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Functional genetic polymorphisms and female reproductive disorders: Part II—endometriosis

C.B. Tempfer[1,5], M. Simoni[2], B. Destenaves[3], and B.C.J.M. Fauser[4]

[1]Department of Obstetrics and Gynecology, Medical University, 1090 Vienna, Austria [2]Department of Medicine, Endocrinology and Metabolism, University of Modena and Reggio Emilia, I-41100 Modena, Italy [3]Stratified Medicine Group, Merck Serono International S.A, 1202 Geneva, Switzerland [4]Department of Reproductive Medicine and Gynecology, University Medical Center, 3508 GA Utrecht, The Netherlands

[5]Correspondence address. E-mail: clemens.tempfer@meduniwien.ac.at

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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 (Levanat *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 evalauation 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 PstI C/T polymorphism of the IL-1 receptor gene, is associated with a reduced risk of endometriosis.

The insulin-like growth factor II (IGF2) ApaI polymorphism was not found to be associated with endometriosis in Taiwanese women (Hsieh *et al*., 2004c). Also, a polymorphism in the *TGF* beta 1 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 (Vigano *et al*., 2003). In Caucasian women, the p.G241R polymorphism in the *ICAM1* gene may influence disease severity (Vigano *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 (Vigano *et al*., 2003; Yamashita *et al*., 2005; Kitawaki *et al*., 2006). The PmlI 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*1403* 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		Association with susceptibility		Phenotype
	Name	dbSNP ID	Positive (number of cases, number of controls)	Negative (number of cases, number of controls)	
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)	PmlI RFLP (3′-UTR C/T)	rs1801026	Taiwanese women (150, 159) (Hsieh *et al*., 2005c) Chinese women (152, 189) (Shan *et al*., 2007)		
	−160C/A	rs1620	Chinese women: −160A −347GA haplotype. (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) (Vigano *et al*., 2005)	
	CT60A/G	rs3087243		Italian women (146, 153) (Vigano *et al*., 2005)	
EGFR (7p12, epidermal growth factor receptor: regulates cell growth and differentiation)	2073A/T	rs17337023	Taiwanese women (122, 139) (Hsieh *et al*., 2005e)		
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)	

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 β1: major histocompatibility II protein)	HLA-DPB1*01-*03, *0401-*0402, *05, *06, *08-*11, *13-*19			Japanese women (83, 222) (Ishii *et al*., 2003)	
HLA-DQB1 (6p21.3, human leukocyte antigen DQ β1: 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 β1: 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, *0103, *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)	Chinese 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	rs1799968	Caucasian women (180, 175) (Vigano *et al*., 2003)	Japanese women (126, 172) (Yamashita *et al*., 2005)	Caucasian women; disease severity (Vigano *et al*., 2003)
	p.K469E	rs5498	Japanese women. Association only seen in combination with IL-6 -634G (202, 236) (Kitawaki *et al*., 2006)	Caucasian women (180, 175) (Vigano *et al*., 2003) Japanese women (126, 172) (Yamashita *et al*., 2005)	
IFNG (12q14, interferon-γ: cytokine)	CA repeat		Japanese women (185, 176) (Kitawaki *et al*., 2004)		
IGF2 (11p15.5, insulin-like growth factor II: cytokine)	ApaI RFLP (17 200G/A)	rs680		Taiwanese women (120, 103) (Hsieh *et al*., 2004c)	
IL4 (5q31.1, interleukin-4: cytokine)	−590C/T	rs2243250		Taiwanese women (120, 106) (Hsieh *et al*., 2002) Japanese women (185, 176) (Kitawaki *et al*., 2004)	
	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) (Bhanoori *et al*., 2005b)	

Continued

Table I *Continued*

Gene (locus, protein name and its function)	Variant		Association with susceptibility		Phenotype
	Name	dbSNP ID	Positive (number of cases, number of controls)	Negative (number of cases, number of controls)	
	−634C/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)	
	−627A/C (−592C/A)	rs1800872	Taiwanese women (130, 133) (Hsieh *et al*., 2003)	Japanese women (196, 160) (Kitawaki *et al*., 2002)	
IL18 (11q22.2-q22.3, interleukin-18: cytokine)	105A/C	rs549908		Taiwanese women (150, 159) (Hsieh *et al*., 2005b)	
IL1B (2q14, interleukin-1β: cytokine)	−511C/T	rs16 944		Taiwanese women (120, 103) (Hsieh *et al*., 2001a) Chinese women (138, 100) (Wen *et al*., 2006)	
	3953C/T	rs1143634		Austrian women (92, 69) (Wieser *et al*., 2003b) Taiwanese women (120, 103) (Hsieh *et al*., 2001a) Chinese women (138, 100) (Wen *et al*., 2006)	
IL1R1 (2q11.2, interleukin-1 receptor 1: cytokine receptor)	PstI RFLP	rs2041748		Brazilian women (109, 114) (D'Amora *et al*., 2006)	
	BsrBI RFLP	No dbSNP ID	Brazilian women (109, 114) (D'Amora *et al*., 2006)		
IL2RB (22q13.1, interleukin-2 receptor β: cytokine receptor)	881T/C	rs228953	Taiwanese women (150, 159) (Hsieh *et al*., 2005b)		
IL1RN (2q14.2, interleukin-1R antagonist: cytokine)	86 bp VNTR (intron 2)		Chinese women (138, 100) (Wen *et al*., 2006)	Taiwanese women (120, 103) (Hsieh *et al*., 2001a)	
IL12RB1 (19p13.1, interleukin-12 receptor β: cytokine receptor)	p.G378R	rs401502		Taiwanese women (150, 159) (Hsieh *et al*., 2005b)	
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)		
TGFB1 (19q13.1, transforming growth factor β1: cytokine)	−509C/T	rs1800469	Taiwanese women (150, 159) (Hsieh *et al*., 2005f)	Dutch women (72, 95 or 93) (van Kaam *et al*., 2007a)	

TNF (6p21.3, tumour necrosis factor α: cytokine)	−1031T/C	rs1799964	Japanese women: −1031T, −863C, −857C haplotype (123, 165) (Teramoto *et al*., 2004) Japanese women (130, 185) (Asghar *et al*., 2004)		Japanese women; disease severity (Asghar *et al*., 2004)
	−863C/A	rs1800630	Japanese women: −1031T, −863C, −857C haplotype (123, 165) (Teramoto *et al*., 2004)		
	−857C/T	rs1799724	Japanese women: −1031T, −863C, −857C haplotype (123, 165) (Teramoto *et al*., 2004)		
	−308G/A	rs1800629		Taiwanese women (120, 106) (Hsieh *et al*., 2002) Korean women (70, 202) (Lee *et al*., 2002) Austrian women (92, 69) (Wieser *et al*., 2002a)	
	−238G/A	rs361525		Korean women (70, 202) (Lee *et al*., 2002) Austrian women (92, 69) (Wieser *et al*., 2002a)	
		rs1800750, rs3093661, rs1800610, rs3093662, rs4645843, rs3093664, rs3091257		Australian women (958, 959) (Zhao *et al*., 2007)	
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)		
		rs2857602, rs2844486, rs3131637, rs2844484, rs2844483, rs4647191, rs2844482, rs2071590, rs1800683, rs2239704, rs909253, rs2857713, rs3093543, rs1041981		Australian women (958, 959) (Zhao *et al*., 2007)	
TNFRSF1B (1p36.3-p36.2, tumour necrosis factor receptor 2: cytokine receptor)	p.M196R	rs1061622		Japanese women (123, 165) (Teramoto *et al*., 2004)	

Continued

Table I *Continued*

Gene (locus, protein name and its function)	Variant	dbSNP ID	Association with susceptibility		Phenotype
	Name		Positive (number of cases, number of controls)	Negative (number of cases, number of controls)	
TP53 (17p13.1, tumour protein p53: regulation of cell cycle)	p.R72P	rs1042522	Chinese women (118, 140) (Chang *et al.*, 2002) Taiwanese women (148, 150) (Hsieh and Lin, 2006)	Japanese women (105, 180 neonates) (Omori *et al.*, 2004) Italian women (104, 88) (Vietri *et al.*, 2007) Italian women (151, 153) (Lattuada *et al.*, 2004b)	

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. RFLP, restriction fragment-length polymorphism; VNTR, variable number of tandem repeats.

HLA-DQB1 genes are in strong linkage disequilibrium (de Bakker *et al.*, 2006), which may explain why they both show an association with endometriosis. Studies of Chinese and Korean women investigating many of the known alleles of the *HLA-DRB1* gene found no association between these alleles and endometriosis susceptibility in these populations (Wang *et al.*, 2002; Whang *et al.*, 2006). Two polymorphisms in the cytotoxic T lymphocyte antigen 4 (*CTLA*-4) gene were found not to be associated with endometriosis (Vigano *et al.*, 2005).

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.

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 PvuII (−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 *et al.*, 2007b). The association between endometriosis and the PvuII 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

Table II Polymorphisms of genes encoding sex hormones and hormone regulators, which have been investigated for their role in endometriosis

Gene (locus, protein name and its function)	Variant		Association with susceptibility		Phenotype
	Name	dbSNP ID	Positive (number of cases, number of controls)	Negative (number of cases, number of controls)	
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)	
ESR1 (6q25.1, estrogen receptor α: hormone receptor)	TA repeat (promoter)		Greek women (57, 57) (Georgiou *et al*., 1999) Taiwanese women (119, 108) (Hsieh *et al*., 2005d) Korean women (180, 165) (Kim *et al*., 2005b)		Korean women; disease stage and disease susceptibility (Kim *et al*., 2005b)
	PvuII RFLP (−397T/C) (IVS1 −401T/C)	rs2234693	Greek women (57, 57) (Georgiou *et al*., 1999) Italian women (61†) (Luisi *et al*., 2006) Japanese women (203, 179) (Kitawaki *et al*., 2001) Taiwanese women (112, 110) (Hsieh *et al*., 2007b)	Korean women (180, 165) (Kim *et al*., 2005b) Japanese women (132, 182) (Wang *et al*., 2004) Austrian women (32, 790) (Huber *et al*., 2005)	German women (98, 98); disease severity, haplotype with rs7340799 (Renner *et al*., 2006) Egyptian women (23†); disease severity (El-Gindi *et al*., 2002)
	XbaI RFLP (−351A/G)	rs7340799	Taiwanese women (112 EM, 106 LM, 110C) (Hsieh *et al*., 2007b)	Italian women (61†) (Luisi *et al*., 2006) Japanese women (132, 182) (Wang *et al*., 2004) Korean women (180, 165) (Kim *et al*., 2005b)	German women (98, 98)); disease severity, haplotype with rs2234693 (Renner *et al*., 2006)
ESR2 (14q23.2, estrogen receptor β: hormone receptor)	RsaI RFLP (1082G/A)	rs1256049		Japanese women (132, 182) (Wang *et al*., 2004)	
	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)	Japanese women; disease severity (Wang *et al*., 2004)
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)
	PROGINS (320 bp PV/HS-1 Alu insertion in intron G and 2 SNPs: rs1042838 in exon 4 and rs104839 in exon 5)		Austrian women (95, 107) (Wieser *et al*., 2002b) Brazilian women (121, 281) (De Carvalho *et al*., 2007) signif. assoc. Italian women (131, 127) (Lattuada *et al*., 2004a)	Australian European women (980 triads‡) (Treloar *et al*., 2005a, b) Dutch women (72, 93) (van Kaam *et al*., 2007b) Indian women (100, 108) (Govindan *et al*., 2007)	

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. RFLP, restriction fragment-length polymorphism; SNP, single-nucleotide polymorphism.

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 AluI 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).

Progesterone 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 1

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 (Tsuchiya *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.L432V, 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 studied in Japanese and Austrian women, but did not appear to influence endometriosis susceptibility (Huber *et al*., 2005; Tsuchiya *et al*., 2005b).

The *GSTM1, GSTP1, 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

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; Iizuka *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.I105V polymorphism in the *GSTP1* gene is associated with an increased risk of endometriosis in Turkish women (Ertunc *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; Iizuka *et al*., 2003; Ivashchenko *et al*., 2003; Babu *et al*., 2004; Deguchi *et al*., 2005; Iskhakova, 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 *AHR* 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* MspI RFLP (6235T/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 (Bhanoori *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 (Bhanoori *et al*., 2005a; Kim *et al*., 2005a). In contrast, the −460C/T polymorphism did not appear to affect susceptibility in either of these populations (Bhanoori *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		Association with susceptibility		Phenotype
	Name	dbSNP ID	Positive	Negative	
AHR (7p15, arylhydrocarbon receptor: transcription factor, detoxification)	p.K554R	rs2066853		Japanese women (79, 59) (Tsuchiya *et al*., 2005a)	
ARNT (7p15, arylhydrocarbon receptor nuclear translocator: transcription factor, detoxification)	567G/C (p.V189V)	rs2228099		Japanese women (79, 59) (Tsuchiya *et al*., 2005a)	
AHRR (5p15.3, arylhydrocarbon receptor repressor: transcription factor repressor, detoxification)	p.A185P	rs2292596	Japanese women (79, 59) (Tsuchiya *et al*., 2005a) Korean women, in association with GSTT1 null deletion (316, 256) (Kim *et al*., 2007b)	Japanese women (45, 108) (Watanabe *et al*., 2001) No differences found	Japanese women; disease severity (79, 59) (Tsuchiya *et al*., 2005a)
COMT (22q11.21, catechol-*O*-methyl transferase: steroid biosynthesis, Estrogen metabolism)	p.V158M	rs4680		Austrian women (91, 92) (Wieser *et al*., 2002c); (32, 790) (Huber *et al*., 2005) Taiwanese women (105, 312) ((Juo *et al*., 2006)	
CYP1A1 (15q22-q24, cytochrome P450 1A1 enzyme: steroid biosynthesis, Estrogen metabolism, phase I detoxification)	MspI RFLP (6235T/C) (3801T/C) (m1)	rs4646903	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) UK, mainly Caucasian women; in combination with GSTM1 null deletion (101; 154 + 192 in sib pair analysis) (Hadfield *et al*., 2001)	Chinese women (76, 80) (Peng *et al*., 2002) Taiwanese women of Chinese descent (105, 312) (Juo *et al*., 2006) Austrian women (32, 790) (Huber *et al*., 2005) South Indian women (310, 215) (Babu *et al*., 2005) Japanese women (35, 37) (Iizuka *et al*., 2003)	
	p.I462V 4889A/G (m2)	rs1048943	Chinese women (76, 80) (Peng *et al*., 2003a)	Chinese women (76, 80) (Peng *et al*., 2002)	
CYP1B1 (2p21, cytochrome P450 1B1 enzyme: steroid biosynthesis, Estrogen metabolism, phase I detoxification)	p.N453S	rs1800440		Austrian women (32, 790) (Huber *et al*., 2005)	
	p.L432V, p.D449D(C/T), p.N453S, p.A119S	rs1056836, rs1056837, rs1800440, rs1056827		Korean women (221, 188) (Cho *et al*., 2007)	

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		Greek women (275, 346) (Arvanitis *et al*., 2003)	Japanese women; chocolate cysts (140, 177) (Kado *et al*., 2002)	
	p.R264C	rs28757190		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)	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)
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)	

Continued

Table III *Continued*

Gene (locus, protein name and its function)	Variant		Association with susceptibility		Phenotype
	Name	dbSNP ID	Positive	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) Russian women; in combination with either GSTM1 null mutation homozygots or NAT2 slow acetylator (*5, *6, *7 homozygots) (74, 40) (Ivashchenko *et al*., 2003)	French women (65, 72) (Baranova *et al*., 1999) Greek women (275, 346) (Arvanitis *et al*., 2003) South Indian women (310, 215) (Babu *et al*., 2005) Korean women (194, 259) (Hur *et al*., 2005); no association) Japanese women (114, 179) (Morizane *et al*., 2004) 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)		Austrian women (32, 790) (Huber *et al*., 2005)		
	p.S312G	rs605059	Japanese women (79, 59) (Tsuchiya *et al*., 2005b)		Japanese women; disease severity (Tsuchiya *et al*., 2005b)
MPO (17q23.1, myeloperoxidase: phase I detoxification, oxidation and activation of carcinogens and nitric oxide)	−463G/A	rs2333227		Taiwanese women (150, 159) (Hsieh *et al*., 2004a)	
NAT1 (8p23.1-p21.3, *N*-acetyltransferase 1: phase II detoxification)	NAT1*3, *4, *10, *11			Japanese women (145, 182) (Deguchi *et al*., 2005)	
NAT2 (8p22, *N*-acetyltransferase 2: phase II detoxification)	Nat2*4-*7		French women NAT2*5 allele (65, 72) (Baranova *et al*., 1999) UK women NAT2*4/NAT2*6 genotype (54, 123) (Nakago *et al*., 2001) Balkan women NAT2*7 allele (102, 153) (Iskhakova, 2006) Russian women; slow acetylator (*5, *6, *7 homozygots) in combination with either GSTT1 or GSTM1 null mutation homozygots (74, 40) (Ivashchenko *et al*., 2003)	South Indian women (252, 264) (Babu *et al*., 2004) Japanese women (145, 182) (Deguchi *et al*., 2005); (35, 37) (Iizuka *et al*., 2003)	

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.

Table IV Polymorphisms encoding genes involved in glucose homeostasis, vascular function and tissue remodelling, which have been investigated for their role in endometriosis

Gene (locus, protein name and its function)	Variant		Association with susceptibility		Phenotype
	Name	dbSNP ID	Positive	Negative	
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)	
	p.Q188R	No dbSNP ID (rare mutation)		Chinese women (325, 310) (He *et al.*, 2006) UK women (78, 248) (Morland *et al.*, 1998)	
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	Japanese women (390 women with EM, leiomyoma or adenomyoma, 144 controls) (Kiyomizu *et al.*, 2006)		
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) (Bhanoori *et al.*, 2005a) Korean women (215, 219 + 70) (Kim *et al.*, 2005a)		

Table IV *Continued*

Gene (locus, protein name and its function)	Variant		Association with susceptibility		Phenotype
	Name	dbSNP ID	Positive	Negative	
	−460C/T	Rs833061	Taiwanese women (122, 131) (Hsieh *et al*., 2004d)	South Indian women (215, 210) (Bhanoori *et al*., 2005a) Korean women (215, 219 + 70) (Kim *et al*., 2005a)	
	936C/T	rs3025039		Korean women (105, 100 + 100) (Kim *et al*., 2007a)	
Genes involved in tissue remodelling					
AHSG (3q27, alpha 2-Heremans Schmidt glycoprotein: mediates tissue development)	p.T230M	rs4917	Korean women (79, 105) (Kim *et al*., 2004)		
	p.T238S	rs4918	Korean women (79, 105) (Kim *et al*., 2004)		
MMP1 (11q22.3, matrix metalloproteinase-1: tissue remodelling)	−1607ins/delG (1G/2G)	rs112925	Chinese women: 2G allele (100, 150) (Kang *et al*., 2005) North China population (100,150) (Shan *et al*., 2005)	Italian women (56, 71) (Ferrari *et al*., 2006)	
MMP3 (11q22.3, matrix metalloproteinase-3: tissue remodelling)	−1171ins/delA (5A/6A)		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) North China population (100,150) (Shan *et al*., 2005) Italian women (56, 71) (Ferrari *et al*., 2006)	
MMP7 (11q21-q22, matrix metalloproteinase-7: tissue remodelling)	−181A/G	rs1799750	Chinese women (143 EM, 76 AM, 160) (Shan *et al*., 2006)		
MMP9 (20q11.2-q13.1, matrix metalloproteinase-9: tissue remodelling)	−1562C/T	rs3918242		Chinese women (143 EM, 76 AM) (Shan *et al*., 2006)	
SERPINE1 (7q21.3−q22, plasminogen activator inhibitor-1: fibrinolysis system. Linked to cardiovascular disease)	−675ins/delG (4G/5G)	Several dbSNP IDs: rs1799768, rs34857375, rs1799762, 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, rs365446, 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)		
Genes involved in malignant transformation					

KRAS (12p12.1, kirsten rat sarcoma viral oncogene homologue: proto-oncogene)	rs7304896, rs7132980, rs4556643, rs11612828, rs12320328, rs11047921, rs11047919, rs7309670, rs17388893, rs10842514, rs6487464, rs4495968, rs17388587, rs11047912, rs17329025, rs17388148, rs11047901, rs12579073, rs12313763, rs1137282, rs9266, rs13096, rs11047892, rs4963857, rs7137734, rs11047889, rs11047887, rs11609324, rs11836162, rs3924649	Australian women (959, 959) (Zhao *et al*., 2006)
PTEN (10q23.3, phosphate and tensin homologue: tumour suppressor)	rs2673836, rs1234220, rs1234219, rs1903858, rs2299939, rs11202597, rs1234224, rs2735343, rs17431184, rs555895, rs2736627, rs926091, rs532678, rs701848, rs478839	Australian women (768, 768) (Treloar *et al*., 2007)

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

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 endoding 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 (*GAL T*,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; He *et al*., 2006; 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 (Treloar *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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