**Functional genetic polymorphisms and female reproductive disorders:**

**Part II—endometriosis**

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**BACKGROUND:** Endometriosis has a strong genetic component, and numerous genetic studies have been reported.

**METHODS:** We have systematically reviewed these studies and included 114 in our final selection.

**RESULTS:** We found no consistent evidence linking endometriosis with specific polymorphisms in genes encoding inflammatory mediators, proteins involved in sex steroid metabolism, vascular function and tissue remodelling. Although a number of polymorphisms have been associated with endometriosis in selected populations, the associations have not been independently confirmed, either because only single studies were carried out on these markers/genes or because other studies reported no association. The most solid evidence linking specific polymorphisms to endometriosis came from studies investigating glutathione-S-transferase, a phase II detoxification enzyme. Carriage of the *GSTT1* null deletion variant showed consistent association with endometriosis with a 29% increased risk; however, it cannot be excluded that this result was due to publication bias, and this association should be independently confirmed in large-scale, well-designed case–control studies.

**CONCLUSIONS:** The evidence of an association between genetic polymorphisms and endometriosis is weak. Carriage of the *GSTT1* null deletion may moderately increase the risk of this disease. We suggest that the methodology of association studies should be improved in order to identify and validate associations in endometriosis.

**Key words:** endometriosis / female reproduction / genetic polymorphisms / detoxification / sex steroids

**Introduction**

The association between genetic polymorphisms and clinical disease has long been recognized. For example, a relationship between blood group and gastrointestinal cancer was described in the 1950s (Billington, 1956).

More recently, technological advances in molecular biology have fuelled the interest in molecular polymorphisms and their influence on the susceptibility and clinical presentation of diseases (Tempfer et al., 2004).

Many aspects of female reproductive function are strongly influenced by genetic factors, and numerous studies have attempted to...
identify susceptibility genes for disorders affecting female fertility such as polycystic ovary syndrome, endometriosis, fibroids, cancer (ovarian, vulvar, cervical), premature ovarian failure, recurrent pregnancy loss and pre-eclampsia (Levan et al., 2004; Modugno, 2004; Escobar-Morreale et al., 2005; Goswami and Conway, 2005; Tempfer et al., 2005; Ferreira et al., 2006; Layman, 2006). For many of these conditions, the search for genetic disease markers is ongoing, and no strong candidate has yet emerged.

Endometriosis is characterized by the presence and growth of endometrial cells outside the uterus, which impair fertility (Wenzl et al., 2003; Halis and Arici, 2004), and the disease has a strong genetic component (Treloar et al., 1999; Bischoff and Simpson, 2004; Vigano et al., 2007). In a study of the genetic influence on endometriosis risk in an Australian twin sample, for example, the risk ratio of affected versus population prevalence was 3.58 for monozygotic twins and 2.32 for dizygotic twins (Treloar et al., 1999). Clarifying the genetic etiology of endometriosis would have implications for diagnosis, identification of individuals at risk and the development of targeted therapeutics.

This disorder has been the focus of a large number of association studies investigating a wide variety of polymorphisms. Previous reviews assessed the possible role of specific polymorphisms or groups of polymorphisms, indicating that the number of robust associations may be low (Falconer et al., 2007). Some have even challenged the evidence for endometriosis having a genetic background (Di and Guo, 2007).

In this review, we assess evidence for the role of genetic polymorphisms in endometriosis. We present a systematic review of the published literature across all polymorphisms investigated in relation to endometriosis. We have evaluated the reliability and strength of the evidence for each of the 114 selected studies and discuss methods for improving association studies. However, to enable proper evaluation of the studies, we first explore the methodology of molecular association.

Genetic association studies of polymorphisms

The genetic basis of disease may be elucidated in different ways. One approach is to scan across the genome to identify markers/genes of interest; a second approach is to investigate specific ‘candidate’ genes. We discuss these approaches below, and provide examples of such studies in endometriosis.

Genome-wide linkage analysis using affected sibling-pairs has been applied to endometriosis by Australian, British and Icelandic groups (Stefansson et al., 1998; Treloar et al., 2000; Kennedy et al., 2001). These studies aim to find chromosomal regions shared by related individuals harbouring disease-predisposing genes. In these linkage studies, which are conceptually different from case-control studies in unrelated individuals, a possible informative locus on chromosome 10q has been reported (Treloar et al., 2000). In addition, in a separate linkage analysis of families with three or more affected members, Zondervan et al. (2007) suggested that there may be one or more high-penetrance susceptibility loci for endometriosis on chromosome 7. A dominant mode of inheritance with reduced penetrance and a recessive mode of inheritance with high penetrance have been suggested for these potential genetic variants. To our knowledge, genome-wide genetic association studies on unrelated individuals have not been carried out.

Genetic case-control studies identify markers/genes that are associated with a trait of interest, such as a given disease. Genetic association studies do not, however, prove an etiological link between the polymorphism and/or the gene in question and the investigated trait. Once identified, the association of a specific genetic marker within a candidate gene with the trait should be investigated further. Specifically, it has to be clarified, whether the allele of interest has a direct biological effect or whether the association is based on biological effects downstream of the allele, which are in linkage disequilibrium. Since linkage disequilibrium may vary in different populations, this is an important source of inconsistency.

A particular problem in interpreting the results from genetic association studies in endometriosis is linked to the fact that this is not a monogenic trait but a complex trait. Therefore, various genetic factors can be expected to have an effect with an additional level of variation regarding the individual effect sizes. Especially small effect sizes may be easily missed in individual studies with small sample sizes. Common methodological problems in genetic association studies include low sample size, chance findings, multiple comparisons and subsequent type I error inflation, different ethnic backgrounds of the study subjects, varying disease definitions and inclusion/exclusion criteria and ascertainment bias. To help overcome these methodological problems, Zondervan et al. (2002) proposed the following criteria for case-control studies to identify an association between genetic polymorphisms and endometriosis: (i) use newly diagnosed, i.e. incident, cases with endometriosis, (ii) collect information predating symptoms and (iii) use at least one population-based female control group matched for unadjustable confounders and ideally also screened for pelvic symptoms. These criteria for high-quality case-control studies, however, have not been fulfilled by the majority of the studies discussed in this review. Therefore, positive associations between genetic polymorphisms and endometriosis have to be interpreted with caution.

Ethnic background is an important source of variation. As illustrated by this review, genetic associations are often inconsistent across ethnic barriers, which may be due to different frequencies of polymorphic alleles as well as gene–gene interactions. In this respect, a genetic association, although valid in a specific ethnic population, may not be relevant for individuals of another ethnicity. This has to be acknowledged when judging the external validity of any genetic association study.

Some of these methodological problems can be overcome—at least in part—by summarizing data from individual studies in the form of a meta-analysis. This tool has been increasingly used to confirm or rule out associations. Applying meta-analysis can be generally expected to confirm only a fraction of associations previously reported in individual small studies. Also, a strong association in individual studies with a P-value < 0.001 has been reported to be a good predictor of confirmation in a meta-analysis (Lohmueller et al., 2003).

In this review, we have assessed the quality of evidence for every group of polymorphisms investigated in endometriosis association studies according to the agreement between studies, the presence or absence of meta-analyses and the strength of the association.
Systematic review search criteria

We systematically searched the PubMed and EMBASE databases for gene association studies published up to the end of August 2007 using the term ‘endometriosis’ combined with ‘polymorphism OR polymorphisms’ or ‘mutation OR mutations’. The search was not limited by language of publication. Translations of non-English papers were not obtained. The principle author (C.B.T.) selected relevant studies using the following criteria: all studies investigating polymorphic genetic variants with cases, i.e. women with a clinical and/or surgical diagnosis of endometriosis irrespective of disease stage, and with controls, i.e. women irrespective of definition of controls, listing absolute numbers of the respective genotype distributions. The interpretation of the consistency of an association with endometriosis always refers to a specific polymorphism and not to any investigated polymorphism in a specific gene.

Results

The search for endometriosis susceptibility polymorphisms was focused mainly on genes involved in inflammation, sex steroid regulation, metabolism, biosynthesis, detoxification, vascular function and tissue remodelling.

Genes of inflammatory mediators

It is widely accepted that endometriosis is an inflammatory process, associated with altered immune cell function, immune cell numbers, and elevated levels of inflammatory cytokines (Agic et al., 2006). This observation has led researchers to investigate the effects of polymorphisms in genes encoding cytokines and other molecules involved in inflammation (see Table I).

Cytokines

In Taiwanese women, the —509C/T promoter polymorphism in the transforming growth factor (TGF) β1 gene (Hsieh et al., 2005f), the 881T/C polymorphism in the interleukin (IL)-2 receptor β gene (Hsieh et al., 2005b) and the —627A/C promoter polymorphism in the IL-10 gene (Hsieh et al., 2003) have all been associated to endometriosis susceptibility. Two polymorphisms in the promoter region of the IL-10 gene, —1082G/A and —592C/A [note that this is the same as the —627A/C single-nucleotide polymorphism (SNP) studied by Hsieh et al. (2003)], have been investigated in Japanese women but do not appear to influence endometriosis susceptibility in this population (Kitawaki et al., 2002). However, the same research group found that the genotype for the CA repeat microsatellite in the interferon-γ gene may have an effect on endometriosis susceptibility in Japanese women (Kitawaki et al., 2004). Polymorphisms in genes encoding other interleukins (IL-1β, IL-4, IL-6 and IL-18) and their receptors (IL-1 receptor and IL-12 receptor β) have been investigated but failed to show a consistent association with endometriosis susceptibility (Hsieh et al., 2001a, 2002, 2005b; Lee et al., 2002; Wieser et al., 2003a, b; Bhanoori et al., 2005b; Kitawaki et al., 2006; Wen et al., 2006). Wieser et al. (2003a) suggest that the IL-6 promoter polymorphism 174G/C predisposes women to endometriosis with chocolate cysts. In one study, carriage of the IL-1 receptor antagonist A2 allele was associated with endometriosis in a Chinese population (Wen et al., 2006). D’Amora et al. (2006) also reported that the BsrBI C/A, but not the Pstl C/T polymorphism of the IL-1 receptor gene, is associated with a reduced risk of endometriosis.

The insulin-like growth factor II (IGF2) Apal polymorphism was not found to be associated with endometriosis in Taiwanese women (Hsieh et al., 2004c). Also, a polymorphism in the TGFbeta1 gene (509C/T) was not associated with deep infiltrating endometriosis in Dutch women (van Kaam et al., 2007a).

A number of groups have investigated a possible link between polymorphisms in the tumour necrosis factor (TNF) gene and increased endometriosis risk. Polymorphisms in the promoter region of the TNF-α gene do not appear to influence endometriosis risk in Korean, Taiwanese or Caucasian women (Hsieh et al., 2002; Lee et al., 2002; Wieser et al., 2002a). An Australian study investigating 26 polymorphisms in the promoter and coding regions of TNF also found no association with endometriosis (Zhao et al., 2007). However, the —1031T/C TNF promoter polymorphism may affect disease severity in Japanese women (Asghar et al., 2004). In Japanese women, the TNF-U01 haplotype (—1031T, —863C, —857C) has also been linked to endometriosis susceptibility, although it should be noted that this haplotype is in strong linkage disequilibrium with the HLA-B*0702 allele, making it difficult to determine which gene is responsible for the association (Teramoto et al., 2004). A Chinese study found an association between endometriosis and the +252 polymorphism in intron 1 of the TNF beta gene (Luo et al., 2006).

Nitric oxide and adhesion molecules

Elevated levels of the pro-inflammatory molecule nitric oxide (NO) have been reported in women with endometriosis (Wu et al., 2003). Endothelial NO synthase catalyses the production of NO, and the p.E298D polymorphism in the NOS3 gene has been associated with endometriosis susceptibility (Zervou et al., 2003). Intercellular adhesion molecule-1 (ICAM-1) is thought to mediate interactions between endometrial cells and lymphocytes during the pathogenesis of endometriosis (Viganò et al., 2003). In Caucasian women, the p.G241R polymorphism in the ICAM1 gene may influence disease severity (Viganò et al., 2003), but neither this nor the p.K469E polymorphism appear to have a direct influence on endometriosis susceptibility in either Caucasian or Japanese women (Viganò et al., 2003; Yamashita et al., 2005; Kitawaki et al., 2006). The Pm11 C/T polymorphism of the epithelial cadherin (CDH1) gene was associated with late-stage endometriosis in Taiwanese women (Hsieh et al., 2005c). In a Chinese study, the CDH1 3’-UTR C/T polymorphism, but not the —160C/A or —347G/GA promoter polymorphisms, was associated with endometriosis (Shan et al., 2007).

Human leukocyte antigens

Human leukocyte antigens (HLAs) are key components of the major histocompatibility complex (MHC), which is involved in immune cell signalling processes such as T-cell activation. HLA genes involved in both MHC I (HLA-A and HLA-B) and MHC II (HLA-DPB1, HLA-DQB1 and HLA-DRB1) have been studied in women with endometriosis. A study of Chinese women found that HLA-B genotype, but not HLA-A genotype, influences endometriosis susceptibility (Wang et al., 2001). In Japanese women, both the HLA-DRB1*0403 and HLA-DQB1*0301 alleles have been linked to increased endometriosis risk, whereas HLA-DPB1 alleles do not appear to affect susceptibility (Ishii et al., 2002, 2003). It should be noted that the HLA-DRB1 and
| Table I Polymorphisms of genes encoding inflammatory mediators, which have been investigated for their role in endometriosis |
|---|
| **Gene (locus, protein name and its function)** | **Variant Name** | **dbSNP ID** | **Association with susceptibility Positive (number of cases, number of controls)** | **Negative (number of cases, number of controls)** | **Phenotype** |
| CCL5 [17q11.2-q12, chemokine (C–C motif) ligand 5 (RANTES): chemokine] | −403G/A | rs2107538 | Spanish women (63, 36 or 110) (Antinolo et al., 2003) |  |
|  | −28C/G | rs2280788 | Spanish women (63, 36 or 110) (Antinolo et al., 2003) |  |
| CCR2 (3p21.31, monocyte chemotactic protein 1 receptor: chemokine receptor) | p.V64I | rs1799864 | Spanish women (63, 36 or 110) (Antinolo et al., 2004) |  |
| CCR5 (3p21.31, chemokine (C–C motif) receptor 5: chemokine receptor) | Delta32 (32 bp deletion) | rs333 | Spanish women (63, 36 or 110) (Antinolo et al., 2004) |  |
| CDH1 (16q22.1, epithelial cadherin 1: adhesion molecule) | P11I RFLP (3'-UTR C/T) | rs1801026 | Taiwanese women (150, 159) (Hsieh et al., 2005c) |  |
|  | −160C/A | rs1620 | Chinese women (152, 189) (Shan et al., 2007) |  |
|  | −347G/GA | rs5030625 | Chinese women: −160A−347GA haplotype (152, 189) (Shan et al., 2007) |  |
| CDKN1A (6p21.2, cyclin-dependent kinase inhibitor 1A (p21): regulation of cell cycle) | p.S31R | rs1801270 | Taiwanese women (102, 119) (Hsieh et al., 2001c) |  |
| CTLa4 (2q33, cytotoxic T lymphocyte antigen-4: T-cell ligand) | 49A/G | rs231775 | Italian women (143, 165) (Vigna et al., 2005) |  |
|  | CT60A/G | rs3087243 | Italian women (146, 153) (Vigna et al., 2005) |  |
| EGFR (7p12, epidermal growth factor receptor: regulates cell growth and differentiation) | 2073A/T | rs17337023 | Taiwanese women (122, 139) (Hsieh et al., 2005c) |  |
| FAS (10q24.1, FAS: mediates apoptosis) | −1377G/A | rs2234767 | Spanish women (78, 57 or 108) (Fernandez et al., 2005) |  |
|  | −670A/G | rs1800682 | Spanish women (78, 57 or 108) (Fernandez et al., 2005) |  |
| FASLG (1q23, FAS ligand: mediates apoptosis) | −844C/T | rs763110 | Spanish women (78, 57 or 108) (Fernandez et al., 2005) |  |
| Gene                        | Chr | Description                          | Ethnicity/Study                                                                 |
|----------------------------|-----|---------------------------------------|---------------------------------------------------------------------------------|
| HLA-A (6p21.3, human leukocyte antigen-A: major histocompatibility I protein) |     | HLA-A                                 | Chinese women (40, 50) (Wang et al., 2001)                                      |
| HLA-B (6p21.3, human leukocyte antigen-B: major histocompatibility I protein) |     | HLA-B                                 | Chinese women: HLA-B46, HLA-B48 alleles (40, 50) (Wang et al., 2001)             |
| HLA-DPB1 (6p21.3, human leukocyte antigen DP B1: major histocompatibility II protein) |     | HLA-DPB1*01-01, *0401-0402, *05, *06, *08-11, *13+19 | Japanese women (83, 222) (Ishii et al., 2003)                                    |
| HLA-DQB1 (6p21.3, human leukocyte antigen DQ B1: major histocompatibility II protein) |     | HLA-DQB1*0201, *0301-0303, *0401-0402, *0501-0503, *0601-0604 | Japanese women: HLA-DQB1*0301 allele (83, 222 or 117) (Ishii et al., 2003)       |
| HLA-DRB1 (6p21.3, human leukocyte antigen DR B1: major histocompatibility II protein) |     | HLA-DRB1*0101, *0301, *0401-0408, *0410, *0701, *0801-0803, *09, *10, *1101, *1104, *1201-1202, *1301-1302, *1401, *1402, *1404, *1405, *1501, *1502, *1602 (+ *0102, *0302, *0804, *1602, *1305 in Japanese study) (+ *1111, *1339, *1406, *1407, *1412 in Korean study) | Japanese women: HLA-DRB1*1403 (83, 222) (Ishii et al., 2002) Japanese women: only looking at HLA-DRB1*1501 & *1502 (40, 50) (Wang et al., 2002) Korean women (100, 800 or 108) (Whang et al., 2006) |
| ICAM1 (19p13.3-p13.2, intercellular adhesion molecule-1: adhesion molecule) |     | p.G241R rs179968                       | Caucasian women (180, 175) (Vigano et al., 2003) Japanese women (126, 172) (Yamashita et al., 2005) Caucasian women: disease severity (Vigano et al., 2003) |
| IFNG (12q14, interferon-γ: cytokine) |     | p.K469E rs5498                        | Japanese women: Association only seen in combination with IL-6 -634G (202, 236) (Kitawaki et al., 2006) Japanese women (126, 172) (Yamashita et al., 2005) |
| IGF2 (11p15.5, insulin-like growth factor II: cytokine) |     | CA repeat rs680                       | Japanese women (185, 176) (Kitawaki et al., 2004)                               |
| IL4 (5q31.1, interleukin-4: cytokine) |     | Apal RFLP (17 200G/A) rs2243250        | Taiwanese women (120, 103) (Hsieh et al., 2004c)
|                          |     | 70 bp VNTR (intron 3)                 | Taiwanese women (120, 106) (Hsieh et al., 2002)
| IL6 (7p21, interleukin-6: cytokine) |     | −174G/C rs1800795                    | Korean women (70, 202) (Lee et al., 2002)
|                          |     |                                      | Austrian women (94, 70) (Wieser et al., 2003a)
|                          |     |                                      | South Indian women (232, 210) (Blanco et al., 2005b)                                  |
| Gene (locus, protein name and its function) | Variant Name | dbSNP ID | Association with susceptibility | Phenotype |
|-------------------------------------------|--------------|----------|---------------------------------|-----------|
| **2634C/G (−572C/G)** rs1800796 | Japanese women. Association only seen in combination with ICAM1 p.469E/E genotype (202, 236) (Kitawaki et al., 2006) | | | |
| **IL10 (1q31-q32, interleukin-10: cytokine)** | −1082G/A rs1800896 | Japanese women (196, 160) (Kitawaki et al., 2002) | | |
| **IL18 (11q22.2-q22.3, interleukin-1β: cytokine)** | −627A/C (< 592C/A) rs1800872 | Taiwanese women (130, 133) (Hsieh et al., 2003) | | |
| **IL1B (2q14, interleukin-1β: cytokine)** | 3953C/T rs143634 | Austrian women (92, 69) (Wieser et al., 2006) | | |
| **IL1RI (2q11.2, interleukin-1 receptor I: cytokine receptor)** | PstI RFLP | Brazilian women (109, 114) (D’Amora et al., 2006) | | |
| **IL2RB (22q13.1, interleukin-2 receptor β: cytokine receptor)** | BsrBI RFLP | No dbSNP ID | | |
| **IL1RN (2q14.2, interleukin-1R antagonist: cytokine)** | 86 bp VNTR (intron 2) | Chinese women (138, 100) (Wen et al., 2006) | | |
| **IL12RB1 (19p13.1, interleukin-12 receptor β: cytokine receptor)** | p.G378R rs401502 | Taiwanese women (150, 159) (Hsieh et al., 2001a) | | |
| **NOS3 (7q36, endothelial nitric oxide synthase: catalyses synthesis of nitric oxide, a pro-inflammatory molecule)** | p.E298D rs1799983 | Caucasian women in Greek population (94, 60) (Zervou et al., 2003) | | |
| **TGFBI (19q13.1, transforming growth factor β1: cytokine)** | −509C/T rs1800469 | Taiwanese women (150, 159) (Hsieh et al., 2005b) | | |
| Polymorphism | Frequencies | Studies |
|--------------|-------------|---------|
| **TNF (6p21.3, tumour necrosis factor α: cytokine)** | | |
| −1031T/C     | rs1799964   | Japanese women: −1031T, −638C, −857C haplotype (123, 165) (Teramoto et al., 2004) |
|              |             | Japanese women (130, 185) (Asghar et al., 2004) |
| −863C/A      | rs1800630   | Japanese women: −1031T, −638C, −857C haplotype (123, 165) (Teramoto et al., 2004) |
| −857C/T      | rs1799724   | Japanese women: −1031T, −638C, −857C haplotype (123, 165) (Teramoto et al., 2004) |
| −308G/A      | rs1800629   | | |
| −238G/A      | rs361525    | | |
|              |             | | |
| **TNF (6p21.3, tumour necrosis factor β: Lymphotoxin-alpha LTA): cytokine** | | |
| Intron 1+252A/G (A1069G) | rs909253    | Chinese women (82, 80) (Luo et al., 2006) |
|              |             | | |
| **TNFRSF1B (1p36.3-p36.2, tumour necrosis factor receptor 2: cytokine receptor)** | | |
| p.M196R      | rs1061622   | Japanese women (123, 165) (Teramoto et al., 2004) |
|              |             | | |
|              |             | Taiwanese women (120, 106) (Hsieh et al., 2002) |
|              |             | Korean women (70, 202) (Lee et al., 2002) |
|              |             | Austrian women (92, 69) (Wieser et al., 2002a) |
|              |             | Korean women (70, 202) (Lee et al., 2002) |
|              |             | Austrian women (92, 69) (Wieser et al., 2002a) |
|              |             | Australian women (958, 959) (Zhao et al., 2007) |

*Continued*
Genes involved in sex hormone activity

Investigations of the influence of polymorphisms in genes encoding sex hormones and hormone regulators are set out in Table II.

### Estrogen receptor

The influence of estrogen receptor gene (ESR1) polymorphisms has been investigated both in European and in Asian women with endometriosis. The XbaI (−351A/G) and the Pvull (−397T/C) restriction fragment-length polymorphisms (RFLPs) were not associated with endometriosis in a Korean population (Kim et al., 2005b), but appear to affect endometriosis susceptibility in Taiwanese women (Hsieh and Lin, 2006). The association between endometriosis and the Pvull RFLP (−397T/C) was also found in Greek and Italian women (Georgiou et al., 1999; Luisi et al., 2006), and has been shown to influence disease severity, but not susceptibility, in German and Egyptian women (El-Gindi et al., 2002; Renner et al., 2006). This polymorphism was not found to affect endometriosis susceptibility in Korean women (Kim et al., 2005b), and studies

### Regulation upon activation normal T-cell expressed and secreted

Regulation upon Activation Normal T cell Expressed and Secreted (RANTES, recently renamed CCL5) is an inflammatory cytokine that has been implicated in the induction of monocyte migration in the peritoneal fluid of women with endometriosis (Pritts et al., 2002). Although the −403G/A and −28C/G polymorphisms in the CCL5 gene and the delta32 and p.V64I polymorphisms in the RANTES receptor genes, CCR5 and CCR2, respectively, do not appear to affect endometriosis susceptibility (Antinolo et al., 2003, 2004), the p.P12A polymorphism in the gene encoding PPAR-γ (PPARG), which regulates the expression of CCL5, has been linked to an increased risk of endometriosis (Dogan et al., 2004). On the other hand, no association was found in Japanese women between the PPARG p.P12A polymorphism and endometriosis, but an association was found with the exon 6 161C/T polymorphism in that same gene (Kiyomizu et al., 2006).

### Summary

No consistent evidence linking endometriosis with specific polymorphisms of genes coding for inflammatory mediators is available. A number of polymorphisms have been found to be associated with endometriosis in selected populations (Table I). However, these associations have not been independently confirmed across ethnic barriers, either because only single studies are available or because other studies investigating these polymorphisms reported no association. Nor have meta-analyses of these studies been published. Therefore, no specific polymorphisms of genes encoding inflammatory mediators have been convincingly shown to play a role in the susceptibility to endometriosis.
| Gene (locus, protein name and its function) | Variant Name | dbSNP ID | Association with susceptibility | Negative (number of cases, number of controls) | Phenotype |
|------------------------------------------|--------------|----------|---------------------------------|-----------------------------------------------|-----------|
| AR (Xq11.2-q12, androgen receptor gene: hormone receptor) | CAG repeat (exon 1) | | Taiwanese women (110, 99) (Hsieh et al., 2001b) | Italian women (105, 92) (Lattuada et al., 2004c) | Korean women; disease stage and disease susceptibility (Kim et al., 2005b) |
| ESR1 (6q25.1, estrogen receptor α: hormone receptor) | TA repeat (promoter) | | Greek women (57, 57) (Georgiou et al., 1999) | Turkish women (110, 108) (Hsieh et al., 2005d) | Italian women (121, 121) (Kim et al., 2005b) |
| | PVuII RFLP (1207T/C) | rs2234693 | Greek women (57, 57) (Georgiou et al., 1999) | Japanese women (132, 182) (Wang et al., 2004) | Korean women (180, 165) (Kim et al., 2005b) |
| | XbaI RFLP (1351A/G) | rs7340799 | Taiwanese women (112 EM, 106 LM, 110C) (Hsieh et al., 2007b) | Malaysian women (239, 287) (Lee et al., 2007) | Japanese women; disease severity (Wang et al., 2004) |
| ESR2 (14q23.2, estrogen receptor β: hormone receptor) | RsaI RFLP (1082G/A) | rs1256049 | Japanese women (132, 182) (Wang et al., 2004) | Italian women (61) (Luisi et al., 2006) | Italian women (61) (Luisi et al., 2006) |
| | AluI RFLP (1730A/G) | rs4986938 | Japanese women (132, 182) (Wang et al., 2004) | Italian women (61) (Luisi et al., 2006) | Korean women (239, 287) (Lee et al., 2007) |
| NRIP1 (21q11.2, receptor interacting protein 140: estrogen and progesterone receptor cofactor) | p.R448G | rs2229742 | Spanish women (59, 141) (Caballero et al., 2005) | | |
| PGR (11q22-q23, progesterone receptor: hormone receptor) | 331A/G | rs10895068 | Dutch women (72, 93) (van Kaam et al., 2007b) | | Dutch women; risk of deep infiltrating endometriosis (van Kaam et al., 2007b) |

Genes are grouped alphabetically, and studies showing positive or negative associations of these genes with disease susceptibility and/or positive associations with phenotype are presented. †Not a case–control study; ‡Parent–offspring study.
investigating its importance in Japanese women have reported conflicting results (Kitawaki et al., 2001; Wang et al., 2004). An Austrian group investigated the effect of the ESR1 -397T/C polymorphism, which they named IVS1 -401T/C, but found no association with endometriosis susceptibility (Huber et al., 2005). A TA repeat microsatellite upstream of the ESR1 gene has been linked to endometriosis susceptibility in Greek, Taiwanese and Korean women (Georgiou et al., 1999; Kim et al., 2005b; Hsieh et al., 2005d), and has been associated with susceptibility to mild endometriosis in Korean women (Kim et al., 2005b). Studies of Japanese, Korean and Italian women found no link between the XbaI RFLP (−351A/C) in the ESR1 gene and endometriosis susceptibility (Wang et al., 2004; Kim et al., 2005b; Luisi et al., 2006), although a study of German women suggested that it may influence lesion severity (Renner et al., 2006). The Alu I RFLP (1730A/G) in the ESR2 gene was linked to an increased risk of stage IV endometriosis in Japanese women (Wang et al., 2004), but was not shown to influence disease susceptibility in groups of Italian and Korean women (Luisi et al., 2006; Lee et al., 2007).

**Progestrone receptor**

Groups in Austria, Brazil and Italy have demonstrated a link between the PROGINS polymorphism in the PGR gene and endometriosis susceptibility (Wieser et al., 2002b; Lattuada et al., 2004a; De Carvalho et al., 2007). A study of Dutch women with deep infiltrating endometriosis found no association with PROGINS, but did observe an association with the PGR 331G/A polymorphism (van Kaam et al., 2007b). A study from India (Govindan et al., 2007) and an analysis of pooled data from an Australian group who conducted several studies investigating the PROGINS polymorphism and five SNPs in the PGR gene, indicated that there was no association with endometriosis susceptibility for any of these variants (Treloar et al., 2005a).

**Androgen receptor**

The CAG repeat microsatellite in the AR gene has been linked to an increased risk of uterine fibroids, and the 21 CAG repeat allele showed an association with endometriosis susceptibility in Taiwanese women (Hsieh et al., 2001b). However, an Italian study found no association between CAG repeat length and endometriosis susceptibility (Lattuada et al., 2004c). Receptor interacting protein 140 co-regulates the activities of estrogen and progesterone receptors and is essential for female fertility (Caballero et al., 2005). The p.R448G polymorphism in the gene encoding this protein (NRIP1) has been linked to endometriosis susceptibility in Spanish women (Caballero et al., 2005).

**Summary**

No consistent evidence linking specific polymorphisms of genes encoding proteins involved in sex hormone activity with endometriosis is available. A number of polymorphisms have been found to be associated with endometriosis in selected populations (Table II). However, these associations have not been independently confirmed across ethnic barriers, either because only single studies are available or because other studies investigating the respective polymorphisms reported no association. A systematic review and meta-analysis of studies investigating sex steroid biosynthesis and sex steroid receptors in women with endometriosis has been published, demonstrating no consistent association of the investigated polymorphisms with endometriosis (Guo, 2006a). Therefore, no specific polymorphisms of genes encoding proteins involved in sex hormone activity have been convincingly shown to play a role in the susceptibility to endometriosis.

**Metabolic enzymes**

**17-β hydroxysteroid dehydrogenase type I**

The 17-β hydroxysteroid dehydrogenase type 1 (HSD17B1) gene encodes a key enzyme involved in testosterone biosynthesis and estrogen metabolism. The p.S312G polymorphism in this gene has been linked to an increased risk of endometriosis in Japanese women (Tsukiya et al., 2005b), and the −27A/C (vIV) polymorphism was associated with an increased risk of endometriosis in a cohort of Austrian women (Huber et al., 2005).

**Detoxification enzymes**

The CYP1A1 and CYP1B1 genes encode phase I detoxification enzymes involved in estrogen metabolism. Studies in Austrian, Indian, Chinese, Japanese and Taiwanese populations found no association between known polymorphisms in the CYP1A1 gene and susceptibility to endometriosis (Peng et al., 2002; Iizuka et al., 2003; Babu et al., 2005; Huber et al., 2005; Juo et al., 2006). However, studies in Greece and the UK indicated that the MspI RFLP (6235T/C) in the CYP1A1 gene may influence endometriosis susceptibility when associated with the GSTM1 null deletion variant (Arvanitis et al., 2001; 2003; Hadfield et al., 2001). Peng et al. (2003a) reported that the CYP1A1 4889A/G polymorphism is associated with endometriosis in Chinese women. An Austrian group investigated the p.N453S polymorphism in the CYP1B1 gene but this did not appear to influence susceptibility to endometriosis (Huber et al., 2005). In a Korean study, the CYP1B1 p.L432Y, Asp(449)C/T and p.A453S polymorphisms were not associated with late stage endometriosis (Cho et al., 2007). Polymorphisms in genes encoding other enzymes involved in estrogen metabolism (COMT) or phase I detoxification (myeloperoxidase) have also been investigated, but failed to show an effect on endometriosis susceptibility (Wieser et al., 2002c; Hsieh et al., 2004a; Huber et al., 2005; Juo et al., 2006).

The CYP17A1 and CYP19A1 genes both code for enzymes involved in estrogen biosynthesis. Whereas studies of Taiwanese women have shown a possible relation between endometriosis susceptibility and the −34T/C polymorphism in the promoter region of the CYP17A1 gene (Hsieh et al., 2004b, 2005d), no strong association with CYP17A1 polymorphisms has been found in UK, Brazilian, Austrian, Taiwanese or Japanese study populations (Kado et al., 2002; Asghar et al., 2005; Huber et al., 2005; Juo et al., 2006; De Carvalho et al., 2007). The TTTA repeat microsatellite in the CYP19A1 gene may increase the risk of endometriosis in Greek women (Arvanitis et al., 2003), and shows a weak association in Japanese women (Kado et al., 2002). Another polymorphism in this gene (p.R264C) was shown to increase the risk of endometriosis in Greek women (Arvanitis et al., 2003), and shows a weak association in Japanese women (Kado et al., 2002). Another polymorphism in this gene (p.R264C) was studied in Japanese and Austrian women, but did not appear to influence endometriosis susceptibility (Huber et al., 2005; Tsukiya et al., 2005b).

The GSTM1, GSTPI, GSTT1, NAT1 and NAT2 genes all encode phase II detoxification enzymes. Null deletions in the glutathione-S-transferase GSTM1 gene have been linked to an increased risk of endometriosis in
Polymorphisms and endometriosis

French, Russian, Indian, Chinese and Taiwanese women (Baranova et al., 1997, 1999; Ivashchenko et al., 2003; Peng et al., 2003b; Hsieh et al., 2004a; Babu et al., 2005). These null deletions were not shown to affect endometriosis susceptibility in Korean, Japanese and Australian study populations (Baxter et al., 2001; Izuka et al., 2003; Morizane et al., 2004; Hur et al., 2005), although the Australian study indicated that GSTM1 null deletion may predispose endometrial lesions to malignant transformation (Baxter et al., 2001). The p.I105Sv polymorphism in the GSTP1 gene is associated with an increased risk of endometriosis in Turkish women (Ertnuc et al., 2005), but does not seem to have an effect on susceptibility in Korean women (Hur et al., 2005). Studies conducted in Greece, France, India, UK, Japan and Korea showed no correlation between the GSTT1 null deletion variant and endometriosis susceptibility (Baranova et al., 1999; Arvanitis et al., 2003; Morizane et al., 2004; Babu et al., 2005; Hur et al., 2005), whereas a study of Russian women did show such an association (Ivashchenko et al., 2003). Several studies have investigated the association between NAT2 polymorphisms and endometriosis susceptibility, but they reported conflicting results (Baranova et al., 1999; Nakago et al., 2001; Izuka et al., 2003; Ivashchenko et al., 2003; Babu et al., 2004; Deguchi et al., 2005; Isshakova, 2006). One study investigated NAT1 polymorphisms and found no association with endometriosis susceptibility (Deguchi et al., 2005).

The arylhydrocarbon receptor (AhR) and the AhR nuclear translocator (ARNT) are transcription factors that promote the expression of a number of genes encoding metabolic enzymes (including CYP1A1 and GST). The action of AhR is suppressed by the AhR repressor (AhRR). In Japanese women, the p.A185P polymorphism in the AHRR gene has been shown to confer endometriosis susceptibility and severity, but polymorphisms in the AHRR and ARNT genes did not have an effect (Tsuchiya et al., 2005a). In a Korean study, concomitant carriage of the p.A185P polymorphism in the AHRR gene and the GSTT1 null deletion, but not carriage of AHRR p.A185P, GSTT1 null deletion or GSTM1 null deletion alone, was associated with endometriosis (Kim et al., 2007b). The AHRR p.A185P polymorphism was not associated with endometriosis in Japanese women (Watanabe et al., 2001).

Summary
The most solid evidence so far linking specific polymorphisms to endometriosis comes from studies investigating phase II detoxification enzymes, namely the GSTT1 null deletion variant. A systematic review and meta-analysis of the GSTM1 and GSTT1 variants demonstrated a consistent association between GSTT1 polymorphisms and endometriosis with a moderate effect size. There was a 29% increased risk of endometriosis in GSTT1 null deletion carriers (Guo, 2005). It has to be mentioned, however, that there was evidence of publication bias in this meta-analysis, indicating that the size of the increased risk associated with the GSTT1 deletion variant may actually be smaller or non-existent. In addition, a number of polymorphisms have been found to be associated with endometriosis in selected populations, e.g. HSD17B1 p.S312G and −27A/C (vIV), CYP1A1 Mspl RFLP (2623T/C), NAT2*5, CYP17A1 −34T/C, CYP19A1 TTTA repeat microsatellite and AHRR p.A185P (Table III). These associations, however, have not been independently confirmed across ethnic barriers either because only single studies are available or because other studies investigating these polymorphisms reported no association.

Genes regulating vascular function and tissue remodelling
Endometriosis shows some of the characteristics typically seen in malignant cells, such as neovascularization and local invasion (Hsieh et al., 2005c). Therefore, polymorphisms in a number of genes involved in vascular and cellular growth and reorganization have been investigated for a possible role in endometriosis.

Vascular endothelial growth factor, epidermal growth factor receptor and endostatin
Vascular endothelial growth factor (VEGF) mediates vascular permeability and angiogenesis, and is known to be a key molecule in the pathogenesis of endometriosis (Bhanaorri et al., 2005a; Kim et al., 2005a). Three polymorphisms in the VEGF gene have been evaluated in women with endometriosis. The 405G/C polymorphism has been linked to endometriosis susceptibility in South Indian women, and with susceptibility to advanced-stage endometriosis in Korean women (Bhanaorri et al., 2005a; Kim et al., 2005a). In contrast, the −460C/T polymorphism did not appear to affect susceptibility in either of these populations (Bhanaorri et al., 2005a; Kim et al., 2005a), but may influence the risk of endometriosis in Taiwanese women (Hsieh et al., 2004d). The VEGF 936C/T polymorphism and the endostatin 4349G/A polymorphism were not associated with endometriosis in Korean women (Kim et al., 2007a) (Table IV). The epidermal growth factor receptor (EGFR) is another molecule involved in angiogenesis, and the EGFR 2073*T allele has been linked to an increased risk of endometriosis in Taiwanese women (Hsieh et al., 2005e) (Table I).

Angiotensin-I-converting enzyme
Angiotensin-I-converting enzyme (ACE) catalyzes the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Three polymorphisms in the gene encoding this enzyme have been investigated in Taiwanese women with endometriosis, and both the 2350A/G and −240A/T variants as well as the insertion/deletion (I/D) polymorphism are associated with endometriosis susceptibility in this population (Hsieh et al., 2005a, 2007a).

Matrix metalloproteinases
Matrix metalloproteinases (MMPs) are thought to be involved in the tissue invasion that occurs during endometriotic lesion formation (Ferrari et al., 2006). Polymorphisms in MMP1, MMP3, MMP7 and MMP9 genes have been investigated in Chinese women with endometriosis. A single I/D polymorphism 1G/2G (also referred to as −1607ins/delG) in the promoter region of the MMP1 gene and the −181A/G polymorphism in the MMP7 gene were associated with an increased risk of endometriosis (Kang et al., 2005; Shan et al., 2006). In contrast, a single I/D polymorphism −1171ins/delA (5A/6A) in the promoter region of the MMP3 gene did not appear to affect endometriosis susceptibility (Kang et al., 2005; Shan et al., 2005). The MMP1(2G)/MMP3(6A) combination showed an
Table III  Polymorphisms of genes encoding enzymes involved in metabolism and biosynthesis, which have been investigated for their role in endometriosis

| Gene (locus, protein name and its function) | Variant Name | dbSNP ID | Association with susceptibility | Phenotype |
|-------------------------------------------|--------------|----------|---------------------------------|-----------|
| AHR (7p15, arylhydrocarbon receptor: transcription factor, detoxification) | p.K554R | rs2066853 | Positive | Japanese women (79, 59) (Tsuchiya et al., 2005a) |
|  | 567G/C (p.V189V) | rs2228099 | Negative | Japanese women (79, 59) (Tsuchiya et al., 2005a) |
| ARNT (7p15, arylhydrocarbon receptor nuclear translocator: transcription factor, detoxification) | p.A185P | rs2292596 | Japanese women (79, 59) (Tsuchiya et al., 2005a) | Japanese women (45, 108) (Watanabe et al., 2001) |
| AHRR (5p15.3, arylhydrocarbon receptor repressor: transcription factor repressor, detoxification) | p.A185P | rs2292596 | Korean women, in association with GSTT1 null deletion (316, 256) (Kim et al., 2007b) | No differences found (Tsuchiya et al., 2005a) |
| COMT (22q11.1, catechol-O-methyl transferase: steroid biosynthesis, Estrogen metabolism) | p.V158M | rs4680 | Greek women; alone or in combination with GSTM1 null deletion (5†, 54) (Arvanitis et al., 2001); in combination with GSTM1 null deletion (275, 346) (Arvanitis et al., 2003; Cretan Greek women) | Chinese women (76, 80) (Peng et al., 2002) |
|  | MspI RFLP (6235T/C) (3801T/C) (m1) | rs4646903 | Korean women, in association with GSTT1 null deletion (316, 256) (Kim et al., 2007b) | Taiwanese women of Chinese descent (105, 312) (Juo et al., 2006) |
|  | p.L462V | rs1048943 | Chinese women (76, 80) (Peng et al., 2003a) | Chinese women (76, 80) (Peng et al., 2002) |
|  | 4889A/G (m2) |  | | Austrian women (32, 790) (Huber et al., 2005) |
| CYP1A1 (15q22-q24, cytochrome P450 1A1 enzyme: steroid biosynthesis, Estrogen metabolism, phase I detoxification) | p.N453S | rs1800440 |  | South Indian women (310, 215) (Babu et al., 2005) |
|  | p.L432V, p.D449D(C/T), p.N453S, p.A119S | rs1056836, rs1056837, rs1800440, rs1056827 |  | Japanese women (35, 37) (Iizuka et al., 2003) |
|  |  |  |  | Korean women (221, 188) (Cho et al., 2007) |
| CYP1B1 (2p21, cytochrome P450 1B1 enzyme: steroid biosynthesis, Estrogen metabolism, phase I detoxification) | p.N455S | rs1800440 |  |  |
| Polymorphism | Description | Reference(s) | Sample Size | Country/Region |
|--------------|-------------|--------------|-------------|----------------|
| CYP17A1 (10q24.3, cytochrome P450 17 enzyme: estrogen biosynthesis) | MspA1 RFLP (−34T/C) rs743572 | Taiwanese women (119, 128) (Hsieh et al., 2004b); (119, 108) (Hsieh et al., 2005d) |  |  |
|  |  | Brazilian women (121, 281) (De Carvalho et al., 2007) |  |  |
|  |  | Japanese women (140, 177) (Kado et al., 2002) |  |  |
|  |  | UK (94, 97) and Japanese women (130, 179) (Asghar et al., 2005) |  |  |
|  |  | Austrian women (32, 790) (Huber et al., 2005) |  |  |
|  |  | Taiwanese women (198, 312) (Juo et al., 2006) |  |  |
| CYP19A1 (15q21.1, aromatase: steroid biosynthesis) | TTTA repeat microsatellite p.R264C rs28757190 | Greek women (275, 346) (Arvanitis et al., 2003) |  |  |
|  |  | Japanese women; chocolate cysts (140, 177) (Kado et al., 2002) |  |  |
|  |  | Austrian women (32, 790) (Huber et al., 2005) |  |  |
|  |  | Japanese women (79, 59) (Tsuchiya et al., 2005b) |  |  |
| GSTM1 (1p13.3, glutathione-S-transferase M1: phase II detoxification) | Null deletion | French women (50, 72) (Baranova et al., 1997); (65, 72) (Baranova et al., 1999) |  |  |
|  |  | Russian women - in combination with either GSTT1 null mutation homozygots or NAT2 slow acetylator (*5, *6, *7 homozygots) (74, 40) (Ivashchenko et al., 2003) |  |  |
|  |  | Chinese women (76, 80) (Peng et al., 2003b) |  |  |
|  |  | Taiwanese women (150, 159) (Hsieh et al., 2004a) |  |  |
|  |  | South Indian women (310, 215) (Babu et al., 2005) |  |  |
|  |  | Greek women; in combination with CYP1A1 6235T/C (5†, 54) (Arvanitis et al., 2001); (275, 346) (Arvanitis et al., 2003; Cretan Greek women) |  |  |
|  |  | UK, mainly Caucasian women; in combination with CYP1A1 6235T/C (101; 154 + 192 in sib pair analysis) (Hadfield et al., 2001) |  |  |
| GSTP1 (11q13, glutathione-S-transferase P1: phase II detoxification) | p.I105V rs1695 | Turkish women (150, 150) (Ertunc et al., 2005) |  |  |
|  |  | Korean women (194, 259) (Hur et al., 2005) |  |  |
|  |  | Australian women (84, 219) (Baxter et al., 2001) |  |  |
|  |  | Japanese women (35, 37) (Iizuka et al., 2003); (114, 179) (Morizane et al., 2004) |  |  |
|  |  | Korean women (194, 259) (Hur et al., 2005) |  |  |
|  |  | Korean women (316, 256) (Kim et al., 2007b) |  |  |
|  |  | Australian women (84, 219) (Baxter et al., 2001) |  |  |

Continued
| Gene (locus, protein name and its function) | Variant Name | dbSNP ID | Association with susceptibility | Phenotype | Negative |
|------------------------------------------|-------------|---------|--------------------------------|-----------|---------|
| GSTT1 (22q11.23, glutathione-S-transferase T1: phase II detoxification) | Null deletion | | Korean women, in association with AHRR p.A185P (316, 256) (Kim et al., 2007b) | French women (65, 72) (Baranova et al., 1999) | Russian women; in combination with either GSTM1 null mutation homozygots or NAT2 slow acetylator (*5, *6, *7 homozygots) (74, 40) (Ivashchenko et al., 2003) |
| | | | | Greek women (275, 346) (Arvanitis et al., 2003) | | South Indian women (310, 215) (Babu et al., 2005) |
| | | | | Japanese women (194, 259) (Hur et al., 2005); no association | | Korean women (114, 179) (Morizane et al., 2004) |
| | | | | French women (65, 72) (Baranova et al., 1999) | | UK, mainly Caucasian women (129, 147) (Hadfield et al., 2001) |
| | | | | | | Greek women (275, 346) (Arvanitis et al., 2003) |
| | | | | | | South Indian women (310, 215) (Babu et al., 2005) |
| | | | | | | Japanese women (194, 259) (Hur et al., 2005); no association |
| | | | | | | Korean women (114, 179) (Morizane et al., 2004) |
| | | | | | | French women (65, 72) (Baranova et al., 1999) |
| | | | | | | UK, mainly Caucasian women (129, 147) (Hadfield et al., 2001) |
| HSD17B1 (17q11-q21, 5 17-β hydroxysteroid dehydrogenase: testosterone biosynthesis, Estrogen metabolism) | −27A/C (vIV) | p.5312G | Austrian women (32, 790) (Huber et al., 2005) | | Japanese women; disease severity (Tsuchiya et al., 2005b) |
| | | rs605059 | Japanese women (79, 59) (Tsuchiya et al., 2005b) | | | |
| MPO (17q23.1, myeloperoxidase: phase I detoxification, oxidation and activation of carcinogens and nitric oxide) | −463G/A | rs233227 | | | Taiwanese women (150, 159) (Hsieh et al., 2004a) |
| NAT1 (8p23.1-p21.3, N-acetyltransferase 1: phase II detoxification) | NAT1*3, *4, *10, *11 | | | | | |
| NAT2 (8p22, N-acetyltransferase 2: phase II detoxification) | Nat2*4-*7 | | | | | |

Genes are grouped alphabetically, and studies showing positive or negative associations of these genes with disease susceptibility and/or positive associations with phenotype are presented.

†Affected family members.
| Gene (locus, protein name and its function) | Variant Name | dbSNP ID | Association with susceptibility | Phenotype |
|-------------------------------------------|--------------|----------|-------------------------------|-----------|
| **Mediators of glucose homeostasis**      |              |          |                               |           |
| GALT (9p13, galactose-1-phosphate uridyl transferase: galactose metabolism) | p.N314D      | rs2070074 | North American women (33, 111) (Cramer et al., 1996) | UK women (148, 148) (Hadfield et al., 1999); (78, 248 C) (Morland et al., 1998) | Icelandic women (85 cases, 103 male controls, 110 female controls) (Stefansson et al., 2001) | Chinese women (325, 310) (He et al., 2006) | Chinese women (325, 310) (He et al., 2006) | UK women (78, 248) (Morland et al., 1998) |
|                                           | p.Q188R      | No dbSNP ID (rare mutation) |                               |           |
| PPARG (3p25, peroxisome proliferator-activated receptor-γ: transcription factor; mediates insulin resistance, regulates CCL5 expression) | p.P12A       | rs1801282 | German women (51, 55) (Dogan et al., 2004) | Japanese women (390 women with endometriosis, leiomyoma or adenomyoma, 144 controls) (Kiyomizu et al., 2006) |
|                                           | p.H447H, 161C/T | rs3856806 |                               |           |
| **Mediators of vascular function or genes linked to cardiovascular risk** |              |          |                               |           |
| ACE (17q23.3, angiotensin-I converting enzyme: mediates vascular homeostasis) | −240A/T      | rs4291   | Taiwanese women (150, 159) (Hsieh et al., 2005a) |             |
|                                           | 2350A/G      | rs4343   | Taiwanese women (150, 159) (Hsieh et al., 2005a) |             |
|                                           | 287 bp ALU ins/del in intron 16 | Several dbSNP IDs: rs4646994 or rs4340, rs1799752 | Taiwanese women (125 endometriosis, 120 leiomyoma, 128 control) (Hsieh et al., 2007a) |             |
| COL18A1 (21q22.3, endostatin: inhibits endothelial cell proliferation and angiogenesis) | 4349G/A (p.D1437 N) (p.D104 N) | rs12483377 |             | Korean women (105, 100 + 100) (Kim et al., 2007a) |
| VEGFA (6p12, vascular endothelial growth factor: mediates vascular permeability and angiogenesis) | 405G/C (− 634G/C) | Rs2010963 | South Indian women (215, 210) (Bhanooori et al., 2005a) | Korean women (215, 219 + 70) (Kim et al., 2005a) |
| Gene (locus, protein name and its function) | Variant Name | dbSNP ID | Association with susceptibility | Phenotype |
|------------------------------------------|--------------|----------|--------------------------------|-----------|
| **Variant Association with susceptibility** |              |          | Taiwanese women (122, 131) (Hsieh et al., 2004d) | South Indian women (215, 210) (Bhanoori et al., 2005a) |
| **Phenotype** |              |          | Korean women (215, 219 + 70) (Kim et al., 2005a) | Korean women (105, 100 + 100) (Kim et al., 2007a) |
| **Gene involved in tissue remodelling** |              |          | Korean women (79, 105) (Kim et al., 2004) | Italian women (56, 71) (Ferrari et al., 2006) |
| **AHSG (3q27, alpha 2-Heremans Schmidt glycoprotein: mediates tissue development)** | p.T230M | rs4917 | Chinese women: 2G allele (100, 150) (Kang et al., 2005) | North China population (100,150) (Shan et al., 2005) |
| | p.T238S | rs4918 | | | |
| **MMP1 (11q22.3, matrix metalloproteinase-1: tissue remodelling)** | −1607ins/deG (1G/2G) | rs112925 | Chinese women MMP1-2G MMP3-6A haplotype (100, 150) (Kang et al., 2005; Shan et al., 2005) | Chinese women (100, 150) (Kang et al., 2005) |
| **MMP3 (11q22.3, matrix metalloproteinase-3: tissue remodelling)** | −1171ins/deA (5A/6A) | | | North China population (100,150) (Shan et al., 2005) |
| **MMP7 (11q21-q22, matrix metalloproteinase-7: tissue remodelling)** | −181A/G | rs1799750 | Chinese women (143 EM, 76 AM, 160) (Shan et al., 2006) | Chinese women (143 EM, 76 AM) (Shan et al., 2006) |
| **MMP9 (20q11.2-q13.1, matrix metalloproteinase-9: tissue remodelling)** | −1562C/T | rs3918242 | | | |
| **SERPINE1 (7q21.3–q22, plasminogen activator inhibitor-1: fibrinolysis system. Linked to cardiovascular disease)** | −675ins/deG (4G/5G) | Several dbSNP IDs: rs1799768, rs34857375, rs1799889 | Canadian and North American women (75, 43) (Bedaiwy et al., 2006) | | |
| **Genes involved in signal transduction** | | | | | |
| **EMX2 (10q26.1, empty spiracles homeobox 2: homeodomain transcription factor)** | | rs1860399, rs82 613, rs82 612, rs242956, rs703409, rs703411, rs1638626, rs2286629, rs385209, rs855769, rs365466, rs8192640, rs740734, rs855768, rs2240776, rs703413, rs4751627, rs242960, rs8181280, rs855766, rs4752078, rs4752079 | | Australian women 768, 768 (Treloar et al., 2007) |
| **STAT6 (12q13, signal transducer and activator of transcription 6: signal transduction and activation of transcription)** | 2964G/A | rs324015 | South Indian women (232, 210) (Bhanoori et al., 2007) | |
association (Kang et al., 2005; Shan et al., 2005), but this is probably due to the effects of the MMP1 (2G) genotype rather than a combined effect of both genes. The −1562C/T polymorphism in the MMP9 gene was not associated with endometriosis susceptibility (Shan et al., 2006). A group that investigated MMP polymorphisms in a population of Italian women found no association between MMP1 or MMP3 gene polymorphisms and susceptibility to endometriosis (Ferrari et al., 2006).

α2-HS glycoprotein, plasminogen activator inhibitor-1

α2-HS glycoprotein (AHSG) has been implicated in tissue development, and polymorphisms in the AHSG gene (p.T230M and p.T238S) have been linked to endometriosis susceptibility in Korean women (Kim et al., 2004). The plasminogen activator inhibitor 1 (PAI-1) 4G/5G promoter polymorphism has been investigated in 75 women with laparoscopically confirmed endometriosis and 43 controls (Bedaiwy et al., 2006). In this study, the 4G/4G genotype, known to be associated with hypofibrinolysis, was found to be over-represented among women with endometriosis.

Summary

No consistent evidence linking specific polymorphisms of genes encoding proteins involved in vascular function and tissue remodelling with endometriosis is available. A number of polymorphisms have been found to be associated with endometriosis in selected populations (Table IV). These associations, however, have not been independently confirmed across ethnic barriers either because only single studies are available or because other studies investigating these polymorphisms reported no association. No meta-analysis of respective studies has been published. Therefore, no specific polymorphisms of genes encoding proteins involved in vascular function and tissue remodelling have been convincingly shown to play a role in the susceptibility to endometriosis.

Other genes linked to endometriosis

Genes involved in signal transduction (STAT6, Table IV), malignant transformation (TP53, P21, KRAS, Table IV; BRAF), apoptosis (FAS, Table I; FASLG, Table I) and galactose metabolism (GALT, Table IV) have been investigated for a role in endometriosis susceptibility, but no consistent association has been found (Tables I–IV) (Cramer et al., 1996; Morland et al., 1998; Hadfield et al., 1999; Hsieh et al., 2001c; Stefansson et al., 2001; Chang et al., 2002; Lattuada et al., 2004b; Omori et al., 2004; Fernandez et al., 2005; Hsieh and Lin, 2006; Zhao et al., 2006; Bhanoori et al., 2007; Vietri et al., 2007). Two exceptions are the STAT6 3′-UTR 2964G/A polymorphism (Bhanoori et al., 2007) and the GALT p.N314D polymorphism (Cramer et al., 1996), which are over-represented among South Indian women and US women with endometriosis, respectively. Hsieh and Lin (2006) found that the TP53 codon p.R72P polymorphism was associated with endometriosis in Taiwanese women and also looked for the presence of mutations at codons 11 and 248 in this population, but did not find any (Table I). An Australian study of 22 polymorphisms in the EMX2 gene and 15 polymorphisms in the PTEN gene found no association with endometriosis (Tarlo et al., 2007).
Summary
No consistent and independently confirmed evidence linking specific polymorphisms of the STAT6, TP53, P21, FAS, FASLG, EMX2, PTEN, CTLA4 and GALT genes is available.

Discussion
In this review, we have summarized the current evidence linking genetic polymorphisms and endometriosis, showing that the majority of polymorphisms investigated so far are not associated with this disease in a methodologically reliable way. This may be because they have been investigated in only a single study or a limited number of studies, or because conflicting results were obtained.

The most solid evidence to date linking specific polymorphisms to endometriosis comes from studies investigating phase II detoxification enzymes. A systematic review and meta-analysis of studies investigating the glutathione-S-transferases GSTM1 and GSTT1 variants demonstrated a consistent association of a GSTT1 polymorphism and endometriosis, with a 29% increased risk of endometriosis in GSTT1 null deletion carriers.

There is no consistent evidence to link specific polymorphisms of genes encoding inflammatory mediators and proteins involved in sex steroid metabolism, vascular function and tissue remodelling with endometriosis. Although a number of polymorphisms have been found associated with endometriosis in selected populations, these associations have not been independently confirmed across ethnic barriers, either because only single studies are available or because other studies reported no association. The majority of polymorphisms have not been subjected to meta-analysis due to the limited availability of comparable studies. However, a systematic review and meta-analysis of sex steroid biosynthesis and sex steroid receptors demonstrated no consistent association of the investigated polymorphisms with endometriosis.

Clearly, absence of evidence of an association between a specific polymorphism and endometriosis does not rule out that this gene in general or other polymorphisms of this gene in particular may be involved in the etiology of this disease.

To date, most studies are retrospective genetic association studies, whereas others are studies with prospectively identified cases. This is a potential source of inconsistency, since studies including prospectively identified cases, i.e. incident cases, may produce different results compared with studies using retrospectively identified cases, i.e. prevalent cases. Other problems facing researchers in this field are well-illustrated in two recent reviews on the genetics of endometriosis (Guo, 2006a, b). The author ruled out many of the previous positive findings, highlighting issues such as lack of independent confirmation for many studies (Guo, 2006b) and faulty analyses (Guo, 2006a).

In order to further explore the importance of known and new polymorphisms in female reproductive function, it is essential that studies are well-designed and sufficiently powered. Whereas retrospective studies are useful for generating hypotheses, a prospective design must be used to test these hypotheses. Exploratory (hypothesis-generating) studies should aim to screen large numbers of genetic variations. This becomes an option for more researchers as high-throughput genotyping technologies improve and become more widely accessible. The exploratory phase should be followed by validation of a limited number of candidate markers (hypothesis testing), and prospective studies should be conducted whenever an association is confirmed. This approach will allow the identification and validation of polymorphisms, and those with strong links to susceptibility may help in developing new drugs or regimens. In addition, the discovery of genes that influence treatment response may enable individualized treatment to be tailored on the basis of genotype.

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