Screening the Hub Genes and Analyzing the Mechanisms in Discharged COVID-19 Patients Retesting Positive through Bioinformatics Analysis

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Abstract

Background: With the worldwide spread of COVID-19, people's health and social order have been exposed to enormous risks. After encountering patients who test positive again after discharge, our study analyzed the pathogenesis to further assess the risk and possibility of virus reactivation.

Methods: A separate microarray was acquired from the Integrated Gene Expression System (GEO), and its samples were divided into two groups: a "convalescent-RTP" group consisting of recovery and "retesting-positive" (RTP) patients (group CR) and a "health-RTP" group consisting of healthy control and RTP patients (group HR). The enrichment analysis was performed with R software, obtaining the gene ontology (GO) and Kyoto pluripotent stem cells (KEGG) of the genes and genomes. Subsequently, the protein–protein interaction (PPI) networks of each group were established and the hub genes were discovered using the cytoHubba plug-in.

Results: In this study, 20 differentially expressed genes were identified, and 6622 genes were identified in the group CR, consisting of 5003 up-regulated and 1619 down-regulated genes. Meanwhile, 7335 genes were screened in the group HR, including 4323 up-regulated and 3012 down-regulated ones. The GO and KEGG analysis of the two groups revealed significant enrichment of these differentially expressed genes in pathways associated with immune response and apoptosis. In the PPI network constructed, 10 hub genes in group CR were identified, including TP53BP1, SNRPD1, SNRPD2, SF3B1, SNRNP200, MRPS16, MRPS9, CALM1, PPP2R1A, YWHAZ. Similarly, TP53BP1, RPS15, EFTUD2, MRPL16, MRPL17, MRPS14, RPL35A, MRPL32, MRPS6, POLR2G were selected as hub genes.

Conclusions: Using the messenger ribonucleic acid (mRNA) expression data from GSE166253, we explore the pathogenesis of retesting positive in COVID-19 from the immune mechanism and molecular level. We found TP53BP1, SNRPD1 and SNRPD2 as hub genes in RTP patients. Hence, their regulatory pathway is vital to the management and prognostic prediction of RTP patients, rendering the further study of these hub genes necessary.

Introduction

The coronavirus disease 2019 (COVID-19), induced by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a global public health crisis. Typical symptoms of the disease are fever, sore throat, fatigue, cough or dyspnea^[1]; droplet transmission is the main route of transmission, with close contact providing an opportunity for such virus transfer^[1, 2]. As of October 1, 2021, there are 233,136,147 confirmed cases throughout the world, including 4,771,408 deaths reported by the World Health Organization (WHO)^[3].

So far, a large number of patients have been cured and discharged from hospitals. However, some, described as "retesting-positive" (RTP) patients, were retested positive for SARS-CoV-2 after discharge. According to a systematic review, the RTP cases accounted for about 12% of discharged patients^[4] with the median duration of viral shedding in RTP patients after admission being 14.0^[5]. Most of these patients' clinical results revealed moderate severity conditions along with clinical symptoms including cough, sputum production, headache and dizziness^[6]. As for the cause of RTP, the related researches focus on the false-negative RT-PCR testing at discharge^[5] or the persistence of the virus and periodic shedding in the gastrointestinal tract^[7]. However, there still remain concerns that discharged patients may be at risk of viral reactivation and should be considered potential sources of SARS-CoV-2 infection, which may become a public health crisis. Therefore, further exploration of the impaired immune function and pathogenesis is required.

Based on the previous study in immunology, a higher level of white blood count (WBC) was independently relevant to RTP by RT-PCR^[8]. Besides, patients infected with COVID-19 also exhibited higher leukocyte numbers and elevated plasma pro-inflammatory cytokine levels^[2]. Additionally, compared with convalescent patients, they presented lower levels in lactate dehydrogenase (LDH) at the first week after admission but higher levels in eosinophil count^[9]. According to Yao MQ et al., patients presenting with decreased leukocyte, platelet and CD4+ T counts were at a higher risk of RTP^[6]. Xiangying Ren et al. revealed that ribonucleic acid (RNA) of viral could still be detected in patients with SARS-CoV-2 specific immunoglobulin M (IgM) and immunoglobulin G (IgG) present^[4]. Besides, a systematic review presented that it's predictive to recognize RTP through a combination of lower high-sensitivity C-reactive protein (hs-CRP) and higher WBC^[8]. Overall, little is known about RTP in immunology and pathogenesis, and many results are in conflict with the previous study.

Therefore, we believe that it is necessary to analyze the biological information of the samples. The research results may further expand the insight into RTP events in COVID-19 by analyzing the RTP immunological characteristics and molecular pathogenesis genes of peripheral blood mononuclear cells containing RTP patients, convalescent patients and healthy control subjects.

Materials And Methods

Data collection

Aiming at analyzing the biological information of RTP patients, initially, we performed a search of the Gene Expression System (GEO) data using SARS-CoV-2 as the keyword (ncbi.nlm.nih.gov/geo/). Dataset GSE166253, contributed by Wang D et al., was found and used in our study (Table 1). The sequencing platform employed was the GLP20795 HiSeq X Ten (Homo sapiens). The dataset consisted of 10 retesting-positive (RTP) samples, six convalescent and 10 healthy ones, with the sample source containing the peripheral blood mononuclear cells (PBMCs) of human beings. To analyze the pathogenesis of RTP occurrence in COVID-19, we divided the samples into two groups: a "convalescent-RTP" group comprising of convalescent patients and RTP patients (group CR) and a "healthy-RTP" group of healthy controls and RTP patients (group HR).

Screening of DEGs

After acquiring the gene expression data, the R pack (R Foundation for statistic computing) was utilized, and the Fold change (FC) and P-value were calculated to identify the differentially expressed genes (DEGs) from the two groups (CR and HR). Following this, in the R language program, $p < 0.05$ and $|\log_2 FC| \geq 1$ were designed as the threshold, and the genes that met the criteria were sifted out as DEGs. Finally, we constructed volcano plots and heatmaps to visualize all the DEGs of GSE166253.

Functional Enrichment Analysis

The GO annotation can be divided into three categories: biological process (BP), cellular component (CC) and molecular function (MF). In our study, we execute the GO function and KEGG pathway enrichment analysis for the DEGs, with the P-value < 0.05 deemed statistically significant.

Establishment of PPI and Screening of Hub Genes

Exploring functional interactions between proteins is crucial to understanding the molecular mechanisms of RTP for the COVID-19 infection. The Search Tool for the Retrieval of Interacting Genes (STRING), an online tool to assess and integrate PPI information, contains physical and functional associations^[10]. To find the potential correlations to the DEGs, we employed STRING to map their PPI network. If the interaction score was > 0.4 , then it will permit protein interaction. To draw an interaction of DEGs, the Cytoscape software was used to visualize the PPI network. To examine the protein interaction further, we employed this on the basis of the PPI associations to screen out hub genes. Finally, the immune infiltration analysis was performed for the two groups to further confirm the results of our study. The results of the immunoblotting analysis are attached to the supplementary document.

Results

Screening of DEGs

Downloading the GSE166253 dataset from the GEO database, we conducted differential expression analysis using the R language. In group CR, 20376 DEGs were identified, containing 5003 up-regulated and 1619 down-regulated genes (Table 2). Simultaneously, 20376 DEGs were found in group HR, consisting of 4323 up-regulated and 3012 down-regulated genes (Table 3). Subsequently, volcano plots and heatmaps were performed to present the DEGs in both groups (Fig.1 and Fig.2). The volcano plots depicted upregulated (blue) and downregulated (red) genes, while the heatmaps presented the expression levels of the DEGs.

Functional Enrichment

With regard to the CR group (Table 4), the GO analysis in the biological processes demonstrated that the DEGs were significantly enriched in the processes that neutrophils are involved in, such as the activation of neutrophil, neutrophil-mediated immune and neutrophil activation participated in immune response. As for the cellular components, the mitochondrial inner membrane and mitochondrial protein complex were predominantly recognized. Besides, the terms of the most enriched in molecular functions were associated with transcription coactivator activity as well as magnesium ion binding (Fig.3a). Moreover, according to the KEGG enrichment analysis results of group CR (Table 5), three significant pathways of DEGs were identified, containing endocytosis, nucleotide-binding oligomerization domain-like receptors (NOD-like receptor) signal path and tumor necrosis factor (TNF) signal path (Fig.3b).

Similarly, the results in group HR were shown as follows (Table 6): the GO enrichment in biological processes revealed that DEGs were primarily located on neutrophil activation, neutrophil-mediated immunity as well as neutrophil activation participating in immune response. In terms of the category of cellular components, the mitochondrial inner membrane, mitochondrial matrix and nuclear speck were chiefly enriched. For molecular functions, the mitochondrial inner membrane, mitochondrial matrix and nuclear speck were significantly identified (Fig.3c). In the KEGG pathway enrichment analysis (Table 7), a total of 10 key pathways were found, especially the pathways associated with prion disease, Huntington's disease and Parkinson's disease, which take part in the corresponding neurodegenerative disorder (Fig.3d).

Establishment of PPI and Screening of Hub Genes

We constructed the PPI networks for both the CR and HR groups, after which the top 10 genes with the highest degree of connectivity were determined using the Cytoscape and cytoHubba plugin (Fig.4 and Fig.5). In group CR, 1246 nodes and 5665 edges were included in the PPI network for up-regulated DEGs (Fig.4a), while 1060 nodes and 613 edges were found in the PPI network of down-regulated DEGs (Fig.4b). Afterwards, TP53BP1, SNRPD1, SNRPD2, SF3B1, SNRNP200, MRPS16, MRPS9, CALM1, PPP2R1A, YWHAZ were identified as hub genes (Fig.4c). As for group HR, 1223 nodes and 1257 edges were found in the PPI network of up-regulated DEGs (Fig.5a), whereas for down-regulated DEGs, 732 nodes and 228 edges were found in the PPI network (Fig.5b). With the same methods, 10 hub genes, including TP53BP1, RPS15, EFTUD2, MRPL16, MRPL17, MRPS14, RPL35A, MRPL32, MRPS6, POLR2G, were screened out and their interactions were displayed in Fig.5c.

Discussion

With the spread of the COVID-19 epidemic, the situation of RTP for SARS-CoV-2 after discharge renders the management of discharged patients a difficult problem^[11], potentially leading to a public health crisis. At present, there is still no definitive conclusion about the cause of RTP, and the possibility of their re-infection and disease transmission cannot be ruled out. In this study, the peripheral blood samples of RTP patients, convalescent patients and healthy people were divided into two groups—CR and HR groups, and the immune mechanism of COVID-19 RTP was explored based on the results of the enrichment analysis.

Through the GO analysis for both the groups, the immune processes' neutrophils involved and the mitochondrial function and contents were significantly enriched. As Cynthia Magro et al. studied, patients with COVID-19 had markedly increased neutrophils^[12]. The extracellular bactericidal networks (NETs) of SARS-CoV-2-activated neutrophils are considered important in the progress of the COVID-19 infection, and releasing NETs in lung tissue could result in the death of lung epithelial cells^[13], indicating that the immune processes that neutrophils are involved in RTP patients may be more activated in lysing infected cells and release the virus. The mitochondria plays a variety of interrelated functions in cellular metabolism, producing adenosine triphosphate (ATP) and many biosynthesis intermediates, as well as participating in stress responses such as autophagy and apoptosis^[14]. Studies have pointed out that the monocytes of patients with COVID-19 accumulate dysfunctional mitochondria, resulting in their metabolic defects, decreased OXPHOS and glycolysis, impaired oxidative burst, altered immune response and possibly increased susceptibility to secondary infections^[15]. RTP patients may experience more intense mitochondrial dysfunction. Additionally, mitochondrial dysfunction was a key factor in neurodegenerative diseases^[14], which also corresponded to the KEGG-rich pathway in the HR group (prion disease, Huntington's disease)—this may be related to the prognosis of RP patients.

Apart from neurodegenerative diseases, the KEGG analysis of both the CR and HR groups also revealed that endocytosis, the NOD-like receptors and TNF pathways were the main enrichment pathways. Endocytosis plays a vital role in the infection of disease and restoration of health. Recent studies have suggested that the key event supporting the SARS-CoV-2 infection may be the endocytosis of viral particles^[16], which may be more intense in RTP patients. NOD-like receptors (NLRs), a class of pattern recognition receptors (PRRs)^[17], can recognize ligands from microbial pathogens, host cells and environmental sources, then activate an inflammatory response^[18]. Similar to mitochondria, NLRs play a significant part in regulating apoptosis, acting as a key regulator of apoptosis as well as aiding in early development^[16] and directing autophagy by recruiting ATG16L1 to the plasma membrane at the site of the bacterial entry sites^[19]. The TNF superfamily is a multifunctional proinflammatory cytokine that participates in the processes of cell survival, apoptosis induction, inflammatory response and cell differentiation^[20]. In the SARS-CoV-2 infection, innate immune cells will produce a variety of inflammatory cytokines, but only the combination of TNF- α and IFN- γ can damage vital organs by inducing the death of inflammatory cells^[21]. In summation, the NOD-like receptors and TNF pathways may contribute extensively to RTP patients through apoptosis and inflammatory response.

Since the results of the HR group cannot exclude the interference with the COVID-19 infection, we selected the hub genes of the CR group for discussion next, with the HR group taken as verification. TP53BP1 was enriched in both groups, and its expression in the CR group was downregulated. TP53BP1, one of the regulator genes of TP53, is known to be highly associated with the DNA damage signal pathway, checkpoint signal and DNA repair capacity^[22]. Moreover, it has been associated with cancer and neurological diseases^[22, 23]. In the immune system, DNA repair factors TP53 can support immunoglobulin class switch recombination^[24]. B cells are critical for the production of antibodies and protective immunity to viruses, and Tan et al. discovered a stronger antibody response is related to delayed viral clearance as well as disease severity^[25]. According to their research, the downregulation of TP53BP1 resulted in a lower antibody response, indicating a higher level of viral clearance in RTP patients. In a study on the mechanisms of the maintenance of foot-and-mouth disease (FMD) virus persistence, TP53BP1 in the persistently positive group was also significantly downregulated. It was reported that the downregulation of TP53BP1 could inhibit the Th17 response, natural killer cell (NK cell) cytotoxicity and apoptosis^[26]. The main effector of Th17 cells is IL-17, while the lymphocytes in COVID-19 patients can produce more IL-17, and blocking IL-17 could be a novel therapeutic strategy for COVID-19^[27]. The lower expression of IL-17 in RTP patients may lead to milder symptoms. Preliminary studies of patients with severe COVID-19 indicate that the decrease in the number or function of NK cells will reduce the clearance of infected and activated cells^[28]. Moreover, the limitation of apoptosis and reduction in clearing infected and activated cells may lead to the slower death of infected cells, resulting in the longer discharge of RNA of SARS-CoV-2 in RTP patients.

SNRPD1 and SNRPD2 are both up-regulated in group CR, with the main regulatory pathway of the former being the mRNA splicing^[29]. The study confirmed that spliceosome machinery is a replicative machinery of SARS-CoV-2 for evading host challenges, which may prove that the replication activity of SARS-CoV-2 is more active in RTP patients^[30]. According to Xiaofeng Dai et al., SNRPD1 over-expression is observably connected to genes involved in the cell cycle, cell mitosis and chromatin replication, and the expression of SNRPD1 in malignant or the number of hyperproliferative cells is higher than in normal cells^[31]. The high correlation with the cell cycle in SNRPD1 expression emphasizes that the cell proliferation of RTP patients may be more active. Similar to SNRPD1, SNRPD2 regulates mRNA splicing and is highly associated with Alzheimer's disease, which is similar to the KEGG results in group HR.

In our study, many enriched pathways and the effects of hub genes are related to apoptosis, which could be evidence of the hypothesis that the cause of reactivation leads to delayed virus clearance^[7]. The immunity in RTP patients, the immune processes' neutrophils involved, endocytosis, NOD-like receptors and TNF pathways, as well as the immune cell function regulated by the hub genes, still require further research to explore their characters in RTP. Besides, the pathway of neurodegenerative diseases was significantly enriched, which makes the management and close attention of the RTP patients crucial.

However, due to the discrepancy in the theory of RTP and the small number of samples, our study has limitations. To make up these limitations, we expect further studies with larger samples to explore the association between each hub gene and the role of the pathways in RTP.

Conclusion

In general, using the biological analyses, we have explored the pathogenesis of RTP occurrence in COVID-19 from the immune mechanism and molecular level. With the analysis of DEGs, we found TP53BP1, SNRPD1 and SNRPD2 as hub genes that are considered vital to apoptosis, changes in immune cell function, cancer and neurodegenerative disease. We regard apoptosis as a key pathway in the persistence of the virus and its periodic release. Besides, the prognosis of RTP patients should be of concern because the pathway is regulated by hub genes in cancer and neurodegenerative disease. With these findings, the mechanism in RTP and related management measures for RTP patients would induce further clarity. However, aiming at deepening the understanding of the immune mechanism in RTP patients, we expect future studies to further explore these at the genetic and immunity levels.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The GSE166253 datasets used during the current study is available from GEO database(<https://www.ncbi.nlm.nih.gov/gds/>).

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Xu-Guang Guo provided the original idea and constructed the article outline. Ke-Ying Fang, Gui-Ning Liang, Zhuo-Qing Zhuang, Yong-Xin Fang, Yu-Qian Dong, Chuang-Jia Liang, Xin-Yan Chen, were responsible for data analysis, table making and manuscript constructing. All the authors read and approve the final version of the manuscript.

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Footnotes

Not applicable.

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Tables

Table1

Details of the data sources for this study.

Table2

Upregulated genes and downregulated genes that meet the screening criteria in group CR

Gene expression profile	Sample collection	Sample genetic data included	Platform	Reference
GSE166253	peripheral blood mononuclear cells	GSM5066812	GPL20795 HiSeq X Ten (Homo sapiens)	
		GSM5066813		
		GSM5066814		
		GSM5066815		
		GSM5066816		
		GSM5066817		
		GSM5066818		
		GSM5066819		
		GSM5066820		
		GSM5066821		
		GSM5066822		
		GSM5066823		
		GSM5066824		
		GSM5066825		
		GSM5066826		
		GSM5066827		
		GSM5066828		
		GSM5066829		
		GSM5066830		
		GSM5066831		
		GSM5066832		
		GSM5066833		
		GSM5066834		
		GSM5066835		
		GSM5066836		
		GSM5066837"		

DEGs	Gene terms
Up-regulated	<p>DUSP11,KANK1,LZTR1,EEF1A1P19,VMAC,FOSL1,CTSZ,IFITM5,ARHGEF1,B3GALNT2,HLA-DRB5,MCM3,H3F3B,SLC25A6,CD79B,HLA-F-AS1,TRBV10,DT,PQLC1,GNAL,ACTR3,PIM2,ZDHH4P1,SNORA9B,MYO6,ALOX5APHSD17B13,AOAH1T1,TBC1D16,WASF2,RTF4,SIGLEC10,CD52,HSP90B1,GIMDOA,PGLYRP1,SF1,HMG5,CASP17P,SLC4A1,APDNAJA3,NADSYN1,SLC25A36,CD48,CD200R1,SLC39A13,ARHGEF10L,CEACAM8,RBM12B-AS1,AS1,FCER2,SCARNA9,CLCF1,RNF181,PECR,GAB2,SCARNA8,SH3TC1,SLC25A40,SMAD1,VBP1,SMG1P5,RASSF2,DOCK9-D,STK10,MAP3K12,MEAS1,RDH14,CD99P1,SEMA3F,NUDC,KRBA1,PYGL,TARS2,ZNF410,HSP90AB1,CAPG,LYAR,MOB2,RNF146,HNRNP3A15,CALU,B3GNT7,Z83843.1,DOB,SERTAD3,RN7SL329PSAT2,XBP1P1,TIMMDC1,UBALD1,APOL3,NMRAL1,APTR,CCDC9,MALSU1,WDR81,FCN1,TXNDC5,RASA2-IT1,SMTNL1,AS1,MAPK8,GIMAP8,LRCH3,PLAGL1,ZMYND8,APOLD1,GASAL1,QPCT,DICER1,NBPFF1,CASTOR2,UACA,CARD9,KAT2B,MARK4,COLQ,OGFOD3,TR805P,CRELD1,AC103810.5,IFI6,LMMB1,DNHD1,XRRA1,ABHD4,HACL1,CCT6A,KLHDC8A,EIF4EBP3,EDF1,PCF11,WASF1,TBC1D30,SLC27A4,TMCCDT,USP15,TRAJ24,Z98752.2,NAP1L4,EFCAB2,ZNF18,MAP4K4,C1QL3,WDR18,CD14B,RAB6B,NPM1P25,PPM1L,RWDD3,CIAO3,COPB1,MYBPH1,1,JRKL,PZPCDK3,TMEM161B,MIAT,GBP6,UBL5,GTTF2IRD2,WAPL,MRPS5,PARS2,ADD2,FRG1,CREBZF,PARP14,STK17B,CUTC,WDR11-AS1,MED28,AS1,MITF,PRR16,ILVBL,FDPSP3,FCRL3,SLC1A4,THOC2,AIMP2,KCNK5,TRIM51BPZSCAN25,ENTPD2,TMEM245,LPP0AS2,ATP5MC1P3,TBCA,ZN59PCDK10,COX6A1,AC243960.3,ZNF318,KCNH3,OXSR1,PDF,PCNPP1,PHF7,DEFA1B,MICAL3,TLN1,COPS7B,LINC01465,SNORA63C,PRKD2,AKR1AS1,NHSL1,GTSCR1,YDJC,TMF1,CDK20,MBD1,TMEM150A,POLR3D,HERC5,ZNF69,NFE2L2,TMEM120A,TMEM126B,SMIM10,IGHV4-59,COCH,M807PGSDMD,TGIF2,MRPL46,DEDD,TMEM158,STX1B,TEKT2,TBC1D2,OR7E140PCLP1,RBBP4P1,CKAP2,AATK,COMMD9,SLC27A4,CHK21,ZNHIT1,AS1,SLC25A42,RNU6-623PCYCS,PIK3AP1,MPV17,AMDH1,NARF,MCMBPAC139530.1,TCEA1P4,ITI4,PRR11,GJB2,NUDT17,SMG9,CASD1,NSL1,AS1,SMAP1,CD27-AS1,TGS1,L3HYPDH,SLC28A3,DCST1,NECTIN4,FRG1DP,PCGF1,CLIC5,MPST,HEXIM1,SIKE1,BBIP1,TRBV12-3,AL096865.1,CLE275PFBLLN2,EOTG,HEATR9,CMT1,POM121B,CCSER2,NDUFA17,WB,UGP2,IMPAT1,CWC15,COX7B,AGAP9,APOL6,TAZ,SPARC,CHMP4B,UQCQRQ,IN,AS1,ZBED1,PMAIP1,MRPS24,AKR1C3,ENTR1,RAD54L,MICAL2,SLC25A34,PRRT4,ATXN2,IKZF1,FKBP1B,CBY1,SMPDL3A,OLFM1,STN1,TRAF7,ADT,ACSS2,C7orf26,COL4A3,ELOB,POLR2H,ENKD1,WDR91,ATP5ME,COP1,RAPGEF1,VPS26A,ZNF573,UQCRRF1,DHRS4L2,MRPL47,MDM1,XCL1,AS1,FKBP5,XPNPEP1,NTSR1,AC025917.1,AP1M1,TRBV10-2,MMP17,NDUFA4P1,FBXO46,CEP120,CAC3C,POMGNT1,WDR3,CYB5B,SLAMF6,ZN,AS1,CD93,NSRP1,NCAPG2,TENT5A,PTPRC,AKAP12,AL662907.1,C2CD4D,HMB5,MIER3,DDX56,ZNF582-AS1,MRPL54,MYO19,TGPS2,NUPL2,CBI,AS1,SLC1A7,SPRY3,CLTB,AGAP1,SPATS2,AL645939.2,ZNF165,SPEN,NAA25,CCNL1,HECA,PRRC2B,AC003072.1,GATAD2B,RRP1B,CYB5A,UBE2D4,DISC1,NBEAL2,CCER2,AQP9,RPL26P9,AL355987.4,USP14,PMS2L3,MS4A4A,IPGK1,TRAJ10,TIPRL,ZBTB25,SNORA80B,DCMFD13,CHK21,ZNHIT1,AS1,RCCD1,CAMK1D,RRBP1,TRPM7,SMARCD1,AES,ODF3B,TPR,ASB14,MEAF6,GP5,USP22,IL12RB2,CLC,MRTFA,GHRL,TUBA1A,NOLC1,ALDH3B6,COASY,DEX1,MICU3,TRAPPC10,COPS9,TRIP11,IARS,IPPK,KDM2B,AC079305.3,C4BPA,BOK,SIGLEC8,MORC3,CD36,SNRPD2,ZDHH4P1B,CITED257P,DEID2,ARL16,FBXW8,ZNF26,PHF21A,ACTR6,NCBP3,C1orf109,BORCS5,CYHR1,GLT8D1,MECP2,MRPS17,AC007342.6,LINC00122,TRGV5,CRIP,AS1,TYW5,ADGRE2,MTMR3,DSC2,ERO1A,XBP1,OMG,ALG9,ATPCKMT,TTHAP9,SMPD4P1,MAN1A2,EXOG,SPTBN1,PTGIR,SPINDOC,DNTTIP1,ST,AS1,AC132192.2,KMT5C,SPRY1,KCNRG,REXO1,CTC1,SOS2,TDP2,MED25,CHCHD2,ADRM1,C6orf203,MMAB,TP53TG1,LRCH4,BEX1,HSPBP1,AN,AS1,KCNMB4,RNF214,NIPAL2,FLI1,ANKRD54,OSBPL9,COX6CP1,JMJD6,MTF2,KNL1,MCMA,AL161757.2,FCMR,NCKG1,GNMT,QKBX1,VPREB3,4,AP001266.2,SNX18,LINC01678,SYNPO,DNASE1L3,CUL1,NPC1,UBE2Q2P1,PRCC,ZNF672,FSCN1,UCN,SLC30A1,ID1,DPP7,TDRD3,GNGT2,PDZD603P,SLC25A12,FMO5,PCYT2,TMEM81,EXOC3-AS1,UCKL1,PSMB9,MTG2,SLC17A9,KLKB1,DYPD-AS1,XPNPEP2,RBM22,PDXP,WIP1,BCL9L,ARSL,AS1,UPF1,LNCAROD,PER3,DPAGT1,HDDC2,PADI2,SDAD1,EZH1,AC025164.1,CRTC3,SOX12,HERC6,EEF1E1,SNRPCP3,SENP7,CETP,NDUFA13,TRA,AS1,SMPD1,MPP5,SNORD12C,ARL15,TRIQK,CMPK2,CHRNA10,GF1B,SPG7,IGHJ5,GRIN2C,ZNF554,DTX4,ACADVL,THRB,HSPE1P11,AC244157.1,IT1,AC011450.1,BNIP3,C12orf65,MYDGF,METTL7A,AP005019.1,ADAP2,C9orf16,DPEP2,PGBD4,WBP2,MAN2A1,GPER1,SKAP2,MICA,ARRDC2,AK13,LHPPLINC02453,AC016999.1,STMN3,POU5F1P3,CARS2,LINC02356,ATRIPNEM,IP07,COPA,AC010326.4,ALG13-AS1,ERMP1,SNX11,PKD1,G,AS1,FAS,RCL1,EMC2,OR2A20PAC008115.2,EID1,KATNAL2,AL133406.2,MIR302CHG,AC138393.2,PEG13,DNA2,AC087741.2,TBC1D23,AL596202,IT2,PIGG,PFKFB4,LAT2,ZDHH41,TNRC6C,SH3YL1,RF00560,AC004477.3,ABCC13,TTCT17,LDHAL6A,COMMD2,HSD17B7P2,MLX,EPMD2A,MINCRL,IT1,SPTAN1,GYPA,TRAV5,PPP1CA,GMEB1,NDUFB11,E1F1AD,ERP44,SLC18B1,CTSO,ZSCAN26,MIR3198-1,RNU6-662PHDLBPNAMPTP1,CIN95C,625PGBP1P1,TTCC22,RPL30,SNORD124,MSANTD2,AC006111.2,RAI1,BBS7,ELAC2,PCOLCE,TRAV20,PRR13P2,LSM12,ABCA1,C1orf35,HLA-DPB1,DT,TLR5,KLHDC8B,EXOSC4,UBA52P5,ST6GALNAC4P1,APOBR,EMB,CLNS1A,MORC4,CADMA4,REXO4,RAB18,AC025171.3,AC087854.1,TIMM23B,AS1,AF131215.6,FRYL,ADARB2,CDH26,NCAPG,NHP2,ZNF607,R3HDM2,LINC00482,UCBD1,AMMECR1L,ZC3H6,EVA1C,C3orf33,PLA2G6,NRDE2,TR,AS1,KIFC3,EMBP1,MTX3,GIPR,AC023509.3,REPS1,TRAJ16,NVL,AC116366.1,SLC22A1,LINC02265,PVR,ADGRB1,AVL9,EBPL,COQ10BP2,NCAPD3,AS1,NUP210,TMEM88,FAM161B,AC027176.2,F0082796.1,IGHG3,SRRM1,MAP3K10,C16orf87,TDRD6,FAM234A,SNHG14,POLD4,PPIP5K2,COMA479PCH2,EFL1,C19orf44,MVD,SNORA38,FAHD2CPT0B2,EZH1,AC008753.3,USP31,STK39,IFT52,TMEM242,CCDC200,ERLIN1,UPK3A,AS1,AASS,GTTF2IP12,SIRT6,FAM49A,ARL2BPPATZ1,PTAR1,HIST2H2AA3,YBX1P2,AC008750.2,WDR19,NCAPD2,AGAP10P,CTEX1D1,AL354877.106PPIGZ,YWHAG,PIEZO1,LINC00847,RF00154,AL353622.2,IGHD,CYP4F29PSPDYE12P,PCLEC9A,PEX10,CRYL1,BUB1B,ERCC4,HERC4,SIK1,CA3-AS1,SLC2A9,RRP12,ATP6V1FNB,MFGE8,TMEM254,COX20,PPARA,ILRLB1,CCDC92,HIBCB,KRBOX4,GALNT2,SNORA40B,GARS,TAS1R3,TRMT10,1,BCL2L15,ANKRD52,AC008035.1,AC090181.2,ZKSCAN5,RAP1GAPDPY19L2P2,PWP1,SNORD72,MINDY3,CCL2,CRYZP1,YIPF2,TRAV38-2DV8,G,DT,AC244197.3,MEIS1,AL158163.1,ARL14EP,AL031963.3,SUCLG1,ZUP1,C8orf33,CD14A,HDAC4,EPHX1,LINC01474,NTNG2,EPB41L4A,ENKUR,AD0PNEIL1,KR11,PRKY,EVI2B,COX14,BCDIN3D,SFXN5,AC009041.2,LINC01988,GOLGA8B,ITPR3,TRAJ5,RF00573,AC006946.1,XKR3,LINC00888,LT,AS1,DGAT2,AC022960.1,LEXM,CLPTM1,CCDC82,Sep_9,AC037459.3,THBS4,POLE4,FITM1,AC124016.2,TEX45,SMDT1,FUND2,MPLKIPLINC022AS2,AP000866.6,HP1BP3,MED6,PIGU,LGALS12,C12orf43,AC006960.3,NLRC5,AL590714.1,AC012313.10,CCDC106,TRAJ21,AC117503.2,ZNF552</p>
Down-regulated	<p>HBEGF,CXCR1,HBD,TARDBP,FTLP3,FTH1P16,MTRNR2L2,HBB,TNFRSF12A,GAPDHP14,LARP1,BCL2L11,CXCR6,C5orf15,HIF1AN,NANS,CXCL5,TC,AS1,SH2D1A,WWC3,ACSL3,PFKM,CXCL16,MOB4,CD84,MAP4K1,LPCAT4,PGM2,ARF3,CCR12P,FOSL2,MMS22L,RNF122,PILRA,IRF4,IREB2,LGALS14,MTCO1P11,B3GNT8,FOXO4,H1FX-AS1,EME2,TRG-AS1,ATP1A1-AS1,ARF4-AS1,KCTD5,P2RX1,RAB24,PHF12,SLC35E4,EHD4,TSHB,GSTP1,SC646P,TIMP2,PTGFRN,ABCA11P,TPPP3,ELK3,ATP13A1,SMURF2,OOSP3,ZNF467,KLF5,GPR89B,STX3,CRIM1,ZBED3,RBBP4P2,ZNF845,MPEG1,ZB50P,HSPA1A,SPIDR,TRAJ3,GPR75,WHAMMP2,EMSY,MYADM,CHPF2,Z97180.1,ZNF677,PPP1R8,ODF2,VIPAS39,SLC25A17,CCDC78,TDP1,ADAM,AS1,ZFR,CHST8,SMC1A,BRD3,TSC1,SPSB2,FTLP2,ZNF79,SLC24A3,HSD17B1,GRN,ITCH,MIR7854,GPATCH1,ZNF655,NFIA,FNTA,MIPPCOR02B487PPDE4D,ISG15,AC004854.2,ZBED4,ZNF185,AC016949.1,MIR6763,PTPRJ,ARL61P4,YPEL5P2,ZNF33B,HOXB2,TFFDPI1,LONRF3,ACSL4,WDR3,AS1,MIR219A1,ANAPC1,NR2C1,PLD2,GK3P,TMEM168,TRIM27,UCK1,ARID4B,PLEKHG5,PARBP,TANC2,TAS2R20,RNF216-IT1,AC010737.1,PSMC79P,PNPLA6,POMPAL591846.1,NME3,TPRA1,AC093627.4,SOCSE6,SPICE1,HMG1,HOXA2,AL590609.3,CXCR5,CHMP2A,GRK6,EFCAB13,PSMA1,1,ABALON,KIAA0355,DRAP1,SLC2A3,SF3B2,PHF5A,NHLRC1,STXBP3,CREB3L4,XRN2,FTL,AL139041.1,HIVEP3,GBGT1,RFXANK,SERAC1,NGS8,TI1266PLAMB1,AL122001.1,CCDC136,P2RY12,RPS20P14,MFAP4,MIR3936,AC092053.2,CCDC189,SPIRE1,EDRF1-AS1,UPF3A,ZNF257,APAF1,CLD,AS1,BRAT1,SNORA12,INSR,TEFM,RN7SL4PCT2orf29,SLIRPLILRA4,PRKAG2,AP001962.1,CAMKMT,RNA55P111,SIL1,GPATCH4,LOXL1,AC132931,1310PHOOK1,LINC00677,HHAT,BCCIP,VPS52,NIPSNAP1,GPRIN1,FBXL13,AC025594.2,AAK1,AC021087.1,KPNA4,MIR4740,CTLA4,SYT2,CHAD,AC8SN1,AC093826.2,ADCY4,GEMIN4,KRT17P8,NFATC2IPRAB11A,AC006460.2,DNAJC16,PJVK,RPL32P3,AL009031.1,SNAP47,UBXN8,AL121820.2,40,MIR373,C5orf66,COX10,L3MBTL1,AC002401.1,ZNF75D,TRGV4,E1F4E3,AC103706.2,MIR4668,Mar_5,ITGB1BP1,LSM10,PLLP,SNORD100,AC06DT,FBXO32,BX679664.3,AC009318.1,WFS1,PMS1,RHOU,PVALB,TCHPRXFP4,CNTNAP1,ARSK,FADS2,MT1XP1,FOXD2-AS1,AL031777.1,PCCB,RF,AS1,ROCK1P1,AC096733.2,AC007969.1,E1F4G2,RF01225,AL138995.1,RBP5,RPS18,RPE,LINC01402,C1orf146,ZNF502,AC022182.1,ZNF830,MIR:188P,POLR2M,ZSWIM7,TNFAIP1,RGS10,AC145098.1,RNA55P345,AC139100.2,CTU2,TMEM87A,ZNF641,LINC02604,AC009299.3,AC034222.2,PI249PZNF140,AC116348.1,FGFBP3,AC245052.6,AL135925.1,PGBD1,SLAMF9,AC108134.1,SNORA22B,RNU7-180P,AC079035.1,AC073641.1,PSN</p>

Table3

Upregulated genes and downregulated genes that meet the screening criteria in group HR

DEGs	Gene terms
Up-regulated	<p>MT-CO2,ZNF599,MT-CO3P23,EEF1A1P19,G3BP1,NFKBIL1,DUSP11,CXCR1,LZTR1,MTRNR2L2,HLA-DRB5,KANK1,PSEN2,FOSL1,FTH1P16,CD79B,IT1,SBN02,HSPA8,E1F1AX,SEMA4C,CTSZ,SCARNA20,CD70,SAE1,MIR1249,RNF31,SGSM3,RSRP1,SGTB,CSR1P,SEMA4F,FCF1,KLF13,SCARNA3,DPB2,RNF144B,GPR25,RPL23AP7,ARL4D,HSPB1,FOSL2,IL1RAP,PDIA5,CLIC3,SHMT2,ZNF600,PPP1R2,HSP90AB4,PSCARF1,UBE2V2,RBM43,USF658PRNF169,PLCB1,ARHGDI1B,MIR26A2,KLF3,NRADD,PTBC1D14,IRF4,RBM4,DNAJB12,FES,EEF1AKMT1,TM9SF1,PTPN2,ETFB,DDO,MOB3A,AIFI1024PMARF1,HIGLEC11,HGDFL3,PTGS1,JPT2,SPRY2,CFH,LINC01629,IRGQ,GABARAP,MORF4L2,ARID5B,E1F3J,PQLC1,BCAS3,DEF8,EHD4,CIB3,IT1,CLK3,GLUD1,NARF-IT1,Z83844.2,COX8A,HES4,GOLGA2,IFNGR2,PIIG,PPP2R2B,E1F3B,APH1B,HES1,PPP1R2B,DUSP12,ARF6,LYAR,GNAI3,KH1AS1,ZNF486,CSF2RB,PLK1,NAP1L4,CCNH,TPRN,STK11,PRG4,GAB2,RAPSN,MT-CO1P11,ITGAX,FUT10,SH3BGR1,LLUL,REM2,ZNF487,CNPGIN1AS1,FUCA1,TRIM58,EID2B,MAPK1,HMGB1P14,ZNF322,SRGAP2B,Z84480.1,PLEC,SLC4A10,CBFA2T2,VARS,BMP1,ARMCT1,CD8B,PLEKHA1,ATP5I652PCFAP36,TBK1,OXLD1,MBD5,LMNTD2,STIM2,KPNA6,ZNF300,ATRN,EME2,BLZF1,ARL6,NDUFB2-AS1,AMIGO1,TAL1,AJ003147.3,ARHGEF34AS1,GHRLOS,NCOA2,TRIM51BPMAPK7,TRAPPC6A,SLTM,CTSC,DNAL1,MRPL13,TBC1D32,FAM57A,ECH1,CLINT1,AP3B1,XPO7,MICOS10,TRAJ3AS1,AC095057.3,ZNF324,NXPH4,CBX8,ZNF33A,RNU1-27PPPP4R3A,BICRA,PAIP2B,BAG5,PSM6,CNPPD1,CSNK1A1,TTK,GATAD2A,SH3AC1,MEATP6,CCZ1,SREK1,MDFIC,MRPL50,HSPA1A,KARS,TCP1L1,KPNA5,YWHAZ,TPRKB,BTLA,PTPRK,COX7B,ZBTB40,NCEH1,WBP11,STRIP1,SNORDAS1,MRPL33,MMP17,TMEM116,SPON1-AS1,THEM5,TTL,ABHD15,GNA15,PSMB6,TLK2P1,CHIT1,PKD2,DRC3,NUP37,AC100810.3,ECI2,CAMSAF646PAB39A,RWDD4,SF3A1,NUDT4,SLC9A8,FBXO8,CHORDC1,MTMR9,FZD2,H2AF2,PRKDC,EPB42,UQCERS1,TRGJP1,MRKL47,ZSCAN18,ENTFDOB,TDFD1,AP1G1,ZNF185,PPM1L,FAHD1,JAM3,DHRS4-AS1,AARS,PRKCZ,VWF,AGA,TMEM198B,MRPS24,MRPL39,PIIPAP40,ETV6,TRAV12-1,ZI4,NR1H3,FOXO1,BCL2A1,TRIM9,CDCA4P4,RBX1,CD7C,ATG16L1,VN1R81P,COMMD9,AC012615.4,GPAM,ZBTB20,AC079305.1,CIAO3,JPT1,LRRCAS1,SCGB1B2PSTTRADA,SEPT14P4,ZNF276,ARF4,TBL2,PHLPP1,LRRCC1,CWC25,TTYH2,MAEA,MMP2B,BLVRP,CCNJ,DRAM2,SPAG1,GADD45G,662PNELFA,CASP8AP2,HCF1-AS1,TIMM9,MED12,TBC1D3L,ABHD12B,CXorf40B,SVIL-AS1,INSIG2,PTK6,EPG5,SHISA8,CRY2,CKAP2L,TRAPPC1AS1,MED24,MECR,OVGP1,TBCCD1,TLDC2,CD42P4,SMARCD1,TIA1,TRIP6,STK3,PPP6R1,SPINT2,ITGB5,POMGNT2,SLC19A2,RBM15,IFI44,BEXAS1,ATP10A,CCDC18,CYP2U1,BRWD1,AKAP9,LTK,MT-CO1P12,B4GALT4-AS1,GPATCH11,LSM4,PDSS1,OXSM,GHITM,NCKAP1,MRPS17P5,DDX3946PKCTD3,TGDF1P6,SUN2,STK25,FBXO30,MPHOSPH8,ZFC3H1,CUL4A,BISPR,EMC2,PDCL3P4,SKA2,IRF2BP1,TMEM44-AS1,TMEM159,DDX55541P,TRAV23DV6,SPNS1,NEDD8,ZFAND3,PIGB,CITED4,CRBN,ZNF529-AS1,LIMS1-AS1,ZNHIT1,YPEL5P2,DBF4,SNORA59A,ALDOA,POLR2E,TNFSAS1,AL162430.1,SLC40A1,LSMEM2,PKFB2,AMN,BIN3,FITM2,MINDY1,ZNF581,BCAS2,DIS3,HID1,C5orf30,SLC25A14,ZFAND2B,VAT1,MRPL12,T762PNODAL,SPTBN5,ANKRD42,AC040160.2,ZNF525,CTSE,LY6G5B,HTR7,NDST1,VPS37D,TCF7,HIVEP3,POLA1,ESD,CCND2,ETFBKMT,VWA7,ZN1,C19orf54,TMEM80,ZNF44,RBMX,SLC25A39,CNOT9,GPR183,NACC2,HEMGN,HEATR5A,LRRFIP1P1,BTBD6,PSMB9,PRKCI,ELOC3P1,FAM151B,FAS1,HNRNPA1,CLIP4,SLC30A1,HAUS8,TRDRP,ZNF527,BCL9L,AC004889.1,STK19B,SLC6A16,MICD,CNRP2,PGRMC2,ASCC1,CNOT4,BCKDHA,NPM1AS1,TNIP1,CHD8,UXS1,HADHA,PSMB2,ZNF770,ZBTB6,DFFA,DCUN1D2,CADM1,NOB1,SH3GL1,FAM210B,TRIM28,VWCE,POLR3H,TMEM134,SPCDDT,ATP5PBP1,ERFE,IQCG,EZR-AS1,MRM3,ZBTB7A,TRAV10,CDCA3,CDK2AP2P2,ZNF41,AC1357078.1,AMZ2P1,SNORA31,ZNF227,MRPL45P2,DLC729PHMGB1P20,AAANT,CCDC25,COX11,SIK2,GPR65,KCNMB4,FBXL17,KCTD20,KYNU,TAPBP,USP12-AS1,LAMTOR4,ALKBH4,PPP3CC,SLC25AAS1,TRIM39,PD2,ISY1,SHMT1,DISC1,GFI1B,OMG,ZBTB49,ZNF121,DCAF1,CALM2,IFT43,IMPAD1,EHBP1,GP5,KLHL36,AC113935.1,NDUFB11,KIIT2,ZFP90,SNX18,ZW10,ADHFE1,CHST8,AMD1,GRAP2,USP13,GAA,SPIRE2,HSPBAP1,POMGNT1,AASS,TOB2,DNAJB14,PMS2,VCPKMT,SPRY3,A,DT,MRPS16,JRK,MLINC1,NDUFB8,LCN12,ASCL2,HABP4,PNKPDCTP1,MRPL24,AGRN,MGPFUOM,HIRA,FHIT,TAKM1,COMMD4,EXOC3-AS1,REC4,PARD6A,SLC26A1,NCR1,MYDGF,LINC01881,SLC7A60S,TAF12,NKD1,TMEM123,AC007386.1,NRIP1,CPNE2,ITI2H,USE1,NUMA1,MED22,PRKAG1AS2,CPSP6,MAP3K1,SOD1P3,PLA2G4C,ZMYM6,LRRC14,MDGA1,ACVR1B,C6orf52,FAM204A,ACP5,MTPN,AC090229.1,ADAP2,QRICH1,PIRMI1,F701P,CNXX3,HOXB4,ZNF280C,ATG14,FAM193A,AC008966.2,HMGB3P22,MPP5,KDELRL,RBAK,PIIP5K1,MHENCRC,UCLK1,RNU6-574PUHRF1BP1,AS1,POP7,TP3A,SPRY1,ACTR8,PDXDC1,EMD,UMAD1,ZNF81,ARSD,CPLANE2,TRMT112,TC2N,MFSD1P1,EXOSC6,PMS2P3,PBDC1,CTNNA1,SYAS,ZNF230,MRPS17,SUPT3H,UBL3,AC021242.3,C1QCQ,DNAH1,TAOK3,FAM183BPCORO6,AC067945.1,SLC18A2,SNRPD1,SPCS1,GSDMB,CHST1AS1,CDA,OAS3,BCLAF1,YPEL3,ARHGEF19,BZW1P2,AC073172.1,STP1R1,PPP2R3C,EMC7,TMEM71,CYB561D2,ARPP19,HSD11B1L,PRPF31,FAN1AS1,PNISR,SH3YL1,LZTS2,AC125437.1,PAGE2B,ARSG,AASDHPT,ZDHHC19,E1F3D,CASSA,RNY1P11,PKHD1L1,CIPC,AC026412.1,RN3S,SEPHS1686PFARSA,KIF20A,AK9,C3H12A,ANAPC16,AL138963.1,AL359183.1,PGAP3,CETPFASKD5,OTULINL,ITPR2,ENKUR,ZFP82,AL050343.1,RNF2459PFRLY,AC087241.4,SOGA1,TRIM65,ZNF100,APH1A,MSL2,TRMT10A,AC011465.1,EFNA4,FAM122C,TRPT1,SETP17,ZNF518B,RCOR3,DCPS,AT1300PFADS3,ADORA3,CLOCK,MRPS31P4,C1orf147,ANAPC11,DEPDC1B,FZD5,TMEM117,EEF2K,MFF,AC026748.1,SPDL1,EMC8,E1F5B,ATRX,DB1IT1,PLCB3,PMPCA,SEC61A1,MIR4514,PTPN18,TRAJ57,FOXJ3,TMEM191C,CUBN,E1F4EP1,LINC01474,MNDA,TAF1A,SQOR,MYOM1,AC119428.3,</p>
Down-regulated	<p>HBEGF,HBD,HBB,MOB1A,IFITM5,FCHO1,SH2B1,CSGALNACT2,MALT1,CXCR3,NANS,SPAG9,SGPP2,SLC25A6,FPR3,AL627311.1,CXCR2P1,AQR,P13,NAP1L1,OLA1,AL627309.7,ST3GAL6,OGFOD2,IQSEC1,LYPD3,MELK,FLT1P1,ADAM9,AC012368.2,PGLYR1,USCUG2P2,CLCF1,UBE2E3,AL3919I1010PCREBL2,ST6GALNAC3,PTPRE,RALGAPA1,PALD1,AC108673.3,MEGF9,ANTXR2,CNN2P9,ZNF137,BCL7B,PAF1,LPAT1,PTGDS,HSD17B1,482PPYCR1,NLGN2,LAMTOR1,TMEM260,ADGRE3,TP53BP2,NRF1,IL16,HAPLN3,DZANK1,RBM3,HEY1,RGS12,SH3BGR2,CASP9,BAZ2A,DENND977PRER1,TCTEX1D2,PAD16,RDH10,TRAJ35,CALR,GDPD1,ANP32B,FNTA,AC007278.2,APOL3,CEACAM6,MIR580,TXNDC9,DGCR11,ULK4,MMP9,AS1,IL18,PNMA1,TPP2,AC018926.1,TDP1,AL513327.3,FAM157C,ISM1,HCG9,MBTPS2,AL049840.5,CARD9,ZBTB38,AL390774.2,URI1,AC020908IT1,AC008735.4,THAP1,AC104763.3,MPIG6B,TRDD2,RPL37AP1,IGF2R,ZNF282,AC104411.1,ERN1,PRADC1,AC018946.1,RO60,RAB6B,MIR8064,AS1,HBQ1,CCDC194,PCNPDSYTYK,RASSF2,CALM3,NCOA4,TTTC16,FBXO9,AC005682.1,RF00593,MIR4269,RPS7P1,AC104564.3,CD5,MIR4324,SL7,KDSR,AC100847.1,ZNF586,CDK13,AC011374.2,JRKL,C4BP4,MIB2,NINL,SLC27A4,MCUB,KIAA1522,LINC01004,MKRN1,AC004687.1,AC035474.4,TG,MIR548AK,HIPK1,RAB2B,AC007365.1,FN1,AC007342.9,YIPF1,SLC25A26,AOAH,ACSL5,MS4A14,ARG2,GPR34,FAM160A2,MASP2,GIHCG,AL391017PATP5P0,TN50CP1,TSPYL1,AL732372.3,TMEM208,AC069287.3,RNY4P7,FLNA,AC066613.2,PTPRG,UBE2A1,TP53I11,VILL,SSBP2,TRAJ45,E59PAC093010.2,ITGA9,AL031432.3,SETDB1,PPP1R14B,KHK,AC0067838.1,SRSF8,TMEM17,BET1,PTMAG12,DBR1,AL139353.2,SLC30A1275PAL353764.1,CCR10,IL1B,FEZ2,AL590609.3,APCDD1,AC010326.4,ME1,EXD3,ZKSCAN4,Mar_7,HIST1H2BF,CPLANE1,AC009570.1,E1F4A2,A50PZNF746,AC055839.1,NTSR1,HIST1H2AH,ZNF680,AC010531.5,RHOBTB2,AC005154.2,CCDC127,POLI,AC130454.1,WASH5PBDH13,ASPSCRDT,PACRGL,SRP68,STARD4,AC005261.5,TIAM1,APC,AC013244.2,RPL26,AC092634.3,TRAV39,ZNF701,HIST1H2B1,SNORA24B,STARD5,DHX57,A223PNUDT17,ING2,AC091185.2,BBIP1,DAPP1,FAM215B,CASC3,FADS1,AC008731.1,AC005332.4,UBL7,SLC25A25,AC244157.2,AMZ2,AC02108729PUBE2G2,MIR4484,RNASE2,NSUN7,DHX30,EP58L1,TRAV25,AC006946.1,OSGIN1,AL591848.3,SLC20A1,RUVBL2,SIRPG,BLOC1S5,PIP4K2A,SLDT,PDLLIM1P4,STAMBPL1,MIR5190,CERK,CAPS2,AL139022.2,CLTB,BNC2,GOLGA2P10,ZNF93,AC099811.6,MTMR12,AL031963.3,LINC02207,AC1,RNU4ATAC,RHEBL1,LINC01063,RBP5,MIR5690,AL512791.1,AL031846.2,AC090607.1,UBE2H,ADCY3,NPHP4,AC010654.1,RSAD1,STEAP4,AP0C141PMYCT1,MDC1,RF02154A,RGL2,PCYOX1L,AC021106.2,AC018665.1,AC005776.2,AC008753.3,EZH2,OSGEPL1-AS1,MIR6731,GBP1,AC099063403PAGAP6,AC106774.3,AC007556.1,AC009506.1,LY6G5C,AC009951.1,MCRIPI1,PSMD5,AC022217.1,LIPC,AC021087.3,LY96,RNU6ATAC39PSPI19,DYNC1H1,AC074032.1,AC009121.1,NENFP1,RN7SL600PAC112173.1,SNRPA1,GAN,AC005154.4,AC008115.1,DNPEPAL445584.2,AC099548.1,AS1,AC006960.1,UBR5,ILNR3C,AC104010.1,TMEM52B,PILRB,NOP53-AS1,AC074132.1,RENBPAC005391.1,RAB5B,AC132942.1,RF00285,GK-AS1,AS1,CYP2T1,PCN0T7,TLL11,AL391832.3,AL162377.1,CCDC144B,AC125232.2,TBD11.1,GABPB2,SNORD98,AC010615.1,NSUN3,AC008753.2,PFRRNR2,AC022150.4,AL022328.2,AL513365.1,AC108718.1,SS18L2,RNA5SP78,AC136475.10,ZNF32,PDCL,RFX7,SOX12,SLC27A3,RPL34P22,AC0055,SFTPD,AP002360.1,FANCF,RF00599,AC092053.2,SC5D,AL136141.1,DNAJA2,PRDM1,AC013356.3,AC009159.3,AC010737.1,STRAD4,AC00424AS1,TRIM14,RUSC1,ABCA1,S1PR5,SRP54-AS1,AL121845.4,SLC4A8,AL031710.2,HECW2,HEATR6,RPSAP5B,GIMAP7,CRACR2B,AC025171.1,GOLAS1,ACTN1,LINC00945,HSD17B7,AC008680.1,TRAJ54,MIR646,AL355480.1,ANKHD1,SMIM10L1,ASMTL,RNA5SP201,RNY3P8,ABHD2,ZCHHC2423PAC005332.6,AP4B1-AS1,AL138724.1,MTCH1,AL162615.1,DGAT2,POLR1B,NHLRC1,RPAP4,AKT3-IT1,EXOC7,AL135818.2,SEC23A,MT-ND5,DI1114PAC009093.7,CASC1,NCF1,KMT2B,AC073073.1,METTL7A,MRPL57,AL353763.2,AC007298.2,SCML4,AC123768.2,AC136475.7,MIR7847,ACADT,ROCK1P1,SAFB,PBX2,AC020658.7,AC018695.6,PSMD10,AC105265.4,AC018682.1,COLGALT2,RPL39P18,GIMAP5,ZNF83,UQCRH,AC073840.1AS1,RF00273,RP30,CYP4F25PCGAS,SYN1,RNU4-8SPSPHK1,SSSCA1-AS1,ZNF480,SDAD1P1,AP005131.2,AL353763.1,FAM86D,PRF01169,ACA731P10orf143,BLOC1S3,ZSWIM7,ZNF155,AC010530.1,AC026634.1,RBM8A,STYX,PIGO,COX6A1P2,APT-X,ATP5M6,BNIP1,ZNF512B,ODC1-DT,45,AC090615.1,AC005726.3,AC007041.1,AC006205.2,SMCO4,MANEAL,AC138150.2,LINC00659,RPL39,AC010285.3,CHI3L1,AL109804.1,ARL4C,553PPDE4B,AL445187.1,AL136441.1,PDK4,AC109454.2,RF01233,MORN2,TNFAIP8L1,AP003108.4,MIR4769,UQCR10,RAB3A,RNVU1-15,AC006214PAC027559.1,AC080023.2,INSR,AL049780.1,AC124798.1,AC024475.1,RF3C,RP12P28,AC021422.1,PHLDB2,AC144530.1,HLA-H,IRMG6075,WIAS1,AC146507.2,AL031005.1,LINGO2,PDGFA,SIRT7,LTN1,AC022868.1,CNTNAP1,MIR4258,MAP9,WWC2,AL513475.1,FAM189B,AC009090.1,RC51143PMIR3671,SECISBP2,ATP5PD,AC020913.3,FLNB,YIPF5,GPSM2,ZDHHC13,AC023389.1,HLF,AC120114.3,NANPAC139495.1,AC087501.4,AC</p>

Table4

The collection of significantly enricher GO pathways (top 10 according to P value) in group CR

ONTOLOGY	ID	Description	Count	P-value	GeneID
BP	GO:0042119	Neutrophil activation	200	1.10E-13	SLC27A2/SLPI/PFKL/PTPRN2/P2RX1/APAF1/LAMP1/ACAA1/FGL2/FCER1G/STXBP3/
BP	GO:0002446	Neutrophil mediated immunity	199	2.81E-13	SLC27A2/SLPI/PFKL/PTPRN2/P2RX1/APAF1/LAMP1/ACAA1/FGL2/FCER1G/STXBP3/
BP	GO:0002283	Neutrophil activation involved in immune response	194	7.92E-13	SLC27A2/SLPI/PFKL/PTPRN2/P2RX1/APAF1/LAMP1/ACAA1/FGL2/FCER1G/STXBP3/
BP	GO:0043312	Neutrophil degranulation	193	8.15E-13	SLC27A2/SLPI/PFKL/PTPRN2/P2RX1/APAF1/LAMP1/ACAA1/FGL2/FCER1G/STXBP3/
BP	GO:0032543	Mitochondrial translation	70	3.01E-11	UQCC2/NSUN3/GATC/COA3/GADD45GIP1/TRMT10C/MTIF3/RMND1/MRPL37/GATB/M
CC	GO:0005743	Mitochondrial inner membrane	193	1.72E-14	TIMM22/SLC25A3/CRLS1/GPD2/UQCC2/COA3/TIMM23/ALAS2/CLU/APOO/SLC25A15
CC	GO:0098798	Mitochondrial protein complex	119	1.58E-13	TIMM22/NSUN3/COA3/TIMM23/TOMM40L/APOO/TRMT10C/ATP5F1B/PPIF/TIMM21,
CC	GO:0005759	Mitochondrial matrix	179	1.27E-10	UQCC2/NSUN3/PCCB/ALAS2/GADD45GIP1/MIPEP/TRMT10C/ATP5F1B/ABHD10/SLC2
CC	GO:0010008	Endosome membrane	179	8.87E-10	SORT1/LAMP1/RABEPK/BAIAP3/CHMP5/GGA3/VPS52/RAB27B/TMEM150B/SNX6/IN
CC	GO:0000315	Organelle large ribosomal subunit	36	1.25E-09	NSUN3/MRPL37/MRPL32/MRPL51/MRPL42/MRPL43/MPV17L2/MRPL14/MRPL44/M
MF	GO:0003713	Transcription coactivator activity	123	1.04E-06	JADE1/PKN1/ASXL1/TAF12/TRERF1/ELF3/TFDP1/TRIP4/MED13/NFYC/FOXC1/ENY2,
MF	GO:0140030	Modification-dependent protein binding	62	9.99E-06	SHARPIN/TP53BP1/MSH6/RNF168/ZMYND11/TNFAIP3/PSME4/SPIN2B/EPS15/L3ME
MF	GO:0032182	Ubiquitin-like protein binding	45	1.21E-05	SHARPIN/RNF185/GGA3/DCUN1D5/UHL3/RNF168/TNFAIP3/SERBP1/DCUN1D3/ASC
MF	GO:0003725	Double-stranded RNA binding	37	1.70E-05	AGO3/DHX36/RC3H1/ZFR/DROSHA/TFRC/DHX9/MRPL44/FXR1/LSM14A/DDX1/LRRF
MF	GO:0000287	Magnesium ion binding	84	1.92E-05	IRAK3/ERN1/MSH6/TREX2/DHX36/PPA1/PGM2/ENO2/PIF1/PRPS1/RP2/ARF1/XYLT2,

Table5

The collection of significantly enricher GO pathways (top 10 according to P value) in group HR

Table6

Ten most significantly enriched KEGG pathways in group CR.

Table7

ONTOLOGY	ID	Description	Count	P-value	GeneID
BP	GO:0140053	mitochondrial gene expression	88	6.01E-15	NGRN/MRRF/MRPL57/MTG1/TEFM/MRPS2/GATC/MTIF3/TRMT10C/TRNT1/NSU
BP	GO:0042119	neutrophil activation	204	2.76E-14	MMP9/ALDOC/MCEMP1/PSMB1/GLIPR1/ERP44/B4GALT1/PSMD2/ORMDL3/LRG1
BP	GO:0002446	neutrophil mediated immunity	203	7.21E-14	MMP9/ALDOC/MCEMP1/PSMB1/GLIPR1/ERP44/B4GALT1/PSMD2/ORMDL3/LRG1
BP	GO:0002283	neutrophil activation involved in immune response	199	9.70E-14	MMP9/ALDOC/MCEMP1/PSMB1/GLIPR1/ERP44/B4GALT1/PSMD2/ORMDL3/LRG1
BP	GO:0043312	neutrophil degranulation	198	9.84E-14	MMP9/ALDOC/MCEMP1/PSMB1/GLIPR1/ERP44/B4GALT1/PSMD2/ORMDL3/LRG1
CC	GO:0005743	mitochondrial inner membrane	199	2.89E-16	ATP5PO/ATP5MD/RDH13/SLC25A26/PPIF/UQCR10/MCUB/MRPL57/CYC1/AFG3L2
CC	GO:0098798	mitochondrial protein complex	124	1.65E-15	ATP5PO/ATP5MD/PPIF/UQCR10/MCUB/MRPL57/CYC1/AFG3L2/MRPS2/MTX3/TR
CC	GO:0005759	mitochondrial matrix	190	1.07E-13	HSPE1/PYCR2/LIAS/PYCR1/ALKBH7/NR3C1/PPIF/STYXL1/TK2/PARS2/MRRF/EC
CC	GO:0016607	nuclear speck	161	7.41E-12	SLU7/SRSF8/SLC2A4RG/FBXL4/NR3C1/SMU1/OIP5/ALKBH5/CASC3/POLI/PRPF6/
CC	GO:0005819	spindle	141	1.25E-10	MYH9/TBL1X/PLK2/KLHL22/NR3C1/PPP2CA/PAFAH1B1/MAP10/DIDO1/MZT2A/P
MF	GO:0043021	ribonucleoprotein complex binding	63	2.43E-07	NAA10/RBM3/SECISBP2/CPEB4/OLA1/EZH2/LTN1/MRRF/NMD3/PRPF6/DDX3X/S
MF	GO:0004674	protein serine/threonine kinase activity	160	3.58E-06	CDK7/TGFBF1/PLK2/ERN1/GRK3/CSNK1G3/MAP3K21/ULK4/MAST4/PAK1/VRK3/
MF	GO:0031072	heat shock protein binding	54	8.52E-06	ERN1/USP19/NR3C1/DNAJB2/DNAJA2/HSP90AB1/CDKN1B/PPP5C/TELO2/SPN/Z
MF	GO:0004842	ubiquitin-protein transferase activity	139	1.67E-05	MALT1/FBXL4/RNF185/WDSUB1/LTN1/FBXO40/HERC5/UBE2G2/MIB2/MKRN1/PP
MF	GO:0003743	translation initiation factor activity	28	1.82E-05	EIF4G2/MTIF3/EIF4A2/EIF4H/EIF4A1/EIF6/EIF3K/EIF3H/EIF3J/EIF3F/MTIF2/EIF4G:

Ten most significantly enriched KEGG pathways in group HR.

Figures

ONTOLOGY	ID	Description	Count	P-value	GeneID
BP	GO:0140053	mitochondrial gene expression	88	6.01E-15	NGRN/MRRF/MRPL57/MTG1/TEFM/MRPS2/GATC/MTIF3/TRMT10C/TRNT1/NSUN
BP	GO:0042119	neutrophil activation	204	2.76E-14	MMP9/ALDOC/MCEMP1/PSMB1/GLIPR1/ERP44/B4GALT1/PSMD2/ORMDL3/LRG1
BP	GO:0002446	neutrophil mediated immunity	203	7.21E-14	MMP9/ALDOC/MCEMP1/PSMB1/GLIPR1/ERP44/B4GALT1/PSMD2/ORMDL3/LRG1
BP	GO:0002283	neutrophil activation involved in immune response	199	9.70E-14	MMP9/ALDOC/MCEMP1/PSMB1/GLIPR1/ERP44/B4GALT1/PSMD2/ORMDL3/LRG1
BP	GO:0043312	neutrophil degranulation	198	9.84E-14	MMP9/ALDOC/MCEMP1/PSMB1/GLIPR1/ERP44/B4GALT1/PSMD2/ORMDL3/LRG1
CC	GO:0005743	mitochondrial inner membrane	199	2.89E-16	ATP5PO/ATP5MD/RDH13/SLC25A26/PPIF/UQCR10/MCUB/MRPL57/CYC1/AFG3L2
CC	GO:0098798	mitochondrial protein complex	124	1.65E-15	ATP5PO/ATP5MD/PPIF/UQCR10/MCUB/MRPL57/CYC1/AFG3L2/MRPS2/MTX3/TR
CC	GO:0005759	mitochondrial matrix	190	1.07E-13	HSPE1/PYCR2/LIAS/PYCR1/ALKBH7/NR3C1/PPIF/STYXL1/TK2/PARS2/MRRF/ECF
CC	GO:0016607	nuclear speck	161	7.41E-12	SLU7/SRSF8/SLC2A4RG/FBXL4/NR3C1/SMU1/OIP5/ALKBH5/CASC3/POLI/PRPF6/
CC	GO:0005819	spindle	141	1.25E-10	MYH9/TBL1X/PLK2/KLHL22/NR3C1/PPP2CA/PAFAH1B1/MAP10/DIDO1/MZT2A/P
MF	GO:0043021	ribonucleoprotein complex binding	63	2.43E-07	NAA10/RBM3/SECISBP2/CPEB4/OLA1/EZH2/LTN1/MRRF/NMD3/PRPF6/DDX3X/S
MF	GO:0004674	protein serine/threonine kinase activity	160	3.58E-06	CDK7/TGFBF1/PLK2/ERN1/GRK3/CSNK1G3/MAP3K21/ULK4/MAST4/PAK1/VRK3/
MF	GO:0031072	heat shock protein binding	54	8.52E-06	ERN1/USP19/NR3C1/DNAJB2/DNAJA2/HSP90AB1/CDKN1B/PPP5C/TELO2/SPN/Z
MF	GO:0004842	ubiquitin-protein transferase activity	139	1.67E-05	MALT1/FBXL4/RNF185/WDSUB1/LTN1/FBXO40/HERC5/UBE2G2/MIB2/MKRN1/PP
MF	GO:0003743	translation initiation factor activity	28	1.82E-05	EIF4G2/MTIF3/EIF4A2/EIF4H/EIF4A1/EIF6/EIF3K/EIF3H/EIF3J/EIF3F/MTIF2/EIF4G:

ID	Descripcion	Count	P-value	P.adjust	GeneID
hsa05020	Prion disease	116	2.04E-08	6.68E-06	=-14.8136129/-13.83319472/-41.2285027/-10.55094562/-17.72900004/-2.5623004
hsa05016	Huntington disease	126	4.64E-08	7.61E-06	=-13.83319472/-41.2285027/-10.55094562/-24.48111328/-173.0376027/-17.72900
hsa05012	Parkinson disease	103	6.15E-07	5.08E-05	=-13.83319472/-41.2285027/-10.55094562/-24.48111328/-17.72900004/-2.562300
hsa04144	Endocytosis	104	6.20E-07	5.08E-05	=-9.971260833/-80.55898765/-10.43336139/-4.052067933/-32.50125904/-4.06412
hsa05010	Alzheimer disease	142	8.51E-07	5.58E-05	=-13.83319472/-41.2285027/-10.55094562/-24.48111328/-173.0376027/-17.72900
hsa03050	Proteasome	28	1.60E-06	8.75E-05	=-25.54134178/-41.2285027/-10.55094562/-17.72900004/-11.60909027/-5.543828
hsa05014	Amyotrophic lateral sclerosis	137	5.37E-06	0.000211928	=-13.83319472/-41.2285027/-10.55094562/-24.48111328/-173.0376027/-17.72900
hsa05022	Pathways of neurodegeneration - multiple diseases	172	5.46E-06	0.000211928	=-13.83319472/-41.2285027/-10.55094562/-24.48111328/-173.0376027/-17.72900
hsa00190	Oxidative phosphorylation	60	5.82E-06	0.000211928	=-13.83319472/-6.454919377/-32.89604088/-2.431090716/-11.55958762/-33.2431
hsa04140	Autophagy - animal	61	8.16E-06	0.000267488	=-17.51223489/-24.48111328/-173.0376027/-6.460668104/-3.517128856/-9.05244

Figure 1

(a) Volcano plot of DEGs in group CR; (b) The heatmap of DEGs in group CR. The colors in (a) indicate different gene expressions in the corresponding group (red for upregulated DEGs and green for downregulated DEGs, gray indicates no difference); for (b), the abscissa axis represents the sample types and the ordinate axis represents the gene names.

Figure 2

(a) Volcano plot of DEGs in group HR; (b) The heatmap of DEGs in group HR. The colors in (a) indicate different gene expressions in the corresponding group (red for up-regulated DEGs and green for down-regulated DEGs, gray indicates no difference); for (b), the abscissa axis represents the sample types and the ordinate axis represents the gene names.

Figure 3

Results of functional analysis in group CR and group HR (a) The GO analysis of group CR; (b) The KEGG analysis of group CR; (c) The GO analysis of group HR; (d) The KEGG analysis of group HR. In (a) and (c), the abscissa axis represents the gene ratio while the ordinate axis represents term names. The size of a single bubble represents the degree of enrichment; the color variety represents the different q-values (those in red are considered to be of significance). For (b) and (d), the abscissa axis represents counts; the ordinate axis represents KEGG pathways; color represents the same meaning as the bubble diagram.

Figure 4
PPI network of up-regulated genes in group CR; (b) PPI network of down-regulated genes in group CR; (c) Hub genes in group CR. Nodes represent genes; lines represent the interactions between gene-encoded proteins; the redder the color, the more significant it is.

Figure 5

(a)PPI network of up-regulated genes in group HR; (b)PPI network of down-regulated genes in group HR; (c)Hub genes in group HR. Nodes represent genes; lines represent the interactions between gene-encoded proteins; the redder the color, the more significant it is.

Supplementary Files

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