Protein-protein interaction analysis to identify biomarker networks for endometriosis

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Abstract. The identification of biomarkers and their interaction network involved in the processes of endometriosis is a critical step in understanding the underlying mechanisms of the disease. The aim of the present study was to construct biomarker networks of endometriosis that integrated human protein-protein interactions and known disease-causing genes. Endometriosis-associated genes were extracted from Genotator and DisGeNet and biomarker network and pathway analyses were constructed using atBioNet. Of 100 input genes, 96 were strongly mapped to six major modules. The majority of the pathways in the first module were associated with the proliferation of cancer cells, the enriched pathways in module B were associated with the immune system and infectious diseases, module C included pathways related to immune and metastasis, the enriched pathways in module D were associated with inflammatory processes, and the majority of the pathways in module E were related to replication and repair. The present approach identified known and potential biomarkers in endometriosis. The identified biomarker networks are highly enriched in biological pathways associated with endometriosis, which may provide further insight into the molecular mechanisms underlying endometriosis.

Introduction

Endometriosis is a benign gynecological disorder that occurs in 10% of women of reproductive age (1). The main symptoms include infertility and chronic pelvic pain (2). Although there are a number of studies on endometriosis, the majority of the mechanisms are not well understood (3-6). Identifying disease biomarkers and their interaction networks is important to improve the understanding of the causes of endometriosis, as well as to improve medical care.

Several databases have been developed that store associations between genes and diseases, such as the Online Mendelian Inheritance in Man (7), the Human Gene Mutation Database (8) and the Genetic Association Database (9). Due to the nature of the database curation process, the data are incomplete. Some gene-disease databases that combine gene-associated diseases from several expert, public and curated data sources also exist (10,11). With the rapid accumulation of gene-disease data, increasing research has been utilizing the gene-disease database as a start-point to mine disease biomarkers (12-14).

Protein-protein interaction (PPI) networks include information on the biological processes and molecular functions of cells and have been widely used to characterize the underlying mechanisms of genes associated with complex diseases (15,16). The majority of human diseases are caused by a group of correlated molecules or a network, rather than a single gene (17). Thus, identification and validation of biomarker networks is critical to disease diagnosis, prognosis and treatment.

In the present study, a disease network of endometriosis that integrated human PPIs and known disease-causing genes was constructed. Endometriosis-causing genes were identified from gene-disease databases. Subsequently, bioinformatics approaches, including PPI network construction, module analysis, functional enrichment analysis and text mining, were utilized in the research. The results of the present study may provide new targets for endometriosis therapy and identify the potential mechanisms of the disease.

Materials and methods

Seed gene selection. Endometriosis-related genes were obtained from Genotator (http://genotator.hms.harvard.edu/) (10) and DisGeNET (http://www.disgenet.org) (11). For each tool, gene lists were extracted using the query term, endometriosis. Genotator provides high quality gene-disease

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associations based upon data from 11 trustworthy resources. DisGeNET is a discovery platform that integrates information on gene-disease associations from several public data sources and literature (11). Thus, a list of genes that had been experimentally validated to be associated with endometriosis were obtained.

Disease-gene network construction. Endometriosis-associated genes were submitted to atBioNet (https://www.fda.gov/ScienceResearch/BioinformaticsTools/ucm285284.htm) and PPIs were obtained. atBioNet is a network analysis tool that provides a systematic insight into gene interactions by examining significant functional modules (18). The default option is 'Human Database' that combines data from a variety of public PPI sources, including BioGRID (19), the Database of Interacting Proteins (20), the Human Protein Reference Database (21), IntAct (22), the Molecular INTeraction database (23), REACTOME (24) and the Signaling Pathways Integrated Knowledge Engine (25). The protein interaction network included 12,043 human proteins and 132,605 interactions. SCAN algorithm was used to identify functional modules and perform assessment of generated gene networks for biomarker discovery (26).

Pathway enrichment analysis. To identify potential roles of genes in endometriosis, the Kyoto Encyclopedia of Genes and Genomes (KEGG) (27) pathway analysis component in atBioNet was used. Overrepresented KEGG pathways for each module were ranked according to the P-value obtained from Fisher's exact tests.

Literature mining. To identify the genes associated with endometriosis, mining from the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed) with keywords 'gene symbol' and 'endometriosis' was conducted. Subsequently, the articles associated with endometriosis were screened manually. A high number of papers indicated that the relationship between potential biomarker genes and endometriosis is well studied and documented.

Results

Screening of seed genes related to endometriosis. A total of 271 and 229 genes were extracted from Genotator and DisGeNET, respectively. The common genes, of which there were 100, were used as seed genes to generate functional modules.

Construction of biomarker networks. Of 100 input genes, 96 were found in GenBank (https://www.ncbi.nlm.nih.gov/genbank/), and network clustering identified six major sub network modules from the original PPI network (Fig. 1). Hub genes in each module were identified (Table I).

Table I. Hub genes in each module.

Module	Gene ID	Gene symbol
A	196	AHR
A	367	AR
A	405	ARNT
A	2099	ESR1
A	8204	NRIP1
A	2100	ESR2
A	7157	TP53
A	2516	NR5A1
A	2908	NR3C1
A	5241	PGR
B	3557	IL1RN
B	3552	IL1A
B	3554	IL1R1
B	3553	IL1B
B	3560	IL2RB
B	3600	IL15
B	3565	IL4
B	3586	IL10
B	3606	IL18
C	4316	MMP7
C	3479	IGF1
C	3484	IGFBP1
C	4312	MMP1
C	5069	PAPPA
C	7077	TIMP2
C	4322	MMP13
C	4321	MMP12
D	3106	HLA-B
D	3105	HLA-A
D	3107	HLA-C
D	3115	HLA-DPB1
D	3117	HLA-DQA1
D	3119	HLA-DQB1
D	3123	HLA-DRB1
E	328	APEX1
E	4968	OGG1
E	7515	XRCC1
E	2068	ERCC2
E	2073	ERCC5
F	355	FAS
F	356	FASLG
F	7132	TNFRSF1A
F	7124	TNF
F	4049	LTA

KEGG pathway analysis. A total of 2,429 genes from the KEGG human database were added to the PPI network and genes in each module were selected for pathway enrichment analysis. The top 10 significantly enriched KEGG pathways for the six modules in endometriosis are demonstrated in Table II. Module A was a cancer cell proliferation module. The majority of the pathways in the first module were related to the proliferation of cancer cells and were associated with pathways in cancer, the cell cycle, oocyte meiosis, adherens junctions and the Wnt signaling pathway. The enriched pathways in module B were associated with the immune system and infectious diseases, including cytokine-cytokine

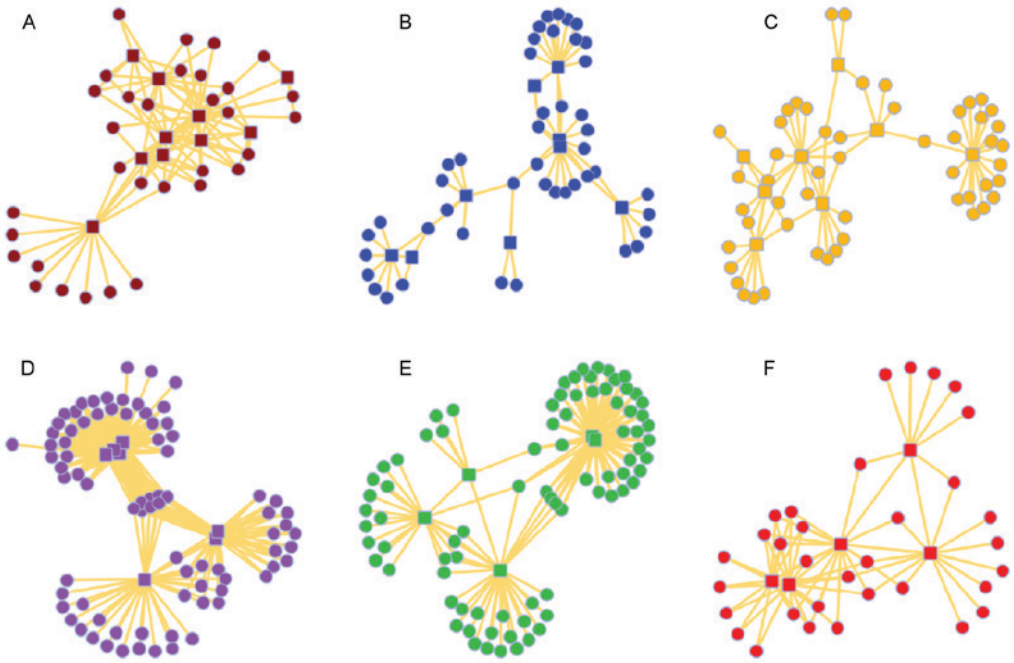

Figure 1. Network constructed from endometriosis-associated genes. Squares represent seed genes and circles represent added genes. (A-F) represent modules A-F, respectively.

receptor interaction, the mitogen-activated protein kinase signaling pathway, the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway, the intestinal immune network for immunoglobulin (Ig) A production and Toll-like receptor signaling pathways. Module C was associated with complement and coagulation cascades, extracellular matrix-receptor interaction, focal adhesion, and proteasome and hematopoietic cell lineages associated with immune and metastasis. The enriched pathways in module D were associated with inflammatory responses, including phagosome, cell adhesion molecules, antigen processing and presentation, natural killer cell mediated cytotoxicity, T cell receptor signaling pathways and the intestinal immune network for IgA production. The majority of the pathways in module E were related to processes of replication and repair, including DNA replication, base excision repair, nucleotide excision repair, mismatch repair and homologous recombination.

Endometriosis-associated genes identified in literature. A total of 15 genes, seven in the first module and eight in the second module, have previously been reported in literature to be candidate biomarkers for endometriosis (Fig. 2). For example, women with endometriosis had significantly higher SOX2 expression levels compared to controls (Fig. 2A) (28). Also, various genes identified in the second module (Fig. 2B), including CASP3, S100A13 and IL1R2, have been reported to be associated with endometriosis (29-31). Details for the 15 literature-confirmed potential endometriosis biomarkers are listed in Table III.

Discussion

The cause of endometriosis is not entirely understood. No single theory is able to explain all cases of endometriosis. The present study implemented PPI for endometriosis biomarker network analysis and identified biologically relevant functional modules. A number of genes and pathways identified in the modules have already been reported to participate in the pathogenesis of endometriosis (32-36).

Although endometriosis is a benign disorder, several common characteristics of this disease are shared with invasive cancer (37). Previous epidemiologic studies have demonstrated that women with endometriosis have an increased risk of ovarian and breast cancer (38,39). Coincidentally, the three chromosomal regions (9p, 11q and 22q) that have demonstrated loss of heterozygosity in ovarian endometriosis were the same that were observed in ovarian tumors (40). These studies have demonstrated that the inactivation of tumor suppressor genes has an important role in the development of endometriosis. The results of the present study demonstrated that expression of cancer-related pathways are significantly imbalanced in endometriosis in module A. The hub genes identified were AHR, AR, ARNT, ESR1, NRIP1, ESR2, TP53, NR5A1, NR3C1 and PGR.

The enriched pathways in module B were associated with the immune system and infectious diseases. The presence of proinflammatory cytokines in the peritoneal fluid of patients with endometriosis has been reported in previous studies (41-43). Cytokines may regulate the actions of leukocytes in the peritoneal fluid or may act directly on the ectopic endometrium (44). Dysregulation of the JAK-STAT pathway is associated with various immune disorders (45), which was also demonstrated in the results of the present study. IL10RA, IL15, IL10 and JAK3 from the Toll-like receptor signaling pathway and CASP1, IL18, IL1B and TRAF6 from the NOD-like receptor signaling pathway, which are important for generating mature proinflammatory cytokines, were also identified in this module and are confirmed by previous studies (35,46). Module B also

Table II. Top 10 KEGG pathways ranked by P-value for the top six modules in endometriosis.

Functional modules (no. of genes)	Map title in KEGG	No. of genes mapped in the pathway	P-value[a]
Module A (n=42)	Pathways in cancer (hsa05200)	7	<0.0001
	Thyroid cancer (hsa05216)	3	<0.0001
	Prostate cancer (hsa05215)	4	0.0001
	Oocyte meiosis (hsa04114)	4	0.0003
	Neurotrophin signaling pathway (hsa04722)	4	0.0005
	Cell cycle (hsa04110)	4	0.0005
	Basal transcription factors (hsa03022)	3	0.0005
	Colorectal cancer (hsa05210)	3	0.0008
	Wnt signaling pathway (hsa04310)	4	0.0009
	Renal cell carcinoma (hsa05211)	3	0.0011
Module B (n=54)	Cytokine-cytokine receptor interaction (hsa04060)	19	<0.0001
	Apoptosis (hsa04210)	11	<0.0001
	JAK-STAT signaling pathway (hsa04630)	15	<0.0001
	Pertussis (hsa05133)	9	<0.0001
	Measles (hsa05162)	11	<0.0001
	Tuberculosis (hsa05152)	11	<0.0001
	Toxoplasmosis (hsa05145)	9	<0.0001
	Leishmaniasis (hsa05140)	7	<0.0001
	Intestinal immune network for IgA production (hsa04672)	6	<0.0001
	Toll-like receptor signaling pathway (hsa04620)	7	<0.0001
Module C (n=60)	Complement and coagulation cascades (hsa04610)	6	<0.0001
	Hypertrophic cardiomyopathy (hsa05410)	4	0.0009
	ECM-receptor interaction (hsa04512)	4	0.0010
	Dilated cardiomyopathy (hsa05414)	4	0.0012
	Hematopoietic cell lineage (hsa04640)	3	0.0111
	Focal adhesion (hsa04510)	4	0.0208
	Proteasome (hsa03050)	2	0.0237
	Pathways in cancer (hsa05200)	5	0.0280
	Vitamin B6 metabolism (hsa00750)	1	0.0316
	Staphylococcus aureus infection (hsa05150)	2	0.0355
Module D (n=87)	Phagosome (hsa04145)	17	<0.0001
	Cell adhesion molecules (hsa04514)	24	<0.0001
	Antigen processing and presentation (hsa04612)	24	<0.0001
	Natural killer cell mediated cytotoxicity (hsa04650)	13	<0.0001
	T cell receptor signaling pathway (hsa04660)	18	<0.0001
	Intestinal immune network for IgA production (hsa04672)	13	<0.0001
	Type I diabetes mellitus (hsa04940)	17	<0.0001
	Leishmaniasis (hsa05140)	14	<0.0001
	Toxoplasmosis (hsa05145)	13	<0.0001
	Staphylococcus aureus infection (hsa05150)	13	<0.0001
Module E (n=87)	Purine metabolism (hsa00230)	19	<0.0001
	Pyrimidine metabolism (hsa00240)	19	<0.0001
	RNA polymerase (hsa03020)	12	<0.0001
	DNA replication (hsa03030)	17	<0.0001
	Base excision repair (hsa03410)	22	<0.0001
	Nucleotide excision repair (hsa03420)	31	<0.0001
	Mismatch repair (hsa03430)	14	<0.0001
	Homologous recombination (hsa03440)	7	<0.0001
	Huntington's disease (hsa05016)	13	<0.0001
	Basal transcription factors (hsa03022)	6	<0.0001

Table II. Continued.

Functional modules (no. of genes)	Map title in KEGG	No. of genes mapped in the pathway	P-value[a]
Module F (n=38)	Cytokine-cytokine receptor interaction (hsa04060)	12	<0.0001
	Apoptosis (hsa04210)	14	<0.0001
	RIG-I-like receptor signaling pathway (hsa04622)	7	<0.0001
	Tuberculosis (hsa05152)	8	<0.0001
	Pathways in cancer (hsa05200)	10	<0.0001
	Natural killer cell mediated cytotoxicity (hsa04650)	7	<0.0001
	Chagas disease (American trypanosomiasis; hsa05142)	6	<0.0001
	Alzheimer's disease (hsa05010)	7	<0.0001
	Osteoclast differentiation (hsa04380)	6	<0.0001
	Type I diabetes mellitus (hsa04940)	4	<0.0001

[a]According to Fisher's exact test. KEGG, Kyoto Encyclopedia of Genes and Genomes; JAK-STAT, Janus kinase-signal transducer and activator of transcription; IgA, immunoglobulin A; ECM, extracellular matrix.

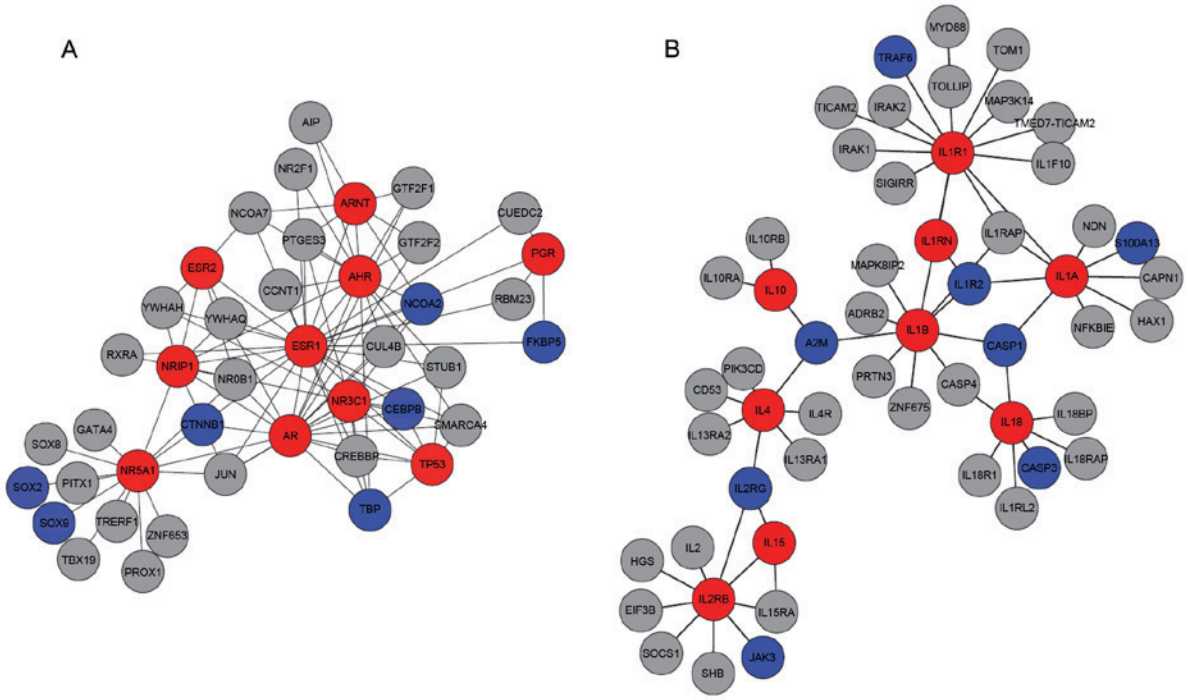

Figure 2. Known and potential endometriosis biomarkers found by protein-protein interaction. The (A) first and (B) second modules are shown. Red circles represent seed genes and blue/grey circles represent the identified endometriosis biomarker genes, based on the seed genes with blue circles being confirmed by literature and grey circles representing currently unconfirmed biomarker genes.

included the osteoclastogenesis pathway, which is predominantly regulated by signaling pathways activated by immune receptors (47).

Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that share a conserved domain structure. MMPs are capable of degrading various types of extracellular matrix (ECM) and serve an important function in tissue remodeling associated with various physiological and pathological processes (48). The expression of several MMPs is maximal during the menstrual phase in the human endometrium (49). MMPs also have a vital role in the pathogenesis of endometriosis and cancer, particularly in the processes of metastasis and invasion (33,50). MMP1, MMP7, MMP12, MMP13, IGF1, IGFBP1, PAPPA and TIMP2 were identified as the hub genes in module C. ECM-receptor interaction, focal adhesion and proteasomes were also identified in this module, as in previous studies (32,51,52).

The immune response is one of the major factors influencing pathogenesis of endometriosis. Numerous genes in the fourth module are involved in the function of the immune system. Hub genes in this module are members of the HLA gene family, including HLA-A, -B, -C, -DPB1,

Table III. Details of the 15 potential endometriosis biomarkers in modules A and B demonstrated in literature.

Gene ID	Gene symbol	Module	PMID	Description
1051	CEBPB	A	23097472	A novel functional link between C/EBPβ and STAT3 that is a critical regulator of endometrial differentiation in women.
1499	CTNNB1	A	23765252	CTNNB1 mutations are significantly different in low-grade ovarian endometrioid carcinomas (53%) compared with low-grade endometrial endometrioid carcinomas (28%; P<0.0057).
2289	FKBP5	A	22279148	No significant endometriosis-related change was observed for FKBP5.
6908	TBP	A	18252806	TBP inhibits the TNF-α-induced expression of endome triotic genes in 12Z endometriotic epithelial cells.
10499	NCOA2	A	12050280	Abnormal increases in endometrial TIF2 and SRC-3 levels are also associated with infertility in women with polycystic ovary syndrome.
6657	SOX2	A	23670619	Samples from endometriosis patients had higher mRNA expression levels of Oct-4, CXCR4, SOX2 and MET compared with that of the normal controls.
6662	SOX9	A	23847113	Cells in ectopic endometriosis lesions also expressed SSEA-1 and nuclear SOX9.
2	A2M	B	2454848	Women with endometriosis had significantly lower amounts of functional α-2M than did women without endometriosis.
836	CASP3	B	24246915	Significantly lower expression of caspase-3 protein was found in ectopic (3.20±1.24) and eutopic endometrium (3.88±1.93) as compared with the control group (6.49±1.85; P<0.01).
7189	TRAF6	B	20130413	TRAF2, TRAF6 and TAK1 were constitutively activated and were unaffected by TSA treatment in endometriotic cells.
834	CASP1	B	17094974	Eutopic and ectopic ECs from women with endome triosis expressed decreased transcript abundance of p53 and Caspase-1 compared to ECs from women without endometriosis.
6284	S100A13	B	15821778	Expression of S100A13 corresponds to the activation of the endothelial cells in the process of endometriotic angiogenesis.
7850	IL1R2	B	17482186	IL-1RII can neutralize IL-1β and counteract its effect on endometrial stromal cells, and may provide a new clinical strategy for the treatment of endometriosis.
3561	IL2RG	B	16759924	IL2RG was demonstrated to be significantly differen tially expressed in blood lymphocytes between endome triosis patients and controls.
3718	JAK3	B	17631002	JAK3 inhibitors, especially JANEX-1, may prove useful to prevent or alleviate the symptoms of endometriosis.

CEBPB, CCAAT/enhancer binding protein β; CTNNB1, catenin β 1; FKBP5, FK506 binding protein 5; TBP, TATA-box binding protein; NCOA2, nuclear receptor coactivator 2; SOX2, SRY-box 2; SOX9, SRY-box 9; A2M, α-2-macroglobulin; CASP3, caspase 3; TRAF6, TNF receptor associated factor 6; CASP1, caspase 1; S100A13, S100 calcium binding protein A13; IL1R2, interleukin 1 receptor type 2; IL2RG, interleukin 2 receptor subunit gamma; JAK3, Janus kinase 3.

-DQA1, -DQB1 and -DRB1, which have key roles in the immune response, and it appears that endometriosis shares many similarities with autoimmune diseases (34,53). It has been demonstrated that patients with endometriosis display a significantly higher expression of HLA I and II molecules compared with individuals without endometriosis (54).

Oxidative stress has been proposed as a potential factor involved in the pathophysiology of endometriosis (55). Accumulation of reactive oxygen species may induce cellular injury, such as DNA damage. The present study demonstrated that the majority of the pathways in module E were related to replication and repair. APEX1, OGG1, XRCC1, ERCC2 and ERCC5 were the seed genes identified in this module. APEX1 and XRCC1 are key genes involved in the base excision repair pathway, which removes DNA adducts induced predominantly by oxidation and alkylation (56). APEX1 is an essential enzyme and has a central role in the DNA repair system; however, a study by Hsu *et al* (57) demonstrated that APEX1 Asp148Glu was not associated with endometriosis in patients in Taiwan. Future studies may confirm the association between APEX1 and the risk of endometriosis. XRCC1 has been demonstrated to physically interact with several enzymes known to be involved in the repair of single-strand breaks in DNA (58). A study by Hsieh *et al* (36) indicated that XRCC1 Arg399Gln polymorphism is correlated with a higher susceptibility to endometriosis.

In conclusion, the pathogenesis of endometriosis is likely multifactorial. The present study constructed a disease network of endometriosis that integrated human protein-protein interactions and known disease-causing genes. The present study has identified a number of biological mechanisms that may be associated with endometriosis. Further studies on the specific function and interactions of the genes in related modules are required to improve the understanding of endometriosis.

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