

ARTICLE Identification of a functional human-unique 351-bp *Alu* insertion polymorphism associated with major depressive disorder in the 1p31.1 GWAS risk loci

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Genome-wide association studies (GWAS) have reported substantial single-nucleotide polymorphisms (SNPs) associated with major depressive disorder (MDD), but the underlying functional variations in the GWAS risk loci are unclear. Here we show that the European MDD genome-wide risk-associated allele of rs12129573 at 1p31.1 is associated with MDD in Han Chinese, and this SNP is in strong linkage disequilibrium (LD) with a human-unique *Alu* insertion polymorphism (rs70959274) in the 5' flanking region of a long non-coding RNA (lncRNA) *LINC01360* (Long Intergenic Non-Protein Coding RNA 1360), which is preferably expressed in human testis in the currently available expression datasets. The risk allele at rs12129573 is almost completely linked with the absence of this *Alu* insertion. The *Alu* insertion polymorphism (rs70959274) is significantly associated with a lower RNA level of *LINC01360* and acts as a transcription silencer likely through modulating the methylation of its internal CpG sites. Luciferase assays confirm that the presence of *Alu* insertion at rs70959274 suppresses transcriptional activities in human cells, and deletion of the *Alu* insertion through CRISPR/Cas9-directed genome editing increases RNA expression of *LINC01360*. Deletion of the *Alu* insertion in human cells also leads to dysregulation of gene expression, biological processes and pathways relevant to MDD, such as the alterations of mRNA levels of *DRD2* and *FLOT1*, transcription of genes involved in synaptic transmission, neurogenesis, learning or memory, and the PI3K-Akt signaling pathway. In summary, we identify a human-unique DNA repetitive polymorphism in robust LD with the MDD risk-associated SNP at the prominent 1p31.1 GWAS loci, and offer insights into the molecular basis of the illness.

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INTRODUCTION

Major depressive disorder (MDD) is a severe mental illness substantially influenced by genetic and environmental risk factors [1]. Recent genome-wide association studies (GWAS) have identified multiple common single-nucleotide polymorphisms (SNPs) conferring risk of MDD [2–4], such as variations spanning *VRK2*, *DRD2*, *TCF4*, and the extended major histocompatibility complex (MHC) region [4–6]. Majority of the risk SNPs for MDD are located in noncoding genomic regions, and identifying the functional variations among the noncoding SNPs is crucial for translating the clinical associations into molecular mechanisms and for understanding the biological basis of the illness [7, 8]. Likewise, there are many studies aiming to characterize the functional causative SNPs in the psychiatric GWAS risk loci [9–13]. However, both GWAS analyses and follow-up functional studies primarily focus on SNPs and small indels, and other types of

sequence variations are relatively less investigated. Nevertheless, accumulating data have shown that sequence variations besides SNPs, such as variable number tandem repeats (VNTRs), *Alu* short interspersed nuclear elements (SINEs), copy number variations (CNVs), and short tandem repeats (STRs), may also confer significant risk of psychiatric disorders, and some of them might be the functional units to which GWAS SNP associations are attributed [14–19].

Among these sequence variations, *Alu* polymorphisms are potentially important players in complex illnesses whose impact remains less characterized. *Alu* polymorphisms refer to the presence or absence of an *Alu* insertion (mobile genetic elements that are ~300-bp stretch of repetitive DNA sequences ancestrally derived from the small cytoplasmic 7SL RNA) [20]. Most *Alu* insertions are fixed in populations, while some are still polymorphic (comprised of presence (insertion) and absence (empty) alleles) [21]. Intriguingly,

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Payer et al. have previously identified many *Alu* polymorphisms in strong linkage disequilibrium (LD) with GWAS risk SNPs of complex diseases [14]. Therefore, a comprehensive post-GWAS analysis of risk loci considering all types of sequence variations is important to identify potential causative variations and will aid in the understanding of genetic mechanisms for psychiatric disorders.

There is a GWAS risk locus at 1p31.1 in which rs12129573 and its index SNPs are genome-wide significantly associated with MDD in Europeans ($p = 4.01 \times 10^{-12}$ in 135,458 cases and 344,901 controls) [4]. Here we replicate the association between rs12129573 and clinical diagnosis of MDD across distinct populations. Moving beyond statistical analysis, we have discovered a human-unique Alu polymorphism (rs70959274), which is in strong LD with rs12129573, in the promoter of LINC01360 (Long Intergenic Non-Protein Coding RNA 1360). Through both in vitro luciferase reporter gene assays and CRISPR/Cas9 editing-generated HEK293T and U251 cells with different Alu polymorphisms, we reveal that absence of the Alu insertion predicts a higher transcription level of LINC01360 in cells; eQTL analyses also suggest that the absence of the Alu insertion correlates to higher expression of LINC01360 in the human tissue. We then show that the Alu insertion likely serves as a transcription silencer of LINC01360 through modulating DNA methylation. Our results describe a novel human-specific Alu insertion as a potential causative variation explaining the GWAS risk associations in the 1p31.1 locus.

METHODS

MDD case-control sample and statistical analysis in Chinese population

1751 MDD cases and 2468 controls of Han Chinese origin were recruited for the current study. MDD patients were diagnosed according to the DSM-IV criteria via standard diagnostic assessments, supplemented with clinical information through thorough review of medical records and interview with family informants [22, 23]. Those who were diagnosed with other psychiatric disorders or neurological disorders, being pregnant, or breastfeeding at the time of study were excluded. Control subjects were local volunteers with no history of self-reported mental illnesses. All the protocols and methods used in this study were approved by the institutional review board of the Kunming Institute of Zoology, Chinese Academy of Sciences and the ethics committees of all participating hospitals and universities. All participants provided informed consents. Genomic DNA was extracted using high-salt method [24]. The PCR primers amplifying the DNA fragments spanning rs12129573 (PCR product length: 458-bp) were 5'-TGTCCTCAGCAAGAGAATGTGG-3' (forward) and 5'-AATGT TAATCTGGATGCTTTCGG-3' (reverse), and SNP genotyping was conducted using the SNaPShot method as previously described [25]. We also confirmed the genotyping of rs12129573 of 50 randomly selected individuals using Sanger sequencing, and no genotyping errors were found. We applied logistic regression to analyze the associations between SNPs and MDD using PLINK v1.9 [26], with sex and residence of participants included in the covariates. Regional association results of the 1p31.1 loci were plotted using LocusZoom (http://locuszoom.sph.umich.edu/ locuszoom/) [27].

Sequence variation analysis and genotyping of the *Alu* polymorphism in human populations

We examined the UCSC website (http://genome.ucsc.edu/) to identify all types of potential sequence variations in the 1p31.1 region. Genotyping of the *Alu* polymorphism (rs70959274) was conducted using PCR in 191 samples (including 135 Han Chinese, 36 European and 20 Pakistani individuals), and amplicons were analyzed with electrophoresis and Sanger sequencing to determine different alleles. The PCR primers for genotyping of

rs70959274 were 5'-GCACAATGCAAATATGCCTTAA-3' (forward) and 5'-CCATCCTCCATACACAAAACAT-3' (reverse) (PCR product length: presence of *Alu* insertion: 495-bp; absence of *Alu* insertion: 144-bp).

Expression quantitative trait loci (eQTL) analysis in human tissues To identify the impact of risk SNP rs12129573 on mRNA expression, we utilized GTEx (Genotype-Tissue Expression project; https:// www.gtexportal.org/) dataset to explore the gene expression regulation in human tissues [28]. Genes within 150-Kb away from the risk SNP rs12129573 were analyzed for its eQTL effects. As described in the original GTEx report [28], linear regression was conducted between genes and normalized expression matrices, with top three genotyping principal components, gender, genotyping platforms included as covariates. Detailed information of the GTEx dataset can be found in the original study and on their official website [28].

Defining candidate regulatory variations

The pairwise LD (r^2) between sequence variations were calculated using the Haploview program [29]. We used the SNP data from the 1000 Genomes Project (https://www.internationalgenome.org/) to identify variations in strong LD ($r^2 \ge 0.8$) with the MDD risk SNP rs12129573 in Europeans [30]. We used HaploReg v4.1 (https:// pubs.broadinstitute.org/mammals/haploreg/haploreg.php) dataset to help prioritize the candidate regulatory SNPs [31], which primarily utilized ChIP-Seq results of histone modifications such as H3K4me1, H3K4me3, H3K9ac and H3K27ac in brain tissues and multiple types of cells from the ENCODE dataset [32]. We then utilized GWAVA (Genome Wide Annotation of VAriants, https:// www.sanger.ac.uk/sanger/StatGen_Gwava, a web-based tool aiming to prioritize the functional variations based on the annotations of noncoding elements primarily from ENCODE/GENCODE, as well as the genome-wide properties such as evolutionary conservation and GC-content), to predict whether the epigenetic features and regulatory elements overlapped with the tested SNPs [33]. We also used AliBaba 2.1 program (http://gene-regulation.com/pub/ programs/alibaba2/index.html), which is developed based on the binding sites resources from TRANSFAC® Public [34], to predict the potential binding sites of transcription factors within the Alu sequence at rs70959274.

Cell culture

The HEK293T (human embryonic kidneys 293T) and U251 (human glioma) cell lines were originally obtained from the Kunming Cell Bank, Kunming Institute of Zoology, and HCC1806 (human mammary gland epithelial) cell line was originally obtained from ATCC. PCR and microscope analyses are regularly performed to ensure that no cells were contaminated with mycoplasma during the study. All cells were cultured in a standard humidified incubator with 5% CO₂ at 37 °C. HEK293T and U251 cells were cultured in a humidified 5% CO₂ incubator at 37 °C in Dulbecco's Modified Eagle's Medium (DMEM) basic (Gibco) supplemented with 10% fetal bovine serum (FBS) (Biological Industries), 1% non-essential amino acids, 1% sodium pyruvate, and 1% penicillin-streptomycin (Life Technologies). HCC1806 cells were cultured in RPMI Medium 1640 Basic (Gibco) supplemented with 5% FBS and 1% penicillin-streptomycin.

LINC01360 promoter activities characterized by luciferase reporter assays

Plasmid construction in pGL3-promoter vector. DNA fragments containing different alleles at rs70959274 were amplified for luciferase assays using the primers 5'-AAAGACTGCAAAGGCTTC CT-3' (forward) and 5'-TCCATATCCATCCTCCATACAC-3' (reverse) (PCR product length: presence of *Alu* insertion: 909-bp; absence of *Alu* insertion: 558-bp). The sequences were then sub-cloned into

pGL3-promoter vector (Promega, #E1761), and Sanger sequencing was performed to ensure that the recombinant clones only differ at rs70959274.

Transfection and luciferase reporter gene assay. The reconstructed pGL3 reporters were transiently co-transfected into HEK293T, U251, and HCC1806 cells together with an internal control reporter pRL-TK (Promega, #E224A) using Lipofectamine 3000 (Life Technologies). These plasmids were all accurately quantified and equal amounts of the plasmids were used for transfection between different wells in 24-well plate. All transfection procedures lasted 24–48 h, and the cells were then collected to measure luciferase activity using the Dual-Luciferase Reporter Assay System (Promega). The activity of firefly luciferase was normalized to that of Renilla luciferase to control for variations in the transfection efficiency between different wells. All assays were performed at least in four biological replicates in independent experiments, and two-tailed *t*-tests were performed to analyze statistical differences between experimental groups.

Prediction of CpG islands within the *Alu* sequence at rs70959274 and bisulfite sequencing

EMBOSS Cpgplot (http://emboss.bioinformatics.nl/cgi-bin/emboss/ cpgplot) was used to identify CpG islands (CGIs) in the *Alu* insertion sequence [35]. The default parameters of prediction were as follows: 1) the observed CpG/expected CpG ratios > 0.6; 2) %C + % G > 50%; and 3) sequence length > 200-bp.

We used ZYMO EZ DNA Methylation-Gold[™] Kit to conduct bisulfite conversions of DNA following the manufacturer's instructions. Sodium bisulfite converts unmethylated cytosine to uracil, which is then PCR amplified as thymidine while methylated cytosine remains cytosine. The Bisulfite sequencing PCR primers were 5'-GTGAAGTTTAGATTTGAGATTTTAA-3' (forward) and 5'-TCCATACA CAAAACATACATTCT-3' (reverse), and PCR was performed at 95 °C for 5 min followed by 40 cycles of 95 °C for 30 sec, 55 °C for 30 sec and 72 °C for 1 min with a final extension at 72 °C for 7 min. PCR products from bisulfite-treated DNA were tested in 2% agarose gel and then cloned into the pEASY-T1 vector (TransGen Biotech, Beijing, China). The colony PCR was undertaken to screen for positive colonies. The clones of PCR products with the right size were sequenced on an ABI sequencer with dye terminators (Applied Biosystems, Foster City, CA, USA). The methylation frequencies of all CpG sites were determined for ten clones.

CRISPR/Cas9 guide selection and genome deletion of rs70959274 region

Protospacer sequences of CRISPR/cas9 against target regions were designed by CRISPOR (http://crispor.tefor.net/crispor.py) [36]. We deleted the 1278-bp DNA sequence encompassing rs70959274 using two Cas9-guide RNA constructs. Annealed oligonucleotides were sub-cloned into the pL-CRISPR.EFS.GFP plasmid, which simultaneously delivers spCas9, GFP, and sgRNA. The sgRNA sequences were 5'-AGACATAATCCCAATATCTG-3' (upstream) and 5'-GAGTTAGAAAATTAGGACAG-3' (downstream).

The HEK293T, U251, and HCC1806 cells were cultured on 6-well plates and allowed to grow to ~85% confluency; HEK293T cells were transiently transfected with the pL-CRISPR.EFS.GFP-sgRNA (or pL-CRISPR.EFS.GFP-control-sgRNA which did not target human genome) constructs using Lipofectamine 3000, while U251 and HCC1806 cells were infected with pL-CRISPR.EFS.GFP-sgRNA (or pL-CRISPR.EFS.GFP-control-sgRNA) lentivirus. In all, 48 h after transfection or 72 h after infection, cells with strong GFP fluorescence signals were identified with a confocal microscopy and proceeded for genomic DNA extraction. The target region was then amplified, and electrophoresis and Sanger sequencing were performed to confirm successful editing of the genome as previously described [37]. Cells with and without editing of the target region were then

allowed to grow to establish sublines. Eventually, three non-deleted and three biallelic deleted sublines after CRISPR/Cas9 genome editing were selected for subsequent RNA extraction, complementary DNA (cDNA) synthesis, real-time quantitative PCR (RT-qPCR), and RNA-sequencing.

Detection of off-target effects in CRISPR/Cas9

Detection of off-target effects during CRISPR/Cas9 was performed following our previous study [37]. We predicted 28 most likely offtarget sites in the genome using the tools provided at http:// crispor.tefor.net/crispor.py. Briefly, DNA fragments differed by less than three nucleotides compared with the target sequence were considered potential off-target sites. These DNA fragments were amplified using PCR from HEK293T cells that were used for the CRISPR/cas9 mediated deletion of the Alu polymorphism at rs70959274. The T7EN1 cleavage assay was then performed to examine the cleavage of off-target sites. Specifically, a total of 200 ng purified PCR products were denatured and reannealed in $1\times$ NEB Buffer 2 (NEB) in 20 μl volume using a thermocycler with the following program: 95 °C, 5 min; 95–85 °C at -2 °C/s; 85–25 °C at -0.1 °C/s; hold at 4 °C. In all, 1 µl of T7EN1 enzymes (NEB) were then added to hybridize PCR products and incubated at 37 °C for 30 min. The PCR products digested by T7EN1 were separated on a 2% agarose gel and images were captured by Tanon 5200 Multi.

Real-time quantitative PCR analyses in cells

Total cellular RNA was isolated from HEK293T, U251 and HCC1806 cells using TRIzol reagent. The cDNA was then synthesized from the total RNA using the RevertAid First Strand cDNA Synthesis Kit (Thermo, #K1622). An aliquot of 2 µg total RNA was used to synthesize cDNA in a 20 µl reaction mixture containing Random Hexamer Primer, RevertAid M-MuLV RT, RiboLock RNase Inhibitor, DNase I, 5× Reaction Buffer and 10 mM dNTP Mix (Thermo). The mRNA expression was quantified through RT-gPCR using the ABI PRISM 7900 real-time PCR system (Applied Biosystems) as previously described [6, 38, 39]. RPS13 was used as the reference gene to normalize the amplification signal between different wells and the amount of input cDNA. The primers used for amplification of RPS13 were 5'-CCCCACTTGGTTGAAGTTGA-3' (forward) and 5'-CTTGTGCAACACCATGTGAA-3' (reverse); primers for LRRIQ3 were 5'-CGATTTGTCTGACTGTGTTGGG-3' (forward) and 5'-CATGACTGGT TAGCTCTTCTGTGA-3' (reverse); primers for NEGR1 were 5'-TGCA GTGCGGAAAATGATGTG-3' (forward) and 5'-CTTATCAGGCCACTGC GTCC-3' (reverse). Relative mRNA levels of these genes were presented as the means of $2^{-\Delta\Delta Ct}$. Statistical tests against different groups were conducted using two-tailed t-test.

Two pairs of primers were used to quantify the expression of LINC01360. The first pair (the forward and reverse primers were located in different exons) were 5'-CAGGCTGAGGGATGTTAGG AAG-3' (forward) and 5'-CTGAGGTGACAGGGAGTTTGGT-3' (reverse); the second pair (the forward and reverse primers were located in the same exon) were 5'-TTCCAAGGGCCAATTTTGAA-3' (forward) and 5'-GAGGCCCAGTTTGCGTCAT-3' (reverse). The first pair of LINC01360 primers is supposed to measure the expression of only part of its transcripts; the second pair is predicted to measure the expression of majority of the LINC01360 transcripts. The predicted transcripts of LINC01360 in the Ensembl website and locations of each primer are shown in Fig. S1. Since LINC01360 is not quantifiable in some samples and cannot be statistically analyzed using RT-qPCR, we conducted semi-quantitative PCR and the amplicons were separated on 2% agarose gels to examine the accuracies and intensities of the PCR product bands. The semi-quantitative PCR of LINC01360 was performed on an Applied Biosystems Veriti Thermal Cycler following the program that firstly 95 °C for 5 min, followed by 40 repeated cycles of 95 °C for 30 s, 60 °C for 30 s and 72 °C for 30 s, with one final annealing cycle at 72 °C for 5 min.

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RNA-sequencing analysis in HEK293T and U251 cells

Paired-end RNA-sequencing analysis was performed for the HEK293T and U251 cells with and without CRISPR-mediated deletion of the Alu insertion. RNA-sequencing was conducted on Illumina NovaSeg 6000 with a 150-bp read length. Fastg data files were retrieved for sequencing quality and trim reads examination using trimmomatic-0.36 [40]. This process yielded results of clean paired-end reads, which were subsequently aligned to the GRCh38 of the human genome using Hisat2 [41]. FeatureCounts were used to quantify mRNA expression of genes annotated in the Ensembl build GRCh38.91 [42], and genes with average FPKM (Fragments Per Kilobase Per Million Mapped Fragments) < 0.1 were excluded from further differential expression analyses. R package DESeg2 was used to analyze the gene expression differences between experimental groups [43]. Genes with false discovery rate (FDR) corrected p-value < 0.05 were identified as significantly differentially expressed.

Biological processes and pathway analyses

To examine whether genes involved in essential pathways in MDD pathogenesis and relevant psychological characteristics are affected by the rs70959274 *Alu* polymorphism, functional annotation analyses with Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway annotation and Gene Ontology (GO) annotation were performed using R package clusterProfiler [44]. KEGG pathways and GO biological process (BP) terms with a gene number <5 were excluded, and KEGG pathways and GO BP terms

with FDR-corrected *p*-value < 0.05 were considered statistically significantly enriched. Semantic similarity analyses were then conducted with GOSemSim [45] to narrow down the enriched GO terms based on their similarity between each other (r > 0.5 was considered highly similar).

RESULTS

rs12129573 is significantly associated with MDD in Han Chinese population

The MDD GWAS in European populations discovered significant associations of 44 independent risk loci, among which rs12129573 in 1p31.1 showed genome-wide significant associations ($p = 4.01 \times 10^{-12}$ in 135,458 cases and 344,901 controls) [4]. In our Han Chinese samples (1751 MDD cases and 2468 controls), the putative risk A-allele of rs12129573 was also significantly overrepresented in MDD patients compared with healthy controls ($p = 2.98 \times 10^{-5}$, OR = 1.239, Table S1). The allele and genotype frequencies of the SNP are shown in Table S1, and there is no deviation of Hardy–Weinberg equilibrium in controls.

rs12129573 is significantly associated with a lower RNA expression of LINC01360 $\,$

The rs12129573 locates in the 5' flanking region of *LINC01360* (Fig. 1). *LINC01360* encodes a lncRNA with unknown function, and is also the only annotated gene within 150-Kb around the SNP. Accumulating evidence have suggested that noncoding risk



Fig. 1 Genetic associations of SNPs spanning 1p31.1 region with major depressive disorder (MDD) in European populations, and schematic of rs12129573 and Alu polymorphism (rs70959274) locations in human genome. A physical map of the region is given and depicts known genes within the region, and the LD is defined based on the SNP rs12129573. The dash line indicates the threshold for genome-wide significance ($p = 5.00 \times 10^{-8}$). Note: in the PGC2 MDD GWAS, rs12129573 showed genome-wide significant association ($p = 4.01 \times 10^{-12}$) with the illness in 135,458 cases and 344,901 controls. However, the summary statistics of 23andMe dataset (75,607 cases and 231,747 controls) in their GWAS were not publicly released, and we thus used the results in the remaining samples (including 59,851 cases and 113,154 controls) to make this figure *via* LocusZoom. Intriguingly, in this smaller dataset, rs12129573 is still the leading variation in the 1p31.1 area showing genome-wide significant association with MDD ($p = 5.45 \times 10^{-9}$).

u serenni te В С Α A^{WINSENDOIE} HEERORONOIE AWORE HONOLOGIC start site of *Alu* sequence in heterozygote 2.0 02000 LINC01360 RNA Level 1.0 2000 bp 0.0 1000 bp 750 bp -10 500 bp -2.0 250 bp p=1.30E-60 сc ĊA ÅА (n=136) (n=140) (n=46) 100 bp rs12129573 GTGAAGTCTAGACTTGAGACT D HEK293T Unmethylated Methylated 0-0-00 -----0-0 0-0-00 0-0-0--0-0 -0-0 -0--0--0 •-o-co 0-0-0 -0-0 -0 0-0-00 0-0-0 -0 -0-0--0-0--0-0 0 0-0-00 0-0-0 -0-C 0-0-00--0 0-0-0-0 -0-0--0-0 -0--0--0 -0--0 0-0-00 -0-0 -0 0-0-00 0-0-0--0-0--0-0 -0--0--0 -0 0 0 0-0-00 0-0-0-0--0 0-0 0-0 -0 C -0 0-0-00 -0 ------0 -0-------0-0 -0--0 0 -0--0-0 **E** U251 Unmethylated Methylated -----0-0-0--0-0 -0 0-0-00 -0-0 0 0 -0-------0-0 0-0--0-0 0 . -0 0 -0-0 -0 0-0-00 0-0-0 0 0 -----0-0 0 0 0 0 0 0-0-00-____ 2 -0-0 0 0 0 0-0-00-0-0-0--0-0 -0-. 0-0-00 0-0-0--0-0 0--0--0 0-0-00 ------0-0--0-0 -0--0--0 0 -0-00 -0-0 -0 0-0-00--0-0-0--0-0--0-0--0--0--0 -0 0 F SH-SY5Y Unmethylated Methylated ┝╋╋ 0-0-**0**0 0-0-00 0-0-0 -0-0 -0 0 0-0-0--0 0-0--0-0 -0-0 -0 0-0-00-0-0-0-0-0--0-0 0 -0--0 0-0-00 0-0-0 -0-0 0-0-00 0-0-0 -0-0 -0-0 -0--0-0-0-00-0-0-0-0-0--0-0 -0--0--0--0 -0--0 -0-0 -0--0 -0-0 0-0-00 -0-0-0 -0-0 00 0 0 -0 0-0-00 0-0-0 0-0-00-0-0-0-0-0--0-0--0--0-0--0--0--0 0 -0-0-0-00 -0-0 -----0-0--0-0 0 0-0-0 0-0 -0-00 0-0

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Fig. 2 Molecular characterization of the linked rs12129573 and rs70959274. a Expression quantitative trait loci (eQTL) analyses of rs12129573 with *LINC01360* RNA expression in GTEx dataset. b Electrophoresis of *Alu* polymorphism (rs70959274) different genotypes. c Sanger sequencing of individual carrying heterozygote at the *Alu* polymorphism (rs70959274). d–f DNA methylation status of the CpG sites within the 351-bp *Alu* sequence at rs70959274 in HEK293T, U251 and SH-SY5Y cells respectively. [Each row means one clone in bisulfite sequencing; the black solid circle donates unmethylation, and empty circle donates methylation].

variations of complex disorders tend to be associated with mRNA expression of nearby or distal genes [7], we therefore examined the associations between rs12129573 and the mRNA expression of all its potential cis-acting genes (<1-Mb) in multiple public brain eQTL datasets (BrainSeq [46], CommonMind [47], Brain xQTL [48] and GTEx-brain [28]). Unfortunately, rs12129573 was not associated with the mRNA expression of any genes in the brain tissues (data not shown).

To examine if rs12129573 exerted regulatory effects in human organs other than the brain, we then retrieved RNA-sequencing data of multiple human tissues from the GTEx dataset [28]. This tissue-wide analysis showed that rs12129573 was significantly associated with *LINC01360* expression in human testis (N = 322 subjects, $p = 1.30 \times 10^{-60}$, Fig. 2a), and a detailed examination found that its risk A-allele indicated a higher RNA level of the lncRNA. The GTEx tissue-wide analysis did not reveal any significant eQTL associations in other tissues. By contrast, rs12129573 was not associated with the mRNA expression of other genes near *LINC01360* at 1p31.1 in the testis, such as *LRRIQ3* (>700-Kb far from rs12129573) or *NEGR1* (>1-Mb far from rs12129573) (p > 0.4, Fig. S2). According to the RNA-sequencing data from GTEx dataset [28], *LINC01360* is preferably expressed in human testis (Fig. S3). To examine the possibility that the relatively rare presence of *LINC01360* expression in the GTEx

dataset was resulted from limitations of RNA-sequencing techniques, we then conducted semi-quantitative PCR to examine the RNA expression of *LINC01360* in human brain tissues (Fig. S4) and several human cell lines (HEK293T, U251, and HCC1806, as shown in the following sections). However, the expression levels of *LINC01360* in these samples and cells were quite low.

Functional prediction analysis of rs12129573 LD linked SNPs To pinpoint the genetic variation(s) conferring functional impact within this locus, we retrieved information of SNPs in high LD $(r^2 \ge 0.8)$ with rs12129573 in Europeans. Briefly, 170 SNPs were in high LD with rs12129573 in Europeans, and all the 171 SNPs were in the noncoding regions near LINC01360. We therefore performed functional prediction of these SNPs using HaploReg v4.1 dataset [31]. However, we found that they unlikely resided in any DNA segments with open-chromatin peaks or transcription factors binding sites or histone markers in the brain (e.g., H3K4me1, H3K4me3, H3K9ac, and H3K27ac) (Fig. S5). Further functional prediction using other programs (e.g., GWAVA [33], Table S2) also suggested that these SNPs were unlikely functional, as the functional prediction scores of almost all SNPs were <0.5 (prediction scores from three different versions of the classifier (Region score, TSS score, Unmatched score) range 0-1, and higher

scores indicate a greater likelihood that the respective variations are functional). In addition, we also utilized data from recently published studies to assess whether any of the 171 SNPs located in the open chromatin peaks in human brain tissues or neurons derived from human induced pluripotent stem cells (hiPSC), so as to examine whether these SNPs exert functions in early neuro-development [11, 49]. However, none of the tested SNPs were overlapped with the open chromatin peaks (data not shown).

Identification of a human-unique *Alu* insertion polymorphism (rs70959274) in strong LD with rs12129573

Although the functional SNPs in the 1p31.1 region and the LINC01360 locus remain unclear, we have identified a 351-bp Alu insertion polymorphism (rs70959274) in 431-bp 3' downstream of rs12129573, which was further confirmed using in silico analysis on the UCSC website (http://genome.ucsc.edu/) and through Sanger DNA sequencing of the target region (Fig. 2b, c). Intriguingly, Alu polymorphisms in strong LD with GWAS risk SNPs of complex diseases have been repeatedly highlighted, and are thought to play putative roles in the pathogenesis of these diseases [14]. We therefore amplified rs70959274 and rs12129573 in 135 Han Chinese individuals, and found that the MDD risk A-allele of rs12129573 was almost completely linked with "absence" of the Alu insertion ($r^2 =$ 0.94). In 36 European and 20 Pakistani individuals, the substantial LD between rs12129573 and rs70959274 was also observed ($r^2 = 0.89$ and 1.00, respectively). Considering that Alu elements are usually conserved in primates [20], we then examined rs70959274 across species and found that it was human-specific. Further characterization of its allelic status in multiple human cell lines revealed homozygous presence of the Alu insertion in U251 and SH-SY5Y (human neuroblastoma) cells, heterozygous in HEK293T cells, and homozygous absence in HCC1806 cells (Fig. S6). However, the Alu polymorphism rs70959274 was not covered in the current GWAS platforms or in public eQTL datasets. Given the tight LD between rs12129573 and rs70959274, we used the genotype of rs12129573 as the proxy of that of rs70959274, and predicted that the presence of the Alu insertion at rs70959274 was linked with a lower RNA level of LINC01360.

Alu insertion at rs70959274 decreases promoter activities in vitro Compared with single base-pair substitution (i.e., rs12129573), the 351-bp Alu insertion polymorphism (i.e., rs70959274) likely exerts a greater impact in the genome. Indeed, Alu insertions have been demonstrated to affect transcription and post-transcription processes through affecting promoter activity, DNA methylation, alternative splicing, and RNA editing [50]. We therefore tested the regulatory effect of the Alu insertion on promoter activities using an in vitro reporter gene assay. We amplified the DNA fragments spanning rs70959274 from individuals carrying different genotypes of this Alu polymorphism. These sequences were then subcloned into the pGL3 promoter vector and transiently cotransfected with an internal control reporter pRL-TK into human HEK293T, U251, and HCC1806 cells. The luciferase activities of these cells were then examined. In all three cells, the transcriptional activity of the pGL3 promoter containing the Alu insertion was significantly lower than that of the promoter without the insertion ($p = 1.36 \times 10^{-5}$ in HEK293T cells, p = 0.01 in U251 cells, and p = 0.001 in HCC1806 cells, two-tailed *t*-test, Fig. 3a-c), suggesting that the Alu insertion at this locus likely exerted repressive effects on transcription, which is also consistent with the eQTL analysis in human tissues.

Alu insertion at rs70959274 contains multiple DNA methylation sites

To explore the mechanisms underlying this repressive effect of the *Alu* insertion on transcriptional activities, we tested whether the *Alu* element could bind transcription repressors, or underwent hypermethylation of the DNA. Since rs70959274 has multiple similar

sequences across the genome, the current genome-wide sequencing based on short reads (such as ChIP-Seq on H3K4me1, H3K4me3 or transcription factors *etc.*) is not able to precisely map to the *Alu* region (Fig. S7). A functional prediction of the 351-bp *Alu* insertion sequence at rs70959274 did not identify any particular transcription repressors of interest using AliBaba 2.1 program (http://generegulation.com/pub/programs/alibaba2/index.html), JASPAR (http:// jaspar.genereg.net/) [51], or AnimaITFDB (v3.0) (http://bioinfo.life. hust.edu.cn/AnimaITFDB/#!/) [52] (Fig. S8). Intriguingly, we identified 23 CpG sites and one CpG island (CGI) within the 351-bp *Alu* insertion sequence, and bisulfite sequencing further found that all 23 CpG sites in HEK293T and U251 cells were completely or near completely methylated under natural condition (Fig. 2d, e). Similarly, hypermethylation of the *Alu* insertion at rs70959274 was also observed in SH-SY5Y cells (Fig. 2f).

Deletion of the *Alu* insertion (rs70959274) in cells increases RNA expression of LINC01360

We further tested whether the Alu insertion at rs70959274 repressed the RNA expression of LINC01360. We used a dual sqRNA-directed CRISPR/Cas9 system to knock out this Alu element in HEK293T and U251 cells, and then examined the alterations of LINC01360. Since rs70959274 is a short stretch of repetitive DNA sequences, and Alu elements generally have abundant presence of similar sequences in the genome, it is difficult to precisely delete the Alu insertion at rs70959274. To resolve this problem, we designed the sgRNAs that could delete the 1278-bp DNA sequence covering rs70959274. After CRISPR/Cas9-directed genome editing in cells, we examined 28 most likely off-target sites; 22 sites did not have any cleavage signals, and 6 sites had detectable cleavage bands, but further verification of these sites using Sanger sequencing did not find genomic DNA cleavage within 100-bp around each site (Fig. S9 and Table S3). Taken together, significant off-target signals were not detected in this CRISPR/Cas9-directed editing experiment.

Following CRISPR/Cas9 editing, clones with and without the *Alu* element were selected in triplicates and expanded from HEK293T and U251 cells. Through semi-quantitative PCR, we found that the RNA level of *LINC01360* was significantly increased after the *Alu* insertion was deleted in both HEK293T and U251 cells (Fig. 3d, e). By contrast, mRNA expression of *LRRIQ3* or *NEGR1* was not altered after the CRISPR/Cas9 editing (Fig. S10).

Since the *Alu* insertion sequence (351-bp) was difficult to precisely target through CRISPR/Cas9 due to the presence of multiple homological sequences, we deleted both the *Alu* insertion and two segments of flanking sequences (i.e., a total of 1278-bp). To exclude the possibility that the alteration of *LINC01360* after genome editing was solely caused by deletion of the flanking sequence, we performed CRISPR/Cas9 editing in the HCC1806 cells (the genotype at rs70959274 is "totally absent of *Alu* insertion" in these cells) using the same plasmids to delete these flanking sequences around rs70959274 (i.e., 928-bp). Deleting these flanking sequences in HCC1806 cells did not alter expression of *LINC01360*, *LRRIQ3* or *NEGR1* (Figs. 3f and S11).

Deletion of the *Alu* insertion (rs70959274) in cells alters expression of genes and biological processes relevant to MDD

We then conducted the RNA-sequencing analysis of the HEK293T and U251 cells respectively with and without CRISPR-mediated deletion of the *Alu* insertion (n = 3 per condition) to identify genes exhibiting significantly different expression levels. In the HEK293T cells, 389 differentially expressed genes (DEGs) with an absolute fold change (FC) > 1.20 ($|\log_2(FC)| > 0.26$) at an FDR < 0.05 between different genotypic groups were defined (Table S4). Among these genes, 200 DEGs had significantly lower mRNA levels and 189 DEGs had higher expression following the deletion of the *Alu* insertion. These DEGs were enriched in pathways related to ribosome and biosynthesis of amino acids (FDR < 0.05,

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Fig. 4a and Table S5). Specifically, gene set enrichment analysis (GSEA) indicated that these DEGs were significantly enriched in the GO terms "ribosome biogenesis", "mitochondrial translation", "mitochondrial gene expression", and "establishment of protein localization to mitochondrion" (FDR < 0.05, Fig. 4a and Table S6).

In U251 cells, 132 genes exhibited significantly altered expression levels in cells with *Alu* insertion deleted compared with the wild-type cells ($|log_2(FC)| > 0.26$ at an FDR < 0.05), among which 47 DEGs were down-regulated and 85 DEGs were upregulated following the *Alu* insertion deletion (Table S7). KEGG pathway analyses revealed significantly enriched signals in the PI3K-Akt

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Fig. 3 Effects of rs70959274 on LINC01360 transcriptional activities and gene expression. a–c Results of the reporter gene assay testing the regulatory activities of rs70959274 in HEK293T, U251, and HCC1806 cell lines. Effects of rs70959274 allele variation on pGL3 promoter activity are shown in the panels for HEK293T, U251, and HCC1806 cells. "Negative control" means pGL3 basic empty vector (which does not have promoter activity). "Empty pGL3 vector" means pGL3 promoter empty vector (which has an internal promoter). The Y-axis values represent fold changes of luciferase activity relative to the "Empty pGL3 vector" group. The means and standard deviations of at least four biological replicates are shown. $p \le 0.05$; $p \le 0.01$; $**p \le 0.001$; $**p \le 0.0001$. **d–f** Semi-quantitative PCR of *LINC01360* RNA in HEK293T, U251 and HCC1806 cell lines with and without CRISPR/Cas9 deletion of the DNA sequence spanning *Alu* insertion at rs70959274 (or flanking sequence only). [Control 1–3 and *Alu* del 1–3 respectively refer the three biological replicates in which the *Alu* insertion elements were either not deleted or deleted]. For the semi-quantitative PCR of *LINC01360* in HEK293T and HCC1806 cells, the gel electrophoresis figure using the first pair of primer for *LINC01360* was presented, and the semi-quantitative PCR using the send pair of primer yielded similar and consistent results (data not shown). For the gel electrophoresis figure in U251 cells, the semi-quantitative PCR of *LINC01360* using the first pair of primer did not observe any bands even after the *Alu* sequence was deleted (data not shown). We then used the second pair of primer which is predicted to cover majority of the *LINC01360* transcripts, and the gel electrophoresis is presented in the figure. Therefore, *LINC01360* likely underwent distinct alternative splicing patterns in different cells despite all expressed in low level, and *LINC01360* transcripts measured by the first pair of primer was not expressed in U251 cells. *Alu* del, de



Fig. 4 KEGG pathway and GO biological processes analyses of dysregulated genes in the HEK293T and U251 cell lines after CRISPR/Cas9 deletion of the *Alu* insertion at rs70959274.

signaling pathway, focal adhesion, regulation of actin cytoskeleton, cell cycle and axon guidance (FDR < 0.05, Fig. 4a and Table S8). More intriguingly, GSEA results indicated that these DEGs were strongly enriched in the GO terms "positive regulation of neurogenesis", "learning or memory", "modulation of chemical synaptic transmission", "regulation of trans-synaptic signaling" and "regulation of stem cell proliferation" etc. (FDR < 0.05, Fig. 4a and Table S9). Besides highlighting essential pathways, RNA-sequencing analysis in U251 cells also revealed some DEGs whose involvement in MDD were supported by particularly strong evidence, such as FLOT1 and DRD2. FLOT1 has been implicated as a MDD susceptibility gene in a recent integrative analysis of GWAS and RNA-sequencing eQTL transcriptomes, and the mRNA expression of FLOT1 was significantly upregulated in the brain and peripheral blood of MDD patients compared with controls [53]. In a recent GWAS of depression, *DRD2* was genome-wide significantly associated with the illness (lowest $p = 3.57 \times 10^{-39}$ for rs61902811 in 660,418 cases and 1,453,489 controls) [2], and dysregulation of the dopamine system has been repeatedly discussed in the pathophysiology of depression [54, 55]. Both FLOT1 and DRD2 showed elevated mRNA expression after deletion of the Alu insertion (which corresponds to higher genetic risk) in the RNA-sequencing analysis (FLOT1, $loq_2(FC) = 0.39$, FDR = 0.00934; DRD2, $loq_2(FC) = 0.63$, FDR = 0.000858; Fig. S12). The current study provides extra evidence suggesting their pivotal roles in MDD pathogenesis.

Overall, results in both cell lines supported certain pathological hypotheses. For example, abnormal mitochondrial function has been reported in MDD [56–58], although the exact mechanisms

linking mitochondrial abnormalities to MDD remain unclear, transcriptomic results in HEK293T cells may provide some insights. Additionally, synaptic dysregulation and impaired learning or memory have been proposed to facilitate MDD pathogenesis [59–63], which is also confirmed in the current transcriptome analysis results in U251 cells. However, there were only six DEGs (*EHD1, C15orf39, DCTPP1, PLK2, HSPB1, RRS1*) highlighted in both HEK293T and U251 cells (Table S10), and these overlapped genes were not enriched in any biological processes or pathways using the currently available pathway analysis platforms.

DISCUSSION

Chromosome 1p31.1 is a lead risk locus identified by MDD GWAS [4]. Here we identify a human-unique *Alu* insertion in this genomic region in strong LD with the MDD risk SNP rs12129573, and this *Alu* insertion acts as a silencer likely through DNA methylation mechanisms. Intriguingly, recent studies have also found altered DNA methylation of the *AluY* subfamily and long interspersed nuclear element (LINE-1) in schizophrenia and bipolar disorder [64, 65]. Therefore, consistent evidence supports the involvement of such mobile retrotransposon elements in psychiatric disorders.

Given that psychiatric disorders are usually considered primarily or dominantly originated from humans (although they appear to decrease Darwinian fitness), there has long been the hypothesis of potential evolutionary mechanisms underlying these illnesses, and many studies have proposed that psychiatric disorders might be relevant to certain human-unique features (e.g., DNA alleles, gene expression, and protein function). For example, we have previously identified a human-specific allele that undergoes Darwinian natural selection. This allele enables humans to adapt to a colder environment in Europe, while simultaneously increases the risk of schizophrenia [66]. A previous study discovered a human-specific tandem repeat in the AS3MT gene increasing risk of psychiatric disorders in human populations [19]. In addition, we previously reported that the primate-specific gene BTN3A2 was a schizophrenia risk gene in the MHC loci [12], and have also recently characterized two human-specific Alu polymorphisms in the GWAS risk loci of psychiatric disorders at 10q24.32 and 3p21.1 respectively, and the "presence" of the Alu insertion at each locus has been recognized as psychiatric risk alleles [17, 18]. Intriguingly, the human-unique alleles at these previously reported psychiatric risk loci all indicate higher risk of psychiatric disorders, supporting the putative origination of psychiatric illnesses in humans. However, there is never an easy answer to etiology of psychiatric illnesses from the perspective of evolution. As mentioned, these diseases and variations are considered to decrease Darwinian fitness (e.g., they result in substantial reproductive disadvantage). Although there have been multiple evolutionary hypothesis (e.g., natural selection hypothesis, mutation-selection-drift hypothesis, and balancing selection hypothesis) discussing why psychiatric disorders and their risk genetic variations still exist in humans, a satisfactory and validated explanation is still lacking [67, 68]. Indeed, we herein have identified a new psychiatric risk locus whose human-unique allele (i.e., Alu insertion) reduced the genetic risk of MDD. This result thus suggests the complexity of the genetic and evolutionary basis of MDD. Considering that numerous genetic variations have pleiotropic effects in human traits, it is possible that MDD is significantly affected by the interactions between environmental exposures and genetic variations, and both evolutionary ancestral and novel alleles at distinct loci may confer risk of this illness.

We have also defined a IncRNA (LINC01360) whose expression is affected by the rs70959274 Alu polymorphism. Therefore, this IncRNA likely plays a role in the pathogenesis of MDD. Nevertheless, the caveats still exist regarding LINC01360 in the present study. Although our results strongly suggest the involvement of this IncRNA in the genetic risk of MDD related to rs12129573 and the rs70959274 Alu polymorphism, we are not able to comprehensively characterize its expression pattern in tissues relevant to MDD (e.g., the brain) using currently available data (Fig. S1) [28]. Instead, our spatial expression analysis shows that LINC01360 is preferably expressed in human testis, suggesting its putative function in spermatogenesis and testosterone production, etc. With little knowledge of the link between testis and MDD, the mechanisms by which LINC01360 participate in MDD remain unclear. Nevertheless, testosterone has been implicated in the pathophysiology and treatment of MDD before. For example, Giltay et al. [69] found that plasma testosterone levels were lower in men with MDD compared with healthy men, and Walther et al. [70] reported that testosterone treatment might to be effective and efficacious in reducing depressive symptoms in men. Therefore, further studies exploring whether LINC01360 affects MDD via modulating testosterone production or function are of great interest.

It is also worth noting that the current failure to detect *LINC01360* expression in brain tissues might not be sufficient to deny its potential function in the brain. Specifically, the GTEx RNA-sequencing data [28] used in the current study is primarily obtained from postnatal brain tissues. As accumulating studies suggest that some genetic risk factors of psychiatric illnesses exert functional impact during particular stages of brain development [71–73], whether the expression of *LINC01360* peaks in the brain during a specific time-window that is not covered in the current dataset remains an interesting question to answer. In addition, it is

gradually recognized that gene expression profiles of different types of cells in the brain differ significantly [74, 75]. Since the data used to examine *LINC01360* expression in the present study does not differentiate different types of cells, it is possible that its expression is altered only in certain cells, and the differences are therefore undetectable when data from all cells are analyzed together. As a result, we believe that quantifying *LINC01360* expression in different cells in the brain during different developmental stages may provide valuable information regarding its functionality.

We have confirmed the functional impact of the rs70959274 Alu polymorphism through CRISPR/Cas9-directed genomic editing in cells. The regulatory effect of rs70959274 on LINC01360 promoter activities are consistent in different cell lines, providing valuable insights into the functional impact of this Alu polymorphism. However, caution is also needed regarding the inconsistent RNAsequencing results between HEK293T and U251 cells following deletion of the rs70959274 Alu insertion. For example, the risk genes highlighted in U251 cells, such as FLOT1 and DRD2, were not altered in HEK293T cells; and we have observed alteration of mitochondrial-relevant pathways following genomic editing in HEK293T cells only. Therefore, we speculate that the Alu insertion and the IncRNA might exert (partially) distinct functions between HEK293T and U251 cells, as reflected in the RNA-sequencing analysis. In addition, previous studies have reported enriched Alu content in the mitochondrial genes, which might disrupt the neuronal mitochondrial homeostasis and lead to brain disorders [76], it is thus also possible that the altered mitochondrial pathway genes in HEK293T cell after deletion of the Alu insertion at rs70959274 is not related to LINC01360, but rather because of other undefined mechanisms.

In summary, our study has described the potential involvement of a novel human-specific Alu polymorphism in the genetic risk of MDD conferred by the 1p31.1 locus, and emphasizes the necessity and importance of considering repetitive DNA polymorphisms in studying psychiatric illnesses. We also reveal that a IncRNA, LINC01360, is likely modulated by this Alu polymorphism. While the exact role of LINC01360 in MDD remains unclear, further studies characterizing its expression and function in MDD-relevant tissues at different developmental stages are urgently needed to gain insights into the etiology and pathogenesis of this illness. In addition, it is well-known that DRD2 is a schizophrenia risk gene, and in previous GWAS study, the LINC01360 locus also exhibited genome-wide significant association with schizophrenia (rs12129573, $p = 8.94 \times 10^{-15}$ in 40,675 cases and 64,643 controls) [77], therefore our investigations on the Alu polymorphism and LINC01360 may also provide insights into the biological mechanisms of schizophrenia albeit further characterization study should be performed.

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AUTHOR CONTRIBUTIONS

W.L., L.L., X.X. and M.L. designed the study and interpreted the results. W.L., W.L., X.C. and Z.Y. conducted the SNP and *Alu* genotyping, the primary functional assays, including molecular cloning, cell line experiments, and analysis of those data. H.L. performed the bioinformatics analysis based on RNA-sequencing data. H.C. and X.X. contributed to design the CRISPR/Cas9 experiments. W.L., X.S., M.S., D.S.Z., X.L., C.Z., M.S., L.Z., Y.Y., Y.Z., J.Z., Y.G.Y., Y.F. and L.L. contributed to collection of clinical samples. X.X. and M.L. drafted the manuscript, and all authors contributed to the final version of the paper.

ADDITIONAL INFORMATION

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Figure S1. The predicted transcripts of *LINC01360* in Ensembl and locations of each primer in the gene.

| | | | | First pair of prir | ners | |
|-----------------------|-----------|---------------------------------------|--------------------|--------------------|---------|--------|
| | | | Forward | | Reverse | |
| LINC01360-204 >linRNA | 5' I | · · · · · · · · · · · · · · · · · · · | | | | 3' |
| LINC01360-212 >linRNA | | | | | | |
| LINC01360-210 >linRNA | | | | | | 0 |
| LINC01360-213 >linRNA | D | | | | | |
| LINC01360-214 >linRNA | J | | 0 | | | |
| LINC01360-208 >linRNA | I | | | | | 0 |
| LINC01360-202 >linRNA | I | | | | | 0 |
| LINC01360-203 >linRNA | M | ── | | | | |
| LINC01360-207 >linRNA | ₩ | ~_₽ | | | | |
| LINC01360-206 >linRNA | | | | | | 0 |
| LINC01360-211 >linRNA | ₩ | | | | | 0 |
| LINC01360-209 >linRNA | ₩ | ~~ | | | | 0 |
| LINC01360-205 >linRNA | ₩ | ~ | | | | |
| LINC01360-216 >linRNA | M | ~~ <u> </u> | | | | 0 |
| LINC01360-217 >linRNA | \bowtie | | | | | 0 |
| LINC01360-201 >linRNA | | | | | | |
| LINC01360-215 >linRNA | J | | | | | 0 |
| | | | | | | |
| | | Forward | | Reverse | | |
| | | Seco | nd pair of primers | 5 | | |

Figure S2. Rs12129573 is not associated with mRNA expression of *LRRIQ3* or *NEGR1* in testis tissue in GTEx dataset.







Figure S4. Expression analysis of *LINC01360* in eight human brain tissues using semi-quantitative

PCR. The semi-quantitative PCR was performed on an Applied Biosystems Veriti Thermal Cycler following the program that firstly 95 °C for 5 min, followed by 40 repeated cycles of 95 °C for 30 s, 60 °C for 30 s and 72 °C for 30 s, with one final annealing cycle at 72 °C for 5 min. The semi-quantitative PCR was conducted using the second pair of primers of *LINC01360*, which is predicted to cover majority of the transcripts.





Figure S5. Functional prediction of rs12129573 and its LD SNPs using HaploReg.

Abbreviation

Chr, chromosome; pos, position; LD, linkage disequilibrium; Ref, reference allele; Alt, alternative allele; AFR freq, frequency of reference allele in African populations; AMR freq, frequency of reference allele in American populations; ASN freq, frequency of reference allele in Asian populations; EUR freq, frequency of reference allele in European populations.

Figure S6. Genotyping of the *Alu* polymorphism rs70959274 in multiple human cell lines.



Figure S7. Examples of genome-wide sequencing based on short reads (such as ChIP-Seq on H3K4me1, H3K4me3 or transcription factors *etc.*) around rs70959274 region.



Figure S8. Functional prediction of the Alu sequence (351-bp) at rs70959274 using Alibaba2 website. Potential binding sites of transcriptional factors were marked in the figure.

| seq(0. Segments: | . 5 | 9) | cggccgggcgggggggctcacgcctgtaatcccagcactttgggaggccgaggcggg |
|--|---|--|---|
| 2.3.1.0 | 2 | 11 | Sp1=== |
| 1.1.3.0 | 26 | 35 | <u>=C/EBPalp=</u> |
| 2.3.1.0 | 43 | 57 | =====Sp1===== ===P1== |
| 2.3.1.0 | 49 51 | 60 | <u>pgr_1</u> ====Sp1== |
| | | | |
| seq(60. | . 11 | 9) | atcacgaggtcaggagatcgagaccatectggetaacacagtgaaaccecgtetetaeta |
| Segments: | - 21 | | |
| 2.3.1.0 | 60 | 69 | = ====IISP=== |
| 9.9.721 | 65 | 74 | ==RAR-beta |
| 2.1.2.2 | 65 | 75 | ==RXR-alpha |
| 2.1.1.1 | 82 | 91 | GR |
| 4.1.1.0 | 100 | 109 | =====]]=== |
| 2310 | 105 | 114 | <u>-Mr-Kappab</u> ====Sp1=== |
| 2.3.2.2 | 117 | 126 | |
| | | | |
| seq(120. Segments: | . 17 | 9) | aaaaacacaaaaaaattagccgggcgtggtggcggggcgcctgtagtcccagctacttggg |
| 2.3.2.2 | 117 | 126 | Hb |
| <u>1.1.3.0</u> | 126 | 135 | =C/EBPalp= |
| 2.3.2.2 | 128 | 137 | <u>=====Hb===</u> |
| 2.3.1.0 | 140 | 150 | |
| 2.3.1.0 | 147 | 159 | ======Sp1==== |
| 2.3.1.0 | 178 | 187 | |
| <u>1.1.3.0</u> | 179 | 188 | ± |
| 1.6.1.0 | 179 | 188 | Ξ |
| seq(180. | . 23 | 9) | aggotgaggoaggagaatggogtgaaccogggaggoggagottgoagtgagoogagatco |
| Segments: | 170 | 107 | |
| <u>2.3.1.0</u> 1.1.3.0 | 179 | 188 | C/FBPaln= |
| 1.6.1.0 | 179 | 188 | AP-2alph= |
| 1.2.1.0 | 186 | 195 | B1=== |
| <u>1.2.2.0</u> | 186 | 195 | <u>====MvoD==</u> |
| 1.6.1.0 | 206 | 215 | <u>=AP-2alph=</u> |
| 2310 | 208 | 245 | Spi |
| | | | |
| | 0.0 | 0) | aganant goost and goost gggogogogogogogogogogogogogogogogogogo |
| seq(240. Segments: | 29 | 9) | -SecareSearessersarasagesagareresterraaaaaaaaaaaaaaaaaaaaaaaaaaaaaa |
| seq(240. Segments: <u>2.3.1.0</u> | 234 | 245 | pl==== |
| seq(240. Segments: <u>2.3.1.0</u> <u>2.3.1.0</u> | 234 253 | 245 263 | p1==== YY1=== |
| seq(240. Segments: 2.3.1.0 2.3.1.0 2.3.1.0 | 234 253 275 | 245 263 284 | p1==== |
| seq(240. Segments: 2.3.1.0 2.3.1.0 2.3.1.0 2.3.2.2 2.2.2 2.2.2 | 234 253 275 283 | 245 263 284 292 | <u>p1====</u> <u>=====YY1===</u> <u>=====Hb===</u> <u>====Hb===</u> |
| seq(240. Segments: 2.3.1.0 2.3.1.0 2.3.1.0 2.3.2.2 3.3.2.0 | 234 253 275 283 297 | 245 263 284 292 306 | <u>p1====</u> <u>=====YY1===</u> <u>=====Hb===</u> |
| seq(240. Segments: 2.3.1.0 2.3.1.0 2.3.1.0 2.3.2.2 3.3.2.0 seq(300. | 234 253 275 283 297 . 35 | 245 263 284 292 306 9) | <u>p1====</u> <u>=====YY1===</u> <u>=====Hb===</u> <u>aaaaaagaaaaagaaaaagaaaaagaaaaagaaaaga</u> |
| seq(240. Segments: 2.3.1.0 2.3.1.0 2.3.2.2 3.3.2.0 seq(300. Segments: 3.3.2.0 | 234 253 275 283 297 . 35 297 | 245 263 284 292 306 9) | pl==== <u>=====YY1===</u> <u>=====Hb===</u> aaaaaagaaaaagaaaaagaaaaagaaaaagaaaaagaaaa |
| seq(240. Segments: 2.3.1.0 2.3.1.0 2.3.2.2 3.3.2.0 seq(300. Segments: 3.3.2.0 3.5.3.0 | 234 253 275 283 297 . 35 297 306 | 245 263 284 292 306 9) 306 315 | pl==== |
| seq(240. Segments: 2.3.1.0 2.3.1.0 2.3.2.2 3.3.2.0 seq(300. Segments: 3.3.2.0 3.5.3.0 4.5.1.0 | 234 253 275 283 297 . 35 297 306 319 | 245 263 284 292 306 9) 306 315 328 | pl==== |
| seq(240. Segments: 2.3.1.0 2.3.1.0 2.3.2.2 3.3.2.0 seq(300. Segments: 3.3.2.0 3.5.3.0 4.5.1.0 4.3.1.1 | 234 253 275 283 297 . 35 297 306 319 345 | 245 263 284 292 306 315 328 354 | p1==== <u>====Sp1===</u> <u>====Hb===</u> <u>aaaaaagaaaaagaaaaagaaaaagaaaaagagactctaaaat</u> <u>HNP-3==</u> <u>===ICSBP==</u> <u>===TBP===</u> <u>===MEB-1==</u> |

Figure S9. Results of off-target effects during genome editing of rs70959274. We examined the 28 most likely off-target sites by T7EN1 analysis, and 6 sites (Off-6, Off-11, Off-14, Off-17, Off-18, Off-19) have detected cleavage bands, which were then verified by Sanger sequencing and no overlap peak was found within 100-bp around each site. These data indicated that potential off-target effects were not existed in our CRISPR/Cas9 system.





Figure S10. No changes in mRNA expression levels of *LRRIQ3* and *NEGR1* after rs70959274 and its flanking sequence were deleted in HEK293T and U251 cells.

The values on Y-axis represent relative expression $(2^{-\Delta\Delta Ct})$ relative to the control group. **Abbreviation:** *Alu* del, deletion of *Alu* insertion.

Figure S11. No changes in mRNA expression level of *LRRIQ3* after the flanking sequence was deleted in HCC1806 cells (*NEGR1* was not expressed in HCC1806 cells).



The values on Y-axis represent relative expression $(2^{A-\Delta\Delta Ct})$ relative to the control group. **Abbreviation:** Flanking del, deletion of flanking sequence.

Figure S12. RNA-sequencing analysis of *FLOT1* and *DRD2* genes in U251 cells after CRISPR/Cas9 deletion of the *Alu* insertion at rs70959274.



Abbreviation: *Alu* del, deletion of *Alu* insertion.

Table S1. Association of rs12129573 with MDD in our Han Chinese samples (1,751 cases and 2,468 controls)

| CIID | CHR SNP | Desition | Location | A 1 | 4.2 | Frequer | ncy of A1 | D valua | OP | $(059/CL_{c})$ |
|------|------------|----------|------------|-----|-----|---------|-------------|-----------------------|---------|-----------------------|
| CHK | SINF | Position | Location | AI | AZ | Cases | Controls | r-value | UK | (95%CIS) |
| 1 | rs12129573 | 73768366 | Intergenic | Α | С | 0.254 | 0.214 | 2.98×10^{-5} | 1.239 (| (1.120–1.370) |
| | | | | | | | | | | |
| CHR | SNP | Position | Location | A1 | A2 | TEST | Case | Cont | trol | P-value |
| 1 | rs12129573 | 73768366 | Intergenic | Α | С | GENO | 144/584/987 | 7 115/825 | 5/1524 | 2.38×10^{-6} |

Note:

Hardy-Weinberg equilibrium (HWE) test for rs12129573 in control: Pearson's p is 0.811.

We have confirmed the genotyping of rs12129573 using Sanger sequencing on 50 randomly selected individuals, and no genotyping error were found.

Abbreviation: CHR, chromosome; SNP, single nucleotide polymorphism; A1, allele 1; A2, allele 2.

Table S2. Functional prediction of rs12129573 and its LD SNPs using GWAVA.

| CHR | SNP | Position | TSS distance | SS distance | Exon | Region score | TSS score | Unmatched score |
|-----|------------------------|----------|--------------|-------------|------|--------------|-----------|-----------------|
| 1 | rs11210201 | 73766431 | -5421 | -5526 | - | 0.23 | 0.29 | 0.1 |
| 1 | rs11210202 | 73767064 | -4788 | -4893 | - | 0.43 | 0.39 | 0.24 |
| 1 | rs12128495 | 73767587 | -4265 | -4370 | - | 0.34 | 0.42 | 0.21 |
| 1 | rs12144370 | 73768276 | -3576 | -3681 | - | 0.4 | 0.38 | 0.3 |
| 1 | rs12129573 | 73768366 | -3486 | -3591 | - | 0.26 | 0.27 | 0.19 |
| 1 | rs12145429 | 73769279 | -2573 | -2678 | - | 0.38 | 0.44 | 0.33 |
| 1 | rs12145432 | 73769330 | -2522 | -2627 | - | 0.3 | 0.28 | 0.33 |
| 1 | rs1923201 | 73771457 | -395 | -500 | - | 0.28 | 0.18 | 0.47 |
| 1 | rs1923202 | 73771528 | -324 | -429 | - | 0.26 | 0.2 | 0.49 |
| 1 | rs9425118 | 73771766 | -86 | -191 | - | 0.37 | 0.18 | 0.54 |
| 1 | rs1475061 | 73772981 | 81 | -65 | 1 | 0.21 | 0.04 | 0.48 |
| 1 | rs4593766 | 73773043 | 143 | -3 | 1 | 0.18 | 0.04 | 0.27 |
| 1 | rs6424545 | 73773048 | 148 | 0 | 1 | 0.22 | 0.03 | 0.25 |
| 1 | rs1475062 | 73773189 | 289 | 140 | 1 | 0.11 | 0.06 | 0.2 |
| 1 | rs1475063 | 73773255 | 355 | 206 | 1 | 0.19 | 0.09 | 0.4 |
| 1 | rs11210203 | 73775513 | 2613 | -1020 | - | 0.29 | 0.02 | 0.02 |
| 1 | rs6424546 | 73776673 | 3773 | 0 | 1 | 0.24 | 0.18 | 0.29 |
| 1 | rs6424547 | 73776696 | 3796 | 20 | - | 0.09 | 0.04 | 0.05 |
| 1 | rs6424548 | 73776850 | 3950 | 174 | - | 0.22 | 0.04 | 0.03 |
| 1 | rs11210204 | 73777991 | 5091 | 1315 | - | 0.19 | 0.03 | 0.05 |
| 1 | rs11210205 | 73778100 | 5200 | 1424 | - | 0.2 | 0.04 | 0.09 |
| 1 | rs12061680 | 73778378 | 5478 | 1702 | - | 0.16 | 0.05 | 0.04 |
| 1 | rs11210207 | 73782938 | 10038 | -2210 | - | 0.41 | 0.26 | 0.19 |
| 1 | rs7517355 | 73784077 | 11177 | -1071 | - | 0.36 | 0.14 | 0.05 |
| 1 | rs7528322 | 73784686 | 11786 | -462 | - | 0.32 | 0.11 | 0.05 |
| 1 | rs1012/961 | 73786469 | 13569 | 1318 | - | 0.31 | 0.07 | 0.05 |
| 1 | rs10/32841 | 73786858 | 13958 | 1707 | - | 0.15 | 0.12 | 0.04 |
| 1 | rs2340398 | /3/88694 | 15/94 | 3543 | - | 0.23 | 0.01 | 0.01 |
| 1 | rs10890032 | 73789324 | 16424 | 41/3 | - | 0.21 | 0.01 | 0 |
| 1 | rs11210209 | 73793245 | 20345 | -/881 | - | 0.19 | 0.02 | 0.01 |
| 1 | rs1885240 | 73793499 | 20599 | -/02/ | - | 0.25 | 0.04 | 0.01 |
| 1 | rs107/0810 | 73793030 | 20730 | -7490 | - | 0.2 | 0.08 | 0.01 |
| 1 | rs10890033 | 73796794 | 22025 | -0203 | | 0.17 | 0.03 | 0.01 |
| 1 | rs2145784 | 73797927 | 25027 | -3199 | - | 0.43 | 0.05 | 0.01 |
| 1 | rs1923206 | 73799968 | 27068 | -1158 | - | 0.15 | 0.00 | 0.04 |
| 1 | rs6684973 | 73801632 | 28732 | 503 | 1 | 0.20 | 0.11 | 0.24 |
| 1 | rs1923207 | 73803542 | 30642 | 2413 | 1 | 0.39 | 0.19 | 0.43 |
| 1 | rs1120979 | 73804712 | 31812 | 3583 | - | 0.27 | 0.02 | 0 |
| 1 | rs1120981 | 73805179 | 32279 | 4050 | - | 0.31 | 0.05 | 0.02 |
| 1 | rs6689226 | 73806923 | 34023 | 5794 | - | 0.37 | 0.03 | 0 |
| 1 | rs2208565 | 73810229 | 37329 | -3585 | - | 0.16 | 0.04 | 0 |
| 1 | rs2208566 | 73810422 | 37522 | -3392 | - | 0.22 | 0.05 | 0 |
| 1 | rs6700324 | 73810915 | 38015 | -2899 | - | 0.18 | 0.03 | 0.01 |
| 1 | rs6702943 | 73810973 | 38073 | -2841 | - | 0.25 | 0.05 | 0.02 |
| 1 | rs1951361 | 73811954 | 39054 | -1860 | - | 0.3 | 0.15 | 0.04 |
| 1 | rs10749820 | 73812598 | 39698 | -1216 | - | 0.26 | 0.15 | 0.01 |
| 1 | rs11210211 | 73813579 | 40679 | -235 | - | 0.34 | 0.07 | 0.05 |
| 1 | rs1923211 | 73814908 | 42008 | 1091 | - | 0.26 | 0.13 | 0.1 |
| 1 | rs1923212 | 73814973 | 42073 | 1156 | - | 0.26 | 0.11 | 0.06 |
| 1 | rs1160682 | 73816564 | 43664 | 2747 | - | 0.25 | 0.16 | 0.03 |
| | rs2008280 | 73816745 | 43845 | 2928 | - | 0.3 | 0.44 | 0.02 |
| 1 | rs6668602 | /381/816 | 44916 | -2937 | - | 0.36 | 0.09 | 0.03 |
| 1 | rs10493516 | /3818516 | 45010 | -223/ | - | 0.31 | 0.08 | 0.05 |
| 1 | 182180940 | 73920227 | 40948 | -905 | - | 0.20 | 0.2 | 0.05 |
| 1 | 181923214 rs2340200 | 73821002 | 4/32/ | -320 | - | 0.24 | 0.15 | 0.04 |
| 1 | 182340399 | 73921093 | 48193 | 507 525 | - | 0.33 | 0.33 | 0.25 |
| 1 | 152340400 | 73821201 | 40301 | 825 821 | - | 0.32 | 0.31 | 0.17 |
| 1 | rs6673702 | 73821377 | 40077 | 1023 | - | 0.29 | 0.2 | 0.15 |
| 1 | rs10890034 | 73824279 | 51379 | 3523 | - | 0.23 | 0.22 | 0.14 |
| 1 | rs10789369 | 73824909 | 52009 | 4153 | - | 0.25 | 0.14 | 0.01 |
| 1 | rs6681595 | 73827012 | 54112 | 6256 | - | 0.23 | 0.1 | 0.01 |
| 1 | rs10890035 | 73828271 | 55371 | 7515 | - | 0.39 | 0 | 0 |
| | | | | | | | | |

| 1 | rs7541529 | 73828831 | 55931 | 8075 | - | 0.19 | 0.07 | 0 |
|----------|--------------------|-----------|----------------|-------|---|------|------|------|
| 1 | rs1923216 | 73829128 | 56228 | 8372 | - | 0.24 | 0.06 | 0 |
| 1 | rs1023218 | 73829120 | 56382 | 8526 | _ | 0.31 | 0.07 | 0.02 |
| 1 | rs6620022 | 73820623 | 56722 | 8967 | _ | 0.11 | 0.07 | 0.02 |
| 1 | 150089032 | 73829023 | 57029 | 0172 | - | 0.11 | 0.07 | 0.02 |
| 1 | rs/41513/ | /3829928 | 57028 | 9172 | - | 0.3 | 0.06 | 0 |
| <u> </u> | rs10890036 | 73830081 | 57181 | 9325 | - | 0.34 | 0.19 | 0.03 |
| 1 | rs1923219 | 73830471 | 57571 | 9715 | - | 0.31 | 0.23 | 0.07 |
| 1 | rs2025080 | 73832675 | 59775 | 11919 | - | 0.26 | 0.25 | 0.08 |
| 1 | rs6702039 | 73833009 | 60109 | 12253 | - | 0.26 | 0.26 | 0.02 |
| 1 | rs10749821 | 73833914 | 61014 | 13158 | - | 0.37 | 0.25 | 0.04 |
| 1 | rs11210215 | 73834346 | 61446 | 13590 | _ | 0.33 | 0.22 | 0.1 |
| 1 | rs2240401 | 72825726 | 62826 | 14070 | _ | 0.35 | 0.12 | 0.04 |
| 1 | 182340401 | 73833720 | (2877 | 14970 | - | 0.38 | 0.10 | 0.04 |
| 1 | rs2340403 | /3835/// | 628// | 15021 | - | 0.27 | 0.3 | 0.01 |
| l | rs1923222 | /3836340 | 63440 | 15584 | - | 0.34 | 0.26 | 0.04 |
| 1 | rs12034860 | 73836769 | 63869 | 16013 | - | 0.21 | 0.04 | 0.01 |
| 1 | rs12128161 | 73837417 | 64517 | 16661 | - | 0.36 | 0.22 | 0.09 |
| 1 | rs12128235 | 73837608 | 64708 | 16852 | - | 0.24 | 0.16 | 0.01 |
| 1 | rs12117304 | 73837640 | 64740 | 16884 | - | 0.3 | 0.11 | 0.01 |
| 1 | rs6677536 | 73837958 | 65058 | 17202 | - | 0.27 | 0.15 | 0.05 |
| 1 | rs1923223 | 73839564 | 66664 | 18808 | _ | 0.3 | 0.17 | 0.03 |
| 1 | rs1023223 | 73830001 | 67021 | 10165 | _ | 0.22 | 0.19 | 0.03 |
| 1 | 151923224 | 73839921 | 67021 | 19103 | - | 0.55 | 0.18 | 0.03 |
| 1 | rs/554968 | /3840843 | 6/943 | 2008/ | - | 0.3 | 0.19 | 0.02 |
| 1 | rs11210216 | /3842480 | 69580 | 21724 | - | 0.28 | 0.07 | 0.04 |
| 1 | rs7544965 | 73842685 | 69785 | 21929 | - | 0.31 | 0.13 | 0.02 |
| 1 | rs7516608 | 73843213 | 70313 | 22457 | - | 0.42 | 0.22 | 0.06 |
| 1 | rs10890037 | 73845254 | 72354 | 24498 | - | 0.25 | 0.03 | 0 |
| 1 | rs10749822 | 73845360 | 72460 | 24604 | - | 0.24 | 0.05 | 0.01 |
| 1 | rs10736419 | 73845941 | 73041 | 25185 | - | 0.42 | 0.38 | 0.16 |
| 1 | rs11210217 | 738/65/2 | 73642 | 25786 | _ | 0.12 | 0.05 | 0.03 |
| 1 | 1511210217 | 73040342 | 75421 | 23780 | - | 0.2 | 0.03 | 0.03 |
| 1 | IS/515828 | /3848331 | 75451 | 2/5/5 | - | 0.33 | 0.17 | 0 |
| 1 | rs/54698/ | /3848505 | /5605 | 27749 | - | 0.16 | 0.09 | 0.02 |
| 1 | rs7547059 | /384853/ | /563/ | 27781 | - | 0.19 | 0.09 | 0.03 |
| 1 | rs11581459 | 73848631 | 75731 | 27875 | - | 0.18 | 0 | 0 |
| 1 | rs12135094 | 73848944 | 76044 | 28188 | - | 0.23 | 0.11 | 0.02 |
| 1 | rs12120214 | 73848985 | 76085 | 28229 | - | 0.19 | 0.13 | 0 |
| 1 | rs12127629 | 73848987 | 76087 | 28231 | - | 0.21 | 0.08 | 0.01 |
| 1 | rs11210219 | 73849016 | 76116 | 28260 | - | 0.16 | 0.08 | 0.02 |
| 1 | rs10789370 | 73849297 | 76397 | 28541 | _ | 0.21 | 0.17 | 0.05 |
| 1 | rs11210220 | 73840655 | 76755 | 20041 | _ | 0.20 | 0.11 | 0.03 |
| 1 | 1511210220 | 73849033 | 70733 | 20077 | - | 0.29 | 0.11 | 0.05 |
| 1 | 11210221 | /38496/3 | /0//3 | 28917 | - | 0.34 | 0.14 | 0.01 |
| 1 | rs11210222 | /384968/ | /6/8/ | 28931 | - | 0.26 | 0.09 | 0.03 |
| l | rs1923228 | /3849//3 | 76873 | 29017 | - | 0.34 | 0.26 | 0 |
| 1 | rs12564336 | 73851675 | 78775 | 30919 | - | 0.4 | 0.3 | 0.12 |
| 1 | rs6671002 | 73851752 | 78852 | 30996 | - | 0.26 | 0.3 | 0.06 |
| 1 | rs6671203 | 73851936 | 79036 | 31180 | - | 0.23 | 0.17 | 0 |
| 1 | rs6673911 | 73852067 | 79167 | 31311 | - | 0.38 | 0.22 | 0.07 |
| 1 | rs6673919 | 73852090 | 79190 | 31334 | - | 0.3 | 0.23 | 0.11 |
| 1 | rs11210223 | 73852445 | 79545 | 31689 | - | 0.33 | 0.18 | 0.04 |
| 1 | rs11210224 | 73852554 | 79654 | 31798 | _ | 0.2 | 0.1 | 0.03 |
| 1 | rs11210224 | 73852585 | 79685 | 31820 | | 0.25 | 0.1 | 0.01 |
| 1 | rs1022220 | 72957765 | 70065 | 22000 | - | 0.23 | 0.14 | 0.01 |
| 1 | 151 <i>72323</i> 0 | 72052020 | 2003 | 22102 | - | 0.32 | 0.1 | 0.02 |
| 1 | 1022222 | /3852939 | 80039 | 32183 | - | 0.37 | 0.18 | 0.05 |
| 1 | rs1923233 | /3853460 | 80560 | 32704 | - | 0.27 | 0.03 | 0.01 |
| 1 | rs1923234 | 73853481 | 80581 | 32725 | - | 0.22 | 0.04 | 0.01 |
| 1 | rs1923236 | 73853826 | 80926 | 33070 | - | 0.21 | 0.04 | 0.02 |
| 1 | rs12044079 | 73854147 | 81247 | 33391 | - | 0.29 | 0.18 | 0.03 |
| 1 | rs11210226 | 73854284 | 81384 | 33528 | - | 0.28 | 0.13 | 0.04 |
| 1 | rs11210227 | 73855015 | 82115 | 34259 | - | 0.25 | 0.16 | 0.03 |
| 1 | rs1338645 | 73855051 | 82151 | 34295 | - | 0.31 | 0.21 | 0.07 |
| 1 | rs34547319 | 73855495 | 82595 | 34739 | _ | 0.38 | 0.07 | 0.02 |
| 1 | rs5500/666 | 73856001 | 83101 | 35335 | | 0.20 | 0.07 | 0.02 |
| 1 | re6701544 | 72956/71 | 03171 02571 | 25715 | - | 0.21 | 0.01 | 0 |
| 1 | 150/01344 | / 38304/1 | 033/1 | 33/13 | - | 0.39 | 0.09 | 0.02 |
| 1 | rs6/043/6 | /3856841 | 83941 | 36085 | - | 0.32 | 0.03 | 0.02 |
| 1 | rs6704461 | 73856933 | 84033 | 36177 | - | 0.27 | 0.08 | 0.02 |
| 1 | rs6689493 | 73857058 | 84158 | 36302 | - | 0.25 | 0.06 | 0.01 |
| 1 | rs1984201 | 73857097 | 84197 | 36341 | - | 0.31 | 0.06 | 0.03 |
| 1 | rs1856410 | 73857494 | 84594 | 36738 | - | 0.18 | 0.03 | 0.03 |

| 1 | rs1338655 | 73857613 | 84713 | 36857 | - | 0.22 | 0.21 | 0.02 |
|---|------------|----------|--------|-------|---|------|------|------|
| 1 | rs1338654 | 73857724 | 84824 | 36968 | - | 0.2 | 0.16 | 0.04 |
| 1 | rs5015579 | 73857839 | 84939 | 37083 | - | 0.24 | 0.11 | 0.03 |
| 1 | rs5015578 | 73857844 | 84944 | 37088 | - | 0.23 | 0.19 | 0.03 |
| 1 | rs11809026 | 73858039 | 85139 | 37283 | - | 0.23 | 0.11 | 0 |
| 1 | rs11805813 | 73858079 | 85179 | 37323 | - | 0.23 | 0.13 | 0.05 |
| 1 | rs12744582 | 73858261 | 85361 | 37505 | - | 0.4 | 0.18 | 0.06 |
| 1 | rs11809098 | 73858561 | 85661 | 37805 | - | 0.2 | 0.04 | 0.01 |
| 1 | rs11809486 | 73858941 | 86041 | 38185 | - | 0.21 | 0.13 | 0.05 |
| 1 | rs6696623 | 73859367 | 86467 | 38611 | - | 0.24 | 0.08 | 0.01 |
| 1 | rs11210229 | 73860028 | 87128 | 39272 | - | 0.28 | 0.1 | 0 |
| 1 | rs1923238 | 73860311 | 87411 | 39555 | - | 0.26 | 0.04 | 0.02 |
| 1 | rs12031120 | 73860821 | 87921 | 40065 | - | 0.27 | 0.19 | 0.05 |
| 1 | rs1338651 | 73861924 | 89024 | 41168 | - | 0.34 | 0.22 | 0.05 |
| 1 | rs10159196 | 73863269 | 90369 | 42513 | - | 0.28 | 0.28 | 0.05 |
| 1 | rs1885249 | 73865740 | 92840 | 44984 | - | 0.32 | 0.14 | 0 |
| 1 | rs1416268 | 73866272 | 93372 | 45516 | - | 0.36 | 0.14 | 0.01 |
| 1 | rs1416269 | 73866598 | 93698 | 45842 | - | 0.34 | 0.15 | 0.03 |
| 1 | rs12035848 | 73870901 | 98001 | 50145 | - | 0.37 | 0.34 | 0.13 |
| 1 | rs12043387 | 73871205 | 98305 | 50449 | - | 0.26 | 0.13 | 0.04 |
| 1 | rs7543202 | 73872885 | 99985 | 52129 | - | 0.32 | 0.13 | 0.02 |
| 1 | rs3964487 | 73873755 | 100855 | 52999 | - | 0.23 | 0.04 | 0 |
| 1 | rs1475064 | 73882478 | 109578 | 61722 | - | 0.29 | 0.17 | 0.03 |
| 1 | rs12731986 | 73884838 | 111938 | 64082 | - | 0.34 | 0.24 | 0.03 |
| 1 | rs4523481 | 73899639 | 126739 | 78883 | - | 0.37 | 0.3 | 0.08 |
| 1 | rs11807366 | 73916648 | 143748 | 95892 | - | 0.28 | 0.12 | 0 |

Abbreviation: SNP, single nucleotide polymorphism; TSS, transcriptional start site; SS, stop site.

| | | | | | | | | Droduct | Predicte |
|-----|--------|--|----------------|--|---------|------------|-------------------------------|----------------|---------------------------|
| sgl | RNAs | Coordinates | Mismatche s | target_seq | PA M | location | gene name | s Size (bp) | Cleavag e Size (bp) |
| | On | <u>chr1:73302733-7</u> <u>3302752</u> | 0 | AGACATAATCCCAATA TCTG | AG G | intergenic | RN7SKP19-LINC0 1360 | NA | NA |
| | Off-1 | <u>chr20:6298785-6</u> <u>298807</u> | 2 | AGGCATAATCCCAACA TCTG | GA G | intergenic | AL109618.1-CASC 20 | 219 | 108/111 |
| | 0ff-2 | <u>chr15:48483907-</u> <u>48483929</u> | 3 | GAAGATAATCCCAATAT CTG | TG A | exonic | FBN1 | 156 | 45/111 |
| | Off-3 | <u>chr2:69468239-6</u> <u>9468261</u> | 3 | AGACATAATCCTAATTT CTC | AG G | exonic | AAK1 | 194 | 83/111 |
| | 0ff-4 | <u>chr1:20077565-2</u> <u>0077587</u> | 3 | AGACATAATCACAATAT TTA | TG G | intronic | PLA2G5 | 164 | 79/85 |
| sgR | Off-5 | <u>chr13:29079701-</u> <u>29079723</u> | 3 | AGAAATAAACCCAATA TTTG | TG G | intronic | MTUS2 | 371 | 145/226 |
| 1 | 0ff-6 | <u>chr8:36916786-3</u> <u>6916808</u> | 3 | AGACATAA <mark>A</mark> CCAAATA TCT T | GG G | intergenic | KCNU1 | 225 | 81/144 |
| | 0ff-7 | <u>chr7:77638720-7</u> <u>7638742</u> | 4 | AAACAAATTACCAATA TCTG | TG G | exonic | PTPN12 | 215 | 63/152 |
| | Off-8 | <u>chr10:63152194-</u> <u>63152216</u> | 2 | AGACATATTCCCAATAT TTG | CG A | intronic | NRBF2 | 300 | 71/229 |
| | 0ff-9 | <u>chr16:62114060-</u> <u>62114082</u> | 4 | AAATACAGTCCCAATA TCTG | AG G | intergenic | CDH8-RNU6-21P | 211 | 47/164 |
| | 0ff-10 | <u>chr8:66137060-6</u> <u>6137082</u> | 4 | AAACATGAACCCAATA TCTT | AG G | intronic | TRIM55 | 163 | 43/120 |
| | 0ff-11 | <u>chr21:27145123-</u> <u>27145145</u> | 3 | AGGCATTATCCCAGTA TCTG | TG G | intergenic | ADAMTS5-AP001 604.1 | 458 | 163/295 |
| | On | <u>chr1:73304011-7</u> <u>3304030</u> | 0 | GAGTTAGAAAATTAGG ACAG | TG G | intergenic | RN7SKP19-LINC0 1360 | NA | NA |
| | 0ff-12 | <u>chr15:67728299-</u> <u>67728321</u> | 4 | GAGTTAAAAGATTAAG ACAA | AG G | intronic | MAP2K5 | 387 | 163/224 |
| | 0ff-13 | <u>chr6:70798437-7</u> <u>0798459</u> | 4 | CTGTTAAAAAATTAAG ACAG | AG G | intronic | SMAP1 | 414 | 152/262 |
| | 0ff-14 | <u>chr12:80731469-</u> <u>80731491</u> | 4 | AAGTTAGAAAATTAGA ATAT | AG G | intergenic | MYF5-LINC01490 | 184 | 73/111 |
| | 0ff-15 | <u>chr1:202572366-</u> 202572388 | 2 | GAGTTAGAAAAATAGG ACTG | AA G | intronic | PPP1R12B | 498 | 181/317 |
| | 0ff-16 | <u>chr15:80915411-</u> <u>80915433</u> | 1 | GAGTTAGAAAATTA <mark>T</mark> G ACAG | TG A | intergenic | RP11-351M8.1 | 357 | 72/285 |
| | 0ff-17 | <u>chr1:235202257-</u> <u>235202279</u> | 1 | GAGTTAGAAAATTAAG ACAG | TG A | intronic | ARID4B | 373 | 109/264 |
| | 0ff-18 | <u>chr5:145021427-</u> <u>145021449</u> | 2 | GAGTTA T AAAATTAGG A <mark>G</mark> AG | AG G | intergenic | AC005371.1-AC13 2803.1 | 374 | 145/229 |
| sgR | 0ff-19 | <u>chr15:27509513-</u> <u>27509535</u> | 2 | GAGTTAAAAAATCAGG ACAG | AG A | intergenic | RP11-100M12.3-G ABRG3 | 505 | 248/257 |
| 2 | 0ff-20 | <u>chrX:124164858-</u> <u>124164880</u> | 2 | CAGTTAGAAAATTAAG ACAG | TG A | intergenic | STAG2-SNORA40 | 251 | 117/134 |
| | 0ff-21 | <u>chr6:131849055-</u> <u>131849077</u> | 2 | GAGCTAGAAAATTAGG ACAA | TG A | intronic | ENPP1 | 357 | 174/183 |
| | 0ff-22 | <u>chr19:50340176-</u> <u>50340198</u> | 2 | AAGTGAGAAAATTAGG ACAG | TG A | intergenic | KCNC3-NAPSA | 243 | 95/148 |
| | 0ff-23 | <u>chr16:15570064-</u> <u>15570086</u> | 2 | CAGTGAGAAAATTAGG ACAG | TG A | intronic | C16orf45 | 241 | 36/205 |
| | 0ff-24 | <u>chr10:49542779-</u> <u>49542801</u> | 2 | CAGTTAGAAAATTATG ACAG | TG A | intergenic | ERCC6-PGBD3-C HAT | 217 | 58/159 |
| | 0ff-25 | <u>chr11:23872238-</u> <u>23872260</u> | 2 | GAGTGAGAAAATTATG ACAG | TG A | intergenic | RNU6-783P-RP11- 2F20.1 | 371 | 141/230 |
| | 0ff-26 | <u>chr5:18554974-1</u> <u>8554996</u> | 2 | CAGTGAGAAAATTAGG ACAG | TG A | intergenic | RN7SL58P-CTD-2 023M8.1 | 233 | 94/139 |
| | 0ff-27 | <u>chr20:37563512-</u> <u>37563534</u> | 2 | CAGTAAGAAAATTAGG ACAG | TG A | intergenic | BLCAP-RP11-425 M5.8 | 215 | 36/179 |
| | 0ff-28 | <u>chr9:82455784-8</u> 2455806 | 2 | GACTTAAAAAAATTAGG ACAG | AG A | intergenic | RP11-15B24.4-RP1 1-333B6.1 | 228 | 41/187 |

Table S3. Information about the off-target effects of the two sgRNAs in HEK293T cells.

| Gene ID | Gene name | BP | log2(FC) | S.E. | stat | p-value | p-adjust | Ctrl-1 | Ctrl-2 | Ctrl-3 | Alu Del-1 | Alu Del-2 | Alu Del-3 |
|-----------------|------------|----------|----------|-------|--------|----------|----------|---------|---------|---------|-----------|-----------|-----------|
| ENSG00000147162 | OGT | Xa13.1 | -0.517 | 0.076 | -6.840 | 7.92E-12 | 8 29E-08 | 22.387 | 23 863 | 27.027 | 19 193 | 17 280 | 14 344 |
| ENSG00000175455 | CCDC14 | 3g21.1 | -0.403 | 0.065 | -6.204 | 5.51E-10 | 2.71E-06 | 5.043 | 5.184 | 5.654 | 3.924 | 4.303 | 3.684 |
| ENSG0000055732 | MCOLN3 | 1p22.3 | -0.524 | 0.085 | -6.149 | 7.78E-10 | 2.71E-06 | 2.866 | 2.941 | 3.358 | 2.153 | 2.221 | 1.944 |
| ENSG00000245532 | NEAT1 | 11a13.1 | -0.434 | 0.074 | -5.892 | 3.80E-09 | 9.95E-06 | 2.076 | 2.134 | 2.427 | 1.797 | 1.625 | 1.451 |
| ENSG00000204681 | GABBR1 | 6p22.1 | -0.591 | 0.101 | -5.830 | 5.54E-09 | 9.99E-06 | 2.787 | 3.329 | 3.826 | 2.523 | 2.131 | 1.884 |
| ENSG00000229807 | XIST | Xq13.2 | -0.415 | 0.072 | -5.798 | 6.73E-09 | 9.99E-06 | 126.646 | 131.529 | 160.512 | 113.934 | 105.977 | 91.260 |
| ENSG00000274012 | RN7SL2 | 14q21.3 | 0.860 | 0.149 | 5.784 | 7.28E-09 | 9.99E-06 | 18.746 | 19.022 | 21.063 | 40.688 | 41.273 | 24.443 |
| ENSG00000251562 | MALAT1 | 11q13.1 | -0.604 | 0.105 | -5.776 | 7.64E-09 | 9.99E-06 | 7.211 | 5.891 | 5.677 | 3.667 | 4.540 | 4.088 |
| ENSG00000211459 | MT-RNR1 | ŃA | 0.328 | 0.058 | 5.656 | 1.55E-08 | 1.81E-05 | 241.193 | 237.493 | 248.514 | 311.819 | 289.740 | 303.480 |
| ENSG00000161996 | WDR90 | 16p13.3 | -0.447 | 0.080 | -5.578 | 2.44E-08 | 2.40E-05 | 3.302 | 3.594 | 3.884 | 2.856 | 2.385 | 2.591 |
| ENSG0000086061 | DNAJA1 | 9p21.1 | 0.486 | 0.087 | 5.572 | 2.52E-08 | 2.40E-05 | 24.256 | 24.351 | 24.000 | 30.538 | 32.394 | 37.696 |
| ENSG0000088986 | DYNLL1 | 12q24.31 | 0.419 | 0.077 | 5.450 | 5.05E-08 | 4.17E-05 | 13.813 | 14.420 | 13.370 | 17.425 | 18.680 | 19.085 |
| ENSG00000116754 | SRSF11 | 1p31.1 | -0.350 | 0.064 | -5.445 | 5.18E-08 | 4.17E-05 | 21.430 | 23.219 | 25.211 | 17.088 | 19.798 | 17.397 |
| ENSG00000173209 | AHSA2 | 2p15 | -0.472 | 0.087 | -5.420 | 5.97E-08 | 4.21E-05 | 2.352 | 2.543 | 2.921 | 2.016 | 1.840 | 1.725 |
| ENSG00000128228 | SDF2L1 | 22q11.21 | 0.475 | 0.088 | 5.418 | 6.03E-08 | 4.21E-05 | 12.330 | 12.545 | 12.034 | 16.777 | 17.225 | 16.927 |
| ENSG00000113108 | APBB3 | 5q31.3 | -0.617 | 0.114 | -5.399 | 6.69E-08 | 4.38E-05 | 2.800 | 2.819 | 3.453 | 2.200 | 1.921 | 1.742 |
| ENSG00000233276 | GPX1 | 3p21.31 | 0.374 | 0.069 | 5.380 | 7.44E-08 | 4.58E-05 | 36.583 | 38.511 | 35.560 | 47.804 | 46.789 | 47.730 |
| ENSG0000075618 | FSCN1 | 7p22.1 | 0.308 | 0.058 | 5.304 | 1.13E-07 | 6.32E-05 | 15.378 | 16.237 | 16.814 | 20.220 | 19.764 | 19.449 |
| ENSG00000179958 | DCTPP1 | 16p11.2 | 0.435 | 0.082 | 5.302 | 1.15E-07 | 6.32E-05 | 16.924 | 17.941 | 17.230 | 21.483 | 23.893 | 24.442 |
| ENSG00000165502 | RPL36AL | 14q21.3 | 0.357 | 0.068 | 5.239 | 1.62E-07 | 8.46E-05 | 34.760 | 36.173 | 38.606 | 46.734 | 48.387 | 44.037 |
| ENSG00000136010 | ALDH1L2 | 12q23.3 | -0.539 | 0.104 | -5.184 | 2.17E-07 | 1.08E-04 | 7.543 | 7.856 | 8.790 | 6.004 | 6.481 | 4.087 |
| ENSG00000120694 | HSPH1 | 13q12.3 | 0.457 | 0.089 | 5.158 | 2.49E-07 | 1.16E-04 | 7.806 | 7.815 | 7.167 | 9.725 | 9.815 | 11.466 |
| ENSG0000008710 | PKD1 | 16p13.3 | -0.421 | 0.082 | -5.155 | 2.54E-07 | 1.16E-04 | 3.179 | 3.118 | 3.547 | 2.808 | 2.207 | 2.275 |
| ENSG00000165655 | ZNF503 | 10q22.2 | 0.405 | 0.079 | 5.122 | 3.02E-07 | 1.32E-04 | 23.323 | 23.010 | 22.081 | 27.800 | 29.890 | 32.141 |
| ENSG00000186834 | HEXIM1 | 17q21.31 | 0.474 | 0.093 | 5.094 | 3.51E-07 | 1.47E-04 | 3.876 | 4.410 | 4.231 | 5.568 | 5.509 | 6.145 |
| ENSG00000214279 | SCART1 | 10q26.3 | -0.711 | 0.140 | -5.081 | 3.75E-07 | 1.51E-04 | 0.924 | 1.147 | 1.279 | 0.810 | 0.576 | 0.639 |
| ENSG00000250067 | YJEFN3 | 19p13.11 | -0.622 | 0.123 | -5.056 | 4.28E-07 | 1.62E-04 | 2.536 | 2.759 | 3.183 | 1.961 | 1.702 | 1.788 |
| ENSG00000127586 | CHTF18 | 16p13.3 | -0.381 | 0.075 | -5.047 | 4.48E-07 | 1.62E-04 | 9.597 | 10.819 | 10.986 | 8.948 | 7.400 | 7.571 |
| ENSG00000223745 | CCDC18-AS1 | NA | -0.774 | 0.154 | -5.040 | 4.66E-07 | 1.62E-04 | 1.384 | 1.435 | 1.617 | 0.984 | 0.991 | 0.605 |
| ENSG00000213903 | LTB4R | 14q12 | -0.511 | 0.102 | -5.037 | 4.73E-07 | 1.62E-04 | 3.349 | 3.544 | 4.119 | 2.911 | 2.548 | 2.202 |
| ENSG00000100029 | PES1 | 22q12.2 | 0.360 | 0.071 | 5.030 | 4.91E-07 | 1.62E-04 | 12.253 | 13.613 | 12.729 | 16.565 | 15.617 | 16.914 |
| ENSG00000214826 | DDX12P | NA | -0.447 | 0.089 | -5.028 | 4.95E-07 | 1.62E-04 | 10.740 | 11.065 | 12.467 | 9.570 | 7.406 | 7.931 |
| ENSG0000007080 | CCDC124 | 19p13.11 | 0.331 | 0.066 | 5.019 | 5.20E-07 | 1.65E-04 | 22.651 | 23.983 | 23.535 | 28.704 | 30.152 | 28.713 |
| ENSG00000110104 | CCDC86 | 11q12.2 | 0.503 | 0.101 | 4.996 | 5.86E-07 | 1.77E-04 | 10.611 | 10.995 | 10.998 | 14.720 | 13.522 | 17.469 |
| ENSG00000183458 | AC138932.1 | NA | -0.610 | 0.122 | -4.993 | 5.94E-07 | 1.77E-04 | 1.225 | 1.146 | 1.432 | 0.900 | 0.796 | 0.772 |
| ENSG00000108465 | CDK5RAP3 | 17q21.32 | -0.609 | 0.122 | -4.988 | 6.10E-07 | 1.77E-04 | 1.578 | 1.548 | 1.915 | 1.277 | 1.010 | 0.988 |
| ENSG00000162733 | DDR2 | 1q23.3 | -0.523 | 0.105 | -4.961 | 7.02E-07 | 1.99E-04 | 5.136 | 5.543 | 5.781 | 4.315 | 4.313 | 2.780 |
| ENSG00000140400 | MAN2C1 | 15q24.2 | -0.405 | 0.082 | -4.953 | 7.31E-07 | 2.01E-04 | 4.480 | 4.813 | 5.468 | 4.109 | 3.352 | 3.575 |
| ENSG00000136942 | RPL35 | 9q33.3 | 0.267 | 0.054 | 4.931 | 8.18E-07 | 2.16E-04 | 134.083 | 150.639 | 151.812 | 175.909 | 181.563 | 163.682 |
| ENSG00000188229 | TUBB4B | 9q34.3 | 0.361 | 0.073 | 4.929 | 8.26E-07 | 2.16E-04 | 49.944 | 50.749 | 48.776 | 61.993 | 60.623 | 67.617 |
| ENSG00000171314 | PGAM1 | 10q24.1 | 0.300 | 0.061 | 4.894 | 9.86E-07 | 2.52E-04 | 62.201 | 66.936 | 62.628 | 76.678 | 79.525 | 78.054 |

Table S4. Differential expression analysis in HEK293T cells after the *Alu* insertion was deleted.

| ENSG0000075826 | SEC31B | 10q24.31 | -0.607 | 0.125 | -4.857 | 1.19E-06 | 2.97E-04 | 0.938 | 1.143 | 1.299 | 0.774 | 0.703 | 0.716 |
|-----------------|------------|----------|--------|-------|--------|----------|----------|---------|---------|---------|---------|---------|---------|
| ENSG00000177700 | POLR2L | 11p15.5 | 0.450 | 0.094 | 4.811 | 1.51E-06 | 3.59E-04 | 14.253 | 16.893 | 13.993 | 20.571 | 20.196 | 20.522 |
| ENSG00000146830 | GIGYF1 | 7q22.1 | -0.320 | 0.067 | -4.808 | 1.53E-06 | 3.59E-04 | 9.624 | 9.969 | 10.240 | 8.695 | 7.576 | 7.446 |
| ENSG00000185189 | NRBP2 | 8q24.3 | -0.589 | 0.123 | -4.804 | 1.56E-06 | 3.59E-04 | 1.793 | 1.785 | 2.052 | 1.448 | 1.219 | 1.049 |
| ENSG00000099800 | TIMM13 | 19p13.3 | 0.363 | 0.076 | 4.801 | 1.58E-06 | 3.59E-04 | 15.050 | 15.204 | 15.223 | 18.571 | 19.316 | 20.093 |
| ENSG00000184381 | PLA2G6 | 22q13.1 | -0.571 | 0.119 | -4.795 | 1.63E-06 | 3.62E-04 | 1.343 | 1.360 | 1.510 | 1.090 | 0.922 | 0.805 |
| ENSG00000168439 | STIP1 | 11q13.1 | 0.320 | 0.067 | 4.787 | 1.69E-06 | 3.70E-04 | 25.467 | 26.185 | 24.946 | 30.681 | 31.477 | 32.713 |
| ENSG00000176978 | DPP7 | 9q34.3 | -0.667 | 0.140 | -4.770 | 1.85E-06 | 3.94E-04 | 2.518 | 2.919 | 3.340 | 2.240 | 1.637 | 1.603 |
| ENSG00000132424 | PNISR | 6q16.2 | -0.306 | 0.064 | -4.765 | 1.89E-06 | 3.95E-04 | 5.718 | 5.916 | 6.616 | 4.758 | 5.211 | 4.663 |
| ENSG00000112715 | VEGFA | 6p21.1 | -0.398 | 0.084 | -4.751 | 2.03E-06 | 4.16E-04 | 2.820 | 3.190 | 3.417 | 2.725 | 2.304 | 2.073 |
| ENSG00000142102 | PGGHG | 11p15.5 | -0.517 | 0.110 | -4.720 | 2.36E-06 | 4.75E-04 | 3.459 | 3.725 | 4.370 | 3.249 | 2.482 | 2.277 |
| ENSG00000181026 | AEN | 15q26.1 | 0.350 | 0.075 | 4.692 | 2.71E-06 | 5.31E-04 | 4.717 | 5.002 | 4.954 | 6.021 | 6.103 | 6.411 |
| ENSG00000158545 | ZC3H18 | 16q24.2 | 0.315 | 0.067 | 4.689 | 2.74E-06 | 5.31E-04 | 4.237 | 4.356 | 4.635 | 5.423 | 5.339 | 5.536 |
| ENSG00000163629 | PTPN13 | 4q21.3 | -0.330 | 0.070 | -4.685 | 2.80E-06 | 5.33E-04 | 7.093 | 6.788 | 7.085 | 6.060 | 5.611 | 4.910 |
| ENSG00000134333 | LDHA | 11p15.1 | 0.263 | 0.056 | 4.665 | 3.09E-06 | 5.77E-04 | 55.150 | 62.681 | 60.945 | 72.173 | 74.747 | 65.974 |
| ENSG00000169976 | SF3B5 | 6q24.2 | 0.320 | 0.069 | 4.650 | 3.31E-06 | 6.08E-04 | 60.989 | 67.214 | 62.337 | 79.850 | 77.950 | 78.337 |
| ENSG00000179115 | FARSA | 19p13.13 | 0.302 | 0.065 | 4.633 | 3.60E-06 | 6.43E-04 | 28.117 | 29.112 | 31.465 | 35.310 | 35.405 | 37.523 |
| ENSG00000104979 | C19orf53 | 19p13.13 | 0.360 | 0.078 | 4.631 | 3.64E-06 | 6.43E-04 | 17.199 | 18.153 | 17.131 | 22.272 | 23.042 | 21.613 |
| ENSG00000185324 | CDK10 | 16q24.3 | -0.400 | 0.086 | -4.628 | 3.68E-06 | 6.43E-04 | 3.508 | 3.550 | 4.029 | 3.018 | 2.528 | 2.773 |
| ENSG0000087088 | BAX | 19q13.33 | 0.384 | 0.083 | 4.625 | 3.75E-06 | 6.43E-04 | 7.583 | 8.570 | 7.837 | 10.107 | 10.384 | 10.565 |
| ENSG00000167615 | LENG8 | 19q13.42 | -0.353 | 0.076 | -4.614 | 3.95E-06 | 6.66E-04 | 16.260 | 18.255 | 20.579 | 16.138 | 13.525 | 13.081 |
| ENSG00000163945 | UVSSA | 4p16.3 | -0.487 | 0.106 | -4.606 | 4.11E-06 | 6.82E-04 | 0.997 | 1.091 | 1.364 | 0.919 | 0.769 | 0.748 |
| ENSG00000261409 | AL035425.3 | NA | -0.280 | 0.061 | -4.598 | 4.26E-06 | 6.97E-04 | 73.257 | 78.010 | 85.930 | 62.672 | 70.873 | 60.094 |
| ENSG00000160200 | CBS | 21q22.3 | -0.450 | 0.098 | -4.576 | 4.74E-06 | 7.63E-04 | 2.396 | 2.630 | 2.662 | 2.159 | 1.822 | 1.612 |
| ENSG00000100591 | AHSA1 | 14q24.3 | 0.312 | 0.068 | 4.567 | 4.94E-06 | 7.84E-04 | 15.496 | 16.508 | 15.746 | 19.323 | 19.548 | 19.934 |
| ENSG00000132635 | PCED1A | 20p13 | -0.409 | 0.091 | -4.508 | 6.56E-06 | 1.02E-03 | 9.954 | 11.153 | 12.449 | 9.532 | 7.844 | 7.662 |
| ENSG0000070669 | ASNS | 7q21.3 | -0.593 | 0.132 | -4.502 | 6.74E-06 | 1.03E-03 | 2.021 | 2.105 | 2.514 | 1.731 | 1.517 | 1.122 |
| ENSG00000197903 | HIST1H2BK | 6p22.1 | 0.516 | 0.115 | 4.501 | 6.78E-06 | 1.03E-03 | 15.768 | 14.978 | 16.479 | 22.876 | 21.978 | 22.089 |
| ENSG00000113758 | DBN1 | 5q35.3 | 0.310 | 0.069 | 4.493 | 7.01E-06 | 1.04E-03 | 9.183 | 9.395 | 9.788 | 11.463 | 11.246 | 12.123 |
| ENSG00000101104 | PABPC1L | 20q13.12 | -0.412 | 0.092 | -4.493 | 7.03E-06 | 1.04E-03 | 3.659 | 4.415 | 4.669 | 3.429 | 3.213 | 2.851 |
| ENSG0000065911 | MTHFD2 | 2p13.1 | -0.361 | 0.081 | -4.480 | 7.47E-06 | 1.08E-03 | 31.487 | 31.293 | 30.791 | 25.307 | 27.334 | 19.912 |
| ENSG00000105447 | GRWD1 | 19q13.33 | 0.400 | 0.089 | 4.478 | 7.55E-06 | 1.08E-03 | 5.802 | 6.137 | 5.816 | 7.231 | 7.367 | 8.607 |
| ENSG00000182154 | MRPL41 | 9q34.3 | 0.394 | 0.089 | 4.452 | 8.52E-06 | 1.19E-03 | 13.475 | 15.153 | 12.967 | 18.242 | 18.692 | 17.431 |
| ENSG0000009694 | TENM1 | Xq25 | -0.397 | 0.090 | -4.422 | 9.78E-06 | 1.35E-03 | 3.270 | 3.468 | 4.561 | 2.889 | 3.027 | 2.572 |
| ENSG00000228253 | MT-ATP8 | NA | -0.449 | 0.102 | -4.408 | 1.04E-05 | 1.42E-03 | 222.354 | 248.850 | 307.612 | 206.287 | 159.274 | 197.248 |
| ENSG00000125445 | MRPS7 | 17q25.1 | 0.347 | 0.079 | 4.385 | 1.16E-05 | 1.53E-03 | 6.693 | 6.817 | 6.550 | 8.124 | 8.921 | 8.285 |
| ENSG00000215252 | GOLGA8B | 15q14 | -0.454 | 0.104 | -4.385 | 1.16E-05 | 1.53E-03 | 1.904 | 2.175 | 2.699 | 1.689 | 1.603 | 1.594 |
| ENSG00000119812 | FAM98A | 2p22.3 | 0.357 | 0.081 | 4.384 | 1.17E-05 | 1.53E-03 | 5.504 | 5.880 | 5.795 | 6.741 | 7.348 | 7.709 |
| ENSG00000250337 | PURPL | 5p14.1 | -0.469 | 0.107 | -4.375 | 1.21E-05 | 1.57E-03 | 4.184 | 4.697 | 5.175 | 3.215 | 3.795 | 3.056 |
| ENSG0000075624 | ACTB | 7p22.1 | 0.320 | 0.073 | 4.370 | 1.24E-05 | 1.57E-03 | 220.042 | 225.625 | 201.791 | 258.795 | 264.316 | 278.849 |
| ENSG00000109046 | WSB1 | 17q11.1 | -0.331 | 0.076 | -4.367 | 1.26E-05 | 1.57E-03 | 4.237 | 4.791 | 5.345 | 3.727 | 4.052 | 3.538 |
| ENSG00000122417 | ODF2L | 1p22.3 | -0.420 | 0.096 | -4.367 | 1.26E-05 | 1.57E-03 | 1.811 | 1.908 | 2.074 | 1.267 | 1.643 | 1.380 |
| ENSG00000160633 | SAFB | 19p13.3 | 0.302 | 0.069 | 4.350 | 1.36E-05 | 1.66E-03 | 9.442 | 9.821 | 9.761 | 11.624 | 11.388 | 12.447 |
| ENSG00000196155 | PLEKHG4 | 16q22.1 | -0.432 | 0.099 | -4.341 | 1.42E-05 | 1.71E-03 | 1.991 | 2.251 | 2.153 | 1.783 | 1.549 | 1.382 |

| ENSG00000167549 | CORO6 | 17q11.2 | -0.608 | 0.141 | -4.320 | 1.56E-05 | 1.85E-03 | 2.030 | 1.991 | 2.208 | 1.710 | 1.093 | 1.253 |
|-----------------|------------|------------|--------|-------|--------|----------|----------|--------|--------|--------|--------|--------|--------|
| ENSG00000223764 | AL645608.1 | 1p36.33 | -0.444 | 0.103 | -4.306 | 1.66E-05 | 1.95E-03 | 3.093 | 3.171 | 3.093 | 2.450 | 2.082 | 2.293 |
| ENSG00000127445 | PIN1 | 19p13.2 | 0.295 | 0.069 | 4.298 | 1.72E-05 | 1.96E-03 | 6.073 | 6.564 | 6.652 | 7.933 | 7.793 | 7.745 |
| ENSG00000235703 | LINC00894 | Xq28 | -0.683 | 0.159 | -4.298 | 1.72E-05 | 1.96E-03 | 0.653 | 0.652 | 0.692 | 0.420 | 0.415 | 0.399 |
| ENSG00000130023 | ERMARD | 6q27 | -0.473 | 0.110 | -4.295 | 1.74E-05 | 1.96E-03 | 2.149 | 2.400 | 2.458 | 1.839 | 1.639 | 1.534 |
| ENSG00000011260 | UTP18 | 17q21.33 | 0.340 | 0.079 | 4.295 | 1.74E-05 | 1.96E-03 | 10.003 | 10.406 | 10.071 | 12.191 | 12.695 | 13.352 |
| ENSG0000074935 | TUBE1 | 6q21 | -0.400 | 0.093 | -4.285 | 1.82E-05 | 2.03E-03 | 3.942 | 4.017 | 4.212 | 2.853 | 3.633 | 2.677 |
| ENSG00000188811 | NHLRC3 | 13q13.3 | -0.440 | 0.103 | -4.281 | 1.86E-05 | 2.05E-03 | 1.752 | 1.970 | 2.048 | 1.367 | 1.559 | 1.294 |
| ENSG00000135473 | PAN2 | 12q13.3 | -0.394 | 0.092 | -4.279 | 1.88E-05 | 2.05E-03 | 3.052 | 3.365 | 3.866 | 2.921 | 2.600 | 2.241 |
| ENSG00000215417 | MIR17HG | 13q31.3 | -0.503 | 0.118 | -4.272 | 1.94E-05 | 2.09E-03 | 2.380 | 2.598 | 2.894 | 1.705 | 2.055 | 1.742 |
| ENSG00000173110 | HSPA6 | 1q23.3 | 0.762 | 0.179 | 4.266 | 1.99E-05 | 2.12E-03 | 1.036 | 1.512 | 1.136 | 1.870 | 1.956 | 2.372 |
| ENSG00000115902 | SLC1A4 | 2p14 | -0.614 | 0.144 | -4.262 | 2.02E-05 | 2.12E-03 | 1.538 | 1.640 | 1.696 | 1.265 | 1.198 | 0.712 |
| ENSG00000135624 | CCT7 | 2p13.2 | 0.265 | 0.062 | 4.258 | 2.06E-05 | 2.13E-03 | 55.252 | 58.007 | 54.160 | 65.068 | 68.085 | 66.527 |
| ENSG0000074842 | MYDGF | 19p13.3 | 0.303 | 0.071 | 4.240 | 2.23E-05 | 2.28E-03 | 16.769 | 19.322 | 18.974 | 22.193 | 23.188 | 21.986 |
| ENSG00000175602 | CCDC85B | 11q13.1 | 0.402 | 0.095 | 4.239 | 2.25E-05 | 2.28E-03 | 10.050 | 11.344 | 11.030 | 13.996 | 13.068 | 15.350 |
| ENSG00000167553 | TUBA1C | 12q13.12 | 0.276 | 0.065 | 4.218 | 2.47E-05 | 2.47E-03 | 17.739 | 17.597 | 17.585 | 21.290 | 20.533 | 21.727 |
| ENSG00000221978 | CCNL2 | 1p36.33 | -0.294 | 0.070 | -4.212 | 2.53E-05 | 2.50E-03 | 8.210 | 9.245 | 9.529 | 7.966 | 6.949 | 6.913 |
| ENSG00000184076 | UQCR10 | 22q12.2 | 0.314 | 0.075 | 4.209 | 2.56E-05 | 2.51E-03 | 28.250 | 32.459 | 29.933 | 36.944 | 38.271 | 36.643 |
| ENSG0000096093 | EFHC1 | 6p12.2 | -0.458 | 0.109 | -4.203 | 2.63E-05 | 2.55E-03 | 0.476 | 0.475 | 0.563 | 0.380 | 0.401 | 0.313 |
| ENSG00000189306 | RRP7A | 22q13.2 | 0.296 | 0.071 | 4.201 | 2.66E-05 | 2.55E-03 | 11.610 | 12.805 | 12.245 | 14.637 | 14.575 | 15.407 |
| ENSG00000147383 | NSDHL | Xq28 | 0.339 | 0.081 | 4.199 | 2.68E-05 | 2.55E-03 | 8.693 | 9.134 | 9.396 | 10.933 | 11.671 | 11.512 |
| ENSG00000168010 | ATG16L2 | 11q13.4 | -0.645 | 0.154 | -4.190 | 2.79E-05 | 2.63E-03 | 0.731 | 0.883 | 1.199 | 0.698 | 0.563 | 0.515 |
| ENSG00000124762 | CDKN1A | 6p21.2 | 0.439 | 0.105 | 4.183 | 2.88E-05 | 2.69E-03 | 2.549 | 2.931 | 3.187 | 3.960 | 4.204 | 3.483 |
| ENSG00000160818 | GPATCH4 | 1q22-q23.1 | 0.336 | 0.081 | 4.169 | 3.06E-05 | 2.82E-03 | 6.454 | 6.924 | 6.436 | 8.041 | 8.069 | 8.690 |
| ENSG00000140939 | NOL3 | 16q22.1 | -0.652 | 0.156 | -4.167 | 3.09E-05 | 2.82E-03 | 1.366 | 1.429 | 1.598 | 0.909 | 0.940 | 0.919 |
| ENSG00000216866 | RPS2P55 | NA | 0.418 | 0.100 | 4.166 | 3.10E-05 | 2.82E-03 | 32.715 | 41.961 | 43.878 | 49.063 | 62.151 | 45.769 |
| ENSG00000126254 | RBM42 | 19q13.12 | 0.331 | 0.080 | 4.160 | 3.18E-05 | 2.87E-03 | 16.436 | 16.101 | 15.158 | 19.668 | 19.322 | 20.567 |
| ENSG00000172531 | PPP1CA | 11q13.2 | 0.274 | 0.066 | 4.141 | 3.45E-05 | 3.06E-03 | 17.983 | 18.864 | 17.915 | 21.810 | 22.148 | 21.769 |
| ENSG00000132382 | MYBBP1A | 17p13.2 | 0.272 | 0.066 | 4.130 | 3.63E-05 | 3.19E-03 | 14.590 | 15.463 | 15.515 | 17.966 | 17.522 | 19.018 |
| ENSG00000130669 | PAK4 | 19q13.2 | 0.276 | 0.067 | 4.099 | 4.14E-05 | 3.61E-03 | 4.092 | 4.155 | 4.315 | 5.117 | 5.050 | 4.919 |
| ENSG00000114857 | NKTR | 3p22.1 | -0.283 | 0.069 | -4.092 | 4.27E-05 | 3.69E-03 | 5.343 | 5.819 | 6.928 | 5.011 | 5.077 | 4.627 |
| ENSG00000112699 | GMDS | 6p25.3 | -0.439 | 0.108 | -4.085 | 4.40E-05 | 3.76E-03 | 3.153 | 3.016 | 3.732 | 2.786 | 2.316 | 2.134 |
| ENSG00000183426 | NPIPA1 | NA | -0.693 | 0.170 | -4.084 | 4.42E-05 | 3.76E-03 | 0.512 | 0.562 | 0.579 | 0.400 | 0.309 | 0.306 |
| ENSG00000126457 | PRMT1 | 19q13.33 | 0.291 | 0.071 | 4.073 | 4.64E-05 | 3.88E-03 | 15.904 | 15.992 | 15.350 | 18.789 | 18.553 | 19.976 |
| ENSG00000264112 | AC015813.1 | NA | -0.410 | 0.101 | -4.068 | 4.74E-05 | 3.92E-03 | 2.606 | 3.070 | 3.387 | 2.318 | 2.506 | 1.939 |
| ENSG00000170606 | HSPA4 | 5q31.1 | 0.279 | 0.069 | 4.058 | 4.96E-05 | 4.00E-03 | 21.280 | 20.124 | 20.465 | 23.917 | 24.847 | 25.691 |
| ENSG00000011028 | MRC2 | 17q23.2 | -0.438 | 0.108 | -4.057 | 4.97E-05 | 4.00E-03 | 2.051 | 2.054 | 2.557 | 1.879 | 1.493 | 1.497 |
| ENSG00000108829 | LRRC59 | 17q21.33 | 0.269 | 0.067 | 4.041 | 5.32E-05 | 4.25E-03 | 14.200 | 14.657 | 14.049 | 16.724 | 17.179 | 17.390 |
| ENSG00000280322 | AL035425.4 | ŇA | -0.293 | 0.073 | -4.028 | 5.63E-05 | 4.44E-03 | 67.026 | 67.431 | 78.345 | 61.908 | 60.867 | 49.561 |
| ENSG0000086504 | MRPL28 | 16p13.3 | 0.285 | 0.071 | 4.024 | 5.71E-05 | 4.44E-03 | 11.657 | 12.226 | 12.696 | 14.289 | 15.007 | 14.861 |
| ENSG0000004777 | ARHGAP33 | 19q13.12 | -0.537 | 0.134 | -4.024 | 5.73E-05 | 4.44E-03 | 1.244 | 1.146 | 1.325 | 0.945 | 0.806 | 0.788 |
| ENSG00000257270 | AL928654.3 | NA | -0.614 | 0.153 | -4.007 | 6.16E-05 | 4.74E-03 | 10.050 | 10.970 | 11.105 | 7.026 | 6.367 | 7.396 |
| ENSG00000145362 | ANK2 | 4q25-q26 | -0.387 | 0.097 | -3.995 | 6.46E-05 | 4.94E-03 | 1.180 | 1.155 | 1.316 | 1.002 | 1.023 | 0.749 |
| ENSG00000248498 | ASNSP1 | NA | -0.677 | 0.170 | -3.985 | 6.74E-05 | 5.08E-03 | 2.302 | 2.601 | 3.043 | 1.926 | 1.969 | 1.051 |

| ENSG00000160193 | WDR4 | 21q22.3 | 0.405 | 0.102 | 3.980 | 6.88E-05 | 5.15E-03 | 4.732 | 4.962 | 4.571 | 5.905 | 6.025 | 6.794 |
|-----------------|------------|----------|--------|-------|--------|----------|----------|--------|--------|--------|--------|--------|--------|
| ENSG00000188747 | NOXA1 | 9q34.3 | -0.665 | 0.168 | -3.962 | 7.42E-05 | 5.47E-03 | 2.574 | 2.518 | 3.476 | 2.093 | 1.751 | 1.502 |
| ENSG00000150990 | DHX37 | 12q24.31 | 0.412 | 0.105 | 3.942 | 8.09E-05 | 5.87E-03 | 5.284 | 4.935 | 4.811 | 6.100 | 6.012 | 7.687 |
| ENSG00000145912 | NHP2 | 5q35.3 | 0.266 | 0.068 | 3.941 | 8.12E-05 | 5.87E-03 | 36.939 | 40.190 | 36.965 | 44.603 | 47.060 | 44.575 |
| ENSG00000225177 | AL590617.2 | ŇA | -0.754 | 0.191 | -3.940 | 8.14E-05 | 5.87E-03 | 4.075 | 4.512 | 5.379 | 3.440 | 3.165 | 1.639 |
| ENSG00000189159 | JPT1 | 17q25.1 | 0.301 | 0.076 | 3.937 | 8.25E-05 | 5.88E-03 | 8.967 | 8.979 | 8.988 | 10.350 | 11.237 | 11.313 |
| ENSG00000154059 | IMPACT | 18q11.2 | -0.346 | 0.088 | -3.937 | 8.26E-05 | 5.88E-03 | 6.568 | 6.432 | 6.148 | 4.899 | 5.675 | 4.418 |
| ENSG00000177595 | PIDD1 | 11p15.5 | -0.366 | 0.093 | -3.925 | 8.67E-05 | 6.08E-03 | 2.986 | 3.055 | 3.489 | 2.777 | 2.328 | 2.226 |
| ENSG00000278041 | AL133325.3 | NA | -0.497 | 0.127 | -3.925 | 8.68E-05 | 6.08E-03 | 3.061 | 3.817 | 4.179 | 3.165 | 2.513 | 2.098 |
| ENSG00000130254 | SAFB2 | 19p13.3 | 0.360 | 0.092 | 3.924 | 8.72E-05 | 6.08E-03 | 4.529 | 4.894 | 4.710 | 5.696 | 5.555 | 6.696 |
| ENSG00000166963 | MAP1A | 15q15.3 | 0.528 | 0.135 | 3.920 | 8.84E-05 | 6.08E-03 | 0.437 | 0.385 | 0.442 | 0.574 | 0.602 | 0.627 |
| ENSG00000106305 | AIMP2 | 7p22.1 | 0.394 | 0.101 | 3.918 | 8.91E-05 | 6.08E-03 | 6.955 | 7.226 | 6.733 | 8.424 | 9.066 | 9.770 |
| ENSG00000100219 | XBP1 | 22q12 | -0.302 | 0.077 | -3.916 | 9.00E-05 | 6.08E-03 | 26.687 | 28.114 | 28.005 | 25.750 | 21.506 | 19.518 |
| ENSG00000130706 | ADRM1 | 20q13.33 | 0.312 | 0.080 | 3.915 | 9.05E-05 | 6.08E-03 | 13.334 | 14.461 | 13.757 | 16.296 | 16.862 | 17.982 |
| ENSG00000277972 | CISD3 | 17q12 | 0.495 | 0.126 | 3.914 | 9.06E-05 | 6.08E-03 | 1.802 | 1.745 | 1.795 | 2.614 | 2.498 | 2.362 |
| ENSG00000250251 | PKD1P6 | NA | -0.406 | 0.104 | -3.914 | 9.06E-05 | 6.08E-03 | 1.927 | 1.836 | 2.236 | 1.609 | 1.497 | 1.378 |
| ENSG00000175265 | GOLGA8A | 15q14 | -0.393 | 0.101 | -3.901 | 9.58E-05 | 6.39E-03 | 3.387 | 4.507 | 4.972 | 3.483 | 3.140 | 3.062 |
| ENSG00000198860 | TSEN15 | 1q25.3 | -0.390 | 0.101 | -3.877 | 1.06E-04 | 6.98E-03 | 12.579 | 12.617 | 11.963 | 8.880 | 11.357 | 8.007 |
| ENSG00000184465 | WDR27 | 6q27 | -0.342 | 0.088 | -3.876 | 1.06E-04 | 6.98E-03 | 2.511 | 2.789 | 3.260 | 2.494 | 2.176 | 2.017 |
| ENSG00000164187 | LMBRD2 | 5p13.2 | -0.482 | 0.124 | -3.872 | 1.08E-04 | 7.05E-03 | 1.459 | 1.425 | 1.696 | 0.936 | 1.351 | 0.965 |
| ENSG00000160298 | C21orf58 | 21q22.3 | -0.405 | 0.105 | -3.857 | 1.15E-04 | 7.42E-03 | 2.622 | 2.835 | 3.433 | 2.494 | 2.247 | 1.913 |
| ENSG00000183856 | IQGAP3 | 1q22 | -0.295 | 0.077 | -3.849 | 1.19E-04 | 7.54E-03 | 6.733 | 7.298 | 8.339 | 6.635 | 6.123 | 5.321 |
| ENSG00000171421 | MRPL36 | 5p15.33 | 0.458 | 0.119 | 3.848 | 1.19E-04 | 7.54E-03 | 5.177 | 5.700 | 5.492 | 7.128 | 6.850 | 8.279 |
| ENSG00000167447 | SMG8 | 17q22 | 0.369 | 0.096 | 3.842 | 1.22E-04 | 7.66E-03 | 2.906 | 3.141 | 2.942 | 3.778 | 3.809 | 3.931 |
| ENSG00000175309 | PHYKPL | 5q35.3 | -0.355 | 0.092 | -3.840 | 1.23E-04 | 7.67E-03 | 3.004 | 3.356 | 3.777 | 3.028 | 2.568 | 2.266 |
| ENSG00000276550 | HERC2P2 | 15q11.2 | -0.322 | 0.084 | -3.836 | 1.25E-04 | 7.75E-03 | 5.795 | 6.161 | 7.400 | 5.740 | 4.797 | 4.794 |
| ENSG00000140398 | NEIL1 | 15q24.2 | -0.457 | 0.119 | -3.830 | 1.28E-04 | 7.87E-03 | 1.652 | 1.747 | 1.991 | 1.587 | 1.152 | 1.156 |
| ENSG00000107815 | TWNK | 10q24.31 | 0.353 | 0.092 | 3.827 | 1.30E-04 | 7.87E-03 | 4.640 | 4.223 | 4.515 | 5.561 | 5.432 | 5.938 |
| ENSG00000150627 | WDR17 | 4q34.2 | -0.432 | 0.113 | -3.826 | 1.30E-04 | 7.87E-03 | 1.278 | 1.322 | 1.421 | 0.982 | 1.137 | 0.840 |
| ENSG00000177239 | MAN1B1 | 9q34.3 | -0.307 | 0.080 | -3.826 | 1.30E-04 | 7.87E-03 | 2.963 | 3.063 | 3.647 | 2.676 | 2.554 | 2.508 |
| ENSG0000053372 | MRTO4 | 1p36.13 | 0.356 | 0.093 | 3.824 | 1.31E-04 | 7.89E-03 | 6.291 | 6.771 | 6.151 | 7.756 | 7.913 | 8.725 |
| ENSG00000125656 | CLPP | 19p13.3 | 0.282 | 0.074 | 3.819 | 1.34E-04 | 8.00E-03 | 14.100 | 14.941 | 13.980 | 16.861 | 17.649 | 17.399 |
| ENSG00000171858 | RPS21 | 20q13.33 | 0.270 | 0.071 | 3.815 | 1.36E-04 | 8.10E-03 | 46.400 | 52.065 | 51.098 | 56.709 | 65.524 | 56.733 |
| ENSG00000160323 | ADAMTS13 | 9q34.2 | -0.558 | 0.146 | -3.814 | 1.37E-04 | 8.10E-03 | 1.826 | 2.483 | 2.920 | 2.048 | 1.368 | 1.438 |
| ENSG00000214425 | LRRC37A4P | NA | -0.448 | 0.117 | -3.812 | 1.38E-04 | 8.10E-03 | 1.078 | 1.162 | 1.176 | 0.860 | 0.806 | 0.818 |
| ENSG00000136045 | PWP1 | 12q23.3 | 0.273 | 0.072 | 3.809 | 1.40E-04 | 8.16E-03 | 10.471 | 10.770 | 10.725 | 12.361 | 13.084 | 12.857 |
| ENSG00000132002 | DNAJB1 | 19p13.12 | 0.342 | 0.090 | 3.801 | 1.44E-04 | 8.29E-03 | 8.494 | 9.261 | 9.233 | 10.212 | 11.042 | 12.589 |
| ENSG00000128626 | MRPS12 | 19q13.2 | 0.434 | 0.114 | 3.801 | 1.44E-04 | 8.29E-03 | 5.425 | 5.920 | 5.422 | 7.032 | 6.803 | 8.599 |
| ENSG00000173275 | ZNF449 | Xq26.3 | -0.387 | 0.102 | -3.794 | 1.48E-04 | 8.48E-03 | 2.280 | 2.403 | 2.660 | 1.896 | 2.067 | 1.610 |
| ENSG00000265972 | TXNIP | 1q21.1 | -0.400 | 0.106 | -3.793 | 1.49E-04 | 8.48E-03 | 4.892 | 5.257 | 6.269 | 4.685 | 4.336 | 3.322 |
| ENSG00000164442 | CITED2 | 6q24.1 | 0.300 | 0.079 | 3.789 | 1.51E-04 | 8.56E-03 | 8.215 | 8.885 | 9.899 | 11.683 | 10.464 | 10.757 |
| ENSG00000120800 | UTP20 | 12q23.2 | 0.320 | 0.085 | 3.787 | 1.52E-04 | 8.57E-03 | 3.269 | 3.365 | 3.015 | 3.816 | 3.959 | 4.185 |
| ENSG00000140450 | ARRDC4 | 15q26.2 | -0.486 | 0.129 | -3.777 | 1.59E-04 | 8.86E-03 | 4.318 | 4.688 | 5.854 | 4.286 | 3.690 | 2.558 |
| ENSG00000145494 | NDUFS6 | 5p15.33 | 0.296 | 0.079 | 3.771 | 1.63E-04 | 8.97E-03 | 14.604 | 14.989 | 14.516 | 17.474 | 19.092 | 17.228 |

| ENSG00000142002 | DPP9 | 19p13.3 | 0.321 | 0.086 | 3.753 | 1.75E-04 | 9.48E-03 | 3.231 | 3.484 | 3.258 | 3.905 | 4.009 | 4.435 |
|--|--|--|---|---|--|--|--|---|--|---|--|--|--|
| ENSG00000179912 | R3HDM2 | 12q13.3 | -0.423 | 0.113 | -3.743 | 1.82E-04 | 9.82E-03 | 2.653 | 2.592 | 3.105 | 2.391 | 2.194 | 1.606 |
| ENSG00000130707 | ASS1 | 9q34.11 | -0.415 | 0.111 | -3.741 | 1.83E-04 | 9.82E-03 | 7.180 | 7.385 | 9.217 | 6.769 | 6.385 | 4.556 |
| ENSG0000004478 | FKBP4 | 12p13.33 | 0.271 | 0.073 | 3.732 | 1.90E-04 | 1.00E-02 | 20.987 | 21.735 | 20.879 | 24.805 | 24.183 | 27.065 |
| ENSG00000138834 | MAPK8IP3 | 16p13.3 | -0.316 | 0.085 | -3.727 | 1.94E-04 | 1.02E-02 | 3.077 | 3.303 | 3.875 | 3.048 | 2.542 | 2.564 |
| ENSG00000187535 | IFT140 | 16p13.3 | -0.316 | 0.085 | -3.715 | 2.03E-04 | 1.06E-02 | 2.630 | 2.613 | 3.132 | 2.402 | 2.243 | 2.020 |
| ENSG00000175548 | ALG10B | 12q12 | -0.468 | 0.126 | -3.713 | 2.05E-04 | 1.07E-02 | 1.732 | 1.710 | 1.847 | 0.976 | 1.600 | 1.214 |
| ENSG0000009950 | MLXIPL | 7q11.23 | -0.488 | 0.132 | -3.705 | 2.11E-04 | 1.09E-02 | 1.977 | 2.035 | 2.301 | 1.881 | 1.303 | 1.285 |
| ENSG00000261236 | BOP1 | 8q24.3 | 0.281 | 0.076 | 3.696 | 2.19E-04 | 1.12E-02 | 14.163 | 14.148 | 13.838 | 17.075 | 15.841 | 17.872 |
| ENSG00000168701 | TMEM208 | 16q22.1 | 0.400 | 0.108 | 3.696 | 2.19E-04 | 1.12E-02 | 4.350 | 5.143 | 4.556 | 5.944 | 6.400 | 6.074 |
| ENSG00000249115 | HAUS5 | 19q13.12 | -0.281 | 0.076 | -3.696 | 2.19E-04 | 1.12E-02 | 6.725 | 6.863 | 7.471 | 6.249 | 5.967 | 5.000 |
| ENSG0000088538 | DOCK3 | 3p21.2 | -0.389 | 0.105 | -3.691 | 2.23E-04 | 1.13E-02 | 1.993 | 2.263 | 2.739 | 2.018 | 1.774 | 1.499 |
| ENSG00000150779 | TIMM8B | 11q23.1 | 0.358 | 0.097 | 3.691 | 2.24E-04 | 1.13E-02 | 10.848 | 12.358 | 11.203 | 14.619 | 13.823 | 15.293 |
| ENSG00000103035 | PSMD7 | 16q23.1 | 0.282 | 0.076 | 3.690 | 2.24E-04 | 1.13E-02 | 8.238 | 8.331 | 8.759 | 9.824 | 10.294 | 10.393 |
| ENSG0000070495 | JMJD6 | 17q25.1 | 0.404 | 0.110 | 3.687 | 2.27E-04 | 1.14E-02 | 1.441 | 1.464 | 1.649 | 1.873 | 1.909 | 2.174 |
| ENSG00000169504 | CLIC4 | 1p36.11 | -0.335 | 0.091 | -3.685 | 2.28E-04 | 1.14E-02 | 18.259 | 18.205 | 17.752 | 13.373 | 17.209 | 12.212 |
| ENSG00000241553 | ARPC4 | 3p25.3 | 0.396 | 0.108 | 3.684 | 2.30E-04 | 1.14E-02 | 2.272 | 2.571 | 2.262 | 3.033 | 3.339 | 2.927 |
| ENSG00000161010 | MRNIP | 5q35.3 | -0.329 | 0.089 | -3.677 | 2.36E-04 | 1.16E-02 | 2.241 | 2.354 | 2.815 | 2.112 | 1.880 | 1.849 |
| ENSG00000104853 | CLPTM1 | 19q13.32 | 0.269 | 0.073 | 3.676 | 2.37E-04 | 1.16E-02 | 9.030 | 9.275 | 8.692 | 10.779 | 10.443 | 11.071 |
| ENSG0000039650 | PNKP | 19q13.33 | -0.297 | 0.081 | -3.672 | 2.40E-04 | 1.17E-02 | 4.004 | 4.119 | 4.431 | 3.479 | 3.477 | 3.178 |
| ENSG00000165810 | BTNL9 | 5q35.3 | -0.450 | 0.123 | -3.670 | 2.42E-04 | 1.17E-02 | 1.607 | 1.727 | 2.045 | 1.520 | 1.305 | 1.082 |
| ENSG00000244754 | N4BP2L2 | 13q13.1 | -0.289 | 0.079 | -3.663 | 2.49E-04 | 1.20E-02 | 2.182 | 2.486 | 2.687 | 1.912 | 2.216 | 1.838 |
| ENSG00000135069 | PSAT1 | 9q21.2 | -0.333 | 0.091 | -3.660 | 2.52E-04 | 1.20E-02 | 103.155 | 106.682 | 100.506 | 88.430 | 93.413 | 63.847 |
| ENSG00000160781 | PAQR6 | 1q22 | -0.574 | 0.157 | -3.658 | 2.54E-04 | 1.20E-02 | 2.243 | 2.457 | 2.815 | 2.107 | 1.626 | 1.281 |
| ENSG00000112578 | BYSL | 6p21.1 | 0.286 | 0.078 | 3.658 | 2.54E-04 | 1.20E-02 | 9.213 | 9.016 | 9.262 | 10.784 | 11.473 | 10.990 |
| ENSG00000105676 | ARMC6 | 19p13.11 | 0.359 | 0.098 | 3.656 | 2.56E-04 | 1.21E-02 | 3.799 | 4.005 | 3.774 | 4.635 | 4.692 | 5.383 |
| ENSG00000153879 | CEBPG | 19q13.11 | -0.278 | 0.076 | -3.650 | 2.62E-04 | 1.23E-02 | 10.587 | 10.777 | 11.483 | 9.584 | 9.734 | 7.608 |
| ENSG00000144736 | SHQ1 | 3p13 | 0.364 | 0.100 | 3.645 | 2.67E-04 | 1.24E-02 | 2.760 | 2.925 | 2.639 | 3.278 | 3.478 | 3.866 |
| ENSG00000159958 | TNFRSF13C | 22q13.2 | -0.564 | 0.155 | -3.645 | 2.68E-04 | 1.24E-02 | 1.703 | 2.604 | 2.973 | 1.900 | 1.559 | 1.410 |
| ENSG00000108592 | FTSJ3 | 17q23.3 | 0.273 | 0.075 | 3.642 | 2.71E-04 | 1 24E-02 | 6 864 | 6.789 | 6.575 | 7.778 | 8.263 | 8.214 |
| ENSG00000128294 | TPST2 | 22a12.1 | | | | | 1.2 12 02 | 0.001 | | | | | |
| ENSG00000114796 | | 22412.1 | 0.401 | 0.110 | 3.637 | 2.76E-04 | 1.25E-02 | 1.211 | 1.140 | 1.295 | 1.508 | 1.544 | 1.710 |
| | KLHL24 | 3q27.1 | 0.401 | 0.110 0.098 | 3.637 -3.636 | 2.76E-04 2.77E-04 | 1.25E-02 1.25E-02 | 1.211 1.351 | 1.140 1.520 | 1.295 1.578 | 1.508 1.114 | 1.544 1.208 | 1.710 1.125 |
| ENSG00000132199 | KLHL24 ENOSF1 | 3q27.1 18p11.32 | $ \begin{array}{r} 0.401 \\ -0.355 \\ -0.324 \end{array} $ | 0.110 0.098 0.089 | 3.637 -3.636 -3.635 | 2.76E-04 2.77E-04 2.78E-04 | 1.25E-02 1.25E-02 1.25E-02 1.25E-02 | 1.211 1.351 2.086 | 1.140 1.520 2.455 | 1.295 1.578 2.530 | 1.508 1.114 2.068 | 1.544 1.208 1.929 | 1.710 1.125 1.611 |
| ENSG00000132199 ENSG00000198089 | KLHL24 ENOSF1 SFI1 | 3q27.1 18p11.32 22q12.2 | $ \begin{array}{r} 0.401 \\ -0.355 \\ -0.324 \\ -0.349 \end{array} $ | 0.110 0.098 0.089 0.096 | $ \begin{array}{r} 3.637 \\ -3.636 \\ -3.635 \\ -3.633 \\ \end{array} $ | 2.76E-04 2.77E-04 2.78E-04 2.80E-04 | 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 | 1.211 1.351 2.086 1.640 | 1.140 1.520 2.455 1.986 | 1.295 1.578 2.530 2.031 | 1.508 1.114 2.068 1.690 | 1.544 1.208 1.929 1.386 | 1.710 1.125 1.611 1.330 |
| ENSG00000132199 ENSG00000198089 ENSG00000072778 | KLHL24 ENOSF1 SFI1 ACADVL | 3q27.1 18p11.32 22q12.2 17p13.1 | $\begin{array}{r} 0.401 \\ -0.355 \\ -0.324 \\ -0.349 \\ -0.298 \end{array}$ | 0.110 0.098 0.089 0.096 0.082 | 3.637 -3.636 -3.635 -3.633 -3.633 | 2.76E-04 2.77E-04 2.78E-04 2.80E-04 2.80E-04 | 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 | 1.211 1.351 2.086 1.640 6.522 | 1.140 1.520 2.455 1.986 7.076 | 1.295 1.578 2.530 2.031 7.685 | 1.508 1.114 2.068 1.690 6.484 | 1.544 1.208 1.929 1.386 5.327 | 1.710 1.125 1.611 1.330 5.352 |
| ENSG00000132199 ENSG00000198089 ENSG00000072778 ENSG00000132467 | KLHL24 ENOSF1 SFI1 ACADVL UTP3 | 3q27.1 18p11.32 22q12.2 17p13.1 4q13.3 | $\begin{array}{r} 0.401 \\ \hline -0.355 \\ \hline -0.324 \\ \hline -0.349 \\ \hline -0.298 \\ \hline 0.305 \end{array}$ | 0.110 0.098 0.089 0.096 0.082 0.084 | $\begin{array}{r} 3.637 \\ \hline -3.636 \\ \hline -3.635 \\ \hline -3.633 \\ \hline -3.633 \\ \hline 3.633 \end{array}$ | 2.76E-04 2.77E-04 2.78E-04 2.80E-04 2.80E-04 2.81E-04 | 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 | 1.211 1.351 2.086 1.640 6.522 6.741 | 1.140 1.520 2.455 1.986 7.076 7.414 | 1.295 1.578 2.530 2.031 7.685 7.347 | 1.508 1.114 2.068 1.690 6.484 8.905 | 1.544 1.208 1.929 1.386 5.327 8.787 | 1.710 1.125 1.611 1.330 5.352 8.662 |
| ENSG00000132199 ENSG00000198089 ENSG0000072778 ENSG00000132467 ENSG00000109066 | KLHL24 ENOSF1 SFI1 ACADVL UTP3 TMEM104 | 3q27.1 18p11.32 22q12.2 17p13.1 4q13.3 17q25.1 | $\begin{array}{r} 0.401 \\ \hline -0.355 \\ \hline -0.324 \\ \hline -0.349 \\ \hline -0.298 \\ \hline 0.305 \\ \hline 0.551 \\ \end{array}$ | 0.110 0.098 0.089 0.096 0.082 0.084 0.152 | $\begin{array}{r} 3.637 \\ \hline -3.636 \\ \hline -3.635 \\ \hline -3.633 \\ \hline -3.633 \\ \hline 3.633 \\ \hline 3.629 \\ \end{array}$ | 2.76E-04 2.77E-04 2.78E-04 2.80E-04 2.80E-04 2.81E-04 2.84E-04 | 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.26E-02 | 1.211 1.351 2.086 1.640 6.522 6.741 1.163 | 1.140 1.520 2.455 1.986 7.076 7.414 1.247 | 1.295 1.578 2.530 2.031 7.685 7.347 1.106 | 1.508 1.114 2.068 1.690 6.484 8.905 1.594 | 1.544 1.208 1.929 1.386 5.327 8.787 1.415 | 1.710 1.125 1.611 1.330 5.352 8.662 2.086 |
| ENSG00000132199 ENSG00000132199 ENSG00000198089 ENSG0000012778 ENSG00000132467 ENSG00000109066 ENSG00000167085 | KLHL24 ENOSF1 SFI1 ACADVL UTP3 TMEM104 PHB | 22q12.1 3q27.1 18p11.32 22q12.2 17p13.1 4q13.3 17q25.1 17q21.33 | $\begin{array}{r} 0.401 \\ -0.355 \\ -0.324 \\ -0.349 \\ -0.298 \\ 0.305 \\ 0.551 \\ 0.283 \end{array}$ | 0.110 0.098 0.089 0.096 0.082 0.084 0.152 0.078 | $\begin{array}{r} 3.637 \\ \hline -3.636 \\ \hline -3.635 \\ \hline -3.633 \\ \hline -3.633 \\ \hline 3.633 \\ \hline 3.629 \\ \hline 3.628 \\ \end{array}$ | 2.76E-04 2.77E-04 2.78E-04 2.80E-04 2.80E-04 2.81E-04 2.84E-04 2.86E-04 | 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.26E-02 1.26E-02 | 1.211 1.351 2.086 1.640 6.522 6.741 1.163 14.983 | 1.140 1.520 2.455 1.986 7.076 7.414 1.247 16.268 | 1.295 1.578 2.530 2.031 7.685 7.347 1.106 13.968 | 1.508 1.114 2.068 1.690 6.484 8.905 1.594 17.911 | 1.544 1.208 1.929 1.386 5.327 8.787 1.415 18.214 | 1.710 1.125 1.611 1.330 5.352 8.662 2.086 18.520 |
| ENSG00000132199 ENSG00000132199 ENSG00000198089 ENSG0000012778 ENSG00000132467 ENSG00000109066 ENSG00000167085 ENSG00000204388 | KLHL24 ENOSF1 SFI1 ACADVL UTP3 TMEM104 PHB HSPA1B | 3q27.1 18p11.32 22q12.2 17p13.1 4q13.3 17q25.1 17q21.33 6p21.33 | $\begin{array}{r} 0.401 \\ \hline -0.355 \\ \hline -0.324 \\ \hline -0.349 \\ \hline -0.298 \\ \hline 0.305 \\ \hline 0.551 \\ \hline 0.283 \\ \hline 0.658 \end{array}$ | 0.110 0.098 0.089 0.096 0.082 0.084 0.152 0.078 0.183 | $\begin{array}{r} 3.637 \\ \hline -3.636 \\ \hline -3.635 \\ \hline -3.633 \\ \hline -3.633 \\ \hline 3.633 \\ \hline 3.629 \\ \hline 3.628 \\ \hline 3.605 \end{array}$ | 2.76E-04 2.77E-04 2.78E-04 2.80E-04 2.80E-04 2.81E-04 2.84E-04 2.86E-04 3.12E-04 | 1.25E-02 1.26E-02 1.26E-02 1.34E-02 | 1.211 1.351 2.086 1.640 6.522 6.741 1.163 14.983 18.996 | 1.140 1.520 2.455 1.986 7.076 7.414 1.247 16.268 22.383 | 1.295 1.578 2.530 2.031 7.685 7.347 1.106 13.968 23.378 | 1.508 1.114 2.068 1.690 6.484 8.905 1.594 17.911 30.096 | 1.544 1.208 1.929 1.386 5.327 8.787 1.415 18.214 30.535 | $\begin{array}{r} 1.710\\ \hline 1.125\\ \hline 1.611\\ \hline 1.330\\ \hline 5.352\\ \hline 8.662\\ \hline 2.086\\ \hline 18.520\\ \hline 40.069\\ \end{array}$ |
| ENSG00000132199 ENSG00000132199 ENSG00000198089 ENSG0000012778 ENSG00000132467 ENSG00000109066 ENSG00000167085 ENSG00000204388 ENSG00000138658 | KLHL24 ENOSF1 SFI1 ACADVL UTP3 TMEM104 PHB HSPA1B ZGRF1 | 3q27.1 3q27.1 18p11.32 22q12.2 17p13.1 4q13.3 17q25.1 17q21.33 6p21.33 4q25 | $\begin{array}{r} 0.401 \\ \hline -0.355 \\ \hline -0.324 \\ \hline -0.349 \\ \hline -0.298 \\ \hline 0.305 \\ \hline 0.551 \\ \hline 0.283 \\ \hline 0.658 \\ \hline -0.339 \end{array}$ | 0.110 0.098 0.089 0.096 0.082 0.084 0.152 0.078 0.183 0.094 | $\begin{array}{r} 3.637 \\ \hline -3.636 \\ \hline -3.635 \\ \hline -3.633 \\ \hline -3.633 \\ \hline 3.633 \\ \hline 3.629 \\ \hline 3.628 \\ \hline 3.605 \\ \hline -3.601 \\ \end{array}$ | 2.76E-04 2.77E-04 2.78E-04 2.80E-04 2.80E-04 2.81E-04 2.84E-04 2.86E-04 3.12E-04 3.17E-04 | 1.25E-02 1.26E-02 1.26E-02 1.34E-02 1.36E-02 | 1.211 1.351 2.086 1.640 6.522 6.741 1.163 14.983 18.996 2.180 | 1.140 1.520 2.455 1.986 7.076 7.414 1.247 16.268 22.383 2.469 | 1.295 1.578 2.530 2.031 7.685 7.347 1.106 13.968 23.378 2.946 | 1.508 1.114 2.068 1.690 6.484 8.905 1.594 17.911 30.096 2.096 | 1.544 1.208 1.929 1.386 5.327 8.787 1.415 18.214 30.535 2.103 | 1.710 1.125 1.611 1.330 5.352 8.662 2.086 18.520 40.069 1.746 |
| ENSG00000132199 ENSG00000132199 ENSG00000198089 ENSG0000012778 ENSG00000132467 ENSG0000019066 ENSG00000167085 ENSG00000204388 ENSG00000138658 ENSG00000239306 | KLHL24 ENOSF1 SFI1 ACADVL UTP3 TMEM104 PHB HSPA1B ZGRF1 RBM14 | 22q12.1 3q27.1 18p11.32 22q12.2 17p13.1 4q13.3 17q25.1 17q21.33 6p21.33 4q25 11q13.2 | $\begin{array}{r} 0.401 \\ -0.355 \\ -0.324 \\ -0.349 \\ -0.298 \\ 0.305 \\ 0.551 \\ 0.283 \\ 0.658 \\ -0.339 \\ 0.291 \end{array}$ | 0.110 0.098 0.089 0.096 0.082 0.084 0.152 0.078 0.183 0.094 0.081 | $\begin{array}{r} 3.637 \\ \hline -3.636 \\ \hline -3.635 \\ \hline -3.633 \\ \hline -3.633 \\ \hline 3.633 \\ \hline 3.629 \\ \hline 3.628 \\ \hline 3.605 \\ \hline -3.601 \\ \hline 3.588 \\ \end{array}$ | 2.76E-04 2.77E-04 2.78E-04 2.80E-04 2.80E-04 2.81E-04 2.84E-04 2.86E-04 3.12E-04 3.17E-04 3.33E-04 | 1.25E-02 1.26E-02 1.26E-02 1.34E-02 1.36E-02 1.41E-02 | 1.211 1.351 2.086 1.640 6.522 6.741 1.163 14.983 18.996 2.180 9.517 | 1.140 1.520 2.455 1.986 7.076 7.414 1.247 16.268 22.383 2.469 10.112 | 1.295 1.578 2.530 2.031 7.685 7.347 1.106 13.968 23.378 2.946 9.100 | 1.508 1.114 2.068 1.690 6.484 8.905 1.594 17.911 30.096 2.096 11.091 | 1.544 1.208 1.929 1.386 5.327 8.787 1.415 18.214 30.535 2.103 11.605 | 1.710 1.125 1.611 1.330 5.352 8.662 2.086 18.520 40.069 1.746 12.191 |
| ENSG00000132199 ENSG00000132199 ENSG00000198089 ENSG0000012778 ENSG00000132467 ENSG00000109066 ENSG00000167085 ENSG00000204388 ENSG00000138658 ENSG00000239306 ENSG00000110888 | KLHL24 ENOSF1 SFI1 ACADVL UTP3 TMEM104 PHB HSPA1B ZGRF1 RBM14 CAPRIN2 | 22q12.1 3q27.1 18p11.32 22q12.2 17p13.1 4q13.3 17q25.1 17q21.33 6p21.33 4q25 11q13.2 12p11.21 | $\begin{array}{r} 0.401 \\ -0.355 \\ -0.324 \\ -0.349 \\ -0.298 \\ 0.305 \\ 0.551 \\ 0.283 \\ 0.658 \\ -0.339 \\ 0.291 \\ -0.358 \end{array}$ | 0.110 0.098 0.089 0.082 0.084 0.152 0.078 0.183 0.094 0.081 0.100 | $\begin{array}{r} 3.637 \\ \hline -3.636 \\ \hline -3.635 \\ \hline -3.633 \\ \hline -3.633 \\ \hline 3.633 \\ \hline 3.629 \\ \hline 3.628 \\ \hline 3.605 \\ \hline -3.601 \\ \hline 3.588 \\ \hline -3.587 \\ \end{array}$ | 2.76E-04 2.77E-04 2.78E-04 2.80E-04 2.80E-04 2.81E-04 2.84E-04 2.86E-04 3.12E-04 3.17E-04 3.33E-04 3.34E-04 | 1.25E-02 1.26E-02 1.36E-02 1.36E-02 1.41E-02 1.41E-02 | 1.211 1.351 2.086 1.640 6.522 6.741 1.163 14.983 18.996 2.180 9.517 1.521 | 1.140 1.520 2.455 1.986 7.076 7.414 1.247 16.268 22.383 2.469 10.112 1.533 | 1.295 1.578 2.530 2.031 7.685 7.347 1.106 13.968 23.378 2.946 9.100 1.851 | 1.508 1.114 2.068 1.690 6.484 8.905 1.594 17.911 30.096 2.096 11.091 1.375 | 1.544 1.208 1.929 1.386 5.327 8.787 1.415 18.214 30.535 2.103 11.605 1.260 | 1.710 1.125 1.611 1.330 5.352 8.662 2.086 18.520 40.069 1.746 12.191 1.154 |
| ENSG00000132199 ENSG00000132199 ENSG00000198089 ENSG0000012467 ENSG00000109066 ENSG00000167085 ENSG00000167085 ENSG00000138658 ENSG00000138658 ENSG00000110888 ENSG00000169490 | KLHL24 ENOSF1 SFI1 ACADVL UTP3 TMEM104 PHB HSPA1B ZGRF1 RBM14 CAPRIN2 TM2D2 | 3q27.1 3q27.1 18p11.32 22q12.2 17p13.1 4q13.3 17q25.1 17q21.33 6p21.33 4q25 11q13.2 12p11.21 8p11.22 | $\begin{array}{r} 0.401 \\ -0.355 \\ -0.324 \\ -0.349 \\ -0.298 \\ 0.305 \\ 0.551 \\ 0.283 \\ 0.658 \\ -0.339 \\ 0.291 \\ -0.358 \\ 0.329 \\ \end{array}$ | 0.110 0.098 0.089 0.096 0.082 0.084 0.152 0.078 0.183 0.094 0.081 0.100 0.092 | $\begin{array}{r} 3.637 \\ \hline -3.636 \\ \hline -3.635 \\ \hline -3.633 \\ \hline -3.633 \\ \hline 3.633 \\ \hline 3.629 \\ \hline 3.628 \\ \hline 3.605 \\ \hline -3.601 \\ \hline 3.588 \\ \hline -3.587 \\ \hline 3.585 \\ \hline \end{array}$ | 2.76E-04 2.77E-04 2.78E-04 2.80E-04 2.80E-04 2.84E-04 2.86E-04 3.12E-04 3.17E-04 3.33E-04 3.34E-04 3.37E-04 | 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.25E-02 1.26E-02 1.26E-02 1.34E-02 1.36E-02 1.41E-02 1.41E-02 1.41E-02 | 1.211 1.351 2.086 1.640 6.522 6.741 1.163 14.983 18.996 2.180 9.517 1.521 2.617 | $\begin{array}{r} 1.140\\ 1.520\\ 2.455\\ 1.986\\ 7.076\\ 7.414\\ 1.247\\ 16.268\\ 22.383\\ 2.469\\ 10.112\\ 1.533\\ 2.764\\ \end{array}$ | 1.295 1.578 2.530 2.031 7.685 7.347 1.106 13.968 23.378 2.946 9.100 1.851 2.780 | 1.508 1.114 2.068 1.690 6.484 8.905 1.594 17.911 30.096 2.096 11.091 1.375 3.237 | $\begin{array}{r} 1.544\\ 1.208\\ 1.929\\ 1.386\\ 5.327\\ 8.787\\ 1.415\\ 18.214\\ 30.535\\ 2.103\\ 11.605\\ 1.260\\ 3.525\\ \end{array}$ | 1.710 1.125 1.611 1.330 5.352 8.662 2.086 18.520 40.069 1.746 12.191 1.154 3.401 |

| ENSG0000060982 | BCAT1 | 12p12.1 | -0.285 | 0.080 | -3.578 | 3.47E-04 | 1.43E-02 | 6.100 | 5.797 | 6.254 | 4.721 | 5.718 | 4.372 |
|-----------------|----------|----------|--------|-------|--------|----------|----------|--------|--------|--------|--------|--------|--------|
| ENSG00000173692 | PSMD1 | 2q37.1 | 0.273 | 0.077 | 3.561 | 3.69E-04 | 1.50E-02 | 11.782 | 11.862 | 10.859 | 13.249 | 13.861 | 14.281 |
| ENSG00000157014 | TATDN2 | 3p25.3 | 0.361 | 0.102 | 3.561 | 3.70E-04 | 1.50E-02 | 2.063 | 2.290 | 2.464 | 2.982 | 2.591 | 3.088 |
| ENSG00000130479 | MAP1S | 19p13.11 | 0.326 | 0.092 | 3.556 | 3.77E-04 | 1.52E-02 | 3.351 | 3.427 | 3.319 | 4.168 | 3.914 | 4.464 |
| ENSG00000265354 | TIMM23 | 10q11.22 | 0.288 | 0.081 | 3.555 | 3.77E-04 | 1.52E-02 | 23.655 | 24.356 | 22.308 | 27.969 | 27.942 | 29.321 |
| ENSG0000079999 | KEAP1 | 19p13.2 | 0.280 | 0.079 | 3.553 | 3.81E-04 | 1.53E-02 | 6.287 | 6.848 | 6.774 | 7.767 | 7.846 | 8.336 |
| ENSG0000038210 | PI4K2B | 4p15.2 | -0.512 | 0.144 | -3.550 | 3.86E-04 | 1.54E-02 | 3.665 | 3.505 | 4.079 | 1.936 | 3.397 | 2.483 |
| ENSG00000171222 | SCAND1 | 20q11.23 | 0.354 | 0.100 | 3.549 | 3.86E-04 | 1.54E-02 | 5.904 | 6.148 | 5.885 | 7.274 | 7.328 | 8.120 |
| ENSG00000173545 | ZNF622 | 5p15.1 | 0.355 | 0.100 | 3.537 | 4.05E-04 | 1.59E-02 | 5.242 | 5.162 | 5.460 | 6.869 | 6.534 | 6.707 |
| ENSG00000247077 | PGAM5 | 12q24.33 | 0.315 | 0.089 | 3.532 | 4.12E-04 | 1.61E-02 | 10.772 | 11.339 | 11.474 | 15.525 | 11.752 | 14.132 |
| ENSG00000198198 | SZT2 | 1p34.2 | -0.276 | 0.078 | -3.527 | 4.20E-04 | 1.62E-02 | 0.927 | 0.996 | 1.080 | 0.883 | 0.822 | 0.754 |
| ENSG00000143106 | PSMA5 | 1p13.3 | 0.261 | 0.074 | 3.525 | 4.24E-04 | 1.62E-02 | 6.519 | 6.352 | 6.050 | 7.464 | 7.641 | 7.417 |
| ENSG00000149231 | CCDC82 | 11q21 | -0.394 | 0.112 | -3.523 | 4.27E-04 | 1.63E-02 | 1.945 | 2.148 | 2.223 | 1.519 | 1.924 | 1.332 |
| ENSG00000173638 | SLC19A1 | 21q22.3 | 0.288 | 0.082 | 3.517 | 4.36E-04 | 1.65E-02 | 2.574 | 2.696 | 2.698 | 3.069 | 3.128 | 3.436 |
| ENSG00000105520 | PLPPR2 | 19p13.2 | 0.356 | 0.101 | 3.516 | 4.39E-04 | 1.66E-02 | 3.607 | 3.271 | 3.174 | 4.266 | 4.296 | 4.220 |
| ENSG00000223749 | MIR503HG | Xq26.3 | -0.446 | 0.127 | -3.513 | 4.43E-04 | 1.67E-02 | 3.786 | 4.595 | 4.611 | 3.420 | 3.227 | 2.818 |
| ENSG0000089775 | ZBTB25 | 14q23.3 | -0.425 | 0.121 | -3.507 | 4.53E-04 | 1.69E-02 | 0.689 | 0.708 | 0.860 | 0.548 | 0.635 | 0.482 |
| ENSG00000144395 | CCDC150 | 2q33.1 | -0.388 | 0.111 | -3.506 | 4.54E-04 | 1.69E-02 | 0.886 | 0.967 | 0.939 | 0.706 | 0.717 | 0.695 |
| ENSG00000179981 | TSHZ1 | 18q22.3 | 0.303 | 0.087 | 3.491 | 4.81E-04 | 1.78E-02 | 1.898 | 1.972 | 2.081 | 2.317 | 2.408 | 2.546 |
| ENSG00000221886 | ZBED8 | 5q33.3 | -0.597 | 0.171 | -3.491 | 4.82E-04 | 1.78E-02 | 1.207 | 1.393 | 1.399 | 0.754 | 0.997 | 0.869 |
| ENSG0000087266 | SH3BP2 | 4p16.3 | -0.288 | 0.083 | -3.490 | 4.84E-04 | 1.78E-02 | 1.338 | 1.470 | 1.607 | 1.257 | 1.197 | 1.129 |
| ENSG00000162129 | CLPB | 11q13.4 | 0.294 | 0.084 | 3.487 | 4.89E-04 | 1.79E-02 | 3.754 | 3.822 | 4.242 | 4.776 | 4.641 | 4.920 |
| ENSG00000100294 | MCAT | 22q13.2 | 0.315 | 0.091 | 3.481 | 5.00E-04 | 1.82E-02 | 5.851 | 5.957 | 6.132 | 7.327 | 7.039 | 7.746 |
| ENSG00000242294 | STAG3L5P | 7q22.1 | -0.535 | 0.154 | -3.480 | 5.02E-04 | 1.82E-02 | 1.561 | 1.723 | 1.979 | 1.352 | 1.070 | 1.174 |
| ENSG0000005206 | SPPL2B | 19p13.3 | -0.273 | 0.079 | -3.477 | 5.07E-04 | 1.83E-02 | 3.225 | 3.350 | 3.724 | 3.025 | 2.746 | 2.676 |
| ENSG00000169692 | AGPAT2 | 9q34.3 | 0.298 | 0.086 | 3.477 | 5.07E-04 | 1.83E-02 | 7.558 | 7.331 | 7.975 | 9.505 | 9.338 | 9.026 |
| ENSG00000183978 | COA3 | 17q21.2 | 0.347 | 0.100 | 3.473 | 5.15E-04 | 1.85E-02 | 5.333 | 5.492 | 5.153 | 6.663 | 6.628 | 6.883 |
| ENSG0000020922 | MRE11 | 11q21 | -0.267 | 0.077 | -3.463 | 5.34E-04 | 1.87E-02 | 5.075 | 5.163 | 5.890 | 4.267 | 4.970 | 4.050 |
| ENSG00000135763 | URB2 | 1q42.13 | 0.295 | 0.085 | 3.456 | 5.48E-04 | 1.91E-02 | 5.908 | 5.756 | 5.798 | 6.570 | 6.931 | 7.720 |
| ENSG00000114383 | TUSC2 | 3p21.31 | 0.302 | 0.088 | 3.452 | 5.56E-04 | 1.92E-02 | 7.204 | 7.682 | 6.953 | 9.070 | 8.644 | 9.031 |
| ENSG00000169021 | UQCRFS1 | 19q12 | 0.269 | 0.078 | 3.440 | 5.81E-04 | 1.99E-02 | 9.290 | 9.897 | 9.535 | 11.382 | 10.859 | 12.055 |
| ENSG00000120437 | ACAT2 | 6q25.3 | 0.354 | 0.103 | 3.438 | 5.86E-04 | 1.99E-02 | 5.831 | 6.120 | 5.107 | 6.531 | 7.205 | 7.903 |
| ENSG00000181085 | MAPK15 | NA | -0.627 | 0.183 | -3.430 | 6.03E-04 | 2.03E-02 | 1.244 | 1.041 | 1.617 | 0.883 | 0.762 | 0.845 |
| ENSG00000155115 | GTF3C6 | 6q21 | 0.268 | 0.078 | 3.428 | 6.09E-04 | 2.04E-02 | 24.753 | 24.281 | 23.404 | 28.038 | 30.172 | 28.427 |
| ENSG00000110906 | KCTD10 | 12q24.11 | 0.268 | 0.078 | 3.422 | 6.21E-04 | 2.07E-02 | 1.977 | 2.089 | 2.092 | 2.407 | 2.459 | 2.483 |
| ENSG00000141378 | PTRH2 | 17q23.1 | 0.398 | 0.116 | 3.422 | 6.22E-04 | 2.07E-02 | 1.539 | 1.850 | 1.756 | 2.114 | 2.152 | 2.448 |
| ENSG00000147894 | C9orf72 | 9p21.2 | -0.371 | 0.109 | -3.415 | 6.38E-04 | 2.11E-02 | 1.646 | 1.763 | 1.938 | 1.275 | 1.537 | 1.285 |
| ENSG00000187961 | KLHL17 | 1p36.33 | -0.353 | 0.103 | -3.409 | 6.52E-04 | 2.14E-02 | 4.076 | 4.155 | 4.492 | 3.867 | 3.134 | 2.896 |
| ENSG00000105699 | LSR | 19q13.12 | 0.279 | 0.082 | 3.405 | 6.63E-04 | 2.17E-02 | 5.444 | 5.767 | 5.612 | 6.764 | 6.866 | 6.630 |
| ENSG00000100105 | PATZ1 | 22q12.2 | 0.274 | 0.081 | 3.397 | 6.81E-04 | 2.22E-02 | 4.420 | 4.338 | 4.301 | 5.199 | 5.036 | 5.427 |
| ENSG00000117410 | ATP6V0B | 1p34.1 | 0.282 | 0.083 | 3.392 | 6.93E-04 | 2.25E-02 | 8.595 | 8.529 | 7.964 | 9.608 | 10.158 | 10.513 |
| ENSG00000106006 | HOXA6 | 7p15.2 | 0.412 | 0.122 | 3.386 | 7.10E-04 | 2.30E-02 | 4.735 | 4.913 | 5.217 | 6.849 | 5.814 | 6.922 |
| ENSG00000129474 | AJUBA | 14q11.2 | -0.346 | 0.102 | -3.385 | 7.11E-04 | 2.30E-02 | 3.047 | 3.066 | 3.282 | 2.600 | 2.797 | 1.955 |
| ENSG00000251493 | FOXD1 | 5q13.2 | 0.542 | 0.160 | 3.381 | 7.23E-04 | 2.30E-02 | 2.261 | 2.381 | 2.811 | 4.915 | 2.896 | 2.962 |

| ENSG00000100216 | TOMM22 | 22q13.1 | 0.272 | 0.081 | 3.379 | 7.27E-04 | 2.30E-02 | 18.782 | 19.262 | 17.480 | 21.591 | 21.734 | 23.228 |
|-----------------|----------|--------------|--------|-------|--------|----------|----------|--------|--------|--------|--------|--------|--------|
| ENSG00000130224 | LRCH2 | Xq23 | -0.331 | 0.098 | -3.379 | 7.27E-04 | 2.30E-02 | 4.420 | 4.419 | 4.775 | 3.180 | 4.236 | 3.318 |
| ENSG00000254858 | MPV17L2 | 19p13.11 | 0.413 | 0.122 | 3.370 | 7.51E-04 | 2.35E-02 | 3.569 | 3.698 | 3.595 | 4.604 | 4.296 | 5.415 |
| ENSG00000132005 | RFX1 | 19p13.12 | 0.308 | 0.091 | 3.366 | 7.62E-04 | 2.38E-02 | 2.346 | 2.381 | 2.628 | 3.143 | 2.811 | 3.061 |
| ENSG00000160877 | NACC1 | 19p13.13 | 0.281 | 0.084 | 3.360 | 7.79E-04 | 2.43E-02 | 8.876 | 8.835 | 8.533 | 10.392 | 9.827 | 11.380 |
| ENSG00000148300 | REXO4 | 9q34.2 | 0.267 | 0.080 | 3.353 | 8.00E-04 | 2.48E-02 | 6.892 | 7.535 | 7.288 | 8.819 | 8.501 | 8.603 |
| ENSG00000166436 | TRIM66 | 11p15.4 | -0.422 | 0.127 | -3.334 | 8.57E-04 | 2.62E-02 | 0.804 | 0.942 | 1.032 | 0.824 | 0.671 | 0.562 |
| ENSG00000167173 | C15orf39 | 15q24.2 | 0.279 | 0.084 | 3.331 | 8.66E-04 | 2.64E-02 | 4.924 | 4.782 | 5.461 | 5.999 | 5.665 | 6.538 |
| ENSG00000104899 | AMH | 19p13.3 | -0.415 | 0.125 | -3.324 | 8.86E-04 | 2.68E-02 | 7.048 | 8.160 | 8.776 | 7.351 | 4.608 | 5.846 |
| ENSG00000103356 | EARS2 | 16p12.2 | 0.296 | 0.089 | 3.323 | 8.90E-04 | 2.68E-02 | 3.417 | 3.173 | 3.337 | 3.846 | 3.967 | 4.261 |
| ENSG00000172534 | HCFC1 | Xq28 | 0.263 | 0.079 | 3.323 | 8.91E-04 | 2.68E-02 | 15.385 | 15.632 | 15.930 | 17.764 | 17.336 | 20.621 |
| ENSG00000114270 | COL7A1 | 3p21.31 | -0.433 | 0.131 | -3.316 | 9.12E-04 | 2.73E-02 | 0.583 | 0.661 | 0.756 | 0.542 | 0.440 | 0.484 |
| ENSG00000188191 | PRKAR1B | 7p22.3 | 0.442 | 0.133 | 3.311 | 9.29E-04 | 2.77E-02 | 1.449 | 1.721 | 1.384 | 1.903 | 1.935 | 2.301 |
| ENSG00000179041 | RRS1 | 8q13.1 | 0.332 | 0.100 | 3.306 | 9.45E-04 | 2.81E-02 | 7.999 | 7.993 | 8.085 | 9.929 | 9.128 | 10.953 |
| ENSG00000173915 | USMG5 | 10q24.33 | 0.312 | 0.094 | 3.304 | 9.52E-04 | 2.82E-02 | 15.133 | 15.803 | 15.517 | 18.052 | 21.594 | 17.630 |
| ENSG00000108511 | HOXB6 | 17q21.32 | 0.296 | 0.090 | 3.303 | 9.55E-04 | 2.82E-02 | 7.275 | 6.988 | 6.984 | 8.232 | 8.495 | 9.144 |
| ENSG00000106479 | ZNF862 | 7q36.1 | -0.537 | 0.163 | -3.299 | 9.70E-04 | 2.82E-02 | 0.421 | 0.483 | 0.500 | 0.312 | 0.349 | 0.299 |
| ENSG00000171492 | LRRC8D | 1p22.2 | -0.388 | 0.118 | -3.298 | 9.74E-04 | 2.82E-02 | 3.821 | 3.345 | 3.632 | 3.182 | 2.959 | 2.087 |
| ENSG00000169230 | PRELID1 | 5q35.3 | 0.275 | 0.084 | 3.297 | 9.76E-04 | 2.82E-02 | 35.215 | 36.002 | 34.608 | 44.817 | 37.238 | 44.919 |
| ENSG00000106211 | HSPB1 | 7q11.23 | 0.289 | 0.088 | 3.297 | 9.76E-04 | 2.82E-02 | 7.870 | 7.603 | 8.305 | 10.052 | 9.671 | 9.103 |
| ENSG00000144935 | TRPC1 | 3q23 | -0.381 | 0.116 | -3.296 | 9.82E-04 | 2.82E-02 | 1.723 | 1.825 | 2.162 | 1.437 | 1.585 | 1.319 |
| ENSG00000182796 | TMEM198B | 12q13.2 | -0.477 | 0.145 | -3.295 | 9.83E-04 | 2.82E-02 | 1.278 | 1.297 | 1.632 | 1.096 | 1.074 | 0.825 |
| ENSG00000198258 | UBL5 | 19p13.2 | 0.298 | 0.091 | 3.295 | 9.84E-04 | 2.82E-02 | 8.548 | 9.851 | 9.093 | 10.358 | 11.770 | 11.403 |
| ENSG00000162687 | KCNT2 | 1q31.3 | -0.575 | 0.175 | -3.294 | 9.88E-04 | 2.82E-02 | 0.549 | 0.567 | 0.667 | 0.419 | 0.476 | 0.293 |
| ENSG00000215375 | MYL5 | 4p16.3 | -0.514 | 0.156 | -3.288 | 1.01E-03 | 2.86E-02 | 1.083 | 1.200 | 1.346 | 1.030 | 0.741 | 0.750 |
| ENSG0000088881 | EBF4 | 20p13 | -0.554 | 0.169 | -3.288 | 1.01E-03 | 2.86E-02 | 1.281 | 1.436 | 1.771 | 1.308 | 0.915 | 0.807 |
| ENSG00000174749 | FAM241A | 4q25 | -0.361 | 0.110 | -3.285 | 1.02E-03 | 2.88E-02 | 1.742 | 1.645 | 1.757 | 1.145 | 1.566 | 1.264 |
| ENSG00000110660 | SLC35F2 | 11q22.3 | 0.276 | 0.084 | 3.283 | 1.03E-03 | 2.89E-02 | 4.229 | 4.135 | 4.463 | 5.105 | 5.076 | 5.207 |
| ENSG00000141252 | VPS53 | 17p13.3 | 0.277 | 0.084 | 3.276 | 1.05E-03 | 2.95E-02 | 0.693 | 0.734 | 0.707 | 0.868 | 0.876 | 0.824 |
| ENSG00000164088 | PPM1M | 3p21.2 | -0.557 | 0.170 | -3.272 | 1.07E-03 | 2.97E-02 | 1.736 | 2.192 | 2.314 | 1.775 | 1.534 | 0.916 |
| ENSG00000185896 | LAMP1 | 13q34 | 0.264 | 0.081 | 3.266 | 1.09E-03 | 3.02E-02 | 5.555 | 5.661 | 5.445 | 7.400 | 6.151 | 6.334 |
| ENSG00000135272 | MDFIC | 7q31.1-q31.2 | -0.375 | 0.115 | -3.262 | 1.10E-03 | 3.04E-02 | 2.145 | 2.061 | 2.302 | 1.602 | 1.974 | 1.408 |
| ENSG00000120697 | ALG5 | 13q13.3 | 0.283 | 0.087 | 3.259 | 1.12E-03 | 3.07E-02 | 6.325 | 6.437 | 6.249 | 7.887 | 7.853 | 7.245 |
| ENSG00000100109 | TFIP11 | 22q12.1 | 0.302 | 0.093 | 3.253 | 1.14E-03 | 3.09E-02 | 2.493 | 2.391 | 2.381 | 2.907 | 2.946 | 3.035 |
| ENSG00000150593 | PDCD4 | 10q25.2 | -0.293 | 0.090 | -3.249 | 1.16E-03 | 3.11E-02 | 12.047 | 12.414 | 12.757 | 10.371 | 11.788 | 8.086 |
| ENSG00000164877 | MICALL2 | 7p22.3 | -0.595 | 0.183 | -3.248 | 1.16E-03 | 3.12E-02 | 0.352 | 0.444 | 0.472 | 0.332 | 0.230 | 0.269 |
| ENSG00000113732 | ATP6V0E1 | 5q35.1 | 0.279 | 0.086 | 3.245 | 1.18E-03 | 3.14E-02 | 9.130 | 9.812 | 9.983 | 11.242 | 11.586 | 11.937 |
| ENSG00000180992 | MRPL14 | 6p21.1 | 0.288 | 0.089 | 3.236 | 1.21E-03 | 3.22E-02 | 14.150 | 14.903 | 14.678 | 18.356 | 16.829 | 17.769 |
| ENSG00000158106 | RHPN1 | 8q24.3 | -0.430 | 0.133 | -3.235 | 1.22E-03 | 3.23E-02 | 1.946 | 2.070 | 2.568 | 1.863 | 1.348 | 1.618 |
| ENSG00000274276 | CBSL | 21p12 | -0.360 | 0.111 | -3.234 | 1.22E-03 | 3.23E-02 | 2.531 | 2.569 | 2.585 | 2.177 | 1.782 | 1.982 |
| ENSG00000175322 | ZNF519 | 18p11.21 | -0.470 | 0.146 | -3.230 | 1.24E-03 | 3.26E-02 | 0.336 | 0.352 | 0.445 | 0.265 | 0.311 | 0.234 |
| ENSG00000160256 | FAM207A | 21q22.3 | 0.319 | 0.099 | 3.228 | 1.25E-03 | 3.27E-02 | 8.009 | 8.045 | 7.454 | 9.455 | 9.999 | 9.673 |
| ENSG00000106948 | AKNA | 9q32 | -0.609 | 0.189 | -3.227 | 1.25E-03 | 3.27E-02 | 0.393 | 0.391 | 0.598 | 0.366 | 0.315 | 0.216 |
| ENSG00000167378 | IRGQ | 19q13.31 | 0.307 | 0.095 | 3.226 | 1.26E-03 | 3.27E-02 | 1.225 | 1.247 | 1.426 | 1.547 | 1.544 | 1.678 |

| ENSG00000155657 | TTN | 2q31.2 | -0.288 | 0.089 | -3.226 | 1.26E-03 | 3.27E-02 | 0.150 | 0.143 | 0.148 | 0.123 | 0.114 | 0.121 |
|-----------------|------------|----------|--------|-------|--------|----------|----------|--------|--------|--------|--------|--------|--------|
| ENSG00000132768 | DPH2 | 1p34.1 | 0.364 | 0.113 | 3.215 | 1.31E-03 | 3.37E-02 | 5.162 | 5.171 | 5.060 | 5.920 | 6.017 | 7.657 |
| ENSG00000139793 | MBNL2 | 13q32.1 | -0.367 | 0.114 | -3.215 | 1.31E-03 | 3.37E-02 | 2.315 | 2.247 | 2.480 | 1.798 | 2.129 | 1.498 |
| ENSG00000174775 | HRAS | 11p15.5 | 0.328 | 0.102 | 3.212 | 1.32E-03 | 3.39E-02 | 5.135 | 5.793 | 6.270 | 7.831 | 6.577 | 6.978 |
| ENSG00000198356 | ASNA1 | 19p13.13 | 0.323 | 0.101 | 3.210 | 1.33E-03 | 3.40E-02 | 10.468 | 10.964 | 8.986 | 12.043 | 13.034 | 12.774 |
| ENSG00000128965 | CHAC1 | 15q15.1 | -0.396 | 0.123 | -3.209 | 1.33E-03 | 3.40E-02 | 5.307 | 5.341 | 5.176 | 4.579 | 4.334 | 3.077 |
| ENSG00000169231 | THBS3 | 1q22 | -0.594 | 0.186 | -3.201 | 1.37E-03 | 3.44E-02 | 0.772 | 0.896 | 1.253 | 0.769 | 0.645 | 0.500 |
| ENSG00000109062 | SLC9A3R1 | 17q25.1 | 0.337 | 0.105 | 3.201 | 1.37E-03 | 3.44E-02 | 4.195 | 4.043 | 4.462 | 5.301 | 4.913 | 5.660 |
| ENSG00000105364 | MRPL4 | 19p13.2 | 0.268 | 0.084 | 3.199 | 1.38E-03 | 3.45E-02 | 6.758 | 7.036 | 6.723 | 7.598 | 8.224 | 8.660 |
| ENSG00000104833 | TUBB4A | 19p13.3 | 0.301 | 0.094 | 3.198 | 1.38E-03 | 3.45E-02 | 3.162 | 3.274 | 3.541 | 4.220 | 4.378 | 3.606 |
| ENSG00000183072 | NKX2-5 | 5q35.1 | 0.278 | 0.087 | 3.196 | 1.39E-03 | 3.46E-02 | 7.140 | 7.364 | 7.099 | 8.591 | 8.629 | 8.774 |
| ENSG00000022277 | RTFDC1 | 20q13.31 | 0.267 | 0.084 | 3.186 | 1.44E-03 | 3.54E-02 | 4.478 | 4.500 | 4.232 | 5.413 | 5.253 | 5.132 |
| ENSG00000164983 | TMEM65 | 8q24.13 | -0.322 | 0.101 | -3.186 | 1.44E-03 | 3.54E-02 | 3.123 | 3.129 | 3.109 | 2.078 | 2.882 | 2.469 |
| ENSG00000185278 | ZBTB37 | 1q25.1 | -0.330 | 0.104 | -3.185 | 1.45E-03 | 3.54E-02 | 0.764 | 0.809 | 1.059 | 0.695 | 0.735 | 0.639 |
| ENSG00000135976 | ANKRD36 | 2q11.2 | -0.374 | 0.118 | -3.184 | 1.45E-03 | 3.54E-02 | 0.901 | 1.016 | 1.098 | 0.898 | 0.734 | 0.675 |
| ENSG00000225138 | SLC9A3-AS1 | NA | -0.374 | 0.118 | -3.182 | 1.46E-03 | 3.55E-02 | 2.088 | 2.673 | 2.928 | 2.155 | 1.922 | 1.797 |
| ENSG00000160213 | CSTB | 21q22.3 | 0.266 | 0.084 | 3.180 | 1.47E-03 | 3.56E-02 | 6.024 | 6.729 | 5.857 | 7.309 | 7.483 | 7.438 |
| ENSG00000187984 | ANKRD19P | 9q22.31 | -0.317 | 0.100 | -3.173 | 1.51E-03 | 3.64E-02 | 4.299 | 5.112 | 5.787 | 4.164 | 4.130 | 3.782 |
| ENSG00000117016 | RIMS3 | 1p34.2 | -0.356 | 0.112 | -3.167 | 1.54E-03 | 3.67E-02 | 1.247 | 1.249 | 1.453 | 1.137 | 0.978 | 0.944 |
| ENSG00000149150 | SLC43A1 | 11q12.1 | -0.378 | 0.120 | -3.156 | 1.60E-03 | 3.77E-02 | 4.125 | 4.628 | 4.501 | 3.935 | 3.714 | 2.513 |
| ENSG00000132361 | CLUH | 17p13.3 | 0.260 | 0.082 | 3.155 | 1.61E-03 | 3.77E-02 | 11.272 | 11.501 | 11.013 | 13.280 | 12.172 | 14.634 |
| ENSG00000167112 | TRUB2 | 9q34.11 | 0.295 | 0.094 | 3.148 | 1.64E-03 | 3.82E-02 | 2.698 | 2.790 | 2.662 | 3.091 | 3.272 | 3.547 |
| ENSG00000263711 | AC079062.1 | 18q22.3 | -0.440 | 0.140 | -3.147 | 1.65E-03 | 3.82E-02 | 0.775 | 0.823 | 0.951 | 0.562 | 0.692 | 0.605 |
| ENSG00000172428 | COPS9 | 2q37.3 | 0.453 | 0.144 | 3.143 | 1.67E-03 | 3.86E-02 | 2.862 | 2.890 | 2.324 | 3.182 | 4.199 | 3.627 |
| ENSG00000155158 | TTC39B | 9p22.3 | -0.358 | 0.114 | -3.139 | 1.69E-03 | 3.89E-02 | 0.651 | 0.694 | 0.732 | 0.581 | 0.547 | 0.481 |
| ENSG00000178896 | EXOSC4 | 8q24.3 | 0.409 | 0.130 | 3.137 | 1.71E-03 | 3.90E-02 | 4.256 | 3.936 | 4.563 | 5.038 | 5.474 | 6.218 |
| ENSG00000148690 | FRA10AC1 | 10q23.33 | -0.330 | 0.105 | -3.136 | 1.71E-03 | 3.90E-02 | 2.261 | 2.390 | 2.510 | 1.712 | 2.297 | 1.648 |
| ENSG0000083444 | PLOD1 | 1p36.22 | 0.274 | 0.088 | 3.134 | 1.72E-03 | 3.91E-02 | 3.579 | 3.351 | 3.582 | 4.078 | 4.087 | 4.433 |
| ENSG00000154265 | ABCA5 | 17q24.3 | -0.365 | 0.116 | -3.130 | 1.75E-03 | 3.96E-02 | 0.582 | 0.655 | 0.688 | 0.513 | 0.536 | 0.435 |
| ENSG00000136463 | TACO1 | 17q23.3 | 0.276 | 0.088 | 3.129 | 1.76E-03 | 3.96E-02 | 6.807 | 6.275 | 7.043 | 8.177 | 7.760 | 8.207 |
| ENSG0000065029 | ZNF76 | 6p21.31 | -0.298 | 0.095 | -3.128 | 1.76E-03 | 3.96E-02 | 2.655 | 2.839 | 3.317 | 2.688 | 2.352 | 2.065 |
| ENSG00000111788 | AC009533.1 | NA | -0.297 | 0.095 | -3.123 | 1.79E-03 | 3.99E-02 | 4.656 | 4.787 | 4.977 | 4.306 | 3.582 | 3.753 |
| ENSG0000063241 | ISOC2 | 19q13.42 | 0.330 | 0.106 | 3.122 | 1.79E-03 | 3.99E-02 | 2.282 | 2.681 | 2.251 | 3.095 | 2.890 | 3.029 |
| ENSG00000173153 | ESRRA | 11q13.1 | 0.299 | 0.096 | 3.121 | 1.80E-03 | 4.01E-02 | 4.206 | 4.167 | 4.846 | 5.887 | 4.931 | 5.280 |
| ENSG00000223960 | AC009948.1 | 2q31.2 | -0.448 | 0.144 | -3.120 | 1.81E-03 | 4.01E-02 | 2.034 | 2.381 | 2.329 | 1.386 | 2.124 | 1.401 |
| ENSG00000153291 | SLC25A27 | 6p12.3 | -0.350 | 0.112 | -3.119 | 1.82E-03 | 4.01E-02 | 2.685 | 2.811 | 3.406 | 2.475 | 2.311 | 2.129 |
| ENSG00000186908 | ZDHHC17 | 12q21.2 | -0.304 | 0.098 | -3.118 | 1.82E-03 | 4.01E-02 | 2.934 | 3.237 | 3.075 | 2.212 | 2.948 | 2.277 |
| ENSG00000117394 | SLC2A1 | 1p34.2 | 0.273 | 0.088 | 3.116 | 1.83E-03 | 4.01E-02 | 5.009 | 6.087 | 6.178 | 7.716 | 7.019 | 5.983 |
| ENSG00000170915 | PAQR8 | 6p12.2 | -0.349 | 0.112 | -3.115 | 1.84E-03 | 4.01E-02 | 2.156 | 1.981 | 2.343 | 1.808 | 1.830 | 1.413 |
| ENSG00000204410 | MSH5 | 6p21.33 | -0.527 | 0.169 | -3.107 | 1.89E-03 | 4.08E-02 | 0.560 | 0.751 | 0.783 | 0.556 | 0.481 | 0.404 |
| ENSG00000116455 | WDR77 | 1p13.2 | 0.313 | 0.101 | 3.105 | 1.90E-03 | 4.09E-02 | 10.606 | 9.812 | 10.484 | 11.421 | 11.956 | 14.601 |
| ENSG00000132819 | RBM38 | 20q13.31 | 0.301 | 0.097 | 3.104 | 1.91E-03 | 4.09E-02 | 4.866 | 4.983 | 4.954 | 5.924 | 5.672 | 6.468 |
| ENSG00000144468 | RHBDD1 | 2q36.3 | -0.284 | 0.091 | -3.104 | 1.91E-03 | 4.09E-02 | 2.178 | 2.195 | 2.325 | 1.871 | 1.976 | 1.618 |
| ENSG00000230590 | FTX | Xq13.2 | -0.394 | 0.127 | -3.099 | 1.94E-03 | 4.13E-02 | 0.261 | 0.289 | 0.349 | 0.203 | 0.255 | 0.219 |

| ENSG00000276045 | ORAI1 | NA | 0.386 | 0.125 | 3.091 | 1.99E-03 | 4.20E-02 | 2.461 | 2.538 | 3.098 | 3.948 | 3.294 | 3.233 |
|-----------------|------------|----------|--------|-------|--------|----------|----------|--------|--------|--------|--------|--------|--------|
| ENSG00000114648 | KLHL18 | 3p21.31 | 0.274 | 0.088 | 3.091 | 2.00E-03 | 4.20E-02 | 2.342 | 2.459 | 2.546 | 2.971 | 2.724 | 3.099 |
| ENSG00000114120 | SLC25A36 | 3q23 | -0.269 | 0.087 | -3.090 | 2.00E-03 | 4.20E-02 | 6.983 | 6.881 | 7.394 | 5.134 | 6.882 | 5.495 |
| ENSG00000174744 | BRMS1 | 11q13.2 | 0.340 | 0.110 | 3.090 | 2.00E-03 | 4.20E-02 | 4.092 | 4.192 | 3.657 | 4.855 | 4.850 | 5.312 |
| ENSG00000167775 | CD320 | 19p13.2 | 0.274 | 0.089 | 3.090 | 2.00E-03 | 4.20E-02 | 12.383 | 11.932 | 11.501 | 13.599 | 13.917 | 15.416 |
| ENSG00000170855 | TRIAP1 | 12q24.31 | 0.296 | 0.096 | 3.088 | 2.01E-03 | 4.22E-02 | 8.226 | 8.814 | 7.950 | 9.980 | 10.348 | 10.156 |
| ENSG00000169992 | NLGN2 | 17p13.1 | -0.299 | 0.097 | -3.085 | 2.04E-03 | 4.24E-02 | 7.944 | 7.768 | 9.557 | 8.088 | 5.910 | 6.343 |
| ENSG00000223705 | NSUN5P1 | 7q11.23 | -0.328 | 0.107 | -3.076 | 2.10E-03 | 4.31E-02 | 2.404 | 2.723 | 3.314 | 2.389 | 2.163 | 2.095 |
| ENSG0000037241 | RPL26L1 | 5q35.1 | 0.312 | 0.101 | 3.076 | 2.10E-03 | 4.31E-02 | 16.012 | 16.834 | 13.415 | 18.490 | 19.760 | 18.917 |
| ENSG00000145214 | DGKQ | 4p16.3 | -0.283 | 0.092 | -3.074 | 2.11E-03 | 4.31E-02 | 2.645 | 2.676 | 3.007 | 2.322 | 2.276 | 2.184 |
| ENSG00000187840 | EIF4EBP1 | 8p11.23 | -0.263 | 0.086 | -3.074 | 2.11E-03 | 4.31E-02 | 77.903 | 81.032 | 83.749 | 75.122 | 72.817 | 53.351 |
| ENSG00000125995 | ROMO1 | 20q11.22 | 0.333 | 0.108 | 3.072 | 2.13E-03 | 4.31E-02 | 11.839 | 14.916 | 12.867 | 16.382 | 17.160 | 16.054 |
| ENSG00000197283 | SYNGAP1 | 6p21.32 | -0.393 | 0.128 | -3.070 | 2.14E-03 | 4.32E-02 | 0.739 | 0.754 | 0.954 | 0.740 | 0.556 | 0.550 |
| ENSG00000180902 | D2HGDH | 2q37.3 | -0.343 | 0.112 | -3.066 | 2.17E-03 | 4.34E-02 | 1.833 | 2.098 | 2.290 | 1.854 | 1.574 | 1.436 |
| ENSG00000100304 | TTLL12 | 22q13.2 | 0.276 | 0.090 | 3.065 | 2.17E-03 | 4.34E-02 | 14.410 | 15.002 | 14.416 | 18.042 | 15.125 | 19.371 |
| ENSG00000101187 | SLCO4A1 | 20q13.33 | 0.360 | 0.117 | 3.064 | 2.18E-03 | 4.34E-02 | 1.682 | 1.770 | 1.895 | 2.194 | 2.119 | 2.473 |
| ENSG00000144120 | TMEM177 | 2q14.2 | 0.260 | 0.085 | 3.064 | 2.18E-03 | 4.34E-02 | 5.866 | 6.329 | 6.112 | 7.307 | 7.144 | 7.301 |
| ENSG00000266338 | NBPF15 | 1q21.1 | -0.263 | 0.086 | -3.062 | 2.20E-03 | 4.36E-02 | 4.594 | 5.298 | 5.997 | 4.508 | 4.703 | 3.906 |
| ENSG00000169660 | HEXDC | 17q25.3 | -0.416 | 0.136 | -3.061 | 2.20E-03 | 4.36E-02 | 1.618 | 1.885 | 1.941 | 1.599 | 1.142 | 1.304 |
| ENSG00000185803 | SLC52A2 | 8q24.3 | 0.342 | 0.112 | 3.057 | 2.24E-03 | 4.40E-02 | 2.880 | 2.767 | 2.893 | 3.374 | 3.479 | 3.866 |
| ENSG00000147852 | VLDLR | 9p24.2 | -0.399 | 0.131 | -3.045 | 2.32E-03 | 4.53E-02 | 0.958 | 0.961 | 0.987 | 0.814 | 0.831 | 0.549 |
| ENSG0000092036 | HAUS4 | 14q11.2 | -0.361 | 0.119 | -3.039 | 2.37E-03 | 4.59E-02 | 2.744 | 2.970 | 2.999 | 2.277 | 2.364 | 2.092 |
| ENSG00000205746 | AC126755.1 | NA | -0.402 | 0.132 | -3.033 | 2.42E-03 | 4.64E-02 | 0.976 | 0.953 | 1.101 | 0.884 | 0.743 | 0.649 |
| ENSG00000113643 | RARS | 5q34 | 0.260 | 0.086 | 3.033 | 2.42E-03 | 4.64E-02 | 13.432 | 13.060 | 12.036 | 14.373 | 15.146 | 16.271 |
| ENSG00000166166 | TRMT61A | 14q32.33 | 0.372 | 0.123 | 3.032 | 2.43E-03 | 4.65E-02 | 2.794 | 2.836 | 2.296 | 3.323 | 3.256 | 3.619 |
| ENSG00000173457 | PPP1R14B | 11q13.1 | 0.318 | 0.105 | 3.030 | 2.45E-03 | 4.66E-02 | 14.172 | 14.820 | 14.306 | 21.855 | 15.280 | 16.527 |
| ENSG00000143578 | CREB3L4 | 1q21.3 | -0.548 | 0.181 | -3.029 | 2.45E-03 | 4.67E-02 | 1.269 | 1.745 | 1.618 | 1.040 | 1.322 | 0.789 |
| ENSG00000172828 | CES3 | 16q22.1 | -0.362 | 0.120 | -3.028 | 2.46E-03 | 4.68E-02 | 1.684 | 1.753 | 2.118 | 1.601 | 1.459 | 1.224 |
| ENSG00000166479 | TMX3 | 18q22.1 | -0.288 | 0.095 | -3.027 | 2.47E-03 | 4.68E-02 | 2.958 | 3.035 | 2.954 | 2.148 | 2.775 | 2.351 |
| ENSG00000132846 | ZBED3 | 5q13.3 | -0.321 | 0.106 | -3.024 | 2.50E-03 | 4.69E-02 | 2.599 | 2.546 | 2.646 | 2.413 | 2.139 | 1.657 |
| ENSG00000110047 | EHD1 | 11q13.1 | 0.290 | 0.096 | 3.022 | 2.51E-03 | 4.71E-02 | 2.065 | 2.205 | 2.188 | 2.645 | 2.367 | 2.807 |
| ENSG00000145632 | PLK2 | 5q11.2 | 0.534 | 0.177 | 3.016 | 2.56E-03 | 4.77E-02 | 0.423 | 0.597 | 0.561 | 0.746 | 0.731 | 0.791 |
| ENSG00000111237 | VPS29 | 12q24.11 | -0.263 | 0.087 | -3.012 | 2.59E-03 | 4.82E-02 | 7.334 | 7.780 | 8.553 | 6.069 | 7.438 | 6.040 |
| ENSG00000131584 | ACAP3 | 1p36.33 | -0.319 | 0.106 | -3.007 | 2.64E-03 | 4.86E-02 | 2.026 | 2.016 | 2.334 | 1.976 | 1.437 | 1.651 |
| ENSG0000060069 | CTDP1 | 18q23 | 0.350 | 0.116 | 3.005 | 2.65E-03 | 4.87E-02 | 1.051 | 1.317 | 1.256 | 1.698 | 1.350 | 1.531 |
| ENSG00000164331 | ANKRA2 | 5q13.2 | -0.394 | 0.131 | -3.005 | 2.66E-03 | 4.87E-02 | 2.310 | 2.380 | 2.681 | 1.957 | 2.036 | 1.575 |
| ENSG00000104231 | ZFAND1 | 8q21.13 | -0.296 | 0.098 | -3.004 | 2.67E-03 | 4.87E-02 | 5.320 | 5.565 | 5.719 | 4.462 | 5.309 | 3.683 |
| ENSG00000113971 | NPHP3 | 3q22.1 | -0.465 | 0.155 | -2.999 | 2.71E-03 | 4.92E-02 | 0.459 | 0.470 | 0.493 | 0.320 | 0.402 | 0.301 |
| ENSG00000165983 | PTER | 10p13 | -0.307 | 0.102 | -2.996 | 2.74E-03 | 4.95E-02 | 3.841 | 4.041 | 4.189 | 2.985 | 3.822 | 2.883 |
| ENSG00000123552 | USP45 | 6a16.2 | -0.288 | 0.096 | -2.992 | 2.77E-03 | 4.98E-02 | 1.562 | 1.577 | 1.756 | 1.271 | 1.348 | 1.348 |

Abbreviation: BP, biological position; FC, fold change; S.E., standard error; Ctrl, control; *Alu* del, deletion of *Alu* insertion.

Table S5. KEGG pathway analysis of DEGs in HEK293T cells.

| term ID | term description | Gene Ratio | Bg Ratio | p-value | adjust p-value | q-value | gene name | Count |
|----------|-----------------------------|------------|----------|----------|----------------|----------|---|-------|
| hsa01230 | Biosynthesis of amino acids | 7/142 | 75/8011 | 3.44E-04 | 4.33E-02 | 4.12E-02 | PGAM1/CBS/ASNS/ASS1/PSAT1/BCAT1/CBSL | 7 |
| hsa03010 | Ribosome | 10/142 | 153/8011 | 3.70E-04 | 4.33E-02 | 4.12E-02 | RPL36AL/RPL35/MRPS7/MRPL28/MRPL36/RPS21/ MRPS12/MRPL14/MRPL4/RPL26L1 | 10 |

Abbreviation: Bg, background.

Table S6. Gene Ontology (GO) BP analysis of DEGs in HEK293T cells.

| ID | Description | Gene Ratio | Bg Ratio | p-value | adjust p-value | q-value | Count |
|------------|---|------------|-----------|----------|----------------|----------|-------|
| GO:0042254 | ribosome biogenesis | 28/332 | 297/18670 | 6.62E-13 | 2.27E-09 | 2.14E-09 | 28 |
| GO:0016072 | rRNA metabolic process | 22/332 | 253/18670 | 9.88E-10 | 1.70E-06 | 1.59E-06 | 22 |
| GO:0006986 | response to unfolded protein | 18/332 | 176/18670 | 2.62E-09 | 2.06E-06 | 1.93E-06 | 18 |
| GO:0032543 | mitochondrial translation | 11/332 | 135/18670 | 3.00E-05 | 5.72E-03 | 5.38E-03 | 11 |
| GO:0140053 | mitochondrial gene expression | 12/332 | 162/18670 | 3.40E-05 | 6.08E-03 | 5.72E-03 | 12 |
| GO:0044773 | mitotic DNA damage checkpoint | 9/332 | 97/18670 | 5.78E-05 | 9.44E-03 | 8.88E-03 | 9 |
| GO:0042149 | cellular response to glucose starvation | 6/332 | 42/18670 | 9.24E-05 | 1.32E-02 | 1.24E-02 | 6 |
| GO:000086 | G2/M transition of mitotic cell cycle | 14/332 | 247/18670 | 1.44E-04 | 1.83E-02 | 1.72E-02 | 14 |
| GO:1901607 | alpha-amino acid biosynthetic process | 7/332 | 66/18670 | 1.67E-04 | 1.97E-02 | 1.85E-02 | 7 |
| GO:0072655 | establishment of protein localization to mitochondrion | 10/332 | 137/18670 | 1.72E-04 | 1.97E-02 | 1.85E-02 | 10 |
| GO:0090199 | regulation of release of cytochrome c from mitochondria | 6/332 | 48/18670 | 1.98E-04 | 2.19E-02 | 2.06E-02 | 6 |
| GO:0042326 | negative regulation of phosphorylation | 20/332 | 468/18670 | 2.91E-04 | 2.91E-02 | 2.73E-02 | 20 |
| GO:0061077 | chaperone-mediated protein folding | 6/332 | 59/18670 | 6.16E-04 | 4.32E-02 | 4.06E-02 | 6 |
| GO:1902115 | regulation of organelle assembly | 11/332 | 194/18670 | 7.31E-04 | 4.56E-02 | 4.29E-02 | 11 |

Abbreviation: Bg, background.

| Gene ID | Gene name | BP | log2(FC) | S.E. | stat | p-value | p-adjust | Ctrl-1 | Ctrl-2 | Ctrl-3 | Alu Del-1 | Alu Del-2 | Alu Del-3 |
|-----------------|------------|----------|----------|-------|--------|----------|----------|--------|--------|--------|-----------|-----------|-----------|
| ENSG0000070404 | FSTL3 | 19p13.3 | 0.752 | 0.099 | 7.608 | 2.79E-14 | 3.53E-10 | 2.659 | 2.432 | 2.656 | 4.046 | 4.457 | 4.604 |
| ENSG00000112139 | MDGA1 | 6p21.2 | 0.835 | 0.112 | 7.460 | 8.68E-14 | 5.49E-10 | 0.281 | 0.277 | 0.289 | 0.500 | 0.474 | 0.542 |
| ENSG00000242808 | SOX2-OT | 3q26.33 | -0.549 | 0.081 | -6.773 | 1.26E-11 | 5.34E-08 | 14.909 | 15.691 | 14.860 | 11.010 | 10.432 | 9.751 |
| ENSG00000106211 | HSPB1 | 7q11.23 | 0.502 | 0.075 | 6.679 | 2.41E-11 | 7.63E-08 | 36.339 | 37.069 | 34.834 | 51.423 | 49.721 | 52.682 |
| ENSG00000145632 | PLK2 | 5q11.2 | 0.510 | 0.084 | 6.041 | 1.53E-09 | 3.87E-06 | 7.798 | 8.065 | 8.826 | 11.599 | 11.762 | 11.964 |
| ENSG00000277775 | HIST1H3F | 6p22.2 | -0.765 | 0.130 | -5.893 | 3.79E-09 | 8.01E-06 | 62.702 | 62.188 | 58.543 | 38.242 | 28.438 | 41.594 |
| ENSG00000170689 | HOXB9 | 17q21.32 | 1.015 | 0.174 | 5.822 | 5.82E-09 | 8.59E-06 | 0.470 | 0.461 | 0.499 | 1.146 | 0.888 | 0.876 |
| ENSG0000087074 | PPP1R15A | 19q13.33 | 0.580 | 0.099 | 5.828 | 5.61E-09 | 8.59E-06 | 4.392 | 3.899 | 4.398 | 6.123 | 5.997 | 6.923 |
| ENSG00000265727 | RN7SL648P | NA | -1.057 | 0.182 | -5.814 | 6.11E-09 | 8.59E-06 | 7.871 | 9.358 | 9.794 | 5.254 | 4.196 | 3.648 |
| ENSG00000162599 | NFIA | 1p31.3 | -0.657 | 0.114 | -5.784 | 7.29E-09 | 9.23E-06 | 0.820 | 0.894 | 0.725 | 0.515 | 0.504 | 0.531 |
| ENSG0000078269 | SYNJ2 | 6q25.3 | 0.689 | 0.127 | 5.417 | 6.06E-08 | 6.98E-05 | 1.918 | 1.488 | 1.693 | 2.386 | 2.622 | 3.237 |
| ENSG00000136997 | MYC | 8q24.21 | 0.835 | 0.155 | 5.390 | 7.04E-08 | 7.43E-05 | 1.744 | 1.378 | 1.527 | 2.277 | 2.600 | 3.435 |
| ENSG00000162496 | DHRS3 | 1p36.21 | 2.221 | 0.418 | 5.311 | 1.09E-07 | 9.87E-05 | 0.752 | 1.506 | 1.645 | 7.608 | 6.461 | 4.251 |
| ENSG00000187840 | EIF4EBP1 | 8p11.23 | 0.626 | 0.118 | 5.312 | 1.09E-07 | 9.87E-05 | 5.656 | 4.964 | 6.002 | 7.906 | 8.430 | 9.448 |
| ENSG00000261326 | LINC01355 | NA | -0.632 | 0.121 | -5.229 | 1.71E-07 | 1.44E-04 | 1.279 | 1.334 | 1.349 | 0.977 | 0.801 | 0.790 |
| ENSG00000163584 | RPL22L1 | 3q26.2 | 0.697 | 0.135 | 5.180 | 2.22E-07 | 1.75E-04 | 0.969 | 0.874 | 0.945 | 1.423 | 1.533 | 1.582 |
| ENSG00000167526 | RPL13 | 17p11.2 | 0.476 | 0.092 | 5.143 | 2.70E-07 | 2.01E-04 | 5.815 | 5.182 | 5.585 | 8.435 | 7.241 | 7.469 |
| ENSG00000197121 | PGAP1 | 2q33.1 | -0.421 | 0.082 | -5.129 | 2.92E-07 | 2.05E-04 | 1.970 | 1.802 | 1.943 | 1.443 | 1.412 | 1.431 |
| ENSG00000131095 | GFAP | 17q21.31 | -0.613 | 0.120 | -5.110 | 3.22E-07 | 2.15E-04 | 33.963 | 41.186 | 32.627 | 23.027 | 27.088 | 20.662 |
| ENSG00000123144 | TRIR | 19p13.13 | 0.449 | 0.088 | 5.098 | 3.43E-07 | 2.17E-04 | 16.172 | 15.217 | 17.276 | 23.132 | 22.238 | 21.376 |
| ENSG00000120833 | SOCS2 | 12q22 | 0.472 | 0.095 | 4.987 | 6.14E-07 | 3.70E-04 | 2.343 | 1.963 | 2.029 | 3.011 | 2.951 | 2.851 |
| ENSG00000210140 | MT-TC | NA | 0.746 | 0.151 | 4.949 | 7.44E-07 | 4.28E-04 | 45.020 | 57.706 | 40.239 | 72.922 | 81.701 | 85.304 |
| ENSG00000133519 | ZDHHC8P1 | NA | -0.624 | 0.127 | -4.905 | 9.35E-07 | 5.15E-04 | 1.268 | 1.332 | 1.170 | 0.809 | 0.841 | 0.802 |
| ENSG00000198729 | PPP1R14C | 6q25.1 | -0.653 | 0.133 | -4.893 | 9.92E-07 | 5.24E-04 | 1.679 | 1.682 | 1.703 | 1.148 | 1.106 | 0.986 |
| ENSG00000167779 | IGFBP6 | 12q13.13 | 0.742 | 0.152 | 4.875 | 1.09E-06 | 5.52E-04 | 1.442 | 1.427 | 1.812 | 2.534 | 2.552 | 2.813 |
| ENSG0000013588 | GPRC5A | 12p13.1 | 0.905 | 0.187 | 4.838 | 1.31E-06 | 5.72E-04 | 0.395 | 0.256 | 0.271 | 0.474 | 0.542 | 0.709 |
| ENSG00000231383 | FGF12-AS1 | 3q28 | 0.636 | 0.131 | 4.839 | 1.30E-06 | 5.72E-04 | 2.293 | 2.305 | 2.262 | 3.281 | 3.571 | 3.840 |
| ENSG00000011422 | PLAUR | 19q13.31 | 0.530 | 0.109 | 4.839 | 1.31E-06 | 5.72E-04 | 2.808 | 2.421 | 2.418 | 3.329 | 3.632 | 4.108 |
| ENSG00000150625 | GPM6A | 4q34.2 | -0.425 | 0.087 | -4.859 | 1.18E-06 | 5.72E-04 | 8.219 | 9.373 | 8.870 | 6.667 | 6.829 | 6.310 |
| ENSG0000092421 | SEMA6A | 5q23.1 | -0.783 | 0.162 | -4.826 | 1.40E-06 | 5.89E-04 | 0.467 | 0.672 | 0.473 | 0.349 | 0.309 | 0.283 |
| ENSG00000239381 | AC125613.1 | NA | -0.456 | 0.095 | -4.779 | 1.76E-06 | 7.18E-04 | 11.186 | 12.616 | 11.324 | 8.473 | 9.074 | 8.170 |
| ENSG00000116106 | EPHA4 | 2q36.1 | 0.745 | 0.156 | 4.773 | 1.82E-06 | 7.19E-04 | 0.267 | 0.295 | 0.279 | 0.419 | 0.436 | 0.561 |
| ENSG0000067082 | KLF6 | 10p15.2 | 0.432 | 0.091 | 4.758 | 1.96E-06 | 7.51E-04 | 3.587 | 3.029 | 3.426 | 4.443 | 4.471 | 4.684 |
| ENSG00000149295 | DRD2 | 11q23.2 | 0.625 | 0.132 | 4.725 | 2.30E-06 | 8.58E-04 | 0.782 | 0.709 | 0.721 | 1.001 | 1.162 | 1.258 |
| ENSG00000179041 | RRS1 | 8q13.1 | 0.774 | 0.167 | 4.651 | 3.31E-06 | 1.20E-03 | 1.133 | 0.785 | 0.969 | 1.591 | 1.560 | 1.801 |
| ENSG00000272888 | LINC01578 | NA | -0.405 | 0.087 | -4.643 | 3.44E-06 | 1.21E-03 | 4.624 | 4.894 | 5.056 | 3.847 | 3.650 | 3.564 |
| ENSG00000186340 | THBS2 | 6q27 | 0.466 | 0.102 | 4.590 | 4.42E-06 | 1.51E-03 | 3.561 | 3.304 | 2.980 | 4.114 | 4.619 | 4.905 |
| ENSG00000240342 | RPS2P5 | NA | 0.448 | 0.099 | 4.543 | 5.54E-06 | 1.85E-03 | 16.161 | 14.759 | 14.042 | 21.213 | 18.802 | 21.462 |
| ENSG00000180611 | MB21D2 | 3q29 | 0.568 | 0.128 | 4.451 | 8.55E-06 | 2.78E-03 | 1.026 | 0.892 | 1.015 | 1.336 | 1.442 | 1.589 |
| ENSG00000197122 | SRC | 20q11.23 | 0.507 | 0.115 | 4.400 | 1.08E-05 | 3.43E-03 | 0.721 | 0.722 | 0.645 | 0.946 | 1.079 | 0.950 |
| ENSG00000172922 | RNASEH2C | 11q13.1 | 0.395 | 0.090 | 4.386 | 1.16E-05 | 3.57E-03 | 2.390 | 2.465 | 2.494 | 3.206 | 3.259 | 3.243 |
| ENSG0000279541 | AC005261.6 | NA | -0748 | 0 173 | -4327 | 1.51E-05 | 4.55E-03 | 2 408 | 1 838 | 2 441 | 1 232 | 1 184 | 1 578 |

Table S7. Differential expression analysis in U251 cells after the Alu insertion was deleted.

| ENSG0000075461 | CACNG4 | 17q24.2 | 0.448 | 0.104 | 4.308 | 1.65E-05 | 4.85E-03 | 4.260 | 3.841 | 3.660 | 4.849 | 5.372 | 5.870 |
|-----------------|------------|----------|--------|-------|--------|----------|----------|--------|--------|--------|--------|--------|--------|
| ENSG00000171992 | SYNPO | 5q33.1 | 0.399 | 0.093 | 4.301 | 1.70E-05 | 4.90E-03 | 1.800 | 1.930 | 2.065 | 2.452 | 2.690 | 2.539 |
| ENSG0000074071 | MRPS34 | 16p13.3 | 0.527 | 0.123 | 4.271 | 1.94E-05 | 5.47E-03 | 5.665 | 5.624 | 5.919 | 7.013 | 8.511 | 9.383 |
| ENSG00000101955 | SRPX | Xp11.4 | 0.443 | 0.104 | 4.266 | 1.99E-05 | 5.48E-03 | 2.610 | 2.501 | 2.506 | 3.577 | 3.491 | 3.328 |
| ENSG00000136026 | CKAP4 | 12q23.3 | 0.354 | 0.083 | 4.255 | 2.09E-05 | 5.64E-03 | 19.468 | 17.399 | 17.427 | 22.801 | 22.287 | 24.518 |
| ENSG0000080298 | RFX3 | 9p24.2 | -0.409 | 0.097 | -4.229 | 2.34E-05 | 6.18E-03 | 2.223 | 2.461 | 2.359 | 1.820 | 1.898 | 1.614 |
| ENSG00000183696 | UPP1 | 7p12.3 | 0.389 | 0.092 | 4.220 | 2.44E-05 | 6.32E-03 | 8.764 | 7.940 | 8.158 | 9.971 | 10.779 | 11.925 |
| ENSG00000197045 | GMFB | 14q22.2 | -0.420 | 0.100 | -4.208 | 2.58E-05 | 6.54E-03 | 1.732 | 1.493 | 1.592 | 1.200 | 1.136 | 1.276 |
| ENSG00000128510 | CPA4 | 7q32.2 | 0.660 | 0.158 | 4.178 | 2.95E-05 | 7.31E-03 | 1.985 | 1.248 | 1.734 | 2.829 | 2.229 | 2.812 |
| ENSG00000279099 | AC090740.1 | NA | -0.994 | 0.241 | -4.127 | 3.68E-05 | 8.96E-03 | 1.133 | 2.149 | 1.699 | 1.014 | 0.945 | 0.562 |
| ENSG00000179271 | GADD45GIP1 | 19p13.13 | 0.738 | 0.179 | 4.117 | 3.83E-05 | 9.15E-03 | 1.624 | 1.403 | 1.416 | 1.775 | 2.666 | 2.985 |
| ENSG00000137312 | FLOT1 | 6p21.33 | 0.389 | 0.095 | 4.108 | 3.98E-05 | 9.34E-03 | 29.664 | 29.344 | 28.360 | 33.975 | 38.433 | 42.455 |
| ENSG00000101974 | ATP11C | Xq27.1 | -0.304 | 0.074 | -4.103 | 4.09E-05 | 9.41E-03 | 8.406 | 8.452 | 7.983 | 6.859 | 6.599 | 6.734 |
| ENSG00000167657 | DAPK3 | 19p13.3 | 0.405 | 0.099 | 4.089 | 4.33E-05 | 9.61E-03 | 3.368 | 2.848 | 3.279 | 3.983 | 4.293 | 4.353 |
| ENSG00000116678 | LEPR | 1p31.3 | -0.475 | 0.116 | -4.090 | 4.30E-05 | 9.61E-03 | 0.730 | 0.658 | 0.618 | 0.473 | 0.445 | 0.527 |
| ENSG00000277443 | MARCKS | 6q21 | -0.307 | 0.075 | -4.072 | 4.66E-05 | 1.02E-02 | 30.514 | 29.567 | 30.392 | 25.585 | 23.370 | 24.474 |
| ENSG00000271533 | Z83843.1 | NA | -0.457 | 0.113 | -4.061 | 4.88E-05 | 1.05E-02 | 3.260 | 3.407 | 3.423 | 2.371 | 2.824 | 2.195 |
| ENSG00000188486 | H2AFX | 11q23.3 | 0.604 | 0.149 | 4.053 | 5.06E-05 | 1.07E-02 | 23.108 | 21.907 | 26.636 | 46.429 | 29.268 | 33.654 |
| ENSG00000133216 | EPHB2 | 1p36.12 | 0.657 | 0.163 | 4.025 | 5.71E-05 | 1.15E-02 | 0.735 | 0.507 | 0.532 | 0.772 | 0.881 | 1.147 |
| ENSG00000163191 | S100A11 | 1q21.3 | 0.384 | 0.095 | 4.025 | 5.71E-05 | 1.15E-02 | 65.500 | 68.378 | 65.427 | 76.793 | 90.157 | 94.136 |
| ENSG00000213639 | PPP1CB | 2p23.2 | -0.558 | 0.138 | -4.028 | 5.62E-05 | 1.15E-02 | 32.151 | 41.920 | 42.944 | 30.757 | 27.172 | 21.979 |
| ENSG00000103966 | EHD4 | 15q15.1 | 0.386 | 0.096 | 4.013 | 5.99E-05 | 1.17E-02 | 3.116 | 2.846 | 2.994 | 4.135 | 3.500 | 4.113 |
| ENSG00000205213 | LGR4 | 11p14.1 | -0.379 | 0.094 | -4.015 | 5.95E-05 | 1.17E-02 | 3.111 | 3.557 | 3.434 | 2.656 | 2.671 | 2.479 |
| ENSG00000215861 | AC245297.1 | NA | 0.483 | 0.121 | 3.993 | 6.54E-05 | 1.25E-02 | 5.433 | 5.209 | 5.045 | 6.320 | 7.768 | 7.905 |
| ENSG0000090975 | PITPNM2 | 12q24.31 | 0.434 | 0.109 | 3.989 | 6.64E-05 | 1.25E-02 | 0.646 | 0.553 | 0.553 | 0.777 | 0.782 | 0.814 |
| ENSG00000123091 | RNF11 | 1p32.3 | -0.394 | 0.099 | -3.987 | 6.69E-05 | 1.25E-02 | 7.010 | 6.328 | 6.522 | 4.672 | 4.892 | 5.602 |
| ENSG00000118503 | TNFAIP3 | 6q23.3 | 0.562 | 0.142 | 3.965 | 7.35E-05 | 1.32E-02 | 0.429 | 0.428 | 0.478 | 0.725 | 0.642 | 0.618 |
| ENSG00000150893 | FREM2 | 13q13.3 | -0.457 | 0.115 | -3.965 | 7.33E-05 | 1.32E-02 | 0.760 | 0.830 | 0.639 | 0.521 | 0.544 | 0.563 |
| ENSG00000125945 | ZNF436 | 1p36.12 | -0.507 | 0.128 | -3.959 | 7.53E-05 | 1.32E-02 | 8.837 | 11.102 | 10.679 | 8.015 | 7.650 | 5.990 |
| ENSG00000100599 | RIN3 | 14q32.12 | 0.402 | 0.103 | 3.903 | 9.48E-05 | 1.64E-02 | 0.900 | 0.836 | 0.756 | 1.093 | 1.079 | 1.129 |
| ENSG00000110047 | EHD1 | 11q13.1 | 0.362 | 0.094 | 3.842 | 1.22E-04 | 2.06E-02 | 2.735 | 2.446 | 2.685 | 3.301 | 3.183 | 3.662 |
| ENSG00000108819 | PPP1R9B | 17q21.33 | 0.345 | 0.090 | 3.844 | 1.21E-04 | 2.06E-02 | 6.064 | 6.805 | 6.788 | 7.945 | 8.599 | 8.546 |
| ENSG00000171385 | KCND3 | 1p13.2 | -0.695 | 0.181 | -3.839 | 1.24E-04 | 2.06E-02 | 1.079 | 1.655 | 1.504 | 1.104 | 0.844 | 0.686 |
| ENSG00000214160 | ALG3 | 3q27.1 | 0.374 | 0.098 | 3.828 | 1.29E-04 | 2.07E-02 | 2.842 | 2.792 | 3.141 | 3.751 | 3.688 | 3.989 |
| ENSG00000166949 | SMAD3 | 15q22.33 | 0.304 | 0.079 | 3.833 | 1.27E-04 | 2.07E-02 | 5.188 | 5.641 | 5.616 | 6.819 | 6.865 | 6.716 |
| ENSG00000185565 | LSAMP | 3q13.31 | -0.430 | 0.112 | -3.830 | 1.28E-04 | 2.07E-02 | 0.822 | 1.018 | 0.936 | 0.690 | 0.692 | 0.689 |
| ENSG00000164951 | PDP1 | 8q22.1 | 0.366 | 0.096 | 3.816 | 1.36E-04 | 2.14E-02 | 4.353 | 4.001 | 4.806 | 5.957 | 5.615 | 5.475 |
| ENSG00000077092 | RARB | 3p24.2 | 0.334 | 0.088 | 3.807 | 1.40E-04 | 2.14E-02 | 4.615 | 4.928 | 4.914 | 6.047 | 5.855 | 6.393 |
| ENSG00000149177 | PTPRJ | 11p11.2 | 0.281 | 0.074 | 3.809 | 1.39E-04 | 2.14E-02 | 3.740 | 3.560 | 3.627 | 4.506 | 4.455 | 4.368 |
| ENSG00000105519 | CAPS | 19p13.3 | -0.395 | 0.104 | -3.809 | 1.39E-04 | 2.14E-02 | 38.385 | 38.535 | 33.173 | 26.423 | 25.915 | 31.684 |
| ENSG00000134013 | LOXL2 | 8p21.3 | 0.300 | 0.079 | 3.782 | 1.56E-04 | 2.35E-02 | 12.249 | 12.876 | 12.350 | 14.834 | 16.440 | 15.076 |
| ENSG00000181904 | C5orf24 | 5q31.1 | -0.351 | 0.093 | -3.771 | 1.62E-04 | 2.42E-02 | 2.606 | 2.531 | 2.718 | 1.947 | 2.046 | 2.193 |
| ENSG00000115648 | MLPH | 2q37.3 | 0.498 | 0.132 | 3.759 | 1.71E-04 | 2.44E-02 | 0.933 | 0.727 | 0.741 | 1.017 | 1.091 | 1.288 |
| ENSG00000196352 | CD55 | 1q32.2 | 0.418 | 0.111 | 3.761 | 1.70E-04 | 2.44E-02 | 1.420 | 1.231 | 1.368 | 1.697 | 1.696 | 1.993 |

| ENSG00000167173 | C15orf39 | 15q24.2 | 0.389 | 0.103 | 3.758 | 1.71E-04 | 2.44E-02 | 1.774 | 1.594 | 1.573 | 2.115 | 2.011 | 2.359 |
|-----------------|------------|----------------|--------|-------|--------|----------|----------|---------|--------|--------|---------|---------|---------|
| ENSG00000149212 | SESN3 | 11q21 | -0.399 | 0.106 | -3.758 | 1.72E-04 | 2.44E-02 | 5.387 | 4.377 | 4.533 | 3.449 | 3.398 | 4.031 |
| ENSG00000111052 | LIN7A | 12q21.31 | -0.660 | 0.176 | -3.750 | 1.77E-04 | 2.49E-02 | 0.297 | 0.363 | 0.365 | 0.238 | 0.233 | 0.183 |
| ENSG0000005884 | ITGA3 | 17q21.33 | 0.285 | 0.076 | 3.744 | 1.81E-04 | 2.52E-02 | 34.811 | 35.441 | 33.731 | 40.169 | 42.392 | 44.626 |
| ENSG00000111206 | FOXM1 | 12p13.33 | 0.368 | 0.098 | 3.739 | 1.85E-04 | 2.54E-02 | 10.648 | 9.556 | 9.202 | 11.588 | 12.399 | 14.087 |
| ENSG00000106278 | PTPRZ1 | 7q31.32 | -0.579 | 0.155 | -3.723 | 1.97E-04 | 2.68E-02 | 1.297 | 1.868 | 1.413 | 1.141 | 1.112 | 0.829 |
| ENSG00000170545 | SMAGP | 12q13.13 | 0.539 | 0.145 | 3.709 | 2.08E-04 | 2.71E-02 | 0.650 | 0.610 | 0.539 | 0.897 | 0.797 | 0.919 |
| ENSG00000179958 | DCTPP1 | 16p11.2 | 0.425 | 0.115 | 3.707 | 2.10E-04 | 2.71E-02 | 4.563 | 3.965 | 3.775 | 5.341 | 5.181 | 6.018 |
| ENSG00000161638 | ITGA5 | 12q13.13 | 0.348 | 0.094 | 3.712 | 2.06E-04 | 2.71E-02 | 1.529 | 1.467 | 1.339 | 1.870 | 1.777 | 1.884 |
| ENSG00000126070 | AGO3 | 1p34.3 | -0.294 | 0.079 | -3.716 | 2.02E-04 | 2.71E-02 | 1.377 | 1.327 | 1.347 | 1.101 | 1.069 | 1.146 |
| ENSG00000269902 | AC234772.3 | NA | -0.503 | 0.135 | -3.711 | 2.07E-04 | 2.71E-02 | 7.191 | 7.476 | 8.161 | 4.807 | 5.888 | 5.510 |
| ENSG00000181104 | F2R | 5q13.3 | 0.483 | 0.130 | 3.704 | 2.12E-04 | 2.72E-02 | 3.761 | 2.742 | 3.027 | 4.828 | 3.842 | 4.684 |
| ENSG00000105810 | CDK6 | 7q21.2 | -0.294 | 0.080 | -3.696 | 2.19E-04 | 2.77E-02 | 11.464 | 12.209 | 11.015 | 9.458 | 9.136 | 9.803 |
| ENSG0000083067 | TRPM3 | 9q21.12-q21.13 | -0.460 | 0.125 | -3.693 | 2.21E-04 | 2.77E-02 | 0.219 | 0.227 | 0.203 | 0.156 | 0.149 | 0.167 |
| ENSG00000166897 | ELFN2 | 22q13.1 | 0.426 | 0.115 | 3.689 | 2.25E-04 | 2.80E-02 | 0.691 | 0.593 | 0.732 | 0.959 | 0.898 | 0.867 |
| ENSG00000114279 | FGF12 | 3q28-q29 | 0.478 | 0.130 | 3.686 | 2.28E-04 | 2.80E-02 | 5.081 | 4.384 | 4.132 | 5.463 | 5.849 | 7.681 |
| ENSG00000158856 | DMTN | 8p21.3 | 0.334 | 0.091 | 3.677 | 2.36E-04 | 2.87E-02 | 2.310 | 2.486 | 2.290 | 2.920 | 3.037 | 3.007 |
| ENSG00000232112 | TMA7 | 3p21.31 | -0.432 | 0.118 | -3.672 | 2.41E-04 | 2.91E-02 | 5.908 | 5.921 | 6.499 | 4.945 | 4.094 | 4.619 |
| ENSG00000179820 | MYADM | 19q13.42 | 0.353 | 0.096 | 3.668 | 2.45E-04 | 2.92E-02 | 6.716 | 6.796 | 6.376 | 8.070 | 7.950 | 9.462 |
| ENSG00000099250 | NRP1 | 10p11.22 | 0.414 | 0.114 | 3.644 | 2.68E-04 | 3.17E-02 | 8.962 | 7.157 | 7.503 | 9.666 | 9.829 | 12.076 |
| ENSG00000150630 | VEGFC | 4q34.3 | 0.986 | 0.274 | 3.596 | 3.23E-04 | 3.76E-02 | 0.349 | 0.205 | 0.225 | 0.391 | 0.466 | 0.681 |
| ENSG0000086289 | EPDR1 | 7p14.1 | 0.376 | 0.105 | 3.593 | 3.27E-04 | 3.76E-02 | 3.913 | 3.172 | 3.461 | 4.724 | 4.315 | 4.690 |
| ENSG00000133083 | DCLK1 | 13q13.3 | 0.351 | 0.098 | 3.593 | 3.27E-04 | 3.76E-02 | 0.863 | 0.889 | 0.931 | 1.140 | 1.244 | 1.056 |
| ENSG00000182768 | NGRN | 15q26.1 | 0.358 | 0.100 | 3.590 | 3.31E-04 | 3.78E-02 | 1.981 | 1.950 | 2.120 | 2.874 | 2.443 | 2.479 |
| ENSG00000231607 | DLEU2 | 13q14.2 | -0.405 | 0.113 | -3.580 | 3.43E-04 | 3.88E-02 | 1.663 | 1.759 | 1.620 | 1.333 | 1.371 | 1.123 |
| ENSG00000177556 | ATOX1 | 5q33.1 | 0.425 | 0.119 | 3.572 | 3.54E-04 | 3.97E-02 | 1.455 | 1.255 | 1.253 | 1.625 | 1.691 | 2.016 |
| ENSG00000176845 | METRNL | 17q25.3 | 0.419 | 0.117 | 3.566 | 3.63E-04 | 4.03E-02 | 1.387 | 1.348 | 1.464 | 1.777 | 1.976 | 1.891 |
| ENSG00000196923 | PDLIM7 | 5q35.3 | 0.452 | 0.128 | 3.541 | 3.99E-04 | 4.39E-02 | 2.219 | 1.782 | 2.038 | 2.401 | 2.683 | 3.206 |
| ENSG00000138685 | FGF2 | 4q28.1 | -0.341 | 0.096 | -3.537 | 4.05E-04 | 4.42E-02 | 2.445 | 2.686 | 2.612 | 2.208 | 1.980 | 1.954 |
| ENSG00000108518 | PFN1 | 17p13.2 | 0.434 | 0.124 | 3.517 | 4.36E-04 | 4.58E-02 | 109.396 | 92.025 | 86.907 | 109.017 | 130.535 | 151.369 |
| ENSG00000168056 | LTBP3 | 11q13.1 | 0.407 | 0.116 | 3.518 | 4.36E-04 | 4.58E-02 | 2.783 | 3.546 | 3.156 | 3.904 | 4.737 | 3.996 |
| ENSG00000141510 | TP53 | 17p13.1 | 0.301 | 0.086 | 3.521 | 4.30E-04 | 4.58E-02 | 7.938 | 8.752 | 7.903 | 9.624 | 10.461 | 10.344 |
| ENSG00000249087 | ZNF436-AS1 | 1p36.12 | -0.572 | 0.163 | -3.516 | 4.38E-04 | 4.58E-02 | 1.079 | 1.349 | 1.083 | 0.757 | 0.915 | 0.701 |
| ENSG00000265185 | SNORD3B-1 | 17p11.2 | -0.694 | 0.197 | -3.521 | 4.30E-04 | 4.58E-02 | 2.690 | 2.722 | 2.505 | 2.125 | 1.410 | 1.384 |
| ENSG00000131459 | GFPT2 | 5q35.3 | 0.473 | 0.135 | 3.509 | 4.50E-04 | 4.59E-02 | 0.934 | 0.952 | 0.810 | 1.056 | 1.390 | 1.303 |
| ENSG00000105329 | TGFB1 | 19q13.2 | 0.325 | 0.093 | 3.507 | 4.53E-04 | 4.59E-02 | 8.640 | 9.492 | 9.990 | 12.298 | 11.930 | 11.187 |
| ENSG00000166311 | SMPD1 | 11p15.4 | 0.296 | 0.084 | 3.512 | 4.45E-04 | 4.59E-02 | 6.882 | 7.505 | 7.347 | 9.031 | 8.850 | 8.922 |
| ENSG00000188647 | PTAR1 | 9q21.12 | -0.278 | 0.079 | -3.509 | 4.50E-04 | 4.59E-02 | 3.150 | 3.162 | 3.129 | 2.742 | 2.519 | 2.555 |
| ENSG00000163631 | ALB | 4q13.3 | -6.068 | 1.731 | -3.505 | 4.57E-04 | 4.59E-02 | 14.463 | 0.179 | 0.104 | 0.084 | 0.066 | 0.068 |
| ENSG00000171823 | FBXL14 | 12p13.33 | 0.406 | 0.116 | 3.498 | 4.68E-04 | 4.65E-02 | 1.987 | 2.090 | 1.902 | 2.433 | 2.647 | 2.863 |
| ENSG00000170043 | TRAPPC1 | 17p13.1 | 0.329 | 0.094 | 3.496 | 4.72E-04 | 4.65E-02 | 13.284 | 13.552 | 11.895 | 15.231 | 17.001 | 16.586 |
| ENSG00000188153 | COL4A5 | Xq22.3 | -0.291 | 0.083 | -3.495 | 4.74E-04 | 4.65E-02 | 3.358 | 3.687 | 3.390 | 2.829 | 2.876 | 2.861 |
| ENSG00000172795 | DCP2 | 5q22.2 | -0.351 | 0.101 | -3.482 | 4.97E-04 | 4.84E-02 | 3.376 | 3.865 | 3.682 | 3.089 | 2.933 | 2.580 |
| ENSG00000044524 | EPHA3 | 3p11.1 | -0.347 | 0.100 | -3.476 | 5.09E-04 | 4.88E-02 | 34.770 | 43.168 | 37.880 | 30.646 | 32.025 | 28.833 |

| ENSG00000161179 YDJC | 22q11.21 | 0.601 | 0.173 | 3.469 | 5.23E-04 | 4.98E-02 | 0.930 | 0.927 | 1.158 | 1.809 | 1.363 | 1.444 |
|-----------------------|----------|-------|-------|-------|----------|----------|-------|-------|-------|-------|-------|-------|
| ENSG00000149260 CAPN5 | 11q13.5 | 0.445 | 0.129 | 3.466 | 5.28E-04 | 4.99E-02 | 0.690 | 0.729 | 0.661 | 0.806 | 1.023 | 1.011 |

Abbreviation: BP, biological position; FC, fold change; S.E., standard error; Ctrl, control; *Alu* del, deletion of *Alu* insertion.

Table S8. KEGG pathway analysis of DEGs in U251 cells.

| ID | Description | Gene Ratio | Bg Ratio | p-value | adjust p-value | q-value | gene name | Count |
|----------|----------------------------------|------------|----------|----------|----------------|----------|--|-------|
| hsa04218 | Cellular senescence | 8/65 | 160/8011 | 4.08E-05 | 6.10E-03 | 4.65E-03 | MYC/EIF4EBP1/PPP1CB/SMAD3/FOXM1/CDK6/TP53/TGFB1 | 8 |
| hsa05222 | Small cell lung cancer | 6/65 | 92/8011 | 9.33E-05 | 6.10E-03 | 4.65E-03 | MYC/RARB/ITGA3/CDK6/TP53/COL4A5 | 6 |
| hsa04151 | PI3K-Akt signaling pathway | 11/65 | 354/8011 | 1.12E-04 | 6.10E-03 | 4.65E-03 | MYC/EIF4EBP1/THBS2/ITGA3/ITGA5/F2R/CDK6/ VEGFC/FGF2/TP53/COL4A5 | 11 |
| hsa05205 | Proteoglycans in cancer | 8/65 | 204/8011 | 2.24E-04 | 9.12E-03 | 6.95E-03 | MYC/PLAUR/SRC/PPP1CB/ITGA5/FGF2/TP53/TGFB1 | 8 |
| hsa05220 | Chronic myeloid leukemia | 5/65 | 76/8011 | 3.57E-04 | 9.69E-03 | 7.38E-03 | MYC/SMAD3/CDK6/TP53/TGFB1 | 5 |
| hsa04512 | ECM-receptor interaction | 5/65 | 88/8011 | 7.02E-04 | 1.63E-02 | 1.25E-02 | THBS2/FREM2/ITGA3/ITGA5/COL4A5 | 5 |
| hsa04510 | Focal adhesion | 7/65 | 199/8011 | 1.08E-03 | 2.20E-02 | 1.68E-02 | THBS2/SRC/PPP1CB/ITGA3/ITGA5/VEGFC/COL4A5 | 7 |
| hsa05226 | Gastric cancer | 6/65 | 149/8011 | 1.25E-03 | 2.27E-02 | 1.73E-02 | MYC/SMAD3/RARB/FGF2/TP53/TGFB1 | 6 |
| hsa04810 | Regulation of actin cytoskeleton | 7/65 | 213/8011 | 1.60E-03 | 2.61E-02 | 1.99E-02 | SRC/PPP1CB/ITGA3/ITGA5/F2R/FGF2/PFN1 | 7 |
| hsa04110 | Cell cycle | 5/65 | 124/8011 | 3.23E-03 | 4.20E-02 | 3.20E-02 | MYC/SMAD3/CDK6/TP53/TGFB1 | 5 |
| hsa04360 | Axon guidance | 6/65 | 181/8011 | 3.35E-03 | 4.20E-02 | 3.20E-02 | SEMA6A/EPHA4/SRC/EPHB2/NRP1/EPHA3 | 6 |

Abbreviation: Bg, background.

Table S9. Gene Ontology (GO) BP analysis of DEGs in U251 cells.

| ID | Description | Gene Ratio | Bg Ratio | p-value | adjust p-value | q-value | Count |
|------------|---|------------|-----------|----------|----------------|----------|-------|
| GO:1901888 | regulation of cell junction assembly | 8/113 | 88/18670 | 6.03E-08 | 5.86E-05 | 4.45E-05 | 8 |
| GO:0010810 | regulation of cell-substrate adhesion | 11/113 | 215/18670 | 7.61E-08 | 5.86E-05 | 4.45E-05 | 11 |
| GO:0001933 | negative regulation of protein phosphorylation | 14/113 | 429/18670 | 3.20E-07 | 1.41E-04 | 1.07E-04 | 14 |
| GO:0001655 | urogenital system development | 12/113 | 330/18670 | 7.62E-07 | 1.96E-04 | 1.49E-04 | 12 |
| GO:0010634 | positive regulation of epithelial cell migration | 9/113 | 171/18670 | 9.70E-07 | 1.98E-04 | 1.50E-04 | 9 |
| GO:0016311 | dephosphorylation | 14/113 | 478/18670 | 1.16E-06 | 1.98E-04 | 1.50E-04 | 14 |
| GO:0007050 | cell cycle arrest | 10/113 | 237/18670 | 1.78E-06 | 2.38E-04 | 1.81E-04 | 10 |
| GO:0018108 | peptidyl-tyrosine phosphorylation | 12/113 | 363/18670 | 2.06E-06 | 2.65E-04 | 2.01E-04 | 12 |
| GO:0072091 | regulation of stem cell proliferation | 6/113 | 70/18670 | 4.11E-06 | 4.53E-04 | 3.44E-04 | 6 |
| GO:0048771 | tissue remodeling | 8/113 | 179/18670 | 1.33E-05 | 1.17E-03 | 8.87E-04 | 8 |
| GO:0001667 | ameboidal-type cell migration | 12/113 | 461/18670 | 2.31E-05 | 1.69E-03 | 1.29E-03 | 12 |
| GO:0050769 | positive regulation of neurogenesis | 12/113 | 474/18670 | 3.03E-05 | 1.94E-03 | 1.48E-03 | 12 |
| GO:0050918 | positive chemotaxis | 5/113 | 68/18670 | 5.72E-05 | 3.09E-03 | 2.35E-03 | 5 |
| GO:0051348 | negative regulation of transferase activity | 9/113 | 285/18670 | 5.92E-05 | 3.09E-03 | 2.35E-03 | 9 |
| GO:0090287 | regulation of cellular response to growth factor stimulus | 9/113 | 292/18670 | 7.14E-05 | 3.55E-03 | 2.69E-03 | 9 |
| GO:1903034 | regulation of response to wounding | 7/113 | 179/18670 | 1.09E-04 | 5.23E-03 | 3.97E-03 | 7 |
| GO:0045926 | negative regulation of growth | 8/113 | 249/18670 | 1.37E-04 | 5.91E-03 | 4.49E-03 | 8 |
| GO:0007611 | learning or memory | 8/113 | 256/18670 | 1.66E-04 | 6.72E-03 | 5.11E-03 | 8 |
| GO:0050921 | positive regulation of chemotaxis | 6/113 | 135/18670 | 1.71E-04 | 6.77E-03 | 5.15E-03 | 6 |
| GO:0048010 | vascular endothelial growth factor receptor signaling pathway | 5/113 | 96/18670 | 2.93E-04 | 1.01E-02 | 7.71E-03 | 5 |
| GO:0050804 | modulation of chemical synaptic transmission | 10/113 | 436/18670 | 3.17E-04 | 1.05E-02 | 7.99E-03 | 10 |
| GO:0099177 | regulation of trans-synaptic signaling | 10/113 | 437/18670 | 3.23E-04 | 1.06E-02 | 8.04E-03 | 10 |
| GO:0001666 | response to hypoxia | 9/113 | 359/18670 | 3.35E-04 | 1.09E-02 | 8.26E-03 | 9 |
| GO:2000278 | regulation of DNA biosynthetic process | 5/113 | 108/18670 | 5.05E-04 | 1.35E-02 | 1.03E-02 | 5 |
| GO:0007569 | cell aging | 5/113 | 116/18670 | 6.99E-04 | 1.63E-02 | 1.24E-02 | 5 |
| GO:0051099 | positive regulation of binding | 6/113 | 179/18670 | 7.73E-04 | 1.75E-02 | 1.33E-02 | 6 |
| GO:0006914 | autophagy | 10/113 | 496/18670 | 8.63E-04 | 1.82E-02 | 1.38E-02 | 10 |
| GO:0061919 | process utilizing autophagic mechanism | 10/113 | 496/18670 | 8.63E-04 | 1.82E-02 | 1.38E-02 | 10 |
| GO:1905477 | positive regulation of protein localization to membrane | 5/113 | 122/18670 | 8.78E-04 | 1.83E-02 | 1.39E-02 | 5 |
| GO:1905475 | regulation of protein localization to membrane | 6/113 | 187/18670 | 9.70E-04 | 1.95E-02 | 1.48E-02 | 6 |
| GO:0110053 | regulation of actin filament organization | 7/113 | 261/18670 | 1.06E-03 | 2.05E-02 | 1.56E-02 | 7 |
| GO:0030100 | regulation of endocytosis | 7/113 | 281/18670 | 1.61E-03 | 2.57E-02 | 1.95E-02 | 7 |
| GO:1990778 | protein localization to cell periphery | 7/113 | 311/18670 | 2.85E-03 | 3.46E-02 | 2.63E-02 | 7 |
| GO:0070588 | calcium ion transmembrane transport | 7/113 | 315/18670 | 3.06E-03 | 3.56E-02 | 2.71E-02 | 7 |
| GO:0046488 | phosphatidylinositol metabolic process | 5/113 | 174/18670 | 4.15E-03 | 4.30E-02 | 3.27E-02 | 5 |
| GO:0007596 | blood coagulation | 7/113 | 336/18670 | 4.36E-03 | 4.45E-02 | 3.38E-02 | 7 |
| GO:0071496 | cellular response to external stimulus | 7/113 | 339/18670 | 4.57E-03 | 4.50E-02 | 3.42E-02 | 7 |

Abbreviation: Bg, background.

| Gene ID | Gene name | BP | НЕК293Т | | | | | U251 | | | | |
|-----------------|-----------|---------|----------|-------|-------|----------|----------|----------|-------|-------|----------|----------|
| | | | log2(FC) | S.E. | stat | p-value | p-adjust | log2(FC) | S.E. | stat | p-value | p-adjust |
| ENSG00000110047 | EHD1 | 11q13.1 | 0.290 | 0.096 | 3.022 | 2.51E-03 | 4.71E-02 | 0.362 | 0.094 | 3.842 | 1.22E-04 | 2.06E-02 |
| ENSG00000167173 | C15orf39 | 15q24.2 | 0.279 | 0.084 | 3.331 | 8.66E-04 | 2.64E-02 | 0.389 | 0.103 | 3.758 | 1.71E-04 | 2.44E-02 |
| ENSG00000179958 | DCTPP1 | 16p11.2 | 0.435 | 0.082 | 5.302 | 1.15E-07 | 6.32E-05 | 0.425 | 0.115 | 3.707 | 2.10E-04 | 2.71E-02 |
| ENSG00000145632 | PLK2 | 5q11.2 | 0.534 | 0.177 | 3.016 | 2.56E-03 | 4.77E-02 | 0.510 | 0.084 | 6.041 | 1.53E-09 | 3.87E-06 |
| ENSG00000106211 | HSPB1 | 7q11.23 | 0.289 | 0.088 | 3.297 | 9.76E-04 | 2.82E-02 | 0.502 | 0.075 | 6.679 | 2.41E-11 | 7.63E-08 |
| ENSG00000179041 | RRS1 | 8q13.1 | 0.332 | 0.100 | 3.306 | 9.45E-04 | 2.81E-02 | 0.774 | 0.167 | 4.651 | 3.31E-06 | 1.20E-03 |

Table S10. The shared DEGs between HEK293T and U251 cells after the *Alu* insertion was deleted.