CIRCADIAN RHYTHMS, INTERMITTENT FASTING, METABOLIC HEALTH

THE UNIVERSITY of ADELAIDE

A thesis submitted by

Lijun Zhao

(MBBS, MSc in Medicine)

For the degree of

Doctor of Philosophy

Discipline of Medicine

Adelaide Medical School

The University of Adelaide

August 2021

TABLE OF CONTENTS

LIST OF TABLES

LIST OF SUPPLEMENTARY TABLES

LIST OF FIGURES

LIST OF SUPPLEMENTARY FIGURES

LIST OF APPENDICES

SUMMARY

Lifestyle induced metabolic diseases such as obesity, type 2 diabetes (T2DM) and cardiovascular diseases (CVD) are often associated with increased energy intake, and reduced levels of physical activity. The feeding and fasting cycle is one of the strong time cues to entrain circadian rhythms in peripheral organs without altering the central clock in the brain. Recently, insulin was shown to be a time cue and thus an important reset signal for peripheral circadian clocks in vitro, in mice and in humans. Therefore, mistimed and erratic eating patterns, known to occur in modern society, may induce circadian disruption, and could contribute to the development of metabolic diseases. The aim of this thesis was to provide the evidence that mistimed eating will associate with markers of obesity and T2DM and intermittent fasting on 3 non-consecutive days per week may impact peripheral clocks, while time restricted eating (TRE) will decrease the risk factors of T2DM via restoring the 24-hour rhythms of blood metabolite and glucoregulatory hormones, as well as the transcriptome in subcutaneous adipose tissue (SAT).

To examine the impact of erratic eating patterns on metabolic health, I enriched the existing concept of eating architecture, to include variations in meal frequency, size, timing and regularity. I first carried out a cross-sectional study to determine the relationship between components of eating architecture on body fat and markers of glycaemic control in 73 healthy adults at increased risk of T2DM. I aligned the datasets from the food diary, accelerometers and continuous glucose monitors in real-time for 1 to 2 weeks collected under free-living conditions. The results from the multivariable linear regression analysis show that lower day-to-day variability in first meal consumption was associated with lower body fat and improved glucose control in adults at increased risk of T2DM.

Intermittent fasting (IF) is a practice of alternating periods of eating and fasting, which has

emerged as an effective therapeutic dietary strategy for combating obesity and improving markers of cardiometabolic diseases. IF regimes include zero or minimal calories consumed 1 to 4 days per week on fasting days, followed by *ad libitum* eating on the remaining days, leading to about 10% calorie restriction overall per day of fasting (e.g., 3 days of fasting is ~30% calorie restriction). However, the day-to-day variation in the patterning of food intake under IF intervention could also lead to circadian disruption, but this is not well tested to date. Therefore, I next examined the effects of eight weeks of IF on mRNA levels of genes involved in circadian regulation in skeletal muscle and SAT. In this study, breakfast was consumed before a 24-hour fast on 3 non-consecutive days/week. The results indicate no universal effect of IF to alter peripheral clocks, which may partly be due to the alignment of the fasting/feeding cycle with the biological clock by initiating the fasting day at breakfast.

TRE, is a circadian rhythm-reinforcing lifestyle that recommends restricting energy intake within a daily shortened period of time during the active phase (6-10 hours in human studies, 8-12 hours in animal studies), alternatively lengthening the daily fasting period, without altering calorie intakes or diet quality. In animal models of obesity and aging, TRE reduced diet-induced weight gain and fat accumulation, improved glucose tolerance and insulin sensitivity, prevented the age- and diet-induced reduction in cardiac contractile function and muscle function, as well as rescued the metabolic consequences induced by clock gene mutants. In humans, TRE also reduced body weight and fat mass, improved glucose control, mitigated risk factors of CVD such as blood pressure, lipids and inflammation in individuals with overweight and obesity. However, most of the TRE clinical trials are pilot studies that have only examined adherence, feasibility and body weight with a limited sample size and number. Few have explored the potential mechanisms involved in restoring the circadian clocks in human tissue and blood. Hence, I conducted the first human trial with a highly controlled metabolic ward stay to examine the effects of eight weeks of 10-hour TRE (self-selected eating duration except consuming the

last meal before 7:30 pm) on glucose metabolism in men with increased risk of T2DM. Fifteen men with obesity but no history of diabetes were enrolled and underwent two weeks of baseline monitoring, before they were instructed to eat their regular diets within a contiguous 10-hour time frame each day for 8-weeks. Metabolic testing was performed at baseline and week 8 during a 35-hour metabolic ward stay, during which all food intake was strictly timed and controlled. Eight weeks of TRE did not alter the primary outcome plasma glucose area under the curve (AUC) at breakfast, but increased glucose AUC at dinner. TRE reduced fasting glucose, glycated haemoglobin (HbA1c), body weight and body fat. In SAT after an overnight fast, 117 genes were upregulated and 202 genes were downregulated by TRE. Pathway analysis revealed the downregulation of genes involved in proteasome function and mitochondrial regulation. These results suggest that TRE had a net effect to reduce glycaemia and dampened energy-consuming pathways in SAT.

To further explore the mechanisms of TRE on these improvements, I evaluated the impacts of TRE on markers of central clocks (dim light melatonin onset, DLMO) and SAT clocks, as well as the 24-hour profiles of blood metabolites, glucoregulatory hormones and transcriptome profiles in human SAT in the same cohort. TRE did not alter DLMO, suggesting central clocks were not altered by TRE. TRE reduced morning cortisol levels, which correlated to the changes in HbA1c, indicating an improved glycaemic control. TRE altered the 24-hour profile of insulin, non-esterified fatty acids (NEFA), triglyceride and glucose-dependent insulinotropic peptide. TRE increased CLOCK and NR1D2 and decreased PER1 and NR1D1 at 12 am. The rhythmicity of 450 genes were altered by TRE. Pathway analysis showed enrichment in transcription co-repressor activity, DNA binding transcription factor binding, regulation of chromatin organization and small GTPase binding pathways. Weighted Gene Co-expression Network Analysis of these 450 genes revealed the three module eigengenes that were strongly correlated with BMI, insulin and NEFA. This study suggests that TRE altered the rhythms of

blood metabolites, insulin, and increased key clock genes, restored the expression of genes involving in chromatin regulation and vesicular translocation of glucose transporters in human SAT.

In conclusion, this research showed that routine consumption of breakfast meals may optimise temporal regulation to anticipate and respond appropriately to a glucose challenge. This was partially supported by the second study showing that IF protocol initiated at breakfast time does not alter peripheral clocks in muscle or fat, which could be essential to prevent circadian misalignment during IF in humans. Finally, I provided novel evidence that TRE could be a preventative tool for individuals with obesity who are at increased risk of T2DM to improve glucose control and reset circadian rhythms, and thus may potentially be a therapeutic strategy for patients with prediabetes or T2DM.

DECLARATION

I, Lijun Zhao, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any University or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any University or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I acknowledge that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Name: Lijun Zhao

Signature: Date: 25 August 2021

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my supervisors Associate Professor Leonie Heilbronn, Professor Gary Wittert and Doctor Amy Hutchison, for their motivation, advice, expertise, belief in my capacity, and unreserved continuous support during my PhD life. It was a great privilege and honour to study under their supervision. I would like to thank Leonie for her mentoring and inspiration with her dynamism, vision, and critical thinking, which equipped me with skills and insightful thoughts that are essential in my future career. Thank her for spending time and effort in improving my writing skills. Her kindness, patience, encouragement, support and expertise have been invaluable in my PhD journey. My sincere thanks to Gary for his encouragement, advice, critically reviewing my work and extended my role to the journal editorial. I would like to thank Amy for her invaluable guidance, kind cooperation and precious time throughout my candidature.

A big thank you to my collaborators Professor Siobhan Banks and Doctor Crystal Grant from University of South Australia, and Professor Satchidananda Panda and his team members (Doctor Emily Manoogian, Hiep Le and April Williams) from Salk Institute for Biological Studies for their technical and financial support and suggestions. My project would not be completed without their engagement.

I would like to thank the wisdom and guidance received from my postgraduate co-ordinators Doctor Christina Bursill and Associated Professor Richard Young.

I am grateful to Doctor Yohannes Melaku, Andrew Vincent and Kylie Lange for their statistical support. I would also like to thank the staffs of the CRE group in the AHMS building (Scott Standfield and Mark Salkeld) for their guidance in my laboratory work. Additionally, I would like to thank my group members (Bo Liu, Prashant Regmi, Rajesh Chaudhary, Xiao Tong

Teong, Kai Liu and Rasha Charrouf), past and present PhD fellows (Yonatal Tefera, Rezanur Rahaman, Sebastian Overduin, Xuyi Wang, Nitish Joat, Qianhui Wan, Rebecca O'rielly, Yoko Wang, Maria Nunez-Salces, and Xiaoliang Tong) for their continuous support and encouragement. A special thank for Xiao Tong and Julia who collected the data which formulate part of my PhD work.

Thanks to my housemates (Zhan Liu, Xiaonan Xiong and Jiajian Wang) for their support, care and bareness in my life. I want to thank my Talk With Aussie partners Jenny and Barry, who have given me care, encouragement, and effort to improve my English speaking skills.

I would like to express my eternal gratitude to my parents Mr Fuyou Zhao & Mrs Yuxiang Shi, for their constant support, attention and encouragement to build up my career. They are pillars of my life. They teach me kindness, integrity, hardworking, fortitude, focus, determination and respectfulness, which help in all aspects of my life, including my PhD journey. I would not be able to be in this position without their support. A sincere thanks to grandparents (I wish my grandpa could see my achievements although he has left during the 1st year of my PhD), my sisters and other family members for their enthusiasm, support, encouragement and understanding.

Last but not least, my special thanks to my boyfriend (YouAreHoney) for his care, mentoring, patience, support and love during my PhD journey. I would not be able to be such strong without him.

I feel privileged to acknowledge and thank everyone who contributed to the completion of this PhD work.

Lijun Zhao

August 2021

DEDICATION

To my parents, grandparents and boyfriend

PUBLICATIONS CONTRIBUTING TO THESIS

Publications and manuscripts are listed in order of appearance in this thesis.

1. **Zhao L**, Hutchison AT, Heilbronn LK. Carbohydrate intake and circadian synchronicity in the regulation of glucose homeostasis. *Curr Opin Clin Nutr Metab Care.* 2021;24(4):342-348.
2. **Zhao L**, Teong XT, Liu K, Liu B, Melaku YA, Vincent AD, Manoogian ENC, Panda S, Wittert G, Hutchison AT, Heilbronn LK. Eating architecture in adults at increased risk of type 2 diabetes: associations with body fat and glycaemic control. *Br J Nutr*. 2021:1-28.
3. **Zhao L**, Hutchison AT, Wittert GA, Thompson CH, Lange K, Liu B, Heilbronn LK. Intermittent Fasting Does Not Uniformly Impact Genes Involved in Circadian Regulation in Women with Obesity. *Obesity (Silver Spring).* 2020;28 Suppl 1:S63-S67.
4. **Zhao L**, Hutchison AT, Liu B, Yates CL, Teong XT, Wittert GA, Thompson CH, Nguyen L, Au J, Manoogian ENC, Le HD, Williams AE, Panda S, Banks S, Heilbronn LK. Time restricted eating improves glycaemic control and attenuates energy-consuming pathways in adipose tissue in men at increased risk of type2 diabetes. *Nutrition*, 2022. **96**: p. 111583.

Under review:

5. **Zhao L**, Hutchison AT, Liu B, Andrew V, Wittert GA, Thompson CH, Nguyen L, Au J, Manoogian ENC, Le HD, Williams AE, Banks S, Panda S, Heilbronn LK. Time restricted eating alters the 24-hour transcriptomic profile in human adipose tissue. Obesity.

CONFERENCE PROCEEDINGS

1. **Lijun Zhao**, Amy T Hutchison, Bo Liu, Gary A Wittert, Campbell H Thompson, Leanne Nguyen, John Au, Andrew Vincent, Emily N. C. Manoogian, Hiep D Le, April E Williams, Siobhan Banks, Satchidananda Panda, Leonie K Heilbronn. Time restricted eating alters the 24-hour transcriptomic profile in human adipose tissue. Australia and New Zealand Obesity Society Virtual Annual Scientific Meeting, Brisbane, Australia 2021 [**oral presentation**].
2. **Lijun Zhao**, Amy Hutchison, Bo Liu, Crystal Yates, Xiao Tong Teong, Gary Wittert, Campbell Thompson, Leanne Nguyen, John Au, Emily Manoogian, Hiep Le, April Williams, Satchidananda Panda, Siobhan Banks, Leonie Heilbronn. Time restricted eating improves glycaemic control and attenuates energy-consuming pathways in human adipose tissue. ASMR South Australian Scientific Meeting, Adelaide, Australia 2021 [**oral presentation**].
3. **Lijun Zhao**, Xiao Tong Teong, Kai Liu, Bo Liu, Yohannes A Melaku, Andrew D. Vincent, Emily N. C. Manoogian, Satchidananda Panda, Gary Wittert , Amy T Hutchison, Leonie K Heilbronn. Eating patterns in adults with obesity: associations with body fat and glycaemic control. The Austral-Asia Obesity Research Update 2020 virtually - Convened by Australia and New Zealand Obesity Society, virtual conference, Australia 2020 [**oral presentation**].
4. **Lijun Zhao**, Xiao Tong Teong, Kai Liu, Bo Liu, Yohannes A Melaku, Andrew D. Vincent, Emily N. C. Manoogian, Satchidananda Panda, Gary Wittert , Amy T Hutchison, Leonie K Heilbronn. Eating patterns in adults with obesity: associations with body fat and glycaemic control. Florey postgraduate research conference, Adelaide, Australia 2020 [**poster presentation**].

5. **Lijun Zhao**, Amy Hutchison, Bo Liu, Crystal Yates, Xiao Tong Teong, Gary Wittert, Campbell Thompson, Leanne Nguyen, John Au, Emily Manoogian, Satchidananda Panda, Siobhan Banks, Leonie Heilbronn. The impact of time restricted eating on glucose response to an identical standard meal in the morning and evening in men at increased risk of type 2 diabetes, Joint scientific meeting of Australian New Zealand Obesity Society (ANZOS), the Australasian Society for Lifestyle Medicine (ASLM) and the International Chair on Cardiometabolic Risk (ICCR), Sydney, Australia 2019 [**oral presentation**].
6. **Lijun Zhao**, Amy Hutchison, Bo Liu, Crystal Yates, Xiao Tong Teong, Gary Wittert, Campbell Thompson, Leanne Nguyen, John Au, Emily Manoogian, Satchidananda Panda, Siobhan Banks, Leonie Heilbronn. Time restricted eating reduces fasting blood glucose but not 24-hour glucose levels in men at increased risk of type 2 diabetes mellitus, Florey Postgraduate Research Conference, Adelaide, Australia 2019 [**poster presentation**].
7. **Lijun Zhao**, Amy Hutchison, Bo Liu, Crystal Yates, Xiao Tong Teong, Gary Wittert, Campbell Thompson, Leanne Nguyen, John Au, Emily Manoogian, Satchidananda Panda, Siobhan Banks, Leonie Heilbronn. Time restricted feeding improves glucose control to a breakfast meal in men with obesity and elevated waist circumference after 8 weeks, Lifelong Health Theme 'Kick-off' Event, South Australia Health and Medical Research Institute, Adelaide, Australia, 2019 [**invited oral presentation**].

ACHIEVEMENTS DURING CANDIDATURE

1. Awarded Best Early Career Researcher Oral Presentation Award from The Austral-Asia Obesity Research Update Virtual Conference 2020 (ANZOS).
2. Awarded Florey Medical Research Foundation Prize - Applied Science Category from Florey Postgraduate Research Conference 2020.
3. Awarded Northern Communities Health Foundation Prize from Florey Postgraduate Research Conference 2020.
4. Awarded High degree research travel scholarship, University of Adelaide (2019).
5. Shortlisted for Australian and New Zealand Obesity Society (ANZOS) Annual Conference Early Career Researcher award 2021/2019.
6. Awarded Beacon of Enlightenment Scholarship for PhD Program, University of Adelaide, Australia (2017-2021)

ABBREVIATIONS

(i)AUC	(Incremental) area under the curve
(p)AKT	(phosphorylated) Protein kinase B
18S	18S ribosomal RNA
Actb	Actin beta
ADF	Alternate-day fasting
ADMF	Alternate-day modified fasting
AEBSF	4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride
ALT	Alanine transaminase
AMP/ATP	Adenosine monophosphate/ adenosine triphosphate ratio
AMPK (Ampk)	AMP-activated protein kinase
ApoB	Apolipoprotein B
ARHAGEF17/18	Rho/Rac guanine nucleotide exchange factor 17 or 18
ARHGDIα	Rho GDP dissociation inhibitor alpha
ARHGEF1	Rho guanine nucleotide exchange factor 1
Arntl	Aryl hydrocarbon receptor nuclear translocator-like protein 1
AST	Aspartate transaminase
ATGL	Adipose triglyceride lipase
ATP5F1E	ATP synthase F1 subunit epsilon
ATP5PD	ATP synthase peripheral stalk subunit d
AUSDRISK	Australian Type 2 Diabetes Risk Assessment Tool
B2m	Beta-2-microglobulin
BCAA	Branched chain amino acids
BDNF	Brain-derived neurotrophic factor

BMAL1 (Bmal1)	Brain and muscle ARNT like protein 1
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
CAR	Cortisol awakening respons
CBX4	Chromobox 4
CCGs	Clock-controlled genes
CCK	Cholecystokinin
CCT7/8	Chaperonin containing TCP1 subunit 7 or 8
CDC42EP1	CDC42 effector protein 1
CGM	Continuous glucose monitoring
CI	Confidence interval
CK1 ε/δ	Casein kinase 1 ε or δ
CLOCK (Clock)	Circadian locomotor output cycles kaput
CR	Calorie restriction
CREB	cAMP-responsive element binding protein
CRP	C-reactive protein
CRTC1	CREB regulated transcription coactivator 1
CRY1 (Cry1)	Cryptochrome 1
CTBP1	C-terminal binding protein 1
CTDP1	Carboxyl-terminal domain phosphatase subunit 1
CVD	Cardiovascular diseases
DBP (Dbp)	D-box binding protein
DEXA	Dual-energy X-ray absorptiometry
DLMO	Dim light melatonin onset
DPP-4	Dipeptidyl peptidase-IV

DVL1	Dishevelled segment polarity protein 1
EDD	Easy Diet Diary
EI	Energy intake
ER	Energy requirements
FASN	Fatty acid synthase
FBG	Fasting blood glucose
FBRS	Fibrosin
FDR	False discovery rate
FFA	Free fatty acids
FFM	Fat free mass
FGF21	Fibroblast growth factor 21
FINS	Fasting plasma insulin
FM	Fat mass
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
fT3	Free tri-iodothyronine
fT4	Free thyroxine
G6-P	Glucose 6-phosphate
GGT	Gamma-glutamyl transpeptidase
GI	Glycemic index
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide-1;
Glut2/4,	Glucose transporter type 2 or 4
GLUT4	Glucose transport type 4
GO	Gene ontology

GSEA	Gene set enrichment analysis
GSK3	Glycogen synthase kinase 3
H1FX	H1 histone family member X
HbA1c	Glycated haemoglobin
HC	High carbohydrate
HCir	Hip circumference
HDAC1/2/3	Histone deacetylase 1 or 2 or 3
HDL-c	High-density lipoprotein-cholesterol
HF	High fat
HMB	β-hydroxy β-methylbutyrate supplementation
HOMA-IR	Homeostatic model assessment of insulin resistance
HP	High protein
Hprt	Hypoxanthine phosphoribosyltransferase
HR	Heart rate
hsCRP	High-sensitivity C-reactive protein
HSL	Hormone-sensitive lipase
HSP90	Heat shock protein 90
HSP90AB1	Heat shock protein 90 alpha family class B member 1
IF	Intermittent fasting
IF70/ IF100	Intermittent fasting with food provided at 70% or 100% of baseline energy requirement
IGF-1	Insulin-like growth factor-1
IGFBP-1/ 3	Insulin-like growth factor binding protein 1 or 3
IL-6/8/1b	Interleukin 6 or 8 or 1b
IRS	Insulin receptor substrate

KMT1/SUV39H	lysine methyltransferase 1 subunit SUV39H1
KMT2B	lysine methyltransferase 2B
LDL-c	Low-density lipoprotein cholesterol
LH	Luteinizing hormone
LM	Lean mass
LPL	Lipoprotein lipase
LTF	Lactotransferrin
MBD3	Methyl-CpG binding domain protein
mCC	myCircadianClock
MRPL33 /51	Mitochondrial ribosomal protein L33 or 51
MRPS35	Mitochondrial ribosomal protein S35
MsigDB	Molecular Signatures Database
MTNR1B	Melatonin receptor 1B gene
mTORC	Mammalian target of rapamycin complex
NAD	Nicotinamide adenine dinucleotide
NAMPT	Nicotinamide phosphoribosyl transferase
NCOR2	Nuclear receptor corepressor 2
NDUFA12	NADH:ubiquinone oxidoreductase subunit A12
NDUFS5	NADH:ubiquinone oxidoreductase subunit S5
NEFA	Non-esterified fatty acid
NR1D1/2 (Nr1d1/2)	Nuclear receptor subfamily 1, group D, member 1 or 2
OGTT	Oral glucose tolerance test
ORA	Overrepresentation analysis
PAK	p21-activated kinases

PARK7	Parkinsonism associated deglycase
PARP1	Poly(ADP-ribose) polymerase 1
PCR	Polymerase chain reaction
PER1/2 (Per1/2)	Period 1 or 2
PGC-1α	Peroxisome proliferator-activated receptor- γ coactivator 1α
PI3K/PIK3	Phosphoinositide 3-kinase
PLEKHG3	Pleckstrin homology and Rho GEF domain containing G3
POCS	Polycystic ovary syndrome
PPARα/γ	Peroxisome proliferator-activated receptor α or γ
PRDM16	PR/SET Domain 16
PSMC2/5	Proteasome 26S subunit, non-ATPase 2 or 5
PSMD2	Proteasome 26S subunit, ATPase 2
PYY	Pepetide YY
RAB11	Ras-related protein Rab-11
RAB11FIP3	RAB11 family interacting protein 3
RAC1	Rac family small GTPase 1
RAI1	Retinoic acid-induced 1
RCT	Randomized control trial
REM	Repaid eye movement
RER	Respiratory exchange ratio
REV-ERB α/β	Nuclear receptor reverse erythroblastosis virus α or β
ROR (Ror)	Retinoic acid related orphan receptor
RORE	ROR-response elements
RPS6K1 or S6K1	Ribosomal protein S6 kinase 1
RPS6KA4	Ribosomal protein S6 kinase A4

RXT	Randomized crossover trial
SAT	Subcutaneous adipose tissue
SCN	Suprachiasmatic nucleus
SD	Standard deviation
SELENOS	Selenoprotein S
SEM	Standard error of mean
SETDB1	SET Domain Bifurcated Histone Lysine Methyltransferase 1
SHBG	Sex hormone-binding globulin
SIRT1 (Sirt1)	Sirtuin 1
SKP1	S-phase kinase associated protein 1
SNPs	Single nucleotide polymorphisms
SREBF1,	Sterol regulatory element binding transcription factor 1
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TCF3	Transcription factor 3
TG	Triglycerides
TNFα	Tumor necrosis factor α
TOMM7 /22	Translocase of outer mitochondrial membrane 7 or 22
TRE	Time restricted eating
TRiC	Chaperonin-containing T-complex
TSC22D4	Transforming growth factor beta-like stimulated clone 22 domain family member 4
TSH	Thyroid stimulating hormone
TXN	Thioredoxin
VAS	Visual analogue scales

VAT	Visceral fat mass
VCP	Valosin containing protein
WC	Waist circumference
WGCNA	Weighted gene co-expression network
WHR	Waist/hip ratio
ZNF587	Zinc finger protein 587
β-HBD	Beta hydroxybutyrate

CHAPTER 1 INTRODUCTION, RESEARCH QUESTIONS, AIMS AND HYPOTHESIS

1.1 Obesity prevalence and impacts

More than 1.9 billion adults were overweight or obese in 2016, globally (World Health Organization, 2018). This figure has tripled since 1975 (World Health Organization, 2018). The latest report from the Australian Institute of Health and Welfare revealed that 36% of Australians were overweight and 31% were obese in 2017–2018 (Australian Institute of Health and Welfare, 2020b). It is predicted that the obesity rate of Australian adults alone will reach 35% by 2025 (Hayes et al., 2017). It is also projected that the rate of severe obesity (body mass index [BMI] $\geq$ 35 kg/m^2) will reach 13% by 2025, from just 5% in 1995 (Hayes et al., 2017).

The National Institute of Health (NIH) in the United States and World Health Organization (WHO) acknowledges obesity as a disease, recognizing its profound effects on individual health outcomes and socioeconomic costs (National Heart, 1998, Bray et al., 2017). Obesity is linked to a range of chronic diseases, such as type 2 diabetes (T2DM), cardiovascular disease (CVD), liver disease, sleep apnoea, reproductive diseases, mood disorders, arthritis, and some types of cancer (Afshin et al., 2017, Swinburn et al., 2011, Romero-Corral et al., 2010, Magliano, 2008, Luppino et al., 2010, Polyzos et al., 2019), and an estimated reduction in life expectancy of 5–20 years lost depending on the severity of the condition and comorbidities (Fontaine et al., 2003, Berrington de Gonzalez et al., 2010, Whitlock et al., 2009) (Figure 1.1).

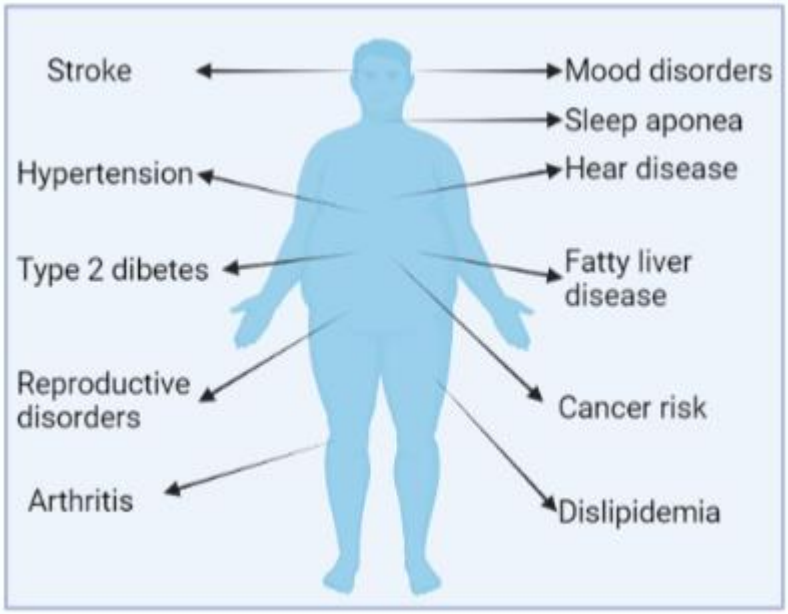


Figure 1.1 Adverse effect of obesity.

Additionally, the rising prevalence of obesity in society will increase the future direct (health burden) and indirect (productivity loss) costs to the society (Keramat et al., 2020b, Keramat et al., 2020a). It has been estimated that the health burden resulting from obesity is 0.7%-2.8% of a country's annual expenditure worldwide (Withrow and Alter, 2011). In Australia, the most recent report disclosed that the disease burden in Australia due to overweight and obesity reached 8.4% in 2015 from 7% in 2011 (Australian Institute of Health and Welfare, 2020a, Australian Institute of Health and Welfare (AIHW), 2017). Furthermore, the World Obesity Federation (WOF) estimated that the total cost of obesity to health services globally is USD 990 billion per year (World Health Organization, 2019, World Obesity Federation, 2017). In Australia, the annual cost of treating obesity-related diseases is projected to increase from $8 billion (in 2012) to $21 billion by 2025 (World Health Organization, 2019, World Obesity Federation, 2017). Therefore, reducing obesity significantly reduces associated disease costs.

Multiple risk factors and complex mechanisms are involved in the increasing prevalence of

overweight and obesity, including genetic, metabolic (i.e., aging, sex, neuroendocrine factors, microbiota, thermogenesis), environmental (i.e., socioeconomic status, social-culture) and behavioural/lifestyle (i.e., overeating, physical inactivity, sleep deficiency, mistimed food intake) factors (Blüher, 2019, St-Onge et al., 2017). The fundamental cause of obesity is a chronic oversupply or consumption of calories and few calories expended, which are the major aspects of the modern lifestyle (Hall et al., 2011, Mindikoglu et al., 2017).

Lifestyle refers to what and how we eat, sleep and exercise. With the development of industrial production, transport systems, entertainment, information technologies, and food production, the modern lifestyles of humans are less governed by the light-dark cycle (~24 hour). What and how we eat have profoundly contributed to the increasing prevalence of obesity and obesity-related diseases (St-Onge et al., 2017, Magklis et al., 2019).

1.2 The erratic eating pattern in modern life

1.2.1 What we eat

Long term overconsumption of energy is linked to obesity, with foods that are ultra-processed clearly contributing to this association. The Western diet pattern is characterized by a high daily intake of saturated fats, refined carbohydrates and salt (López-Taboada et al., 2020). Conversely, the Mediterranean diet is underpinned by a high intake of vegetables, fruits, nuts, cereals, whole grains, and olive oil, a moderate consumption of fish and poultry, and a low intake of sweets, red meat and dairy products (Bach-Faig et al., 2011, D'Innocenzo et al., 2019). This much healthier diet is low in saturated fatty acids and rich in fibre, and glutathione and antioxidants. It is well established that habitual consumption of a Western or high-fat diet is associated with chronic disease, including obesity, T2DM, and CVD (López-Taboada et al., 2020). The Mediterranean diet has been associated with a lower risk of obesity, T2DM and metabolic syndrome and CVD in adults (Estruch et al., 2018, Huo et al., 2015, D'Innocenzo et al., 2019).

1.2.2 How we eat

Eating architecture refers to how, rather than what, we eat and encompasses four main components: 1) meal frequency, 2) meal size (calorie density), 3) meal timing (i.e., daily eating duration, and timing in relation to the sleep-wake cycle) and 4) meal regularity (the day-to-day variation in all of the above components) (Magklis et al., 2019, Pot et al., 2016b).

These components particularly cannot be accurately assessed with a single questionnaire or 24-hour food recall. Further, the methodology of collecting information on eating patterns and the definition of a meal or eating event varies from study to study (Leech et al., 2015), which may impact the outcomes. *Leech et al* found that 57% of men and 59% of women in Australia had either a "late lunch" (i.e. eating occasions peak at one hour later than the "conventional" pattern) or "grazing" eating pattern (i.e. frequent but no distinct peaks in the probability of eating occasions) using a latent-class analysis (Leech et al., 2017b). The estimated eating duration via 24-hour food recall in a 15,000 American cohort was 12 h for most individuals (Kant, 2018). Using a photograph-based smartphone application, *Gill et al* showed an irregular "breakfast-lunch-dinner temporal pattern" in healthy and non-shift-worker adults (Gill and Panda, 2015). In this study, over 75% of total calories were consumed after midday, and "metabolic jet-lag" was displayed between weekdays and weekends (Gill and Panda, 2015). A prolonged daily eating duration of ~15 hour/day was also observed with the definition of a meal as all eating events occurred within 15 minutes from one to the next, and each eating event was defined as any of the events that showed a unique time stamp measured by a smartphone application (Gill and Panda, 2015, Gupta et al., 2017b).

Meal timing

Prospective studies have demonstrated positive associations between breakfast skipping and weight gain as well as increased risk of developing T2DM (St-Onge et al., 2017, Bi et al., 2015,

Ballon et al., 2019, Ma et al., 2020, Wicherski et al., 2021). However, randomized clinical trials (RCTs) have shown mixed results (Schlundt et al., 1992, Geliebter et al., 2014, Dhurandhar et al., 2014). A recent meta-analysis of seven randomized clinical trials that included 425 participants showed that breakfast skipping reduced body weight by 0.5 kg, but increased low-density lipoprotein cholesterol (LDL-c) by 9 mg/dL (Bonnet et al., 2020). Late-night eating is also associated with an increased risk of obesity, poorer glucose control and CVD (Nas et al., 2017, Xiao et al., 2019, Gu et al., 2020, Lopez-Minguez et al., 2018, McHill et al., 2017, Allison et al., 2020). A higher percentage of total daily energy intake consumed within 2 hours of waking and a lower percentage of total energy intake consumed within 2 hours before bedtime was associated with lower BMI in 872 middle-to-old aged adults by six non-consecutive 24-hour dietary recalls over one year (Xiao et al., 2019).

Meal size

In regard to the meal size, a higher proportion of energy consumed in the evening is associated with the risk of obesity (Kahleova et al., 2017, Aljuraiban et al., 2015). For example, eating the largest meal at dinner was associated with higher BMI compared with those who ate their largest meal at breakfast or lunch in a relatively healthy cohort of 50,660 North American in the Adventist Health Study 2 (Kahleova et al., 2017). One possible mechanism could be the proximity of meal consumption to the rise time of nocturnal melatonin (known as dim light melatonin onset, DLMO, a marker of body circadian clock). *McHill et al* showed that later eating closer to DLMO was linked with increased adiposity and impaired glucose control (McHill et al., 2017, McHill et al., 2019). In RCTs, skewing food intake towards breakfast (i.e., high calorie in the morning versus high calorie in the evening) improves glycaemic control and promotes weight loss (Jakubowicz et al., 2015a, Jakubowicz et al., 2013).

Meal frequency

A greater meal frequency has been associated with a lower risk of obesity (St-Onge et al., 2017). However, The Adventist Health Study 2 showed that eating one or two meals/day was associated with a relative lower BMI compared with 3meals/day, and eating >3 meals/day (snacking) was associated with an increased BMI (Kahleova et al., 2017). The authors attributed these positive effects of reduced meal frequency to the combination of meal timing, frequency, and longer overnight fasting. Reduced meal frequency from 6 times/day to 3 times/day also improved glycaemic management, decreased hunger and cravings, and restored peripheral clocks in patients with T2DM (Jakubowicz et al., 2019).

Meal regularity

This encompasses the day-to-day variation in meal size, frequency and meal timing. Irregular meal size was associated with increased risk factors of cardiometabolic diseases (Pot et al., 2016b, Pot et al., 2014, Sierra-Johnson et al., 2008, Shin et al., 2009, Wennberg et al., 2016). Compared to irregular breakfast eaters (3-4 days/week), regular daily breakfast eaters (7days/week) and those who never ate breakfast (0 day/week) were less likely to be obese (Guinter et al., 2020). Regularity of breakfast consumption may partially explain the inconsistent outcomes of the impact of breakfast skipping on weight control between population-based studies and across RCTs, as none of these studies have examined breakfast regularity. Only a handful of small RCTs have examined the impact of meal irregularity on biomarkers of disease risk. Irregular meal frequency (3-9 meals/day) decreased postprandial thermogenesis (Farshchi et al., 2004a), and increased insulin resistance (Farshchi et al., 2004b, Farshchi et al., 2005) and fasting lipids (Farshchi et al., 2005) compared with regular meal frequency (6 meals/day) in lean or obese women.

The rapid development of technologies, such as smartphone applications, provides us with new abilities to investigate individuals' eating behaviours under free-living conditions

comprehensively. The reliability of digital photographs to estimate calorie intake has been validated against weighed food records with underestimation bias <5% for energy and all macronutrients (Naaman et al., 2021). The usage of smartphone applications allows tracking of what, how much, where, and when foods are consumed (Yong et al., 2020). For example, *myCircadianClock* (mCC) was developed at the Salk Institute for Biological Studies (La Jolla, CA, USA), and serves as an electronic food, activity, and sleep diary to record all food intake, physical activity, and sleep quantity/quality every day during diet intervention in real time (Chow et al., 2020, Wilkinson et al., 2019, Gill and Panda, 2015, Gupta et al., 2017b). Simultaneously, tracking cardiometabolic risk factors monitors by continuous glucose monitoring, dynamic 24-hour blood pressure monitoring, and activity and sleep patterns tracking through accelerometers, can also provide dynamic changes over the same time periods. These can be aligned with food records via smartphone application and physical activity status to develop a more comprehensive understanding of eating architecture and cardiometabolic health.

1.3 Circadian rhythms

1.3.1 Definition

Circadian rhythms are endogenous, self-sustaining, daily oscillating physiological rhythms with a period of approximately 24 hours (Bass and Takahashi, 2010, Panda, 2016, Reppert and Weaver, 2002). In an environment free of time cues, the circadian rhythms of plasma melatonin in humans are on average period of 24.2 hours (Czeisler et al., 1999). Under normal conditions of the light-dark cycle, circadian rhythms have a period of exactly 24 hours. Therefore, circadian rhythms need to be reset daily to synchronise to the external 24-hour environment, so called entrainment by a time giver (i.e., Zeitgeber) (Czeisler et al., 1999). Zeitgebers have a phase response curve profile that determines the direction of the rhythms move as a result of

the Zeitgeber and the magnitude that a Zeitgeber has on the timing of rhythms across the circadian period. A positive phase shift means the system has advanced its timing by moving rhythms to peak earlier whereas a negative phase shift means the system has delayed its timing by moving rhythms to peak later (Bass and Takahashi, 2010). Besides, the magnitude of phase shift emphasizes how the responsiveness of the system differs across the circadian phase.

Circadian rhythms control internal biological processes which direct behaviour and metabolism such as hormone synthesis and secretion, body temperature, nutrient absorption, sleep-active cycles and feeding-fasting cycles (Bass and Takahashi, 2010, Panda, 2016, Reppert and Weaver, 2002, Manoogian and Panda, 2017, Huang et al., 2011, Banks et al., 2016).

1.3.2 Circadian system organization and clock machinery

Central and peripheral clock organization

The mammalian circadian system contains a central master clock located in the hypothalamic superchiasmatic nucleus (SCN) and peripheral clocks in other brain regions and almost all other tissues, including adipose tissue, muscle, liver, gut and pancreas (Sinturel et al., 2020, Bass and Takahashi, 2010, Panda, 2016, Yoo et al., 2004). The SCN exhibits autonomous timekeeping, which oscillates robustly, even after removing all external time cues (Patton and Hastings, 2018). In an environment free of time information, circadian rhythms of plasma melatonin in humans are shown to free run with an average period of 24.2 hours (Czeisler et al., 1999). Therefore, circadian rhythms need to be reset daily to synchronise to the external 24-hour environment, so-called entrainment. The SCN is entrained by the external 24-hour environmental light/dark cycle via retinal photoreceptors in the retinohypothalamic tract (Panda, 2016). The entrained timing signal from the SCN is transmitted to the peripheral clocks by the autonomic nervous system, neural and hormonal signals (i.e., cortisol and melatonin), body temperature, and behavioural signals such as physical activity and food intake (Lowrey and

Takahashi, 2011). Importantly, the strength of behavioural and physiological cycles can reinforce SCN and peripheral clocks (e.g., hormones such as insulin and cortisol generated in a rhythmic pattern under the influence of our behaviour and the action of peripheral clock activity, which can in turn influence clock function). Therefore, it is an orchestra network of body clocks that consolidate highly rhythmic physiology (Bass and Takahashi, 2010) (Figure 1.1).

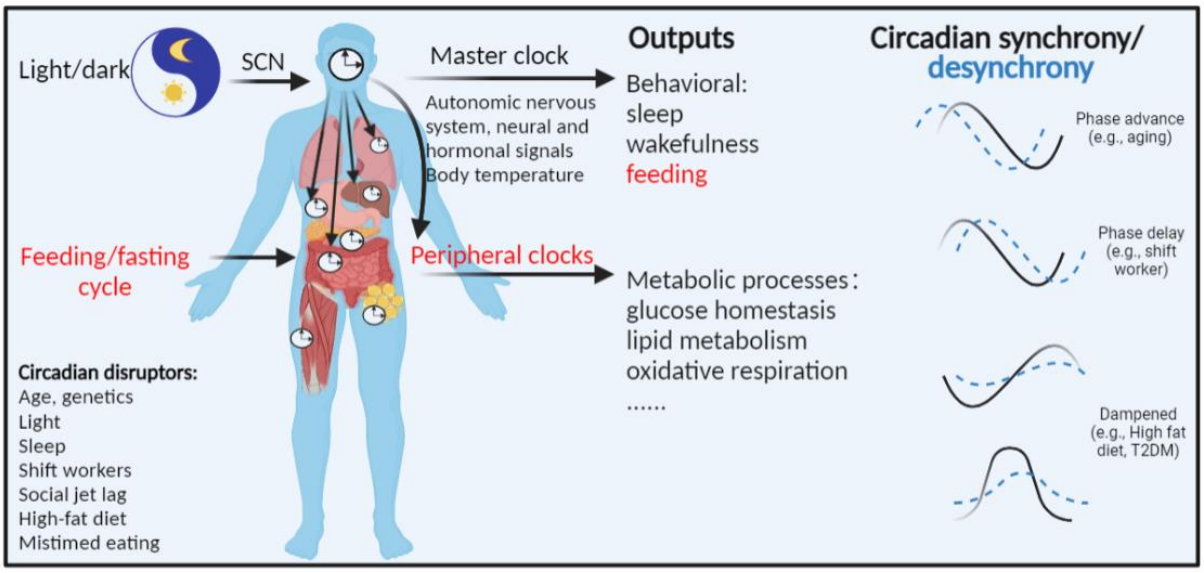


Figure 1.2 Organization of central and peripheral clocks with external cues and behaviour and metabolic outputs.

[The master clock in the suprachiasmatic nucleus (SCN), is entrained by the ~24-hour environmental light/dark cycle. The entrained timing signal from the SCN is transmitted to the peripheral clocks by the autonomic nervous system, neural and hormonal signals (i.e., cortisol and melatonin), body temperature, and behavioural signals. Peripheral clocks exist in almost all other tissues, such as adipose tissue, muscle, liver, gut and pancreas. Brain clock outputs include behavioural rhythms (i.e., sleep, wakefulness and feeding), while peripheral clock outputs include metabolic rhythms (i.e., glucose and lipid homeostasis, etc.). An orchestrated network of body clocks consolidates our robust rhythmic physiology. Circadian desynchrony will be induced when these rhythms are disrupted by the circadian disruptors (i.e., age, genetic,

light, sleep, shift work and mistimed eating etc.). Adapted from (Bass and Takahashi, 2010, Panda, 2016)]

The molecular clock

The molecular mechanism of the central and peripheral clocks is based on the interlocked transcriptional-translational feedback loops (Sinturel et al., 2020, Bass and Takahashi, 2010, Panda, 2016) (Figure 1.2). CLOCK (Circadian locomotor output cycles kaput) : BMAL1/ARNTL (Brain and muscle ARNT-like 1 or Aryl hydrocarbon receptor nuclear translocator-like protein 1) heterodimer activates the expression of Cryptochrome homolog (Cry1/2) and Period homolog (Per1/2/3) by binding to E-box sequences in the promoter region of these genes (Gekakis et al., 1998). Per and Cry proteins accumulate and translocate to nucleus and repress their own transcription by binding with CLOCK: BMAL1/ARNTL complex (Kume et al., 1999, Zheng et al., 2001). The level of Per and Cry proteins decreases due to the protein degradation over the time, thereby decreasing the inhibition on CLOCK: BMAL1 mediated transcription, allowing the cycle to continue. This process takes around 24 hours.

Additionally, CLOCK: BMAL1/ARNTL also increases the expression of retinoic acid receptor-related orphan receptors (Ror-α/β/γ) and nuclear receptor reverse erythroblastosis virus α/β (Rev-erb α/β) via E-box (Sato et al., 2004, Guillaumond et al., 2005, Preitner et al., 2002). BMAL1 transcription is activated and repressed by RORs and REV-ERBs, respectively, by competing for binding on the REV-ERB/ROR-response elements (ROREs) in the BMAL1 promoter region (Emery and Reppert, 2004, Guillaumond et al., 2005). RORα formulates a complex with peroxisome proliferator-activated receptor- γ coactivator 1α (PGC-1α) to enhance the transcription, while REV-ERB recruits nuclear receptor co-repressor 1/2 (NCoR1/2) and histone deacetylase 3 (HDAC3) co-repressors to repress Bmal1 expression (Yin et al., 2010, Alenghat et al., 2008).

Post-transcriptional modifications induced by the feeding/fasting status regulate the molecular clock

Post-transcriptional modifications induced by the feeding/fasting status play a critical role in maintaining the 24-hour period of the molecular clock (Greenwell et al., 2019, Ye et al., 2020, Vollmers et al., 2009, de Goede et al., 2018, Hatori et al., 2012, Sherman et al., 2012) (Figure 1.2). During feeding, activation of insulin-pAKT (protein kinase B)-mTOR (mammalian target of rapamycin) pathway promotes the phosphorylation of glycogen synthase kinase 3 (GSK3), which increases the stability of Per protein (Zheng and Sehgal, 2010), and activates ribosomal S6 protein kinase 1 (S6K1) phosphorylation to increase the synthesis of Per protein (Crosby et al., 2019), and induces Cry1 through an unknown mechanism (Ramanathan et al., 2018). During fasting, mTOR is inhibited and protein kinase AMP-activated protein kinase (AMPK) is activated by increased AMP/ATP or ADP/ATP ratio, reducing the stability of CRY1 and PER2 through phosphorylation of CRY1-Ser 71 and activation of casein kinase 1 (CK1), respectively (Brenna and Albrecht, 2020, Lamia et al., 2009). Fasting also activates nicotinamide phosphoribosyl transferase (NAMPT), which is the rate-limiting enzyme of NAD+ (nicotinamide adenine dinucleotide) salvage pathway. NAD+ inhibits the CLOCK: BMAL1 by increasing activity of Sirtuin 1 (SIRT1, SIRT-family protein, regulate histone acetyltransferase activity of CLOCK) and the poly-ADP-ribosylation mediated by poly (ADP-ribose) polymerase 1 (PARP1) (Xie et al., 2020, Asher et al., 2010, Ramsey et al., 2009, Nakahata et al., 2009).

Clock control genes

Furthermore, the metabolic output of the clock machinery is to drive the transcription of thousands of clock-controlled genes (CCGs) either directly via the CLOCK: BMAL1/ARNTL complex recruitment to the E-box of the promotor and REV-REBs or RORs binding to the

RORE of the promotor (Bass and Takahashi, 2010, Panda, 2016, Lowrey and Takahashi, 2011), or indirectly via other essential clock output proteins such as D-box element-binding proteins (DBP) (Ripperger et al., 2000).

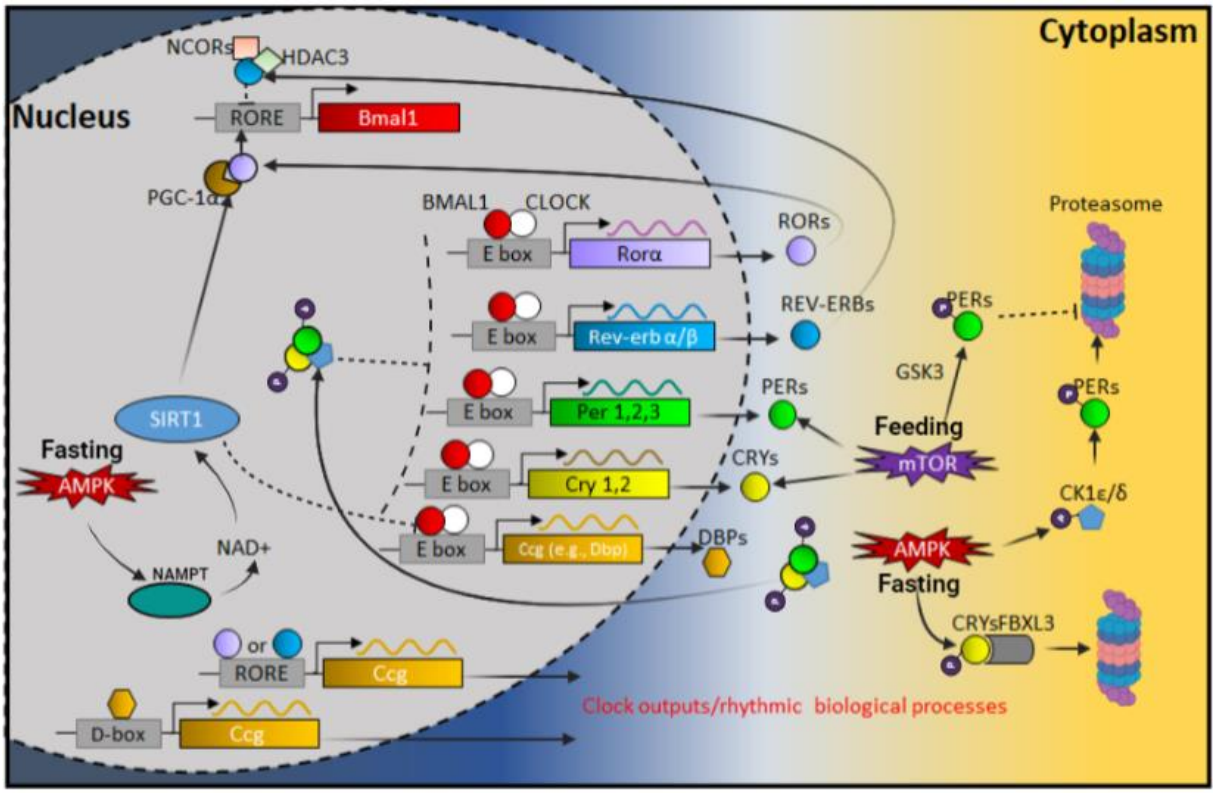


Figure 1.3 The mammalian molecular clock feedback loops and interaction with metabolic signals in response to fasting and feeding.

[In response to fasting and feeding, the molecular clock encompasses two transcriptional-translational feedback loops: 1) Per/Cry gene expression are positively regulated by transcription factors CLOCK (white circle):BMAL1 (red circle) by binding the E-box region, and repressed (dash line) by their own translation protein products PER (green circle)/CRY (yellow circle); 2) additional loop established via the nuclear activators RORα/β/γ (purple circle) and repressors REV-ERBα/β (blue circle) which are induced by CLOCK:BMAL1. RORα formulates a complex with peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) to enhance the transcription, while REV-ERB recruits nuclear receptor co-repressor 1/2

(NCoR1/2) and histone deacetylase 3 (HDAC3) co-repressors to repress Bmal1 expression. The positive loop also induces the expression of the clock control genes (CCG) which either binds to the E-box or RORE in promotor genes or induces the expression of D-element binding protein (DBP, hexagon) which binds to the D-box region of promotor genes. These CCGs are the outputs of the circadian rhythms involved in multiple biological processes. In the fed state, nutrients- activated mTOR induces Cry and Per, which represses CLOCK: BMAL1. mTOR also increases the stability of PER by promoting the phosphorylation of glycogen synthase kinase 3 (GSK3). In the fasting state, mTOR is inhibited and protein kinase AMP-activated protein kinase (AMPK) is activated, reducing the stability of CRY1 and PER2 through phosphorylation of CRY1-Ser 71 and activation of casein kinase 1ε/δ (CK1ε/δ), respectively, thereby reduced the PERs and CRYs degradation by 26S proteasome. AMPK also enhances SIRT1 (sirtuin 1) activity via increasing the expression of nicotinamide phosphoribosyl transferase (NAMPT), which is the rate-limiting enzyme of the NAD+ (nicotinamide adenine dinucleotide) salvage pathway, leading to the inhibition of CLOCK:BMAL1. SIRT1 also activates the deacetylation and modulation of the activity of downstream SIRT1 targets such as PGC-1α. Adapted from (Bass and Takahashi, 2010, Lee and Kim, 2013)]

1.3.3 Key factors entraining the circadian clock

Light

Daylight is the primary driver of the central clock though the photosensitive opsin, so-called melanopsin, presented in retinal ganglion cells (Gooley et al., 2001). Light exposure early during the night can lead to a phase delay in rhythms, while late light exposure at night causes a phase advance (Czeisler et al., 1989, Khalsa et al., 2003, St Hilaire et al., 2012). Compared with individuals who lived in a larger city with more artificial light exposure, those living in rural areas displayed a rhythm more closely coupled with the solar system, suggesting that light

intensity also entrains the phase of circadian rhythms (Roenneberg and Merrow, 2007, Wright et al., 2013, Tähkämö et al., 2019). Our modern lifestyle is now characterised by reduced natural light exposure during the day and increased artificial light exposure at night. A recent systematic review of 12 observational studies has shown that light exposure at night is a significant risk factor for overweight and obesity (Lai et al., 2020). Under the condition of controlled food intake and physical activity, bright light at night decreases insulin sensitivity in healthy individuals (Cheung et al., 2016), and increases plasma glucose and insulin levels (Albreiki et al., 2017). Additional factors such as shift work (work outside of conventional daytime hours) and social jet lag (discrepancy between biological and social rhythms during workdays and weekends) also substantially desynchronize the circadian system and are associated with metabolic health consequences (Lai et al., 2020).

Feeding-fasting cycles

Peripheral clocks are highly sensitive to metabolic signals resulting from food intake (Damiola et al., 2000, Hamaguchi et al., 2015, Nováková et al., 2011, Wehrens et al., 2017). Altering feeding patterns disrupts molecular clocks and has consequent impacts on metabolism in animal models (Zarrinpar et al., 2016, Salgado-Delgado et al., 2010, Yasumoto et al., 2016, Sherman et al., 2011, Chaix et al., 2014). Under the normal light/dark cycles, restricting mice to only feeding during the inactive phase (daytime) produced a 6-hour phase-advance for the expression of liver clock genes (Arntl, Nr1d1, Per2, and Dbp), inverted the phase of liver Per1 and dampened the clock genes (Nr1d1, Per1, Per2, Dbp) and metabolic genes (fatty acid synthase, acetyl CoA carboxylase alpha and stearoyl-CoA desaturase-1) in white adipose tissue, as compared to the mice fed at night time (active phase) (Yasumoto et al., 2016). This resulted in obesity, glucose elevation, hepatic steatosis, inflammation and other metabolic disturbances (Zarrinpar et al., 2016, Salgado-Delgado et al., 2010, Yasumoto et al., 2016, Sherman et al., 2011, Chaix et al., 2014). Expression of clock genes in muscle was less responsive than adipose

tissue and liver to the altered feeding-fasting cycles (Yasumoto et al., 2016), suggesting there are tissue-specific impacts of restricted feeding.

Mice with clock gene mutations or deletions also show a functional deficiency of circadian oscillator, altered feeding\fasting rhythms, and impaired metabolic health such as increased weight gain and fat accumulation, glucose intolerance, hyperinsulinemia, hyperlipidaemia and hepatic steatosis (Vollmers et al., 2009, Marcheva et al., 2013, Turek et al., 2005, Shostak et al., 2013, Chaix et al., 2018). However, these metabolic consequences are rescued when these mice are fed solely in the active phase (Chaix et al., 2018) with restored diurnal oscillation of several hundred of transcripts involved in glucose metabolism and lipid homeostasis (Vollmers et al., 2009, Adamovich et al., 2014, Chaix et al., 2018).

Similarly, disordered feeding (such as rotating the light cycle to mimic shift work) and diet-induced obesity (i.e,. high-fat diet) have been shown to disturb the circadian rhythms in mice (Salgado-Delgado et al., 2008, Chaix et al., 2014, Hatori et al., 2012). For example, mice that underwent “shift work” (rotating light: dark cycle) altered the peak and phase of Per1 and Per2 compared to control mice (Salgado-Delgado et al., 2008). These shift work mice gained more weight, lost diurnal locomotor activity (decreased nocturnal activity), decreased nocturnal food intake in the first week and then displayed an inverted feeding pattern after 4 weeks, and dampened glucose and lipid rhythmicity (Salgado-Delgado et al., 2008). Furthermore, when mice were fed high-fat diet solely during nighttime, the dampened rhythms in the gene expression of fatty acid synthase, acetyl CoA carboxylase and pyruvate carboxylase in liver and muscle were rescued along with improved glucose tolerance (Chaix et al., 2014, Hatori et al., 2012).

In humans, manipulating meal timing also affects the circadian rhythms in peripheral clocks (Wehrens et al., 2017, Jakubowicz et al., 2017b). In a highly controlled clinical trial, delaying

breakfast by 5 hours for 6 days delayed the glucose rhythm and the phase of PER2 mRNA rhythm in adipose tissue (Wehrens et al., 2017). In contrast, others showed that breakfast consumption increased Bmal1, Rorα, and Sirt1 expression in healthy individuals, and increased the expression Bmal1, Per1, Per2, Rev-erbα and Ampk in individuals with T2DM compared with breakfast skipping (Jakubowicz et al., 2017b).

Insulin has been recently identified as a zeitgeber to drive peripheral clocks in mice and humans both *in vitro* and *in vivo* (Crosby et al., 2019). Insulin regulates the circadian clocks via increasing the translation of Per2 mRNA to PER2 protein *in vitro*, in a dose-dependent manner, and in mice (Crosby et al., 2019). In this study, pharmacological attenuation of insulin/insulin growth factor -1 signalling via inhibition of mTOR via torin 1 or rapamycin was capable of delaying entrainment of PER::LUC rhythms to changes in the meal timing. Recently, this was confirmed in human adipose tissue. In that study, the expression of core clock genes Per2, Per3 and Nr1d1 were altered in subcutaneous adipose tissue (SAT) of individuals with obesity, during a hyperinsulinemic-euglycemic clamp (Tuvia et al., 2021). Furthermore, insulin also induced a phase-shift of Per1 and Per2 in human stem cell-derived adipocytes, mouse 3T3-L1 cells and adipose tissue explants from mPer2Luc knock-in mice, suggesting that insulin may be the primary mechanism of feeding-induced adipose tissue clock entrainment (Tuvia et al., 2021).

1.3.4 Evidence of circadian disruption to induce obesity and impair glucose metabolism (Figure 1.1)

Clock genes in humans

Human mutations in several core clock genes increase the genetic susceptibility to obesity and metabolic diseases. For example, observational studies have shown associations between two BMAL1 haplotypes and T2DM (Woon et al., 2007), between single nucleotide polymorphisms

(SNPs) of CLOCK and obesity (Scott et al., 2008, Sookoian et al., 2008), between genetic loci in CRY2 and increased fasting glucose (Barker et al., 2011), as well as between REV-ERBα polymorphisms and obesity (Ruano et al., 2014). Further, lifestyle management such as diet and sleep show potential to improve cardiometabolic abnormalities conferred by common circadian-related genetic variants, including body weight (Loria-Kohen et al., 2016), fasting glucose (Dashti et al., 2015), insulin resistance and T2DM (Dashti et al., 2014, Garcia-Rios et al., 2014).

Effect of sleep-wake rhythms

Accumulated evidence from both epidemiological studies and clinical trials shows that disturbed sleep-wake rhythms affect the risk of developing obesity and T2DM (Shan et al., 2015, Cappuccio et al., 2010, Zerón-Rugerio et al., 2020). A dose-response meta-analysis of prospective studies showed a U-shaped relationship. Namely, both short and long sleep duration are associated with increased risk of T2DM, with the lowest T2DM risk at 7 to 8 hours sleep per day (Shan et al., 2015). Both short and long duration of sleep are predictors of cardiovascular outcomes (Cappuccio et al., 2011). Poor sleep quality also increases the risk of obesity and T2DM (Cappuccio et al., 2010, Zerón-Rugerio et al., 2020). Accordingly, patients with obstructive sleep apnoea are at increased risk of developing T2DM, partially due to disturbed sleep (Rundo, 2019). Patients with T2DM also show a high incidence of obstructive sleep apnoea and poor glycaemic control (Tahrani and Ali, 2014).

The relationship between sleep deprivation and its metabolic consequences is also presented under highly controlled food intake and physical activity in humans (Broussard et al., 2012, Donga et al., 2010). For instance, in healthy young adults, reduced glucose tolerance was observed after five nights of sleep loss (4 hours per night) compared with five well-rested nights (12 hours per night) (Spiegel et al., 1999). Subsequently, reduced insulin sensitivity was

observed in liver, adipose tissue and the whole body of sleep restricted in healthy individuals (Broussard et al., 2012, Donga et al., 2010).

Shift work

Shift workers are at higher risk of developing obesity and obesity-related diseases, including T2DM (Saulle et al., 2018, Gao et al., 2020). A recent systematic review and dose-response meta-analysis of 12 cohort studies showed that shift work was associated with an increased risk of T2DM, and that the greater number of shift working days, the higher risk of T2DM (Gao et al., 2020). This study supports the findings from UK biobank data that working more night shifts per month was associated with a higher risk of T2DM (Vetter et al., 2018).

Several well-controlled human experimental circadian misalignment studies shed further light on the relationship between shift work and risk factors of CVD in healthy shift and non-shift workers (Morris et al., 2016a, Morris et al., 2016b, Morris et al., 2015, Reid and Abbott, 2015, Sharma et al., 2017). The shift work conditions lead people to consume their food at a time of day when the β-cell response is reduced due to its normal daily variation (Sharma et al., 2017). *Morris et al* showed that healthy individuals under three days of mimicked night shifts reduced glucose tolerance and decreased pancreatic β-cell function and insulin sensitivity compared with a circadian alignment condition (Morris et al., 2015). When ten healthy adults were exposed to a 28 -hour “day” for eight days with controlled food and activity, the resulting circadian misalignment was associated with increased blood glucose and insulin (Scheer et al., 2009).

Chronotype and social jet lag

Individuals differ in circadian phase (the natural propensity of behavioural manifestation relative to light-dark cycle) preference, known as chronotype, which may be a risk factor of

cardiometabolic diseases (Almoosawi et al., 2019). For example, individuals with an evening chronotype are at increased risk of abdominal obesity and developing T2DM compared with the morning type (Merikanto et al., 2013, De Amicis et al., 2020), independent of sleep duration and physical activity. In individuals with T2DM or prediabetes, evening chronotypes have poorer glycaemic control, independent from sleep disturbances (Reutrakul et al., 2013) (Anothaisintawee et al., 2017). Metabolically unhealthy individuals with obesity had lower physical activity in the morning, later bedtimes, and were less likely to consume breakfast as compared with those individuals with obesity that were classified as metabolically healthy(Torres-Castillo et al., 2020, Yu et al., 2015).

1.3.5 Circadian variation of glucose metabolism and macronutrient intakes (refer to the Chapter 2)

Glucose homeostasis is controlled primarily by the liver, adipose tissue, and skeletal muscle. The balance between the utilization and production of glucose is primarily maintained at equilibrium by two opposing hormones, insulin and glucagon (Komatsu et al., 2013). In response to an elevation in plasma glucose and amino acids after consumption of a meal during active phase, insulin is released from the β cells of the islets of Langerhans in the pancreas (Sinturel et al., 2020). Insulin acts to skeletal muscle to promote the glucose uptake through glucose transporter 4 (GLUT4) from circulation, which is the largest insulin-sensitive organ and responsible for 70-80% of insulin-stimulated glucose uptake in the post-prandial state (DeFronzo and Tripathy, 2009). Insulin also profoundly inhibits lipolysis in adipocytes, primarily through inhibition of the enzyme hormone-sensitive lipase (Anthonsen et al., 1998). In adipose tissue, insulin also stimulate adipocyte glucose uptake and stored primarily as lipid by activation of lipid synthetic enzymes, including pyruvate dehydrogenase, fatty acid synthase and acetyl-CoA carboxylase (Saltiel and Kahn, 2001, Kitamura et al., 1999). In the hepatocyte, insulin stimulates the utilization and storage of glucose as lipid and glycogen through stimulates

the expression of genes encoding glycogenesis (liver-specific glycogen synthase kinase 3) and fatty-acid synthetic enzymes (sterol regulatory element-binding protein 1), while repressing glucose synthesis and release via blocking gluconeogenesis (phosphoenolpyruvate carboxykinase 1) and glycogenolysis (Pilkis and Granner, 1992, Sinturel et al., 2020, Saltiel and Kahn, 2001). Insulin serves as the major physiological anabolic agent, promoting the synthesis and storage of glucose, lipids, and proteins and inhibiting their degradation and release back into the circulation. Therefore, high circulating insulin levels in response to over calories consumption and continuous energy consumption will contribute to the development of obesity, insulin resistance and T2DM.

When plasma glucose falls (i.e., during fasting), glucagon is secreted by α cells, which surround the β cells in the pancreas. Glucose is excreted from liver by glucagon-promoted glycolysis and gluconeogenesis during the fasting/resting phase (Komatsu et al., 2013), which maintain the fasting blood glucose (Saltiel and Kahn, 2001). Incretins such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinoptropic polypeptide (GIP), enhances glucose-dependent insulin secretion in islet β cell after nutrients ingestion (Martchenko et al., 2020).

The rhythmic secretion of insulin and glucagon from pancreases and incretin hormone such as GLP-1 from the gut coordinate the blood glucose homeostasis throughout the day (Gachon et al., 2017). The well-established circadian variation in glucose tolerance is characterized by better glucose tolerance in the morning than in the evening (Poggiogalle et al., 2018), which has been extensively described in my recently published review, along with the impact of varying macronutrient timing in Chapter 2.

1.4 Intermittent fasting and time restricted eating

1.4.1 Intermittent fasting

Intermittent fasting (IF) is the practice of alternating periods of eating and fasting, which is emerging as an alternative dietary strategy for combating obesity and improving markers of cardiometabolic diseases (Antoni et al., 2017, Harvie and Howell, 2017, Harris et al., 2018). There are a variety of intermittent fasting regimes with regards to feed-fast cycles, meal timing and energy intake, in which complete fasting for one to four times per week (i.e., 5:2 diet; every other day fasting/alternate-day fasting [ADF] or alternate-day modified fasting [ADMF], whereby up to 30% of calorie requirements are prescribed during a fasting day) are the most commonly studied in humans (Table 1.1).

Table 1.1 Description of different protocols in intermittent fasting

IF regimen	Weekly fasting days	Energy allowance		Eating duration[1]	
		Fed day	Fasting day	Fed day	Fasting day
Alternate-day fasting (ADF) (Templeman et al., 2021, Catenacci et al., 2016, Varady et al., 2011, Beaulieu et al., 2020)	3-4 days	100-150% or *ad libitum*	0		 or or
Alternate-day modified fasting (ADMF) (Hutchison et al., 2019a, Bowen et al., 2018, Trepanowski et al., 2017, Coutinho et al., 2018)	3-4 days	100-150% or *ad libitum*	~25-30%		 or or *
5:2 diet (Conley et al., 2018, Headland et al., 2019)	2 (sometimes consecutive)	100% or *ad libitum*	~25-30%		 or *
Time restricted eating (TRE)(Gill and Panda, 2015, Parr et al., 2020b)	7 days	100%	100%		

[1]The circle represents a 24 hour day split into day and night from 6 am to 6 pm; arrow represents the eating duration in different studies; the weight of the line represents the energy density.

* Meals on fasting day was split into small meals consumed at lunch and dinner or mimic the habitual three meals and snacks

IF regimes that include zero or minimal calories on the fasting days, followed by *ad libitum* eating on the remaining days, 10% restriction overall per day of fasting (e.g., 3 days of fasting is ~30% restriction) (Harris et al., 2018). Different types of IF trials were conducted in humans, including ADF (Heilbronn et al., 2005b), ADMF (Bowen et al., 2018, Coutinho et al., 2018, Beaulieu et al., 2020, Catenacci et al., 2016, Trepanowski et al., 2017, Varady et al., 2011, Johnson et al., 2007, Hoddy et al., 2014), and 5:2 diet (Antoni et al., 2018, Carter et al., 2016, Fitzgerald et al., 2018, Harvie et al., 2013, Schübel et al., 2018, Sundfør et al., 2018, Harvie et al., 2011). Data from these clinical trials indicate that several benefits are produced by IF, that are similar in magnitude to the responses produced in response to calorie restriction (CR) in humans (Bales and Kraus, 2013, Heilbronn and Ravussin, 2003, Liu et al., 2020). These outcomes include reducing body weight or fat mass and blood pressure, improving insulin sensitivity, glycaemic control and lipid profiles, and decreasing parameters of inflammation and oxidative stress (Carter et al., 2016, Catenacci et al., 2016, Harvie et al., 2013, Harvie et al., 2011, Heilbronn et al., 2005b, Heilbronn et al., 2005a, Hoddy et al., 2014, Varady et al., 2013, Varady et al., 2011, Johnson et al., 2007, Klempel et al., 2012) (Table 1.2).

A handful of studies have shown that the improvements in cardiometabolic risk factors produced by IF are superior to CR (Hutchison et al., 2019a, Harvie et al., 2013, Harvie et al., 2011, Varady et al., 2013, Antoni et al., 2018, Templeman et al., 2021, Trepanowski et al., 2017). Those studies reported a greater reduction in weight loss (Hutchison et al., 2019a), fat mass (Hutchison et al., 2019a, Harvie et al., 2013), fasting insulin (Harvie et al., 2013, Harvie et al., 2011), insulin sensitivity assessed by homoeostatic model assessment of insulin resistance (HOMA-IR) (Hutchison et al., 2019a, Harvie et al., 2013, Harvie et al., 2011), triglycerides (Hutchison et al., 2019a, Varady et al., 2013, Antoni et al., 2018, Templeman et al., 2021), total cholesterol and LDL-c (Hutchison et al., 2019a), and blood pressure (Antoni et al., 2018) and greater increases in high-density lipoprotein cholesterol (HDL-c) (Trepanowski et al., 2017).

However, other trials have shown no difference between IF versus CR in weight loss or improved cardiometabolic profiles (Beaulieu et al., 2020, Headland et al., 2020, Headland et al., 2019, Sundfør et al., 2018, Coutinho et al., 2018, Conley et al., 2018, Bowen et al., 2018, Catenacci et al., 2016, Carter et al., 2016). However, higher fat mass, lower fat loss rate (Templeman et al., 2021, Fitzgerald et al., 2018) and higher fasting blood glucose were also observed following IF versus CR (Schübel et al., 2018).

Some of these controversies may be due to the great heterogeneity in trial design when fasting protocol is implemented, including studies initiating fasts at breakfast (8 am) (Hutchison et al., 2019a), lunch (12 pm-2 pm) (Trepanowski et al., 2017), mid-afternoon (3 pm) (Templeman et al., 2021), dinner (Catenacci et al., 2016) and late-night (Varady et al., 2011, Soeters et al., 2009) or by breaking into small meals consumed at lunch and dinner (Trepanowski et al., 2017, Conley et al., 2018, Varady et al., 2011, Hoddy et al., 2014) or mimicking the habitual three meals and snacks (Coutinho et al., 2018, Bowen et al., 2018), resulting in different fasting duration (i.e., ~18-24 hours). Many of these studies did not specify the meal timing on fasting days with self-selected consecutive or non-consecutive fasting days. Also, none of these studies have reported the timing of meal consumption during the intervention. The protocol on fed days also varies among trials with respect to the meal timing and calories such as *ad labium* eating, 120%-150% of energy requirements or habitual eating, leading to erratic eating patterns and meal irregularity.

Acute 24-hour fasting has been shown to blunt the rhythmicity of core clock genes and proteins in mice, which can be reversed by refeeding (Kinouchi et al., 2018, Barnea et al., 2010). However, the effect of IF on the circadian clock has not been studied extensively. So far, only one animal study reported that IF altered the circadian rhythmicity in mouse liver (Froy et al., 2009). In this study, IF dampened the amplitudes of Per1, Per2, Cry1, Clock and Arntl when the fasting/feeding cycle was initiated at the onset of the rest phase. Initiation of IF at the onset

of the active phase (i.e., equivalent to breakfast) did not alter the amplitude of expression, although a short phase advance was observed in clock genes that was in alignment with the small advance in peak food intakes, as the animals were hungry (Froy et al., 2009). No human clinical trials have examined the impact of IF on circadian clocks as yet.

Table 1.2 Intermittent fasting regimens and outcome comparison with daily calorie restriction[1]

Reference	Population, sample size	IF diet protocol				IF vs CR outcomes	
		Study design, % CR, duration	Fasting days	Fed days	Timing of fasting initiated/meal timing on fasting days	Adiposity	Cardiometabolic health risk factors
(Templeman et al., 2021)	Healthy, lean adults IF n= 12 CR n= 12	ADF 0% CR 25% 3 weeks	Fasting every other day Zero ER	150% habitual eating	3 pm	↔ weight, BMI **↑FM, % body FM, FM index**	↔ FBG, insulin, NEFA, glycerol, TG, TC, HDL-c, LDL-c ↔ postprandial glucose and insulin ↔ NEFA, glycerol AUC **↓ TG AUC**
(Beaulieu et al., 2020)	Overweight/obese IF n= 24 CR n= 22	ADMF 25% CR 25% Until 5% weight loss achieved	Fasting every other day ~25% ER	*Ad libitum*	Not specified	↔weight, FM, FFM	
(Headland et al., 2020)	Overweight/obese adults IF n= 31 CR n= 40	5:2 diet or 2d/week ~30% CR ~30% 24 months follow up	2 consecutive or non-consecutive fasting days as preferred ~500 kcal ER for female ~600 kcal ER for men Self-selected	Habitual eating	Not specified	↔ weight	↔ TC, HDL-c,LDL-c, TG
(Headland et al., 2019)	Overweight/obese adults IF n= 104 CR n= 118	5:2 diet or 2 d/week ~30% CR ~30% 12months	2 consecutive or non-consecutive fasting days as preferred ~2100 kj for female ~2520 kj for men	Habitual eating	Not specified	↔ weight, BMI, FM, LM	↔HDL-c ↔FBG ↔LDL-c, TC, TG

Reference	Population, sample size	IF diet protocol				IF vs CR outcomes	
		Study design, % CR, duration	Fasting days	Fed days	Timing of fasting initiated/meal timing on fasting days	Adiposity	Cardiometabolic health risk factors
(Hutchison et al., 2019a)	Overweight/obese adults IF n= 25 CR n= 25	ADMF ~30% CR ~30% 8 weeks All foods provided	Fasting every other day ~32% ER	145% ER	8 am	**↓weight** **↓FM** ↔ FFM	↔insulin sensitivity ↔ FBG, insulin **↓ HOMA-IR (fasting day)** **↓TC, TG, LDL-c** ↔FGF21, AST
(Sundfør et al., 2018)	Obese adults IF n= 54 CR n= 58	2d/week 28% CR 26% 6 months	2 non-consecutive fasting days ~400 kcal for female ~500 kcals for male	*Ad libitum* Mediterranean diet	Not specified, but served as one meal or 2-3 snacks	↔ weight, WC	↔blood pressure, HR ↔FBG, HbA1C ↔TG, HDL-c, TC, LDL-c, ApoB ↔CRP
(Schübel et al., 2018)	Overweight/obese adults IF n= 49 CR n= 49	2d/week ~20% CR ~20% 12 weeks	2 non-consecutive fasting days ~25% ER	100% ER	Not specified	↔weight	**↑FBG** ↔ Insulin, HOMA-IR ↔LDL-c, HDL-c, TC, TG ↔CRP, IL-6/8, TNFα, interferon γ ↔IGF-1 ↔% liver fat, GGT, AST, ALT ↔SHBG
(Fitzgerald et al., 2018)	Multiple sclerosis adults with overweight/obesity IF n= 12 CR n= 12	5:2 diets 25% CR 22% 8 weeks All foods provided	2 consecutive fasting days 25% ER	100%ER	Not specified	↔weight, BMI, WC, HCir, LM, % body FM, % visceral FM **↑ FM** **↓fat loss rate**	↔ FBG ↔TG, TC, LDL-c, HDL-c
(Coutinho et al., 2018)	Adults with obesity IF n= 14	3d/week 33% CR 33%	3 non-consecutive fasting days	100%ER	3 meals + 2 snack, allow to	↔ weight, FM, FFM, % FM	↔ fasting and postprandial insulin,

Reference	Population, sample size	IF diet protocol				IF vs CR outcomes	
		Study design, % CR, duration	Fasting days	Fed days	Timing of fasting initiated/meal timing on fasting days	Adiposity	Cardiometabolic health risk factors
	CR n= 14	12 weeks	550 kcal for female 660 kcal for male		have low-starch vegetables ≤2cups/day		ghrelin, GLP-1, CCK, PYY
(Conley et al., 2018)	Males with obesity IF n= 11 CR n= 12	2d/week 600 kcal CR 500kcals 6 months	2 non-consecutive fasting days 600 kcal ER	*Ad libitum*	Not specified, encouraged to consume calorie-free beverages	↔weight, BMI, WC	↔FBG ↔TG, TC, LDL-c, HDL-c ↔blood pressure
(Bowen et al., 2018)	Adults with overweight/ obesity IF n= 67 CR n= 68	3d/week+CR ~53% CR ~50%	3 non-consecutive fasting days 2400 kj ER	3 non-consecutive fed days 5000kj ER 1 *ad libitum* day 10000kj ER	3 meals (2 commercial meals at breakfast and lunch, low energy vegetables at dinner)	↔weight, FM, visceral FM, LM	↔FBG, fasting insulin ↔TC, LDL-c, HDL-c, TG ↔hsCRP ↔blood pressure
(Antoni et al., 2018)	Adults with overweight/obesity IF n= 15 CR n= 12	5:2 diet 22% CR 23% Until 5%weight loss achieved	2 consecutive fasting days ~25% ER	100% ER	Not specified	↔weight, FM, FFM, WC, HCir	↔FBG, fasting insulin, C-peptide, HOMA-IR ↔TC, LDL-c, HDL-c, TG, NEFA **↓postprandial TG** **↓systolic blood pressure**
(Trepanowski et al., 2017)	Adults with obesity IF n= 34 CR n= 35	ADMF 25% CR 25% 6 months All food provided for first 3 months	Fast every other day ~25% ER	125%ER 3 meals	Lunch (12 pm to 2 pm)	↔weight ↔FM, LM, visceral FM	↔FBG, fasting insulin, HOMA-IR ↔blood pressure, HR ↔TC, LDL-c, TG **↑HDL-c** ↔hsCRP

Reference	Population, sample size	IF diet protocol				IF vs CR outcomes	
		Study design, % CR, duration	Fasting days	Fed days	Timing of fasting initiated/meal timing on fasting days	Adiposity	Cardiometabolic health risk factors
(Catenacci et al., 2016)	Adults with obesity IF n= 14 CR n= 12	ADF 47% CR 28% 8weeks All foods provided	Fast every other day Zero ER	100% ER+ *Ad libitum* access to 5-7 snacks (~200kcal/serve)	After evening meal	↔weight, BMI, FM, LM, visceral FM, trunk FM, % FM, %LM, % visceral FM, % trunk FM	↔FBG, fasting insulin, insulin sensitivity index[‡] ↔TC, LDL-c, HDL-c, TG ↔ghrelin, BDNF
(Carter et al., 2016)	Overweight/obese adults with T2DM IF n= 31 CR n= 32	2d/week 1670-2500kj CR 5000-6500 kj/day 12 weeks	2 non-specified fasting days 1670-2500 kj ER	Habitual eating	Not specified	↔weight, %FM, FM, FFM	↔HbA1c ↔use of oral hypoglycaemic agent and insulin
(Harvie et al., 2013)	Women with overweight and breast cancer family history IF n= 53 CR n= 54	5:2 diet 25% CR 25% 3 months	2 consecutive fasting days 2500-2717 kj	100%ER Mediterranean diet	Not specified	↔weight **↓FM**	**↓Fasting insulin** **↓HOMA-IR** ↔FBG, HbA1c, IGF-1 ↔TC, TG, LDL-c, HDL-c ↔blood pressure ↔IL-6, TNFα
(Varady et al., 2011)	Adults with overweight/obesity IF n= 15 CR n= 15	ADF 25% CR 25% 12 weeks	Fast every other day 25%ER	*Ad libitum*	At midnight, but meals were consumed between 12 pm to 2 pm	↔weight	**↓TG** ↔LDL-c, HDL-c, TC ↔LDL particle size, HDL particle size
(Harvie et al., 2011)	Premenopausal women with overweight/obesity IF n= 53 CR n= 54	5:2 diet 25% CR 25% 3 months	2 consecutive fasting days 25% ER	100% ER	Not specified	↔weight, FM, FFM, WC, HCir	**↓Fasting insulin** **↓HOMA-IR** ↔FBG, ghrelin ↔TC, TG, LDL-c ↔blood pressure ↔CRP ↔BDNF

[1]ADF, alternate day fasting (zero calorie intake on fasting days); ADMF, alternate day modified fasting (minimal calorie intake on fasting days), 5:2 diet (2 consecutive fasting days per week); IF, intermittent fasting; CR, calorie restriction; FBG, fasting blood glucose; HOMA-IR, Homeostatic model assessment of insulin resistance; HbA1c, glycated haemoglobin A1c; IGF-1, insulin growth factor-1; FM, fat mass; FFM, fat free mass; LM, lean mass; WC, waist circumference; HCir, hip circumference; TG, triglycerides; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; CRP, C-reactive protein; hsCRP, high-sensitivity C-reactive protein; BDNF, brain-derived neurotrophic factor; IL-6/8, interleukin 6 or 8; TNFα, tumour necrosis factor α; NEFA, non-esterified fatty acid; ApoB, Apolipoprotein B; FGF21, fibroblast growth factor 21; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase; ALT, alanine transaminase; GLP-1, glucagon-like peptide 1; CCK, cholecystokinin; PYY, peptide YY; SHBG, sex hormone-binding globulin. ER: calculated energy requirements based on the different methods described in the paper.

[†] Insulin sensitivity index calculated through MINMOD program.

1.4.2 Time restricted eating

TRE can be included as a subtype of intermittent fasting, but as a circadian rhythm-reinforcing lifestyle that recommends restricting energy intake within a daily shortened period of time (6-10 hours in human studies, 8-12 hours in animal studies), which lengthens the daily fasting period (Ye et al., 2020, Hatori et al., 2012, Chaix et al., 2014, Chaix et al., 2018) (Table 1.1).

TRE acts as a powerful regulator in metabolic health and aging in rodent models

Eating during the active phase has been shown to induce pleiotropic metabolic health benefits in animal models of obesity and aging (Ye et al., 2020, Mehus et al., 2020, Schafer et al., 2019, Wang et al., 2018, Duncan et al., 2016). These benefits include blunted weight gain and fat accumulation (Chaix et al., 2014, Sherman et al., 2012, Hatori et al., 2012, Chaix et al., 2018, Sundaram and Yan, 2016, Olsen et al., 2017, Duncan et al., 2016, Woodie et al., 2017, Cisse et al., 2018, Delahaye et al., 2018, Das et al., 2021, Ye et al., 2020, Sherman et al., 2011, Arble et al., 2009) and protected mice from the metabolic disorders induced by a high-fat diet, including improved glucose tolerance and insulin sensitivity (Sherman et al., 2012, Chaix et al., 2014, Duncan et al., 2016, Sundaram and Yan, 2016, Woodie et al., 2017, Regmi et al., 2021) as well as fat mobilization and oxidation (Sherman et al., 2012, Hatori et al., 2012, Chaix et al., 2014, Woodie et al., 2017, Ye et al., 2020, Mehus et al., 2020), enhanced bile acid production and restored cholesterol homeostasis (Hatori et al., 2012, Chaix et al., 2014) thereby decreasing circulating total cholesterol level (Sherman et al., 2012, Chaix et al., 2014). TRE also reduced inflammation in diet-induced obesity (Delahaye et al., 2018, Sherman et al., 2011, Sherman et al., 2012, Hatori et al., 2012, Chaix et al., 2014, Sundaram and Yan, 2016) and enhanced immune responses (Cisse et al., 2018). In addition, TRE restored dampened circadian rhythms caused by diet-induced obesity in core clock genes and genes involved in energy metabolism (i.e., AMPK, SIRT1, G6-P [glucose 6-phosphate], FASN [fatty acid synthase], PPAR

[peroxisome proliferator-activated receptor] α, PPARγ, and PGC-1α [PPARγ coactivator 1α]) (Sherman et al., 2012, Sherman et al., 2011, Hatori et al., 2012, Regmi et al., 2021), and diurnal rhythms in gut microbiota (Ye et al., 2020, Zarrinpar et al., 2014, Hu et al., 2018). TRE also prevented the age- and diet-induced reduction in cardiac contractile function (Tsai et al., 2013) and cancer (Das et al., 2021), restored the high-fat diet-induced loss of gastric vagal afferent mechanosensitivity (Kentish et al., 2018), and improved the circadian dysfunction and motor symptoms of a mouse model with neurodegenerative diseases (Wang et al., 2018). Some studies even suggested that these benefits are independent of calorie intake (Chaix et al., 2014, Arble et al., 2009, Hatori et al., 2012, Zarrinpar et al., 2014), although other studies showed there is a modest reduction in food intake, particularly initially when high-fat diet animals adopt a TRE routine (Delahaye et al., 2018, Sundaram and Yan, 2016) partially driven by the improved metabolic flexibility (Chaix et al., 2018). Collectively, there is a potential to adopt TRE for preventing and improving cardiometabolic health in humans, particularly individuals with metabolic disorders, including obesity and T2DM (Chaix et al., 2019, Sulli et al., 2018).

The effect of TRE on metabolic health in humans

There are now a number of pilot clinical trials that also show favourable health benefits of TRE in humans, which include moderate weight loss, improved glucose control and risk markers of cardiometabolic diseases (Table 1.3, Figure 1.3). TRE protocols with daily energy intakes limited from 4 to 10 hours either early or later in the day have been implemented in individuals with normal weight (LeCheminant et al., 2013, Jones et al., 2020, Moro et al., 2020, Zeb et al., 2020, Martens et al., 2020, McAllister et al., 2020, Tinsley et al., 2019, Tinsley et al., 2017, Moro et al., 2016, Ravussin et al., 2019, Smith S.T., 2017, Jamshed et al., 2019, Antoni, 2018. , Cienfuegos et al., 2020b), overweight or obesity (Gabel et al., 2019, Gabel et al., 2018a, Gabel et al., 2018b, Anton et al., 2019, Hutchison et al., 2019b, Gill et al., 2015, Lee et al., 2020, Kesztyus et al., 2019, Chow et al., 2020, Parr et al., 2020b, Lundell et al., 2020, Gabel et al.,

2020a, Schroder et al., 2021), prediabetes (Sutton et al., 2018), as well as T2DM and metabolic syndrome (Wilkinson et al., 2019, Parr et al., 2020a). In the past four years, 30 TRE clinical trials have been published, including 11 within-participants design, seven randomized cross-over designs (RXT), nine RCTs and four non-RCT designs (includes one within-participants design that compared with historical controls). All clinical trials except one were conducted in a small number of participants (N = 8 to 56) with short-term intervention (ranged from four days to 16 weeks). The following section aims to update current evidence and research gaps on TRE in humans.

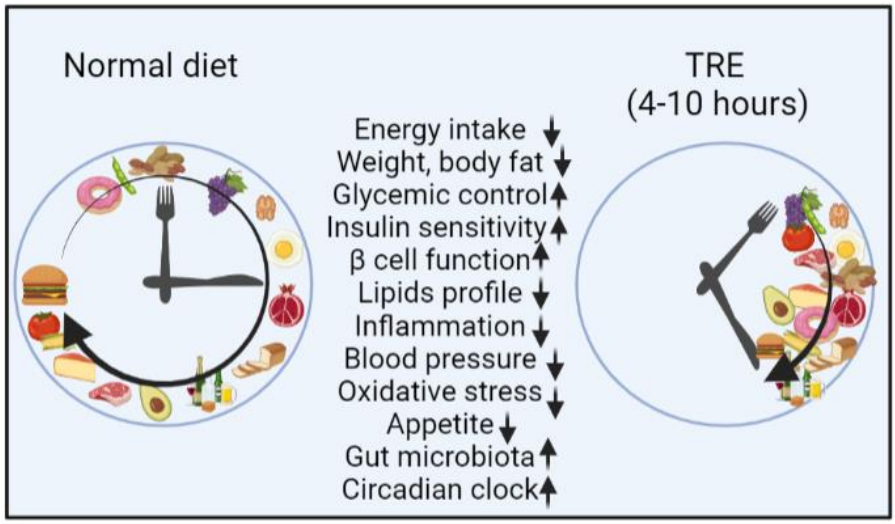


Figure 1.4 Metabolic benefits of time restricted eating (TRE).

Body weight and composition

Body weight and fat mass are markers of adiposity. Recent systematic reviews and meta-analysis show that TRE significantly reduced body weight and fat mass (Moon et al., 2020, Marianna et al., 2019). Previous clinical trials that investigated the effect of TRE on body weight and composition are summarised in Table 1.3. The majority of within-participants design trials showed a reduction of body weight (from 1.7kg to 3.3kg) and fat mass (from 1kg to 2kg) or percentage of fat mass (~1%) in individuals with obesity and/or metabolic syndrome

after 4 to 16 weeks of TRE intervention with various eating windows of 8–10 hours (Gill and Panda, 2015, Gabel et al., 2019, Kesztyus et al., 2019, Wilkinson et al., 2019, Gabel et al., 2020a, Li et al., 2021). Some of these trials have demonstrated modest reductions in energy intake during 10 hour TRE (8-20% of calorie restriction) (Gill and Panda, 2015, Wilkinson et al., 2019, Gabel et al., 2019). In RCTs or RXT trials, TRE also reduced body weight and fat mass compared with control groups (Schroder et al., 2021, de Oliveira Maranhão Pureza et al., 2021, Pureza et al., 2020, Cienfuegos et al., 2021, Cienfuegos et al., 2020b, Moro et al., 2020, Chow et al., 2020, Tinsley et al., 2019, Gabel et al., 2018a, Moro et al., 2016, Stote et al., 2007, Carlson et al., 2007). A few trials have observed that TRE reduced fat mass without altering energy intake in resistance-trained young adults (Tinsley et al., 2017, Tinsley et al., 2019) and men with obesity (Pureza et al., 2020, de Oliveira Maranhão Pureza et al., 2021). Additionally, only one trial has examined TRE for 12 months in conjunction with a hypoenergyetic diet. TRE showed a greater reduction in the percentage of fat mass and waist circumference compared with the controls with hypoenergetic diet (Pureza et al., 2020, de Oliveira Maranhão Pureza et al., 2021). However, an RCT published in JAMA showed that the reduction in body weight in response to an 8-hour TRE for 12 weeks was not significantly different from the energy intake matched three structured meals in control group (Lowe et al., 2020). Of note, this study had a high dropout rate which may minimise the statistical power and introduce bias. Further, most participants self-reported their weight changes using a Bluetooth weighing scale that was linked to a custom app. These studies suggest that TRE may result in weight and fat loss without specifically instructing individuals to reduce energy intakes, but more evidence is required.

Lean mass was maintained after TRE in healthy normal-weight individuals who underwent regular strength training (Moro et al., 2016, Tinsley et al., 2017, Tinsley et al., 2019, Gonzalez et al., 2021, Martens et al., 2020, Moro et al., 2020, Schroder et al., 2021). However, the loss of lean mass was observed in adults with overweight (Chow et al., 2020) and/or obesity (Lowe

et al., 2020, Cienfuegos et al., 2020b, Cienfuegos et al., 2021) alongside the reduction of body weight and fat mass. Lean mass loss is typically reported in response to caloric restriction and weight loss (5-8% of body weight loss, 10-20% of fat loss) (Varady, 2011), and studies are yet to compare whether lean mass loss is different in comparison to CR.

Calorie intake

Despite no recommendations to change the quality and quantity of the diet during the TRE intervention, a decrease in calorie intake of approximately 8–30% is typically reported in response to TRE in individuals with overweight or obesity, or patients with T2DM or metabolic syndrome (LeCheminant et al., 2013, Gill and Panda, 2015, Tinsley et al., 2017, Antoni, 2018. , Gabel et al., 2018b, Gabel et al., 2019, Wilkinson et al., 2019, Jones et al., 2020, Cienfuegos et al., 2020b, Cienfuegos et al., 2021) (Table 1.3) . Calorie intake was also decreased by 20% in eight non-shift worker young adults who followed ~10-hour TRE for 16 weeks, which could reflect reduced late-night eating and drinking (Gill and Panda, 2015). Other 4 and 6 hour TRE protocols with greater time restriction have reduced calorie intake by ~30% (~550kcal/day) (Cienfuegos et al., 2020b). This is opposite to the results observed in mice, whereby improvements in health are observed without marked reductions in energy intake. This raises the question as to whether the benefits of TRE on metabolic outcomes are independent of the reduction in calorie intake and subsequent weight loss. Only one five-week highly-controlled RXT has examined this, by providing all foods at calculated energy requirements. The authors observed significant improvements in insulin sensitivity, β cell function and reduction in blood pressure and oxidative stress as a result of TRE (8 am - 2 pm; 6h reduction) in the absence of calorie restriction and weight loss (Sutton et al., 2018).

Glucose metabolism

Parameters related to improved glycaemic control (i.e., fasting and postprandial glucose and

insulin, glycated haemoglobin [HbA1c]) were reported in several studies (Antoni, 2018. , Jamshed et al., 2019, Sutton et al., 2018, Moro et al., 2016, Hutchison et al., 2019b, Kesztyus et al., 2019, Parr et al., 2020b, Parr et al., 2020a, Martens et al., 2020, Moro et al., 2020, Jones et al., 2020, Cienfuegos et al., 2020b, Li et al., 2021) (Table 1.3). Recent systematic reviews and meta-analysis show that TRE significantly reduces fasting blood glucose levels (Moon et al., 2020). Four days of early TRE (eating between 8 am to 2 pm) reduced 24-hour glucose levels by 4 mg/dl as measured by continuous glucose monitors (CGM), and reduced fasting glucose and fasting insulin, and 24-hour C-peptide in men with obesity (Jamshed et al., 2019). Early TRE (8 am to 2 pm) also showed improved markers of β cell responsiveness and insulin resistance independent from weight loss in eight individuals with obesity and prediabetes after five weeks (Sutton et al., 2018). However, TRE as a single isocaloric meal during the evening-time (5 pm to 9 pm) for eight weeks, impaired glucose tolerance and insulin sensitivity the following morning in normal adults (Carlson et al., 2007, Stote et al., 2007). In individuals with obesity, delayed TRE (eating between 1 pm to 7 pm or 3 pm to 7 pm), significantly reduced body weight, fat mass, fasting insulin and HOMA-IR, oxidative stress compared to the control group (Cienfuegos et al., 2020b). An RCT comparing early TRE (eating between 8 am to 4 pm) versus *ad libitum* energy matched calorie restriction control (N = 8 per arm) reported reduced postprandial glucose and insulin and increased skeletal muscle uptake of glucose after two weeks (Jones et al., 2020). So far, there is limited data comparing the impacts of TRE in a feeding window prescribed to the early or late time of the day. *Hutchison et al* reported that TRE improved glycaemic responses to a test meal in men at risk for T2DM regardless of early or delayed TRE (Hutchison et al., 2019b).

Aside from three studies that have assessed 24-hour glucose by CGM (Chow et al., 2020, Jones et al., 2020, Parr et al., 2020b), most studies have solely assessed the postprandial glucose responses at breakfast following TRE or control. *Parr et al* recently examined the effects of

self-selected TRE (8hours/day) over 24-hours as compared to a prolonged eating pattern (Parr et al., 2020b). In this study, five days of TRE reduced night-time glucose by CGM, peak glucose and insulin after breakfast and post-lunch glucose and insulin levels in men with overweight or obesity. Longer-term RCTs examining the day-long effects of TRE on glucose control are warranted.

Lipid metabolism

A handful of studies show TRE reduced triglyceride(Moro et al., 2016, Hutchison et al., 2019b, Zeb et al., 2020), total cholesterol (Zeb et al., 2020, Wilkinson et al., 2019), LDL-c (Wilkinson et al., 2019) and HDL-c (Wilkinson et al., 2019) , while some studies also show that TRE increased blood lipids (Sutton et al., 2018, Carlson et al., 2007, Stote et al., 2007, Jamshed et al., 2019, Martens et al., 2020, Zeb et al., 2020) (Table 1.3). Six studies showed no changes in fasting lipid levels in adults with overweight and/or obesity (Gabel et al., 2018b, Lowe et al., 2020, Cienfuegos et al., 2020b, Gabel et al., 2020a, Schroder et al., 2021, Li et al., 2021). The discrepancy between trials could be related to the study population and TRE protocols. For example, eating one isocaloric meal within a 4-hour evening-time frame increased total cholesterol, LDL-c and HDL-c in normal healthy adults (Carlson et al., 2007, Stote et al., 2007). However, TRE decreased total cholesterol, LDL-c, non-HDL-c and HDL-c in adults with metabolic syndrome (Wilkinson et al., 2019). Early TRE (without weight loss) increased fasting triglycerides and total cholesterol in adults with prediabetes (Sutton et al., 2018). These studies suggest that TRE effects on lipid profiles are more likely to be pronounced in patients with metabolic diseases.

TRE also increased the 24-hour non-esterified fatty acids (NEFA) levels, reflecting increased adipose tissue lipolysis. However, TRE did not alter fasting levels of NEFA in two other studies (Jones et al., 2020, Hutchison et al., 2019b). Collectively, larger well-designed RCTs are needed.

Neuro-endocrine hormones and subjective appetite

The impact of TRE on metabolic and neuroendocrine hormones in humans is poorly evaluated. TRE decreased fasting glucagon-like-peptite-1 (GLP-1) (Hutchison et al., 2019b), fasting and mean ghrelin, increased PYY in the evening (Jamshed et al., 2019, Ravussin et al., 2019) and fasting insulin-like growth factor-1 (IGF-1) (Moro et al., 2016, Jamshed et al., 2019, Ravussin et al., 2019, Hutchison et al., 2019b), as well as altered adipokines (lower leptin, high adiponectin) (Sutton et al., 2018, Moro et al., 2016, Jamshed et al., 2019, Ravussin et al., 2019). However, 10-hour TRE did not change the 24-hour responses of GLP-1, gastric inhibitory polypeptide (GIP), PYY, leptin and cortisol in sedentary men with overweight or obesity compared with the control condition (15hours/day eating duration) in a five-day RXT.

The impact of TRE on subjective appetite assessed by visual analogue scale has also been examined (Stote et al., 2007, LeCheminant et al., 2013, Moro et al., 2016, Sutton et al., 2018, Carlson et al., 2007, Parr et al., 2020b, Lundell et al., 2020, Martens et al., 2020). TRE reduced appetite in the evening (Sutton et al., 2018, Parr et al., 2020b, Lundell et al., 2020, Martens et al., 2020) and increased feelings of fullness after a meal (Hutchison et al., 2019b).

Blood pressure

TRE decreased systolic and diastolic blood pressure in four of 10 studies in individuals with obesity (Gabel et al., 2020a, Gabel et al., 2018a), patients with metabolic syndrome (Wilkinson et al., 2019) and prediabetes (Sutton et al., 2018) (Table 1.3). The reductions observed was comparable to other lifestyle interventions such as diet and exercise and/or therapeutic interventions (Zomer et al., 2016). Furthermore, reductions in both systolic and diastolic blood pressure were observed in the study of early TRE (Sutton et al., 2018), the magnitudes of which were similar to the antihypertensive effects of angiotensin-converting enzyme inhibitors (Zomer et al., 2016). Conversely, restricting eating to one meal in the evening increased blood

pressure in healthy men with normal weight (Carlson et al., 2007, Stote et al., 2007). Dietary salt intake is associated with blood pressure (Huang et al., 2020) and has entraining effects on human blood pressure circadian rhythm (Itoh et al., 1996, Kimura et al., 2010). These studies suggest that reduced insulin resistance and shifting salt intake during the early time may partially drive the improvements in blood pressure control (Sutton et al., 2018, Carlson et al., 2007, Stote et al., 2007). However, blood pressure was unchanged by TRE in several other studies of adults with obesity (Anton et al., 2019, Chow et al., 2020, Lowe et al., 2020, Cienfuegos et al., 2020b, Cienfuegos et al., 2021). Thus, further evidence of the impact of TRE on blood pressure, particularly the 24-hour dynamic profile of blood pressure, is required (Quist et al., 2020).

Oxidative stress, inflammation and liver function

A few studies have evaluated the impact of TRE on oxidative stress in individuals with prediabetes and/or obesity (Sutton et al., 2018, Cienfuegos et al., 2021, Cienfuegos et al., 2020b) (Table 1.3). Decreased 8-isoprostane, which represents a reduction of lipid peroxidation, was observed with TRE (Cienfuegos et al., 2020b, Sutton et al., 2018, Cienfuegos et al., 2021). At the molecular level, early TRE (8 am to 2 pm, 6 hours/day) did not alter the expression of genes involved in oxidative stress in adults with overweight (Jamshed et al., 2019).

The impacts of TRE on inflammation in humans are limited (Moro et al., 2016, Martens et al., 2020, Moro et al., 2020, Zeb et al., 2020, Cienfuegos et al., 2020b, Schroder et al., 2021, Li et al., 2021, McAllister et al., 2021a, Sutton et al., 2018, Wilkinson et al., 2019) (Table 1.3). One reported reduced circulating tumour necrosis factor-α (TNF- α) and interleukin-1β (IL-1β) in normal-weight adults (Moro et al., 2016), another found reduced high-sensitivity C reactive protein (CRP) in polycystic ovary syndrome (PCOS) (Li et al., 2021). The third study showed reduced salivary IL-6 and IL-1β but increased CRP measured via saliva in healthy male

firefighters after eight weeks of self-selected 10-hour TRE (McAllister et al., 2021a). No significant changes in high-sensitivity CRP levels were detected in patients with metabolic syndrome (Wilkinson et al., 2019). TRE also did not affect circulating high-sensitivity CRP, TNF- α, and IL-6 in individuals with prediabetes and/or obesity (Sutton et al., 2018, Cienfuegos et al., 2020b). Improved liver function was also reported in followed an 8-hour TRE for 25 days in healthy young adults (Zeb et al., 2020) and for five weeks in women with PCOS (Li et al., 2021) as compared with the control group, which was not observed in adults with obesity (Schroder et al., 2021). Further studies are required.

Clock genes and rhythms in microbiome, transcriptome and metabolome

Evidence of the mechanisms by which TRE facilitates the cardiometabolic impacts via optimized peripheral clocks in humans is under-explored. Several circadian clock genes in peripheral white blood cells were altered in people with overweight and obesity as compared to controls (Jamshed et al., 2019, Zeb et al., 2020) (Table 1.3). Early TRE (8 am to 2 pm) surprisingly altered five out of eight circadian clock genes, including increased mRNA levels of morning and evening Cry1, Cry2 and Rorα, and morning Bmal1, and decreased evening Per1 expression in peripheral blood white blood cells after four days. TRE also altered the diurnal rhythm of key circadian clock regulators, including nutrient-sensing phosphatidylinositol 3-kinase-related kinase (mTOR) and NAD-dependent deacetylase Sirt1, indicating the cross-talk between the energy status and circadian clock in response to TRE also occurs in humans. The gene expression of Bmal1, Clock and Sirt1 in blood samples was also upregulated after 25 days of 8-hour TRE (7:30 pm to 3:30 am) in healthy young adults (Zeb et al., 2020). However, both studies measured the clock gene expression in blood samples with one or two sampling time points, which limits the interpretation of the overall phase-shift, period or amplitude of peripheral clocks. The existing evidence for assessing diurnal rhythm in peripheral tissue is at least 3 time points over 24 hour period but the outcome may differ due to the different statistical

analysis methods. Particularly in the context of cortisol and melatonin, frequent time course sampling are required.

Gut microbiome is associated with the aetiology of obesity and obesity-related complications such as non-alcoholic fatty liver disease, insulin resistance and T2DM (Canfora et al., 2019). Most studies have noted that the ratio of *Firmicutes* to *Bacteroidetes* is significantly higher in obese subjects (John and Mullin, 2016). TRE (8 hours/day) increased the diversity of gut microbiota and beneficial bacteria such as *Prevotellaceae*, *Prevotella_9* and *Bacteroidia*, which showed positive associations with the change in Bmal1 and Sirt1 gene expression (Zeb et al., 2020) (Table 1.3). The authors postulated that TRE could produce health benefit via restoring the diurnal rhythms of the gut microbiome. However, no changes in gut microbiota was observed in 14 adults with obesity who followed 8-hour TRE for eight weeks in a within-participants design trial (Gabel et al., 2020a) (Table 1.3).. The reason for the discrepancy between trials is unclear.

To date, there is only one study that has examined the effects of TRE on clock gene expression, transcriptome and metabolome in skeletal muscle and serum metabolome with five serial samples over a 24-hour period in humans (Lundell et al., 2020, Parr et al., 2020b) (Table 1.3). In this randomized cross-over trial, five days of TRE did not perturb the core clock gene expression in muscle, but increased the amplitude of other rhythmic transcripts in skeletal muscle, and increased the rhythmicity of several amino acid transporter genes and metabolites in muscle, as well as phase-shifted the amino-acid related metabolites in serum. In humans, it is not possible to obtain serial liver biopsies and the effects of TRE on subcutaneous adipose tissue to date, has not been tested yet.

Table 1.3 Summary of time restricted eating human studies[1]

Reference	Population, sample size (M/F)	TRE protocol (fasting: eating period), duration, trial design	Comparisons	Energy Balance	Metabolic Effects (primary outcome in bold)	Other Results (primary outcome in bold)
(Carlson et al., 2007, Stote et al., 2007)	Normal weight adults n= 15 (5/10)	4:20 8 weeks RXT	**TRE**: 1 isocaloric meal 5 pm-9 pm **Control**: 3 meals/day	↔PA ↔EI	↓ weight, FM ↓ oral glucose tolerance and insulin sensitivity ↔ HOMA-IR ↓ cortisol ↑ TC, LDL-c, HDL-c ↑ blood pressure	↑ hunger, desire to eat, prospective consumption ↓ fullness
(LeCheminant et al., 2013)	Normal weight males n= 27 (27/0)	11:13 2 weeks RXT	**TRE**: 6 am-7 pm **Control**: *ad libitum*	↓9%EI Not reported PA	↓ weight	↑ hunger
(Gill and Panda, 2015)	Young adults with obesity n= 8 (5/3)	10:14 16 weeks Within participants	**Pre**: >14hours eating **Post**: 10-11h, self-selected	↓ 20%EI	↓ weight, BMI	↑ sleep quality ↓ hunger
(Moro et al., 2016)	Normal weight adults with resistance trained TRE n= 17 (17/0) Control n= 17 (17/0)	8:16 8-week RCT	**TRE**: 1 pm - 8 pm **Control**: 8 am -8 pm	↔ EI ↔ PA during training sessions	↓ FM ↔ muscular mass and strength ↓ FBG ↓ insulin resistance ↓ TG ↔ HDL-c, LDL-c, TC	↓ TNF-α, IL-1β ↓ IGF 1, leptin ↑ adiponectin ↓ respiratory ratio (↑lipid oxidation)
(Smith S.T., 2017)	Healthy young adults n= 20 (0/20)	8:16 4 weeks Within participants	**Pre**: habitual **Post**: 12 pm to 8 pm		↓ weight ↔ FM	↔ appetite score
(Tinsley et al., 2017)	Young adults with strength-trained TRE n= 10 (10/0)	4:20 8-week RCT	**TRE**: anytime 4 pm to midnight for 4 days a week	↓ of 650 kcals/day between fasting days and non-	↔ weight, FM ↔ lean soft tissue, muscular volume,	

Reference	Population, sample size (M/F)	TRE protocol (fasting: eating period), duration, trial design	Comparisons	Energy Balance	Metabolic Effects (primary outcome in bold)	Other Results (primary outcome in bold)
	Control n= 8 (8/0)		**Control**: *ad libitum*	fasting days ↓ weekly EI	muscular strength	
(Antoni, 2018.)	Healthy adults TRE n= 7 (1/6) Control n= 6 (0/6)	↓habitual eating duration of 3 h 10 weeks non-RCT	**TRE**: delayed breakfast and advanced dinner by 1.5hrs **Control**: habitual	↔ daily EI	↔ weight ↓ %FM ↓ FBG	
(Sutton et al., 2018)	Adults with pre-diabetes and overweight n= 8 (8/0)	6:18 5 weeks RXT	self-selected breakfast between 6:30 am-8:30 am **eTRE**: spaced lunch and dinner by 3hrs, dinner before 3 pm **Control**: spaced lunch and dinner by 6 hrs	↔ EI (iso-caloric food provided)	↔ weight ↔ oral glucose tolerance ↓ insulin (fasting, mean and peak) ↑ insulin sensitivity, β cell responsiveness ↓ insulin resistance ↑ TG, TC ↔ LDL-c, HDL-c ↓ blood pressure ↔ hsCRP, IL-6	↓ desire to eat ↓ 8-isoprostane (oxidative stress)
(Gabel et al., 2018a)	Adults with obesity TRE n= 23 (3/20) Control n= 23 (2/21)	8:16 12 weeks non-RCT with matched historical control	**TRE**: 10 am-6 pm **Control**: habitual	↓ 20% EI (350 kcal/day) ↔PA	↓ weight ↓ BMI ↓ systolic blood pressure ↔ FBG, insulin, HOMA-IR ↔ LDL-c, HDL-c, TG, TC	
(Gabel et al., 2019)	Adults with obesity TRE n= 23 (3/20)	8:16 12 weeks Within participants	**Pre**: regular eating **Post**: 10 am-6 pm	↓ 20% EI (350 kcal/day) ↔PA	↓ weight, FM ↔LM, visceral FM	↔ β-HBD ↔ sleep quality
(Jamshed et al., 2019, Ravussin et al., 2019)	Adults with normal or overweight n= 11 (7/4)	6:18 4 days RXT	**eTRE**: 8 am -2 pm **Control**: 8 am to 8 pm	↔ EI (iso-caloric)	↓ 24-hour mean blood glucose, hyperglycaemic excursion ↓ morning fasting insulin,	↑ β-HBD ↔ BDNF ↔ IGF1, IGFBP-1, IGFBP-3, growth

Reference	Population, sample size (M/F)	TRE protocol (fasting: eating period), duration, trial design	Comparisons	Energy Balance	Metabolic Effects (primary outcome in bold)	Other Results
					HOMA-IR ↑ evening insulin, HOMA-IR ↑ morning fasting TC, LDL-c, HDL-c ↔ TG, FFA ↔ morning cortisol ↓ evening cortisol ↑ day time energy expenditure, metabolic flexibility	hormone ↓ 24-hour profile of hunger, desire to eat, capacity to eat ↓ morning ghrelin, leptin and GLP-1 ↓ average ghrelin ↑ evening PYY (satiety) Modification of genes expressions involved in glucose uptake, circadian rhythm, longevity, autophagy in whole blood cells
(Anton et al., 2019, Lee et al., 2020)	Elder adults with overweight n= 10(4/6)	8:16 4 weeks within participants	**Pre**: >12hrs/day **Post**: 12 pm to 8 pm		↓ weight ↔ FBG ↔ blood pressure few treatment-emergent adverse events, adherence (84%)	↑ walking speed ↑ mental and physical function (based on the effect size)
(Hutchison et al., 2019b)	Adults with increased risk of T2DM n= 15 (15/0)	9:15 1 week RXT	**dTRE**: 12 pm to 9 pm **eTRE**: 8 am to 5 pm **Baseline**: *ad libitum*	↔ PA Not reported EI	↓ weight ↓ mean fasting glucose by CGM in eTRE ↑glucose tolerance ↓ fasting TG ↔ NEFA	↔ hunger, fullness, or desire to eat ↑ fullness in eTRE ↓ fasting GLP-1
(Tinsley et al., 2019)	Young adults with strength-trained TRE n= 13 (0/13) TRE+HMB n= 13	8:16 8 weeks RCT	**TRE**: 12 pm- 8 pm **TRE+HMB**: 12 pm – 8 pm **Control**: breakfast as	↔ EI ↔ PA	↓ FM of 4%–7% in per protocol analysis for the 2 TRE groups ↔ FFM, muscle	

Reference	Population, sample size (M/F)	TRE protocol (fasting: eating period), duration, trial design	Comparisons	Energy Balance	Metabolic Effects (primary outcome in bold)	Other Results
	(0/13) Control n= 14 (0/14)		soon as waking, *ad libitum*		performance	
(Kesztyus et al., 2019)	Primary care patients with abdominal obesity n= 40 (9/31)	8-9:16-15 12 weeks Within participants	**Pre**: *ad libitum* **Post**: self-selected 8-9hrs/day		↓eating duration ↓ weight, BMI , WC ↓ HbAc1	
(Wilkinson et al., 2019)	Adults with metabolic syndrome n= 19 (13/6)	10:14 12 weeks Within participants	**Pre**: >14 hrs/day **Post**: 10hrs/day, self-selection, dinner before 8 pm	↓ EI by 8.62% ± 14.47% ↔ PA	↓ weight, BMI, %FM, visceral fat rating, WC ↔ FBG, insulin, HOMA-IR, HbA1c, mean glucose by CGM ↓ TC, LDL-c, non-HDL-c, HDL-c ↔ TG ↔ hsCRP ↓ blood pressure ↔ ALT, AST	↑ sleep duration ↑ sleep duration and efficiency in 84% of participants
(Chow et al., 2020)	Adults with overweight and prolonged eating window TRE n= 11 (2/9) Control n= 9 (1/8)	8:16 12 weeks RCT	**TRE**: self-selected 8hrs/day **Control**: >14hrs/day	↔ PA Not reported EI	↓ weight, LM, VFM ↔ insulin, HOMA-IR ↔ blood pressure ↔ average glucose by CGM	
(Parr et al., 2020b, Lundell et al., 2020)	Sedentary adults with overweight/obesity n= 11 (11/0)	8:16 5 days RXT	**TRE**: 10 am-6 pm **Control**: 15 hrs/day	↔ EI (iso-caloric) ↔ PA	↔ 24-hour glucose AUC ↓ night-time glucose AUC, glucose and insulin iAUC after lunch, peak insulin and glucose at breakfast, 24-hour C-peptide ↑ post-lunch TG, 24-hour	↑ subjective feelings (well-being and satisfaction) ↓ evening hunger ↔clock gene expression in muscle ↑ amplitude of

Reference	Population, sample size (M/F)	TRE protocol (fasting: eating period), duration, trial design	Comparisons	Energy Balance	Metabolic Effects (primary outcome in bold)	Other Results
					NEFA AUC ↔ 24-hour TG AUC	oscillating muscle transcripts ↑ rhythmicity of several amino acid transporter genes in muscle and metabolites phase-shifted amino acid related metabolites
(Parr et al., 2020a)	Adults with T2DM n= 19 (9/10)	9:15 4 weeks Within participants	**Pre**: habitual **Post**: 10 am- 7 pm	↔overall EI Adherence to TRE ↓ 16% EI	↔ weight ↔ HbA1c feasible, adhere, safe	↔ Cognitive function
(Lowe et al., 2020)	Adults with overweight/ obese TRE n= 25 (13/12) Control n= 25 (15/10)	8:16 12 weeks RCT	**TRE**: 12 pm- 8 pm **Control**: 3 structure meal/day	↔ EI ↓ daily movement, steps count	↔ weight ↓ appendicular LM (index) ↔ FBG, fasting insulin, HOMA-IR, HbA1C ↔ TG, TC, LDL-c, HDL-c ↔ blood pressure	↔ self-reported sleep measures
(Martens et al., 2020)	Healthy normal weight midlife and older adults n= 22 (10/12)	8:16 6 weeks RXT	**TRE**: self-selected **Control**: normal eating	↔ EI (isocaloric)	↔ weight, leg LM, bone mineral density ↑ leg FM (2.5%); ↔FBG ↑ oral glucose tolerance ↔ fasting insulin or insulin AUC, insulinogenic index (β cell function) ↑ TC, LDL-c ↔ oxidized-LDL-c ↔ acetoacetate, β-HBD ↔ blood pressure ↑ cardiorespiratory fitness ↔ CRP, IL-6	↓ hunger ↔ endothelium dependent dilation

Reference	Population, sample size (M/F)	TRE protocol (fasting: eating period), duration, trial design	Comparisons	Energy Balance	Metabolic Effects (primary outcome in bold)	Other Results
					↔ RER	
(Moro et al., 2020)	Young healthy elite cyclists TRE n= 8 (8/0) Control n= 8 (8/0)	8:16 4 weeks RCT	**TRE**: 10 am-6 pm **Control**: 7 am-9 pm		↓ weight ↔ FM, FFM ↔ FBG, insulin ↔ IL-6, TNFα ↔ adiponectin, IGF-1, TSH	↑ PPO/body weight ratio (sport performance) ↔ Maximal oxygen consumption
(Zeb et al., 2020)	Young healthy adults TRE n= 56 (56/0) Control n= 24 (24/0)	8:16 25 days Non-RCT	**TRE**: 7:30 pm-3:30 am **Control**: regular diet		↑ HDL-c ↓ TC, TG, ↔ LDL-c ↔ IL-1β, TNFα ↓ ALT, AST, ALP, GGT, serum albumin	↑ microbiome diversity in gut ↑ Bmal1, Clock, Sirt1 gene expression
(Jones et al., 2020)	Healthy young lean adults TRE n= 8 (8/0) Control n= 8 (8/0)	8:16 2 weeks RCT	**eTRE**: 8 am-4 pm **Control**: calorie restriction, *ad libitum*, food provided to match eTRE group	↓15% EI (~400kcal/day) in eTRE ↔ EI between eTRE and control ↔ PA	↔ weight, FM, LM, android fat, gynoid fat ↔ FBG, mean 24-hour glucose by CGM, RMR ↑ insulin sensitivity, skeletal muscle glucose uptake, BCAA ↑ fasting insulin ↓ postprandial glucose and insulin ↓ mean glucose (8 pm to 8 am) ↑ glucose variability(8 am to 8 pm) ↔ TG, FFA	↑ fasting ghrelin
(Cienfuegos et al., 2020b, Cienfuegos	Adults with obesity 4h TRE n= 16 (2/14)	4:20 6:18	**4h TRE**: 3 pm-7 pm **6h TRE**: 1 pm-7 pm	↓ 30% EI (~550Kcal)	*Vs. control, ↔ between 4 and 6:*	↓ 8-isoprostane (oxidative stress)

Reference	Population, sample size (M/F)	TRE protocol (fasting: eating period), duration, trial design	Comparisons	Energy Balance	Metabolic Effects (primary outcome in bold)	Other Results
et al., 2021)	6h TRE n= 19 (1/18) Control n= 14 (2/12)	8 weeks RCT	**Control**: routine eating		↓ weight, FM, LM ↓fasting insulin, HOMA-IR, ↔ FBG, HbA1c ↔ LDL-c, HDL-c, TG ↔ TNFα, IL-6 ↔ blood pressure, HR	↔ No serious adverse events were reported ↔ sleep quality, duration, insomnia severity, obstructive sleep apnoea
(Gabel et al., 2020a)	Adults with obesity n= 14 (unclear)	8:16 12 weeks Within participants	**Pre**: regular eating **Post**: 10 am-6 pm		↓ weight, FM ↔ LM, VFM ↔ FBG, insulin ↔ TC, LDL-c, HDL-c, TG ↓ systolic blood pressure ↑ HR	↔ gut microbiota phylogenetic diversity ↔ abundance of any phyla
(Pureza et al., 2020, de Oliveira Maranhão Pureza et al., 2021)	Adults with obesity TRE n= 31 (0/31) Control n= 27 (0/27)	12:12 21 days/12 months RCT	**TRE**: self-selected (hypoenergetic diet) **Control**: habitual eating (hypoenergetic diet)	↔ EI Not reported PA	*21 days:* ↔ weight ↓ %FM ↑ axillary temperature ↔ FBG, fasting insulin, T3, T4, TSH *12 months:* ↔ weight ↓ %FM, WC	
(Schroder et al., 2021)	Adults with obesity TRE n= 20 (0/20) Control n= 12 (0/20)	8:16 non-RCT 3 months	**TRE**: 12 pm-8 pm **Control**: habitual eating		↓ weight, BMI, FM, WC, %fat, FM index, muscle mass, muscle mass index related to height ↔ FBG, insulin, HOMA-IR ↔ TC, LDL-c, HDL-c, TG ↔ blood pressure ↔ CRP	↔ probability of general cardiovascular events to happen ↑ self-perception of a better quality of life

Reference	Population, sample size (M/F)	TRE protocol (fasting: eating period), duration, trial design	Comparisons	Energy Balance	Metabolic Effects (primary outcome in bold)	Other Results
					↔ ALP,AST,GGT	
(Gonzalez et al., 2021)	Healthy professional adult firefighters n= 16 (16/0)	10:14 7 weeks Within participants	**Pre**: habitual eating **Post**: self-selected 10hrs/day		↔ FM, BMI	↑ endurance exercise performance
(Li et al., 2021)	Women with anovulatory polycystic ovary syndrome n= 15 (0/15)	8:16 5 weeks Within participants	**Pre**: habitual eating **Post**: 8 am-4 pm		↓ weight, BMI, FM, % FM, VFM ↔ muscle mass ↔ WHR ↓ fasting insulin, HOMA-IR ↓ insulin AUC, insulin AUC/glucose AUC ↔ FBG, glucose AUC ↔ TG, TC, LDL-c ↓ hsCRP ↓ ALT	↑ improvement in menstrual cycle irregularity ↑ SHBG, IGF-1 ↓ total testosterone, free androgen index ↔ LH,FSH, LH/FSH
(McAllister et al., 2021a)	Healthy adult firefighters n= 13 (13/0)	10:14 8 weeks Within participants	**Pre**: habitual eating **Post**: self-selected 10hrs/day	↔ EI	↔ fire grounds test ↔ HR ↓ Salivary IL-6 and IL-1b ↑ Salivary CRP	↓ cortisol response to the simulated fire grounds test

[1] RXT, randomised cross-over clinical trial; RCT, randomized clinical trial; EI, energy intake; TRE, time restricted eating; eTRE: early time restricted eating; HMB, β-hydroxy β-methylbutyrate supplementation; SHBG, sex hormone-binding globulin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; FM, fat mass; VAT, visceral fat mass; FFM, fat free mass; LM, lean mass; BMI, body mass index; WC, waist circumference; WHR. Waist/hip ratio; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, glycosylated haemoglobin; HR: heart rate; FBG, fasting blood glucose; IGF-1, insulin-like growth factor 1; IGFBP-1 or 3, insulin-like growth factor binding protein 1 or 3; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; TG, triglycerides; TNFα, tissue necrosis factor alpha; IL-6/1b, interleukin 6 or 1b; CGM, continuous glucose monitoring; FFA, free fatty acids; NEFA, non-esterified fatty acid; BCAA, branched chain amino acids; RER: respiratory exchange ratio; AUC, incremental area under the curve; CRP, C-reactive protein; hsCRP, high-sensitive C-reactive protein; β-HBD, beta hydroxybutyrate; ALT, alanine

aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; WC, waist circumference; fT3, free tri-iodothyronine; fT4, free thyroxine; TSH, thyroid stimulating hormone; GLP-1, glucagon-like peptide 1; PYY, peptide YY; BDNF brain derived neuronal factor ; Bmal1, Brain and Muscle ARNT-Like 1; Clock, Circadian Locomotor Output Cycles Kaput; Sirt1, sirtuin 1.

1.5 Summary

Food intake is one of the strongest cues to entrain peripheral clocks, probably partially via elevated insulin levels. Therefore, mistimed and erratic eating patterns could induce circadian disruption, leading to obesity and metabolic health consequences. However, few studies have simultaneously captured objective behavioural rhythms (such as daily sleep patterns, eating patterns, blood pressure and glucose patterns) to explore the critical contributors that are associated with developing obesity. Furthermore, the day-to-day variation in eating patterns could also lead to circadian disruption, and is not well tested to date. TRE, which is designed to reinforce peripheral circadian rhythms, has shown pleiotropic metabolic health benefits in both animals and humans. However, most of the TRE clinical trials to date are pilot studies that have only examined adherence, feasibility and body weight with a limited sample size and number. Very few have explored the potential mechanisms involved in restoring the peripheral circadian clocks in humans, indicating a need for further clinical research.

1.6 Research questions

This research aims to answer the following questions:

1. Are components of eating architecture associated with markers of adiposity and glycaemic control in individuals who are at increased risk of developing T2DM?
2. Does IF disturb the clock gene expression in peripheral tissues in humans?
3. Does TRE improve metabolic health in humans?
4. Does TRE alter the markers of central clocks?
5. Does TRE alter 24-hour profiles of metabolites and glucoregulatory hormones in humans?
6. Does TRE restore the circadian clocks and rhythmic genes in human peripheral tissues?

1.7 Overall and specific aims and hypothesis

1.7.1 Overall aims

The overall aim of my research project was to provide evidence that erratic eating will increase the risk of obesity and T2DM, while TRE will decrease the risk factors of T2DM, such as body weight and markers of glucose control, via restoring the 24-hour rhythms of blood metabolite and glucoregulatory hormones, as well as transcriptome in adipose tissue.

1.7.2 Specific aims and hypothesis

Study 1: Cross-sectional study

Aim: To determine the relationship between components of eating architecture and body fat and markers of glycaemic control, in adults at increased risk of T2DM.

Hypothesis: High variability in eating architecture components, particularly the first meal of the day, will be positively associated with body fat mass as a marker of obesity, HbA1c and mean 24-hour glucose by CGM as markers of overall glycaemic control in men and women at increased risk of T2DM.

Study 2: Sub-study from an eight-week randomized clinical trial

Aim: To examine the effects of 8-week IF (fast:feast 3:4 days/week) on mRNA levels of genes involved in circadian regulation in muscle and adipose tissue in women with obesity.

Hypothesis: IF will reduce the expression of genes involved in circadian regulation in muscle and adipose tissue following 24-hour fasting days in both IF groups, but that there would be a differential response between IF groups on refeeding days.

Study 3: Highly controlled metabolic ward stay pre and post eight weeks of 10 hour TRE

clinical trial

Aims:

1. To examine the effects of eight weeks of TRE on glucose metabolism during a metabolic ward stay in men with obesity.
2. To test the effect of TRE on 24-hour profile of blood metabolites, glucoregulatory hormones, and transcriptomic profiles in human adipose tissue.

Hypotheses:

1. TRE will reduce body weight, improve glycaemic control in men.
2. TRE will alter the 24-hour profile of glucose, NEFA, triglycerides, and glucoregulatory hormones and restore adipose tissue clocks and rhythmic gene expression, without altering central clock marker melatonin.

1.8 Outline of the thesis

In addition to the research questions, aims and hypothesis, this thesis is organized into a series of published and unpublished articles (Figure 1.4). This includes a review of the current literature (published) and four original research articles (2 published, 1 under review, and 1 written in manuscript format and soon to be submitted).

The first chapter of this thesis contains an introduction, research questions, aims and hypotheses. The introduction section encompassed the current prevalence of obesity, the impact of mistimed eating on the risk of obesity and glycaemic control, the interaction among circadian rhythms, food intake and metabolism, as well as the solution to combat obesity and risk of T2DM by timed eating such as intermittent fasting and time restricted eating.

Chapter 2 is entitled "Carbohydrate intake and circadian synchronicity in the regulation of glucose homeostasis" and was published in *Current Opinion Clinical Nutrition & Metabolism Care* in 2021. This invited review article summarised the current research in meal timing which is increasingly being used as a tool to improve glucose control and reset circadian clocks. This review highlighted carbohydrate timing as a potential key in regulating peripheral clocks as insulin is a cue to synchronize biological rhythms *in vitro* and in mice. It also identified the research gaps in manipulating macronutrient timing to modify glucose metabolism or clocks in human for future studies.

Chapter 3 is entitled "Eating architecture in adults at increased risk of T2DM: associations with body fat and glycaemic control" and is in press in *British Journal of Nutrition*. This original research examined the relationship between components of eating architecture and body fat and markers of glycaemic control, in adults at increased risk of T2DM. We aimed to identify the aspects of eating architecture components associated with obesity and markers of glycaemic control.

Chapter 4 is entitled “Intermittent Fasting Does Not Uniformly Impact Genes Involved in Circadian Regulation in Women with Obesity” and was published in *Obesity* in 2020. This paper examined the effect of 24-hour alternate day fasting (initiated at breakfast time) on the core clock gene expression in women with obesity. We proposed that alternate day intermittent fasting could dampen the clock gene expression in peripheral tissues such as muscle and adipose tissue. This paper highlighted that the timing of initiation of fasting might be important to maintain a robust circadian clock in women with obesity.

Chapter 5 is entitled “Time restricted eating improves glycaemic control and dampens energy-consuming pathways in human adipose tissue” and is published online in *Nutrition Journal (International Journal of Applied and Basic Nutritional Sciences)* in January 2022. This is the primary outcome paper for Study 3, which examined the effects of self-selected 10-hour TRE on body weight, glycaemic control and adipose tissue transcriptome in men with increased risk of T2DM. This study showed that TRE produced a moderate weight and fat loss, improved markers of glucose control such as fasting blood glucose and HbA1c, as well as downregulated the transcripts enriched in energy-consuming pathways. Thus, this finding suggests that TRE could be a preventative or therapeutic strategy to assist glycaemic management for patients with prediabetes or T2DM.

Chapter 6 is entitled “Time restricted eating alters the 24-hour transcriptomic profile in human adipose tissue” and will be submitted for publication. This paper is the secondary outcomes of Study 3. We examined the effect of TRE on the markers of central clocks and peripheral clock adipose tissue, as well as 24-hour profiles of blood metabolites, glucoregulatory hormones and adipose tissue transcriptome. TRE did not alter melatonin but reduced morning cortisol levels, altered the 24-hour profile of insulin, triglycerides and non-esterified fatty acids. TRE also altered key clock genes and restored genes involved in chromatin regulation and vesicular translocation of glucose transporters in human SAT.

Chapter 7 is conclusions and future directions.

The last chapter contains conclusions and future directions.

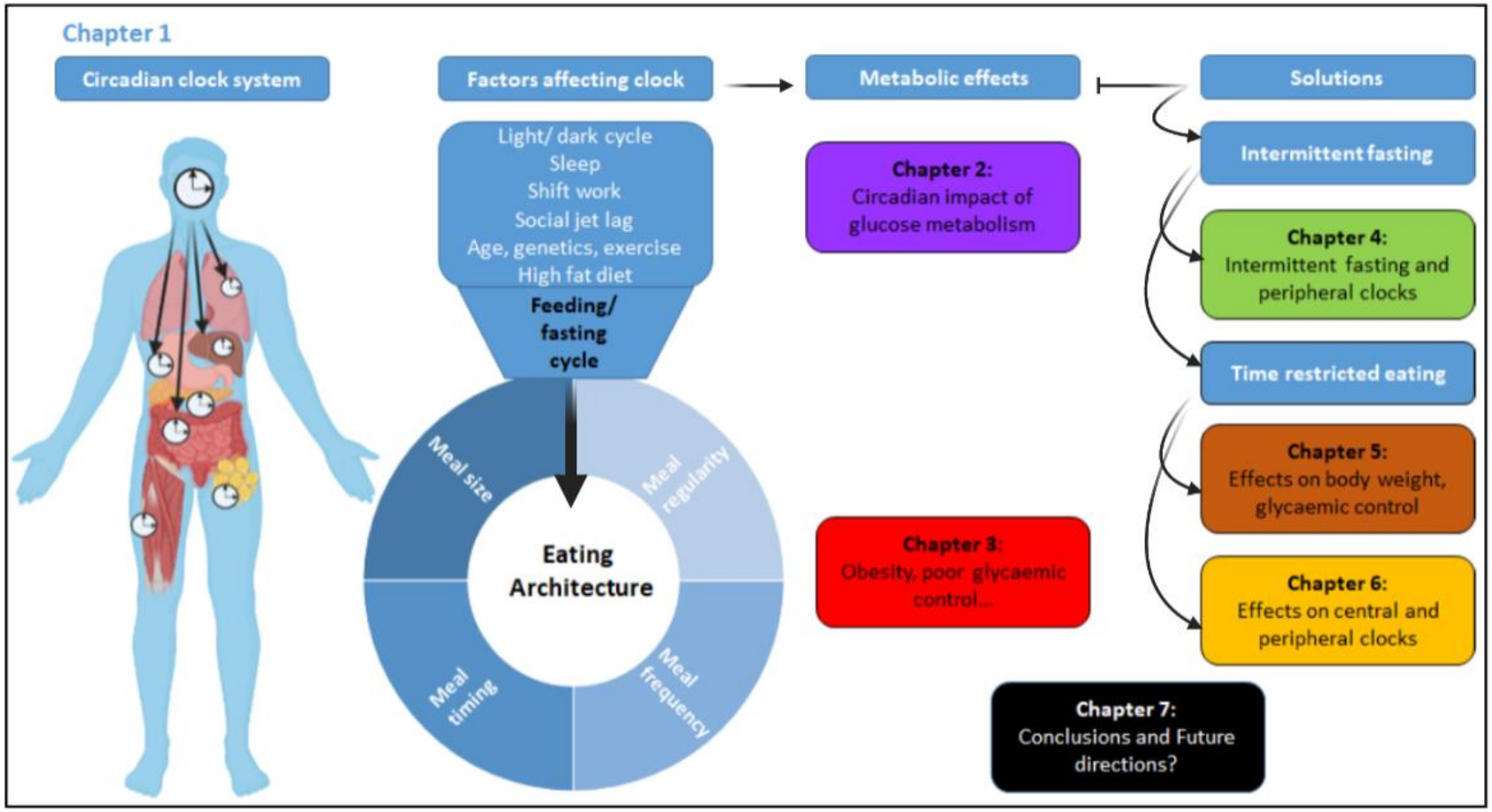


Figure 1.5 Format and outline of the thesis.

CHAPTER 2 CARBOHYDRATE INTAKE AND CIRCADIAN SYNCHRONICITY IN THE REGULATION OF GLUCOSE HOMEOSTASIS

Lijun Zhao[1,2], Amy T Hutchison[1,2], Leonie K Heilbronn[1,2,3]

[1] Adelaide Medical School, University of Adelaide, South Australia 5000, Australia

[2] Lifelong Health Theme, South Australian Health and Medical Research Institute, South Australia 5000, Australia

[3] Corresponding author and lead contact

Statement of Authorship

Title of Paper	Carbohydrate intake and circadian synchronicity in the regulation of glucose homeostasis
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Zhao L, Hutchison AT, Heilbronn LK. Carbohydrate intake and circadian synchronicity in the regulation of glucose homeostasis. Curr Opin Clin Nutr Metab Care. 2021;24(4):342-348.

Principal Author

Name of Principal Author (Candidate)	Lijun Zhao		
Contribution to the Paper	Searched and reviewed literature, interpreted data, wrote the manuscript, and approved final manuscript.		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	23 July 2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Amy T Hutchison		
Contribution to the Paper	Searched literature, interpreted data and approved final manuscript.		
Signature		Date	17/08/2021

Name of Co-Author	Leonie Heilbronn		
Contribution to the Paper	Interpreted data, wrote the manuscript, and approved final manuscript.		
Signature		Date	26/7/21

2.1 Key points

- Meal timing is increasingly being used as a tool to improve glucose control and reset circadian clocks.
- New evidence shows that insulin is a cue that synchronizes biological rhythms, and an important reset signal for peripheral circadian clocks *in vitro* and in mice, suggesting carbohydrate timing could be key in regulating peripheral clocks.
- Few studies to date have tested the impacts of carbohydrate timing on glucose metabolism or clocks in humans.

2.2 Abstract

Purpose of review

Glucose metabolism is under circadian regulation, with insulin secretion and sensitivity being highest in the morning as compared to the evening. This review will discuss the existing evidence for the role of meal and macronutrient timing to improve glucose metabolism and reset circadian clocks, with a focus on the evidence in humans.

Recent findings

Shortening the daily eating window (also known as time restricted eating), or skewing food intake towards breakfast and away from the evening meal both improve glucose control in people with impaired glucose metabolism. Insulin is recently purported to be a zeitgeber and thus an important reset signal for peripheral circadian clocks *in vitro* and in mice. Whilst few studies have tested the impact of macronutrient timing in humans, eating a greater proportion of carbohydrates earlier, rather than later, in the day is associated with better glucose control.

Summary

The impact of carbohydrate intake timing on endogenous central and peripheral clocks, and its potential to optimize circadian regulation and improve glycemic control, are not well understood but are currently under intense exploration.

Keywords: Carbohydrate, meal timing, insulin, cortisol, glucose

2.3 Introduction

Perturbations in eating architecture, such as breakfast skipping, all-day grazing, and late night eating are associated with an increased risk of obesity and chronic diseases in humans (Dashti et al., 2020, Martínez-Lozano et al., 2020, Yamamoto et al., 2021). In mice, high fat diet disturbs eating architecture, and the animals graze significantly more during their sleeping phase. This is associated with a dampening in the amplitude of transcription of core clock genes in peripheral tissues, misalignment between central and peripheral clocks, and impaired glucose metabolism (Sinturel et al., 2020, Lewis et al., 2020). Time restricted eating (TRE), defined as limiting daily food intake to a 6-10 hour period during the active phase, restores the robust oscillation of clock genes and glucose control in mouse models of circadian disruption, aging, and diet-induced obesity (Regmi and Heilbronn, 2020). Whilst only pilot TRE studies have been conducted in humans with obesity, the health benefits of TRE include modest weight losses, reduced cardiovascular risk markers and improved glucose control, although it is still unclear whether TRE alters the amplitude of peripheral clocks in humans (Jamshed et al., 2019, Jones et al., 2020, Hutchison et al., 2019b, Kesztyus et al., 2019, Parr et al., 2020a, Wilkinson et al., 2019, Parr et al., 2020b, Schroder et al., 2021, Peeke et al., 2021, Pureza et al., 2020, McAllister et al., 2021b, Zeb et al., 2020, Moro et al., 2020, Cienfuegos et al., 2020a). More recently, insulin was reported to be a zeitgeber, an important reset signal for circadian clocks (Crosby et al., 2019). This new evidence highlights the need to consider the importance of macronutrient timing in humans. This review will discuss the circadian regulation of glucose homeostasis, the evidence that altering meal timing will improve glucose control, and emerging evidence that carbohydrate timing could harness peripheral clocks, synchronize circadian rhythms and improve glycemic control in humans.

2.4 Circadian rhythms control glucose metabolism

Glucose homeostasis is under regulation by the circadian system (Sinturel et al., 2020, Leung et al., 2020). In humans, there are smaller glucose excursions in response to an oral glucose tolerance test that is performed at 8 am as compared to a test that is performed at 8pm, even when there is an equivalent fasting time between tests (Leung et al., 2019). This finding is mirrored when the more physiological mixed-nutrients meal test is conducted at 8 am, 8 pm and 12 am (Leung et al., 2019). Diurnal variation in glucose tolerance is the result of rhythms in β-cell responsiveness, hepatic insulin clearance and peripheral insulin sensitivity (Oosterman et al., 2020). There is a marked increase in β-cell sensitivity and insulin secretion in response to carbohydrate intake in the morning as compared to the same carbohydrate intake in the evening. Some of this effect may be mediated by the incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinoptropic polypeptide (GIP), whose secretion is highest in the morning, and which potentiate insulin secretion (Martchenko et al., 2020). It may also be linked with lower levels of melatonin in the morning, whose night time rise coincides with a decrease in glucose homeostasis (Rubio-Sastre et al., 2014). Melatonin has been shown to reduce cAMP (cyclic adenosine monophosphate) and inhibit insulin release in islets , while acute treatment with melatonin reduces insulin secretion in humans *in vivo* (Campbell and Newgard, 2021), with a greater effect when melatonin was given in the morning versus the evening (Rubio-Sastre et al., 2014).

Approximately nine to fifteen percent of the human muscle and adipose tissue transcriptome exhibits circadian oscillation (Stenvers et al., 2019a, Lundell et al., 2020). There is a marked reduction in insulin sensitivity at midnight versus midday in human muscle and subcutaneous adipose tissue (Oosterman et al., 2020). This is likely linked to impaired GLUT4 (glucose transport type 4) translocation to the cell surface, which is required for insulin mediated glucose uptake, at night versus during the day (Gutierrez-Monreal et al., 2020). Interestingly, GLUT4

expression, translocation and recycling remains rhythmic under constant protocol conditions (i.e., during which time sleep, activity, light and food intake were controlled), and knockdown of CLOCK (circadian locomotor output cycles kaput) by siRNA in primary human muscle cultures was sufficient to impair basal and insulin-stimulated glucose uptake (Perrin et al., 2018).

Hydrocortisone treatment impairs insulin signalling in C2C12 myotubes (Negri et al., 2020). In humans, cortisol release is rhythmic, peaking shortly after awakening, and declining over the day, following a periodic non-linear oscillation with brisk cortisol increases in response to psychological and nutritional stimuli (see Figure 2.1) (Minnetti et al., 2020). An acute physiological morning elevation in plasma cortisol begins to inhibit insulin secretion and induces peripheral insulin resistance 4-6 hours later, an effect which persisted for 12-16 hours (Oster et al., 2017). The insulin-desensitizing effects of cortisol were more pronounced when it was given in the evening, instead of the morning (Negri et al., 2020, Oster et al., 2017). Thus, high cortisol levels at night may be more deleterious for insulin sensitivity, although impairment in the cortisol awakening response and elevated cortisol nadir are both associated with future incidence of T2DM and insulin resistance (Panagiotou et al., 2021).

2.5 The role of meal timing in glucose regulation- is eating early in the day optimal for glucose control?

Given extensive evidence that insulin sensitivity and secretion are under circadian regulation and highest in the morning, it makes sense that skewing food intake, and particularly carbohydrate intake, towards breakfast would improve day-long glucose control. Whilst skipping breakfast and late night eating are both independently associated with increased risk of obesity and T2DM in cross-sectional studies (Yaguchi-Tanaka and Tabuchi, 2020, Hashimoto et al., 2020, Dashti et al., 2020, Martínez-Lozano et al., 2020), some studies suggest

that the risk is only elevated when breakfast skipping is combined with late night eating (Azami et al., 2019, Yaguchi et al., 2020). In fact, many randomized controlled trials do not detect negative consequences of skipping breakfast (Ogata et al., 2019, Bonnet et al., 2020), and a recent systematic review and meta-analysis synthesizing this evidence also showed that breakfast skipping did not alter fasting insulin or glucose (Bonnet et al., 2020). Interestingly, individuals with fixed breakfast habits (i.e. they report never, or always, consuming breakfast) were both less likely to be obese than those who reported occasionally skipping breakfast (3 to 4 days per week) (Guinter et al., 2020), which suggests erratic eating habits increases risk of obesity.

Delaying breakfast and all subsequent meals by 2.5 hours mitigated weight loss and the improvements in markers of cardiovascular risk and insulin resistance in women with overweight and obesity who were placed under caloric restriction (Madjd et al., 2020). Skewing food intake to a large breakfast and small dinner was also optimal for weight loss and glycemic control in individuals with T2DM versus the reverse (Morgan et al., 2012, Richter et al., 2020). These benefits was associated with greater diet-induced thermogenesis and lower cortisol levels (Richter et al., 2020). Eating a high carbohydrate snack after lunch versus after dinner also reduced glucose excursions in the evening and the next morning (Nitta et al., 2019). Together, these studies show that eating more energy in the morning and less in the evening, are optimal for weight control and health. However, this pattern of eating is the reverse from societal norms and general lifestyles, and thus whether individuals can adhere to this distribution of food intake, long-term, is unclear.

Surprisingly, evidence has indicated that eating earlier may not be necessary if implementing TRE. In mice, delaying the initiation of TRE (akin to breakfast skipping) delayed key clock and nutrient signaling genes (i.e., Bmal1, Cry1, Per2, Reverbα, Nampt, NAD, Sirt1), and mitigated weight and fat losses, but did not impact the improvements in glucose tolerance (Regmi et al.,

2021). Similarly, TRE initiated at breakfast or lunch resulted in identical improvements in glucose tolerance in men with obesity (Hutchison et al., 2019b). However, this was a small pilot study, conducted for one week per condition, and larger and longer trials are required to confirm these results.

2.6 The role of macronutrient timing in glucose regulation

Whilst a number of studies have examined the impact of meal timing on glucose regulation in humans, few have examined the role of macronutrient timing (Morgan et al., 2012, Nitta et al., 2019, Kräuchi et al., 2002, Leung et al., 2019, Davis et al., 2020, Davis et al., 2021) (Table 1), and even fewer have examined the response longer-term (Jakubowicz et al., 2017a, Kessler et al., 2017, Kessler et al., 2018, Alves et al., 2014). Postprandial glucose responses to a high-protein or high-carbohydrate meal consumed at 8 am or 8 pm were examined over four separate metabolic testing days in 10 healthy lean individuals (Davis et al., 2020, Davis et al., 2021). The high-carbohydrate breakfast did not differentially impact glucose control as compared to the high-protein breakfast. However, the high-carbohydrate dinner resulted in a 71% increase in postprandial glucose response versus the high-protein dinner, highlighting the diurnal regulation in insulin sensitivity and secretion. This study did not examine the effects of these single meals on 24-hour glucose profiles. Eating a high glycemic index (GI) diet with more of the energy load in the evening increased 20-hour glucose levels, postprandial insulin and HOMA-IR (homeostatic model assessment for insulin resistance) compared with high GI morning loading, or low GI evening loading. Of note, there were no differences between the high GI morning and low GI evening diet groups, except that insulin levels were higher in the high GI morning condition to compensate (Morgan et al., 2012). In individuals with pre-existing impairments in glucose metabolism however, a high-energy and protein breakfast (50% carbohydrates, 25% protein) with low-energy dinner was optimal to decrease glucose and increase postprandial insulin, C-peptide and GLP-1 at breakfast, and at the subsequent lunch

and dinner versus a high-energy and carbohydrate breakfast (64% carbohydrates, 11% protein) (Jakubowicz et al., 2017a). Whey protein was most favorable as compared to mixed protein ingestion, and linked to greater stimulation of GLP-1 (Jakubowicz et al., 2017a).

In longer term studies, weight loss and fasting glucose and insulin levels were not different when a protein enriched lunch and carbohydrate enriched dinner versus the reverse were consumed. Contrary to expectations, insulin resistance by HOMA-IR was lowest when participants consumed the protein enriched lunch and carbohydrate enriched dinner (Alves et al., 2014). Another study examined consumption of isocaloric diets enriched with carbohydrate until 1:30 pm and then fat-enriched diets between 4:30 pm and 10 pm (HC-HF) or the inverse (HF-HC) for four weeks each (Kessler et al., 2017, Kessler et al., 2018). Eating carbohydrates earlier in the day promoted fat oxidation in the morning, but had no impact on blood lipids or cortisol rhythm (Kessler et al., 2018). Eating carbohydrates early significantly reduced day-long glucose, although this was significant only in men who had impaired glucose metabolism at baseline (Kessler et al., 2017). Collectively, these studies provide some indication that manipulating carbohydrate intake towards the beginning of the day and fat and protein towards the end of the day could improve glucose metabolism, particularly in those who are overweight and at risk of insulin resistance (Figure 2.1B). However, these studies are small and typically have not evaluated the effects of macronutrient timing on endogenous central rhythms or peripheral clocks.

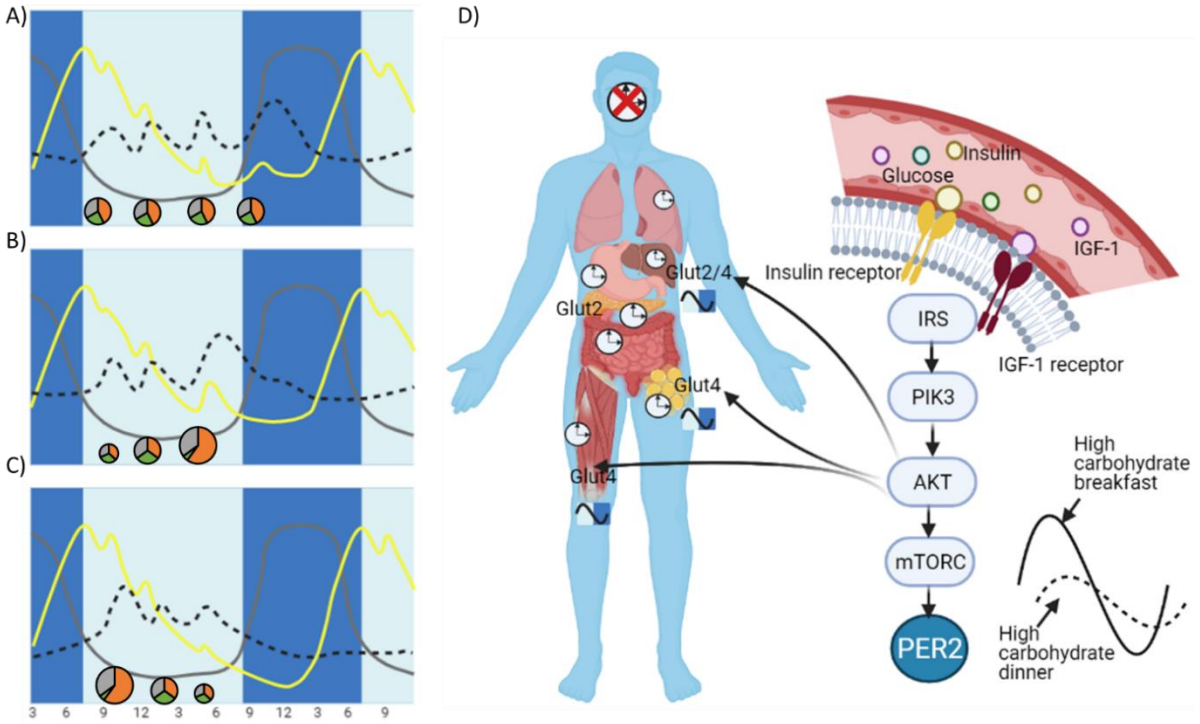


Figure 2.1 Predicted temporal glucose, cortisol and melatonin responses to alterations in meal and macronutrient timing.

[**A)** Predicted glucose and cortisol responses to four identical meals divided across the waking period, with a late dinner meal served around the physiological elevation of melatonin. **B)** Predicted glucose and cortisol responses to a small breakfast and large, carbohydrate-enriched dinner which elevating the cortisol nadir and overnight glucose levels, with residual effects the following day, which may also adversely affect PER2 and peripheral clocks. **C)** Predicted glucose and cortisol responses to a large carbohydrate-enriched breakfast and a smaller, low carbohydrate dinner will be optimal for overnight cortisol and glucose. **D)** Insulin is proposed as a zeitgeber, and thus a high-carbohydrate breakfast may be optimal to drive PER2 protein translation maximally in the morning, particularly if the meal is timed to coincide within 4 hours after the cortisol awakening response, as compared to high-carbohydrate dinner which may flatten the amplitude in PER2. Size of the circle represents size of a meal. Orange, green and grey panel represent the percentage of carbohydrate, protein and fat, respectively. Glucose (black dash line), melatonin (grey line) and cortisol (yellow line). IGF-1, insulin-like growth factor-1; Glut2/4, glucose transporter type 2/4; IRS, insulin receptor substrate; PIK3, Phosphoinositide 3-kinases; AKT, Protein kinase B; mTORC, mammalian target of rapamycin complex; PER2, period 2 protein.]

Table 2.1 Summary of macronutrient timing studies in humans and their major findings[1]

References	n	Study design	Trial length	Group	Comparison group	Effect on glycaemia/circadian rhythms
(23)	10 healthy lean adults	RXT	1 day	OGTT at 8 am	OGTT at 8 pm	↑ OGTT glucose iAUC and insulin iAUC
				Low GI meal consumed at 8 am	Low GI meal consumed at 8 pm and midnight	↑ meal test glucose iAUC and insulin iAUC at 8 pm and 12 am ↔ meal test glucose and insulin iAUC at 8 pm vs 12 am
(46)	17 young healthy women adults	RXT	1 day	Sweet snack at 3:30 pm, B:17%, L:27%, D: 32%, S:24%	Sweet snack at 7:30 pm, B:17%, L:27%, D: 32%, S:24%	↑ mean amplitude of glycemic excursions and standard deviation of glucose ↑ glucose iAUC from 12 pm to 7 am ↑ glucose iAUC at 7 am to 10 am next day
(49)	10 lean, healthy adults	RXT	1 day	HC meal (c: 46%, p:15%, f:34%), consumed at 8 am or 8 pm	HP meal, (c: 29%, p: 41%, f:28%), consumed at 8 am or 8 pm	↔ glucose iAUC at 8 am ↓ glucose iAUC at 8 pm ↔ Insulin
2012 (44)	6 healthy lean adults	RXT	1 day	Low GI, large breakfast (B: 60%, L: 20%, D: 20%) or Low GI, large dinner (B: 20%, L: 20%, D: 60%)	High GI, large dinner, B:20%, L:20%, D: 60%	↑ 24-hour glucose AUC, postprandial insulin and HOMA-IR ↔ triglycerides ↔ non-esterified fatty acid
				Low GI, large dinner (B: 20%, L: 20%, D: 60%)	High GI, large breakfast, B:60%, L:20%, D: 20%	↑ postprandial insulin ↔ triglycerides ↔ non-esterified fatty acid
2017 (51)	56 adults with T2DM	RCT	12 weeks	HC breakfast (c: 64%, p: 11%, f: 25%)	HP whey breakfast (c: 50%, p: 25%, f: 25%, 28g whey protein) or HP breakfast (c: 50%, p: 25%, f: 25%, no whey protein)	↓ body weight, HbA1c, postprandial glucose, ghrelin, hunger ↑ postprandial insulin, C-peptide, satiety

References	n	Study design	Trial length	Group	Comparison group	Effect on glycaemia/circadian rhythms
				HP breakfast (c: 50%, p: 25%, f: 25%, no whey protein)	HP whey breakfast (c: 50%, p: 25%, f: 25%, 28g whey protein)	↓ body weight, postprandial glucose, HbA1c, ghrelin, hunger ↑ postprandial insulin, c-peptide, GLP-1 satiety
(52, 53)	29 non-obese men	RXT	4 weeks	HC meals until 13.30 (c: 65%, p: 15%, f: 20%), HF meals between 4:30 pm and 10 pm (c: 35%, p: 15%, f: 50%)	Inverse sequence of meals	All subjects: ↓ leptin and visfatin, altered daily leptin and visfatin profiles In normal glucose tolerance subjects: ↑ 24-hour GLP-1 IFG/IGT subjects: ↑ 24 hour glucose AUC ↓ fasting GLP-1, peptide YY, ↓fasting HDL-c
(48)	10 healthy young men	RXT, in a constant protocol	3 days	One HC meal in the morning during 8:30 am to 9 am (c: 75%, p: 11%, f: 14%)	One HC meal in the evening during 9:30 pm-10 pm (c: 75%, p: 11%, f: 14%)	↑ core body temperature, advance phase ↑ heart rate, advance phase ↓nocturnal melatonin secretion
(54)	58 men, obese	RCT, ~10% caloric restriction for weight loss	8 weeks	Diurnal carbohydrate/nocturnal protein (L, c: 69%, p:7%; D, c:42%, p: 19%)	Nocturnal carbohydrate/diurnal protein (L, c: 18%, p: 41%; D, c: 68%, p: 8%)	↔ anthropometry and body composition ↓ HOMA-IR

[1] B, breakfast; L, lunch; D, dinner; S, snack; c, carbohydrates, f, fat; p, protein; HC, high carbohydrate; HF, high fat; HP, high protein; OGTT, oral glucose tolerance test; AUC, area under the curve; iAUC, incremental AUC; RXT, randomized crossover trial; RCT, randomized control trial; BMI, body mass index; GI, glycemic index; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance. GLP-1, glucagon-like peptide-1; T2DM, type 2 diabetes mellitus; ↑, increase; ↓ decrease; ↔ no change.

2.7 The role of meal and macronutrient timing on cortisol, melatonin and peripheral clocks

The cortisol response to meals is dependent on the energy and macronutrient content of the meal, with a large, high carbohydrate meal resulting in an increased cortisol peak compared with small, low carbohydrate meal (Richter et al., 2020, Martens et al., 2010). The cortisol response is also dependent on meal timing, with a reduced cortisol response to an identical meal that is eaten in the evening as compared to the morning (Van Cauter et al., 1992) (Figure 2.1A). In lean healthy individuals, the cortisol response was examined in response to eating dinner at 6 pm followed by a snack at 10pm, or the reverse (Gu et al., 2020). The early-snack/late-dinner combination increased mean cortisol levels and the overnight cortisol nadir, impairing glucose tolerance the following morning (Gu et al., 2020). The early-snack/late-dinner condition also induced a 4-hour phase shift in metabolites, increasing overnight glucose, delaying the triglyceride peak, and reducing fatty acid oxidation. This study shows the deleterious effects of late night eating on glucose metabolism even in lean, healthy individuals, which was partly mediated by cortisol (Figure 2.1A).

There is also emerging evidence that insulin acts as a zeitgeber, driving the translation of Per2 (Period 2) mRNA to PER2 protein (which is the core protein of circadian molecular machinery) *in vitro*, in a dose dependent manner, and in mice (Crosby et al., 2019). Of note, stimulating PER2::LUC fibroblasts with insulin 6 hours after cortisol produced the greatest induction of PER2 protein as compared to when insulin was administered 6 hours prior to, or simultaneously with cortisol (Figure 2.1D). In rats, giving a single piece of chocolate at the onset of the active phase versus onset of the rest phase enhanced re-entrainment of the superchiasmatic nucleus in a jet-lag model, and prevented circadian desynchrony and weight gain in a shift work model (Escobar et al., 2020). In a 3 day constant-protocol human study, eating a single large

carbohydrate-rich meal at 9:30 pm led to a phase advance in core body temperature, heart rate and lower melatonin versus eating the same meal at 8:30 am (Kräuchi et al., 2002). Together, these studies suggest that temporal spikes in insulin, induced by carbohydrate-loading can alter peripheral clocks in humans. However, the long term effects are unknown.

If insulin is an entraining signal in humans, eating a high carbohydrate meal within four hours of waking should provide the greatest drive to increase insulin secretion, and thus Per2 translation, potentially restoring the amplitude of peripheral clocks in humans with obesity. This timing would also coincide with the peak in insulin sensitivity, and have the least impact on the overnight cortisol nadir (Figure 2.1C). On the other hand, eating a high carbohydrate dinner at night, could drive Per2 translation in the evening, at a time when PER2 levels should be low, desynchronizing peripheral clocks as well as increasing the overnight cortisol nadir, and impairing glucose homeostasis in the following morning (Figure 2.1B). This remains to be tested, however.

2.8 Conclusions

The effects of meal timing on metabolic health is currently under intense scrutiny. Manipulation of macronutrient timing may provide another avenue to optimize regulation of circadian clocks and glycemic control, and enable compensation for the individual's genetic and lifestyle vulnerabilities.

Acknowledgements: None

Financial support and sponsorship: LZ is supported by a Beacon of Enlightenment Scholarship from The University of Adelaide.

Conflicts of interest: There are no conflicts of interest.

CHAPTER 3 EATING ARCHITECTURE IN ADULTS AT INCREASED RISK OF TYPE 2 DIABETES: ASSOCIATIONS WITH BODY FAT AND GLYCAEMIC CONTROL

Lijun Zhao[1,2,3], Xiao Tong Teong[1,2,3], Kai Liu[1,2,3], Bo Liu[1,2,3], Yohannes A Melaku[4], Andrew D. Vincent[1], Emily N. C. Manoogian[5], Satchidananda Panda[5], Gary Wittert[1,2,3], Amy T Hutchison[1,2,3], Leonie K Heilbronn[1,2,3,6]

[1] Adelaide Medical School, University of Adelaide, Adelaide, South Australia 5000, Australia

[2] NHMRC Centre of Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide, Adelaide, South Australia, Australia

[3] Lifelong Health Theme, South Australian Health and Medical Research Institute, Adelaide, South Australia 5000, Australia

[4] Adelaide Institute for Sleep Health, College of Medicine and Public Health, Flinders University, Adelaide, South Australia 5000, Australia

[5] Salk Institute for Biological Studies, La Jolla, California, USA

[6] Corresponding author and lead contact

Statement of Authorship

Title of Paper	Eating architecture in adults at increased risk of type 2 diabetes: associations with body fat and glycaemic control
Publication Status	☑ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Lijun Zhao, Xiao Tong Teong, Kai Liu, Bo Liu, Yohannes A Melaku, Andrew D. Vincent, Emily N. C. Manoogian, Satchidananda Panda, Gary Wittert, Amy T Hutchison, Leonie K Heilbronn. Eating architecture in adults at increased risk of type 2 diabetes: associations with body fat and glycaemic control.

Principal Author

Name of Principal Author (Candidate)	Lijun Zhao		
Contribution to the Paper	Collected data, analysed data, wrote manuscript and approved final manuscript.		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	23 July 2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Xiao Tong Teong		
Contribution to the Paper	Collected data and approved final manuscript.		
Signature		Date	26/7/2021

Name of Co-Author	Kai Liu		
Contribution to the Paper	Collected data and approved final manuscript.		
Signature		Date	26/7/2021

Name of Co-Author	Bo Liu		
Contribution to the Paper	Collected data, contributed to data interpretation and approved final manuscript.		
Signature		Date	06/08/2021

Name of Co-Author	Yohannes A Melaku		
Contribution to the Paper	Asissted statistics for analysing data and approved final manuscript.		
Signature		Date	27/07/2021

Name of Co-Author	Andrew Vincent		
Contribution to the Paper	Asissted statistics for analysing data and approved final manuscript.		
Signature		Date	09-08-2021

Name of Co-Author	Emily N. C. Manoogian		
Contribution to the Paper	Supplied the myCircadianClock application, contributed to data interpretation and approved final manuscript.		
Signature		Date	8/12/2021

Name of Co-Author	Satchidananda Panda		
Contribution to the Paper	Supplied the myCircadianClock application, contributed to data interpretation and approved final manuscript.		
Signature		Date	08/23/21

Name of Co-Author	Gary Wittert		
Contribution to the Paper	Designed the study, provided clinical support and supervison, contributed to data interpretation and approved final manuscript.		
Signature		Date	5/08/21

Name of Co-Author	Amy T Hutchison		
Contribution to the Paper	Designed the study, contributed to data interpretation and approved final manuscript.		
Signature		Date	17/08/2021

Name of Co-Author	Leonie Heilbronn		
Contribution to the Paper	Designed, conducted and supervised the study, interpreted the data, approved final manuscript, and primary responsibility for the study and publication.		
Signature		Date	26/7/21

3.1 Key points

3.2 Abstract

Eating architecture is a term that describes meal frequency, meal timing, and meal size and the daily variation in each of these. The aim of this study was to determine the relationship between components of eating architecture on body fat and markers of glycaemic control in healthy adults at increased risk of type 2 diabetes (T2DM). Participants (N=73, 39 males, age 58.8 [8.1] years, BMI 33.4 [4.4] kg/m^2) recorded food intake and wore accelerometers and continuous glucose monitors (CGM) for 7-14 days under free-living conditions. Body fat and glycated haemoglobin (HbA1c) were also measured. The mean and day-to-day variation (calculated as the standard deviation during the monitoring period) of each component of eating architecture were calculated. Multivariable linear regression models were constructed for three separate outcome variables (body fat mass, mean CGM glucose, and HbA1c) for each component of eating architecture before and after adjustment for confounders. Higher variability in the time of first meal consumption was associated with increased body fat mass after adjusting for confounders (β=0.227, 95% CI: 0.019, 0.434, p=0.033). Increased variability in the time lag from waking to first meal consumption was also positively associated with increased HbA1c after adjustment (β=0.285, 95%CI: 0.040, 0.530, p=0.023). Low day-to-day variability in first meal consumption was associated with lower body fat and improved glucose control in adults at increased risk of T2DM. Routine consumption of meals may optimise temporal regulation to anticipate and respond appropriately to a glucose challenge.

Keywords: Meal timing, meal regularity, obesity, glycaemia control, breakfast

3.3 Introduction

Eating architecture refers to when and how much, rather than what, we eat (Leech et al., 2015, Magklis et al., 2019), and encompasses the concepts of meal frequency, meal size (or caloric density), meal regularity, and meal timing (Figure 3.1). There is renewed interest in the concept of eating architecture as meal timing has emerged as a strong external cue that regulate circadian clock genes in peripheral tissues, such as liver, gut and adipose tissue in rodent models (Wehrens et al., 2017, Hatori et al., 2012). In humans, delaying breakfast by five hours delayed the expression of Period 2 (Per2) by 1-hour in adipose tissue from healthy individuals (Wehrens et al., 2017). Whereas eating dinner late at night inverted the daily rhythm of salivary microbiota (Collado et al., 2018), and increases the cortisol nadir, impairing glycaemic control the following morning (Gu et al., 2020). The most studied form of eating architecture in the literature is 'breakfast skipping'. Breakfast skipping is associated with an increased risk of developing type 2 diabetes (T2DM) in epidemiological studies (Bi et al., 2015, Ballon et al., 2019, Ma et al., 2020, Wicherski et al., 2021). Other studies suggest that skipping breakfast plus concomitant late evening meals was associated with poorer glycaemic control in patients with T2DM (Azami et al., 2019, St-Onge et al., 2017). Randomized controlled trials investigating whether breakfast skipping alters health have produced mixed results (Schlundt et al., 1992, Geliebter et al., 2014, Dhurandhar et al., 2014). In the largest study conducted to date, breakfast skipping did not produce a greater body weight loss in 147 free-living adults attempting to lose weight over 16 weeks versus breakfast eaters (Dhurandhar et al., 2014). However, a recent systematic review of seven randomized clinical trials showed that breakfast skipping reduced body weight by 0.5kg, but increased low density cholesterol by 9 mg/dL (Bonnet et al., 2020). Late night eating and irregular energy intake and snacking between meals are also associated with increased risk of adiposity and cardiovascular diseases (CVD), and poorer glucose control (Nas et al., 2017, Xiao et al., 2019, Gu et al., 2020, Lopez-Minguez et

al., 2018, McHill et al., 2017, Allison et al., 2020). Irregular energy intake and snacking between meals has also been positively associated with body mass index (BMI), waist circumference (Pot et al., 2014) and increased CVD risk at > 10 years follow up (Pot et al., 2016a).

Typically, all of the epidemiological studies referenced above have relied on 24-hour recalls or have asked a single question regarding usual eating habits. However, meals are highly personalized and highly variable from day to day (Zeevi et al., 2015, Guinter et al., 2020, Pot et al., 2014). To our knowledge, there is no study that has investigated the variation in components of eating architecture and measures of obesity or glucose control in real time over 1 – 2 weeks either in the general population or in those at increased risk of obesity or T2DM, who would likely benefit most from this knowledge given they are more likely to have irregular eating patterns (Leech et al., 2017b, Leech et al., 2017a) and dampened peripheral clocks in adipose tissue and skeletal muscle (Stenvers et al., 2019a, Wefers et al., 2020). Therefore, we hypothesised that high variability in components of eating architecture, and particularly the first meal of the day, would positively associate with outcomes, body fat mass as a marker of obesity, HbA1c and mean 24-hour glucose by CGM as markers of overall glycaemic control in men and women at increased risk of T2DM.

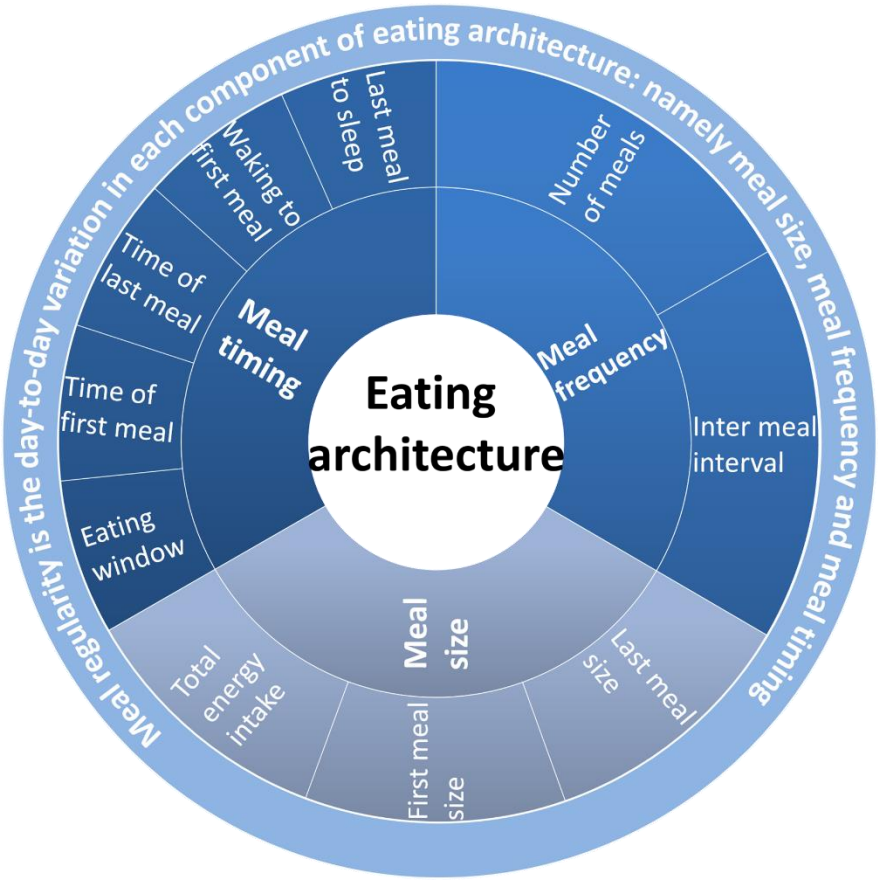


Figure 3.1 Eating architecture components.

[Eating architecture refers to how food is eaten and encompasses four components: meal frequency, meal size, meal timing and meal regularity. Meal size covers total energy intake, size of the first and last meal. Meal timing includes time of first and last meal, eating window, and time lag from last meal to sleep and from waking to first meal. Meal frequency includes number of meals per day and inter-meal intervals. Meal regularity is the day-to-day variation in the other three components.]

3.4 Materials and Methods

Participants

Data analysed in this study was baseline information from two registered clinical trials (ClinicalTrials.gov Identifier: NCT03590158 and NCT03689608, respectively), which were

collected between July 2018 and June 2020. Ethics approval for both studies was obtained from Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee and participants provided written informed consent. Use of the *MyCircadianClock* application was approved by Salk Institute Institutional Review Board (PRASAD et al., 2020, Gill and Panda, 2015). Inclusion criteria were: aged between 35-75 years old, score 12 or greater on the Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK) calculator (Chen et al., 2010), without diabetes, non-shift workers, weight-stable (<5% fluctuation in their body weight for past 6-months at study entry). All participants were assessed for their risk of developing diabetes by AUSDRISK score determined by gender, ethnicity, BMI, waist circumference, exercise level, family or personal hypoglycaemia history and vegetable and fruit consumption (Chen et al., 2010). A score of 9 to 11 indicates intermediate risk (1 in 30 will develop diabetes within 5 years), 12 to 15 indicates high risk (1 in 14,), 16 to 19 indicates very high risk (1 in 7), and ≥ 20 indicates 1 in 3 will develop diabetes within 5 years. Participants who took medications that might affect glucose metabolism and HbA1c, and smokers were excluded. Women who were pregnant or lactating at the time of study enrolment were not eligible.

Eligible participants underwent a 1 to 2-week baseline monitoring period prior to the baseline metabolic test. During this monitoring period, participants were fitted with an Actigraph (wGT3X-BT, ActiGraph LLC, Pensacola, Fla., USA) to measure sleep patterns and physical activity (steps per day) (ActiLife software, version 6.13.3). A continuous glucose monitor (CGM; FreeStyle Libre Pro, Abbott, UK) was also fitted on the back of the upper arm of the non-dominant hand. This measured blood glucose levels every 15 minutes for the duration of the baseline monitoring period. One of two smartphone applications (app), myCircadianClock (mCC; https://mycircadianclock.org/) (PRASAD et al., 2020, Gill and Panda, 2015) and Easy Diet Diary (EDD, https://xyris.com.au/products/easy-diet-diary/) (Ambrosini et al., 2018), were used to photograph and annotate meal timing and eating/drinking events.

Of the 122 participants from both studies who wore CGM, 49 participants excluded from the analysis for the following reasons: incomplete food records (34 participants; meal timing not documented or poorly documented), missing ActiGraph data (4 participants), and missing CGM data (7 participants with <72 hours CGM data, 4 participants with technical issues where the CGM failed to collect data). As such, a total of 73 (46.6 % females) participants were included in the final analysis (Figure 3.2).

At the end of the baseline monitoring period, whole body composition was assessed by Dual-energy X-ray absorptiometry (DEXA, Lunar Prodigy; GE Health care, Madison, Wisconsin) and analysed by EnCore software (GE Healthcare, Chicago, Illinois; version 16.2). Body weight was measured on calibrated scales with participants in the fasted state, in a gown and after voiding. Waist circumference was measured at the mid-point between the participant's lowest rib and the top of the iliac crest. Blood samples were taken to evaluate HbA1cusing commercially available enzymatic kits on an AU480 clinical analyzer (Beckman Coulter, Inc., Brea, California). Sleep on and sleep off time were obtained from ActiGraph and markers reflecting sleep-meal relationship were calculated as defined in the following section.

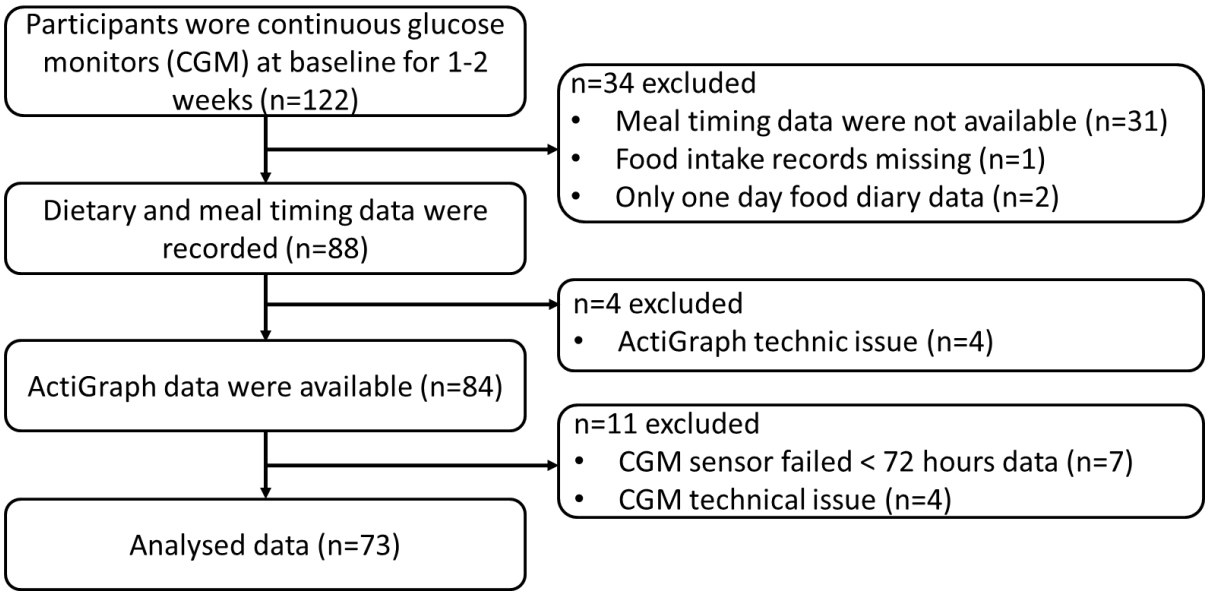


Figure 3.2 Participant flow chart.

Continuous glucose monitoring (CGM)

Days for which any of CGM data was not recorded was excluded from the analysis, including the day when the CGM was put on, and the day when it was taken off. If the CGM accidentally fell off at any point prior to the scheduled end of testing, that day was also excluded. 24-hour mean blood glucose was calculated as the mean of the daily 96 readings, and 24-hour SD as the standard deviation of these 96 readings. The 24-hour mean glucose in the following analysis was calculated as the average glucose on all recording days. Each CGM glucose reading was counted as one data point and the data was summarized from mid-night to mid-night for each participant. For diurnal variations of glucose metrics, daytime was defined as 06:00 AM to 00:59 AM and night time as 01:00 AM to 05:59 AM (only less than 0.5% of eating events occurred during these hours, Figure 3.3B).

Smart phone applications for food intake

Participants who used the mCC app were asked to photograph all eating events prior to any food and/or drink consumption (N = 28). Annotation was used to describe what they ate, while the app provides a time-stamp to note when they ate. Participants who used the EDD app also photographed all eating events and annotated the food they ate (N = 45). They were required to record the time the meal was consumed manually as an annotation. Only participants with ≥2 recording days and meal frequency ≥2 times per day were included in the analysis. Total energy, fat, protein, carbohydrate and fibre intakes were estimated from the food images and annotations by nutritionally trained researchers using FoodWorks (Version 10, Xyris Software, Australia) with meal timing aligned from the apps. The reliability of digital photographs to estimate energy intake by trained investigators, has previously been validated against weighed food records. In this study they were utilised to obtain a time stamp of food consumption as we were primarily interested in meal timing (Naaman et al., 2021).

Definition of eating event, meal and snacks and eating architecture components

The metabolic recording day was defined as from 03:00 AM on day 1 to 03:00 AM on day 2 in our dataset as very few eating events occurred between 03:00 AM and 04:00 AM (Figure 3.3B). The following definitions were applied to food intake data which generated through FoodWorks based on the information from smartphone apps.

1. *Eating event*: Any food/drink (except water) consumed at a unique time was considered an eating event (Gill and Panda, 2015, Gupta et al., 2017b); this included drinks such as black coffee or artificial sweeteners (Reis et al., 2019, Sylvetsky, 2018).
2. *Hourly percentage of eating events*: percentage of all eating events in 1 hour bin. It was calculated as eating events at each hour divided by the total eating events.
3. *Meal*: classified as all eating event only if they occurred within 15minutes of a preceding eating event, including main meals and snacks.
4. *Meal frequency*: the number of meals on each recording day including meals after mid-night.
5. *Inter-meal* interval: the average time difference between two subsequent meals during each recording day (e.g., if there were two eating events 14 minutes apart within a meal, and then another meal 2 hours later, inter-meal interval was counted from the second eating event); then mean values of recording days were calculated.
6. *Time of the first meal*: depicted as the time of first meal (HH:MM) which occurred after 03:00 AM.
7. *Time of the last meal:* depicted as the time of last meal (HH:MM). If the time of a meal occurred after mid-night but before 03:00 AM, this was recorded as the time of the last meal of the previous day.
8. *Eating window:* the duration between first and the last meal within a day (hours) and was obtained by subtracting the first from the last recorded time of eating from the 95%

(2.5%tile to 97.5%tile) of all calorie-containing eating events occur during the monitoring period.

9. *Percentage of energy in first/last meal:* the energy content of the first/last meal divided by total energy intake on each recording day.
10. *Total energy intake:* the mean daily energy intake.
11. *Meal timing relative to sleep onset/wake*: time lag from wake to the first meal (wake to first meal), and time lag from the last meal to sleep onset (last meal to sleep onset).
12. *Meal regularity*: day-to-day variation of each component of the eating architecture. Calculated as the standard deviation of each eating architecture component during the monitoring period for each participant.

Outcome measures

Outcome measures included body fat mass, 24-hour mean glucose and HbA1c. The body fat mass covariate-unadjusted model (Model 1) was first adjusted for age, sex, fat free mass, app type (shown as Model 2) and further adjusted for physical activity, total energy intake and total sleep time (shown as Model 3). The HbA1c and glucose unadjusted models (Model 1) were first adjusted for age, sex, app type, waist circumference, BMI (shown as Model 2) and further adjusted for the percentage of energy intake from carbohydrates (shown as Model 3).

Statistical methods

Calculations of eating architecture components were performed after synchronizing data from food records, activity and sleep patterns, and continuous glucose levels in real time. Data are presented as mean ± SD. Mann-Whitney U test was applied to assess the difference between mean percentage of energy in first meal and mean percentage of energy in last meal. Linear regression models were constructed with each eating architecture component as predictors. To ensure that the assumption of normality did not affect the performance of the models, we

assessed quanitle-quanitle plots of the residuals of each model. Where necessary, dependent variables were log-transformed before the regression (body fat mass). Each eating architecture variable was investigated independently of the others, i.e. each model had only one eating architecture component included as the predictor. All regression coefficients (β) were reported as standardised estimates with a 95% confidence interval. Plots and statistical analysis were performed using R software (version 3.6.1; The R Foundation for Statistical Computing, Vienna, Austria) and its interaction software jamovi (Version 1.1) with the significance level set at 0.05.

3.5 Results

Baseline characteristics

Caucasians (N=73, 34 females, 39 males, mean ± SD, age 58.8 ± 8.1 years, BMI 33.4 ± 4.4 kg/m^2) with elevated waist circumference (113 ± 13 cm) were included in the final analysis (Table 3.1). The average body fat mass and lean mass were 38.6 ± 10.4 kg and 59.2 ± 11.9 kg, respectively. Sleep patterns showed that the total sleep time was 7.7 ±1.1 hours with sleep onset time at 22:48 ± 1:07 and sleep offset time at 6:56 ± 0:59. The group mean of average 24-hour glucose was 5.3 ± 0.6 mmol/L (Figure 3.3A) and HbA1c was 5.5 ± 0.4 %. The glucose distribution over 24-hour is shown in Figure 3.3A; mean glucose during the daytime was 5.4 ± 0.6 mmol/L and 4.9 ± 0.6 mmol/L during the night.

Table 3.1 Participants characteristics[1]

	All (n=73)
Sex (N, female/male)	34/39
Age at recruitment (year)	58.8 ± 8.1
Height (m)	1.7 ± 0.1
Weight (kg)	98.2 ± 16.3
BMI (kg/m^2)	33.4 ± 4.4

	All (n=73)
Waist circumference (cm)	113 ± 13
Glycated haemoglobin (%)	5.5 ± 0.4
Body fat mass (kg)[2]	38.6 ± 10.4
Fat free mass (kg) [2]	59.2 ± 11.9
Sleep onset time (HH:MM)[3]	22:48 ± 01:07
Sleep offset time (HH:MM)[3]	06:56 ± 00:59
Total sleep time (Hours)[3]	7.7 ±1.1
Steps per day (steps)[3]	10351 ± 5447

[1]All data are Mean ± SD. [2] n=67. [3] n=69. BMI, body mass index.

Eating architecture

Eating events peaks occurred at 8:00 AM, 12:00 PM and 6:00 PM (Figure 3.3B). The 95% (2.5 - 97.5 percentile) eating window was 11.5 ± 2.0 hours, with a variation in the day-to-day eating window of 2.0 ± 1.5 hours (Table 3.2, note: the SD in this table represents the variation between participants). A polar plot shows the eating events spread against the clock time (Figure 3.3C) and more clearly depicts the day-to-day within-individual variation in meal timing. The mean inter-meal duration was 187 ± 59 minutes with a mean day-to-day variation of 46 ± 24 minutes. The mean time of the first meal and last meal were 08:30 ± 01:24 AM and 07:48 ± 01:24 PM, respectively, with a similar day-to-day variation of 84 minutes. Meal frequency was on average 5.0 ± 1.5 times/day with 1.2 ± 0.6 times/day variation between days. Average reported daily total energy intake was 8405 ± 2056 kJ with 2250 ± 1326 kJ day-to-day variation in daily energy intake, and more food was consumed during the last meal of the day than the first meal of the day (26.1 ± 13.7 % vs 19.6 ± 9.44 %, $p < 0.001$). Substantial day-to-day variations in percentage of energy intake in the first (10.5 ± 6.7 %) and last (14.6 ± 7.1%) meals were observed. The average time lag from waking to first meal was 114 ± 57 minutes, and time lag from last meal to sleep was 197 ± 90 minutes, with 78 ± 48 minutes and 88 ± 81 minutes daily variation, respectively.

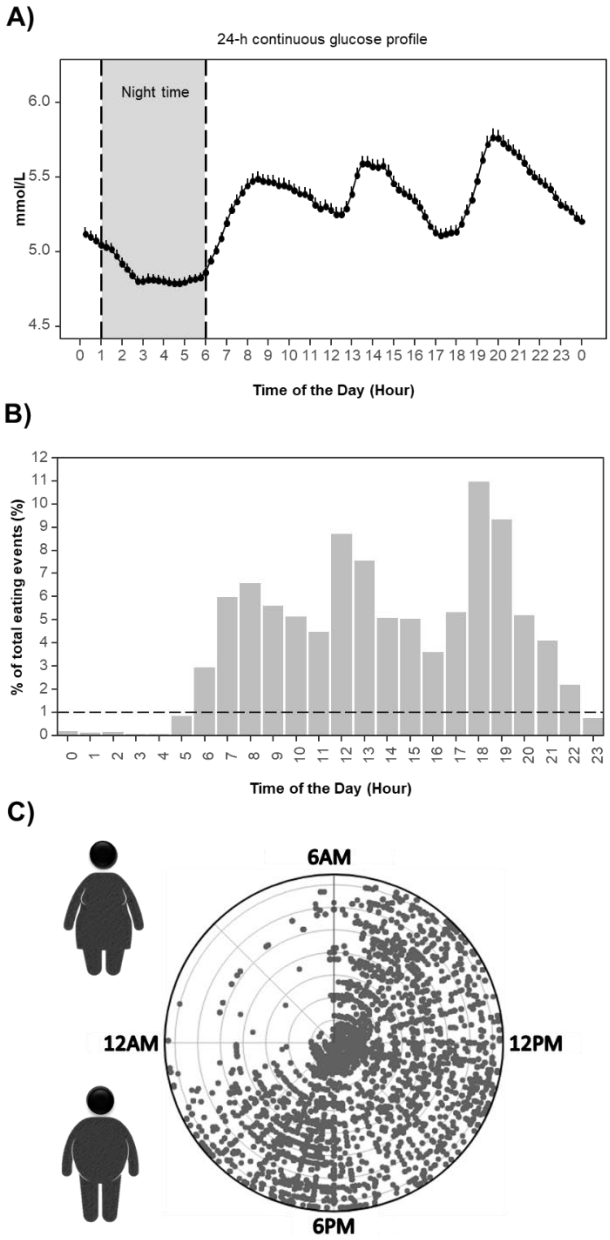


Figure 3.3 Distribution of eating events around the day and 24-hour continuous glucose profile.

[**A)** 24 hour continuous glucose profile every 15 minutes. Data from 73 individuals are shown; **B)** Percentage of all eating events in 1 hour bin shows the nadir at 03:00 to 04:00 AM and the peaks of eating events occurred at 08:00 AM, 12:00 PM and 06:00 PM; **C)** Polar plot of eating events of each individual plotted against time of the day in each concentric circle (each circle represents a different participant).]

Table 3.2 Characteristics of eating architecture components[1,2]

	All (n=73)
Meal timing	
Eating window (hours)	11.5 ± 2.0
Inter-meal interval (minutes)	187 ± 59
Time of first meal (HH:MM)	08:30 ± 01:24
Time of last meal (HH:MM)	19:48 ± 01:24
Time lag from last meal to sleep (minutes) [2]	197 ±90
Time lag from wake to first meal (minutes) [2]	114± 57
Meal frequency	
Number of meals/day (times/day)	5.0 ± 1.5
Meal size	
Total daily energy intake (kJ)	8405 ± 2056
Percentage of energy in first meal (%)	19.6 ± 9.4
Percentage of energy in last meal (%)	26.1 ± 13.7
Meal regularity	
Eating window (hours)	2.0 ± 1.5
Time of first meal (minutes)	84 ± 78
Time of last meal (minutes)	84 ± 60
Inter-meal interval (minutes)	46 ± 24
Time lag from last meal to sleep onset (minutes) [2]	88 ± 81
Time lag from wake to first meal (minutes) [2]	78 ± 48
Meal frequency (times/day)	1.2 ± 0.6
Total daily energy intake (kJ)	2252 ± 1326
Percentage of energy in first meal (%)	10.5 ± 6.7
Percentage of energy in last meal (%)	14.6 ± 7.1

[1] Data presented as mean ± SD, presented SD is the variation between participants. [2] n=69.

Associations between components of eating architecture and metabolic health markers

As shown in Table 3.3, later consumption of the first meal was associated with increased body fat mass before (Model 1, $p = 0.05$, $\beta = 0.26$, 95% confidence interval [CI]: 0.01, 0.51) and

after adjustment of age, sex, fat free mass and app type (Model 2, p = 0.03, β = 0.22, 95% [CI]: 0.02, 0.41). A trend was evident after further adjustment of physical activity, total energy intake and total sleep time (Model 3, p = 0.09, β = 0.17, 95% CI: -0.03, 0.37) (Table 3). Higher day-to-day variability in the time of first meal consumption was associated with higher body fat mass after adjusted for age, sex, fat free mass and app type (Model 2: p = 0.03, β = 0.22, 95% CI: 0.02, 0.42) and further adjusted by physical activity, total energy intake and total sleep time (Model 3: p = 0.03, β = 0.23, 95% CI: 0.02, 0.43) (Table 3.3). There were no significant associations between other eating architecture components and body fat mass after adjustment for confounders as shown in Table 3. There were no significant associations between any eating architecture components and mean glucose by CGM as shown in Supplementary Table 3.1. There was a positive association between HbA1c and day-to-day variation in the time lag from waking to the first meal before (Model 1, p= 0.02, β= 0.30, 95% CI: 0.06, 0.54), and after adjustment for age, sex, app type, BMI and waist circumference (Model 2, p= 0.02, β= 0.28, 95% CI: 0.04, 0.52) and further adjustment for percentage of energy intake from carbohydrates (Model 3, p= 0.02, β= 0.29, 95% CI: 0.04, 0.53) (Table 3.4).

Table 3.3 Associations between body fat mass and each component of eating architecture after adjustment of confounders[1]

	Model 1			Model 2			Model 3		
	P trend	β	95% CI	P trend	β	95% CI	P trend	β	95% CI
Meal timing									
Eating window	**0.02**	**-0.30**	**(-0.54, -0.05)**	0.14	-0.16	(-0.36, 0.05)	0.25	-0.12	(-0.32, 0.09)
Inter-meal intervals	0.69	0.05	(-0.21, 0.31)	0.77	0.03	(-0.19, 0.25)	0.59	0.07	(-0.18, 0.31)
Time of first meal	**0.05**	**0.26**	**(0.01, 0.51)**	**0.03**	**0.22**	**(0.02, 0.41)**	**0.09**	**0.17**	**(-0.03, 0.37)**
Time of last meal	0.22	-0.16	(-0.41, 0.10)	0.84	-0.02	(-0.24, 0.19)	0.99	0.11	(-0.21, 0.21)
Last meal - sleep	**0.04**	**0.27**	**(0.02, 0.52)**	0.55	0.07	(-0.15, 0.28)	0.69	0.05	(-0.18, 0.27)
Waking - first meal	0.29	0.14	(-0.12, 0.40)	0.60	0.05	(-0.15, 0.25)	0.82	0.02	(-0.18, 0.23)
Meal frequency									
Number of meals	0.27	-0.14	(-0.40, 0.11)	0.40	-0.09	(-0.30, 0.12)	0.36	-0.11	(-0.34, 0.12)
Meal size									
First meal size	0.97	0.01	(-0.25, 0.26)	0.53	0.07	(-0.14, 0.27)	0.63	0.05	(-0.16, 0.26)
Last meal size	**0.04**	**0.26**	**(0.01, 0.51)**	0.30	0.12	(-0.11, 0.34)	0.33	0.11	(-0.12, 0.33)
Meal regularity									
Meal timing									
Eating window	0.82	-0.03	(-0.29, 0.23)	0.13	0.16	(-0.05, 0.37)	0.17	0.16	(-0.07, 0.38)
Inter-meal intervals	0.81	-0.03	(-0.29, 0.23)	0.76	0.03	(-0.17, 0.23)	0.61	0.05	(-0.14, 0.24)

	Model 1			Model 2			Model 3		
	P trend	**β**	**95% CI**	**P trend**	**β**	**95% CI**	**P trend**	**β**	**95% CI**
Time of first meal	0.52	0.08	(-0.17, 0.34)	**0.03**	**0.22**	**(0.02, 0.42)**	**0.03**	**0.23**	**(0.02, 0.43)**
Time of last meal	0.46	-0.10	(-0.35, 0.16)	0.92	-0.01	(-0.22, 0.19)	0.67	-0.04	(-0.25, 0.16)
Last meal - sleep	0.78	-0.04	(-0.31, 0.23)	0.81	0.03	(-0.19, 0.25)	0.87	0.02	(-0.21, 0.25)
Waking - first meal	0.85	-0.03	(-0.29, 0.24)	0.86	-0.02	(-0.23, 0.19)	0.51	-0.07	(-0.26, 0.13)
Meal frequency									
Number of meals	0.18	-0.17	(-0.43, 0.08)	0.99	0.00	(-0.23, 0.23)	0.71	-0.04	(-0.28, 0.19)
Meal size									
First meal size	0.50	-0.09	(-0.35, 0.17)	0.94	0.01	(-0.21, 0.23)	0.66	-0.05	(-0.28, 0.18)
Last meal size	0.96	-0.01	(-0.27, 0.25)	0.87	-0.02	(-0.22, 0.18)_	0.33	-0.10	(-0.29, 0.10)

[1] Linear regression analyses were performed to estimate strength of associations between log 10 transformed body fat mass and each component of eating architecture without covariate adjustment (Model 1) and multivariable models adjusting for age, gender, fat free mass, application type (Model 2), and Model 2 plus the physical activity, total energy intake and total sleep time (Model 3). β are the standardized coefficients; 95% CI, 95% confidence interval.

Table 3.4 Associations between glycated haemoglobin (HbA1c) and each component of eating architecture after adjustment of confounders[1]

	Model 1			Model 2			Model 3		
	P trend	β	95% CI	P trend	β	95% CI	P trend	β	95% CI
Meal timing									
Eating window	0.97	0.01	(-0.23, 0.24)	0.30	-0.13	(-0.38, 0.12)	0.30	-0.13	(-0.39, 0.12)
Inter-meal intervals	0.38	-0.11	(-0.34, 0.13)	0.53	-0.08	(-0.33, 0.17)	0.53	-0.01	(-0.33, 0.17)
Time of first meal	0.91	-0.01	(-0.25, 0.22)	0.74	0.04	(-0.21, 0.29)	0.74	0.04	(-0.22, 0.30)
Time of last meal	0.99	0.00	(-0.24, 0.24)	0.50	-0.09	(-0.34, 0.17)	0.49	-0.09	(-0.36, 0.17)
Last meal - sleep	0.94	0.01	(-0.24, 0.26)	0.34	0.13	(-0.14, 0.39)	0.34	0.13	(-0.14, 0.39)
Waking - first meal	0.22	0.15	(-0.09, 0.39)	0.08	0.21	(-0.02, 0.44)	0.08	0.21	(-0.03, 0.45)
Meal frequency									
Number of meals	0.86	0.02	(-0.21, 0.26)	0.79	-0.03	(-0.27, 0.21)	0.79	-0.33	(-0.28, 0.21)
Meal size									
Total daily energy intake	0.40	0.10	(-0.14, 0.34)	0.96	0.00	(-0.25, 0.25)	0.99	0.00	(-0.26, 0.25)
First meal size	0.56	-0.07	(-0.31, 0.17)	0.83	-0.03	(-0.26, 0.21)	0.08	-0.03	(-0.03, 0.22)
Last meal size	0.95	-0.01	(-0.24, 0.23)	0.54	0.08	(-0.18, 0.33)	0.54	0.80	(-0.18, 0.34)
Meal regularity									
Meal timing									

	Model 1			Model 2			Model 3		
	P trend	**β**	**95% CI**	**P trend**	**β**	**95% CI**	**P trend**	**β**	**95% CI**
Eating window	0.99	0.00	(-0.24, 0.24)	0.78	-0.04	(-0.28, 0.21)	0.780	-0.04	(-0.29, 0.22)
Inter-meal intervals	0.58	0.06	(-0.17, 0.30)	0.72	0.04	(-0.19, 0.28)	0.714	0.05	(-0.20, 0.29)
Time of first meal	0.98	0.00	(-0.23, 0.24)	0.69	-0.05	(-0.31, 0.20)	0.694	-0.05	(-0.31, 0.21)
Time of last meal	0.93	0.01	(-0.24, 0.25)	0.99	-0.00	(-0.24, 0.24)	0.990	-0.00	(-0.24, 0.24)
Last meal - sleep	0.39	-0.11	(-0.36, 0.14)	0.39	-0.11	(-0.38, 0.15)	0.387	-0.12	(-0.39, 0.15)
Waking - first meal	**0.02**	**0.30**	**(0.06, 0.54)**	**0.02**	**0.28**	**(0.04, 0.52)**	**0.023**	**0.29**	**(0.04, 0.53)**
Meal frequency									
Number of meals	0.97	-0.01	(-0.24, 0.23)	0.60	-0.07	(-0.34, 0.19)	0.600	-0.07	(-0.34, 0.20)
Meal size									
Total daily energy intake	0.80	0.03	(-0.21, 0.27)	0.64	-0.59	(-0.31, 0.19)	0.644	-0.59	(-0.31, 0.19)
First meal size	0.82	-0.03	(-0.26, 0.21)	0.83	-0.03	(-0.29, 0.23)	0.827	-0.03	(-0.29, 0.24)
Last meal size	0.33	0.12	(-0.12, 0.35)	0.17	0.16	(-0.07, 0.40)	0.166	0.17	(-0.07, 0.41)

[1] Linear regression analyses were performed to estimate strength of associations between glycated haemoglobin (HbA1c) and each component of eating architecture without covariate adjustment (Model 1) and multivariable models adjusting for age, gender, body mass index, waist circumference, application type (Model 2), and Model 2 plus the percentage of carbohydrates (Model 3). β are the standardized coefficients; 95% CI, 95% confidence interval.

3.6 Discussion

In this cross-sectional study in adults at risk of T2DM, both eating breakfast earlier and smaller variation in the daily timing of breakfast were associated with decreased body fat mass. Less day-to-day variation in the size of the first meal and the time lag from waking to the first meal were also associated with improved glycaemic control in this population.

Observational studies have shown associations between meal irregularity and cardio-metabolic health (Shin et al., 2009, Wennberg et al., 2016, Pot et al., 2014, Pot et al., 2016b, Guinter et al., 2020, Uemura et al., 2015, Xiao et al., 2019, Ha and Song, 2019, Wang et al., 2020, Ma et al., 2020, Mekary et al., 2013, Mekary et al., 2012). Most of the previous population-based studies have investigated the relationship between frequency of breakfast consumption and weight status by categorising participants into either daily breakfast consumers or have combined never eating breakfast with irregular breakfast consumption (Mekary et al., 2013, Guinter et al., 2020, Ha and Song, 2019, Uemura et al., 2015, Wang et al., 2020, Wennberg et al., 2016, Mekary et al., 2012). Additionally, the data are typically collected by a single 24-hour recall or a single question about breakfast habits (Wang et al., 2020, Sierra-Johnson et al., 2008, Shin et al., 2009), which may not represent habitual eating patterns (McHill et al., 2020). *Guinter et al* were first to investigate the day-to-day regularity in breakfast consumption in the Sister study cohort of 46,037 women in relation to weight status after stratifying the frequencies of breakfast consumption per week (0 day/week, 1-2 days/week, 3-4 days/week, 5-6 days/week and 7 days/week) (Guinter et al., 2020). Compared to irregular breakfast eaters (3-4 days/week), regular daily breakfast eaters (7 days/week) and those who never ate breakfast (0 day/week) were less likely to be obese and showed a decreased risk of 5-year incidence of overweight and obesity (Guinter et al., 2020). However, this study did not examine the relationship between day-to-day variation in breakfast size or timing and obesity, and did not assess cardiometabolic risk. Pot 's research team developed a method to score meal regularity based on the variability

in energy intake per meal relative to the 5-consecutive-day mean energy intake of that meal (i.e., calculated breakfast, lunch, evening meal, between meals and total daily energy intake separately), with a higher score reflecting a more irregular eating pattern (Pot et al., 2016b, Pot et al., 2014). In that study, more irregular energy intake at breakfast was associated with an increased risk of metabolic syndrome in 1768 adults (Pot et al., 2014). Further prospective analysis confirmed the positive association between irregular energy intake, particularly at breakfast, lunch and between meals, and cardiometabolic risk after 10 and 17 years follow up (Pot et al., 2016b). In the present study, we only observed associations with the first meal of the day and did not observe any significant relationships between the last meal of the day and glucose control or obesity.

In the present study, we found that higher day-to-day variability in the time lag from waking to the first meal was associated with higher HbA1c. Adults with type 1 and type 2 diabetes who eat regular meals have better glycaemic control than those who eat irregularly timed meals (Ahola et al., 2019, Azami et al., 2019). *Xiao et al* examined the associations between timing of energy intake relative to sleep and BMI in 872 middle-to-old aged adults utilising six non-consecutive 24-hour dietary recalls over 12 months. In that study, a higher percent of total daily energy intake consumed within 2 hours after waking and a lower percent of total energy intake consumed within 2 hours before bedtime was associated with lower BMI (Xiao et al., 2019). However, glucose status was not evaluated.

Randomized clinical trials have reported the importance of breakfast consumption and breakfast size in glucose control (Jakubowicz et al., 2013, Jakubowicz et al., 2015a, Jakubowicz et al., 2017a, Jakubowicz et al., 2015b). *Jakubowicz et al* established that high-energy breakfast with low-energy dinner improved glucose tolerance in women with obesity (Jakubowicz et al., 2013) and improved glycaemic control in patients with T2DM (Jakubowicz et al., 2015a) as compared to the reverse feeding pattern. A high-energy breakfast rich in carbohydrates also upregulated

clock gene expression in white blood cells as compared with breakfast skipping (Jakubowicz et al., 2017b). Consuming a large breakfast (47% energy requirements) and small dinner (13% of energy requirements) also upregulated expression of clock genes and reduced HbA1c after 12 weeks versus eating 6 isocaloric meals over the day in 14 adults with T2DM (Jakubowicz et al., 2019). In the latter study, meal frequency, inter-meal interval, time of the last meal, the length of eating window, the size of the first meal and the last meal, time lag from last meal to sleep were all different between the two arms making it impossible to untangle which factor was the main contributing factor to the glycaemic benefit. Overall, these studies suggest that skewing food intake towards earlier in the day allows for appropriate temporal regulation of glucose metabolism, a finding that is supported by the results of the present study.

Meal timing considerations could also be important during intermittent fasting (IF) diets. IF is a diet pattern in which zero or minimal calories are consumed 1 to 4 days per week, followed by *ad libitum* eating on the remaining days (Zhao et al., 2020). Some controversial results exists as to whether IF is superior for metabolic health when compared with continuous calorie restriction (Hutchison et al., 2019a, Trepanowski et al., 2017, Harvie et al., 2011). Some of the discrepancies could be the result of meal timing on fasting and non-fasting days. In anticipation of a fasting day, it is possible that some individuals may choose to eat late-night snacks. Furthermore, fasting protocols have been initiated after breakfast (Hutchison et al., 2019a), lunch (Hoddy et al., 2014) and dinner (Hoddy et al., 2014, Varady et al., 2013, Halberg et al., 2005). Ending the fasting period at the onset of the rest phase (akin to dinner in humans) inverted peripheral clock gene expression in mice (Froy et al., 2009). Whilst the impacts of meal timing during IF have not been adequately studied in humans, IF initiated after breakfast did not alter clock genes in human adipose tissue and skeletal muscle (Zhao et al., 2020). However, future studies should assess eating architecture in both CR and IF interventions. In addition, time restricted eating (TRE, a subtype of IF, in which daily energy intake is restricted to between 6–11 hours) is a dietary tool that has emerged as a practical intervention for

improving cardiometabolic health (Parr et al., 2020b, Jamshed et al., 2019, Gabel et al., 2018a, Sutton et al., 2018, Hutchison et al., 2019b, Ravussin et al., 2019, Gabel et al., 2020b, Moro et al., 2016). However, many questions as to the optimal time to initiate TRE also remain to be tested.

The present analysis was a cross-sectional study with a relatively small sample size, which limited the number of multi-variables that could be adjusted for. This also limited exploration of the impact of combining components of eating architecture which are likely to interact with each other (Azami et al., 2019, Kahleova et al., 2017, Mekary et al., 2013, Mekary et al., 2012). Additional limitations include that food intake was not assessed by weighed food records, subjective appetite was not measured, and that data was lost from a number of participants due to incomplete food records (28%), technical issues with accelerometry (3%) or CGM loss (9%) resulting in the final sample size was 73. Finally, the outcomes from the present study cannot be extrapolated to the general population. Thus, more prospective studies with larger sample sizes and in wider population groups are needed to evaluate the long-term risk of obesity or chronic diseases with respect to irregular eating patterns. The strengths of this work are that this is the first study synchronizing data from objective food records, activity and sleep patterns, and continuous glucose levels in real time for 1-2 weeks to capture meal size, frequency, timing and meal regularity. The use of smartphone apps may offer a practical tool for collecting personalised food diaries in real time in the future, as opposed to paper-based questionnaires or 24-hour diet recall. This is also the first study to evaluate the components of eating architecture in relation to body fat mass and glucose control among adults at increased risk of T2DM.

In conclusion, the results from the present analysis show that eating breakfast earlier, and at a consistent time each day was associated with decreased body fat mass, and improved glycaemic control as indicated by lower HbA1c, in adults with increased risk of T2DM. Routine consumption of meals may therefore optimise temporal regulation to anticipate and respond appropriately to a glucose challenge.

Funding Statement: The research was funded by Diabetes Australia and National Health and Medical Research Council (NHMRC) Project grant. LZ is supported by a Beacon of Enlightenment Scholarship from The University of Adelaide.

Author Contributions: Trials in this study were conducted in South Australia Health and Medical Research Institute, Adelaide. LKH, ATH, GAW designed the research. LKH, ATH, BL, XTT, KL and LZ collected data. LZ, XTT and KL estimated energy intake via FoodWorks. GAW provided clinical support and supervision. ECM and SP supplied the *myCircadianClock* application. YAM and AV provided statistical support. LZ performed the statistical analysis and draft the manuscript. All authors contributed to data interpretation and preparation of the manuscript. LKH had full access to the data and had primary responsibility for the final publication.

Competing Interests: Satchidananda Panda is the author of the book "The Circadian Code" for which he receives author royalty from PenguinRandomHouse Company. The other authors declared no conflict of interest.

Acknowledgment: We thank the participants who participated in this study and acknowledge that the software and dashboard to calculate the time lag of the meal relative to sleep was created by Aran Wittert.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT03590158 and NCT03689608

SUPPLEMENTARY MATERIAL FOR CHAPTER 3

Supplementary Table 3.1 Associations between mean glucose measured by continuous glucose monitors and each component of eating architecture after adjustment of confounders[1]

	Model 1			Model 2			Model 3		
	P trend	β	95% CI	P trend	β	95% CI	P trend	β	95% CI
Meal timing									
Eating window	0.79	0.03	(-0.21, 0.27)	0.70	-0.05	(-0.28, 0.19)	0.69	-0.05	(-0.29, 0.19)
Inter-meal intervals	0.59	-0.06	(-0.30, 0.17)	0.56	0.07	(-0.17, 0.30)	0.54	0.07	(-0.16, 0.31)
Time of first meal	0.32	0.12	(-0.12, 0.35)	0.85	0.02	(-0.21, 0.26)	0.87	0.02	(-0.22, 0.26)
Time of last meal	0.61	0.06	(-0.18,0.30)	0.51	-0.08	(-0.32, 0.16)	0.45	-0.09	(-0.34, 0.15)
Last meal - sleep	0.99	0.00	(-0.25,0.25)	0.45	0.10	(-0.16, 0.35)	0.45	0.10	(-0.16, 0.36)
Waking - first meal	0.80	0.03	(0.21,0.28)	0.70	0.05	(-0.19, 0.28)	0.70	0.05	(-0.19, 0.28)
Meal frequency									
Number of meals	0.93	-0.01	(0.25, 0.23)	0.37	-0.10	(-0.33, 0.12)	0.36	-0.11	(-0.33, 0.12)
Meal size									
Total daily energy intake	0.81	0.03	(-0.21, 0.27)	0.92	-0.01	(-0.25, 0.23)	0.94	-0.01	(-0.25, 0.23)
First meal size	0.15	0.17	(-0.07, 0.40)	0.26	0.13	(-0.10, 0.35)	0.27	0.13	(-0.10, 0.35)

	Model 1			Model 2			Model 3		
	P trend	β	95% CI	P trend	β	95% CI	P trend	β	95% CI
Last meal size	0.44	-0.09	(-0.33, 0.14)	0.76	0.04	(-0.20, 0.28)	0.74	0.04	(-0.20, 0.28)
Meal regularity									
Meal timing									
Eating window	0.88	-0.02	(-0.26, 0.22)	0.19	-0.15	(-0.39, 0.08)	0.19	-0.16	(-0.39, 0.08)
Inter-meal intervals	0.87	-0.02	(-0.26, 0.22)	0.49	-0.08	(-0.30, 0.14)	0.52	-0.08	(-0.31, 0.16)
Time of first meal	0.79	0.31	(-0.21, 0.27)	0.17	-0.16	(-0.34, 0.07)	0.17	-0.17	(-0.41, 0.07)
Time of last meal	0.84	-0.02	(-0.26, 0.21)	0.40	-0.10	(-0.32, 0.13)	0.39	-0.10	(-0.32, 0.13)
Last meal - sleep	0.82	-0.03	(0.28, 0.22)	0.95	0.01	(-0.25, 0.26)	0.94	0.01	(-0.25, 0.27)
Waking - first meal	0.98	0.00	(-0.25, 0.26)	0.49	-0.08	(-0.33, 0.16)	0.45	-0.09	(-0.34, 0.15)
Meal frequency									
Number of meals	0.63	0.06	(-0.18, 0.29)	0.27	-0.14	(-0.39, 0.11)	0.27	-0.14	(-0.39, 0.11)
Meal size									
Total daily energy intake	0.94	-0.01	(-0.25, 0.23)	0.37	-0.11	(-0.34, 0.13)	0.39	-0.10	(-0.34, 0.13)
First meal size	**0.04**	**0.24**	**(0.01, 0.47)**	0.37	0.11	(-0.13, 0.36)	0.36	0.11	(-0.13, 0.36)
Last meal size	0.61	0.06	(-0.18, 0.30)	0.94	0.01	(-0.21, 0.23)	0.90	0.01	(-0.21, 0.24)

[1] Linear regression analyses were performed to estimate strength of associations between mean 24-hour glucose measured by continuous glucose monitors and each component of eating architecture without covariate adjustment (Model 1) and multivariable models adjusting for age, gender, body mass index, waist circumference, application type (Model 2), and Model 2 plus the percentage of carbohydrates (Model 3). β are the

standardized coefficients; 95% CI, 95% confidence interval

CHAPTER 4 INTERMITTENT FASTING DOES NOT UNIFORMLY IMPACT GENES INVOLVED IN CIRCADIAN REGULATION IN WOMEN WITH OBESITY

Lijun Zhao [1,2,3], Amy T. Hutchison[1,2,3], Gary A. Wittert[1,2,3], Campbell H. Thompson[1], Kylie Lange[1,2], Bo Liu[1,2], Leonie K. Heilbronn[1,2,3,4]

[1] Adelaide Medical School, University of Adelaide, Adelaide, South Australia 5000, Australia

[2] NHMRC Centre of Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide, Adelaide, South Australia, Australia

[3] Lifelong Health Theme, South Australian Health and Medical Research Institute, Adelaide, South Australia 5000, Australia

[4] Corresponding author and lead contact

Statement of Authorship

Title of Paper	Intermittent Fasting Does Not Uniformly Impact Genes Involved in Circadian Regulation in Women with Obesity
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Zhao L, Hutchison AT, Wittert GA, Thompson CH, Lange K, Liu B, Heilbronn LK. Intermittent Fasting Does Not Uniformly Impact Genes Involved in Circadian Regulation in Women with Obesity. Obesity (Silver Spring). 2020;28 Suppl 1:S63-S67.

Principal Author

Name of Principal Author (Candidate)	Lijun Zhao		
Contribution to the Paper	Performed experiments, analysed the data, interpreted the data, wrote the manuscript and approved the final manuscript.		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	23 July 2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Amy T. Hutchison		
Contribution to the Paper	Commenced study and collected samples, interpreted the dats and approved final manuscript.		
Signature		Date	17/08/2021

Name of Co-Author	Gary A Wittert		
Contribution to the Paper	Designed the study, collected biopsies and provided clinical supervision, interpreted the data and approved final manuscript.		
Signature		Date	05/08/21

Name of Co-Author	Campbell H. Thompson		
Contribution to the Paper	Collected biopsies and approved final manuscript.		
Signature		Date	6/8/2021

Name of Co-Author	Kylie Lange		
Contribution to the Paper	Asissted statistics for analysing data and approved final manuscript.		
Signature		Date	28/Jul/2021

Name of Co-Author	Bo Liu		
Contribution to the Paper	Commenced study and collected samples, interpreted the data and approved final manuscript.		
Signature		Date	06/08/2021

Name of Co-Author	Leonie K. Heilbronn		
Contribution to the Paper	Designed, conducted and supervised the study, interpreted the data, approved final manuscript, and primary responsibility for the study and publication.		
Signature		Date	26/7/21

4.1 Study importance

What is already known about this subject?

- Behavioural and metabolic processes are regulated via central and peripheral clocks
- Prolonged fasting and overfeeding both dampen peripheral clocks in mouse tissues
- Intermittent fasting reduces the risk factors for diabetes and heart diseases in humans

What are the new findings in your manuscript?

- Intermittent fasting did not have a universal effect to blunt peripheral clocks in human skeletal muscle and adipose tissue
- Intermittent overfeeding reduced genes involved in circadian regulation in muscle

How might your results change the direction of research or the focus of clinical practice?

- Optimizing intermittent fasting protocols could be important to prevent circadian misalignment in humans.

4.2 Abstract

Objective

To examine the effects of intermittent fasting (IF) on mRNA levels of peripheral clock genes in skeletal muscle and subcutaneous adipose tissue (SAT) in women with obesity.

Methods

Women were randomized to one of two IF protocols and provided with all foods at 100% (IF100) or 70% (IF70) of calculated weekly energy requirements for 8-week. Breakfast was consumed before a 24-hour fast which was initiated on 3 non-consecutive days/week. Muscle and SAT biopsies were performed at 8 am after an overnight fast at baseline and at week 8 on a refed day and again following a 24-hour fasting at week 8 for analysis of the mRNA levels of key genes involved in circadian regulation.

Results

A group by time interaction was observed in *Per2* in muscle (F=3.497, P=0.044) and SAT (F=6.686, P=0.008), but significance was lost upon post hoc adjustment. A time effect was observed in *Rorα* in muscle, which was decreased by refeeding in both groups (F=7.225, P=0.003).

Conclusion

There was no universal effect of IF to alter peripheral clocks, which may partly be due to the alignment of the fasting/feeding cycle with the biological clock. Optimizing intermittent fasting protocols could be important to prevent circadian misalignment in humans.

Keywords: Intermittent fasting, circadian rhythm, clock gene expression, weight loss, breakfast

4.3 Introduction

The circadian system controls behavioural and metabolic processes via a central clock located in the suprachiasmatic nucleus (SCN), which communicates with peripheral clocks that exist in most tissues including liver, adipose tissue, muscle and pancreas (Otway et al., 2011, van Moorsel et al., 2016, Panda, 2016). At the molecular level, the circadian clock is generated by a transcriptional-translational feedback loop (Panda, 2016). The positive regulators of this loop are Clock (Circadian locomotor output cycles kaput) and Arntl (Aryl hydrocarbon receptor nuclear translocator-like protein 1). These form a heterodimer to increase the expression of Cryptochrome homolog (*Cry1/2*) and Period homolog (*Per1/2/3*) genes. Per and Cry accumulate and translocate to the nucleus where they bind with Clock:Arntl heterodimers and repress their own transcription. *Arntl* is also positively regulated by Ror-α/β/γ (Retinoic acid receptor-related orphan receptors) and negatively regulated by Nr1d1/2 (nuclear receptor subfamily 1 group D member 1/ 2) nuclear hormone receptors (Panda, 2016).

Transcriptional programs of clock-controlled genes oscillate in a tissue specific manner (Kinouchi et al., 2018, Panda, 2016) and have been confirmed to be rhythmic in human muscle (van Moorsel et al., 2016) and subcutaneous adipose tissue (SAT) (Otway et al., 2011). Peripheral clocks are exquisitely sensitive to feeding/fasting cycles (Vollmers et al., 2009, de Goede et al., 2018, Hatori et al., 2012). During feeding, activation of mTOR promotes the phosphorylation of glycogen synthase kinase 3 (GSK3), which increase the stability of Per (Zheng and Sehgal, 2010), lengthening the period which leads to a phase delay (Lee and Kim, 2013). During fasting, protein kinase AMPK is activated reducing the stability of Cry1 and Per2, leading to a phase advance(Lee and Kim, 2013).

Intermittent fasting (IF) is an eating pattern in which zero or minimal calories are consumed 1-4 days per week, followed by *ad libitum* eating on the remaining days (Heilbronn and Panda,

2019). IF reduces risk factors for diabetes and heart disease in humans (Heilbronn et al., 2005a, Hoddy et al., 2014, Varady et al., 2013, Halberg et al., 2005, Hutchison et al., 2019a). It is controversial as to whether IF produces greater metabolic health benefits versus calorie restriction (CR) (Hutchison et al., 2019a, Trepanowski et al., 2017, Harvie et al., 2011). Some of these controversies may be due to when the fasting protocol is implemented, with studies initiating fasts at breakfast (Hutchison et al., 2019a), lunch (Hoddy et al., 2014) and dinner (Hoddy et al., 2014, Varady et al., 2013, Halberg et al., 2005). There is only one study that has examined the effects of IF on peripheral clocks (Froy et al., 2009). In this study, IF abolished circadian rhythmicity of *Per2*, *Cry1* and *Arntl* in mouse liver, but only when the fasting/feeding cycle was initiated at the onset of the rest phase.

We recently completed an 8 week IF intervention where we provided all food at 70% (IF70) or 100% (IF100) of energy requirements in women with obesity (Hutchison et al., 2019a, Liu et al., 2019). The exploratory aim of this sub-study was to examine the effects of IF on mRNA levels of genes involved in circadian regulation in muscle and SAT. We hypothesized that IF would reduce the expression of genes involved in circadian regulation in muscle and SAT following 24-hour fasting days in both IF groups, but there would be a differential response between IF groups on refeeding days.

4.4 Methods

This study was approved by Royal Adelaide Hospital Research Ethics Committee and participants provided written informed consent. It was registered with ClinicalTrials.gov (NCT01769976).

Participants and study design

The study design has been described previously (Hutchison et al., 2019a). Since we were

primarily interested in whether fasting alters clock expression, we limited analysis to IF groups (Supplementary Figure 4.1). Briefly, 50 females, aged 35-70 years and body mass index (BMI) 25 to 42 kg/m^2 were randomized into two IF groups for 8 weeks. Individuals who completed muscle and fat biopsies at baseline and week 8 were included for analysis (n=37, aged 35-68 years and BMI 25-41 kg/m^2) (Supplementary Figure 4.1). The IF70 and IF100 groups were provided foods at 70% and 100% of calculated baseline energy requirements per week, respectively. Both groups were instructed to consume a breakfast (containing 30-35% of energy requirements) before 8 am initiating a ~24-hour "fast" until 8am the following day on three non-consecutive days per week. On the 4 refeeding days per week, the IF70 group consumed foods at ~100% of energy requirements, whereas the IF100 consumed ~145% of energy requirements to hit their weekly assigned energy targets.

Metabolic testing, muscle and adipose tissue biopsies

Participants underwent three metabolic visits in this study including two after 12-hour fasting at baseline (BL,V0) and week 8 (Refed, V8A), and one after 24-hour fast (Fast, V8B). Premenopausal women (N=16/37) were studied in the follicular phase to minimize the influence of the menstrual cycle. Individuals were weighed in a hospital gown and fasting blood samples were drawn. Fasting glucose and insulin were measured and homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as (fasting serum insulin [milliunits/litre] X fasting plasma glucose [millimoles/litre])/22.5 (Matthews et al., 1985). Vastus lateralis muscle and abdominal fat tissue were collected at ~8:00 am (Liu et al., 2019). All samples were immediately frozen in liquid nitrogen and stored at -80°C.

Quantitative real-time PCR

RNA extraction, cDNA reverse transcription protocols and gene expression analysis (quantitative real-time polymerase-chain reaction) have been described elsewhere (Liu et al.,

2019). Six clock genes were measured in SAT and skeletal muscle, *Cry1* was below detection limits in SAT. Clock genes evaluated were *Arntl* (aryl hydrocarbon receptor nuclear translocator-Like, Hs00154147_m1), *Clock* (circadian locomotor output cycles kaput, Hs00231857_m1), *Per2* (period 2, Hs01007553_m1), *Cry1* (cryptochrome 1, Hs00172734_m1), *Nr1d1* (nuclear receptor subfamily 1 group D member 1, Hs00253876_m1) and *Rorα* (retinoic acid receptor-related orphan receptor α, Hs00536545_m1). As described previously (Liu et al., 2019), the relative expression of each gene was normalized for the mean of *B2m* and *18s* for SAT, and *Actb* and *Hprt* for skeletal muscle.

Statistics

Data are presented as mean ± SEM. A restricted maximum likelihood mixed effects model was conducted to examine the group effects of 8-week intervention following an overnight 12-h fast and 24-hour fast, as well as the time effects within each group. The model included fixed factors for group (IF70, IF100), time (BL/V0, Refed/V8A and Fast/V8B) and the group by time interaction, and a random factor for subject with an unstructured covariance matrix to account for the repeated visits. Within-group comparisons of the effect of time were conducted using Bonferroni-adjusted pairwise comparisons of the estimated marginal means with significance set at $p<0.05$ (two-sided). Between-group comparisons of the changes between visits were conducted using unadjusted planned contrasts. Data were log-transformed if the skewness or heteroscedasticity in the residuals were observed. Statistical analysis was performed using SPSS (Version 25, Armonk, New York).

4.5 Results

Anthropometric and biochemical results

As previously reported, body weight was significantly decreased by the intervention, with

greater reduction in IF70 as compared with IF100 (Table 4.1). The same trend was also observed in fat mass, but did not reach significance in this smaller cohort as was previously reported (Hutchison et al., 2019a, Liu et al., 2019). Group by time differences were also observed in the change in fasting insulin and HOMA-IR (Table 4.1). Following refeeding, fasting insulin and HOMA-IR were reduced in IF70, but were transiently elevated above baseline in the IF100 group, likely reflecting the overfeeding prescribed to this group. Following the 24-hour fast, insulin levels were reduced in both IF groups. Fasting glucose levels were reduced from baseline after a 24-hour fast in the IF70 group only (Table 4.1).

mRNA levels of circadian genes in muscle and adipose tissue

Group by time differences were observed in *Per2* in muscle (F=3.497, P=0.044, Figure 1C), and adipose tissue (F=6.686, P=0.008, Figure 1I), but significance was lost upon post hoc adjustment. A time effect was observed in *Rorα* in muscle, which was decreased by refeeding in both groups (time, F=7.225, P=0.003, Figure 1E). Within group analysis showed reduced muscle mRNA levels of *Per2* (P=0.021), *Rorα* (P=0.034, Figure 1E) and *Cry1* (P=0.022, Figure 1F) following refed days and reduced levels of *Clock* (V0 vs V8B, P=0.019; V8A vs V8B, P=0.043, Figure 1B) and *Nr1d1* (P=0.035, Figure 1D) following fast days in the IF100 group. In the IF70 group, *Per2* mRNA levels were increased in muscle (P=0.013, Figure 1C) but reduced in adipose tissue (P=0.027, Figure 1I) during the fed to fast transition. No other genes were altered by the interventions.

Table 4.1 Changes in anthropometric measures at baseline and after 8 weeks intervention (N=37, participants who had muscle and/or subcutaneous adipose tissue biopsies)[1]

	IF100 (N=17)			IF70 (N=20)			Between group comparison (p-value)		
	BL (12h fast)	V8A (12h fast)	V8B (24h-fast)	BL (12h fast)	V8A (12h fast)	V8B (24h-fast)	Δ (V8A-BL)	Δ (V8B-BL)	Δ (V8A-V8B)
Weight (kg)	84.4 ± 3.2	81.2 ± 3.2*	-	88.7 ± 3.0	83.5 ± 3.2*	-	**0.007**	-	-
BMI (kg/m^2)	31.3 ± 1.1	30.1 ± 1.1*	-	32.7 ± 0.9	30.8 ± 0.9*	-	**0.012**	-	-
Fat (%)	46.5 ± 1.6	44.8 ± 1.8*	-	49.1 ± 1.5	47.0 ± 1.6*	-	0.358	-	-
FPG (mmol/L)	4.9 ± 0.1	5.0 ± 0.1	4.8 ± 0.1	4.9 ± 0.1	4.7 ± 0.1	4.7 ± 0.1*	0.124	0.414	0.415
FINS (mU/L)	18.4 ± 1.8	22.9 ± 2.6*	14.5 ± 1.7*#	20.1 ± 1.7	16.2 ± 1.2*	14.0 ± 1.3*	**<0.001**	0.486	**0.021**
HOMA-IR	4.1 ± 0.5	4.7 ± 0.5	3.4 ± 0.5#	4.4 ± 0.4	3.4 ± 0.3*	2.9 ± 0.3*	**0.001**	0.226	0.143

[1]Data are shown as mean ± SEM. Mixed effects model was performed to test the group differences of 8-week intervention following overnight 12-h fast (Refed, V8A) and 24-h fast (Fast, V8B), as well as time effects within each group. P values are bold if the significance is presented between group comparisons. *P<0.05 difference within each group vs baseline; #P<0.001 difference within each group from V8A to V8B. IF70: intermittent fasting diet at 70% baseline energy requirements; IF100: intermittent fasting diet at 100% baseline energy requirements; BL: baseline; BMI: body mass index; FPG: fasting plasma glucose; FINS: fasting plasma insulin; HOMA-IR: Homeostatic model of assessment-insulin resistance; h,hour.

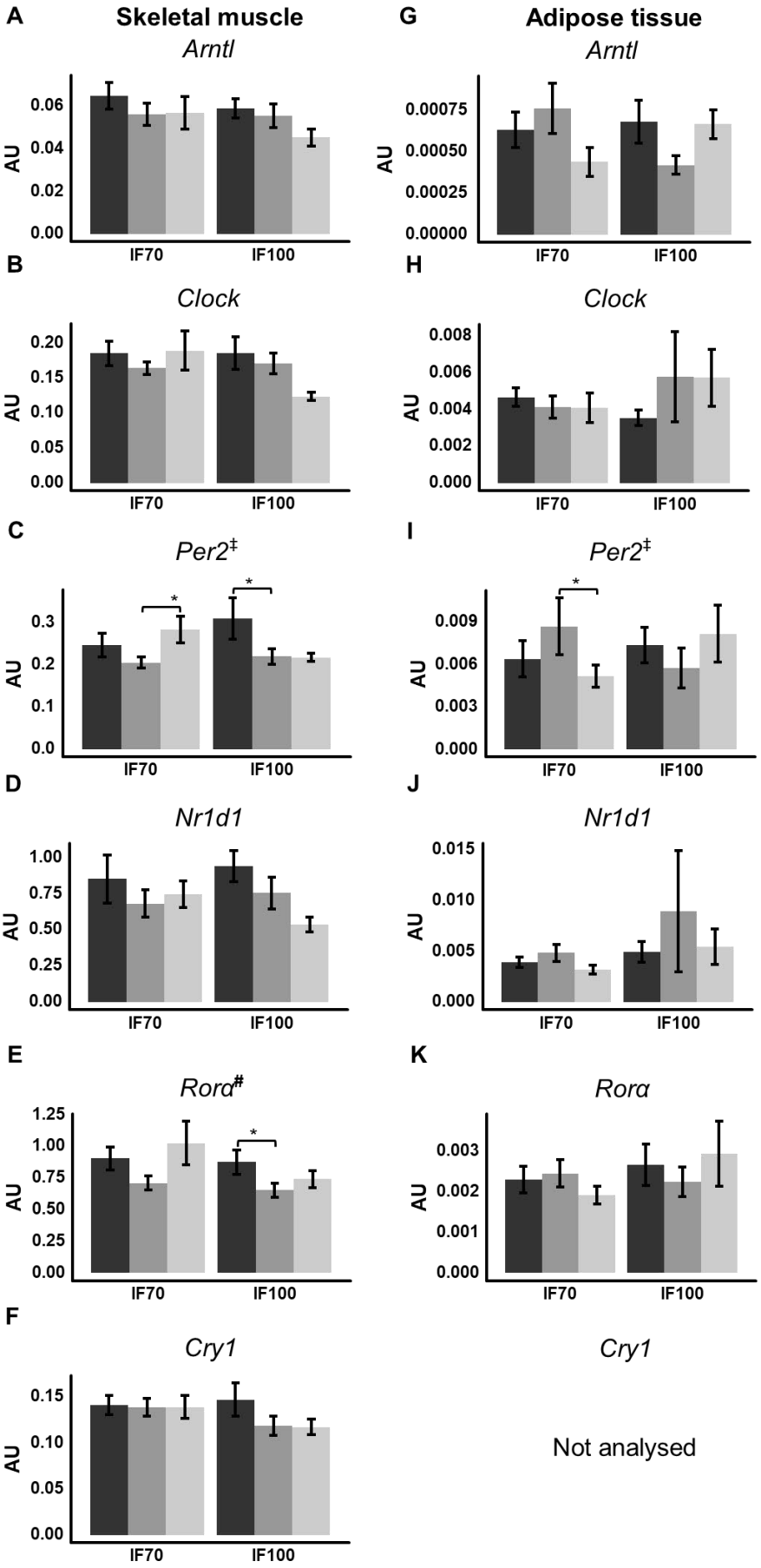

A
Skeletal muscle
Arntl
AU
0.06
0.04
0.02
0.00
IF70
IF100
G
Adipose tissue
Arntl
0.00075
0.00050
0.00025
0.00000
B
Clock
0.20
0.15
0.10
0.05
H
Clock
0.008
0.006
0.004
0.002
0.000
C
Per2‡
*
0.3
0.2
0.1
0.0
I
Per2‡
0.009
0.006
0.003
D
Nr1d1
1.00
0.75
0.50
0.25
J
Nr1d1
0.015
0.010
0.005
E
Rorα#
1.25
1.00
0.75
0.50
0.25
K
Rorα
F
Cry1
0.15
0.10
0.05
Cry1
Not analysed

Figure 4.1 (A, G) Arntl, (B, H) Clock, (C, I) Per2, (D, J) Nr1d1, (E, K) Rorα and (F) Cry1 gene expression after 8-week of IF intervention in skeleton muscle (IF70, N = 17; IF100, N = 14) and subcutaneous adipose tissue (N = 9 per group), respectively.

[Mixed effects model was performed to test the group effects of 8-week intervention following overnight 12-hour fast (Refed, V8A) and 24-hour fast (Fast, V8B), as well as time effects within each group. Black bar: baseline following 12-hour fast; grey bar: week 8 following 12-hour fast (Refed); light grey bar: week 8 following 24-hour fast (Fast). $^{\#}$ P<0.05 time effect; $^{\ddagger}P$<0.05 group by time interaction effect; $^{*}P$<0.05 difference within each group.]

4.6 Discussion

Peripheral clocks exhibit circadian rhythmicity in human muscle (van Moorsel et al., 2016) and adipose tissue (Otway et al., 2011), and are exquisitely sensitive to feeding/fasting cycle (Vollmers et al., 2009, de Goede et al., 2018, Hatori et al., 2012). Based on preclinical findings (Froy et al., 2009, Kinouchi et al., 2018), we hypothesized that IF would reduce expression of peripheral clocks in human muscle and adipose tissue following a fasting day, but that mRNA levels would be restored by refeeding particularly in the IF70 group, which was under CR. Reassuringly, we observed that 24 hours of fasting did not produce universal changes in genes involved in circadian regulation in human muscle or adipose tissue.

Acute 24-hours of fasting completely blunted the rhythmicity of *Arntl* protein and downstream genes including *Dbp, Nr1d1, Per2, Per3* in mouse liver and muscle (Kinouchi et al., 2018). This was sustained when the fasting duration was extended to 48-hour but was rapidly reversed by refeeding (Kinouchi et al., 2018). In the present study in humans, 24 hours of fasting reduced *Clock* and *Nr1d1* mRNA levels only in muscle in the IF100 group and *Per2* levels only in adipose tissue in the IF70 group. In contrast, *Per2* was increased by fasting in muscle in the IF70 group, potentially indicating there may be tissue specific regulation in humans. We

speculate that CR may have mediated the fasting induced increase in *Per2*. In mouse liver, CR increased the amplitude in *Per1*, *Per2*, *Cry2* and *Arntl* (Patel et al., 2016). To our knowledge, the effects of CR on the phase or amplitude of peripheral clocks have not been reported in human tissue. However, weight loss induced by low calorie diet increased the mRNA levels of *Per2* and *Nr1d1* in human adipose tissue samples that were taken at 9 am (Pivovarova et al., 2016). In skeletal muscle, morning *Cry1* mRNA levels were increased in women with obesity and decreased to the level of lean controls following weight loss induced by bariatric surgery (Sardon Puig et al., 2020).

The effects of IF on peripheral clocks have previously only been tested during a fed day in mice (Froy et al., 2009). IF initiated at the onset of the rest phase dampened the amplitude of expression in *Per1*, *Per2*, *Cry1*, *Clock* and *Arntl* during a refeeding day. Initiation of IF at the onset of active phase did not alter the amplitude of expression, but induced a short phase advance in clock genes that was in alignment with an advance in peak food intakes (Froy et al., 2009). This mouse study shows the clear entraining effect of food intake on peripheral clocks, and advocates for alignment of initiation of IF with the biological clock. In the present study, we selected to initiate the fasting/feeding protocol at breakfast and observed minimal changes in clock genes in muscle or fat in the IF70 group. This meal timing on fasting days potentially limited the negative consequences of IF on molecular clocks (Froy et al., 2009) and contrasts a number of IF studies in humans that advocate to start/end the fasting periods at lunch or dinner (Hoddy et al., 2014, Varady et al., 2013, Halberg et al., 2005). At the transcriptomic level, delaying the initiation of food intake by 6-h or "skipping breakfast" resulted in ~500 genes differentially expressed in human adipose tissue (Loboda et al., 2009). Genes upregulated with fasting were positively correlated with *Per1*, suggesting that skipping breakfast delayed the molecular clock in adipose tissue (Loboda et al., 2009). Similar results have been reported in other studies of breakfast delay in adipose tissue (Wehrens et al., 2017) and blood leukocytes

(Jakubowicz et al., 2017b). This difference in meal timing on fasting days could also explain some of the discrepancy in health outcomes between studies of IF (Hutchison et al., 2019a, Trepanowski et al., 2017, Harvie et al., 2011), since circadian desynchrony has been linked to increased disease risk and reduced lifespan in animal models (Logan and McClung, 2018).

The IF100 group was included to test the effects of IF independently of weight loss. This group was therefore overfed on feeding days in order to maintain overall energy balance and experienced minimal weight loss, no improvements in blood lipids and transient elevations in insulin following refeeding days (Hutchison et al., 2019a). Insulin stimulates *Per2* protein accumulation by increasing *Per2* mRNA translation (Crosby et al., 2019). The net result is to suppress expression of Arntl target genes including *Per2*, *Cry1*, *Nr1d1* and *Rorα* (Panda, 2016). Reductions in *Per2*, *Cry1* and *Rorα* mRNA levels were observed in muscle in response to refeeding in the IF100 group. These results could also have occurred due to a lengthened daily eating cycle. Whilst we aligned the start of feeding/fasting cycle, we neglected to control, or track, the time that individuals completed their prescribed food intakes each day. It is possible that the IF100 group required longer to eat the large volume of food prescribed on this day, contributing to a phase delay or dampening of clock gene expression (Hatori et al., 2012).

Since only one-time point was sampled, we cannot determine whether there was a dampening or shifting in the phase of these genes limiting interpretation. As we were primarily interested in the effects of fasting, we chose not to include samples from the CR group arm for analysis, meaning we cannot differentiate between the effects of IF and CR. The present study was also limited by small sample size and to females. Whilst premenopausal participants were studied in the follicular phase, the impact of the menstrual cycle on the molecular clock was not taken into consideration (Shechter and Boivin, 2010). Finally, glucose profiles were not assessed by continuous glucose monitoring.

The present study is the first to examine the impacts of IF on clock gene expression in human muscle and adipose tissue. Genes involved in circadian regulation were sensitive to intermittent overfeeding in skeletal muscle, but we did not observe a universal effect of fasting across groups or tissues. This may have partly been due to the alignment of the fasting/feeding cycle with the biological clock (i.e at breakfast). Given the potential for IF to promote day-to-day variation in meal timing, further consideration should be given to the optimal design of IF protocols in humans. These studies should compare the effects of initiating IF after breakfast vs. dinner on health, and the amplitude and phase of peripheral clocks, during both fed and fasting days.

Acknowledgement: Individual deidentified participant data will be made available on request.

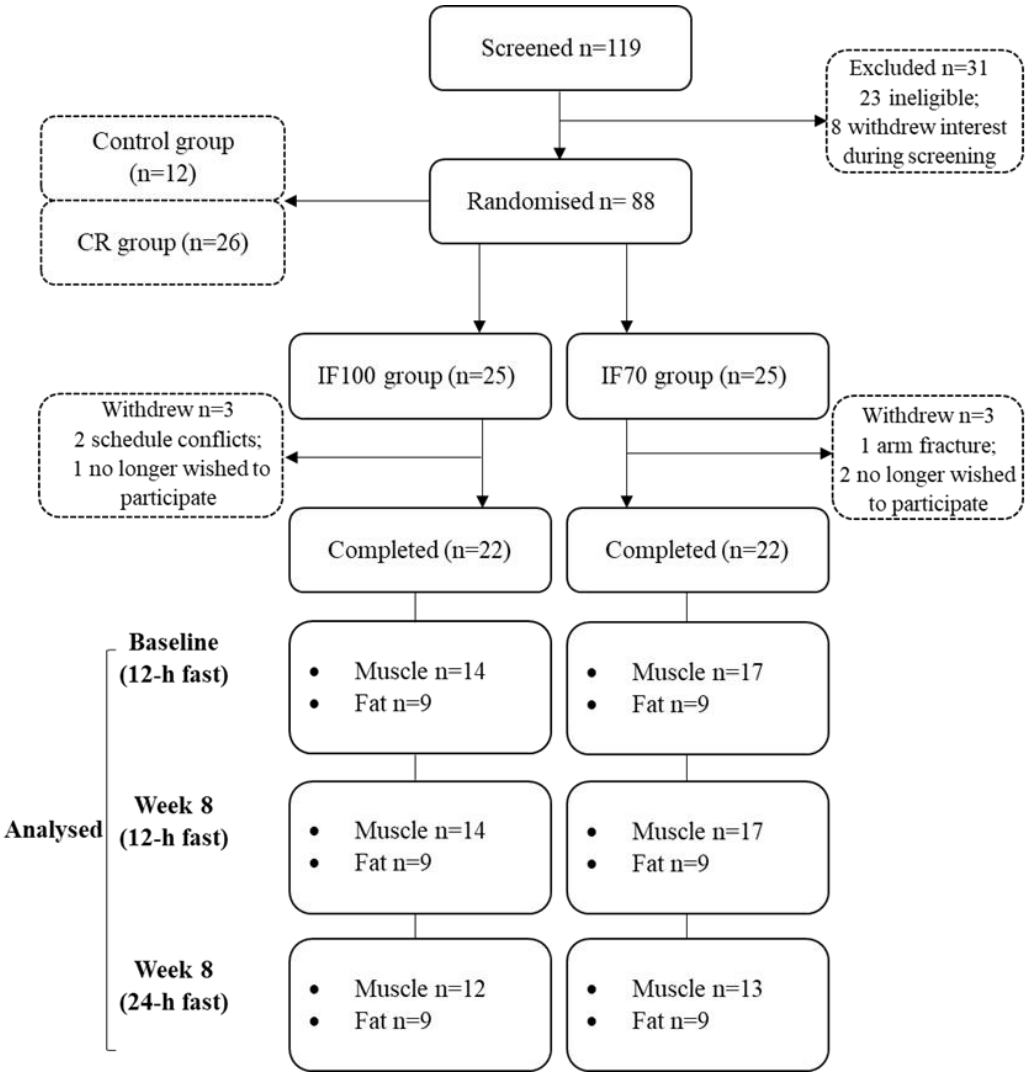
Funding Sources: The research was funded by a National Health and Medical Research Council (NHMRC) Project Grant APP1023401. LZ is supported by a Beacon of Enlightenment Scholarship from University of Adelaide.

Disclosure: The authors declared no conflicts of interest.

Author Contributions: LKH and GAW designed the research. ATH and BL collected data and analysed plasma biomarkers. BL and LZ performed experiments. GAW and CHT provided clinical support, supervised clamps and performed muscle and adipose tissue biopsies. LZ and KL performed statistical analysis. All authors contributed to data interpretation and preparation of the manuscript. LKH had full access to the data and had primary responsibility for the final publication.

Clinical trial registration: ClinicalTrials.gov. identifier NCT01769976

SUPPLEMENTARY MATERIAL FOR CHAPTER 4



Supplementary Figure 4.1 CONSORT flow diagram.

[88 females were randomized into four groups (IF70, IF100, calorie restriction [CR] 70 and control) for 8 weeks. 50 participants were randomized into IF groups (N=25 per group, N=22 per group completed the study). Analysis was limited to IF groups as we were primarily interested in whether fasting shifts clock expression. Individuals who completed at least 2 muscle biopsies (IF70, n=17; IF100, n=14) and completed 3 fat biopsies (n=9 per group) were included for analysis. Twelve participants had both fat and muscle biopsies (n=6 in each group).]

CHAPTER 5 TIME RESTRICTED EATING IMPROVES GLYCAEMIC CONTROL AND DAMPENS ENERGY-CONSUMING PATHWAYS IN HUMAN ADIPOSE TISSUE

Lijun Zhao[1,2], Amy T Hutchison[1,2], Bo Liu[1,2], Crystal L Yates [3], Xiao Tong Teong[1,2], Gary A Wittert[1,2], Campbell H Thompson[1,4], Leanne Nguyen[4], John Au[4], Emily N. C. Manoogian[5], Hiep D Le[5], April E Williams[5], Satchidananda Panda[5], Siobhan Banks[3], Leonie K Heilbronn[1,2,6]

[1] Adelaide Medical School, The University of Adelaide, Adelaide, South Australia 5000, Australia

[2] Lifelong Health Theme, South Australian Health and Medical Research Institute, Adelaide, South Australia 5000, Australia

[3] University of South Australia, Justice and Society, Behaviour-Brain Body Research Centre, South Australia, 5000, Australia

[4] Royal Adelaide Hospital, Adelaide, South Australia 5000, Australia

[5] Salk Institute for Biological Studies, La Jolla, California, 92182, USA

[6] Corresponding author and lead contact

Statement of Authorship

Title of Paper	Time restricted eating improves glycaemic control and dampens energy-consuming pathways in human adipose tissue
Publication Status	✓ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Lijun Zhao, Amy T Hutchison, Bo Liu, Crystal L Yates, Xiao Tong Toong, Gary A Wittert, Campbell H Thompson, Leanne Nguyen, John Au, Emily N. C. Manoogian, Hiep D Le, April E Williams, Satchidananda Panda, Siobhan Banks, Leonie K Heilbronn. Time restricted eating improves glycaemic control and dampens energy-consuming pathways in human adipose tissue.

Principal Author

Name of Principal Author (Candidate)	Lijun Zhao		
Contribution to the Paper	Commenced the study, collected data, performed lab work, analysed data, wrote manuscript and approved final manuscript.		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	23 July 2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Amy T Hutchison		
Contribution to the Paper	Designed the study, collected data and interpreted the data and approved final manuscript.		
Signature		Date	17/08/2021

Name of Co-Author	Bo Liu		
Contribution to the Paper	Collected data and approved final manuscript.		
Signature		Date	06/08/2021

Name of Co-Author	Crystal L Yates		
Contribution to the Paper	Collected data and approved final manuscript.		
Signature		Date	28/7/21

Name of Co-Author	Xiao Tong Teong		
Contribution to the Paper	Collected data and approved final manuscript.		
Signature		Date	26/7/2021

Name of Co-Author	Gary A Wittert		
Contribution to the Paper	Designed the study, collected biopsies and provided clinical supervision, interpreted the data and approved final manuscript.		
Signature		Date	05/08/21

Name of Co-Author	Campbell H Thompson		
Contribution to the Paper	Collected biopsies and approved final manuscript.		
Signature		Date	6/8/21

Name of Co-Author	Leanne Nguyen		
Contribution to the Paper	Collected biopsies and approved final manuscript.		
Signature		Date	19/8/21

Name of Co-Author	John Au		
Contribution to the Paper	Collected biopsies and approved final manuscript.		
Signature		Date	19/8/21

Name of Co-Author	Emily N. C. Manoogian		
Contribution to the Paper	Supplied the myCircadianClock application, contributed to data interpretation and approved final manuscript.		
Signature		Date	8/12/2021

Name of Co-Author	Hiep D Le		
Contribution to the Paper	Performed RNA sequencing and approved final manuscript.		
Signature		Date	13/08/21

Name of Co-Author	April E Williams		
Contribution to the Paper	Analysed RNA sequencing data and approved final manuscript.		
Signature		Date	12/08/21

Name of Co-Author	Satchidananda Panda		
Contribution to the Paper	Supplied the myCircadianClock application, funded adipose tissue RNA sequencing, contributed to data interpretation and approved final manuscript.		
Signature		Date	08/23/21

Name of Co-Author	Siobhan Banks		
Contribution to the Paper	Designed the study, supervised metabolic test days during the ward stay at the sleep and chronobiology laboratory, contributed to the data interpretation and approved final manuscript.		
Signature		Date	19/8/21

Name of Co-Author	Leonie K Heilbronn		
Contribution to the Paper	Designed, conducted and supervised the study, interpreted the data, approved final manuscript, and primary responsibility for the study and publication.		
Signature		Date	26/7/21

5.1 Highlights

- Under highly controlled conditions, time restricting eating (TRE) reduces fasting glucose and glycated haemoglobin and tended to improve 24 hour glucose in men with obesity, but impaired glucose response to a dinner meal.
- TRE alters the adipose tissue transcriptome, downregulating genes involved in mitoribosome regulation and proteasome function which may be an adaptive response to lowered energy availability and reduced mitochondrial oxidative stress.
- TRE could be a preventative or therapeutic strategy to assist glycaemic management for patients with prediabetes or type 2 diabetes

5.2 Abstract

Aim

To examine the effects of eight weeks of TRE on glucose metabolism and adipose tissue transcriptome during a metabolic ward stay in men with obesity.

Methods

In a single-arm, pre-post trial, 15 men (aged 62.9 ± 4 years, body mass index 30.5 ± 2.4 kg/m^2, waist circumference 113 ± 4 cm) with obesity but no history of diabetes were enrolled and underwent two weeks of baseline monitoring, before they were instructed to eat their regular diets within a contiguous 10-hour time frame each day for 8-weeks. Metabolic testing was performed at baseline and week 8 during a 35-hour metabolic ward stay, during which all food intake was strictly timed and controlled. Identical meal tolerance tests were performed at breakfast and dinner. Blood glucose, glucoregulatory hormones and subjective appetite score were measured. Subcutaneous adipose tissue (SAT) biopsies were performed and the transcriptome was assessed.

Results

The primary outcome, plasma glucose area under the curve (AUC), was altered by TRE being unchanged at breakfast, but increased at dinner. TRE reduced fasting glucose, glycated haemoglobin, body weight and body fat and increased glucose-dependent insulinotropic peptide AUC at dinner. In SAT, 117 genes were upregulated and 202 genes were downregulated by TRE. Pathway analysis revealed the downregulation of genes involved in proteasome function and mitochondrial regulation.

Conclusion

TRE had a net effect to reduce glycaemia and dampened energy-consuming pathways in

adipose tissue.

Keywords: Time restricted eating, weight loss, glycaemia control, breakfast, dinner, adipose tissue transcriptome

5.3 Introduction

Obesity has been associated with an increase in the duration of the contiguous daily eating pattern (Si Hassen et al., 2018, Ducrot et al., 2018, Leech et al., 2017a). The average eating duration was more than 14 hours in 156 college-age adults in the United States (Gill and Panda, 2015) and in 94 adults aged 19-58 in India (Gupta et al., 2017b). Time restricting eating, or TRE, therefore represents an alternative dietary strategy to manage obesity and associated metabolic diseases. Pilot studies have shown that TRE improves markers of glucose regulation in individuals with obesity (Regmi and Heilbronn, 2020, Jamshed et al., 2019). TRE also improved pancreatic β cell responsiveness and insulin resistance measured by oral glucose tolerant test at habitual breakfast time in 8 adult males aged 35-70 with prediabetes after 5 weeks (Sutton et al., 2018), and reduced glycated haemoglobin (HbA1c) in 40 individuals aged 35-65 with one or more components of the metabolic syndrome after 12 weeks (Kesztyus et al., 2019). However, self-selected TRE did not alter fasting glucose, fasting insulin, 24-hour glucose, or HbA1c in 19 adults aged 48-70 with metabolic syndrome after 12 weeks (Wilkinson et al., 2019). The majority of TRE studies to date have limited metabolic assessments to the morning (Sutton et al., 2018, Kesztyus et al., 2019, Wilkinson et al., 2019). Only two have examined responses during in-patient stays of 4-5 days (Jamshed et al., 2019, Parr et al., 2020b), reporting reduced 24-hour glucose.

Adipose tissue is the major energy depot and plays a critical role in the adaptive response to fasting. These adaptions include switching from lipid synthesis to lipolysis, elevating non-esterified fatty acid (NEFA) levels, suppressing mitochondria translation and insulin signalling (Defour et al., 2020). An acute 24-hour fast was previously reported to upregulate 260 genes and downregulate 557 genes in human adipose tissue in 11 healthy non-obese individuals (Defour et al., 2020). The downregulated genes were enriched in multiple pathways involved in energy metabolism and proteasome (Defour et al., 2020). In mouse, TRE reduced

inflammatory pathways (Hatori et al., 2012, Chaix et al., 2014). However, the effects of TRE on the subcutaneous adipose tissue (SAT) transcriptome have not previously been reported in humans.

The objectives of this study were to determine, in a controlled metabolic environment, 1) the effects of eight weeks of TRE on overall and meal specific glycaemia as measured by area under the curve (primary outcome) and postprandial NEFA, triglyceride, insulin, ghrelin, ghrelin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP) and subjective appetite score in response to mixed nutrient meal tests at breakfast and dinner in men on a metabolic ward; 2) the effect of TRE on adipose tissue transcriptome. We hypothesised that TRE would improve glycaemic control and appetite regulation at breakfast and dinner, and alter the transcriptomic profiles in adipose tissue.

5.4 Materials and methods

Participants

This study was designed as an open-label, single-arm, pre-post trial. Fifteen men were recruited between July 17, 2018, and April 3, 2019. Inclusion criteria were: aged 40-70 years; waist circumference ≥ 94 cm; weight-stable (< 5 % fluctuation in body weight for 6-months prior to study entry) (Supplementary Figure 5.1). Participants were excluded if they reported: personal history and/or diagnosis of diabetes, cancer, major psychiatric disorders, liver disease, gastrointestinal surgery or disease, eating disorders, anaemia, insomnia or cardiovascular disease deemed unstable by the study physician; use of prescribed or non-prescribed medications which may affect energy metabolism, gastrointestinal function, perform >2 sessions per week of high-intensity exercise; intake of >140g alcohol/week; smoking; consumption of any illicit substance; unable to comprehend study protocol; shift work; had undertaken, or was planning to undertake, trans-meridian travel during the study period or the

preceding 60 days; serum ferritin level of <30ng/mL; or a self-reported habitual eating window of less than 12 hours/day. Eleven participants took medications for hypertension, and/or high cholesterol, and/or gastro-oesophageal reflux disease. One participant ceased taking anti-hypertension medication at week 2 and another participant stopped taking statins at week 2. Removing these patients from the analysis did not affect the outcomes (data not shown) and so they are included in the analysis.

The study was approved by the Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee, University of Adelaide, and the University of South Australia, and registered with ClinicalTrials.gov (NCT03590158). Written, informed consent was obtained from all participants prior to their enrolment.

Study design

The trial period was 10 weeks, including 2-week baseline monitoring and an 8-week TRE intervention (Figure 5.1A). In the two weeks prior to baseline and week 8, participants were fitted with an Actigraph to measure daily energy expenditure, activity levels, step counts and sleep patterns (wGT3X-BT, ActiGraph LLC, FL, USA) and a continuous glucose monitoring (CGM, FreeStyle Libre Pro, Abbott, UK) to measure interstitial glucose. Participants downloaded the photograph-based smartphone application "*myCircadianClock"* (mCC; https://mycircadianclock.org/, Satchidananda Panda, Salk Institute, La Jolla, CA, USA) and photographed and annotated all eating and drinking events for the entire 10-week study duration. Whole-body composition was assessed by Dual-energy X-ray absorptiometry (DEXA, Lunar Prodigy; GE Health care, Madison, Wisconsin) and analysed by enCore software (GE Healthcare, Chicago, Illinois; version 16.2). Blood pressure was measured when the participant seated after 10 minutes of rest. Waist circumference was measured by the same investigator at the mid-point between the participant's lowest rib and the top of his hip bone. In order to

standardise food intake, all foods were provided at 100% of calculated total daily energy requirements (50% of carbohydrate, 30% fat, 20% protein) for 3 days prior to the metabolic testing visit at baseline and week 8 (Medicine, 2005). Participants also attended the clinical facility every 2 weeks for adherence and health assessments.

Dietary intervention

Eating durations of 4 -12 hours have been trialled in TRE studies in humans (Regmi and Heilbronn, 2020). However, the optimal duration is not yet clear, as only one study has compared 4 hour and 6 hour eating windows (Cienfuegos et al., 2020a). We selected 10 hour TRE based on past literature showing improvements in weight and health (Peeke et al., 2021, Gill and Panda, 2015, Wilkinson et al., 2019), while very short TRE lengths are accompanied with several adverse effects (nausea, headache, sleep disruption) (Sutton et al., 2018, Cienfuegos et al., 2020a) which might lessen long-term adherence. Participants were instructed to eat their habitual diets, within a consistent 10-hour time frame each day for 8 weeks. Participants could self-selected the precise time window, with the exception that the latest eating occasion was to be completed by 1930h. Water and energy-free beverage consumption were allowed *ad libitum*. No other dietary instructions were provided, but participants were asked to maintain their usual daily physical activity and sleep patterns.

Daily eating duration, food intake and adherence

Participants used the mCC application to photograph all eating events, which provides a timestamp of the event and annotated the photo to describe what they ate. Adherence to a designated eating window was determined by the number of days in which a participant was adherent to logging (a minimum of two calorie-containing entries over a minimum of 5 h for a given day) and when all caloric food items were contained within a 15-min buffer on each side of the self-selected 10-hour eating window. We define the eating window as the time interval

during which 95% (2.5 percentile to 97.5 percentile) of all calorie-containing ingestion events occur during baseline or intervention period (Gill and Panda, 2015, Wilkinson et al., 2019). A trained researcher estimated total daily energy intake, macronutrient intakes from the food images and annotations obtained from the mCC app server using Foodworks (Xyris Software, version 10, Australia).

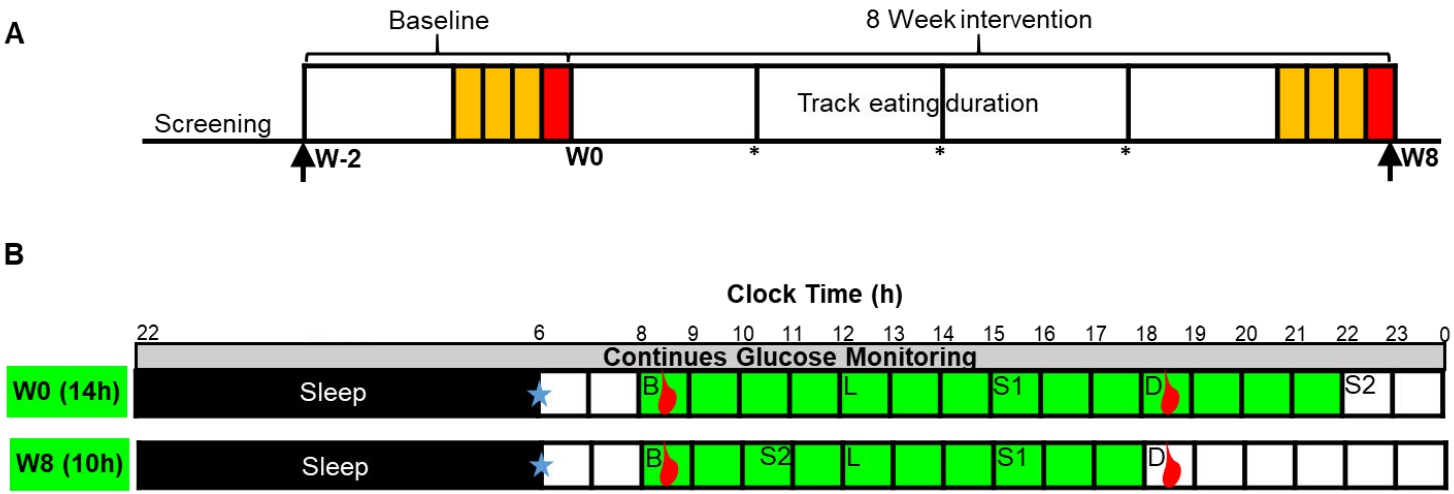


Figure 5.1 Study design

[Schematic of the study design. Following a successful screening, participants entered the baseline phase of the study. Physical activity was recorded for 2 weeks at baseline (W-2 to W0) and 2 weeks prior to the study conclusion (W6 to W8). The daily eating duration was tracked throughout the entire 10 weeks of the study. All foods were provided at 100% of calculated energy requirements for the three-days prior to metabolic testing (orange box). Participants attended the sleep laboratory lab for a 35-hour metabolic testing visit (red box) at baseline and week 8. Adherence checks were completed 2-weekly (star). A DEXA scan was conducted after an overnight fast at baseline and at the completion of the study (arrow). **(B)** Metabolic testing day study protocol and meal plan for participants with estimated energy requirements. Identical meals were provided within a 14-h time frame at W0 (upper panel, 0800-2200h) and 10-h time frame at W8 (lower panel, 0800-1800h) (green). Snack 2 was utilized to maintain the different time frames (consumed at 2200h at W0 but 1030h at W8). Abdominal subcutaneous adipose tissue biopsies were performed at 0600 AM (blue star). Meal tests were performed following an identical standard meal at breakfast and dinner (red blood dot).]

Metabolic testing at the Sleep and Chronobiology Laboratory

Metabolic testing was performed in a light, noise, and temperature-controlled sleep and chronobiology laboratory at the University of South Australia as previously described (Gupta et al., 2017a). Four participants per run arrived at 1630h, the afternoon prior to testing. Dinner was provided at 1830h, and an 8-hour sleep opportunity was provided at 2200h. Light intensity was < 50 lx and < 0.03 lx during periods of wakefulness and sleep, respectively. All foods were provided at calculated energy balance based on sedentary activity levels (Medicine, 2005). At baseline, three meals (breakfast at 0800h, lunch at 1200h, dinner at 1800h) and two snacks (snack 1 at 1500h and snack 2 at 2200h) were provided over a 14-hour time period. The breakfast and dinner meals provided were identical (753 kcal, 60 % carbohydrate, 20 % fat, 17 % protein, 3 % fibre). At week 8, identical meals were provided at identical times, except snack 2, which was moved to 1030h to hit the 10-hour TRE eating window. The description of the standardized meal is presented in Supplementary Table 5.1. Water was allowed *ad libitum*.

Body weight was measured with a calibrated scale, in a hospital gown, after voiding. An in-dwelling intravenous cannula was placed at 0600h and SAT biopsies were performed as previously described (Tam et al., 2010). Pre-meal blood samples were taken at 0800h (breakfast) and 1800h (dinner), immediately prior to consumption of the standard meal. Postprandial venous blood samples were collected at 15, 30, 60, 90, 120, and 150 minutes (Figure 5.1B). Blood was collected in ice-chilled EDTA tubes, and 20 µL of 200mM 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF, Gold Biotechnology, St Louis, Missouri; Cat# A-540-5, CAS 30827-99-7) and 10 µL of dipeptidyl peptidase-IV inhibitor (Sigma-Aldrich, North Ryde, NSW, Australia; Cat#: 634867) were added to 1 millilitre of whole blood for the measurement of gastrointestinal hormones (ghrelin, GLP-1, GIP). Samples were immediately placed on ice, centrifuged at 4°C, and snap-frozen to −80°C for later analysis. Blood glucose, HbA1c, fasting total cholesterol, high-density lipoprotein-cholesterol (HDL-c)

and triglycerides, NEFA, plasma ghrelin, GLP-1, GIP and visual analogue scales (VAS) assessing measures of appetite were measured (for details, see the supplementary Appendix associated with this article online).

Biochemical measures

Blood glucose, HbA1c, fasting total cholesterol, HDL-c and triglycerides were measured using commercially available enzymatic kits on an AU480 clinical analyzer (Beckman Coulter, Inc., Brea, California). NEFA were measured using a colorimetric assay (NEFA; Randox Laboratories Ltd. Co. Antrim, United Kingdom). Plasma insulin was measured by radioimmunology assay (EMD Millipore, Billeria, USA). Plasma ghrelin, GLP-1, and GIP were measured by magnetic bead-based quantitative immunoassay (MilliporeSigma, Burlington, Massachusetts). Samples from each participant were analysed within the same run to minimise interassay variation. As a result of failed cannulas, two participants did not have blood samples at the dinner meal test. CGM data was lost from one participant at baseline (W0) and another participant at week 8 (W8) due to technical issues. CGM data from one participant was excluded at baseline from the analysis due to vasovagal syncope as a result of a failed cannula.

Appetite responses

Participants completed visual analogue scales (VAS) assessing measures of appetite at 0, 15, 30, 60, 90, 120, 150 minutes during the meal test (Flint et al., 2000). The scales assessed hunger (“not at all hungry” to “very hungry”), fullness (“not at all full” to “very full”), desire to eat (“not at all strong” to “very strong”) and prospective consumption (“none at all” to “a large amount”).

RNA isolation, sequencing and transcriptomic analysis

Total RNA was extracted from SAT using the RNEasy Lipid Tissue Mini kit (Qiagen, Hilden,

Germany) according to the manufacturer's recommendations. RNA quality was assessed using Agilent 2200 TapeStation system (Agilent Technologies, Amsterdam, Netherlands) and RNA-seq libraries were performed using Illumina's TruSeq RNA library Preparation kit (Illumina, San Diego, CA, USA). Libraries were sequenced using an Illumina HiSeq 2500 with 50-bp single-read chemistry. Sequenced reads were mapped and annotated to the human genome using Star v2.5.3a (Dobin et al., 2013). After removing genes with < 10 counts combined across all samples, the remaining genes were normalized using Trimmed Mean of M-values normalization and dispersion was estimated using edgeR (Robinson et al., 2010). Analysis of differentially expressed genes was carried out via edgeR, with designs that accounted for pre- and post- intervention. Statistically differentially expressed gene expression was assessed using a likelihood ratio test and corrected for multiple hypotheses testing using the Benjamini-Hochberg method (false discovery rate [FDR] <0.05). The lists of differentially expressed genes after TRE were imported in Molecular Signatures Database (MSigDB) for enrichment analysis of Gene Ontology (GO) pathways (overrepresentation analysis, ORA). The fold changes and FDR values from all available genes for gene set enrichment analysis (GSEA) (Subramanian et al., 2005), GSEA algorithm and MSigDB collection (http://software.broadinstitute.org/gsea/msigdb) were used for querying C5: GO pathways. Only gene sets consisting of more than 10 and fewer than 500 genes were taken into account. Statistical significance of GSEA results was determined using 1,000 permutations.

Statistical analysis

The AUC was calculated using the trapezoidal rule. Statistical analysis was conducted using linear mixed model regression, with effects of TRE (baseline vs week 8) and mealtime (breakfast vs. dinner) as fixed factors, and a random factor for participant ID with an unstructured covariance matrix to account for the repeated visits (at baseline and week 8). All other anthropometric and biochemical results were analyzed using a paired sample t-test (two-

sided) with the level of significance set at <0.05. Correlation between weight loss and the changes in fasting glucose, HbA1c, glucose AUC at breakfast and dinner were performed by Spearman. Statistical analysis was performed using R software (version 3.6.1; The R Foundation for Statistical Computing, Vienna, Austria) and SPSS (Version 25, IBM, Armonk, New York).

Power calculation

Sample size requirements were calculated on the primary endpoint reduction in glucose AUC in response to a mixed meal. The study was powered to detect a 0.6 mmol/L/hour change in glucose AUC from baseline, assuming the within-group variance is 0.7 mmol/L/hour (Hutchison et al., 2019b), with two-sided $\alpha = 0.05$ and statistical power of 80%.

5.5 Results

Fifteen men (Mean ± standard deviation [SD], age 63 ± 4 years, BMI 30.5 ± 2.4 kg/m^2, waist circumference 113 ± 4 cm) were recruited into and completed the study. Baseline characteristics are presented in Table 5.1.

Daily eating duration, adherence, calorie intake, and physical activity

Mean percent adherence to logging was 87 ± 26 % during baseline, and 88 ± 10 % during TRE. The 95% eating window at baseline was 14.6 ± 1.0 hours and was reduced to 10.6 ± 1.0 hours after TRE (P<0.0001; Figure 5.2A-B). Participants chose to shorten both ends of their eating window with an average time of the first or last caloric event occurring 1.3 ± 0.5 hours later or 1.7 ± 0.7 hours earlier than baseline (Figure 5.2C-D). The estimated average daily energy intake was not significantly changed by the intervention (Supplementary Table 5.2). There was no effect of TRE on sleep duration, sleep onset time, and sleep end time. The number of steps per day and average energy expenditure by accelerometers was decreased by TRE (both P<0.05)

(Supplementary Table 5.3).

Anthropometric and biochemical results

A significant reduction in body weight (*P*=0.015), waist circumference (*P*=0.014), visceral fat mass (*P*=0.020), percent body fat (*P*=0.010), fasting plasma glucose (*P*=0.026) and HbA1c (*P*=0.008) was observed (Table 1). There was no change in blood pressure, fasting insulin, total cholesterol, HDL-c, triglycerides, or NEFA (all *P*>0.05). There was no correlation between weight loss and the changes in any measure of glycaemia (*P*>0.05).

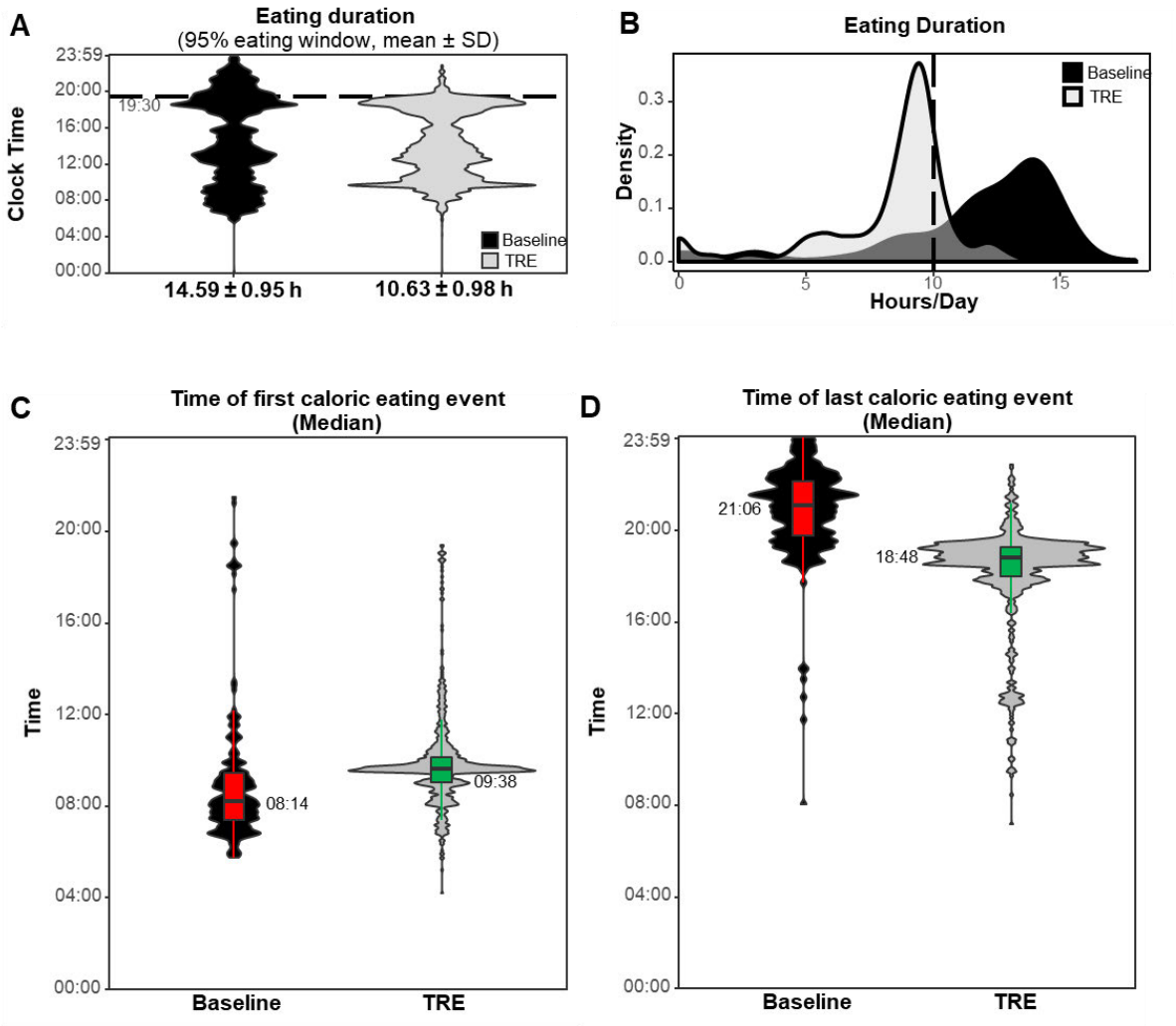


Figure 5.2 Eating duration and time of first and last meal pre- and post- time restricted eating.

[**A)** Violin plot of the time of caloric eating events at baseline and during the intervention. This figure depicts the density of daily caloric eating events at baseline (black, W-2 to W0) and during the intervention (grey, W0 to W8). A reference horizontal black long dash line is presented at (0, 1930), which was the latest eating time frame allowed (0930 to 1930 PM). Data are presented as mean ± SD. **B)** Density plot of daily eating duration at baseline and during time restricted eating (TRE). Daily eating intervals were calculated as the time interval during which 95% of all calorie-containing ingestion events occurred during baseline or intervention period. Adherence to a designated eating window was determined by the number of days in which a participant was adherent to logging and all caloric food items were contained within a 15-min buffer on each side of the self-selected 10-h eating window. A reference vertical long dash line is presented at (10hours/day, 0). **C, D)** Violin plot of the time of first (C) and last (D) caloric eating events at baseline and during TRE intervention. This figure depicts the density of daily first and last caloric eating events at baseline (black/red, 2 weeks prior to the TRE) and during the intervention (grey/green, 8 weeks). Data were presented as median.]

Table 5.1 Body composition and metabolic disease risk factors at baseline and after 8 weeks of 10-hour time restricted eating (N=15)[1]

	Baseline	Week 8	P-value[1]
Body weight (kg)	95.2 ± 12.2	92.9 ± 10.8	**0.015**
BMI (kg/m^2)	30.5 ± 2.4	29.8 ± 2.1	**0.010**
Waist circumference (cm)	113 ± 9	109 ± 8	**0.014**
Total fat mass (kg)	32.8 ± 7.1	30.7 ± 1.5	**0.020**
Visceral fat mass (kg)	3.0 ± 1.2	2.7 ± 1.0	**0.020**
Fat mass (%)	34.3 ± 1.2	32.9 ± 1.2	**0.010**
SBP(mmHg)	136 ± 19	131 ± 14	0.229
DBP(mmHg)	83 ± 10	82 ± 9	0.732
Fasting glucose (mmol/L)	5.7 ± 0.4	5.4 ± 0.4	**0.026**
Fasting insulin (mU/L)	11.0 ±6.9	10.4 ± 7.1	0.278
HbA1c (%)	6.1 ± 0.3	5.9 ± 0.3	**0.008**
Triglyceride (mmol/L)	1.7 ± 0.6	1.8 ± 0.7	0.474
NEFA (mmol/L)	0.46 ± 0.18	0.43 ± 0.24	0.414
Total Cholesterol (mmol/L)	5.1 ±1.1	5.2 ± 1.0	0.495
HDL-c (mmol/L)	1.06 ± 0.21	1.08 ± 0.26	0.406

[1]Data are presented as Mean ± SD. Statistical analysis was performed using paired *t*-test. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, haemoglobin A1c; NEFA, non-esterified fatty acids; HDL-c, high-density lipoprotein-cholesterol.

Glucose response to standard meal test from laboratory measurement and CGM

A mealtime by TRE interaction was observed for the primary outcome glucose AUC (*F*=16.418, *P*<0.001, Figure 5.3A). TRE did not significantly reduce breakfast glucose AUC (-0.25 ± 0.16 mmol/L/h, *P*=0.131) and increased the dinner glucose AUC (0.51 ± 0.11 mmol/L/h, P<0.001). We observed a similar result from the CGM as the laboratory-based glucose measures in the mealtime by TRE interaction (*F*=11.780, *P*=0.004, Figure 5.3B), except glucose AUC was significantly reduced at breakfast (-0.5 ± 0.2 mmol/L/h, *P*=0.012), and tended to increase at dinner (0.4 ± 0.2 mmol/L/h, *P*=0.124). A trend towards a reduction in 24-hour mean glucose by CGM (-0.21 ± 0.11 mmol/L, *P*=0.089, Figure 5.3B) was also observed.

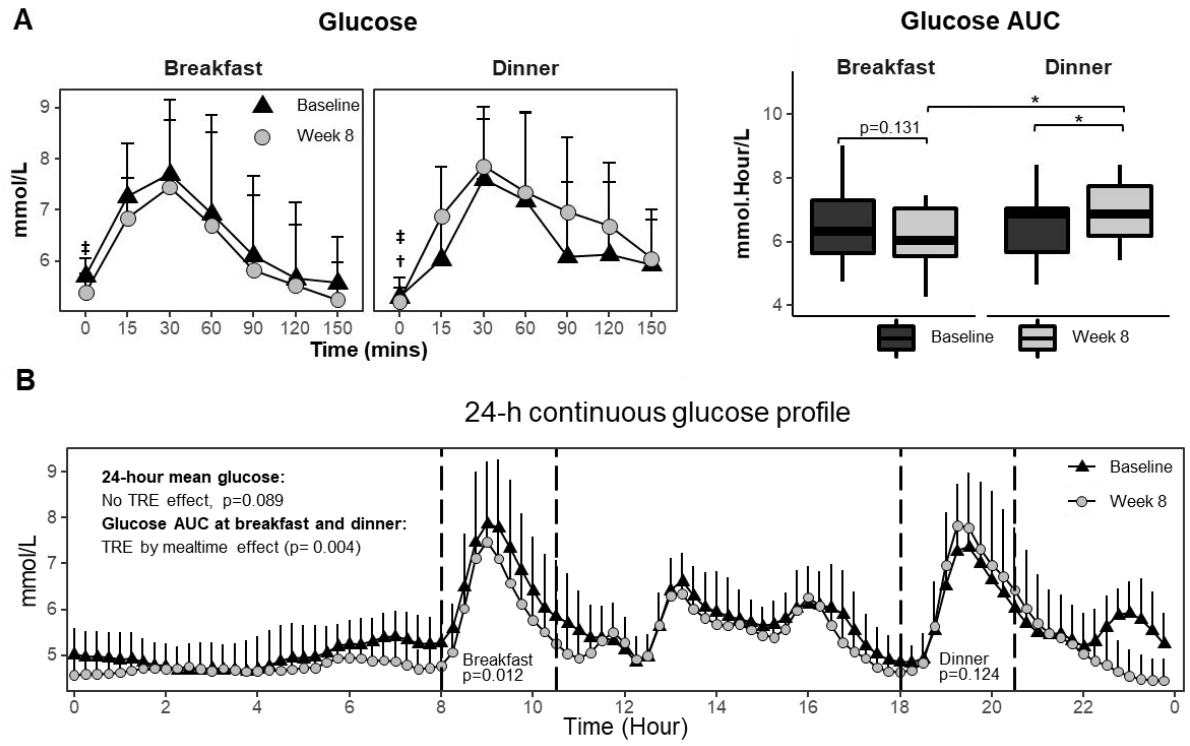


Figure 5.3 Glucose response to standard meal test from laboratory measurement and continuous glucose monitors (CGM).

[**A)** Glucose area under curve (AUC) responses to a standardized, mixed meal test over 2.5 hours at baseline and after 8 weeks of time restricted eating (TRE). Data are presented as mean

± SD (N=15). Boxplots are showing AUCs in median (interquartile range). Statistical analysis was performed using linear mixed-effects modelling, with effects of mealtime (breakfast vs dinner) and TRE (baseline vs Week 8) as fixed factors and ID as a random factor. * Mealtime by TRE interactions (P<0.01) on AUC; ‡ TRE effect (P<0.05, vs baseline) on pre-meal glucose; † mealtime effect (P<0.05, breakfast vs dinner) on pre-meal glucose (Time 0). AUC, area under the curve. **B)** 24-hour 15-minutely glucose profile from continuous glucose monitoring (CGM) at baseline (black triangle, N = 13) and after 8 weeks of TRE (grey circle, N = 14). Vertical lines represent meal tests conducted at breakfast and dinner. Data were plotted as mean ± SEM at each time point on metabolic test days, from midnight to midnight at baseline (black bar) and week 8 (grey bar). Glucose AUC calculated from CGM data aligns with the meal tests over 2.5 hours at baseline and week 8. Statistical analysis was performed using linear mixed effect modelling, with effects of mealtime (breakfast vs dinner) and TRE (baseline vs week 8) as fixed factors and ID as a random factor. There was a mealtime by TRE interaction (*P*=0.004), *post-hoc* tests showed that glucose AUC by CGM was lower after TRE than at baseline (*P*=0.012).]

Insulin, gastrointestinal hormone, triglyceride, and NEFA responses to meal test

There were no significant effects of TRE or mealtime on pre-meal and postprandial insulin (Figure 5.4A). There was an effect of mealtime on pre-meal ghrelin (*F*=10.442, *P*=0.007, Figure 5.4B) and postprandial ghrelin AUC (*F*=13.244, *P*=0.003, Figure 5.4B), with both being higher at dinner vs breakfast. Pre-meal GLP-1 was also higher at dinner (mealtime effect, *F*=12.945, *P*=0.003, Figure 5.4C) and tended to be increased by TRE (TRE effect, *F*=4.588, *P*=0.056). There were no significant effects on postprandial GLP-1. There was a TRE by mealtime interaction for pre-meal GIP (*F*=9.200, *P*=0.009, Figure 5.4D), which was increased by TRE at dinner (*P*=0.003). There was an effect of TRE (*F*=10.452, *P*=0.007, Figure 5.4D) and mealtime (*F*=9.046, *P*=0.010, Figure 5.4D) on postprandial GIP, which was increased by TRE, and at dinner. Pre-meal and postprandial triglyceride was higher at dinner (mealtime effect, *F*=21.287,

P<0.001; *F*=23.070, *P*=0.003, respectively, Figure 5.4E). Pre-meal NEFA was higher at breakfast (mealtime effect, *F*=10.375, *P*=0.006, Figure 5.4F) while the suppression of postprandial NEFA tended to be greater following TRE (TRE effect, *F*=4.334, *P*=0.056).

Subjective appetite responses to standard meal test

There were no significant mealtime by TRE interactions for subjective measures of appetite, except postprandial desire to eat (*F*=5.349, *P*=0.035, Supplementary Figure 5.2A), which was reduced at dinner vs breakfast following TRE (*P*=0.001). TRE reduced pre-meal desire to eat (*F*=8.593, *P*=0.011, Supplementary Figure 5.2A), hunger (*F*=6.388, *P*=0.024, Supplementary Figure 5.2B), prospective consumption (*F*=13.066, *P*=0.003, Supplementary Figure 5.2D) and increased feelings of pre-meal (*F*=4.810, *P*=0.046, Supplementary Figure 5.2C) and post-prandial fullness (*F*=7.145, *P*=0.018, Supplementary Figure 5.2C). Mealtime effects were also evident with reduced feelings of postprandial hunger (*F*=11.637, *P*=0.004; Supplementary Figure 5.2B), and prospective consumption (*F*=5.484, *P*=0.034; Supplementary Figure 5.2D) and increased feeling of fullness (*F*=6.048, *P*=0.028; Supplementary Figure 5.2C) at dinner versus breakfast.

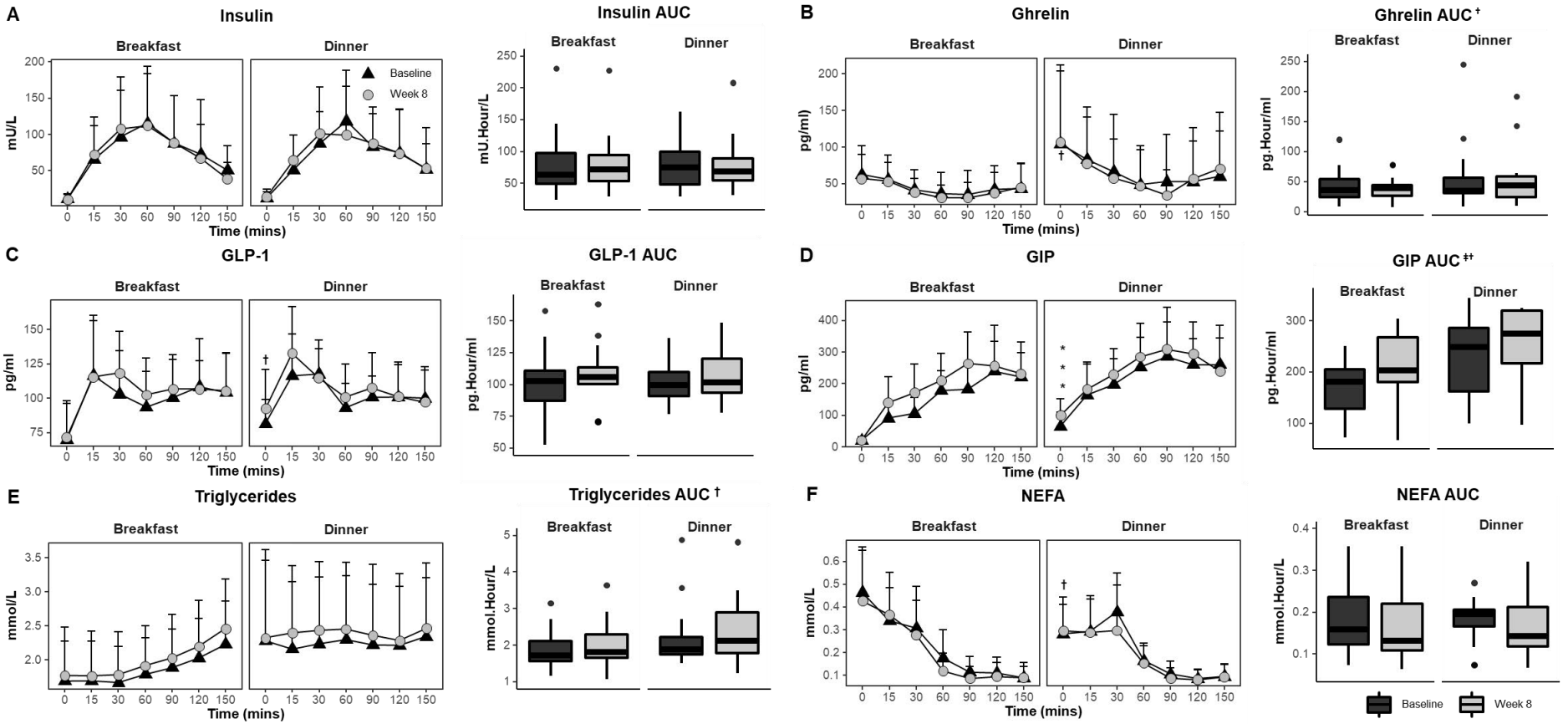


Figure 5.4 (A) insulin, (B) ghrelin, (C) glucagon-like peptide-1 (GLP-1), (D) glucose-dependent insulinotropic peptide (GIP), (D) triglycerides and (E) Non-esterified fatty acid (NEFA) area under curve (AUC) responses to a 2.5 hour, standardized, mixed-nutrient meal test at baseline and after 8 weeks of time restricted eating.

[Data are presented as mean ± SD (N=15). Boxplots are showing AUCs in median (interquartile range). Statistical analysis was performed using linear mixed effect modelling, with effects of mealtime (Breakfast vs Dinner) and TRE (Baseline vs Week 8) as fixed factors and ID as a random factor. * P<0.01 Mealtime by TRE interactions (Pre-meal GIP levels were higher at 1800h vs 0800h at baseline and week 8; pre-meal GIP at 1800h were increased by TRE, therefore three * presented in the figure); ‡ TRE effect (P<0.05, Baseline vs Week 8) on AUC; † mealtime effect (P<0.05, Breakfast vs Dinner) on AUC or pre-meal values (Time 0). mins, minutes.]

Biological pathways enriched in human adipose tissue in response to TRE

We assessed transcriptional changes in adipose tissue in response to TRE and observed 319 genes were differentially expressed, 117 genes were upregulated and 202 genes were downregulated (APPENDIX A-1). To analyse the effects of TRE on biological pathways, we first performed GO pathways ORA analysis of differentially expressed genes. With a cut-off value of FDR<0.05, 107 pathways were downregulated by TRE and none were upregulated (APPENDIX A-2). We report the top ten terms ranked by enrichment ratio of significantly enriched terms with FDR < 0.05. These terms are involved in phospholipase and lipase inhibitor activity, proteasome function, telomerase activity, chaperone complex, apoptotic signalling pathway, and oxidoreductase activity (Figure 5.5). Subsequent GSEA analysis of GO terms revealed 4 upregulated gene sets and 34 downregulated gene sets (APPENDIX A-3 and Supplementary Figure 5.3). Mitochondrial function were enriched in the top 10 pathways from the GSEA analysis, and were also significant downregulated in ORA, but not within the top 10 pathways. The upregulated sets included antimicrobial humoral immune response, cytokine receptor activity and disruption of cells of other organism involved in symbiotic interaction. The list of genes that were significantly altered in each pathway is provided in APPENDIX A-4.

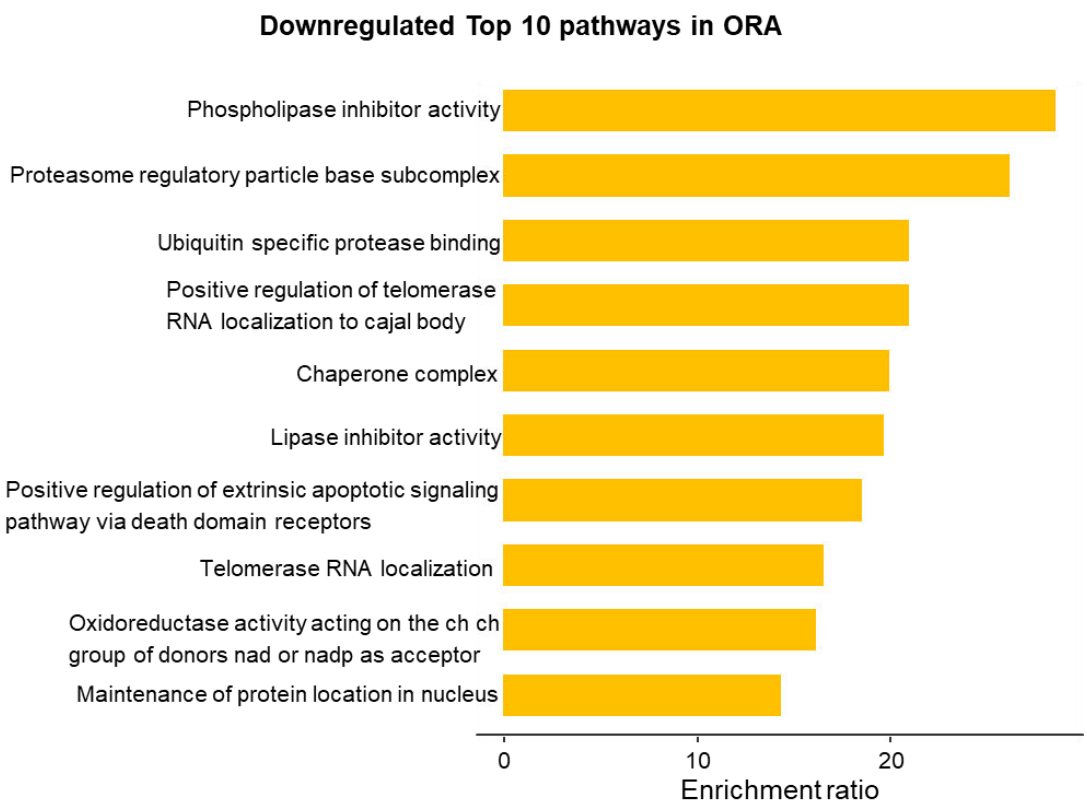


Figure 5.5 Gene ontology (GO) pathway analysis of downregulated gene list after time restricted eating in human abdominal subcutaneous adipose tissue.

[GO was performed using overrepresented analysis (ORA) with up or downregulated genes. Bars represent the enrichment ratio of downregulated pathways (in orange) (APPENDIX A-2)]

5.6 Discussion

The study showed that TRE did not alter glucose responses to breakfast and increased the glucose response at dinner, but reduced body weight and fat mass, fasting glucose, glycated haemoglobin and 24-hour glucose profiles and increased GIP, suggesting that TRE likely had a net beneficial effect on glucose metabolism. TRE also attenuated energy-dependent pathways involved in proteasome function and mito-ribosome regulation in adipose tissue.

The postprandial glucose and insulin responses to a breakfast meal were not significantly altered by TRE. Previous studies have shown that TRE improved glucose tolerance in mice

(Hatori et al., 2012, Chaix et al., 2014) and in men with obesity when assessed at breakfast (Hutchison et al., 2019b). Other studies have shown no change in postprandial glucose response at breakfast after 5 days (Parr et al., 2020b) or 5 weeks of TRE (Sutton et al., 2018). Postprandial insulin levels were reduced in the latter study, suggesting TRE improved insulin sensitivity (Sutton et al., 2018). In the present study, TRE tended to increase the suppression of NEFA after breakfast and dinner, suggesting an improvement in adipose tissue insulin sensitivity (Karpe et al., 2011), but this requires qualification by tracer studies. Improved adipose tissue insulin sensitivity is associated with improved systemic glucose tolerance (Morley et al., 2015), but there was no change in genes involved in insulin signalling in adipose tissue in this study.

Reductions in fasting blood glucose are universally reported in response to TRE (Wilkinson et al., 2019, Chow et al., 2020), and may reflect an improvement in hepatic insulin sensitivity or are a result of the longer fasting period imposed by a TRE protocol as partial depletion of hepatic glycogen stores likely contribute to reduced fasting glucose (Cherkas and Golota, 2014, Cherkas et al., 2020). However, few studies have investigated day long glucose control, and thus TRE may only be shifting the glycaemic profile. Unexpectedly, we observed a poorer glucose response at dinner following TRE. The underpinning reason for this is unclear. Light exposure, caloric, and macronutrient intakes and the 3-day lead-in diet prior to testing were identical pre- and post-intervention, but there was a greater cumulative energy intake at dinner post TRE by design. In the only other study that has investigated glucose response at dinner, there was no change in postprandial glucose or insulin after 5 days of TRE (Parr et al., 2020b). Reassuringly, fasting glucose and HbA1c was reduced by TRE in the present study and there was a tendency for TRE to reduce 24-hour mean glucose by CGM, suggesting a net effect to improve glycaemia, which was independent of weight loss. The majority of previous studies have not observed changes in 24-hour glucose by CGM (Hutchison et al., 2019b, Wilkinson et al., 2019, Chow et al., 2020), which may be related to small sample size and the free-living

environment. One other study conducted in a metabolic chamber, also showed a significant (0.22 mmol/L) reduction in 24-hour glucose by CGM (Sutton et al., 2018), which is similar in magnitude to the reduction observed in our study.

Our data are in agreement with some studies suggesting that TRE increased fullness and reduced pre-meal hunger, desire to eat, and prospective consumption in the evening (Sutton et al., 2018, Gill and Panda, 2015). Interestingly, altered subjective appetite feeling in response to TRE may induce a shift in preference to eat earlier in the day, which could promote weight loss and glyceamic control (Jakubowicz et al., 2013, Jakubowicz et al., 2015a, Jakubowicz et al., 2017a, Fuse et al., 2012). However, there was no detectable effect on postprandial ghrelin or GLP-1, but GIP was elevated by TRE. GIP displays a bi-functional regulation of glucose homeostasis (Christensen, 2016, Christensen et al., 2011), stimulating glucagon secretion in the fasting state and insulin secretion when glucose levels are elevated (Christensen, 2016, Christensen et al., 2011). An increase GIP AUC at dinner should therefore have stimulated insulin secretion (Christensen, 2016, Christensen et al., 2011), slowed gastric emptying, and flattened the glucose curve, which did not occur. Potentially increased insulin clearance or the complicated interplay between different incretins (Tong et al., 2010) could explain this result.

Consistent with a recent systematic review and some RCTs, we found that TRE reduced body weight and fat mass (Peeke et al., 2021, Adafer et al., 2020, Moon et al., 2020). However, another RCT showed no difference in body weight in response to 8-hour TRE versus control (Lowe et al., 2020). Of note, the latter study had a high dropout rate, and no measurement of patient adherence to TRE. At least part of the appeal of TRE is that health benefits may occur independently of reduced food intake (Sutton et al., 2018). In this study, despite giving no instruction to reduce food intake, we observed modest reductions in body weight and fat mass, alongside a small reduction in the number of steps per day. This suggests there was a small spontaneous reduction in food intake, as has been reported previously (Gabel et al., 2018a,

LeCheminant et al., 2013), although this was not statistically significant.

Our pathway analysis of differentially expressed genes in SAT revealed the downregulation of key genes in mitochondrial biogenesis and oxidative phosphorylation. In particular, genes encoding subunits of mito-ribosome (MRPS35, MRPL33, MRPL51), mitochondrial ribosome proteins translocation (TOMM7, TOMM 22), and the electron transport chain and ATP synthase (NDUFA12, NDUFS5, ATP5F1E, ATP5PD). Whilst changes in mitochondrial biogenesis and oxidative phosphorylation in humans in response to TRE has not been previously evaluated, caloric restriction is known to attenuate pathways involved in oxidative phosphorylation in adipose tissue (Lam et al., 2016). Potentially, this could reduce mitochondrial reactive oxygen species production, and slow aging (Pamplona and Barja, 2006). In mice, TRE increased mitochondrial density in liver (Hatori et al., 2012), but reduced mitochondrial electron transport chain activity in *Drosophila* heart (Gill et al., 2015). Thus, there may be species and tissue-specific mitochondrial adaptions in response to TRE.

Chaperone complexes assist the conformational folding of macromolecular structures (Gestaut et al., 2019). TRE also decreased the expression of molecular chaperone HSP90, and components of the chaperonin-containing T-complex (TRiC), namely CCT7 and CCT8. HSP90 plays a principal role in assembly and maintenance of the 26S proteasome, which is responsible for the degradation of intracellular proteins for recycling (Tanaka, 2009). Several other genes involved in proteasome function were also downregulated by TRE, including subunits of the 26S proteasome (PSMC2 and PSMC5, PSMD2), ubiquitin-specific protease binding (SELENOS, PARK7, VCP) and maintenance of protein location in the nucleus (SKP1, TXN, PARK7. Inhibition of proteasome activity is linked to adipocyte aging and insulin resistance (Díaz-Ruiz et al., 2015), and thus may be a negative consequence of TRE. Interestingly, downregulation of the proteasome pathway has also been reported in SAT following CR and 24-hour fasting in humans (Lam et al., 2016, Defour et al., 2020), and may be an adaptive

response to lowered energy availability and reduced mitochondrial oxidative stress (Masschelin et al., 2019). TRiC is also involved in the proper folding of cytoskeletal proteins (Gestaut et al., 2019) and telomerase biogenesis and localization (Freund et al., 2014). TRE was previously shown to increase the abundance of TRiC subunit RNAs in the *Drosophila* heart (Gill et al., 2015). Collectively, this study suggests that highly energetic pathways such as oxidative phosphorylation, proteasome and telomerase were downregulated by TRE. Similar to CR (Lam et al., 2016), this may be an adaptive response to the reduction in energy storage requirements or as a result from less damage created by mitochondrial reactive oxygen species (Pamplona and Barja, 2006). However, diurnal variations in the proteasome and telomerase pathways have also been reported (Park et al., 2019, Kim and Somers, 2017) and it is possible that TRE may have shifted the amplitude or phase, rather than induced a net dampening effect.

In mouse, pathway analysis of the SAT transcriptome showed downregulation of inflammatory pathways (Hatori et al., 2012, Chaix et al., 2014), which were not observed in this study in humans. However, TRE upregulated genes involved in anti-microbial humoral immune response, including lactoferrin. Lactoferrin plays a key role in the host defence against a broad range of microbial infections and anti-inflammatory activity and adaptive immunity (Ward et al., 2005). Individuals with obesity and T2DM displayed low levels of LTF gene expression in subcutaneous adipose tissue (Moreno-Navarrete et al., 2013). TRE could therefore be increasing adaptive immunity and may therefore be protective against pathogen infection in humans, but this requires further study.

The study has several limitations. It was an uncontrolled, short term, pre-post study with a small sample size to explore the day-long effects of TRE. The study was conducted solely in white males with obesity, and thus findings cannot be directly extended to females, people with T2DM, and individuals of other races. Modest weight loss was co-observed, and this rather than TRE, could have accounted for the beneficial health effects, although significance held after

adjustment for weight loss. TRE would likely have a more pronounced effect in liver as compared with adipose tissue, but this was not possible to obtain in this study. Finally, TRE may have resulted in a phase shift rather than any net effect on the adipose tissue transcriptome, which can only be assessed by serial sampling.

In conclusion, TRE had a net effect to improve glycaemic control and dampened energy-consuming pathways in the adipose tissue transcriptome, providing novel evidence that it could be a preventative tool for individuals with obesity who are at increased risk of T2DM, and may potentially be a therapeutic strategy for patients with prediabetes or T2DM.

Acknowledgements: The authors thank research in the SP lab is supported by NIH grants DK115214, and DK118278 and Robertwood Johnson Foundation grant 76014.

Funding: The research was funded by Diabetes Australia (Grant number Y18H-HEIL). LZ is supported by a Beacon of Enlightenment Scholarship from The University of Adelaide.

Data and resource availability: RNA-seq data from adipose tissue of this study are deposited in the Gene Expression Omnibus (GEO) repository (accession number GSE168705) and are available upon reasonable request.

Disclosure of interests: Gary A Wittert has received research funding for testosterone pharmacology studies (Weight Watchers, Bayer), speakers (Besins, Bayer, World Obesity), expert testimony (Australian Health Practitioners Regulation Agency), International Advisory Board (Bayer) and consultancy (Elsevier) fees. Satchidananda Panda is the author of the book "The Circadian Code" for which he receives author royalty from PenguinRandomHouse Company. The other authors declared no conflict of interest.

Author contributions: LKH, ATH, SB, GAW designed the research. LKH, ATH, BL, XTT and LZ collected data. LZ and LKH analysed plasma biomarkers and extracted high quality

mRNA from adipose tissue. LZ and CLY scored the visual analogue scales. GAW and CHT provided clinical support and supervision, LN and JA provided clinical support. ECM and SP supplied the *myCircadianClock* application. ECM, SP and HDL prepared adipose tissue for RNA sequencing. AEW performed adipose tissue RNA-seq data analysis. SB supervised metabolic test days during the ward stay at the sleep and chronobiology laboratory. LZ performed statistical analysis and data visualization. All authors contributed to the data interpretation and preparation of the manuscript. LKH had full access to the data and had primary responsibility for the final publication.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT03590158

SUPPLEMENTARY MATERIAL FOR CHAPTER 5

Supplementary Table 5.1 Standard meal macronutrient composition

Foods(Quanity)	Energy (kJ)	Carbohydrate (g)	Protein (g)	Total fat (g)	Fibre (g)
Honey (10g)	142	8.3	0	0	0
White loaf (40g)	432	19.1	3.8	0.9	1.2
Fruit salad in juice (130g)	333	18.5	0.4	0.1	1.7
Quiche (140g)	1652	28.1	11.6	25.9	2.1
Chocolate milk (250ml)	588	17.3	9.8	3.5	0

g, grams; mL, millilitres; kJ, kilojoules.

Supplementary Table 5.2 Calculated energy and macronutrient intakes at baseline and after 8 weeks of 10-hour time restricted eating[1, 2]

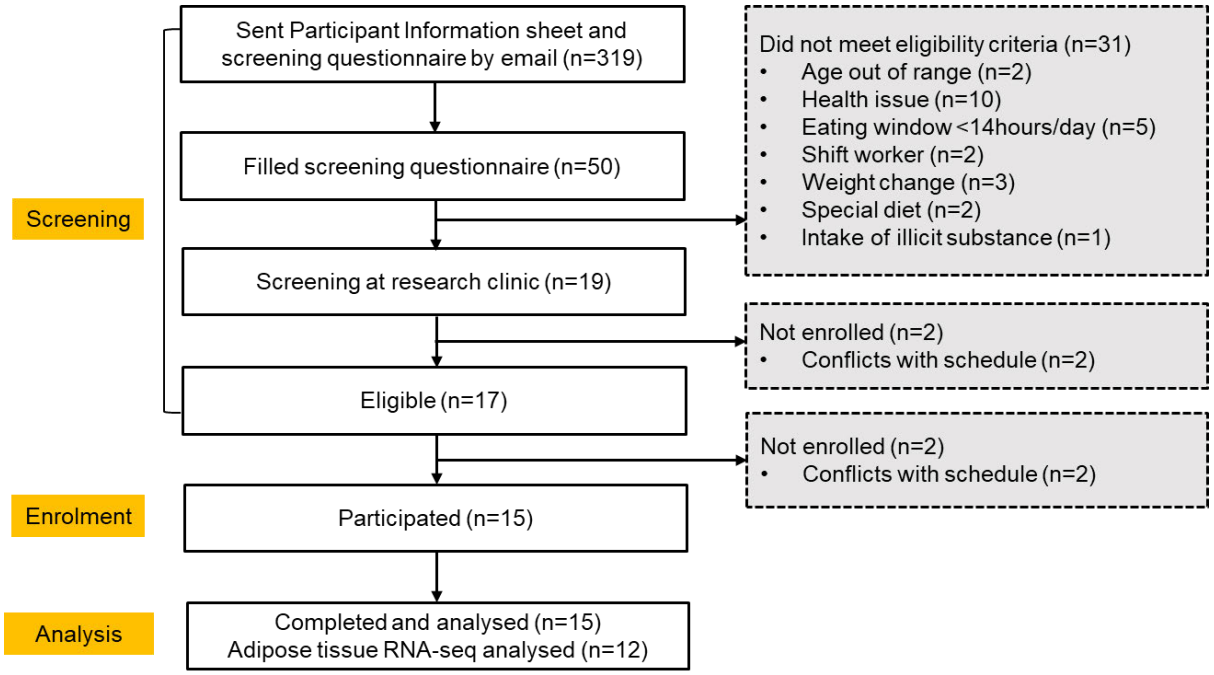
	Baseline	Week 8	P-value
Daily calorie intake(kcal/day)	2365±82	2246±75	0.295
Carbohydrate (g/day)	254±12	231±11	0.063
Total fat (g/day)	92±4	90±3	0.704
Saturated fat (g/day)	39±2	37±1	0.536
Protein (g/day)	97±3	97±3	0.869

[1]Data are mean ± SEM. [2]Energy and macronutrient intakes were calculated based on food intake photographs and descriptions from the *myCircadianClock* application. [3]Statistical analysis was performed using paired *t*-test. kcal, kilo calorie; g, gram.

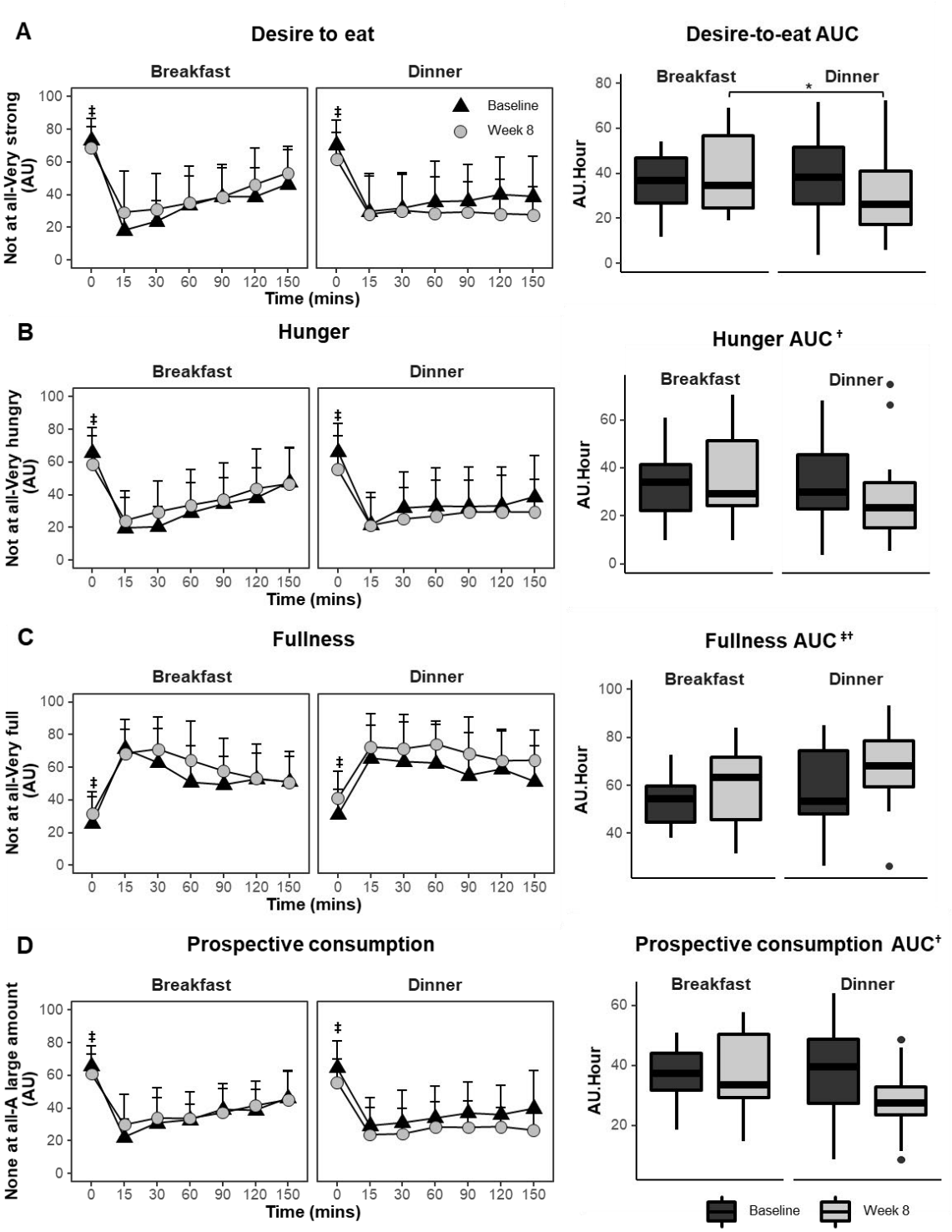
Supplementary Table 5.3 Daily physical activity and sleep patterns at baseline and after 8 weeks of 10-hour time restricted eating[1,2]

Parameters	Baseline	Week 8	P-value[3]
Wear time (%)	98.5 ± 0.6	98.8 ± 0.3	0.506
Non-wear time (%)	1.5 ± 0.6	1.2 ± 0.3	0.839
Sedentary PA/Day (Hours)	11.9 ± 0.3	12.5 ± 0.3	**0.015**
Light PA/Day (Hours)	8.9 ± 0.3	8.8 ± 0.3	0.385
Moderate PA/Day (Hours)	2.7 ± 0.2	2.4 ± 0.1	**0.034**
Vigorous PA/Day (Hours)	0	0	
Average MVPA /Day (Hours)	2.7 ± 0.2	2.4 ± 0.1	**0.034**
Steps/Day	12764 ± 844	11662 ± 740	**0.039**
Sleep duration (hh:mm)	06:53 ± 00:12	06:48 ± 00:10	0.510
Sleep onset time (hh:mm)	23:10 ± 00:11	23:17 ± 00:12	0.288
Sleep end time (hh:mm)	06:36 ± 00:11	06:37 ± 00:11	0.834

[1]Data are presented as mean ± SEM, N=15. [2]Measures of activity assessed by ActiGraph accelerometer for 2 weeks at baseline and 2 weeks prior to time restricted eating conclusion. [3]Statistical analysis was performed using paired *t*-test. PA: physical activity, MVPA: Moderate to vigorous physical activity.

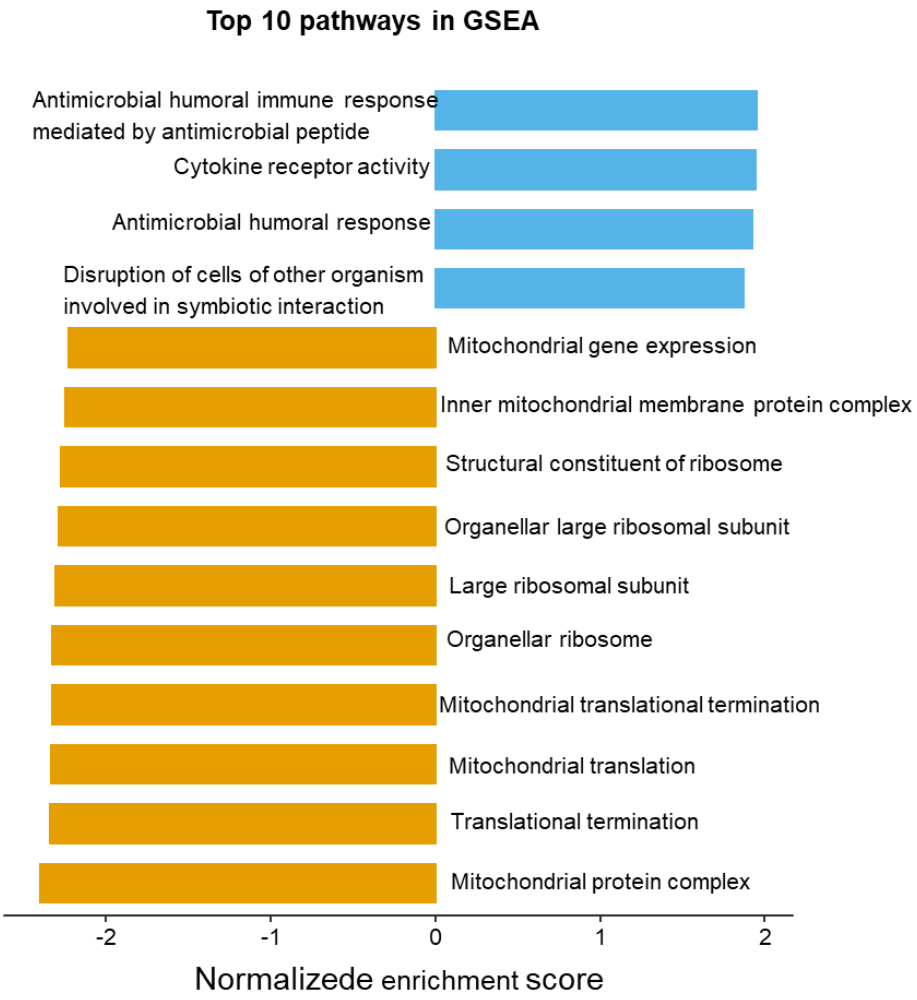


Supplementary Figure 5.1 Participant recruitment and study flow diagram.



Supplementary Figure 5.2 (A) Desire to eat, (B) Hunger, (C) Fullness, and (D-d) prospective consumption area under the curve (AUC) responses to a 2.5 hour, standardized, mixed-nutrient meal test at baseline and after 8 weeks of time restricted eating.

[Data are presented as mean ± SD (N=15). Boxplots are showing AUCs in median (interquartile range). Statistical analysis was performed using linear mixed effect modelling, with effects of mealtime (Breakfast vs Dinner) and TRE (Baseline vs Week 8) as fixed factors and ID as a random factor. * Mealtime by TRE interactions (P<0.001, vs dinner at Week 8) on AUC; ‡ TRE effect (P<0.05, Baseline vs Week 8) on AUC or pre-meal values (Time 0); † mealtime effect (P<0.05, Breakfast vs Dinner) on AUC. AUC, area under the curve; AU, arbitrary unit; mins, minutes.]



Supplementary Figure 5.3 Gene ontology (GO) pathway analysis of ranked gene list after time restricted eating in human abdominal subcutaneous adipose tissue.

[GO was performed using gene sets enrichment analysis (GSEA). Bars represent the normalized enrichment score of upregulated (in blue) or downregulated (in orange) pathways (APPENDIX A-3).]

CHAPTER 6 TIME RESTRICTED EATING ALTERS THE 24-HOUR TRANSCRIPTOMIC PROFILE IN HUMAN ADIPOSE TISSUE

Lijun Zhao [1,2], Amy T Hutchison[1,2], Bo Liu[1,2], Gary A Wittert[1,2], Campbell H Thompson[1,3], Leanne Nguyen[3], John Au[3], Andrew Vincent[1], Emily N. C. Manoogian[4], Hiep D Le[4], April E Williams[4], Siobhan Banks[5], Satchidananda Panda[4], Leonie K Heilbronn[1,2,6]

[1] Adelaide Medical School, University of Adelaide, Adelaide, South Australia 5000, Australia

[2] Lifelong Health Theme, South Australian Health and Medical Research Institute, Adelaide, South Australia 5000, Australia

[3] Royal Adelaide Hospital, Adelaide, South Australia 5000, Australia

[4] Salk Institute for Biological Studies, La Jolla, California, 92037, USA

[5] University of South Australia, Justice and Society, Behaviour-Brain Body Research Centre, South Australia, 5000, Australia

[6] Corresponding author and lead contact

Statement of Authorship

Title of Paper	Time restricted eating alters the 24-hour transcriptomic profile in human adipose tissue
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Lijun Zhao, Amy T Hutchison, Bo Liu, Gary A Wittert, Campbell H Thompson, Leanne Nguyen, John Au, Andrew Vincent, Emily N. C. Manoogian, Hiep D Le, April E Williams, Siobhan Banks, Satchidananda Panda, Leonie K Heilbronn. Time restricted eating alters the 24-hour transcriptomic profile in human adipose tissue.

Principal Author

Name of Principal Author (Candidate)	Lijun Zhao		
Contribution to the Paper	Commenced the study, collected data, performed lab work, analysed data, wrote manuscript and approved final manuscript.		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	23 July 2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis: and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Amy T Hutchison		
Contribution to the Paper	Designed the study, collected data and interpreted the data and approved final manuscript. Edited the manuscript.		
Signature		Date	20/08/2021

Name of Co-Author	Bo Liu		
Contribution to the Paper	Collected data and approved final manuscript. Edited the manuscript.		
Signature		Date	20/08/2021

Name of Co-Author	Gary A Wittert		
Contribution to the Paper	Gary A Wittert Designed the study, collected biopsies and edited and approved the final manuscript clinical supervision, interpreted the data and approved final manuscript. Edited the manuscript.		
Signature		Date	19/08/2021

Name of Co-Author	Campbell H Thompson		
Contribution to the Paper	Collected biopsies and approved final manuscript.		
Signature		Date	20. AUG. 2021

Name of Co-Author	Leanne Nguyen		
Contribution to the Paper	Collected biopsies and approved final manuscript.		
Signature		Date	19/8/21

Name of Co-Author	John Au		
Contribution to the Paper	Collected biopsies and approved final manuscript.		
Signature		Date	19/8/21

Name of Co-Author	Andrew Vincent		
Contribution to the Paper	Asissted statistics for analysing data and approved final manuscript. Edited the manuscript.		
Signature		Date	24/8/21

Name of Co-Author	Emily N. C. Manoogian		
Contribution to the Paper	Supplied the myCircadianClock application, contributed to data interpretation and approved final manuscript. Edited the manuscript.		
Signature		Date	8/19/2021

Name of Co-Author	Hiep D Le		
Contribution to the Paper	Performed RNA sequencing and approved final manuscript.		
Signature		Date	19/08/21

Name of Co-Author	April E Williams		
Contribution to the Paper	Analysed RNA sequencing data and approved final manuscript. Edited the manuscript.		
Signature		Date	20/8/21

Name of Co-Author	Siobhan Banks		
Contribution to the Paper	Designed the study, supervised metabolic test days during the ward stay at the sleep and chronobiology laboratory, contributed to the data interpretation and approved final manuscript. Edited the manuscript.		
Signature		Date	20/8/21

Name of Co-Author	Satchidananda Panda		
Contribution to the Paper	Supplied the myCircadianClock application, funded adipose tissue RNA sequencing, contributed to data interpretation and approved final manuscript. Edited the manuscript.		
Signature		Date	08/23/21

Name of Co-Author	Leonie K Heilbronn		
Contribution to the Paper	Designed, conducted and supervised the study, interpreted the data, approved final manuscript, and primary responsibility for the study and publication.		
Signature		Date	18/8/21

6.1 Study importance

What is already known about this subject?

- Time restricted eating (TRE) restores circadian rhythms in the animal model
- TRE improves glucose metabolism in humans
- TRE altered the circadian rhythm of amino acid metabolism in skeletal muscle

What are the new findings in your manuscript?

- TRE restored circadian rhythms in metabolites and glucoregulatory hormones
- TRE altered the clock gene expression and restored the circadian rhythms in genes controlling transcriptional regulation and vesicular translocation of glucose transporters in human adipose tissue

How might your results change the direction of research or the focus of clinical practice?

- The study provides the first evidence the TRE restores circadian rhythms to genes in adipose tissue in humans
- Providing potential mechanisms of TRE in regulating metabolic health in humans could be critical to translating the TRE into clinical practice

6.2 Abstract

Background

Time restricted eating (TRE) alters the transcriptomic profile and metabolome in human skeletal muscle. However, the effect of TRE on subcutaneous adipose tissue (SAT) clock genes and transcriptomic profile in humans have not been tested yet.

Aims: To investigate the effects of TRE on 24-hour metabolites, glucoregulatory hormones and SAT transcriptome.

Methods: Men with overweight and obesity (N=15, aged 63 ± 4 years, BMI 30.5 ± 2.4 kg/m^2) were recruited (NCT03590158). A 35-hour metabolic ward stay was conducted at baseline and after eight weeks of TRE (10 hours/day). Plasma glucose, non-esterified fatty acid (NEFA), triglyceride, insulin, ghrelin, glucagon-like peptide-1, and glucose-dependent insulinotropic peptide (GIP) were measured three hourly, and the SAT transcriptome was assessed six hourly. Dim light melatonin onset (DLMO) and cortisol area under the curve (AUC) were also examined.

Results: TRE did not alter DLMO but reduced morning cortisol AUC. TRE altered the 24-hour profile of insulin, NEFA, triglyceride and GIP. TRE increased CLOCK and NR1D2 and decreased PER1 and NR1D1 at 12am. The rhythmicity of 450 genes were altered by TRE detected by Spline regression analysis. Pathway analysis showed enrichment in transcription co-repressor activity, DNA binding transcription factor binding, regulation of chromatin organization and small GTPase binding pathways. Weighted Gene Co-expression Network Analysis of these 450 genes revealed three module eigengenes that were strongly correlated with BMI, insulin and NEFA.

Conclusion: TRE altered the rhythms of blood metabolites, insulin, and increased key clock genes, and restored the expression of genes involving in chromatin regulation and vesicular translocation of glucose transporters in human SAT.

Keywords: time restricted eating, circadian rhythms, adipose tissue, transcriptome, glucose, weighted gene co-expression network analysis

6.3 Introduction

The circadian system controls multiple behavioural and metabolic processes (Panda, 2016). At a molecular level, two transcriptional-translational feedback loops exist: period (Per1/2/3) and cryptochrome (Cry1/2) genes are positively regulated by transcription factors circadian locomotor output cycles kaput and brain and muscle ARNT like protein 1 complex (CLOCK:BMAL1/ARNTL), and are repressed by their own translation protein products PER/CRY; an additional loop established via the nuclear activators retinoic acid related orphan receptor (RORα/β/γ) and repressors nuclear receptor subfamily 1, group D, member 1 and 2 (NR1D1 and NR1D2), which regulate Bmal1 transcription (Sinturel et al., 2020). Nutrient signalling molecules are strong regulators of the clock genes in peripheral tissues such as liver and adipose tissue. Recently, insulin has been established as a time cue of circadian rhythms by driving the translation of PER2 in mouse liver and human adipose tissue (Crosby et al., 2019, Tuvia et al., 2021). Activation of insulin-pAKT-mTOR pathway also promotes the phosphorylation of glycogen synthase kinase 3 (GSK3), which increases the stability of PER proteins (Zheng and Sehgal, 2010). Whereas fasting activates AMP-activated protein kinase (AMPK) and nicotinamide phosphoribosyl transferase (NAMPT) pathways, reducing the stability and/or transcription of CRY and PER proteins (Lamia et al., 2009, Ramsey et al., 2009, Nakahata et al., 2009). Therefore, meal timing is a cue that entrains peripheral clocks and mistimed eating and shortened overnight fasting periods dampen peripheral clocks in mice (Hatori et al., 2012, Chaix et al., 2018).

Time restricted eating (TRE) limits the continuous eating duration to 6-10 hours by extending the time spent fasting (Sutton et al., 2018, Jones et al., 2020, Cienfuegos et al., 2020a, Wilkinson et al., 2019, Hatori et al., 2012, Chaix et al., 2014). In mice that are fed a high-fat diet, TRE reduced body weight gain and body fat accumulation, improved glucose tolerance and restored diurnal rhythms of core clock gene expression (Regmi et al., 2021, Hatori et al., 2012, Chaix et

al., 2014, Chaix et al., 2018). In humans, TRE decreased body weight by reducing calorie intake (Gabel et al., 2018a, LeCheminant et al., 2013, Gabel et al., 2018b, Cienfuegos et al., 2020a) and improved insulin sensitivity and β cell responsiveness independently of weight loss and reduced energy intake (Sutton et al., 2018). TRE also regulated the rhythmicity of transcriptional profiles involved in amino acid transport, but did not alter core clock gene expression in human skeletal muscle (Lundell et al., 2020). The effect of TRE on 24-hour adipose tissue transcriptomic profiles in humans remains untested.

Adipose tissue plays a vital role in the body's adaptive response to fasting by inhibiting de novo fatty acid synthesis and adipogenesis, and stimulating lipolysis, elevating circulating non-esterified fatty acid (NEFA) levels (Defour et al., 2020). There is clear evidence that individuals with obesity and type 2 diabetes (T2DM) have a flattened amplitude in the adipose tissue transcriptome, with <2% of expressed genes showing a diurnal rhythm, compared with 8% in lean individuals (Stenvers et al., 2019a). Acute fasting also alters the transcripts involved in circadian clocks in human adipose tissue (Loboda et al., 2009, Defour et al., 2020, Couto Alves et al., 2018). Accordingly, we hypothesised that TRE would alter 24-hour profiles of metabolites, glucoregulatory hormones, clock genes and rhythmic genes in human SAT.

6.4 Methods

Participants

Fifteen men (aged 40-70 years) with obesity (BMI 30.5 ± 2.4 kg/m^2; waist circumference 113 ± 4 cm). Other clinical characteristics of the study participants have been previously reported in Chapter 1.

Design

This study was designed as an open-label, pre-post trial, including 2-week baseline monitoring

and an 8-week TRE intervention. Individuals following a prolonged daily eating duration lifestyle (>12hr/day) during the baseline monitoring period were recruited to participate the study in the South Australia Health and Medical Research Institute (SAHMRI). First enrolment of participants was on July 17, 2018, and the trial was completed on April 3, 2019. The study was approved by the Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee, University of Adelaide, and the University of South Australia, and registered with ClinicalTrials.gov (NCT03590158). Written, informed consent was obtained from each participant prior to the enrolment.

In the two weeks prior to baseline and week 8 metabolic testing visit, activity levels and sleep patterns were measured by Actigraph (wGT3X-BT, ActiGraph LLC, FL, USA). All eating and drinking events for the entire 10-week study duration were photographed and annotated by photograph-based smartphone application "*myCircadianClock"* (mCC; https://mycircadianclock.org/, Satchidnanda Panda, Salk Institute, La Jolla, CA, USA). Prior to the metabolic testing visit, standardised foods were provided at 100% of calculated total daily energy requirements (50% of carbohydrate, 30% fat, 20% protein) for three days. Whole-body composition was assessed by Dual-energy X-ray absorptiometry.

Dietary intervention

Participants were instructed to eat their habitual diets within a self-selected consistent 10-hour time frame each day for 8 weeks (the latest eating occasion was to be completed by 7:30 pm). Water and energy-free beverage consumption were allowed *ad libitum*. No other dietary instructions were provided, but participants were asked to maintain their usual daily physical activity and sleep patterns.

Procedures during metabolic ward stay

Metabolic testing was performed in a light, noise, and temperature-controlled sleep and chronobiology laboratory (Figure 6.1A). Four participants per run arrived at 4:30 pm, the afternoon prior to testing. Dinner was provided at 6:30 pm, and an 8-hour sleep opportunity was provided at 10 pm. For periods of wakefulness, light intensity was < 50 lx and < 0.03 lx during sleep. On the metabolic testing day, three meals and two snacks were provided at calculated energy balance based on the sedentary activity levels. The timing of meals differed between baseline and week 8, where snack 2 was either consumed between a 14-hour prolonged eating window of 8 am to 10 pm (10 pm at baseline) or a 10-hour restricted eating window of 8 am to 6 pm (10:30 am at week 8). Water was allowed *ad libitum*.

The metabolic testing day started at 6 am followed by an overnight fast and completed at 3 am the following day (i.e., for a 24-hour period) to obtain a total of four subcutaneous adipose tissue (SAT) biopsies every 6 hours as previously described (Tam et al., 2010) and eight blood samples every 3 hours from 6 am (Figure 6.1A). 3 hourly blood samples were used to measure glucose, glucoregulatory hormones (insulin, ghrelin, glucagon like peptide 1 [GLP-1], glucose-dependent insulinotropic peptide [GIP]) and metabolites (triglycerides and NEFA). 20 µL of 200mM 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF, Gold Biotechnology, St Louis, Missouri; Cat# A-540-5, CAS 30827-99-7) and 10 µL of dipeptidyl peptidase-IV (DPP-4) inhibitor (Sigma-Aldrich, North Ryde, NSW, Australia; Cat#: 634867) were added to 1 millilitre of 3hourly whole blood samples for the measurement of glucoregulatory hormones (ghrelin, GLP-1, GIP). Blood samples were also taken every hour from 6 am to 12 am and 5 pm to 3 am to measure morning cortisol levels, and evening melatonin and cortisol levels, respectively (Figure 6.1A).

Plasma hormone and metabolite measurements

Blood glucose and triglycerides were measured using commercially available enzymatic kits

on an AU480 clinical analyzer (Beckman Coulter, Inc., Brea, California). NEFA were measured using a colorimetric assay (NEFA; Randox Laboratories Ltd. Co. Antrim, United Kingdom). Plasma insulin (EMD Millipore, Billeria, USA), cortisol (DIAsource ImmunoAssays S.A., Louvain-la-Neuve, Belgium) and melatonin (Bühlmann Laboratories AG, Schönenbuch, Switzerland) were measured by radioimmunology assay as described elsewhere (Riad-Fahmy et al., 1979, Fraser et al., 1983, Morgan and Lazarow, 1963). Plasma ghrelin, GLP-1, and GIP were measured by magnetic bead-based quantitative immunoassay (MilliporeSigma, Burlington, Massachusetts). Samples from each participant were analysed within the same run to minimise inter-assay variation.

Adipose tissue biopsy

Subcutaneous adipose tissue samples (~250mg) will be collected at 6 hour intervals from 6am to 12 am at baseline and after TRE intervention. A subcutaneous adipose biopsy will be performed using the technique of Bergstrom: after cleansing the skin on the abdomen lateral to the umbilicus with chlorhexidine solution, and placing a fenestrated drape, anaesthesia is administered (5mL of Xylocaine 2%, no adrenaline). A 0.75 cm incision is made in the skin (#11 scalpel) and a 5mm Bergstrom needle inserted to collect approximately 250mg of adipose tissue with suction. Two to three passes will be used to obtain approximately 250mg of adipose tissue. The sample is washed in sterile PBS and snap frozen in liquid nitrogen. Upon completion of the biopsy, pressure is applied and the incision is closed with a sterile bandage, and a sterile dressing applied. Samples will be assessed by RNA sequencing.

Adipose tissue RNA sequencing

Total RNA was extracted from 50-100mg SAT using the RNEasy Lipid Tissue Mini kit (Qiagen, Hilden, Germany) according to the manufacturer's recommendations. RNA integrity number was verified with Agilent 2200 TapeStation system (Agilent Technologies, Amsterdam,

Netherlands). RNA-seq libraries (cDNA libraries from polyA mRNA) and sequencing were performed using Illumina's TruSeq RNA library Preparation kit according to manufacturer's instructions (Illumina, San Diego, CA, USA), starting with 200 ng of total RNA. Libraries were pooled into groups of 12 to a lane and sequenced using an Illumina HiSeq 2500 (Illumina, San Diego, CA, USA) with 50-bp single-read chemistry.

Statistic methods

Baseline measurements and plasma values

The dim light melatonin onset (DLMO) was calculated as the absolute threshold >10 pM for each participant (Benloucif et al., 2008), which used for determining the endogenous circadian phase. Melatonin and cortisol data were plotted relative to clock time. Data were grouped into time bins, 3 hr for blood metabolites and glucoregulatery hormones and 6 hr for adipose tissue transcriptome (6 am to 12 am). Paired Student t-test (two-sided) or Wilcox- test was applied to analyse the DLMO, morning and evening cortisol area under the curve (AUC), cortisol meal response and objective sleep measurement. The correlation between the change in morning cortisol AUC and the change in HbA1c were tested via Pearson correlation analysis. Analysis of all temporal profiles of metabolites was first carried out using a linear mixed effect model fit by restricted maximum likelihood, with the time-of-day (6 am, 9 am, 12 pm, 3 pm, 6 pm, 9 pm, 12 am, 3 am), TRE (baseline, week 8) and time-of-day by TRE interaction as the fixed factors and subject ID as a random factor. Data were log-transformed if the skewness or heteroscedasticity in the residuals were observed. Statistical analysis was performed using R software (version 3.6.1; The R Foundation for Statistical Computing, Vienna, Austria).

RNA sequencing data screening and pre-processing

Sequence images were transformed FastQ files through Illumina software (BaseCaller, Illumina,

San Diego, CA, BCL2FastQ, version 2.17.1.14). The quality check was done by using FastQC, version 0.11.5 (Babraham Bioinformatics, Cambridge, UK). Sequence alignments were performed using Star v2.5.3a, and data were pre-processed and analysed in the R/Bioconductor environment (R, 2019). Sequenced reads were mapped and annotated to the human genome (Dobin et al., 2013, Heinz et al., 2010). After removing genes with less than 10 counts combined across all samples, the remaining genes were normalized using Trimmed Mean of M-values normalization and their dispersion was estimated using edgeR (Robinson et al., 2010, McCarthy et al., 2012).

Analysis of differentially expressed genes by edgR

Analysis of differentially expressed genes was carried out via edgeR (Chen et al., 2016), with designs that accounted for pre- and post- intervention at each time point. Statistically differentially expressed gene expression was assessed using a likelihood ratio test and corrected for multiple hypotheses testing using the Benjamini-Hochberg method (false discovery rate [FDR] <0.05).

Spline regression analysis

Rhythmic analysis was not applicable for this dataset as our adipose tissue biopsies were only sampled at four-time points. Therefore, time-series samples were treated independently, and a Spline regression model was applied to identify the transcripts which followed the different 24-hour profile after TRE versus baseline using the R package splineTimeR version 1.18.0 (Michna A, 2020), which was corrected for multiple hypotheses testing using the Benjamini-Hochberg method (false discovery rate [FDR] <0.05).

Enrichment analysis

Enriched pathways were found using WebGestaltR to perform overrepresentation analysis

(ORA) against the Molecular Signatures Database (MSigDB) and Gene ontology (GO) enrichment analysis (Liao et al., 2019, Ashburner et al., 2000, 2021). Only gene sets consisting of more than 10 and fewer than 500 genes were taken into account.

Construction of weighted gene co-expression network (WGCNA), identification of significant modules and hub genes

WGCNA was used to cluster groups of strongly co-expressed genes into co-expression network modules among the genes found to have significant rhythmicity over time in TRE versus baseline by spline analysis (Zhao et al., 2010, Zhang and Horvath, 2005). A network module is a cluster of closely interconnected genes, so-called eigengenes. Eigengenes were then correlated with external traits to identify modules that are significantly associated with the clinical traits and to find the most significant associations. To determine whether the modules were associated with phenotype (BMI, percentage of body fat mass, glucose, NEFA, triglycerides, insulin, GIP, GLP-1), we calculated the significance of the Pearson correlation between modules and traits using an asymptotic t test (Zhang and Horvath, 2005). The top hub gene of each module, defined as the central to the network that defines each module. Enrichment analysis of the network module genes was also conducted according to the above methods.

6.5 Results

Participants

The protocol and clinical characteristics of the cohort been reported in Chapter 5 and are briefly summarised here. Fifteen men (mean ± SD, age: 63 ± 4 years; waist circumference: 113 ± 4 cm, body mass index: 30.5 ± 2.4 kgm^2; body mass: 95.2 ± 12.2 kg; body fat percentage: 34.3 ± 1.2%) started and completed the study without adverse events. As reported previously,

photograph-based food diary records showed excellent adherence to TRE with a significant reduction in eating hours per day (14.6 ± 1.0 hrs versus 10.6 ± 1.0 hrs, p<0.0001; Figure 6.1B, polar plot).

TRE reduced stress hormone and increased rapid eye movement sleep stage, but did not alter melatonin rhythm

TRE reduced morning cortisol AUC by -17.4 ± 9.4 ug/L.Hour (p=0.02, Figure 6.1C-D), but did not significant alter evening cortisol AUC (change = -4.4 ± 4.5 ug/L.Hour, p=0.35, Figure 6.1C). The change in morning cortisol AUC was positively correlated with the change in HbA1c (r=0.60, p=0.02). TRE also significantly reduced the meal-induced cortisol response after dinner only -10.7 ug/L.Hour (p=0.04). TRE did not alter the DLMO (p= 0.86, Figure 6.1E-F), but increased the percentage of REM (repaid eye movement) sleep without changing sleep onset latency, total sleep time, sleep efficiency, percentage of sleep stage 1, 2 and 3 (Supplementary Table 6.1).

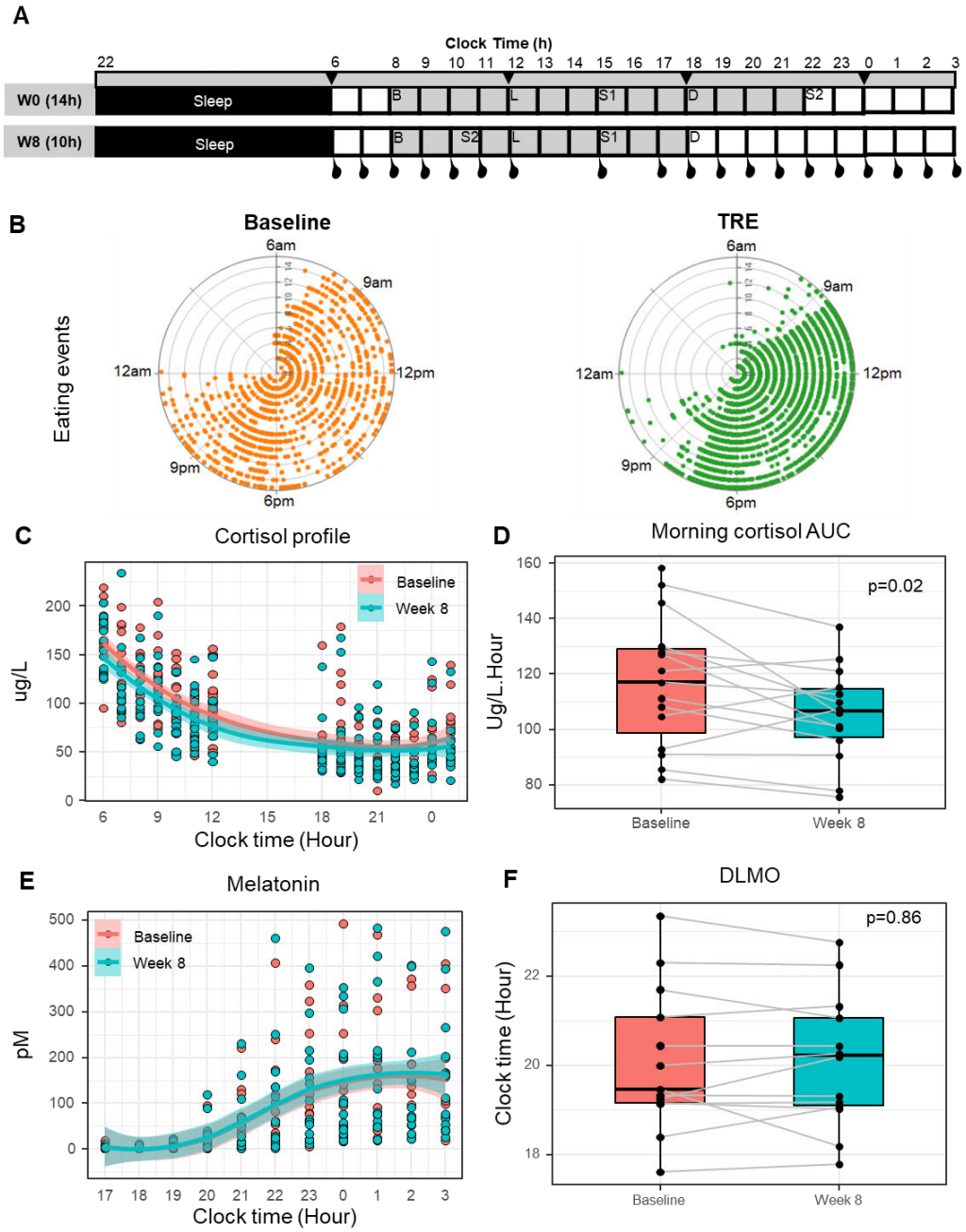


Figure 6.1 Schematic of study and effect of time restricted eating on eating events distribution and levels of cortisol and melatonin.

[**A)** Schematic of the study design: participants attended the sleep laboratory lab for a 35-hour metabolic testing visit at baseline and week 8. Identical meals were provided within a 14-h time frame at Week 0 (W0, upper panel, 8 am-10 pm) and 10-h time frame at Week 8 (W8, lower panel, 8 am-6 pm) (grey area). Abdominal subcutaneous adipose tissue biopsies were

performed every 6 hours from 6 am (black arrows) and blood samples were collected 3 hourly from 6 am to 3 am, hourly from 6 am to 12 pm and 5 pm to 3 am (black dots). **B)** Polar plot of eating events of each individual plotted against time of the day in each concentric circle (each circle represents a different participant) during the baseline monitoring period (orange) and during time restricted eating intervention (green). **C-D**) Levels of cortisol from 6 am to 12 pm and from 6 pm to 1 am in hourly plasma samples collected during the metabolic ward stay (C) and morning cortisol area under the curve (D). **E-F)** Levels of melatonin from 5 pm to 3 am in hourly samples collected during the metabolic ward stay (E) and dim light melatonin onset (DLMO) at 10 pm (F).]

TRE altered 24-hour profile of insulin, NEFA, triglycerides and GIP concentrations

A time of day by TRE interaction was observed in 24-hour profile of insulin ($F=2.39$, $p<0.02$, Figure 6.2B), NEFA ($F=4.76$, $p<0.001$, Figure 6.2C), triglyceride ($F=3.71$, $p<0.001$, Figure 6.2D) and GIP ($F=5.55$, $p<0.001$, Figure 2F). Post-hoc analysis showed that in response to TRE, insulin was increased at midday ($p=0.02$), and decreased at midnight ($p=0.01$) (Figure 6.2B). NEFA concentrations decreased at 9 am and midday ($p=0.04$ and 0.03, respectively) and increased at midnight ($p<0.001$) (Figure 6.2C), whereas triglycerides were lower at midnight and 3 am ($p<0.001$ and 0.003, respectively) (Figure 6.2D). There were no changes in the concentrations of NEFA and triglycerides at other time points. Only GIP levels were higher at 9 am, 12 pm and 6 pm ($p=0.05$, 0.003, 0.01, respectively), and lower at midnight ($p<0.001$) (Figure 6.2F). There were no changes were observed in glucose (Figure 6.2A), GLP-1 (Figure 6.2E), ghrelin (Supplementary Figure 6.1 and Supplementary Table 6.2).

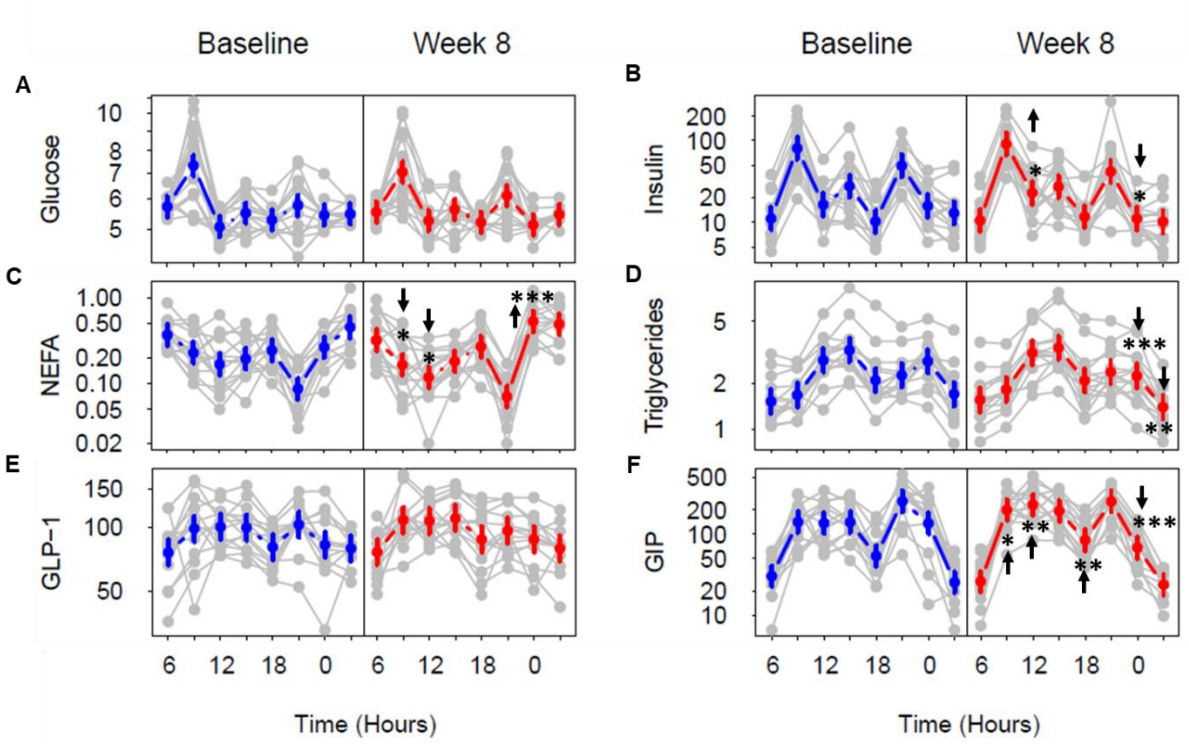


Figure 6.2 Prediction of time restricted eating on 24-hour profiles of plasma metabolites (glucose, non-esterified fatty acids [NEFA], triglycerides), and glucoregulatory hormones (insulin and glucose-dependent insulinotropic peptide [GIP]).

[Time of day by TRE effect, post hoc test: * p<0.05, ** p<0.01, ***p<0.001. Up direction arrow represents increase; down direction arrow represents decrease; Blue color: baseline; red color: week 8.]

TRE altered SAT transcriptional profiles

RNA sequencing of SAT samples detected that 319, 610 and 3407 transcripts were differentially expressed by TRE at 6 am, 6 pm and 12 am, respectively (Figure 6.3A, APPENDIX B-1, APPENDIX B-2 and APPENDIX B-3, respectively). Only five genes were altered at all of these time points (Figure 6.3B-D), namely, ZNF587 (zinc finger protein 587), CTDP1 (carboxyl-terminal domain phosphatase subunit 1), RAI1 (retinoic acid-induced 1), CBX4 (chromobox 4) and TSC22D4 (transforming growth factor beta-like stimulated clone 22

domain family member 4).

First, we examined the 24-hour profile of the known core clock genes. TRE increased CLOCK (FDR= 0.054) and NR1D2 (FDR=0.011) gene expression, whereas TRE decreased the expression of PER1 (FDR=0.023) and NR1D1 (FDR=0.016) at 12 am (Figure 6.4). To analyse the impact of TRE on the temporal profile of adipose tissue transcripts, we used spline regression models (N= 450, APPENDIX B-4, with top 25 genes are presented in Figure 6.5). The. Pathway analysis yielded four GO pathways (Table 6.1): 15 genes were enriched in transcription co-repressor activity pathway (FDR=0.045, Supplementary Table 6.2); 19 genes were enriched in DNA-binding transcription factor binding pathway (FDR<0.001, Supplementary Table 6.2),; 13 genes in the regulation of chromatin organization pathway (FDR<0.001, Supplementary Table 6.2); and 24 genes were enriched in small GTPase binding (FDR=0.008, Supplementary Table 6.2). **Network analysis indicates basic gene alteration in response to TRE in human adipose tissue**

Four distinct co-expression module eigengenes were identified from the 450 rhythmic genes from spline analysis by using WGCNA (Figure 6.6A). The calculating module-trait correlation are presented as a heatmap (Figure 6.6B). Genes that clustered in the grey module (N=71) were negatively correlated with BMI, percentage of body fat mass, insulin and GIP and positively correlated with NEFA. Genes in the brown (n=43) and blue (n=105) module were positively correlated with BMI, percentage of body fat and insulin, and negatively correlated with NEFA. The top hub gene for the blue module was FBRS (fibrosin), brown was ARHGEF1 (Rho guanine nucleotide exchange factor 1), turquoises was MBD3 (Methyl-CpG binding domain protein) and grey was HSP90AB1 (heat shock protein 90 alpha family class B member 1) (Figure 6.6C). To further explore the key regulatory nodes, we applied pathway analysis of genes each module. Only the genes in grey model, showing the strongest correlations with the clinical traits, were enriched in specific pathways, including chaperone medicated protein

complex assembly, response to topologically incorrect protein, post-translational protein modification and RNA splicing, after ranking the top gene sets while maximizing gene coverage (Figure 6.6D).

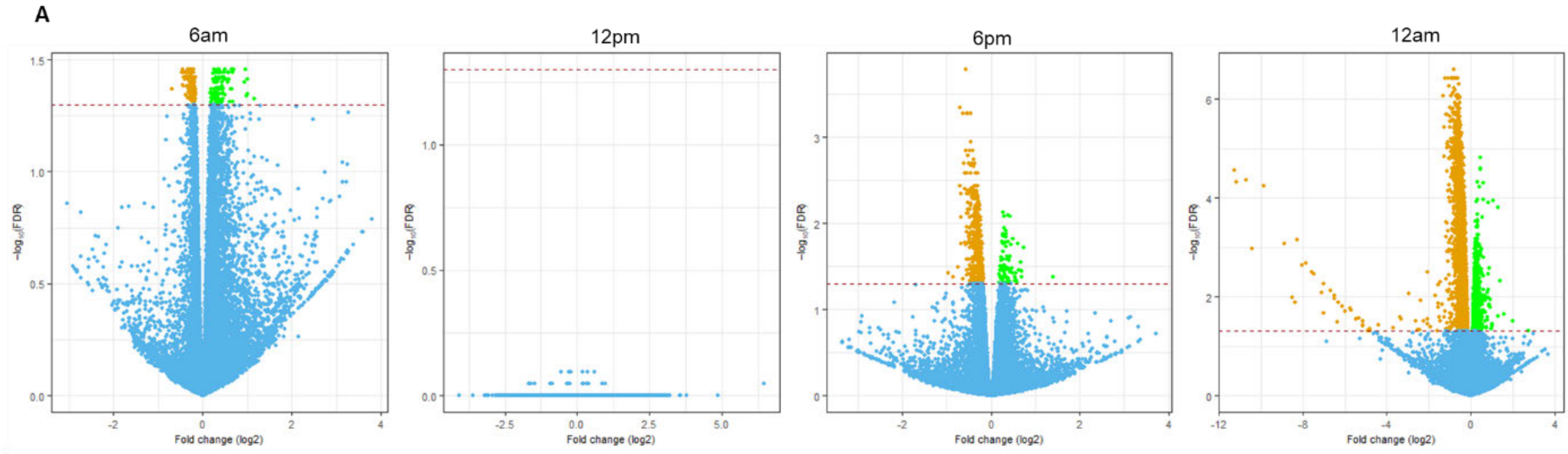

A
6am
12pm
6pm
12am
Fold change (log2)
B
All differentially expressed genes
6am
6pm
12am
12pm
72
2830
528
5
265
5
0
44
C
Upregulated genes
40
1221
51
3
106
1
7
D
Downregulated genes
32
1644
481
2
198
2

Figure 6.3 Volcano plots and Venn diagrams of differentially expressed genes in adipose tissue at baseline versus week 8.

[**A)** Volcano plot representation of differential expression analysis of genes in adipose tissue at baseline versus week 8 comparisons at 6 am, 12 pm, 6 pm and 12 am datasets, respectively. Green and orange points mark the genes with significantly increased or decreased expression respectively by time restricted eating compared to baseline samples (FDR<0.05). The x-axis shows log2 fold-changes in expression and the y-axis the log FDR of a gene being differentially expressed (red dash line represents FDR=0.05). **B-D)** Venn diagrams shows the overlaps of differentially expressed (B), upregulated (C) and downregulated (D) genes at each time point, respectively.]

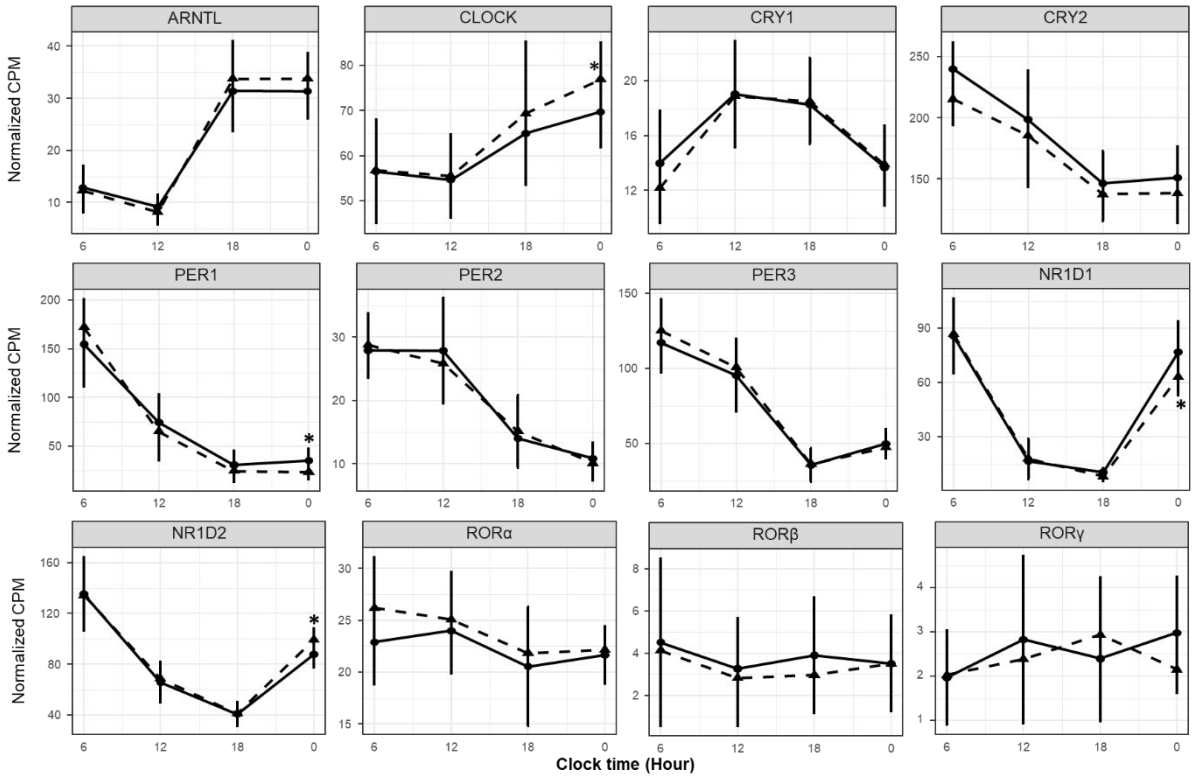


Figure 6.4 24 hour profiles of core clock genes.

[Average (± SD, n = 12) normalized counts of core clock genes in subcutaneous adipose tissue at different times of the day. Solid line represents baseline, dash line represents TRE. * false discovery rate (FDR) <0.05.]

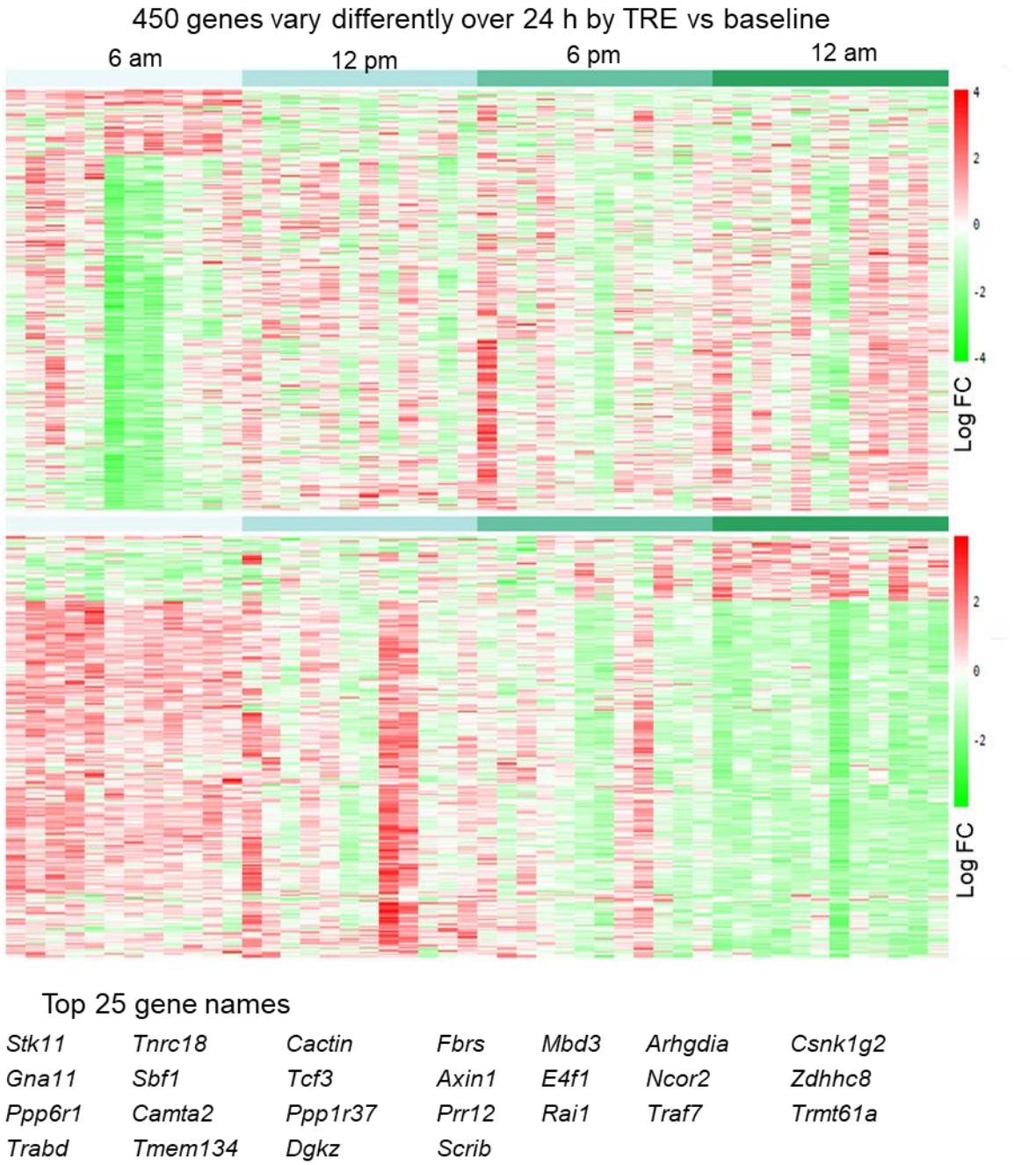


Figure 6.5 Spline regression analysis.

[Spline regression analysis identified 450 profile of genes displayed different rhythmicity by time restricted eating (lower panel) versus baseline (upper panel) (top 25 gene names are presented).]

Table 6.1 Gene ontology enrichment analysis of 450 genes that showed altered rhythmicity in response to time restricted eating.

ID	Category	Gene Set term	Overlap	Enrichment ratio	p-Value	FDR
GO_MF (molecular function)	GO:0031267	GO_SMALL_GTPASE_BINDING	24	2.538	0.000	0.008
GO_BP (biological process)	GO:0006325	GO_REGULATION_OF_CHROMATIN_ORGANIZATION	13	3.367	0.000	0.025
GO_ MF (molecular function)	GO:0140297	GO_DNA_BINDING_TRANSCRIPTION_FACTOR_BINDING	19	2.599	0.000	0.026
GO_ MF (molecular function)	GO:0003714	GO_TRANSCRIPTION_COREPRESSOR_ACTIVITY	15	2.834	0.000	0.045

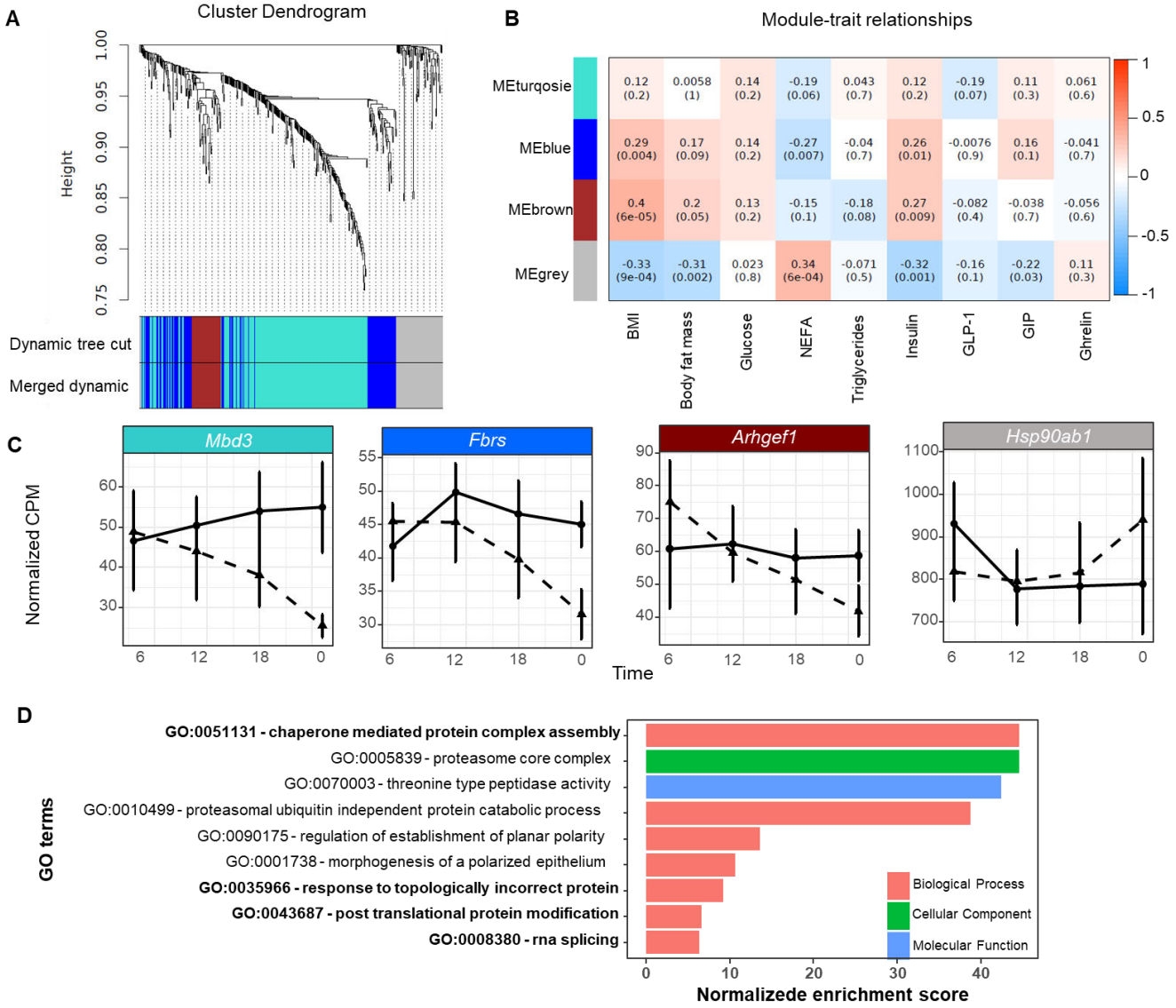

A
Cluster Dendrogram
Height
1.00
0.95
0.90
0.85
0.80
0.75
Dynamic tree cut
Merged dynamic
B
Module-trait relationships
MEturqosie
MEblue
MEbrown
MEgrey
0.12 (0.2) 0.0058 (1) 0.14 (0.2) -0.19 (0.06) 0.043 (0.7) 0.12 (0.2) -0.19 (0.07) 0.11 (0.3) 0.061 (0.6)
0.29 (0.004) 0.17 (0.09) 0.14 (0.2) -0.27 (0.007) -0.04 (0.7) 0.26 (0.01) -0.0076 (0.9) 0.16 (0.1) -0.041 (0.7)
0.4 (6e-05) 0.2 (0.05) 0.13 (0.2) -0.15 (0.1) -0.18 (0.08) 0.27 (0.009) -0.082 (0.4) -0.038 (0.7) -0.056 (0.6)
-0.33 (9e-04) -0.31 (0.002) 0.023 (0.8) 0.34 (6e-04) -0.071 (0.5) -0.32 (0.001) -0.16 (0.1) -0.22 (0.03) 0.11 (0.3)
1
0.5
0
-0.5
-1
BMI
Body fat mass
Glucose
NEFA
Triglycerides
Insulin
GLP-1
GIP
Ghrelin
C
Mbd3
Fbrs
Arhgef1
Hsp90ab1
Normalized CPM
Time
6
12
18
0
D
GO terms
GO:0051131 - chaperone mediated protein complex assembly
GO:0005839 - proteasome core complex
GO:0070003 - threonine type peptidase activity
GO:0010499 - proteasomal ubiquitin independent protein catabolic process
GO:0090175 - regulation of establishment of planar polarity
GO:0001738 - morphogenesis of a polarized epithelium
GO:0035966 - response to topologically incorrect protein
GO:0043687 - post translational protein modification
GO:0008380 - rna splicing
Biological Process
Cellular Component
Molecular Function
0
10
20
30
40
Normalizede enrichment score

Figure 6.6 Weighted gene co-expression network analysis (WGCNA) and target modules and hub genes screening.

[**A)** Network analysis of 450 genes generated from spline analysis to identify distinct modules of co-expression genes. **B)** Pearson correlation coefficient between the eigengene of modules and the sample feature vector. Numbers in rectangular represent the correlation coefficients and numbers in brackets indicate the corresponding P values. BMI, body mass index; NEFA, Non-esterified fatty acid. **C)** Top hub gene in each eigengene of module. MBD3 (Methyl-CpG binding domain protein), FBRS (fibrosin), ARHGEF1 (Rho/Rac guanine nucleotide exchange factor 18), and HSP90AB1 (heat shock protein 90 alpha family class B member 1). **D)** Significant gene ontology (GO) terms that enriched in the grey module (FDR<0.05). Bolded four GO terms represents the top gene sets while maximizing gene coverage.]

6.6 Discussion

TRE is purported to improve metabolic health by resetting circadian rhythms in rodents (Hatori et al., 2012, Chaix et al., 2018). However, the evidence for this in humans is currently lacking, with only one study performing serial time point sampling over 24 hours under unrestricted or time restricted eating conditions (Lundell et al., 2020). In that study, TRE altered the rhythmicity of amino acid transport in human skeletal muscle transcriptome and metabolome, but did not alter core clock gene expression (Lundell et al., 2020). In our study, TRE did not alter the phase of central clock marker DLMO, but decreased morning cortisol level, and insulin, GIP and triglycerides at midnight and increased NEFA at midnight. TRE also altered four out of 12 core clock genes at midnight. Spline analysis revealed that 450 genes that were arrhythmic at baseline, became rhythmic in response to TRE. Over-representation analysis indicated that pathways involved in transcription corepressor activity pathway, DNA binding transcription factor binding, regulation of chromatin organization and small GTPase binding all fit this

pattern. The expression of these genes was then grouped into egiengenes and were correlated with the purported systemic circadian synchronizer insulin, as well as factors that often co-correlate with insulin namely, BMI and percentage body fat and inversely with the metabolite NEFA.

Previous studies indicate that TRE improves insulin sensitivity in response to meals given at breakfast time (Sutton et al., 2018, Martens et al., 2020). In this cohort, we previously reported improved adipose tissue insulin sensitivity to a breakfast and dinner meal in Chapter 6, but did not observe a change in insulin response to these meals. One previous study showed that 24-hour C-peptide AUC was decreased (Parr et al., 2020b), suggesting that improved insulin sensitivity. In the present study, TRE altered the 24-hour profiles in plasma insulin, NEFA and triglycerides, and GIP. TRE did not alter DLMO in our hands or previously cycle (Wehrens et al., 2017), which is primarily regulated by the light-dark cycle (Zeitzer et al., 2000, Pandi-Perumal et al., 2007). However, we anticipated that evening cortisol levels may be reduced by TRE, as consuming meals late at night elevates the cortisol nadir (Gu et al., 2020, Richter et al., 2020). However, evening cortisol was not elevated in our cohort, which could be the results of the small size of the meal (~200 kcals) that was given late at night in the baseline condition (Zhao et al., 2021a). However, morning cortisol was reduced by TRE in the present study, which could have contributed to the lower rise in morning glucose (Rybicka et al., 2011) and lower HbA1c (Ortiz et al., 2019).

Individuals with obesity and T2DM have a dampened amplitude of core clock genes (including CLOCK, PER1, NR1D1 and NR1D2) (Stenvers et al., 2019a), along with mice that are fed high fat diets (Chaix et al., 2014, Chaix et al., 2018, Hatori et al., 2012). TRE restores the amplitude of peripheral clocks in liver and adipose tissue (Chaix et al., 2014, Chaix et al., 2018, Hatori et al., 2012) in mouse models of aging and obesity. In the present study, TRE increased CLOCK and NR1D2, and decreased PER1 and NR1D1 transcripts at midnight. TRE did not alter clock

genes in human muscle (Lundell et al., 2020). However, muscle is known to be less responsive to food cues than liver or adipose tissue in mice (Yasumoto et al., 2016) and TRE downregulated PER1 at 8 pm and upregulated CRY1/2 and RORα at 8 am and 8 pm in whole blood (Jamshed et al., 2019). Shortening the eating window by reducing meal frequency from 6 to 3 meals also upregulated BMAL1, CRY1, PER2 and RORα gene expression in patients with T2DM (Jakubowicz et al., 2019).

Insulin induced a phase shift of PER2 and PER1 in human stem cell-derived adipocytes (Tuvia et al., 2021), mouse 3T3-L1 cells and adipose tissue explants from mPer2Luc knockin mice (Crosby et al., 2019).In humans, PER2 and PER3 were upregulated and NR1D1 and NR1D2 were downregulated in adipose tissue by insulin versus saline infusion (Tuvia et al., 2021).In total, approximately 1.8% of the transcripts were altered by insulin versus saline, which included AMPK, phosphatidylinositol and mTOR pathways (Tuvia et al., 2021). This work suggests that insulin may be a mediator of adipose tissue clock entrainment in response to food intake and we postulate that the reduction in evening insulin as a result of TRE may drive changes in clocks and downstream genes, and other metabolites.

Mice on high-fat diet *ad libitum* also displayed dampening rhythms of liver transcripts (Chaix et al., 2018) and metabolites (Chaix et al., 2014, Hatori et al., 2012), which were restored by TRE. TRE phase-advanced a larger proportion of gene expression in human skeletal muscle (Lundell et al., 2020). Temporal fasting induced by breakfast omission positively affected genes that were on the diurnal decline whereas temporal feeding induced by breakfast consumption positively affected genes that were on the diurnal incline in human adipose tissue, suggesting TRE may phase-advance genes related to PER1 (Loboda et al., 2009). In another highly controlled randomized cross-over clinical trials, delaying food intake for 5 hours phase-delayed adipose tissue PER2 for one hour (Wehrens et al., 2017). We observed that the 450 transcripts became rhythmic in response to TRE, suggesting that TRE restored the genes in adipose tissue

(Lundell et al., 2020, Loboda et al., 2009, Wehrens et al., 2017).

The molecular components of the circadian clock are a combination of transcriptional activators and repressors coordinately acting at thousands of sites in the chromatin fiber and ultimately driving a highly specific program of gene expression around the day to maintain metabolic homeostasis (Sinturel et al., 2020, Goldstein and Hager, 2015, Zhu and Belden, 2020). TRE induced oscillations of genes encoding histone deacetylation activity and transcriptional regulation activity (including DNA-binding transcription repressor, protein serine/threonine phosphatase, and transcription corepressor/coregulatory /cofactor) in human muscle (Lundell et al., 2020). In this study, TRE induced rhythms in adipose tissue genes involved in the regulation of chromatin organisation (e.g., KMT2B, H1FX, TRIM28, SREBF1, CTBP1, RPS6KA4), transcription co-repressor activity and DNA binding transcription factor binding (e.g., NCOR2, CTBP1, CBX4, TCF3). The nuclear PERIOD complex guides deacetylation and recruitment of KMT1 (lysine methyltransferase 1) subunit SUV39H1 to Per1 and Per2 promoters causing circadian di-methylation and tri-methylation of histone H3 lysine 9, suggesting PER complex delivers the relevant chromatin-modifying enzymes to the circadian target gene (Duong and Weitz, 2014). (Milazzo et al., 2020). TRIM28 shown to interact with CRY1 and CRY2 (Hirano et al., 2016), is a large multi-domain protein that supports heterochromatin deposition and silencing by bridging interactions between KRAB-zinc finger transcription factors and histone de-acetylases (HDAC1/2) and methyltransferases (SETDB1), which may trigger epigenetic obesity (Dalgaard et al., 2016). HDAC3 is also recruited by NR1D1 and is needed for rhythms in hepatic lipid metabolism (Alenghat et al., 2008, Yin et al., 2010). In our study, increased CLOCK at midnight may result from reduced NR1D1 and NCOR1/2 which reduced the repression of BMAL1/ARNTL expression, leading to increased or maintain the levels of BMAL1/CLOCK, inducing the expression of E-box controlled core clock genes (i.e., NR1D2) and other clock controlled genes involved in adipose tissue

physiological pathways such as the expression of key enzymes in the regulation of lipolysis including HSL (hormone-sensitive lipase), LPL (lipoprotein lipase) and ATGL (adipose triglyceride lipase), and adipogenesis such as genes involved in Wnt signalling (TCF3 and DVL) (Shostak et al., 2013, Stenvers et al., 2019b, Guo et al., 2012). The downregulated PER1 may resulted from the reduced insulin level (Crosby et al., 2019, Tuvia et al., 2021). TRE also altered the rhythmicity transcription factors involved in adipose tissue remodelling such as CREB regulated transcription coactivator 1 (CRTC1)-CREB complex (Altarejos et al., 2008, Jagannath et al., 2013), CTBP1(a co-repressor of PPARγ), and CBX4 (a polycomb group protein for maintaining stability of transcriptional co-activator PRDM16 (Chen et al., 2018). Thus, TRE may impact adipose tissue physiology by circadian regulation of chromatin modification and transcription factors.

Insulin mediated PI3K-Akt pathways are downregulated by fasting, dampening mTORc and SREBP, inhibiting lipogenesis and cell growth (Crewe et al., 2019, Nagao et al., 2021, Olson, 2012). SREBF1 or SREB protein 1 (SREBP1) is a transcription factor whose activity is strongly regulated by nutrient availability through the insulin-mTORC1 signalling pathway, peaking during the nocturnal feeding period in mice (Gilardi et al., 2014) and suppressed during the fasting period (Le Martelot et al., 2009). TRE was previously shown to restore circadian rhythms in SREBP1 (Chaix et al., 2014) and target genes in the liver of cry1$^{-/-}$, cry2$^{-/-}$, Bmal1$^{-/-}$ knockout mice (Vollmers et al., 2009, Gilardi et al., 2014), suggesting a dominant role of the feeding-fasting cycle in the regulation of SREBP1. Our results support this evidence with the expression higher during feeding and lowered during fasting period by TRE, and perhaps indicate TRE may restored rhythmic regulation of lipogenesis in SAT (Chaix et al., 2018).

TRE also restored rhythmicity of RPS6KA4, with lower levels at midnight and greater peaks at 6am. Ribosomal S6 kinase is a group of serine/threonine kinases, of which ribosomal S6 protein

kinase 1 (RPS6K1) is an mTOR-effector kinase (Lipton et al., 2015). RPS6K1 is an important regulator of translation, and rhythmically associates with the clock translational machinery by phosphorylating BMAL1and stimulating protein synthesis (Crosby et al., 2019, Lipton et al., 2015). RPS6KA4 also can phosphorylate histone H3 to modulate the accessibility and transcriptional competence of specific chromatin regions regulating genes involved in inflammation via activation CREB1 (Cheng et al., 2015).

In the present study, TRE altered different subfamily of small GTPase such as Rho GTPases (ARHGEF18, ARHGDIA, PLEKHG3, ARHGEF17, ARHGEF1, RAC1, CDC42EP1) and Rab GTPases (RAB11FIP3), which is involved in glucose stimulated insulin secretion in pancreases and glucose uptake through increasing GLUT4 translocation in metabolically active tissues such as skeletal muscles (Wang et al., 2011), liver (Gendaszewska-Darmach et al., 2021), or adipocytes (Welsh et al., 2007, Balamatsias et al., 2011, Usui et al., 2003). In adipose tissue, RAB11 promotes GLUT4 transport from the endosomal compartments to glucose transporter storage vesicles via scaffolding protein Rip11 (Welsh et al., 2007), whereas RAC1, facilitates GLUT4 plasma membrane association via regulation of the actin cytoskeleton at physiological insulin concentrations (Balamatsias et al., 2011). CDC42 also assist GLUT4 translocation and glucose transport in 3T3-L1 (Usui et al., 2003). In muscle, RAC1 stimulates actin cytoskeleton reorganization and activates PAK to insulin-promoted GLUT4 translocation (Wang et al., 2011). The altered rhythmicity of small GTPase with a significant downregulation in the evening in response to TRE may contribute to the rhythmicity of insulin secretion and insulin sensitivity that is known to occur in peripheral tissues (Zhao et al., 2021a) and could be the alternative therapeutics to against the upregulated of small GTPase induced by hyperglycaemia (Gendaszewska-Darmach et al., 2021).

The calculating module-trait relationships analysis showed that the positive correlations between two modules that had lower expression at midnight and insulin, BMI and NEFA, but

the reverse for genes that mapped to the grey module. Pathway analysis of genes from the grey module were enriched in chaperone mediated protein complex assembly, post-translational protein modification, response to topologically incorrect protein and RNA splicing, with the hub gene being HSP90AB1. HSP90AB1 is one of the HSP90 co-chaperone isoforms involving in maintaining proper cellular levels of BMAL1 protein *in vivo* (Schneider et al., 2014), and thus may contribute to TRE induced restoration of clocks. HPS90 is also involved in the protein complex assembly of the 26S proteasome to assist in the degradation of misfolded or unfolded protein (Gusarova et al., 2001, Maxwell et al., 1999). The proteasome displays circadian variation (Desvergne et al., 2016) and is dysregulated in obesity and aging (Díaz-Ruiz et al., 2015, Otoda et al., 2013), and reduced in humans in response to daily calorie restriction (Lam et al., 2016), acute fasting (Defour et al., 2020) and TRE reported in Chapter 5.

The changes in adipose tissue transcriptome could be partially resulted from the study protocol which entailed different lengths of fasting prior to the adipose tissue biopsy at midnight. Since sampling was not performed at more than 4 time points, we did not perform a cosine model to predict the mesor, amplitude and phase shift of the 24-hour profile of adipose tissue transcriptome and glucoregulatory hormones. Spline analysis displayed a group of altered gene expression profiles, we assuming the rhythmicity of these genes may be restored by TRE, however, these needs to be further confirmed in the constant routine protocol.

In conclusion, TRE altered the 24-hour rhythm of insulin, and restored the rhythmicity of 450 genes in adipose tissue, which were suggestive of a phase-advance in pathways involved in transcription co-repressor activity, DNA-binding transcription factor binding, regulation of chromatin organization and small GTPase binding and genes that are known to be involved in multiple physiological processes in adipose tissue.

Ethics declarations: Central Adelaide Local Health Network (CALHN) Human Research

Ethics Committee, University of Adelaide, and the University of South Australia.

Data availability: The raw sequencing data and have been deposited in are deposited in the NCBI Gene Expression Omnibus (GEO) repository (accession number GSE168705) and are available upon request.

Acknowledgement: The authors thank research in the SP lab is supported by NIH grants DK115214, and DK118278 and Robertwood Johnson Foundation grant 76014. The authors also thank Mark Salkeld and Scott Standfield for the technical support in melatonin extraction and measurement.

Disclosure of conflict interest: Gary A Wittert has received research funding for testosterone pharmacology studies (Weight Watchers, Bayer), speakers (Besins, Bayer, World Obesity), expert testimony (Australian Health Practitioners Regulation Agency), International Advisory Board (Bayer) and consultancy (Elsevier) fees. Satchidananda Panda is the author of the book "The Circadian Code" for which he receives author royalty from PenguinRandomHouse Company. The other authors declared no conflict of interest.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT03590158

SUPPLEMENTARY MATERIAL FOR CHAPTER 6

Supplementary Table 6.1 Effect of time restricted eating on sleep architectures (N=15)[1]

	Baseline	Week 8	P-value
Total sleep time (min)	346.0 ± 18.0	363.3 ± 15.5	0.236
WASO	99.1 ± 14.5	96.1 ± 13.2	0.816
Sleep onset latency (min)	21.9 ± 6.0	17.1±3.8	0.553
REM sleep latency (min)	141.9 ± 29.3	153.7 ± 25.4	0.386
Sleep efficiency (%)	73.7 ± 3.8	76.1 ± 3.2	0.406
% N1	22.7 ± 2.6	24.3 ± 2.4	0.355
% N2	56.0 ± 2.6	52.1 ± 2.6	0.269
% SWS	15.4 ± 1.8	15.1 ± 3.0	0.874
% REM	6.4 ± 1.2	8.5 ± 1.3	0.021
AHI (events/hr)	15.7 ± 3.8	18.6 ± 5.3	0.488

[1]Data are mean ± SEM; N=15. WASO, wake time after sleep onset; REM, rapid eye movement; %N1, percentage of sleep stage 1, %N2, percentage of sleep stage 2; %N3, percentage of sleep stage 3; %SWS, percentage of slow wave sleep; % REM, percentage of rapid eye movement sleep stage; AHI, apnoea hypopnea index.

Supplementary Table 6.2 Linear mixed model effects of metabolites, and glucoregulatary hormones in response to time restricted eating[1]

	TRE effect		Time effect		Time * TRE effect		
	F	P value	F	P value	F	P value	Post hoc test results
Glucose (mmol/L)	0.07	0.79	28.26	**<0.001**	1.01	0.43	
Insulin (mIU/L)	0.38	0.54	111.03	**<0.001**	2.39	**0.02**	↑ at 12pm (p=0.02); ↓at 12am (p=0.01)
NEFA (mmol/L)	0.23	0.64	58.49	**<0.001**	4.76	**<0.001**	↓ at 9am (p=0.04) and 12pm (p=0.03); ↑ at 12am (p<0.001)
Triglycerides (mmol/L)	0.41	0.52	81.58	**<0.001**	3.71	**<0.001**	↓at 12am (p<0.001) and 3am (p=0.003)
GLP-1(pg/ml)	2.66	0.10	12.45	**<0.001**	0.62	0.74	
GIP(pg/ml)	2.04	0.10	105.51	**<0.001**	5.55	**<0.001**	↑at 9am (p=0.05), 12pm(p=0.003) and 6pm (p=0.009); ↓ at 12am (p<0.001)
Ghrelin(pg/ml)	2.71	0.10	18.94	**<0.001**	1.50	0.17	

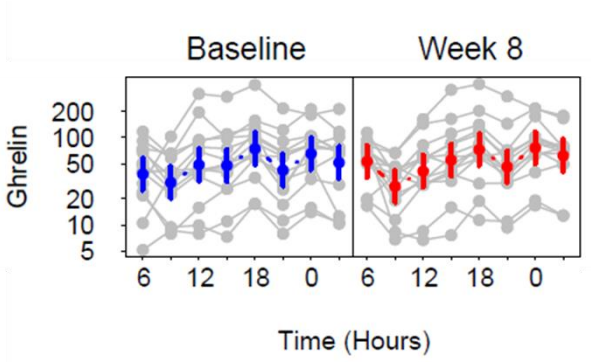
[1]Data are presented as the size and P values of fixed effect Omnibus tests from linear mixed model regression. Post hoc tests were performed if the interaction effect was observed and only the tests with paired time point were reported. NEFA, non-esterified fatty acids; GIP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic peptide.

Supplementary Table 6.3 Gene names enriched in each pathway (pathway analysis of 450 rhythmic altered genes by time restricted eating).

Gene set	Gene symbol	Gene name	FDR
GO_SMALL_GTPASE_BINDING			0.008
	OCRL	OCRL, inositol polyphosphate-5-phosphatase	
	TRAPPC5	trafficking protein particle complex 5	
	ARHGEF18	Rho/Rac guanine nucleotide exchange factor 18	
	GGA1	golgi associated, gamma adaptin ear containing, ARF binding protein 1	
	ARHGDIA	Rho GDP dissociation inhibitor alpha	
	PLEKHG3	pleckstrin homology and RhoGEF domain containing G3	
	YIPF2	Yip1 domain family member 2	
	DVL1	dishevelled segment polarity protein 1	
	MAP3K11	mitogen-activated protein kinase kinase kinase 11	
	PKN1	protein kinase N1	
	SBF1	SET binding factor 1	
	LLGL1	LLGL scribble cell polarity complex component 1	
	RAB11FIP3	RAB11 family interacting protein 3	
	ARHGEF17	Rho guanine nucleotide exchange factor 17	
	SGSM2	small G protein signaling modulator 2	
	PPP6R1	protein phosphatase 6 regulatory subunit 1	
	TBC1D10B	TBC1 domain family member 10B	
	RAC1	Rac family small GTPase 1	
	SPHK2	sphingosine kinase 2	
	INF2	inverted formin, FH2 and WH2 domain containing	
	CDC42EP1	CDC42 effector protein 1	
	MICALL2	MICAL like 2	
	ARHGEF1	Rho guanine nucleotide exchange factor 1	

Gene set	Gene symbol	Gene name	FDR
GO_REGULATION_OF_CHROMATIN_ORGANIZATION			0.025
	SREBF1	sterol regulatory element binding transcription factor 1	
	CTBP1	C-terminal binding protein 1	
	BRD7	bromodomain containing 7	
	ZBTB7B	zinc finger and BTB domain containing 7B	
	PARP10	poly(ADP-ribose) polymerase family member 10	
	RPS6KA4	ribosomal protein S6 kinase A4	
	TAF7	TATA-box binding protein associated factor 7	
	TRIM28	tripartite motif containing 28	
	H1FX	H1 histone family member X	
	KAT7	lysine acetyltransferase 7	
	KMT2B	lysine methyltransferase 2B	
	NOC2L	NOC2 like nucleolar associated transcriptional repressor	
	MAP1S	microtubule associated protein 1S	
GO_DNA_BINDING_TRANSCRIPTION_FACTOR_BINDING			0.026
	CTBP1	C-terminal binding protein 1	
	DDX54	DEAD-box helicase 54	
	MAP3K10	mitogen-activated protein kinase kinase kinase 10	
	PKN1	protein kinase N1	
	TCF3	transcription factor 3	
	TRIP6	thyroid hormone receptor interactor 6	
	CTDP1	CTD phosphatase subunit 1	
	HCFC1	host cell factor C1	
	TAF7	TATA-box binding protein associated factor 7	
	NCOR2	nuclear receptor corepressor 2	
	GAS2L1	growth arrest specific 2 like 1	
	FAF1	Fas associated factor 1	

Gene set	Gene symbol	Gene name	FDR
	CRTC1	CREB regulated transcription coactivator 1	
	NOC2L	NOC2 like nucleolar associated transcriptional repressor	
	ZBTB7A	zinc finger and BTB domain containing 7A	
	BBS10	Bardet-Biedl syndrome 10	
	MED25	mediator complex subunit 25	
	ZFPM1	zinc finger protein, FOG family member 1	
	MKKS	McKusick-Kaufman syndrome	
GO_TRANSCRIPTION_COREPRESSOR_ACTIVITY			0.045
	CTBP1	C-terminal binding protein 1	
	DDX54	DEAD-box helicase 54	
	BRD7	bromodomain containing 7	
	ATN1	atrophin 1	
	JUNB	JunB proto-oncogene, AP-1 transcription factor subunit	
	MAP3K10	mitogen-activated protein kinase kinase kinase 10	
	CBX4	chromobox 4	
	E4F1	E4F transcription factor 1	
	TRIM28	tripartite motif containing 28	
	NCOR2	nuclear receptor corepressor 2	
	DRAP1	DR1 associated protein 1	
	MXD4	MAX dimerization protein 4	
	MYBBP1A	MYB binding protein 1a	
	NOC2L	NOC2 like nucleolar associated transcriptional repressor	
	ZBTB7A	zinc finger and BTB domain containing 7A	



Supplementary Figure 6.1 Prediction of time restricted eating on 24-hour profiles of plasma ghrelin.

[Blue color: baseline; red color: week 8.]

CHAPTER 7 FUTURE DIRECTIONS AND CONCLUSIONS

7.1 Summary of the findings

The findings in this thesis can be summarised in three major parts: 1) the association between eating architecture components and markers of obesity and T2DM; 2) the impact of IF on 3 non-consecutive days per week on muscle and adipose tissue clock gene expression; 3) the effect of 10-hour TRE on glycaemic control and adipose tissue transcriptome. The results revealed that lower day-to-day variability in first meal consumption was associated with lower body fat and improved glucose control in adults at increased risk of T2DM. IF on 3 non-consecutive days per week had no universal effect to alter peripheral clocks. 10-hour TRE reduced fasting glucose, HbA1c, body weight and body fat, and downregulated genes involved in proteasome function and mitochondrial regulation in adipose tissue at 6 am. TRE did not alter DLMO but reduced morning cortisol levels. TRE altered the 24-hour profile of insulin, NEFA, triglyceride and GIP. CLOCK and NR1D2 were increased and PER1 and NR1D1 were decreased at 12 am by TRE. TRE restored the rhythmicity of 450 genes, which enriched in transcription co-repressor activity, DNA binding transcription factor binding, regulation of chromatin organization and small GTPase binding pathways. Weighted Gene Co-expression Network Analysis of these 450 genes revealed the three module eigengenes that were strongly correlated with BMI, insulin and NEFA.

7.2 Discussion

1. Which component of eating architecture matters most?

Whilst we were able to examine individual components of eating architecture (Zhao et al., 2021b), due to the small sample size, we could not examine how these components interact with each other to influence body fat and glycaemic markers. For instance, the time of the first meal and the last meal will determine the daily eating duration. Furthermore, meal frequency

and the inter-meal intervals may be highly correlated, further affecting the meal timing and size. Thus, one component could be a confounder for the association between another component and metabolic outcomes (Azami et al., 2019, Kahleova et al., 2017, Mekary et al., 2013, Mekary et al., 2012), which requires further examination with large datasets from multiple populations.

2. What are the impacts of IF on 24-hour profile of circadian clock and nutrients sensitive genes?

In animal models, acute 24-hour fasting blunted the rhythmicity of BMAL1 and REV-ERBα genes in both liver and muscle, and produced a temporal gene expression response via fasting-sensitive transcription factors including glucocorticoid receptor, cAMP responsive element binding protein, forkhead box proteins, transcription factor EB and peroxisome proliferator-activated receptors (Kinouchi et al., 2018), and phase-delayed Per2 gene expression in muscle (Barnea et al., 2010). IF also dampened the amplitudes of clock gene expression when the fasting/feeding cycle was initiated at the onset of the rest phase in mice. These changes were not observed when IF was initiated at the onset of the active phase, although a short phase advance was observed in clock genes aligned with the small advance in peak food intakes (Froy et al., 2009). In humans, an acute 24-hour fast downregulated metabolic pathways, such as triglyceride synthesis, tricarboxylic acid cycle, glycolysis, oxidative phosphorylation, insulin signalling, SREBP signalling, and mitochondrial translation in adipose tissue (Defour et al., 2020). However, the changes in circadian clocks were not reported. Whilst we observed that 8-week of IF did not alter circadian clock gene expression in adipose tissue and muscle, we still cannot determine whether there was a dampening or shifting in phase, as there was only one-time point sampled (Zhao et al., 2020). Therefore, further studies should establish the impact of IF on the 24-hour profile of clock gene expression in humans, and should determine whether the optimal metabolic responses are presented when the fasting periods are initiated at breakfast, lunch or dinner, as well as the feasibility and preferences that individuals have for following

one dietary pattern over the other.

3. Does CR require for restore the circadian clock during the IF intervention in humans?

Although our research showed that IF did not produce a uniform effect on the single time point of clock gene expression, we did not examine whether CR have contributed to this effect. In rodent models, CR increases the amplitude clock gene expression in the liver (Patel et al., 2016, Astafev et al., 2017). *Patel et al* demonstrated that mice with 30% of CR showed a remarkably robust oscillation in the expression of Per1, Per2, Cyr2 and Bmal1 compared to the mice fed *ad libitum* (Patel et al., 2016). The impact of CR on clocks was also independent of Bmal1, as shown by increased amplitude of Cry1 in CR with Bmal1 knockout mice (Patel et al., 2016). IF regimes that include zero or minimal calories on the fasting days, followed by *ad libitum* eating on the remaining days, restrict energy intake by about 10% restriction per day of fasting (e.g., 3 days of fasting is ~30% restriction) (Harris et al., 2018). Recently, *Templeman et al* examined the impact of IF on clock gene expression versus CR in adipose tissue (Templeman et al., 2021). Lean, healthy individuals were randomised into three groups, including 24-hour fasting with 150% energy intake on alternate days (0:150; n = 12) and two control groups involved a matched degree of daily CR without fasting (75% energy intake daily; 75:75; n = 12) or a matched pattern of fasting without net energy restriction (200% energy intake on alternate days; 0:200; n = 12) (Templeman et al., 2021). In this study, the time of the fast was initiated at 3 pm. A significant group by time effect were observed for Per1. However, post hoc analysis showed that Per1 was significant upregulated by CR, there was no change in IF (0:150) group, and Per1 trended downward in IF (0:200) group (Templeman et al., 2021). This suggests that IF without weight loss may perturb clocks, but the study still cannot determine whether there was a shift in the amplitude or phase of clocks due to the single time point sampling of the tissues. Therefore, further studies should isolate the effects of IF and energy restriction on the 24-hour profile of clock gene expression and explore whether CR is required for restoring the circadian

clock during the IF diet in humans.

4. What is the optimal meal timing to initiate the fast? And does the meal timing during a fed day impact health?

IF protocols on fasting days varies among trials, including initiating the fasts after breakfast (Hutchison et al., 2019a), lunch (Trepanowski et al., 2017), mid-afternoon (Templeman et al., 2021), and dinner (Catenacci et al., 2016) and late-night (Varady et al., 2011, Soeters et al., 2009). Some studies have also repeatedly broken the fasting period by multiple small meals (Trepanowski et al., 2017, Conley et al., 2018, Varady et al., 2011, Hoddy et al., 2014, Coutinho et al., 2018, Bowen et al., 2018). Furthermore, the protocol on fed days is also inconsistent among trials regarding the meal timing and calories such as *ad libutm* eating, 120%-150% of energy requirements or habitual eating. Given the potential for IF to promote day-to-day variation in meal timing and that none of the existing IF trials have ever tracked the eating patterns on fasting and fed days, further consideration should be given to the optimal design of IF protocols in humans. These studies should compare the effects of initiating IF after breakfast vs. dinner on health, and the amplitude and phase of peripheral clocks, during both fed and fasting days.

5. Does TRE improve metabolic health in individuals with established metabolic diseases?

In this research, we showed that TRE reduced fasting blood glucose and HbA1c and tended to reduce 24-hour mean glucose levels in males with obesity. These findings may provide evidence that TRE could assist glycaemic management in patients with prediabetes and T2DM. However, this finding cannot directly be implemented/translated in those individuals with established metabolic disorders such as T2DM or metabolic syndrome. To date, only one study showed that eight weeks of 10-hour TRE produced the benefits in 19 adults with metabolic syndrome (Wilkinson et al., 2019), and another study reported no changes of Hb1Ac after four

weeks of TRE in patients with T2DM (Parr et al., 2020a). One of the potential reasons could be short-time intervention. In addition, the safety and feasibility of translation TRE to those individuals with specific metabolic disorders are still unknown; thus, future studies are warranted.

6. What are the long-term effects of TRE in humans?

The evidence from previous studies and our study provides promising data regarding the benefits of TRE on human metabolic health. However, the majority of the intervention duration have ranged from 4 days to 16 weeks in a small sample size (less than 56 individuals). Only one trial has reported that TRE in conjunction with a hypoenergyetic diet, produced greater reductions in body fat mass and waist circumference versus controls with hypoenergyetic diet for 12 months in 31 individuals with obesity (Pureza et al., 2020, de Oliveira Maranhão Pureza et al., 2021). Yet, the long-term impacts of TRE and subsequent adherence in humans are not clear. Future studies should establish whether the metabolic health benefits of TRE are validated in the long term and in larger populations.

7. What is the best window for TRE? (length, early or late)

TRE protocols with daily energy intakes limited from 4 to 12 hours either early or later in the day have been implemented in humans, but the optimal time window of TRE to recommend for people has not been well tested. In rodent models, 9-hour protocol produced a greater reduction in body weight and fat mass, and better improvement in glucose tolerance versus 12-hour or 15-hour protocols (Sundaram and Yan, 2016, Chaix et al., 2014). Further, the evidence from animal models show that delaying the initiation of TRE (akin to breakfast skipping) delayed key clock and nutrient signaling genes, and mitigated weight and fat losses but did not impact the improvements in glucose tolerance (Regmi et al., 2021). In humans, metabolic improvements have been observed with 4-hour, 6-hour, 8-hour, 9-hour and 10-hour TRE

protocols (Hutchison et al., 2019b, Wilkinson et al., 2019, Cienfuegos et al., 2020a, Sutton et al., 2018, Martens et al., 2020). A shorter window located either early or late of the daytime can exhibit better metabolic improvements with (Cienfuegos et al., 2020a, Cienfuegos et al., 2021) or without (Sutton et al., 2018) weight loss. *Cienfuegos et al* for the first time, showed that 4-hour TRE did not produce superior metabolic health as compared with 6-hour late TRE in 12 adults with obesity (Cienfuegos et al., 2020a, Cienfuegos et al., 2021). In that study, the latest eating time was 7 pm for both studies. A 4-hour window prescribed in the late evening (5 pm to 9 pm) or beyond 10 hours have not shown health benefits (Carlson et al., 2007, Stote et al., 2007, LeCheminant et al., 2013, Pureza et al., 2020, de Oliveira Maranhão Pureza et al., 2021). TRE initiated at breakfast or lunch resulted in improvements in glucose tolerance in men with obesity (Hutchison et al., 2019b). When designing TRE trials, consideration should also be given to increase participant compliance. Collectively, larger and longer trials are required to confirm whether TRF has dose-dependent effects and, if so, the optimal time of eating window to recommend and that can be followed long term.

8. Should a personalised TRE window be prescribed?

Carriers of specific genetic variants in the circadian gene, such as BMAL1 (rs7950226, rs11022775) (Woon et al., 2007), CLOCK (rs3749474, rs1801260, rs4580704) (Scott et al., 2008, Sookoian et al., 2008), CRY2 (rs11605924) (Barker et al., 2011), and REV-REBα (rs939347) (Ruano et al., 2014), as well as carriers of a common variant in melatonin receptor 1B gene (MTNR1B, rs10830963) (Garaulet et al., 2020, de Luis et al., 2020a, de Luis et al., 2020b, Pacheco et al., 2020, Goni et al., 2019), are more likely to be obese and increased risk of developing T2DM. Further, a late eating window may not maximise the benefits of TRE in individuals with MTNR1B variant. Therefore, personal chronotype and potentially genotype when prescribing TRE. and should be further explored in future studies.

9. What is the impact of TRE on cortisol?

Cortisol is one of the critical outputs of endogenous clock. In humans, cortisol peaks shortly before activity starts (cortisol awakening response, CAR) and declines during the remaining 24-hour, following a periodic non-linear oscillation with brisk cortisol increases in response to psychological and nutritional stimuli (Minnetti et al., 2020). A flattened diurnal cortisol slope resulted from low CAR or raised evening cortisol levels, is predictive for the future incidence of T2DM (Hackett et al., 2016). The effects of TRE on cortisol levels vary among studies. Our study found that 10-hour self-selected TRE reduced morning cortisol Area under the curve (AUC) (6 am to 12 pm) and did not alter the evening cortisol AUC (6 pm to 1 am). Early 6-hour TRE altered the decreased evening cortisol at 8 pm without changing the fasting cortisol levels at 8 am in a four-day randomised cross-over trial (Jamshed et al., 2019, Ravussin et al., 2019). Reduced cortisol stress responses were also observed in healthy adult firefighters after eight weeks of TRE (8 hours/day) (McAllister et al., 2021a). However, TRE (8hours/day from 10 am to 6 pm) for five days did not alter the 24-hour cortisol levels measured by area under the curve (AUC) in sedentary men with overweight/obesity (Parr et al., 2020b, Lundell et al., 2020). However, none of the TRE studies evaluated CAR and the early, late, and overall cortisol slope changes.

10. Does TRE impact the proteome in peripheral tissues?

In this research, we demonstrated that TRE altered the 24-hour rhythmicity of genes which are enriched in transcription co-repressor activity, DNA binding transcription factor binding, regulation of chromatin organisation and small GTPase binding pathways at the transcription level. However, we did not measure this at the level of the proteome. The fundamental molecular mechanism of circadian physiology is based on the orchestration of transcriptional/translational feedback loops (Huang et al., 2011, Bass and Takahashi, 2010,

Panda, 2016). Some of the clock proteins coded by the clock genes are transcription factors and transcriptional regulators, which activate or repress their own expression or other clock proteins. Those target genes driven by the core clock are termed 'CCG', which enrich the output of circadian rhythms (Luck et al., 2014). Extensive transcriptomic studies revealed that 43% of all protein-coding genes showed circadian expression in a tissue-specific manner in mice (Zhang et al., 2014). However, the rhythmic phases of proteins abundance throughout the day are usually different from the abundance of transcripts. For instance, *Reddy et al* demonstrated that nearly half of the cycling proteins were not cycling at the transcriptional level in mouse liver (Reddy et al., 2006). Thus the rhythmicity of proteome is regulated not only at the transcriptional level but also translational and posttranslational levels.

Furthermore, the organism needs an accurate, rapid and temporal regulation of proteins such as phosphorylation to coordinate metabolic homeostasis (Robles et al., 2017). *Mauvoisin et al* found that the proteins displayed circadian rhythmicity involve in multiple key hepatic physiological processes in mice with nighttime feeding (Mauvoisin et al., 2014). Additionally, more than 25% of phosphorylating sites are robust oscillated in a daily rhythm with significant higher amplitudes, which is more sensitive than the dynamic changes in the proteome (Robles et al., 2017). As protein phosphorylating and dephosphorylating acts like a power that temporarily turns on and off the physiological processes, multiple signalling pathways coordinate by this temporally regulation. Circadian proteomic profile studies in humans are extremely limited. So far, only one study has provided evidence that endogenous and non-endogenous rhythms regulate the human proteome. *Depner et al* measured one circadian cycle every 4 hours from 6 healthy males who were subjected to eat during daytime within 13 hours and sleep during nighttime (aligned with the endogenous circadian rhythm) or eat during nighttime within and sleep during daytime (misaligned with the endogenous circadian rhythm), and found the acute impacts of misalignment of food intake and sleep on human plasma

proteome (Depner et al., 2018). Therefore, the effects of TRE on peripheral proteome and phosphorolome requires further study in humans.

11. Does TRE impact the diurnal rhythm of microbiota in humans?

The microbiome influences metabolism and contributes to metabolic disorders and obesity (Hartstra et al., 2015). Specific microbiota and essential microbially-derived products, such as short-chain fatty acids and bile acids, exhibit diurnal rhythms in relative abundance over a 24-hour cycle (Leone et al., 2015, Voigt et al., 2014, Thaiss et al., 2014). Erratic eating patterns and diet-induced obesity can disrupt and dampen these rhythms (Zarrinpar et al., 2014). Circadian disruption caused by behavior and genetics also decreased the taxonomic diversity and induced intestinal dysbiosis(Voigt et al., 2014, Voigt et al., 2016). In mice, TRE can restore oscillations in some gut microbiota (Zarrinpar et al., 2014). The recent systematic review for six human clinical trials showed that intermittent fasting increases the diversity and abundance of gut microbiome, which may be associated with improved immune function and metabolic health (Llewellyn-Waters and Abdullah, 2021). Only two studies examined the impact of TRE on human gut microbiota (Zeb et al., 2020, Gabel et al., 2020b). *Zeb et al* found that 8-hour TRE (7:30 pm to 3:30 am) for 25 days increased the diversity of gut microbiota and beneficial bacteria in healthy young adults compared with the control group, while *Gabel et al* reported no change in gut microbiota phylogenetic diversity and abundance of any phyla after 12 weeks TRE (10 am to 6 pm). However, the evidence of the impact of TRE on the diurnal oscillation of the human gut microbiome with multiple fecal sampling, through rectal swabs, is still not tested. Further studies are required.

12. What is the relationship between insulin and circadian clock in response to TRE?

This research revealed that the genes that altered the rhythmicity in response to TRE were correlated with insulin. Unfortunately, our analysis cannot uncover the mechanisms of this

correlation. However, the evidence from mice and humans showed that insulin acts as a time cue to regulate the molecular clock by inducing the transcription and translation of Per (Crosby et al., 2019, Tuvia et al., 2021). *Crosby et al* showed that insulin increased the Per2 translation in mouse fibroblasts through the mTOR-Akt pathways. In contrast, *Tucia et al* showed that insulin acutely induced the Per2 transcripts and protein levels in human and mouse adipose tissue plants, suggesting the cell- and tissue-specific mechanisms of insulin in the regulation of the circadian clock in peripheral tissues. However, our study was limited to interpreting insulin's role in the regulation of adipose tissue transcriptomic profile. Thus, future studies are needed to examine whether altered insulin levels are the mechanisms of restoring peripheral clocks in response to TRE. Studies with multiple time-point-matched plasma insulin and peripheral tissues (such as peripheral white blood cells) along with each meal response are required.

13. What is the proper timing for the macronutrients in optimising the effects of TRE? Does the sequence of the macronutrients within a meal matter in optimising the effects of TRE?

Different macronutrients will produce different insulin responses to a meal. Limited evidence has evaluated the effects of manipulating macronutrient timing on circadian rhythm and metabolic health (extensively reviewed in chapter 2). Therefore, more studies are required.

The sequence of macronutrient intakes within a meal may also affect postprandial responses. Several studies have shown that consuming carbohydrates-last within a meal improves glycaemic control in healthy individuals (Sun et al., 2020), prediabetes (Shukla et al., 2019) or type 2 diabetes (Shukla et al., 2017, Shukla et al., 2015). In a randomised cross-over study, 16 healthy adults were served five identical test meals with different sequences of rice, vegetables and meat in 5 separate occasions at breakfast, *Sun et al* reported that eating rice last attenuated the glycaemic response and increased GLP-1 stimulation, but did not differentially alter insulin

levels (Sun et al., 2020). After a protein preload, improved postprandial glucose responses have been observed, but solely following a breakfast meal (Rigamonti et al., 2019, Watson et al., 2019, Nesti et al., 2019, Tricò et al., 2020). Metabolome analysis found that temporal changes in postprandial metabolic pattern in response to a preload protein could predict the glucose and insulin response after the main meal in subjects with metabolic syndrome, suggesting that pre-consumption of protein may facilitate the glucose and lipid disposal from plasma (Pekmez et al., 2020). Optimising micronutrient intake within a meal during the TRE intervention could provide new avenues to maximise the benefits of TRE and improve glycaemic control.

7.3 Implications

The implications of the studies in this thesis are two parts: implications of the findings for dietary interventions in health clinical practice guidelines and methodological implications in eating patterns

7.3.1 Health and clinical practice guidelines

This thesis provides the novel evidence in circadian rhythm and metabolic health with a special focus on when we eat. Regular consumption of meals daily, particularly breakfast is easy and low-cost to translate to the clinical practice. In general, the type of IF is selected based on the potential increased adherence but neglected the impact of the meal timing on fasting day on body circadian system and metabolic health, which implies to the dietitian to be cautious to recommend IF as an intervention.

Reduced HbA1c along with reduced fasting blood glucose in response to 10-hour TRE could be a preventative or therapeutic strategy to assist glycaemic management for patients with prediabetes or T2DM. The study delivers the first evidence the TRE restores circadian rhythms to genes in adipose tissue in humans, providing potential mechanisms of TRE in regulating

metabolic health in humans could be critical to translating the TRE into clinical practice.

These recommendations could readily be translated to existing dietary guidelines, and be a simple, safe and effective means of reducing the significant and increasing burden of T2DM in community.

7.3.2 Methodological implications in nutritional clinical trials and epidemiological studies

This thesis also enriched the concept of the eating architecture by calculating meal regularity as a day-to-day variation through the data collected objectively. To our knowledge, for the first time we have aligned three datasets, including photograph-based food diary with meal timing, sleep pattern monitored by accelerometer and blood glucose levels measured by continuous glucose monitors in real time, to capture the components of the eating architecture and their associations with glucose control. The novel methodological significance could provide the new approach for the nutritional clinical trials and epidemiological studies to further understand the importance of eating architecture in larger population.

7.4 Limitations

Although the limitations of each study are detailed in the respective chapters, I mention some of the major ones below. In common, the studies in this thesis had small sample size and limited to male and/or female adults with obesity. Thus, more prospective studies with larger sample sizes and in wider population groups are needed to evaluate the long-term risk of obesity or chronic diseases with respect to IF and TRE.

An inability to adjust for many variables was the major limitations in the first study (Chapter 3). In addition, the interaction of eating architecture components could not be explored in this study. The average number of days that dietary data was collected varied between participants,

which was not adjusted for. The terminology of eating event was not determined based on the characteristics of our own data but referred to a study published in the United States population.

The one-time point tissue sampling in study 2 (Chapter 4) limited us to determine whether IF dampened or shifted in the phase of clock genes and the lack of a CR group meant that we could not differentiate between the effects of IF and CR.

7.5 Future directions

Future studies should consider two major directions, including identifying the optimal initiation time of fasting during IF and/or TRE to maximise the weight and health benefit, and the application of new novel technologies in nutritional research.

CR has been reported to increases the amplitude clock gene expression in rodent models (Patel et al., 2016, Astafev et al., 2017). However, the evidence in the impact of IF on clocks independent from CR is less explored. Future studies should isolate the effects of IF from CR and examine health and longevity pathways as well as the impact of these separately on the 24-hour transcriptome. It is unclear whether CR is required for restoring the circadian clock during the IF diet in humans. In addition, the impact of fast initiation time on fasting days under the same IF protocol on metabolic health needs to be investigated. Given the potential for IF to promote day-to-day variation in meal timing and the fact that none of the existing IF trials have ever tracked eating patterns on fasting and fed days, further consideration should be given to the optimal design of IF protocols in humans including standardising/measuring meal timing. These studies should compare the effects of initiating IF after breakfast vs. dinner on health, and the amplitude and phase of peripheral clocks, during both fed and fasting days.

Trials on the metabolic benefits of TRE have increased exponentially in recent years. In animal models, the health benefits from CR mouse model can be partially attributed to TRE (Duregon

et al., 2021, Pak et al., 2021). Recently, *Pak et al* demonstrated that fasting alone recapitulates many of the physiological and molecular effects of CR by using a series of feeding regimens to dissect the effects of calories and fasting. In humans, early and late short TRE produces metabolic benefit (Sutton et al., 2018, Cienfuegos et al., 2020a) and similar results are observed in mice (Regmi et al., 2021). In order to improving compliance to TRE interventions (Regmi and Heilbronn, 2020), late TRE may a better option (Cienfuegos et al., 2020a). However, the long-term effect of delayed TRE as compared to the early TRE is still not tested. Therefore, further investigation is required in this matter, including whether the health benefits of TRE is greater than CR with or with same length of fasting duration and what length of eating window is optimal in humans.

Whether manipulating carbohydrate intake towards the beginning of the day and fat and protein towards the end of the day could improve glucose metabolism, particularly in those who are overweight and at risk of insulin resistance (Zhao et al., 2021a). A meal with vegetable first followed by meat and rice attenuates postprandial responses (Sun et al., 2020). These strategies should also be used to optimize the IF and TRE protocol and studies testing this in future should be designed.

Last but not the least, emerging technologies provide us with new abilities to investigate individuals' behaviours under free-living conditions. The traditional methods for collecting behavioural and physiological rhythms to predict the risk of metabolic health over a certain period of time is slowly being replaced by more convenient technologies, such as smartphone applications, continuous glucose monitors, blood pressure, as well as heart rate, body temperature, activity, light exposure and sleep patterns through accelerometers. Smartphone applications have allowed tracking what, where and when foods are consumed with time-stamped pictures and annotations (Yong et al., 2020, Chow et al., 2020, Wilkinson et al., 2019, Gill and Panda, 2015, Gupta et al., 2017b) and some have been validated against weighed food

records (Naaman et al., 2021). Continuous glucose monitors may also be able to track carbohydrate intake, although the responses to individual meals depend on their individual glucose tolerance, glycaemic index of the carbohydrate, fibre, fat and protein content of the meals as well as meal format, rate of gastric emptying and the time of day. Machine learning may also prove to be useful in identifying adherence of the diet to interventions (Zeevi et al., 2015). Simultaneously, tracking cardiometabolic risk factors monitors by CGM, dynamic 24-hour blood pressure monitoring, and activity and sleep patterns tracking through accelerometers, will also provide dynamic changes over the same time periods. These can then be aligned with food records via smartphone application and physical activity status to develop a comprehensive understanding of eating architecture and health.

7.6 Conclusions

Our behavioural and physiological processes are driven by internal circadian rhythms orchestrated with external environmental cues. Food intake is a strong entraining cue for peripheral clocks, which may be partially driven by the feeding-related hormone insulin. Therefore, mistimed and erratic eating patterns, could induce circadian disruption and promote obesity and metabolic disorders. Few studies have simultaneously captured objective behavioural rhythms under free-living conditions to explore the contributors associated with obesity and T2DM.

This doctoral work demonstrated that eating breakfast earlier and at a consistent time each day was associated with decreased body fat mass, and improved glycaemic control as indicated by lower HbA1c, in adults with increased risk of T2DM. There are some concerns that IF protocols may induce circadian disruption due to the day-to-day variation in daily eating patterns, but this has not been well tested to date. Reassuringly, we showed that IF did not uniformly alter clock gene expression, which may partly be due to the alignment of the fasting/feeding cycle with the

biological clock by initiating the fasting day at breakfast. This partially supports the above findings from the cross-sectional study.

Finally, TRE protocols are designed to reinforce circadian rhythms in peripheral tissues and improve metabolic health in animals and humans. However, very few have explored the potential mechanisms involved in restoring the peripheral circadian clocks in humans. In our hands, TRE had a net effect of reducing body weight and glycaemia, and dampened energy-consuming pathways in adipose tissue after overnight fasting in men with obesity. The 24-hour data indicate that TRE altered the rhythms of blood metabolites, insulin, and increased key clock genes and restored genes expression involving in chromatin regulation and vesicular translocation of glucose transporters in human SAT. Additionally, our study further supports the emerging evidence that insulin as a systematic time cue may be the driver of the changes in 24-hour profiles of metabolites in blood and transcripts in adipose tissue in response to TRE.

To summarise, routine consumption of breakfast may optimise temporal regulation to anticipate and respond appropriately to a meal challenge, and TRE will decrease the risk factors of T2DM, and restore 24-hour rhythms of blood metabolites and glucoregulatory hormones and transcriptome in adipose tissue. Collectively, this thesis suggests that TRE could be a preventative or therapeutic strategy to assist glycaemic management for individuals with obesity who are at high risk of T2DM.

REFERENCES

2021. The Gene Ontology resource: enriching a GOld mine. *Nucleic Acids Res,* 49**,** D325-D334.

ADAFER, R., MESSAADI, W., MEDDAHI, M., PATEY, A., HADERBACHE, A., BAYEN, S. & MESSAADI, N. 2020. Food Timing, Circadian Rhythm and Chrononutrition: A Systematic Review of Time-Restricted Eating's Effects on Human Health. *Nutrients,* 12.

ADAMOVICH, Y., ROUSSO-NOORI, L., ZWIGHAFT, Z., NEUFELD-COHEN, A., GOLIK, M., KRAUT-COHEN, J., WANG, M., HAN, X. & ASHER, G. 2014. Circadian clocks and feeding time regulate the oscillations and levels of hepatic triglycerides. *Cell Metab,* 19**,** 319-30.

AFSHIN, A., FOROUZANFAR, M. H., REITSMA, M. B., SUR, P., ESTEP, K., LEE, A., MARCZAK, L., MOKDAD, A. H., MORADI-LAKEH, M., NAGHAVI, M., SALAMA, J. S., VOS, T., ABATE, K. H., ABBAFATI, C., AHMED, M. B., AL-ALY, Z., ALKERWI, A., AL-RADDADI, R., AMARE, A. T., AMBERBIR, A., AMEGAH, A. K., AMINI, E., AMROCK, S. M., ANJANA, R. M., ARNLOV, J., ASAYESH, H., BANERJEE, A., BARAC, A., BAYE, E., BENNETT, D. A., BEYENE, A. S., BIADGILIGN, S., BIRYUKOV, S., BJERTNESS, E., BONEYA, D. J., CAMPOS-NONATO, I., CARRERO, J. J., CECILIO, P., CERCY, K., CIOBANU, L. G., CORNABY, L., DAMTEW, S. A., DANDONA, L., DANDONA, R., DHARMARATNE, S. D., DUNCAN, B. B., ESHRATI, B., ESTEGHAMATI, A., FEIGIN, V. L., FERNANDES, J. C., FURST, T., GEBREHIWOT, T. T., GOLD, A., GONA, P. N., GOTO, A., HABTEWOLD, T. D., HADUSH, K. T., HAFEZI-NEJAD, N., HAY, S. I., HORINO, M., ISLAMI, F., KAMAL, R., KASAEIAN, A., KATIKIREDDI, S. V., KENGNE, A. P., KESAVACHANDRAN, C. N., KHADER, Y. S., KHANG, Y. H., KHUBCHANDANI, J., KIM, D., KIM, Y. J., KINFU, Y., KOSEN, S., KU, T., DEFO, B. K., KUMAR, G. A., LARSON, H. J., LEINSALU, M., LIANG, X., LIM, S. S., LIU, P., LOPEZ, A. D., LOZANO, R., MAJEED, A., MALEKZADEH, R., MALTA, D. C., MAZIDI, M., MCALINDEN, C., MCGARVEY, S. T., MENGISTU, D. T., MENSAH, G. A., MENSINK, G. B. M., MEZGEBE, H. B., MIRRAKHIMOV, E. M., MUELLER, U. O., NOUBIAP, J. J., OBERMEYER, C. M., OGBO, F. A., OWOLABI, M. O., PATTON, G. C., et al. 2017. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med,* 377**,** 13-27.

AHOLA, A. J., MUTTER, S., FORSBLOM, C., HARJUTSALO, V. & GROOP, P. H. 2019. Meal timing, meal frequency, and breakfast skipping in adult individuals with type 1 diabetes - associations with glycaemic control. *Sci Rep,* 9**,** 20063.

ALBREIKI, M. S., MIDDLETON, B. & HAMPTON, S. M. 2017. A single night light exposure acutely alters hormonal and metabolic responses in healthy participants. *Endocr Connect,* 6**,** 100-110.

ALENGHAT, T., MEYERS, K., MULLICAN, S. E., LEITNER, K., ADENIJI-ADELE, A., AVILA, J., BUĆAN, M., AHIMA, R. S., KAESTNER, K. H. & LAZAR, M. A. 2008. Nuclear receptor corepressor and histone deacetylase 3 govern circadian metabolic physiology. *Nature,* 456**,** 997-1000.

ALJURAIBAN, G. S., CHAN, Q., OUDE GRIEP, L. M., BROWN, I. J., DAVIGLUS, M. L., STAMLER, J., VAN HORN, L., ELLIOTT, P. & FROST, G. S. 2015. The impact of eating frequency and time of intake on nutrient quality and Body Mass Index: the INTERMAP Study, a Population-Based Study. *J Acad Nutr Diet,* 115**,** 528-36 e1.

ALLISON, K. C., HOPKINS, C. M., RUGGIERI, M., SPAETH, A. M., AHIMA, R. S., ZHANG, Z., TAYLOR, D. M. & GOEL, N. 2020. Prolonged, Controlled Daytime versus Delayed Eating Impacts Weight and Metabolism. *Curr Biol*.

ALMOOSAWI, S., VINGELIENE, S., GACHON, F., VOORTMAN, T., PALLA, L., JOHNSTON, J. D., VAN DAM, R. M., DARIMONT, C. & KARAGOUNIS, L. G. 2019. Chronotype: Implications for Epidemiologic Studies on Chrono-Nutrition and Cardiometabolic Health. *Adv Nutr,* 10**,** 30-42.

ALTAREJOS, J. Y., GOEBEL, N., CONKRIGHT, M. D., INOUE, H., XIE, J., ARIAS, C. M., SAWCHENKO, P. E. & MONTMINY, M. 2008. The Creb1 coactivator Crtc1 is required for energy balance and fertility. *Nat Med,* 14**,** 1112-7.

ALVES, R. D., DE OLIVEIRA, F. C., HERMSDORFF, H. H., ABETE, I., ZULET, M. A., MARTÍNEZ, J. A. & BRESSAN, J. 2014. Eating carbohydrate mostly at lunch and protein mostly at dinner within a covert hypocaloric diet influences morning glucose homeostasis in overweight/obese men. *Eur*

J Nutr, 53**,** 49-60.

AMBROSINI, G. L., HURWORTH, M., GIGLIA, R., TRAPP, G. & STRAUSS, P. 2018. Feasibility of a commercial smartphone application for dietary assessment in epidemiological research and comparison with 24-h dietary recalls. *Nutr J,* 17**,** 5.

ANOTHAISINTAWEE, T., LERTRATTANANON, D., THAMAKAISON, S., KNUTSON, K. L., THAKKINSTIAN, A. & REUTRAKUL, S. 2017. Later chronotype is associated with higher hemoglobin A1c in prediabetes patients. *Chronobiol Int,* 34**,** 393-402.

ANTHONSEN, M. W., RÖNNSTRAND, L., WERNSTEDT, C., DEGERMAN, E. & HOLM, C. 1998. Identification of novel phosphorylation sites in hormone-sensitive lipase that are phosphorylated in response to isoproterenol and govern activation properties in vitro. *J Biol Chem,* 273**,** 215-21.

ANTON, S. D., LEE, S. A., DONAHOO, W. T., MCLAREN, C., MANINI, T., LEEUWENBURGH, C. & PAHOR, M. 2019. The Effects of Time Restricted Feeding on Overweight, Older Adults: A Pilot Study. *Nutrients,* 11.

ANTONI, R., JOHNSTON, K. L., COLLINS, A. L. & ROBERTSON, M. D. 2017. Effects of intermittent fasting on glucose and lipid metabolism. *Proc Nutr Soc,* 76**,** 361-368.

ANTONI, R., JOHNSTON, K. L., COLLINS, A. L. & ROBERTSON, M. D. 2018. Intermittent v. continuous energy restriction: differential effects on postprandial glucose and lipid metabolism following matched weight loss in overweight/obese participants. *Br J Nutr,* 119**,** 507-516.

ANTONI, R., ROBERTSON, T., ROBERTSON, M., & JOHNSTON, J. 2018. . A pilot feasibility study exploring the effects of a moderate time-restricted feeding intervention on energy intake, adiposity and metabolic physiology in free-living human subjects. *Journal of Nutritional Science,* 7.

ARBLE, D. M., BASS, J., LAPOSKY, A. D., VITATERNA, M. H. & TUREK, F. W. 2009. Circadian timing of food intake contributes to weight gain. *Obesity (Silver Spring),* 17**,** 2100-2.

ASHBURNER, M., BALL, C. A., BLAKE, J. A., BOTSTEIN, D., BUTLER, H., CHERRY, J. M., DAVIS, A. P., DOLINSKI, K., DWIGHT, S. S., EPPIG, J. T., HARRIS, M. A., HILL, D. P., ISSEL-TARVER, L., KASARSKIS, A., LEWIS, S., MATESE, J. C., RICHARDSON, J. E., RINGWALD, M., RUBIN, G. M. & SHERLOCK, G. 2000. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. *Nat Genet,* 25**,** 25-9.

ASHER, G., REINKE, H., ALTMEYER, M., GUTIERREZ-ARCELUS, M., HOTTIGER, M. O. & SCHIBLER, U. 2010. Poly(ADP-ribose) polymerase 1 participates in the phase entrainment of circadian clocks to feeding. *Cell,* 142**,** 943-53.

ASTAFEV, A. A., PATEL, S. A. & KONDRATOV, R. V. 2017. Calorie restriction effects on circadian rhythms in gene expression are sex dependent. *Sci Rep,* 7**,** 9716.

AUSTRALIAN INSTITUTE OF HEALTH AND WELFARE 2020a. Australian Burden of Disease Study 2015: Interactive data on risk factor burden, viewed 12 July 2021. *https://www.aihw.gov.au/reports/burden-of-disease/interactive-data-risk-factor-burden*.

AUSTRALIAN INSTITUTE OF HEALTH AND WELFARE 2020b. Overweight and obesity: an interactive insight. Cat. no. PHE 251. . *Canberra: AIHW. Viewed 22 March 2021, https://www.aihw.gov.au/reports/overweight-obesity/overweight-and-obesity-an-interactive-insight*.

AUSTRALIAN INSTITUTE OF HEALTH AND WELFARE (AIHW) 2017. Impact of overweight and obesity as a risk factor for chronic conditions, AIHW, Canberra.

AZAMI, Y., FUNAKOSHI, M., MATSUMOTO, H., IKOTA, A., ITO, K., OKIMOTO, H., SHIMIZU, N., TSUJIMURA, F., FUKUDA, H., MIYAGI, C., OSAWA, S., OSAWA, R. & MIURA, J. 2019. Long working hours and skipping breakfast concomitant with late evening meals are associated with suboptimal glycemic control among young male Japanese patients with type 2 diabetes. *J Diabetes Investig,* 10**,** 73-83.

BACH-FAIG, A., BERRY, E. M., LAIRON, D., REGUANT, J., TRICHOPOULOU, A., DERNINI, S., MEDINA, F. X., BATTINO, M., BELAHSEN, R., MIRANDA, G. & SERRA-MAJEM, L. 2011. Mediterranean diet pyramid today. Science and cultural updates. *Public Health Nutr,* 14**,** 2274-84.

BALAMATSIAS, D., KONG, A. M., WATERS, J. E., SRIRATANA, A., GURUNG, R., BAILEY, C. G., RASKO, J. E.,

TIGANIS, T., MACAULAY, S. L. & MITCHELL, C. A. 2011. Identification of P-Rex1 as a novel Rac1-guanine nucleotide exchange factor (GEF) that promotes actin remodeling and GLUT4 protein trafficking in adipocytes. *J Biol Chem,* 286**,** 43229-40.

BALES, C. W. & KRAUS, W. E. 2013. Caloric restriction: implications for human cardiometabolic health. *J Cardiopulm Rehabil Prev,* 33**,** 201-8.

BALLON, A., NEUENSCHWANDER, M. & SCHLESINGER, S. 2019. Breakfast Skipping Is Associated with Increased Risk of Type 2 Diabetes among Adults: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *J Nutr,* 149**,** 106-113.

BANKS, G., NOLAN, P. M. & PEIRSON, S. N. 2016. Reciprocal interactions between circadian clocks and aging. *Mamm Genome,* 27**,** 332-40.

BARKER, A., SHARP, S. J., TIMPSON, N. J., BOUATIA-NAJI, N., WARRINGTON, N. M., KANONI, S., BEILIN, L. J., BRAGE, S., DELOUKAS, P., EVANS, D. M., GRONTVED, A., HASSANALI, N., LAWLOR, D. A., LECOEUR, C., LOOS, R. J., LYE, S. J., MCCARTHY, M. I., MORI, T. A., NDIAYE, N. C., NEWNHAM, J. P., NTALLA, I., PENNELL, C. E., ST POURCAIN, B., PROKOPENKO, I., RING, S. M., SATTAR, N., VISVIKIS-SIEST, S., DEDOUSSIS, G. V., PALMER, L. J., FROGUEL, P., SMITH, G. D., EKELUND, U., WAREHAM, N. J. & LANGENBERG, C. 2011. Association of genetic Loci with glucose levels in childhood and adolescence: a meta-analysis of over 6,000 children. *Diabetes,* 60**,** 1805-12.

BARNEA, M., MADAR, Z. & FROY, O. 2010. High-fat diet followed by fasting disrupts circadian expression of adiponectin signaling pathway in muscle and adipose tissue. *Obesity (Silver Spring),* 18**,** 230-8.

BASS, J. & TAKAHASHI, J. S. 2010. Circadian integration of metabolism and energetics. *Science,* 330**,** 1349-54.

BEAULIEU, K., CASANOVA, N., OUSTRIC, P., TURICCHI, J., GIBBONS, C., HOPKINS, M., VARADY, K., BLUNDELL, J. & FINLAYSON, G. 2020. Matched Weight Loss Through Intermittent or Continuous Energy Restriction Does Not Lead To Compensatory Increases in Appetite and Eating Behavior in a Randomized Controlled Trial in Women with Overweight and Obesity. *J Nutr,* 150**,** 623-633.

BENLOUCIF, S., BURGESS, H. J., KLERMAN, E. B., LEWY, A. J., MIDDLETON, B., MURPHY, P. J., PARRY, B. L. & REVELL, V. L. 2008. Measuring melatonin in humans. *J Clin Sleep Med,* 4**,** 66-9.

BERRINGTON DE GONZALEZ, A., HARTGE, P., CERHAN, J. R., FLINT, A. J., HANNAN, L., MACINNIS, R. J., MOORE, S. C., TOBIAS, G. S., ANTON-CULVER, H., FREEMAN, L. B., BEESON, W. L., CLIPP, S. L., ENGLISH, D. R., FOLSOM, A. R., FREEDMAN, D. M., GILES, G., HAKANSSON, N., HENDERSON, K. D., HOFFMAN-BOLTON, J., HOPPIN, J. A., KOENIG, K. L., LEE, I. M., LINET, M. S., PARK, Y., POCOBELLI, G., SCHATZKIN, A., SESSO, H. D., WEIDERPASS, E., WILLCOX, B. J., WOLK, A., ZELENIUCH-JACQUOTTE, A., WILLETT, W. C. & THUN, M. J. 2010. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med,* 363**,** 2211-9.

BI, H., GAN, Y., YANG, C., CHEN, Y., TONG, X. & LU, Z. 2015. Breakfast skipping and the risk of type 2 diabetes: a meta-analysis of observational studies. *Public Health Nutr,* 18**,** 3013-9.

BLÜHER, M. 2019. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol,* 15**,** 288-298.

BONNET, J. P., CARDEL, M. I., CELLINI, J., HU, F. B. & GUASCH-FERRÉ, M. 2020. Breakfast Skipping, Body Composition, and Cardiometabolic Risk: A Systematic Review and Meta-Analysis of Randomized Trials. *Obesity (Silver Spring),* 28**,** 1098-1109.

BOWEN, J., BRINDAL, E., JAMES-MARTIN, G. & NOAKES, M. 2018. Randomized Trial of a High Protein, Partial Meal Replacement Program with or without Alternate Day Fasting: Similar Effects on Weight Loss, Retention Status, Nutritional, Metabolic, and Behavioral Outcomes. *Nutrients,* 10.

BRAY, G. A., KIM, K. K. & WILDING, J. P. H. 2017. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. *Obes Rev,* 18**,** 715-723.

BRENNA, A. & ALBRECHT, U. 2020. Phosphorylation and Circadian Molecular Timing. *Front Physiol,* 11**,** 612510.

BROUSSARD, J. L., EHRMANN, D. A., VAN CAUTER, E., TASALI, E. & BRADY, M. J. 2012. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. *Ann Intern Med,* 157**,** 549-57.

CAMPBELL, J. E. & NEWGARD, C. B. 2021. Mechanisms controlling pancreatic islet cell function in insulin secretion. *Nat Rev Mol Cell Biol,* 22**,** 142-158.

CANFORA, E. E., MEEX, R. C. R., VENEMA, K. & BLAAK, E. E. 2019. Gut microbial metabolites in obesity, NAFLD and T2DM. *Nat Rev Endocrinol,* 15**,** 261-273.

CAPPUCCIO, F. P., COOPER, D., D'ELIA, L., STRAZZULLO, P. & MILLER, M. A. 2011. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J,* 32**,** 1484-92.

CAPPUCCIO, F. P., D'ELIA, L., STRAZZULLO, P. & MILLER, M. A. 2010. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care,* 33**,** 414-20.

CARLSON, O., MARTIN, B., STOTE, K. S., GOLDEN, E., MAUDSLEY, S., NAJJAR, S. S., FERRUCCI, L., INGRAM, D. K., LONGO, D. L., RUMPLER, W. V., BAER, D. J., EGAN, J. & MATTSON, M. P. 2007. Impact of reduced meal frequency without caloric restriction on glucose regulation in healthy, normal-weight middle-aged men and women. *Metabolism,* 56**,** 1729-34.

CARTER, S., CLIFTON, P. M. & KEOGH, J. B. 2016. The effects of intermittent compared to continuous energy restriction on glycaemic control in type 2 diabetes; a pragmatic pilot trial. *Diabetes Res Clin Pract,* 122**,** 106-112.

CATENACCI, V. A., PAN, Z., OSTENDORF, D., BRANNON, S., GOZANSKY, W. S., MATTSON, M. P., MARTIN, B., MACLEAN, P. S., MELANSON, E. L. & TROY DONAHOO, W. 2016. A randomized pilot study comparing zero-calorie alternate-day fasting to daily caloric restriction in adults with obesity. *Obesity (Silver Spring),* 24**,** 1874-83.

CHAIX, A., LIN, T., LE, H. D., CHANG, M. W. & PANDA, S. 2018. Time-Restricted Feeding Prevents Obesity and Metabolic Syndrome in Mice Lacking a Circadian Clock. *Cell Metab*.

CHAIX, A., MANOOGIAN, E. N. C., MELKANI, G. C. & PANDA, S. 2019. Time-Restricted Eating to Prevent and Manage Chronic Metabolic Diseases. *Annu Rev Nutr,* 39**,** 291-315.

CHAIX, A., ZARRINPAR, A., MIU, P. & PANDA, S. 2014. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. *Cell Metab,* 20**,** 991-1005.

CHEN, L., MAGLIANO, D. J., BALKAU, B., COLAGIURI, S., ZIMMET, P. Z., TONKIN, A. M., MITCHELL, P., PHILLIPS, P. J. & SHAW, J. E. 2010. AUSDRISK: an Australian Type 2 Diabetes Risk Assessment Tool based on demographic, lifestyle and simple anthropometric measures. *Med J Aust,* 192**,** 197-202.

CHEN, Q., HUANG, L., PAN, D., ZHU, L. J. & WANG, Y. X. 2018. Cbx4 Sumoylates Prdm16 to Regulate Adipose Tissue Thermogenesis. *Cell Rep,* 22**,** 2860-2872.

CHEN, Y., LUN, A. & SMYTH, G. 2016. From reads to genes to pathways: differential expression analysis of RNA-Seq experiments using Rsubread and the edgeR quasi-likelihood pipeline [version 2; peer review: 5 approved]. *F1000Research,* 5.

CHENG, F., SAWANT, T. V., LAN, K., LU, C., JUNG, J. U. & GAO, S. J. 2015. Screening of the Human Kinome Identifies MSK1/2-CREB1 as an Essential Pathway Mediating Kaposi's Sarcoma-Associated Herpesvirus Lytic Replication during Primary Infection. *J Virol,* 89**,** 9262-80.

CHERKAS, A. & GOLOTA, S. 2014. An intermittent exhaustion of the pool of glycogen in the human organism as a simple universal health promoting mechanism. *Med Hypotheses,* 82**,** 387-9.

CHERKAS, A., HOLOTA, S., MDZINARASHVILI, T., GABBIANELLI, R. & ZARKOVIC, N. 2020. Glucose as a Major Antioxidant: When, What for and Why It Fails? *Antioxidants (Basel),* 9.

CHEUNG, I. N., ZEE, P. C., SHALMAN, D., MALKANI, R. G., KANG, J. & REID, K. J. 2016. Morning and Evening Blue-Enriched Light Exposure Alters Metabolic Function in Normal Weight Adults. *PLoS One,* 11**,** e0155601.

CHOW, L. S., MANOOGIAN, E. N. C., ALVEAR, A., FLEISCHER, J. G., THOR, H., DIETSCHE, K., WANG, Q., HODGES, J. S., ESCH, N., MALAEB, S., HARINDHANAVUDHI, T., NAIR, K. S., PANDA, S. & MASHEK, D. G. 2020. Time-Restricted Eating Effects on Body Composition and Metabolic Measures in Humans with Overweight: A Feasibility Study. *Obesity (Silver Spring),* 28**,** 860-869.

CHRISTENSEN, M., VEDTOFTE, L., HOLST, J. J., VILSBOLL, T. & KNOP, F. K. 2011. Glucose-dependent insulinotropic polypeptide: a bifunctional glucose-dependent regulator of glucagon and insulin

secretion in humans. *Diabetes,* 60**,** 3103-9.
CHRISTENSEN, M. B. 2016. Glucose-dependent insulinotropic polypeptide: effects on insulin and glucagon secretion in humans. *Dan Med J,* 63.
CIENFUEGOS, S., GABEL, K., KALAM, F., EZPELETA, M., PAVLOU, V., LIN, S., WISEMAN, E. & VARADY, K. A. 2021. The effect of 4-h versus 6-h time restricted feeding on sleep quality, duration, insomnia severity and obstructive sleep apnea in adults with obesity. *Nutr Health***,** 2601060211002347.
CIENFUEGOS, S., GABEL, K., KALAM, F., EZPELETA, M., WISEMAN, E., PAVLOU, V., LIN, S., OLIVEIRA, M. L. & VARADY, K. A. 2020a. Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity. *Cell Metab,* 32**,** 366-378.e3.
CIENFUEGOS, S., GABEL, K., KALAM, F., EZPELETA, M., WISEMAN, E., PAVLOU, V., LIN, S., OLIVEIRA, M. L. & VARADY, K. A. 2020b. Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity. *Cell Metab*.
CISSE, Y. M., BORNIGER, J. C., LEMANSKI, E., WALKER, W. H., 2ND & NELSON, R. J. 2018. Time-Restricted Feeding Alters the Innate Immune Response to Bacterial Endotoxin. *J Immunol,* 200**,** 681-687.
COLLADO, M. C., ENGEN, P. A., BANDIN, C., CABRERA-RUBIO, R., VOIGT, R. M., GREEN, S. J., NAQIB, A., KESHAVARZIAN, A., SCHEER, F. & GARAULET, M. 2018. Timing of food intake impacts daily rhythms of human salivary microbiota: a randomized, crossover study. *FASEB J,* 32**,** 2060-2072.
CONLEY, M., LE FEVRE, L., HAYWOOD, C. & PROIETTO, J. 2018. Is two days of intermittent energy restriction per week a feasible weight loss approach in obese males? A randomised pilot study. *Nutr Diet,* 75**,** 65-72.
COUTINHO, S. R., HALSET, E. H., GASBAKK, S., REHFELD, J. F., KULSENG, B., TRUBY, H. & MARTINS, C. 2018. Compensatory mechanisms activated with intermittent energy restriction: A randomized control trial. *Clin Nutr,* 37**,** 815-823.
COUTO ALVES, A., GLASTONBURY, C. A., EL-SAYED MOUSTAFA, J. S. & SMALL, K. S. 2018. Fasting and time of day independently modulate circadian rhythm relevant gene expression in adipose and skin tissue. *BMC Genomics,* 19**,** 659.
CREWE, C., ZHU, Y., PASCHOAL, V. A., JOFFIN, N., GHABEN, A. L., GORDILLO, R., OH, D. Y., LIANG, G., HORTON, J. D. & SCHERER, P. E. 2019. SREBP-regulated adipocyte lipogenesis is dependent on substrate availability and redox modulation of mTORC1. *JCI Insight,* 5.
CROSBY, P., HAMNETT, R., PUTKER, M., HOYLE, N. P., REED, M., KARAM, C. J., MAYWOOD, E. S., STANGHERLIN, A., CHESHAM, J. E., HAYTER, E. A., ROSENBRIER-RIBEIRO, L., NEWHAM, P., CLEVERS, H., BECHTOLD, D. A. & O'NEILL, J. S. 2019. Insulin/IGF-1 Drives PERIOD Synthesis to Entrain Circadian Rhythms with Feeding Time. *Cell,* 177**,** 896-909 e20.
CZEISLER, C. A., DUFFY, J. F., SHANAHAN, T. L., BROWN, E. N., MITCHELL, J. F., RIMMER, D. W., RONDA, J. M., SILVA, E. J., ALLAN, J. S., EMENS, J. S., DIJK, D. J. & KRONAUER, R. E. 1999. Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science,* 284**,** 2177-81.
CZEISLER, C. A., KRONAUER, R. E., ALLAN, J. S., DUFFY, J. F., JEWETT, M. E., BROWN, E. N. & RONDA, J. M. 1989. Bright light induction of strong (type 0) resetting of the human circadian pacemaker. *Science,* 244**,** 1328-33.
D'INNOCENZO, S., BIAGI, C. & LANARI, M. 2019. Obesity and the Mediterranean Diet: A Review of Evidence of the Role and Sustainability of the Mediterranean Diet. *Nutrients,* 11.
DALGAARD, K., LANDGRAF, K., HEYNE, S., LEMPRADL, A., LONGINOTTO, J., GOSSENS, K., RUF, M., ORTHOFER, M., STROGANTSEV, R., SELVARAJ, M., LU, T. T., CASAS, E., TEPERINO, R., SURANI, M. A., ZVETKOVA, I., RIMMINGTON, D., TUNG, Y. C., LAM, B., LARDER, R., YEO, G. S., O'RAHILLY, S., VAVOURI, T., WHITELAW, E., PENNINGER, J. M., JENUWEIN, T., CHEUNG, C. L., FERGUSON-SMITH, A. C., COLL, A. P., KÖRNER, A. & POSPISILIK, J. A. 2016. Trim28 Haploinsufficiency Triggers Bi-stable Epigenetic Obesity. *Cell,* 164**,** 353-64.
DAMIOLA, F., LE MINH, N., PREITNER, N., KORNMANN, B., FLEURY-OLELA, F. & SCHIBLER, U. 2000. Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes Dev,* 14**,** 2950-61.

DAS, M., ELLIES, L. G., KUMAR, D., SAUCEDA, C., OBERG, A., GROSS, E., MANDT, T., NEWTON, I. G., KAUR, M., SEARS, D. D. & WEBSTER, N. J. G. 2021. Time-restricted feeding normalizes hyperinsulinemia to inhibit breast cancer in obese postmenopausal mouse models. *Nat Commun,* 12**,** 565.

DASHTI, H. S., FOLLIS, J. L., SMITH, C. E., TANAKA, T., GARAULET, M., GOTTLIEB, D. J., HRUBY, A., JACQUES, P. F., KIEFTE-DE JONG, J. C., LAMON-FAVA, S., SCHEER, F. A., BARTZ, T. M., KOVANEN, L., WOJCZYNSKI, M. K., FRAZIER-WOOD, A. C., AHLUWALIA, T. S., PERÄLÄ, M. M., JONSSON, A., MUKA, T., KALAFATI, I. P., MIKKILÄ, V. & ORDOVÁS, J. M. 2015. Gene-Environment Interactions of Circadian-Related Genes for Cardiometabolic Traits. *Diabetes Care,* 38**,** 1456-66.

DASHTI, H. S., GÓMEZ-ABELLÁN, P., QIAN, J., ESTEBAN, A., MORALES, E., SCHEER, F. & GARAULET, M. 2020. Late eating is associated with cardiometabolic risk traits, obesogenic behaviors, and impaired weight loss. *Am J Clin Nutr,* 113**,** 154-61.

DASHTI, H. S., SMITH, C. E., LEE, Y. C., PARNELL, L. D., LAI, C. Q., ARNETT, D. K., ORDOVÁS, J. M. & GARAULET, M. 2014. CRY1 circadian gene variant interacts with carbohydrate intake for insulin resistance in two independent populations: Mediterranean and North American. *Chronobiol Int,* 31**,** 660-7.

DAVIS, R., BONHAM, M. P., NGUO, K. & HUGGINS, C. E. 2020. Glycaemic response at night is improved after eating a high protein meal compared with a standard meal: A cross-over study. *Clin Nutr,* 39**,** 1510-1516.

DAVIS, R., MURGIA, C., DORDEVIC, A. L., BONHAM, M. P. & HUGGINS, C. E. 2021. Diurnal variation in gene expression of human peripheral blood mononuclear cells after eating a standard meal compared with a high protein meal: A cross-over study. *Clin Nutr,* S0261-5614(21)00021-2.

DE AMICIS, R., GALASSO, L., LEONE, A., VIGNATI, L., DE CARLO, G., FOPPIANI, A., MONTARULI, A., ROVEDA, E., CÈ, E., ESPOSITO, F., VANZULLI, A., BATTEZZATI, A. & BERTOLI, S. 2020. Is Abdominal Fat Distribution Associated with Chronotype in Adults Independently of Lifestyle Factors? *Nutrients,* 12.

DE GOEDE, P., SEN, S., OOSTERMAN, J. E., FOPPEN, E., JANSEN, R., LA FLEUR, S. E., CHALLET, E. & KALSBEEK, A. 2018. Differential effects of diet composition and timing of feeding behavior on rat brown adipose tissue and skeletal muscle peripheral clocks. *Neurobiol Sleep Circadian Rhythms,* 4**,** 24-33.

DE LUIS, D. A., IZAOLA, O., PRIMO, D. & ALLER, R. 2020a. A circadian rhythm-related MTNR1B genetic variant (rs10830963) modulate body weight change and insulin resistance after 9 months of a high protein/low carbohydrate vs a standard hypocaloric diet. *J Diabetes Complications,* 34**,** 107534.

DE LUIS, D. A., IZAOLA, O., PRIMO, D. & ALLER, R. 2020b. Dietary-fat effect of the rs10830963 polymorphism in MTNR1B on insulin resistance in response to 3 months weight-loss diets. *Endocrinol Diabetes Nutr,* 67**,** 43-52.

DE OLIVEIRA MARANHÃO PUREZA, I. R., DA SILVA JUNIOR, A. E., SILVA PRAXEDES, D. R., LESSA VASCONCELOS, L. G., DE LIMA MACENA, M., VIEIRA DE MELO, I. S., DE MENEZES TOLEDO FLORÊNCIO, T. M. & BUENO, N. B. 2021. Effects of time-restricted feeding on body weight, body composition and vital signs in low-income women with obesity: A 12-month randomized clinical trial. *Clin Nutr,* 40**,** 759-766.

DEFOUR, M., MICHIELSEN, C., O'DONOVAN, S. D., AFMAN, L. A. & KERSTEN, S. 2020. Transcriptomic signature of fasting in human adipose tissue. *Physiol Genomics,* 52**,** 451-467.

DEFRONZO, R. A. & TRIPATHY, D. 2009. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care,* 32 Suppl 2**,** S157-63.

DELAHAYE, L. B., BLOOMER, R. J., BUTAWAN, M. B., WYMAN, J. M., HILL, J. L., LEE, H. W., LIU, A. C., MCALLAN, L., HAN, J. C. & VAN DER MERWE, M. 2018. Time-restricted feeding of a high fat diet in C57BL/6 male mice reduces adiposity, but does not protect against increased systemic inflammation. *Appl Physiol Nutr Metab*.

DEPNER, C. M., MELANSON, E. L., MCHILL, A. W. & WRIGHT, K. P., JR. 2018. Mistimed food intake and sleep alters 24-hour time-of-day patterns of the human plasma proteome. *Proc Natl Acad Sci*

U S A, 115**,** E5390-E5399.

DESVERGNE, A., UGARTE, N., RADJEI, S., GAREIL, M., PETROPOULOS, I. & FRIGUET, B. 2016. Circadian modulation of proteasome activity and accumulation of oxidized protein in human embryonic kidney HEK 293 cells and primary dermal fibroblasts. *Free Radic Biol Med,* 94**,** 195-207.

DHURANDHAR, E. J., DAWSON, J., ALCORN, A., LARSEN, L. H., THOMAS, E. A., CARDEL, M., BOURLAND, A. C., ASTRUP, A., ST-ONGE, M. P., HILL, J. O., APOVIAN, C. M., SHIKANY, J. M. & ALLISON, D. B. 2014. The effectiveness of breakfast recommendations on weight loss: a randomized controlled trial. *Am J Clin Nutr,* 100**,** 507-13.

DÍAZ-RUIZ, A., GUZMÁN-RUIZ, R., MORENO, N. R., GARCÍA-RIOS, A., DELGADO-CASADO, N., MEMBRIVES, A., TÚNEZ, I., EL BEKAY, R., FERNÁNDEZ-REAL, J. M., TOVAR, S., DIÉGUEZ, C., TINAHONES, F. J., VÁZQUEZ-MARTÍNEZ, R., LÓPEZ-MIRANDA, J. & MALAGÓN, M. M. 2015. Proteasome Dysfunction Associated to Oxidative Stress and Proteotoxicity in Adipocytes Compromises Insulin Sensitivity in Human Obesity. *Antioxid Redox Signal,* 23**,** 597-612.

DOBIN, A., DAVIS, C. A., SCHLESINGER, F., DRENKOW, J., ZALESKI, C., JHA, S., BATUT, P., CHAISSON, M. & GINGERAS, T. R. 2013. STAR: ultrafast universal RNA-seq aligner. *Bioinformatics,* 29**,** 15-21.

DONGA, E., VAN DIJK, M., VAN DIJK, J. G., BIERMASZ, N. R., LAMMERS, G. J., VAN KRALINGEN, K. W., CORSSMIT, E. P. & ROMIJN, J. A. 2010. A single night of partial sleep deprivation induces insulin resistance in multiple metabolic pathways in healthy subjects. *J Clin Endocrinol Metab,* 95**,** 2963-8.

DUCROT, P., MEJEAN, C., BELLISLE, F., ALLES, B., HERCBERG, S. & PENEAU, S. 2018. Adherence to the French Eating Model is inversely associated with overweight and obesity: results from a large sample of French adults. *Br J Nutr,* 120**,** 231-239.

DUNCAN, M. J., SMITH, J. T., NARBAIZA, J., MUEEZ, F., BUSTLE, L. B., QURESHI, S., FIESELER, C. & LEGAN, S. J. 2016. Restricting feeding to the active phase in middle-aged mice attenuates adverse metabolic effects of a high-fat diet. *Physiol Behav,* 167**,** 1-9.

DUONG, H. A. & WEITZ, C. J. 2014. Temporal orchestration of repressive chromatin modifiers by circadian clock Period complexes. *Nat Struct Mol Biol,* 21**,** 126-32.

DUREGON, E., POMATTO-WATSON, L., BERNIER, M., PRICE, N. L. & DE CABO, R. 2021. Intermittent fasting: from calories to time restriction. *Geroscience,* 43**,** 1083-1092.

EMERY, P. & REPPERT, S. M. 2004. A rhythmic Ror. *Neuron,* 43**,** 443-6.

ESCOBAR, C., ESPITIA-BAUTISTA, E., GUZMÁN-RUIZ, M. A., GUERRERO-VARGAS, N. N., HERNÁNDEZ-NAVARRETE, M., ÁNGELES-CASTELLANOS, M., MORALES-PÉREZ, B. & BUIJS, R. M. 2020. Chocolate for breakfast prevents circadian desynchrony in experimental models of jet-lag and shift-work. *Sci Rep,* 10**,** 6243.

ESTRUCH, R., ROS, E., SALAS-SALVADÓ, J., COVAS, M. I., CORELLA, D., ARÓS, F., GÓMEZ-GRACIA, E., RUIZ-GUTIÉRREZ, V., FIOL, M., LAPETRA, J., LAMUELA-RAVENTOS, R. M., SERRA-MAJEM, L., PINTÓ, X., BASORA, J., MUÑOZ, M. A., SORLÍ, J. V., MARTÍNEZ, J. A., FITÓ, M., GEA, A., HERNÁN, M. A. & MARTÍNEZ-GONZÁLEZ, M. A. 2018. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med,* 378**,** e34.

FARSHCHI, H. R., TAYLOR, M. A. & MACDONALD, I. A. 2004a. Decreased thermic effect of food after an irregular compared with a regular meal pattern in healthy lean women. *Int J Obes Relat Metab Disord,* 28**,** 653-60.

FARSHCHI, H. R., TAYLOR, M. A. & MACDONALD, I. A. 2004b. Regular meal frequency creates more appropriate insulin sensitivity and lipid profiles compared with irregular meal frequency in healthy lean women. *Eur J Clin Nutr,* 58**,** 1071-7.

FARSHCHI, H. R., TAYLOR, M. A. & MACDONALD, I. A. 2005. Beneficial metabolic effects of regular meal frequency on dietary thermogenesis, insulin sensitivity, and fasting lipid profiles in healthy obese women. *Am J Clin Nutr,* 81**,** 16-24.

FITZGERALD, K. C., VIZTHUM, D., HENRY-BARRON, B., SCHWEITZER, A., CASSARD, S. D., KOSSOFF, E., HARTMAN, A. L., KAPOGIANNIS, D., SULLIVAN, P., BAER, D. J., MATTSON, M. P., APPEL, L. J. & MOWRY, E. M. 2018. Effect of intermittent vs. daily calorie restriction on changes in weight and patient-reported outcomes in people with multiple sclerosis. *Mult Scler Relat Disord,* 23**,**

33-39.
FLINT, A., RABEN, A., BLUNDELL, J. E. & ASTRUP, A. 2000. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. *Int J Obes Relat Metab Disord,* 24**,** 38-48.
FONTAINE, K. R., REDDEN, D. T., WANG, C., WESTFALL, A. O. & ALLISON, D. B. 2003. Years of life lost due to obesity. *JAMA,* 289**,** 187-93.
FRASER, S., COWEN, P., FRANKLIN, M. & LEWY, A. J. 1983. Direct radioimmunoassay and gas chromatography-mass spectrometry compared for determination of melatonin in plasma. *Clin Chem,* 29**,** 1703-4.
FREUND, A., ZHONG, F. L., VENTEICHER, A. S., MENG, Z., VEENSTRA, T. D., FRYDMAN, J. & ARTANDI, S. E. 2014. Proteostatic control of telomerase function through TRiC-mediated folding of TCAB1. *Cell,* 159**,** 1389-403.
FROY, O., CHAPNIK, N. & MISKIN, R. 2009. Effect of intermittent fasting on circadian rhythms in mice depends on feeding time. *Mech Ageing Dev,* 130**,** 154-60.
FUSE, Y., HIRAO, A., KURODA, H., OTSUKA, M., TAHARA, Y. & SHIBATA, S. 2012. Differential roles of breakfast only (one meal per day) and a bigger breakfast with a small dinner (two meals per day) in mice fed a high-fat diet with regard to induced obesity and lipid metabolism. *J Circadian Rhythms,* 10**,** 4.
GABEL, K., HODDY, K. K., BURGESS, H. J. & VARADY, K. A. 2019. Effect of 8-h time-restricted feeding on sleep quality and duration in adults with obesity. *Appl Physiol Nutr Metab,* 44**,** 903-906.
GABEL, K., HODDY, K. K., HAGGERTY, N., SONG, J., KROEGER, C. M., TREPANOWSKI, J. F., PANDA, S. & VARADY, K. A. 2018a. Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: A pilot study. *Nutr Healthy Aging,* 4**,** 345-353.
GABEL, K., HODDY, K. K. & VARADY, K. A. 2018b. Safety of 8-h time restricted feeding in adults with obesity. *Appl Physiol Nutr Metab*.
GABEL, K., MARCELL, J., CARES, K., KALAM, F., CIENFUEGOS, S., EZPELETA, M. & VARADY, K. A. 2020a. Effect of time restricted feeding on the gut microbiome in adults with obesity: A pilot study. *Nutr Health,* 26**,** 79-85.
GABEL, K., MARCELL, J., CARES, K., KALAM, F., CIENFUEGOS, S., EZPELETA, M. & VARADY, K. A. 2020b. Effect of time restricted feeding on the gut microbiome in adults with obesity: A pilot study. *Nutr Health***,** 260106020910907.
GACHON, F., LOIZIDES-MANGOLD, U., PETRENKO, V. & DIBNER, C. 2017. Glucose Homeostasis: Regulation by Peripheral Circadian Clocks in Rodents and Humans. *Endocrinology,* 158**,** 1074-1084.
GAO, Y., GAN, T., JIANG, L., YU, L., TANG, D., WANG, Y., LI, X. & DING, G. 2020. Association between shift work and risk of type 2 diabetes mellitus: a systematic review and dose-response meta-analysis of observational studies. *Chronobiol Int,* 37**,** 29-46.
GARAULET, M., QIAN, J., FLOREZ, J. C., ARENDT, J., SAXENA, R. & SCHEER, F. 2020. Melatonin Effects on Glucose Metabolism: Time To Unlock the Controversy. *Trends Endocrinol Metab*.
GARCIA-RIOS, A., GOMEZ-DELGADO, F. J., GARAULET, M., ALCALA-DIAZ, J. F., DELGADO-LISTA, F. J., MARIN, C., RANGEL-ZUÑIGA, O. A., RODRIGUEZ-CANTALEJO, F., GOMEZ-LUNA, P., ORDOVAS, J. M., PEREZ-JIMENEZ, F., LOPEZ-MIRANDA, J. & PEREZ-MARTINEZ, P. 2014. Beneficial effect of CLOCK gene polymorphism rs1801260 in combination with low-fat diet on insulin metabolism in the patients with metabolic syndrome. *Chronobiol Int,* 31**,** 401-8.
GEKAKIS, N., STAKNIS, D., NGUYEN, H. B., DAVIS, F. C., WILSBACHER, L. D., KING, D. P., TAKAHASHI, J. S. & WEITZ, C. J. 1998. Role of the CLOCK protein in the mammalian circadian mechanism. *Science,* 280**,** 1564-9.
GELIEBTER, A., ASTBURY, N. M., AVIRAM-FRIEDMAN, R., YAHAV, E. & HASHIM, S. 2014. Skipping breakfast leads to weight loss but also elevated cholesterol compared with consuming daily breakfasts of oat porridge or frosted cornflakes in overweight individuals: a randomised controlled trial. *J Nutr Sci,* 3**,** e56.
GENDASZEWSKA-DARMACH, E., GARSTKA, M. A. & BŁAŻEWSKA, K. M. 2021. Targeting Small GTPases

and Their Prenylation in Diabetes Mellitus. *J Med Chem,* 64**,** 9677-9710.
GESTAUT, D., ROH, S. H., MA, B., PINTILIE, G., JOACHIMIAK, L. A., LEITNER, A., WALZTHOENI, T., AEBERSOLD, R., CHIU, W. & FRYDMAN, J. 2019. The Chaperonin TRiC/CCT Associates with Prefoldin through a Conserved Electrostatic Interface Essential for Cellular Proteostasis. *Cell,* 177**,** 751-765 e15.
GILARDI, F., MIGLIAVACCA, E., NALDI, A., BARUCHET, M., CANELLA, D., LE MARTELOT, G., GUEX, N. & DESVERGNE, B. 2014. Genome-wide analysis of SREBP1 activity around the clock reveals its combined dependency on nutrient and circadian signals. *PLoS Genet,* 10**,** e1004155.
GILL, S., LE, H. D., MELKANI, G. C. & PANDA, S. 2015. Time-restricted feeding attenuates age-related cardiac decline in Drosophila. *Science,* 347**,** 1265-9.
GILL, S. & PANDA, S. 2015. A Smartphone App Reveals Erratic Diurnal Eating Patterns in Humans that Can Be Modulated for Health Benefits. *Cell Metab,* 22**,** 789-98.
GOLDSTEIN, I. & HAGER, G. L. 2015. Transcriptional and Chromatin Regulation during Fasting - The Genomic Era. *Trends Endocrinol Metab,* 26**,** 699-710.
GONI, L., GONI, L., SUN, D., SUN, D., HEIANZA, Y., HEIANZA, Y., WANG, T., WANG, T., HUANG, T., HUANG, T., MARTÍNEZ, J. A., MARTÍNEZ, J. A., SHANG, X., SHANG, X., BRAY, G. A., BRAY, G. A., SMITH, S. R., SMITH, S. R., SACKS, F. M., SACKS, F. M., QI, L. & QI, L. 2019. A circadian rhythm-related MTNR1B genetic variant modulates the effect of weight-loss diets on changes in adiposity and body composition: the POUNDS Lost trial. *European journal of nutrition,* 58**,** 1381-1389.
GONZALEZ, A. E., WALDMAN, H. S., ABEL, M. G., MCCURDY, K. W. & MCALLISTER, M. J. 2021. Impact of Time Restricted Feeding on Fitness Variables in Professional Resistance Trained Firefighters. *J Occup Environ Med,* 63**,** 343-349.
GOOLEY, J. J., LU, J., CHOU, T. C., SCAMMELL, T. E. & SAPER, C. B. 2001. Melanopsin in cells of origin of the retinohypothalamic tract. *Nat Neurosci,* 4**,** 1165.
GREENWELL, B. J., TROTT, A. J., BEYTEBIERE, J. R., PAO, S., BOSLEY, A., BEACH, E., FINEGAN, P., HERNANDEZ, C. & MENET, J. S. 2019. Rhythmic Food Intake Drives Rhythmic Gene Expression More Potently than the Hepatic Circadian Clock in Mice. *Cell Rep,* 27**,** 649-657 e5.
GU, C., BRERETON, N., SCHWEITZER, A., COTTER, M., DUAN, D., BØRSHEIM, E., WOLFE, R. R., PHAM, L. V., POLOTSKY, V. Y. & JUN, J. C. 2020. Metabolic Effects of Late Dinner in Healthy Volunteers-A Randomized Crossover Clinical Trial. *J Clin Endocrinol Metab,* 105**,** 2789-802.
GUILLAUMOND, F., DARDENTE, H., GIGUÈRE, V. & CERMAKIAN, N. 2005. Differential control of Bmal1 circadian transcription by REV-ERB and ROR nuclear receptors. *J Biol Rhythms,* 20**,** 391-403.
GUINTER, M. A., PARK, Y. M., STECK, S. E. & SANDLER, D. P. 2020. Day-to-day regularity in breakfast consumption is associated with weight status in a prospective cohort of women. *Int J Obes (Lond),* 44**,** 186-194.
GUO, B., CHATTERJEE, S., LI, L., KIM, J. M., LEE, J., YECHOOR, V. K., MINZE, L. J., HSUEH, W. & MA, K. 2012. The clock gene, brain and muscle Arnt-like 1, regulates adipogenesis via Wnt signaling pathway. *FASEB J,* 26**,** 3453-63.
GUPTA, C. C., DORRIAN, J., GRANT, C. L., PAJCIN, M., COATES, A. M., KENNAWAY, D. J., WITTERT, G. A., HEILBRONN, L. K., DELLA VEDOVA, C. B. & BANKS, S. 2017a. It's not just what you eat but when: The impact of eating a meal during simulated shift work on driving performance. *Chronobiol Int,* 34**,** 66-77.
GUPTA, N. J., KUMAR, V. & PANDA, S. 2017b. A camera-phone based study reveals erratic eating pattern and disrupted daily eating-fasting cycle among adults in India. *PLoS One,* 12**,** e0172852.
GUSAROVA, V., CAPLAN, A. J., BRODSKY, J. L. & FISHER, E. A. 2001. Apoprotein B degradation is promoted by the molecular chaperones hsp90 and hsp70. *J Biol Chem,* 276**,** 24891-900.
GUTIERREZ-MONREAL, M. A., HARMSEN, J. F., SCHRAUWEN, P. & ESSER, K. A. 2020. Ticking for Metabolic Health: The Skeletal-Muscle Clocks. *Obesity (Silver Spring),* 28 Suppl 1**,** S46-S54.
HA, K. & SONG, Y. 2019. Associations of Meal Timing and Frequency with Obesity and Metabolic Syndrome among Korean Adults. *Nutrients,* 11.
HACKETT, R. A., KIVIMÄKI, M., KUMARI, M. & STEPTOE, A. 2016. Diurnal Cortisol Patterns, Future Diabetes, and Impaired Glucose Metabolism in the Whitehall II Cohort Study. *J Clin Endocrinol*

Metab, 101**,** 619-25.
HALBERG, N., HENRIKSEN, M., SODERHAMN, N., STALLKNECHT, B., PLOUG, T., SCHJERLING, P. & DELA, F. 2005. Effect of intermittent fasting and refeeding on insulin action in healthy men. *J Appl Physiol (1985),* 99**,** 2128-36.
HALL, K. D., SACKS, G., CHANDRAMOHAN, D., CHOW, C. C., WANG, Y. C., GORTMAKER, S. L. & SWINBURN, B. A. 2011. Quantification of the effect of energy imbalance on bodyweight. *Lancet,* 378**,** 826-37.
HAMAGUCHI, Y., TAHARA, Y., HITOSUGI, M. & SHIBATA, S. 2015. Impairment of Circadian Rhythms in Peripheral Clocks by Constant Light Is Partially Reversed by Scheduled Feeding or Exercise. *J Biol Rhythms,* 30**,** 533-42.
HARRIS, L., HAMILTON, S., AZEVEDO, L. B., OLAJIDE, J., DE BRÚN, C., WALLER, G., WHITTAKER, V., SHARP, T., LEAN, M., HANKEY, C. & ELLS, L. 2018. Intermittent fasting interventions for treatment of overweight and obesity in adults: a systematic review and meta-analysis. *JBI Database System Rev Implement Rep,* 16**,** 507-547.
HARTSTRA, A. V., BOUTER, K. E., BACKHED, F. & NIEUWDORP, M. 2015. Insights into the role of the microbiome in obesity and type 2 diabetes. *Diabetes Care,* 38**,** 159-65.
HARVIE, M. & HOWELL, A. 2017. Potential Benefits and Harms of Intermittent Energy Restriction and Intermittent Fasting Amongst Obese, Overweight and Normal Weight Subjects-A Narrative Review of Human and Animal Evidence. *Behav Sci (Basel),* 7.
HARVIE, M., WRIGHT, C., PEGINGTON, M., MCMULLAN, D., MITCHELL, E., MARTIN, B., CUTLER, R. G., EVANS, G., WHITESIDE, S., MAUDSLEY, S., CAMANDOLA, S., WANG, R., CARLSON, O. D., EGAN, J. M., MATTSON, M. P. & HOWELL, A. 2013. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. *Br J Nutr,* 110**,** 1534-47.
HARVIE, M. N., PEGINGTON, M., MATTSON, M. P., FRYSTYK, J., DILLON, B., EVANS, G., CUZICK, J., JEBB, S. A., MARTIN, B., CUTLER, R. G., SON, T. G., MAUDSLEY, S., CARLSON, O. D., EGAN, J. M., FLYVBJERG, A. & HOWELL, A. 2011. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. *Int J Obes (Lond),* 35**,** 714-27.
HASHIMOTO, Y., KAJI, A., SAKAI, R., OSAKA, T., USHIGOME, E., HAMAGUCHI, M., YAMAZAKI, M. & FUKUI, M. 2020. Skipping breakfast is associated with glycemic variability in patients with type 2 diabetes. *Nutrition,* 71**,** 110639.
HATORI, M., VOLLMERS, C., ZARRINPAR, A., DITACCHIO, L., BUSHONG, E. A., GILL, S., LEBLANC, M., CHAIX, A., JOENS, M., FITZPATRICK, J. A., ELLISMAN, M. H. & PANDA, S. 2012. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. *Cell Metab,* 15**,** 848-60.
HAYES, A. J., LUNG, T. W., BAUMAN, A. & HOWARD, K. 2017. Modelling obesity trends in Australia: unravelling the past and predicting the future. *Int J Obes (Lond),* 41**,** 178-185.
HEADLAND, M. L., CLIFTON, P. M. & KEOGH, J. B. 2019. Effect of intermittent compared to continuous energy restriction on weight loss and weight maintenance after 12 months in healthy overweight or obese adults. *Int J Obes (Lond),* 43**,** 2028-2036.
HEADLAND, M. L., CLIFTON, P. M. & KEOGH, J. B. 2020. Impact of intermittent vs. continuous energy restriction on weight and cardiometabolic factors: a 12-month follow-up. *Int J Obes (Lond),* 44**,** 1236-1242.
HEILBRONN, L. K., CIVITARESE, A. E., BOGACKA, I., SMITH, S. R., HULVER, M. & RAVUSSIN, E. 2005a. Glucose tolerance and skeletal muscle gene expression in response to alternate day fasting. *Obes Res,* 13**,** 574-81.
HEILBRONN, L. K. & PANDA, S. 2019. Alternate-Day Fasting Gets a Safe Bill of Health. *Cell Metab,* 30**,** 411-413.
HEILBRONN, L. K. & RAVUSSIN, E. 2003. Calorie restriction and aging: review of the literature and implications for studies in humans. *Am J Clin Nutr,* 78**,** 361-9.
HEILBRONN, L. K., SMITH, S. R., MARTIN, C. K., ANTON, S. D. & RAVUSSIN, E. 2005b. Alternate-day

fasting in nonobese subjects: effects on body weight, body composition, and energy metabolism. *Am J Clin Nutr,* 81**,** 69-73.

HEINZ, S., BENNER, C., SPANN, N., BERTOLINO, E., LIN, Y. C., LASLO, P., CHENG, J. X., MURRE, C., SINGH, H. & GLASS, C. K. 2010. Simple combinations of lineage-determining transcription factors prime cis-regulatory elements required for macrophage and B cell identities. *Mol Cell,* 38**,** 576-89.

HIRANO, A., NAKAGAWA, T., YOSHITANE, H., OYAMA, M., KOZUKA-HATA, H., LANJAKORNSIRIPAN, D. & FUKADA, Y. 2016. USP7 and TDP-43: Pleiotropic Regulation of Cryptochrome Protein Stability Paces the Oscillation of the Mammalian Circadian Clock. *PLoS One,* 11**,** e0154263.

HODDY, K. K., KROEGER, C. M., TREPANOWSKI, J. F., BARNOSKY, A., BHUTANI, S. & VARADY, K. A. 2014. Meal timing during alternate day fasting: Impact on body weight and cardiovascular disease risk in obese adults. *Obesity (Silver Spring),* 22**,** 2524-31.

HU, D., MAO, Y., XU, G., LIAO, W., REN, J., YANG, H., YANG, J., SUN, L., CHEN, H., WANG, W., WANG, Y., SANG, X., LU, X., ZHANG, H. & ZHONG, S. 2018. Time-restricted feeding causes irreversible metabolic disorders and gut microbiota shift in pediatric mice. *Pediatr Res*.

HUANG, L., TRIEU, K., YOSHIMURA, S., NEAL, B., WOODWARD, M., CAMPBELL, N. R. C., LI, Q., LACKLAND, D. T., LEUNG, A. A., ANDERSON, C. A. M., MACGREGOR, G. A. & HE, F. J. 2020. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: systematic review and meta-analysis of randomised trials. *Bmj,* 368**,** m315.

HUANG, W., RAMSEY, K. M., MARCHEVA, B. & BASS, J. 2011. Circadian rhythms, sleep, and metabolism. *J Clin Invest,* 121**,** 2133-41.

HUO, R., DU, T., XU, Y., XU, W., CHEN, X., SUN, K. & YU, X. 2015. Effects of Mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: a meta-analysis. *Eur J Clin Nutr,* 69**,** 1200-8.

HUTCHISON, A. T., LIU, B., WOOD, R. E., VINCENT, A. D., THOMPSON, C. H., O'CALLAGHAN, N. J., WITTERT, G. A. & HEILBRONN, L. K. 2019a. Effects of Intermittent Versus Continuous Energy Intakes on Insulin Sensitivity and Metabolic Risk in Women with Overweight. *Obesity (Silver Spring),* 27**,** 50-58.

HUTCHISON, A. T., REGMI, P., MANOOGIAN, E. N. C., FLEISCHER, J. G., WITTERT, G. A., PANDA, S. & HEILBRONN, L. K. 2019b. Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover Trial. *Obesity (Silver Spring),* 27**,** 724-732.

ITOH, K., KAWASAKI, T. & CUGINI, P. 1996. Effects of timing of salt intake to 24-hour blood pressure and its circadian rhythm. *Ann N Y Acad Sci,* 783**,** 324-5.

JAGANNATH, A., BUTLER, R., GODINHO, S. I. H., COUCH, Y., BROWN, L. A., VASUDEVAN, S. R., FLANAGAN, K. C., ANTHONY, D., CHURCHILL, G. C., WOOD, M. J. A., STEINER, G., EBELING, M., HOSSBACH, M., WETTSTEIN, J. G., DUFFIELD, G. E., GATTI, S., HANKINS, M. W., FOSTER, R. G. & PEIRSON, S. N. 2013. The CRTC1-SIK1 pathway regulates entrainment of the circadian clock. *Cell,* 154**,** 1100-1111.

JAKUBOWICZ, D., BARNEA, M., WAINSTEIN, J. & FROY, O. 2013. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity (Silver Spring),* 21**,** 2504-12.

JAKUBOWICZ, D., LANDAU, Z., TSAMERET, S., WAINSTEIN, J., RAZ, I., AHREN, B., CHAPNIK, N., BARNEA, M., GANZ, T., MENAGED, M., MOR, N., BAR-DAYAN, Y. & FROY, O. 2019. Reduction in Glycated Hemoglobin and Daily Insulin Dose Alongside Circadian Clock Upregulation in Patients With Type 2 Diabetes Consuming a Three-Meal Diet: A Randomized Clinical Trial. *Diabetes Care*.

JAKUBOWICZ, D., WAINSTEIN, J., AHREN, B., BAR-DAYAN, Y., LANDAU, Z., RABINOVITZ, H. R. & FROY, O. 2015a. High-energy breakfast with low-energy dinner decreases overall daily hyperglycaemia in type 2 diabetic patients: a randomised clinical trial. *Diabetologia,* 58**,** 912-9.

JAKUBOWICZ, D., WAINSTEIN, J., AHREN, B., LANDAU, Z., BAR-DAYAN, Y. & FROY, O. 2015b. Fasting until noon triggers increased postprandial hyperglycemia and impaired insulin response after lunch and dinner in individuals with type 2 diabetes: a randomized clinical trial. *Diabetes Care,*

38**,** 1820-6.
JAKUBOWICZ, D., WAINSTEIN, J., LANDAU, Z., AHREN, B., BARNEA, M., BAR-DAYAN, Y. & FROY, O. 2017a. High-energy breakfast based on whey protein reduces body weight, postprandial glycemia and HbA1C in Type 2 diabetes. *J Nutr Biochem,* 49**,** 1-7.
JAKUBOWICZ, D., WAINSTEIN, J., LANDAU, Z., RAZ, I., AHREN, B., CHAPNIK, N., GANZ, T., MENAGED, M., BARNEA, M., BAR-DAYAN, Y. & FROY, O. 2017b. Influences of Breakfast on Clock Gene Expression and Postprandial Glycemia in Healthy Individuals and Individuals With Diabetes: A Randomized Clinical Trial. *Diabetes Care,* 40**,** 1573-1579.
JAMSHED, H., BEYL, R. A., DELLA MANNA, D. L., YANG, E. S., RAVUSSIN, E. & PETERSON, C. M. 2019. Early Time-Restricted Feeding Improves 24-Hour Glucose Levels and Affects Markers of the Circadian Clock, Aging, and Autophagy in Humans. *Nutrients,* 11**,** 1234.
JOHN, G. K. & MULLIN, G. E. 2016. The Gut Microbiome and Obesity. *Curr Oncol Rep,* 18**,** 45.
JOHNSON, J. B., SUMMER, W., CUTLER, R. G., MARTIN, B., HYUN, D. H., DIXIT, V. D., PEARSON, M., NASSAR, M., TELLJOHANN, R., MAUDSLEY, S., CARLSON, O., JOHN, S., LAUB, D. R. & MATTSON, M. P. 2007. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Radic Biol Med,* 42**,** 665-74.
JONES, R., PABLA, P., MALLINSON, J., NIXON, A., TAYLOR, T., BENNETT, A. & TSINTZAS, K. 2020. Two weeks of early time-restricted feeding (eTRF) improves skeletal muscle insulin and anabolic sensitivity in healthy men. *Am J Clin Nutr,* 112**,** 1015-1028.
KAHLEOVA, H., LLOREN, J. I., MASHCHAK, A., HILL, M. & FRASER, G. E. 2017. Meal Frequency and Timing Are Associated with Changes in Body Mass Index in Adventist Health Study 2. *J Nutr,* 147**,** 1722-1728.
KANT, A. K. 2018. Eating patterns of US adults: Meals, snacks, and time of eating. *Physiol Behav,* 193**,** 270-278.
KARPE, F., DICKMANN, J. R. & FRAYN, K. N. 2011. Fatty acids, obesity, and insulin resistance: time for a reevaluation. *Diabetes,* 60**,** 2441-9.
KENTISH, S. J., HATZINIKOLAS, G., LI, H., FRISBY, C. L., WITTERT, G. A. & PAGE, A. J. 2018. Time-Restricted Feeding Prevents Ablation of Diurnal Rhythms in Gastric Vagal Afferent Mechanosensitivity Observed in High-Fat Diet-Induced Obese Mice. *J Neurosci,* 38**,** 5088-5095.
KERAMAT, S. A., ALAM, K., GOW, J. & BIDDLE, S. J. H. 2020a. Gender differences in the longitudinal association between obesity, and disability with workplace absenteeism in the Australian working population. *PLoS One,* 15**,** e0233512.
KERAMAT, S. A., ALAM, K., GOW, J. & BIDDLE, S. J. H. 2020b. Obesity, Long-Term Health Problems, and Workplace Satisfaction: A Longitudinal Study of Australian Workers. *J Community Health,* 45**,** 288-300.
KESSLER, K., HORNEMANN, S., PETZKE, K. J., KEMPER, M., KRAMER, A., PFEIFFER, A. F., PIVOVAROVA, O. & RUDOVICH, N. 2017. The effect of diurnal distribution of carbohydrates and fat on glycaemic control in humans: a randomized controlled trial. *Sci Rep,* 7**,** 44170.
KESSLER, K., HORNEMANN, S., PETZKE, K. J., KEMPER, M., MARKOVA, M., RUDOVICH, N., GRUNE, T., KRAMER, A., PFEIFFER, A. F. H. & PIVOVAROVA-RAMICH, O. 2018. Diurnal distribution of carbohydrates and fat affects substrate oxidation and adipokine secretion in humans. *Am J Clin Nutr,* 108**,** 1209-1219.
KESZTYUS, D., CERMAK, P., GULICH, M. & KESZTYUS, T. 2019. Adherence to Time-Restricted Feeding and Impact on Abdominal Obesity in Primary Care Patients: Results of a Pilot Study in a Pre-Post Design. *Nutrients,* 11**,** 2854.
KHALSA, S. B., JEWETT, M. E., CAJOCHEN, C. & CZEISLER, C. A. 2003. A phase response curve to single bright light pulses in human subjects. *J Physiol,* 549**,** 945-52.
KIM, J. & SOMERS, D. E. 2017. An HSP90 co-chaperone controls circadian proteostasis. *Cell Cycle,* 16**,** 1483-1484.
KIMURA, G., DOHI, Y. & FUKUDA, M. 2010. Salt sensitivity and circadian rhythm of blood pressure: the keys to connect CKD with cardiovascular events. *Hypertens Res,* 33**,** 515-20.

KINOUCHI, K., MAGNAN, C., CEGLIA, N., LIU, Y., CERVANTES, M., PASTORE, N., HUYNH, T., BALLABIO, A., BALDI, P., MASRI, S. & SASSONE-CORSI, P. 2018. Fasting Imparts a Switch to Alternative Daily Pathways in Liver and Muscle. *Cell Rep,* 25**,** 3299-3314 e6.

KITAMURA, T., KITAMURA, Y., KURODA, S., HINO, Y., ANDO, M., KOTANI, K., KONISHI, H., MATSUZAKI, H., KIKKAWA, U., OGAWA, W. & KASUGA, M. 1999. Insulin-induced phosphorylation and activation of cyclic nucleotide phosphodiesterase 3B by the serine-threonine kinase Akt. *Mol Cell Biol,* 19**,** 6286-96.

KLEMPEL, M. C., KROEGER, C. M., BHUTANI, S., TREPANOWSKI, J. F. & VARADY, K. A. 2012. Intermittent fasting combined with calorie restriction is effective for weight loss and cardio-protection in obese women. *Nutr J,* 11**,** 98.

KOMATSU, M., TAKEI, M., ISHII, H. & SATO, Y. 2013. Glucose-stimulated insulin secretion: A newer perspective. *J Diabetes Investig,* 4**,** 511-6.

KRÄUCHI, K., CAJOCHEN, C., WERTH, E. & WIRZ-JUSTICE, A. 2002. Alteration of internal circadian phase relationships after morning versus evening carbohydrate-rich meals in humans. *J Biol Rhythms,* 17**,** 364-76.

KUME, K., ZYLKA, M. J., SRIRAM, S., SHEARMAN, L. P., WEAVER, D. R., JIN, X., MAYWOOD, E. S., HASTINGS, M. H. & REPPERT, S. M. 1999. mCRY1 and mCRY2 are essential components of the negative limb of the circadian clock feedback loop. *Cell,* 98**,** 193-205.

LAI, K. Y., SARKAR, C., NI, M. Y., GALLACHER, J. & WEBSTER, C. 2020. Exposure to light at night (LAN) and risk of obesity: A systematic review and meta-analysis of observational studies. *Environ Res,* 187**,** 109637.

LAM, Y. Y., GHOSH, S., CIVITARESE, A. E. & RAVUSSIN, E. 2016. Six-month Calorie Restriction in Overweight Individuals Elicits Transcriptomic Response in Subcutaneous Adipose Tissue That is Distinct From Effects of Energy Deficit. *J Gerontol A Biol Sci Med Sci,* 71**,** 1258-65.

LAMIA, K. A., SACHDEVA, U. M., DITACCHIO, L., WILLIAMS, E. C., ALVAREZ, J. G., EGAN, D. F., VASQUEZ, D. S., JUGUILON, H., PANDA, S., SHAW, R. J., THOMPSON, C. B. & EVANS, R. M. 2009. AMPK regulates the circadian clock by cryptochrome phosphorylation and degradation. *Science,* 326**,** 437-40.

LE MARTELOT, G., CLAUDEL, T., GATFIELD, D., SCHAAD, O., KORNMANN, B., LO SASSO, G., MOSCHETTA, A. & SCHIBLER, U. 2009. REV-ERBalpha participates in circadian SREBP signaling and bile acid homeostasis. *PLoS Biol,* 7**,** e1000181.

LECHEMINANT, J. D., CHRISTENSON, E., BAILEY, B. W. & TUCKER, L. A. 2013. Restricting night-time eating reduces daily energy intake in healthy young men: a short-term cross-over study. *Br J Nutr,* 110**,** 2108-13.

LEE, S. A., SYPNIEWSKI, C., BENSADON, B. A., MCLAREN, C., DONAHOO, W. T., SIBILLE, K. T. & ANTON, S. 2020. Determinants of Adherence in Time-Restricted Feeding in Older Adults: Lessons from a Pilot Study. *Nutrients,* 12.

LEE, Y. & KIM, E. K. 2013. AMP-activated protein kinase as a key molecular link between metabolism and clockwork. *Exp Mol Med,* 45**,** e33.

LEECH, R. M., TIMPERIO, A., LIVINGSTONE, K. M., WORSLEY, A. & MCNAUGHTON, S. A. 2017a. Temporal eating patterns: associations with nutrient intakes, diet quality, and measures of adiposity. *Am J Clin Nutr,* 106**,** 1121-1130.

LEECH, R. M., WORSLEY, A., TIMPERIO, A. & MCNAUGHTON, S. A. 2015. Understanding meal patterns: definitions, methodology and impact on nutrient intake and diet quality. *Nutr Res Rev,* 28**,** 1-21.

LEECH, R. M., WORSLEY, A., TIMPERIO, A. & MCNAUGHTON, S. A. 2017b. Temporal eating patterns: a latent class analysis approach. *Int J Behav Nutr Phys Act,* 14**,** 3.

LEONE, V., GIBBONS, S. M., MARTINEZ, K., HUTCHISON, A. L., HUANG, E. Y., CHAM, C. M., PIERRE, J. F., HENEGHAN, A. F., NADIMPALLI, A., HUBERT, N., ZALE, E., WANG, Y., HUANG, Y., THERIAULT, B., DINNER, A. R., MUSCH, M. W., KUDSK, K. A., PRENDERGAST, B. J., GILBERT, J. A. & CHANG, E. B. 2015. Effects of diurnal variation of gut microbes and high-fat feeding on host circadian clock function and metabolism. *Cell Host Microbe,* 17**,** 681-9.

LEUNG, G. K. W., HUGGINS, C. E. & BONHAM, M. P. 2019. Effect of meal timing on postprandial glucose responses to a low glycemic index meal: A crossover trial in healthy volunteers. *Clin Nutr,* 38**,** 465-471.

LEUNG, G. K. W., HUGGINS, C. E., WARE, R. S. & BONHAM, M. P. 2020. Time of day difference in postprandial glucose and insulin responses: Systematic review and meta-analysis of acute postprandial studies. *Chronobiol Int,* 37**,** 311-326.

LEWIS, P., OSTER, H., KORF, H. W., FOSTER, R. G. & ERREN, T. C. 2020. Food as a circadian time cue - evidence from human studies. *Nat Rev Endocrinol,* 16**,** 213-223.

LI, C., XING, C., ZHANG, J., ZHAO, H., SHI, W. & HE, B. 2021. Eight-hour time-restricted feeding improves endocrine and metabolic profiles in women with anovulatory polycystic ovary syndrome. *J Transl Med,* 19**,** 148.

LIAO, Y., WANG, J., JAEHNIG, E. J., SHI, Z. & ZHANG, B. 2019. WebGestalt 2019: gene set analysis toolkit with revamped UIs and APIs. *Nucleic Acids Res,* 47**,** W199-W205.

LIPTON, J. O., YUAN, E. D., BOYLE, L. M., EBRAHIMI-FAKHARI, D., KWIATKOWSKI, E., NATHAN, A., GÜTTLER, T., DAVIS, F., ASARA, J. M. & SAHIN, M. 2015. The Circadian Protein BMAL1 Regulates Translation in Response to S6K1-Mediated Phosphorylation. *Cell,* 161**,** 1138-1151.

LIU, B., HUTCHISON, A. T., THOMPSON, C. H., LANGE, K. & HEILBRONN, L. K. 2019. Markers of adipose tissue inflammation are transiently elevated during intermittent fasting in women who are overweight or obese. *Obes Res Clin Pract,* 13**,** 408-415.

LIU, K., LIU, B. & HEILBRONN, L. K. 2020. Intermittent fasting: What questions should we be asking? *Physiol Behav,* 218**,** 112827.

LLEWELLYN-WATERS, K. & ABDULLAH, M. M. H. Intermittent fasting - a potential approach to modulate the gut microbiota in humans? A systematic review. 2021.

LOBODA, A., KRAFT, W. K., FINE, B., JOSEPH, J., NEBOZHYN, M., ZHANG, C., HE, Y., YANG, X., WRIGHT, C., MORRIS, M., CHALIKONDA, I., FERGUSON, M., EMILSSON, V., LEONARDSON, A., LAMB, J., DAI, H., SCHADT, E., GREENBERG, H. E. & LUM, P. Y. 2009. Diurnal variation of the human adipose transcriptome and the link to metabolic disease. *BMC Med Genomics,* 2**,** 7.

LOGAN, R. W. & MCCLUNG, C. A. 2018. Rhythms of life: circadian disruption and brain disorders across the lifespan. *Nat Rev Neurosci*.

LOPEZ-MINGUEZ, J., SAXENA, R., BANDIN, C., SCHEER, F. A. & GARAULET, M. 2018. Late dinner impairs glucose tolerance in MTNR1B risk allele carriers: A randomized, cross-over study. *Clin Nutr,* 37**,** 1133-1140.

LÓPEZ-TABOADA, I., GONZÁLEZ-PARDO, H. & CONEJO, N. M. 2020. Western Diet: Implications for Brain Function and Behavior. *Front Psychol,* 11**,** 564413.

LORIA-KOHEN, V., ESPINOSA-SALINAS, I., MARCOS-PASERO, H., LOURENÇO-NOGUEIRA, T., HERRANZ, J., MOLINA, S., REGLERO, G. & RAMIREZ DE MOLINA, A. 2016. Polymorphism in the CLOCK gene may influence the effect of fat intake reduction on weight loss. *Nutrition,* 32**,** 453-60.

LOWE, D. A., WU, N., ROHDIN-BIBBY, L., MOORE, A. H., KELLY, N., LIU, Y. E., PHILIP, E., VITTINGHOFF, E., HEYMSFIELD, S. B., OLGIN, J. E., SHEPHERD, J. A. & WEISS, E. J. 2020. Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity: The TREAT Randomized Clinical Trial. *JAMA Intern Med*.

LOWREY, P. L. & TAKAHASHI, J. S. 2011. Genetics of circadian rhythms in Mammalian model organisms. *Adv Genet,* 74**,** 175-230.

LUCK, S., THURLEY, K., THABEN, P. F. & WESTERMARK, P. O. 2014. Rhythmic degradation explains and unifies circadian transcriptome and proteome data. *Cell Rep,* 9**,** 741-51.

LUNDELL, L. S., PARR, E. B., DEVLIN, B. L., INGERSLEV, L. R., ALTıNTAŞ, A., SATO, S., SASSONE-CORSI, P., BARRÈS, R., ZIERATH, J. R. & HAWLEY, J. A. 2020. Time-restricted feeding alters lipid and amino acid metabolite rhythmicity without perturbing clock gene expression. *Nat Commun,* 11**,** 4643.

LUPPINO, F. S., DE WIT, L. M., BOUVY, P. F., STIJNEN, T., CUIJPERS, P., PENNINX, B. W. & ZITMAN, F. G. 2010. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry,* 67**,** 220-9.

MA, X., CHEN, Q., PU, Y., GUO, M., JIANG, Z., HUANG, W., LONG, Y. & XU, Y. 2020. Skipping breakfast

is associated with overweight and obesity: A systematic review and meta-analysis. *Obes Res Clin Pract,* 14**,** 1-8.

MADJD, A., TAYLOR, M. A., DELAVARI, A., MALEKZADEH, R., MACDONALD, I. A. & FARSHCHI, H. R. 2020. Effects of consuming later evening meal versus earlier evening meal on weight loss during a Weight Loss Diet: a randomized clinical trial. *Br J Nutr***,** 1-25.

MAGKLIS, E., HOWE, L. D. & JOHNSON, L. 2019. Eating Style and the Frequency, Size and Timing of Eating Occasions: A cross-sectional analysis using 7-day weighed dietary records. *Sci Rep,* 9**,** 15133.

MAGLIANO, M. 2008. Obesity and arthritis. *Menopause Int,* 14**,** 149-54.

MANOOGIAN, E. N. C. & PANDA, S. 2017. Circadian rhythms, time-restricted feeding, and healthy aging. *Ageing Res Rev,* 39**,** 59-67.

MARCHEVA, B., RAMSEY, K. M., PEEK, C. B., AFFINATI, A., MAURY, E. & BASS, J. 2013. Circadian clocks and metabolism. *Handb Exp Pharmacol***,** 127-55.

MARIANNA, P., IOLANDA, C., ANDREA, E., VALENTINA, P., ILARIA, G., GIOVANNINO, C., EZIO, G. & SIMONA, B. 2019. Effects of time-restricted feeding on body weight and metabolism. A systematic review and meta-analysis. *Rev Endocr Metab Disord*.

MARTCHENKO, A., MARTCHENKO, S. E., BIANCOLIN, A. D. & BRUBAKER, P. L. 2020. Circadian Rhythms and the Gastrointestinal Tract: Relationship to Metabolism and Gut Hormones. *Endocrinology,* 161**,** bqaa167.

MARTENS, C. R., ROSSMAN, M. J., MAZZO, M. R., JANKOWSKI, L. R., NAGY, E. E., DENMAN, B. A., RICHEY, J. J., JOHNSON, S. A., ZIEMBA, B. P., WANG, Y., PETERSON, C. M., CHONCHOL, M. & SEALS, D. R. 2020. Short-term time-restricted feeding is safe and feasible in non-obese healthy midlife and older adults. *Geroscience*.

MARTENS, M. J., RUTTERS, F., LEMMENS, S. G., BORN, J. M. & WESTERTERP-PLANTENGA, M. S. 2010. Effects of single macronutrients on serum cortisol concentrations in normal weight men. *Physiol Behav,* 101**,** 563-7.

MARTÍNEZ-LOZANO, N., TVARIJONAVICIUTE, A., RÍOS, R., BARÓN, I., SCHEER, F. & GARAULET, M. 2020. Late Eating Is Associated with Obesity, Inflammatory Markers and Circadian-Related Disturbances in School-Aged Children. *Nutrients,* 12.

MASSCHELIN, P. M., COX, A. R., CHERNIS, N. & HARTIG, S. M. 2019. The Impact of Oxidative Stress on Adipose Tissue Energy Balance. *Front Physiol,* 10**,** 1638.

MATTHEWS, D. R., HOSKER, J. P., RUDENSKI, A. S., NAYLOR, B. A., TREACHER, D. F. & TURNER, R. C. 1985. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia,* 28**,** 412-9.

MAUVOISIN, D., WANG, J., JOUFFE, C., MARTIN, E., ATGER, F., WARIDEL, P., QUADRONI, M., GACHON, F. & NAEF, F. 2014. Circadian clock-dependent and -independent rhythmic proteomes implement distinct diurnal functions in mouse liver. *Proc Natl Acad Sci U S A,* 111**,** 167-72.

MAXWELL, P. H., WIESENER, M. S., CHANG, G. W., CLIFFORD, S. C., VAUX, E. C., COCKMAN, M. E., WYKOFF, C. C., PUGH, C. W., MAHER, E. R. & RATCLIFFE, P. J. 1999. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature,* 399**,** 271-5.

MCALLISTER, M. J., GONZALEZ, A. E. & WALDMAN, H. S. 2021a. Time Restricted Feeding Reduces Inflammation and Cortisol Response to a Firegrounds Test in Professional Firefighters. *J Occup Environ Med,* 63**,** 441-447.

MCALLISTER, M. J., GONZALEZ, A. E. & WALDMAN, H. S. 2021b. Time Restricted Feeding Reduces Inflammation and Cortisol Response to a Firegrounds Test in Professional Firefighters. *Journal of Occupational and Environmental Medicine,* Publish Ahead of Print.

MCALLISTER, M. J., PIGG, B. L., RENTERIA, L. I. & WALDMAN, H. S. 2020. Time-restricted feeding improves markers of cardiometabolic health in physically active college-age men: a 4-week randomized pre-post pilot study. *Nutr Res,* 75**,** 32-43.

MCCARTHY, D. J., CHEN, Y. & SMYTH, G. K. 2012. Differential expression analysis of multifactor RNA-Seq experiments with respect to biological variation. *Nucleic Acids Res,* 40**,** 4288-97.

MCHILL, A. W., CZEISLER, C. A., PHILLIPS, A. J. K., KEATING, L., BARGER, L. K., GARAULET, M., SCHEER, F. & KLERMAN, E. B. 2019. Caloric and Macronutrient Intake Differ with Circadian Phase and between Lean and Overweight Young Adults. *Nutrients,* 11.

MCHILL, A. W., HILDITCH, C. J., FISCHER, D., CZEISLER, C. A., GARAULET, M., SCHEER, F. & KLERMAN, E. B. 2020. Stability of the timing of food intake at daily and monthly timescales in young adults. *Sci Rep,* 10**,** 20849.

MCHILL, A. W., PHILLIPS, A. J., CZEISLER, C. A., KEATING, L., YEE, K., BARGER, L. K., GARAULET, M., SCHEER, F. A. & KLERMAN, E. B. 2017. Later circadian timing of food intake is associated with increased body fat. *Am J Clin Nutr,* 106**,** 1213-1219.

MEDICINE, I. O. 2005. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids,* Washington, DC, The National Academies Press.

MEHUS, A. A., RUST, B., IDSO, J. P., HANSON, B., ZENG, H., YAN, L., BUKOWSKI, M. R. & PICKLO, M. J. 2020. Time-restricted feeding mice a high-fat diet induces a unique lipidomic profile. *J Nutr Biochem,* 88**,** 108531.

MEKARY, R. A., GIOVANNUCCI, E., CAHILL, L., WILLETT, W. C., VAN DAM, R. M. & HU, F. B. 2013. Eating patterns and type 2 diabetes risk in older women: breakfast consumption and eating frequency. *Am J Clin Nutr,* 98**,** 436-43.

MEKARY, R. A., GIOVANNUCCI, E., WILLETT, W. C., VAN DAM, R. M. & HU, F. B. 2012. Eating patterns and type 2 diabetes risk in men: breakfast omission, eating frequency, and snacking. *Am J Clin Nutr,* 95**,** 1182-9.

MERIKANTO, I., LAHTI, T., PUOLIJOKI, H., VANHALA, M., PELTONEN, M., LAATIKAINEN, T., VARTIAINEN, E., SALOMAA, V., KRONHOLM, E. & PARTONEN, T. 2013. Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. *Chronobiol Int,* 30**,** 470-7.

MICHNA A, B. H. 2020. splineTimeR: Time-course differential gene expression data analysis using spline regression models followed by gene association network reconstruction. *R package version 1.18.0.*

MILAZZO, G., MERCATELLI, D., DI MUZIO, G., TRIBOLI, L., DE ROSA, P., PERINI, G. & GIORGI, F. M. 2020. Histone Deacetylases (HDACs): Evolution, Specificity, Role in Transcriptional Complexes, and Pharmacological Actionability. *Genes (Basel),* 11.

MINDIKOGLU, A. L., OPEKUN, A. R., GAGAN, S. K. & DEVARAJ, S. 2017. Impact of Time-Restricted Feeding and Dawn-to-Sunset Fasting on Circadian Rhythm, Obesity, Metabolic Syndrome, and Nonalcoholic Fatty Liver Disease. *Gastroenterol Res Pract,* 2017**,** 3932491.

MINNETTI, M., HASENMAJER, V., POFI, R., VENNERI, M. A., ALEXANDRAKI, K. I. & ISIDORI, A. M. 2020. Fixing the broken clock in adrenal disorders: focus on glucocorticoids and chronotherapy. *J Endocrinol,* 246**,** R13-R31.

MOON, S., KANG, J., KIM, S. H., CHUNG, H. S., KIM, Y. J., YU, J. M., CHO, S. T., OH, C. M. & KIM, T. 2020. Beneficial Effects of Time-Restricted Eating on Metabolic Diseases: A Systemic Review and Meta-Analysis. *Nutrients,* 12.

MORENO-NAVARRETE, J. M., SERRANO, M., SABATER, M., ORTEGA, F., SERINO, M., PUEYO, N., LUCHE, E., WAGET, A., RODRIGUEZ-HERMOSA, J. I., RICART, W., BURCELIN, R. & FERNÁNDEZ-REAL, J. M. 2013. Study of lactoferrin gene expression in human and mouse adipose tissue, human preadipocytes and mouse 3T3-L1 fibroblasts. Association with adipogenic and inflammatory markers. *J Nutr Biochem,* 24**,** 1266-75.

MORGAN, C. R. & LAZAROW, A. 1963. Immunoassay of Insulin: Two Antibody System: Plasma Insulin Levels of Normal, Subdiabetic and Diabetic Rats. *Diabetes,* 12**,** 115-126.

MORGAN, L. M., SHI, J. W., HAMPTON, S. M. & FROST, G. 2012. Effect of meal timing and glycaemic index on glucose control and insulin secretion in healthy volunteers. *Br J Nutr,* 108**,** 1286-91.

MORLEY, T. S., XIA, J. Y. & SCHERER, P. E. 2015. Selective enhancement of insulin sensitivity in the mature adipocyte is sufficient for systemic metabolic improvements. *Nat Commun,* 6**,** 7906.

MORO, T., TINSLEY, G., BIANCO, A., MARCOLIN, G., PACELLI, Q. F., BATTAGLIA, G., PALMA, A., GENTIL, P., NERI, M. & PAOLI, A. 2016. Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk

factors in resistance-trained males. *J Transl Med,* 14**,** 290.
MORO, T., TINSLEY, G., LONGO, G., GRIGOLETTO, D., BIANCO, A., FERRARIS, C., GUGLIELMETTI, M., VENETO, A., TAGLIABUE, A., MARCOLIN, G. & PAOLI, A. 2020. Time-restricted eating effects on performance, immune function, and body composition in elite cyclists: a randomized controlled trial. *J Int Soc Sports Nutr,* 17**,** 65.
MORRIS, C. J., PURVIS, T. E., HU, K. & SCHEER, F. A. 2016a. Circadian misalignment increases cardiovascular disease risk factors in humans. *Proc Natl Acad Sci U S A,* 113**,** E1402-11.
MORRIS, C. J., PURVIS, T. E., MISTRETTA, J. & SCHEER, F. A. 2016b. Effects of the Internal Circadian System and Circadian Misalignment on Glucose Tolerance in Chronic Shift Workers. *J Clin Endocrinol Metab,* 101**,** 1066-74.
MORRIS, C. J., YANG, J. N., GARCIA, J. I., MYERS, S., BOZZI, I., WANG, W., BUXTON, O. M., SHEA, S. A. & SCHEER, F. A. 2015. Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. *Proc Natl Acad Sci U S A,* 112**,** E2225-34.
NAAMAN, R., PARRETT, A., BASHAWRI, D., CAMPO, I., FLEMING, K., NICHOLS, B., BURLEIGH, E., MURTAGH, J., REID, J. & GERASIMIDIS, K. 2021. Assessment of Dietary Intake Using Food Photography and Video Recording in Free-Living Young Adults: A Comparative Study. *J Acad Nutr Diet,* 121**,** 749-761 e1.
NAGAO, H., CAI, W., WEWER ALBRECHTSEN, N. J., STEGER, M., BATISTA, T. M., PAN, H., DREYFUSS, J. M., MANN, M. & KAHN, C. R. 2021. Distinct signaling by insulin and IGF-1 receptors and their extra- and intracellular domains. *Proc Natl Acad Sci U S A,* 118.
NAKAHATA, Y., SAHAR, S., ASTARITA, G., KALUZOVA, M. & SASSONE-CORSI, P. 2009. Circadian control of the NAD+ salvage pathway by CLOCK-SIRT1. *Science,* 324**,** 654-7.
NAS, A., MIRZA, N., HÄGELE, F., KAHLHÖFER, J., KELLER, J., RISING, R., KUFER, T. A. & BOSY-WESTPHAL, A. 2017. Impact of breakfast skipping compared with dinner skipping on regulation of energy balance and metabolic risk. *Am J Clin Nutr,* 105**,** 1351-1361.
NATIONAL HEART, L., AND BLOOD INSTITUTE OBESITY EDUCATION INITIATIVE EXPERT PANEL ON THE IDENTIFICATION, EVALUATION, AND TREATMENT OF OBESITY IN ADULTS (US). 1998. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. . *Bethesda (MD): National Heart, Lung, and Blood Institute,* 98.
NEGRI, M., PIVONELLO, C., SIMEOLI, C., DI GENNARO, G., VENNERI, M. A., SCIARRA, F., FERRIGNO, R., DE ANGELIS, C., SBARDELLA, E., DE MARTINO, M. C., COLAO, A., ISIDORI, A. M. & PIVONELLO, R. 2020. Cortisol circadian rhythm and insulin resistance in muscle: effect of dosing and timing of hydrocortisone exposure on insulin sensitivity in synchronized muscle cells. *Neuroendocrinology*.
NESTI, L., MENGOZZI, A. & TRICÒ, D. 2019. Impact of Nutrient Type and Sequence on Glucose Tolerance: Physiological Insights and Therapeutic Implications. *Front Endocrinol (Lausanne),* 10**,** 144.
NITTA, A., IMAI, S., KAJIYAMA, S., MIYAWAKI, T., MATSUMOTO, S., OZASA, N., KAJIYAMA, S., HASHIMOTO, Y., TANAKA, M. & FUKUI, M. 2019. Impact of different timing of consuming sweet snack on postprandial glucose excursions in healthy women. *Diabetes Metab,* 45**,** 369-374.
NOVÁKOVÁ, M., POLIDAROVÁ, L., SLÁDEK, M. & SUMOVÁ, A. 2011. Restricted feeding regime affects clock gene expression profiles in the suprachiasmatic nucleus of rats exposed to constant light. *Neuroscience,* 197**,** 65-71.
OGATA, H., KAYABA, M., TANAKA, Y., YAJIMA, K., IWAYAMA, K., ANDO, A., PARK, I., KIYONO, K., OMI, N., SATOH, M. & TOKUYAMA, K. 2019. Effect of skipping breakfast for 6 days on energy metabolism and diurnal rhythm of blood glucose in young healthy Japanese males. *Am J Clin Nutr,* 110**,** 41-52.
OLSEN, M. K., CHOI, M. H., KULSENG, B., ZHAO, C. M. & CHEN, D. 2017. Time-restricted feeding on weekdays restricts weight gain: A study using rat models of high-fat diet-induced obesity. *Physiol Behav,* 173**,** 298-304.
OLSON, A. L. 2012. Regulation of GLUT4 and Insulin-Dependent Glucose Flux. *ISRN Mol Biol,* 2012**,** 856987.
OOSTERMAN, J. E., WOPEREIS, S. & KALSBEEK, A. 2020. The Circadian Clock, Shift Work, and Tissue-

Specific Insulin Resistance. *Endocrinology,* 161**,** bqaa180.
ORTIZ, R., KLUWE, B., ODEI, J. B., ECHOUFFO TCHEUGUI, J. B., SIMS, M., KALYANI, R. R., BERTONI, A. G., GOLDEN, S. H. & JOSEPH, J. J. 2019. The association of morning serum cortisol with glucose metabolism and diabetes: The Jackson Heart Study. *Psychoneuroendocrinology,* 103**,** 25-32.
OSTER, H., CHALLET, E., OTT, V., ARVAT, E., DE KLOET, E. R., DIJK, D. J., LIGHTMAN, S., VGONTZAS, A. & VAN CAUTER, E. 2017. The Functional and Clinical Significance of the 24-Hour Rhythm of Circulating Glucocorticoids. *Endocr Rev,* 38**,** 3-45.
OTODA, T., TAKAMURA, T., MISU, H., OTA, T., MURATA, S., HAYASHI, H., TAKAYAMA, H., KIKUCHI, A., KANAMORI, T., SHIMA, K. R., LAN, F., TAKEDA, T., KURITA, S., ISHIKURA, K., KITA, Y., IWAYAMA, K., KATO, K., UNO, M., TAKESHITA, Y., YAMAMOTO, M., TOKUYAMA, K., ISEKI, S., TANAKA, K. & KANEKO, S. 2013. Proteasome dysfunction mediates obesity-induced endoplasmic reticulum stress and insulin resistance in the liver. *Diabetes,* 62**,** 811-24.
OTWAY, D. T., MANTELE, S., BRETSCHNEIDER, S., WRIGHT, J., TRAYHURN, P., SKENE, D. J., ROBERTSON, M. D. & JOHNSTON, J. D. 2011. Rhythmic diurnal gene expression in human adipose tissue from individuals who are lean, overweight, and type 2 diabetic. *Diabetes,* 60**,** 1577-81.
PACHECO, D., IZAOLA JÁUREGUI, O., PRIMO MARTÍN, D. & DE LUIS ROMÁN, D. A. 2020. A circadian rhythm-related MTNR1B genetic variant (rs10830963) modulates glucose metabolism and insulin resistance after body weight loss secondary to biliopancreatic diversion surgery. *Nutr Hosp,* 37**,** 1143-1149.
PAK, H. H., HAWS, S. A., GREEN, C. L., KOLLER, M., LAVARIAS, M. T., RICHARDSON, N. E., YANG, S. E., DUMAS, S. N., SONSALLA, M., BRAY, L., JOHNSON, M., BARNES, S., DARLEY-USMAR, V., ZHANG, J., YEN, C. E., DENU, J. M. & LAMMING, D. W. 2021. Fasting drives the metabolic, molecular and geroprotective effects of a calorie-restricted diet in mice. *Nat Metab,* 3**,** 1327-1341.
PAMPLONA, R. & BARJA, G. 2006. Mitochondrial oxidative stress, aging and caloric restriction: the protein and methionine connection. *Biochim Biophys Acta,* 1757**,** 496-508.
PANAGIOTOU, C., LAMBADIARI, V., MARATOU, E., GEROMERIATI, C., ARTEMIADIS, A., DIMITRIADIS, G. & MOUTSATSOU, P. 2021. Insufficient glucocorticoid receptor signaling and flattened salivary cortisol profile are associated with metabolic and inflammatory indices in type 2 diabetes. *J Endocrinol Invest,* 44**,** 37-48.
PANDA, S. 2016. Circadian physiology of metabolism. *Science,* 354**,** 1008-1015.
PANDI-PERUMAL, S. R., SMITS, M., SPENCE, W., SRINIVASAN, V., CARDINALI, D. P., LOWE, A. D. & KAYUMOV, L. 2007. Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. *Prog Neuropsychopharmacol Biol Psychiatry,* 31**,** 1-11.
PARK, J., ZHU, Q., MIREK, E., NA, L., RADUWAN, H., ANTHONY, T. G. & BELDEN, W. J. 2019. BMAL1 associates with chromosome ends to control rhythms in TERRA and telomeric heterochromatin. *PLoS One,* 14**,** e0223803.
PARR, E. B., DEVLIN, B. L., LIM, K. H. C., MORESI, L. N. Z., GEILS, C., BRENNAN, L. & HAWLEY, J. A. 2020a. Time-Restricted Eating as a Nutrition Strategy for Individuals with Type 2 Diabetes: A Feasibility Study. *Nutrients,* 12**,** 3228.
PARR, E. B., DEVLIN, B. L., RADFORD, B. E. & HAWLEY, J. A. 2020b. A Delayed Morning and Earlier Evening Time-Restricted Feeding Protocol for Improving Glycemic Control and Dietary Adherence in Men with Overweight/Obesity: A Randomized Controlled Trial. *Nutrients,* 12**,** 505.
PATEL, S. A., VELINGKAAR, N., MAKWANA, K., CHAUDHARI, A. & KONDRATOV, R. 2016. Calorie restriction regulates circadian clock gene expression through BMAL1 dependent and independent mechanisms. *Sci Rep,* 6**,** 25970.
PATTON, A. P. & HASTINGS, M. H. 2018. The suprachiasmatic nucleus. *Curr Biol,* 28**,** R816-R822.
PEEKE, P. M., GREENWAY, F. L., BILLES, S. K., ZHANG, D. & FUJIOKA, K. 2021. Effect of time restricted eating on body weight and fasting glucose in participants with obesity: results of a randomized, controlled, virtual clinical trial. *Nutr Diabetes,* 11**,** 6.
PEKMEZ, C. T., BJØRNSHAVE, A., PRATICO, G., HERMANSEN, K. & DRAGSTED, L. O. 2020. Pre-meal

protein intake alters postprandial plasma metabolome in subjects with metabolic syndrome. *Eur J Nutr,* 59**,** 1881-1894.

PERRIN, L., LOIZIDES-MANGOLD, U., CHANON, S., GOBET, C., HULO, N., ISENEGGER, L., WEGER, B. D., MIGLIAVACCA, E., CHARPAGNE, A., BETTS, J. A., WALHIN, J. P., TEMPLEMAN, I., STOKES, K., THOMPSON, D., TSINTZAS, K., ROBERT, M., HOWALD, C., RIEZMAN, H., FEIGE, J. N., KARAGOUNIS, L. G., JOHNSTON, J. D., DERMITZAKIS, E. T., GACHON, F., LEFAI, E. & DIBNER, C. 2018. Transcriptomic analyses reveal rhythmic and CLOCK-driven pathways in human skeletal muscle. *Elife,* 7.

PILKIS, S. J. & GRANNER, D. K. 1992. Molecular physiology of the regulation of hepatic gluconeogenesis and glycolysis. *Annu Rev Physiol,* 54**,** 885-909.

PIVOVAROVA, O., GOGEBAKAN, O., SUCHER, S., GROTH, J., MURAHOVSCHI, V., KESSLER, K., OSTERHOFF, M., RUDOVICH, N., KRAMER, A. & PFEIFFER, A. F. 2016. Regulation of the clock gene expression in human adipose tissue by weight loss. *Int J Obes (Lond),* 40**,** 899-906.

POGGIOGALLE, E., JAMSHED, H. & PETERSON, C. M. 2018. Circadian regulation of glucose, lipid, and energy metabolism in humans. *Metabolism*.

POLYZOS, S. A., KOUNTOURAS, J. & MANTZOROS, C. S. 2019. Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics. *Metabolism,* 92**,** 82-97.

POT, G. K., ALMOOSAWI, S. & STEPHEN, A. M. 2016a. Meal irregularity and cardiometabolic consequences: results from observational and intervention studies. *Proc Nutr Soc,* 75**,** 475-486.

POT, G. K., HARDY, R. & STEPHEN, A. M. 2014. Irregular consumption of energy intake in meals is associated with a higher cardiometabolic risk in adults of a British birth cohort. *Int J Obes (Lond),* 38**,** 1518-24.

POT, G. K., HARDY, R. & STEPHEN, A. M. 2016b. Irregularity of energy intake at meals: prospective associations with the metabolic syndrome in adults of the 1946 British birth cohort. *Br J Nutr,* 115**,** 315-23.

PRASAD, M. A., MANOOGIAN, E., ZURAIKAT, F. M., NAIR, N., ST-ONGE, M.-P., PANDA, S. & LAFERRERE, B. 2020. 2005-P: A Smartphone Intervention to Promote Time-Restricted Eating Reduces Body Weight and Blood Pressure in Adults with Overweight and Obesity. *Diabetes,* 69**,** 2005-P.

PREITNER, N., DAMIOLA, F., LOPEZ-MOLINA, L., ZAKANY, J., DUBOULE, D., ALBRECHT, U. & SCHIBLER, U. 2002. The orphan nuclear receptor REV-ERBalpha controls circadian transcription within the positive limb of the mammalian circadian oscillator. *Cell,* 110**,** 251-60.

PUREZA, I., MELO, I. S. V., MACENA, M. L., PRAXEDES, D. R. S., VASCONCELOS, L. G. L., SILVA-JÚNIOR, A. E., FLORÊNCIO, T. & BUENO, N. B. 2020. Acute effects of time-restricted feeding in low-income women with obesity placed on hypoenergetic diets: Randomized trial. *Nutrition,* 77**,** 110796.

QUIST, J. S., JENSEN, M. M., CLEMMENSEN, K. K. B., PEDERSEN, H., BJERRE, N., STØRLING, J., BLOND, M. B., WEWER ALBRECHTSEN, N. J., HOLST, J. J., TOREKOV, S. S., VISTISEN, D., JØRGENSEN, M. E., PANDA, S., BROCK, C., FINLAYSON, G. & FÆRCH, K. 2020. Protocol for a single-centre, parallel-group, randomised, controlled, superiority trial on the effects of time-restricted eating on body weight, behaviour and metabolism in individuals at high risk of type 2 diabetes: the REStricted Eating Time (RESET) study. *BMJ Open,* 10**,** e037166.

R, C., TEAM 2019. R: A language and environment for statistical computing. *R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/.*

RAMANATHAN, C., KATHALE, N. D., LIU, D., LEE, C., FREEMAN, D. A., HOGENESCH, J. B., CAO, R. & LIU, A. C. 2018. mTOR signaling regulates central and peripheral circadian clock function. *PLoS Genet,* 14**,** e1007369.

RAMSEY, K. M., YOSHINO, J., BRACE, C. S., ABRASSART, D., KOBAYASHI, Y., MARCHEVA, B., HONG, H. K., CHONG, J. L., BUHR, E. D., LEE, C., TAKAHASHI, J. S., IMAI, S. & BASS, J. 2009. Circadian clock feedback cycle through NAMPT-mediated NAD+ biosynthesis. *Science,* 324**,** 651-4.

RAVUSSIN, E., BEYL, R. A., POGGIOGALLE, E., HSIA, D. S. & PETERSON, C. M. 2019. Early Time-Restricted Feeding Reduces Appetite and Increases Fat Oxidation But Does Not Affect Energy Expenditure in Humans. *Obesity (Silver Spring),* 27**,** 1244-1254.

REDDY, A. B., KARP, N. A., MAYWOOD, E. S., SAGE, E. A., DEERY, M., O'NEILL, J. S., WONG, G. K., CHESHAM, J., ODELL, M., LILLEY, K. S., KYRIACOU, C. P. & HASTINGS, M. H. 2006. Circadian orchestration of the hepatic proteome. *Curr Biol,* 16**,** 1107-15.

REGMI, P., CHAUDHARY, R., PAGE, A. J., HUTCHISON, A. T., VINCENT, A. D., LIU, B. & HEILBRONN, L. 2021. Early or delayed time-restricted feeding prevents metabolic impact of obesity in mice. *J Endocrinol,* 248**,** 75-86.

REGMI, P. & HEILBRONN, L. K. 2020. Time-Restricted Eating: Benefits, Mechanisms, and Challenges in Translation. *iScience,* 23**,** 101161.

REID, K. J. & ABBOTT, S. M. 2015. Jet Lag and Shift Work Disorder. *Sleep Med Clin,* 10**,** 523-35.

REIS, C. E. G., DÓREA, J. G. & DA COSTA, T. H. M. 2019. Effects of coffee consumption on glucose metabolism: A systematic review of clinical trials. *J Tradit Complement Med,* 9**,** 184-191.

REPPERT, S. M. & WEAVER, D. R. 2002. Coordination of circadian timing in mammals. *Nature,* 418**,** 935-41.

REUTRAKUL, S., HOOD, M. M., CROWLEY, S. J., MORGAN, M. K., TEODORI, M., KNUTSON, K. L. & VAN CAUTER, E. 2013. Chronotype is independently associated with glycemic control in type 2 diabetes. *Diabetes Care,* 36**,** 2523-9.

RIAD-FAHMY, D., READ, G. F., GASKELL, S. J., DYAS, J. & HINDAWI, R. 1979. A simple, direct radioimmunoassay for plasma cortisol, featuring a 125I radioligand and a solid-phase separation technique. *Clin Chem,* 25**,** 665-8.

RICHTER, J., HERZOG, N., JANKA, S., BAUMANN, T., KISTENMACHER, A. & OLTMANNS, K. M. 2020. Twice as High Diet-Induced Thermogenesis After Breakfast vs Dinner On High-Calorie as Well as Low-Calorie Meals. *J Clin Endocrinol Metab,* 105**,** dgz311.

RIGAMONTI, A. E., LEONCINI, R., CASNICI, C., MARELLI, O., COL, A., TAMINI, S., LUCCHETTI, E., CICOLINI, S., ABBRUZZESE, L., CELLA, S. G. & SARTORIO, A. 2019. Whey Proteins Reduce Appetite, Stimulate Anorexigenic Gastrointestinal Peptides and Improve Glucometabolic Homeostasis in Young Obese Women. *Nutrients,* 11.

RIPPERGER, J. A., SHEARMAN, L. P., REPPERT, S. M. & SCHIBLER, U. 2000. CLOCK, an essential pacemaker component, controls expression of the circadian transcription factor DBP. *Genes Dev,* 14**,** 679-89.

ROBINSON, M. D., MCCARTHY, D. J. & SMYTH, G. K. 2010. edgeR: a Bioconductor package for differential expression analysis of digital gene expression data. *Bioinformatics,* 26**,** 139-40.

ROBLES, M. S., HUMPHREY, S. J. & MANN, M. 2017. Phosphorylation Is a Central Mechanism for Circadian Control of Metabolism and Physiology. *Cell Metab,* 25**,** 118-127.

ROENNEBERG, T. & MERROW, M. 2007. Entrainment of the human circadian clock. *Cold Spring Harb Symp Quant Biol,* 72**,** 293-9.

ROMERO-CORRAL, A., CAPLES, S. M., LOPEZ-JIMENEZ, F. & SOMERS, V. K. 2010. Interactions between obesity and obstructive sleep apnea: implications for treatment. *Chest,* 137**,** 711-9.

RUANO, E. G., CANIVELL, S. & VIEIRA, E. 2014. REV-ERB ALPHA polymorphism is associated with obesity in the Spanish obese male population. *PLoS One,* 9**,** e104065.

RUBIO-SASTRE, P., SCHEER, F. A., GÓMEZ-ABELLÁN, P., MADRID, J. A. & GARAULET, M. 2014. Acute melatonin administration in humans impairs glucose tolerance in both the morning and evening. *Sleep,* 37**,** 1715-9.

RUNDO, J. V. 2019. Obstructive sleep apnea basics. *Cleve Clin J Med,* 86**,** 2-9.

RYBICKA, M., KRYSIAK, R. & OKOPIEŃ, B. 2011. The dawn phenomenon and the Somogyi effect - two phenomena of morning hyperglycaemia. *Endokrynol Pol,* 62**,** 276-84.

SALGADO-DELGADO, R., ANGELES-CASTELLANOS, M., BUIJS, M. R. & ESCOBAR, C. 2008. Internal desynchronization in a model of night-work by forced activity in rats. *Neuroscience,* 154**,** 922-31.

SALGADO-DELGADO, R., ANGELES-CASTELLANOS, M., SADERI, N., BUIJS, R. M. & ESCOBAR, C. 2010. Food intake during the normal activity phase prevents obesity and circadian desynchrony in a rat model of night work. *Endocrinology,* 151**,** 1019-29.

SALTIEL, A. R. & KAHN, C. R. 2001. Insulin signalling and the regulation of glucose and lipid metabolism.

Nature, 414**,** 799-806.

SARDON PUIG, L., PILLON, N. J., NASLUND, E., KROOK, A. & ZIERATH, J. R. 2020. Influence of obesity, weight loss, and free fatty acids on skeletal muscle clock gene expression. *Am J Physiol Endocrinol Metab,* 318**,** E1-E10.

SATO, T. K., PANDA, S., MIRAGLIA, L. J., REYES, T. M., RUDIC, R. D., MCNAMARA, P., NAIK, K. A., FITZGERALD, G. A., KAY, S. A. & HOGENESCH, J. B. 2004. A functional genomics strategy reveals Rora as a component of the mammalian circadian clock. *Neuron,* 43**,** 527-37.

SAULLE, R., BERNARDI, M., CHIARINI, M., BACKHAUS, I. & LA TORRE, G. 2018. Shift work, overweight and obesity in health professionals: a systematic review and meta-analysis. *Clin Ter,* 169**,** e189-e197.

SCHAFER, M. J., MAZULA, D. L., BROWN, A. K., WHITE, T. A., ATKINSON, E., PEARSALL, V. M., AVERSA, Z., VERZOSA, G. C., SMITH, L. A., MATVEYENKO, A., MILLER, J. D. & LEBRASSEUR, N. K. 2019. Late-life time-restricted feeding and exercise differentially alter healthspan in obesity. *Aging Cell,* 18**,** e12966.

SCHEER, F. A., HILTON, M. F., MANTZOROS, C. S. & SHEA, S. A. 2009. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci U S A,* 106**,** 4453-8.

SCHLUNDT, D. G., HILL, J. O., SBROCCO, T., POPE-CORDLE, J. & SHARP, T. 1992. The role of breakfast in the treatment of obesity: a randomized clinical trial. *Am J Clin Nutr,* 55**,** 645-51.

SCHNEIDER, R., LINKA, R. M. & REINKE, H. 2014. HSP90 affects the stability of BMAL1 and circadian gene expression. *J Biol Rhythms,* 29**,** 87-96.

SCHRODER, J. D., FALQUETO, H., MÂNICA, A., ZANINI, D., DE OLIVEIRA, T., DE SÁ, C. A., CARDOSO, A. M. & MANFREDI, L. H. 2021. Effects of time-restricted feeding in weight loss, metabolic syndrome and cardiovascular risk in obese women. *J Transl Med,* 19**,** 3.

SCHÜBEL, R., NATTENMÜLLER, J., SOOKTHAI, D., NONNENMACHER, T., GRAF, M. E., RIEDL, L., SCHLETT, C. L., VON STACKELBERG, O., JOHNSON, T., NABERS, D., KIRSTEN, R., KRATZ, M., KAUCZOR, H. U., ULRICH, C. M., KAAKS, R. & KÜHN, T. 2018. Effects of intermittent and continuous calorie restriction on body weight and metabolism over 50 wk: a randomized controlled trial. *Am J Clin Nutr,* 108**,** 933-945.

SCOTT, E. M., CARTER, A. M. & GRANT, P. J. 2008. Association between polymorphisms in the Clock gene, obesity and the metabolic syndrome in man. *Int J Obes (Lond),* 32**,** 658-62.

SHAN, Z., MA, H., XIE, M., YAN, P., GUO, Y., BAO, W., RONG, Y., JACKSON, C. L., HU, F. B. & LIU, L. 2015. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care,* 38**,** 529-37.

SHARMA, A., LAURENTI, M. C., DALLA MAN, C., VARGHESE, R. T., COBELLI, C., RIZZA, R. A., MATVEYENKO, A. & VELLA, A. 2017. Glucose metabolism during rotational shift-work in healthcare workers. *Diabetologia,* 60**,** 1483-1490.

SHECHTER, A. & BOIVIN, D. B. 2010. Sleep, Hormones, and Circadian Rhythms throughout the Menstrual Cycle in Healthy Women and Women with Premenstrual Dysphoric Disorder. *Int J Endocrinol,* 2010**,** 259345.

SHERMAN, H., FRUMIN, I., GUTMAN, R., CHAPNIK, N., LORENTZ, A., MEYLAN, J., LE COUTRE, J. & FROY, O. 2011. Long-term restricted feeding alters circadian expression and reduces the level of inflammatory and disease markers. *J Cell Mol Med,* 15**,** 2745-59.

SHERMAN, H., GENZER, Y., COHEN, R., CHAPNIK, N., MADAR, Z. & FROY, O. 2012. Timed high-fat diet resets circadian metabolism and prevents obesity. *FASEB J,* 26**,** 3493-502.

SHIN, A., LIM, S. Y., SUNG, J., SHIN, H. R. & KIM, J. 2009. Dietary intake, eating habits, and metabolic syndrome in Korean men. *J Am Diet Assoc,* 109**,** 633-40.

SHOSTAK, A., MEYER-KOVAC, J. & OSTER, H. 2013. Circadian regulation of lipid mobilization in white adipose tissues. *Diabetes,* 62**,** 2195-203.

SHUKLA, A. P., ANDONO, J., TOUHAMY, S. H., CASPER, A., ILIESCU, R. G., MAUER, E., SHAN ZHU, Y., LUDWIG, D. S. & ARONNE, L. J. 2017. Carbohydrate-last meal pattern lowers postprandial glucose and insulin excursions in type 2 diabetes. *BMJ Open Diabetes Res Care,* 5**,** e000440.

SHUKLA, A. P., DICKISON, M., COUGHLIN, N., KARAN, A., MAUER, E., TRUONG, W., CASPER, A.,

EMILIANO, A. B., KUMAR, R. B., SAUNDERS, K. H., IGEL, L. I. & ARONNE, L. J. 2019. The impact of food order on postprandial glycaemic excursions in prediabetes. *Diabetes Obes Metab,* 21**,** 377-381.

SHUKLA, A. P., ILIESCU, R. G., THOMAS, C. E. & ARONNE, L. J. 2015. Food Order Has a Significant Impact on Postprandial Glucose and Insulin Levels. *Diabetes Care,* 38**,** e98-9.

SI HASSEN, W., CASTETBON, K., TICHIT, C., PENEAU, S., NECHBA, A., DUCROT, P., LAMPURE, A., BELLISLE, F., HERCBERG, S. & MEJEAN, C. 2018. Energy, nutrient and food content of snacks in French adults. *Nutr J,* 17**,** 33.

SIERRA-JOHNSON, J., UNDÉN, A. L., LINESTRAND, M., ROSELL, M., SJOGREN, P., KOLAK, M., DE FAIRE, U., FISHER, R. M. & HELLÉNIUS, M. L. 2008. Eating meals irregularly: a novel environmental risk factor for the metabolic syndrome. *Obesity (Silver Spring),* 16**,** 1302-7.

SINTUREL, F., PETRENKO, V. & DIBNER, C. 2020. Circadian Clocks Make Metabolism Run. *J Mol Biol,* 432**,** 3680-3699.

SMITH S.T., L. J. C., LEMON P.W. 2017. Time-Restricted Eating In Women—A Pilot Study. . *West. Undergrad. Res. J. Health Nat. Sci. ,* 2017;8.

SOETERS, M. R., LAMMERS, N. M., DUBBELHUIS, P. F., ACKERMANS, M., JONKERS-SCHUITEMA, C. F., FLIERS, E., SAUERWEIN, H. P., AERTS, J. M. & SERLIE, M. J. 2009. Intermittent fasting does not affect whole-body glucose, lipid, or protein metabolism. *Am J Clin Nutr,* 90**,** 1244-51.

SOOKOIAN, S., GEMMA, C., GIANOTTI, T. F., BURGUEÑO, A., CASTAÑO, G. & PIROLA, C. J. 2008. Genetic variants of Clock transcription factor are associated with individual susceptibility to obesity. *Am J Clin Nutr,* 87**,** 1606-15.

SPIEGEL, K., LEPROULT, R. & VAN CAUTER, E. 1999. Impact of sleep debt on metabolic and endocrine function. *Lancet,* 354**,** 1435-9.

ST-ONGE, M. P., ARD, J., BASKIN, M. L., CHIUVE, S. E., JOHNSON, H. M., KRIS-ETHERTON, P. & VARADY, K. 2017. Meal Timing and Frequency: Implications for Cardiovascular Disease Prevention: A Scientific Statement From the American Heart Association. *Circulation,* 135**,** e96-e121.

ST HILAIRE, M. A., GOOLEY, J. J., KHALSA, S. B., KRONAUER, R. E., CZEISLER, C. A. & LOCKLEY, S. W. 2012. Human phase response curve to a 1 h pulse of bright white light. *J Physiol,* 590**,** 3035-45.

STENVERS, D. J., JONGEJAN, A., ATIQI, S., VREIJLING, J. P., LIMONARD, E. J., ENDERT, E., BAAS, F., MOERLAND, P. D., FLIERS, E., KALSBEEK, A. & BISSCHOP, P. H. 2019a. Diurnal rhythms in the white adipose tissue transcriptome are disturbed in obese individuals with type 2 diabetes compared with lean control individuals. *Diabetologia,* 62**,** 704-716.

STENVERS, D. J., SCHEER, F., SCHRAUWEN, P., LA FLEUR, S. E. & KALSBEEK, A. 2019b. Circadian clocks and insulin resistance. *Nat Rev Endocrinol,* 15**,** 75-89.

STOTE, K. S., BAER, D. J., SPEARS, K., PAUL, D. R., HARRIS, G. K., RUMPLER, W. V., STRYCULA, P., NAJJAR, S. S., FERRUCCI, L., INGRAM, D. K., LONGO, D. L. & MATTSON, M. P. 2007. A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults. *Am J Clin Nutr,* 85**,** 981-8.

SUBRAMANIAN, A., TAMAYO, P., MOOTHA, V. K., MUKHERJEE, S., EBERT, B. L., GILLETTE, M. A., PAULOVICH, A., POMEROY, S. L., GOLUB, T. R., LANDER, E. S. & MESIROV, J. P. 2005. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. *Proceedings of the National Academy of Sciences,* 102**,** 15545-15550.

SULLI, G., MANOOGIAN, E. N. C., TAUB, P. R. & PANDA, S. 2018. Training the Circadian Clock, Clocking the Drugs, and Drugging the Clock to Prevent, Manage, and Treat Chronic Diseases. *Trends Pharmacol Sci,* 39**,** 812-827.

SUN, L., GOH, H. J., GOVINDHARAJULU, P., LEOW, M. K. & HENRY, C. J. 2020. Postprandial glucose, insulin and incretin responses differ by test meal macronutrient ingestion sequence (PATTERN study). *Clin Nutr,* 39**,** 950-957.

SUNDARAM, S. & YAN, L. 2016. Time-restricted feeding reduces adiposity in mice fed a high-fat diet. *Nutr Res,* 36**,** 603-11.

SUNDFØR, T. M., SVENDSEN, M. & TONSTAD, S. 2018. Effect of intermittent versus continuous energy restriction on weight loss, maintenance and cardiometabolic risk: A randomized 1-year trial.

Nutr Metab Cardiovasc Dis, 28**,** 698-706.
SUTTON, E. F., BEYL, R., EARLY, K. S., CEFALU, W. T., RAVUSSIN, E. & PETERSON, C. M. 2018. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metab,* 27**,** 1212-1221e3.
SWINBURN, B. A., SACKS, G., HALL, K. D., MCPHERSON, K., FINEGOOD, D. T., MOODIE, M. L. & GORTMAKER, S. L. 2011. The global obesity pandemic: shaped by global drivers and local environments. *Lancet,* 378**,** 804-14.
SYLVETSKY, A. C. 2018. Metabolic Effects of Low-Calorie Sweeteners: A Brief Review. *Obesity (Silver Spring),* 26 Suppl 3**,** S25-S31.
TÄHKÄMÖ, L., PARTONEN, T. & PESONEN, A. K. 2019. Systematic review of light exposure impact on human circadian rhythm. *Chronobiol Int,* 36**,** 151-170.
TAHRANI, A. A. & ALI, A. 2014. Obstructive Sleep Apnoea and Type 2 Diabetes. *Eur Endocrinol,* 10**,** 43-50.
TAM, C. S., VIARDOT, A., CLEMENT, K., TORDJMAN, J., TONKS, K., GREENFIELD, J. R., CAMPBELL, L. V., SAMOCHA-BONET, D. & HEILBRONN, L. K. 2010. Short-term overfeeding may induce peripheral insulin resistance without altering subcutaneous adipose tissue macrophages in humans. *Diabetes,* 59**,** 2164-70.
TANAKA, K. 2009. The proteasome: overview of structure and functions. *Proc Jpn Acad Ser B Phys Biol Sci,* 85**,** 12-36.
TEMPLEMAN, I., SMITH, H. A., CHOWDHURY, E., CHEN, Y. C., CARROLL, H., JOHNSON-BONSON, D., HENGIST, A., SMITH, R., CREIGHTON, J., CLAYTON, D., VARLEY, I., KARAGOUNIS, L. G., WILHELMSEN, A., TSINTZAS, K., REEVES, S., WALHIN, J. P., GONZALEZ, J. T., THOMPSON, D. & BETTS, J. A. 2021. A randomized controlled trial to isolate the effects of fasting and energy restriction on weight loss and metabolic health in lean adults. *Sci Transl Med,* 13.
THAISS, C. A., ZEEVI, D., LEVY, M., ZILBERMAN-SCHAPIRA, G., SUEZ, J., TENGELER, A. C., ABRAMSON, L., KATZ, M. N., KOREM, T., ZMORA, N., KUPERMAN, Y., BITON, I., GILAD, S., HARMELIN, A., SHAPIRO, H., HALPERN, Z., SEGAL, E. & ELINAV, E. 2014. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell,* 159**,** 514-29.
TINSLEY, G. M., FORSSE, J. S., BUTLER, N. K., PAOLI, A., BANE, A. A., LA BOUNTY, P. M., MORGAN, G. B. & GRANDJEAN, P. W. 2017. Time-restricted feeding in young men performing resistance training: A randomized controlled trial. *Eur J Sport Sci,* 17**,** 200-207.
TINSLEY, G. M., MOORE, M. L., GRAYBEAL, A. J., PAOLI, A., KIM, Y., GONZALES, J. U., HARRY, J. R., VANDUSSELDORP, T. A., KENNEDY, D. N. & CRUZ, M. R. 2019. Time-restricted feeding plus resistance training in active females: a randomized trial. *Am J Clin Nutr*.
TONG, J., PRIGEON, R. L., DAVIS, H. W., BIDLINGMAIER, M., KAHN, S. E., CUMMINGS, D. E., TSCHOP, M. H. & D'ALESSIO, D. 2010. Ghrelin suppresses glucose-stimulated insulin secretion and deteriorates glucose tolerance in healthy humans. *Diabetes,* 59**,** 2145-51.
TORRES-CASTILLO, N., MARTINEZ-LOPEZ, E., VIZMANOS-LAMOTTE, B. & GARAULET, M. 2020. Healthy Obese Subjects Differ in Chronotype, Sleep Habits, and Adipose Tissue Fatty Acid Composition from Their Non-Healthy Counterparts. *Nutrients,* 13.
TREPANOWSKI, J. F., KROEGER, C. M., BARNOSKY, A., KLEMPEL, M. C., BHUTANI, S., HODDY, K. K., GABEL, K., FREELS, S., RIGDON, J., ROOD, J., RAVUSSIN, E. & VARADY, K. A. 2017. Effect of Alternate-Day Fasting on Weight Loss, Weight Maintenance, and Cardioprotection Among Metabolically Healthy Obese Adults: A Randomized Clinical Trial. *JAMA Intern Med,* 177**,** 930-938.
TRICÒ, D., NESTI, L., FRASCERRA, S., BALDI, S., MENGOZZI, A. & NATALI, A. 2020. A Protein/Lipid Preload Attenuates Glucose-Induced Endothelial Dysfunction in Individuals with Abnormal Glucose Tolerance. *Nutrients,* 12.
TSAI, J. Y., VILLEGAS-MONTOYA, C., BOLAND, B. B., BLASIER, Z., EGBEJIMI, O., GONZALEZ, R., KUEHT, M., MCELFRESH, T. A., BREWER, R. A., CHANDLER, M. P., BRAY, M. S. & YOUNG, M. E. 2013. Influence of dark phase restricted high fat feeding on myocardial adaptation in mice. *J Mol Cell Cardiol,* 55**,** 147-55.

TUREK, F. W., JOSHU, C., KOHSAKA, A., LIN, E., IVANOVA, G., MCDEARMON, E., LAPOSKY, A., LOSEE-OLSON, S., EASTON, A., JENSEN, D. R., ECKEL, R. H., TAKAHASHI, J. S. & BASS, J. 2005. Obesity and metabolic syndrome in circadian Clock mutant mice. *Science,* 308**,** 1043-5.

TUVIA, N., PIVOVAROVA-RAMICH, O., MURAHOVSCHI, V., LÜCK, S., GRUDZIECKI, A., OST, A.-C., KRUSE, M., NIKIFOROVA, V. J., OSTERHOFF, M., GOTTMANN, P., GÖGEBAKAN, Ö., STICHT, C., GRETZ, N., SCHUPP, M., SCHÜRMANN, A., RUDOVICH, N., PFEIFFER, A. F. H. & KRAMER, A. 2021. Insulin directly regulates the circadian clock in adipose tissue. *Diabetes***,** db200910.

UEMURA, M., YATSUYA, H., HILAWE, E. H., LI, Y., WANG, C., CHIANG, C., OTSUKA, R., TOYOSHIMA, H., TAMAKOSHI, K. & AOYAMA, A. 2015. Breakfast Skipping is Positively Associated With Incidence of Type 2 Diabetes Mellitus: Evidence From the Aichi Workers' Cohort Study. *J Epidemiol,* 25**,** 351-8.

USUI, I., IMAMURA, T., HUANG, J., SATOH, H. & OLEFSKY, J. M. 2003. Cdc42 is a Rho GTPase family member that can mediate insulin signaling to glucose transport in 3T3-L1 adipocytes. *J Biol Chem,* 278**,** 13765-74.

VAN CAUTER, E., SHAPIRO, E. T., TILLIL, H. & POLONSKY, K. S. 1992. Circadian modulation of glucose and insulin responses to meals: relationship to cortisol rhythm. *Am J Physiol,* 262**,** E467-75.

VAN MOORSEL, D., HANSEN, J., HAVEKES, B., SCHEER, F., JORGENSEN, J. A., HOEKS, J., SCHRAUWEN-HINDERLING, V. B., DUEZ, H., LEFEBVRE, P., SCHAPER, N. C., HESSELINK, M. K. C., STAELS, B. & SCHRAUWEN, P. 2016. Demonstration of a day-night rhythm in human skeletal muscle oxidative capacity. *Mol Metab,* 5**,** 635-645.

VARADY, K. A. 2011. Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss? *Obes Rev,* 12**,** e593-601.

VARADY, K. A., BHUTANI, S., KLEMPEL, M. C. & KROEGER, C. M. 2011. Comparison of effects of diet versus exercise weight loss regimens on LDL and HDL particle size in obese adults. *Lipids Health Dis,* 10**,** 119.

VARADY, K. A., BHUTANI, S., KLEMPEL, M. C., KROEGER, C. M., TREPANOWSKI, J. F., HAUS, J. M., HODDY, K. K. & CALVO, Y. 2013. Alternate day fasting for weight loss in normal weight and overweight subjects: a randomized controlled trial. *Nutr J,* 12**,** 146.

VETTER, C., DASHTI, H. S., LANE, J. M., ANDERSON, S. G., SCHERNHAMMER, E. S., RUTTER, M. K., SAXENA, R. & SCHEER, F. 2018. Night Shift Work, Genetic Risk, and Type 2 Diabetes in the UK Biobank. *Diabetes Care,* 41**,** 762-769.

VOIGT, R. M., FORSYTH, C. B., GREEN, S. J., ENGEN, P. A. & KESHAVARZIAN, A. 2016. Circadian Rhythm and the Gut Microbiome. *Int Rev Neurobiol,* 131**,** 193-205.

VOIGT, R. M., FORSYTH, C. B., GREEN, S. J., MUTLU, E., ENGEN, P., VITATERNA, M. H., TUREK, F. W. & KESHAVARZIAN, A. 2014. Circadian disorganization alters intestinal microbiota. *PLoS One,* 9**,** e97500.

VOLLMERS, C., GILL, S., DITACCHIO, L., PULIVARTHY, S. R., LE, H. D. & PANDA, S. 2009. Time of feeding and the intrinsic circadian clock drive rhythms in hepatic gene expression. *Proc Natl Acad Sci U S A,* 106**,** 21453-8.

WANG, H. B., LOH, D. H., WHITTAKER, D. S., CUTLER, T., HOWLAND, D. & COLWELL, C. S. 2018. Time-Restricted Feeding Improves Circadian Dysfunction as well as Motor Symptoms in the Q175 Mouse Model of Huntington's Disease. *eNeuro,* 5.

WANG, W., GRECH, A., GEMMING, L. & RANGAN, A. 2020. Breakfast size is associated with daily energy intake and diet quality. *Nutrition,* 75-76**,** 110764.

WANG, Z., OH, E., CLAPP, D. W., CHERNOFF, J. & THURMOND, D. C. 2011. Inhibition or ablation of p21-activated kinase (PAK1) disrupts glucose homeostatic mechanisms in vivo. *J Biol Chem,* 286**,** 41359-41367.

WARD, P. P., PAZ, E. & CONNEELY, O. M. 2005. Multifunctional roles of lactoferrin: a critical overview. *Cell Mol Life Sci,* 62**,** 2540-8.

WATSON, L. E., PHILLIPS, L. K., WU, T., BOUND, M. J., CHECKLIN, H. L., GRIVELL, J., JONES, K. L., CLIFTON, P. M., HOROWITZ, M. & RAYNER, C. K. 2019. A whey/guar "preload" improves postprandial glycaemia and glycated haemoglobin levels in type 2 diabetes: A 12-week, single-blind,

randomized, placebo-controlled trial. *Diabetes Obes Metab,* 21**,** 930-938.
WEFERS, J., CONNELL, N. J., FEALY, C. E., ANDRIESSEN, C., DE WIT, V., VAN MOORSEL, D., MOONEN-KORNIPS, E., JÖRGENSEN, J. A., HESSELINK, M. K. C., HAVEKES, B., HOEKS, J. & SCHRAUWEN, P. 2020. Day-night rhythm of skeletal muscle metabolism is disturbed in older, metabolically compromised individuals. *Mol Metab,* 41**,** 101050.
WEHRENS, S. M. T., CHRISTOU, S., ISHERWOOD, C., MIDDLETON, B., GIBBS, M. A., ARCHER, S. N., SKENE, D. J. & JOHNSTON, J. D. 2017. Meal Timing Regulates the Human Circadian System. *Curr Biol,* 27**,** 1768-1775 e3.
WELSH, G. I., LENEY, S. E., LLOYD-LEWIS, B., WHERLOCK, M., LINDSAY, A. J., MCCAFFREY, M. W. & TAVARÉ, J. M. 2007. Rip11 is a Rab11- and AS160-RabGAP-binding protein required for insulin-stimulated glucose uptake in adipocytes. *J Cell Sci,* 120**,** 4197-208.
WENNBERG, M., GUSTAFSSON, P. E., WENNBERG, P. & HAMMARSTRÖM, A. 2016. Irregular eating of meals in adolescence and the metabolic syndrome in adulthood: results from a 27-year prospective cohort. *Public Health Nutr,* 19**,** 667-73.
WHITLOCK, G., LEWINGTON, S., SHERLIKER, P., CLARKE, R., EMBERSON, J., HALSEY, J., QIZILBASH, N., COLLINS, R. & PETO, R. 2009. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet,* 373**,** 1083-96.
WICHERSKI, J., SCHLESINGER, S. & FISCHER, F. 2021. Association between Breakfast Skipping and Body Weight-A Systematic Review and Meta-Analysis of Observational Longitudinal Studies. *Nutrients,* 13.
WILKINSON, M. J., MANOOGIAN, E. N. C., ZADOURIAN, A., LO, H., FAKHOURI, S., SHOGHI, A., WANG, X., FLEISCHER, J. G., NAVLAKHA, S., PANDA, S. & TAUB, P. R. 2019. Ten-Hour Time-Restricted Eating Reduces Weight, Blood Pressure, and Atherogenic Lipids in Patients with Metabolic Syndrome. *Cell Metab,* 31**,** 92-104 e5.
WITHROW, D. & ALTER, D. A. 2011. The economic burden of obesity worldwide: a systematic review of the direct costs of obesity. *Obes Rev,* 12**,** 131-41.
WOODIE, L. N., LUO, Y., WAYNE, M. J., GRAFF, E. C., AHMED, B., O'NEILL, A. M. & GREENE, M. W. 2017. Restricted feeding for 9h in the active period partially abrogates the detrimental metabolic effects of a Western diet with liquid sugar consumption in mice. *Metabolism*.
WOON, P. Y., KAISAKI, P. J., BRAGANÇA, J., BIHOREAU, M. T., LEVY, J. C., FARRALL, M. & GAUGUIER, D. 2007. Aryl hydrocarbon receptor nuclear translocator-like (BMAL1) is associated with susceptibility to hypertension and type 2 diabetes. *Proc Natl Acad Sci U S A,* 104**,** 14412-7.
WORLD HEALTH ORGANIZATION 2018. Obesity and Overweight. WHO, Fact sheet, 2018. [Availabel at: http://www.who.int/mediacentre/factsheets/fs311/en/ ; Accessed on 12 July 2021).
WORLD HEALTH ORGANIZATION 2019. https://www.who.int/gho/publications/world_health_statistics/2019/EN_WHS_2019_Main.pdf.
WORLD OBESITY FEDERATION 2017. https://www.worldobesity.org/resources/resource-library/calculating-the-costs-of-the-consequences-of-obesity.
WRIGHT, K. P., JR., MCHILL, A. W., BIRKS, B. R., GRIFFIN, B. R., RUSTERHOLZ, T. & CHINOY, E. D. 2013. Entrainment of the human circadian clock to the natural light-dark cycle. *Curr Biol,* 23**,** 1554-8.
XIAO, Q., GARAULET, M. & SCHEER, F. 2019. Meal timing and obesity: interactions with macronutrient intake and chronotype. *Int J Obes (Lond),* 43**,** 1701-1711.
XIE, N., ZHANG, L., GAO, W., HUANG, C., HUBER, P. E., ZHOU, X., LI, C., SHEN, G. & ZOU, B. 2020. NAD(+) metabolism: pathophysiologic mechanisms and therapeutic potential. *Signal Transduct Target Ther,* 5**,** 227.
YAGUCHI-TANAKA, Y. & TABUCHI, T. 2020. Skipping breakfast and subsequent overweight/obesity in children: A nationwide prospective study of 2.5 to 13- year olds in Japan. *J Epidemiol***,** Online ahead of print.
YAGUCHI, Y., FUJIHARA, K., YAMADA, M. H., MATSUBAYASHI, Y., KITAZAWA, M., OSAWA, T., YAMAMOTO, M., KANEKO, M., YAMANAKA, N., SEIDA, H., KODAMA, S. & SONE, H. 2020. Skipping breakfast, late-night eating and current smoking are associated with medication

adherence in Japanese patients with diabetes. *Prim Care Diabetes,* 14**,** 753-759.
YAMAMOTO, R., TOMI, R., SHINZAWA, M., YOSHIMURA, R., OZAKI, S., NAKANISHI, K., IDE, S., NAGATOMO, I., NISHIDA, M., YAMAUCHI-TAKIHARA, K., KUDO, T. & MORIYAMA, T. 2021. Associations of Skipping Breakfast, Lunch, and Dinner with Weight Gain and Overweight/Obesity in University Students: A Retrospective Cohort Study. *Nutrients,* 13**,** 271.
YASUMOTO, Y., HASHIMOTO, C., NAKAO, R., YAMAZAKI, H., HIROYAMA, H., NEMOTO, T., YAMAMOTO, S., SAKURAI, M., OIKE, H., WADA, N., YOSHIDA-NORO, C. & OISHI, K. 2016. Short-term feeding at the wrong time is sufficient to desynchronize peripheral clocks and induce obesity with hyperphagia, physical inactivity and metabolic disorders in mice. *Metabolism,* 65**,** 714-27.
YE, Y., XU, H., XIE, Z., WANG, L., SUN, Y., YANG, H., HU, D. & MAO, Y. 2020. Time-Restricted Feeding Reduces the Detrimental Effects of a High-Fat Diet, Possibly by Modulating the Circadian Rhythm of Hepatic Lipid Metabolism and Gut Microbiota. *Frontiers in Nutrition,* 7.
YIN, L., WU, N. & LAZAR, M. A. 2010. Nuclear receptor Rev-erbalpha: a heme receptor that coordinates circadian rhythm and metabolism. *Nucl Recept Signal,* 8**,** e001.
YONG, J. Y. Y., TONG, E. M. W. & LIU, J. C. J. 2020. When the camera eats first: Exploring how meal-time cell phone photography affects eating behaviours. *Appetite,* 154**,** 104787.
YOO, S. H., YAMAZAKI, S., LOWREY, P. L., SHIMOMURA, K., KO, C. H., BUHR, E. D., SIEPKA, S. M., HONG, H. K., OH, W. J., YOO, O. J., MENAKER, M. & TAKAHASHI, J. S. 2004. PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. *Proc Natl Acad Sci U S A,* 101**,** 5339-46.
YU, J. H., YUN, C. H., AHN, J. H., SUH, S., CHO, H. J., LEE, S. K., YOO, H. J., SEO, J. A., KIM, S. G., CHOI, K. M., BAIK, S. H., CHOI, D. S., SHIN, C. & KIM, N. H. 2015. Evening chronotype is associated with metabolic disorders and body composition in middle-aged adults. *J Clin Endocrinol Metab,* 100**,** 1494-502.
ZARRINPAR, A., CHAIX, A. & PANDA, S. 2016. Daily Eating Patterns and Their Impact on Health and Disease. *Trends Endocrinol Metab,* 27**,** 69-83.
ZARRINPAR, A., CHAIX, A., YOOSEPH, S. & PANDA, S. 2014. Diet and feeding pattern affect the diurnal dynamics of the gut microbiome. *Cell Metab,* 20**,** 1006-17.
ZEB, F., WU, X., CHEN, L., FATIMA, S., HAQ, I. U., CHEN, A., MAJEED, F., FENG, Q. & LI, M. 2020. Effect of time-restricted feeding on metabolic risk and circadian rhythm associated with gut microbiome in healthy males. *Br J Nutr***,** 1-11.
ZEEVI, D., KOREM, T., ZMORA, N., ISRAELI, D., ROTHSCHILD, D., WEINBERGER, A., BEN-YACOV, O., LADOR, D., AVNIT-SAGI, T., LOTAN-POMPAN, M., SUEZ, J., MAHDI, J. A., MATOT, E., MALKA, G., KOSOWER, N., REIN, M., ZILBERMAN-SCHAPIRA, G., DOHNALOVA, L., PEVSNER-FISCHER, M., BIKOVSKY, R., HALPERN, Z., ELINAV, E. & SEGAL, E. 2015. Personalized Nutrition by Prediction of Glycemic Responses. *Cell,* 163**,** 1079-1094.
ZEITZER, J. M., DIJK, D. J., KRONAUER, R., BROWN, E. & CZEISLER, C. 2000. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol,* 526 Pt 3**,** 695-702.
ZERÓN-RUGERIO, M. F., DIEZ-NOGUERA, A., IZQUIERDO-PULIDO, M. & CAMBRAS, T. 2020. Adiposity and body mass index of young women are associated with altered 24-hour profile of wrist temperature and sleep quality. *Chronobiol Int,* 37**,** 1580-1590.
ZHANG, B. & HORVATH, S. 2005. A general framework for weighted gene co-expression network analysis. *Stat Appl Genet Mol Biol,* 4**,** Article17.
ZHANG, R., LAHENS, N. F., BALLANCE, H. I., HUGHES, M. E. & HOGENESCH, J. B. 2014. A circadian gene expression atlas in mammals: implications for biology and medicine. *Proc Natl Acad Sci U S A,* 111**,** 16219-24.
ZHAO, L., HUTCHISON, A. T. & HEILBRONN, L. K. 2021a. Carbohydrate intake and circadian synchronicity in the regulation of glucose homeostasis. *Curr Opin Clin Nutr Metab Care,* 24**,** 342-348.
ZHAO, L., HUTCHISON, A. T., WITTERT, G. A., THOMPSON, C. H., LANGE, K., LIU, B. & HEILBRONN, L. K. 2020. Intermittent Fasting Does Not Uniformly Impact Genes Involved in Circadian Regulation

in Women with Obesity. *Obesity (Silver Spring),* 28 Suppl 1**,** S63-S67.
ZHAO, L., TEONG, X. T., LIU, K., LIU, B., MELAKU, Y. A., VINCENT, A. D., MANOOGIAN, E. N. C., PANDA, S., WITTERT, G., HUTCHISON, A. T. & HEILBRONN, L. K. 2021b. Eating architecture in adults at increased risk of type 2 diabetes: associations with body fat and glycaemic control. *Br J Nutr***,** 1-28.
ZHAO, W., LANGFELDER, P., FULLER, T., DONG, J., LI, A. & HOVARTH, S. 2010. Weighted gene coexpression network analysis: state of the art. *J Biopharm Stat,* 20**,** 281-300.
ZHENG, B., ALBRECHT, U., KAASIK, K., SAGE, M., LU, W., VAISHNAV, S., LI, Q., SUN, Z. S., EICHELE, G., BRADLEY, A. & LEE, C. C. 2001. Nonredundant roles of the mPer1 and mPer2 genes in the mammalian circadian clock. *Cell,* 105**,** 683-94.
ZHENG, X. & SEHGAL, A. 2010. AKT and TOR signaling set the pace of the circadian pacemaker. *Curr Biol,* 20**,** 1203-8.
ZHU, Q. & BELDEN, W. J. 2020. Molecular Regulation of Circadian Chromatin. *J Mol Biol,* 432**,** 3466-3482.
ZOMER, E., GURUSAMY, K., LEACH, R., TRIMMER, C., LOBSTEIN, T., MORRIS, S., JAMES, W. P. & FINER, N. 2016. Interventions that cause weight loss and the impact on cardiovascular risk factors: a systematic review and meta-analysis. *Obes Rev,* 17**,** 1001-11.

APPENDICES

APPENDIX A

Appendix A-1 Differential expressed gene list upon time restricted eating.

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NM_000078	CETP	1.164	3.194	16.746	0.001	0.047	up
NM_001287005	SUSD3	1.014	0.482	22.067	0.000	0.039	up
NM_001013838	CARMIL2	1.012	0.440	17.403	0.001	0.045	up
NM_080608	SPATA25	0.980	-0.023	17.070	0.001	0.046	up
NM_019609	CPXM1	0.953	5.524	35.447	0.000	0.035	up
NM_002214	ITGB8	0.930	0.093	21.021	0.000	0.040	up
NM_001040272	ADAMTSL1	0.695	3.359	33.415	0.000	0.035	up
NM_005522	HOXA1	0.673	0.514	16.382	0.001	0.048	up
NM_020469	ABO	0.672	1.898	27.672	0.000	0.036	up
NR_033738	LOC440300	0.658	0.647	18.646	0.000	0.043	up
NM_004915	ABCG1	0.653	3.579	31.179	0.000	0.035	up
NM_001012455	ZSCAN23	0.621	0.575	19.117	0.000	0.043	up
NM_001199149	LTF	0.601	4.210	16.379	0.001	0.048	up
NR_026921	LOC202181	0.586	2.604	25.007	0.000	0.036	up
NM_052854	CREB3L1	0.579	2.242	21.756	0.000	0.039	up
NM_001029864	KIAA1755	0.572	2.227	25.242	0.000	0.036	up
NM_020335	VANGL2	0.557	1.965	20.637	0.000	0.040	up
NR_026947	C1RL-AS1	0.519	2.093	22.359	0.000	0.039	up

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NR_003530	MEG3	0.504	5.623	22.567	0.000	0.039	up
NM_020883	ZSWIM5	0.501	1.549	17.099	0.001	0.046	up
NM_001320537	SLC37A1	0.501	2.746	41.110	0.000	0.035	up
NR_040058	RAD51-AS1	0.482	2.428	21.846	0.000	0.039	up
NM_004031	IRF7	0.474	3.039	23.125	0.000	0.038	up
NM_018988	GFOD1	0.472	3.466	26.731	0.000	0.036	up
NM_005358	LMO7	0.460	2.114	16.664	0.001	0.047	up
NR_023386	CROCCP3	0.455	2.919	18.486	0.000	0.043	up
NM_006820	IFI44L	0.455	6.005	18.975	0.000	0.043	up
NM_001305225	LOC100506127	0.454	2.690	17.543	0.001	0.045	up
NM_001309242	MYO15B	0.450	6.616	19.591	0.000	0.042	up
NM_000222	KIT	0.448	3.771	17.726	0.001	0.045	up
NM_033517	SHANK3	0.440	7.328	16.385	0.001	0.048	up
NM_001013627	NHSL2	0.438	3.477	20.890	0.000	0.040	up
NM_032206	NLRC5	0.430	5.933	23.714	0.000	0.038	up
NM_002403	MFAP2	0.428	2.596	18.505	0.000	0.043	up
NM_004456	EZH2	0.426	1.752	20.089	0.000	0.041	up
NM_001164741	ARHGAP4	0.425	4.713	18.783	0.000	0.043	up
NR_027487	ARHGAP27P1	0.419	3.789	27.137	0.000	0.036	up
NM_015660	GIMAP2	0.406	4.093	16.549	0.001	0.048	up
NM_144682	SLFN13	0.398	3.831	16.602	0.001	0.048	up
NM_025092	PGGHG	0.397	5.400	19.644	0.000	0.042	up
NM_020246	SLC12A9	0.397	4.482	17.317	0.001	0.045	up
NM_001127217	SMAD9	0.392	3.377	17.363	0.001	0.045	up
NM_001127671	LIFR	0.383	7.805	18.844	0.000	0.043	up
NM_000612	IGF2	0.382	7.574	27.023	0.000	0.036	up
NR_003512	INS-IGF2	0.374	7.538	25.754	0.000	0.036	up

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NM_001098479	HLA-F	0.374	6.084	17.271	0.001	0.045	up
NM_015512	DNAH1	0.373	5.374	22.551	0.000	0.039	up
NR_002728	KCNQ1OT1	0.369	4.473	23.736	0.000	0.038	up
NM_020379	MAN1C1	0.369	4.520	30.222	0.000	0.035	up
NM_021224	ZNF462	0.365	4.443	27.604	0.000	0.036	up
NM_153252	BRWD3	0.364	4.343	27.479	0.000	0.036	up
NM_020717	SHROOM4	0.362	6.126	16.190	0.001	0.050	up
NM_003655	CBX4	0.355	3.027	18.564	0.000	0.043	up
NM_015133	MAPK8IP3	0.353	5.543	17.789	0.000	0.044	up
NM_001136022	NFATC4	0.352	5.163	19.601	0.000	0.042	up
NM_001318480	SH3TC1	0.350	3.601	19.070	0.000	0.043	up
NM_001291813	SLC25A29	0.349	4.535	19.841	0.000	0.042	up
NM_014718	CLSTN3	0.348	4.643	16.872	0.001	0.047	up
NM_199002	ARHGEF1	0.340	6.087	22.378	0.000	0.039	up
NM_001012967	DDX60L	0.338	5.189	31.742	0.000	0.035	up
NM_001017995	SH3PXD2B	0.337	5.373	27.572	0.000	0.036	up
NM_005014	OMD	0.337	3.817	16.281	0.001	0.049	up
NM_001159293	ZNF737	0.335	3.490	16.853	0.001	0.047	up
NM_003088	FSCN1	0.331	4.823	20.886	0.000	0.040	up
NM_001204410	SEC14L1	0.328	7.350	16.303	0.001	0.049	up
NM_030935	TSC22D4	0.324	4.796	21.736	0.000	0.039	up
NM_001037335	HELZ2	0.322	4.376	18.187	0.000	0.044	up
NM_000022	ADA	0.320	4.098	17.317	0.001	0.045	up
NM_001174108	ZBED6	0.319	5.078	17.202	0.001	0.045	up
NM_003737	DCHS1	0.316	6.457	20.817	0.000	0.040	up
NM_030665	RAI1	0.316	4.473	17.862	0.000	0.044	up
NM_001127208	TET2	0.312	5.059	16.483	0.001	0.048	up

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NM_173690	SCAI	0.312	4.322	26.114	0.000	0.036	up
NM_015136	STAB1	0.312	7.537	19.748	0.000	0.042	up
NR_024448	GUSBP11	0.311	4.703	21.266	0.000	0.040	up
NM_001329998	TRANK1	0.308	5.695	17.839	0.000	0.044	up
NM_015038	KIAA0754	0.298	5.178	19.690	0.000	0.042	up
NM_022835	PLEKHG2	0.296	5.442	23.293	0.000	0.038	up
NM_003023	SH3BP2	0.296	6.576	27.258	0.000	0.036	up
NM_001080424	KDM6B	0.290	4.925	18.637	0.000	0.043	up
NM_020461	TUBGCP6	0.285	6.158	21.369	0.000	0.040	up
NM_020654	SENP7	0.285	4.966	18.292	0.000	0.044	up
NM_033449	FCHSD1	0.281	4.078	16.185	0.001	0.050	up
NM_003560	PLA2G6	0.280	5.894	19.163	0.000	0.043	up
NM_052925	LENG8	0.276	7.834	17.198	0.001	0.045	up
NM_001146116	DIP2A	0.274	5.756	25.981	0.000	0.036	up
NM_014705	DOCK4	0.274	5.181	19.346	0.000	0.043	up
NM_001318202	FHOD1	0.273	5.599	19.417	0.000	0.043	up
NM_032270	LRRC8C	0.266	5.707	21.644	0.000	0.039	up
NM_003482	KMT2D	0.265	6.971	29.424	0.000	0.035	up
NM_004715	CTDP1	0.263	3.878	16.815	0.001	0.047	up
NM_001270507	TNFAIP3	0.263	4.822	20.902	0.000	0.040	up
NM_001136049	LMLN	0.259	3.870	17.124	0.001	0.046	up
NM_001308143	JADE2	0.257	5.517	17.257	0.001	0.045	up
NM_001099269	ZNF506	0.256	4.234	17.464	0.001	0.045	up
NR_026943	LOC642852	0.254	4.234	16.738	0.001	0.047	up
NM_020830	WDFY1	0.251	5.761	22.437	0.000	0.039	up
NM_001282474	AP1G2	0.250	4.506	18.561	0.000	0.043	up
NM_001204817	ZNF587	0.249	4.906	19.280	0.000	0.043	up

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NM_001330358	MTHFR	0.248	5.334	24.636	0.000	0.036	up
NM_014634	PPM1F	0.244	6.437	21.623	0.000	0.039	up
NM_014686	KIAA0355	0.243	6.302	17.419	0.001	0.045	up
NM_001297776	RIMKLB	0.243	6.265	16.676	0.001	0.047	up
NM_000052	ATP7A	0.236	4.446	17.298	0.001	0.045	up
NM_001243756	PXN	0.236	7.176	21.887	0.000	0.039	up
NM_058243	BRD4	0.226	4.719	21.895	0.000	0.039	up
NM_001080437	SNED1	0.225	6.522	16.727	0.001	0.047	up
NM_003331	TYK2	0.224	6.110	16.966	0.001	0.046	up
NM_001281482	ARFGAP1	0.223	5.532	17.106	0.001	0.046	up
NM_020729	ODF2L	0.213	5.032	17.298	0.001	0.045	up
NM_138714	NFAT5	0.210	6.911	17.811	0.000	0.044	up
NM_014727	KMT2B	0.201	5.689	18.982	0.000	0.043	up
NM_015144	ZCCHC14	0.197	5.354	17.550	0.001	0.045	up
NM_053043	RBM33	0.193	6.764	16.308	0.001	0.049	up
NR_037945	STX16-NPEPL1	0.193	6.714	16.842	0.001	0.047	up
NM_181489	ZNF445	0.183	5.365	16.243	0.001	0.049	up
NM_001109662	HECTD4	0.169	6.484	18.213	0.000	0.044	up
NM_001130089	KARS	-0.151	6.972	17.444	0.001	0.045	down
NM_001206540	CAPZB	-0.153	7.644	19.137	0.000	0.043	down
NM_001320525	DDX19A	-0.155	5.729	17.173	0.001	0.045	down
NM_001288976	XRCC6	-0.157	7.707	18.353	0.000	0.044	down
NM_006513	SARS	-0.158	6.813	18.147	0.000	0.044	down
NM_001780	CD63	-0.164	9.627	17.853	0.000	0.044	down
NM_001313943	RHOA	-0.165	9.694	16.723	0.001	0.047	down
NM_032020	FUCA2	-0.166	6.063	18.496	0.000	0.043	down
NM_007126	VCP	-0.166	8.631	17.658	0.001	0.045	down

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NM_016085	ATRAID	-0.168	6.772	18.501	0.000	0.043	down
NM_001305840	TCEAL4	-0.168	6.304	18.827	0.000	0.043	down
NM_002793	PSMB1	-0.169	7.425	18.919	0.000	0.043	down
NR_073470	SUPT4H1	-0.170	5.885	23.386	0.000	0.038	down
NM_015530	GORASP2	-0.171	6.362	18.573	0.000	0.043	down
NM_004147	DRG1	-0.172	5.742	16.558	0.001	0.048	down
NR_104099	VPS29	-0.173	6.345	17.182	0.001	0.045	down
NM_002027	FNTA	-0.173	6.572	19.852	0.000	0.042	down
NM_001791	CDC42	-0.174	7.748	20.083	0.000	0.041	down
NM_018462	BRK1	-0.176	7.652	19.364	0.000	0.043	down
NM_001172415	BAG1	-0.176	5.987	17.336	0.001	0.045	down
NM_014230	SRP68	-0.177	6.452	20.656	0.000	0.040	down
NM_001253823	BLVRA	-0.178	5.919	19.929	0.000	0.042	down
NM_001984	ESD	-0.178	6.771	20.072	0.000	0.041	down
NM_001242614	CD99L2	-0.178	7.786	21.719	0.000	0.039	down
NM_006191	PA2G4	-0.178	6.640	18.722	0.000	0.043	down
NM_016134	CPQ	-0.178	6.506	16.558	0.001	0.048	down
NM_001288	CLIC1	-0.178	7.895	17.763	0.001	0.044	down
NM_001696	ATP6V1E1	-0.179	7.161	17.973	0.000	0.044	down
NM_001321243	VOPP1	-0.179	4.926	16.404	0.001	0.048	down
NM_015292	ESYT1	-0.180	8.995	18.818	0.000	0.043	down
NM_000671	ADH5	-0.180	8.089	16.480	0.001	0.048	down
NM_001267809	ILF2	-0.180	6.676	20.982	0.000	0.040	down
NM_001156	ANXA7	-0.183	7.647	21.245	0.000	0.040	down
NM_000191	HMGCL	-0.183	5.834	20.548	0.000	0.040	down
NM_007355	HSP90AB1	-0.183	9.773	17.941	0.000	0.044	down
NM_053041	COMMD7	-0.184	5.587	17.794	0.000	0.044	down

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NM_001270896	TRAPPC3	-0.185	5.966	17.377	0.001	0.045	down
NM_005801	EIF1	-0.186	9.124	20.230	0.000	0.041	down
NM_005870	SAP18	-0.186	7.365	18.087	0.000	0.044	down
NM_006930	SKP1	-0.186	7.879	18.042	0.000	0.044	down
NM_000454	SOD1	-0.187	7.856	17.613	0.001	0.045	down
NM_001009552	PPP2CB	-0.187	6.978	16.481	0.001	0.048	down
NM_014413	EIF2AK1	-0.187	6.972	20.587	0.000	0.040	down
NM_032233	SETD3	-0.187	6.976	16.924	0.001	0.047	down
NM_006156	NEDD8	-0.188	6.919	18.373	0.000	0.044	down
NM_021821	MRPS35	-0.188	5.192	16.474	0.001	0.048	down
NM_005701	SNUPN	-0.188	4.862	17.370	0.001	0.045	down
NM_001330259	ACOT9	-0.189	5.734	16.313	0.001	0.049	down
NM_000127	EXT1	-0.189	5.959	21.658	0.000	0.039	down
NM_016104	RWDD1	-0.190	5.843	17.060	0.001	0.046	down
NR_134473	NDUFS4	-0.190	5.808	17.485	0.001	0.045	down
NM_145080	NSMCE1	-0.192	5.283	20.025	0.000	0.041	down
NM_012111	AHSA1	-0.192	6.123	16.260	0.001	0.049	down
NM_001282907	CCT8	-0.192	6.513	23.279	0.000	0.038	down
NM_002808	PSMD2	-0.192	7.654	23.486	0.000	0.038	down
NM_018648	NOP10	-0.194	5.877	29.602	0.000	0.035	down
NM_002803	PSMC2	-0.194	6.591	16.600	0.001	0.048	down
NM_058246	DNAJB6	-0.195	6.250	18.320	0.000	0.044	down
NM_032412	CYSTM1	-0.196	6.873	17.912	0.000	0.044	down
NM_006923	SDF2	-0.196	5.133	20.957	0.000	0.040	down
NM_001163280	HTATSF1	-0.197	6.934	23.445	0.000	0.038	down
NM_001282500	TTC1	-0.198	5.920	17.422	0.001	0.045	down
NM_003487	TAF15	-0.198	7.427	19.744	0.000	0.042	down

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NM_016406	UFC1	-0.199	6.222	17.816	0.000	0.044	down
NM_001166285	CCT7	-0.199	7.223	21.801	0.000	0.039	down
NM_014280	DNAJC8	-0.199	6.647	27.279	0.000	0.036	down
NM_006819	STIP1	-0.199	6.360	25.952	0.000	0.036	down
NM_031266	HNRNPAB	-0.200	5.975	19.661	0.000	0.042	down
NM_001605	AARS	-0.202	7.346	18.560	0.000	0.043	down
NM_006292	TSG101	-0.203	6.040	21.342	0.000	0.040	down
NM_016039	C14orf166	-0.204	6.712	21.410	0.000	0.040	down
NM_138389	FAM114A1	-0.204	6.604	25.011	0.000	0.036	down
NM_152653	UBE2E2	-0.204	5.312	16.838	0.001	0.047	down
NM_001123377	PARK7	-0.204	7.691	20.720	0.000	0.040	down
NM_015475	FAM98A	-0.205	6.250	21.983	0.000	0.039	down
NM_014188	SSU72	-0.205	6.334	17.546	0.001	0.045	down
NM_015933	TMA7	-0.206	5.466	17.841	0.000	0.044	down
NM_006571	DCTN6	-0.206	5.569	17.646	0.001	0.045	down
NM_001317963	PWP1	-0.206	5.784	22.045	0.000	0.039	down
NM_012138	AATF	-0.206	5.281	19.245	0.000	0.043	down
NM_001322038	NUTF2	-0.207	5.637	17.991	0.000	0.044	down
NM_000100	CSTB	-0.207	7.467	23.950	0.000	0.038	down
NM_004517	ILK	-0.207	7.442	20.602	0.000	0.040	down
NM_144723	ZMAT2	-0.208	6.352	26.588	0.000	0.036	down
NM_014248	RBX1	-0.209	5.231	19.132	0.000	0.043	down
NM_001007027	ALG8	-0.209	5.192	16.521	0.001	0.048	down
NM_001287742	FDFT1	-0.210	7.391	18.584	0.000	0.043	down
NM_003124	SPR	-0.210	5.159	17.253	0.001	0.045	down
NM_018697	LANCL2	-0.210	4.632	18.975	0.000	0.043	down
NR_048568	ACTR6	-0.210	4.330	16.743	0.001	0.047	down

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NM_020243	TOMM22	-0.210	5.694	22.004	0.000	0.039	down
NM_001291163	EPHX1	-0.212	8.992	22.689	0.000	0.039	down
NR_015432	LINC00493	-0.213	5.084	18.231	0.000	0.044	down
NM_001316363	EIF2S2	-0.213	5.970	19.842	0.000	0.042	down
NM_001199163	PSMC5	-0.214	6.772	22.903	0.000	0.039	down
NM_018445	SELENOS	-0.214	5.323	22.094	0.000	0.039	down
NM_001318966	EIF2B4	-0.215	5.342	23.425	0.000	0.038	down
NR_045639	UQCRB	-0.215	7.368	18.622	0.000	0.043	down
NM_021237	SELENOK	-0.216	5.314	22.587	0.000	0.039	down
NM_019059	TOMM7	-0.216	7.590	25.329	0.000	0.036	down
NM_001330727	COPS4	-0.216	5.247	19.417	0.000	0.043	down
NM_001324220	HMGCS1	-0.216	5.973	24.158	0.000	0.038	down
NM_001017973	P4HA2	-0.217	4.575	17.015	0.001	0.046	down
NM_016429	COPZ2	-0.217	6.367	20.744	0.000	0.040	down
NR_003573	ANXA2P2	-0.217	8.635	18.744	0.000	0.043	down
NM_024605	ARHGAP10	-0.217	5.890	20.447	0.000	0.041	down
NM_021019	MYL6	-0.218	10.437	18.888	0.000	0.043	down
NM_004891	MRPL33	-0.218	5.126	18.074	0.000	0.044	down
NR_036625	VDAC1	-0.218	6.914	19.609	0.000	0.042	down
NM_181696	PRDX1	-0.219	7.792	25.435	0.000	0.036	down
NM_170784	MKKS	-0.219	5.638	17.945	0.000	0.044	down
NM_001199671	CALU	-0.220	7.991	23.231	0.000	0.038	down
NM_014412	CACYBP	-0.220	5.385	18.849	0.000	0.043	down
NR_037929	SLMO2-ATP5E	-0.221	7.755	16.324	0.001	0.049	down
NM_014183	DYNLRB1	-0.223	6.380	17.675	0.001	0.045	down
NM_004905	PRDX6	-0.224	9.225	25.761	0.000	0.036	down
NM_207118	GTF2H5	-0.224	5.619	16.442	0.001	0.048	down

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NM_001012456	SEC61G	-0.224	4.939	20.160	0.000	0.041	down
NM_021908	ST7	-0.225	4.948	17.709	0.001	0.045	down
NM_012180	FBXO8	-0.226	5.040	18.958	0.000	0.043	down
NM_003610	RAE1	-0.226	4.552	20.954	0.000	0.040	down
NM_032359	CMSS1	-0.227	4.429	16.688	0.001	0.047	down
NM_025075	THOC7	-0.227	5.188	19.047	0.000	0.043	down
NM_174923	CCDC107	-0.228	6.298	16.835	0.001	0.047	down
NM_002789	PSMA4	-0.228	6.277	30.045	0.000	0.035	down
NM_020532	RTN4	-0.231	9.861	16.893	0.001	0.047	down
NM_014463	LSM3	-0.232	5.352	20.939	0.000	0.040	down
NR_047676	TARS	-0.232	5.999	18.962	0.000	0.043	down
NM_001142648	SAR1A	-0.232	8.152	20.564	0.000	0.040	down
NM_001319066	ITGB1BP1	-0.233	8.372	25.942	0.000	0.036	down
NM_018838	NDUFA12	-0.233	5.359	23.178	0.000	0.038	down
NM_003329	TXN	-0.233	5.953	17.633	0.001	0.045	down
NM_001006605	FAM69A	-0.233	5.881	17.972	0.000	0.044	down
NM_032194	RPF2	-0.233	4.362	20.263	0.000	0.041	down
NM_006886	ATP5E	-0.234	7.839	18.118	0.000	0.044	down
NM_006356	ATP5H	-0.235	6.923	19.310	0.000	0.043	down
NM_001324165	ZNF32	-0.236	5.435	20.785	0.000	0.040	down
NM_001316772	GARS	-0.236	5.947	17.866	0.000	0.044	down
NM_016497	MRPL51	-0.237	6.036	21.937	0.000	0.039	down
NM_006519	DYNLT1	-0.242	5.395	21.240	0.000	0.040	down
NM_004939	DDX1	-0.243	7.025	25.567	0.000	0.036	down
NM_032273	TMEM126A	-0.243	4.542	18.091	0.000	0.044	down
NM_014169	CHMP4A	-0.245	6.071	35.714	0.000	0.035	down
NM_003256	TIMP4	-0.246	7.386	17.923	0.000	0.044	down

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NM_182679	GPATCH4	-0.246	4.920	19.500	0.000	0.043	down
NM_001204858	ELOC	-0.247	5.284	30.934	0.000	0.035	down
NM_022157	RRAGC	-0.247	6.973	19.743	0.000	0.042	down
NM_004344	CETN2	-0.247	5.441	21.836	0.000	0.039	down
NM_002032	FTH1	-0.248	11.101	18.585	0.000	0.043	down
NM_015621	CCDC69	-0.249	9.302	21.864	0.000	0.039	down
NM_016038	SBDS	-0.249	7.729	24.865	0.000	0.036	down
NM_014282	HABP4	-0.251	5.702	29.732	0.000	0.035	down
NM_138408	GTF3C6	-0.255	4.642	20.880	0.000	0.040	down
NM_001316961	AAMDC	-0.258	5.823	16.578	0.001	0.048	down
NM_006834	RAB32	-0.259	4.562	16.683	0.001	0.047	down
NM_007051	FAF1	-0.259	5.576	29.892	0.000	0.035	down
NM_004552	NDUFS5	-0.260	6.925	23.729	0.000	0.038	down
NM_016002	SCCPDH	-0.260	5.798	18.586	0.000	0.043	down
NM_017867	HPF1	-0.262	4.104	17.718	0.001	0.045	down
NM_015957	APIP	-0.263	4.931	17.413	0.001	0.045	down
NM_001002857	ANXA2	-0.265	10.266	25.201	0.000	0.036	down
NM_002023	FMOD	-0.266	9.445	18.151	0.000	0.044	down
NM_199342	SVBP	-0.267	4.710	29.645	0.000	0.035	down
NM_004853	STX8	-0.267	5.329	17.199	0.001	0.045	down
NM_000898	MAOB	-0.267	7.837	19.220	0.000	0.043	down
NM_024657	MORC4	-0.269	5.434	18.134	0.000	0.044	down
NR_137440	BRE	-0.269	4.964	31.753	0.000	0.035	down
NM_016283	AK6	-0.270	4.671	31.123	0.000	0.035	down
NM_001297576	PEA15	-0.272	9.348	32.640	0.000	0.035	down
NM_018405	COPRS	-0.274	6.207	19.259	0.000	0.043	down
NM_001442	FABP4	-0.279	12.470	19.059	0.000	0.043	down

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NM_000146	FTL	-0.280	12.823	17.304	0.001	0.045	down
NM_001286124	MARK1	-0.284	5.499	25.135	0.000	0.036	down
NM_012151	F8A1	-0.289	4.013	31.813	0.000	0.035	down
NM_001260512	MGST1	-0.290	10.170	20.740	0.000	0.040	down
NM_025243	SLC19A3	-0.292	8.574	20.358	0.000	0.041	down
NM_017549	EPDR1	-0.293	6.705	24.618	0.000	0.036	down
NM_013363	PCOLCE2	-0.305	8.384	18.325	0.000	0.044	down
NM_006366	CAP2	-0.310	6.105	23.427	0.000	0.038	down
NM_183240	TMEM37	-0.312	8.183	27.215	0.000	0.036	down
NM_019554	S100A4	-0.315	8.495	16.893	0.001	0.047	down
NM_020689	SLC24A3	-0.320	6.645	18.535	0.000	0.043	down
NM_001154	ANXA5	-0.326	9.881	23.873	0.000	0.038	down
NM_001018100	MYZAP	-0.329	8.154	16.877	0.001	0.047	down
NM_001286968	JUND	-0.331	6.241	22.558	0.000	0.039	down
NM_000700	ANXA1	-0.332	10.018	32.257	0.000	0.035	down
NM_002966	S100A10	-0.344	8.573	29.362	0.000	0.035	down
NM_001354	AKR1C2	-0.347	9.540	20.193	0.000	0.041	down
NM_001860	SLC31A2	-0.363	5.332	24.636	0.000	0.036	down
NM_001282696	FAM107B	-0.371	7.745	23.411	0.000	0.038	down
NM_052886	MAL2	-0.376	5.551	17.096	0.001	0.046	down
NM_021021	SNTB1	-0.386	5.079	28.518	0.000	0.036	down
NR_024204	CYTOR	-0.400	3.625	23.868	0.000	0.038	down
NR_027622	LOC100128164	-0.411	4.953	21.715	0.000	0.039	down
NM_001353	AKR1C1	-0.413	9.026	28.616	0.000	0.036	down
NM_014467	SRPX2	-0.424	6.496	23.488	0.000	0.038	down
NR_135480	LOC102724532	-0.431	3.151	20.170	0.000	0.041	down
NM_001289808	CRYAB	-0.433	10.774	26.056	0.000	0.036	down

Gene ID	Gene name	logFC	logCPM	F	P-Value	FDR	Regulation direction
NM_001937	DPT	-0.438	10.677	32.245	0.000	0.035	down
NM_003012	SFRP1	-0.451	8.437	20.359	0.000	0.041	down
NM_014762	DHCR24	-0.469	7.835	25.381	0.000	0.036	down
NR_045784	CHIT1	-0.678	4.520	19.229	0.000	0.043	down

Appendix A-2 Gene Ontology pathway overrepresentation analysis (ORA) of differentially expressed genes (downregulated) after time restricted eating.

Gene Set	Enrichment ratio	p-Value	FDR
GO_PHOSPHOLIPASE_INHIBITOR_ACTIVITY	28.479	0.000	0.009
GO_PROTEASOME_REGULATORY_PARTICLE_BASE_SUBCOMPLEX	26.105	0.000	0.011
GO_POSITIVE_REGULATION_OF_TELOMERASE_RNA_LOCALIZATION_TO_CAJAL_BODY	20.884	0.000	0.019
GO_UBIQUITIN_SPECIFIC_PROTEASE_BINDING	20.884	0.000	0.019
GO_CHAPERONE_COMPLEX	19.890	0.000	0.005
GO_LIPASE_INHIBITOR_ACTIVITY	19.579	0.000	0.022
GO_POSITIVE_REGULATION_OF_EXTRINSIC_APOPTOTIC_SIGNALING_PATHWAY_VIA_DEATH_DOMAIN_RECEPTORS	18.427	0.001	0.026
GO_TELOMERASE_RNA_LOCALIZATION	16.488	0.001	0.029
GO_OXIDOREDUCTASE_ACTIVITY_ACTING_ON_THE_CH_CH_GROUP_OF_DONORS_NAD_OR_NADP_AS_ACCEPTOR	16.065	0.000	0.009
GO_MAINTENANCE_OF_PROTEIN_LOCATION_IN_NUCLEUS	14.239	0.001	0.041
GO_NUCLEOTIDE_EXCISION_REPAIR_DNA_DUPLEX_UNWINDING	14.239	0.001	0.041
GO_INCLUSION_BODY_ASSEMBLY	13.620	0.001	0.046
GO_MACROMOLECULE_TRANSMEMBRANE_TRANSPORTER_ACTIVITY	13.620	0.001	0.046
GO_RESPONSE_TO_X_RAY	13.474	0.000	0.013
GO_REGULATION_OF_CELL_MIGRATION_INVOLVED_IN_SPROUTING_ANGIOGENESIS	10.992	0.000	0.023
GO_ANTIBIOTIC_METABOLIC_PROCESS	10.327	0.000	0.000
GO_LIGASE_ACTIVITY_FORMING_CARBON_OXYGEN_BONDS	10.187	0.001	0.027
GO_CALCIUM_DEPENDENT_PHOSPHOLIPID_BINDING	10.041	0.000	0.009
GO_POSITIVE_REGULATION_OF_STRESS_FIBER_ASSEMBLY	10.041	0.000	0.009
GO_ENDOPEPTIDASE_COMPLEX	9.639	0.000	0.004
GO_REGULATION_OF_TRANSCRIPTION_FROM_RNA_POLYMERASE_II_PROMOTER_IN_RESPONSE_TO_HYPOXIA	9.618	0.000	0.001

Gene Set	Enrichment ratio	p-Value	FDR
GO_TAU_PROTEIN_BINDING	9.282	0.001	0.033
GO_FICOLIN_1_RICH_GRANULE	9.263	0.000	0.000
GO_CELLULAR_DETOXIFICATION	8.702	0.000	0.000
GO_REGULATION_OF_CELLULAR_AMINO_ACID_METABOLIC_PROCESS	8.702	0.000	0.015
GO_ANTIOXIDANT_ACTIVITY	8.599	0.000	0.003
GO_AMINO_ACID_ACTIVATION	8.524	0.001	0.043
GO_ANTIBIOTIC_CATABOLIC_PROCESS	8.524	0.001	0.043
GO_CALCIUM_DEPENDENT_PROTEIN_BINDING	8.421	0.000	0.017
GO_POSITIVE_REGULATION_OF_ACTIN_FILAMENT_BUNDLE_ASSEMBLY	8.421	0.000	0.017
GO_POSITIVE_REGULATION_OF_CELL_MATRIX_ADHESION	8.354	0.001	0.046
GO_CELLULAR_IRON_ION_HOMEOSTASIS	8.287	0.000	0.018
GO_SCF_DEPENDENT_PROTEASOMAL_UBIQUITIN_DEPENDENT_PROTEIN_CATABOLIC_PROCESS	8.213	0.000	0.003
GO_AZUROPHIL_GRANULE_LUMEN	8.122	0.000	0.003
GO_HEMATOPOIETIC_STEM_CELL_DIFFERENTIATION	8.032	0.000	0.009
GO_REGULATION_OF_CELLULAR_AMINE_METABOLIC_PROCESS	7.931	0.000	0.009
GO_REGULATION_OF_ESTABLISHMENT_OF_PLANAR_POLARITY	7.664	0.000	0.002
GO_DETOXIFICATION	7.641	0.000	0.001
GO_INTERLEUKIN_1_MEDIATED_SIGNALING_PATHWAY	7.383	0.000	0.005
GO_IRON_ION_HOMEOSTASIS	7.371	0.000	0.011
GO_NEGATIVE_REGULATION_OF_CELL_CYCLE_G2_M_PHASE_TRANSITION	7.237	0.000	0.005
GO_REGULATION_OF_ACTOMYOSIN_STRUCTURE_ORGANIZATION	7.120	0.000	0.012
GO_PEPTIDASE_COMPLEX	7.040	0.000	0.013
GO_CONTRACTILE_ACTIN_FILAMENT_BUNDLE_ASSEMBLY	6.810	0.000	0.015
GO_REGULATION_OF_ACTIN_FILAMENT_BUNDLE_ASSEMBLY	6.810	0.000	0.015
GO_DNA_GEOMETRIC_CHANGE	6.737	0.000	0.015
GO_ANTIGEN_PROCESSING_AND_PRESENTATION_OF_EXOGENOUS_PEPTIDE_ANTIGEN_VIA_MHC_CLASS_I	6.694	0.001	0.034
GO_REGULATION_OF_CELLULAR_RESPONSE_TO_HEAT	6.609	0.001	0.035

Gene Set	Enrichment ratio	p-Value	FDR
GO_ANAPHASE_PROMOTING_COMPLEX_DEPENDENT_CATABOLIC_PROCESS	6.446	0.001	0.039
GO_REGULATION_OF_HEMATOPOIETIC_PROGENITOR_CELL_DIFFERENTIATION	6.367	0.001	0.041
GO_AZUROPHIL_GRANULE	6.142	0.000	0.003
GO_REACTIVE_OXYGEN_SPECIES_BIOSYNTHETIC_PROCESS	6.142	0.000	0.023
GO_POSITIVE_REGULATION_OF_CANONICAL_WNT_SIGNALING_PATHWAY	6.053	0.000	0.006
GO_PIGMENT_GRANULE	6.024	0.000	0.025
GO_MORPHOGENESIS_OF_A_POLARIZED_EPITHELIUM	6.010	0.000	0.006
GO_UNFOLDED_PROTEIN_BINDING	5.991	0.000	0.011
GO_OXIDATIVE_PHOSPHORYLATION	5.895	0.000	0.012
GO_REGULATION_OF_DNA_TEMPLATED_TRANSCRIPTION_IN_RESPONSE_TO_STRESS	5.848	0.000	0.012
GO_NIK_NF_KAPPAB_SIGNALING	5.837	0.000	0.003
GO_CELLULAR_TRANSITION_METAL_ION_HOMEOSTASIS	5.748	0.001	0.027
GO_FC_EPSILON_RECEPTOR_SIGNALING_PATHWAY	5.696	0.001	0.027
GO_NON_CANONICAL_WNT_SIGNALING_PATHWAY	5.683	0.000	0.008
GO_REGULATION_OF_STEM_CELL_DIFFERENTIATION	5.644	0.001	0.027
GO_INNATE_IMMUNE_RESPONSE_ACTIVATING_CELL_SURFACE_RECEPTOR_SIGNALING_PATHWAY	5.448	0.001	0.032
GO_TRANSITION_METAL_ION_HOMEOSTASIS	5.375	0.000	0.018
GO_HEAT_SHOCK_PROTEIN_BINDING	5.310	0.001	0.035
GO_FC_RECEPTOR_SIGNALING_PATHWAY	5.280	0.000	0.006
GO_TUMOR_NECROSIS_FACTOR_MEDIATED_SIGNALING_PATHWAY	5.189	0.000	0.011
GO_PROTEASE_BINDING	5.094	0.001	0.042
GO_MICROTUBULE_CYTOSKELETON_ORGANIZATION_INVOLVED_IN_MITOSIS	5.053	0.001	0.044
GO_POSITIVE_REGULATION_OF_WNT_SIGNALING_PATHWAY	4.943	0.000	0.013
GO_VESICLE_LUMEN	4.943	0.000	0.000
GO_VACUOLAR_LUMEN	4.914	0.000	0.014
GO_RESPONSE_TO_INTERLEUKIN_1	4.819	0.000	0.009
GO_RESPONSE_TO_HEAT	4.801	0.000	0.016

Gene Set	Enrichment ratio	p-Value	FDR
GO_REGULATION_OF_MORPHOGENESIS_OF_AN_EPITHELIUM	4.746	0.000	0.017
GO_ORGANIC_ACID_BINDING	4.630	0.000	0.010
GO_CELLULAR_RESPONSE_TO_TOXIC_SUBSTANCE	4.520	0.000	0.008
GO_POSITIVE_REGULATION_OF_PROTEIN_KINASE_B_SIGNALING	4.457	0.001	0.038
GO_CELLULAR_KETONE_METABOLIC_PROCESS	4.397	0.001	0.025
GO_PROTEIN_FOLDING	4.351	0.000	0.014
GO_MIDBODY	4.275	0.001	0.046
GO_MITOCHONDRIAL_PROTEIN_COMPLEX	4.144	0.000	0.011
GO_RNA_LOCALIZATION	4.140	0.000	0.019
GO_UBIQUITIN_LIKE_PROTEIN_LIGASE_BINDING	4.122	0.000	0.004
GO_DRUG_METABOLIC_PROCESS	4.052	0.000	0.003
GO_CELLULAR_AMINO_ACID_METABOLIC_PROCESS	3.988	0.000	0.009
GO_REGULATION_OF_CELL_CYCLE_G2_M_PHASE_TRANSITION	3.959	0.001	0.036
GO_REGULATION_OF_CELLULAR_PROTEIN_CATABOLIC_PROCESS	3.883	0.001	0.026
GO_POSITIVE_REGULATION_OF_PROTEIN_COMPLEX_ASSEMBLY	3.867	0.001	0.027
GO_CELLULAR_RESPONSE_TO_OXYGEN_LEVELS	3.814	0.001	0.044
GO_PROTEIN_LOCALIZATION_TO_NUCLEUS	3.805	0.001	0.027
GO_ANTIGEN_PROCESSING_AND_PRESENTATION	3.797	0.001	0.045
GO_REGULATION_OF_PROTEIN_COMPLEX_ASSEMBLY	3.703	0.000	0.002
GO_ATPASE_ACTIVITY_COUPLED	3.580	0.000	0.010
GO_COFACTOR_METABOLIC_PROCESS	3.576	0.000	0.003
GO_CADHERIN_BINDING	3.556	0.000	0.016
GO_RESPONSE_TO_TUMOR_NECROSIS_FACTOR	3.504	0.001	0.027
GO_REGULATION_OF_SMALL_MOLECULE_METABOLIC_PROCESS	3.470	0.000	0.019
GO_RESPONSE_TO_OXIDATIVE_STRESS	3.440	0.000	0.006
GO_REGULATION_OF_SUPRAMOLECULAR_FIBER_ORGANIZATION	3.429	0.000	0.021
GO_ATPASE_ACTIVITY	3.400	0.000	0.007

Gene Set	Enrichment ratio	p-Value	FDR
GO_POST_TRANSLATIONAL_PROTEIN_MODIFICATION	3.182	0.001	0.029
GO_PROTEASOMAL_PROTEIN_CATABOLIC_PROCESS	3.164	0.000	0.010
GO_REGULATION_OF_PROTEIN_CATABOLIC_PROCESS	3.113	0.001	0.033
GO_CELL_ADHESION_MOLECULE_BINDING	3.002	0.000	0.015
GO_RNA_SPLICING	2.969	0.001	0.030

Appendix A-3 Gene Ontology pathway analysis of ranked gene list after time restricted eating via gene sets enrichment analysis (GSEA).

Gene Set	Normalized Enrichment Score	p-Value	FDR	size	Leading Edge Number
Upregulated pathways					
GO_ANTIMICROBIAL_HUMORAL_IMMUNE_RESPONSE_MEDIATED_BY_ANTIMICROBIAL_PEPTIDE	1.955	0.000	0.006	44	17
GO_ANTIMICROBIAL_HUMORAL_RESPONSE	1.927	0.000	0.006	73	24
GO_CYTOKINE_RECEPTOR_ACTIVITY	1.943	0.000	0.007	80	35
GO_DISRUPTION_OF_CELLS_OF_OTHER_ORGANISM_INVOLVED_IN_SYMBIOTIC_INTERACTION	1.870	0.000	0.030	14	9
Downregulated pathways					
GO_ATP_SYNTHESIS_COUPLED_ELECTRON_TRANSPORT	-2.108	0.000	0.005	75	54
GO_CERAMIDE_CATABOLIC_PROCESS	-1.952	0.004	0.032	17	2
GO_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE	-2.045	0.000	0.012	95	65
GO_ENERGY_COUPLED_PROTON_TRANSPORT_DOWN_ELECTROCHEMICAL_GRADIENT	-1.996	0.000	0.020	20	16
GO_ESTABLISHMENT_OF_PROTEIN_LOCALIZATION_TO_ENDOPLASMIC_RETICULUM	-1.925	0.000	0.042	108	69
GO_INNER_MITOCHONDRIAL_MEMBRANE_PROTEIN_COMPLEX	-2.250	0.000	0.001	111	70
GO_LARGE_RIBOSOMAL_SUBUNIT	-2.307	0.000	0.000	108	76
GO_MITOCHONDRIAL_ELECTRON_TRANSPORT_NADH_TO_UBIQUINONE	-2.066	0.005	0.009	40	31
GO_MITOCHONDRIAL_GENE_EXPRESSION	-2.230	0.000	0.001	149	94
GO_MITOCHONDRIAL_MEMBRANE_PART	-2.010	0.000	0.018	188	119
GO_MITOCHONDRIAL_PROTEIN_COMPLEX	-2.404	0.000	0.000	231	155
GO_MITOCHONDRIAL_RESPIRATORY_CHAIN_COMPLEX_I	-2.008	0.000	0.018	40	31
GO_MITOCHONDRIAL_TRANSLATION	-2.337	0.000	0.000	125	86
GO_MITOCHONDRIAL_TRANSLATIONAL_TERMINATION	-2.331	0.000	0.000	85	65
GO_NADH_DEHYDROGENASE_ACTIVITY	-1.993	0.000	0.021	36	27

Gene Set	Normalized Enrichment Score	p-Value	FDR	size	Leading Edge Number
GO_ORGANELLAR_LARGE_RIBOSOMAL_SUBUNIT	-2.285	0.000	0.000	54	41
GO_ORGANELLAR_RIBOSOME	-2.326	0.000	0.000	81	62
GO_ORGANELLAR_SMALL_RIBOSOMAL_SUBUNIT	-2.038	0.000	0.013	26	21
GO_OXIDATIVE_PHOSPHORYLATION	-2.218	0.000	0.001	111	70
GO_OXIDOREDUCTASE_ACTIVITY_ACTING_ON_NAD_P_H_QUINONE_OR_SIMILAR_COMPOUND_AS_ACCEPTOR	-1.978	0.000	0.024	49	37
GO_PROTON_TRANSPORTING_ATP_SYNTHASE_COMPLEX	-2.135	0.000	0.003	18	16
GO_RIBOSOMAL_SUBUNIT	-2.003	0.000	0.019	174	120
GO_RIBOSOME	-1.985	0.000	0.023	209	146
GO_STRUCTURAL_CONSTITUENT_OF_RIBOSOME	-2.275	0.000	0.000	144	110
GO_TRANSLATION_FACTOR_ACTIVITY_RNA_BINDING	-1.967	0.000	0.027	81	57
GO_TRANSLATION_INITIATION_FACTOR_ACTIVITY	-1.989	0.000	0.022	48	40
GO_TRANSLATION_REGULATOR_ACTIVITY_NUCLEIC_ACID_BINDING	-1.934	0.000	0.039	99	65
GO_TRANSLATIONAL_ELONGATION	-2.217	0.000	0.001	125	79
GO_TRANSLATIONAL_INITIATION	-2.085	0.000	0.007	180	126
GO_TRANSLATIONAL_TERMINATION	-2.340	0.000	0.000	99	75
GO_URONIC_ACID_METABOLIC_PROCESS	-2.192	0.000	0.002	12	10
GO_VERY_LONG_CHAIN_FATTY_ACID_METABOLIC_PROCESS	-1.925	0.007	0.041	11	8

Appendix A-4 Differentially expressed gene names under each top 10 pathway.

	Gene names	FDR
Downregulated pathways (ORA)		
phospholipase inhibitor activity		**0.009**
ANXA1	annexin A1	
ANXA2	annexin A2	
ANXA5	annexin A5	
proteasome regulatory particle base subcomplex		**0.011**
PSMD2	proteasome 26S subunit, non-ATPase 2	
PSMC5	proteasome 26S subunit, ATPase 5	
PSMC2	proteasome 26S subunit, ATPase 2	
positive regulation of telomerase rna localization to cajal body		**0.019**
NOP10	NOP10 ribonucleoprotein	
CCT7	chaperonin containing TCP1 subunit 7	
CCT8	chaperonin containing TCP1 subunit 8	
ubiquitin specific protease binding		**0.019**
SELENOS	selenoprotein S	
PARK7	Parkinsonism associated deglycase	
VCP	valosin containing protein	
chaperone complex		**0.005**
STIP1	stress induced phosphoprotein 1	
CCT8	chaperonin containing TCP1 subunit 8	
HSP90AB1	heat shock protein 90 alpha family class B member 1	
CCT7	chaperonin containing TCP1 subunit 7	
lipase inhibitor activity		**0.022**
ANXA1	annexin A1	
ANXA2	annexin A2	
ANXA5	annexin A5	
positive regulation of extrinsic apoptotic signaling pathway via death domain receptors		**0.026**
PEA15	proliferation and apoptosis adaptor protein 15	
FAF1	Fas associated factor 1	
SFRP1	secreted frizzled related protein 1	
telomerase rna localization		**0.029**
NOP10	NOP10 ribonucleoprotein	
CCT8	chaperonin containing TCP1 subunit 8	
CCT7	chaperonin containing TCP1 subunit 7	
oxidoreductase activity acting on the ch-ch group of donors, nad or nadp as acceptor		**0.009**
AKR1C1	aldo-keto reductase family 1 member C1	
DHCR24	24-dehydrocholesterol reductase	
AKR1C2	aldo-keto reductase family 1 member C2	
BLVRA	biliverdin reductase A	
maintenance of protein location in nucleus		**0.041**
PARK7	Parkinsonism associated deglycase	
SKP1	S-phase kinase associated protein 1	

	Gene names	FDR
TXN	thioredoxin	
Downregulated pathways (GSEA)		
mitochondrial protein complex		**<0.001**
TOMM7	translocase of outer mitochondrial membrane 7	
NDUFA12	NADH:ubiquinone oxidoreductase subunit A12	
NDUFS5	NADH:ubiquinone oxidoreductase subunit S5	
TOMM22	translocase of outer mitochondrial membrane 22	
MRPL51	mitochondrial ribosomal protein L51	
PARK7	Parkinsonism associated deglycase	
ATP5PD	ATP synthase peripheral stalk subunit d	
MRPL33	mitochondrial ribosomal protein L33	
ATP5F1E	ATP synthase F1 subunit epsilon	
MRPS35	mitochondrial ribosomal protein S35	
translational termination		**<0.001**
MRPS35	mitochondrial ribosomal protein S35	
MRPL33	mitochondrial ribosomal protein L33	
MRPL51	mitochondrial ribosomal protein L51	
organellar ribosome		**<0.001**
MRPS35	mitochondrial ribosomal protein S35	
MRPL33	mitochondrial ribosomal protein L33	
MRPL51	mitochondrial ribosomal protein L51	
mitochondrial translation		**<0.001**
MRPS35	mitochondrial ribosomal protein S35	
MRPL33	mitochondrial ribosomal protein L33	
MRPL51	mitochondrial ribosomal protein L51	
GARS	glycyl-tRNA synthetase	
mitochondrial translational termination		**<0.001**
MRPS35	mitochondrial ribosomal protein S35	
MRPL33	mitochondrial ribosomal protein L33	
MRPL51	mitochondrial ribosomal protein L51	
large ribosomal subunit		**<0.001**
MRPL33	mitochondrial ribosomal protein L33	
MRPL51	mitochondrial ribosomal protein L51	
oxidative phosphorylation		**<0.001**
NDUFA12	NADH:ubiquinone oxidoreductase subunit A12	
NDUFS5	NADH:ubiquinone oxidoreductase subunit S5	
VCP	valosin containing protein	
PARK7	Parkinsonism associated deglycase	
ATP5PD	ATP synthase peripheral stalk subunit d	
RHOA	ras homolog family member A	
ATP5F1E	ATP synthase F1 subunit epsilon	
inner mitochondrial membrane protein complex		**<0.001**
NDUFA12	NADH:ubiquinone oxidoreductase subunit A12	
NDUFS5	NADH:ubiquinone oxidoreductase subunit S5	
PARK7	Parkinsonism associated deglycase	

	Gene names	FDR
ATP5PD	ATP synthase peripheral stalk subunit d	
ATP5F1E	ATP synthase F1 subunit epsilon	
organellar large ribosomal subunit		**<0.001**
MRPL33	mitochondrial ribosomal protein L33	
MRPL51	mitochondrial ribosomal protein L51	
structural constituent of ribosome		**<0.001**
MRPS35	mitochondrial ribosomal protein S35	
MRPL33	mitochondrial ribosomal protein L33	
MRPL51	mitochondrial ribosomal protein L51	
Upregulated pathways (GSEA)		
disruption of cells of other organism involved in symbiotic interaction		**0.049**
No genes were significant expressed		
antimicrobial humoral response		**0.017**
LTF	lactotransferrin	
cytokine receptor activity		**0.008**
LIFR	LIF receptor alpha	
antimicrobial humoral immune response mediated by antimicrobial peptide		**0.011**
LTF	lactotransferrin	

APPENDIX B

Appendix B-1 Differential expressed gene list at 6 am upon time restricted eating.

Refer to APPENDIX A-1

Appendix B-2 Differential expressed gene list at 6 pm upon time restricted eating.

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_000097	CPOX	0.230	4.116	14.277	0.001	0.045	up
NM_000139	MS4A2	0.557	2.687	14.222	0.001	0.045	up
NM_000450	SELE	1.396	2.381	14.687	0.001	0.042	up
NM_001017995	SH3PXD2B	0.283	5.145	22.945	0.000	0.013	up
NM_001037813	ZNF284	0.396	2.361	17.622	0.000	0.026	up
NM_001039618	CREBZF	0.285	6.299	16.389	0.001	0.032	up
NM_001042601	TTC14	0.393	6.304	16.079	0.001	0.034	up
NM_001077195	ZNF436	0.245	6.039	14.535	0.001	0.043	up
NM_001081	CUBN	0.380	3.373	13.656	0.001	0.050	up
NM_001098504	DDX17	0.273	9.522	14.448	0.001	0.044	up
NM_001105549	ZNF83	0.279	6.203	16.097	0.001	0.034	up
NM_001127217	SMAD9	0.420	3.317	13.861	0.001	0.048	up
NM_001127372	ZNF84	0.265	5.293	13.719	0.001	0.049	up
NM_001136499	ZNF841	0.337	4.418	23.739	0.000	0.012	up
NM_001204817	ZNF587	0.351	4.713	13.973	0.001	0.048	up
NM_001257293	HNRNPH1	0.285	8.062	16.495	0.001	0.032	up
NM_001282356	SLC26A7	0.672	1.664	17.071	0.001	0.029	up
NM_001282757	TRA2A	0.283	5.937	17.508	0.000	0.026	up
NM_001286259	ADAT2	0.367	4.118	17.604	0.000	0.026	up
NM_001288980	C18orf54	0.461	1.928	16.177	0.001	0.034	up
NM_001300822	ZCCHC10	0.298	3.261	15.383	0.001	0.037	up
NM_001300850	RC3H1	0.218	5.234	17.965	0.000	0.025	up
NM_001303246	RASA2	0.282	4.648	15.891	0.001	0.035	up
NM_001312909	FAM111A	0.348	5.455	19.779	0.000	0.019	up

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_001321103	SLC4A7	0.375	4.259	21.288	0.000	0.016	up
NM_001321685	ZNF225	0.331	2.938	13.768	0.001	0.049	up
NM_001330314	SLC35F5	0.179	6.283	15.071	0.001	0.039	up
NM_001330330	LUC7L3	0.317	7.606	22.389	0.000	0.014	up
NM_001330415	LARP4	0.273	5.498	15.865	0.001	0.035	up
NM_001330462	ATL2	0.183	5.599	13.682	0.001	0.050	up
NM_002158	FOXN2	0.306	5.130	14.895	0.001	0.041	up
NM_002345	LUM	0.263	8.583	13.664	0.001	0.050	up
NM_002393	MDM4	0.346	5.955	22.868	0.000	0.013	up
NM_002687	PNN	0.269	6.739	18.937	0.000	0.021	up
NM_003763	STX16	0.260	7.208	13.702	0.001	0.050	up
NM_004229	MED14	0.219	5.403	16.556	0.001	0.031	up
NM_004830	MED23	0.267	5.287	22.482	0.000	0.014	up
NM_005057	RBBP5	0.260	4.853	21.289	0.000	0.016	up
NM_005603	ATP8B1	0.298	4.461	15.381	0.001	0.037	up
NM_005623	CCL8	0.696	2.104	14.594	0.001	0.042	up
NM_005711	EDIL3	0.551	2.784	15.281	0.001	0.038	up
NM_005759	ABI2	0.256	4.951	17.531	0.000	0.026	up
NM_005763	AASS	0.331	5.784	16.026	0.001	0.034	up
NM_005933	KMT2A	0.271	6.677	14.278	0.001	0.045	up
NM_006469	IVNS1ABP	0.306	6.214	15.997	0.001	0.034	up
NM_012194	KIAA1549L	0.544	1.757	14.789	0.001	0.042	up
NM_014585	SLC40A1	0.303	7.431	24.143	0.000	0.011	up
NM_014911	AAK1	0.237	5.761	17.396	0.000	0.027	up
NM_015100	POGZ	0.333	6.742	16.385	0.001	0.032	up
NM_015207	OTUD3	0.254	4.530	17.629	0.000	0.026	up
NM_017680	ASPN	0.342	4.633	22.283	0.000	0.014	up

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_018638	ETNK1	0.311	5.172	20.567	0.000	0.017	up
NM_019083	TRMT13	0.381	4.133	16.167	0.001	0.034	up
NM_020297	ABCC9	0.265	6.466	28.157	0.000	0.007	up
NM_020343	RALGAPA2	0.385	6.695	27.435	0.000	0.008	up
NM_020762	SRGAP1	0.315	4.292	15.679	0.001	0.035	up
NM_020964	EPG5	0.276	5.830	16.596	0.001	0.031	up
NM_021045	ZNF248	0.394	4.177	14.514	0.001	0.043	up
NM_021201	MS4A7	0.369	4.998	18.167	0.000	0.025	up
NM_021240	DMRT3	0.729	2.296	19.518	0.000	0.019	up
NM_021629	GNB4	0.269	5.328	13.667	0.001	0.050	up
NM_022173	TIA1	0.324	6.175	14.977	0.001	0.040	up
NM_022894	PAPOLG	0.269	3.966	14.596	0.001	0.042	up
NM_024116	TAF1D	0.242	4.218	14.649	0.001	0.042	up
NM_024590	ARSJ	0.686	0.813	15.532	0.001	0.036	up
NM_032682	FOXP1	0.206	5.328	15.912	0.001	0.035	up
NM_032726	PLCD4	0.453	3.591	20.109	0.000	0.018	up
NM_033014	OGN	0.492	4.811	15.234	0.001	0.038	up
NM_033050	SUCNR1	0.315	3.765	16.044	0.001	0.034	up
NM_080284	ABCA6	0.260	6.153	13.659	0.001	0.050	up
NM_145254	TMEM170A	0.310	3.898	14.668	0.001	0.042	up
NM_152347	EFCAB13	0.597	2.192	20.207	0.000	0.017	up
NM_152475	ZNF417	0.495	3.319	21.958	0.000	0.015	up
NM_153240	NPHP3	0.266	5.712	20.248	0.000	0.017	up
NM_173601	GXYLT1	0.300	4.638	26.869	0.000	0.008	up
NM_181672	OGT	0.299	8.000	16.678	0.001	0.031	up
NM_194247	HNRNPA3	0.213	7.435	16.559	0.001	0.031	up
NM_194292	SASS6	0.431	2.098	18.132	0.000	0.025	up

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_207333	ZNF320	0.324	4.070	13.734	0.001	0.049	up
NM_212482	FN1	0.259	9.206	17.809	0.000	0.026	up
NR_003530	MEG3	0.383	5.222	14.310	0.001	0.045	up
NR_026777	ZNF37BP	0.283	4.605	15.689	0.001	0.035	up
NR_026938	ADCY10P1	0.539	2.591	14.130	0.001	0.046	up
NR_029410	LOC389765	0.417	1.810	15.756	0.001	0.035	up
NR_029434	PSMA3-AS1	0.309	5.581	20.733	0.000	0.017	up
NR_034089	CCDC18-AS1	0.424	4.732	26.987	0.000	0.008	up
NR_036650	WHAMMP1	0.437	2.600	15.372	0.001	0.037	up
NR_038397	DNM3OS	0.274	4.941	15.589	0.001	0.036	up
NR_045128	TXLNGY	0.259	4.709	17.586	0.000	0.026	up
NR_073506	TMEM39A	0.255	4.850	15.921	0.001	0.035	up
NR_103844	NPTN-IT1	0.634	1.981	15.790	0.001	0.035	up
NR_104111	OSBPL3	0.404	3.192	17.326	0.001	0.027	up
NR_108027	LINC01484	0.574	1.672	13.826	0.001	0.049	up
NR_136326	PNISR	0.314	7.563	15.836	0.001	0.035	up
NR_144477	ZKSCAN1	0.213	6.965	14.663	0.001	0.042	up
NM_000017	ACADS	-0.296	6.390	17.857	0.000	0.026	down
NM_000033	ABCD1	-0.312	4.436	20.508	0.000	0.017	down
NM_000152	GAA	-0.254	5.794	16.738	0.001	0.031	down
NM_000156	GAMT	-0.370	3.572	14.794	0.001	0.042	down
NM_000199	SGSH	-0.239	5.069	13.939	0.001	0.048	down
NM_000285	PEPD	-0.261	6.520	29.801	0.000	0.006	down
NM_000398	CYB5R3	-0.379	9.465	34.459	0.000	0.004	down
NM_000455	STK11	-0.278	5.008	23.443	0.000	0.013	down
NM_000485	APRT	-0.282	5.527	21.890	0.000	0.015	down
NM_000754	COMT	-0.317	5.769	26.094	0.000	0.009	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_000852	GSTP1	-0.269	7.612	14.706	0.001	0.042	down
NM_000853	GSTT1	-0.226	6.178	14.069	0.001	0.049	down
NM_000858	GUK1	-0.332	6.548	19.580	0.000	0.019	down
NM_000883	IMPDH1	-0.215	6.070	17.576	0.000	0.026	down
NM_001001410	TSR3	-0.264	5.111	15.114	0.001	0.039	down
NM_001001522	TAGLN	-0.407	8.645	15.502	0.001	0.037	down
NM_001002021	PFKL	-0.366	6.731	36.686	0.000	0.004	down
NM_001002913	PTRH1	-0.419	2.189	14.658	0.001	0.042	down
NM_001003	RPLP1	-0.335	8.742	20.350	0.000	0.017	down
NM_001003891	MED15	-0.228	6.048	17.640	0.000	0.026	down
NM_001004	RPLP2	-0.278	9.484	19.071	0.000	0.021	down
NM_001004019	FBLN2	-0.262	9.495	17.551	0.000	0.026	down
NM_001006617	MAPKAP1	-0.201	7.142	20.336	0.000	0.017	down
NM_001008701	ADGRL1	-0.288	6.512	23.168	0.000	0.013	down
NM_001010858	RNF187	-0.196	6.379	13.851	0.001	0.048	down
NM_001012426	FOXP4	-0.270	5.518	13.897	0.001	0.048	down
NM_001012614	CTBP1	-0.221	6.486	22.508	0.000	0.014	down
NM_001012973	PLAC9	-0.539	6.252	64.158	0.000	0.001	down
NM_001017405	MAEA	-0.212	5.346	17.448	0.000	0.027	down
NM_001018050	POLR3H	-0.196	5.793	14.386	0.001	0.044	down
NM_001018078	FPGS	-0.272	5.933	20.552	0.000	0.017	down
NM_001024732	MECR	-0.272	5.652	14.501	0.001	0.043	down
NM_001025237	TSPAN4	-0.342	6.067	20.443	0.000	0.017	down
NM_001029885	CPTP	-0.385	3.604	20.553	0.000	0.017	down
NM_001037806	NCKAP5L	-0.294	5.408	18.624	0.000	0.023	down
NM_001037984	SLC38A10	-0.367	7.004	35.605	0.000	0.004	down
NM_001039847	GPX4	-0.271	9.645	21.987	0.000	0.015	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_001039877	STRN4	-0.261	6.037	16.542	0.001	0.031	down
NM_001040197	AGTRAP	-0.326	4.126	22.943	0.000	0.013	down
NM_001040427	HAGH	-0.227	5.847	18.319	0.000	0.024	down
NM_001040661	SLC29A4	-0.441	6.658	19.732	0.000	0.019	down
NM_001042461	TRAPPC5	-0.644	3.230	62.914	0.000	0.001	down
NM_001077399	PNKD	-0.201	5.492	15.201	0.001	0.039	down
NM_001078171	FAM127A	-0.233	7.013	16.057	0.001	0.034	down
NM_001080453	INTS1	-0.346	5.584	35.237	0.000	0.004	down
NM_001080543	CACTIN	-0.344	3.936	25.705	0.000	0.009	down
NM_001080779	MYO1C	-0.213	10.115	13.898	0.001	0.048	down
NM_001083538	POTEE	-0.625	1.030	14.384	0.001	0.044	down
NM_001083601	NAA60	-0.278	5.095	16.545	0.001	0.031	down
NM_001100112	MYH2	-0.864	0.520	14.590	0.001	0.042	down
NM_001100913	PACS2	-0.243	6.345	18.230	0.000	0.024	down
NM_001102564	IFT43	-0.294	4.041	21.075	0.000	0.016	down
NM_001105079	FBRS	-0.235	5.435	15.866	0.001	0.035	down
NM_001110556	FLNA	-0.331	10.164	18.386	0.000	0.024	down
NM_001111322	DDX54	-0.255	5.131	16.773	0.001	0.031	down
NM_001113324	TEN1	-0.344	3.917	21.787	0.000	0.015	down
NM_001113756	TYMP	-0.354	5.354	17.983	0.000	0.025	down
NM_001120	MFSD10	-0.329	4.275	14.464	0.001	0.043	down
NM_001122957	BCKDK	-0.225	4.862	18.570	0.000	0.023	down
NM_001127229	AURKAIP1	-0.268	5.529	16.455	0.001	0.032	down
NM_001130	AES	-0.326	8.274	35.806	0.000	0.004	down
NM_001130012	SLC9A3R2	-0.399	5.780	31.773	0.000	0.005	down
NM_001130517	MPST	-0.347	5.051	31.589	0.000	0.005	down
NM_001130969	NSMF	-0.343	5.056	18.557	0.000	0.023	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_001135054	SIGIRR	-0.321	3.923	16.125	0.001	0.034	down
NM_001136203	CCDC124	-0.485	4.562	52.114	0.000	0.001	down
NM_001136498	CISD3	-0.292	5.088	23.533	0.000	0.013	down
NM_001142500	FLYWCH2	-0.364	3.758	17.631	0.000	0.026	down
NM_001142864	PIEZO1	-0.230	7.348	14.061	0.001	0.047	down
NM_001145165	DOHH	-0.402	2.557	17.086	0.001	0.029	down
NM_001145809	MYH14	-0.305	5.972	19.910	0.000	0.018	down
NM_001145853	WFS1	-0.250	6.438	24.785	0.000	0.011	down
NM_001146175	ZNF414	-0.670	1.898	26.570	0.000	0.009	down
NM_001166102	NDUFV1	-0.251	6.838	16.721	0.001	0.031	down
NM_001166426	WDR13	-0.258	5.597	21.312	0.000	0.016	down
NM_001169111	SCO2	-0.275	3.944	17.935	0.000	0.025	down
NM_001170535	ATAD3A	-0.441	3.155	20.686	0.000	0.017	down
NM_001173523	PCDH7	-0.372	3.899	14.260	0.001	0.045	down
NM_001173988	RABL6	-0.300	5.926	27.950	0.000	0.008	down
NM_001190716	DNM2	-0.207	6.687	16.117	0.001	0.034	down
NM_001195072	TMEM184B	-0.176	6.569	15.140	0.001	0.039	down
NM_001198869	CAPN1	-0.252	6.324	21.344	0.000	0.016	down
NM_001199173	MLST8	-0.328	4.350	20.748	0.000	0.017	down
NM_001199196	ARMC6	-0.284	4.315	19.521	0.000	0.019	down
NM_001203260	NDUFC2-KCTD14	-0.306	5.864	32.726	0.000	0.005	down
NM_001204240	TBC1D10A	-0.276	4.687	18.097	0.000	0.025	down
NM_001243177	ALDOA	-0.306	9.628	38.647	0.000	0.004	down
NM_001251888	ASPSCR1	-0.326	3.623	18.023	0.000	0.025	down
NM_001252406	ZBTB7B	-0.295	6.808	32.301	0.000	0.005	down
NM_001256269	KIF22	-0.287	4.264	14.980	0.001	0.040	down
NM_001256530	TSPO	-0.576	6.448	91.879	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_001257975	CIZ1	-0.213	6.611	13.837	0.001	0.049	down
NM_001267549	ARFRP1	-0.243	4.981	15.731	0.001	0.035	down
NM_001267552	PEMT	-0.555	6.468	23.473	0.000	0.013	down
NM_001270639	JOSD2	-0.484	2.749	16.007	0.001	0.034	down
NM_001270888	SLC25A10	-0.329	5.307	16.417	0.001	0.032	down
NM_001271098	PUF60	-0.244	6.394	26.440	0.000	0.009	down
NM_001271441	C21orf2	-0.343	3.739	15.897	0.001	0.035	down
NM_001271875	CUEDC1	-0.237	5.659	17.403	0.000	0.027	down
NM_001271944	TFEB	-0.322	3.995	20.387	0.000	0.017	down
NM_001272083	SHISA5	-0.167	6.900	14.373	0.001	0.044	down
NM_001281426	DCTN3	-0.244	5.338	19.117	0.000	0.021	down
NM_001281453	MBD3	-0.513	5.527	49.667	0.000	0.002	down
NM_001281715	PHB	-0.198	6.716	14.150	0.001	0.046	down
NM_001282144	NLRX1	-0.227	5.271	14.316	0.001	0.045	down
NM_001282176	CLPTM1	-0.200	6.307	15.245	0.001	0.038	down
NM_001282311	FAM3A	-0.279	5.066	17.003	0.001	0.029	down
NM_001282670	FAAP20	-0.521	2.941	30.306	0.000	0.006	down
NM_001284497	FAM234A	-0.324	6.730	41.516	0.000	0.003	down
NM_001284501	NUBP2	-0.508	4.275	22.522	0.000	0.014	down
NM_001285829	CEBPA	-0.296	9.058	17.839	0.000	0.026	down
NM_001286435	NME4	-0.313	7.249	27.053	0.000	0.008	down
NM_001287	CLCN7	-0.282	5.700	16.075	0.001	0.034	down
NM_001287427	CCND3	-0.192	5.449	15.596	0.001	0.036	down
NM_001288708	DBNDD1	-0.549	2.471	17.464	0.000	0.027	down
NM_001289419	ANAPC11	-0.266	5.214	18.417	0.000	0.024	down
NM_001290002	ZNF385A	-0.260	6.420	15.042	0.001	0.040	down
NM_001291780	RBM38	-0.404	3.618	25.179	0.000	0.010	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_001297556	MAP2K7	-0.249	4.909	14.620	0.001	0.042	down
NM_001297658	TSSC4	-0.445	4.176	32.429	0.000	0.005	down
NM_001300900	MRPS34	-0.297	5.024	20.910	0.000	0.017	down
NM_001300946	GATAD2A	-0.212	5.721	19.379	0.000	0.020	down
NM_001301020	OAZ1	-0.236	8.733	25.700	0.000	0.009	down
NM_001301061	BCL7B	-0.224	6.300	16.888	0.001	0.030	down
NM_001301129	POLR2F	-0.294	4.458	15.134	0.001	0.039	down
NM_001301243	ARHGDIA	-0.323	7.374	32.460	0.000	0.005	down
NM_001303007	DDAH2	-0.230	7.131	14.762	0.001	0.042	down
NM_001303024	SSSCA1	-0.391	3.202	21.842	0.000	0.015	down
NM_001303501	CNN2	-0.242	6.941	13.770	0.001	0.049	down
NM_001304547	MVB12A	-0.282	4.597	15.196	0.001	0.039	down
NM_001308240	C19orf70	-0.371	5.192	33.430	0.000	0.005	down
NM_001308632	POLD1	-0.482	2.387	19.592	0.000	0.019	down
NM_001312	CRIP2	-0.323	5.345	18.208	0.000	0.024	down
NM_001313726	ANO3	-0.320	4.774	15.450	0.001	0.037	down
NM_001316307	RAC3	-0.475	3.386	22.903	0.000	0.013	down
NM_001316332	MAP2K3	-0.245	5.618	15.778	0.001	0.035	down
NM_001318016	ZDHHC12	-0.524	3.730	36.203	0.000	0.004	down
NM_001318099	LZTS2	-0.319	6.508	20.015	0.000	0.018	down
NM_001318236	LAMTOR4	-0.245	5.972	17.338	0.000	0.027	down
NM_001318252	C7orf50	-0.457	4.688	29.701	0.000	0.006	down
NM_001318711	KIFC3	-0.292	5.006	13.959	0.001	0.048	down
NM_001318867	DOK1	-0.313	6.136	25.848	0.000	0.009	down
NM_001318918	GLIS2	-0.404	3.574	15.688	0.001	0.035	down
NM_001319	CSNK1G2	-0.399	4.907	32.435	0.000	0.005	down
NM_001320484	TRABD	-0.481	3.599	28.742	0.000	0.007	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_001321089	GPS1	-0.263	5.920	21.185	0.000	0.016	down
NM_001321190	RUVBL2	-0.235	4.628	13.683	0.001	0.050	down
NM_001321241	SLC25A39	-0.249	6.083	22.154	0.000	0.015	down
NM_001321263	EPN1	-0.325	5.643	34.499	0.000	0.004	down
NM_001321439	YIPF2	-0.329	4.409	22.252	0.000	0.015	down
NM_001321463	NCLN	-0.319	5.199	25.308	0.000	0.010	down
NM_001322487	HPS1	-0.217	5.949	14.596	0.001	0.042	down
NM_001323552	TRADD	-0.259	4.260	23.330	0.000	0.013	down
NM_001324086	RPUSD1	-0.460	2.992	16.190	0.001	0.034	down
NM_001324229	STOML1	-0.326	4.256	22.903	0.000	0.013	down
NM_001329444	PPP1R16A	-0.352	3.755	21.392	0.000	0.016	down
NM_001329919	UNC13C	-0.967	0.582	15.332	0.001	0.038	down
NM_001330120	SNCG	-0.293	7.677	18.162	0.000	0.025	down
NM_001330282	MZT2B	-0.454	3.674	20.639	0.000	0.017	down
NM_001330311	DVL1	-0.426	5.152	38.154	0.000	0.004	down
NM_001330469	COPE	-0.404	5.766	35.365	0.000	0.004	down
NM_001346082	TP53I13	-0.377	5.375	35.665	0.000	0.004	down
NM_001348	DAPK3	-0.327	4.454	22.926	0.000	0.013	down
NM_001398	ECH1	-0.240	7.797	19.446	0.000	0.020	down
NM_001541	HSPB2	-0.335	5.677	20.775	0.000	0.017	down
NM_001569	IRAK1	-0.304	6.402	19.695	0.000	0.019	down
NM_001606	ABCA2	-0.235	6.328	13.790	0.001	0.049	down
NM_001658	ARF1	-0.192	8.259	13.926	0.001	0.048	down
NM_001687	ATP5D	-0.511	4.507	33.250	0.000	0.005	down
NM_001694	ATP6V0C	-0.225	5.726	17.995	0.000	0.025	down
NM_001728	BSG	-0.357	8.329	28.658	0.000	0.007	down
NM_001810	CENPB	-0.315	6.684	31.235	0.000	0.005	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_001848	COL6A1	-0.249	9.697	14.695	0.001	0.042	down
NM_001849	COL6A2	-0.393	9.377	21.085	0.000	0.016	down
NM_001864	COX7A1	-0.259	6.680	20.910	0.000	0.017	down
NM_001913	CUX1	-0.190	6.095	14.114	0.001	0.046	down
NM_001916	CYC1	-0.244	6.279	26.618	0.000	0.009	down
NM_001919	ECI1	-0.387	4.485	33.739	0.000	0.004	down
NM_001970	EIF5A	-0.225	7.306	19.033	0.000	0.021	down
NM_001985	ETFB	-0.309	7.149	31.031	0.000	0.005	down
NM_002046	GAPDH	-0.227	9.583	18.141	0.000	0.025	down
NM_002067	GNA11	-0.326	6.099	32.068	0.000	0.005	down
NM_002070	GNAI2	-0.212	8.580	17.925	0.000	0.025	down
NM_002081	GPC1	-0.401	6.292	27.545	0.000	0.008	down
NM_002082	GRK6	-0.257	4.240	16.210	0.001	0.033	down
NM_002305	LGALS1	-0.333	10.038	26.144	0.000	0.009	down
NM_002333	LRP3	-0.432	5.590	34.160	0.000	0.004	down
NM_002335	LRP5	-0.352	7.063	28.272	0.000	0.007	down
NM_002337	LRPAP1	-0.267	6.487	22.753	0.000	0.014	down
NM_002360	MAFK	-0.279	4.650	19.711	0.000	0.019	down
NM_002412	MGMT	-0.270	4.952	18.269	0.000	0.024	down
NM_002415	MIF	-0.579	3.894	41.709	0.000	0.003	down
NM_002434	MPG	-0.454	4.293	30.224	0.000	0.006	down
NM_002446	MAP3K10	-0.503	3.180	22.349	0.000	0.014	down
NM_002496	NDUFS8	-0.336	5.265	34.212	0.000	0.004	down
NM_002528	NTHL1	-0.484	2.827	21.779	0.000	0.015	down
NM_002579	PALM	-0.522	7.445	67.085	0.000	0.001	down
NM_002676	PMM1	-0.236	5.485	16.651	0.001	0.031	down
NM_002695	POLR2E	-0.397	7.678	48.338	0.000	0.002	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_002741	PKN1	-0.347	6.398	41.468	0.000	0.003	down
NM_002795	PSMB3	-0.217	6.081	20.808	0.000	0.017	down
NM_002801	PSMB10	-0.297	4.622	21.593	0.000	0.016	down
NM_002813	PSMD9	-0.244	5.617	23.799	0.000	0.012	down
NM_002917	RFNG	-0.268	4.936	19.122	0.000	0.021	down
NM_002972	SBF1	-0.236	6.302	17.520	0.000	0.026	down
NM_003021	SGTA	-0.269	5.399	23.637	0.000	0.013	down
NM_003025	SH3GL1	-0.322	5.816	25.900	0.000	0.009	down
NM_003040	SLC4A2	-0.265	5.980	18.329	0.000	0.024	down
NM_003132	SRM	-0.279	5.200	13.673	0.001	0.050	down
NM_003200	TCF3	-0.283	4.841	20.009	0.000	0.018	down
NM_003214	TEAD3	-0.279	4.853	16.999	0.001	0.029	down
NM_003260	TLE2	-0.400	5.229	34.278	0.000	0.004	down
NM_003302	TRIP6	-0.320	5.822	21.245	0.000	0.016	down
NM_003365	UQCRC1	-0.192	6.873	14.724	0.001	0.042	down
NM_003502	AXIN1	-0.340	4.320	26.984	0.000	0.008	down
NM_003573	LTBP4	-0.334	6.820	18.123	0.000	0.025	down
NM_003655	CBX4	-0.422	3.265	14.168	0.001	0.046	down
NM_003731	SSNA1	-0.351	4.856	26.110	0.000	0.009	down
NM_003801	GPAA1	-0.419	6.046	35.445	0.000	0.004	down
NM_003952	RPS6KB2	-0.242	4.231	14.950	0.001	0.040	down
NM_004003	CRAT	-0.307	6.219	28.674	0.000	0.007	down
NM_004074	COX8A	-0.274	6.338	21.990	0.000	0.015	down
NM_004146	NDUFB7	-0.504	5.781	46.072	0.000	0.002	down
NM_004168	SDHA	-0.176	7.158	14.554	0.001	0.043	down
NM_004204	PIGQ	-0.420	4.286	23.080	0.000	0.013	down
NM_004218	RAB11B	-0.334	5.590	26.501	0.000	0.009	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_004322	BAD	-0.400	4.755	31.357	0.000	0.005	down
NM_004357	CD151	-0.289	9.443	20.963	0.000	0.017	down
NM_004424	E4F1	-0.383	3.527	16.547	0.001	0.031	down
NM_004429	EFNB1	-0.219	6.643	22.456	0.000	0.014	down
NM_004549	NDUFC2	-0.220	6.381	18.704	0.000	0.023	down
NM_004565	PEX14	-0.317	4.548	34.620	0.000	0.004	down
NM_004699	FAM50A	-0.213	6.115	20.309	0.000	0.017	down
NM_004704	RRP9	-0.292	4.109	15.460	0.001	0.037	down
NM_004710	SYNGR2	-0.228	6.531	22.518	0.000	0.014	down
NM_004715	CTDP1	-0.247	3.832	15.129	0.001	0.039	down
NM_004765	BCL7C	-0.368	4.438	15.185	0.001	0.039	down
NM_004793	LONP1	-0.321	5.935	29.479	0.000	0.006	down
NM_004813	PEX16	-0.355	3.833	15.680	0.001	0.035	down
NM_004913	VPS9D1	-0.253	3.888	13.796	0.001	0.049	down
NM_004924	ACTN4	-0.233	8.443	18.560	0.000	0.023	down
NM_005098	MSC	-0.421	5.152	17.627	0.000	0.026	down
NM_005163	AKT1	-0.218	7.629	21.206	0.000	0.016	down
NM_005273	GNB2	-0.289	6.817	24.264	0.000	0.011	down
NM_005319	HIST1H1C	-0.438	5.098	27.241	0.000	0.008	down
NM_005357	LIPE	-0.568	9.740	51.358	0.000	0.001	down
NM_005716	GIPC1	-0.240	6.083	16.612	0.001	0.031	down
NM_005781	TNK2	-0.332	5.213	14.242	0.001	0.045	down
NM_005809	PRDX2	-0.256	7.554	15.568	0.001	0.036	down
NM_005860	FSTL3	-0.341	7.325	16.584	0.001	0.031	down
NM_005861	STUB1	-0.337	6.465	24.960	0.000	0.010	down
NM_005984	SLC25A1	-0.256	7.296	15.681	0.001	0.035	down
NM_006012	CLPP	-0.314	4.321	24.131	0.000	0.011	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_006026	H1FX	-0.550	5.343	42.289	0.000	0.003	down
NM_006056	NMUR1	-0.397	4.472	19.951	0.000	0.018	down
NM_006097	MYL9	-0.351	9.871	29.672	0.000	0.006	down
NM_006233	POLR2I	-0.380	4.086	21.914	0.000	0.015	down
NM_006234	POLR2J	-0.337	4.330	16.250	0.001	0.033	down
NM_006285	TESK1	-0.250	6.611	28.850	0.000	0.007	down
NM_006312	NCOR2	-0.291	6.213	26.637	0.000	0.009	down
NM_006319	CDIPT	-0.187	6.442	13.852	0.001	0.048	down
NM_006339	HMG20B	-0.310	5.305	25.161	0.000	0.010	down
NM_006349	ZNHIT1	-0.307	5.855	31.934	0.000	0.005	down
NM_006354	TADA3	-0.192	6.096	13.857	0.001	0.048	down
NM_006412	AGPAT2	-0.451	8.848	41.743	0.000	0.003	down
NM_006423	RABAC1	-0.327	5.242	24.491	0.000	0.011	down
NM_006427	SIVA1	-0.702	4.411	38.759	0.000	0.004	down
NM_006428	MRPL28	-0.369	5.143	31.769	0.000	0.005	down
NM_006440	TXNRD2	-0.350	3.850	19.384	0.000	0.020	down
NM_006442	DRAP1	-0.406	5.500	52.056	0.000	0.001	down
NM_006453	TBL3	-0.340	3.956	18.268	0.000	0.024	down
NM_006454	MXD4	-0.295	6.773	20.833	0.000	0.017	down
NM_006478	GAS2L1	-0.447	4.510	63.747	0.000	0.001	down
NM_006556	PMVK	-0.252	5.618	23.129	0.000	0.013	down
NM_006612	KIF1C	-0.290	9.134	25.536	0.000	0.010	down
NM_006712	FASTK	-0.281	5.439	23.428	0.000	0.013	down
NM_006744	RBP4	-0.270	10.128	20.172	0.000	0.017	down
NM_006764	IFRD2	-0.228	5.296	15.804	0.001	0.035	down
NM_006779	CDC42EP2	-0.492	5.210	20.695	0.000	0.017	down
NM_006782	ZFPL1	-0.365	4.459	35.982	0.000	0.004	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_006795	EHD1	-0.311	6.495	42.329	0.000	0.003	down
NM_006829	ADIRF	-0.280	10.029	17.703	0.000	0.026	down
NM_006830	UQCR11	-0.264	6.111	20.763	0.000	0.017	down
NM_006844	ILVBL	-0.275	5.754	17.633	0.000	0.026	down
NM_006848	CCDC85B	-0.537	2.414	15.011	0.001	0.040	down
NM_007108	ELOB	-0.425	6.354	36.366	0.000	0.004	down
NM_007121	NR1H2	-0.337	5.593	21.154	0.000	0.016	down
NM_007165	SF3A2	-0.422	4.201	22.987	0.000	0.013	down
NM_007283	MGLL	-0.233	10.308	20.761	0.000	0.017	down
NM_007322	RANBP3	-0.213	5.517	17.341	0.000	0.027	down
NM_012088	PGLS	-0.304	4.768	21.408	0.000	0.016	down
NM_012094	PRDX5	-0.221	7.084	13.962	0.001	0.048	down
NM_012155	EML2	-0.220	4.740	13.704	0.001	0.050	down
NM_012181	FKBP8	-0.423	7.500	36.533	0.000	0.004	down
NM_012265	RHBDD3	-0.426	3.334	14.421	0.001	0.044	down
NM_012396	PHLDA3	-0.381	7.157	19.293	0.000	0.020	down
NM_012398	PIP5K1C	-0.230	5.483	17.773	0.000	0.026	down
NM_012401	PLXNB2	-0.249	6.966	17.494	0.000	0.026	down
NM_012458	TIMM13	-0.246	4.997	18.263	0.000	0.024	down
NM_013265	VPS51	-0.332	5.759	19.633	0.000	0.019	down
NM_013321	SNX8	-0.296	5.453	14.637	0.001	0.042	down
NM_013373	ZDHHC8	-0.353	5.033	21.406	0.000	0.016	down
NM_013379	DPP7	-0.398	5.794	31.356	0.000	0.005	down
NM_013400	REPIN1	-0.257	6.318	30.012	0.000	0.006	down
NM_014045	LRP10	-0.213	7.558	15.770	0.001	0.035	down
NM_014183	DYNLRB1	-0.182	6.253	16.258	0.001	0.033	down
NM_014216	ITPK1	-0.317	8.453	34.997	0.000	0.004	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_014235	UBL4A	-0.188	5.789	14.838	0.001	0.041	down
NM_014578	RHOD	-0.409	2.911	21.337	0.000	0.016	down
NM_014580	SLC2A8	-0.317	4.049	13.901	0.001	0.048	down
NM_014604	TAX1BP3	-0.251	6.850	15.543	0.001	0.036	down
NM_014855	AP5Z1	-0.378	4.595	19.719	0.000	0.019	down
NM_014931	PPP6R1	-0.245	5.470	24.746	0.000	0.011	down
NM_015005	CEP170B	-0.401	5.858	44.405	0.000	0.002	down
NM_015015	KDM4B	-0.224	4.919	17.668	0.000	0.026	down
NM_015104	ATG2A	-0.272	4.396	13.829	0.001	0.049	down
NM_015366	PRR5	-0.334	5.257	22.896	0.000	0.013	down
NM_015399	BRMS1	-0.208	4.731	14.363	0.001	0.044	down
NM_015456	NELFB	-0.275	5.358	18.451	0.000	0.024	down
NM_015492	C15orf39	-0.309	4.820	19.343	0.000	0.020	down
NM_015629	PRPF31	-0.238	5.206	14.713	0.001	0.042	down
NM_015670	SENP3	-0.185	5.589	15.459	0.001	0.037	down
NM_015710	GLTSCR2	-0.334	6.873	14.405	0.001	0.044	down
NM_015950	MRPL2	-0.231	4.758	14.488	0.001	0.043	down
NM_015965	NDUFA13	-0.235	6.514	18.799	0.000	0.022	down
NM_016111	TELO2	-0.331	3.965	15.591	0.001	0.036	down
NM_016172	UBAC1	-0.227	5.298	14.600	0.001	0.042	down
NM_016263	FZR1	-0.246	4.420	13.968	0.001	0.048	down
NM_016381	TREX1	-0.249	3.953	16.572	0.001	0.031	down
NM_016423	ZNF219	-0.459	6.377	55.631	0.000	0.001	down
NM_016466	ANKRD39	-0.474	2.655	24.235	0.000	0.011	down
NM_016496	MARCH2	-0.216	6.724	15.762	0.001	0.035	down
NM_016539	SIRT6	-0.428	2.461	15.096	0.001	0.039	down
NM_016547	SDF4	-0.233	6.685	19.197	0.000	0.020	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_016732	RALY	-0.200	6.521	16.738	0.001	0.031	down
NM_017432	PTOV1	-0.237	5.288	16.639	0.001	0.031	down
NM_017607	PPP1R12C	-0.298	6.461	25.357	0.000	0.010	down
NM_017721	CC2D1A	-0.328	4.563	17.972	0.000	0.025	down
NM_017797	BTBD2	-0.376	5.472	22.553	0.000	0.014	down
NM_017838	NHP2	-0.242	5.039	15.912	0.001	0.035	down
NM_017914	C19orf24	-0.543	3.673	33.296	0.000	0.005	down
NM_018067	MAP7D1	-0.291	7.958	25.444	0.000	0.010	down
NM_018083	ZNF358	-0.386	5.898	20.330	0.000	0.017	down
NM_018174	MAP1S	-0.478	3.176	26.537	0.000	0.009	down
NM_018226	RNPEPL1	-0.363	6.393	45.750	0.000	0.002	down
NM_018389	SLC35C1	-0.298	5.932	15.271	0.001	0.038	down
NM_018670	MESP1	-0.382	3.550	23.449	0.000	0.013	down
NM_018694	ARL6IP4	-0.262	6.704	18.512	0.000	0.023	down
NM_018973	DPM3	-0.392	3.387	16.266	0.001	0.033	down
NM_018998	FBXW5	-0.418	6.063	37.384	0.000	0.004	down
NM_019009	TOLLIP	-0.227	5.861	14.445	0.001	0.044	down
NM_019037	EXOSC4	-0.476	2.583	22.562	0.000	0.014	down
NM_019070	DDX49	-0.296	4.370	26.924	0.000	0.008	down
NM_020132	AGPAT3	-0.220	6.906	16.969	0.001	0.029	down
NM_020376	PNPLA2	-0.322	9.779	39.010	0.000	0.004	down
NM_020441	CORO1B	-0.316	5.451	22.813	0.000	0.014	down
NM_020470	YIF1A	-0.321	5.181	25.119	0.000	0.010	down
NM_020664	DECR2	-0.360	4.264	29.185	0.000	0.007	down
NM_020680	SCYL1	-0.225	6.101	17.982	0.000	0.025	down
NM_021107	MRPS12	-0.367	3.655	20.989	0.000	0.017	down
NM_021128	POLR2L	-0.324	7.088	25.964	0.000	0.009	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_021228	SCAF1	-0.350	5.007	28.722	0.000	0.007	down
NM_021259	TMEM8A	-0.266	4.673	20.755	0.000	0.017	down
NM_021727	FADS3	-0.256	8.284	17.713	0.000	0.026	down
NM_021923	FGFRL1	-0.246	5.919	19.722	0.000	0.019	down
NM_021943	ZFAND3	-0.222	6.712	14.141	0.001	0.046	down
NM_022039	FBXW4	-0.358	6.777	27.827	0.000	0.008	down
NM_022144	TNMD	-0.535	6.763	15.949	0.001	0.035	down
NM_022338	C11orf24	-0.299	5.751	21.434	0.000	0.016	down
NM_022464	SIL1	-0.248	5.664	21.516	0.000	0.016	down
NM_022489	INF2	-0.436	7.337	46.309	0.000	0.002	down
NM_022748	TNS3	-0.204	8.320	15.530	0.001	0.036	down
NM_022773	LMF1	-0.333	3.386	18.130	0.000	0.025	down
NM_023933	FAM173A	-0.464	1.655	15.986	0.001	0.034	down
NM_023935	DDRGK1	-0.201	5.017	15.786	0.001	0.035	down
NM_023937	MRPL34	-0.253	4.640	18.473	0.000	0.023	down
NM_024036	LRFN4	-0.525	3.714	27.883	0.000	0.008	down
NM_024042	METRN	-0.338	3.361	15.773	0.001	0.035	down
NM_024050	DDA1	-0.311	4.858	26.242	0.000	0.009	down
NM_024100	WDR18	-0.387	3.257	24.476	0.000	0.011	down
NM_024108	TRAPPC6A	-0.483	3.648	16.801	0.001	0.030	down
NM_024112	C9orf16	-0.619	4.154	46.219	0.000	0.002	down
NM_024299	PPDPF	-0.369	5.878	20.500	0.000	0.017	down
NM_024309	TNIP2	-0.221	5.312	16.768	0.001	0.031	down
NM_024321	RBM42	-0.268	5.116	15.498	0.001	0.037	down
NM_024326	FBXL15	-0.494	1.895	21.267	0.000	0.016	down
NM_024407	NDUFS7	-0.703	3.841	74.085	0.000	0.000	down
NM_024496	IRF2BPL	-0.286	6.000	15.811	0.001	0.035	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_024531	SLC52A2	-0.345	4.127	27.773	0.000	0.008	down
NM_024591	CHMP6	-0.386	3.987	32.966	0.000	0.005	down
NM_024682	TBC1D17	-0.226	5.455	16.961	0.001	0.029	down
NM_024706	ZNF668	-0.571	2.184	20.050	0.000	0.018	down
NM_024954	UBTD1	-0.389	3.854	14.971	0.001	0.040	down
NM_025072	PTGES2	-0.258	4.548	21.201	0.000	0.016	down
NM_025078	PQLC1	-0.402	5.793	31.440	0.000	0.005	down
NM_025207	FLAD1	-0.165	5.519	14.272	0.001	0.045	down
NM_025219	DNAJC5	-0.212	6.643	19.337	0.000	0.020	down
NM_025241	UBXN6	-0.389	6.606	33.368	0.000	0.005	down
NM_030573	THAP7	-0.431	3.400	24.598	0.000	0.011	down
NM_030587	B4GALT2	-0.340	6.241	31.020	0.000	0.005	down
NM_030662	MAP2K2	-0.227	5.410	21.480	0.000	0.016	down
NM_030665	RAI1	-0.320	4.766	19.435	0.000	0.020	down
NM_030782	CLPTM1L	-0.246	6.741	26.572	0.000	0.009	down
NM_030935	TSC22D4	-0.297	4.542	17.330	0.001	0.027	down
NM_030974	SHARPIN	-0.310	5.241	31.495	0.000	0.005	down
NM_030981	RAB1B	-0.253	7.855	27.194	0.000	0.008	down
NM_031209	QTRT1	-0.286	4.215	14.063	0.001	0.047	down
NM_031213	ABHD17A	-0.459	3.233	20.371	0.000	0.017	down
NM_031297	RNF208	-0.680	1.360	20.401	0.000	0.017	down
NM_031434	TMUB1	-0.370	3.545	26.982	0.000	0.008	down
NM_032017	STK40	-0.182	7.005	15.524	0.001	0.036	down
NM_032038	SPNS1	-0.290	4.425	21.080	0.000	0.016	down
NM_032271	TRAF7	-0.245	5.681	17.571	0.000	0.026	down
NM_032272	MAF1	-0.213	6.696	15.620	0.001	0.036	down
NM_032319	PRADC1	-0.273	5.219	28.773	0.000	0.007	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_032344	NUDT22	-0.400	3.636	19.913	0.000	0.018	down
NM_032356	NAA38	-0.263	4.709	13.740	0.001	0.049	down
NM_032375	AKT1S1	-0.239	5.479	16.073	0.001	0.034	down
NM_032409	PINK1	-0.212	7.472	18.018	0.000	0.025	down
NM_032412	CYSTM1	-0.210	6.814	14.038	0.001	0.047	down
NM_032477	MRPL41	-0.352	4.602	31.106	0.000	0.005	down
NM_032514	MAP1LC3A	-0.317	4.576	20.277	0.000	0.017	down
NM_032515	BOK	-0.334	7.740	36.927	0.000	0.004	down
NM_032552	DAB2IP	-0.298	6.450	24.821	0.000	0.011	down
NM_032683	MPV17L2	-0.411	3.412	27.280	0.000	0.008	down
NM_032800	C1orf198	-0.359	7.669	13.944	0.001	0.048	down
NM_033025	SYDE1	-0.272	5.143	14.907	0.001	0.041	down
NM_033200	LMF2	-0.371	5.873	25.909	0.000	0.009	down
NM_033256	PPP1R14A	-0.539	4.463	27.937	0.000	0.008	down
NM_033257	DGCR6L	-0.348	4.110	14.330	0.001	0.044	down
NM_033271	BTBD6	-0.296	7.628	30.450	0.000	0.006	down
NM_033630	SCAND1	-0.672	2.901	33.436	0.000	0.005	down
NM_052850	GADD45GIP1	-0.321	4.522	20.915	0.000	0.017	down
NM_052876	NACC1	-0.273	5.235	20.693	0.000	0.017	down
NM_053050	MRPL53	-0.248	4.677	14.569	0.001	0.043	down
NM_079834	SCAMP4	-0.262	5.133	21.047	0.000	0.017	down
NM_080732	EGLN2	-0.237	6.515	14.429	0.001	0.044	down
NM_080748	ROMO1	-0.336	4.876	25.713	0.000	0.009	down
NM_133467	CITED4	-0.404	3.385	14.779	0.001	0.042	down
NM_138346	KIAA2013	-0.275	5.525	29.520	0.000	0.006	down
NM_138392	SHKBP1	-0.279	4.542	20.513	0.000	0.017	down
NM_138440	VASN	-0.477	3.609	14.060	0.001	0.047	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_138795	ARL8A	-0.266	5.435	20.824	0.000	0.017	down
NM_139343	BIN1	-0.193	6.191	14.933	0.001	0.040	down
NM_144653	NACC2	-0.184	6.505	16.353	0.001	0.032	down
NM_144716	CCDC12	-0.298	4.764	22.006	0.000	0.015	down
NM_145166	ZBTB47	-0.282	6.457	15.405	0.001	0.037	down
NM_145245	EVI5L	-0.355	4.103	28.621	0.000	0.007	down
NM_145253	UBALD1	-0.518	2.618	28.996	0.000	0.007	down
NM_145806	ZNF511	-0.261	4.276	14.490	0.001	0.043	down
NM_145869	ANXA11	-0.203	8.378	13.968	0.001	0.048	down
NM_146388	MRPL4	-0.310	4.625	25.820	0.000	0.009	down
NM_152243	CDC42EP1	-0.405	5.760	32.095	0.000	0.005	down
NM_152307	TRMT61A	-0.348	4.107	19.214	0.000	0.020	down
NM_152743	BRAT1	-0.377	4.590	35.396	0.000	0.004	down
NM_152914	NATD1	-0.288	6.946	24.280	0.000	0.011	down
NM_153329	ALDH16A1	-0.326	4.132	17.314	0.001	0.027	down
NM_153818	PEX10	-0.282	4.792	20.619	0.000	0.017	down
NM_170711	DAZAP1	-0.179	5.661	14.711	0.001	0.042	down
NM_172367	TUSC5	-0.373	9.570	38.850	0.000	0.004	down
NM_175063	EMC10	-0.231	5.640	14.699	0.001	0.042	down
NM_175573	ADRM1	-0.378	5.797	33.804	0.000	0.004	down
NM_176795	HRAS	-0.306	4.537	23.694	0.000	0.012	down
NM_177533	NUDT14	-0.298	3.683	13.772	0.001	0.049	down
NM_177924	ASAH1	-0.254	9.728	14.059	0.001	0.047	down
NM_177925	H2AFJ	-0.292	6.694	21.936	0.000	0.015	down
NM_178557	NAT8L	-0.246	8.226	20.540	0.000	0.017	down
NM_181843	NUDT8	-0.597	2.711	37.347	0.000	0.004	down
NM_182703	ANKDD1A	-0.372	5.257	21.829	0.000	0.015	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NM_182706	SCRIB	-0.319	4.545	18.903	0.000	0.022	down
NM_182981	OSGIN1	-0.450	4.207	16.195	0.001	0.034	down
NM_183241	C9orf142	-0.429	2.997	14.651	0.001	0.042	down
NM_194460	RNF126	-0.538	3.417	24.426	0.000	0.011	down
NM_198475	FAM171A2	-0.744	1.968	16.376	0.001	0.032	down
NM_198582	KLHL30	-0.386	3.471	21.923	0.000	0.015	down
NM_198868	TBC1D9B	-0.247	8.340	20.349	0.000	0.017	down
NM_199069	NDUFAF3	-0.253	5.476	19.819	0.000	0.019	down
NM_201397	GPX1	-0.453	8.092	44.966	0.000	0.002	down
NM_201532	DGKZ	-0.337	4.659	21.416	0.000	0.016	down
NM_203387	RNH1	-0.391	6.902	33.827	0.000	0.004	down
NM_206967	C16orf74	-0.516	1.597	15.104	0.001	0.039	down
NM_207340	ZDHHC24	-0.592	2.570	20.554	0.000	0.017	down
NM_207368	MCRIP1	-0.467	5.588	37.665	0.000	0.004	down
NR_024194	TOM1	-0.276	6.225	30.611	0.000	0.006	down
NR_024388	NCBP2-AS2	-0.341	3.861	15.880	0.001	0.035	down
NR_026581	MLF2	-0.191	7.153	17.775	0.000	0.026	down
NR_026845	URB1-AS1	-0.505	2.382	17.440	0.000	0.027	down
NR_027063	LINC00116	-0.403	3.401	18.000	0.000	0.025	down
NR_027889	TMEM189	-0.241	5.846	20.534	0.000	0.017	down
NR_028582	G6PC3	-0.216	5.818	14.705	0.001	0.042	down
NR_030717	SNAPC2	-0.402	3.307	24.761	0.000	0.011	down
NR_030770	CCM2	-0.259	5.615	23.403	0.000	0.013	down
NR_033338	FAAP100	-0.297	4.335	15.931	0.001	0.035	down
NR_034166	NDUFA11	-0.324	5.776	17.771	0.000	0.026	down
NR_037576	TMEM222	-0.194	5.355	15.399	0.001	0.037	down
NR_037651	HSPB2-C11orf52	-0.344	3.347	18.849	0.000	0.022	down

Gene ID	Gene names	logFC	logCPM	F	P-Value	FDR	Regulated direction
NR_037709	TEN1-CDK3	-0.256	4.819	16.719	0.001	0.031	down
NR_037715	RNASEK	-0.208	6.568	19.548	0.000	0.019	down
NR_037717	RNASEK-C17orf49	-0.197	6.953	17.362	0.000	0.027	down
NR_037791	RAB4B-EGLN2	-0.235	6.680	15.023	0.001	0.040	down
NR_037928	P2RX5-TAX1BP3	-0.261	6.764	17.371	0.000	0.027	down
NR_038422	PIN1	-0.311	5.226	24.915	0.000	0.010	down
NR_038942	PARTICL	-0.473	1.601	15.163	0.001	0.039	down
NR_045724	CLTB	-0.323	5.695	27.088	0.000	0.008	down
NR_046202	C19orf47	-0.424	3.025	23.389	0.000	0.013	down
NR_046418	CHMP1A	-0.210	6.104	19.517	0.000	0.019	down
NR_073565	DNLZ	-0.388	2.013	15.019	0.001	0.040	down
NR_104432	ZNF213	-0.314	3.567	15.395	0.001	0.037	down
NR_110612	ATP6V0E2	-0.379	5.754	27.147	0.000	0.008	down
NR_126522	EXOC3-AS1	-0.451	2.381	13.762	0.001	0.049	down
NR_130151	RPS19BP1	-0.233	5.635	14.094	0.001	0.047	down
NR_134464	CARD19	-0.282	4.039	16.145	0.001	0.034	down
NR_136651	JMJD8	-0.285	6.077	22.474	0.000	0.014	down
NR_138144	PYCRL	-0.310	2.939	16.477	0.001	0.032	down
NR_138610	MCRIP2	-0.467	2.583	20.811	0.000	0.017	down

Appendix B-3 Differential expressed gene list at 12 am upon time restricted eating.

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_000024	ADRB2	0.329	4.444	10.127	0.005	0.037	up
NM_000052	ATP7A	0.188	4.513	12.181	0.003	0.023	up
NM_000078	CETP	0.904	3.266	14.337	0.001	0.014	up
NM_000110	DPYD	0.256	5.760	12.427	0.002	0.022	up
NM_000124	ERCC6	0.251	3.901	10.457	0.005	0.034	up
NM_000165	GJA1	0.248	6.393	13.551	0.002	0.017	up
NM_000176	NR3C1	0.266	8.009	15.863	0.001	0.010	up
NM_000233	LHCGR	0.447	4.282	15.124	0.001	0.012	up
NM_000251	MSH2	0.177	4.252	10.225	0.005	0.036	up
NM_000255	MUT	0.172	5.986	10.065	0.005	0.037	up
NM_000267	NF1	0.135	6.258	10.216	0.005	0.036	up
NM_000276	OCRL	0.156	6.165	13.163	0.002	0.018	up
NM_000368	TSC1	0.227	6.218	18.682	0.000	0.006	up
NM_000391	TPP1	0.232	7.359	17.936	0.001	0.007	up
NM_000401	EXT2	0.215	6.473	27.225	0.000	0.001	up
NM_000408	GPD2	0.248	5.305	17.531	0.001	0.008	up
NM_000410	HFE	0.211	4.020	10.745	0.004	0.032	up
NM_000484	APP	0.216	8.918	12.167	0.003	0.023	up
NM_000534	PMS1	0.229	4.416	19.250	0.000	0.005	up
NM_000601	HGF	0.362	3.392	13.766	0.002	0.016	up
NM_000623	BDKRB2	0.477	3.597	16.321	0.001	0.009	up
NM_000706	AVPR1A	0.338	5.513	14.626	0.001	0.013	up
NM_000819	GART	0.215	6.066	17.819	0.001	0.007	up
NM_000821	GGCX	0.200	6.129	12.304	0.003	0.022	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_000824	GLRB	0.347	3.544	9.727	0.006	0.040	up
NM_000848	GSTM2	0.273	5.545	25.443	0.000	0.002	up
NM_000849	GSTM3	0.194	6.033	17.837	0.001	0.007	up
NM_000851	GSTM5	0.386	4.595	23.583	0.000	0.002	up
NM_000856	GUCY1A3	0.388	5.311	10.452	0.005	0.034	up
NM_000876	IGF2R	0.155	8.217	11.995	0.003	0.024	up
NM_000895	LTA4H	0.160	5.962	10.806	0.004	0.031	up
NM_000919	PAM	0.290	7.997	15.822	0.001	0.010	up
NM_000969	RPL5	0.137	9.179	9.454	0.007	0.043	up
NM_000971	RPL7	0.317	5.063	29.604	0.000	0.001	up
NM_000983	RPL22	0.203	7.219	21.256	0.000	0.004	up
NM_000984	RPL23A	0.169	7.067	15.868	0.001	0.010	up
NM_000987	RPL26	0.236	8.362	23.388	0.000	0.003	up
NM_000998	RPL37A	0.151	9.291	10.179	0.005	0.036	up
NM_001001	RPL36AL	0.152	6.976	13.724	0.002	0.016	up
NM_001001396	ATP2B4	0.192	9.950	11.859	0.003	0.025	up
NM_001001668	ZNF470	0.211	3.512	11.242	0.004	0.028	up
NM_001001788	RAET1G	1.568	-1.605	12.182	0.003	0.023	up
NM_001002860	BTBD7	0.143	5.686	11.661	0.003	0.026	up
NM_001003679	LEPR	0.208	6.119	11.302	0.004	0.028	up
NM_001004023	DYRK3	0.350	3.044	11.543	0.003	0.026	up
NM_001004304	ZNF740	0.146	5.930	9.886	0.006	0.039	up
NM_001004343	MAP1LC3C	0.725	1.289	9.635	0.006	0.041	up
NM_001005404	YPEL2	0.273	6.345	16.831	0.001	0.009	up
NM_001005851	ZNF780B	0.344	4.330	23.968	0.000	0.002	up
NM_001006610	SIAH1	0.282	5.108	23.520	0.000	0.002	up
NM_001007027	ALG8	0.192	5.190	20.766	0.000	0.004	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001007189	IGIP	0.223	5.062	14.054	0.002	0.015	up
NM_001007544	C1orf186	0.520	0.904	9.169	0.007	0.046	up
NM_001008	RPS4Y1	0.132	7.373	9.804	0.006	0.040	up
NM_001008390	CGGBP1	0.181	6.816	16.370	0.001	0.009	up
NM_001008938	CKAP5	0.144	6.655	9.742	0.006	0.040	up
NM_001009608	SLX4IP	0.288	3.163	12.268	0.003	0.023	up
NM_001009881	ZCCHC11	0.205	5.067	16.862	0.001	0.009	up
NM_001009924	TMEM230	0.196	7.518	11.851	0.003	0.025	up
NM_001010	RPS6	0.155	9.994	9.682	0.006	0.041	up
NM_001010853	PM20D2	0.304	3.182	10.502	0.005	0.034	up
NM_001010887	ACER2	0.410	3.517	22.363	0.000	0.003	up
NM_001010989	HERPUD1	0.125	6.506	9.136	0.007	0.047	up
NM_001012279	SOGA3	0.356	6.410	16.999	0.001	0.008	up
NM_001012506	CCDC66	0.202	4.024	13.684	0.002	0.016	up
NM_001012756	ZNF260	0.177	4.150	10.428	0.005	0.034	up
NM_001013649	C2orf68	0.202	5.331	17.624	0.001	0.007	up
NM_001014972	ZNF638	0.147	6.857	12.748	0.002	0.020	up
NM_001017368	RFFL	0.198	5.125	18.950	0.000	0.006	up
NM_001017923	C14orf28	0.237	3.241	11.224	0.004	0.028	up
NM_001019	RPS15A	0.176	8.245	14.287	0.001	0.014	up
NM_001023560	ZSCAN26	0.344	4.425	36.483	0.000	0.000	up
NM_001024924	EXOC1	0.132	6.048	11.542	0.003	0.026	up
NM_001025	RPS23	0.173	8.458	17.224	0.001	0.008	up
NM_001028	RPS25	0.176	8.181	14.745	0.001	0.013	up
NM_001029997	ZNF181	0.178	3.639	8.897	0.008	0.050	up
NM_001030	RPS27	0.955	-0.621	13.689	0.002	0.016	up
NM_001030006	AP2B1	0.174	7.774	22.745	0.000	0.003	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001030007	AP1G1	0.175	6.889	19.660	0.000	0.005	up
NM_001031812	CSNK1G3	0.216	4.751	8.867	0.008	0.050	up
NM_001031835	PHKB	0.226	6.782	20.396	0.000	0.004	up
NM_001032363	MINOS1	0.189	5.773	14.214	0.001	0.015	up
NM_001033045	GPR155	0.157	4.780	8.930	0.008	0.049	up
NM_001033050	MTERF2	0.205	4.430	14.626	0.001	0.013	up
NM_001033719	ZNF404	0.592	1.532	17.637	0.001	0.007	up
NM_001033858	DCLRE1C	0.193	3.689	8.889	0.008	0.050	up
NM_001034850	FAM134B	0.304	5.190	13.968	0.002	0.015	up
NM_001037442	RUFY3	0.179	5.560	14.057	0.002	0.015	up
NM_001039886	ZNF808	0.308	2.745	9.183	0.007	0.046	up
NM_001040199	CLDND1	0.150	5.819	10.313	0.005	0.035	up
NM_001040402	DCUN1D4	0.169	5.989	13.738	0.002	0.016	up
NM_001040653	ZXDC	0.151	4.793	10.541	0.005	0.033	up
NM_001042493	SMIM8	0.284	2.644	12.103	0.003	0.023	up
NM_001042496	SLC12A6	0.272	5.365	11.657	0.003	0.026	up
NM_001042548	FEZ2	0.180	6.982	14.404	0.001	0.014	up
NM_001042549	NSL1	0.156	4.793	11.111	0.004	0.029	up
NM_001042601	TTC14	0.266	6.330	12.542	0.002	0.021	up
NM_001042603	KDM5A	0.188	6.191	20.261	0.000	0.004	up
NM_001042683	SHPRH	0.182	4.970	16.908	0.001	0.008	up
NM_001042734	SEC24B	0.180	5.800	17.455	0.001	0.008	up
NM_001058	TACR1	0.575	4.300	21.434	0.000	0.004	up
NM_001068	TOP2B	0.127	7.041	12.436	0.002	0.022	up
NM_001076678	ZNF493	0.395	3.164	22.833	0.000	0.003	up
NM_001077181	CDC14B	0.163	6.068	10.918	0.004	0.030	up
NM_001077195	ZNF436	0.228	6.092	11.320	0.004	0.028	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001077394	DPH5	0.200	4.184	14.306	0.001	0.014	up
NM_001077691	ALG9	0.170	5.846	10.126	0.005	0.037	up
NM_001079673	FNDC3A	0.210	6.244	15.045	0.001	0.012	up
NM_001079802	FKTN	0.170	5.042	10.376	0.005	0.035	up
NM_001079872	CUL4B	0.172	6.248	23.280	0.000	0.003	up
NM_001080392	KIAA1147	0.174	5.862	9.958	0.006	0.038	up
NM_001080412	ZBTB38	0.237	6.712	9.405	0.007	0.044	up
NM_001080432	FTO	0.226	6.474	18.814	0.000	0.006	up
NM_001080479	ARHGEF28	0.185	4.950	10.250	0.005	0.036	up
NM_001080480	MBOAT1	0.250	4.165	10.943	0.004	0.030	up
NM_001081	CUBN	0.430	3.392	10.415	0.005	0.034	up
NM_001081573	GAB3	0.204	4.439	12.321	0.003	0.022	up
NM_001082538	TCTN1	0.202	4.013	10.057	0.005	0.037	up
NM_001083335	ZNF112	0.411	2.879	19.157	0.000	0.005	up
NM_001083893	STRN3	0.167	5.314	11.669	0.003	0.026	up
NM_001083953	THADA	0.174	5.201	14.725	0.001	0.013	up
NM_001083956	ZNF655	0.155	6.066	12.974	0.002	0.019	up
NM_001085458	CTNND1	0.159	8.397	8.886	0.008	0.050	up
NM_001098398	COPA	0.127	8.224	8.959	0.008	0.049	up
NM_001098475	TDRD10	0.292	2.835	8.884	0.008	0.050	up
NM_001098504	DDX17	0.228	9.478	12.794	0.002	0.020	up
NM_001098638	RNF169	0.236	4.573	15.438	0.001	0.011	up
NM_001099269	ZNF506	0.299	4.076	16.464	0.001	0.009	up
NM_001099693	RPL31	0.148	8.836	9.951	0.006	0.038	up
NM_001099922	ALG13	0.276	4.980	12.508	0.002	0.021	up
NM_001102420	ZFAND5	0.287	7.423	24.343	0.000	0.002	up
NM_001102608	COL6A6	1.078	2.746	46.334	0.000	0.000	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001102653	OTUD4	0.143	5.682	9.011	0.008	0.048	up
NM_001104587	SLFN11	0.272	5.657	12.397	0.003	0.022	up
NM_001105207	LAMA4	0.210	9.948	15.657	0.001	0.011	up
NM_001105549	ZNF83	0.269	6.189	24.402	0.000	0.002	up
NM_001106	ACVR2B	0.308	3.800	12.975	0.002	0.019	up
NM_001111283	IGF1	0.559	7.734	11.658	0.003	0.026	up
NM_001112734	ZSCAN30	0.190	4.654	9.037	0.008	0.048	up
NM_001122752	SERPINI1	0.496	2.824	22.103	0.000	0.003	up
NM_001122838	NAPEPLD	0.363	3.719	14.901	0.001	0.013	up
NM_001122964	PPP4R3B	0.126	6.830	8.945	0.008	0.049	up
NM_001123226	MTO1	0.210	4.234	12.420	0.002	0.022	up
NM_001123329	ZBTB1	0.158	5.812	11.428	0.003	0.027	up
NM_001127228	CBX1	0.144	5.625	9.827	0.006	0.039	up
NM_001127372	ZNF84	0.232	5.322	17.924	0.001	0.007	up
NM_001127401	YPEL5	0.177	6.881	15.149	0.001	0.012	up
NM_001127582	ING4	0.193	5.143	16.947	0.001	0.008	up
NM_001128126	AP4S1	0.232	3.207	9.739	0.006	0.040	up
NM_001128159	VPS53	0.166	5.565	13.530	0.002	0.017	up
NM_001128217	PSIP1	0.196	5.495	12.601	0.002	0.021	up
NM_001128304	PLSCR4	0.228	6.760	14.813	0.001	0.013	up
NM_001128310	SPARCL1	0.275	9.846	17.177	0.001	0.008	up
NM_001128430	SMARCAD1	0.158	5.037	10.675	0.004	0.032	up
NM_001128610	USP8	0.150	6.053	13.663	0.002	0.016	up
NM_001128615	ARHGEF3	0.371	4.816	13.773	0.002	0.016	up
NM_001129899	KRBOX4	0.268	3.855	24.255	0.000	0.002	up
NM_001129993	KIAA1841	0.270	4.112	14.767	0.001	0.013	up
NM_001130031	ZNF562	0.279	4.034	12.746	0.002	0.020	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001130142	VWA5A	0.183	5.402	11.070	0.004	0.029	up
NM_001130147	CCDC77	0.242	2.884	13.599	0.002	0.017	up
NM_001130158	MYO1B	0.204	6.244	13.337	0.002	0.018	up
NM_001130688	HMGB2	0.405	5.421	27.736	0.000	0.001	up
NM_001134296	AP3M2	0.196	4.822	23.501	0.000	0.003	up
NM_001134381	TBC1D5	0.161	6.697	14.105	0.001	0.015	up
NM_001134438	PHLDB2	0.249	7.438	13.809	0.002	0.016	up
NM_001134673	NFIA	0.200	6.865	11.149	0.004	0.029	up
NM_001134831	AHI1	0.163	4.688	9.917	0.006	0.039	up
NM_001135178	ZNF397	0.345	4.829	35.935	0.000	0.000	up
NM_001135197	CCDC36	0.340	3.385	12.050	0.003	0.024	up
NM_001135643	DCTN4	0.138	6.544	11.632	0.003	0.026	up
NM_001135733	TP53INP1	0.259	5.817	11.775	0.003	0.025	up
NM_001136040	CPSF7	0.142	6.548	13.505	0.002	0.017	up
NM_001136127	DNM3	0.370	2.992	13.222	0.002	0.018	up
NM_001136156	ZNF507	0.178	4.963	10.359	0.005	0.035	up
NM_001136262	ATXN7L3B	0.117	6.652	10.127	0.005	0.037	up
NM_001136499	ZNF841	0.303	4.465	11.189	0.004	0.028	up
NM_001136501	ZNF844	0.558	3.278	39.393	0.000	0.000	up
NM_001141980	TP53BP1	0.236	5.680	22.065	0.000	0.003	up
NM_001142416	AIMP1	0.210	5.619	24.470	0.000	0.002	up
NM_001142443	EDC3	0.163	4.956	12.229	0.003	0.023	up
NM_001142579	ZNF780A	0.253	3.293	12.501	0.002	0.021	up
NM_001142651	NEURL1B	0.268	6.055	11.497	0.003	0.027	up
NM_001142683	CCDC121	0.250	2.999	11.710	0.003	0.026	up
NM_001143770	ZNF438	0.158	4.751	10.277	0.005	0.035	up
NM_001143887	COPS2	0.192	6.349	15.748	0.001	0.011	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001145009	BTN3A1	0.348	5.858	31.730	0.000	0.001	up
NM_001145415	SETDB1	0.185	5.487	15.259	0.001	0.012	up
NM_001145425	NR1D2	0.178	6.547	15.447	0.001	0.011	up
NM_001146	ANGPT1	0.319	6.803	15.112	0.001	0.012	up
NM_001146071	TDRD3	0.173	4.475	9.419	0.007	0.043	up
NM_001146214	TBC1D15	0.141	5.862	10.162	0.005	0.036	up
NM_001159293	ZNF737	0.393	3.210	21.794	0.000	0.003	up
NM_001160223	RNF170	0.149	4.944	10.325	0.005	0.035	up
NM_001162501	TNRC6B	0.175	5.387	10.358	0.005	0.035	up
NM_001164213	LRCH1	0.189	5.082	10.393	0.005	0.034	up
NM_001164273	MGA	0.154	5.688	14.199	0.001	0.015	up
NM_001164343	ZBTB20	0.250	7.127	10.101	0.005	0.037	up
NM_001164380	STAU2	0.203	5.295	14.044	0.002	0.015	up
NM_001166279	PAN2	0.252	6.164	18.633	0.000	0.006	up
NM_001166693	AFF1	0.254	7.400	14.150	0.001	0.015	up
NM_001167608	RHBDD1	0.188	5.040	11.993	0.003	0.024	up
NM_001167671	LPP	0.199	7.708	11.504	0.003	0.027	up
NM_001170781	FAM122C	0.521	1.022	12.109	0.003	0.023	up
NM_001171606	PREPL	0.271	6.448	14.695	0.001	0.013	up
NM_001171796	TRIQK	0.261	4.381	19.342	0.000	0.005	up
NM_001172435	RAB3GAP1	0.149	6.556	16.422	0.001	0.009	up
NM_001172671	ZNF430	0.272	2.755	10.239	0.005	0.036	up
NM_001173984	BRD7	0.176	5.514	21.505	0.000	0.004	up
NM_001174061	SMG7	0.208	6.240	13.376	0.002	0.018	up
NM_001174108	ZBED6	0.250	5.054	9.620	0.006	0.041	up
NM_001178099	ZNF182	0.292	3.633	17.673	0.001	0.007	up
NM_001184742	ZBTB33	0.178	4.834	11.504	0.003	0.027	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001184819	GNL3L	0.341	4.767	33.169	0.000	0.001	up
NM_001184998	KIAA0430	0.163	6.997	15.913	0.001	0.010	up
NM_001185094	NIT1	0.162	5.138	9.916	0.006	0.039	up
NM_001190241	IFT80	0.236	4.528	21.114	0.000	0.004	up
NM_001190737	NFIB	0.217	7.547	18.379	0.000	0.006	up
NM_001190828	FCGR2B	0.373	4.507	9.820	0.006	0.039	up
NM_001190839	MGP	0.336	8.670	18.554	0.000	0.006	up
NM_001190850	CNOT4	0.202	4.416	9.849	0.006	0.039	up
NM_001193314	VIPAS39	0.160	4.972	11.325	0.004	0.028	up
NM_001193465	KANSL1	0.145	5.644	11.080	0.004	0.029	up
NM_001193538	TMEM126B	0.167	5.307	18.567	0.000	0.006	up
NM_001194955	MATR3	0.142	7.896	13.567	0.002	0.017	up
NM_001194998	CEP152	0.455	3.072	15.683	0.001	0.011	up
NM_001195156	TMEM35B	0.213	4.748	17.852	0.001	0.007	up
NM_001195434	MLF1	0.321	2.243	9.828	0.006	0.039	up
NM_001195470	SATB1	0.149	5.276	10.495	0.005	0.034	up
NM_001197247	BTN3A2	0.252	5.616	10.007	0.005	0.038	up
NM_001197294	DPYSL3	0.198	7.350	9.097	0.008	0.047	up
NM_001198595	STON1	0.356	5.456	12.473	0.002	0.022	up
NM_001198625	RUNX1T1	0.228	5.249	16.838	0.001	0.009	up
NM_001198759	LY75-CD302	0.235	7.175	16.221	0.001	0.010	up
NM_001198777	CUL2	0.129	5.589	9.212	0.007	0.046	up
NM_001198801	EIF4G3	0.184	6.943	11.747	0.003	0.025	up
NM_001199181	ATP2C1	0.263	6.674	20.408	0.000	0.004	up
NM_001199397	NEK1	0.158	4.450	9.404	0.007	0.044	up
NM_001199462	PDCD2	0.156	5.074	11.792	0.003	0.025	up
NM_001199649	PTK2	0.170	6.676	9.255	0.007	0.045	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001199973	RPL36A-HNRNPH2	0.127	6.771	9.618	0.006	0.041	up
NM_001201362	HMGN3	0.210	6.009	16.712	0.001	0.009	up
NM_001201536	TAF1A	0.473	1.840	11.595	0.003	0.026	up
NM_001202409	ZNF559	0.187	4.272	13.334	0.002	0.018	up
NM_001202554	PIGV	0.265	4.295	15.764	0.001	0.011	up
NM_001204077	UBE4A	0.212	6.624	30.279	0.000	0.001	up
NM_001204366	MGST2	0.184	4.991	13.214	0.002	0.018	up
NM_001204477	CDRT4	0.323	3.956	14.704	0.001	0.013	up
NM_001204478	TVP23C-CDRT4	0.319	4.009	15.845	0.001	0.010	up
NM_001204747	RFC1	0.154	6.276	14.486	0.001	0.014	up
NM_001204803	ANO6	0.242	8.481	14.252	0.001	0.014	up
NM_001204817	ZNF587	0.237	4.803	11.293	0.004	0.028	up
NM_001205315	STEAP4	0.460	7.169	26.657	0.000	0.001	up
NM_001206938	TCAF1	0.200	4.935	11.795	0.003	0.025	up
NM_001225	CASP4	0.220	5.462	14.952	0.001	0.013	up
NM_001240	CCNT1	0.164	5.294	9.068	0.008	0.048	up
NM_001242318	PDE7A	0.239	3.715	10.096	0.005	0.037	up
NM_001242401	GHR	0.182	8.616	9.651	0.006	0.041	up
NM_001242546	ANAPC16	0.168	7.278	10.948	0.004	0.030	up
NM_001242844	RNF146	0.144	6.031	10.547	0.005	0.033	up
NM_001242875	ELP2	0.131	6.224	10.422	0.005	0.034	up
NM_001243571	MTMR2	0.199	5.571	19.049	0.000	0.006	up
NM_001243597	CDON	0.213	6.062	11.993	0.003	0.024	up
NM_001244262	HBP1	0.307	6.886	25.524	0.000	0.002	up
NM_001244638	ARID5B	0.595	6.732	26.149	0.000	0.002	up
NM_001244972	NRP1	0.210	8.807	20.072	0.000	0.005	up
NM_001251882	VIPR1	0.246	4.460	16.965	0.001	0.008	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001253	CDC5L	0.135	5.384	8.949	0.008	0.049	up
NM_001256165	TMCO1	0.121	6.233	11.203	0.004	0.028	up
NM_001257118	CASP1	0.232	4.681	9.174	0.007	0.046	up
NM_001257293	HNRNPH1	0.216	8.124	10.167	0.005	0.036	up
NM_001258249	UTY	0.216	4.411	14.467	0.001	0.014	up
NM_001258313	PDE1A	0.382	3.565	20.570	0.000	0.004	up
NM_001261459	ZNF484	0.330	2.399	10.156	0.005	0.037	up
NM_001267550	TTN	0.836	3.164	21.703	0.000	0.003	up
NM_001267578	TOR1AIP1	0.156	6.686	10.805	0.004	0.031	up
NM_001268	RCBTB2	0.206	5.697	14.328	0.001	0.014	up
NM_001270928	IFIT1	0.216	5.530	13.776	0.002	0.016	up
NM_001271314	ZNF266	0.169	5.612	9.003	0.008	0.048	up
NM_001271318	ZNF512	0.273	5.283	20.135	0.000	0.005	up
NM_001271427	EMC1	0.171	5.954	16.989	0.001	0.008	up
NM_001271685	SLC35A3	0.211	5.045	10.396	0.005	0.034	up
NM_001271920	SEC11A	0.161	7.047	13.168	0.002	0.018	up
NM_001271999	DOCK7	0.188	6.036	10.829	0.004	0.031	up
NM_001276318	PPP1R3E	0.208	4.892	14.266	0.001	0.014	up
NM_001276506	SDHD	0.181	6.616	12.234	0.003	0.023	up
NM_001278119	ZKSCAN8	0.221	5.975	10.597	0.004	0.033	up
NM_001278344	ACTN2	1.044	-0.976	10.299	0.005	0.035	up
NM_001278412	AMN1	0.224	2.708	10.191	0.005	0.036	up
NM_001278470	MON2	0.168	6.427	15.205	0.001	0.012	up
NM_001278480	SUPT20H	0.184	4.990	18.373	0.000	0.006	up
NM_001278503	STT3A	0.165	6.596	12.058	0.003	0.024	up
NM_001278594	ALDH6A1	0.287	6.339	9.463	0.007	0.043	up
NM_001278628	CRNKL1	0.184	4.731	12.822	0.002	0.020	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001281463	SMC1A	0.190	6.321	10.543	0.005	0.033	up
NM_001282188	CYSLTR1	0.363	2.949	9.285	0.007	0.045	up
NM_001282524	NPIPB6	1.995	-2.087	10.784	0.004	0.031	up
NM_001282656	ZNF143	0.226	4.043	11.085	0.004	0.029	up
NM_001282730	SUPT7L	0.240	6.000	21.749	0.000	0.003	up
NM_001282757	TRA2A	0.257	5.968	23.856	0.000	0.002	up
NM_001282860	GON4L	0.175	5.773	13.405	0.002	0.017	up
NM_001282913	TCAIM	0.160	4.464	10.329	0.005	0.035	up
NM_001282917	RALGAPB	0.183	6.438	22.147	0.000	0.003	up
NM_001282959	CCAR1	0.178	6.253	11.966	0.003	0.024	up
NM_001286174	C2CD5	0.260	5.465	21.769	0.000	0.003	up
NM_001286259	ADAT2	0.324	4.185	33.155	0.000	0.001	up
NM_001286514	ATF7IP	0.191	6.733	21.983	0.000	0.003	up
NM_001286569	ZRANB3	0.315	2.399	14.762	0.001	0.013	up
NM_001286577	C2CD3	0.182	4.610	10.271	0.005	0.035	up
NM_001286631	RBM26	0.192	5.479	16.534	0.001	0.009	up
NM_001286657	TMEM68	0.205	3.379	9.625	0.006	0.041	up
NM_001286748	MRPS27	0.155	6.007	12.182	0.003	0.023	up
NM_001287349	ZNF852	0.421	1.850	11.916	0.003	0.024	up
NM_001287393	COMMD6	0.143	5.840	11.166	0.004	0.029	up
NM_001288659	METTL9	0.117	6.358	9.265	0.007	0.045	up
NM_001288980	C18orf54	0.434	1.835	9.300	0.007	0.045	up
NM_001289	CLIC2	0.273	4.839	15.884	0.001	0.010	up
NM_001290184	NCSTN	0.179	7.264	14.372	0.001	0.014	up
NM_001290259	PHF3	0.148	6.530	9.724	0.006	0.040	up
NM_001290261	ZNF337	0.255	5.196	30.902	0.000	0.001	up
NM_001290768	TBCK	0.291	5.102	9.891	0.006	0.039	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001291490	ZNF285	0.555	1.560	15.005	0.001	0.012	up
NM_001291981	PTPRK	0.302	5.161	25.950	0.000	0.002	up
NM_001291999	NCK1	0.163	5.855	16.130	0.001	0.010	up
NM_001297765	CETN3	0.237	3.600	15.640	0.001	0.011	up
NM_001300821	EIF4B	0.203	8.341	18.518	0.000	0.006	up
NM_001300850	RC3H1	0.158	5.179	11.309	0.004	0.028	up
NM_001301022	NUDT4	0.282	5.597	15.729	0.001	0.011	up
NM_001301039	C1orf54	0.328	3.052	11.084	0.004	0.029	up
NM_001302769	PARD3B	0.182	6.618	13.310	0.002	0.018	up
NM_001303251	ZBED8	0.439	3.268	23.417	0.000	0.003	up
NM_001303433	FUBP1	0.223	5.933	18.163	0.000	0.007	up
NM_001304947	KRBA2	0.379	3.002	24.061	0.000	0.002	up
NM_001305040	ZNF33B	0.289	4.435	11.422	0.003	0.027	up
NM_001308116	PHC3	0.177	6.240	9.028	0.008	0.048	up
NM_001308120	FAM179B	0.206	4.569	13.735	0.002	0.016	up
NM_001308142	MKL2	0.247	6.987	11.401	0.003	0.027	up
NM_001308317	CCDC14	0.220	5.531	10.749	0.004	0.032	up
NM_001314042	KDM5B	0.256	5.317	29.011	0.000	0.001	up
NM_001315507	PCM1	0.115	7.068	9.530	0.006	0.042	up
NM_001316	CSE1L	0.154	5.881	9.140	0.007	0.047	up
NM_001316311	RPL35A	0.185	8.357	14.618	0.001	0.013	up
NM_001316345	RECK	0.257	4.983	11.565	0.003	0.026	up
NM_001317156	PLAGL1	0.210	5.903	13.719	0.002	0.016	up
NM_001317784	SCYL2	0.132	5.671	8.980	0.008	0.049	up
NM_001318005	ZNF514	0.246	5.258	16.439	0.001	0.009	up
NM_001318120	SEC31A	0.142	8.111	11.599	0.003	0.026	up
NM_001318135	ZNF3	0.185	4.930	13.686	0.002	0.016	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001318153	JMJD1C	0.189	6.481	15.561	0.001	0.011	up
NM_001318240	NCOA6	0.160	6.024	13.505	0.002	0.017	up
NM_001318381	INVS	0.255	4.736	15.713	0.001	0.011	up
NM_001318728	ZNF532	0.178	6.377	12.942	0.002	0.019	up
NM_001318736	CCDC82	0.151	5.637	11.363	0.003	0.028	up
NM_001318758	NFX1	0.137	5.718	10.215	0.005	0.036	up
NM_001318844	SNW1	0.116	6.055	8.886	0.008	0.050	up
NM_001318926	RPE	0.185	5.408	9.169	0.007	0.046	up
NM_001319073	SACM1L	0.134	6.130	9.421	0.007	0.043	up
NM_001319236	RPL34	0.192	8.198	13.208	0.002	0.018	up
NM_001319238	ZC3H11A	0.148	7.448	12.145	0.003	0.023	up
NM_001319998	FAM63A	0.213	4.693	10.496	0.005	0.034	up
NM_001320032	ABCC5	0.307	5.031	9.846	0.006	0.039	up
NM_001320137	RPL6	0.152	7.470	15.576	0.001	0.011	up
NM_001320219	U2SURP	0.181	6.782	9.532	0.006	0.042	up
NM_001320593	ADD3	0.276	7.081	27.773	0.000	0.001	up
NM_001320660	PCID2	0.146	4.916	10.994	0.004	0.030	up
NM_001320724	RWDD2B	0.186	4.859	9.807	0.006	0.040	up
NM_001320727	SETDB2-PHF11	0.184	5.402	16.939	0.001	0.008	up
NM_001320767	ZNF544	0.229	4.082	10.106	0.005	0.037	up
NM_001320836	N4BP2L2	0.207	6.006	26.090	0.000	0.002	up
NM_001320882	DYNC1I2	0.135	6.379	9.912	0.006	0.039	up
NM_001320953	ZNF232	0.223	3.088	9.096	0.008	0.047	up
NM_001321194	TBL1XR1	0.152	7.061	9.860	0.006	0.039	up
NM_001321356	ZNF667	0.335	2.350	11.099	0.004	0.029	up
NM_001321376	ZNF671	0.351	3.112	8.869	0.008	0.050	up
NM_001321501	SEPT10	0.154	6.724	12.526	0.002	0.021	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001321532	USPL1	0.165	5.040	10.805	0.004	0.031	up
NM_001321685	ZNF225	0.242	2.916	9.403	0.007	0.044	up
NM_001321731	EXOC6B	0.238	6.124	28.851	0.000	0.001	up
NM_001321855	JAK1	0.144	8.683	13.758	0.002	0.016	up
NM_001321903	HACD4	0.327	3.372	14.913	0.001	0.013	up
NM_001322139	ZNF160	0.164	5.602	10.427	0.005	0.034	up
NM_001322352	LMAN2L	0.281	4.871	18.478	0.000	0.006	up
NM_001322427	CARF	0.233	4.166	9.181	0.007	0.046	up
NM_001322434	HNRNPH3	0.278	6.808	12.053	0.003	0.024	up
NM_001322940	DSE	0.248	6.045	11.572	0.003	0.026	up
NM_001323017	PFKFB3	0.799	9.265	16.954	0.001	0.008	up
NM_001323029	IQCG	0.332	4.152	19.142	0.000	0.006	up
NM_001323423	RBM39	0.174	7.536	16.713	0.001	0.009	up
NM_001323890	AASDH	0.196	3.913	10.247	0.005	0.036	up
NM_001323903	LEO1	0.275	4.053	11.406	0.003	0.027	up
NM_001323906	GABPB2	0.275	4.354	15.504	0.001	0.011	up
NM_001324027	ZNF717	0.228	2.575	9.200	0.007	0.046	up
NM_001324062	MIA3	0.128	6.752	10.123	0.005	0.037	up
NM_001324087	VDAC2	0.183	4.923	15.859	0.001	0.010	up
NM_001324094	GLCE	0.267	5.801	21.093	0.000	0.004	up
NM_001324101	EBF1	0.258	7.282	10.223	0.005	0.036	up
NM_001324151	ZNF41	0.169	4.129	8.946	0.008	0.049	up
NM_001324242	RBM41	0.196	4.750	10.105	0.005	0.037	up
NM_001324263	TMC7	0.320	3.070	9.021	0.008	0.048	up
NM_001324366	ADAL	0.192	4.092	9.049	0.008	0.048	up
NM_001324393	HMBOX1	0.307	3.613	11.170	0.004	0.029	up
NM_001324445	ADAT1	0.154	5.311	10.368	0.005	0.035	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001326297	ZC3H14	0.170	5.858	18.411	0.000	0.006	up
NM_001329237	NEK9	0.196	7.685	19.605	0.000	0.005	up
NM_001329239	TFPI	0.215	5.033	11.932	0.003	0.024	up
NM_001329456	ZNF304	0.169	4.375	8.931	0.008	0.049	up
NM_001329998	TRANK1	0.291	5.228	18.399	0.000	0.006	up
NM_001330177	PCNX4	0.163	5.246	16.365	0.001	0.009	up
NM_001330183	SLFN5	0.173	7.557	12.100	0.003	0.023	up
NM_001330239	TJP1	0.263	7.447	21.169	0.000	0.004	up
NM_001330288	SMARCC2	0.150	7.445	14.442	0.001	0.014	up
NM_001330314	SLC35F5	0.146	6.259	12.794	0.002	0.020	up
NM_001330330	LUC7L3	0.227	7.588	15.539	0.001	0.011	up
NM_001330360	POLA1	0.327	4.066	18.440	0.000	0.006	up
NM_001330447	HELZ	0.179	6.451	9.802	0.006	0.040	up
NM_001330462	ATL2	0.165	5.547	13.551	0.002	0.017	up
NM_001330564	ZC3H13	0.176	6.884	12.874	0.002	0.020	up
NM_001330617	ZNF17	0.303	2.980	11.076	0.004	0.029	up
NM_001330637	MPDZ	0.259	7.018	17.494	0.001	0.008	up
NM_001330679	NMRK1	0.167	5.196	9.913	0.006	0.039	up
NM_001330691	CEP78	0.290	3.336	17.230	0.001	0.008	up
NM_001330698	YTHDC1	0.162	6.178	11.912	0.003	0.024	up
NM_001330733	ZNF518A	0.184	5.478	9.986	0.006	0.038	up
NM_001330766	ZNF415	0.346	2.791	12.894	0.002	0.020	up
NM_001331036	ELF2	0.206	5.228	23.250	0.000	0.003	up
NM_001331037	GPBP1	0.171	6.186	21.042	0.000	0.004	up
NM_001331088	FAM122B	0.203	4.828	9.343	0.007	0.044	up
NM_001334	CTSO	0.152	5.737	10.662	0.004	0.032	up
NM_001346270	USP28	0.277	4.152	15.111	0.001	0.012	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001347424	A2M	0.271	10.473	18.843	0.000	0.006	up
NM_001347664	ACVR1	0.227	5.190	14.376	0.001	0.014	up
NM_001347712	FRA10AC1	0.176	4.512	12.374	0.003	0.022	up
NM_001347828	PDGFRA	0.215	7.205	10.270	0.005	0.035	up
NM_001347893	TMX2	0.169	6.253	15.169	0.001	0.012	up
NM_001349	DARS	0.135	6.451	14.496	0.001	0.014	up
NM_001382	DPAGT1	0.199	4.924	14.474	0.001	0.014	up
NM_001386	DPYSL2	0.209	7.217	20.561	0.000	0.004	up
NM_001393	ECM2	0.265	8.264	10.906	0.004	0.030	up
NM_001415	EIF2S3	0.182	6.831	27.397	0.000	0.001	up
NM_001424	EMP2	0.205	6.408	13.934	0.002	0.016	up
NM_001431	EPB41L2	0.207	8.836	9.580	0.006	0.042	up
NM_001512	GSTA4	0.242	4.669	16.929	0.001	0.008	up
NM_001546	ID4	0.469	6.398	11.265	0.004	0.028	up
NM_001551	IGBP1	0.152	5.737	13.538	0.002	0.017	up
NM_001568	EIF3E	0.239	7.688	37.841	0.000	0.000	up
NM_001668	ARNT	0.172	6.641	21.876	0.000	0.003	up
NM_001678	ATP1B2	0.447	2.169	9.707	0.006	0.041	up
NM_001867	COX7C	0.164	6.669	9.697	0.006	0.041	up
NM_001875	CPS1	0.341	3.685	16.638	0.001	0.009	up
NM_001876	CPT1A	0.193	5.954	11.822	0.003	0.025	up
NM_001895	CSNK2A1	0.146	5.524	10.331	0.005	0.035	up
NM_001918	DBT	0.202	5.513	15.852	0.001	0.010	up
NM_001967	EIF4A2	0.413	7.996	22.698	0.000	0.003	up
NM_001979	EPHX2	0.339	5.524	30.449	0.000	0.001	up
NM_001990	EYA3	0.217	4.399	11.711	0.003	0.026	up
NM_001991	EZH1	0.231	7.356	29.569	0.000	0.001	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_002006	FGF2	0.304	6.741	12.880	0.002	0.020	up
NM_002019	FLT1	0.373	6.481	12.981	0.002	0.019	up
NM_002065	GLUL	0.340	9.717	9.552	0.006	0.042	up
NM_002069	GNAI1	0.223	7.062	9.130	0.007	0.047	up
NM_002092	GRSF1	0.125	6.458	9.864	0.006	0.039	up
NM_002107	H3F3A	0.252	3.250	12.438	0.002	0.022	up
NM_002152	HRC	0.579	2.412	14.258	0.001	0.014	up
NM_002156	HSPD1	0.230	7.360	12.219	0.003	0.023	up
NM_002157	HSPE1	0.274	5.327	14.678	0.001	0.013	up
NM_002291	LAMB1	0.236	8.156	10.156	0.005	0.037	up
NM_002293	LAMC1	0.217	9.793	15.729	0.001	0.011	up
NM_002336	LRP6	0.197	6.175	13.874	0.002	0.016	up
NM_002345	LUM	0.226	8.549	9.703	0.006	0.041	up
NM_002372	MAN2A1	0.160	5.860	10.716	0.004	0.032	up
NM_002387	MCC	0.247	5.967	11.560	0.003	0.026	up
NM_002389	CD46	0.144	8.736	9.313	0.007	0.045	up
NM_002397	MEF2C	0.219	6.228	10.380	0.005	0.035	up
NM_002444	MSN	0.132	9.444	9.107	0.008	0.047	up
NM_002480	PPP1R12A	0.199	6.090	9.682	0.006	0.041	up
NM_002482	NASP	0.140	5.520	9.371	0.007	0.044	up
NM_002486	NCBP1	0.177	4.963	9.507	0.007	0.043	up
NM_002526	NT5E	0.404	4.999	11.172	0.004	0.029	up
NM_002537	OAZ2	0.153	6.465	9.929	0.006	0.039	up
NM_002547	OPHN1	0.337	4.529	21.472	0.000	0.004	up
NM_002556	OSBP	0.134	6.595	10.043	0.005	0.037	up
NM_002612	PDK4	0.864	8.751	45.326	0.000	0.000	up
NM_002669	PLRG1	0.162	5.822	12.266	0.003	0.023	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_002687	PNN	0.235	6.781	17.241	0.001	0.008	up
NM_002716	PPP2R1B	0.359	8.328	20.327	0.000	0.004	up
NM_002786	PSMA1	0.141	6.799	11.599	0.003	0.026	up
NM_002814	PSMD10	0.149	5.288	11.603	0.003	0.026	up
NM_002884	RAP1A	0.146	6.321	9.513	0.007	0.042	up
NM_002906	RDX	0.162	7.050	9.786	0.006	0.040	up
NM_002954	RPS27A	0.169	8.524	10.228	0.005	0.036	up
NM_002979	SCP2	0.173	7.408	12.572	0.002	0.021	up
NM_002989	CCL21	1.402	1.338	19.927	0.000	0.005	up
NM_003005	SELP	0.528	4.796	12.634	0.002	0.021	up
NM_003022	SH3BGRL	0.164	6.969	12.327	0.003	0.022	up
NM_003074	SMARCC1	0.173	5.786	11.314	0.004	0.028	up
NM_003092	SNRPB2	0.179	5.040	20.186	0.000	0.005	up
NM_003144	SSR1	0.128	7.247	10.163	0.005	0.036	up
NM_003217	TMBIM6	0.172	9.639	13.908	0.002	0.016	up
NM_003265	TLR3	0.372	4.344	17.219	0.001	0.008	up
NM_003266	TLR4	0.179	6.186	9.789	0.006	0.040	up
NM_003268	TLR5	0.440	3.385	12.903	0.002	0.020	up
NM_003291	TPP2	0.152	5.745	10.855	0.004	0.031	up
NM_003298	NR2C2	0.172	6.074	10.677	0.004	0.032	up
NM_003324	TULP3	0.195	4.867	12.096	0.003	0.023	up
NM_003337	UBE2B	0.175	5.486	17.422	0.001	0.008	up
NM_003363	USP4	0.151	6.504	15.592	0.001	0.011	up
NM_003366	UQCRC2	0.165	7.553	12.618	0.002	0.021	up
NM_003400	XPO1	0.229	7.222	21.076	0.000	0.004	up
NM_003417	ZNF264	0.173	4.702	9.841	0.006	0.039	up
NM_003430	ZNF91	0.287	3.691	11.108	0.004	0.029	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_003472	DEK	0.136	6.267	10.125	0.005	0.037	up
NM_003477	PDHX	0.198	5.419	10.630	0.004	0.033	up
NM_003596	TPST1	0.370	3.969	16.743	0.001	0.009	up
NM_003611	OFD1	0.267	4.411	22.253	0.000	0.003	up
NM_003613	CILP	0.461	7.826	11.284	0.004	0.028	up
NM_003617	RGS5	0.305	8.698	15.303	0.001	0.012	up
NM_003640	IKBKAP	0.208	5.772	9.429	0.007	0.043	up
NM_003747	TNKS	0.154	5.845	10.859	0.004	0.031	up
NM_003749	IRS2	0.630	6.172	55.018	0.000	0.000	up
NM_003763	STX16	0.166	7.174	9.233	0.007	0.046	up
NM_003772	JRKL	0.263	4.470	21.096	0.000	0.004	up
NM_003797	EED	0.215	3.784	11.621	0.003	0.026	up
NM_003800	RNGTT	0.241	4.430	10.377	0.005	0.035	up
NM_003810	TNFSF10	0.225	7.189	10.400	0.005	0.034	up
NM_003825	SNAP23	0.137	6.103	10.322	0.005	0.035	up
NM_003870	IQGAP1	0.166	8.430	10.937	0.004	0.030	up
NM_003909	CPNE3	0.174	7.004	12.988	0.002	0.019	up
NM_003916	AP1S2	0.238	4.987	9.157	0.007	0.046	up
NM_004087	DLG1	0.214	6.873	10.693	0.004	0.032	up
NM_004096	EIF4EBP2	0.262	8.760	27.121	0.000	0.001	up
NM_004136	IREB2	0.130	6.298	11.256	0.004	0.028	up
NM_004229	MED14	0.141	5.415	10.599	0.004	0.033	up
NM_004277	SLC25A27	0.376	4.246	25.644	0.000	0.002	up
NM_004354	CCNG2	0.488	5.937	26.907	0.000	0.001	up
NM_004459	BPTF	0.140	6.457	11.856	0.003	0.025	up
NM_004501	HNRNPU	0.178	8.317	19.321	0.000	0.005	up
NM_004537	NAP1L1	0.219	7.766	25.612	0.000	0.002	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_004606	TAF1	0.151	6.500	16.692	0.001	0.009	up
NM_004615	TSPAN7	0.307	5.896	11.615	0.003	0.026	up
NM_004698	PRPF3	0.144	5.945	10.556	0.005	0.033	up
NM_004713	NEMF	0.151	5.831	12.089	0.003	0.023	up
NM_004719	SCAF11	0.148	7.358	10.638	0.004	0.032	up
NM_004772	NREP	0.406	4.777	29.946	0.000	0.001	up
NM_004774	MED1	0.177	6.276	16.237	0.001	0.010	up
NM_004830	MED23	0.217	5.270	11.449	0.003	0.027	up
NM_004867	ITM2A	0.268	6.406	15.863	0.001	0.010	up
NM_004874	BAG4	0.392	4.820	19.711	0.000	0.005	up
NM_004891	MRPL33	0.202	5.084	14.979	0.001	0.012	up
NM_004896	VPS26A	0.162	6.312	11.249	0.004	0.028	up
NM_004961	GABRE	0.207	7.826	9.372	0.007	0.044	up
NM_005012	ROR1	0.399	3.621	14.050	0.002	0.015	up
NM_005038	PPID	0.212	5.123	17.028	0.001	0.008	up
NM_005047	PSMD5	0.155	5.557	12.572	0.002	0.021	up
NM_005082	TRIM25	0.236	6.520	11.833	0.003	0.025	up
NM_005087	FXR1	0.170	6.720	20.563	0.000	0.004	up
NM_005095	ZMYM4	0.177	6.166	22.190	0.000	0.003	up
NM_005127	CLEC2B	0.219	4.639	11.500	0.003	0.027	up
NM_005131	THOC1	0.222	4.701	14.375	0.001	0.014	up
NM_005171	ATF1	0.188	3.980	9.833	0.006	0.039	up
NM_005204	MAP3K8	0.393	4.790	11.486	0.003	0.027	up
NM_005238	ETS1	0.221	7.864	10.611	0.004	0.033	up
NM_005246	FER	0.220	5.569	14.594	0.001	0.013	up
NM_005261	GEM	0.238	4.248	10.634	0.004	0.033	up
NM_005266	GJA5	0.411	4.286	9.371	0.007	0.044	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_005328	HAS2	0.637	2.468	16.313	0.001	0.010	up
NM_005338	HIP1	0.163	6.720	9.549	0.006	0.042	up
NM_005384	NFIL3	0.320	5.581	9.772	0.006	0.040	up
NM_005399	PRKAB2	0.123	5.758	9.305	0.007	0.045	up
NM_005419	STAT2	0.208	7.432	27.029	0.000	0.001	up
NM_005436	CCDC6	0.149	5.600	12.538	0.002	0.021	up
NM_005455	ZRANB2	0.197	6.912	11.441	0.003	0.027	up
NM_005467	NAALAD2	0.288	3.678	9.329	0.007	0.044	up
NM_005502	ABCA1	0.368	7.368	21.849	0.000	0.003	up
NM_005534	IFNGR2	0.185	6.570	11.262	0.004	0.028	up
NM_005540	INPP5B	0.188	5.017	21.555	0.000	0.004	up
NM_005570	LMAN1	0.160	6.722	11.557	0.003	0.026	up
NM_005611	RBL2	0.217	7.195	21.783	0.000	0.003	up
NM_005625	SDCBP	0.170	8.395	12.899	0.002	0.020	up
NM_005642	TAF7	0.152	6.566	11.603	0.003	0.026	up
NM_005653	TFCP2	0.176	5.601	16.100	0.001	0.010	up
NM_005707	PDCD7	0.158	4.778	11.599	0.003	0.026	up
NM_005760	CEBPZ	0.173	5.489	10.321	0.005	0.035	up
NM_005761	PLXNC1	0.396	3.928	13.173	0.002	0.018	up
NM_005763	AASS	0.216	5.764	11.454	0.003	0.027	up
NM_005777	RBM6	0.261	6.948	18.508	0.000	0.006	up
NM_005778	RBM5	0.205	7.433	14.209	0.001	0.015	up
NM_005795	CALCRL	0.282	6.369	12.701	0.002	0.020	up
NM_005824	LRRC17	0.655	2.183	12.683	0.002	0.021	up
NM_005885	MARCH6	0.121	7.442	9.644	0.006	0.041	up
NM_005898	CAPRIN1	0.168	7.848	15.139	0.001	0.012	up
NM_005908	MANBA	0.340	5.031	29.378	0.000	0.001	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_005933	KMT2A	0.281	6.699	24.512	0.000	0.002	up
NM_005981	TSPAN31	0.214	5.571	13.666	0.002	0.016	up
NM_006022	TSC22D1	0.213	6.600	12.402	0.003	0.022	up
NM_006079	CITED2	0.334	6.593	23.926	0.000	0.002	up
NM_006218	PIK3CA	0.192	6.162	9.115	0.008	0.047	up
NM_006265	RAD21	0.181	7.179	15.426	0.001	0.011	up
NM_006281	STK3	0.279	4.756	16.714	0.001	0.009	up
NM_006310	NPEPPS	0.176	6.578	11.300	0.004	0.028	up
NM_006311	NCOR1	0.135	7.116	10.698	0.004	0.032	up
NM_006380	APPBP2	0.148	6.226	10.053	0.005	0.037	up
NM_006390	IPO8	0.228	6.023	20.821	0.000	0.004	up
NM_006430	CCT4	0.160	6.696	10.528	0.005	0.033	up
NM_006437	PARP4	0.164	6.577	15.102	0.001	0.012	up
NM_006459	ERLIN1	0.190	6.056	18.357	0.000	0.006	up
NM_006463	STAMBP	0.163	5.272	11.698	0.003	0.026	up
NM_006469	IVNS1ABP	0.244	6.274	21.226	0.000	0.004	up
NM_006472	TXNIP	0.605	10.886	46.850	0.000	0.000	up
NM_006499	LGALS8	0.155	7.131	13.385	0.002	0.018	up
NM_006515	SETMAR	0.191	4.710	12.738	0.002	0.020	up
NM_006526	ZNF217	0.223	5.404	11.056	0.004	0.029	up
NM_006565	CTCF	0.154	5.655	12.067	0.003	0.024	up
NM_006614	CHL1	0.352	5.790	17.895	0.001	0.007	up
NM_006626	ZBTB6	0.190	3.555	10.947	0.004	0.030	up
NM_006630	ZNF234	0.213	4.041	17.431	0.001	0.008	up
NM_006660	CLPX	0.156	5.364	16.832	0.001	0.009	up
NM_006682	FGL2	0.261	6.028	15.535	0.001	0.011	up
NM_006696	BRD8	0.306	5.570	46.797	0.000	0.000	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_006703	NUDT3	0.200	5.023	12.531	0.002	0.021	up
NM_006714	SMPDL3A	0.332	2.920	9.118	0.007	0.047	up
NM_006729	DIAPH2	0.337	4.948	20.111	0.000	0.005	up
NM_006759	UGP2	0.210	9.404	9.005	0.008	0.048	up
NM_006802	SF3A3	0.129	6.144	9.621	0.006	0.041	up
NM_006813	PNRC1	0.232	6.204	17.453	0.001	0.008	up
NM_006835	CCNI	0.169	7.386	20.584	0.000	0.004	up
NM_006837	COPS5	0.154	5.915	9.087	0.008	0.047	up
NM_006856	ATF7	0.220	6.637	22.739	0.000	0.003	up
NM_006859	LIAS	0.204	3.918	11.068	0.004	0.029	up
NM_006904	PRKDC	0.167	7.490	12.660	0.002	0.021	up
NM_006909	RASGRF2	0.272	6.112	21.427	0.000	0.004	up
NM_006963	ZNF22	0.307	5.503	37.500	0.000	0.000	up
NM_006994	BTN3A3	0.294	5.312	17.097	0.001	0.008	up
NM_007006	NUDT21	0.135	6.338	10.036	0.005	0.037	up
NM_007018	CNTRL	0.274	4.575	15.721	0.001	0.011	up
NM_007021	C10orf10	1.309	9.327	43.478	0.000	0.000	up
NM_007034	DNAJB4	0.261	5.541	11.469	0.003	0.027	up
NM_007045	FGFR1OP	0.220	4.026	10.869	0.004	0.031	up
NM_007067	KAT7	0.201	5.230	17.949	0.001	0.007	up
NM_007124	UTRN	0.256	8.705	15.467	0.001	0.011	up
NM_007131	ZNF75D	0.208	4.743	12.254	0.003	0.023	up
NM_007137	ZNF81	0.314	3.190	14.939	0.001	0.013	up
NM_007147	ZNF175	0.259	3.404	10.266	0.005	0.036	up
NM_007175	ERLIN2	0.161	6.238	9.450	0.007	0.043	up
NM_007195	POLI	0.176	6.109	10.834	0.004	0.031	up
NM_007202	AKAP10	0.212	5.036	26.022	0.000	0.002	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_007223	GPR176	0.375	3.919	15.853	0.001	0.010	up
NM_007247	SYNRG	0.149	5.751	13.173	0.002	0.018	up
NM_007259	VPS45	0.240	5.934	30.219	0.000	0.001	up
NM_007271	STK38	0.151	6.414	10.053	0.005	0.037	up
NM_007282	RNF13	0.136	6.120	11.579	0.003	0.026	up
NM_007294	BRCA1	0.389	3.282	14.390	0.001	0.014	up
NM_007355	HSP90AB1	0.252	9.755	17.726	0.001	0.007	up
NM_012082	ZFPM2	0.206	4.943	8.963	0.008	0.049	up
NM_012086	GTF3C3	0.181	5.091	17.158	0.001	0.008	up
NM_012117	CBX5	0.138	6.641	11.464	0.003	0.027	up
NM_012197	RABGAP1	0.142	6.327	12.865	0.002	0.020	up
NM_012215	MGEA5	0.284	8.314	27.316	0.000	0.001	up
NM_012231	PRDM2	0.176	5.748	12.706	0.002	0.020	up
NM_012238	SIRT1	0.229	4.885	10.396	0.005	0.034	up
NM_012311	KIN	0.261	3.699	15.540	0.001	0.011	up
NM_012338	TSPAN12	0.239	4.219	12.169	0.003	0.023	up
NM_012414	RAB3GAP2	0.186	6.145	9.869	0.006	0.039	up
NM_012426	SF3B3	0.235	6.597	30.974	0.000	0.001	up
NM_012428	NPTN	0.153	6.137	11.385	0.003	0.027	up
NM_012433	SF3B1	0.154	8.850	12.284	0.003	0.022	up
NM_013255	MKLN1	0.183	7.231	9.361	0.007	0.044	up
NM_013262	MYLIP	0.228	5.882	9.366	0.007	0.044	up
NM_013283	MAT2B	0.219	5.807	15.573	0.001	0.011	up
NM_013302	EEF2K	0.158	6.297	9.711	0.006	0.041	up
NM_013346	SNX12	0.163	5.648	12.153	0.003	0.023	up
NM_013390	TMEM2	0.313	6.567	11.134	0.004	0.029	up
NM_013450	BAZ2B	0.187	5.572	13.772	0.002	0.016	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_013451	MYOF	0.171	7.561	9.832	0.006	0.039	up
NM_014000	VCL	0.175	8.722	11.766	0.003	0.025	up
NM_014139	SCN11A	0.533	2.198	28.656	0.000	0.001	up
NM_014153	ZC3H7A	0.197	6.217	28.852	0.000	0.001	up
NM_014167	CCDC59	0.182	3.861	10.625	0.004	0.033	up
NM_014171	CRIPT	0.234	4.154	11.699	0.003	0.026	up
NM_014230	SRP68	0.169	6.402	16.258	0.001	0.010	up
NM_014280	DNAJC8	0.114	6.604	8.933	0.008	0.049	up
NM_014296	CAPN7	0.160	5.790	14.795	0.001	0.013	up
NM_014369	PTPN18	0.149	6.231	11.191	0.004	0.028	up
NM_014444	TUBGCP4	0.254	3.816	11.379	0.003	0.027	up
NM_014454	SESN1	0.268	5.477	19.571	0.000	0.005	up
NM_014494	TNRC6A	0.155	7.269	10.651	0.004	0.032	up
NM_014547	TMOD3	0.205	5.740	11.612	0.003	0.026	up
NM_014548	TMOD2	0.227	4.944	10.889	0.004	0.031	up
NM_014607	UBXN4	0.128	7.186	10.260	0.005	0.036	up
NM_014611	MDN1	0.210	6.537	12.498	0.002	0.021	up
NM_014633	CTR9	0.172	5.957	11.062	0.004	0.029	up
NM_014637	MTFR1	0.164	4.295	9.762	0.006	0.040	up
NM_014639	TTC37	0.166	6.949	12.576	0.002	0.021	up
NM_014653	WSCD2	0.455	2.061	9.920	0.006	0.039	up
NM_014672	KIAA0391	0.176	4.721	11.292	0.004	0.028	up
NM_014676	PUM1	0.143	6.943	9.175	0.007	0.046	up
NM_014691	AQR	0.161	5.653	17.847	0.001	0.007	up
NM_014702	KIAA0408	0.362	6.458	17.110	0.001	0.008	up
NM_014705	DOCK4	0.299	5.108	16.815	0.001	0.009	up
NM_014706	SART3	0.133	5.341	10.621	0.004	0.033	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_014739	BCLAF1	0.144	6.945	8.921	0.008	0.049	up
NM_014742	TM9SF4	0.155	6.081	11.597	0.003	0.026	up
NM_014774	EFCAB14	0.168	7.880	11.477	0.003	0.027	up
NM_014789	ZNF623	0.196	4.376	11.279	0.004	0.028	up
NM_014800	ELMO1	0.278	4.747	11.889	0.003	0.025	up
NM_014804	KIAA0753	0.240	4.183	11.203	0.004	0.028	up
NM_014828	TOX4	0.169	6.520	19.008	0.000	0.006	up
NM_014880	CD302	0.237	7.106	14.510	0.001	0.014	up
NM_014895	CEP162	0.261	3.681	11.252	0.004	0.028	up
NM_014911	AAK1	0.229	5.887	19.480	0.000	0.005	up
NM_014924	ATG14	0.164	5.561	12.348	0.003	0.022	up
NM_014949	KIAA0907	0.194	5.693	11.678	0.003	0.026	up
NM_014967	FAN1	0.165	5.542	10.119	0.005	0.037	up
NM_014991	WDFY3	0.175	6.484	9.359	0.007	0.044	up
NM_014997	KLHDC10	0.132	6.747	11.442	0.003	0.027	up
NM_015024	XPO7	0.126	6.532	11.225	0.004	0.028	up
NM_015041	CLUAP1	0.163	4.608	10.140	0.005	0.037	up
NM_015049	TRAK2	0.160	7.351	8.996	0.008	0.048	up
NM_015058	VWA8	0.238	5.586	12.657	0.002	0.021	up
NM_015072	TTLL5	0.221	4.305	16.198	0.001	0.010	up
NM_015076	CDK19	0.216	4.538	14.268	0.001	0.014	up
NM_015087	SPG20	0.166	6.547	9.860	0.006	0.039	up
NM_015100	POGZ	0.265	6.684	20.257	0.000	0.004	up
NM_015120	ALMS1	0.183	4.997	13.916	0.002	0.016	up
NM_015135	NUP205	0.167	5.626	17.345	0.001	0.008	up
NM_015143	METAP1	0.198	4.892	15.214	0.001	0.012	up
NM_015161	ARL6IP1	0.145	7.330	11.822	0.003	0.025	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_015172	PRRC2C	0.179	7.348	17.757	0.001	0.007	up
NM_015188	TBC1D12	0.214	4.448	9.483	0.007	0.043	up
NM_015191	SIK2	0.262	8.458	14.382	0.001	0.014	up
NM_015203	RPRD2	0.300	5.778	35.690	0.000	0.000	up
NM_015231	NUP160	0.205	5.875	19.680	0.000	0.005	up
NM_015255	UBR2	0.219	6.241	18.354	0.000	0.006	up
NM_015268	DNAJC13	0.149	6.721	12.300	0.003	0.022	up
NM_015295	SMCHD1	0.273	5.929	19.347	0.000	0.005	up
NM_015303	VPS8	0.216	5.465	16.393	0.001	0.009	up
NM_015310	PSD3	0.182	4.342	11.983	0.003	0.024	up
NM_015342	PPWD1	0.226	4.877	19.065	0.000	0.006	up
NM_015348	TMEM131	0.134	5.853	10.103	0.005	0.037	up
NM_015358	MORC3	0.233	5.234	17.191	0.001	0.008	up
NM_015360	SKIV2L2	0.133	5.780	11.336	0.004	0.028	up
NM_015361	R3HDM1	0.183	5.230	17.290	0.001	0.008	up
NM_015375	DSTYK	0.134	5.247	10.899	0.004	0.031	up
NM_015393	PARM1	0.325	6.609	16.317	0.001	0.009	up
NM_015416	LETMD1	0.221	6.431	20.833	0.000	0.004	up
NM_015429	ABI3BP	0.410	6.183	11.995	0.003	0.024	up
NM_015439	CCDC28A	0.199	4.292	9.954	0.006	0.038	up
NM_015483	KBTBD2	0.167	5.712	9.564	0.006	0.042	up
NM_015484	SYF2	0.138	5.627	11.642	0.003	0.026	up
NM_015496	KIAA1429	0.150	6.258	16.797	0.001	0.009	up
NM_015534	ZZZ3	0.134	5.460	12.224	0.003	0.023	up
NM_015562	UBXN7	0.218	4.719	11.427	0.003	0.027	up
NM_015662	IFT172	0.203	5.017	9.882	0.006	0.039	up
NM_015665	AAAS	0.124	5.665	9.148	0.007	0.047	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_015690	STK36	0.196	4.663	10.974	0.004	0.030	up
NM_015693	INTU	0.453	3.211	27.604	0.000	0.001	up
NM_015852	ZNF117	0.287	7.915	9.177	0.007	0.046	up
NM_015878	AZIN1	0.153	6.862	11.654	0.003	0.026	up
NM_015902	UBR5	0.147	7.477	15.556	0.001	0.011	up
NM_015909	NBAS	0.221	6.022	19.188	0.000	0.005	up
NM_015975	TAF9B	0.254	4.792	15.869	0.001	0.010	up
NM_015994	ATP6V1D	0.173	5.741	11.479	0.003	0.027	up
NM_016006	ABHD5	0.189	6.186	9.445	0.007	0.043	up
NM_016091	EIF3L	0.159	8.285	14.507	0.001	0.014	up
NM_016127	SARAF	0.123	7.816	9.775	0.006	0.040	up
NM_016242	EMCN	0.374	6.327	18.014	0.001	0.007	up
NM_016245	HSD17B11	0.201	5.732	16.566	0.001	0.009	up
NM_016287	HP1BP3	0.171	7.832	13.865	0.002	0.016	up
NM_016302	CRBN	0.158	5.706	18.252	0.000	0.007	up
NM_016320	NUP98	0.128	6.801	11.239	0.004	0.028	up
NM_016355	DDX47	0.121	5.486	10.135	0.005	0.037	up
NM_016395	HACD3	0.227	5.923	16.691	0.001	0.009	up
NM_016403	CWC15	0.163	5.415	13.923	0.002	0.016	up
NM_016410	CHMP5	0.166	5.797	16.174	0.001	0.010	up
NM_016436	PHF20	0.141	5.822	11.130	0.004	0.029	up
NM_016467	ORMDL1	0.173	5.448	19.758	0.000	0.005	up
NM_016470	OSER1	0.157	5.410	11.371	0.003	0.027	up
NM_016497	MRPL51	0.167	5.897	9.476	0.007	0.043	up
NM_016530	RAB8B	0.163	5.409	10.692	0.004	0.032	up
NM_016551	TM7SF3	0.234	5.844	17.341	0.001	0.008	up
NM_016570	ERGIC2	0.183	5.012	10.698	0.004	0.032	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_016593	CYP39A1	0.609	1.475	15.872	0.001	0.010	up
NM_016603	FAM13B	0.134	5.893	10.151	0.005	0.037	up
NM_016604	KDM3B	0.130	6.958	9.553	0.006	0.042	up
NM_016817	OAS2	0.275	4.647	10.621	0.004	0.033	up
NM_016836	RBMS1	0.143	6.800	10.682	0.004	0.032	up
NM_016946	F11R	0.232	7.143	22.353	0.000	0.003	up
NM_016955	SEPSECS	0.216	4.506	9.831	0.006	0.039	up
NM_017415	KLHL3	0.313	4.795	12.339	0.003	0.022	up
NM_017520	MPHOSPH8	0.148	6.325	12.684	0.002	0.021	up
NM_017526	LEPROT	0.138	7.954	12.845	0.002	0.020	up
NM_017583	TRIM44	0.123	7.366	8.908	0.008	0.049	up
NM_017631	DDX60	0.205	4.745	13.436	0.002	0.017	up
NM_017637	BNC2	0.293	5.077	10.599	0.004	0.033	up
NM_017640	CARMIL1	0.194	3.849	9.733	0.006	0.040	up
NM_017643	MBTD1	0.294	4.824	20.964	0.000	0.004	up
NM_017644	KLHL24	0.367	6.103	16.940	0.001	0.008	up
NM_017654	SAMD9	0.241	4.198	9.516	0.007	0.042	up
NM_017655	GIPC2	0.297	3.094	10.402	0.005	0.034	up
NM_017661	ZNF280D	0.334	5.507	24.715	0.000	0.002	up
NM_017680	ASPN	0.517	4.699	16.571	0.001	0.009	up
NM_017693	BIVM	0.164	5.208	11.275	0.004	0.028	up
NM_017747	ANKHD1	0.177	7.134	17.304	0.001	0.008	up
NM_017752	TBC1D8B	0.248	3.597	10.238	0.005	0.036	up
NM_017761	PNRC2	0.159	6.057	9.689	0.006	0.041	up
NM_017794	FOCAD	0.190	4.995	10.433	0.005	0.034	up
NM_017799	TMEM260	0.235	4.290	9.739	0.006	0.040	up
NM_017830	OCIAD1	0.160	6.618	15.334	0.001	0.012	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_017831	RNF125	0.366	4.955	18.194	0.000	0.007	up
NM_017847	C1orf27	0.140	5.325	12.090	0.003	0.023	up
NM_017890	VPS13B	0.169	6.064	9.617	0.006	0.041	up
NM_017902	HIF1AN	0.138	6.295	9.414	0.007	0.044	up
NM_017940	NBPF1	0.184	6.357	15.859	0.001	0.010	up
NM_017952	PTCD3	0.199	5.989	21.745	0.000	0.003	up
NM_017990	PDPR	0.216	6.829	21.729	0.000	0.003	up
NM_018023	YEATS2	0.220	5.270	14.348	0.001	0.014	up
NM_018047	RBM22	0.161	5.465	13.300	0.002	0.018	up
NM_018050	MANSC1	0.158	4.856	12.671	0.002	0.021	up
NM_018079	SRBD1	0.281	4.062	9.272	0.007	0.045	up
NM_018091	ELP3	0.162	5.458	11.468	0.003	0.027	up
NM_018129	PNPO	0.158	5.162	9.679	0.006	0.041	up
NM_018133	MSL2	0.181	4.701	11.877	0.003	0.025	up
NM_018178	GOLPH3L	0.264	5.081	45.713	0.000	0.000	up
NM_018200	HMG20A	0.128	5.307	9.354	0.007	0.044	up
NM_018227	UBA6	0.157	5.391	9.217	0.007	0.046	up
NM_018230	NUP133	0.133	5.744	14.207	0.001	0.015	up
NM_018257	PCMTD2	0.309	6.125	24.852	0.000	0.002	up
NM_018259	TTC17	0.214	6.340	22.557	0.000	0.003	up
NM_018288	PHF10	0.140	5.257	9.823	0.006	0.039	up
NM_018292	QRSL1	0.195	4.488	14.909	0.001	0.013	up
NM_018320	RNF121	0.146	4.542	10.070	0.005	0.037	up
NM_018327	SPTLC3	0.230	3.749	11.613	0.003	0.026	up
NM_018328	MBD5	0.252	3.930	14.989	0.001	0.012	up
NM_018360	TXLNG	0.267	5.563	35.769	0.000	0.000	up
NM_018362	LIN7C	0.176	4.097	9.561	0.006	0.042	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_018367	ACER3	0.184	6.552	9.064	0.008	0.048	up
NM_018368	LMBRD1	0.212	6.146	22.688	0.000	0.003	up
NM_018373	SYNJ2BP	0.171	6.497	12.259	0.003	0.023	up
NM_018375	SLC39A9	0.127	6.308	9.051	0.008	0.048	up
NM_018376	NIPSNAP3B	0.348	5.657	15.538	0.001	0.011	up
NM_018388	MBNL3	0.198	6.075	9.809	0.006	0.040	up
NM_018418	SPATA7	0.351	2.936	14.930	0.001	0.013	up
NM_018428	UTP6	0.150	5.417	9.801	0.006	0.040	up
NM_018433	KDM3A	0.189	5.634	14.463	0.001	0.014	up
NM_018471	ZC3H15	0.146	5.975	9.245	0.007	0.045	up
NM_018489	ASH1L	0.142	7.472	11.815	0.003	0.025	up
NM_018490	LGR4	0.208	6.060	11.150	0.004	0.029	up
NM_018530	GSDMB	0.282	3.704	10.487	0.005	0.034	up
NM_018675	ZNF302	0.223	5.468	23.853	0.000	0.002	up
NM_018847	KLHL9	0.215	5.710	10.099	0.005	0.037	up
NM_018948	ERRFI1	0.278	5.574	9.008	0.008	0.048	up
NM_019022	TMX3	0.140	6.246	8.973	0.008	0.049	up
NM_019035	PCDH18	0.256	7.595	21.607	0.000	0.004	up
NM_019051	MRPL50	0.209	4.052	10.118	0.005	0.037	up
NM_019069	WDR5B	0.209	3.732	10.986	0.004	0.030	up
NM_019071	ING3	0.228	3.576	11.412	0.003	0.027	up
NM_019083	TRMT13	0.215	4.160	9.739	0.006	0.040	up
NM_019087	ARL15	0.251	3.834	8.961	0.008	0.049	up
NM_019095	CRLS1	0.200	5.875	13.198	0.002	0.018	up
NM_019589	YLPM1	0.121	6.270	9.318	0.007	0.045	up
NM_019592	RNF20	0.247	6.041	28.310	0.000	0.001	up
NM_019593	GPCPD1	0.288	5.887	19.620	0.000	0.005	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_019597	HNRNPH2	0.131	6.807	10.632	0.004	0.033	up
NM_019607	C8orf44	0.361	2.678	11.140	0.004	0.029	up
NM_019619	PARD3	0.170	5.330	11.461	0.003	0.027	up
NM_020200	PRTFDC1	0.262	2.847	12.719	0.002	0.020	up
NM_020225	STOX2	0.252	3.512	8.955	0.008	0.049	up
NM_020234	DTWD1	0.221	4.716	14.076	0.002	0.015	up
NM_020297	ABCC9	0.310	6.390	20.184	0.000	0.005	up
NM_020314	C16orf62	0.136	5.912	10.948	0.004	0.030	up
NM_020342	SLC39A10	0.251	4.661	11.161	0.004	0.029	up
NM_020343	RALGAPA2	0.246	6.652	11.212	0.004	0.028	up
NM_020374	C12orf4	0.181	4.547	12.429	0.002	0.022	up
NM_020395	INTS12	0.170	4.148	9.918	0.006	0.039	up
NM_020399	GOPC	0.164	5.971	11.300	0.004	0.028	up
NM_020401	NUP107	0.151	5.501	8.888	0.008	0.050	up
NM_020440	PTGFRN	0.293	4.933	10.376	0.005	0.035	up
NM_020453	ATP10D	0.221	4.619	10.691	0.004	0.032	up
NM_020666	CLK4	0.264	5.122	18.426	0.000	0.006	up
NM_020690	ANKHD1-EIF4EBP3	0.166	7.265	17.623	0.001	0.007	up
NM_020699	GATAD2B	0.188	5.222	13.604	0.002	0.017	up
NM_020725	ATXN7L1	0.243	3.567	11.859	0.003	0.025	up
NM_020738	KIDINS220	0.194	7.066	16.640	0.001	0.009	up
NM_020747	ZNF608	0.246	4.827	14.212	0.001	0.015	up
NM_020802	CEP126	0.194	5.188	14.011	0.002	0.015	up
NM_020806	GPHN	0.316	4.365	17.026	0.001	0.008	up
NM_020810	TRMT5	0.161	4.669	9.377	0.007	0.044	up
NM_020813	ZNF471	0.228	4.370	9.597	0.006	0.042	up
NM_020823	TMEM181	0.128	5.993	9.170	0.007	0.046	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_020844	KIAA1456	0.691	1.813	15.850	0.001	0.010	up
NM_020872	CNTN3	0.261	3.397	16.485	0.001	0.009	up
NM_020879	CCDC146	0.222	4.149	10.110	0.005	0.037	up
NM_020925	CACHD1	0.323	6.155	25.956	0.000	0.002	up
NM_020943	CWC22	0.172	4.592	11.141	0.004	0.029	up
NM_020964	EPG5	0.189	5.842	11.697	0.003	0.026	up
NM_020978	AMY2B	0.300	5.376	10.241	0.005	0.036	up
NM_021045	ZNF248	0.256	4.190	11.942	0.003	0.024	up
NM_021073	BMP5	0.451	1.899	11.503	0.003	0.027	up
NM_021163	RBAK	0.184	4.501	9.252	0.007	0.045	up
NM_021215	RPRD1B	0.169	5.137	13.004	0.002	0.019	up
NM_021249	SNX6	0.196	6.384	16.444	0.001	0.009	up
NM_021639	GPBP1L1	0.149	6.503	16.804	0.001	0.009	up
NM_021807	EXOC4	0.139	6.390	8.972	0.008	0.049	up
NM_021818	SAV1	0.248	5.787	20.621	0.000	0.004	up
NM_021916	ZNF70	0.293	2.706	13.397	0.002	0.017	up
NM_021977	SLC22A3	0.488	5.037	11.330	0.004	0.028	up
NM_021994	ZNF277	0.228	3.831	13.015	0.002	0.019	up
NM_022068	PIEZO2	0.498	1.049	14.956	0.001	0.013	up
NM_022079	HERC4	0.211	5.864	15.459	0.001	0.011	up
NM_022147	RTP4	0.446	1.684	11.200	0.004	0.028	up
NM_022173	TIA1	0.256	6.173	16.127	0.001	0.010	up
NM_022373	HERPUD2	0.183	5.009	12.275	0.003	0.022	up
NM_022455	NSD1	0.132	6.855	8.942	0.008	0.049	up
NM_022469	GREM2	1.327	-0.476	11.754	0.003	0.025	up
NM_022491	SUDS3	0.215	5.194	19.531	0.000	0.005	up
NM_022494	ZDHHC6	0.199	5.169	18.668	0.000	0.006	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_022497	MRPS25	0.152	6.077	13.640	0.002	0.016	up
NM_022553	VPS52	0.129	6.029	9.550	0.006	0.042	up
NM_022659	EBF2	0.235	5.403	16.972	0.001	0.008	up
NM_022753	S100PBP	0.180	4.608	11.927	0.003	0.024	up
NM_022780	RMND5A	0.266	6.211	22.236	0.000	0.003	up
NM_022787	NMNAT1	0.235	4.494	15.272	0.001	0.012	up
NM_022818	MAP1LC3B	0.168	6.655	14.287	0.001	0.014	up
NM_022918	TMEM135	0.185	6.624	9.572	0.006	0.042	up
NM_023015	INTS3	0.308	7.005	24.908	0.000	0.002	up
NM_024015	HOXB4	0.271	3.325	11.880	0.003	0.025	up
NM_024039	MIS12	0.162	4.331	10.877	0.004	0.031	up
NM_024045	DDX50	0.156	5.502	15.322	0.001	0.012	up
NM_024087	ASB9	0.386	2.019	14.000	0.002	0.015	up
NM_024093	C2orf49	0.175	4.811	9.491	0.007	0.043	up
NM_024104	SMIM7	0.196	6.262	14.338	0.001	0.014	up
NM_024106	ZNF426	0.254	4.110	11.419	0.003	0.027	up
NM_024116	TAF1D	0.247	4.238	10.022	0.005	0.038	up
NM_024541	C10orf76	0.158	5.370	11.413	0.003	0.027	up
NM_024592	SRD5A3	0.149	4.669	9.035	0.008	0.048	up
NM_024597	MAP7D3	0.228	5.980	10.156	0.005	0.037	up
NM_024611	ICE2	0.177	5.750	20.755	0.000	0.004	up
NM_024612	DHX40	0.136	5.504	9.673	0.006	0.041	up
NM_024615	PARP8	0.204	4.523	14.275	0.001	0.014	up
NM_024654	NOL9	0.301	4.381	28.939	0.000	0.001	up
NM_024657	MORC4	0.249	5.279	9.776	0.006	0.040	up
NM_024662	NAT10	0.168	5.517	16.736	0.001	0.009	up
NM_024675	PALB2	0.228	3.747	13.184	0.002	0.018	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_024685	BBS10	0.437	4.664	20.546	0.000	0.004	up
NM_024699	ZFAND1	0.209	4.784	16.215	0.001	0.010	up
NM_024721	ZFHX4	0.257	5.790	9.867	0.006	0.039	up
NM_024733	ZNF665	0.313	1.540	9.073	0.008	0.047	up
NM_024734	CLMN	0.233	6.767	15.248	0.001	0.012	up
NM_024776	PEAK1	0.230	7.646	20.082	0.000	0.005	up
NM_024782	NHEJ1	0.194	4.018	9.797	0.006	0.040	up
NM_024784	ZBTB3	0.343	2.347	13.202	0.002	0.018	up
NM_024790	CSPP1	0.259	3.711	18.650	0.000	0.006	up
NM_024829	PLBD1	0.233	5.192	11.380	0.003	0.027	up
NM_024852	AGO3	0.325	3.400	24.308	0.000	0.002	up
NM_024896	ERMP1	0.223	4.883	16.094	0.001	0.010	up
NM_024901	DENND2D	0.249	4.478	13.956	0.002	0.015	up
NM_025009	CEP135	0.378	2.994	12.413	0.002	0.022	up
NM_025074	FRAS1	0.844	0.749	17.653	0.001	0.007	up
NM_025114	CEP290	0.171	4.693	9.931	0.006	0.039	up
NM_025137	SPG11	0.231	6.279	23.243	0.000	0.003	up
NM_025195	TRIB1	0.424	5.467	18.029	0.001	0.007	up
NM_025203	WDCP	0.225	3.754	12.354	0.003	0.022	up
NM_025208	PDGFD	0.398	4.871	10.795	0.004	0.031	up
NM_025211	GKAP1	0.265	3.185	9.101	0.008	0.047	up
NM_025243	SLC19A3	0.495	7.606	21.572	0.000	0.004	up
NM_030641	APOL6	0.288	8.338	18.005	0.001	0.007	up
NM_030771	CCDC34	0.452	2.141	12.390	0.003	0.022	up
NM_030877	CTNNBL1	0.206	5.200	16.214	0.001	0.010	up
NM_030918	SNX27	0.184	5.066	17.004	0.001	0.008	up
NM_030934	TRMT1L	0.164	4.615	9.691	0.006	0.041	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_030939	C6orf62	0.127	7.039	8.986	0.008	0.049	up
NM_030962	SBF2	0.126	6.785	8.925	0.008	0.049	up
NM_030979	PABPC3	0.220	3.887	16.656	0.001	0.009	up
NM_031157	HNRNPA1	0.179	6.593	10.566	0.005	0.033	up
NM_031243	HNRNPA2B1	0.145	9.203	9.328	0.007	0.044	up
NM_031314	HNRNPC	0.150	7.615	13.570	0.002	0.017	up
NM_031370	HNRNPD	0.142	6.785	11.884	0.003	0.025	up
NM_031407	HUWE1	0.196	8.211	18.463	0.000	0.006	up
NM_031442	TMEM47	0.207	6.256	9.650	0.006	0.041	up
NM_031463	HSDL1	0.167	4.964	11.983	0.003	0.024	up
NM_031490	LONP2	0.159	6.816	9.845	0.006	0.039	up
NM_031850	AGTR1	0.422	5.430	52.894	0.000	0.000	up
NM_031905	ARMC10	0.151	4.473	8.978	0.008	0.049	up
NM_032012	TMEM245	0.165	7.614	9.390	0.007	0.044	up
NM_032013	NDRG3	0.161	5.559	14.160	0.001	0.015	up
NM_032025	EIF2A	0.137	6.344	14.372	0.001	0.014	up
NM_032208	ANTXR1	0.238	6.630	10.781	0.004	0.031	up
NM_032217	ANKRD17	0.187	6.823	19.502	0.000	0.005	up
NM_032236	USP48	0.149	6.032	13.198	0.002	0.018	up
NM_032256	TMEM117	0.260	2.844	8.936	0.008	0.049	up
NM_032316	NICN1	0.188	5.040	10.155	0.005	0.037	up
NM_032351	MRPL45	0.201	5.189	15.828	0.001	0.010	up
NM_032368	LZIC	0.161	5.536	13.783	0.002	0.016	up
NM_032385	FAXDC2	0.231	6.618	12.772	0.002	0.020	up
NM_032423	ZNF528	0.210	4.348	13.225	0.002	0.018	up
NM_032427	MAML2	0.252	5.702	11.990	0.003	0.024	up
NM_032458	PHF6	0.207	4.484	9.273	0.007	0.045	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_032587	CARD6	0.230	4.888	13.291	0.002	0.018	up
NM_032664	FUT10	0.261	3.124	12.375	0.003	0.022	up
NM_032682	FOXP1	0.245	5.610	9.496	0.007	0.043	up
NM_032765	TRIM52	0.246	5.071	14.238	0.001	0.015	up
NM_032773	LRCH3	0.237	3.626	14.691	0.001	0.013	up
NM_032812	PLXDC2	0.136	6.277	10.098	0.005	0.037	up
NM_032842	TMEM209	0.190	4.449	10.310	0.005	0.035	up
NM_032846	RAB2B	0.154	5.030	9.780	0.006	0.040	up
NM_032852	ATG4C	0.232	3.832	10.708	0.004	0.032	up
NM_032875	FBXL20	0.456	4.898	69.204	0.000	0.000	up
NM_032962	CCL14	0.292	7.361	10.837	0.004	0.031	up
NM_032999	GTF2I	0.205	6.364	12.122	0.003	0.023	up
NM_033014	OGN	0.434	4.881	10.073	0.005	0.037	up
NM_033050	SUCNR1	0.447	3.853	22.977	0.000	0.003	up
NM_033091	TRIM4	0.150	5.277	9.380	0.007	0.044	up
NM_033092	TRIM5	0.222	4.654	13.636	0.002	0.016	up
NM_033208	TIGD7	0.289	3.444	15.129	0.001	0.012	up
NM_033395	CEP295	0.198	4.010	8.906	0.008	0.049	up
NM_033418	METTL18	0.378	2.655	12.219	0.003	0.023	up
NM_033439	IL33	0.293	6.327	12.266	0.003	0.023	up
NM_033515	ARHGAP18	0.173	5.359	11.120	0.004	0.029	up
NM_033547	INTS4	0.185	4.335	10.467	0.005	0.034	up
NM_033637	BTRC	0.172	4.833	12.682	0.002	0.021	up
NM_052817	MID2	0.161	5.625	9.147	0.007	0.047	up
NM_052818	N4BP2L1	0.261	4.031	16.217	0.001	0.010	up
NM_052852	ZNF486	0.300	2.090	10.295	0.005	0.035	up
NM_052864	TIFA	0.357	2.384	14.547	0.001	0.014	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_052880	PIK3IP1	0.252	6.508	14.168	0.001	0.015	up
NM_052905	FMNL2	0.360	6.983	14.151	0.001	0.015	up
NM_057159	LPAR1	0.235	5.176	14.168	0.001	0.015	up
NM_058165	MOGAT1	0.897	0.608	23.079	0.000	0.003	up
NM_058172	ANTXR2	0.227	7.751	9.587	0.006	0.042	up
NM_058229	FBXO32	0.367	5.176	13.662	0.002	0.016	up
NM_080424	SP110	0.294	4.262	19.650	0.000	0.005	up
NM_080546	SLC44A1	0.141	6.110	12.325	0.003	0.022	up
NM_080597	OSBPL1A	0.169	7.088	9.692	0.006	0.041	up
NM_100264	WAC	0.124	7.181	9.619	0.006	0.041	up
NM_101395	DYRK1A	0.139	5.996	9.000	0.008	0.048	up
NM_133259	LRPPRC	0.130	7.083	10.929	0.004	0.030	up
NM_133264	WIPF2	0.150	5.673	8.931	0.008	0.049	up
NM_133372	FNIP1	0.188	5.554	10.283	0.005	0.035	up
NM_138367	ZNF251	0.234	4.886	11.489	0.003	0.027	up
NM_138376	TTC5	0.239	2.954	9.706	0.006	0.041	up
NM_138467	TYW3	0.192	5.132	20.892	0.000	0.004	up
NM_138473	SP1	0.210	7.336	26.223	0.000	0.002	up
NM_138782	FCHO2	0.281	5.104	14.737	0.001	0.013	up
NM_138806	CD200R1	0.495	1.628	10.997	0.004	0.030	up
NM_138809	CMBL	0.246	5.799	16.321	0.001	0.009	up
NM_139056	ADAMTS16	0.807	2.283	11.015	0.004	0.030	up
NM_139281	WDR36	0.164	5.410	9.849	0.006	0.039	up
NM_144607	CYB5D1	0.156	5.084	11.585	0.003	0.026	up
NM_144660	SAMD8	0.158	6.215	9.706	0.006	0.041	up
NM_144665	SESN3	0.384	5.922	20.483	0.000	0.004	up
NM_144695	BROX	0.170	5.398	16.356	0.001	0.009	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_144982	ZFC3H1	0.239	6.123	19.803	0.000	0.005	up
NM_145165	CHURC1	0.135	7.095	10.731	0.004	0.032	up
NM_145212	MRPL30	0.130	5.579	9.150	0.007	0.047	up
NM_145243	OMA1	0.292	3.807	13.468	0.002	0.017	up
NM_145259	ACVR1C	0.332	7.179	8.948	0.008	0.049	up
NM_147223	NCOA1	0.140	6.757	10.605	0.004	0.033	up
NM_147686	TRAF3IP2	0.182	4.829	10.706	0.004	0.032	up
NM_148894	BOD1L1	0.152	6.410	9.376	0.007	0.044	up
NM_152283	ZFP62	0.238	4.577	16.316	0.001	0.009	up
NM_152289	ZNF561	0.244	4.539	19.514	0.000	0.005	up
NM_152316	ARL14EP	0.147	4.895	11.277	0.004	0.028	up
NM_152320	ZNF641	0.146	5.542	9.448	0.007	0.043	up
NM_152347	EFCAB13	0.488	2.275	14.150	0.001	0.015	up
NM_152360	ZNF573	0.429	1.964	11.038	0.004	0.029	up
NM_152434	CWF19L2	0.264	4.460	26.088	0.000	0.002	up
NM_152475	ZNF417	0.416	3.406	18.109	0.000	0.007	up
NM_152519	KANSL1L	0.237	4.495	12.903	0.002	0.020	up
NM_152527	SLC16A14	0.319	3.764	19.916	0.000	0.005	up
NM_152542	PPM1K	0.260	4.137	12.040	0.003	0.024	up
NM_152551	SNRNP48	0.158	4.124	8.939	0.008	0.049	up
NM_152599	MFSD6L	2.776	-2.792	9.461	0.008	0.049	up
NM_152605	ZNF781	0.475	2.156	14.870	0.001	0.013	up
NM_152655	ZNF585A	0.316	3.435	15.737	0.001	0.011	up
NM_152703	SAMD9L	0.238	5.957	12.389	0.003	0.022	up
NM_152729	NT5DC1	0.156	5.342	13.919	0.002	0.016	up
NM_152765	C8orf46	0.445	2.227	11.832	0.003	0.025	up
NM_152772	TCP11L2	0.541	3.213	21.504	0.000	0.004	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_152900	MAGI3	0.175	4.076	9.534	0.006	0.042	up
NM_152989	SOX5	0.385	4.559	9.420	0.007	0.043	up
NM_153235	TXLNB	0.529	1.001	9.698	0.006	0.041	up
NM_153240	NPHP3	0.229	5.625	16.959	0.001	0.008	up
NM_153366	SVEP1	0.283	8.501	15.513	0.001	0.011	up
NM_153607	CREBRF	0.333	5.738	20.571	0.000	0.004	up
NM_153618	SEMA6D	0.369	4.658	33.060	0.000	0.001	up
NM_153702	ELMOD2	0.159	5.064	9.466	0.007	0.043	up
NM_153809	TAF1L	0.381	1.361	8.875	0.008	0.050	up
NM_153816	SNX14	0.131	5.733	11.931	0.003	0.024	up
NM_170606	KMT2C	0.235	7.263	16.284	0.001	0.010	up
NM_170784	MKKS	0.154	5.648	12.051	0.003	0.024	up
NM_172037	RDH10	0.341	4.995	23.393	0.000	0.003	up
NM_172311	STON1-GTF2A1L	0.364	4.382	8.944	0.008	0.049	up
NM_173348	FAM149B1	0.191	4.789	11.602	0.003	0.026	up
NM_173480	ZNF57	0.349	1.558	9.517	0.007	0.042	up
NM_173505	ANKRD29	0.333	5.035	9.670	0.006	0.041	up
NM_173566	PRR14L	0.134	5.517	9.738	0.006	0.040	up
NM_173569	UBN2	0.226	5.256	13.115	0.002	0.019	up
NM_173611	FAM98B	0.155	5.208	10.013	0.005	0.038	up
NM_173653	SLC9A9	0.357	4.891	10.390	0.005	0.035	up
NM_173800	LVRN	0.281	6.695	18.380	0.000	0.006	up
NM_173812	DPY19L2	0.519	3.919	22.913	0.000	0.003	up
NM_173825	RABL3	0.163	6.330	13.702	0.002	0.016	up
NM_173872	CLCN3	0.138	6.592	9.366	0.007	0.044	up
NM_175859	CTPS2	0.235	4.453	26.173	0.000	0.002	up
NM_175907	ZADH2	0.147	5.823	10.851	0.004	0.031	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_176877	PATJ	0.258	4.369	17.355	0.001	0.008	up
NM_177444	PPFIBP1	0.249	6.074	18.473	0.000	0.006	up
NM_177525	MEST	0.245	8.870	9.430	0.007	0.043	up
NM_177538	CYP20A1	0.306	4.860	40.488	0.000	0.000	up
NM_178127	ANGPTL5	0.568	2.180	14.405	0.001	0.014	up
NM_178509	STXBP4	0.321	2.214	9.462	0.007	0.043	up
NM_178544	ZNF546	0.361	2.795	16.403	0.001	0.009	up
NM_178822	IGSF10	0.453	4.908	26.828	0.000	0.001	up
NM_181506	LRRC70	0.341	2.478	10.871	0.004	0.031	up
NM_181507	HPS5	0.163	5.060	13.529	0.002	0.017	up
NM_181578	RFC5	0.247	3.110	11.140	0.004	0.029	up
NM_181656	C17orf58	0.323	4.090	9.447	0.007	0.043	up
NM_181672	OGT	0.346	8.063	27.917	0.000	0.001	up
NM_181861	APAF1	0.276	4.355	16.673	0.001	0.009	up
NM_182487	OLFML2A	0.416	5.487	17.237	0.001	0.008	up
NM_182633	ZNF713	0.299	1.518	8.972	0.008	0.049	up
NM_182715	SYPL1	0.153	6.887	11.336	0.004	0.028	up
NM_182898	CREB5	0.488	4.453	14.938	0.001	0.013	up
NM_182916	TRNT1	0.253	3.957	14.887	0.001	0.013	up
NM_182920	ADAMTS9	0.291	5.867	12.347	0.003	0.022	up
NM_183238	ZNF605	0.256	4.561	14.583	0.001	0.014	up
NM_194247	HNRNPA3	0.196	7.516	11.692	0.003	0.026	up
NM_194328	RNF38	0.208	5.794	13.452	0.002	0.017	up
NM_198129	LAMA3	0.419	5.470	11.067	0.004	0.029	up
NM_198141	GANC	0.191	4.735	13.696	0.002	0.016	up
NM_198148	CPXM2	0.522	5.258	11.925	0.003	0.024	up
NM_198428	BBS9	0.223	3.774	16.200	0.001	0.010	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_198485	TPRG1	0.201	5.288	10.846	0.004	0.031	up
NM_198557	RBM43	0.256	4.423	18.317	0.000	0.006	up
NM_198578	LRRK2	0.168	4.781	10.523	0.005	0.033	up
NM_198721	COL25A1	0.264	3.921	10.092	0.005	0.037	up
NM_199168	CXCL12	0.252	8.209	12.660	0.002	0.021	up
NM_199418	PRCP	0.173	7.308	11.569	0.003	0.026	up
NM_201263	WARS2	0.286	3.774	17.536	0.001	0.008	up
NM_203284	RBPJ	0.165	7.142	17.434	0.001	0.008	up
NM_203447	DOCK8	0.207	5.941	14.510	0.001	0.014	up
NM_203487	PCDH9	0.303	5.711	23.438	0.000	0.003	up
NM_205860	NR5A2	0.454	3.691	14.426	0.001	0.014	up
NM_206808	CLYBL	0.408	2.993	18.332	0.000	0.006	up
NM_206827	RASL11A	0.432	3.233	29.313	0.000	0.001	up
NM_207038	TCF12	0.153	6.418	14.282	0.001	0.014	up
NM_207123	GAB1	0.337	5.083	26.219	0.000	0.002	up
NM_207352	CYP4V2	0.226	5.389	17.676	0.001	0.007	up
NM_207435	C12orf76	0.348	2.280	11.467	0.003	0.027	up
NM_212482	FN1	0.332	9.352	10.804	0.004	0.031	up
NR_002212	NUDT4P1	0.277	5.510	13.892	0.002	0.016	up
NR_002315	H3F3AP4	0.252	3.250	12.438	0.002	0.022	up
NR_002323	TUG1	0.137	7.783	9.943	0.006	0.038	up
NR_002578	GAS5	0.288	5.345	25.634	0.000	0.002	up
NR_002722	ZNF204P	0.198	4.004	10.822	0.004	0.031	up
NR_002944	HNRNPA1P10	0.183	6.299	9.562	0.006	0.042	up
NR_003108	NBR2	0.281	2.241	9.625	0.006	0.041	up
NR_003249	HNRNPDL	0.180	7.506	16.097	0.001	0.010	up
NR_003579	FRG1BP	0.203	3.802	9.453	0.007	0.043	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NR_015353	LINC01278	0.308	4.315	27.562	0.000	0.001	up
NR_015367	NBDY	0.264	3.499	13.338	0.002	0.018	up
NR_015451	LINC00294	0.253	3.916	12.257	0.003	0.023	up
NR_023311	ZNF137P	0.394	1.872	12.650	0.002	0.021	up
NR_023915	IPW	0.385	2.793	13.460	0.002	0.017	up
NR_023917	PTENP1	0.237	3.836	12.956	0.002	0.019	up
NR_024188	PPP1R21	0.181	5.157	14.907	0.001	0.013	up
NR_024199	CBLL1	0.213	4.473	13.021	0.002	0.019	up
NR_024408	PSMD5-AS1	0.245	4.740	22.605	0.000	0.003	up
NR_024549	DMTF1	0.259	6.320	27.159	0.000	0.001	up
NR_024565	ZNF271P	0.186	5.523	13.189	0.002	0.018	up
NR_026730	TPTE2P1	0.924	-0.601	15.296	0.001	0.012	up
NR_026777	ZNF37BP	0.254	4.529	16.901	0.001	0.008	up
NR_026790	HCG11	0.223	5.182	26.634	0.000	0.001	up
NR_026804	KLF3-AS1	0.512	1.556	9.395	0.007	0.044	up
NR_026808	ANP32A-IT1	0.908	0.442	13.782	0.002	0.016	up
NR_026837	TRHDE-AS1	0.305	6.635	13.335	0.002	0.018	up
NR_026867	ZNF300P1	0.481	2.635	12.509	0.002	0.021	up
NR_026885	LOC100270804	0.329	2.350	11.479	0.003	0.027	up
NR_026903	AMZ2P1	0.217	4.181	12.446	0.002	0.022	up
NR_026938	ADCY10P1	0.532	2.613	28.547	0.000	0.001	up
NR_027107	LOC90768	0.387	2.932	9.940	0.006	0.038	up
NR_027130	ZNF738	0.315	2.522	9.413	0.007	0.044	up
NR_027183	LINC00847	0.273	4.734	29.744	0.000	0.001	up
NR_027455	LINC00893	0.444	2.320	19.567	0.000	0.005	up
NR_027456	LINC00894	0.623	2.446	21.132	0.000	0.004	up
NR_027671	UGGT1	0.315	6.698	38.321	0.000	0.000	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NR_027696	TAPT1-AS1	0.498	1.768	15.369	0.001	0.011	up
NR_027856	CLK1	0.288	7.576	16.405	0.001	0.009	up
NR_027873	PAXBP1	0.228	4.878	15.679	0.001	0.011	up
NR_027921	CCL15-CCL14	0.293	7.350	10.889	0.004	0.031	up
NR_028477	RBMX	0.167	6.519	13.332	0.002	0.018	up
NR_029410	LOC389765	0.333	1.936	9.072	0.008	0.047	up
NR_029434	PSMA3-AS1	0.233	5.619	22.174	0.000	0.003	up
NR_033327	EFHC1	0.300	4.663	14.840	0.001	0.013	up
NR_034053	TNPO3	0.118	6.326	10.045	0.005	0.037	up
NR_034070	CASP12	0.977	-0.403	9.359	0.007	0.044	up
NR_034089	CCDC18-AS1	0.466	4.719	62.331	0.000	0.000	up
NR_034127	LOC100132356	0.539	0.792	12.570	0.002	0.021	up
NR_036508	LOC100128398	0.378	2.037	12.965	0.002	0.019	up
NR_036634	TGFBR3	0.177	7.982	9.319	0.007	0.045	up
NR_036650	WHAMMP1	0.390	2.615	13.034	0.002	0.019	up
NR_036680	DPY19L1P1	0.573	1.019	12.963	0.002	0.019	up
NR_037144	PLEKHA8P1	0.428	3.489	27.086	0.000	0.001	up
NR_037155	SEPT4	0.241	4.719	11.110	0.004	0.029	up
NR_037701	LINC01963	0.174	4.209	9.328	0.007	0.044	up
NR_037714	RAD51L3-RFFL	0.176	5.026	15.454	0.001	0.011	up
NR_037803	BACE1-AS	0.396	1.323	9.510	0.007	0.043	up
NR_037804	NPHP3-ACAD11	0.229	7.141	20.112	0.000	0.005	up
NR_037859	PIR-FIGF	0.241	5.199	10.798	0.004	0.031	up
NR_037870	CADM3-AS1	0.798	2.980	11.593	0.003	0.026	up
NR_037934	SEPSECS-AS1	0.853	-0.020	15.770	0.001	0.011	up
NR_038337	OSER1-AS1	0.309	3.367	16.117	0.001	0.010	up
NR_038426	LINC01354	0.706	2.134	15.120	0.001	0.012	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NR_038889	LOC401320	0.322	4.786	24.365	0.000	0.002	up
NR_038903	RAB30-AS1	0.281	2.696	10.815	0.004	0.031	up
NR_039891	MIR3064	0.252	4.319	10.592	0.005	0.033	up
NR_040071	TNRC6C-AS1	0.238	3.870	11.801	0.003	0.025	up
NR_040079	LOC399715	1.032	-0.648	9.811	0.006	0.040	up
NR_040662	HCP5	0.290	4.882	12.618	0.002	0.021	up
NR_045639	UQCRB	0.199	7.226	15.080	0.001	0.012	up
NR_045769	ATF2	0.176	5.965	15.694	0.001	0.011	up
NR_046106	NOL8	0.169	5.301	10.637	0.004	0.032	up
NR_046386	UHRF2	0.284	5.048	19.794	0.000	0.005	up
NR_048570	EXTL2	0.260	4.600	22.625	0.000	0.003	up
NR_049734	MS4A14	0.387	3.015	10.209	0.005	0.036	up
NR_049752	ZNF211	0.211	3.903	8.919	0.008	0.049	up
NR_049763	CNOT1	0.131	7.519	10.559	0.005	0.033	up
NR_072999	JAM2	0.404	5.957	22.448	0.000	0.003	up
NR_073040	NET1	0.757	7.052	9.402	0.007	0.044	up
NR_073062	MCU	0.174	4.536	13.086	0.002	0.019	up
NR_073206	SEL1L2	0.714	1.696	12.599	0.002	0.021	up
NR_073366	DNAJC10	0.163	6.605	12.579	0.002	0.021	up
NR_073405	PRKXP1	0.440	2.505	11.753	0.003	0.025	up
NR_073428	CWC25	0.184	4.988	12.287	0.003	0.022	up
NR_073470	SUPT4H1	0.139	5.872	9.686	0.006	0.041	up
NR_073562	RABGGTB	0.285	5.400	23.698	0.000	0.002	up
NR_102279	HOXB-AS1	0.317	3.801	8.940	0.008	0.049	up
NR_103448	ZNF192P1	0.546	1.313	12.373	0.003	0.022	up
NR_103469	C11orf57	0.241	4.778	20.511	0.000	0.004	up
NR_103720	STAG3L5P	0.250	2.786	9.429	0.007	0.043	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NR_104005	NUDT4P2	0.278	5.510	13.859	0.002	0.016	up
NR_104461	PARP11	0.195	3.694	10.763	0.004	0.031	up
NR_109852	LINC-PINT	0.276	3.672	14.440	0.001	0.014	up
NR_110001	LOC101926935	0.758	0.721	15.737	0.001	0.011	up
NR_110458	HAGLR	0.414	3.112	9.810	0.006	0.040	up
NR_111983	CASP8	0.161	4.809	11.884	0.003	0.025	up
NR_120425	MAP3K4	0.191	5.235	17.891	0.001	0.007	up
NR_121191	PGM5-AS1	0.560	1.212	10.273	0.005	0.035	up
NR_121587	LOC101929331	0.633	0.733	12.879	0.002	0.020	up
NR_122113	DUXAP8	0.587	0.745	9.736	0.006	0.040	up
NR_125376	LOC100419583	0.195	5.213	8.904	0.008	0.050	up
NR_126557	LINC01402	0.715	-0.082	10.859	0.004	0.031	up
NR_130929	LOC644285	0.483	3.457	22.068	0.000	0.003	up
NR_131186	LOC105377348	0.547	0.889	9.486	0.007	0.043	up
NR_132426	ACAD11	0.203	6.783	10.699	0.004	0.032	up
NR_132782	SNORA100	0.295	2.947	11.621	0.003	0.026	up
NR_133914	PCF11-AS1	0.617	1.245	13.029	0.002	0.019	up
NR_134525	TTF1	0.167	4.023	10.623	0.004	0.033	up
NR_134654	LOC401261	0.285	2.985	9.377	0.007	0.044	up
NR_134945	BCKDHB	0.253	5.120	12.690	0.002	0.021	up
NR_135143	RSRP1	0.290	6.676	10.561	0.005	0.033	up
NR_135299	C1orf132	0.424	3.726	19.127	0.000	0.006	up
NR_135323	PHF11	0.200	5.088	17.610	0.001	0.007	up
NR_135583	COA1	0.136	5.200	8.973	0.008	0.049	up
NR_135747	NIPAL2	0.203	5.183	13.141	0.002	0.018	up
NR_136326	PNISR	0.271	7.561	17.994	0.001	0.007	up
NR_136662	TIAL1	0.200	6.114	26.019	0.000	0.002	up

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NR_136705	KLF8	0.376	6.316	22.149	0.000	0.003	up
NR_136718	DDX3Y	0.147	6.551	9.989	0.006	0.038	up
NR_136736	MLLT10	0.159	5.563	11.836	0.003	0.025	up
NR_137440	BRE	0.170	5.030	11.920	0.003	0.024	up
NR_137637	ERAP2	0.233	6.279	25.905	0.000	0.002	up
NR_138072	ARRDC3	0.449	5.941	63.169	0.000	0.000	up
NR_138485	CEPT1	0.308	5.515	55.252	0.000	0.000	up
NR_138575	L3HYPDH	0.170	5.406	9.466	0.007	0.043	up
NR_144356	PPIEL	0.266	3.277	14.346	0.001	0.014	up
NR_144378	EMX2OS	0.276	5.397	13.575	0.002	0.017	up
NR_144394	SUZ12P1	0.351	2.884	15.129	0.001	0.012	up
NR_144401	WDR48	0.227	5.880	31.982	0.000	0.001	up
NR_144477	ZKSCAN1	0.174	6.999	10.614	0.004	0.033	up
NR_144931	EPB41L4A	0.220	5.013	11.202	0.004	0.028	up
NM_000017	ACADS	-0.538	6.211	35.138	0.000	0.000	down
NM_000020	ACVRL1	-0.236	6.325	16.367	0.001	0.009	down
NM_000033	ABCD1	-0.527	4.355	76.022	0.000	0.000	down
NM_000086	CLN3	-0.223	4.807	11.515	0.003	0.027	down
NM_000101	CYBA	-0.638	4.799	59.872	0.000	0.000	down
NM_000116	TAZ	-0.194	4.629	15.825	0.001	0.010	down
NM_000118	ENG	-0.250	7.754	9.463	0.007	0.043	down
NM_000152	GAA	-0.532	5.696	72.828	0.000	0.000	down
NM_000154	GALK1	-0.807	2.679	65.768	0.000	0.000	down
NM_000156	GAMT	-0.614	3.357	29.087	0.000	0.001	down
NM_000190	HMBS	-0.251	4.323	10.972	0.004	0.030	down
NM_000199	SGSH	-0.438	5.037	39.748	0.000	0.000	down
NM_000203	IDUA	-0.492	3.235	35.106	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_000229	LCAT	-0.366	3.783	27.262	0.000	0.001	down
NM_000263	NAGLU	-0.376	6.070	29.603	0.000	0.001	down
NM_000285	PEPD	-0.217	6.446	11.658	0.003	0.026	down
NM_000398	CYB5R3	-0.452	9.421	42.773	0.000	0.000	down
NM_000400	ERCC2	-0.316	3.601	20.393	0.000	0.004	down
NM_000402	G6PD	-0.270	5.656	20.486	0.000	0.004	down
NM_000413	HSD17B1	-0.693	1.114	26.682	0.000	0.001	down
NM_000423	KRT2	-10.401	3.724	67.808	0.000	0.001	down
NM_000427	LOR	-7.013	0.998	17.665	0.003	0.022	down
NM_000431	MVK	-0.480	4.213	46.008	0.000	0.000	down
NM_000435	NOTCH3	-0.394	7.574	34.105	0.000	0.000	down
NM_000445	PLEC	-0.671	6.960	76.163	0.000	0.000	down
NM_000455	STK11	-0.480	4.905	52.335	0.000	0.000	down
NM_000476	AK1	-0.178	5.632	9.881	0.006	0.039	down
NM_000485	APRT	-0.461	5.485	53.496	0.000	0.000	down
NM_000487	ARSA	-0.386	5.358	65.847	0.000	0.000	down
NM_000528	MAN2B1	-0.319	6.801	23.975	0.000	0.002	down
NM_000548	TSC2	-0.257	5.863	26.916	0.000	0.001	down
NM_000597	IGFBP2	-0.439	3.903	24.054	0.000	0.002	down
NM_000660	TGFB1	-0.287	4.273	15.975	0.001	0.010	down
NM_000674	ADORA1	-0.392	4.851	17.544	0.001	0.008	down
NM_000694	ALDH3B1	-0.254	3.971	8.981	0.008	0.049	down
NM_000713	BLVRB	-0.415	6.153	41.332	0.000	0.000	down
NM_000754	COMT	-0.529	5.648	96.744	0.000	0.000	down
NM_000820	GAS6	-0.277	6.357	11.273	0.004	0.028	down
NM_000837	GRINA	-0.321	7.630	31.208	0.000	0.001	down
NM_000852	GSTP1	-0.412	7.563	51.807	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_000858	GUK1	-0.628	6.407	81.552	0.000	0.000	down
NM_000873	ICAM2	-0.200	5.576	12.782	0.002	0.020	down
NM_000883	IMPDH1	-0.328	6.085	43.496	0.000	0.000	down
NM_000918	P4HB	-0.174	9.072	9.027	0.008	0.048	down
NM_000941	POR	-0.428	6.253	59.950	0.000	0.000	down
NM_000954	PTGDS	-0.706	4.468	22.894	0.000	0.003	down
NM_000964	RARA	-0.338	4.258	27.736	0.000	0.001	down
NM_000967	RPL3	-0.196	9.782	14.315	0.001	0.014	down
NM_000979	RPL18	-0.184	8.003	12.623	0.002	0.021	down
NM_000981	RPL19	-0.182	9.277	15.592	0.001	0.011	down
NM_000992	RPL29	-0.534	7.636	68.307	0.000	0.000	down
NM_001001410	TSR3	-0.478	4.990	37.685	0.000	0.000	down
NM_001001479	SLC35E4	-0.688	0.867	17.867	0.001	0.007	down
NM_001001520	HDGFRP2	-0.222	4.184	8.916	0.008	0.049	down
NM_001001522	TAGLN	-0.352	8.655	9.556	0.006	0.042	down
NM_001001795	C8orf82	-0.351	3.346	17.038	0.001	0.008	down
NM_001001852	PIM3	-0.767	5.819	126.539	0.000	0.000	down
NM_001002021	PFKL	-0.621	6.630	92.615	0.000	0.000	down
NM_001002034	FAM109B	-0.257	3.906	9.356	0.007	0.044	down
NM_001002836	ZNF787	-0.545	3.244	57.722	0.000	0.000	down
NM_001002913	PTRH1	-0.697	2.095	37.813	0.000	0.000	down
NM_001002914	KCTD11	-0.288	5.094	13.211	0.002	0.018	down
NM_001003	RPLP1	-0.508	8.606	65.078	0.000	0.000	down
NM_001003800	BICD2	-0.168	5.986	14.262	0.001	0.014	down
NM_001003891	MED15	-0.435	5.929	67.397	0.000	0.000	down
NM_001004	RPLP2	-0.335	9.371	26.571	0.000	0.002	down
NM_001004019	FBLN2	-0.377	9.291	17.151	0.001	0.008	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001004125	TUSC1	-0.225	3.447	10.481	0.005	0.034	down
NM_001004431	METRNL	-0.545	4.372	35.673	0.000	0.000	down
NM_001005291	SREBF1	-0.615	7.944	26.456	0.000	0.002	down
NM_001007468	SMARCB1	-0.170	5.165	9.822	0.006	0.039	down
NM_001008404	C14orf180	-0.538	7.395	14.038	0.002	0.015	down
NM_001008701	ADGRL1	-0.389	6.427	20.138	0.000	0.005	down
NM_001008739	C6orf226	-0.836	1.984	26.866	0.000	0.001	down
NM_001009	RPS5	-0.273	7.868	30.979	0.000	0.001	down
NM_001009944	PKD1	-0.739	6.328	173.903	0.000	0.000	down
NM_001010858	RNF187	-0.252	6.315	23.583	0.000	0.002	down
NM_001010866	TMEM201	-0.406	3.034	26.880	0.000	0.001	down
NM_001012426	FOXP4	-0.536	5.333	53.704	0.000	0.000	down
NM_001012614	CTBP1	-0.373	6.414	55.303	0.000	0.000	down
NM_001012973	PLAC9	-0.628	6.008	41.654	0.000	0.000	down
NM_001012984	C16orf86	-0.622	1.817	16.623	0.001	0.009	down
NM_001013251	SLC3A2	-0.224	5.762	12.020	0.003	0.024	down
NM_001013253	LSP1	-0.355	6.401	18.940	0.000	0.006	down
NM_001013842	C8orf58	-0.290	3.502	9.651	0.006	0.041	down
NM_001013845	CXorf40B	-0.285	4.158	18.624	0.000	0.006	down
NM_001014342	FLG2	-10.696	2.704	332.371	0.000	0.000	down
NM_001014440	ODF3B	-0.969	2.770	68.742	0.000	0.000	down
NM_001014764	EMC6	-0.358	3.374	32.542	0.000	0.001	down
NM_001014765	FBXO44	-0.277	3.948	10.141	0.005	0.037	down
NM_001014831	PAK4	-0.534	2.637	30.243	0.000	0.001	down
NM_001015053	HDAC5	-0.233	5.721	19.669	0.000	0.005	down
NM_001017402	LAMB3	-0.367	6.854	18.745	0.000	0.006	down
NM_001017405	MAEA	-0.291	5.256	36.118	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001018	RPS15	-0.321	7.049	35.666	0.000	0.000	down
NM_001018050	POLR3H	-0.350	5.735	31.126	0.000	0.001	down
NM_001018078	FPGS	-0.332	5.902	21.869	0.000	0.003	down
NM_001024679	C1orf68	-7.553	0.032	56.253	0.000	0.003	down
NM_001024943	ASL	-0.298	4.537	26.586	0.000	0.002	down
NM_001025160	ADGRE5	-0.265	5.358	13.676	0.002	0.016	down
NM_001025231	KPRP	-6.990	-0.379	43.432	0.000	0.006	down
NM_001025237	TSPAN4	-0.699	5.839	91.088	0.000	0.000	down
NM_001029882	AHDC1	-0.646	4.179	44.628	0.000	0.000	down
NM_001029885	CPTP	-0.780	3.481	103.084	0.000	0.000	down
NM_001029896	WDR45	-0.174	5.940	13.514	0.002	0.017	down
NM_001031734	FDX1L	-0.222	3.467	10.806	0.004	0.031	down
NM_001031738	TMEM150A	-0.229	4.118	17.859	0.001	0.007	down
NM_001031803	LLGL2	-0.712	1.590	13.685	0.002	0.016	down
NM_001033026	TMEM259	-0.530	6.783	86.301	0.000	0.000	down
NM_001035254	FAM102A	-0.352	4.570	22.995	0.000	0.003	down
NM_001037160	CYS1	-0.645	2.534	9.992	0.006	0.038	down
NM_001037161	ACOT1	-0.281	4.839	11.329	0.004	0.028	down
NM_001037335	HELZ2	-0.495	3.832	53.587	0.000	0.000	down
NM_001037666	GATSL3	-0.533	3.543	19.664	0.000	0.005	down
NM_001037806	NCKAP5L	-0.713	5.049	123.161	0.000	0.000	down
NM_001037984	SLC38A10	-0.620	6.883	85.219	0.000	0.000	down
NM_001039140	C20orf27	-0.474	5.450	33.961	0.000	0.000	down
NM_001039141	TRIOBP	-0.329	6.829	36.459	0.000	0.000	down
NM_001039469	MARK2	-0.300	4.508	42.017	0.000	0.000	down
NM_001039503	PRSS53	-0.550	1.106	11.956	0.003	0.024	down
NM_001039614	C15orf59	-0.773	2.943	47.722	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001039707	SDCCAG3	-0.157	4.546	10.084	0.005	0.037	down
NM_001039792	HRCT1	-0.556	4.304	32.963	0.000	0.001	down
NM_001039803	CDK20	-0.344	2.042	10.550	0.005	0.033	down
NM_001039847	GPX4	-0.402	9.576	31.890	0.000	0.001	down
NM_001039877	STRN4	-0.525	5.845	70.487	0.000	0.000	down
NM_001039999	FAM83G	-0.835	0.529	14.161	0.001	0.015	down
NM_001040125	PQLC2	-0.517	3.524	62.914	0.000	0.000	down
NM_001040167	LFNG	-0.320	4.990	15.806	0.001	0.010	down
NM_001040197	AGTRAP	-0.504	4.004	41.757	0.000	0.000	down
NM_001040427	HAGH	-0.393	5.783	53.871	0.000	0.000	down
NM_001040661	SLC29A4	-0.682	6.477	48.637	0.000	0.000	down
NM_001040694	INCENP	-0.297	3.023	18.560	0.000	0.006	down
NM_001040716	PC	-0.245	7.468	10.751	0.004	0.032	down
NM_001042371	PGP	-0.479	4.070	50.791	0.000	0.000	down
NM_001042454	TGFB1I1	-0.261	4.183	12.973	0.002	0.019	down
NM_001042461	TRAPPC5	-1.145	2.956	109.970	0.000	0.000	down
NM_001042539	MAZ	-0.262	6.374	40.777	0.000	0.000	down
NM_001042573	ENGASE	-0.174	5.442	10.160	0.005	0.037	down
NM_001042576	RRBP1	-0.232	7.338	22.762	0.000	0.003	down
NM_001042633	SNX21	-0.420	6.591	33.319	0.000	0.001	down
NM_001070	TUBG1	-0.204	4.918	12.375	0.003	0.022	down
NM_001077191	GPBAR1	-0.633	3.625	26.071	0.000	0.002	down
NM_001077198	ATG9A	-0.258	6.132	24.534	0.000	0.002	down
NM_001077621	VPS37D	-0.630	0.361	9.465	0.007	0.043	down
NM_001078171	FAM127A	-0.292	6.951	23.283	0.000	0.003	down
NM_001078172	FAM127B	-0.187	5.068	11.300	0.004	0.028	down
NM_001080395	AATK	-0.762	0.653	26.549	0.000	0.002	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001080400	PLIN4	-0.409	13.258	15.347	0.001	0.012	down
NM_001080419	UNK	-0.267	4.134	16.039	0.001	0.010	down
NM_001080424	KDM6B	-0.359	4.491	33.847	0.000	0.001	down
NM_001080436	WTIP	-0.328	4.169	13.296	0.002	0.018	down
NM_001080453	INTS1	-0.598	5.419	114.133	0.000	0.000	down
NM_001080464	ASPG	-1.692	-0.466	16.178	0.001	0.010	down
NM_001080495	TNRC18	-0.531	5.879	127.089	0.000	0.000	down
NM_001080543	CACTIN	-0.506	3.815	52.012	0.000	0.000	down
NM_001080779	MYO1C	-0.219	10.085	11.873	0.003	0.025	down
NM_001080826	PRAG1	-0.325	4.040	8.941	0.008	0.049	down
NM_001081563	DMPK	-0.507	5.870	78.775	0.000	0.000	down
NM_001082486	ACD	-0.272	3.059	9.688	0.006	0.041	down
NM_001082968	TOM1L2	-0.187	6.710	11.745	0.003	0.025	down
NM_001083538	POTEE	-0.444	1.174	9.198	0.007	0.046	down
NM_001083601	NAA60	-0.453	4.856	62.617	0.000	0.000	down
NM_001083613	TMEM219	-0.206	6.506	12.966	0.002	0.019	down
NM_001084	PLOD3	-0.230	5.599	16.113	0.001	0.010	down
NM_001085365	MZT2A	-1.118	1.866	81.429	0.000	0.000	down
NM_001085372	UQCC3	-0.755	3.047	100.204	0.000	0.000	down
NM_001085454	GIT1	-0.408	5.418	48.545	0.000	0.000	down
NM_001089	ABCA3	-0.418	5.166	62.172	0.000	0.000	down
NM_001092	ABR	-0.192	6.680	18.318	0.000	0.006	down
NM_001098201	GPER1	-0.526	4.621	42.242	0.000	0.000	down
NM_001098479	HLA-F	-0.401	5.583	25.786	0.000	0.002	down
NM_001098515	MRGPRF	-0.489	4.442	55.681	0.000	0.000	down
NM_001098537	PNPLA7	-0.410	4.603	39.029	0.000	0.000	down
NM_001098784	FAM89B	-0.527	5.086	134.739	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001098797	TOX2	-0.394	1.666	12.181	0.003	0.023	down
NM_001099737	WDR83	-0.431	2.451	23.898	0.000	0.002	down
NM_001099781	GGT5	-0.306	5.227	15.071	0.001	0.012	down
NM_001100176	HOOK2	-0.333	6.683	9.205	0.007	0.046	down
NM_001100418	C19orf60	-0.652	2.822	51.240	0.000	0.000	down
NM_001100913	PACS2	-0.446	6.281	98.305	0.000	0.000	down
NM_001101	ACTB	-0.210	11.494	12.864	0.002	0.020	down
NM_001105079	FBRS	-0.518	5.262	95.153	0.000	0.000	down
NM_001105203	RUSC1	-0.245	4.653	18.654	0.000	0.006	down
NM_001110556	FLNA	-0.411	10.204	53.990	0.000	0.000	down
NM_001111308	PDE4A	-0.275	5.374	25.729	0.000	0.002	down
NM_001111322	DDX54	-0.498	5.059	55.524	0.000	0.000	down
NM_001113324	TEN1	-0.450	3.800	28.155	0.000	0.001	down
NM_001113756	TYMP	-0.745	5.360	49.936	0.000	0.000	down
NM_001114600	SZRD1	-0.174	7.232	16.232	0.001	0.010	down
NM_001114618	MGAT1	-0.220	7.506	17.645	0.001	0.007	down
NM_001120	MFSD10	-0.637	4.067	102.243	0.000	0.000	down
NM_001122819	KIF17	-0.371	2.409	10.857	0.004	0.031	down
NM_001122823	GTF3C5	-0.227	5.134	23.323	0.000	0.003	down
NM_001122890	GGT6	-5.336	-1.851	20.023	0.003	0.027	down
NM_001122956	DBNL	-0.179	6.570	13.616	0.002	0.017	down
NM_001122957	BCKDK	-0.246	4.821	18.145	0.000	0.007	down
NM_001124758	SPNS2	-0.408	5.135	16.474	0.001	0.009	down
NM_001127198	TMC6	-0.560	4.677	98.193	0.000	0.000	down
NM_001127229	AURKAIP1	-0.524	5.413	63.116	0.000	0.000	down
NM_001127240	BBC3	-0.824	1.644	36.847	0.000	0.000	down
NM_001127266	TMEM129	-0.451	5.796	43.185	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001128225	SLC39A13	-0.612	5.124	118.440	0.000	0.000	down
NM_001128228	TPRN	-0.673	1.855	26.451	0.000	0.002	down
NM_001128425	MUTYH	-0.327	3.100	11.509	0.003	0.027	down
NM_001128844	SMARCA4	-0.171	5.477	12.844	0.002	0.020	down
NM_001128854	SRRT	-0.156	5.987	10.131	0.005	0.037	down
NM_001129727	PLEKHG4	-0.313	4.066	11.234	0.004	0.028	down
NM_001130	AES	-0.438	8.207	61.784	0.000	0.000	down
NM_001130004	ACTN1	-0.166	8.362	10.303	0.005	0.035	down
NM_001130012	SLC9A3R2	-0.715	5.801	72.977	0.000	0.000	down
NM_001130028	CLK3	-0.170	4.979	14.098	0.001	0.015	down
NM_001130144	LTBP3	-0.294	6.448	13.355	0.002	0.018	down
NM_001130413	SCNN1D	-0.713	1.811	22.444	0.000	0.003	down
NM_001130517	MPST	-0.614	4.903	49.917	0.000	0.000	down
NM_001130524	AP1M1	-0.341	6.282	38.445	0.000	0.000	down
NM_001130823	DNMT1	-0.170	5.168	11.006	0.004	0.030	down
NM_001130861	CLDN5	-0.341	5.718	19.366	0.000	0.005	down
NM_001130955	ARHGEF18	-0.283	4.535	30.924	0.000	0.001	down
NM_001130969	NSMF	-0.481	4.977	46.241	0.000	0.000	down
NM_001134231	NT5DC2	-0.247	4.657	28.797	0.000	0.001	down
NM_001134382	IQSEC1	-0.178	7.474	10.639	0.004	0.032	down
NM_001134775	KLC2	-0.377	4.081	21.509	0.000	0.004	down
NM_001134875	C14orf80	-1.050	0.628	28.347	0.000	0.001	down
NM_001135004	DNAJB5	-0.214	4.008	11.051	0.004	0.029	down
NM_001135049	JDP2	-0.285	5.215	13.150	0.002	0.018	down
NM_001135054	SIGIRR	-0.556	3.739	48.342	0.000	0.000	down
NM_001135243	TCOF1	-0.160	5.312	9.831	0.006	0.039	down
NM_001135635	C11orf68	-0.258	5.273	24.732	0.000	0.002	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001135707	ACBD4	-0.289	4.914	15.970	0.001	0.010	down
NM_001135999	RUSC2	-0.368	5.803	54.779	0.000	0.000	down
NM_001136019	FCGRT	-0.275	7.564	19.584	0.000	0.005	down
NM_001136026	SEC13	-0.154	6.701	9.706	0.006	0.041	down
NM_001136035	TRMT1	-0.253	4.502	16.207	0.001	0.010	down
NM_001136037	LIMS2	-0.435	5.835	25.236	0.000	0.002	down
NM_001136053	TPRA1	-0.307	4.530	26.093	0.000	0.002	down
NM_001136108	R3HCC1	-0.357	4.984	26.693	0.000	0.001	down
NM_001136134	RPL28	-0.244	7.686	18.878	0.000	0.006	down
NM_001136203	CCDC124	-0.822	4.459	119.857	0.000	0.000	down
NM_001136263	C2CD4C	-0.768	1.309	21.210	0.000	0.004	down
NM_001136265	IFFO2	-0.457	4.691	19.713	0.000	0.005	down
NM_001136498	CISD3	-0.377	5.034	41.840	0.000	0.000	down
NM_001137601	ZBTB42	-0.770	2.830	70.391	0.000	0.000	down
NM_001142290	MGRN1	-0.317	5.222	50.129	0.000	0.000	down
NM_001142397	CTIF	-0.197	8.140	9.008	0.008	0.048	down
NM_001142500	FLYWCH2	-0.690	3.606	83.349	0.000	0.000	down
NM_001142623	GHDC	-0.305	4.041	18.441	0.000	0.006	down
NM_001142641	FBRSL1	-0.540	3.797	56.711	0.000	0.000	down
NM_001142674	CHID1	-0.185	5.479	9.186	0.007	0.046	down
NM_001142798	C17orf49	-0.182	5.009	9.664	0.006	0.041	down
NM_001142854	SPATC1L	-0.767	0.629	13.150	0.002	0.018	down
NM_001142864	PIEZO1	-0.508	7.268	86.651	0.000	0.000	down
NM_001143944	LEMD2	-0.164	5.307	10.137	0.005	0.037	down
NM_001143993	RASSF7	-1.060	0.849	34.253	0.000	0.000	down
NM_001144026	NDOR1	-0.637	3.711	38.255	0.000	0.000	down
NM_001144759	PHLDB1	-0.302	8.944	14.321	0.001	0.014	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001144825	RUNDC3A	-2.430	-2.431	9.379	0.008	0.047	down
NM_001144856	PLEKHG6	-0.511	5.438	15.182	0.001	0.012	down
NM_001144996	ITGA7	-0.234	9.626	9.881	0.006	0.039	down
NM_001145018	CCDC153	-0.439	0.851	10.480	0.005	0.034	down
NM_001145023	SCRN2	-0.470	7.071	41.677	0.000	0.000	down
NM_001145165	DOHH	-0.935	2.433	74.364	0.000	0.000	down
NM_001145437	LSS	-0.367	7.558	25.552	0.000	0.002	down
NM_001145463	YIF1B	-0.403	4.115	32.135	0.000	0.001	down
NM_001145638	GPSM1	-0.553	2.464	28.572	0.000	0.001	down
NM_001145809	MYH14	-0.340	5.881	16.504	0.001	0.009	down
NM_001145815	AMDHD2	-0.664	3.651	61.841	0.000	0.000	down
NM_001145853	WFS1	-0.318	6.337	28.449	0.000	0.001	down
NM_001146151	AVPR2	-0.610	2.777	30.892	0.000	0.001	down
NM_001146175	ZNF414	-0.880	1.773	32.342	0.000	0.001	down
NM_001161344	CHFR	-0.203	4.281	11.092	0.004	0.029	down
NM_001161357	FCHO1	-0.787	1.057	24.275	0.000	0.002	down
NM_001162383	ARHGEF2	-0.166	6.952	11.258	0.004	0.028	down
NM_001163257	PLXNB3	-0.547	3.527	21.841	0.000	0.003	down
NM_001163809	WDR81	-0.428	5.220	47.021	0.000	0.000	down
NM_001164	APBB1	-0.237	4.760	15.364	0.001	0.011	down
NM_001164189	PLIN3	-0.393	5.606	10.953	0.004	0.030	down
NM_001164692	LTB4R2	-0.438	1.887	9.995	0.006	0.038	down
NM_001164741	ARHGAP4	-0.532	4.368	57.619	0.000	0.000	down
NM_001164783	BCKDHA	-0.213	5.220	9.536	0.006	0.042	down
NM_001166034	SBSN	-6.358	2.280	12.021	0.004	0.032	down
NM_001166102	NDUFV1	-0.393	6.739	53.216	0.000	0.000	down
NM_001166111	PNPLA6	-0.486	4.783	44.843	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001166237	GSDMD	-0.420	4.420	28.305	0.000	0.001	down
NM_001166286	RGMA	-0.509	3.422	28.488	0.000	0.001	down
NM_001166426	WDR13	-0.411	5.458	45.876	0.000	0.000	down
NM_001167676	FAM229A	-2.228	-1.978	10.813	0.004	0.031	down
NM_001167947	TIMM17B	-0.358	4.220	23.246	0.000	0.003	down
NM_001168243	C4orf48	-2.064	-1.686	11.415	0.004	0.028	down
NM_001169111	SCO2	-0.642	3.812	66.932	0.000	0.000	down
NM_001170535	ATAD3A	-0.692	3.294	50.010	0.000	0.000	down
NM_001170543	PGAM5	-0.197	4.516	9.878	0.006	0.039	down
NM_001170719	BCAR1	-0.767	4.022	78.371	0.000	0.000	down
NM_001170820	IFITM10	-0.675	2.776	11.958	0.003	0.024	down
NM_001170880	GPR137	-0.408	3.605	33.441	0.000	0.001	down
NM_001171816	RNF166	-0.608	3.297	65.733	0.000	0.000	down
NM_001171868	TMEM200B	-0.490	6.303	12.530	0.002	0.021	down
NM_001171909	CXorf40A	-0.209	4.404	12.477	0.002	0.022	down
NM_001171948	KXD1	-0.174	6.167	16.947	0.001	0.008	down
NM_001172630	ARHGAP33	-0.472	2.688	27.734	0.000	0.001	down
NM_001172659	ZFYVE28	-0.549	2.594	38.906	0.000	0.000	down
NM_001172663	RAB40C	-0.668	3.611	67.611	0.000	0.000	down
NM_001172688	GGA1	-0.435	5.217	72.046	0.000	0.000	down
NM_001173431	OBSL1	-0.465	5.688	33.708	0.000	0.001	down
NM_001173988	RABL6	-0.512	5.839	77.174	0.000	0.000	down
NM_001174100	PCBP4	-0.326	4.976	28.744	0.000	0.001	down
NM_001177802	RANGRF	-0.168	4.746	11.125	0.004	0.029	down
NM_001177996	FAM109A	-0.409	3.291	22.740	0.000	0.003	down
NM_001184975	PACSIN3	-0.598	3.168	39.103	0.000	0.000	down
NM_001185011	NCAPH2	-0.408	4.948	47.756	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001188	BAK1	-0.251	3.511	9.220	0.007	0.046	down
NM_001190716	DNM2	-0.269	6.667	40.966	0.000	0.000	down
NM_001193333	CORO1A	-0.711	3.944	49.188	0.000	0.000	down
NM_001193388	UNKL	-0.267	5.109	18.951	0.000	0.006	down
NM_001193452	NUDT16L1	-0.329	3.896	18.029	0.001	0.007	down
NM_001193524	FAM65A	-0.324	6.181	40.424	0.000	0.000	down
NM_001193646	ATF5	-0.498	5.895	36.222	0.000	0.000	down
NM_001193655	C17orf62	-0.244	5.116	20.689	0.000	0.004	down
NM_001195001	PTPRU	-0.359	4.895	27.789	0.000	0.001	down
NM_001195056	DDIT3	-0.289	5.284	12.775	0.002	0.020	down
NM_001195072	TMEM184B	-0.346	6.527	44.974	0.000	0.000	down
NM_001195381	GPR35	-0.685	0.030	10.961	0.004	0.030	down
NM_001195605	ZNF865	-0.462	3.177	28.598	0.000	0.001	down
NM_001195736	FAM213B	-0.299	4.265	20.175	0.000	0.005	down
NM_001195753	THAP3	-0.322	3.964	25.686	0.000	0.002	down
NM_001196	BID	-0.243	4.006	11.606	0.003	0.026	down
NM_001197181	TUBB3	-1.522	-0.494	18.848	0.000	0.006	down
NM_001198690	PPAN-P2RY11	-0.524	3.673	44.194	0.000	0.000	down
NM_001198869	CAPN1	-0.393	6.269	58.868	0.000	0.000	down
NM_001198994	NADK	-0.218	6.331	18.905	0.000	0.006	down
NM_001199039	SERINC2	-0.642	2.904	28.285	0.000	0.001	down
NM_001199107	TBC1D24	-0.238	4.603	14.324	0.001	0.014	down
NM_001199120	RPP21	-0.400	2.846	16.345	0.001	0.009	down
NM_001199173	MLST8	-0.663	4.213	57.330	0.000	0.000	down
NM_001199196	ARMC6	-0.483	4.327	49.308	0.000	0.000	down
NM_001199281	CABIN1	-0.309	5.288	33.463	0.000	0.001	down
NM_001199417	ARHGAP23	-0.288	5.241	11.272	0.004	0.028	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001199580	SUN2	-0.310	8.390	26.747	0.000	0.001	down
NM_001199867	MARK4	-0.228	4.285	12.916	0.002	0.019	down
NM_001200016	NAT6	-0.396	2.997	17.248	0.001	0.008	down
NM_001201459	ZNF513	-0.445	3.975	30.878	0.000	0.001	down
NM_001201479	CORO7-PAM16	-0.573	4.090	70.502	0.000	0.000	down
NM_001201552	ZNF821	-0.321	2.461	12.237	0.003	0.023	down
NM_001203260	NDUFC2-KCTD14	-0.355	5.754	32.948	0.000	0.001	down
NM_001204240	TBC1D10A	-0.462	4.533	34.416	0.000	0.000	down
NM_001204299	ZNF664-RFLNA	-0.387	1.858	9.037	0.008	0.048	down
NM_001204527	SSR4	-0.202	5.634	10.285	0.005	0.035	down
NM_001204872	NPEPL1	-0.397	5.687	53.191	0.000	0.000	down
NM_001204887	RAB43	-0.517	3.007	35.022	0.000	0.000	down
NM_001206670	PLA2G4E	-4.791	-1.636	13.979	0.008	0.049	down
NM_001206951	SLC16A3	-0.557	2.738	13.946	0.002	0.015	down
NM_001207011	CNTFR	-0.524	5.838	51.665	0.000	0.000	down
NM_001214906	ZNF48	-0.487	2.359	20.547	0.000	0.004	down
NM_001215	CA6	-7.083	-0.672	35.882	0.001	0.008	down
NM_001242369	CACFD1	-0.749	2.558	33.628	0.000	0.001	down
NM_001242820	DEF8	-0.279	5.591	23.704	0.000	0.002	down
NM_001242898	PPP6R2	-0.315	5.727	69.454	0.000	0.000	down
NM_001243177	ALDOA	-0.358	9.605	34.577	0.000	0.000	down
NM_001243247	NPRL3	-0.265	4.670	19.372	0.000	0.005	down
NM_001245002	NFIC	-0.260	7.596	21.123	0.000	0.004	down
NM_001251888	ASPSCR1	-0.593	3.551	58.709	0.000	0.000	down
NM_001252039	RAB5C	-0.176	7.466	18.553	0.000	0.006	down
NM_001252197	IRX5	-0.763	2.244	25.432	0.000	0.002	down
NM_001252406	ZBTB7B	-0.516	6.649	55.399	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001253792	ZNF444	-0.318	3.248	18.150	0.000	0.007	down
NM_001254757	ST3GAL4	-0.239	4.550	14.099	0.001	0.015	down
NM_001256182	ANKRD11	-0.214	6.032	31.894	0.000	0.001	down
NM_001256269	KIF22	-0.427	4.148	32.069	0.000	0.001	down
NM_001256456	INTS11	-0.317	5.399	36.953	0.000	0.000	down
NM_001256494	MAN2C1	-0.313	6.873	39.388	0.000	0.000	down
NM_001256530	TSPO	-0.754	6.240	68.647	0.000	0.000	down
NM_001256617	TUBGCP2	-0.208	5.582	24.148	0.000	0.002	down
NM_001256964	CCDC51	-0.199	4.120	10.289	0.005	0.035	down
NM_001257360	AMPD2	-0.310	4.555	16.829	0.001	0.009	down
NM_001257370	EME2	-1.455	-0.287	19.540	0.000	0.005	down
NM_001257975	CIZ1	-0.257	6.598	27.857	0.000	0.001	down
NM_001258373	SPATA20	-0.400	5.679	44.209	0.000	0.000	down
NM_001261	CDK9	-0.171	5.799	16.325	0.001	0.009	down
NM_001261403	NFKB2	-0.237	4.519	10.549	0.005	0.033	down
NM_001261826	AP3D1	-0.212	6.646	19.408	0.000	0.005	down
NM_001265582	URM1	-0.163	5.886	15.467	0.001	0.011	down
NM_001267549	ARFRP1	-0.505	4.919	71.465	0.000	0.000	down
NM_001267552	PEMT	-0.611	6.348	58.174	0.000	0.000	down
NM_001267723	CCDC61	-0.435	2.549	23.246	0.000	0.003	down
NM_001268284	LRRC8E	-0.763	0.850	19.505	0.000	0.005	down
NM_001270550	MDK	-0.403	3.235	15.270	0.001	0.012	down
NM_001270639	JOSD2	-1.060	2.480	82.690	0.000	0.000	down
NM_001270691	SMOX	-0.524	1.987	16.400	0.001	0.009	down
NM_001270888	SLC25A10	-0.502	5.230	19.875	0.000	0.005	down
NM_001271044	NFIX	-0.214	8.108	9.989	0.006	0.038	down
NM_001271098	PUF60	-0.367	6.349	55.413	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001271441	C21orf2	-0.704	3.614	54.231	0.000	0.000	down
NM_001271610	STX10	-0.247	4.880	17.657	0.001	0.007	down
NM_001271765	SLC16A5	-0.317	2.697	9.517	0.007	0.042	down
NM_001271818	ORAI2	-0.269	4.602	9.205	0.007	0.046	down
NM_001271875	CUEDC1	-0.373	5.615	34.250	0.000	0.000	down
NM_001271938	MEGF8	-0.240	6.833	15.480	0.001	0.011	down
NM_001271944	TFEB	-0.675	3.583	40.201	0.000	0.000	down
NM_001271977	STK25	-0.274	6.218	45.552	0.000	0.000	down
NM_001272036	LRRC14	-0.403	4.369	50.209	0.000	0.000	down
NM_001272051	C16orf91	-0.555	2.818	29.614	0.000	0.001	down
NM_001272083	SHISA5	-0.285	6.853	47.541	0.000	0.000	down
NM_001276252	WDTC1	-0.148	6.007	10.540	0.005	0.033	down
NM_001276319	NOL3	-0.246	5.706	13.285	0.002	0.018	down
NM_001277764	CIB1	-0.213	5.631	17.083	0.001	0.008	down
NM_001278158	ZNF205	-0.651	2.399	53.964	0.000	0.000	down
NM_001278195	TEX264	-0.287	5.085	28.275	0.000	0.001	down
NM_001278529	ARHGEF40	-0.239	8.094	13.871	0.002	0.016	down
NM_001278559	ZNF316	-0.206	5.202	19.018	0.000	0.006	down
NM_001278651	RANGAP1	-0.270	5.592	29.834	0.000	0.001	down
NM_001278669	NFATC1	-0.281	3.915	16.267	0.001	0.010	down
NM_001280561	TMEM249	-0.629	0.088	9.189	0.007	0.046	down
NM_001280794	EPHB6	-0.375	4.153	13.914	0.002	0.016	down
NM_001281	TBCB	-0.183	5.245	16.250	0.001	0.010	down
NM_001281297	EDF1	-0.268	6.962	34.031	0.000	0.000	down
NM_001281444	PKIG	-0.208	5.533	12.039	0.003	0.024	down
NM_001281453	MBD3	-1.091	5.332	177.422	0.000	0.000	down
NM_001281460	SLC35C2	-0.291	5.145	13.414	0.002	0.017	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001281482	ARFGAP1	-0.571	5.315	64.367	0.000	0.000	down
NM_001281504	ATG4D	-0.545	2.942	42.670	0.000	0.000	down
NM_001282144	NLRX1	-0.374	5.118	23.598	0.000	0.002	down
NM_001282176	CLPTM1	-0.167	6.283	9.929	0.006	0.039	down
NM_001282290	ARHGAP27	-0.327	4.859	26.284	0.000	0.002	down
NM_001282291	ABCB8	-0.383	4.469	40.673	0.000	0.000	down
NM_001282311	FAM3A	-0.448	4.930	36.034	0.000	0.000	down
NM_001282328	PES1	-0.173	5.396	12.481	0.002	0.022	down
NM_001282351	FBXL19	-0.560	2.707	31.224	0.000	0.001	down
NM_001282434	HES6	-0.669	0.504	12.143	0.003	0.023	down
NM_001282533	LZTS3	-0.288	3.547	17.311	0.001	0.008	down
NM_001282662	MKL1	-0.226	4.729	14.666	0.001	0.013	down
NM_001282670	FAAP20	-0.794	2.772	43.860	0.000	0.000	down
NM_001283009	RTEL1	-0.280	4.024	11.720	0.003	0.026	down
NM_001284251	GUCD1	-0.229	7.477	15.216	0.001	0.012	down
NM_001284260	WDR86	-0.910	0.252	17.072	0.001	0.008	down
NM_001284351	SLC9A3	-0.726	1.028	28.879	0.000	0.001	down
NM_001284497	FAM234A	-0.424	6.556	38.714	0.000	0.000	down
NM_001284498	SLC43A2	-0.330	5.096	17.429	0.001	0.008	down
NM_001284501	NUBP2	-0.991	4.101	108.262	0.000	0.000	down
NM_001285829	CEBPA	-0.518	8.856	20.631	0.000	0.004	down
NM_001285878	CEBPB	-0.494	5.903	25.475	0.000	0.002	down
NM_001286134	RIC8A	-0.178	6.595	20.881	0.000	0.004	down
NM_001286205	GAS8	-0.201	4.182	12.115	0.003	0.023	down
NM_001286435	NME4	-0.392	7.159	27.588	0.000	0.001	down
NM_001286464	BAIAP3	-0.562	2.130	27.551	0.000	0.001	down
NM_001286499	PIF1	-0.766	0.208	11.073	0.004	0.029	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001286572	RNF40	-0.194	6.303	17.554	0.001	0.008	down
NM_001286581	PHRF1	-0.527	4.869	100.184	0.000	0.000	down
NM_001286606	CRACR2B	-0.808	3.233	80.856	0.000	0.000	down
NM_001286798	NTMT1	-0.387	3.852	24.085	0.000	0.002	down
NM_001286968	JUND	-0.249	6.156	12.485	0.002	0.021	down
NM_001287	CLCN7	-0.628	5.562	79.559	0.000	0.000	down
NM_001287427	CCND3	-0.267	5.358	14.080	0.002	0.015	down
NM_001287603	ZBTB17	-0.549	3.811	64.102	0.000	0.000	down
NM_001288708	DBNDD1	-0.567	2.501	16.995	0.001	0.008	down
NM_001288723	B3GAT3	-0.488	4.517	49.479	0.000	0.000	down
NM_001288794	RMND5B	-0.163	5.024	9.687	0.006	0.041	down
NM_001288805	ZNF707	-0.267	2.838	9.619	0.006	0.041	down
NM_001288962	TRIP10	-0.234	7.070	13.215	0.002	0.018	down
NM_001289103	PRKCSH	-0.255	6.778	24.351	0.000	0.002	down
NM_001289419	ANAPC11	-0.559	5.048	50.636	0.000	0.000	down
NM_001289824	FURIN	-0.498	7.046	69.704	0.000	0.000	down
NM_001289912	LOC400927-CSNK1E	-0.261	6.364	30.548	0.000	0.001	down
NM_001289922	C22orf34	-0.558	1.098	9.979	0.006	0.038	down
NM_001289933	ZASP	-1.025	0.551	21.438	0.000	0.004	down
NM_001290002	ZNF385A	-0.372	6.384	22.457	0.000	0.003	down
NM_001290076	URGCP	-0.157	5.526	10.706	0.004	0.032	down
NM_001290149	C19orf48	-0.608	3.484	30.615	0.000	0.001	down
NM_001291324	BAHCC1	-0.589	4.565	39.244	0.000	0.000	down
NM_001291428	BAX	-0.270	3.682	9.962	0.006	0.038	down
NM_001291780	RBM38	-0.767	3.512	72.552	0.000	0.000	down
NM_001291860	HSPG2	-0.433	10.084	79.486	0.000	0.000	down
NM_001291920	RXRA	-0.414	7.618	54.707	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001291931	TSNARE1	-0.414	3.112	40.932	0.000	0.000	down
NM_001294335	ADGRB2	-0.748	2.889	31.076	0.000	0.001	down
NM_001294340	ZC3H18	-0.182	4.868	11.683	0.003	0.026	down
NM_001294341	MFSD7	-0.369	3.350	24.357	0.000	0.002	down
NM_001297427	TMEM175	-0.408	4.042	25.424	0.000	0.002	down
NM_001297556	MAP2K7	-0.395	4.849	56.185	0.000	0.000	down
NM_001297658	TSSC4	-0.948	3.986	138.266	0.000	0.000	down
NM_001297760	ETNK2	-0.571	2.693	9.425	0.007	0.043	down
NM_001300804	MDFI	-0.654	5.207	24.102	0.000	0.002	down
NM_001300854	DCD	-11.144	4.709	90.810	0.000	0.000	down
NM_001300862	MPND	-0.329	3.330	11.931	0.003	0.024	down
NM_001300868	SLC29A2	-0.541	3.362	12.782	0.002	0.020	down
NM_001300900	MRPS34	-0.425	4.946	50.708	0.000	0.000	down
NM_001300946	GATAD2A	-0.373	5.641	47.801	0.000	0.000	down
NM_001301020	OAZ1	-0.325	8.648	34.147	0.000	0.000	down
NM_001301061	BCL7B	-0.247	6.250	30.745	0.000	0.001	down
NM_001301078	AP2S1	-0.224	5.655	14.444	0.001	0.014	down
NM_001301129	POLR2F	-0.272	4.439	18.105	0.000	0.007	down
NM_001301132	BAHD1	-0.185	4.758	13.249	0.002	0.018	down
NM_001301243	ARHGDIA	-0.615	7.325	110.973	0.000	0.000	down
NM_001301782	LENG9	-0.464	1.186	11.239	0.004	0.028	down
NM_001301838	C12orf57	-0.634	5.126	76.717	0.000	0.000	down
NM_001302545	AAMP	-0.218	7.056	18.873	0.000	0.006	down
NM_001302691	APOE	-0.716	6.875	36.139	0.000	0.000	down
NM_001303007	DDAH2	-0.411	7.052	44.099	0.000	0.000	down
NM_001303024	SSSCA1	-0.622	3.141	32.496	0.000	0.001	down
NM_001303100	ERICH1	-0.222	3.745	8.944	0.008	0.049	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001303437	HEXIM2	-0.403	2.486	12.462	0.002	0.022	down
NM_001303501	CNN2	-0.246	6.818	11.427	0.003	0.027	down
NM_001303506	PPP4C	-0.255	5.426	19.516	0.000	0.005	down
NM_001303530	TUBB6	-0.262	8.060	14.893	0.001	0.013	down
NM_001304461	SERPINA12	-7.852	0.255	66.626	0.000	0.002	down
NM_001304547	MVB12A	-0.426	4.501	44.501	0.000	0.000	down
NM_001304722	PLEKHO1	-0.263	5.059	17.296	0.001	0.008	down
NM_001304762	EVA1B	-1.010	1.554	30.460	0.000	0.001	down
NM_001304763	ZNF687	-0.302	4.575	43.904	0.000	0.000	down
NM_001304799	NARFL	-0.458	3.757	34.158	0.000	0.000	down
NM_001304808	BRD1	-0.272	4.890	20.931	0.000	0.004	down
NM_001304815	CIC	-0.594	5.639	108.668	0.000	0.000	down
NM_001304835	OGFOD2	-0.398	3.213	19.552	0.000	0.005	down
NM_001304958	CCDC92	-0.195	6.193	10.797	0.004	0.031	down
NM_001304993	SDSL	-0.457	2.562	16.329	0.001	0.009	down
NM_001304999	OXLD1	-0.388	3.905	24.388	0.000	0.002	down
NM_001305141	NMRAL1	-0.305	3.687	13.036	0.002	0.019	down
NM_001305275	AGRN	-0.594	4.403	34.152	0.000	0.000	down
NM_001305654	LIME1	-0.864	2.061	62.952	0.000	0.000	down
NM_001306085	ATP9B	-0.177	4.446	9.380	0.007	0.044	down
NM_001307980	DNAJC4	-0.365	4.282	33.568	0.000	0.001	down
NM_001308068	FLYWCH1	-0.596	4.886	59.451	0.000	0.000	down
NM_001308090	HDAC7	-0.213	6.729	10.142	0.005	0.037	down
NM_001308147	PLEKHG3	-0.306	4.957	20.319	0.000	0.004	down
NM_001308240	C19orf70	-0.606	5.132	105.294	0.000	0.000	down
NM_001308370	ESPNL	-0.927	0.540	16.287	0.001	0.010	down
NM_001308632	POLD1	-0.840	2.357	37.235	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001309242	MYO15B	-0.327	6.233	14.769	0.001	0.013	down
NM_001310315	TUBB2A	-0.325	6.579	10.179	0.005	0.036	down
NM_001310321	MFGE8	-0.233	7.174	20.819	0.000	0.004	down
NM_001312	CRIP2	-0.590	5.199	31.809	0.000	0.001	down
NM_001316307	RAC3	-0.725	3.188	25.487	0.000	0.002	down
NM_001316321	CCDC57	-0.293	3.888	15.125	0.001	0.012	down
NM_001316327	PRKCD	-0.304	7.118	9.845	0.006	0.039	down
NM_001316332	MAP2K3	-0.499	5.540	22.749	0.000	0.003	down
NM_001316766	C2orf81	-0.799	0.003	17.072	0.001	0.008	down
NM_001316938	FBXL12	-0.211	3.980	10.475	0.005	0.034	down
NM_001316978	ZBTB45	-0.574	2.785	42.773	0.000	0.000	down
NM_001317007	S100A16	-0.219	6.617	14.441	0.001	0.014	down
NM_001317199	CXXC5	-0.571	5.687	38.208	0.000	0.000	down
NM_001317238	ATAD3B	-0.619	3.369	31.633	0.000	0.001	down
NM_001317782	RPL8	-0.224	8.905	19.398	0.000	0.005	down
NM_001317895	PARP10	-0.730	5.287	161.814	0.000	0.000	down
NM_001317950	AKNA	-0.261	5.256	13.694	0.002	0.016	down
NM_001317968	ARRDC1	-0.473	3.254	24.017	0.000	0.002	down
NM_001318016	ZDHHC12	-0.842	3.497	76.428	0.000	0.000	down
NM_001318087	SMPD1	-0.171	5.419	9.266	0.007	0.045	down
NM_001318099	LZTS2	-0.568	6.385	82.201	0.000	0.000	down
NM_001318202	FHOD1	-0.399	5.727	43.904	0.000	0.000	down
NM_001318217	TMEM208	-0.194	4.511	8.903	0.008	0.050	down
NM_001318234	SNPH	-0.488	3.120	43.145	0.000	0.000	down
NM_001318236	LAMTOR4	-0.378	5.846	34.754	0.000	0.000	down
NM_001318252	C7orf50	-0.709	4.586	50.091	0.000	0.000	down
NM_001318477	TSKU	-0.553	7.667	12.065	0.003	0.024	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001318480	SH3TC1	-0.644	3.295	33.805	0.000	0.001	down
NM_001318507	CTU2	-0.747	2.629	80.672	0.000	0.000	down
NM_001318711	KIFC3	-0.668	5.018	81.603	0.000	0.000	down
NM_001318733	RHBDL1	-1.234	-0.639	12.801	0.002	0.020	down
NM_001318821	PDDC1	-0.233	5.907	37.036	0.000	0.000	down
NM_001318833	EHMT2	-0.198	5.318	10.408	0.005	0.034	down
NM_001318853	OPRL1	-0.535	1.513	10.515	0.005	0.033	down
NM_001318867	DOK1	-0.427	6.060	28.908	0.000	0.001	down
NM_001318878	STK32C	-0.501	2.844	34.776	0.000	0.000	down
NM_001318918	GLIS2	-0.879	3.489	49.882	0.000	0.000	down
NM_001319	CSNK1G2	-0.769	4.826	162.031	0.000	0.000	down
NM_001319085	ARID5A	-0.293	3.453	9.612	0.006	0.041	down
NM_001319119	DNPEP	-0.170	6.146	10.194	0.005	0.036	down
NM_001319170	DPH2	-0.234	4.429	14.357	0.001	0.014	down
NM_001319302	RILPL1	-0.216	4.271	14.948	0.001	0.013	down
NM_001319670	SPSB2	-0.535	2.390	14.686	0.001	0.013	down
NM_001320038	LOC730098	-0.490	1.006	11.857	0.003	0.025	down
NM_001320247	IGSF8	-0.620	4.873	56.050	0.000	0.000	down
NM_001320309	IMP4	-0.263	5.502	34.115	0.000	0.000	down
NM_001320327	CHCHD2	-0.190	6.564	13.150	0.002	0.018	down
NM_001320444	TMEM102	-0.452	0.815	9.388	0.007	0.044	down
NM_001320484	TRABD	-0.790	3.495	112.560	0.000	0.000	down
NM_001320566	CCDC130	-0.539	4.181	55.295	0.000	0.000	down
NM_001320747	EVPL	-0.964	0.497	9.566	0.006	0.042	down
NM_001320905	DTYMK	-0.347	3.987	19.182	0.000	0.005	down
NM_001321089	GPS1	-0.414	5.843	51.542	0.000	0.000	down
NM_001321102	TRAPPC12	-0.284	4.863	20.542	0.000	0.004	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001321149	TMEM94	-0.180	5.830	15.690	0.001	0.011	down
NM_001321190	RUVBL2	-0.413	4.571	40.023	0.000	0.000	down
NM_001321241	SLC25A39	-0.437	5.995	51.928	0.000	0.000	down
NM_001321263	EPN1	-0.581	5.511	95.916	0.000	0.000	down
NM_001321439	YIPF2	-0.601	4.311	68.803	0.000	0.000	down
NM_001321463	NCLN	-0.653	5.151	97.637	0.000	0.000	down
NM_001321484	RPS19	-0.184	7.928	10.336	0.005	0.035	down
NM_001322141	TANGO2	-0.166	5.525	10.321	0.005	0.035	down
NM_001322397	ENTPD6	-0.311	5.730	60.323	0.000	0.000	down
NM_001322464	SH3BP5L	-0.198	5.106	18.440	0.000	0.006	down
NM_001322487	HPS1	-0.256	5.905	25.429	0.000	0.002	down
NM_001323551	ZC3H12A	-0.692	2.628	28.707	0.000	0.001	down
NM_001323552	TRADD	-0.285	4.214	23.982	0.000	0.002	down
NM_001323627	ZDHHC1	-0.528	3.132	35.984	0.000	0.000	down
NM_001324086	RPUSD1	-0.964	2.800	51.220	0.000	0.000	down
NM_001324229	STOML1	-0.646	4.271	52.919	0.000	0.000	down
NM_001324309	KLHL21	-0.315	6.670	21.746	0.000	0.003	down
NM_001326416	PISD	-0.342	6.889	14.619	0.001	0.013	down
NM_001326609	AIMP2	-0.260	4.582	15.024	0.001	0.012	down
NM_001329444	PPP1R16A	-0.913	3.609	77.421	0.000	0.000	down
NM_001329544	PTDSS2	-0.381	4.217	27.912	0.000	0.001	down
NM_001329722	TMEM54	-0.483	3.456	15.644	0.001	0.011	down
NM_001330120	SNCG	-0.361	7.564	9.152	0.007	0.047	down
NM_001330236	LOC107984640	-2.057	-1.727	10.373	0.005	0.036	down
NM_001330282	MZT2B	-0.949	3.483	83.082	0.000	0.000	down
NM_001330306	C1orf159	-0.887	2.099	77.572	0.000	0.000	down
NM_001330311	DVL1	-0.840	5.017	165.089	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001330395	WIZ	-0.500	5.570	83.473	0.000	0.000	down
NM_001330400	SFXN5	-0.260	3.566	12.468	0.002	0.022	down
NM_001330466	SLC8B1	-0.288	5.685	11.602	0.003	0.026	down
NM_001330469	COPE	-0.643	5.623	71.525	0.000	0.000	down
NM_001330518	PCYT2	-0.320	5.596	23.073	0.000	0.003	down
NM_001330536	CENPX	-0.409	4.218	41.403	0.000	0.000	down
NM_001330990	DHX30	-0.291	5.712	38.220	0.000	0.000	down
NM_001331039	TRMT2A	-0.550	4.958	91.875	0.000	0.000	down
NM_001345970	ZNF629	-0.264	5.209	12.108	0.003	0.023	down
NM_001346082	TP53I13	-0.777	5.110	70.208	0.000	0.000	down
NM_001346116	PUSL1	-0.606	2.241	28.350	0.000	0.001	down
NM_001346186	RHBDD2	-0.339	5.500	21.564	0.000	0.004	down
NM_001347	DGKQ	-0.544	3.539	37.011	0.000	0.000	down
NM_001348	DAPK3	-0.583	4.466	113.661	0.000	0.000	down
NM_001407	CELSR3	-0.607	1.504	15.335	0.001	0.012	down
NM_001519	BRF1	-0.603	4.544	75.066	0.000	0.000	down
NM_001540	HSPB1	-0.630	6.716	103.104	0.000	0.000	down
NM_001541	HSPB2	-0.386	5.553	25.059	0.000	0.002	down
NM_001567	INPPL1	-0.278	6.629	39.524	0.000	0.000	down
NM_001569	IRAK1	-0.451	6.399	80.682	0.000	0.000	down
NM_001606	ABCA2	-0.475	6.235	57.572	0.000	0.000	down
NM_001614	ACTG1	-0.251	10.264	14.070	0.002	0.015	down
NM_001619	GRK2	-0.452	5.753	68.513	0.000	0.000	down
NM_001626	AKT2	-0.307	8.311	13.958	0.002	0.015	down
NM_001654	ARAF	-0.182	5.925	13.854	0.002	0.016	down
NM_001658	ARF1	-0.236	8.227	22.575	0.000	0.003	down
NM_001662	ARF5	-0.306	6.164	24.514	0.000	0.002	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_001665	RHOG	-0.262	5.171	22.864	0.000	0.003	down
NM_001667	ARL2	-0.271	6.103	14.621	0.001	0.013	down
NM_001670	ARVCF	-0.774	2.747	40.641	0.000	0.000	down
NM_001687	ATP5D	-0.926	4.238	102.237	0.000	0.000	down
NM_001694	ATP6V0C	-0.282	5.651	25.478	0.000	0.002	down
NM_001728	BSG	-0.508	8.234	67.764	0.000	0.000	down
NM_001761	CCNF	-0.391	2.016	8.864	0.008	0.050	down
NM_001810	CENPB	-0.492	6.656	101.843	0.000	0.000	down
NM_001823	CKB	-0.275	5.714	10.666	0.004	0.032	down
NM_001846	COL4A2	-0.326	10.352	28.099	0.000	0.001	down
NM_001848	COL6A1	-0.481	9.702	34.126	0.000	0.000	down
NM_001849	COL6A2	-0.759	9.304	60.359	0.000	0.000	down
NM_001856	COL16A1	-0.357	6.142	22.604	0.000	0.003	down
NM_001864	COX7A1	-0.240	6.599	12.406	0.003	0.022	down
NM_001897	CSPG4	-0.364	7.514	30.345	0.000	0.001	down
NM_001909	CTSD	-0.600	8.902	60.036	0.000	0.000	down
NM_001916	CYC1	-0.291	6.279	33.031	0.000	0.001	down
NM_001919	ECI1	-0.564	4.371	30.870	0.000	0.001	down
NM_001928	CFD	-0.351	8.444	17.589	0.001	0.007	down
NM_001940	ATN1	-0.288	7.522	52.852	0.000	0.000	down
NM_001944	DSG3	-4.845	-2.108	14.438	0.007	0.047	down
NM_001950	E2F4	-0.180	5.834	18.018	0.001	0.007	down
NM_001961	EEF2	-0.348	10.780	27.511	0.000	0.001	down
NM_001970	EIF5A	-0.231	7.365	20.932	0.000	0.004	down
NM_001983	ERCC1	-0.254	6.001	19.774	0.000	0.005	down
NM_001985	ETFB	-0.478	7.013	48.738	0.000	0.000	down
NM_001997	FAU	-0.350	7.324	43.564	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_002005	FES	-0.317	4.552	30.923	0.000	0.001	down
NM_002016	FLG	-8.479	2.087	27.699	0.001	0.010	down
NM_002018	FLII	-0.149	7.507	13.385	0.002	0.018	down
NM_002046	GAPDH	-0.188	9.624	15.876	0.001	0.010	down
NM_002051	GATA3	-0.449	2.815	14.102	0.001	0.015	down
NM_002067	GNA11	-0.608	5.967	162.451	0.000	0.000	down
NM_002070	GNAI2	-0.262	8.546	35.933	0.000	0.000	down
NM_002081	GPC1	-0.839	6.276	60.935	0.000	0.000	down
NM_002082	GRK6	-0.519	4.075	63.265	0.000	0.000	down
NM_002087	GRN	-0.424	7.731	31.476	0.000	0.001	down
NM_002096	GTF2F1	-0.194	5.683	15.021	0.001	0.012	down
NM_002105	H2AFX	-0.975	2.029	45.783	0.000	0.000	down
NM_002117	HLA-C	-0.204	8.616	12.454	0.002	0.022	down
NM_002166	ID2	-0.273	5.364	21.415	0.000	0.004	down
NM_002178	IGFBP6	-0.470	6.465	14.726	0.001	0.013	down
NM_002180	IGHMBP2	-0.224	3.772	11.033	0.004	0.030	down
NM_002193	INHBB	-0.304	6.261	15.178	0.001	0.012	down
NM_002226	JAG2	-0.588	4.623	71.261	0.000	0.000	down
NM_002229	JUNB	-1.272	3.751	70.283	0.000	0.000	down
NM_002230	JUP	-0.382	6.089	14.137	0.001	0.015	down
NM_002231	CD82	-0.415	4.852	29.335	0.000	0.001	down
NM_002275	KRT15	-9.875	1.505	294.735	0.000	0.000	down
NM_002305	LGALS1	-0.417	9.987	25.541	0.000	0.002	down
NM_002314	LIMK1	-0.470	4.252	30.223	0.000	0.001	down
NM_002318	LOXL2	-0.406	7.371	20.073	0.000	0.005	down
NM_002319	LRCH4	-0.544	4.578	91.124	0.000	0.000	down
NM_002332	LRP1	-0.226	11.489	11.141	0.004	0.029	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_002333	LRP3	-0.842	5.339	62.181	0.000	0.000	down
NM_002335	LRP5	-0.589	6.957	140.039	0.000	0.000	down
NM_002337	LRPAP1	-0.382	6.383	48.836	0.000	0.000	down
NM_002342	LTBR	-0.242	6.469	16.887	0.001	0.009	down
NM_002346	LY6E	-0.376	5.276	21.595	0.000	0.004	down
NM_002360	MAFK	-0.609	4.486	71.834	0.000	0.000	down
NM_002386	MC1R	-0.433	1.231	8.945	0.008	0.049	down
NM_002412	MGMT	-0.353	4.781	19.411	0.000	0.005	down
NM_002415	MIF	-1.105	3.804	110.338	0.000	0.000	down
NM_002419	MAP3K11	-0.562	5.854	69.315	0.000	0.000	down
NM_002428	MMP15	-0.365	5.573	39.686	0.000	0.000	down
NM_002434	MPG	-0.742	4.141	93.675	0.000	0.000	down
NM_002446	MAP3K10	-0.672	3.067	52.454	0.000	0.000	down
NM_002461	MVD	-0.818	4.400	30.254	0.000	0.001	down
NM_002496	NDUFS8	-0.497	5.152	43.912	0.000	0.000	down
NM_002513	NME3	-0.923	3.691	187.684	0.000	0.000	down
NM_002528	NTHL1	-0.612	2.616	44.643	0.000	0.000	down
NM_002536	TBC1D25	-0.232	4.578	20.494	0.000	0.004	down
NM_002555	SLC22A18	-0.741	1.877	24.909	0.000	0.002	down
NM_002566	P2RY11	-0.764	1.435	15.842	0.001	0.010	down
NM_002579	PALM	-0.669	7.161	55.668	0.000	0.000	down
NM_002616	PER1	-0.596	4.878	12.157	0.003	0.023	down
NM_002629	PGAM1	-0.161	4.911	10.327	0.005	0.035	down
NM_002639	SERPINB5	-4.408	0.117	12.830	0.005	0.037	down
NM_002652	PIP	-8.861	0.654	97.774	0.000	0.001	down
NM_002673	PLXNB1	-0.264	5.826	24.807	0.000	0.002	down
NM_002676	PMM1	-0.270	5.435	17.209	0.001	0.008	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_002695	POLR2E	-0.616	7.615	72.770	0.000	0.000	down
NM_002705	PPL	-0.287	6.888	11.188	0.004	0.029	down
NM_002741	PKN1	-0.559	6.298	107.636	0.000	0.000	down
NM_002751	MAPK11	-0.293	5.089	15.348	0.001	0.012	down
NM_002792	PSMA7	-0.165	7.575	10.035	0.005	0.038	down
NM_002801	PSMB10	-0.519	4.525	40.403	0.000	0.000	down
NM_002812	PSMD8	-0.216	8.064	10.364	0.005	0.035	down
NM_002813	PSMD9	-0.243	5.572	13.931	0.002	0.016	down
NM_002819	PTBP1	-0.266	6.841	23.242	0.000	0.003	down
NM_002821	PTK7	-0.440	2.752	10.833	0.004	0.031	down
NM_002826	QSOX1	-0.281	6.546	27.472	0.000	0.001	down
NM_002856	NECTIN2	-0.440	4.962	40.404	0.000	0.000	down
NM_002862	PYGB	-0.321	7.597	36.723	0.000	0.000	down
NM_002910	RENBP	-0.291	3.985	13.685	0.002	0.016	down
NM_002911	UPF1	-0.270	6.489	32.175	0.000	0.001	down
NM_002917	RFNG	-0.550	4.821	75.956	0.000	0.000	down
NM_002918	RFX1	-0.447	2.398	24.305	0.000	0.002	down
NM_002926	RGS12	-0.295	4.880	18.809	0.000	0.006	down
NM_002952	RPS2	-0.188	7.840	9.993	0.006	0.038	down
NM_002972	SBF1	-0.592	6.176	130.816	0.000	0.000	down
NM_003021	SGTA	-0.511	5.331	108.423	0.000	0.000	down
NM_003025	SH3GL1	-0.613	5.734	86.555	0.000	0.000	down
NM_003036	SKI	-0.204	6.572	9.673	0.006	0.041	down
NM_003040	SLC4A2	-0.530	5.889	118.942	0.000	0.000	down
NM_003047	SLC9A1	-0.263	4.776	18.069	0.001	0.007	down
NM_003086	SNAPC4	-0.428	3.330	27.917	0.000	0.001	down
NM_003088	FSCN1	-0.494	4.934	42.031	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_003091	SNRPB	-0.299	5.952	34.862	0.000	0.000	down
NM_003098	SNTA1	-0.413	6.372	23.919	0.000	0.002	down
NM_003102	SOD3	-0.348	6.944	17.459	0.001	0.008	down
NM_003119	SPG7	-0.241	6.258	13.826	0.002	0.016	down
NM_003120	SPI1	-0.497	3.971	16.284	0.001	0.010	down
NM_003131	SRF	-0.293	5.544	38.095	0.000	0.000	down
NM_003132	SRM	-0.481	5.278	51.576	0.000	0.000	down
NM_003155	STC1	-0.519	2.642	10.586	0.005	0.033	down
NM_003192	TBCC	-0.192	3.703	8.901	0.008	0.050	down
NM_003200	TCF3	-0.525	4.774	79.176	0.000	0.000	down
NM_003214	TEAD3	-0.246	4.732	9.506	0.007	0.043	down
NM_003249	THOP1	-0.327	3.587	21.162	0.000	0.004	down
NM_003251	THRSP	-0.480	9.754	12.621	0.002	0.021	down
NM_003260	TLE2	-0.594	5.209	48.293	0.000	0.000	down
NM_003278	CLEC3B	-0.639	7.484	35.361	0.000	0.000	down
NM_003294	TPSAB1	-0.442	3.483	12.166	0.003	0.023	down
NM_003302	TRIP6	-0.531	5.704	66.220	0.000	0.000	down
NM_003312	TST	-0.374	5.592	16.344	0.001	0.009	down
NM_003313	TSTA3	-0.342	4.362	19.660	0.000	0.005	down
NM_003327	TNFRSF4	-1.163	-0.027	32.473	0.000	0.001	down
NM_003331	TYK2	-0.351	5.919	58.899	0.000	0.000	down
NM_003364	UPP1	-0.296	3.592	13.187	0.002	0.018	down
NM_003367	USF2	-0.190	6.739	13.229	0.002	0.018	down
NM_003370	VASP	-0.234	5.471	9.292	0.007	0.045	down
NM_003461	ZYX	-0.524	6.811	80.346	0.000	0.000	down
NM_003481	USP5	-0.162	6.770	12.430	0.002	0.022	down
NM_003491	NAA10	-0.197	5.460	17.597	0.001	0.007	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_003498	SNN	-0.172	7.708	10.903	0.004	0.031	down
NM_003502	AXIN1	-0.529	4.144	84.487	0.000	0.000	down
NM_003549	HYAL3	-0.402	1.290	11.467	0.003	0.027	down
NM_003550	MAD1L1	-0.296	3.917	15.599	0.001	0.011	down
NM_003565	ULK1	-0.393	4.793	36.901	0.000	0.000	down
NM_003573	LTBP4	-0.527	6.709	15.121	0.001	0.012	down
NM_003575	ZNF282	-0.331	3.982	27.640	0.000	0.001	down
NM_003581	NCK2	-0.233	5.082	14.516	0.001	0.014	down
NM_003636	KCNAB2	-0.373	4.525	13.408	0.002	0.017	down
NM_003655	CBX4	-0.724	3.049	63.918	0.000	0.000	down
NM_003660	PPFIA3	-0.632	0.835	12.833	0.002	0.020	down
NM_003683	RRP1	-0.281	4.043	19.061	0.000	0.006	down
NM_003685	KHSRP	-0.184	5.928	20.102	0.000	0.005	down
NM_003687	PDLIM4	-0.682	2.034	28.533	0.000	0.001	down
NM_003721	RFXANK	-0.226	4.354	17.321	0.001	0.008	down
NM_003731	SSNA1	-0.666	4.744	79.688	0.000	0.000	down
NM_003740	KCNK5	-0.554	2.329	13.099	0.002	0.019	down
NM_003755	EIF3G	-0.237	6.439	21.424	0.000	0.004	down
NM_003775	S1PR4	-1.026	0.413	17.828	0.001	0.007	down
NM_003782	B3GALT4	-0.528	3.640	41.688	0.000	0.000	down
NM_003801	GPAA1	-0.651	5.908	103.075	0.000	0.000	down
NM_003820	TNFRSF14	-0.428	5.161	42.934	0.000	0.000	down
NM_003823	TNFRSF6B	-1.157	-0.125	9.366	0.007	0.044	down
NM_003824	FADD	-0.185	4.470	11.997	0.003	0.024	down
NM_003827	NAPA	-0.241	7.000	14.795	0.001	0.013	down
NM_003834	RGS11	-0.303	4.742	9.640	0.006	0.041	down
NM_003900	SQSTM1	-0.239	9.661	10.340	0.005	0.035	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_003942	RPS6KA4	-0.377	4.723	51.524	0.000	0.000	down
NM_003952	RPS6KB2	-0.452	4.140	45.649	0.000	0.000	down
NM_003959	HIP1R	-0.468	4.947	35.629	0.000	0.000	down
NM_003969	UBE2M	-0.242	4.681	15.219	0.001	0.012	down
NM_003974	DOK2	-0.335	3.688	9.228	0.007	0.046	down
NM_003977	AIP	-0.215	4.589	9.140	0.007	0.047	down
NM_004003	CRAT	-0.391	6.167	41.756	0.000	0.000	down
NM_004031	IRF7	-0.858	2.583	57.222	0.000	0.000	down
NM_004058	CAPS	-0.576	2.950	48.382	0.000	0.000	down
NM_004074	COX8A	-0.311	6.275	24.890	0.000	0.002	down
NM_004095	EIF4EBP1	-0.288	4.348	10.364	0.005	0.035	down
NM_004104	FASN	-0.655	10.016	34.931	0.000	0.000	down
NM_004111	FEN1	-0.256	3.840	10.016	0.005	0.038	down
NM_004140	LLGL1	-0.452	4.545	61.504	0.000	0.000	down
NM_004145	MYO9B	-0.270	6.330	20.804	0.000	0.004	down
NM_004146	NDUFB7	-0.954	5.571	117.952	0.000	0.000	down
NM_004148	NINJ1	-0.437	5.174	29.718	0.000	0.001	down
NM_004173	SLC7A4	-0.430	3.597	12.008	0.003	0.024	down
NM_004204	PIGQ	-0.720	4.145	66.623	0.000	0.000	down
NM_004218	RAB11B	-0.446	5.481	37.936	0.000	0.000	down
NM_004227	CYTH3	-0.166	6.401	13.961	0.002	0.015	down
NM_004252	SLC9A3R1	-0.325	4.661	24.496	0.000	0.002	down
NM_004257	TGFBRAP1	-0.173	5.719	13.914	0.002	0.016	down
NM_004260	RECQL4	-0.685	0.854	10.987	0.004	0.030	down
NM_004292	RIN1	-0.679	1.223	13.368	0.002	0.018	down
NM_004317	ASNA1	-0.234	5.603	17.313	0.001	0.008	down
NM_004322	BAD	-0.645	4.631	52.552	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_004356	CD81	-0.271	9.692	16.976	0.001	0.008	down
NM_004357	CD151	-0.386	9.359	22.809	0.000	0.003	down
NM_004359	CDC34	-0.436	4.713	40.847	0.000	0.000	down
NM_004383	CSK	-0.499	4.441	38.172	0.000	0.000	down
NM_004395	DBN1	-0.291	5.919	21.670	0.000	0.003	down
NM_004420	DUSP8	-0.713	2.485	26.808	0.000	0.001	down
NM_004422	DVL2	-0.268	4.921	29.278	0.000	0.001	down
NM_004424	E4F1	-0.738	3.359	70.118	0.000	0.000	down
NM_004429	EFNB1	-0.401	6.466	30.125	0.000	0.001	down
NM_004431	EPHA2	-0.279	3.828	14.877	0.001	0.013	down
NM_004435	ENDOG	-0.463	2.440	26.079	0.000	0.002	down
NM_004451	ESRRA	-0.573	4.901	70.897	0.000	0.000	down
NM_004461	FARSA	-0.293	4.781	18.381	0.000	0.006	down
NM_004481	GALNT2	-0.212	6.866	13.765	0.002	0.016	down
NM_004486	GOLGA2	-0.164	7.186	11.116	0.004	0.029	down
NM_004502	HOXB7	-0.196	4.657	13.184	0.002	0.018	down
NM_004514	FOXK2	-0.240	5.144	29.239	0.000	0.001	down
NM_004542	NDUFA3	-0.274	4.921	12.467	0.002	0.022	down
NM_004549	NDUFC2	-0.180	6.297	10.238	0.005	0.036	down
NM_004565	PEX14	-0.433	4.472	34.631	0.000	0.000	down
NM_004579	MAP4K2	-0.249	4.060	15.045	0.001	0.012	down
NM_004584	RAD9A	-0.319	3.310	13.097	0.002	0.019	down
NM_004603	STX1A	-0.693	1.060	13.400	0.002	0.017	down
NM_004636	SEMA3B	-0.581	5.927	23.194	0.000	0.003	down
NM_004638	PRRC2A	-0.237	7.403	28.358	0.000	0.001	down
NM_004639	BAG6	-0.133	7.424	9.820	0.006	0.039	down
NM_004656	BAP1	-0.246	6.250	36.664	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_004672	MAP3K6	-0.516	5.514	60.222	0.000	0.000	down
NM_004689	MTA1	-0.239	5.233	28.233	0.000	0.001	down
NM_004691	ATP6V0D1	-0.167	6.431	13.267	0.002	0.018	down
NM_004700	KCNQ4	-0.389	1.849	10.760	0.004	0.032	down
NM_004704	RRP9	-0.329	4.133	22.935	0.000	0.003	down
NM_004710	SYNGR2	-0.449	6.464	56.755	0.000	0.000	down
NM_004711	SYNGR1	-0.267	3.910	10.127	0.005	0.037	down
NM_004712	HGS	-0.388	5.581	66.061	0.000	0.000	down
NM_004715	CTDP1	-0.445	3.665	33.537	0.000	0.001	down
NM_004716	PCSK7	-0.167	5.614	16.559	0.001	0.009	down
NM_004749	TBRG4	-0.242	4.894	24.853	0.000	0.002	down
NM_004756	NUMBL	-0.410	5.181	23.445	0.000	0.003	down
NM_004759	MAPKAPK2	-0.212	6.688	16.802	0.001	0.009	down
NM_004765	BCL7C	-0.670	4.307	69.201	0.000	0.000	down
NM_004793	LONP1	-0.558	5.855	95.868	0.000	0.000	down
NM_004807	HS6ST1	-0.278	3.922	11.673	0.003	0.026	down
NM_004813	PEX16	-0.601	3.681	53.867	0.000	0.000	down
NM_004819	SYMPK	-0.214	5.575	20.802	0.000	0.004	down
NM_004860	FXR2	-0.163	5.815	11.082	0.004	0.029	down
NM_004886	APBA3	-0.823	2.728	70.385	0.000	0.000	down
NM_004890	SPAG7	-0.253	5.671	19.953	0.000	0.005	down
NM_004907	IER2	-0.334	4.583	16.689	0.001	0.009	down
NM_004910	PITPNM1	-0.450	3.120	13.381	0.002	0.018	down
NM_004913	VPS9D1	-0.568	3.885	64.238	0.000	0.000	down
NM_004924	ACTN4	-0.270	8.415	27.407	0.000	0.001	down
NM_004943	DMWD	-0.355	4.670	30.357	0.000	0.001	down
NM_004974	KCNA2	-0.440	2.824	11.481	0.003	0.027	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_005007	NFKBIL1	-0.350	3.503	20.861	0.000	0.004	down
NM_005035	POLRMT	-0.512	4.290	72.979	0.000	0.000	down
NM_005046	KLK7	-6.506	-0.713	33.931	0.001	0.009	down
NM_005049	PWP2	-0.192	4.358	16.635	0.001	0.009	down
NM_005053	RAD23A	-0.260	6.849	30.445	0.000	0.001	down
NM_005072	SLC12A4	-0.243	6.802	20.716	0.000	0.004	down
NM_005078	TLE3	-0.389	5.382	20.232	0.000	0.005	down
NM_005090	JMJD7-PLA2G4B	-0.183	4.561	14.142	0.001	0.015	down
NM_005094	SLC27A4	-0.363	4.620	52.698	0.000	0.000	down
NM_005098	MSC	-0.942	4.983	85.830	0.000	0.000	down
NM_005099	ADAMTS4	-0.483	3.952	29.903	0.000	0.001	down
NM_005101	ISG15	-0.828	2.558	59.624	0.000	0.000	down
NM_005115	MVP	-0.337	6.977	22.060	0.000	0.003	down
NM_005125	CCS	-0.321	4.299	23.798	0.000	0.002	down
NM_005133	RCE1	-0.312	3.137	15.037	0.001	0.012	down
NM_005137	DGCR2	-0.337	6.198	37.183	0.000	0.000	down
NM_005144	HR	-0.395	2.463	10.293	0.005	0.035	down
NM_005146	SART1	-0.345	5.375	48.172	0.000	0.000	down
NM_005163	AKT1	-0.364	7.590	61.236	0.000	0.000	down
NM_005224	ARID3A	-0.396	2.167	10.070	0.005	0.037	down
NM_005231	CTTN	-0.160	7.830	13.191	0.002	0.018	down
NM_005234	NR2F6	-0.496	4.644	34.161	0.000	0.000	down
NM_005255	GAK	-0.340	5.499	49.152	0.000	0.000	down
NM_005258	GCHFR	-0.529	3.481	23.864	0.000	0.002	down
NM_005262	GFER	-0.295	4.121	21.543	0.000	0.004	down
NM_005273	GNB2	-0.521	6.752	89.336	0.000	0.000	down
NM_005275	GNL1	-0.146	6.432	11.581	0.003	0.026	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_005309	GPT	-0.682	3.755	27.629	0.000	0.001	down
NM_005319	HIST1H1C	-0.366	5.035	10.568	0.005	0.033	down
NM_005334	HCFC1	-0.252	5.413	21.964	0.000	0.003	down
NM_005357	LIPE	-0.689	9.637	48.509	0.000	0.000	down
NM_005392	PHF2	-0.144	6.034	10.758	0.004	0.032	down
NM_005427	TP73	-3.314	-2.856	11.881	0.004	0.029	down
NM_005453	ZBTB22	-0.174	4.555	9.210	0.007	0.046	down
NM_005456	MAPK8IP1	-0.639	2.686	40.639	0.000	0.000	down
NM_005461	MAFB	-0.293	5.803	20.178	0.000	0.005	down
NM_005480	TROAP	-1.432	-0.368	10.740	0.004	0.032	down
NM_005481	MED16	-0.470	3.077	21.930	0.000	0.003	down
NM_005507	CFL1	-0.156	8.879	11.242	0.004	0.028	down
NM_005518	HMGCS2	-5.995	-1.315	23.412	0.002	0.020	down
NM_005524	HES1	-0.547	3.563	41.962	0.000	0.000	down
NM_005526	HSF1	-0.351	4.974	42.526	0.000	0.000	down
NM_005547	IVL	-5.148	-1.551	18.355	0.004	0.031	down
NM_005555	KRT6B	-5.718	-1.493	24.028	0.002	0.019	down
NM_005560	LAMA5	-0.608	5.602	45.419	0.000	0.000	down
NM_005567	LGALS3BP	-0.300	8.727	14.317	0.001	0.014	down
NM_005576	LOXL1	-0.505	3.710	31.895	0.000	0.001	down
NM_005583	LYL1	-0.665	1.861	29.889	0.000	0.001	down
NM_005608	PTPRCAP	-0.575	0.952	13.302	0.002	0.018	down
NM_005619	RTN2	-0.324	2.467	9.432	0.007	0.043	down
NM_005629	SLC6A8	-0.302	5.921	22.753	0.000	0.003	down
NM_005632	CAPN15	-0.979	3.311	121.226	0.000	0.000	down
NM_005641	TAF6	-0.191	4.925	17.945	0.001	0.007	down
NM_005663	NELFA	-0.404	3.490	30.323	0.000	0.001	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_005675	DGCR6	-0.705	2.965	58.639	0.000	0.000	down
NM_005679	TAF1C	-0.315	5.403	25.897	0.000	0.002	down
NM_005694	COX17	-0.171	4.229	9.082	0.008	0.047	down
NM_005698	SCAMP3	-0.203	5.791	22.359	0.000	0.003	down
NM_005716	GIPC1	-0.532	5.975	59.228	0.000	0.000	down
NM_005720	ARPC1B	-0.387	6.028	24.888	0.000	0.002	down
NM_005735	ACTR1B	-0.179	6.082	17.751	0.001	0.007	down
NM_005749	TOB1	-0.241	4.681	19.434	0.000	0.005	down
NM_005762	TRIM28	-0.341	6.412	41.100	0.000	0.000	down
NM_005775	SORBS3	-0.351	6.741	35.155	0.000	0.000	down
NM_005781	TNK2	-0.684	4.994	136.493	0.000	0.000	down
NM_005782	ALYREF	-0.330	4.268	27.694	0.000	0.001	down
NM_005804	DDX39A	-0.236	4.739	12.254	0.003	0.023	down
NM_005837	POP7	-0.359	3.666	25.879	0.000	0.002	down
NM_005850	SF3B4	-0.184	5.211	12.870	0.002	0.020	down
NM_005851	CDK2AP2	-0.331	4.578	27.702	0.000	0.001	down
NM_005858	AKAP8	-0.199	5.018	14.005	0.002	0.015	down
NM_005860	FSTL3	-0.614	7.215	42.694	0.000	0.000	down
NM_005861	STUB1	-0.405	6.372	43.039	0.000	0.000	down
NM_005873	RGS19	-0.600	2.701	22.101	0.000	0.003	down
NM_005886	KATNB1	-0.566	3.724	74.758	0.000	0.000	down
NM_005892	FMNL1	-0.309	5.207	19.403	0.000	0.005	down
NM_005920	MEF2D	-0.154	6.012	12.018	0.003	0.024	down
NM_005929	MELTF	-0.476	2.603	13.061	0.002	0.019	down
NM_005934	MLLT1	-0.311	5.822	31.820	0.000	0.001	down
NM_005967	NAB2	-0.334	3.952	17.871	0.001	0.007	down
NM_005982	SIX1	-0.714	5.208	19.863	0.000	0.005	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_005984	SLC25A1	-0.307	7.309	18.793	0.000	0.006	down
NM_005993	TBCD	-0.252	5.822	28.776	0.000	0.001	down
NM_005994	TBX2	-0.449	3.786	20.608	0.000	0.004	down
NM_006012	CLPP	-0.441	4.212	23.108	0.000	0.003	down
NM_006026	H1FX	-0.691	5.037	60.762	0.000	0.000	down
NM_006035	CDC42BPB	-0.137	7.724	12.079	0.003	0.023	down
NM_006053	TCIRG1	-0.503	5.047	44.275	0.000	0.000	down
NM_006056	NMUR1	-0.459	4.186	14.095	0.001	0.015	down
NM_006067	EMC8	-0.183	4.429	10.180	0.005	0.036	down
NM_006088	TUBB4B	-0.426	7.649	41.607	0.000	0.000	down
NM_006097	MYL9	-0.313	9.909	32.607	0.000	0.001	down
NM_006114	TOMM40	-0.491	4.664	37.765	0.000	0.000	down
NM_006116	TAB1	-0.172	4.736	10.813	0.004	0.031	down
NM_006133	DAGLA	-0.561	2.793	24.087	0.000	0.002	down
NM_006150	PRICKLE3	-0.258	3.042	11.808	0.003	0.025	down
NM_006184	NUCB1	-0.239	8.234	15.598	0.001	0.011	down
NM_006231	POLE	-0.180	5.172	16.105	0.001	0.010	down
NM_006233	POLR2I	-0.350	4.008	21.558	0.000	0.004	down
NM_006234	POLR2J	-0.495	4.256	48.036	0.000	0.000	down
NM_006238	PPARD	-0.296	4.831	36.295	0.000	0.000	down
NM_006247	PPP5C	-0.223	4.837	14.467	0.001	0.014	down
NM_006266	RALGDS	-0.280	6.268	21.301	0.000	0.004	down
NM_006270	RRAS	-0.342	6.903	21.920	0.000	0.003	down
NM_006285	TESK1	-0.423	6.573	44.742	0.000	0.000	down
NM_006295	VARS	-0.266	5.293	37.744	0.000	0.000	down
NM_006302	MOGS	-0.229	5.651	21.957	0.000	0.003	down
NM_006312	NCOR2	-0.544	6.261	155.338	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_006319	CDIPT	-0.276	6.355	26.621	0.000	0.001	down
NM_006336	ZER1	-0.290	5.929	23.376	0.000	0.003	down
NM_006337	MCRS1	-0.199	5.596	18.057	0.001	0.007	down
NM_006339	HMG20B	-0.469	5.206	64.285	0.000	0.000	down
NM_006341	MAD2L2	-0.248	3.669	11.874	0.003	0.025	down
NM_006349	ZNHIT1	-0.380	5.771	40.086	0.000	0.000	down
NM_006351	TIMM44	-0.227	4.549	12.236	0.003	0.023	down
NM_006354	TADA3	-0.229	6.067	22.830	0.000	0.003	down
NM_006383	CIB2	-0.209	3.842	9.825	0.006	0.039	down
NM_006387	CHERP	-0.338	4.574	34.583	0.000	0.000	down
NM_006388	KAT5	-0.174	5.439	13.473	0.002	0.017	down
NM_006412	AGPAT2	-0.799	8.704	45.587	0.000	0.000	down
NM_006423	RABAC1	-0.411	5.091	28.695	0.000	0.001	down
NM_006427	SIVA1	-1.224	4.054	176.017	0.000	0.000	down
NM_006428	MRPL28	-0.495	5.008	50.684	0.000	0.000	down
NM_006440	TXNRD2	-0.383	3.702	17.589	0.001	0.007	down
NM_006442	DRAP1	-0.557	5.483	90.320	0.000	0.000	down
NM_006453	TBL3	-0.614	3.857	42.343	0.000	0.000	down
NM_006454	MXD4	-0.545	6.563	67.796	0.000	0.000	down
NM_006460	HEXIM1	-0.419	6.277	36.001	0.000	0.000	down
NM_006473	TAF6L	-0.259	3.567	15.192	0.001	0.012	down
NM_006478	GAS2L1	-0.732	4.208	62.239	0.000	0.000	down
NM_006480	RGS14	-0.509	2.547	15.877	0.001	0.010	down
NM_006494	ERF	-0.498	4.021	46.986	0.000	0.000	down
NM_006497	HIC1	-0.709	3.122	36.721	0.000	0.000	down
NM_006516	SLC2A1	-0.569	2.887	10.398	0.005	0.034	down
NM_006532	ELL	-0.338	3.589	20.933	0.000	0.004	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_006551	SCGB1D2	-8.015	-0.028	63.930	0.000	0.002	down
NM_006555	YKT6	-0.162	6.987	9.887	0.006	0.039	down
NM_006556	PMVK	-0.248	5.606	16.063	0.001	0.010	down
NM_006589	FAM189B	-0.231	3.784	10.298	0.005	0.035	down
NM_006598	SLC12A7	-0.290	5.331	20.214	0.000	0.005	down
NM_006612	KIF1C	-0.281	9.099	17.612	0.001	0.007	down
NM_006634	VAMP5	-0.223	5.400	10.686	0.004	0.032	down
NM_006640	SEPT9	-0.320	6.595	22.514	0.000	0.003	down
NM_006647	NOXA1	-0.971	1.290	19.135	0.000	0.006	down
NM_006651	CPLX1	-0.428	1.665	14.697	0.001	0.013	down
NM_006663	PPP1R13L	-0.533	2.843	15.099	0.001	0.012	down
NM_006675	TSPAN9	-0.171	6.389	9.732	0.006	0.040	down
NM_006676	USP20	-0.232	4.587	14.768	0.001	0.013	down
NM_006694	JTB	-0.128	6.179	8.949	0.008	0.049	down
NM_006705	GADD45G	-0.818	0.362	19.084	0.000	0.006	down
NM_006712	FASTK	-0.536	5.406	80.267	0.000	0.000	down
NM_006736	DNAJB2	-0.219	6.499	22.389	0.000	0.003	down
NM_006739	MCM5	-0.325	4.070	24.412	0.000	0.002	down
NM_006742	PSKH1	-0.255	5.665	17.569	0.001	0.007	down
NM_006744	RBP4	-0.270	10.062	9.804	0.006	0.040	down
NM_006753	SURF6	-0.297	4.883	34.116	0.000	0.000	down
NM_006764	IFRD2	-0.385	5.282	41.954	0.000	0.000	down
NM_006767	LZTR1	-0.240	6.421	33.668	0.000	0.001	down
NM_006779	CDC42EP2	-0.824	5.017	85.169	0.000	0.000	down
NM_006782	ZFPL1	-0.508	4.412	71.610	0.000	0.000	down
NM_006795	EHD1	-0.491	6.416	68.952	0.000	0.000	down
NM_006804	STARD3	-0.249	4.728	20.034	0.000	0.005	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_006808	SEC61B	-0.199	5.864	15.272	0.001	0.012	down
NM_006816	LMAN2	-0.270	5.853	21.088	0.000	0.004	down
NM_006829	ADIRF	-0.383	9.898	23.337	0.000	0.003	down
NM_006830	UQCR11	-0.311	5.989	26.183	0.000	0.002	down
NM_006844	ILVBL	-0.495	5.724	43.321	0.000	0.000	down
NM_006848	CCDC85B	-1.089	2.094	79.124	0.000	0.000	down
NM_006858	TMED1	-0.511	4.340	48.948	0.000	0.000	down
NM_006876	B4GAT1	-0.212	4.869	11.544	0.003	0.026	down
NM_006927	ST3GAL2	-0.248	4.609	13.838	0.002	0.016	down
NM_006986	MAGED1	-0.198	6.841	10.754	0.004	0.032	down
NM_006987	RPH3AL	-0.226	4.182	12.416	0.002	0.022	down
NM_007022	CYB561D2	-0.272	3.895	16.955	0.001	0.008	down
NM_007024	TMEM115	-0.330	5.180	39.979	0.000	0.000	down
NM_007046	EMILIN1	-0.642	4.751	49.664	0.000	0.000	down
NM_007056	CLASRP	-0.212	4.521	11.004	0.004	0.030	down
NM_007065	CDC37	-0.228	7.391	27.944	0.000	0.001	down
NM_007076	FICD	-0.341	2.863	14.911	0.001	0.013	down
NM_007108	ELOB	-0.661	6.174	94.242	0.000	0.000	down
NM_007109	TCF19	-0.348	3.574	16.936	0.001	0.008	down
NM_007121	NR1H2	-0.550	5.414	50.565	0.000	0.000	down
NM_007165	SF3A2	-0.638	4.108	68.994	0.000	0.000	down
NM_007171	POMT1	-0.299	4.863	25.022	0.000	0.002	down
NM_007181	MAP4K1	-0.321	2.000	9.184	0.007	0.046	down
NM_007184	NISCH	-0.176	6.503	15.341	0.001	0.012	down
NM_007209	RPL35	-0.253	7.594	20.026	0.000	0.005	down
NM_007254	PNKP	-0.359	4.045	46.541	0.000	0.000	down
NM_007255	B4GALT7	-0.432	4.552	31.073	0.000	0.001	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_007260	LYPLA2	-0.438	4.216	41.021	0.000	0.000	down
NM_007274	ACOT7	-0.565	3.282	40.082	0.000	0.000	down
NM_007277	EXOC3	-0.175	5.827	15.621	0.001	0.011	down
NM_007279	U2AF2	-0.212	6.423	21.566	0.000	0.004	down
NM_007284	TWF2	-0.524	5.788	132.583	0.000	0.000	down
NM_007313	ABL1	-0.296	7.005	29.873	0.000	0.001	down
NM_007322	RANBP3	-0.188	5.488	12.677	0.002	0.021	down
NM_007346	OGFR	-0.593	4.418	77.163	0.000	0.000	down
NM_007353	GNA12	-0.152	7.193	9.201	0.007	0.046	down
NM_007371	BRD3	-0.202	5.190	17.207	0.001	0.008	down
NM_012067	AKR7A3	-0.684	0.039	13.783	0.002	0.016	down
NM_012079	DGAT1	-0.340	7.210	24.749	0.000	0.002	down
NM_012088	PGLS	-0.363	4.734	30.433	0.000	0.001	down
NM_012094	PRDX5	-0.300	7.019	22.255	0.000	0.003	down
NM_012099	CD3EAP	-0.315	2.905	19.013	0.000	0.006	down
NM_012114	CASP14	-7.459	-0.036	53.341	0.000	0.004	down
NM_012121	CDC42EP4	-0.263	6.528	11.728	0.003	0.025	down
NM_012135	FAM50B	-0.290	3.030	11.305	0.004	0.028	down
NM_012162	FBXL6	-0.569	3.100	47.546	0.000	0.000	down
NM_012163	LRRC29	-0.526	0.844	10.933	0.004	0.030	down
NM_012181	FKBP8	-0.670	7.314	89.917	0.000	0.000	down
NM_012203	GRHPR	-0.178	6.345	11.272	0.004	0.028	down
NM_012235	SCAP	-0.168	5.885	16.589	0.001	0.009	down
NM_012265	RHBDD3	-0.850	3.147	71.936	0.000	0.000	down
NM_012267	HSPBP1	-0.461	3.353	43.413	0.000	0.000	down
NM_012268	PLD3	-0.429	7.457	25.552	0.000	0.002	down
NM_012292	ARHGAP45	-0.601	3.536	25.645	0.000	0.002	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_012318	LETM1	-0.223	5.634	15.176	0.001	0.012	down
NM_012320	PLA2G15	-0.338	5.201	17.217	0.001	0.008	down
NM_012324	MAPK8IP2	-1.104	1.009	27.896	0.000	0.001	down
NM_012339	TSPAN15	-0.311	6.909	18.038	0.001	0.007	down
NM_012384	GMEB2	-0.360	3.685	21.506	0.000	0.004	down
NM_012396	PHLDA3	-0.674	7.021	82.090	0.000	0.000	down
NM_012398	PIP5K1C	-0.469	5.419	83.756	0.000	0.000	down
NM_012401	PLXNB2	-0.474	6.870	81.866	0.000	0.000	down
NM_012407	PICK1	-0.300	3.607	13.740	0.002	0.016	down
NM_012427	KLK5	-6.660	-0.629	38.134	0.001	0.007	down
NM_012435	SHC2	-0.767	3.384	38.295	0.000	0.000	down
NM_012445	SPON2	-0.609	5.465	39.022	0.000	0.000	down
NM_012458	TIMM13	-0.474	4.905	46.482	0.000	0.000	down
NM_012469	PRPF6	-0.145	6.718	11.220	0.004	0.028	down
NM_012478	WBP2	-0.256	6.834	27.573	0.000	0.001	down
NM_013258	PYCARD	-0.393	2.586	11.843	0.003	0.025	down
NM_013265	VPS51	-0.589	5.628	47.073	0.000	0.000	down
NM_013284	POLM	-0.176	4.167	9.021	0.008	0.048	down
NM_013286	RBM15B	-0.178	6.423	15.705	0.001	0.011	down
NM_013291	CPSF1	-0.447	5.673	88.026	0.000	0.000	down
NM_013299	SAC3D1	-0.585	2.295	19.490	0.000	0.005	down
NM_013301	CCDC106	-0.652	3.403	64.520	0.000	0.000	down
NM_013321	SNX8	-0.548	5.276	43.955	0.000	0.000	down
NM_013327	PARVB	-0.118	5.472	9.427	0.007	0.043	down
NM_013328	PYCR2	-0.159	5.573	12.731	0.002	0.020	down
NM_013334	GMPPB	-0.329	4.090	26.696	0.000	0.001	down
NM_013342	TFPT	-0.462	3.286	26.308	0.000	0.002	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_013355	PKN3	-0.498	3.752	32.026	0.000	0.001	down
NM_013366	ANAPC2	-0.444	4.763	62.743	0.000	0.000	down
NM_013373	ZDHHC8	-0.792	4.905	236.534	0.000	0.000	down
NM_013375	ABT1	-0.303	4.195	27.967	0.000	0.001	down
NM_013376	SERTAD1	-0.587	2.900	32.231	0.000	0.001	down
NM_013379	DPP7	-0.848	5.672	105.927	0.000	0.000	down
NM_013400	REPIN1	-0.451	6.251	45.949	0.000	0.000	down
NM_013401	RAB3IL1	-0.382	4.318	22.032	0.000	0.003	down
NM_013432	TONSL	-0.582	0.702	16.539	0.001	0.009	down
NM_013443	ST6GALNAC6	-0.161	8.107	11.334	0.004	0.028	down
NM_013982	NRG2	-0.407	1.950	9.767	0.006	0.040	down
NM_014002	IKBKE	-0.403	3.102	13.951	0.002	0.015	down
NM_014008	CCDC22	-0.344	3.667	25.156	0.000	0.002	down
NM_014015	DEXI	-0.206	4.779	15.456	0.001	0.011	down
NM_014045	LRP10	-0.290	7.509	35.104	0.000	0.000	down
NM_014047	C19orf53	-0.226	5.427	25.881	0.000	0.002	down
NM_014062	NOB1	-0.162	4.801	8.890	0.008	0.050	down
NM_014079	KLF15	-0.532	4.916	19.969	0.000	0.005	down
NM_014205	ZNHIT2	-1.126	0.830	37.218	0.000	0.000	down
NM_014214	IMPA2	-0.294	4.495	16.713	0.001	0.009	down
NM_014216	ITPK1	-0.393	8.431	41.952	0.000	0.000	down
NM_014225	PPP2R1A	-0.181	7.464	10.180	0.005	0.036	down
NM_014235	UBL4A	-0.331	5.661	43.355	0.000	0.000	down
NM_014262	P3H3	-0.425	3.005	25.973	0.000	0.002	down
NM_014272	ADAMTS7	-0.543	3.341	31.872	0.000	0.001	down
NM_014291	GCAT	-0.587	2.164	19.298	0.000	0.005	down
NM_014292	CBX6	-0.150	5.852	12.408	0.002	0.022	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_014329	EDC4	-0.322	5.202	32.201	0.000	0.001	down
NM_014337	PPIL2	-0.139	5.443	11.672	0.003	0.026	down
NM_014346	TBC1D22A	-0.222	4.968	18.749	0.000	0.006	down
NM_014357	LCE2B	-6.498	-0.698	31.918	0.001	0.011	down
NM_014389	PELP1	-0.218	5.041	15.102	0.001	0.012	down
NM_014424	HSPB7	-0.405	9.212	10.945	0.004	0.030	down
NM_014431	PALD1	-0.330	3.783	9.809	0.006	0.040	down
NM_014448	ARHGEF16	-0.725	2.549	24.095	0.000	0.002	down
NM_014516	CNOT3	-0.228	4.338	19.244	0.000	0.005	down
NM_014520	MYBBP1A	-0.356	5.243	49.100	0.000	0.000	down
NM_014550	CARD10	-0.308	3.881	9.279	0.007	0.045	down
NM_014572	LATS2	-0.169	5.594	13.065	0.002	0.019	down
NM_014578	RHOD	-0.367	2.867	13.058	0.002	0.019	down
NM_014580	SLC2A8	-0.539	3.916	36.200	0.000	0.000	down
NM_014593	CXXC1	-0.268	4.899	29.673	0.000	0.001	down
NM_014595	NT5C	-0.338	3.929	18.694	0.000	0.006	down
NM_014603	CDR2L	-0.301	3.803	11.429	0.003	0.027	down
NM_014604	TAX1BP3	-0.333	6.795	43.886	0.000	0.000	down
NM_014634	PPM1F	-0.252	6.232	26.390	0.000	0.002	down
NM_014652	IPO13	-0.246	5.286	25.484	0.000	0.002	down
NM_014654	SDC3	-0.180	7.421	10.121	0.005	0.037	down
NM_014661	FAM53B	-0.250	5.969	17.050	0.001	0.008	down
NM_014675	CROCC	-0.512	3.895	76.918	0.000	0.000	down
NM_014694	ADAMTSL2	-0.847	0.984	15.647	0.001	0.011	down
NM_014699	ZNF646	-0.262	4.235	20.562	0.000	0.004	down
NM_014700	RAB11FIP3	-0.466	5.032	66.063	0.000	0.000	down
NM_014712	SETD1A	-0.403	4.658	53.797	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_014716	ACAP1	-0.488	2.015	12.343	0.003	0.022	down
NM_014726	TBKBP1	-0.354	4.407	39.493	0.000	0.000	down
NM_014727	KMT2B	-0.388	5.449	52.144	0.000	0.000	down
NM_014786	ARHGEF17	-0.299	6.477	29.888	0.000	0.001	down
NM_014798	PLEKHM1	-0.345	5.710	30.169	0.000	0.001	down
NM_014807	C2CD2L	-0.346	3.748	20.076	0.000	0.005	down
NM_014811	PPP1R26	-0.417	4.123	39.485	0.000	0.000	down
NM_014844	TECPR2	-0.172	5.147	11.206	0.004	0.028	down
NM_014853	SGSM2	-0.295	5.587	35.416	0.000	0.000	down
NM_014855	AP5Z1	-0.834	4.468	83.692	0.000	0.000	down
NM_014891	PDAP1	-0.160	6.548	15.477	0.001	0.011	down
NM_014931	PPP6R1	-0.539	5.342	100.631	0.000	0.000	down
NM_014938	MLXIP	-0.182	6.932	19.566	0.000	0.005	down
NM_014940	MON1B	-0.153	5.192	11.901	0.003	0.024	down
NM_014948	UBOX5	-0.286	3.735	15.576	0.001	0.011	down
NM_014963	SBNO2	-0.579	4.611	47.135	0.000	0.000	down
NM_014972	TCF25	-0.219	6.480	14.746	0.001	0.013	down
NM_014984	CEP131	-0.488	2.325	23.882	0.000	0.002	down
NM_015005	CEP170B	-0.767	5.807	169.958	0.000	0.000	down
NM_015015	KDM4B	-0.393	4.852	48.927	0.000	0.000	down
NM_015037	ZSWIM8	-0.205	6.289	23.157	0.000	0.003	down
NM_015048	SETD1B	-0.357	5.262	23.563	0.000	0.002	down
NM_015099	CAMTA2	-0.273	6.130	44.304	0.000	0.000	down
NM_015103	PLXND1	-0.215	8.219	15.369	0.001	0.011	down
NM_015104	ATG2A	-0.470	4.330	57.289	0.000	0.000	down
NM_015117	ZC3H3	-0.533	3.387	35.685	0.000	0.000	down
NM_015124	GRAMD4	-0.410	5.288	46.051	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_015133	MAPK8IP3	-0.626	5.209	81.257	0.000	0.000	down
NM_015140	TTLL12	-0.334	4.415	23.648	0.000	0.002	down
NM_015160	PMPCA	-0.208	5.050	13.769	0.002	0.016	down
NM_015164	PLEKHM2	-0.436	6.165	57.542	0.000	0.000	down
NM_015168	ZC3H4	-0.159	4.820	11.550	0.003	0.026	down
NM_015175	NBEAL2	-0.276	5.519	13.572	0.002	0.017	down
NM_015178	RHOBTB2	-0.323	4.241	24.748	0.000	0.002	down
NM_015229	CLUH	-0.449	6.738	60.573	0.000	0.000	down
NM_015242	ARAP1	-0.311	6.626	29.893	0.000	0.001	down
NM_015254	KIF13B	-0.145	5.712	9.136	0.007	0.047	down
NM_015260	SIN3B	-0.270	6.131	35.715	0.000	0.000	down
NM_015274	MAN2B2	-0.227	6.658	13.703	0.002	0.016	down
NM_015321	CRTC1	-0.353	4.453	30.217	0.000	0.001	down
NM_015329	MAU2	-0.170	5.685	10.324	0.005	0.035	down
NM_015366	PRR5	-0.515	5.038	42.546	0.000	0.000	down
NM_015392	NPDC1	-0.439	4.257	8.904	0.008	0.050	down
NM_015395	TECPR1	-0.320	5.106	29.324	0.000	0.001	down
NM_015399	BRMS1	-0.286	4.646	21.481	0.000	0.004	down
NM_015404	WHRN	-0.413	1.873	12.588	0.002	0.021	down
NM_015414	RPL36	-0.424	6.951	52.540	0.000	0.000	down
NM_015456	NELFB	-0.438	5.248	72.922	0.000	0.000	down
NM_015466	PTPN23	-0.352	5.594	76.620	0.000	0.000	down
NM_015492	C15orf39	-0.786	4.699	149.680	0.000	0.000	down
NM_015503	SH2B1	-0.206	6.229	18.884	0.000	0.006	down
NM_015527	TBC1D10B	-0.363	5.149	45.186	0.000	0.000	down
NM_015533	TKFC	-0.229	4.191	12.061	0.003	0.024	down
NM_015545	PTCD1	-0.313	4.009	35.252	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_015603	CCDC9	-0.366	3.754	24.683	0.000	0.002	down
NM_015627	LDLRAP1	-0.276	4.990	33.321	0.000	0.001	down
NM_015629	PRPF31	-0.336	5.100	34.008	0.000	0.000	down
NM_015649	IRF2BP1	-0.401	3.265	17.161	0.001	0.008	down
NM_015656	KIF26A	-0.775	3.428	60.921	0.000	0.000	down
NM_015658	NOC2L	-0.332	5.437	35.168	0.000	0.000	down
NM_015666	MTG2	-0.326	4.462	27.117	0.000	0.001	down
NM_015675	GADD45B	-0.565	4.354	19.897	0.000	0.005	down
NM_015680	CNPPD1	-0.174	6.715	11.648	0.003	0.026	down
NM_015694	ZNF777	-0.281	3.396	14.816	0.001	0.013	down
NM_015698	GPKOW	-0.212	4.735	14.642	0.001	0.013	down
NM_015703	RRP7A	-0.199	5.286	18.865	0.000	0.006	down
NM_015705	SGSM3	-0.251	5.104	29.036	0.000	0.001	down
NM_015710	GLTSCR2	-0.464	6.719	44.142	0.000	0.000	down
NM_015711	GLTSCR1	-0.407	2.507	16.098	0.001	0.010	down
NM_015714	G0S2	-0.780	9.463	42.855	0.000	0.000	down
NM_015719	COL5A3	-0.245	8.197	10.528	0.005	0.033	down
NM_015720	PODXL2	-0.350	2.950	13.383	0.002	0.018	down
NM_015846	MBD1	-0.148	5.622	12.070	0.003	0.024	down
NM_015853	UBXN1	-0.290	6.316	26.329	0.000	0.002	down
NM_015871	ZNF593	-0.372	2.577	12.843	0.002	0.020	down
NM_015873	VILL	-0.277	3.434	9.549	0.006	0.042	down
NM_015897	PIAS4	-0.368	3.308	32.705	0.000	0.001	down
NM_015898	ZBTB7A	-0.410	5.687	61.105	0.000	0.000	down
NM_015916	CALHM2	-0.229	4.916	11.646	0.003	0.026	down
NM_015949	GET4	-0.449	4.616	39.533	0.000	0.000	down
NM_015953	NOSIP	-0.405	4.369	30.082	0.000	0.001	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_015963	THAP4	-0.461	4.958	61.927	0.000	0.000	down
NM_015965	NDUFA13	-0.443	6.417	39.802	0.000	0.000	down
NM_015997	RRNAD1	-0.271	4.147	18.301	0.000	0.006	down
NM_016035	COQ4	-0.300	4.620	15.255	0.001	0.012	down
NM_016068	FIS1	-0.210	7.003	15.872	0.001	0.010	down
NM_016069	PAM16	-0.309	2.736	9.803	0.006	0.040	down
NM_016084	RASD1	-0.450	6.993	10.643	0.004	0.032	down
NM_016111	TELO2	-0.815	3.835	94.675	0.000	0.000	down
NM_016151	TAOK2	-0.266	6.087	20.542	0.000	0.004	down
NM_016154	RAB4B	-0.305	4.094	20.546	0.000	0.004	down
NM_016155	MMP17	-0.811	2.280	42.539	0.000	0.000	down
NM_016172	UBAC1	-0.293	5.287	31.282	0.000	0.001	down
NM_016199	LSM7	-0.394	3.005	20.829	0.000	0.004	down
NM_016201	AMOTL2	-0.370	8.162	26.050	0.000	0.002	down
NM_016215	EGFL7	-0.824	5.698	83.077	0.000	0.000	down
NM_016219	MAN1B1	-0.307	5.770	31.155	0.000	0.001	down
NM_016256	NAGPA	-0.329	3.631	19.782	0.000	0.005	down
NM_016263	FZR1	-0.555	4.267	77.890	0.000	0.000	down
NM_016292	TRAP1	-0.189	5.842	14.105	0.001	0.015	down
NM_016307	PRRX2	-0.663	1.331	15.844	0.001	0.010	down
NM_016310	POLR3K	-0.190	3.093	9.142	0.007	0.047	down
NM_016337	EVL	-0.263	5.594	22.872	0.000	0.003	down
NM_016381	TREX1	-0.512	3.851	41.067	0.000	0.000	down
NM_016390	SPOUT1	-0.237	4.885	31.539	0.000	0.001	down
NM_016423	ZNF219	-0.750	6.303	91.180	0.000	0.000	down
NM_016453	NCKIPSD	-0.221	4.834	12.962	0.002	0.019	down
NM_016457	PRKD2	-0.287	4.815	11.741	0.003	0.025	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_016466	ANKRD39	-0.430	2.544	15.887	0.001	0.010	down
NM_016496	MARCH2	-0.291	6.660	18.005	0.001	0.007	down
NM_016526	BET1L	-0.194	6.304	16.296	0.001	0.010	down
NM_016538	SIRT7	-0.338	3.439	16.591	0.001	0.009	down
NM_016539	SIRT6	-0.733	2.356	40.320	0.000	0.000	down
NM_016547	SDF4	-0.443	6.605	81.125	0.000	0.000	down
NM_016579	CD320	-0.296	3.866	9.304	0.007	0.045	down
NM_016581	ECSIT	-0.223	4.151	11.239	0.004	0.028	down
NM_016582	SLC15A3	-0.345	4.660	11.469	0.003	0.027	down
NM_016639	TNFRSF12A	-0.969	3.174	12.452	0.002	0.022	down
NM_016647	THEM6	-0.535	4.907	47.991	0.000	0.000	down
NM_016732	RALY	-0.292	6.471	34.340	0.000	0.000	down
NM_016938	EFEMP2	-0.395	6.540	48.508	0.000	0.000	down
NM_016948	PARD6A	-0.660	1.410	34.178	0.000	0.000	down
NM_017422	CALML5	-8.244	0.488	105.057	0.000	0.001	down
NM_017432	PTOV1	-0.335	5.157	48.245	0.000	0.000	down
NM_017436	A4GALT	-0.585	3.945	32.808	0.000	0.001	down
NM_017514	PLXNA3	-0.403	5.384	25.813	0.000	0.002	down
NM_017525	CDC42BPG	-1.187	-0.207	20.430	0.000	0.004	down
NM_017550	MIER2	-0.505	3.421	34.852	0.000	0.000	down
NM_017556	FBLIM1	-0.517	4.989	22.838	0.000	0.003	down
NM_017566	KLHDC4	-0.202	3.783	9.648	0.006	0.041	down
NM_017570	OPLAH	-0.717	3.715	53.308	0.000	0.000	down
NM_017592	MED29	-0.166	5.805	10.273	0.005	0.035	down
NM_017607	PPP1R12C	-0.553	6.356	105.302	0.000	0.000	down
NM_017617	NOTCH1	-0.637	5.931	134.616	0.000	0.000	down
NM_017621	ALKBH4	-0.260	2.994	9.660	0.006	0.041	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_017622	BORCS6	-0.500	2.975	24.865	0.000	0.002	down
NM_017636	TRPM4	-0.461	4.517	57.921	0.000	0.000	down
NM_017721	CC2D1A	-0.610	4.536	132.488	0.000	0.000	down
NM_017723	TOR4A	-0.304	2.445	9.828	0.006	0.039	down
NM_017728	TMEM104	-0.266	5.095	25.738	0.000	0.002	down
NM_017758	ALKBH5	-0.240	6.244	26.716	0.000	0.001	down
NM_017789	SEMA4C	-0.407	4.567	45.015	0.000	0.000	down
NM_017793	RPP25	-0.264	2.850	11.464	0.003	0.027	down
NM_017797	BTBD2	-0.724	5.321	95.525	0.000	0.000	down
NM_017814	TMEM161A	-0.511	3.444	30.493	0.000	0.001	down
NM_017818	WRAP73	-0.212	3.644	12.709	0.002	0.020	down
NM_017820	EXD3	-0.959	2.629	102.896	0.000	0.000	down
NM_017825	ADPRHL2	-0.265	4.805	21.965	0.000	0.003	down
NM_017827	SARS2	-0.318	3.756	27.219	0.000	0.001	down
NM_017838	NHP2	-0.230	5.049	18.891	0.000	0.006	down
NM_017854	TMEM160	-0.571	1.180	13.710	0.002	0.016	down
NM_017857	SSH3	-0.436	4.922	42.238	0.000	0.000	down
NM_017859	UCKL1	-0.395	4.549	40.326	0.000	0.000	down
NM_017870	TMEM132A	-0.591	1.337	12.098	0.003	0.023	down
NM_017873	ASB6	-0.280	4.275	20.460	0.000	0.004	down
NM_017882	CLN6	-0.187	4.615	9.454	0.007	0.043	down
NM_017908	ZNF446	-0.411	2.855	14.369	0.001	0.014	down
NM_017914	C19orf24	-0.970	3.493	95.873	0.000	0.000	down
NM_017916	PIH1D1	-0.207	5.011	17.297	0.001	0.008	down
NM_017921	NPLOC4	-0.160	7.645	9.391	0.007	0.044	down
NM_017966	VPS37C	-0.319	4.315	27.842	0.000	0.001	down
NM_017999	RNF31	-0.225	5.137	14.861	0.001	0.013	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_018006	TRMU	-0.278	3.736	20.911	0.000	0.004	down
NM_018009	TAPBPL	-0.227	5.091	16.087	0.001	0.010	down
NM_018044	NSUN5	-0.421	3.531	32.004	0.000	0.001	down
NM_018049	PLEKHJ1	-0.335	4.719	32.832	0.000	0.001	down
NM_018052	VAC14	-0.253	4.965	14.816	0.001	0.013	down
NM_018059	RADIL	-0.476	1.377	9.710	0.006	0.041	down
NM_018067	MAP7D1	-0.376	7.786	29.388	0.000	0.001	down
NM_018074	CCDC94	-0.291	3.445	12.600	0.002	0.021	down
NM_018083	ZNF358	-0.608	5.713	74.786	0.000	0.000	down
NM_018174	MAP1S	-0.883	2.987	71.066	0.000	0.000	down
NM_018210	NAXD	-0.168	5.548	17.251	0.001	0.008	down
NM_018216	PANK4	-0.289	3.949	19.897	0.000	0.005	down
NM_018226	RNPEPL1	-0.668	6.258	205.169	0.000	0.000	down
NM_018275	C7orf43	-0.230	3.611	10.585	0.005	0.033	down
NM_018358	ABCF3	-0.126	5.745	9.032	0.008	0.048	down
NM_018378	FBXL8	-0.884	0.924	16.870	0.001	0.009	down
NM_018389	SLC35C1	-0.341	6.033	12.714	0.002	0.020	down
NM_018419	SOX18	-0.615	3.058	19.629	0.000	0.005	down
NM_018641	CHST12	-0.419	3.033	31.693	0.000	0.001	down
NM_018670	MESP1	-0.658	3.284	25.694	0.000	0.002	down
NM_018690	APOBR	-0.565	3.153	11.125	0.004	0.029	down
NM_018694	ARL6IP4	-0.324	6.602	38.577	0.000	0.000	down
NM_018708	FEM1A	-0.248	4.776	19.927	0.000	0.005	down
NM_018957	SH3BP1	-0.560	2.335	17.855	0.001	0.007	down
NM_018973	DPM3	-0.796	3.083	46.747	0.000	0.000	down
NM_018992	KCTD5	-0.346	3.661	26.043	0.000	0.002	down
NM_018998	FBXW5	-0.742	5.927	113.291	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_019009	TOLLIP	-0.392	5.821	45.069	0.000	0.000	down
NM_019015	CHPF2	-0.484	5.306	77.748	0.000	0.000	down
NM_019020	TBC1D16	-0.233	8.731	14.358	0.001	0.014	down
NM_019037	EXOSC4	-0.692	2.503	35.284	0.000	0.000	down
NM_019055	ROBO4	-0.290	6.703	9.103	0.008	0.047	down
NM_019070	DDX49	-0.514	4.279	58.445	0.000	0.000	down
NM_019103	ZMAT5	-0.395	3.493	21.066	0.000	0.004	down
NM_019108	SMG9	-0.164	4.412	10.082	0.005	0.037	down
NM_019112	ABCA7	-0.439	3.617	29.279	0.000	0.001	down
NM_019121	PPP1R37	-0.619	3.668	73.295	0.000	0.000	down
NM_019613	WDR45B	-0.186	6.524	15.262	0.001	0.012	down
NM_019848	SLC10A3	-0.474	4.370	45.335	0.000	0.000	down
NM_019885	CYP26B1	-0.420	5.663	34.317	0.000	0.000	down
NM_019892	INPP5E	-0.304	4.154	18.309	0.000	0.006	down
NM_020062	SLC2A4RG	-0.454	6.616	39.349	0.000	0.000	down
NM_020126	SPHK2	-0.628	3.333	48.306	0.000	0.000	down
NM_020127	TUFT1	-0.386	4.408	12.127	0.003	0.023	down
NM_020132	AGPAT3	-0.241	6.872	17.921	0.001	0.007	down
NM_020135	WRNIP1	-0.132	4.700	8.983	0.008	0.049	down
NM_020142	NDUFA4L2	-0.733	4.192	86.371	0.000	0.000	down
NM_020145	SH3GLB2	-0.346	5.425	37.841	0.000	0.000	down
NM_020158	EXOSC5	-0.546	2.798	33.427	0.000	0.001	down
NM_020160	MEIS3	-0.428	1.489	14.040	0.002	0.015	down
NM_020175	DUS3L	-0.661	3.118	58.249	0.000	0.000	down
NM_020195	SDR39U1	-0.202	5.334	15.564	0.001	0.011	down
NM_020196	XAB2	-0.483	4.808	59.789	0.000	0.000	down
NM_020201	NT5M	-0.722	1.190	21.990	0.000	0.003	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_020218	ATXN7L3	-0.221	6.035	15.418	0.001	0.011	down
NM_020223	FAM20C	-0.500	5.360	34.915	0.000	0.000	down
NM_020230	PPAN	-0.431	3.753	50.106	0.000	0.000	down
NM_020246	SLC12A9	-0.526	4.156	52.574	0.000	0.000	down
NM_020248	CTNNBIP1	-0.323	6.207	11.318	0.004	0.028	down
NM_020310	MNT	-0.203	4.594	9.533	0.006	0.042	down
NM_020315	PDXP	-0.613	3.175	25.256	0.000	0.002	down
NM_020338	ZMIZ1	-0.220	7.303	17.551	0.001	0.008	down
NM_020360	PLSCR3	-0.189	4.932	9.879	0.006	0.039	down
NM_020376	PNPLA2	-0.506	9.714	41.273	0.000	0.000	down
NM_020404	CD248	-0.422	8.678	21.973	0.000	0.003	down
NM_020410	ATP13A1	-0.361	4.753	50.051	0.000	0.000	down
NM_020427	SLURP1	-6.303	-0.818	28.840	0.001	0.013	down
NM_020438	DOLPP1	-0.362	3.794	31.502	0.000	0.001	down
NM_020441	CORO1B	-0.652	5.317	181.751	0.000	0.000	down
NM_020451	SELENON	-0.268	7.095	28.024	0.000	0.001	down
NM_020457	THAP11	-0.204	4.530	17.630	0.001	0.007	down
NM_020461	TUBGCP6	-0.277	5.692	47.348	0.000	0.000	down
NM_020470	YIF1A	-0.436	5.193	62.365	0.000	0.000	down
NM_020529	NFKBIA	-0.230	5.901	9.934	0.006	0.039	down
NM_020533	MCOLN1	-0.304	4.340	20.450	0.000	0.004	down
NM_020632	ATP6V0A4	-4.927	-1.868	13.951	0.008	0.050	down
NM_020649	CBX8	-0.740	1.630	26.862	0.000	0.001	down
NM_020650	RCN3	-0.358	4.811	14.724	0.001	0.013	down
NM_020664	DECR2	-0.472	4.122	31.647	0.000	0.001	down
NM_020680	SCYL1	-0.427	6.016	59.085	0.000	0.000	down
NM_020695	REXO1	-0.649	3.981	124.695	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_020709	PNMAL2	-0.342	4.570	14.701	0.001	0.013	down
NM_020710	LRRC47	-0.149	5.532	9.476	0.007	0.043	down
NM_020713	ZNF512B	-0.453	5.142	66.649	0.000	0.000	down
NM_020719	PRR12	-0.618	4.450	75.068	0.000	0.000	down
NM_020753	CASKIN2	-0.530	4.996	62.549	0.000	0.000	down
NM_020761	RPTOR	-0.352	4.724	30.655	0.000	0.001	down
NM_020812	DOCK6	-0.251	7.177	18.885	0.000	0.006	down
NM_020820	PREX1	-0.353	5.257	15.280	0.001	0.012	down
NM_020857	VPS18	-0.249	5.092	18.053	0.001	0.007	down
NM_020888	KIAA1522	-0.228	4.362	12.063	0.003	0.024	down
NM_020892	DTX2	-0.602	2.975	42.000	0.000	0.000	down
NM_020895	GRAMD1A	-0.452	4.361	40.022	0.000	0.000	down
NM_020896	OSBPL5	-0.377	4.700	44.596	0.000	0.000	down
NM_020904	PLEKHA4	-0.392	4.150	11.734	0.003	0.025	down
NM_020946	DENND1A	-0.218	4.459	19.222	0.000	0.005	down
NM_020950	KIAA1614	-0.395	3.170	17.734	0.001	0.007	down
NM_020956	PRX	-0.321	3.544	16.098	0.001	0.010	down
NM_020959	ANO8	-0.270	3.735	11.382	0.003	0.027	down
NM_020971	SPTBN4	-0.443	2.724	14.266	0.001	0.014	down
NM_021008	DEAF1	-0.329	4.101	20.576	0.000	0.004	down
NM_021020	LZTS1	-0.503	2.184	11.141	0.004	0.029	down
NM_021107	MRPS12	-0.491	3.574	34.650	0.000	0.000	down
NM_021128	POLR2L	-0.567	6.959	59.331	0.000	0.000	down
NM_021134	MRPL23	-0.372	4.532	24.943	0.000	0.002	down
NM_021138	TRAF2	-0.350	3.202	16.901	0.001	0.008	down
NM_021184	C6orf47	-0.186	5.015	15.542	0.001	0.011	down
NM_021198	CTDSP1	-0.298	7.390	30.111	0.000	0.001	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_021216	ZNF71	-0.329	3.134	19.975	0.000	0.005	down
NM_021228	SCAF1	-0.637	4.931	139.648	0.000	0.000	down
NM_021242	MID1IP1	-0.295	5.680	25.949	0.000	0.002	down
NM_021259	TMEM8A	-0.598	4.530	102.404	0.000	0.000	down
NM_021630	PDLIM2	-0.596	4.360	54.649	0.000	0.000	down
NM_021640	C12orf10	-0.193	4.658	11.274	0.004	0.028	down
NM_021724	NR1D1	-0.271	6.130	13.872	0.002	0.016	down
NM_021727	FADS3	-0.467	8.295	41.826	0.000	0.000	down
NM_021923	FGFRL1	-0.465	5.837	34.451	0.000	0.000	down
NM_021933	MIIP	-0.507	3.292	28.949	0.000	0.001	down
NM_021934	ATG101	-0.198	4.413	10.037	0.005	0.037	down
NM_021937	EEFSEC	-0.204	3.842	9.515	0.007	0.042	down
NM_021958	HLX	-0.408	3.348	19.816	0.000	0.005	down
NM_021975	RELA	-0.223	5.976	21.797	0.000	0.003	down
NM_021978	ST14	-0.642	3.397	12.822	0.002	0.020	down
NM_022036	GPRC5C	-0.642	3.860	34.673	0.000	0.000	down
NM_022039	FBXW4	-0.298	6.709	24.647	0.000	0.002	down
NM_022044	SDF2L1	-0.346	2.097	9.625	0.006	0.041	down
NM_022061	MRPL17	-0.184	4.609	13.814	0.002	0.016	down
NM_022089	ATP13A2	-0.575	4.715	93.258	0.000	0.000	down
NM_022092	CHTF18	-1.025	1.641	47.714	0.000	0.000	down
NM_022095	ZNF335	-0.270	4.870	17.995	0.001	0.007	down
NM_022104	PCIF1	-0.313	5.118	26.108	0.000	0.002	down
NM_022149	MAGEF1	-0.288	4.493	14.769	0.001	0.013	down
NM_022153	VSIR	-0.296	6.559	22.694	0.000	0.003	down
NM_022156	DUS1L	-0.495	5.808	80.728	0.000	0.000	down
NM_022165	LIN7B	-0.842	1.035	27.872	0.000	0.001	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_022167	XYLT2	-0.479	4.108	29.416	0.000	0.001	down
NM_022338	C11orf24	-0.460	5.778	39.813	0.000	0.000	down
NM_022450	RHBDF1	-0.427	4.784	89.820	0.000	0.000	down
NM_022460	HS1BP3	-0.171	4.606	11.220	0.004	0.028	down
NM_022464	SIL1	-0.276	5.614	25.315	0.000	0.002	down
NM_022480	KLHL25	-0.476	4.537	24.740	0.000	0.002	down
NM_022489	INF2	-0.722	7.182	109.895	0.000	0.000	down
NM_022574	GIGYF1	-0.203	6.419	10.039	0.005	0.037	down
NM_022719	DGCR14	-0.388	3.804	33.674	0.000	0.001	down
NM_022737	PLPPR2	-0.196	4.167	10.682	0.004	0.032	down
NM_022744	C16orf58	-0.230	6.263	25.121	0.000	0.002	down
NM_022749	FAM160B2	-0.349	5.776	64.651	0.000	0.000	down
NM_022752	ZNF574	-0.526	3.325	43.810	0.000	0.000	down
NM_022772	EPS8L2	-0.446	2.741	9.449	0.007	0.043	down
NM_022773	LMF1	-0.352	3.251	13.134	0.002	0.018	down
NM_022830	TUT1	-0.215	4.819	13.834	0.002	0.016	down
NM_022833	FAM129B	-0.428	5.971	38.914	0.000	0.000	down
NM_022834	VWA1	-0.745	4.582	103.447	0.000	0.000	down
NM_022836	DCLRE1B	-0.211	3.596	9.129	0.007	0.047	down
NM_022903	CCDC71	-0.354	4.027	38.526	0.000	0.000	down
NM_022917	NOL6	-0.158	5.564	10.412	0.005	0.034	down
NM_023007	JMJD4	-0.399	3.946	29.434	0.000	0.001	down
NM_023083	CAPN10	-0.645	3.083	47.423	0.000	0.000	down
NM_023931	ZNF747	-0.282	4.053	17.893	0.001	0.007	down
NM_023933	FAM173A	-1.097	1.371	61.093	0.000	0.000	down
NM_023935	DDRGK1	-0.240	4.973	15.394	0.001	0.011	down
NM_023948	MOSPD3	-0.509	2.985	35.112	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_024031	PRR14	-0.327	4.358	27.605	0.000	0.001	down
NM_024036	LRFN4	-1.040	3.606	152.358	0.000	0.000	down
NM_024042	METRN	-0.532	3.194	37.868	0.000	0.000	down
NM_024050	DDA1	-0.320	4.803	34.562	0.000	0.000	down
NM_024066	ERI3	-0.166	5.519	9.029	0.008	0.048	down
NM_024067	C7orf26	-0.165	4.460	13.184	0.002	0.018	down
NM_024075	TSEN34	-0.245	4.453	10.051	0.005	0.037	down
NM_024078	NOC4L	-0.621	2.678	44.093	0.000	0.000	down
NM_024100	WDR18	-0.398	3.019	13.986	0.002	0.015	down
NM_024105	ALG12	-0.272	4.136	14.940	0.001	0.013	down
NM_024108	TRAPPC6A	-0.770	3.477	63.348	0.000	0.000	down
NM_024112	C9orf16	-1.107	3.954	77.099	0.000	0.000	down
NM_024164	TPSB2	-0.579	3.734	18.368	0.000	0.006	down
NM_024165	PHF1	-0.177	5.685	9.534	0.006	0.042	down
NM_024297	PHF23	-0.268	4.967	15.214	0.001	0.012	down
NM_024299	PPDPF	-0.563	5.780	77.438	0.000	0.000	down
NM_024309	TNIP2	-0.319	5.278	34.104	0.000	0.000	down
NM_024321	RBM42	-0.464	4.989	48.765	0.000	0.000	down
NM_024326	FBXL15	-0.725	1.787	53.153	0.000	0.000	down
NM_024329	EFHD2	-0.531	5.024	58.612	0.000	0.000	down
NM_024336	IRX3	-0.745	2.285	19.451	0.000	0.005	down
NM_024337	IRX1	-0.705	2.429	35.994	0.000	0.000	down
NM_024407	NDUFS7	-1.255	3.544	95.769	0.000	0.000	down
NM_024496	IRF2BPL	-0.509	5.895	32.655	0.000	0.001	down
NM_024516	PAGR1	-0.176	4.572	10.192	0.005	0.036	down
NM_024527	ABHD8	-0.713	2.259	37.944	0.000	0.000	down
NM_024531	SLC52A2	-0.664	4.095	75.944	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_024535	CORO7	-0.654	3.953	78.830	0.000	0.000	down
NM_024536	CHPF	-0.854	3.986	113.938	0.000	0.000	down
NM_024552	CERS4	-0.329	3.934	17.977	0.001	0.007	down
NM_024591	CHMP6	-0.585	3.915	56.373	0.000	0.000	down
NM_024599	RHBDF2	-0.451	3.075	22.730	0.000	0.003	down
NM_024600	TMEM204	-0.406	4.322	41.965	0.000	0.000	down
NM_024608	NEIL1	-0.323	3.353	17.337	0.001	0.008	down
NM_024660	IGFLR1	-0.540	2.441	19.112	0.000	0.006	down
NM_024667	VPS37B	-0.261	4.320	16.769	0.001	0.009	down
NM_024671	ZNF768	-0.279	4.912	27.086	0.000	0.001	down
NM_024698	SLC25A22	-0.824	2.564	69.983	0.000	0.000	down
NM_024706	ZNF668	-1.080	1.956	51.073	0.000	0.000	down
NM_024710	ISOC2	-0.462	4.817	39.466	0.000	0.000	down
NM_024712	ELMO3	-0.693	0.748	11.178	0.004	0.029	down
NM_024735	FBXO31	-0.176	5.600	12.143	0.003	0.023	down
NM_024741	ZNF408	-0.298	2.454	9.826	0.006	0.039	down
NM_024742	ARMC5	-0.565	2.419	31.489	0.000	0.001	down
NM_024747	HPS6	-0.385	3.868	39.073	0.000	0.000	down
NM_024757	EHMT1	-0.168	5.775	17.497	0.001	0.008	down
NM_024815	NUDT18	-0.374	3.440	25.786	0.000	0.002	down
NM_024816	RABEP2	-0.782	2.652	63.775	0.000	0.000	down
NM_024827	HDAC11	-0.215	4.581	9.829	0.006	0.039	down
NM_024830	LPCAT1	-0.156	5.048	9.850	0.006	0.039	down
NM_024832	RIN3	-0.280	3.858	10.556	0.005	0.033	down
NM_024876	COQ8B	-0.387	4.336	44.518	0.000	0.000	down
NM_024919	FRMD1	-0.448	3.317	11.253	0.004	0.028	down
NM_024927	PLEKHH3	-0.954	3.566	70.464	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_024954	UBTD1	-0.863	3.512	47.454	0.000	0.000	down
NM_024963	FBXL18	-0.319	3.951	16.875	0.001	0.009	down
NM_025069	ZNF703	-0.710	4.678	70.048	0.000	0.000	down
NM_025072	PTGES2	-0.520	4.478	117.759	0.000	0.000	down
NM_025078	PQLC1	-0.696	5.562	114.607	0.000	0.000	down
NM_025082	CENPT	-0.186	5.318	10.014	0.005	0.038	down
NM_025092	PGGHG	-0.305	4.863	14.739	0.001	0.013	down
NM_025108	C16orf59	-1.562	-1.191	14.546	0.001	0.014	down
NM_025128	MUS81	-0.236	4.527	25.853	0.000	0.002	down
NM_025182	FAM214B	-0.421	5.051	22.407	0.000	0.003	down
NM_025193	HSD3B7	-0.406	5.285	20.038	0.000	0.005	down
NM_025194	ITPKC	-0.342	4.749	20.730	0.000	0.004	down
NM_025201	PLEKHO2	-0.483	7.162	31.515	0.000	0.001	down
NM_025215	PUS1	-0.385	3.334	19.370	0.000	0.005	down
NM_025219	DNAJC5	-0.330	6.577	47.952	0.000	0.000	down
NM_025224	ZBTB46	-0.322	3.818	15.340	0.001	0.012	down
NM_025232	REEP4	-0.330	2.785	10.916	0.004	0.030	down
NM_025233	COASY	-0.157	5.424	11.303	0.004	0.028	down
NM_025241	UBXN6	-0.608	6.497	67.726	0.000	0.000	down
NM_025248	SRCIN1	-0.497	1.018	10.327	0.005	0.035	down
NM_025250	TTYH3	-0.587	5.148	23.721	0.000	0.002	down
NM_025251	ARHGAP39	-0.762	0.952	34.208	0.000	0.000	down
NM_030573	THAP7	-0.647	3.263	51.826	0.000	0.000	down
NM_030576	LIMD2	-0.376	3.044	9.331	0.007	0.044	down
NM_030587	B4GALT2	-0.434	6.172	54.249	0.000	0.000	down
NM_030615	KIF25	-0.802	1.428	23.441	0.000	0.003	down
NM_030649	ACAP3	-0.399	4.812	41.300	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_030662	MAP2K2	-0.438	5.337	42.621	0.000	0.000	down
NM_030665	RAI1	-0.739	4.674	146.649	0.000	0.000	down
NM_030782	CLPTM1L	-0.197	6.683	11.639	0.003	0.026	down
NM_030792	GDPD5	-0.302	6.826	16.486	0.001	0.009	down
NM_030926	ITM2C	-0.244	5.424	15.588	0.001	0.011	down
NM_030930	UNC93B1	-0.585	3.763	46.759	0.000	0.000	down
NM_030935	TSC22D4	-0.589	4.425	123.999	0.000	0.000	down
NM_030952	NUAK2	-0.590	1.145	16.501	0.001	0.009	down
NM_030957	ADAMTS10	-0.257	4.610	11.134	0.004	0.029	down
NM_030973	MED25	-0.663	3.458	79.666	0.000	0.000	down
NM_030974	SHARPIN	-0.575	5.112	89.879	0.000	0.000	down
NM_030981	RAB1B	-0.230	7.802	15.955	0.001	0.010	down
NM_031209	QTRT1	-0.580	4.109	72.683	0.000	0.000	down
NM_031213	ABHD17A	-0.768	3.125	55.485	0.000	0.000	down
NM_031219	HDHD3	-0.357	4.144	20.234	0.000	0.005	down
NM_031229	RBCK1	-0.368	5.437	61.530	0.000	0.000	down
NM_031232	NECAB3	-0.508	3.763	31.921	0.000	0.001	down
NM_031283	TCF7L1	-0.236	5.569	13.275	0.002	0.018	down
NM_031287	SF3B5	-0.220	5.935	10.790	0.004	0.031	down
NM_031297	RNF208	-1.044	1.231	68.706	0.000	0.000	down
NM_031300	MXD3	-0.878	0.858	28.234	0.000	0.001	down
NM_031430	RILP	-0.187	4.913	10.485	0.005	0.034	down
NM_031434	TMUB1	-0.729	3.452	98.448	0.000	0.000	down
NM_031449	ZMIZ2	-0.339	6.035	42.474	0.000	0.000	down
NM_031454	SELENOO	-0.593	3.798	59.350	0.000	0.000	down
NM_031459	SESN2	-0.486	4.416	30.035	0.000	0.001	down
NM_031464	RPS6KL1	-0.306	3.738	11.539	0.003	0.026	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_031477	YPEL3	-0.218	5.037	12.704	0.002	0.020	down
NM_031485	GRWD1	-0.197	4.677	13.393	0.002	0.017	down
NM_031904	FRMD8	-0.373	4.823	30.598	0.000	0.001	down
NM_031910	C1QTNF6	-0.293	3.140	10.383	0.005	0.035	down
NM_031918	KLF16	-0.397	2.650	18.817	0.000	0.006	down
NM_031946	AGAP3	-0.437	5.470	47.394	0.000	0.000	down
NM_031968	NARF	-0.167	4.932	9.210	0.007	0.046	down
NM_032017	STK40	-0.329	7.011	35.908	0.000	0.000	down
NM_032019	HDAC10	-0.638	3.498	65.659	0.000	0.000	down
NM_032038	SPNS1	-0.465	4.281	38.592	0.000	0.000	down
NM_032108	SEMA6B	-0.400	3.551	12.927	0.002	0.019	down
NM_032112	MRPL43	-0.213	4.924	16.604	0.001	0.009	down
NM_032140	ENKD1	-0.343	2.665	12.899	0.002	0.020	down
NM_032223	PCNX3	-0.557	5.033	91.577	0.000	0.000	down
NM_032242	PLXNA1	-0.507	5.890	82.067	0.000	0.000	down
NM_032251	CCDC88B	-0.626	2.679	32.268	0.000	0.001	down
NM_032259	WDR24	-0.550	2.578	58.930	0.000	0.000	down
NM_032271	TRAF7	-0.472	5.600	83.062	0.000	0.000	down
NM_032272	MAF1	-0.256	6.597	21.132	0.000	0.004	down
NM_032283	ZDHHC18	-0.171	5.285	14.204	0.001	0.015	down
NM_032301	FBXW9	-0.438	1.983	12.531	0.002	0.021	down
NM_032302	PSMG3	-0.235	3.894	11.710	0.003	0.026	down
NM_032306	ALKBH7	-0.691	3.606	51.279	0.000	0.000	down
NM_032309	CHCHD5	-0.532	3.152	28.833	0.000	0.001	down
NM_032344	NUDT22	-0.641	3.529	38.962	0.000	0.000	down
NM_032348	MXRA8	-0.300	7.818	11.858	0.003	0.025	down
NM_032355	MON1A	-0.251	3.497	13.921	0.002	0.016	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_032356	NAA38	-0.550	4.543	59.928	0.000	0.000	down
NM_032367	ZBED3	-0.348	3.622	16.181	0.001	0.010	down
NM_032375	AKT1S1	-0.265	5.402	23.810	0.000	0.002	down
NM_032377	ELOF1	-0.317	4.944	35.180	0.000	0.000	down
NM_032378	EEF1D	-0.359	7.685	47.408	0.000	0.000	down
NM_032409	PINK1	-0.245	7.424	17.407	0.001	0.008	down
NM_032421	CLIP2	-0.414	4.406	38.719	0.000	0.000	down
NM_032431	SYVN1	-0.178	6.386	13.376	0.002	0.018	down
NM_032444	SLX4	-0.284	3.330	15.897	0.001	0.010	down
NM_032449	CC2D1B	-0.170	5.697	17.945	0.001	0.007	down
NM_032450	MROH1	-0.442	2.214	20.359	0.000	0.004	down
NM_032477	MRPL41	-0.611	4.435	67.401	0.000	0.000	down
NM_032478	MRPL38	-0.416	5.072	54.890	0.000	0.000	down
NM_032482	DOT1L	-0.608	3.896	43.297	0.000	0.000	down
NM_032514	MAP1LC3A	-0.397	4.415	23.286	0.000	0.003	down
NM_032515	BOK	-0.462	7.610	23.352	0.000	0.003	down
NM_032520	GNPTG	-0.356	5.740	38.969	0.000	0.000	down
NM_032527	ZGPAT	-0.553	4.146	93.643	0.000	0.000	down
NM_032534	KRBA1	-0.372	2.691	15.002	0.001	0.012	down
NM_032548	ABTB1	-0.346	4.973	34.540	0.000	0.000	down
NM_032552	DAB2IP	-0.466	6.360	79.500	0.000	0.000	down
NM_032595	PPP1R9B	-0.270	5.900	18.863	0.000	0.006	down
NM_032611	PTP4A3	-0.338	3.695	13.778	0.002	0.016	down
NM_032627	SSBP4	-0.657	3.333	50.962	0.000	0.000	down
NM_032630	CINP	-0.188	4.325	9.884	0.006	0.039	down
NM_032656	DHX37	-0.286	4.021	16.832	0.001	0.009	down
NM_032683	MPV17L2	-0.279	3.278	12.378	0.003	0.022	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_032687	CYHR1	-0.289	4.380	16.170	0.001	0.010	down
NM_032701	KMT5C	-0.441	2.056	16.781	0.001	0.009	down
NM_032711	MAFG	-0.241	5.170	16.800	0.001	0.009	down
NM_032728	PLPP7	-0.291	3.046	9.320	0.007	0.045	down
NM_032737	LMNB2	-0.405	4.272	35.284	0.000	0.000	down
NM_032772	ZNF503	-0.533	4.205	27.745	0.000	0.001	down
NM_032775	KLHL22	-0.266	4.952	25.585	0.000	0.002	down
NM_032790	ORAI1	-0.681	2.666	54.365	0.000	0.000	down
NM_032800	C1orf198	-0.292	7.485	9.005	0.008	0.048	down
NM_032818	ARHGEF39	-0.878	0.024	12.189	0.003	0.023	down
NM_032827	ATOH8	-0.361	4.700	20.447	0.000	0.004	down
NM_032848	RITA1	-0.264	3.532	9.472	0.007	0.043	down
NM_032862	TIGD5	-0.995	1.082	31.553	0.000	0.001	down
NM_032881	LSM10	-0.247	5.012	12.044	0.003	0.024	down
NM_032928	TMEM141	-0.247	4.458	14.907	0.001	0.013	down
NM_032951	MLXIPL	-0.276	7.714	19.790	0.000	0.005	down
NM_032995	ARHGEF4	-0.417	3.520	12.349	0.003	0.022	down
NM_033018	CDK16	-0.170	6.496	10.410	0.005	0.034	down
NM_033025	SYDE1	-0.392	4.997	37.425	0.000	0.000	down
NM_033027	CSRNP1	-0.669	3.320	45.634	0.000	0.000	down
NM_033070	CECR5	-0.272	4.651	24.635	0.000	0.002	down
NM_033113	ZNF628	-1.189	0.445	37.368	0.000	0.000	down
NM_033133	CNP	-0.190	6.463	12.356	0.003	0.022	down
NM_033158	HYAL2	-0.497	5.615	16.622	0.001	0.009	down
NM_033200	LMF2	-0.671	5.712	101.111	0.000	0.000	down
NM_033212	CCDC102A	-0.595	1.894	20.018	0.000	0.005	down
NM_033215	PPP1R3F	-0.537	1.501	16.077	0.001	0.010	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_033254	BOC	-0.214	5.618	8.983	0.008	0.049	down
NM_033256	PPP1R14A	-0.522	4.273	15.785	0.001	0.011	down
NM_033257	DGCR6L	-0.644	4.006	49.691	0.000	0.000	down
NM_033271	BTBD6	-0.351	7.635	28.816	0.000	0.001	down
NM_033386	MICALL1	-0.289	4.766	16.157	0.001	0.010	down
NM_033396	TNKS1BP1	-0.309	8.654	24.663	0.000	0.002	down
NM_033446	MVB12B	-0.233	4.208	17.244	0.001	0.008	down
NM_033449	FCHSD1	-0.291	3.849	11.068	0.004	0.029	down
NM_033452	TRIM47	-0.443	4.180	28.042	0.000	0.001	down
NM_033513	TPGS1	-2.063	-0.622	22.190	0.000	0.003	down
NM_033517	SHANK3	-0.394	6.985	17.660	0.001	0.007	down
NM_033549	TRIM41	-0.262	5.545	22.965	0.000	0.003	down
NM_033630	SCAND1	-1.325	2.607	136.823	0.000	0.000	down
NM_052821	WDR5	-0.160	5.206	9.237	0.007	0.046	down
NM_052844	WDR34	-0.408	2.986	19.185	0.000	0.005	down
NM_052850	GADD45GIP1	-0.534	4.401	58.084	0.000	0.000	down
NM_052853	ADCK2	-0.296	4.384	19.565	0.000	0.005	down
NM_052876	NACC1	-0.465	5.209	76.884	0.000	0.000	down
NM_052893	BTBD9	-0.159	4.533	10.325	0.005	0.035	down
NM_052897	MBD6	-0.211	5.915	12.603	0.002	0.021	down
NM_052901	SLC25A25	-0.330	4.141	10.545	0.005	0.033	down
NM_052902	STK11IP	-0.404	3.875	30.582	0.000	0.001	down
NM_052988	CDK10	-0.230	4.749	15.479	0.001	0.011	down
NM_053004	GNB1L	-0.906	0.571	16.029	0.001	0.010	down
NM_053005	MOB2	-0.277	4.831	28.264	0.000	0.001	down
NM_053044	HTRA3	-0.302	5.601	8.880	0.008	0.050	down
NM_053050	MRPL53	-0.355	4.544	17.542	0.001	0.008	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_054012	ASS1	-0.207	8.235	10.244	0.005	0.036	down
NM_054013	MGAT4B	-0.238	5.650	14.840	0.001	0.013	down
NM_054035	UNC119	-0.183	4.735	13.470	0.002	0.017	down
NM_057092	FKBP2	-0.270	4.946	16.422	0.001	0.009	down
NM_058173	MUCL1	-11.257	2.808	404.941	0.000	0.000	down
NM_058190	FAM207A	-0.569	1.684	20.995	0.000	0.004	down
NM_058243	BRD4	-0.229	4.583	14.491	0.001	0.014	down
NM_079421	CDKN2D	-0.317	2.527	11.962	0.003	0.024	down
NM_079834	SCAMP4	-0.411	5.022	42.721	0.000	0.000	down
NM_080430	SELENOM	-0.426	4.983	36.942	0.000	0.000	down
NM_080604	TJAP1	-0.252	4.755	28.518	0.000	0.001	down
NM_080621	SAMD10	-0.640	1.445	17.063	0.001	0.008	down
NM_080662	PEX11G	-0.610	1.636	17.790	0.001	0.007	down
NM_080732	EGLN2	-0.491	6.405	73.317	0.000	0.000	down
NM_080748	ROMO1	-0.550	4.751	69.270	0.000	0.000	down
NM_080861	SPSB3	-0.523	5.005	50.607	0.000	0.000	down
NM_080875	MIB2	-0.993	3.077	101.929	0.000	0.000	down
NM_130443	DPP3	-0.176	4.898	10.492	0.005	0.034	down
NM_130445	COL18A1	-0.428	6.740	48.445	0.000	0.000	down
NM_130459	TOR2A	-0.317	2.672	14.016	0.002	0.015	down
NM_130465	TSPAN17	-0.262	4.992	19.062	0.000	0.006	down
NM_130787	AP2A1	-0.372	5.961	55.970	0.000	0.000	down
NM_130807	MOB3A	-0.157	5.859	10.835	0.004	0.031	down
NM_133328	DEDD2	-0.287	3.604	12.164	0.003	0.023	down
NM_133373	PLCD3	-0.331	5.837	21.833	0.000	0.003	down
NM_133452	RAVER1	-0.429	4.013	46.781	0.000	0.000	down
NM_133467	CITED4	-0.957	3.033	69.283	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_133644	GTPBP3	-0.280	3.173	9.257	0.007	0.045	down
NM_134268	CYGB	-0.499	5.576	40.808	0.000	0.000	down
NM_134269	SMTN	-0.527	4.928	41.964	0.000	0.000	down
NM_134323	TARBP2	-0.338	3.504	25.384	0.000	0.002	down
NM_138300	PYGO2	-0.140	5.694	9.574	0.006	0.042	down
NM_138346	KIAA2013	-0.415	5.398	57.506	0.000	0.000	down
NM_138352	SAMD1	-0.206	4.657	14.073	0.002	0.015	down
NM_138353	DCAF15	-0.458	3.547	34.978	0.000	0.000	down
NM_138368	AP5B1	-0.251	5.207	18.916	0.000	0.006	down
NM_138370	PKDCC	-0.278	7.204	20.286	0.000	0.004	down
NM_138383	MTSS1L	-0.506	5.198	69.191	0.000	0.000	down
NM_138384	MTG1	-0.219	4.014	16.758	0.001	0.009	down
NM_138392	SHKBP1	-0.420	4.485	40.468	0.000	0.000	down
NM_138393	REEP6	-0.626	2.635	16.019	0.001	0.010	down
NM_138414	SGF29	-0.278	3.408	10.992	0.004	0.030	down
NM_138431	MFSD3	-0.733	2.526	74.277	0.000	0.000	down
NM_138440	VASN	-1.013	3.588	53.667	0.000	0.000	down
NM_138462	ZMYND19	-0.342	3.083	13.242	0.002	0.018	down
NM_138465	GLI4	-0.697	2.564	38.069	0.000	0.000	down
NM_138471	C11orf84	-0.407	2.504	22.017	0.000	0.003	down
NM_138481	CHADL	-0.658	1.058	9.612	0.006	0.041	down
NM_138499	PWWP2B	-0.693	3.758	51.945	0.000	0.000	down
NM_138689	PPP1R14B	-0.492	3.357	23.620	0.000	0.002	down
NM_138769	RHOT2	-0.586	5.463	103.407	0.000	0.000	down
NM_138774	R3HDM4	-0.379	4.826	27.299	0.000	0.001	down
NM_138783	ZNF653	-0.661	0.558	10.000	0.006	0.038	down
NM_138795	ARL8A	-0.380	5.310	31.012	0.000	0.001	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_138797	ANKRD54	-0.209	4.176	14.322	0.001	0.014	down
NM_138802	ZFAND2B	-0.181	4.766	12.789	0.002	0.020	down
NM_139033	MAPK7	-0.418	3.630	30.975	0.000	0.001	down
NM_139062	CSNK1D	-0.234	6.953	28.711	0.000	0.001	down
NM_139159	DPP9	-0.205	5.403	14.581	0.001	0.014	down
NM_139162	MIEF2	-0.375	2.797	16.162	0.001	0.010	down
NM_139343	BIN1	-0.241	6.294	15.597	0.001	0.011	down
NM_139355	MATK	-0.787	2.320	9.983	0.006	0.038	down
NM_144505	KLK8	-4.804	-1.710	14.878	0.007	0.044	down
NM_144585	SLC22A12	-1.042	0.575	15.331	0.001	0.012	down
NM_144589	COMTD1	-0.821	0.447	14.373	0.001	0.014	down
NM_144635	FAM131A	-0.412	3.556	31.162	0.000	0.001	down
NM_144653	NACC2	-0.361	6.432	38.346	0.000	0.000	down
NM_144679	TEPSIN	-0.318	3.639	14.615	0.001	0.013	down
NM_144716	CCDC12	-0.295	4.638	20.128	0.000	0.005	down
NM_144947	KLK11	-5.144	-1.432	16.375	0.006	0.038	down
NM_144999	LRRC45	-0.723	2.250	69.811	0.000	0.000	down
NM_145040	PRKCDBP	-0.375	4.639	25.482	0.000	0.002	down
NM_145057	CDC42EP5	-0.605	1.620	18.730	0.000	0.006	down
NM_145059	FUK	-0.225	3.557	12.499	0.002	0.021	down
NM_145065	PELI3	-0.358	3.943	17.599	0.001	0.007	down
NM_145166	ZBTB47	-0.401	6.389	45.499	0.000	0.000	down
NM_145201	NAPRT	-0.817	3.813	86.760	0.000	0.000	down
NM_145245	EVI5L	-0.462	4.070	42.397	0.000	0.000	down
NM_145253	UBALD1	-0.918	2.465	57.917	0.000	0.000	down
NM_145260	OSR1	-0.445	2.885	15.907	0.001	0.010	down
NM_145271	ZNF688	-0.353	3.033	13.969	0.002	0.015	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_145272	C17orf50	-3.351	-2.994	12.851	0.003	0.026	down
NM_145294	WDR90	-0.628	3.037	49.473	0.000	0.000	down
NM_145296	CADM4	-0.405	2.559	20.536	0.000	0.004	down
NM_145652	WFDC5	-5.123	-1.445	16.221	0.006	0.039	down
NM_145725	TRAF3	-0.329	5.549	34.351	0.000	0.000	down
NM_145730	AP1B1	-0.238	6.309	28.630	0.000	0.001	down
NM_145754	KIFC2	-0.266	4.220	14.536	0.001	0.014	down
NM_145806	ZNF511	-0.261	4.215	13.717	0.002	0.016	down
NM_145869	ANXA11	-0.186	8.364	12.639	0.002	0.021	down
NM_145886	PIDD1	-0.712	2.948	43.607	0.000	0.000	down
NM_145901	HMGA1	-0.643	4.802	16.622	0.001	0.009	down
NM_146388	MRPL4	-0.548	4.535	120.619	0.000	0.000	down
NM_147193	GLIS1	-1.095	-0.168	17.339	0.001	0.008	down
NM_148179	RPP25L	-0.239	3.174	9.751	0.006	0.040	down
NM_148965	TNFRSF25	-0.552	3.787	34.748	0.000	0.000	down
NM_152221	CSNK1E	-0.270	6.333	33.321	0.000	0.001	down
NM_152243	CDC42EP1	-0.748	5.632	82.652	0.000	0.000	down
NM_152260	RPUSD2	-0.294	2.926	13.396	0.002	0.017	down
NM_152274	FAM58A	-0.432	3.663	44.140	0.000	0.000	down
NM_152287	ZNF276	-0.226	4.547	11.297	0.004	0.028	down
NM_152293	TADA2B	-0.277	5.091	18.554	0.000	0.006	down
NM_152307	TRMT61A	-0.704	3.985	110.492	0.000	0.000	down
NM_152326	ANKRD9	-0.319	2.095	9.857	0.006	0.039	down
NM_152339	SPATA2L	-0.847	0.831	34.429	0.000	0.000	down
NM_152384	BBS5	-0.312	3.881	16.334	0.001	0.009	down
NM_152421	FAM69B	-0.421	3.837	17.923	0.001	0.007	down
NM_152441	FBXL14	-0.683	2.170	29.662	0.000	0.001	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_152443	RDH12	-3.684	-1.840	10.978	0.006	0.042	down
NM_152482	C19orf25	-0.628	3.244	48.066	0.000	0.000	down
NM_152493	ZNF362	-0.269	5.017	15.261	0.001	0.012	down
NM_152499	CCDC24	-0.518	1.182	19.264	0.000	0.005	down
NM_152558	IQCE	-0.255	4.587	23.769	0.000	0.002	down
NM_152600	ZNF579	-0.698	1.373	17.056	0.001	0.008	down
NM_152704	AMER2	-1.565	0.600	8.996	0.008	0.048	down
NM_152743	BRAT1	-0.588	4.427	49.901	0.000	0.000	down
NM_152783	D2HGDH	-0.515	3.864	36.424	0.000	0.000	down
NM_152833	C9orf69	-0.487	5.112	79.605	0.000	0.000	down
NM_152892	LRWD1	-0.478	2.544	34.738	0.000	0.000	down
NM_152911	PAOX	-0.320	1.978	11.615	0.003	0.026	down
NM_152914	NATD1	-0.359	6.838	16.114	0.001	0.010	down
NM_152988	SPPL2B	-0.672	4.331	75.311	0.000	0.000	down
NM_153219	ZNF524	-0.643	3.098	48.750	0.000	0.000	down
NM_153221	CILP2	-1.138	-1.090	10.418	0.005	0.034	down
NM_153253	SIPA1	-0.422	3.873	46.837	0.000	0.000	down
NM_153265	EML3	-0.336	6.460	46.773	0.000	0.000	down
NM_153329	ALDH16A1	-0.592	3.962	52.805	0.000	0.000	down
NM_153334	SCARF2	-0.768	2.396	38.141	0.000	0.000	down
NM_153367	ZCCHC24	-0.243	8.079	19.485	0.000	0.005	down
NM_153693	HOXC6	-0.202	4.602	9.273	0.007	0.045	down
NM_153818	PEX10	-0.213	4.776	11.845	0.003	0.025	down
NM_153827	MINK1	-0.167	6.275	13.068	0.002	0.019	down
NM_170600	SH2D3C	-0.319	4.441	11.865	0.003	0.025	down
NM_170707	LMNA	-0.466	8.462	75.457	0.000	0.000	down
NM_170711	DAZAP1	-0.272	5.620	34.108	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_170713	RASSF1	-0.296	5.571	20.043	0.000	0.005	down
NM_170746	SELENOH	-0.318	4.559	21.601	0.000	0.004	down
NM_170754	TNS2	-0.402	8.319	42.417	0.000	0.000	down
NM_172251	MRPL54	-0.188	5.165	12.866	0.002	0.020	down
NM_172367	TUSC5	-0.487	9.313	28.794	0.000	0.001	down
NM_173546	KLHDC8B	-0.325	6.621	12.890	0.002	0.020	down
NM_173547	TRIM65	-0.186	4.847	9.837	0.006	0.039	down
NM_173564	NYAP1	-0.473	0.829	10.008	0.005	0.038	down
NM_173587	RCOR2	-0.559	1.106	12.803	0.002	0.020	down
NM_173620	HEXDC	-0.457	3.260	23.974	0.000	0.002	down
NM_173680	ZNF775	-0.532	1.287	18.204	0.000	0.007	down
NM_173828	RELL2	-0.688	0.115	13.017	0.002	0.019	down
NM_173832	ZFP41	-0.303	3.302	22.394	0.000	0.003	down
NM_173852	KRTCAP2	-0.137	5.461	9.111	0.008	0.047	down
NM_174869	IDH3G	-0.215	5.428	20.413	0.000	0.004	down
NM_174905	FAM98C	-0.313	2.892	9.135	0.007	0.047	down
NM_174922	ADCK5	-0.648	1.900	24.424	0.000	0.002	down
NM_174923	CCDC107	-0.234	6.535	9.419	0.007	0.043	down
NM_174953	ATP2A3	-0.476	3.795	11.824	0.003	0.025	down
NM_174983	MFSD12	-0.701	4.128	25.449	0.000	0.002	down
NM_175039	ST6GALNAC4	-0.482	3.226	16.377	0.001	0.009	down
NM_175063	EMC10	-0.384	5.515	30.175	0.000	0.001	down
NM_175573	ADRM1	-0.599	5.717	63.508	0.000	0.000	down
NM_175744	RHOC	-0.233	7.396	21.531	0.000	0.004	down
NM_175875	SIX5	-0.649	3.882	39.840	0.000	0.000	down
NM_175902	OGFOD3	-0.349	4.576	36.934	0.000	0.000	down
NM_176782	FAM151A	-0.746	-0.469	10.589	0.005	0.033	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_176795	HRAS	-0.544	4.499	79.137	0.000	0.000	down
NM_177401	MIDN	-0.532	4.493	31.027	0.000	0.001	down
NM_177439	FTSJ1	-0.171	4.812	12.092	0.003	0.023	down
NM_177457	LYNX1	-0.301	5.375	20.165	0.000	0.005	down
NM_177533	NUDT14	-0.479	3.579	17.058	0.001	0.008	down
NM_177925	H2AFJ	-0.551	6.529	59.237	0.000	0.000	down
NM_177938	P4HTM	-0.231	3.771	10.797	0.004	0.031	down
NM_178001	PTPA	-0.177	6.301	19.107	0.000	0.006	down
NM_178012	TUBB2B	-0.498	2.649	22.366	0.000	0.003	down
NM_178167	ZNF598	-0.650	4.289	87.802	0.000	0.000	down
NM_178326	ATG4B	-0.315	4.908	39.747	0.000	0.000	down
NM_178348	LCE1A	-6.109	-0.932	26.099	0.002	0.016	down
NM_178349	LCE1B	-6.140	-0.914	26.525	0.002	0.016	down
NM_178429	LCE2C	-5.464	-1.265	18.975	0.004	0.029	down
NM_178443	FERMT3	-0.590	4.552	19.898	0.000	0.005	down
NM_178507	OAF	-0.339	6.469	16.267	0.001	0.010	down
NM_178508	C6orf1	-0.421	3.503	25.114	0.000	0.002	down
NM_178526	SLC25A42	-0.267	4.486	9.885	0.006	0.039	down
NM_178536	LCN12	-2.515	-2.672	9.259	0.008	0.047	down
NM_178557	NAT8L	-0.303	8.130	11.254	0.004	0.028	down
NM_178568	RTN4RL1	-0.579	4.275	21.913	0.000	0.003	down
NM_178570	RTN4RL2	-1.009	-0.284	9.227	0.007	0.046	down
NM_181462	MRPL55	-0.652	3.832	42.483	0.000	0.000	down
NM_181491	MED22	-0.325	5.521	36.749	0.000	0.000	down
NM_181719	TMCO4	-0.181	4.850	10.345	0.005	0.035	down
NM_181843	NUDT8	-0.657	2.604	36.010	0.000	0.000	down
NM_182498	ZNF428	-0.326	3.806	16.944	0.001	0.008	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_182557	BCL9L	-0.652	6.716	77.680	0.000	0.000	down
NM_182703	ANKDD1A	-0.376	5.343	11.842	0.003	0.025	down
NM_182706	SCRIB	-0.695	4.490	182.149	0.000	0.000	down
NM_182919	TICAM1	-0.454	2.737	18.761	0.000	0.006	down
NM_182924	MICALL2	-0.875	2.964	59.485	0.000	0.000	down
NM_182981	OSGIN1	-0.877	3.944	35.229	0.000	0.000	down
NM_183006	DLGAP4	-0.335	6.191	21.411	0.000	0.004	down
NM_183008	UBXN11	-0.305	4.104	17.960	0.001	0.007	down
NM_183057	VPS28	-0.374	5.864	53.158	0.000	0.000	down
NM_183241	C9orf142	-0.576	2.962	61.907	0.000	0.000	down
NM_183357	ADCY5	-0.308	6.369	9.778	0.006	0.040	down
NM_183373	PXDC1	-0.299	6.686	16.128	0.001	0.010	down
NM_194255	SLC19A1	-0.457	3.108	25.609	0.000	0.002	down
NM_194278	ELMSAN1	-0.270	5.937	23.618	0.000	0.002	down
NM_194458	UBE2J2	-0.239	4.797	19.382	0.000	0.005	down
NM_194460	RNF126	-0.841	3.182	73.947	0.000	0.000	down
NM_197956	NAIF1	-0.300	2.922	13.498	0.002	0.017	down
NM_197964	FMC1	-0.354	3.839	12.890	0.002	0.020	down
NM_198075	LRRC56	-1.334	-0.816	14.304	0.001	0.014	down
NM_198149	SHISA4	-0.242	3.306	9.278	0.007	0.045	down
NM_198219	ING1	-0.257	3.192	13.487	0.002	0.017	down
NM_198291	SRC	-0.252	4.596	10.514	0.005	0.033	down
NM_198317	KLHL17	-0.602	1.490	14.511	0.001	0.014	down
NM_198471	KANK3	-0.466	4.251	35.788	0.000	0.000	down
NM_198472	FUOM	-0.654	2.871	33.958	0.000	0.000	down
NM_198475	FAM171A2	-0.833	1.614	25.871	0.000	0.002	down
NM_198488	FAM83H	-0.462	2.571	12.309	0.003	0.022	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_198507	FAM174A	-0.421	3.173	26.641	0.000	0.001	down
NM_198525	KIF7	-0.350	3.502	10.025	0.005	0.038	down
NM_198526	ZNF710	-0.525	2.870	26.539	0.000	0.002	down
NM_198536	TMEM205	-0.276	5.365	34.047	0.000	0.000	down
NM_198540	B3GNT8	-1.048	0.262	27.716	0.000	0.001	down
NM_198565	NRROS	-0.300	3.755	14.203	0.001	0.015	down
NM_198580	SLC27A1	-0.196	5.368	15.506	0.001	0.011	down
NM_198582	KLHL30	-0.584	3.357	37.853	0.000	0.000	down
NM_198679	RAPGEF1	-0.179	7.163	14.598	0.001	0.013	down
NM_198681	PLEKHG5	-0.532	6.553	20.222	0.000	0.005	down
NM_198722	AMIGO3	-0.657	0.869	15.971	0.001	0.010	down
NM_198723	TCEA2	-0.430	3.561	19.050	0.000	0.006	down
NM_198868	TBC1D9B	-0.294	8.315	43.175	0.000	0.000	down
NM_198949	NUDT1	-0.346	3.161	14.061	0.002	0.015	down
NM_199002	ARHGEF1	-0.501	5.654	88.626	0.000	0.000	down
NM_199054	MKNK2	-0.419	7.038	51.874	0.000	0.000	down
NM_199069	NDUFAF3	-0.276	5.411	19.955	0.000	0.005	down
NM_199141	CARM1	-0.207	4.961	17.443	0.001	0.008	down
NM_199184	DNPH1	-0.392	3.694	20.839	0.000	0.004	down
NM_199242	UNC13D	-0.407	2.887	9.290	0.007	0.045	down
NM_199287	CCDC137	-0.289	4.053	20.641	0.000	0.004	down
NM_199341	C19orf68	-0.249	3.583	11.813	0.003	0.025	down
NM_199360	TPD52L2	-0.159	7.739	10.985	0.004	0.030	down
NM_201397	GPX1	-0.608	7.898	49.333	0.000	0.000	down
NM_201400	EEF2KMT	-0.210	3.440	8.899	0.008	0.050	down
NM_201532	DGKZ	-0.723	4.616	166.705	0.000	0.000	down
NM_203344	SERTAD3	-0.585	3.996	50.310	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NM_203370	FAM212A	-0.696	1.817	23.799	0.000	0.002	down
NM_203387	RNH1	-0.719	6.792	91.305	0.000	0.000	down
NM_203500	KEAP1	-0.261	6.157	21.061	0.000	0.004	down
NM_205834	LSR	-0.585	2.669	22.202	0.000	0.003	down
NM_206967	C16orf74	-0.509	1.543	11.820	0.003	0.025	down
NM_207111	RNF216	-0.141	5.869	12.497	0.002	0.021	down
NM_207336	ZNF467	-0.459	2.368	18.668	0.000	0.006	down
NM_207340	ZDHHC24	-0.528	2.417	12.533	0.002	0.021	down
NM_207346	TSEN54	-0.305	2.658	10.819	0.004	0.031	down
NM_207368	MCRIP1	-0.848	5.417	143.405	0.000	0.000	down
NM_207370	GPR153	-0.302	5.131	15.492	0.001	0.011	down
NM_207392	KRTDAP	-8.380	2.011	25.068	0.001	0.013	down
NM_207510	LCNL1	-1.526	-0.733	13.647	0.002	0.016	down
NM_213568	SLC39A3	-0.285	3.600	11.520	0.003	0.027	down
NM_213600	PLA2G4F	-5.757	-1.274	25.004	0.002	0.018	down
NR_002196	H19	-0.538	8.809	20.629	0.000	0.004	down
NR_002211	MEIS3P1	-0.249	4.195	16.947	0.001	0.008	down
NR_002312	RPPH1	-1.936	-2.066	9.691	0.006	0.041	down
NR_002773	AOC4P	-0.516	2.927	14.088	0.002	0.015	down
NR_002786	CIDECP	-0.318	3.666	11.542	0.003	0.026	down
NR_003089	OTUB1	-0.217	5.511	18.947	0.000	0.006	down
NR_003186	NCF1B	-1.007	-0.756	8.999	0.008	0.048	down
NR_003225	LGALS3	-0.170	8.599	12.452	0.002	0.022	down
NR_003659	WASH3P	-0.627	2.712	57.269	0.000	0.000	down
NR_004380	SNORD104	-1.127	-1.521	9.228	0.007	0.046	down
NR_015434	LOC148413	-0.246	4.152	16.586	0.001	0.009	down
NR_024019	FAM193B	-0.255	5.816	17.145	0.001	0.008	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NR_024071	PLCD1	-0.355	5.513	17.005	0.001	0.008	down
NR_024077	WASH2P	-0.456	1.973	12.588	0.002	0.021	down
NR_024194	TOM1	-0.340	6.124	25.442	0.000	0.002	down
NR_024247	MUM1	-0.284	5.742	21.708	0.000	0.003	down
NR_024279	FLJ37453	-0.376	2.242	10.956	0.004	0.030	down
NR_024421	ZNF503-AS2	-0.382	1.646	11.082	0.004	0.029	down
NR_024497	LINC00999	-0.452	1.288	10.811	0.004	0.031	down
NR_024525	FAM96B	-0.224	4.759	18.088	0.000	0.007	down
NR_024540	WASH7P	-0.655	1.006	14.024	0.002	0.015	down
NR_024542	SNHG7	-0.333	4.910	25.020	0.000	0.002	down
NR_026581	MLF2	-0.176	7.135	11.245	0.004	0.028	down
NR_026712	RPL13AP5	-0.321	8.403	30.407	0.000	0.001	down
NR_026845	URB1-AS1	-0.495	2.187	19.902	0.000	0.005	down
NR_027033	MIRLET7BHG	-0.518	3.185	34.443	0.000	0.000	down
NR_027052	THAP7-AS1	-0.418	1.927	9.156	0.007	0.046	down
NR_027063	LINC00116	-0.454	3.352	25.616	0.000	0.002	down
NR_027297	HOMER3	-0.492	3.810	29.051	0.000	0.001	down
NR_027307	BORCS8-MEF2B	-0.567	2.938	31.625	0.000	0.001	down
NR_027329	PSMG3-AS1	-0.321	4.708	14.524	0.001	0.014	down
NR_027487	ARHGAP27P1	-0.342	3.592	25.374	0.000	0.002	down
NR_027889	TMEM189	-0.388	5.819	27.070	0.000	0.001	down
NR_028502	MIR22HG	-0.392	6.947	17.323	0.001	0.008	down
NR_028582	G6PC3	-0.231	5.832	12.333	0.003	0.022	down
NR_029409	TOLLIP-AS1	-0.616	1.023	10.807	0.004	0.031	down
NR_029494	MIR22	-0.538	1.688	16.602	0.001	0.009	down
NR_030366	MIR636	-2.923	-2.486	17.096	0.001	0.009	down
NR_030533	MIR675	-0.784	3.778	36.429	0.000	0.000	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NR_030717	SNAPC2	-0.747	3.170	90.093	0.000	0.000	down
NR_030767	ANKRD13D	-0.489	4.059	53.452	0.000	0.000	down
NR_030770	CCM2	-0.508	5.506	73.245	0.000	0.000	down
NR_033230	SMPD4	-0.310	5.336	40.774	0.000	0.000	down
NR_033338	FAAP100	-0.771	4.239	110.794	0.000	0.000	down
NR_033339	CTBP1-AS2	-0.194	4.060	9.016	0.008	0.048	down
NR_033348	RAI2	-0.253	5.677	14.296	0.001	0.014	down
NR_033397	PRMT1	-0.326	5.592	34.240	0.000	0.000	down
NR_033403	BMP1	-0.215	5.769	12.224	0.003	0.023	down
NR_033902	CCAR2	-0.136	6.389	9.266	0.007	0.045	down
NR_034166	NDUFA11	-0.503	5.631	55.511	0.000	0.000	down
NR_036447	PKD1P1	-0.776	1.467	49.907	0.000	0.000	down
NR_036515	LOC284454	-0.342	4.656	18.468	0.000	0.006	down
NR_037146	TNFSF12	-0.225	6.007	13.910	0.002	0.016	down
NR_037164	ASB13	-0.207	4.272	11.417	0.003	0.027	down
NR_037401	MIR3606	-0.288	3.437	11.377	0.003	0.027	down
NR_037425	MIR3652	-0.778	3.005	62.811	0.000	0.000	down
NR_037576	TMEM222	-0.309	5.237	22.984	0.000	0.003	down
NR_037608	SLX1A-SULT1A3	-1.474	-1.410	11.649	0.003	0.026	down
NR_037609	SLX1B-SULT1A4	-1.474	-1.410	11.649	0.003	0.026	down
NR_037661	FKBP1A-SDCBP2	-0.379	3.166	23.873	0.000	0.002	down
NR_037675	INAFM1	-0.309	3.012	13.273	0.002	0.018	down
NR_037709	TEN1-CDK3	-0.287	4.678	19.054	0.000	0.006	down
NR_037715	RNASEK	-0.214	6.485	21.590	0.000	0.004	down
NR_037717	RNASEK-C17orf49	-0.206	6.892	20.876	0.000	0.004	down
NR_037719	TMEM256-PLSCR3	-0.189	5.177	10.816	0.004	0.031	down
NR_037775	MIA-RAB4B	-0.291	4.079	18.278	0.000	0.006	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NR_037791	RAB4B-EGLN2	-0.469	6.569	69.892	0.000	0.000	down
NR_037807	IL17RC	-0.359	4.323	16.410	0.001	0.009	down
NR_037882	RTEL1-TNFRSF6B	-0.314	4.013	14.458	0.001	0.014	down
NR_037928	P2RX5-TAX1BP3	-0.357	6.710	49.031	0.000	0.000	down
NR_037945	STX16-NPEPL1	-0.196	6.543	20.031	0.000	0.005	down
NR_038118	MMAB	-0.211	5.181	10.815	0.004	0.031	down
NR_038262	MIR210HG	-0.854	1.835	30.166	0.000	0.001	down
NR_038422	PIN1	-0.363	5.084	25.897	0.000	0.002	down
NR_038942	PARTICL	-0.409	1.606	9.204	0.007	0.046	down
NR_039835	MIR4687	-2.371	-1.460	15.216	0.001	0.012	down
NR_039872	MIR4721	-0.574	0.972	17.648	0.001	0.007	down
NR_039905	MIR4750	-1.139	-1.032	17.552	0.001	0.008	down
NR_039906	MIR4751	-0.673	1.792	36.208	0.000	0.000	down
NR_039983	LOC729737	-0.591	1.609	19.138	0.000	0.006	down
NR_040252	ANKS3	-0.337	3.220	13.220	0.002	0.018	down
NR_045058	UBTF	-0.174	6.976	11.574	0.003	0.026	down
NR_045568	IRF3	-0.319	4.979	26.452	0.000	0.002	down
NR_045724	CLTB	-0.468	5.604	42.517	0.000	0.000	down
NR_046202	C19orf47	-0.588	2.993	45.913	0.000	0.000	down
NR_046266	TBC1D10C	-0.589	1.541	11.256	0.004	0.028	down
NR_046411	POLD4	-0.198	5.437	10.051	0.005	0.037	down
NR_046418	CHMP1A	-0.345	5.997	56.106	0.000	0.000	down
NR_046762	ALMS1-IT1	-0.961	-1.206	9.158	0.007	0.046	down
NR_048551	SLC4A3	-0.651	2.150	15.516	0.001	0.011	down
NR_048577	ADAM15	-0.296	7.115	27.433	0.000	0.001	down
NR_051968	MRPS2	-0.255	4.303	17.419	0.001	0.008	down
NR_051979	IPO4	-0.239	4.461	8.899	0.008	0.050	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NR_073024	RPL13A	-0.208	8.943	14.735	0.001	0.013	down
NR_073409	TMEM134	-0.808	3.414	56.506	0.000	0.000	down
NR_073448	REEP2	-0.630	3.035	24.471	0.000	0.002	down
NR_073517	PIK3R2	-0.296	4.163	22.412	0.000	0.003	down
NR_073565	DNLZ	-0.375	1.977	12.884	0.002	0.020	down
NR_075070	STMN3	-0.392	3.760	18.833	0.000	0.006	down
NR_077061	LOC440311	-0.554	2.251	22.770	0.000	0.003	down
NR_102409	SCARF1	-0.413	4.947	24.708	0.000	0.002	down
NR_103728	PVRIG2P	-0.263	4.033	9.147	0.007	0.047	down
NR_103804	PDLIM7	-0.470	4.152	15.795	0.001	0.011	down
NR_104201	BCL2L12	-0.322	2.144	10.223	0.005	0.036	down
NR_104293	ACSF3	-0.270	3.766	14.924	0.001	0.013	down
NR_104295	CRELD2	-0.252	4.403	16.617	0.001	0.009	down
NR_104307	ULK3	-0.285	5.080	22.199	0.000	0.003	down
NR_104312	COMMD4	-0.339	4.990	22.914	0.000	0.003	down
NR_104432	ZNF213	-0.524	3.402	32.313	0.000	0.001	down
NR_106773	MIR6716	-0.690	1.698	31.803	0.000	0.001	down
NR_106775	MIR6511B1	-2.628	-2.483	11.015	0.004	0.031	down
NR_106837	MIR6779	-0.953	-0.731	11.652	0.003	0.026	down
NR_106854	MIR6796	-0.909	0.055	15.526	0.001	0.011	down
NR_106863	MIR6805	-0.634	1.995	27.334	0.000	0.001	down
NR_106865	MIR6807	-0.996	-0.648	11.323	0.004	0.028	down
NR_106879	MIR6821	-1.097	-0.198	8.902	0.008	0.050	down
NR_106908	MIR6849	-0.858	-0.999	9.956	0.006	0.038	down
NR_107001	MIR7847	-0.948	1.991	46.009	0.000	0.000	down
NR_108061	VIM-AS1	-0.473	2.843	10.517	0.005	0.033	down
NR_109807	PHPT1	-0.257	5.430	20.746	0.000	0.004	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NR_109828	PCBP2-OT1	-0.290	4.317	20.329	0.000	0.004	down
NR_109909	CTC-338M12.4	-0.359	2.615	11.593	0.003	0.026	down
NR_109931	LOC101928796	-1.073	0.654	25.056	0.000	0.002	down
NR_109978	METTL26	-0.315	4.128	26.522	0.000	0.002	down
NR_110172	U2AF1L4	-0.282	3.616	13.668	0.002	0.016	down
NR_110612	ATP6V0E2	-0.430	5.603	19.761	0.000	0.005	down
NR_110730	PTOV1-AS2	-0.498	1.978	13.353	0.002	0.018	down
NR_110933	KCTD13	-0.284	3.024	11.124	0.004	0.029	down
NR_111987	NPHP4	-0.310	3.064	12.250	0.003	0.023	down
NR_120586	LOC101928069	-0.429	1.499	9.649	0.006	0.041	down
NR_125375	LOC100288152	-0.612	2.294	13.628	0.002	0.017	down
NR_126522	EXOC3-AS1	-0.667	2.310	22.294	0.000	0.003	down
NR_130151	RPS19BP1	-0.387	5.587	41.819	0.000	0.000	down
NR_130745	LOC100288778	-0.458	3.348	30.590	0.000	0.001	down
NR_130747	CHRD	-0.441	3.498	21.384	0.000	0.004	down
NR_130975	C1orf35	-0.453	3.202	29.309	0.000	0.001	down
NR_132114	SNHG19	-0.710	1.997	26.628	0.000	0.001	down
NR_134464	CARD19	-0.587	3.861	38.087	0.000	0.000	down
NR_134612	TP53I11	-0.296	6.096	42.552	0.000	0.000	down
NR_134616	LOC105374952	-0.952	-0.766	10.689	0.004	0.032	down
NR_134666	UCK1	-0.198	5.328	12.443	0.002	0.022	down
NR_134855	INO80E	-0.272	5.122	40.328	0.000	0.000	down
NR_135087	LOC105369340	-1.263	-0.016	11.547	0.003	0.026	down
NR_135180	LOC101928659	-0.889	-0.353	9.608	0.006	0.041	down
NR_135762	RPS9	-0.227	8.340	18.997	0.000	0.006	down
NR_136651	JMJD8	-0.352	5.982	38.465	0.000	0.000	down
NR_136910	KMT5A	-0.165	4.986	12.319	0.003	0.022	down

Gene ID	Gene names	logFC	logCPM	F	PValue	FDR	Regulated direction
NR_137287	ARHGEF10L	-0.463	5.399	44.226	0.000	0.000	down
NR_138144	PYCRL	-0.434	2.883	17.084	0.001	0.008	down
NR_138423	MIGA2	-0.444	4.695	47.523	0.000	0.000	down
NR_138479	PREB	-0.270	6.868	14.132	0.001	0.015	down
NR_138610	MCRIP2	-0.896	2.568	76.400	0.000	0.000	down
NR_144321	TRIM8	-0.414	7.728	30.997	0.000	0.001	down
NR_144402	LOC108783654	-0.488	3.626	44.299	0.000	0.000	down
NR_144474	DPH1	-0.177	5.068	15.457	0.001	0.011	down

Appendix B-4 Spline regression identified 24-hour rhythmicity of 450 genes were altered by time restricted eating.

	Baseline				Week 8							
Gene names	6am	12pm	6pm	12am	6am	12pm	6pm	12am	Average Expression	F	P-Value	FDR
CSNK1G2	695.036	131.864	269.445	150.340	95.643	-234.134	-548.747	-374.069	740.029	25.433	0.000	0.000
PPP6R1	1051.762	117.806	267.786	84.109	121.271	-193.970	-641.946	-355.164	1090.191	23.780	0.000	0.000
GNA11	1571.930	182.092	700.798	77.300	112.301	-349.303	-966.708	-563.992	1685.234	18.770	0.000	0.000
TCF3	642.572	56.458	335.080	46.033	105.482	-163.328	-480.040	-238.811	718.657	17.546	0.000	0.000
STK11	820.417	39.197	115.384	19.703	63.809	-141.754	-428.747	-211.898	810.417	16.987	0.000	0.000
SBF1	2006.101	49.025	306.759	85.091	115.335	-188.492	-1035.014	-617.345	1973.839	15.937	0.000	0.000
PRR12	615.122	8.990	109.913	7.220	84.893	-92.074	-373.019	-241.287	620.499	15.743	0.000	0.000
E4F1	270.962	23.498	116.191	5.662	63.526	-114.110	-237.635	-150.988	293.449	15.243	0.000	0.000
DGKZ	620.900	68.497	155.925	127.677	98.387	-151.523	-513.189	-289.475	635.100	14.969	0.000	0.000
NCOR2	1861.992	44.840	515.641	300.809	113.362	-356.165	-949.600	-669.530	1916.411	14.667	0.000	0.000
PPP1R37	373.120	-7.895	10.965	10.862	7.748	-48.342	-131.128	-132.940	351.851	14.460	0.000	0.000
TRAF7	1226.708	137.724	292.064	122.063	37.667	-188.607	-498.608	-349.980	1260.008	14.510	0.000	0.000
TNRC18	1589.898	35.891	178.832	127.551	202.515	-244.902	-859.240	-578.852	1588.498	14.222	0.000	0.000
CAMTA2	1886.026	-84.392	-54.663	78.023	116.809	-1.376	-537.133	-312.352	1824.257	14.256	0.000	0.000
FBRS	1034.918	28.562	334.560	-54.322	89.873	-147.073	-567.408	-292.233	1077.473	14.050	0.000	0.000
TMEM134	282.302	18.307	91.878	28.868	35.130	-50.799	-209.481	-138.613	291.996	13.677	0.000	0.000
ZDHHC8	892.190	-1.926	78.214	40.904	61.171	-155.166	-546.743	-355.069	840.910	13.805	0.000	0.000
AXIN1	515.113	47.980	46.197	-3.787	50.325	-138.412	-289.894	-152.745	499.929	13.700	0.000	0.000
SCRIB	699.579	-38.971	-80.369	37.892	66.780	-145.999	-381.341	-267.795	625.955	13.810	0.000	0.000
TRABD	300.050	24.534	105.628	22.482	56.804	-116.508	-272.934	-151.120	311.126	13.704	0.000	0.000
CACTIN	372.829	34.702	100.856	5.615	51.173	-124.547	-228.965	-134.268	386.729	13.820	0.000	0.000
ARHGDIA	3843.293	675.687	1342.892	806.007	-12.016	-660.246	-1853.814	-1405.387	4015.506	13.435	0.000	0.000
MBD3	1155.784	193.537	298.859	180.342	52.495	-361.919	-848.004	-679.916	1130.575	13.393	0.000	0.000

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
TRMT61A	378.777	79.753	183.017	64.846	19.329	-98.143	-225.268	-177.932	412.812	13.184	0.000	0.000
RAI1	492.308	70.612	662.044	50.962	110.295	-237.480	-434.753	-393.388	677.964	13.178	0.000	0.000
SLC25A22	115.729	10.406	89.872	50.533	36.961	-13.225	-143.950	-84.160	141.074	13.228	0.000	0.000
TSC22D4	616.337	-32.202	117.018	-30.840	137.714	-188.765	-476.397	-251.581	621.483	13.123	0.000	0.000
FAAP100	489.946	43.861	137.147	78.827	68.586	-98.090	-383.691	-234.842	502.964	12.713	0.000	0.000
CC2D1A	684.798	-53.557	4.076	16.364	78.292	-137.335	-422.958	-228.501	636.659	12.709	0.000	0.000
SH3GL1	1293.157	166.095	549.316	163.935	45.814	-320.192	-589.471	-567.123	1391.464	12.761	0.000	0.000
C19orf47	189.572	29.395	79.218	26.483	8.992	-70.902	-95.052	-80.234	202.873	12.771	0.000	0.000
GGA1	916.610	74.977	229.391	98.786	129.579	-137.835	-501.332	-298.149	971.352	12.530	0.000	0.000
STOML1	468.833	33.299	149.153	85.885	36.932	-100.001	-300.146	-185.124	484.858	12.384	0.000	0.001
ZBTB17	431.036	-16.439	-31.170	-2.675	46.956	-66.343	-217.004	-134.409	398.680	12.172	0.000	0.001
PHRF1	857.103	-1.335	47.478	-14.730	76.358	-174.294	-384.344	-282.985	827.658	12.127	0.000	0.001
DVL1	983.831	0.335	102.266	28.423	55.530	-237.275	-594.968	-423.978	922.449	12.081	0.000	0.001
PCNX3	776.310	106.401	346.487	97.979	91.218	-128.051	-495.956	-294.547	854.840	11.971	0.000	0.001
TMEM8A	658.134	22.201	83.168	13.480	97.074	-126.426	-463.187	-219.078	646.907	11.946	0.000	0.001
PARP10	1131.510	132.502	-31.355	180.464	170.248	-202.010	-715.631	-538.380	1085.590	11.977	0.000	0.001
CEP170B	1323.887	227.323	639.308	302.423	5.469	-284.873	-805.327	-623.589	1411.984	11.831	0.000	0.001
MIB2	256.748	-30.186	85.907	-25.256	63.196	-73.359	-263.250	-138.857	259.823	11.825	0.000	0.001
FZR1	590.642	-58.186	46.213	-60.567	62.162	-68.564	-345.251	-152.598	561.114	11.741	0.000	0.001
MED22	1091.884	97.030	185.019	180.838	33.632	-11.354	-360.566	-200.139	1125.184	11.679	0.000	0.001
CBX4	176.939	53.800	195.827	6.435	45.243	-98.352	-191.327	-110.923	229.307	11.686	0.000	0.001
MAP3K10	243.685	19.114	28.188	6.624	39.322	-93.426	-202.542	-88.772	233.881	11.601	0.000	0.001
PIP5K1C	1076.441	59.598	306.779	69.951	34.366	-111.304	-482.957	-266.672	1110.818	11.579	0.000	0.001
NDOR1	329.936	44.657	183.556	-0.750	74.079	-132.190	-269.827	-175.234	374.369	11.545	0.000	0.001
CAPN15	298.247	-36.609	8.202	31.459	43.005	-50.182	-215.692	-168.050	277.115	11.456	0.000	0.001
TMEM259	2877.214	217.005	544.426	293.124	243.822	-449.231	-1477.717	-990.402	2919.840	11.431	0.000	0.001

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
SGTA	1104.729	-11.663	167.870	18.590	50.381	-159.567	-508.237	-300.009	1082.987	11.391	0.000	0.001
CTU2	152.002	24.475	44.658	35.233	6.776	-15.161	-93.652	-65.106	156.546	11.329	0.000	0.001
PFKL	2805.509	237.783	205.806	247.481	182.631	-682.116	-1518.760	-999.398	2686.578	11.264	0.000	0.001
INPPL1	2407.792	91.039	611.935	104.992	262.049	-261.851	-892.282	-558.149	2576.573	11.279	0.000	0.001
PACS2	2113.615	114.495	108.246	166.121	113.904	-342.705	-838.914	-579.394	2053.817	11.163	0.000	0.001
ARFGAP1	1062.926	18.824	244.069	43.861	161.506	-215.894	-682.566	-406.734	1091.330	11.086	0.000	0.001
CHMP6	381.641	51.802	115.519	44.503	25.813	-97.652	-237.936	-129.840	392.222	11.108	0.000	0.001
SLC39A13	915.534	22.231	217.445	77.139	63.683	-103.131	-511.343	-318.638	925.937	11.082	0.000	0.001
CLCN7	1340.977	55.130	154.853	67.782	125.003	-212.871	-787.786	-472.888	1307.670	11.065	0.000	0.001
MAP1S	256.943	-12.537	26.417	-19.615	35.738	-71.453	-212.406	-99.393	238.803	11.011	0.000	0.001
ESRRA	709.133	95.324	147.204	195.713	13.757	-38.104	-301.620	-259.303	727.194	10.999	0.000	0.001
SCAF1	844.858	-14.157	186.541	11.427	32.105	-138.538	-469.014	-262.751	828.169	11.023	0.000	0.001
CTDP1	329.633	31.366	110.599	-7.990	64.574	-81.162	-247.837	-96.020	352.554	10.973	0.000	0.001
RNPEPL1	2219.043	176.980	188.740	137.087	78.048	-473.695	-1143.648	-765.435	2108.535	10.935	0.000	0.001
DPP7	1464.824	63.930	247.972	133.441	147.876	-402.157	-998.712	-739.051	1425.492	10.868	0.000	0.001
DUS3L	198.393	-10.384	124.759	15.864	35.820	-20.607	-159.762	-91.855	226.788	10.760	0.000	0.001
WIZ	1356.045	-13.217	40.970	35.468	80.940	-154.913	-560.682	-385.096	1297.547	10.728	0.000	0.001
ABHD17A	265.732	-5.230	21.094	-0.079	36.809	-88.437	-195.536	-113.390	249.945	10.667	0.000	0.002
ZNF512B	785.061	96.196	396.487	121.975	110.615	-61.070	-507.660	-255.974	893.236	10.670	0.000	0.002
TSSC4	440.833	20.067	202.581	-0.983	26.061	-109.184	-340.187	-208.673	453.426	10.637	0.000	0.002
CORO1B	1163.349	44.432	87.224	45.336	39.438	-166.284	-598.308	-357.596	1099.968	10.626	0.000	0.002
TRMT2A	797.022	47.141	201.666	73.146	96.659	-136.654	-470.931	-295.268	826.733	10.580	0.000	0.002
RNF126	229.299	49.548	163.121	-1.594	39.548	-113.914	-224.913	-123.981	260.326	10.511	0.000	0.002
GATAD2A	1079.378	215.385	663.107	117.637	58.041	-156.954	-515.179	-256.553	1254.226	10.504	0.000	0.002
PKD1	2401.279	-252.565	447.007	-135.000	319.905	-343.511	-1630.126	-966.705	2353.382	10.494	0.000	0.002
VPS45	1676.724	20.981	-506.723	-62.990	-152.283	-61.264	557.937	220.085	1528.330	10.533	0.000	0.002

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
RHOT2	1152.349	121.215	264.678	124.943	195.770	-314.610	-745.619	-528.313	1201.031	10.529	0.000	0.002
NUBP2	503.695	43.898	117.756	38.286	45.349	-156.468	-403.336	-259.266	488.778	10.429	0.000	0.002
MIR3652	225.440	-12.459	1.408	34.456	21.536	-2.895	-160.625	-79.848	208.544	10.401	0.000	0.002
KDM6B	678.610	-72.166	77.819	-121.624	141.206	-44.350	-519.769	-92.290	667.905	10.378	0.000	0.002
SRP68	2301.616	-187.512	-501.475	-151.829	-274.381	52.358	758.717	283.322	2107.651	10.368	0.000	0.002
PPP6R2	1350.845	43.583	164.340	89.857	83.491	-147.995	-486.532	-264.843	1360.581	10.341	0.000	0.002
NCLN	919.555	88.600	178.860	151.163	32.902	-161.969	-479.444	-345.499	915.216	10.311	0.000	0.002
GRAMD1A	660.896	-48.394	-158.536	-7.263	120.265	-71.724	-361.071	-186.876	594.094	10.313	0.000	0.002
BRE	844.670	61.286	-85.291	-36.041	-147.237	-38.875	356.515	116.996	807.334	10.320	0.000	0.002
MED25	338.861	7.789	-8.330	4.790	29.669	-51.602	-181.603	-119.253	315.388	10.223	0.000	0.002
PTRH1	117.576	26.275	-1.898	25.899	20.154	-52.296	-85.052	-59.645	112.803	10.152	0.000	0.002
ADCK5	102.515	18.754	4.567	16.003	31.938	-39.624	-99.879	-51.792	102.770	10.160	0.000	0.002
SLC12A9	485.883	-32.795	86.033	-0.771	130.748	-86.733	-448.405	-153.192	492.743	10.169	0.000	0.002
TAF15	4552.673	-114.179	-820.231	-168.717	-591.456	344.188	1313.655	547.578	4216.725	10.138	0.000	0.002
SMPD4	1010.645	24.249	127.896	88.883	47.311	-83.697	-259.876	-234.660	1029.814	10.113	0.000	0.002
KIFC3	933.115	-89.981	3.010	76.266	87.734	-72.256	-628.568	-284.461	857.560	9.938	0.000	0.002
SMOX	78.493	0.070	77.950	4.758	28.025	-15.628	-101.883	-29.727	99.864	9.939	0.000	0.002
PDCD7	780.794	-49.637	-250.085	-39.908	-88.037	69.078	285.268	69.810	699.661	9.952	0.000	0.002
PPP1R16A	357.105	14.756	46.088	39.958	43.171	-82.719	-268.519	-189.888	343.118	9.925	0.000	0.002
RAVER1	415.958	37.171	92.681	19.880	53.344	-53.549	-241.482	-108.248	431.955	9.842	0.000	0.003
TBC1D10B	958.682	16.342	201.172	-55.730	49.737	-137.169	-306.883	-223.269	981.835	9.874	0.000	0.003
DDX49	522.854	35.944	85.003	28.472	25.967	-99.403	-248.614	-151.437	518.134	9.859	0.000	0.003
C15orf39	764.295	-147.171	280.934	-110.999	39.916	-97.117	-465.213	-281.822	762.368	9.840	0.000	0.003
ZBTB45	203.621	0.229	9.929	-2.524	18.325	-54.206	-109.238	-67.248	192.825	9.864	0.000	0.003
TBL3	377.830	57.605	75.616	53.405	5.611	-114.670	-121.486	-173.622	383.106	9.858	0.000	0.003
PKN1	2234.944	95.012	236.673	57.327	29.004	-367.649	-1040.289	-564.561	2131.242	9.783	0.000	0.003

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
AGAP3	1110.203	39.522	561.293	-83.122	128.250	-177.015	-624.082	-318.315	1233.594	9.744	0.000	0.003
SBNO2	666.207	-85.999	145.399	-11.575	109.055	4.265	-409.777	-238.081	683.390	9.728	0.000	0.003
C1orf159	107.769	2.387	63.200	4.436	25.336	-10.689	-114.189	-57.504	120.375	9.731	0.000	0.003
BAHCC1	606.090	-109.367	376.254	-95.434	124.289	-169.256	-401.203	-304.169	688.618	9.716	0.000	0.003
SNAPC2	225.082	35.922	107.921	21.663	16.534	-52.116	-177.224	-85.571	239.120	9.705	0.000	0.003
LLGL1	605.033	40.685	72.541	67.659	73.528	-105.287	-339.708	-179.124	607.087	9.694	0.000	0.003
APBA3	190.201	1.199	37.773	6.040	13.644	-49.128	-113.539	-87.667	185.721	9.683	0.000	0.003
AP5Z1	578.202	40.647	239.949	55.457	47.160	-116.944	-432.122	-275.845	601.842	9.669	0.000	0.003
SPHK2	220.280	76.587	138.891	53.380	37.430	-83.693	-163.899	-125.621	260.428	9.653	0.000	0.003
CPTP	345.778	-29.462	32.413	-13.391	27.235	-65.734	-220.434	-128.776	322.027	9.622	0.000	0.003
UBALD1	157.752	24.202	22.224	20.396	6.876	-50.392	-101.428	-74.394	150.519	9.591	0.000	0.003
MXD4	3055.439	-54.706	-96.813	-260.572	266.384	-598.238	-1514.414	-858.650	2823.091	9.586	0.000	0.003
RHBDD3	228.573	40.826	104.120	25.444	18.965	-60.531	-176.102	-113.732	242.082	9.591	0.000	0.003
C9orf69	871.958	72.603	159.038	121.421	-1.258	-99.779	-279.572	-262.479	879.178	9.535	0.000	0.003
ATG2A	542.919	-21.568	123.449	-14.025	75.608	-116.922	-337.555	-162.105	550.996	9.519	0.000	0.003
EPN1	1275.609	112.459	169.515	60.789	97.366	-289.452	-703.785	-413.447	1250.617	9.458	0.000	0.003
PLEC	3634.059	-279.924	296.998	51.960	688.153	-637.795	-2797.778	-1380.434	3510.787	9.424	0.000	0.003
C19orf24	329.266	44.081	67.367	31.201	42.140	-119.158	-289.874	-167.757	319.509	9.391	0.000	0.003
PTPN23	1184.991	45.158	231.028	118.683	121.531	-178.463	-538.317	-293.717	1226.829	9.368	0.000	0.004
DOHH	142.987	25.035	35.149	30.248	10.284	-39.453	-102.775	-78.619	142.666	9.359	0.000	0.004
RNF208	69.099	10.700	6.577	9.878	8.833	-35.617	-59.418	-40.473	64.467	9.348	0.000	0.004
RPUSD1	178.615	35.897	90.262	24.841	3.092	-46.223	-126.689	-95.868	188.574	9.319	0.000	0.004
IRF7	173.044	-9.508	-17.845	34.715	57.629	-39.926	-180.807	-97.963	162.384	9.275	0.000	0.004
KATNB1	366.822	4.959	12.570	33.202	9.117	-20.452	-186.006	-85.351	343.778	9.243	0.000	0.004
PPP1R12C	2282.098	112.741	272.721	105.555	70.924	-363.429	-1026.048	-665.555	2215.318	9.214	0.000	0.004
OPLAH	390.556	9.868	39.119	8.583	47.140	-60.067	-248.569	-161.808	378.913	9.186	0.000	0.004

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
SLC38A10	3032.663	511.044	960.957	348.786	155.605	-686.406	-1872.465	-1047.674	3122.422	9.173	0.000	0.004
EHMT1	1435.616	19.424	-30.659	55.005	75.386	-173.894	-374.893	-144.020	1393.824	9.165	0.000	0.004
PTGES2	572.471	107.095	38.511	122.149	0.772	-100.415	-177.871	-197.664	563.642	9.156	0.000	0.004
KAT7	1013.887	-26.156	-166.815	-93.461	-80.406	31.805	231.635	159.921	954.952	9.115	0.000	0.004
POLD1	158.337	-0.760	-15.388	16.741	24.407	-63.695	-113.678	-80.874	141.887	9.120	0.000	0.004
LMF2	1438.951	148.552	371.666	67.321	168.745	-382.283	-990.816	-574.739	1462.461	9.121	0.000	0.004
XYLT2	486.987	10.353	49.835	-3.575	75.095	-109.063	-275.563	-162.426	485.123	9.097	0.000	0.004
CCDC130	483.708	43.164	67.827	42.734	68.037	-80.223	-210.936	-214.531	500.972	9.028	0.000	0.005
DRAP1	1200.481	106.088	125.697	141.385	5.440	-353.365	-447.345	-410.578	1159.408	8.928	0.000	0.005
MAP3K11	1769.875	-32.567	53.940	-95.949	354.572	-324.380	-1190.240	-613.445	1720.955	8.928	0.000	0.005
EXT2	2210.442	92.708	-310.543	14.501	-175.697	79.258	712.893	284.661	2162.188	8.937	0.000	0.005
BCL9L	2868.406	-228.401	2070.530	-795.243	540.479	-557.400	-2130.789	-1195.986	3316.650	8.876	0.000	0.005
CIC	1373.177	-150.919	322.333	-37.321	237.564	-197.449	-1046.809	-449.587	1382.164	8.857	0.000	0.005
ANAPC2	699.467	15.379	257.827	-27.757	92.927	-77.782	-421.094	-189.737	750.174	8.842	0.000	0.005
SF3A2	496.109	-12.740	99.914	-20.767	75.442	-145.590	-393.528	-161.013	486.202	8.786	0.000	0.006
RAB40C	336.249	15.609	121.376	-11.567	39.276	-60.502	-224.024	-133.801	351.787	8.769	0.000	0.006
ZBTB7A	1365.236	-68.378	600.283	-216.809	93.761	-134.505	-616.072	-296.316	1467.967	8.750	0.000	0.006
BRF1	610.053	-30.508	175.869	22.948	60.938	-100.731	-345.478	-235.004	626.650	8.723	0.000	0.006
RAB4B-EGLN2	2720.673	-37.172	208.277	-46.755	104.270	-340.523	-1049.972	-683.090	2620.047	8.706	0.000	0.006
CAPN10	265.837	-26.290	-14.313	-6.293	47.415	-35.314	-198.351	-86.868	244.332	8.706	0.000	0.006
ZNF598	486.724	15.300	262.521	3.829	39.116	-54.860	-328.177	-174.560	531.293	8.681	0.000	0.006
ZGPAT	510.606	-38.674	21.782	4.127	30.710	-28.300	-222.210	-151.019	486.220	8.662	0.000	0.006
BRD1	868.932	-45.721	11.674	-87.800	94.540	-95.091	-359.905	-139.797	840.258	8.664	0.000	0.006
TMEM39A	779.533	-116.399	-176.466	-33.627	-65.555	237.130	207.731	79.804	723.607	8.641	0.000	0.006
LZTS2	2369.385	48.659	371.047	-1.530	130.807	-469.007	-1162.704	-747.504	2320.026	8.645	0.000	0.006
ADRM1	1261.051	257.956	537.673	198.298	-4.829	-322.169	-603.606	-461.183	1343.260	8.596	0.000	0.006

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
GET4	592.889	53.430	229.599	41.166	25.058	-139.692	-208.817	-210.725	640.188	8.600	0.000	0.006
PLEKHA8P1	384.923	-70.104	-316.344	-29.292	-55.849	73.101	200.191	91.770	283.936	8.605	0.000	0.006
QTRT1	502.040	19.497	-8.939	31.720	44.756	-117.587	-228.181	-187.405	475.641	8.593	0.000	0.006
AMDHD2	393.592	-23.746	-28.294	2.195	55.985	-76.953	-249.166	-145.617	360.116	8.559	0.000	0.007
ARFRP1	895.673	26.264	-140.671	85.337	-1.283	-139.323	-204.126	-273.538	807.343	8.520	0.000	0.007
C10orf10	16122.030	-1447.550	-16869.377	27.825	-2615.882	-5066.169	-14592.937	-15651.663	12353.302	8.490	0.000	0.007
NDUFS7	417.229	56.279	-17.856	16.728	36.077	-194.983	-320.134	-238.337	365.340	8.487	0.000	0.007
RTN4RL1	370.270	141.169	265.073	176.609	52.340	-98.541	-265.590	-223.916	453.651	8.473	0.000	0.007
FBRSL1	394.059	-28.210	110.544	-46.147	67.206	-73.834	-266.781	-128.889	405.655	8.478	0.000	0.007
CCDC106	247.020	83.272	135.483	45.047	35.788	-93.405	-197.654	-120.175	279.463	8.483	0.000	0.007
DGCR2	1899.294	206.328	461.454	-1.146	37.525	-179.914	-560.491	-366.625	1975.577	8.441	0.000	0.007
OGFR	608.795	38.447	133.431	-18.351	88.281	-75.262	-434.349	-188.601	617.324	8.456	0.000	0.007
UQCC3	229.485	41.768	38.244	28.097	16.676	-44.881	-136.823	-100.184	228.233	8.449	0.000	0.007
GALK1	172.833	-0.369	56.358	10.022	21.006	-20.348	-139.487	-74.617	175.911	8.444	0.000	0.007
TPGS1	13.202	4.233	8.968	9.498	2.965	-14.640	-18.752	-20.873	14.176	8.455	0.000	0.007
ZNF668	103.919	24.706	50.610	10.904	3.746	-54.666	-65.599	-71.506	109.564	8.464	0.000	0.007
HCFC1	1092.052	38.633	31.648	92.648	127.667	-118.838	-401.891	-225.172	1096.826	8.424	0.000	0.007
BORCS8-MEF2B	207.840	-6.927	52.016	-3.265	28.903	-38.704	-128.107	-77.570	212.675	8.393	0.000	0.007
PSMA1	2626.283	316.709	-25.242	136.544	-221.046	10.986	648.112	298.622	2666.537	8.364	0.000	0.007
ATAD3A	247.045	6.927	19.318	68.819	3.885	-53.703	-129.728	-101.803	233.378	8.370	0.000	0.007
BTBD2	1237.376	12.443	15.976	21.924	94.960	-251.616	-743.241	-444.818	1142.326	8.388	0.000	0.007
JUNB	387.179	-137.152	-17.515	110.166	56.766	49.110	-371.932	-239.580	336.953	8.369	0.000	0.007
FAM53B	1560.741	123.221	447.224	-25.143	182.910	-296.306	-593.989	-354.566	1684.258	8.396	0.000	0.007
RBM38	254.166	19.446	243.088	4.765	55.375	-64.516	-313.918	-106.913	305.295	8.365	0.000	0.007
MPG	483.111	61.243	149.758	24.112	34.082	-156.685	-327.447	-199.445	488.364	8.371	0.000	0.007

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
NME3	383.184	38.289	84.667	14.690	67.721	-133.014	-323.672	-210.579	382.324	8.330	0.000	0.008
STRN4	1541.493	116.730	524.699	-53.411	91.739	-218.021	-818.506	-425.938	1606.579	8.325	0.000	0.008
MCRIP1	1243.361	149.034	214.387	103.503	45.897	-347.781	-760.968	-556.534	1196.607	8.335	0.000	0.008
EDC4	919.449	74.101	224.974	34.167	104.680	-80.284	-406.522	-209.756	977.118	8.290	0.000	0.008
GNB2	2841.066	197.005	513.637	242.511	52.064	-444.752	-1218.261	-807.422	2821.498	8.289	0.000	0.008
VPS9D1	355.577	16.330	116.894	56.621	41.077	-59.261	-229.558	-136.881	374.632	8.284	0.000	0.008
ACTR6	533.615	-53.190	-155.347	-41.116	-75.473	56.947	204.301	61.959	475.239	8.279	0.000	0.008
TRAPPC5	228.999	58.972	74.082	19.788	19.900	-127.560	-182.852	-148.137	228.824	8.206	0.000	0.008
SPPL2B	541.131	74.944	167.649	27.807	105.335	-166.548	-404.120	-266.548	573.992	8.200	0.000	0.008
NDUFB7	1494.813	154.427	110.635	92.145	74.553	-460.030	-968.237	-708.141	1382.964	8.182	0.000	0.008
MAP2K2	1066.848	98.123	98.297	110.199	64.775	-195.289	-407.642	-324.840	1060.851	8.177	0.000	0.008
MKKS	1325.162	43.758	-318.580	18.362	-188.842	74.909	489.943	170.170	1222.171	8.177	0.000	0.008
ATAD3B	222.183	67.197	131.844	58.029	52.183	-66.444	-191.822	-117.040	263.391	8.180	0.000	0.008
NUDT22	297.998	62.911	62.673	50.767	16.189	-109.144	-135.048	-140.428	303.908	8.164	0.000	0.009
OCRL	1743.685	36.074	-69.498	2.134	-135.680	130.814	439.868	218.357	1743.365	8.131	0.000	0.009
EGLN2	2437.520	-43.545	174.908	-28.079	89.295	-286.451	-962.307	-629.415	2338.204	8.113	0.000	0.009
STK32C	180.935	14.609	9.737	37.198	2.400	-41.105	-43.505	-71.194	177.720	8.089	0.000	0.009
INTS1	1315.974	20.458	35.022	-39.462	109.740	-265.302	-768.010	-372.287	1228.784	8.090	0.000	0.009
SNX21	2326.849	323.590	913.131	162.878	136.105	-299.157	-882.274	-734.995	2552.065	8.095	0.000	0.009
SDF4	2608.423	147.243	303.864	165.129	16.094	-260.085	-913.707	-604.313	2557.982	8.075	0.000	0.009
LRRC14	524.541	-5.395	93.702	34.973	23.503	-45.397	-171.488	-140.343	533.556	8.076	0.000	0.009
RPS6KA4	708.646	-24.402	-2.361	55.143	13.942	-26.131	-218.604	-136.347	674.322	8.028	0.000	0.010
ZBTB42	170.856	10.819	141.635	-8.936	15.138	-9.620	-140.677	-68.432	199.266	8.011	0.000	0.010
SLC9A3	47.897	8.778	13.176	12.836	11.949	-8.235	-47.485	-23.358	50.951	8.013	0.000	0.010
VWA1	730.251	-31.390	10.363	20.091	89.201	-163.760	-438.211	-319.388	684.970	8.000	0.000	0.010
FBXL20	1071.724	-158.234	-813.129	-157.494	-72.223	65.415	318.171	247.169	806.119	7.989	0.000	0.010

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
GAK	1184.760	16.360	164.342	28.089	121.921	-104.994	-535.354	-251.031	1201.134	7.977	0.000	0.010
ARHGEF1	1507.620	-112.603	18.275	-68.883	345.243	-296.234	-1091.646	-489.513	1458.473	7.958	0.000	0.010
SIVA1	476.695	148.196	285.130	13.889	33.621	-307.533	-383.162	-357.930	511.611	7.957	0.000	0.010
CHPF2	811.278	177.453	606.787	157.415	56.693	-73.154	-426.281	-296.120	983.407	7.950	0.000	0.010
FBXW5	1784.209	125.943	199.090	106.808	87.590	-440.365	-1062.905	-684.005	1692.475	7.945	0.000	0.010
GLI4	178.692	7.382	-25.551	23.231	29.793	-45.635	-111.381	-85.516	163.981	7.846	0.000	0.011
MAEA	1072.174	70.153	-49.836	26.448	32.996	-182.369	-262.446	-201.322	1021.771	7.809	0.000	0.012
LIME1	125.748	-5.649	20.192	-2.204	37.521	-50.899	-124.788	-72.603	124.776	7.808	0.000	0.012
AP2B1	5503.036	-96.105	-625.202	-83.428	-225.007	77.540	866.528	716.072	5341.909	7.791	0.000	0.012
ARMC6	488.822	87.874	48.512	125.960	-14.067	-83.767	-132.709	-150.542	484.183	7.782	0.000	0.012
GRK2	1531.243	-38.419	248.753	-109.770	234.553	-178.209	-909.344	-399.738	1545.754	7.785	0.000	0.012
SRM	902.101	84.922	219.951	222.346	-6.295	-96.042	-388.543	-244.534	918.330	7.771	0.000	0.012
SLC4A2	1642.560	101.451	102.844	130.822	-0.974	-263.703	-491.012	-524.378	1582.676	7.763	0.000	0.012
SURF6	732.931	80.829	96.847	77.926	28.218	-105.271	-207.583	-151.977	747.693	7.752	0.000	0.012
FLYWCH2	329.260	16.581	116.632	-0.360	14.840	-57.605	-207.247	-109.111	335.734	7.755	0.000	0.012
ZMAT2	2167.563	-50.459	-318.573	-169.991	-295.185	108.997	710.337	286.883	2030.441	7.736	0.000	0.012
AIMP1	1243.837	-43.207	-114.998	-73.582	-111.199	18.314	350.328	195.604	1206.375	7.735	0.000	0.012
BRAT1	644.504	18.065	65.180	-26.541	59.991	-165.337	-385.667	-196.274	617.129	7.734	0.000	0.012
TOMM40	514.275	161.461	301.836	173.513	-4.649	-116.062	-155.581	-224.757	600.156	7.743	0.000	0.012
TMC6	625.739	72.512	157.762	116.554	107.793	-134.819	-397.362	-286.164	664.780	7.732	0.000	0.012
ARHGEF17	2283.357	-156.884	652.583	-144.965	397.333	-371.871	-1081.174	-651.233	2450.526	7.727	0.000	0.012
C9orf142	225.550	7.100	-7.287	15.433	33.821	-92.821	-127.487	-96.137	212.884	7.719	0.000	0.012
PUF60	1941.919	317.852	530.077	265.581	-52.540	-308.186	-437.502	-457.925	2036.675	7.707	0.000	0.012
SPNS1	559.050	40.211	23.236	6.324	39.220	-135.381	-225.355	-170.724	540.830	7.648	0.000	0.013
BCAR1	473.913	26.465	217.087	-68.358	56.265	-85.617	-326.681	-199.096	505.818	7.645	0.000	0.013
BRD7	1230.616	-30.067	-268.135	-54.769	-145.328	54.475	386.227	174.910	1135.441	7.648	0.000	0.013

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
SCO2	313.197	68.747	214.155	48.353	12.273	-75.042	-155.943	-155.632	364.959	7.640	0.000	0.013
LRP5	3624.232	-33.848	392.738	-32.380	413.831	-895.928	-2246.152	-1219.259	3497.015	7.620	0.000	0.013
GPAA1	1702.695	201.757	239.501	105.691	53.014	-425.510	-923.710	-560.568	1642.425	7.610	0.000	0.013
LRCH4	584.763	3.665	214.291	50.242	108.878	-52.763	-432.427	-216.996	632.075	7.576	0.000	0.014
AHDC1	461.242	-34.335	527.867	-192.211	116.852	-106.506	-447.029	-198.498	589.606	7.577	0.000	0.014
YIPF2	537.409	39.603	97.890	40.318	16.759	-82.789	-287.402	-159.352	527.710	7.566	0.000	0.014
DNM2	2495.162	218.748	459.746	192.995	104.942	-401.843	-759.215	-443.306	2573.601	7.551	0.000	0.014
TELO2	433.942	-8.155	10.548	24.144	33.730	-76.378	-250.581	-190.357	403.392	7.551	0.000	0.014
RAE1	625.129	-28.811	-76.881	-20.272	-92.880	-27.626	220.421	18.671	584.609	7.556	0.000	0.014
CHTF18	83.871	-18.330	21.721	8.599	35.360	-25.292	-114.376	-56.422	85.418	7.534	0.000	0.014
REXO1	503.053	-70.526	-0.096	-41.095	31.278	-25.682	-224.142	-160.092	464.804	7.521	0.000	0.014
SEC31A	6100.536	192.948	239.361	646.576	-521.187	299.785	1320.033	911.768	6249.365	7.508	0.000	0.014
SGSM2	1337.954	-19.936	2.195	-13.450	187.663	-212.121	-507.730	-344.118	1323.213	7.499	0.000	0.014
FURIN	3594.007	80.332	343.832	256.224	-12.692	-219.982	-1258.382	-905.721	3476.756	7.448	0.000	0.015
RNH1	3147.035	301.416	318.143	351.491	-11.651	-648.146	-1462.058	-1195.392	2985.541	7.445	0.000	0.015
SIX5	441.010	35.084	102.836	-39.622	59.138	-91.453	-337.510	-129.141	440.298	7.449	0.000	0.015
MIGA2	754.731	-8.593	-13.575	2.471	54.651	-124.622	-231.573	-246.082	723.802	7.418	0.000	0.015
PGP	361.073	96.570	242.668	57.060	0.682	-42.791	-138.608	-125.196	425.332	7.410	0.000	0.016
PRRC2A	4172.781	295.035	678.828	267.809	238.518	-400.161	-1245.869	-648.849	4315.648	7.392	0.000	0.016
C19orf25	293.526	-9.152	-54.195	21.324	39.682	-30.874	-193.278	-86.126	259.859	7.393	0.000	0.016
TRAF3	976.511	140.859	453.747	225.711	20.215	-119.631	-265.945	-268.288	1106.566	7.397	0.000	0.016
GIT1	1316.685	-124.330	20.647	-163.883	163.895	-112.014	-672.528	-270.487	1255.415	7.395	0.000	0.016
SF3B3	2449.497	-29.575	-469.544	-15.578	-155.551	47.329	760.917	316.212	2352.301	7.384	0.000	0.016
RAB11FIP3	873.939	33.731	208.563	-5.170	32.080	-78.591	-351.844	-219.910	891.743	7.380	0.000	0.016
DUS1L	1399.994	207.658	303.004	212.470	16.320	-193.678	-480.287	-453.084	1438.720	7.370	0.000	0.016

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
HBP1	4487.417	-1144.231	-3614.134	-622.995	-572.646	18.686	1508.505	791.265	3133.847	7.370	0.000	0.016
FAM160B2	1459.093	29.979	184.037	19.539	146.283	-225.037	-539.162	-397.962	1482.913	7.345	0.000	0.016
SREBF1	3457.911	2399.791	4749.200	-3221.486	305.491	-1313.334	-878.585	-3664.369	5298.601	7.322	0.000	0.016
ZNF48	139.934	26.169	43.638	-9.838	15.059	-51.013	-59.282	-53.260	149.462	7.333	0.000	0.016
ATP13A2	604.687	95.015	264.777	116.348	21.227	-61.079	-269.681	-237.019	664.156	7.336	0.000	0.016
KMT2B	1192.978	-69.614	110.850	-9.955	163.528	15.440	-572.818	-287.418	1199.808	7.330	0.000	0.016
ZNF628	39.734	8.637	6.524	4.874	5.371	-14.233	-30.795	-26.299	39.055	7.320	0.000	0.016
TRIM28	2178.562	48.592	233.136	174.024	71.053	-286.029	-568.267	-519.386	2181.764	7.322	0.000	0.016
POMT1	700.465	41.102	147.970	71.139	52.164	-93.760	-194.088	-192.507	740.852	7.303	0.000	0.017
FASTK	1200.881	5.372	-25.700	106.043	9.105	-181.179	-391.512	-371.089	1118.541	7.285	0.000	0.017
POLRMT	542.543	25.665	41.527	28.885	26.751	-21.489	-223.984	-149.047	530.947	7.277	0.000	0.017
ZNF414	82.475	31.589	39.444	21.518	2.117	-47.623	-59.194	-50.199	87.273	7.239	0.000	0.018
NACC1	823.663	193.731	336.429	195.380	-25.809	-142.394	-262.553	-253.504	895.202	7.242	0.000	0.018
CLUH	2136.921	677.697	572.345	-1147.308	55.806	-247.862	-768.136	-835.211	2334.617	7.237	0.000	0.018
TP53I13	936.881	166.379	412.367	14.763	42.600	-289.284	-490.186	-474.074	999.006	7.227	0.000	0.018
CRACR2B	232.485	3.558	92.719	38.711	29.116	-17.557	-209.101	-98.562	241.873	7.229	0.000	0.018
CTBP1	2258.160	131.301	279.690	98.789	67.724	-375.788	-687.772	-552.168	2252.428	7.227	0.000	0.018
ZNF438	694.952	8.468	-184.821	36.530	-84.028	75.957	239.332	90.132	642.107	7.216	0.000	0.018
COPE	1389.513	217.895	151.485	134.411	29.752	-341.409	-718.632	-460.745	1333.870	7.211	0.000	0.018
LRFN4	368.571	8.761	42.175	37.280	16.460	-103.611	-253.655	-191.872	340.488	7.176	0.000	0.018
MAPK8IP3	1029.571	-54.437	159.592	32.120	244.477	-132.662	-823.234	-431.593	1043.771	7.156	0.000	0.019
PIM3	1632.306	-241.237	58.247	142.050	177.177	-172.645	-995.395	-726.548	1528.157	7.152	0.000	0.019
FSCN1	624.400	134.409	158.002	309.461	147.921	-56.157	-435.518	-309.031	700.576	7.136	0.000	0.019
PLXNB2	3291.137	-160.827	526.159	-152.641	268.586	-463.265	-1660.165	-832.245	3245.392	7.133	0.000	0.019

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
CORO7-PAM16	441.773	35.858	117.176	36.265	60.157	-58.875	-303.306	-153.560	458.220	7.119	0.000	0.019
C10orf76	980.815	43.175	-40.204	39.642	-63.739	-36.936	233.986	94.209	982.912	7.121	0.000	0.019
CABIN1	1063.706	-32.548	142.518	-60.033	138.949	-73.108	-555.560	-167.506	1071.476	7.124	0.000	0.019
TIGD5	64.246	2.310	14.527	-2.864	7.078	-5.983	-53.601	-25.451	62.554	7.116	0.000	0.019
FBXL8	51.006	13.203	4.624	11.093	11.157	-19.472	-41.691	-31.449	51.267	7.106	0.000	0.019
KDM4B	769.493	-6.439	139.261	-4.634	91.885	-122.268	-430.834	-178.743	776.905	7.085	0.000	0.020
MYBBP1A	797.035	129.999	392.902	170.319	45.976	-87.284	-307.707	-222.583	911.309	7.083	0.000	0.020
UPF1	2607.191	-164.105	-205.638	-95.681	164.662	-198.026	-693.316	-448.743	2458.930	7.087	0.000	0.020
DGCR6L	466.887	31.560	4.600	39.868	14.278	-140.941	-151.230	-210.207	442.117	7.088	0.000	0.020
RABL6	1581.461	103.643	146.005	97.359	12.555	-265.201	-606.166	-430.440	1524.738	7.069	0.000	0.020
THAP7	241.674	2.363	167.392	-27.026	19.611	-83.793	-166.215	-95.633	269.764	7.060	0.000	0.020
CCDC71	424.325	-20.624	133.794	-36.582	14.574	-94.170	-119.243	-106.657	442.691	7.057	0.000	0.020
GRK6	473.808	26.112	71.870	-4.612	42.432	-70.276	-267.730	-122.648	468.981	7.060	0.000	0.020
SYNGR2	2365.533	111.000	240.800	157.019	-37.580	-295.711	-563.175	-629.842	2318.198	7.054	0.000	0.020
PDXP	170.064	84.052	251.287	5.164	7.965	-84.731	-85.839	-99.042	243.305	7.047	0.000	0.020
RPS6KB2	454.933	43.391	89.923	34.930	14.991	-76.009	-166.537	-132.001	462.879	7.040	0.000	0.020
PIEZO1	5235.248	-1173.132	-697.363	-744.733	385.272	-731.956	-1973.441	-1433.480	4616.424	7.039	0.000	0.020
DOT1L	371.966	47.508	137.884	33.129	61.397	-45.611	-263.965	-145.725	404.148	7.033	0.000	0.020
PSMA3	1697.233	223.861	32.652	193.739	-196.121	67.706	480.927	236.225	1737.031	7.032	0.000	0.020
TRIP6	1268.631	207.266	577.913	94.254	40.302	-299.659	-619.383	-422.741	1373.931	7.040	0.000	0.020
SNAPC4	272.818	-18.696	43.797	-5.925	53.209	-16.040	-170.050	-84.253	279.746	7.031	0.000	0.020
INF2	4068.616	304.703	1157.136	94.435	181.077	-1242.317	-2172.481	-1807.550	4092.076	7.023	0.000	0.020
ARHGAP39	42.843	17.350	20.823	13.861	11.816	-22.342	-39.154	-32.186	49.609	7.017	0.000	0.020
DGCR14	349.357	-11.949	144.110	-21.722	23.261	3.402	-171.887	-61.239	375.241	7.004	0.000	0.020
UCKL1	661.936	-44.368	-48.758	29.709	42.832	-63.911	-216.618	-168.079	620.301	7.007	0.000	0.020

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
LMAN2L	833.437	-98.064	-210.957	-131.669	-78.044	56.045	279.564	154.294	760.154	7.007	0.000	0.020
TUBGCP6	1606.120	-307.459	-304.639	-130.693	319.021	24.189	-811.455	-305.612	1482.647	6.995	0.000	0.020
TRAPPC6A	304.310	53.283	89.131	25.957	12.897	-101.226	-188.234	-135.794	306.328	6.978	0.000	0.021
RABEP2	194.135	-0.664	-28.058	21.800	6.162	-38.139	-67.009	-91.700	173.310	6.935	0.000	0.022
PWWP2B	375.497	-28.964	115.676	-13.184	44.805	-39.702	-254.581	-144.424	383.030	6.928	0.000	0.022
LDLRAP1	872.751	32.062	-34.392	31.890	23.675	-138.318	-137.693	-195.666	842.235	6.916	0.000	0.022
DDA1	710.722	56.941	174.023	3.742	1.586	-188.582	-168.884	-158.359	731.710	6.911	0.000	0.022
POLR2E	5466.348	348.978	561.505	462.730	-11.596	-1091.312	-2500.749	-1648.529	5188.695	6.910	0.000	0.022
STAMBP	1035.730	-50.072	-132.124	-97.931	-70.290	-0.421	185.137	141.332	980.642	6.907	0.000	0.022
C16orf62	1585.886	25.558	-267.111	-30.456	-166.876	18.772	374.882	204.797	1485.012	6.894	0.000	0.022
NSMF	767.237	135.752	261.040	87.405	62.207	-196.865	-445.314	-225.508	812.779	6.895	0.000	0.022
STX16-NPEPL1	2433.510	-11.103	69.178	64.930	325.304	-104.744	-810.878	-446.855	2467.991	6.885	0.000	0.022
HSP90AB1	23071.381	-1709.693	-7338.259	-370.413	-2843.830	1708.952	8941.641	4182.417	20749.490	6.883	0.000	0.022
SLC52A2	385.182	76.364	198.985	92.352	21.370	-81.013	-266.653	-156.901	421.973	6.875	0.000	0.023
ZNF513	394.568	28.679	93.587	33.370	15.037	-18.082	-137.948	-110.041	410.527	6.873	0.000	0.023
ATG4D	223.043	-0.101	52.568	-23.709	31.024	-45.109	-153.673	-63.335	224.312	6.870	0.000	0.023
COPS5	1628.604	-85.053	-361.716	-68.677	-176.063	102.051	513.910	185.525	1504.589	6.861	0.000	0.023
SUPT4H1	1548.671	46.282	-175.774	-85.087	-175.808	-8.591	395.736	196.764	1473.141	6.856	0.000	0.023
KIF22	454.604	52.833	130.582	10.101	26.979	-100.510	-211.085	-114.647	473.121	6.852	0.000	0.023
ABCB8	548.587	65.098	75.049	83.099	48.832	-109.871	-217.239	-169.898	562.859	6.844	0.000	0.023
CDC42EP1	1498.991	-247.191	497.903	-262.331	36.159	-387.027	-690.591	-589.336	1482.908	6.833	0.000	0.023
DHX30	1355.474	-11.611	132.495	52.823	-4.491	-103.957	-250.404	-236.830	1344.545	6.836	0.000	0.023
SHARPIN	1046.567	23.782	-35.261	20.008	4.477	-179.250	-356.012	-312.520	962.378	6.824	0.000	0.023
OCIAD1	2607.960	-14.404	-360.388	-167.315	-224.546	-28.228	676.895	283.834	2483.813	6.828	0.000	0.023
SSBP4	300.940	-17.156	2.403	6.093	34.253	-17.044	-189.716	-96.681	282.109	6.825	0.000	0.023

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
PIGQ	523.212	2.461	83.030	-6.122	32.378	-130.308	-302.466	-199.785	503.087	6.805	0.000	0.023
HSPG2	30252.818	484.947	2372.595	441.538	5081.891	-5948.607	-16380.887	-10176.602	30299.642	6.809	0.000	0.023
LINC01278	573.580	-74.759	-213.750	-63.355	-40.985	78.410	177.716	113.145	508.096	6.804	0.000	0.023
APRT	1134.179	98.833	254.944	108.926	74.990	-209.740	-592.825	-298.358	1154.535	6.788	0.000	0.024
TOLLIP	1459.299	108.159	170.470	138.457	-0.086	-183.293	-408.584	-333.206	1447.740	6.779	0.000	0.024
SCYL1	1744.399	114.534	147.705	111.802	-52.729	-196.161	-359.479	-429.701	1701.637	6.766	0.000	0.024
WDR24	177.541	-15.914	1.437	-5.165	23.092	-11.102	-105.597	-50.530	167.892	6.756	0.000	0.025
ZNF844	243.299	-15.712	-122.437	3.002	10.683	-16.709	44.872	87.042	216.840	6.732	0.000	0.025
C20orf27	1129.726	83.890	189.019	111.980	128.396	-179.864	-663.127	-321.152	1143.012	6.717	0.000	0.026
RHBDD1	787.090	9.270	-82.501	33.055	-64.019	68.784	190.595	136.244	770.979	6.707	0.000	0.026
COQ8B	566.139	29.092	-22.236	34.313	50.539	-118.361	-195.015	-173.619	545.313	6.697	0.000	0.026
TNK2	1008.638	-135.002	223.117	-189.808	220.240	-346.998	-705.674	-477.924	1014.396	6.691	0.000	0.026
NOL9	511.961	-41.720	-31.746	-46.745	-38.937	73.201	231.294	75.764	518.868	6.692	0.000	0.026
LRRC45	142.438	17.746	-3.158	12.234	16.073	-30.507	-91.015	-56.181	133.597	6.688	0.000	0.026
TFEB	402.917	-19.774	124.183	-125.536	36.632	-103.224	-219.065	-134.949	404.900	6.670	0.000	0.026
SNRPB2	869.730	-38.737	-112.883	-69.723	-109.874	85.886	302.361	128.748	827.385	6.670	0.000	0.026
FAF1	1287.110	202.578	-168.013	168.238	-215.823	48.690	444.253	143.793	1236.923	6.664	0.000	0.027
PDDC1	1486.633	47.198	118.379	145.342	79.438	-80.163	-281.823	-306.332	1519.093	6.662	0.000	0.027
RAB3A	29.822	10.512	2.540	9.614	11.774	-15.893	-32.978	-14.978	31.541	6.653	0.000	0.027
PRMT1	1210.092	84.458	111.115	149.510	-5.152	-130.849	-292.747	-231.575	1200.291	6.639	0.000	0.027
TMBIM6	20781.563	-328.029	-3504.660	-594.389	-2372.637	1367.897	6702.644	2861.401	19641.146	6.640	0.000	0.027
CAPN1	2057.154	123.676	192.754	122.037	57.102	-264.540	-820.757	-390.061	2008.126	6.640	0.000	0.027
C19orf60	188.218	4.162	33.320	19.870	25.283	-48.901	-114.878	-88.169	189.172	6.634	0.000	0.027
GUK1	2483.380	83.883	231.960	50.698	121.741	-396.603	-1351.760	-755.963	2363.405	6.632	0.000	0.027
TSNARE1	294.309	-59.078	-51.360	-47.829	51.683	-27.504	-170.342	-61.807	262.404	6.627	0.000	0.027

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
ZBTB7B	2517.264	602.201	744.158	306.692	-17.614	-443.955	-952.920	-732.869	2629.562	6.617	0.000	0.027
CTNNBL1	1000.458	-64.410	-236.552	-67.417	-75.643	-15.368	229.671	144.654	915.923	6.606	0.000	0.028
ZNF687	599.591	-1.920	160.572	-9.204	44.277	-89.256	-232.528	-118.730	626.660	6.600	0.000	0.028
NCSTN	3790.646	168.928	-280.167	-14.141	-336.842	77.362	1049.634	511.512	3740.663	6.595	0.000	0.028
DDX54	854.880	81.625	178.271	86.902	-4.071	-85.027	-340.155	-209.677	858.095	6.587	0.000	0.028
FTO	2162.935	101.327	-257.336	34.110	-236.055	132.624	787.973	370.721	2122.339	6.571	0.000	0.028
SDF2	926.021	-42.085	-256.414	-52.873	-118.798	-59.116	329.297	15.064	826.116	6.566	0.000	0.028
C7orf50	601.443	147.999	208.923	116.638	15.883	-207.130	-356.173	-271.374	622.510	6.565	0.000	0.028
DMWD	649.888	40.950	159.659	10.063	83.059	-142.817	-325.514	-174.659	681.753	6.554	0.000	0.029
STK25	2111.470	-126.449	-90.040	-54.313	51.550	-243.309	-364.908	-402.588	2004.644	6.544	0.000	0.029
FAM65A	1993.157	-142.548	254.592	-131.217	202.585	-152.128	-853.325	-371.303	1993.248	6.544	0.000	0.029
YIF1A	895.412	127.782	142.804	167.059	-67.056	-180.606	-118.003	-257.425	895.886	6.523	0.000	0.030
ZNF574	308.994	-8.028	18.785	-32.479	17.010	-68.938	-118.148	-91.738	294.360	6.498	0.001	0.030
NAA60	841.259	22.738	210.039	-120.213	53.971	-177.386	-355.018	-219.113	855.634	6.477	0.001	0.031
EXOSC5	204.669	-4.239	-18.742	12.672	13.826	-45.604	-89.777	-67.487	186.491	6.476	0.001	0.031
NPEPL1	1380.158	40.746	159.980	48.069	108.130	-215.657	-537.131	-381.390	1381.555	6.478	0.001	0.031
CACFD1	144.460	2.220	68.145	14.948	26.709	-14.059	-126.725	-69.818	157.452	6.465	0.001	0.031
TOX4	2242.698	-94.806	-171.156	-6.860	-127.519	46.043	333.361	354.574	2182.795	6.463	0.001	0.031
GANAB	8652.901	11.559	-866.013	-55.993	-616.438	46.392	1884.498	804.687	8398.394	6.458	0.001	0.031
ARL14EP	771.440	-84.894	-116.239	-32.755	-85.688	67.796	275.936	72.405	730.931	6.452	0.001	0.031
ZNF213	308.989	19.664	17.015	-3.695	33.602	-57.799	-195.145	-71.987	295.550	6.449	0.001	0.031
TYK2	1591.312	-29.578	92.774	105.297	232.783	-113.687	-744.635	-426.692	1599.550	6.441	0.001	0.032
TSPAN31	1300.654	-88.063	-342.827	-84.146	-111.013	27.687	410.558	164.363	1192.529	6.438	0.001	0.032
STK3	745.473	-95.799	-265.768	-45.514	-80.317	89.516	226.161	179.691	653.398	6.429	0.001	0.032
EFNB1	2196.162	549.113	605.877	208.241	231.380	-593.567	-929.577	-729.561	2371.700	6.433	0.001	0.032
CUEDC1	1123.538	198.884	420.585	165.720	-18.914	-150.541	-329.861	-256.374	1212.934	6.428	0.001	0.032

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
PTBP1	2698.031	181.280	714.620	247.794	36.620	-223.759	-521.420	-533.508	2870.759	6.423	0.001	0.032
DNAJC8	2655.409	-73.688	-488.040	-142.366	-353.106	36.944	839.471	257.634	2449.992	6.422	0.001	0.032
CCDC102A	125.961	-22.445	-9.901	-19.720	16.052	3.912	-68.471	-34.282	114.790	6.419	0.001	0.032
TMUB1	327.707	-34.929	53.605	-17.145	8.076	-46.403	-182.001	-106.823	308.576	6.389	0.001	0.033
PSMA4	2071.184	246.294	30.145	216.462	-307.815	76.218	752.286	153.220	2100.102	6.378	0.001	0.033
MLST8	496.457	57.401	117.849	46.024	-0.357	-81.452	-223.055	-180.261	496.786	6.380	0.001	0.033
LIN7B	54.180	-3.606	9.858	6.964	5.792	-8.834	-24.566	-34.443	54.738	6.373	0.001	0.033
HGS	1329.814	-43.250	47.602	13.572	48.958	-152.677	-418.950	-300.073	1279.394	6.370	0.001	0.033
ATXN7L3	1561.395	67.885	471.158	28.275	102.713	-110.949	-430.050	-254.401	1690.805	6.363	0.001	0.034
RNF166	288.739	-27.385	19.622	-5.471	29.113	-10.722	-161.749	-89.610	276.291	6.352	0.001	0.034
LRP3	1341.711	121.371	-63.496	25.375	39.973	-327.403	-723.502	-520.202	1200.862	6.337	0.001	0.034
C9orf16	421.524	86.378	209.024	51.816	57.875	-177.472	-463.408	-251.417	437.397	6.329	0.001	0.035
AGPAT2	11709.507	1878.284	2151.164	1484.176	-230.348	-4230.764	-4256.432	-6157.422	11462.113	6.314	0.001	0.035
IGSF8	893.000	-147.411	362.300	-245.036	58.397	-20.040	-486.800	-235.653	919.168	6.306	0.001	0.035
ARHGEF18	615.873	-15.988	76.684	-15.032	41.843	-63.551	-202.077	-113.024	618.859	6.295	0.001	0.036
LYPLA2	485.255	-10.158	125.548	-5.808	45.501	-45.810	-234.214	-127.622	502.426	6.297	0.001	0.036
MICALL2	143.608	23.939	159.595	60.976	43.486	-25.684	-180.847	-118.176	189.283	6.280	0.001	0.036
RABGGTB	1214.051	-146.503	-432.408	-124.446	-114.077	68.429	436.385	195.098	1073.653	6.278	0.001	0.036
PLEKHG3	765.513	-0.112	264.127	-18.121	119.209	-97.999	-393.295	-189.977	834.149	6.281	0.001	0.036
ZFPM1	25.371	-8.074	12.093	-9.232	11.112	-1.925	-39.618	-0.772	26.800	6.268	0.001	0.036
BBS10	695.774	-110.283	-415.887	11.895	-57.394	128.131	299.186	191.118	582.966	6.268	0.001	0.036
EXOSC4	130.803	37.883	67.103	26.568	-3.777	-54.476	-55.147	-62.602	142.593	6.252	0.001	0.037
ASPSCR1	320.655	7.323	50.006	17.216	10.703	-58.182	-150.962	-103.693	312.969	6.235	0.001	0.038
GAS2L1	560.081	126.393	82.661	4.257	-3.815	-205.779	-210.706	-235.570	544.775	6.235	0.001	0.038
H1FX	960.199	218.994	357.407	-79.422	76.268	-465.677	-656.109	-366.866	987.425	6.208	0.001	0.039

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
C19orf70	957.055	94.461	99.571	113.476	13.388	-228.502	-429.623	-327.390	920.317	6.205	0.001	0.039
MCRIP2	170.554	-7.016	19.693	18.043	3.471	-45.214	-91.780	-85.561	158.959	6.189	0.001	0.039
FKBP8	4984.543	205.878	207.242	-142.454	269.053	-1128.968	-2934.990	-1459.232	4606.482	6.173	0.001	0.040
ZDHHC12	327.931	61.268	84.721	11.698	4.443	-99.252	-216.812	-123.088	319.898	6.161	0.001	0.041
FAM173A	72.595	17.414	21.279	9.740	-0.926	-17.211	-45.719	-39.093	71.769	6.135	0.001	0.042
TAF7	2759.342	-458.998	-751.653	-336.713	-308.508	321.231	812.823	350.880	2450.521	6.135	0.001	0.042
SLC9A3R2	2951.642	-1291.049	-2141.350	-661.178	520.644	-561.747	-1749.922	-754.372	1990.996	6.102	0.001	0.043
NOC2L	1084.780	67.927	170.558	93.305	-14.262	-119.441	-183.854	-244.220	1102.160	6.101	0.001	0.043
ARID5B	2316.846	-109.983	-870.119	180.212	-83.242	210.675	1305.483	1016.007	2253.631	6.083	0.001	0.044
LOC108783654	291.771	30.559	175.470	-1.306	36.145	-85.880	-169.701	-113.114	334.132	6.083	0.001	0.044
CACYBP	1112.834	-75.637	-274.679	9.384	-161.670	187.129	401.415	171.384	1016.436	6.073	0.001	0.044
RAC1	5889.970	-222.768	-677.592	-148.531	-468.209	28.801	1200.571	396.474	5613.505	6.074	0.001	0.044
HPF1	462.387	13.752	-70.443	2.370	-77.373	46.036	207.558	52.446	440.362	6.070	0.001	0.044
OSBPL5	715.019	-176.224	144.399	-93.475	98.739	14.923	-374.444	-141.530	721.659	6.065	0.001	0.044
MFSD7	283.935	-16.741	-19.368	13.156	48.350	-15.573	-147.914	-72.018	273.395	6.058	0.001	0.045
NONO	4787.033	-149.433	-162.012	-178.114	-280.586	257.204	787.411	461.640	4724.543	6.043	0.001	0.045
ABHD8	148.737	-24.589	15.148	-14.768	22.281	-28.561	-102.750	-58.311	140.942	6.035	0.001	0.046
F11R	4364.103	-705.459	-1543.979	-723.924	-321.000	437.796	1131.922	621.830	3804.434	6.025	0.001	0.046
ATP5D	619.344	81.711	21.709	8.716	34.303	-231.315	-374.986	-288.727	568.848	6.018	0.001	0.046
EPHX2	1237.079	-17.965	-306.363	-121.119	-125.225	18.515	443.176	291.872	1147.599	6.012	0.001	0.046
XAB2	881.718	-64.643	-31.532	-77.793	67.652	-125.205	-442.129	-185.485	807.636	6.014	0.001	0.046
CXXC5	1086.453	-129.441	1227.822	-107.885	40.931	-220.756	-455.610	-549.574	1383.392	6.005	0.001	0.047
ATN1	5052.332	-78.147	563.232	-290.792	303.735	-595.565	-1684.012	-847.455	5023.420	6.000	0.001	0.047
ARVCF	191.333	-4.295	15.692	18.539	33.939	-27.750	-152.728	-86.951	184.779	5.995	0.001	0.047
NBAS	1791.235	-177.605	-657.411	-33.905	-132.972	96.479	489.798	259.849	1583.601	5.985	0.001	0.047

Gene names	Baseline				Week 8				Average Expression	F	P-Value	FDR
	6am	12pm	6pm	12am	6am	12pm	6pm	12am				
USP20	734.009	-87.653	-98.933	-70.965	72.144	-73.086	-236.929	-113.878	677.132	5.974	0.001	0.048
TOLLIP-AS1	43.936	18.378	19.236	14.402	11.585	-32.426	-34.933	-32.264	50.397	5.979	0.001	0.048
SELENOO	439.821	-12.166	22.101	-42.540	42.699	-84.829	-210.602	-152.249	419.816	5.976	0.001	0.048
RPRD1B	938.339	-112.584	-71.473	-124.803	-48.009	86.203	161.681	127.331	906.073	5.973	0.001	0.048
MZT2B	342.132	6.731	63.697	2.824	33.687	-109.605	-239.013	-180.846	329.519	5.970	0.001	0.048
TRMU	335.579	4.765	28.818	27.790	6.375	-36.351	-26.288	-93.022	341.217	5.966	0.001	0.048
THOC7	972.938	27.164	-137.325	0.614	-144.776	27.829	294.632	127.700	912.595	5.966	0.001	0.048
SPATA25	15.292	-3.354	3.125	3.827	13.725	-0.951	-26.116	-6.681	18.551	5.964	0.001	0.048
JAK1	10777.023	-55.087	-1431.588	-452.076	-628.575	323.145	2239.782	1011.642	10374.922	5.957	0.001	0.048
NARFL	371.119	10.135	78.537	-13.246	33.338	-28.760	-197.785	-88.458	376.498	5.948	0.001	0.048
SLC10A3	505.371	81.462	219.914	22.926	9.589	-115.048	-190.536	-161.118	549.229	5.942	0.001	0.049
D2HGDH	465.368	-34.890	-61.879	-16.050	60.985	-65.078	-191.399	-172.815	430.012	5.930	0.001	0.049
ARRDC1	281.050	-16.314	20.836	-23.462	54.355	-39.115	-175.714	-82.886	277.954	5.926	0.001	0.049
GPSM1	156.906	-6.433	1.528	5.618	41.126	-25.959	-129.651	-56.162	153.141	5.920	0.001	0.049
TFCP2	1318.194	-143.365	-256.816	-113.880	-111.382	135.393	359.559	172.420	1227.720	5.921	0.001	0.049
ABCA3	932.707	77.168	91.239	100.960	0.572	-115.973	-257.246	-234.996	921.419	5.924	0.001	0.049
CRTC1	517.911	-15.885	176.833	30.235	83.033	-118.230	-283.785	-159.407	559.862	5.921	0.001	0.049
VPS26A	2058.965	-143.392	-270.753	-104.226	-227.911	200.056	650.152	280.457	1961.168	5.928	0.001	0.049
LONP1	1557.306	106.771	277.772	101.434	31.148	-292.130	-696.638	-460.965	1536.433	5.909	0.001	0.050
ATXN10	1588.737	57.034	-85.728	72.611	-139.484	89.760	303.635	204.261	1563.508	5.909	0.001	0.050