Identification of Long Non-Coding RNA Expression Profiles and Co-Expression Genes in Thyroid Carcinoma Based on The Cancer Genome Atlas (TCGA) Database

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Background: Thyroid carcinoma is a malignancy with high morbidity and mortality. Genetic alterations play pivot roles in the pathogenesis of thyroid carcinoma, where long noncoding RNA (lncRNA) have been identified to be crucial. This study sought to investigate the biological functions of lncRNA expression profiles in thyroid carcinoma.

Material/Methods: The lncRNAs expression profiles were acquired from The Cancer Genome Atlas (TCGA) database according to 510 thyroid cancer tissues and 58 normal thyroid tissues. By using R package edgeR, differentially expressed RNAs were obtained. Also, an overall survival model was established based on Cox regression and clinical data then testified by Kaplan-Meier plot, receiver operating characteristic (ROC)-curve and C-index analysis. We investigated the co-expressed genes with lncRNAs involved in the prognostic model, as well as Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis was conducted R package clusterProfile.

Results: A total of 352 lncRNAs were identified as differentially expressed in thyroid carcinoma, and an overall survival model consisting of 8 signature lncRNAs was proposed (ROC=0.862, C-index=0.893, P<0.05), 3 of which (DOCK9-DT, FAM111A-DT, and LINC01736) represent co-expressed mRNAs. However, as an oncogene, only FAM111A-DT increased the prognostic risk in thyroid carcinoma. Furthermore, we found differential genes LINC01016, LHX1-DT, IGF2-AS, ND MIR1-1HG-AS1, significantly related to lymph node metastasis (P<0.05).

Conclusions: In this study, we clarified the differential lncRNA expression profiles which were related to the tumorigenesis and prognosis in thyroid carcinoma. Our results provide new rationale and understandings to the pathogenesis and regulatory mechanisms of thyroid carcinoma.

MeSH Keywords: Carcinogenesis • RNA, Long Noncoding • Thyroid Neoplasms

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Background

Thyroid carcinoma is one of the most malignant tumors and it is postulated that morbidity and mortality by thyroid carcinoma in USA are increasing observed in 2019 [1]. Pathologically, papillary thyroid carcinoma (PTC) represents 80% of thyroid tumors which derived from parafollicular C-cells, where follicular cell originated carcinomas are most common. Except for PTC, follicular thyroid carcinoma (FTC) (15%), poorly differentiated thyroid carcinoma (PDTC) (≤2%) and anaplastic thyroid carcinoma (ATC) (≤2%) have constituted follicular cell-derived thyroid carcinoma. FTC and PDTC have a decent prognosis, while ATC has high mortality a survival 3-month to 5-month survival rate after first diagnosis [2,3]. Over the past few decades, the increased incidence of thyroid carcinoma is not only attributed to environmental changes, but also mainly attributed to improvements in early diagnosis of thyroid carcinoma [4–6]. Although thyroid carcinoma is a multifactorial disease (as many studies have shown), pathogenesis, including genetic alterations, plays vital roles in carcinogenesis. The phosphatidylinositol-3-kinase AKT and mitogen-activated protein kinase (MAPK) has been extensively revealed alternations in thyroid carcinoma with different molecular mechanisms [7–9].

With the development of high-throughput sequencing technologies, more than 20 000 lncRNAs have been drawn attention since these noncoding transcripts were regarding as gene trash elements before [10]. It is widely recognized that lncRNAs are participated in the regulation of transcription, splicing, translation, and imprinting [11–15]. Increasing studies of lncRNAs show that they play vital roles in various human diseases, especially in cancer [16,17], where lncRNAs may exhibit as tumorigenic or tumor suppressor genes. Ding et al. demonstrated that lncRNA TpteP1 could inhibit hepatocellular carcinoma cell development and occurrence by controlling IL-6/STAT3 signaling [18]. Yu et al. suggested AFAP1-AS1 was an oncogenic gene and that the AFAP1-AS1/LSD1/HBP1 axis could be a new therapeutic target in non-small cell lung cancer [19]. Similarly, thousands of lncRNAs are involved in tumorigenesis in thyroid carcinoma, but the characterization of differential lncRNA expressions and functional profiles in thyroid carcinoma remain unclear.

In our study, we sought to analyze the differentiated lncRNA profiles in thyroid carcinomas by extracting from The Cancer Genome Atlas (TCGA) database. Additionally, investigated the relationship between differentiated lncRNAs and overall survival rate on patients. Also, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional analyses were conducted to show the functional mRNAs. To this end, we demonstrated that the lymph node metastasis was associated lncRNAs. Taken together, our results provide new insights for tumorigenesis and lncRNA related pathogenesis in thyroid carcinoma.

Material and Methods

Datasets and differentially expressed lncRNAs

The transcriptome profiling data of 510 thyroid carcinoma samples and 58 normal thyroid samples were obtained from The Cancer Genome Atlas (TCGA) in January 2019. The lncRNA sequencing data and related clinical information were generated and we download them by utilizing The GDC Data Transfer Tool (https://gdc.cancer.gov/access-data/gdc-data-transfer-tool). Our study abides by the TCGA publication guidelines (http://cancergenome.nih.gov/publications/publicationguidelines). By comparing thyroid carcinoma tissues to normal tissues and using R package edgeR in R software (version 3.4.1), differentially expressed lncRNAs were identified with thresholds |log2FoldChange| >2 as well as adjusted P value <0.05. The lncRNAs were annotated by ENSEMBL (https://www.ensembl.org/) and depicted using the pheatmap package in R program. Ethical consent was not required because all the data in this study were obtained from the TCGA database.

Cox regression and survival analysis

All differentially expressed lncRNAs were subjected to univariate Cox regression with P value cutoff <0.01. Then the significant lncRNAs which related to univariate Cox regression were subsequently analyzed in a multivariate Cox proportional hazards model. By following the results of the multivariate Cox model and median risk score point, a total of 251 patients were grouped into “High risk” and “Low risk” respectively, where the risk score formula was shown as following:

\[
\text{Risk score} = \beta_1 \text{gene}_1 \times \text{expr}_1 + \beta_2 \text{gene}_2 \times \text{expr}_2 + \ldots + \beta_n \text{gene}_n \times \text{expr}_n
\]

[Cox regression analysis and Kaplan-Meier survival analysis were performed by using R package “survival”. The receiver operating characteristic (ROC)-curve analysis and C-index analysis were conducted to evaluate the consequence of the risk system we established, which were performed by using R package survivalROC and BiocManager, respectively. The log-rank test was employed to evaluate the statistical differences in overall survival, and survival curves were depicted by Kaplan-Meier analysis, where P<0.05 was considered as statistically significant.

LncRNAs-proteins correlations

The correlations between differentially expressed lncRNAs and related mRNAs were determined by using package limma in R program. The minimum interaction absolute value was set at medium confidence 0.400 with P value cutoff <0.001. Based on the results, all correlated genes were submitted to enrichment analysis for further validation.
Functional analysis

In order to demonstrate the biological functions of the differential expressed lncRNAs which involved in our predictive model, functional enrichment analysis was performed by analysis of GO and KEGG pathway. By analyzing all the lncRNAs correlated genes, as indicated, we used clusterProfiler package in R software to determine the molecular function, biological process and cellular component for GO analysis and pathway analysis in KEGG. The histograms for GO and KEGG were acquired by the R package GOplot.

LncRNAs related to lymph nodes metastasis

A total of 352 differentially expressed lncRNAs, as indicated, were analyzed in relation to 230 nonlymph nodes metastasis (N0) patients and 225 lymph nodes metastasis (N1) with thresholds |log2FoldChange| >2 as well as adjusted P value <0.05. Moreover, these lncRNAs which link to lymph nodes metastasis were visualized using the pheatmap package in R program.

Results

Differentially expressed lncRNAs in thyroid carcinoma

A total of 352 lncRNAs were identified as differentially expressed in thyroid carcinoma (510 thyroid carcinoma samples versus 58 normal thyroid tissues) (Supplementary Table 1). Of these, 166 lncRNAs (47.2%) were considered to be downregulated while 186 lncRNAs (52.8%) were upregulated. By visualizing the lncRNAs expression profiles, we performed volcano plot and heatmap to depict the overall differences among each gene (Figure 1A, 1B).

Cox regression and overall survival model

A total of 352 differentially expressed lncRNAs were determined with univariate Cox analysis, as shown in Table 1. We found 12 lncRNAs to be significantly related to overall survival with univariate Cox regression at a significant level of P<0.01. Subsequently, we then performed a multivariate Cox regression analysis where a total 8 lncRNAs were found to be as coupled to a prognosis model for overall survival (P=5.2405e-06), of which DOCK9-DT, LINCO0900, C8orf34-AS1, LINCO1736 were suggested as protective factors while ATP2C2-AS1, FAM111A-DT, LINCO2550, LINCO1896 increased the risk in thyroid carcinoma (Figure 2). However, ATP2C2-AS1 and LINCO2550 were downregulated genes, while the other 6 genes determine the opposite functions (Table 2). According to the overall survival model, we grouped patients into “high risk” and “low risk” groups, where the high-risk patients showed worse overall survival to low-risk group (P=1.0627e-04) (Figure 3A).

Additionally, ROC-curve analysis depicted the discriminative value of our established risk scoring system, where we found an AUC=0.862 (Figure 3B). Our risk scoring system was found to be highly sensitivity and specificity (100% and 94%) respectively in predicting overall survival, and the high-risk scoring group could be used for an impressive method for overall survival prediction. The heatmap represents the expression profiles of overall survival model based on the risk scoring system (Figure 3C). Also, we calculated the C-index value of our overall survival model, which is well proven (Table 3). Furthermore, the risk scores and survival status of all patients were visualized in Figure 4A and 4B where high-risk patients were significantly correlated to death as expected. Only 1 patient dead in the low-risk group (0.4%), while 15 patients dead in high-risk group (6.0%). Together, these data demonstrated that the impressive overall survival model based on the Cox regression could be a decent method for prognosis prediction.

LncRNAs correlated mRNAs and functional analysis

A total of 3 lncRNAs (DOCK9-DT, FAM111A-DT, and LINCO1736) were involved in the overall survival model and were found to be correlated to mRNAs expressions which co-expressed with 3274, 3412, and 31 mRNAs respectively. Based on the predicted Pearson correlation score, the top 5 correlating mRNAs of DOCK9-DT, FAM111A-DT, and LINCO1736 are presented in Figure 5. We found a significantly strong correlation between DOCK9-DT and SDC4 (Cor=0.826, P=6.156e-143) and between FAM111A and FAM111A-DT (Cor=0.839, P=2.212e-151).

To further investigate the biological functions of these co-expressed mRNAs, we conducted GO and KEGG functional analysis. As shown in Figure 6A, the results indicated that for GO analysis, most of the mRNAs were assembled in cell adhesion molecule binding with the lowest P-value at 8.33e-05 in FAM111A-DT while oxidoreductase activity, acting on the aldehyde or oxo group of donors represented the lowest value P=6.82e-05 in DOCK9-DT. In addition, a total of 4 mRNAs were related to phospholipid binding in LINCO1736. By analyzing the results of KEGG enrichment pathways, we found that in DOCK9-DT, a total of 70 genes were gathering in MAPK signaling pathway, while human papillomavirus infection reflects the most significant pathway including 85 genes in FAM111A-DT and Staphylococcus aureus infection represents the highest cancer associated pathway in LINCO1736 (Figure 6B). These results indicated that these 3 lncRNAs might play vital roles in the tumorigenesis by targeting functional mRNAs.

Lymph nodes metastasis-related lncRNAs

Since lymph nodes metastasis is a critical predictive factor in thyroid carcinoma [21,22], we further analyzed the relationship between differentially expressed lncRNAs and lymph nodes
metastasis. Among 352 differentially expressed lncRNAs, we found that 4 upregulated genes (LINC01016, LHX1-DT, IGF2-AS, and MIR1-1HG-AS1) were significantly expressed across patients with N1 than N0 (Table 4), and the results were visualized by heatmap (Figure 7).

Discussion

The screening of RNAs transcripts was facilitated in the past 20 years and lncRNAs were testified to be an emerging factor which strongly associated with tumorigenesis and metastasis in thyroid carcinoma [23–26]. To understand the mechanism of genetic and epigenetic alterations in thyroid carcinoma, we investigated the transcriptomes files of thyroid carcinoma and normal thyroid samples based on TCGA database. We clarified that some lncRNAs have significantly interactions with overall survival, and the predictive survival model was established where some gene expression signatures were well elucidated. Furthermore, LINC01016, LHX1-DT, IGF2-AS, and MIR1-1HG-AS1 showed the possibility related to lymph node metastasis in the thyroid.
We found in our overall survival prediction survival model that DOCK9-DT, LINC00900, C8orf34-AS1, and LINC01736 exerted as protective factors in prognosis, while ATP2C2-AS1, FAM111A-DT, LINC02550, and LINC01896 increased the risks; however, only FAM111A-DT and LINC02550 exerted as oncogenes in thyroid carcinoma as well as significantly positively correlated with poor outcomes in patients. Interestingly, these lncRNAs have not been reported or studied before, the prognostic value of these bundles of genes and our overall survival model remains to be confirmed and demonstrated.

Table 1. Significant IncRNAs in univariate Cox regression (P<0.01).

| Gene           | HR       | z        | P-value       |
|----------------|----------|----------|---------------|
| LINC00900      | 0.578188577 | -3.232009209 | 0.001229231   |
| LINC02471      | 0.799698308 | -3.18117259 | 0.001466802   |
| LINC02550      | 1.587458096 | 3.109803736 | 0.001872117   |
| DOCK9-DT       | 0.507389188 | -3.021875971 | 0.002512135   |
| LINC02555      | 0.814930817 | -2.888049273 | 0.003876391   |
| ATP2C2-AS1     | 1.929219328 | 2.841530213 | 0.00448976    |
| LINCO1896      | 1.317107839 | 2.767740738 | 0.005644634   |
| FAM111A-DT     | 0.510951459 | -2.708395538 | 0.006760939   |
| PAX8-AS1       | 2.027929188 | 2.601271103 | 0.009287902   |
| C8orf34-AS1    | 0.660496757 | -2.580697317 | 0.009860099   |
| LINCO1929      | 1.549979462 | 2.599584878 | 0.009333659   |
| LINCO1736      | 0.631751329 | -2.580697317 | 0.009860099   |

Figure 2. Eight lncRNA expression profiles for prediction of overall survival in thyroid carcinoma by multivariate Cox regression.

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Previous results [27] suggested that \textit{FAM111A-DT} could be the most promising genes in tumorigenesis of thyroid carcinoma, by numerous binding mRNAs with high correlation index. \textit{FAM111A-DT}, which named as \textit{FAM111A divergent transcript}, ubiquitously expressed in 25 tissues including thyroid gland.

This study validated that there is a significant correlation between \textit{FAM111A-DT} and \textit{FAM111A}, which confirmed early findings [28] that new susceptibility loci reached on chromosomes 11q12 (\textit{FAM111A-FAM111B}) were linked to the carcinogenesis of prostate cancer. Fernandez et al. indicated that \textit{FAM111A-DElncRNAs Regulation Log fold change FDR}

| DElncRNAs | Regulation | Log fold change | FDR        |
|-----------|------------|-----------------|------------|
| DOCK9-DT  | Upregulation | 1.907135801     | 3.87E-38   |
| LINC0900  | Upregulation | 1.12286421      | 5.38E-18   |
| C8orf34-AS1 | Upregulation | 1.431387442     | 4.08E-08   |
| LINC0736  | Upregulation | 1.001949864     | 0.00258681 |
| ATP2C2-AS1 | Downregulation | -1.382854376    | 4.18E-24   |
| FAM111A-DT | Upregulation | 1.31734235      | 5.38E-24   |
| LINC02550 | Downregulation | -1.012245336    | 1.46E-05   |
| LINC01896 | Upregulation | 2.692433265     | 0.006280554|

Table 2. Differentially expressed lncRNAs in overall survival model.

| Type          | Survival curve (p=1.627e–04) | ROC curve (AUC=0.862) |
|---------------|-------------------------------|-----------------------|
| Life expectancy (year) | ![Survival curve](image) | ![ROC curve](image) |

Figure 3. Cox regression and overall survival model. (A) Kaplan Meier plot showed significance between high-risk and low-risk patients in overall survival by the prognostic model (P<0.05). (B) The ROC curve analysis for the overall survival model (AUC=0.862) (C) The heatmap of 8 lncRNA expression profiles for prediction of overall survival model. ROC – receiver operating characteristics; AUC – area under the ROC; lncRNA – long noncoding RNA.

Table 3. C-index value of the overall survival model.

| C-index   | SE      | Lower    | Upper    | P-value       |
|-----------|---------|----------|----------|---------------|
| 0.8926066 | 0.04260484 | 0.8091026 | 0.9761105 | 3.110781e-20 |

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expression could predict the possibility of local advanced cervical cancer patients who are developing distal metastasis [29]. Our results showed for thyroid carcinoma were consistent with the insulin family of polypeptide growth factors, which promotes factors in thyroid carcinoma, but the relationship with lncRNAs expression profiles remains obscured. In our study, one of the novel and potentially important findings was that LINC01736. lncRNAs – long noncoding RNAs, mRNA – messenger RNA.

It is well known that the clinicopathological features, such as distal tumor metastasis and lymph node metastasis, as well tumor grade or staging have been proven to be pivotal prognostic factors in thyroid carcinoma, but the relationship with lncRNAs expression profiles remains obscured. In our study, one of the novel and potentially important findings was that LINC01736, LHX1-DT, IGF2-AS, and MIR1-1HG-AS1 were significantly linked to tumorigenesis and lymph node metastasis. None of the IncRNAs have been investigated except IGF2-AS. It has been proposed that IGF2 encodes a member of the insulin family of polypeptide growth factors, which promote growth-promoting activity possess. Consequently, as

Figure 4. (A) Scatter diagram showed risk scores of thyroid carcinoma patients based on TCGA database. (B) Scatter diagram showed survivals statuses of thyroid carcinoma patients based on TCGA database. TCGA – The Cancer Genome Atlas.

Figure 5. The correlation plots between differentially expressed lncRNAs and mRNAs. (A) The correlation plots of the top 5 correlated mRNAs of DOCK-DT. (B) The correlation plots of the top 5 correlated mRNAs of FAM111A-DT. (C) The correlation plots of the top 5 correlated mRNAs of LINC01736. lncRNAs – long noncoding RNAs, mRNA – messenger RNA.
Table 4. Differentially expressed LncRNAs related to lymph node metastasis.

| DElncRNAs   | Regulation | Log fold change | FDR      |
|-------------|------------|-----------------|----------|
| LINC01016   | Upregulation | 3.865146393 | 1.06E-28 |
| LHX1-DT     | Upregulation | 5.243275683 | 6.43E-28 |
| IGF2-AS     | Upregulation | 5.085826129 | 8.86E-38 |
| MIR1-1HG-AS1| Upregulation | 4.019136688 | 8.86E-38 |

Figure 6. Functional enrichment analysis for DOCK-DT, FAM111A-DT, and LINC01736 co-expressed genes. (A) Top 10 biological processes of GO analysis. (B) Top 10 pathways of KEGG enrichment analysis. GO – Gene Ontology; KEGG – Kyoto Encyclopedia of Genes and Genomes.
an antisense RNA of \( IGF2 \), \( IGF2-AS \) plays an important role in various cancers, including neuroblastoma and prostate cancer [34,35]. However, the function of \( IGF2-AS \) in thyroid carcinoma has not been elucidated yet; larger cohort is needed to testify the role and mechanisms.

**Conclusions**

We have identified differentially expressed IncRNAs based on TCGA database which associated with oncogenesis and prognosis of thyroid carcinoma. Although many IncRNAs showed promising and novel roles as biomarkers, lack of literature support limits the determinacy of these gene signatures. Future mechanistic studies are needed to validate these findings using functional experiments in vivo and in vitro. Importantly, our study provides new understandings for future studies of IncRNAs in thyroid carcinoma.

**Conflicts of interests**

None.

**Supplementary Data**

**Supplementary Table 1.** A list of 352 differentially expressed IncRNAs.

| LncRNA       | logFC    | logCPM  | PValue   | FDR     |
|--------------|----------|---------|----------|---------|
| ADD3-AS1     | –1.54462734 | –0.99910347 | 7.41E-64 | 2.41E-61 |
| LINCO1977    | 3.843510161 | 0.480401174 | 3.30E-62 | 9.70E-60 |
| RUNCDA3-A51  | 1.952999031 | 2.819115059 | 1.60E-57 | 3.27E-55 |
| LINCO2454    | 4.588997022 | 0.89782849 | 1.61E-57 | 3.27E-55 |
| LINCO2580    | –2.495858713 | –2.33679796 | 5.59E-57 | 1.09E-54 |
| STK2A-A51    | 3.034463136 | 1.06838602 | 1.13E-54 | 1.85E-52 |
| ST7-A51      | –1.448121092 | 1.639916538 | 3.98E-53 | 5.75E-51 |
| LINCO2471    | 5.22739754 | 3.40062735 | 4.33E-53 | 6.20E-51 |
| GASAL1       | –1.59528068 | –1.059362756 | 5.43E-51 | 6.43E-49 |
| UNC5B-A51    | 4.973040329 | 0.130580513 | 5.60E-51 | 6.59E-49 |
| ATP2B1-A51   | –1.307528781 | 1.42251738 | 3.19E-50 | 3.59E-48 |
| LPP-A52      | –1.308820155 | 0.367428007 | 4.66E-50 | 5.12E-48 |
| LNTCTM34A    | 1.644647087 | 0.883915622 | 1.87E-48 | 1.74E-46 |
| LINCO2432    | –2.18236897 | 0.03975372 | 2.50E-48 | 2.30E-46 |
| SEPT7-A51    | –1.271664294 | 1.166809574 | 5.28E-47 | 4.43E-45 |
| LINCO1354    | –2.298558579 | –0.743544878 | 5.17E-46 | 3.95E-44 |
| LRP4-A51     | 4.203658038 | –0.081468552 | 5.23E-44 | 3.24E-42 |
| STARD13-A51  | –1.594861034 | –1.853468472 | 9.54E-44 | 5.81E-42 |
| LINCO2158    | –1.762893598 | –2.434775175 | 6.45E-43 | 3.65E-41 |
| LINCO2560    | 3.846613199 | 1.279416149 | 4.80E-41 | 2.34E-39 |
| LYPAL1-DT    | –1.420355734 | –2.28151519 | 1.36E-40 | 6.33E-39 |
| HAGLROS      | 3.855389888 | –0.487304666 | 1.88E-40 | 8.69E-39 |
| LINCO2555    | 6.186581911 | 4.08600787 | 8.26E-40 | 3.63E-38 |
| LncRNA         | logFC       | logCPM       | PValue      | FDR         |
|---------------|-------------|--------------|-------------|-------------|
| DOCK9-DT      | 1.907135801 | 3.415634107  | 8.85E-40    | 3.87E-38    |
| TNC6G4A245    | -2.31701745 | -4.6628907   | 3.08E-37    | 1.26E-36    |
| LINC01770     | -3.033484056| 0.776786468  | 9.92E-39    | 3.95E-37    |
| LINC01539     | -2.546623831| -0.740040233 | 2.60E-38    | 1.01E-36    |
| LINC01220     | -1.429512524| -1.210742776 | 9.94E-38    | 3.65E-36    |
| TDRKH-A51     | -2.471672    | -5.3325932   | 4.37E-38    | 1.61E-36    |
| RARA-AS1      | 1.443101238  | 2.55332964   | 1.83E-36    | 6.13E-35    |
| NR2F1-A51     | -2.546623831| -0.740040233 | 2.60E-38    | 1.01E-36    |
| LINC01672     | -2.533325932| -2.658901068 | 4.37E-38    | 1.61E-36    |
| LINC01220     | -1.429512524| -1.210742776 | 9.94E-38    | 3.65E-36    |
| TNR6G4A245    | 1.38188595   | 0.208416671  | 1.17E-37    | 4.24E-36    |
| LINC01220     | -1.429512524| -1.210742776 | 9.94E-38    | 3.65E-36    |
| LINC01539     | -2.546623831| -0.740040233 | 2.60E-38    | 1.01E-36    |
| LINC01220     | -1.429512524| -1.210742776 | 9.94E-38    | 3.65E-36    |
| TNR6G4A245    | 1.38188595   | 0.208416671  | 1.17E-37    | 4.24E-36    |
| LINC01220     | -1.429512524| -1.210742776 | 9.94E-38    | 3.65E-36    |
| LINC01539     | -2.546623831| -0.740040233 | 2.60E-38    | 1.01E-36    |
| LINC01220     | -1.429512524| -1.210742776 | 9.94E-38    | 3.65E-36    |
| TNR6G4A245    | 1.38188595   | 0.208416671  | 1.17E-37    | 4.24E-36    |
| LINC01220     | -1.429512524| -1.210742776 | 9.94E-38    | 3.65E-36    |
| TNR6G4A245    | 1.38188595   | 0.208416671  | 1.17E-37    | 4.24E-36    |
| LncRNA      | logFC   | logCPM   | PValue    | FDR      |
|------------|---------|----------|-----------|----------|
| LBX2-AS1   | 1.46326 | 1.75583  | 8.58E-28  | 1.45E-26 |
| RPL34-AS1  | –1.203 | –1.458  | 3.09E-27  | 4.93E-26 |
| LINC01510  | 4.2295  | –1.319  | 3.05E-28  | 1.45E-26 |
| SYNE1-AS1  | –1.966  | –2.977  | 3.19E-27  | 5.06E-26 |
| BLACAT1    | 1.126   | 0.287   | 1.13E-26  | 1.72E-25 |
| KCNB2-AS1  | 3.030   | –2.798  | 3.19E-27  | 5.06E-26 |
| FAM170B-AS1| 4.141   | –2.095  | 3.24E-26  | 4.18E-24 |
| LINC01747  | 3.363   | –1.268  | 6.05E-27  | 9.08E-26 |
| MPPED2-AS1 | –2.779  | –0.982  | 6.64E-27  | 1.02E-25 |
| SNRK-AS1   | –1.562  | –1.629  | 1.10E-26  | 1.67E-25 |
| DCST1-AS1  | 1.126   | 0.287   | 1.13E-26  | 1.72E-25 |
| A2M-AS1    | –1.079  | 0.139   | 1.55E-26  | 2.33E-25 |
| LINC01137  | 1.085   | 2.724   | 3.30E-26  | 4.93E-25 |
| LINC00891  | 2.471   | 0.766   | 3.68E-25  | 5.06E-24 |
| LINC00607  | 2.564   | 0.766   | 3.68E-25  | 5.06E-24 |
| FAM111A-GT | 1.317   | 3.855   | 4.07E-25  | 5.38E-24 |
| KIZ-AS1    | –1.361  | –2.770  | 5.53E-25  | 7.25E-24 |
| HAGLR      | 3.234   | 2.671   | 9.06E-25  | 1.17E-23 |
| TMEM92-AS1 | –1.619  | –3.063  | 6.05E-27  | 9.08E-26 |
| LINC0092   | 3.368   | –2.701  | 1.56E-24  | 1.96E-23 |
| LINC01136  | –1.632  | –3.044  | 1.77E-24  | 2.20E-23 |
| LINC01126  | –1.382  | –3.061  | 2.10E-24  | 2.66E-23 |
| LINC00926  | –1.817  | 0.848   | 2.66E-24  | 3.27E-23 |
| LINC02345  | 2.808   | –0.709  | 3.40E-24  | 4.14E-23 |
| SNX29P2    | –1.777  | 3.54E   | 3.54E-24  | 4.31E-23 |
| THR8-AS1   | –1.228  | –1.417  | 3.61E-24  | 4.38E-23 |
| WDR11-AS1  | –1.258  | –1.879  | 4.62E-24  | 5.55E-23 |
| LINC01918  | 2.321   | –1.165  | 1.16E-23  | 1.35E-22 |
| LINC00612  | –1.559  | –2.039  | 1.91E-23  | 2.18E-22 |
| CDKN2B-AS1 | –2.328  | –1.370  | 4.54E-23  | 5.03E-22 |
| DCTN1-AS1  | 2.320   | –1.881  | 5.69E-23  | 6.27E-22 |
| NAMA       | –1.695  | 2.785   | 9.82E-23  | 1.06E-21 |
| MIR31HG    | 2.772   | 1.189   | 1.63E-22  | 1.72E-21 |
| LINC01614  | 3.956   | –1.067  | 1.65E-22  | 1.74E-21 |
| ELN-AS1    | –1.073  | 0.518   | 1.99E-22  | 2.07E-21 |
| CLIP1-AS1  | –1.396  | –3.097  | 2.02E-22  | 2.10E-21 |
| LINC01659  | –2.151  | –3.196  | 2.73E-22  | 2.82E-21 |
| LINC02343  | 3.189   | –2.726  | 3.24E-22  | 3.32E-21 |
| LINC01267  | 2.401   | –2.709  | 7.65E-22  | 7.67E-21 |
| LINC00609  | –1.636  | –2.515  | 7.98E-22  | 7.98E-21 |

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| LncRNA          | logFC     | logCPM         | PValue       | FDR          |
|-----------------|-----------|----------------|--------------|--------------|
| DUXAP8          | 2.525692559 | -1.151147476   | 9.78E-22     | 9.72E-21     |
| LINC0146       | -1.151147476 | -1.247590878   | 3.35E-20     | 3.24E-19     |
| LINC00506      | -1.384523233 | -1.817503745   | 1.55E-21     | 1.52E-20     |
| TCEG1L-AS1      | 2.049627044 | -1.24742241    | 6.35E-20     | 6.16E-19     |
| LINC005381     | -2.599270665 | -2.300678546   | 3.88E-20     | 3.37E-19     |
| PARAL1          | 4.346540422 | -1.773215312   | 1.68E-20     | 1.50E-19     |
| UCKL1-AS1       | -1.165628262 | -1.427590888   | 2.71E-20     | 2.39E-19     |
| LINC00853      | 1.898942986 | -0.028798475   | 2.46E-19     | 2.01E-18     |
| LINC01975      | -2.599270665 | -2.300678546   | 3.88E-20     | 3.37E-19     |
| TBILA           | 2.049627044 | -1.24742241    | 6.35E-20     | 6.16E-19     |
| LINC01550      | -1.249560267 | 0.839350621    | 1.39E-18     | 1.23E-17     |
| WWTR1-AS1       | -1.017125584 | 0.223947847    | 9.82E-19     | 8.55E-18     |
| LINC00887      | 2.178988373 | 0.122886421    | 5.38E-18     | 4.46E-17     |
| LINC01426      | 1.898942986 | -0.028798475   | 2.06E-18     | 1.70E-17     |
| MID1P1-AS1      | -1.121699853 | -1.71060927    | 4.35E-18     | 3.47E-17     |
| LINC01985      | -1.462693538 | -0.70321875    | 6.41E-18     | 5.29E-17     |
| TNFRSF10A-AS1  | 1.068417568 | 0.129805675    | 6.41E-18     | 5.29E-17     |
| LINC01814      | -1.067329139 | -0.18296878   | 9.82E-19     | 8.55E-18     |
| NCAM1-AS1       | -1.876475157 | 0.439873595    | 1.76E-18     | 1.46E-17     |
| LINC00900      | 1.122886421 | 2.205956467    | 5.38E-18     | 4.46E-17     |
| LINC0167       | -1.151147476 | -1.247590878   | 3.35E-20     | 3.24E-19     |
| PGMS-AS1        | -1.75993484 | -2.956305355   | 5.49E-18     | 4.46E-17     |
| LINC01018      | -1.267726684 | 0.765169818    | 1.52E-20     | 1.41E-19     |
| HAND2-AS1       | -1.800404947 | -1.05377541    | 1.13E-17     | 8.93E-17     |
| FAM181A-AS1     | -1.666658115 | -1.38650436   | 1.20E-17     | 9.57E-17     |
| LINC02593       | -1.531899488 | -1.539817408   | 1.46E-17     | 1.19E-16     |
| LINC0067       | -1.278875217 | -2.971124274   | 1.71E-17     | 1.38E-16     |
| LINC01704      | 3.331082757 | 2.69009325     | 2.00E-17     | 1.51E-16     |
| SH3PD2A-AS1     | 1.683732006 | -2.733975495   | 3.10E-17     | 2.34E-16     |
| LINC00982      | -1.339058009 | 3.307059677    | 3.26E-17     | 2.34E-16     |
| ZNF571-AS1      | 1.471778093 | 1.485743805    | 4.06E-17     | 3.08E-16     |
| CATIP-AS2       | -1.455702841 | -2.102456882   | 5.57E-17     | 4.19E-16     |
| HCG2040054     | -1.071754441 | -3.058694113   | 8.48E-18     | 6.30E-17     |
| NAD2-R2-AS1     | -1.267726684 | -2.345071094   | 7.37E-17     | 5.44E-16     |
| FAM182A         | -1.525124056 | -2.38769015   | 1.14E-16     | 8.53E-16     |
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| HCG22    | 2.532702  | 2.327072   | 1.82E-17    | 1.25E-16   |
| LINC0117 | -1.106311 | -0.303572  | 1.94E-17    | 1.37E-16   |
| VAC14-AS1| 2.016076  | 1.403521   | 4.29E-17    | 2.87E-16   |
| SOX9-AS1 | -1.377769 | 0.522131   | 5.26E-17    | 3.49E-16   |
| TMEM108-AS1| 4.104907| 2.164907   | 6.17E-17    | 4.10E-16   |
| LINC02461| 5.681571 | 1.639718   | 8.87E-17    | 5.80E-16   |
| LINC02257| 3.694696 | -2.804992  | 9.62E-17    | 6.27E-16   |
| LINC02173| -1.00803  | -0.903572  | 2.40E-17    | 1.64E-16   |
| VAC14-AS1| 2.016076  | -1.403521  | 4.29E-17    | 2.87E-16   |
| LINC01615| 3.395239 | -1.347501  | 5.26E-17    | 3.49E-16   |
| LINC01204| -2.191001 | -2.048930  | 4.52E-17    | 2.76E-16   |
| LINC02491| -2.316587 | -2.438486  | 4.68E-17    | 2.85E-16   |
| LINC01615| 1.805083  | -1.800514  | 1.22E-16    | 7.86E-16   |
| LINC00942| 1.832226  | -1.347501  | 2.06E-16    | 1.30E-15   |
| SEPT4-AS1| -1.108555 | -2.120540  | 2.06E-16    | 1.30E-15   |
| LINC01878| 2.737430  | -1.282814  | 3.20E-16    | 1.98E-15   |
| NAV2-AS4 | -1.646324 | -0.249631  | 1.05E-16    | 6.83E-16   |
| LINC02397| -1.911008 | -2.048930  | 4.52E-16    | 2.76E-16   |
| LINC02458| 2.316587  | -2.438486  | 4.68E-17    | 2.85E-16   |
| LINC00942| 1.832226  | -1.347501  | 2.06E-16    | 1.30E-15   |
| LINC01615| 1.805083  | -1.800514  | 1.22E-16    | 7.86E-16   |
| LncRNA          | logFC   | logCPM  | PValue         | FDR         |
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| SNAP25-AS1      | 1.569   | -1.98   | 4.81E-14       | 2.44E-13    |
| HRAS-AS1        | -1.017  | -0.88   | 6.66E-14       | 3.33E-13    |
| LINC01571       | -1.199  | 2.32    | 7.30E-14       | 3.65E-13    |
| LINC02600       | 2.37    | 0.44    | 8.40E-14       | 4.18E-13    |
| DGUOK-AS1       | 1.00    | 0.14    | 8.57E-14       | 4.28E-13    |
| UBXN10-AS1      | 1.01    | 1.00    | 9.08E-14       | 4.50E-13    |
| SPANXA2-OT1     | 1.30    | -2.22   | 1.28E-14       | 6.28E-13    |
| SNRPN           | 0.67    | 0.12    | 1.42E-14       | 7.10E-13    |
| CFLAR-AS1       | -1.03   | -0.29   | 1.58E-13       | 7.68E-13    |
| HOXA11-AS1      | 4.17    | -2.38   | 1.80E-13       | 8.67E-13    |
| LINC01257       | -2.18   | -1.69   | 1.84E-13       | 8.86E-13    |
| ZBTB20-AS1      | -1.04   | -2.98   | 1.92E-13       | 9.24E-13    |
| LINC02185       | -1.02   | -2.89   | 1.95E-13       | 9.38E-13    |
| LINC01968       | 1.48    | -2.03   | 1.96E-13       | 9.42E-13    |
| LINC01978       | 1.95    | -2.90   | 2.03E-12       | 9.38E-13    |
| LINC01268       | 1.19    | -1.83   | 2.09E-13       | 9.42E-13    |
| LINC02159       | 2.39    | -0.93   | 1.14E-12       | 5.36E-12    |
| LINC01260       | 1.09    | -1.30   | 1.17E-12       | 5.27E-12    |
| CLDN10-AS1      | 1.19    | -2.90   | 1.23E-12       | 5.36E-12    |
| LINC01013       | 1.19    | -1.83   | 1.24E-12       | 5.62E-12    |
| CLDN10-AS1      | 4.00    | -2.97   | 1.25E-12       | 5.62E-12    |
| FENDRR          | -1.08   | -2.87   | 1.76E-12       | 7.85E-12    |
| LINC0365        | 1.85    | -1.73   | 1.77E-12       | 7.85E-12    |
| LINC01268       | 1.09    | -1.30   | 1.17E-12       | 5.27E-12    |
| LINC01013       | 1.19    | -2.90   | 1.23E-12       | 5.36E-12    |
| CLDN10-AS1      | 4.00    | -2.97   | 1.25E-12       | 5.62E-12    |
| LINC0365        | 1.85    | -1.73   | 1.77E-12       | 7.85E-12    |
| LINC01268       | 1.09    | -1.30   | 1.17E-12       | 5.27E-12    |
| LINC01013       | 1.19    | -2.90   | 1.23E-12       | 5.36E-12    |
| CLDN10-AS1      | 4.00    | -2.97   | 1.25E-12       | 5.62E-12    |
| LINC0365        | 1.85    | -1.73   | 1.77E-12       | 7.85E-12    |
| LncRNA    | logFC  | logCPM  | PValue   | FDR     |
|----------|--------|---------|----------|---------|
| SRGAP3-AS4 | -1.09460423 | -3.018458492 | 6.20E-11 | 2.40E-10 |
| LINC01715 | 0.983380567  | 6.61543209  | 7.13E-11 | 2.72E-10 |
| MEG9     | 2.480937047  | 2.417027462 | 7.48E-11 | 2.88E-10 |
| LINC02516 | 1.681214882  | -2.606906768 | 8.63E-11 | 3.30E-10 |
| LINC01933 | 1.360700071  | 0.775510846 | 1.08E-10 | 4.09E-10 |
| LINC01451 | 1.738266137  | -3.016532722 | 1.19E-10 | 4.49E-10 |
| UCA1     | 3.111031028  | -1.662934778 | 1.32E-10 | 4.94E-10 |
| LINC02516 | -2.086388338 | -2.423911662 | 1.38E-10 | 4.62E-10 |
| PACERR   | 1.32108611   | -1.739672921 | 1.71E-10 | 6.35E-10 |
| PLAC4    | -1.179131972 | -3.187321626 | 1.73E-10 | 6.41E-10 |
| LINC00402 | -0.208638838 | -2.423911662 | 1.79E-10 | 6.61E-10 |
| LINC00113 | 1.878237395  | -2.20315245  | 2.18E-10 | 7.99E-10 |
| PRR29-AS1| -1.295589209 | 0.676313736  | 2.53E-09 | 8.51E-09 |
| MLIP-IT1 | 1.180959368  | -2.20315245  | 2.75E-10 | 9.17E-10 |
| NAV2-ASS | -1.202851563 | -3.044836102 | 2.99E-10 | 9.17E-10 |
| TMC3-AS1 | -1.011789762 | -1.059725645 | 4.11E-09 | 1.10E-08 |
| MYOSLID | 1.742193737   | -2.93689052  | 4.23E-09 | 1.18E-08 |
| LINC00861 | -1.17952809  | -2.85902371 | 4.60E-09 | 1.38E-08 |
| FALEC    | 2.187742734   | -1.382164308 | 4.92E-09 | 1.57E-08 |
| RNU6ATAC35P | -1.295589209 | -0.756313736 | 5.15E-09 | 1.72E-08 |
| TMC5-AS1 | -1.001789762 | -1.059725645 | 5.45E-09 | 1.72E-08 |
| MYOSLID | 1.742193737   | -2.93689052  | 6.02E-09 | 1.91E-08 |
| LINC0078 | -1.499956986 | -1.95421177 | 6.02E-09 | 1.91E-08 |
| TCL6     | -1.947664766 | -1.819781972 | 6.02E-09 | 1.91E-08 |
| LINC01705 | 3.38082231   | -2.821752802 | 6.02E-09 | 1.91E-08 |
| LINC0242 | 1.284297799   | -0.49372608  | 6.02E-09 | 1.91E-08 |
| LINC01857 | -1.517930886 | -1.450805986 | 6.02E-09 | 1.91E-08 |
| LINC02347 | 2.51584231   | -3.178109564 | 6.02E-09 | 1.91E-08 |
| LINC02384 | -1.161842833 | -1.106399342 | 6.02E-09 | 1.91E-08 |
| LINC00897 | -1.30558597  | 1.896209333  | 6.02E-09 | 1.91E-08 |
| C8orf34-AS1 | 1.431387442 | -2.031569466 | 6.02E-09 | 1.91E-08 |
| PRK27AS1 | -1.068066842 | -3.198234381 | 6.02E-09 | 1.91E-08 |

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| LncRNA     | logFC    | logCPM   | PValue       | FDR        |
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| MIR4527HG | 2.188066145 | -2.951448562 | 2.85E-08  | 8.39E-08  |
| LINC0179  | -2.822249698 | -3.158271112 | 3.10E-08  | 9.32E-08  |
| DPP10-A51 | 2.176483838 | -1.655100877 | 3.13E-08  | 9.20E-08  |
| LINC01293 | 2.967538508 | -1.723191923 | 3.21E-08  | 9.42E-08  |
| LINC00134 | 2.125301434 | -3.76E-07  | 1.00E-07  | 1.00E-07  |
| KCCAT333  | 1.89311652  | -2.130586927 | 4.04E-08  | 1.17E-07  |
| LINC01934 | -1.301524233 | -2.654274876 | 4.18E-08  | 1.21E-07  |
| LINC0836  | 3.169311285  | -3.126967444 | 5.69E-08  | 1.63E-07  |
| HPN-AS1   | 1.197442278  | -1.9946336  | 5.94E-08  | 1.69E-07  |
| LINC01983 | -1.486025422 | -2.743801026 | 4.34E-08  | 1.26E-07  |
| LINC01480 | -1.134594996 | -2.50279128  | 4.91E-08  | 1.41E-07  |
| LINC01293 | 2.967538508 | -1.723191923 | 3.21E-08  | 9.42E-08  |
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| LINC0836  | 3.169311285  | -3.126967444 | 5.69E-08  | 1.63E-07  |
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| LINC01983 | -1.486025422 | -2.743801026 | 4.34E-08  | 1.26E-07  |
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| HPN-AS1   | 1.197442278  | -1.9946336  | 5.94E-08  | 1.69E-07  |
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| LINC01480 | -1.134594996 | -2.50279128  | 4.91E-08  | 1.41E-07  |
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| LINC01293 | 2.967538508 | -1.723191923 | 3.21E-08  | 9.42E-08  |
| LINC01934 | -1.301524233 | -2.654274876 | 4.18E-08  | 1.21E-07  |
| LINC0836  | 3.169311285  | -3.126967444 | 5.69E-08  | 1.63E-07  |
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| LINC01976| -1.235919046 | -2.611455982 | 2.95E-05  | 6.21E-05  |
| LINC01597| 1.18039492 | -2.038545166 | 6.32E-05  | 0.000128067 |
| DLX6-AS1 | 1.026349641 | -1.509082087 | 7.11E-05  | 0.000142994 |
| LINC00525| 1.174432004 | -2.731294734 | 8.64E-05  | 0.000172065 |
| LINC02576| -1.187034556 | -2.141219796 | 0.000102011 | 0.000201612 |
| IFNG-AS1 | -1.300736035 | -1.972370504 | 0.000102388 | 0.000202312 |
| SLC26A4-AS1 | -1.007653022 | 8.553744747 | 0.000108694 | 0.000213992 |
| LINC01783| 1.058124593 | -2.587925042 | 0.000118932 | 0.000235289 |
| LINC01736| 1.001949864 | -2.238306481 | 0.000133039 | 0.000258681 |
| LINC02544| 1.125663027 | -1.252983739 | 0.000205176 | 0.000389425 |
| DGCR10  | 1.008940155 | -2.906238751 | 0.000323916 | 0.000598487 |
| LINC01016| -1.397984509 | -0.746262465 | 0.00080403 | 0.001413638 |
| LINC00261| -1.065417538 | -1.644636073 | 0.001219267 | 0.002090539 |
| MIR1-1HG-AS1 | 1.54132604 | -2.042767475 | 0.001324837 | 0.002628781 |
| LINC01896| 2.692432365 | -2.185760354 | 0.00392824 | 0.006280554 |
| LINC00648| 1.296137264 | -2.152158054 | 0.004458972 | 0.007064917 |
| LINC01014| -1.014153989 | -3.084912065 | 0.004587855 | 0.007252895 |
| ZFY-AS1  | -1.51394898 | -0.614803453 | 0.004705264 | 0.007420158 |
| LINC02506| 1.825073446 | -2.948303371 | 0.00535615 | 0.008366998 |

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