



Characterization of IncRNA Profiles of Plasma-Derived Exosomes From Type 1 Diabetes Mellitus

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Pang H, Fan W, Shi X, Li J, Wang Y, Luo S, Lin J, Huang G, Li X, Xie Z and Zhou Z (2022) Characterization of IncRNA Profiles of Plasma-Derived Exosomes From Type 1 Diabetes Mellitus. Front. Endocrinol. 13:822221. doi: 10.3389/fendo.2022.822221 **Backgrounds:** Exosomes contain several types of transcripts, including long non-coding RNAs (IncRNAs), and have been shown to exert important effects in human diseases. However, the roles of exosomal IncRNAs in type 1 diabetes mellitus (T1DM) have not been well investigated. In the present study, we characterized the plasma-derived exosomal IncRNAs expression profiles of T1DM and predict their potential function in the pathogenesis of T1DM.

Material and Methods: Exosomal IncRNA expression profiles were detected by Illumina Hiseq platform (T1DM subjects N=10; age-, sex- matched Control subjects N=10). Six exosomal IncRNAs were selected to validate their expression level by using quantitative real-time PCR (qRT-PCR) (T1DM subjects N=30; age-, sex- matched Control subjects N=30). Bioinformatics analysis approaches were carried out to explore the potential biological function of differentially expressed IncRNAs.

Results: A total of 162 differentially expressed exosomal IncRNAs were identified in T1DM patients compared with control subjects, among which 77 up-regulated and 85 down-regulated. The expression level of the selected six IncRNAs didn't show significant difference in the following qRT-PCR analysis. Gene Ontology analysis enriched terms such as activation of phospholipase D activity, neuronal cell body membrane, and calcium sensitive guanylate cyclase activator activity for cis-acting genes of IncRNAs, and metal ion binding for trans-acting genes. The most enriched Kyoto Encyclopedia of Genes and Genomes pathways for the IncRNAs were associated with oxidative phosphorylation and Parkinson's disease for cis-acting genes, and pathways in cancer as well as focal adhesion for trans-acting genes.

Conclusions: This study characterized the IncRNA profiles of plasma-derived exosomes from T1DM for the first time and these results highlighted the potential role of exosomal IncRNAs in T1DM pathogenesis. A better understanding of exosomal IncRNA profiling will provide novel insights into its molecular mechanisms.

Keywords: type 1 diabetes mellitus, exosomes, long non-coding RNA, plasma-derived, bioinformatics analysis

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by absolute insulin deficiency and resultant hyperglycemia (1, 2). The incidence and prevalence of T1DM are increasing worldwide and more than 463 million people are affected (3, 4). This disease is incurable at present and patients with T1DM have to rely on lifelong insulin administration. Besides, the high prevalence of diabetic complications, such as retinopathy, nephropathy, as well as neuropathy, severely influence the life quality of T1DM patients and impose a considerable financial burden. The pathogenesis of T1DM is extremely complex and multiple factors, including genetic backgrounds, environmental triggers, and behavioral changes, may contribute to the onset and development of T1DM (5-7). An improved understanding of T1DM pathophysiology will render early identification and intervene of T1DM.

Growing evidence has suggested that a small extracellular vesicle (EV), namely exosome, plays an important role in multiple pathogenic processes, including T1DM (8). Exosomes, which can be released by virtually all cell types, are significant mediators of intercellular communication and interorgan crosstalk through transferring bioactive molecules, including proteins, lipids, and RNAs between cells (9, 10). Moreover, the content of exosomes is strictly regulated in response to all kinds of endogenous or exogenous stimulations, thus reflecting the biological events or disease conditions (11). Therefore, a better understanding of exosomes may provide a valuable target for disease diagnosis and treatment.

Long non-coding RNAs (lncRNAs), a sub-class of noncoding RNA family, have emerged as crucial regulators in multiple pathophysiological conditions (12). LncRNAs are more than 200 nucleotides in length and take part in the regulation of various cellular and biological processes, such as gene silencing, histone modifications and DNA methylation (13, 14). Accumulating evidence has highlighted the role of lncRNAs in pancreatic islets and development of T1DM (15–18). However, the research about the exosomal lncRNA is relatively lacking, especially in T1DM. Here, we investigated the plasmaderived exosomal lncRNA expression profiles in patients with T1DM and explored their biological function. This present work provided a novel insight into the pathogenesis of T1DM and laid a foundation for using exosomal lncRNAs as biomarkers and therapeutic targets for T1DM.

MATERIALS AND METHODS

Study Subjects

Patients with T1DM attending the Diabetes Clinic at the Second Xiangya Hospital were recruited. The inclusion criteria of case group were as follows: (1) fulfilling the WHO diagnostic criteria for diabetes (1999); (2) acute onset and insulin dependency within 6 months after diagnosis; (3) positive for at least one following islet autoantibodies: GADA (glutamic acid decarboxylase antibody), IA-2A (protein tyrosine phosphatase antibody), or ZnTA8 (zinc transporter 8 antibody); (4) diabetes duration less than 5 years. Exclusion criteria included pregnancy, combined with other autoimmune diseases, malignant tumors, or a recent cardiovascular event. Non-diabetic subjects without autoimmune diseases, cancers, or family history of diabetes were recruited as health control. This case-control study was approved by the Ethics Committee of the Second Xiangya Hospital and all the research methods were conducted in accordance with the ethical guidelines of the Declaration of Helsinki. All the participants or their guardians indicated that they fully understand the research goals and procedures, and written informed consent was obtained. A total of 10 cases and 10 controls were included in the discovery phase. There was no significant difference in age (P=0.97) and sex (P=0.36) between two groups (Table 1). Besides, we used a new cohort (T1DM subjects N=30; age-, sex- matched Control subjects N=30) for the following qRT-PCR analysis.

Isolation of Plasma

Peripheral blood was collected in the EDTA blood tubes from each participant and plasma was separated by centrifugation at 3000 g for 15 min at 4°C. The plasm samples were stored at -80°C before use.

Isolation of Exosome

Size exclusion chromatography methods were adopted to isolate exosomes. In brief, 1 mL of 0.8 μ m filtered plasma was 1.5-fold diluted with phosphate-buffered saline (PBS) and the further purification was made by using Exosupur[®] columns (Echobiotech, China). Next, we eluted the samples with 0.1M PBS and collected about 2 mL elute fractions. The collected fractions were then concentrated to 200 μ L by 100 kDa molecular weight cut-off Amicon[®] Ultra spin filters (Merck, Germany). All procedures were operated according to the manufacture's institutions.

TABLE 1 | Characteristics of T1DM and control subjects.

Characteristic	T1DM (n=10)	Control (n=10)	P value	
Sex (male/female)	3/7	5/5	0.36	
Age (year)	25.20 ± 7.24	25.10 ± 2.96	0.97	
BMI (kg/m2)	21.26 ± 2.71	20.40 ± 2.24	0.47	
Duration (months)	25.40 ± 14.94	-	-	
FPG (mmol/L)	7.79 ± 3.32	-	-	
HbA1c %	8.01 ± 2.20	-	-	

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, Hemoglobin A1c.

Transmission Electron Microscopy (TEM)

We put 10 μ L purified exosome on a copper mesh and the sample was incubated at room temperature for 1 min. The exosome was negatively stained with uranyl acetate solution for 1 min after washing with sterile distilled water. After dried for 2 min under incandescent light, the exosome was examined under a TEM (H-7650, Hitachi Ltd., Tokyo, Japan).

Nanoparticle Tracking Analysis (NTA)

The size distribution and quality of isolated particle (concentrations between 1×10^7 /mL and 1×10^9 /mL) were determined by the ZetaView PMX 110 (Particle Metrix, Meerbusch, Germany), which equipped with 405 nm laser. A 60 second video was taken with a frame rate of 30 frames/second. The, the particle movement was analyzed by NTA software (ZetaView 8.02.28).

Western Blot Analysis (WB)

The exosome supernatant was denatured in $5 \times$ sodium dodecyl sulfonate (SDS) buffer and subjected to WB analysis (10% SDS-polyacrylamide gel electrophoresis; 50 µg protein/lane) using rabbit polyclonal antibody CD63, TSG101, Alix and calnexin. The proteins were visualized on the Tanon4600 Automatic chemiluminescence image analysis system (Tanon, Shanghai, China). The identification of exosome, including TEM, NTA, and WB analysis, was entrusted the company (Echo Biotech Co., Ltd, Beijing, P. R. China).

Total RNA Isolation

The miRNeasy Serum/Plasma Advanced Kit (Qiagen, cat. No. 217204) was used to extract and purify the exosomal RNA in compliance with the kit instruction. The concentration and purity of RNA were evaluated using the RNA Nano 6000 Assay Kit of the Agilent Bioanalyzer 2100 System (Agilent Technologies, CA, USA).

Library Preparation and Sequencing

The extracted RNA was used as input material for sequencing libraries using the SMARTer Stranded Total RNA-Seq Kit (Takara Bio USA, Inc.) according to manufacturer's recommendations. Index codes were added to attribute sequences to each sample. At last, library quality was evaluated on the Agilent Bioanalyzer 2100 and qPCR. The clustering of the index-coded samples was performed on acBot Cluster Generation System using TruSeq PE Cluster Kitv3-cBot-HS (Illumina, San Diego, CA, USA). After cluster generation, the library preparations were sequenced on an Illumina Hiseq platform and paired-end reads were generated.

LncRNA Analysis

The transcriptome was assembled using the Stringtie and Scripture based on the reads mapped to the reference genome. The assembled transcripts were annotated using the Cuffcompare program from the Cufflinks package. The unknown transcripts were used to screen for putative lncRNAs. Four computational approaches including CPC, CNCI, Pfam, and CPAT were combined to elect ncRNA candidates from presumed proteincoding RNAs in the unknown transcripts. Presumed proteincoding RNAs were filtered out using exon number threshold and a minimum length. Transcripts having more than two exons and with lengths more than 200 nt were selected as lncRNA candidates and further screened using CPC, CNCI, Pfam, and CPAT that have the power to distinguish the proteincoding genes from the non-coding genes. As well as the different types of lncRNAs include long intergenic lncRNA (lincRNA), intronic lncRNA, anti-sense lncRNA were selected using cuff compare. Stringtie was used to calculate FPKMs of lncRNAs in each sample. Gene FPKMs (fragments per kilo-base of exon per million fragments) were computed by summing the FPKMs of transcripts in each gene group. The lncRNA sequencing and lncRNA analysis were entrusted the company (Echo Biotech Co., Ltd, Beijing, P. R. China).

GO and KEGG Pathway Enrichment Analysis

Gene Ontology (GO) enrichment analysis of the differentially expressed lncRNAs was implemented by the topGO R packages. We used KOBAS (19) software to test the statistical enrichment of differential expression genes in Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (http://www.genome.jp/kegg/).

Quantitative Real-Time PCR (qRT-PCR) Assay

The total RNA from exosomes was extracted using miRNeasy Serum/Plasma Advanced Kit (Qiagen, cat. No. 217204) according to the manufacturer's protocol. The total RNA was then reverse transcribed to synthesize cDNA using PrimeScriptTM RT reagent Kit (Perfect Real Time) (TAKARA, RR037A). The abundance of target gene expression was detected by TaqMan[®] probe using qRT-PCR. 2 μ L of cDNA was used as the template for each PCR reaction. The GADPH was selected as the internal reference gene. The sequence of primers and probes were shown as **Table 2**.

Statistical Analysis

We used SPSS software version 20.0 to perform the statistical analysis. The data were presented as mean \pm SD (standard deviation). Differential expression analysis of lncRNAs between two groups was performed using the Mann Whitney U test with cutoff FPKM > 5, *P*-value < 0.05 and Fold change > 1.5. The comparisons of the relative expression level of candidate lncRNAs in qRT-PCR were analyzed by the unpaired t-test. A *P*-value less than 0.05 was considered as statistically significant.

RESULTS

Characterization of Exosome

We used TEM and NTA to evaluate the morphology and sizes distribution of isolated exosome. As shown by **Figure 1**, the isolated particles were oval and cup-shaped with diameter range between 30 nm to 200 nm (median, 91.7 nm). WB analysis indicated that the presence of exosomal positive protein markers Alix, Tsg101, and CD63, and the absence of Calnexin, the negative

LncRNA	Symbol	Primer Sequence (5'-3')
ENST00000533796	TALDO1-209	F-GATGCTACCACCCACCCG
		R-AATTCGGTCCTTGCTGATCC
		P-CCGGAAGCTGGGCGGGTCAC
ENST00000472614	GNB1-207	F-GAGGGCGCTGAGACAAATT
		R-GTGCTCTTCAATGCCACCTT
		P-CCAGACCAGAAGCCCTTCTGAATTAAG
ENST00000525207	SF3B2-204	F-GCTGAAGGAGAGCCGC
		R-TGTCCTCCTCAGTCTCTGAC
		P-AGGAAATGGAAACAGATGCTCGCT
ENST00000495420	ANP32A-208	F-GAGCCTTCAAAGTCCTAAAACG
		R-TTCATTCGACCGACTGTTGT
		P-AGAGCTGCGGAACAGGACG
ENST00000488260	EIF1B-204	F-CGGCAGGGACTGAGGATT
		R-ATCACAGTACCATTACAGGCAAA
		P-ATCCAGCAACGGAACGGCA
ENST00000505090	CANX-210	F-TTTCAGCCAGGCGTTGTG
		R-CTCCTCATCTCCCTTGTCCT
		P-CCCGTGGCTGTGGGTAGTC

protein marker for exosome. All these results suggested that the isolated exosomes were well-prepared and with good purity.

An Overview of the RNA Sequencing Results

The procedures of lncRNA sequencing and bioinformatics analysis were summarized in **Figure 2**. A total of 20 samples, including 10 patients and 10 healthy controls were constructed and analyzed. The percentage of Q30 base was at least 91.94%. A total of 40065 lncRNAs, including 33453 known lncRNAs and 6612 novel lncRNAs were generated. Among these identified

IncRNAs, lincRNAs accounted for the largest proportion (69.1%), followed by intronic lncRNAs (15.5%), sense lncRNAs (8.6%), and antisense lncRNAs (6.8%). Then, we predicted the target genes of lncRNA. On the one hand, it is predicted that the adjacent genes within 100 kb were its cis-acting gene because lncRNA could regulate the expression of neighboring genes. On the other hand, the trans-acting genes of the lncRNA were predicted by analyzing the expression correlation between lncRNA and corresponding mRNA. The genes with absolute Pearson correlation coefficient greater than 0.9 and *P*-value less than 0.01 were taken as the trans-acting genes of the lncRNA.





Differentially Expressed Exosomal IncRNAs

Based on the plasma-derived exosomal lncRNA expression profiles, differentially expressed lncRNAs were distinguished between T1DM patients and control subjects. Hierarchical clustering analysis was performed to cluster lncRNAs according to their expression level (**Figure 3A**). As shown by volcano diagram (**Figure 3B**) and MA plot (**Figure 3C**), total of 162 differentially expressed lncRNAs were identified, in which 77 up-regulated and 85 down-regulated (**Table 3**). These results indicated that plasma-derived exosomal lncRNA expression profiles were distinguishable between T1DM patients and control subjects.

Functional Analysis of Exosomal IncRNAs

To explore the potential biological function of 162 differentially expressed lncRNAs, GO enrichment analysis and the KEGG pathway analysis were employed. The lncRNAs exert biological effects by acting as cis- or trans- regulators (20, 21). We summarized the significantly enriched GO terms of cis-acting genes of differentially expressed lncRNAs regarding to the biological process (BP), cellular component (CC), and molecular function (MF), respectively (**Figure 4A**). For BP, the term with the most genes and with the highest enrichment score was the activation of phospholipase D activity (GO:0031584) (**Figure 4B**). For CC, the term with the most genes was the extracellular exosome (GO:0070062) and with the highest score was neuronal cell body membrane (GO:0032809) (Figure 4C). In addition, for MF the terms DNA binding transcription factor activity (GO:0003700) and protein binding (GO:0005515) ware associated with most genes, and the most enriched term was calcium sensitive guanylate cyclase activator activity (GO:0008048) (Figure 4D). We also summarized the GO terms of trans-acting genes (Figure 5A). For BP, the term with the most genes was the positive regulation of transcription from RNA polymerase II promoter (GO:0045944) (Figure 5B). For CC, the term cytosol (GO:0005829) was correlated to most genes (Figure 5C). For MF, the term with protein binding (GO:0005515) was most genes, and metal ion binding (GO:0046872) was most significantly enriched term (Figure 5D). Besides, the enriched pathways of target genes of lncRNA were analyzed by KEGG. For cis-acting genes, the most significantly enriched terms were involved in oxidative phosphorylation (ko00190) and Parkinson's disease (ko05012) (Figure 6A). For trans-acting genes, the terms pathways in cancer (ko05200) and focal adhesion (ko04510) were related to most genes (Figure 6B). We also performed the disease annotation of identified lncRNAs through sequence alignment with LncRNADisease database. The results showed some IncRNAs were associated with autoimmune diseases, including dermatomyositis and polymyositis. LncRNA can be precursor molecule of miRNA. We also detected the lncRNAs which serve as precursor of miRNA through comparing and predicting the miRNA sequence in miRbase database.



expressed exosomal IncRNAs in T1DM and control subjects. G1: control group; G2: case group.

TABLE 3	The detailed information	of the differentially e	expressed exosomal IncRNAs.
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ID	Symbol	P-value	log2FC	Regulated
ENST00000533796	TALDO1-209	6.24E-06	-6.22261	down
ENST00000547703	MYL6-208	7.84E-06	-7.97936	down
ENST00000472614	GNB1-207	1.28E-05	-5.81213	down
ENST00000525207	SF3B2-204	6.42E-05	5.004214	up
ENST00000514674	CCT5-212	9.56E-05	4.352669	up
ENST00000514918	NSA2-203	0.00013006	-4.66882	down
ENST00000515015	IK-208	0.00016215	5.635708	up
ENST00000436115	NDUFS7-204	0.000189895	-5.98882	down
ENST00000496582	RPL35A-208	0.000212962	-4.83713	down
ENST00000620389	SRSF3-207	0.000245529	-5.60859	down
ENST00000495420	ANP32A-208	0.000265961	-4.70741	down
ENST00000585223	DDX5-233	0.000385727	3.60407	up
ENST00000587642	WBP2-207	0.000387307	4.236054	up
ENST00000565031	NDUFB10-203	0.00054778	4.086463	up
ENST00000472568	ADD3-207	0.000589455	-3.97259	down
ENST00000531008	RPS13-207	0.000641612	4.050101	up
ENST00000573505	ALDH3A2-210	0.000700788	-4.38782	down
ENST00000550184	MYL6-216	0.00078891	-4.29868	down
ENST00000484600	ARPC1B-218	0.000864268	-5.89173	down
ENST00000466129	RPS24-207	0.000999187	3.280526	up
ENST00000492519	PABPC4-217	0.001059294	3.753608	up
ENST00000488260	EIF1B-204	0.001073793	-4.21143	down
ENST00000561048	PPIB-203	0.001105467	-4.49263	down
ENST00000489109	ANXA1-206	0.001150385	-4.69253	down

(Continued)

TABLE 3 | Continued

NEXTCO00202009 IPACI-1072 0.001114/24. -9.6524 down NEXTCO000202000 IPACI-1020 0.001201/17. -9.6524 up NEXTCO0001472680 AIPAL-116 0.001201/07. -9.81000 up DESTCO000460203 PRLA_201 0.00150307 -9.81007 up DESTCO000460203 PRLA_201 0.00160004 -4.66075 up DESTCO000460204 HA_2021-213 0.00160743 -4.66075 up DESTCO00046074 PRLA_203 0.00160743 -4.80074 up DESTCO00046074 PRLA_203 0.00160744 -4.06075 up DESTCO00046074 PRLA_203 0.00160747 -4.10406 up DESTCO000477207 PLMB-1235 0.00220503 -5.61764 down DESTCO000520203 PRLA_201 0.00027777 -4.10406 down DESTCO000520203 PRLA_201 0.00027777 -4.10406 down DESTCO000520203 PRLA_201 0.00027777 -4.10406 down DESTCO000520203	ID	Symbol	P-value	log2FC	Regulated
ENSTODUCTORSPRING ENSPIRED 0.00120172 4.45234 0.007 ENSTODUCTORSPRING PAPIN1-716 0.001203881 4.14.07914 1.001200801 3.81007 0.001 ENSTODUCTORSPRING PAPIN1-716 0.001503057 3.81007 0.001	ENST00000502548	RACK1-202	0.00119424	-3.65467	down
ENSTODO0472800 AP2M.716 0.001238068 4.078642 up ENSTODO048008 HPLS-217 0.00163827 -3.81907 down ENSTODO048008 HPLS-213 0.00163827 -3.212781 up ENSTODO048002 HPLS-213 0.00178328 -4.48675 down ENSTOD002805 UP1M-205 0.01187820 2.314167 up ENSTOD00048002 HTEFR-208 0.002387200 4.141541 up ENSTOD00048002 HTEFR-208 0.002237200 4.141541 down ENSTOD00058167 PSMA06-12 0.00223803 -5.51764 down ENSTOD00058169 HPS-204 0.00228303 -5.51764 down ENSTOD00058169 HPS-204 0.00248032 -3.5869 down ENSTOD00058169 HPS-204 0.00024737 3.4769 down ENSTOD00058169 HPS-204 0.00024734 3.43627 down ENSTOD0005777 HUBP-206 0.00074734 3.43627 down ENSTOD0005778 HUBP-207	ENST00000526990	EHBP1L1-202	0.001204172	-4.95234	down
BNTCOD005490393 HLA-DPB1:217 0.001582037 -3.81907 down BNTCOD00546030 BY15-710 0.001582047 3.212781 up BNTCOD00540502 SPTB11-715 0.00158205 4.64177 down BNTCOD0052205 C110656205 0.001592278 2.814192 up BNTCOD0052206 C110656205 0.00159278 2.814192 up BNTCOD0050500 CANX-210 0.002355077 4.30016 down BNTCOD0050500 CANX-210 0.002355077 4.41046 down BNTCOD0050500 CANX-210 0.002355077 4.4205 down BNTCOD0050500 CANX-214 0.000450381 4.36737 down BNTCOD0050500 R28-204 0.000316635 -3.53590 down BNTCOD00505005 R28-204 0.00047174 -3.63590 down BNTCOD00505016 R28-204 0.00047144 -3.63590 down BNTCOD00505016 R28-204 0.000471444 -3.63590 down BNTCOD00505016 R28-2	ENST00000472560	AP2M1-216	0.001238868	4.079642	up
Distruction Display 3.21271 up Distruction Display 4.461172 up ENTODOL048123 HLA-DPI-213 0.00176823 4.461172 up ENTODOL048124 HLA-DPI-213 0.00176723 4.23227 up ENTODOL048124 PPI-384-205 0.00122473 4.23227 up ENTODOL048124 PPI-384-205 0.00223703 4.11141 up ENTODOL048074 PPI-4926 0.00223717 -4.10495 0.0011 ENTODOL048077 PLIAP1-205 0.0028303 -5.51764 0.0011 ENTODOL047087 PLIAP1-205 0.0028303 -5.51764 0.0011 ENTODOL047087 PLIAP1-205 0.00283163 -3.55666 0.0011 ENTODOL047087 PLIAP1-207 0.004314632 -3.55666 0.0011 ENTODOL0570840 SIREF-202 0.00445144 -3.37671 0.0011 ENTODOL0570840 SIREF-202 0.00267143 -3.58671 0.0011 ENTODOL0570840 SIREF-202 0.000267143	ENST00000498038	HLA-DPB1-217	0.001533537	-3.81907	down
ENTODOLOGIESICS SPITENT-0056 0.007/88233 4.64172 up ENTODOLOGIESICS C11 cm8.206 0.00187/205 2.814122 up ENTODOLOGIESICS C11 cm8.206 0.00187/205 2.814122 up ENTODOLOGIESICS ATREM-206 0.00227/301 4.1151.41 up ENTODOLOGIESICS PSIAM0 0.00227/301 4.1151.41 up ENTODOLOGIESICS PSIAM0 0.00227/301 4.1151.41 up ENTODOLOGIESICS PSIAM0 0.00228/301 4.1151.41 up ENTODOLOGIESICS PSIAM0 0.00228/302 -5.87741 down ENTODOLOGIESICS PSIAM0 0.00288/302 -3.87897 down ENTODOLOGIESICS PSIAM0 0.00288/302 -3.87897 down ENTODOLOGIESICS PSIE-122 0.00288/302 -3.87897 down ENTODOLOGIESICS PSIE-122 0.00450645 -3.37807 down ENTODOLOGIESICS PSIE-122 0.00450645 -3.57807 down ENTODOLOGIESICS	ENST00000645908	RPL5-210	0.001592047	3.212761	up
ENERGOOGNEGE20 HLA DEB1/213 0.001805199 -4.6075 down ENERGOODNEESE2 C11 off8-205 0.00187265 2.2141452 up ENTODODNESE20 AT79FF-208 0.00224530 4.141541 up ENTODODNESE20 CANK-210 0.002245507 -3.00011 down ENTODODNESE20 CANK-210 0.00227171 -4.10499 down ENTODODNESE27 IF2A-02 0.00227171 -4.10499 down ENTODODNESE27 IF2A-02 0.0023700 -9.97671 down ENTODODNESE20 EIFA-02 0.00237140 -9.97671 down ENTODODNESE30 FPS-204 0.002371462 -3.93633 down ENTODODNESE198 FP1-204 0.00451462 -3.7477 down ENTODODNESE198 FP1-202 0.00451474 3.93633 down ENTODODNESE198 FP1-202 0.004514542 3.31647 down ENTODODNESE198 FP1-202 0.004571452 -3.26473 down ENTODODNESE199 FP3-202 <td>ENST00000496323</td> <td>SPTBN1-205</td> <td>0.001789333</td> <td>4.641172</td> <td>up</td>	ENST00000496323	SPTBN1-205	0.001789333	4.641172	up
ENSTOD000582526 C11058-205 0.01878295 2.814152 up ENSTOD0046002 ATPSPF-205 0.00222730 4.141541 up ENSTOD0046002 ATPSPF-205 0.00222730 4.141541 up ENSTOD0050000 CAMS-210 0.00225700 4.140495 0.0007 ENSTOD00056167 PIMA-212 0.00227177 -3.4225 0.001 ENSTOD0005727 FLBH-205 0.00228303 -6.51744 0.0001 ENSTOD000582527 ESA-202 0.00228303 -3.1789 0.001 ENSTOD000582530 CASP1>14 0.0014652 -3.1789 0.001 ENSTOD000582540 CASP1>14 0.0014652 -3.1789 0.001 ENSTOD00058119 ENSTOD00058119 ENSTOD00058119 ENSTOD00058119 0.00011114 4.00737 down ENSTOD00058119 ENSTOD0007724 3.55666 0.0007 2.94675 down ENSTOD00077755 TMF2:02 0.00577474 3.55666 0.0007 2.94675 down ENSTOD000781725 ENSTO0007772	ENST00000469120	HLA-DPB1-213	0.001805199	-4.60675	down
ENTODOD046574 PRIS0000 ATPSPF-208 0.00324573 4.23797 up ENTOD00500000 CANK21D 0.002345947 -3.30911 down ENTOD00505000 CANK21D 0.0023709 -1.410496 down ENTOD00515902 IK.209 0.00277177 -3.4285 down ENTOD0070277 FUBP1-205 0.0028303 -3.51764 down ENTOD00702877 FUBP1-205 0.0028033 -3.51769 down ENTOD00220062006 PRE-3.204 0.00280729 -3.1769 down ENTOD002020161716 PAPL-9.207 0.004281748 -3.55677 down ENTOD002021740 SHR1-3.222 0.005060114 -3.57677 down ENTOD0020161716 PAPL-207 0.000517743 -3.55677 down ENTOD002016172 PAPG 207 0.000507743 -3.55677 down ENTOD00201752 TMFS-302 0.00077743 -3.55679 down ENTOD0021755 TMFS-302 0.000774485 2.896793 up ENTOD00217	ENST00000525256	C11orf58-206	0.001879295	2.814152	up
ENSTOD000488002 ATFSPF-208 0.002327309 4.14141 up ENSTOD00050600 CANK-210 0.002857/17 -3.30511 down ENSTOD00056167 PSMAR-212 0.002877/17 -3.42825 down ENSTOD00057207 FLBP1-205 0.0027277/7 -3.42825 down ENSTOD000583820 CASP-114 0.0014653 -3.57637 down ENSTOD000583820 CASP-114 0.0014653 -3.57837 up ENSTOD000583820 CASP-124 0.0024729 -3.1789 down ENSTOD000583820 CASP-124 0.0024729 -3.1789 down ENSTOD000581110 EPAS-2019 0.004493042 -3.556367 down ENSTOD000581112 EPAS-2019 0.0059071734 3.855666 down ENSTOD00058112 EPAS-203 0.00597774 3.456767 down ENSTOD000582468 ZETS4-206 0.00577744 3.456768 down ENSTOD000582468 ZETS4-206 0.00577743 3.45877 down ENSTOD000582468	ENST00000465744	RPL36A-205	0.001922473	4.237297	up
ENSTOD0050500 CANA2210 0.002245547 3.30811 down ENSTOD00505197 PSMA6-212 0.00227177 -3.42825 down ENSTOD0070277 EIRA.202 0.002220383 -3.51764 down ENSTOD0070277 EIRA.202 0.00220383 -3.51764 down ENSTOD00702827 EIRA.202 0.00220383 -3.51764 down ENSTOD0070282696 PR1-9.206 0.00421714 -3.55563 down ENSTOD00052896 PR1-9.206 0.00421714 -3.55663 down ENSTOD00051876 PAR-PC-207 0.00421714 -3.55663 up ENSTOD000517440 SRF1-3.422 0.00560473 -3.51617 down ENSTOD000527440 ERA-212 0.0056043 -3.51617 down ENSTOD000527440 ERA-212 0.0056043 -3.51617 down ENSTOD000527440 ERA-212 0.0057743 -3.54637 down ENSTOD00052725 TNF2-322 0.0057743 -4.5274 down ENSTOD00052725 T	ENST00000486002	ATP5PF-208	0.002327309	4.141541	up
ENSTD0000566167 FBMA6-212 0.002637017 -1.04086 down ENSTD00004706587 FURPI-205 0.00263803 -5.5774 down ENSTD0000466677 FURPI-205 0.00263803 -5.5774 down ENSTD0000528200 CASP1-214 0.00314652 -3.58989 down ENSTD000053899 FPI-2026 0.004011114 -3.33323 up ENSTD000056919 FPI-2026 0.00459045 -3.57807 down ENSTD0000576430 SFR5-1202 0.00459045 -3.00237 down ENSTD0000576430 SFR5-1202 0.00574734 -3.56666 up ENSTD000046112 FFR-202 0.00574734 -3.56666 up ENSTD000058914 27874-08 0.00574734 -3.86266 up ENSTD0000576430 SFR5-202 0.00574734 -3.86266 up ENSTD0000576430 EFR5-202 0.005778269 -3.7428 down ENSTD0000477555 TVF2-202 0.005778269 -3.7428 down ENSTD0000477550	ENST00000505090	CANX-210	0.002345547	-3.90611	down
ENSTD00004756592 IK-020 0.002727177 -3.8285 down ENST0000476257 EIF3A-022 0.002920933 -3.57697 down ENST0000042527 EIF3A-022 0.003829729 -3.1769 down ENST00000356908 PR52-204 0.003829729 -3.1769 down ENST00000516716 PAPC1-207 0.004281746 -3.38333 down ENST000003616716 PAPC1-207 0.00430945 -3.57807 down ENST0000048101 EIFA-219 0.004513042 -3.57807 down ENST00000269412 PPG-309 0.0050913 -3.81647 down ENST0000026943 21F94-208 0.005074734 3.55566 down ENST0000026943 21F94-208 0.00574468 4.8602 up ENST00000269425 NCP53-203 0.00574468 3.58973 up ENST00000269425 NCP53-203 0.00574468 3.59878 up ENST00000269455 NCP53-203 0.005764468 3.74238 up ENST000000469569	ENST00000556167	PSMA6-212	0.002637017	-4.10496	down
ENSTODOUCH70287 FUBPH-205 0.02283803 -5.1764 down ENSTODOUCH20527 EIR3A-202 0.0228063 -3.97697 down ENSTODOUCS28260 CASH-1214 0.003146652 -3.55697 down ENSTODOUCS28260 PAS2-204 0.0049729 -3.1769 down ENSTODOUCS1819 PALPC1-207 0.00493048 -3.3923 down ENSTODOUCS1819 FIR3A-219 0.00459045 -3.30237 down ENSTODOUCS18130 SIR5A-219 0.005074734 -3.55666 up ENSTODOUCS18142 MSTRG.562314.2 0.005074734 -3.85666 up ENSTODOUCS1825 NDP5-203 0.0057483 -4.84672 up ENSTODOUCS1825 NDP5-203 0.00574828 -2.88771 down ENSTODOUCS1825 NDP5-203 0.00574828 -2.88771 up ENSTODOUCS1825 NDP5-203 0.00574828 -3.84875 down ENSTODOUCS1825 NDP5-203 0.00574828 -3.84875 up ENSTODOUCA9506	ENST00000515592	IK-209	0.002727177	-3.42825	down
ENST00000462527 EIF3A-202 0.002920983 -3.97697 down ENST00000326608 PRS2-204 0.003829729 -3.1769 down ENST00000326608 PRS2-204 0.003829729 -3.1769 down ENST000003519718 PAPL19-205 0.004281746 -3.57807 down ENST00000378430 SRSF1-202 0.00450945 -3.57807 down ENST00000485101 EIFA-2219 0.0050945 -3.57807 down ENST000004612 PPIG-209 0.005074734 3.55566 up ENST0000058861 EIF3-204 0.00508171027 -2.94875 down ENST0000058863 ZBT64-208 0.00574468 2.88771 up ENST000005863 SOGP-210 0.005674468 2.88761 up ENST000005864 RPS2-8021 0.00676468 2.88761 up ENST000005864 RPS2-8021 0.0066781 3.58978 up ENST000005864 RPS2-8021 0.0066781 3.7423 up ENST0000058764 RAPM1-	ENST00000470287	FUBP1-205	0.00283803	-5.51764	down
ENST00000632520 CASP1-214 0.003146322 -3.65969 down ENST0000065196 RPS-204 0.004011114 3.457337 up ENST0000065196 RPS-204 0.004211746 3.35923 down ENST0000057840 SRSF1-202 0.004500465 3.35707 down ENST0000045142 PTG-209 0.004500465 -3.65566 up ENST0000045142 PTG-209 0.0065074734 -3.65566 up ENST0000045142 PTG-209 0.00657773 -2.94875 down ENST00000508901 BTF3-204 0.005777448 4.48402 up ENST0000050891 BTF3-204 0.005777428 2.94875 down ENST00000472755 TVF2-202 0.005778486 2.88701 up ENST00000472755 TVF2-202 0.005778486 2.88712 up ENST0000049573 S.74238 down epst712 2.88153 up ENST0000049573 D.0050776486 2.88712 up epst7200 down ENST	ENST00000462527	EIF3A-202	0.002920393	-3.97697	down
ENST00000526908 PR52-204 0.003829/29 3.1769 down ENST0000055199 PR10-206 0.004281746 3.39322 down ENST00000518746 PAPC1-207 0.00459045 -3.57677 down ENST0000074540 SFSF1-702 0.00459045 -3.57677 down ENST0000074540 PF16-209 0.00570734 3.81647 down ENST0000050801 BTF3-204 0.00570977 -2.94675 down ENST0000050384 ZBTB4-208 0.00578448 4.84602 up ENST0000052344 ZBTB4-208 0.00578428 3.85616 up ENST0000052343 SDCEP-210 0.00568811 3.85616 up ENST0000052344 SDCEP-210 0.00668913 3.85816 up ENST00000045086 AP241-214 0.0066737 3.37403 down ENST00000045086 SP525 0.00678913 1.194766 up ENST0000045086 SP421-214 0.0066657 3.37403 down ENST00000457724 NUMB-226 <td>ENST00000532520</td> <td>CASP1-214</td> <td>0.003146632</td> <td>-3.55369</td> <td>down</td>	ENST00000532520	CASP1-214	0.003146632	-3.55369	down
ENST0000685199 PPL19-206 0.004011114 4.467337 up ENST0000678430 SRSP1-202 0.00459045 -3.35207 down ENST0000465142 PPG-203 0.00574734 -3.55666 up ENST000045142 PPG-203 0.005074734 -3.51647 down ENST000045142 PPG-203 0.005074734 -3.81647 down ENST000004525 MSTR.662314.2 0.005074734 -3.81647 down ENST000000472755 TVP2-202 0.005714269 -4.52274 down ENST00000472755 TVP2-202 0.005774269 2.48275 down ENST00000472755 TVP2-202 0.00577429 3.4228 down ENST00000472765 TVP2-202 0.00577429 3.628153 up ENST00000476586 PD99-13 0.00677429 3.628153 up ENST00000477050 ENST00000477050 S.14723 0.00676829 3.344141 down ENST0000047720 S.145203 0.00768297 3.447234 up EN	ENST00000526908	RPS2-204	0.003829729	-3.1769	down
ENST000005/8716 PABPC1-207 0.004/81746 -3.3923 down ENST0000078430 SISF1-502 0.004950945 -3.57807 down ENST00000785101 EIFA2-219 0.005674734 3.555666 up MSTRG.562314.2 0.00567077 -9.8475 down ENST0000059801 ETF3-204 0.00567077 -9.8475 down ENST0000059348 287544.208 0.005671459 -4.52274 down ENST00000593275 TVPE-202 0.005778239 -3.7428 down ENST0000049658 AP2M-214 0.00579381 3.528216 up ENST0000049658 AP2M-214 0.005693815 3.528153 up ENST0000049658 AP2M-214 0.0065785 -3.77403 down ENST0000049708 ENST000004977829 -3.84491 down ENST00000497782 ENST000004977829 -3.84491 down ENST00000497784 S.55897 -3.77403 up ENST0000049774 ENST0000049777 -3.84491 down	ENST00000585199	RPL19-206	0.004011114	3.457337	up
ENST000004676430 SPSP1-202 0.004913042 -3.07807 clown ENST00000466142 PPG-209 0.005674734 3.555666 up ENST0000046742 PPG-209 0.00567973 -3.81647 clown ENST00000472755 TMF3-5024 0.005796486 4.84002 up ENST00000259345 ZETB44-208 0.005778129 -4.52274 clown ENST000002594525 NDF3-202 0.005778485 2.889701 up ENST000002594525 NDF3-203 -3.74238 clown ENST00000262643 SDCBP-210 0.0056391 3.595216 up ENST00000465650 CD699-213 0.00616171 3.59578 up ENST00000472650 SLK-203 0.0061617 3.535813 up ENST00000472760 SLK-203 0.00769291 5.353611 up ENST0000047276 SLX-203 0.00769297 3.24487 up ENST000005774 NLMB-226 0.00769297 3.24857 up ENST0000057774 NLMB-233 0.0076	ENST00000518716	PABPC1-207	0.004281746	-3.39323	down
ENST00000485101 EIF4A2.219 0.004613042 -3.0287 down ENST00000466142 PIG.209 0.005067473 3.555066 up MSTRG.562314.2 0.005067473 -3.81647 down ENST0000059901 ETF3-204 0.00571529 -4.52274 down ENST00000572755 TVF2-202 0.005764486 2.889701 up ENST0000046032 COPS3-203 0.00577429 -3.74238 down ENST0000046032 COPS3-203 0.005784486 2.889701 up ENST0000046032 COPS3-203 0.005784486 3.622153 up ENST0000046032 COPS3-203 0.005781529 -3.74238 down ENST00000470708 FP28-201 0.0066917 3.539578 up ENST00000474200 SLK-203 0.00678913 4.194786 up ENST0000049848 STRADB-210 0.0066878 -3.77403 down ENST0000049873 EP315-209 0.007699271 5.333651 up ENST0000058774 NLMB-226 <td< td=""><td>ENST00000578430</td><td>SRSF1-202</td><td>0.004590845</td><td>-3.57807</td><td>down</td></td<>	ENST00000578430	SRSF1-202	0.004590845	-3.57807	down
ENST0000466142 PPG-209 0.005074734 3.565666 up ENST0000528142 MSTRG.562314.2 0.005061913 -3.31647 down ENST00000529051 ETF3-204 0.00567077 -2.94875 down ENST00000529053 ZTB44-208 0.0056711529 -4.52274 down ENST0000048052 NPF2-202 0.005778239 -3.74238 down ENST0000048052 NPF2-202 0.005778239 -3.74238 down ENST0000048052 SDC8P-210 0.005639818 3.958216 up ENST00000466668 AP24/1-214 0.0060951 4.194786 up ENST00000466668 AP24/1-214 0.006678 -3.77403 down ENST0000047266 STK4DB-210 0.0067678 -3.77403 down ENST0000047266 STK4DB-210 0.0076827 -3.74403 up ENST0000047266 STK4DB-210 0.0076827 -3.84491 down ENST0000047266 FAB2118-203 0.0076827 -3.84491 up ENST0000046733	ENST00000485101	EIF4A2-219	0.004613042	-3.00297	down
MSTHG.582314.2 MSTRG.582314.2 0.00508011 -3.81647 down ENST00000550801 ETF3-204 0.0057177 -2.94875 down ENST00000528048 ZSTB44-208 0.00571529 -4.82274 down ENST0000046032 COP53-038 0.00571529 -4.82274 down ENST0000046032 COP53-038 0.005778239 -3.74238 down ENST00000466032 COP53-038 0.00567818 3.985216 up ENST0000046603 RP2828-201 0.006971702 -2.88162 up ENST00000447260 SLK-203 0.006158913 4.194786 up ENST000004474260 SLK-203 0.00670695 -3.84491 down ENST000004474260 SLK-203 0.00729271 5.363631 up ENST0000044673 EP515-209 0.00729271 5.363631 up ENST0000044673 EP515-209 0.00729271 5.363631 up ENST0000044673 EP515-209 0.00729271 5.363631 up ENST0000054774	ENST00000466142	PPIG-209	0.005074734	3.555666	up
ENST00000528801 BTR3-204 0.005170977 -2.94875 down ENST00000522848 ZBTB44-208 0.005581484 4.44602 up ENST000005228455 NDP55-203 0.0055711529 -4.52274 down ENST00000542852 NDP55-203 0.005778299 -3.74238 down ENST00000522843 SDCBP-210 0.00563818 3.956216 up ENST00000466698 AP2M1-214 0.0066091 3.528153 up ENST0000047086 RP528-201 0.00615813 4.194786 up ENST000004466590 CD99-213 0.00616817 3.539578 up ENST00000498648 STRADB-210 0.0066059 -3.84491 down ENST0000049873 EP515-209 0.00798021 4.567347 up ENST0000049873 EP515-209 0.007829057 3.24837 up ENST00000552774 NLMB-226 0.007829057 3.24837 up ENST00000567774 RP417-207 0.00856999 3.108377 up ENST0000056766	MSTRG.562314.2	MSTRG.562314.2	0.005080913	-3.81647	down
ENST00000529348 ZBTB44-208 0.005571529 4.45227 down ENST000005472755 TWP2-202 0.005771529 -4.52274 down ENST00000549525 NOP63-203 0.005774486 2.88701 up ENST0000466596 AP2M1-214 0.006030811 3.528153 up ENST0000046596 AP2M1-214 0.00605781 4.194786 up ENST00000465960 CD99-213 0.006158913 4.194786 up ENST000047280 SLK-203 0.0066578 -3.77403 down ENST00004498648 STFADB-210 0.0066578 -3.77403 up ENST00004497420 SLK-203 0.007329302 4.457347 up ENST0000044973 LDHA-211 0.007329302 4.57347 up ENST0000054976 RAB11B-203 0.0078292 2.35549 up ENST0000054976 RAB12-217 0.00850599 3.108377 up ENST0000054976 RAB12-207 0.0086507 3.42491 up ENST00000549864 TMM-212<	ENST00000508901	BTF3-204	0.005170977	-2.94875	down
ENS1000034/2765 IVME2202 0.00571429 -4.32274 down ENST0000548555 IVDFS-203 0.0057742486 2.889701 up ENST0000548032 COPS3-203 0.005778239 -3.74238 down ENST0000046032 SDCBP-210 0.00693918 3.989216 up ENST0000047708 RPS28-201 0.00616917 3.539576 up ENST0000047280 SLK-203 0.00616917 3.539576 up ENST0000044280 STRADB-210 0.0066778 -3.77403 down ENST00000498048 STRADB-210 0.006776578 -3.77403 down ENST00000498048 STRADB-210 0.00763276 3.402206 up ENST00000493703 EPS15-209 0.007329302 4.457347 up ENST00000493703 EPS15-209 0.00782957 3.224837 up ENST0000052522 RPL8-203 0.00789527 3.234837 up ENST0000056355 RPL7-207 0.008650899 3.089377 up ENST0000057562 <td< td=""><td>ENST00000529348</td><td>ZBTB44-208</td><td>0.005368448</td><td>4.84602</td><td>up</td></td<>	ENST00000529348	ZBTB44-208	0.005368448	4.84602	up
ENST00000694255 NOP53-203 0.005764486 2.889701 up ENST00000622843 SDCBP-210 0.00593818 3.356216 up ENST0000046598 AP2M1-214 0.00600961 3.522153 up ENST0000046598 AP2M1-214 0.006071702 -2.86162 down ENST0000044708 RFS28-201 0.006163913 4.194786 up ENST00000447280 SLK-203 0.00616617 3.539578 up ENST0000048648 STFADB-210 0.0066558 -3.7403 down ENST00000587774 NUME-226 0.00709271 5.353631 up ENST00000494573 LPH-211 0.007329302 4.467347 up ENST00000494573 LPH-211 0.007329302 4.467347 up ENST00000494573 LPH-211 0.0078297 3.324837 up ENST00000588706 RPL27A-207 0.00850699 3.108377 up ENST0000058654 RPL27A-207 0.009683951 -2.82256 down ENST00000586854 RPL	ENS100000472755	IWF2-202	0.005711529	-4.52274	down
ENS10000028243 COPS3-2008 0.0057/8239 -3.74238 down ENST0000028243 SDCBP-210 0.00639316 3.852163 up ENST00000282843 DCDB-211 0.006071702 -2.86162 down ENST00000445960 CDB9-213 0.006158913 4.194766 up ENST0000047280 SLK-203 0.006161617 3.539578 up ENST0000089648 STRADB-210 0.00666578 -3.77403 down ENST00000498648 STRADB-210 0.00676659 -3.84491 down ENST00000498733 EPS15-209 0.00739202 4.457347 up ENST0000049473 LDHA-211 0.007682476 3.402206 up ENST00000494573 LDHA-211 0.007869297 3.244837 up ENST00000589706 RAB118-203 0.00786929 3.108377 up ENST000005825212 RPL8-203 0.0078692 2.585649 up ENST0000058655 RPL27A-207 0.00898591 -2.82285 down ENST00000686454	ENST00000594525	NOP53-203	0.005764486	2.889701	up
ENS100000262843 SUC8F-210 0.00894818 3.98276 up ENST0000046558 AP2H1-214 0.006030961 3.528153 up ENST000045850 C099-213 0.006168913 4.194786 up ENST000045850 C099-213 0.00616617 3.539578 up ENST0000045850 C099-213 0.006706059 -3.7403 down ENST00000581741 RPL7-213 0.006706059 -3.84491 up ENST00000581741 RPL3-211 0.007392977 3.53631 up ENST00000581741 RPL9-203 0.00768297 3.324837 up ENST0000058705 RAB118-203 0.00768297 3.324837 up ENST0000052822 RPL3-203 0.0076892 2.53549 up ENST000005855 RPL3-207 0.008950919 3.108377 up ENST000005856 RPL3-207 0.00896891 -2.82285 down ENST000005865 RPL3-207 0.009683951 -2.82285 down ENST000005865 RPL3-207	ENS100000486032	COPS3-208	0.005778239	-3.74238	down
ENS100000466589 AP2M1-214 0.006030661 3.528153 up ENST00000471028 RPS8-201 0.006156913 4.194786 up ENST0000047088 RPS8-201 0.00616617 3.539578 up ENST0000047660 SLK-203 0.00616617 3.539578 up ENST00000498648 STRADB-210 0.0066578 -3.77403 down ENST00000498676 RAIDB-210 0.007329302 4.457347 up ENST0000049673 LDHA-211 0.007329302 4.457347 up ENST0000058706 RAI118-203 0.007829597 3.242367 up ENST0000058706 RPL3-203 0.00789299 3.108377 up ENST00000582623 RPL27A-207 0.00850599 3.108377 up ENST00000530585 RPL27A-207 0.00863051 -2.82285 down ENST0000054442 RPL9-210 0.009683951 -2.82285 down ENST000006514842 RPL37-207 0.01093959 3.08422 up ENST000006614424 <t< td=""><td>ENS100000522843</td><td>SDCBP-210</td><td>0.00593818</td><td>3.958216</td><td>up</td></t<>	ENS100000522843	SDCBP-210	0.00593818	3.958216	up
ENS10000047/088 FHS28-201 0.00607/02 -2.86162 00W1 ENS700006496560 C99-213 0.00616617 3.539578 up ENS700006496560 SLK-203 0.00616617 3.539578 up ENS700006581741 FRL17-213 0.006706059 -3.84491 down ENS700000581741 RL17-213 0.00739202 4.457347 up ENS700000494573 LDHA-211 0.007682276 3.402206 up ENS70000058706 FAB118-203 0.007829597 3.324337 up ENS700000582632 RPL8-203 0.0078692 2.55549 up ENS700000582632 RPL3-207 0.00863061 -2.82285 down ENS700000588254 TPM3-213 0.009863051 -2.82285 down ENS700000588254 TPM3-213 0.009863051 -2.82285 down ENS700000588254 TPM3-213 0.009863051 -2.82285 down ENS700000588273 SELENOW-206 0.010074218 -3.84098 down ENS7000001698273	ENS10000466598	AP2M1-214	0.006030961	3.528153	up
ENST 0000049350 CD39-213 CD006 156913 4.194766 Up ENST 00000474260 SLK-203 0.00616617 3.539578 up ENST 0000498648 STRADB-210 0.006676659 -3.84491 down ENST 00000587774 NUMB-226 0.007392902 4.457347 up ENST 00000587774 NUMB-226 0.007329302 4.457347 up ENST 0000058773 LPH-211 0.007682476 3.04226 up ENST 00000598706 RAB11B-203 0.007829597 3.324837 up ENST 00000585232 RPL8-203 0.007879014 2.683607 up ENST 00000580585 RPL27A-207 0.00863951 -2.82285 down ENST 0000058442 RPL9-210 0.009643951 -2.82285 down ENST 0000058055 RPL7A-207 0.0099643951 -2.82285 down ENST 0000054842 RPL9-200 0.010033959 3.08422 up ENST 00000614842 RPL7A-207 0.01093959 3.08422 up ENST 00000617745<	ENS10000417088	RPS28-201	0.006071702	-2.86162	down
ENST000004/4260 SLR.203 0.0001601/ 3.539676 up ENST0000048648 STRADB.210 0.00666578 -3.77403 down ENST00000498793 EPS15-209 0.0073929302 -4.457347 up ENST00000498793 EPS15-209 0.007829276 3.324837 up ENST00000498793 EPS15-209 0.00786927 3.324837 up ENST00000525232 RPL3-203 0.00786929 2.535549 up ENST00000525232 RPL2-703 0.0086508999 3.108377 up ENST0000053865 RPL27A-207 0.0086508991 3.442714 up ENST00000548242 RPL3-207 0.008952126 3.442714 up ENST00000548242 RPL7-207 0.0089551 -2.82285 down ENST000006885 ATP6VTE1-205 0.100943959 3.984422 up ENST0000046085 ATP6VTE1-205 0.01063957 4.04501 down ENST0000046085 ATP6VTE1-205 0.01074218 -3.84098 down ENST0000046085	ENS10000645950	CD99-213	0.006158913	4.194786	up
ENST000004980945 STRAUB-210 0.00060767 -3.7140.3 000ml ENST00000581741 RPL17-213 0.006706059 -3.84491 down ENST00000493793 EPS15-209 0.00739302 4.457347 up ENST00000494573 LDHA-211 0.007829476 3.402206 up ENST00000494573 LDHA-211 0.007829597 3.324837 up ENST00000525232 RPL3-203 0.0078692 2.535549 up ENST00000530585 RPL3-207 0.008606999 3.108377 up ENST00000368545 TPM3-213 0.00983951 -2.82285 down ENST000005488292 RPL3-207 0.009940847 3.616313 up ENST00000548392 RPL9-210 0.009940847 3.616313 up ENST00000489392 RPL47-207 0.009940847 3.616313 up ENST0000046085 ATP6V1E1-205 0.010073959 3.098422 up ENST0000046026 AMD1-207 0.01129415 4.406694 up ENST0000061784	ENS10000474260	SLK-203	0.00616617	3.539578	up
ENSTO000058774 INUMB-226 0.007099271 5.353631 up ENST0000635774 NUMB-226 0.007399271 5.353631 up ENST0000543733 LDHA-211 0.007632476 3.402206 up ENST000058706 RAB118-203 0.007829597 3.324837 up ENST00000525232 RPL8-203 0.007879014 2.663607 up ENST00000530585 RPL27A-207 0.008506999 3.108377 up ENST00000530585 RPL27A-207 0.00985212 3.442714 up ENST00000538853 RPL9-210 0.00985212 3.442714 up ENST00000548422 RPL9-210 0.009940847 3.616313 up ENST00000548232 RPL7A-207 0.009940847 3.616313 up ENST00000480392 RPL7A-207 0.01074218 -3.84098 down ENST0000046085 ATP6V1E1-205 0.010535877 -4.04501 down ENST0000046085 ATP6V1E1-205 0.0101535877 -4.04501 down ENST00000462420	ENS10000498648	STRADB-210	0.00666578	-3.77403	down
ENST 100000597/74 ND/MB-226 0.007329302 4.457347 up ENST 00000494573 LDHA-211 0.007329302 4.457347 up ENST 00000598706 RAB 118-203 0.007829507 3.324837 up ENST 00000521046 PCMTD1-205 0.0078692 2.535549 up ENST 00000521046 PCMTD1-205 0.0078699 3.108377 up ENST 0000058565 RPL2-702 0.00863951 -2.82285 down ENST 00000588645 TPM3-213 0.009683951 -2.82285 down ENST 00000588645 RPL9-210 0.009683951 -2.82285 down ENST 00000588645 RPL9-210 0.010074218 -3.84098 down ENST 00000480392 RPL7-207 0.01003959 3.089422 up ENST 00000460265 ATF8/11-205 0.101033959 3.98498 down ENST 00000460265 ATB9/11-202 0.011129415 4.04501 down ENST 00000461242 AMD1-207 0.11129415 4.046694 up ENST	ENS100000561741	RPL17-213	0.0007000031	-3.64491	down
ENST0000493733 EPS 19-203 0.007832922 4.407347 up ENST0000494573 LDHA-211 0.007832957 3.324837 up ENST00000525232 RPL8-203 0.0078692 2.535549 up ENST00000530656 RPL27A-207 0.008506999 3.108377 up ENST00000530585 RPL27A-207 0.00986951 -2.82285 down ENST00000588232 RPL7A-207 0.009940847 3.616313 up ENST0000058823 RPL7A-207 0.009940847 3.616313 up ENST00000489392 RPL7A-207 0.010074218 -3.84098 down ENST00000460085 ATP6V1E1-205 0.010033959 3.088422 up ENST00000460240 LAMTOR5-202 0.011110826 -3.51861 down ENST00000517545 POM1-207 0.011229415 4.406694 up ENST00000561743 PKM-214 0.012431727 3.41881 up ENST00000561743 PKM-214 0.013241519 -3.13868 down ENST0000066143	ENS100000557774	NUIVIB-220	0.007099271	0.303031	up
ENST00000599706 RAB11B-203 0.00782476 3.424837 up ENST00000525232 RPL8-203 0.0078692 2.535549 up ENST00005250366 RPL27A-207 0.00856999 3.108377 up ENST000053855 TPM3-213 0.009829212 3.442714 up ENST0000514842 RPL-27A-207 0.009683951 -2.82285 down ENST00000589273 SELENOW-206 0.010074218 -3.84098 down ENST00000585 ATPEVIE1-205 0.010035857 -4.04501 down ENST00000685 ATPEVIE1-205 0.010135877 -4.04501 down ENST00000612642 AMD1-207 0.01110826 -3.51861 down ENST00000612642 AMD1-207 0.011229415 4.406694 up ENST00000612642 AMD1-207 0.01129415 -3.324716 down ENST00000612642 AMD1-207 0.01129415 -4.046694 up ENST00000612642 AMD1-207 0.01129415 -4.046694 up ENST00000612642 <td>ENST00000493793</td> <td></td> <td>0.007329302</td> <td>4.457347</td> <td>up</td>	ENST00000493793		0.007329302	4.457347	up
ENST0000052/036 PRDI-B-203 0.00782937 3.524857 up ENST0000052/036 PRUE-203 0.0078692 2.535549 up ENST0000052/046 PCMTD1-205 0.00789014 2.663607 up ENST00000530585 RPL27A-207 0.0089629212 3.442714 up ENST00000514842 RPL9-210 0.009863951 -2.82285 down ENST000005489392 RPL7A-207 0.009940847 3.616313 up ENST00000548273 SELENCW-206 0.010074218 -3.84098 down ENST00000460085 ATF6VtF1-205 0.01110826 -3.51861 down ENST00000460240 LAWTOR5-202 0.01110826 -3.51861 down ENST00000471419 NDNO-209 0.0196858 -3.24716 down ENST00000471419 NDNO-209 0.0196858 -3.24716 down ENST0000048122 RPLP1-204 0.012715911 -2.21776 down ENST00000561738 UQCRC2-203 0.01384842 -3.20313 down ENST0000	ENST00000494573		0.007832476	3.402200	up
ENST 00000521232 PCM 205 0.007692 2.53049 0.00 ENST 00000521046 PCMTD1-205 0.007879014 2.663607 up ENST 00000530585 RPL27A-207 0.008506999 3.108377 up ENST 0000048392 RPL7A-207 0.009683951 -2.82285 down ENST 0000048392 RPL7A-207 0.009940847 3.616313 up ENST 0000048392 RPL7A-207 0.009940847 3.84098 down ENST 00000460265 ATF6V1E1-205 0.010073218 -3.84098 down ENST 00000460240 LAMTOR5-202 0.01110826 -3.51861 down ENST 00000617545 PCM1-202 0.01110826 -3.51861 down ENST 00000617545 PCM1-207 0.012231727 3.411681 up ENST 00000661798 UQCRC2-203 0.013241519 -3.13668 down ENST 00000561798 UQCRC2-203 0.013241519 -3.13668 down ENST 00000648735 HBG1-203 0.01326708 -3.22171 down <	ENST00000525222	RAD 110-203	0.0078602	3.324037	up
ENST 0000052 (040 PCMIT D1203 0.007 6780 14 2.00807 up ENST 00000530885 RPL27A-207 0.08806999 3.108377 up ENST 00000514842 RPL9-210 0.00983951 -2.82285 down ENST 0000514842 RPL7A-207 0.00983951 -2.82285 down ENST 0000598273 SELENOW-206 0.01074218 -3.84098 down ENST 0000646085 ATP6V1E1-205 0.01093959 3.098422 up ENST 0000046026440 LAMTOR5-202 0.011209415 4.04601 down ENST 00000612642 AMD1-207 0.01129415 4.046694 up ENST 00000612642 AMD1-207 0.012431727 3.411681 up ENST 00000612642 AMD1-204 0.012415191 -3.13868 down ENST 00000612643 PKM-214 0.012415191 -3.13868 down ENST 00000661743 PLP1-204 0.013241519 -3.20313 down ENST 00000648735 HBG1-203 0.013241519 -3.20313 down	ENS100000525252	NFL0-200 DOMID1 205	0.007820014	2.000049	up
ENST 00000386545 IPIC 21 A-207 0.008309999 3.108377 0.008 ENST 00000386545 TPM3-213 0.008952212 3.442714 up ENST 0000386545 RPL7A-207 0.009940847 3.616313 up ENST 00000489392 RPL7A-207 0.009940847 3.616313 up ENST 00000480365 ATP6V1E1-206 0.010074218 -3.84098 down ENST 00000460265 ATP6V1E1-205 0.01093959 3.098422 up ENST 00000460240 LAMTORS-202 0.011129815 4.04501 down ENST 00000471419 NONO-209 0.011299415 4.406694 up ENST 0000048122 RPLP1-204 0.012715911 -2.21776 down ENST 0000048122 RPLP1-204 0.013284542 -3.20313 down ENST 00000488735 HBG1-203 0.013384842 -3.20313 down ENST 00000488722 NAMPT-212 0.013977634 2.846161 up ENST 00000489732 NAMPT-212 0.01460306 4.127691 up	ENST00000521040		0.007575014	2.003007	up
ENST00000514842 RPL9-210 0.009683951 -2.82285 down ENST00000514842 RPL7A-207 0.009940847 3.616313 up ENST00000598273 SELENOW-206 0.010074218 -3.84098 down ENST0000046085 ATP6V1E1-205 0.01093959 3.098422 up ENST00000612642 LAMTOR5-202 0.011110826 -3.51861 down ENST00000612642 AMD1-207 0.011229415 4.406694 up ENST00000612642 AMD1-207 0.0112431727 3.411681 up ENST0000065143 PKM-214 0.0122715911 -2.21776 down ENST00000651758 UQCRC2-203 0.01324842 -3.20313 down ENST00000561798 UQCRC2-203 0.0132650708 -3.22111 down ENST0000057552 AKT1-218 0.013650708 -3.22111 down ENST00000571551 ZNF224-208 0.01491183 -3.06762 down ENST00000513816 RAPGEF2-212 0.014928653 3.037927 up EN	ENST00000368545	TPM3-213	0.0080500999	3.100377	up
ENST00000489392 FPL7A-207 0.009940847 3.616313 up ENST00000489392 FPL7A-207 0.009940847 3.84098 down ENST0000460085 ATP6V1E1-205 0.01003959 3.098422 up ENST0000460240 LAMTOR5-202 0.010535877 -4.04501 down ENST00000462420 LAMTOR5-202 0.01110826 -3.51861 down ENST00000471419 NONO-209 0.01129415 4.406694 up ENST00000488122 RPLP1-204 0.012715911 -2.21776 down ENST00000561738 UQCRC2-203 0.013241519 -3.13868 down ENST000005677552 AKT1-218 0.013384842 -3.22171 down ENST000005677552 AKT1-218 0.013384842 -3.22111 down ENST00000577552 AKT1-218 0.01360708 -3.22111 up ENST00000591551 ZNF224-208 0.01460306 4.127691 up ENST00000591551 ZNF224-208 0.01492853 -3.06762 down ENST00	ENST0000051/842	RPI 0-210	0.000683251	-2 82285	down
EINST00000598273 SELENCU: 0.010074218 0.010074218 0.010074008 EINST00000598273 SELENOW-206 0.010093959 3.098422 up EINST00000460085 ATP6V1E1-205 0.010073218 -3.84098 down EINST00000517545 PCM1-202 0.011110826 -3.51861 down EINST00000612642 AMD1-207 0.011229415 4.406694 up EINST00000471419 NONO-209 0.011969858 -3.24716 down EINST0000048122 RPLP1-204 0.012431727 3.411681 up EINST00000561798 UQCRC2-203 0.013241519 -3.13868 down EINST00000648735 HBG1-203 0.013650708 -3.221776 down EINST00000557552 AKT1-218 0.013650708 -3.22111 down EINST00000591551 ZNF224-208 0.01492853 -3.06762 down EINST00000591551 ZNF224-208 0.014928853 3.037927 up EINST00000591581 ZNF224-208 0.014928853 3.037927 up	ENST00000489392	RPI 74-207	0.009040847	3 616313	
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ENST00000464240LAMTOR5-2020.010535877-4.04501downENST00000517545PCM1-2020.011110826-3.51861downENST00000517545PCM1-2020.01112294154.406694upENST00000517545NONO-2090.011969858-3.24716downENST00000565143PKM-2140.012317273.411681upENST00000561798UQCRC2-2030.013241519-3.13868downENST00000581752AKT1-2180.01384842-3.20313downENST00000587552AKT1-2180.01360708-3.22111downENST00000489732NAMPT-2120.0139776342.846161upMSTRG.255299.33MSTRG.255299.330.014603064.127691upENST00000517551ZNF224-2080.014911883-3.06762downENST00000513816RAPGEF2-2120.0153054-4.09493downENST0000060178ECH1-2120.01513054-4.09493downENST00000564440PKM-2120.015477651-2.72849down	ENST00000460085	ATP6V1E1-205	0.010003959	3 098422	up
Environmentation Driving Self 0.010000017 1.01001 0.0111 ENST00000617545 PCM1-202 0.011110826 -3.51861 down ENST00000612642 AMD1-207 0.011229415 4.406694 up ENST00000565143 PKM-214 0.012431727 3.411681 up ENST000005651798 UQCRC2-203 0.013241519 -3.13868 down ENST00000548735 HBG1-203 0.01384842 -3.20313 down ENST00000547552 AKT1-218 0.013650708 -3.2111 down ENST00000489732 NAMPT-212 0.013977634 2.846161 up MSTRG.255299.33 0.01460306 4.127691 up ENST00000517551 ZNF224-208 0.014911883 -3.06762 down ENST00000513816 RAPGEF2-212 0.01513054 -4.09493 down ENST0000060178 ECH1-212 0.01542483 2.704678 up ENST0000060178 FCH1-212 0.015477651 -2.72849 down	ENST00000464240	LAMTOR5-202	0.010535877	-4 04501	down
EnvironmentForm LocGiven LocGiven LocGiven LocENST0000612642AMD1-2070.0112294154.406694upENST00000471419NONO-2090.011969858-3.24716downENST00000565143PKM-2140.0124317273.411681upENST00000561798UQCRC2-2030.013241519-3.13868downENST00000557552HBG1-2030.013384842-3.20313downENST00000489732NAMPT-2120.0139776342.846161upENST00000591551ZNF224-2080.014603064.127691upENST00000513816RAPGEF2-2120.0149288533.037927upENST00000600178ECH1-2120.01513054-4.09493downENST00000664440FRIM22-2090.015424832.704678up	ENST00000517545	PCM1-202	0.011110826	-3.51861	down
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EnvironmentHole LeftOut of the constraint of the c	ENST00000471419	NONO-209	0.011969858	-3 24716	down
ENST00000488122RPLP1-2040.012715911-2.21776downENST00000488122RPLP1-2030.01221519-3.13868downENST00000648735HBG1-2030.01384842-3.20313downENST00000557552AKT1-2180.013650708-3.22111downENST00000489732NAMPT-2120.0139776342.846161upMSTRG.255299.33MSTRG.255299.330.014603064.127691upENST00000591551ZNF224-2080.014911883-3.06762downENST000005013816RAPGEF2-2120.01513054-4.09493downENST00000600178ECH1-2120.01513054-4.09493downENST0000060454TRIM22-2090.015424832.704678upENST000005644400PKM-2120.015477651-2.72849down	ENST00000565143	PKM-214	0.012431727	3 411681	up
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ENST00000557552 AKT1-218 0.013650708 -3.22111 down ENST00000489732 NAMPT-212 0.013850708 -3.22111 up MSTRG.255299.33 MSTRG.255299.33 0.01460306 4.127691 up ENST00000591551 ZNF224-208 0.014911883 -3.06762 down ENST00000513816 RAPGEF2-212 0.014928853 3.037927 up ENST00000600178 ECH1-212 0.01513054 -4.09493 down ENST00000564440 TRIM22-209 0.01542483 2.704678 up ENST00000564440 PKM-212 0.015477651 -2.72849 down	ENST00000648735	HBG1-203	0.013384842	-3.20313	down
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ENST00000513816 RAPGEF2-212 0.014928853 3.037927 up ENST00000600178 ECH1-212 0.01513054 -4.09493 down ENST00000460454 TRIM22-209 0.01542483 2.704678 up ENST00000564440 PKM-212 0.015477651 -2.72849 down	ENST00000591551	ZNF224-208	0.014911883	-3.06762	down
ENST00000600178 ECH1-212 0.01513054 -4.09493 down ENST00000460454 TRIM22-209 0.01542483 2.704678 up ENST00000564440 PKM-212 0.015477651 -2.72849 down	ENST00000513816	RAPGEF2-212	0.014928853	3.037927	up
ENST00000460454TRIM22-2090.015424832.704678upENST00000564440PKM-2120.015477651-2.72849down	ENST0000600178	ECH1-212	0.01513054	-4.09493	down
ENST00000564440 PKM-212 0.015477651 -2.72849 down	ENST00000460454	TRIM22-209	0.01542483	2.704678	up
	ENST00000564440	PKM-212	0.015477651	-2.72849	down

(Continued)

TABLE 3 | Continued

ID	Symbol	P-value	log2FC	Regulated
ENST00000555863	NEMF-207	0.016201769	-2.83837	down
ENST00000492144	EIF4A2-222	0.016368381	3.027909	up
ENST00000505854	SNX2-202	0.016442341	4.485358	up
ENST00000460378	EPB41-208	0.016492727	3.034939	up
ENST00000503439	ANAPC13-202	0.017240099	-4.01868	down
ENST00000527304	MAP3K11-206	0.018546951	-3.0729	down
ENST00000475808	GLUL-208	0.018551696	-2.92786	down
ENST00000432675	EIF3D-205	0.018957454	-2.80598	down
ENST00000436354	UBXN1-203	0.019178124	2.954689	up
ENST00000521112	RPL30-208	0.019372092	-2.7188	down
ENST00000564276	PKM-211	0.019467707	2.308757	up
ENST00000518657	NDUFB9-205	0.020492678	-3.82501	down
ENST00000490221	CCT3-214	0.021255056	3.750684	up
ENS100000490613	PSMB8-205	0.021316098	-3.24049	down
ENS100000581631	SMCHD1-206	0.021359933	-3.83403	down
ENS100000484615	RPL3-217	0.022749903	-2.36799	down
ENS100000561554	RPL4-202	0.023050097	-2.59119	down
ENS10000561707	CO1L1-202	0.023163569	2.919411	up
ENS100000573807	GP52-213	0.023431442	0.5961	qu
ENST00000646220		0.02348098	2.0001	up down
ENS100000678005	PIPRO-217 SMADOE1 215	0.023923100	-3.19077	down
ENST00000578995	PPP1CA-206	0.02/28061	-2.47998	down
ENST00000470944	SOD1-203	0.024250001	-2.47330	down
ENST00000472217	LISE1-204	0.02430032	3 260114	uo
MSTBG 314430 5	MSTRG 314430 5	0.025574578	-3 07342	down
ENST00000481353	PDCD4-206	0.025896515	2 12976	au
ENST00000531282	NDUES8-213	0.026490099	-2.77951	down
ENST00000472202	ATP5F1C-207	0.026862338	-3.52936	down
ENST00000527808	BIRC2-203	0.027777176	3.512334	au
MSTRG.739926.2	MSTRG.739926.2	0.02792067	-1.75089	down
ENST00000488537	TXNIP-203	0.02824563	-2.7104	down
ENST00000515481	HNRNPH1-227	0.029065048	-2.62042	down
MSTRG.926466.1	MSTRG.926466.1	0.03085915	1.863832	up
ENST00000517801	CYRIB-204	0.031092289	-2.41059	down
ENST00000534765	SF3B2-216	0.031187865	3.422181	up
ENST00000553252	SLC38A2-213	0.03125579	3.678198	up
MSTRG.505966.1	MSTRG.505966.1	0.031515408	-2.5263	down
ENST00000480304	YWHAZ-212	0.032040453	-2.55559	down
ENST00000474582	RPS8-205	0.032559983	-2.28222	down
MSTRG.505964.56	MSTRG.505964.56	0.032725433	-3.80789	down
ENST00000461935	SRSF11-206	0.032876738	2.915137	up
ENST00000497196	DDX17-210	0.033142368	-2.75023	down
ENST00000467349	MRPL53-203	0.033214202	3.922429	up
ENST00000484221	SLAMF7-208	0.033344736	-3.25879	down
ENS100000644260	DDX3X-240	0.033743268	-2.55081	down
ENS100000519594	LCP2-203	0.033881721	2.208504	up
ENS100000491294	ARPC1B-219	0.034432197	2.016897	up
ENS100000479338	EIF4H-203	0.036070802	-3.09132	down
ENS10000467371	SP1BN1-204	0.037587984	3.216338	up
ENS100000210019		0.029257697	-3.43430	down
ENST00000580226	MRD2 200	0.038003347	-2.90309	UOWIT
ENST000000000000000000000000000000000000	DDI 104 205	0.03006520	2.000074	up
ENST00000490333	TMEM131_208	0.039873678	3 134736	up
ENST00000484513	MYD88-208	0.040371938	2 666172	up
ENST00000434385	STK38I -203	0.041597845	-2 50685	down
ENST00000602712	MARCHE8-207	0.041761876	2 7343	un
ENST00000517569	SARAF-202	0.042059641	2 656393	un
MSTRG.255299.32	MSTBG.255299.32	0.043398782	3.823257	un
ENST00000612499	IFI27-205	0.043600733	2.662225	un
ENST00000551678	MARF1-210	0.04372356	2.509668	au
ENST00000509797	RUFY1-213	0.043942792	1.86348	up

(Continued)

TABLE 3 | Continued

DISCUSSION

ID	Symbol	P-value	log2FC	Regulated
ENST00000592372	SLC25A39-215	0.044425736	-3.28037	down
ENST00000585695	SLC25A39-206	0.045292114	3.294733	up
ENST00000472760	PRPF40A-208	0.045362214	-2.4923	down
ENST00000507273	RACK1-216	0.045566475	2.184397	up
ENST00000555267	CALM1-211	0.046144992	1.959441	up
ENST00000548485	OSBPL8-208	0.046195315	-2.79872	down
ENST00000522823	LCP2-208	0.04718699	2.405215	up
ENST00000602252	RPS11-209	0.047579066	2.795051	up
ENST00000594264	USF2-206	0.048591173	2.165011	up
ENST00000460633	HLA-DQA1-205	0.048849575	-2.73019	down
ENST00000493362	HNRNPK-211	0.049736378	2.755326	up
ENST00000548622	HSP90B1-204	0.049899032	1.839573	up

Validation of Exosomal IncRNA Expression by qRT-PCR

To further verify the sequencing data, six differentially expressed exosomal lncRNAs, including one up-regulated (ENST00000525207) and five down-regulated (ENST00000495420, ENST00000488260, ENST00000505090, ENST00000472614, and ENST00000533796), were randomly selected to perform the qRT-PCR analysis (T1DM subjects N=30; age-, sex- matched Control subjects N=30). However, the results indicated that the expression levels of selected lncRNAs were similar between T1DM patients and control individuals (**Figure 7**).

Nowadays, it has been reached a consensus that T1DM is a multifactorial disease, and the precise pathogenic mechanisms

are still obscure. Mounting evidence has suggested exosomes play an important role in the onset and development of T1DM (8, 22). However, research about the expression profiles of exosomal lncRNA in T1DM has not yet been reported. Here, we performed the transcriptome-wide expression patterns of plasma-derived exosomal lncRNAs in the T1DM using Illumina Hiseq platform, and further explore their function by bioinformatics analysis.

In the present study, 162 aberrantly expressed exosomal lncRNAs, including 77 up-regulated and 85 down-regulated, were identified. The lincRNA accounted for the most proportion of differentially expressed lncRNAs, which was in accordance with previous study (23). To further validate the expression level of identified exosomal lncRNA, six of them, one up-regulated and five down-regulated, were randomly selected to perform qRT-PCR analysis. However, no significant difference was detected between T1DM patients and control subjects.



enriched biological processes (B), cellular components (C), and molecular functions (D) of differentially expressed inclines (A). The



The relatively limited sample size may contribute to the negative results more or less. Nevertheless, there were still 156 differentially expressed lncRNAs to be further test in future studies. We believe that some of these may have the potential to become novel biomarkers for T1DM given the fact that both exosome (22) and lncRNA (15) have been reported to be significantly associated with T1DM. It has been indicated that islet-derived exosomes can activate immune response and lead to autoimmune attack (24). Also, T lymphocyte-derived exosomes are associated with beta-cell dysfunction and death (25). Some studies also evaluated the diagnostic potential of exosomes in the context of T1DM. It has been demonstrated that human islet-derived exosomal RNAs were differentially expressed when exposed to proinflammatory cytokines (26). Another study investigated the plasma-derived exosomes and reported a

distinct exosomes miRNAs signature in patients with longduration T1DM (27). Some studies have also investigated the potential role of lncRNA in the T1DM pathogenesis. LncRNAs usually expressed in a cell-specific manner. Previous transcriptome profiling studies have identified more than 1000 islet-specific lncRNAs (28, 29). The dysfunction of lncRNAs may lead to autoimmune response and alter the progression of T1DM (30, 31). A recent whole genome RNA sequencing study in circulating leukocytes identified 393 differentially expressed lncRNAs, potentially providing novel targets for diagnosis and treatment of T1DM (32). Another study conducted a comparative analysis of the expression profiles of lncRNA by analyzing published microarray data set and proposed a specific 26-lncRNA signature, which could be used to effectively identify T1DM susceptible individuals (33). In addition, *in vitro*





N=30). G1: control group; G2: case group.

experiment using MIN6 cells found that the expression of lncRNA was modified by cytokine treatment and overexpression of these lncRNA favored beta-cell apoptosis, indicating dysregulation of lncRNA contributes to the beta-cell failure during the development of T1DM (18). Furthermore, some specific lncRNAs have been reported to be implicated in beta-cell function and T1DM. It has been indicated that lncRNA MALAT1 could induce beta-cell dysfunction through inhibiting the expression of PDX-1 by reducing its H3 histone acetylation (34). The lncRNA Lnc13 could regulate the inflammation of pancreatic beta-cell by allele-specific stabilization of STAT1 mRNA (35). All the aforementioned studies suggested that both exosome and lncRNA were involved in the T1DM pathogenesis.

Next, to predict the potential biological functions of identified differentially expressed lncRNAs, we performed GO enrichment analysis and the KEGG pathway analysis. The terms such as activation of phospholipase D activity, neuronal cell body membrane, calcium sensitive guanylate cyclase activator activity, and metal ion binding were significantly enriched in the identified differentially exosomal lncRNAs. These terms were associated with diabetes or its complication to some extent. For instance, it has been shown that glycosylphosphatidylinositol-specific phospholipase D level were correlated to the insulin resistance of adipose tissue in obese subjects (36). Also, the expression of glycoprotein phospholipase D (GPLD1) was found to be increased in mouse models of T1DM (37, 38), and GPLD1 levels in autoimmune diabetes were higher than that in T2DM or healthy controls (39).

KEGG pathway analysis indicated that the differentially expressed lncRNAs were involved in oxidative phosphorylation, Parkinson's disease (PD) and pathways in cancer. PD is also a multifactorial disease and both genetic and environmental factors contribute to the pathogenesis of this progressive neurodegenerative disease (40). The primary pathogenic mechanisms of PD remain unclear. However, some pathophysiological processes, such as mitochondrial dysfunction, oxidative stress, and chronic inflammation, are identified to be associated with PD (41). These processes are also involved in the onset and development of T1DM (42, 43), which suggested that PD and T1DM might share some common pathological features. Interestingly, another progressive neurodegeneration disease, Alzheimer's disease (AD), has been proposed as "type 3 diabetes mellitus" because of the shared molecular and cellular characteristics with T1DM and T2DM (44).

LncRNAs were frequently precursor RNAs of miRNAs. We identified the precursor lncRNAs of miRNA through comparing miRNA sequence in miRbase database. Some identified miRNAs such as miR-21 (45) and miR-424 (46) has been implicated in the progression of T1DM. Therefore, the lncRNA combined miRNA might contribute to the T1DM collectively.

Both exosome and lncRNA have been implicated in the progression of T1DM. However, the exact role of exosomal lncRNA in T1DM lacks full investigation and research. The present study identified the expression profiles of exosomal lncRNA and laid foundation for further study in this field. There are some limitations of our study. First, the sample size was relatively small. Future study should include more samples to decrease the random errors. Second, we only selected six lncRNAs to validate their expression level by qRT-PCR and the sample size was relatively small. Further study should focus on more lncRNAs based on the sequencing results and assess the biomarker potential of exosomal lncRNAs in a larger sample set. Third, we didn't investigate the function of exosomal lncRNAs and some *in vitro* or *in vivo* study are required in future study.

In conclusion, this study identified the characteristics of the plasma-derived exosomal lncRNA transcriptome of T1DM for

the first time and threw insights into the biomarker potential and pathogenic factor of exosomal lncRNA in T1DM.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are publicly available. This data can be found here: [https://db.cngb.org/cnsa/ accession number CNP0002574].

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Xiangya Hospital. The patients/participants provided their written informed consent to participate in this study.

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AUTHOR CONTRIBUTIONS

ZZ, ZX, and HP conceived and designed the experiments. HP, WF, JLi, YW, SL, JLin, GH, and XL collected samples. HP, XS, and WF performed the experiments and analyzed the data. HP wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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