Understanding the role of epigenomic, genomic and genetic alterations in the development of endometriosis (Review)

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Abstract. Endometriosis is a complex disease influenced by genetic, epigenetic and environmental factors. The aim of the present study was to describe genomic instability, genetic polymorphisms and their haplotype, epigenetic alterations associated with predisposition to endometriosis, and the key factors associated with endometriosis-related ovarian neoplasms. Focus has been given on the developing paradigm that epigenetic alterations or genetic mutations in endometriosis may start in utero or in adolescent and young adults. A search was conducted between 1966 and 2010 through the English language literature (online Medline PubMed database) using the keywords endometriosis combined with epigenetic, genetic and environment. Genetic/epigenetic alterations include single-nucleotide polymorphisms (SNPs), copy number variation, loss of heterozygosity (LOH), and promoter methylation. Several genes with genetic polymorphisms analyzed in the present study tended to overlap previously reported endometriosis susceptibility genes. Retrograde menstruation leads to iron overload, which facilitates the accumulation of somatic mutations through Fenton reaction-mediated oxidative stress. The epigenetic disruption of gene expression plays an important role in the development of endometriosis through interaction with environmental changes. There seems to be at least three spatiotemporally distinct phases of the development of endometriosis: the initial phase of genetic background inherited from parents; followed by epigenetic modifications in the female offspring; and iron overload, which is subject to dynamic modulation later in life. In conclusion, the marked regulation of endometriosis susceptibility genes may stem from a mechanism responsible for epigenetic and genetic mutations based on the microenvironmental changes.

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1. Introduction

Endometriosis is a common gynecologic disease with an estimated frequency of 5-10% among the female population of reproductive age. This disorder is characterized by inflammation, but the pathogenesis of the disease remains unclear. A stepwise process of accumulation of genetic mutations or epigenetic alterations may contribute to the development of endometriosis under the influence of environmental factors such as inflammatory responses (1). Endometriosis is reported to be associated with the frequent up- and downregulation of disease susceptibility genes in several pathways including cytokines, inflammation, immune, oxidative stress, detoxification, hormone receptors, metabolism, matrix remodeling, adhesion molecules, growth factors, cell cycle regulation, signaling, oncogenes, and transcriptional regulation (2). The marked regulation of disease may be associated with genetic alterations (1). The common mechanisms leading to loss- or gain-of-function have a causal relationship to genomic instability, including microsatellite instability (MSI), chromosomal instability (CIN), loss of heterozygosity (LOH), single-nucleotide polymorphism (SNP), gene mutations, and mitochondrial DNA (mtDNA) mutations (3,4). In addition, evidence has emerged indicating that a specific gene has been shown to regulate its neighbor genes by epigenetic mechanisms (5). Insights have emerged from various lines of evidence, including that endometriosis may be an epigenetic disease (6).

This review focused on the relationship between genomic instability, gene mutations and epigenetic alterations associated with increased risk of the development of endometriosis.

2. Literature search

A computerized literature search was performed to identify relevant studies reported in the English language. We searched MEDLINE electronic databases (http://www.ncbi.nlm.nih.gov/sites/entrez) published between January 1966 and December 2013, combining the keywords 'endometriosis', 'genetic', 'epigenetic', and 'environment'. Various combinations of the terms were used, depending on the database searched. Each gene was also linked to the NCBI Entrez Gene pages (http://www.ncbi.nlm.nih.gov/sites/entrez). In addition, references in each article were searched to identify potentially missed studies.

3. Microenvironment

Transtubal retrograde flow and hemolysis occurring during menstruation result in the accumulation of high levels of pro-oxidant factors, such as heme and iron, into the peritoneal cavity (7). Free heme catalyzes oxidative reactions, but impairs lipid bilayers of mitochondria. Mitochondria are a major source for reactive oxygen species (ROS) production. Heme also acts as a pro-inflammatory molecule, leading to cellular injury and DNA damage (2). Furthermore, iron overload initiates a Fenton chemical reaction, which causes oxidative stress and large-scale genomic alterations (2). Persistent oxidative stress induces destruction of the peritoneal mesothelium followed by the overexpression of inflammatory cytokines and adhesion molecules for ectopic endometrial cells, which may cause the development of endometriosis (7). Increased ROS generation, secondary to the influx of heme and iron during retrograde menstruation, have been found in endometriosis (8,9). Oxidative signals from the microenvironment may be required for the development, maintenance and progression of endometriotic precursor lesions. Therefore, endometriosis has been considered to be associated with a chronic inflammatory state leading to pro-inflammatory cytokine excess by oxidative stress (10).

It is well known that the fine-tuning of alterations in oxidant and antioxidant pathways as well as endogenous redox regulators have been reported in the endometrium, serum, or peritoneal fluid (8). Antioxidant defense enzymes provide protection against oxidative DNA damage from carcinogen-specific mutations. It is likely that endometriosis is inherited in a polygenic manner (11). Therefore, inherited sequence variations in specific genes that encode inflammatory and antioxidant defense proteins may alter disease predisposition and thus individual susceptibility to endometriosis.

Endometriosis is a benign disease, however, it shares some features with malignancy, and has been associated with an increased risk of malignant tumors, including epithelial ovarian carcinomas (endometrioid adenocarcinoma and clear cell carcinoma), other Müllerian-type tumors (Müllerian-type mucinous borderline tumor and serous borderline tumor) and sarcomas such as adenosarcoma and endometrial stromal sarcoma in the female pelvic cavity (12-14). The precise cellular and molecular mechanisms leading to endometriosis-associated ovarian carcinogenesis recently became more evident (15-19). Excessive iron accumulation in the pelvic cavity or endometriotic cysts leads to increased oxidative stress and inflammation. Abundant iron-induced ROS is thought to be mutagenic, and chronic exposure of ectopic endometrium to this microenvironment facilitates the accumulation of somatic mutations, which can cause non-regulated mitotic division, growth and migration, similar to malignant mechanisms (3,10,18). This microenvironment is a possible link between endometriosis and tumor development (3). Environment-gene interactions may persistently occur in endometriosis as well as in endometriosis-related carcinogenesis.

4. Genetic instability

General. Endometriosis is characterized by genetic instability, which may play a role in disease establishment, maintenance and progression (3,4). Three phenotypes of genomic instability are generally recognized in cancer: the phenotypes associated with microsatellite instability (MSI), chromosomal instability (CIN) and loss of heterozygosity (LOH).

Microsatellite instability (MSI). Mutations in DNA mismatch repair (MMR) genes result in failure to repair errors that occur during spontaneous DNA replication and are identified as responsible for Lynch syndrome (also known as hereditary non-polyposis colorectal cancer). MSI is a common feature of cancer, but may be uncommon in endometriosis and atypical endometriosis bordering the cancerous region (20,21). The expression of MMR proteins was very weak in endometriosis, but was increased in ovarian carcinoma accompanied by endometriosis and ovarian carcinoma stepwisely with significant differences (22). A higher frequency of MSI was found in endometrioid adenocarcinoma of the ovary (20). However, Ali-Fehmi *et al* showed that a high frequency of MSI was detected in endometriosis (83%) and atypical endometriosis (75%), indicating no significant differences in the MSI between endometriosis and ovarian carcinoma (23). Differences in study design, sample size and methodological issues have been suggested as an explanation for the contradictory data. It is likely that MMR abnormalities may be involved in the malignant transformation of endometriosis. However, there are no data that provide biological and clinical significance of MMR genes in endometriosis itself. Additional studies are needed to confirm the validity and reproducibility of MSI in endometriosis.

Chromosomal instability (CIN). Chromosomal instability (CIN), also known as unequal chromosome distribution during cell division, or DNA copy number alteration underlies the transformation of cells toward malignancy. This phenomenon is a characteristic feature of the majority of cancer cells. Findings of recent studies have shown that there are tissue-specific loss of DNA copy number on chromosomal arms 1p, 22q and X, while gain of somatic DNA copy number alterations was identified on 6p, 17q and 20q in women with endometriosis, suggesting that chromosomal instability is important in the development of endometriosis (24,25). However, not all investigators identified chromosomal aberrations (26). Therefore, expert consensus was not achieved on the importance of CIN in endometriosis.

Loss of heterozygosity (LOH). Numerous studies have documented loss of heterozygosity (LOH) in endometriosis (3,23,27-33). LOH is relatively common in endometriosis. Even small endometriotic cysts harbor LOH on chromosomal arms 9p, 11q or 22q (32). Findings of previous studies have demonstrated that LOH on chromosomal arms 6q (28), 7p (31), 9p (29,30,32), 10q (23,27,28), 11q (30,32), 13q (29), 16q (33) and 22q (30,32), was frequently (15-50%) found in endometriosis, while no LOH was observed in normal endometrium (30). Such LOH may be involved in the development and maintenance of endometriosis. In total 30-60% of endometriotic lesions showed LOH at one or more sites (23,27,30). LOH was frequently observed on chromosome 6q (60.0%) and 10q (40.0%) in atypical endometriosis (28).

A recent genome-wide study identified a locus at 7p15.2 as an endometriosis-specific LOH (31). The chromosome 7p15.2 contains the homeobox A (HOXA) cluster, an important gene for endometriosis (http://www.ncbi.nlm.nih.gov/gene/3206). Some genes on chromosome 7p15.2 also showed a promising association with malignancy, including leukemia, non-small cell lung cancer, prostate cancer, and pancreatic cancer (34). The gene cadherin 1 (CDH1) located on chromosome 16q22.1 encodes the cell-cell adhesion molecule, E-cadherin. Many genes of the CDH family, CDH1, 3, 5, 8, 11 and 16 exist on chromosome 16q22.1. E-cadherin is lost during the process of epithelial-mesenchymal transition, which plays a role in the metastatic process. Goumenou *et al* found that LOH on cyclin-dependent kinase inhibitor 2A [CDKN2A, also known as p16(Ink4), chromosomal location, 9p21], galactose-1-phosphate uridylyltransferase (GALT, 9p13), tumor protein p53 (TP53, 17p13.1) and apolipoprotein A-II (APOA2, 1q23.3), occurs in endometriosis (35). Mutations in the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) gene are associated with endometriosis (36). The PTEN gene on chromosome 10q23.3 is also the most frequently deleted tumor suppressor gene in human cancers. In general, LOH on chromosome 10q23.3 was associated with more than half of solitary endometriotic cysts and approximately one third of ovarian carcinomas (23,27).

Endometriosis has been shown to be associated with an increased risk of developing ovarian endometrioid and clear cell carcinoma. LOH was common in endometrioid adenocarcinoma (43%) but not common in clear cell carcinoma (27,28). Some LOH states are common to all of the endometriotic, transitional and ovarian carcinoma tissues (27). Other cases have revealed that LOH events are detected in cancer cells alone, but not in transitional and endometriotic tissues (29). No cases show LOH events in endometriosis alone (27). Thus, LOH may be a step in the development of endometriosis as well as endometriosis-associated ovarian cancer.

5. Single-nucleotide polymorphism (SNP) haplotype analysis

Endometriosis is considered a genetic disease. This disorder is aggregated in families and individuals with an affected twin, suggesting that some subjects may have a genetic predisposition to developing endometriosis (37). Genetic background inherited from parents may confer susceptibility to endometriosis. The SNP represents a variation in the DNA sequence when a single nucleotide differs in an individual. Genome-wide SNP analysis data (37) have provided valuable insights into the genetic basis of complex traits to identify common and rare variants underlying complex diseases.

Specific SNP alterations of genes and their highly interconnected genes have been previously identified (Table I). Table I shows genetic polymorphisms and their haplotype in selected functional category lists. The genetic polymorphisms in each gene significantly appear to differ in relation to endometriosis risk. The biological categories include inflammation and immune response, oxidative stress and detoxification, hormone receptors and metabolism, matrix remodeling, adhesion molecules, growth factors, cell cycle regulation, signaling and oncogenes, transcriptional regulation, human leukocyte antigens and microRNA regulation (Tables I and II). Endometriosis undergoes a variety of molecular changes depending on the ability to survive, attach, grow, and invade. Many molecular events involved in endometriosis pathogenesis contribute to its development and maintenance. Genes in the category of inflammation showed that endometriosis is characterized by an imbalance between the oxidative and antioxidative arms of the inflammatory system, resulting in the over production of proinflammatory cytokines, oxidative stress and detoxification molecules (7,8). Since the results of some genes have been inconsistent, genetic polymorphism data are considered to be limited and conflicting. A majority of association studies are based on very simple models including one SNP or haplotype and small sample sizes. Thus, the evidence of an association between genetic polymorphisms in a single gene and endometriosis risk may be weak.

6. Somatic mutations and alterations in endometriosis-related carcinogenesis

Epithelial ovarian carcinomas have been divided into at least five subgroups: high-grade serous, endometrioid, clear cell, mucinous, and low-grade serous (38). Endometriosis is associated with an increased risk of developing ovarian endometrioid and clear cell carcinoma (14). In this section, we mainly focus on genetic alterations of atypical endometriosis and endometriosis-associated ovarian carcinomas (EAOC). EAOC carcinogenesis generally follows a gradual and stepwise accumulation of genetic mutations under the influence of chronic inflammation and hyperestrogenism for clear cell carcinoma and endometrioid adenocarcinoma, respectively (13). We describe specific genetic/genomic alterations that are aberrantly expressed in solitary endometriosis, endometriosis distant from ovarian carcinomas, contiguous endometriosis associated with ovarian carcinomas, and ovarian carcinomas. Endometriosis susceptibility genes are defined as specific genes with a higher frequency of chromosomal aberrations, somatic gain- or loss-of-function mutations, or hypermethylation in solitary endometriosis than in normal endometrium. These genes are highly sensitive to microenvironmental changes, particularly to alterations in the inflammatory milieu, and in the induction of (epi)genomic changes in endometriosis precursor lesions, which may eventually lead to endometriosis. These genes may only be involved in the development and maintenance of endometriosis. Genes responsible for tumor promotion are dervied

Table I. Genetic polymorphisms in the selected functional category lists[a].

Categories	Genetic polymorphisms
Cytokines, inflammation, immune and oxidative stress	COX-2 (114), FCRL3 (115-117), IFNG (118-120), IL1A (121), IL1R1 (122,123), IL2 (124), IL6 (125,126), IL10 (127-133), IL16 (134), IL18 (135), KIR3DS1 (136), NFKB1 (137,138), NOS3 (139), TNFA (125,140-144), TNFR2 (141), TNFSF13B (145), TGFB1 (146,147), TLR4 (148), XRCC1 (45) and XRCC4 (46)
Detoxification	CYP1A1 (58,149), CYP1B1 (149), CYP2C19 (150), CYP17 (151-154), CYP19 (155-158), GSTM1 (56-60), GSTT1 (52), GSTP1 (159) and NAT2 (59,62)
Hormone receptors and metabolism	AHRR (52,160), AR (161), CETP (25), DRD2 (162), ESR1 (130,153,163-170), ESR2 (165,171-174), HSD17B1 (165,175,176), FSHR (155,177), HSD17B3 (155), LHB (178), NRIP1 (179) and PGR (176,180-184)
Matrix remodeling	LOXL4 (185), MMP-1 (96,186,187), MMP-2 (188-190), MMP-3 (186), MMP-7 (191), MMP-9 (186,190,192), MMP-12 (193), MMP-13 (193), PAI-1 (194,195) and TIMP-2 (189,196)
Growth factors	BDNF (197), IGF-II (198), IGFBP3 (199), IRS2 (200), FGF2 (201), EGFR (202), VEGF (203-211) and VEGFR-2 (212)
Cell cycle regulation, signaling and oncogenes	CDKN1B (213), CDKN2BAS (214,215), PDCD6 (206), PTPN22 (217,218), TP53 (122,219-224), WNT4 (214) and STAT6 (225)
Adhesion molecules	CDH1 (226-228), FN1 (214), ICAM1 (126,158,229), MUC2 (230) and MUC4 (231)
Transcriptional regulation	CHD5 (232), FOXP3 (115), HOXA10 (233) and PPARG2 (234,235)
Human leukocyte antigens	HLA-D (236) and HLA-DR (237)
microRNA	let-7 microRNA (238)
Others	ACE (237,240), AHSG (241), C3 (185), DNMT3L (242), GALT (35,53), MTHFR (243), PEMT (243), SLC22A23 (244) and WHSC1 (244)

[a]The candidate SNPs represented 10 major functional categories. References are indicated in parentheses. SNPs, single-nucleotide polymorphisms.

from genes with further aberrations required for promotion to a premalignant state in contiguous endometriosis associated with ovarian carcinomas than in endometriosis distant from ovarian carcinomas or solitary endometriosis. Genes responsible for the malignant transformation of endometriosis and cancer progression are involved in malignant transformation in ovarian carcinomas as compared to contiguous endometriosis associated with ovarian carcinomas. Tables III and IV show (epi)genetically relevant information of endometriosis susceptibility genes, genes responsible for tumor promotion and genes responsible for the malignant transformation of endometriosis and cancer progression.

Endometriosis susceptibility gene candidates. These genes are associated with the transition from normal endometrium to non-atypical endometriosis components. Endometriosis susceptibility genes include PTEN (3,23,27,28,36), v-myc avian myelocytomatosis viral oncogene homolog (MYC) (39,40), catenin (cadherin-associated protein), β 1, 88 kDa (CTNNB1) (30,41-44), X-ray repair complementing defective repair in Chinese hamster cells (XRCC) (45-48), B-cell CLL/lymphoma 2 (BCL2) (49-51), galactose-1-phosphate uridylyltransferase (GALT) (35,52-55), glutathione S-transferase mu 1 (GSTM1) (56-61) and N-acetyltransferase 2 (NAT2) (59,62). These genes are associated with important aspects of tumor biology, including the regulation of cell growth and proliferation, detoxification, DNA base excision repair, cell adhesion, metabolism, differentiation, anti-apoptosis, angiogenesis, tumor suppression, and tumorigenesis. However, oncogenic events, including promoter hypermethylation and genetic mutations, associated with endometrial and ovarian cancers are uncommon in solitary endometriosis (63).

Gene candidates responsible for tumor promotion. Previous studies (Table III) have shown EAOC and coexisting endometriosis exhibit common molecular genetic alterations that were widely detected in ovarian carcinoma tissue and contiguous endometriotic tissue associated with ovarian carcinomas. These are defined as genes responsible for tumor promotion, including genes responsible for the malignant transformation of endometriosis and those responsible for ovarian cancer progression. Genetic mutations detected in the carcinoma samples were almost detected in the corresponding contiguous endometriosis samples. In a few genes, however, genetic alteration events are found in ovarian carcinoma tissue alone, but not in contiguous atypical endometriosis.

These specific genes are responsible for carcinoma progression. However, it is unlikely that patients showed genetic alteration events in the endometriotic tissue only (27).

Gene candidates responsible for malignant transformation of endometriosis. These genes play a role in the transition from

Table II. Genetic polymorphisms and their haplotype in endometriosis.

Name	Description	Genetic polymorphisms and their haplotypes
Cytokines, inflammation, immune and oxidative stress		
COX-2	Cyclooxygenase-2	A significant genetic association between the COX-2 gene -765G/C polymorphism and advanced-stage endometriosis was demonstrated in Korean women (114).
FCRL3	Fc receptor-like 3	A possible FOXP3 and FCRL3 interaction leads to a cumulative effect on the development of endometriosis (115). Data from this study point to a possible association of the FCRL3 -169C/T polymorphisms with endometriosis, especially minimal/mild endometriosis, and the haplotype AGAT may be protective against the development of the disease in Brazilian women (116). The FCRL3 C-169T polymorphism may play an important role in the pathogenesis of endometriosis and/or infertility (117). FCRL3 may play a role in regulation of the immune system.
IFNG	Interferon-γ	The IFNG gene CA-repeat polymorphism is associated with susceptibility to endometriosis in South Indian women (120). The CA repeat polymorphism in the IFN-γ gene may be associated with a risk of endometriosis in the South Korean population (199).
IL1A	Interleukin 1α	Candidate SNPs are located in and around the IL1A gene (121).
IL1R1	Interleukin 1 receptor, type I	The IL1R1 1498T/C polymorphism is associated with early-stage endometriosis in Korean women (245). Polymorphisms at a C/A transition at position 52 in exon 1C of the IL-1R1 gene showed protective risk for the development of endometriosis (123).
IL-2R	Interleukin-2 receptor	IL-2R -627*C homozygote and C allele are related to higher susceptibility to endometriosis (124).
IL-6	Interleukin-6	IL-6 -174C/G gene polymorphisms may be a risk factor for endometriosis for Asians (125). IL-6 -634C/G and ICAM-1 469K/E polymorphisms synergistically affect the susceptibility for endometriosis in the Japanese population (126).
IL-10	Interleukin-10	The IL-10 ACC/ACC genotype, which is known to be a 'low-producer' of IL-10, is associated with endometriosis (128). The IL10 -592 A/C polymorphisms conferred susceptibility to endometriosis (127). The functional promoter polymorphism at IL-10 may play a role in the development of endometriosis (129). The -592 or -819 C allele of IL-10 are associated with endometriosis (130). IL-10 gene promoter polymorphisms at -819 and -592 sites are associated with endometriosis risk (131). An association between endometriosis and IL-10 gene promoter polymorphism exists, and the IL-10 -627 A allele is related to a higher susceptibility to endometriosis (132). IL-10 promoter polymorphisms were associated with the production of anti-CA II ab in patients with endometriosis (133).
IL-16	Interleukin-16	The rs4778889 T/C polymorphism of the IL-16 gene may be associated with risk of endometriosis in the Chinese population, especially in patients with pain phenotype (134).
IL-18	Interleukin-18	IL-18 -607*A homozygote and A allele were positively correlated with the risk of developing endometriosis or the stage of endometriosis (135).
KIR3DS1	Killer cell immunoglobulin-like, receptor three domains, long cytoplasmic tail, 1	Polymorphism in KIRs may be associated with susceptibility for endometriosis (136).

Table II. Continued.

Name	Description	Genetic polymorphisms and their haplotypes
NFKB1	Nuclear factor of κ light polypeptide gene enhancer in B-cells 1	The -94 insertion/deletion ATTG polymorphism in the NFKB1 gene was positively associated both with moderate/severe endometriosis and idiopathic infertility (137). NFKB is a transcription regulator that is activated by various intracellular and extracellular stimuli such as cytokines, oxidant-free radicals, ultraviolet irradiation, and bacterial or viral products.
NOS3	Nitric oxide synthase 3	The T allele, encoding aspartic acid, of the Glu298Asp polymorphism of the NOS3 may be associated with advanced stage endometriosis in the Korean population (139). Nitric oxide, a reactive-free radical, is synthesized from L-arginine by NOS3, nitric oxide synthase 3 (endothelial cell).
TNFA	Tumor nectosis factor-α	The genotype frequencies at the TNFA:g.[-1031T/C] and the TNFA:g.[-863C/A] sites may be associated with advanced stage endometriosis in the Korean population (142). TNF-α -238A/G gene polymorphisms may be a risk factor for endometriosis for Asians (125). TNFA promoter polymorphism was associated with susceptibility to endometriosis (144). The variability of the -1031T/C polymorphism of the TNF-α gene may be associated with susceptibility to endometriosis (143). The -C850T TNFA gene polymorphism may be used as a relevant molecular marker to identify women with risk of developing endometriosis in Asian Indian women (140).
TNFR2	Tumor necrosis factor receptor 2	The haplotype alleles of the TNF-α and TNFR2 gene polymorphisms are genetic factors associated with endometriosis (141).
TNFSF13B and BLyS	B lymphocyte stimulator, is also known as TNFSF13B, tumor necrosis factor (ligand) superfamily, member 13b	The results point to a possible association between BLyS -817C/T polymorphism and idiopathic infertility in a Brazilian population (145). BLyS is a cytokine that belongs to the TNF ligand family and plays an important role in the proliferation and differentiation of B cells.
TGFB1	Transforming growth factor-β1	The TC haplotype allele of TGFB1-509C/T and 868T/C polymorphisms may be associated with early-stage endometriosis in Korean women (146). T homozygote and T allele for TGFB1 are associated with higher susceptibility to endometriosis (191).
TLR4	Toll-like receptor 4	TLR4 896A/G polymorphism (rs4986790) is a functional polymorphism resulting in hypo-responsiveness of the receptor, thus resulting in peritoneal inflammation and the initiation of endometriosis (148).
XRCC1	X-ray repair complementing defective repair in Chinese hamster cells 1	XRCC1 Arg399Gln polymorphism is associated with higher susceptibility to endometriosis (45). The protein encoded by this gene is involved in the efficient repair of DNA single-strand breaks formed by exposure to ionizing radiation and alkylating agents.
XRCC4	X-ray repair complementing defective repair in Chinese hamster cells 4	XRCC4 codon 247*A and XRCC4 promoter -1394*T related genotypes and alleles might be associated with endometriosis susceptibilities and pathogenesis (46).
Detoxification		
CYP1A1 m1	Cytochrome P450, family 1, subfamily A, polypeptide 1	The combination of CYP1A1 m1 polymorphism and GSTM1 null deletion is closely associated with penetration of the endometriosis phenotype (58).

Table II. Continued.

Name	Description	Genetic polymorphisms and their haplotypes
CYP2C19	Cytochrome P450, family 2, subfamily C, polypeptide 19	CYP2C19*2 heterozygote genotype has a higher risk of developing endometriosis (150).
CYP17-34	Cytochrome P450, family 17-34	The CYP17-34 G variant, previously associated with increased 17β-estradiol production, contributed to stage I-II endometriosis in women from a Polish population (151).
CYP17	Cytochrome P450, family 17, subfamily A, polypeptide 1	A2A2 type mutation of the CYP17 gene was observed to be more frequent in patients with endometriosis (152). The CYP17* T allele appears to be associated with a trend of increased risk of endometriosis (154).
CYP19	Cytochrome P450, family 19 (CYP19A1)	Non-synonymous polymorphisms of CYP19A1 gene may modulate the risk of endometriosis in Taiwanese Chinese women (155,156). AA and CC genotypes were significantly represented in Val80 and 1558G/T polymorphisms of CYP19 in patients affected with endometriosis (157). The 3 bp I/D polymorphism of the CYP19 gene may be weakly associated with the susceptibility of endometriosis in a Japanese population (158).
GSTM1	Glutathione S-transferase mu 1	An association was observed between endometriosis and the GSTM1 null deletion in South Indian women (56). The GSTM1* null genotype is associated with a higher risk of endometriosis development (57). The combination of CYP1A1 m1 polymorphism and GSTM1 null deletion is closely associated with penetration of the endometriosis phenotype (58). Involvement of NAT2 and GSTM1 detoxification system genes in the pathogenesis of endometriosis and the possible impact of NAT2 gene polymorphism in the development of different forms of this disease was noted (59). The unusually high frequency of homozygotes for the GSTM1 gene deletion among patients with endometriosis suggests a possible contribution of environmental toxins in the pathogenesis of this disease due to the absence or low activity of GSTM1 enzyme (60).
NAT2	N-acetyltransferase 2 (arylamine N-acetyltransferase)	Altered NAT 2 enzyme activity may be a predisposition factor in endometriosis. Alternatively NAT 2 alleles may be in linkage disequilibrium with a susceptibility allele in the same chromosomal region (62). NAT2 is an enzyme that functions to activate and deactivate arylamine and hydrazine drugs and carcinogens.
Hormone receptors and metabolism		
AHRR	Aryl-hydrocarbon receptor repressor	The AHRR codon 185 and GSTT1 polymorphisms are associated with the risk of advanced stage endometriosis (52). AHRR codon 185 polymorphism was associated with susceptibility to and severity of endometriosis in Japanese women (160).
AR	Androgen receptor	The 19 and 20 CAG repeats of the AR gene are associated with endometriosis (161).
CETP	Cholesteryl ester transfer protein, plasma	The I405V polymorphism of the CETP gene plays an important role as an independent factor in the risk of endometriosis in women (25).
DRD2	Dopamine receptor D2	An excess of DRD2 polymorphism was found in exon 7 in women with peritoneal moderate/severe endometriosis (162).
ESR1	Estrogen receptor 1, also known as estrogen receptor-α	The X allele of ERα-*Xba*I is associated with endometriosis (130). The ERα (*Pvu*II and *Xba*I) gene polymorphisms may be included among the genetic risk factors for endometriosis (167). Estrogen receptor-α thymine-adenine (TA) repeat polymorphisms may be a genetic risk factor for minimal or mild endometriosis (168). ERα-351 *Xba*I*G- and -397 *Pvu*II*C-related genotypes/alleles were correlated with higher susceptibilities of endometriosis (166).

Table II. Continued.

Name	Description	Genetic polymorphisms and their haplotypes
ESR1	Estrogen receptor 1, also known as estrogen receptor-α	The ESR1 polymorphism rs3798573 A/G was associated with risk of endometriosis and infertile endometriosis in Han women from central China (164). ER α* 14 TA repeats and the CYP17* A1 allele are associated with an increased risk of endometriosis (153). The restriction enzyme *Pvu*II polymorphism of the ERα gene is associated with the risk for endometriosis (169). The variability of the estrogen receptor gene likely contributes to the pathogenesis of endometriosis (170). Genetic variants in ESR1 gene may modify susceptibility to endometriosis and influence the fertility status in endometriosis patients (165).
ESR2	Estrogen receptor-β	The *Alu*I polymorphism in the ERβ gene is associated with an increased risk of stage IV endometriosis in a Japanese population (174). The frequency of the heterozygous A/G polymorphism of the ER-β gene was 9 times higher in patients with endometriosis than in the control group (171). The ESR2 +1730 G/A polymorphism can be associated with risk of infertility and endometriosis-associated infertility (172). The ERβ gene +1730 G/A polymorphism can be associated with the risk of the development of endometriosis, regardless of the stage of the disease (173). The proline allele is associated with substantial complaints (infertility associated with pain), when compared to the homozygous arginine genotype; we also found that the proline allele was more frequent in endometriosis patients (222).
FSHR	Follicle stimulating hormone receptor	Non-synonymous polymorphisms of the FSHR gene may modulate the risk of endometriosis in Taiwanese Chinese women (155,156). Both the GG (680Ser/Ser) and GA (680Ser/Asn) genotypes of FSHR were associated with a significantly lower risk of endometriosis (177).
HSD17B1	Hydroxysteroid (17-β) dehydrogenase 1	Genetic variants in the HSD17B1 gene may modify susceptibility to endometriosis and influence the fertility status in endometriosis patients (165). HSD17B1 polymorphisms are associated with an increased risk of endometriosis (176).
HSD17B3	Hydroxysteroid (17-β) dehydrogenase 3	Non-synonymous polymorphisms of HSD17B3 gene may modulate the risk of endometriosis in Taiwanese Chinese women (155,156).
LHβ	Luteinizing hormone β	The LHβ 1502G/A polymorphism may be involved in the predisposition to infertility and minimal/mild endometriosis-associated infertility (178).
PGR	Progesterone receptor	PGR polymorphisms are associated with an increased risk of endometriosis (176). There is a significant correlation between PGR polymorphism and endometriosis (180). PGR heterozygosis genotype frequencies were shown to be statistically higher in endometriosis cases compared with controls (181). The presence of the PGR gene polymorphic allele +331A is associated with a reduced risk of deep infiltrating endometriosis compared with the healthy population controls (182).The PROGINS polymorphism of the PGR may be associated with an increased risk of endometriosis (183). PROGINS appears to be associated with endometriosis in Caucasian individuals (184).
Matrix remodeling		
LOXL4	Lysyl oxidase-like 4	Statistically significant differences in the allelic frequencies and genotype distribution of genetic variants in LOXL4 and C3 were documented in patients with endometriosis-associated infertility versus controls, and in patients with endometriosis versus controls, respectively in a Puerto Rican population (185).
MMP	Matrix metalloproteinase	Haplotypes of MMP-1, -3, and -9 genes were related to a high risk for endometriosis (186).

Table II. Continued.

Name	Description	Genetic polymorphisms and their haplotypes
MMP-1	Matrix metalloproteinase-1	The MMP-1 promoter SNP may modify susceptibility to endometriosis (187).
MMP-2	Matrix metalloproteinase-2	Polymorphisms in MMP-2 (-735 C/T) were associated with an elevated risk of endometriosis (190). The MMP-2 G/6A haplotype may modify susceptibility to endometriosis (187). The MMP-2 polymorphisms are associated with advanced-stage endometriosis (189).
MMP-7	Matrix metalloproteinase-7	MMP-7-181A/G polymorphism has the potential to be a susceptibility factor for endometriosis in women from North China (191).
MMP-9	Matrix metalloproteinase-9	Polymorphisms in MMP-9 (-1562 C/T) were associated with elevated risk of endometriosis (190). The haplotypes in the MMP-9 gene may correlate with the progression of endometriosis (192).
MMP-12 and MMP-13	Matrix metalloproteinase-12 and -13	A potential role for MMP-12 -82 A/G- and MMP-13 -77 A/G-combined polymorphisms was demonstrated in superficial endometriosis (193).
PAI-1	Plasminogen activator inhibitor type-1	Hypofibrinolysis, associated with the 4G allele of the PAI-1 gene, was found significantly more often in women with endometriosis compared with controls (195). The PAI-1 4G/5G polymorphism may be associated with a risk of endometriosis-associated infertility in Brazilian women (194).
TIMP-2	Tissue inhibitor of metalloproteinase 2	The TIMP-2 -418C/C homozygote may be a protective factor against the development of endometriosis in North Chinese women (196). The TIMP-2 polymorphisms are associated with advanced-stage endometriosis (189).
Growth factors		
BDNF	Brain-derived neurotrophic factor	The BDNF(Met) SNP may contribute to the increased susceptibility to Stage III-IV endometriosis and endometriosis-related infertility (197). BDNF is a member of the nerve growth factor family and is overexpressed in endometriosis.
EGFR	Epidermal growth factor receptor	EGFR gene 2073*T-related genotypes and allele are associated with higher susceptibilities to endometriosis (202).
IGF-II	Insulin-like growth factor-II	The IGF-II 820G/A polymorphism is a genetic factor that may be associated with the development of endometriosis in Korean women (198).
IGFBP3	Insulin-like growth factor binding protein 3	The AAG haplotype allele of the -672A/G, -202A/C and c.95C/G polymorphisms in the IGFBP3 gene may be associated with advanced endometriosis in Korean women (199).
IRS2	Insulin receptor substrate 2	The IRS2 1057G/D polymorphism may be associated with an increased risk for endometriosis (200).
NRIP1	Nuclear receptor interacting protein 1	NRIP1 gene variants might act as predisposing factors for endometriosis (179). NRIP1 gene modulates transcriptional activity of the estrogen receptor.
VEGF	Vascular endothelial growth factor	The VEGF -2578 A/C SNP may influence susceptibility to endometriosis in the Estonian population (206). The VEGF +936T/C polymorphism is capable of causing endometriosis susceptibility and is a risk factor for endometriosis (204). The CC genotype of VEGF +405 and 460T/405C haplotypes of VEGF may be associated with the risk of endometriosis (207). The VEGF-460/-1154/-2578 TGC, CAA, TAA and TAC haplotypes were associated with endometriosis. The -1154A and -2578A alleles may be protective against the development of endometriosis in North Chinese women (208).

Table II. Continued.

Name	Description	Genetic polymorphisms and their haplotypes
VEGF	Vascular endothelial growth factor	The -460T/+405C haplotype in the VEGF gene, which is associated with lower promoter activity, was significantly less common in women with endometriosis than in controls. These data suggest that the +405G allele may influence the likelihood of a woman developing the disease (210). The VEGF +405 C/G polymorphism may be associated with the risk of advanced stage endometriosis in the Korean population (209). The T/T homozygotes and the T allele of the VEGF-460 gene are associated with a higher risk of endometriosis (211). The VEGF +405 G/C polymorphism is associated with the risk of endometriosis, and endometriosis associated with adenomyosis and chocolate cysts (203). The +405G/C polymorphism in VEGF may be associated with a higher risk of endometriosis in northern Iran (205).
VEGFR-2	Vascular endothelial growth factor receptor-2	The 1192C/T polymorphisms on the VEGFR-2 gene might affect the risk of developing endometriosis in Northern Chinese women of Han ethnicity (212).
Cell cycle regulation, signaling and oncogenes		
CDKN1B	Cyclin-dependent kinase inhibitor 1B (p27, Kip1)	The 109V/G polymorphism of the CDKN1B gene seems to be associated with a higher risk of the development of endometriosis (213).
CDKN2BAS	CDKN2B antisense RNA 1	CDKN2BAS is a new susceptibility locus for endometriosis (215). We confirm CDKN2BAS to be the first identified common loci for endometriosis (217).
KRAS	Kirsten rat sarcoma viral oncogene homolog	An inherited polymorphism of a let-7 miRNA binding site in KRAS leads to abnormal endometrial growth and endometriosis. The KRAS let-7 (LCS6) polymorphism is the first described genetic marker of endometriosis risk (238).
PDCD6	Programmed cell death 6	PDCD6 gene may be a new susceptibility gene to endometriosis (216). PDCD6 participates in T cell receptor-, Fas-, and glucocorticoid-induced programmed cell death.
PTPN22	Protein tyrosine phosphatase, non-receptor type 22 (lymphoid)	Female carriers of the PTPN22(*)T variant are significantly more susceptible to endometriosis than controls (218). In Brazilian women, the PTPN22 1858C/T polymorphism may be an important genetic predisposing factor for endometriosis, especially, in advanced disease (217). PTPN22 plays a role in the T-cell receptor signaling pathway. Mutations in this gene may be associated with a range of autoimmune disorders including type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus and Graves' disease.
STAT6	Signal transducer and activator of transcription 6	The G2964A 3'-untranslated region polymorphism of the STAT6 gene is associated with endometriosis in South Indian women (225).
TP53	Tumor protein p53	Specific TP53 polymorphisms are associated with an increased risk of endometriosis-associated infertility and with post-IVF failure (219). Genotype Pro/Pro of codon 72 polymorphism in TP53 contributes significantly to susceptibility to endometriosis in the Mexican population (122). The 16-bp duplication polymorphism in TP53 contributes significantly to susceptibility to endometriosis in the Mexican population (220). The TP53 codon 72 Pro/Pro + Arg/Pro genotypes are associated with increased risk of endometriosis in the Asian population (221). TP53 codon 72*Pro-related genotype is related with a higher susceptibility of endometriosis (223). Endometriosis is associated with the TP53 polymorphism. p53 arginine homozygotes have a lower risk for endometriosis. Heterozygotes and proline homozygotes have a higher risk for endometriosis (224).

Table II. Continued.

Name	Description	Genetic polymorphisms and their haplotypes
WNT4	Wingless-type MMTV integration site family, member 4	We confirm WNT4 as the first identified common loci for endometriosis (214). WNT4 is involved in oncogenesis and in several developmental processes, including the regulation of cell fate and patterning during embryogenesis.
Adhesion molecules		
CDH1	Cadherin 1, also known as E-cadherin	The E-cadherin gene polymorphism rs4783689 was marginally associated with endometriosis in the Japanese population, suggesting that E-cadherin might be involved in genetic susceptibility to endometriosis (226). The E-cadherin -347GA/GA and -160A/A genotypes and -347GA/-160A/+54C and -347G/-160A/+54C haplotypes may jointly modify the risk of endometriosis in Indian women (227). There is a relation between the CDH1 3'-UTR C/T polymorphism, the -160 A/-347 GA haplotype of two promoter polymorphisms and risk of endometriosis, suggesting a potential role in endometriosis development, at least in North Chinese women (228).
FN1	Fibronectin 1	FN1 has been confirmed as the first identified common loci for endometriosis (214).
ICAM1	Intercellular adhesion molecule 1	ICAM1 polymorphism in codon 241 is associated with the development of susceptibility to endometriosis in the population of northern Iran (229). IL-6 -634C/G and ICAM-1 469K/E polymorphisms synergistically affect the susceptibility for endometriosis in the Japanese population (126). A genetic polymorphism in the ICAM-1 gene domain may contribute to the susceptibility to endometriosis (246).
MUC2	Mucin 2	MUC2 polymorphisms, especially rs10794288 and rs10902088, are associated with endometriosis as well as endometriosis-related infertility (230). MUC2 is a mucous barrier that protects the lumen.
MUC4	Mucin 4	MUC4 polymorphisms are associated with development of endometriosis and endometriosis-related infertility in the Taiwanese population (231).
Transcriptional regulation		
CHD5	Chromodomain helicase DNA binding protein 5	Endometriosis may be associated with the tumor-suppressor gene CHD5 in the Caucasian population (232). CHD5 functions in chromatin remodeling and gene transcription. This gene is a potential tumor suppressor gene that may play a role in the development of neuroblastoma.
FOXP3	Forkhead box P3	A possible FOXP3 and FCRL3 interaction leads to a cumulative effect on the development of endometriosis (115). FOXP3 is a member of the forkhead/winged-helix family of transcriptional regulators.
HOXA10	Homeo box A10	Patients with HOXA10 polymorphism were associated with a lower American Fertility Society score and less severe obliterated cul-de-sac (233).
PPARG	Peroxisome proliferator-activated receptor γ	The results suggest that the PPAR-γ 161CC genotype may be a genetic risk factor for endometriosis (235).
PPARG2	Peroxisome proliferator-activated receptor γ 2	The PPARG2 Pro12Ala polymorphism is associated with advanced-stage endometriosis in the Korean population (234). PPAR-γ is a regulator of adipocyte differentiation. Additionally, PPAR-γ is involved in the pathology of numerous diseases including obesity, diabetes, atherosclerosis and cancer.
Human leukocyte antigens		
HLA-DQB1	Major histocompatibility, complex class II, DQ β 1	The prevalence of the HLA-DQB1*0301 allele was significantly greater in patients with endometriosis, compared with the general controls (236). The HLA-DRB1*1403 allele may play a role in the development of endometriosis (237).
microRNAs		
let-7 microRNA		An inherited polymorphism of a let-7 miRNA binding site in KRAS leads to abnormal endometrial growth and endometriosis. The KRAS let-7 (LCS6) polymorphism is the first described genetic marker of endometriosis risk (238).

Table II. Continued.

Name	Description	Genetic polymorphisms and their haplotypes
Others		
ACE	Angiotensin I converting enzyme	ACE*I/D gene polymorphisms are associated with endometriosis (239). ACE 2350*G and ACE-240*T-related genotypes and alleles are associated with higher susceptibility to endometriosis (240).
AHSG	α-2-Heremans Schmidt (HS)-glycoprotein	Endometriosis is associated with the AHSG gene polymorphism in Korean women (241). AHSG is involved in several functions, such as endocytosis, brain development and the formation of bone tissue.
C3	Complement component 3	Statistically significant differences in the allelic frequencies and genotype distribution of genetic variants in LOXL4 and C3 were documented in patients with endometriosis-associated infertility versus controls, and in patients with endometriosis versus controls, respectively, in a Puerto Rican population (185).
DNMT3L	DNA (cytosine-5)-methyltransferase 3-like	The association of DNMT3L genetic variants and endometrioma was detected (242). DNMT3L stimulates *de novo* methylation by DNA cytosine methyltransferase 3 α and is thought to be required for the establishment of maternal genomic imprints.
GALT	Galactose-1-phosphate uridylyltransferase	Loss of heterozygosity on GALT occurs in endometriosis (35). The N314D mutation of GALT is associated with endometriosis (53).
MTHFR	Methylenetetrahydrofolate reductase (NAD(P)H)	The exhaustive multifactor dimensionality reduction analysis revealed an epistatic interaction between rs1801133 of MTHFR and rs4244593 of PEMT in endometriosis-associated infertility (243).
PEMT	Phosphatidylethanolamine N-methyltransferase	MTHFR is a co-substrate for homocysteine remethylation to methionine. PEMT converts phosphatidylethanolamine to phosphatidylcholine by sequential methylation.
SLC22A23	Solute carrier family 22, member 23, transports organic ions across cell membranes	Significant associations between SLC22A23 haplotypes and the severe stage of the disease were identified (244).
WHSC1	Wolf-Hirschhorn syndrome candidate 1	Significant associations between WHSC1 alleles and endometriosis-related infertility were identified (244). Wolf-Hirschhorn syndrome (WHS) is a malformation syndrome associated with a hemizygous deletion of the distal short arm of chromosome 4.

normal endometriosis development to preneoplastic atypical lesions. Genes responsible for the malignant transformation of endometriosis include AT-rich interactive domain 1A (SWI-like) (ARID1A) (3,15,17-19), tumor protein p53 (TP53) (3,10,30,64,65), v-raf murine sarcoma viral oncogene homolog B (BRAF) (63,66,67), phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α (PIK3CA) (16,17,68), actinin, α 4 (ACTN4) (69), telomerase reverse transcriptase (TERT) (70), mindbomb E3 ubiquitin protein ligase 1 (MIB1) (49), v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2, also known as HER2 (ERBB2) (71), cyclin-dependent kinase inhibitor 1A (p21, Cip1) (CDKN1A) (50,72-74) and met proto-oncogene (MET) (75).

Gene candidates responsible for cancer progression. These genes are associated with an increased susceptibility to ovarian carcinomas, through transition from atypical endometriosis to carcinoma. Sequential progression from benign endometriosis to atypical forms culminates in neoplasia in endometriosis-associated ovarian carcinoma. Genes responsible for cancer progression include Kirsten rat sarcoma viral oncogene homolog (KRAS) (76).

Benign, solitary endometriosis has shown somatic mutations in the PTEN and XRCC genes, but may be uncommon in ARID1A, TP53 and KRAS gene mutations. Endometriotic lesions adjacent to carcinomas have loss- or gain-of-function mutations, amplifications or overexpression in genes and proteins directly related to neoplasms, in particular the PTEN, ARID1A, MYC, TP53, CTNNB1 and PIK3CA genes. KRAS mutations may be associated with the malignant transformation of atypical endometriosis into ovarian carcinomas (76).

7. Mitochondrial DNA (mtDNA) mutations

Somatic mitochondrial DNA (mtDNA) mutations have been regarded as a hallmark of neoplasms and chronic inflammatory

Table III. Information concerning endometriosis susceptibility genes, genes responsible for tumor promotion and genes responsible for malignant transformation of endometriosis and cancer progression.

Genes	Endometriosis susceptibility genes	Genes responsible for tumor promotion	
		Genes responsible for malignant transformation of endometriosis	Genes responsible for cancer progression
PTEN	-/+	+	+
MYC	+	ND	+
CTNNB1	-/+	ND	+
XRCC	+	ND	ND
BCL2	-/+	-/+	+
GALT	+	ND	+
GSTM1	+	ND	+
ARID1A	-	+	+
TP53	-	+	+
BRAF	-	ND	-
PIK3CA	-	+	+
ACTN4	-	+	+
TERT	-	+	+
MIB1	-	+	+
ERBB2	-	ND	+
CDKN1A	ND	ND	+
MET	-	+	+
KRAS	-	-	+

ND, not determined.

diseases such as aging, neurodegenerative disease and endometriosis (77). mtDNA is highly vulnerable to mutagenesis through the production of ROS. Specific mtDNA mutations also increase ROS overproduction and enhance tumor progression. Several types of mtDNA alterations, including point mutations, deletions, insertions and copy number changes, have been associated with carcinogenesis (78). Findings of previous studies have demonstrated the possible association between mtDNA polymorphisms and susceptibility to endometriosis, including A189G, A13603G, 310C insertion, T16189C polymorphisms, 189G/310TC/16189C haplotype, and 5,335-bp deletion (77,79-81). Therefore, mtDNA genetic alterations may exhibit risk of endometriosis development. No evidence has emerged indicating that these mtDNA mutations are functional and pathogenic.

8. Epigenetic alterations

Beyond genetic/genomic alterations, the development of endometriosis is also influenced by epigenetic mechanisms. Accumulating evidence suggest various epigenetic aberrations in endometriosis (6,82). Epigenetic alterations reported in endometriosis thus far include the genomic DNA methylation of progesterone receptor (PGR)-B, E-cadherin (CDH1), homeobox A10 (HOXA10) (83), estrogen receptor-β (ESR2), aromatase (CYP19A1) (84), histone deacetylase inhibition (HDACi) (82), CDKN2A/B (85), IGFBP-1 (83), leukemia inhibitory factor (LIF) (83) and DNA-methyltransferase (DNMTs) (86). Downregulated genes are associated with embryogenesis (the downstream targets of HOXA10), growth factors (IGF and IGFBP) and immuno-endocrine behavior [prolactin (PRL)], interleukin-11 (IL-11), leukemia inhibitory factor (LIF), transforming growth factor (TGF)-β, FK506 binding protein 4, 59 kDa (FKBP4), cyclooxygenase (COX)-2, prostaglandins (PGs), forkhead box O1 (FOXO1) and CCAAT/enhancer binding protein (C/EBP), β (C/EBPβ) (6,82,84-94). Target genes are important for the embryogenesis and decidualization process, which includes hormonal regulation, cytokine expression and transcription factors (89,95). A previous study has shed new light on the overlapping epigenetic signatures between the development of endometriosis and insufficient decidualization process (89). Large-scale epigenetic silencing of decidualization-related genes might play important roles in the development of endometriosis (95).

9. Epidemiology

Endometriosis has been successfully identified a novel gene-environment interaction (96). Previous studies have described a positive relationship and inverse association between endometriosis risk and social, environmental and biological factors, as well as their interactions (97-107). Factors contributing to an increased risk are low birth weight, a multiple gestation, exposure to diethylstilbestrol in utero (97), overweight during late childhood (106), level of indoor exposure to passive smoking during childhood, experiencing food deprivation during World War II, walking activity at 8-15 years of age, exposure to pet animals, living in a farm for ≥3 consecutive months during childhood (100), a flight attendant, service station attendant, or health worker, a nurse (105), night shift work (107), alcohol consumption (98), cutaneous melanoma, skin sensitivity to sun exposure, nevi, freckles (108), pigmentary traits, family history of melanoma, periodontal disease (107), and caesarean section (99). On the other hand, a decreased risk of endometriosis is associated with the factors such as menarcheal age (100), increasing body size during childhood and early adulthood (102), body mass index, long-chain omega-3 fatty acid consumption (101), and in utero cigarette exposure (108). Results of those studies suggest that specific adverse exposures throughout fetal life, in early life, or during childhood or adolescence may influence the risk of endometriosis (100). Evidence of endometriosis risk of dioxin is not sufficient and remains limited (103). Based on insufficient data, it is currently not clear whether each factor is a true characteristic of women who develop endometriosis (106).

10. Discussion

Endometriosis is a chronic inflammatory disease with genetic, epigenetic and environmental background (109). Firstly, independent analysis of many cohorts have suggested genetic/epigenetic alterations such as SNPs, copy number

Table IV. Epigenetically and genetically relevant information of endometriosis susceptibility genes, genes responsible for tumor promotion and genes responsible for malignant transformation of endometriosis and cancer progression.

Name	Description	Characteristics and functions
Endometriosis susceptibility genes		
PTEN	Phosphatase and tensin homolog	Tumor suppressor gene PTEN, located on chromosome 10q23.3, is frequently deleted in human carcinomas. PTEN is a negative regulator of the PIK3/Akt survival signaling pathway. No PTEN mutations were identified in normal endometrium, endometriosis and atypical endometriosis (28). However, it has been demonstrated that somatic mutations in the PTEN gene have been associated with 20-30% of solitary endometrial cysts (27,36). Genetic mutations leading to functional inactivation of the PTEN gene were identified in one third of ovarian carcinomas (23,27). An increased frequency of the PTEN gene mutations has been reported in endometrioid carcinoma, but not in clear cell or serous tumors (3,30). These data suggest that somatic PTEN gene mutations play a part in the development of endometriosis itself and mainly malignant transformation of endometriosis.
MYC	v-myc avian myelocytomatosis viral oncogene homolog	The protein encoded by this gene is associated with important aspects of tumor biology including the regulation of cell growth and proliferation, cell adhesion, metabolism, differentiation, apoptosis, and angiogenesis. Mutations, overexpression, rearrangement and translocation of the MYC gene have been associated with a variety of hematopoietic tumors, leukemias and lymphomas. The gene expression levels were increased in ectopic tissue in comparison with normal and eutopic endometrium (40). MYC amplifications have been observed in ovarian carcinomas, particularly in endometriosis-associated endometrioid adenocarcinomas (39). The MYC amplifications possibly reflect the importance for initiation and/or progression of the development of endometriosis itself and mainly endometrioid adenocarcinomas.
CTNNB1	Catenin (cadherin-associated protein), β 1, 88 kDa	Both loss- and gain-of-function mutations of β-catenin have been established as the driving force of tumorigenesis in many carcinomas (44). Aberrant activation of the Wnt/β-catenin signaling pathway can generate chromosomal instability (44). Although there are no genetic mutation analyses, endometriotic tissues exhibited markedly reduced staining when compared with proliferative endometrium (43). Shaco-Levy *et al* reported that immunophenotypic abnormalities were present in 23% of histologically benign endometriotic lesions (43). The CTNNB1 gene mutations were detected in low-grade endometrioid carcinomas (41), suggesting that endometrioid carcinomas arise from endometriosis via CTNNB1 gene mutations. Common genetic alterations may therefore be a dependent event from endometriosis to endometrioid carcinoma that are consistent with a common lineage (30).
XRCC	X-ray repair complementing defective repair in Chinese hamster cells	XRCC1 is essential for DNA base excision repair, single-strand break repair and nucleotide excision repair. Oxidative DNA damage due to chronic inflammatory stimuli and oxidative stress due to lower DNA repair activity are associated with endometriosis progression (47). Several polymorphisms in the DNA repair gene, the genotypes of XRCC1 Arg/Gln and XRCC3 Thr/Thr, are associated with endometriosis risk (45,46), demonstrating somatic XRCC gene mutations in endometriosis risk. Defective DNA repair generates chromosomal instability that can cause subsequent alterations in gene expression. XRCC1 expression was also associated with serous type ovarian carcinomas. This gene is a predictive biomarker in ovarian carcinomas, but not a carcinoma susceptibility gene (48).
BCL2	B-cell CLL/lymphoma 2	No genetic BCL2 mutations have been reported in endometriosis. Immunohistochemical studies demonstrated that anti-apoptotic factor Bcl-2 was reported to stain 23% of benign endometriotic cysts, 42% of benign endometriotic lesions adjacent to the endometrioid carcinoma, 67% of endometrioid carcinomas, 73% of clear cell carcinomas, and 50% of papillary serous carcinomas (51). No differences have been previously found in the expression of Bcl-2 in endometriosis and ovarian carcinomas (49,50).

Table IV. Continued.

Name	Description	Characteristics and functions
GALT	Galactose-1-phosphate uridylyltransferase, 9p13	N314D mutation of GALT gene revealed a significant association with endometriosis patients compared to general population controls (30% compared with 14%) (53). However, findings of recent reports provide no evidence supporting involvement of the GALT locus in the development of endometriosis (54,55). GALT locus is a region frequently lost in ovarian carcinomas (35).
GSTM1	Glutathione S-transferase mu 1, and NAT2, N-acetyltransferase 2	GSTM1 and NAT2 (genes encoding for the detoxification enzymes) act as possible disease susceptibility genes. GSTM1 null type was associated with a significantly increased risk of endometriosis [odds ratio (OR)=2.38] (see 'A SNP haplotype analysis' section).
Genes responsible for malignant transformation of endometriosis		
ARID1A	AT rich interactive domain 1A (SWI-like)	ARID1A modulates the chromatin remodeling complex, through interactions with p53, SMAD family member 3 (SMAD3), or hormonal receptors. This complex plays a role in a variety of DNA activities such as replication, repair, methylation, recombination, transcription and gene expression by regulating key chromatin functions (246). ARID1A is frequently mutated in a variety of human cancers (15,17,18). Immunohistochemistry showed that a high frequency of the negative expression of ARID1A was 86-100% of the cases, including endometriotic cyst epithelium of non-atypical endometriosis, atypical endometriosis, the endometriotic lesions adjacent to carcinomas with deficient ARID1A expression (15). On the other hand, endometriosis distant from ARID1A-deficient carcinomas and solitary endometriosis were positive for ARID1A (15,19). Mutation of ARID1A seems to be an early event, which develops at the stage of endometriosis and is reliably detectable in the precursor lesion (3).
TP53	Tumor protein p53	TP53 genetic alterations were absent in solitary endometriosis (64). Ovarian carcinomas and adjacent endometriotic lesions have shown TP53 gene mutations, suggesting a possible malignant genetic transition spectrum (3,10). The TP53 gene alterations were not seen in endometriotic lesions that were distant from each other (30). The mutations were positive in 31% of endometriosis coexisting with clear cell carcinoma, whereas no mutations were detected in endometriosis coexisting with endometrioid adenocarcinoma (65). High-grade serous and possibly endometrioid carcinomas probably arise from cells with TP53 mutations and possibly the dysfunction of BRCA1 and/or BRCA2.
BRAF	v-raf murine sarcoma viral oncogene homolog B	Genomic data are limited. BRAF mutations are rare in endometriosis (63). BRAF mutations do not have an essential role in endometriosis-associated and endometriosis-independent endometrioid adenocarcinoma (66). It was recognized that low-grade serous carcinomas are characterized by BRAF mutations (67).
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α	Several studies have reported PI3K/AKT pathway activation in the solitary endometriosis (17), but no PIK3CA gene mutations were detected (68). PIK3CA activating H1047R mutations have been reported to show a high sensitivity for ovarian clear cell carcinoma (33-46%) (16). Same mutations were frequently found in the endometriotic epithelium adjacent to clear cell carcinomas (16).
ACTN4	Actinin, α 4	α actinin is an actin-binding protein. ACTN4 mutations, gains of ACTN4, or actinin-4 overexpression are not detected in endometriosis (69). More than half of the atypical endometrioses exhibited low-level gains of ACTN4 and actinin-4 overexpression (69).
TERT	Telomerase reverse transcriptase	Current knowledge on TERT gene mutations is very limited. Somatic gain-of-function mutations at the TERT promoter act as one of the mechanisms of ovarian clear cell carcinogenesis (70). TERT gene mutations were not detected in the endometriotic lesions adjacent to the clear cell carcinoma, suggesting that they do not appear to be an early event in the carcinogenic sequence.
MIB1	Mindbomb E3 ubiquitin protein ligase 1	MIB1 functions as an E3 ubiquitin ligase. The encoded protein may promote the ubiquitination and degradation of death-associated protein kinase 1 (DAPK1),

Table IV. Continued.

Name	Description	Characteristics and functions
MIB1	Mindbomb E3 ubiquitin protein ligase 1	an apoptosis-related tumor suppressor gene. A high expression of MIB1 protein was detected in high-grade ovarian carcinoma and atypical endometriosis (49). Transitions from atypical endometriosis to carcinoma may be documented.
ERBB2	v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2, also known as HER2	c-erb-B2 is a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases. No expression of c-erb B2 protein was detected in endometriotic tissues, suggesting that ERBB2 gene may not play an important role in the physiopathology of endometriosis. The overexpression of c-erb-B2 protein was found in endometriosis-related endometrioid adenocarcinomas (71). Genomic data are limited.
CDKN1A	Cyclin-dependent kinase inhibitor 1A (p21, Cip1)	This gene encodes a potent cyclin-dependent kinase inhibitor. p21, a downstream effector of ARID1A. No difference was detected in the distribution of the CDKN1A genotype between the endometriosis and control groups (72). Increased p21 expression was found in endometriosis and ovarian clear cell carcinoma (50,73,74). Genomic data are limited.
MET	met proto-oncogene	The proto-oncogene MET product is the hepatocyte growth factor receptor and encodes tyrosine-kinase activity. The results of previous studies revealed amplification of the MET gene and overexpression of the MET protein, especially in ovarian clear cell carcinoma (75). Endometriosis is negative for MET gain (75). A step-wise increase in MET levels was noted from paired endometriosis (0%), to atypical endometriosis (67%) and clear cell carcinoma (>90%) (75). MET gain predisposes to the malignant transformation of endometriosis and might cause the development and progression of clear cell carcinoma (75).
Genes responsible for cancer progression		
KRAS	Kirsten rat sarcoma viral oncogene homolog	KRAS is one of the most important downstream effectors coupling epidermal growth factor receptor (EGFR) to intracellular signaling cascades, leading to cell growth and inhibition of apoptosis. KRAS gene mutations were detectable in clear cell carcinoma, endometrioid adenocarcinoma and mucinous adenocarcinoma (76). KRAS mutations were not detected in endometriosis or atypical endometriosis bordering the cancerous region (20, 42). It is possible that KRAS mutations are associated with malignant transformation of atypical endometriosis into ovarian carcinomas (76).

variation, loss of heterozygosity, and promoter methylation on the development of endometriosis (Table I). Polymorphic variants of the specific alleles were found to exhibit a significant positive or inverse association between the risk for endometriosis compared to the controls. Genome-wide gene expression profiling studies (88) showed that differentially regulated (ectopic-to-eutopic) genes in endometriosis were classified into several functional categories, including inflammation and immune response, cell cycle regulation, cytokine and growth factor signaling, endocrine function, matrix remodeling, cell adhesion, DNA damage and detoxification, regulation of glucose and lipid metabolism and transcription factors (88). These data allow us to hypothesize that the previously reported endometriosis susceptibility genes (88) tend to overlap those with genetic polymorphisms analyzed in this study (Tables I and II).

Many susceptibility genes have been reported as candidate genes for the development of endometriosis. However, a majority of genes are not key drivers of somatic expansion, but likely candidate modifiers that bridge inflammation, detoxification, growth and immune escape to license eutopic and ectopic outgrowth. Epistatic modifier genes are known to participate in a wide range of essential processes: one such mechanism is inflammation and oxidative stress (2,7,8,10,110,111). This finding supports the previous hypothesis that iron-induced oxidative stress and detoxification seems to play a key role in the development of endometriosis (2). Many modifier genes are considered to complement the actions of causative genes and play a significant role in variable phenotypic expression of the disease. Although genetic alterations inherited from parents confers susceptibility to endometriosis, wide variations in the penetrance of gene mutations may reflect the genetic background of the phenotypic diversity. Variable penetrance reflects the action of modifier genes. Even particular mutations or their variant transcripts associated with disease onset may fail to cause endometriosis, due to reduced or incomplete penetrance. Despite the identification of mutations associated with the development of endometriosis, the precise functional genetic alterations remain poorly understood.

Secondly, the epigenetic disruption of gene expression also plays an important role in the development of endometriosis through interaction with environmental changes. The 'thrifty phenotype hypothesis' demonstrated that maternal diet during fetal development has many epigenetic implications, which affect the offspring's risk factors for obesity during childhood and adulthood, and even in subsequent generations (112). Similar adverse effects may be seen in other aspects of biological functions such as endometriosis. Low birthweight and multiple pregnancy are associated with subsequent endometriosis risk (97). Specific adverse environmental exposures in fetal and neonatal life, in childhood or adolescence may influence the risk of endometriosis (100). A recent study showed that environmental changes in utero such as maternal dietary energy intakes or prenatal exposures induce altered epigenetic regulation in the offspring affecting the expression of specific modifier genes that are mainly associated with endometrial decidualization processes (89,95). Epigenetic alterations may be associated with altered tissue function in fetal endometrium and influence later-life disease. The developmental origins of health and disease (DOHaD) approach may be used to elucidate the pathogenesis and epigenetic alterations of endometriosis. If gene mutations associated with endometrial decidualization are susceptible to epigenetic alterations, they have subsequent effects on disease mechanisms, such as impaired decidualization and endometriosis (89,95). The demonstration of such a sequence of genetic and epigenetic events has been shown for disease processes such as obesity, metabolic syndrome and type 2 diabetes, cardiovascular disease, cancer and possibly endometriosis. Gene-environment interactions can promote the acquisition of epigenetic alterations, genetic mutations and a different profile of gene expression. However, the precise link between epigenetics and disease is missing. The regulation of these processes in which the individuals more predisposed to endometriosis remain to be elucidated.

Mounting evidence suggests that women with endometriosis have a higher risk for ovarian cancer. In this study, ovarian cancer susceptibility genes have been defined as candidate genes responsible for malignant transformation (from endometriosis to atypical endometriosis) and candidate genes responsible for cancer progression (from atypical endometriosis to ovarian cancer) (Tables III and IV). A majority of genes function as genes responsible for malignant transformation.

Environmental factors including iron, redox and inflammatory modifications may originate from retrograde menstruation and accumulate in endometriotic lesions. Iron is an extremely reactive transition metal and generates hydroxyl radicals via a Fenton reaction (2,3,7-10,18). It is well known that iron is involved in a wide range of oxidative stress, and iron accumulation introduces point mutations as well as DNA single and double-strand breaks (110). Iron overload can also cause genetic and epigenetic changes, including DNA hypermethylation and chromatin remodeling, which lead to genomic instability and a significant increase in cancer risk (2,109,110,113). Iron contributes to carcinogenesis via three major processes: step one, by generating iron-mediated oxidative stress (genetic/epigenetic changes); step two, by promoting DNA mutagenesis, histone modification, chromatin remodeling (EAOC initiation); and step three, by enhancing genome instability (cancer promotion and progression) (111).

In conclusion, genetic and genomic factors have been unable to explain the full etiology of endometriosis. It is tempting to hypothesis that there are at least three distinct phases of the development of endometriosis: the initial wave of genetic background inherited from parents; followed by epigenetic modifications in the female offspring; and the iron overload, which is subject to dynamic modulation later in life. Stress in utero or during adolescence may compromise the future oxidative stress response to an iron insult. The present study may provide new insights into the potential mechanisms by which microenvironmental changes such as iron overload induces endometriosis and enhances endometriosis-associated carcinogenesis. Future investigations should focus on how such epigenetic changes continue to regulate risk of endometriosis from infancy through to adulthood. For example, hypermethylation of the decidualization-related genes in fetal life may cause a decrease in expression, and have a direct impact on uterine endometrial functions such as decidualization, thus influencing risk of endometriosis and infertility later in life. Of note, specific (epi)genetic signatures have led to emerging efforts to apply the knowledge to early detection, diagnosis and development of molecularly targeted therapy.

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