27 CME REVIEW ARTICLE

Volume 62, Number 9
OBSTETRICAL AND GYNECOLOGICAL SURVEY

CHIEF EDITOR'S NOTE: This article is part of a series of continuing education activities in this Journal through which a total of 36 *AMA/PRA Category 1 Credits™* can be earned in 2007. Instructions for how CME credits can be earned appear on the last page of the Table of Contents.

Endometriosis and Genetic Polymorphisms

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Endometriosis is a benign gynecological disease with an unclear pathophysiology characterized by ectopic endometrium causing endometrium-like inflammatory lesions outside the uterine cavity. Recently, a number of studies have investigated genetic polymorphisms as a possible factor contributing to the development of endometriosis. In this review, we have summarized current data regarding genes with nucleotide polymorphisms investigated with regard to endometriosis. We searched PubMed for publications on endometriosis and polymorphism and found 108 publications between January 1979 and September 2005. These were classified according to the type of genetic polymorphism investigated and whether the result favored or did not favor association with endometriosis. We found a strikingly large amount of conflicting results. About 50% of the reviewed studies demonstrated positive correlations between different polymorphisms and endometriosis. This relation is most clearly seen in groups 1 (cytokines and inflammation), 2 (steroid-synthesizing enzymes and detoxifying enzymes and receptors), 4 (estradiol metabolism), 5 (other enzymes and metabolic systems), and 7 (adhesion molecules and matrix enzymes). Group 8 (apoptosis, cell-cycle regulation, and oncogenes) seemed to be negatively correlated with the disease, whereas group 3 (hormone receptors), 6 (growth factor systems), and especially 9 (human leukocyte antigen system components) showed a relatively strong correlation. The review indicates that polymorphisms may have a limited value in assessing possible development of endometriosis.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader should be able to recall the complexity of attempting to link endometriosis to single nucleotide polymorphisms (SNPs), explain that the literature is varied on results and recommendations and is population specific, and state that there are some SNP relationships that are clinically stronger than others.

Endometriosis is a benign gynecological disease characterized by ectopic endometrium causing endometrium-like inflammatory lesions outside the uterine cavity. The cause of endometriosis is unclear. Genetic, endocrine, immune, and environmental factors have been suggested in the pathogenesis. Familial studies of endometriosis have suggested an increased risk of about 6% for close relatives to have

Dr. D'Hooghe has disclosed that he was/is the recipient of direct Grant/Research support from Serono and Pfizer and was a Consultant/Advisor for Ferring. All other authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

This study was supported by the Swedish Science Council (72X-14952, to G.F.) and Karolinska Institutets Fonder.

Lippincott Continuing Medical Education Institute, Inc. has identified and resolved all faculty conflicts of interest regarding this educational activity.

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the disease, suggesting a genetic component (1–3). Over the past 10 years, a number of studies have addressed the question of genetic polymorphisms as one contributing factor to the development of endometriosis (4). More than 20 candidate genes have been detected as being associated with endometriosis, using a variety of techniques for the analysis of genetic polymorphisms. The clinical relevance of the way single nucleotide polymorphisms (SNPs) can modify physiology can be illustrated by the occurrence of follicle stimulating hormone (FSH) receptor polymorphisms. At least 3 genetic variants of the human FSH receptor have been described, with different sensitivity to FSH, resulting in the clinical observation that women with the less sensitive form of FSH receptor need more FSH during controlled ovarian hyperstimulation (5–7). The association between hypertension and different variants of the angiotensinogen gene (AGT) (8) illustrates the clinical relevance of genetic polymorphisms in other areas of medicine. The purpose of this review is to summarize current data regarding the various genes investigated, the techniques used, and the evidence for or against an involvement in the pathogenesis of endometriosis.

MATERIALS AND METHODS

A search of PubMed, using the search terms "endometriosis" and "polymorphism," revealed 124 publications between January 1979 and September 2006. The 124 articles were classified according to the type of genetic polymorphism investigated and whether the result favored or did not favor association with endometriosis.

The methods to study genetic polymorphisms in these studies (as well as generally) involve polymerase chain reaction (PCR) of DNA extracted from peripheral blood, followed by restriction fragment length polymorphism (RLFP) analysis or DNA sequencing. Several different sequence methods exist, including automated DNA sequencing (ABI PRISM DNA sequencer), pyrosequencing, and different forms of real-time PCR (RT-PCR).

Population sizes in the reviewed publications range from 50 to 200 (mean 129 $\pm$ 70). The vast majority of studies included premenopausal women with surgically confirmed endometriosis as cases and women with a negative history of endometriosis-associated symptoms as controls. In some studies, the endometriosis group was divided based on American Society of Reproductive Medicine (ASRM) severity (ASRM 1997). Few studies have presented a power calculation, but for most polymorphisms, authors have assumed that a population of about 100 should be adequate to achieve statistical significance. However, in genetic epidemiology, the issue of study design sample size and controls are crucial, and recently, it was pointed out that the standards of statistical proof that have become acceptable in the general biomedical literature are not appropriate for genetic association studies (9). In genetic association studies, risk factors such as smoking or obesity have been replaced by the presence or absence of a particular genetic polymorphism. Risk can be considered in terms of either a predisposing allele or genotype, or in terms of multiple categories of disease risk, such as the risks associated with the 3 possible genotypes 1/1, 1/2, and 2/2 at a single diallelic locus (9). However, the prior probabilities that determine appropriate standards of evidence remain largely subjective. Given the small a priori probability that any genetic locus is associated with disease, and the typical observation of both small effect sizes and inadequate study sizes, it is not surprising that most findings judged to be positive with conventional methods of statistical significance have not been replicated (9), as will be illustrated in our review.

SPECIFIC GENE POLYMORPHISMS

Cytokines/Inflammation

- Interferon-γ (IFN-γ)
- Interleukins (IL-1-β, IL-4, IL-6, IL-10, IL-1 receptor, IL-2 receptor β)
- Tumor necrosis factor (TNF)-α and β, TNF-receptor 2

Immunological factors and the inflammatory response have been reported to play important roles in the pathogenesis of endometriosis. Several cytokines, such as IL-1, IL-6, IL-8, and TNF-α, have been found to be elevated in women with endometriosis (10). A total of 20 studies of genetic polymorphisms in the inflammatory system and their possible correlations with endometriosis (from 12 unique study populations) have been reviewed. Study populations varied between 70 and 232 women with surgically confirmed endometriosis in all cases. Control populations were defined surgically in 6 studies and clinically (no history of endometriosis) in the remaining ones. Eight of these studies correlated positively with the disease.

TNF-α is a major multifunctional proinflammatory cytokine involved in inflammatory and immune function. Elevated TNF-α levels in peritoneal fluid have been reported in women with endometriosis, suggesting that TNF-α may be involved in the de-

velopment of endometriosis. Several polymorphic sites within the promoter region of TNF-α have been described, including 5 biallelic polymorphisms at -1031, -863, -857, -308, and -238. Two of the 5 reviewed studies show positive correlations between specific polymorphic sites and endometriosis. Teramoto et al and Ahsgar et al reported an association between the polymorphic site 1031 T/C in the TNF-α promoter gene and endometriosis in Japanese women (11,12). Studies of the remaining 4 sites and polymorphisms in the TNF-α receptor 2 have not shown associations with endometriosis. One recent study of TNF-β polymorphisms found an increased risk of endometriosis in women with the AA genotype in the $+252$ site (13).

Several members and regulatory components of the interleukin family have been examined for polymorphisms, including IFN-γ, IL-1β, IL-4, IL-6, IL-10, the IL1-receptor 1, the IL-1 receptor antagonist, and the IL-2 receptor. Fourteen studies have been reviewed from 8 unique study populations. Studies of IL-1β (exon 5, 511 promotor), IL-4 (-590 C/T) and IL-6 (-174 G/C) polymorphisms have shown negative correlations with endometriosis in all cases, although Wieser et al reported a higher prevalence of endometriomas in women with the IL-6 -174 G allele (14). On the other hand, polymorphisms at 3 different sites of the IL-10 gene promoter (-1082, -592, and -627) all seem to correlate with endometriosis in Taiwanese and Japanese women. IL-10 affects the growth and differentiation of various cell types in the immune system and inhibits the production of other cytokines, such as IL-1, IL-6, and TNF. Furthermore, 1 study of IFN-γ CA-repeat polymorphisms and 1 on IL-2 receptor β (-627 C) have shown associations with endometriosis in Taiwanese and Japanese women.

In summary, polymorphisms in some specific cytokines may be associated with endometriosis. In total, 42.9% of the reviewed studies showed positive correlations between the examined polymorphisms and endometriosis. The most interesting genes in this respect are TNF-α (-1031), IL-10 (-1082, -592, -627), IFN-γ CA-repeat, and IL-2Rβ (-627). It should be noted that these associations have been found in Japanese and Taiwanese women, and these findings may not be relevant in other ethnic groups.

Steroid-Synthesizing Enzymes and Detoxifying Enzymes and Receptors

- Cytochrome P450c17, c19 (CYP17, CYP19)
- Arylhydrocarbon receptor (AHR), AHR repressor (AHRR), AHR nuclear translocator (ARNT)
- Glutathione S-transferases M1, T1 and P1 (GSTM1, GSTT1, GSTP1)
- N-Acetyl transferases 1 and 2 (NAT1, NAT2)
- Peroxisome proliferator-activated receptor (PPAR)-γ

Endometriosis is a complex trait, and multiple susceptibility genes interact with one another and the environment to produce the phenotype. Among the many genes implicated are steroid-synthesizing enzymes and detoxifying enzymes and receptors. CYP17 and CYP19, coding for cytochrome P-450, part of the phase I xenobiotic detoxification enzyme system and also playing a vital role in steroid biosynthesis in the ovary, have been studied, because polymorphisms in these genes may affect circulating estrogen levels. Phase II detoxifying enzymes and receptors such as glutathione S-tranferases (GSTs), the AHR gene, and NAT1 and NAT2 have been implicated in both endometriosis and cancer, because allelic variants of these genes with impaired detoxification function might increase risks for genetic changes. Studies on association between endometriosis and the various phase I and phase II detoxification genes have produced inconsistent results, possibly because of ethnic differences. Many polymorphism studies have now been performed on components of these systems.

There are 9 studies in which various polymorphisms in either CYP17, CYP19 or in both genes have been examined. They were performed in mainly Japanese, Indian, Chinese, and European populations. Some of these studies simultaneously investigated polymorphisms in other genes such as 17-β-hydroxysteroid dehydrogenase type 1 (HSD17B1), gluthathione reductase, and estrogen receptor α(ER-α). Two studies report positive correlations between endometriosis and occurrence of a tetranucleotide (TTTA) tandem-repeat polymorphism in CYP19 (15,16), and 3 studies report positive correlations to CYP17 A1 allele polymorphisms (17–19). However, for both genes, there were also negative studies, regarding the CYP17 MspA1 polymorphisms, 5 studies found no correlation with endometriosis (15,16,20–22), and for CYP19, 2 studies were negative (22,23).

The AHR gene may be regulated by structural variations in AHR itself, in the AHRR, in the ARNT, or in AHR target molecules such as cytochrome P-4501A1 (CYP1A1) and GST. Polymorphisms have been detected in several of these components, e.g., at the AhR codon 554, at the ARNT codon 189 and at the AHRR codon 185. Two groups in Japan have studied these polymorphisms; 1 group found no

association between uterine endometriosis and any polymorphisms (24), whereas the other group found an association between endometriosis and the AHRR codon 185 polymorphism (25).

GSTs are part of the key phase II detoxifying enzyme system, responsible for metabolism of xenobiotics and carcinogens. Also myeloperoxidase (MPO) plays an important role in the oxidation and activation of carcinogens and nitric oxide. Ten studies have addressed the association between endometriosis and gene polymorphisms in the GSTs, many studies dealing with the role of GSTM1 and GSTT1, whereas fewer were on the GSTTP1 gene. The 1 study on the MPO-463*G/A gene polymorphism showed no relation to the susceptibility of endometriosis (26).

An association between endometriosis and the GSTM1 null mutation has been reported in many populations, including French, Slavic, Indian, and Greek (16,21,26–29). Baranova et al (1997) concluded that 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 (27). However, there are also a few studies that found no association between the GSTM1 null mutation and endometriosis (30–32). Hadfield et al (2001) however saw a small increased risk for endometriosis in the combination of the GSTM1 null genotype and the CYP1A1 MspI polymorphism (31).

The GSTT1 null phenotype was found not to be associated with endometriosis in most studies (16,21,28,31,32); only 1 study reported a positive association (29). In addition, the GSTTP ile/ile polymorphism was not significantly associated with endometriosis in the studies published (32,33).

Arylamine-N-acetyl transferase is a phase II detoxification enzyme encoded by the gene NAT2. Wide interindividual variation of expression of compound metabolic enzymes is determined by polymorphisms and may predispose the development of diseases provoked by environmental factors. SNP changes from the wild-type NAT2 *4 allele result in allelic variants *5, *6, and *7. Homozygotes for the NAT2 *4 wild type are fast acetylators; heterozygotes with 1 wild-type allele and a variant NAT2 *5, *6, or *7 allele have reduced enzyme activity; and individuals with 2 variant alleles are slow acetylators. Some studies have implicated NAT2 *4/*6 as a susceptibility factor in endometriosis (see e.g., 28,29,34). However, 2 recent studies in Japan and India found no association between NAT2 and endometriosis (35,36).

Dogan et al (2004) explored the association of the PPAR-γ2 Pro-12-Ala polymorphism with endometriosis in a case–control study with 51 women with endometriosis stages I–IV and 55 control women without endometriosis. They found that the 12-Pro allele of PPAR-γ2 may have protective effects, avoiding the development and progression of endometriosis (37). In contrast, Kiyomizu et al found no correlation between the Pro-12-Ala polymorphism and endometriosis, but did find an association between the 161CC genotype and endometriosis as well as adenomyosis (38).

To summarize, the data in the articles presented here seem to favor an association between endometriosis and CYP17, CYP19, GSTTM1, and NAT2. In total, 46.2% of the studies showed reviewed positive correlations between the polymorphisms examined and endometriosis. However, 3 recent detailed meta-analyses of the studies on detoxifying enzymes and the association with endometriosis propose that the evidence to date does not show any association at all for CYP17, CYP19, GSTTM1, and NAT2 (39,40). According to the meta-analyses, this paradox is likely explained by the fact that most association studies test multiple markers, with no attempt made to control for multiple comparisons. This issue is not only relevant in cases of multiple loci but also in the case of a single locus with multiple genotypes (39,40).

Hormone Receptors

- Androgen receptor (AR)
- Estrogen receptors (ER)-α and β
- Progesterone receptors (PRs)

Endometriosis, adenomyosis and leiomyomata develop in women of reproductive age, regress after menopause or ovariectomy, and are generally thought to grow in an estrogen-dependent fashion. The induction of a hypoestrogenic state through the use of GnRH-agonists and gestagens is the gold standard in medical therapy of endometriosis. Furthermore, an increase in AR caused by estrogen is recognized as one of the biological phenomena related to estrogen-induced growth in uterine endometrium, and a genetic variation in the AR has been associated with the risk of developing endometriosis (41,42). The third hormone of interest, progesterone, is widely used in the medical treatment of endometriosis. Interestingly, recent studies have shown that modulation of the progesterone receptor with selec-

tive progesterone receptor modulators (SPRMs) may reduce endometriosis-associated pain. SPRMs are currently used in the management of medical abortions, but may have a therapeutic potential in endometriosis (43).

Genetic variations of these hormonal receptors in association with endometriosis have been the focus of 13 studies. Study populations range between 43 and 203 women with surgically confirmed endometriosis. Eight of these studies correlated positively with endometriosis.

The AR gene is located on the X chromosome and contains a highly polymorphic trinucleotide repeat (cytosine, adenine, and guanine: CAG) in its first exon, whose length and methylation pattern affect both AR expression and function. The methylation pattern of the human AR alleles was investigated by Yano et al in 1999. They found that the methylation patterns of all samples from a single endometrial cyst were identical, which indicated that endometrial cysts are monoclonal in origin and suggested that they might have neoplastic potential (44). Fujimoto et al determined the number of CAG repeats in AR mRNA to understand clonality in ovarian endometriosis. They found that an individual ovarian endometrioma might be formed from an independent monoclonal ovarian endometriotic endometrial cell after inactivation of either AR allele in the X chromosome (41). These 2 studies were questioned recently by Mayr et al (45), who stated that the human AR used as a marker in these studies was of highly questionable reliability due to the instability of its methylation pattern in nonmalignant cells and during the course of malignancy. Mayr et al re-addressed the question of clonality of endometriotic foci by using an alternative assay based on a polymorphism of the phosphoglycerate kinase 1 gene and by using laser-capture microdissection defined tissue fractions of interest. They found that only 2 of 32 samples from different patients bore monoclonal tissue. Therefore, their conclusion was that former studies stating that endometriosis is premalignant have to be cautiously reinterpreted (45). The same conclusion was found in a similar study using the same technique by Nabeshima et al (46). Two additional studies on AR receptor polymorphisms have focused directly on the possible association with endometriosis. Hsieh et al concluded that AR gene polymorphisms likely contribute to the pathogenesis of endometriosis (47), whereas Lattuada et al came to the opposite conclusion (42).

Of the 10 studies of ER-α and β polymorphisms, 6 have been able to establish a positive link to endometriosis. Georgiou et al explored the association of the ER 2-allele (point) polymorphism and multiallelic (microsatellite) polymorphism with endometriosis. They found a statistically significant difference between the patients and the controls in the frequency of the 2-allele PvuII polymorphism and in the median repeats of the (TA)n multiallelic polymorphism. The authors concluded that variability of the ER gene likely contributes to the pathogenesis of endometriosis (48). This was further supported by Kitawaki et al through studies of PvuII polymorphisms in 4 groups of endometriosis, adenomyosis/leiomyomata, disease-free, and reference population (49). However, Wang et al were not able to correlate polymorphisms in the ER-α gene, although a positive association was noted between the AluI polymorphism in the ER-β gene and stage IV endometriosis (50). Renner et al and Kim et al found no significant association between PvuII and XbaI ER-α polymorphisms and endometriosis, although Kim et al reported that ER dinucleotide TA-repeat polymorphism is associated with minimal or mild endometriosis (51,52).

Oehler et al (2004) addressed the question of why induction of hypoestrogenic states sometimes fails to improve endometriosis or adenomyosis, and hypothesized that mutations/polymorphisms in ERs, rendering them less sensitive to estrogen, might in part be responsible. Functional characterization of somatic ER-α gene mutations revealed that 2 of the mutant ER-α proteins display severely impaired DNA-binding and transactivation properties secondary to an altered response to estrogens or changes in epidermal growth factor-mediated ligand-independent activation. They suggested that mutation-related silencing of estrogen responsiveness might render endometriotic cells resistant to hypoestrogenic conditions, thereby accounting for failure of estrogen-ablative therapy in adenomyosis (53).

Berchuck et al (2004) determined whether progesterone receptor polymorphisms affect ovarian cancer risk. They genotyped the +331 G/A polymorphism in an unusually large population-based, case–control study from North Carolina that included 942 Caucasian subjects (438 cases, 504 controls) and in a confirmatory group from Australia (535 cases, 298 controls). The authors concluded that the +331 G/A progesterone receptor promoter polymorphism may modify the molecular epidemiologic pathway that encompasses both the development of endometriosis and its subsequent transformation into endometrioid/clear cell ovarian cancer (54). The recent study by van Kaam et al (55) showed that the +331 G/A

polymorphism was associated with a decreased risk for deep infiltrating endometriosis. Two studies of polymorphisms in intron G of the progesterone receptor in Caucasian populations have demonstrated associations with endometriosis (56,57), but a recent large study by Treloar et al (58) showed no association between polymorphisms in the progesterone receptor gene and endometriosis (58).

In summary, polymorphisms in the ER-α gene may be linked to the pathogenesis of endometriosis, whereas polymorphisms in the progesterone receptor and the AR seem to have a weaker correlation. In total, 60% of the reviewed studies showed positive correlations between the examined polymorphisms and endometriosis. The studies of these receptor polymorphisms have been conducted in Caucasian, Japanese, and Taiwanese populations.

Estradiol Metabolism

- Catechol-O-methyltransferase (COMT)
- 17-β-hydroxysteroid dehydrogenase type 1 (HSD17B1)

COMT inactivates the estradiol metabolites, 2-hydroxy and 4-hydroxy catechols, which have been implicated in the pathogenesis of endometriosis (59). A COMT valine to methionine polymorphism (G-to-A) in exon 4 of the COMT gene is polymorphic in the human population, with 25% of Caucasians being homozygous for the low-activity allele (COMT-L) of the enzyme. Wieser et al (2002) investigated whether this COMT polymorphism is associated with endometriosis by PCR in 91 women with and 92 women without endometriosis. They found no difference in allele frequencies, and concluded that the valine to methionine polymorphism in exon 4 of the COMT gene is not associated with the risk of endometriosis compared with a surgical control population (60). The same result for COMT was reported by Juo et al (2005) (22). Similarly, the possible association between polymorphisms in estradiol-synthesizing enzyme genes was investigated in a Japanese population with or without endometriosis. The authors conclude that evidence for association between the Ser312Gly polymorphism in HSD17B1 and endometriosis exists and suggested that the A-allele of HSD17B1 seems to confer higher risk for endometriosis (23). Further evidence of this association was recently provided by Huber et al in an attempt to develop a multiple genetic model of 10 SNPs involved in estrogen metabolism (61).

Other Enzymes and Metabolic Systems

- α2-Heremans Schmidt glycoprotein (AHSG)
- Endothelial nitric oxide synthase (eNOS)
- Galactose metabolism: galactose-1-phosphate uridyl transferase (GALT)

Several enzymes and metabolic systems, such as the AHSG, eNOS, and GALT may be involved in the pathogenesis of endometriosis. It has been demonstrated that the AHSG gene is expressed in the endometrium of patients with endometriosis, and that these patients have high levels of AHSG in serum and peritoneal fluid and significant antibodies to this protein (62). Kim et al observed that women not carrying the AHSG 2 allele had twice the risk of endometriosis than those carrying at least 1 copy of this allele and suggested that endometriosis is associated with the AHSG gene polymorphism in Korean women (63).

Similarly, the endothelial isoform of NOS has been detected in peritoneal fluid from women with endometriosis (64,65). In a Greek population, Zervou et al were able to present strong evidence that a common polymorphism of exon 7 at nucleotide 894 in the endothelial NOS gene is associated with the incidence of endometriosis (66).

The N314D specific mutation in the gene encoding GALT has been proposed as a risk factor for ovarian cancer and endometriosis (67). This mutation is common, with carrier frequencies of 14% to 18% in different populations. Cramer et al reported that women in a North American population with endometriosis were more likely to carry at least 1 N314D allele (30% compared with 14%) and more likely to report a medical history of scoliosis (21% compared with 2%) compared with general population controls (n = 111); these were 2 features they previously had described in women with vaginal agenesis. They speculated that endometriosis may arise due to defects of canalization of the cervix leading to cervical stenosis and retrograde menstruation (67). However, several attempts to reproduce these findings have failed to demonstrate associations between the N314D mutation and endometriosis in British, Icelandic, and Chinese populations (68–71).

In summary, 42.9% of the reviewed studies showed positive correlations between the examined polymorphisms and endometriosis. However, 3 of 4 studies of GALT polymorphisms failed to demonstrate an association with endometriosis.

Growth Factor Systems

- Epidermal growth factor receptor (EGFR)
- Regulated upon activation normal T cells expressed and secreted (RANTES)
- Transforming growth factor (TGF)-β-receptor 1 (TβR-I)
- Vascular endothelial growth factor (VEGF)

Six studies of polymorphisms in different growth factor systems have been reviewed, with study populations ranging between 63 and 215 women with endometriosis. These systems are involved in growth, differentiation, and vascularization of normal and tumor cells. Activation of the EGFR results in effects that include DNA synthesis and cellular differentiation, and dysregulated EGFR expression is implicated in the pathogenesis of numerous illnesses. Hsieh et al (72) evaluated whether EGFR gene polymorphism with A→T base change at the 2073 position of exon 21 could be a useful marker for predicting susceptibility to endometriosis or leiomyoma. They found that the EGFR gene 2073*T-related genotypes and alleles were associated with higher susceptibilities to endometriosis and leiomyoma (72).

The RANTES (regulated upon activation normal T cells expressed and secreted) chemokine is known to be expressed in endometriotic lesions in a concentration which correlated with the severity of endometriosis. Antiñolo et al (73) genotyped and evaluated the role of the variants −403G→A and −28C→G, located within the promoter region of the gene, as susceptibility factors in a cohort of Spanish women with endometriosis. No differences were found in the allelic frequencies of both variants, nor in the haplotype/genotype distribution between patients and controls. These data are consistent with the lack of association between these polymorphisms and endometriosis in the population studied (73).

The inactivation or altered expression of TGF-β receptors or other components of the TGF-β signaling pathway are common in many cancer types. A germline sequence variant of transforming growth factor-β receptor 1 (TβR-I), which involves the deletion of 3 alanines (6A) from a 9-alanine stretch (9A), impaired mediation of TGF-β antiproliferative signaling. The TβR-I (6A) variant has been reported to occur at an increased frequency in a variety of cancer types and may represent an important hereditary predisposing factor. Baxter et al (74) investigated the possible influence of the TβR-I (6A) allele on cancer risk in a case–control study of 248 controls; 304 women with ovarian cancer; 98 women with endometriosis; and 355 women with breast cancer occurring under the age of 40 years, bilateral breast cancer, or a family history of breast cancer. The study provides additional evidence for an association of the TβR-I (6A) allele with cancer predisposition, but did not indicate a link to endometriosis (74).

VEGF is a major mediator of angiogenesis, and plays a key role in the pathophysiology of endometriosis. Both the −460C→T and +405G→C polymorphisms in the 5′-untranslated region of the VEGF gene may influence the likelihood of a woman developing endometriosis according to 3 studies of Indian, Korean, and Taiwanese women (75–77).

In total, 66.7% of the reviewed studies showed positive correlations between the examined polymorphisms and endometriosis. Polymorphisms in the 5′ untranslated region of the VEGF gene may be of interest in future association studies.

Adhesion Molecules and Matrix Enzymes

- Intercellular adhesion molecule 1 (ICAM-1)
- Matrix metalloproteinases 1 and 3 (MMP1, MMP3)
- MUC9
- Plasminogen activator inhibitor 1 (PAI-1)

Cell adhesion molecules are expressed in endometriotic lesions, and in cells and tissues that are involved in the development and progression of the disease (78). ICAM-1 is one such surface glycoprotein that promotes adhesion in immunological and inflammatory reactions. Both the surface and the soluble forms of ICAM-1 have been proposed to be involved in the pathogenic mechanisms underlying various autoimmune and immune-mediated diseases including disorders of the female reproductive system, such as preeclampsia, ovarian hyperstimulation syndrome, and endometriosis (79–83). The 2 existing studies of the 2 polymorphic sites in codons 241 (G/R241) and 469 (E/K469) have reached opposite results in terms of increased endometriosis susceptibility (84,85). Yamashita et al (85) were not able to correlate ICAM-1 polymorphisms with endometriosis in a Japanese population, whereas Viganó et al (84) noticed a strikingly high frequency of the R241 allele in patients with stage IV endometriosis.

MMP1 is involved in tissue remodeling and bleeding and possibly in the secondary shedding and reimplantation of endometriotic lesions (86), whereas MMP3 in ectopic endometrium may participate in the process of invasion and tissue remodeling that is hypothesized to occur in the pathogenesis of endometriosis (87). Shan et al (88) assessed how gene

polymorphisms in the MMP1 and MMP3 promoters affect the risk of development of endometriosis. They genotyped 100 women with endometriosis and 150 control subjects in North China and concluded that the MMP1 promoter SNP and MMP 2G/6A haplotype may modify susceptibility to endometriosis. However, the MMP3 promoter SNP was unlikely to be associated with endometriosis in the population of North China (88). Kang et al (89) similarly found that individuals with the MMP-1 2G haplotype had a significantly increased risk of developing endometriosis and adenomyosis, whereas the MMP-3 promoter SNP was not associated with susceptibility to endometriosis and adenomyosis (89). In contrast, Ferrari et al (90) found no associations between MMP polymorphisms and endometriosis.

Bedaiwy et al (91) studied polymorphisms of the PAI-1 gene in a group of women with or without endometriosis. They found a positive association between the 4G allele of the PAI-1 gene in women with endometriosis compared with controls, indicating that hypofibrinolysis and persistence of fibrin matrix could support the initiation of endometriotic lesions in the peritoneal cavity (91).

In total, 40% of the reviewed studies showed positive correlations between the examined polymorphisms and endometriosis. (It should be borne in mind that some of the associations may not be causal.)

Apoptosis, Cell-Cycle Regulation, and Oncogenes

- FAS, FASL
- p21, p53, ras

The suggestions for pathophysiological mechanisms leading to endometriosis include dysregulation of the normal apoptotic process, which takes place in the endometrium. One of the apoptotic pathways playing a crucial role in programmed cell death within the endometrium is the FAS-FASL system. Furthermore, cell-cycle regulator genes and tumor suppressor genes such as p21, p53, and ras have been implicated in the pathogenesis of endometriosis. p21, an important regulator of the cell cycle, acts as a mediator of the growth-suppressing and promoting functions of p53. The monoclonal origin of most endometriotic lesions (as indicated by recent investigations) indicates their neoplastic nature. p53, a tumor suppressor, regulates cell proliferation, and genetic alterations in p53 are involved in carcinogenesis in a wide variety of human cancers.

Fernández et al evaluated 3 polymorphisms located within FAS (−1377G→A and −670A→G) and FASL (−843C→T) genes, as susceptibility factors for endometriosis. The authors reported that the differences in the distribution of the polymorphic variants were not statistically significant when the group of endometriosis patients was compared with the control group. They concluded that the variants analyzed are not involved in the pathogenesis of the disease in their population (92). A study by Hsieh et al of codon 31 polymorphisms of p21 and endometriosis led to the conclusion that this particular SNP is not a useful marker for prediction of endometriosis susceptibility (93). Vercellini et al came to similar conclusions regarding the presence of activating mutations in codons 12, 13, and 61 of ras genes and endometriosis in an Italian population (94).

The possible association between polymorphisms in p53 and endometriosis has been evaluated by 6 different groups. The majority of these studies have focused on the p53 codon 72 polymorphisms (arginine homozygosity, heterozygosity, and proline homozygosity). Chang et al reported that endometriosis may be associated with p53 polymorphism, and that p53 arginine homozygotes have lower risk for endometriosis, whereas heterozygotes and proline homozygotes have higher risk for endometriosis (95), and Hsieh et al reported that p53 codon 72 polymorphisms are related with higher susceptibility of endometriosis (96). The remaining studies have failed to support this possible pathogenetic mechanism (94,97–99).

In summary, only 2 (22.2%) of the abovementioned studies (95,96) correlated positively to endometriosis. It is unlikely that polymorphisms in these systems are associated with the pathogenesis of endometriosis.

Human Leukocyte Antigen System and Immune Components

An increasing number of reports suggests that endometriosis is associated with abnormal immune function involving changes in both cell-mediated and humoral immunity, although the etiology of the disease remains undefined (100). The human leukocyte antigen (HLA) system is known to play a role in the etiology of a number of diseases, such as insulin-dependent diabetes mellitus (101) and SLE (102). In 2 studies by Ishii et al, the possible role of HLA polymorphisms was evaluated in a population of 83 Japanese women with surgically confirmed endometriosis. The authors concluded that the incidence of

both the HLA-DQB1*0301 allele and the HLA-DRB1*1403 allele was significantly greater in patients with endometriosis compared with a control population (103,104).

The latter study by Ishii et al was to some extent confirmatory of a study by Wang et al (105). In a Chinese group of 40 women with endometriosis, the HLA-DRB1 15 allele was found to be significantly higher in the endometriosis group as compared with the normal control group (105). Wang et al had reported earlier that the occurrence of endometriosis may be associated with the presence of HLA-I B46 antigen and that the HLA-I B48 antigen might play a protective role against endometriosis (106).

Viganó et al (107) examined polymorphisms in the cytotoxic T lymphocyte antigen (CTLA) 4 gene, a primary determinant for autoimmunity, because specific polymorphisms have been associated with predisposition to most autoimmune disorders. They found no association (107).

Although only demonstrated in Asian women, polymorphisms in the HLA-system may be associated with the risk of developing endometriosis. Further studies in other ethnic groups are warranted.

DISCUSSION

Currently, more than 10 million DNA sequence variations have been uncovered in the human genome. The most detailed variation discovery efforts have focused on candidate genes involved in cardiovascular disease or in susceptibilities associated with exposure to environmental agents. The average human gene contains 126 biallelic polymorphisms, 46 of which are common (≥5% minor allele frequency) and 5 of which are found in coding regions (108). Individual genetic variation has also been proposed as a significant contributor to the etiology of endometriosis. Several epidemiologic studies suggest that endometriosis is highly inheritable (109) and a number of SNPs have been found to be associated with the clinical course of, and the susceptibility to, the disease.

This review reveals a strikingly large amount of conflicting results. About 50% of the reviewed studies have demonstrated positive correlations between different polymorphisms and endometriosis. This relation is most clearly seen in groups 1 (cytokines and inflammation), 2 (steroid-synthesizing enzymes and detoxifying enzymes and receptors), 4 (estradiol metabolism), 5 (other enzymes and metabolic systems), and 7 (adhesion molecules and matrix enzymes). Group 8 (apoptosis, cell-cycle regulation, and oncogenes) seems to be negatively correlated with the disease, whereas group 3 (hormone receptors), 6 (growth factor systems), and especially groups 9 (HLA-system components) show a relatively strong correlation.

The validity of the results ultimately depends on the selection of the study population, which translates into the crucial question: do the women studied have endometriosis? In over 90% of the studies, endometriosis was diagnosed by laparoscopy. This is generally considered to be the gold standard in diagnosing endometriosis, and the high frequency of the procedure should ensure a correct selection of the study population. However, control patients have in most cases been included through a negative medical history of endometriosis-associated symptoms. This method cannot ascertain a completely endometriosis-free control group but the alternative of choosing an invasive approach must be considered unethical in a healthy population. Choosing adequate control groups is a complex and often overseen problem in endometriosis research (110). It is necessary that the control group is free from other causes of pain or subfertility in order to study the effects of endometriosis itself. Women undergoing tubal ligation, preferably through laparoscopy, could serve as a much better control group than women with just a negative history of endometriosis. Unfortunately, few studies have used this kind of control group.

The validity of the association studies between different SNPs and endometriosis was recently questioned by Guo in a series of meta-analyses. The analyses included all publications in 3 of the abovementioned systems: sex steroid synthesis, GSTM1/GSTT1, and dioxin detoxification enzymes (39,40). The author criticized a large number of association studies on the basis of publication bias, poorly defined control groups and data analysis. Furthermore, several genetic variants with a reported association with endometriosis are single studies without independent confirmation studies. The author concluded that there is little evidence that SNPs in these systems are associated with endometriosis. Guo further suggested that in future association studies, efforts should be made to control for other risk factors in endometriosis and select the control group more carefully. The problem of interpreting and extrapolating association studies has been addressed in several reviews. The simplicity of identifying genetic markers through PCR has led to a large number of association studies with sometimes contradictory results. Gambaro et al (111) discussed the risk of jumping to conclusions in population association

studies, because complex diseases often arise from an interaction between several genetic and environmental factors. The inability to replicate many results clearly illustrates the shortcomings of current association studies. Colhoun et al (112) recently concluded that this inability is the result of publication bias, failure to attribute results to chance and inadequate sample size. As phrased by Newton-Cheh and Hirschhorn: "Ultimately, the strongest evidence in support of a reported association will be replication of association with *the same allele, the same phenotype and the same direction of effect* in an independent population sample" (113).

The meta-analyses and reviews cited above illustrate some of the problems with these association studies and raise the question whether any of the evaluated SNPs are associated with endometriosis or not.

Conflicting results may further arise from ethnic variance. Approximately 50% of the reviewed studies have been conducted in Asian populations and the remainder in Caucasian populations. Results from many studies that were performed in one ethnic population were not confirmed when repeated in another population. It is well known that the distribution of gene polymorphisms vary in different ethnic populations, and this is one major factor in the ascertainment bias that has given concern regarding SNP data analysis (114–116). This variance makes it difficult to draw valid conclusions about whether a certain polymorphism is relevant in the biology of endometriosis or not. In this context, it is also appropriate to point out that several research groups have used the same population material to analyze a large variety of polymorphisms, which means that in those studies, the possible ethnic population bias might also be accompanied by patient/control selection bias (see above).

SNPs thus seem to have a limited value in assessing increased susceptibility of developing endometriosis. The conflicting results of the reviewed studies indicate that a single SNP contributes to a relatively small fraction of the underlying genetics of endometriosis. As pointed out by Guo, the human genome contains more than 1.8 million SNPs (http://snp.cshl.org/) and the probability that a particular gene polymorphism may increase the risk of endometriosis is miniscule. Some investigated SNP systems may be more interesting than others, such as the HLA system, TNFα-1031, VEGF and progestins. An ongoing web project (http://www.well.ox.ac.uk/~krinaz/) describes allele and genotype frequencies of SNPs in association studies and provides a useful tool for the study of genetic variants and the pathogenesis of endometriosis (117).

An interesting approach was that of Huber et al in an attempt to develop a multiple genetic model by combining genotyping of 10 associated SNPs (61). Although the authors were not able to demonstrate an interaction model, the idea of integrating several SNPs into a combined model may be more attractive than the current investigation of single SNPs.

Promising results were recently reported in a multiple SNP model attempting to predict the risk of prostate cancer (118). The ongoing international HapMap project (http://www.hapmap.org), with the aim to determine the common patterns of DNA sequence variation in the human genome, may provide a powerful tool in future general association studies, and may also help to further illuminate the role for gene polymorphisms in the pathogenesis of endometriosis.

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