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Screening and identification of key biomarkers associated with endometriosis using bioinformatics and next-generation sequencing data analysis

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Abstract

Background Endometriosis is a common cause of endometrial-type mucosa outside the uterine cavity with symptoms such as painful periods, chronic pelvic pain, pain with intercourse and infertility. However, the early diagnosis of endometriosis is still restricted. The purpose of this investigation is to identify and validate the key biomarkers of endometriosis.

Methods Next-generation sequencing dataset GSE243039 was obtained from the Gene Expression Omnibus database, and differentially expressed genes (DEGs) between endometriosis and normal control samples were identified. After screening of DEGs, gene ontology (GO) and REACTOME pathway enrichment analyses were performed. Furthermore, a protein–protein interaction (PPI) network was constructed and modules were analyzed using the Human Integrated Protein–Protein Interaction rEference database and Cytoscape software, and hub genes were identified. Subsequently, a network between miRNAs and hub genes, and network between TFs and hub genes were constructed using the miRNet and NetworkAnalyst tool, and possible key miRNAs and TFs were predicted. Finally, receiver operating characteristic curve analysis was used to validate the hub genes.

Results A total of 958 DEGs, including 479 upregulated genes and 479 downregulated genes, were screened between endometriosis and normal control samples. GO and REACTOME pathway enrichment analyses of the 958 DEGs showed that they were mainly involved in multicellular organismal process, developmental process, signaling by GPCR and muscle contraction. Further analysis of the PPI network and modules identified 10 hub genes, including *vcam1, snca, prkcb, adrb2, foxq1, mdfi, actbl2, prkd1, dapk1* and *actc1*. Possible target miRNAs, including *hsa-mir-3143* and hsa-mir-2110, and target TFs, including *tcf3 (transcription factor 3)* and *clock* (clock circadian regulator), were predicted by constructing a miRNA-hub gene regulatory network and TF-hub gene regulatory network.

Conclusions This investigation used bioinformatics techniques to explore the potential and novel biomarkers. These biomarkers might provide new ideas and methods for the early diagnosis, treatment and monitoring of endometriosis.

Keywords Bioinformatics, Biomarkers, Differentially expressed genes, Endometriosis, Hub genes, Next-generation sequencing, Signaling pathways

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Background

Endometriosis is one of the most important chronic inflammatory diseases and has become the key cause of serious reproductive and general health condition [1]. Endometriosis is characterized by the presence of endometrial-type mucosa outside the uterine cavity [2]. The outbreak of their first period occurs through menopause, disregarding of ethnic origin or social status [2]. The clinical incidence of endometriosis is high, and its main features include dysmenorrhea, dyspareunia, chronic pelvic pain, irregular uterine bleeding and infertility [3], which places a great burden on the economy of health and reduces quality of life in worldwide; 10% of women of reproductive age are diagnosed with endometriosis each year [4]. These patients might have various complications including gynecological cancer (ovarian, endometrial and cervical cancers) [5], polycystic ovary syndrome [6], cardiovascular diseases [7], obesity [8], gestational diabetes mellitus [9], diabetes mellitus [10] and hypertension [11]. Endometriosis is recognized to be vulnerable on sex hormone estrogen, which rise the inflammation, growth and pain linked with the disease [6]. Studies have revealed that the progression of endometriosis is related to genetic risk factors [12] as well as environmental factors [13]. Because of this disorder complex pathogenesis, it is mainly treated by gynecological surgery [14], oral contraceptives [15], progestins [16], nonsteroidal anti-inflammatory drugs [17] and gonadotropin-releasing hormone agonists [18]. But these treatments have not been effective for longer period. Therefore, it is urgent to find specific molecular biomarkers for early assessment of the prognosis of patients with endometriosis, so as to further advancing the treatment and prognosis of patients. In current years, molecular biomarkers were demonstrated highly useful as clinical tools for endometriosis diagnosis and treatment [19].

The underlying complex molecular mechanisms in endometriosis pose a special challenge to daily clinical practice. Studies have found that genes including *cyr61* [20], *esr2* and *cyp19a1* [21], *hoxa10* [22], *foxd3* [23], *loxl1* and *htra1* [24] can be used as an important marker for early diagnosis, prognosis and treatment of endometriosis. Studies have shown that signaling pathways including AKT and ERK signaling pathways [25], Wnt/β-catenin signaling pathway [26], PI3K-Akt-mTOR and MAPK signaling pathways [27], notch signaling pathway [28] and MAPK/ERK signal pathway [29] are involved in the progression of endometriosis. Taken together, current evidence suggests that the genes and signaling pathways are closely related to the progression of endometriosis.

The mechanisms of endometriosis at the molecular level are essentially for treating the disease. With the wide application of next-generation sequencing (NGS) technology, endometriosis-related genes have been widely identified, which is a key step in exploring the complex pathology of endometriosis and finding drugs that combat the illness. Numerous NGS data of gene expression have been published in public databases such as NCBI Gene Expression Omnibus (GEO) [https://www.ncbi.nlm.nih.gov/geo/] [30] during the past few years, and they are being increasingly used in bioinformatics and NGS data analysis to explore target genes or proteins associated in various diseases [31, 32].

Bioinformatics and network analysis of NGS data are an effective way to explore biomarkers in the pathogenesis of various diseases. Therefore, this investigation aimed to use bioinformatics analysis to identify hub genes and molecular pathways involved in endometriosis, to identify key diagnostic or therapeutic biomarkers. We obtained DEGs between endometriosis and normal control samples from GSE243039, a gene expression profile downloaded from the GEO database. Immediately after, we performed gene ontology (GO) and REACTOME pathway enrichment analysis on these DEGs. By constructing PPI networks, we screened for the significant modules and hub genes. We constructed miRNA-hub gene regulatory network and TF-hub gene regulatory network, and we screened for the miRNAs, TFs and hub genes. To validate that these hub genes can serve as molecular markers of endometriosis, we determined hub genes by using receiver operating characteristic curve (ROC) analysis. This investigation might offer better insight into potential molecular mechanisms to explore preventive and therapeutic strategies for endometriosis.

Methods

Next-generation sequencing (NGS) data source

The NGS dataset GSE243039 was obtained from the GEO database (Accession Date: 11/09/2023). The GSE243039 dataset included 20 endometriosis samples and 20 normal control samples. The platform used was the GPL24676 Illumina NovaSeq 6000 (Homo sapiens).

Identification of DEGs

The limma R/Bioconductor software package [33] was used to perform the identification of DEGs between endometriosis samples and normal control samples. We adjusted *p*-value to correct the false positive error caused by the multiple tests and determined it by the Benjamini and Hochberg method [34], which is the common tools to minimize the false discovery rate. The cutoff criteria were $|\text{logFC}| > 1.304$ (log2 fold change) for upregulated genes, $|\text{logFC}| > 1.304$ (log2 fold change) < -1.2644 for downregulated genes and a adj.*P*.Val < 0.05. Thereafter, we used R packages “ggplot2” and “gplot” to show the

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

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
PLPPR4	6.76335	6.20E−15	2.24E−11	12.15991	Up	Phospholipid phosphatase related 4
PCSK9	5.07288	5.03E−12	2.78E−09	9.713276	Up	Proprotein convertase subtilisin/kexin type 9
ADAMTS19	4.976936	1.00E−14	2.25E−11	11.97438	Up	ADAM metallopeptidase with thrombospondin type 1 motif 19
KIF26A	4.329184	9.75E−08	4.69E−06	6.504061	Up	Kinesin family member 26A
GRIA4	4.296838	2.87E−08	1.91E−06	6.886288	Up	Glutamate ionotropic receptor AMPA-type subunit 4
CNTN4	4.108296	6.99E−08	3.70E−06	6.608031	Up	Contactin 4
APCDD1	4.052813	4.17E−06	9.09E−05	5.335862	Up	APC downregulated 1
SEMA3A	4.047205	3.35E−07	1.28E−05	6.120174	Up	Semaphorin 3A
TMEM26	4.037968	1.59E−12	1.10E−09	10.11548	Up	Transmembrane protein 26
GRIN2A	4.022587	2.01E−08	1.44E−06	6.998121	Up	Glutamate ionotropic receptor NMDA-type subunit 2A
LAMC3	3.98438	7.26E−06	0.000141	5.162268	Up	Laminin subunit gamma 3
L1CAM	3.939758	1.85E−06	4.86E−05	5.589465	Up	L1 cell adhesion molecule
CBLN2	3.905839	1.06E−07	5.03E−06	6.477874	Up	Cerebellin 2 precursor
HPSE2	3.800586	2.29E−07	9.22E−06	6.238608	Up	Heparanase 2 (inactive)
CILP	3.794436	0.000108	0.001167	4.301899	Up	Cartilage intermediate layer protein
SDK1	3.794238	3.57E−07	1.34E−05	6.100051	Up	Sidekick cell adhesion molecule 1
ROBO2	3.793291	1.94E−09	2.38E−07	7.73845	Up	Roundabout guidance receptor 2
LPAR3	3.77025	2.07E−08	1.47E−06	6.988144	Up	Lysophosphatidic acid receptor 3
GALNT17	3.764892	1.28E−06	3.70E−05	5.703322	Up	Polypeptide N-acetylgalactosaminyltransferase 17
PALMD	3.746961	1.97E−06	5.08E−05	5.569086	Up	Palmdelphin
JAKMIP2	3.740977	2.39E−09	2.79E−07	7.671792	Up	Janus kinase and microtubule interacting protein 2
SLC35F3	3.733243	4.47E−09	4.41E−07	7.472579	Up	Solute carrier family 35 member F3
CACNA1G	3.652448	1.35E−07	6.07E−06	6.403646	Up	Calcium voltage-gated channel subunit alpha1 G
AJAP1	3.630833	9.51E−06	0.000175	5.077432	Up	Adherens junctions-associated protein 1
RORB	3.592522	0.000505	0.003859	3.789292	Up	RAR-related orphan receptor B
HSD17B2	3.586894	5.44E−06	0.000112	5.252487	Up	Hydroxysteroid 17-beta dehydrogenase 2
PCDH19	3.462986	8.50E−08	4.28E−06	6.54683	Up	Protocadherin 19
S100A4	3.361421	7.83E−15	2.24E−11	12.06958	Up	S100 calcium binding protein A4
NLGN4X	3.346885	4.69E−05	0.000609	4.570634	Up	Neuroligin 4 X-linked
VCAM1	3.305329	0.000134	0.001387	4.230696	Up	Vascular cell adhesion molecule 1
STRA6	3.252045	0.0002	0.001881	4.098793	Up	Signaling receptor and transporter of retinol STRA6
COL6A6	3.23629	1.92E−08	1.39E−06	7.011592	Up	Collagen type VI alpha 6 chain
SIX2	3.233347	0.000242	0.002174	4.035541	Up	SIX homeobox 2
CLEC3B	3.219362	6.86E−08	3.64E−06	6.613763	Up	C-type lectin domain family 3 member B
ST8SIA4	3.210139	2.46E−06	6.00E−05	5.500511	Up	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 4
MMP3	3.201862	3.29E−05	0.000461	4.684818	Up	Matrix metallopeptidase 3
PLCH1	3.175137	0.000139	0.001428	4.217957	Up	Phospholipase C eta 1
CABCOCO1	3.141923	7.85E−12	3.96E−09	9.56007	Up	Ciliary-associated calcium binding coiled-coil 1
DPP6	3.141142	2.99E−06	6.98E−05	5.439696	Up	Dipeptidyl peptidase-like 6
COL28A1	3.064911	2.00E−05	0.000311	4.842314	Up	Collagen type XXVIII alpha 1 chain
COCH	3.05674	9.67E−06	0.000178	5.071932	Up	Cochlin
EFNA5	3.05662	5.11E−08	2.96E−06	6.705933	Up	Ephrin A5
GRP	3.056161	1.13E−08	9.17E−07	7.178938	Up	Gastrin releasing peptide

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
AVPR1A	3.052514	0.000105	0.001144	4.309966	Up	Arginine vasopressin receptor 1A
ADGRL3	3.042869	5.00E−06	0.000105	5.278659	Up	Adhesion G protein-coupled receptor L3
EPHA6	3.029344	1.31E−09	1.78E−07	7.865147	Up	EPH receptor A6
CNTN5	3.004363	4.15E−08	2.53E−06	6.770742	Up	Contactin 5
TUBA3E	3.003025	1.70E−05	0.000275	4.894684	Up	Tubulin alpha 3e
RGS7	2.977539	3.87E−10	7.39E−08	8.259352	Up	Regulator of G protein signaling 7
AQP8	2.973723	2.61E−09	2.99E−07	7.643696	Up	Aquaporin 8
WNT6	2.964101	1.91E−06	4.98E−05	5.57843	Up	Wnt family member 6
FABP4	2.95997	7.51E−08	3.90E−06	6.585421	Up	Fatty acid binding protein 4
PSG1	2.955976	0.000331	0.002783	3.931445	Up	Pregnancy-specific beta-1-glycoprotein 1
ANO1	2.949958	6.03E−08	3.33E−06	6.65401	Up	Anoctamin 1
SOX6	2.938951	2.83E−10	6.16E−08	8.361581	Up	SRY-box transcription factor 6
NDP	2.91885	0.000663	0.004802	3.696355	Up	Norrincystine knot growth factor NDP
ERVMER34-1	2.886936	3.13E−06	7.21E−05	5.425421	Up	Endogenous retrovirus group MER34 member 1, envelope
PREX2	2.876737	2.03E−06	5.18E−05	5.560168	Up	Phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 2
TFAP2C	2.864072	0.00077	0.005349	3.644851	Up	Transcription factor AP-2 gamma
NTRK1	2.855604	0.00041	0.003283	3.859591	Up	Neurotrophic receptor tyrosine kinase 1
CNTN1	2.853904	3.97E−05	0.000531	4.624175	Up	Contactin 1
GALNT13	2.842063	7.03E−05	0.000834	4.440753	Up	Polypeptide N-acetylgalactosaminyltransferase 13
SYT9	2.839815	3.44E−06	7.81E−05	5.395487	Up	Synaptotagmin 9
FGF10	2.839506	8.05E−10	1.29E−07	8.021417	Up	Fibroblast growth factor 10
RAMP3	2.832349	2.64E−06	6.33E−05	5.478637	Up	Receptor activity modifying protein 3
ALDH1L1	2.799	1.51E−06	4.19E−05	5.651506	Up	Aldehyde dehydrogenase 1 family member L1
PLA2G7	2.794211	1.73E−07	7.33E−06	6.326221	Up	Phospholipase A2 group VII
MMP12	2.792426	8.64E−05	0.000983	4.373945	Up	Matrix metallopeptidase 12
FAIM2	2.790032	1.17E−09	1.62E−07	7.902043	Up	Fas apoptotic inhibitory molecule 2
SEMA6A	2.781374	8.57E−10	1.34E−07	8.001094	Up	Semaphorin 6A
ADCY1	2.747518	0.000609	0.004472	3.725191	Up	Adenylatecyclase 1
MDGA2	2.743823	4.06E−07	1.50E−05	6.060738	Up	MAM domain containing glycosylphosphatidylinositol anchor 2
COL14A1	2.740007	1.47E−09	1.93E−07	7.827594	Up	Collagen type XIV alpha 1 chain
LCP1	2.739277	2.89E−06	6.80E−05	5.450181	Up	Lymphocyte cytosolic protein 1
MMP27	2.734557	8.62E−07	2.69E−05	5.826621	Up	Matrix metallopeptidase 27
LRP1B	2.727044	6.97E−07	2.30E−05	5.892855	Up	LDL receptor-related protein 1B
LY6K	2.697355	1.17E−05	0.000206	5.012773	Up	Lymphocyte antigen 6 family member K
PIP5K1B	2.685746	3.33E−09	3.59E−07	7.566542	Up	Phosphatidylinositol-4-phosphate 5-kinase type 1 beta
ZNF726	2.675392	2.65E−08	1.81E−06	6.911657	Up	Zinc finger protein 726
ADRA1D	2.663313	5.86E−07	2.03E−05	5.946796	Up	Adrenoceptor alpha 1D
SNCA	2.646582	0.002632	0.013959	3.210533	Up	Synuclein alpha
ST6GALNAC3	2.636022	1.03E−07	4.92E−06	6.486685	Up	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 3
TMEM52B	2.627669	1.79E−05	0.000287	4.877499	Up	Transmembrane protein 52B
TMEM37	2.616893	0.000162	0.001595	4.169509	Up	Transmembrane protein 37
CLIC2	2.612803	2.04E−09	2.45E−07	7.722159	Up	Chloride intracellular channel 2
NAALAD2	2.599709	9.33E−08	4.57E−06	6.517728	Up	N-acetylated alpha-linked acidic dipeptidase 2
LMTK3	2.580405	1.71E−07	7.29E−06	6.32841	Up	Lemur tyrosine kinase 3

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
STAR	2.573317	1.36E−05	0.000232	4.965242	Up	Steroidogenic acute regulatory protein
ACP3	2.532701	8.27E−06	0.000158	5.121323	Up	Acid phosphatase 3
IL31RA	2.523753	1.20E−09	1.64E−07	7.893868	Up	Interleukin 31 receptor A
APOD	2.520315	2.01E−05	0.000312	4.840658	Up	Apolipoprotein D
ANO4	2.518658	0.002076	0.011589	3.296307	Up	Anoctamin 4
LRATD1	2.518289	5.35E−11	1.62E−08	8.911076	Up	LRAT domain containing 1
INSRR	2.495802	0.000526	0.003994	3.774937	Up	Insulin receptor-related receptor
LAG3	2.494584	3.41E−05	0.000473	4.672734	Up	Lymphocyte activating 3
SOX18	2.481299	3.15E−06	7.25E−05	5.423675	Up	SRY-box transcription factor 18
F2RL2	2.478309	2.13E−06	5.38E−05	5.545123	Up	Coagulation factor II thrombin receptor-like 2
TMEM132B	2.476601	1.49E−05	0.00025	4.934886	Up	Transmembrane protein 132B
CCR1	2.473974	1.88E−05	0.000297	4.862981	Up	C–C motif chemokine receptor 1
NCKAP5	2.473105	0.000694	0.004962	3.680433	Up	NCK-associated protein 5
C2orf88	2.472711	2.18E−10	5.04E−08	8.446715	Up	Chromosome 2 open reading frame 88
ICA1	2.471974	1.03E−06	3.11E−05	5.77108	Up	Islet cell autoantigen 1
CST1	2.470675	0.000727	0.00514	3.664434	Up	Cystatin SN
NKAIN1	2.460596	0.001948	0.011011	3.319084	Up	Sodium/potassium transporting ATPase interacting 1
IP6K3	2.457598	0.000285	0.002469	3.981865	Up	Inositol hexakisphosphate kinase 3
RETREG1	2.457043	1.48E−06	4.10E−05	5.659324	Up	Reticulophagy regulator 1
CYP39A1	2.447117	1.10E−06	3.28E−05	5.75072	Up	Cytochrome P450 family 39 subfamily A member 1
S100A3	2.444216	9.86E−15	2.25E−11	11.98095	Up	S100 calcium binding protein A3
ISM1	2.438578	2.07E−05	0.000319	4.831004	Up	Isthmin 1
CHST1	2.432231	2.51E−06	6.10E−05	5.493885	Up	Carbohydrate sulfotransferase 1
ATCAY	2.424636	1.58E−06	4.30E−05	5.63875	Up	ATCAY kinesin light chain interacting caytaxin
PREX1	2.422015	7.44E−07	2.40E−05	5.872563	Up	Phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 1
CARD16	2.415338	6.30E−06	0.000126	5.206741	Up	Caspase recruitment domain family member 16
ADRA2C	2.405717	0.001481	0.008888	3.41651	Up	Adrenoceptor alpha 2C
FLT1	2.40555	4.08E−05	0.000544	4.615809	Up	Fms-related receptor tyrosine kinase 1
FABP5	2.404621	2.66E−08	1.81E−06	6.910337	Up	Fatty acid binding protein 5
PRDM1	2.398435	0.003852	0.018662	3.070723	Up	PR/SET domain 1
TRPC3	2.393228	1.51E−12	1.10E−09	10.13214	Up	Transient receptor potential cation channel subfamily C member 3
TUNAR	2.38405	1.98E−06	5.08E−05	5.568021	Up	TCL1 upstream neural differentiation-associated RNA
IGSF3	2.379319	1.48E−09	1.93E−07	7.825786	Up	Immunoglobulin superfamily member 3
THSD7A	2.376559	0.00529	0.024026	2.951945	Up	Thrombospondin type 1 domain containing 7A
ADAMTS17	2.37201	1.42E−06	3.98E−05	5.672089	Up	ADAM metallopeptidase with thrombospondin type 1 motif 17
DKK2	2.371245	1.51E−06	4.17E−05	5.653171	Up	Dickkopf WNT signaling pathway inhibitor 2
PROK1	2.361571	0.012248	0.045333	2.625366	Up	Prokineticin 1
SCTR	2.355346	2.76E−06	6.58E−05	5.464606	Up	Secretin receptor
FOXL2NB	2.341574	0.001967	0.0111	3.315561	Up	FOXL2 neighbor
WNT16	2.336909	0.002059	0.011516	3.299158	Up	Wnt family member 16
ZNF804A	2.332815	0.000402	0.003239	3.865913	Up	Zinc finger protein 804A
RNF157	2.321389	0.000916	0.006147	3.584773	Up	Ring finger protein 157

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
FILNC1	2.313159	2.61E−10	5.75E−08	8.387101	Up	FOXO-induced long non-coding RNA 1
COL5A3	2.302619	3.26E−08	2.11E−06	6.846013	Up	Collagen type V alpha 3 chain
F13A1	2.302086	3.45E−05	0.000476	4.669571	Up	Coagulation factor XIII A chain
SH3GL2	2.296048	7.55E−10	1.23E−07	8.042216	Up	SH3 domain containing GRB2-like 2, endophilin A1
PRKCB	2.295018	0.0001	0.001103	4.326301	Up	Protein kinase C beta
DHCR24	2.292674	1.76E−12	1.18E−09	10.07839	Up	24-dehydrocholesterol reductase
GPR20	2.290641	1.69E−06	4.53E−05	5.617085	Up	G protein-coupled receptor 20
PDE3B	2.290631	5.46E−08	3.11E−06	6.68473	Up	Phosphodiesterase 3B
CHST2	2.281982	1.57E−07	6.76E−06	6.355455	Up	Carbohydrate sulfotransferase 2
BMP4	2.278367	9.72E−13	7.87E−10	10.28843	Up	Bone morphogenetic protein 4
IL1RL1	2.271743	0.013247	0.048129	2.59379	Up	Interleukin 1 receptor-like 1
MYPN	2.259711	9.70E−06	0.000178	5.071057	Up	Myopalladin
HS3ST5	2.254222	3.44E−07	1.31E−05	6.111664	Up	Heparan sulfate-glucosamine 3-sulfotransferase 5
PLCG2	2.246402	2.57E−13	3.06E−10	10.76548	Up	Phospholipase C gamma 2
KCNH5	2.245021	8.24E−07	2.60E−05	5.840638	Up	Potassium voltage-gated channel subfamily H member 5
PRL	2.243593	0.01139	0.042843	2.654416	Up	Prolactin
FOXQ1	2.24188	0.001101	0.007076	3.520892	Up	Forkhead box Q1
ALPP	2.240977	5.86E−08	3.29E−06	6.662879	Up	Alkaline phosphatase, placental
SEMA6D	2.239721	0.000164	0.001613	4.164838	Up	Semaphorin 6D
NEFL	2.235525	0.000173	0.001684	4.147159	Up	Neurofilament light chain
WNT5A	2.234375	0.000779	0.005402	3.640615	Up	Wnt family member 5A
MACC1	2.218788	3.88E−05	0.00052	4.631753	Up	MET transcriptional regulator MACC1
TRPC6	2.214357	0.000918	0.006155	3.583976	Up	Transient receptor potential cation channel subfamily C member 6
MEOX1	2.213199	0.002772	0.014517	3.191701	Up	Mesenchyme homeobox 1
DOCK4	2.198954	2.50E−06	6.07E−05	5.495826	Up	Dedicator of cytokinesis 4
HTR1B	2.174988	0.001557	0.009248	3.398983	Up	5-Hydroxytryptamine receptor 1B
PRAME	2.156065	1.78E−08	1.31E−06	7.035603	Up	PRAME nuclear receptor transcriptional regulator
THSD7B	2.152357	6.08E−08	3.33E−06	6.651165	Up	Thrombospondin type 1 domain containing 7B
TIMP3	2.150985	2.16E−05	0.000331	4.818136	Up	TIMP metallopeptidase inhibitor 3
SLCO4A1	2.150798	1.71E−06	4.55E−05	5.613756	Up	Solute carrier organic anion transporter family member 4A1
EGFL6	2.146157	2.05E−07	8.48E−06	6.272113	Up	EGF-like domain multiple 6
SERPINB2	2.144838	0.000271	0.002375	3.997832	Up	Serpin family B member 2
CYP4B1	2.142878	0.000609	0.004473	3.725041	Up	Cytochrome P450 family 4 subfamily B member 1
COL7A1	2.141664	3.70E−05	0.000501	4.64651	Up	Collagen type VII alpha 1 chain
FRZB	2.138613	5.90E−09	5.48E−07	7.38458	Up	Frizzled-related protein
PSG3	2.122902	0.000211	0.001955	4.081503	Up	Pregnancy-specific beta-1-glycoprotein 3
VWC2	2.119857	0.000176	0.001702	4.142014	Up	Von Willebrand factor C domain containing 2
CFD	2.113436	0.000635	0.004631	3.710733	Up	Complement factor D
CRACD	2.113112	3.13E−05	0.000443	4.700251	Up	Capping protein inhibiting regulator of actin dynamics
LANCL3	2.108051	2.95E−06	6.92E−05	5.443294	Up	LanC-like family member 3
RAB6C	2.105403	3.52E−10	6.81E−08	8.290269	Up	RAB6C, member RAS oncogene family
NLRP2	2.101201	0.001176	0.007429	3.497735	Up	NLR family pyrin domain containing 2

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
CPE	2.098622	1.22E−07	5.60E−06	6.435386	Up	Carboxypeptidase E
ADAMTS9	2.097533	8.34E−06	0.000158	5.118628	Up	ADAM metallopeptidase with thrombospondin type 1 motif 9
SAMD13	2.094561	4.87E−08	2.86E−06	6.720529	Up	Sterile alpha motif domain containing 13
GPBAR1	2.089881	0.000529	0.004012	3.773206	Up	G protein-coupled bile acid receptor 1
DNAJC6	2.089319	1.38E−05	0.000235	4.960018	Up	DnaJ heat shock protein family (Hsp40) member C6
NPW	2.089175	1.98E−08	1.43E−06	7.001975	Up	Neuropeptide W
XK	2.08758	2.05E−06	5.23E−05	5.55645	Up	X-linked Kx blood group antigen, Kell and VPS13A binding protein
EREG	2.078451	0.0007	0.004995	3.677405	Up	Epiregulin
GABRA2	2.07472	0.000126	0.00132	4.249985	Up	Gamma-aminobutyric acid type A receptor subunit alpha 2
TMCC3	2.069775	2.54E−06	6.15E−05	5.490304	Up	Transmembrane and coiled-coil domain family 3
NDNF	2.06	0.000881	0.005955	3.598115	Up	Neuron-derived neurotrophic factor
DCHS1	2.055197	9.01E−06	0.000169	5.094397	Up	Dachsous cadherin-related 1
CNTN6	2.043284	2.55E−06	6.17E−05	5.488599	Up	Contactin 6
MEGF10	2.040746	6.01E−05	0.000737	4.491082	Up	Multiple EGF-like domains 10
MEI4	2.023279	2.05E−06	5.21E−05	5.557795	Up	Meiotic double-stranded break formation protein 4
SNAP25	1.995428	0.002541	0.013588	3.223379	Up	Synaptosome-associated protein 25
CARD9	1.992794	3.15E−09	3.46E−07	7.584141	Up	Caspase recruitment domain family member 9
ELMO1	1.991602	0.001782	0.010277	3.350853	Up	Engulfment and cell motility 1
SYT1	1.990573	0.000161	0.001593	4.170655	Up	Synaptotagmin 1
NETO1	1.982914	0.007261	0.030523	2.831024	Up	Neuropilin and tolloid-like 1
CD24	1.974298	9.23E−05	0.001036	4.352364	Up	CD24 molecule
SLC26A7	1.966152	0.000434	0.00343	3.84067	Up	Solute carrier family 26 member 7
ZBTB7C	1.9647	1.56E−05	0.000257	4.922019	Up	Zinc finger and BTB domain containing 7C
KIAA1210	1.957336	0.007147	0.030161	2.837133	Up	KIAA1210
LHCGR	1.957307	7.93E−05	0.000917	4.401541	Up	Luteinizing hormone/choriogonadotropin receptor
CLSTN2	1.95386	3.67E−07	1.37E−05	6.092016	Up	Calsyntenin 2
SCD	1.948808	2.97E−10	6.26E−08	8.345503	Up	Stearoyl-CoA desaturase
DTX1	1.943827	0.000125	0.001307	4.254768	Up	Deltex E3 ubiquitin ligase 1
COL24A1	1.939722	0.000211	0.001955	4.081409	Up	Collagen type XXIV alpha 1 chain
SYTL5	1.939593	7.69E−05	0.000894	4.411666	Up	Synaptotagmin-like 5
PDGFB	1.938244	0.002996	0.015394	3.16336	Up	Platelet-derived growth factor subunit B
ZNF608	1.936373	0.000242	0.002174	4.035469	Up	Zinc finger protein 608
RASL11B	1.935406	0.00167	0.009794	3.374029	Up	RAS-like family 11 member B
LSAMP	1.933966	0.00022	0.00202	4.068241	Up	Limbic system-associated membrane protein
WFDC1	1.928958	3.44E−05	0.000476	4.669817	Up	WAP four-disulfide core domain 1
MMP7	1.928028	0.008602	0.034662	2.765233	Up	Matrix metallopeptidase 7
PIK3CG	1.927056	2.85E−05	0.000413	4.730577	Up	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma
ACSM5	1.925101	0.000743	0.005206	3.65709	Up	acyl-CoA synthetase medium chain family member 5
DGCR6	1.920838	1.73E−06	4.59E−05	5.609382	Up	DiGeorge syndrome critical region gene 6
CYYR1	1.919394	5.50E−05	0.000692	4.519664	Up	Cysteine and tyrosine-rich 1
EFHB	1.919312	0.000592	0.004376	3.734642	Up	EF-hand domain family member B

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
MMRN1	1.917217	0.006887	0.029355	2.851399	Up	Multimerin 1
APOL4	1.916085	0.000867	0.005878	3.603849	Up	Apolipoprotein L4
LDLR	1.915435	8.92E−10	1.37E−07	7.988438	Up	Low-density lipoprotein receptor
SOAT2	1.912507	0.000132	0.001367	4.235818	Up	Sterol O-acyltransferase 2
RGCC	1.911303	2.83E−07	1.11E−05	6.172257	Up	Regulator of cell cycle
CD4	1.910165	0.000151	0.001516	4.191808	Up	CD4 molecule
FOXL2	1.904983	0.003288	0.016488	3.129183	Up	Forkhead box L2
MYZAP	1.89753	0.000551	0.004128	3.759569	Up	Myocardial zonulaadherens protein
AKNAD1	1.896549	1.37E−07	6.12E−06	6.398722	Up	AKNA domain containing 1
AIF1L	1.894951	2.32E−06	5.77E−05	5.518188	Up	Allograft inflammatory factor 1-like
DPF3	1.890886	4.46E−05	0.000582	4.587222	Up	Double PHD fingers 3
LRRC9	1.888336	1.71E−06	4.54E−05	5.614477	Up	Leucine-rich repeat containing 9
GPR183	1.887312	0.000178	0.001718	4.137994	Up	G protein-coupled receptor 183
GPAT3	1.885466	8.31E−05	0.000953	4.386524	Up	Glycerol-3-phosphate acyltransferase 3
CYP2S1	1.876127	0.000157	0.00156	4.179408	Up	Cytochrome P450 family 2 subfamily S member 1
TRPA1	1.874787	2.39E−05	0.000361	4.785926	Up	Transient receptor potential cation channel subfamily A member 1
PTGER4	1.871058	7.25E−08	3.81E−06	6.596382	Up	Prostaglandin E receptor 4
GUCY1A2	1.87003	0.002926	0.015117	3.1719	Up	Guanylatecyclase 1 soluble subunit alpha 2
EPHA5	1.869065	0.00017	0.001659	4.153086	Up	EPH receptor A5
F2RL3	1.867425	2.40E−06	5.91E−05	5.507821	Up	F2R-like thrombin or trypsin receptor 3
DOC2B	1.865626	0.003349	0.01673	3.122408	Up	Double C2 domain beta
KCNMB4	1.863178	1.01E−11	4.66E−09	9.475144	Up	Potassium calcium-activated channel subfamily M regulatory beta subunit 4
C1QL1	1.861516	6.16E−07	2.11E−05	5.930949	Up	Complement C1q-like 1
TOX	1.860898	0.008698	0.034956	2.760886	Up	Thymocyte selection-associated high-mobility group box
ADAMTS5	1.858577	2.85E−06	6.74E−05	5.454439	Up	ADAM metallopeptidase with thrombospondin type 1 motif 5
CST4	1.854793	0.000981	0.006477	3.561072	Up	Cystatin S
DENND2A	1.849173	1.49E−05	0.000249	4.936687	Up	DENN domain containing 2A
RSPO3	1.838526	0.003545	0.017522	3.101462	Up	R-spondin 3
WNK2	1.834822	0.004199	0.020035	3.03863	Up	WNK lysine-deficient protein kinase 2
CD163L1	1.832977	0.000434	0.003431	3.840479	Up	CD163 molecule-like 1
MYO7A	1.832212	1.08E−06	3.24E−05	5.755675	Up	Myosin VIIA
LAMB4	1.830346	0.000255	0.002255	4.018242	Up	Laminin subunit beta 4
C1orf115	1.829301	0.001783	0.010279	3.350666	Up	Chromosome 1 open reading frame 115
KRT17	1.826069	0.007054	0.029863	2.842174	Up	Keratin 17
SLCO2A1	1.824825	0.011356	0.042777	2.655589	Up	Solute carrier organic anion transporter family member 2A1
ADGRB3	1.824244	0.011341	0.042738	2.656129	Up	Adhesion G protein-coupled receptor B3
AP1M2	1.81959	8.53E−07	2.67E−05	5.829938	Up	Adaptor-related protein complex 1 subunit mu 2
KRT23	1.815768	0.006914	0.02944	2.849908	Up	Keratin 23
CACNA2D3	1.812351	0.000448	0.003511	3.829647	Up	Calcium voltage-gated channel auxiliary subunit alpha2delta 3
CNNM1	1.81155	2.43E−08	1.69E−06	6.93773	Up	Cyclin and CBS domain divalent metal cation transport mediator 1
MAP2K6	1.806928	2.08E−05	0.00032	4.829723	Up	Mitogen-activated protein kinase kinase 6
ADAMTS1	1.799871	9.71E−05	0.001078	4.33595	Up	ADAM metallopeptidase with thrombospondin type 1 motif 1

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
PDE4B	1.797337	3.32E–05	0.000465	4.681741	Up	Phosphodiesterase 4B
LONRF2	1.796485	0.000406	0.003259	3.862741	Up	LON peptidase N-terminal domain and ring finger 2
PRODH	1.796094	0.000202	0.001894	4.095604	Up	Proline dehydrogenase 1
NES	1.795876	2.81E–08	1.88E–06	6.89227	Up	Nestin
PPM1K-DT	1.790804	0.000253	0.002235	4.021614	Up	PPM1K divergent transcript
SH2D2A	1.784919	0.002087	0.011636	3.294392	Up	SH2 domain containing 2A
FLVCR1-DT	1.76383	2.84E–06	6.72E–05	5.4554	Up	FLVCR1 divergent transcript
IL2RB	1.762693	1.59E–07	6.84E–06	6.351329	Up	Interleukin 2 receptor subunit beta
TH	1.759115	0.000387	0.003149	3.878918	Up	Tyrosine hydroxylase
TMEM119	1.757054	0.000451	0.00353	3.827295	Up	Transmembrane protein 119
IRX6	1.754264	5.32E–05	0.000672	4.530268	Up	Iroquois homeobox 6
PSG9	1.74561	0.000334	0.002807	3.928326	Up	Pregnancy-specific beta-1-glycoprotein 9
GSG1	1.745508	0.000363	0.002994	3.900141	Up	Germ cell associated 1
RIPOR3	1.744933	0.002066	0.011541	3.298045	Up	RIPOR family member 3
PADI2	1.744161	0.008207	0.033553	2.783561	Up	Peptidyl arginine deiminase 2
MUC12	1.743784	1.10E–07	5.12E–06	6.467978	Up	Mucin 12, cell surface associated
CACNA1D	1.742432	9.20E–06	0.000171	5.087788	Up	Calcium voltage-gated channel subunit alpha1 D
LRFN5	1.741517	0.004516	0.021256	3.011478	Up	Leucine-rich repeat and fibronectin type III domain containing 5
MMP8	1.741159	0.000474	0.003672	3.810273	Up	Matrix metallopeptidase 8
KDR	1.735916	0.000728	0.005141	3.663967	Up	Kinase insert domain receptor
SHISA9	1.727647	0.000861	0.005851	3.606041	Up	Shisa family member 9
CNFN	1.725304	8.97E–06	0.000168	5.095699	Up	Cornifelin
TMEM179	1.720603	0.001031	0.006725	3.543782	Up	Transmembrane protein 179
KRT36	1.707213	5.96E–08	3.31E–06	6.657399	Up	Keratin 36
ADRB2	1.707123	0.012557	0.046242	2.615362	Up	Adrenoceptor beta 2
NAP1L3	1.704244	6.36E–06	0.000127	5.203771	Up	Nucleosome assembly protein 1-like 3
ACKR3	1.704237	0.001281	0.00795	3.467756	Up	Atypical chemokine receptor 3
P2RX6	1.701605	6.86E–08	3.64E–06	6.613663	Up	Purinergic receptor P2X 6
RGL3	1.698453	1.70E–07	7.24E–06	6.331144	Up	Ral guanine nucleotide dissociation stimulator-like 3
OLFML2A	1.697944	0.000135	0.001392	4.228681	Up	Olfactomedin-like 2A
CNGA1	1.689869	9.69E–05	0.001077	4.336457	Up	Cyclic nucleotide gated channel subunit alpha 1
ZNF385D	1.68789	0.000248	0.002208	4.027498	Up	Zinc finger protein 385D
CDHR3	1.685844	6.74E–09	6.16E–07	7.342318	Up	Cadherin-related family member 3
GJA3	1.682527	8.54E–05	0.000976	4.377758	Up	Gap junction protein alpha 3
MGAT3	1.682319	2.46E–06	6.00E–05	5.500659	Up	Beta-1,4-mannosyl-glycoprotein 4-beta-N-acetylglucosaminyltransferase
COL21A1	1.680805	0.001948	0.011011	3.319004	Up	Collagen type XXI alpha 1 chain
MSMO1	1.674252	8.37E–10	1.34E–07	8.008722	Up	Methylsterolmonooxygenase 1
ATP6V0D2	1.673953	0.001215	0.007617	3.486263	Up	ATPase H + transporting V0 subunit d2
TNFRSF9	1.672028	1.68E–05	0.000274	4.897474	Up	TNF receptor superfamily member 9
PTPRC	1.670463	0.00115	0.007314	3.505535	Up	Protein tyrosine phosphatase receptor type C
APOBEC3B	1.669855	0.000729	0.005142	3.663748	Up	Apolipoprotein B mRNA editing enzyme catalytic subunit 3B
SEMA3D	1.665302	0.000472	0.003657	3.812069	Up	Semaphorin 3D
ANK1	1.660532	0.000278	0.002421	3.989632	Up	Ankyrin 1
DIRAS2	1.659017	0.012554	0.04624	2.615447	Up	DIRAS family GTPase 2

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
B4GALNT2	1.658134	0.000614	0.004498	3.722662	Up	Beta-1,4-N-acetyl-galactosaminyltransferase 2
CCDC144A	1.657617	0.006513	0.02811	2.872803	Up	Coiled-coil domain containing 144A
ZNF474	1.655783	1.24E−05	0.000215	4.993492	Up	Zinc finger protein 474
MARK1	1.653507	0.000873	0.005913	3.601391	Up	Microtubule affinity regulating kinase 1
PITX1	1.652387	0.003109	0.015818	3.149696	Up	Paired-like homeodomain 1
EYA1	1.650534	0.000544	0.004096	3.763743	Up	EYA transcriptional coactivator and phosphatase 1
TXK	1.639055	1.06E−06	3.18E−05	5.762193	Up	TXK tyrosine kinase
KL	1.638649	0.000243	0.002178	4.034235	Up	Klotho
PCARE	1.635391	0.000312	0.002658	3.951005	Up	Photoreceptor cilium actin regulator
PRECSIT	1.633825	0.002252	0.012361	3.267025	Up	p53-regulated carcinoma-associated Stat3 activating long intergenic non-protein coding transcript
ST8SIA1	1.633014	0.000571	0.004251	3.747217	Up	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 1
PLAU	1.631288	5.97E−07	2.07E−05	5.940868	Up	Plasminogen activator, urokinase
EPHA7	1.62913	0.005243	0.023861	2.955306	Up	EPH receptor A7
ZNF365	1.624049	0.000217	0.002005	4.071338	Up	Zinc finger protein 365
PIK3R3	1.62296	0.001303	0.008059	3.461725	Up	Phosphoinositide−3-kinase regulatory subunit 3
GALNT14	1.618549	0.002579	0.013742	3.21792	Up	Polypeptide N-acetylgalactosaminyltransferase 14
ADGRL4	1.618549	0.000762	0.005307	3.64825	Up	Adhesion G protein-coupled receptor L4
GJB2	1.618325	0.007075	0.029917	2.841034	Up	Gap junction protein beta 2
SYN3	1.618277	0.001316	0.00812	3.458311	Up	Synapsin III
CCDC141	1.614116	0.000716	0.005087	3.669619	Up	Coiled-coil domain containing 141
HECW2	1.612933	0.000636	0.004637	3.710178	Up	HECT, C2 and WW domain containing E3 ubiquitin protein ligase 2
SOX8	1.609757	8.04E−05	0.000927	4.39731	Up	SRY-box transcription factor 8
CCND2	1.609603	5.94E−07	2.06E−05	5.942393	Up	Cyclin D2
ATP1B2	1.609317	3.49E−05	0.00048	4.665774	Up	ATPase Na + /K + transporting subunit beta 2
RTN4R	1.60759	2.91E−09	3.25E−07	7.608653	Up	Reticulon 4 receptor
HMGCS1	1.606762	2.67E−09	3.04E−07	7.636955	Up	3-Hydroxy-3-methylglutaryl-CoA synthase 1
PTGS1	1.601971	2.41E−05	0.000363	4.782843	Up	Prostaglandin-endoperoxide synthase 1
CRABP2	1.599948	3.53E−07	1.33E−05	6.10377	Up	Cellular retinoic acid binding protein 2
KRTAP2-3	1.597381	0.000586	0.004334	3.738465	Up	Keratin-associated protein 2–3
PCOTH	1.596003	0.000192	0.001826	4.11299	Up	Prostate and testis expressed opposite C1QTNF9B and MIPEP
NPIPB2	1.593271	0.003013	0.015455	3.161236	Up	Nuclear pore complex interacting protein family member B2
HECW1	1.58806	0.00442	0.020879	3.019552	Up	HECT, C2 and WW domain containing E3 ubiquitin protein ligase 1
PTPRD	1.587373	2.59E−12	1.59E−09	9.943946	Up	Protein tyrosine phosphatase receptor type D
ZNF114	1.585505	1.17E−06	3.42E−05	5.732094	Up	Zinc finger protein 114
MCTP1	1.58428	0.000679	0.004886	3.688218	Up	Multiple C2 and transmembrane domain containing 1
PCDH9	1.582512	9.60E−07	2.94E−05	5.793167	Up	Protocadherin 9
MASP1	1.58163	0.000666	0.004822	3.694404	Up	MBL-associated serine protease 1
NALF1	1.578515	0.005281	0.024012	2.95261	Up	NALCN channel auxiliary factor 1
TOGARAM2	1.576442	2.67E−07	1.05E−05	6.191049	Up	TOG array regulator of axonemal microtubules 2

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
ST6GALNAC2	1.576212	9.42E−05	0.001053	4.345596	Up	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 2
LNCOG	1.57379	8.65E−06	0.000163	5.106912	Up	lncRNA osteogenesis associated
QPRT	1.572637	1.33E−07	6.02E−06	6.408497	Up	Quinolinate phosphoribosyltransferase
INSIG1	1.570033	3.38E−07	1.29E−05	6.117312	Up	Insulin-induced gene 1
TRIM9	1.56912	0.010349	0.0399	2.692488	Up	Tripartite motif containing 9
BMP8A	1.568731	0.000269	0.002359	4.000743	Up	Bone morphogenetic protein 8a
DYNLT5	1.560446	1.07E−07	5.03E−06	6.475716	Up	Dynein light chain Tctex-type family member 5
SORCS1	1.558679	0.008327	0.033886	2.777893	Up	Sortilin-related VPS10 domain containing receptor 1
IMPA2	1.557806	1.84E−05	0.000292	4.869246	Up	Inositol monophosphatase 2
MACC1-DT	1.554741	0.000276	0.002403	3.992735	Up	MACC1 divergent transcript
CHRM2	1.550458	0.00899	0.035819	2.747955	Up	Cholinergic receptor muscarinic 2
HKDC1	1.549584	6.00E−05	0.000736	4.491685	Up	Hexokinase domain containing 1
EPCAM	1.547502	0.002885	0.014961	3.177114	Up	Epithelial cell adhesion molecule
WNT9A	1.535805	0.00015	0.001506	4.194741	Up	Wnt family member 9A
UCA1	1.535128	0.012638	0.046442	2.612777	Up	Urothelial cancer associated 1
PPM1H	1.532532	0.010359	0.03992	2.692121	Up	Protein phosphatase, Mg2+/Mn2+dependent 1H
PRXL2A	1.531991	0.006859	0.02927	2.852957	Up	Peroxiredoxin-like 2A
KRT37	1.531948	2.39E−05	0.000361	4.786092	Up	Keratin 37
FSIP2	1.531	0.0005	0.003829	3.792398	Up	Fibrous sheath interacting protein 2
TRIM55	1.530497	0.000422	0.003361	3.849581	Up	Tripartite motif containing 55
GRM4	1.529606	7.85E−08	4.01E−06	6.57182	Up	Glutamate metabotropic receptor 4
IRX2	1.527283	0.002829	0.014726	3.184301	Up	Iroquois homeobox 2
SEMA3B	1.523654	1.97E−08	1.42E−06	7.004789	Up	Semaphorin 3B
TSPAN12	1.521905	3.93E−08	2.44E−06	6.787408	Up	Tetraspanin 12
SNTB1	1.519848	7.66E−13	7.58E−10	10.37296	Up	Syntrophin beta 1
BATF2	1.517422	9.31E−05	0.001041	4.349725	Up	Basic leucine zipper ATF-like transcription factor 2
SIGLEC1	1.51605	2.89E−05	0.000416	4.725468	Up	Sialic acid binding Ig-like lectin 1
GCOM1	1.509491	0.002311	0.012631	3.257672	Up	GCOM1, MYZAP-POLR2M combined locus
SLC37A2	1.509308	2.96E−06	6.92E−05	5.442942	Up	Solute carrier family 37 member 2
CLDN23	1.509024	0.003664	0.017942	3.089276	Up	Claudin 23
KRT34	1.506734	0.000158	0.001571	4.176501	Up	Keratin 34
MBOAT1	1.503727	3.60E−06	8.08E−05	5.381682	Up	Membrane-bound O-acyltransferase domain containing 1
UCN2	1.501515	0.001732	0.010056	3.361125	Up	Urocortin 2
CRTAC1	1.501044	0.000227	0.002071	4.056501	Up	Cartilage acidic protein 1
ADGRG6	1.500022	0.000505	0.003859	3.789317	Up	Adhesion G protein-coupled receptor G6
TNFRSF18	1.499245	0.000345	0.00288	3.917721	Up	TNF receptor superfamily member 18
ACAT2	1.498762	5.90E−09	5.48E−07	7.384612	Up	Acetyl-CoA acetyltransferase 2
CYP2J2	1.496024	2.63E−05	0.000389	4.755929	Up	Cytochrome P450 family 2 subfamily J member 2
CLEC14A	1.495564	0.00037	0.003041	3.893644	Up	C-type lectin domain containing 14A
CYP1A1	1.491253	0.00975	0.038182	2.716075	Up	Cytochrome P450 family 1 subfamily A member 1
NEFM	1.490799	0.001644	0.009686	3.379503	Up	Neurofilament medium chain
RUBCNL	1.489824	3.29E−05	0.000462	4.684258	Up	Rubicon-like autophagy enhancer
CDO1	1.486353	7.93E−05	0.000917	4.401608	Up	Cysteine dioxygenase type 1

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
H2AC20	1.485079	0.000107	0.00116	4.304163	Up	H2A clustered histone 20
ASTN2	1.483569	2.17E−09	2.56E−07	7.70268	Up	Astrotactin 2
NTN1	1.479365	0.011399	0.042871	2.654087	Up	Netrin 1
P3H2	1.479255	3.81E−05	0.000512	4.637609	Up	Prolyl 3-hydroxylase 2
FBXW10	1.477472	2.41E−05	0.000362	4.784075	Up	F-box and WD repeat domain containing 10
GRIP2	1.474979	7.91E−07	2.52E−05	5.853548	Up	Glutamate receptor interacting protein 2
ATP1A2	1.473718	0.010376	0.03997	2.691488	Up	ATPase Na + /K + transporting subunit alpha 2
STAC2	1.469529	0.004907	0.022687	2.980292	Up	SH3 and cysteine-rich domain 2
ARPP21	1.46692	0.001824	0.010466	3.342611	Up	cAMP-regulated phosphoprotein 21
PDGFD	1.46332	4.95E−05	0.000633	4.553809	Up	Platelet-derived growth factor D
AFF3	1.461558	0.000108	0.001167	4.301496	Up	ALF transcription elongation factor 3
ADGRG1	1.453238	0.000199	0.001869	4.101306	Up	Adhesion G protein-coupled receptor G1
HS3ST1	1.446114	0.003511	0.017392	3.105029	Up	Heparan sulfate-glucosamine 3-sulfotransferase 1
PNPLA3	1.441511	1.37E−06	3.89E−05	5.681647	Up	Patatin-like phospholipase domain containing 3
TNFRSF19	1.440266	0.002116	0.011764	3.289401	Up	TNF receptor superfamily member 19
CCDC188	1.433143	1.51E−05	0.000251	4.932387	Up	Coiled-coil domain containing 188
CLDN3	1.432576	0.00114	0.00727	3.508451	Up	Claudin 3
MSTN	1.43247	0.000702	0.005005	3.676601	Up	Myostatin
TMC1	1.431978	0.008233	0.033618	2.782322	Up	Transmembrane channel-like 1
CCDC85A	1.427842	0.003586	0.017671	3.097223	Up	Coiled-coil domain containing 85A
VPREB3	1.425686	1.32E−05	0.000226	4.973789	Up	V-set pre-B cell surrogate light chain 3
ERMP1	1.425535	5.89E−08	3.30E−06	6.661374	Up	Endoplasmic reticulum metallopeptidase 1
LEPR	1.418868	0.000184	0.001768	4.126541	Up	Leptin receptor
FADS1	1.418126	9.06E−10	1.37E−07	7.983374	Up	Fatty acid desaturase 1
SDK2	1.416107	0.002872	0.014912	3.178806	Up	Sidekick cell adhesion molecule 2
DMRTA2	1.413035	0.000639	0.004655	3.708625	Up	DMRT-like family A2
CEROX1	1.410648	0.00155	0.009217	3.400537	Up	Cytoplasmic endogenous regulator of oxidative phosphorylation 1
RTKN2	1.409168	0.00655	0.028242	2.870656	Up	Rhotekin 2
CD248	1.408077	4.55E−08	2.72E−06	6.741817	Up	CD248 molecule
IL15	1.40691	0.004192	0.020011	3.039324	Up	Interleukin 15
STK32B	1.406641	0.000785	0.005428	3.63813	Up	Serine/threonine kinase 32B
GSTT2B	1.406073	2.50E−05	0.000374	4.771519	Up	Glutathione S-transferase theta 2B
CPED1	1.403905	1.89E−07	7.85E−06	6.298593	Up	Cadherin-like and PC-esterase domain containing 1
KREMEN1	1.403521	7.96E−07	2.53E−05	5.851322	Up	Kringle containing transmembrane protein 1
CACNA1H	1.402919	0.005026	0.023107	2.971315	Up	Calcium voltage-gated channel subunit alpha1 H
BMP2	1.402331	0.002908	0.015056	3.174247	Up	Bone morphogenetic protein 2
PCDHB15	1.401583	1.31E−07	5.97E−06	6.412115	Up	Protocadherin beta 15
GIMAP2	1.400683	0.000251	0.002227	4.023704	Up	GTPase, IMAP family member 2
GLUD2	1.400362	1.17E−05	0.000206	5.011695	Up	Glutamate dehydrogenase 2
FAM169A	1.399373	4.26E−05	0.000563	4.601522	Up	Family with sequence similarity 169 member A
PCOLCE	1.398122	1.53E−08	1.16E−06	7.084186	Up	Procollagen C-endopeptidase enhancer
LPAR4	1.391463	0.00028	0.002431	3.987885	Up	Lysophosphatidic acid receptor 4
LAMA5	1.390713	1.56E−06	4.30E−05	5.6425	Up	Laminin subunit alpha 5
SYT7	1.389911	0.000605	0.004453	3.727472	Up	Synaptotagmin 7

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
SLC2A8	1.387939	1.41E−05	0.000238	4.953929	Up	Solute carrier family 2 member 8
NTNG1	1.387735	0.005839	0.025811	2.91451	Up	Netrin G1
NELL2	1.387296	0.00387	0.018726	3.069057	Up	Neural EGFL-like 2
TCIM	1.386703	4.85E−05	0.000624	4.560422	Up	Transcriptional and immune response regulator
OGFRL1	1.385353	2.05E−05	0.000317	4.834026	Up	Opioid growth factor receptor-like 1
CRYBG1	1.382787	0.00034	0.002847	3.922792	Up	Crystallin beta-gamma domain containing 1
TAS2R1	1.382739	0.00365	0.017882	3.090739	Up	Taste 2 receptor member 1
ZBTB46	1.380412	6.99E−07	2.31E−05	5.891925	Up	Zinc finger and BTB domain containing 46
PAK3	1.377753	0.003696	0.018063	3.086095	Up	p21 (RAC1) activated kinase 3
KRT19	1.377283	2.40E−05	0.000361	4.785049	Up	Keratin 19
FABP3	1.376442	2.80E−05	0.000408	4.735269	Up	Fatty acid binding protein 3
IDI1	1.37204	3.14E−10	6.40E−08	8.326735	Up	Isopentenyl-diphosphate delta isomerase 1
ROS1	1.371129	0.002688	0.01419	3.202863	Up	ROS proto-oncogene 1, receptor tyrosine kinase
ATRNL1	1.370951	1.82E−05	0.00029	4.871979	Up	Attractin-like 1
MME	1.370733	0.002971	0.0153	3.16643	Up	Membrane metalloendopeptidase
APOE	1.369649	0.006638	0.028528	2.865549	Up	Apolipoprotein E
SFMBT2	1.369082	0.001173	0.007418	3.498669	Up	Scm-like with four mbt domains 2
CUBN	1.367232	5.16E−05	0.000656	4.540303	Up	Cubilin
ACSL5	1.366293	2.81E−08	1.88E−06	6.892859	Up	Acyl-CoA synthetase long chain family member 5
SIPA1L2	1.365666	0.001365	0.008339	3.445393	Up	Signal-induced proliferation associated 1-like 2
PTCH1	1.361587	1.34E−09	1.80E−07	7.857233	Up	Patched 1
OSR2	1.360422	0.005582	0.02499	2.931623	Up	Odd-skipped-related transcription factor 2
ITPKA	1.359673	1.02E−06	3.08E−05	5.775409	Up	Inositol-trisphosphate 3-kinase A
RAB7B	1.359256	1.56E−07	6.74E−06	6.358232	Up	RAB7B, member RAS oncogene family
RBM20	1.353082	0.004207	0.02006	3.037929	Up	RNA binding motif protein 20
CASP1	1.343594	1.22E−05	0.000213	4.999578	Up	Caspase 1
PDE9A	1.341431	0.002844	0.014796	3.182322	Up	Phosphodiesterase 9A
PTPRN2	1.340227	1.74E−05	0.000281	4.887206	Up	Protein tyrosine phosphatase receptor type N2
MGLL	1.33916	9.37E−11	2.50E−08	8.724848	Up	Monoglyceride lipase
EFNB2	1.336805	0.000908	0.006098	3.587838	Up	Ephrin B2
GYPE	1.335653	0.000109	0.001173	4.298897	Up	Glycophorin E (MNS blood group)
STAMBPL1	1.335123	0.000565	0.00422	3.750655	Up	STAM binding protein-like 1
HLA-C	1.331822	9.95E−10	1.47E−07	7.953065	Up	Major histocompatibility complex, class I, C
NID1	1.330925	7.14E−07	2.35E−05	5.885025	Up	Nidogen 1
ABCG2	1.328504	0.000181	0.001743	4.132914	Up	ATP binding cassette subfamily G member 2 (Junior blood group)
XCR1	1.327928	0.003631	0.017807	3.092625	Up	X-C motif chemokine receptor 1
HMGCR	1.327709	6.18E−10	1.05E−07	8.107146	Up	3-Hydroxy-3-methylglutaryl-CoA reductase
ACE	1.32685	2.56E−06	6.17E−05	5.487931	Up	Angiotensin I converting enzyme
GRASLND	1.326126	0.000509	0.003885	3.78638	Up	Glycosaminoglycan regulatory-associated long non-coding RNA
PPFIA2	1.323272	0.001732	0.010057	3.361016	Up	PTPRF interacting protein alpha 2
ENTREP1	1.322912	0.004413	0.020852	3.02012	Up	Endosomal transmembrane epsin interactor 1
RNF17	1.32049	0.01074	0.041023	2.677805	Up	Ring finger protein 17
CORT	1.318854	0.000189	0.0018	4.118604	Up	Cortistatin

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
BFSP1	1.3175	3.77E−12	2.19E−09	9.813358	Up	Beaded filament structural protein 1
PGR	1.317315	0.000265	0.002329	4.005569	Up	Progesterone receptor
RENBP	1.316502	0.000375	0.003067	3.889321	Up	Renin binding protein
WLS	1.313999	7.40E−07	2.40E−05	5.8742	Up	Wnt ligand secretion mediator
RIMS1	1.313761	0.00186	0.010619	3.335646	Up	Regulating synaptic membrane exocytosis 1
KLK3	1.31258	0.006761	0.028959	2.858486	Up	Kallikrein-related peptidase 3
MCOLN2	1.311284	0.004696	0.021935	2.996798	Up	Mucolipin TRP cation channel 2
ST3GAL5	1.310723	1.91E−06	4.98E−05	5.578951	Up	ST3 beta-galactoside alpha-2,3-sialyltransferase 5
STMN2	1.310233	0.008348	0.033934	2.776924	Up	Stathmin 2
ARSL	1.307945	0.000358	0.00296	3.905428	Up	Arylsulfatase L
GREM2	1.306505	0.004675	0.021874	2.99854	Up	Gremlin 2, DAN family BMP antagonist
C1QTNF7	1.304475	0.001677	0.009816	3.37246	Up	C1q and TNF related 7
PTGIS	−5.23674	3.67E−08	2.30E−06	−6.80923	Down	Prostaglandin I2 synthase
SFRP4	−5.07827	6.79E−11	1.84E−08	−8.83175	Down	Secreted frizzled-related protein 4
MFAP5	−4.50412	0.00014	0.001432	−4.21667	Down	Microfibril-associated protein 5
BMP6	−4.46815	1.78E−10	4.45E−08	−8.51213	Down	Bone morphogenetic protein 6
CDH6	−4.39935	1.13E−09	1.60E−07	−7.91281	Down	Cadherin 6
TSPAN2	−4.37263	3.01E−10	6.26E−08	−8.34126	Down	Tetraspanin 2
PDE1C	−4.30317	1.98E−06	5.09E−05	−5.56744	Down	Phosphodiesterase 1C
GPC6	−4.22114	2.48E−10	5.61E−08	−8.40467	Down	Glypican 6
PIEZO2	−4.10461	4.39E−08	2.65E−06	−6.75297	Down	Piezo-type mechanosensitive ion channel component 2
PKP2	−4.02356	3.01E−10	6.26E−08	−8.34141	Down	Plakophilin 2
RARRES1	−3.93563	5.18E−17	5.87E−13	−14.1022	Down	Retinoic acid receptor responder 1
MDFI	−3.75278	2.44E−10	5.58E−08	−8.40984	Down	MyoD family inhibitor
NALCN	−3.73823	2.85E−09	3.22E−07	−7.61577	Down	Sodium leak channel, non−selective
EMB	−3.71037	2.54E−07	1.00E−05	−6.20599	Down	Embigin
PDLIM3	−3.69103	0.00088	0.005951	−3.59883	Down	PDZ and LIM domain 3
MGAM	−3.5935	4.99E−11	1.53E−08	−8.93413	Down	Maltase-glucoamylase
COL11A1	−3.56036	2.26E−06	5.64E−05	−5.52742	Down	Collagen type XI alpha 1 chain
RERG	−3.556	0.000342	0.002863	−3.92067	Down	RAS-like estrogen-regulated growth inhibitor
GDNF	−3.5355	6.42E−11	1.80E−08	−8.85003	Down	Glial cell-derived neurotrophic factor
CHRDL2	−3.51084	2.03E−07	8.40E−06	−6.27594	Down	Chordin-like 2
FOXL1	−3.49556	2.80E−08	1.88E−06	−6.89356	Down	Forkhead box L1
PLPP4	−3.43759	7.45E−18	1.69E−13	−14.9443	Down	Phospholipid phosphatase 4
C5orf46	−3.32884	0.000143	0.001451	−4.2099	Down	Chromosome 5 open reading frame 46
ANXA8	−3.32023	8.43E−12	4.16E−09	−9.53561	Down	Annexin A8
FIBIN	−3.29706	1.84E−09	2.27E−07	−7.75512	Down	Fin bud initiation factor homolog
LMO3	−3.28827	1.01E−05	0.000184	−5.05759	Down	LIM domain only 3
CABLES1	−3.2806	1.65E−10	4.20E−08	−8.53847	Down	Cdk5 and Abl enzyme substrate 1
ITGBL1	−3.26694	1.22E−07	5.60E−06	−6.43497	Down	Integrin subunit beta-like 1
NFASC	−3.25827	4.61E−08	2.74E−06	−6.7377	Down	Neurofascin
FGFR2	−3.25145	6.44E−07	2.19E−05	−5.91735	Down	Fibroblast growth factor receptor 2
ANXA8L1	−3.24754	4.18E−11	1.37E−08	−8.99366	Down	Annexin A8-like 1
KCNJ12	−3.23099	1.52E−09	1.97E−07	−7.81704	Down	Potassium inwardly rectifying channel subfamily J member 12
NPY4R	−3.17277	6.04E−07	2.08E−05	−5.93721	Down	Neuropeptide Y receptor Y4
GALNT12	−3.16958	2.96E−10	6.26E−08	−8.34597	Down	Polypeptide N-acetylgalactosaminyltransferase 12

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
TMEM215	−3.15136	0.000603	0.004439	−3.72871	Down	Transmembrane protein 215
IL33	−3.14699	3.03E−09	3.35E−07	−7.59651	Down	Interleukin 33
GAL3ST3	−3.07934	1.32E−11	5.77E−09	−9.38217	Down	Galactose−3-O-sulfotransferase 3
PLCB4	−3.07703	6.02E−10	1.04E−07	−8.11536	Down	Phospholipase C beta 4
NGF	−3.05568	2.83E−07	1.11E−05	−6.17229	Down	Nerve growth factor
PAPPA2	−3.02516	6.76E−06	0.000134	−5.18461	Down	Pappalysin 2
CD200	−3.00614	7.69E−09	6.92E−07	−7.30053	Down	CD200 molecule
BST2	−2.99884	8.75E−06	0.000165	−5.10331	Down	Bone marrow stromal cell antigen 2
TENM2	−2.99726	7.57E−05	0.000885	−4.41665	Down	Teneurin transmembrane protein 2
ARHGEF4	−2.97645	3.76E−09	3.95E−07	−7.52717	Down	Rho guanine nucleotide exchange factor 4
SEL1L3	−2.97399	3.91E−06	8.64E−05	−5.35617	Down	SEL1L family member 3
TBX18	−2.93338	5.69E−06	0.000116	−5.23831	Down	T-box transcription factor 18
MN1	−2.92877	4.16E−05	0.000552	−4.6095	Down	MN1 proto-oncogene, transcriptional regulator
FAM110C	−2.92689	0.00014	0.00143	−4.21713	Down	Family with sequence similarity 110 member C
HAPLN1	−2.92354	3.12E−06	7.21E−05	−5.42614	Down	Hyaluronan and proteoglycan link protein 1
KIAA1549L	−2.91526	7.15E−07	2.35E−05	−5.88491	Down	KIAA1549-like
GDF6	−2.89617	0.003217	0.016242	−3.13726	Down	Growth differentiation factor 6
NPY4R2	−2.88311	5.68E−07	1.98E−05	−5.95614	Down	Neuropeptide Y receptor Y4-2
FOXC2	−2.85881	5.18E−06	0.000108	−5.26771	Down	Forkhead box C2
ERG	−2.84212	0.000503	0.003853	−3.79014	Down	ETS transcription factor ERG
COMP	−2.84085	0.001248	0.00778	−3.47699	Down	Cartilage oligomeric matrix protein
CECR2	−2.83971	6.76E−08	3.61E−06	−6.61824	Down	CECR2 histone acetyl-lysine reader
FST	−2.83619	3.30E−10	6.56E−08	−8.31108	Down	Follistatin
GOLGA8M	−2.82467	7.78E−09	6.97E−07	−7.29701	Down	Golgin A8 family member M
FMO2	−2.82238	2.18E−07	8.84E−06	−6.25419	Down	Flavin containing dimethylaniline monoxygenase 2
AK4	−2.81954	3.84E−05	0.000516	−4.63504	Down	Adenylate kinase 4
SORBS2	−2.8058	0.000102	0.001116	−4.32079	Down	Sorbin and SH3 domain containing 2
CACNG7	−2.79309	1.93E−06	5.01E−05	−5.5752	Down	Calcium voltage-gated channel auxiliary subunit gamma 7
ZMAT1	−2.78465	3.16E−10	6.40E−08	−8.32498	Down	Zinc finger matrin-type 1
BEND7	−2.77362	2.41E−15	1.36E−11	−12.5293	Down	BEN domain containing 7
TPD52L1	−2.76596	5.49E−06	0.000113	−5.2496	Down	TPD52-like 1
TCF23	−2.75207	0.007372	0.030866	−2.82513	Down	Transcription factor 23
FGF14	−2.74619	1.20E−07	5.53E−06	−6.4404	Down	Fibroblast growth factor 14
ITGA7	−2.73939	1.02E−08	8.46E−07	−7.2129	Down	Integrin subunit alpha 7
PLN	−2.7368	0.000946	0.0063	−3.57356	Down	Phospholamban
EFEMP1	−2.73301	2.81E−06	6.66E−05	−5.45894	Down	EGF containing fibulin extracellular matrix protein 1
GATA6	−2.71505	9.68E−09	8.19E−07	−7.22789	Down	GATA binding protein 6
CXADR	−2.67583	1.39E−06	3.93E−05	−5.67788	Down	CXADR Ig-like cell adhesion molecule
BHLHE41	−2.67205	5.13E−08	2.96E−06	−6.70473	Down	Basic helix-loop-helix family member e41
ACAN	−2.65447	0.00106	0.006881	−3.53408	Down	Aggrecan
MYH1	−2.65008	0.003197	0.016158	−3.1395	Down	Myosin heavy chain 1
LRRN2	−2.6404	0.000231	0.002093	−4.05193	Down	Leucine-rich repeat neuronal 2
CSGALNACT1	−2.63549	6.22E−08	3.40E−06	−6.6444	Down	Chondroitin sulfate N-acetylgalactosaminyltransferase 1
TCF21	−2.63196	0.004002	0.019265	−3.05653	Down	Transcription factor 21

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
CACNG6	−2.62787	2.46E−06	6.00E−05	−5.5005	Down	Calcium voltage-gated channel auxiliary subunit gamma 6
PTGS2	−2.61561	0.000993	0.006533	−3.5567	Down	Prostaglandin-endoperoxide synthase 2
MTSS1	−2.5969	3.28E−08	2.12E−06	−6.84404	Down	MTSS I-BAR domain containing 1
LRRC32	−2.5596	9.10E−12	4.29E−09	−9.50977	Down	Leucine-rich repeat containing 32
APCDD1L	−2.55771	1.78E−06	4.70E−05	−5.6015	Down	APC downregulated 1-like
GDF10	−2.52375	8.52E−06	0.000161	−5.11174	Down	Growth differentiation factor 10
APCDD1L-DT	−2.52144	0.000121	0.00128	−4.26316	Down	APCDD1L divergent transcript
CPNE5	−2.50055	3.14E−05	0.000445	−4.69907	Down	Copine 5
RASSF9	−2.48511	0.000533	0.004036	−3.77084	Down	Ras association domain family member 9
TNFAIP8L3	−2.46545	4.02E−05	0.000537	−4.61998	Down	TNF alpha-induced protein 8-like 3
KCNN3	−2.46136	4.68E−07	1.69E−05	−6.01633	Down	Potassium calcium-activated channel subfamily N member 3
DHRS3	−2.45497	1.30E−08	1.02E−06	−7.13549	Down	Dehydrogenase/reductase 3
HMCN1	−2.44784	3.66E−05	0.000497	−4.64995	Down	Hemicentin 1
DACT1	−2.43049	9.85E−09	8.27E−07	−7.22242	Down	Disheveled binding antagonist of beta catenin 1
SPINT2	−2.42485	6.05E−08	3.33E−06	−6.65307	Down	Serine peptidase inhibitor, Kunitz type 2
NKX3-1	−2.41903	4.50E−10	8.23E−08	−8.20991	Down	NK3 homeobox 1
CMKLR2	−2.41878	2.94E−05	0.000421	−4.72009	Down	Chemerin chemokine-like receptor 2
CHN2	−2.41303	0.00019	0.001815	−4.11517	Down	Chimerin 2
HOXC8	−2.41049	0.001204	0.007561	−3.48945	Down	Homeobox C8
DGAT2	−2.3977	1.91E−06	4.98E−05	−5.57954	Down	Diacylglycerol O-acyltransferase 2
PITX2	−2.38971	0.000544	0.004096	−3.76375	Down	Paired-like homeodomain 2
MEGF6	−2.38799	1.44E−06	4.03E−05	−5.66645	Down	Multiple EGF-like domains 6
TCEAL2	−2.38755	3.09E−06	7.16E−05	−5.42892	Down	Transcription elongation factor A-like 2
SLC2A5	−2.38396	4.28E−05	0.000564	−4.60045	Down	Solute carrier family 2 member 5
AKR1C3	−2.37252	8.03E−05	0.000927	−4.39752	Down	Aldo-ketoreductase family 1 member C3
TNFSF10	−2.36958	0.000237	0.00214	−4.04219	Down	TNF superfamily member 10
SCGB3A2	−2.35953	4.24E−05	0.000561	−4.60308	Down	Secretoglobin family 3A member 2
BDNF	−2.35866	1.27E−09	1.73E−07	−7.87543	Down	Brain-derived neurotrophic factor
KRT7	−2.35066	7.32E−06	0.000142	−5.15962	Down	Keratin 7
ADAMTSL1	−2.34915	0.000201	0.001888	−4.09725	Down	ADAMTS-like 1
RGS4	−2.34753	0.001356	0.008304	−3.44775	Down	Regulator of G protein signaling 4
KCNE4	−2.34479	1.96E−06	5.06E−05	−5.57154	Down	Potassium voltage-gated channel subfamily E regulatory subunit 4
SMIM43	−2.34033	9.83E−07	3.00E−05	−5.78594	Down	Small integral membrane protein 43
SBSPON	−2.33756	1.88E−05	0.000297	−4.86278	Down	Somatomedin B and thrombospondin type 1 domain containing
RAPGEF5	−2.33731	0.000947	0.006305	−3.57308	Down	Rap guanine nucleotide exchange factor 5
NDRG2	−2.33365	3.13E−10	6.40E−08	−8.3278	Down	NDRG family member 2
IGFN1	−2.33352	0.00021	0.001948	−4.0831	Down	Immunoglobulin-like and fibronectin type III domain containing 1
THEM5	−2.31898	2.19E−06	5.50E−05	−5.53726	Down	Thioesterase superfamily member 5
SCG2	−2.31212	0.000444	0.003496	−3.83241	Down	Secretogranin II
MT1F	−2.29146	5.10E−10	9.17E−08	−8.16938	Down	Metallothionein 1F
EPHA3	−2.27945	0.010466	0.040236	−2.68805	Down	EPH receptor A3
PLA2G5	−2.27384	0.001836	0.010509	−3.34033	Down	Phospholipase A2 group V
OLAH	−2.27268	1.47E−05	0.000246	−4.94049	Down	Oleoyl-ACP hydrolase
EYA2	−2.27257	8.10E−05	0.000934	−4.39458	Down	EYA transcriptional coactivator and phosphatase 2

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
GMNC	−2.26975	6.58E−06	0.000131	−5.19309	Down	Geminin coiled-coil domain containing
PCDHA12	−2.26677	1.73E−09	2.19E−07	−7.77547	Down	Protocadherin alpha 12
KCNJ2	−2.26148	1.99E−05	0.00031	−4.84451	Down	Potassium inwardly rectifying channel subfamily J member 2
EVA1A	−2.2484	2.10E−06	5.32E−05	−5.54978	Down	Eva-1 homolog A, regulator of programmed cell death
INHBA	−2.24796	3.67E−09	3.89E−07	−7.53531	Down	Inhibin subunit beta A
ALPL	−2.2474	0.000123	0.001295	−4.25866	Down	Alkaline phosphatase, biomineralization associated
C10orf90	−2.24435	8.67E−08	4.35E−06	−6.5408	Down	Chromosome 10 open reading frame 90
LXN	−2.2373	1.21E−16	9.11E−13	−13.7459	Down	Latexin
MECOM	−2.23059	3.12E−06	7.21E−05	−5.42619	Down	MDS1 and EVI1 complex locus
SGK1	−2.22874	7.04E−14	1.14E−10	−11.2391	Down	Serum/glucocorticoid-regulated kinase 1
CSTA	−2.22764	1.34E−05	0.000228	−4.97019	Down	Cystatin A
ATP10A	−2.20744	4.70E−07	1.69E−05	−6.01505	Down	ATPase phospholipid transporting 10A (putative)
RAP1GAP	−2.20507	4.84E−09	4.73E−07	−7.44742	Down	RAP1 GTPase activating protein
ULBP1	−2.20094	1.57E−06	4.30E−05	−5.64097	Down	UL16 binding protein 1
HOXC9	−2.19532	0.001264	0.007861	−3.47228	Down	Homeobox C9
PLEKHB1	−2.17758	2.38E−07	9.51E−06	−6.22619	Down	Pleckstrin homology domain containing B1
FHIP1A	−2.17607	3.08E−05	0.000437	−4.70586	Down	FHF complex subunit HOOK interacting protein 1A
VEPH1	−2.17448	7.23E−05	0.000852	−4.43137	Down	Ventricular zone expressed PH domain containing 1
PRR15	−2.17303	0.000208	0.001932	−4.08688	Down	Proline-rich 15
SLC2A12	−2.16601	2.10E−08	1.49E−06	−6.98398	Down	Solute carrier family 2 member 12
RGS7BP	−2.16065	0.00015	0.001506	−4.19413	Down	Regulator of G protein signaling 7 binding protein
COL4A4	−2.15631	0.000804	0.005533	−3.63009	Down	Collagen type IV alpha 4 chain
TMEM252	−2.1552	0.001179	0.007441	−3.49684	Down	transmembrane protein 252
TFPI2	−2.15359	3.66E−07	1.37E−05	−6.09249	Down	Tissue factor pathway inhibitor 2
MYH3	−2.14535	7.26E−05	0.000855	−4.43002	Down	Myosin heavy chain 3
DIO3	−2.14233	0.000107	0.001161	−4.30373	Down	Iodothyronine deiodinase 3
DYSF	−2.14228	1.95E−05	0.000304	−4.85115	Down	Dysferlin
EPB41L3	−2.14036	0.013569	0.049032	−2.58408	Down	Erythrocyte membrane protein band 4.1-like 3
TLR3	−2.14034	0.000506	0.003864	−3.78855	Down	Toll-like receptor 3
ANGPTL1	−2.13393	0.005354	0.024253	−2.9474	Down	Angiopoietin-like 1
SPTLC3	−2.13272	0.000242	0.002174	−4.03589	Down	Serine palmitoyltransferase long chain base subunit 3
PPP1R12B	−2.12791	6.22E−09	5.76E−07	−7.3677	Down	Protein phosphatase 1 regulatory subunit 12B
VSTM2L	−2.12654	1.64E−07	7.01E−06	−6.34319	Down	V-set and transmembrane domain containing 2-like
CELF2	−2.12104	8.02E−05	0.000926	−4.39815	Down	CUGBP Elav-like family member 2
MARCHF3	−2.1184	2.49E−07	9.90E−06	−6.21202	Down	Membrane-associated ring-CH-type finger 3
ANGPTL4	−2.11488	1.09E−05	0.000195	−5.03512	Down	Angiopoietin-like 4
SLC1A7	−2.11257	1.46E−07	6.43E−06	−6.37842	Down	Solute carrier family 1 member 7
EPHB2	−2.11095	2.06E−13	2.59E−10	−10.8454	Down	EPH receptor B2
ZBED9	−2.10312	3.24E−12	1.93E−09	−9.86565	Down	Zinc finger BED-type containing 9
FLI1	−2.09763	7.54E−09	6.81E−07	−7.30668	Down	Fli-1 proto-oncogene, ETS transcription factor

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
RASSF5	−2.09562	1.06E−07	5.03E−06	−6.47681	Down	Ras association domain family member 5
THBS1	−2.09173	1.78E−07	7.50E−06	−6.31621	Down	Thrombospondin 1
SLC66A1L	−2.08339	0.00011	0.001177	−4.29665	Down	Solute carrier family 66 member 1-like
GCH1	−2.08255	2.26E−06	5.64E−05	−5.52711	Down	GTP cyclohydrolase 1
MBP	−2.07759	6.50E−07	2.20E−05	−5.91444	Down	Myelin basic protein
PPP1R14A	−2.07597	8.56E−06	0.000162	−5.11027	Down	Protein phosphatase 1 regulatory inhibitor subunit 14A
MFAP3L	−2.0747	1.04E−06	3.12E−05	−5.76892	Down	Microfibril-associated protein 3-like
NXPH4	−2.066	2.63E−05	0.000389	−4.75555	Down	Neurexophilin 4
ID3	−2.06263	1.48E−07	6.45E−06	−6.37456	Down	Inhibitor of DNA binding 3
TNNT2	−2.06055	0.002524	0.013521	−3.22568	Down	Troponin T2, cardiac type
LIMCH1	−2.06017	4.90E−08	2.86E−06	−6.7188	Down	LIM and calponin homology domains 1
NOX4	−2.0487	1.70E−08	1.26E−06	−7.05129	Down	NADPH oxidase 4
CTRB2	−2.0478	4.57E−06	9.78E−05	−5.30672	Down	Chymotrypsinogen B2
CGREF1	−2.04395	0.001147	0.007301	−3.50646	Down	Cell growth regulator with EF-hand domain 1
LHX9	−2.04248	0.00036	0.002971	−3.90358	Down	LIM homeobox 9
S1PR5	−2.02711	1.44E−07	6.36E−06	−6.38316	Down	Sphingosine−1-phosphate receptor 5
NXPH3	−2.02511	1.51E−07	6.55E−06	−6.36811	Down	Neurexophilin 3
CACNG8	−2.02501	1.26E−08	9.95E−07	−7.14593	Down	Calcium voltage-gated channel auxiliary subunit gamma 8
PLA2G4A	−2.02297	0.0054	0.024408	−2.94417	Down	Phospholipase A2 group IVA
SERPINE2	−2.02191	5.41E−05	0.000682	−4.52496	Down	Serpin family E member 2
OR2W3	−2.01915	4.71E−05	0.00061	−4.56978	Down	Olfactory receptor family 2 subfamily W member 3
RAPGEF4	−2.01695	1.31E−07	5.97E−06	−6.41194	Down	Rap guanine nucleotide exchange factor 4
ALDH1B1	−2.01467	2.16E−07	8.79E−06	−6.25731	Down	Aldehyde dehydrogenase 1 family member B1
PRUNE2	−2.00548	7.40E−06	0.000144	−5.15609	Down	Prune homolog 2 with BCH domain
TRH	−1.99889	3.24E−07	1.25E−05	−6.13018	Down	Thyrotropin releasing hormone
TINAGL1	−1.99794	7.06E−07	2.33E−05	−5.88874	Down	Tubulointerstitial nephritis antigen-like 1
SYTL2	−1.99772	6.49E−08	3.51E−06	−6.63095	Down	Synaptotagmin-like 2
ADAP1	−1.9933	1.87E−08	1.37E−06	−7.02063	Down	ArfGAP with dual PH domains 1
SHANK2	−1.98828	2.21E−07	8.96E−06	−6.24956	Down	SH3 and multiple ankyrin repeat domains 2
IGSF9	−1.98524	3.33E−05	0.000466	−4.68027	Down	Immunoglobulin superfamily member 9
PI16	−1.98436	0.000958	0.00636	−3.56934	Down	Peptidase inhibitor 16
TLR1	−1.9714	1.04E−06	3.12E−05	−5.7691	Down	Toll-like receptor 1
STXBP6	−1.97135	0.000136	0.001404	−4.22513	Down	Syntaxin binding protein 6
CRLF1	−1.96167	0.002322	0.012654	−3.25588	Down	Cytokine receptor-like factor 1
EN1	−1.94422	0.005523	0.024788	−2.93568	Down	Engrailed homeobox 1
RSPO1	−1.94117	0.007895	0.032555	−2.79861	Down	R-spondin 1
PCSK1	−1.93847	0.012658	0.04649	−2.61212	Down	Proprotein convertase subtilisin/kexin type 1
CALB2	−1.93536	0.00306	0.015621	−3.15552	Down	Calbindin 2
TGFBI	−1.93292	8.67E−13	7.58E−10	−10.3288	Down	Transforming growth factor beta-induced
IGF2BP1	−1.93152	0.00046	0.003586	−3.82035	Down	Insulin-like growth factor 2 mRNA binding protein 1
SALL4	−1.92736	9.28E−05	0.001039	−4.35048	Down	Spalt-like transcription factor 4
EYA4	−1.91854	0.000274	0.002389	−3.99513	Down	EYA transcriptional coactivator and phosphatase 4
KLHL4	−1.91835	0.012076	0.044816	−2.63101	Down	Kelch-like family member 4
KRT18	−1.91099	2.60E−08	1.79E−06	−6.91712	Down	Keratin 18

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
ITGB1BP2	−1.90746	0.004274	0.020316	−3.03203	Down	Integrin subunit beta 1 binding protein 2
CCDC80	−1.90172	3.46E−07	1.31E−05	−6.10983	Down	Coiled-coil domain containing 80
DAPK1	−1.89532	0.000177	0.001711	−4.13957	Down	Death-associated protein kinase 1
WNK4	−1.89353	9.28E−08	4.56E−06	−6.51956	Down	WNK lysine deficient protein kinase 4
KRT13	−1.89249	0.008927	0.03562	−2.7507	Down	Keratin 13
DLX5	−1.89124	0.001255	0.007816	−3.47494	Down	Distal-less homeobox 5
FMO3	−1.88354	9.88E−05	0.001093	−4.33029	Down	Flavin containing dimethylaniline monoxygenase 3
VLDLR	−1.87827	2.11E−09	2.51E−07	−7.71161	Down	Very low density lipoprotein receptor
VDR	−1.87723	7.82E−07	2.51E−05	−5.85697	Down	Vitamin D receptor
GPC4	−1.86856	1.06E−07	5.02E−06	−6.47928	Down	Glypican 4
FAM20A	−1.86013	9.50E−08	4.63E−06	−6.51229	Down	FAM20A golgi-associated secretory pathway pseudokinase
FOXS1	−1.85885	0.002611	0.013865	−3.21349	Down	Forkhead box S1
LZTS1	−1.85517	1.62E−05	0.000265	−4.90959	Down	Leucine zipper tumor suppressor 1
RARB	−1.85254	6.68E−08	3.57E−06	−6.62213	Down	Retinoic acid receptor beta
KISS1	−1.85075	0.008338	0.033908	−2.77737	Down	KiSS-1 metastasis suppressor
GEM	−1.85038	4.00E−10	7.44E−08	−8.24801	Down	GTP binding protein overexpressed in skeletal muscle
FZD7	−1.84689	4.94E−05	0.000632	−4.55449	Down	Frizzled class receptor 7
HOXB6	−1.8464	0.000111	0.00119	−4.29191	Down	Homeobox B6
PTPRN	−1.84327	1.64E−05	0.000268	−4.90588	Down	Protein tyrosine phosphatase receptor type N
ZFHX2	−1.84083	1.18E−08	9.47E−07	−7.16493	Down	Zinc finger homeobox 2
CELSR2	−1.83846	1.08E−08	8.88E−07	−7.1931	Down	Cadherin EGF LAG seven-pass G-type receptor 2
OR51E2	−1.83269	0.000424	0.003368	−3.84843	Down	Olfactory receptor family 51 subfamily E member 2
OMG	−1.82461	0.00021	0.00195	−4.0825	Down	Oligodendrocyte myelin glycoprotein
TLCD4	−1.8233	1.34E−07	6.05E−06	−6.40593	Down	TLC domain containing 4
EPHA4	−1.81892	4.29E−06	9.30E−05	−5.32687	Down	EPH receptor A4
EN2	−1.81816	1.65E−06	4.45E−05	−5.62445	Down	Engrailed homeobox 2
LRRC38	−1.81694	0.003933	0.01899	−3.06297	Down	Leucine-rich repeat containing 38
PODN	−1.81065	3.33E−06	7.59E−05	−5.4062	Down	Podocan
SCN4B	−1.80981	1.91E−06	4.98E−05	−5.57981	Down	Sodium voltage-gated channel beta subunit 4
FMO1	−1.80856	0.001182	0.007455	−3.49585	Down	Flavin containing dimethylaniline monoxygenase 1
DAW1	−1.80436	2.04E−05	0.000316	−4.83563	Down	Dynein assembly factor with WD repeats 1
SORCS2	−1.80129	0.00011	0.001185	−4.29419	Down	Sortilin-related VPS10 domain containing receptor 2
CDH8	−1.798	0.000148	0.001495	−4.19805	Down	Cadherin 8
ENC1	−1.78484	8.51E−07	2.67E−05	−5.83061	Down	Ectodermal-neural cortex 1
IFNE	−1.78476	9.46E−07	2.90E−05	−5.79788	Down	Interferon epsilon
TNNT1	−1.78213	1.64E−05	0.000268	−4.90515	Down	Troponin T1, slow skeletal type
ANKRD1	−1.7785	0.000493	0.003783	−3.79748	Down	Ankyrin repeat domain 1
TBILA	−1.77649	9.15E−06	0.00017	−5.08928	Down	TGF-beta-induced lncRNA
SGCA	−1.77282	0.009194	0.036483	−2.73918	Down	Sarcoglycan alpha
ZFPM2	−1.76616	1.92E−08	1.39E−06	−7.01159	Down	Zinc finger protein, FOG family member 2
SOX9	−1.76309	0.000564	0.004211	−3.75153	Down	SRY-box transcription factor 9
SLC22A23	−1.76019	1.74E−08	1.29E−06	−7.04295	Down	Solute carrier family 22 member 23
MGP	−1.75918	1.22E−05	0.000213	−5.00007	Down	Matrix Gla protein

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
SULF1	−1.75807	4.24E−06	9.22E−05	−5.3303	Down	Sulfatase 1
IL20RA	−1.75316	0.006167	0.02697	−2.8937	Down	Interleukin 20 receptor subunit alpha
PIPOX	−1.75171	1.39E−09	1.85E−07	−7.84567	Down	Pipecolic acid and sarcosine oxidase
DEPP1	−1.75008	0.000166	0.001626	−4.16145	Down	DEPP autophagy regulator 1
CYP24A1	−1.74299	9.00E−06	0.000169	−5.09464	Down	Cytochrome P450 family 24 subfamily A member 1
BACH2	−1.73896	4.49E−08	2.70E−06	−6.74624	Down	BTB domain and CNC homolog 2
DNAH11	−1.73836	5.56E−06	0.000114	−5.24577	Down	Dynein axonemal heavy chain 11
PKIA	−1.7378	6.72E−07	2.25E−05	−5.90405	Down	cAMP-dependent protein kinase inhibitor alpha
ID2	−1.73319	5.43E−09	5.12E−07	−7.41108	Down	Inhibitor of DNA binding 2
MCTP2	−1.73276	0.011965	0.044491	−2.63472	Down	Multiple C2 and transmembrane domain containing 2
WSCD1	−1.72857	2.68E−05	0.000395	−4.74914	Down	WSC domain containing 1
STEAP1B	−1.72452	1.39E−06	3.93E−05	−5.67797	Down	STEAP family member 1B
TLR2	−1.72425	2.42E−06	5.95E−05	−5.50499	Down	Toll-like receptor 2
ARHGEF37	−1.7203	8.61E−09	7.56E−07	−7.26502	Down	Rho guanine nucleotide exchange factor 37
IL6	−1.71293	0.002096	0.011676	−3.29281	Down	Interleukin 6
KLHL23	−1.70426	2.22E−09	2.61E−07	−7.69491	Down	Kelch-like family member 23
NPPB	−1.70388	0.004912	0.022698	−2.97995	Down	Natriuretic peptide B
DIO3OS	−1.70365	2.75E−05	0.000402	−4.74205	Down	DIO3 opposite strand upstream RNA
OVCH2	−1.70131	0.000263	0.002311	−4.00871	Down	Ovochymase 2
FRMD5	−1.69745	1.82E−09	2.25E−07	−7.75951	Down	FERM domain containing 5
SPINK1	−1.6942	0.000938	0.006255	−3.57646	Down	Serine peptidase inhibitor Kazal type 1
GAS6	−1.69335	8.35E−07	2.63E−05	−5.83652	Down	Growth arrest specific 6
GPC3	−1.69025	0.008756	0.035122	−2.75827	Down	Glypican 3
NTRK3	−1.688	3.78E−05	0.000508	−4.64039	Down	Neurotrophic receptor tyrosine kinase 3
SLC6A15	−1.68799	0.001765	0.010206	−3.35421	Down	Solute carrier family 6 member 15
FBXO32	−1.68771	1.37E−07	6.12E−06	−6.39812	Down	F-box protein 32
CCNA1	−1.68516	0.000112	0.001194	−4.29037	Down	Cyclin A1
AMIGO2	−1.68485	2.17E−05	0.000332	−4.81716	Down	Adhesion molecule with Ig-like domain 2
F11R	−1.68051	0.000754	0.005261	−3.65216	Down	F11 receptor
HPGDS	−1.67767	0.000369	0.003033	−3.89491	Down	Hematopoietic prostaglandin D synthase
MPP2	−1.67247	3.88E−05	0.000521	−4.63125	Down	MAGUK p55 scaffold protein 2
RAB11FIP1	−1.66972	3.72E−11	1.28E−08	−9.03219	Down	RAB11 family interacting protein 1
SIGLEC15	−1.66662	0.010585	0.040571	−2.68356	Down	Sialic acid binding Ig-like lectin 15
LNCSRLR	−1.66631	6.95E−05	0.000829	−4.44413	Down	lncRNA sorafenib resistance in renal cell carcinoma associated
FOXD1	−1.66456	0.000243	0.002178	−4.03439	Down	Forkhead box D1
CCNO	−1.6641	1.93E−05	0.000302	−4.85415	Down	Cyclin O
ADAM12	−1.65893	8.34E−09	7.36E−07	−7.27483	Down	ADAM metallopeptidase domain 12
BISPR	−1.65887	1.88E−05	0.000297	−4.86248	Down	BST2 interferon stimulated positive regulator
BEGAIN	−1.65732	0.004062	0.019486	−3.05102	Down	Brain-enriched guanylate kinase associated
RASSF2	−1.65325	0.009	0.035841	−2.74754	Down	Ras association domain family member 2
CCDC110	−1.65218	0.0077	0.031935	−2.80834	Down	Coiled-coil domain containing 110
CTRB1	−1.64621	0.001089	0.007023	−3.52466	Down	Chymotrypsinogen B1
ALDH8A1	−1.64599	4.97E−05	0.000635	−4.55206	Down	Aldehyde dehydrogenase 8 family member A1
LGALS2	−1.64481	2.30E−07	9.25E−06	−6.23679	Down	Galectin 2
SEL1L2	−1.63989	0.005162	0.023628	−2.96122	Down	SEL1L2 adaptor subunit of ERAD E3 ligase
HAS3	−1.63832	0.000108	0.001167	−4.30132	Down	Hyaluronan synthase 3

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
NCAM1	−1.63777	0.002841	0.014783	−3.18274	Down	Neural cell adhesion molecule 1
LGI2	−1.62905	0.00797	0.032818	−2.79492	Down	Leucine-rich repeat LGI family member 2
ABCA9	−1.62869	0.000622	0.004553	−3.71794	Down	ATP binding cassette subfamily A member 9
CALHM5	−1.62299	6.38E−08	3.47E−06	−6.63653	Down	Calcium homeostasis modulator family member 5
MYOC	−1.62137	0.004188	0.019999	−3.03963	Down	Myocilin
ZFHX4	−1.61935	1.93E−06	5.01E−05	−5.57544	Down	Zinc finger homeobox 4
PPFIA4	−1.61786	8.60E−06	0.000162	−5.10896	Down	PTPRF interacting protein alpha 4
HAS1	−1.61211	0.002204	0.012145	−3.27468	Down	Hyaluronan synthase 1
GCSAM	−1.60977	0.000286	0.002475	−3.9807	Down	Germinal center-associated signaling and motility
HOXB7	−1.60906	0.000289	0.002504	−3.97632	Down	Homeobox B7
GALNT9	−1.60616	0.000323	0.002731	−3.93973	Down	Polypeptide N-acetylgalactosaminyltransferase 9
DUSP2	−1.60389	0.000427	0.003391	−3.84547	Down	Dual specificity phosphatase 2
USP2	−1.60125	6.08E−08	3.33E−06	−6.65132	Down	Ubiquitin specific peptidase 2
RAB3IP	−1.60019	8.70E−13	7.58E−10	−10.3278	Down	RAB3A interacting protein
ABCA10	−1.59931	0.000167	0.001636	−4.15891	Down	ATP binding cassette subfamily A member 10
KLF2	−1.59915	0.000152	0.001521	−4.19038	Down	KLF transcription factor 2
SIK1	−1.59191	0.004429	0.020911	−3.01874	Down	Salt inducible kinase 1
EEF1A2	−1.58379	0.004251	0.020235	−3.03407	Down	Eukaryotic translation elongation factor 1 alpha 2
OR2A7	−1.58343	6.96E−06	0.000137	−5.17537	Down	Olfactory receptor family 2 subfamily A member 7
SIX1	−1.58277	7.30E−06	0.000142	−5.16045	Down	SIX homeobox 1
FGF7	−1.57915	5.70E−10	1.01E−07	−8.13309	Down	Fibroblast growth factor 7
ESYT3	−1.5739	2.49E−05	0.000373	−4.77272	Down	Extended synaptotagmin 3
CCN2	−1.56954	4.32E−06	9.33E−05	−5.32471	Down	Cellular communication network factor 2
JCAD	−1.56924	3.80E−09	3.97E−07	−7.5239	Down	Junctional cadherin 5 associated
MAP3K9	−1.56819	9.01E−06	0.000169	−5.09419	Down	Mitogen-activated protein kinase kinase kinase 9
SUPT20HL1	−1.56464	0.000373	0.003056	−3.89128	Down	SUPT20H-like 1
MYOZ3	−1.56364	0.000805	0.005542	−3.62926	Down	Myozenin 3
SMIM10L2A	−1.56314	0.000163	0.001606	−4.16698	Down	Small integral membrane protein 10-like 2A
ABCA8	−1.55861	0.001604	0.009481	−3.3883	Down	ATP binding cassette subfamily A member 8
EXPH5	−1.55444	5.56E−05	0.000697	−4.51595	Down	Exophilin 5
DAB1	−1.55404	0.003521	0.017423	−3.10397	Down	DAB adaptor protein 1
PKDCC	−1.55391	7.68E−06	0.000148	−5.14443	Down	Protein kinase domain containing, cytoplasmic
PLPPR3	−1.54125	0.004043	0.019408	−3.05277	Down	Phospholipid phosphatase related 3
MYH10	−1.53969	8.54E−07	2.67E−05	−5.82944	Down	Myosin heavy chain 10
FRMPD4	−1.53684	8.55E−05	0.000977	−4.37704	Down	FERM and PDZ domain containing 4
IGFBP3	−1.53514	5.73E−05	0.000709	−4.50655	Down	Insulin-like growth factor binding protein 3
FANK1	−1.52718	8.24E−09	7.29E−07	−7.27887	Down	Fibronectin type III and ankyrin repeat domains 1
IFITM10	−1.52693	9.56E−09	8.12E−07	−7.23185	Down	Interferon-induced transmembrane protein 10
MPP7	−1.52412	2.20E−05	0.000336	−4.81221	Down	MAGUK p55 scaffold protein 7
PLXDC2	−1.52327	0.002033	0.0114	−3.30371	Down	Plexin domain containing 2
GRAMD1B	−1.51361	1.09E−14	2.25E−11	−11.9416	Down	GRAM domain containing 1B
ARHGDIG	−1.50611	0.004765	0.022182	−2.99136	Down	Rho GDP dissociation inhibitor gamma

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
TRIM63	−1.50548	0.002381	0.012902	−3.24686	Down	Tripartite motif containing 63
SLC4A4	−1.50352	3.21E−08	2.09E−06	−6.85153	Down	Solute carrier family 4 member 4
SH3RF2	−1.50251	0.011665	0.043547	−2.64489	Down	SH3 domain containing ring finger 2
HRNR	−1.49315	0.001072	0.006929	−3.53015	Down	Hornerin
SLC9C1	−1.49104	5.78E−06	0.000117	−5.23371	Down	Solute carrier family 9 member C1
HUNK	−1.48709	1.56E−05	0.000258	−4.92035	Down	Hormonally up-regulated Neu-associated kinase
CYRIA	−1.48637	0.003429	0.017064	−3.11375	Down	CYFIP-related Rac1 interactor A
LYVE1	−1.48603	4.33E−05	0.00057	−4.59653	Down	Lymphatic vessel endothelial hyaluronan receptor 1
TMEM38A	−1.48316	4.11E−09	4.20E−07	−7.49924	Down	Transmembrane protein 38A
BEND5	−1.48116	0.00269	0.014195	−3.20264	Down	BEN domain containing 5
SLAIN1	−1.48056	0.000233	0.002111	−4.04819	Down	SLAIN motif family member 1
PRKD1	−1.47989	2.42E−09	2.82E−07	−7.66775	Down	Protein kinase D1
CYP3A7	−1.47698	0.002711	0.01429	−3.19973	Down	Cytochrome P450 family 3 subfamily A member 7
TTC9	−1.4755	0.000904	0.006079	−3.58943	Down	Tetratricopeptide repeat domain 9
CHL1	−1.47355	0.003068	0.015656	−3.15461	Down	Cell adhesion molecule L1-like
CILP2	−1.47199	0.000823	0.005642	−3.62168	Down	Cartilage intermediate layer protein 2
KCNG2	−1.46863	0.002174	0.012006	−3.27964	Down	Potassium voltage-gated channel modifier subfamily G member 2
PLD5	−1.46805	0.000466	0.003624	−3.81645	Down	Phospholipase D family member 5
BGN	−1.46712	0.000467	0.00363	−3.81575	Down	Biglycan
SLC35F2	−1.4638	8.63E−10	1.34E−07	−7.99901	Down	Solute carrier family 35 member F2
EPPK1	−1.46283	0.010978	0.041646	−2.66907	Down	Epiplakin 1
SIRPB1	−1.4611	0.000175	0.001699	−4.1432	Down	Signal regulatory protein beta 1
EDA	−1.46025	0.003186	0.016118	−3.14073	Down	Ectodysplasin A
MYEF2	−1.45681	4.38E−07	1.60E−05	−6.03714	Down	Myelin expression factor 2
STEAP2	−1.4563	0.000201	0.001889	−4.09682	Down	STEAP2 metalloreductase
PARP15	−1.45533	5.85E−05	0.000721	−4.50001	Down	Poly(ADP-ribose) polymerase family member 15
ACTBL2	−1.45475	0.003908	0.018897	−3.06536	Down	Actin beta-like 2
CPEB1	−1.45421	4.20E−06	9.13E−05	−5.33383	Down	Cytoplasmic polyadenylation element binding protein 1
NTRK2	−1.45301	0.00721	0.030366	−2.83373	Down	Neurotrophic receptor tyrosine kinase 2
SYT15	−1.45278	4.46E−06	9.58E−05	−5.31449	Down	Synaptotagmin 15
HSD17B6	−1.45106	2.74E−05	0.000402	−4.74239	Down	Hydroxysteroid 17-beta dehydrogenase 6
FPR3	−1.45054	0.013294	0.048282	−2.59237	Down	Formyl peptide receptor 3
SLIT2	−1.44843	0.000778	0.005397	−3.64129	Down	Slit guidance ligand 2
IRX3	−1.448	0.008462	0.034258	−2.77161	Down	Iroquois homeobox 3
MPO	−1.44767	9.22E−06	0.000171	−5.08704	Down	Myeloperoxidase
MANEA-DT	−1.44692	7.82E−06	0.00015	−5.13889	Down	MANEA divergent transcript
COL8A2	−1.44373	0.000319	0.002698	−3.94428	Down	Collagen type VIII alpha 2 chain
ACTC1	−1.44263	0.001093	0.007041	−3.52346	Down	Actin alpha cardiac muscle 1
FLG	−1.43718	2.18E−05	0.000333	−4.81474	Down	Filaggrin
HEG1	−1.43712	9.45E−08	4.62E−06	−6.51394	Down	Heart development protein with EGF-like domains 1
NRP2	−1.43679	1.83E−11	7.17E−09	−9.27083	Down	Neuropilin 2
B3GALT5	−1.43583	0.007636	0.031726	−2.81152	Down	Beta-1,3-galactosyltransferase 5
NNMT	−1.42889	2.33E−11	8.81E−09	−9.18978	Down	Nicotinamide N-methyltransferase
CHI3L1	−1.42851	0.002587	0.013767	−3.21683	Down	Chitinase 3-like 1

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
TNIK	−1.42153	2.61E−05	0.000387	−4.75795	Down	TRAF2 and NCK interacting kinase
LMCD1	−1.42114	0.000221	0.002026	−4.06669	Down	LIM and cysteine-rich domains 1
RHD	−1.41493	0.004381	0.020742	−3.02287	Down	Rh blood group D antigen
STEAP1	−1.41	3.84E−06	8.53E−05	−5.36171	Down	STEAP family member 1
SP6	−1.40925	0.000606	0.004456	−3.72701	Down	Sp6 transcription factor
EXTL1	−1.40841	9.26E−05	0.001038	−4.35128	Down	Exostosin-like glycosyltransferase 1
RUNX1	−1.40441	1.85E−07	7.71E−06	−6.30475	Down	RUNX family transcription factor 1
NFIB	−1.40425	1.88E−06	4.94E−05	−5.5835	Down	Nuclear factor I B
APLN	−1.39953	0.010642	0.04075	−2.68144	Down	Apelin
ANKRD29	−1.39607	7.42E−07	2.40E−05	−5.87325	Down	Ankyrin repeat domain 29
SORBS1	−1.39462	0.001393	0.008472	−3.43827	Down	Sorbin and SH3 domain containing 1
EPB41	−1.39438	4.81E−07	1.72E−05	−6.00756	Down	Erythrocyte membrane protein band 4.1
GZMM	−1.38989	0.000363	0.002991	−3.90077	Down	Granzyme M
PDGFRL	−1.38791	2.18E−05	0.000333	−4.81524	Down	Platelet-derived growth factor receptor-like
ART4	−1.38626	0.001104	0.007088	−3.51966	Down	ADP-ribosyltransferase 4 (inactive) (Dombrock blood group)
ACKR2	−1.38274	0.006722	0.028841	−2.86071	Down	Atypical chemokine receptor 2
MGST1	−1.37937	2.58E−05	0.000384	−4.76127	Down	Microsomal glutathione S-transferase 1
FAM180A	−1.37911	1.42E−05	0.00024	−4.95043	Down	Family with sequence similarity 180 member A
FPR1	−1.3785	2.49E−06	6.07E−05	−5.49678	Down	Formyl peptide receptor 1
STOX2	−1.37795	0.000718	0.005098	−3.66866	Down	Storkhead box 2
ST3GAL6	−1.37756	9.44E−09	8.10E−07	−7.23598	Down	ST3 beta-galactoside alpha-2,3-sialyltransferase 6
PLP1	−1.37284	0.000225	0.002056	−4.05966	Down	Proteolipid protein 1
MYOM2	−1.37149	0.00055	0.004123	−3.76021	Down	Myomesin 2
NBPF14	−1.36956	7.92E−15	2.24E−11	−12.0651	Down	NBPF member 14
NAV2	−1.36928	5.56E−11	1.66E−08	−8.8983	Down	Neuron navigator 2
PDE7B	−1.36867	8.42E−07	2.65E−05	−5.8338	Down	Phosphodiesterase 7B
INSYN2A	−1.36767	4.47E−05	0.000583	−4.58645	Down	Inhibitory synaptic factor 2A
MYOZ1	−1.36713	0.000202	0.001894	−4.09555	Down	Myozenin 1
PMEL	−1.36522	0.006691	0.028726	−2.86246	Down	Premelanosome protein
SLC35F4	−1.3639	0.000534	0.004042	−3.76997	Down	Solute carrier family 35 member F4
COL4A3	−1.36303	0.007824	0.032335	−2.80209	Down	Collagen type IV alpha 3 chain
GAS6-DT	−1.36132	1.02E−05	0.000185	−5.05604	Down	GAS6 divergent transcript
KCNQ4	−1.36021	2.07E−06	5.26E−05	−5.55373	Down	Potassium voltage-gated channel subfamily Q member 4
SSPN	−1.35519	1.41E−06	3.95E−05	−5.67467	Down	Sarcospan
PPP1R13L	−1.35489	4.31E−05	0.000568	−4.59787	Down	Protein phosphatase 1 regulatory subunit 13-like
SEMA3C	−1.35338	1.20E−05	0.00021	−5.004	Down	Semaphorin 3C
BMAL2	−1.35187	1.74E−05	0.000281	−4.88662	Down	Basic helix-loop-helix ARNT-like 2
ZNF334	−1.35102	1.77E−09	2.22E−07	−7.76728	Down	Zinc finger protein 334
SLFNL1	−1.34826	1.10E−05	0.000197	−5.03039	Down	Schlafen-like 1
FNDC1	−1.34778	0.003748	0.018272	−3.08084	Down	Fibronectin type III domain containing 1
DCLK2	−1.34715	1.44E−08	1.11E−06	−7.10315	Down	Doublecortin-like kinase 2
NOTCH2	−1.34466	1.59E−12	1.10E−09	−10.1137	Down	Notch receptor 2
DSE	−1.34245	5.19E−13	5.71E−10	−10.5116	Down	Dermatan sulfate epimerase
ZNF185	−1.33924	1.72E−09	2.18E−07	−7.77811	Down	Zinc finger protein 185 with LIM domain
IQSEC3	−1.33771	1.44E−07	6.36E−06	−6.38305	Down	IQ motif and Sec7 domain ArfGEF 3
P4HA3	−1.33558	0.00265	0.014033	−3.20809	Down	Prolyl 4-hydroxylase subunit alpha 3

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
JPH3	−1.33528	0.000135	0.001393	−4.22789	Down	Junctophilin 3
SLC38A3	−1.33466	0.000348	0.002899	−3.91474	Down	Solute carrier family 38 member 3
PTGDR	−1.33221	0.005916	0.026081	−2.90954	Down	Prostaglandin D2 receptor
TMEM255A	−1.33178	0.002105	0.011716	−3.29122	Down	Transmembrane protein 255A
PALM2AKAP2	−1.33037	0.000609	0.004471	−3.72537	Down	PALM2 and AKAP2 fusion
SEC14L6	−1.32791	0.005769	0.02558	−2.91909	Down	SEC14-like lipid binding 6
PDK4	−1.32376	0.009379	0.037081	−2.73135	Down	Pyruvate dehydrogenase kinase 4
PITPNM3	−1.32314	2.40E−06	5.91E−05	−5.50838	Down	PITPNM family member 3
GNG7	−1.32272	0.001096	0.007055	−3.52242	Down	G protein subunit gamma 7
PGF	−1.32205	0.003132	0.015905	−3.1471	Down	Placental growth factor
THBS2	−1.31978	2.70E−05	0.000396	−4.74785	Down	Thrombospondin 2
DBNDD1	−1.31563	0.000102	0.001117	−4.32009	Down	Dysbindin domain containing 1
GPR143	−1.31545	6.83E−07	2.27E−05	−5.8991	Down	G protein-coupled receptor 143
GSTO2	−1.31528	1.57E−08	1.18E−06	−7.07604	Down	Glutathione S-transferase omega 2
LRRC2	−1.31492	4.15E−06	9.08E−05	−5.33705	Down	Leucine-rich repeat containing 2
DNAH6	−1.31229	0.001233	0.007709	−3.4811	Down	Dynein axonemal heavy chain 6
ANK3	−1.30956	0.001305	0.008066	−3.46113	Down	Ankyrin 3
DES	−1.30838	0.005578	0.024982	−2.93188	Down	Desmin
KRT86	−1.30784	0.001565	0.009285	−3.39716	Down	Keratin 86
PDLIM5	−1.30783	2.97E−09	3.30E−07	−7.60251	Down	PDZ and LIM domain 5
PRDM6	−1.30782	0.000118	0.001252	−4.27173	Down	PR/SET domain 6
RPS6KA2-IT1	−1.30648	0.002511	0.013464	−3.22766	Down	RPS6KA2 intronic transcript 1
IGFBPL1	−1.30493	0.000887	0.005985	−3.59605	Down	Insulin-like growth factor binding protein-like 1
TRABD2A	−1.30183	0.008619	0.034725	−2.76445	Down	TraB domain containing 2A
HTR6	−1.30181	0.000196	0.001852	−4.10637	Down	5-Hydroxytryptamine receptor 6
NAV1	−1.30062	2.60E−14	4.67E−11	−11.6111	Down	Neuron navigator 1
HSPB7	−1.29905	0.000499	0.003828	−3.79288	Down	Heat shock protein family B (small) member 7
NPAS1	−1.29461	0.000511	0.003897	−3.78524	Down	Neuronal PAS domain protein 1
PNPLA1	−1.29452	0.001027	0.006704	−3.54508	Down	Patatin-like phospholipase domain containing 1
NFIX	−1.29301	1.81E−07	7.57E−06	−6.31162	Down	Nuclear factor I X
PIK3AP1	−1.29075	0.002458	0.013241	−3.23532	Down	Phosphoinositide−3-kinase adaptor protein 1
NRG1	−1.28956	0.001135	0.007242	−3.51	Down	Neuregulin 1
DMRT2	−1.2883	0.001355	0.008303	−3.44799	Down	Doublesex and mab-3-related transcription factor 2
CCDC71L	−1.28655	1.36E−05	0.000232	−4.96414	Down	Coiled-coil domain containing 71-like
LIF	−1.28585	0.001024	0.006695	−3.54602	Down	LIF interleukin 6 family cytokine
MCUB	−1.28452	9.52E−09	8.12E−07	−7.23327	Down	Mitochondrial calcium uniporter dominant negative subunit beta
ADH1C	−1.28217	0.005486	0.024689	−2.93817	Down	Alcohol dehydrogenase 1C (class I), gamma polypeptide
SLC16A11	−1.28094	0.001365	0.008339	−3.44544	Down	Solute carrier family 16 member 11
SIRPA	−1.28048	5.30E−09	5.06E−07	−7.41881	Down	Signal regulatory protein alpha
B3GNT7	−1.27747	5.43E−07	1.91E−05	−5.9701	Down	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 7
NUAK1	−1.27407	4.13E−05	0.00055	−4.61137	Down	NUAK family kinase 1
CHRM4	−1.27138	9.69E−05	0.001076	−4.33666	Down	Cholinergic receptor muscarinic 4
FAM131C	−1.2709	0.000197	0.001861	−4.10365	Down	Family with sequence similarity 131 member C

Table 1 (continued)

Gene symbol	logFC	*p* Value	adj.*P*.Val	tvalue	Regulation	Gene name
CACNA1I	−1.26965	0.000148	0.00149	−4.19925	Down	Calcium voltage-gated channel subunit alpha1 I
PLK2	−1.26873	1.57E−06	4.30E−05	−5.64037	Down	Polo-like kinase 2
STX11	−1.2683	0.000107	0.001159	−4.30497	Down	Syntaxin 11
PALM	−1.26784	2.42E−05	0.000364	−4.78214	Down	Paralemmin
SPSB1	−1.26633	2.13E−07	8.72E−06	−6.26124	Down	splA/Ryanodine receptor domain and SOCS box containing 1
PFKP	−1.26587	5.77E−07	2.01E−05	−5.95129	Down	Phosphofructokinase, platelet
TMSB15B	−1.26556	0.002332	0.012706	−3.25431	Down	Thymosin beta 15B
CDKL2	−1.26526	0.010003	0.038886	−2.70594	Down	Cyclin-dependent kinase-like 2
CTAGE9	−1.2644	2.56E−06	6.17E−05	−5.48824	Down	CTAGE family member 9

DEGs with upregulated and downregulated expression in volcano plot and heatmap, respectively.

GO and pathway enrichment analyses of DEGs

GO enrichment analysis (http://www.geneontology.org) [35] (Accession Date: 26/02/2024) was frequently used to annotate the degree of gene function terms in DEGs, which included biological process (BP), cellular component (CC) and molecular function (MF). REACTOME (https://reactome.org/) (Accession Date: 26/02/2024) [36] pathway enrichment analysis was used to demonstrate enriched signaling pathways in DEGs. The g:Profiler (http://biit.cs.ut.ee/gprofiler/) (Accession Date: 26/02/2024) [37] was used to perform GO and REACTOME pathway enrichment analysis of DEGs. $P < 0.05$ was considered to represent statistical significance.

Construction of the PPI network and module analysis

To ensure the optimal graphical display of protein interactions of DEGs, Human Integrated Protein–Protein Interaction rEference (HIPIE) (https://cn.string-db.org/) [38] (Accession Date: 23/02/2024) was used to generate the PPI network. The software Cytoscape (version 3.10.1) (http://www.cytoscape.org/) [39] (Accession Date: 23/02/2024) was used to visualize the PPI network. The Network Analyzer in Cytoscape was utilized to calculate node degree [40], betweenness [41], stress [42] and closeness [43]. The PEWCC Cytoscape software plugin [44] was used to create modules in the PPI network of endometriosis.

Construction of the miRNA-hub gene regulatory network

The significant miRNAs were identified from miRNA-hub gene regulatory network analysis through the TarBase, miRTarBase, miRecords, miRanda (S mansoni only), miR2Disease, HMDD, PhenomiR, SM2miR, PharmacomiR, EpimiR, starBase, TransmiR, ADmiRE and TAM 2 via miRNet database (https://www.mirnet.ca/) [45] (Acession Date: 26/02/2024). This network was visualized with Cytoscape [39] (Accession Date: 26/02/2024), and the significant hub genes and miRNAs were selected via the Network Analyzer plugin in Cytoscape based on the degree connectivity.

Construction of the TF-hub gene regulatory network

The significant transcription factors (TFs) were identified from TF-hub gene regulatory network analysis through the CHEA via NetworkAnalyst database (https://www.networkanalyst.ca/) [46] (Acession Date: 01/05/2024). This network was visualized with Cytoscape [39] (Accession Date: 01/05/2024), and the significant hub genes and TFs were selected via the Network Analyzer plugin in Cytoscape based on the degree connectivity.

Receiver operating characteristic curve (ROC) analysis

ROC analysis was performed to predict the diagnostic effectiveness of biomarkers by pROC package of R software [47]. The area under the curve (AUC) value was utilized to determine the diagnostic effectiveness in discriminating endometriosis from normal control samples.

Results

Identification of DEGs

The DEGs were screened by “limma” package ($|\text{logFC}| > 1.304$ (log2 fold change) for upregulated genes and $|\text{logFC}| > 1.304$ (log2 fold change) < -1.2644 for downregulated genes and adj.P.Val < 0.05). The GSE243039 dataset contained 958 DEGs, including 479 upregulated genes and 479 downregulated genes, and is listed in Table 1. The volcano plot (Fig. 1) was used to show the expression pattern of DEGs in endometriosis. The heatmap of the DEGs is shown in Fig. 2.

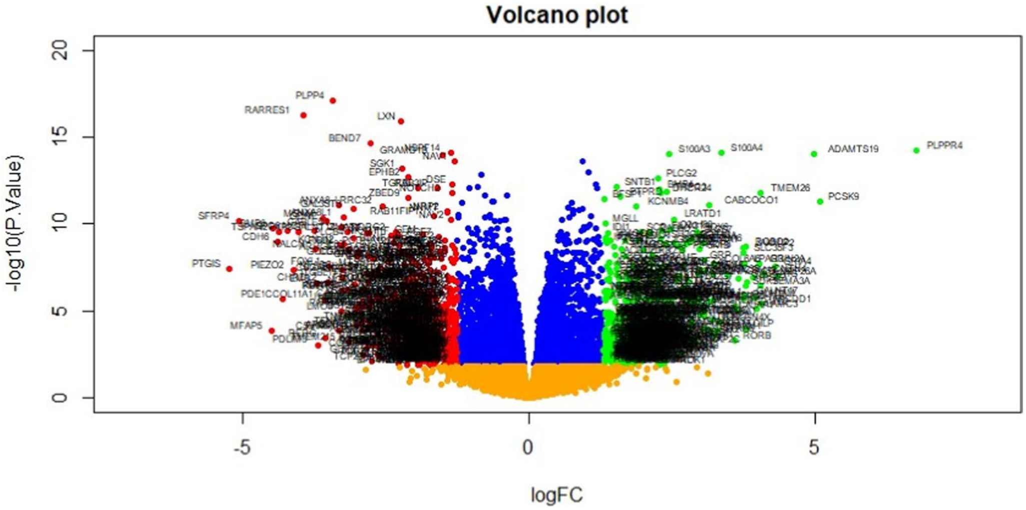

Fig. 1 Volcano plot of differentially expressed genes. Genes with a significant change of more than twofold were selected. Green dot represented upregulated significant genes and red dot represented downregulated significant genes

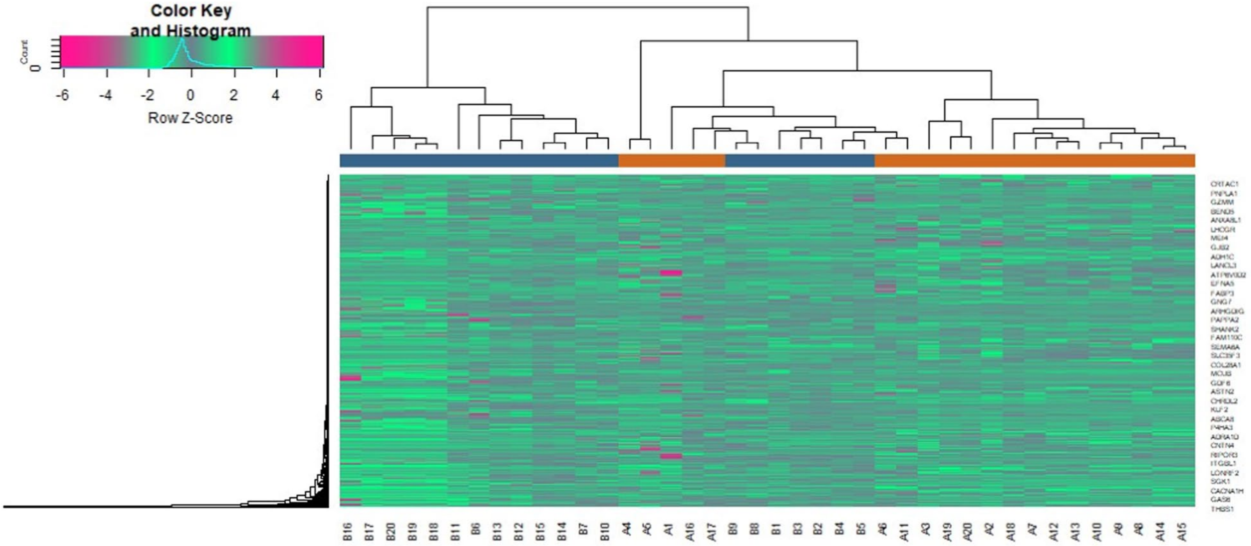

Fig. 2 Heat map of differentially expressed genes. Legend on the top left indicates log fold change of genes. (A1 – A20 = Endometriosis samples; B1 – B20 = Normal control samples)

GO and pathway enrichment analyses of DEGs

GO enrichment and REACTOME pathway enrichment analyses were performed on the DEGs using the g:Profiler database. GO enrichment analysis covers three aspects: BP, CC and MF (Table 2). The upregulated genes were mainly related to multicellular organismal process, regulation of biological process, membrane, extracellular region, signaling receptor binding and molecular transducer activity, while the downregulated genes were mainly involved in developmental process, biological regulation, cell periphery, cytoplasm, molecular function regulator activity and calcium ion binding. The REACTOME pathway enrichment analysis showed that the genes upregulated genes in endometriosis were enriched in signaling by GPCR, extracellular matrix organization, muscle contraction and glycosaminoglycan metabolism (Table 3).

Construction of the PPI network and module analysis

Considering the critical role of protein interactions in protein function, we used the HIPIE database and Cytoscape software to generate PPI network once we had

Table 2 The enriched GO terms of the up- and downregulated differentially expressed genes

GO ID	CATEGORY	GO Name	adjusted_*p*_value	negative_log10_of_adjusted_*p*_value	Gene Count	Gene
Upregulated genes						
GO:0032501	BP	multicellular organismal process	8.48E−28	27.07135732	279	PLPPR4,PCSK9,KIF26A,CNTN4,APCDD1,SEMA3A,GRIN2A,LAMC3,L1CAM,CBLN2,SDK1,ROBO2,LPAR3,CACNA1G,AJAP1,RORB,HSD17B2,NLGN4X,VCAM1,STRA6,SIX2,CLEC3B,ST8SIA4,COCH,EFNA5,GRP,AVPR1A,ADGRL3,EPHA6,CNTN5,AQP8,WNT6,FABP4,PSG1,ANO1,SOX6,NDP,PREX2,TFAP2C,NTRK1,CNTN1,FGF10,RAMP3,PLA2G7,MMP12,FAIM2,SEMA6A,ADCY1,MDGA2,COL14A1,LCP1,ADRA1D,SNCA,CLIC2,ACP3,IL31RA,APOD,INSRR,LAG3,SOX18,F2RL2,CCR1,CST1,RETREG1,CYP39A1,ISM1,ATCAY,PREX1,CARD16,ADRA2C,FLT1,FABP5,PRDM1,TRPC3,TUNAR,IGSF3,THSD7A,DKK2,PROK1,SCTR,WNT16,ZNF804A,RNF157,F13A1,SH3GL2,PRKCB,DHCR24,PDE3B,BMP4,IL1RL1,MYPN,HS3ST5,PLCG2,PRL,FOXQ1,SEMA6D,NEFL,WNT5A,MEOX1,DOCK4,HTR1B,TIMP3,SERPINB2,COL7A1,FRZB,PSG3,VWC2,CRACD,NLRP2,CPE,ADAMTS9,NPW,XK,EREG,GABRA2,NDNF,DCHS1,CNTN6,MEGF10,MEI4,SNAP25,SYT1,NETO1,CD24,SLC26A7,LHCGR,CLSTN2,SCD,DTX1,PDGFB,LSAMP,PIK3CG,MMRN1,LDLR,SOAT2,RGCC,CD4,FOXL2,DPF3,GPR183,TRPA1,PTGER4,EPHA5,F2RL3,KCNMB4,C1QL1,TOX,ADAMTS5,CST4,RSPO3,MYO7A,KRT17,ADGRB3,MAP2K6,ADAMTS1,PDE4B,NES,SH2D2A,TH,TMEM119,IRX6,PSG9,PADI2,CACNA1D,LRFN5,MMP8,KDR,CNFN,KRT36,ADRB2,ACKR3,P2RX6,CNGA1,GJA3,MGAT3,TNFRSF9,PTPRC,SEMA3D,MARK1,PITX1,EYA1,TXK,KL,PCARE,PLAU,EPHA7,ZNF365,PIK3R3,GJB2,CCDC141,HECW2,SOX8,CCND2,ATP1B2,RTN4R,PTGS1,CRABP2,HECW1,PTPRD,PCDH9,INSIG1,BMP8A,CHRM2,EPCAM,WNT9A,PRXL2A,FSIP2,IRX2,SEMA3B,TSPAN12,SNTB1,BATF2,SIGLEC1,MBOAT1,UCN2,CRTAC1,ADGRG6,CYP2J2,CLEC14A,CYP1A1,ASTN2,NTN1,GRIP2,ATP1A2,STAC2,PDGFD,AFF3,ADGRG1,TNFRSF19,CLDN3,MSTN,TMC1,LEPR,SDK2,DMRTA2,CD248,IL15,KREMEN1,CACNA1H,BMP2,PCDHB15,LAMA5,SYT7,NTNG1,NELL2,TCIM,TAS2R1,ZBTB46,PAK3,KRT19,ROS1,MME,APOE,CUBN,PTCH1,OSR2,ITPKA,RAB7B,RBM20,CASP1,PDE9A,MGLL,EFNB2,NID1,ABCG2,HMGCR,ACE,PPFIA2,RNF17,BFSP1,PGR,RENBP,WLS,RIMS1,KLK3,MCOLN2,STMN2,ARSL,GREM2

Table 2 (continued)

GO ID	CATEGORY	GO Name	adjusted_*p*_value	negative_log10_of_adjusted_*p*_value	Gene Count	Gene
GO:0050789	BP	regulation of biological process	9.83E−12	11.00739244	330	PLPPR4,PCSK9,KIF26A,GRIA4,CNTN4,APCDD1,SEMA3A,GRIN2A,L1CAM,CBLN2,HPSE2,CILP,SDK1,ROBO2,LPAR3,PALMD,CACNA1G,AJAP1,RORB,S100A4,NLGN4X,VCAM1,STRA6,SIX2,CLEC3B,MMP3,PLCH1,DPP6,COCH,EFNA5,GRP,AVPR1A,ADGRL3,EPHA6,RGS7,AQP8,WNT6,FABP4,PSG1,ANO1,SOX6,NDP,PREX2,TFAP2C,NTRK1,CNTN1,SYT9,FGF10,RAMP3,PLA2G7,MMP12,FAIM2,SEMA6A,ADCY1,COL14A1,LCP1,PIP5K1B,ZNF726,ADRA1D,SNCA,CLIC2,STAR,ACP3,IL31RA,APOD,INSRR,LAG3,SOX18,F2RL2,CCR1,ICA1,NKAIN1,RETREG1,ISM1,ATCAY,PREX1,CARD16,ADRA2C,FLT1,FABP5,PRDM1,TRPC3,TUNAR,DKK2,PROK1,SCTR,WNT16,ZNF804A,RNF157,SH3GL2,PRKCB,DHCR24,GPR20,PDE3B,CHST2,BMP4,IL1RL1,HS3ST5,PLCG2,KCNH5,PRL,FOXQ1,SEMA6D,NEFL,WNT5A,MACC1,TRPC6,MEOX1,DOCK4,HTR1B,PRAME,TIMP3,EGFL6,SERPINB2,FRZB,PSG3,VWC2,CFD,CRACD,RAB6C,NLRP2,CPE,ADAMTS9,GPBAR1,DNAJC6,NPW,XK,EREG,GABRA2,NDNF,DCHS1,CNTN6,MEGF10,SNAP25,ELMO1,SYT1,NETO1,CD24,ZBTB7C,LHCGR,CLSTN2,SCD,DTX1,PDGFB,ZNF608,RASL11B,WFDC1,MMP7,PIK3CG,EFHB,MMRN1,LDLR,SOAT2,RGCC,CD4,FOXL2,MYZAP,DPF3,GPR183,GPAT3,TRPA1,PTGER4,GUCY1A2,EPHA5,F2RL3,DOC2B,KCNMB4,C1QL1,TOX,ADAMTS5,CST4,RSPO3,WNK2,C1ORF115,KRT17,ADGRB3,MAP2K6,ADAMTS1,PDE4B,PRODH,NES,SH2D2A,IL2RB,TH,TMEM119,IRX6,PSG9,PADI2,MUC12,CACNA1D,LRFN5,MMP8,KDR,SHISA9,KRT36,ADRB2,ACKR3,P2RX6,RGL3,OLFML2A,CDHR3,GJA3,MGAT3,ATP6V0D2,TNFRSF9,PTPRC,APOBEC3B,SEMA3D,ANK1,DIRAS2,B4GALNT2,MARK1,PITX1,EYA1,TXK,KL,ST8SIA1,PLAU,EPHA7,ZNF365,PIK3R3,ADGRL4,GJB2,SYN3,HECW2,SOX8,CCND2,ATP1B2,RTN4R,PTGS1,CRABP2,HECW1,PTPRD,ZNF114,MCTP1,MASP1,TOGARAM2,INSIG1,BMP8A,SORCS1,IMPA2,CHRM2,EPCAM,WNT9A,UCA1,PRXL2A,TRIM55,GRM4,IRX2,SEMA3B,TSPAN12,BATF2,SIGLEC1,GCOM1,MBOAT1,UCN2,ADGRG6,TNFRSF18,CYP2J2,CLEC14A,CYP1A1,RUBCNL,ASTN2,NTN1,P3H2,GRIP2,ATP1A2,STAC2,PDGFD,AFF3,ADGRG1,TNFRSF19,CLDN3,MSTN,TMC1,ERMP1,LEPR,FADS1,DMRTA2,RTKN2,CD248,IL15,STK32B,KREMEN1,CACNA1H,BMP2,LPAR4,LAMA5,SYT7,SLC2A8,NTNG1,TCIM,TAS2R1,ZBTB46,PAK3,KRT19,FABP3,ROS1,ATRNL1,MME,APOE,SFMBT2,ACSL5,SIPA1L2,PTCH1,OSR2,ITPKA,RAB7B,RBM20,CASP1,PDE9A,PTPRN2,MGLL,EFNB2,STAMBPL1,HLA-C,NID1,XCR1,HMGCR,ACE,PPFIA2,ENTREP1,CORT,PGR,WLS,RIMS1,KLK3,MCOLN2,STMN2,GREM2

Table 2 (continued)

GO ID	CATEGORY	GO Name	adjusted_*p*_value	negative_log10_of_adjusted_*p*_value	Gene Count	Gene
GO:0016020	CC	membrane	4.72E−15	14.32631317	295	PLPPR4,PCSK9,GRIA4,CNTN4,APCDD1,TMEM26,GRIN2A,LAMC3,L1CAM,HPSE2,SDK1,ROBO2,LPAR3,GALNT17,PALMD,SLC35F3,CACNA1G,AJAP1,HSD17B2,PCDH19,NLGN4X,VCAM1,STRA6,ST8SIA4,PLCH1,DPP6,EFNA5,AVPR1A,ADGRL3,EPHA6,CNTN5,RGS7,AQP8,WNT6,PSG1,ANO1,ERVMER34-1,PREX2,NTRK1,CNTN1,GALNT13,SYT9,FGF10,RAMP3,FAIM2,SEMA6A,ADCY1,MDGA2,LCP1,MMP27,LRP1B,LY6K,PIP5K1B,ADRA1D,SNCA,ST6GALNAC3,TMEM52B,TMEM37,CLIC2,NAALAD2,LMTK3,ACP3,IL31RA,ANO4,INSRR,LAG3,F2RL2,TMEM132B,CCR1,C2ORF88,ICA1,NKAIN1,RETREG1,CYP39A1,S100A3,CHST1,ATCAY,PREX1,ADRA2C,FLT1,FABP5,TRPC3,TUNAR,IGSF3,THSD7A,SCTR,ZNF804A,SH3GL2,PRKCB,DHCR24,GPR20,PDE3B,CHST2,IL1RL1,MYPN,HS3ST5,PLCG2,KCNH5,ALPP,SEMA6D,WNT5A,TRPC6,DOCK4,HTR1B,PRAME,THSD7B,SLCO4A1,EGFL6,SERPINB2,CYP4B1,COL7A1,FRZB,PSG3,VWC2,LANCL3,CPE,GPBAR1,DNAJC6,XK,EREG,GABRA2,TMCC3,DCHS1,CNTN6,MEGF10,SNAP25,ELMO1,SYT1,NETO1,CD24,SLC26A7,LHCGR,CLSTN2,SCD,SYTL5,PDGFB,LSAMP,PIK3CG,CYYR1,LDLR,SOAT2,CD4,MYZAP,AIF1L,GPR183,GPAT3,CYP2S1,TRPA1,PTGER4,EPHA5,F2RL3,DOC2B,KCNMB4,WNK2,CD163L1,MYO7A,LAMB4,C1ORF115,KRT17,SLCO2A1,ADGRB3,AP1M2,CACNA2D3,CNNM1,PDE4B,PRODH,IL2RB,TH,TMEM119,PSG9,GSG1,MUC12,CACNA1D,LRFN5,KDR,SHISA9,CNFN,TMEM179,ADRB2,ACKR3,P2RX6,RGL3,CNGA1,CDHR3,GJA3,MGAT3,MSMO1,ATP6V0D2,TNFRSF9,PTPRC,SEMA3D,ANK1,DIRAS2,B4GALNT2,ZNF474,MARK1,TXK,KL,ST8SIA1,PLAU,EPHA7,PIK3R3,GALNT14,ADGRL4,GJB2,SYN3,CCND2,ATP1B2,RTN4R,PTGS1,PTPRD,MCTP1,PCDH9,NALF1,ST6GALNAC2,INSIG1,SORCS1,CHRM2,HKDC1,EPCAM,GRM4,TSPAN12,SNTB1,SIGLEC1,SLC37A2,CLDN23,MBOAT1,ADGRG6,TNFRSF18,CYP2J2,CLEC14A,CYP1A1,RUBCNL,ASTN2,GRIP2,ATP1A2,STAC2,PDGFD,ADGRG1,PNPLA3,TNFRSF19,CCDC188,CLDN3,TMC1,ERMP1,LEPR,FADS1,SDK2,RTKN2,CD248,KREMEN1,CACNA1H,BMP2,PCDHB15,GIMAP2,FAM169A,LPAR4,SYT7,SLC2A8,NTNG1,TCIM,OGFRL1,TAS2R1,PAK3,KRT19,ROS1,ATRNL1,MME,APOE,CUBN,ACSL5,PTCH1,RAB7B,CASP1,PDE9A,PTPRN2,MGLL,EFNB2,GYPE,STAMBPL1,HLA-C,ABCG2,XCR1,HMGCR,ACE,PPFIA2,ENTREP1,BFSP1,PGR,WLS,RIMS1,MCOLN2,ST3GAL5,STMN2,ARSL

Table 2 (continued)

GO ID	CATEGORY	GO Name	adjusted_*p*_value	negative_log10_of_adjusted_*p*_value	Gene Count	Gene
GO:0005576	CC	extracellular region	1.97E−13	12.7052702	159	PCSK9,ADAMTS19,GRIA4,CNTN4,SEMA3A,LAMC3,CBLN2,HPSE2,CILP,ROBO2,S100A4,VCAM1,COL6A6,CLEC3B,MMP3,COL28A1,COCH,GRP,CNTN5,WNT6,FABP4,PSG1,ANO1,NDP,ERVMER34-1,CNTN1,FGF10,ALDH1L1,PLA2G7,MMP12,ADCY1,MDGA2,COL14A1,LCP1,MMP27,LY6K,SNCA,TMEM52B,ACP3,APOD,LAG3,F2RL2,CST1,ISM1,FLT1,FABP5,THSD7A,ADAMTS17,DKK2,PROK1,WNT16,COL5A3,F13A1,PRKCB,BMP4,IL1RL1,PLCG2,PRL,WNT5A,TIMP3,EGFL6,SERPINB2,COL7A1,FRZB,PSG3,VWC2,CFD,CPE,ADAMTS9,NPW,EREG,NDNF,NETO1,LHCGR,COL24A1,PDGFB,LSAMP,WFDC1,MMP7,MMRN1,APOL4,LDLR,AIF1L,F2RL3,C1QL1,ADAMTS5,CST4,RSPO3,CD163L1,LAMB4,ADGRB3,ADAMTS1,PSG9,PADI2,MMP8,KDR,KRT36,OLFML2A,CDHR3,COL21A1,ATP6V0D2,PTPRC,SEMA3D,KL,PLAU,RTN4R,PTGS1,CRABP2,PTPRD,ZNF114,MASP1,QPRT,BMP8A,EPCAM,WNT9A,PRXL2A,KRT37,SEMA3B,SIGLEC1,SLC37A2,KRT34,UCN2,CRTAC1,TNFRSF18,ACAT2,CYP2J2,H2AC20,NTN1,ATP1A2,PDGFD,ADGRG1,MSTN,VPREB3,LEPR,CD248,IL15,GSTT2B,BMP2,PCOLCE,LAMA5,SYT7,NTNG1,NELL2,KRT19,FABP3,MME,APOE,CUBN,HLA-C,NID1,ACE,PPFIA2,CORT,RENBP,WLS,KLK3,ARSL,GREM2,C1QTNF7
GO:0005102	MF	signaling receptor binding	9.33E−07	6.030222484	71	PCSK9,SEMA3A,S100A4,NLGN4X,VCAM1,EFNA5,GRP,AVPR1A,WNT6,FABP4,ANO1,NDP,NTRK1,FGF10,SEMA6A,LCP1,LAG3,F2RL2,ADRA2C,DKK2,PROK1,WNT16,BMP4,PRL,SEMA6D,WNT5A,MACC1,DOCK4,EGFL6,CPE,NPW,EREG,MEGF10,SYT1,NETO1,DTX1,SYTL5,PDGFB,RASL11B,PIK3CG,CD4,C1QL1,ADAMTS5,RSPO3,NES,KDR,PTPRC,SEMA3D,KL,EPHA7,PTPRD,BMP8A,WNT9A,SEMA3B,UCN2,GRIP2,PDGFD,MSTN,IL15,BMP2,LAMA5,TCIM,ATRNL1,APOE,PTCH1,EFNB2,HLA-C,ACE,CORT,PGR,GREM2
GO:0060089	MF	molecular transducer activity	4.32026E−05	4.364490249	64	GRIA4,GRIN2A,L1CAM,ROBO2,LPAR3,RORB,NLGN4X,STRA6,AVPR1A,ADGRL3,EPHA6,NTRK1,RAMP3,ADRA1D,IL31RA,INSRR,LAG3,F2RL2,CCR1,ADRA2C,FLT1,SCTR,GPR20,IL1RL1,HTR1B,GPBAR1,GABRA2,LHCGR,CD4,GPR183,PTGER4,EPHA5,F2RL3,ADGRB3,IL2RB,KDR,ADRB2,ACKR3,P2RX6,TNFRSF9,PTPRC,EPHA7,ADGRL4,RTN4R,PTPRD,SORCS1,CHRM2,GRM4,ADGRG6,TNFRSF18,ADGRG1,TNFRSF19,CLDN3,LEPR,LPAR4,OGFRL1,TAS2R1,ROS1,CUBN,PTCH1,PTPRN2,NID1,XCR1,PGR
Downregulated genes						

Table 2 (continued)

GO ID	CATEGORY	GO Name	adjusted_*p*_value	negative_log10_of_adjusted_*p*_value	Gene Count	Gene
GO:0032502	BP	developmental process	1.56E−20	19.80631915	232	PTGIS,SFRP4,MFAP5,BMP6,CDH6,TSPAN2,PKP2,MDFI,EMB,PDLIM3,COL11A1,GDNF,CHRDL2,FOXL1,PLPP4,LMO3,CABLES1,NFASC,FGFR2,TMEM215,IL33,NGF,PAPPA2,TENM2,TBX18,HAPLN1,GDF6,FOXC2,COMP,CECR2,FST,SORBS2,CACNG7,TCF23,FGF14,ITGA7,PLN,EFEMP1,GATA6,CXADR,BHLHE41,ACAN,CSGALNACT1,TCF21,PTGS2,MTSS1,LRRC32,GDF10,CPNE5,DHRS3,DACT1,SPINT2,NKX3-1,HOXC8,DGAT2,PITX2,AKR1C3,TNFSF10,BDNF,KRT7,ADAMTSL1,RGS4,SMIM43,RAPGEF5,NDRG2,SCG2,EPHA3,PLA2G5,EYA2,INHBA,ALPL,MECOM,SGK1,CSTA,ATP10A,RAP1GAP,HOXC9,PLEKHB1,SLC2A12,COL4A4,MYH3,DIO3,EPB41L3,TLR3,ANGPTL4,EPHB2,FLI1,THBS1,MBP,ID3,TNNT2,NOX4,LHX9,S1PR5,SERPINE2,SHANK2,IGSF9,PI16,CRLF1,EN1,PCSK1,TGFBI,IGF2BP1,SALL4,EYA4,KRT18,ITGB1BP2,WNK4,KRT13,DLX5,VLDLR,VDR,GPC4,FAM20A,FOXS1,LZTS1,RARB,FZD7,HOXB6,PTPRN,ZFHX2,CELSR2,OR51E2,OMG,EPHA4,EN2,DAW1,CDH8,ENC1,IFNE,TNNT1,ANKRD1,SGCA,ZFPM2,SOX9,MGP,SULF1,CYP24A1,DNAH11,ID2,TLR2,IL6,NPPB,SPINK1,GAS6,GPC3,NTRK3,CCNA1,AMIGO2,F11R,SIGLEC15,FOXD1,CCNO,ADAM12,RASSF2,NCAM1,LGI2,MYOC,HOXB7,DUSP2,USP2,KLF2,SIK1,SIX1,FGF7,CCN2,JCAD,EXPH5,DAB1,PKDCC,MYH10,IGFBP3,ARHGDIG,HRNR,SLC9C1,LYVE1,PRKD1,TTC9,CHL1,BGN,EPPK1,EDA,MYEF2,ACTBL2,NTRK2,SLIT2,IRX3,COL8A2,ACTC1,FLG,HEG1,NRP2,NNMT,CHI3L1,TNIK,SP6,EXTL1,RUNX1,NFIB,APLN,STOX2,PLP1,MYOM2,NAV2,MYOZ1,COL4A3,KCNQ4,PPP1R13L,SEMA3C,DCLK2,NOTCH2,PTGDR,PALM2AKAP2,PGF,THBS2,ANK3,DES,KRT86,PDLIM5,PRDM6,TRABD2A,HTR6,NAV1,HSPB7,NPAS1,PNPLA1,NRG1,DMRT2,LIF,PLK2,PALM,CDKL2

Table 2 (continued)

GO ID	CATEGORY	GO Name	adjusted_*p*_value	negative_log10_of_adjusted_*p*_value	Gene Count	Gene
GO:0065007	BP	biological regulation	3.68E−14	13.43418786	342	PTGIS,SFRP4,BMP6,CDH6,PDE1C,GPC6,PIEZO2,PKP2,RARRES1,MDFI,NALCN,RERG,GDNF,CHRDL2,FOXL1,PLPP4,FIBIN,LMO3,CABLES1,ITGBL1,FGFR2,KCNJ12,NPY4R,TMEM215,IL33,PLCB4,NGF,PAPPA2,CD200,BST2,TENM2,ARHGEF4,TBX18,MN1,FAM110C,HAPLN1,GDF6,NPY4R2,FOXC2,ERG,COMP,FST,FMO2,AK4,SORBS2,CACNG7,TPD52L1,TCF23,FGF14,ITGA7,PLN,EFEMP1,GATA6,CXADR,BHLHE41,ACAN,LRRN2,TCF21,CACNG6,PTGS2,MTSS1,LRRC32,APCDD1L,GDF10,CPNE5,RASSF9,TNFAIP8L3,DHRS3,DACT1,SPINT2,NKX3-1,CMKLR2,CHN2,HOXC8,DGAT2,PITX2,SLC2A5,AKR1C3,TNFSF10,BDNF,RGS4,KCNE4,SMIM43,RAPGEF5,NDRG2,SCG2,MT1F,EPHA3,PLA2G5,EYA2,GMNC,KCNJ2,INHBA,ALPL,C10ORF90,MECOM,SGK1,CSTA,ATP10A,RAP1GAP,ULBP1,HOXC9,PLEKHB1,VEPH1,RGS7BP,TFPI2,DIO3,DYSF,EPB41L3,TLR3,ANGPTL1,PPP1R12B,VSTM2L,CELF2,ANGPTL4,SLC1A7,EPHB2,ZBED9,FLI1,RASSF5,THBS1,GCH1,MBP,PPP1R14A,NXPH4,ID3,TNNT2,LIMCH1,NOX4,CGREF1,LHX9,S1PR5,NXPH3,CACNG8,PLA2G4A,SERPINE2,OR2W3,RAPGEF4,TRH,ADAP1,SHANK2,IGSF9,PI16,TLR1,STXBP6,CRLF1,EN1,RSPO1,PCSK1,CALB2,TGFBI,IGF2BP1,SALL4,EYA4,KRT18,ITGB1BP2,CCDC80,DAPK1,WNK4,KRT13,DLX5,VLDLR,VDR,GPC4,FAM20A,FOXS1,LZTS1,RARB,KISS1,GEM,FZD7,HOXB6,PTPRN,ZFHX2,CELSR2,OR51E2,EPHA4,EN2,LRRC38,PODN,SCN4B,FMO1,SORCS2,CDH8,ENC1,IFNE,TNNT1,ANKRD1,SGCA,ZFPM2,SOX9,MGP,SULF1,IL20RA,DEPP1,CYP24A1,BACH2,DNAH11,PKIA,ID2,MCTP2,TLR2,IL6,NPPB,FRMD5,SPINK1,GAS6,GPC3,NTRK3,FBXO32,AMIGO2,F11R,HPGDS,MPP2,RAB11FIP1,SIGLEC15,FOXD1,ADAM12,RASSF2,ALDH8A1,LGALS2,HAS3,NCAM1,MYOC,ZFHX4,HAS1,GCSAM,HOXB7,DUSP2,USP2,RAB3IP,KLF2,SIK1,EEF1A2,OR2A7,SIX1,FGF7,CCN2,JCAD,MAP3K9,SUPT20HL1,ABCA8,EXPH5,DAB1,PKDCC,PLPPR3,MYH10,FRMPD4,IGFBP3,FANK1,MPP7,ARHGDIG,TRIM63,SLC4A4,SH3RF2,SLC9C1,HUNK,CYRIA,LYVE1,TMEM38A,BEND5,SLAIN1,PRKD1,CYP3A7,CHL1,KCNG2,EPPK1,SIRPB1,EDA,PARP15,CPEB1,NTRK2,SYT15,HSD17B6,FPR3,SLIT2,IRX3,MPO,ACTC1,HEG1,NRP2,NNMT,CHI3L1,TNIK,LMCD1,SP6,RUNX1,NFIB,APLN,SORBS1,EPB41,PDGFRL,ACKR2,FPR1,STOX2,PLP1,NAV2,PDE7B,INSYN2A,MYOZ1,PMEL,COL4A3,PPP1R13L,SEMA3C,BMAL2,ZNF334,DCLK2,NOTCH2,IQSEC3,JPH3,SLC38A3,PTGDR,PALM2AKAP2,PDK4,GNG7,PGF,THBS2,GPR143,LRRC2,ANK3,DES,PDLIM5,PRDM6,IGFBPL1,TRABD2A,HTR6,HSPB7,NPAS1,NFIX,PIK3AP1,NRG1,DMRT2,LIF,ADH1C,SIRPA,NUAK1,CHRM4,CACNA1I,PLK2,STX11,PALM,CDKL2

Table 2 (continued)

GO ID	CATEGORY	GO Name	adjusted_*p*_value	negative_log10_of_adjusted_*p*_value	Gene Count	Gene
GO:0071944	CC	cell periphery	1.05E−11	10.97687663	204	PTGIS,MFAP5,CDH6,TSPAN2,GPC6,PIEZO2,PKP2,NALCN,EMB,MGAM,COL11A1,RERG,PLPP4,ITGBL1,NFASC,FGFR2,ANXA8L1,KCNJ12,NPY4R,PAPPA2,CD200,BST2,TENM2,ARHGEF4,FAM110C,HAPLN1,NPY4R2,COMP,SORBS2,CACNG7,ITGA7,EFEMP1,CXADR,ACAN,LRRN2,CACNG6,PTGS2,LRRC32,APCDD1L,GDF10,CPNE5,TNFAIP8L3,KCNN3,DHRS3,HMCN1,SPINT2,CMKLR2,SLC2A5,TNFSF10,ADAMTSL1,RGS4,KCNE4,SMIM43,SBSPON,RAPGEF5,EPHA3,PLA2G5,PCDHA12,KCNJ2,EVA1A,ALPL,C10ORF90,SGK1,CSTA,ATP10A,ULBP1,VEPH1,SLC2A12,RGS7BP,COL4A4,TFPI2,DIO3,DYSF,EPB41L3,TLR3,ANGPTL1,ANGPTL4,SLC1A7,EPHB2,THBS1,MBP,MFAP3L,NOX4,S1PR5,CACNG8,SERPINE2,OR2W3,RAPGEF4,TINAGL1,SYTL2,ADAP1,SHANK2,IGSF9,TLR1,CRLF1,TGFBI,KRT18,CCDC80,DAPK1,VLDLR,GPC4,LZTS1,KISS1,GEM,FZD7,PTPRN,CELSR2,OR51E2,OMG,EPHA4,LRRC38,PODN,SCN4B,SORCS2,CDH8,SGCA,SLC22A23,MGP,SULF1,IL20RA,STEAP1B,TLR2,IL6,GPC3,NTRK3,SLC6A15,AMIGO2,F11R,MPP2,SIGLEC15,ADAM12,RASSF2,HAS3,NCAM1,MYOC,HAS1,GCSAM,OR2A7,ESYT3,CCN2,JCAD,ABCA8,MYH10,IFITM10,MPP7,GRAMD1B,ARHGDIG,SLC4A4,HRNR,SLC9C1,LYVE1,PRKD1,CHL1,KCNG2,BGN,EPPK1,SIRPB1,EDA,STEAP2,NTRK2,SYT15,FPR3,COL8A2,FLG,HEG1,NRP2,CHI3L1,TNIK,RHD,STEAP1,SORBS1,EPB41,ART4,ACKR2,MGST1,FPR1,PLP1,NAV2,PMEL,COL4A3,KCNQ4,SSPN,NOTCH2,IQSEC3,JPH3,SLC38A3,PTGDR,PALM2AKAP2,GNG7,THBS2,GPR143,ANK3,DES,IGFBPL1,TRABD2A,HTR6,PIK3AP1,NRG1,ADH1C,SIRPA,CHRM4,CACNA1I,STX11,PALM

Table 2 (continued)

GO ID	CATEGORY	GO Name	adjusted_*p*_value	negative_log10_of_adjusted_*p*_value	Gene Count	Gene
GO:0005737	CC	cytoplasm	0.000756935	3.120941328	297	PTGIS,SFRP4,PDE1C,GPC6,PKP2,MDFI,PDLIM3,MGAM,COL11A1,RERG,GDNF,CHRDL2,FIBIN,LMO3,CABLES1,NFASC,FGFR2,ANXA8L1,GALNT12,IL33,GAL3ST3,PLCB4,NGF,BST2,TENM2,ARHGEF4,FAM110C,ERG,FST,FMO2,AK4,SORBS2,CACNG7,TPD52L1,FGF14,PLN,CXADR,ACAN,MYH1,CSGALNACT1,PTGS2,MTSS1,RASSF9,TNFAIP8L3,KCNN3,DHRS3,HMCN1,DACT1,SPINT2,NKX3-1,CHN2,DGAT2,SLC2A5,AKR1C3,SCGB3A2,BDNF,KRT7,ADAMTSL1,RGS4,NDRG2,IGFN1,THEM5,SCG2,MT1F,EPHA3,PLA2G5,OLAH,EYA2,EVA1A,INHBA,ALPL,C10ORF90,LXN,MECOM,SGK1,CSTA,ATP10A,RAP1GAP,ULBP1,PLEKHB1,SLC2A12,RGS7BP,COL4A4,MYH3,DIO3,DYSF,EPB41L3,TLR3,SPTLC3,PPP1R12B,VSTM2L,CELF2,MARCHF3,EPHB2,ZBED9,FLI1,RASSF5,THBS1,GCH1,MBP,PPP1R14A,MFAP3L,ID3,TNNT2,LIMCH1,NOX4,S1PR5,CACNG8,PLA2G4A,SERPINE2,RAPGEF4,ALDH1B1,PRUNE2,TRH,TINAGL1,SYTL2,ADAP1,SHANK2,TLR1,STXBP6,CRLF1,PCSK1,CALB2,TGFBI,IGF2BP1,SALL4,EYA4,KLHL4,KRT18,ITGB1BP2,DAPK1,WNK4,KRT13,DLX5,FMO3,VLDLR,VDR,GPC4,FAM20A,LZTS1,RARB,FZD7,PTPRN,CELSR2,OR51E2,TLCD4,EPHA4,PODN,FMO1,DAW1,SORCS2,ENC1,TNNT1,ANKRD1,SGCA,ZFPM2,SULF1,PIPOX,DEPP1,CYP24A1,BACH2,DNAH11,PKIA,ID2,MCTP2,WSCD1,STEAP1B,TLR2,ARHGEF37,IL6,NPPB,GAS6,GPC3,FBXO32,CCNA1,HPGDS,MPP2,RAB11FIP1,CCNO,BEGAIN,RASSF2,CCDC110,ALDH8A1,SEL1L2,HAS3,NCAM1,MYOC,PPFIA4,HAS1,GCSAM,HOXB7,GALNT9,DUSP2,USP2,RAB3IP,SIK1,EEF1A2,SIX1,FGF7,ESYT3,CCN2,JCAD,MYOZ3,ABCA8,EXPH5,DAB1,PKDCC,MYH10,IGFBP3,FANK1,MPP7,GRAMD1B,ARHGDIG,TRIM63,HRNR,HUNK,TMEM38A,BEND5,SLAIN1,PRKD1,CYP3A7,BGN,EPPK1,SIRPB1,EDA,STEAP2,PARP15,ACTBL2,CPEB1,NTRK2,SYT15,HSD17B6,SLIT2,IRX3,MPO,COL8A2,ACTC1,FLG,B3GALT5,NNMT,CHI3L1,TNIK,LMCD1,STEAP1,SP6,EXTL1,SORBS1,EPB41,ACKR2,MGST1,FPR1,STOX2,ST3GAL6,MYOM2,PDE7B,MYOZ1,PMEL,COL4A3,SSPN,PPP1R13L,BMAL2,DCLK2,NOTCH2,DSE,ZNF185,IQSEC3,P4HA3,JPH3,SEC14L6,PDK4,PITPNM3,THBS2,DBNDD1,GPR143,GSTO2,DNAH6,ANK3,DES,KRT86,PDLIM5,NAV1,HSPB7,PNPLA1,PIK3AP1,LIF,MCUB,ADH1C,SIRPA,B3GNT7,NUAK1,PLK2,STX11,PALM,SPSB1,PFKP,CDKL2,CTAGE9
GO:0098772	MF	molecular function regulator activity	7.91485E−05	4.101557094	80	BMP6,PKP2,RARRES1,MDFI,RERG,GDNF,IL33,NGF,BST2,ARHGEF4,GDF6,FST,CACNG7,TCF23,FGF14,PLN,EFEMP1,CACNG6,GDF10,SPINT2,NKX3-1,CHN2,TNFSF10,BDNF,RGS4,KCNE4,RAPGEF5,SCG2,INHBA,LXN,SGK1,CSTA,RAP1GAP,TFPI2,PPP1R12B,ANGPTL4,THBS1,PPP1R14A,ID3,CACNG8,SERPINE2,RAPGEF4,TRH,ADAP1,PI16,CRLF1,WNK4,FAM20A,GEM,LRRC38,SCN4B,IFNE,PKIA,ID2,ARHGEF37,IL6,NPPB,SPINK1,GAS6,GPC3,CCNA1,CCNO,RAB3IP,FGF7,IGFBP3,ARHGDIG,SH3RF2,PRKD1,EDA,SLIT2,APLN,MYOZ1,COL4A3,SEMA3C,IQSEC3,PGF,NRG1,LIF,MCUB,SIRPA
GO:0005509	MF	calcium ion binding	0.000143688	3.842578472	38	CDH6,ANXA8L1,PLCB4,TENM2,COMP,EFEMP1,ACAN,HMCN1,MEGF6,PLA2G5,PCDHA12,ALPL,DYSF,THBS1,GCH1,CGREF1,PLA2G4A,CALB2,ITGB1BP2,VLDLR,CELSR2,CDH8,SGCA,MGP,SULF1,MCTP2,GAS6,HPGDS,ESYT3,HRNR,SYT15,SLIT2,FLG,HEG1,RUNX1,NOTCH2,PITPNM3,THBS2

Table 3 The enriched pathway terms of the up- and downregulated differentially expressed genes

Pathway ID	Pathway Name	adjusted_*p*_value	negative_log10_of_adjusted_*p*_value	Gene Count	Gene
Upregulated genes					
REAC:R-HSA-372790	Signaling by GPCR	0.000169138	3.771759438	44	PLPPR4,LPAR3,MMP3,AVPR1A,RGS7,WNT6,RAMP3,ADCY1,ADRA1D,F2RL2,CCR1,PREX1,ADRA2C,TRPC3,PROK1,SCTR,WNT16,PRKCB,GPR20,PDE3B,WNT5A,TRPC6,HTR1B,GPBAR1,NPW,XK,LHCGR,PIK3CG,GPR183,PTGER4,F2RL3,ADRB2,ACKR3,PIK3R3,CHRM2,WNT9A,GRM4,UCN2,LPAR4,TAS2R1,PTCH1,MGLL,XCR1,CORT
REAC:R-HSA-1474244	Extracellular matrix organization	0.000724319	3.140069834	24	LAMC3,VCAM1,COL6A6,MMP3,COL28A1,MMP12,COL14A1,COL5A3,BMP4,COL7A1,ADAMTS9,COL24A1,PDGFB,MMP7,ADAMTS5,ADAMTS1,MMP8,KDR,COL21A1,P3H2,BMP2,PCOLCE,LAMA5,NID1
REAC:R-HSA-373076	Class A/1 (Rhodopsin-like receptors)	0.011143325	1.952985185	22	PLPPR4,LPAR3,AVPR1A,ADRA1D,F2RL2,CCR1,ADRA2C,PROK1,HTR1B,GPBAR1,NPW,XK,LHCGR,GPR183,PTGER4,F2RL3,ADRB2,ACKR3,CHRM2,LPAR4,XCR1,CORT
REAC:R-HSA-9675108	Nervous system development	0.017667803	1.752817451	31	SEMA3A,L1CAM,ROBO2,CACNA1G,COL6A6,ST8SIA4,EFNA5,EPHA6,TUBA3E,CNTN1,SEMA6A,TRPC3,COL5A3,SH3GL2,SEMA6D,TRPC6,CNTN6,CD24,EPHA5,CACNA1D,PTPRC,ANK1,EPHA7,PIK3R3,ADGRG6,NTN1,CACNA1H,NELL2,PAK3,EFNB2,HMGCR
REAC:R-HSA-162582	Signal Transduction	0.033015787	1.481278352	94	PLPPR4,LAMC3,CILP,LPAR3,COL6A6,MMP3,AVPR1A,TUBA3E,RGS7,WNT6,SOX6,PREX2,NTRK1,CNTN1,FGF10,RAMP3,ADCY1,PIP5K1B,ADRA1D,APOD,F2RL2,CCR1,PREX1,ADRA2C,FLT1,FABP5,PRDM1,TRPC3,DKK2,PROK1,SCTR,WNT16,COL5A3,SH3GL2,PRKCB,GPR20,PDE3B,IL1RL1,PLCG2,NEFL,WNT5A,TRPC6,DOCK4,HTR1B,GPBAR1,NPW,XK,EREG,ELMO1,LHCGR,SCD,DTX1,COL24A1,PDGFB,MMP7,PIK3CG,GPR183,PTGER4,F2RL3,RSPO3,SH2D2A,IL2RB,KDR,ADRB2,ACKR3,RGL3,ATP6V0D2,PIK3R3,RTN4R,CRABP2,HECW1,CHRM2,WNT9A,GRM4,UCN2,H2AC20,PDGFD,KREMEN1,BMP2,FAM169A,LPAR4,LAMA5,TAS2R1,PAK3,APOE,PTCH1,MGLL,XCR1,CORT,PGR,WLS,KLK3,STMN2,GREM2
REAC:R-HSA-109582	Hemostasis	0.053792682	1.269276802	32	KIF26A,L1CAM,CLEC3B,TUBA3E,PSG1,F2RL2,ADRA2C,TRPC3,F13A1,PRKCB,PLCG2,TRPC6,DOCK4,TIMP3,SERPINB2,PSG3,CFD,PDGFB,PIK3CG,MMRN1,GUCY1A2,F2RL3,KCNMB4,PSG9,P2RX6,PLAU,PIK3R3,ATP1B2,EPCAM,VPREB3,PDE9A,MGLL
Downregulated genes					
REAC:R-HSA-397014	Muscle contraction	0.005754659	2.23998037	17	KCNJ12,CACNG7,FGF14,PLN,CACNG6,KCNE4,KCNJ2,MYH3,DYSF,TNNT2,CACNG8,SCN4B,TNNT1,ACTC1,SORBS1,DES,CACNA1I
REAC:R-HSA-1630316	Glycosaminoglycan metabolism	0.01248541	1.903597196	12	GPC6,ACAN,CSGALNACT1,GPC4,GPC3,HAS3,HAS1,LYVE1,BGN,ST3GAL6,DSE,B3GNT7

Table 3 (continued)

Pathway ID	Pathway Name	adjusted_*p*_value	negative_log10_of_ adjusted_*p*_value	Gene Count	Gene
REAC:R-HSA-1474244	Extracellular matrix organization	0.051293235	1.289939908	18	MFAP5,COL11A1,HAPLN1,COMP,ITGA7,EFEMP1,ACAN,COL4A4,THBS1,CTRB2,F11R,ADAM12,CTRB1,NCAM1,BGN,COL8A2,COL4A3,P4HA3
REAC:R-HSA-3000178	ECM proteoglycans	0.051461154	1.288520482	8	HAPLN1,COMP,ITGA7,ACAN,COL4A4,NCAM1,BGN,COL4A3
REAC:R-HSA-5362517	Signaling by Retinoic Acid	0.051461154	1.288520482	6	DHRS3,AKR1C3,RARB,ALDH8A1,PDK4,ADH1C
REAC:R-HSA-3781865	Diseases of glycosylation	0.051461154	1.288520482	11	GPC6,GALNT12,ACAN,ADAMTSL1,SBSPON,THBS1,GPC4,GPC3,BGN,NOTCH2,THBS2

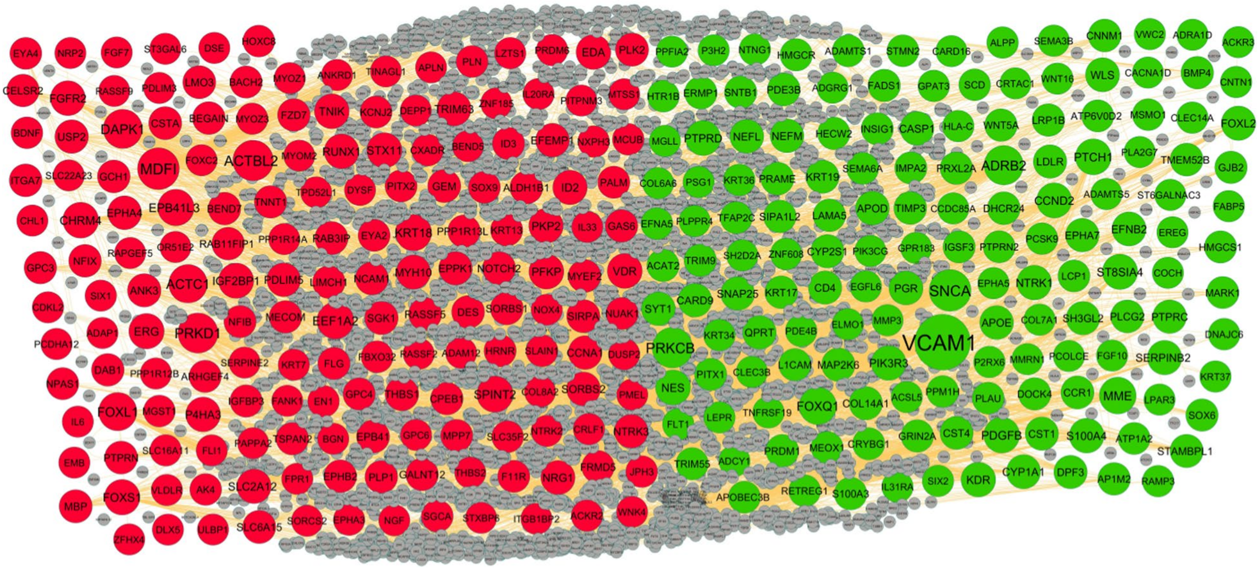

Fig. 3 PPI network of DEGs. Upregulated genes are marked in parrot green; downregulated genes are marked in red

identified the 958 DEGs. The results showed that there were dense regions in PPI, that is, genes closely related to endometriosis. A total of 4871 nodes and 8009 edges were selected to plot the PPI network (Fig. 3). The Network Analyzer plugin of Cytoscape was used to score each node gene by four selected algorithms, including node degree, betweenness, stress and closeness. Finally, we identified ten hub genes (*vcam1*, *snca*, *prkcb*, *adrb2*, *foxq1*, *mdfi*, *actbl2*, *prkd1*, dapk1 and *actc1*) and are listed in Table 4. The top two significant modules from PEWCC were selected for future analysis. Module 1 included 22 nodes and 41 edges (Fig. 4A). The functional enrichment analysis of genes in module 1 was conducted by g:Profiler. These genes were significantly enriched in multicellular organismal process and regulation of biological process. Module 2 included 8 nodes and 14 edges (Fig. 4B). The functional enrichment analysis of genes in module 2 was conducted by g:Profiler. These genes were significantly enriched in developmental process and biological regulation.

Construction of the miRNA-hub gene regulatory network

We searched for target-regulated hub gene miRNAs using miRNet database and then used the results of this database. By constructing miRNA-hub gene regulatory network networks, we found 2495 nodes (miRNA: 2168; Hub Gene: 327) and 14,692 edges (Fig. 5). We identified 365 miRNAs (ex; *hsa-mir-3143*) targeting regulation of *ccnd2*, 102 mirnas (ex; *hsa-mir-6888-5p*) targeting regulation of *vcam1*, 89 mirnas (ex; *hsa-mir-200a-3p*) targeting regulation of *ptprd*, 88 mirnas (ex; *hsa-mir-3122*) targeting regulation of *pdgfb*, 81 mirnas (ex; *hsa-mir-17-5p*) targeting regulation of *prkcb*, 241 mirnas (ex; *hsa-mir-2110*) targeting regulation of i*gf2bp1*, 77 mirnas (ex; *hsa-mir-4432*) targeting regulation of *actc1*, 53 mirnas

Table 4 Topology table for up- and downregulated genes

Regulation	Node	Degree	Betweenness	Stress	Closeness
Up	VCAM1	416	0.184904	86,834,622	0.341594
Up	SNCA	180	0.086564	32,935,316	0.326731
Up	PRKCB	156	0.05443	19,551,102	0.310589
Up	ADRB2	136	0.056876	10,503,780	0.316941
Up	FOXQ1	102	0.022891	20,702,630	0.264141
Up	MME	93	0.029423	14,457,318	0.274745
Up	PTCH1	78	0.028409	7,457,792	0.26486
Up	PDGFB	76	0.022264	6,008,890	0.261024
Up	ST8SIA4	67	0.023812	5,175,380	0.271404
Up	CCND2	64	0.020133	4,021,362	0.290612
Up	PTPRD	63	0.019057	5,697,616	0.263326
Up	NES	62	0.016543	4,851,666	0.279575
Up	S100A4	58	0.018352	5,689,768	0.278232
Up	PIK3R3	58	0.019257	6,819,154	0.280639
Up	NTRK1	56	0.013319	5,744,746	0.272529
Up	KDR	56	0.011496	7,778,812	0.275476
Up	SERPINB2	52	0.014458	5,702,426	0.255581
Up	FOXL2	51	0.009024	7,152,922	0.25159
Up	CYP1A1	48	0.01608	2,790,170	0.277882
Up	EFNB2	47	0.013517	2,651,168	0.267657
Up	WLS	47	0.013043	3,634,828	0.24982
Up	PGR	46	0.011767	3,597,166	0.275976
Up	SYT1	43	0.008774	2,229,078	0.26394
Up	CASP1	43	0.013201	3,495,008	0.247848
Up	NEFL	43	0.010016	1,997,222	0.276493
Up	SNAP25	42	0.014293	1,986,420	0.284695
Up	APOD	42	0.014537	3,155,838	0.267201
Up	APOE	41	0.012455	1,705,636	0.280963
Up	PTPRC	40	0.010061	2,818,146	0.2708
Up	CARD9	40	0.011367	3,316,374	0.241309
Up	NEFM	40	0.01491	2,636,816	0.293522
Up	QPRT	38	0.009819	8,934,012	0.225947
Up	SH3GL2	37	0.008529	3,627,714	0.25839
Up	EPHA7	37	0.010685	3,258,698	0.263269
Up	CD4	36	0.010006	1,469,630	0.281337
Up	LDLR	36	0.009886	1,569,128	0.256754
Up	MAP2K6	36	0.008317	1,723,230	0.264672
Up	CYP2S1	35	0.010486	1,835,320	0.267966
Up	DPF3	34	0.006119	3,159,488	0.241034
Up	COL14A1	34	0.008718	4,017,460	0.243861
Up	STAMBPL1	33	0.007553	4,960,736	0.233437
Up	CST1	33	0.007158	2,170,272	0.231714
Up	CST4	32	0.006271	2,740,472	0.226906
Up	PLCG2	31	0.008121	1,680,216	0.275476
Up	KRT19	31	0.008239	1,459,230	0.2835
Up	CCR1	29	0.009532	3,308,298	0.246917
Up	PRAME	27	0.006029	2,712,304	0.235482
Up	TMEM52B	27	0.008366	1,251,782	0.265394
Up	DHCR24	26	0.008117	1,620,290	0.284645

Table 4 (continued)

Regulation	Node	Degree	Betweenness	Stress	Closeness
Up	TIMP3	25	0.007343	1,887,972	0.250437
Up	CNNM1	25	0.005697	1,036,690	0.225111
Up	KRT17	25	0.004783	2,178,508	0.269854
Up	PDE3B	25	0.006554	2,226,676	0.246031
Up	PRDM1	24	0.004603	2,157,456	0.257883
Up	S100A3	23	0.005112	2,081,396	0.233628
Up	LAMA5	22	0.004812	1,668,084	0.252819
Up	SIPA1L2	22	0.004587	2,681,374	0.250592
Up	LRP1B	22	0.004855	1,903,866	0.242572
Up	PRXL2A	22	0.005952	857,154	0.244756
Up	AP1M2	21	0.005745	1,327,148	0.25295
Up	BMP4	21	0.005918	1,465,568	0.211152
Up	ERMP1	21	0.005252	1,833,162	0.242307
Up	WNT5A	21	0.005621	839,274	0.243361
Up	GRIN2A	20	0.004087	2,097,912	0.237981
Up	SNTB1	19	0.004951	1,366,392	0.21671
Up	DOCK4	19	0.004269	1,553,902	0.262445
Up	HECW2	19	0.004944	1,653,624	0.23112
Up	FADS1	19	0.003917	1,034,182	0.223786
Up	TRIM9	18	0.003815	745,666	0.244707
Up	SOX6	18	0.003932	1,523,690	0.236042
Up	GJB2	18	0.00357	1,889,844	0.220141
Up	L1CAM	17	0.002057	874,050	0.249079
Up	HMGCR	17	0.003664	1,039,586	0.22993
Up	ACAT2	17	0.003431	920,074	0.241214
Up	MARK1	16	0.002652	1,684,916	0.259313
Up	TRIM55	16	0.001206	524,732	0.240036
Up	HMGCS1	16	0.003905	954,734	0.219377
Up	INSIG1	15	0.003029	1,038,904	0.223047
Up	PITX1	15	0.003043	1,063,398	0.219288
Up	CRYBG1	15	0.002626	695,160	0.262106
Up	IGSF3	15	0.00201	920,740	0.242717
Up	IMPA2	15	0.00307	1,138,144	0.227266
Up	MEOX1	14	0.003339	829,668	0.222802
Up	ATP6V0D2	14	0.002463	486,050	0.221524
Up	TFAP2C	13	0.002502	1,073,038	0.244769
Up	PTPRN2	13	0.002218	428,790	0.226631
Up	ATP1A2	12	0.002637	1,131,342	0.233035
Up	ADAMTS1	12	0.0024	617,034	0.225842
Up	SEMA6A	12	0.003041	437,668	0.233437
Up	APOBEC3B	12	0.001441	744,566	0.221746
Up	PLAU	11	0.003237	803,628	0.243617
Up	LCP1	11	0.002165	543,558	0.22579
Up	EFNA5	10	8.84E−04	151,924	0.243922
Up	RETREG1	10	0.001241	470,002	0.215797
Up	STMN2	10	0.002634	545,182	0.208403
Up	PPM1H	9	0.001276	937,346	0.238098
Up	HTR1B	9	0.00207	271,180	0.241681
Up	MSMO1	8	0.001453	551,916	0.229042

Table 4 (continued)

Regulation	Node	Degree	Betweenness	Stress	Closeness
Up	KRT36	8	7.68E−04	350,894	0.240059
Up	PCSK9	7	3.29E−04	54,918	0.224446
Up	DNAJC6	7	0.001693	628,446	0.220171
Up	SCD	7	0.001379	435,390	0.231021
Up	KRT34	7	0.003303	1,108,236	0.179504
Up	ALPP	5	0.001644	337,932	0.19351
Up	PDE4B	5	7.08E−04	200,632	0.228311
Up	CLEC14A	5	0.001237	443,264	0.182555
Up	GPAT3	5	8.73E−04	87,548	0.215234
Up	NTNG1	4	0.00111	125,664	0.21288
Up	P2RX6	4	5.27E−04	122,142	0.203863
Up	TNFRSF19	4	9.59E−04	559,034	0.234359
Up	ZNF608	4	8.37E−04	272,030	0.208296
Up	HLA-C	4	4.32E−04	96,322	0.228365
Up	SIX2	3	0.002226	1,176,074	0.232756
Up	RAMP3	3	8.22E−04	758,918	0.155682
Up	FLT1	3	2.74E−04	63,344	0.237412
Up	FABP5	3	4.57E−04	103,188	0.213702
Up	SH2D2A	3	4.10E−04	212,434	0.243678
Up	EGFL6	3	2.04E−04	63,224	0.222151
Up	COL7A1	3	9.87E−04	306,868	0.253622
Up	KRT37	3	8.22E−04	275,598	0.132128
Up	CNTN1	3	4.36E−04	235,384	0.249705
Up	SEMA3B	3	1	6	1
Up	MMP3	2	4.76E−05	19,768	0.225049
Up	GPR183	2	5.02E−05	27,508	0.203684
Up	EPHA5	2	8.99E−06	2564	0.215691
Up	IL31RA	2	3.46E−05	26,030	0.212973
Up	CCDC85A	2	1.60E−05	5982	0.186687
Up	WNT16	2	0	0	0.207099
Up	PSG1	2	2.29E−04	125,530	0.232345
Up	ACSL5	2	1.08E−04	106,606	0.247181
Up	PIK3CG	2	2.70E−04	137,430	0.238506
Up	LEPR	2	2.99E−04	76,112	0.231847
Up	FGF10	1	0	0	0.21491
Up	ELMO1	1	0	0	0.207895
Up	ADRA1D	1	0	0	0.178118
Up	P3H2	1	0	0	0.200313
Up	MMRN1	1	0	0	0.219347
Up	COCH	1	0	0	0.209407
Up	PLA2G7	1	0	0	0.200033
Up	PLPPR4	1	0	0	0.196606
Up	VWC2	1	0	0	0.193656
Up	ST6GALNAC3	1	0	0	0.209407
Up	MGLL	1	0	0	0.240677
Up	CLEC3B	1	0	0	0.242005
Up	CARD16	1	0	0	0.198628
Up	COL6A6	1	0	0	0.195886
Up	EREG	1	0	0	0.209389

Table 4 (continued)

Regulation	Node	Degree	Betweenness	Stress	Closeness
Up	ADGRG1	1	0	0	0.240677
Up	PCOLCE	1	0	0	0.207187
Up	LPAR3	1	0	0	0.165313
Up	ADCY1	1	0	0	0.188751
Up	ACKR3	1	0	0	0.180429
Up	CRTAC1	1	0	0	0.203038
Up	ADAMTS5	1	0	0	0.200288
Up	CACNA1D	1	0	0	0.176234
Up	PPFIA2	1	0	0	0.208448
Down	MDFI	180	0.067201	24,938,630	0.277565
Down	ACTBL2	159	0.059788	16,984,080	0.312604
Down	PRKD1	151	0.049413	25,348,404	0.299078
Down	DAPK1	135	0.043258	14,691,546	0.296454
Down	ACTC1	125	0.043583	13,786,990	0.30907
Down	FOXL1	119	0.031148	26,714,620	0.26612
Down	EEF1A2	96	0.030658	12,573,334	0.292657
Down	EPB41L3	88	0.027315	13,917,190	0.278966
Down	KRT18	86	0.033018	9,650,494	0.319249
Down	SPINT2	85	0.027392	6,835,460	0.266689
Down	CHRM4	78	0.024102	10,167,440	0.263869
Down	FOXS1	72	0.016114	9,987,450	0.261276
Down	ERG	70	0.015816	8,115,936	0.283484
Down	IGF2BP1	68	0.018742	4,590,692	0.29807
Down	STX11	67	0.018202	6,035,790	0.271495
Down	VDR	63	0.017576	4,272,470	0.275569
Down	PFKP	63	0.019322	10,071,716	0.289505
Down	FGFR2	62	0.017882	4,630,474	0.273724
Down	TNIK	61	0.017992	5,615,768	0.280526
Down	EDA	61	0.017336	5,807,424	0.250476
Down	RUNX1	60	0.018065	4,954,702	0.282973
Down	P4HA3	59	0.019144	7,280,554	0.270709
Down	ID2	55	0.016051	4,769,732	0.275678
Down	PKP2	55	0.020937	6,848,742	0.291937
Down	SLC2A12	55	0.015964	7,708,246	0.235084
Down	MYH10	52	0.016668	3,589,202	0.30441
Down	NRG1	50	0.016348	3,547,318	0.264831
Down	TRIM63	48	0.012682	4,517,170	0.262615
Down	SORBS2	45	0.00868	6,589,870	0.267186
Down	EPHA4	43	0.013734	2,446,220	0.275429
Down	NTRK3	42	0.010949	4,470,618	0.254578
Down	CCNA1	42	0.009251	3,433,956	0.256971
Down	PDLIM5	42	0.013999	2,000,086	0.281548
Down	EFEMP1	42	0.014364	2,399,978	0.254751
Down	THBS1	41	0.012427	2,896,698	0.261318
Down	ANK3	40	0.010421	4,772,040	0.248506
Down	USP2	40	0.012325	2,824,276	0.271343
Down	SGK1	38	0.007985	3,779,252	0.269659
Down	EPPK1	38	0.007359	4,225,478	0.276414
Down	SIRPA	35	0.008354	4,887,612	0.273248

Table 4 (continued)

Regulation	Node	Degree	Betweenness	Stress	Closeness
Down	RAB3IP	34	0.008005	2,997,686	0.246805
Down	PLK2	34	0.011158	1,806,358	0.269003
Down	SLC6A15	33	0.00856	4,749,196	0.239752
Down	RASSF5	32	0.007015	3,193,748	0.249705
Down	MBP	32	0.010185	1,574,138	0.275008
Down	NOTCH2	32	0.007274	2,605,336	0.262106
Down	EPB41	32	0.008073	4,217,818	0.277123
Down	GEM	32	0.006616	4,083,892	0.257488
Down	CSTA	31	0.007847	3,030,162	0.254192
Down	LMO3	31	0.009479	1,668,282	0.254485
Down	NCAM1	30	0.009068	1,465,722	0.279977
Down	SORBS1	30	0.004624	2,039,478	0.267878
Down	DES	29	0.005178	1,191,798	0.262814
Down	PTPRN	29	0.00818	1,615,368	0.250039
Down	MYEF2	29	0.006925	2,882,312	0.252124
Down	EPHB2	28	0.005108	1,607,522	0.262885
Down	ALDH1B1	28	0.007171	3,795,748	0.243592
Down	ITGA7	27	0.007364	1,448,790	0.24742
Down	BEGAIN	27	0.005823	1,454,784	0.243849
Down	GCH1	26	0.006139	2,464,430	0.240558
Down	MECOM	25	0.005644	2,581,520	0.241789
Down	NFIX	25	0.004898	1,145,270	0.242102
Down	RAB11FIP1	25	0.005257	2,872,472	0.269749
Down	PLP1	25	0.006069	1,380,662	0.25009
Down	DAB1	24	0.005216	1,464,652	0.258472
Down	LIMCH1	24	0.00482	2,909,102	0.245745
Down	PPP1R13L	23	0.003793	1,790,426	0.243714
Down	GAS6	23	0.004951	1,039,182	0.213496
Down	FRMD5	23	0.008404	1,763,548	0.260297
Down	BEND7	23	0.005734	1,408,600	0.237632
Down	CELSR2	23	0.006178	1,023,294	0.238074
Down	FZD7	23	0.005034	1,869,974	0.232656
Down	GALNT12	22	0.005278	1,572,318	0.221878
Down	CPEB1	22	0.003768	839,108	0.260451
Down	TNNT1	21	0.002906	698,182	0.250257
Down	GPC3	21	0.004711	1,741,574	0.228012
Down	TSPAN2	21	0.0057	972,012	0.248379
Down	IGFBP3	19	0.004017	1,687,726	0.236363
Down	ID3	18	0.001278	690,358	0.212211
Down	NFIB	18	0.006922	1,031,030	0.260982
Down	GPC4	18	0.003629	1,410,500	0.24296
Down	KRT13	18	0.001814	1,014,686	0.248392
Down	FLG	18	0.002769	1,392,370	0.234846
Down	BACH2	17	0.004043	1,105,092	0.231593
Down	NUAK1	17	0.002249	854,382	0.242053
Down	ARHGEF4	17	0.002473	1,190,348	0.242681
Down	HRNR	17	0.002458	1,173,000	0.254698
Down	F11R	16	0.002671	1,064,048	0.24369
Down	MPP7	16	0.003136	1,190,282	0.243495

Table 4 (continued)

Regulation	Node	Degree	Betweenness	Stress	Closeness
Down	PALM	16	0.003087	1,250,900	0.236489
Down	PITX2	15	0.002541	901,710	0.225267
Down	NPAS1	15	0.00459	1,076,534	0.226199
Down	EYA2	14	0.00257	759,552	0.228129
Down	KCNJ2	14	0.002222	782,768	0.215119
Down	FBXO32	13	0.002724	515,166	0.242476
Down	SGCA	13	0.003283	940,578	0.222619
Down	SOX9	13	0.003999	579,538	0.246068
Down	EYA4	12	0.00376	1,740,072	0.201699
Down	PLN	12	0.002418	280,268	0.216142
Down	SLAIN1	12	0.001293	817,642	0.236328
Down	HOXC8	11	0.00227	382,190	0.215539
Down	CXADR	11	0.001515	411,744	0.239941
Down	AK4	10	0.002393	770,268	0.214257
Down	BDNF	9	0.001499	722,196	0.218746
Down	MGST1	9	0.001054	383,496	0.220891
Down	JPH3	9	0.001571	342,404	0.213928
Down	SLC35F2	9	0.002137	334,890	0.208127
Down	MCUB	8	0.001343	376,614	0.228773
Down	EN1	7	0.001288	650,718	0.214239
Down	NXPH3	7	0.001042	394,474	0.225685
Down	PRDM6	6	8.27E−04	180,818	0.199541
Down	ACKR2	6	0.001234	909,848	0.168077
Down	SIX1	5	0.003887	1,852,370	0.236581
Down	CRLF1	5	4.88E−04	106,980	0.20325
Down	LZTS1	5	8.75E−04	197,898	0.219357
Down	CDKL2	5	0.001644	383,036	0.220071
Down	EPHA3	4	8.78E−05	38,542	0.232634
Down	SLC16A11	4	0.001233	310,374	0.20308
Down	MYOZ3	4	8.48E−04	232,490	0.20818
Down	DUSP2	3	8.09E−06	4042	0.210113
Down	VLDLR	3	1.30E−04	45,712	0.232179
Down	FPR1	3	1.55E−05	5552	0.223858
Down	PCDHA12	3	8.37E−04	124,810	0.228472
Down	SERPINE2	2	3.16E−04	17,692	0.221949
Down	NTRK2	2	2.65E−04	169,496	0.24658
Down	BGN	2	5.42E−05	11,718	0.190197
Down	IL20RA	2	3.31E−04	115,232	0.234925
Down	PPP1R12B	2	6.15E−05	31,120	0.224054
Down	KRT7	2	4.36E−05	26,098	0.228784
Down	NOX4	2	1.13E−04	68,694	0.246442
Down	ANKRD1	2	0	0	0.208582
Down	PPP1R14A	2	1.75E−04	131,520	0.245497
Down	NGF	1	0	0	0.214173
Down	FGF7	1	0	0	0.21491
Down	RASSF2	1	0	0	0.199819
Down	ADAM12	1	0	0	0.191183
Down	ZFHX4	1	0	0	0.210194
Down	EMB	1	0	0	0.168806

Table 4 (continued)

Regulation	Node	Degree	Betweenness	Stress	Closeness
Down	ST3GAL6	1	0	0	0.209407
Down	DSE	1	0	0	0.209389
Down	OR51E2	1	0	0	0.18939
Down	GPC6	1	0	0	0.195477
Down	NRP2	1	0	0	0.213477
Down	THBS2	1	0	0	0.207187
Down	CHL1	1	0	0	0.199051
Down	ULBP1	1	0	0	0.185683
Down	SLC22A23	1	0	0	0.174346
Down	RAPGEF5	1	0	0	0.199051
Down	IL33	1	0	0	0.198628
Down	ADAP1	1	0	0	0.230234
Down	MYOZ1	1	0	0	0.208002
Down	DYSF	1	0	0	0.208127
Down	DLX5	1	0	0	0.177326
Down	FLI1	1	0	0	0.220881
Down	COL8A2	1	0	0	0.196059
Down	TINAGL1	1	0	0	0.217271
Down	PMEL	1	0	0	0.208448
Down	APLN	1	0	0	0.217271
Down	MTSS1	1	0	0	0.208448
Down	DEPP1	1	0	0	0.220891
Down	IL6	1	0	0	0.205342
Down	BEND5	1	0	0	0.21344
Down	RASSF9	1	0	0	0.202682
Down	MYOM2	1	0	0	0.200173
Down	FOXC2	1	0	0	0.183859
Down	FANK1	1	0	0	0.254631
Down	ZNF185	1	0	0	0.238167
Down	ITGB1BP2	1	0	0	0.18209
Down	PDLIM3	1	0	0	0.172315
Down	SORCS2	1	0	0	0.179491
Down	PITPNM3	1	0	0	0.195886
Down	TPD52L1	1	0	0	0.228676
Down	PAPPA2	1	0	0	0.191183
Down	WNK4	1	0	0	0.212396
Down	STXBP6	1	0	0	0.221615

(ex; *hsa-mir-556-3p*) targeting regulation of *epb41l3*, 48 mirnas (ex; hsa-mir-10b-5p) targeting regulation of *dapk1* and 41 mirnas (ex; *hsa-mir-1229-5p*) targeting regulation of *mdfi*, and are listed in Table 5.

Construction of the TF-hub gene regulatory network

We searched for target-regulated hub gene TFs using NetworkAnalyst database and then used the results of this database. By constructing TF-hub gene regulatory network networks, we found 520 nodes (TF: 198; Hub Gene: 322) and 8331 edges (Fig. 6). We identified 59 TFs (ex; *tcf3*) targeting regulation of *ptch1*, 42 tfs (ex; *phc1)* targeting regulation of *ccnd2*, 37 tfs (ex; *nr1i2*) targeting regulation of *prkcb*, 36 tfs (ex; *hoxc9*) targeting regulation of *st8sia4*, 34 tfs (ex; *rnf2*) targeting regulation of *foxq1*, 44 tfs (ex; *clock*) targeting regulation of *dapk1*, 38 tfs (ex; *prdm14*) targeting regulation of *igf2bp1*, 36 tfs (ex; *smarca4*) targeting regulation of *krt18*, 34 tfs (ex; *trim28*) targeting regulation of *stx11* and 31 tfs (ex; *htt*) targeting regulation of *epb41l3*, and are listed in Table 5.

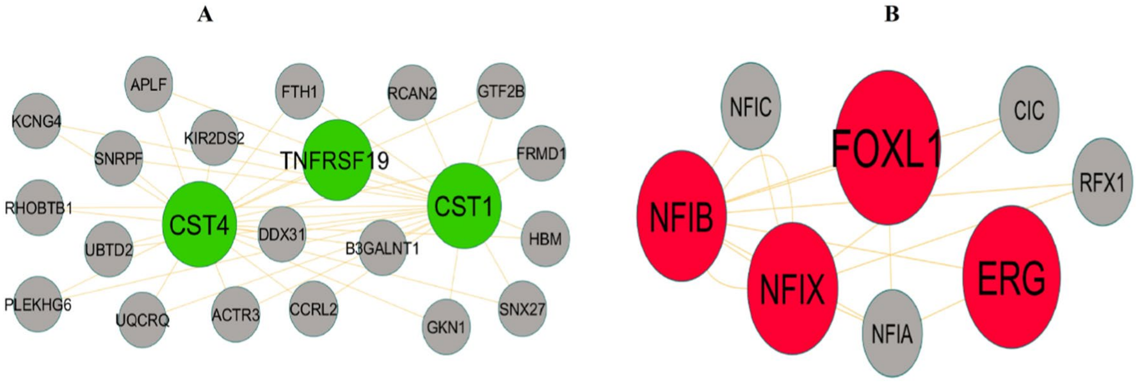

Fig. 4 Modules selected from the PPI network. **A** The most significant module was obtained from PPI network with 22 nodes and 41 edges for upregulated genes **B** The most significant module was obtained from PPI network with 8 nodes and 14 edges for downregulated genes. Upregulated genes are marked in parrot green; downregulated genes are marked in red

Fig. 5 Hub gene—miRNA regulatory network. The olive green color diamond nodes represent the key miRNAs; upregulated genes are marked in green; downregulated genes are marked in red

Receiver operating characteristic curve (ROC) analysis

The ROC curve was used to evaluate the diagnostic value of hub genes. As shown in Fig. 7, the AUC values of *vcam1*, *snca*, *prkcb*, *adrb2*, *foxq1*, *mdfi*, *actbl2*, *prkd1*, *dapk1* and *actc1* in endometriosis were 0.904, 0.907, 0.903, 0.926, 0.901, 0.910, 0.923, 0.892, 0.895 and 0.898, respectively. Thus, the hub genes have good diagnostic efficiency in endometriosis and normal control samples.

Discussion

Endometriosis is a key cause of serious reproductive disorder in the female population and leads to a public health burden. Lack of early screening and diagnosis of endometriosis result in progressive worsening including dysmenorrhea, dyspareunia, chronic pelvic pain, irregular uterine bleeding and infertility. The advance stage of endometriosis seriously affects the recovery from female reproductive diseases. Therefore, it is necessary to identify potential novel biomarkers for early diagnosis and targeted therapy of endometriosis. With the advancement of bioinformatics methods and NGS technology, it has started to be widely applied to identify potential novel biomarkers. This investigation used NGS data to conduct bioinformatics analysis for identifying novel target genes and pathways involved in the occurrence and development of endometriosis. Bioinformatics and NGS

Table 5 MiRNA–hub gene and TF–hub gene topology table

Regulation	Hub Genes	Degree	MicroRNA	Regulation	Hub Genes	Degree	TF
Up	CCND2	365	hsa-mir-3143	Up	PTCH1	59	TCF3
Up	VCAM1	102	hsa-mir-6888-5p	Up	CCND2	42	PHC1
Up	PTPRD	89	hsa-mir-200a-3p	Up	PRKCB	37	NR1I2
Up	PDGFB	88	hsa-mir-3122	Up	ST8SIA4	36	HOXC9
Up	PRKCB	81	hsa-mir-17-5p	Up	FOXQ1	34	RNF2
Up	PIK3R3	78	hsa-mir-93-5p	Up	PDGFB	34	RELA
Up	FOXQ1	62	hsa-mir-5706	Up	NES	32	KLF4
Up	MME	54	hsa-mir-186-5p	Up	MME	31	BMI1
Up	PTCH1	52	hsa-mir-372-3p	Up	PIK3R3	30	RUNX1
Up	SNCA	37	hsa-mir-369-3p	Up	PTPRD	27	PAX3
Up	S100A4	36	hsa-mir-194-3p	Up	ADRB2	27	GATA2
Up	ST8SIA4	31	hsa-mir-181c-5p	Up	SNCA	25	SCLY
Up	ADRB2	22	hsa-mir-10b-5p	Up	S100A4	20	ARNT
Up	NES	21	hsa-mir-487b-5p	Up	VCAM1	16	SMAD3
Up	NTRK1	4	hsa-mir-147a	Up	NTRK1	13	JARID2
Down	IGF2BP1	241	hsa-mir-2110	Down	DAPK1	44	CLOCK
Down	ACTC1	77	hsa-mir-4432	Down	IGF2BP1	38	PRDM14
Down	EPB41L3	53	hsa-mir-556-3p	Down	KRT18	36	SMARCA4
Down	DAPK1	48	hsa-mir-10b-5p	Down	STX11	34	TRIM28
Down	MDFI	41	hsa-mir-1229-5p	Down	EPB41L3	31	HTT
Down	FOXL1	36	hsa-mir-7-5p	Down	FOXL1	29	STAT3
Down	SPINT2	29	hsa-mir-4677-3p	Down	ERG	28	TFAP2C
Down	KRT18	27	hsa-mir-126-3p	Down	SPINT2	26	NACC1
Down	EEF1A2	27	hsa-mir-16-5p	Down	EEF1A2	24	DNAJC2
Down	STX11	21	hsa-mir-373-3p	Down	CHRM4	22	SOX9
Down	PRKD1	19	hsa-mir-34a-5p	Down	PRKD1	21	MTF2
Down	ACTBL2	14	hsa-mir-599	Down	ACTBL2	18	YAP1
Down	ERG	9	hsa-mir-145-5p	Down	MDFI	17	TET1
Down	FOXS1	8	hsa-mir-101-3p	Down	ACTC1	15	TBX5
Down	CHRM4	4	hsa-mir-146a-5p	Down	FOXS1	11	EP300

data analysis might become to identify effective drugs for treating endometriosis in future.

In this investigation, we analyzed the endometriosis GSE243039 screened from the GEO database. It includes 20 normal control samples and 20 endometriosis samples. Compared to normal controls, we found 958 DEGs (including 479 upregulated genes and 479 downregulated genes). Research has shown that *pcsk9* [48], *cntn4* [49], *sema3a* [50], *sfrp4* [51], *mfap5* [52], *bmp6* [53], *cdh6* [54], *piezo2* [55] and *pkp2* [56] play an important role in the pathogenesis of inflammation. Some studies have shown that altered expression of genes includes *pcsk9* [57], *sema3a* [58] and *sfrp4* [59] promotes the pain. Studies have revealed that genes including *pcsk9* [60], *cntn4* [61], *sema3a* [62], *ptgis* [63], *sfrp4* [64], *mfap5* [65], *cdh6* [66], *gpc6* [67] and *pkp2* [68] play a key role in ovarian cancer. A study indicates that genes including *pcsk9* [69], *sfrp4* [70] and *bmp6* [71] have been identified in polycystic ovarian syndrome. Genes including *pcsk9* [72], *cntn4* [49], sema3a [73], *sfrp4* [74], *mfap5* [75], *bmp6* [76], *pde1c* [77] and *pkp2* [78] are altered expressed in cardiovascular diseases. The genes including *pcsk9* [79], *apcdd1* [80], *sfrp4* [81], *mfap5* [82] and *pkp2* [83] have been identified to be involved in the development of obesity. Studies show that genes including *pcsk9* [84] and *sfrp4* [85] have been known to be involved in gestational diabetes mellitus. Recent reports have revealed that genes including *pcsk9* [86], *sema3a* [87], *sfrp4* [81] and *bmp6* [88] play an important role in the pathogenesis of diabetes mellitus. Recent reports have revealed that genes including *pcsk9* [89], *sema3a* [90], *ptgis* [91] and *piezo2* [92] have a significant prognostic potential in hypertension. Studies have found that genes including *adamts19* [93] and *bmp6* [94] play an indispensable role in infertility. Previous studies have reported that the genes including *sema3a* [95], *sfrp4* [96] and *bmp6* [94] are a key regulator of endometriosis.

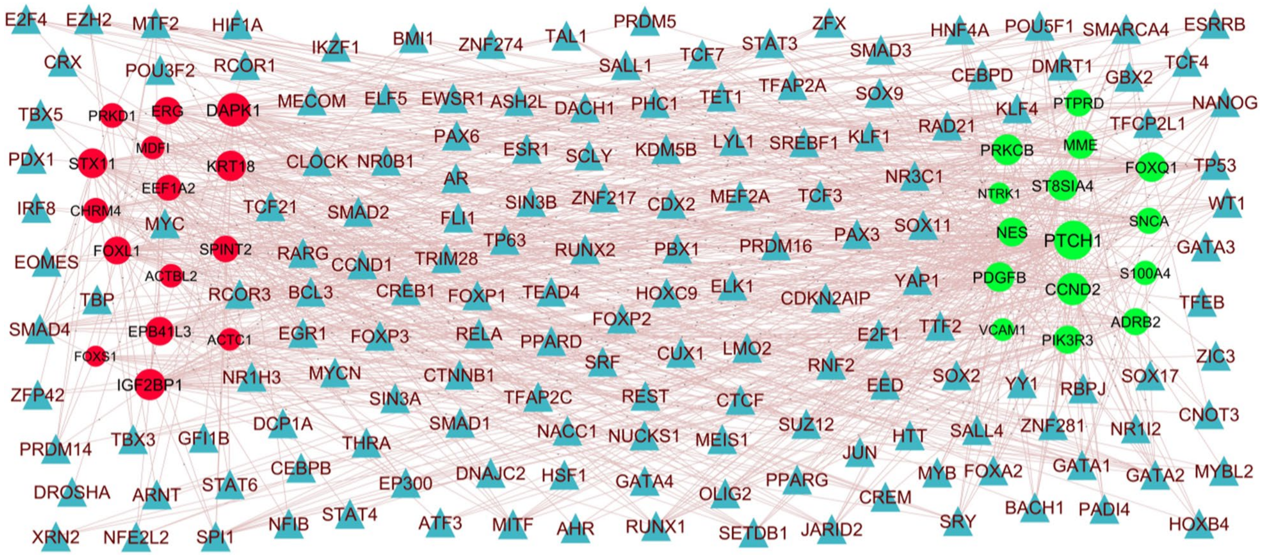

Fig. 6 Hub gene—TF regulatory network. The blue color triangle nodes represent the key TFs; upregulated genes are marked in dark green; downregulated genes are marked in dark red

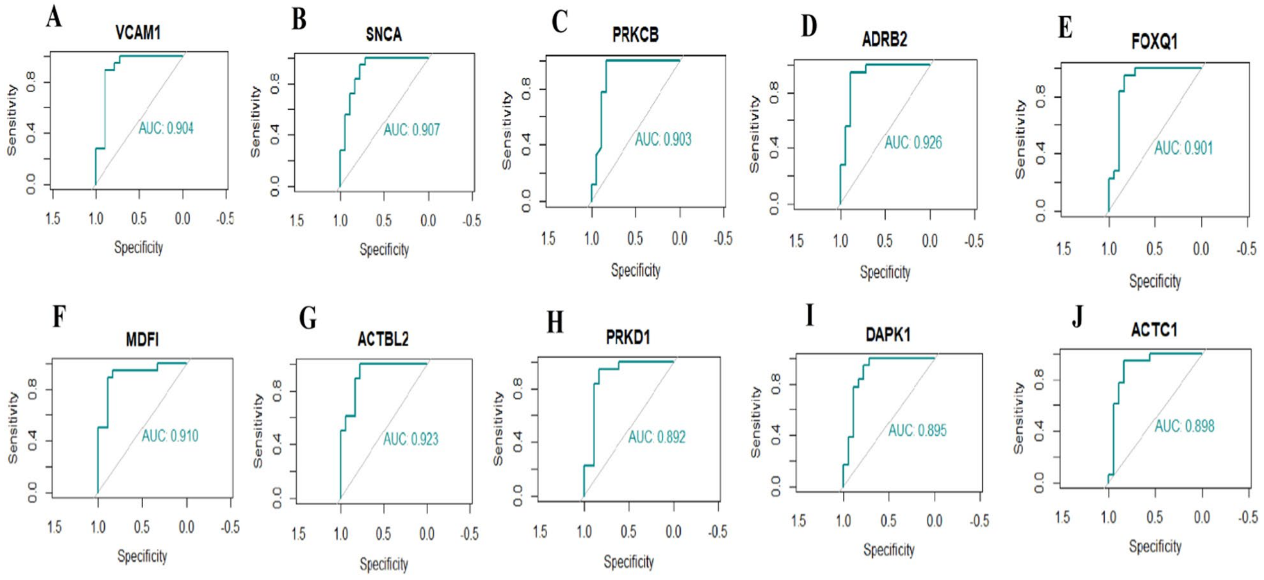

Fig. 7 ROC curve analyses of hub genes. **A** VCAM1 **B** SNCA **C** PRKCB **D** ADRB2 **E** FOXQ1 **F** MDFI **G** ACTBL2 **H** PRKD1 **I** DAPK1 **J** ACTC1

Recently, increasing evidence demonstrated that genes including *ptgis* [97] and *sfrp4* [98] might be potential therapeutic targets for endometrial cancer treatment. Studies have found that genes including *sfrp4* [99] and mfap5 [100] are used as prognostic markers for cervical cancer. This result suggests that these genes might play a key role in the progression of endometriosis.

In this investigation, we identified enriched genes in GO terms and signaling pathways that might be utilized as diagnostic, prognostic and therapeutic targets in endometriosis. Signaling pathways including extracellular matrix organization [101], nervous system development [102], signal transduction [103], hemostasis [104], muscle contraction [105], signaling by retinoic acid [106] and diseases of glycosylation [107] were responsible for advancement of endometriosis. Recently, mounting researches have revealed that genes including *l1cam* [108], *hsd17b2* [109], *vcam1* [110], *sox6* [111], *fgf10* [112], *mmp12* [113], *ccr1* [114], *prok1* [115], *prl* [116], *timp3* [117], *adamts9* [118], *ndnf* [119], *lhcgr* [120], *pdgfb* [121], *ldlr* [122], *cd4* [123], *foxl2* [124], *trpa1* [125], *adrb2* [126], *plau* 127], *epcam* [128], *ucn2* [129], *cyp1a1* [130], *ntn1* [131], *il15* [132], *bmp2* [133], *apoe* [134], *casp1* [135], *abcg2* [136], *ace* [137], *pgr* [138], *alpp* [139], *lpar4* [140], *atrnl1* [141], *hla-c* [142], *mmp3* [143], *pdlim3* [144], *nfasc* [145], *il33* [146], *ngf* [147], comp [148], *fst* [149], *efemp1* [150], *gata6* [151], *tcf21* [152], *ptgs2* [153], *hoxc8* [154], *akr1c3* [155], *bdnf* [119], *epha3* [156], *inhba* [157], *rap-1gap* [158], *tlr3* [159], *nox4* [160], *tgfbi* [161], *igf2bp1* [162], *dlx5* [163], *vdr* [164], *fzd7* [165], *id2* [166], *tlr2* [167], *il6* [168], *gas6* [169], *dusp2* [170], *fgf7* [171], *ccn2* [172], *igfbp3* [173], *chl1* [174], *bgn* [175], *ntrk2* [176], *slit2* [177], *notch2* [178], lif [179], *cd200* [180], *bst2* [181], *dysf* [182], *dapk1* [183], *kiss1* [184], *fpr1* [185] and *trh* [186] were vital for the onset and developmental process of endometriosis. A great number of studies have indicated that genes including *l1cam* [187], *ajap1* [188], *hsd17b2* [189], *vcam1* [190], *grp* [191], *aqp8* [192], *wnt6* [193], *fabp4* [194], *sox6* [195], *ntrk1* [196], *cntn1* [197], *mmp12* [198], *lag3* [199], *sox18* [200], *ccr1* [201], *flt1* [202], *prdm1* [203], *trpc3* [204], *dkk2* [205], *rnf157* [206], *dhcr24* [207], *bmp4* [208], *prl* [209], *foxq1* [210], *wnt5a* [211], *meox1* [212], *dock4* [213], *timp3* [214], *adamts9* [215], *ndnf* [216], *neto1* [217], *cd24* [218], *lhcgr* [219], *scd* [220], *pdgfb* [221], *mmrn1* [222], *ldlr* [223], *cd4* [224], *foxl2* [225], *trpa1* [226], *epha5* [227], *tox* [228], *cst4* [229], *rspo3* [230], *map2k6* [231], *nes* [232], *tmem119* [233], *padi2* [234], *mmp8* [235], *kdr* [236], *adrb2* [237], *mgat3* [238], *ptprc* [239], *pitx1* [240], *kl* [241], *plau* [242], *znf365* [243], *pik3r3* [244], *sox8* [245], *ccnd2* [246], *crabp2* [247], *pcdh9* [248], *epcam* [249], *clec14a* [250], *cyp1a1* [251], *ntn1* [252], *pdgfd* [253], *cldn3* [254], *lepr* [255], *il15* [256], *bmp2* [257], *lama5* [258], *ntng1* [259], *krt19* [260], *ros1* [261], *apoe* [262], *ptch1* [263], *itpka* [264], *casp1* [265], *nid1* [266], *abcg2* [267], ace [268], *pgr* [269], *wls* [270], *klk3* [271], *lrp1b* [272], *ly6k* [273], *alpp* [274], *prame* [275], *slco4a1* [276], *egfl6* [277], *gpbar1* [278], *elmo1* [279], *wnk2* [280], *il2rb* [281], *diras2* [282], *galnt14* [283], *rtkn2* [284], *atrnl1* [285], *s100a4* [286], *macc1* [287], *mmp3* [288], *col11a1* [289], *cables1* [290], *fgfr2* [291], *il33* [292], *ngf* [293], *foxc2* [294], *comp* [295], *fst* [296], *sorbs2* [297], *efemp1* [298], *gata6* [299], *tcf21* [300], *ptgs2* [301], *mtss1* [302], *dact1* [303], *hoxc8* [304], *pitx2* [305], *tnfsf10* [306], *bdnf* [307] *krt7* [308], *ndrg2* [309], *eya2* [310], *inhba* [311], *sgk1* [312], *slc2a12* [313], *dio3* [314], *epb41l3* [315], *tlr3* [316], *angptl4* [317], *ephb2* [318], *fli1* [319], *thbs1* [320], *id3* [321], *nox4* [322], *tgfbi* [323], *igf2bp1* [324], *sall4* [325], *dlx5* [326], *vdr* [327], *lzts1* [328], *fzd7* [329], *en2* [330], *enc1* [331], *ifne* [332], *tnnt1* [333], *ankrd1* [334], *sox9* [335], *mgp* [336], *sulf1* [337], *cyp24a1* [338], *dnah11* [339], *tlr2* [340], *il6* [341], *nppb* [342], *spink1* [343], *gpc3* [344], *ntrk3* [345], *amigo2* [346], *foxd1* [347], *adam12* [348], *dusp2* [349], *usp2* [350], *klf2* [351], *sik1* [352], *six1* [310], *fgf7* [353], *myh10* [354], *igfbp3* [355], *lyve1* [356], *actbl2* [357], *slit2* [358], *actc1* [359], *nnmt* [360], *chi3l1* [361], *runx1* [362], *nfib* [363], notch2 [364], *pgf* [365], *thbs2* [366], *nav1* [367], *nrg1* [368], *plk2* [369], *itgbl1* [370], *cd200* [371], *bst2* [372], *kcnn3* [373], *hmcn1* [374], *veph1* [375], *tfpi2* [376], *sytl2* [377], *ccdc80* [378], *dapk1* [379], *kiss1* [380], *il20ra* [381], *has3* [382], *has1* [382], *mgst1* [383], *fpr1* [384] and *sh3rf2* [385] are closely associated with the onset and progression of ovarian cancer. A previous study reported that the genes including *l1cam* [386], *hsd17b2* [387], *grp* [388], *fabp4* [389], *sox6* [390]. *mmp12* [391], *apod* [392], *lag3* [393], *cst1* [394], *flt1* [395], *dhcr24* [396], *prl* [397], *wnt5a* [398], *timp3* [399], *cd24* [400], *lhcgr* [401], *mmrn1* [402], *cd4* [403], *adamts5* [404], *adamts1* [405], *padi2* [406], *mark1* [407], *kl* [408], *plau* [409], *sox8* [410], *crabp2* [411], *ptprd* [412], *epcam* [413], *irx2* [414], *sema3b* [415], *cyp1a1* [416], *pdgfd* [417], *lepr* [418], *apoe* [419], *casp1* [420], *mgll* [421], *nid1* [422], *abcg2* [423], *ace* [424], *pgr* [425], *hpse2* [426], *lmtk3* [427], *alpp* [428], *egfl6* [429], *cacna2d3* [430], *mctp1* [431], *hkdc1* [432], *s100a4* [433], *macc1* [434], *mmp3* [435], *fgfr2* [436], *il33* [437], *foxc2* [438], *itga7* [439], *efemp1* [440], *gata6* [441], *bhlhe41* [442], *tcf21* [443], *gdf10* [444], *nkx3-1* [445], *akr1c3* [446], *sgk1* [447], *rap1gap* [448], *fli1* [449], *nox4* [450], *serpine2* [451], *igsf9* [452], *igf2bp1* [453], *sall4* [454], *vdr* [455], *celsr2* [456], *enc1* [457], *sox9* [458], *cyp24a1* [338], *il6* [459], *gas6* [460], *klf2* [461], *six1* [462], *igfbp3* [463], *lyve1* [464], *chl1* [465], *bgn* [466], *slit2* [467], *nrp2* [468], nnmt [469], *runx1* [470], *thbs2* [471], *hspb7* [472], *nrg1* [473], *tfpi2* [474], *dapk1* [183], *has3* [475], *has1* [475], *steap1* [476] and *mgst1* [477] play an important role in the pathophysiology of endometrial cancer. Study demonstrated that genes including *vcam1* [478], *aqp8* [479], *l1cam* [480], *fabp4* [481], *psg1* [482], *sox6* [483], *mmp12* [484], *apod* [485], *lag3* [486], *sox18* [487], *flt1* [488], *fabp5* [489], *bmp4* [490], *prl* [491], *foxq1* [492], *wnt5a* [493], *frzb* [494], *cpe* [495], *ereg* [496], *ndnf* [497], *cd24* [498], *scd* [499], *ldlr* [500], *cd4* [501], *foxl2* [502], *krt17* [503], *nes* [504], *mgat3* [505], *mark1* [506], *kl* [507], *plau* [508], *epha7* [509], *pik3r3* [510], *ccnd2* [511], *hecw1* [512], *epcam* [513], *batf2* [514], *cyp1a1* [515], *mstn* [516], *il15* [517], *syt7* [518], *pak3* [519], *krt19* [520], *ros1* [521], *cubn* [522], *ptch1* [523], *casp1* [524], *abcg2* [525], *pgr* [526], *hpse2* [527], *lrp1b* [528], *alpp* [529], *cyp2s1* [530], *doc2b* [531], *msmo1* [532], *sorcs1* [533], hla-c [534], *s100a4* [535], *macc1* [536], *mmp3* [537], *fgfr2* [538], *il33* [539], *ngf* [540], *foxc2* [541], *sorbs2* [542], *itga7* [543], *efemp1* [544], *gata6* [545], *tcf21* [546], *ptgs2* [547], *mtss1* [548], *dact1* [549], *spint2* [550], *nkx3-1* [551], *hoxc8* [552], *bdnf* [497], *ndrg2* [553], *epha3* [554], *eya2* [555], *inhba* [556], *alpl* [557], *sgk1* [558], *rap1gap* [559], *epb41l3* [560], *tlr3* [561], *angptl4* [562], *ephb2* [563], *fli1* [564], *thbs1* [565], *nox4* [566], *tgfbi* [567], *igf2bp1* [568], *sall4* [569], *vdr* [570], *rarb* [571], *epha4* [572], *enc1* [573], *sox9* [574], *sulf1* [575], *tlr2* [576], *il6* [577], *gpc3* [578], *ntrk3* [579], *ccna1* [580], *amigo2* [581], *foxd1* [582], *ccno* [583], *adam12* [584], *rassf2* [585], *hoxb7* [586], *klf2* [587], *sik1* [588], *six1* [589], *fgf7* [590], *igfbp3* [591], *chl1* [592], *eppk1* [593], *slit2* [594], *flg* [595], *nrp2* [596], *nnmt* [597], *chi3l1* [598], *runx1* [599], *apln* [600], *sema3c* [601], *notch2* [602], *thbs2* [603], *pnpla1* [604], *bst2* [605], *hmcn1* [606], *ulbp1* [607], *tfpi2* [608], *dapk1* [609], *kiss1* [610], *fpr1* [611] and *pik3ap1* [612] can participate in the occurrence and development of cervical cancer. The abnormal expression of genes including *cbln2* [613], *sdk1* [614], *vcam1* [615], *six2* [616], *avpr1a* [617], *epha6* [618], *fabp4* [619], *psg1* [620], *ano1* [621], *sox6* [622], *fgf10* [623], *pla2g7* [624], *mmp12* [625], *adra1d* [626], *lag3* [627], *flt1* [628], *fabp5* [629], *prdm1* [630], *trpc3* [631], *igsf3* [632], *bmp4* [633], *il1rl1* [634], *prl* [635], *nefl* [636], *wnt5a* [637], *timp3* [638], *ndnf* [639], *snap25* [640], *cd24* [641], *pdgfb* [642], *ldlr* [643], *cd4* [644], *trpa1* [645], *adamts1* [646], *pde4b* [647], *nes* [648], *th* [649], *psg9* [650], *cacna1d* [651], *mmp8* [652], *adrb2* [653], *kl* [654], *plau* [655], *ptprd* [656], *sema3b* [657], *ucn2* [658], *cyp2j2* [659], *cyp1a1* [660], *atp1a2* [661], *cldn3* [662], *mstn* [663], *lepr* [664], *il15* [665], *cacna1h* [666], *bmp2* [667], *lama5* [668], *ros1* [669], *apoe* [670], *casp1* [671], *pde9a* [672], *efnb2* [673], *abcg2* [674], *ace* [675], *pgr* [676], *slc35f3* [677], *ica1* [678], *alpp* [679], *trpc6* [680], *gpbar1* [681], *pnpla3* [682], *hla-c* [683], *s100a4* [684], *macc1* [685], *mmp3* [686], *gdnf* [687], *fgfr2* [688], *il33* [689], *ngf* [690], *pappa2* [691], *comp* [692], *gata6* [693], *acan* [694], *tcf21* [695], *ptgs2* [696], *pitx2* [697], *akr1c3* [698], *bdnf* [699], *sgk1* [700], *tlr3* [701], *angptl4* [702], *fli1* [703], *thbs1* [704], *id3* [705], *nox4* [706], *pcsk1* [707], *itgb1bp2* [708], *wnk4* [709], *dlx5* [710], *vdr* [711], *epha4* [712], *mgp* [713], *cyp24a1* [714], *id2* [715], *tlr2* [716], *il6* [717], *nppb* [718], *gas6* [719], *f11r* [720], *foxd1* [721], *adam12* [722], *ncam1* [723], *usp2* [724], *klf2* [725], *sik1* [726], *fgf7* [727], *igfbp3* [728], *bgn* [729], *ntrk2* [730], *nnmt* [731], *chi3l1* [732], *runx1* [733], *apln* [734], *stox2* [735], *kcnq4* [736], *notch2* [737], *pgf* [738], *thbs2* [739], *pdlim5* [740], *prdm6* [741], *htr6* [742], *nrg1* [743], *cd200* [744], *bst2* [745], *kcnn3* [746], *slc2a5* [747], *tfpi2* [748], *dysf* [749], *ccdc80* [750], *dapk1* [751], *kiss1* [752], *slc4a4* [753], *steap2* [754], *sorbs1* [755], *ackr2* [756], *fpr1* [757], *gpr143* [758] and *trh* [759] contributes to the progression of hypertension. Study showed that the genes including *robo2* [760], *vcam1* [761], *grp* [762], *fabp4* [763], *ano1* [764], *sox6* [765], *tfap2c* [766], *ramp3* [767], *pla2g7* [768], *mmp12* [769], *faim2* [770], *apod* [771], *lag3* [772], *sox18* [773], *f2rl2* [774], *ccr1* [775], *flt1* [776], *fabp5* [629], *trpc3* [777]. *thsd7a* [778], *dkk2* [779], *prkcb* [780], *dhcr24* [781], *pde3b* [782], *bmp4* [783], *il1rl1* [784], *mypn* [785], *plcg2* [786], prl [787], *wnt5a* [788], *meox1* [789], *timp3* [790], *frzb* [791], *cpe* [792], *adamts9* [793], *ndnf* [794], *pdgfb* [795], *pik3cg* [796], *ldlr* [797], *cd4* [798], *trpa1* [799], *f2rl3* [800], *c1ql1* [801], *adamts5* [802], *pde4b* [803], *nes* [804], *th* [805], *mmp8* [806], *kdr* [807], *adrb2* [808], ackr3 [809], *ptprc* [810], *kl* [811, 812], *plau* [813], *ccnd2* [814], *ptgs1* [815], *insig1* [816], *irx2* [817], *siglec1* [818], *ucn2* [819], *cyp2j2* [820], *cyp1a1* [821], *astn2* [822], *ntn1* [823], *pdgfd* [824], *mstn* [663], lepr [664], *il15* [825], *cacna1h* [826], *bmp2* [827], *syt7* [828], *zbtb46* [829], *ros1* [830], *apoe* [831], *cubn* [832], *rbm20* [833], *casp1* [834], *pde9a* [835], abcg2 [836], *hmgcr* [837], *ace* [838], *grem2* [839], *palmd* [840], *lrp1b* [841], *alpp* [842], *trpc6* [843], *gpbar1* [844], *myzap* [845], *prodh* [846], *il2rb* [847], *cdhr3* [848], *pnpla3* [849], *fads1* [850], *hla-c* [851], *s100a4* [852], *mmp3* [853], *pdlim3* [854], *gdnf* [855], *fgfr2* [856], *il33* [857], ngf [858], *hapln1* [859], *foxc2* [860], *comp* [861], *fst* [862], *sorbs2* [863], *itga7* [864], *pln* [865], *gata6* [866], *bhlhe41* [867], *acan* [868], *tcf21* [869], *ptgs2* [870], *dact1* [871], *pitx2* [872], *akr1c3* [873], *bdnf* [874], *ndrg2* [875], *eya2* [876], *sgk1* [877], *rap1gap* [878], *dio3* [879], *tlr3* [880], *angptl4* [881], *ephb2* [882], *thbs1* [883], *tnnt2* [884], *nox4* [885], *s1pr5* [886], *serpine2* [887], *pcsk1* [888], *tgfbi* [889], *sall4* [890], *eya4* [891], *itgb1bp2* [708], *vdr* [892], *gpc4* [893], *celsr2* [894], *epha4* [895], *tnnt1* [896], *ankrd1* [897], *zfpm2* [898], sox9 [899], *mgp* [900], *cyp24a1* [901], *dnah11* [902], *tlr2* [903], *il6* [904], *gas6* [905], *gpc3* [906], *ntrk3* [907], *amigo2* [908], *f11r* [909], *adam12* [722], *ncam1* [910], *usp2* [911], *klf2* [912], *sik1* [913], *six1* [914], *fgf7* [915], *ccn2* [916], *jcad* [917], *igfbp3* [918], *lyve1* [919], *prkd1* [920], *bgn* [921], *eda* 922], *slit2* [923], *actc1* [924], *nrp2* [925], *chi3l1* [926], *runx1* [927], *apln* [928], *myom2* [929], *myoz1* [930], *ppp1r13l* [931], *thbs2* [932], *des* [933], *pdlim5* [934], *hspb7* [935], *nrg1* [936], *plk2* [937], *itgbl1* [938], *cd200* [939], *kcnn3* [940], *kcnj2* [941], *eva1a* [942], *tfpi2* [943], *dysf* [944], *adap1* [945], *ccdc80* [946], *dapk1* [947], *scn4b* [948], *esyt3* [949], *abca8* [950], *heg1* [951], *fpr1* [952], *sspn* [953], *adh1c* [954], *sirpa* [955] and *trh* [956] might be related to the pathophysiology of cardiovascular diseases. A study showed genes including *hsd17b2* [109], *efna5* [957], *mmp12* [958], *prok1* [959], *prl* [960], *nlrp2* [961], *ndnf* [962], *mei4* [963], *cd24* [964], *lhcgr* [965], *cd4* [966], *foxl2* [967], *kdr* [968], *adrb2* [969], *cyp1a1* [970], *ntn1* [971], *mstn* [972], *bmp2* [973], *apoe* [974], *ace* [975], *pgr* [976], *grem2* [977], *alpp* [978], *mmp3* [979], *gdnf* [980], *fgfr2* [981], *il33* [982], *ngf* [983], *comp* [984], *cecr2* [985], *fst* [986], *gata6* [987], *ptgs2* [153], *bdnf* [988], *sgk1* [989], *angptl4* [990], *thbs1* [991], *id3* [992], *nox4* [993], *igf2bp1* [994], *sall4* [995], *vdr* [996], *sulf1* [997], *tlr2* [998], *il6*

[999], *gpc3* [1000], *ccno* [1001], *igfbp3* [1002], *chl1* [1003], *ntrk2* [1004], *slit2* [1005], *apln* [1006], *notch2* [1007], *pgf* [1008], *lif* [1009], *cd200* [1010], *tfpi2* [1011], *kiss1* [752] and *trh* [1012] are highly prone to infertility. A study indicated that activation of genes including *vcam1* [761], *stra6* [1013], *coch* [1014], *grp* [1015], *aqp8* [1016], *fabp4* [1017], *ano1* [1018], *sox6* [1019], *tfap2c* [1020], *ntrk1* [1021], *cntn1* [1022], *fgf10* [1023], *pla2g7* [768], *mmp12* [1024], *lcp1* [1025], *snca* [1026], *apod* [1027], *lag3* [1028], *ccr1* [1029], *cst1* [1030], *retreg1* [1031], *flt1* [1032], *fabp5* [1033], *prdm1* [1034], *trpc3* [1035], *prok1* [1036], *wnt16* [1037], *f13a1* [1038], *dhcr24* [1039], *pde3b* [1040], *bmp4* [783], *il1rl1* [1041], *plcg2* [1042], *prl* [1043], *foxq1* [1044], *nefl* [1045], *wnt5a* [1046], *timp3* [1047], *serpinb2* [1048], *frzb* [1049], *nlrp2* [1050], *cpe* [1051], *adamts9* [1052], *npw* [1053], *ereg* [1054], *ndnf* [1055], *snap25* [1056], *syt1* [1057], *scd* [1058], *pdgfb* [1059], *ldlr* [1060], *cd4* [1061], *gpr183* [1062], *trpa1* [125], *ptger4* [1063], *adamts5* [1064], *rspo3* [1065], *krt17* [1066], *adamts1* [1067], *pde4b* [1068], *nes* [804], *sh2d2a* [1069], *th* [1070], *tmem119* [1071], *mmp8* [1072], *adrb2* [1073], *ackr3* [1074], *mgat3* [1075], *tnfrsf9* [1076], *txk* [1077], *kl* [811], *plau* [1078], *epha7* [1079], *znf365* [1080], *pik3r3* [1081], *sox8* [1082], *ccnd2* [1083], *ptgs1* [1084], *batf2* [1085], *ucn2* [1086], *cyp2j2* [1087], *clec14a* [1088], *cyp1a1* [1089], *ntn1* [1090], *mstn* [1091], *lepr* [1092], *cd248* [1093], *il15* [825], *bmp2* [1094], *ros1* [1095], *mme* [1096], *apoe* [1097], *ptch1* [1098], *casp1* [1099], *mgll* [1100], efnb2 [1101], abcg2 [1102], *hmgcr* [1103], *ace* [1104], *pgr* [1105], *grem2* [839], *rgs7* [1106], *chst1* [1107], *alpp* [1108], *trpc6* [1109], *slco4a1* [276], *cyp4b1* [1110], *gpbar1* [844], *elmo1* [1111], *doc2b* [1112], *cd163l1* [1113], *slco2a1* [1114], *il2rb* [1115], *b4galnt2* [1116], *slc37a2* [1117], *pnpla3* [1118], *fads1* [1119], *hla-c* [1120], *st3gal5* [1121], *s100a4* [1122], *macc1* [1123], *cort* [1124], *mmp3* [1125], *gdnf* [1126], *lmo3* [1127], *nfasc* [1128], *fgfr2* [1129], *il33* [1130], *ngf* [1131], *hapln1* [1132], *gdf6* [1133], *foxc2* [1134], *comp* [1135], *fst* [1136], *itga7* [1137], *gata6* [1138], *acan* [1139], *tcf21* [1140], *ptgs2* [1141], *mtss1* [1142], *dhrs3* [1143], *nkx3-1* [1144], *tnfsf10* [1145], *bdnf* [1146], *ndrg2* [1147], epha3 [1148], *pla2g5* [1149], *mecom* [1150], *sgk1* [1151], *tlr3* [1152], *angptl4* [1153], *ephb2* [1154], *fli1* [1155], *thbs1* [1156], *mbp* [1157], *id3* [1158], *nox4* [1159], *s1pr5* [1160], *pi16* [1161], *igf2bp1* [1162], *sall4* [1163], *vldlr* [1164], *vdr* [1165], *fam20a* [1166], *epha4* [1167], *ankrd1* [1168], *sgca* [1169], *sox9* [1170], *mgp* [1171], *cyp24a1* [1172], *tlr2* [1173], *il6* [1174], *gas6* [1175], *ntrk3* [1176], *adam12* [1177], *ncam1* [1178], *myoc* [1179], *usp2* [1180], *klf2* [1181], *sik1* [1182], *six1* [1183], *fgf7* [1184], *ccn2* [1185], *igfbp3* [1186], *lyve1* [1187], *prkd1* [1188], *bgn* [1189], *slit2* [1190], *irx3* [1191], *actc1* [1192], *flg* [1193], *nrp2* [1194], *nnmt* [1195], *chi3l1* [1196], *runx1* [1197], *nfib* [1198], *apln* [1199], *plp1* [1200], *nav2* [1201], *notch2* [1202], *pgf* [1203], *thbs2* [1204], *nrg1* [1205], *lif* [1206], *plk2* [1207], *nalcn* [1208], *cd200* [1209], *kcnn3* [1210], *eva1a* [1211], *tfpi2* [1212], *dysf* [1213], *sytl2* [1214], *tlr1* [1215], *ccdc80* [946], *dapk1* [947], *kiss1* [1216], *gem* [1217], *il20ra* [1218], *has3* [1219], *has1* [1220], *slc4a4* [1221], *sirpb1* [1222], *steap1* [1223], *ackr2* [1224], *fpr1* [1225], gng7 [1226], *igfbpl1* [1227], *pik3ap1* [1228], *adh1c* [1229], *lxn* [1230] and *trh* [1231] has been observed in inflammation. Studies have suggested that genes including *vcam1* [1232], *aqp8* [1233], *fabp4* [1234], *fabp5* [1235], *bmp4* [1236], *prl* [960], *wnt5a* [1237], *adamts9* [1238], *ndnf* [1239], *lhcgr* [1240], *ldlr* [1241], *cd4* [1242], *adamts5* [1243], *map2k6* [1244], *adamts1* [1245], *pde4b* [1246], *th* [1247], *mmp8* [1248], *adrb2* [969], *kl* [1249], *epha7* [1250], *ucn2* [1251], *cyp1a1* [970], *lepr* [1252], *il15* [1253], *bmp2* [1254], *apoe* [1255], *casp1* [1256], *ace* [1257], *pgr* [1258], *grem2* [1259], *sorcs1* [1260], *hkdc1* [1261], *fads1* [1262], *s100a4* [1263], *il33* [1243], *ngf* [1264], *comp* [1265], *fst* [1266], *gata6* [1267], *acan* [1268], *akr1c3* [1269], *bdnf* [1270], *angptl4* [1271], *nox4* [1272], *vdr* [1273], *gpc4* [1274], *tlr2* [1275], *il6* [1276], *igfbp3* [1277], *tnik* [1278], *apln* [1279], *pgf* [1280], *nrg1* [1281], lif [1282], *angptl1* [1283], *kiss1* [1284], *sorbs1* [1285] and *trh* [1286] can be used as important therapeutic targets for polycystic ovarian syndrome. A recent study found that genes including *vcam1* [1287], *stra6* [1288], *aqp8* [1289], *fabp4* [1290], *sox6* [1291], *ramp3* [1292], *mmp12* [1293], *faim2* [770], *ccr1* [1294], *ism1* [1295], flt1 [1296], *fabp5* [1297], *thsd7a* [1298], *sctr* [1299], *wnt16* [1300], *prkcb* [1301], *pde3b* [1302], *il1rl1* [1041], *prl* [1303], *wnt5a* [1304], *htr1b* [1305], *timp3* [1306], *cpe* [1051], *ereg* [1307], *ndnf* [1308], *snap25* [1309], *cd24* [1310], *scd* [1058], *pdgfb* [1311], *ldlr* [1312], *cd4* [1313], *trpa1* [1314], *map2k6* [1315], *pde4b* [1316], *th* [1317], *mmp8* [1318], *adrb2* [1319], *kl* [1320], *plau* [1321], *ptgs1* [1084], *insig1* [1322], *bmp8a* [1323], ucn2 [1324], ntn1 [1090], *pdgfd* [1325], *mstn* [1326], *lepr* [1092], *il15* [1327], *bmp2* [1328], *apoe* [1329], *casp1* [1330], *mgll* [1331], *nid1* [1332], *abcg2* [1333], *ace* [1334], *pgr* [1335], *grem2* [1336], *lrp1b* [1337], *alpp* [1338], *trpc6* [1339], *egfl6* [1340], *gpbar1* [1341], *aif1l* [1342], *gpat3* [1343], *sorcs1* [1260], *slc37a2* [1344], *fads1* [1345], *acsl5* [1346], *ptprn2* [1347], *s100a4* [1348], *macc1* [1349], *cort* [1350], *mmp3* [1351], *gdnf* [1352], *lmo3* [1353], *cables1* [1354], il33 [1355], *ngf* [1356], *foxc2* [1357], *fst* [1136], *pln* [1358], *acan* [1359], *ptgs2* [1360], *gdf10* [1361], *cpne5* [1362], *dgat2* [1363], *bdnf* [1364], *rgs4* [1365], *epha3* [1366], *pla2g5* [1367], *sgk1* [700], *tlr3* [1368], *angptl4* [1369], *ephb2* [1370], *thbs1* [1371], *id3* [1372], *nox4* [1373], *pcsk1* [1374], *wnk4* [1375], *vldlr* [1376], *vdr* [1377], *gpc4* [1378], *ifne* [1379], *zfpm2* [1380], *tlr2* [1381], il6 [1382], *spink1* [1383], *gas6* [1384], *f11r* [1385], *siglec15* [1386], *adam12* [1387], *myoc* [1388], *usp2* [1389], *sik1* [1390], *ccn2* [1391], *igfbp3* [1392], *lyve1*

[1393], *bgn* [1394], *eda* [1395], *ntrk2* [1396], *slit2* [1397], *irx3* [1191], *nnmt* [1398], *chi3l1* [1399], *runx1* [1400], *apln* [1401], *pgf* [1402], *htr6* [742], *nrg1* [1403], *npy4r* [1404], *ccdc80* [1405], *kiss1* [1406], *slc6a15* [1407], *esyt3* [1408], *sorbs1* [1409], *slc38a3* [1410], *lxn* [1411] and *trh* [1412] are potential targets for obesity. Studies have shown that genes including *vcam1* [1413], *stra6* [1414], *aqp8* [1415], *fabp4* [1416], *flt1* [1417], *bmp4* [633], *prl* [1418], *adamts9* [1419], *ndnf* [1420], *dtx1* [1421], *cd4* [1422], *adamts5* [1423], *mmp8* [1424], *adrb2* [1425], *ptprd* [1426], *insig1* [1427], *lepr* [1428], *il15* [1429], *apoe* [1430], *ace* [1431], *lrp1b* [1432], *alpp* [1433], *hkdc1* [1434], *pnpla3* [1435], *fads1* [1436], *mmp3* [1437], *fgfr2* [1438], *il33* [1439], *foxc2* [1440], *fst* [1441], *hoxc8* [1442], *bdnf* [1443], *ndrg2* [1444], *angptl4* [1445], *tgfbi* [1446], *vdr* [1447], *gpc4* [1448], *cyp24a1* [1449], *tlr2* [1450], *il6* [1451], *klf2* [1452], *igfbp3* [1453], *slit2* [1454], *apln* [1455], *notch2* [1456], *pgf* [1457], *nrg1* [1458], *tlr1* [1459], *ccdc80* [1460] and *kiss1* [1461] are the contributing factors to gestational diabetes mellitus pathogenesis. A previous study identified genes including *vcam1* [1462], *stra6* [1013], *wnt6* [1463], *fabp4* [1464], *sox6* [1465], *pla2g7* [1466], *mmp12* [1467], *faim2* [770], *snca* [1468], *apod* [1469], *lag3* [1470], *prex1* [1471], *flt1* [1472], *fabp5* [1473], *trpc3* [1474], *thsd7a* [1475], *prkcb* [1476], *pde3b* [1477], *bmp4* [1478], *prl* [1479], *nefl* [1480], *wnt5a* [1481], *timp3* [1306], *cpe* [1482], *adamts9* [1483], ndnf [1484], *snap25* [1485], *scd* [1058], *ldlr* [1486], *cd4* [1487], *trpa1* [1488], *rspo3* [1489], *pde4b* [1490], *th* [1491], *cacna1d* [1492], *mmp8* [1318], *kdr* [1493], *adrb2* [653], *kl* [1494], *plau* [1321], *ccnd2* [1495], *ptprd* [1496], *siglec1* [1497], *ucn2* [1324], *cyp2j2* [1498], *cyp1a1* [1499], *ntn1* [1090], *mstn* [1326], *lepr* [1500], *il15* [1501], *bmp2* [1502], *apoe* [1503], *cubn* [1504], *casp1* [1505], *mgll* [1506], *efnb2* [1507], *nid1* [1508], *abcg2* [1102], *ace* [1509], *stmn2* [1510], *ica1* [1511], *trpc6* [1512], *gpbar1* [1513], *elmo1* [1514], *doc2b* [1515], *ank1* [1516], *sorcs1* [1517], *hkdc1* [1518], *pnpla3* [1519], *fads1* [1520], *acsl5* [1521], *hla-c* [1522], *s100a4* [1523], *cort* [1524], *mmp3* [1525], *gdnf* [1526], *cables1* [1354], *il33* [1527], *ngf* [1528], *foxc2* [1529], *comp* [1530], *fst* [1531], *sorbs2* [1532], *gata6* [1533], *ptgs2* [1141], *dact1* [1534], *dgat2* [1535], *bdnf* [1484], *ndrg2* [1536], *sgk1* [1537], *tlr3* [1152], *angptl4* [1538], *ephb2* [1539], *thbs1* [1540], *mbp* [1541], *nox4* [1542], *pi16* [1543], *pcsk1* [888], *tgfbi* [1544], *igf2bp1* [1545], *wnk4* [1546], *vldlr* [1547], *vdr* [1548], *gpc4* [1274], *ptprn* [1549], *epha4* [712], *sox9* [1550], *mgp* [1551], *cyp24a1* [1552], *tlr2* [1553], *il6* [1554], *nppb* [1555], *spink1* [1556], *gas6* [1557], *f11r* [1558], *foxd1* [1559], *adam12* [1560], *klf2* [1561], *sik1* [1562], *fgf7* [1563], *igfbp3* [918], *lyve1* [1393], *eda* [1395], *slit2* [1564], *irx3* [1565], *nnmt* [1398], *chi3l1* [1566], *runx1* [1567], *apln* [1568], *col4a3* [1569], *notch2* [1570], *pdlim5* [740], *nrg1* [1571], *dmrt2* [1572], *npy4r* [1573], *cd200* [1574], *bst2* [1575], *tfpi2* [1576], *kiss1* [1406], *mpp7* [1577], *sorbs1* [1409], *slc38a3* [1578], *chn2* [1579] and *trh* [1580] have been implicated in diabetes mellitus pathology. A previous bioinformatics study suggested that genes including *grp* [1581], *avpr1a* [1582], *ano1* [1583], *ntrk1* [1584], *fgf10* [1585], *mmp12* [1586], *snca* [1587], *ccr1* [1588], *flt1* [1589], *fabp5* [1590], *trpc3* [1591], *bmp4* [1592], *prl* [1593], *wnt5a* [1594], *timp3* [1595], *serpinb2* [1596], *nlrp2* [1050], *npw* [1053], *ereg* [1597], *ndnf* [1598], *snap25* [1056], *syt1* [1599], *cd4* [1600], *gpr183* [1601], *trpa1* [1602], *pde4b* [1603], *th* [1604], *mmp8* [1605], *adrb2* [1606], *mgat3* [1607], *plau* [1608], *astn2* [1609], *il15* [1610], *bmp2* [1611], *apoe* [1612], *pde9a* [1613], *mgll* [1100], *efnb2* [1101], *hmgcr* [1614], *ace* [1615], *syt9* [1616], *trpc6* [1617], *xcr1* [1618], *s100a4* [1619], *mmp3* [1620], *gdnf* [1621], *il33* [1622], *ngf* [1623], *gdf6* [1133], *comp* [1624], *acan* [1625], *ptgs2* [1626], *gdf10* [1627], *bdnf* [1628], *ndrg2* [1629], *sgk1* [1630], *tlr3* [1631], *ephb2* [1632], *mbp* [1633], *nox4* [1619], *shank2* [1634], *pi16* [1635], *dlx5* [1636], *vdr* [1637], *zfhx2* [1638], *epha4* [1639], *cyp24a1* [1640], *id2* [1641], *tlr2* [1642], *il6* [1643], *spink1* [1644], *gas6* [1645], *klf2* [1646], *six1* [1647], *chl1* [1648], *slit2* [1649], *runx1* [1650], *notch2* [1651], *pgf* [1652], *nrg1* [1653], *nalcn* [1654], *lxn* [1655] and *trh* [1656] might play a role in the development of pain. Therefore, studying the enriched genes involved in the regulation of endometriosis might be helpful to clarify the incidence or molecular pathogenic mechanisms of various complications including ovarian cancer, endometrial cancer, cervical cancer, hypertension, cardiovascular diseases, infertility, inflammation, polycystic ovarian syndrome, obesity, gestational diabetes mellitus, diabetes mellitus and pain.

Establishing PPI network and module analysis is friendly for researchers to investigate the underlying molecular mechanism of endometriosis for the reason that the DEGs would be grouped and ordered in the network judging by their interactions. PPI network and module analyses could help to find hub genes involved in the regulation of endometriosis. A recent study suggested that the hub genes including *vcam1* [110], *adrb2* [126] and *dapk1* [183] might take part in the progression of endometriosis. Recent evidence indicates that the hub genes including *vcam1* [190], *adrb2* [237], *foxq1* [210], *actbl2* [357], *dapk1* [379], *actc1* [359], *cst4* [229], *nfib* [363], *nfix* [1657] and *erg* [1658] are potential therapeutic targets in ovarian cancer. Previous studies have reported that hub genes including *vcam1* [478], *foxq1* [492], *dapk1* [609] and *erg* [1659] participate in the progression of cervical cancer. Studies have shown that hub genes including *vcam1* [615], *adrb2* [653] and *dapk1* [751] are involved in the regulation of hypertension.

Several studies have found hub genes including *vcam1* [761], *prkcb* [780], *adrb2* [808], *prkd1* [920], *dapk1* [947], *actc1* [924] and *nfix* [1660] expression levels were significantly altered in cardiovascular diseases. Studies show that hub genes including *vcam1* [761], *snca* [1026], *adrb2* [1073], *foxq1* [1044], *prkd1* [1188], *dapk1* [947], *actc1* [1192], *cst1* [1030], *nfib* [1198] and *erg* [1661] are mainly involved in progression of inflammation. Previous studies have shown that hub genes including *vcam1* [1232] and *adrb2* [969] were identified to be closely associated with polycystic ovarian syndrome. Many studies have confirmed that hub genes including *vcam1* [1287], *prkcb* [1301] and *adrb2* [1319] were an important participant in obesity. Previous studies have found that hub genes including *vcam1* [1413] and *adrb2* [1425] were shown to be primarily involved in gestational diabetes mellitus. A growing number of studies have demonstrated that hub genes including *vcam1* [1462], *snca* [1468], *prkcb* [1476] and *adrb2* [653] play an important role in progression of diabetes mellitus. Accumulating evidence shows that hub gene *adrb2* [969] is an important risk factor for infertility. Recent study reported that hub gene *adrb2* [1606] plays a crucial role in pain progression. A recent study showed that hub genes including *dapk1* [183], cst1 [394] and nfix [1662] plays an important role in the pathogenesis of endometrial cancer. Our findings suggested *mdfi*, *tnfrsf19* and *foxl1* as potential novel diagnostic biomarkers for endometriosis. This investigation identified the possible hub genes that were highly correlated with the PPI network to find the novel biomarkers associated in the pathogenesis of endometriosis. Our ROC curve analysis showed that hub genes have diagnostic value for endometriosis.

In this investigation, the miRNA-hub gene regulatory network and TF-hub gene regulatory network of the hub genes in endometriosis were analyzed by using miRNet and NetworkAnalyst database. These analyses could help to find some miRNAs, TFs and hub genes involved in the regulation of endometriosis. Studies have shown that biomarkers including *ccnd2* [246], *vcam1* [190], *pdgfb* [221], *ptch1* [263], *foxq1* [210], *igf2bp1* [324], *actc1* [359], *epb41l3* [315], *dapk1* [379], *hsa-mir-17-5p* [1663], *tcf3* [1664], *rnf2* [1665], *clock* [1666], *smarca4* [1667] and *trim28* [1668] can lead to ovarian cancer. Studies reported that biomarkers including *ccnd2* [511], *vcam1* [478], *ptch1* [523], *foxq1* [492], *igf2bp1* [568], *epb41l3* [560], dapk1 [609], *hsa-mir-17-5p* [1669], *tcf3* [1670] and *trim28* [1671] were proposed to contribute to the development of cervical cancer. A previous study reported that biomarkers including *ccnd2* [814], *vcam1* [615], *pdgfb* [795], *prkcb* [780], *actc1* [924], *dapk1* [947], *hsa-mir-17-5p* [1672], *hsa-mir-2110* [1673], *tcf3* [1674] and *smarca4* [1675] play a key role in cardiovascular diseases. Accumulated evidence has demonstrated that biomarkers including *ccnd2* [1083], *vcam1* [761], *pdgfb* [1059], *ptch1* [1098], *foxq1* [1044], *igf2bp1* [1162], *actc1* [1192], *dapk1* [947], *hsa-mir-2110* [1676], *hsa-mir-10b-5p* [1677], *tcf3* [1678], *nr1i2* [1679] and *trim28* [1680] are associated with inflammation. Studies have shown that biomarkers including *ccnd2* [1495], *vcam1* [1462], *ptprd* [1496], *prkcb* [1476], *igf2bp1* [1545], *hsa-mir-200a-3p* [1681] and *hsa-mir-10b-5p* [1682] were identified to be associated with diabetes mellitus. A previous study found that biomarkers including *vcam1* [110], *pdgfb* [121], *igf2bp1* [162], *dapk1* [183] and *hsa-mir-17-5p* [1683] have been found in endometriosis. Recent studies have identified biomarkers including *vcam1* [1232], *hsa-mir-17-5p* [1684] and hsa-mir-2110 [1685] are involved in the pathogenesis and progression of polycystic ovarian syndrome. A previous study reported that biomarkers including *vcam1* [1287], *pdgfb* [1311], *prkcb* [1301], *hsa-mir-17-5p* [1686], *hsa-mir-10b-5p* [1687] and *trim28* [1688] are associated with the pathogenesis and development of obesity. Many studies have shown that biomarkers including *vcam1* [1413], *ptprd* [1426] and *hsa-mir-17-5p* [1689] are likely to be important in the development of gestational diabetes mellitus. Recent studies have demonstrated that biomarkers including *igf2bp1* [453], *dapk1* [183], *ptprd* [412], tcf3 [1690], *smarca4* [1691] and *trim28* [1692] are important in the development of endometrial cancer. Research has shown that biomarkers including *ptprd* [656], *pdgfb* [642], *dapk1* [751], *hsa-mir-4432* [1693], *smarca4* [1694] and *trim28* [1695] might be potential therapeutic targets for hypertension. Recent studies have proposed that the biomarkers including *igf2bp1* [994], *hsa-mir-17-5p* [1696] and *smarca4* [1697] serve a vital role in infertility. Study has suggested that *TRIM28* [1698] might be involved in the development of pain. New biomarkers associated with diagnosis were identified in this study: *st8sia4*, *mdfi*, *krt18*, *stx11*, *hsa-mir-3143*, *hsa-mir-6888-5p*, hsa-mir-3122, *hsa-mir-556-3p*, *hsa-mir-1229-5p*, *phc1*, *hoxc9*, prdm14 and *htt* (huntingtin). We suggest that exercise can regulate the expression of these miRNAs, TFs and hub genes, thereby inhibiting the occurrence and development of endometriosis.

There are few limitations in our investigation. While our investigation presents promising results, several limitations should be accepted. In vivo and in vitro validation experiments for hub genes and clinical trials are required to assess the correlation linking clinical parameters and the hub genes in endometriosis pathogenesis. In this investigation, we did not account for the potential confounding effects of demographic variables. We will conduct more in-depth research in the future.

Conclusions

The current investigation identified biomarkers and pathways which might be involved in endometriosis progression through the integrated analysis of NGS dataset. These results might contribute to a better understanding of the molecular mechanisms which underlie endometriosis and provide a series of potential biomarkers. However, further experiments are required to verify the findings of the current investigations. Therefore, further experiments with additional patient cohorts are also required to confirm the results of these investigations. In vivo and in vitro investigation of gene and pathway interaction is essential to delineate the specific roles of the identified biomarkers, which might help to confirm biomarker functions and reveal the molecular mechanisms underlying endometriosis.

Abbreviations

DEGs	Differentially expressed genes
NGS	Next-generation sequencing
GEO	Gene expression omnibus
GO	Gene ontology
PPI	Protein–protein interaction
miRNA	Micro-ribonuclic acid
TF	Transcription factor
ROC	Receiver operating characteristic curve
VCAM1	Vascular cell adhesion molecule 1
SNCA	Synuclein alpha
PRKCB	Protein kinase C beta
ADRB2	Adrenoceptor beta 2
FOXQ1	Forkhead box Q1
MDFI	MyoD family inhibitor
ACTBL2	Actin beta-like 2
PRKD1	Protein kinase D1
DAPK1	Death-associated protein kinase 1
ACTC1	Actin alpha cardiac muscle 1

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Availability of data and materials

The datasets supporting the conclusions of this article are available in the GEO (Gene Expression Omnibus) (https://www.ncbi.nlm.nih.gov/geo/) repository. [(GSE243039) https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE243039].

Declarations

Ethics approval and consent to participate

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

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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