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ORIGINAL RESEARCH

Revealing lncRNA Biomarkers Related to Chronic Obstructive Pulmonary Disease Based on Bioinformatics

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Background: Chronic obstructive pulmonary disease (COPD) is a common chronic disease of the respiratory tract, with high prevalence, high disability, and poor prognosis. However, the molecular mechanism of COPD needs to be further revealed.

Methods: We obtained the gene expression profile and miRNA expression profile of COPD patients from Gene Expression Omnibus (GEO) database, and the differentially expressed genes (DEGs) and differentially expressed miRNAs (DEmis) in COPD were identified. Subsequently, the COPD-related ceRNA network was constructed based on the interaction between lncRNA, miRNA, and mRNA using the lncACTdb database. Finally, the Cytoscape software was used to analyze the network topology and COPD-related lncRNAs.

Results: Firstly, the 519 DEGs and 17 DEmis were identified from COPD GEO datasets. GO enrichment showed that leukocyte chemotaxis, cell chemotaxis, and myeloid leukocyte migration were upregulated, and muscle and membrane repolarization-related biological progress were downregulated in COPD. KEGG pathway enrichment shows that the p53 pathway was upregulated in COPD. Hallmark enrichment showed that chronic neutrophil inflammation was a sign of the pathogenesis of COPD. Next, a ceRNA network including 93 DEGs, 2 DEmi, 463 lncRNAs, and 1157 DEG-lncRNA, DEmi-lncRNA, and DEmi-DEG interactions were obtained. The hub-lncRNA (the network is ranked in the top 10) as the core marker of COPD, including SNHG12, SLFNL1-AS1, KCNQ1OT1, XIST, EAF1-AS1, FOXD2-AS1, NORAD, PINK1-AS and RP11-69E11.4. And the cytoHubba analysis identified ATM, SMAD7 and HIF1A as hub genes of ceRNA network.

Conclusion: This study provides a landscape of ceRNA network of COPD, which help to reveal the underlying pathophysiological mechanisms of COPD and shed light on novel therapeutic strategies for COPD.

Keywords: chronic obstructive pulmonary disease, lncRNA, miRNA, bioinformatics

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic bronchitis or emphysema hallmarked by chronic respiratory symptoms and airflow restriction, which can further develop into common chronic diseases of pulmonary heart disease and respiratory failure.[1] The prevalence of COPD is increasingly worldwide, which become a great individual and society burden.[2] As the COPD is often punctuated by rhinoviruses (RVs), the acute exacerbations frequently lead to morbidity and mortality of these patients.[3] Although smoking and aging are the main causes of COPD.[4] However, the pathological mechanism of COPD remains limited. The underlying pathophysiological mechanism is urgent for developing new therapies for COPD.

The dysregulation of mRNA and miRNA expression was also observed in COPD.[5] A microarray of epithelium from COPD survey the TLR family gene expression and revealed that TLR5 is essential for the activation of innate immune responses in COPD. The aging-related genes were also differently expressed in COPD.[6] The distinct miRNA profile was also observed in COPD.[7] Moreover, the study showed that MicroRNA-218 regulated the overproduction of MUC5AC

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and inflammation of COPD by targeting TNFR1-mediated NF-κB pathway. Recently, microRNA-21 was reported to mediate COPD pathogenesis by regulating SATB1/S100A9/NF-κB axis.[8]

Emerging studies showed that the genetic factors are also important determinants of COPD. Long non-coding RNA (lncRNA) is a type of single-stranded non-coding RNA with the length of longer than 200 nucleotides that participate in various biological processes by manipulating gene expression.[9] Recently, lncRNAs have been documented to play a key role in diverse biological functions and be involved in various disease including COPD and airway disease.[10] A recent study revealed the significant different lncRNA expression profiles in smokers with or without COPD. Moreover, lncRNAs was reported to perform essential functions in the progression of COPD. lncRNA TUG1 was reported to reduce proliferation in COPD by inducing -β.[11] Research by Li et al showed that lncRNA MIR155HG regulates/ macrophage polarization in COPD.[12] Zheng et al found that lncRNA COPDA1 promotes the proliferation of human bronchial smooth muscle cells in COPD.[13] As the key regulator of miRNA, lncRNA was reported to regulate the COPD progression by targeting miRNA and mRNA.[14,15] However, the landscape of COPD ceRNA network is limited.

In this study, we performed differential analysis of genes and miRNA expression profiles in COPD patients to obtain COPD-related genes and miRNAs, and constructed a COPD ceRNA network based on the interaction between genes, miRNAs and lncRNAs in the lncACTdb database. And then Cytoscape was used to perform topological analysis on the ceRNA network, and we obtained 10 lncRNAs as hub nodes, which were expected to become potential therapeutic targets for COPD.

Materials and Methods

Data Collection

We searched the mRNA and miRNA expression profiles of patients with COPD in the Gene Expression Omnibus (GEO) database based on the keywords "COPD", "Home sapiens", "mRNA profiles" and "miRNA profiles". A total of 16 items were identified. Finally, after screening for the presence or absence of normal samples and the source of the samples, 148 samples from the four studies were used for subsequent analysis. The detailed information of the data set is shown in Table 1.

Data Preprocessing and Differential Expression Analysis

The original data was downloaded and the R package "limma" was used for analysis. Firstly, the original data was normalized (log2), and then differently expressed genes between COPD and normal samples were analyzed (lmFit and eBay functions) with the threshold used is fold change (log2) cutoff of 1 and p value cutoff of 0.05. Each data set was analyzed separately. Volcano maps and gene expression heat maps were performed by R package "ggplot2 and pheatmap".

PPI Network Analysis

The protein–protein interaction (PPI) network can help us identify the key genes for the occurrence and development of COPD from the level of interaction. Get the PPI information of DEGs from the Search tool for the retrieval of Interacting Genes (STRING) database (http://www.string-db.org/).[10] Then, Cytoscape v3.7.0 software was used to analyze the topology of the PPI network in COPD, and the PPI network was constructed.

Table 1 Datasets

Accession	Experiment	Platform	*COPD*	Normal	Mrna/microRNA
GSE38974	Array	GPL7723	19	8	microRNA
GSE38974	Array	GPL4133	23	9	mRNA
GSE103174	Array	GPL13667	37	16	mRNA
GSE135188	RNA-seq	GPL21290	18	18	mRNA

GO/KEGG Enrichment Analysis

In order to study the biological functions of DEG, the R package ClusterProfiler was used to analyze and visualize the functional map of DEGs (Gene Ontology (GO) annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway) and the annotative R package (org.Hs.eg.db) was selected as background. P value <0.05 is statistically significant.

Hallmark Feature Enrichment

In order to explore the enrichment of DEG in the biological state and process, the Hallmark gene set was downloaded from the MsigDB database, and the gene set of each pathway in the hallmark and the overlap of DEG were calculated by hypergeometric analysis. The enrichment threshold is P value <0.05.

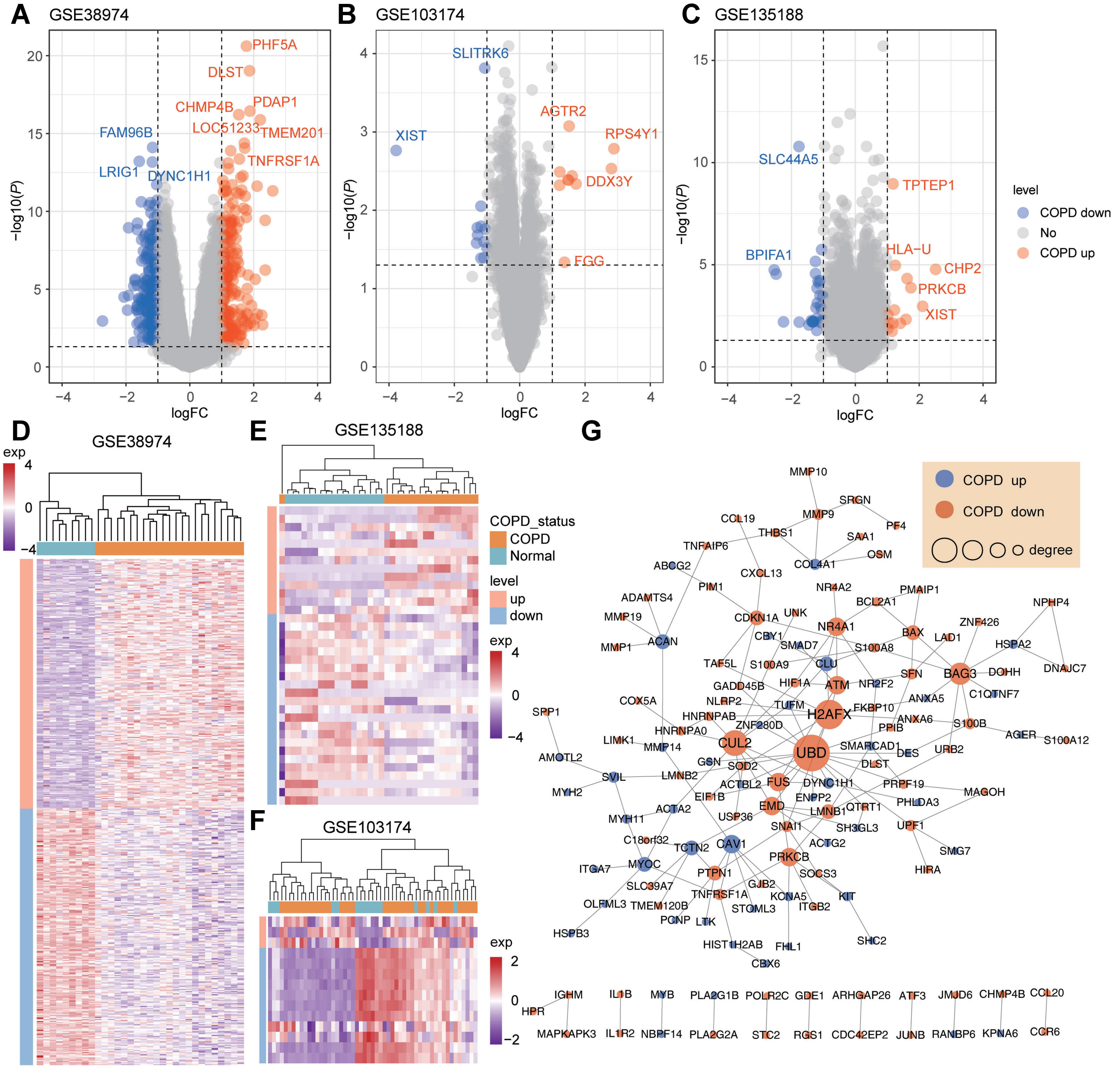

Figure 1 The DEG in COPD samples and normal samples. (**A**) The volcano plots of DEGs in COPD using GSE38974 dataset. (**B**) The volcano plots of DEGs in COPD using GSE103174 dataset. (**C**) The volcano plots of DEGs in COPD using GSE135188 datasets. The upregulated gene were red and the down-regulated genes were blue. The filter parameter of DEGs were |log2 (FC)|> 1 and P <0.05. (**D**) The heat maps of DEGs in COPD samples and normal samples using GSE38974. (**E**) The heat maps of DEGs in COPD samples and normal samples in the GSE103174. (**F**) The heat maps of DEGs in COPD samples and normal samples in the GSE135188 datasets. (**G**) The network of DEGs in COPD.

Construction of ceRNA Network

The lncACTdb 2.0 (http://www.bio-bigdata.net/LncACTdb/) database contained the ceRNA interaction relationships from multiple documents. The DEGs and DEmis were submitted to the database, and then the related lncRNA, the interactions between DEGs and lncRNA, DEmi and lncRNA, and DEG and DEmiRNA were obtained. According to the ceRNA theory, the selected DEmi and DEG, DEmi and lncRNA, and DEG and lncRNA were integrated and interacted with each other, and the DEmi-DEG-lncRNA ceRNA network was constructed using Cytoscape v3.7.0 software.

Statistical Analysis

All data were analyzed using R (v 4.0.3). The different expression analysis was performed using R "limma" packages. Student's t-tests were used to calculate P-values by t.test function. The heatmaps were generated by pheatmap R package (v 1.0.12).

Result

DEG and DEmi Related to COPD Was Screened

Firstly, the 519 DEGs from the mRNA expression between COPD samples and normal samples from three GEO datasets were obtained with a threshold of p value <0.05 and |logFC|>1. Among them, 233 up-regulated DEGs, 240 down-regulated DEGs were identified in the data set GSE38974; 10 up-regulated DEGs and 12 down-regulated DEGs were identified in the data set GSE103174, and 16 up-regulated DEGs and 31 down-regulated DEGs were identified in the data set GSE135188. The DEGs volcano map of the above three datasets are shown in Figure 1A–C, and the heatmap is shown in Figure 1D–F. In the DEG expression heatmap, there was significant heterogeneity between the expression of DEGs in COPD samples and normal samples. Next, we use all 519 DEGs to construct a PPI network in Figure 1G. In the constructed PPI-DEG network, there were a total of 139 DEGs and 166 interaction relationships. Among them, UBD, H2AFX, BAG3, and CDKN1A were key genes in the network of COPD. Zhang et al determined the modular gene markers containing H2AFX by analyzing the protein interaction network as a marker for distinguishing COPD and NSCLC.[16] Sun et al identified 40 potential COPD-related genes through bioinformatics analysis and found that HIF1A, CDKN1A, BAG3, ERBB2, and ATG16L1 may affect the development of COPD by regulating autophagy.[17]

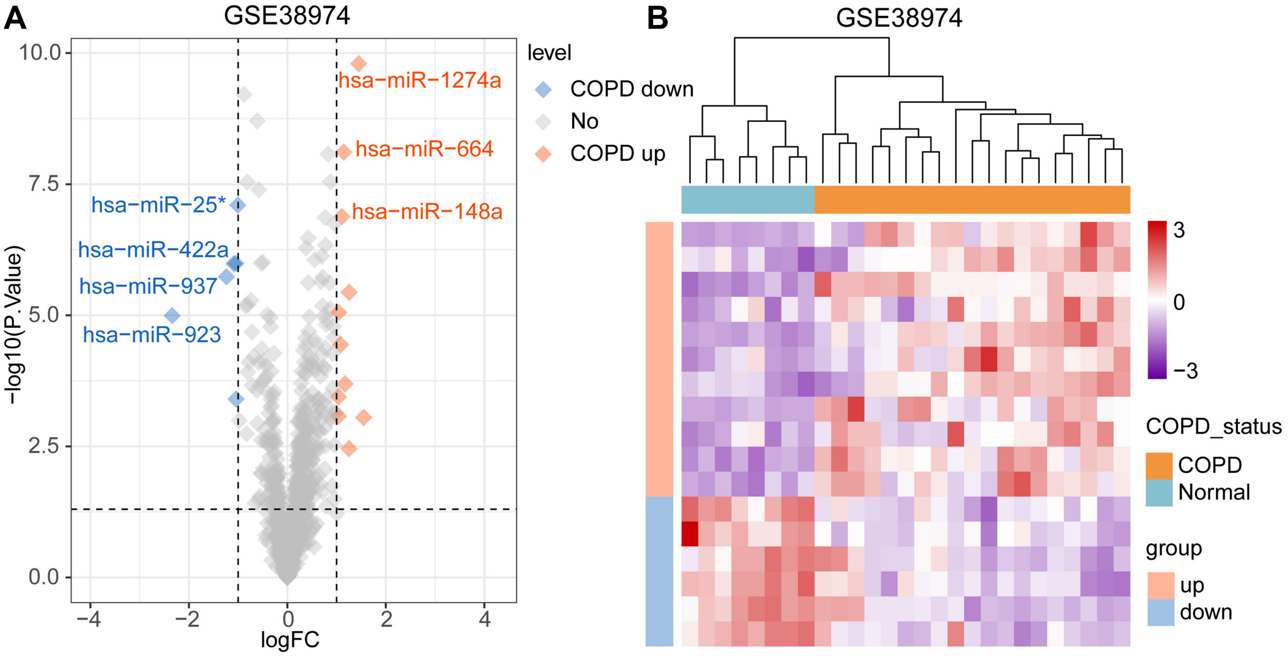

Figure 2 The differential microRNAs (DEmi) in COPD samples and normal samples. (**A**) The volcano plots of DEmi obtained from the data set GSE38974 with P <0.05 and |log2 (FC)|> 1. The small diamond presents the microRNAs. (**B**) The heat map of DEmis of COPD samples and normal samples in the data set GSE38974.

We next selected 17 DEmis from the data set GSE38974 by using the same threshold as that used to obtain DEGs, including 11 up-regulated DEmis and 6 down-regulated DEmis. The volcano map and heatmap of DEmis are shown in Figure 2A and B, respectively.

Functional Enrichment of DEG in COPD

In order to explore the biological significance of COPD features, all DEGs from GSE38974, GSE103174 and GSE135188 were used for GO/KEGG analysis using the Hallmark gene sets in MSigDB. As shown in Figure 3A, GO enrichment showed that leukocyte chemotaxis, cell chemotaxis and myeloid leukocyte migration were upregulated, and muscle and membrane repolarization-related biological progresses were downregulated in COPD. The cytokine receptor CXCR2 antagonist (MK-7123) reduced the chemotaxis of neutrophils, which may alleviate the airway inflammation of COPD,[18] and aerobic training combined with respiratory muscle stretching improved the functional exercise capacity of COPD patients and reduced dyspnea.[19] In Figure 3B, KEGG pathway enrichment shows that p53 pathway was upregulated in COPD. The p53 signaling pathway polymorphism was associated with changes in emphysema in COPD patients,[20] and compared with non-smokers, healthy smokers and COPD smokers due to the apoptosis of active pulmonary capillary endothelial cells, the level of circulating endothelial cells increased.[21] Dinesh et al also revealed the

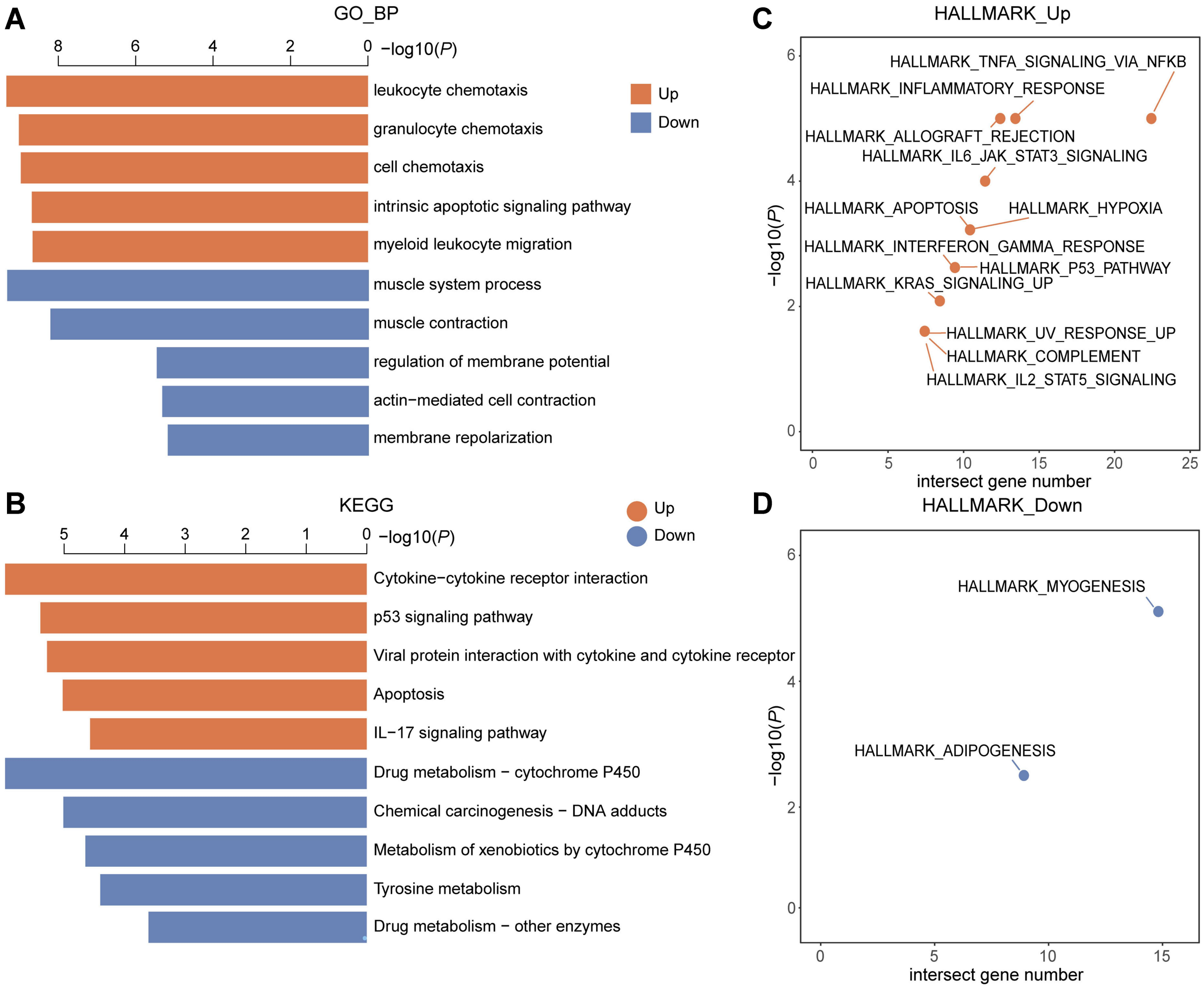

Figure 3 The functional enrichment analysis of DEG in COPD. (**A**) GO_BP function enrichment of DEG in COPD. (**B**) KEGG function enrichment of DEG in COPD. The enrichment results of DEG up (**C**) and down (**D**) in Hallmark respectively. The abscissa was the number of intersections between DEG and the pathway gene set, and the ordinate was -log10 of the significance p-value of the hypergeometric test.

increased apoptotic cell death in airway epithelial cells in COPD.[10] We also found in the Hallmark enrichment results of Figure 3C and D that chronic neutrophil inflammation was a sign of the pathogenesis of COPD, which persists after smoking cessation.[22] And COPD patients may be particularly vulnerable to hypoxia-induced autonomic disorders.[23]

lncRNA Marker is Screened Based on DEG and DEmi

We obtained the RNA interaction relationship from the database lncACTdb 2.0, and constructed the interaction relationship network containing 519 DEGs and 17 DEmis. The ceRNA network we obtained (Figure 4) contains 93 DEGs, 2 DEmi, 463 lncRNAs, and 1157 DEG-lncRNA, DEmi-lncRNA, and DEmi-DEG interactions. The network nodedegree is shown in Table 2. In the constructed ceRNA network, we selected hub-lncRNA (the network is ranked in the top 10) as the core marker of COPD, including SNHG12, SLFNL1-AS1, KCNQ1OT1, XIST, EAF1-AS1, FOXD2-AS1, NORAD, PINK1-AS and RP11-69E11.4. Next, basing on the cytoHubba analysis of cytoscape, ATM, SMAD7 and HIF1A were identified as hub genes in this network and are used for the treatment of COPD in the future (Figure 5).

Discussion

COPD is a chronic progressive inflammatory disease with poor prognosis and low long-term survival rate.[24] Pulmonary rehabilitation is traditionally recommended for patients with moderate to severe COPD. Although pulmonary rehabilitation, bronchodilators and anti-inflammatory agents provides the greatest improvement in dyspnea, exercise tolerance, and health-related quality of life,[25] it is very difficult to change physical activity and with poor outcome.[26] Therefore, COPD is a major heterogeneous disease and one of the world's leading causes of death, and it is urgent for diagnostic and prognostic biomarkers for COPD.

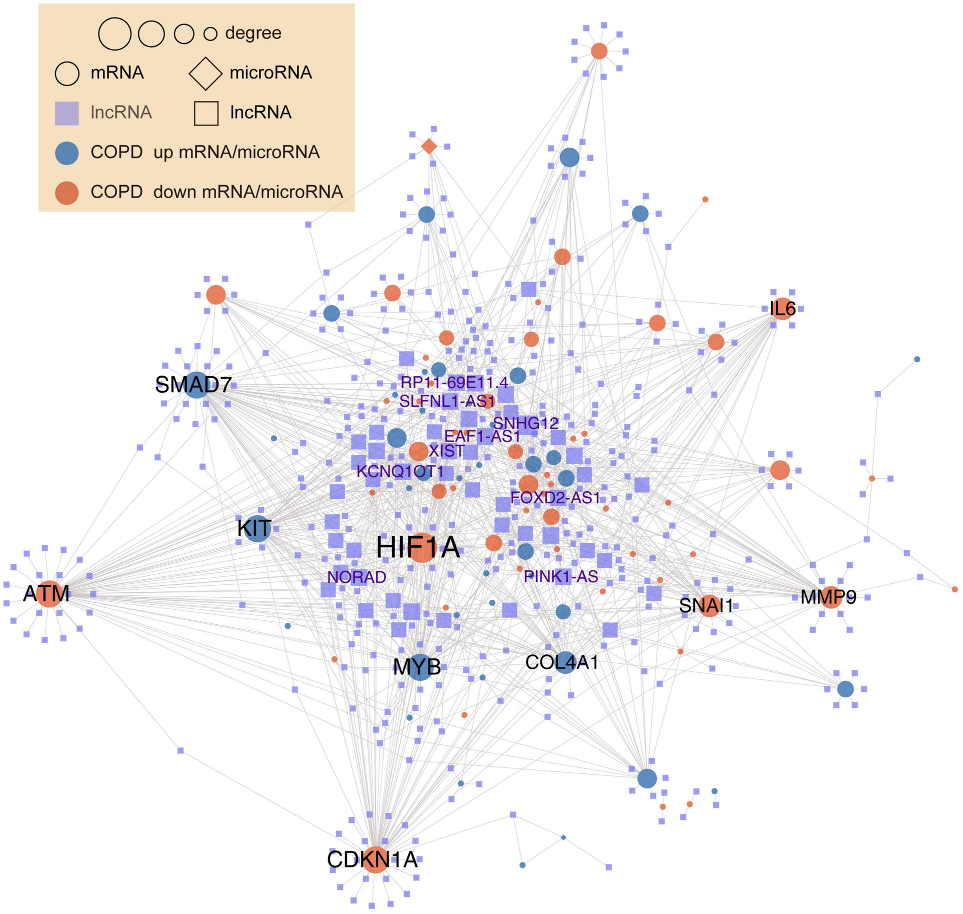

Figure 4 ceRNA network in COPD.

Table 2 The Network Node Degree

Gene	RNA	Upordown	Degree
AADAC	mRNA	Down	0
ABCG2	mRNA	Down	17
AC002117.1	lncRNA	Plane	1
AC002467.7	lncRNA	Plane	1
AC003104.1	lncRNA	Plane	4
AC003991.3	lncRNA	Plane	3
AC004069.2	lncRNA	Plane	1
AC004448.5	lncRNA	Plane	1
AC005154.6	lncRNA	Plane	6
AC005532.5	lncRNA	Plane	2
AC007228.9	lncRNA	Plane	1
AC007292.6	lncRNA	Plane	1
AC008079.10	lncRNA	Plane	2
AC008697.1	lncRNA	Plane	1
AC009133.12	lncRNA	Plane	2
AC009948.5	lncRNA	Plane	5
AC010136.2	lncRNA	Plane	1
AC010226.4	lncRNA	Plane	1
AC012123.1	lncRNA	Plane	1
AC015849.16	lncRNA	Plane	2
AC015933.2	lncRNA	Plane	1
AC016747.3	lncRNA	Plane	1
AC017060.1	lncRNA	Plane	1
AC017101.10	lncRNA	Plane	5
AC018890.6	lncRNA	Plane	2
AC023347.1	lncRNA	Plane	1
AC034220.3	lncRNA	Plane	1
AC058791.1	lncRNA	Plane	2
AC069363.1	lncRNA	Plane	2
AC073254.1	lncRNA	Plane	1
AC073641.2	lncRNA	Plane	3
AC074117.10	lncRNA	Plane	1
AC074286.1	lncRNA	Plane	3
AC074366.3	lncRNA	Plane	2
AC084219.4	lncRNA	Plane	2
AC092066.1	lncRNA	Plane	1
AC093627.10	lncRNA	Plane	1
AC097662.2	lncRNA	Plane	1
AC104134.2	lncRNA	Plane	2
AC107081.5	lncRNA	Plane	2
AC108142.1	lncRNA	Plane	1
AC116366.5	lncRNA	Plane	1
AC139100.4	lncRNA	Plane	1
AC141928.1	lncRNA	Plane	1
ACAN	mRNA	Down	0
ACSL5	mRNA	Up	0
ACTA2	mRNA	Down	12
ACTBL2	mRNA	Down	0
ACTG2	mRNA	Down	0
ACTN3	mRNA	Down	0
ADAMTS4	mRNA	Up	1

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
ADH1A	mRNA	Down	0
ADH1C	mRNA	Down	0
ADORA2A-AS1	lncRNA	Plane	1
AF127936.9	lncRNA	Plane	1
AF146191.4	lncRNA	Plane	1
AGBL1	mRNA	Down	0
AGBL2	mRNA	Down	0
AGER	mRNA	Down	0
AGTR2	mRNA	Up	0
AK2P2	mRNA	Up	0
AKAP14	mRNA	Down	0
AKIRIN1	mRNA	Up	0
AL133243.1	lncRNA	Plane	1
ALAS2	mRNA	Up	0
ALG6	mRNA	Down	0
ALKBH3-AS1	lncRNA	Plane	1
ALMS1-IT1	lncRNA	Plane	1
ALOX12-AS1	lncRNA	Plane	2
AMOTL2	mRNA	Down	0
ANKMY2	mRNA	Down	0
ANKRD22	mRNA	Up	0
ANO8	mRNA	Up	0
ANXA2P3	mRNA	Down	0
ANXA5	mRNA	Down	0
ANXA6	mRNA	Up	0
AP001258.4	lncRNA	Plane	1
AP006621.8	lncRNA	Plane	1
APAF1	mRNA	Up	23
APOBEC3A	mRNA	Up	0
APOBEC3C	mRNA	Up	0
ARHGAP26	mRNA	Up	2
ARL4C	mRNA	Up	2
ARNTL2	mRNA	Up	0
ART4	mRNA	Down	0
ASPHD1	mRNA	Up	0
ASPN	mRNA	Down	0
ATF3	mRNA	Up	5
ATM	mRNA	Up	72
ATP1A2	mRNA	Down	0
ATP1B2	mRNA	Down	0
AXUD1	mRNA	Up	0
BACE1-AS	lncRNA	Plane	1
BAG3	mRNA	Up	1
BAI3	mRNA	Down	0
BAIAP2-AS1	lncRNA	Plane	1
BAX	mRNA	Up	22
BCDIN3D-AS1	lncRNA	Plane	1
BCHE	mRNA	Down	0
BCL2A1	mRNA	Up	0
BDKRB1	mRNA	Up	0

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
BPIFA1	mRNA	Down	0
BVES-AS1	lncRNA	Plane	1
C10orf116	mRNA	Down	0
C10orf28	mRNA	Down	0
C11orf10	mRNA	Down	0
C11orf88	mRNA	Down	0
C13orf33	mRNA	Up	0
C15orf48	mRNA	Up	0
C17orf102	lncRNA	Plane	1
C18orf32	mRNA	Up	0
C1orf105	mRNA	Up	0
C1orf132	lncRNA	Plane	1
C1orf195	lncRNA	Plane	1
C1QTNF5	mRNA	Down	0
C1QTNF7	mRNA	Down	0
C1RL-AS1	lncRNA	Plane	4
C20orf46	mRNA	Down	0
C20orf85	mRNA	Down	0
C2orf40	mRNA	Down	0
C2orf54	mRNA	Up	0
C2orf83	mRNA	Down	0
C4orf7	mRNA	Up	0
C6	mRNA	Down	0
C6orf124	mRNA	Up	0
C6orf192	mRNA	Down	0
C7orf23	mRNA	Down	0
C9orf117	mRNA	Down	0
C9orf171	mRNA	Down	0
C9orf24	mRNA	Down	0
CABP7	mRNA	Down	0
CACNA1E	mRNA	Up	0
CACNA1H	mRNA	Down	0
CAPS	mRNA	Down	0
CARD8-AS1	lncRNA	Plane	1
CASC2	lncRNA	Plane	3
CASC8	lncRNA	Plane	1
CASK-AS1	lncRNA	Plane	1
CASQ2	mRNA	Down	0
CATIP-AS2	lncRNA	Plane	2
CAV1	mRNA	Down	25
CBX6	mRNA	Down	0
CBY1	mRNA	Down	0
CCDC103	mRNA	Down	0
CCDC137	mRNA	Up	0
CCDC17	mRNA	Down	0
CCDC18-AS1	lncRNA	Plane	10
CCDC19	mRNA	Down	0
CCDC3	mRNA	Down	0
CCDC37	mRNA	Down	0
CCDC48	mRNA	Down	0

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
CCDC77	mRNA	Down	0
CCDC81	mRNA	Down	0
CCL19	mRNA	Up	0
CCL20	mRNA	Up	4
CCL8	mRNA	Up	2
CCR6	mRNA	Up	0
CD70	mRNA	Up	0
CD86	mRNA	Down	4
CDC42EP2	mRNA	Up	0
CDH3	mRNA	Up	0
CDKN1A	mRNA	Up	70
CDKN2B-AS1	lncRNA	Plane	1
CES1	mRNA	Down	0
CFLAR-AS1	lncRNA	Plane	6
CGB1	mRNA	Down	0
CH25H	mRNA	Up	0
CHI3L1	mRNA	Up	0
CHI3L2	mRNA	Up	0
CHIT1	mRNA	Up	0
CHMP4B	mRNA	Up	0
CHP2	mRNA	Up	0
CHST2	mRNA	Up	0
CKMT2-AS1	lncRNA	Plane	2
CLC	mRNA	Up	0
CLEC4E	mRNA	Up	0
CLU	mRNA	Down	20
CMIP	mRNA	Up	0
CNN1	mRNA	Down	0
COL21A1	mRNA	Down	3
COL4A1	mRNA	Down	41
COL4A2-AS1	lncRNA	Plane	7
COX10-AS1	lncRNA	Plane	3
COX5A	mRNA	Up	0
CPA3	mRNA	Down	0
CPT2	mRNA	Up	0
CREB3L4	mRNA	Down	0
CRNDE	lncRNA	Plane	2
CSF3	mRNA	Up	0
CTB-111H14.1	lncRNA	Plane	1
CTC-204F22.1	lncRNA	Plane	6
CTC-351M12.1	lncRNA	Plane	7
CTC-444N24.11	lncRNA	Plane	1
CTC-444N24.7	lncRNA	Plane	4
CTC-459F4.3	lncRNA	Plane	1
CTC-459F4.9	lncRNA	Plane	2
CTC-479C5.10	lncRNA	Plane	4
CTC-487M23.5	lncRNA	Plane	5
CTD-2047H16.3	lncRNA	Plane	2
CTD-2095E4.5	lncRNA	Plane	5
CTD-2292P10.4	lncRNA	Plane	2

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
CTD-2337I7.1	lncRNA	Plane	1
CTD-2369P2.5	lncRNA	Plane	1
CTD-2410N18.4	lncRNA	Plane	3
CTD-2510F5.4	lncRNA	Plane	3
CTD-2517M22.14	lncRNA	Plane	4
CTD-2587H24.14	lncRNA	Plane	2
CTD-2619J13.14	lncRNA	Plane	1
CTD-2630F21.1	lncRNA	Plane	2
CTD-3032J10.2	lncRNA	Plane	1
CTD-3099C6.9	lncRNA	Plane	1
CTD-3131K8.2	lncRNA	Plane	5
CTGF	mRNA	Down	9
CTSS	mRNA	Up	0
CUL2	mRNA	Up	7
CXCL13	mRNA	Up	0
CYorf15B	mRNA	Up	0
CYP1B1	mRNA	Up	3
CYP3A4	mRNA	Down	3
CYP3A7	mRNA	Down	0
CYTOR	lncRNA	Plane	1
DAW1	mRNA	Down	0
DDC	mRNA	Down	1
DDR2	mRNA	Down	0
DENND4B	mRNA	Down	0
DES	mRNA	Down	0
DGUOK-AS1	lncRNA	Plane	3
DHRS4-AS1	lncRNA	Plane	1
DLEU2L	lncRNA	Plane	1
DLST	mRNA	Up	0
DLX6-AS1	lncRNA	Plane	5
DNAJC5	mRNA	Up	0
DNAJC7	mRNA	Up	0
DNASE1L3	mRNA	Down	0
DOHH	mRNA	Up	10
DPH6-AS1	lncRNA	Plane	2
DPYD-AS1	lncRNA	Plane	5
DUSP15	mRNA	Down	0
DUSP2	mRNA	Up	4
DYNC1H1	mRNA	Down	0
DYNLRB2	mRNA	Down	0
EAF1-AS1	lncRNA	Plane	12
EBLN3P	lncRNA	Plane	8
EEF1A1P11	mRNA	Down	0
EFHB	mRNA	Down	0
EGFL7	mRNA	Down	0
EIF1B	mRNA	Up	0
EIF3J-AS1	lncRNA	Plane	2
ELOA-AS1	lncRNA	Plane	3
EMD	mRNA	Up	0
EML2-AS1	lncRNA	Plane	1

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
ENPP2	mRNA	Down	0
ENPP4	mRNA	Down	0
ENTPD1-AS1	lncRNA	Plane	1
ERF	mRNA	Up	0
EXTL3-AS1	lncRNA	Plane	3
F8A1	mRNA	Down	0
FAM162B	mRNA	Down	0
FAM166B	mRNA	Up	0
FAM183A	mRNA	Down	0
FAM201A	lncRNA	Plane	5
FAM5C	mRNA	Down	0
FAM95C	lncRNA	Plane	1
FAM96B	mRNA	Down	0
FAT4	mRNA	Down	0
FENDRR	lncRNA	Plane	3
FGFBP2	mRNA	Down	0
FGG	mRNA	Up	2
FHL1	mRNA	Down	0
FIBIN	mRNA	Down	0
FILIP1L	mRNA	Down	0
FKBP10	mRNA	Up	0
FLJ21511	mRNA	Down	0
FLJ34515	mRNA	Down	0
FLJ37453	lncRNA	Plane	3
FLJ46284	lncRNA	Plane	3
FOLR1	mRNA	Down	0
FOXD2-AS1	lncRNA	Plane	11
FSTL1	mRNA	Down	8
FTX	lncRNA	Plane	9
FUS	mRNA	Up	0
GABBR1	mRNA	Down	0
GABRE	mRNA	Down	0
GADD45B	mRNA	Up	0
GAGE3	mRNA	Up	0
GAS1	mRNA	Down	21
GAS5	lncRNA	Plane	2
GBP6	mRNA	Down	0
GDE1	mRNA	Up	0
GDF10	mRNA	Down	0
GDF15	mRNA	Up	0
GFPT2	mRNA	Up	0
GJB2	mRNA	Up	0
GLT1D1	mRNA	Up	0
GLT25D2	mRNA	Down	0
GLYCTK-AS1	lncRNA	Plane	1
GNA11	mRNA	Down	0
GNG12-AS1	lncRNA	Plane	2
GNG13	mRNA	Down	2
GPC3	mRNA	Down	1
GPM6A	mRNA	Down	0

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
GPR172A	mRNA	Up	0
GPR177	mRNA	Up	0
GRB14	mRNA	Down	0
GRM8	mRNA	Down	0
GSN	mRNA	Down	0
GSTA2	mRNA	Down	0
GSTA5	mRNA	Down	0
GSTM1	mRNA	Down	0
GSTT1	mRNA	Down	0
GUSBP11	lncRNA	Plane	1
H19	lncRNA	Plane	4
H2AFX	mRNA	Up	29
HAGLR	lncRNA	Plane	3
HAS1	mRNA	Up	0
HCG18	lncRNA	Plane	3
HCRT	mRNA	Down	0
HELLPAR	lncRNA	Plane	1
HIF1A	mRNA	Up	79
HIRA	mRNA	Up	0
HIST1H2AB	mRNA	Down	0
HIST1H4B	mRNA	Down	0
HK3	mRNA	Up	0
HLA-U	mRNA	Up	0
HMBOX1	mRNA	Down	3
HMGB3L1	mRNA	Up	0
HMOX1	mRNA	Up	5
HNRNPA0	mRNA	Up	0
HNRNPAB	mRNA	Up	0
HORMAD2-AS1	lncRNA	Plane	1
HOTAIRM1	lncRNA	Plane	1
HOXA-AS2	lncRNA	Plane	4
HOXA-AS3	lncRNA	Plane	3
HOXA2	mRNA	Down	0
HOXC-AS2	lncRNA	Plane	1
HPR	mRNA	Up	0
HRASLS5	mRNA	Up	0
hsa-miR-105	miRNA	Up	0
hsa-miR-10a	miRNA	Up	0
hsa-miR-1274a	miRNA	Up	0
hsa-miR-144	miRNA	Up	0
hsa-miR-148a	miRNA	Up	0
hsa-miR-223	miRNA	Up	0
hsa-miR-25*	miRNA	Down	0
hsa-miR-374a	miRNA	Up	0
hsa-miR-422a	miRNA	Down	0
hsa-miR-454	miRNA	Up	0
hsa-miR-486-5p	miRNA	Up	12
hsa-miR-513a-5p	miRNA	Down	3
hsa-miR-576-3p	miRNA	Down	0
hsa-miR-664	miRNA	Up	0

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
hsa-miR-766	miRNA	Up	0
hsa-miR-923	miRNA	Down	0
hsa-miR-937	miRNA	Down	0
HSPA2	mRNA	Down	0
HSPB3	mRNA	Down	0
HSPD1P6	mRNA	Up	0
ID4	mRNA	Down	4
IER3	mRNA	Up	0
IFIT1	mRNA	Down	4
IFT20	mRNA	Up	0
IGFBP7-AS1	lncRNA	Plane	1
IGHM	mRNA	Up	0
IGSF6	mRNA	Up	0
IL1B	mRNA	Up	1
IL1R2	mRNA	Up	0
IL20RB	mRNA	Up	0
IL33	mRNA	Down	0
IL6	mRNA	Up	31
IL8	mRNA	Up	0
INMT	mRNA	Down	0
IPO9-AS1	lncRNA	Plane	1
IQCD	mRNA	Down	0
IQGAP2	mRNA	Up	0
IRX5	mRNA	Down	0
ITGA7	mRNA	Down	4
ITGA9-AS1	lncRNA	Plane	4
ITGB2	mRNA	Up	0
ITLN2	mRNA	Down	0
ITPKC	mRNA	Up	0
JMJD6	mRNA	Up	0
JPX	lncRNA	Plane	1
JUNB	mRNA	Up	2
KB-1208A12.3	lncRNA	Plane	2
KB-1517D11.4	lncRNA	Plane	1
KB-1572G7.2	lncRNA	Plane	1
KB-1615E4.2	lncRNA	Plane	3
KB-318B8.7	lncRNA	Plane	3
KC6	lncRNA	Plane	1
KCNA5	mRNA	Down	0
KCNIP2-AS1	lncRNA	Plane	1
KCNQ1OT1	lncRNA	Plane	16
KDM4A-AS1	lncRNA	Plane	10
KIAA0644	mRNA	Down	0
KIT	mRNA	Down	56
KLK12	mRNA	Down	0
KPNA6	mRNA	Down	0
KRT17P3	mRNA	Up	0
KRT4	mRNA	Down	0
KRT7	mRNA	Up	6
KRT7-AS	lncRNA	Plane	2

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
L1TD1	mRNA	Down	0
LA16c-358B7.3	lncRNA	Plane	1
LACTB2-AS1	lncRNA	Plane	1
LAD1	mRNA	Up	0
LDB2	mRNA	Down	0
LEFTY2	mRNA	Down	0
LILRB1	mRNA	Up	0
LILRB2	mRNA	Up	0
LIMD1-AS1	lncRNA	Plane	1
LIMK1	mRNA	Up	24
LIMS2	mRNA	Down	0
LINC-PINT	lncRNA	Plane	6
LINC00158	lncRNA	Plane	1
LINC00304	lncRNA	Plane	1
LINC00339	lncRNA	Plane	4
LINC00461	lncRNA	Plane	1
LINC00472	lncRNA	Plane	1
LINC00511	lncRNA	Plane	3
LINC00525	lncRNA	Plane	2
LINC00630	lncRNA	Plane	1
LINC00641	lncRNA	Plane	2
LINC00645	lncRNA	Plane	1
LINC00661	lncRNA	Plane	1
LINC00664	lncRNA	Plane	1
LINC00665	lncRNA	Plane	9
LINC00667	lncRNA	Plane	3
LINC00670	lncRNA	Plane	2
LINC00707	lncRNA	Plane	1
LINC00869	lncRNA	Plane	7
LINC00893	lncRNA	Plane	2
LINC00894	lncRNA	Plane	7
LINC00907	lncRNA	Plane	1
LINC00909	lncRNA	Plane	1
LINC00910	lncRNA	Plane	1
LINC00958	lncRNA	Plane	10
LINC00960	lncRNA	Plane	2
LINC00963	lncRNA	Plane	6
LINC01085	lncRNA	Plane	1
LINC01090	lncRNA	Plane	2
LINC01116	lncRNA	Plane	1
LINC01128	lncRNA	Plane	10
LINC01134	lncRNA	Plane	2
LINC01140	lncRNA	Plane	7
LINC01184	lncRNA	Plane	1
LINC01197	lncRNA	Plane	1
LINC01257	lncRNA	Plane	1
LINC01278	lncRNA	Plane	2
LINC01358	lncRNA	Plane	2
LINC01362	lncRNA	Plane	2
LINC01521	lncRNA	Plane	1

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
LINC01569	lncRNA	Plane	1
LINC01578	lncRNA	Plane	1
LINC01605	lncRNA	Plane	1
LINC01619	lncRNA	Plane	1
LINC01783	lncRNA	Plane	1
LINC01934	lncRNA	Plane	4
LINC01965	lncRNA	Plane	1
LIPE-AS1	lncRNA	Plane	1
LIX1L-AS1	lncRNA	Plane	1
LLNLR-268E12.1	lncRNA	Plane	1
LLNLR-470E3.1	lncRNA	Plane	1
LMCD1	mRNA	Down	0
LMNB1	mRNA	Up	0
LMNB2	mRNA	Up	3
LMOD1	mRNA	Down	0
LOC100128164	mRNA	Down	0
LOC100128178	mRNA	Down	0
LOC100128548	mRNA	Down	0
LOC100128977	mRNA	Up	0
LOC100131582	mRNA	Up	0
LOC100132247	mRNA	Down	0
LOC100134228	mRNA	Up	0
LOC23117	mRNA	Down	0
LOC338799	mRNA	Down	0
LOC389831	mRNA	Down	0
LOC391132	mRNA	Up	0
LOC391532	mRNA	Up	0
LOC402360	mRNA	Down	0
LOC51233	mRNA	Up	0
LOC595101	mRNA	Up	0
LOC646909	mRNA	Up	0
LOC646949	mRNA	Up	0
LOC649294	mRNA	Up	0
LOC650392	mRNA	Up	0
LOC728763	mRNA	Down	0
LOC728820	mRNA	Up	0
LOC729046	mRNA	Up	0
LOC729259	mRNA	Up	0
LOC729652	mRNA	Up	0
LOC780529	mRNA	Up	0
LRIG1	mRNA	Down	9
LRP5L	mRNA	Up	0
LRRC2	mRNA	Down	0
LRRC36	mRNA	Down	0
LRRC45	mRNA	Down	0
LRRC46	mRNA	Down	0
LRRC75A-AS1	lncRNA	Plane	2
LTBP2	mRNA	Down	0
LTBP4	mRNA	Down	0
LTC4S	mRNA	Down	0

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
LTK	mRNA	Down	0
MACC1-AS1	lncRNA	Plane	1
MAGOH	mRNA	Up	0
MALAT1	lncRNA	Plane	10
MAOB	mRNA	Down	0
MAP4K3	mRNA	Down	11
MAPKAPK3	mRNA	Up	0
MATN1-AS1	lncRNA	Plane	1
MBD4	mRNA	Up	0
MBNL1-AS1	lncRNA	Plane	1
MCF2L-AS1	lncRNA	Plane	1
MCM3AP-AS1	lncRNA	Plane	1
MED18	mRNA	Up	2
MELTF-AS1	lncRNA	Plane	1
METTL7A	mRNA	Up	3
MFAP4	mRNA	Down	2
MGC70870	mRNA	Up	0
MIR124-2HG	lncRNA	Plane	1
MIR155HG	lncRNA	Plane	1
MIR17HG	lncRNA	Plane	1
MIR22HG	lncRNA	Plane	2
MIR4435-2HG	lncRNA	Plane	2
MIR4458HG	lncRNA	Plane	1
MIR583HG	lncRNA	Plane	1
MIRLET7BHG	lncRNA	Plane	4
MKNK1-AS1	lncRNA	Plane	1
MMP1	mRNA	Up	1
MMP10	mRNA	Up	0
MMP14	mRNA	Down	12
MMP19	mRNA	Up	0
MMP9	mRNA	Up	49
MNT	mRNA	Down	0
MOP-1	mRNA	Up	0
MRTO4	mRNA	Up	0
MS4A2	mRNA	Down	0
MS4A8B	mRNA	Down	0
MSC	mRNA	Up	7
MST1	mRNA	Down	13
MSTP9	mRNA	Down	0
MT1F	mRNA	Up	0
MT1H	mRNA	Up	0
MT1L	mRNA	Up	0
MT1M	mRNA	Up	7
MTND1P23	mRNA	Up	0
MXD1	mRNA	Up	13
MYB	mRNA	Down	59
MYH11	mRNA	Down	0
MYH2	mRNA	Down	1
MYO15B	mRNA	Down	0
MYOC	mRNA	Down	1

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
MYOZ1	mRNA	Down	0
MYRIP	mRNA	Down	0
NBPF14	mRNA	Down	0
NBPF20	mRNA	Up	0
NCR2	mRNA	Up	0
NEAT1	lncRNA	Plane	7
NEUROG1	mRNA	Up	0
NFKBIZ	mRNA	Up	0
NFYC-AS1	lncRNA	Plane	2
NKILA	lncRNA	Plane	1
NKX2-8	mRNA	Down	0
NLRP2	mRNA	Up	0
NMNAT3	mRNA	Down	0
NNT-AS1	lncRNA	Plane	1
NORAD	lncRNA	Plane	11
NOV	mRNA	Down	0
NPHP4	mRNA	Up	0
NPIP	mRNA	Down	0
NPM3	mRNA	Up	0
NPNT	mRNA	Down	15
NPPA-AS1	lncRNA	Plane	1
NPTN	mRNA	Down	0
NR2F1-AS1	lncRNA	Plane	7
NR2F2	mRNA	Down	5
NR4A1	mRNA	Up	0
NR4A2	mRNA	Up	18
NSBP1	mRNA	Down	0
NTF3	mRNA	Down	8
NTM	mRNA	Up	1
NUAK2	mRNA	Up	0
NUTM2A-AS1	lncRNA	Plane	1
NUTM2B-AS1	lncRNA	Plane	2
OGN	mRNA	Down	0
OIP5-AS1	lncRNA	Plane	5
OLFML3	mRNA	Down	0
OLIG3	mRNA	Up	0
OMD	mRNA	Down	0
OPN1LW	mRNA	Up	0
OR2A1-AS1	lncRNA	Plane	2
OSM	mRNA	Up	0
OSTbeta	mRNA	Down	0
PABPC4L	mRNA	Down	0
PADI3	mRNA	Up	0
PAX8-AS1	lncRNA	Plane	1
PCA3	lncRNA	Plane	1
PCBP1-AS1	lncRNA	Plane	5
PCDH18	mRNA	Down	0
PCNP	mRNA	Down	0
PCOLCE2	mRNA	Down	0
PDAP1	mRNA	Up	0

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
PDCD4-AS1	lncRNA	Plane	1
PF4	mRNA	Up	0
PFDN6	mRNA	Up	0
PHF1	mRNA	Down	0
PHF5A	mRNA	Up	0
PHLDA1	mRNA	Up	0
PHLDA2	mRNA	Up	0
PHLDA3	mRNA	Down	0
PI16	mRNA	Down	0
PI3	mRNA	Up	0
PIK3CD-AS1	lncRNA	Plane	1
PIK3CD-AS2	lncRNA	Plane	1
PIM1	mRNA	Up	19
PINK1-AS	lncRNA	Plane	11
PLA2G1B	mRNA	Down	0
PLA2G2A	mRNA	Up	0
PLA2G7	mRNA	Up	0
PLEKHG4	mRNA	Up	0
PLEKHH3	mRNA	Down	0
PLN	mRNA	Down	0
PMAIP1	mRNA	Up	5
POLR2C	mRNA	Up	0
POLR2J4	lncRNA	Plane	1
POU2AF1	mRNA	Up	0
PPIB	mRNA	Up	0
PPP1R14A	mRNA	Down	0
PPP1R3C	mRNA	Down	0
PPP3CB-AS1	lncRNA	Plane	5
PRDM6	mRNA	Down	0
PRKCB	mRNA	Up	3
PRKY	mRNA	Down	0
PROS1	mRNA	Down	1
PROSER2-AS1	lncRNA	Plane	1
PRPF19	mRNA	Up	0
PRR13P5	mRNA	Up	0
PRRG4	mRNA	Up	0
PRRT2	mRNA	Down	0
PRSS36	mRNA	Up	0
PSMA3-AS1	lncRNA	Plane	7
PTCHD1-AS	lncRNA	Plane	1
PTOV1-AS1	lncRNA	Plane	1
PTPN1	mRNA	Up	2
PTPRD	mRNA	Down	12
PTX3	mRNA	Up	3
PVT1	lncRNA	Plane	2
QTRT1	mRNA	Up	0
RAB13	mRNA	Up	3
RAB20	mRNA	Up	0
RAB23	mRNA	Down	4
RAET1E-AS1	lncRNA	Plane	1

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
RANBP6	mRNA	Down	0
RAP1GAP	mRNA	Down	0
RAPGEF5	mRNA	Down	0
RBM26-AS1	lncRNA	Plane	1
RERG	mRNA	Down	0
RFX3-AS1	lncRNA	Plane	4
RGL2	mRNA	Down	0
RGL4	mRNA	Up	0
RGS1	mRNA	Up	0
RGS22	mRNA	Down	0
RND1	mRNA	Up	0
RNF125	mRNA	Up	0
RNF145	mRNA	Up	0
RP1-117O3.2	lncRNA	Plane	1
RP1-118J21.5	lncRNA	Plane	6
RP1-158P9.1	lncRNA	Plane	1
RP1-191J18.66	lncRNA	Plane	10
RP1-193H18.2	lncRNA	Plane	1
RP1-199J3.7	lncRNA	Plane	4
RP1-224A6.9	lncRNA	Plane	1
RP1-253P7.4	lncRNA	Plane	1
RP1-27K12.2	lncRNA	Plane	1
RP1-283E3.8	lncRNA	Plane	2
RP1-37C10.3	lncRNA	Plane	2
RP1-92O14.6	lncRNA	Plane	3
RP11-1000B6.5	lncRNA	Plane	1
RP11-1007O24.3	lncRNA	Plane	4
RP11-106M3.3	lncRNA	Plane	1
RP11-108M9.3	lncRNA	Plane	2
RP11-108M9.6	lncRNA	Plane	2
RP11-10K16.1	lncRNA	Plane	1
RP11-1149O23.2	lncRNA	Plane	1
RP11-120D5.1	lncRNA	Plane	2
RP11-120E11.2	lncRNA	Plane	1
RP11-133K1.11	lncRNA	Plane	1
RP11-140H17.2	lncRNA	Plane	1
RP11-147L13.12	lncRNA	Plane	2
RP11-154D6.1	lncRNA	Plane	1
RP11-156E6.1	lncRNA	Plane	3
RP11-157P1.4	lncRNA	Plane	3
RP11-158K1.3	lncRNA	Plane	1
RP11-160H22.5	lncRNA	Plane	1
RP11-161H23.9	lncRNA	Plane	1
RP11-161M6.2	lncRNA	Plane	3
RP11-16E12.2	lncRNA	Plane	1
RP11-186B7.4	lncRNA	Plane	1
RP11-197N18.2	lncRNA	Plane	1
RP11-197N18.8	lncRNA	Plane	1
RP11-228B15.4	lncRNA	Plane	2
RP11-244H3.1	lncRNA	Plane	1

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
RP11-267M23.1	lncRNA	Plane	1
RP11-277P12.20	lncRNA	Plane	1
RP11-278C7.3	lncRNA	Plane	3
RP11-288L9.4	lncRNA	Plane	3
RP11-295P9.3	lncRNA	Plane	1
RP11-299J3.8	lncRNA	Plane	3
RP11-29G8.3	lncRNA	Plane	3
RP11-2C24.3	lncRNA	Plane	1
RP11-2C24.4	lncRNA	Plane	2
RP11-303E16.2	lncRNA	Plane	2
RP11-304L19.13	lncRNA	Plane	1
RP11-305E6.4	lncRNA	Plane	7
RP11-314B1.2	lncRNA	Plane	7
RP11-317N8.5	lncRNA	Plane	8
RP11-328C8.4	lncRNA	Plane	7
RP11-334C17.5	lncRNA	Plane	4
RP11-342K2.1	lncRNA	Plane	2
RP11-342M1.3	lncRNA	Plane	2
RP11-345P4.4	mRNA	Down	0
RP11-348N5.7	lncRNA	Plane	1
RP11-348P10.2	lncRNA	Plane	1
RP11-352G18.2	lncRNA	Plane	3
RP11-355B11.2	lncRNA	Plane	1
RP11-357H14.17	lncRNA	Plane	5
RP11-359B12.2	lncRNA	Plane	1
RP11-360N9.2	lncRNA	Plane	1
RP11-372K14.2	lncRNA	Plane	4
RP11-373N22.3	lncRNA	Plane	1
RP11-378J18.8	lncRNA	Plane	1
RP11-380L11.4	lncRNA	Plane	1
RP11-381N20.1	lncRNA	Plane	3
RP11-386G11.5	lncRNA	Plane	5
RP11-394O2.3	lncRNA	Plane	1
RP11-395G23.3	lncRNA	Plane	3
RP11-399K21.14	lncRNA	Plane	2
RP11-405O10.2	lncRNA	Plane	1
RP11-412P11.1	lncRNA	Plane	1
RP11-415J8.3	lncRNA	Plane	5
RP11-416N4.4	lncRNA	Plane	2
RP11-421L21.3	lncRNA	Plane	6
RP11-446H18.5	lncRNA	Plane	1
RP11-452F19.3	lncRNA	Plane	1
RP11-45P15.4	lncRNA	Plane	3
RP11-468E2.5	lncRNA	Plane	7
RP11-46O21.2	lncRNA	Plane	1
RP11-477D19.2	lncRNA	Plane	1
RP11-478C19.2	lncRNA	Plane	2
RP11-481C4.2	lncRNA	Plane	1
RP11-493P1.2	lncRNA	Plane	3
RP11-519G16.3	lncRNA	Plane	1

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
RP11-531A24.7	lncRNA	Plane	1
RP11-539I5.1	lncRNA	Plane	2
RP11-545I5.3	lncRNA	Plane	4
RP11-54O7.1	lncRNA	Plane	1
RP11-54O7.3	lncRNA	Plane	10
RP11-574K11.29	lncRNA	Plane	1
RP11-57H12.5	lncRNA	Plane	5
RP11-588H23.3	lncRNA	Plane	1
RP11-588K22.2	lncRNA	Plane	4
RP11-58K22.5	lncRNA	Plane	1
RP11-5C23.1	lncRNA	Plane	1
RP11-60A24.3	lncRNA	Plane	1
RP11-626G11.5	lncRNA	Plane	1
RP11-631M21.2	mRNA	Down	0
RP11-656D10.6	lncRNA	Plane	1
RP11-656D10.7	lncRNA	Plane	2
RP11-65L3.2	lncRNA	Plane	2
RP11-661A12.5	lncRNA	Plane	1
RP11-661A12.8	lncRNA	Plane	1
RP11-677I18.3	lncRNA	Plane	1
RP11-677M14.8	lncRNA	Plane	3
RP11-69E11.4	lncRNA	Plane	11
RP11-69E11.8	lncRNA	Plane	3
RP11-701H24.4	lncRNA	Plane	1
RP11-702F3.1	lncRNA	Plane	1
RP11-714G18.1	lncRNA	Plane	1
RP11-715F3.2	lncRNA	Plane	3
RP11-73M18.8	lncRNA	Plane	1
RP11-77H9.2	lncRNA	Plane	1
RP11-793H13.3	lncRNA	Plane	2
RP11-799B12.4	lncRNA	Plane	1
RP11-802E16.3	lncRNA	Plane	1
RP11-815J21.4	lncRNA	Plane	1
RP11-819C21.1	lncRNA	Plane	2
RP11-81K13.1	lncRNA	Plane	2
RP11-822E23.8	lncRNA	Plane	5
RP11-829H16.3	lncRNA	Plane	1
RP11-834C11.4	lncRNA	Plane	6
RP11-843B15.4	lncRNA	Plane	3
RP11-84G21.1	lncRNA	Plane	1
RP11-861E21.2	lncRNA	Plane	1
RP11-968A15.8	lncRNA	Plane	1
RP11-96D1.10	lncRNA	Plane	2
RP11-983P16.4	lncRNA	Plane	1
RP13-143G15.4	lncRNA	Plane	1
RP13-36C9.6	mRNA	Down	0
RP13-39P12.3	lncRNA	Plane	1
RP13-516M14.1	lncRNA	Plane	1
RP3-323N1.2	lncRNA	Plane	1
RP3-467L1.4	lncRNA	Plane	2

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
RP4-569M23.2	lncRNA	Plane	1
RP4-605O3.4	lncRNA	Plane	1
RP4-613B23.1	lncRNA	Plane	1
RP4-622L5.7	lncRNA	Plane	1
RP4-625H18.2	lncRNA	Plane	1
RP4-635E18.7	lncRNA	Plane	2
RP4-639F20.1	lncRNA	Plane	1
RP4-665N4.8	lncRNA	Plane	2
RP4-669K10.8	lncRNA	Plane	3
RP4-671G15.2	lncRNA	Plane	2
RP4-671O14.6	lncRNA	Plane	3
RP4-758J18.13	lncRNA	Plane	1
RP4-758J18.2	lncRNA	Plane	1
RP4-761J14.8	lncRNA	Plane	1
RP4-794H19.1	lncRNA	Plane	1
RP5-1021I20.5	lncRNA	Plane	1
RP5-1024G6.2	lncRNA	Plane	2
RP5-1024G6.5	lncRNA	Plane	6
RP5-1033H22.2	lncRNA	Plane	1
RP5-1039K5.19	lncRNA	Plane	3
RP5-1071N3.1	lncRNA	Plane	1
RP5-1074L1.4	lncRNA	Plane	3
RP5-1101C3.1	lncRNA	Plane	1
RP5-1126H10.2	lncRNA	Plane	3
RP5-1198O20.4	lncRNA	Plane	8
RP5-864K19.7	lncRNA	Plane	7
RP5-884C9.2	lncRNA	Plane	1
RP5-894A10.6	lncRNA	Plane	1
RP5-899E9.1	lncRNA	Plane	4
RP5-991G20.1	lncRNA	Plane	1
RP5-997D16.2	lncRNA	Plane	1
RP6-24A23.7	lncRNA	Plane	1
RPA4	mRNA	Down	0
RPS14P8	mRNA	Up	0
RPS6P1	mRNA	Down	0
RRP12	mRNA	Up	0
RSPH10B	mRNA	Down	0
S100A12	mRNA	Up	0
S100A8	mRNA	Up	0
S100A9	mRNA	Up	1
S100B	mRNA	Up	3
SAA1	mRNA	Up	0
SAPS1	mRNA	Down	0
SCAMP1-AS1	lncRNA	Plane	1
SCN4B	mRNA	Down	0
SEC14L3	mRNA	Down	0
14-Sep	mRNA	Up	0
SERPIND1	mRNA	Up	0
SERTAD1	mRNA	Up	0
SETBP1	mRNA	Down	0

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
SFN	mRNA	Up	0
SFTPA1B	mRNA	Down	0
SGCE	mRNA	Down	0
SGMS1-AS1	lncRNA	Plane	1
SGPP2	mRNA	Up	5
SH3BP5-AS1	lncRNA	Plane	1
SH3GL3	mRNA	Down	0
SHANK3	mRNA	Down	0
SHC2	mRNA	Down	0
SLAMF7	mRNA	Up	0
SLC16A1-AS1	lncRNA	Plane	1
SLC25A22	mRNA	Up	0
SLC26A4	mRNA	Up	0
SLC2A1-AS1	lncRNA	Plane	3
SLC39A7	mRNA	Up	0
SLC44A5	mRNA	Down	0
SLC45A4	mRNA	Down	0
SLC6A19	mRNA	Up	0
SLC6A4	mRNA	Down	10
SLC7A8	mRNA	Up	0
SLCO4A1	mRNA	Up	0
SLFNL1-AS1	lncRNA	Plane	17
SLIT2	mRNA	Down	0
SLITRK6	mRNA	Down	0
SMAD7	mRNA	Down	75
SMARCAD1	mRNA	Down	0
SMG7	mRNA	Down	0
SNAI1	mRNA	Up	41
SNHG1	lncRNA	Plane	2
SNHG12	lncRNA	Plane	22
SNHG14	lncRNA	Plane	1
SNHG15	lncRNA	Plane	2
SNHG16	lncRNA	Plane	6
SNHG17	lncRNA	Plane	1
SNHG20	lncRNA	Plane	1
SNHG22	lncRNA	Plane	2
SNHG3	lncRNA	Plane	3
SNHG5	lncRNA	Plane	3
SNHG7	lncRNA	Plane	5
SNORA70	mRNA	Down	0
SNTN	mRNA	Down	0
SOCS3	mRNA	Up	15
SOD2	mRNA	Up	7
SOSTDC1	mRNA	Down	0
SPAG8	mRNA	Down	0
SPARCL1	mRNA	Down	0
SPEG	mRNA	Down	0
SPP1	mRNA	Up	10
SPSB2	mRNA	Down	0
SRD5A3-AS1	lncRNA	Plane	1

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
SRGN	mRNA	Up	0
SSBP3-AS1	lncRNA	Plane	4
SSPN	mRNA	Down	0
ST20-AS1	lncRNA	Plane	2
ST6GALNAC3	mRNA	Down	0
ST6GALNAC5	mRNA	Down	0
STARD13-AS	lncRNA	Plane	3
STARD4-AS1	lncRNA	Plane	4
STC2	mRNA	Up	5
STK32C	mRNA	Up	0
STOML3	mRNA	Down	0
STX18-AS1	lncRNA	Plane	1
SULT1A1	mRNA	Down	0
SVIL	mRNA	Down	0
TAF5L	mRNA	Up	0
TARID	lncRNA	Plane	1
TBC1D9	mRNA	Down	1
tcag7.873	mRNA	Up	0
TCEAL4	mRNA	Down	0
TCF21	mRNA	Down	2
TCTN2	mRNA	Down	0
TDRD10	mRNA	Down	0
TEP1	mRNA	Up	0
TEX41	lncRNA	Plane	2
THBS1	mRNA	Up	14
THCAT158	lncRNA	Plane	1
THUMPD3-AS1	lncRNA	Plane	5
TLX1NB	lncRNA	Plane	1
TMC3-AS1	lncRNA	Plane	1
TMED9	mRNA	Up	0
TMEM100	mRNA	Down	2
TMEM120B	mRNA	Up	0
TMEM147-AS1	lncRNA	Plane	2
TMEM178	mRNA	Down	0
TMEM201	mRNA	Up	0
TMEM212	mRNA	Down	0
TMEM254-AS1	lncRNA	Plane	1
TNFAIP6	mRNA	Up	3
TNFRSF1A	mRNA	Up	0
TNFRSF6B	mRNA	Up	0
TONSL-AS1	lncRNA	Plane	1
TPTEP1	mRNA	Up	0
TRAM2-AS1	lncRNA	Plane	1
TREM2	mRNA	Up	2
TRG-AS1	lncRNA	Plane	7
TSC22D1-AS1	lncRNA	Plane	1
TSIX	lncRNA	Plane	3
TTMA	mRNA	Up	0
TTN-AS1	lncRNA	Plane	5
TTTY15	mRNA	Down	0

(*Continued*)

Table 2 (Continued).

Gene	RNA	Upordown	Degree
TUBA4B	mRNA	Down	0
TUFM	mRNA	Down	0
TUG1	lncRNA	Plane	6
TXLNGY	mRNA	Down	0
TYRP1	mRNA	Down	0
UBD	mRNA	Up	5
UNK	mRNA	Up	0
UNQ6494	lncRNA	Plane	1
UNQ9419	mRNA	Up	0
UPF1	mRNA	Up	0
URB2	mRNA	Up	0
USP36	mRNA	Up	0
VCAN-AS1	lncRNA	Plane	3
VLDLR-AS1	lncRNA	Plane	1
VPS18	mRNA	Down	1
VPS9D1-AS1	lncRNA	Plane	2
WDR67	mRNA	Down	0
WFDC1	mRNA	Down	0
WFDC21P	lncRNA	Plane	2
XAGE1D	mRNA	Up	0
XIST	lncRNA	Plane	16
XX-FW83563B9.5	lncRNA	Plane	1
XXbac-B461K10.4	lncRNA	Plane	5
YEATS2-AS1	lncRNA	Plane	1
ZACN	mRNA	Down	0
ZBBX	mRNA	Down	0
ZBED2	mRNA	Down	0
ZBTB20-AS1	lncRNA	Plane	1
ZC3H12A	mRNA	Up	2
ZEB1-AS1	lncRNA	Plane	2
ZFHX2-AS1	lncRNA	Plane	1
ZFP62	mRNA	Down	0
ZFPM2-AS1	lncRNA	Plane	7
ZIM2-AS1	lncRNA	Plane	1
ZNF117	mRNA	Up	0
ZNF213-AS1	lncRNA	Plane	2
ZNF264	mRNA	Up	0
ZNF280D	mRNA	Down	0
ZNF337-AS1	lncRNA	Plane	4
ZNF426	mRNA	Up	0
ZNF572	mRNA	Down	0
ZNF652	mRNA	Up	2
ZNF674-AS1	lncRNA	Plane	3
ZNF675	mRNA	Up	0
ZNF728	mRNA	Up	0
ZNF790-AS1	lncRNA	Plane	8
ZRANB2-AS2	lncRNA	Plane	1
ZSCAN10	mRNA	Up	0

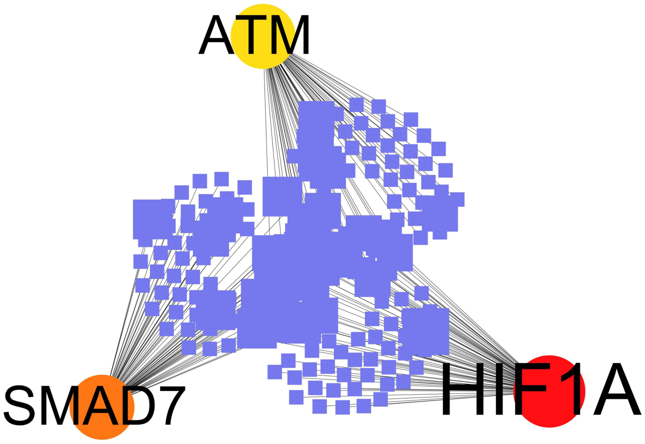

Figure 5 The hub genes of COPD in ceRNA network.

High-throughput sequencing technologies have implied in various disease for detecting potential diagnostic and prognostic biomarkers at the transcriptome level. Accumulation of studies revealed the disease-related RNAs which correlated with disease pathology. lncRNAs and miRNAs regulated mRNAs network implied in the various diseases, and some of them was identified as potentially suitable biomarkers.[27] In this study, we identified the differentially expressed RNAs, which have significant associations with immune and cancer-related signaling pathway. Among of these, the cytokine receptor CXCR2 antagonist (MK-7123) reduced the chemotaxis of neutrophils, which may alleviate the airway inflammation of COPD.[18] The p53 signaling pathway polymorphism was associated with changes in emphysema in COPD patients.[20]

In addition, ceRNAs network related to COPD was evaluated, implying new molecular mechanism and potential therapeutic target for COPD. Among of the network genes, 10 lncRNAs might be used as COPD marker including SNHG12, SLFNL1-AS1, KCNQ1OT1, XIST, EAF1-AS1, FOXD2-AS1, NORAD, PINK1-AS and RP11-69E11.4. Among them, SNHG12 participated in the unfolded protein response and function as a potential therapeutic target and biomarker for human cancer.[28] Many tumor cells avoided immune-mediated attacks and enhanced the polarization of effector immune cells (such as macrophages and T cells) via SNHG12.[29] SNHG12 also actED as a competitive endogenous RNA (ceRNA) by containing multiple miRNA binding sites, thereby “sponging” these miRNAs to regulate its downstream targets.[30] Recent studies have described the emerging role of ceRNAs in the etiology of cancer, where various ncRNA molecules including lncRNAs, miRNAs, pseudogenes and circular RNAs (circRNAs) share common miRNA response elements (MREs), thereby passing through complex RNA networks Mutual regulation through cellular processes.[31] XIST/miR-200c-3p/EGR3 axis promotes 16HBE cell apoptosis and inflammatory response stimulated by cigarette smoke extract. These findings may provide new insights for the treatment of COPD by reducing lung inflammation.[32]

In conclusion, our research has revealed the DEGs and DEmis related to COPD, and constructed the ceRNA network in COPD, which may provide potential new insights for the treatment of COPD. However, we have some limitations on the mechanism of action of lncRNA involved in the progression of chronic obstructive pulmonary disease. Next, we will further study the related functions and mechanisms through cell, tissue and animal experiments.

Abbreviations

COPD, Chronic obstructive pulmonary disease; GEO, Gene Expression Omnibus; DEGs, differentially expressed genes; DEmi, differentially expressed miRNAs; lncRNA, Long non-coding RNA; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available in the Gene Expression Omnibus (GEO) datasets (http://www.ncbi.nlm.nih.gov/geo/).

Ethical Approval

This study has been exempted from the medical ethics committee of the Affiliated Hospital of Inner Mongolia Medical University. The public database mentioned in this study is publicly available for re-analyzing, and no ethical approval was required by the local ethics committees, so that this study does not require ethics approval.

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Disclosure

The authors declare that they have no competing interests in this work.

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