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Original Article

Screening of a panel of steroid-related genes showed polymorphisms of aromatase genes confer susceptibility to advanced stage endometriosis in the Taiwanese Han population

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Abstract

Objective: To establish a multilocus model for studying the effect of steroid-related genes on advanced stage endometriosis.
Materials and methods: A total of 121 patients with advanced stage endometriosis and 171 control women were included. Eighteen single-nucleotide polymorphisms (SNPs) from nine genes (*HSD17B1*, *HSD17B2*, *HSD17B5*, *HSD17B6*, *CYP17*, *CYP19*, *ERα*, *ERβ*, and *PGR*) were genotyped using the TaqMan assays. Logistic regression models were used to evaluate the genetic effects, with adjustment for other covariates.
Results: Only the presence of the mutant *CYP19* (aromatase gene) was associated with a significantly increased risk of endometriosis after adjusting for age, BMI, and parity ($p = 0.002$, OR = 2.69; 95% CI = 1.44–5.02). No association was ascertained between the other investigated SNPs and endometriosis.
Conclusion: Polymorphisms of the aromatase gene confer susceptibility to advanced stage endometriosis in the Taiwanese Han population.

Keywords: endometriosis; polymorphism; steroid-related genes

Introduction

Endometriosis, the presence of endometrium-like tissue in sites outside the uterine cavity, is an estrogen-dependent inflammatory disease that affects 6–10% of women of reproductive age in the United States [1]. Their common histologic features are the presence of endometrial stromal or epithelial cells, chronic bleeding, and signs of inflammation. These lesions can occur singly or in combination and are associated with an increased risk of infertility or chronic pelvic pain [2,3].

Endometriosis develops mostly in women of reproductive age and regresses after the menopause or ovariectomy, and the lesion relapses in postmenopausal women under estrogen replacement therapy, suggesting that the growth of endometriosis is estrogen-dependent [4]. Clinical evidence clearly points to a deleterious effect of uninterrupted ovulatory cycles on the development and persistence of endometriosis [5]. An increase in the local concentration of estrogen resulting from the absence of 17β-hydroxysteroid dehydrogenase (HSD17B) type 2 in pelvic endometriotic implants was found [6]. No

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steroidogenic acute regulatory protein (StAR) or aromatase was detectable in disease-free uterine endometrium, but there were increased StAR and aromatase levels in extra-ovarian endometriotic implants and endometriomas [7–10]. These studies and the presence of estrogen receptors (ER) and aromatase in endometriosis lesions indicate that local estrogen production may stimulate the growth of lesions [11]. Biologically significant quantities of progesterone and estrogen are produced locally in endometriotic tissue through an abnormally active aromatase and steroidogenic cascade [11]. In studies on humans and other primates, estrogen stimulates the growth of endometriotic tissue, whereas aromatase inhibitors that block estrogen formation are beneficial in patients with endometriosis [12–14].

Endometriosis is evolving from a local disorder to a complex, chronic systemic disease, as its underlying cellular and molecular mechanisms are being uncovered [15]. Endometriosis can be inherited in a polygenic manner given that its incidence in relatives of affected women is up to seven times the incidence in women without such a family history [16], and with a five- to eightfold increase in the risk of occurrence in first-degree relatives [17]. Numerous studies have attempted to identify susceptible alleles for endometriosis [18–20]. Some genetic studies have revealed an association between the development of endometriosis and the polymorphisms of several genes, including the genes related to estrogen metabolism [4, 21]. The *Pvu*II polymorphism of the *ERα* gene is associated with the risk of endometriosis [22,23]. ERα14 thymine-adenine repeats polymorphism and the cytochrome P450, family 17, subfamily A, polypeptide 1 (CYP17 A1) allele polymorphism were shown to be associated with an increased risk of endometriosis in Taiwanese women [24]. It was also found that ER-351 *Xba*I*G- and -397 *Pvu*II*C-related genotypes alleles were correlated with higher susceptibilities of endometriosis [25]. The 3 bp I/D polymorphism of the *CYP19 A1* gene was shown to be weakly associated with susceptibility to endometriosis [21]. The A-allele of HSD17B1, the Ser312Gly polymorphism, appeared to confer a higher risk of endometriosis in Japanese women [26]. Although efforts have been devoted to explore the role of ER complex components and aromatase enzymes in endometriosis, these studies usually focused on a single gene or just several genes. Moreover, results of these studies were quite often not consistent [18–20].

In this study, we aimed to investigate the association between endometriosis and a more complete panel of multiple gene polymorphisms in estrogen synthesis and estrogen targets in the Taiwanese Han population. Eighteen genetic variants from nine genes (*HSD17B1*, *HSD17B2*, *HSD17B5*, *HSD17B6*, *CYP17*, *CYP19*, *ERα*, *ER*β, and *PGR*) were genotyped. The above listed single-nucleotide polymorphisms (SNPs) were selected because the respective gene products are involved in estrogen metabolism or targets, and can thus be seen as candidate genes for endometriosis. For example, variant CYP17, and CYP19 enzymes have been noted to be associated with significant changes in serum hormone concentrations [14]. Variations of the *ERα* gene lead to significant alterations in the response to therapy with estrogen [12]. HSD17B catalyzes the final step of estradiol (E2) biosynthesis. Type 1 and 7 HSD17B catalyzes the transformation of estrone (E1) into E2 [27]. We thus attempted to establish a multiple genetic model based on gene–gene interactions to define potentially critical SNP combinations in the susceptibility to endometriosis.

Materials and methods

Participants

The study was approved by the institutional review board of Changhua Christian Hospital (CCH060708) and informed written consent was obtained from each woman. The participants of the study are the same as in the previous study [28]. From September 2006 and December 2009, we recruited 121 infertile women who had pathologic confirmation of stage III/IV (advanced stage) endometriosis and underwent laparotomy or laparoscopy. The extent of the disease was staged according to the guidelines of the American Society for Reproductive Medicine [29]. This is a case-control study where we enrolled 171 women as controls who had delivered at least one full-term healthy baby without the aid of assisted reproductive technologies and had not experienced miscarriage or pregnancy complications. Women with the following conditions were excluded: infertility, dysmenorrhea, hypermenorrhea, irregular menstruation, surgical history of any gynecologic diseases, or previous diagnosis of endometriosis and adenomyosis. All individuals belonged to the Taiwanese Han, the major ethnic group in Taiwan (making up >95% of the country's population). All patients underwent a comprehensive examination, including a detailed history, physical examination, and hormone assays.

Genotyping

Peripheral venous blood samples were obtained from participants. Genomic DNA was extracted from lymphocytes using a Puregene DNA isolation kit (Gentra, Minneapolis, MN, USA). We searched polymorphisms, which are available online at http://www.ncbi.nlm.nih.gov/SNP/ or http://www.ensembl.org, for estrogen synthesizing/transporting genes (*HSD17B1*, *HSD17B2*, *HSD17B5*, *HSD17B6*, *CYP17*, *CYP19*), ER genes (*ERa*, *ERb*), and progesterone receptor gene (*PGR*). SNPs of these genes had been reported to be associated with at least two of the following steroid hormone-related disorders: breast cancer, endometrial cancer, prostate cancer, endometriosis, precocious puberty, and polycystic ovarian syndrome in peer-review articles (http://www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed). A total of 18 SNPs were chosen out of nine genes. These SNPs were detected by primer extension analysis using endpoint TaqMan assays (Applied Biosystems, Warrington, UK) in 96-well arrays, and genotypes were subsequently read on a 7900 Sequence Detector (Applied Biosystems). The detailed protocol of SNP typing is available on request to the corresponding investigator. The control samples for TaqMan assay had been

Table 1
Demographic distribution among participants.

	Age (y)	BMI (kg/m^2)	Parity
Endometriosis (n = 121)	30.9 ± 6.3*	22.1 ± 3.6	0.7 ± 1.1**
Control (n = 171)	29.1 ± 4.3	22.7 ± 1.3	1.7 ± 0.6

*p = 0.004.
**p < 0.001 compared with controls.
BMI = body mass index.

confirmed by direct genomic DNA sequence analysis performed using an automatic sequencer (Applied Biosystems).

Statistical analysis

Logistic regression models were used to evaluate the genetic effect, with adjustment for other covariates. Any variant with a p value <0.05 was considered significant. Throughout statistical analysis, SNPs were considered binary variables using a dominant gene model, i.e., homozygous wild-type compared with heterozygous and homozygous mutant (wild-type to wild-type, compared with wild-type to mutant and mutant to mutant). The association of SNPs with the presence of endometriosis was evaluated and expressed as odds ratios (OR) and 95% confidence intervals (CI).

Results

The study included a total of 121 patients with advanced stage endometriosis and 171 control women (Table 1). The mean age was 30.9 ± 6.3 versus 29.1 ± 4.3 years for endometriosis patients and controls, respectively. The BMI and parity were 22.1 ± 3.6 versus 22.7 ± 1.3 kg/m^2 and 0.7 ± 1.1 versus 1.7 ± 0.6 for endometriosis patients and controls, respectively. There were significant differences between patients with endometriosis and control participants in age and parity; therefore, they were adjusted in the multivariable logistic regression models for analyses. The genotype distributions of each SNP were in Hardy–Weinberg equilibrium for both endometriosis patients and controls.

Only the presence of the mutant rs8042086 *CYP19* (aromatase gene) was associated with a significantly increased risk of endometriosis after adjusting for age, BMI, and parity. The C/T + C/C genotypes of *CYP19* showed a statistically significant association with endometriosis compared with the T/T genotype (p = 0.002, OR = 2.69; 95% CI = 1.44–5.02) (Table 2). No association was ascertained between the other investigated SNPs and the presence or absence of endometriosis (Tables 3 and 4).

Discussion

Implementation of genetic testing has been applied to clinical practice in medical subspecialties such as hematology and clinical pharmacology [30]. Candidate genes are generally chosen based on biological mechanisms relevant to the disease. Genetic variants in these candidate genes are genotyped in samples from cases and controls, or in affected families to test for association by statistical analysis. For endometriosis, candidates tested include genes from detoxification pathways, sex steroid pathways, cytokine signaling pathways, adhesion molecules and matrix enzymes, and cell-cycle regulators [18]. In the past decade, a considerable number of genetic studies have been carried out to explore the association of various pathways with endometriosis, such as catechol-O-methyltransferase (COMT) [31], intron G of the progesterone receptor [32], ER [23,24,33,34], IL-6 [35], vascular endothelial growth factor [36], HSD17B1, HSD17B2, and HSD17B7 [37], CYP17 and CYP19 [21,38], and AhRR [39]. Many of these studies have been reviewed recently in detail for association with endometriosis susceptibility [18,19,40–42]. Most of the studies investigated only a

Table 2
Distribution of CYP gene polymorphisms among endometriosis patients and controls.

Genotype	SNP ID	Patients, n (%)	Controls, n (%)	p	OR (95% CI)
CYP17	rs743572				
Genotype frequency					
AG[a]		52 (43.0)	89 (52.0)		
AA + GG		69 (57.0)	82 (48.0)	0.366	1.31 (0.73–2.34)
CYP17	rs10786712				
Genotype frequency					
CT[a]		50 (41.3)	88 (51.4)		
CC + TT		71 (59.7)	83 (48.6)	0.322	1.34 (0.75–2.40)
CYP19	rs10046				
Genotype frequency					
AG[a]		60 (49.6)	87 (50.9)		
AA + GG		61 (50.4)	84 (49.1)	0.874	0.95 (0.54–1.70)
CYP19	rs8042086				
Genotype frequency					
TT[a]		30 (24.8)	84 (49.1)		
CT + CC		91 (75.2)	87 (50.9)	0.002	2.69 (1.44–5.02)

CI = confidence interval; CYP = cytochrome P450; OR = odds ratio; SNP = single-nucleotide polymorphisms. Results adjusted for age, body mass index, and parity.
[a] Denotes the reference group for pairwise comparisons.

Table 3
Distribution of HSDs gene polymorphisms among endometriosis patients and controls.

Genotype	SNP ID	Patients, *n* (%)	Controls, *n* (%)	*p*	OR (95% CI)
HSD17B1	rs605059				
Genotype frequency					
AG[a]		61 (50.4)	87 (50.9)		
AA + GG		60 (49.6)	84 (49.1)	0.441	1.27 (0.69–2.32)
HSD17B1	rs676387				
Genotype frequency					
AC[a]		57 (47.1)	85 (49.7)		
AA + CC		64 (52.9)	86 (50.3)	0.272	1.40 (0.77–2.53)
HSD17B2	rs8191246				
Genotype frequency					
AA[a]		115 (95.0)	157 (91.8)		
AG + GG		6 (5.0)	14 (8.2)	0.491	1.40 (0.20–2.18)
HSD17B2	rs11642323				
Genotype frequency					
CT[a]		59 (48.8)	85 (49.7)		
CC + TT		62 (51.2)	86 (50.3)	0.572	1.40 (0.47–1.51)
HSD17B2	rs8191138				
Genotype frequency					
GG[a]		59 (48.8)	89 (52.0)		
AG + AA		62 (51.2)	82 (48.0)	0.425	1.27 (0.71–2.28)
HSD17B5	rs12529				
Genotype frequency					
GG[a]		88 (72.7)	127 (74.3)		
CG + CC		33 (27.3)	44 (25.7)	0.820	1.08 (0.55–2.11)
HSD17B6	rs898611				
Genotype frequency					
TT[a]		64 (52.9)	96 (56.1)		
CT + CC		57 (47.1)	75 (43.9)	0.289	1.38 (0.76–2.52)
HSD17B6	rs7967600				
Genotype frequency					
GG[a]		64 (52.9)	96 (56.1)		
AG + AA		57 (47.1)	75 (43.9)	0.332	1.34 (0.74–2.40)

CI = confidence interval; HSD = hydroxysteroid dehydrogenase; OR = odds ratio; SNP = single-nucleotide polymorphisms. Results adjusted for age, body mass index, and parity.

[a] Denotes the reference group for pairwise comparisons.

single SNP or a single gene and thus the interaction models or correction of multiple comparisons could not be obtained. Thus far, only a few additive effects of multiple SNPs have been described [28,30]. Identifying critical combinations of SNPs conferring additive risks of developing endometriosis would be of clinical interest for defining high-risk populations, or for identifying women most likely to benefit from pharmacologic interventions related to the gene product of the respective SNPs, e.g., antiestrogens [30]. We thus set out to investigate a combination of multiple SNPs (*HSD17B1*, *HSD17B2*, *HSD17B5*, *HSD17B6*, *CYP17*, *CYP19*, *ERα*, *ERβ*, and *PGR*) involved in estrogen metabolism simultaneously. This study demonstrates that the presence of the mutant rs8042086 of *CYP19* (aromatase gene) is associated with a significant risk of developing advanced endometriosis. Except for *HSD17B2*, *HSD17B5*, and *HSD17B6*, most SNPs chosen for genotyping in this study have been shown to be significantly associated with endometriosis or other estrogen-related diseases. However, the correlation could not be replicated in our samples.

The net production of 17β-E2 is the result of a delicate balance between the synthesis and the inactivation of E2 [43]. Enzymes encoded by the HSD17B family catalyze the interconversion between higher activity 17β-hydroxysteroids and lower activity 17-ketosteroids, and thus regulate the biological activity of sex steroids, including estrogen. In humans, aromatase produces mainly E1 and some HSD17Bs play the role for the synthesis of E2 from E1. The production of E2 is mediated through the HSD17B type 1, 3, 5, 7, and 12, as well as steroid sulfatase (STS), which converts the sulfated estrogens to biologically active estrogens [44–46]. Gene transcripts for types 1 and 7 HSD17B and estrogen sulfatase were found to be overexpressed in endometriotic tissues when compared with normal endometrium [43]. The conversion of E2 into less active metabolites in endometrium tissue is based on enzymatic actions of HSD17Bs types 2, 4, and 8, which form by an oxidative reaction to androstenedione and E1 [47]. The type 2 HSD17B is believed to be one of the most important E2-inactivating enzymes in the endometrium [48]. The general consensus is that the expression of type 2 HSD17B is reduced or absent in eutopic and ectopic endometrium of endometriosis patients [43,49]. The expression pattern of aromatase and the regulation of 17βHSD-2 were found to be altered in the eutopic endometrium of women with endometriosis compared to that of women without disease [4]. Inactivation of 17β-E2 is impaired in endometriotic tissues due to deficient expression of 17βHSD-2,

Table 4
Distribution of estrogen and progesterone receptor gene polymorphisms among endometriosis patients and controls.

Genotype	SNP ID	Patients, *n* (%)	Controls, *n* (%)	*p*	OR (95% CI)
ERα	rs1801132				
Genotype frequency					
CG[a]		65 (53.7)	80 (46.8)		
CC + GG		56 (46.3)	91 (53.2)	0.524	0.83 (0.46–1.48)
ERα	rs2077647				
Genotype frequency					
CT[a]		48 (39.7)	77 (45.1)		
CC + TT		73 (60.3)	94 (54.9)	0.841	1.06 (0.59–1.93)
ERα	rs2228480				
Genotype frequency					
GG[a]		67 (55.4)	111 (64.9)		
AG + AA		54 (44.6)	60 (35.1)	0.133	1.59 (0.87–2.92)
ERβ	rs4986938				
Genotype frequency					
CC[a]		97 (80.2)	140 (81.9)		
CT + TT		24 (19.8)	31 (18.1)	0.369	1.41 (0.67–2.99)
ERβ	rs1256049				
Genotype frequency					
CT[a]		61 (50.4)	82 (48.0)		
CC + TT		60 (49.6)	89 (52.0)	0.810	1.07 (0.60–1.92)
PGR	rs1042838				
Genotype frequency					
CC[a]		116 (95.9)	167 (97.7)		
AC + AA		5 (4.1)	4 (2.3)	0.491	1.40 (0.20–2.18)

CI = confidence interval; ER = estrogen receptor; OR = odds ratio; PGR = progesterone receptor; SNP = single-nucleotide polymorphisms. Results adjusted for age, body mass index, and parity.
[a] Denotes the reference group for pairwise comparisons.

which is normally expressed in eutopic endometrium in response to progesterone [6].

The haplotypes of the *HSD17B1* gene have been associated with elevated E2 levels and breast cancer, an estrogen-dependent disease [50]. It has been suggested that the presence of SNP vlV A->C of *HSD17B1* promotes the development of endometriosis [30]. The transcripts of the reductive HSD17B type 1, which catalyzes the conversion of E1 to E2, are expressed in both eutopic endometrium and endometriosis. In contrast, HSD17B type 2 messenger ribonucleic acids are present in all samples of secretory eutopic endometrium, but not in secretory samples of endometriotic lesions [6]. Evidence for association between the Ser312Gly polymorphism in HSD17B1 and endometriosis was found in a Japanese population. The A-allele of HSD17B1 appears to confer higher risk for endometriosis in Japanese women [26]. The study also provided evidence of HSD17B1 vlV A->C as a low penetrance genetic marker of endometriosis in a population of middle-European origin [30]. Besides *HSD17B1* and *HSD17B2*, other members of the *HSD17B* family in relation to the risk of endometriosis have not been explored. We have thus investigated a more comprehensive panel of *HSD17B* genes. For the first time, an attempt was made to explore the association of *HSD17B5*, and *HSD17B6* genes in endometriosis. We did not identify a positive association in all SNPs tested. For the progesterone receptor gene, rs1042838 was in complete linkage disequilibrium with the most representative functional SNP (PROGIN) in the Taiwanese. In addition, rs1042838-PROGIN was significantly associated with recurrent pregnancy loss in our population [51]. Although only two to four SNPs were genotyped for each of the remaining genes, these SNPs have been shown to be associated with steroid hormone-related diseases in our previous publications [51,52].

Aromatase overexpression has been confirmed in numerous reports on endometriosis in terms of the transcript level [7,37,53], protein level [8,9,54,55], as well as the enzymatic activity level [8,54]. The *CYP17* gene mediates both steroid 17α-hydroxylase and 17,20-lyase activities and plays a key role in androgen biosynthesis. The *CYP19A1* gene codes for aromatase enzymes involved in conversion of androgen to estrogen. Previous studies on Taiwanese women have shown a possible relation between endometriosis susceptibility and the 234T/C polymorphism in the promoter region of the *CYP17A1* gene [24,56]. However, no strong association with *CYP17A1* polymorphisms has been found in other studies of UK, Brazilian, Austrian, Taiwanese, or Japanese populations [21,30,57–59]. Although of similar ethnic background, we also could not prove the association between the CYP17A1 SNP and endometriosis. The TTTA repeat microsatellite in the *CYP19A1* gene showed no association in Japanese women with endometriosis [21] and the risk of endometriosis was increased in Greek women [60]. Another polymorphism in this gene (CYP19 Arg264Cys C->T) was studied in Japanese and Austrian women, but did not appear to influence endometriosis susceptibility [26,30]. The 3 bp I/D polymorphism of the *CYP19A1* gene was shown to be only weakly associated with the susceptibility to endometriosis [21]. The polymorphisms

C1558T (rs700519) of *CYP19* were related to endometriosis in an Italian population [38]. In this study, we demonstrated that the polymorphism of the *CYP19* SNP (rs8042086) was associated with susceptibility to endometriosis.

A review of association studies for CYP17A1, CYP19A1, androgen receptor (AR), PGR and ERα, ERβ concluded that many reported positive findings were unsound because of problems with data analysis in the original reports [42]. Almost all previous published studies were limited by the small sample size, only single SNP in each gene, and many results were controversial in different studies and/or different population groups [19,20]. Thus, population difference may be an important factor in the genetic association study based on SNPs of a single gene. Meta-analysis of the studies provided some, although limited, support for an association between endometriosis and both the PGR-PROGINS polymorphism and ESR1-PvuII polymorphism [42]. However, another study in a large family-based sample failed to support any association between PGR and endometriosis [61]. In this study, no significant finding was noted on the study of *ERα*, *ERβ*, and PGR relevant to the endometriosis. Recently, an international collaborative study also failed to support the association between PGR-PROGIN and endometriosis [62]. Taken together, our results are in accordance with those of Trabert et al [63]. They used a tagSNP approach to characterize a panel of sex hormone metabolizing genes in endometriosis. Of all genes (*ESR1*, *ESR2*, *PGR*, *CYP17A1*, *CYP19A1*, *HSD17B1*, *HSD17B2*, *CYP1A1*, *CYP1A2*, *COMT*, and *GSTM1*) tested, only *CYP19* showed a significant association [63].

Although as many SNPs for each gene as possible have been analyzed in the present study, some limitations must be considered when evaluating the results of this study. First, some estrogen-related genes were not included in our model. We only chose *CYP17A1*, *CYP19A1*, and *HSD17B* in our study. Second, the sample size was still small for this study, and this restricts the statistical power to detect associations at very stringent levels of significance. Finally, our control group consisted primarily of asymptomatic volunteers. Without surgical diagnosis, the control population could contain a substantial number of women with mild endometriosis. Considering the high frequency of minimal/mild endometriosis in asymptomatic women, some investigations considered early-stage endometriosis as a physiological process. It appears logical to investigate the early-stage and advanced stage diseases separately [64].

On the basis of the most recent studies, a hypothesis for the pathophysiology of endometriosis was proposed in our institute [65]. In this model, retrograded menses cause inflammation in the pelvic cavity and the immune cells, led by macrophages, producing cytokines (IL-1α) that induce overexpression of cyclooxygenase (COX)-2 in macrophages and ectopic endometriotic tissues. Expression of COX-2 leads to increased production and accumulation of prostanoids, especially prostaglandin E2 (PGE2), in the peritoneal fluid. A link between inflammation and estrogen production in endometriosis was uncovered in a feedback cycle that favors the overexpression of key steroidogenic genes (most notably aromatase), overexpression of COX-2, and continuous local production of E2 and PGE2 in endometriotic tissue [11,15]. The autonomous positive-feedback loop between PGE2 and estrogen in the ectopic endometriotic lesion might explain the importance in the pathogenesis of this disorder [65]. The present results further substantiate the positive findings on the aromatase gene, the key factor for the synthesis of estrogen, and the risk of endometriosis. While some enzymes involved in estrogen metabolism may play no role in the cell growth of endometriosis due to an altered microenvironment in endometriotic lesions, this study along with previous studies, seems to suggest that genetic variants of steroid-hormone metabolic pathways may have only minimal effects on the pathogenesis of endometriosis [30].

Conclusion

Based on this study, we support previously published data that genetic variation of the *CYP19A1* gene may play a significant role in this respect. Our data demonstrate an association between an SNP of the *CYP19A1* gene and endometriosis, indicating that the *CYP19A1* polymorphism is a candidate genetic susceptibility marker of this disease. Although previous studies have shown association of *ERα*, *ERβ*, *PGR*, *CYP17*, *HSD17B1*, and *HSD17B2* with endometriosis, these associations could not be replicated in this study. We also tried to explore the association between *HSD17B5* and *HSD17B6* with endometriosis, but a negative association was yielded. This study suggests that genetic variants of steroid-hormone metabolic pathway genes may have only minimal effects on the pathogenesis of endometriosis.

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