

**RNA-sequencing identifies dysregulation of the human pancreatic islet transcriptome
by the saturated fatty acid palmitate**

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Abstract

Pancreatic β -cell dysfunction and death are central in the pathogenesis of type 2 diabetes.

Saturated fatty acids cause β -cell failure and contribute to diabetes development in genetically predisposed individuals.

Here we used RNA-sequencing to map transcripts expressed in five palmitate-treated human islet preparations, observing 1,325 modified genes. Palmitate induced fatty acid metabolism and endoplasmic reticulum (ER) stress. Functional studies identified novel mediators of adaptive ER stress signaling. Palmitate modified genes regulating ubiquitin and proteasome function, autophagy and apoptosis. Inhibition of autophagic flux and lysosome function contributed to lipotoxicity. Palmitate inhibited transcription factors controlling β -cell phenotype including PAX4 and GATA6. 59 type 2 diabetes candidate genes were expressed in human islets, and 11 were modified by palmitate. Palmitate modified expression of 17 splicing factors and shifted alternative splicing of 3,525 transcripts. Ingenuity Pathway Analysis of modified transcripts and genes confirmed that top changed functions related to cell death. DAVID analysis of transcription binding sites in palmitate-modified transcripts revealed a role for PAX4, GATA and the ER stress response regulators XBP1 and ATF6.

This human islet transcriptome study identified novel mechanisms of palmitate-induced β -cell dysfunction and death. The data point to crosstalk between metabolic stress and candidate genes at the β -cell level.

Pancreatic β -cells are long-lived cells (1) that face protracted metabolic challenges in insulin resistant individuals (2). This includes the chronic exposure to saturated free fatty acids (FFAs), present in a high fat Western diet and released from the adipose tissue in obesity (3). High levels of saturated FFAs are predictive of the future development of type 2 diabetes (T2D) (3). High fat feeding impairs the β -cells' ability to compensate for insulin resistance (4; 5). Prolonged exposure to FFAs impairs insulin secretion *in vivo* and *in vitro* (6; 7), and induces β -cell death (8) in a phenomenon called lipotoxicity.

Palmitate is the most common saturated FFA in man, and has been used in *in vitro* studies to examine the mechanisms of lipotoxicity. Palmitate functionally impairs β -cells by inhibition of insulin transcription (9), inducing mitochondrial uncoupling (10), and inhibiting exocytosis by disrupting the coupling between Ca^{2+} channels and insulin granules (11). The production of reactive oxygen species (10) and ceramides (12) has also been implicated in palmitate-induced β -cell dysfunction and death. We and others have previously shown that FFAs induce endoplasmic reticulum (ER) stress in β -cells (13-16). The ER plays a central role in the synthesis and folding of secretory proteins. In β -cells, insulin represents up to 50% of the protein synthesized (17). ER stress, defined as an imbalance between protein folding demand and ER capacity, leads to accumulation of misfolded proteins. ER stress is sensed by the ER stress transducers PERK, IRE1 and ATF6 that activate the unfolded protein response (UPR). The UPR attenuates protein translation to relieve the load on the ER and induces ER chaperones, ER-associated degradation and ER expansion. It is an adaptive response, but when prolonged or exaggerated, it triggers apoptosis. Saturated FFAs elicit marked PERK activity and the resulting eIF2 α phosphorylation contributes to β -cell death (13; 18) via the mitochondrial apoptosis pathway (19).

Unbiased approaches to examine the β -cell response to palmitate include microarray studies of clonal INS-1 and MIN6 cells. These studies showed induction of genes involved in FFA β -oxidation, FFA desaturation, steroid biosynthesis, cell cycle, chemokines and acute phase response genes and inhibition of genes involved in glycolysis and aminoacyl tRNA

biosynthesis (20-23). Time course microarrays of palmitate-treated INS-1E cells by us led to the identification of the pro-apoptotic Bcl-2 proteins that mediate lipotoxic β-cell death (19). Oleate-treated human islet arrays showed transcriptional induction of FFA oxidation, inflammatory genes and antioxidant enzymes (24).

One of the intrinsic limitations of microarrays is that transcript detection is limited to transcripts for which probes are present on the arrays. RNA-sequencing (RNA-seq) has become the gold standard for transcriptomic studies, allowing detection of low-expressed genes, alternative splice variants, and novel transcripts (25). It has been used by our group to map the transcriptome of human islets (26) and this has been recently replicated in human islets and purified human β-cells (27); the latter study showed that islets are a good proxy for β-cell transcript expression.

Environmental challenges interact with the genetic background of individuals to generate disease. Recent genome-wide association studies (GWAS) have linked a number of genetic variants to susceptibility to T2D (28). Many of these variants seem to be related to pancreatic β-cell function, but there is little information on the expression and function of these genes in human β-cells faced with prolonged metabolic stress. The known candidate genes for T2D explain less than 10% of the heritability of the disease (28). Epigenetic alterations, such as changes in DNA methylation, have been described in pancreatic islets from T2D patients (29) and may explain part of the missing heritability. Whether the expression of these epigenetic T2D candidate genes is modified by metabolic stress has never been investigated.

In order to better understand the global responses of human islets exposed to metabolic stress, we have used RNA-seq to identify all transcripts, including splice variants, expressed in human islets of Langerhans following a 48-h exposure to the saturated FFA palmitate. This *in vitro* model of lipotoxicity arguably induces more rapid and harmful effects than what may occur *in vivo*. Nonetheless, this analysis provides a snapshot of the cellular responses under conditions that may prevail in T2D. Key findings were validated and followed-up by functional

studies in independent human islet samples and clonal or primary rat β -cells. We also examined whether putative candidate genes for T2D are expressed in human islets and modified by palmitate.

Research design and methods

Human and rat islet isolation and cell culture

Human islet collection and handling were approved by the local Ethical Committee in Pisa, Italy. Human pancreatic islets were isolated in Pisa using collagenase digestion and density gradient purification from heart-beating organ donors with no medical history of diabetes or metabolic disorders (30). The donor characteristics are provided in Table S1. The first five preparations were used for RNA-seq (2F/3M, donor age 55 \pm 9 years, BMI 24.8 \pm 0.7 kg/m 2) and the other preparations (15F/16M, donor age 63 \pm 3 years, BMI 25.0 \pm 0.5 kg/m 2) for confirmation and functional studies. In Pisa, the islets were cultured in M199 culture medium containing 5.5 mM glucose. The islets were shipped to Brussels within 1-5 days of isolation. In Brussels, the human islets were cultured in Ham's F-10 medium containing 6.1 mM glucose, 10% heat-inactivated fetal bovine serum (FBS), 2 mM GlutaMAX, 50 μ M 3-isobutyl-1-methylxanthine, 1% charcoal-absorbed BSA, 50 U/ml penicillin and 50 μ g/ml streptomycin. Islet β -cell purity was evaluated in dispersed islet cells by insulin immunocytochemistry and averaged 52 \pm 3% (26). The islets were exposed or not to 0.5 mM palmitate in the same medium without FBS for 2 days (8; 13; 31). The serum-free culture conditions have previously been validated (32). Human islet viability, assessed after Hoechst 33342 and propidium iodide staining (see below), was similar in serum-free or 10% FBS-containing medium (respectively 93 \pm 1% vs 95 \pm 1% viable cells after 72 h, n=8, p=0.3).

Rat insulin-producing INS-1E cells, kindly provided by C. Wollheim, University of Geneva, Geneva, Switzerland (33) were cultured in RPMI 1640 medium supplemented with 5% FBS, 10 mM HEPES, 1 mM Na-pyruvate and 50 μ M 2-mercaptoethanol (34). The INS-1E cells were exposed to palmitate as described (13).

Rats were used according to the Belgian Regulations for Animal Care with approval of the Ethical Committee for Animal Experiments of the ULB, Brussels, Belgium. Islets were isolated from adult male Wistar rats (Charles River Laboratories, Brussels, Belgium) and primary β -cells FACS-purified (FACSAria; BD Bioscience, San Jose, CA) and cultured as described (13).

RNA-seq and data analysis

Five human islet preparations were sequenced and data analyzed as previously described in detail (26). In brief, polyA-selected mRNA was purified from total RNA isolated with the RNeasy Mini Kit (Qiagen, Venlo, The Netherlands). mRNAs were reverse transcribed to cDNA, paired-end repaired, 3'-monoadenylated and adaptor ligated. 200 bp cDNA products were amplified and libraries submitted to quality control with the Agilent bioanalyzer 2100 (Agilent Technologies, Wokingham, UK). The RNA integrity number (RIN) values for all samples were >7.5. cDNA was sequenced on one sequencing lane of an Illumina Genome Analyzer II system (Illumina). The raw data will be deposited in Gene Expression Omnibus (GEO), submission number GSExxxx.

Paired-end reads were mapped to the human genome (version GRCh37/hg19) using gem-mapper from GEM suite (<http://gemlibrary.sourceforge.net>). Mapped reads were used to quantify transcripts from the RefSeq reference database (35), using the Flux Capacitor (<http://flux.sammeth.net>) (36). Genes and transcripts were assigned a relative coverage rate as measured in RPKM units ("reads per kilobase of exon model per million mapped reads") (37). Lists of differentially expressed genes and transcripts were generated from the Flux Capacitor output using scripts in Perl or R. Palmitate-modified genes were defined by taking the \log_2 of the proportion between the sum of the RPKM for all gene transcripts under palmitate condition and control condition. A Fisher exact test (number of reads mapped to the gene and number of reads mapped to all other genes in palmitate vs control) was Benjamini-Hochberg corrected (taking for each gene the 5 samples as independent tests) and a difference in gene expression considered significant if the p-value was <0.05. A gene was considered modified by palmitate if its expression changed significantly in one direction

in at least 4 out of 5 islet preparations and no significant change in the opposite direction was observed. Differences in splice indices - the proportion between the RPKM for a transcript and the sum of the RPKM for all the transcripts from the same gene - were compared between palmitate and control condition. Splicing analysis was done using Gencode version 16 annotations datasets (38-40). The GENCODE annotation used dataset contains 153,008 transcripts corresponding to 25,492 genes remained after processing and keeping protein coding genes and lincRNA only. Changes in splicing were statistically tested as above, i.e. by Benjamini-Hochberg-corrected Fisher exact test-defined p-value <0.05 in at least 4 out of 5 islet samples and no sample pair exhibiting a significant change in the opposite direction.

Human islet and rat β-cell RNA extraction and RT-PCR

Human islets (Table S1), INS-1E and primary rat β-cells were used for validation and mechanistic experiments. PolyA mRNA was isolated using the Dynabeads mRNA DIRECT kit (Invitrogen, Paisley, UK) and reverse transcribed as previously described (34). qRT-PCR was done using the iQ SYBR Green Supermix (BIO-RAD, Nazareth Eke, Belgium) on a LightCycler (Roche Diagnostics, Mannheim, Germany) or iCycler MyiQ Single Color (BIO-RAD) instrument (41; 42). Data were expressed as number of copies using the standard curve method and corrected for the housekeeping gene β-actin or glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Primers used for qRT- and RT-PCR are listed in Table S2.

RNA interference

Human and rat β-cells were transfected with 30 nM siRNA and Lipofectamine RNAiMAX (Invitrogen) diluted in Opti-MEM I (Invitrogen) as described (43), resulting in a transfection efficiency of >90% (43; 44). After overnight transfection the cells were cultured for 48 h before further use. The siRNAs are listed in Table S3.

Western blot

Western blots were performed using equal amounts of whole cell extract protein as described (18). Briefly, cell lysates were run on SDS-PAGE, washed in transfer buffer and

proteins transferred to a nitrocellulose membrane. The primary antibodies were anti- β -actin (1:2,000), GATA6 and LC3B (both 1:1,000) from Cell Signaling (Beverly, MA), LONP1 from Protein Tech Group and anti- α -tubulin (1:10,000) from Sigma. Horseradish peroxidase-labeled donkey anti-rabbit or donkey anti-mouse (1:10,000, Jackson Immuno Research, Baltimore Pike, PA) antibodies were used as secondary antibodies. Protein signal was visualized using chemiluminescence Supersignal (Pierce) and quantified using Scion Image (Scion Corporation, Frederick, MD).

Assessment of apoptosis

The percentage of apoptotic cells was determined in at least 500 cells per condition by staining with the DNA-binding dyes propidium iodide and Hoechst 33342 (Sigma-Aldrich) as previously described (18).

Electron microscopy

Electron microscopy studies were performed on isolated human islets as previously described (30).

Statistical analyses

The statistical analysis of the RNA-seq data is described in supplemental material. Data for confirmation and functional studies are shown as means \pm SEM. Comparisons were performed by paired two-tailed Student's t test or ratio t test. A p-value ≤ 0.05 was considered statistically significant.

Results

Sequencing of palmitate-treated human islets and analysis of transcripts

Five human islet preparations, exposed or not to palmitate for 48 h, were RNA-sequenced. The characteristics of the organ donors and islet preparations are shown in Table S1. The percent cell death in palmitate-treated human islets was 12 \pm 2%, compared to 6 \pm 2% in control condition (48 h, $p < 0.05$). The reads were mapped to the human genome (version GRCh37/hg19) using GEM software, mapping on average 85% of raw reads. Transcript expression and splicing was evaluated using Flux Capacitor software. As reference transcript

annotation, we employed the 42,012 annotated human mRNA and ncRNA sequences from RefSeq.

Of the 18,463 genes detected by the RNA-seq, a total of 1,325 (7%) were significantly modified by a 48-h exposure to palmitate, with 428 being up- and 897 being downregulated. Compared to our previous RNA-seq analysis of cytokine-exposed human islets (26), there was limited overlap between the two stress conditions (Figure S1A-C). Of the genes upregulated by cytokines, 10% were also induced by palmitate, and of the cytokine-inhibited genes 19% were palmitate-regulated, showing that palmitate induced specific transcript expression changes.

The genes detected as modified by palmitate by RNA-seq were compared to microarray data of human islets from T2D donors and/or donors with HbA1c $\geq 6\%$ (45). Of the genes differentially expressed in T2D and hyperglycemia, 7-16% were modified by palmitate in non-diabetic islets. In 82% of these genes the change in expression occurred in the same direction for palmitate exposure and T2D (Figure S1D).

For internal validation, expression data were confirmed for 7 genes by qRT-PCR in the same islet samples used for RNA-seq. The gene expression data were essentially superimposable (Figure S2). Additional validation was done by comparing RNA-seq data to qRT-PCR in independent human islet samples for 30 genes, showing a correlation coefficient of 0.63 (Figure S2).

Expression of candidate genes for T2D in human islets

We examined whether known T2D candidate genes (28) are expressed (median RPKM >1) in human islets. We defined a set of 69 genes using the convention typically used in naming GWAS loci, i.e. in the absence of a strong biological candidate to choose the nearest gene to the peak GWAS signal. It is likely that this gene set is enriched for transcripts that mediate the GWAS locus effects. We did not exclude genes from loci that have been shown to act through non-islet mechanisms. Of the 69 candidate genes, 59 (86%) were present in human islets (Figure 1A). This was a significantly higher proportion than that of candidate genes associated with ulcerative colitis (46) or body height (47), or a random set of 60 genes

(Figure 1B). The T2D genes were also more abundantly expressed with higher RPKM. Similarly, a large proportion of genes previously identified to harbor differential DNA methylation in T2D islets (29) were well expressed in human islets (Figure S3), with median expression of 8 RPKM compared to 6 RPKM for all detected genes.

Analysis of palmitate-modified genes

We next analyzed the human islet genes that were modified by palmitate (complete list accessible at <http://lmedex.ulb.ac.be/data.php> with password provided upon request). These genes were analyzed using Ingenuity Pathway Analysis (IPA, Figure S4) and DAVID software (see below), and they were manually curated (Table S4 and Figure 2). IPA showed that upregulated genes belong to the functions “Cell Death”, “Cellular Movement” (mainly chemokines), “Cellular Development”, “Gene expression” and “Lipid Metabolism” (Figure S4A). Downregulated genes fell into the functional categories “Cellular Movement”, “Cell Morphology”, “Lipid Metabolism”, “Molecular Transport” and “Small Molecule Biochemistry” (Figure S4B). The manual annotation was performed taking a pancreatic β-cell perspective. It showed induction of genes involved in lipid metabolism, including the transcription factor SREBP2, and early response genes which are part of an adaptive response (Figure 2). Palmitate inhibited expression of key β-cell transcription factors, including PDX1, PAX4, MAFA and MAFB, hormones and receptors, genes involved in ATP production, and channels and transporters, thereby likely contributing to induce β-cell dysfunction. Upregulation of a large number of UPR genes and inhibition of protein degradation pathways are likely to further contribute to β-cell dysfunction and death. Growth and regeneration genes were inhibited. Inflammatory responses were extensively modified, with upregulation of cytokines and chemokines and inhibition of HLA (Table S4 and Figure 2).

FFA metabolism

Palmitate exposure induced gene expression of fatty acid metabolic pathways (Figure 3A). It induced ACSL1 and 3, involved in FFA activation to acyl-CoA moieties, CPT-1, which mediates mitochondrial FFA uptake, ACADVL, ECH1 and HADHA, three enzymes involved

in mitochondrial FFA β -oxidation, and two FFA desaturases that introduce double bonds into saturated FFAs and as such are β -cell protective (21). Interestingly, palmitate inhibited expression of enzymes involved in the *de novo* synthesis of ceramide (including SERINC5, SPTSSB and CERS2). In parallel, it inhibited genes involved in the lysosomal breakdown of ceramide and sphingolipids (Figure 3A).

Protein synthesis/processing and ER stress

Palmitate induced the aminoacyl tRNA synthetases IARS, GARS, MARS, WARS, VARS, CARS and SARS and the translation elongation factor EEF1A2, involved in delivery of aminoacyl tRNAs to the ribosome. Protein translation initiation factors were modulated, with induction of EIF4A1 and inhibition of EIF4A2 expression, and inhibition of the translational repressor EIF4G2. Hormone processing was affected with an induction of CPE and PCSK1 and inhibition of PCSK4 and SCG5 (Figure 3B).

The RNA-seq data indicated transcriptional activation of the three branches of the UPR, including PERK-dependent induction of ATF4, ATF3, TRIB3 and GADD34, ATF6-dependent induction of BiP and its cofactor DNAJB11, and IRE1-dependent induction of chaperones and protein disulfide isomerases (Figure 3B). In line with this, DAVID analysis using UCSC_TFBS showed enrichment for potential binding sites for the transcription factors ATF6 and IRE1-dependent XBP1 (Figure 4A).

Interestingly, palmitate induced expression of the ER stress transducers CREB3 and CREB3L3 (Figure 3B), which may play roles similar to ATF6 in a tissue-specific way (48; 49). Because their role in β -cells is unknown, we studied these ER stress transducers further. CREB3 was well expressed in human islets, with an RPKM of 15, and mildly induced by palmitate (Figure 5A). The induction was not detected in independent human islet samples (Figure 5B), but palmitate did induce CREB3 expression in INS-1E cells (Figure 5C). CREB3 silencing (using two independent siRNAs, Figure 5C) markedly sensitized the cells to palmitate-induced apoptosis (Figure 5D). Similarly, efficient CREB3 knockdown in primary rat β -cells enhanced lipotoxicity, nearly doubling palmitate-induced apoptosis (Figure 5E and F).

This was confirmed in human islets, where CREB3 mRNA knockdown by 67-72% potentiated lipotoxicity in two independent preparations (Figure 5G). CREB3L3 is expressed at lower levels in human islets but it was markedly induced by palmitate (Figure 5H); this was confirmed in independent human islet samples by qRT-PCR (Figure 5I). CREB3L3 was also induced by oleate, but inhibited by synthetic ER stressors (Figure 5I), suggesting it mediates an adaptive UPR in response to FFAs, but fails to do so in the face of severe chemical ER stress. Taken together, these data suggest a novel role for CREB3 and CREB3L3 in adaptive β -cell UPR signaling.

Proteasomal function and autophagy

Palmitate inhibited expression of the ubiquitin-conjugating enzymes UBE2H and UBE3A, the deubiquitinating enzymes USP2, USP54 and USP30, ubiquitin D, a proteasomal degradation signal, and modulated expression of components of the proteasome (Figure 3B).

FFAs have previously been shown to induce autophagosome formation (50; 51) and impair autophagic flux in β -cells (52). We confirmed that palmitate induces conversion of microtubule-associated protein 1 light chain 3 (LC3) from its native (I) to the lipidated form (II) in INS-1E cells (Figure 6A and B) and human islets (Figure 6C and D), resulting in an increased LC3 II/I ratio (Figure 6B and D) and accumulation of autophagosomes in human β -cells (Figure 6E). The present RNA-seq data identified inhibition of a number of autophagy- and lysosomal function-related genes that may directly affect lysosome - autophagosome fusion (Figure 3B). Thus, ATG7 and WIPI2 were inhibited, as were the positive regulators of autophagy SCOC, DRAM2 and KIAA1324. ATP6AP2, an accessory protein to the H⁺-ATPase, and the adaptor-related protein complex subunit AP2M1, both of which contribute to lysosomal acidification, were inhibited. The inhibition of adaptor-related protein complex subunits AP3B1 and AP3M2 and cathepsins F, O, S, A and D may also affect lysosomal function. To examine whether stimulating autophagic flux would protect β -cells, we used the autophagy enhancing drug carbamazepine (53). Carbamazepine protected INS-1E cells from lipotoxicity in a dose-dependent manner (Figure 6F). In human islets carbamazepine

promoted LC3 II disappearance (Figure 6G and H), suggesting increased clearance of autophagosomes (54), and it effectively protected against palmitate-induced cell death (Figure 6I).

Mitochondrial dynamics and quality control

We searched the human islet RNA-seq data for genes involved in mitochondrial movement, biogenesis, fusion-fission and mitophagy (Table S5). Mitochondrial fragmentation, which plays a role in lipotoxic β -cell apoptosis (55), was detected ultrastructurally in palmitate-treated human islets (Figure S5A). Genes involved in mitochondrial fission (DNM1L, FIS1, MFF) and fusion (MFN1, MFN2, OPA1) were well expressed in human islets, with a median RPKM of 12, compared to a median expression of 6 RPKM for all human islet transcripts. Palmitate did not modify their expression, suggesting that the mechanism(s) leading to impaired mitochondrial fusion is not transcriptional.

Among the mitochondrial enzymes induced by palmitate was Lon peptidase 1 (LONP1, Figure S5B). This AAA⁺ protease is involved in mitochondrial protein quality control. It degrades misfolded or oxidized proteins and acts as a chaperone in the assembly of protein complexes (56). We confirmed that LonP1 is induced under lipotoxic conditions in rat β -cells (Figure S5C and D). LonP1 induction by palmitate (57) may occur in response to a stoichiometric imbalance in nuclear- and mitochondrial-encoded proteins.

Insulin secretion

Palmitate is known to inhibit glucose-induced insulin release and this was confirmed here. Palmitate-treated human islets increased insulin secretion following high glucose stimulation by 1.4 \pm 0.1-fold, compared to a stimulation index of 2.1 \pm 0.2 for non-exposed islets ($p<0.01$, Figure S6). We performed a detailed analysis of the impact of palmitate on the expression of human islet genes that modulate insulin secretion mostly at the level of membrane depolarization and Ca²⁺ entry (58). Palmitate inhibited only 2 of the 48 genes (Table S6), including the Ca²⁺-sensing receptor CaSR, whose activation contributes to human islet insulin secretion (59). Palmitate did inhibit expression of genes involved in ATP production in the Krebs cycle and respiratory chain, including citrate synthase, 2 isocitrate

dehydrogenases and components of complexes I, II, III and IV and mitochondrial ATP synthase (Figure 3A and Table S4). This inhibition, but not transcriptional inhibition of the distal steps of the stimulus-secretion pathway, may contribute to loss of insulin secretion (60; 61).

Interestingly, several of the genes implicated in stimulus-secretion coupling have splice variants. For at least some (KCNMA1, CASR and CLCN3), palmitate alters splicing (Table S6). Future studies should investigate the functional impact of these changes in splicing.

Transcription factors

Palmitate downregulated PDX1, MAFA, MAFB, PAX4, and NEUROD1 that are important for the maintenance of β-cell function and its differentiated state (Figure 2). The RNA-seq data also pointed to a mild inhibition of GATA6, a well expressed transcription factor (RPKM 7, Figure 7A). Heterozygous GATA6 mutations cause pancreatic agenesis and neonatal diabetes (62) and milder phenotypes such as adult-onset diabetes. We confirmed that palmitate inhibits GATA6 expression by qRT-PCR in independent human islet samples and in primary rat β-cells (Figure 7B and C). GATA6 was silenced by transfecting rat or human islet cells with 2 different siRNAs (Figure 7D-F). GATA6 knockdown induced apoptosis under basal condition and accentuated lipotoxicity (Figure 7G-I). These data point to a novel role for GATA6 in adult β-cells and suggest that its inhibition by palmitate contributes to lipotoxicity. Interestingly, the promoter regions of transcripts that were downregulated by palmitate were enriched in potential GATA binding sites (Figure 4B).

Cell death and inflammatory responses

Palmitate induced mRNAs encoding both pro- and anti-apoptotic proteins (Figure 2 and Table S4). For example, palmitate induced GRAMD4 that inhibits the anti-apoptotic Bcl-2 protein and promotes Bax translocation to the mitochondria. Some pro-apoptotic genes were inhibited, including TP53INP1, caspase 2 and 10, the pro-apoptotic Bcl-2 family members BMF and BCL2L11, which encodes Bim. The latter is in keeping with our previous findings that Bim does not play a role in lipotoxic β-cell apoptosis (19). Palmitate also inhibited genes

with anti-apoptotic functions, including c-Flip, DDX17, TM7SF3, DCAF7, ADCYAP1, ANXA4, NMT1 and PRDX6. TXNIP expression was inhibited by palmitate; this was confirmed by qRT-PCR (Figure S7A). High glucose tended to increase TXNIP expression, but palmitate prevented the induction of TXNIP by glucose (Figure S7A). TXNIP inhibits insulin secretion and promotes apoptosis; its inhibition indicates it does not mediate lipotoxicity. This is in keeping with an earlier report showing that TXNIP deficiency protects against gluco- but not lipotoxicity (63). Chen et al also suggested that TXNIP does not mediate thapsigargin-induced β -cell apoptosis (63). In contrast, a recent report indicated that ER stress induces TXNIP and thereby causes NLRP3 inflammasome activation and IL-1 β -driven human islet apoptosis (64). We previously showed that an IL-1 receptor antagonist does not protect human islets from palmitate (31). Similarly, the IL-1 receptor antagonist did not protect human islets against apoptosis induced by thapsigargin or brefeldin A, while it effectively protected against the cytokines IL-1 β + IFN- γ (Figure S7B). Notably, the NLRP3 inflammasome is very lowly expressed in human islets. The RPKM sum of the five NLRP3 transcripts has a mean value of 0.12 and NLRP3 is not induced by palmitate (0.06 RPKM), one of the priming steps for NLRP3 activation. PYCARD and caspase 1 are expressed (mean RPKM of 7.9 and 4.1, respectively) but not modified by palmitate. These data argue against a pro-apoptotic role of TXNIP and the inflammasome in human islets facing lipotoxicity or ER stress.

Palmitate upregulated chemokines and cytokines, including IL6, IL1A, IL33, IL8, CXCL1 and CXCL2 (Figure 2 and Table S4), in line with previous findings (31); the role of these mediators remain to be defined.

Long non-coding RNA

Our experimental design and analysis was not directed at long non-coding RNA (lncRNA) discovery. From the RefSeq database, 1297 out of the 3267 known non-coding RNAs (a global class of non-coding RNAs, including lncRNAs, miRNAs, pseudogenes, unspliced transcripts, etc) were present in human islets (RPKM > 1). Recently, a large number of

previously unknown lncRNA were identified in human islets and β-cells (65). We detected 349 out of these 1128 lncRNA. Of these, 9 (2%) were modified by palmitate, showing their responsiveness to metabolic stimuli. The induction of MALAT1, one of the most abundant lncRNA, was confirmed by qRT-PCR (Figure S2).

Palmitate-induced changes in T2D candidate gene expression

Palmitate inhibited expression of TSPAN8, KCNK16, ADCY5, ADRA2A, TP53INP1, CDC123 and PRC1, while it induced C2CD4A, ADAMTS9 and SPRY2 (Figure 1). For one of these, we evaluated the functional consequence of its downregulation. ADCY5 silencing (by 50%) markedly sensitized rat β-cells to apoptosis, both basally and following palmitate exposure (Figure S8).

Palmitate-induced alternative splicing in human islets

Of the 212 human islet expressed splicing factors, 17 were modified by palmitate (Figure 8A). Among these was SRSF3. We confirmed that palmitate induces SRSF3 in independent human islet samples and in rat β-cells by qRT-PCR (Figure 8B and C).

Exposure of human islets to palmitate altered splicing of 574 genes, with 363 and 462 splice variants being up- and downregulated, respectively, using RefSeq annotation (Figure S9A). IPA of palmitate-modified splice variants identified “Cell Growth and Proliferation” and “Cell Death” as the main categories (Figure S9B). Because RefSeq provides a conservative catalogue of splice variants, we reanalyzed the RNA-seq data using the ENCODE-based GENCODE dataset (version 16), which provides 4-5-fold more transcripts. This increased the number of splice transcripts modified by palmitate by > 6-fold, to 3,525, corresponding to 2,858 genes (Figure 8D). Compared to the splicing induced in human islets by cytokines, there was little overlap (14% only, Figure S1C), showing a stress-specific splicing response. IPA of palmitate-modified splice variants identified “Cell Death and Survival”, “Organismal Survival” and “Gene Expression” as the main categories (Figure 8E). DAVID analysis against UCSC_TFBS identified among the palmitate-modified splice variants enrichment for potential binding sites for the transcription factors ATF6, ELK1, PAX4 and PPARA (Figure 4C).

Discussion

RNA-seq is a highly reproducible method to interrogate the whole transcriptome and identify novel cellular responses to environmental cues (25). Different from microarrays, it allows detection of high and low abundance genes, alternative splice variants and novel transcripts, identifying 25-75% more genes than conventional arrays and more differentially expressed transcripts (25; 66-68). We used it here to map the global response of human islets facing metabolic stress induced by palmitate. The presently used *in vitro* model of lipotoxicity induces cellular responses in the islets over a 48-h period, compared to slower and more heterogeneous events *in vivo*. *In vivo* the effects may also be attenuated by the presence of unsaturated FFAs that decrease the lipotoxicity of saturated FFAs (8). The picture emerging from the analysis of palmitate-treated human islets indicates a complex adaptive response, including upregulation of lipid metabolism and disposal, paralleled by inhibition of the Krebs cycle and oxidative phosphorylation. There are several signals of cellular stress responses, including cytosolic stress, mitochondrial quality control, and activation of an array of genes regulating the UPR and pathways of apoptosis. There was also inhibition of genes regulating protein degradation and autophagy, which may aggravate the ER stress by preventing disposal of misfolded proteins. The transcriptome data further suggest that palmitate leads to loss of the β-cell differentiated phenotype, with inhibition of key β-cell transcription factors, hormones and receptors. Some cytokines and chemokines were induced while HLA genes were inhibited. Palmitate also induced changes in the alternative splicing of more than 3,500 transcripts. These data extend significantly beyond previous microarray findings (19-24). Thus, the RNA-seq analysis identified modulation of the transcription factors GATA6, PAX4, CREB3 and CREB3L3 by palmitate (see below).

GWAS have identified more than 60 loci associated with T2D. The present and previous observations (26; 27) indicate that >80% of the putative candidate genes are expressed in human islets, and we show here that some are modified by palmitate exposure.

Palmitate inhibited the transcription factors PDX1, MAFA, MAFB, NEUROD1, PAX4 and GATA6, all of which play important roles in β -cell differentiation. GATA6 and PAX4 expression has not been previously reported to be modified by palmitate. In the DAVID analysis, GATA and PAX4 binding sites were overrepresented in the promoter region of both palmitate-modified genes and transcripts with modified splicing (Figure 4). These data suggest that palmitate modulates gene networks contributing to lipotoxic loss of β -cell function and survival. On the other hand, the data suggest that the β -cell functional impairment is not related to transcriptional inhibition of distal steps of insulin secretion.

A key cellular stress response activated by palmitate in human islets is the UPR (present data). ER stress has been shown to contribute to lipotoxic β -cell death (13; 16). What governs the transition from adaptive to fatal ER stress is probably cell specific and remains ill understood. Saturated FFAs elicit marked PERK activity and the resulting eIF2 α phosphorylation contributes to β -cell death (13), while ATF6 and IRE1 mediate protective UPR signaling (69). There are a number of structural homologs of ATF6 that may play tissue-specific roles. Here we found that CREB3 and CREB3L3 are upregulated by palmitate. CREB3 may promote protective UPR signaling, given that CREB3 silencing markedly sensitized β -cells to lipotoxicity. A better understanding of the (mal)adaptive facets of the ER stress response in β -cells is important, in light of the evidence for UPR markers in β -cells from T2D patients (16; 17; 30) and the fact that T2D drugs modulate the UPR (69).

The present RNA-seq analysis indicates that palmitate inhibits several protein degradation mechanisms, including autophagy and lysosomal function. In line with the present findings, palmitate has been shown to impair autophagic flux in β -cells and thereby contribute to lipotoxicity (52). β -Cells from T2D patients show signs of altered autophagy, including increased autophagic vacuole and autophagosome volume density and reduced LAMP2 and cathepsin B and D expression in T2D islets (51), in keeping with our RNA-seq findings. We used carbamazepine to stimulate autophagic flux (53), and showed marked β -cell protection from lipotoxicity (Figure 6F and I). Carbamazepine is an anti-epileptic and mood-stabilizing

drug. Compared to other anti-epileptics and atypical antipsychotics, carbamazepine is associated with lesser diabetes risk, but no study reported protection from diabetes, possibly because it can impair β -cell function (70).

Palmitate modified splicing of 3,525 transcripts, detection of which is missed by conventional microarrays. The alternative splicing is different from that observed following exposure of human islets to pro-inflammatory cytokines (26), suggesting that different forms of β -cell stress lead to different splicing signatures probably through the activation of distinct splicing factors.

In conclusion, the present transcriptomic study provides a snapshot of the β -cell responses to conditions that may contribute to T2D pathogenesis. The transcript changes induced by palmitate differ from cytokine-induced stress (26), showing activation of stress-specific signatures in β -cells. The RNA-seq data identify novel players in palmitate-induced β -cell dysfunction and death and indicate several novel areas for investigation in the field.

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Author contributions: MC, MIMC, PM, DLE designed the experiments, MC, BA, GB, DAC, MIE, MM, JVT, TG, OV, IS, MB, LL LM, MS performed experiments and analyzed data, and MC and DLE wrote the manuscript. BA, GB, DAC, MIE, MM, JVT, TG, OV, IS, LM, MIMC, PM and MS reviewed and edited the manuscript. MC is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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The authors declare that they have no conflict of interest associated with this manuscript.

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Figure 5: Role of novel ER stress transducers in lipotoxic β -cell death

(A) RNA-seq data of CREB3 expression in 5 human islet preparations exposed to palmitate for 48 h. (B) CREB3 mRNA expression assessed by qRT-PCR in human islets exposed to 0.5 mM oleate (OL), 0.5 mM palmitate (PAL), 1 μ M thapsigargin (THA), 5 μ g/ml tunicamycin or 0.1 μ g/ml brefeldin A (n=3-6). (C) CREB3 mRNA expression assessed by qRT-PCR and (D) apoptosis in INS-1E cells transfected with control (negative, N) or 2 different CREB3 siRNAs and then treated with 0.5 mM palmitate for 16 h (n=3). (E) CREB3 mRNA expression and (F) apoptosis in FACS-purified primary rat β -cells transfected with control or CREB3 siRNAs and then treated with 0.5 mM palmitate for 24 h (n=3). (G) Apoptosis in dispersed human islet cells transfected with control or CREB3 siRNAs and exposed to palmitate for 24 h. Individual data for two independent human islet preparations are shown. (H) RNA-seq

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Figure 6: Role of autophagy in lipotoxic β-cell death

LC3 conversion in INS-1E cells (A-B) and human islets (C-D) exposed to 0.5 mM palmitate for the indicated times (n=3-4). (B, D) LC3 I and II protein expression was quantified by densitometry and normalized to tubulin or β-actin, or expressed as the ratio of LC3 II/I. (E) Accumulation of autophagosomes (double membrane organelles containing rough ER and mitochondria and/or partially degraded ER, arrows) in human islets exposed to palmitate for 48 h. (F) Apoptosis in INS-1E cells exposed to 0.5 mM palmitate alone or in combination with the indicated concentrations (in μM) of carbamazepine for 24 h (n=5-7). (G-H) LC3 conversion in human islets exposed to 0.5 mM palmitate and/or 30 μM carbamazepine for 24 h (n=3). (I) Human islet cell death after 24 h exposure to palmitate and/or carbamazepine (n=4). *p<0.05, **p<0.01, ***p<0.001 vs control (CTL), #p<0.05 as indicated.

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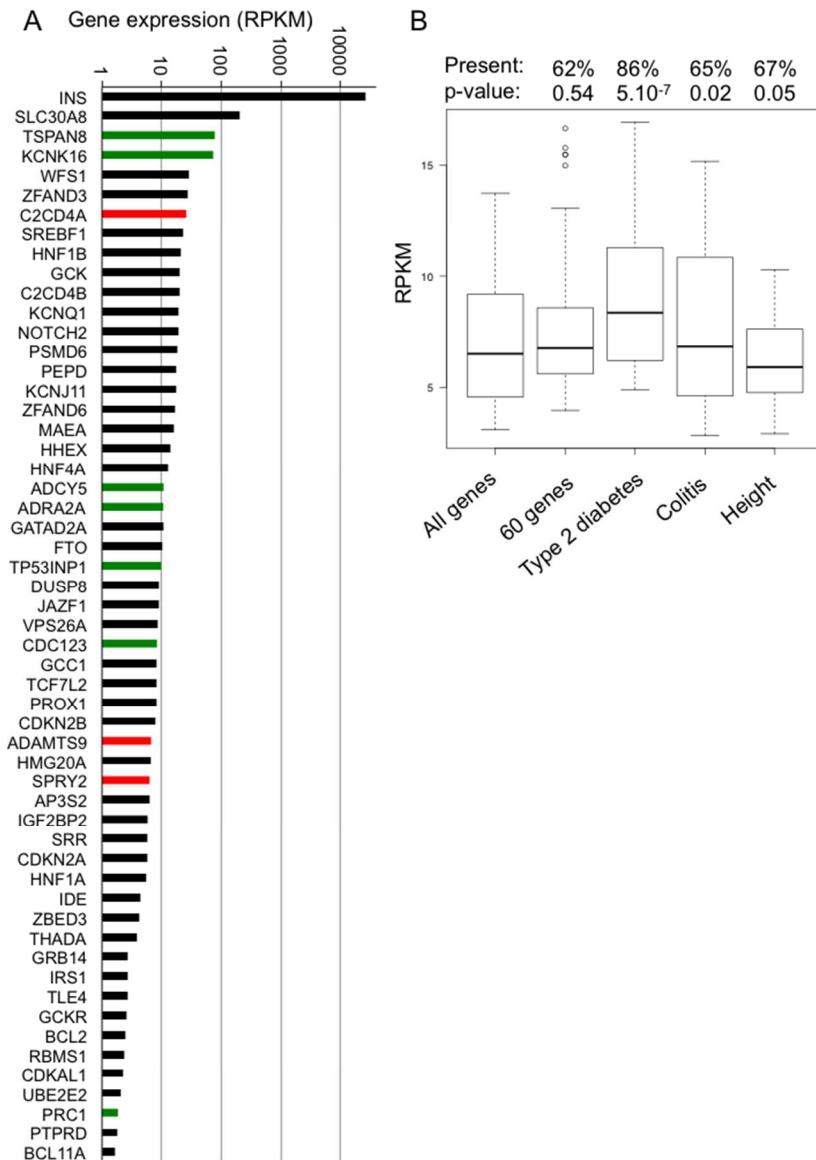


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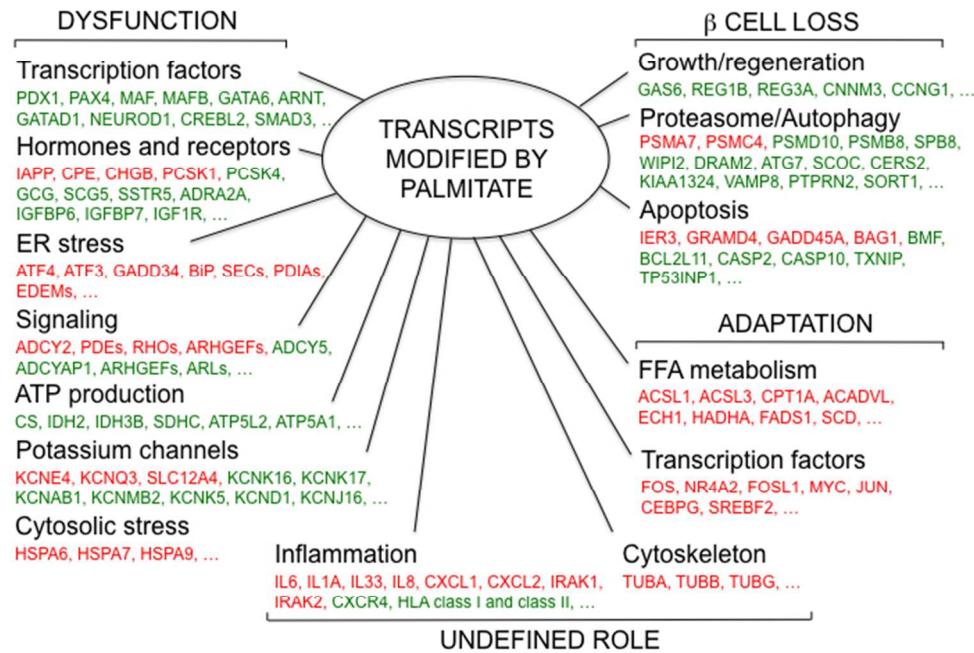


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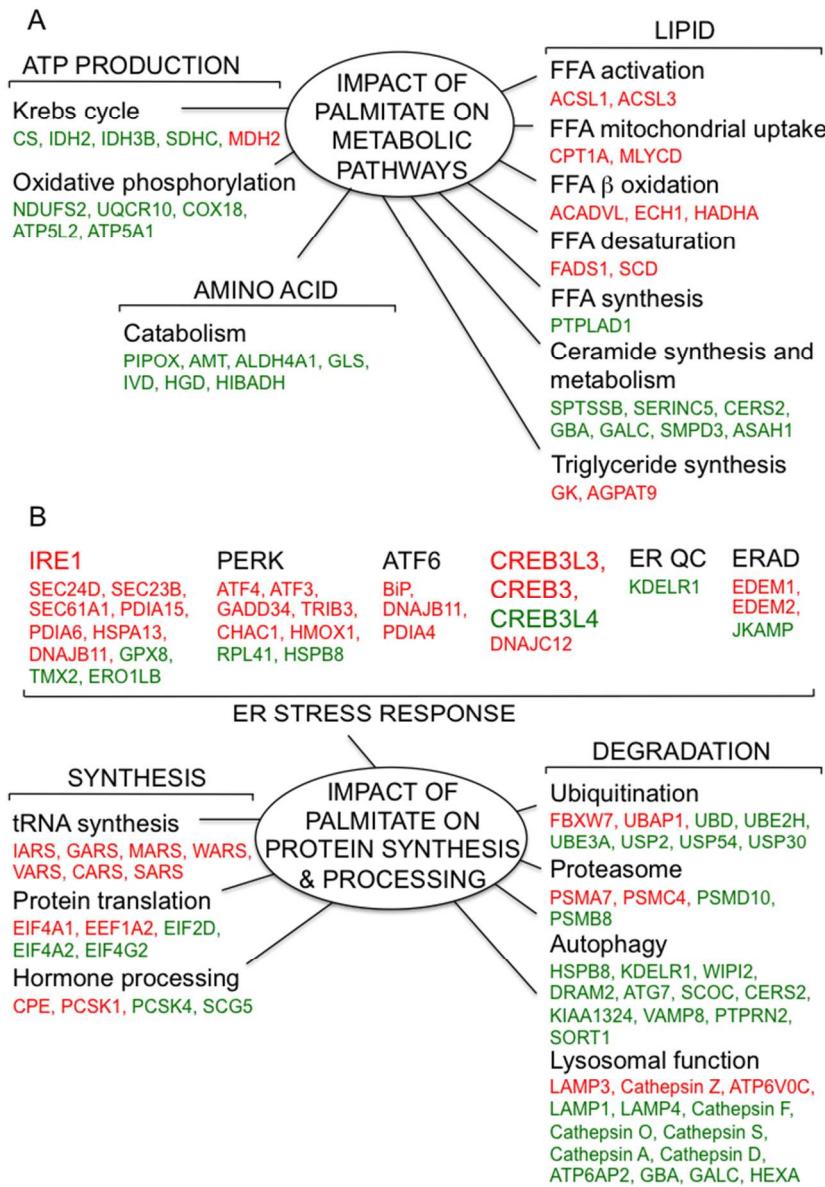


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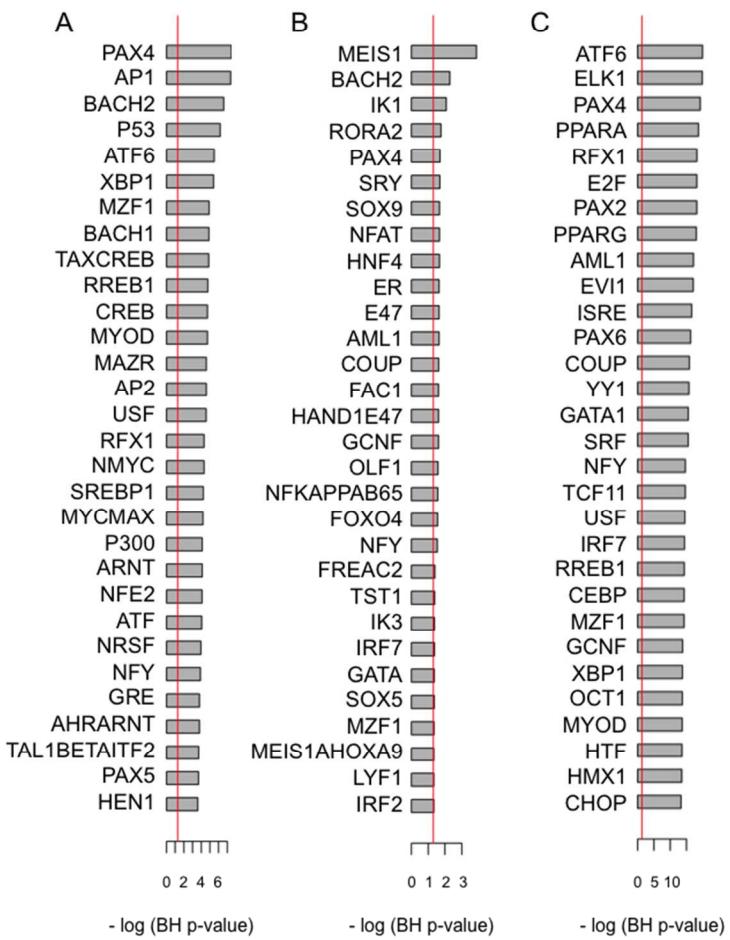


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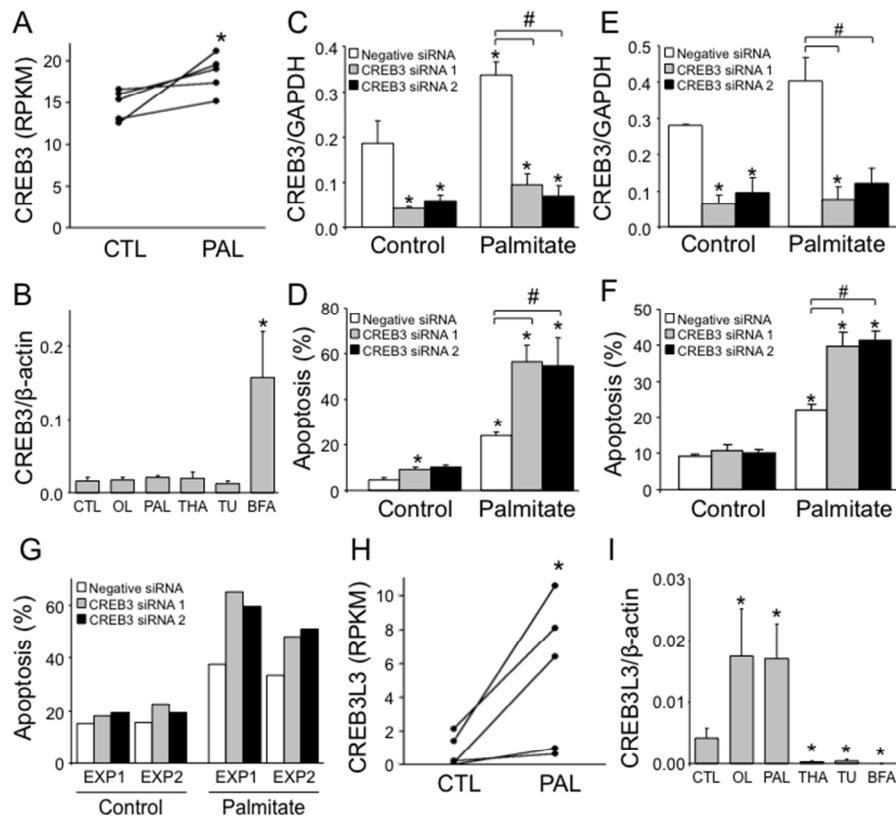


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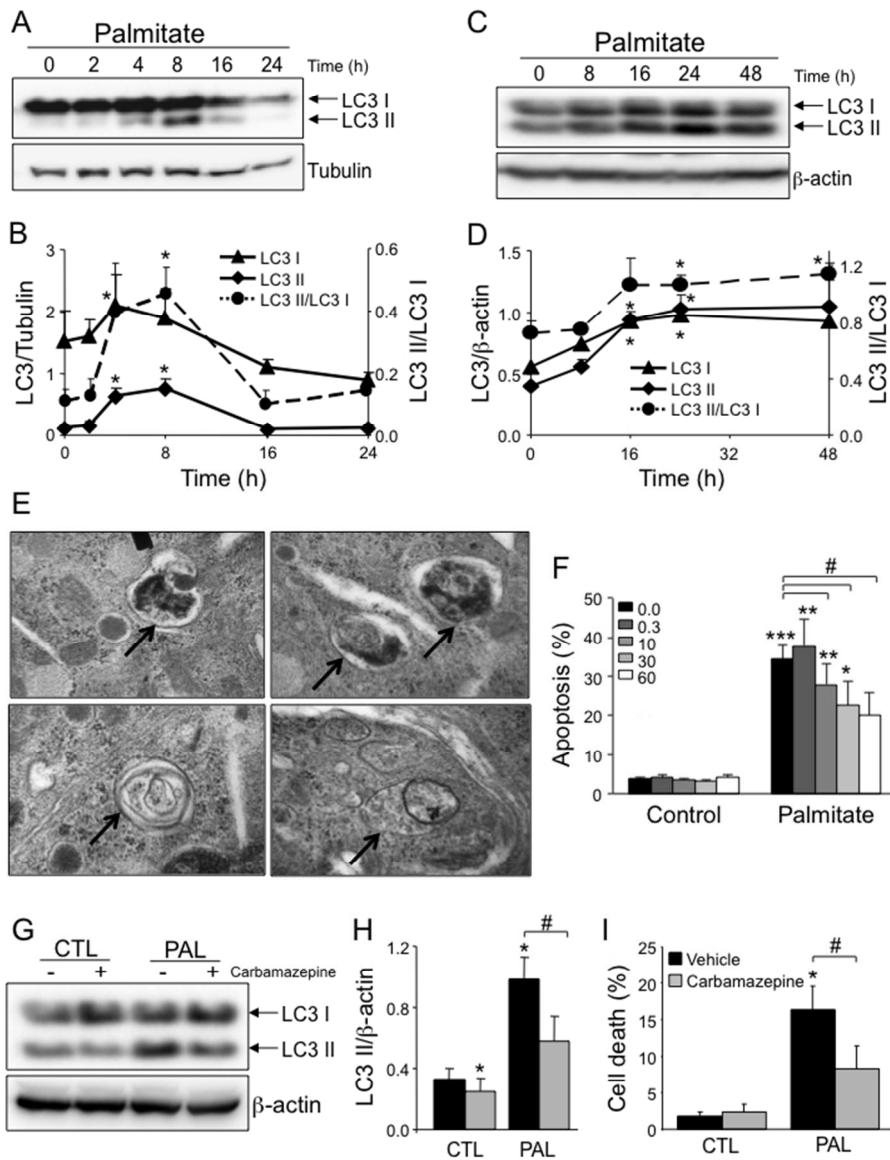


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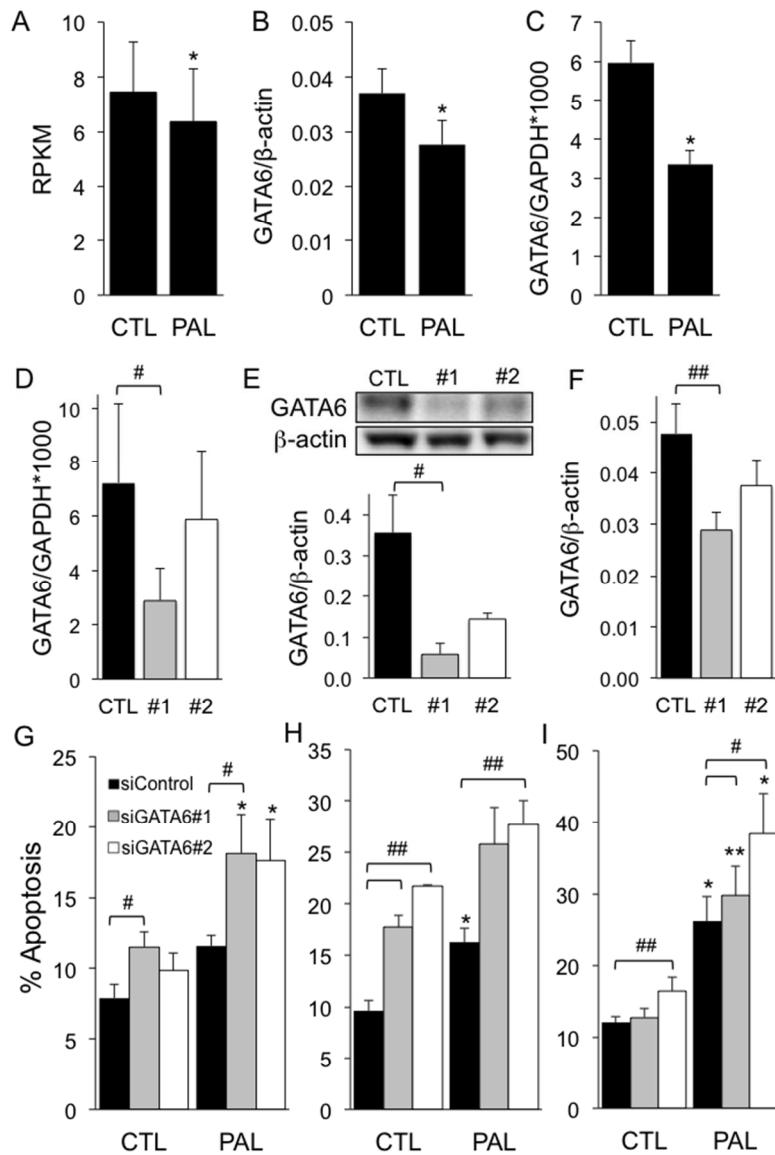


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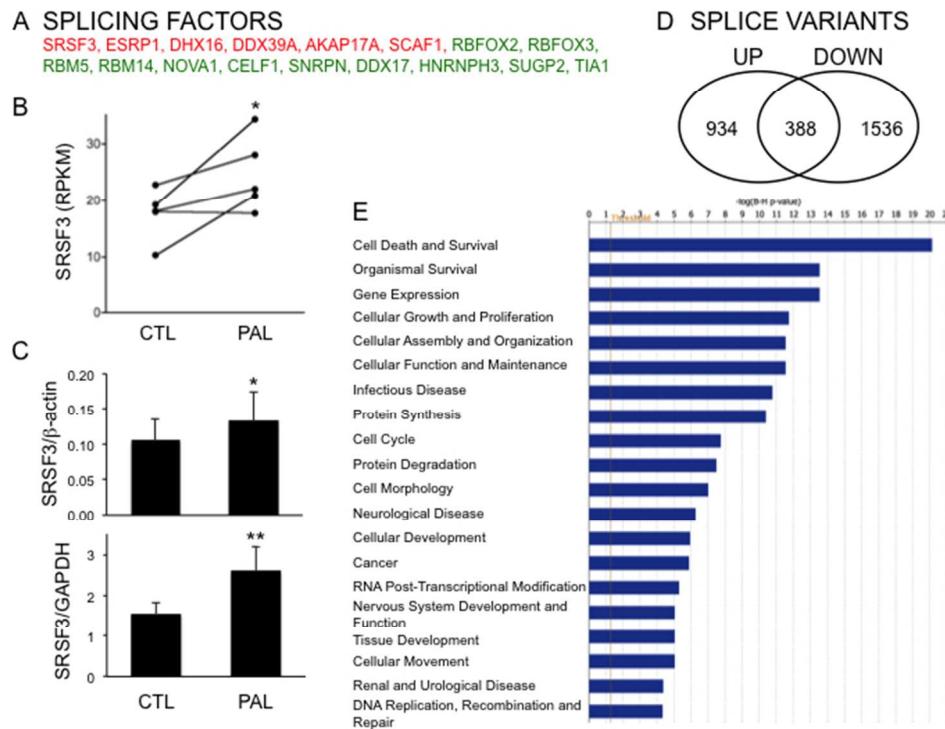


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Supplemental Figure Legends**Figure S1: Comparison of human islet transcript expression changes induced by palmitate versus the cytokines IL-1 β + IFN- γ and versus genes differentially expressed in T2D human islets**

Venn diagram of (A) up- or (B) downregulated genes in islets exposed for 48 h to palmitate (present findings) or the cytokines IL-1 β + IFN- γ (1). (C) Venn diagram of transcripts with modified splicing following palmitate or cytokine exposure. (D) Of the genes that are differentially expressed in human islets from T2D donors compared to non-diabetic donors and from donors with HbA1c \geq 6% compared to those with HbA1c <6% (2), 28 genes were up- or downregulated by palmitate. The fold change is plotted of gene expression changes in T2D or hyperglycemic islets, assessed by microarrays, and in palmitate-treated islets, assessed by RNA-seq. The changes were largely in the same direction, with a correlation coefficient of 0.59 ($p=0.001$).

Figure S2: Validation of RNA-seq gene expression data by qRT-PCR in palmitate-treated human islets

Human islets from 5 organ donors were cultured for 48 h in the presence or absence (CTL) of palmitate (PAL). RNA-seq gene expression results (black bars) were compared to gene expression assessed by qRT-PCR (gray bars) in the same human islet preparations used for RNA-seq. Data were normalized to the geometric mean of β -actin and GAPDH expression and expressed as fold induction of control. * $p<0.05$, ** $p<0.01$ for CYT vs PAL by ratio t test. Bottom right panel: Palmitate-induced transcript expression changes of 30 genes assessed by RNA-seq were compared to expression changes measured by qRT-PCR in independent islet preparations. There was good agreement between the two datasets, with a correlation coefficient of 0.63 ($p<0.001$). Plotted RNA-seq data are the median of the fold change of RPKM in

palmitate vs control condition; qRT-PCR data are expressed as the average fold change in gene expression corrected for the reference gene β -actin.

Figure S3: DNA methylation profiling-derived T2D candidate genes are well expressed in human islets

Transcript expression levels are shown of genes that showed differential DNA methylation in a previous DNA methylation profiling study (3). Panels A and B show hypomethylated genes with RPKM >1, ranked by expression level, and panel C shows RNA-seq expression levels of the hypermethylated genes. Red bars indicate palmitate-upregulated and green bars downregulated transcripts.

Figure S4: IPA of palmitate-modified genes

(A) 428 genes were significantly upregulated by palmitate in at least 4 out of 5 islet samples, and significantly downregulated in none. These genes were mapped to 417 unique entries in the IPA database and submitted to gene set enrichment analysis based on Benjamini-Hochberg corrected Fisher tests. IPA of these upregulated genes is shown for “Molecular and Cellular Function”. (B) 897 genes were significantly downregulated by palmitate in at least 4 out of 5 islet samples, and significantly upregulated in none. They were mapped to 885 unique entries in the IPA database. IPA of these cytokine-downregulated genes is shown for “Molecular and Cellular Function”. The length of the blue bars indicates the significance of the association between the set of genes and the keyword, and is expressed as minus the logarithm of the probability that a random set of genes from the human genome would be associated with the same keyword. The straight orange line indicates a threshold of 0.05 (corresponding to a -log(BH p-value) of 1.3).

Figure S5: Palmitate alters mitochondrial morphology in human β -cells and induces LonP1 expression

(A) Human islets exposed to palmitate for 48 h were examined by electron microscopy. Mitochondria (M) in β -cells were often elongated with signs of fragmentation (arrows) or they appeared swollen (Ms). Magnification: top panel \times 21000, other panels \times 64000. (B) LonP1 mRNA expression by RNA-seq in palmitate (PAL)-treated human islets. (C) LonP1 protein expression in INS-1E cells treated or not for 6, 24 and 48 h with 0.5 mM palmitate (P or PAL). (D) Densitometric quantification of Western blots as in panel C, n=2-7 independent experiments, *p<0.05 vs control (C or CT).

Figure S6: Palmitate impairs human islet glucose-stimulated insulin secretion

Human islets were exposed or not (CTL) to palmitate (PAL) for 48 h. Insulin secretion was measured at 3.3 and 16.7 mM glucose (n=4).

Figure S7: Role of TXNIP and IL-1 β in lipotoxic and chemical ER stress-induced apoptosis

(A) Palmitate inhibited TXNIP mRNA expression in human islets. Human islets were cultured in the presence of palmitate (PAL, 0.5 mM), 28 mM glucose (G28) or the combination of both (G28 PAL) for 48 h. TXNIP mRNA expression was measured by qRT-PCR and normalized to β -actin expression levels (n=5-7). *p<0.05 vs control (CTL) by ratio t test. (B) IL-1 receptor antagonist does not protect human islets from chemical ER stress. Human islets were cultured for 24, 48 and 72 h in the presence of thapsigargin (Thap, 1 μ M) or brefeldin A (Bref, 0.1 μ g/ml) alone or in combination with the IL-1 receptor antagonist (300 ng/ml). The cytokines (Cyt) IL-1 β (50 U/ml) plus IFN- γ (1,000 U/ml) were used as a positive control. Cell death was assessed in

3-5 independent human islet preparations. *p<0.05, **p<0.01 vs control (CT), ***p<0.01 as indicated.

Figure S8: Inhibition of the type 2 diabetes candidate gene ADCY5 triggers β-cell apoptosis

(A) ADCY5 mRNA expression by RNA-seq in palmitate (PAL)-treated human islets.
(B) Apoptosis in INS-1E cells transfected with control siRNA (white bars) or ADCY5 siRNA (black bars) and then treated with palmitate for 16 h (n=4). *p<0.05 vs control (CTL), #p<0.05, ##p<0.01 as indicated.

Figure S9: Palmitate-induced changes in alternative splicing according to RefSeq annotation

(A) Palmitate exposure led to changes in alternative splicing. Using RefSeq annotation, 363 transcripts were significantly upregulated in at least 4 out of 5 islet samples and significantly downregulated in none, and 462 transcripts were significantly downregulated using similar criteria. The Venn diagram illustrates the number of genes which have transcripts modified in both directions (intersection) and in only one direction. (B) IPA of the 574 genes with modified splicing. The length of the blue bars indicates the significance of the association between the set of transcripts and the keyword, and is expressed as minus the logarithm of the probability that a random set of transcripts from the human genome would be associated with the same keyword. The straight orange line indicates a threshold of 0.05 (corresponding to a -log(BH p-value) of 1.3).

Table S1: Characteristics of the organ donors and human islet preparations used for RNA-seq and independent confirmation and mechanistic studies

Gender	Age (years)	BMI (kg/m ²)	Cause of death	Purity (%)
F	77	23.8	Trauma	45
M	36	26.3	CVD	51
M	77	25.2	CVD	62
F	46	22.5	CVD	60
M	40	26.2	Trauma	34
M	59	26.7	NA	58
M	51	26.2	Trauma	54
F	79	29.7	CH	21
M	68	27.5	CH	42
F	76	25.4	CH	30
F	75	29.4	CVD	24
F	73	30.0	CVD	16
M	63	NA	NA	46
F	64	23.4	CH	76
M	69	25.1	CH	68
F	23	19.7	Trauma	70
M	47	27.7	CVD	48
F	65	24.6	CH	58
F	87	21.5	Trauma	61
F	72	23.9	CH	62
M	69	25	CVD	85
M	85	25.5	CH	39
M	59	27.7	Trauma	56

F	76	19.5	CH	35
F	50	20.2	CH	70
F	42	23	CVD	48
M	52	24.5	CH	60
F	79	27.5	CH	89
M	56	24.7	Cerebral ischemia	47
M	69	24.2	CVD	57
F	79	28.1	Trauma	61
M	79	23.7	NA	13
M	82	23	CH	61
M	32	NA	NA	75
F	23	22.5	Cardiac arrest	46
M	51	NA	Trauma	37

Abbreviations: F: Female; M: Male; BMI: Body mass index; CVD: Cardiovascular disease; CH: Cerebral hemorrhage. Purity indicates the percentage of β -cells in the human islet preparations as determined by immunostaining for insulin. The first five preparations were used for RNA-seq, the others for confirmation and mechanistic studies.

Table S2: Primer sequences

Gene	Species	RefSeq ID	STD or qRT	Forward primer	Reverse primer	Product length (bp)
ACTB	Homo sapiens	NM_001101	STD	AAATCTGGCACCAACACCTTC	CCGATCCACACGGAGTACTT	805
			qRT	CTGTACGCCAACACAGTGCT	GCTCAGGAGGAGCAATGATC	127
CCL2	Homo sapiens	NM_002982	STD	TTCTGTGCCTGCTGCTCATA	GTCTTCGGAGTTGGGTTTG	277
			qRT	AGCAAGTGTCCCAAAGAAGC	CATGGAATCCTGAACCCACT	93
GAPDH	Rattus norvegicus	NM_017008	STD	ATGACTCTACCCACGGCAAG	TGTGAGGGAGATGTCAGTG	975
			qRT	AGTTCAACGGCACAGTCAAG	TACTCAGCACCAGCATCACC	118
IL1B	Homo sapiens	NM_000576	STD	GCTGAGGAAGATGCTGGTTC	TTCTGCTTGAGAGGTGCTGA	514
			qRT	TCCAGGGACAGGGATATGGAG	TCTTTCAACACGCAGGACAG	133
IL6	Homo sapiens	NM_000600	STD	AGTACCCCCAGGAGAAGATT	TACTCATCTGCACAGCTCTG	354
			qRT	AAAAGATGGCTGAAAAAGATGG	CTACTCTCAAATCTGTTCTGG	129
IL8	Homo sapiens	NM_000584	STD	AGGAAGAAACCACCGGAAG	TCTTCAAAAACCTCTCCACAAC	325
			qRT	TGTAAACATGACTTCCAAGCT	TTGGAGTATGTCTTTATGCAC	131
MALAT1	Homo sapiens	NR_002819	STD	GCTTGAGGAACCGCAGATA	TTCTTCGCCTTCCCGTACTT	603
			qRT	GACGGAGGTTGAGATGAAGC	ATTGGGGCTCTGTAGTCCT	84
GATA6	Homo sapiens	NM_005257	STD	ACCTGCTGGAGGACCTGTC	ATACTTGAGCTCGCTGTTCTC	504
			qRT	AGACCACTTGCTATGAAAAAAG	TCATGGGAATGGAATTATTGC	109
GATA6	Rattus norvegicus	NM_019185.1	STD	TGCCAACCTTGAGAACAGTGACC	TGGAAGCAGACCCAGGCTGACA	372
			qRT	CGGTGCGACAGGATTCTGGTGT	TTTGCCTCCATCTGGACTGCT	117
KCNK16	Rattus norvegicus	NM_001109520	STD	ATATCTGCTACCTGCTGCTTG	ACGTGGCTGAAGAACATGGG	520
			qRT	AAAGGCAACTCCACCAACC	TAGAAGACACAGAACGACTG	134
KCNK16	Homo sapiens	NM_001135105, NM_001135106, NM_001135107, NM_032115	STD	AGAACTACACCTGCCTGGAC	TAGTCCCCAAAGCCAATGGTG	486
			qRT	AGGCACAGTCGTCACTACC	TTGAGGAAGATCACGTTAAC	107
CREB3	Homo sapiens	NM_006368.4	STD	CACCCTTCCGTAGTTGTCC	GGGAGCACAGCAAATCATCT	192
			qRT	AAAGTGGAGATTGGGGACG	CGCTCGGTACCTCAGAAAG	84

CREB3	Rattus norvegicus	NM_001013092.2	STD	CTGACGGAGGAAGAGAAAAGG	GTTCAGGCAGGAAACATTGC	202
			qRT	GAGTATGTTGTGTTGCACCG	TTCTGAGCTCTCCAAGTGGT	123
CREB3L3	Homo sapiens	NM_001012115	STD	AATATGGTCCCCAGCTGACA	AGCAGCAATTCCCTTCACAGT	306
			qRT	GTGTCATCCAAGCAAGCAAG	CACATGTCAGGTCAATGGC	120
SRSF3	Homo sapiens	NM_003017, NR_036610	STD	GCAGTCCGAGAGCTAGATGG	CACCACTTCTCTGCAAAGT	337
			qRT	GTCGCAGATCTCCAAGAAGG	GGACGGCTTGTGATTCTCT	110
SRSF3	Rattus norvegicus	NM_00147907.3	STD	ATCGTGATTCCCTGTCCCTTG	ACCACTTTGCCAAGTGGTC	513
			qRT	AGAACGGGCTTTGGCTATT	TTCACCATTGACAGTTCCA	175
ADCY5	Homo sapiens	NM_001199642, NM_183357	STD	ATTTTCTCCTGCACCAACATC	ATCCCCAAGGATCTTAATACG	403
			qRT	TCCCAGAGACAGGCTTCC	TTTCATCTCCATGGCAACATG	129
ADCY5	Rattus norvegicus	NM_022600.1	STD	ATCTATAACCATCTACACCCCT	ACATTGTCATGTTCTGGATG	398
			qRT	ACCAGTTCTGCTGAAACAG	TCGGGTGGGTAGTGAGTG	88
<u>TXNIP</u>	<u>Homo sapiens</u>	<u>NM_006472.4</u>	<u>STD</u>	<u>ATGTTCCCGAATTGTGGTC</u>	<u>ATCTGCTGCCAATTACCAAG</u>	<u>270</u>
			<u>qRT</u>	<u>ATCATGGCGTGGCAAGAG</u>	<u>ITCTTGGATCCAGGAACGC</u>	<u>117</u>

STD: primers used for conventional PCR, qRT: primers used for real time qRT-PCR. The RefSeq ID of the sequence used to design the primers is provided.

Table S3: siRNAs

Gene	Species	siRNA name	Distributor	Sequence
None		Allstars Negative Control siRNA	Qiagen, Venlo, the Netherlands	Not provided
GATA6	Homo sapiens	GATA6HSS104009(3_RNAI)	Invitrogen, Paisley, UK	AAGAAGUGGAAGUUGGAGUCAUGGG
		GATA6HSS178134(3_RNAI)	Invitrogen	UUGACCCGAAUACUUGAGCUCGCUG
	Rattus norvegicus	Gata6RSS334002(3_RNAI)	Invitrogen	GCUCCGGUAACAGCUCUGUUCCUAU
		GataRSS334003(3_RNAI)	Invitrogen	GCAACGCAUGCGGUCUCUACAGUAA
CREB3	Homo sapiens	<u>Creb3HSS116089(3_RNAI)</u>	<u>Invitrogen</u>	<u>CCACGGAAACUGUCUUAUGGAUC</u>
		<u>Creb3HSS116090(3_RNAI)</u>	<u>Invitrogen</u>	<u>GGACCCAGAUGACUCCACAGCAUAU</u>
CREB3	Rattus norvegicus	Creb3RSS335120(3_RNAI)	Invitrogen	UCAUCGCCGGAUGUUUCUCAACUCUU
		CrebRSS356125(3_RNAI)	Invitrogen	CCUUCCACAGGAGCACGUCUCCAUA
ADCY5	Rattus norvegicus	Adcy5RSS329997(3_RNAI)	Invitrogen	AUGACAUGCGUUCACCUGGUUCACC

Table S4: Functional classification of human islet genes modified by palmitate

Gene name	Gene description	Median RPKM	Log ₂ fold change
Glucose metabolism			
PDK4	pyruvate dehydrogenase kinase, isozyme 4	21	1.17E+00
AKR1B10	aldo-keto reductase family 1, member B10	13	9.81E-01
G6PD	glucose-6-phosphate dehydrogenase	14	6.74E-01
PMM2	phosphomannomutase 2	8.1	5.67E-01
PFKP	phosphofructokinase, platelet	26	5.20E-01
HKDC1	hexokinase domain containing 1	11	3.82E-01
GAPDH	glyceraldehyde-3-phosphate dehydrogenase	518	3.32E-01
ENO1	enolase 1, (alpha)	202	2.85E-01
GPT	glutamic-pyruvate transaminase (alanine aminotransferase)	1.9	-8.18E-01
PFKFB2	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2	23	-6.94E-01
PPP1R3E	protein phosphatase 1, regulatory subunit 3E	5.6	-5.28E-01
SORD	sorbitol dehydrogenase		-3.86E-01
CRYL1	crystallin, lambda 1	13	-2.72E-01
H6PD	hexose-6-phosphate dehydrogenase (glucose 1-dehydrogenase)	10	-2.15E-01
Lipid metabolism			
PLIN2	perilipin 2	6.0	2.67E+00
AGPAT9	1-acylglycerol-3-phosphate O-acyltransferase 9	1.2	1.17E+00
AKR1C2	aldo-keto reductase family 1, member C2	29	9.08E-01
FABP5	fatty acid binding protein 5 (psoriasis-associated)	13	8.85E-01
GK	glycerol kinase	1.4	8.33E-01
ACSL1	acyl-CoA synthetase long-chain family member 1	11	7.99E-01
FADS1	fatty acid desaturase 1	13	7.99E-01
LRP8	low density lipoprotein receptor-related protein 8, apolipoprotein e receptor	1.2	7.69E-01
AKR1C1	aldo-keto reductase family 1, member C1	63	7.69E-01
ACADVL	acyl-CoA dehydrogenase, very long chain	95	7.56E-01
CPT1A	carnitine palmitoyltransferase 1A (liver)	9.8	7.02E-01
LDLR	low density lipoprotein receptor	20	6.48E-01
ECH1	enoyl CoA hydratase 1, peroxisomal	38	6.48E-01
SCD	stearoyl-CoA desaturase (delta-9-desaturase)	86	6.44E-01
FA2H	fatty acid 2-hydroxylase	11	6.14E-01
PITPNM1	phosphatidylinositol transfer protein, membrane-associated 1	15	5.91E-01
MGLL	monoglyceride lipase	5.6	5.85E-01

OSBPL10	oxysterol binding protein-like 10	2.8	5.55E-01
HILPDA	hypoxia inducible lipid droplet-associated	8.9	5.45E-01
MLYCD	malonyl-CoA decarboxylase	6.2	5.35E-01
ACLY	ATP citrate lyase	76	4.63E-01
SC4MOL	sterol-C4-methyl oxidase-like	33	4.10E-01
SREBF2	sterol regulatory element binding transcription factor 2	34	3.74E-01
ACSL3	acyl-CoA synthetase long-chain family member 3	7.1	3.73E-01
HADHA	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit	36	3.69E-01
HSD11B2	hydroxysteroid (11-beta) dehydrogenase 2	6.3	-1.51E+00
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	5.8	-1.44E+00
FFAR3	free fatty acid receptor 3	2.0	-1.17E+00
SERPINA6	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 6	9.7	-1.13E+00
STARD4-AS1	STARD4 antisense RNA 1 (LOC100505678)	1.0	-1.09E+00
FFAR1	free fatty acid receptor 1	17	-9.85E-01
C5orf13	Chromosome 5 open reading frame 13	12	-8.75E-01
CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5	21	-8.68E-01
SCARA3	scavenger receptor class A, member 3	1.7	-8.67E-01
LIPT1	lipoyltransferase 1	3.1	-8.50E-01
STS	steroid sulfatase (microsomal), isozyme S	5.4	-8.42E-01
APOE	apolipoprotein E	6.4	-8.33E-01
VNN2	vanin 2	14	-7.98E-01
PLCH2	phospholipase C, eta 2	5.2	-7.90E-01
METTL7A	methyltransferase like 7A	11	-7.88E-01
EBPL	emopamil binding protein-like	6.5	-6.63E-01
C3orf57, aka SPTSSB	serine palmitoyltransferase, small subunit B	3.7	-6.53E-01
ARSE	arylsulfatase E (chondrodysplasia punctata 1)	12	-6.44E-01
CBR4	carbonyl reductase 4	6.3	-6.42E-01
LDLRAD2	low density lipoprotein receptor class A domain containing 2	14	-6.33E-01
NPC1L1	NPC1 (Niemann-Pick disease, type C1, gene)-like 1	10	-6.22E-01
PPAP2B	phosphatidic acid phosphatase type 2B	8.5	-5.66E-01
RORC	RAR-related orphan receptor C	13	-5.56E-01
ABCG1	ATP-binding cassette, sub-family G (WHITE), member 1	7.7	-5.39E-01
GPRC5B	G protein-coupled receptor, family C, group 5, member B	24	-5.36E-01
SMPD3	sphingomyelin phosphodiesterase 3, neutral membrane (neutral sphingomyelinase II)	2.9	-5.28E-01
O3FAR1	omega-3 fatty acid receptor 1 (GPR120)	4.0	-5.09E-01
HSD3B7	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 7	12	-4.98E-01

NAPEPLD	N-acyl phosphatidylethanolamine phospholipase D	4.1	-4.80E-01
MBOAT1	membrane bound O-acyltransferase domain containing 1	2.9	-4.75E-01
GPD1	glycerol-3-phosphate dehydrogenase 1 (soluble)	8.6	-4.72E-01
AGK	acylglycerol kinase	5.2	-4.28E-01
PCTP	phosphatidylcholine transfer protein	5.2	-4.00E-01
AACS	acetoacetyl-CoA synthetase	17	-3.67E-01
LCLAT1	lysocardiolipin acyltransferase 1	3.3	-3.48E-01
CERS2	ceramide synthase 2	73	-3.19E-01
GBA	glucosidase, beta, acid	32	-3.14E-01
GALC	galactosylceramidase	6.9	-3.06E-01
NPC2	Niemann-Pick disease, type C2	81	-3.04E-01
ASAH1	N-acylsphingosine amidohydrolase (acid ceramidase) 1	34	-2.93E-01
LIPA	lipase A, lysosomal acid, cholesterol esterase	17	-2.92E-01
SORL1	sortilin-related receptor, L(DLR class) A repeats containing	30	-2.66E-01
SERINC5	serine incorporator 5	8.9	-2.46E-01
PTPLAD1	protein tyrosine phosphatase-like A domain containing 1	36	-2.28E-01
NMT1	N-myristoyltransferase 1	17	-1.73E-01
CDS2	CDP-diacylglycerol synthase (phosphatidate cytidylyltransferase) 2	9.3	-1.68E-01
HEXA	hexosaminidase A (alpha polypeptide)	23	-1.67E-01
SOAT1	sterol O-acyltransferase 1	9.0	-1.47E-01

Aminoacid metabolism

GCLM	glutamate-cysteine ligase, modifier subunit	8.0	1.07E+00
GCLC	glutamate-cysteine ligase, catalytic subunit	8.5	9.59E-01
PYCR1	pyrroline-5-carboxylate reductase 1	6.5	7.84E-01
GPT2	glutamic pyruvate transaminase (alanine aminotransferase) 2	4.1	3.99E-01
PIPOX	pipecolic acid oxidase	3.1	-1.32E+00
AMT	aminomethyltransferase	9.1	-1.23E+00
SHMT1	serine hydroxymethyltransferase 1 (soluble)	2.9	-9.75E-01
ALDH4A1	aldehyde dehydrogenase 4 family, member A1	3.7	-9.07E-01
GPT	glutamic-pyruvate transaminase (alanine aminotransferase)	1.9	-8.18E-01
DPH1	DPH1 homolog (<i>S. cerevisiae</i>)	11	-6.82E-01
DDC	dopa decarboxylase (aromatic L-amino acid decarboxylase)	4.3	-6.65E-01
GLS	glutaminase	31	-5.13E-01
ADI1	acireductone dioxygenase 1	26	-4.94E-01
AHCYL2	adenosylhomocysteinase-like 2	9.2	-4.20E-01
IVD	isovaleryl-CoA dehydrogenase	9.5	-3.93E-01
GLUL	glutamate-ammonia ligase	50	-3.88E-01
HIBCH	3-hydroxyisobutyryl-CoA hydrolase	6.6	-3.49E-01

HGD	homogentisate 1,2-dioxygenase	8.5	-2.31E-01
HIBADH	3-hydroxisobutyrate dehydrogenase	14	-1.91E-01
Krebs cycle/ATP production			
PCK2	phosphoenolpyruvate carboxykinase 2 (mitochondrial)	10	3.87E-01
MDH2	malate dehydrogenase 2, NAD (mitochondrial)	62	3.24E-01
ATP5L2	ATP synthase, H ⁺ transporting, mitochondrial Fo complex, subunit G2	9.8	-2.01E+00
ACSS1	acyl-CoA synthetase short-chain family member 1	11	-7.72E-01
UQCR10	ubiquinol-cytochrome c reductase, complex III subunit X	37	-4.60E-01
SDHC	succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa	21	-3.96E-01
IDH2	isocitrate dehydrogenase 2 (NADP ⁺), mitochondrial	60	-3.22E-01
COX18	cytochrome c oxidase assembly homolog (S. cerevisiae)	2.2	-2.92E-01
ATP5A1	ATP synthase, H ⁺ transporting, mitochondrial F1 complex, alpha subunit 1, cardiac muscle	65	-2.77E-01
CS	citrate synthase	47	-2.38E-01
IDH3B	isocitrate dehydrogenase 3 (NAD ⁺) beta	19	-2.24E-01
NDUFS2	NADH dehydrogenase (ubiquinone) Fe-S protein 2, 49kDa (NADH-coenzyme Q reductase)	22	-1.95E-01
Metabolism – miscellaneous			
UGDH	UDP-glucose 6-dehydrogenase	16	8.68E-01
NANS	N-acetylneuraminc acid synthase	14	7.28E-01
TSTA3	tissue specific transplantation antigen P35B	11	5.82E-01
TALDO1	transaldolase 1	29	3.48E-01
OAZ1	ornithine decarboxylase antizyme 1	187	2.39E-01
HNMT	histamine N-methyltransferase	9.3	-9.08E-01
ADHFE1	alcohol dehydrogenase, iron containing, 1	2.9	-8.45E-01
GGTLC1	gamma-glutamyltransferase light chain 1	8.0	-8.41E-01
ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	5.1	-8.18E-01
AOC2	amine oxidase, copper containing 2 (retina-specific)	2.3	-7.65E-01
DDC	dopa decarboxylase (aromatic L-amino acid decarboxylase)	4.3	-6.65E-01
AOC3	amine oxidase, copper containing 3	1.7	-6.21E-01
NMNAT3	nicotinamide nucleotide adenylyltransferase 3	3.4	-6.06E-01
NMRK1	nicotinamide riboside kinase 1 (C9orf95)	11	-4.83E-01
FDX1	ferredoxin 1	4.8	-4.74E-01
CMBL	carboxymethylenebutenolidase homolog (Pseudomonas)	7.5	-4.63E-01
HSD17B11	hydroxysteroid (17-beta) dehydrogenase 11	9.0	-4.58E-01
ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide	12	-4.33E-01
ESD	esterase D	23	-4.06E-01
GNPDA1	glucosamine-6-phosphate deaminase 1	13	-4.05E-01
GGT1	gamma-glutamyltransferase 1	16	-4.04E-01
N6AMT1	N-6 adenine-specific DNA methyltransferase 1 (putative)	2.3	-3.79E-01

NUDT2	nudix (nucleoside diphosphate linked moiety X)-type motif 2	10	-3.53E-01
SAT2	spermidine/spermine N1-acetyltransferase family member 2	31	-3.23E-01
NDST2	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 2	6.7	-2.61E-01
PRPS1	phosphoribosyl pyrophosphate synthetase 1	16	-1.90E-01
Hormones/growth factors/receptors/neuropeptides and exocytosis			
IGFBP1	insulin-like growth factor binding protein 1	0.3	2.76E+00
FGF18	fibroblast growth factor 18	0.2	2.51E+00
ANGPTL4	angiopoietin-like 4	14	2.08E+00
PYY	peptide YY	0.4	2.07E+00
GPR3	G protein-coupled receptor 3	0.5	1.84E+00
INHBA	inhibin, beta A	9.5	1.44E+00
VGF	nerve growth factor inducible	381	1.16E+00
GAP43	growth associated protein 43	6.4	1.12E+00
GDF15	growth differentiation factor 15	62	1.11E+00
ADM	adrenomedullin	10	1.06E+00
FGF2	fibroblast growth factor 2 (basic)	1.4	1.04E+00
CHRNA5	cholinergic receptor, nicotinic, alpha 5	1.0	8.93E-01
NRP2	neuropilin 2	2.1	8.36E-01
IAPP	islet amyloid polypeptide	348	8.38E-01
NRG1	neuregulin 1	0.6	8.04E-01
SYT5	synaptotagmin V	13	7.94E-01
RAB3B	RAB3B, member RAS oncogene family	15	7.65E-01
IGFBP4	insulin-like growth factor binding protein 4	74	7.62E-01
PTGER4	prostaglandin E receptor 4 (subtype EP4)	1.0	7.60E-01
CHGB	chromogranin B (secretogranin 1)	885	7.32E-01
PAM	peptidylglycine alpha-amidating monooxygenase	107	6.84E-01
BDKRB2	bradykinin receptor B2	8.8	5.49E-01
UNC13A	unc-13 homolog A (<i>C. elegans</i>)	11	5.38E-01
ADM2	adrenomedullin 2	2.4	4.54E-01
RIMS2	regulating synaptic membrane exocytosis 2	1.8	4.16E-01
FGFR1	fibroblast growth factor receptor 1	18	3.11E-01
EDN3	endothelin 3	27	2.33E-01
RPH3A	rabphilin 3A homolog (mouse)	5.1	-1.51E+00
FOLR1	folate receptor 1 (adult)	3.4	-1.31E+00
GREM2	gremlin 2	1.3	-1.31E+00
IGFBP6	insulin-like growth factor binding protein 6	4.8	-1.20E+00
SSTR5	somatostatin receptor 5	1.2	-1.09E+00
GLRA1	glycine receptor, alpha 1	1.4	-1.02E+00
HNMT	histamine N-methyltransferase	9.3	-9.08E-01

GRIA4	glutamate receptor, ionotropic, AMPA 4	2.9	-8.57E-01
RTP4	receptor (chemosensory) transporter protein 4	6.5	-8.47E-01
PAQR5	progestin and adipoQ receptor family member V	4.8	-6.60E-01
PAQR7	progestin and adipoQ receptor family member VII	7.0	-6.42E-01
GPRC5B	G protein-coupled receptor, family C, group 5, member B	24	-5.36E-01
ADRA2A	adrenoceptor alpha 2A	9.7	-5.22E-01
MAOA	monoamine oxidase A	9.0	-5.12E-01
O3FAR1	omega-3 fatty acid receptor 1	4.0	-5.09E-01
SH2B1	SH2B adaptor protein 1	15	-4.98E-01
GLCE	glucuronic acid epimerase	5.7	-4.97E-01
IGFBP7	insulin-like growth factor binding protein 7	115	-4.33E-01
GCG	glucagon	5101	-4.02E-01
IGF1R	insulin-like growth factor 1 receptor	20	-4.01E-01
LEPR	leptin receptor	3.8	-4.00E-01
GPR39	G protein-coupled receptor 39	8.9	-3.98E-01
CASR	calcium-sensing receptor	24	-3.64E-01
AGT	angiotensinogen (serpin peptidase inhibitor, clade A, member 8)	26	-3.57E-01
LCN2	lipocalin 2	331	-3.46E-01
FAM3B	family with sequence similarity 3, member B	19	-3.42E-01
ABAT	4-aminobutyrate aminotransferase	14	-3.35E-01
EPB41L1	erythrocyte membrane protein band 4.1-like 1	15	-2.92E-01
NOTCH2	notch 2	13	-2.68E-01
PTPRN2	protein tyrosine phosphatase, receptor type, N polypeptide 2	50	-2.49E-01
NISCH	nischarin	20	-2.45E-01
SCG3	secretogranin III	49	-2.32E-01
SCG5	secretogranin V (7B2 protein)	250	-2.04E-01
GNRHR2	gonadotropin-releasing hormone (type 2) receptor 2	5.3	-1.88E-01
ADCYAP1	adenylate cyclase activating polypeptide 1 (pituitary)	14	-1.78E-01
APLP2	amyloid beta (A4) precursor-like protein 2	147	-1.45E-01
SEPT8	septin 8	14	-1.34E-01

Protein synthesis/translation regulation/protein folding/endoplasmic reticulum stress

CREB3L3	cAMP responsive element binding protein 3-like 3	0.2	2.92E+00
ATF3	activating transcription factor 3	15	1.36E+00
AGR2	anterior gradient 2 homolog (<i>Xenopus laevis</i>)	8.9	1.22E+00
DOHH	deoxyhypusine hydroxylase/monooxygenase	12	9.12E-01
HSPA7	heat shock 70kDa protein 7 (HSP70B)	1.9	9.08E-01
PPP1R15A	protein phosphatase 1, regulatory subunit 15A	21	9.08E-01
TRIB3	tribbles homolog 3 (<i>Drosophila</i>)	20	8.72E-01
HSPA6	heat shock 70kDa protein 6 (HSP70B')	2.3	8.11E-01

HMOX1	heme oxygenase (decycling) 1	6.2	7.85E-01
HSPA5	heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	120	7.47E-01
SEC24D	SEC24 family, member D (<i>S. cerevisiae</i>)	17	7.40E-01
DNAJC12	DnaJ (Hsp40) homolog, subfamily C, member 12	35	7.17E-01
CRELD2	cysteine-rich with EGF-like domains 2	9.0	6.60E-01
CHAC1	ChaC, cation transport regulator homolog 1 (<i>E. coli</i>)	4.7	6.34E-01
EDEM1	ER degradation enhancer, mannosidase alpha-like 1	9.8	6.05E-01
ERN1	endoplasmic reticulum to nucleus signaling 1	5.7	6.00E-01
XPOT	exportin, tRNA	8.2	5.80E-01
HSPA13	heat shock protein 70kDa family, member 13	9.8	5.70E-01
IARS	isoleucyl-tRNA synthetase	17	5.17E-01
GARS	glycyl-tRNA synthetase	19	5.17E-01
SELS	selenoprotein S	20	5.01E-01
CPE	carboxypeptidase E	469	5.00E-01
TXNDC5	thioredoxin domain containing 5 (endoplasmic reticulum)	40	4.82E-01
SSR3	signal sequence receptor, gamma (translocon-associated protein gamma)	25	4.72E-01
PCSK1	proprotein convertase subtilisin/kexin type 1	145	4.70E-01
PDIA4	protein disulfide isomerase family A, member 4	42	4.51E-01
ORMDL2	ORM1-like 2 (<i>S. cerevisiae</i>)	14	4.36E-01
MARS	methionyl-tRNA synthetase	22	4.21E-01
SEC23B	Sec23 homolog B (<i>S. cerevisiae</i>)	18	4.11E-01
EEF1A2	eukaryotic translation elongation factor 1 alpha 2	90	4.09E-01
DNAJB11	DnaJ (Hsp40) homolog, subfamily B, member 11	18	3.97E-01
SEC61A1	Sec61 alpha 1 subunit (<i>S. cerevisiae</i>)	90	3.84E-01
RPL8	ribosomal protein L8	393	3.84E-01
GOSR2	golgi SNAP receptor complex member 2	11	3.59E-01
EDEM2	ER degradation enhancer, mannosidase alpha-like 2	12	3.43E-01
HSPA9	heat shock 70kDa protein 9 (mortalin)	34	3.38E-01
ABCF1	ATP-binding cassette, sub-family F (GCN20), member 1	14	3.31E-01
WARS	tryptophanyl-tRNA synthetase	25	3.28E-01
RCN1	reticulocalbin 1, EF-hand calcium binding domain	32	3.23E-01
ATF4	activating transcription factor 4 (tax-responsive enhancer element B67)	139	3.17E-01
PPIB	peptidylprolyl isomerase B (cyclophilin B)	181	3.01E-01
VARS	valyl-tRNA synthetase	9.9	2.98E-01
CREB3	cAMP responsive element binding protein 3	15	2.48E-01
NOL6	nucleolar protein family 6 (RNA-associated)	6.7	2.45E-01
CARS	cysteinyl-tRNA synthetase	8.6	2.41E-01
EIF4A1	eukaryotic translation initiation factor 4A1	60	2.39E-01

PDIA6	protein disulfide isomerase family A, member 6	59	2.31E-01
SARS	seryl-tRNA synthetase	60	2.25E-01
RPS6KA1	ribosomal protein S6 kinase, 90kDa, polypeptide 1	9.0	2.16E-01
LMAN2	lectin, mannose-binding 2	41	1.36E-01
NANOS1	nanos homolog 1 (<i>Drosophila</i>)	2.9	-9.13E-01
FKBP1B	FK506 binding protein 1B, 12.6 kDa	8.0	-8.06E-01
FKBP7	FK506 binding protein 7	1.7	-8.04E-01
PIGV	phosphatidylinositol glycan anchor biosynthesis, class V	6.5	-7.75E-01
DPH1	DPH1 homolog (<i>S. cerevisiae</i>)	11	-6.82E-01
GPX8	glutathione peroxidase 8 (putative)	2.8	-6.53E-01
CREB3L4	cAMP responsive element binding protein 3-like 4	4.3	-6.38E-01
ALG8	asparagine-linked glycosylation 8, alpha-1,3-glucosyltransferase homolog (<i>S. cerevisiae</i>)	6.0	-5.43E-01
MRPL36	mitochondrial ribosomal protein L36	16	-4.72E-01
MRPS33	mitochondrial ribosomal protein S33	22	-4.67E-01
PEX19	peroxisomal biogenesis factor 19	12	-3.89E-01
N6AMT1	N-6 adenine-specific DNA methyltransferase 1 (putative)	2.3	-3.79E-01
JKAMP	JNK1/MAPK8-associated membrane protein	12	-3.74E-01
ARL6IP5	ADP-ribosylation-like factor 6 interacting protein 5	57	-3.66E-01
EIF2D	eukaryotic translation initiation factor 2D	9.5	-3.57E-01
ERMP1	endoplasmic reticulum metallopeptidase 1	7.8	-3.51E-01
EIF4A2	eukaryotic translation initiation factor 4A2	145	-3.10E-01
FKBP9	FK506 binding protein 9, 63 kDa	30	-2.98E-01
MPPE1	metallophosphoesterase 1	6.1	-2.86E-01
HSPB8	heat shock 22kDa protein 8	15	-2.74E-01
RPL41	ribosomal protein L41	1148	-2.62E-01
SRP14	signal recognition particle 14kDa (homologous Alu RNA binding protein)	59	-2.53E-01
TMX2	thioredoxin-related transmembrane protein 2	26	-2.32E-01
PTPLAD1	protein tyrosine phosphatase-like A domain containing 1	36	-2.28E-01
RPL5	ribosomal protein L5	169	-2.15E-01
EIF4G2	eukaryotic translation initiation factor 4 gamma, 2	122	-2.02E-01
ERO1LB	ERO1-like beta (<i>S. cerevisiae</i>)	66	-1.66E-01
MRPS27	mitochondrial ribosomal protein S27	12	-1.64E-01
KDELR1	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 1	86	-1.62E-01

Posttranslational modification/ubiquitination

MGAT2	mannosyl (alpha-1,6-)glycoprotein beta-1,2-N-acetylglucosaminyltransferase	9.0	4.21E-01
FBXW5	F-box and WD repeat domain containing 5	33	4.14E-01
FBXW7	F-box and WD repeat domain containing 7, E3 ubiquitin protein ligase	7.8	4.05E-01

GCNT1	glucosaminyl (N-acetyl) transferase 1, core 2	3.9	3.71E-01
UBAP1	ubiquitin associated protein 1	19	1.78E-01
RBBP6	retinoblastoma binding protein 6	8.1	1.12E-01
TRIM74	tripartite motif containing 74	1.9	-1.55E+00
RNF122	ring finger protein 122	5.1	-9.94E-01
PCSK4	proprotein convertase subtilisin/kexin type 4	1.2	-9.38E-01
MUC20	mucin 20, cell surface associated	10	-7.48E-01
DTX4	deltex homolog 4 (<i>Drosophila</i>)	5.3	-7.14E-01
UBD	ubiquitin D	77	-6.85E-01
USP2	ubiquitin specific peptidase 2	4.5	-6.08E-01
KLHL3	kelch-like 3 (<i>Drosophila</i>)	3.9	-5.95E-01
NEURL	neuralized homolog (<i>Drosophila</i>)	27	-5.32E-01
ST6GALNAC2	ST6 (alpha-N-acetyl-neuraminy-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 2	5.3	-5.25E-01
CHST9	carbohydrate (N-acetylgalactosamine 4-0)sulfotransferase 9	8.9	-4.69E-01
FUT2	fucosyltransferase 2 (secretor status included)	3.3	-4.44E-01
MKRN1	makorin ring finger protein 1	25	-4.30E-01
FANCL	Fanconi anemia, complementation group L	6.3	-4.19E-01
USP54	ubiquitin specific peptidase 54	7.2	-3.74E-01
ST6GAL1	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	16	-3.64E-01
USP30	ubiquitin specific peptidase 30	4.1	-3.58E-01
SLC35A1	solute carrier family 35 (CMP-sialic acid transporter), member A1	7.8	-3.44E-01
SAT2	spermidine/spermine N1-acetyltransferase family member 2	31	-3.23E-01
UBE2H	ubiquitin-conjugating enzyme E2H	35	-3.13E-01
DCUN1D1	DCN1, defective in cullin neddylation 1, domain containing 1 (<i>S. cerevisiae</i>)	4.4	-3.13E-01
DCAF11	DDB1 and CUL4 associated factor 11	15	-2.98E-01
SUMF2	sulfatase modifying factor 2	76	-2.82E-01
B4GALT1	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 1	33	-2.59E-01
UBE3A	ubiquitin protein ligase E3A	11	-2.52E-01
DCAF7	DDB1 and CUL4 associated factor 7	16	-2.39E-01
FBXO28	F-box protein 28	5.0	-2.07E-01
SCG5	secretogranin V (7B2 protein)	250	-2.04E-01
NMT1	N-myristoyltransferase 1	17	-1.73E-01
Proteasome/lysosome/autophagy			
LAMP3	lysosomal-associated membrane protein 3	3.0	8.43E-01
CTSZ	cathepsin Z	105	7.22E-01
IDS	iduronate 2-sulfatase	90	5.58E-01
PSMA7	proteasome (prosome, macropain) subunit, alpha type, 7	31	3.23E-01

PSMC4	proteasome (prosome, macropain) 26S subunit, non-ATPase, 4		19	3.21E-01
ATP6V0C	ATPase, H ⁺ transporting, lysosomal 16kDa, V0 subunit c		124	2.24E-01
CD63	CD63 molecule		253	2.17E-01
MUTED	muted homolog (mouse)		2.6	-1.71E+00
PPT2	palmitoyl-protein thioesterase 2		5.2	-1.06E+00
WIPI2	WD repeat domain, phosphoinositide interacting 2		9.5	-8.30E-01
LAPTM5	lysosomal protein transmembrane 5		9.4	-7.43E-01
ULK3	unc-51-like kinase 3 (C. elegans)		10	-5.64E-01
CTSF	cathepsin F		14	-5.26E-01
CTSO	cathepsin O		6.9	-5.23E-01
CTSS	cathepsin S		11	-4.94E-01
DRAM2	DNA-damage regulated autophagy modulator 2		10	-4.86E-01
ARSD	arylsulfatase D		22	-4.60E-01
AP3M2	adaptor-related protein complex 3, mu 2 subunit		4.6	-4.58E-01
PSMD10	proteasome (prosome, macropain) 26S subunit, non-ATPase, 10		12	-4.36E-01
ATG7	autophagy related 7		8.6	-4.21E-01
CLN5	ceroid-lipofuscinosis, neuronal 5		14	-3.89E-01
ARL8B	ADP-ribosylation factor-like 8B		19	-3.74E-01
TMEM9	transmembrane protein 9		35	-3.60E-01
SCOC	short coiled-coil protein		23	-3.53E-01
AP3B1	adaptor-related protein complex 3, beta 1 subunit		11	-3.25E-01
TMEM9B	TMEM9 domain family, member B		17	-3.20E-01
CERS2	ceramide synthase 2		73	-3.19E-01
GBA	glucosidase, beta, acid		32	-3.14E-01
GALC	galactosylceramidase		6.9	-3.06E-01
NPC2	Niemann-Pick disease, type C2		81	-3.04E-01
ASAH1	N-acylsphingosine amidohydrolase (acid ceramidase) 1		34	-2.93E-01
LIPA	lipase A, lysosomal acid, cholesterol esterase		17	-2.92E-01
HSPB8	heat shock 22kDa protein 8		15	-2.74E-01
VIPAS39	VPS33B interacting protein, apical-basolateral polarity regulator, spe-39 homolog (C14orf133)		5.3	-2.71E-01
KIAA1324	KIAA1324		48	-2.67E-01
SORL1	sortilin-related receptor, L(DLR class) A repeats containing		30	-2.66E-01
VAMP8	vesicle-associated membrane protein 8 (endobrevin)		56	-2.65E-01
ATP6AP2	ATPase, H ⁺ transporting, lysosomal accessory protein 2		46	-2.55E-01
CTSA	cathepsin A		64	-2.50E-01
PTPRN2	protein tyrosine phosphatase, receptor type, N polypeptide 2		50	-2.49E-01
SIDT2	SID1 transmembrane family, member 2		12	-2.37E-01

PSMB8	proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional peptidase 7)	33	-2.34E-01
HGSNAT	heparan-alpha-glucosaminide N-acetyltransferase	19	-2.21E-01
CTSD	cathepsin D	371	-2.07E-01
SORT1	sortilin 1	22	-2.03E-01
HEXA	hexosaminidase A (alpha polypeptide)	23	-1.67E-01
KDELR1	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 1	86	-1.62E-01
GLB1	galactosidase, beta 1	31	-1.61E-01
AP2M1	adaptor-related protein complex 2, mu 1 subunit	65	-1.59E-01
PRDX6	peroxiredoxin 6	34	-1.31E-01
LAMP1	lysosomal-associated membrane protein 1	116	-1.26E-01
CD68	CD68 molecule	44	-9.91E-02
Vesicle transport			
SNX22	sorting nexin 22	31	3.56E-01
COPG1	coatomer protein complex, subunit gamma 1	44	3.48E-01
AP3D1	adaptor-related protein complex 3, delta 1 subunit	32	2.85E-01
VCP	valosin containing protein	43	2.06E-01
LMAN2	lectin, mannose-binding 2	41	1.36E-01
SYNGR4	synaptogyrin 4	2.7	-1.36E+00
COPG2	coatomer protein complex, subunit gamma 2	5.0	-6.72E-01
STX6	syntaxin 6	5.6	-4.75E-01
VPS52	vacuolar protein sorting 52 homolog (S. cerevisiae)	12	-4.65E-01
SYNGR1	synaptogyrin 1	11	-4.55E-01
SNX27	sorting nexin family member 27	9.3	-4.45E-01
SNAP23	synaptosomal-associated protein, 23kDa	8.5	-4.07E-01
RAB2B	RAB2B, member RAS oncogene family	7.0	-3.93E-01
RAB11FIP4	RAB11 family interacting protein 4 (class II)	8.0	-3.91E-01
NIPSNAP1	nipsnap homolog 1 (C. elegans)	21	-3.42E-01
SNX29	sorting nexin 29 (RUNDC2A)	5.5	-3.35E-01
COG4	component of oligomeric golgi complex 4	12	-3.24E-01
FAM21C	family with sequence similarity 21, member C	15	-2.91E-01
SH3GL2	SH3-domain GRB2-like 2	9.9	-2.90E-01
SNX6	sorting nexin 6	11	-2.89E-01
MPPE1	metallophosphoesterase 1	6.1	-2.86E-01
VIPAS39	VPS33B interacting protein, apical-basolateral polarity regulator, spe-39 homolog (C14orf133)	5.3	-2.71E-01
AMOT	angiromotin	4.6	-2.71E-01
SORL1	sortilin-related receptor, L(DLR class) A repeats containing	30	-2.66E-01
VAMP8	vesicle-associated membrane protein 8 (endobrevin)	56	-2.65E-01
ATP6AP2	ATPase, H ⁺ transporting, lysosomal accessory protein 2	46	-2.55E-01

RUFY1	RUN and FYVE domain containing 1	11	-2.38E-01
FLOT2	flotillin 2	37	-2.36E-01
AP2B1	adaptor-related protein complex 2, beta 1 subunit	35	-2.06E-01
SORT1	sortilin 1	22	-2.03E-01
CLSTN1	calsyntenin 1	45	-1.15E-01

Mitochondrial enzymes

MTHFD2	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase	7.7	8.45E-01
LONP1	lon peptidase 1, mitochondrial	17	5.63E-01
MTHFD1L	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like	3.6	3.48E-01
ATAD3A	ATPase family, AAA domain containing 3A	5.9	3.08E-01
PITRM1	pitrilysin metallopeptidase 1	17	2.99E-01
IMMP2L	IMP2 inner mitochondrial membrane peptidase-like (S. cerevisiae)	5.1	-9.11E-01
CBR4	carbonyl reductase 4	6.3	-6.42E-01
NMNAT3	nicotinamide nucleotide adenylyltransferase 3	3.4	-6.06E-01
MAOA	monoamine oxidase A	9.0	-5.12E-01
HMGCL	3-hydroxymethyl-3-methylglutaryl-CoA lyase	20	-4.67E-01
AGK	acylglycerol kinase	5.2	-4.28E-01
IVD	isovaleryl-CoA dehydrogenase	9.5	-3.93E-01
USP30	ubiquitin specific peptidase 30	4.1	-3.58E-01
NFS1	NFS1 nitrogen fixation 1 homolog (S. cerevisiae)	7.1	-3.56E-01
NIPSNAP1	nipsnap homolog 1 (C. elegans)	21	-3.42E-01
TIMMDC1	translocase of inner mitochondrial membrane domain containing 1 (C3orf1)	15	-2.34E-01
CDS2	CDP-diacylglycerol synthase (phosphatidate cytidylyltransferase) 2	9.3	-1.68E-01

Channels and transporters

SLC7A11	solute carrier family 7, (cationic amino acid transporter, y+ system) member 11	1.0	2.18E+00
SLC5A4	solute carrier family 5 (low affinity glucose cotransporter), member 4	0.9	1.64E+00
AQP3	aquaporin 3 (Gill blood group)	42	9.98E-01
SLC7A5	solute carrier family 7 (amino acid transporter light chain, L system), member 5	28	9.95E-01
CNGA3	cyclic nucleotide gated channel alpha 3	5.0	9.66E-01
BEST1	bestrophin 1	1.0	9.50E-01
KCNE4	potassium voltage-gated channel, Isk-related family, member 4	3.8	9.33E-01
KCNQ3	potassium voltage-gated channel, KQT-like subfamily, member 3	1.7	7.05E-01
SLC35D3	solute carrier family 35, member D3	1.1	7.02E-01

Diabetes

SLC45A3	solute carrier family 45, member 3	2.9	6.39E-01
SLC7A1	solute carrier family 7 (cationic amino acid transporter, y+ system), member 1	15	5.87E-01
TMCO3	transmembrane and coiled-coil domains 3	32	5.34E-01
SLC38A5	solute carrier family 38, member 5	1.4	4.93E-01
SLC6A6	solute carrier family 6 (neurotransmitter transporter, taurine), member 6	24	4.72E-01
IPO4	importin 4	5.1	4.31E-01
ABCB6	ATP-binding cassette, sub-family B (MDR/TAP), member 6	6.0	4.27E-01
SLC9A1	solute carrier family 9, subfamily A (NHE1, cation proton antiporter 1), member 1	9.7	4.01E-01
SLC39A7	solute carrier family 39 (zinc transporter), member 7	53	3.95E-01
SLC38A2	solute carrier family 38, member 2	16	3.88E-01
CLIC1	chloride intracellular channel 1	97	3.74E-01
SLC35B1	solute carrier family 35, member B1	15	3.40E-01
ABCF1	ATP-binding cassette, sub-family F (GCN20), member 1	14	3.31E-01
SLC12A4	solute carrier family 12 (potassium/chloride transporters), member 4	7.2	2.93E-01
SLC25A25	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 25	7.3	2.67E-01
TCN1	transcobalamin I (vitamin B12 binding protein, R binder family)	17	-1.74E+00
SLC9A3	solute carrier family 9, subfamily A (NHE3, cation proton antiporter 3), member 3	1.3	-1.14E+00
SLC15A3	solute carrier family 15, member 3	1.5	-1.12E+00
KCNK16	potassium channel, subfamily K, member 16	51	-1.27E+00
KCNK17	potassium channel, subfamily K, member 17	9.8	-1.23E+00
CLCNKB	chloride channel, voltage-sensitive Kb	1.4	-1.23E+00
AQP1	aquaporin 1 (Colton blood group)	179	-1.11E+00
GLRA1	glycine receptor, alpha 1	1.4	-1.02E+00
SLC25A34	solute carrier family 25, member 34	8.9	-8.80E-01
GJB2	gap junction protein, beta 2, 26kDa	3.3	-8.57E-01
SLC16A9	solute carrier family 16, member 9 (monocarboxylic acid transporter 9)	4.2	-8.16E-01
CACNG4	calcium channel, voltage-dependent, gamma subunit 4	2.2	-7.95E-01
SLC46A3	solute carrier family 46, member 3	6.1	-6.97E-01
TMEM37	transmembrane protein 37	18	-6.65E-01
SLC3A1	solute carrier family 3 (cystine, dibasic and neutral amino acid transporters, activator of cystine, dibasic and neutral amino acid transport), member 1	68	-6.59E-01
KCNAB1	potassium voltage-gated channel, shaker-related subfamily, beta member 1	1.1	-6.59E-01
KCNMB2	potassium large conductance calcium-activated channel, subfamily M, beta member 2	8.3	-6.02E-01

KCNK5	potassium channel, subfamily K, member 5	9.8	-5.61E-01
SLC35E2	solute carrier family 35, member E2	20	-5.43E-01
KCND1	potassium voltage-gated channel, Shal-related subfamily, member 1	3.0	-5.43E-01
ABCG1	ATP-binding cassette, sub-family G (WHITE), member 1	7.7	-5.39E-01
ABCC5	ATP-binding cassette, sub-family C (CFTR/MRP), member 5	8.5	-5.04E-01
GJB1	gap junction protein, beta 1, 32kDa	28	-4.87E-01
SLC44A2	solute carrier family 44, member 2	22	-4.58E-01
KCTD2	potassium channel tetramerisation domain containing 2	10	-4.33E-01
SLC25A10	solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10	8.4	-3.69E-01
SLC18B1	solute carrier family 18, subfamily B, member 1 (C6orf192)	6.0	-3.58E-01
SLC35A1	solute carrier family 35 (CMP-sialic acid transporter), member A1	7.8	-3.44E-01
KCNJ16	potassium inwardly-rectifying channel, subfamily J, member 16	11	-2.95E-01
ABCF2	ATP-binding cassette, sub-family F (GCN20), member 2	7.0	-2.86E-01
SERINC5	serine incorporator 5	8.9	-2.46E-01
SLC39A9	solute carrier family 39 (zinc transporter), member 9	21	-2.08E-01
FXYD6	FXYD domain containing ion transport regulator 6	21	-1.91E-01
KCTD7	potassium channel tetramerisation domain containing 7	3.5	-1.87E-01
SLC34A2	solute carrier family 34 (sodium phosphate), member 2	27	-1.58E-01
SLC23A2	solute carrier family 23 (nucleobase transporters), member 2	9.4	-1.40E-01
SLC25A3	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 3	83	-1.34E-01

Cytoskeleton and related proteins

TUBB2B	tubulin, beta 2B	23	9.28E-01
ABLIM3	actin binding LIM protein family, member 3	1.9	8.83E-01
TUBB2A	tubulin, beta 2A	33	8.67E-01
TUBB6	tubulin, beta 6	8.5	7.64E-01
MAP7	microtubule-associated protein 7	11	6.77E-01
TUBB2C	tubulin, beta 2C (TUBB4B tubulin, beta 4b)	67	6.64E-01
LMO7	LIM domain 7	11	6.50E-01
LIMCH1	LIM and calponin homology domains 1	13	6.39E-01
MARK1	MAP/microtubule affinity-regulating kinase 1	2.7	5.91E-01
MAP2	microtubule-associated protein 2	20	5.72E-01
TUBB4	tubulin, beta 4 (TUBB4A, tubulin beta 4a)	8.17	5.59E-01
TUBA4A	tubulin, alpha 4a	68	4.74E-01
VIM	vimentin	85	4.68E-01
TUBG1	tubulin, gamma 1	8.9	4.06E-01
MAP1B	microtubule-associated protein 1B	17	3.95E-01
TMOD1	tropomodulin 1	38	3.83E-01

CAMSAP1	calmodulin regulated spectrin-associated protein 1	6.0	3.72E-01
NDEL1	nudE nuclear distribution E homolog (A. nidulans)-like 1	11	3.54E-01
PALLD	palladin, cytoskeletal associated protein	14	3.04E-01
SPIRE1	spire homolog 1 (<i>Drosophila</i>)	8.1	3.00E-01
MAST2	microtubule associated serine/threonine kinase 2	6.0	2.98E-01
PDLIM7	PDZ and LIM domain 7 (enigma)	14	2.69E-01
TUBB	tubulin, beta	133	2.63E-01
SEPT11	septin 11	8.0	1.77E-01
CNN1	calponin 1, basic, smooth muscle	1.0	-1.49E+00
MNS1	meiosis-specific nuclear structural 1	1.3	-1.34E+00
PRC1	protein regulator of cytokinesis 1	2.0	-1.05E+00
LSP1	lymphocyte-specific protein 1	1.8	-8.06E-01
BBS4	Bardet-Biedl syndrome 4	5.8	-7.91E-01
CNN2	calponin 2	8.6	-6.43E-01
DNAH5	dynein, axonemal, heavy chain 5	1.3	-6.31E-01
NES	nestin	2.0	-6.25E-01
STMN1	stathmin 1	21	-5.64E-01
IFFO2	intermediate filament family orphan 2	5.7	-5.57E-01
CNP	2',3'-cyclic nucleotide 3' phosphodiesterase	12	-5.44E-01
MKS1	Meckel syndrome, type 1	3.6	-4.99E-01
SH2B1	SH2B adaptor protein 1	15	-4.98E-01
MARCKSL1	MARCKS-like 1	42	-4.78E-01
CEP41	centrosomal protein 41kDa (TSGA14)	5.2	-4.76E-01
BBIP1	BBSome interacting protein 1	8.1	-3.89E-01
COBL	cordon-bleu homolog (mouse)	12	-3.72E-01
ARL6IP5	ADP-ribosylation-like factor 6 interacting protein 5	57	-3.66E-01
RANBP10	RAN binding protein 10	9.2	-3.42E-01
MPP1	membrane protein, palmitoylated 1, 55kDa	13	-3.36E-01
SSH3	slingshot homolog 3 (<i>Drosophila</i>)	9.3	-3.20E-01
IPP	intracisternal A particle-promoted polypeptide	4.2	-3.08E-01
EPB41L1	erythrocyte membrane protein band 4.1-like 1	15	-2.92E-01
AMOT	angiomotin	4.6	-2.71E-01
MYH10	myosin, heavy chain 10, non-muscle	14	-2.70E-01
ARL3	ADP-ribosylation factor-like 3	5.4	-2.56E-01
NUDCD3	NudC domain containing 3	15	-2.28E-01
ARHGEF11	Rho guanine nucleotide exchange factor (GEF) 11	7.0	-2.25E-01
NUMA1	nuclear mitotic apparatus protein 1	44	-2.24E-01
EPB41L5	erythrocyte membrane protein band 4.1 like 5	6.1	-2.16E-01
MTUS2	microtubule associated tumor suppressor candidate 2	3.4	-2.08E-01
SDC1	syndecan 1	20	-1.88E-01

DPYSL2	dihydropyrimidinase-like 2	21	-1.86E-01
KIF1C	kinesin family member 1C	12	-1.59E-01
KIF3B	kinesin family member 3B	34	-1.57E-01
SDC2	syndecan 2	19	-1.40E-01
LASP1	LIM and SH3 protein 1	57	-1.34E-01
SEPT8	septin 8	14	-1.34E-01
Peptidase/protease			
CAPN8	calpain 8	0.9	1.82E+00
TLL2	tolloid-like 2	0.5	1.37E+00
MMP1	matrix metallopeptidase 1	13	1.09E+00
ECEL1	endothelin converting enzyme-like 1	25	9.59E-01
CTSZ	cathepsin Z	105	7.22E-01
ADAMTS9	ADAM metallopeptidase with thrombospondin type 1 motif, 9	5.6	5.79E-01
FKBP11	FK506 binding protein 11, 19 kDa	20	5.52E-01
PITRM1	pitrilysin metallopeptidase 1	17	2.99E-01
C9orf3	chromosome 9 open reading frame 3	6.2	2.01E-01
ADAM28	ADAM metallopeptidase domain 28	1.5	-1.38E+00
MMP11	matrix metallopeptidase 11 (stromelysin 3)	3.9	-1.21E+00
CAPN3	calpain 3, (p94)	4.4	-1.15E+00
MMP7	matrix metallopeptidase 7 (matrilysin, uterine)	271	-1.03E+00
PCSK4	proprotein convertase subtilisin/kexin type 4	1.2	-9.38E-01
MMP9	matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	19	-8.42E-01
WFDC2	WAP four-disulfide core domain 2	43	-8.08E-01
MMP19	matrix metallopeptidase 19	2.6	-8.04E-01
PLAU	plasminogen activator, urokinase	9.3	-7.90E-01
FAP	fibroblast activation protein, alpha	8.7	-6.56E-01
SERPINA3	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3	1796	-6.25E-01
SERPINA5	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 5	58	-5.61E-01
CTSF	cathepsin F	14	-5.26E-01
CTSO	cathepsin O	6.9	-5.23E-01
CTSS	cathepsin S	11	-4.94E-01
SPOCK1	sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 1	4.1	-4.86E-01
MMP14	matrix metallopeptidase 14 (membrane-inserted)	70	-4.77E-01
PREPL	prolyl endopeptidase-like	30	-4.15E-01
SERPINA4	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 4	29	-3.92E-01
APH1B	anterior pharynx defective 1 homolog B (C. elegans)	7.4	-3.88E-01
MMP15	matrix metallopeptidase 15 (membrane-inserted)	18	-3.80E-01

BACE1	beta-site APP-cleaving enzyme 1	22	-3.73E-01
ERMP1	endoplasmic reticulum metallopeptidase 1	7.8	-3.51E-01
THSD4	thrombospondin, type I, domain containing 4	4.4	-3.46E-01
CTSA	cathepsin A	64	-2.50E-01
CTSD	cathepsin D	371	-2.07E-01
Transcription factors			
FOS	FBJ murine osteosarcoma viral oncogene homolog	7.8	1.26E+00
ZNF165	zinc finger protein 165	2.1	9.88E-01
ETV5	ets variant 5	4.8	9.22E-01
NR4A2	nuclear receptor subfamily 4, group A, member 2	2.2	8.34E-01
CITED2	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2	30	8.21E-01
FOSL1	FOS-like antigen 1	1.6	8.18E-01
BHLHA15	basic helix-loop-helix family, member a15	2.1	7.88E-01
MSC	musculin	4.3	7.85E-01
TSHZ3	teashirt zinc finger homeobox 3	2.8	7.64E-01
EGR1	early growth response 1	18	6.88E-01
EPAS1	endothelial PAS domain protein 1	47	6.78E-01
TSC22D2	TSC22 domain family, member 2	4.2	6.68E-01
KLF4	Kruppel-like factor 4 (gut)	4.0	6.59E-01
CEBPG	CCAAT/enhancer binding protein (C/EBP), gamma	9.3	6.37E-01
BACH2	BTB and CNC homology 1, basic leucine zipper transcription factor	0.8	6.30E-01
TGIF1	TGFB-induced factor homeobox 1	17	5.80E-01
KLF6	Kruppel-like factor 6	25	5.57E-01
ZNF331	zinc finger protein 331	8.5	5.51E-01
ZNF395	zinc finger protein 395	35	5.08E-01
FAM50A	family with sequence similarity 50, member A	23	4.92E-01
MYC	v-myc myelocytomatosis viral oncogene homolog (avian)	4.5	4.46E-01
JUN	jun proto-oncogene	56	3.99E-01
NFIL3	nuclear factor, interleukin 3 regulated	16	3.85E-01
SREBF2	sterol regulatory element binding transcription factor 2	34	3.74E-01
MAFK	v-maf musculoaponeurotic fibrosarcoma oncogene homolog K (avian)	14	3.65E-01
NPAS2	neuronal PAS domain protein 2	8.0	3.62E-01
EDF1	endothelial differentiation-related factor 1	105	3.37E-01
ZNF404	zinc finger protein 404	1.4	-2.21E+00
PAX4	paired box 4	1.7	-1.19E+00
CDX2	caudal type homeobox 2	3.5	-9.35E-01
ZNF763	zinc finger protein 763	1.6	-8.84E-01
ZNF85	zinc finger protein 85	2.0	-8.54E-01

ZNF691	zinc finger protein 691	4.8	-7.50E-01
AEBP1	AE binding protein 1	11	-6.98E-01
RUNX1T1	runt-related transcription factor 1; translocated to, 1 (cyclin D-related)	1.5	-6.69E-01
CREB3L4	cAMP responsive element binding protein 3-like 4	4.3	-6.38E-01
ZFP14	zinc finger protein 14 homolog (mouse)	1.8	-6.14E-01
ZNF211	zinc finger protein 211	5.5	-5.98E-01
TFDP2	transcription factor Dp-2 (E2F dimerization partner 2)	2.6	-5.60E-01
RORC	RAR-related orphan receptor C	13	-5.56E-01
ZBTB7C	zinc finger and BTB domain containing 7C	1.4	-5.41E-01
KANK2	KN motif and ankyrin repeat domains 2	5.8	-5.40E-01
EAPP	E2F-associated phosphoprotein	9.3	-5.37E-01
MAF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian)	3.7	-5.29E-01
PATZ1	POZ (BTB) and AT hook containing zinc finger 1	12	-5.22E-01
SIX5	SIX homeobox 5	5.4	-5.20E-01
MAFB	v-maf musculoaponeurotic fibrosarcoma oncogene homolog B (avian)	55	-5.14E-01
PBXIP1	pre-B-cell leukemia homeobox interacting protein 1	34	-5.12E-01
VGLL4	vestigial like 4 (Drosophila)	22	-4.84E-01
ZNF671	zinc finger protein 671	4.3	-4.75E-01
BCAS3	breast carcinoma amplified sequence 3	3.1	-4.62E-01
CREG1	cellular repressor of E1A-stimulated genes 1	20	-4.61E-01
ARNT	aryl hydrocarbon receptor nuclear translocator	10	-4.58E-01
ZHX3	zinc fingers and homeoboxes 3	4.8	-4.20E-01
CRY2	cryptochrome 2 (photolyase-like)	12	-4.18E-01
EYA3	eyes absent homolog 3 (Drosophila)	6.2	-4.07E-01
PBX2	pre-B-cell leukemia homeobox 2	20	-4.05E-01
ZNF462	zinc finger protein 462	4.0	-4.02E-01
ZNF429	zinc finger protein 429	4.6	-4.01E-01
ZNF192	zinc finger protein 192	5.3	-4.01E-01
NFYC	nuclear transcription factor Y, gamma	9.4	-4.00E-01
ERH	enhancer of rudimentary homolog (Drosophila)	30	-3.99E-01
MEIS2	Meis homeobox 2	24	-3.93E-01
ZNF280D	zinc finger protein 280D	5.3	-3.90E-01
ZNF14	zinc finger protein 14	2.2	-3.81E-01
UBTF	upstream binding transcription factor, RNA polymerase I	16	-3.66E-01
GTF3C3	general transcription factor IIIC, polypeptide 3, 102kDa	6.8	-3.42E-01
PBX3	pre-B-cell leukemia homeobox 3	13	-3.40E-01
PER3	period homolog 3 (Drosophila)	4.7	-3.39E-01
RFX1	regulatory factor X, 1	6.8	-3.34E-01
SOX13	SRY (sex determining region Y)-box 13	7.6	-3.33E-01

SMAD3	SMAD family member 3	17	-3.26E-01
GTF2I	general transcription factor Ili	83	-3.15E-01
ZNF445	zinc finger protein 445	3.9	-2.94E-01
ZNF561	zinc finger protein 561	5.3	-2.89E-01
GATA6	GATA binding protein 6	6.6	-2.86E-01
ZSCAN29	zinc finger and SCAN domain containing 29	4.5	-2.81E-01
SALL2	sal-like 2 (<i>Drosophila</i>)	7.0	-2.74E-01
PDX1	pancreatic and duodenal homeobox 1	57	-2.71E-01
BRD8	bromodomain containing 8	12	-2.71E-01
CREBL2	cAMP responsive element binding protein-like 2	21	-2.26E-01
PTTG1IP	pituitary tumor-transforming 1 interacting protein	70	-2.23E-01
BHLHE41	basic helix-loop-helix family, member e41	9.8	-2.15E-01
ELF3	E74-like factor 3 (ets domain transcription factor, epithelial-specific)	71	-2.08E-01
NEUROD1	neuronal differentiation 1	29	-1.83E-01
GATAD1	GATA zinc finger domain containing 1	9.5	-1.59E-01
DPF2	D4, zinc and double PHD fingers family 2	12	-1.44E-01
PRDM2	PR domain containing 2, with ZNF domain	7.0	-9.55E-02

NF-κB regulation

SQSTM1	sequestosome 1	158	6.54E-01
NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	46	6.45E-01
IRAK2	interleukin-1 receptor-associated kinase 2	4.3	6.28E-01
STK40	serine/threonine kinase 40	17	6.08E-01
IRAK1	interleukin-1 receptor-associated kinase 1	25	4.99E-01
NFKBIZ	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta	11	4.32E-01
NFKBIB	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, beta	7.0	4.14E-01
NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	9.5	4.08E-01
NFKB2	nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)	16	3.37E-01
AEBP1	AE binding protein 1	11	-6.98E-01
UNC5CL	unc-5 homolog C (<i>C. elegans</i>)-like	35	-6.51E-01
TRIM22	tripartite motif containing 22	6.4	-6.44E-01
TMEM9	transmembrane protein 9	35	-3.60E-01
HIF1AN	hypoxia inducible factor 1, alpha subunit inhibitor	10	-3.33E-01
SAT2	spermidine/spermine N1-acetyltransferase family member 2	31	-3.23E-01
TMEM9B	TMEM9 domain family, member B	17	-3.20E-01

DPF2	D4, zinc and double PHD fingers family 2	12	-1.44E-01
ANXA4	annexin A4	109	-1.34E-01
PRDM2	PR domain containing 2, with ZNF domain	7.0	-9.55E-02
PEBP1	phosphatidylethanolamine binding protein 1	127	-8.37E-02
Chemokines/cytokines/adhesion molecules/innate immunity and related proteins			
IL6	interleukin 6 (interferon, beta 2)	1.5	2.23E+00
IL1A	interleukin 1, alpha	0.7	1.19E+00
FAM19A5	family with sequence similarity 19 (chemokine (C-C motif)-like), member A5	0.8	1.17E+00
C2CD4A	C2 calcium-dependent domain containing 4A	27	1.16E+00
ISG20	interferon stimulated exonuclease gene 20kDa	3.5	1.01E+00
IER3	immediate early response 3	205	9.88E-01
IL33	interleukin 33	1.1	9.50E-01
CXCL1	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	44	9.15E-01
IL8	interleukin 8	36	8.94E-01
TNFRSF11B	tumor necrosis factor receptor superfamily, member 11b	6.2	8.36E-01
IRAK2	interleukin-1 receptor-associated kinase 2	4.3	6.28E-01
TREM1	triggering receptor expressed on myeloid cells 1	2.3	5.84E-01
CDHR3	cadherin-related family member 3	0.7	5.75E-01
SPSB1	splA/ryanodine receptor domain and SOCS box containing 1	8.6	5.56E-01
CTNNA2	catenin (cadherin-associated protein), alpha 2	2.1	5.51E-01
CXCL2	chemokine (C-X-C motif) ligand 2	22	5.07E-01
SELS	seleoprotein S	20	5.01E-01
IRAK1	interleukin-1 receptor-associated kinase 1	25	4.99E-01
MFHAS1	malignant fibrous histiocytoma amplified sequence 1	3.6	4.28E-01
NFIL3	nuclear factor, interleukin 3 regulated	16	3.85E-01
TNFRSF1A	tumor necrosis factor receptor superfamily, member 1A	25	3.74E-01
GAB2	GRB2-associated binding protein 2	5.8	3.65E-01
C4BPB	complement component 4 binding protein, beta	2.4	-2.15E+00
TYROBP	TYRO protein tyrosine kinase binding protein	5.8	-1.94E+00
LILRB4	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 4	1.5	-1.92E+00
DEFB1	defensin, beta 1	123	-1.85E+00
KLKB1	kallikrein B, plasma (Fletcher factor) 1	2.5	-1.26E+00
C4BPA	complement component 4 binding protein, alpha	3.6	-1.01E+00
RARRES3	retinoic acid receptor responder (tazarotene induced) 3	9.5	-9.23E-01
C1QTNF6	C1q and tumor necrosis factor related protein 6	7.1	-9.20E-01
C1QB	complement component 1, q subcomponent, B chain	6.0	-8.69E-01

SCARA3	scavenger receptor class A, member 3	1.7	-8.67E-01
CD74	CD74 molecule, major histocompatibility complex, class II invariant chain	238	-8.54E-01
IFI44	interferon-induced protein 44	2.6	-8.20E-01
VNN2	vanin 2	14	-7.98E-01
MTCP1NB	mature T-cell proliferation 1 neighbor	6.8	-7.86E-01
TLR5	toll-like receptor 5	2.1	-7.30E-01
AEBP1	AE binding protein 1	11	-6.98E-01
TGFB2	transforming growth factor, beta 2	4.6	-6.56E-01
UNC5CL	unc-5 homolog C (<i>C. elegans</i>)-like	35	-6.51E-01
FCGRT	Fc fragment of IgG, receptor, transporter, alpha	23	-6.46E-01
TRIM22	tripartite motif containing 22	6.4	-6.44E-01
CDH22	cadherin 22, type 2	14	-6.08E-01
CHL1	cell adhesion molecule with homology to L1CAM (close homolog of L1)	3.5	-5.92E-01
CXCR4	chemokine (C-X-C motif) receptor 4	4.7	-5.88E-01
PILRA	paired immunoglobulin-like type 2 receptor alpha	8.0	-5.69E-01
CFI	complement factor I	20	-5.64E-01
ZFYVE21	zinc finger, FYVE domain containing 21	14	-5.60E-01
IFIT1	interferon-induced protein with tetratricopeptide repeats 1	8.0	-5.22E-01
VTCN1	V-set domain containing T cell activation inhibitor 1	22	-5.06E-01
TSC22D3	TSC22 domain family, member 3	18	-4.81E-01
CD59	CD59 molecule, complement regulatory protein	94	-4.45E-01
TGFB3	transforming growth factor, beta 3	8.4	-4.11E-01
EDA	ectodysplasin A	1.4	-4.11E-01
CFHR1	complement factor H-related 1	6.5	-4.01E-01
SEMA4D	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	6.6	-3.64E-01
TMEM9	transmembrane protein 9	35	-3.60E-01
ARL16	ADP-ribosylation factor-like 16	9.6	-3.47E-01
LCN2	lipocalin 2	331	-3.46E-01
CMTM6	CKLF-like MARVEL transmembrane domain containing 6	24	-3.23E-01
TMEM9B	TMEM9 domain family, member B	17	-3.20E-01
NEO1	neogenin 1	14	-3.05E-01
PALM3	paralemmin 3	18	-2.61E-01
B2M	beta-2-microglobulin	1936	-2.58E-01
PSMB8	proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional peptidase 7)	33	-2.34E-01
CD46	CD46 molecule, complement regulatory protein	72	-2.17E-01
IL20RA	interleukin 20 receptor, alpha	4.6	-2.01E-01
SDC1	syndecan 1	20	-1.88E-01

F11R	F11 receptor	26	-1.41E-01
CDC42SE1	CDC42 small effector 1	26	-1.40E-01
ATRN	attractin	13	-1.28E-01
CD68	CD68 molecule	44	-9.91E-02
CMTM4	CKLF-like MARVEL transmembrane domain containing 4	21	-9.69E-02
HLA-related			
HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	1.3	-1.71E+00
HLA-DRA	major histocompatibility complex, class II, DR alpha	35	-1.48E+00
HLA-DPB1	major histocompatibility complex, class II, DP beta 1	3.4	-1.40E+00
HLA-DMB	major histocompatibility complex, class II, DM beta	3.9	-1.35E+00
HLA-DPA1	major histocompatibility complex, class II, DP alpha 1	6.4	-1.13E+00
HLA-DRB1	major histocompatibility complex, class II, DR beta 1	21	-1.05E+00
HLA-DMA	major histocompatibility complex, class II, DM alpha	14	-1.05E+00
HLA-DRB5	major histocompatibility complex, class II, DR beta 5	8.0	-8.87E-01
HLA-B	major histocompatibility complex, class I, B	466	-3.93E-01
MR1	major histocompatibility complex, class I-related	4.0	-3.83E-01
RFX1	regulatory factor X, 1	6.8	-3.34E-01
HLA-C	major histocompatibility complex, class I, C	427	-3.07E-01
Signal transduction			
SHC4	SHC (Src homology 2 domain containing) family, member 4	0.3	2.16E+00
ADCY2	adenylate cyclase 2 (brain)	0.5	1.56E+00
DKK4	dickkopf homolog 4 (<i>Xenopus laevis</i>)	1.8	1.14E+00
PDE10A	phosphodiesterase 10A	1.5	8.18E-01
RAB3B	RAB3B, member RAS oncogene family	15	7.65E-01
IRS2	insulin receptor substrate 2	6.6	7.46E-01
PAK3	p21 protein (Cdc42/Rac)-activated kinase 3	8.3	7.23E-01
FICD	FIC domain containing	6.4	6.75E-01
TMEM158	transmembrane protein 158 (gene/pseudogene)	4.1	6.74E-01
PDE9A	phosphodiesterase 9A	4.4	6.63E-01
RHOB	ras homolog family member B	46	6.44E-01
RHOQ	ras homolog family member Q	13	5.72E-01
ARHGEF2	Rho/Rac guanine nucleotide exchange factor (GEF) 2	7.3	5.52E-01
MICALL1	MICAL-like 1	4.6	4.80E-01
KIAA1244	KIAA1244	15	4.28E-01
AXIN1	axin 1	5.6	4.24E-01
RAP2B	RAP2B, member of RAS oncogene family	5.0	4.02E-01
RASSF1	Ras association (RaiGDS/AF-6) domain family member 1	7.1	3.99E-01

ARHGEF5	Rho guanine nucleotide exchange factor (GEF) 5	19	3.49E-01
TBL2	transducin (beta)-like 2	8.5	3.29E-01
PKIA	protein kinase (cAMP-dependent, catalytic) inhibitor alpha	2.2	2.92E-01
YWHAH	tyrosine 3-monooxygenase/tryptophan monooxygenase activation protein, eta polypeptide	5-	2.87E-01
RPTOR	regulatory associated protein of MTOR, complex 1	4.1	2.43E-01
RAPGEF1	Rap guanine nucleotide exchange factor (GEF) 1	13	2.18E-01
GNAS	GNAS complex locus	1432	1.92E-01
GNB1	guanine nucleotide binding protein (G protein), beta polypeptide 1	89	6.78E-02
TYROBP	TYRO protein tyrosine kinase binding protein	5.8	-1.94E+00
LPAR6	lysophosphatidic acid receptor 6	2.2	-1.31E+00
ARHGDIIB	Rho GDP dissociation inhibitor (GDI) beta	5.0	-1.21E+00
FFAR3	free fatty acid receptor 3	2.0	-1.17E+00
SMO	smoothened, frizzled family receptor	3.1	-1.04E+00
DOK3	docking protein 3	1.3	-1.01E+00
SFRP5	secreted frizzled-related protein 5	27	-9.40E-01
CALML4	calmodulin-like 4	3.1	-8.83E-01
VANGL2	vang-like 2 (van gogh, Drosophila)	3.5	-8.51E-01
PIK3IP1	phosphoinositide-3-kinase interacting protein 1	9.9	-8.45E-01
LGALS9	lectin, galactoside-binding, soluble, 9	13	-8.25E-01
SRGAP3	SLIT-ROBO Rho GTPase activating protein 3	2.3	-8.18E-01
PRKAR2B	protein kinase, cAMP-dependent, regulatory, type II, beta	2.9	-7.97E-01
PLCH2	phospholipase C, eta 2	5.2	-7.90E-01
RASA4	RAS p21 protein activator 4	34	-7.85E-01
RHOV	ras homolog family member V	34	-7.17E-01
PLCD1	phospholipase C, delta 1	4.8	-7.12E-01
RASL11A	RAS-like, family 11, member A	6.0	-7.09E-01
FARP2	FERM, RhoGEF and pleckstrin domain protein 2	5.6	-6.96E-01
RASSF4	Ras association (RalGDS/AF-6) domain family member 4	15	-6.81E-01
SRGAP1	SLIT-ROBO Rho GTPase activating protein 1	2.5	-6.77E-01
PIK3C2B	phosphoinositide-3-kinase, class 2, beta polypeptide	3.4	-6.54E-01
ARRDC2	arrestin domain containing 2	16	-6.45E-01
PLD1	phospholipase D1, phosphatidylcholine-specific	5.1	-6.20E-01
GIPC2	GIPC PDZ domain containing family, member 2	3.1	-6.16E-01
ASAP3	ArfGAP with SH3 domain, ankyrin repeat and PH domain 3	10	-5.99E-01
SUFU	suppressor of fused homolog (Drosophila)	3.9	-5.99E-01

ARRDC4	arrestin domain containing 4	12	-5.90E-01
MAP3K15	mitogen-activated protein kinase kinase kinase 15	4.1	-5.84E-01
PPAP2B	phosphatidic acid phosphatase type 2B	8.5	-5.66E-01
RASGRP1	RAS guanyl releasing protein 1 (calcium and DAG-regulated)	4.7	-5.38E-01
TXNIP	thioredoxin interacting protein	118	-5.20E-01
SH2B1	SH2B adaptor protein 1	15	-4.98E-01
RGN	regucalcin (senescence marker protein-30)	7.0	-4.95E-01
FZD4	frizzled family receptor 4	1.8	-4.89E-01
NOTCH3	notch 3	11	-4.82E-01
CTNNBIP1	catenin, beta interacting protein 1	6.8	-4.82E-01
MARCKSL1	MARCKS-like 1	42	-4.78E-01
IP6K2	inositol hexakisphosphate kinase 2	36	-4.44E-01
PILRB	paired immunoglobulin-like type 2 receptor beta	44	-4.44E-01
ADCY5	adenylyl cyclase 5	8.0	-4.42E-01
MCF2L	MCF.2 cell line derived transforming sequence-like	7.4	-4.31E-01
DMXL2	Dmx-like 2	5.0	-4.30E-01
PORCN	porcupine homolog (Drosophila)	2.8	-4.30E-01
RAB20	RAB20, member RAS oncogene family	15	-4.27E-01
ELMO2	engulfment and cell motility 2	13	-4.03E-01
ARHGEF3	Rho guanine nucleotide exchange factor (GEF) 3	7.3	-4.02E-01
RAB2B	RAB2B, member RAS oncogene family	7.0	-3.93E-01
RAB11FIP4	RAB11 family interacting protein 4 (class II)	8.0	-3.91E-01
APH1B	anterior pharynx defective 1 homolog B (C. elegans)	7.4	-3.88E-01
ARHGEF10L	Rho guanine nucleotide exchange factor (GEF) 10-like	19	-3.78E-01
ASB8	ankyrin repeat and SOCS box containing 8	9.5	-3.76E-01
ARL8B	ADP-ribosylation factor-like 8B	19	-3.74E-01
ARL6IP5	ADP-ribosylation-like factor 6 interacting protein 5	57	-3.66E-01
ARL16	ADP-ribosylation factor-like 16	9.6	-3.47E-01
RANBP10	RAN binding protein 10	6.0	-3.42E-01
DLG2	discs, large homolog 2 (Drosophila)	1.4	-3.37E-01
MPP1	membrane protein, palmitoylated 1, 55kDa	13	-3.36E-01
SNX29	sorting nexin 29	5.5	-3.35E-01
HIF1AN	hypoxia inducible factor 1, alpha subunit inhibitor	10	-3.33E-01
RGL1	ral guanine nucleotide dissociation stimulator-like 1	5.1	-3.26E-01
GNG10	guanine nucleotide binding protein (G protein), gamma 10	18	-3.12E-01
ARHGEF9	Cdc42 guanine nucleotide exchange factor (GEF) 9	8.8	-2.93E-01
DIXDC1	DIX domain containing 1	2.6	-2.92E-01
SRGAP2	SLIT-ROBO Rho GTPase activating protein 2	9.5	-2.83E-01
NOTCH2	notch 2	13	-2.68E-01

ARL3	ADP-ribosylation factor-like 3	5.4	-2.56E-01
CHN1	chimerin (chimaerin) 1	5.9	-2.54E-01
MADD	MAP-kinase activating death domain	13	-2.43E-01
RAP1GAP	RAP1 GTPase activating protein	54	-2.37E-01
FLOT2	flotillin 2	37	-2.36E-01
ARHGEF11	Rho guanine nucleotide exchange factor (GEF) 11	7.0	-2.25E-01
RAB11A	RAB11A, member RAS oncogene family	25	-2.11E-01
RALBP1	ralA binding protein 1	13	-1.83E-01
ADCYAP1	adenylate cyclase activating polypeptide 1 (pituitary)	14	-1.78E-01
CDS2	CDP-diacylglycerol synthase (phosphatidate cytidylyltransferase) 2	9.3	-1.68E-01
CALM2	calmodulin 2 (phosphorylase kinase, delta)	122	-1.62E-01
TSPAN3	tetraspanin 3	78	-1.60E-01
WLS	wntless homolog (Drosophila)	44	-9.65E-02
PEBP1	phosphatidylethanolamine binding protein 1	127	-8.37E-02

Kinases/phosphatases

DUSP1	dual specificity phosphatase 1	20	9.12E-01
SIK1	salt-inducible kinase 1	7.7	8.60E-01
STK40	serine/threonine kinase 40	17	6.08E-01
MAPK7	mitogen-activated protein kinase 7	3.6	5.15E-01
DUSP4	dual specificity phosphatase 4	15	4.67E-01
OXSR1	oxidative-stress responsive 1	9.7	3.29E-01
MAST2	microtubule associated serine/threonine kinase 2	6.0	2.98E-01
RPS6KA1	ribosomal protein S6 kinase, 90kDa, polypeptide 1	9.0	2.16E-01
DUSP3	dual specificity phosphatase 3	25	1.01E-01
PHPT1	phosphohistidine phosphatase 1	37	7.11E-02
PPP1R1B	protein phosphatase 1, regulatory (inhibitor) subunit 1B	34	-1.33E+00
ELFN2	extracellular leucine-rich repeat and fibronectin type III domain containing 2	7.8	-8.86E-01
HDHD1	haloacid dehalogenase-like hydrolase domain containing 1	7.1	-6.41E-01
PPP1R3E	protein phosphatase 1, regulatory subunit 3E	5.6	-5.28E-01
STK38	serine/threonine kinase 38	9.9	-4.94E-01
NEK6	NIMA (never in mitosis gene a)-related kinase 6	13	-4.80E-01
PIP4K2B	phosphatidylinositol-5-phosphate 4-kinase, type II, beta	12	-4.70E-01
WNK2	WNK lysine deficient protein kinase 2	8.9	-4.67E-01
HUNK	hormonally up-regulated Neu-associated kinase	3.7	-4.51E-01
PPP1R12B	protein phosphatase 1, regulatory subunit 12B	3.9	-4.50E-01
SGK2	serum/glucocorticoid regulated kinase 2	5.6	-4.40E-01
PPP2R5A	protein phosphatase 2, regulatory subunit B', alpha	11	-4.32E-01
AGK	acylglycerol kinase	5.2	-4.28E-01
EYA3	eyes absent homolog 3 (Drosophila)	6.2	-4.07E-01

PPM1H	protein phosphatase, Mg ²⁺ /Mn ²⁺ dependent, 1H	7.1	-3.77E-01
VRK3	vaccinia related kinase 3	6.1	-3.40E-01
DSTYK	dual serine/threonine and tyrosine protein kinase	4.9	-3.33E-01
PTPN18	protein tyrosine phosphatase, non-receptor type 18 (brain-derived)	18	-3.15E-01
PRKCH	protein kinase C, eta	5.1	-3.00E-01
CAMK2N1	calcium/calmodulin-dependent protein kinase II inhibitor 1	35	-2.94E-01
MPPE1	metallophosphoesterase 1	6.1	-2.86E-01
CTDSPL	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase-like	10	-2.79E-01
PTPRN2	protein tyrosine phosphatase, receptor type, N polypeptide 2	50	-2.49E-01
INPP4A	inositol polyphosphate-4-phosphatase, type I, 107kDa	4.1	-2.30E-01
ARPP19	cAMP-regulated phosphoprotein, 19kDa	29	-2.28E-01
PIP5K1A	phosphatidylinositol-4-phosphate 5-kinase, type I, alpha	10	-2.23E-01
PTPRA	protein tyrosine phosphatase, receptor type, A	17	-1.47E-01

Transcription regulation/alternative splicing

EGR4	early growth response 4	0.9	9.96E-01
ELL2	elongation factor, RNA polymerase II, 2	20	7.05E-01
SRSF3	serine/arginine-rich splicing factor 3	18	5.67E-01
ESRP1	epithelial splicing regulatory protein 1	13	4.85E-01
DHX16	DEAH (Asp-Glu-Ala-His) box polypeptide 16	8.4	3.84E-01
DDX39A	DEAD (Asp-Glu-Ala-Asp) box polypeptide 39A	9.4	3.76E-01
AKAP17A	A kinase (PRKA) anchor protein 17A chr:X	15	3.06E-01
AKAP17A	A kinase (PRKA) anchor protein 17A chr:Y	15	2.99E-01
SCAF1	SR-related CTD-associated factor 1	14	2.02E-01
TCERG1L	transcription elongation regulator 1-like	2.7	-9.39E-01
NANOS1	nanos homolog 1 (Drosophila)	2.9	-9.13E-01
RBFOX3	RNA binding protein, fox-1 homolog (C. elegans) 3	1.6	-8.98E-01
MEPCE	methylphosphate capping enzyme	16	-7.22E-01
DIS3L	DIS3 mitotic control homolog (S. cerevisiae)-like	6.7	-6.05E-01
RBM14	RNA binding motif protein 14	8.7	-5.83E-01
NOVA1	neuro-oncological ventral antigen 1	3.8	-5.74E-01
CNP	2',3'-cyclic nucleotide 3' phosphodiesterase	12	-5.44E-01
CELF1	CUGBP, Elav-like family member 1	22	-5.32E-01
ADI1	acireductone dioxygenase 1	26	-4.94E-01
TSC22D3	TSC22 domain family, member 3	18	-4.81E-01
CSTF3	cleavage stimulation factor, 3' pre-RNA, subunit 3, 77kDa	8.5	-4.20E-01
HMGN3	high mobility group nucleosomal binding domain 3	32	-3.77E-01
RBFOX2	RNA binding protein, fox-1 homolog (C. elegans) 2	14	-3.69E-01
SNRPN	small nuclear ribonucleoprotein polypeptide N	94	-3.67E-01

UBTF	upstream binding transcription factor, RNA polymerase I	16	-3.66E-01
SMARCD3	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 3	13	-3.61E-01
PHC1	polyhomeotic homolog 1 (<i>Drosophila</i>)	20	-3.51E-01
POLDIP3	polymerase (DNA-directed), delta interacting protein 3	22	-3.47E-01
THOC7	THO complex 7 homolog (<i>Drosophila</i>)	16	-3.46E-01
HMGN1	high mobility group nucleosome binding domain 1	54	-3.42E-01
SMARCD2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 2	14	-3.25E-01
SMARCE1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1	22	-3.23E-01
DDX17	DEAD (Asp-Glu-Ala-Asp) box helicase 17	96	-3.18E-01
SUGP2	SURP and G patch domain containing 2	17	-2.99E-01
LDB1	LIM domain binding 1	22	-2.82E-01
TJP2	tight junction protein 2 (zonula occludens-2)	24	-2.81E-01
PCGF3	polycomb group ring finger 3	12	-2.77E-01
POLR2G	polymerase (RNA) II (DNA directed) polypeptide G	18	-2.59E-01
TIA1	TIA1 cytotoxic granule-associated RNA binding protein	8.9	-2.26E-01
HNRNPH3	heterogeneous nuclear ribonucleoprotein H3 (2H9)	29	-1.76E-01
RBM5	RNA binding motif protein 5	22	-1.38E-01
Non-coding RNA			
SLC7A5P2	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5 pseudogene 2	2.3	1.60E+00
SLC7A5P1	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5 pseudogene 1	8.2	1.54E+00
LINC00473	long intergenic non-protein coding RNA 473	7.0	1.35E+00
ZSCAN12P1	zinc finger and SCAN domain containing 12 pseudogene 1	0.8	1.20E+00
FABP5P3	fatty acid binding protein 5 pseudogene 3	9.6	9.36E-01
DGCR5	DiGeorge syndrome critical region gene 5 (non-protein coding)	3.7	5.87E-01
MALAT1	metastasis associated lung adenocarcinoma transcript 1	306	5.75E-01
TUBA4B	tubulin, alpha 4b (pseudogene)	13	5.43E-01
HSP90B3P	heat shock protein 90kDa beta (Grp94), member 3, pseudogene	23	4.40E-01
LOC100170939	glucuronidase, beta pseudogene	0.6	2.59E-01
LINC00671	long intergenic non-protein coding RNA 671 (LOC388387)	2.5	-1.97E+00
SSTR5-AS1	SSTR5 antisense RNA 1 (LOC146336)	8.7	-1.96E+00
M1	uncharacterized LOC100507027	3.8	-1.90E+00
LOC100505624	uncharacterized LOC100505624	1.2	-1.80E+00
LOC100271722	uncharacterized LOC100271722	1.1	-1.66E+00
LOC645638	WDNM1-like pseudogene	2.2	-1.25E+00
LOC441204	uncharacterized LOC441204	1.3	-1.10E+00
PCBP1-AS1	PCBP1 antisense RNA 1	1.1	-1.09E+00
STARD4-AS1	STARD4 antisense RNA 1 (LOC100505678)	1.0	-1.09E+00

LINC00622	long intergenic non-protein coding RNA (LOC644242)	622	3.5	-9.46E-01
PTOV1-AS1	PTOV1 antisense RNA 1 (LOC100506033)		4.7	-8.86E-01
TRAPPC2P1	trafficking protein particle complex 2 pseudogene 1		6.0	-8.58E-01
HNRNPUL2-BSCL2	HNRNPUL2-BSCL2 readthrough		13	-7.67E-01
MST1P2	macrophage stimulating 1 (hepatocyte growth factor-like) pseudogene 2		24	-7.55E-01
GGT3P	gamma-glutamyltransferase 3 pseudogene		11	-6.72E-01
SENP3-EIF4A1	SENP3-EIF4A1 readthrough		1.3	-6.43E-01
LOC93622	Morf4 family associated protein 1-like 1 pseudogene		4.2	-6.24E-01
LINC00339	long intergenic non-protein coding RNA 339 (HSPC157)		6.9	-5.81E-01
HCP5	HLA complex P5 (non-protein coding)		8.1	-5.63E-01
LOC729678	uncharacterized LOC729678		8.7	-5.51E-01
C15orf48	chromosome 15 open reading frame 48		63	-5.32E-01
SKP1P2	S-phase kinase-associated protein 1 pseudogene 2 (loc728622)		16	-4.51E-01
CD27-AS1	CD27 antisense RNA 1 (non-protein coding) (loc678655)		5.1	-4.32E-01
GTF2IRD2P1	GTF2I repeat domain containing 2 pseudogene 1		12	-4.18E-01
FKBP9L	FK506 binding protein 9-like		28	-3.79E-01
LRRC37A4P	leucine rich repeat containing 37, member A4, pseudogene		18	-3.60E-01
LOC220906	uncharacterized LOC220906		11	-3.49E-01
LOC147727	uncharacterized LOC147727		5.9	-3.48E-01
RPSAP9	ribosomal protein SA pseudogene 9		67	-3.37E-01
HCG11	HLA complex group 11 (non-protein coding)		8.7	-3.21E-01
LOC100506548	uncharacterized LOC100506548		6.8	-3.09E-01
MST1P9	macrophage stimulating 1 (hepatocyte growth factor-like) pseudogene 9		13	-2.85E-01
DHRS4-AS1	DHRS4 antisense RNA 1 (non-protein coding) (C14orf167)		8.2	-2.43E-01
TUG1	taurine upregulated 1 (non-protein coding)		19	-2.35E-01
RPSAP58	ribosomal protein SA pseudogene 58		177	-6.95E-02

Epigenetic regulation

SFMBT2	Scm-like with four mbt domains 2	0.8	6.17E-01
ARID5B	AT rich interactive domain 5B (MRF1-like)	5.9	4.71E-01
CBX4	chromobox homolog 4	6.1	3.76E-01
KDM6B	lysine (K)-specific demethylase 6B	9.6	2.73E-01
APOBEC3C	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3C	7.5	-8.13E-01
APOBEC3D	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3D	2.0	-7.47E-01
H2AFV	H2A histone family, member V	23	-6.97E-01
CBX7	chromobox homolog 7	18	-6.64E-01
HIST1H2AC	histone cluster 1, H2ac	14	-6.75E-01

APOBEC2	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 2	4.4	-5.29E-01
ZMYM3	zinc finger, MYM-type 3	11	-5.26E-01
ING3	inhibitor of growth family, member 3	4.5	-5.17E-01
DPY30	dpy-30 homolog (<i>C. elegans</i>)	15	-5.08E-01
SETDB2	SET domain, bifurcated 2	1.7	-4.52E-01
ERI2	ERI1 exoribonuclease family member 2	2.5	-4.48E-01
FKBP3	FK506 binding protein 3, 25kDa	14	-3.69E-01
ING4	inhibitor of growth family, member 4	9.2	-3.28E-01
EZH1	enhancer of zeste homolog 1 (<i>Drosophila</i>)	10	-3.05E-01
APOBEC3F	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3F	5.1	-2.79E-01
PCGF3	polycomb group ring finger 3	12	-2.77E-01
CBX3	chromobox homolog 3	18	-2.52E-01
PHF8	PHD finger protein 8	10	-2.52E-01
MPHOSPH8	M-phase phosphoprotein 8	10	-2.47E-01
KANSL1	KAT8 regulatory NSL complex subunit 1 (KIAA1267)	10	-2.38E-01
CBX1	chromobox homolog 1	19	-2.18E-01
PHF15	PHD finger protein 15	11	-1.41E-01
WDR82	WD repeat domain 82	22	-1.24E-01
PRDM2	PR domain containing 2, with ZNF domain	7.0	-9.55E-02

Oxidative stress/DNA damage response

HMOX1	heme oxygenase (decycling) 1	6.2	7.85E-01
DDIT4	DNA-damage-inducible transcript 4	83	7.42E-01
TXN	thioredoxin	19	7.05E-01
MSRA	methionine sulfoxide reductase A	3.8	6.18E-01
SESN2	sestrin 2	13	5.95E-01
TXNDC11	thioredoxin domain containing 11	15	4.38E-01
RAD23A	RAD23 homolog A (<i>S. cerevisiae</i>)	29	4.22E-01
TALDO1	transaldolase 1	29	3.48E-01
OXSR1	oxidative-stress responsive 1	97	3.29E-01
PON1	paraoxonase 1	4.9	-2.06E+00
GSTM1	glutathione S-transferase mu 1	15	-1.03E+00
SEPP1	selenoprotein P, plasma, 1	20	-8.76E-01
SCARA3	scavenger receptor class A, member 3	1.7	-8.67E-01
DDB2	damage-specific DNA binding protein 2, 48kDa	14	-8.03E-01
ENC1	ectodermal-neural cortex 1 (with BTB-like domain)	18	-7.31E-01
GSTM4	glutathione S-transferase mu 4	12	-7.07E-01
GGCT	gamma-glutamylcyclotransferase	14	-7.04E-01
PCYOX1L	prenylcysteine oxidase 1 like	5.7	-5.49E-01
GSTK1	glutathione S-transferase kappa 1	55	-5.12E-01

GTF2H5	general transcription factor IIH, polypeptide 5	2.3	-5.12E-01
PARP3	poly (ADP-ribose) polymerase family, member 3	5.7	-4.33E-01
RPA2	replication protein A2, 32kDa	9.4	-4.14E-01
EEP1D1	endonuclease/exonuclease/phosphatase family domain containing 1	4.5	-3.79E-01
XPC	xeroderma pigmentosum, complementation group C	13	-2.54E-01
RPA1	replication protein A1, 70kDa	8.4	-2.01E-01
PRDX6	peroxiredoxin 6	34	-1.31E-01
Apoptosis			
IER3	immediate early response 3	205	9.88E-01
GRAMD4	GRAM domain containing 4	14	7.55E-01
GADD45A	growth arrest and DNA-damage-inducible, alpha	16	7.50E-01
TP53BP2	tumor protein p53 binding protein, 2	7.8	5.11E-01
BAG1	BCL2-associated athanogene	12	2.68E-01
LRG1	leucine-rich alpha-2-glycoprotein 1	28	-1.01E+00
DNASE1	deoxyribonuclease I	1.3	-9.55E-01
BMF	Bcl2 modifying factor	17	-8.62E-01
FAS	Fas (TNF receptor superfamily, member 6)	2.7	-8.23E-01
CFLAR	CASP8 and FADD-like apoptosis regulator	21	-8.02E-01
UACA	veal autoantigen with coiled-coil domains and ankyrin repeats	3.0	-7.99E-01
MAP3K15	mitogen-activated protein kinase kinase kinase 15	4.1	-5.84E-01
CASP10	caspase 10, apoptosis-related cysteine peptidase	2.8	-5.55E-01
EAPP	E2F-associated phosphoprotein	9.3	-5.37E-01
TP53INP1	tumor protein p53 inducible nuclear protein 1	7.5	-5.28E-01
PATZ1	POZ (BTB) and AT hook containing zinc finger 1	12	-5.22E-01
TXNIP	thioredoxin interacting protein	118	-5.20E-01
RGN	regucalcin (senescence marker protein-30)	7.0	-4.95E-01
NEK6	NIMA (never in mitosis gene a)-related kinase 6	13	-4.80E-01
CREG1	cellular repressor of E1A-stimulated genes 1	20	-4.61E-01
IP6K2	inositol hexakisphosphate kinase 2	36	-4.44E-01
CASP2	caspase 2, apoptosis-related cysteine peptidase	6.3	-4.20E-01
ELMO2	engulfment and cell motility 2	13	-4.03E-01
ARL6IP5	ADP-ribosylation-like factor 6 interacting protein 5	57	-3.66E-01
LCN2	lipocalin 2	331	-3.46E-01
DSTYK	dual serine/threonine and tyrosine protein kinase	4.9	-3.33E-01
SMARCE1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1	22	-3.23E-01
DDX17	DEAD (Asp-Glu-Ala-Asp) box helicase 17	96	-3.18E-01
BCL2L11	BCL2-like 11 (apoptosis facilitator)	7.7	-3.06E-01
SNN	stannin	7.0	-3.02E-01
TJP2	tight junction protein 2	24	-2.81E-01

SALL2	sal-like 2 (Drosophila)	7.0	-2.74E-01
XPC	xeroderma pigmentosum, complementation group C	13	-2.54E-01
NISCH	nischarin	20	-2.45E-01
MADD	MAP-kinase activating death domain	13	-2.43E-01
DCAF7	DDB1 and CUL4 associated factor 7	16	-2.39E-01
INPP4A	inositol polyphosphate-4-phosphatase, type I, 107kDa	4.1	-2.30E-01
TIA1	TIA1 cytotoxic granule-associated RNA binding protein	8.9	-2.26E-01
PERP	PERP, TP53 apoptosis effector	46	-2.23E-01
PIP5K1A	phosphatidylinositol-4-phosphate 5-kinase, type I, alpha	10	-2.23E-01
TM7SF3	transmembrane 7 superfamily member 3	15	-2.21E-01
SORT1	sortilin 1	22	-2.03E-01
EIF4G2	eukaryotic translation initiation factor 4 gamma, 2	122	-2.02E-01
PRPS1	phosphoribosyl pyrophosphate synthetase 1	16	-1.90E-01
ADCYAP1	adenylate cyclase activating polypeptide 1 (pituitary)	14	-1.78E-01
NMT1	N-myristoyltransferase 1	17	-1.73E-01
DPF2	D4, zinc and double PHD fingers family 2	12	-1.44E-01
ANXA4	annexin A4	109	-1.34E-01
PRDX6	peroxiredoxin 6	34	-1.31E-01
Cell cycle			
PCDHGA5	protocadherin gamma subfamily A, 5	0.4	1.83E+00
PCDHAC2	protocadherin alpha subfamily C, 2	1.8	1.12E+00
CDKN1C	cyclin-dependent kinase inhibitor 1C	35	8.30E-01
PCDHGA3	protocadherin gamma subfamily A, 3	1.0	6.66E-01
PCDHB7	protocadherin beta 7	0.8	6.58E-01
LGALS4	lectin, galactoside-binding, soluble, 4	41	3.20E-01
ADRM1	adhesion regulating molecule 1	22	2.91E-01
ITGA3	integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)	39	1.98E-01
GAS6	growth arrest-specific 6	19	-7.65E-01
CETN3	centrin, EF-hand protein, 3	4.6	-7.62E-01
REG1B	regenerating islet-derived 1 beta	1803	-7.08E-01
DPH1	DPH1 homolog (S. cerevisiae)	11	-6.82E-01
CCNDBP1	cyclin D-type binding-protein 1	6.3	-6.67E-01
CBX7	chromobox homolog 7	18	-6.64E-01
CNNM3	cyclin M3	13	-5.75E-01
TFDP2	transcription factor Dp-2 (E2F dimerization partner 2)	2.6	-5.60E-01
REG3G	regenerating islet-derived 3 gamma	49	-5.42E-01
CEP68	centrosomal protein 68kDa	3.9	-5.42E-01
EAPP	E2F-associated phosphoprotein	9.3	-5.37E-01
URGCP	upregulator of cell proliferation	14	-4.94E-01

REG3A	regenerating islet-derived 3 alpha	2785	-4.82E-01
NEK6	NIMA (never in mitosis gene a)-related kinase 6	13	-4.80E-01
CEP41	centrosomal protein 41kDa (TSGA14)	5.2	-4.76E-01
HEPACAM2	HEPACAM family member 2	27	-4.56E-01
CLMN	calmin (calponin-like, transmembrane)	11	-4.45E-01
RPA2	replication protein A2, 32kDa	9.4	-4.14E-01
NUP43	nucleoporin 43kDa	5.4	-4.09E-01
ERH	enhancer of rudimentary homolog (<i>Drosophila</i>)	30	-3.99E-01
HAUS4	HAUS augmin-like complex, subunit 4	9.4	-3.89E-01
MCM6	minichromosome maintenance complex component 6	1.9	-3.68E-01
IST1	increased sodium tolerance 1 homolog (<i>yeast</i>) (KIAA0174)	37	-3.46E-01
SNN	stannin	7.0	-3.02E-01
CDKN2C	cyclin-dependent kinase inhibitor 2C	5.8	-3.02E-01
CCNG1	cyclin G1	27	-3.01E-01
CAMK2N1	calcium/calmodulin-dependent protein kinase II inhibitor 1	35	-2.94E-01
CTDSPL	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase-like	10	-2.79E-01
ARPP19	cAMP-regulated phosphoprotein, 19kDa	29	-2.28E-01
NUMA1	nuclear mitotic apparatus protein 1	44	-2.24E-01
PTTG1IP	pituitary tumor-transforming 1 interacting protein	70	-2.23E-01
TMEM30B	transmembrane protein 30B	22	-2.10E-01
RALBP1	ralA binding protein 1	13	-1.83E-01
CMTM4	CKLF-like MARVEL transmembrane domain containing 4	21	-9.69E-02

Extracellular matrix

MFAP4	microfibrillar-associated protein 4	1.2	-2.43E+00
CHAD	chondroadherin	1.7	-1.80E+00
ITGB1BP1	integrin beta 1 binding protein 1	32	-1.42E+00
OLFML2B	olfactomedin-like 2B	1.2	-1.04E+00
EFEMP1	EGF containing fibulin-like extracellular matrix protein 1	8.2	-9.49E-01
ABI3BP	ABI family, member 3 (NESH) binding protein	1.5	-9.32E-01
COL10A1	collagen, type X, alpha 1	1.6	-1.20E+00
VWA2	von Willebrand factor A domain containing 2	1.4	-1.04E+00
COL1A2	collagen, type I, alpha 2	39	-5.05E-01
COL4A2	collagen, type IV, alpha 2	23	-4.39E-01
COL1A1	collagen, type I, alpha 1	60	-3.59E-01
COL18A1	collagen, type XVIII, alpha 1	34	-3.43E-01
MATN2	matrilin 2	4.4	-5.98E-01
ENG	endoglin (transforming growth factor beta receptor complex)	8.4	-5.95E-01
CD82	CD82 molecule	24	-5.73E-01

SPARC	secreted protein, acidic, cysteine-rich (osteonectin)	25	-5.72E-01
PCOLCE	procollagen C-endopeptidase enhancer	8.3	-5.44E-01
MMP9	matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	19	-8.42E-01
ITGB4	integrin, beta 4	11	-3.32E-01
HSPG2	heparan sulfate proteoglycan 2 (perlecan)	14	-2.46E-01
CHST3	carbohydrate (chondroitin 6) sulfotransferase 3	3.3	-2.07E-01
CRTAP	cartilage associated protein	9.2	-2.02E-01
AGRN	agrin	46	-1.40E-01
Other/unknown function			
PTGS2	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	1.7	2.25E+00
AREG	amphiregulin	5.5	2.19E+00
SFN	stratifin	3.2	1.58E+00
C6orf223	chromosome 6 open reading frame 223	0.8	1.49E+00
PRG4	proteoglycan 4	23	1.43E+00
LOC441177	hypothetical LOC441177	2.1	1.38E+00
FEZ1	fasciculation and elongation protein zeta 1 (zygin I)	2.0	1.24E+00
STC2	stanniocalcin 2	4.0	1.13E+00
CCDC48	coiled-coil domain containing 48	0.6	1.04E+00
KIAA1199	KIAA1199	2.3	9.94E-01
SMOC1	SPARC related modular calcium binding 1	12	9.76E-01
TTC39B	tetratricopeptide repeat domain 39B	1.9	9.41E-01
PHLDA2	pleckstrin homology-like domain, family A, member 2	3.8	9.13E-01
TRIM9	tripartite motif containing 9	4.3	9.05E-01
JPH1	junctophilin 1	1.33	8.11E-01
TRIM16	tripartite motif containing 16	6.0	7.84E-01
FLJ35776	hypothetical LOC649446	2.6	7.76E-01
GTPBP2	GTP binding protein 2	20	7.75E-01
KLHDC8A	kelch domain containing 8A	12	7.47E-01
TRIM16L	tripartite motif containing 16-like	7.0	7.42E-01
VAT1L	vesicle amine transport protein 1 homolog (T. californica)-like	6.5	7.04E-01
LOC100507034	uncharacterized LOC100507034	2.1	6.90E-01
TCP11L2	t-complex 11 (mouse)-like 2	4.4	6.73E-01
LOC154761	hypothetical LOC154761	8.5	6.58E-01
EML5	echinoderm microtubule associated protein like 5	1.7	6.48E-01
SMOX	spermine oxidase	6.0	6.36E-01
KIAA0319	KIAA0319	1.4	6.27E-01
BEX2	brain expressed X-linked 2	50	6.20E-01
C10orf108	chromosome 10 open reading frame 108	1.9	6.16E-01

PEG10	paternally expressed 10	25	6.15E-01
MRPL23	mitochondrial ribosomal protein L23	16	6.09E-01
C12orf68	chromosome 12 open reading frame 68	2.6	6.08E-01
FAM135A	family with sequence similarity 135, member A	3.5	6.03E-01
ZNF841	zinc finger protein 841	4.2	6.03E-01
CSRNP1	cysteine-serine-rich nuclear protein 1	12	5.97E-01
NEDD9	neural precursor cell expressed, developmentally down-regulated 9	7.8	5.95E-01
GNL3	guanine nucleotide binding protein-like 3 (nucleolar)	14	5.94E-01
LURAP1L	leucine rich adaptor protein 1-like	14	5.94E-01
FEM1C	fem-1 homolog c (<i>C. elegans</i>)	3.9	5.92E-01
PIGA	phosphatidylinositol glycan anchor biosynthesis, class A	3.4	5.79E-01
WDR25	WD repeat domain 25	4.7	5.72E-01
MTRF1L	mitochondrial translational release factor 1-like	4.7	5.58E-01
TMEM200A	transmembrane protein 200A	7.0	5.56E-01
NACAD	NAC alpha domain containing	20	5.46E-01
CCDC104	coiled-coil domain containing 104	17	5.41E-01
TMEM39A	transmembrane protein 39A	7.3	5.33E-01
SOGA2	SOGA family member 2	3.4	5.32E-01
CNIH4	cornichon homolog 4 (<i>Drosophila</i>)	14	5.20E-01
TSPYL2	TSPY-like 2	20	4.96E-01
AMPD2	adenosine monophosphate deaminase 2	29	4.93E-01
BHLHE40	basic helix-loop-helix family, member e40	57	4.87E-01
BEX5	brain expressed, X-linked 5	8.6	4.83E-01
PARM1	prostate androgen-regulated mucin-like protein 1	48	4.68E-01
DNTTIP2	deoxynucleotidyltransferase, terminal, interacting protein 2	12	4.66E-01
FAM83G	family with sequence similarity 83, member G	6.5	4.58E-01
KPNA2	karyopherin alpha 2 (RAG cohort 1, importin alpha 1)	8.9	4.37E-01
KIAA0284	KIAA0284	13	4.33E-01
ODZ4	odz, odd Oz/ten-m homolog 4 (<i>Drosophila</i>)	1.7	4.20E-01
LRRC59	leucine rich repeat containing 59	24	4.20E-01
TRIB1	tribbles homolog 1 (<i>Drosophila</i>)	14	4.00E-01
TESC	tescalcin	25	3.91E-01
KIAA0754	KIAA0754	8.2	3.91E-01
STBD1	starch binding domain 1	16	3.85E-01
FRY	furry homolog (<i>Drosophila</i>)	3.7	3.79E-01
UAP1	UDP-N-acetylglucosamine pyrophosphorylase 1	10	3.78E-01
CTAGE4	CTAGE family, member 4	13	3.78E-01

LOXL2	lysyl oxidase-like 2	4.9	3.71E-01
SIPA1L2	signal-induced proliferation-associated 1 like 2	7.2	3.71E-01
SYNJ2	synaptojanin 2	8.0	3.65E-01
HTATIP2	HIV-1 Tat interactive protein 2, 30kDa	24	3.65E-01
MYBBP1A	MYB binding protein (P160) 1a	6.2	3.55E-01
LOC100271836	SMG1 homolog, phosphatidylinositol 3-kinase-related kinase pseudogene	5.1	3.54E-01
WIPI1	WD repeat domain, phosphoinositide interacting 1	8.1	3.51E-01
CLPB	ClpB caseinolytic peptidase B homolog (E. coli)	3.5	3.49E-01
PFDN2	prefoldin subunit 2	19	3.47E-01
SPRY2	sprouty homolog 2 (Drosophila)	5.8	3.41E-01
TBC1D30	TBC1 domain family, member 30	1.9	3.36E-01
FLII	flightless I homolog (Drosophila)	23	3.28E-01
ZFYVE28	zinc finger, FYVE domain containing 28	4.1	3.11E-01
ZNF275	zinc finger protein 275	4.2	3.05E-01
MYO1C	myosin IC	26	2.84E-01
TANC2	tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 2	5.9	2.68E-01
TMEM163	transmembrane protein 163	17	2.43E-01
CDCP1	CUB domain containing protein 1	23	2.40E-01
ASCC2	activating signal cointegrator 1 complex subunit 2	10	2.24E-01
BRD4	bromodomain containing 4	17	1.92E-01
C15orf24	chromosome 15 open reading frame 24	35	1.89E-01
NOMO2	NODAL modulator 2	81	1.79E-01
NOMO3	NODAL modulator 3	79	1.78E-01
NOMO1	NODAL modulator 1	80	1.73E-01
PRNP	prion protein	32	1.64E-01
NAV1	neuron navigator 1	7.5	1.62E-01
ANKRD11	ankyrin repeat domain 11	14	1.54E-01
TYMP	thymidine phosphorylase	11	1.49E-01
ALKBH5	alkB, alkylation repair homolog 5 (E. coli)	28	1.43E-01
COMM3-BMI1	COMM3-BMI1 readthrough	5.2	-Inf
AGR3	anterior gradient 3 homolog (Xenopus laevis)	2.1	-2.44E+00
CHI3L2	chitinase 3-like 2	2.7	-1.72E+00
SULT1C2	sulfotransferase family, cytosolic, 1C, member 2	2.9	-1.66E+00
FAM159B	family with sequence similarity 159, member B	15	-1.42E+00
ZCCHC4	zinc finger, CCHC domain containing 4	1.8	-1.20E+00
CCDC121	coiled-coil domain containing 121	1.9	-1.17E+00
LOC100128288	uncharacterized LOC100128288	2.6	-1.17E+00
C1orf127	chromosome 1 open reading frame 127	7.8	-1.16E+00
PYROXD2	pyridine nucleotide-disulphide oxidoreductase domain 2	3.5	-1.14E+00

TSPAN8	tetraspanin 8	58	-1.10E+00
PRR15L	proline rich 15-like	24	-1.09E+00
KIAA1614	KIAA1614	1.1	-1.09E+00
WSCD2	WSC domain containing 2	8.3	-1.08E+00
STAC3	SH3 and cysteine rich domain 3	1.2	-1.07E+00
C11orf92	chromosome 11 open reading frame 92	2.4	-1.04E+00
CD248	CD248 molecule, endosialin	2.5	-1.04E+00
CCDC152	coiled-coil domain containing 152	9.4	-1.04E+00
NWD1	NACHT and WD repeat domain containing 1	1.2	-1.00E+00
C6orf222	chromosome 6 open reading frame 222	11	-9.81E-01
UPK1B	uroplakin 1B	3.9	-9.81E-01
HYPK	Huntingtin interacting protein K (C15orf63)	5.3	-9.56E-01
MSS51	mitochondrial translational activator homolog (S. cerevisiae)	1.1	-9.54E-01
HHLA2	HERV-H LTR-associating 2	6.4	-9.16E-01
LOC100131089	uncharacterized LOC100131089	3.6	-8.91E-01
TMEM145	transmembrane protein 145	4.6	-8.75E-01
PROM2	prominin 2	6.2	-8.63E-01
FAM108B1	family with sequence similarity 108, member B1	3.8	-8.36E-01
AMPH	amphiphysin	5.1	-8.12E-01
GPNMB	glycoprotein (transmembrane) nmb	9.1	-8.06E-01
TMEM196	transmembrane protein 196	1.9	-7.91E-01
NBPF14	neuroblastoma breakpoint family, member 14	18	-7.87E-01
LUM	lumican	16	-7.83E-01
C2orf72	chromosome 2 open reading frame 72	4.5	-7.82E-01
C15orf40	chromosome 15 open reading frame 40	8.3	-7.81E-01
NDRG2	NDRG family member 2	20	-7.64E-01
IQCC	IQ motif containing C	1.9	-7.64E-01
C20orf196	chromosome 20 open reading frame 196	1.4	-7.61E-01
C1orf63	chromosome 1 open reading frame 63	24	-7.59E-01
IGSF1	immunoglobulin superfamily, member 1	5.4	-7.48E-01
EPDR1	ependymin related protein 1 (zebrafish)	7.0	-7.47E-01
FAM155B	family with sequence similarity 155, member B	2.6	-7.35E-01
FLJ35390	uncharacterized LOC255031	14	-7.33E-01
LOC100216545	uncharacterized LOC100216545	1.4	-7.30E-01
MTRNR2L6	MT-RNR2-like 6	34	-7.23E-01
MGC27345	uncharacterized protein MGC27345	1.1	-7.07E-01
GATS	GATS, stromal antigen 3 opposite strand	12	-7.02E-01
TTC18	tetratricopeptide repeat domain 18	1.6	-7.00E-01
LOC100131564	uncharacterized LOC100131564	5.8	-6.97E-01
COQ10A	coenzyme Q10 homolog A (S. cerevisiae)	5.4	-6.95E-01
NOTCH2NL	notch 2 N-terminal like	6.0	-6.82E-01

GRAMD1C	GRAM domain containing 1C	2.2	-6.56E-01
PCMTD2	protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 2	9.7	-6.52E-01
LOC646471	uncharacterized LOC646471	4.0	-6.46E-01
HSBP1L1	heat shock factor binding protein 1-like 1	11	-6.44E-01
LOC100422737	uncharacterized LOC100422737	8.2	-6.39E-01
PVRIG	poliovirus receptor related immunoglobulin domain containing	5.5	-6.26E-01
LRRC4	leucine rich repeat containing 4	3.2	-6.25E-01
N4BP2L1	NEDD4 binding protein 2-like 1	3.7	-6.25E-01
SFTPA2	surfactant protein A2	2.3	-6.23E-01
C1orf226	chromosome 1 open reading frame 226	2.0	-6.21E-01
C7orf43	chromosome 7 open reading frame 43	8.4	-5.88E-01
PRUNE	prune homolog (<i>Drosophila</i>)	8.1	-5.85E-01
TMEM229B	transmembrane protein 229B	5.2	-5.84E-01
TSPAN6	tetraspanin 6	8.0	-5.71E-01
CA11	carbonic anhydrase XI	9.7	-5.70E-01
ABHD14B	abhydrolase domain containing 14B	17	-5.61E-01
NBPF16	neuroblastoma breakpoint family, member 16	56	-5.54E-01
HRSP12	heat-responsive protein 12	5.2	-5.49E-01
IQCB1	IQ motif containing B1	4.7	-5.42E-01
C15orf48	chromosome 15 open reading frame 48	63	-5.32E-01
TMCC3	transmembrane and coiled-coil domain family 3	4.6	-5.31E-01
THNSL1	threonine synthase-like 1 (<i>S. cerevisiae</i>)	4.2	-5.23E-01
EPN3	epsin 3	4.9	-5.18E-01
CCDC61	coiled-coil domain containing 61	2.6	-5.16E-01
OLFM2	olfactomedin 2	33	-5.14E-01
IGIP	IgA-inducing protein homolog (<i>Bos taurus</i>)	11	-5.10E-01
NBPF24	neuroblastoma breakpoint family, member 24	40	-5.06E-01
FAM117A	family with sequence similarity 117, member A	7.8	-4.97E-01
TRIQQK	triple QxxK/R motif containing (C8orf83)	9.4	-4.96E-01
SLAIN1	SLAIN motif family, member 1	3.7	-4.96E-01
GTF2IRD1P1	GTF2I repeat domain containing 1 pseusogene 1 (loc729156)	4.6	-4.18E-01
C16orf88	chromosome 16 open reading frame 88	7.7	-4.82E-01
PXMP4	peroxisomal membrane protein 4, 24kDa	2.0	-4.80E-01
IQCK	IQ motif containing K	3.3	-4.62E-01
ANXA9	annexin A9	7.7	-4.51E-01
C14orf93	chromosome 14 open reading frame 93	4.8	-4.51E-01
FAM53B	family with sequence similarity 53, member B	5.1	-4.49E-01
GPR98	G protein-coupled receptor 98	1.2	-4.48E-01

C15orf38	chromosome 15 open reading frame 38	7.1	-4.36E-01
C11orf93	chromosome 11 open reading frame 93	8.2	-4.27E-01
ZDHHC4	zinc finger, DHHC-type containing 4	19	-4.25E-01
SELENBP1	selenium binding protein 1	12	-4.19E-01
TMEM206	transmembrane protein 206	2.1	-4.19E-01
MYL9	myosin, light chain 9, regulatory	16	-4.17E-01
RPUSD4	RNA pseudouridylate synthase domain containing 4	5.5	-4.15E-01
SPG11	spastic paraplegia 11 (autosomal recessive)	9.1	-4.14E-01
NCMAP	noncompact myelin associated protein (c1orf130)	8.3	-4.07E-01
CAB39L	calcium binding protein 39-like	3.9	-4.05E-01
C1orf126	chromosome 1 open reading frame 126	3.4	-4.02E-01
CYS1	cystin 1	6.7	-4.00E-01
FAM219B	family with sequence similarity 219, member B (C15orf17)	17	-3.98E-01
PQLC3	PQ loop repeat containing 3	7.1	-3.97E-01
TMEM63A	transmembrane protein 63A	15	-3.96E-01
GRAMD3	GRAM domain containing 3	5.5	-3.92E-01
SPATA20	spermatogenesis associated 20	20	-3.82E-01
C8orf42	chromosome 8 open reading frame 42	7.6	-3.82E-01
C8orf33	chromosome 8 open reading frame 33	9.8	-3.78E-01
FAM115A	family with sequence similarity 115, member A	24	-3.76E-01
CCDC28A	coiled-coil domain containing 28A	9.5	-3.76E-01
PLEKHA6	pleckstrin homology domain containing, family A member 6	15	-3.72E-01
TMEM19	transmembrane protein 19	4.2	-3.68E-01
TMEM50B	transmembrane protein 50B	8.9	-3.66E-01
C22orf39	chromosome 22 open reading frame 39	7.8	-3.64E-01
C1orf115	chromosome 1 open reading frame 115	8.1	-3.63E-01
LMBR1L	limb region 1 homolog (mouse)-like	7.3	-3.60E-01
FAM46C	family with sequence similarity 46, member C	14	-3.56E-01
TMEM126B	transmembrane protein 126B	11	-3.56E-01
MTRNR2L1	MT-RNR2-like 1	96	-3.52E-01
TMEM87A	transmembrane protein 87A	13	-3.49E-01
NBPF3	neuroblastoma breakpoint family, member 3	3.1	-3.44E-01
SAMD12	sterile alpha motif domain containing 12	4.5	-3.44E-01
CASC4	cancer susceptibility candidate 4	21	-3.43E-01
TMTC2	transmembrane and tetratricopeptide repeat containing 2	4.4	-3.36E-01
NARG2	NMDA receptor regulated 2	3.4	-3.36E-01
TRANK1	tetratricopeptide repeat and ankyrin repeat containing 1	2.1	-3.33E-01
C1orf198	chromosome 1 open reading frame 198	14	-3.30E-01
ATXN7L3B	ataxin 7-like 3B	27	-3.19E-01

TMCC1	family 1 transmembrane and coiled-coil domain	5.4	-3.15E-01
ITM2B	integral membrane protein 2B	161	-3.09E-01
SH3BP5L	SH3-binding domain protein 5-like	8.4	-3.09E-01
PCED1A	PC-esterase domain containing 1A (FAM113A)	15	-2.99E-01
C5orf22	chromosome 5 open reading frame 22	3.5	-2.98E-01
NIPAL3	NIPA-like domain containing 3	9.0	-2.97E-01
FAM213B	family with sequence similarity 213, member B (C1orf93)	8.7	-2.96E-01
R3HDM2	R3H domain containing 2	16	-2.95E-01
TSPYL4	TSPY-like 4	13	-2.92E-01
PLCL2	phospholipase C-like 2	7.9	-2.90E-01
SUN2	Sad1 and UNC84 domain containing 2	25	-2.87E-01
HEBP1	heme binding protein 1	24	-2.87E-01
C10orf76	chromosome 10 open reading frame 76	5.3	-2.82E-01
C6orf120	chromosome 6 open reading frame 120	6.6	-2.79E-01
VWA5A	von Willebrand factor A domain containing 5A	23	-2.75E-01
IFT172	intraflagellar transport 172 homolog (Chlamydomonas)	4.2	-2.71E-01
C6orf89	chromosome 6 open reading frame 89	19	-2.64E-01
C22orf13	chromosome 22 open reading frame 13	21	-2.60E-01
C22orf29	chromosome 22 open reading frame 29	3.6	-2.54E-01
ZC3H7A	zinc finger CCCH-type containing 7A	12	-2.49E-01
CHURC1	churchill domain containing 1	8.8	-2.45E-01
DENND2D	DENN/MADD domain containing 2D	12	-2.44E-01
SUN1	Sad1 and UNC84 domain containing 1	30	-2.34E-01
RPRD2	regulation of nuclear pre-mRNA domain containing 2	8.5	-2.30E-01
CYB561D1	cytochrome b-561 domain containing 1	7.2	-2.28E-01
TBC1D2B	TBC1 domain family, member 2B	8.2	-2.27E-01
KIAA1191	KIAA1191	27	-2.11E-01
GPR107	G protein-coupled receptor 107	15	-2.09E-01
TSPYL1	TSPY-like 1	24	-2.08E-01
RNF145	ring finger protein 145	19	-1.98E-01
TACSTD2	tumor-associated calcium signal transducer 2	238	-1.95E-01
FAM134C	family with sequence similarity 134, member C	16	-1.84E-01
RBMS6	RNA binding motif protein 6	27	-1.81E-01
PHLDB1	pleckstrin homology-like domain, family B, member 1	7.4	-1.75E-01
NUCKS1	nuclear casein kinase and cyclin-dependent kinase substrate 1	33	-1.70E-01
METTL9	methyltransferase like 9	14	-1.62E-01
TOR1AIP2	torsin A interacting protein 2	10	-1.54E-01
CCDC93	coiled-coil domain containing 93	12	-1.39E-01
KIAA1522	KIAA1522	65	-1.13E-01

RNA-seq gene expression in 5 human islet preparations. The sum of the RPKM for all the transcripts of the same gene under control condition is taken as measure of gene expression and the median of the 5 values is provided. Genes that were not detected or had an RPKM <1 in the control and in the palmitate condition are not mentioned. The \log_2 of the proportion between the sum of the RPKM for all the transcripts from the same gene under palmitate treatment and the same sum obtained under control conditions was taken as measure of change in gene expression. A difference in gene expression was considered significant if the corrected p value was <0.05. Genes were only taken up in the list when they were significantly changed in expression in one direction for at least 4 islet samples and changed in the other direction for none. The table contains the median \log_2 fold change of the samples with significantly modified gene expression.

Table S5: Expression of genes involved in mitochondrial movement, biogenesis, fusion-fission and mitophagy

Gene name	Gene description	Median RPKM control	Median RPKM palmitate
FIS1	fission 1 (mitochondrial outer membrane) homolog (S. cerevisiae)	55	58
PINK1	PTEN induced putative kinase 1	23	22
ESRRA	estrogen-related receptor alpha	19	23
MFN2	mitofusin 2	19	17
BNIP3L	BCL2/adenovirus E1B 19kDa interacting protein 3-like	18	22
RHOT2	ras homolog family member T2	17	16
TRAK1	trafficking protein, kinesin binding 1	15	18
DNM1L	dynamin 1-like	13	9.5
MFF	mitochondrial fission factor	11	9.0
TRAK2	trafficking protein, kinesin binding 2	8.1	9.0
FUNDC1	FUN14 domain containing 1	6.5	5.5
OPA1	optic atrophy 1 (autosomal dominant)	6.4	6.0
RHOT1	ras homolog family member T1	6.0	6.2
NRF1	nuclear respiratory factor 1	5.1	5.0
MFN1	mitofusin 1	4.8	5.6
SMCR7	Smith-Magenis syndrome chromosome region, candidate 7	3.7	3.2
PPARGC1A	peroxisome proliferator-activated receptor gamma, coactivator 1 alpha	3.7	3.7
GABPA	GA binding protein transcription factor, alpha subunit 60kDa	3.6	3.9
PARK2	parkinson protein 2, E3 ubiquitin protein ligase (parkin)	0.9	1.3
PPARGC1B	peroxisome proliferator-activated receptor gamma, coactivator 1 beta	0.3	0.3

RNA-seq gene expression in 5 human islet preparations. The sum of the RPKM for all the transcripts of the same gene is taken as measure of gene expression and the median of the 5 values is provided.

Table S6: Expression of genes involved in regulation of insulin secretion in human islets

Gene name	Gene description	Median RPKM control	Median RPKM palmitate
Glucose transporters			
SLC2A1	solute carrier family 2 (facilitated glucose transporter), member 1	12	18
SLC2A3	solute carrier family 2 (facilitated glucose transporter), member 3	2.9	3.6
SLC2A2	solute carrier family 2 (facilitated glucose transporter), member 2	1.5	1.0
Voltage gated Ca²⁺ channels			
CACNA1H	calcium channel, voltage-dependent, T type, alpha 1H subunit	9.4	14
CACNA1A	calcium channel, voltage-dependent, P/Q type, alpha 1A subunit	8.1	13
CACNA1D	calcium channel, voltage-dependent, L type, alpha 1D subunit	6.3	6.3
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit	3.0	3.4
CACNA1E	calcium channel, voltage-dependent, R type, alpha 1E subunit	0.04	0.03
Voltage gated Na⁺ channels			
SCN1B	sodium channel, voltage-gated, type I, beta subunit	4.2	6.1
SCN3B	sodium channel, voltage-gated, type III, beta subunit	2.7	3.4
SCN9A	sodium channel, voltage-gated, type IX, alpha subunit	2.2	2.0
SCN8A	sodium channel, voltage gated, type VIII, alpha subunit	1.4	1.2
Large conductance Ca²⁺-activated and voltage-gated delayed rectifying K⁺ channels			
KCNH2	potassium voltage-gated channel, subfamily H (eag-related), member 2	34	20
KCNQ1	potassium voltage-gated channel, KQT-like subfamily, member 1	21	22
KCNMA1	potassium large conductance calcium-activated channel, subfamily M, alpha member 1	10	9.0
KCNB2	potassium voltage-gated channel, Shab-related subfamily, member 2	2.6	2.7
Inwardly rectifying K⁺ channels			

KCNJ11	potassium inwardly-rectifying channel, subfamily J, member 11	13	18
KCNJ15	potassium inwardly-rectifying channel, subfamily J, member 15	5.4	3.0
KCNJ4	potassium inwardly-rectifying channel, subfamily J, member 4	0.06	0.14
KCNJ12	potassium inwardly-rectifying channel, subfamily J, member 12	0.01	0

Small conductance Ca^{2+} -activated channels

KCNN4	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4	0.3	0.3
KCNN3	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3	0.3	0.3
KCNN2	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 2	0.2	0.1
KCNN1	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 1	0.04	0.02

Background conductance

CASR	calcium-sensing receptor	24	22
NALCN	sodium leak channel, non-selective	1.4	1.3

Intracellular ion channels

ITPR3	inositol 1,4,5-trisphosphate receptor, type 3	31	32
CLCN3	chloride channel, voltage-sensitive 3	22	23
ITPR2	inositol 1,4,5-trisphosphate receptor, type 2	2.4	3.2
ITPR1	inositol 1,4,5-trisphosphate receptor, type 1	1.8	2.4
RYR2	ryanodine receptor 2 (cardiac)	0.3	0.4
RYR3	ryanodine receptor 3	0.02	0.007

G-protein coupled inwardly rectifying K^+ channels

KCNJ6	potassium inwardly-rectifying channel, subfamily J, member 6	2.4	3.2
KCNJ3	potassium inwardly-rectifying channel, subfamily J, member 3	1.4	1.3

Receptors

GABBR1	gamma-aminobutyric acid (GABA) B receptor, 1	9.5	7.5
SSTR2	somatostatin receptor 2	8.1	10
SSTR3	somatostatin receptor 3	5.5	6.8
SSTR1	somatostatin receptor 1	5.1	6.2
SSTR5	somatostatin receptor 5	1.2	0.7
SSTR4	somatostatin receptor 4	0.06	0.2

Proteins involved in exocytosis

STX1A	syntaxin 1A (brain)	50	47
VAMP2	vesicle-associated membrane protein 2 (synaptobrevin 2)	44	50
SYT7	synaptotagmin VII	37	47
SNAP25	synaptosomal-associated protein, 25kDa	28	36
GCK	glucokinase (hexokinase 4)	22	17
SYT5	synaptotagmin V	13	21
GLP1R	glucagon-like peptide 1 receptor	7.9	9.9
SENP1	SUMO1/sentrin specific peptidase 1	1.8	2.2

RNA-seq gene expression in 5 human islet preparations. The sum of the RPKM for all the transcripts of the same gene is taken as measure of gene expression and the median of the 5 values is provided. A difference in gene expression was considered significant if the corrected p value was <0.05 in at least 4 islet samples and changed in the other direction for none. Significantly induced genes are shown in red, significantly downregulated genes in green, and genes with significantly modified splice variants in blue.

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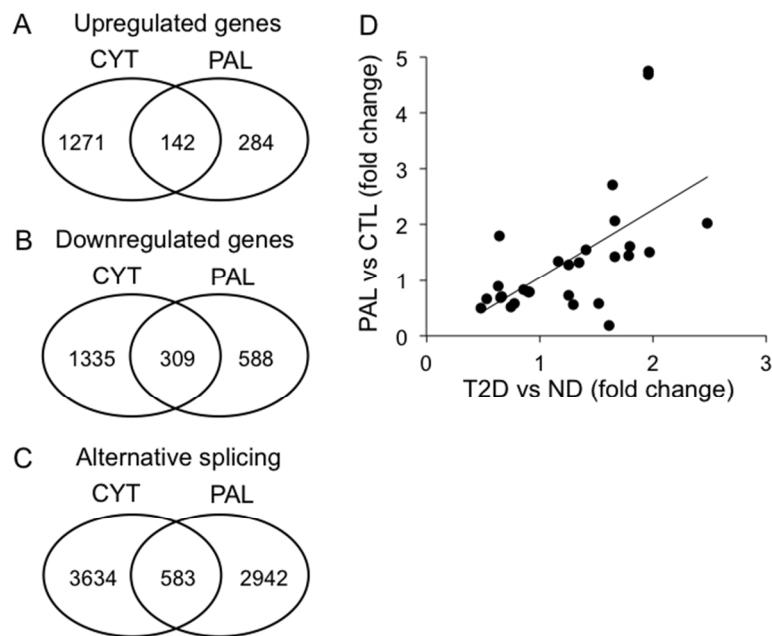


Figure S1: Comparison of human islet transcript expression changes induced by palmitate versus the cytokines IL-1 β + IFN- γ and versus genes differentially expressed in T2D human islets

Venn diagram of (A) up- or (B) downregulated genes in islets exposed for 48 h to palmitate (present findings) or the cytokines IL-1 β + IFN- γ (1). (C) Venn diagram of transcripts with modified splicing following palmitate or cytokine exposure. (D) Of the genes that are differentially expressed in human islets from T2D donors compared to non-diabetic donors and from donors with HbA1c $\geq 6\%$ compared to those with HbA1c $< 6\%$ (2), 28 genes were up- or downregulated by palmitate. The fold change is plotted of gene expression changes in T2D or hyperglycemic islets, assessed by microarrays, and in palmitate-treated islets, assessed by RNA-seq. The changes were largely in the same direction, with a correlation coefficient of 0.59 ($p=0.001$).

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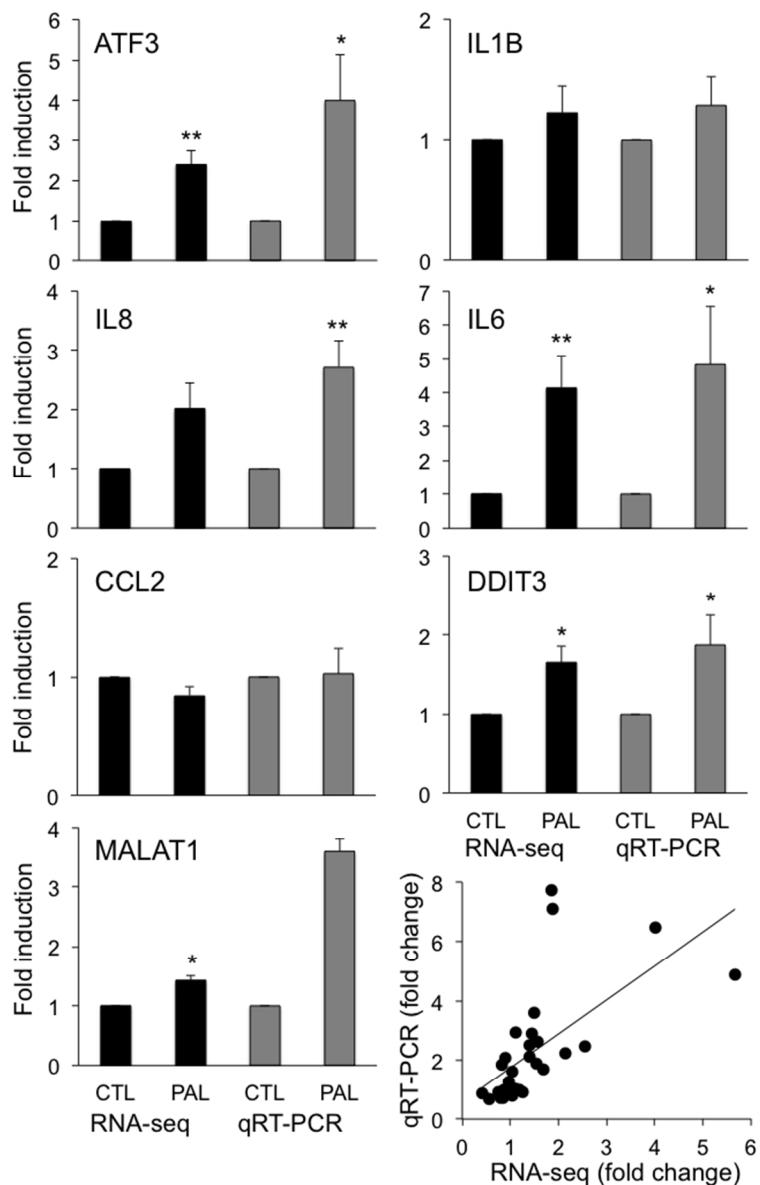
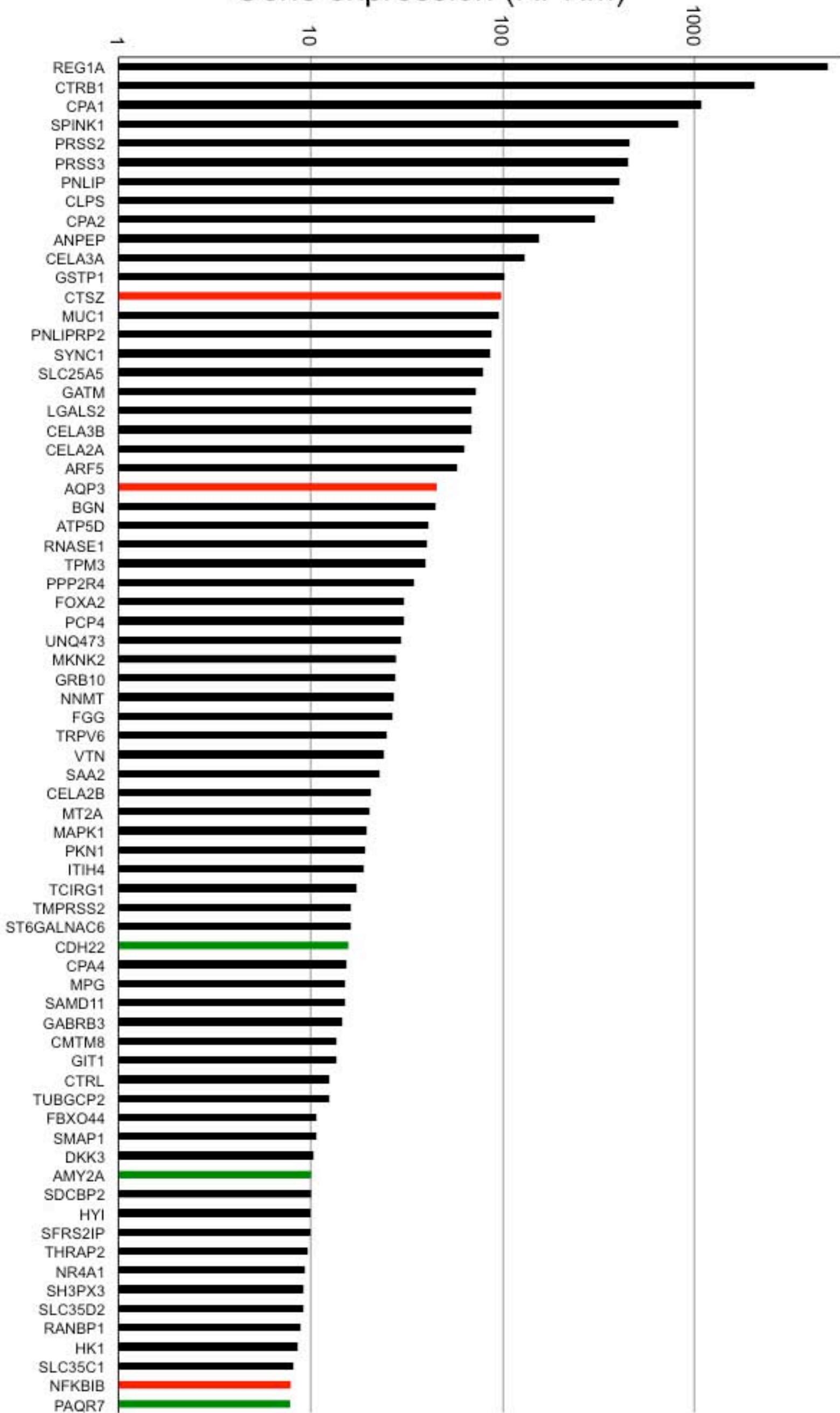


Figure S2: Validation of RNA-seq gene expression data by qRT-PCR in palmitate-treated human islets
Human islets from 5 organ donors were cultured for 48 h in the presence or absence (CTL) of palmitate (PAL). RNA-seq gene expression results (black bars) were compared to gene expression assessed by qRT-PCR (gray bars) in the same human islet preparations used for RNA-seq. Data were normalized to the geometric mean of β -actin and GAPDH expression and expressed as fold induction of control. * $p<0.05$, ** $p<0.01$ for CYT vs PAL by ratio t test. Bottom right panel: Palmitate-induced transcript expression changes of 30 genes assessed by RNA-seq were compared to expression changes measured by qRT-PCR in independent islet preparations. There was good agreement between the two datasets, with a correlation coefficient of 0.63 ($p<0.001$). Plotted RNA-seq data are the median of the fold change of RPKM in palmitate vs control condition; qRT-PCR data are expressed as the average fold change in gene expression corrected for the reference gene β -actin.

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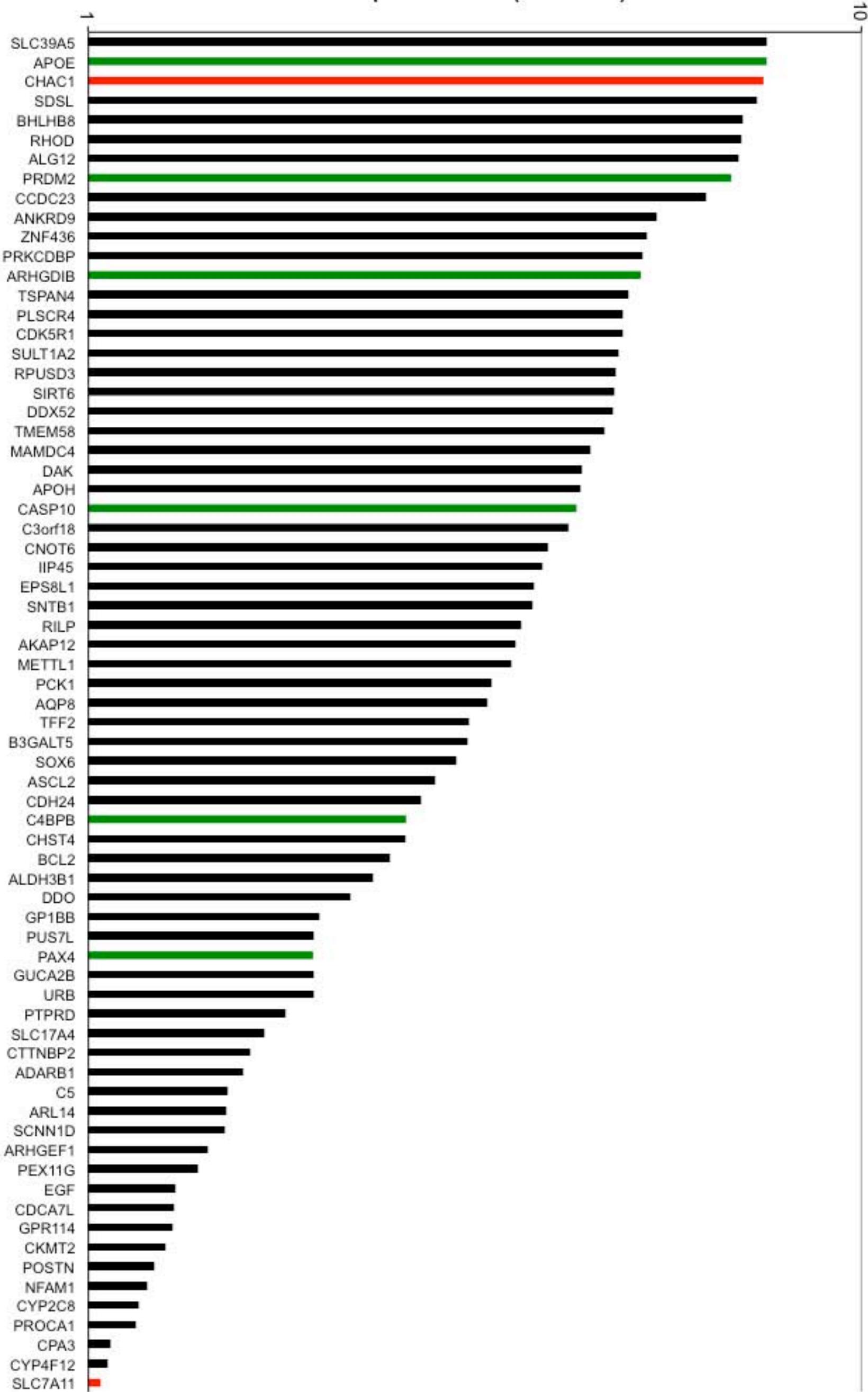
A

Gene expression (RPKM)



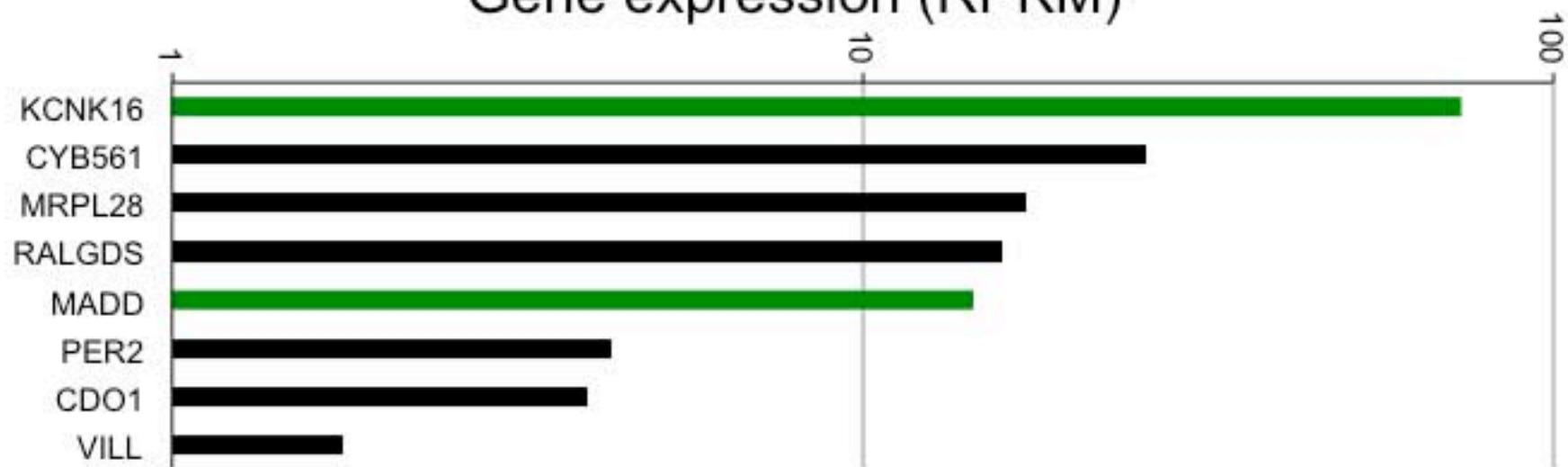
B

Gene expression (RPKM)



C

Gene expression (RPKM)



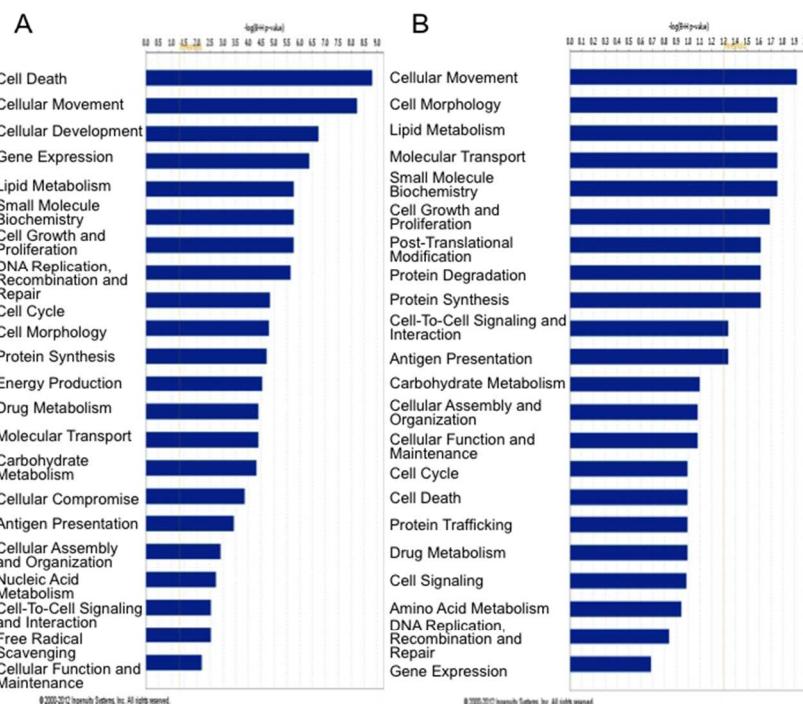


Figure S4: IPA of palmitate-modified genes

(A) 428 genes were significantly upregulated by palmitate in at least 4 out of 5 islet samples, and significantly downregulated in none. These genes were mapped to 417 unique entries in the IPA database and submitted to gene set enrichment analysis based on Benjamini-Hochberg corrected Fisher tests. IPA of these upregulated genes is shown for "Molecular and Cellular Function". (B) 897 genes were significantly downregulated by palmitate in at least 4 out of 5 islet samples, and significantly upregulated in none. They were mapped to 885 unique entries in the IPA database. IPA of these cytokine-downregulated genes is shown for "Molecular and Cellular Function". The length of the blue bars indicates the significance of the association between the set of genes and the keyword, and is expressed as minus the logarithm of the probability that a random set of genes from the human genome would be associated with the same keyword. The straight orange line indicates a threshold of 0.05 (corresponding to a -log(BH p-value) of 1.3).

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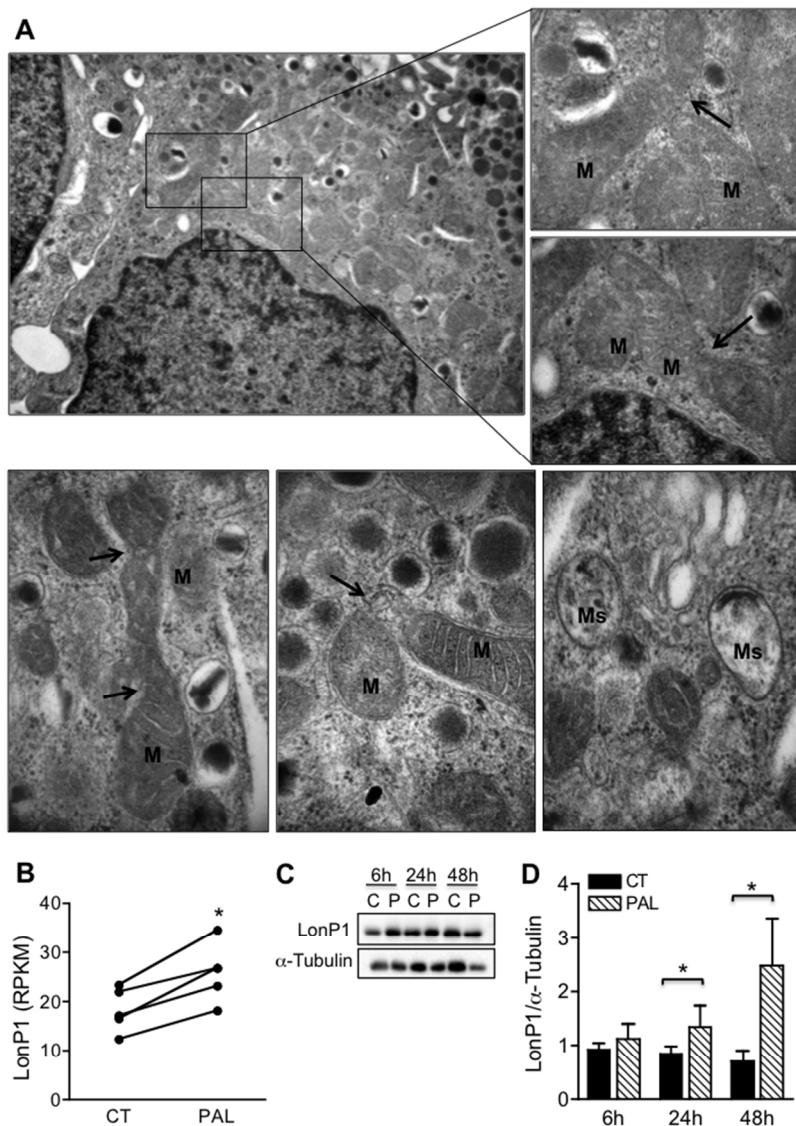


Figure S5: Palmitate alters mitochondrial morphology in human β -cells and induces LonP1 expression
(A) Human islets exposed to palmitate for 48 h were examined by electron microscopy. Mitochondria (M) in β -cells were often elongated with signs of fragmentation (arrows) or they appeared swollen (Ms). Magnification: top panel $\times 21000$, other panels $\times 64000$. (B) LonP1 mRNA expression by RNA-seq in palmitate (PAL)-treated human islets. (C) LonP1 protein expression in INS-1E cells treated or not for 6, 24 and 48 h with 0.5 mM palmitate (P or PAL). (D) Densitometric quantification of Western blots as in panel C, n=2-7 independent experiments, *p<0.05 vs control (C or CT).

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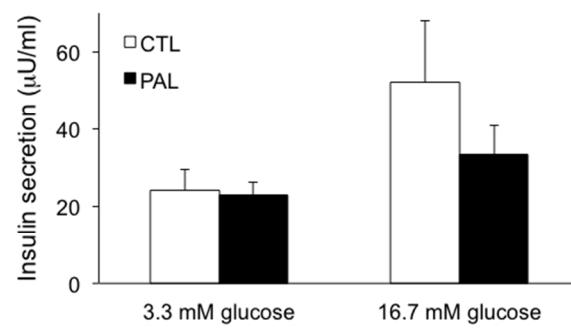


Figure S6: Palmitate impairs human islet glucose-stimulated insulin secretion
Human islets were exposed or not (CTL) to palmitate (PAL) for 48 h. Insulin secretion was measured at 3.3 and 16.7 mM glucose (n=4).
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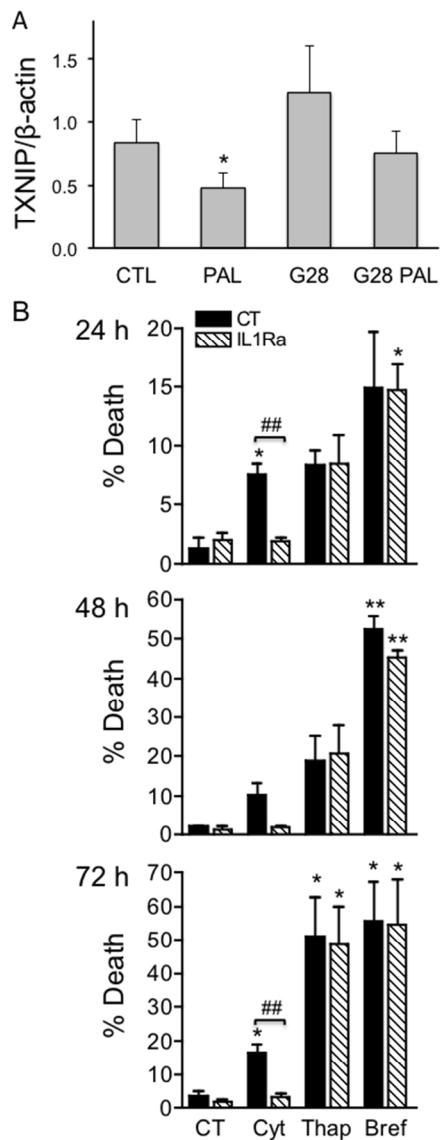


Figure S7: Role of TXNIP and IL-1 β in lipotoxic and chemical ER stress-induced apoptosis
(A) Palmitate inhibited TXNIP mRNA expression in human islets. Human islets were cultured in the presence of palmitate (PAL, 0.5 mM), 28 mM glucose (G28) or the combination of both (G28 PAL) for 48 h. TXNIP mRNA expression was measured by qRT-PCR and normalized to β -actin expression levels ($n=5-7$). * $p<0.05$ vs control (CTL) by ratio t test. **(B)** IL-1 receptor antagonist does not protect human islets from chemical ER stress. Human islets were cultured for 24, 48 and 72 h in the presence of thapsigargin (Thap, 1 μ M) or brefeldin A (Bref, 0.1 μ g/ml) alone or in combination with the IL-1 receptor antagonist (300 ng/ml). The cytokines (Cyt) IL-1 β (50 U/ml) plus IFN- γ (1,000 U/ml) were used as a positive control. Cell death was assessed in 3-5 independent human islet preparations. * $p<0.05$, ** $p<0.01$ vs control (CT), # $p<0.01$ as indicated.

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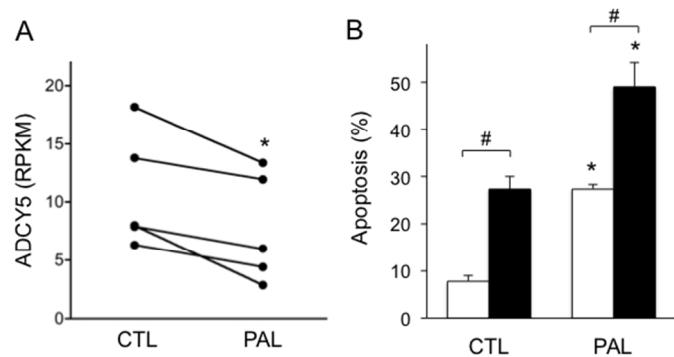


Figure S8: Inhibition of the type 2 diabetes candidate gene ADCY5 triggers β -cell apoptosis
(A) ADCY5 mRNA expression by RNA-seq in palmitate (PAL)-treated human islets. (B) Apoptosis in INS-1E cells transfected with control siRNA (white bars) or ADCY5 siRNA (black bars) and then treated with palmitate for 16 h (n=4). *p<0.05 vs control (CTL), #p<0.05, ##p<0.01 as indicated.
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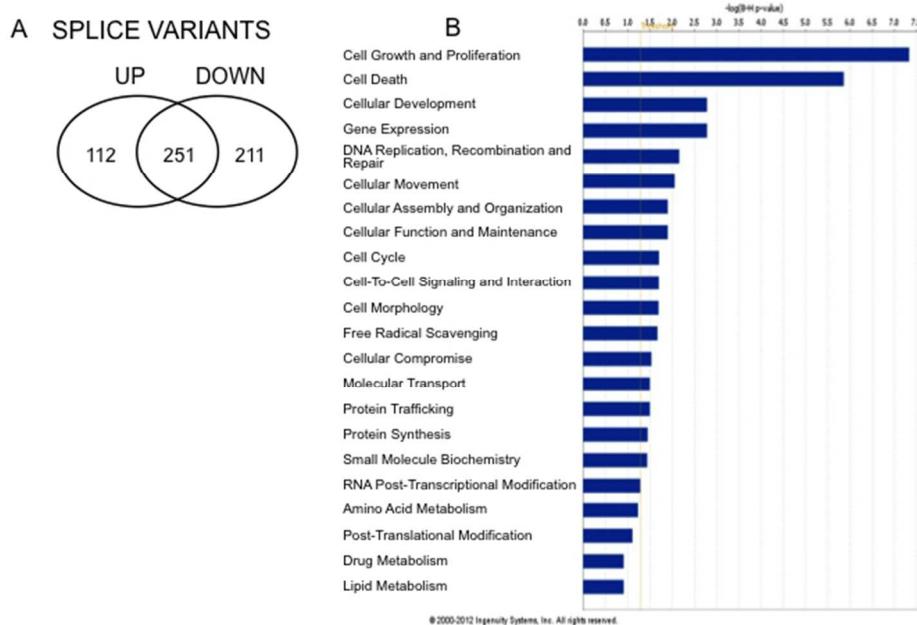


Figure S9: Palmitate-induced changes in alternative splicing according to RefSeq annotation
 (A) Palmitate exposure led to changes in alternative splicing. Using RefSeq annotation, 363 transcripts were significantly upregulated in at least 4 out of 5 islet samples and significantly downregulated in none, and 462 transcripts were significantly downregulated using similar criteria. The Venn diagram illustrates the number of genes which have transcripts modified in both directions (intersection) and in only one direction. (B) IPA of the 574 genes with modified splicing. The length of the blue bars indicates the significance of the association between the set of transcripts and the keyword, and is expressed as minus the logarithm of the probability that a random set of transcripts from the human genome would be associated with the same keyword. The straight orange line indicates a threshold of 0.05 (corresponding to a $-\log(\text{BH } p\text{-value})$ of 1.3).

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