Research Article

Network Pharmacology and Bioinformatics Methods Reveal the Mechanism of Zao-Jiao-Ci in the Treatment of LSCC

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Objective. Zao-Jiao-Ci (ZJC), a traditional Chinese medicine, is considered as a promising candidate to treat laryngeal squamous cell carcinoma (LSCC). However, the underlying molecular mechanism remains unclear. Methods. Gene expression profiles of GSE36668 were available from the GEO database, and differentially expressed genes (DEGs) of LSCC were obtained by *R* package; subsequently, enrichment analysis on KEGG and GO of DEGs was performed. The active ingredients of ZJC were screened from the TCMSP database, and the matched candidate targets were obtained by PharmMapper. Furthermore, we constructed proteinprotein interaction (PPI) networks of DEGs and candidate targets, respectively, and we screened the core network from the merged network through combining the two PPI networks using Cytoscape 3.7.2. The key targets derived from the core network were analyzed to find out the associated KEGG signal enrichment pathway. By the GEPIA online website, Kaplan-Meier analysis was used to complete the overall survival and disease-free survival of the selected genes in the core module. Results. We identified 96 candidate targets of ZJC and 86 DEGs of LSCC, the latter including 50 upregulated genes and 36 downregulated genes. DEGs were obviously enriched in the following biological functions: extracellular structure organization, the extracellular matrix organization, and endodermal cell differentiation. The 60 key targets from the core network were enriched in the signal pathways including transcriptional misregulation cancer, cell cycle, and so on. We found that LSCC patients with high expression of HIST1H3J, HIST1H3F, and ITGA4 had worse overall survival, while higher expression of NTRK1, COPS5, HIST1H3A, and HIST1H3G had significantly worse disease-free survival. Conclusion. It suggested that the interaction between ZJC and LSCC was related to the signal pathways of transcriptional misregulation cancer and cell cycle, revealing that it may be the mechanism of ZJC in the treatment of LSCC.

1. Introduction

Laryngeal squamous cell carcinoma (LSCC) is the most common malignancy of the larynx, and its clinical manifestations are hoarseness, stridor, dyspnea, and even dysphagia [1, 2]. Disappointingly, despite various technologies such as surgery, laser therapy, and chemoradiation have advanced recently, and the survival rate has not improved because of a high rate of recurrence and metastasis [3, 4]. Therefore, in order to improve survival rates of the patients, there is an urgent need for effective treatment.

An increasing number of studies confirmed that traditional Chinese medicine (TCM) including multiple ingredients and targets play a critical role in the treatment of cancer. Zao-Jiao-Ci (ZJC), also known as *Gleditsia sinensis*, is a traditional Chinese medicine with a variety of bioactivities, especially antitumor activity, which has been widely used in clinic [5]. It was investigated that the ethanol extract of *Gleditsia sinensis* (EEGS) could suppress the growth of human colon cancer HCT116 cells in vitro and in vivo [6]. The extract of *Gleditsia sinensis* fruit performed inhibitory effects on esophageal squamous cell carcinoma (ESCC) cells, breast cancer MCF-7 cells, hepatoblastoma HepG2 cells, and so on [7, 8]. However, there is no study to investigate the anticancer effect of *Gleditsia sinensis* on LSCC, and the mechanism remains unclear. Network pharmacology has exhibited specific utility in analyzing multicomponent and multitarget, consistent with the therapy hypothesis of complex diseases. By constructing a multilevel, multifaceted network model comprised of components, targets, pathways, and diseases, we can investigate TCM in the treatment of disease involved in the regulation of a variety of signaling pathways, key targets taxa, and biological process analysis, aiming to reveal the mechanism from the molecular level [9].

In this study, we used network pharmacology to investigate whether ZJC exerts anticancer effects on LSCC based on the GEO microarray dataset. And through the pathway enrichment analysis of the interaction targets between differentially expressed gene (DEGs) of LSCC and key node targets of ZJC, we further predicted the therapeutic mechanism of ZJC on LSCC. To our knowledge, this study is the first to explore the efficacy and mechanism of ZJC on LSCC, providing theoretical support and directions for further basic research.

2. Methods

2.1. Active Ingredients Screening and Targets Prediction for ZJC. Through the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), all components of ZJC could be found by searching the term "Zao-Jiao-Ci." We set oral bioavailability (OB) > 30% and drug-likeness (DL) > 0.18 as screening conditions supported by the published literatures to obtain the final active ingredients [10, 11]. PharmMapper server is the first webserver for potential drug targets identification through large-scale reverse pharmacophore mapping strategy [12]. The MOL structure of active ingredients provided by TCMSP was input into PharmMapper server (http://lilab.ecust.edu.cn/pharmmapper/) to get the targets of the pharmacophore model. The first 15 targets sorted by the fit score were seemed as candidate targets of ZJC.

2.2. Active Ingredient-Target PPI Network Construction. To explore the association between ingredients and targets, we established an interaction network. Cytoscape 3.7.2, one of the most favorite open-source software tools, provides visually biomedical interaction networks composed of protein, gene, and other types of interactions. It was used to develop an active ingredient-target PPI network to visualize the relationship between the active ingredients and their targets of ZJC.

2.3. GEO Data Collection and DEGs Identification. The original data series GSE84957 was downloaded from the Gene Expression Omnibus (GEO) microarray dataset, which contained gene expression profiles of 18 tissue samples (9 LSCC tumor tissues and 9 normal tissues). The R language was used to process the original data sets, and the RMA algorithm of Affy software package was used to perform background correction and quartile standardization of the expression matrix. The gene ID, the gene probe name of the expression matrix, was replaced by the gene symbol

provided by the GPL17843 Agilent-042818 Human lncRNA Microarray 8_24_v2 platform, and the average value of multiple probes for the same gene was used for analysis. Limma package was used to identify the significant differentially expressed genes (DEGs) according to P < 0.01, |log2 (FC)| > 3.

The screened DEGs were mapped into a volcano map using the R language heatmap package for intuitive vision; finally, the clusterProfiler package was used to carry out GO enrichment analysis and KEGG pathway enrichment analysis for DEGs.

2.4. PPI Network Construction. BisoGenet plugin, comprising of six available PPI databases (the Biological General Repository for Interaction Datasets (BioGRID), Biomolecular Interaction Network Database (BIND), Molecular Interaction Database (MINT), Human Protein Reference Database (HPRD), and Database of Interacting Proteins (DIP)), was used to build the PPI network for DEGs and candidate target genes, respectively [13]. Then, the merged network was conducted for the two PPI networks. We filtered the output nodes with degrees of freedom greater than 2 times the median of all nodes according to the indicators of degree and betweenness centrality. Then, a core PPI network was constructed using CytoNCA, a Cytoscape plugin. The ClueGO plugin was used for the KEGG signaling pathway enrichment analysis. P < 0.01 was taken as the inclusion standard for pathway items. The results of enrichment analysis were presented in the form of the pie chart and nodes.

2.5. Cluster of the Core PPI Network. The MCODE plugin in Cytoscape software was used to screen the highly clustered important modules in the core PPI network. We set the parameters as degree cutoff = 2 and κ -core = 2 and conducted KEGG signaling pathway enrichment analysis for the most significantly clustered modules.

2.6. Gene Expression Data of the Core Cluster for LSCC. The correlation between survival rates of LSCC patients (disease-free survival rate and overall survival rate) and the gene expression levels (NTRK1, COPS5, HIST1H3A, HIST1H3G, HIST1H3J, HIST1H3J, HIST1H3F, and ITGA4) were calculated using GEPIA online database (http://GEPIA. cancer pku.cn/) [14].

3. Results

3.1. Active Ingredients and Targets of ZJC. Searching for all the reported components in the TCMSP database, 30 active ingredients of ZJC were collected. Sequentially, only 11 active ingredients were retained which conformed to OB > 30% and DL > 0.18, such as fisetin, fustin, flavanone, and kaempferol (Table 1). Then, 96 candidate targets of the above 11 active components were obtained after the duplicate targets were excluded.

No.	Component	OB (%)	DL
1	Fisetin	52.60	0.24
2	Fustin	50.91	0.24
3	(-)-Taxifolin	60.51	0.27
4	Flavanone	41.35	0.24
5	Beta-sitosterol	36.91	0.75
6	Sitosterol	36.91	0.75
7	Kaempferol	41.88	0.24
8	Stigmasterol	43.83	0.76
9	Stigmast-4-ene-3,6-dione	39.12	0.79
10	Ent-epicatechin	48.96	0.24
11	Quercetin	46.43	0.28

TABLE 1: The active ingredients in ZJC.



FIGURE 1: Active ingredients-targets network of ZJC. The blue circles represent the active ingredients, the red diamonds represent the targets, and the interaction between the two is represented by gray edges.

3.2. Active Ingredients-Targets PPI Network Construction. A PPI network of the active components and relevant targets, containing 107 nodes and 165 edges, was constructed by the network graphing tool Cytoscape 3.7.2. The 11 active ingredients could be connected with multiple targets, respectively, and each target also could be connected with multiple active ingredients, which directly demonstrated the relationship between active ingredients and targets of ZJC (Figure 1).

3.3. LSCC Differentially Expressed Genes (DEGs). By analyzing the gene chip of GSE84957, a total of 81 genes with significant different expression of the LSCC tissues compared with adjacent nonneoplastic tissues were obtained, among which 50 genes were upregulated and 31 genes were downregulated in tumor tissues (Table 2; Figure 2).

3.4. GO Enrichment Analysis and KEGG Pathway Analysis for DEGs. GO enrichment analysis was used to explore the molecular mechanism of DEGs. The results were given as follows: (i) in the BP category, DEGs were mostly enriched in the extracellular structure organization, the extracellular matrix organization, endodermal cell differentiation, endoderm formation, and endoderm development; (ii) in the category of CC, DEGs were mainly enriched in the extracellular matrix, collagen-containing extracellular matrix, endoplasmic reticulum lumen, collagen trimer, and extracellular matrix component; (iii) in the MF category, extracellular matrix structural constituent, cytokine activity, and receptor ligand activity were selected for main MF. The results of KEGG pathway analysis showed that ECM-receptor interaction, protein digestion and absorption, focal adhesion, Staphylococcus aureus infection, and viral protein interaction with cytokine and cytokine receptor were the major pathways involved in DEGs (Figure 3).

TABLE 2: Differently expressed genes from GSE84957.

CST 4.45518022 7.41759678 1.4977-11 3.717-07 1.551198442 XLOC OUH24 3.0412-028733 1.5925332 4.507-10 3.6112-06 12.7375038 MMP11 3.903325333 6.966977144 11.58573097 4.367-10 3.6112-06 12.7375038 GCUTA1 3.19737644 9.238542733 10.78042002 1.437-09 7.221-06 11.71297431 COLTA1 3.19737644 9.2385407 2.920013 -10.07924 3.447-09 7.221-06 11.71297431 LRP12 3.530821556 4.005204877 9.1064728 1.54F-08 4.26E-05 9.4231143 LCO10050027 4.14287378 4.568671189 8.999347485 2.06F-08 4.97E-05 8.9885142 LCEEP3 3.064138167 1.055244692 8.893742313 3.20F-08 4.97E-05 8.987220302 PLAUR 3.02747033 7.82422043 3.89E-07 0.00012333 7.875178695 PLAUR 3.0274733 7.82422043 3.89E-07 0.00013132 7.87434366 MSR1	GeneSample	logFC	AveExpr	t	P value	Adi. P value	В
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PLAUR 3.027472033 7.824632761 8.051498015 1.46E-07 0.000165132 7.584034636 MSR1 3.915547922 4.49770906 7.705572 2.80E-07 0.000311941 6.67808428 SPP1 4.85309722 7.31872101 7.296233787 6.17E-07 0.000495582 5.941304536 CTP4H1 -3.938406289 5.17450178 -7.14999436 8.57E-07 0.000495582 5.941304558 DC100653149 3.266119356 5.443807811 7.078044014 9.50E-07 0.000152005 5.84474163 MMP1 4.862459922 6.78305694 7.00232661 1.10E-06 0.000055605 5.463280919 COL5A2 3.504323078 7.584409283 6.59758252 2.94E-06 0.00115171 4.7842804 CXCL10 4.59198284 5.640723644 6.497758643 3.07E-06 0.00115171 4.7842804 CXCL10 4.51992844 5.640723644 6.498763364 3.07E-06 0.00115171 4.78738076 PTHLH 4.094722111 1.151599561 6.240735069 3.02E-06 </td <td>TMEM158</td> <td>3.718106033</td> <td>4.697089117</td> <td>8.222894187</td> <td>1.06E - 07</td> <td>0.000132353</td> <td>7.875178695</td>	TMEM158	3.718106033	4.697089117	8.222894187	1.06E - 07	0.000132353	7.875178695
MSR1 3.918547922 4.497970906 7.705672 2.80E-07 0.000248682 6.98290287 SPP1 4.85309722 7.318721011 7.296283387 6.17E-07 0.000415016 6.247440183 SPP1 4.953097222 7.318721011 7.296283387 6.17E-07 0.00045016 6.247440183 SP1 4.953097222 7.318721011 7.296283387 6.17E-07 0.000495582 5.941304558 LOC100653149 3.266119356 5.44380711 7.00223601 1.10E-06 0.0000520061 5.70320204 TMASP19 4.052795578 5.81407245 6.547338071 1.83E-06 0.00015742 5.243053393 HOXD11 3.550990856 5.087563172 6.54672159 2.94E-06 0.0011714 4.78102804 CXCL11 4.51979286 6.465006439 6.502326246 3.05E-06 0.00115171 4.7802804 CXICL1 4.519792865 6.44530693 3.30E-06 0.00113171 4.673287016 LOC100652832 3.25860656 6.465006429 6.31274545 4.226-06 0.00113	PLAUR	3.027472033	7.824632761	8.051498015	1.46E - 07	0.000165132	7.584034636
TGFBI 3.415596633 9.235027294 7.534242043 3.89E-07 0.000311941 6.678084284 CYP4B1 -3.938406289 5.174530178 -7.129943877 6.17E-07 0.0004192116 5.96686977 SH3BGRL2 -4.01528089 6.443807811 7.078044014 9.50E-07 0.0005582 5.94139458 MMP1 4.862459922 6.783056994 7.022323691 1.10E-06 0.00059569 5.463280919 COL5A2 3.504323078 7.584409283 6.5795129 2.78E-06 0.000117349 4.38402889 CXCL11 4.763231211 4.652769394 6.51975825 2.94E-06 0.00115171 4.74802804 CXCL10 4.519192844 5.640273644 6.498769364 3.07E-06 0.00115171 4.74802804 CXCL10 4.49172111 1.151998561 6.441235069 3.30E-06 0.00115171 4.74802804 CXCL12 -3.47615767 3.3039317 -6.24022991 5.26E-06 0.00115171 4.673287016 CXL02 -3.06515767 3.03939117 -6.24092991 5.26E	MSR1	3.918547922	4.497970906	7.705672	2.80E - 07	0.000248682	6.98290287
SPP1 4.85309722 7.318721011 7.296283387 6.17E - 07 0.000415016 6.247440183 CYP4B1 -4.938406289 5.174530178 -7.145914333 8.37E - 07 0.000492716 5.96986977 SH3BGRL2 -4.071528089 6.438324422 -7.1299436 8.57E - 07 0.000525005 5.844794163 DC10065149 3.268119356 5.44380781 7.078446014 9.50E - 07 0.0005925005 5.443280819 COL5A2 3.5032078 5.81647465 6.87433807 1.43E - 06 0.00015742 5.243033891 HOXD11 3.550990856 5.087563172 6.54672159 2.78E - 06 0.00115171 4.781590785 LOC100652832 3.25380656 6.46006439 6.502326246 3.05E - 06 0.00115171 4.74073422 XLOC_006053 -3.635899633 9.15639624 -6.475756406 3.22E - 06 0.00115171 4.69579809 KRT17 4.404712111 1.15326978 6.2496340 3.02E - 06 0.00115171 4.69579809 KRT14 4.0882033 7.74967984 6.34	TGFBI	3.415596633	9.235072794	7.534242043	3.89E - 07	0.000311941	6.678084284
CYP4R1 -3.938406289 5.174530178 -7.145413133 8.31 <i>E</i> -07 0.000495216 5.96986977 SH3BCRL2 -4.071520898 6.43832642 -7.12999436 8.57 <i>E</i> -07 0.0004955x2 5.844794163 MMP1 4.8625795678 5.81647465 6.87435807 1.10 <i>E</i> -06 0.0006950601 5.70320204 TM4SF19 4.052795678 5.81647465 6.87435807 1.80 <i>E</i> -06 0.000117349 4.834020859 COL5A2 3.504332078 7.584409283 6.5795032897 1.80 <i>E</i> -06 0.0011571 4.748025804 CXCL10 4.762232121 4.652769334 6.509758265 2.94 <i>E</i> -06 0.00115171 4.748025804 CXCL00 4.519192844 5.640273644 6.498769364 3.07 <i>E</i> -06 0.00115171 4.748025804 XLOC_00603 -3.635899633 9.156396294 -6.475756406 3.02 <i>E</i> -06 0.00115171 4.69579809 XRT1 4.404712111 1.51599561 6.44235069 3.30 <i>E</i> -06 0.00115171 4.673287016 CXCL12 -3.47515767 8.30393117 -6.	SPP1	4.853097222	7.318721011	7.296283387	6.17E - 07	0.000415016	6.247440183
SH3BGRL2 -4.071520089 6.43822422 -7.12999436 8.57E - 07 0.000495582 5.5441304558 LOC100653149 3.268119356 5.443807811 7.078040614 9.50E - 07 0.000525005 5.544734163 MMP1 4.862459922 6.783056994 7.002232691 1.10E - 06 0.000852605 5.76320204 TMASF19 4.052795678 5.81647465 6.673032897 1.43E - 06 0.000115742 5.24305389 HOXD11 3.550990856 5.087563172 6.54672159 2.78E - 06 0.00115171 4.781590755 LOC100652832 3.233860566 6.460230649 6.502526246 3.05E - 06 0.00115171 4.7481590755 LOC1006053 -3.635899633 9.156396294 -6.477576406 3.20E - 06 0.00115171 4.673287016 PTHLH 4.09820033 7.949679894 6.34121265 4.26E - 06 0.00115171 4.673287016 VLOC_106021 4.372459256 1.50269782 6.229963809 5.38E - 06 0.001142786 4.23314024 XLOC_106021 4.372459256 1.50269782 6.229963809 5.38E - 06 0.001142781 4.211342414 <td>CYP4B1</td> <td>-3.938406289</td> <td>5.174530178</td> <td>-7.145413133</td> <td>8.31E - 07</td> <td>0.000492716</td> <td>5.96986977</td>	CYP4B1	-3.938406289	5.174530178	-7.145413133	8.31E - 07	0.000492716	5.96986977
LOC100653149 3.268119356 5.443807811 7.078046014 9.50E -07 0.00052005 5.844794163 TM4SF19 4.052795678 5.81647465 6.87435807 1.43E -06 0.000956569 5.46238019 COL5A2 3.504323078 7.584409236 6.759032897 1.43E -06 0.000815742 5.243053839 HOXD11 3.550990856 5.087563172 6.54672159 2.78E -06 0.001115171 4.781590785 CXCL11 4.762321211 4.652769394 6.519758265 2.94E -06 0.00115171 4.78050785 CXCL10 4.519192844 5.640273644 6.498769364 3.07E -06 0.00115171 4.748026804 CXCL10 4.519192844 5.640273644 6.498769364 3.07E -06 0.00115171 4.748026804 CXCL10 4.519192844 5.640273649 -6.457576406 3.30E -06 0.00115171 4.6673287016 PTHLH 4.098820033 7.949679894 -6.477576406 3.30E -06 0.00115171 4.6673287016 PTHLH 4.098820033 7.949679894 -6.477576406 3.30E -06 0.00115171 4.6673287016 PTHLH 4.098820033 7.949679894 -6.477576406 3.30E -06 0.00115171 4.673287016 PTHLH 4.09882003 7.949679894 -6.47730972 6.010115171 4.673287016 PTHLH 4.09882003 7.94967982 6.229963809 5.38E -06 0.001142594 4.341701824 CXCL12 -3.476515767 6.105022078 6.17730972 6.01E -06 0.00115214 4.01370397 KIDC_2 0.00621 4.372459256 11.50269782 6.229963809 5.38E -06 0.00116254 4.003977039 HMGA2 3.706329122 3.703429261 6.117033971 6.83E -06 0.001163274 4.003977039 HMGA2 3.706329122 3.703429261 6.117033971 6.83E -06 0.001183877 8.3829512486 NRGI 3.430506311 6.615773067 6.013403137 8.51E -06 0.001987878 3.3829512486 NRGI 3.430506311 6.615773067 5.968266129 4.35E -06 0.001985485 3.66592943 MYOC -3.299936644 3.378123278 -5.96421662 9.45E -06 0.001985485 3.66592144 DNAPTP3 4.162512589 8.355008817 5.948057503 9.77E -06 0.001965485 3.66592943 MYOC -3.299936641 3.37812397 -5.58621646 9.45E -06 0.001985485 3.66592144 DNAPTP3 4.16251167 3.1043818 5.70928488 1.54E -05 0.002228048 3.344198953 COL1A2 3.096446333 11.78684306 5.800402532 1.34E -05 0.002286888 3.34417863 CXCL9 3.067348622 6.516563178 5.759709415 1.47E -05 0.002286888 3.34417863 CXCL9 3.067348622 6.516563178 5.759709415 1.47E -05 0.00228743 3.340074185 CXCL9 3.0067348622 6.516563178 5.759709415 1.47E	SH3BGRL2	-4.071528089	6.438326422	-7.12999436	8.57E - 07	0.000495582	5.941304558
MMPI 4.862459922 6.783056994 7.002232691 1.10E-06 0.00090601 5.7032024 TMASPIP 4.052795678 5.81647465 6.87435807 1.48E-06 0.000096559 5.462380919 COL5A2 3.504323078 7.884409283 6.759032897 1.80E-06 0.000115742 5.243053891 HOXD11 4.762321211 4.652769394 6.519758265 2.94E-06 0.00115171 4.78190785 LOC100652832 3.253800656 6.465006439 6.502526246 3.05E-06 0.00115171 4.740703422 XLOC_000053 -3.635899633 9.156396294 -6.475756406 3.22E-06 0.00115171 4.69579809 KRT17 4.404712111 11.51599561 6.464235069 3.30E-06 0.001135184 4.431701824 CXL12 -3.476515767 8.33393117 -6.24092991 5.26E-06 0.00124781 4.231344214 CULA4 3.21121667 6.0692078 6.177430972 6.01E-06 0.00126438 4.100669064 CLCA4 -5.919341655 5.955450789 6.039266244	LOC100653149	3.268119356	5.443807811	7.078046014	9.50E - 07	0.000525005	5.844794163
1MASP19 4.052/795/8 5.8164/465 6.87/435807 1.43E - 06 0.000085669 5.46236078 COL5A2 3.504920856 5.087563172 6.54672159 2.78E - 06 0.00115171 4.7834020889 CXCL11 4.762321211 4.652769394 6.519758265 2.94E - 06 0.00115171 4.748026804 CXCL10 4.519192844 5.640273644 6.498769364 3.07E - 06 0.00115171 4.748026804 CXLO_00053 -3.35899633 9.15639624 -6.47756406 3.32E - 06 0.00115171 4.69728809 KRT17 4.404712111 1.151599561 6.464235069 3.30E - 06 0.001125174 4.4372487263 CXCL12 -3.4776515767 8.33039117 -6.24092991 5.26E - 06 0.0011224781 4.21134214 CXL14 -5.919341656 8.217143061 -6.126082361 6.070E - 06 0.0011827481 4.103666904 CLCA4 -5.919341656 8.217143061 -6.126082361 6.070E - 06 0.0011827481 4.00666906 VISP1 3.027104311 6.964110233 -5.99450777 8.92E - 06 0.001987368 3.3732590438	MMP1	4.862459922	6.783056994	7.002232691	1.10E - 06	0.000590601	5.70320204
COL5A2 3.504324078 7.584409283 6.799032897 1.800-106 0.000115742 3.24305889 HOXD11 3.550990856 5.087563172 6.54672159 2.78E-06 0.00111571 4.743020899 CXCL11 4.762321211 4.652769394 6.519758265 2.94E-06 0.00115171 4.748026804 CXCL10 4.519192844 5.640273644 6.488769364 3.07E-06 0.00115171 4.748026804 XLOC_006053 -3.655896633 9.156396294 -6.475756406 3.22E-06 0.00115171 4.69578809 KRT17 4.40471211 11.151599561 6.464235069 3.30E-06 0.001422596 4.23314024 XLOC_12_06021 4.372459256 1.50269782 6.229963809 5.38E-06 0.001422781 4.211342414 CLEAA -5.919341656 6.327143061 -6.12082361 6.70E-06 0.0016615 3.985842669 VISP1 3.02198156 5.395450789 6.0326244 8.06E-06 0.001838778 3.829512486 NRG1 3.4030504311 6.615773067 6.01340337	TM4SF19	4.052795678	5.81647465	6.87435807	1.43E - 06	0.000696569	5.462380919
HOXD11 3:530990856 3:08/5631/2 6:340/2139 2:78E - 06 0.001117/349 4:834020889 CXCL11 4:762321211 4:652703946 6:50758265 2:94E - 06 0.00115171 4:748026804 CXCL10 4:519192844 5:640273644 6:498769364 3:07E - 06 0.00115171 4:69579809 KRT17 4:404712111 11:51599561 6:44235069 3:02E - 06 0.00115171 4:69579809 KRT17 4:404712111 11:51599561 6:44235069 3:02E - 06 0.00115171 4:69579809 KRT17 4:404712111 11:51599561 6:44235069 3:02E - 06 0.00113174 4:71718124 CXL12 -3:476515767 8:330393117 -6:24092991 5:26E - 06 0.001242781 4:21142414 CXL14 -5:919341656 8:217143061 -6:120082361 6:70E - 06 0.001661254 4:003977039 HMGA2 3:706329122 3:703429261 6:117033971 6:82E - 06 0.0018678 3:82512486 NKG1 3:433500222 5:808183467 -5:968076797 9:38E - 06 0.001963485 3:665672938 MYOC	COL5A2	3.504323078	7.584409283	6.759032897	1.80E - 06	0.000815742	5.243053839
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	HOXDII	3.550990856	5.087563172	6.54672159	2.78E - 06	0.001117349	4.834020589
LOC.100622832 3.233800536 6.463006439 6.50222476 3.035 - 06 0.00115171 4.748028064 XLOC_006053 -3.638899633 9.156396294 -6.475756406 3.22E - 06 0.00115171 4.69579809 KRT17 4.404712111 11.51599561 6.464235069 3.30E - 06 0.00115171 4.673287016 PTHLH 4.098820033 7.949679894 6.341212465 4.26E - 06 0.001315184 4.431701824 CXCL12 -3.476515767 8.330393117 -6.24092991 5.26E - 06 0.00142596 4.233143024 CXLCL2_006021 4.372459256 11.5020782 6.0229963809 5.38E - 06 0.0016615 3.985842669 VILOC_12_006021 3.3704329261 6.117033971 6.83E - 06 0.00186615 3.985842669 MIGA2 3.706329122 3.703429261 6.013403137 8.92E - 06 0.0019778 3.829512486 NRG1 3.430506311 6.615773067 6.033405137 8.92E - 06 0.001965485 3.6685672938 MYOC -3.2090936644 3.37812378 -5.9680767	CXCLII LOC100(52022	4.762321211	4.652769394	6.519758265	2.94E - 06	0.00115171	4./81590/85
CACL10 4.31912844 5.8402/3644 6.486.09364 3.012 = 06 0.00115171 4.740/03422 KRT17 4.404712111 11.51599561 6.464235069 3.30E = 06 0.00115171 4.673287016 PTHLH 4.098820033 7.949679894 6.341212465 4.26E = 06 0.001125184 4.431701824 CXCL12 -3.476515767 8.330393117 -6.2409291 5.26E = 06 0.00142781 4.211342414 COL8A1 3.211121667 6.060922078 6.177430972 6.01E = 06 0.001661524 4.003977039 HMGA2 3.706329122 3.703429261 6.117033971 6.83E = 06 0.00186155 3.985842669 WISP1 3.021981556 5.595450789 6.039266244 8.06E = 06 0.00189778 3.829512486 NRG1 3.430506311 6.615773067 6.01340313 8.51E = 06 0.001965485 3.66752934 GCNT3 -3.42300222 5.80818467 -5.964261662 9.45E = 06 0.001965485 3.667592443 GDNAPTP3 4.162512588 8.3550008817 5.9480575	LUC100652852	3.253860656	6.465006439	6.502526246	3.05E - 06	0.00115171	4.748026804
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	VLOC 006053	4.519192844	5.0402/3044	6.498/09304	3.0/E = 06	0.00115171	4.740703422
$\begin{array}{llllllllllllllllllllllllllllllllllll$	KDT17	-5.055699055	9.130390294	-0.4/3/30400	3.22E - 00 3.30E - 06	0.00115171	4.09379609
Intern Intern <thintern< th=""> <thintern< th=""> <thintern< td="" tr<=""><td>РТНІ Н</td><td>4 098820033</td><td>7 949679894</td><td>6 341212465</td><td>3.30E = 00 4 26E = 06</td><td>0.0011315184</td><td>4.075287010</td></thintern<></thintern<></thintern<>	РТНІ Н	4 098820033	7 949679894	6 341212465	3.30E = 00 4 26E = 06	0.0011315184	4.075287010
Chichi Chichi <thchichi< th=""> <thchichi< th=""> <thchichi< td="" th<=""><td>CXCL12</td><td>-3 476515767</td><td>8 330393117</td><td>-6 24092991</td><td>4.20E = 00 5.26E - 06</td><td>0.001313104</td><td>4 233143024</td></thchichi<></thchichi<></thchichi<>	CXCL12	-3 476515767	8 330393117	-6 24092991	4.20E = 00 5.26E - 06	0.001313104	4 233143024
COL&A1 3.211121667 6.060922078 6.177430972 6.01E - 06 0.001526438 4.106669044 CLCA4 -5.919341656 8.217143061 -6.126082361 6.70E - 06 0.001661254 4.003977039 HMGA2 3.706329122 3.703429261 6.117033971 6.83E - 06 0.0016615 3.985842669 WISP1 3.02191556 5.595450789 6.03926244 8.06E - 06 0.00197796 3.777336092 ANKRD20A9P -3.027104311 6.6615773067 6.013403137 8.51E - 06 0.001965485 3.685672933 GCNT3 -3.48336022 5.808183467 -5.96676797 9.38E - 06 0.001965485 3.660592194 DNAPTP3 4.162512589 8.355008817 5.948057503 9.79E - 06 0.00197924 3.645098841 FUT3 -3.452809133 7.136305 -5.832221646 1.25E - 05 0.002217034 3.388254529 CFD -3.520037456 9.269488272 -5.800510125 1.34E - 05 0.00228688 3.344398953 COL1A2 3.096744633 1.78684306 5.80	XLOC 12 006021	4.372459256	11.50269782	6.229963809	5.38E - 06	0.001424781	4.211342414
CLCA4 -5.919341656 8.217143061 -6.126082361 6.70E - 06 0.001661254 4.003977039 HMGA2 3.706329122 3.703492261 6.117033971 6.83E - 06 0.00166615 3.985842669 WISP1 3.021981556 5.595450789 6.039266244 8.06E - 06 0.00186778 3.829512486 NRG1 3.430506311 6.615773067 6.013403137 8.51E - 06 0.001907796 3.777336092 ANKRD20A9P -3.027104311 6.964110233 -5.991259577 8.92E - 06 0.001965485 3.685672938 MYOC -3.290936644 3.378123278 -5.964261662 9.45E - 06 0.001965485 3.660592194 DNAPTP3 4.162512589 8.355008817 5.948057503 9.79E - 06 0.00121345 3.409270286 CFD -3.52007456 9.369048272 -5.8019125 1.34E - 05 0.002286888 3.344398953 COL1A2 3.096446333 11.78684306 5.800402532 1.34E - 05 0.002286888 3.3447863 CXL9 3.067348622 6.615663178 5.75	COL8A1	3.211121667	6.060922078	6.177430972	6.01E - 06	0.001526438	4.106669064
HMGA23.7063291223.7034292616.1170339716.83E - 060.001666153.985842669WISP13.0219815565.5954507896.039266248.06E - 060.0018387783.829512486NRG13.4305063116.6157730676.0134031378.51E - 060.0019077963.772590438GCNT3-3.0271043116.964110233-5.9680767979.38E - 060.0019654853.685672938MYOC-3.2909366443.378123278-5.9642616629.45E - 060.0019654853.665052194DNAPTP34.1625125898.3550088175.9480575039.79E - 060.0019654853.660592194DNAPTP34.1625125898.3550088175.9480575039.79E - 060.001972243.64509841FUT3-3.452091337.136305-5.8212916461.25E - 050.002213453.409270286CRNN-6.5247332789.72241585-5.8219412971.28E - 050.0022868883.344398953COL1A23.09644633311.786843065.8004025321.34E - 050.0022868883.34417863CXCL93.0673486226.615663175.7597094151.47E - 050.0022868883.3447864PDPN3.1702757331.004381885.7092849881.64E - 050.0022675473.003115853COL5A13.20939372211.038862925.6343062531.92E - 050.0026875473.00315853COL5A13.2051796228.6743017445.6044076532.95E - 050.002792322.979773593COL5A13.2051796228.674301744 <td>CLCA4</td> <td>-5.919341656</td> <td>8.217143061</td> <td>-6.126082361</td> <td>6.70E - 06</td> <td>0.001661254</td> <td>4.003977039</td>	CLCA4	-5.919341656	8.217143061	-6.126082361	6.70E - 06	0.001661254	4.003977039
WISP13.0219815565.5954507896.0392662448.06E - 060.0018387783.829512486NRG13.4305063116.6157730676.013403178.51E - 060.0019077963.777336092ANKRD20A9P-3.0271043116.964110233-5.9912595778.92E - 060.0019654853.685672938MYOC-3.2909366443.378123278-5.9642616629.45E - 060.0019654853.660572194DD223.0308502117.342800395.9556987689.63E - 060.0019654853.660592194DNAPTP34.1625125898.3550088175.9480575039.79E - 060.0012979243.645098841FUT3-3.4528091337.136305-5.8219412971.28E - 050.0022170343.388254529CFD-3.5200374569.369048272-5.8005101251.34E - 050.0022868883.344398953COL1A23.09644633311.786843065.8004025321.34E - 050.0022868883.3441398953CXL593.6074486226.6156631785.7957094151.47E - 050.0022697473.0171081PDPN3.17027573310.04381885.7092849881.64E - 050.0022697473.0171185PDPN3.1702757331.004381885.7092849881.64E - 050.00226875473.00171405CALA5-3.8610034677.10638656-5.6348062531.92E - 050.0022697473.01710913SCARA5-3.861034677.10638656-5.634307391.97E - 050.00226975473.001318533COLA13.2051796228.6743017	HMGA2	3.706329122	3.703429261	6.117033971	6.83E - 06	0.00166615	3.985842669
NRG1 3.430506311 6.615773067 6.013403137 8.51E - 06 0.001907796 3.777336092 ANKRD20A9P -3.027104311 6.964110233 -5.991259577 8.92E - 06 0.001947336 3.732590438 GCNT3 -3.483360222 5.808183467 -5.968076797 9.38E - 06 0.001965485 3.66567238 MYOC -3.290936644 3.378123278 -5.964261662 9.45E - 06 0.001965485 3.660592194 DNAPTP3 4.162512589 8.355008817 5.948057503 9.79E - 06 0.001979224 3.645098841 FUT3 -3.452809133 7.136305 -5.83221646 1.25E - 05 0.002227034 3.388254529 CFD -3.52037456 9.369048272 -5.800510125 1.34E - 05 0.002286888 3.344398953 COL1A2 3.096446333 11.78684306 5.800402532 1.34E - 05 0.002286888 3.34417863 CXCL9 3.067348622 6.615663178 5.759709415 1.47E - 05 0.002269549 3.260741185 PDPN 3.170275733 10.0438188 5.7	WISP1	3.021981556	5.595450789	6.039266244	8.06E - 06	0.001838778	3.829512486
ANKRD20A9P-3.0271043116.964110233-5.9912595778.92E - 060.0019473363.732590438GCNT3-3.4833602225.808183467-5.9680767979.38E - 060.0019654853.685672938MYOC-3.2909366443.378123278-5.9642616629.45E - 060.0019654853.66759194DDZ23.0308502117.3428003395.9556987689.63E - 060.0019654853.660592194DNAPTP34.1625125898.3550088175.9480575039.79E - 060.0019792243.645098841FUT3-3.4528091337.136305-5.8322216461.25E - 050.0022270343.388254529CFD-3.5200374569.369048272-5.8005101251.34E - 050.0022868883.34419863COL1A23.09644633311.786843065.8004025321.34E - 050.0022868883.34417863CXCL93.0673486226.6156631785.7597094151.47E - 050.0022868883.34417863CXCL93.07027573310.04381885.7092849881.64E - 050.0026404633.04722486NMP124.1625211673.7365494175.6388645841.91E - 050.0026875473.017110913SCARA5-3.8610034677.106386856-5.6348062531.92E - 050.002792322.979773593COL5A13.2051796228.6743017445.6044076532.05E - 050.002792322.979773593COL5A13.2051796228.6743017445.6044076532.05E - 050.002781172.877727019ANKRD20A5P-3.18826611<	NRG1	3.430506311	6.615773067	6.013403137	8.51E - 06	0.001907796	3.777336092
GCNT3-3.4833602225.808183467-5.9680767979.38E - 060.0019654853.685672938MYOC-3.2909366443.378123278-5.9642616629.45E - 060.0019654853.660592194DNAPTP34.1625125898.3550088175.9480575039.79E - 060.0019792243.64509841DNAPTP3-3.4528091337.136305-5.8322216461.25E - 050.002217343.482097286CRNN-6.5247332789.72241585-5.8219412971.28E - 050.0022270343.388254529CFD-3.5200374569.369048272-5.8005101251.34E - 050.0022868883.344398953COL1A23.09644633311.786843065.800425321.34E - 050.0022868883.34417863CXCL93.0673486226.6156631785.7597094151.47E - 050.002695493.260741185PDPN3.17027573310.04381885.7092849881.64E - 050.002529113.15705467INHBA3.0998870785.8097533175.6560436611.84E - 050.0026875473.011710913SCARA5-3.8610034677.106386856-5.6348062531.92E - 050.0026875473.003315853COL4A13.29399372211.038862925.6234307391.97E - 050.0027092322.979773593ANKRD20A5P-3.118266115.357065783-5.574210892.19E - 050.0028731172.877727019TNXB-3.3901475448.386793894-5.464372672.79E - 050.0033455262.648949986CCDC25-3.340572133 <td< td=""><td>ANKRD20A9P</td><td>-3.027104311</td><td>6.964110233</td><td>-5.991259577</td><td>8.92E - 06</td><td>0.001947336</td><td>3.732590438</td></td<>	ANKRD20A9P	-3.027104311	6.964110233	-5.991259577	8.92E - 06	0.001947336	3.732590438
MYOC-3.2909366443.378123278-5.9642616629.45E - 060.0019654853.6677944815ODZ23.0308502117.3428003395.9556987689.63E - 060.0019654853.660592194DNAPTP34.1625125898.3550088175.9480575039.79E - 060.0019792243.645098841FUT3-3.4528091337.136305-5.8322216461.25E - 050.002213453.409270286CRNN-6.5247332789.72241585-5.8219412971.28E - 050.0022270343.388254529CFD-3.5200374569.369048272-5.8005101251.34E - 050.0022868883.344398953COL1A23.09644633311.786843065.8004025321.34E - 050.0022868883.34417863CXCL93.0673486226.6156631785.7597094151.47E - 050.0026875473.067741185PDPN3.17027573310.04381885.7092849881.64E - 050.0026875473.017110913SCARA5-3.8610034677.106386856-5.6348062531.92E - 050.0026875473.00315853COL4A13.2051796228.6743017445.6044076532.05E - 050.0027092322.979773593COL5A13.2051796228.6743017445.6044076532.05E - 050.0023731172.877727019TNXB-3.3901475448.386793894-5.464372672.79E - 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E - 050.0033455262.6421014FN13.58053544411.63254756 <td>GCNT3</td> <td>-3.483360222</td> <td>5.808183467</td> <td>-5.968076797</td> <td>9.38E - 06</td> <td>0.001965485</td> <td>3.685672938</td>	GCNT3	-3.483360222	5.808183467	-5.968076797	9.38E - 06	0.001965485	3.685672938
ODZ23.0308502117.3428003395.9556987689.63E - 060.0019654853.660592194DNAPTP34.1625125898.3550088175.9480575039.79E - 060.0019792243.645098841FUT3-3.4528091337.136305-5.8322216461.25E - 050.002213453.409270286CRNN-6.5247332789.72241585-5.8019412971.28E - 050.0022260343.388254529CFD-3.5200374569.369048272-5.8005101251.34E - 050.0022868883.34417863CXCL93.09644633311.786843065.8004025321.34E - 050.0022868883.34417863CXCL93.0673486226.6156631785.7597094151.47E - 050.0022695493.260741185PDPN3.17027573310.04381885.7092849881.64E - 050.0022697473.01710913SCARA5-3.8610034677.10638656-5.634866131.84E - 050.0026875473.017110913SCARA5-3.8610034677.10638656-5.6348062531.92E - 050.0026875473.003315853COL5A13.29399372211.038862925.6234307391.97E - 050.002792952.940368581ANKRD20A5P-3.118266115.357065783-5.5742108892.19E - 050.0023455262.648949986CCDC25-3.3405721337.218539933-5.4610950792.81E - 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E - 050.0033455262.6421014FN13.58053544411.63254756	MYOC	-3.290936644	3.378123278	-5.964261662	9.45E - 06	0.001965485	3.677944815
DNAPTP34.1625125898.3550088175.9480575039.79E - 060.0019792243.645098841FUT3-3.4528091337.136305-5.8322216461.25E - 050.002213453.409270286CRNN-6.524732789.72241585-5.8219412971.28E - 050.0022270343.388254529CFD-3.5200374569.369048272-5.8005101251.34E - 050.0022868883.344398953COL1A23.09644633311.786843065.8004025321.34E - 050.0023695493.260741185PDPN3.17027573310.04381885.7092849881.64E - 050.002529113.157054667INHBA3.0998870785.8097533175.6560436611.84E - 050.0026875473.011710913SCARA5-3.8610034677.106386856-5.6348062531.92E - 050.002792322.979773593COL4A13.29399372211.038862925.6234307391.97E - 050.002792322.979773593COL5A13.2051796228.6743017445.6044076532.05E - 050.002792322.979773593COL5A13.2051796228.6743017445.6044076532.05E - 050.0028731172.877727019TNXB-3.3901475448.386793894-5.464372672.79E - 050.0033455262.648949986CCDC25-3.3405721337.218539933-5.464172672.79E - 050.0033455262.6421014FN13.58053544411.63247565.4279580083.02E - 050.0033455262.6421014FN13.58053544411.6324756<	ODZ2	3.030850211	7.342800339	5.955698768	9.63E - 06	0.001965485	3.660592194
FUT3-3.4528091337.136305-5.8322216461.25E - 050.002213453.409270286CRNN-6.5247332789.72241585-5.8219412971.28E - 050.0022270343.388254529CFD-3.5200374569.369048272-5.8005101251.34E - 050.0022868883.344398953COL1A23.09644633311.786843065.8004025321.34E - 050.0022868883.34417863CXCL93.0673486226.6156631785.7597094151.47E - 050.0023695493.260741185PDPN3.17027573310.04381885.7092849881.64E - 050.0026404633.04722486MMP124.1625211673.7365494175.6388645841.91E - 050.0026875473.011710913SCARA5-3.8610034677.106386856-5.6348062531.92E - 050.0027092322.979773593COL5A13.2051796228.6743017445.6044076532.05E - 050.002792952.940368581ANKRD20A5P-3.1188266115.357065783-5.5742108892.19E - 050.0033455262.648949986CCDC25-3.3405721337.218539933-5.4610950792.81E - 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E - 050.0033455262.642894986CCDC25-3.3405721337.218539933-5.4610950792.81E - 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E - 050.0033455262.6421014FN13.58053544411.6325475	DNAPTP3	4.162512589	8.355008817	5.948057503	9.79 <i>E</i> – 06	0.001979224	3.645098841
CRNN-6.5247332789.72241585-5.8219412971.28E - 050.0022270343.388254529CFD-3.5200374569.369048272-5.8005101251.34E - 050.0022868883.344398953COL1A23.09644633311.786843065.8004025321.34E - 050.0022868883.34417863CXCL93.0673486226.6156631785.7597094151.47E - 050.0023695493.260741185PDPN3.17027573310.04381885.7092849881.64E - 050.002529113.157054467INHBA3.0998870785.8097533175.6560436611.84E - 050.0026875473.011710913SCARA5-3.8610034677.106386856-5.6348062531.92E - 050.0026875473.003315853COL4A13.29399372211.038862925.6234307391.97E - 050.002792322.979773593COL5A13.2051796228.6743017445.6044076532.05E - 050.0028731172.877727019TNXB-3.3901475448.386793894-5.4610950792.81E - 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E - 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E - 050.0033455262.6421014FN13.5805311338.9132381-5.3804985083.36E - 050.0037267742.473306046FBN23.7020987674.6470011285.3175403913.86E - 050.0039636982.340945176KRT4-5.78358505612.44990214	FUT3	-3.452809133	7.136305	-5.832221646	1.25E - 05	0.00221345	3.409270286
CFD-3.5200374569.369048272-5.8005101251.34E - 050.0022868883.344398953COL1A23.09644633311.786843065.8004025321.34E - 050.0022868883.34417863CXCL93.0673486226.6156631785.7597094151.47E - 050.0023695493.260741185PDPN3.17027573310.04381885.7092849881.64E - 050.002229113.157054467INHBA3.099870785.8097533175.6560436611.84E - 050.0026404633.04722486MMP124.1625211673.7365494175.6388645841.91E - 050.0026875473.011710913SCARA5-3.8610034677.106386856-5.6348062531.92E - 050.0022875473.003315853COL4A13.29399372211.038862925.6234307391.97E - 050.0027092322.979773593COL5A13.2051796228.6743017445.6044076532.05E - 050.0027893172.840368581ANKRD20A5P-3.1188266115.357065783-5.5742108892.19E - 050.0033455262.64420194FN13.58053544411.632547565.4279580083.02E - 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E - 050.0037267742.473306046FBN23.7020987674.6470011285.3175403913.86E - 050.0039636982.340945176KRT4-5.78358505612.44990214-5.275014984.24E - 050.0043045412.251297748	CRNN	-6.524733278	9.72241585	-5.821941297	1.28E - 05	0.002227034	3.388254529
COLLA23.09644633311.786843065.8004025321.34E - 050.0022868883.34417863CXCL93.0673486226.6156631785.7597094151.47E - 050.0023695493.260741185PDPN3.17027573310.04381885.7092849881.64E - 050.002529113.157054467INHBA3.0998870785.8097533175.6560436611.84E - 050.0026404633.04722486MMP124.1625211673.7365494175.6388645841.91E - 050.0026875473.011710913SCARA5-3.8610034677.106386856-5.6348062531.92E - 050.0026875473.003315853COL4A13.29399372211.038862925.6234307391.97E - 050.0027092322.979773593COL5A13.2051796228.6743017445.6044076532.05E - 050.002792952.940368581ANKRD20A5P-3.1188266115.357065783-5.5742108892.19E - 050.0033455262.648949986CCDC25-3.3405721337.218539933-5.4610950792.81E - 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E - 050.0033455262.6421014FN13.58053544411.632547565.427958083.06E - 050.0037267742.473306046FBN23.7020987674.6470011285.3175403913.86E - 050.0039636982.340945176KRT4-5.78358505612.44990214-5.275014984.24E - 050.0043045412.251297748	CFD	-3.520037456	9.369048272	-5.800510125	1.34E - 05	0.002286888	3.344398953
CXCL93.0673486226.6156631785.7597094151.47E = 050.0023695493.26074185PDPN3.17027573310.04381885.7092849881.64E = 050.002529113.157054467INHBA3.0998870785.8097533175.6560436611.84E = 050.0026404633.04722486MMP124.1625211673.7365494175.6388645841.91E = 050.0026875473.011710913SCARA5-3.8610034677.106386856-5.6348062531.92E = 050.0026875473.003315853COL4A13.29399372211.038862925.6234307391.97E = 050.0027092322.979773593COL5A13.2051796228.6743017445.6044076532.05E = 050.0028731172.877727019TNXB-3.3901475448.386793894-5.464372672.79E = 050.0033455262.648949986CCDC25-3.3405721337.218539933-5.4610950792.81E = 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E = 050.0037267742.473306046FBN23.7020987674.6470011285.3175403913.86E = 050.0039636982.340945176KRT4-5.78358505612.44990214-5.275014984.24E = 050.0043045412.251297748	COL1A2	3.096446333	11.78684306	5.800402532	1.34E - 05	0.002286888	3.34417863
PDPN3.1702/573310.04381885.7092849881.64E = 050.002529113.157054467INHBA3.0998870785.8097533175.6560436611.84E = 050.0026404633.04722486MMP124.1625211673.7365494175.6388645841.91E = 050.0026875473.011710913SCARA5-3.8610034677.106386856-5.6348062531.92E = 050.0027092322.979773593COL4A13.29399372211.038862925.6234307391.97E = 050.0027092322.979773593COL5A13.2051796228.6743017445.6044076532.05E = 050.0028731172.877727019TNXB-3.3901475448.386793894-5.464372672.79E = 050.0033455262.648949986CCDC25-3.3405721337.218539933-5.4610950792.81E = 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E = 050.0033455262.6421014FN23.7020987674.6470011285.3175403913.86E = 050.0037267742.473306046FBN23.7020987674.6470011285.3175403913.86E = 050.0039636982.340945176KRT4-5.78358505612.44990214-5.275014984.24E = 050.0043045412.251297748	CXCL9	3.06/348622	6.615663178	5.759709415	1.4/E - 05	0.002369549	3.260/41185
INHBA3.09988/0785.809/533175.6560436611.84E - 050.0026404633.04/22486MMP124.1625211673.7365494175.6388645841.91E - 050.0026875473.011710913SCARA5-3.8610034677.106386856-5.6348062531.92E - 050.0026875473.003315853COL4A13.29399372211.038862925.6234307391.97E - 050.0027092322.979773593COL5A13.2051796228.6743017445.6044076532.05E - 050.002731172.877727019TNXB-3.3901475448.386793894-5.464372672.79E - 050.0033455262.648949986CCDC25-3.3405721337.218539933-5.4610950792.81E - 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E - 050.0037267742.473306046FBN23.7020987674.6470011285.3175403913.86E - 050.0039636982.340945176KRT4-5.78358505612.44990214-5.275014984.24E - 050.0043045412.251297748	PDPN	3.1/02/5/33	10.0438188	5./09284988	1.64E - 05	0.00252911	3.15/05446/
MMP124.1625211675.7365494175.6588643841.91E - 050.0026875475.011710915SCARA5-3.8610034677.106386856-5.6348062531.92E - 050.0026875473.003315853COL4A13.29399372211.038862925.6234307391.97E - 050.0027092322.979773593COL5A13.2051796228.6743017445.6044076532.05E - 050.002792952.940368581ANKRD20A5P-3.1188266115.357065783-5.5742108892.19E - 050.0028731172.877727019TNXB-3.3901475448.386793894-5.464372672.79E - 050.0033455262.648949986CCDC25-3.3405721337.218539933-5.4610950792.81E - 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E - 050.0037267742.473306046FBN23.7020987674.6470011285.3175403913.86E - 050.0039636982.340945176KRT4-5.78358505612.44990214-5.275014984.24E - 050.0043045412.251297748	INHBA MMD12	3.099887078	5.809/5551/	5.050045001	1.84E - 05	0.002640463	3.04/22486
SCARAS -3.861005467 7.106386856 -5.634806253 1.92E - 05 0.002687547 3.003313853 COL4A1 3.293993722 11.03886292 5.623430739 1.97E - 05 0.002709232 2.979773593 COL5A1 3.205179622 8.674301744 5.604407653 2.05E - 05 0.002709295 2.940368581 ANKRD20A5P -3.118826611 5.357065783 -5.574210889 2.19E - 05 0.002873117 2.877727019 TNXB -3.390147544 8.386793894 -5.46437267 2.79E - 05 0.003345526 2.648949986 CCDC25 -3.340572133 7.218539933 -5.461095079 2.81E - 05 0.003345526 2.6421014 FN1 3.580535444 11.63254756 5.427958008 3.02E - 05 0.003726774 2.473306046 FBN2 3.702098767 4.647001128 5.317540391 3.86E - 05 0.003963698 2.340945176 KRT4 -5.783585056 12.44990214 -5.27501498 4.24E - 05 0.004304541 2.251297748	MMP12	4.162521167	3./3654941/	5.638864584	1.91E - 05	0.002687547	3.011/10913
COL4A15.29599572211.058862925.6254307391.97E = 050.0027092522.979773595COL5A13.2051796228.6743017445.6044076532.05E = 050.0027092952.940368581ANKRD20A5P-3.1188266115.357065783-5.5742108892.19E = 050.0028731172.877727019TNXB-3.3901475448.386793894-5.464372672.79E = 050.0033455262.648949986CCDC25-3.3405721337.218539933-5.4610950792.81E = 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E = 050.0033259592.572791248MAL-6.3603311338.9132381-5.3804985083.36E = 050.0037267742.473306046FBN23.7020987674.6470011285.3175403913.86E = 050.0039636982.340945176KRT4-5.78358505612.44990214-5.275014984.24E = 050.0043045412.251297748	SCARAS	-3.80100340/	/.100380830	-5.054800255	1.92E - 05	0.002087547	3.003313833 2.070772502
CCDLSAT 5.205175022 6.07501744 5.004407055 2.05E = 05 0.00275295 2.940388881 ANKRD20A5P -3.118826611 5.357065783 -5.574210889 2.19E = 05 0.002873117 2.877727019 TNXB -3.390147544 8.386793894 -5.46437267 2.79E = 05 0.003345526 2.648949986 CCDC25 -3.340572133 7.218539933 -5.461095079 2.81E = 05 0.003345526 2.6421014 FN1 3.580535444 11.63254756 5.427958008 3.02E = 05 0.003345526 2.6421014 FN1 3.580535444 11.63254756 5.427958008 3.02E = 05 0.003726774 2.473306046 FBN2 3.702098767 4.647001128 5.317540391 3.86E = 05 0.003963698 2.340945176 KRT4 -5.783585056 12.44990214 -5.27501498 4.24E = 05 0.004304541 2.251297748	COL4AI	3.273773/22 3.205170622	11.03080292 8.674301744	5.025450755	1.9/L = 0.5 2.05E = 0.5	0.002/09232	2.7/7//3373
Invited 26000-5.1765260115.57605765-5.5742108672.17E = 050.0026751172.877727019TNXB-3.3901475448.386793894-5.464372672.79E - 050.0033455262.648949986CCDC25-3.3405721337.218539933-5.4610950792.81E - 050.0033455262.6421014FN13.58053544411.632547565.4279580083.02E - 050.0035259592.572791248MAL-6.3603311338.9132381-5.3804985083.36E - 050.0037267742.473306046FBN23.7020987674.6470011285.3175403913.86E - 050.0039636982.340945176KRT4-5.78358505612.44990214-5.275014984.24E - 050.0043045412.251297748	ANKRD2045D	-3 118826611	0.0/4301/44 5 357065783	-5 574210880	2.03E = 05 2 19F = 05	0.002/9293 0.002873117	2.740308381 2.877727010
Trans 5.550147544 6.560755054 -5.40457207 2.75E = 05 6.000545520 2.048949980 CCDC25 -3.340572133 7.218539933 -5.461095079 2.81E - 05 0.003345526 2.6421014 FN1 3.580535444 11.63254756 5.427958008 3.02E - 05 0.003525959 2.572791248 MAL -6.360331133 8.9132381 -5.380498508 3.36E - 05 0.003726774 2.473306046 FBN2 3.702098767 4.647001128 5.317540391 3.86E - 05 0.003963698 2.340945176 KRT4 -5.783585056 12.44990214 -5.27501498 4.24E - 05 0.004304541 2.251297748	TNXR	-3 390147544	8 386793894	-5.57 +210005	2.19E = 0.5 2 79F = 0.5	0.0023/511/	2.677727019
FN13.58053544411.632547565.4279580083.02E - 050.0035259592.572791248MAL-6.3603311338.9132381-5.3804985083.36E - 050.0037267742.473306046FBN23.7020987674.6470011285.3175403913.86E - 050.0039636982.340945176KRT4-5.78358505612.44990214-5.275014984.24E - 050.0043045412.251297748	CCDC25	-3 340572133	7 218539933	-5 461095079	2.77E = 0.5 2.81F = 0.5	0.003345526	2.6421014
MAL -6.360331133 8.9132381 -5.380498508 3.36E - 05 0.003726774 2.473306046 FBN2 3.702098767 4.647001128 5.317540391 3.86E - 05 0.003963698 2.340945176 KRT4 -5.783585056 12.44990214 -5.27501498 4.24E - 05 0.004304541 2.251297748	FN1	3.580535444	11.63254756	5.427958008	3.02E - 05	0.003525959	2.572791248
FBN2 3.702098767 4.647001128 5.317540391 3.86E - 05 0.003963698 2.340945176 KRT4 -5.783585056 12.44990214 -5.27501498 4.24E - 05 0.004304541 2.251297748	MAL	-6.360331133	8.9132381	-5.380498508	3.36E - 05	0.003726774	2.473306046
KRT4 -5.783585056 12.44990214 -5.27501498 4.24E - 05 0.004304541 2.251297748	FBN2	3.702098767	4.647001128	5.317540391	3.86E - 05	0.003963698	2.340945176
	KRT4	-5.783585056	12.44990214	-5.27501498	4.24E - 05	0.004304541	2.251297748

5

GeneSample	logFC	AveExpr	t	P value	Adj. P value	В
MSC	3.021481811	5.778950494	5.273063535	4.25E - 05	0.004304541	2.247179302
MYZAP	-3.966621	6.975986556	-5.218924365	4.80E - 05	0.00453758	2.132761995
CHI3L1	3.447755856	8.454925183	5.212706409	4.86E - 05	0.004565936	2.119601631
XLOC_008370	-4.086801056	5.071876417	-5.195774385	5.05E - 05	0.004618685	2.083744902
AMY1C	-3.066162922	4.171807861	-5.181124682	5.22E - 05	0.004702673	2.052698071
FAM107 A	-3.366929044	6.613174211	-5.153177492	5.55E - 05	0.004829406	1.993410827
CA9	4.004719489	4.832498267	5.105740988	6.17E - 05	0.005199505	1.89260426
SFI1	-3.172654489	7.898643289	-5.038975245	7.16E - 05	0.005657681	1.75036129
KRT24	-4.307497756	6.663276378	-4.903497209	9.71 <i>E</i> – 05	0.006802832	1.460515802
FAM3B	-3.002864178	7.472917967	-4.851035631	0.000109236	0.007385034	1.347873623
PSCA	-4.424161267	6.177034822	-4.836697273	0.000112824	0.007525305	1.317050516
TREM1	3.132156567	5.329140306	4.802412753	0.000121894	0.007755997	1.243287728
MMP7	4.0077695	8.433879583	4.797447382	0.000123267	0.007808567	1.232597743
XLOC_l2_007931	-3.335940244	10.48608082	-4.789159173	0.000125595	0.007875182	1.214750103
KRT6B	4.076616322	9.703940506	4.773184049	0.000130209	0.007978995	1.180336064
SERPINE1	3.5038576	7.4466057	4.752919626	0.00013631	0.008152053	1.136656679
ABCA8	-3.2918408	5.542601178	-4.749840302	0.000137262	0.008169717	1.130016856
SNX31	-3.294362333	3.714450967	-4.727065435	0.000144517	0.008363625	1.080888859
KRT16	3.956891967	10.74006252	4.71119429	0.000149801	0.008567571	1.046633089
RSAD2	3.410952911	5.3110705	4.667343136	0.000165442	0.009086152	0.951904596
CEACAM5	-3.982757711	9.060092478	-4.649201732	0.000172387	0.009343839	0.912681384





FIGURE 2: Volcano plot of gene expression and heatmap of DEGs. (a) The rows represent genes and the columns represent samples. The first 9 columns are tumor samples and the last 9 columns are normal samples. Red represents high gene expression, and blue represents low gene expression. (b) The red, blue, and green dots represent the differentially expressed genes between the tumor tissues and normal tissues of LSCC, among which the red represents the upregulated genes in the tumor tissues, the blue represents the downregulated genes, and the green represents the genes of logFC > 4, while the black represents the insignificantly different genes.

3.5. PPI Network Construction and Key Targets Screening. A PPI network based on the targets of ZJC active ingredients was constructed. It showed that ZJC had direct or indirect correlation with the 1572 targets, and there were 29,098 interconnections between these targets. At the same time, the PPI network was mapped for DEGs, and 2,262 targets were directly or indirectly related to LSCC, with 50,181 interconnections between these targets. Then, the intersections of the two PPI networks were used to construct a merged network with 510 nodes and 10950 edges (Figures 4(a)-4(c)). Furthermore, we analyzed the topological properties of the nodes in the merged network of the protein interactions to find the key nodes. Finally, 60 key nodes were identified through the network topology analysis (Figure 4(d) and Table 3).

3.6. KEGG Pathway Analysis and Main Module of the Core PPI Network. The KEGG signaling pathways analysis suggested that 60 key targets were mainly enriched in cell cycle, central



FIGURE 3: GO enrichment analysis and KEGG pathways analysis on DEGs. (a) GO enrichment analysis: the top 10 terms of biological process, cellular component, and molecular function with P < 0.05. (b) KEGG pathways analysis: the top 3 terms of KEGG enrichment pathway with P < 0.05.



FIGURE 4: Continued.





FIGURE 4: Identification of key targets for ZJC against LSCC. (a) PPI of ZJC targets. (b) PPI of DEGs in LSCC. (c) The intersections of the two PPI networks of ZJC and DEGs. (d) Topological screening of the interactive PPI network based on degree and betweenness centrality. The same type of the signaling pathway is represented by nodes of the same color, and the size of the node represents the significance of the signaling pathway. The higher the significance of the signaling pathway is, the larger the node is, indicating that the importance of the pathway is higher.

TABLE 3: The topological properties of the 60 key nodes.

Name (the key targets)	Degree	Betweenness	Betweenness centrality	Closeness	Closeness centrality	Topological coefficient
YWHAZ	155	3001.377571	0.01183919	0.585365854	0.58536585	0.14373835
YWHAG	87	816.3912445	0.00322033	0.537313433	0.53731343	0.16424877
MCM5	101	1080.133008	0.00426068	0.542518837	0.54251884	0.14457089
STAU1	114	1407.485881	0.00555195	0.550218341	0.55021834	0.13468492
ITGA4	208	7021.25165	0.02769593	0.616891065	0.61689106	0.10712371
АРР	125	5666 777349	0.02235309	0 557522124	0 55752212	0 10929128
CIII 3	211	7900 538977	0.03116436	0.626865672	0.62686567	0.1083315
CUL2	121	2103 400854	0.00865241	0.556906077	0.55690608	0.1311238
	121 Q4	1104 388860	0.00435636	0.510052523	0.51005252	0.14961657
CUL4A CUL1	150	2727 270054	0.00455050	0.519052525	0.51905252	0.12774442
CODE	158	2/3/.2/0054	0.010/9/4	0.5/99/0985	0.5/99/699	0.12774443
COPSS	1/3	4596.081368	0.01812964	0.592941176	0.59294118	0.11812865
YWHAQ	116	2340.926//	0.00923399	0.5532382	0.5532382	0.139556/1
EEFIAI	111	2303.865101	0.0090878	0.553846154	0.55384615	0.15/26594
OBSL1	151	2614.051749	0.01031135	0.572077185	0.57207719	0.11367624
TARDBP	99	902.4212542	0.00355968	0.540192926	0.54019293	0.14812918
HSPA8	102	1110.484051	0.0043804	0.549019608	0.54901961	0.1617004
HSPA5	124	2786.82878	0.01099289	0.56187291	0.56187291	0.15308876
HSP90AA1	115	3058.241745	0.0120635	0.558139535	0.55813953	0.13921995
EIF4A3	94	923.5252369	0.00364293	0.535031847	0.53503185	0.14405585
HSP90AB1	111	2024.466508	0.00798568	0.555066079	0.55506608	0.14751182
MYC	88	1227.898615	0.00484355	0.536741214	0.53674121	0.11599255
CCDC8	145	2628.810161	0.01036957	0.568848758	0.56884876	0.11392955
HDAC1	84	1756.679856	0.00692938	0.525547445	0.52554745	0.11154264
RPA1	106	1443.910092	0.00569563	0.544864865	0.54486486	0.13668578
RPA2	98	1508.905701	0.00595201	0.541353383	0.54135338	0.13008096
HNRNPA1	130	1803.567503	0.00711433	0.565656566	0.56565657	0.14709052
EGFR	143	4724.066642	0.01863449	0.572727273	0.57272727	0.1103327
HIST1H3F	86	437.5273205	0.00172586	0.529411765	0.52941176	0.14705882
UBC	133	3538 655204	0.01395853	0 566929134	0 56692913	012972445
CUL7	174	4304 231567	0.01697841	0 594339623	0 59433962	0.10695547
HNRNPK	90	914 3729176	0.00360682	0.535600425	0.53560043	0.17748918
TURE	95	1017 885462	0.00300002	0.537886873	0.53788687	0.16372140
HNDNDI	106	2301 609719	0.00401314	0.5378360875	0.537886087	0.15722622
CDV2	170	2391.090/10	0.00943420	0.547820087	0.54782009	0.13722022
EWSD1	172 95	1514 216962	0.02120079	0.592941170	0.59294118	0.15192716
CDCEL	05	1514.510602	0.00597333	0.552200909	0.55220097	0.13183/10
NEDD	06	2102.934909	0.00855196	0.530619072	0.53061907	0.13024984
	80 06	333.4510/89	0.00210425	0.528501887	0.52850189	0.14705092
HISTIHJA	86	437.5273205	0.00172586	0.529411765	0.52941176	0.14/05882
HISTIH3D	86	437.5273205	0.001/2586	0.529411/65	0.52941176	0.14/05882
TRAF6	100	2757.045931	0.01087541	0.538461538	0.53846154	0.09652163
HISTIH3C	86	437.5273205	0.00172586	0.529411765	0.52941176	0.14/05882
NPM1	156	3506.462925	0.01383155	0.58400927	0.58400927	0.14115178
HIST1H3E	86	437.5273205	0.00172586	0.529411765	0.52941176	0.14705882
HIST1H3I	86	437.5273205	0.00172586	0.529411765	0.52941176	0.14705882
HIST1H3G	86	437.5273205	0.00172586	0.529411765	0.52941176	0.14705882
FUS	109	1065.023899	0.00420108	0.551422319	0.55142232	0.157963
HIST1H3J	86	437.5273205	0.00172586	0.529411765	0.52941176	0.14705882
HIST1H3H	86	437.5273205	0.00172586	0.529411765	0.52941176	0.14705882
HIST1H3B	86	437.5273205	0.00172586	0.529411765	0.52941176	0.14705882
NTRK1	270	16394.02825	0.06466766	0.673796791	0.67379679	0.09989618
FLNA	89	1820.058448	0.00717938	0.537313433	0.53731343	0.15216314
FN1	307	27515.32665	0.10853658	0.708860759	0.70886076	0.09048518
SIRT7	128	2444.801055	0.00964373	0.5532382	0.5532382	0.11177503
GRB2	136	4533.847683	0.01788415	0.570135747	0.57013575	0.12538522
FBXO6	12.9	2240,28371	0.00883699	0.558139535	0.55813953	0.11844315
VCP	103	1651 524516	0.00651458	0.544864865	0.54486486	0.14998166
CAND1	152	2355 429527	0.0092912	0 578645235	0 57864524	0 12845528
XPO1	106	2555.425527	0.0072912	0.543103449	0.57004524	0.120+3520
MCM2	207	6633 522707	0.0261665	0.621454004	0.621/5/00	0.12403074
VWHAE	02	1174 474077	0.0201005	0.021404994	0.02143477	0.1100/275
I W FIAE	73	11/4.4/09//	0.00403283	0.33/313433	0.33731343	0.10200331



FIGURE 5: Vital terms of KEGG enrichment analysis of the key targets.





FIGURE 6: The two main modules of the core PPI network of ZJC against LSCC.



FIGURE 7: Continued.



FIGURE 7: Disease-free survival analyses and overall survival analyses of LSCC. (a)–(d) Disease-free survival analyses of NTRK1, COPS5, HIST1H3A, and HIST1H3G about LSCC. (e)–(g) Overall survival analyses of HIST1H3J, HIST1H3F, and ITGA4 about LSCC.

carbon metabolism in cancer, and DNA replication, indicating the mechanisms of ZJC in the treatment of LSCC. The other signaling pathways included prostate cancer, protein processing in endoplasmic reticulum, spliceosome, transcriptional misregulation in cancer, and ubiquitin-mediated proteolysis (Figure 5). Through the MCODE plugin, two main modules of the core PPI network were obtained, one of which was functionally enriched in alcoholism, transcriptional misregulation in cancer, and systemic lupus erythematosus (Figure 6).

3.7. LSCC Survival Analysis. To demonstrate the relationship between key genes and LSCC, we analyzed the genes in core module through the GEPIA online database and Kaplan-Meier curve. We found that LSCC patients with high expression of HIST1H3J, HIST1H3F, and ITGA4 had worse overall survival, while LSCC patients with high expression of NTRK1, COPS5, HIST1H3A, and HIST1H3G had significantly worse disease-free survival (Figure 7).

4. Discussion

Based on the network pharmacology analysis of drug and disease target, collateral relationship can effectively reveal the mechanism of ZJC in the treatment of LSCC. Here, we found 96 candidate targets of ZJC and 81 DEGs of LSCC. Then, we constructed the PPI network for them separately. The huge genes involved in the interacted PPI network were analyzed to derive the possible mechanisms of anti-LSCC of ZJC, including transcriptional misregulation cancer, alcoholism, and cell cycle.

In our study, we identified 11 active ingredients of ZJC, which synergistically regulated 96 candidate targets. A large number of published literatures showed that the 11 active ingredients had anticancer activities, respectively. As reported, fisetin could inhibit the proliferation and migration of human laryngeal cancer via ERK1/2 and AKT/NF-KB/mTOR signaling pathways and induce apoptosis in human lung cancer through the MAPK signaling pathway [15, 16]. It was also revealed that kaempferol and quercetin were potential to inhibit cell migration and invasion in human head and neck

squamous cell carcinoma [17, 18]. Li et al. emphasized that taxifolin may arrest aggressive breast cancer by promoting the MET progress through decreasing the expression of β -catenin [19]. Additionally, the inhibitory potency of flavanone on human breast cancer and gastric cancer has been reported previously [20, 21]. To our knowledge, no previous studies have explored the synergistic effect of the 11 active ingredients deriving from ZJC in suppressing LSCC development.

To investigate the possible mechanism of anti-LSCC of ZJC at a system level, we applied GlueGO to complete KEGG enrichment signaling pathway analysis, through analyzing the huge targets of the core PPI network in tight corresponding to LSCC and ZJC. We identified 11 items, in particular, transcriptional misregulation in cancer, alcoholism, cell cycle, and central carbon metabolism in cancer (all P < 0.01). It is apparent that both signal pathways of transcriptional misregulation in cancer and central carbon metabolism in cancer were closely associated with cancer [22, 23]. Sequentially, transcriptional misregulation in cancer was the most significant pathway following ZJC acting on LSCC (P < 0.001). As reported, cancer is more likely to occur in the mucous membrane in direct contact with alcohol; therefore, an intermediate increase in the risk of laryngeal cancer was found among alcoholics [24]. Aberrant cell cycle results in uncontrolled proliferation of cells, which is the common nature of cancer [25]. Zhou et al. demonstrated that Erchen decoction plus Huiyanzhuyu decoction was promising medicine in treatment of LSCC through inhibiting the cell cycle and inducing apoptosis of LSCC cells [26]. Protein processing in endoplasmic reticulum (ER) is crucial for the pathogenesis of cancer, with severe ER stress closely related to the development and invasion of cancer [27, 28]. These findings were consistent with the network pharmacology analysis.

5. Conclusion

Our study revealed that the anti-LSCC mechanism of ZJC was closely connected to transcriptional misregulation cancer, alcoholism, and cell cycle signaling pathway, which provided an important basis for further discussion of the follow-up experiment al design, making the experimental research more reasonable and more instructive.

Data Availability

The original data series GSE84957 used to support the findings of this study is downloaded from the Gene Expression Omnibus (GEO) microarray dataset.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Feng Xiang conceived the study and drafted the manuscript. Guiyuan Peng analyzed and interpreted the data and reviewed the manuscript. Shasha Li instructed the research and reviewed the manuscript. Linman Li and Jieling Lin contributed to conception and design of the study. All authors revised, read, and approved the manuscript.

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