



Identification of potential mRNA panels for severe acute respiratory syndrome coronavirus 2 (COVID-19) diagnosis and treatment using microarray dataset and bioinformatics methods

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Abstract

The goal of the present investigation is to identify the differentially expressed genes (DEGs) between SARS-CoV-2 infected and normal control samples to investigate the molecular mechanisms of infection with SARS-CoV-2. The microarray data of the dataset E-MTAB-8871 were retrieved from the ArrayExpress database. Pathway and Gene Ontology (GO) enrichment study, protein–protein interaction (PPI) network, modules, target gene–miRNA regulatory network, and target gene–TF regulatory network have been performed. Subsequently, the key genes were validated using an analysis of the receiver operating characteristic (ROC) curve. In SARS-CoV-2 infection, a total of 324 DEGs (76 up- and 248 down-regulated genes) were identified and enriched in a number of associated SARS-CoV-2 infection pathways and GO terms. Hub and target genes such as TP53, HRAS, MAPK11, RELA, IKZF3, IFNAR2, SKI, TNFRSF13C, JAK1, TRAF6, KLRF2, CD1A were identified from PPI network, target gene–miRNA regulatory network, and target gene–TF regulatory network. Study of the ROC showed that ten genes (CCL5, IFNAR2, JAK2, MX1, STAT1, BID, CD55, CD80, HAL-B, and HLA-DMA) were substantially involved in SARS-CoV-2 patients. The present investigation identified key genes and pathways that deepen our understanding of the molecular mechanisms of SARS-CoV-2 infection, and could be used for SARS-CoV-2 infection as diagnostic and therapeutic biomarkers.

Keywords SARS-CoV-2 infection · Bioinformatics analysis · Biomarkers · Protein–protein interaction (PPI) network · Differentially expressed genes

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is known as novel coronavirus disease-2019 (COVID-19) and has spread widely throughout the globe in an epidemic proportion with the current pandemic risk (Li et al. 2020). This infection is related to respiratory diseases, and this virus mainly infects respiratory

epithelial cells and transmits from human to human primarily through the respiratory tract, contributing to more deaths (Zou et al. 2020; Madurai Elavarasan and Pugazhendhi 2020). In the present situation, the survival rate of patients with SARS-CoV-2 infection has been slightly increased, and patients with this infection have no apparent benefit from the current antiviral drugs (Hoffmann et al. 2020). Knowing the molecular pathogenesis of the viral infections and their routes of transmission is completely necessary for the creation of new therapeutic targets.

Present situation for investigating the pathogenesis of SARS-CoV-2 infection is needed in molecular biology. Although the pathogenesis of SARS-CoV-2 infection remains to be clarified, abnormal gene expression in nasal epithelial cells can serve significant roles (Sungnak et al. 2020). Entry factors related genes such as angiotensin-converting enzyme 2 (ACE2) (Zhang et al. 2020); TMPRSS2 (Sungnak et al. 2020); and inflammatory related genes (IL-2, IL-7, IL-10, GCSF, IP-10, MCP-1, MIP-1A, and TNF- α) (Fu

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et al. 2020) were linked with pathogenesis of SARS-CoV-2 infections. Therefore, targeted regulation of these genes may reveal potential strategies for the treatment of SARS-CoV-2 infections. Therefore, targeted regulation of entry factors and inflammatory-related genes could become potential strategies for the treatment of SARS-CoV-2 infection.

Throughout this investigation, we used bioinformatics methods to examine differentially expressed genes (DEGs) between SARS-CoV-2-infected samples and standard control samples. We performed pathway enrichment and gene ontology (GO) analysis of DEGs, and established the protein–protein interactions (PPI) network, modules analysis, target gene–miRNA regulatory network, and target gene–TF regulatory network to reveal molecular mechanisms in SARS-CoV-2 infection. Finally, we performed validation hub genes by receiver operating characteristic (ROC) curve analysis. Finally, through receiver operating characteristic (ROC) curve analysis, we conducted validation hub genes. The aim of this study is thus to have a better understanding of the exact mechanisms of SARS-CoV-2 infection and to identify potential novel diagnostic or therapeutic targets through bioinformatics analysis.

Materials and methods

Microarray data selection

Microarray data of gene expression profile (E-MTAB-8871) was downloaded from ArrayExpress (<https://www.ebi.ac.uk/arrayexpress>), which is the largest resource of gene

expression publicly available (Kolesnikov et al. 2015). Samples from this dataset were RNA extracted from the blood sample and processed for hybridization on NanoString nCounter Human Immunology V2 Panel Array. A total of 32 samples were investigated, including 22 SARS-CoV-2-infected samples, and 10 normal control samples. The study was designed according to the flowchart (Fig. 1).

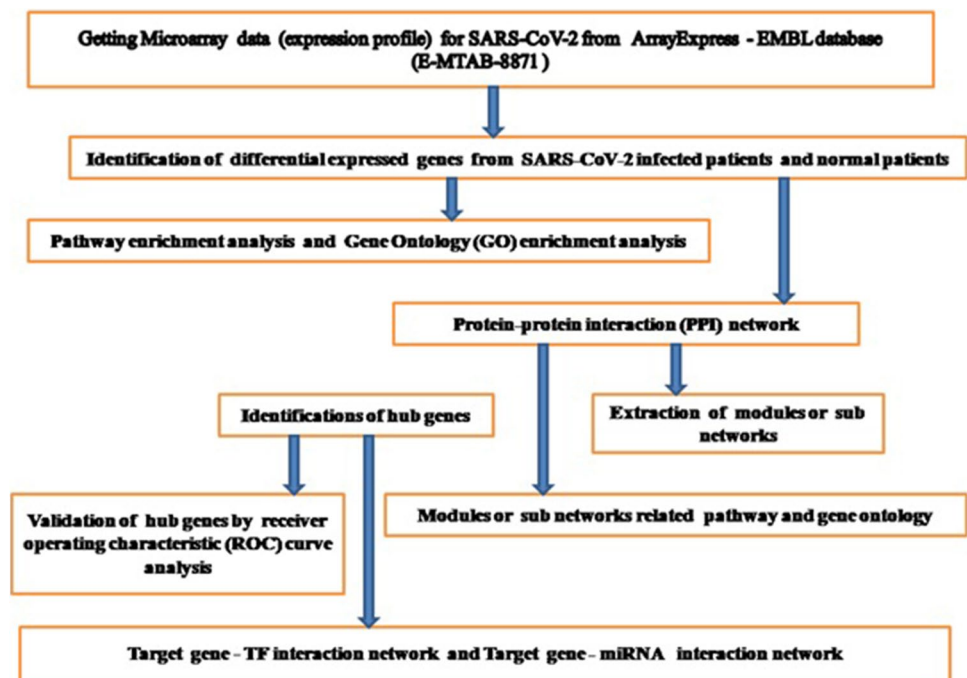
Identification of DEGs

The DEGs between the SARS-CoV-2-infected samples and normal control samples were analyzed with various methods including data preparation (data normalization and summarization) and DEGs identification (up- and down-regulated genes). The limma package in R Software was used for background correction, quantile normalization and probe summarization, and limma package was also applied for DEGs identification (Ritchie et al. 2015). The development of DEGs choice included model design, linear model fitness, contrast matrix generation, bayesian model building and gene filtering, all of which were managed by the functions in the limma package. Genes with the $p < 0.05$, \log_2 Fcl (fold change) > 1.5 were considered as DEGs (up- and down-regulated genes).

Pathway enrichment analysis for DEGs

BIOCYC (<https://biocyc.org/>) (Caspi et al. 2016), Kyoto Encyclopedia of Genes and Genomes (KEGG) (<http://www.genome.jp/kegg/pathway.html>) (Kanehisa et al. 2019), Pathway Interaction Database (PID) (<https://wiki.nci.nih.gov/>

Fig. 1 The workflow representing the methodology and the major outcome of the study. SARS-CoV-2—Severe acute respiratory syndrome coronavirus 2 infection - breast cancer, GO—gene ontology, miRNA—MicroRNA, TF—transcription factor, DEGs—differential expressed genes



pages/viewpage.action?pageId=315491760) (Schaefer et al. 2009), REACTOME (<https://reactome.org/>) (Fabregat et al. 2018), GenMAPP (<http://www.genmapp.org/>) (Dahlquist et al. 2002), MSigDB C2 BIOCARTA (<http://software.broadinstitute.org/gsea/msigdb/collections.jsp>) (Subramanian et al. 2005), PantherDB (<http://www.pantherdb.org/>) (Mi et al. 2017), Pathway Ontology (<http://www.obofoundry.org/ontology/pw.html>) (Petri et al. 2014) and Small Molecule Pathway Database (SMPDB) (<http://smpdb.ca/>) (Jewison et al. 2014) are a data resource for genes and genomes with assigned corresponding functional importance. The TopGene (ToppFun) (<https://toppgene.cchmc.org/enrichment.jsp>) (Chen et al. 2009) is an online resource for interpreting genes originating from genomic investigation with bioinformatics data. The p value < 0.05 was considered statistically significant.

Gene ontology (GO) enrichment analysis for DEGs

GO (<http://www.geneontology.org/>) (Lewis et al. 2017) was used to determine gene actions in three aspects: biological process (BP), cellular component (CC) and molecular function (MF). TopGene (ToppFun) (<https://toppgene.cchmc.org/enrichment.jsp>) (Chen et al. 2009) is an online website that provides an extensive set of functional annotation tools to understand the biological meaning behind a massive list of genes. In the current investigation, the GO enrichment analyses for statistically important DEGs. The p value < 0.05 was considered statistically significant.

PPI network construction and module analysis

The common up and down-regulated genes of E-MTAB-8871 was analyzed using the online website STRING (<https://string-db.org/>, version 11) (Szklarczyk et al. 2019), with 0.700 (moderate confidence) as the minimum required interaction score. Then, the software Cytoscape (<http://www.cytoscape.org/>, version 3.8.0) (Shannon et al. 2003) was used to establish a PPI network. The Network Analyzer in Cytoscape was utilized to calculate node degree (Przulj et al. 2004), betweenness centrality (Nguyen et al. 2011), stress centrality (Shi and Zhang 2011), closeness centrality (Nguyen and Liu 2011) and clustering coefficient (Wang et al. 2012). PEWCC1 (<http://apps.cytoscape.org/apps/PEWCC1>) (Zaki et al. 2013) was used to perform module analysis.

Construction of target gene–miRNA regulatory network

miRNet database (<https://www.mirnet.ca/>) (Fan and Xia 2018) provides certain target gene–miRNA regulatory association pairs, which are verified by experiments and

predicted by ten programs, including TarBase (<http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=tarbase/index>) (Vlachos et al. 2015), miRTarBase (<http://mirtarbase.mbc.nctu.edu.tw/php/download.php>) (Chou et al. 2018), miRecords (<http://miRecords.umn.edu/miRecords>) (Xiao et al. 2009), miR2Disease (<http://www.mir2disease.org/>) (Jiang et al. 2009), HMDD (<http://www.cuilab.cn/hmdd>) (Huang et al. 2019), PhenomiR (<http://mips.helmholtz-muenchen.de/phenomir/>) (Ruepp et al. 2010), SM2miR (<http://bioinfo.hrbmu.edu.cn/SM2miR/>) (Liu et al. 2013), PharmacomiR (<http://www.pharmaco-mir.org/>) (Rukov et al. 2014), EpimiR (<http://bioinfo.hrbmu.edu.cn/EpimiR/>) (Dai et al. 2014) and starBase (<http://starbase.sysu.edu.cn/>) (Li et al. 2014). This investigation inputted the up- and down-regulated genes into the database to examine the regulatory association pairs between target gene and miRNA. Target gene–miRNA regulatory network was constructed and visualized by Cytoscape 3.8.0 software to show the target genes and miRNA. Therefore, these target genes and miRNA might play a potential role in the pathogenesis and treatment of SARS-CoV-2 infection.

Construction of target gene–TF regulatory network

NetworkAnalyst database (<https://www.networkanalyst.ca/>) (Zhou et al. 2019) provides certain target gene–TF regulatory association pairs, which are verified by experiments and predicted by JASPAR (<http://jaspar.genereg.net/>) (Khan et al. 2018) database. This investigation inputted the up- and down-regulated genes into the database to examine the regulatory association pairs between target gene and TF. Target gene–TF regulatory network was constructed and visualized by Cytoscape 3.8.0 software to show the target genes and TF. Therefore, these target genes and TF may play a potential role in the pathogenesis and treatment of SARS-CoV-2 infection.

Validation of hub genes

Receiver-operating characteristic (ROC) analyses were operated to calculate the diagnostic value of the hub genes for SARS-CoV-2 infection. The ROC curve with area under curve (AUC) was determined using R “pROC” package (Robin et al. 2011).

Results

Identification of DEGs

Microarray dataset (E-MTAB-8871) was obtained from ArrayExpress database and normalized mRNA expression data through R language (Fig. 2). Volcano plot was

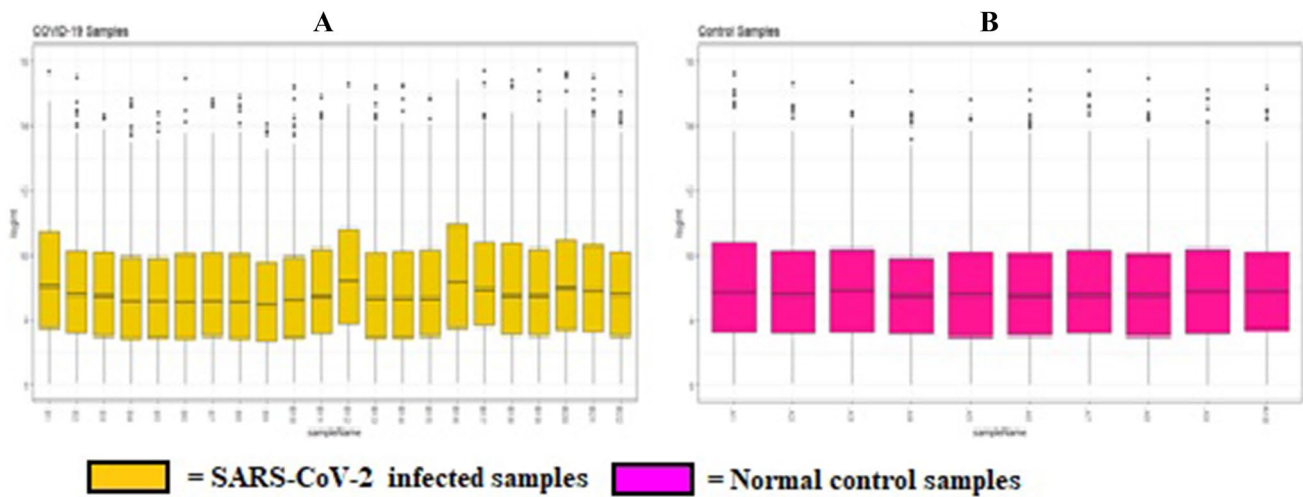


Fig. 2 Box plots of the normalized data. **a** 22 SARS-CoV-2 infected samples **b** 10 normal control samples. Horizontal axis represents the sample symbol and the vertical axis represents the gene expression values. The black line in the box plot represents the median value of gene expression

generated to manifest up-regulated (green) and down-regulated (red) genes between SARS-CoV-2-infected samples and normal controls samples (Fig. 3) and were also visualized on a heatmap for up- and down-regulated genes (Figs. 4, 5). This approach indicated presence of a total of 324 statistically significant genes ($P < 0.05$, $\log_2 \text{FC}$ (fold change) > 1.5), of which 76 genes were up-regulated and 248 genes were down-regulated (Table 1).

Pathway enrichment analysis for DEGs

Pathway enrichment analysis of integrated DEGs showed the up-regulated genes were mainly involved in measles, herpes simplex infection, IL12-mediated signaling events, IL2-mediated signaling events, cytokine signaling in immune system, innate immune system, IL22 soluble receptor signaling pathway, bioactive peptide-induced signaling pathway, JAK/STAT signaling pathway, Inflammation mediated by chemokine and cytokine signaling pathway, G protein signaling, platelet-derived growth factor signaling, intracellular signalling through adenosine receptor A2a and adenosine,

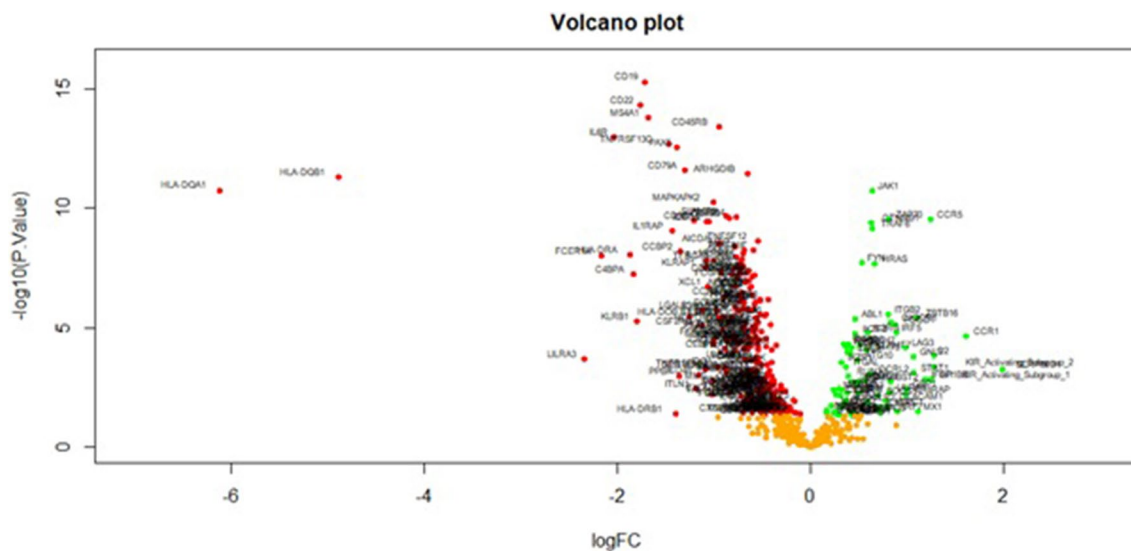


Fig. 3 Volcano plot of differentially expressed genes. Genes with a significant change of more than twofold were selected. Green dot on right side (■) represented up regulated significant genes and red dot on left side (●) represented down regulated significant genes

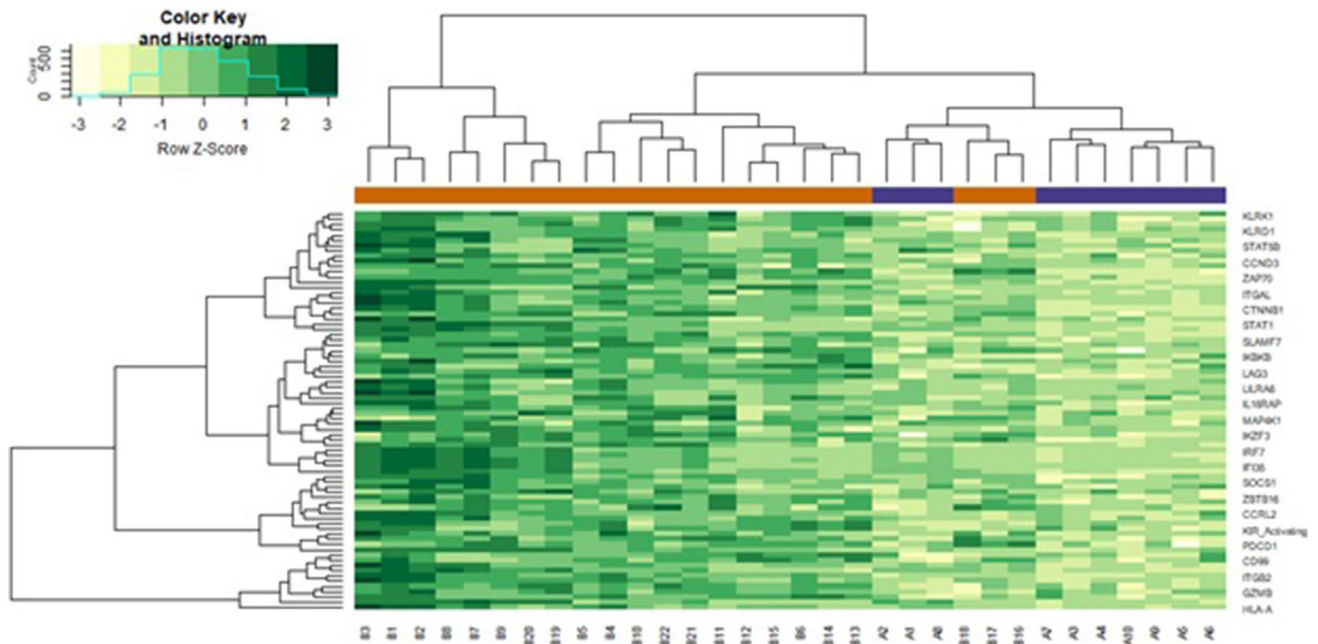


Fig. 4 Heat map of up regulated differentially expressed genes. Legend on the top left indicate log fold change of genes. White represents decreased expression of genes; light green represents not significant

expression of genes; dark green represents increased expression of genes. (A1–A10=Normal control samples; B1–B22=SARS-CoV-2 infected samples)

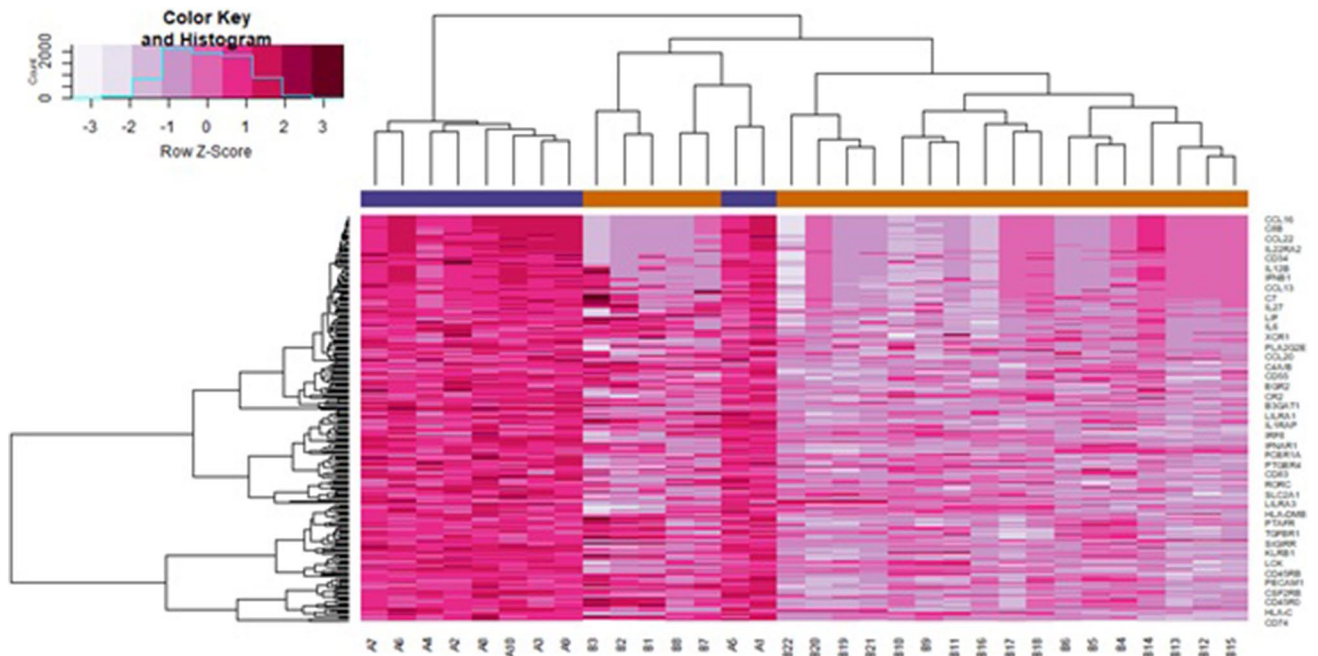


Fig. 5 Heat map of down regulated differentially expressed genes. Legend on the top left indicate log fold change of genes. White represents decreased expression of genes; light pink represents not significant

expression of genes; dark pink represents increased expression of genes. (A1–A10=Normal control samples; B1–B22=SARS-CoV-2 infected samples)

insulin signalling and other pathways (Table 2); the down-regulated genes were mainly involved in citrulline–nitric oxide cycle, phospholipases, cytokine–cytokine receptor

interaction, hematopoietic cell lineage, IL4-mediated signaling events, IL12-mediated signaling events, cytokine signaling in immune system, signaling by interleukins,

Table 1 The statistical metrics for key differentially expressed genes (DEGs)

Gene Symbol	logFC	pValue	adj.P.Val	t value	Regulation	Gene Name
JAK1	0.641818	1.84E-11	1.84E-11	9.973193	Up	Janus kinase 1
ZAP70	0.810545	2.91E-10	2.91E-10	8.897328	Up	Zeta chain of T cell receptor associated protein kinase 70
CCR5	1.239182	3.04E-10	3.04E-10	8.880753	Up	C-C motif chemokine receptor 5 (gene/pseudogene)
CTNNB1	0.633545	4.11E-10	4.11E-10	8.766907	Up	Catenin beta 1
TRAF6	0.644773	7.11E-10	7.11E-10	8.561082	Up	TNF receptor associated factor 6
FYN	0.536182	1.96E-08	1.96E-08	7.357891	Up	FYN proto-oncogene, Src family tyrosine kinase
HRAS	0.668773	2.14E-08	2.14E-08	7.325507	Up	HRas proto-oncogene, GTPase
ITGB2	0.805182	2.8E-06	2.8E-06	5.644273	Up	Integrin subunit beta 2
ZBTB16	1.099955	3.88E-06	3.88E-06	5.53388	Up	Zinc finger and BTB domain containing 16
ABL1	0.468091	4.46E-06	4.46E-06	5.486138	Up	ABL proto-oncogene 1, non-receptor tyrosine kinase
CX3CR1	0.834227	6.3E-06	6.3E-06	5.369313	Up	C-X3-C motif chemokine receptor 1
PDCD1	0.880955	7.79E-06	7.79E-06	5.297093	Up	Programmed cell death 1
IRF5	0.884364	1.56E-05	1.56E-05	5.062275	Up	Interferon regulatory factor 5
IL2RG	0.590818	1.7E-05	1.7E-05	5.032467	Up	Interleukin 2 receptor subunit gamma
IKZF3	0.467273	1.78E-05	1.78E-05	5.016592	Up	IKAROS family zinc finger 3
CCR1	1.613727	2.3E-05	2.3E-05	4.929543	Up	C-C motif chemokine receptor 1
CD99	0.398773	4.76E-05	4.76E-05	4.681138	Up	CD99 molecule (Xg blood group)
SMAD5	0.349818	5.02E-05	5.02E-05	4.662446	Up	SMAD family member 5
CD247	0.51	5.34E-05	5.34E-05	4.641555	Up	CD247 molecule
TP53	0.372273	5.85E-05	5.85E-05	4.609909	Up	Tumor protein p53
LAG3	0.988591	6.64E-05	6.64E-05	4.566916	Up	Lymphocyte activating 3
LCP2	0.432682	6.74E-05	6.74E-05	4.561553	Up	Lymphocyte cytosolic protein 2
SLAMF7	0.577409	8.58E-05	8.58E-05	4.478485	Up	SLAM family member 7
TMEM173	0.377318	0.000103	0.000103	4.416144	Up	Transmembrane protein 173
CUL9	0.4155	0.000119	0.000119	4.366647	Up	Cullin 9
C2	1.280182	0.000153	0.000153	4.279415	Up	Complement C2
GNLY	1.067364	0.000167	0.000167	4.248083	Up	Granulysin
ATG10	0.490955	0.000234	0.000234	4.130655	Up	Autophagy related 10
IKZF1	0.321682	0.000285	0.000285	4.061503	Up	IKAROS family zinc finger 1
KIR_Activating_Subgroup_2	1.279318	0.00043	0.00043	3.915229	Up	Killer-cell immunoglobulin-like receptor-Subgroup 2
ITGAL	0.370273	0.000461	0.000461	3.890576	Up	Integrin subunit alpha L
SERPING1	1.992773	0.00057	0.00057	3.815201	Up	Serpin family G member 1
STAT1	1.066864	0.000762	0.000762	3.711251	Up	signal transducer and activator of transcription 1
CCRL2	0.621773	0.000844	0.000844	3.674266	Up	C-C motif chemokine receptor like 2
RUNX1	0.392409	0.001035	0.001035	3.600334	Up	RUNX family transcription factor 1
KIR_Activating_Subgroup_1	1.243455	0.001444	0.001444	3.478418	Up	Killer-cell immunoglobulin-like receptor Subgroup 1
IFIH1	1.189	0.001492	0.001492	3.466339	Up	Interferon induced with helicase C domain 1
GP1BB	1.252364	0.001517	0.001517	3.460324	Up	Glycoprotein Ib platelet subunit beta
TBX21	0.557591	0.001716	0.001716	3.414736	Up	T-box transcription factor 21
BST2	0.825727	0.00183	0.00183	3.390875	Up	Bone marrow stromal cell antigen 2
JAK2	0.436727	0.001927	0.001927	3.371677	Up	Janus kinase 2
PSMB9	0.490864	0.001928	0.001928	3.371431	Up	Proteasome 20S subunit beta 9
XBP1	0.485455	0.002051	0.002051	3.348399	Up	X-box binding protein 1
GBP1	0.999545	0.003627	0.003627	3.133218	Up	Guanylate binding protein 1

Table 1 (continued)

Gene Symbol	logFC	pValue	adj.P.Val	t value	Regulation	Gene Name
STAT4	0.295591	0.003667	0.003667	3.129061	Up	Signal transducer and activator of transcription 4
MAP4K1	0.2385	0.003959	0.003959	3.099644	Up	Mitogen-activated protein kinase kinasekinasekinase 1
CCND3	0.326591	0.004076	0.004076	3.08846	Up	cyclin D3
LILRA6	0.817091	0.004839	0.004839	3.022071	Up	Leukocyte immunoglobulin like receptor A6
GFI1	0.495591	0.005741	0.005741	2.955427	Up	Growth factor independent 1 transcriptional repressor
HLA-A	0.385909	0.005824	0.005824	2.949825	Up	Major histocompatibility complex, class I, A
IL18RAP	0.982227	0.006135	0.006135	2.929331	Up	Interleukin 18 receptor accessory protein
C1QBP	0.264182	0.006145	0.006145	2.928686	Up	Complement C1q binding protein
CCL5	0.3105	0.006563	0.006563	2.902767	Up	C–C motif chemokine ligand 5
SOCS1	0.704318	0.007115	0.007115	2.870801	Up	Suppressor of cytokine signaling 1
STAT3	0.370545	0.010179	0.010179	2.72698	Up	Signal transducer and activator of transcription 3
CEACAM1	0.784909	0.011682	0.011682	2.670737	Up	CEA cell adhesion molecule 1
TLR2	0.589773	0.013287	0.013287	2.617647	Up	toll like receptor 2
KLRK1	0.358136	0.014239	0.014239	2.588898	Up	killer cell lectin like receptor K1
MAP4K2	0.221227	0.018828	0.018828	2.471244	Up	Mitogen-activated protein kinase kinasekinasekinase 2
KLRC1	0.7945	0.019896	0.019896	2.4477	Up	Killer cell lectin like receptor C1
ATG5	0.327	0.020137	0.020137	2.44253	Up	Autophagy related 5
IL18R1	0.713136	0.020905	0.020905	2.426467	Up	Interleukin 18 receptor 1
IKBKB	0.1695	0.027641	0.027641	2.304841	Up	Inhibitor of nuclear factor kappa B kinase subunit beta
STAT5B	0.2575	0.032278	0.032278	2.235871	Up	Signal transducer and activator of transcription 5B
MX1	1.111727	0.032817	0.032817	2.228441	Up	MX dynamin like GTPase 1
IRF7	0.898909	0.033248	0.033248	2.222589	Up	Interferon regulatory factor 7
TRAF2	0.171955	0.034273	0.034273	2.208908	Up	TNF receptor associated factor 2
IFI35	0.725909	0.035093	0.035093	2.198229	Up	Interferon induced protein 35
IKBKE	0.236545	0.035149	0.035149	2.197514	Up	Inhibitor of nuclear factor kappa B kinase subunit epsilon
CLEC7A	0.421227	0.037828	0.037828	2.164155	Up	C-type lectin domain containing 7A
LTB4R	0.465227	0.03902	0.03902	2.149988	Up	Leukotriene B4 receptor
GZMB	0.437364	0.040654	0.040654	2.131179	Up	Granzyme B
NLRP3	0.290364	0.04286	0.04286	2.106829	Up	NLR family pyrin domain containing 3
LILRB2	0.299364	0.042931	0.042931	2.106059	Up	Leukocyte immunoglobulin like receptor B2
IFNAR2	0.184136	0.048633	0.048633	2.047965	Up	Interferon alpha and beta receptor subunit 2
KLRD1	0.4455	0.049759	0.049759	2.037205	Up	Killer cell lectin like receptor D1
CD19	-1.7175	5.18E-16	5.18E-16	-14.7177	Down	CD19 molecule
CD22	-1.757	4.93E-15	4.93E-15	-13.592	Down	CD22 molecule
MS4A1	-1.67741	1.67E-14	1.67E-14	-13.0082	Down	Membrane spanning 4-domains A1
CD45RB	-0.94709	4.17E-14	4.17E-14	-12.5832	Down	Receptor-Type Tyrosine-Protein Phosphatase C
IL6R	-2.0375	1.05E-13	1.05E-13	-12.164	Down	interleukin 6 receptor
TNFRSF13C	-1.46186	2.18E-13	2.18E-13	-11.8375	Down	TNF receptor superfamily member 13C
PAX5	-1.37636	2.92E-13	2.92E-13	-11.7085	Down	Paired box 5
CD79A	-1.29577	2.53E-12	2.53E-12	-10.7841	Down	CD79a molecule
ARHGDI3	-0.65064	3.68E-12	3.68E-12	-10.6278	Down	Rho GDP dissociation inhibitor beta
HLA-DQB1	-4.88305	5.18E-12	5.18E-12	-10.4865	Down	Major histocompatibility complex, class II, DQ beta 1

Table 1 (continued)

Gene Symbol	logFC	pValue	adj.P.Val	t value	Regulation	Gene Name
HLA-DQA1	-6.1155	1.8E-11	1.8E-11	-9.98021	Down	Major histocompatibility complex, class II, DQ alpha 1
MAPKAPK2	-0.99755	5.49E-11	5.49E-11	-9.53915	Down	MAPK activated protein kinase 2
SLAMF6	-0.87414	2.16E-10	2.16E-10	-9.01008	Down	SLAM family member 6
PTGER4	-0.76932	2.43E-10	2.43E-10	-8.96519	Down	Prostaglandin E receptor 4
CD79B	-0.84082	2.75E-10	2.75E-10	-8.91788	Down	CD79b molecule
CD97	-1.1985	3.22E-10	3.22E-10	-8.85915	Down	Leukocyte antigen CD97
IL1RL2	-1.04873	3.57E-10	3.57E-10	-8.81964	Down	Interleukin 1 receptor like 2
CD1A	-1.07114	3.6E-10	3.6E-10	-8.81626	Down	CD1a molecule
IL1RAP	-1.43418	8.92E-10	8.92E-10	-8.47672	Down	Interleukin 1 receptor accessory protein
TNFSF12	-0.53718	2.42E-09	2.42E-09	-8.10915	Down	TNF superfamily member 12
AICDA	-0.94759	2.89E-09	2.89E-09	-8.04473	Down	Activation induced cytidine deaminase
MBP	-0.77614	4.02E-09	4.02E-09	-7.92468	Down	myelin basic protein
TRAF4	-0.67777	5.69E-09	5.69E-09	-7.79888	Down	TNF receptor associated factor 4
MIF	-0.59309	5.94E-09	5.94E-09	-7.78344	Down	Macrophage migration inhibitory factor
CCBP2	-1.34027	6.31E-09	6.31E-09	-7.76207	Down	Chemokine-binding protein 2
CCL22	-0.68986	8.3E-09	8.3E-09	-7.66358	Down	C-C motif chemokine ligand 22
HLA-DRA	-1.87223	9.28E-09	9.28E-09	-7.62328	Down	Major histocompatibility complex, class II, DR alpha
FCER1A	-2.15768	9.79E-09	9.79E-09	-7.60411	Down	Fc fragment of IgE receptor 1a
LILRB5	-0.76595	1.11E-08	1.11E-08	-7.55809	Down	Leukocyte immunoglobulin like receptor B5
CCL15	-0.7105	1.48E-08	1.48E-08	-7.4567	Down	C-C motif chemokine ligand 15
IL12B	-0.99886	1.5E-08	1.5E-08	-7.45174	Down	Interleukin 12B
TFRC	-1.07782	1.61E-08	1.61E-08	-7.42698	Down	Transferrin receptor
EBI3	-0.72195	1.86E-08	1.86E-08	-7.37653	Down	Epstein-Barr virus induced 3
IL4	-0.69941	2.72E-08	2.72E-08	-7.24189	Down	Interleukin 4
ICAM2	-0.74745	2.86E-08	2.86E-08	-7.22422	Down	Intercellular adhesion molecule 2
KLRAP1	-1.0865	3.09E-08	3.09E-08	-7.19683	Down	Killer cell lectin-like receptor subfamily A pseudogene 1
CD40	-0.79436	3.29E-08	3.29E-08	-7.17439	Down	CD40 molecule
IL22RA2	-0.6365	4.34E-08	4.34E-08	-7.07766	Down	Interleukin 22 receptor subunit alpha 2
IL2	-0.64395	4.65E-08	4.65E-08	-7.05298	Down	Interleukin 2
IL29	-0.64395	4.65E-08	4.65E-08	-7.05298	Down	Interleukin 29
CD3E	-0.73018	5.24E-08	5.24E-08	-7.01159	Down	CD3e molecule
CD55	-0.92114	5.29E-08	5.29E-08	-7.00828	Down	CD55 molecule (Cromer blood group)
IL19	-0.6555	5.33E-08	5.33E-08	-7.00515	Down	Interleukin 19
NOS2	-0.81432	5.6E-08	5.6E-08	-6.98829	Down	Nitric oxide synthase 2
C4BPA	-1.83359	5.78E-08	5.78E-08	-6.97697	Down	Complement component 4 binding protein alpha
CCL26	-0.57677	6.5E-08	6.5E-08	-6.93596	Down	C-C motif chemokine ligand 26
CDH5	-0.60586	7.09E-08	7.09E-08	-6.90577	Down	Cadherin 5
IL9	-0.60586	7.09E-08	7.09E-08	-6.90577	Down	Interleukin 9
FCGRT	-0.75709	8.18E-08	8.18E-08	-6.85603	Down	Fc fragment of IgG receptor and transporter
C8B	-0.6555	1.1E-07	1.1E-07	-6.75159	Down	Complement C8 beta chain
IL5	-0.64086	1.16E-07	1.16E-07	-6.7344	Down	Interleukin 5
PIGR	-0.66695	1.33E-07	1.33E-07	-6.68821	Down	Polymeric immunoglobulin receptor
XCL1	-1.06423	1.98E-07	1.98E-07	-6.54928	Down	X-C motif chemokine ligand 1
AIRE	-0.78032	2.01E-07	2.01E-07	-6.5441	Down	Autoimmune regulator
IL3	-0.60723	2.08E-07	2.08E-07	-6.53283	Down	Interleukin 3
CCL16	-0.6195	2.31E-07	2.31E-07	-6.4973	Down	C-C motif chemokine ligand 16

Table 1 (continued)

Gene Symbol	logFC	pValue	adj.P.Val	t value	Regulation	Gene Name
CCL7	-0.6195	2.31E-07	2.31E-07	-6.4973	Down	C-C motif chemokine ligand 7
CSF2	-0.6195	2.31E-07	2.31E-07	-6.4973	Down	Colony stimulating factor 2
ITLN2	-0.6195	2.31E-07	2.31E-07	-6.4973	Down	Intelectin 2
THY1	-0.6195	2.31E-07	2.31E-07	-6.4973	Down	Thy-1 cell surface antigen
IL21	-0.70245	3.28E-07	3.28E-07	-6.37574	Down	Interleukin 21
BCL2	-0.7385	4.11E-07	4.11E-07	-6.29854	Down	BCL2 apoptosis regulator
EDNRB	-0.60541	4.11E-07	4.11E-07	-6.29833	Down	Endothelin receptor type B
CCR6	-0.88205	4.78E-07	4.78E-07	-6.24666	Down	C-C motif chemokine receptor 6
TIRAP	-0.70182	5.91E-07	5.91E-07	-6.17398	Down	TIR domain containing adaptor protein
STAT6	-0.52186	6.37E-07	6.37E-07	-6.14848	Down	Signal transducer and activator of transcription 6
PSMB10	-0.43945	6.43E-07	6.43E-07	-6.14519	Down	Proteasome 20S subunit beta 10
SKI	-0.52182	7.16E-07	7.16E-07	-6.10886	Down	SKI proto-oncogene
RAG2	-0.56723	8.47E-07	8.47E-07	-6.05149	Down	Recombination activating 2
CD209	-0.7285	8.56E-07	8.56E-07	-6.04758	Down	CD209 molecule
VTN	-0.68305	9.43E-07	9.43E-07	-6.01488	Down	Vitronectin
IFNB1	-0.57768	9.97E-07	9.97E-07	-5.99573	Down	Interferon beta 1
EOMES	-0.77505	1.47E-06	1.47E-06	-5.8643	Down	Eomesodermin
CD74	-0.69905	1.52E-06	1.52E-06	-5.85145	Down	CD74 molecule
CCR10	-0.60368	1.7E-06	1.7E-06	-5.81503	Down	C-C motif chemokine receptor 10
LGALS3	-1.12309	1.85E-06	1.85E-06	-5.78563	Down	Galectin 3
PDGFB	-0.64241	1.86E-06	1.86E-06	-5.78395	Down	Platelet derived growth factor subunit B
ICAM4	-0.96814	1.96E-06	1.96E-06	-5.76557	Down	Intercellular adhesion molecule 4 (Landsteiner-Wiener blood group)
ICOSLG	-0.74791	2.07E-06	2.07E-06	-5.74698	Down	Inducible T cell costimulator ligand
C9	-0.52132	2.66E-06	2.66E-06	-5.66169	Down	Complement C9
IL16	-0.45973	2.88E-06	2.88E-06	-5.63467	Down	Interleukin 16
RELA	-0.47205	3.09E-06	3.09E-06	-5.61097	Down	RELA proto-oncogene, NF-kB subunit
DEFB1	-0.8105	3.38E-06	3.38E-06	-5.58051	Down	Defensin beta 1
IL13RA1	-0.90159	3.41E-06	3.41E-06	-5.57755	Down	Interleukin 13 receptor subunit alpha 1
HLA-DOB	-1.24595	3.65E-06	3.65E-06	-5.55493	Down	Major histocompatibility complex, class II, DO beta
KIR3DL3	-0.56905	3.78E-06	3.78E-06	-5.54244	Down	Killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 3
HLA-C	-0.93941	3.97E-06	3.97E-06	-5.52568	Down	Major histocompatibility complex, class I, C
KLRB1	-1.79632	5.31E-06	5.31E-06	-5.42732	Down	Killer cell lectin like receptor B1
HLA-DMB	-0.85005	5.86E-06	5.86E-06	-5.39367	Down	Major histocompatibility complex, class II, DM beta
KLRF2	-0.53859	6E-06	6E-06	-5.3857	Down	Killer cell lectin like receptor F2
ICAM3	-0.66718	6.38E-06	6.38E-06	-5.36481	Down	Intercellular adhesion molecule 3
IL28A	-0.55718	7.03E-06	7.03E-06	-5.33194	Down	Interleukin 28A
SIGIRR	-0.41545	7.52E-06	7.52E-06	-5.30925	Down	Single Ig and TIR domain containing
MASP2	-0.68927	7.93E-06	7.93E-06	-5.29109	Down	Mannan binding lectin serine peptidase 2
CSF2RB	-1.12332	8.36E-06	8.36E-06	-5.27318	Down	Colony stimulating factor 2 receptor beta common subunit
CD46	-0.59905	9.11E-06	9.11E-06	-5.24408	Down	CD46 molecule
S1PR1	-0.60436	9.23E-06	9.23E-06	-5.23966	Down	Sphingosine - 1-phosphate receptor 1
TLR9	-0.56841	1.05E-05	1.05E-05	-5.19438	Down	Toll like receptor 9
HLA-DPB1	-0.70064	1.07E-05	1.07E-05	-5.19046	Down	Major histocompatibility complex, class II, DP beta 1

Table 1 (continued)

Gene Symbol	logFC	pValue	adj.P.Val	t value	Regulation	Gene Name
CCL13	-0.57018	1.16E-05	1.16E-05	-5.16161	Down	C-C motif chemokine ligand 13
PLA2G2E	-0.67155	1.19E-05	1.19E-05	-5.15362	Down	Phospholipase A2 group IIE
IL20	-0.67032	1.29E-05	1.29E-05	-5.12687	Down	Interleukin 20
PTAFR	-0.91373	1.37E-05	1.37E-05	-5.10671	Down	Platelet activating factor receptor
TGFBI	-0.59209	1.44E-05	1.44E-05	-5.08943	Down	Transforming growth factor beta induced
IL26	-0.50514	1.52E-05	1.52E-05	-5.07029	Down	Interleukin 26
IFNAR1	-0.78755	2.03E-05	2.03E-05	-4.97214	Down	Interferon alpha and beta receptor subunit 1
LTA	-0.56282	2.17E-05	2.17E-05	-4.94915	Down	Lymphotoxin alpha
FCGR2B	-0.85355	2.4E-05	2.4E-05	-4.91443	Down	Fc fragment of IgG receptor IIb
EGR1	-0.63082	2.41E-05	2.41E-05	-4.9133	Down	Early growth response 1
CD86	-0.76691	2.54E-05	2.54E-05	-4.89525	Down	CD86 molecule
CD82	-0.99568	2.76E-05	2.76E-05	-4.86674	Down	CD82 molecule
CD34	-0.56045	2.79E-05	2.79E-05	-4.86293	Down	CD34 molecule
TRAF3	-0.46214	2.87E-05	2.87E-05	-4.85429	Down	TNF receptor associated factor 3
CTLA4	-0.53577	3E-05	3E-05	-4.83886	Down	Cytotoxic T-Lymphocyte Associated Protein 4
HAMP	-0.61205	3E-05	3E-05	-4.83856	Down	Hepcidin antimicrobial peptide
EGR2	-0.78873	3.15E-05	3.15E-05	-4.82228	Down	Early growth response 2
ICAM5	-0.53214	3.22E-05	3.22E-05	-4.81493	Down	Intercellular adhesion molecule 5
CSF1R	-0.70273	3.45E-05	3.45E-05	-4.79056	Down	Colony stimulating factor 1 receptor
NT5E	-0.85836	3.68E-05	3.68E-05	-4.76884	Down	5'-nucleotidase ecto
IL7	-0.74464	4.3E-05	4.3E-05	-4.71548	Down	Interleukin 7
CTSS	-0.62991	4.34E-05	4.34E-05	-4.71277	Down	Cathepsin S
IL17B	-0.55268	4.82E-05	4.82E-05	-4.6769	Down	Interleukin 17B
CR2	-1.00786	4.86E-05	4.86E-05	-4.67369	Down	Complement C3d receptor 2
CD44	-0.35164	5.25E-05	5.25E-05	-4.64701	Down	CD44 molecule (Indian blood group)
PLA2G2A	-0.53655	5.77E-05	5.77E-05	-4.61492	Down	Phospholipase A2 group IIA
BTK	-0.45495	5.87E-05	5.87E-05	-4.60896	Down	Bruton tyrosine kinase
C6	-0.65964	5.95E-05	5.95E-05	-4.60439	Down	Complement C6
IRGM	-0.62291	6.21E-05	6.21E-05	-4.58953	Down	Immunity related GTPase M
IL22	-0.65314	7.15E-05	7.15E-05	-4.54121	Down	Interleukin 22
CEBPB	-0.88709	7.69E-05	7.69E-05	-4.51625	Down	CCAAT enhancer binding protein beta
IL6	-0.69105	7.91E-05	7.91E-05	-4.50639	Down	Interleukin 6
IFNA2	-0.77586	8.23E-05	8.23E-05	-4.49296	Down	Interferon alpha 2
TGFBR1	-0.40336	8.66E-05	8.66E-05	-4.47511	Down	Transforming growth factor beta receptor 1
IL17F	-0.54009	8.83E-05	8.83E-05	-4.4686	Down	Interleukin 17F
IL28A/B	-0.55282	0.000163	0.000163	-4.25674	Down	Interleukin 28A/B
IL17A	-0.53723	0.00018	0.00018	-4.22236	Down	Interleukin 17A
LILRA2	-0.68495	0.000195	0.000195	-4.194	Down	Leukocyte immunoglobulin like receptor A2
LILRA3	-2.33691	0.000203	0.000203	-4.18055	Down	Leukocyte immunoglobulin like receptor A3
VCAM1	-0.60605	0.000219	0.000219	-4.15259	Down	Vascular cell adhesion molecule 1
SPP1	-0.6555	0.000221	0.000221	-4.1496	Down	Secreted phosphoprotein 1
CARD9	-0.55227	0.000269	0.000269	-4.0818	Down	Caspase recruitment domain family member 9
LCK	-0.40364	0.000299	0.000299	-4.04398	Down	LCK proto-oncogene, Src family tyrosine kinase
SELE	-0.52332	0.000306	0.000306	-4.03551	Down	selectin E
SLC2A1	-0.44118	0.00036	0.00036	-3.97865	Down	solute carrier family 2 member 1
LIF	-0.50555	0.000368	0.000368	-3.97037	Down	LIF interleukin 6 family cytokine
IDO1	-0.95541	0.000417	0.000417	-3.92685	Down	Indoleamine 2,3-dioxygenase 1

Table 1 (continued)

Gene Symbol	logFC	pValue	adj.P.Val	t value	Regulation	Gene Name
TNFRSF10C	-0.88564	0.000471	0.000471	-3.88294	Down	TNF receptor superfamily member 10c
IL23A	-0.87541	0.000557	0.000557	-3.82374	Down	interleukin 23 subunit alpha
CD80	-0.58964	0.000567	0.000567	-3.81702	Down	CD80 molecule
GPR183	-1.088	0.00057	0.00057	-3.81527	Down	G protein-coupled receptor 183
C1R	-0.41727	0.000592	0.000592	-3.8018	Down	Complement C1r
CCL11	-0.55055	0.000611	0.000611	-3.79064	Down	C-C motif chemokine ligand 11
HLA-DPA1	-0.6385	0.000637	0.000637	-3.77577	Down	major histocompatibility complex, class II, DP alpha 1
IFNG	-0.877	0.00073	0.00073	-3.72658	Down	Interferon gamma
DUSP4	-0.70741	0.000789	0.000789	-3.69861	Down	Dual specificity phosphatase 4
IL27	-0.44905	0.000852	0.000852	-3.67089	Down	Interleukin 27
CD48	-1.15805	0.000953	0.000953	-3.6304	Down	CD48 molecule
FN1	-0.56177	0.001005	0.001005	-3.61111	Down	fibronectin 1
CD244	-0.39427	0.001018	0.001018	-3.60646	Down	CD244 molecule
PPBP	-1.35464	0.001091	0.001091	-3.58105	Down	pro-platelet basic protein
IL13	-0.599	0.001204	0.001204	-3.54515	Down	interleukin 13
CCL24	-0.45395	0.001221	0.001221	-3.53987	Down	C-C motif chemokine ligand 24
GATA3	-0.55041	0.001228	0.001228	-3.53797	Down	GATA binding protein 3
BID	-0.46636	0.001281	0.001281	-3.52243	Down	BH3 interacting domain death agonist
BCL2L11	-0.40091	0.001565	0.001565	-3.44881	Down	BCL2 like 11
KIT	-0.52868	0.001589	0.001589	-3.44316	Down	KIT proto-oncogene, receptor tyrosine kinase
MME	-1.00591	0.001596	0.001596	-3.44151	Down	Membrane metalloendopeptidase
ZEB1	-0.38082	0.001667	0.001667	-3.42548	Down	Zinc finger E-box binding homeobox 1
C4A/B	-0.62314	0.001738	0.001738	-3.40994	Down	Complement C4A/B
FCAR	-0.50423	0.00198	0.00198	-3.36169	Down	Fc fragment of IgA receptor
BTLA	-0.45623	0.002033	0.002033	-3.35183	Down	B and T lymphocyte associated
TAGAP	-0.38886	0.002261	0.002261	-3.31206	Down	T cell activation RhoGTPase activating protein
CD83	-0.39914	0.002292	0.002292	-3.307	Down	CD83 molecule
SELPLG	-0.37564	0.002362	0.002362	-3.29575	Down	Selectin P ligand
B3GAT1	-0.66791	0.002423	0.002423	-3.28614	Down	Beta-1,3-glucuronyltransferase 1
CCRL1	-0.39195	0.002543	0.002543	-3.26788	Down	C-C chemokine receptor type 11
TNFRSF14	-0.29986	0.002557	0.002557	-3.26588	Down	TNF receptor superfamily member 14
CSF3R	-0.65318	0.003003	0.003003	-3.20507	Down	Colony stimulating factor 3 receptor
CD9	-0.87091	0.003004	0.003004	-3.20497	Down	CD9 molecule
C1S	-0.52059	0.003211	0.003211	-3.17969	Down	complement C1s
PECAM1	-0.30873	0.003251	0.003251	-3.17496	Down	platelet and endothelial cell adhesion molecule 1
DEFB103B	-0.4315	0.003466	0.003466	-3.15055	Down	Defensin beta 103B
ITLN1	-1.17682	0.003488	0.003488	-3.14815	Down	Intelectin 1
CXCL13	-0.46586	0.003554	0.003554	-3.14101	Down	C-X-C motif chemokine ligand 13
RAG1	-0.47836	0.003917	0.003917	-3.10376	Down	Recombination activating 1
TNFRSF4	-0.55123	0.004154	0.004154	-3.08112	Down	TNF receptor superfamily member 4
C14orf166	-0.35727	0.004255	0.004255	-3.07189	Down	Chromosome 14 open reading frame 166
IL10RA	-0.26059	0.004423	0.004423	-3.0569	Down	Interleukin 10 receptor subunit alpha
POU2F2	-0.292	0.004614	0.004614	-3.04059	Down	POU class 2 homeobox 2
C7	-0.41223	0.004688	0.004688	-3.03441	Down	complement C7
RORC	-0.52768	0.005006	0.005006	-3.00891	Down	RAR related orphan receptor C
CXCL11	-0.83891	0.005151	0.005151	-2.99784	Down	C-X-C motif chemokine ligand 11

Table 1 (continued)

Gene Symbol	logFC	pValue	adj.P.Val	t value	Regulation	Gene Name
MASP1	-0.50677	0.005182	0.005182	-2.99543	Down	Mannan binding lectin serine peptidase 1
MAP4K4	-0.37777	0.005449	0.005449	-2.97583	Down	Mitogen-activated protein kinase kinasekinasekinase 4
CX3CL1	-0.50445	0.005597	0.005597	-2.96535	Down	C-X3-C motif chemokine ligand 1
BATF3	-0.62586	0.005862	0.005862	-2.94725	Down	Basic leucine zipper ATF-like transcription factor 3
CCR8	-0.51627	0.005946	0.005946	-2.94164	Down	C-C motif chemokine receptor 8
TAL1	-1.01455	0.006016	0.006016	-2.93707	Down	TAL bHLH transcription factor 1, erythroid differentiation factor
NFIL3	-0.723	0.007	0.007	-2.87725	Down	Nuclear factor, interleukin 3 regulated
CD8A	-0.50595	0.007337	0.007337	-2.85858	Down	CD8a molecule
CLEC6A	-0.62323	0.007445	0.007445	-2.85274	Down	C-type lectin domain containing 6A
TCF4	-0.37827	0.007904	0.007904	-2.8289	Down	Transcription factor 4
FCGR2A	-0.664	0.009089	0.009089	-2.77283	Down	Fc fragment of IgG receptor IIa
HLA-B	-0.31677	0.00918	0.00918	-2.76877	Down	major histocompatibility complex, class I, B
IRF8	-0.39477	0.009346	0.009346	-2.76157	Down	Interferon regulatory factor 8
MAPK11	-0.60427	0.010152	0.010152	-2.72804	Down	Mitogen-activated protein kinase 11
ILF3	-0.17055	0.010366	0.010366	-2.71958	Down	Interleukin enhancer binding factor 3
XCR1	-0.34541	0.01065	0.01065	-2.70856	Down	X-C motif chemokine receptor 1
ITGAE	-0.33509	0.011424	0.011424	-2.67988	Down	Integrin subunit alpha E
IL4R	-0.69064	0.012538	0.012538	-2.64162	Down	Interleukin 4 receptor
CTSC	-0.16718	0.012619	0.012619	-2.63897	Down	Cathepsin C
ETS1	-0.39405	0.013255	0.013255	-2.61865	Down	ETS proto-oncogene 1, transcription factor
CFI	-0.30082	0.013335	0.013335	-2.61614	Down	Complement factor I
STAT5A	-0.27168	0.014802	0.014802	-2.57273	Down	Signal transducer and activator of transcription 5A
C8A	-0.37964	0.016204	0.016204	-2.53478	Down	Complement C8 alpha chain
DEFB4A	-0.36691	0.017835	0.017835	-2.49428	Down	Defensin beta 4A
RELB	-0.45095	0.019351	0.019351	-2.45958	Down	RELB proto-oncogene, NF-kB subunit
ATG7	-0.32859	0.01984	0.01984	-2.4489	Down	Autophagy related 7
DPP4	-0.38823	0.01999	0.01999	-2.44568	Down	Dipeptidyl peptidase 4
GPI	-0.21382	0.020424	0.020424	-2.43646	Down	Glucose-6-phosphate isomerase
CD59	-0.24032	0.020561	0.020561	-2.43359	Down	CD59 molecule (CD59 blood group)
CASP3	-0.40573	0.025629	0.025629	-2.33807	Down	Caspase 3
TIGIT	-0.3615	0.025963	0.025963	-2.33239	Down	T cell immunoreceptor with Ig and ITIM domains
CFD	-0.36627	0.026073	0.026073	-2.33053	Down	Complement factor D
CCL18	-0.42077	0.026944	0.026944	-2.3161	Down	C-C motif chemokine ligand 18
PLAU	-0.34086	0.028132	0.028132	-2.29706	Down	Plasminogen activator, urokinase
PTPN22	-0.20086	0.028829	0.028829	-2.28623	Down	Protein tyrosine phosphatase non-receptor type 22
TOLLIP	-0.27377	0.028911	0.028911	-2.28497	Down	Toll interacting protein
CXCR2	-0.49195	0.029438	0.029438	-2.27696	Down	C-X-C motif chemokine receptor 2
CCL20	-0.34555	0.029871	0.029871	-2.27048	Down	C-C motif chemokine ligand 20
IL12A	-0.40759	0.03046	0.03046	-2.26179	Down	Interleukin 12A
IL10	-0.33555	0.03205	0.03205	-2.23904	Down	Interleukin 10
LILRA1	-0.26991	0.033542	0.033542	-2.21862	Down	leukocyte immunoglobulin like receptor A1
PTPN6	-0.16109	0.034722	0.034722	-2.20304	Down	protein tyrosine phosphatase non-receptor type 6
CCL19	-0.37718	0.035605	0.035605	-2.19168	Down	C-C motif chemokine ligand 19
IKBKAP	-0.15505	0.035624	0.035624	-2.19144	Down	IκB kinase complex-associated protein

Table 1 (continued)

Gene Symbol	logFC	pValue	adj.P.Val	t value	Regulation	Gene Name
TNFRSF9	-0.50786	0.036235	0.036235	-2.18372	Down	TNF receptor superfamily member 9
TCF7	-0.60091	0.036564	0.036564	-2.17963	Down	Transcription factor 7
HLA-DMA	-0.30777	0.036925	0.036925	-2.17516	Down	Major histocompatibility complex, class II, DM alpha
CXCL12	-0.69291	0.037168	0.037168	-2.17218	Down	C-X-C motif chemokine ligand 12
MBL2	-0.37009	0.037623	0.037623	-2.16664	Down	Mannose binding lectin 2
IKZF2	-0.46655	0.039489	0.039489	-2.14452	Down	IKAROS family zinc finger 2
BCAP31	-0.10632	0.04075	0.04075	-2.13009	Down	B cell receptor associated protein 31
HLA-DRB1	-1.39495	0.041403	0.041403	-2.12278	Down	Major histocompatibility complex, class II, DR beta 1
IRAK4	-0.23727	0.041428	0.041428	-2.12251	Down	Interleukin 1 receptor associated kinase 4
CXCR1	-0.49741	0.041833	0.041833	-2.11802	Down	C-X-C motif chemokine receptor 1
PTK2	-0.33609	0.043242	0.043242	-2.10272	Down	Protein tyrosine kinase 2
CD45R0	-0.46514	0.043373	0.043373	-2.10132	Down	A member of leucocyte common antigen family

phenylalanine tyrosine and tryptophan biosynthesis, MAP kinase activity, genes encoding secreted soluble factors, cytokine network, interleukin signaling pathway, inflammation mediated by chemokine and cytokine signaling pathway, intrinsic apoptotic, interleukin-10 signaling, sulindac pathway, glycolysis and other pathways (Table 3).

Gene ontology (GO) enrichment analysis for DEGs

The GO enrichment analysis of up- and down-regulated genes can be split into three groups: BP, CC, and MF are listed in Tables 4, 5. In terms of BP, the up-regulated genes were mainly involved in regulation of immune system process, response to biotic stimulus and other functions; the down-regulated genes were mainly associated in regulation of immune system process, cytokine-mediated signaling pathway and other functions. As far as CC is concerned, the up-regulated genes were mainly involved in the side of membrane, receptor complex and other functions; the down-regulated genes were mainly located in the cell surface, leaflet of membrane layers and other functions. As for MF, the up-regulated genes mainly participated in kinase binding, signaling receptor binding and other functions; the down-regulated genes mainly participated in cytokine receptor binding, signaling receptor binding and other functions (Tables 4, 5).

PPI network construction and module analysis

To determine the expression relationships among up- and down-regulated genes, we inputted the up- and down-regulated genes to STRING PPI database. Then, PPI networks were visualized using the cytoscape software. As a result, a PPI network for up-regulated genes had 2912 nodes and

5967 edges (Fig. 6). Among these nodes, TP53, HRAS, CTNBN1, FYN, ABL1, STAT3, STAT1, JAK2, C1QBP, XBP1, BST2, CD99 and IFI35 were identified as hub genes with highest node degree distribution, betweenness centrality, stress centrality, closeness centrality and lowest clustering coefficient are listed in Table 6. The scatter plots for this network are shown in Fig. 7a–e. Enrichment analysis showed that the genes were mainly associated with measles, natural killer cell mediated cytotoxicity, HTLV-I infection, regulation of immune system process, viral myocarditis, Jak-STAT signaling pathway, herpes simplex infection, hemostasis, response to biotic stimulus, cytokine signaling in immune system, integral component of plasma membrane and response to biotic stimulus. A PPI network for down-regulated genes had 3083 nodes and 6491 edges (Fig. 8). Among these nodes, MAPK11, RELA, LCK, KIT, EGR1, IL20, ILF3, CASP3, IL19, ATG7, GPI and S1PR1 were identified as hub genes with highest node degree distribution, betweenness centrality, stress centrality, closeness centrality and lowest clustering coefficient are listed in Table 6. The scatter plots for this network are shown in Fig. 9a–e. Enrichment analysis showed that the genes were mainly associated with tuberculosis, inflammatory bowel disease (IBD), HTLV-I infection, cytokine–cytokine receptor interaction, cytokine-mediated signaling pathway, regulation of immune system process, response to biotic stimulus, response to cytokine, cytokine production, innate immune system, glycolysis, gluconeogenesis and the extracellular signal-regulated RAF/MEK/ERK signaling.

Based on STRING database, plug-ins PEWCC1 was used to carry out module analysis in Cytoscape software. We identified total 566 and 548 modules from the PPI network of up- and down-regulated genes according to the degree of importance and further analyzed with the plug-in

Table 2 The enriched pathway terms of the up regulated differentially expressed genes

KEGG	Pathway Name	P-value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
213306	Measles	3.21E-17	4.46E-15	2.46E-14	4.46E-15	16	CCND3, JAK1, JAK2, IFIH1, TRAF6, IKKBE, TLR2, IRF7, FYN, IL2RG, STAT1, TP53, STAT3, MX1, STAT5B, IFNAR2
377873	Herpes simplex infection	1.19E-13	8.24E-12	4.54E-11	1.65E-11	15	JAK1, JAK2, IFIH1, TRAF2, TRAF6, HLA-A, IKKBE, TLR2, C1QBP, CCL5, IRF7, IKKKB, STAT1, TP53, IFNAR2
83079	Natural killer cell mediated cytotoxicity	5.40E-13	2.50E-11	1.38E-10	7.51E-11	13	KLRK1, CD247, HLA-A, GZMB, HRAS, LCP2, ITGAL, FYN, ITGB2, KLRC1, ZAP70, KLRD1, IFNAR2
193147	Osteoclast differentiation	1.85E-10	3.32E-09	1.83E-08	2.57E-08	11	JAK1, TRAF2, TRAF6, LILRB2, LILRA6, SOCS1, IKKKB, LCP2, FYN, STAT1, IFNAR2
83077	Jak-STAT signaling pathway	1.31E-09	1.83E-08	1.01E-07	1.83E-07	11	CCND3, JAK1, JAK2, HRAS, SOCS1, IL2RG, STAT1, STAT3, STAT4, STAT5B, IFNAR2
217173	Influenza A	3.94E-09	4.56E-08	2.51E-07	5.47E-07	11	JAK1, JAK2, IFIH1, IKKBE, CCL5, IRF7, IKKKB, STAT1, NLRP3, MX1, IFNAR2
373901	HTLV-1 infection	2.27E-08	2.11E-07	1.16E-06	3.16E-06	12	CCND3, JAK1, HLA-A, HRAS, XBPI, CTNNB1, IKKKB, ITGAL, ITGB2, IL2RG, TP53, STAT5B
658418	Viral carcinogenesis	2.16E-07	1.67E-06	9.20E-06	3.00E-05	10	CCND3, JAK1, TRAF2, HLA-A, HRAS, IRF7, CCR5, TP53, STAT3, STAT5B
83080	T cell receptor signaling pathway	2.05E-06	1.36E-05	7.47E-05	2.85E-04	7	PDCD1, CD247, HRAS, IKKKB, LCP2, FYN, ZAP70
125138	Viral myocarditis	2.21E-05	1.18E-04	6.51E-04	3.07E-03	5	ABL1, HLA-A, ITGAL, FYN, ITGB2
213780	Tuberculosis	7.57E-05	3.63E-04	2.00E-03	1.05E-02	7	JAK1, JAK2, TRAF6, TLR2, CLEC7A, ITGB2, STAT1
83051	Cytokine-cytokine receptor interaction	1.59E-04	6.69E-04	3.69E-03	2.21E-02	8	CCR1, CCL5, CCR5, IL18RAP, IL2RG, IL18R1, CX3CRI, IFNAR2
152665	Malaria	1.79E-04	7.32E-04	4.04E-03	2.49E-02	4	KLRK1, TLR2, ITGAL, ITGB2
Pathway interaction database							
137922	IL12-mediated signaling events	1.37E-17	1.56E-15	8.29E-15	1.56E-15	13	JAK2, CD247, HLA-A, TBX21, GZMB, SOCS1, CCR5, IL18RAP, IL2RG, IL18R1, STAT1, STAT3, STAT4
137976	IL2-mediated signaling events	5.15E-10	2.94E-08	1.56E-07	5.88E-08	8	JAK1, IKZF3, SOCS1, FYN, IL2RG, STAT1, STAT3, STAT5B
138055	TCR signaling in naive CD8 + T cells	9.79E-09	2.35E-07	1.25E-06	1.12E-06	7	TRAF6, CD247, HLA-A, IKKKB, LCP2, FYN, ZAP70
138071	PDGFR-beta signaling pathway	6.28E-07	7.16E-06	3.81E-05	7.16E-05	6	ABL1, HRAS, FYN, STAT1, STAT3, STAT5B
137988	IL2 signaling events mediated by STAT5	2.52E-05	2.21E-04	1.17E-03	2.87E-03	4	CCND3, JAK1, IL2RG, STAT5B
138019	p75(NTR)-mediated signaling	5.25E-03	2.32E-02	1.23E-01	5.99E-01	3	TRAF6, IKKKB, TP53
138021	Paxillin-dependent events mediated by a4b1	5.29E-03	2.32E-02	1.23E-01	6.03E-01	2	ITGAL, ITGB2
137940	Signaling events mediated by VEGFR1 and VEGFR2	5.75E-03	2.43E-02	1.29E-01	6.55E-01	3	HRAS, CTNNB1, FYN



Table 2 (continued)

Pathway ID	Pathway Name	P-value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
137983	ALK2 signaling events	6.18E-02	1.22E-01	6.47E-01	1.00E+00	1	SMAD5
138046	Syndecan-1-mediated signaling events	9.40E-02	1.70E-01	9.04E-01	1.00E+00	1	CCL5
REACTOME							
1269310	Cytokine Signaling in Immune system	3.94E-16	2.05E-13	1.40E-12	2.05E-13	28	JAK1, JAK2, TRAF2, TRAF6, HLA-A, BST2, HRAS, PSMB9, GBP1, SOCS1, CCR1, IRF5, CCL5, IRF7, CCR5, IKKBK, FYN, IFI35, IL18RAP, ITGB2, IL2RG, IL18R1, STAT1, TP53, STAT3, MX1, STAT5B, IFNAR2
1269203	Innate Immune System	1.61E-13	4.19E-11	2.86E-10	8.38E-11	32	KLRK1, ATG5, JAK1, JAK2, IFIH1, TRAF2, TRAF6, CD247, ABL1, HLA-A, IKBKE, BST2, LILRB2, TLR2, HRAS, PSMB9, CLEC7A, SOCS1, C2, IRF7, GNLY, CTNNB1, IKBKB, LCP2, ITGAL, FYN, ITGB2, IL2RG, KLRD1, TP53, NLRP3, CEACAM1
1269318	Signaling by Interleukins	9.69E-11	1.06E-08	7.24E-08	5.04E-08	19	JAK1, JAK2, TRAF6, HRAS, PSMB9, SOCS1, CCR1, CCL5, CCR5, IKBKB, FYN, IL18RAP, ITGB2, IL2RG, IL18R1, STAT1, TP53, STAT3, STAT5B
1269171	Adaptive Immune System	1.02E-10	1.06E-08	7.24E-08	5.30E-08	23	KLRK1, PDCD1, TRAF6, CD247, ZBTB16, HLA-A, LILRB2, TLR2, LAG3, HRAS, LILRA6, PSMB9, SOCS1, SLAMF7, IKBKB, LCP2, ITGAL, FYN, ITGB2, KLRD1, ZAP70, KLRD1, TP53
1269340	Hemostasis	5.49E-07	2.20E-05	1.50E-04	2.86E-04	16	JAK1, JAK2, ABL1, CD99, HRAS, CIQBP, SERPING1, IRF7, LCP2, ITGAL, FYN, ITGB2, IL2RG, TP53, CEACAM1, GPIIB
1269260	TRAF3-dependent IRF activation pathway	9.84E-05	1.55E-03	1.06E-02	5.12E-02	3	IFIH1, IKBKE, IRF7
1268854	Disease	1.26E-03	1.24E-02	8.44E-02	6.55E-01	13	JAK2, CD247, HLA-A, TLR2, HRAS, PSMB9, CCR5, CTNNB1, IKBKB, FYN, STAT1, STAT3, STAT5B
1268855	Diseases of signal transduction	1.35E-03	1.30E-02	8.90E-02	7.03E-01	8	JAK2, HRAS, PSMB9, CTNNB1, FYN, STAT1, STAT3, STAT5B
1269562	Leukotriene receptors	2.86E-02	8.96E-02	6.12E-01	1.00E+00	1	LTB4R
1269248	Activation of C3 and C5	3.98E-02	1.18E-01	8.08E-01	1.00E+00	1	C2
MSigDB C2 BIOCARTEA (v6.0)							
M8066	IL22 Soluble Receptor Signaling Pathway	2.31E-10	3.56E-08	2.00E-07	3.56E-08	6	JAK1, JAK2, STAT1, STAT3, STAT4, STAT5B
M13494	Bioactive Peptide Induced Signaling Pathway	4.38E-09	3.38E-07	1.90E-06	6.75E-07	7	JAK2, HRAS, FYN, STAT1, STAT3, STAT4, STAT5B
M1462	CTL mediated immune response against target cells	1.61E-08	7.50E-07	4.21E-06	2.48E-06	5	CD247, HLA-A, GZMB, ITGAL, ITGB2
M6231	NO2-dependent IL 12 Pathway in NK cells	2.31E-06	3.24E-05	1.82E-04	3.56E-04	4	JAK2, CD247, CCR5, STAT4
M13863	MAPKinase Signaling Pathway	1.06E-05	1.08E-04	6.09E-04	1.63E-03	6	TRAF2, MAP4K1, HRAS, IKBKB, MAP4K2, STAT1
M6427	T Helper Cell Surface Molecules	6.45E-05	4.73E-04	2.66E-03	9.93E-03	3	CD247, ITGAL, ITGB2

Table 2 (continued)

KEGG	Pathway Name	P-value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
M4047	Selective expression of chemokine receptors during T-cell polarization	6.08E-04	3.12E-03	1.75E-02	9.37E-02	3	CCR1, CCR5, IL18R1
M11358	Tumor Suppressor Arf Inhibits Ribosomal Biogenesis	4.24E-03	1.28E-02	7.19E-02	6.53E-01	2	ABL1, TP53
M17400	ALK in cardiac myocytes	1.93E-02	4.37E-02	2.45E-01	1.00E+00	2	CTNNB1, SMAD5
M5885	Ensemble of genes encoding ECM-associated proteins including ECM-affiliated proteins, ECM regulators and secreted factors	8.19E-01	8.30E-01	1.00E+00	1.00E+00	3	CLEC7A, SERPING1, CCL5
Panther DB							
P00038	JAK/STAT signaling pathway	1.76E-12	5.64E-11	2.29E-10	5.64E-11	7	JAK1, JAK2, SOCS1, STAT1, STAT3, STAT4, STAT5B
P00031	Inflammation mediated by chemokine and cytokine signaling pathway	1.44E-06	2.31E-05	9.37E-05	4.62E-05	9	JAK2, CCR2, CCR1, CCL5, CCR5, IKKB, ITGAL, CX3CR1, STAT3
P00054	Toll receptor signaling pathway	1.94E-04	1.03E-03	4.19E-03	6.20E-03	4	TRAF6, IKBKE, TLR2, IKKB
P00006	Apoptosis signaling pathway	3.03E-04	1.39E-03	5.62E-03	9.69E-03	5	TRAF2, GZMB, IKKB, MAP4K2, TP53
P00010	B cell activation	4.43E-02	9.45E-02	3.83E-01	1.00E+00	2	HRAS, IKKB
P00052	TGF-beta signaling pathway	9.73E-02	1.67E-01	6.78E-01	1.00E+00	2	HRAS, SMAD5
P00011	Blood coagulation	2.07E-01	2.89E-01	1.00E+00	1.00E+00	1	GP1BB
P00012	Cadherin signaling pathway	2.34E-01	3.00E-01	1.00E+00	1.00E+00	2	CTNNB1, FYN
P00057	Wntsignaling pathway	2.59E-01	3.07E-01	1.00E+00	1.00E+00	3	CTNNB1, TP53, SMAD5
P00056	VEGF signaling pathway	2.86E-01	3.27E-01	1.00E+00	1.00E+00	1	HRAS
Pathway Ontology							
PW:0000125	G protein signaling	5.82E-03	3.10E-02	1.26E-01	1.86E-01	1	LTB4R
PW:0000297	platelet-derived growth factor signaling	5.82E-03	3.10E-02	1.26E-01	1.86E-01	1	JAK2
PW:0000143	insulin signaling	1.05E-02	3.36E-02	1.36E-01	3.37E-01	2	SOCS1, STAT5B
PW:0000330	Bone morphogenetic proteins signaling	2.86E-02	6.53E-02	2.65E-01	9.15E-01	1	SMAD5
PW:0000599	altered canonical Wntsignaling	2.86E-02	6.53E-02	2.65E-01	9.15E-01	1	CTNNB1
PW:0000508	platelet aggregation	3.42E-02	6.84E-02	2.78E-01	1.00E+00	1	GP1BB
PW:0000234	innate immune response	6.18E-02	1.10E-01	4.46E-01	1.00E+00	1	TLR2
PW:0000278	autophagy	1.04E-01	1.39E-01	5.65E-01	1.00E+00	1	ATG10
PW:0000243	vascular endothelial growth factor signaling	1.30E-01	1.49E-01	6.03E-01	1.00E+00	1	FYN
PW:0000490	transforming growth factor-beta Smad dependent signaling	1.40E-01	1.55E-01	6.28E-01	1.00E+00	1	RUNX1
SMPDB							
SMP00320	Intracellular Signalling Through Adenosine Receptor A2a and Adenosine	1.55E-02	2.46E-02	4.52E-02	4.65E-02	2	HRAS, IKKB
SMP00391	Insulin Signalling	1.89E-01	1.89E-01	3.46E-01	5.66E-01	1	HRAS

Table 3 The enriched pathway terms of the down regulated differentially expressed genes

Pathway ID	Pathway Name	P-value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
703092	Citrulline-nitric oxide cycle	8.83E-02	2.53E-01	8.24E-01	1.00E+00	1	NOS2
142419	Phospholipases	9.82E-02	2.53E-01	8.24E-01	1.00E+00	1	PLA2G2E, PLA2G2A
545273	Glycoaminoglycan-protein linkage region biosynthesis	1.05E-01	2.53E-01	8.24E-01	1.00E+00	1	B3GAT1
545323	Urate biosynthesis/inosine 5'-phosphate degradation	1.05E-01	2.53E-01	8.24E-01	1.00E+00	1	NT5E
142383	Tryptophan degradation to 2-amino-3-carboxymuconate semialdehyde	1.21E-01	2.53E-01	8.24E-01	1.00E+00	1	IDO1
KEGG							
83051	Cytokine-cytokine receptor interaction	3.05E-61	5.54E-59	3.21E-58	5.54E-59	69	IL10, IL10RA, IL12A, IL12B, IL13, IL13RA1, TNFRSF9, IL17A, PDGFB, TNFSF12, IL17B, TNFRSF14, TNFRSF10C, CCL26, IL17F, TNFRSF4, IL22RA2, IL21, CCL7, CCR6, CCL11, CCL13, CCR8, CCL15, CCL16, CCL18, CCL19, CCL20, CCL22, CCL24, CXCL11, CXCL1, KIT, CX3CL1, CXCL12, IL19, CCR10, XCR1, CXCL13, PPBP, IL23A, IFNA2, IFNAR1, IFNB1, IFNG, TGFBR1, LIF, CSF1R, CSF2, CSF2RB, CSF3R, IL20, IL22, CD40, TNFRSF13C, LTA, IL1RAP, IL2, IL3, IL4, IL4R, IL5, IL6, IL6R, IL7, IL26, CXCR1, IL9, CXCR2
83078	Hematopoietic cell lineage	4.22E-35	3.84E-33	2.22E-32	7.67E-33	34	HLA-DMA, HLA-DMB, HLA-DOB, HLA-DPA1, HLA-DPB1, HLA-DQAI, HLA-DQB1, HLA-DRA, HLA-DRB1, CD55, MME, KIT, CR2, TFRC, CD1A, CD3E, CSF1R, CSF2, CD8A, CD9, CSF3R, CD19, MS4A1, CD22, CD34, CD44, CD59, IL3, IL4, IL4R, IL5, IL6, IL6R, IL7
842771	Inflammatory bowel disease (IBD)	4.58E-32	2.78E-30	1.61E-29	8.34E-30	28	IL10, IL12A, IL12B, IL13, IL17A, HLA-DMA, HLA-DMB, HLA-DOB, HLA-DPA1, HLA-DPB1, HLA-DQAI, HLA-DQB1, HLA-DRA, HLA-DRB1, GATA3, IL17F, STAT6, IL21, RELA, IL23A, IFNG, IL22, RORC, IL2, IL4, IL4R, IL5, IL6

Table 3 (continued)

BIOCYC Pathway ID	Pathway Name	P-value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
83077	Jak-STAT signaling pathway	4.56E-26	1.19E-24	6.86E-24	8.30E-24	33	IL10, IL10RA, IL12A, IL12B, IL13, IL13RA1, BCL2, STAT5A, STAT6, PTPN6, IL22RA2, IL21, IL19, IL23A, IFNA2, IFNAR1, IFNB1, IFNG, LIF, CSF2, CSF2RB, CSF3R, IL20, IL22, IL2, IL3, IL4, IL4R, IL5, IL6, IL6R, IL7, IL9
213780	Tuberculosis	3.41E-25	6.89E-24	3.99E-23	6.20E-23	34	IL10, IL10RA, IL12A, IL12B, CEBPB, HLADMA, HLADMB, HLADOB, HLADPA1, HLADPBI, HLADQAI, HLADQBI, HLADRA, HLADRB1, BCL2, CD209, BID, FCGR2A, FCGR2B, CARD9, NOS2, CASP3, REL, TLR9, IL23A, IFNA2, IFNB1, IFNG, TIRAP, IRAK4, CD74, MAPK11, CTSS, IL6
83120	Asthma	4.56E-24	8.30E-23	4.80E-22	8.30E-22	18	IL10, IL13, HLADMA, HLADMB, HLADOB, HLADPA1, HLADPBI, HLADQAI, HLADQBI, HLADRA, HLADRB1, FCERIA, CCL11, CD40, IL3, IL4, IL5, IL9
125138	Viral myocarditis	2.26E-16	2.06E-15	1.19E-14	4.12E-14	17	HLA-B, HLA-C, HLA-DMA, HLA-DMB, HLADOB, HLADPA1, HLADPBI, HLADQAI, HLADQBI, HLA-DRA, HLADRB1, CD55, BID, CASP3, CD80, CD86, CD40
373901	HTLV-I infection	2.85E-15	2.35E-14	1.36E-13	5.18E-13	29	HLA-B, PDGFB, HLA-C, HLADMA, HLADMB, HLADOB, HLADPA1, HLADPBI, HLADQAI, HLADQBI, HLADRA, HLADRB1, ETS1, STAT5A, VCAMI, REL, RELB, LCK, SLC2A1, TGFBR1, CD3E, CSF2, EGRI, EGR2, CD40, TNFRSF13C, LTA, IL2, IL6
213306	Measles	4.04E-12	2.53E-11	1.47E-10	7.35E-10	19	IL12A, IL12B, IL13, CD46, TNFRSF10C, CD209, STAT5A, FCGR2B, REL, TLR9, IFNA2, IFNAR1, IFNB1, IFNG, CD3E, IRAK4, IL2, IL4, IL6
83074	Antigen processing and presentation	7.12E-12	4.32E-11	2.50E-10	1.30E-09	15	HLA-B, HLA-C, HLADMA, HLADMB, HLADOB, HLADPA1, HLADPBI, HLADQAI, HLADQBI, HLADRA, HLADRB1, IFNG, CD8A, CD74, CTSS

Table 3 (continued)

Pathway ID	Pathway Name	P-value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
217173	Influenza A	4.98E-11	2.75E-10	1.59E-09	9.07E-09	20	IL12A, IL12B, HLA-DMA, HLA-DMB, HLA-DOB, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, HLA-DRB1, TNFRSF10C, REL, IFNA2, IFNARI, IFNB1, IFNG, IRAK4, MAPK11, IL6
Pathway interaction database							
137933	IL4-mediated signaling events	7.74E-16	8.36E-14	4.40E-13	8.36E-14	17	IL10, IL13RA1, CEBPB, AICDA, ETS1, CCL26, STAT5A, STAT6, PTPN6, PI3K, CCL11, THY1, EGR2, LTA, IL4, IL4R, IL5
137922	IL12-mediated signaling events	9.23E-15	4.99E-13	2.62E-12	9.97E-13	16	IL12A, IL12B, HLA-DRA, HLA-DRB1, STAT5A, STAT6, EOMES, NOS2, REL, RELB, LCK, IFNG, CD3E, CD8A, IL2, IL4
138000	IL23-mediated signaling events	1.32E-12	4.75E-11	2.50E-10	1.42E-10	12	IL12B, IL17A, IL17F, STAT5A, NOS2, IL19, REL, IL23A, IFNG, CD3E, IL2, IL6
137929	IL27-mediated signaling events	1.43E-11	3.87E-10	2.04E-09	1.55E-09	10	IL12A, IL12B, IL17A, GATA3, STAT5A, IFNG, EBI3, IL2, IL6, IL27
138058	BCR signaling pathway	3.00E-07	4.05E-06	2.13E-05	3.24E-05	10	ETS1, PTPN6, FCGR2B, BTK, POU2F2, REL, CD19, CD22, CD79A, CD79B
138055	TCR signaling in naive CD8+ T cells	2.28E-04	1.30E-03	6.82E-03	2.46E-02	6	PTPN6, LCK, CD3E, CD8A, CD80, CD86
137939	Direct p53 effectors	2.95E-03	1.33E-02	7.00E-02	3.18E-01	8	SPP1, BCL2, TNFRSF10C, BID, CD82, MAP4K4, CX3CL1, LIF
138081	FAS (CD95) signaling pathway	3.67E-03	1.42E-02	7.46E-02	3.97E-01	4	BID, BTK, CASP3, MAPK11
137995	HIV-1 Nef: Negative effector of Fas and TNF-alpha	3.67E-03	1.42E-02	7.46E-02	3.97E-01	4	BCL2, BID, CASP3, REL
137944	IL1-mediated signaling events	2.58E-02	6.45E-02	3.40E-01	1.00E+00	3	TOLLIP, REL, IRAK4

REACTOME

Table 3 (continued)

BIOCYC Pathway ID	Pathway Name	P-value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
1269310	Cytokine Signaling in Immune system	3.81E-46	2.02E-43	1.39E-42	2.02E-43	86	IL10, IL10RA, IL12A, IL12B, IL13, IL13RA1, IL16, TRAF3, TNFRSF9, IL17A, HLA-B, PDGFB, HLA-C, TNFSF12, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRB1, HLA-DRB1, HLA-DRB1, TNFRSF14, GATA3, PSMB10, BCL2, PTAFR, IL1RL2, IL17F, PTK2, STAT5A, STAT6, TNFRSF4, PTPN6, IL22RA2, TOLLIP, CCL11, CCL19, CCL20, CCL22, KIT, NOS2, VCAMI, IL19, RAG1, RAG2, ZEB1, FNI, DUSP4, IRF8, CASP3, RELA, RELB, LCK, IL23A, SIPR1, IFNA2, IFNAR1, IFNB1, IFNG, LIF, CSF1R, CSF2, CSF2RB, CSF3R, EBI3, EGRI, IL20, CD80, CD86, IL22, CD40, IRAK4, CD44, TNFRSF13C, LTA, RORC, IL1RAP, IL2, IL3, IL4, IL4R, IL5, IL6, IL6R, IL7, IL27, IL9
1269318	Signaling by Interleukins	2.98E-33	7.91E-31	5.42E-30	1.58E-30	62	IL10, IL10RA, IL12A, IL12B, IL13, IL13RA1, IL16, IL17A, PDGFB, GATA3, PSMB10, BCL2, PTAFR, IL1RL2, IL17F, PTK2, STAT5A, STAT6, PTPN6, IL22RA2, TOLLIP, CCL11, CCL19, CCL20, CCL22, KIT, NOS2, VCAMI, IL19, RAG1, RAG2, ZEB1, FNI, DUSP4, CASP3, RELA, LCK, IL23A, SIPR1, LIF, CSF1R, CSF2, CSF2RB, CSF3R, EBI3, IL20, CD80, CD86, IL22, IRAK4, RORC, IL1RAP, IL2, IL3, IL4, IL4R, IL5, IL6, IL6R, IL7, IL27, IL9

Table 3 (continued)

BIOCYC Pathway ID	Pathway Name	P-value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
1269203	Innate Immune System	4.93E-25	8.72E-23	5.98E-22	2.62E-22	82	MASPI, TRAF3, HLA-B, PDGFB, HLA-C, MAPKAPK2, CTSC, PECAM1, MBL2, PSMB10, CD55, CD46, BCL2, DEFB103B, PTAFR, CD209, PTK2, STAT6, DEFB1, DEFB4A, CFD, PTPN6, FCAR, FCER1A, PIGR, FCGR2A, CARD9, BTK, MIF, PLA2G2A, TOLLIP, CIR, C1S, C4A, PLAU, C4BPA, CCR6, MME, C6, C7, C8A, C8B, C9, KIT, NOS2, GPI, LILRA3, VTN, CLEC6A, FN1, ATG7, ITLN1, DUSP4, ICAM2, ICAM3, RELA, RELB, TLR9, LCK, PPBP, CFI, IFNA2, LGALS3, IFNB1, CSF2, CSF2RB, CD19, SIGIRR, CD80, CD86, TIRAP, IRAK4, CD44, CD59, MAPK11, IL2, IL3, IL5, CTSS, CXCR1, MASP2, CXCR2
1269171	Adaptive Immune System	1.51E-15	1.15E-13	7.86E-13	8.03E-13	52	HLA-B, PDGFB, HLA-C, HLA-DMA, HLA-DMB, HLA-DOB, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, CTSC, HLA-DRB1, TNFRSF14, PSMB10, PTPN22, CD209, PTPN6, SLAMF6, FCGR2B, BTK, KIT, KLRB1, LILRB5, VCAM1, ICOSLG, LILRA1, LILRA3, LILRA2, ATG7, ICAM2, ICAM3, ICAM4, RELA, BTLA, LCK, CD1A, CD3E, CD8A, CD19, CD22, CD80, CD86, ICAM5, TIRAP, CD34, CD40, CD74, CD79A, CD79B, CTLA4, CTSS
1269201	Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	5.01E-14	2.66E-12	1.82E-11	2.66E-11	21	HLA-B, HLA-C, SLAMF6, FCGR2B, KLRB1, LILRB5, VCAM1, LILRA1, LILRA3, LILRA2, ICAM2, ICAM3, ICAM4, CD1A, CD3E, CD8A, CD19, CD22, ICAM5, CD34, CD40
1269546	Peptide ligand-binding receptors	6.17E-08	1.82E-06	1.25E-05	3.27E-05	17	CCR6, CCL13, CCR8, CCL16, CCL19, CCL20, CXCL11, XCL1, CX3CL1, CXCL12, CCR10, XCR1, CXCL13, PPBP, EDNRB, CXCR1, CXCR2
1269545	Class A/1 (Rhodopsin-like receptors)	4.71E-07	1.14E-05	7.79E-05	2.50E-04	21	PTAFR, PTGER4, CCR6, CCL13, CCR8, CCL16, CCL19, CCL20, CXCL11, XCL1, CX3CL1, CXCL12, CCR10, XCR1, CXCL13, GPR183, PPBP, SIPRI, EDNRB, CXCR1, CXCR2

Table 3 (continued)

BIOCYC Pathway ID	Pathway Name	P-value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
1269340	Hemostasis	1.15E-04	1.47E-03	1.01E-02	6.09E-02	26	CD244, PDGFB, PECAMI, GATA3, PTK2, CFD, PTPN6, MIF, PLAU, NOS2, SELE, SELPLG, FNI, LCK, PPBP, IFNA2, IFNB1, CSF2, CSF2RB, CD9, CD44, CD48, CD74, IL2, IL3, IL5
1269501	MAPK family signaling cascades	3.27E-04	3.40E-03	2.33E-02	1.74E-01	15	PDGFB, PSMB10, PTK2, KIT, RAG1, RAG2, FNI, DUSP4, CSF2, CSF2RB, IL2, IL3, IL5, IL6, IL6R
1269240	Toll Like Receptor TLR6:TLR2 Cascade	3.46E-04	3.40E-03	2.33E-02	1.84E-01	8	MAPKAPK2, BTK, DUSP4, RELA, SIGIRR, TIRAP, IRAK4, MAPK11
<i>Gen MAPP</i>							
MAP00400	Phenylalanine tyrosine and tryptophan biosynthesis	1.38E-01	5.02E-01	1.00E+00	1.00E+00	1	BID
MAP_kinase_activity	MAP kinase activity	1.38E-01	5.02E-01	1.00E+00	1.00E+00	1	MAPK11
MAP00010	Glycolysis Gluconeogenesis	2.47E-01	5.02E-01	1.00E+00	1.00E+00	2	BID, GPI
MAP00030	Pentose phosphate	2.70E-01	5.02E-01	1.00E+00	1.00E+00	1	GPI
MAP00590	Prostaglandin and leukotriene metabolism	2.96E-01	5.02E-01	1.00E+00	1.00E+00	1	PLA2G2A
MAP00500	Starch and sucrose metabolism	3.34E-01	5.02E-01	1.00E+00	1.00E+00	1	GPI
MAP00330	Arginine and proline metabolism	5.05E-01	5.81E-01	1.00E+00	1.00E+00	1	NOS2
MAP00380	Tryptophan metabolism	5.73E-01	5.81E-01	1.00E+00	1.00E+00	1	IDO1
MAP00561	Glycerolipid metabolism	5.81E-01	5.81E-01	1.00E+00	1.00E+00	1	PLA2G2A
MSigDB C2 BIOCARTA (v6.0)							
M5883	Genes encoding secreted soluble factors	4.86E-27	7.82E-25	4.43E-24	7.82E-25	46	IL10, IL12A, IL12B, IL13, IL16, IL17A, PDGFB, TNFSF12, IL17B, CCL26, IL17F, CCL7, CCL11, CCL13, CCL15, CCL16, CCL18, CCL19, CCL20, CCL22, CCL24, CXCL11, XCL1, CX3CL1, CXCL12, IL19, CXCL13, PPBP, IL23A, IFNA2, IFNB1, IFNG, LIF, CSF2, EBI3, IL20, IL22, LTA, IL2, IL3, IL4, IL5, IL6, IL7, IL26, IL9
M17406	Cytokine Network	2.71E-22	2.18E-20	1.24E-19	4.36E-20	15	IL10, IL12A, IL12B, IL13, IL16, IL17A, IFNB1, IFNG, LTA, IL2, IL3, IL4, IL5, IL6, IL9
M6910	Cytokines and Inflammatory Response	5.19E-21	2.78E-19	1.58E-18	8.35E-19	16	IL10, IL12A, IL12B, IL13, HLA-DRA, HLA-DRB1, IFNB1, IFNG, CSF2, LTA, IL2, IL3, IL4, IL5, IL6, IL7

Table 3 (continued)

Pathway ID	Pathway Name	P-value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
M5885	Ensemble of genes encoding ECM-associated proteins including ECM-affiliated proteins, ECM regulators and secreted factors	7.80E-21	3.14E-19	1.78E-18	1.26E-18	57	IL10, IL12A, IL12B, IL13, MASP1, IL16, IL17A, PDGFB, TNFSF12, CTSC, IL17B, MBL2, CCL26, IL17F, CD209, PLAU, CCL7, CCL11, CCL13, CCL15, CCL16, CCL18, CCL19, CCL20, CCL22, CCL24, CXCL11, XCL1, CX3CL1, CXCL12, IL19, CLEC6A, ITLN1, CXCL13, ITLN2, PPBP, IL23A, IFNA2, LGALS3, IFNB1, IFNG, IL2, CSF2, EBI3, IL20, IL22, LTA, IL2, IL3, IL4, IL5, CTSS, IL6, IL7, IL26, IL9, MASP2
M5889	Ensemble of genes encoding extracellular matrix and extracellular matrix-associated proteins	4.62E-17	1.49E-15	8.43E-15	7.44E-15	61	IL10, IL12A, IL12B, IL13, MASP1, IL16, IL17A, PDGFB, TNFSF12, SPP1, CTSC, IL17B, MBL2, CCL26, IL17F, CD209, PLAU, CCL7, CCL11, CCL13, CCL15, CCL16, CCL18, CCL19, CCL20, CCL22, CCL24, CXCL11, XCL1, CX3CL1, CXCL12, IL19, CLEC6A, ITLN1, CXCL13, ITLN2, PPBP, FNI, ITLN1, CXCL13, ITLN2, PPBP, IL23A, IFNA2, LGALS3, IFNB1, IFNG, TGFB1, LIF, CSF2, EBI3, IL20, IL22, LTA, IL2, IL3, IL4, IL5, CTSS, IL6, IL7, IL26, IL9, MASP2
M1467	The Co-Stimulatory Signal During T-cell Activation	4.81E-11	7.03E-10	3.98E-09	7.74E-09	9	HLA-DRA, HLA-DRB1, ICOSLG, LCK, CD3E, CD80, CD86, CTLA4, IL2
M3952	Cells and Molecules involved in local acute inflammatory response	1.02E-05	7.46E-05	4.22E-04	1.64E-03	5	C6, C7, VCAM1, SELPLG, IL6
M18215	Role of Tob in T-cell activation	3.16E-05	2.21E-04	1.25E-03	5.08E-03	5	IFNG, TGFB1, CD3E, IL2, IL4
M13968	HIV-1 Nef: negative effector of Fas and TNF	6.46E-04	3.15E-03	1.78E-02	1.04E-01	6	BCL2, PTK2, BID, CASP3, RELA, ARHG-DIB
M13247	T Cytotoxic Cell Surface Molecules	1.90E-03	6.80E-03	3.85E-02	3.06E-01	3	CD3E, CD8A, THY1
Panther DB P00036	Interleukin signaling pathway	6.51E-19	2.47E-17	1.05E-16	2.47E-17	22	IL10, IL10RA, IL12A, IL13, IL13RA1, IL17A, MAPKAPK2, IL17F, STAT5A, STAT6, IL21, IL23A, IL2, IL4, IL4R, IL5, IL6, IL6R, IL7, CXCR1, IL9, CXCR2
P00031	Inflammation mediated by chemokine and cytokine signaling pathway	4.36E-07	8.28E-06	3.50E-05	1.66E-05	16	CCL26, CCL7, CCR6, CCL11, CCL13, CCR8, CCL18, CCL20, CCL22, CX3CL1, CCR10, XCRI, IFNAR1, IFNG, CXCR1, CXCR2

Table 3 (continued)

BIOCYC Pathway ID	Pathway Name	P-value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
P00053	T cell activation	7.23E-05	8.13E-04	3.44E-03	2.75E-03	8	HLA-DPA1, HLA-DQA1, HLA-DRA, LCK, CD3E, CD80, CD86, CD74
P00010	B cell activation	8.56E-05	8.13E-04	3.44E-03	3.25E-03	7	PTPN6, BTK, CD19, CD22, CD79A, CD79B, MAPK11
P00054	Toll receptor signaling pathway	2.14E-03	1.62E-02	6.86E-02	8.12E-02	5	TOLLIP, RELA, TLR9, IFNB1, IRAK4
P00006	Apoptosis signaling pathway	2.67E-03	1.69E-02	7.14E-02	1.01E-01	7	BCL2, BID, BCL2L11, CASP3, RELA, RELB, LTA
P00035	Interferon-gamma signaling pathway	1.42E-02	7.69E-02	3.25E-01	5.39E-01	3	PTPN6, IFNG, MAPK11
P00046	Oxidative stress response	5.17E-02	1.86E-01	7.88E-01	1.00E+00	3	BCL2, DUSP4, MAPK11
P00047	PDGF signaling pathway	8.39E-02	2.44E-01	1.00E+00	1.00E+00	5	PDGFB, MAPKAPK2, ETS1, STAT5A, STAT6
P00034	Integrin signalling pathway	5.94E-01	7.28E-01	1.00E+00	1.00E+00	3	ITGAE, PTK2, FN1
Pathway Ontology							
PW:0000104	intrinsic apoptotic	1.82E-03	7.63E-02	3.30E-01	7.63E-02	4	BCL2, BID, BCL2L11, CASP3
PW:0000515	Interleukin-10 signaling	7.84E-01	1.57E-01	6.78E-01	6.78E-01	1	IL10
PW:0000516	Interleukin-6 signaling	7.84E-01	1.57E-01	6.78E-01	6.78E-01	1	IL6
PW:0000499	Nuclear Factor Kappa B signaling	9.58E-01	1.60E-01	6.91E-01	6.91E-01	2	RELA, RELB
PW:0000009	programmed cell death	1.00E+00	1.80E-01	7.78E-01	7.78E-01	2	BCL2, CASP3
PW:0000102	The extracellular signal-regulated RAF/MEK/ERK signaling	8.14E-02	2.18E-01	9.44E-01	1.00E+00	2	SPP1, S1PR1
PW:0000529	angiotensin (1-7) signaling	8.83E-02	2.18E-01	9.44E-01	1.00E+00	1	MME
PW:0000106	extrinsic apoptotic	1.05E-01	2.45E-01	1.00E+00	1.00E+00	1	CASP3
PW:0000559	hexosamine biosynthetic	1.21E-01	2.55E-01	1.00E+00	1.00E+00	1	GPI
PW:0000228	G protein signaling via Galphai family	1.53E-01	2.80E-01	1.00E+00	1.00E+00	1	S1PR1
SMPDB							
SMP00094	Sulindac Pathway	1.21E-01	4.52E-01	1.00E+00	1.00E+00	1	PLA2G2A
SMP00040	Glycolysis	2.14E-01	4.52E-01	1.00E+00	1.00E+00	1	GPI
SMP00063	Tryptophan Metabolism	2.70E-01	4.52E-01	1.00E+00	1.00E+00	1	IDO1
SMP00379	NifedipinePathway	2.83E-01	4.52E-01	1.00E+00	1.00E+00	1	EDNRB
SMP00006	Tyrosine Metabolism	3.59E-01	4.84E-01	1.00E+00	1.00E+00	1	MIF
SMP00320	Intracellular Signalling Through Adenosine Receptor A2a and Adenosine	4.57E-01	4.84E-01	1.00E+00	1.00E+00	1	MAPK11

Table 4 The enriched GO terms of the up regulated differentially expressed genes

GO ID	CATEGORY	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0002682	BP	Regulation of immune system process	1.53E-44	5.68E-41	5.00E-40	5.68E-41	56	KLRK1, ATG5, JAK1, JAK2, IFIH1, PDCD1, TRAF2, TRAF6, IKZF3, CD247, ZBTB16, ABL1, HLA-A, IKBKE, CD99, BST2, LILRB2, TBX21, TLR2, LAG3, HRAS, PSMB9, CIQBP, CLEC7A, SERPING1, XBP1, GBPI, SOCS1, C2, CCR1, IKZF1, CCL5, IRF7, CTNNA1, RUNX1, SLAMF7, IKBKB, LCP2, ITGAL, FYN, IL18RAP, ITGB2, IL2RG, IL18R1, KLRC1, ZAP70, GFI1, KLRD1, CX3CR1, STAT1, TP53, NLRP3, STAT3, STAT5B, CEACAM1, IFNAR2
GO:0009607	BP	Response to biotic stimulus	6.86E-35	6.36E-32	5.59E-31	2.54E-31	48	KLRK1, ATG5, JAK1, JAK2, IFIH1, TRAF6, IKZF3, ATG10, ABL1, HLA-A, IKBKE, BST2, LILRB2, TBX21, TLR2, GZMB, LAG3, HRAS, PSMB9, CIQBP, CLEC7A, SERPING1, XBP1, GBPI, SOCS1, C2, IRF5, CCL5, IRF7, CCR5, GNL5, SLAMF7, IKBKB, FYN, IFI35, IL18RAP, ITGB2, MAP4K2, GFI1, KLRD1, CX3CR1, STAT1, TP53, NLRP3, MX1, STAT5B, CEACAM1, IFNAR2
GO:0006952	BP	Defense response	1.12E-33	5.92E-31	5.21E-30	4.14E-30	49	KLRK1, JAK1, JAK2, IFIH1, TRAF6, HLA-A, IKBKE, BST2, LILRB2, TLR2, GZMB, LAG3, HRAS, PSMB9, CIQBP, CLEC7A, SERPING1, GBPI, CCRL2, SOCS1, C2, CCR1, IRF5, CCL5, IRF7, CCR5, GNL5, LTB4R, SLAMF7, IKBKB, ITGAL, FYN, IFI35, IL18RAP, ITGB2, IL18R1, MAP4K2, GFI1, KLRD1, CX3CR1, STAT1, TP53, NLRP3, STAT3, STAT4, MX1, STAT5B, CEACAM1, IFNAR2
GO:0001816	BP	Cytokine production	3.84E-27	1.29E-24	1.14E-23	1.42E-23	34	KLRK1, ATG5, JAK2, IFIH1, TRAF2, TRAF6, CD247, ABL1, IKBKE, BST2, LILRB2, TBX21, TLR2, LAG3, HRAS, CIQBP, CLEC7A, XBP1, GBPI, SOCS1, IRF5, CCL5, IRF7, CTNNA1, RUNX1, LCP2, IL18RAP, IL18R1, CX3CR1, STAT1, NLRP3, STAT3, STAT5B, CEACAM1

Table 4 (continued)

GO ID	CATEGORY	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0034097	BP	Response to cytokine	2.23E-26	6.90E-24	6.07E-23	8.28E-23	38	JAK1, JAK2, IFIH1, TRAF2, TRAF6, HLA-A, IKBKE, BST2, TLR2, PSMB9, XBPI, GBP1, CCR2, SOCS1, CCR1, IRF5, CCL5, IRF7, CCR5, CTNNB1, RUNX1, IKBKB, FYN, IFI35, IL18RAP, ITGB2, IL2RG, IL18R1, GFII, CX3CRI, STAT1, TP53, STAT3, STAT4, MX1, STAT5B, CEACAM1, IFNAR2
GO:0042110	BP	T cell activation	1.68E-25	4.43E-23	3.90E-22	6.21E-22	28	CCND3, KLRK1, ATG5, PDCD1, TRAF6, ZBTB16, ABL1, LILRB2, TBX21, LAG3, CLEC7A, XBPI, SOCS1, IKZF1, CCL5, CTNNB1, RUNX1, ITGAL, FYN, ITGB2, IL2RG, IL18R1, ZAP70, TP53, NLRP3, STAT3, STAT5B, CEACAM1
GO:0045321	BP	Leukocyte activation	6.65E-23	1.30E-20	1.14E-19	2.47E-19	36	CCND3, KLRK1, ATG5, JAK2, PDCD1, TRAF6, IKZF3, ZBTB16, ABL1, BST2, LILRB2, TBX21, TLR2, LAG3, CLEC7A, XBPI, SOCS1, IKZF1, CCL5, CTNNB1, RUNX1, SLAMF7, LCP2, ITGAL, FYN, IL18RAP, ITGB2, IL2RG, IL18R1, ZAP70, CX3CRI, TP53, NLRP3, STAT3, STAT5B, CEACAM1
GO:0001775	BP	Cell activation	2.83E-22	5.00E-20	4.40E-19	1.05E-18	37	CCND3, KLRK1, ATG5, JAK2, PDCD1, TRAF6, IKZF3, ZBTB16, ABL1, BST2, LILRB2, TBX21, TLR2, LAG3, CLEC7A, XBPI, SOCS1, IKZF1, CCL5, CTNNB1, RUNX1, SLAMF7, LCP2, ITGAL, FYN, IL18RAP, ITGB2, IL2RG, IL18R1, ZAP70, CX3CRI, TP53, NLRP3, STAT3, STAT5B, CEACAM1, GPIBB
GO:0080134	BP	Regulation of response to stress	3.88E-18	3.59E-16	3.16E-15	1.44E-14	34	KLRK1, JAK1, JAK2, IFIH1, TRAF2, TRAF6, ABL1, IKBKE, MAP4K1, TLR2, LAG3, HRAS, PSMB9, CIQBP, CLEC7A, SERPING1, XBPI, SOCS1, CCL5, IRF7, CTNNB1, IKBKB, FYN, IL18RAP, ITGB2, MAP4K2, GFII, CX3CRI, STAT1, TP53, NLRP3, STAT5B, CEACAM1, IFNAR2
GO:0051094	BP	Positive regulation of developmental process	1.52E-15	1.00E-13	8.79E-13	5.64E-12	31	JAK1, JAK2, TRAF6, ZBTB16, ABL1, LILRB2, TBX21, TLR2, CIQBP, CLEC7A, XBPI, SOCS1, CCR1, IKZF1, CCL5, CTNNB1, RUNX1, IKBKB, FYN, ITGB2, IL2RG, ZAP70, GFII, CX3CRI, STAT1, TP53, NLRP3, STAT3, STAT5B, SMAD5, CEACAM1

Table 4 (continued)

GO ID	CATEGORY	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0098552	CC	Side of membrane	1.17E-11	1.54E-09	9.47E-09	3.08E-09	18	KLRK1, PDCD1, TRAF2, TRAF6, HLA-A, TLR2, LAG3, CCRL2, CCR1, CCR5, SLAMF7, IKBKB, ITGAL, FYN, ITGB2, IL2RG, KLRD1, CX3CR1
GO:0043235	CC	Receptor complex	3.20E-10	2.81E-08	1.73E-07	8.44E-08	15	TRAF2, TRAF6, CD247, TLR2, IKBKB, LCP2, ITGAL, IL18RAP, ITGB2, IL2RG, IL18R1, KLRC1, ZAP70, KLRD1, CEACAM1
GO:0009986	CC	Cell surface	2.20E-09	9.68E-08	5.96E-07	5.81E-07	19	KLRK1, PDCD1, HLA-A, BST2, LILRB2, TLR2, LAG3, CIQBP, CLEC7A, CCRL2, CCR1, CCR5, SLAMF7, ITGAL, ITGB2, IL2RG, KLRD1, CX3CR1, CEACAM1
GO:0005887	CC	Integral component of plasma membrane	2.88E-07	6.90E-06	4.25E-05	7.59E-05	21	KLRK1, TRAF2, TRAF6, CD99, LILRB2, TLR2, CCRL2, CCR1, CCR5, LTB4R, IKBKB, ITGAL, IL18RAP, ITGB2, IL2RG, IL18R1, KLRC1, CX3CR1, CEACAM1, GPIBB, IFNAR2
GO:0098805	CC	Whole membrane	8.24E-06	1.55E-04	9.56E-04	2.18E-03	19	ATG5, JAK2, TRAF2, TRAF6, HLA-A, IKBKE, BST2, LILRB2, TLR2, IRF7, LTB4R, CTNNB1, IKBKB, LCP2, ITGAL, FYN, ITGB2, ZAP70, CEACAM1
GO:0044194	CC	cytolytic granule	1.84E-04	2.70E-03	1.66E-02	4.87E-02	2	GZMB, GNLY
GO:0000790	CC	Nuclear chromatin	9.72E-04	1.17E-02	7.18E-02	2.57E-01	16	IKZF3, ZBTB16, TBX21, XBPI, IRF5, IKZF1, IRF7, CTNNB1, RUNX1, GFI1, STAT1, TP53, STAT3, STAT4, STAT5B, SMAD5
GO:0090575	CC	RNA polymerase II transcription factor complex	5.30E-03	4.21E-02	2.59E-01	1.00E+00	4	CTNNB1, RUNX1, TP53, STAT3
GO:0005667	CC	Transcription factor complex	5.46E-03	4.21E-02	2.59E-01	1.00E+00	6	IKZF1, CTNNB1, RUNX1, TP53, STAT3, SMAD5
GO:0048471	CC	Perinuclear region of cytoplasm	8.69E-03	4.78E-02	2.94E-01	1.00E+00	8	TRAF6, ABL1, HRAS, CTNNB1, FYN, CX3CR1, STAT1, MX1
GO:0019900	MF	Kinase binding	6.20E-10	1.90E-07	1.27E-06	2.82E-07	19	CCND3, KLRK1, JAK2, TRAF2, TRAF6, CD247, ABL1, CIQBP, XBPI, SOCS1, CCL5, CTNNB1, IKBKB, ITGB2, MAP4K2, TP53, STAT3, CEACAM1, IFNAR2
GO:0005102	MF	Signaling receptor binding	7.06E-08	3.57E-06	2.39E-05	3.21E-05	23	KLRK1, JAK1, JAK2, TRAF2, TRAF6, ABL1, HLA-A, LILRB2, TLR2, LAG3, CIQBP, CLEC7A, CCRL2, SOCS1, CCL5, CTNNB1, FYN, ITGB2, KLRD1, STAT1, TP53, STAT3, STAT5B

Table 4 (continued)

GO ID	CATEGORY	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0044212	MF	Transcription regulatory region DNA binding	1.45E-07	5.42E-06	3.63E-05	6.57E-05	17	TRAF6, IKZF3, ZBTB16, TBX21, XBPI, IRF5, IKZF1, IRF7, CTNNB1, RUNX1, GFII1, STAT1, TP53, STAT3, STAT4, STAT5B, SMAD5
GO:0038023	MF	Signaling receptor activity	3.46E-07	1.13E-05	7.54E-05	1.58E-04	21	KLRK1, CD247, LILRB2, TLR2, LAG3, CLEC7A, CCR1, CCR5, CCR5, CCR5, LTB4R, ITGAL, IL18RAP, ITGB2, IL2RG, IL18R1, KLRC1, KLRD1, CX3CR1, GPIBB, IFNAR2
GO:0043565	MF	Sequence-specific double-stranded DNA binding	5.76E-06	9.35E-05	6.27E-04	2.62E-03	16	IKZF3, ZBTB16, ABL1, TBX21, XBPI, IRF5, IKZF1, IRF7, RUNX1, STAT1, TP53, NLRP3, STAT3, STAT4, STAT5B, SMAD5
GO:0016772	MF	Transferase activity, transferring phosphorus-containing groups	8.11E-06	1.19E-04	7.98E-04	3.69E-03	20	CCND3, JAK1, JAK2, TRAF2, TRAF6, ABL1, IKBKE, MAP4K1, HRAS, SOCS1, CCL5, CTNNB1, IKBKB, LCP2, FYN, ZAP70, MAP4K2, TP53, STAT3, CEACAM1
GO:0070011	MF	Peptidase activity, acting on L-amino acid peptides	1.03E-05	1.38E-04	9.27E-04	4.66E-03	16	ATG5, JAK2, IFIH1, TRAF2, TRAF6, BST2, GZMB, PSMB9, CLEC7A, SERPING1, C2, FYN, STAT1, TP53, NLRP3, STAT3
GO:0000977	MF	RNA polymerase II regulatory region sequence-specific DNA binding	1.25E-05	1.58E-04	1.06E-03	5.67E-03	13	IKZF3, ZBTB16, TBX21, XBPI, IKZF1, IRF7, RUNX1, STAT1, TP53, STAT3, STAT4, STAT5B, SMAD5
GO:0035639	MF	Purine ribonucleoside triphosphate binding	3.00E-04	1.75E-03	1.17E-02	1.37E-01	17	JAK1, JAK2, IFIH1, ABL1, IKBKE, MAP4K1, HRAS, CUL9, GBP1, RUNX1, IKBKB, FYN, ZAP70, MAP4K2, TP53, NLRP3, MX1
GO:0032559	MF	Adenylylribonucleotide binding	1.44E-03	6.51E-03	4.36E-02	6.57E-01	14	JAK1, JAK2, IFIH1, ABL1, IKBKE, MAP4K1, CUL9, RUNX1, IKBKB, FYN, ZAP70, MAP4K2, TP53, NLRP3

BP biological process, *CC* cellular component, *MF* molecular functions

Table 5 The enriched GO terms of the down regulated differentially expressed genes

GO ID	Category	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0002682	BP	Regulation of immune system process	1.87E-103	9.66E-100	8.82E-99	9.66E-100	153	IL10, IL12A, IL12B, IL13, IRGM, MASP1, TRAF3, IL17A, CEBPB, CD244, HLA-B, HLA-C, IDO1, HLA-DMA, HLA-DMB, HLA-DOB, HLA-DPA1, HLA-DPB1, HLA-DQA1, MAPKAPK2, HLA-DQB1, HLA-DRA, CTSC, HLA-DRB1, PECAM1, MBL2, TNFRSF14, GATA3, ETS1, PSMB10, CD55, PTPN22, CD46, BCL2, PTAFR, CD83, PTGER4, IL1RL2, CD209, PTK2, STAT5A, STAT6, TNFRSF4, CFD, PTPN6, SLAMF6, FCER1A, PIGR, FCGR2A, FCGR2B, CARD9, BTK, MIF, IL21, CIR, C1S, C4A, C4BPA, CCL7, CCR6, C6, C7, C8A, CCL19, C8B, CCL20, C9, CCL24, TAL1, XCL1, KIT, CX3CL1, KLRB1, CXCL12, VCAM1, SELE, GPI, RAG1, DPP4, ICOSLG, LILRA1, LILRA2, ZEB1, VTN, CLEC6A, ATG7, ICAM2, ICAM3, ICAM4, CXCL13, CASP3, AIRE, RELA, BTLA, RELB, GPR183, TLR9, LCK, CFI, CR2, IL23A, IFNA2, LGALS3, TFRC, IFNB1, IFNG, LIF, CD1A, CD3E, CSF1R, CSF2, CD8A, THY1, CD9, CSF3R, CD19, TIGIT, MS4A1, EBI3, CD22, IL20, CD80, CD86, ICAM5, TIRAP, CD34, CD40, IRAK4, CD44, CD48, TNFRSF13C, CD59, CD74, CD79A, CD79B, LTA, RORC, CTLA4, PAX5, HAMP, MAPK11, IL2, IL3, IL4, IL4R, IL5, CTSS, IL6, IL6R, IL7, IL27, MASP2, CXCR2

Table 5 (continued)

GO ID	Category	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0019221	BP	Cytokine-mediated signaling pathway	1.05E-84	1.35E-81	1.23E-80	5.40E-81	131	IL10, IL10RA, IL12A, IL12B, IL13, IRGM, MASP1, TRAF3, IL17A, ILF3, CE2BPB, CD244, HLA-B, AICDA, HLA-C, IDO1, TAGAP, HLA-DPA1, HLA-DPB1, HLA-DQA1, MAPKAPK2, HLA-DQB1, HLA-DRA, HLA-DRB1, MBL2, TNFRSF14, GATA3, PSMB10, CD55, PTPN22, CD46, BCL2, DEFB103B, PTAFR, PTGER4, IL1RL2, CCL26, CD209, STAT5A, BID, DEFB1, DEFB4A, CFD, PTPN6, SLAMF6, FCGR2B, CARD9, BTK, KLRF2, MIF, IL21, PLA2G2A, TOLLIP, CIR, C1S, C4A, C4BPA, CCL7, CCL11, CCL13, BATT3, CCL15, CCL16, C6, C7, CCL18, C8A, CCL19, C8B, CCL20, CCL22, C9, CCL24, CXCL11, XCL1, CX3CL1, NOS2, CXCL12, VCAM1, SELE, RAG2, LILRA2, CLEC6A, BCL2L11, ATG7, ITLN1, ICAM2, ICAM3, IRF8, CXCL13, CASP3, RELA, RELB, TLR9, PPBP, CFI, CR2, IL23A, IFNA2, EDNRB, LGALS3, IFNARI, IFNBI, IFNG, CSF1R, CSF2, CD8A, CSF2RB, MS4A1, EGR1, SIGIRR, CD80, CD86, TIRAP, CD40, IRAK4, CD44, CD74, CD79B, LTA, HAMP, MAPK11, IL1RAP, IL2, IL4, IL4R, CTSS, IL6, IL6R, IL27, MASP2
GO:0009607	BP	RESPONSE to biotic stimulus	7.42E-81	7.65E-78	6.99E-77	3.83E-77	120	IL10, IL10RA, IL12A, IL12B, IL13, IL13RA1, IRGM, IL16, TRAF3, TNFRSF9, IL17A, CE2BPB, HLA-B, PDGFB, HLA-C, TNFSF12, SPP1, HLA-DPA1, HLA-DPB1, HLA-DQA1, MAPKAPK2, HLA-DQB1, HLA-DRA, HLA-DRB1, TNFRSF14, GATA3, ETS1, PSMB10, BCL2, PTAFR, IL1RL2, CCL26, IL17F, STAT5A, STAT6, TNFRSF4, PTPN6, IL22RA2, NFIL3, BTK, MIF, IL21, TOLLIP, CCL7, CCR6, CCL11, CCL13, CCR8, CCL15, MME, CCL16, CCL18, CCL19, CCL20, CCL22, CCL24, CXCL11, XCL1, KIT, CX3CL1, NOS2, CXCL12, VCAM1, IL19, SELE, SELPLG, CCR10, XCR1, TCF7, ZEB1, FNI, IRF8, CXCL13, CASP3, RELA, RELB, PPBP, IL23A, SIPR1, IFNA2, TFR3, IFNARI, IFNBI, IFNG, LIF, CSF1R, CSF2, CSF2RB, CSF3R, EBI3, EGRI, SIGIRR, IL20, CD80, CD86, TIRAP, IL22, CD40, IRAK4, CD44, TNFRSF13C, CD74, LTA, RORC, HAMP, MAPK11, IL1RAP, IL2, IL3, IL4, IL4R, IL5, IL6, IL6R, IL7, IL26, IL27, CXCR1, IL9, CXCR2

Table 5 (continued)

GO ID	Category	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0009607	BP	Response to biotic stimulus	7.42E-81	7.65E-78	6.99E-77	3.83E-77	131	IL10, IL10RA, IL12A, IL12B, IL13, IRGM, MASPI, TRAF3, IL17A, ILF3, CEPPB, CD244, HLA-B, AICDA, HLA-C, IDO1, TAGAP, HLA-DPA1, HLA-DPB1, HLA-DQA1, MAPKAPK2, HLA-DQB1, HLA-DRA, HLA-DRB1, MBL2, TNFRSF14, GATA3, PSMB10, CD55, PTPN22, CD46, BCL2, DEFB103B, PTAFR, PTGER4, IL1RL2, CCL26, CD209, STAT5A, BID, DEFB1, DEFB4A, CFD, PTPN6, SLAMF6, FCGR2B, CARD9, BTK, KLRF2, MIF, IL21, PLA2G2A, TOLLIP, CIR, C1S, C4A, C4BPA, CCL7, CCL11, CCL13, BATT3, CCL15, CCL16, C6, C7, CCL18, C8A, CCL19, C8B, CCL20, CCL22, C9, CCL24, CXCL11, XCL1, CX3CL1, NOS2, CXCL12, VCAM1, SELE, RAG2, LILRA2, CLEC6A, BCL2L11, ATG7, ITLN1, ICAM2, ICAM3, IRF8, CXCL13, CASP3, RELA, RELB, TLR9, PPBP, CFI, CR2, IL23A, IFNA2, EDNRB, LGALS3, IFNARI, IFNB1, IFNG, CSF1R, CSF2, CD8A, CSF2RB, MS4A1, EGR1, SIGIRR, CD80, CD86, TIRAP, CD40, IRAK4, CD44, CD74, CD79B, LTA, HAMP, MAPK11, IL1RAP, IL2, IL4, IL4R, CTSS, IL6, IL6R, IL27, MASP2
GO:0034097	BP	Response to cytokine	3.04E-80	2.61E-77	2.39E-76	1.57E-76	120	IL10, IL10RA, IL12A, IL12B, IL13, IL13RA1, IRGM, IL16, TRAF3, TNFRSF9, IL17A, CEPPB, HLA-B, PDGFB, HLA-C, TNFSF12, SPP1, HLA-DPA1, HLA-DPB1, HLA-DQA1, MAPKAPK2, HLA-DQB1, HLA-DRA, HLA-DRB1, TNFRSF14, GATA3, ETS1, PSMB10, BCL2, PTAFR, IL1RL2, CCL26, IL17F, STAT5A, STAT6, TNFRSF4, PTPN6, IL22RA2, NFIL3, BTK, MIF, IL21, TOLLIP, CCL7, CCR6, CCL11, CCL13, CCR8, CCL15, MME, CCL16, CCL18, CCL19, CCL20, CCL22, CCL24, CXCL11, XCL1, KIT, CX3CL1, NOS2, CXCL12, VCAM1, IL19, SELE, SELPLG, CCR10, XCR1, TCF7, ZEB1, FN1, IRF8, CXCL13, CASP3, RELA, RELB, PPBP, IL23A, SIPR1, IFNA2, TFR3, IFNAR1, IFNB1, IFNG, LIF, CSF1R, CSF2, CSF2RB, CSF3R, EB13, EGR1, SIGIRR, IL20, CD80, CD86, TIRAP, IL22, CD40, IRAK4, CD44, TNFRSF13C, CD74, LTA, RORC, HAMP, MAPK11, IL1RAP, IL2, IL3, IL4, IL4R, IL5, IL6, IL6R, IL7, IL26, IL27, CXCR1, IL9, CXCR2

Table 5 (continued)

GO ID	Category	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0042110	BP	T cell activation	8.30E-63	2.25E-60	2.06E-59	4.28E-59	77	IL10, IL12A, IL12B, CEBPB, CD244, IDO1, HLA-DMA, HLA-DMB, HLA-DPA1, HLA-DPB1, HLA-DQA1, TNFRSF14, GATA3, PSMB10, CD55, PTPN22, CD46, BCL2, CD83, PTGER4, IL1RL2, CD209, STAT5A, STAT6, TNFRSF4, EOMES, PTPN6, SLAMF6, FCGR2B, IL21, CCR6, CCL19, CCL20, XCL1, KIT, CXCL12, VCAM1, RAG1, RAG2, DPP4, ICOSLG, TCF7, ZEB1, CASP3, AIRE, BTLA, RELB, GPR183, LCK, IL23A, IFNA2, LGALS3, TFR3, IFNAR1, IFNB1, IFNG, CD3E, CD8A, THY1, TIGIT, EBI3, EGR1, CD80, CD86, CD44, CD48, TNFRSF13C, CD74, RORC, CTLA4, IL2, IL4, IL4R, IL6, IL6R, IL7, IL27
GO:0001816	BP	Cytokine production	8.07E-58	1.81E-55	1.65E-54	4.16E-54	87	IL10, IL12A, IL12B, IL13, TRAF3, TNFRSF9, IL17A, CEBPB, CD244, IDO1, HLA-DPA1, HLA-DPB1, MAPKAPK2, IL17B, MBP, TNFRSF14, GATA3, CD55, PTPN22, CD46, PTAFR, CD83, PTGER4, IL1RL2, IL17F, STAT5A, STAT6, TNFRSF4, EOMES, PTPN6, SLAMF6, FCER1A, FCGR2B, CARD9, BTK, KLRF2, MIF, IL21, CCL19, CCL20, XCL1, KIT, CX3CL1, NOS2, IL19, ICOSLG, LILRA2, CLEC6A, FN1, IRF8, AIRE, RELA, RELB, TLR9, IL23A, IFNA2, IFNAR1, IFNB1, IFNG, CD3E, CSF1R, CSF2, TIGIT, EBI3, EGR1, SIGIRR, CD80, CD86, TIRAP, CD34, CD40, IRAK4, TNFRSF13C, CD74, LTA, RORC, MAPK11, IL1RAP, IL2, IL4, IL4R, IL6, IL6R, IL7, IL26, IL27, IL9
GO:0002694	BP	Regulation of leukocyte activation	7.07E-57	1.52E-54	1.39E-53	3.65E-53	77	IL10, IL12A, IL12B, IL13, CEBPB, CD244, IDO1, HLA-DMA, HLA-DMB, HLA-DPA1, HLA-DPB1, HLA-DQA1, CTSC, TNFRSF14, GATA3, CD55, PTPN22, CD46, BCL2, PTAFR, CD83, IL1RL2, CD209, STAT5A, STAT6, TNFRSF4, PTPN6, FCER1A, FCGR2B, BTK, MIF, IL21, CCR6, CCL19, CCL20, XCL1, CX3CL1, VCAM1, RAG1, DPP4, ICOSLG, ZEB1, CASP3, BTLA, GPR183, TLR9, LCK, IL23A, IFNA2, LGALS3, TFR3, IFNB1, IFNG, CD3E, THY1, CD19, TIGIT, EBI3, CD22, CD80, CD86, TIRAP, CD40, CD44, TNFRSF13C, CD74, RORC, CTLA4, HAMP, IL2, IL4, IL4R, IL5, IL6, IL6R, IL7, IL27

Table 5 (continued)

GO ID	Category	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0006954	BP	Inflammatory response	5.64E-55	1.12E-52	1.02E-51	2.91E-51	82	IL10, IL12B, IL13, IRGM, IL17A, CEBPB, IDO1, SPPI, MAPKAPK2, CTSC, IL17B, MBL2, GATA3, ETS1, PTAFR, PLA2G2E, PTGER4, IL1RL2, CCL26, IL17F, STAT5A, TNFRSF4, IL22RA2, FCER1A, FCGR2B, BTK, MIF, IL21, PLA2G2A, TOLLIP, C4A, CCL7, CCR6, CCL11, CCL13, CCL15, CCL16, CCL18, CCL19, CCL20, CCL22, CCL24, CXCL11, XCL1, KIT, CX3CL1, NOS2, VCAM1, SELE, XCRI, FNI, NT5E, CXCL13, REL, RELB, TLR9, PPBP, IL23A, IFNA2, EDNRB, IFNG, CSF1R, SIGIRR, IL20, TIRAP, IL22, CD40, CD44, LTA, HAMP, IL1RAP, IL2, CDH5, IL4, IL4R, IL5, CTSS, IL6, IL6R, IL27, IL9, CXCR2
GO:0007155	BP	Cell adhesion	3.87E-42	3.50E-40	3.20E-39	2.00E-38	91	IL10, IL12A, IL12B, CEBPB, CD244, IDO1, HLA-DMA, HLA-DMB, SPPI, HLA-DPA1, HLA-DPB1, HLA-DQA1, PECAM1, MBP, TNFRSF14, GATA3, ETS1, CD55, PTPN22, CD46, BCL2, PTAFR, CD83, ITGAE, PTGER4, IL1RL2, CD209, PTK2, STAT5A, PTPN6, FCGR2B, IL21, PLAU, CCL11, CCR8, CCL19, XCL1, KIT, MAP4K4, CX3CL1, CXCL12, VCAM1, SELE, SELPLG, RAG1, DPP4, ICOSLG, VTN, FNI, BCL2L11, NT5E, ICAM2, ICAM3, ICAM4, CXCL13, CASP3, REL, BTLA, LCK, IL23A, SIPR1, IFNA2, LGALS3, TFRC, IFNB1, IFNG, TGFBI, ARHGAP1, CD3E, THY1, CD9, CSF3R, TIGIT, EBI3, CD22, CD80, CD86, ICAM5, CD34, CD44, TNFRSF13C, CD74, CTLA4, IL1RAP, IL2, CDH5, IL4, IL4R, IL6, IL6R, IL7

Table 5 (continued)

GO ID	Category	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0009986	CC	Cell surface	8.40E-48	1.04E-45	6.72E-45	3.09E-45	83	IL12A, IL12B, IL13, IL13RA1, TNFRSF9, IL17A, CD244, HLA-B, PDGFB, HLA-C, HLA-DMA, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DRA, HLA-DRB1, PECAM1, MBL2, MBP, TNFRSF14, CD55, CD46, TNFRSF10C, CD83, ITGAE, CD209, TNFRSF4, FCER1A, FCGR2B, FCGR2, MIF, PLAU, CCR6, CCR8, MME, KIT, CX3CL1, CXCL12, VCAM1, CCR10, DPP4, ICOSLG, XCR1, NT5E, BTLA, CR2, SIPRI1, LGALS3, TFR3, IFNG, TGFBRI, CD1A, CD3E, CSF1R, CD8A, THY1, CD9, CSF3R, CD19, TIGIT, MS4A1, EBI3, CD22, CD80, CD86, CD34, CD40, CD44, CD48, TNFRSF13C, CD59, CD74, CD79A, CD79B, RORC, CTLA4, CDH5, IL4, CTSS, IL6, IL6R, CXCR1, CXCR2
GO:0097478	CC	Leaflet of membrane bilayer	8.80E-48	1.04E-45	6.72E-45	3.24E-45	70	IL12B, IL13, IL13RA1, TRAF3, TNFRSF9, IL17A, CD244, HLA-B, HLA-C, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, HLA-DRB1, PECAM1, TNFRSF14, PTPN22, CD83, ITGAE, CD209, TNFRSF4, FCER1A, FCGR2B, FCGR2, CCR6, CCR8, KIT, CXCL12, VCAM1, CCR10, ICOSLG, XCR1, BTLA, LCK, CR2, S1PR1, LGALS3, TFR3, IFNG, CD1A, CD3E, BCAP31, CD8A, THY1, CD9, CSF3R, CD19, MS4A1, EBI3, CD22, CD80, CD86, CD34, CD40, CD44, CD48, TNFRSF13C, CD59, CD74, CD79A, CD79B, RORC, CTLA4, CDH5, IL4, IL6, IL6R, CXCR1, CXCR2
GO:0031226	CC	Intrinsic component of plasma membrane	4.10E-24	3.01E-22	1.96E-21	1.51E-21	75	IL13RA1, TRAF3, TNFRSF9, TNFSF12, HLA-DPA1, HLA-DQA1, HLA-DRA, CD46, PTAFR, CD83, ITGAE, IL1RL2, TNFRSF4, CD82, SLAMF6, FCAR, FCER1A, PI3R, FCGR2B, KLRF2, TOLLIP, CCR6, CCR8, MME, C6, C7, C8A, C8B, C9, KIT, VCAM1, SELP, SELPLG, CCR10, ICOSLG, XCR1, LILRA2, ICAM2, ICAM3, ICAM4, BTLA, GPR183, S1PR1, SLC2A1, EDNRB, TFR3, IFNAR1, TGFBRI, CD1A, CD3E, BCAP31, CSF1R, CD8A, THY1, CSF2RB, CD9, CSF3R, CD19, MS4A1, EBI3, CD22, ICAM5, CD34, CD40, CD44, CD48, CD59, CD74, CD79B, CTLA4, IL1RAP, IL4R, IL6, IL6R, CXCR2

Table 5 (continued)

GO ID	Category	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0098589	CC	Membrane region	7.35E-11	1.93E-09	1.25E-08	2.70E-08	24	PECAM1, CD55, CD46, STAT6, FCER1A, BTK, MME, SELE, SELPLG, DPP4, ITLN1, CASP3, LCK, S1PR1, SLC2A1, EDNRB, TGFBRI1, CD1A, CD8A, THY1, CD19, MS4A1, CD48, CD79A
GO:0043235	CC	Receptor complex	3.10E-10	6.71E-09	4.35E-08	1.14E-07	26	IL12B, IL13RA1, TRAF3, ITGAE, PTPN6, PIGR, TOLLIP, KIT, ITLN1, CR2, TFR3, TGFBRI1, CD3E, CSF1R, CD8A, CSF2RB, CSF3R, EBI3, CD40, CD44, CD74, CD79A, CD79B, IL4R, IL6, IL6R
GO:0030141	CC	Secretory granule	3.67E-07	5.20E-06	3.37E-05	1.35E-04	29	PDGFB, CTSC, PECAM1, CD55, CD46, PTAFR, CFD, PTPN6, FCAR, PIGR, FCGR2A, MIF, PLA2G2A, TOLLIP, PLAU, MME, KIT, GPI, LILRA3, FN1, ATG7, PPBP, LGALS3, CD9, CD44, CD59, CTSS, CXCR1, CXCR2
GO:0005764	CC	Lysosome	1.31E-06	1.49E-05	9.69E-05	4.81E-04	25	IL13, HLA-DMA, HLA-DMB, HLA-DOB, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, CTSC, HLA-DRB1, FCER1A, PIGR, BTK, TOLLIP, KIT, DPP4, TLR9, IFNAR1, CD34, CD74, IL4, IL4R, CTSS, CXCR2
GO:0005794	CC	Golgi apparatus	4.18E-03	2.00E-02	1.30E-01	1.00E+00	31	IRGM, HLA-B, PDGFB, HLA-C, SPPI, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, CTSC, HLA-DRB1, CD55, CD46, DEFB103B, DEFB1, DEFB4A, MME, VCAM1, DPP4, VTN, TLR9, SLC2A1, TGFB1, BCAP31, CD44, CD59, CD74, CD79B, B3GAT1, CTLA4
GO:0048471	CC	Perinuclear region of cytoplasm	2.87E-02	8.46E-02	5.49E-01	1.00E+00	16	TNFSF12, SPPI, PTPN22, BCL2, BTK, PLA2G2A, TOLLIP, CX3CL1, NOS2, SELE, ATG7, TFR3, TRAF4, BCAP31, CD34, CTLA4
GO:0044297	CC	Cell body	9.03E-02	2.08E-01	1.00E+00	1.00E+00	14	PDGFB, MBP, PTGER4, FCGR2B, C4A, MME, CX3CL1, CASP3, IFNG, CD3E, THY1, CD22, CD40, IL6R
GO:0030054	CC	Cell junction	9.70E-02	2.20E-01	1.00E+00	1.00E+00	21	PECAM1, CD46, PTK2, PTPN6, C4A, PLAU, MME, KIT, MAP4K4, DPP4, LCK, SLC2A1, TGFBRI1, TRAF4, CD3E, THY1, CD9, CD44, CD59, HAMP, CDH5

Table 5 (continued)

GO ID	Category	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0005126	MF	Cytokine receptor binding	8.37E-54	6.01E-51	4.30E-50	6.01E-51	59	IL10, IL12A, IL12B, IL13, TRAF3, TNFSF12, GATA3, DEFB103B, CCL26, IL17F, BID, DEFB1, DEFB4A, MIF, IL21, TOLLIP, CCL7, CCL11, CCL13, CCL15, CCL16, CCL18, CCL19, CCL20, CCL22, CCL24, CXCL11, XCL1, CX3CL1, CXCL12, CXCL13, CASP3, TLR9, PPBP, IL23A, IFNA2, IFNB1, IFNG, TGFBRI, LIF, TRAF4, CSF2, EBI3, IL20, IL22, IRAK4, CD44, LTA, IL1RAP, IL2, IL3, CDH5, IL4, IL5, IL6, IL6R, IL7, IL27, IL9
GO:0005102	MF	Signaling receptor binding	3.78E-49	9.05E-47	6.48E-46	2.72E-46	108	IL10, IL12A, IL12B, IL13, IL16, TRAF3, IL17A, CEBPB, CD244, HLA-B, PDGFB, HLA-C, TNFSF12, HLA-DOB, SPPI, HLA-DPA1, HLA-DQA1, HLA-DQB1, HLA-DRA, IL17B, MBL2, GATA3, DEFB103B, CCL26, IL17F, PTK2, BID, DEFB1, DEFB4A, PTPN6, PI3R, MIF, IL21, TOLLIP, CCL7, CCL11, CCL13, CCL15, CCL16, CCL18, CCL19, CCL20, CCL22, CCL24, CXCL11, XCL1, CX3CL1, CXCL12, VCAM1, IL19, SELPLG, GPI, DPP4, ICOSLG, VTN, FNI, ATG7, ICAM2, ICAM3, ICAM4, CXCL13, CASP3, TLR9, LCK, PPBP, IL23A, SIPRI, IFNA2, EDNRB, LGALS3, IFNB1, IFNG, TGFBRI, TGFBRI, LIF, TRAF4, CD3E, BCAP31, CSF2, CD8A, THY1, CD9, TIGIT, MS4A1, EBI3, CD22, IL20, CD86, ICAM5, TIRAP, IL22, IRAK4, CD44, CD74, LTA, HAMP, IL1RAP, IL2, IL3, CDH5, IL4, IL5, IL6, IL6R, IL7, IL26, IL27, IL9
GO:0030545	MF	Chemokine receptor binding	2.63E-22	2.36E-20	1.69E-19	1.89E-19	20	DEFB103B, CCL26, DEFB1, DEFB4A, CCL7, CCL11, CCL13, CCL15, CCL16, CCL18, CCL19, CCL20, CCL22, CCL24, CXCL11, XCL1, CX3CL1, CXCL12, CXCL13, PPBP
GO:0098772	MF	Molecular function regulator	1.42E-18	6.80E-17	4.86E-16	1.02E-15	71	IL10, IL12A, IL12B, IL13, IRGM, IL16, IL17A, PDGFB, TNFSF12, SPP1, TAGAP, CTSC, IL17B, CD46, BCL2, DEFB103B, CCL26, IL17F, EOMES, DEFB4A, MIF, IL21, C4A, CCL7, CCL11, CCL13, CCL15, CCL16, CCL18, CCL19, CCL20, CCL22, CCL24, CXCL11, XCL1, CX3CL1, NOS2, CXCL12, IL19, GPI, FNI, CXCL13, CASP3, SKI, PPBP, IL23A, IFNA2, LGALS3, IFNB1, IFNG, LIF, ARHGDI3, TRAF4, CSF2, THY1, EBI3, IL20, TIRAP, IL22, LTA, HAMP, IL2, IL3, IL4, IL5, IL6, IL6R, IL7, IL26, IL27, IL9

Table 5 (continued)

GO ID	Category	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0004888	MF	Transmembranesignaling receptor activity	2.09E-12	8.81E-11	6.31E-10	1.50E-09	50	IL10RA, IL12B, IL13RA1, HLA-DOB, HLA-DPA1, HLA-DQA1, HLA-DQB1, HLA-DRA, TNFRSF14, TNFRSF10C, PTAFR, PTGER4, IL1RL2, TNFRSF4, PTPN6, IL22RA2, FCER1A, PIGR, FCGR2B, CCR6, CCR8, KIT, KLRB1, LILRB5, SELE, CCR10, XCR1, LILRA1, GPR183, TLR9, CR2, SIPRI, EDNRB, IFNARI, IFNG, TGFBRI, CD3E, CSF1R, CSF2RB, CSF3R, EBI3, CD44, CD74, CD79A, CD79B, IL1RAP, IL4R, IL6R, CXCR1, CXCR2
GO:0001664	MF	G protein-coupled receptor binding	3.80E-12	1.52E-10	1.08E-09	2.73E-09	23	DEFB103B, CCL26, DEFB1, DEFB4A, CCL7, CCL11, CCL13, CCL15, CCL16, CCL18, CCL19, CCL20, CCL22, CCL24, CXCL11, XCL1, CX3CL1, CXCL12, CXCL13, PPBP, SIPRI1, EDNRB, IL2
GO:0044877	MF	Protein-containing complex binding	1.24E-11	4.46E-10	3.19E-09	8.92E-09	48	PDGFB, HLA-DMA, HLA-DMB, HLA-DOB, SPPI1, HLA-DRA, HLA-DRB1, PTK2, FCAR, FCERIA, PIGR, FCGR2A, FCGR2B, FCGRT, MIF, C8A, C8B, CX3CL1, CXCL12, VCAMI1, DPP4, LILRA2, VTN, FN1, BCL2L1, ICAM2, ICAM3, ICAM4, CASP3, RELA, LCK, IFNA2, LGALS3, IFNB1, TGFB1, TGFBRI, CD3E, BCAP31, CD8A, THY1, CD9, MS4A1, CD22, ICAM5, CD44, CD74, CDH5, CTSS
GO:0042802	MF	IDENTICAL protein binding	1.81E-07	3.93E-06	2.81E-05	1.30E-04	51	IL12B, MASP1, CEBPB, AICDA, PDGFB, CTSC, PECAMI, ETS1, BCL2, IL17F, PTK2, STAT6, DEFB1, CARD9, BTK, KLRF2, MIF, C1S, MME, XCL1, KIT, NOS2, RAG1, DPP4, ICOSLG, TCF4, IKZF2, VTN, FN1, ATG7, ITLN1, AIRE, RELA, RELB, TLR9, LCK, CR2, SLC2A1, LGALS3, TRFC, TRAF4, CD3E, CSF1R, CD8A, TIGIT, TIRAP, CD74, CD79A, CD79B, CDH5, IL6R
GO:0046983	MF	Protein dimerization activity	6.79E-07	1.19E-05	8.51E-05	4.88E-04	42	IL10, IL12A, IL12B, MASP1, CEBPB, PDGFB, HLA-DQA1, PECAMI, GATA3, BCL2, IL17F, BID, CARD9, KLRF2, CCL11, MME, TAL1, XCL1, KIT, NOS2, RAG1, DPP4, TCF4, IKZF2, BCL2L11, ATG7, CXCL13, RELA, TLR9, CR2, LGALS3, TRFC, TGFBRI, TRAF4, CD3E, CSF1R, CD8A, TIRAP, CD79A, CD79B, CDH5, IL6R

Table 5 (continued)

GO ID	Category	GO Name	P Value	FDR B&H	FDR B&Y	Bonferroni	Gene Count	Gene
GO:0016301	MF	Kinase activity	1.16E-05	1.54E-04	1.10E-03	8.29E-03	40	IL12B, IRGM, PDGFB, MAPKAPK2, PTPN22, PTK2, TNFRSF4, PTPN6, FCER1A, BTK, MIF, CCL19, TALI, KIT, MAP4K4, NOS2, GPI, DUSP4, CASP3, TLR9, LCK, IL23A, IFNG, TGFBRL, TRAF4, CSF1R, THY1, CD19, EGR1, TIRAP, CD40, IRAK4, CD44, CD74, MAPK11, IL2, IL3, IL4, IL6, IL6R

BP biological process, *CC* cellular component, *MF* molecular functions

PEWCC1. The top four significant modules of up-regulated were selected for further analysis (Fig. 10). Module 48 had 10 nodes and 34 edges, module 50 had 10 nodes and 33 edges, Module 64 had 10 nodes and 17 edges and module 65 had 10 nodes and 17 edges, respectively. Enrichment analysis showed that the genes in these modules were mainly involved in natural killer cell-mediated cytotoxicity, measles, Jak-STAT signaling pathway, viral myocarditis, herpes simplex infection, influenza A, osteoclast differentiation, HTLV-I infection, IL12-mediated signaling events, IL2-mediated signaling events, tuberculosis, malaria, paxillin-dependent events mediated by a4b1, TCR signaling in naive CD8 + T cells and cytokine signaling in Immune system. The top four significant modules of down-regulated were selected for further analysis (Fig. 11). Module 18 had 17 nodes and 44 edges, module 23 had 15 nodes and 20 edges, module 58 had 9 nodes and 22 edges and module 104 had 7 nodes and 12 edges, respectively. Enrichment analysis showed that the genes in these modules were mainly involved in apoptosis signaling pathway, tuberculosis, viral myocarditis, Jak-STAT signaling pathway, cytokine signaling in immune system, measles, innate immune system, cytokine–cytokine receptor interaction, influenza A, hematopoietic cell lineage, HTLV-I infection, signaling by interleukins, adaptive immune system, IL12-mediated signaling events, interleukin signaling pathway, inflammation mediated by chemokine and cytokine signaling pathway, inflammatory bowel disease (IBD), FAS (CD95) signaling pathway, cytokine-mediated signaling pathway, response to biotic stimulus, IL4-mediated signaling events, MAPK family signaling cascades and regulation of immune system process.

Construction of target gene–miRNA regulatory network

Using the miRNet database, target gene–miRNA regulatory network for up-regulated genes had 1008 nodes and 1613 interactions (Fig. 12). The network marked that each target genes have interactions with miRNAs. IKZF3 regulates 134 miRNAs (ex, hsa-mir-6860), TP53 regulates 130 miRNAs (ex, hsa-mir-5703), IFNAR2 regulates 109 miRNAs (ex, hsa-mir-4510), SMAD5 regulates 83 miRNAs (ex, hsa-mir-6086) and STAT3 regulates by 80 miRNAs (ex, hsa-mir-4270) are listed in Table 8. Enrichment analysis showed that the target genes in this network were mainly involved in IL2-mediated signaling events, measles, herpes simplex infection, ALK2 signaling events and cytokine signaling in immune system. Similarly, target gene–miRNA regulatory network for down-regulated genes had 1791 nodes and 3951 interactions (Fig. 13). SKI regulates 210 miRNAs (ex, hsa-mir-5100), TNFRSF13C regulates 136 miRNAs (ex, hsa-mir-3197), BCL2L11 regulates 122 miRNAs (ex, hsa-mir-8064), ICOSLG regulates 119 miRNAs

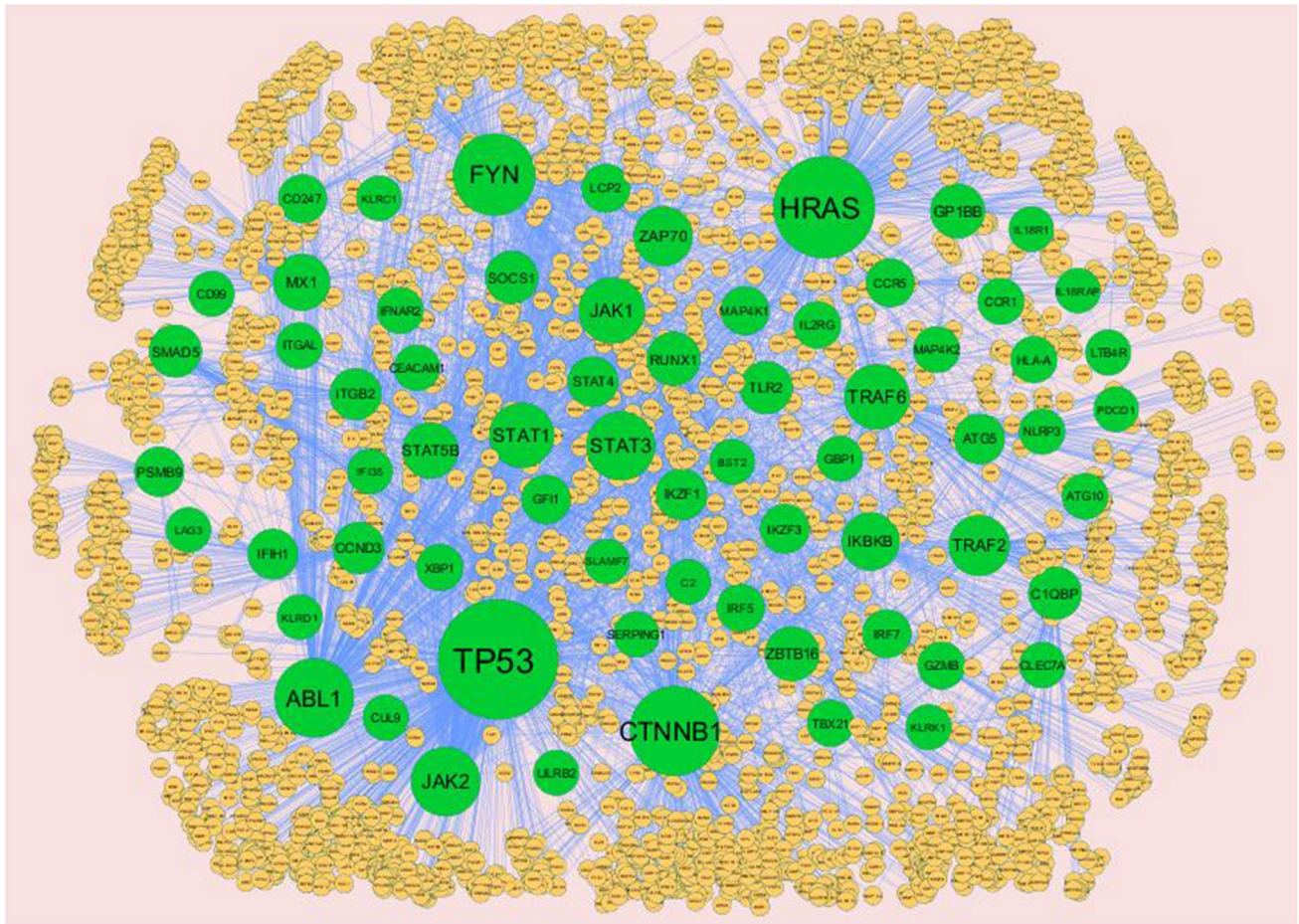


Fig. 6 Protein–protein interaction network of up regulated genes. Green nodes (●) denotes up regulated genes; Blue lines (—) denotes edges (Interactions)

(ex, hsa-mir-3672) and IL6R regulates 94 miRNAs (ex, hsa-mir-7641) are listed in Table 7. Enrichment analysis showed that the target genes in this network were mainly involved in molecular function regulator, cytokine–cytokine receptor interaction, apoptosis signaling pathway, adaptive immune system and cytokine–cytokine receptor interaction.

Construction of target gene–TF regulatory network

Using the NetworkAnalyst database, target gene–TF regulatory network for up-regulated genes had 145 nodes and 634 interactions (Fig. 14). The network marked that each target genes have interactions with transcription factors (TFs). JAK1 regulates 46 TFs (ex, FOXC1), TRAF6 regulates 31 TFs (ex, GATA2), CLEC7A regulates 25 TFs (ex, YY1), STAT1 regulates 22 TFs (ex, CREB1) and IKZF1 regulates 22 TFs (ex, TFAP2A) are listed in Table 8. Enrichment analysis showed that the target genes in this network were mainly involved in measles, herpes simplex infection, tuberculosis, osteoclast differentiation

and regulation of immune system process. Similarly, target gene–TF regulatory network of down-regulated genes had 1788 nodes and 235 interactions (Fig. 15). KLRF2 regulates 127 TFs (ex, FOXC1), CD1A regulates 102 TFs (ex, GATA2), TNFRSF4 regulates 75 TFs (ex, YY1), MME regulates 63 TFs (ex, FOXL1) and CXCL12 regulates 63 TFs (ex, FOXL1) are listed in Table 7. Enrichment analysis showed that the target genes in this network were mainly involved in cytokine-mediated signaling pathway, hematopoietic cell lineage, cytokine–cytokine receptor interaction, innate immune system and peptide ligand-binding receptors.

Validation of hub genes

The ROC curve analysis was accomplished to assess the diagnostic values of hub genes. Our finding revealed that CCL5 (AUC = 0.784), IFNAR2 (AUC = 0.750), JAK2 (AUC = 0.859), MX1 (AUC = 0.773), STAT1

Table 6 Topology table for up and down regulated genes

Regulation	Node	Degree	Betweenness	Stress	Closeness	Clustering Coefficient
Up	TP53	682	0.308256	69419762	0.44613	0.001042
Up	HRAS	543	0.243425	36147274	0.454702	0.003568
Up	CTNNB1	454	0.17049	60805652	0.403018	0.002042
Up	FYN	396	0.117564	12570856	0.436236	0.010907
Up	ABL1	362	0.118179	7631538	0.470883	0.015228
Up	JAK2	258	0.054758	7164820	0.434802	0.021748
Up	STAT3	253	0.05294	16470742	0.398767	0.02108
Up	JAK1	223	0.032981	6336566	0.40235	0.019876
Up	TRAF6	216	0.074546	12176648	0.395301	0.010207
Up	STAT1	213	0.045072	12845532	0.387307	0.023031
Up	TRAF2	171	0.047572	11238720	0.357837	0.007981
Up	ZAP70	153	0.018814	3346658	0.375226	0.028294
Up	IKBKB	140	0.040639	5153454	0.403521	0.017575
Up	MX1	125	0.057134	6475242	0.352549	0.002194
Up	STAT5B	118	0.012758	2934924	0.377415	0.057801
Up	ZBTB16	105	0.029011	4339392	0.371064	0.00696
Up	GP1BB	104	0.024662	2308816	0.350596	0.009335
Up	RUNX1	95	0.021204	3579930	0.370309	0.010526
Up	CIQBP	89	0.043687	7011558	0.334675	0
Up	TLR2	85	0.019615	2401022	0.374839	0.034734
Up	SOCS1	85	0.019595	1846156	0.398713	0.072829
Up	SMAD5	82	0.024208	4462604	0.336687	0.003011
Up	ITGB2	72	0.025976	3349086	0.351061	0.008607
Up	IKZF1	72	0.011714	1722502	0.373157	0.034038
Up	CCND3	71	0.025956	2361424	0.357661	0.008048
Up	ATG5	60	0.020131	2294688	0.333219	0.00678
Up	IFIH1	59	0.023459	2059722	0.333945	0.001753
Up	STAT4	58	0.002561	797810	0.366902	0.082275
Up	PSMB9	55	0.0248	2740768	0.310739	0
Up	IKZF3	47	0.005026	756292	0.361346	0.053654
Up	GFI1	46	0.007563	811180	0.357266	0.013527
Up	IRF7	44	0.010411	1198488	0.338804	0.008457
Up	MAP4K1	44	0.006432	851692	0.348957	0.046512
Up	CD247	43	0.00724	710792	0.349292	0.058693
Up	LCP2	41	0.003353	442356	0.338331	0.07439
Up	CCR5	39	0.010719	942222	0.343359	0.043185
Up	IRF5	34	0.006222	736764	0.339277	0.012478
Up	GZMB	29	0.01009	1297184	0.313584	0
Up	IL2RG	27	0.005284	347620	0.3463	0.071225
Up	TBX21	23	0.003781	493896	0.328704	0.023715
Up	XBP1	21	0.004344	440004	0.329933	0
Up	HLA-A	19	0.007447	822622	0.311637	0
Up	MAP4K2	18	0.002038	190802	0.334636	0.045752
Up	CCR1	18	0.004542	722956	0.323912	0.019608
Up	IFNAR2	17	0.003686	214358	0.335872	0.169118
Up	ITGAL	17	0.004258	302784	0.285588	0.058824
Up	ATG10	16	0.00303	204222	0.278618	0.075
Up	CEACAM1	15	0.003567	815206	0.308991	0
Up	CLEC7A	13	0.006223	422114	0.302253	0
Up	CUL9	10	0.001917	66468	0.352806	0.111111
Up	SERPING1	10	0.004857	805696	0.203225	0

Table 6 (continued)

Regulation	Node	Degree	Betweenness	Stress	Closeness	Clustering Coefficient
Up	NLRP3	10	0.002325	208526	0.304371	0
Up	LTB4R	9	0.002812	970594	0.242059	0
Up	GBP1	9	0.001571	66852	0.307489	0
Up	LILRB2	9	0.004803	191694	0.287677	0
Up	CD99	8	0.002792	99752	0.324129	0
Up	KLRK1	7	0.003445	544176	0.26256	0
Up	BST2	7	1.93E-04	36836	0.324273	0
Up	KLRD1	7	0.001389	97132	0.22517	0.047619
Up	KLRC1	5	0.003221	307724	0.286234	0.1
Up	IL18R1	4	0.00118	348338	0.245924	0
Up	PDCD1	4	0.001374	55018	0.303894	0.166667
Up	SLAMF7	4	0.00206	191070	0.233272	0
Up	C2	4	0.001446	96444	0.245447	0
Up	IFI35	3	6.93E-04	23710	0.323301	0
Up	LAG3	2	4.23E-06	1074	0.245695	0
Up	IL18RAP	2	1.95E-04	52194	0.233609	0
Down	MAPK11	421	0.179413	26118522	0.388195	0.003744
Down	RELA	285	0.126824	20931198	0.37804	0.004645
Down	LCK	267	0.108492	11305268	0.405534	0.014108
Down	KIT	221	0.051071	10158794	0.36783	0.015014
Down	EGR1	195	0.060886	6334914	0.384414	0.016178
Down	ILF3	179	0.093546	7805892	0.330116	3.14E-04
Down	CASP3	175	0.070326	10842834	0.355181	0.005123
Down	PTK2	153	0.049652	8738870	0.356704	0.005246
Down	PTPN6	150	0.044684	5323296	0.365645	0.021477
Down	BCL2	150	0.062256	5772430	0.365862	0.009128
Down	BTK	137	0.022999	3449618	0.35359	0.019429
Down	STAT5A	126	0.024378	5096524	0.35745	0.027429
Down	TGFBR1	123	0.048955	6050368	0.349257	0.007464
Down	CSF1R	117	0.01327	3411424	0.344835	0.005894
Down	FN1	116	0.052141	5201654	0.335331	0.003148
Down	TCF4	115	0.044569	5794596	0.333586	0.005492
Down	TRAF3	113	0.038869	4088284	0.341886	0.010588
Down	STAT6	102	0.026319	3212830	0.363486	0.039216
Down	GATA3	97	0.03064	3006348	0.350689	0.018471
Down	IRAK4	90	0.015953	2526624	0.344064	0.010986
Down	TCF7	90	0.029254	4190222	0.323796	9.99E-04
Down	ATG7	88	0.032475	4557368	0.323761	0
Down	PSMB10	86	0.037084	3948650	0.316536	0
Down	EGR2	78	0.014472	2942228	0.323966	0.002331
Down	CEBPB	77	0.01563	2080316	0.347208	0.028708
Down	TLR9	75	0.01613	2504516	0.335623	0.017658
Down	ETS1	74	0.015119	2229504	0.345493	0.023695
Down	MBP	69	0.02034	1946892	0.33211	0.008099
Down	CD40	63	0.012367	1565636	0.343144	0.030722
Down	PTPN22	63	0.005103	648768	0.333009	0.039939
Down	CXCL13	62	0.033409	4616616	0.255924	0.002644
Down	CD44	61	0.027234	2621678	0.352941	0.016393
Down	DUSP4	56	0.005964	877004	0.343106	0.046753
Down	TOLLIP	55	0.020841	1681614	0.32948	0.011448
Down	TRAF4	54	0.017367	1322968	0.327447	0.012579

Table 6 (continued)

Regulation	Node	Degree	Betweenness	Stress	Closeness	Clustering Coefficient
Down	TFRC	51	0.020865	2030850	0.323932	7.84E-04
Down	TAL1	49	0.012074	1294452	0.327273	0.02551
Down	BATF3	48	0.009925	1237560	0.309471	0.011525
Down	SKI	47	0.009912	1441494	0.325026	0.010176
Down	MAP4K4	46	0.00723	923942	0.334966	0.025121
Down	ARHGDI3	43	0.008007	998356	0.325267	0.00443
Down	BID	40	0.007734	665116	0.336026	0.046154
Down	BCL2L11	39	0.006742	718322	0.327935	0.032389
Down	NOS2	39	0.012743	915032	0.332218	0.010796
Down	AICDA	38	0.016444	2864544	0.288094	0
Down	GPI	37	0.009895	1400722	0.322202	0
Down	CSF2RB	37	0.005071	681430	0.345571	0.100601
Down	TIRAP	37	0.009595	1070880	0.324	0.033033
Down	CD9	36	0.01001	838100	0.302685	0.019048
Down	CDH5	35	0.00845	737334	0.306177	0.013445
Down	AIRE	35	0.010893	2140272	0.292753	0
Down	CD82	32	0.008605	911074	0.323659	0.020161
Down	IFNAR1	31	0.006943	536824	0.340902	0.062366
Down	CD3E	30	0.006779	602042	0.338614	0.078161
Down	LGALS3	30	0.009645	633882	0.302536	0
Down	VTN	30	0.009755	750034	0.299445	0.006897
Down	CD8A	29	0.008368	709958	0.334638	0.029557
Down	CSF3R	28	0.008229	711320	0.334093	0.029101
Down	EOMES	28	0.005201	513270	0.277597	0.018519
Down	VCAM1	28	0.008841	718322	0.31732	0.010582
Down	ZEB1	27	0.006122	1257304	0.288851	0
Down	MME	27	0.009061	1835908	0.290624	0.014245
Down	MIF	27	0.00826	611016	0.321596	0.005698
Down	IKZF2	26	0.003358	390862	0.3129	0
Down	MAPKAPK2	26	0.004801	451358	0.310909	0.024615
Down	PLAU	25	0.008975	593824	0.317844	0.01
Down	DPP4	25	0.010538	1418468	0.265231	0.006667
Down	RORC	25	0.00722	1661398	0.278729	0.013333
Down	CD55	24	0.010279	705586	0.303102	0
Down	IL4R	24	0.00238	270352	0.331181	0.083333
Down	CD19	23	0.001702	211728	0.304301	0.090909
Down	IRF8	23	0.005195	372574	0.329904	0.019763
Down	IL4	23	0.004905	441962	0.296246	0.019763
Down	RELB	23	0.003464	286340	0.326336	0.055336
Down	PAX5	22	0.002896	300204	0.291726	0.021645
Down	CXCR2	22	0.006344	1097670	0.26098	0.047619
Down	IL16	22	0.008141	455702	0.300821	0
Down	SPP1	21	0.005095	320668	0.307124	0.014286
Down	THY1	21	0.008614	468640	0.309285	0.004762
Down	SLC2A1	20	0.00547	544898	0.316244	0
Down	EDNRB	20	0.006473	488214	0.313729	0
Down	SELE	20	0.005852	411150	0.300615	0.031579
Down	HLA-DRA	18	0.004735	398954	0.319992	0.052288
Down	CD79A	18	0.00478	297512	0.338726	0.176471
Down	HLA-B	17	0.006176	428434	0.315111	0.022059
Down	BCAP31	17	0.005172	568664	0.289476	0.058824

Table 6 (continued)

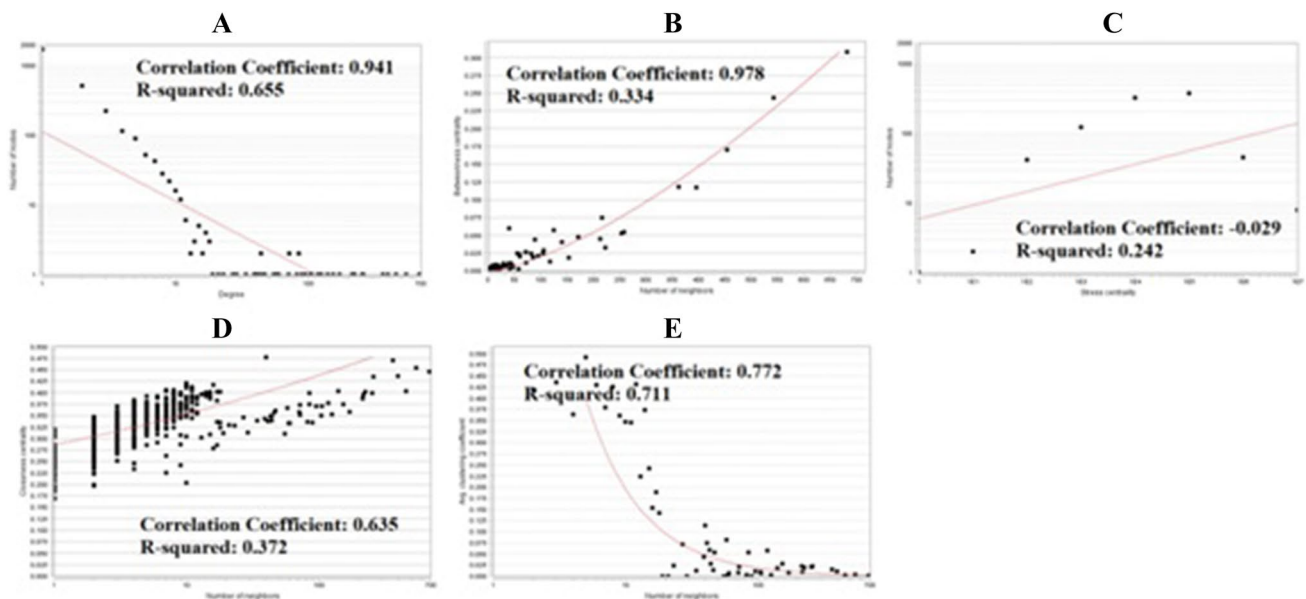
Regulation	Node	Degree	Betweenness	Stress	Closeness	Clustering Coefficient
Down	IL1RAP	17	0.003059	257852	0.322101	0.088235
Down	PDGFB	16	0.003308	533330	0.27399	0
Down	S1PR1	16	0.002256	404754	0.320025	0
Down	CD46	15	0.004006	360234	0.31814	0.047619
Down	RAG1	15	0.002698	229148	0.267304	0.019048
Down	CD22	15	0.003395	414458	0.289123	0.07619
Down	POU2F2	14	0.00252	256428	0.313506	0
Down	TNFRSF14	14	0.002863	205148	0.290131	0.054945
Down	FCGR2B	14	0.001419	233096	0.299854	0.087912
Down	CSF2	14	0.001964	189924	0.271764	0.076923
Down	SELPLG	14	0.004641	618406	0.266933	0.010989
Down	IL10	13	0.001286	131502	0.275387	0.025641
Down	CCL7	13	0.002891	346838	0.240789	0
Down	CD79B	13	3.06E-04	78608	0.337796	0.423077
Down	HLA-C	13	0.003625	407006	0.310407	0.025641
Down	IL6R	13	0.004275	289876	0.288689	0.051282
Down	IL17A	13	0.002334	388710	0.280328	0.025641
Down	FCGR2A	13	0.002143	252800	0.318403	0
Down	LTA	12	0.002886	476206	0.257315	0
Down	CXCL12	12	0.005496	372448	0.27655	0.030303
Down	CTSS	12	0.00407	451030	0.260472	0
Down	CD59	12	0.004363	207460	0.290405	0.030303
Down	CXCR1	12	8.07E-04	176404	0.242095	0.166667
Down	IL2	12	0.002493	217616	0.290487	0.030303
Down	C6	12	9.26E-04	133246	0.24911	0
Down	CD74	12	0.003192	267306	0.315369	0.121212
Down	CR2	11	0.001319	143504	0.267072	0.036364
Down	CCR10	11	0.003702	303034	0.222963	0.072727
Down	CTSC	11	0.004925	257558	0.302268	0
Down	TGFBI	10	7.77E-04	51700	0.253167	0.155556
Down	CD209	10	4.47E-04	37928	0.243628	0.044444
Down	NT5E	10	0.003249	169846	0.314627	0.022222
Down	IL10RA	10	0.001722	123836	0.32116	0.155556
Down	MBL2	9	0.002733	247190	0.248106	0.027778
Down	TNFRSF9	9	0.001065	77604	0.309005	0.305556
Down	HLA-DQA1	9	8.50E-04	84902	0.306147	0.194444
Down	NFIL3	9	0.002148	269802	0.253063	0
Down	MS4A1	9	6.53E-04	54246	0.308664	0.083333
Down	PTAFR	9	0.001839	146258	0.315401	0.055556
Down	MASP1	9	0.002137	326806	0.225528	0.083333
Down	PLA2G2A	8	0.002039	625578	0.228338	0
Down	TNFRSF4	8	7.20E-04	87330	0.26198	0.321429
Down	IL13RA1	8	6.92E-04	54632	0.3129	0.214286
Down	CD48	8	0.001004	75166	0.297881	0.142857
Down	CD244	8	0.001314	270208	0.265574	0.071429
Down	HLA-DRB1	8	0.001343	119046	0.273066	0.142857
Down	IL12A	8	0.003272	296440	0.241412	0.071429
Down	ICAM3	8	6.74E-04	94610	0.255118	0.035714
Down	ICAM2	7	7.74E-04	115578	0.242687	0.047619
Down	CD86	7	0.00143	76566	0.302417	0.190476
Down	IL6	7	0.001988	115352	0.260582	0.095238

Table 6 (continued)

Regulation	Node	Degree	Betweenness	Stress	Closeness	Clustering Coefficient
Down	CD80	7	0.001335	74000	0.254317	0.190476
Down	CCL13	7	3.79E-04	117758	0.239347	0
Down	CARD9	6	0.001358	152030	0.262583	0
Down	MASP2	6	8.34E-04	73116	0.210649	0.2
Down	HLA-DMA	6	0.001965	186844	0.252792	0.2
Down	FCER1A	6	0.001958	462984	0.26283	0
Down	IL13	6	9.18E-04	81904	0.260164	0.2
Down	PIGR	6	0.001383	46460	0.267211	0
Down	ICAM4	6	7.08E-04	122662	0.244131	0
Down	CCL11	6	4.36E-04	106892	0.239682	0
Down	FCAR	6	0.001325	60556	0.281404	0.066667
Down	PTGER4	6	0.001594	111600	0.311981	0
Down	RAG2	6	0.002235	108180	0.302893	0.133333
Down	PPBP	6	0.00149	101978	0.25057	0.066667
Down	IL3	6	1.42E-05	4398	0.276848	0.133333
Down	HLA-DQB1	5	1.37E-04	32052	0.304361	0.5
Down	IDO1	5	0.002598	124836	0.300263	0
Down	TNFRSF10C	5	6.74E-04	112660	0.252006	0
Down	TNFRSF13C	5	6.50E-04	58590	0.256308	0.3
Down	IL17F	5	2.32E-04	81308	0.256031	0.2
Down	CFD	5	0.001535	135276	0.301765	0
Down	CCL19	5	8.76E-05	9268	0.219387	0.4
Down	CD34	5	0.001329	226272	0.243224	0
Down	IFNG	5	0.001405	110736	0.270285	0
Down	IL23A	5	0.00132	310874	0.180846	0.1
Down	EBI3	5	0.001288	90012	0.222769	0.1
Down	C8B	4	2.59E-04	21386	0.208212	0.166667
Down	CCL20	4	0.001697	215266	0.242974	0
Down	C4BPA	4	0.001305	202342	0.207217	0
Down	C8A	4	5.17E-04	27442	0.225528	0.333333
Down	SLAMF6	4	6.38E-06	766	0.274209	0.333333
Down	CCR6	4	0.001956	273648	0.209231	0
Down	BTLA	4	6.84E-04	61880	0.275584	0.333333
Down	CCR8	4	6.64E-04	48144	0.196954	0
Down	CXCL11	4	8.55E-05	11782	0.220629	0
Down	SIGIRR	4	3.08E-06	666	0.277147	0.333333
Down	ITLN1	4	0.001313	85710	0.272679	0
Down	ICAM5	4	3.97E-05	5052	0.242936	0
Down	FCGRT	4	0.001307	236680	0.210779	0
Down	CCL22	4	5.04E-04	43848	0.247169	0
Down	IL12B	4	1.64E-04	39054	0.194859	0.5
Down	IL27	3	2.87E-04	26194	0.215697	0.333333
Down	IL22	3	6.54E-04	37474	0.199417	0
Down	C7	3	1.54E-04	29126	0.226657	0
Down	TIGIT	3	0.001299	79710	0.18742	0
Down	DEFB4A	3	0.002265	309432	0.250917	0
Down	IL22RA2	3	8.49E-04	82918	0.216806	0
Down	IL21	3	2.06E-05	882	0.21301	0
Down	C9	3	1.97E-05	976	0.229359	0.333333
Down	LIF	3	1.35E-05	994	0.252689	0
Down	ITGAE	3	6.54E-04	122018	0.226607	0

Table 6 (continued)

Regulation	Node	Degree	Betweenness	Stress	Closeness	Clustering Coefficient
Down	IL5	3	2.60E-05	1936	0.26283	0.333333
Down	HLA-DPB1	2	0	0	0.240356	1
Down	CFI	2	6.50E-04	65960	0.196527	0
Down	IFNB1	2	0	0	0.254275	1
Down	IFNA2	2	0	0	0.254275	1
Down	XCL1	2	0.001299	97076	0.208706	0
Down	CD1A	2	6.50E-04	79654	0.20475	0
Down	XCR1	2	6.50E-04	48540	0.172698	0
Down	DEFB103B	2	6.50E-04	91060	0.173057	0
Down	IL7	2	6.20E-07	68	0.219497	0
Down	KLRB1	2	6.50E-04	58078	0.267815	0
Down	IL20	2	0.666667	4	0.75	0
Down	HLA-DMB	1	0	0	0.201796	0
Down	HLA-DOB	1	0	0	0.16794	0
Down	ICOSLG	1	0	0	0.200469	0
Down	CD83	1	0	0	0.300029	0
Down	GPR183	1	0	0	0.300029	0
Down	IKBKAP	1	0	0	0.250938	0
Down	DEFB1	1	0	0	0.173038	0
Down	IL1RL2	1	0	0	0.20772	0
Down	IL19	1	0	0	0.5	0

**Fig. 7** Scatter plot for up regulated genes. (A—Node degree; B—Betweenness centrality; C—Stress centrality; D—Closeness centrality; E—Clustering coefficient)

(AUC = 0.873), BID (AUC = 0.848), CD55 (AUC = 0.973), CD80 (AUC = 0.870), HAL-B (AUC = 0.816) and HLA-DMA (AUC = 0.730) had significant diagnostic values for discriminating SARS-CoV-2 samples and normal controls (Fig. 16).

Discussion

Currently, genetic and genomic-related exploration progress speedily and provide new prospect to illuminate the molecular pathogenesis of SARS-CoV-2 infections. And

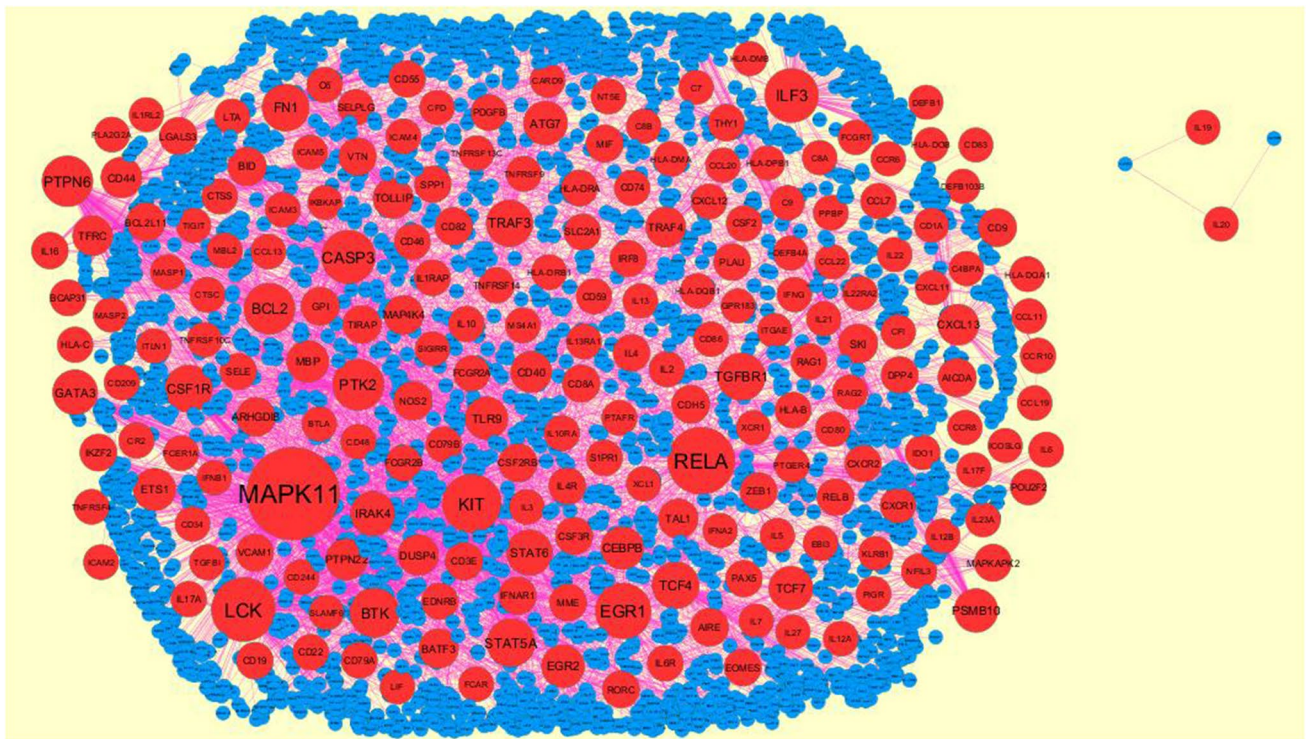


Fig. 8 Protein–protein interaction network of down regulated genes. Red nodes (●) denotes down regulated genes; Pink lines (—) denotes edges (Interactions)

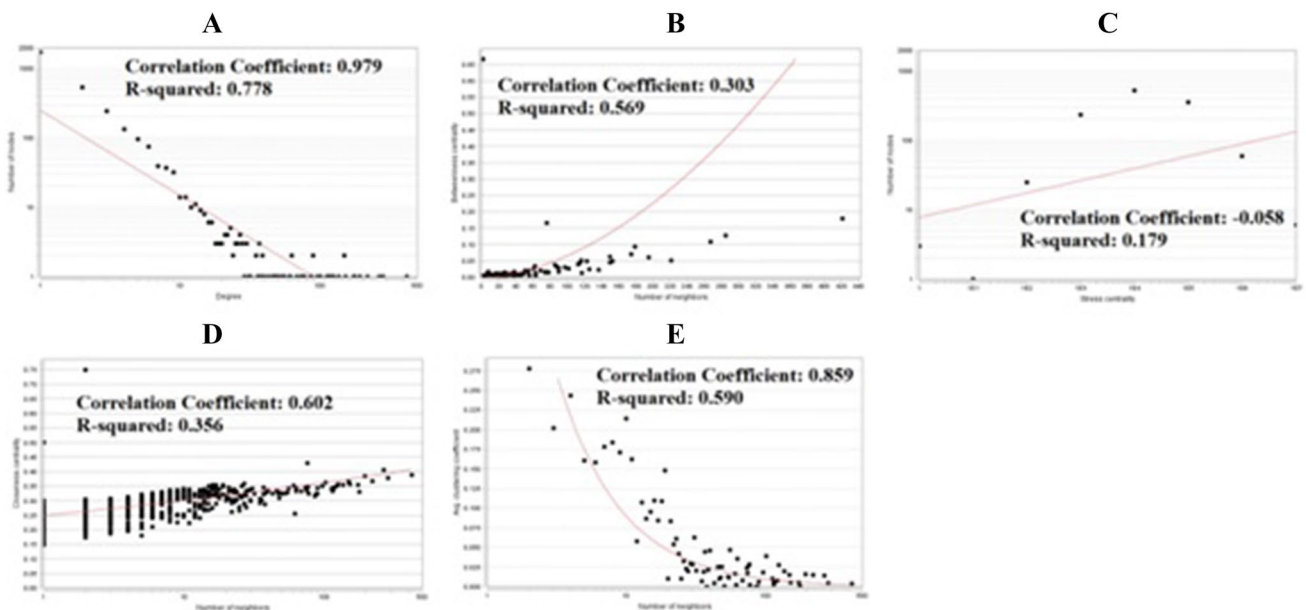


Fig. 9 Scatter plot for down regulated genes. (A—Node degree; B—Betweenness centrality; C—Stress centrality; D—Closeness centrality; E—Clustering coefficient)

bioinformatics analysis also has developed phenomenally and is committed to search for candidate biomarkers to implement more correct screening, prompt diagnosis for

SARS-CoV-2-infected patients based on enormous genetic and genomics data.

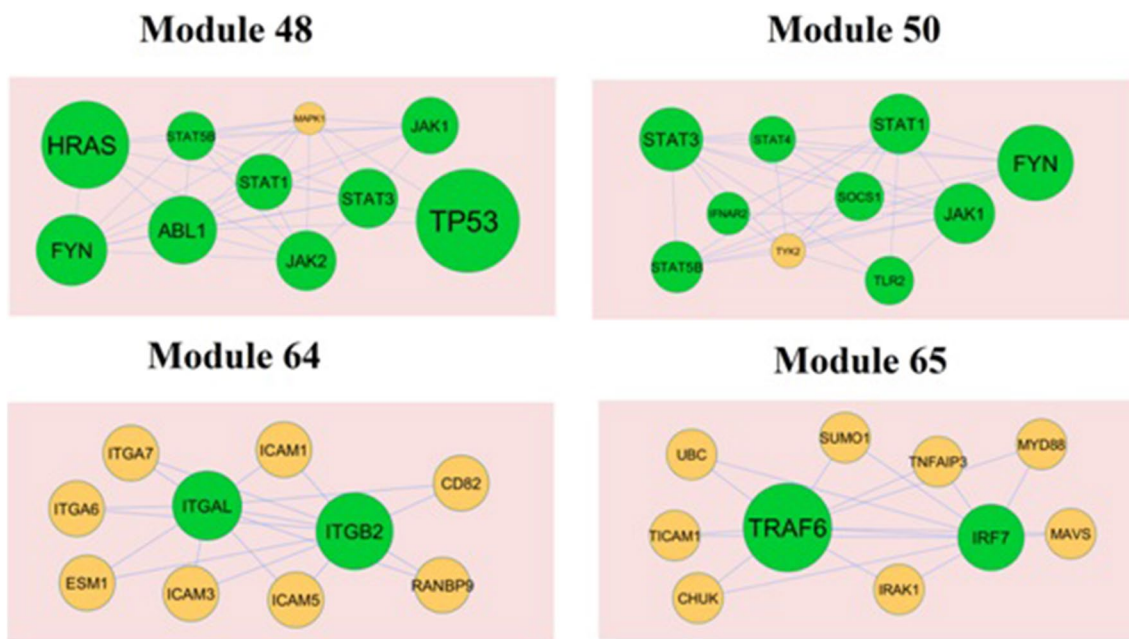


Fig. 10 Modules in PPI network. The green nodes denote the up regulated genes. Green nodes (●) denotes up regulated genes; Blue lines (—) denotes edges (Interactions)

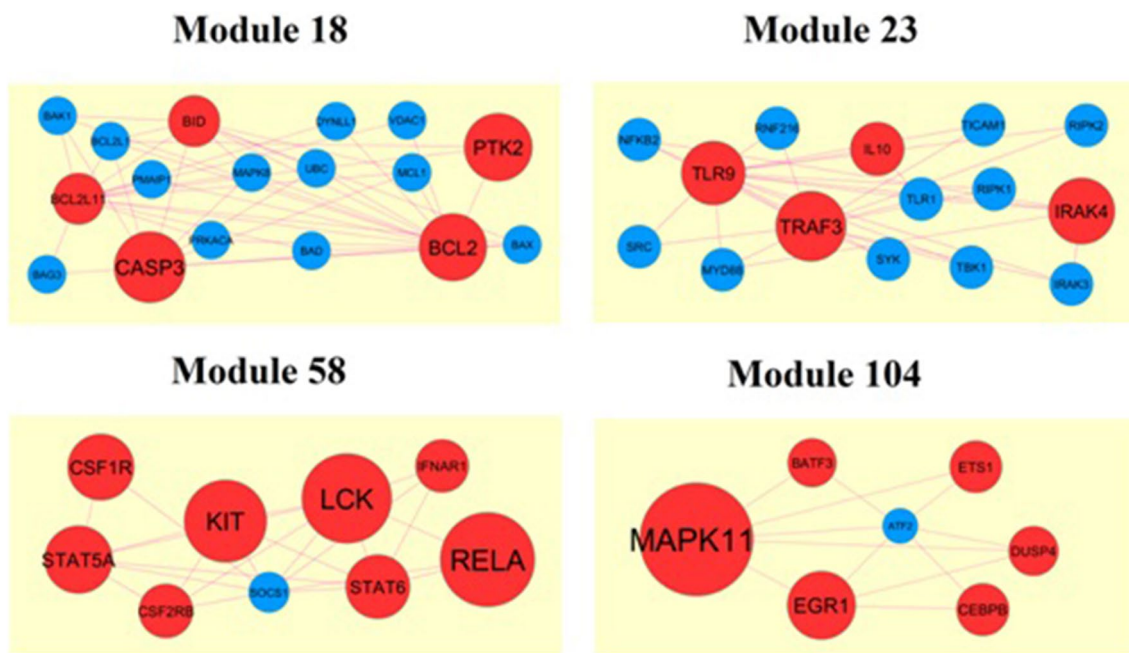


Fig. 11 Modules in PPI network. The red nodes denote the down regulated genes. Red nodes (●) denotes down regulated genes; Pink lines (—) denotes edges (Interactions)

In the current investigation, a bioinformatics approach was used to identify candidate biomarker and therapeutic targets of SARS-CoV-2 infection. Following the analysis, 324 DEGs, including 76 up-regulated genes and 248 down-regulated genes were identified. Shi et al. (2007)

found that expression of JAK1 was responsible for progression of adenovirus infection, but this gene may be linked with advancement of SARS-CoV-2 infection. Previously reported genes such as ZAP70 (Guntermann et al. 1997), CD22 (Ma et al. 2013) and MAPKAPK2 (Yang

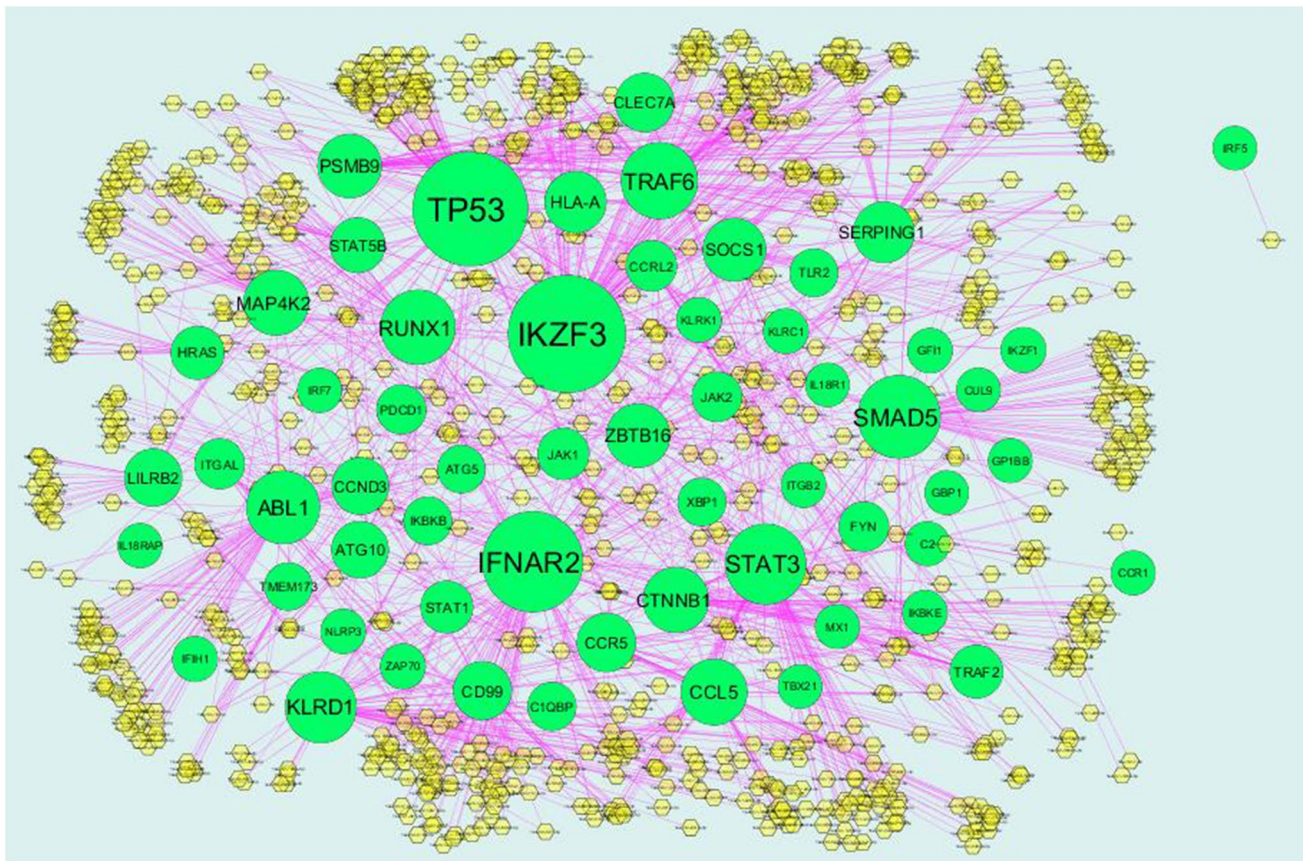


Fig. 12 The network of up regulated genes and their related miRNAs. The green circles nodes (●) are the up regulated genes; yellow diamond nodes (◆) are the miRNAs; Pink lines (—) denotes edges (Interactions)

et al. 2012) are expressed and responsible for progression various viral infections, but our study found that these genes may important for development of SARS-CoV-2 infection. Previously reported genes such as CCR5 (Dawson et al. 2000) and TRAF6 (Tian et al. 2018) were highly expressed and involved in progression of influenza A viral infections, but these genes may be liable for advancement of SARS-CoV-2 infection. Zhivaki et al. (2017) noticed that expression of CX3CR1 is associated in progression of respiratory syncytial virus infection, but this gene may be linked with development of SARS-CoV-2 infection. Previous studies had reported that expression of CD45RB was key for progression of sendai virus infection (Hou and Doherty 1993), but this gene may liable for advancement of SARS-CoV-2 infection. Corominas et al. (2020) showed the possible involvement of IL6R in the development of SARS-CoV-2 infection. Evidence from Chi et al. (2013) study indicated that the HLA-DQB1 expression level is down-regulated in varicella-zoster virus infection, but low expression of this gene may be associated in progression of SARS-CoV-2 infection.

Pathway enrichment analysis results for up- and down-regulated gene might play important roles in the SARS-CoV-2 infection. Studies have found that over expression of enriched genes such as CCND3 (Fan et al. 2017), IRF7 (Rosenberger et al. 2017), MX1 (Pillai et al. 2016) and STAT4 (Bot et al. 2003) in influenza viral infection, but these genes may be important for progression of SARS-CoV-2 infection. JAK2 is a protein-coding gene which was first reported aberrantly expressed and plays important roles in SARS-CoV-2 infection (Wu and Yang 2020). After that, enriched up-regulated genes such as IFIH1 (Asgari et al. 2017), FYN (FYN proto-oncogene, Src family tyrosine kinase) (Kenney and Meng 2015), STAT1 (Patel et al. 2010), GZMB (granzyme B) (Loebbermann et al. 2012a, b), TRAF2 (Liu et al. 2019) and BST2 (Wang et al. 2019) were found to be involved in development of severe viral respiratory infections. Rice et al. (2016) suggested that TLR2 activity was involved in progression of pneumovirus infection, but this gene may be involved in development of SARS-CoV-2 infection. IL2RG has been shown to have an important role in adeno-associated viral infection (Hiramoto et al. 2018), but this gene may be involved in progression

Table 7 miRNA - target gene interaction table

Regulation	Target Genes	Degree	MicroRNA	Regulation	Target Genes	Degree	MicroRNA
Up	IKZF3	134	hsa-mir-6860	Down	SKI	210	hsa-mir-5100
Up	TP53	130	hsa-mir-5703	Down	TNFRSF13C	136	hsa-mir-3197
Up	IFNAR2	109	hsa-mir-4510	Down	BCL2L11	122	hsa-mir-8064
Up	SMAD5	83	hsa-mir-6086	Down	ICOSLG	119	hsa-mir-3672
Up	STAT3	80	hsa-mir-4270	Down	IL6R	94	hsa-mir-7641
Up	TRAF6	71	hsa-mir-6745	Down	VCAM1	86	hsa-mir-4270
Up	RUNX1	67	hsa-mir-4467	Down	LILRA2	83	hsa-mir-4780
Up	ABL1	64	hsa-mir-4511	Down	IRAK4	78	hsa-mir-520e
Up	KLRD1	60	hsa-mir-5094	Down	BTLA	72	hsa-mir-3133
Up	CCL5	49	hsa-mir-4775	Down	CD55	71	hsa-mir-6124
Up	CTNNB1	48	hsa-mir-4255	Down	CCL22	71	hsa-mir-5190
Up	MAP4K2	47	hsa-mir-6131	Down	CD44	70	hsa-mir-5696
Up	PSMB9	44	hsa-mir-3658	Down	PDGFB	69	hsa-mir-6132
Up	ZBTB16	43	hsa-mir-4287	Down	BCL2	68	hsa-mir-184
Up	SOCS1	42	hsa-mir-4495	Down	TFRC	67	hsa-mir-6070
Up	HLA-A	39	hsa-mir-6129	Down	PIGR	66	hsa-mir-4486
Up	SERPING1	38	hsa-mir-1262	Down	CCL16	63	hsa-mir-7703
Up	CCR5	33	hsa-mir-3183	Down	IFNAR1	61	hsa-mir-4430
Up	CLEC7A	33	hsa-mir-4792	Down	TIRAP	61	hsa-mir-4325
Up	CD99	32	hsa-mir-3199	Down	ETS1	58	hsa-mir-3972
Up	LILRB2	30	hsa-mir-3941	Down	CD59	56	hsa-mir-3919
Up	ATG10	29	hsa-mir-4309	Down	IKZF2	55	hsa-mir-5096
Up	CCND3	29	hsa-mir-1321	Down	CEBPB	54	hsa-mir-4510
Up	STAT5B	25	hsa-mir-8485	Down	CD209	54	hsa-mir-3188
Up	TRAF2	21	hsa-mir-6165	Down	HLA-C	53	hsa-mir-4660
Up	HRAS	21	hsa-mir-1268a	Down	DUSP4	53	hsa-mir-6089
Up	STAT1	19	hsa-mir-1183	Down	CCR6	52	hsa-mir-4539
Up	JAK1	17	hsa-mir-107	Down	TGFBR1	51	hsa-mir-8083
Up	CCRL2	16	hsa-mir-4469	Down	MAPKAPK2	50	hsa-mir-4468
Up	ITGAL	14	hsa-mir-764	Down	SLC2A1	50	hsa-mir-4448
Up	FYN	14	hsa-mir-3924	Down	POU2F2	49	hsa-mir-4307
Up	JAK2	14	hsa-mir-5692a	Down	LIF	47	hsa-mir-3655
Up	PDCD1	13	hsa-mir-922	Down	MBL2	47	hsa-mir-3689c
Up	C1QBP	11	hsa-mir-484	Down	HLA-B	44	hsa-mir-5047
Up	IKBKB	10	hsa-mir-451a	Down	ZEB1	43	hsa-mir-2113
Up	TLR2	10	hsa-mir-105-5p	Down	RELA	41	hsa-mir-7515
Up	XBP1	10	hsa-mir-320c	Down	CD46	39	hsa-mir-4780
Up	TMEM173	9	hsa-mir-5093	Down	PAX5	37	hsa-mir-6127
Up	ATG5	9	hsa-mir-299-5p	Down	CASP3	36	hsa-mir-4666b
Up	ZAP70	4	hsa-mir-631	Down	STAT5A	34	hsa-mir-4457
Up	IFIH1	4	hsa-mir-424-5p	Down	PTAFR	33	hsa-mir-4301
Up	KLRC1	4	hsa-mir-9-5p	Down	THY1	32	hsa-mir-4269
Up	IKZF1	4	hsa-mir-19a-3p	Down	ATG7	29	hsa-mir-4518
Up	KLRK1	3	hsa-mir-148b-3p	Down	S1PR1	29	hsa-mir-7977
Up	IKBKE	3	hsa-mir-296-5p	Down	C8A	29	hsa-mir-1299
Up	GFI1	3	hsa-mir-142-3p	Down	CDH5	28	hsa-mir-544a
Up	NLRP3	3	hsa-mir-223-3p	Down	GPI	27	hsa-mir-760
Up	ITGB2	3	hsa-mir-146a-5p	Down	ILF3	27	hsa-mir-4314
Up	IL18RAP	2	hsa-mir-4677-3p	Down	KIT	25	hsa-mir-4490
Up	IRF7	2	hsa-mir-762	Down	GPR183	24	hsa-mir-1303

Table 7 (continued)

Regulation	Target Genes	Degree	MicroRNA	Regulation	Target Genes	Degree	MicroRNA
Up	C2	2	hsa-mir-335-5p	Down	TRAF3	24	hsa-mir-8085
Up	MX1	2	hsa-mir-211-5p	Down	PTPN6	24	hsa-mir-4525
Up	CCR1	2	hsa-mir-181d-3p	Down	SELPLG	23	hsa-mir-1470
Up	CUL9	1	hsa-mir-335-5p	Down	RAG1	23	hsa-mir-3666
Up	IL18R1	1	hsa-mir-124-3p	Down	HLA-DRB1	23	hsa-mir-3978
Up	GBP1	1	hsa-mir-124-3p	Down	TAL1	23	hsa-mir-4719
Up	TBX21	1	hsa-mir-29b-3p	Down	CCL11	23	hsa-mir-6077
Up	GP1BB	1	hsa-mir-26b-5p	Down	IL6	22	hsa-mir-451a
Up	IRF5	1	hsa-mir-22-3p	Down	TGFBI	22	hsa-mir-1322
				Down	CTSS	22	hsa-mir-8066
				Down	CXCL12	20	hsa-mir-886-3p
				Down	BID	20	hsa-mir-623
				Down	TOLLIP	20	hsa-mir-6078
				Down	CD86	20	hsa-mir-8056
				Down	TIGIT	20	hsa-mir-3941
				Down	CD3E	20	hsa-mir-4510
				Down	TNFRSF9	19	hsa-mir-1305
				Down	CXCR2	18	hsa-mir-588
				Down	C6	18	hsa-mir-4310
				Down	IL5	17	hsa-mir-604
				Down	EBI3	17	hsa-mir-6069
				Down	TCF4	15	hsa-let-7e-5p
				Down	BCAP31	15	hsa-mir-4514
				Down	CD82	15	hsa-mir-1470
				Down	FCAR	15	hsa-mir-1976
				Down	SELE	14	hsa-mir-630
				Down	HLA-DRA	14	hsa-mir-3915
				Down	IFNB1	13	hsa-mir-6080
				Down	CD9	13	hsa-mir-5688
				Down	IL10RA	12	hsa-mir-8064
				Down	IL1RL2	12	hsa-mir-4301
				Down	IL1RAP	11	hsa-mir-4635
				Down	IL7	11	hsa-mir-203a-3p
				Down	CD19	11	hsa-mir-466
				Down	IFNG	10	hsa-mir-15b-5p
				Down	EGR2	10	hsa-mir-100-5p
				Down	PTGER4	10	hsa-mir-101-3p
				Down	C1S	10	hsa-mir-548 s
				Down	CX3CL1	10	hsa-mir-5093
				Down	CD244	10	hsa-mir-5702
				Down	C7	10	hsa-mir-1827
				Down	PTK2	9	hsa-mir-543
				Down	MS4A1	9	hsa-mir-644a
				Down	AIRE	9	hsa-mir-4770
				Down	HLA-DOB	9	hsa-mir-1260a
				Down	MAP4K4	8	hsa-mir-520e
				Down	TRAF4	8	hsa-mir-4284
				Down	FN1	8	hsa-mir-200b-3p
				Down	STAT6	8	hsa-mir-361-5p
				Down	CXCL11	8	hsa-mir-4511

Table 7 (continued)

Regulation	Target Genes	Degree	MicroRNA
Down	EGR1	8	hsa-mir-377-3p
Down	C1R	8	hsa-mir-326
Down	IL10	7	hsa-mir-106a-5p
Down	IL12B	7	hsa-mir-103b
Down	PLAU	7	hsa-mir-23b-3p
Down	GATA3	7	hsa-mir-10b-5p
Down	FCGR2A	7	hsa-mir – 4275
Down	AICDA	7	hsa-mir-6873-3p
Down	NT5E	6	hsa-mir – 422a
Down	CTLA4	6	hsa-mir-3924
Down	SPP1	6	hsa-mir-299-5p
Down	BTK	6	hsa-mir-1253
Down	MIF	6	hsa-mir-320a
Down	IL13	5	hsa-let-7i-5p
Down	CD34	5	hsa-mir-106b-5p
Down	IL4	5	hsa-mir – 429
Down	RORC	5	hsa-mir-148b-3p
Down	CTSC	5	hsa-mir-199a-5p
Down	CD40	5	hsa-mir-503-5p
Down	IL2	5	hsa-mir-181c-5p
Down	TCF7	4	hsa-mir-22-3p
Down	ICAM5	4	hsa-mir – 4707-5p
Down	CD83	4	hsa-mir-122-5p
Down	HLA-DQA1	4	hsa-mir – 4673
Down	IL4R	4	hsa-mir-331-3p
Down	MAPK11	3	hsa-let-7a-5p
Down	TNFSF12	3	hsa-mir-17-5p
Down	CCL7	3	hsa-mir-135b-3p
Down	IL12A	3	hsa-mir-10a-5p
Down	CSF1R	3	hsa-mir-155-5p
Down	CFI	3	hsa-mir-181a-5p
Down	IL3	3	hsa-mir – 452-5p
Down	NFIL3	3	hsa-mir-183-5p
Down	ICAM3	3	hsa-mir-3943
Down	EOMES	3	hsa-mir-7855-5p
Down	PTPN22	3	hsa-mir-624-3p
Down	LGALS3	3	hsa-mir-744-5p
Down	CCL19	3	hsa-mir-148b-3p
Down	IL17A	3	hsa-mir-16-1-3p
Down	CD22	2	hsa-mir-19a-3p
Down	CCL20	2	hsa-mir-21-5p
Down	CCL26	2	hsa-mir-25-3p
Down	DEFB4A	2	hsa-mir-26b-5p
Down	CXCR1	2	hsa-mir-335-5p
Down	MME	2	hsa-mir-1-3p
Down	VTN	2	hsa-mir-26b-5p
Down	LILRB5	2	hsa-mir-128-3p
Down	IL13RA1	2	hsa-mir-143-3p
Down	SIGIRR	2	hsa-mir-149-5p
Down	C14orf166	2	hsa-mir-331-3p

Table 7 (continued)

Regulation	Target Genes	Degree	MicroRNA	Regulation	Target Genes	Degree	MicroRNA
				Down	CD8A	2	hsa-mir-196b-5p
				Down	IRF8	2	hsa-mir-646
				Down	FCGR2B	1	hsa-mir-18a-5p
				Down	NOS2	1	hsa-mir-26a-5p
				Down	RELB	1	hsa-mir-26b-5p
				Down	CXCL13	1	hsa-mir-26b-5p
				Down	BATF3	1	hsa-mir-26b-5p
				Down	ICAM4	1	hsa-mir-93-5p
				Down	IL23A	1	hsa-mir-10a-5p
				Down	ARHGDIB	1	hsa-mir-34a-5p
				Down	LTA	1	hsa-mir-34a-5p
				Down	ICAM2	1	hsa-mir-125b-5p
				Down	CR2	1	hsa-mir-132-3p
				Down	B3GAT1	1	hsa-mir-132-3p
				Down	IDO1	1	hsa-mir-153-3p
				Down	MASP1	1	hsa-mir-153-3p
				Down	CD80	1	hsa-mir-146a-5p
				Down	HLA-DPA1	1	hsa-mir-155-5p
				Down	TAGAP	1	hsa-mir-374a-5p
				Down	CD79A	1	hsa-mir-335-5p
				Down	FCGRT	1	hsa-mir-335-5p
				Down	HLA-DMA	1	hsa-mir-335-5p
				Down	KLRB1	1	hsa-mir-335-5p
				Down	LCK	1	hsa-mir-335-5p
				Down	PPBP	1	hsa-mir-335-5p
				Down	CCL15	1	hsa-mir-335-5p
				Down	CCL24	1	hsa-mir-335-5p
				Down	LILRA1	1	hsa-mir-335-5p
				Down	LILRA3	1	hsa-mir-335-5p
				Down	PLA2G2E	1	hsa-mir-335-5p
				Down	IL22	1	hsa-mir-335-5p
				Down	IL27	1	hsa-mir-335-5p
				Down	MBP	1	hsa-mir-127-5p
				Down	IL20	1	hsa-mir-624-3p

Degree – No of miRNA interact with target gene. We taken any one miRNA in table

of SARS-CoV-2 infection. Reported enriched up-regulated genes such as STAT3 (Mizutani et al. 2004) and HLA-A (Ohno et al. 2009) contributes to the progression of SARS coronavirus infection, but this gene may be involved in SARS-CoV-2 infection. Several studies have reported that enriched genes such as STAT5B (Mukherjee et al. 2014), SOCS1 (Zheng et al. 2015), CCR1 (Miller et al. 2006) and CCL5 (Sali mi et al. 2017) were highly expressed in respiratory syncytial virus infection, but elevated expression these genes may be involved in development of SARS-CoV-2 infection. Increasing evidence shows that the enriched genes such as IFNAR2 (Romporn et al. 2013), TBX21 (Zhu et al. 2015), GBP1 (Anderson et al. 1999), IRF5 (Vandenbroeck

et al. 2011) and IFI35 (Estrabaud et al. 2015) were over expressed in various viral infections, but high expression of these genes may be involved in infection of SARS-CoV-2 infection. Novel biomarkers such as IKBKE (inhibitor of nuclear factor kappa B kinase subunit epsilon), TP53, CD247, IL18RAP, IL18R1, HRAS (HRas proto-oncogene, GTPase), PSMB9, IKBKB (inhibitor of nuclear factor kappa B kinase subunit beta), ITGB2 and LTB4R were highly expressed and might be involved in progression of SARS-CoV-2 infection. Sanders et al. (2001) revealed that NOS2 was down-regulated in rhinovirus infection, but this gene may be involved in development of SARS-CoV-2 infection. The enriched down-regulated genes found in this study

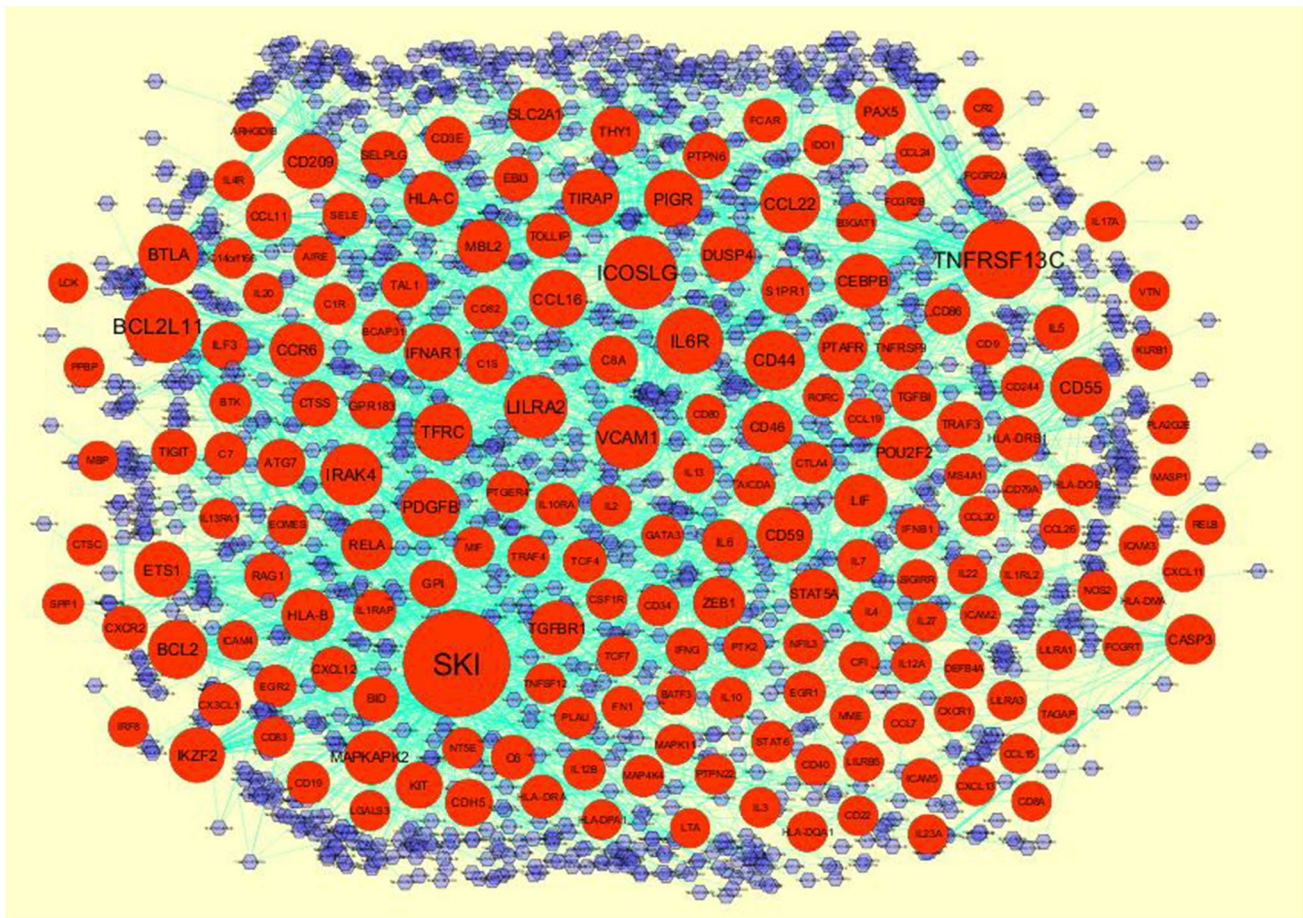


Fig. 13 The network of down regulated genes and their related miRNAs. The red circles nodes (●) are the down regulated genes; blue diamond nodes (◆) are the miRNAs; blue lines (—) denotes edges (Interactions)

include IL10 (Loebbermann et al. 2012a, b), IL13 (Castilow et al. 2008), IL21 (Antunes et al. 2019), CCR6 (Shi et al. 2017), CXCL13 (Alturaiqi et al. 2018), CCL20 (Shi et al. 2017), IL19 (Ermers et al. 2011), IL20 (Ermers et al. 2011), CD40 (Harcourt et al. 2003a, b), IL2 (Noma et al. 1996), IL3 (Bertrand et al. 2015), IL4 (Puthothu et al. 2006), IL9 (Dodd et al. 2009) and STAT6 (Srinivasa et al. 2016) were responsible for progression of respiratory syncytial virus infection, but these genes may be linked with progression of SARS-CoV-2 infection. Many previous studies have confirmed the roles of enriched down-regulated genes such as IL12B (Mueller et al. 2004), TNFRSF9 (Rodriguez et al. 2019), TNFRSF14 (Soroosh et al. 2014), IL17F (Wang et al. 2016), CCR8 (Calado et al. 2010), CCL18 (Malhotra et al. 2019), CCL22 (Yang et al. 2012), CXCL11 (Pineda-Tenor et al. 2014), CX3CL1 (Bertin et al. 2014), CXCL12 (Durrant et al. 2014), CCR10 (Nakayama et al. 2002), IFNA2 (Chen et al. 2017), IFNB1 (Gagné et al. 2017), IL7 (Golden-Mason et al. 2006), IL26 (Miot et al. 2015), CXCR1 (Xu et al. 2016), CEBPB (CCAAT enhancer binding protein

beta) (Liu et al. 2009), ETS1 (Posada et al. 2000), STAT5A (Warby et al. 2003), THY1 (Lu et al. 2011), IL16 (Caufour et al. 2001), HLA-B (Martin et al. 2007), HLA-C (Apps et al. 2013), HLA-DPA1 (Wasityastuti et al. 2016), HLA-DPB1 (Lambert et al. 2015), HLA-DQA1 (Tibbs et al. 1996), HLA-DRB1 (Chi et al. 2013), PSMB10 (Deng et al. 2019), BCL2 (Zuckerman et al. 2001), TOLLIP (toll interacting protein) (Li et al. 2016a, b), VCAM1 (Koraka et al. 2004), RAG1 (Winkler et al. 2017), IRF8 (Terry et al. 2015), EB13 (Gehlert et al. 2004), EGR1 (Baer et al. 2016), IL27 (Swaminathan et al. 2013) and BID (BH3 interacting domain death agonist) (Hsu et al. 2003) were linked with development of various viral infections, but these genes may be associated with advancement of SARS-CoV-2 infection. Previous investigation demonstrated that enriched down-regulated genes such as IL17A (Wang et al. 2016), CCL11 (Suryadevara et al. 2013), CCL19 (Fleming-Canepa et al. 2011), XCR1 (Fossum et al. 2015), IFNAR1 (Lin et al. 2014), IL22 (Kumar et al. 2013), LTA (lymphotoxin alpha) (Morales-García et al. 2012), IL5 (Gorski et al. 2013), EGR2

Table 8 TF—target gene interaction table

Regulation	TF	Degree	Target Gene	Regulation	TF	Degree	Target Gene
Up	FOXC1	46	JAK1	Down	FOXC1	127	KLRF2
Up	GATA2	31	TRAF6	Down	GATA2	102	CD1A
Up	YY1	25	CLEC7A	Down	YY1	75	TNFRSF4
Up	CREB1	22	STAT1	Down	FOXL1	63	MME
Up	TFAP2A	21	IKZF1	Down	NFKB1	61	CXCL12
Up	PPARG	20	IRF7	Down	USF2	48	DEFB1
Up	NFKB1	20	TRAF2	Down	SRF	48	STAT5A
Up	E2F1	19	PSMB9	Down	CREB1	46	TNFRSF10C
Up	RELA	18	IFI35	Down	TP53	45	C1S
Up	USF2	17	LTB4R	Down	STAT3	45	IL26
Up	SREBF1	16	CCND3	Down	PPARG	43	ICAM4
Up	HINFP	15	GP1BB	Down	JUN	42	FCGRT
Up	JUN	15	TLR2	Down	E2F1	42	GATA3
Up	FOXL1	12	LCP2	Down	HINFP	40	BCL2L11
Up	BRCA1	11	CD99	Down	TFAP2A	38	EOMES
Up	NFIC	11	FYN	Down	NFIC	38	IFNA2
Up	SRF	11	IL18RAP	Down	MEF2A	31	CTSS
Up	GATA3	9	CX3CR1	Down	NFYA	29	GPI
Up	PRDM1	9	GNLY	Down	TEAD1	28	LTA
Up	POU2F2	9	SLAMF7	Down	HOXA5	28	PPBP
Up	USF1	8	ATG5	Down	MAX	27	IL12B
Up	FOS	8	CCL5	Down	SREBF2	26	CD80
Up	TEAD1	8	CCR1	Down	SREBF1	26	DEFB4A
Up	TFAP2C	8	CEACAM1	Down	JUND	26	HLA-DPB1
Up	ELK4	8	GBP1	Down	TFAP2C	26	HLA-DQA1
Up	HOXA5	8	GZMB	Down	RUNX2	25	C1R
Up	E2F6	8	HRAS	Down	ARID3A	24	SKI
Up	HNF4A	8	IFNAR2	Down	HNF4A	23	CR2
Up	RUNX2	8	KLRK1	Down	ZNF354C	22	C8A
Up	NFYA	7	ATG10	Down	NR3C1	22	FCGR2B
Up	SREBF2	7	C1QBP	Down	IRF2	22	XCR1
Up	MAX	7	CCRL2	Down	PRDM1	21	IL13
Up	CEBPB	7	CD247	Down	FOS	20	CCL15
Up	PRRX2	7	CTNNB1	Down	USF1	20	IRAK4
Up	ZNF354C	7	GFI1	Down	FOXA1	19	ITLN1
Up	MEF2A	7	IL18R1	Down	PRRX2	19	TLR9
Up	ARID3A	6	ABL1	Down	STAT1	18	LCK
Up	ESR1	6	C2	Down	SP1	16	CD82
Up	PDX1	6	HLA-A	Down	ELK4	16	PAX5
Up	NR3C1	6	ITGAL	Down	NKX3-2	16	PLA2G2E
Up	KLF5	6	ITGB2	Down	KLF5	15	ICOSLG
Up	ELK1	6	JAK2	Down	ELK1	15	IDO1
Up	SP1	6	MAP4K2	Down	BRCA1	15	LGALS3
Up	EGR1	6	MX1	Down	ESR1	15	MASP2
Up	EN1	6	SMAD5	Down	TP63	12	CD19
Up	IRF2	5	RUNX1	Down	PAX2	12	CD48
Up	PAX2	5	STAT5B	Down	NR2F1	12	CEBPB
Up	NR2F1	4	CUL9	Down	E2F6	11	CD8A
Up	FOXF2	4	IKBKE	Down	EN1	11	IL22
Up	TP63	4	IKZF3	Down	SPIB	11	PTAFR
Up	FOXA1	4	IL2RG	Down	FOXF2	10	SELE

Table 8 (continued)

Regulation	TF	Degree	Target Gene	Regulation	TF	Degree	Target Gene
Up	NRF1	4	MAP4K1	Down	SOX10	9	POU2F2
Up	JUND	4	NLRP3	Down	SRY	8	EDNRB
Up	SPIB	4	ZBTB16	Down	NRF1	8	IFNAR1
Up	REL	3	IKZF3	Down	SOX17	7	TNFRSF14
Up	NKX3-1	3	IRF5	Down	SOX5	6	BTK
Up	SOX5	3	KLRD1	Down	NKX2-5	6	PIGR
Up	SOX10	3	STAT3	Down	ELF5	5	BATF3
Up	MYB	3	JAK2	Down	NFATC2	5	IL4
Up	SRY	2	KLRK1	Down	PDX1	5	ITGAE
Up	ELF5	2	TLR2	Down	NFYB	3	PTPN6
Up	NFIL3	1	CX3CR1	Down	ZFX	3	THY1
Up	NR4A2	1	C2	Down	NR4A2	2	CSF2
Up	FEV	1	ATG5	Down	FEV	2	IL23A
Up	FOXI1	1	CCL5	Down	MYB	2	MIF
Up	NKX3-2	1	GZMB	Down	HNF1B	2	SPP1
Up	E2F4	1	IKZF1	Down	REL	2	STAT6
Up	TFCP2L1	1	LCP2	Down	ESR2	1	CCL22
Up	NR2E3	1	HLA-A	Down	FOXI1	1	CD209
Up	GATA1	1	HLA-A	Down	FOXD1	1	HLA-DOB
Up	HNF1B	1	IL18R1	Down	ESRRB	1	ICAM2
Up	SOX17	1	LILRA6	Down	NR2E3	1	IL2
				Down	E2F4	1	S1PR1
				Down	GATA1	1	PDGFB

Degree—No of TF interact with target gene. We taken any one TF in table

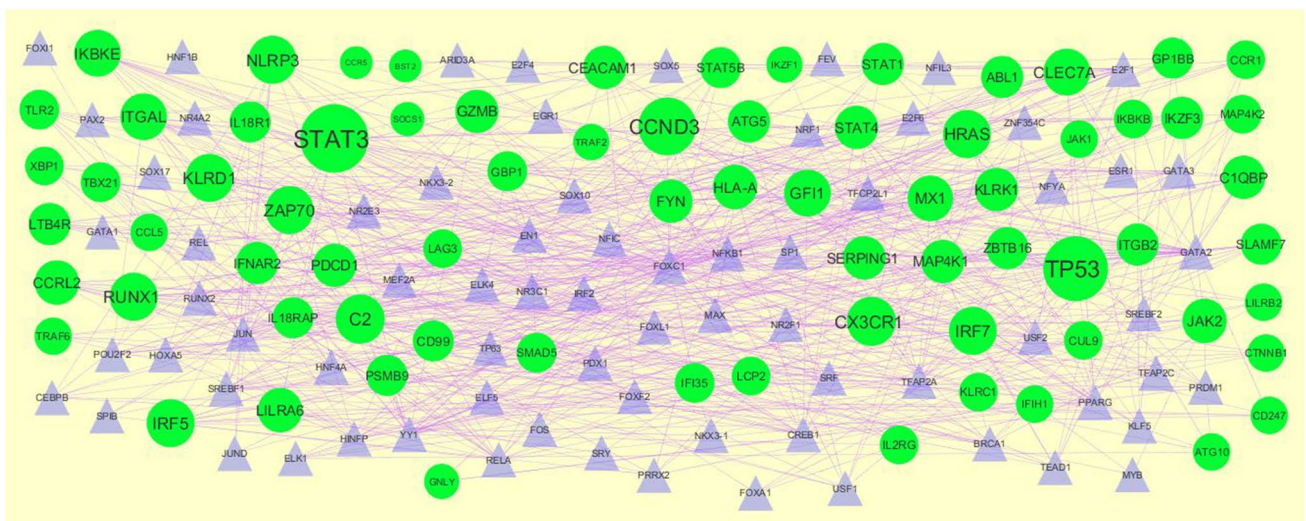


Fig. 14 The network of up regulated genes and their related TFs. The green circles nodes (●) are the up regulated genes; Blue triangle nodes (▲) are the TFs; Purple line (—) denotes edges (Interactions)

(Du et al. 2014), RAG2 (Wu et al. 2010), CASP3 (Takahashi et al. 2013), S1PR1 (Zhao et al. 2019), CD80 (Lumsden et al. 2000), CD86 (Lumsden et al. 2000) and CD44 (Liu et al. 2014) were key for advancement of influenza virus

infection, but these genes may be involved in progression of SARS-CoV-2 infection. Enriched down-regulated genes such as CCL7 (Girkin et al. 2015) and CXCR2 (Nagarkar et al. 2009) have been reported to be associated with

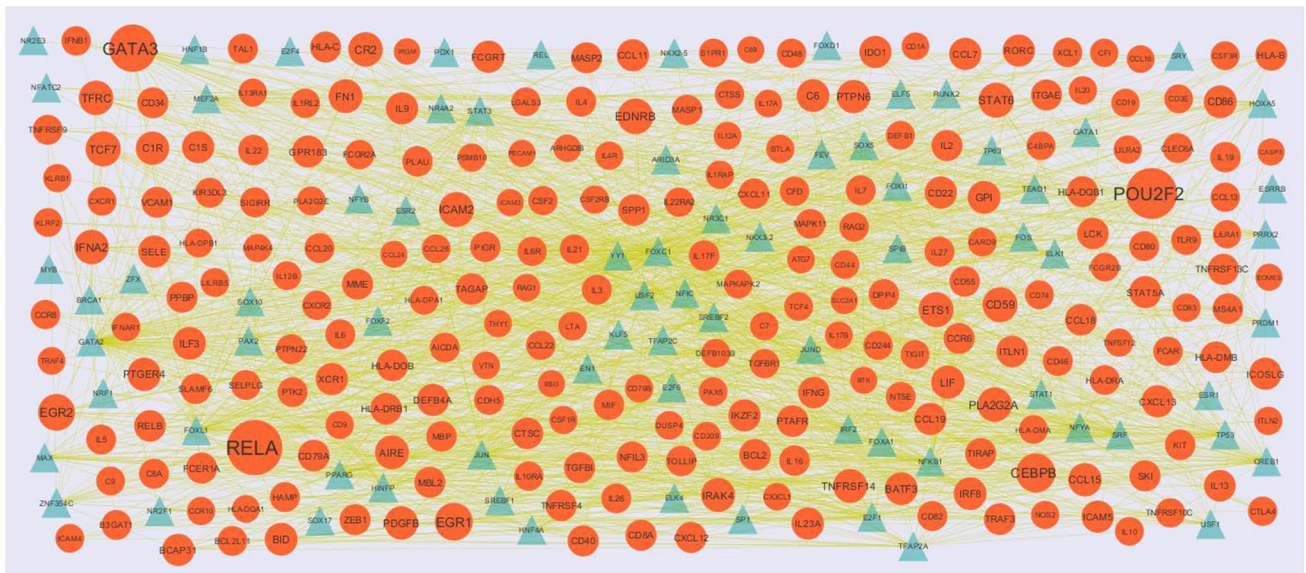


Fig. 15 The network of down regulated genes and their related TFs. The Red circles nodes (●) are the down regulated genes; Blue triangle nodes (▲) are the TFs; Yellow line (—) denotes edges (Interactions)

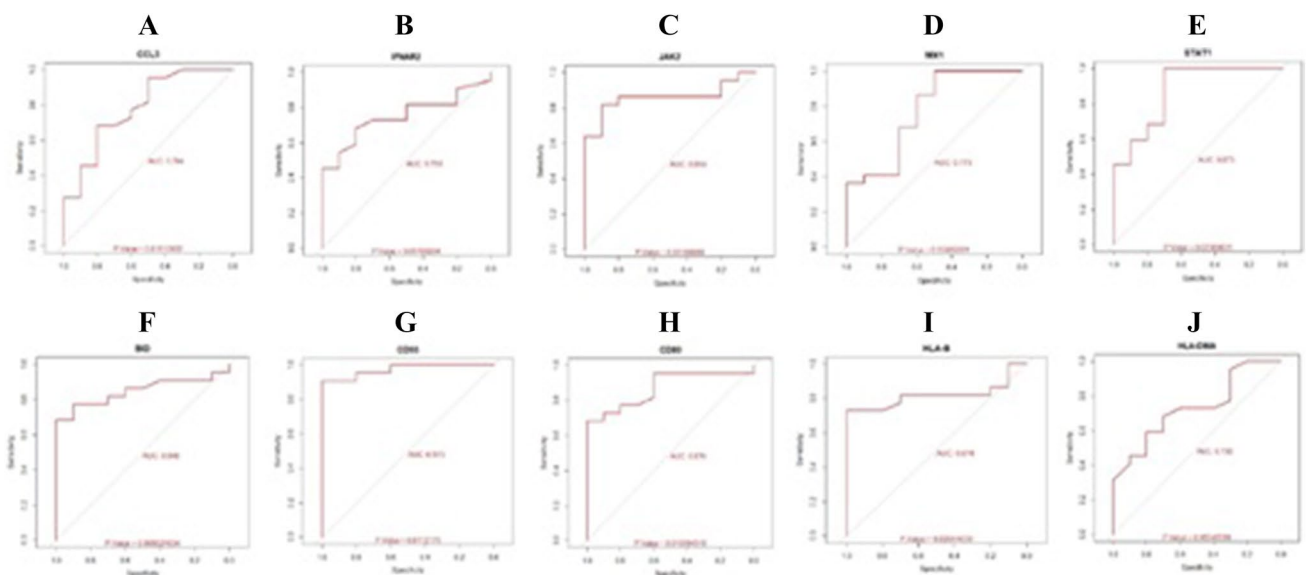


Fig. 16 ROC curve validated the sensitivity, specificity of hub genes as a predictive biomarker for SARS-CoV-2 diagnosis. **a** CCL5 **b** IFNAR2 **c** JAK2 **d** MX1 **e** STAT1 **f** BID **g** CD55 **h** CD80 **i** HAL-B **j** HLA-DMA

rhinovirus 1B infection, but these genes may be responsible for infection of SARS-CoV-2. Accumulating evidence shows that enriched genes such as IFNG (interferon gamma) (Sainz et al. 2004) and TRAF3 (Siu et al. 2009) were low expressed in SARS-CoV, but decreased expression of these genes may be key for progression of SARS-CoV-2 infection. Conti et al. (2020) showed that IL6 was liable for progression of SARS-CoV-2 infection. Novel biomarkers such as IL10RA, IL12A, IL13RA1, PDGFB (platelet-derived

growth factor subunit B), TNFSF12, IL17B, TNFRSF10C, CCL26, TNFRSF4, IL22RA2, CCL15, CCL16, CCL24, XCL1, KIT (KIT proto-oncogene, receptor tyrosine kinase), CCL13, PPBP (pro-platelet basic protein), IL23A, TGFBR1, LIF (LIF interleukin 6 family cytokine), CSF1R, CSF2, CSF2RB, CSF3R, TNFRSF13C, IL1RAP, IL4R, AICDA (activation-induced cytidinedeaminase), PTPN6, PIGR (polymeric immunoglobulin receptor), GATA3, PTAFR (platelet activating factor receptor), IL1RL2, PTK2, FN1,

DUSP4, RELA (RELA proto-oncogene, NF- κ A subunit), RELB (RELB proto-oncogene, NF- κ B subunit), LCK (LCK proto-oncogene, Src family tyrosine kinase), IRAK4, RORC (RAR-related orphan receptor C), BCL2L1 and PLA2G2A were low expressed and might be involved in progression of SARS-CoV-2 infection.

GO enrichment analysis results for up- and down-regulated gene might play important roles in the SARS-CoV-2 infection. Enriched up-regulated genes such as ATG5 (Guévin et al. 2010), PDCD1 (Nasi et al. 2013), ABL1 (García et al. 2012), CD99 (Tochikura et al. 2003), LILRB2 (Alaoui et al. 2018), LAG3 (Tian et al. 2015), SERPING1 (Sanfilippo et al. 2017), XBP1 (Sharma et al. 2017), CTNNA1 (Tucci et al. 2013), RUNX1 (Zhao et al. 2016), SLAMF7 (O'Connell et al. 2019), ITGAL (integrin subunit alpha L) (Xu et al. 2018) and CEACAM1 (Hirai et al. 2010) appeared to be related in various types of viral infections, but these genes may be responsible for progression of SARS-CoV-2 infection. Hu et al. (2017) observed that high expression of C1QBP was liable for progression of respiratory syncytial viral infection, but elevated expression this gene may be associated with advancement of SARS-CoV-2 infection. Evidence demonstrated that high expression of enriched genes such as KLRD1 (Bongen et al. 2018) and NLRP3 (Pothlichet et al. 2013) were important for progression of influenza virus infection, but increased expression of these genes may be involved in advancement of SARS-CoV-2 infection. Novel biomarkers such as KLRK1, IKZF3, ZBTB16, CLEC7A, C2 (complement C2), IKZF1, LCP2, KLRC1, GFI1, CCRL2 and MAP4K2 were highly expressed and might be involved in progression of SARS-CoV-2 infection. Studies have reported that low expression of enriched genes such as IRGM (immunity-related GTPase M) (Hansen et al. 2017), MASP1 (El Saadany et al. 2011), CD244 (Raziorrouh et al. 2010), MBL2 (Spector et al. 2010), CD46 (Gagar et al. 2003), C4A (Imakiire et al. 2012), C9 (Kim et al. 2013), ZEB1 (Lacher et al. 2011), ICAM2 (Wang et al. 2009), BTLA (B and T lymphocyte associated) (Cai et al. 2013), CD1A (Sacchi et al. 2007), CD19 (Zehender et al. 1997), ICAM5 (Wei et al. 2016), CD34 (Fahrbach et al. 2007), CD48 (Ezinne et al. 2014), CD59 (Amet et al. 2012), CD74 (Le Noury et al. 2015) and DEFB1 (Estrada-Aguirre et al. 2014) were linked with development of various viral infections, but low expression of these genes may be liable for progression of SARS-CoV-2 infection. Recent studies reported that enriched genes such as IDO1 (Fox et al. 2015), CD55 (Li et al. 2016), PTPN22 (Crabtree et al. 2016), FCGR2A (Maestri et al. 2016), CARD9 (Uematsu et al. 2015), MIF (macrophage migration inhibitory factor) (Arndt et al. 2002) and PLAU (plasminogen activator, urokinase) (Sidenius et al. 2000) were low expressed in influenza virus infection, but decrease expression of these genes may be key for progression of SARS-CoV-2 infection. Low expression

of genes such as PECAM1 (Wang et al. 1998), TLR9 (Shafique et al. 2012) and CTLA4 (Ayukawa et al. 2004) were observed in respiratory syncytial virus infection, but decrease expression these genes may be associated with progression of SARS-CoV-2 infection. Chen et al. (2017) demonstrated CD83 was important for progression of respiratory syndrome virus, but decrease expression of this gene may be linked with advancement of SARS-CoV-2 infection. Many studies have reported the enriched down-regulated gene such as CD209 (Chan et al. 2010), DPP4 (Letko et al. 2018), ICAM3 (Chan et al. 2007), CD9 (Earnest et al. 2017) and MASP2 (Wang et al. 2009) were liable for advancement of SARS-CoV, but these genes may be linked with progression of SARS-CoV-2 infection. Treon et al. (2020) indicated that low expression of BTK (Bruton tyrosine kinase) was key for progression of SARS-CoV-2 infection. Novel biomarkers such as HLA-DMA, HLA-DMB, HLA-DOB, HLA-DRA, CTSC (cathepsin C), PTGER4, CFD (complement factor D), SLAMF6, FCER1A, FCGR2B, C1R, C1S, C4BPA, C6, C7, C8A, C8B, TAL1, KLRB1, SELE (selectin E), GPI (glucose-6-phosphate isomerase), ICOSLG (inducible T cell costimulator ligand), LILRA1, LILRA2, VTN (vitronectin), CLEC6A, ATG7, ICAM4, AIRE (autoimmune regulator), GPR183, CFI, CR2, LGALS3, TFRC (transferrin receptor), CD3E, CD8A, TIGIT (T cell immunoreceptor with Ig and ITIM domains), MS4A1, TIRAP (TIR domain containing adaptor protein), CD79A, CD79B, PAX5, HAMP (hepcidin antimicrobial peptide), MAPK11, CTSS (cathepsin S), MBP (myelin basic protein), ITGAE (integrin subunit alpha E), FCGRT (Fc fragment of IgG receptor and transporter), MME (membrane metalloendopeptidase), NT5E, CDH5, DEFB103B, DEFB4A and TRAF4 were low expressed and might be involved in progression of SARS-CoV-2 infection.

Construction of PPI network of up- and down-regulated genes might be helpful for understanding the relationship of developmental SARS-CoV-2 infection. Desai et al. (2018) showed that BATF3 was involved in progression of respiratory poxvirus infection, but this gene may be key for development of SARS-CoV-2 infection. Novel biomarker ILF3 was low expressed and might be involved in progression of SARS-CoV-2 infection.

A target gene-miRNA regulatory and target gene-TF regulatory network for up- and down-regulated genes were generated to determine the key target genes and provide valuable information for the analysis of cellular functions and biological processes in SARS-CoV-2 infection. SMAD5 was highly expressed in SARS-CoV-2 infection and might be consider as novel biomarker. Novel biomarkers such as SKI (SKI proto-oncogene) and KLRF2 were low expressed and might be involved in progression of SARS-CoV-2 infection.

Conclusion

It is earnestly hoped that this research will help in enhancing attempts to further understand the molecular characteristics of SARS-CoV-2 infection progression. CCL5, IFNAR2, JAK2, MX1, STAT1, BID, CD55, CD80, HAL-B and HLA-DMA may be used as biomarkers and therapeutic targets in patients with SARS-CoV-2 infection. This research, it is hoped promote ultimate molecularly targeted therapies for SARS-CoV-2 infection and provide acceptable local control and survival.

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Author contributions Basavaraj Vastrad participated in writing original draft and investigation, Chanabasayya Vastrad performed software, supervision, formal analysis and validation. Anandkumar Tengli performed editing and reviewing the manuscript.

Availability of data and materials The datasets supporting the conclusions of this article are available in the ArrayExpress (<https://www.ebi.ac.uk/arrayexpress>) repository. [(E-MTAB-8871) (<https://www.ebi.ac.uk/arrayexpress/experiments/E-MTAB-8871/>)].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No informed consent, because this study does not contain human or animals participants.

Consent for publication Not applicable.

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