SRp55 regulates a splicing network that controls human pancreatic beta cell function and survival

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ABSTRACT
Progressive failure of insulin-producing beta cells is the central event leading to diabetes, but the signalling networks controlling beta cell fate remain poorly understood. Here we show that SRp55, a splicing factor regulated by the diabetes susceptibility gene GLIS3, has a major role in maintaining function and survival of human beta cells. RNA-seq analysis revealed that SRp55 regulates the splicing of genes involved in cell survival and death, insulin secretion and JNK signalling. Specifically, SRp55-mediated splicing changes modulate the function of the pro-apoptotic proteins BIM and BAX, JNK signalling and endoplasmic reticulum stress, explaining why SRp55 depletion triggers beta cell apoptosis. Furthermore, SRp55 depletion inhibits beta cell mitochondrial function, explaining the observed decrease in insulin release. These data unveil a novel layer of regulation of human beta cell function and survival, namely alternative splicing modulated by key splicing regulators such as SRp55 that may crosstalk with candidate genes for diabetes.

INTRODUCTION
Diabetes is caused by loss and/or functional impairment of insulin-producing pancreatic beta cells. Type 1 diabetes (T1D) and type 2 diabetes (T2D) differ in their genetic background, associated environmental factors and clinical history, but both forms of diabetes show loss of beta cell mass, which is near total in long-term T1D and in the range of 20-50% in T2D (1-3). The mechanisms leading to this decrease in functional beta cell mass remain elusive, which may explain why intervention trials aiming to halt or revert beta loss in diabetes have consistently failed.
Genetic variations in the transcription factor GLIS3 are associated with susceptibility to both T1D and T2D (4, 5). GLIS3 mutations also cause a neonatal diabetes syndrome characterized by neonatal diabetes, congenital hypothyroidism and polycystic kidney (6). Functional studies have shown that GLIS3 regulates beta cell differentiation and insulin transcription (7, 8). We have shown that GLIS3 is also required for adult beta cell survival, increasing basal apoptosis when depleted in rodent and human beta cells and sensitizing these cells to cytokine- and palmitate-induced apoptosis (9). Increased beta cell apoptosis in Glis3-depleted rat beta cells is associated with inhibition of the splicing factor SRp55 (also known as Srsf6), leading to a splicing shift in the pro-apoptotic protein Bim that favours the expression of the most pro-death splice variant Bim S (9).

Alternative splicing (AS) is a key post-transcriptional mechanism in which different combinations of splice sites in the pre-mRNA are selected to generate structurally and functionally distinct mRNA and protein variants. Functionally-related transcript populations are regulated by master splicing factors in coordinated “splicing networks” that modulate cell-, tissue-, or developmental-specific functions (10, 11). Little is known on the role of AS in diabetes, but recent findings from our group indicate that neuron-enriched splicing factors play important roles for beta cell function and survival (12, 13) and that inflammatory and metabolic stresses induce different “AS signatures” in human beta cells (14, 15).

The splicing factor SRp55 has been implicated in wound healing and oncogenesis, acting as an oncoprotein that promotes proliferation, survival and hyperplasia in cancer (16, 17). In the present study, we analysed the global role of SRp55 in beta cell function and survival using human pancreatic islets and the insulin-producing EndoC-βH1 human cell line. We found that SRp55 deficiency leads to increased
beta cell apoptosis, impaired mitochondrial respiration and defective insulin secretion. These findings indicate that SRp55 is a key down-stream mediator of GLIS3 function, suggesting that splicing networks regulated by the cross-talk between master splicing factors and candidate genes may contribute to beta cell dysfunction and death in diabetes.

RESEARCH DESIGN AND METHODS

Culture of human islets and EndoC-βH1 cells

Human islets from non-diabetic donors were isolated in Pisa, Italy, using collagenase digestion and density gradient purification. Islets were cultured at 6.1 mmol/liter glucose as described previously (14). Donor characteristics are described in Table S1. Human insulin-producing EndoC-βH1 cells kindly provided by Dr. R. Sharfmann (Institut Cochin, Université Paris Descartes, Paris, France) were grown on matrigel/fibronectin (100 and 2 µg/mL, respectively) coated plates and cultured in DMEM medium as previously described (18). EndoC-βH1 cells were exposed in some experiments to the human cytokines IL-1β (50 U/ml, R&D Systems, Abingdon, UK) and IFN-γ (1,000 U/ml, Peprotech, London, UK) for 48 h as described (14).

Gene/ splice variant silencing and overexpression

The small interfering RNAs targeting human genes/ splice variants used in this study are described in Table S2; Allstars Negative Control siRNA (Qiagen, Venlo, Netherlands) was used as a negative control (siCTL). Transient transfection was performed using 30nM siRNA and Lipofectamine RNAiMAX (Invitrogen, Carlsbad, CA). A pcDNA FLAG plasmid containing the human cDNA sequence of SRSF6 (SRp55), kindly provided by Prof. Hirokazu Hara (Gifu Pharmaceutical University, Japan), was used to exogenously express SRp55 in EndoC-βH1 cells.
Assessment of Cell Viability

Cell viability was determined using fluorescence microscopy after incubation with the DNA-binding dyes Hoechst 33342 and propidium iodide as described previously (19). Apoptosis was further confirmed in some experiments by immunostaining for cleaved caspase-3.

RNA sequencing

Total RNA was isolated from five independent preparations of EndoC-βH1 cells exposed to control (siCTL) or SRp55 (siSR#2) siRNAs using the RNeasy Mini kit (Qiagen, Venlo, Netherlands). RNA sequencing was performed on an Illumina HiSeq 2000 system as previously described (12, 20). The raw data generated are deposited in Gene Expression Omnibus (GEO) under submission number GSE98485.

RNA sequencing analysis

RNA-seq reads were mapped to the human reference genome GRCh37/hg19 using TopHat 2 (21) and the Gencode annotation dataset. Transcript abundance and differential expression was calculated using Flux Capacitor (22). All genes and transcripts have been assigned a relative expression level as measured in RPKM units (reads per kilobase per million mapped reads). A gene/isoform was considered as expressed if it had a RPKM greater or equal to 0.5. Identification of up- and down-regulated genes was performed by computing the Fisher’s exact test and corrected by the Benjamini-Hochberg method, as previously described (14). A minimum of 17% change (log2 fold change of ±0.23) in the expression level between SRp55 KD and control was considered as “modified expression”.

Alternative splicing events were analysed using rMATS (23). rMATS computes percentage splicing index (PSI) and the false discovery rate (FDR) for 5 different
splicing events: skipped exons, mutually exclusive exons, retained introns, 5’ and 3’ alternative splice site. To be considered significantly changed, the cut-off of 5% on ΔPSI and of 0.01% on FDR were used. Motif enrichment analysis in the vicinity of alternatively spliced exons was performed using rMAPS (24) by comparing the spatial occurrence of two SRp55 motifs (17, 25) between cassette exons whose inclusion is affected by SRp55 KD and non-modified exons showing a FDR ≥50%.

Functional annotation and pathway enrichment analysis of genes presenting splicing and/or gene expression alterations was performed using the DAVID and IPA (Ingenuity Pathway Analysis) platforms (26).

Validation of splicing changes by RT-PCR

The validation of selected alternative splicing changes identified by RNA-seq was performed by RT-PCR using exonic primers (Table S3) encompassing the predicted splicing event. The primers were designed against flanking constitutive exons, allowing to distinguish different splice variants based on fragment size. cDNA amplification was performed using MangoTaq DNA polymerase (Bioline), and PCR products separated using the LabChip electrophoretic Agilent 2100 Bioanalyzer system and the DNA 1000 LabChip kit (Agilent Technologies, Wokingham, UK). The molarity of each PCR band corresponding to a specific splice variant was quantified using the 2100 Expert Software (Agilent Technologies, Belgium), and used to calculate the ratio between inclusion and exclusion of the alternative event.

mRNA Extraction and Quantitative Real Time PCR

Poly(A)+ mRNA was isolated using the Dynabeads mRNA DIRECT kit (Invitrogen, Carlsbad, CA) and reverse transcribed as described (19). Quantitative real-time PCR was performed using SYBR and concentrations calculated as copies/µl using the
standard curve method (27). Gene expression was corrected for the reference gene β-Actin. The primers used are listed in Table S3.

**Western Blot and Immunofluorescence**

For Western blot, cells were washed with cold PBS and lysed in Laemmli buffer. Total proteins were resolved by 8-14% SDS-PAGE, transfected to a nitrocellulose membrane and immunoblotted using specific primary antibodies listed in Table S4. Densitometric values were corrected by the housekeeping protein α-tubulin as loading control, after background subtraction. Double immunostaining was performed as previously described (9).

**Insulin secretion**

EndoC-βH1 cells were pre-incubated with culture medium containing 2.8 mM glucose for 18 h. Cells were incubated in Krebs-Ringer buffer for 1 h and sequentially stimulated with 1 mM glucose, 20 mM glucose, or 20 mM glucose 10 µM forskolin for 40 min, as described (28). Insulin release and insulin content were measured using the human insulin ELISA kit (Mercodia, Uppsala, Sweden) in cell-free supernatants and acid-ethanol extracted cell lysates, respectively. Results were normalized by total protein content.

**Mitochondrial respiration**

Oxygen consumption rates (OCR) of EndoC-βH1 cells were measured using the XFp Extracellular Flux Analyzer (Seahorse Bioscience, North Billerica, MA) as previously described (28). Following transfection, cells were pre-incubated in assay medium containing 1 mM glucose for 1 h at 37°C in air. After that, respiration was measured following sequential injections of 20 mM glucose, 5 µM oligomycin, 4 µM carbonyl cyanide-p-trifluoromethoxy-phenylhydrazone (FCCP) and 1 µM rotenone plus 1 µM antimycin A. All data was normalized with total DNA content.
Statistical analysis

Data are show as means ± SD. Significant differences between experimental conditions were assessed by a paired Student’s t-test or by ANOVA followed by Bonferroni correction as indicated. P-values < 0.05 were considered statistically significant.

RESULTS

SRp55 regulates human beta cell survival

Fluorescence microscopy analysis indicates that SRp55 is highly expressed in pancreatic beta cells (Figure 1A). SRp55 mRNA expression is higher in human pancreatic islets and human insulin producing EndoC-βH1 cells as compared to eight other human tissues (Figure 1B). To study the functional impact of SRp55 depletion on human beta cell survival we silenced SRp55 by using two specific siRNAs in human islets and EndoC-βH1 cells, reaching ≥50% inhibition at both mRNA and protein levels (Figure 1C, 1E and 1F). SRp55 silencing significantly increased beta cell death in both dispersed human islets and in EndoC-βH1 cells (Figures 1D and 1G). The observed increase in cleaved caspase-3 expression in SRp55-depleted cells confirmed that beta cell loss is mediated by apoptosis (Figure 1H and 1I). Next, we analysed whether SRp55 expression is affected by pro-inflammatory cytokines. Exposure of EndoC-βH1 cells to IL-1β + IFN-γ significantly decreased SRp55 protein expression (Supplementary Figure S1A). Overexpression of SRp55 in EndoC-βH1 cells (Supplementary Figure S1B) protected these cells against cytokine-induced apoptosis (Supplementary Figure S1B), suggesting that decreased SRp55 expression may contribute to beta cell death during islet inflammation.
Identification of SRp55-regulated splicing events by RNA-seq

SRp55-regulated splicing events were detected by RNA sequencing of five independent EndoC-βH1 preparations under control conditions or following SRp55 knockdown (KD), obtaining an average coverage of 166 million reads. A total of 8769 AS events modified after SRp55 KD were detected (Figure 2A and Supplementary Table S5). The majority of modified AS events correspond to cassette exons (59%), followed by mutually exclusive exons (22%), alternative 5’ splice site (9%), alternative 3’ splice site (7%), and intron retention (3%) (Figure 2B).

Modified AS events affected 4055 different genes (Table S5). Functional enrichment analysis indicated that genes showing AS changes after SRp55 KD depletion are involved in diverse molecular and cellular functions, including cell cycle, DNA repair and replication, cell death and survival, and cellular function and maintenance (Figure 2C). Enriched pathways included several pathways involved in pancreatic beta cell function, dysfunction and death (Figure 2D), including genes related to type 2 diabetes and insulin secretion, regulation of apoptosis and JNK signalling (Figure 2D).

SRp55 KD had a less marked impact on gene transcription when compared to RNA splicing (Supplementary Figures S2A and S2B). Nevertheless, SRp55 KD modified the expression of 2981 genes, inducing predominantly gene up-regulation (Supplementary Figure S2C and Supplementary Table S6). Of note, 28% of differentially expressed genes also presented changes on alternative splicing (Supplementary Figure S2D). Up-regulated genes were enriched in pathways involved in cell cycle, DNA repair and replication, and MAPK signalling among others (Supplementary Table S6).
SRp55 binding-motif analysis

To study whether alternatively spliced genes are directly regulated by SRp55 and identify spatial patterns of SRp55 binding, we performed an enrichment analysis of the SRp55 binding-motifs. We compared the occurrence of SRp55 motifs between modified cassette exons and exons unaffected by SRp55 silencing. The enrichment of two SRp55 motifs were analyzed: a 6-mer motif identified by SELEX (25), and a 9-mer motif identified by de novo discovery in modified exons after SRp55 overexpression in mouse skin (17) (Supplementary Figure S3A). Significant enrichment for both motifs in exonic regions was found in down-regulated exons (Supplementary Figure S3C and S3D). These results support the notion that SRp55, like most SR proteins (29), acts as a splicing activator, promoting exon inclusion when bound to exonic splicing enhancers (ESE). In line with this, the majority of modified cassette exons (73%) displayed exon-skipping after SRp55 depletion (Supplementary Figure S2B), suggesting that a large proportion of modified splicing events are directly regulated by SRp55. Motif enrichment also indicated that up-regulated events were not directly regulated by SRp55, and probably result from the impact of SRp55 on other splicing regulators, as we previously observed following Nova1 KD (12).

Validation of splicing events

We next used independent EndoC-βH1 samples, different from the ones used for RNA-seq, to confirm SRp55-regulated events. Representative genes of pathways regulating beta cell function and survival were selected for further validation. We used RT-PCR followed by automated electrophoresis analysis, based on primers
that amplify isoforms presenting both inclusion and skipping of alternative fragments
and were able to validate 12 out of 12 AS events tested (Figure 3), indicating a good
reliability of the RNA-seq-generated data.

**SRp55 silencing impairs insulin release and leads to mitochondrial
dysfunction**

SRp55-depleted cells showed impaired insulin secretion at 20 mM glucose and in
the presence of glucose plus forskolin stimulation, but had no changes in insulin
content (Figure 4A and 4B). Insulin release is regulated by ATP generation, and we
next analysed mitochondrial respiration by assessing the oxygen consumption rate
using a Seahorse metabolic analyser. SRp55-depleted EndoC-βH1 cells showed
decreased mitochondrial respiration when compared to control cells, exhibiting lower
basal respiration, impaired ATP production (response to oligomycin) and decreased
maximal respiration (response to FCCP following oligomycin) (Figure 4C-4G),
suggesting that SRp55 silencing-induced mitochondrial dysfunction explains the
observed defective glucose-induced insulin release.

Interestingly, RNA-seq analysis indicated that several transcription factors that
regulate the beta cell phenotype and affect insulin secretion were modified after
SRp55 KD (Figure 4H). This includes up-regulation of **FOXO1** and **NEUROD1**,
genes expressed in poorly differentiated endocrine cells (30), and down-regulation of
**PDX-1** and **NKX6.1**, key transcription factors for the maintenance of a differentiated
beta cell phenotype (31, 32).

**SRp55 contributes to beta cell apoptosis via regulation of the expression of
pro-apoptotic splice variants of BCL-2 proteins**
BCL-2 proteins are a family of apoptotic regulators that play a central role in beta cell survival (33). RNA-seq analysis indicated that SRp55 regulates splicing of the BCL-2 proteins BIM (BCL2L11), BAX and BOK, and related apoptotic proteins DIABLO and BCLAF1 (Figures 2 and 3). We have previously shown that SRp55 KD in rat beta cells increases the expression of the most pro-apoptotic isoform Bim S (contributing to beta cell apoptosis (9). Here we confirmed, at both mRNA and protein level, that SRp55 regulates BIM splicing also in human beta cells, increasing the proportion of BIM S over BIM L after SRp55 depletion (Figure 3B, Supplementary Figure S4A and S4B). There was also an overall increase of BIM isoforms following SRp55 silencing (Supplementary Figure S4A and S4C). To assess the functional role of BIM in SRp55 KD-induced apoptosis, we performed a double KD of SRp55 and BIM (Supplementary Figure S4D-S4F). BIM Inhibition decreased EndoC-βH1 apoptosis to basal levels (Supplementary Figure S4F), indicating that BIM plays a central role in regulating cell death in SRp55-depleted cells, and suggesting that SRp55 depletion triggers the intrinsic or mitochondrial pathway of apoptosis.

SRp55 depletion also affected the splicing of the apoptotic effector protein BAX, leading to increased intron 5 retention (Figures 3A and 5A). Unspliced intron 5 leads to the production of BAX β, a constitutively active isoform that may trigger cell death independent of up-stream signalling (34) (Figure 5B). To test whether alteration of BAX splicing by SRp55 KD contributes to the observed increase in apoptosis, we designed a specific BAX β siRNA and performed single and double knock-down experiments in combination with SRp55 siRNA (Figures 5C-5F). The up-regulation of BAX β following SRp55 KD (Figure 5E) correlated with increased BAX translocation to the mitochondria (Figure 5C) and increased apoptosis (Figure 5F). Prevention of BAX β increase by a specific siRNA in SRp55-depleted cells (Figure 5E) reduced
BAX translocation to the mitochondria (Figure 5C), and protected EndoC-βH1 cells (Figure 5F) and human islets (Figure 5G) against apoptosis, indicating a contributory role for BAX β in the observed phenotype.

**SRp55 depletion affects the JNK signalling pathway leading to pathway hyper-activation and increased beta cell apoptosis**

The JNK pathway has a pro-apoptotic role in pancreatic beta cells (35, 36). RNA-seq analysis indicated that SRp55 KD affects the splicing of several members of the JNK pathway (Figures 2D, 3E-3G and 6A). Moreover, several JNK signalling genes are up-regulated following SRp55 silencing (Supplementary Table S6). To understand how these alterations affect the JNK pathway activity, we first analysed the phosphorylation state of the kinases MKK7 and JNK1, and the target transcription factor c-JUN. We observed that MKK7, JNK1 and c-JUN are hyper-phosphorylated in SRp55-depleted cells, while no changes in total protein levels were observed for MKK7 and JNK1 (Figure 6B). We hypothesized that splicing alterations in JNK-related signalling genes alter the pathway activity contributing to increase beta cell death. To test this, we first performed a double KD of JNK1 and SRp55 KD. Inhibition of JNK1 in both EndoC-βH1 cells and human islets protected them against SRp55 KD-induced apoptosis (Figure 6C-F). Next, we mimicked the impact of SRp55 depletion on the splicing of three JNK signalling kinases (MAP3K7, JNK1 and JNK2) by using specific siRNAs against the SRp55-modified cassette exons in these genes. These siRNAs significantly increased the skipping of the cassette exons, recapitulating the effect of SRp55 KD (Figures 6G-I). Interestingly, increased exon skipping in all three JNK-related genes was associated with increased apoptosis (Figure 6J) and JNK hyper-phosphorylation (Figure 6K) in EndoC-βH1 cells. This
supports the hypothesis that splicing alterations induced by SRp55 KD lead to hyper-activation of the JNK-regulated pathway and contribute to beta cell death.

**SRp55 depletion induces endoplasmic reticulum stress**

RNA-seq analysis showed that several genes of the endoplasmic-reticulum-associated protein degradation (ERAD) pathway displayed alternative splicing alterations after SRp55 depletion, and that some ER stress markers were up-regulated at gene expression level (Figure 7A). These findings suggested that reduced SRp55 levels affect the ER function and may contribute to increase beta cell apoptosis. In order to test this hypothesis, we analysed the expression of several ER stress markers at protein and mRNA level. Increased levels of phosphorylated and total IRE1α (Figure 7B and 7C), and phospho-eIF2α (Figure 7B and 7E) were observed following SRp55 silencing. Moreover, induction of BIP (Figure 7F) and XBP1 spliced (Figure 7G) mRNAs was detected by qPCR, indicating that SRp55 deficiency may directly or indirectly lead to ER stress. No significant changes, however, were observed for phosphorylated and total PERK, and CHOP (Figure 7D and 7H). In order to determine whether ER stress indeed contributes to SRp55 KD-induced apoptosis, we performed a double knock down experiment of IRE1α and SRp55 (Figure 7I and 7J). IRE1α silencing protected EndoC-βH1 against cell death induced by SRp55 deficiency (Figure 7K), demonstrating that defects in ER homeostasis and consequent ER stress promote apoptosis in SRp55-depleted cells.

**DISCUSSION**

The present findings indicate that SRp55 drives a crucial splicing program for the preservation of human pancreatic beta cell survival and function. SRp55 is highly
expressed in human pancreatic beta cells, and its depletion leads to beta cell apoptosis and impaired insulin secretion. SRp55 levels are down-regulated by pro-inflammatory cytokines and may contribute to cytokine-induced beta cell apoptosis. These observations suggest that SRp55 acts as a master splicing regulator of beta cell survival under both basal and immune-induced stress conditions. In line with these observations, SRp55 regulates AS of multiple transcripts involved in cell death, JNK signalling, insulin secretion and ER stress, providing a mechanistic link between the observed phenotype and SRp55 targets.

Our group has previously shown that SRp55 is transcriptionally regulated by the transcription factor Glis3 (9). The GLIS3 locus is associated with T1D and T2D (4, 5), with glucose metabolism traits in non-diabetic subjects (37) and its inactivation leads to a severe form of monogenic diabetes in humans (6, 38). GLIS3 is also required for beta cell survival (9), and defective Glis3 expression affects the unfolded protein response promoting beta cell fragility (39). We presently observed that decreased SRp55 expression recapitulates many of the pathological features induced by GLIS3 deficiency, i.e. increased beta cell apoptosis, defective insulin release and ER stress, suggesting that SRp55 may acts as an important down-stream mediator of GLIS3 function.

The function of many BCL-2 proteins and other apoptotic regulators is modulated by AS, producing variants that differ in their localization, post-translation regulation or pro-apoptotic activity (40, 41). Our RNA-seq analysis revealed that SRp55 regulates several genes involved in pancreatic beta cell apoptosis, including several BCL-2 proteins. Importantly, SRp55 depletion affects the splicing of the apoptotic activator BAX, promoting the expression of the constitutively active isoform BAX β. The canonical isoform BAX α contains a C-terminal transmembrane domain tucked into
the dimerization pocket that maintains BAX α in an auto-inhibited monomeric conformation in the cytosol. Following pro-apoptotic signalling, BH3-only activators such as BIM and PUMA induce a conformational change on BAX α promoting its oligomerization, translocation to the mitochondria, permeabilization of the outer membrane, and activation of apoptosis (42). BAX β, on the other hand, retains intron 5, creating a distinct C-terminal domain that maintains it in a permanently activated conformation, leading to its spontaneous oligomerization and activation of apoptosis (34). In addition, BAX β can also act as a BH3-only activator, being able to activate BAX α (34). BAX α may also be activated by BIM S (43), presently shown to be induced by SRp55 KD. The fact that independent KD of BAX β or BIM nearly completely prevents the increase in beta cell apoptosis observed following SRp55 KD suggest that both mechanisms are required to trigger the intrinsic pathway of apoptosis under the present experimental conditions.

Interestingly, our data indicate that SRp55 regulates two other pathways potentially involved in beta cell death in cross-talk with BCL-2 proteins, namely the JNK signalling cascade and ER stress. The JNK pathway has a pivotal role in integrating different stress signals and in promoting beta cell death (33, 44, 45). JNK1 signalling stimulates transcription and activity of pro-apoptotic BCL-2 proteins through activation of the transcription factor c-JUN and via direct phosphorylation (33). Moreover, the JNK pathway is also activated by endoplasmic reticulum stress via the transmembrane protein IRE1α (46). Different JNK splice variants may differ in their enzymatic activities, substrates and activation/deactivation kinetics (47, 48). For instance, a single splice change in MKK7 is able to increase the JNK pathway activity in T-cells (49). SRp55 depletion affects the splicing of several kinases of the JNK signalling cascade (present data). These findings indicate that some of these
changes modify the basal activity of the pathway, leading to JNK hyper-activation and contributing to beta cell to apoptosis. JNK hyper-activation may also be secondary to the unfolded protein response (UPR) via IRE1α signalling (46). We presently observed that SRp55 silencing induces basal endoplasmic reticulum stress. The mechanisms by which SRp55 deficiency triggers ER stress remains to be clarified, but splicing alterations in ER-associated protein degradation genes suggest that the ER function may be compromised via defective disposal of terminally misfolded proteins.

Reduced SRp55 expression also leads to impaired insulin release. Insulin exocytosis is tightly coupled to glucose metabolism, requiring mitochondrial ATP production to induce the closure of $K_{ATP}$ channels and the generation of $Ca^{2+}$ influx that ultimately triggers the release of insulin (50). Our present findings suggest that impaired glucose-induced insulin release is related to mitochondrial dysfunction. Furthermore, SRp55 silencing modifies expression of genes and splice variants related to metabolic pathways, exocytosis and calcium signalling, all potentially impacting on the regulation of insulin secretion. The findings described above are, however, correlative and the precise mechanisms by which SRp55 depletion impairs beta cell function remain to be clarified.

In conclusion, the present observations indicate that SRp55 coordinates a splicing network of functionally interconnected genes in beta cells. These genes are required for beta cell survival and functional phenotype. This suggests that alterations in SRp55 – for instance downstream of polymorphisms that decrease activity of the diabetes candidate gene $GLIS3$ – may promote beta cell failure and loss in diabetes.

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DUALITY OF INTERESTS
The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS
J.J-M., M.I.A. and D.L.E. conceived and designed the experiments. J.J-M., M.I.A., J.-V.T, O.V., E.L-M., F.A.G. and L.M. acquired data. M.B. and P.M. contributed with material and reagents. J.J-M, M.I.A and D.L.E. wrote the manuscript. All authors
revised the manuscript. J.J.M. and D.L.E. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**FIGURE LEGENDS**

Figure 1. SRp55 is highly expressed in human pancreatic beta cells and its depletion leads to increased beta cell apoptosis. **(A)** Fluorescence microscopy analysis of insulin and SRp55 in human islets (left panel) and in the human beta cell line EndoC-βH1 (right panel), showing staining of SRp55 in red, insulin in green and nuclei in blue. **(B)** mRNA expression of SRp55 in human islets, EndoC-βH1 cells and in a panel of normal human tissues was measured by qRT-PCR and normalized by the housekeeping gene β-actin. **(C-D)** Human islets were transfected with control (siCTL) or specific siRNAs against SRp55 (siSR#1 and siSR#2) for 48h. **(C)** SRp55 knock-down levels were assessed by qRT-PCR, and **(D)** apoptosis evaluated by
Hoechst/PI staining. (E-I) EndoC-βH1 cells were transfected with control or specific siRNAs against SRp55 for 48h. SRp55 knock-down levels were assessed by qRT-PCR (E) and by western blot (F). Apoptosis of EndoC-βH1 cells following SRp55 KD was evaluated by Hoechst/PI staining (G) and by cleaved caspase 3 immunofluorescence (H, I). Scale bars, 1 µm. Results are mean ± SEM of three to nine independent experiments. *p < 0.05, **p < 0.01 and ***p < 0.001 vs. siCTL. Paired t-test.

**Figure 2. RNA sequencing of EndoC-βH1 cells following SRp55 depletion.** (A) Pairwise comparison of control versus SRp55 KD EndoC-βH1 cassette exons shown as a volcano plot. Alternative splicing events presenting a difference of percent spliced index (ΔPSI) higher than 5% and a FDR ≤0.01% were considered modified as indicated by doted lines. (B) Number and proportion of the different alternative splicing events modified after SRp55 silencing as identified by rMATS analysis. (C) Ingenuity pathway analysis of genes showing differential alternative splicing (enhanced or inhibited) subsequent to SRp55 depletion. (D) Heat-maps showing genes enriched with Gene Ontology terms involved in cell survival and beta cell function. PSI values are represented by gradient colours and shown for each individual control and SRp55 KD sample. Red, higher PSI; blue, lower PSI. Results are based on five RNA-seq samples.

**Figure 3. Confirmation of SRp55-regulated splicing events.** Representative RT-PCR validations of SRp55-regulated alternative splicing events. cDNAs were amplified by RT-PCR using primers located in the up-stream and down-stream exons of the modified splicing event. PCR fragments were analysed by automated
electrophoresis using a Bioanalyzer machine and quantified by comparison with a loading control. For each gene, representative gel images showing different splice variants affected by SRp55 KD and the corresponding inclusion/exclusion ratio are shown. The structure of each isoform is indicated with blocks representing exons and solid lines introns. Alternatively spliced regions are indicated in red, green or blue. Results are mean ± SEM of three to eight independent experiments. *p < 0.05, **p < 0.01 and ***p < 0.001 vs. siCTL. Paired t-test.

Figure 4. SRp55 depletion impairs insulin secretion and mitochondrial respiration. A) Insulin secretion in EndoC-βH1 cells was evaluated by ELISA after 1 h stimulation with 1 mM glucose, 20 mM glucose or 20 mM glucose plus forskolin. Here and below, black bars indicate transfection with control siRNA and white bars with siRNA against SRp55. B) Insulin content after SRp55 KD was evaluated by ELISA. C-G) Analysis of mitochondrial respiration parameters in EndoC-βH1 cells using a Seahorse oximeter. C) Oxygen consumption rates (OCR) profiles of control and SRp55 KD cells in basal conditions (1 mM glucose) and after sequential treatment with glucose (20 mM), oligomycin (5 μM), FCCP (4 μM) and rotenone plus antimycin A (1 μM each). Injection of different compounds is indicated by arrows. D) Basal respiration (1 mM glucose), calculated by subtracting non-mitochondrial respiration to the last measurement before 20 mM glucose injection. E) Response to high glucose, calculated by subtracting the last basal respiration measurement to the last measurement after injection of 20 mM glucose. F) ATP production, calculated by subtracting the minimum measurement after oligomycin injection to the last measurement after glucose injection. G) Maximal respiration, calculated by subtracting non-mitochondrial respiration to the maximum measurement after FCCP
injection. **H** mRNA expression of transcription factors regulating beta cell identity and phenotype. In the upper panel RNA-seq expression values in RPKM are shown and in the lower panel confirmation by qRT-PCR normalized by the housekeeping gene β-actin are indicated. Results are means ± SEM of three to nine experiments. *p < 0.05, **p < 0.01 and ***p < 0.001 vs. siCTL. **A** ANOVA followed by Bonferroni post hoc test. **B and D-H** Paired t-test.

Figure 5. SRp55 controls the expression of a constitutively active isoform of the apoptotic inducer BAX contributing to increased beta cell apoptosis. **A** Schematic representation of BAX isoforms α and β, and RNA-seq reads in control and SRp55 KD cells mapping to the distal part of the gene. Boxes represent exons; grey are untranslated regions and black are coding regions. Solid lines represent introns. **B** Model of activation of apoptosis by BAX α and BAX β isoforms proposed by Fu and colleagues (35). Upon apoptotic signalling, BH3-only molecules such as BIM activate BAX α to promote its translocation and oligomerization to the mitochondria outer membrane, leading to cytochrome c release and activation of apoptosis. On the other hand, BAX β spontaneously targets, oligomerizes, and permeabilizes mitochondria, behaving as a constitutively active isoform. Double KD of SRp55 and BAX β in EndoC-βH1 cells (C-F) and in human islets (G). Cells were transfected with siCTL, siSRp55#2, siBaxβ or siSRp55#2 + siBaxβ for 48 h. **C** Fluorescence microscopy analysis of BAX and the mitochondrial marker ATP synthase in EndoC-βH1 cells, showing that SRp55 KD leads to increased translocation of BAX to the mitochondria, a phenomenon prevented by BAX β silencing. Scale bars, 1 µm. mRNA expression of SRp55 (D) and BAX β (E) was measured by qRT-PCR and normalized by the housekeeping gene β-actin. mRNA
expression values were normalized by the highest value of each experiment, considered as 1. **F**) Proportion of apoptotic cells in EndoC-βH1 cells. **G**) Proportion of apoptotic cells in dispersed human islets. Results are mean ± SEM of four to five independent experiments. *p < 0.05, **p < 0.01 and ***p < 0.001 vs. siCTL; #p < 0.05, ##p < 0.01 and ###p < 0.001 as indicated by bars. ANOVA followed by Bonferroni post hoc test.

**Figure 6. SRp55 modifies the splicing of JNK signalling cascade genes leading to JNK1 hyper-activation and beta cell apoptosis. A**) Schematic representation of the JNK signalling pathway. In blue, proteins showing splicing alterations detected by RNA-seq following SRp55 KD are shown. In red, proteins exhibiting overphosphorylation upon SRp55 depletion are shown. **B**) Representative western blots and densitometric measurements of total and phosphorylated forms of MKK7, JNK1 and c-JUN in EndoC-βH1 cells in control conditions and after SRp55 KD. Double KD of SRp55 and JNK1 in EndoC-βH1 cells (C-E) and in human islets (F). Cells were transfected with siCTL, siSRp55#2, siJNK1 or siSRp55#2 + siJNK1 for 48 h. mRNA expression of SRp55 (C) and JNK1 (D) was measured by qRT-PCR and normalized by the housekeeping gene β-actin. mRNA expression values were normalized by the highest value of each experiment, considered as 1. **E**) Proportion of apoptotic cells in EndoC-βH1 cells. **F**) Proportion of apoptotic cells in dispersed human islets. **G-K**) Specific KD of three SRp55-regulated spliced variants of the JNK cascade. EndoC-βH1 cells were transfected with siCTL, siSRp55#2 or specific siRNAs targeting cassette exons of MAP3K7 (exon 12, siMAP3K7e12), JNK1 (exon 3, siJNK1e3) and JNK2 (exon 2, siJNK2e2). **(G-I**) Representative RT-PCR validations showing increased exon skipping in MAP3K7 (G), JNK1 (H) and JNK2 (I).
J) Percentage of apoptotic cells, and (K) JNK phosphorylation after SRp55 KD or skipping of MAP3K7, JNK1 and JNK2 cassette exons. Results are mean ± SEM of four to five independent experiments. *p < 0.05, **p < 0.01 and ***p < 0.001 vs. siCTL; ##p < 0.01 and ###p < 0.001 as indicated by bars. B, G-K) Paired t-test. C-F) ANOVA followed by Bonferroni post hoc test.

Figure 7. SRp55 KD-induced endoplasmic reticulum stress contributes to beta cell demise. A) Heat map showing alternative splicing and gene expression changes in genes involved in ER-associated protein degradation process (upper panel) and markers of the unfolded protein response (lower panel). Red, higher and blue, lower expression. B-E) Representative western blots and densitometric measurements of total and phosphorylated forms of IRE1α (C), PERK (D) and eIF2α (E). mRNA expression of BIP (F), XBP1 spliced (G) and CHOP (H) after SRp55 KD was measured by qRT-PCR and normalized by the housekeeping gene β-actin. I-K) Double KD of SRp55 and IRE1α in EndoC.βH1 cells. Cells were transfected with siCTL, siSRp55#2, siIRE1α or siSRp55#2 + siIRE1α for 48 h. mRNA expression of SRp55 (I) and IRE1α (J) was measured by qRT-PCR and normalized by the housekeeping gene β-actin. mRNA expression values were normalized by the highest value of each experiment, considered as 1. K) The proportion of apoptotic cells was evaluated by Hoechst/PI staining. Results are mean ± SEM of four to nine independent experiments. *p < 0.05, **p < 0.01 and ***p < 0.001 vs. siCTL; #p < 0.05 and ###p < 0.001 as indicated by bars. C-H) Paired t-test. I-K) ANOVA followed by Bonferroni post hoc test.
FIGURE 1

A

Human islets EndoC-βH1

SRp55
Insulin
Hoechst
Merge

C

SRp55/β-actin

siCTL
siSR#1
siSR#2

% apoptosis

D

SRp55/β-actin

% apoptosis

E

SRp55/tubulin

% C-casp3 positive cells

F

G

H

Cleaved Caspase 3 Merge

siCTL
sSR#2

I

% C-casp3 positive cells
FIGURE 2

A

-\log_{10} p-value

\Delta PSI

-log10 p-value

0.5

0

-0.5

-1.0

B

Alternative 5' ss, 781, 9%

Alternative 3' ss, 665, 7%

Cassette exons, 5269, 59%

Intron retention, 278, 3%

Mutually exclusive exons, 1970, 22%

C

| Molecular and Cellular Functions                     | P-value range      | # Genes |
|-----------------------------------------------------|--------------------|---------|
| Cellular Assembly and Organization                 | 5.28E-03 – 8.07E-12 | 754     |
| Cellular Function and Maintenance                  | 4.94E-03 – 1.08E-11 | 723     |
| Cell Cycle                                          | 5.47E-03 – 5.17E-09 | 582     |
| DNA Replication, Recombination and Repair           | 4.14E-03 – 5.17E-09 | 368     |
| Cell Death and Survival                             | 5.47E-03 – 3.45E-08 | 580     |

D

Type 2 diabetes

Positive regulation of apoptotic process

Insulin secretion

JNK signalling cascade
FIGURE 3

A. BAX

B. BCL2L11

C. DIABLO

D. INSR

E. JNK2

F. MAP3K7

G. JNK1

H. SMARCC2

I. DNM2

J. SNAP25

K. CACNA2C

L. CACNA1D

[Diagrams showing various gene expression levels for different conditions and controls.]
FIGURE 5

A

BAX α  
BAX β

B

C

siCTL  siSR#2  siBaxβ  siSR#2 + siBaxβ

BAX

ATP synthase

MERGE

D

E

F

G

SRp55/β-actin

Bax/β-actin

% apoptosis

% apoptosis

Diabetes
**FIGURE 7**

A

Alternative splicing

Log PSI

-3 0 3

Gene expression

Log RPKMI

-3 0 3

B

siCTL siSR#2

p-IRE1α

IRE1α

tubulin

siCTL siSR#2

p-PERK

PERK

tubulin

siCTL siSR#2

p-eIF2α

eIF2α

tubulin

C

p-IRE1α / IRE1α

siCTL

siSR#2

D

p-PERK / PERK

PERK / tubulin

E

p-eIF2α / eIF2α

eIF2α / tubulin

F

BIP / β-actin

G

XBP1 spl / β-actin

H

CHOP / β-actin

I

SRp55 / β-actin

J

IRE1α / β-actin

K

% apoptosis

siCTL

siSR#2

siIRE1α #1

siSR#2+siIRE1α #1
SUPPLEMENTARY FIGURE S2

A. Scatter plot showing the relationship between siCTL and siSR#2 log2 RPKM.

B. Scatter plot showing the relationship between siCTL and siSR#2 log2 RPKM.

C. Bar chart showing the number of differentially spliced genes.

D. Venn diagram illustrating the overlap of differentially spliced and expressed genes.

- 4055 differentially spliced genes
- 841 differentially expressed genes
- 2981 genes co-expressed and spliced

Diabetes
SUPPLEMENTARY FIGURE S3

A

B

C

D

SUPPLEMENTARY FIGURE S3

A

B

C

D
SUPPLEMENTARY FIGURE S4

A

siCTL  siSR#2
BIM L
BIM S
tubulin

B

siCTL    siSR#2

Bim S/Bim L

C

siCTL    siSR#2

total Bim/tubulin

D

SRp55/β-actin

0.0  0.4  0.8  1.2

F

Bim S/β-actin

0.0  0.4  0.8  1.2

G

% apoptosis

0  5  10  15  20  25

- siCTL- siSR#2- siBim- siSR#2 + siBim

*  ***  ###  ###
### SUPPLEMENTAL DATA

### SUPPLEMENTARY TABLE AND FIGURE LEGENDS

**Supplementary Table S1. Characteristics of the organ donors and human islet preparations used.**

| ID  | Gender | Age (years) | BMI (kg/m²) | Cause of death | Purity (%) |
|-----|--------|-------------|-------------|----------------|------------|
| ID1 | M      | 69          | 25          | CVD            | 85         |
| ID2 | M      | 85          | 25.5        | CH             | 39         |
| ID3 | M      | 59          | 27.7        | TR             | 56         |
| ID4 | F      | 76          | 19.5        | CH             | 35         |
| ID5 | F      | 64          | 23.4        | CH             | 76         |
| ID6 | M      | 42          | 32.6        | TR             | 36         |
| ID7 | M      | 78          | 23.4        | TR             | 43         |
| ID8 | F      | 63          | 27.3        | ST             | 58         |
| ID9 | F      | 63          | 26          | CH             | 45         |

The abbreviations used are as follows: F, female; M, male; BMI, body mass index; CVD, cardiovascular disease; CH, cerebral hemorrhage; TR, trauma; ST, stroke. Purity indicates the percentage of beta cells in the human islet preparations as determined by immunostaining for insulin.

**Supplementary Table S2. Sequences of siRNAs used to knock down gene expression.**

| Name | Supplier | Sequence |
|------|----------|----------|
| siCTL (Allstars Negative Control siRNA) | Qiagen, Venlo, Netherlands | Not provided |
| siSRp55#1 Silencer Select siRNAi | Invitrogen, Pasley, UK | 5’GCGUCUACAUAGGACGCUGACUA 3’ |
| siSRp55#2 Silencer Select siRNAi | Invitrogen, Pasley, UK | 5’CCUGUUCGUACAGAAUCAGCCGCUUA3’ |
| siBAXβ Custom designed | Dharmacon, Lafayette, USA | Sense 5’ UCGCUAUGUGUCGAGCAGUUU 3’ Antisense 5’ AACCUGGGCAACAUAGCGAUU 3’ |
siBIM Silencer Select
siRNAi Invitrogen, Pasley, UK 5’ ACGAAUGGUUAUCUUACGACUGUU 3’
siJNK1 Silencer Select siRNAi Invitrogen, Pasley, UK 5’GGGCCUACAGAGCUAGUUCUUAU3’
siRE1α Silencer Select siRNAi Invitrogen, Pasley, UK 5’CCCACCACCGUGGACACUUU3’
siMAP3K7e12 Custom designed Dharmacon Sense 5’ UGGAUGUCCUGAGAUCGUU 3’
Antisense 5’ ACAGUCUCAGGGACACAGUAAU 3’
siJNK1e3 Custom designed Dharmacon Sense 5’ UCACAGAGGAAGCAUCAUU 3’
Antisense 5’ UGAUGCUUUACCUCUGGAU 3’
siJNK2e2 Custom designed Lafayette, USA Sense 5’ AGUGUCUCAGGGACACAGUAAU 3’
Antisense 5’ UAACGUUCAAGGGUCAAGACUUAU 3’

Supplementary Table S3. Sequences of primers used for splicing analyses and real time.

| Gene       | Target | Application | Forward (5’-3’)                          | Reverse (5’-3’)                          |
|------------|--------|-------------|-----------------------------------------|-----------------------------------------|
| BAX        | SPL    | AGCAAACTGGTGCTCAAGG | CGTCCAAAGTAGAGAGAGGA                  |
| BIM        | SPL    | ATGGCAAAGCAACCTTCTG | CTCCTGCAATAGTAAGCGT                  |
| SMARCC2    | SPL    | CGACTGAAACCCCAAGAGTA | CCTCGTCTGCCCATCAGA                  |
| DNM2       | SPL    | CCCCGGACTTGGCATTCGAG | CTGGTACACTGCTAAGCTG                   |
| SNAP25     | SPL    | CGTGTGGAAGAGCAGAACC | GAACATTGAAAAGGCCACACG                 |
| CACNA2D1   | SPL    | GTGTGATGGGAGTAGATGTGC | CATTCTCTAACTCGCATC                  |
| CACNA1D    | SPL    | GCCTCAGAGAAGGTTCCAGTG | AGTGGGGGTTCCCTGAATAAG                 |
| MAPK9      | SPL    | GCAAGTGGCGACTCAACTT | TTTGTTGTTAACACATTTACAAAA              |
| MAP3K7     | SPL    | GTGGGAGCAGTGTTGAGAG | TGGACAGTTTCTGTCTTACGTT                |
| MAPK8      | SPL    | CGCTCTTCTGGTAGATTTT | CTTTGAGCTCTGACGGCTAT                 |
| DIABLO     | SPL    | CGCTCTGGAAGAGTTGGCTG | CTCCTGAATTCTTTTCCAAG                  |
| INSR       | SPL    | TGAAGATTACCTGCACAGC | GAGAAGTGTGGGGAAGAC                  |
| ACTB       | qRT    | CTGTACGCAAACGACAGT | GCTAGAGGAGGACATGATC                  |
| SRSF6      | qRT    | CATAGAGCAGTGGCTACA | TGCCCTACGACTCTAGAAAC                  |
| FOXO1      | qRT    | CGTGCGCTACTTTGAGAT | CAGAATGAAAATTGCGTAG                     |
| NEUROD1    | qRT    | CATACCTGCTAGGACTACT | CCACTCCTCGCTAGATTT                   |
The abbreviations used are as follows: SPL, primers used to analyse splicing variants; qRT, primers used for real time qRT-PCR;

**Supplementary Table S4.** Antibodies used for Western blotting and immunofluorescence are listed.

| Antibodies                  | Source                          | Identifier | Dilution |
|-----------------------------|---------------------------------|------------|----------|
| Insulin (mouse)             | Sigma-Aldrich, Bornem, Belgium  | I2018      | IHC: 1:500 |
| SRSF6/ SRp55 (rabbit)       | LifeSpan Bioscience             | LS-B5712   | IHC: 1:500 |
| SAPK/JNK (mouse)            | Cell Signaling Technology       | 9251S      | WB: 1:1000 |
| JNK1 (mouse)                | Cell Signaling Technology       | 3708S      | WB: 1:1000 |
| Phospho-JNK (rabbit)        | Cell Signaling Technology       | #9251      | WB: 1:1000 |
| MKK7 (rabbit)               | Cell Signaling Technology       | #4172      | WB: 1:1000 |
| Phospho-MKK7 (rabbit)       | Merck Millipore                 | 36-013     | WB: 1:1000 |
| c-JUN (rabbit)              | Cell Signaling Technology       | #9165      | WB: 1:1000 |
| Phospho-c-JUN (rabbit)      | Cell Signaling Technology       | #9164      | WB: 1:1000 |
| eIF2α (rabbit)              | Cell Signaling Technology       | #5324      | WB: 1:1000 |
| Phospho-eIF2α (rabbit)      | Cell Signaling Technology       | #3597      | WB: 1:1000 |
| PERK (rabbit)               | Cell Signaling Technology       | #3192      | WB: 1:1000 |
| Phospho-PERK (rabbit)       | Cell Signaling Technology       | #3179      | WB: 1:1000 |
| Phospho-IRE1α (rabbit)      | Novusbio, Littleton, USA        | NB100-2323 | WB: 1:500  |
Supplementary Table S5. Alternative splicing events modified by SRp55 depletion in EndoC-βH1 cells. List of modified cassette exons (S5.1), mutually exclusive exons (S5.2), alternative 3’ splice sites (S5.3), alternative 5’ splice sites (S5.4) and retained introns (S5.5). For each event the genomic coordinates, gene name and difference in PSI (ΔPSI) are indicated. S5.6) List of gene ontology (biological process) enriched terms in all alternatively-spliced genes. S5.7) List of KEGG enriched pathways in all alternatively-spliced genes.

Supplementary Table S6. Genes modified by SRp55 depletion in EndoC-βH1 cells. S6.1) List of down-regulated genes. Median RPKM expression for each condition and log2 fold change are indicated. S6.2) List of gene ontology (biological process) enriched terms in down-regulated genes. S6.3) List of KEGG enriched pathways in down-regulated genes. S6.4) List of up-regulated genes. Median RPKM expression for each condition and log2 fold change are indicated. S6.5) List of gene ontology (biological process) enriched terms in up-regulated genes. S6.6) List of KEGG enriched pathways in up-regulated genes.
Supplementary Figure 1. SRp55 is down-regulated by pro-inflammatory cytokines and this contributes to cytokine-induced beta cell death. A) Representative western blot and densitometric measurements showing the expression of SRp55 in EndoC-βH1 cells non-treated (NT) or following a 48 h exposure to IL-1β + IFN-γ (cytokines). B and C) EndoC-βH1 cells were transfected with an empty vector (pFLAG) or a vector expressing SRp55 (pSRp55). After transfection, cells were left untreated or exposed to IL-1β plus IFN-γ for 48 h. B) SRp55 protein expression was evaluated by Western-blot. Expression values were normalized by the highest value of each experiment, considered as 1. C) Apoptosis was evaluated by Hoechst/PI staining. Results are mean ± SEM of three to six independent experiments. A) *p < 0.05 non-treated (NT) vs cytokines by paired t test. B and C) **p < 0.01 pFLAG vs pSRp55 under non-treated conditions, ###p<0.001 pFLAG vs pSRp55 under cytokines exposure, and &&&p<0.001 as indicated by a bar by ANOVA followed by Bonferroni post hoc test.

Supplementary Figure 2. Impact of SRp55 depletion on alternative splicing as compared to gene expression. A) Expression profiles of splice variants in control versus SRp55-KD cells. B) Expression profiles of genes in control versus SRp55-KD cells. C) Number of up- and down-regulated genes following SRp55 silencing. D) Venn diagram showing the overlap between differentially spliced and differentially expressed genes. Results are based on five independent experiments.

Supplementary Figure 3. Enrichment analysis of SRp55 binding-motifs in modified cassette exons. A) Position weight matrices of SRp55 binding-motifs identified by SELEX (6-mer on the upper side) and by de novo prediction after SRp55 overexpression (9-mer on the lower side). B) Distribution of ΔPSI values in
modified cassette exons, showing a clear predominance of exon skipping. (C-D) Representation of the spatial distribution of SRp55 binding-motifs in the vicinity of alternatively spliced cassette exons. The position weigh matrices shown in (A) were used to scan the occurrence of binding motifs in respectively 1,449 and 3,820 up-regulated or down-regulated exons whose inclusion is impacted by SRp55 KD, and compared against 134,507 non-modified cassette exons (FDR ≥50%). The solid lines indicate the mean SRp55 binding motif score for each nucleotide position. Doted lines indicate log10 p-values obtained by statistical comparison of motif scores between modified exons (down- or up-regulated) against non-modified background exons, showing significant enrichment of the SRp55 binding motif in exonic sequences of down-regulated exons. The green box represents an average cassette exon, while solid lines and grey boxes represent neighbouring introns and up- and down-stream exons respectively. The numbers shown above indicate the relative nucleotide position from exon-intron junctions. Enrichment of the 6-mer motif is shown in (C), while enrichment of the 9-mer motif is shown in (D). Results are based on five independent RNA-seq experiments.

Supplementary Figure 4. SRp55 KD affects splicing and expression of the pro-apoptotic protein BIM contributing to beta cell apoptosis. A) Representative western blot showing the expression of BIM isoforms in control and SRp55 KD EndoC-βH1 cells. B) Ratio between BIM small (S) and BIM large (L) isoforms was calculated by densitometry. C) Protein expression of total BIM was measured by densitometry of all BIM isoforms and normalized by α-tubulin as loading control. Protein expression values were normalized by the highest value of each experiment, considered as 1. D-F) Double KD of SRp55 and BIM in EndoC-βH1 cells. Cells were
transfected with siCTL, siSRp55#2, siBim or siSRp55#2 + siBim for 48 h. mRNA expression of SRp55 (D) and BIM S (E) was measured by qRT-PCR and normalized by the housekeeping gene β-actin. mRNA expression values were normalized by the highest value of each experiment, considered as 1. F) Proportion of apoptotic cells was evaluated by Hoechst/PI staining. Results are mean ± SEM of four to five independent experiments. *p < 0.05, **p < 0.01 and ***p < 0.001 vs. siCTL; ##p < 0.01 and ###p < 0.001 as indicated by bars. B, C) Paired t-test. D-F) ANOVA followed by Bonferroni post hoc test.
| KEGG term                                                      | Gene count | %   | P-Value     |
|---------------------------------------------------------------|------------|-----|-------------|
| Metabolic pathways                                           | 286        | 7.2 | 3.40E-06    |
| Ubiquitin mediated proteolysis                                | 48         | 1.2 | 7.00E-06    |
| Glucagon signaling pathway                                    | 34         | 0.9 | 2.90E-04    |
| Shigellosis                                                    | 24         | 0.6 | 7.30E-04    |
| Insulin resistance                                            | 35         | 0.9 | 7.80E-04    |
| Fructose and mannose metabolism                               | 15         | 0.4 | 8.80E-04    |
| Insulin secretion                                             | 29         | 0.7 | 1.00E-03    |
| AMPK signaling pathway                                        | 38         | 1   | 1.00E-03    |
| Lysosome                                                      | 37         | 0.9 | 1.70E-03    |
| Fanconi anemia pathway                                        | 20         | 0.5 | 2.10E-03    |
| RNA degradation                                               | 26         | 0.7 | 2.30E-03    |
| Phosphatidylinositol signaling system                         | 31         | 0.8 | 2.50E-03    |
| Adherens junction                                             | 24         | 0.6 | 3.50E-03    |
| Homologous recombination                                      | 13         | 0.3 | 3.60E-03    |
| Oocyte meiosis                                                | 33         | 0.8 | 3.80E-03    |
| Amino sugar and nucleotide sugar metabolism                   | 18         | 0.5 | 4.20E-03    |
| Biosynthesis of antibiotics                                   | 55         | 1.4 | 6.90E-03    |
| Dopaminergic synapse                                          | 36         | 0.9 | 8.90E-03    |
| Aldosterone synthesis and secretion                           | 25         | 0.6 | 1.00E-02    |
| Lysine degradation                                            | 18         | 0.5 | 1.00E-02    |
| Type II diabetes mellitus                                     | 17         | 0.4 | 1.00E-02    |
| Pyrimidine metabolism                                         | 30         | 0.8 | 1.20E-02    |
| Bacterial invasion of epithelial cells                        | 24         | 0.6 | 1.20E-02    |
| GnRH signaling pathway                                        | 27         | 0.7 | 1.30E-02    |
| Inositol phosphate metabolism                                 | 22         | 0.6 | 1.60E-02    |
| Endocytosis                                                   | 62         | 1.6 | 2.20E-02    |
| Protein processing in endoplasmic reticulum                   | 43         | 1.1 | 2.40E-02    |
| Insulin signaling pathway                                     | 36         | 0.9 | 2.80E-02    |
| N-Glycan biosynthesis                                         | 16         | 0.4 | 2.80E-02    |
| Base excision repair                                          | 12         | 0.3 | 3.10E-02    |
| Glycerophospholipid metabolism                                | 26         | 0.7 | 3.80E-02    |
| Citrate cycle (TCA cycle)                                     | 11         | 0.3 | 3.90E-02    |
| Nucleotide excision repair                                    | 15         | 0.4 | 4.20E-02    |
| Tight junction                                                | 34         | 0.9 | 6.10E-02    |
| Purine metabolism                                             | 42         | 1.1 | 6.50E-02    |
| Thyroid hormone signaling pathway                             | 29         | 0.7 | 6.50E-02    |
| Regulation of actin cytoskeleton                              | 49         | 1.2 | 6.90E-02    |
| Central carbon metabolism in cancer                           | 18         | 0.5 | 7.20E-02    |
| Non-homologous end-joining                                    | 6          | 0.2 | 7.60E-02    |
| Glycosylphosphatidylinositol(GPI)-anchor biosynthesis          | 9          | 0.2 | 7.60E-02    |
| Pancreatic cancer                                             | 18         | 0.5 | 8.10E-02    |
| Adipocytokine signaling pathway                               | 19         | 0.5 | 8.50E-02    |
| Adrenergic signaling in cardiomyocytes                        | 35         | 0.9 | 8.60E-02    |
| Axon guidance                                                 | 31         | 0.8 | 8.80E-02    |
| Gene ID            | Gene Symbol | siCTL Median RPKM | siSR#2 Median RPKM | Log2 Fold Change |
|-------------------|-------------|-------------------|--------------------|-----------------|
| ENSG00000124193   | SRSF6       | 99.52             | 23.78              | -2.065          |
| ENSG00000264527   | WI2-1959D15.1 | 1.09             | 0.29              | -1.910          |
| ENSG00000239697   | TNFSF12     | 1.20              | 0.48              | -1.785          |
| ENSG00000196337   | CGB7        | 1.03              | 0.39              | -1.749          |
| ENSG00000230454   | U73166.2    | 0.59              | 0.18              | -1.743          |
| ENSG00000188011   | CXXC11      | 3.94              | 1.29              | -1.613          |
| ENSG00000117289   | TXNIP       | 1.65              | 0.50              | -1.594          |
| ENSG00000165272   | AQP3        | 15.79             | 6.26              | -1.571          |
| ENSG00000116661   | FBXO2       | 6.03              | 2.18              | -1.468          |
| ENSG00000075089   | ACTR6       | 10.36             | 3.82              | -1.459          |
| ENSG00000140623   | SEPT12      | 0.72              | 0.41              | -1.455          |
| ENSG00000113048   | MRPS27      | 23.74             | 9.54              | -1.447          |
| ENSG00000104883   | PEX11G      | 1.09              | 0.41              | -1.442          |
| ENSG00000184481   | FOXO4       | 3.02              | 1.13              | -1.422          |
| ENSG00000163754   | GYG1        | 12.05             | 5.17              | -1.353          |
| ENSG00000126903   | SLCL0A3     | 5.18              | 2.12              | -1.315          |
| ENSG00000214736   | TOMM6       | 59.56             | 42.60             | -1.304          |
| ENSG00000108576   | SLC6A4      | 1.58              | 0.60              | -1.282          |
| ENSG00000070985   | TRPM5       | 1.04              | 0.41              | -1.276          |
| ENSG00000104951   | IL4I1       | 5.23              | 3.39              | -1.258          |
| ENSG00000261720   | RP11-161M6.5 | 5.81             | 2.52              | -1.250          |
| ENSG00000140465   | CYP1A1      | 2.63              | 1.47              | -1.241          |
| ENSG00000181004   | BBS12       | 3.34              | 1.48              | -1.230          |
| ENSG00000145337   | PYURF       | 53.87             | 24.73             | -1.214          |
| ENSG00000131374   | TBC1D5      | 38.25             | 26.37             | -1.214          |
| ENSG00000171867   | PRNP        | 57.97             | 24.23             | -1.205          |
| ENSG00000088386   | SLC15A1     | 3.51              | 1.64              | -1.203          |
| ENSG00000261713   | SSTR5-AS1   | 15.87             | 6.11              | -1.199          |
| ENSG00000089157   | RPLP0       | 390.91            | 209.63            | -1.182          |
| ENSG00000152672   | CLEC4F      | 0.53              | 0.20              | -1.157          |
| ENSG00000143162   | CREG1       | 36.23             | 16.73             | -1.151          |
| ENSG00000196358   | NTNG2       | 2.53              | 1.50              | -1.125          |
| ENSG00000170271   | FAXDC2      | 3.41              | 1.57              | -1.123          |
| ENSG00000260539   | RP11-252A24.7 | 8.86             | 4.36              | -1.108          |
| ENSG00000260588   | RP11-930P14.2 | 0.71             | 0.42              | -1.094          |
| ENSG00000258839   | MC1R        | 4.45              | 2.06              | -1.081          |
| ENSG00000189157   | FAM47E      | 14.61             | 8.29              | -1.070          |
| ENSG00000121351   | IAPP        | 29.71             | 12.53             | -1.066          |
| ENSG00000152700   | SAR1B       | 46.26             | 22.81             | -1.065          |
| ENSG00000103671   | TRIP4       | 10.79             | 5.73              | -1.059          |
| ENSG00000084110   | HAL         | 2.79              | 1.23              | -1.058          |
| ENSG00000114779   | ABHD14B     | 29.84             | 15.43             | -1.052          |
| ENSG00000091317   | CMTM6       | 46.74             | 22.82             | -1.045          |
| ENSG00000157654   | PALM2-AKAP2 | 1.35              | 0.54              | -1.041          |
| ENSG00000067955   | CBFB        | 48.54             | 30.84             | -1.028          |
| ENSG00000105419   | MEIS3       | 7.02              | 3.35              | -1.012          |
| ENSG00000065243   | PKN2        | 14.33             | 6.68              | -1.012          |
| ENSG00000165923   | AGBL2       | 1.45              | 0.83              | -1.011          |
| ENSG00000115107   | STEAP3      | 0.66              | 0.33              | -1.004          |
| ENSG00000166866   | MYO1A       | 1.51              | 1.23              | -1.004          |
| Gene Symbol | Gene Name | Fold Change | ΔCt | Log2 Ratios |
|-------------|-----------|-------------|-----|-------------|
| ENSG00000176928 | GCNT4 | 3.89 | 1.97 | -1.003 |
| ENSG00000187266 | EPOR | 20.17 | 11.50 | -1.002 |
| ENSG00000188677 | PARVB | 37.58 | 17.12 | -1.000 |
| ENSG00000267954 | AP000349.1 | 1.75 | 0.90 | -1.000 |
| ENSG00000140481 | CCDC33 | 1.07 | 0.63 | -0.986 |
| ENSG00000150977 | RILPL2 | 0.76 | 0.40 | -0.932 |
| ENSG00000133101 | CCNA1 | 1.80 | 0.80 | -0.846 |
| ENSG00000110906 | KCTD10 | 11.58 | 8.35 | -0.837 |
| ENSG0000008441 | NFIX | 6.76 | 3.32 | -0.837 |
| ENSG00000267143 | RP11-677O4.6 | 2.35 | 1.49 | -0.835 |
| ENSG00000138641 | HERC3 | 57.02 | 32.83 | -0.857 |
| ENSG00000170526 | APOBEC3G | 3.83 | 2.14 | -0.858 |
| ENSG00000137642 | SORL1 | 8.38 | 5.45 | -0.861 |
| ENSG00000182718 | ANXA2 | 10.45 | 5.17 | -0.859 |
| ENSG00000138018 | EPT1 | 55.40 | 33.24 | -0.865 |
| ENSG00000138623 | SEMA7A | 1.27 | 0.77 | -0.826 |
| ENSG00000142273 | CBLC | 0.55 | 0.24 | -0.825 |
| Gene ID    | Gene Symbol | Log2 FC | Log2 pVal | Log2 fold Change |
|-----------|-------------|---------|-----------|-----------------|
| ENSG00000162461 | SLC25A34   | 0.51    | 0.32      | -0.820          |
| ENSG00000105227  | PRX        | 0.50    | 0.28      | -0.818          |
| ENSG00000160781  | PAQR6      | 0.96    | 0.56      | -0.817          |
| ENSG00000116957  | TBCE       | 16.60   | 9.19      | -0.816          |
| ENSG00000064999  | ANKS1A     | 7.43    | 4.23      | -0.815          |
| ENSG00000136144  | RCBTB1     | 19.84   | 11.26     | -0.812          |
| ENSG00000100439  | ABHD4      | 26.21   | 14.92     | -0.812          |
| ENSG00000271643  | RP11-10C24.3 | 2.09  | 1.19      | -0.812          |
| ENSG00000157600  | TMEM164    | 22.54   | 13.11     | -0.811          |
| ENSG00000163703  | CRELD1     | 35.49   | 18.46     | -0.809          |
| ENSG00000205730  | ITPRIPL2   | 1.14    | 0.74      | -0.808          |
| ENSG00000205436  | EXOC3L4    | 0.99    | 0.51      | -0.805          |
| ENSG00000112164  | GLP1R      | 4.37    | 2.73      | -0.799          |
| ENSG00000105639  | JAK3       | 1.98    | 1.14      | -0.797          |
| ENSG00000181392  | SYNE4      | 14.11   | 9.38      | -0.793          |
| ENSG00000076344  | RGS11      | 0.82    | 0.37      | -0.793          |
| ENSG00000119946  | CNNM1      | 22.81   | 11.63     | -0.792          |
| ENSG00000077713  | SLC25A43   | 4.89    | 2.94      | -0.788          |
| ENSG00000166037  | CEP57      | 36.41   | 22.48     | -0.782          |
| ENSG00000140682  | TGFB1I1    | 0.40    | 0.50      | -0.781          |
| ENSG00000137449  | CPEB2      | 8.72    | 5.66      | -0.780          |
| ENSG00000172382  | PRSS27     | 1.15    | 0.59      | -0.779          |
| ENSG00000106524  | ANKMY2     | 3.01    | 2.15      | -0.769          |
| ENSG00000144674  | GOLGA4     | 30.89   | 19.11     | -0.769          |
| ENSG00000110628  | SLC22A18   | 1.45    | 0.86      | -0.767          |
| ENSG00000183762  | KREMEN1    | 2.78    | 1.57      | -0.765          |
| ENSG00000060642  | PIGV       | 6.99    | 4.11      | -0.765          |
| ENSG00000105887  | MTPN       | 82.04   | 46.33     | -0.762          |
| ENSG00000171109  | MFN1       | 20.17   | 13.83     | -0.760          |
| ENSG00000169570  | DTWD2      | 2.71    | 1.69      | -0.759          |
| ENSG00000099953  | MMP11      | 3.44    | 2.07      | -0.755          |
| ENSG00000169621  | APLF       | 0.52    | 0.30      | -0.754          |
| ENSG00000104381  | GDAP1      | 22.18   | 11.94     | -0.753          |
| ENSG00000105829  | BET1       | 9.57    | 4.92      | -0.751          |
| ENSG00000124587  | PEX6       | 6.83    | 4.06      | -0.749          |
| ENSG00000203727  | SAMD5      | 71.61   | 42.10     | -0.749          |
| ENSG00000179965  | ZNF771     | 3.57    | 2.09      | -0.746          |
| ENSG00000039523  | FAM65A     | 10.29   | 6.56      | -0.745          |
| ENSG00000090863  | GLG1       | 47.84   | 28.80     | -0.744          |
| ENSG00000215915  | ATAD3C     | 16.15   | 10.83     | -0.744          |
| ENSG00000124098  | FAM210B    | 21.38   | 12.47     | -0.743          |
| ENSG00000177042  | TMEM80     | 17.02   | 10.17     | -0.743          |
| ENSG00000101194  | SLC17A9    | 5.94    | 3.22      | -0.741          |
| ENSG00000167711  | SERPINF2   | 4.35    | 2.80      | -0.740          |
| ENSG00000166340  | TPP1       | 68.31   | 42.97     | -0.733          |
| ENSG00000163626  | COX18      | 7.68    | 4.63      | -0.732          |
| ENSG00000118276  | B4GALT6    | 16.62   | 10.38     | -0.731          |
| ENSG00000114446  | IFT57      | 19.59   | 15.35     | -0.728          |
| ENSG00000169962  | TAS1R3     | 2.08    | 1.37      | -0.728          |
| ENSG00000139209  | SLC38A4    | 6.65    | 3.89      | -0.725          |
| ENSG0000004776   | HSPB6      | 1.38    | 0.84      | -0.719          |
| ENSG00000198911  | SREBF2     | 92.69   | 62.77     | -0.719          |
| Gene       | Symbol | Log2 FC | Z score | p value |
|------------|--------|---------|---------|---------|
| RGS14      | ENSG00000169220 | 6.89    | 4.17    | -0.714  |
| LARP4      | ENSG00000189067  | 56.64   | 30.14   | -0.713  |
| LITAF      | ENSG00000139988  | 4.45    | 2.95    | -0.713  |
| RH12       | ENSG00000147041  | 0.63    | 0.44    | -0.706  |
| SYTL5      | ENSG00000169507  | 0.98    | 0.59    | -0.705  |
| SLC38A11   | ENSG0000011638   | 4.48    | 2.88    | -0.705  |
| BMF        | ENSG00000104081  | 8.88    | 4.93    | -0.703  |
| VMA21      | ENSG00000160131  | 13.94   | 8.41    | -0.703  |
| TMLHE      | ENSG00000187994  | 4.45    | 2.95    | -0.703  |
| AMT        | ENSG00000134352  | 3.23    | 1.87    | -0.698  |
| P4HA1      | ENSG00000122884  | 7.90    | 4.87    | -0.698  |
| RINL       | ENSG00000187994  | 11.00   | 6.85    | -0.697  |
| BNIP3L     | ENSG00000104765  | 46.76   | 30.73   | -0.696  |
| LMO2       | ENSG00000135363  | 9.69    | 5.81    | -0.692  |
| RXFP3      | ENSG00000182631  | 2.08    | 1.29    | -0.691  |
| ACSF3      | ENSG00000176715  | 15.17   | 8.53    | -0.689  |
| AGER       | ENSG00000204305  | 1.47    | 0.97    | -0.687  |
| LAMP5      | ENSG00000125869  | 1.69    | 1.03    | -0.683  |
| RP11-10C24.1 | ENSG00000271020 | 2.01    | 1.40    | -0.683  |
| EFNA2      | ENSG00000099617  | 2.16    | 1.73    | -0.682  |
| C15orf38   | ENSG00000242498  | 3.97    | 2.92    | -0.681  |
| SLC32A1    | ENSG00000101438  | 1.01    | 0.58    | -0.676  |
| NADK2      | ENSG00000152620  | 8.26    | 5.26    | -0.675  |
| PRKAA1     | ENSG00000132356  | 41.68   | 26.18   | -0.675  |
| CYP2D6     | ENSG00000100197  | 1.32    | 0.84    | -0.674  |
| UCN3       | ENSG00000178473  | 19.52   | 13.26   | -0.671  |
| MTDH       | ENSG00000147649  | 51.30   | 34.35   | -0.669  |
| FSBP       | ENSG00000265817  | 0.79    | 0.35    | -0.665  |
| SLC45A2    | ENSG00000164175  | 3.69    | 2.13    | -0.664  |
| BATF2      | ENSG00000168062  | 0.93    | 0.64    | -0.661  |
| TMEM194B   | ENSG00000189362  | 2.12    | 1.17    | -0.660  |
| DNAJB11    | ENSG00000090520  | 65.82   | 39.35   | -0.660  |
| CYS1       | ENSG00000205795  | 7.03    | 4.64    | -0.659  |
| MON2       | ENSG00000061987  | 19.70   | 12.50   | -0.657  |
| FGD1       | ENSG00000102302  | 5.30    | 3.59    | -0.656  |
| NPC1L1     | ENSG0000015520   | 2.65    | 1.80    | -0.653  |
| IGFALS     | ENSG00000099769  | 4.29    | 2.30    | -0.651  |
| PACRG      | ENSG00000112530  | 1.69    | 1.23    | -0.651  |
| LINC00858  | ENSG00000229404  | 0.54    | 0.33    | -0.647  |
| PPP1R3B    | ENSG00000173281  | 4.09    | 2.67    | -0.646  |
| SLC22A11   | ENSG00000168065  | 1.01    | 0.64    | -0.646  |
| LRC73      | ENSG00000204052  | 1.04    | 0.63    | -0.645  |
| FGFI8      | ENSG00000156427  | 5.77    | 4.04    | -0.642  |
| TMEM101    | ENSG00000091947  | 15.46   | 9.23    | -0.641  |
| ZMAT3      | ENSG00000172667  | 4.00    | 2.35    | -0.641  |
| AC004840.9 | ENSG00000175873  | 0.53    | 0.35    | -0.639  |
| S100A4     | ENSG00000196154  | 10.04   | 10.04   | -0.639  |
| CPEB1      | ENSG00000214575  | 1.61    | 0.98    | -0.638  |
| Ensembl ID | Gene Symbol | log2 Fitted | log2 Control | log2 Fitted/Control | log2 Fold Change | Ensembl ID | Gene Symbol | log2 Fitted | log2 Control | log2 Fitted/Control | log2 Fold Change |
|------------|--------------|-------------|--------------|---------------------|-----------------|------------|--------------|-------------|--------------|-------------------|-----------------|
| ENSG00000165507 | C10orf10 | 26.64 | 20.57 | -0.637 |
| ENSG00000174358 | SLC6A19 | 21.92 | 13.89 | -0.637 |
| ENSG00000175832 | ETV4 | 9.30 | 6.40 | -0.637 |
| ENSG00000196850 | PPTC7 | 8.90 | 6.24 | -0.636 |
| ENSG00000153551 | CMTM7 | 5.16 | 4.00 | -0.633 |
| ENSG00000065361 | ERBB3 | 37.01 | 26.31 | -0.632 |
| ENSG00000205084 | TMEM231 | 1.91 | 0.72 | -0.629 |
| ENSG00000116971 | AKTIP | 8.15 | 6.69 | -0.628 |
| ENSG00000131725 | WDR44 | 4.73 | 4.06 | -0.628 |
| ENSG00000143473 | KCHN1 | 1.69 | 1.09 | -0.627 |
| ENSG00000120063 | GNA13 | 21.85 | 14.62 | -0.627 |
| ENSG00000154928 | EPHB1 | 10.55 | 6.40 | -0.625 |
| ENSG00000166192 | SENP8 | 2.45 | 1.64 | -0.623 |
| ENSG00000157184 | CPT2 | 11.90 | 7.54 | -0.622 |
| ENSG00000137825 | ITPKA | 3.79 | 2.59 | -0.621 |
| ENSG00000085063 | CD59 | 132.62 | 95.02 | -0.620 |
| ENSG00000144191 | CNGA3 | 24.18 | 15.68 | -0.620 |
| ENSG00000267950 | AC136297.1 | 12.44 | 7.68 | -0.617 |
| ENSG00000163083 | INHBB | 0.83 | 0.54 | -0.617 |
| ENSG00000185924 | RTN4RL1 | 0.60 | 0.42 | -0.617 |
| ENSG00000106772 | PRUNE2 | 28.04 | 14.18 | -0.616 |
| ENSG00000179119 | SPTY2D1 | 14.23 | 9.25 | -0.615 |
| ENSG00000185561 | TLC2 | 0.79 | 0.55 | -0.614 |
| ENSG00000134330 | IAH1 | 56.61 | 46.14 | -0.613 |
| ENSG00000176853 | FAM91A1 | 32.53 | 20.66 | -0.612 |
| ENSG00000268397 | ACO08443.1 | 4.20 | 2.74 | -0.609 |
| ENSG00000129187 | DCTD | 43.87 | 29.31 | -0.608 |
| ENSG00000108784 | NAGLU | 29.44 | 19.33 | -0.607 |
| ENSG00000089818 | NECAP1 | 30.66 | 21.37 | -0.606 |
| ENSG00000197444 | OGDHL | 7.69 | 5.75 | -0.606 |
| ENSG00000101384 | JAG1 | 1.14 | 0.74 | -0.603 |
| ENSG00000169446 | MMGT1 | 11.13 | 7.32 | -0.603 |
| ENSG00000125845 | BMP2 | 2.93 | 2.11 | -0.602 |
| ENSG00000137575 | SDCBP | 55.96 | 33.34 | -0.600 |
| ENSG00000141756 | FKB10 | 11.55 | 5.96 | -0.599 |
| ENSG00000186998 | EMID1 | 43.85 | 29.92 | -0.598 |
| ENSG00000168394 | TAP1 | 2.07 | 1.35 | -0.597 |
| ENSG00000107201 | DDX58 | 2.53 | 1.74 | -0.595 |
| ENSG00000136271 | DDX56 | 24.61 | 15.71 | -0.594 |
| ENSG0000014919 | COX15 | 16.05 | 10.96 | -0.593 |
| ENSG00000156671 | SAMD8 | 6.81 | 4.52 | -0.592 |
| ENSG00000162923 | WDR26 | 18.83 | 13.10 | -0.591 |
| ENSG00000163623 | NXX6-1 | 23.03 | 15.30 | -0.591 |
| ENSG00000213888 | AC005003.1 | 2.88 | 1.83 | -0.589 |
| ENSG00000232434 | C9orf172 | 2.62 | 1.75 | -0.587 |
| ENSG00000242282 | AC108488.4 | 1.32 | 0.98 | -0.587 |
| ENSG00000183780 | SLC35F3 | 10.36 | 7.20 | -0.587 |
| ENSG00000182795 | C1orf116 | 7.84 | 4.77 | -0.586 |
| ENSG00000226479 | TME185B | 8.40 | 5.59 | -0.584 |
| ENSG00000170379 | FAM115C | 1.66 | 1.20 | -0.584 |
| ENSG00000110931 | CAMKK2 | 7.03 | 4.10 | -0.583 |
| Gene ID     | Gene Symbol | Fold Change | Expression | z-Score |
|------------|-------------|-------------|------------|---------|
| ENSG00000066926 | FECH       | 9.80        | 5.95       | -0.582  |
| ENSG00000125457 | MIF4GD     | 9.66        | 7.28       | -0.582  |
| ENSG00000123342 | MMP19      | 0.57        | 0.40       | -0.581  |
| ENSG00000167968 | DNASE1L2   | 2.32        | 1.56       | -0.581  |
| ENSG00000140406 | MESDC1     | 7.34        | 5.53       | -0.580  |
| ENSG00000139318 | DUSP6      | 12.70       | 9.25       | -0.578  |
| ENSG00000131910 | NR0B2      | 6.05        | 4.19       | -0.578  |
| ENSG00000239264 | TXNDC5     | 25.37       | 18.13      | -0.578  |
| ENSG00000139410 | SDSL       | 2.98        | 1.89       | -0.577  |
| ENSG00000182749 | PAQR7      | 2.78        | 1.95       | -0.576  |
| ENSG00000175414 | ARL10      | 7.30        | 4.96       | -0.574  |
| ENSG00000262445 | CTD-2545H1.2 | 1.23    | 0.87       | -0.574  |
| ENSG00000162391 | FAM151A    | 0.85        | 0.57       | -0.573  |
| ENSG00000214039 | RP11-474D1.3 | 2.80    | 1.89       | -0.573  |
| ENSG00000123080 | CDKN2C     | 91.59       | 64.94      | -0.572  |
| ENSG00000162881 | OXER1      | 4.83        | 3.25       | -0.570  |
| ENSG00000134070 | IRAK2      | 0.79        | 0.55       | -0.569  |
| ENSG00000243477 | NAT6       | 9.14        | 3.38       | -0.568  |
| ENSG00000245468 | RP11-367J11.3 | 0.72    | 0.44       | -0.568  |
| ENSG00000197775 | DHR54-AS1  | 6.63        | 4.25       | -0.567  |
| ENSG00000117054 | ACADM      | 51.55       | 30.72      | -0.562  |
| ENSG00000167977 | KCTD5      | 34.45       | 26.60      | -0.562  |
| ENSG00000271912 | RP11-661A12.14 | 1.95    | 1.44       | -0.561  |
| ENSG00000260359 | RP11-4F5.2 | 4.45        | 3.19       | -0.559  |
| ENSG00000066135 | KDM4A      | 26.32       | 17.47      | -0.558  |
| ENSG00000177791 | MYOZ1      | 1.20        | 0.83       | -0.558  |
| ENSG00000116147 | TNR        | 9.10        | 6.25       | -0.557  |
| ENSG00000145476 | CYP4V2     | 11.36       | 7.90       | -0.557  |
| ENSG00000164742 | ADCY1      | 25.16       | 17.77      | -0.556  |
| ENSG00000271303 | SRXN1      | 20.15       | 14.08      | -0.556  |
| ENSG00000171227 | TMEM37     | 109.22      | 74.46      | -0.556  |
| ENSG00000155016 | CYP2U1     | 20.75       | 13.64      | -0.555  |
| ENSG00000153560 | UBP1       | 19.93       | 15.54      | -0.555  |
| ENSG00000114812 | VIPR1      | 0.93        | 0.48       | -0.555  |
| ENSG00000164708 | PGAM2      | 1.70        | 1.06       | -0.555  |
| ENSG00000163462 | TRIM46     | 5.43        | 3.95       | -0.552  |
| ENSG00000171714 | ANOS5      | 7.60        | 5.19       | -0.552  |
| ENSG00000175938 | ORAI3      | 9.41        | 6.53       | -0.552  |
| ENSG00000114378 | HYAL1      | 1.77        | 1.30       | -0.551  |
| ENSG00000176393 | RNPEP      | 30.73       | 20.98      | -0.551  |
| ENSG00000234155 | RP11-30P6.6 | 0.62        | 0.48       | -0.549  |
| ENSG0000014914 | MTRMR11    | 4.48        | 3.03       | -0.549  |
| ENSG00000100426 | ZBED4      | 8.09        | 5.94       | -0.549  |
| ENSG00000259040 | BLOC155-TXNDC5 | 22.71    | 16.57      | -0.548  |
| ENSG00000172830 | SSH3       | 8.77        | 5.47       | -0.548  |
| ENSG00000160844 | GATS       | 6.22        | 4.58       | -0.547  |
| ENSG00000204442 | FAM155A    | 0.81        | 0.52       | -0.547  |
| ENSG00000177000 | MTHFR      | 9.54        | 6.82       | -0.547  |
| ENSG00000176402 | GJC3       | 1.26        | 0.94       | -0.546  |
| ENSG00000185250 | PPI6       | 0.96        | 0.68       | -0.546  |
| ENSG00000120256 | LRP11      | 92.14       | 66.35      | -0.545  |
| Gene ID     | Description | Log2 Fold | Log2 Fold | p-value |
|------------|-------------|-----------|-----------|---------|
| ENSG00000204390 | HSPA1L | 0.64 | 0.45 | -0.544 |
| ENSG00000123427 | METTL21B | 1.27 | 0.93 | -0.543 |
| ENSG00000179546 | HTR1D | 10.80 | 6.24 | -0.541 |
| ENSG00000160683 | CXCR5 | 2.11 | 1.45 | -0.541 |
| ENSG00000161664 | ASB16 | 1.01 | 0.83 | -0.540 |
| ENSG00000166260 | COX11 | 98.01 | 66.89 | -0.540 |
| ENSG00000010318 | PHF7 | 2.12 | 1.50 | -0.538 |
| ENSG00000138760 | SCARB2 | 175.04 | 122.03 | -0.537 |
| ENSG00000166128 | RAB8B | 12.38 | 8.56 | -0.536 |
| ENSG00000179403 | VWA1 | 82.63 | 63.48 | -0.536 |
| ENSG00000156735 | BAG4 | 7.00 | 4.75 | -0.535 |
| ENSG00000167780 | SOAT2 | 1.09 | 0.77 | -0.534 |
| ENSG0000007866 | TEAD3 | 2.80 | 1.96 | -0.533 |
| ENSG00000213057 | C1orf220 | 0.70 | 0.35 | -0.532 |
| ENSG00000147459 | DOCK5 | 0.90 | 0.60 | -0.531 |
| ENSG00000140057 | AK7 | 9.42 | 7.00 | -0.531 |
| ENSG0000020129 | NCDN | 7.29 | 5.05 | -0.530 |
| ENSG00000162068 | NTN3 | 7.40 | 5.32 | -0.529 |
| ENSG00000162852 | CNST | 8.15 | 5.63 | -0.529 |
| ENSG0000025796 | SEC63 | 113.07 | 88.80 | -0.528 |
| ENSG0000056998 | GYG2 | 14.75 | 9.88 | -0.527 |
| ENSG00000159403 | C1R | 1.01 | 0.70 | -0.526 |
| ENSG00000130184 | SEC14L5 | 1.78 | 1.35 | -0.524 |
| ENSG00000136122 | BORA | 5.88 | 4.10 | -0.524 |
| ENSG00000177674 | AGTRAP | 6.30 | 4.33 | -0.523 |
| ENSG00000127831 | VIL1 | 471.16 | 320.05 | -0.521 |
| ENSG00000228133 | AC099684.1 | 0.79 | 0.63 | -0.521 |
| ENSG00000116035 | VAX2 | 10.71 | 7.11 | -0.520 |
| ENSG00000130513 | GDF15 | 0.53 | 0.32 | -0.520 |
| ENSG00000167588 | GPD1 | 27.34 | 22.18 | -0.520 |
| ENSG00000267034 | RP11-38408.1 | 1.88 | 1.42 | -0.519 |
| ENSG00000117115 | PADI2 | 0.60 | 0.39 | -0.519 |
| ENSG00000102595 | UGGT2 | 22.68 | 16.05 | -0.518 |
| ENSG00000162496 | DHR53 | 4.56 | 3.14 | -0.517 |
| ENSG00000166589 | CDH16 | 20.36 | 13.55 | -0.516 |
| ENSG0000006459 | JHDM1D | 8.83 | 6.16 | -0.516 |
| ENSG00000197943 | PLCG2 | 21.69 | 15.98 | -0.516 |
| ENSG00000150776 | C11orf57 | 16.89 | 12.11 | -0.516 |
| ENSG00000135124 | P2RX4 | 24.08 | 17.16 | -0.512 |
| ENSG00000197461 | PDGFA | 2.71 | 1.81 | -0.512 |
| ENSG00000103150 | MLYCD | 15.50 | 10.53 | -0.510 |
| ENSG00000071564 | TCF3 | 21.18 | 18.18 | -0.510 |
| ENSG00000198053 | SIRPA | 9.83 | 6.92 | -0.506 |
| ENSG00000084674 | APOB | 10.58 | 7.67 | -0.505 |
| ENSG00000248866 | USP46-AS1 | 1.08 | 0.72 | -0.504 |
| ENSG00000170558 | CDH2 | 57.83 | 40.79 | -0.504 |
| ENSG00000105971 | CAV2 | 1.64 | 1.28 | -0.503 |
| ENSG00000145779 | TNFAIP8 | 5.52 | 4.08 | -0.503 |
| ENSG00000080561 | MID2 | 4.76 | 3.40 | -0.503 |
| ENSG00000140398 | NEIL1 | 6.76 | 4.45 | -0.503 |
| ENSG00000103067 | ESRP2 | 12.56 | 7.93 | -0.502 |
| ENSG00000112378 | PERP | 38.48 | 27.49 | -0.502 |
| Gene ID          | Gene Symbol | Fold Change 1 | Fold Change 2 | |   |
|------------------|-------------|---------------|---------------|---------|
| ENSG00000186529  | CYP4F3      | 3.93          | 2.88          | -0.501  |
| ENSG00000071205  | ARHGAP10    | 5.72          | 3.88          | -0.501  |
| ENSG00000146833  | TRIM4       | 17.67         | 14.27         | -0.500  |
| ENSG00000140332  | TLE3        | 2.83          | 2.10          | -0.498  |
| ENSG00000270011  | ZNF177      | 17.80         | 10.93         | -0.497  |
| ENSG00000171116  | HSFX1       | 0.57          | 0.42          | -0.497  |
| ENSG00000168246  | UBDT2       | 23.19         | 17.02         | -0.496  |
| ENSG00000075785  | RAB7A       | 117.92        | 93.71         | -0.495  |
| ENSG00000182890  | GLUD2       | 0.63          | 0.45          | -0.494  |
| ENSG00000184665  | WDR27       | 6.83          | 5.00          | -0.493  |
| ENSG00000185745  | IFIT1       | 1.16          | 0.98          | -0.492  |
| ENSG00000075785  | FAM117B     | 4.88          | 3.47          | -0.491  |
| ENSG00000148356  | LRSAM1      | 4.80          | 3.55          | -0.491  |
| ENSG00000162999  | DUSP19      | 1.38          | 1.09          | -0.490  |
| ENSG00000101150  | TPDS5L2     | 43.34         | 29.81         | -0.489  |
| ENSG00000170881  | RNF139      | 19.33         | 13.78         | -0.489  |
| ENSG00000103269  | RHBDL1      | 1.70          | 1.21          | -0.488  |
| ENSG00000147162  | OGT         | 35.20         | 26.43         | -0.488  |
| ENSG00000226137  | BAIAP2-AS1  | 8.03          | 5.47          | -0.488  |
| ENSG00000116406  | EDEM3       | 15.54         | 12.01         | -0.487  |
| ENSG00000152128  | TMEM163     | 11.29         | 8.29          | -0.487  |
| ENSG00000159733  | ZFYVE28     | 4.39          | 3.14          | -0.486  |
| ENSG00000158604  | TMED4       | 50.37         | 34.73         | -0.485  |
| ENSG00000084444  | KIAA1467    | 8.01          | 5.88          | -0.485  |
| ENSG00000185043  | CIB1        | 16.17         | 11.89         | -0.484  |
| ENSG00000182957  | SPATA13     | 16.96         | 12.30         | -0.484  |
| ENSG00000102890  | ELMO3       | 7.63          | 5.46          | -0.484  |
| ENSG00000250021  | C15orf38-AP3S2 | 10.32    | 7.67          | -0.483  |
| ENSG00000140093  | SERPINA10   | 13.98         | 10.78         | -0.483  |
| ENSG00000184014  | DENND5A     | 16.46         | 14.34         | -0.479  |
| ENSG00000168917  | SLC35G2     | 24.03         | 17.70         | -0.478  |
| ENSG00000165171  | WBSCR27     | 4.73          | 3.71          | -0.478  |
| ENSG00000105664  | COMP        | 3.04          | 2.08          | -0.477  |
| ENSG00000229180  | GS1-124K5.11| 0.53          | 0.37          | -0.477  |
| ENSG00000120029  | C10orf76    | 11.23         | 8.44          | -0.476  |
| ENSG00000156232  | WHAMM       | 5.84          | 3.94          | -0.474  |
| ENSG00000167972  | ABCA3       | 30.53         | 22.11         | -0.474  |
| ENSG00000197635  | DPP4        | 66.48         | 44.94         | -0.474  |
| ENSG0000114670   | NEK11       | 1.44          | 1.00          | -0.472  |
| ENSG00000198743  | SLC5A3      | 6.64          | 5.84          | -0.472  |
| ENSG00000078487  | ZCWPW1      | 1.68          | 1.42          | -0.471  |
| ENSG00000164535  | DAGL8       | 4.86          | 3.66          | -0.470  |
| ENSG00000126562  | WNK4        | 9.97          | 7.14          | -0.470  |
| ENSG00000072133  | RPS6KA6     | 11.67         | 8.89          | -0.469  |
| ENSG00000184454  | NCMAP       | 0.92          | 0.66          | -0.469  |
| ENSG00000260065  | CTA-445C9.15| 2.56          | 1.93          | -0.469  |
| ENSG00000138041  | SMEK2       | 30.53         | 21.32         | -0.467  |
| ENSG00000109079  | TNFAIP1     | 17.36         | 12.38         | -0.465  |
| ENSG00000109705  | NKX3-2      | 1.03          | 0.74          | -0.464  |
| ENSG00000099957  | P2RX6       | 0.96          | 0.50          | -0.464  |
| ENSG00000029534  | ANK1        | 19.82         | 15.02         | -0.464  |
| ENSG00000185736  | ADARB2      | 2.27          | 2.01          | -0.464  |
| Gene ID      | Gene Symbol | Fold Change | Expression Level | Expression Level |
|-------------|-------------|-------------|------------------|------------------|
| ENSG00000172890 | NADSYN1     | 11.36       | 10.18            | -0.464           |
| ENSG00000155903 | RASA2       | 4.83        | 3.28             | -0.464           |
| ENSG00000126945 | HNRNPH2     | 55.08       | 39.88            | -0.463           |
| ENSG00000102100 | SLC35A2     | 26.93       | 19.63            | -0.463           |
| ENSG00000188158 | NHS         | 1.04        | 0.72             | -0.463           |
| ENSG00000235169 | SMIM1       | 2.71        | 2.07             | -0.462           |
| ENSG00000162949 | CAPN13      | 13.96       | 10.06            | -0.462           |
| ENSG00000170099 | SERPINA6    | 46.16       | 29.11            | -0.459           |
| ENSG00000143882 | ATP6V1C2    | 43.07       | 28.42            | -0.458           |
| ENSG00000110871 | COQ5        | 22.50       | 15.72            | -0.458           |
| ENSG00000114738 | MAPKAPK3    | 22.82       | 15.50            | -0.457           |
| ENSG00000138751 | NP5S1       | 1.53        | 1.11             | -0.457           |
| ENSG00000118902 | SHISA7      | 1.79        | 1.32             | -0.457           |
| ENSG00000244405 | ETV5        | 5.73        | 4.84             | -0.456           |
| ENSG00000108671 | PSMD11      | 54.36       | 42.86            | -0.455           |
| ENSG00000123384 | LRP1        | 11.07       | 8.17             | -0.454           |
| ENSG00000130940 | CASZ1       | 6.47        | 4.67             | -0.454           |
| ENSG00000135926 | TMBIM1      | 3.79        | 2.67             | -0.453           |
| ENSG00000158195 | WASF2       | 19.93       | 14.88            | -0.452           |
| ENSG00000272214 | AC079602.1  | 3.73        | 2.68             | -0.451           |
| ENSG00000174628 | IQCK        | 3.19        | 2.62             | -0.450           |
| ENSG00000120693 | SMAD9       | 8.22        | 5.81             | -0.448           |
| ENSG00000172955 | ADH6        | 6.02        | 4.41             | -0.447           |
| ENSG00000111961 | SASH1       | 9.40        | 7.70             | -0.446           |
| ENSG00000175262 | C1orf127    | 1.86        | 1.49             | -0.446           |
| ENSG00000079112 | CDH17       | 151.04      | 111.13           | -0.445           |
| ENSG00000172794 | RAB37       | 21.06       | 10.52            | -0.445           |
| ENSG00000108091 | CCDC6       | 13.69       | 11.16            | -0.444           |
| ENSG00000171129 | HSFX2       | 0.67        | 0.47             | -0.442           |
| ENSG000000214300 | SPDY3       | 1.97        | 1.48             | -0.442           |
| ENSG00000261589 | CTC-462L7.1 | 3.77        | 2.78             | -0.441           |
| ENSG000000224201 | PNMA6A      | 3.24        | 2.52             | -0.440           |
| ENSG00000174939 | ASPH1D1     | 14.44       | 10.85            | -0.440           |
| ENSG00000173083 | HPSE        | 20.65       | 14.96            | -0.439           |
| ENSG00000135272 | MDFIC       | 10.06       | 8.15             | -0.439           |
| ENSG00000179598 | PLD6        | 0.60        | 0.51             | -0.439           |
| ENSG00000186204 | CYP4F12     | 3.46        | 2.64             | -0.437           |
| ENSG00000183798 | EMILIN3     | 9.77        | 7.89             | -0.437           |
| ENSG00000149577 | SITD2       | 22.95       | 14.10            | -0.436           |
| ENSG00000175895 | PLEKHF2     | 12.05       | 9.65             | -0.436           |
| ENSG00000134193 | REG4        | 1.68        | 1.27             | -0.435           |
| ENSG00000179833 | SERTAD2     | 6.25        | 4.71             | -0.435           |
| ENSG00000073969 | NSF         | 58.51       | 42.58            | -0.434           |
| ENSG00000171885 | AQP4        | 2.90        | 2.33             | -0.434           |
| ENSG00000187678 | SPRY4       | 4.51        | 3.23             | -0.433           |
| ENSG00000139163 | ETNK1       | 76.51       | 61.99            | -0.433           |
| ENSG00000182400 | TRAPPC6B    | 9.55        | 7.14             | -0.432           |
| ENSG00000174013 | FBXO45      | 11.92       | 9.27             | -0.431           |
| ENSG00000118508 | RAB32       | 21.05       | 16.12            | -0.431           |
| ENSG00000116711 | PLA2G4A     | 34.43       | 25.62            | -0.429           |
| ENSG00000257088 | PNMA6D      | 3.33        | 2.70             | -0.429           |
| ENSG00000160058 | BSDC1       | 23.22       | 16.93            | -0.429           |
| Gene             | Fold Change | Expression | Expression Ratio |
|------------------|-------------|------------|------------------|
| ENSEMBL000125650 | PSNP        | 1.29       | 0.92             |
| ENSEMBL000257335 | MGAM        | 18.81      | 15.77            |
| ENSEMBL000241839 | PLEKHO2     | 2.34       | 1.69             |
| ENSEMBL000141753 | IGFBP4      | 12.78      | 9.59             |
| ENSEMBL000171475 | WIPF2       | 10.59      | 7.90             |
| ENSEMBL000165152 | TEMEM246    | 7.70       | 5.60             |
| ENSEMBL000183049 | CAMK1D      | 1.53       | 1.34             |
| ENSEMBL000081177 | EXD2        | 14.86      | 10.79            |
| ENSEMBL000184678 | HIST2H2BE   | 8.13       | 6.05             |
| ENSEMBL000131389 | SLCA6       | 43.82      | 32.84            |
| ENSEMBL000254087 | LYN         | 1.20       | 0.92             |
| ENSEMBL00017261 | KIAA0319    | 4.66       | 3.49             |
| ENSEMBL000141569 | TRIM65      | 1.80       | 1.34             |
| ENSEMBL000157518 | TSC2D3      | 49.76      | 37.16            |
| ENSEMBL000261088 | RP11-61A14.3| 4.76       | 3.79             |
| ENSEMBL000015452 | INPP4B      | 3.97       | 2.97             |
| ENSEMBL000176125 | UFSP1       | 1.35       | 1.02             |
| ENSEMBL000269486 | CTC-360G5.9 | 1.77       | 1.08             |
| ENSEMBL000070019 | GUCY2C      | 73.88      | 55.23            |
| ENSEMBL000102316 | MAGED2      | 131.73     | 97.64            |
| ENSEMBL000178031 | ADAMTS1     | 22.87      | 17.87            |
| ENSEMBL000005513 | SOX8        | 0.62       | 0.48             |
| ENSEMBL000166959 | MS4A8       | 16.66      | 10.95            |
| ENSEMBL000174721 | FGFBP3      | 1.33       | 1.04             |
| ENSEMBL000213889 | PPM1N       | 2.93       | 2.43             |
| ENSEMBL000171150 | SOC55       | 9.12       | 7.01             |
| ENSEMBL000259959 | RP11-121C2.2| 0.71       | 0.52             |
| ENSEMBL000119711 | ALDHA1      | 4.64       | 3.49             |
| ENSEMBL000198435 | NRARP       | 0.68       | 0.63             |
| ENSEMBL000104435 | STMN2       | 132.81     | 101.18           |
| ENSEMBL000143147 | GPR161      | 4.20       | 2.92             |
| ENSEMBL000172824 | CES4A       | 6.61       | 5.68             |
| ENSEMBL000152315 | KCNK13      | 0.76       | 0.54             |
| ENSEMBL000141744 | PNMT        | 3.13       | 2.53             |
| ENSEMBL000015532 | XYL2        | 3.24       | 2.31             |
| ENSEMBL00006432 | MAP3K9      | 5.98       | 4.32             |
| ENSEMBL000164010 | ERMAP       | 5.42       | 4.25             |
| ENSEMBL000268573 | RP11-158H5.7| 1.69       | 1.04             |
| ENSEMBL000100228 | RAB36       | 6.79       | 5.24             |
| ENSEMBL000164949 | GEM         | 4.06       | 3.33             |
| ENSEMBL000163945 | UVSSA       | 2.60       | 1.84             |
| ENSEMBL000130779 | CLIP1       | 9.58       | 7.35             |
| ENSEMBL000262468 | RP11-95P2.1 | 0.66       | 0.40             |
| ENSEMBL000119630 | PGF         | 35.10      | 26.84            |
| ENSEMBL000168610 | STAT3       | 30.93      | 24.99            |
| ENSEMBL000102401 | ARMCX3      | 40.31      | 30.25            |
| ENSEMBL000160233 | LRR3C       | 2.37       | 1.71             |
| ENSEMBL000120526 | NUDCD1      | 8.01       | 6.23             |
| ENSEMBL000163162 | RNF149      | 13.92      | 10.44            |
| ENSEMBL000031003 | FAM13B      | 24.72      | 18.01            |
| ENSEMBL000170540 | ARL6IP1     | 255.44     | 207.05           |
| Gene         | Expression 1 | Expression 2 | Log2 Fold Change |
|--------------|--------------|--------------|-----------------|
| ENSG00000129625 | 36.19        | 26.41        | -0.404          |
| ENSG00000182575 | 3.25         | 2.33         | -0.404          |
| ENSG00000105939  | 12.38        | 9.62         | -0.404          |
| ENSG00000082516   | 6.46         | 4.73         | -0.403          |
| ENSG00000165066   | 273.17       | 206.69       | -0.402          |
| ENSG00000105357   | 33.69        | 25.52        | -0.401          |
| ENSG00000162390   | 2.74         | 2.02         | -0.400          |
| ENSG00000185112   | 0.55         | 0.43         | -0.399          |
| ENSG00000110665   | 1.66         | 1.26         | -0.398          |
| ENSG00000259439   | 1.96         | 1.44         | -0.397          |
| ENSG00000176485   | 6.57         | 4.41         | -0.397          |
| ENSG00000089876   | 13.55        | 9.12         | -0.397          |
| ENSG00000250067   | 2.18         | 1.88         | -0.396          |
| ENSG00000139200   | 1.59         | 1.17         | -0.395          |
| ENSG00000165637   | 79.20        | 63.61        | -0.395          |
| ENSG00000179163   | 39.69        | 32.68        | -0.395          |
| ENSG00000159761   | 1.45         | 1.44         | -0.393          |
| ENSG00000188976   | 31.67        | 26.40        | -0.393          |
| ENSG00000144802   | 8.17         | 5.53         | -0.393          |
| ENSG00000188580   | 4.67         | 3.23         | -0.392          |
| ENSG00000100767   | 1.33         | 0.94         | -0.392          |
| ENSG00000223768   | 4.09         | 2.96         | -0.392          |
| ENSG00000198719   | 2.32         | 1.87         | -0.392          |
| ENSG00000157259   | 13.96        | 10.47        | -0.392          |
| ENSG00000173726   | 48.89        | 38.95        | -0.391          |
| ENSG00000197930   | 46.81        | 37.66        | -0.390          |
| ENSG00000177034   | 5.47         | 4.45         | -0.390          |
| ENSG00000198707   | 4.79         | 3.76         | -0.390          |
| ENSG00000260804   | 3.65         | 3.53         | -0.389          |
| ENSG00000179918   | 60.82        | 47.56        | -0.389          |
| ENSG00000205808   | 10.14        | 8.24         | -0.388          |
| ENSG00000165943   | 19.81        | 14.81        | -0.387          |
| ENSG00000175073   | 2.89         | 2.23         | -0.387          |
| ENSG00000180398   | 41.17        | 31.74        | -0.387          |
| ENSG00000146007   | 59.21        | 49.19        | -0.387          |
| ENSG00000186350   | 40.13        | 31.51        | -0.385          |
| ENSG00000169762   | 21.83        | 18.18        | -0.385          |
| ENSG00000174928   | 2.72         | 2.33         | -0.384          |
| ENSG00000146151   | 52.24        | 40.16        | -0.384          |
| ENSG00000164169   | 4.88         | 3.85         | -0.384          |
| ENSG00000153208   | 0.91         | 0.73         | -0.383          |
| ENSG00000126226   | 18.16        | 12.51        | -0.383          |
| ENSG00000162817   | 4.93         | 3.43         | -0.382          |
| ENSG00000176438   | 1.42         | 1.00         | -0.381          |
| ENSG00000164096   | 19.74        | 14.97        | -0.381          |
| ENSG00000029153   | 10.04        | 8.25         | -0.379          |
| ENSG00000133597   | 19.05        | 15.48        | -0.378          |
| ENSG00000111271   | 34.48        | 24.72        | -0.378          |
| ENSG00000110911   | 28.98        | 23.00        | -0.378          |
| ENSG00000178796   | 15.81        | 12.18        | -0.377          |
| ENSG00000203772   | 1.86         | 1.43         | -0.377          |
| Ensembl ID     | Gene Symbol | Fold Change | Expression | Log2 Fold |
|---------------|-------------|-------------|------------|-----------|
| ENSG00000167703 | SLC43A2     | 20.51       | 15.12      | -0.376    |
| ENSG00000230761 | RP11-342C24.8 | 1.48        | 1.20       | -0.376    |
| ENSG00000189007 | ADAT2       | 1.23        | 0.95       | -0.375    |
| ENSG00000175264 | CHST1       | 2.90        | 2.09       | -0.375    |
| ENSG00000175662 | TOM1L2      | 10.41       | 8.09       | -0.375    |
| ENSG00000121297 | TSH3        | 2.20        | 1.72       | -0.375    |
| ENSG00000181284 | TMEM102     | 3.14        | 2.58       | -0.375    |
| ENSG00000067248 | DHX29       | 12.84       | 10.56      | -0.374    |
| ENSG00000182534 | MXRA7       | 162.15      | 125.38     | -0.374    |
| ENSG00000188636 | LDOC1L      | 25.98       | 20.50      | -0.373    |
| ENSG00000148672 | GLUD1       | 41.11       | 32.09      | -0.371    |
| ENSG00000181444 | IVNS1ABP    | 29.40       | 21.68      | -0.371    |
| ENSG00000251169 | AC005355.2 | 3.50        | 2.61       | -0.370    |
| ENSG00000121297 | TSH3        | 2.20        | 1.72       | -0.375    |
| ENSG00000181284 | TMEM102     | 3.14        | 2.58       | -0.375    |
| ENSG00000067248 | DHX29       | 12.84       | 10.56      | -0.374    |
| ENSG00000182534 | MXRA7       | 162.15      | 125.38     | -0.374    |
| ENSG00000188636 | LDOC1L      | 25.98       | 20.50      | -0.373    |
| ENSG00000148672 | GLUD1       | 41.11       | 32.09      | -0.371    |
| ENSG00000181444 | IVNS1ABP    | 29.40       | 21.68      | -0.371    |
| ENSG00000251169 | AC005355.2 | 3.50        | 2.61       | -0.370    |
| ENSG00000121297 | TSH3        | 2.20        | 1.72       | -0.375    |
| ENSG00000181284 | TMEM102     | 3.14        | 2.58       | -0.375    |
| ENSG00000067248 | DHX29       | 12.84       | 10.56      | -0.374    |
| Gene ID          | Gene Symbol | Log2FoldChange | Log2FoldChange | Log2FoldChange |
|-----------------|-------------|----------------|----------------|----------------|
| ENSG00000085377 | PREP        | 13.39          | 10.45          | -0.356         |
| ENSG00000122971 | ACADS       | 9.99           | 7.85           | -0.356         |
| ENSG00000255455 | RP11-890B15.3 | 1.75           | 1.63           | -0.356         |
| ENSG00000269430 | LRR3C3DN    | 1.36           | 1.06           | -0.356         |
| ENSG00000152291 | TGOLN2      | 74.19          | 62.59          | -0.355         |
| ENSG00000105270 | CLIP3       | 11.75          | 8.98           | -0.355         |
| ENSG00000261211 | RP1-80N2.3  | 1.17           | 0.91           | -0.354         |
| ENSG00000118454 | ANKRD13C    | 11.57          | 9.62           | -0.354         |
| ENSG00000171448 | ZBTB26      | 4.92           | 4.07           | -0.354         |
| ENSG00000090971 | NAT14       | 33.58          | 32.76          | -0.354         |
| ENSG00000272514 | C6orf165    | 1.11           | 0.84           | -0.353         |
| ENSG00000168056 | LTBP3       | 2.94           | 2.39           | -0.353         |
| ENSG00000272447 | RP11-182L21.6 | 4.82           | 3.51           | -0.352         |
| ENSG00000124140 | SLC12A5     | 1.52           | 1.19           | -0.352         |
| ENSG00000162836 | ACN6        | 5.81           | 4.83           | -0.352         |
| ENSG00000166946 | CCND1P1     | 20.17          | 15.74          | -0.351         |
| ENSG00000188707 | ZBED6C1     | 7.81           | 6.12           | -0.351         |
| ENSG00000113719 | ERGIC1      | 30.73          | 24.08          | -0.351         |
| ENSG00000171303 | KCN3        | 3.27           | 2.56           | -0.351         |
| ENSG00000168994 | PXDC1       | 2.03           | 1.66           | -0.350         |
| ENSG00000148082 | SHC3        | 2.84           | 2.68           | -0.350         |
| ENSG00000166886 | NAB2        | 4.04           | 3.03           | -0.350         |
| ENSG00000156150 | ALX3        | 1.36           | 1.17           | -0.350         |
| ENSG00000198863 | RUNDC1      | 10.83          | 8.92           | -0.350         |
| ENSG00000143870 | PDIA6       | 219.87         | 174.21         | -0.349         |
| ENSG00000128829 | EIF2AK4     | 7.69           | 6.20           | -0.349         |
| ENSG00000266753 | RP11-690G19.3 | 1.20           | 0.92           | -0.348         |
| ENSG00000118564 | FBXL5       | 21.74          | 19.27          | -0.348         |
| ENSG00000136045 | PWP1        | 16.42          | 11.87          | -0.348         |
| ENSG00000148943 | LIN7C       | 14.70          | 12.55          | -0.348         |
| ENSG00000269996 | RP11-343N15.5 | 5.33           | 4.40           | -0.347         |
| ENSG00000196878 | LAMB3       | 7.82           | 5.79           | -0.346         |
| ENSG00000146282 | RAR52       | 11.66          | 9.12           | -0.346         |
| ENSG00000129195 | FAM64A      | 9.93           | 7.73           | -0.346         |
| ENSG00000163082 | SGPP2       | 10.90          | 7.94           | -0.346         |
| ENSG00000204271 | SPIN3       | 4.71           | 3.72           | -0.346         |
| ENSG00000197926 | FITM2       | 17.56          | 14.11          | -0.346         |
| ENSG00000144468 | RHBDD1      | 12.05          | 7.32           | -0.346         |
| ENSG00000230567 | FAM203B     | 12.13          | 8.40           | -0.345         |
| ENSG00000167113 | COQ4        | 16.11          | 12.67          | -0.345         |
| ENSG00000204174 | NPY4R       | 1.76           | 1.15           | -0.344         |
| ENSG00000135587 | SMPD2       | 7.32           | 6.13           | -0.344         |
| ENSG00000197177 | GPR123      | 5.71           | 4.52           | -0.344         |
| ENSG00000181830 | SLC35C1     | 6.81           | 5.44           | -0.344         |
| ENSG00000126259 | KIRREL2     | 20.75          | 16.89          | -0.343         |
| ENSG00000118855 | MFSD1       | 24.32          | 19.27          | -0.343         |
| ENSG00000241399 | CD302       | 30.24          | 24.95          | -0.343         |
| ENSG00000261128 | RP11-18F14.2 | 5.79           | 4.94           | -0.343         |
| ENSG00000029333 | TMEM176A     | 2.45           | 1.98           | -0.341         |
| ENSG00000160539 | PPAPDC3      | 2.57           | 2.15           | -0.341         |
| ENSG00000119396 | RAB14       | 50.23          | 39.17          | -0.341         |
| ENSG00000146085 | MUT         | 30.16          | 25.28          | -0.340         |
| Ensembl ID        | Gene   | MESDC2 | ASMTL | LIN9 | IFNGR2 | TRAPPC9 | HPS6 | AGAP10 | GM2A | CDH6 | CYB5D2 | TMC4 | KIAA1430 | CTPS2 | WDR25 | KBLN3 | SLC4A11 | RP11-44F14.8 | KCTD11 | EPS8L2 | KIAA2026 | ELP3 | DDX18 | KCNK17 | ACTR1B | CDH22 | PHF2 | UTP3 | GOT2 | AKR1C2 | PTGES3 | CHMP7 | SMAD5 | PGR | SERPINA1 | PIFO | SLC26A1 | SLC39A8 | TMEM9 | PCDH17 | ZBTB42 | GLYCTK | RBM6 | VPS54 | TIAL1 | BCL2L13 | ARMCX6 | NBEA | STRN3 |
|------------------|--------|--------|-------|------|--------|---------|------|--------|------|------|--------|------|-----------|-------|-------|-------|--------|-----------------|-------|-------|--------|-------|-------|-------|------|------|------|-------|--------|-------|------|-------|-----|-------|-------|-------|-------|-------|------|-------|-------|-------|-------|-------|-----|------|-------|------|-------|-------|-------|------|-------|-------|-------|-------|-------|-----|------|
| Gene             | RETSAT   | 12.13 | 9.42 | -0.319 |
|------------------|----------|-------|------|--------|
| ENSG00000156687  | UNC5D    | 4.22  | 3.52 | -0.318 |
| ENSG00000229645  | LINC00341| 0.95  | 0.72 | -0.318 |
| ENSG00000154035  | C17orf103| 0.94  | 0.78 | -0.318 |
| ENSG00000197979  | CRIPAK   | 1.42  | 1.07 | -0.318 |
| ENSG0000011897   | SERINC1  | 167.88| 136.19| -0.318 |
| ENSG00000111186  | WNT5B    | 5.13  | 4.64 | -0.316 |
| ENSG00000160226  | C21orf2  | 6.16  | 4.95 | -0.316 |
| ENSG0000021890   | NPTXR    | 13.36 | 11.29| -0.315 |
| ENSG00000250742  | RP11-834C11.4| 19.78| 16.01| -0.315 |
| ENSG00000271738  | RP11-137H2.6| 24.15| 19.42| -0.314 |
| ENSG00000069535  | MAOB     | 23.96 | 19.28| -0.314 |
| ENSG00000134871  | COL4A2   | 5.09  | 4.38 | -0.313 |
| ENSG00000168286  | THAP11   | 16.62 | 13.50| -0.313 |
| ENSG00000176055  | MBLAC2   | 2.36  | 1.80 | -0.313 |
| ENSG00000113916  | BCL6     | 7.55  | 7.65 | -0.313 |
| ENSG00000122687  | FTSJ2    | 12.47 | 10.24| -0.312 |
| ENSG00000196865  | NHLRC2   | 2.14  | 1.76 | -0.311 |
| ENSG00000151208  | DLG5     | 20.06 | 15.92| -0.311 |
| ENSG00000079387  | SENP1    | 12.81 | 10.68| -0.310 |
| ENSG00000135002  | RFK      | 58.59 | 48.97| -0.310 |
| ENSG00000172943  | PHF8     | 7.38  | 6.04 | -0.310 |
| ENSG00000116237  | ICMT     | 85.10 | 72.01| -0.310 |
| ENSG00000198035  | AGAP9    | 5.03  | 4.55 | -0.310 |
| ENSG00000143367  | TUFT1    | 10.01 | 8.18 | -0.309 |
| ENSG00000164347  | GFM2     | 12.41 | 10.02| -0.308 |
| ENSG00000107816  | LZTS2    | 3.26  | 3.05 | -0.308 |
| ENSG00000064115  | TM7SF3   | 34.34 | 28.76| -0.307 |
| ENSG00000065154  | OAT      | 26.16 | 22.89| -0.307 |
| ENSG00000172057  | ORMDL3   | 17.94 | 15.86| -0.307 |
| ENSG00000182158  | CREB3L2  | 14.78 | 11.84| -0.307 |
| ENSG00000231925  | TAPBP    | 12.23 | 8.81 | -0.307 |
| ENSG00000196151  | WDSUB1   | 5.81  | 4.70 | -0.306 |
| ENSG00000143627  | PKLR     | 3.85  | 3.11 | -0.306 |
| ENSG00000272005  | RP11-91J19.4| 4.15| 3.58 | -0.306 |
| ENSG00000105953  | OGDH     | 23.21 | 18.69| -0.305 |
| ENSG00000163050  | ADCK3    | 21.93 | 20.01| -0.303 |
| ENSG00000119227  | PIGZ     | 1.23  | 1.14 | -0.303 |
| ENSG00000101346  | POFUT1   | 32.05 | 26.43| -0.303 |
| ENSG00000185340  | GAS2L1   | 1.32  | 1.07 | -0.303 |
| ENSG00000112078  | KCTD20   | 19.25 | 13.91| -0.303 |
| ENSG00000196569  | LAMA2    | 1.10  | 1.02 | -0.302 |
| ENSG00000104936  | DMPK     | 10.79 | 8.75 | -0.302 |
| ENSG00000149571  | KIRREL3  | 4.60  | 3.45 | -0.302 |
| ENSG00000269337  | ALS91479.1| 1.53| 1.23 | -0.302 |
| ENSG00000198018  | ENTPD7   | 7.15  | 5.84 | -0.302 |
| ENSG00000163624  | CDS1     | 18.39 | 15.27| -0.301 |
| ENSG00000165586  | UBTD1    | 4.10  | 3.45 | -0.301 |
| ENSG0000006377   | DLX6     | 3.81  | 2.88 | -0.301 |
| ENSG00000157911  | PEX10    | 11.55 | 9.61 | -0.300 |
| ENSG00000127540  | UQCR11   | 57.07 | 49.47| -0.300 |
| ENSG00000100906  | NFKBIA   | 10.90 | 8.85 | -0.300 |
| Gene Symbol | Gene Name | Log2 Fold Change | Log10 Fold Change | P-Value |
|-------------|-----------|-----------------|------------------|---------|
| ENSG00000151835 | SACS | 2.41 | 1.96 | -0.300 |
| ENSG00000123575 | FAM199X | 15.40 | 13.76 | -0.299 |
| ENSG00000203499 | FAM83H-AS1 | 1.47 | 1.07 | -0.299 |
| ENSG00000164850 | GPER | 10.95 | 8.48 | -0.298 |
| ENSG00000006555 | TTC22 | 7.11 | 5.38 | -0.298 |
| ENSG00000114988 | LMAN2L | 13.85 | 11.26 | -0.298 |
| ENSG00000006210 | CX3CL1 | 7.04 | 5.58 | -0.297 |
| ENSG00000137700 | SLC37A4 | 117.59 | 93.47 | -0.296 |
| ENSG00000063180 | CA11 | 4.91 | 3.19 | -0.296 |
| ENSG00000198876 | DCAF12 | 37.55 | 31.11 | -0.295 |
| ENSG00000072682 | P4HA2 | 23.51 | 19.03 | -0.295 |
| ENSG00000161243 | FBXO27 | 5.07 | 4.05 | -0.295 |
| ENSG00000137218 | FRS3 | 2.23 | 1.77 | -0.295 |
| ENSG00000112033 | PPARD | 7.43 | 5.83 | -0.294 |
| ENSG00000197324 | LRP10 | 37.57 | 30.64 | -0.294 |
| ENSG00000171160 | MORN4 | 3.58 | 2.93 | -0.293 |
| ENSG00000164414 | SLC35A1 | 18.50 | 16.31 | -0.293 |
| ENSG00000089289 | IGBP1 | 16.14 | 13.18 | -0.292 |
| ENSG00000125945 | ZNF436 | 4.95 | 4.28 | -0.292 |
| ENSG00000004660 | CAMKK1 | 9.34 | 7.26 | -0.292 |
| ENSG0000013725 | TTC4 | 8.32 | 6.92 | -0.291 |
| ENSG00000136059 | VILL | 2.81 | 2.30 | -0.291 |
| ENSG00000157500 | APPL1 | 25.61 | 23.28 | -0.291 |
| ENSG000001118231 | CRYGD | 3.62 | 3.17 | -0.290 |
| ENSG00000140986 | RPL3L | 0.62 | 0.55 | -0.290 |
| ENSG00000099330 | OCEL1 | 15.53 | 12.10 | -0.289 |
| ENSG00000029725 | RABEP1 | 44.76 | 36.65 | -0.289 |
| ENSG00000144655 | CSRNP1 | 7.69 | 6.29 | -0.288 |
| ENSG00000175265 | GOLGA8A | 30.24 | 21.72 | -0.288 |
| ENSG00000173114 | LLRN3 | 1.01 | 0.83 | -0.287 |
| ENSG00000214046 | SMIM7 | 50.05 | 50.50 | -0.287 |
| ENSG00000106404 | CLDN15 | 5.28 | 4.32 | -0.286 |
| ENSG00000178988 | MRFAP1L1 | 53.38 | 45.51 | -0.286 |
| ENSG00000198589 | LRBA | 26.97 | 22.36 | -0.286 |
| ENSG00000187498 | COL4A1 | 1.64 | 1.28 | -0.286 |
| ENSG00000115275 | MOGS | 24.96 | 20.99 | -0.286 |
| ENSG00000171467 | ZNF318 | 9.07 | 7.58 | -0.285 |
| ENSG00000099139 | PCSK5 | 1.92 | 1.65 | -0.285 |
| ENSG00000020181 | GPR124 | 1.64 | 1.35 | -0.285 |
| ENSG00000085449 | WDFY1 | 23.58 | 20.02 | -0.285 |
| ENSG00000111725 | PRKAB1 | 12.16 | 10.87 | -0.285 |
| ENSG00000119681 | LTBP2 | 0.52 | 0.45 | -0.284 |
| ENSG00000133466 | C1QTNF6 | 17.54 | 16.29 | -0.284 |
| ENSG00000132793 | LPIN3 | 18.50 | 15.29 | -0.283 |
| ENSG00000198408 | MGEA5 | 24.30 | 17.45 | -0.283 |
| ENSG00000250506 | CDK3 | 4.13 | 3.27 | -0.283 |
| ENSG0000008083 | JARID2 | 7.10 | 5.86 | -0.283 |
| ENSG00000099834 | CDHR5 | 51.33 | 43.11 | -0.282 |
| ENSG00000175573 | C11orf68 | 6.58 | 5.38 | -0.282 |
| ENSG00000138448 | ITGA7 | 15.38 | 12.73 | -0.282 |
| ENSG00000156521 | TYSND1 | 4.57 | 3.66 | -0.282 |
| ENSG00000172269 | DPAGT1 | 18.07 | 15.36 | -0.282 |
| Gene Symbol | Description | Log2 Fold Change | p-Value |
|-------------|-------------|-----------------|---------|
| ENSG00000188554 | NBR1 | 34.99 | 29.47 | -0.282 |
| ENSG00000159479 | MED8 | 15.93 | 13.19 | -0.281 |
| ENSG00000204128 | C2orf72 | 24.04 | 19.67 | -0.281 |
| ENSG00000104419 | NDRG1 | 41.69 | 28.47 | -0.281 |
| ENSG00000053108 | FSTL4 | 0.87 | 0.76 | -0.281 |
| ENSG00000179104 | TMTC2 | 4.48 | 3.34 | -0.280 |
| ENSG00000198585 | NUDT16 | 11.75 | 9.67 | -0.280 |
| ENSG00000161328 | LRRC56 | 1.90 | 1.61 | -0.280 |
| ENSG00000163702 | IL17RC | 5.57 | 5.16 | -0.280 |
| ENSG00000144043 | TEX261 | 49.43 | 41.75 | -0.279 |
| ENSG00000213463 | SYNJ2BP | 18.85 | 15.54 | -0.278 |
| ENSG00000175130 | MARCKSL1 | 133.82 | 113.02 | -0.278 |
| ENSG00000008735 | MAPK8IP2 | 27.26 | 23.00 | -0.277 |
| ENSG00000184949 | FAM227A | 2.48 | 2.00 | -0.276 |
| ENSG00000056558 | TRAF1 | 1.09 | 0.92 | -0.275 |
| ENSG00000067167 | TRAM1 | 79.62 | 65.82 | -0.275 |
| ENSG00000121104 | FAM117A | 10.88 | 9.62 | -0.275 |
| ENSG00000249158 | PCDHA11 | 5.18 | 4.58 | -0.274 |
| ENSG00000132128 | LRRC41 | 19.58 | 16.22 | -0.274 |
| ENSG00000186094 | AGBL4 | 1.40 | 1.01 | -0.274 |
| ENSG00000059588 | TARBP1 | 7.64 | 6.53 | -0.272 |
| ENSG00000182934 | SRPR | 70.77 | 56.94 | -0.272 |
| ENSG00000148396 | SEC16A | 27.26 | 22.48 | -0.272 |
| ENSG00000119004 | CYP20A1 | 8.31 | 7.08 | -0.271 |
| ENSG00000136828 | RALGPS1 | 21.95 | 18.95 | -0.271 |
| ENSG00000136169 | SETDB2 | 3.33 | 2.85 | -0.271 |
| ENSG00000130723 | PRRC2B | 35.82 | 29.29 | -0.271 |
| ENSG00000102978 | POLR2C | 36.83 | 31.29 | -0.269 |
| ENSG00000247400 | DNAJC3-AS1 | 3.56 | 2.70 | -0.269 |
| ENSG00000078177 | N4BP2 | 9.55 | 9.19 | -0.268 |
| ENSG00000083223 | ZCCHC6 | 6.13 | 5.04 | -0.268 |
| ENSG00000198130 | HIBCH | 10.59 | 8.80 | -0.267 |
| ENSG00000148090 | AUH | 10.84 | 8.74 | -0.267 |
| ENSG00000183919 | FAM53B | 2.81 | 2.46 | -0.267 |
| ENSG0000005100 | DHX33 | 5.29 | 4.20 | -0.267 |
| ENSG00000150760 | DOCK1 | 10.81 | 9.05 | -0.266 |
| ENSG00000100220 | RTCB | 41.44 | 34.43 | -0.265 |
| ENSG00000204592 | HLA-E | 69.48 | 57.84 | -0.264 |
| ENSG00000152256 | PDK1 | 4.09 | 3.41 | -0.264 |
| ENSG00000114450 | GNB4 | 5.40 | 4.50 | -0.264 |
| ENSG00000158435 | CNOT11 | 31.58 | 26.90 | -0.264 |
| ENSG00000057704 | TMCC3 | 25.77 | 22.79 | -0.263 |
| ENSG00000178537 | SLC25A20 | 13.77 | 10.89 | -0.263 |
| ENSG00000126882 | FAM78A | 0.58 | 0.60 | -0.262 |
| ENSG00000247596 | TWF2 | 15.48 | 12.91 | -0.262 |
| ENSG00000143811 | PYCR2 | 20.28 | 16.62 | -0.262 |
| ENSG00000187650 | VMAC | 1.38 | 1.01 | -0.262 |
| ENSG00000155792 | DEPTOR | 2.56 | 2.14 | -0.261 |
| ENSG00000197681 | TBC1D3 | 8.73 | 6.92 | -0.259 |
| Gene ID         | Gene Symbol | Expression1 | Expression2 | log2 Fold Change |
|----------------|-------------|-------------|-------------|-----------------|
| ENSG00000145990 | GFOD1       | 2.39        | 2.00        | -0.259          |
| ENSG00000138293 | NCOA4       | 94.51       | 79.26       | -0.259          |
| ENSG00000101350 | KIF3B       | 44.03       | 38.08       | -0.258          |
| ENSG00000070214 | SLC44A1     | 23.18       | 21.36       | -0.257          |
| ENSG00000255545 | RP11-627G23.1 | 3.92       | 3.09        | -0.257          |
| ENSG00000213199 | ASIC3       | 1.62        | 1.21        | -0.257          |
| ENSG00000089053 | ANAPC5      | 59.67       | 48.07       | -0.256          |
| ENSG00000189652 | TMEM232     | 1.58        | 1.33        | -0.256          |
| ENSG00000182809 | CRIP2       | 76.49       | 52.42       | -0.256          |
| ENSG00000154310 | TNK         | 5.93        | 4.84        | -0.256          |
| ENSG00000079482 | OPHN1       | 1.95        | 1.64        | -0.255          |
| ENSG00000160113 | NR2F6       | 24.85       | 22.39       | -0.255          |
| ENSG00000149485 | FADS1       | 105.14      | 85.14       | -0.255          |
| ENSG00000129595 | EPB41L14A   | 1.60        | 1.48        | -0.254          |
| ENSG00000197111 | PCBP2       | 458.47      | 412.26      | -0.253          |
| ENSG00000070214 | SLC44A1     | 23.18       | 21.36       | -0.257          |
| ENSG00000182809 | CRIP2       | 76.49       | 52.42       | -0.256          |
| ENSG00000154310 | TNK         | 5.93        | 4.84        | -0.256          |
| ENSG00000079482 | OPHN1       | 1.95        | 1.64        | -0.255          |
| ENSG00000160113 | NR2F6       | 24.85       | 22.39       | -0.255          |
| ENSG00000149485 | FADS1       | 105.14      | 85.14       | -0.255          |
| ENSG00000129595 | EPB41L14A   | 1.60        | 1.48        | -0.254          |
| ENSG00000100183 | PKM         | 59.67       | 48.07       | -0.256          |
| ENSG00000182809 | CRIP2       | 76.49       | 52.42       | -0.256          |
| ENSG00000154310 | TNK         | 5.93        | 4.84        | -0.256          |
| ENSG00000079482 | OPHN1       | 1.95        | 1.64        | -0.255          |
| ENSG00000160113 | NR2F6       | 24.85       | 22.39       | -0.255          |
| ENSG00000149485 | FADS1       | 105.14      | 85.14       | -0.255          |
| ENSG00000129595 | EPB41L14A   | 1.60        | 1.48        | -0.254          |
| ENSG00000197111 | PCBP2       | 458.47      | 412.26      | -0.253          |
| ENSG00000070214 | SLC44A1     | 23.18       | 21.36       | -0.257          |
| ENSG00000182809 | CRIP2       | 76.49       | 52.42       | -0.256          |
| ENSG00000154310 | TNK         | 5.93        | 4.84        | -0.256          |
| ENSG00000079482 | OPHN1       | 1.95        | 1.64        | -0.255          |
| ENSG00000160113 | NR2F6       | 24.85       | 22.39       | -0.255          |
| ENSG00000149485 | FADS1       | 105.14      | 85.14       | -0.255          |
| ENSG00000129595 | EPB41L14A   | 1.60        | 1.48        | -0.254          |
| ENSG00000070214 | SLC44A1     | 23.18       | 21.36       | -0.257          |
| ENSG00000182809 | CRIP2       | 76.49       | 52.42       | -0.256          |
| ENSG00000154310 | TNK         | 5.93        | 4.84        | -0.256          |
| ENSG00000079482 | OPHN1       | 1.95        | 1.64        | -0.255          |
| ENSG00000160113 | NR2F6       | 24.85       | 22.39       | -0.255          |
| ENSG00000149485 | FADS1       | 105.14      | 85.14       | -0.255          |
| ENSG00000129595 | EPB41L14A   | 1.60        | 1.48        | -0.254          |
| Ensembl ID     | Gene Symbol | Allotype 1 | Allotype 2 | Log2 (Ratio) |
|---------------|-------------|------------|------------|--------------|
| ENSG00000117868 | ESYT2       | 22.86      | 19.00      | -0.235       |
| ENSG00000106348 | IMPDH1      | 14.54      | 12.36      | -0.235       |
| ENSG00000112624 | GLTSCR1L    | 5.91       | 5.24       | -0.235       |
| ENSG00000159346 | ADIPOR1     | 74.75      | 62.29      | -0.235       |
| ENSG00000085511 | MAP3K4      | 32.18      | 27.75      | -0.235       |
| ENSG00000162729 | IGSF8       | 11.50      | 9.12       | -0.235       |
| ENSG00000244045 | TMEM199     | 24.10      | 22.29      | -0.235       |
| ENSG00000071994 | PDCD2       | 27.13      | 23.46      | -0.235       |
| ENSG00000145349 | CAMK2D      | 19.48      | 15.76      | -0.234       |
| ENSG00000091536 | MYO15A      | 1.23       | 0.75       | -0.234       |
| ENSG00000122203 | KIAA1191    | 28.43      | 24.17      | -0.234       |
| ENSG00000198689 | SLC9A6      | 10.36      | 9.68       | -0.234       |