

REVIEW

Advances in the genetics of endometriosis

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Abstract

Endometriosis is a gynecological disease characterized by implantation of endometrial tissue outside of the uterus. Early familial aggregation and twin studies noted a higher risk of endometriosis among relatives. Studies on the roles of the environment, genetics and aberrant regulation in the endometrium and endometriotic lesions of women with endometriosis suggest that endometriosis arises from the interplay between genetic variants and environmental factors. Elucidating the hereditary component has proven difficult because multiple genes seem to produce a susceptibility to developing endometriosis. Molecular techniques, including linkage and genome-wide analysis, have identified candidate genes located near known loci related to development and regulation of the female reproductive tract. As new candidate genes are discovered and hereditary pathways identified using technologies such as genome-wide analysis, the possibility of prevention and treatment becomes more tangible for millions of women affected by endometriosis. Here, we discuss the advances of genetic research in endometriosis and describe technologies that have contributed to the current understanding of the genetic variability in endometriosis, variability that includes regulatory polymorphisms in key genes.

Introduction

The complete sequencing of the human genome in 2001 revolutionized the molecular era of human disease [1]. Of the 3 billion chemical bases comprising the 46 human chromosomes, approximately 30,000 genes have been mapped. For complex human conditions, such as type 2 diabetes mellitus, coronary artery disease and endometriosis, the allelic architectures are difficult to characterize because they fail to show classic Mendelian

inheritance. Multifactorial or polygenic disorders, such as endometriosis, are determined by multiple genes with allelic variations. Early studies by the groups of Simpson and Lamb [2,3] suggested that endometriosis has a heritable component.

Endometriosis is a common, chronic, inflammatory and estrogen-dependent gynecological disease that develops as a consequence of a combination of genetic predisposition and environmental factors. It affects 10 to 15% of women in their reproductive years [4] and is characterized by the implantation of endometrial (womb lining) tissue outside of the uterus (ectopic endometrium). Common locations of ectopic endometrial implantation are the pelvic peritoneum, ovaries, bowel, bladder, and less frequently, the pleural cavity, liver and kidneys.

Endometriosis is diagnosed in 30 to 40% of women with infertility and pelvic pain [5]. Women frequently experience symptoms of dysmenorrhea (painful menstruation), dyspareunia (pain during sexual intercourse), dysuria (pain during urination) and dyschezia (difficulty with defecating). The severity of the disease is graded on a scale of I to IV by the revised American Fertility Society classification system [6], which quantifies disease according to the amount of ectopic endometrial tissue present, its location and the amount of scarring in the pelvis. Stages I and II are described as minimal to mild and stages III and IV are described as moderate to severe [6]. Endometriosis accounts for \$22 billion annually in total US healthcare costs [7]. Medical treatments are often of limited efficacy, counterproductive to fertility and can cause untoward side effects owing to suppression of endogenous steroid hormone levels. Regardless of treatment, endometriotic lesions recur in more than 30% of patients with reduced fecundity and pelvic pain [8]. Women with endometriosis who have pelvic pain have an increased risk of several conditions, including allergies, asthma, autoimmune diseases, hypothyroidism and chronic fatigue syndrome [8].

Familial aggregation and twin studies

Beginning in the 1940s, research into the cause of endometriosis included multiple reports of affected relatives, suggesting a familial occurrence [9,10]. In a 1971 questionnaire study of 350 women with endometriosis, 22.4% of the respondents reported a first- or second-degree relative

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with endometriosis [11]. Simpson *et al.* [2] published the first formal genetic studies on women with histologically proven endometriosis in 1980. In this study, he found that 6.9% of first-degree relatives also had endometriosis; by contrast, less than 1% of their husbands' female relatives had endometriosis [2]. In a follow-up study by Malinak *et al.* [12], the clinical characteristics of patients with histologically confirmed pelvic endometriosis who had affected relatives were compared with patients who had endometriosis without affected relatives. The primary difference was the finding that women who had relatives with endometriosis had more severe disease, defined as stages III to IV. The result further supported the role of genetics in the pathophysiology of endometriosis and established a 7% risk of developing endometriosis for first-degree relatives. Lamb *et al.* [3] later estimated an overall risk of 1.9% for second-degree relatives. In subsequent familial aggregation studies in the UK, Coxhead and Thomas [13] compared 64 women with laparoscopically confirmed endometriosis and 128 controls and found that 9.4% of the patients had first-degree relatives with endometriosis, yet only 1.6% in the control group had relatives with endometriosis. They found a sixfold increased risk for first-degree relatives of women with laparoscopically confirmed diagnosis of endometriosis. Moen and Magnus [14] conducted a large Norwegian study composed of 522 cases, which supported the findings of earlier studies looking at familial aggregation; 3.9% of mothers and 4.8% of sisters of affected individuals had endometriosis compared with only 0.6% of sisters in the control group. Interestingly, this Norwegian study [14] also concluded that symptom severity was increased among women who had relatives with endometriosis, a conclusion originally reported in a smaller study by Malinak *et al.* [12].

Icelandic people, who have been geographically and genetically isolated, have been an interesting population in which to study familial aggregation. A computerized database includes all 283,000 presently living Icelanders in addition to most of their ancestors since the island was settled in the late 9th century. Stefansson *et al.* [15] used this database to study women diagnosed with endometriosis over a 12-year period (1981 to 1993). They calculated the contribution of genetic factors by comparing average kinship coefficients. The calculated kinship coefficient in 750 women with endometriosis was 1.82×10^{-4} , which was significantly higher ($P < 0.001$) than that of matched controls (1.45×10^{-4}).

Twin studies have been used to discern the separate contributions of genes and environment. A small Norwegian twin trial reported that six of eight monozygotic twin pairs were concordant for endometriosis [16]. Hadfield *et al.* [17] described concordance in 9 out of 16 monozygotic pairs for stage III to IV endometriosis in a

larger British population of twin pairs. Of the seven discordant pairs, there were five pairs in which one twin had stage I to II disease and the other had stage III to IV disease. Interestingly, the women in the two discordant monozygotic twin pairs were all infertile. The observation suggests that genes associated with the development of endometriosis may be linked to genes that cause infertility.

Linkage analysis studies

Linkage analysis has been an important technique for discovering the chromosomal location of disease-related genes. Many monogenetic Mendelian disorders, including mutations in the familial breast and ovarian cancer genes *BRCA1* and *BRCA2*, have been successfully mapped using linkage analysis [18,19]. This technique has been used for detection of genetic markers of endometriosis. A large linkage study by Treloar *et al.* [20] combined Australian and UK families and genotyped 4,985 women, including 2,709 with endometriosis. The collaborative International Endogene Study [20] brought together two independent groups: the UK-based Oxford Endometriosis Gene Study and the Australian Genes behind Endometriosis Study. The study [20] used linkage analysis techniques to find two loci of significant linkage on chromosome 10q26 and another region of suggestive linkage on chromosome 20p13. Chromosome 10q26 had previously been implicated in a candidate gene study [21] that reported aberrant endometrial *EMX2* expression in women with endometriosis. *EMX2* encodes a transcription factor required for reproductive-tract development [22], but variants of *EMX2* have not been confirmed to contribute to the development of endometriosis [23]. Although promising, linkage analysis has yielded few significant genetic markers [24].

Genetic association studies

Candidate genes are chosen on the basis of their pathophysiological relevance and variants of candidate genes are assessed in samples of endometriosis cases and controls. Table 1 summarizes the most commonly studied candidate genes. Generally, candidate genes can be divided into several classes: genes involved in regulating xenobiotic metabolism, those involved in steroid action and receptors, and those involved in inflammatory or angiogenic responses (Table 1) [25].

Human endometrium, whether in its normal place (eutopic) or ectopic, is a hormone-responsive tissue, which also produces steroids, including estrogen, that have been shown to promote endometriosis [26]. Risk factors of endometriosis include prolonged exposure to endogenous estrogen, such as that resulting from early menarche or late menopause, and exogenous estrogens. Dysregulation of progesterone signaling in the eutopic

Table 1. Commonly reported endometriosis candidate genes from association studies

Process regulated	Candidate gene	Gene symbol	Chromosomal locus	Number of positive studies	Number of negative studies
Xenobiotic metabolism	Glutathione <i>M</i> -transferase 1	<i>GSTM1</i>	1p13.3	9	12
	Glutathione <i>S</i> -transferase 1	<i>GSTT1</i>	22q11.2	7	7
	<i>N</i> -acetyl-transferase 2	<i>NAT2</i>	8p22	1	4
	Aryl hydrocarbon receptor repressor	<i>AHRR</i>	5p15	3	1
Hormone receptors or metabolism	Estrogen receptor α	<i>ESR1</i>	6q24-27	8	3
	Progesterone receptor	<i>PR</i>	11q22-33	4	2
	Cytochrome P450, family 17, subfamily A, polypeptide 1	<i>CYP17A1</i>	10q24	3	6
	Cytochrome P450, family 19, subfamily A, polypeptide 1	<i>CYP19A1</i>	15q21	5	2
	Cytochrome P450, family 1, subfamily A, polypeptide 1	<i>CYP1A1</i>	15q24	1	3
	Hydroxysteroid (17- β) dehydrogenase 1	<i>HSD17B1</i>	17q11-21	3	0
Inflammation or angiogenesis	Tumor necrosis factor α	<i>TNFA</i>	6p21.3	2	7
	Interleukin-6	<i>IL-6</i>	7p15.3	4	4
	Interleukin-10	<i>IL-10</i>	1q31-32	7	0
	Vascular endothelial growth factor A	<i>VEGFA</i>	6p21-12	5	1
	Intercellular adhesion molecule 1	<i>ICAM1</i>	19p13	2	3
Other processes	Galactose-1-phosphate uridyl transferase	<i>GALT</i>	9p13	2	2
	Tumor suppressor p53	<i>TP53</i>	17p13	2	7
	HLA class II histocompatibility antigen, DRB1-9 β chain	<i>HLA-DRB1</i>	6p21	3	4

Association studies in English on the most commonly studied candidate genes were identified by performing a PubMed literature search up to 23 June 2010. If a published study identified one or more positive associations, we identified this study as positive, otherwise negative. Variants of the *ESR2*, peroxisome proliferator-activated receptor $\gamma 2$ (*PPAR- $\gamma 2$*), nuclear factor $\kappa B 1$ (*NFKB1*), E-cadherin, matrix metalloproteinase 1 (*MMP1*), *MMP9*, cyclin dependent kinase inhibitor p27 (*CDKN1B*), neurokinin-1 (*TAC1*), nitric oxide synthase 3 (*NOS3*), fibroblast growth factor 1 (*FGF1*), *FGF2* and catechol-O-methyltransferase (*COMT*) genes have also been investigated as candidate genes potentially associated with endometriosis.

and ectopic endometrium leads to impaired physiological functions, including infertility and endometriosis in women [27-29].

Several association studies on single nucleotide polymorphisms (SNPs) of steroid receptor genes and steroid metabolizing genes and endometriosis have been performed. Results on the association of estrogen receptor polymorphisms and endometriosis are inconsistent. Some studies showed an association of a polymorphism (*PvuII*) in the estrogen receptor 1 (*ESR1*) and endometriosis [30,31], whereas other studies did not support this association [32,33]. These inconsistencies are probably caused by ethnic differences and small sample size of association studies. Huber *et al.* [34] analyzed the genotype frequencies of ten estrogen-metabolizing SNPs in patients with endometriosis compared with controls. Of these, the *vIV* A \rightarrow C variant in the hydroxysteroid (17- β) dehydrogenase 1 (*HSD17B1*) gene was significantly associated with an increased risk of endometriosis in both univariate and multivariate analyses.

Insensitivity to progesterone has been suggested to affect both implantation and inflammation in endometriosis [26]. The *PROGINS* polymorphism identified in the progesterone receptor (*PR*) gene contributes to growth

dysregulation in hormone-sensitive tissues and has been associated with breast and ovarian cancer [35]. The receptor change caused by the *PROGINS* mutation is hypothesized to affect ligand- and hormone-binding properties, leading to inadequate control of estrogen-receptor-driven proliferation and estrogen overactivation. The *PROGINS* polymorphism is found more frequently in women diagnosed with endometriosis [36-38], but data using genetic variants in the *PR* gene to predict endometriosis are inconclusive in various ethnic populations [35,39].

Polymorphisms in cytokine genes, including tumor necrosis factor (*TNF*)- α , interleukin (*IL*)-1 β , *IL-6* and *IL-10*, and their receptors (*IL-1RN* and *IL-2R β*), have been extensively studied because of the involvement of cytokines in the pathogenesis of endometriosis [40]; however, genetic variants of cytokine genes have not always shown an association with endometriosis. For example, several studies have reported that polymorphisms in the promoter region of the *TNF- α* gene do not influence endometriosis risk in Korean, Taiwanese or Caucasian women [41-43]. Similarly, inconsistent findings on the association of genetic variants and endometriosis have been shown for *IL-6* and intercellular adhesion molecule 1 (*ICAM1*) genes [44].

Exposures to endocrine-disrupting chemicals, such as dioxin, have been implicated in the pathogenesis of endometriosis in rhesus macaques [45] and in women [46,47]. Glutathione *S*-transferases (GSTs) are enzymes involved in the detoxification of a broad range of toxic compounds and carcinogens, including dioxin [48]. Two of the most studied SNPs in detoxification enzymes are in the GST genes *GSTM1* and *GSTT1*, which are located on chromosome 1p13.3 and 22q11.2, respectively. A meta-analysis by Guo [49] involving 14 studies on *GSTM1* and 9 studies on *GSTT1* concluded that there was no increased risk for women with the *GSTM1* null genotype and a slightly increased risk for those with a *GSTT1* polymorphism.

Table 1 summarizes the variable results of the endometriosis and gene polymorphism association studies. These discrepancies may be due to methodological problems, including relatively small numbers of cases and controls and selection of control populations [44]. Another explanation may be the use of different genotyping techniques. In addition, there is difficulty controlling environmental factors and problems replicating results among different ethnic populations. Large, multi-center prospective cohort studies with DNA genotyping arrays and gene-gene and gene-environment studies of endometriosis are needed.

Genome-wide association studies

High-resolution genomic tools enabling genome-wide association studies (GWASs) [50] offer the prospect of making real progress in the discovery of genes contributing to risk of multi-factorial diseases such as endometriosis. GWASs have been performed successfully in the discovery of new genomic regions that are associated with multifactorial diseases [51,52]. The methodology examines variation across the genome using computational models to compare the genotypes of people with and without disease to identify SNPs associated with disease. Sufficient power using this approach necessitates thousands of subjects, but this can be achieved by collaboration of large consortia. The advantage of this method is that hundreds of thousands of SNPs can be quickly examined for potential associations [53]. Another advantage of GWASs is that they are unbiased and do not depend on biologically plausible candidate genes or specific polymorphisms [54]. Disadvantages are that very large sample sizes are necessary to derive meaningful and reproducible conclusions valuable for characterizing polygenic diseases such as endometriosis.

Several large population-based prospective cohorts in the United States, Europe, Australia and Japan have gathered endometriosis data and represent potential sources for GWASs. These include the American California Teacher Study [55], the Nurses' Health Study II [56,57], the National Health and Nutrition Examination

Survey [58], the French E3N Cohort study [59], the Australian Genes behind Endometriosis Study [60], the Oxford Endometriosis Gene Study [61], the Icelandic Endometriosis Cohort Study [15] and the BioBank Japan project [62]. From these different cohorts, extensive time-dependent covariate data have been collected [56]. The cohorts differ in prevalence of current infertility, surgical diagnosis, age distribution, selection of controls and ethnicity. The first large endometriosis GWAS was published by Uno *et al.* [63] using the endometriosis cohort from the Biobank Japan project (1,907 Japanese endometriosis cases and 5,292 controls). They identified an association of endometriosis with the SNP *rs10965235* located in the cyclin-dependent kinase inhibitor 2B anti-sense RNA (*CDKN2BAS*) gene on chromosome 9p21 (with an odds ratio of 1.44) and with *rs16826658m* in the linkage disequilibrium block that includes the signaling gene *WNT4* on chromosome 1p36 [63]. *WNT4* signaling has a role in the coordination of female ovarian follicle development and of the development of the fallopian tubes and uterus from the Müllerian (paramesonephric) ducts [64]. *CDKN2BAS* regulates the expression of *CDKN2A*, a cell-cycle kinase inhibitor that controls endometrial proliferation and has been attributed with a role in endometriosis [65].

Interestingly, this GWAS [63] has confirmed loci such as 9p21 that are shared with conditions previously thought to be unrelated to endometriosis, including coronary artery disease. Recent studies have revealed that genetic variants in 9p21 are associated with multifactorial diseases, including coronary artery disease, type 2 diabetes, malignant melanoma, basal cell carcinoma, nevi (moles) and glioma [66-69]. The clinical relevance of identified genetic variants for predicting risk of endometriosis is unclear because the overall increase in risk caused by the known variants is small [70]. However, GWASs represent a new frontier in the investigation of gene-gene and gene-environment interactions. Predictive power may improve as more susceptibility loci are identified and new computational tools are applied.

Conclusions

We have seen progress in the understanding of endometriosis in the past decade through linkage analysis and association studies. However, the pathophysiology and genetics of endometriosis are still unclear. The long-term goals in discovering the genetic basis of endometriosis are early detection and improved treatment of endometriosis-associated symptoms, including infertility and pelvic pain. GWASs may bring insight into gene-environment interaction and identify candidate genes that are associated with endometriosis. This promising new technology has the potential for finding modest associations for polygenic diseases such as endometriosis.

However, GWASs are prone to error and bias arising from the predominantly case-control study design and the difficulty of interpreting statistics that result from multiple hypothesis testing. They need to be further validated through replication studies that find similar associations among independent samples with large, appropriately powered populations. The credibility and validity of GWASs will be further increased when consistent statistical results are combined with evidence of biological functionality for the variants found. Thereafter, data from GWASs could be used to assess individual risk for endometriosis and may be useful in counseling women for early treatment in order to avoid sequelae such as infertility. In addition, GWAS discoveries could be implemented in the development of novel therapies for the treatment of endometriosis. Genetics-based diagnostic tests for endometriosis and genetically targeted therapies hold the promise to diagnose and treat women at a younger age and allow physicians to better advise women regarding prognosis.

Abbreviations

EMX2, empty spiracles homeobox 2; GST, glutathione S-transferase; GWAS, genome-wide association study; IL, interleukin; SNP, single nucleotide polymorphism; TNF, tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ED drafted the manuscript. FW drafted and edited the manuscript. RNT advised on the manuscript content and relevance and edited the manuscript.

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