

# S-Adenosylmethionine Treatment Diminishes the Proliferation of Castration-Resistant Prostate Cancer Cells by Modulating the Expression of miRNAs

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## Abstract

AdoMet (S-adenosylmethionine) inhibits cancer cell proliferation and migration via epigenetic alterations. This study aimed to investigate whether AdoMet may cause alterations in microRNA (miRNA) expression profiles that are important for the initiation and progression of prostate cancer. PC-3 cells were treated with AdoMet before miRNA sequencing. A total of 17 differentially expressed miRNAs were detected. Target gene prediction was performed by means of databases. Results were aligned to transcriptomic data. The bioinformatic analysis revealed upregulation of anticancerogenic genes, downregulation of cancerogenic-related processes and pathways. Knocking down hsa-miR-192-5p in PC-3 cells resulted in downregulation of cancer cell proliferation, thus confirming these results.

## Keywords

Ado-Met • PC-3 cells • miRNAs • TGF-beta pathway

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## 1. Introduction

In recent years, next-generation sequencing technologies have shed light on epigenetic signatures in malignant tumors (Hussen et al. 2022). Creating an epigenetic landscape of different cancer entities is helpful for revealing the biological mechanisms involved in carcinogenesis (Davies et al. 2020), likely leading to more personalized molecularly targeted therapies in the future (Hussen et al. 2022; Davies et al. 2020). For cancer cells, epigenetic mechanisms seem to be advantageous over genetic alterations since the changes in gene expression are not attributable to mutations in the sequence of DNA (Takeshima and Ushijima 2019). To date, known epigenetic mechanisms involved in carcinogenesis include DNA methylation, posttranslational histone modification, and the regulation of noncoding RNAs (ncRNAs) (Perri et al. 2017). In 1993, Victor Ambros and Gary Ruvkun discovered small ncRNA types that are obviously involved in the posttranscriptional silencing of target genes while working on *Caenorhabditis elegans* (Lee et al. 1993, Reinhart et al. 2000). Moreover, it is widely accepted that microRNA (miRNAs) are crucial for the regulation of gene expression and participate in the control of almost all biological processes (BP) regulating the maintenance of cellular integrity (Galagali and Kim 2020). Furthermore, during

the last two decades, it has become evident that pathophysiological conditions, diseases, and even viral infections can be related to specific miRNA expression patterns (Vaghef et al. 2022). Genes encoding small RNAs often reside within fragile chromosome sites; thus, the loss of heterozygosity concerning miRNAs acting as tumor suppressors may promote carcinogenesis (Calin et al. 2004). In fact, more than 50% of miRNA genes are in genomic regions associated with the emergence of cancer (Calin et al. 2004). Moreover, copy number variations, epigenetic mechanisms, transcriptional regulation, impaired processing, effects on miRNA binding sites, and the expression of competing endogenous RNAs can alter the expression and function of miRNAs and thus may contribute to carcinogenesis (Misiewicz-Krzeminska et al. 2019).

Recently, we and others found that cancer cell lines treated with AdoMet, the second most extensively used enzyme cofactor after ATP, exhibited significant decreases in proliferation, migration, and invasion (Schmidt et al. 2016). Transcriptome data from PC-3 cells, a prostate cancer cell line that was treated with AdoMet S-adenosylmethionine (SAM), revealed the upregulation of numerous tumor suppressor genes and the downregulation of proto-oncogenes. We determined interconnections between AdoMet and alterations in histone methylation (Mathes et al. 2024) as well as promoter methylation (Schmidt et al. 2016). In recent literature, links between SAM and ncRNAs have been reported and discussed (Mosca et al. 2021). For example, Chu et al. (2019) showed changes in the promoter methylation status

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of cancer-related long ncRNAs and miRNAs in hepatocellular carcinoma cells, which displayed an increase in the intracellular concentration of AdoMet. Furthermore, the regulation of miRNA expression profiles by SAM has been shown in head and neck cancer cells as well as in breast cancer cells (Chu et al. 2019; Pagano et al. 2020).

The aim of this work was to investigate the regulation of the miRNA expression profile through AdoMet in prostate cancer cells (PC-3).

## 2. Materials and Methods

### 2.1. Cell culture and treatment with SAM

PC-3 cells were grown in a RPMI 1640 medium supplemented with 10% fetal calf serum and 1.2% penicillin/streptomycin as described previously (Schmidt et al. 2016) (PAN-Biotech GmbH, Aidenbach, Germany). For RNA analysis, cells were grown to a subconfluence of 70–80%. The cells were treated with vehicle (0.005 M H<sub>2</sub>SO<sub>4</sub> and 10% Ethanol) or 200 µM of SAM (32 mM prepared in 5 mM sulfuric acid and 10% ethanol; New England Biolabs, Ipswich, MA, USA) for 120 h. Under both conditions, the medium was changed once per 24 h. Cells were trypsinized and counted. A number of 1 Mio cells was used for the isolation of RNA.

### 2.2. Isolation of total RNA, library preparation, and miRNA-seq

The total RNA was isolated from PC-3 cells using a NucleoSpin miRNA Kit Macherey Nagel (Düren, Germany) according to the manufacturer's instructions. By following ligation of the RNA to modified 3' and 5' adaptors, the products were reverse transcribed (Super Script III; Thermo Fisher Scientific, Waltham, MA, USA), purified (SPRIselect reagent kit, Beckman Coulter, Brea CA, USA), and PCR amplified for 14 cycles (KAPA HiFi HotStart PCR Kit, KAPA Biosystems, Wilmington, MA, USA). After size selection by polyacrylamide gel electrophoresis, miRNAs containing flanking p5 and p7 adapters were sequenced on a HiSeq 2000 instrument (Illumina; library preparation and sequencing were performed by GenXPro GmbH, Frankfurt, Germany). The results were uploaded to EMBL Array Express. The accession number is E-MTAB-14388.

### 2.3. Reverse transcription-quantitative PCR (RT-qPCR)

The total RNA was reverse transcribed into cDNA using Super Script III (Thermo Fisher Scientific) according to the manufacturer's instructions. qPCR was subsequently performed using a TaqMan miRNA assay kit Applied Biosystems (Waltham MA, USA); (Thermo Fisher Scientific) according

to the manufacturer's protocol to amplify miRNAs on an ABI 7500 Real-Time PCR system (Applied Biosystems; Thermo Fisher Scientific). The thermocycling reactions were performed in the following three steps: initial denaturation at 95°C for 5 min, 40 cycles of 95°C for 10 s, and 60°C for 30 s; and the following primer pairs for qPCR are as follows: miR-192-5p forward, 5'-GGACTTTCTTCATTACAC CCG-3'; reverse, 5'-GACCACTGAGGTTAGAGCCA-3'; and U6 forward, 5'-TCGCTTCGGCAGCACATATACT-3' and reverse, 5'-ACGCTTCGGAATTTGCGTGTC-3'. StarD13 forward, 5'-ACTGTCTGTGGTGGGAAACA-3'; StarD13 reverse, TGAGGCACACTTGTTC AACG-3'; GAPDH forward, 5'-TCAAGAAGGTGGTGAAGCAGG-3'; and GAPDH reverse, 5'-TCAAAGGTGGAGGAGTGGGT-3'. The expression levels were quantified using the 2<sup>-ΔΔC<sub>t</sub></sup> method, miRNA expression was normalized to that of U6, and mRNA expression was normalized to that of GAPDH. The reactions were performed in triplicate for each sample, with at least three independent runs.

### 2.4. miRNA inhibitor transfection

PC-3 cells were seeded in 6-well plates. Transfection of the miR-192-5p antagomir (CUGACCUAUGAAUUGACAGCC) and the corresponding negative control miRNA (miR-NC, UUUGUACUACACAAAAGUACUG) were purchased from Thermo Fisher Scientific Company. Transfection into PC-3 cells was performed using Lipofectamine 3000 in 250 µL of Opti-MeM (Reduced Serum Medium) (Invitrogen, Waltham MA, USA) according to the manufacturer's instructions. Then, the cells were trypsinized and counted for subsequent analyses of hsa-microRNA-192-5p expression or for use in cell proliferation assays.

### 2.5. Cell proliferation assay

To assess the proliferation of transfected or treated PC-3 cells, the CellTiter 96® AQ<sub>ueous</sub> Nonradioactive Cell Proliferation Assay (MTS) was used (Promega, Mannheim, Germany). Transfected or treated PC-3 cells were seeded in 96-well plates (2000 cells per well), after which MTS was added, and the absorbance was measured after 24 h, 48 h, and 120 h. At least three independent experiments were performed in triplicate. The data are expressed as percentages of proliferation, where the proliferation rates for the control were arbitrarily set to 100%.

### 2.6. Fluorogenic caspase activity assay

PC-3 cells were washed with phosphate buffered saline. Cell lysis buffer was added (#70108, Cell Signaling Technology, Danvers, MA, USA), and cell lysates were collected in Eppendorf cups. Subsequently, the caspase

activity assay (Caspase-3 Activity Assay Kit #5723, Cell Signaling Technology) was performed according to the manufacturer's instructions. Fluorescence was measured using a plate reader (excitation wavelength: 490 nm; emission wavelength: 525 nm) and expressed in relative fluorescence units.

### 2.7. Data analysis – quantification of miRNA expression by omiRas

The analysis of the miRNA-seq libraries was conducted using omiRas (Müller et al. 2013). After removing adapters and low-quality reads, the remaining reads were summarized as tags, and singletons were excluded from the dataset. Subsequently, the tags were mapped to the human genome (hg19) with bowtie (Li and Durbin 2009). The annotation of tags and mapping to the hg19 were performed using various databases of coding and ncRNAs retrieved from the UCSC Table Browser. ncRNAs that are not mapped to exonic regions of coding genes were quantified in each library. By following normalization of the read number for each tag to the number of mapping loci, the differential expression analysis was performed between treated samples and controls for each miRNA using the DEGseq bioconductor package (Wang et al. 2010). A clustered heatmap was generated using the heatmap package of R software (version 3.5.0). A volcano plot was created using the R package ggplot.

### 2.8. Target prediction and identification of miRNA–mRNA pairs

To identify miRNA-correlated genes, a two-step approach was used. First, three miRNA databases were used to predict potential mRNA targets of miRNAs (miRDB, TargetScan, and miRanda). Second, Pearson correlation coefficients of the intersecting miRNA–mRNA pairs were calculated. ( $R < -0.7$  and  $p < 0.05$ ) for the downstream analysis. The results intersected with previously published RNA-seq data (GSE71070).

### 2.9. Gene ontology (GO) term and KEGG pathway enrichment analyses

GO and KEGG pathway enrichment analyses of the DEGs were performed using the DAVID bioinformatics resource (Dennis et al. 2003). We used a false discovery rate (FDR)  $< 0.01$  as screening threshold to determine the significance of the functions and pathways, and the “GO KEGG bar dot” function of the bioinformatics analysis software “SR plot” (Tang et al. 2023) was used to visualize the GO terms and KEGG enrichment.

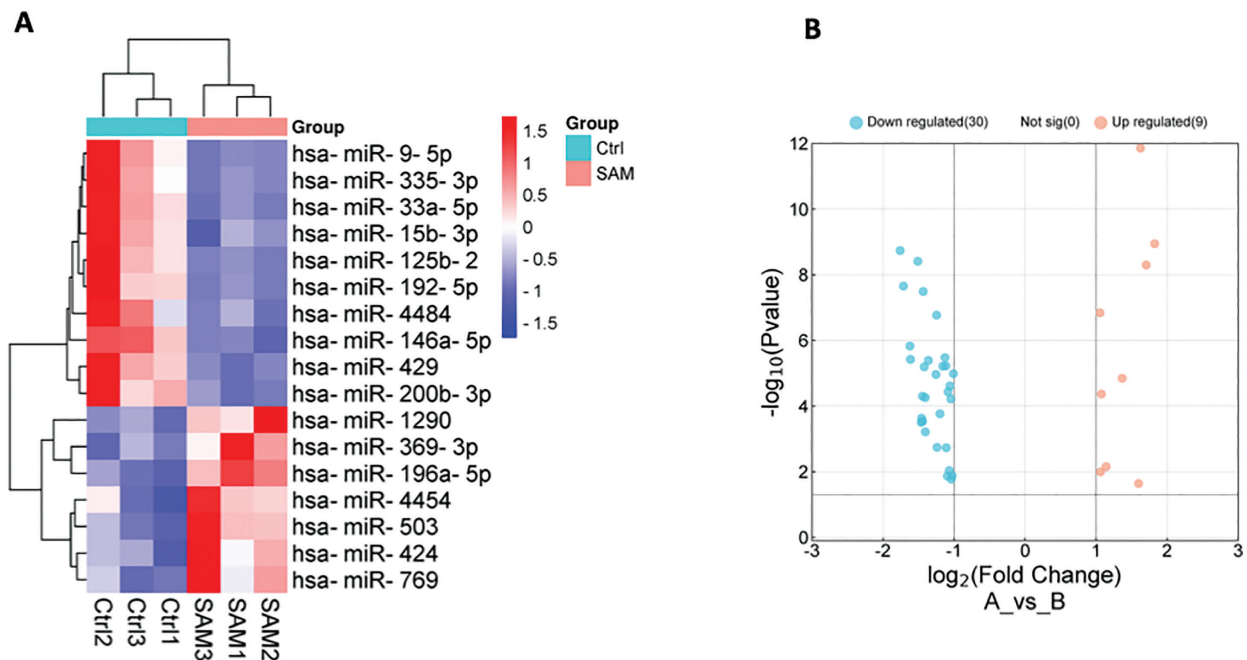
## 3. Results

### 3.1. miRNA prediction and expression

We analyzed the miRNA-seq dataset of PC-3 cell samples treated with SAM and untreated controls by means of omiRas. We detected 17 differentially expressed mature miRNAs that satisfied the criterion of an FDR-corrected  $P < 0.005$ . The set of miRNAs included a total of seven upregulated miRNAs in the treated samples (Figure 1a), many of them with tumor suppressor function, for example, hsa-miR-4454 and hsa-miR-503. In contrast, we detected 10 downregulated miRNAs, displaying mainly oncogenic functions (Figure 1a), such as hsa-miR-429 and also hsa-miR-9-5p, which is highly expressed in prostate cancer cells under normal conditions. The volcano plot in Figure 1b displays the differential expression of upregulated and downregulated miRNAs between SAM-treated samples and controls, whereas the heatmap in Figure 1a clearly shows that the hierarchical clustering analysis performed with omiRas completely discriminated the two groups (SAM-treated and control samples) as well as those upregulated from downregulated samples. Target identification of the respective miRNAs was performed using three different miRNA databases (miRDB, TargetScan, and miRanda) to predict potential mRNA targets of miRNAs. We selected only those miRNAs that were found to be predicted in at least two of the three databases. In total, we found 2775 predicted mRNA targets for upregulated miRNAs (Figure 2a) and 5384 predicted target genes for downregulated miRNAs (Figure 2b).

### 3.2. Transcripts regulated by miRNAs

Based on the results of the target identification, we concentrated especially on those potential transcript-miRNA interactions in which the differential expression of transcripts and miRNAs among the treated samples and controls exhibited the opposite trend, i.e., when transcripts were upregulated in a particular comparison, the miRNA was downregulated, and *this was the opposite*. Hence, 92 target transcripts were downregulated (Figure 2a), 32 of which exhibited oncogenic functions, while the expression of the mature miRNA was upregulated in the treated samples compared with the control samples. Among those downregulated transcripts, we identified, for example, *transforming growth factor beta 2 (TGFB2)* (Figure 2a), which is known to promote cancer progression in later stages of prostate cancer. In contrast, 41 targets were upregulated (Figure 2b) in the treated samples compared with the control samples, while the mature miRNAs were downregulated. Eleven of those upregulated genes are known to act as tumor suppressor genes. Among the upregulated genes, *SERPINE1* (Figure 2b), which encodes plasminogen



**Fig 1.** Detection of differentially expressed miRNAs in PC-3 cells treated with SAM and controls. **(A)** Heatmap of differentially expressed miRNAs in PC-3 cells treated with SAM and untreated controls. Seventeen differentially expressed mature miRNAs (7 upregulated and 10 downregulated) were detected ( $P < 0.005$ ). Clustering clearly distinguished between the treated samples and controls as well as between the upregulated and downregulated groups. **(B)** A volcano plot displaying the differentially expressed miRNAs. miRNAs, microRNA; SAM, S-adenosylmethionine.

activator inhibitor-1 (PAI-1) and is known to be increased in prostate cancer cell lines as well as in tumor samples of patients (Kubala and De Clerck 2019), was detected. PAI-1 usually inhibits the urokinase plasminogen activator (uPA), which has been implicated in tumor cell invasion, survival, and metastasis in a variety of cancer entities, including prostate cancer (Kubala and De Clerck 2019). Since an increase in StarD13 gene expression in the transcriptome could not be detected despite the significant upregulation of hsa-miR-9-5p, we performed real-time PCR for StarD13 in SAM-treated PC-3 cells and ultimately found significant upregulation of its expression (211% of the untreated control) (Figure 2c).

### 3.3. Downregulation of hsa-miR-192-5p diminishes the proliferation of PC-3 cells

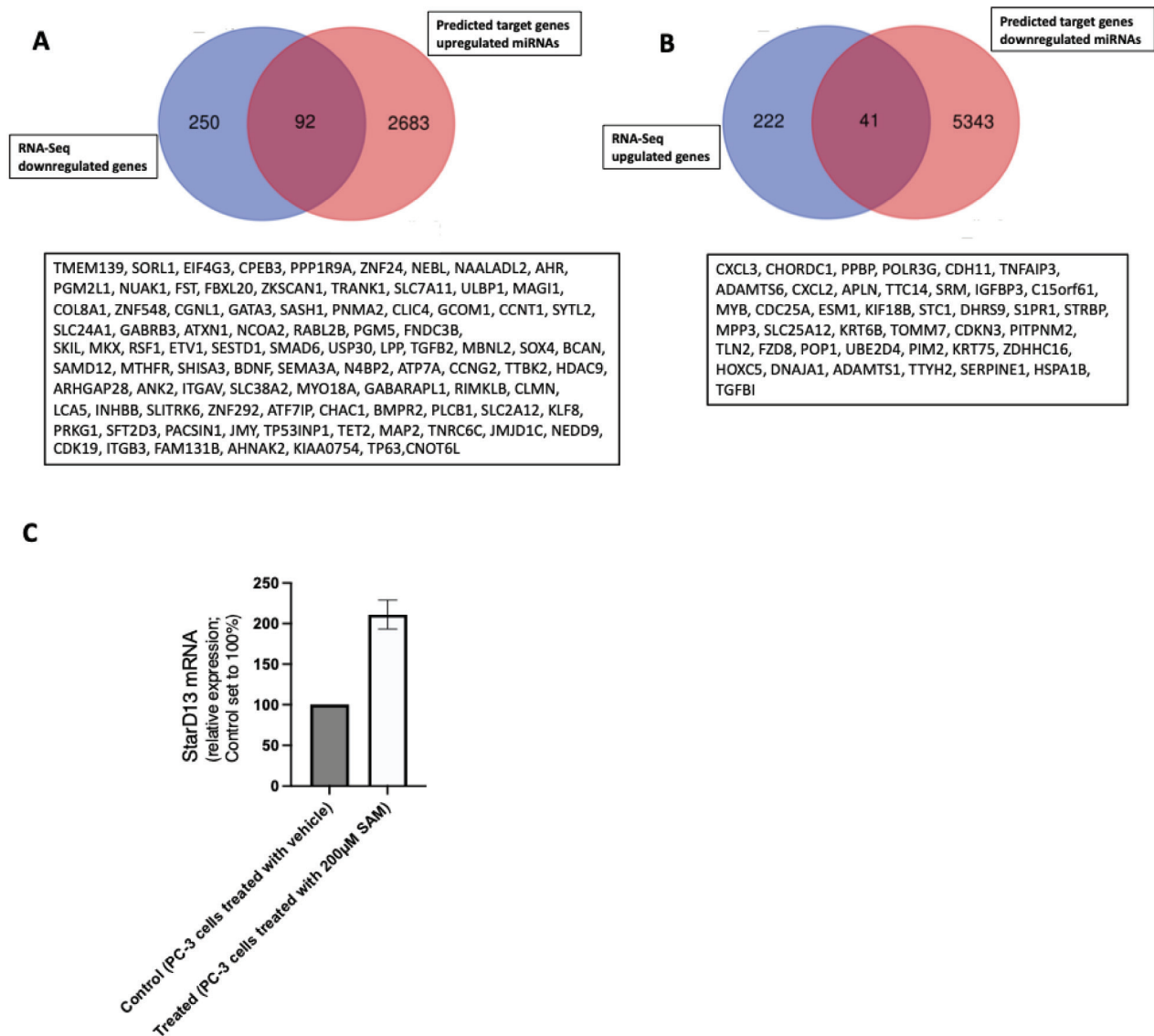
To confirm the impact of SAM on the differential expression of miRNAs in PC-3 cells, we carried out quantitative PCR on PC-3 cells treated with SAM. We used primers against hsa-miR-192-5p since it is known to be overexpressed and promote cell proliferation in prostate cancer cells (Chen et al. 2019b). SAM treatment caused significant downregulation of hsa-miR-192-5p expression after 48 h and 120 h (Figure 3a). After transfection of cells with an inhibitor against hsa-miR-192-5p, the expression significantly decreased after 24 h, 48 h, and 120 h (Figure 3a). A combination of both treatments even increased

the downregulation of hsa-miR-192-5p expression (Figure 3a). We also examined if the downregulation of hsa-miR-192-5p causes downregulation of proliferation. After 48 h and 120 h, the proliferation of the samples transfected with the hsa-miR-192-5p agomir significantly decreased (Figure 3b). A combination of SAM and the hsa-miR-192-5p agomir had the most significant downregulatory effect on PC-3 cell proliferation after 120 h (decrease of 77% compared with that of the untreated controls) (Figure 3b). To clarify if the results of the MTS assay are linked to a loss in cell proliferation or to cell death, a fluorescent caspase-3 activity assay was performed, wherein we could detect a significantly induced caspase-3 activity in PC-3 cells transfected with the hsa-miR-192-5p agomir after 120 h of cell culture (Figure 3c). Again, a combination of SAM-treatment and transfection with the hsa-miR-192-5p agomir had the strongest effect after 120 h of cell culture (Figure 3c). We conclude that downregulation of hsa-miR-192-5p may induce apoptosis in PC-3 cells.

### 3.4. GO and KEGG pathway enrichment analysis

GO term enrichment and KEGG pathway analysis of the differentially expressed genes were performed by comparing the treatment group (treated with SAM) and the control group. Among the significantly enriched GO terms for the downregulated transcripts, “cellular response for

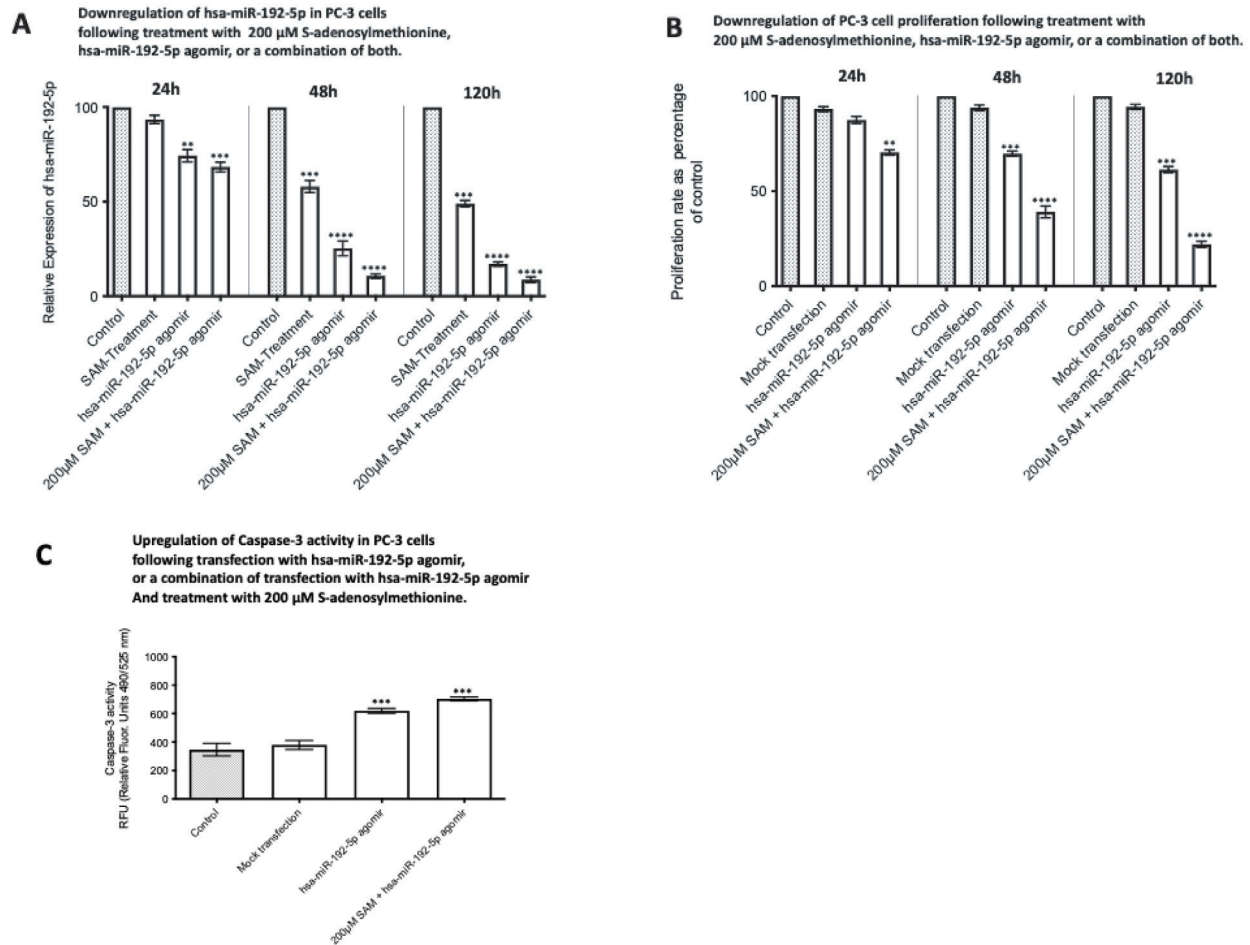




**Fig 2.** Combined analyses of miRNA expression and RNA-seq data. The differentially expressed genes of the transcriptome that were matched to target genes were detected via three different miRNA databases (miRDB, TargetScan, and miRanda). **(A)** A total of 92 downregulated genes were associated with upregulated miRNAs, and **(B)** 41 upregulated genes were associated with downregulated miRNAs. The genes are shown in the boxes. **(C)** Gene expression levels of StarD13 following treatment with 200 µm SAM. A significant increase in the expression of StarD13 was observed (211% of the control). miRNA, microRNA; SAM, S-adenosylmethionine; StarD13, STAR-related lipid transfer domain containing 13.

bone morphogenic protein (BMP) stimulus" (GO:0071773), "response to BMP" (GO:0071772), "regulation of BMP signaling pathway" (GO:0030510), "BMP signaling pathway" (GO:0030509), "positive regulation of epithelial cell migration" (GO:0010634), "regulation of epithelial cell migration" (GO:0010632), "regulation of cellular response to growth factor stimulus" (GO:0090287), and "negative regulation of cytoskeleton organization" (GO:0051494) were found in the BP category (Figure 4a and Table S2). In terms of molecular functions, "insulin-like growth factor I binding" (GO:0031994),

"transcription coregulator activity" (GO:0003712), "fibroblast growth factor binding" (GO:0017134), and "transforming growth factor beta receptor binding" (GO:0005160) were found to be enriched significantly in the set of downregulated mRNAs (Figure 4a and Table S2); whereas, for the cellular component (CC) category, we detected enrichment in the set of downregulated transcripts for "actin-based cell projection" (GO:0098858), "actomyosin" (GO:0042641), and "cell-cell junction" (GO:0005911) (Figure 4a and Table S3). The KEGG pathway analysis revealed particular enrichment of miRNAs

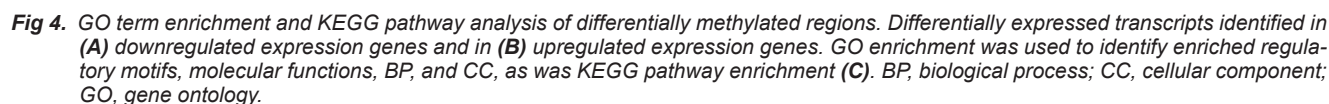


**Fig 3.** (A) Differential expression of hsa-miR-192-5p (after 24, 48, and 120 h) in untreated PC-3 cells or mock-transfected PC-3 cells. Since both groups displayed almost no differences, we described them as controls and set them to 100%. The expression of hsa-miR-192-5p was significantly downregulated following treatment with SAM (60% of the control after 48 h and 45% after 120 h), after transfection with the miRNA agomir (70% of the control after 24 h, 29% of the control after 48 h, and 19% after 120 h), or after combination treatment (68% of the control after 24 h, 13% of the control after 48 h, and 9% of the control after 120 h). (B) Transfection with the hsa-miR-192-5p agomir alone or in combination with SAM inhibited the proliferation of PC-3 cells. Twenty-four hours after PC-3 cells were transfected with the hsa-miR-192-5p agomir, and the cells were seeded in 96-well plates and grown for 24 h, 48 h, or 120 h. Proliferation was measured using the 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide assay. Differences between untransfected PC-3 cells (PC-3) and mock-transfected PC-3 cells (miR-NC) were hardly detectable. Transfection with the hsa-miR-192-5p agomir resulted in significantly diminished proliferation of 71% (after 48 h) and 62% (after 120 h) compared to that of the controls. A combination of SAM treatment and transfection with the miRNA agomir decreased the proliferation rate of PC-3 cells even more clearly (70% of the control after 24 h, 40% of the control after 48 h, and 23% of the control after 120 h). (C) A fluorogenic caspase activity assay revealed a significant upregulation of the caspase-3 activity in PC-3 cells after transfection with hsa-miR-192-5p agomir or a combination of SAM treatment and hsa-miR-192-5p agomir transfection for 120 h. The results are expressed as the means  $\pm$  SDs of three independent experiments: \* $P < 0.01$ , \*\* $P < 0.001$ , \*\*\* $P < 0.0001$ , and \*\*\*\* $P < 0.00001$ . miRNA, microRNA; SAM, S-adenosylmethionine.

in cancer and the TGF- $\beta$  signaling pathway (Figure 4a and Table S4). For the TGF- $\beta$  signaling pathway, five downregulated transcripts, i.e., *FST*, *SMAD6*, *TGFB2*, *INHBB*, and *BMP2*, were detected (Figure 4c).

Considering upregulated gene expression, we detected, for example, significant enrichment for “cell–cell adhesion via plasma-membrane adhesion molecules” (GO:0098742), “cell killing” (GO:0001906), “negative regulation of cytokine production” (GO:0001818), and “positive regulation of cell killing”

(GO:0031343) in the BP category (Figure 4b and Table S5); “growth factor binding” (GO:0031343), “extracellular matrix structural constituent” (GO:0005201), and “cytokine activity” (GO:0005201) in the molecular functions category (Figure 4b and Table S6); and “plasma membrane bounded cell projection cytoplasm” (GO:0032838), “cytoplasmic region” (GO:0099568), and “collagen-containing extracellular matrix” (GO:0062023) in the CC category (Figure 4b and Table S7). The KEGG pathway analysis of the upregulated transcripts



e.g., a recently published study linked the treatment of cancer cells with SAM or methyladenosine to the combat of metastasis by targeting specific miRNAs (Tomasi et al. 2017). In the present publication, the differential expression of miRNAs in prostate cancer cells following treatment with SAM was investigated for the first time. Treatment of prostate cancer cells (PC-3 cells) with AdoMet resulted in upregulation and downregulation of miRNAs. Prediction of target

genes and alignment with a recently performed transcriptome study revealed 92 downregulated and 41 upregulated genes. Thirty-one of the downregulated genes were identified as proto-oncogenes, and 11 of the upregulated transcripts were identified as tumor suppressor genes. Among the differentially expressed miRNAs, hsa-miR-9-5p was detected; under normal conditions, hsa-miR-9-5p is highly expressed in prostate cancer cells and targets StAR-related lipid transfer domain containing 13 (StarD13), thus leading to an increase in the expression of vimentin and N-cadherin, which are the two key factors involved in epithelial–mesenchymal transformation (Chen et al. 2019a). In conjunction with this, a decrease in the expression of StarD13 is usually tightly associated with an increase in the viability and invasion and migration potential of prostate cancer cells (Chen et al. 2019a). In the present study, hsa-miR-9-5p was clearly downregulated following SAM treatment; however, an increase in the expression of StarD13 could not be detected in the associated transcriptome. Real-time quantitative PCR revealed significant upregulation of StarD13, suggesting the presence of a functional system. Additionally, hsa-miR-192-5p, which is usually overexpressed and known to promote cell proliferation in prostate cancer, was found to be downregulated in treated samples (Chen et al. 2019b). One of the predicted targets of hsa-miR-192-5p is *SERPINE1* (urokinase PAI-1), which was simultaneously upregulated in the transcriptome of SAM-treated samples in this study. *SERPINE1* may generally be considered a prognostic factor for disease progression and relapse in several cancer types (Kubala and De Clerck 2019). However, in prostate cancer, the upregulation of *SERPINE1* seems to be favorable since the uPA/PAI-1 ratio and urokinase-type plasminogen activator receptor (uPAR) were found to be higher in prostate carcinoma samples than in benign prostatic hyperplasia samples. Generally, uPAR binds the proactive form of uPA, which subsequently cleaves plasminogen into plasmin, converting growth factors and matrix metalloproteinases to their active forms, leading to the degradation of components of the extracellular matrix (ECM) and the basement membrane. In this way, metastasis could be promoted (Kubala and De Clerck 2019). PAI-1 inhibits the catalytic activity of uPA and plasmin, preventing the degradation of ECM and basement membrane constituents, and thus may impede metastasis (Kubala and De Clerck 2019). Additionally, uPAR can be cleaved between catalytic domains, allowing it to interact with G protein-coupled receptors and activating different signaling pathways involved in cancer progression (Kubala and De Clerck 2019). To obtain additional information about the effects of hsa-miR-192-5p on prostate cancer cells (PC-3 cells), a knockdown of the miRNA was performed by the transfection with the respective agomir, followed by MTS assays, which revealed a significant decrease of viable cancer cells, clearly indicating its anticancer effects. To clarify,

if this decrease was linked to a loss in cell proliferation or the upregulation of apoptosis, we performed fluorometric caspase-3 assays that showed a significant increase of the caspase-3 activity in transfected cells. Recently, it was reported that the downregulation of miRNA-888-5p induced apoptosis in laryngeal squamous cancer cells (Pagano et al. 2020). Upregulated miRNAs, e.g., hsa-miR-503, which is known to suppress tumor cell proliferation and metastasis in prostate cancer cells (Hu et al. 2023), were also found in this study.

To further clarify the biological impact of the predicted target genes aligned to the previously conducted transcriptome, GO term enrichment and KEGG pathway analyses were performed for the 133 upregulated and downregulated genes. In the BP category, downregulated genes associated with cellular responses to BMP stimulus were detected. BMP ligand dimers bind to type I and type II serine/threonine receptor monomers, resulting in the formation of a heterotetrameric kinase complex. Subsequently, the active type I kinase, in turn, activates the receptor-mediated Smad protein via phosphorylation followed by translocation of the complex to the nucleus, where it affects the transcription of BMP target genes involved in proliferation (Provera et al. 2023). Further significantly downregulated BP terms are involved, for example, in the control of epithelial cell migration and cellular response to growth factor stimulus, all of which are crucial features for cancer initiation, progression, and metastasis (Grant and Kyprianou 2013; Joshi et al. 2015). The KEGG pathway analysis revealed that downregulation of the TGF- $\beta$  pathway, which is well known to act in tumor suppression in early-stage prostate cancer cells and in tumor promotion in later stages of the disease (Thompson-Elliott et al. 2021), occurred. The turning point is likely the development of resistance to the inhibitory effects of TGF- $\beta$  signaling on cell proliferation (Thompson-Elliott et al. 2021). The cell line we used (PC-3) represents a model for later stages of prostate cancer; therefore, downregulation of the TGF- $\beta$  pathway seems to be favorable in this respect. Among the downregulated members of the pathway, we found, e.g., SMAD6, leading to a decrease in SMAD2/SMAD3 activity, which is usually necessary for the regulation of target genes in the nucleus (among others involved in proliferation, migration, and invasion) (Thompson-Elliott et al. 2021). As expected, the KEGG pathway analysis also revealed the downregulation of miRNAs in cancer. Upregulated gene targets corresponding to downregulated miRNAs in the BP category were involved in the positive regulation of cell killing and the negative production of cytokine factors, which, under normal conditions, may contribute to the proliferation of cancer cells (Joshi et al. 2015; Pejčić et al. 2023). In the molecular function category, upregulation of ECM constituents was associated with upregulation of collagen containing ECM in the CC category. This seems to be important since the integrity of the ECM, as mentioned



above, is crucial for the origination of cancer and metastasis (Luthold et al. 2022).

A clear limitation of the study is the lack of information concerning the mechanisms by which AdoMet may affect the regulation of differentially expressed miRNAs in PC-3 cells, for which alterations in promoter or histone methylation may be the cause (Schmidt et al. 2016; Mathes et al. 2024). However, in previous studies focused on promoter and histone methylation (H3K4me3/H3K27me3), we could not detect any of the differentially expressed miRNAs found in this study (Schmidt et al. 2016; Mathes et al. 2024). Extending the experiments to further histone marks and the analysis of different genomic elements other than promoter regions may be helpful in the future (Del Valle-Morales et al. 2022). Recently, it was reported that differentially methylated intronic regions could be involved in the expression of intragenic miRNAs (Del Valle-Morales et al. 2022). Moreover, during the last decade, it became obvious that N6-methyladenosine (m6A) methylation, one of the most common RNA modifications, may regulate the generation and degradation of ncRNAs, thus being especially crucial for cancer initiation and progression (Mosca et al. 2021). These points should be considered in future studies.

In conclusion, treatment with SAM leads to differential expression of miRNAs in castration-resistant prostate cancer cells and subsequent gene-to-peak annotation alignment

with the results of a transcriptome study as well as GO term analysis and knockdown experiments revealed the biological relevance of the SAM.

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## Ethics Approval

Not applicable.

## Author Contributions

TS designed the study, carried out the experiments, and performed the bioinformatic analysis. TS analyzed the data and wrote the manuscript.

## Competing Interest

The author declares no conflict of interest.

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Supplementary Tables

Table S1. Functional enrichment analysis (BP) of the downregulated genes

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0048485	Sympathetic nervous system development	4/86	21/18866	2.27016E-06	0.002377266	0.001927173	GATA3/SOX4/SEMA3A/TP63	4
GO:0003283	Atrial septum development	4/86	23/18866	3.3355E-06	0.002377266	0.001927173	TGFB2/SOX4/ANK2/BMPR2	4
GO:0003179	Heart valve morphogenesis	5/86	52/18866	3.8427E-06	0.002377266	0.001927173	GATA3/SMAD6/TGFB2/SOX4/BMPR2	5
GO:0003181	Atrioventricular valve morphogenesis	4/86	24/18866	3.9887E-06	0.002377266	0.001927173	SMAD6/TGFB2/SOX4/BMPR2	4
GO:0003171	Atrioventricular valve development	4/86	26/18866	5.57292E-06	0.002481207	0.002011434	SMAD6/TGFB2/SOX4/BMPR2	4
GO:0031069	Hair follicle morphogenesis	4/86	28/18866	7.57961E-06	0.002481207	0.002011434	FST/TGFB2/ATP7A/TP63	4
GO:0003170	Heart valve development	5/86	61/18866	8.51768E-06	0.002481207	0.002011434	GATA3/SMAD6/TGFB2/SOX4/BMPR2	5
GO:0003183	Mitral valve morphogenesis	3/86	10/18866	1.07242E-05	0.002481207	0.002011434	SMAD6/SOX4/BMPR2	3
GO:0071772	Response to BMP	7/86	168/18866	1.16587E-05	0.002481207	0.002011434	SORL1/FST/GATA3/SKIL/SMAD6/TGFB2/BMPR2	7
GO:0071773	Cellular response to BMP stimulus	7/86	168/18866	1.16587E-05	0.002481207	0.002011434	SORL1/FST/GATA3/SKIL/SMAD6/TGFB2/BMPR2	7
GO:0048880	Sensory system development	10/86	394/18866	1.2143E-05	0.002481207	0.002011434	SLC7A11/COL8A1/GATA3/CLIC4/SKIL/TGFB2/BDNF/SEMA3A/SLITRK6/BMPR2	10
GO:0048730	Epidermis morphogenesis	4/86	32/18866	1.31282E-05	0.002481207	0.002011434	FST/TGFB2/ATP7A/TP63	4
GO:0003279	Cardiac septum development	6/86	114/18866	1.35301E-05	0.002481207	0.002011434	GATA3/SMAD6/TGFB2/SOX4/ANK2/BMPR2	6
GO:0003174	Mitral valve development	3/86	11/18866	1.46971E-05	0.002502712	0.002028868	SMAD6/SOX4/BMPR2	3
GO:0003230	Cardiac atrium development	4/86	36/18866	2.12083E-05	0.003370699	0.002732516	TGFB2/SOX4/ANK2/BMPR2	4
GO:1905314	Semi-lunar valve development	4/86	37/18866	2.36965E-05	0.003515909	0.002850233	GATA3/SMAD6/TGFB2/BMPR2	4
GO:0003281	Ventricular septum development	5/86	76/18866	2.50715E-05	0.003515909	0.002850233	GATA3/SMAD6/TGFB2/SOX4/BMPR2	5
GO:0060413	Atrial septum morphogenesis	3/86	16/18866	4.9065E-05	0.006498385	0.00526803	TGFB2/SOX4/BMPR2	3
GO:0048483	Autonomic nervous system development	4/86	47/18866	6.18134E-05	0.007400207	0.005999108	GATA3/SOX4/SEMA3A/TP63	4
GO:0001654	Eye development	9/86	384/18866	6.30723E-05	0.007400207	0.005999108	SLC7A11/COL8A1/GATA3/CLIC4/SKIL/TGFB2/BDNF/SLITRK6/BMPR2	9
GO:0030510	Regulation of BMP signaling pathway	5/86	93/18866	6.63775E-05	0.007400207	0.005999108	SORL1/FST/SKIL/SMAD6/BMPR2	5
GO:0150063	Visual system development	9/86	388/18866	6.82905E-05	0.007400207	0.005999108	SLC7A11/COL8A1/GATA3/CLIC4/SKIL/TGFB2/BDNF/SLITRK6/BMPR2	9
GO:0030509	BMP signaling pathway	6/86	155/18866	7.63551E-05	0.007914368	0.006415922	SORL1/FST/SKIL/SMAD6/TGFB2/BMPR2	6
GO:0003215	Cardiac right ventricle morphogenesis	3/86	20/18866	9.85737E-05	0.009791656	0.007937778	GATA3/TGFB2/SOX4	3
GO:0003177	Pulmonary valve development	3/86	21/18866	0.000114624	0.010930574	0.008861062	SMAD6/TGFB2/BMPR2	3

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0016358	Dendrite development	7/86	247/18866	0.000135064	0.012023407	0.009746987	CPEB3/PPP1R9A/ BDNF/SEMA3A/PRKG1/ PACSIN1/MAP2	7
GO:0043010	Camera-type eye deve- lopment	8/86	332/18866	0.000136171	0.012023407	0.009746987	SLC7A11/COL8A1/GATA3/ CLIC4/SKIL/TGFB2/ SLITRK6/BMPR2	8
GO:0003205	Cardiac chamber deve- lopment	6/86	174/18866	0.000144194	0.012277131	0.009952673	GATA3/SMAD6/TGFB2/ SOX4/ANK2/BMPR2	6
GO:0010634	Positive regulation of epithelial cell migration	6/86	176/18866	0.000153468	0.01261616	0.010227512	GATA3/SASH1/TGFB2/ HDAC9/BMPR2/ITGB3	6
GO:0090092	Regulation of trans- membrane receptor protein serine/thre- onine kinase signaling pathway	7/86	254/18866	0.000160478	0.012752643	0.010338155	SORL1/FST/SKIL/SMAD6/ TGFB2/INHBB/BMPR2	7
GO:0060393	Regulation of pathway- restricted SMAD prote- in phosphorylation	4/86	62/18866	0.000183531	0.014114136	0.011441873	SMAD6/TGFB2/INHBB/ BMPR2	4
GO:0060037	Pharyngeal system development	3/86	26/18866	0.000220418	0.015457062	0.012530539	GATA3/TGFB2/BMPR2	3
GO:0060384	Innervation	3/86	26/18866	0.000220418	0.015457062	0.012530539	GABRB3/SEMA3A/ SLITRK6	3
GO:0060389	Pathway-restricted SMAD protein phospho- rylation	4/86	65/18866	0.000220445	0.015457062	0.012530539	SMAD6/TGFB2/INHBB/ BMPR2	4
GO:0003148	Outflow tract septum morphogenesis	3/86	27/18866	0.000247155	0.016834784	0.013647414	SMAD6/TGFB2/BMPR2	3
GO:0031032	Actomyosin structure organization	6/86	200/18866	0.000306151	0.020274023	0.016435493	PPP1R9A/NEBL/CGNL1/ PGM5/ARHGAP28/MY- O18A	6
GO:0003206	Cardiac chamber mor- phogenesis	5/86	131/18866	0.000331986	0.020492366	0.016612497	GATA3/SMAD6/TGFB2/ SOX4/BMPR2	5
GO:0003231	Cardiac ventricle deve- lopment	5/86	131/18866	0.000331986	0.020492366	0.016612497	GATA3/SMAD6/TGFB2/ SOX4/BMPR2	5
GO:0003209	Cardiac atrium morpho- genesis	3/86	30/18866	0.00033969	0.020492366	0.016612497	TGFB2/SOX4/BMPR2	3
GO:0010595	Positive regulation of endothelial cell migration	5/86	132/18866	0.000343832	0.020492366	0.016612497	GATA3/SASH1/HDAC9/ BMPR2/ITGB3	5
GO:0032535	Regulation of cellular component size	8/86	383/18866	0.000358164	0.020825902	0.016882884	PPP1R9A/BDNF/SEMA3A/ ATP7A/ARHGAP28/ BMPR2/JMY/MAP2	8
GO:0051497	Negative regulation of stress fiber assembly	3/86	31/18866	0.00037485	0.021277191	0.017248729	PPP1R9A/CGNL1/ ARHGAP28	3
GO:0003176	Aortic valve develop- ment	3/86	32/18866	0.000412269	0.022856978	0.018529411	GATA3/SMAD6/BMPR2	3
GO:0060411	Cardiac septum mor- phogenesis	4/86	77/18866	0.00042271	0.022903202	0.018566884	SMAD6/TGFB2/SOX4/ BMPR2	4
GO:0010632	Regulation of epithelial cell migration	7/86	301/18866	0.000449424	0.023809483	0.019301576	GATA3/SASH1/TGFB2/ SEMA3A/HDAC9/BMPR2/ ITGB3	7
GO:0021675	Nerve development	4/86	79/18866	0.000466089	0.024155573	0.01958214	GABRB3/BDNF/SEMA3A/ SLITRK6	4
GO:0032232	Negative regulation of actin filament bundle assembly	3/86	34/18866	0.000494123	0.025063604	0.020318252	PPP1R9A/CGNL1/ ARHGAP28	3

(Continued)



Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0010769	Regulation of cell morphogenesis involved in differentiation	7/86	310/18866	0.000535603	0.025683957	0.020821152	PPP1R9A/SKIL/BDNF/SEMA3A/BMPR2/MAP2/NEDD9	7
GO:0090287	Regulation of cellular response to growth factor stimulus	7/86	310/18866	0.000535603	0.025683957	0.020821152	SORL1/FST/GATA3/SKIL/SMAD6/BMPR2/ITGB3	7
GO:0110111	Negative regulation of animal organ morphogenesis	3/86	35/18866	0.000538674	0.025683957	0.020821152	GATA3/TGFB2/BMPR2	3
GO:0002088	Lens development in camera-type eye	4/86	83/18866	0.000562221	0.026281074	0.021305215	SLC7A11/GATA3/SKIL/SLITRK6	4
GO:0000289	Nuclear-transcribed mRNA poly(A) tail shortening	3/86	36/18866	0.000585716	0.026852821	0.021768712	CPEB3/TNRC6C/CNOT6L	3
GO:0016331	Morphogenesis of embryonic epithelium	5/86	151/18866	0.000635718	0.028595307	0.023181289	GATA3/TGFB2/SOX4/MTHFR/TP63	5
GO:0001942	Hair follicle development	4/86	87/18866	0.00067167	0.029652983	0.024038713	FST/TGFB2/ATP7A/TP63	4
GO:0007050	Cell cycle arrest	6/86	234/18866	0.000702266	0.030276819	0.024544437	SKIL/TGFB2/SOX4/JMY/TP53INP1/CNOT6L	6
GO:0022404	Molting cycle process	4/86	89/18866	0.000731697	0.030276819	0.024544437	FST/TGFB2/ATP7A/TP63	4
GO:0022405	Hair cycle process	4/86	89/18866	0.000731697	0.030276819	0.024544437	FST/TGFB2/ATP7A/TP63	4
GO:1902904	Negative regulation of supramolecular fiber organization	5/86	156/18866	0.0007366	0.030276819	0.024544437	PPP1R9A/CGNL1/TTBK2/ARHGAP28/MAP2	5
GO:0098773	Skin epidermis development	4/86	90/18866	0.000763091	0.030834037	0.024996155	FST/TGFB2/ATP7A/TP63	4
GO:1902895	Positive regulation of pri-miRNA transcription by RNA polymerase II	3/86	40/18866	0.000799907	0.031782969	0.025765423	GATA3/SMAD6/TGFB2	3
GO:0048286	Lung alveolus development	3/86	41/18866	0.000860228	0.03260155	0.026429021	SLC7A11/ATP7A/BMPR2	3
GO:0014909	Smooth muscle cell migration	4/86	93/18866	0.000862978	0.03260155	0.026429021	SORL1/ATP7A/PRKG1/ITGB3	4
GO:0009267	Cellular response to starvation	5/86	163/18866	0.000897377	0.03260155	0.026429021	NUAK1/SLC38A2/GABARAPL1/INHBB/BMPR2	5
GO:0051494	Negative regulation of cytoskeleton organization	5/86	163/18866	0.000897377	0.03260155	0.026429021	PPP1R9A/CGNL1/TTBK2/ARHGAP28/MAP2	5
GO:0045713	Low-density lipoprotein particle receptor biosynthetic process	2/86	10/18866	0.00090256	0.03260155	0.026429021	ITGAV/ITGB3	2
GO:1904526	Regulation of microtubule binding	2/86	10/18866	0.00090256	0.03260155	0.026429021	TTBK2/MAP2	2
GO:0051100	Negative regulation of binding	5/86	169/18866	0.001054847	0.037420693	0.030335744	SORL1/RSF1/TTBK2/ARHGAP28/MAP2	5
GO:0050673	Epithelial cell proliferation	8/86	453/18866	0.001072913	0.037420693	0.030335744	FST/COL8A1/GATA3/TGFB2/ATP7A/BMPR2/ITGB3/TP63	8
GO:0098917	Retrograde trans-synaptic signaling	2/86	11/18866	0.001099862	0.037420693	0.030335744	BDNF/PLCB1	2
GO:0032924	Activin receptor signaling pathway	3/86	45/18866	0.001130155	0.037420693	0.030335744	FST/INHBB/BMPR2	3
GO:0046189	Phenol-containing compound biosynthetic process	3/86	45/18866	0.001130155	0.037420693	0.030335744	SLC7A11/GATA3/TGFB2	3

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0060412	Ventricular septum morphogenesis	3/86	45/18866	0.001130155	0.037420693	0.030335744	TGFB2/SOX4/BMPR2	3
GO:0060840	Artery development	4/86	102/18866	0.001217645	0.038883859	0.031521885	SMAD6/TGFB2/SOX4/BMPR2	4
GO:0007178	Transmembrane receptor protein serine/threonine kinase signaling pathway	7/86	359/18866	0.001263006	0.038883859	0.031521885	SORL1/FST/SKIL/SMAD6/TGFB2/INHBB/BMPR2	7
GO:0050919	Negative chemotaxis	3/86	47/18866	0.001282991	0.038883859	0.031521885	SEMA3A/ITGAV/ITGB3	3
GO:0070997	Neuron death	7/86	360/18866	0.001283364	0.038883859	0.031521885	SORL1/SLC7A11/GATA3/GABRB3/TGFB2/BDNF/TP63	7
GO:0051798	Positive regulation of hair follicle development	2/86	12/18866	0.001315929	0.038883859	0.031521885	FST/TGFB2	2
GO:0060213	Positive regulation of nuclear-transcribed mRNA poly(A) tail shortening	2/86	12/18866	0.001315929	0.038883859	0.031521885	CPEB3/TNRC6C	2
GO:0010862	Positive regulation of pathway-restricted SMAD protein phosphorylation	3/86	48/18866	0.001364044	0.038883859	0.031521885	TGFB2/INHBB/BMPR2	3
GO:0072331	Signal transduction by p53 class mediator	6/86	267/18866	0.001386923	0.038883859	0.031521885	NUAK1/SOX4/JMY/TP53INP1/TP63/CNOT6L	6
GO:0010631	Epithelial cell migration	7/86	365/18866	0.001389051	0.038883859	0.031521885	GATA3/SASH1/TGFB2/SEMA3A/HDAC9/BMPR2/ITGB3	7
GO:0014812	Muscle cell migration	4/86	106/18866	0.001403922	0.038883859	0.031521885	SORL1/ATP7A/PRKG1/ITGB3	4
GO:0008361	Regulation of cell size	5/86	181/18866	0.001430229	0.038883859	0.031521885	BDNF/SEMA3A/ATP7A/BMPR2/MAP2	5
GO:0048736	Appendage development	5/86	181/18866	0.001430229	0.038883859	0.031521885	SLC7A11/TGFB2/SOX4/BMPR2/TP63	5
GO:0060173	Limb development	5/86	181/18866	0.001430229	0.038883859	0.031521885	SLC7A11/TGFB2/SOX4/BMPR2/TP63	5
GO:0051098	Regulation of binding	7/86	367/18866	0.001433187	0.038883859	0.031521885	SORL1/GATA3/RSF1/BDNF/TTBK2/ARHGAP28/MAP2	7
GO:0090132	Epithelium migration	7/86	368/18866	0.001455662	0.038883859	0.031521885	GATA3/SASH1/TGFB2/SEMA3A/HDAC9/BMPR2/ITGB3	7
GO:0061014	Positive regulation of mRNA catabolic process	3/86	50/18866	0.001535648	0.038883859	0.031521885	CPEB3/TNRC6C/CNOT6L	3
GO:0010745	Negative regulation of macrophage derived foam cell differentiation	2/86	13/18866	0.001550587	0.038883859	0.031521885	ITGAV/ITGB3	2
GO:0042415	Norepinephrine metabolic process	2/86	13/18866	0.001550587	0.038883859	0.031521885	GATA3/ATP7A	2
GO:0042635	Positive regulation of hair cycle	2/86	13/18866	0.001550587	0.038883859	0.031521885	FST/TGFB2	2
GO:1903651	Positive regulation of cytoplasmic transport	2/86	13/18866	0.001550587	0.038883859	0.031521885	SORL1/MAP2	2
GO:0018958	Phenol-containing compound metabolic process	4/86	109/18866	0.001556068	0.038883859	0.031521885	SLC7A11/GATA3/TGFB2/ATP7A	4

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0007409	Axonogenesis	8/86	482/18866	0.001590594	0.038883859	0.031521885	GATA3/SKIL/ETV1/ BDNF/SEMA3A/SLITRK6/ BMPR2/MAP2	8
GO:0090130	Tissue migration	7/86	374/18866	0.00159637	0.038883859	0.031521885	GATA3/SASH1/TGFB2/ SEMA3A/HDAC9/BMPR2/ ITGB3	7
GO:0051051	Negative regulation of transport	8/86	483/18866	0.001611458	0.038883859	0.031521885	PPP1R9A/SESTD1/ ATP7A/HDAC9/ITGAV/IN- HBB/PACSIN1/ITGB3	8
GO:0050770	Regulation of axono- genesis	5/86	186/18866	0.001612647	0.038883859	0.031521885	SKIL/BDNF/SEMA3A/ BMPR2/MAP2	5
GO:0090102	Cochlea development	3/86	51/18866	0.001626288	0.038883859	0.031521885	GATA3/GABRB3/SLITRK6	3
GO:1902893	Regulation of pri- miRNA transcription by RNA polymerase II	3/86	51/18866	0.001626288	0.038883859	0.031521885	GATA3/SMAD6/TGFB2	3
GO:0042303	Molting cycle	4/86	111/18866	0.001663655	0.038883859	0.031521885	FST/TGFB2/ATP7A/TP63	4
GO:0042633	Hair cycle	4/86	111/18866	0.001663655	0.038883859	0.031521885	FST/TGFB2/ATP7A/TP63	4
GO:0061387	Regulation of extent of cell growth	4/86	111/18866	0.001663655	0.038883859	0.031521885	BDNF/SEMA3A/BMPR2/ MAP2	4
GO:0030514	Negative regulation of BMP signaling pathway	3/86	52/18866	0.001720211	0.039815365	0.032277027	SORL1/SKIL/SMAD6	3
GO:0007548	Sex differentiation	6/86	280/18866	0.001764948	0.040458044	0.032798026	FST/GATA3/TGFB2/ SEMA3A/INHBB/TP63	6
GO:0060211	Regulation of nuclear- transcribed mRNA poly(A) tail shortening	2/86	14/18866	0.001803668	0.040875705	0.03313661	CPEB3/TNRC6C	2
GO:0061614	Pri-miRNA transcription by RNA polymerase II	3/86	53/18866	0.00181746	0.040875705	0.03313661	GATA3/SMAD6/TGFB2	3
GO:0006584	Catecholamine meta- bolic process	3/86	54/18866	0.001918077	0.042339775	0.034323484	GATA3/TGFB2/ATP7A	3
GO:0009712	Catechol-containing compound metabolic process	3/86	54/18866	0.001918077	0.042339775	0.034323484	GATA3/TGFB2/ATP7A	3
GO:0030900	Forebrain development	7/86	391/18866	0.002053275	0.044167892	0.03580548	SLC7A11/BCAN/SEMA3A/ ATP7A/SLC38A2/PLCB1/ PRKG1	7
GO:0048839	Inner ear development	5/86	197/18866	0.002073551	0.044167892	0.03580548	GATA3/GABRB3/TGFB2/ BDNF/SLITRK6	5
GO:0007638	Mechanosensory behavior	2/86	15/18866	0.002075002	0.044167892	0.03580548	ETV1/SLITRK6	2
GO:0050746	Regulation of lipoprote- in metabolic process	2/86	15/18866	0.002075002	0.044167892	0.03580548	ITGAV/ITGB3	2
GO:0010976	Positive regulation of neuron projection development	6/86	290/18866	0.002105428	0.044418936	0.036008992	CPEB3/PPP1R9A/SKIL/ BDNF/BMPR2/PACSIN1	6
GO:0031346	Positive regulation of cell projection organi- zation	7/86	394/18866	0.002143474	0.044824937	0.036338124	CPEB3/PPP1R9A/SKIL/ BDNF/ATP7A/BMPR2/ PACSIN1	7
GO:0007613	Memory	4/86	121/18866	0.002280062	0.047266679	0.038317566	CPEB3/ATXN1/BDNF/ PLCB1	4
GO:0042035	Regulation of cytokine biosynthetic process	2/86	16/18866	0.002364421	0.048592932	0.039392716	GATA3/INHBB	2
GO:0048675	Axon extension	4/86	123/18866	0.00241989	0.049307834	0.039972264	BDNF/SEMA3A/BMPR2/ MAP2	4
GO:0042594	Response to starvation	5/86	206/18866	0.002516912	0.050850145	0.041222566	NUAK1/SLC38A2/GABA- RAPL1/INHBB/BMPR2	5

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0001838	Embryonic epithelial tube formation	4/86	125/18866	0.002565513	0.051396495	0.041665474	GATA3/TGFB2/SOX4/MTHFR	4
GO:0035904	Aorta development	3/86	60/18866	0.002594751	0.051549046	0.041789142	SMAD6/TGFB2/SOX4	3
GO:0003184	Pulmonary valve morphogenesis	2/86	17/18866	0.00267176	0.051784349	0.041979895	SMAD6/TGFB2	2
GO:0006750	Glutathione biosynthetic process	2/86	17/18866	0.00267176	0.051784349	0.041979895	SLC7A11/CHAC1	2
GO:1900363	Regulation of mRNA polyadenylation	2/86	17/18866	0.00267176	0.051784349	0.041979895	CPEB3/CCNT1	2
GO:0001704	Formation of primary germ layer	4/86	127/18866	0.002717051	0.052237505	0.042347253	COL8A1/ITGAV/BMPR2/ITGB3	4
GO:0070527	Platelet aggregation	3/86	62/18866	0.002849026	0.054336625	0.044048942	SLC7A11/PRKG1/ITGB3	3
GO:0060080	Inhibitory postsynaptic potential	2/86	18/18866	0.002996851	0.055816359	0.045248514	GABRB3/BDNF	2
GO:0061298	Retina vasculature development in camera-type eye	2/86	18/18866	0.002996851	0.055816359	0.045248514	CLIC4/BMPR2	2
GO:1900153	Positive regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay	2/86	18/18866	0.002996851	0.055816359	0.045248514	CPEB3/TNRC6C	2
GO:0072175	Epithelial tube formation	4/86	133/18866	0.003208333	0.058835885	0.047696346	GATA3/TGFB2/SOX4/MTHFR	4
GO:0090101	Negative regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	4/86	133/18866	0.003208333	0.058835885	0.047696346	SORL1/FST/SKIL/SMAD6	4
GO:0019184	Nonribosomal peptide biosynthetic process	2/86	19/18866	0.003339532	0.060550663	0.049086461	SLC7A11/CHAC1	2
GO:0045785	Positive regulation of cell adhesion	7/86	428/18866	0.003395248	0.060550663	0.049086461	MAGI1/COL8A1/GATA3/TGFB2/SOX4/ITGAV/NEDD9	7
GO:0042490	Mechanoreceptor differentiation	3/86	66/18866	0.00340238	0.060550663	0.049086461	GABRB3/BDNF/SLITRK6	3
GO:0031669	Cellular response to nutrient levels	5/86	221/18866	0.003403435	0.060550663	0.049086461	NUAK1/SLC38A2/GABA-RAPL1/INHBB/BMPR2	5
GO:1901214	Regulation of neuron death	6/86	321/18866	0.003481234	0.061476012	0.049836611	SORL1/SLC7A11/GATA3/GABRB3/TGFB2/BDNF	6
GO:0008406	Gonad development	5/86	223/18866	0.00353664	0.06199522	0.050257517	FST/GATA3/TGFB2/SEMA3A/INHBB	5
GO:0043583	Ear development	5/86	224/18866	0.003604631	0.062552759	0.050709496	GATA3/GABRB3/TGFB2/BDNF/SLITRK6	5
GO:0007015	Actin filament organization	7/86	434/18866	0.003664496	0.062552759	0.050709496	PPP1R9A/NEBL/CGNL1/ARHGAP28/PACSIN1/JMY/NEDD9	7
GO:0002320	Lymphoid progenitor cell differentiation	2/86	20/18866	0.003699639	0.062552759	0.050709496	GATA3/SOX4	2
GO:0042089	Cytokine biosynthetic process	2/86	20/18866	0.003699639	0.062552759	0.050709496	GATA3/INHBB	2
GO:1900151	Regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay	2/86	20/18866	0.003699639	0.062552759	0.050709496	CPEB3/TNRC6C	2

(Continued)



Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0045137	Development of primary sexual characteristics	5/86	229/18866	0.003958763	0.065577145	0.053161267	FST/GATA3/TGFB2/SEMA3A/INHBB	5
GO:0001655	Urogenital system development	6/86	330/18866	0.003983793	0.065577145	0.053161267	GATA3/SMAD6/TGFB2/SOX4/BDNF/TP63	6
GO:0009713	Catechol-containing compound biosynthetic process	2/86	21/18866	0.004077009	0.065577145	0.053161267	GATA3/TGFB2	2
GO:0042107	Cytokine metabolic process	2/86	21/18866	0.004077009	0.065577145	0.053161267	GATA3/INHBB	2
GO:0042423	Catecholamine biosynthetic process	2/86	21/18866	0.004077009	0.065577145	0.053161267	GATA3/TGFB2	2
GO:0051797	Regulation of hair follicle development	2/86	21/18866	0.004077009	0.065577145	0.053161267	FST/TGFB2	2
GO:0060065	Uterus development	2/86	21/18866	0.004077009	0.065577145	0.053161267	GATA3/TGFB2	2
GO:0048608	Reproductive structure development	7/86	443/18866	0.004098572	0.065577145	0.053161267	FST/GATA3/TGFB2/SEMA3A/INHBB/BMPR2/TP63	7
GO:0015800	Acidic amino acid transport	3/86	71/18866	0.004180801	0.066006816	0.053509587	SLC7A11/BDNF/SLC38A2	3
GO:0033627	Cell adhesion mediated by integrin	3/86	71/18866	0.004180801	0.066006816	0.053509587	TGFB2/ITGAV/ITGB3	3
GO:0061458	Reproductive system development	7/86	447/18866	0.004303588	0.06749838	0.05471875	FST/GATA3/TGFB2/SEMA3A/INHBB/BMPR2/TP63	7
GO:0070988	Demethylation	3/86	72/18866	0.004348359	0.067754826	0.054926642	GATA3/TET2/JMJD1C	3
GO:0043254	Regulation of protein-containing complex assembly	7/86	449/18866	0.004408972	0.068253172	0.055330636	SORL1/PPP1R9A/SMAD6/ARHGAP28/ATF7IP/JMY/MAP2	7
GO:0010888	Negative regulation of lipid storage	2/86	22/18866	0.004471481	0.068774263	0.055753068	ITGAV/ITGB3	2
GO:0003208	Cardiac ventricle morphogenesis	3/86	73/18866	0.004519944	0.069074013	0.055996065	GATA3/TGFB2/SOX4	3
GO:0051047	Positive regulation of secretion	6/86	340/18866	0.00460332	0.069900087	0.056665737	SORL1/SYTL2/TGFB2/SOX4/MYO18A/INHBB	6
GO:0010594	Regulation of endothelial cell migration	5/86	238/18866	0.004657999	0.070185555	0.056897156	GATA3/SASH1/HDAC9/BMPR2/ITGB3	5
GO:0050804	Modulation of chemical synaptic transmission	7/86	454/18866	0.004681	0.070185555	0.056897156	CPEB3/PPP1R9A/FBXL20/SLC7A11/SLC24A1/BDNF/PLCB1	7
GO:0099177	Regulation of trans-synaptic signaling	7/86	455/18866	0.004736897	0.070579766	0.05721673	CPEB3/PPP1R9A/FBXL20/SLC7A11/SLC24A1/BDNF/PLCB1	7
GO:0048844	Artery morphogenesis	3/86	75/18866	0.004875303	0.070980628	0.057541696	TGFB2/SOX4/BMPR2	3
GO:0050805	Negative regulation of synaptic transmission	3/86	75/18866	0.004875303	0.070980628	0.057541696	PPP1R9A/SLC24A1/BDNF	3
GO:1900006	Positive regulation of dendrite development	3/86	75/18866	0.004875303	0.070980628	0.057541696	CPEB3/PPP1R9A/PAC-SIN1	3
GO:0032799	Low-density lipoprotein receptor particle metabolic process	2/86	23/18866	0.004882896	0.070980628	0.057541696	ITGAV/ITGB3	2
GO:0035148	Tube formation	4/86	150/18866	0.004922269	0.071119327	0.057654135	GATA3/TGFB2/SOX4/MTHFR	4
GO:0051402	Neuron apoptotic process	5/86	245/18866	0.005259584	0.075535237	0.06123397	GATA3/GABRB3/TGFB2/BDNF/TP63	5

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0010869	Regulation of receptor biosynthetic process	2/86	24/18866	0.005311093	0.075818242	0.061463393	ITGAV/ITGB3	2
GO:0050708	Regulation of protein secretion	6/86	352/18866	0.005437537	0.076277029	0.061835316	SORL1/TGFB2/SOX4/HDAC9/MYO18A/INHBB	6
GO:0000288	Nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay	3/86	78/18866	0.005439218	0.076277029	0.061835316	CPEB3/TNRC6C/CNOT6L	3
GO:0060395	SMAD protein signal transduction	3/86	78/18866	0.005439218	0.076277029	0.061835316	SMAD6/TGFB2/INHBB	3
GO:0009636	Response to toxic substance	5/86	250/18866	0.005721706	0.079503569	0.064450968	PPP1R9A/AHR/SLC7A11/ATP7A/TP53INP1	5
GO:0010770	Positive regulation of cell morphogenesis involved in differentiation	4/86	157/18866	0.00577791	0.079503569	0.064450968	SKIL/BDNF/BMPR2/NEDD9	4
GO:0051017	Actin filament bundle assembly	4/86	157/18866	0.00577791	0.079503569	0.064450968	PPP1R9A/CGNL1/ARHGAP28/NEDD9	4
GO:0031667	Response to nutrient levels	7/86	473/18866	0.005832	0.079503569	0.064450968	SORL1/NUAK1/MTHFR/SLC38A2/GABARAPL1/INHBB/BMPR2	7
GO:0003151	Outflow tract morphogenesis	3/86	80/18866	0.005836042	0.079503569	0.064450968	SMAD6/TGFB2/BMPR2	3
GO:0031668	Cellular response to extracellular stimulus	5/86	253/18866	0.006012367	0.081440239	0.066020964	NUAK1/SLC38A2/GABARAPL1/INHBB/BMPR2	5
GO:0021884	Forebrain neuron development	2/86	26/18866	0.006217208	0.082775094	0.067103088	SEMA3A/ATP7A	2
GO:1903649	Regulation of cytoplasmic transport	2/86	26/18866	0.006217208	0.082775094	0.067103088	SORL1/MAP2	2
GO:0021954	Central nervous system neuron development	3/86	82/18866	0.006249797	0.082775094	0.067103088	SEMA3A/ATP7A/MAP2	3
GO:1903313	Positive regulation of mRNA metabolic process	3/86	82/18866	0.006249797	0.082775094	0.067103088	CPEB3/TNRC6C/CNOT6L	3
GO:0061572	Actin filament bundle organization	4/86	161/18866	0.006308804	0.08305588	0.067330711	PPP1R9A/CGNL1/ARHGAP28/NEDD9	4
GO:0001667	Ameboidal-type cell migration	7/86	481/18866	0.006375514	0.08305588	0.067330711	GATA3/SASH1/TGFB2/SEMA3A/HDAC9/BMPR2/ITGB3	7
GO:0016569	Covalent chromatin modification	7/86	481/18866	0.006375514	0.08305588	0.067330711	GATA3/RSF1/MTHFR/HDAC9/ATF7IP/TET2/JMJD1C	7
GO:2000146	Negative regulation of cell motility	6/86	365/18866	0.006461198	0.083286412	0.067517597	GATA3/CLIC4/SEMA3A/PLCB1/PRKG1/TP53INP1	6
GO:2000243	Positive regulation of reproductive process	3/86	83/18866	0.006463081	0.083286412	0.067517597	SEMA3A/INHBB/PLCB1	3
GO:0003007	Heart morphogenesis	5/86	258/18866	0.006519717	0.083564546	0.067743071	GATA3/SMAD6/TGFB2/SOX4/BMPR2	5
GO:0021537	Telencephalon development	5/86	259/18866	0.006624687	0.084002275	0.068097923	SLC7A11/BCAN/SEMA3A/SLC38A2/PLCB1	5
GO:0050769	Positive regulation of neurogenesis	7/86	485/18866	0.006661076	0.084002275	0.068097923	CPEB3/PPP1R9A/SKIL/BDNF/SEMA3A/BMPR2/PACSIN1	7
GO:0007214	Gamma-aminobutyric acid signaling pathway	2/86	27/18866	0.006694812	0.084002275	0.068097923	GABRB3/BDNF	2
GO:0072337	Modified amino acid transport	2/86	27/18866	0.006694812	0.084002275	0.068097923	SLC7A11/SLC38A2	2

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0007611	Learning or memory	5/86	260/18866	0.006730839	0.084012142	0.068105922	CPEB3/SLC7A11/ATXN1/ BDNF/PLCB1	5
GO:0014910	Regulation of smooth muscle cell migration	3/86	86/18866	0.007128822	0.086118398	0.069813396	SORL1/ATP7A/PRKG1	3
GO:0034109	Homotypic cell-cell adhesion	3/86	86/18866	0.007128822	0.086118398	0.069813396	SLC7A11/PRKG1/ITGB3	3
GO:0050772	Positive regulation of axonogenesis	3/86	86/18866	0.007128822	0.086118398	0.069813396	SKIL/BDNF/BMPR2	3
GO:1902903	Regulation of supramolecular fiber organization	6/86	373/18866	0.007157109	0.086118398	0.069813396	PPP1R9A/CGNL1/TTBK2/ ARHGAP28/JMY/MAP2	6
GO:0003180	Aortic valve morphogenesis	2/86	28/18866	0.007188574	0.086118398	0.069813396	GATA3/SMAD6	2
GO:0031440	Regulation of mRNA 3'-end processing	2/86	28/18866	0.007188574	0.086118398	0.069813396	CPEB3/CCNT1	2
GO:0032800	Receptor biosynthetic process	2/86	28/18866	0.007188574	0.086118398	0.069813396	ITGAV/ITGB3	2
GO:0080111	DNA demethylation	2/86	28/18866	0.007188574	0.086118398	0.069813396	GATA3/TET2	2
GO:0032874	Positive regulation of stress-activated MAPK cascade	4/86	170/18866	0.007619707	0.090826908	0.073630433	SASH1/TGFB2/SEMA3A/ PLCB1	4
GO:0042634	Regulation of hair cycle	2/86	29/18866	0.007698341	0.091302546	0.074016017	FST/TGFB2	2
GO:0022604	Regulation of cell morphogenesis	7/86	499/18866	0.007736206	0.091302546	0.074016017	PPP1R9A/SKIL/BDNF/ SEMA3A/BMPR2/MAP2/ NEDD9	7
GO:0045666	Positive regulation of neuron differentiation	6/86	380/18866	0.007809358	0.091370068	0.074070754	CPEB3/PPP1R9A/SKIL/ BDNF/BMPR2/PACSIN1	6
GO:0002791	Regulation of peptide secretion	6/86	381/18866	0.007905929	0.091370068	0.074070754	SORL1/TGFB2/SOX4/ HDAC9/MYO18A/INHBB	6
GO:0050714	Positive regulation of protein secretion	4/86	172/18866	0.007933559	0.091370068	0.074070754	SORL1/TGFB2/SOX4/ MYO18A	4
GO:0070304	Positive regulation of stress-activated protein kinase signaling cascade	4/86	172/18866	0.007933559	0.091370068	0.074070754	SASH1/TGFB2/SEMA3A/ PLCB1	4
GO:1990138	Neuron projection extension	4/86	172/18866	0.007933559	0.091370068	0.074070754	BDNF/SEMA3A/BMPR2/ MAP2	4
GO:0045682	Regulation of epidermis development	3/86	91/18866	0.008325904	0.094971077	0.076989976	FST/TGFB2/TP63	3
GO:0051492	Regulation of stress fiber assembly	3/86	91/18866	0.008325904	0.094971077	0.076989976	PPP1R9A/CGNL1/ ARHGAP28	3
GO:0060292	Long-term synaptic depression	2/86	31/18866	0.008765276	0.099506758	0.080666905	PPP1R9A/SLC24A1	2
GO:0045778	Positive regulation of ossification	3/86	94/18866	0.009097485	0.102722925	0.083274148	TGFB2/BMPR2/TP63	3
GO:1901796	Regulation of signal transduction by p53 class mediator	4/86	180/18866	0.009273809	0.102722925	0.083274148	NUAK1/JMY/TP53INP1/ TP63	4
GO:0010743	Regulation of macrophage derived foam cell differentiation	2/86	32/18866	0.009322144	0.102722925	0.083274148	ITGAV/ITGB3	2
GO:0048841	Regulation of axon extension involved in axon guidance	2/86	32/18866	0.009322144	0.102722925	0.083274148	SEMA3A/BMPR2	2
GO:0061157	mRNA destabilization	2/86	32/18866	0.009322144	0.102722925	0.083274148	CPEB3/CNOT6L	2

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0030198	Extracellular matrix organization	6/86	395/18866	0.009350199	0.102722925	0.083274148	COL8A1/TGFB2/BCAN/ATP7A/ITGAV/ITGB3	6
GO:0050678	Regulation of epithelial cell proliferation	6/86	395/18866	0.009350199	0.102722925	0.083274148	GATA3/TGFB2/ATP7A/BMPR2/ITGB3/TP63	6
GO:0043062	Extracellular structure organization	6/86	396/18866	0.009460121	0.103453798	0.083866643	COL8A1/TGFB2/BCAN/ATP7A/ITGAV/ITGB3	6
GO:0001822	Kidney development	5/86	283/18866	0.009514131	0.103569356	0.083960322	GATA3/SMAD6/TGFB2/SOX4/BDNF	5
GO:0040013	Negative regulation of locomotion	6/86	397/18866	0.009570966	0.103635943	0.084014302	GATA3/CLIC4/SEMA3A/PLCB1/PRKG1/TP53INP1	6
GO:0090288	Negative regulation of cellular response to growth factor stimulus	4/86	182/18866	0.009630517	0.103635943	0.084014302	SORL1/GATA3/SKIL/SMAD6	4
GO:0007411	Axon guidance	5/86	284/18866	0.009650662	0.103635943	0.084014302	GATA3/ETV1/BDNF/SEMA3A/BMPR2	5
GO:0097485	Neuron projection guidance	5/86	285/18866	0.00978854	0.103806173	0.084152302	GATA3/ETV1/BDNF/SEMA3A/BMPR2	5
GO:0055001	Muscle cell development	4/86	183/18866	0.009812177	0.103806173	0.084152302	NEBL/PGM5/HDAC9/ANK2	4
GO:2000758	Positive regulation of peptidyl-lysine acetylation	2/86	33/18866	0.00989441	0.103806173	0.084152302	GATA3/SOX4	2
GO:0051271	Negative regulation of cellular component movement	6/86	400/18866	0.009909083	0.103806173	0.084152302	GATA3/CLIC4/SEMA3A/PLCB1/PRKG1/TP53INP1	6
GO:0030516	Regulation of axon extension	3/86	97/18866	0.009909621	0.103806173	0.084152302	SEMA3A/BMPR2/MAP2	3
GO:0043542	Endothelial cell migration	5/86	286/18866	0.009927772	0.103806173	0.084152302	GATA3/SASH1/HDAC9/BMPR2/ITGB3	5
GO:0007416	Synapse assembly	4/86	184/18866	0.009996053	0.104063714	0.084361082	PPP1R9A/GABRB3/BDNF/SLITRK6	4
GO:0001657	Ureteric bud development	3/86	98/18866	0.010189417	0.104705042	0.084880986	GATA3/SMAD6/BDNF	3
GO:0006835	Dicarboxylic acid transport	3/86	98/18866	0.010189417	0.104705042	0.084880986	SLC7A11/BDNF/SLC38A2	3
GO:0044728	DNA methylation or demethylation	3/86	98/18866	0.010189417	0.104705042	0.084880986	GATA3/ATF7IP/TET2	3
GO:0072163	Mesonephric epithelium development	3/86	99/18866	0.010473779	0.105981576	0.085915831	GATA3/SMAD6/BDNF	3
GO:0072164	Mesonephric tubule development	3/86	99/18866	0.010473779	0.105981576	0.085915831	GATA3/SMAD6/BDNF	3
GO:0035510	DNA dealkylation	2/86	34/18866	0.010481928	0.105981576	0.085915831	GATA3/TET2	2
GO:0018205	Peptidyl-lysine modification	6/86	405/18866	0.010491465	0.105981576	0.085915831	GATA3/RSF1/SOX4/ATP7A/HDAC9/TET2	6
GO:0072001	Renal system development	5/86	292/18866	0.010791921	0.108556703	0.088003403	GATA3/SMAD6/TGFB2/SOX4/BDNF	5
GO:0007369	Gastrulation	4/86	189/18866	0.010949043	0.108906117	0.088286661	COL8A1/ITGAV/BMPR2/ITGB3	4
GO:0007435	Salivary gland morphogenesis	2/86	35/18866	0.01108455	0.108906117	0.088286661	TGFB2/SEMA3A	2
GO:0035909	Aorta morphogenesis	2/86	35/18866	0.01108455	0.108906117	0.088286661	TGFB2/SOX4	2
GO:0050779	RNA destabilization	2/86	35/18866	0.01108455	0.108906117	0.088286661	CPEB3/CNOT6L	2
GO:0070306	Lens fiber cell differentiation	2/86	35/18866	0.01108455	0.108906117	0.088286661	SLC7A11/SKIL	2

(Continued)



Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0006575	Cellular modified amino acid metabolic process	4/86	190/18866	0.011146431	0.108906117	0.088286661	SLC7A11/GATA3/MTHFR/CHAC1	4
GO:0030308	Negative regulation of cell growth	4/86	190/18866	0.011146431	0.108906117	0.088286661	TGFB2/SEMA3A/BMPR2/MAP2	4
GO:0048167	Regulation of synaptic plasticity	4/86	191/18866	0.011346106	0.110036081	0.089202686	CPEB3/PPP1R9A/SLC24A1/BDNF	4
GO:0110020	Regulation of actomyosin structure organization	3/86	102/18866	0.011354394	0.110036081	0.089202686	PPP1R9A/CGNL1/ARHGAP28	3
GO:0021953	Central nervous system neuron differentiation	4/86	192/18866	0.011548076	0.111010541	0.089992649	SOX4/SEMA3A/ATP7A/MAP2	4
GO:0044272	Sulfur compound biosynthetic process	4/86	192/18866	0.011548076	0.111010541	0.089992649	SLC7A11/BCAN/MTHFR/CHAC1	4
GO:0001823	Mesonephros development	3/86	103/18866	0.011657152	0.111591497	0.090463612	GATA3/SMAD6/BDNF	3
GO:0071634	Regulation of transforming growth factor beta production	2/86	36/18866	0.011702128	0.111591497	0.090463612	TGFB2/ITGAV	2
GO:0002793	Positive regulation of peptide secretion	4/86	193/18866	0.011752352	0.111623928	0.090489903	SORL1/TGFB2/SOX4/MYO18A	4
GO:0010639	Negative regulation of organelle organization	6/86	416/18866	0.011857924	0.112179729	0.090940473	PPP1R9A/CGNL1/USP30/TTBK2/ARHGAP28/MAP2	6
GO:0032231	Regulation of actin filament bundle assembly	3/86	104/18866	0.011964538	0.112740945	0.091395432	PPP1R9A/CGNL1/ARHGAP28	3
GO:0048846	Axon extension involved in axon guidance	2/86	37/18866	0.012334518	0.11495818	0.093192873	SEMA3A/BMPR2	2
GO:1902284	Neuron projection extension involved in neuron projection guidance	2/86	37/18866	0.012334518	0.11495818	0.093192873	SEMA3A/BMPR2	2
GO:0050890	Cognition	5/86	302/18866	0.012344503	0.11495818	0.093192873	CPEB3/SLC7A11/ATXN1/BDNF/PLCB1	5
GO:0001841	Neural tube formation	3/86	106/18866	0.012593245	0.11502795	0.093249434	TGFB2/SOX4/MTHFR	3
GO:0030038	Contractile actin filament bundle assembly	3/86	106/18866	0.012593245	0.11502795	0.093249434	PPP1R9A/CGNL1/ARHGAP28	3
GO:0032091	Negative regulation of protein binding	3/86	106/18866	0.012593245	0.11502795	0.093249434	SORL1/TTBK2/MAP2	3
GO:0034446	Substrate adhesion-dependent cell spreading	3/86	106/18866	0.012593245	0.11502795	0.093249434	ITGAV/NEDD9/ITGB3	3
GO:0043149	Stress fiber assembly	3/86	106/18866	0.012593245	0.11502795	0.093249434	PPP1R9A/CGNL1/ARHGAP28	3
GO:0051963	Regulation of synapse assembly	3/86	107/18866	0.012914585	0.116346145	0.094318051	PPP1R9A/BDNF/SLITRK6	3
GO:0007223	Wnt signaling pathway, calcium modulating pathway	2/86	38/18866	0.012981575	0.116346145	0.094318051	PLCB1/TNRC6C	2
GO:0010742	Macrophage derived foam cell differentiation	2/86	38/18866	0.012981575	0.116346145	0.094318051	ITGAV/ITGB3	2
GO:0071604	Transforming growth factor beta production	2/86	38/18866	0.012981575	0.116346145	0.094318051	TGFB2/ITGAV	2
GO:0090077	Foam cell differentiation	2/86	38/18866	0.012981575	0.116346145	0.094318051	ITGAV/ITGB3	2
GO:0007229	Integrin-mediated signaling pathway	3/86	108/18866	0.013240598	0.117782039	0.095482084	ITGAV/NEDD9/ITGB3	3

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0008593	Regulation of Notch signaling pathway	3/86	108/18866	0.013240598	0.117782039	0.095482084	TGFB2/CHAC1/TP63	3
GO:0001662	Behavioral fear response	2/86	39/18866	0.013643155	0.120019487	0.097295911	FBXL20/BDNF	2
GO:0007431	Salivary gland development	2/86	39/18866	0.013643155	0.120019487	0.097295911	TGFB2/SEMA3A	2
GO:0031111	Negative regulation of microtubule polymerization or depolymerization	2/86	39/18866	0.013643155	0.120019487	0.097295911	TTBK2/MAP2	2
GO:0090100	Positive regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	3/86	110/18866	0.013906677	0.121887936	0.098810602	TGFB2/INHBB/BMPR2	3
GO:0050808	Synapse organization	6/86	433/18866	0.01421063	0.122354017	0.099188438	PPP1R9A/SLC7A11/GABRB3/BCAN/BDNF/SLITRK6	6
GO:1903532	Positive regulation of secretion by cell	5/86	313/18866	0.014220651	0.122354017	0.099188438	SORL1/TGFB2/SOX4/MYO18A/INHBB	5
GO:0000096	Sulfur amino acid metabolic process	2/86	40/18866	0.014319115	0.122354017	0.099188438	SLC7A11/MTHFR	2
GO:0002209	Behavioral defense response	2/86	40/18866	0.014319115	0.122354017	0.099188438	FBXL20/BDNF	2
GO:0010719	Negative regulation of epithelial to mesenchymal transition	2/86	40/18866	0.014319115	0.122354017	0.099188438	GATA3/TGFB2	2
GO:0042417	Dopamine metabolic process	2/86	40/18866	0.014319115	0.122354017	0.099188438	TGFB2/ATP7A	2
GO:0043902	Positive regulation of multi-organism process	2/86	40/18866	0.014319115	0.122354017	0.099188438	INHBB/PLCB1	2
GO:0098656	Anion transmembrane transport	5/86	315/18866	0.014581278	0.123355537	0.100000338	SLC7A11/CLIC4/SLC24A1/GABRB3/SLC38A2	5
GO:0010927	Cellular component assembly involved in morphogenesis	3/86	112/18866	0.014591553	0.123355537	0.100000338	NEBL/PGM5/ANK2	3
GO:0099565	Chemical synaptic transmission, postsynaptic	3/86	112/18866	0.014591553	0.123355537	0.100000338	PPP1R9A/GABRB3/BDNF	3
GO:0007009	Plasma membrane organization	3/86	113/18866	0.014941059	0.125112608	0.101424739	TGFB2/ANK2/PACSIN1	3
GO:0042596	Fear response	2/86	41/18866	0.015009315	0.125112608	0.101424739	FBXL20/BDNF	2
GO:0050434	Positive regulation of viral transcription	2/86	41/18866	0.015009315	0.125112608	0.101424739	CCNT1/RSF1	2
GO:2000826	Regulation of heart morphogenesis	2/86	41/18866	0.015009315	0.125112608	0.101424739	TGFB2/BMPR2	2
GO:0043200	Response to amino acid	3/86	114/18866	0.015295288	0.127052153	0.102997065	CPEB3/MTHFR/ATP7A	3
GO:0043393	Regulation of protein binding	4/86	211/18866	0.015833518	0.13061283	0.105883591	SORL1/BDNF/TTBK2/MAP2	4
GO:0050679	Positive regulation of epithelial cell proliferation	4/86	211/18866	0.015833518	0.13061283	0.105883591	ATP7A/BMPR2/ITGB3/TP63	4
GO:0030278	Regulation of ossification	4/86	212/18866	0.016083232	0.131760911	0.106814303	SMAD6/TGFB2/BMPR2/TP63	4

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:1901215	Negative regulation of neuron death	4/86	212/18866	0.016083232	0.131760911	0.106814303	SORL1/SLC7A11/GA-BRB3/BDNF	4
GO:0030517	Negative regulation of axon extension	2/86	43/18866	0.016431868	0.133243447	0.108016147	SEMA3A/MAP2	2
GO:0040019	Positive regulation of embryonic development	2/86	43/18866	0.016431868	0.133243447	0.108016147	GATA3/PLCB1	2
GO:0060119	Inner ear receptor cell development	2/86	43/18866	0.016431868	0.133243447	0.108016147	GABRB3/SLITRK6	2
GO:0043523	Regulation of neuron apoptotic process	4/86	214/18866	0.016590079	0.134070337	0.108686479	GATA3/GABRB3/TGFB2/BDNF	4
GO:0071496	Cellular response to external stimulus	5/86	326/18866	0.016675122	0.134302338	0.108874555	NUAK1/SLC38A2/GABA-RAPL1/INHBB/BMPR2	5
GO:0046660	Female sex differentiation	3/86	119/18866	0.017137505	0.135942997	0.110204584	FST/INHBB/TP63	3
GO:0045684	Positive regulation of epidermis development	2/86	44/18866	0.017163944	0.135942997	0.110204584	FST/TGFB2	2
GO:0060999	Positive regulation of dendritic spine development	2/86	44/18866	0.017163944	0.135942997	0.110204584	CPEB3/PPP1R9A	2
GO:1901985	Positive regulation of protein acetylation	2/86	44/18866	0.017163944	0.135942997	0.110204584	GATA3/SOX4	2
GO:1902667	Regulation of axon guidance	2/86	44/18866	0.017163944	0.135942997	0.110204584	SEMA3A/BMPR2	2
GO:0006304	DNA modification	3/86	120/18866	0.017520203	0.137848726	0.111749497	GATA3/ATF7IP/TET2	3
GO:0051588	Regulation of neurotransmitter transport	3/86	120/18866	0.017520203	0.137848726	0.111749497	PPP1R9A/FBXL20/ITGB3	3
GO:0006338	Chromatin remodeling	4/86	218/18866	0.017633653	0.138177114	0.11201571	GATA3/RSF1/ATF7IP/TP63	4
GO:0060562	Epithelial tube morphogenesis	5/86	331/18866	0.017689868	0.138177114	0.11201571	GATA3/CLIC4/TGFB2/SOX4/MTHFR	5
GO:0002065	Columnar/cuboidal epithelial cell differentiation	3/86	121/18866	0.017907664	0.138177114	0.11201571	SOX4/SLITRK6/TP63	3
GO:0001974	Blood vessel remodeling	2/86	45/18866	0.017909701	0.138177114	0.11201571	ATP7A/BMPR2	2
GO:0003197	Endocardial cushion development	2/86	45/18866	0.017909701	0.138177114	0.11201571	TGFB2/BMPR2	2
GO:0014047	Glutamate secretion	2/86	45/18866	0.017909701	0.138177114	0.11201571	BDNF/SLC38A2	2
GO:0007163	Establishment or maintenance of cell polarity	4/86	220/18866	0.01817049	0.139736926	0.1132802	GATA3/CLIC4/MYO18A/MAP2	4
GO:0097237	Cellular response to toxic substance	3/86	122/18866	0.018299893	0.140279566	0.1137201	PPP1R9A/ATP7A/TP53INP1	3
GO:0032570	Response to progesterone	2/86	46/18866	0.018669004	0.142194587	0.115272545	NCOA2/TGFB2	2
GO:0035987	Endodermal cell differentiation	2/86	46/18866	0.018669004	0.142194587	0.115272545	COL8A1/ITGAV	2
GO:0009306	Protein secretion	6/86	462/18866	0.018947479	0.143856018	0.116619414	SORL1/TGFB2/SOX4/HDAC9/MYO18A/INHBB	6
GO:0022612	Gland morphogenesis	3/86	124/18866	0.019098668	0.144306981	0.116984995	TGFB2/SEMA3A/TP63	3
GO:0035592	Establishment of protein localization to extracellular region	6/86	463/18866	0.019127939	0.144306981	0.116984995	SORL1/TGFB2/SOX4/HDAC9/MYO18A/INHBB	6
GO:0006378	mRNA polyadenylation	2/86	47/18866	0.019441716	0.144389565	0.117051943	CPEB3/CCNT1	2

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Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0032369	Negative regulation of lipid transport	2/86	47/18866	0.019441716	0.144389565	0.117051943	ITGAV/ITGB3	2
GO:0060986	Endocrine hormone secretion	2/86	47/18866	0.019441716	0.144389565	0.117051943	GATA3/INHBB	2
GO:1904738	Vascular associated smooth muscle cell migration	2/86	47/18866	0.019441716	0.144389565	0.117051943	ATP7A/PRKG1	2
GO:1904752	Regulation of vascular associated smooth muscle cell migration	2/86	47/18866	0.019441716	0.144389565	0.117051943	ATP7A/PRKG1	2
GO:0016570	Histone modification	6/86	468/18866	0.02004796	0.148094346	0.120055289	GATA3/RSF1/MTHFR/HDAC9/TET2/JMJD1C	6
GO:0009101	Glycoprotein biosynthetic process	5/86	342/18866	0.020064796	0.148094346	0.120055289	BCAN/ATP7A/BMPR2/PLCB1/TET2	5
GO:0043631	RNA polyadenylation	2/86	48/18866	0.020227701	0.148835926	0.120656465	CPEB3/CCNT1	2
GO:0007596	Blood coagulation	5/86	343/18866	0.020290572	0.14883915	0.120659078	SLC7A11/GATA3/PRKG1/JMJD1C/ITGB3	5
GO:0071692	Protein localization to extracellular region	6/86	470/18866	0.0204243	0.149360526	0.12108174	SORL1/TGFB2/SOX4/HDAC9/MYO18A/INHBB	6
GO:1903311	Regulation of mRNA metabolic process	5/86	344/18866	0.020518013	0.149586983	0.121265322	CPEB3/CCNT1/MBNL2/TNRC6C/CNOT6L	5
GO:0050807	Regulation of synapse organization	4/86	229/18866	0.020712003	0.150540902	0.122038633	PPP1R9A/SLC7A11/BDNF/SLITRK6	4
GO:0015695	Organic cation transport	2/86	49/18866	0.021026827	0.151902896	0.123142758	SLC38A2/ITGB3	2
GO:0042398	Cellular modified amino acid biosynthetic process	2/86	49/18866	0.021026827	0.151902896	0.123142758	SLC7A11/CHAC1	2
GO:0032271	Regulation of protein polymerization	4/86	231/18866	0.021305014	0.153447596	0.124394996	PPP1R9A/ARHGAP28/JMY/MAP2	4
GO:0007599	Hemostasis	5/86	348/18866	0.021444515	0.153987119	0.12483237	SLC7A11/GATA3/PRKG1/JMJD1C/ITGB3	5
GO:0050817	Coagulation	5/86	349/18866	0.021680346	0.154492818	0.125242323	SLC7A11/GATA3/PRKG1/JMJD1C/ITGB3	5
GO:0008544	Epidermis development	6/86	477/18866	0.02177946	0.154492818	0.125242323	FST/CLIC4/TGFB2/ATP7A/SLITRK6/TP63	6
GO:0008038	Neuron recognition	2/86	50/18866	0.02183896	0.154492818	0.125242323	BDNF/SEMA3A	2
GO:0021695	Cerebellar cortex development	2/86	50/18866	0.02183896	0.154492818	0.125242323	ATP7A/TTBK2	2
GO:0043616	Keratinocyte proliferation	2/86	50/18866	0.02183896	0.154492818	0.125242323	FST/TP63	2
GO:0030336	Negative regulation of cell migration	5/86	350/18866	0.021917868	0.1545923	0.12532297	CLIC4/SEMA3A/PLCB1/PRKG1/TP53INP1	5
GO:0045667	Regulation of osteoblast differentiation	3/86	131/18866	0.022045008	0.155030383	0.12567811	SMAD6/BMPR2/TP63	3
GO:0001101	Response to acid chemical	3/86	132/18866	0.022485065	0.155708635	0.126227947	CPEB3/MTHFR/ATP7A	3
GO:0042476	Odontogenesis	3/86	132/18866	0.022485065	0.155708635	0.126227947	FST/TGFB2/TP63	3
GO:0045444	Fat cell differentiation	4/86	235/18866	0.022522167	0.155708635	0.126227947	GATA3/SMAD6/INHBB/PLCB1	4
GO:0048638	Regulation of developmental growth	5/86	353/18866	0.022640619	0.155708635	0.126227947	BDNF/SEMA3A/BMPR2/PLCB1/MAP2	5
GO:0021545	Cranial nerve development	2/86	51/18866	0.022663967	0.155708635	0.126227947	SEMA3A/SLITRK6	2

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Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0021879	Forebrain neuron differentiation	2/86	51/18866	0.022663967	0.155708635	0.126227947	SEMA3A/ATP7A	2
GO:0035272	Exocrine system development	2/86	51/18866	0.022663967	0.155708635	0.126227947	TGFB2/SEMA3A	2
GO:0043277	Apoptotic cell clearance	2/86	51/18866	0.022663967	0.155708635	0.126227947	ITGAV/ITGB3	2
GO:0060560	Developmental growth involved in morphogenesis	4/86	236/18866	0.022832971	0.156325812	0.126728272	BDNF/SEMA3A/BMPR2/MAP2	4
GO:0051222	Positive regulation of protein transport	5/86	354/18866	0.022884945	0.156325812	0.126728272	SORL1/TGFB2/SOX4/MYO18A/TP63	5
GO:0032872	Regulation of stress-activated MAPK cascade	4/86	237/18866	0.023146391	0.157210815	0.127445716	SASH1/TGFB2/SEMA3A/PLCB1	4
GO:0048588	Developmental cell growth	4/86	237/18866	0.023146391	0.157210815	0.127445716	BDNF/SEMA3A/BMPR2/MAP2	4
GO:0007498	Mesoderm development	3/86	134/18866	0.023379551	0.158271449	0.128305537	BMPR2/ITGB3/TP63	3
GO:0034249	Negative regulation of cellular amide metabolic process	4/86	238/18866	0.023462432	0.158271449	0.128305537	SORL1/CPEB3/TNRC6C/CNOT6L	4
GO:0010883	Regulation of lipid storage	2/86	52/18866	0.023501717	0.158271449	0.128305537	ITGAV/ITGB3	2
GO:0050803	Regulation of synapse structure or activity	4/86	240/18866	0.024102395	0.161152503	0.130641115	PPP1R9A/SLC7A11/BDNF/SLITRK6	4
GO:0070302	Regulation of stress-activated protein kinase signaling cascade	4/86	240/18866	0.024102395	0.161152503	0.130641115	SASH1/TGFB2/SEMA3A/PLCB1	4
GO:0031589	Cell-substrate adhesion	5/86	359/18866	0.024132317	0.161152503	0.130641115	COL8A1/SMAD6/ITGAV/NEDD9/ITGB3	5
GO:0042073	Intraciliary transport	2/86	53/18866	0.02435208	0.162165805	0.131462566	RABL2B/LCA5	2
GO:0006749	Glutathione metabolic process	2/86	54/18866	0.025214926	0.167052167	0.135423781	SLC7A11/CHAC1	2
GO:0046330	Positive regulation of JNK cascade	3/86	138/18866	0.025225998	0.167052167	0.135423781	SASH1/SEMA3A/PLCB1	3
GO:0001706	Endoderm formation	2/86	55/18866	0.026090127	0.171820063	0.139288959	COL8A1/ITGAV	2
GO:0030199	Collagen fibril organization	2/86	55/18866	0.026090127	0.171820063	0.139288959	TGFB2/ATP7A	2
GO:0008584	Male gonad development	3/86	141/18866	0.026661088	0.174456189	0.141425982	GATA3/TGFB2/SEMA3A	3
GO:0030010	Establishment of cell polarity	3/86	141/18866	0.026661088	0.174456189	0.141425982	GATA3/MYO18A/MAP2	3
GO:0006977	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest	2/86	56/18866	0.026977555	0.174456189	0.141425982	SOX4/CNOT6L	2
GO:0044273	Sulfur compound catabolic process	2/86	56/18866	0.026977555	0.174456189	0.141425982	BCAN/CHAC1	2
GO:0060563	Neuroepithelial cell differentiation	2/86	56/18866	0.026977555	0.174456189	0.141425982	SOX4/SLITRK6	2
GO:1904951	Positive regulation of establishment of protein localization	5/86	370/18866	0.027029446	0.174456189	0.141425982	SORL1/TGFB2/SOX4/MYO18A/TP63	5
GO:0031333	Negative regulation of protein-containing complex assembly	3/86	142/18866	0.027149013	0.174456189	0.141425982	SORL1/SMAD6/MAP2	3

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0046546	Development of primary male sexual characteristics	3/86	142/18866	0.027149013	0.174456189	0.141425982	GATA3/TGFB2/SEMA3A	3
GO:0072073	Kidney epithelium development	3/86	142/18866	0.027149013	0.174456189	0.141425982	GATA3/SMAD6/BDNF	3
GO:0016571	Histone methylation	3/86	143/18866	0.027641714	0.176752565	0.143287579	GATA3/MTHFR/TET2	3
GO:0045747	Positive regulation of Notch signaling pathway	2/86	57/18866	0.027877082	0.176752565	0.143287579	TGFB2/TP63	2
GO:0051568	Histone H3-K4 methylation	2/86	57/18866	0.027877082	0.176752565	0.143287579	GATA3/TET2	2
GO:0072431	Signal transduction involved in mitotic G1 DNA damage checkpoint	2/86	57/18866	0.027877082	0.176752565	0.143287579	SOX4/CNOT6L	2
GO:1902400	Intracellular signal transduction involved in G1 DNA damage checkpoint	2/86	57/18866	0.027877082	0.176752565	0.143287579	SOX4/CNOT6L	2
GO:0060078	Regulation of post-synaptic membrane potential	3/86	144/18866	0.028139189	0.177941187	0.144251156	PPP1R9A/GABRB3/BDNF	3
GO:0045926	Negative regulation of growth	4/86	254/18866	0.02887904	0.181656023	0.147262653	TGFB2/SEMA3A/BMPR2/ MAP2	4
GO:2000027	Regulation of animal organ morphogenesis	4/86	254/18866	0.02887904	0.181656023	0.147262653	GATA3/TGFB2/BDNF/ BMPR2	4
GO:0048813	Dendrite morphogenesis	3/86	146/18866	0.029148446	0.182868148	0.148245284	PPP1R9A/SEMA3A/MAP2	3
GO:0050707	Regulation of cytokine secretion	2/86	59/18866	0.029711935	0.183505836	0.148762237	SORL1/HDAC9	2
GO:0051058	Negative regulation of small GTPase mediated signal transduction	2/86	59/18866	0.029711935	0.183505836	0.148762237	CGNL1/TGFB2	2
GO:0060113	Inner ear receptor cell differentiation	2/86	59/18866	0.029711935	0.183505836	0.148762237	GABRB3/SLITRK6	2
GO:0072413	Signal transduction involved in mitotic cell cycle checkpoint	2/86	59/18866	0.029711935	0.183505836	0.148762237	SOX4/CNOT6L	2
GO:1902402	Signal transduction involved in mitotic DNA damage checkpoint	2/86	59/18866	0.029711935	0.183505836	0.148762237	SOX4/CNOT6L	2
GO:1902403	Signal transduction involved in mitotic DNA integrity checkpoint	2/86	59/18866	0.029711935	0.183505836	0.148762237	SOX4/CNOT6L	2
GO:0042093	T-helper cell differentiation	2/86	60/18866	0.03064701	0.187339672	0.151870204	GATA3/ATP7A	2
GO:0048747	Muscle fiber development	2/86	60/18866	0.03064701	0.187339672	0.151870204	NEBL/HDAC9	2
GO:0061098	Positive regulation of protein tyrosine kinase activity	2/86	60/18866	0.03064701	0.187339672	0.151870204	BDNF/NEDD9	2
GO:0097755	Positive regulation of blood vessel diameter	2/86	60/18866	0.03064701	0.187339672	0.151870204	BMPR2/PRKG1	2
GO:0035107	Appendage morphogenesis	3/86	150/18866	0.031224077	0.189410176	0.153548695	TGFB2/SOX4/TP63	3
GO:0035108	Limb morphogenesis	3/86	150/18866	0.031224077	0.189410176	0.153548695	TGFB2/SOX4/TP63	3

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0060041	Retina development in camera-type eye	3/86	150/18866	0.031224077	0.189410176	0.153548695	CLIC4/TGFB2/BMPR2	3
GO:0021872	Forebrain generation of neurons	2/86	61/18866	0.031593687	0.190681897	0.154579637	SEMA3A/ATP7A	2
GO:2000756	Regulation of peptidyl-lysine acetylation	2/86	61/18866	0.031593687	0.190681897	0.154579637	GATA3/SOX4	2
GO:0050684	Regulation of mRNA processing	3/86	152/18866	0.032290377	0.194394591	0.157589398	CPEB3/CCNT1/MBNL2	3
GO:0002294	CD4-positive, alpha-beta T cell differentiation involved in immune response	2/86	62/18866	0.032551842	0.194858921	0.157965815	GATA3/ATP7A	2
GO:0034113	Heterotypic cell-cell adhesion	2/86	62/18866	0.032551842	0.194858921	0.157965815	ITGAV/ITGB3	2
GO:0048863	Stem cell differentiation	4/86	264/18866	0.032612714	0.194858921	0.157965815	GATA3/TGFB2/SEMA3A/TP63	4
GO:0042692	Muscle cell differentiation	5/86	390/18866	0.032848287	0.195775793	0.158709094	NEBL/PGM5/BDNF/HDAC9/ANK2	5
GO:0002287	Alpha-beta T cell activation involved in immune response	2/86	63/18866	0.033521355	0.197809181	0.160357496	GATA3/ATP7A	2
GO:0002293	Alpha-beta T cell differentiation involved in immune response	2/86	63/18866	0.033521355	0.197809181	0.160357496	GATA3/ATP7A	2
GO:0010830	Regulation of myotube differentiation	2/86	63/18866	0.033521355	0.197809181	0.160357496	BDNF/HDAC9	2
GO:0031571	Mitotic G1 DNA damage checkpoint	2/86	63/18866	0.033521355	0.197809181	0.160357496	SOX4/CNOT6L	2
GO:0050773	Regulation of dendrite development	3/86	155/18866	0.033925312	0.199698629	0.16188921	CPEB3/PPP1R9A/PAC-SIN1	3
GO:0006865	Amino acid transport	3/86	156/18866	0.03447973	0.200587288	0.162609617	SLC7A11/BDNF/SLC38A2	3
GO:0043484	Regulation of RNA splicing	3/86	156/18866	0.03447973	0.200587288	0.162609617	MBNL2/SLC38A2/AHNAK2	3
GO:0030166	Proteoglycan biosynthetic process	2/86	64/18866	0.034502103	0.200587288	0.162609617	BCAN/BMPR2	2
GO:0044783	G1 DNA damage checkpoint	2/86	64/18866	0.034502103	0.200587288	0.162609617	SOX4/CNOT6L	2
GO:0044819	Mitotic G1/S transition checkpoint	2/86	64/18866	0.034502103	0.200587288	0.162609617	SOX4/CNOT6L	2
GO:0090596	Sensory organ morphogenesis	4/86	269/18866	0.034581114	0.200587288	0.162609617	COL8A1/GATA3/BDNF/SLITRK6	4
GO:0045787	Positive regulation of cell cycle	5/86	396/18866	0.034735534	0.200993965	0.162939297	CCNT1/TGFB2/SOX4/PLCB1/CNOT6L	5
GO:0046782	Regulation of viral transcription	2/86	65/18866	0.035493968	0.204390387	0.165692666	CCNT1/RSF1	2
GO:1905953	Negative regulation of lipid localization	2/86	65/18866	0.035493968	0.204390387	0.165692666	ITGAV/ITGB3	2
GO:0030168	Platelet activation	3/86	158/18866	0.035602685	0.20452241	0.165799693	SLC7A11/PRKG1/ITGB3	3
GO:0032922	Circadian regulation of gene expression	2/86	66/18866	0.03649683	0.208154171	0.168743844	AHR/NCOA2	2
GO:0034394	Protein localization to cell surface	2/86	66/18866	0.03649683	0.208154171	0.168743844	BDNF/ANK2	2
GO:0045669	Positive regulation of osteoblast differentiation	2/86	66/18866	0.03649683	0.208154171	0.168743844	BMPR2/TP63	2

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0045927	Positive regulation of growth	4/86	274/18866	0.03661755	0.208344248	0.168897933	TGFB2/BDNF/BMPR2/PLCB1	4
GO:0010970	Transport along microtubule	3/86	161/18866	0.037322311	0.211407097	0.171380886	RABL2B/LCA5/MAP2	3
GO:0030239	Myofibril assembly	2/86	67/18866	0.037510571	0.211407097	0.171380886	NEBL/PGM5	2
GO:0031060	Regulation of histone methylation	2/86	67/18866	0.037510571	0.211407097	0.171380886	GATA3/MTHFR	2
GO:0051965	Positive regulation of synapse assembly	2/86	67/18866	0.037510571	0.211407097	0.171380886	BDNF/SLITRK6	2
GO:0032970	Regulation of actin filament-based process	5/86	405/18866	0.037690922	0.211922541	0.17179874	PPP1R9A/CGNL1/ARHGAP28/ANK2/JMY	5
GO:0110053	Regulation of actin filament organization	4/86	278/18866	0.038295803	0.213645618	0.173195582	PPP1R9A/CGNL1/ARHGAP28/JMY	4
GO:0021915	Neural tube development	3/86	163/18866	0.038492103	0.213645618	0.173195582	TGFB2/SOX4/MTHFR	3
GO:0072577	Endothelial cell apoptotic process	2/86	68/18866	0.038535074	0.213645618	0.173195582	GATA3/BMPR2	2
GO:0098840	Protein transport along microtubule	2/86	68/18866	0.038535074	0.213645618	0.173195582	RABL2B/LCA5	2
GO:0099118	Microtubule-based protein transport	2/86	68/18866	0.038535074	0.213645618	0.173195582	RABL2B/LCA5	2
GO:1904888	Cranial skeletal system development	2/86	68/18866	0.038535074	0.213645618	0.173195582	TGFB2/TP63	2
GO:0001764	Neuron migration	3/86	164/18866	0.039083988	0.215208675	0.174462702	GATA3/SEMA3A/PRKG1	3
GO:0046661	Male sex differentiation	3/86	164/18866	0.039083988	0.215208675	0.174462702	GATA3/TGFB2/SEMA3A	3
GO:0071230	Cellular response to amino acid stimulus	2/86	69/18866	0.039570221	0.215208675	0.174462702	CPEB3/ATP7A	2
GO:1903317	Regulation of protein maturation	2/86	69/18866	0.039570221	0.215208675	0.174462702	SOX4/CHAC1	2
GO:1903531	Negative regulation of secretion by cell	3/86	166/18866	0.040281693	0.215208675	0.174462702	PPP1R9A/HDAC9/INHBB	3
GO:2001233	Regulation of apoptotic signaling pathway	5/86	413/18866	0.040444458	0.215208675	0.174462702	SKIL/BDNF/ITGAV/INHBB/TP63	5
GO:0009880	Embryonic pattern specification	2/86	70/18866	0.040615897	0.215208675	0.174462702	SMAD6/SEMA3A	2
GO:0050771	Negative regulation of axonogenesis	2/86	70/18866	0.040615897	0.215208675	0.174462702	SEMA3A/MAP2	2
GO:0009100	Glycoprotein metabolic process	5/86	415/18866	0.041151564	0.215208675	0.174462702	BCAN/ATP7A/BMPR2/PLCB1/TET2	5
GO:0002292	T cell differentiation involved in immune response	2/86	71/18866	0.041671986	0.215208675	0.174462702	GATA3/ATP7A	2
GO:0051403	Stress-activated MAPK cascade	4/86	286/18866	0.041783498	0.215208675	0.174462702	SASH1/TGFB2/SEMA3A/PLCB1	4
GO:0055002	Striated muscle cell development	3/86	169/18866	0.042112957	0.215208675	0.174462702	NEBL/PGM5/HDAC9	3
GO:2000241	Regulation of reproductive process	3/86	170/18866	0.042732596	0.215208675	0.174462702	SEMA3A/INHBB/PLCB1	3
GO:0050663	Cytokine secretion	2/86	72/18866	0.042738376	0.215208675	0.174462702	SORL1/HDAC9	2
GO:0001558	Regulation of cell growth	5/86	420/18866	0.042952231	0.215208675	0.174462702	TGFB2/BDNF/SEMA3A/BMPR2/MAP2	5
GO:0030307	Positive regulation of cell growth	3/86	171/18866	0.043356828	0.215208675	0.174462702	TGFB2/BDNF/BMPR2	3

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0060485	Mesenchyme development	4/86	290/18866	0.043592995	0.215208675	0.174462702	GATA3/TGFB2/SEMA3A/BMPR2	4
GO:0097193	Intrinsic apoptotic signaling pathway	4/86	290/18866	0.043592995	0.215208675	0.174462702	SKIL/CHAC1/JMY/TP63	4
GO:0015807	L-amino acid transport	2/86	73/18866	0.043814951	0.215208675	0.174462702	SLC7A11/SLC38A2	2
GO:0072401	Signal transduction involved in DNA integrity checkpoint	2/86	73/18866	0.043814951	0.215208675	0.174462702	SOX4/CNOT6L	2
GO:0072422	Signal transduction involved in DNA damage checkpoint	2/86	73/18866	0.043814951	0.215208675	0.174462702	SOX4/CNOT6L	2
GO:0002244	Hematopoietic progenitor cell differentiation	3/86	172/18866	0.043985644	0.215208675	0.174462702	FST/GATA3/SOX4	3
GO:0018394	Peptidyl-lysine acetylation	3/86	172/18866	0.043985644	0.215208675	0.174462702	GATA3/RSF1/SOX4	3
GO:0021543	Pallium development	3/86	173/18866	0.044619032	0.215208675	0.174462702	BCAN/SLC38A2/PLCB1	3
GO:0002524	Hypersensitivity	1/86	10/18866	0.044671283	0.215208675	0.174462702	GATA3	1
GO:0003149	Membranous septum morphogenesis	1/86	10/18866	0.044671283	0.215208675	0.174462702	TGFB2	1
GO:0003211	Cardiac ventricle formation	1/86	10/18866	0.044671283	0.215208675	0.174462702	SOX4	1
GO:0010603	Regulation of cytoplasmic mRNA processing body assembly	1/86	10/18866	0.044671283	0.215208675	0.174462702	CNOT6L	1
GO:0021562	Vestibulocochlear nerve development	1/86	10/18866	0.044671283	0.215208675	0.174462702	SLITRK6	1
GO:0021859	Pyramidal neuron differentiation	1/86	10/18866	0.044671283	0.215208675	0.174462702	ATP7A	1
GO:0032025	Response to cobalt ion	1/86	10/18866	0.044671283	0.215208675	0.174462702	ATP7A	1
GO:0032926	Negative regulation of activin receptor signaling pathway	1/86	10/18866	0.044671283	0.215208675	0.174462702	FST	1
GO:0035860	Glial cell-derived neurotrophic factor receptor signaling pathway	1/86	10/18866	0.044671283	0.215208675	0.174462702	GATA3	1
GO:0035871	Protein K11-linked deubiquitination	1/86	10/18866	0.044671283	0.215208675	0.174462702	USP30	1
GO:0035999	Tetrahydrofolate interconversion	1/86	10/18866	0.044671283	0.215208675	0.174462702	MTHFR	1
GO:0042428	Serotonin metabolic process	1/86	10/18866	0.044671283	0.215208675	0.174462702	ATP7A	1
GO:0044557	Relaxation of smooth muscle	1/86	10/18866	0.044671283	0.215208675	0.174462702	PRKG1	1
GO:0045793	Positive regulation of cell size	1/86	10/18866	0.044671283	0.215208675	0.174462702	ATP7A	1
GO:0048251	Elastic fiber assembly	1/86	10/18866	0.044671283	0.215208675	0.174462702	ATP7A	1
GO:0051541	Elastin metabolic process	1/86	10/18866	0.044671283	0.215208675	0.174462702	ATP7A	1
GO:0060513	Prostatic bud formation	1/86	10/18866	0.044671283	0.215208675	0.174462702	TP63	1
GO:0060600	Dichotomous subdivision of an epithelial terminal unit	1/86	10/18866	0.044671283	0.215208675	0.174462702	SEMA3A	1
GO:0086070	SA node cell to atrial cardiac muscle cell communication	1/86	10/18866	0.044671283	0.215208675	0.174462702	ANK2	1

(Continued)

Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0090527	Actin filament reorganization	1/86	10/18866	0.044671283	0.215208675	0.174462702	NEDD9	1
GO:1902946	Protein localization to early endosome	1/86	10/18866	0.044671283	0.215208675	0.174462702	SORL1	1
GO:1904672	Regulation of somatic stem cell population maintenance	1/86	10/18866	0.044671283	0.215208675	0.174462702	TP63	1
GO:1904684	Negative regulation of metalloendopeptidase activity	1/86	10/18866	0.044671283	0.215208675	0.174462702	SORL1	1
GO:2000018	Regulation of male gonad development	1/86	10/18866	0.044671283	0.215208675	0.174462702	SEMA3A	1
GO:2000271	Positive regulation of fibroblast apoptotic process	1/86	10/18866	0.044671283	0.215208675	0.174462702	TP63	1
GO:0043588	Skin development	5/86	425/18866	0.044800039	0.215208675	0.174462702	FST/CLIC4/TGFB2/ATP7A/TP63	5
GO:0072395	Signal transduction involved in cell cycle checkpoint	2/86	74/18866	0.0449016	0.215208675	0.174462702	SOX4/CNOT6L	2
GO:0030833	Regulation of actin filament polymerization	3/86	174/18866	0.045256984	0.215208675	0.174462702	PPP1R9A/ARHGAP28/JMY	3
GO:0010921	Regulation of phosphatase activity	3/86	175/18866	0.045899487	0.215208675	0.174462702	NUAK1/SYTL2/TGFB2	3
GO:0050768	Negative regulation of neurogenesis	4/86	295/18866	0.045916409	0.215208675	0.174462702	SORL1/BDNF/SEMA3A/MAP2	4
GO:0051146	Striated muscle cell differentiation	4/86	295/18866	0.045916409	0.215208675	0.174462702	NEBL/PGM5/BDNF/HDAC9	4
GO:0001707	Mesoderm formation	2/86	75/18866	0.045998211	0.215208675	0.174462702	BMPR2/ITGB3	2
GO:0035019	Somatic stem cell population maintenance	2/86	75/18866	0.045998211	0.215208675	0.174462702	SOX4/TP63	2
GO:0043627	Response to estrogen	2/86	75/18866	0.045998211	0.215208675	0.174462702	GATA3/SMAD6	2
GO:1901983	Regulation of protein acetylation	2/86	75/18866	0.045998211	0.215208675	0.174462702	GATA3/SOX4	2
GO:0033555	Multicellular organismal response to stress	2/86	76/18866	0.047104673	0.215208675	0.174462702	FBXL20/BDNF	2
GO:0071229	Cellular response to acid chemical	2/86	76/18866	0.047104673	0.215208675	0.174462702	CPEB3/ATP7A	2
GO:0030324	Lung development	3/86	177/18866	0.047198109	0.215208675	0.174462702	SLC7A11/ATP7A/BMPR2	3
GO:0048771	Tissue remodeling	3/86	178/18866	0.047854205	0.215208675	0.174462702	ATP7A/BMPR2/ITGB3	3
GO:0007422	Peripheral nervous system development	2/86	77/18866	0.048220875	0.215208675	0.174462702	ETV1/BDNF	2
GO:0048332	Mesoderm morphogenesis	2/86	77/18866	0.048220875	0.215208675	0.174462702	BMPR2/ITGB3	2
GO:0034329	Cell junction assembly	5/86	434/18866	0.048245354	0.215208675	0.174462702	PPP1R9A/GABRB3/BDNF/ANK2/SLITRK6	5
GO:0031098	Stress-activated protein kinase signaling cascade	4/86	300/18866	0.048308144	0.215208675	0.174462702	SASH1/TGFB2/SEMA3A/PLCB1	4
GO:0051258	Protein polymerization	4/86	300/18866	0.048308144	0.215208675	0.174462702	PPP1R9A/ARHGAP28/JMY/MAP2	4
GO:0002182	Cytoplasmic translational elongation	1/86	11/18866	0.049028425	0.215208675	0.174462702	CPEB3	1
GO:0002328	Pro-B cell differentiation	1/86	11/18866	0.049028425	0.215208675	0.174462702	SOX4	1

(Continued)



Table S1. Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0006751	Glutathione catabolic process	1/86	11/18866	0.049028425	0.215208675	0.174462702	CHAC1	1
GO:0006857	Oligopeptide transport	1/86	11/18866	0.049028425	0.215208675	0.174462702	SLC7A11	1
GO:0009950	Dorsal/ventral axis specification	1/86	11/18866	0.049028425	0.215208675	0.174462702	SMAD6	1
GO:0021561	Facial nerve development	1/86	11/18866	0.049028425	0.215208675	0.174462702	SEMA3A	1
GO:0021604	Cranial nerve structural organization	1/86	11/18866	0.049028425	0.215208675	0.174462702	SEMA3A	1
GO:0021610	Facial nerve morphogenesis	1/86	11/18866	0.049028425	0.215208675	0.174462702	SEMA3A	1
GO:0031442	Positive regulation of mRNA 3'-end processing	1/86	11/18866	0.049028425	0.215208675	0.174462702	CPEB3	1
GO:0032253	Dense core granule localization	1/86	11/18866	0.049028425	0.215208675	0.174462702	MAP2	1
GO:0032276	Regulation of gonadotropin secretion	1/86	11/18866	0.049028425	0.215208675	0.174462702	INHBB	1
GO:0032754	Positive regulation of interleukin-5 production	1/86	11/18866	0.049028425	0.215208675	0.174462702	GATA3	1
GO:0034776	Response to histamine	1/86	11/18866	0.049028425	0.215208675	0.174462702	GABRB3	1
GO:0035457	Cellular response to interferon-alpha	1/86	11/18866	0.049028425	0.215208675	0.174462702	GATA3	1
GO:0043455	Regulation of secondary metabolic process	1/86	11/18866	0.049028425	0.215208675	0.174462702	SLC7A11	1
GO:0043589	Skin morphogenesis	1/86	11/18866	0.049028425	0.215208675	0.174462702	TP63	1
GO:0044848	Biological phase	1/86	11/18866	0.049028425	0.215208675	0.174462702	TGFB2	1
GO:0046643	Regulation of gamma-delta T cell activation	1/86	11/18866	0.049028425	0.215208675	0.174462702	SOX4	1
GO:0048021	Regulation of melanin biosynthetic process	1/86	11/18866	0.049028425	0.215208675	0.174462702	SLC7A11	1
GO:0048102	Autophagic cell death	1/86	11/18866	0.049028425	0.215208675	0.174462702	TP53INP1	1
GO:0048103	Somatic stem cell division	1/86	11/18866	0.049028425	0.215208675	0.174462702	TGFB2	1
GO:0048672	Positive regulation of collateral sprouting	1/86	11/18866	0.049028425	0.215208675	0.174462702	BDNF	1
GO:0048742	Regulation of skeletal muscle fiber development	1/86	11/18866	0.049028425	0.215208675	0.174462702	HDAC9	1
GO:0051610	Serotonin uptake	1/86	11/18866	0.049028425	0.215208675	0.174462702	ITGB3	1
GO:0060174	Limb bud formation	1/86	11/18866	0.049028425	0.215208675	0.174462702	SOX4	1
GO:0060525	Prostate glandular acinus development	1/86	11/18866	0.049028425	0.215208675	0.174462702	TP63	1
GO:0061085	Regulation of histone H3-K27 methylation	1/86	11/18866	0.049028425	0.215208675	0.174462702	GATA3	1
GO:0061299	Retina vasculature morphogenesis in camera-type eye	1/86	11/18866	0.049028425	0.215208675	0.174462702	CLIC4	1
GO:0070254	Mucus secretion	1/86	11/18866	0.049028425	0.215208675	0.174462702	SYTL2	1
GO:0070933	Histone H4 deacetylation	1/86	11/18866	0.049028425	0.215208675	0.174462702	HDAC9	1
GO:0071281	Cellular response to iron ion	1/86	11/18866	0.049028425	0.215208675	0.174462702	ATP7A	1

(Continued)

**Table S1.** Continued

ID	Description	GeneRatio	BgRatio	p value	p.adjust	q-value	geneID	Count
GO:0090084	Negative regulation of inclusion body assembly	1/86	11/18866	0.049028425	0.215208675	0.174462702	SORL1	1
GO:0090309	Positive regulation of DNA methylation-dependent heterochromatin assembly	1/86	11/18866	0.049028425	0.215208675	0.174462702	ATF7IP	1
GO:0099519	Dense core granule cytoskeletal transport	1/86	11/18866	0.049028425	0.215208675	0.174462702	MAP2	1
GO:1900247	Regulation of cytoplasmic translational elongation	1/86	11/18866	0.049028425	0.215208675	0.174462702	CPEB3	1
GO:1900376	Regulation of secondary metabolite biosynthetic process	1/86	11/18866	0.049028425	0.215208675	0.174462702	SLC7A11	1
GO:1901950	Dense core granule transport	1/86	11/18866	0.049028425	0.215208675	0.174462702	MAP2	1
GO:1902513	Regulation of organelle transport along microtubule	1/86	11/18866	0.049028425	0.215208675	0.174462702	MAP2	1
GO:1904321	Response to forskolin	1/86	11/18866	0.049028425	0.215208675	0.174462702	AHR	1
GO:1904322	Cellular response to forskolin	1/86	11/18866	0.049028425	0.215208675	0.174462702	AHR	1
GO:1905245	Regulation of aspartic-type peptidase activity	1/86	11/18866	0.049028425	0.215208675	0.174462702	SORL1	1
GO:2000551	Regulation of T-helper 2 cell cytokine production	1/86	11/18866	0.049028425	0.215208675	0.174462702	GATA3	1
GO:2000574	Regulation of microtubule motor activity	1/86	11/18866	0.049028425	0.215208675	0.174462702	MAP2	1
GO:2000615	Regulation of histone H3-K9 acetylation	1/86	11/18866	0.049028425	0.215208675	0.174462702	GATA3	1
GO:0043367	CD4-positive, alpha-beta T cell differentiation	2/86	78/18866	0.049346708	0.215208675	0.174462702	GATA3/ATP7A	2
GO:0043900	Regulation of multi-organism process	2/86	78/18866	0.049346708	0.215208675	0.174462702	INHBB/PLCB1	2
GO:0060998	Regulation of dendritic spine development	2/86	78/18866	0.049346708	0.215208675	0.174462702	CPEB3/PPP1R9A	2
GO:0072332	Intrinsic apoptotic signaling pathway by p53 class mediator	2/86	78/18866	0.049346708	0.215208675	0.174462702	JMY/TP63	2
GO:1903522	Regulation of blood circulation	4/86	303/18866	0.049775935	0.215208675	0.174462702	TGFB2/SEMA3A/ANK2/BMPR2	4
GO:0030323	Respiratory tube development	3/86	181/18866	0.049849498	0.215208675	0.174462702	SLC7A11/ATP7A/BMPR2	3

**Table S2.** Functional enrichment analysis (MF) of genes associated with the downregulated genes

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0031994	Insulin-like growth factor I binding	2/87	13/18352	0.001675018	0.273507638	0.253388116	ITGAV/ITGB3	2
GO:0003712	Transcription coregulator activity	8/87	498/18352	0.002489608	0.273507638	0.253388116	GATA3/NCOA2/RSF1/SOX4/HDAC9/ATF7IP/JMY/JMJD1C	8
GO:0017134	Fibroblast growth factor binding	2/87	23/18352	0.005268487	0.273507638	0.253388116	ITGAV/ITGB3	2
GO:0005160	Transforming growth factor beta receptor binding	2/87	24/18352	0.005729821	0.273507638	0.253388116	SMAD6/TGFB2	2
GO:0005546	Phosphatidylinositol-4,5-bisphosphate binding	3/87	82/18352	0.006959505	0.273507638	0.253388116	SYTL2/SESTD1/PLCB1	3
GO:0001968	Fibronectin binding	2/87	27/18352	0.007220079	0.273507638	0.253388116	ITGAV/ITGB3	2
GO:0005520	Insulin-like growth factor binding	2/87	29/18352	0.008300389	0.273507638	0.253388116	ITGAV/ITGB3	2
GO:0005126	Cytokine receptor binding	5/87	271/18352	0.009355786	0.273507638	0.253388116	GATA3/SMAD6/TGFB2/BDNF/ITGB3	5
GO:0019956	Chemokine binding	2/87	33/18352	0.010663192	0.273507638	0.253388116	ITGAV/ITGB3	2
GO:0015175	Neutral amino acid transmembrane transporter activity	2/87	34/18352	0.011295035	0.273507638	0.253388116	SLC7A11/SLC38A2	2
GO:0008022	Protein C-terminus binding	4/87	189/18352	0.012493832	0.273507638	0.253388116	PPP1R9A/MAGI1/SASH1/ATXN1	4
GO:0051015	Actin filament binding	4/87	206/18352	0.016646672	0.273507638	0.253388116	PPP1R9A/NEBL/MYO18A/CLMN	4
GO:1902936	Phosphatidylinositol bisphosphate binding	3/87	119/18352	0.018993105	0.273507638	0.253388116	SYTL2/SESTD1/PLCB1	3
GO:0048156	Tau protein binding	2/87	45/18352	0.019274238	0.273507638	0.253388116	TTBK2/MAP2	2
GO:0015026	Coreceptor activity	2/87	48/18352	0.021761265	0.273507638	0.253388116	ITGAV/ITGB3	2
GO:0016538	Cyclin-dependent protein serine/threonine kinase regulator activity	2/87	50/18352	0.023489237	0.273507638	0.253388116	CCNT1/CCNG2	2
GO:0070888	E-box binding	2/87	50/18352	0.023489237	0.273507638	0.253388116	AHR/GATA3	2
GO:0022853	Active ion transmembrane transporter activity	4/87	229/18352	0.023508097	0.273507638	0.253388116	SLC7A11/SLC24A1/ATP7A/SLC38A2	4
GO:0019955	Cytokine binding	3/87	135/18352	0.026361093	0.273507638	0.253388116	ITGAV/BMP2/ITGB3	3
GO:0019838	Growth factor binding	3/87	136/18352	0.026865607	0.273507638	0.253388116	ITGAV/BMP2/ITGB3	3
GO:0008509	Anion transmembrane transporter activity	5/87	357/18352	0.027380166	0.273507638	0.253388116	SLC7A11/CLIC4/SLC24A1/GABRB3/SLC38A2	5
GO:0005080	Protein kinase C binding	2/87	55/18352	0.028045437	0.273507638	0.253388116	HDAC9/ITGAV	2
GO:0050840	Extracellular matrix binding	2/87	57/18352	0.029959408	0.273507638	0.253388116	ITGAV/ITGB3	2
GO:0015179	L-amino acid transmembrane transporter activity	2/87	59/18352	0.031923969	0.273507638	0.253388116	SLC7A11/SLC38A2	2

(Continued)

**Table S2.** *Continued*

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0003713	Transcription coactivator activity	4/87	267/18352	0.038154759	0.273507638	0.253388116	GATA3/NCOA2/SOX4/JMY	4
GO:0002039	p53 binding	2/87	66/18352	0.039182529	0.273507638	0.253388116	NUAK1/TP63	2
GO:0008083	Growth factor activity	3/87	162/18352	0.041782078	0.273507638	0.253388116	TGFB2/BDNF/INHBB	3
GO:0072509	Divalent inorganic cation transmembrane transporter activity	3/87	162/18352	0.041782078	0.273507638	0.253388116	SLC24A1/ATP7A/ITGAV	3
GO:0001094	TFIID-class transcription factor complex binding	1/87	10/18352	0.046418788	0.273507638	0.253388116	AHR	1
GO:0002162	Dystroglycan binding	1/87	10/18352	0.046418788	0.273507638	0.253388116	MAP2	1
GO:0004690	Cyclic nucleotide-dependent protein kinase activity	1/87	10/18352	0.046418788	0.273507638	0.253388116	PRKG1	1
GO:0005432	Calcium:sodium antiporter activity	1/87	10/18352	0.046418788	0.273507638	0.253388116	SLC24A1	1
GO:0016868	Intramolecular transferase activity, phosphotransferases	1/87	10/18352	0.046418788	0.273507638	0.253388116	PGM2L1	1
GO:0017002	Activin-activated receptor activity	1/87	10/18352	0.046418788	0.273507638	0.253388116	BMPR2	1
GO:0030957	Tat protein binding	1/87	10/18352	0.046418788	0.273507638	0.253388116	GABARAPL1	1
GO:0031078	Histone deacetylase activity (H3-K14 specific)	1/87	10/18352	0.046418788	0.273507638	0.253388116	HDAC9	1
GO:0032041	NAD-dependent histone deacetylase activity (H3-K14 specific)	1/87	10/18352	0.046418788	0.273507638	0.253388116	HDAC9	1
GO:0140104	Molecular carrier activity	1/87	10/18352	0.046418788	0.273507638	0.253388116	ATP7A	1
GO:0001618	Virus receptor activity	2/87	74/18352	0.048161835	0.273507638	0.253388116	ITGAV/ITGB3	2
GO:0140272	Exogenous protein binding	2/87	74/18352	0.048161835	0.273507638	0.253388116	ITGAV/ITGB3	2
GO:0005254	Chloride channel activity	2/87	75/18352	0.049332465	0.273507638	0.253388116	CLIC4/GABRB3	2

**Table S3.** Functional enrichment analysis (CC) of downregulated genes

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0043034	Costamere	3/89	19/19559	8.37177E-05	0.018250458	0.013835451	PGM5/ANK2/AHNAK2	3
GO:0042641	Actomyosin	4/89	79/19559	0.000463912	0.036256484	0.027485601	NEBL/PGM5/LPP/MYO18A	4
GO:0098858	Actin-based cell projection	6/89	220/19559	0.000505501	0.036256484	0.027485601	PPP1R9A/CLIC4/ATP7A/ITGAV/MAP2/ITGB3	6
GO:0031252	Cell leading edge	8/89	421/19559	0.000665257	0.036256484	0.027485601	PPP1R9A/ATP7A/ITGAV/GABARAPL1/PACSIN1/JMY/NEDD9/ITGB3	8
GO:0005902	Microvillus	4/89	93/19559	0.000858959	0.037450592	0.02839084	CLIC4/ATP7A/ITGAV/ITGB3	4
GO:0044214	Spanning component of plasma membrane	2/89	12/19559	0.001311795	0.043519068	0.032991278	SLC24A1/BMPR2	2
GO:0030175	Filopodium	4/89	106/19559	0.001397401	0.043519068	0.032991278	PPP1R9A/ITGAV/MAP2/ITGB3	4
GO:0030014	CCR4-NOT complex	2/89	16/19559	0.002357022	0.052272891	0.039627445	CPEB3/CNOT6L	2
GO:0030018	Z disc	4/89	128/19559	0.002782162	0.052272891	0.039627445	NEBL/PGM5/ANK2/AHNAK2	4
GO:0031527	Filopodium membrane	2/89	18/19559	0.002987491	0.052272891	0.039627445	ITGAV/ITGB3	2
GO:0097440	Apical dendrite	2/89	18/19559	0.002987491	0.052272891	0.039627445	CPEB3/MAP2	2
GO:0089717	Spanning component of membrane	2/89	19/19559	0.003329111	0.052272891	0.039627445	SLC24A1/BMPR2	2
GO:0042383	Sarcolemma	4/89	135/19559	0.003369092	0.052272891	0.039627445	PGM5/ANK2/SLC38A2/AHNAK2	4
GO:0001725	Stress fiber	3/89	68/19559	0.003687104	0.052272891	0.039627445	NEBL/PGM5/LPP	3
GO:0097517	Contractile actin filament bundle	3/89	68/19559	0.003687104	0.052272891	0.039627445	NEBL/PGM5/LPP	3
GO:0031674	I band	4/89	140/19559	0.003836542	0.052272891	0.039627445	NEBL/PGM5/ANK2/AHNAK2	4
GO:0031258	Lamellipodium membrane	2/89	22/19559	0.004457567	0.057161747	0.043333628	ITGAV/ITGB3	2
GO:0031253	Cell projection membrane	6/89	344/19559	0.004845054	0.057814402	0.043828397	SLC7A11/ATP7A/ITGAV/GABARAPL1/PACSIN1/ITGB3	6
GO:0032432	Actin filament bundle	3/89	76/19559	0.00503887	0.057814402	0.043828397	NEBL/PGM5/LPP	3
GO:0031528	Microvillus membrane	2/89	26/19559	0.006197936	0.067557503	0.051214524	ITGAV/ITGB3	2
GO:0005911	Cell-cell junction	7/89	493/19559	0.007222799	0.074979535	0.056841077	MAG1/CGNL1/CLIC4/PGM5/ANK2/BMPR2/ITGB3	7
GO:0031256	Leading edge membrane	4/89	175/19559	0.008381702	0.082823288	0.062787331	ITGAV/GABARAPL1/PACSIN1/ITGB3	4
GO:0008305	Integrin complex	2/89	31/19559	0.008738237	0.082823288	0.062787331	ITGAV/ITGB3	2
GO:0032587	Ruffle membrane	3/89	95/19559	0.009326562	0.08471627	0.064222378	ITGAV/PACSIN1/ITGB3	3
GO:0032839	Dendrite cytoplasm	2/89	34/19559	0.010449687	0.091121271	0.069077931	GABARAPL1/MAP2	2
GO:0098636	Protein complex involved in cell adhesion	2/89	36/19559	0.011666204	0.097816632	0.074153603	ITGAV/ITGB3	2
GO:0005903	Brush border	3/89	106/19559	0.012543653	0.10127838	0.076777912	SLC7A11/ATP7A/SLC38A2	3
GO:0030027	Lamellipodium	4/89	201/19559	0.013409681	0.104403946	0.079147366	PPP1R9A/ITGAV/NEDD9/ITGB3	4
GO:0030017	Sarcomere	4/89	207/19559	0.014792138	0.111196071	0.084296394	NEBL/PGM5/ANK2/AHNAK2	4
GO:0000307	Cyclin-dependent protein kinase holoenzyme complex	2/89	43/19559	0.016381768	0.119040851	0.090243426	CCNT1/CCNG2	2

(Continued)

Table S3. Continued

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0030016	Myofibril	4/89	227/19559	0.020039059	0.140919836	0.106829619	NEBL/PGM5/ANK2/AHNAK2	4
GO:0034707	Chloride channel complex	2/89	50/19559	0.021772834	0.144876464	0.109829091	CLIC4/GABRB3	2
GO:0034399	Nuclear periphery	3/89	131/19559	0.021959481	0.144876464	0.109829091	CLIC4/ATXN1/MAP2	3
GO:0014704	Intercalated disc	2/89	51/19559	0.022595412	0.144876464	0.109829091	PGM5/ANK2	2
GO:0043292	Contractile fiber	4/89	238/19559	0.023357656	0.145484828	0.110290285	NEBL/PGM5/ANK2/AHNAK2	4
GO:0098978	Glutamatergic synapse	5/89	361/19559	0.024523154	0.147057064	0.111482178	PPP1R9A/FBXL20/BCAN/PLCB1/ITGB3	5
GO:0030315	T-tubule	2/89	54/19559	0.025138884	0.147057064	0.111482178	ANK2/AHNAK2	2
GO:0005802	Trans-Golgi network	4/89	245/19559	0.0256338	0.147057064	0.111482178	SORL1/ATP7A/MYO18A/CHAC1	4
GO:0016459	Myosin complex	2/89	57/19559	0.027793265	0.155357222	0.117774427	CGNL1/MYO18A	2
GO:0031526	Brush border membrane	2/89	58/19559	0.028702113	0.156426515	0.118585046	SLC7A11/ATP7A	2
GO:0036064	Ciliary basal body	3/89	155/19559	0.033795659	0.175834844	0.133298264	RABL2B/TTBK2/LCA5	3
GO:0098862	Cluster of actin-based cell projections	3/89	159/19559	0.036033328	0.175834844	0.133298264	SLC7A11/ATP7A/SLC38A2	3
GO:0035869	Ciliary transition zone	2/89	68/19559	0.038420498	0.175834844	0.133298264	TTBK2/LCA5	2
GO:0005912	Adherens junction	3/89	166/19559	0.040128844	0.175834844	0.133298264	MAG1/PGM5/BMPR2	3
GO:0005667	Transcription regulator complex	5/89	413/19559	0.040249424	0.175834844	0.133298264	AHR/SKIL/SMAD6/HDAC9/ATF7IP	5
GO:0005925	Focal adhesion	5/89	415/19559	0.040953218	0.175834844	0.133298264	PGM5/LPP/ITGAV/NEDD9/ITGB3	5
GO:0030055	Cell-substrate junction	5/89	423/19559	0.043843336	0.175834844	0.133298264	PGM5/LPP/ITGAV/NEDD9/ITGB3	5
GO:0005641	Nuclear envelope lumen	1/89	10/19559	0.044592867	0.175834844	0.133298264	SORL1	1
GO:1990124	Messenger ribonucleoprotein complex	1/89	10/19559	0.044592867	0.175834844	0.133298264	CPEB3	1
GO:0044291	Cell-cell contact zone	2/89	74/19559	0.044768917	0.175834844	0.133298264	PGM5/ANK2	2
GO:0098982	GABA-ergic synapse	2/89	74/19559	0.044768917	0.175834844	0.133298264	GABRB3/PLCB1	2
GO:0045177	Apical part of cell	5/89	433/19559	0.047625364	0.175834844	0.133298264	SLC7A11/CLIC4/ATP7A/ANK2/BMPR2	5
GO:0000118	Histone deacetylase complex	2/89	77/19559	0.048078825	0.175834844	0.133298264	HDAC9/JMJD1C	2
GO:0001726	Ruffle	3/89	179/19559	0.048332303	0.175834844	0.133298264	ITGAV/PACSIN1/ITGB3	3
GO:0031010	ISWI-type complex	1/89	11/19559	0.048942513	0.175834844	0.133298264	RSF1	1
GO:0034992	Microtubule organizing center attachment site	1/89	11/19559	0.048942513	0.175834844	0.133298264	CLMN	1
GO:0034993	Meiotic nuclear membrane microtubule tethering complex	1/89	11/19559	0.048942513	0.175834844	0.133298264	CLMN	1
GO:0097470	Ribbon synapse	1/89	11/19559	0.048942513	0.175834844	0.133298264	PACSIN1	1
GO:0106083	Nuclear membrane protein complex	1/89	11/19559	0.048942513	0.175834844	0.133298264	CLMN	1
GO:0106094	Nuclear membrane microtubule tethering complex	1/89	11/19559	0.048942513	0.175834844	0.133298264	CLMN	1
GO:0016234	Inclusion body	2/89	78/19559	0.049201493	0.175834844	0.133298264	ATXN1/KLF8	2



**Table S4.** Functional enrichment analysis (KEGG) of genes associated with the downregulated genes

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
hsa04350	TGF-beta signaling pathway	5/45	96/8223	0.00016491	0.022922444	0.02187223	FST/SMAD6/TGFB2/INHBB/BMPR2	5
hsa04919	Thyroid hormone signaling pathway	4/45	121/8223	0.004173019	0.290024833	0.276737062	NCOA2/ITGAV/PLCB1/ITGB3	4
hsa04727	GABAergic synapse	3/45	89/8223	0.012533392	0.426926226	0.407366183	GABRB3/SLC38A2/GABA-RAPL1	3
hsa05410	Hypertrophic cardiomyopathy	3/45	90/8223	0.012916633	0.426926226	0.407366183	TGFB2/ITGAV/ITGB3	3
hsa05414	Dilated cardiomyopathy	3/45	96/8223	0.015357058	0.426926226	0.407366183	TGFB2/ITGAV/ITGB3	3
hsa05205	Proteoglycans in cancer	4/45	205/8223	0.025196801	0.497873197	0.475062649	TGFB2/ANK2/ITGAV/ITGB3	4
hsa05206	MicroRNAs in cancer	5/45	310/8223	0.026240318	0.497873197	0.475062649	TGFB2/SOX4/BMPR2/ITGB3/TP63	5
hsa04611	Platelet activation	3/45	124/8223	0.029996051	0.497873197	0.475062649	PLCB1/PRKG1/ITGB3	3
hsa04068	FoxO signaling pathway	3/45	131/8223	0.034496116	0.497873197	0.475062649	TGFB2/CCNG2/GABARAPL1	3
hsa05418	Fluid shear stress and atherosclerosis	3/45	139/8223	0.040045963	0.497873197	0.475062649	ITGAV/BMPR2/ITGB3	3
hsa04730	Long-term depression	2/45	60/8223	0.04241652	0.497873197	0.475062649	PLCB1/PRKG1	2
hsa04550	Signaling pathways regulating pluripotency of stem cells	3/45	143/8223	0.042981859	0.497873197	0.475062649	SKIL/INHBB/BMPR2	3
hsa05321	Inflammatory bowel disease	2/45	65/8223	0.049000918	0.523932893	0.499928395	GATA3/TGFB2	2

**Table S5.** Functional enrichment analysis (BP) of the DEGs associated with the upregulated genes

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0048660	Regulation of smooth muscle cell proliferation	5/38	173/18866	2.40386E-05	0.014098915	0.011725698	TNFAIP3/APLN/IGFBP3/MYB/S1PR1	5
GO:0048659	Smooth muscle cell proliferation	5/38	175/18866	2.54034E-05	0.014098915	0.011725698	TNFAIP3/APLN/IGFBP3/MYB/S1PR1	5
GO:0071222	Cellular response to lipopolysaccharide	5/38	208/18866	5.79563E-05	0.020270505	0.016858447	CXCL3/PPBP/TNFAIP3/CXCL2/SERPINE1	5
GO:0071219	Cellular response to molecule of bacterial origin	5/38	222/18866	7.88877E-05	0.020270505	0.016858447	CXCL3/PPBP/TNFAIP3/CXCL2/SERPINE1	5
GO:0030595	Leukocyte chemotaxis	5/38	232/18866	9.70957E-05	0.020270505	0.016858447	CXCL3/PPBP/CXCL2/S1PR1/SERPINE1	5
GO:0033002	Muscle cell proliferation	5/38	244/18866	0.000123037	0.020270505	0.016858447	TNFAIP3/APLN/IGFBP3/MYB/S1PR1	5
GO:0071216	Cellular response to biotic stimulus	5/38	246/18866	0.000127832	0.020270505	0.016858447	CXCL3/PPBP/TNFAIP3/CXCL2/SERPINE1	5
GO:0070424	Regulation of nucleotide-binding oligomerization domain containing signaling pathway	2/38	10/18866	0.000175971	0.024415911	0.020306073	TNFAIP3/HSPA1B	2
GO:0061043	Regulation of vascular wound healing	2/38	13/18866	0.000303854	0.0350297	0.029133283	TNFAIP3/SERPINE1	2
GO:0070431	Nucleotide-binding oligomerization domain containing 2 signaling pathway	2/38	14/18866	0.000354046	0.0350297	0.029133283	TNFAIP3/HSPA1B	2
GO:0048662	Negative regulation of smooth muscle cell proliferation	3/38	69/18866	0.000360371	0.0350297	0.029133283	TNFAIP3/APLN/IGFBP3	3
GO:0060326	Cell chemotaxis	5/38	311/18866	0.000378699	0.0350297	0.029133283	CXCL3/PPBP/CXCL2/S1PR1/SERPINE1	5
GO:0061844	Antimicrobial humoral immune response mediated by antimicrobial peptide	3/38	75/18866	0.000460592	0.039327508	0.032707657	CXCL3/PPBP/CXCL2	3
GO:0032496	Response to lipopolysaccharide	5/38	334/18866	0.000524346	0.041184338	0.034251934	CXCL3/PPBP/TNFAIP3/CXCL2/SERPINE1	5
GO:0031397	Negative regulation of protein ubiquitination	3/38	80/18866	0.000556545	0.041184338	0.034251934	TNFAIP3/DNAJA1/HSPA1B	3
GO:0002237	Response to molecule of bacterial origin	5/38	356/18866	0.000699847	0.048000435	0.039920704	CXCL3/PPBP/TNFAIP3/CXCL2/SERPINE1	5
GO:0070098	Chemokine-mediated signaling pathway	3/38	88/18866	0.000735142	0.048000435	0.039920704	CXCL3/PPBP/CXCL2	3
GO:0061042	Vascular wound healing	2/38	21/18866	0.000809794	0.048876902	0.040649638	TNFAIP3/SERPINE1	2
GO:1903321	Negative regulation of protein modification by small protein conjugation or removal	3/38	92/18866	0.000836632	0.048876902	0.040649638	TNFAIP3/DNAJA1/HSPA1B	3
GO:1990868	Response to chemokine	3/38	97/18866	0.000975483	0.050782909	0.042234813	CXCL3/PPBP/CXCL2	3
GO:1990869	Cellular response to chemokine	3/38	97/18866	0.000975483	0.050782909	0.042234813	CXCL3/PPBP/CXCL2	3
GO:0097529	Myeloid leukocyte migration	4/38	222/18866	0.001006508	0.050782909	0.042234813	CXCL3/PPBP/CXCL2/SERPINE1	4
GO:0000079	Regulation of cyclin-dependent protein serine/threonine kinase activity	3/38	102/18866	0.001128148	0.053244499	0.044282054	TNFAIP3/CDC25A/CDKN3	3

(Continued)

Table S5. Continued

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0030593	Neutrophil chemotaxis	3/38	103/18866	0.001160384	0.053244499	0.044282054	CXCL3/PPBP/CXCL2	3
GO:2001234	Negative regulation of apoptotic signaling pathway	4/38	233/18866	0.001203717	0.053244499	0.044282054	TNFAIP3/DNAJA1/SERPINE1/HSPA1B	4
GO:1904029	Regulation of cyclin-dependent protein kinase activity	3/38	106/18866	0.001260569	0.053244499	0.044282054	TNFAIP3/CDC25A/CDKN3	3
GO:2001237	Negative regulation of extrinsic apoptotic signaling pathway	3/38	107/18866	0.001295136	0.053244499	0.044282054	TNFAIP3/SERPINE1/HSPA1B	3
GO:0060055	Angiogenesis involved in wound healing	2/38	30/18866	0.001658373	0.065742634	0.054676425	TNFAIP3/SERPINE1	2
GO:1990266	Neutrophil migration	3/38	122/18866	0.001886881	0.072222009	0.060065151	CXCL3/PPBP/CXCL2	3
GO:0071621	Granulocyte chemotaxis	3/38	127/18866	0.002115914	0.076192697	0.063367468	CXCL3/PPBP/CXCL2	3
GO:2000352	Negative regulation of endothelial cell apoptotic process	2/38	34/18866	0.002127904	0.076192697	0.063367468	TNFAIP3/SERPINE1	2
GO:0070423	Nucleotide-binding oligomerization domain containing signaling pathway	2/38	37/18866	0.002516584	0.084138903	0.069976119	TNFAIP3/HSPA1B	2
GO:0019730	Antimicrobial humoral response	3/38	137/18866	0.002624222	0.084138903	0.069976119	CXCL3/PPBP/CXCL2	3
GO:0014912	Negative regulation of smooth muscle cell migration	2/38	38/18866	0.002653028	0.084138903	0.069976119	IGFBP3/SERPINE1	2
GO:0035872	Nucleotide-binding domain, leucine rich repeat containing receptor signaling pathway	2/38	38/18866	0.002653028	0.084138903	0.069976119	TNFAIP3/HSPA1B	2
GO:1902042	Negative regulation of extrinsic apoptotic signaling pathway via death domain receptors	2/38	41/18866	0.003082827	0.095053839	0.079053785	TNFAIP3/SERPINE1	2
GO:0071901	Negative regulation of protein serine/threonine kinase activity	3/38	148/18866	0.003263895	0.096472101	0.080233317	CHORDC1/TNFAIP3/DNAJA1	3
GO:0045124	Regulation of bone resorption	2/38	43/18866	0.003386278	0.096472101	0.080233317	TNFAIP3/S1PR1	2
GO:0097530	Granulocyte migration	3/38	150/18866	0.00338956	0.096472101	0.080233317	CXCL3/PPBP/CXCL2	3
GO:1904036	Negative regulation of epithelial cell apoptotic process	2/38	48/18866	0.004203334	0.113869229	0.094702052	TNFAIP3/SERPINE1	2
GO:2001236	Regulation of extrinsic apoptotic signaling pathway	3/38	162/18866	0.004205981	0.113869229	0.094702052	TNFAIP3/SERPINE1/HSPA1B	3
GO:0009408	Response to heat	3/38	166/18866	0.004502401	0.117537332	0.097752717	CHORDC1/DNAJA1/HSPA1B	3
GO:0046850	Regulation of bone remodeling	2/38	50/18866	0.004553248	0.117537332	0.097752717	TNFAIP3/S1PR1	2
GO:0060976	Coronary vasculature development	2/38	51/18866	0.004733101	0.119403217	0.099304525	ADAMTS6/APLN	2
GO:0048260	Positive regulation of receptor-mediated endocytosis	2/38	52/18866	0.004916199	0.121266244	0.100853955	APLN/SERPINE1	2

(Continued)

Table S5. Continued

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0032757	Positive regulation of interleukin-8 production	2/38	54/18866	0.005292082	0.127700239	0.10620494	SERPINE1/HSPA1B	2
GO:0062197	Cellular response to chemical stress	4/38	360/18866	0.005769905	0.135973274	0.113085407	TNFAIP3/MYB/DNAJA1/HSPA1B	4
GO:0070936	Protein K48-linked ubiquitination	2/38	57/18866	0.005879925	0.135973274	0.113085407	TNFAIP3/UBE2D4	2
GO:0061077	Chaperone-mediated protein folding	2/38	60/18866	0.006496281	0.147160652	0.122389655	CHORDC1/HSPA1B	2
GO:1902041	Regulation of extrinsic apoptotic signaling pathway via death domain receptors	2/38	61/18866	0.006708009	0.147776298	0.122901673	TNFAIP3/SERPINE1	2
GO:0010803	Regulation of tumor necrosis factor-mediated signaling pathway	2/38	62/18866	0.006922854	0.147776298	0.122901673	TNFAIP3/HSPA1B	2
GO:2000351	Regulation of endothelial cell apoptotic process	2/38	62/18866	0.006922854	0.147776298	0.122901673	TNFAIP3/SERPINE1	2
GO:0045453	Bone resorption	2/38	64/18866	0.007361842	0.154181978	0.128229108	TNFAIP3/S1PR1	2
GO:0031331	Positive regulation of cellular catabolic process	4/38	390/18866	0.007622996	0.155713474	0.129502813	TNFAIP3/TOMM7/PIM2/HSPA1B	4
GO:0030198	Extracellular matrix organization	4/38	395/18866	0.007965878	0.155713474	0.129502813	ADAMTS6/ADAMTS14/SERPINE1/TGFBI	4
GO:0043062	Extracellular structure organization	4/38	396/18866	0.008035657	0.155713474	0.129502813	ADAMTS6/ADAMTS14/SERPINE1/TGFBI	4
GO:0002753	Cytoplasmic pattern recognition receptor signaling pathway	2/38	68/18866	0.008276662	0.155713474	0.129502813	TNFAIP3/HSPA1B	2
GO:0016239	Positive regulation of macroautophagy	2/38	68/18866	0.008276662	0.155713474	0.129502813	TOMM7/PIM2	2
GO:0072577	Endothelial cell apoptotic process	2/38	68/18866	0.008276662	0.155713474	0.129502813	TNFAIP3/SERPINE1	2
GO:0031396	Regulation of protein ubiquitination	3/38	211/18866	0.008724015	0.161394284	0.134227394	TNFAIP3/DNAJA1/HSPA1B	3
GO:0001503	Ossification	4/38	412/18866	0.009207614	0.166220297	0.138241063	CDH11/IGFBP3/STC1/S1PR1	4
GO:2001233	Regulation of apoptotic signaling pathway	4/38	413/18866	0.009284377	0.166220297	0.138241063	TNFAIP3/DNAJA1/SERPINE1/HSPA1B	4
GO:1903747	Regulation of establishment of protein localization to mitochondrion	2/38	73/18866	0.009488233	0.167173623	0.139033919	TOMM7/DNAJA1	2
GO:0006457	Protein folding	3/38	230/18866	0.011020819	0.185670592	0.154417363	CHORDC1/DNAJA1/HSPA1B	3
GO:0097191	Extrinsic apoptotic signaling pathway	3/38	230/18866	0.011020819	0.185670592	0.154417363	TNFAIP3/SERPINE1/HSPA1B	3
GO:1900034	Regulation of cellular response to heat	2/38	79/18866	0.011039873	0.185670592	0.154417363	CHORDC1/HSPA1B	2
GO:0009266	Response to temperature stimulus	3/38	233/18866	0.011412487	0.189072545	0.157246678	CHORDC1/DNAJA1/HSPA1B	3
GO:0001933	Negative regulation of protein phosphorylation	4/38	444/18866	0.011876361	0.193864123	0.161231708	CHORDC1/TNFAIP3/IGFBP3/DNAJA1	4
GO:0001819	Positive regulation of cytokine production	4/38	447/18866	0.012149539	0.195449108	0.162549898	POLR3G/MYB/SERPINE1/HSPA1B	4

(Continued)

Table S5. Continued

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:1903320	Regulation of protein modification by small protein conjugation or removal	3/38	242/18866	0.012635607	0.200132614	0.166445047	TNFAIP3/DNAJA1/HSPA1B	3
GO:0009896	Positive regulation of catabolic process	4/38	454/18866	0.01280268	0.200132614	0.166445047	TNFAIP3/TOMM7/PIM2/HSPA1B	4
GO:0014910	Regulation of smooth muscle cell migration	2/38	86/18866	0.012981575	0.200132614	0.166445047	IGFBP3/SERPINE1	2
GO:0006469	Negative regulation of protein kinase activity	3/38	246/18866	0.013202523	0.200750689	0.166959084	CHORDC1/TNFAIP3/DNAJA1	3
GO:0008625	Extrinsic apoptotic signaling pathway via death domain receptors	2/38	89/18866	0.013856109	0.205070406	0.17055168	TNFAIP3/SERPINE1	2
GO:0043506	Regulation of JUN kinase activity	2/38	89/18866	0.013856109	0.205070406	0.17055168	FZD8/DNAJA1	2
GO:0034103	Regulation of tissue remodeling	2/38	91/18866	0.014453019	0.208348715	0.173278163	TNFAIP3/S1PR1	2
GO:0046849	Bone remodeling	2/38	91/18866	0.014453019	0.208348715	0.173278163	TNFAIP3/S1PR1	2
GO:0014909	Smooth muscle cell migration	2/38	93/18866	0.01506093	0.211615603	0.175995148	IGFBP3/SERPINE1	2
GO:0032677	Regulation of interleukin-8 production	2/38	93/18866	0.01506093	0.211615603	0.175995148	SERPINE1/HSPA1B	2
GO:1904035	Regulation of epithelial cell apoptotic process	2/38	94/18866	0.015368982	0.213244626	0.177349964	TNFAIP3/SERPINE1	2
GO:0042326	Negative regulation of phosphorylation	4/38	484/18866	0.015856817	0.217297123	0.18072032	CHORDC1/TNFAIP3/IGFBP3/DNAJA1	4
GO:0033673	Negative regulation of kinase activity	3/38	268/18866	0.01657976	0.219402235	0.182471086	CHORDC1/TNFAIP3/DNAJA1	3
GO:0062207	Regulation of pattern recognition receptor signaling pathway	2/38	99/18866	0.016949739	0.219402235	0.182471086	TNFAIP3/HSPA1B	2
GO:0045807	Positive regulation of endocytosis	2/38	100/18866	0.017273909	0.219402235	0.182471086	APLN/SERPINE1	2
GO:0070301	Cellular response to hydrogen peroxide	2/38	100/18866	0.017273909	0.219402235	0.182471086	TNFAIP3/MYB	2
GO:0032637	Interleukin-8 production	2/38	101/18866	0.017600726	0.219402235	0.182471086	SERPINE1/HSPA1B	2
GO:1990542	Mitochondrial transmembrane transport	2/38	101/18866	0.017600726	0.219402235	0.182471086	SLC25A12/TOMM7	2
GO:0035335	Peptidyl-tyrosine dephosphorylation	2/38	103/18866	0.018262253	0.219402235	0.182471086	CDC25A/CDKN3	2
GO:0048661	Positive regulation of smooth muscle cell proliferation	2/38	103/18866	0.018262253	0.219402235	0.182471086	MYB/S1PR1	2
GO:0048259	Regulation of receptor-mediated endocytosis	2/38	105/18866	0.018934228	0.219402235	0.182471086	APLN/SERPINE1	2
GO:0014812	Muscle cell migration	2/38	106/18866	0.019274106	0.219402235	0.182471086	IGFBP3/SERPINE1	2
GO:0000082	G1/S transition of mitotic cell cycle	3/38	287/18866	0.019853233	0.219402235	0.182471086	CDC25A/CDKN3/PIM2	3
GO:0002676	Regulation of chronic inflammatory response	1/38	10/18866	0.019965185	0.219402235	0.182471086	TNFAIP3	1
GO:0003376	Sphingosine-1-phosphate receptor signaling pathway	1/38	10/18866	0.019965185	0.219402235	0.182471086	S1PR1	1

(Continued)

Table S5. Continued

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0034135	Regulation of toll-like receptor 2 signaling pathway	1/38	10/18866	0.019965185	0.219402235	0.182471086	TNFAIP3	1
GO:0035871	Protein K11-linked deubiquitination	1/38	10/18866	0.019965185	0.219402235	0.182471086	TNFAIP3	1
GO:0042756	Drinking behavior	1/38	10/18866	0.019965185	0.219402235	0.182471086	APLN	1
GO:0051409	Response to nitrosative stress	1/38	10/18866	0.019965185	0.219402235	0.182471086	DNAJA1	1
GO:0051918	Negative regulation of fibrinolysis	1/38	10/18866	0.019965185	0.219402235	0.182471086	SERPINE1	1
GO:0098779	Positive regulation of mitophagy in response to mitochondrial depolarization	1/38	10/18866	0.019965185	0.219402235	0.182471086	TOMM7	1
GO:0031647	Regulation of protein stability	3/38	296/18866	0.021520184	0.219402235	0.182471086	TOMM7/PIM2/HSPA1B	3
GO:0051348	Negative regulation of transferase activity	3/38	296/18866	0.021520184	0.219402235	0.182471086	CHORDC1/TNFAIP3/DNAJA1	3
GO:0032963	Collagen metabolic process	2/38	113/18866	0.021724827	0.219402235	0.182471086	MYB/ADAMTS14	2
GO:0070268	Cornification	2/38	113/18866	0.021724827	0.219402235	0.182471086	KRT6B/KRT75	2
GO:0016078	tRNA catabolic process	1/38	11/18866	0.021940223	0.219402235	0.182471086	POP1	1
GO:0031652	Positive regulation of heat generation	1/38	11/18866	0.021940223	0.219402235	0.182471086	APLN	1
GO:0051574	Positive regulation of histone H3-K9 methylation	1/38	11/18866	0.021940223	0.219402235	0.182471086	MYB	1
GO:0070778	L-aspartate transmembrane transport	1/38	11/18866	0.021940223	0.219402235	0.182471086	SLC25A12	1
GO:0090084	Negative regulation of inclusion body assembly	1/38	11/18866	0.021940223	0.219402235	0.182471086	HSPA1B	1
GO:1901526	Positive regulation of mitophagy	1/38	11/18866	0.021940223	0.219402235	0.182471086	TOMM7	1
GO:1903265	Positive regulation of tumor necrosis factor-mediated signaling pathway	1/38	11/18866	0.021940223	0.219402235	0.182471086	HSPA1B	1
GO:0031109	Microtubule polymerization or depolymerization	2/38	117/18866	0.023180502	0.220532534	0.183411126	KIF18B/HSPA1B	2
GO:0045446	Endothelial cell differentiation	2/38	117/18866	0.023180502	0.220532534	0.183411126	STC1/S1PR1	2
GO:1904019	Epithelial cell apoptotic process	2/38	117/18866	0.023180502	0.220532534	0.183411126	TNFAIP3/SERPINE1	2
GO:0010755	Regulation of plasminogen activation	1/38	12/18866	0.023911386	0.220532534	0.183411126	SERPINE1	1
GO:0033629	Negative regulation of cell adhesion mediated by integrin	1/38	12/18866	0.023911386	0.220532534	0.183411126	SERPINE1	1
GO:0060536	Cartilage morphogenesis	1/38	12/18866	0.023911386	0.220532534	0.183411126	STC1	1
GO:0072537	Fibroblast activation	1/38	12/18866	0.023911386	0.220532534	0.183411126	MYB	1
GO:0090520	Sphingolipid mediated signaling pathway	1/38	12/18866	0.023911386	0.220532534	0.183411126	S1PR1	1

(Continued)



Table S5. Continued

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0034599	Cellular response to oxidative stress	3/38	310/18866	0.024262434	0.220532534	0.183411126	TNFAIP3/MYB/HSPA1B	3
GO:0044843	Cell cycle G1/S phase transition	3/38	310/18866	0.024262434	0.220532534	0.183411126	CDC25A/CDKN3/PIM2	3
GO:0010906	Regulation of glucose metabolic process	2/38	121/18866	0.024675494	0.220532534	0.183411126	IGFBP3/SLC25A12	2
GO:0001682	tRNA 5'-leader removal	1/38	13/18866	0.02587868	0.220532534	0.183411126	POP1	1
GO:0006596	Polyamine biosynthetic process	1/38	13/18866	0.02587868	0.220532534	0.183411126	SRM	1
GO:0031650	Regulation of heat generation	1/38	13/18866	0.02587868	0.220532534	0.183411126	APLN	1
GO:0031665	Negative regulation of lipopolysaccharide-mediated signaling pathway	1/38	13/18866	0.02587868	0.220532534	0.183411126	TNFAIP3	1
GO:0034144	Negative regulation of toll-like receptor 4 signaling pathway	1/38	13/18866	0.02587868	0.220532534	0.183411126	TNFAIP3	1
GO:0043568	Positive regulation of insulin-like growth factor receptor signaling pathway	1/38	13/18866	0.02587868	0.220532534	0.183411126	IGFBP3	1
GO:0032479	Regulation of type I interferon production	2/38	125/18866	0.026209113	0.220532534	0.183411126	POLR3G/TNFAIP3	2
GO:0034605	Cellular response to heat	2/38	125/18866	0.026209113	0.220532534	0.183411126	CHORDC1/HSPA1B	2
GO:0006470	Protein dephosphorylation	3/38	323/18866	0.026971601	0.220532534	0.183411126	IGFBP3/CDC25A/CDKN3	3
GO:0032606	Type I interferon production	2/38	127/18866	0.026990194	0.220532534	0.183411126	POLR3G/TNFAIP3	2
GO:0002576	Platelet degranulation	2/38	129/18866	0.027780676	0.220532534	0.183411126	PPBP/SERPINE1	2
GO:0001886	Endothelial cell morphogenesis	1/38	14/18866	0.027842114	0.220532534	0.183411126	STC1	1
GO:0043650	Dicarboxylic acid biosynthetic process	1/38	14/18866	0.027842114	0.220532534	0.183411126	SLC25A12	1
GO:0051917	Regulation of fibrinolysis	1/38	14/18866	0.027842114	0.220532534	0.183411126	SERPINE1	1
GO:0090399	Replicative senescence	1/38	14/18866	0.027842114	0.220532534	0.183411126	SERPINE1	1
GO:1904925	Positive regulation of autophagy of mitochondrion in response to mitochondrial depolarization	1/38	14/18866	0.027842114	0.220532534	0.183411126	TOMM7	1
GO:0010508	Positive regulation of autophagy	2/38	131/18866	0.028580476	0.220532534	0.183411126	TOMM7/PIM2	2
GO:0046887	Positive regulation of hormone secretion	2/38	131/18866	0.028580476	0.220532534	0.183411126	APLN/MYB	2
GO:0002467	Germinal center formation	1/38	15/18866	0.029801694	0.220532534	0.183411126	TNFAIP3	1
GO:0006089	Lactate metabolic process	1/38	15/18866	0.029801694	0.220532534	0.183411126	SLC25A12	1
GO:0007638	Mechanosensory behavior	1/38	15/18866	0.029801694	0.220532534	0.183411126	STRBP	1
GO:0016114	Terpenoid biosynthetic process	1/38	15/18866	0.029801694	0.220532534	0.183411126	DHRS9	1

(Continued)

Table S5. Continued

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0023035	CD40 signaling pathway	1/38	15/18866	0.029801694	0.220532534	0.183411126	TNFAIP3	1
GO:0034134	Toll-like receptor 2 signaling pathway	1/38	15/18866	0.029801694	0.220532534	0.183411126	TNFAIP3	1
GO:0045779	Negative regulation of bone resorption	1/38	15/18866	0.029801694	0.220532534	0.183411126	TNFAIP3	1
GO:1904923	Regulation of autophagy of mitochondrion in response to mitochondrial depolarization	1/38	15/18866	0.029801694	0.220532534	0.183411126	TOMM7	1
GO:2000345	Regulation of hepatocyte proliferation	1/38	15/18866	0.029801694	0.220532534	0.183411126	TNFAIP3	1
GO:2001171	Positive regulation of ATP biosynthetic process	1/38	15/18866	0.029801694	0.220532534	0.183411126	SLC25A12	1
GO:0003158	Endothelium development	2/38	135/18866	0.030207696	0.220595672	0.183463636	STC1/S1PR1	2
GO:0015748	Organophosphate ester transport	2/38	135/18866	0.030207696	0.220595672	0.183463636	SLC25A12/PITPNM2	2
GO:0006595	Polyamine metabolic process	1/38	16/18866	0.031757427	0.224527035	0.186733247	SRM	1
GO:0043508	Negative regulation of JUN kinase activity	1/38	16/18866	0.031757427	0.224527035	0.186733247	DNAJA1	1
GO:0048012	Hepatocyte growth factor receptor signaling pathway	1/38	16/18866	0.031757427	0.224527035	0.186733247	ESM1	1
GO:0090083	Regulation of inclusion body assembly	1/38	16/18866	0.031757427	0.224527035	0.186733247	HSPA1B	1
GO:0099116	tRNA 5'-end processing	1/38	16/18866	0.031757427	0.224527035	0.186733247	POP1	1
GO:0072655	Establishment of protein localization to mitochondrion	2/38	140/18866	0.032292653	0.224646621	0.186832704	TOMM7/DNAJA1	2
GO:0009615	Response to virus	3/38	349/18866	0.032859219	0.224646621	0.186832704	POLR3G/TNFAIP3/PIM2	3
GO:0030336	Negative regulation of cell migration	3/38	350/18866	0.033098116	0.224646621	0.186832704	IGFBP3/STC1/SERPINE1	3
GO:0002031	G protein-coupled receptor internalization	1/38	17/18866	0.033709322	0.224646621	0.186832704	APLN	1
GO:0009084	Glutamine family amino acid biosynthetic process	1/38	17/18866	0.033709322	0.224646621	0.186832704	SLC25A12	1
GO:0031649	Heat generation	1/38	17/18866	0.033709322	0.224646621	0.186832704	APLN	1
GO:0042448	Progesterone metabolic process	1/38	17/18866	0.033709322	0.224646621	0.186832704	DHRS9	1
GO:0046851	Negative regulation of bone remodeling	1/38	17/18866	0.033709322	0.224646621	0.186832704	TNFAIP3	1
GO:1901673	Regulation of mitotic spindle assembly	1/38	17/18866	0.033709322	0.224646621	0.186832704	HSPA1B	1
GO:0050921	Positive regulation of chemotaxis	2/38	144/18866	0.03400057	0.224646621	0.186832704	S1PR1/SERPINE1	2
GO:0070585	Protein localization to mitochondrion	2/38	144/18866	0.03400057	0.224646621	0.186832704	TOMM7/DNAJA1	2
GO:0042542	Response to hydrogen peroxide	2/38	146/18866	0.034867623	0.229012195	0.190463438	TNFAIP3/MYB	2

(Continued)

Table S5. Continued

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0007043	Cell-cell junction assembly	2/38	147/18866	0.035304388	0.22932859	0.190726575	CDH11/TLN2	2
GO:0051571	Positive regulation of histone H3-K4 methylation	1/38	18/18866	0.035657386	0.22932859	0.190726575	MYB	1
GO:1901524	Regulation of mitophagy	1/38	18/18866	0.035657386	0.22932859	0.190726575	TOMM7	1
GO:0010675	Regulation of cellular carbohydrate metabolic process	2/38	148/18866	0.035743298	0.22932859	0.190726575	IGFBP3/SLC25A12	2
GO:1903364	Positive regulation of cellular protein catabolic process	2/38	149/18866	0.036184345	0.22932859	0.190726575	TNFAIP3/HSPA1B	2
GO:2000146	Negative regulation of cell motility	3/38	365/18866	0.036791555	0.22932859	0.190726575	IGFBP3/STC1/SERPINE1	3
GO:0061041	Regulation of wound healing	2/38	151/18866	0.037072807	0.22932859	0.190726575	TNFAIP3/SERPINE1	2
GO:0003417	Growth plate cartilage development	1/38	19/18866	0.037601625	0.22932859	0.190726575	STC1	1
GO:0030150	Protein import into mitochondrial matrix	1/38	19/18866	0.037601625	0.22932859	0.190726575	TOMM7	1
GO:0031643	Positive regulation of myelination	1/38	19/18866	0.037601625	0.22932859	0.190726575	SLC25A12	1
GO:0035988	Chondrocyte proliferation	1/38	19/18866	0.037601625	0.22932859	0.190726575	STC1	1
GO:0060252	Positive regulation of glial cell proliferation	1/38	19/18866	0.037601625	0.22932859	0.190726575	MYB	1
GO:0090026	Positive regulation of monocyte chemotaxis	1/38	19/18866	0.037601625	0.22932859	0.190726575	SERPINE1	1
GO:0002544	Chronic inflammatory response	1/38	20/18866	0.039542047	0.232485102	0.193351763	TNFAIP3	1
GO:0032495	Response to muramyl dipeptide	1/38	20/18866	0.039542047	0.232485102	0.193351763	TNFAIP3	1
GO:0034138	Toll-like receptor 3 signaling pathway	1/38	20/18866	0.039542047	0.232485102	0.193351763	TNFAIP3	1
GO:0071636	Positive regulation of transforming growth factor beta production	1/38	20/18866	0.039542047	0.232485102	0.193351763	MYB	1
GO:2001169	Regulation of ATP biosynthetic process	1/38	20/18866	0.039542047	0.232485102	0.193351763	SLC25A12	1
GO:0006959	Humoral immune response	3/38	377/18866	0.039894013	0.232485102	0.193351763	CXCL3/PPBP/CXCL2	3
GO:0002029	Desensitization of G protein-coupled receptor signaling pathway	1/38	21/18866	0.04147866	0.232485102	0.193351763	APLN	1
GO:0022401	Negative adaptation of signaling pathway	1/38	21/18866	0.04147866	0.232485102	0.193351763	APLN	1
GO:0034471	ncRNA 5'-end processing	1/38	21/18866	0.04147866	0.232485102	0.193351763	POP1	1
GO:0072574	Hepatocyte proliferation	1/38	21/18866	0.04147866	0.232485102	0.193351763	TNFAIP3	1
GO:0072575	Epithelial cell proliferation involved in liver morphogenesis	1/38	21/18866	0.04147866	0.232485102	0.193351763	TNFAIP3	1
GO:0090280	Positive regulation of calcium ion import	1/38	21/18866	0.04147866	0.232485102	0.193351763	STC1	1

(Continued)

Table S5. Continued

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0098780	Response to mitochondrial depolarisation	1/38	21/18866	0.04147866	0.232485102	0.193351763	TOMM7	1
GO:1903599	Positive regulation of autophagy of mitochondrion	1/38	21/18866	0.04147866	0.232485102	0.193351763	TOMM7	1
GO:0007398	Ectoderm development	1/38	22/18866	0.04341147	0.232485102	0.193351763	KRT6B	1
GO:0023058	Adaptation of signaling pathway	1/38	22/18866	0.04341147	0.232485102	0.193351763	APLN	1
GO:0034104	Negative regulation of tissue remodeling	1/38	22/18866	0.04341147	0.232485102	0.193351763	TNFAIP3	1
GO:0044342	Type B pancreatic cell proliferation	1/38	22/18866	0.04341147	0.232485102	0.193351763	IGFBP3	1
GO:0045624	Positive regulation of T-helper cell differentiation	1/38	22/18866	0.04341147	0.232485102	0.193351763	MYB	1
GO:0045663	Positive regulation of myoblast differentiation	1/38	22/18866	0.04341147	0.232485102	0.193351763	IGFBP3	1
GO:0072576	Liver morphogenesis	1/38	22/18866	0.04341147	0.232485102	0.193351763	TNFAIP3	1
GO:0000966	RNA 5'-end processing	1/38	23/18866	0.045340485	0.232485102	0.193351763	POP1	1
GO:0006359	Regulation of transcription by RNA polymerase III	1/38	23/18866	0.045340485	0.232485102	0.193351763	POLR3G	1
GO:0015813	L-glutamate transmembrane transport	1/38	23/18866	0.045340485	0.232485102	0.193351763	SLC25A12	1
GO:0031639	Plasminogen activation	1/38	23/18866	0.045340485	0.232485102	0.193351763	SERPINE1	1
GO:0032703	Negative regulation of interleukin-2 production	1/38	23/18866	0.045340485	0.232485102	0.193351763	TNFAIP3	1
GO:0042026	Protein refolding	1/38	23/18866	0.045340485	0.232485102	0.193351763	HSPA1B	1
GO:0042401	Cellular biogenic amine biosynthetic process	1/38	23/18866	0.045340485	0.232485102	0.193351763	SRM	1
GO:0043576	Regulation of respiratory gaseous exchange	1/38	23/18866	0.045340485	0.232485102	0.193351763	APLN	1
GO:0051570	Regulation of histone H3-K9 methylation	1/38	23/18866	0.045340485	0.232485102	0.193351763	MYB	1
GO:0040013	Negative regulation of locomotion	3/38	397/18866	0.045353407	0.232485102	0.193351763	IGFBP3/STC1/SERPINE1	3
GO:0034614	Cellular response to reactive oxygen species	2/38	170/18866	0.04592247	0.232485102	0.193351763	TNFAIP3/MYB	2
GO:0051271	Negative regulation of cellular component movement	3/38	400/18866	0.046203141	0.232485102	0.193351763	IGFBP3/STC1/SERPINE1	3
GO:0051302	Regulation of cell division	2/38	171/18866	0.046408056	0.232485102	0.193351763	PPBP/KIF18B	2
GO:0002244	Hematopoietic progenitor cell differentiation	2/38	172/18866	0.046895559	0.232485102	0.193351763	MYB/KRT75	2
GO:0009309	Amine biosynthetic process	1/38	24/18866	0.047265713	0.232485102	0.193351763	SRM	1
GO:0034143	Regulation of toll-like receptor 4 signaling pathway	1/38	24/18866	0.047265713	0.232485102	0.193351763	TNFAIP3	1
GO:0044062	Regulation of excretion	1/38	24/18866	0.047265713	0.232485102	0.193351763	STC1	1
GO:0051446	Positive regulation of meiotic cell cycle	1/38	24/18866	0.047265713	0.232485102	0.193351763	CDC25A	1

(Continued)

Table S5. Continued

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0070841	Inclusion body as- sembly	1/38	24/18866	0.047265713	0.232485102	0.193351763	HSPA1B	1
GO:0090169	Regulation of spindle assembly	1/38	24/18866	0.047265713	0.232485102	0.193351763	HSPA1B	1
GO:0033209	Tumor necrosis factor- mediated signaling pathway	2/38	173/18866	0.047384968	0.232485102	0.193351763	TNFAIP3/HSPA1B	2
GO:0016241	Regulation of macroau- tophagy	2/38	176/18866	0.048864544	0.232485102	0.193351763	TOMM7/PIM2	2
GO:0000423	Mitophagy	1/38	25/18866	0.04918716	0.232485102	0.193351763	TOMM7	1
GO:0002092	Positive regulation of receptor internalization	1/38	25/18866	0.04918716	0.232485102	0.193351763	APLN	1
GO:0015740	C4-dicarboxylate transport	1/38	25/18866	0.04918716	0.232485102	0.193351763	SLC25A12	1
GO:0046697	Decidualization	1/38	25/18866	0.04918716	0.232485102	0.193351763	STC1	1
GO:0050927	Positive regulation of positive chemotaxis	1/38	25/18866	0.04918716	0.232485102	0.193351763	S1PR1	1
GO:0071677	Positive regulation of mononuclear cell migration	1/38	25/18866	0.04918716	0.232485102	0.193351763	SERPINE1	1
GO:1905564	Positive regulation of vascular endothelial cell proliferation	1/38	25/18866	0.04918716	0.232485102	0.193351763	APLN	1
GO:0048771	Tissue remodeling	2/38	178/18866	0.049860292	0.232485102	0.193351763	TNFAIP3/S1PR1	2

**Table S6.** Functional enrichment analysis (MF) of the genes associated with the upregulated genes

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0001664	G protein-coupled receptor binding	7/40	293/18352	2.92192E-06	0.000514258	0.000387539	CXCL3/PPBP/ CXCL2/APLN/ S1PR1/DNAJA1/ HSPA1B	7
GO:0045236	CXCR chemokine receptor binding	3/40	18/18352	7.6518E-06	0.000673358	0.000507435	CXCL3/PPBP/ CXCL2	3
GO:0008009	Chemokine activity	3/40	49/18352	0.000164861	0.009671818	0.007288571	CXCL3/PPBP/ CXCL2	3
GO:0042379	Chemokine receptor binding	3/40	70/18352	0.000474548	0.020880096	0.015735001	CXCL3/PPBP/ CXCL2	3
GO:0005520	Insulin-like growth factor binding	2/40	29/18352	0.001811907	0.063779118	0.048063211	IGFBP3/ESM1	2
GO:0031072	Heat shock protein binding	3/40	127/18352	0.002652501	0.072483606	0.054622813	CHORDC1/DNAJA1/ HSPA1B	3
GO:0005178	Integrin binding	3/40	144/18352	0.003779843	0.072483606	0.054622813	ESM1/TLN2/TGFB1	3
GO:0031625	Ubiquitin protein ligase binding	4/40	297/18352	0.003884332	0.072483606	0.054622813	FZD8/UBE2D4/ DNAJA1/HSPA1B	4
GO:0048018	Receptor ligand activity	5/40	487/18352	0.003943689	0.072483606	0.054622813	CXCL3/PPBP/ CXCL2/APLN/STC1	5
GO:0030546	Signaling receptor activator activity	5/40	492/18352	0.004118387	0.072483606	0.054622813	CXCL3/PPBP/ CXCL2/APLN/STC1	5
GO:0044389	Ubiquitin-like protein ligase binding	4/40	316/18352	0.004838462	0.077415397	0.058339354	FZD8/UBE2D4/ DNAJA1/HSPA1B	4
GO:0005125	Cytokine activity	3/40	235/18352	0.014454634	0.16029063	0.120793178	CXCL3/PPBP/ CXCL2	3
GO:0004725	Protein tyrosine phosphatase activity	2/40	101/18352	0.020420482	0.16029063	0.120793178	CDC25A/CDKN3	2
GO:0005126	Cytokine receptor binding	3/40	271/18352	0.021045942	0.16029063	0.120793178	CXCL3/PPBP/ CXCL2	3
GO:0005200	Structural constituent of cytoskeleton	2/40	104/18352	0.02156948	0.16029063	0.120793178	KRT6B/TLN2	2
GO:0051087	Chaperone binding	2/40	104/18352	0.02156948	0.16029063	0.120793178	CDC25A/DNAJA1	2
GO:0018455	Alcohol dehydrogenase [NAD(P)+] activity	1/40	10/18352	0.02158869	0.16029063	0.120793178	DHRS9	1
GO:0030957	Tat protein binding	1/40	10/18352	0.02158869	0.16029063	0.120793178	DNAJA1	1
GO:0033204	Ribonuclease P RNA binding	1/40	10/18352	0.02158869	0.16029063	0.120793178	POP1	1
GO:0004222	Metalloendopeptidase activity	2/40	108/18352	0.023142512	0.16029063	0.120793178	ADAMTS6/ ADAMTS14	2
GO:0008525	Phosphatidylcholine transporter activity	1/40	11/18352	0.023722397	0.16029063	0.120793178	PITPNM2	1
GO:0004526	Ribonuclease P activity	1/40	12/18352	0.025851567	0.16029063	0.120793178	POP1	1
GO:0061578	Lys63-specific deubiquitinase activity	1/40	12/18352	0.025851567	0.16029063	0.120793178	TNFAIP3	1
GO:0051082	Unfolded protein binding	2/40	118/18352	0.027274787	0.16029063	0.120793178	DNAJA1/HSPA1B	2
GO:0031994	Insulin-like growth factor I binding	1/40	13/18352	0.027976209	0.16029063	0.120793178	IGFBP3	1
GO:0072542	Protein phosphatase activator activity	1/40	13/18352	0.027976209	0.16029063	0.120793178	IGFBP3	1
GO:0005179	Hormone activity	2/40	122/18352	0.029005294	0.16029063	0.120793178	APLN/STC1	2

(Continued)



Table S6. Continued

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0005313	l-glutamate transmembrane transporter activity	1/40	14/18352	0.030096333	0.16029063	0.120793178	SLC25A12	1
GO:0004549	tRNA-specific ribonuclease activity	1/40	15/18352	0.032211948	0.16029063	0.120793178	POP1	1
GO:0042813	Wnt-activated receptor activity	1/40	15/18352	0.032211948	0.16029063	0.120793178	FZD8	1
GO:0005229	Intracellular calcium activated chloride channel activity	1/40	16/18352	0.034323063	0.16029063	0.120793178	TTYH2	1
GO:0008574	ATP-dependent microtubule motor activity, plus-end-directed	1/40	16/18352	0.034323063	0.16029063	0.120793178	KIF18B	1
GO:0015172	Acidic amino acid transmembrane transporter activity	1/40	16/18352	0.034323063	0.16029063	0.120793178	SLC25A12	1
GO:0015556	C4-dicarboxylate transmembrane transporter activity	1/40	16/18352	0.034323063	0.16029063	0.120793178	SLC25A12	1
GO:0019211	Phosphatase activator activity	1/40	16/18352	0.034323063	0.16029063	0.120793178	IGFBP3	1
GO:0045125	Bioactive lipid receptor activity	1/40	16/18352	0.034323063	0.16029063	0.120793178	S1PR1	1
GO:0061778	Intracellular chloride channel activity	1/40	16/18352	0.034323063	0.16029063	0.120793178	TTYH2	1
GO:0019838	Growth factor binding	2/40	136/18352	0.035395696	0.16029063	0.120793178	IGFBP3/ESM1	2
GO:0002020	Protease binding	2/40	137/18352	0.035871398	0.16029063	0.120793178	TNFAIP3/SERPINE1	2
GO:0016854	Racemase and epimerase activity	1/40	17/18352	0.036429689	0.16029063	0.120793178	DHRS9	1
GO:0004745	Retinol dehydrogenase activity	1/40	20/18352	0.042722715	0.164575436	0.124022159	DHRS9	1
GO:0008320	Protein transmembrane transporter activity	1/40	20/18352	0.042722715	0.164575436	0.124022159	TOMM7	1
GO:0140318	Protein transporter activity	1/40	20/18352	0.042722715	0.164575436	0.124022159	TOMM7	1
GO:0005355	Glucose transmembrane transporter activity	1/40	21/18352	0.044811472	0.164575436	0.124022159	PPBP	1
GO:0015149	Hexose transmembrane transporter activity	1/40	21/18352	0.044811472	0.164575436	0.124022159	PPBP	1
GO:0050750	Low-density lipoprotein particle receptor binding	1/40	21/18352	0.044811472	0.164575436	0.124022159	DNAJA1	1
GO:0070530	K63-linked polyubiquitin modification-dependent protein binding	1/40	21/18352	0.044811472	0.164575436	0.124022159	TNFAIP3	1
GO:0022884	Macromolecule transmembrane transporter activity	1/40	22/18352	0.046895785	0.164575436	0.124022159	TOMM7	1
GO:0120014	Phospholipid transfer activity	1/40	22/18352	0.046895785	0.164575436	0.124022159	PITPNM2	1
GO:0015145	Monosaccharide transmembrane transporter activity	1/40	23/18352	0.048975663	0.164575436	0.124022159	PPBP	1

**Table S7.** Functional enrichment analysis (CC) of the DEGs associated with the upregulated genes

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
GO:0031093	Platelet alpha granule lumen	2/39	67/19559	0.007893629	0.247850692	0.220518786	PPBP/SERPINE1	2
GO:0031091	Platelet alpha granule	2/39	91/19559	0.01418764	0.247850692	0.220518786	PPBP/SERPINE1	2
GO:0045095	Keratin filament	2/39	95/19559	0.015392516	0.247850692	0.220518786	KRT6B/KRT75	2
GO:0030681	Multimeric ribonuclease P complex	1/39	10/19559	0.019766209	0.247850692	0.220518786	POP1	1
GO:0000235	Astral microtubule	1/39	11/19559	0.021721763	0.247850692	0.220518786	KIF18B	1
GO:0002177	Manchette	1/39	11/19559	0.021721763	0.247850692	0.220518786	STRBP	1
GO:0005818	Aster	1/39	11/19559	0.021721763	0.247850692	0.220518786	KIF18B	1
GO:0030677	Ribonuclease P complex	1/39	14/19559	0.027565644	0.247850692	0.220518786	POP1	1
GO:1990023	Mitotic spindle midzone	1/39	14/19559	0.027565644	0.247850692	0.220518786	KIF18B	1
GO:0098554	Cytoplasmic side of endoplasmic reticulum membrane	1/39	15/19559	0.029506035	0.247850692	0.220518786	DNAJA1	1
GO:0005666	RNA polymerase III complex	1/39	18/19559	0.035304599	0.269598759	0.23986857	POLR3G	1
GO:0035371	Microtubule plus-end	1/39	23/19559	0.044893941	0.285010639	0.253580895	KIF18B	1
GO:0098799	Outer mitochondrial membrane protein complex	1/39	24/19559	0.046800633	0.285010639	0.253580895	TOMM7	1

**Table S8.** Functional enrichment analysis (KEGG) of genes associated with the upregulated genes

ID	Description	GeneRatio	BgRatio	p-value	p.adjust	q-value	geneID	Count
hsa05134	Legionellosis	3/21	57/8223	0.000384425	0.027678575	0.022256164	CXCL3/CXCL2/ HSPA1B	3
hsa04657	IL-17 signaling pathway	3/21	94/8223	0.001657299	0.039867397	0.032057118	CXCL3/TNFAIP3/ CXCL2	3
hsa04061	Viral protein interaction with cytokine and cytokine receptor	3/21	100/8223	0.001979642	0.039867397	0.032057118	CXCL3/PPBP/ CXCL2	3
hsa04064	NF-kappa B signaling pathway	3/21	104/8223	0.002214855	0.039867397	0.032057118	CXCL3/TNFAIP3/ CXCL2	3
hsa04668	TNF signaling pathway	3/21	114/8223	0.002877066	0.041429752	0.033313397	CXCL3/TNFAIP3/ CXCL2	3
hsa04218	Cellular senescence	3/21	156/8223	0.006931269	0.083175226	0.066880664	IGFBP3/CDC25A/ SERPINE1	3
hsa04141	Protein processing in endoplasmic reticulum	3/21	171/8223	0.008922601	0.091775328	0.073795951	UBE2D4/DNA- JA1/HSPA1B	3
hsa04621	NOD-like receptor signaling pathway	3/21	186/8223	0.011219936	0.095815294	0.077044462	CXCL3/TNFAIP3/ CXCL2	3
hsa04062	Chemokine signaling pathway	3/21	192/8223	0.012226679	0.095815294	0.077044462	CXCL3/PPBP/ CXCL2	3
hsa05120	Epithelial cell signaling in Helicobacter pylori infection	2/21	70/8223	0.013513912	0.095815294	0.077044462	CXCL3/CXCL2	2
hsa04115	p53 signaling pathway	2/21	73/8223	0.014638448	0.095815294	0.077044462	IGFBP3/SERPINE1	2
hsa05417	Lipid and atherosclerosis	3/21	215/8223	0.016561503	0.099369018	0.079901988	CXCL3/CXCL2/ HSPA1B	3
hsa05323	Rheumatoid arthritis	2/21	93/8223	0.023111727	0.128003412	0.102926721	CXCL3/CXCL2	2
hsa05146	Amoebiasis	2/21	102/8223	0.027448456	0.141163486	0.113508651	CXCL3/CXCL2	2
hsa04060	Cytokine-cytokine receptor interaction	3/21	295/8223	0.037680574	0.180866757	0.145433796	CXCL3/PPBP/ CXCL2	3
hsa04371	Apelin signaling pathway	2/21	139/8223	0.048309475	0.200783275	0.16144854	APLN/SERPINE1	2
hsa05162	Measles	2/21	139/8223	0.048309475	0.200783275	0.16144854	TNFAIP3/HSPA1B	2