

# CYP17, CYP1A1 and COMT polymorphisms and the risk of adenomyosis and endometriosis in Taiwanese women

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**BACKGROUND:** The aim of the study was to test whether the *COMT*, *CYP1A1* and *CYP17* genes influence the risk of developing adenomyosis and endometriosis. **METHODS:** We conducted two case-control studies, where the cases ( $n = 198$ ) had either of the two diseases, and controls ( $n = 312$ ) were disease-free women. For the *COMT* gene, we selected the G/A nonsynonymous single-nucleotide polymorphism (SNP) that leads to valine-to-methionine (Val/Met) substitution. For the *CYP1A1* gene, we used a functional T/C SNP in the 3'-noncoding region, and we genotyped a T/C functional SNP in the 5' region of the *CYP17* gene for the present study. Hardy-Weinberg equilibrium was checked in both cases and controls. Logistic regression models were used to evaluate the genetic effect, with adjustment for other covariates. **RESULTS:** We found that the homozygous *COMT* genotype that encodes low enzyme activity had an increased risk for adenomyosis with an age-adjusted odds ratio of 3.2 (95% confidence interval 1.3–7.8;  $P = 0.006$ ). The *COMT* gene, however, was not associated with endometriosis. Neither the *CYP1A1* nor *CYP17* genes had any significant association with either of the two diseases. **CONCLUSION:** The *COMT* gene significantly influences the risk of adenomyosis but not endometriosis. The present study does not provide evidence to support any of the three genes exerting pleiotropic effects on both diseases.

*Key words:* adenomyosis/endometriosis/estrogen/gene/polymorphism

## Introduction

Endometriosis and adenomyosis are two common gynaecological disorders. Both diseases are characterized by the presence of endometrial glands and stroma outside their normal locations. When endometrial glands and stroma are present outside the uterine cavity, it is called endometriosis. When they are within the myometrium, the disease is defined as adenomyosis. Both disease entities develop in women of reproductive ages and regress after menopause, which suggests they are estrogen-dependent disorders. Adenomyosis and endometriosis contain estrogen receptors, and interestingly both have aromatase that catalyzes the conversion of androgens to estrogens, suggesting local estrogen production (Noble *et al.*, 1996; Kitawaki *et al.*, 1997). Studies have also found increased estrogen concentrations in the adenomyotic and endometriotic lesions (Yamamoto *et al.*, 1993; Zeitoun *et al.*, 1999). A growing body of evidence indicates that both diseases are partially determined

by genetic factors (Hadfield *et al.*, 1997; Simpson and Bischoff, 2002). Given that estrogen is involved in both the diseases, we proposed to investigate whether estrogen-metabolizing genes have a pleiotropic effect to influence the risk for both diseases. The three genes investigated in this study are the catechol-O-methyltransferase (*COMT*), cytochrome P450c17 $\alpha$  (*CYP17*) and cytochrome P450IA1 (*CYP1A1*) genes.

The G/A nonsynonymous single-nucleotide polymorphism (SNP) at codon 158 in the *COMT* gene leads to valine-to-methionine (Val/Met) substitution, which apparently influences the enzyme activity (Lachman *et al.*, 1996). For the *CYP1A1* gene, four polymorphisms are commonly investigated in many studies (see review by Masson *et al.*, 2005), but the T/C SNP in the 3'-noncoding region (also known as 3801 T/C) is the most prevalent in the Asian population. In addition, this T/C SNP has been suggested to be a functional related site (Landi *et al.*, 1994; Taioli *et al.*, 1999). The 5' region of the *CYP17* gene contains the

T/C SNP that can be detected by the MspA1 restriction enzyme, and thus its alleles have been also denoted as A1 (i.e. allele T) and A2 (allele C). The A2 allele is associated with elevated levels of estradiol in young women (Feigelson *et al.*, 1998). Given the biological consequence of the three SNPs, they are conceivable candidate polymorphisms for our study. We conducted two case–control studies to test the hypothesis of a common estrogen-metabolizing gene conferring the risk for both gynaecological diseases. The first case–control study focused on adenomyosis, and the second study focused on endometriosis.

## Methods

### Subjects

The study was approved by the Kaohsiung Medical University Hospital (KMUH) Institutional Review Board. All participants gave their informed consent. For the endometriosis cases, we only included the patients who underwent laparotomy or laparoscopy at KMUH and had pathological confirmation of the disease. The diagnosis of adenomyosis in the present study was based on the pathological finding of the presence of endometrium in the myometrium. All the patients previously had conservative treatments but failed to have satisfied response before surgery. All the cases that met the above criteria were consecutively recruited from the Department of Obstetrics and Gynecology at the KMUH, Taiwan, between December 2002 and July 2004. The controls were from two sources. The first source provided a subset of the subjects who participated in a community-based Papanicolaou (Pap) smear screening on the southwestern coastal plain of Taiwan (Chia-Yi city) between October 1999 and December 2000 (Wu *et al.*, 2003). The second source offered a subset of the participants in another community-based Pap smear screening conducted in Kaohsiung County, Taiwan, between January 2003 and September 2004 (Tsai *et al.*, 2005). The demographic information and reproductive histories were obtained by trained public health nurses who interviewed the study subjects in both Pap smear screening programs. Healthy controls were excluded from the present study if they had infertility, dysmenorrhea, hypermenorrhea, irregular menstruation, surgical history for any obstetrical diseases, previous diagnosis of endometriosis or adenomyosis or no available DNA sample. The final number of controls enrolled in the first study were 155 healthy subjects from the first source and 147 from the second source. All cases and controls were of Chinese descent.

### Genotyping

Genomic DNA was extracted from the peripheral blood using a standard method. The PCR-based restriction fragment length polymorphism (RFLP) methods for *COMT*, *CYP1A1* and *CYP17* genotyping have been described elsewhere (Carey *et al.*, 1994; Feigelson *et al.*, 1998; Huang *et al.*, 1999). The G/A SNP at the *COMT* gene is also designated as the H/L polymorphism, where the H allele has high enzyme activity and the L allele low enzyme activity. The T allele of the T/C SNP at the *CYP1A1* gene is also called the wt allele and the C allele corresponds to the vt allele described by other investigators. For the polymorphism at the *CYP17* gene, some reports used the A1 allele to represent the T allele and A2 to represent the C allele.

### Statistical analysis

A goodness-of-fit chi-squared test was used to test for Hardy–Weinberg equilibrium in both cases and controls. We compared the mean age, BMI and parity between each type of diseases and controls. Because these three variables may also influence disease risk, they were

included in the multivariate regression models. The difference of genotype distributions between controls and each type of diseases was assessed by both univariate and multivariate logistic regression models. We used all adenomyosis cases (i.e. 93 patients of only adenomyosis plus 17 patients of both diseases) while analysing genetic effects on adenomyosis. Similarly, all endometriosis patients were used for analysis, regardless of coexistent adenomyosis. Each genotype was first treated as a dummy variable to avoid assumption of a genetic dominant effect. We also tested for the dominant effect by combining one homozygous genotype and the heterozygous genotype as one group to compare with the other homozygous genotype. Appropriate covariates were adjusted in the logistic regression models. Odds ratio (OR) was calculated to assess the genetic effect. Statistical analyses were conducted by the SAS software (SAS, Cary, NC). A two-sided *P*-value <0.05 was considered significant.

## Results

A total of 198 cases and 312 controls were included in this study. Among the total cases, 93 patients had only adenomyosis, 88 had only endometriosis and 17 had both diseases (Table I). The mean age (year) and SD was  $46.2 \pm 7.6$  for adenomyosis cases,  $35.5 \pm 8.6$  for endometriosis cases and  $49.2 \pm 12.0$  for controls. Other demographic information is summarized in Table I. Age was significantly different between controls and any of the two diseases. BMI and parity were associated with the status of endometriosis but not adenomyosis. Therefore, age was included in the multivariate regression models for analyses of adenomyosis and endometriosis. BMI and parity were only included in the analysis of endometriosis.

Tables II–IV summarize the genotypic distributions for the *COMT*, *CYP1A1* and *CYP17* genes among our patients and controls. The genotype distributions of each SNP were in

**Table I.** Mean and SD of age, BMI and parity among participants

	Age (years)	BMI (kg/m <sup>2</sup> )	Parity
Adenomyosis (only, <i>n</i> = 93)	46.7 ± 7.8 <sup>a</sup>	24.0 ± 4.1	2.6 ± 1.5
Endometriosis (only, <i>n</i> = 88)	34.0 ± 8.4 <sup>a</sup>	21.4 ± 3.8 <sup>a</sup>	1.4 ± 1.0 <sup>a</sup>
Adenomyosis and endometriosis ( <i>n</i> = 17)	43.4 ± 4.2 <sup>a</sup>	23.5 ± 5.3	1.6 ± 1.3 <sup>a</sup>
Adenomyosis (all, <i>n</i> = 110)	46.2 ± 7.6 <sup>a</sup>	23.9 ± 4.3	2.5 ± 1.5
Endometriosis (all, <i>n</i> = 105)	35.5 ± 8.6 <sup>a</sup>	21.7 ± 4.1 <sup>a</sup>	1.4 ± 1.1 <sup>a</sup>
Control ( <i>n</i> = 312)	49.2 ± 12.0	23.3 ± 3.7	2.6 ± 1.0

<sup>a</sup>*P* < 0.05 compared with controls.

**Table II.** *COMT* gene and the two gynaecological diseases

	H/H	H/L	L/L
Controls (%)	186 (60.8)	109 (35.6)	11 (3.6)
Adenomyosis (all) (%)	57 (52.3)	41 (37.6)	11 (10.1)
Unadjusted OR	1	1.2 (0.8–2.0)	3.3 (1.3–7.9)
Adjusted OR <sup>a</sup>	1	1.2 (0.7–1.9)	3.2 (1.3–7.8, <i>P</i> = 0.006)
Endometriosis (all) (%)	61 (58.7)	37 (35.6)	6 (5.8)
Unadjusted OR	1	1.0 (0.6–1.7)	1.7 (0.6–4.7)
Adjusted OR <sup>b</sup>	1	0.6 (0.3–1.4)	1.0 (0.2–6.0)

<sup>a</sup>Adjusted for age.

<sup>b</sup>Adjusted for age, BMI and parity.

**Table III.** *CYP1A1* gene and the two gynaecological diseases

	T/T	T/C	C/C
Controls (%)	107 (35.8)	144 (48.2)	48 (16.1)
Adenomyosis (all) (%)	33 (30.6)	52 (48.1)	23 (21.3)
Unadjusted OR	1	1.2 (0.7–1.9)	1.6 (0.8–2.9)
Adjusted OR <sup>a</sup>	1	1.2 (0.7–2.0)	1.5 (0.8–2.9)
Endometriosis (all) (%)	42 (40.4)	52 (50.0)	10 (9.6)
Unadjusted OR	1	0.9 (0.6–1.5)	0.6 (0.2–1.1)
Adjusted OR <sup>b</sup>	1	0.9 (0.4–2.0)	0.6 (0.2–1.9)

<sup>a</sup>Adjusted for age.<sup>b</sup>Adjusted for age, BMI and parity.**Table IV.** *CYP17* gene and the two gynaecological diseases

	T/T	T/C	C/C
Controls (%)	57 (18.8)	140 (46.1)	107 (35.2)
Adenomyosis (all) (%)	18 (16.5)	55 (50.5)	36 (33.0)
Unadjusted OR	1	1.2 (0.7–2.3)	1.1 (0.6–2.0)
Adjusted OR <sup>a</sup>	1	1.2 (0.7–2.3)	1.1 (0.6–2.0)
Endometriosis (all) (%)	25 (24.0)	45 (43.3)	34 (32.7)
Unadjusted OR	1	0.7 (0.4–1.3)	0.7 (0.4–1.3)
Adjusted OR <sup>b</sup>	1	0.4 (0.1–0.9)	0.4 (0.2–1.1)

<sup>a</sup>Adjusted for age.<sup>b</sup>Adjusted for age, BMI and parity.

Hardy–Weinberg equilibrium for both case and control groups. Using the H/H genotype of the *COMT* gene as the reference, the L/L genotype had an increased risk for adenomyosis (adjusted OR = 3.2; 95% confidence interval [CI] 1.3–7.8;  $P = 0.006$ ) but not for endometriosis (Table II). Because the OR increased with the number of the L allele (H/H : H/L : L/L = 1 : 1.2 : 3.2), and because the COMT enzyme activity also proportionally decreases to the number of the L allele, the L allele may have an additive effect on adenomyosis development. We further analysed the *COMT* effect on 93 adenomyosis cases that did not have coexistent endometriosis. The new results improved slightly: the adjusted OR for H/L was 1.24 (95% CI, 0.75–2.05) and for L/L was 3.53 (95% CI, 1.4–8.8). The *CYP1A1* gene did not have a significant association with either of the two diseases (Table III). We also tested for the dominant effect by either the T or C allele, and the results remained insignificant for all tests. Similarly, we did not find any genotype of *CYP17* as a risk factor for the two diseases (Table IV).

## Discussion

In our present study, we analysed the relationships between two estrogen-dependent gynaecological diseases and three estrogen-metabolizing genes. The polymorphism at each of the three genes is common in the general population and may have a functional consequence. We found that the *COMT* gene is only associated with adenomyosis but not with endometriosis. The *CYP17* and *CYP1A1* genes are not significantly related to either of the two diseases. To our knowledge, this is the first study to demonstrate a potential genetic effect on adenomyosis but not on endometriosis. We have not found any previous publications specifically investigating the relationship between adenomyosis and the three estrogen-metabolizing genes. The estimated prevalence of adenomyosis varies widely among

studies, but adenomyosis is much more frequently seen in endometriotic patients than in healthy women (Kunz *et al.*, 2005). Therefore, our results may be only applicable to adenomyotic patients with severe clinical presentations.

The different results between adenomyosis and endometriosis with regard to the *COMT* genotypes can be partially attributed to their different pathogeneses. Although adenomyosis might be considered a special form of endometriosis, distinct processes have been found in the two diseases. The precise aetiology for adenomyosis is poorly understood. The conventional view is that adenomyosis results from the abnormal down-growth and invagination of the endometrium into the myometrium. Endometriosis formation is generally believed to involve retrograde menstruation, attachment of endometrial fragments to the epithelium of the peritoneum, invasion of the epithelium, establishment of a blood supply and generation of a suboptimal immune response that does not adequately clear the implants. The immune system is considered to play a crucial role in the development of endometriosis (Lebovic *et al.*, 2001). The complicated underlying mechanisms for endometriosis may indicate that a single gene effect can be too small to be detected in our limited sample size. In addition, adenomyosis and endometriosis differ with respect to clinical symptoms and treatment, which may further support different pathophysiological mechanisms between the two diseases.

The principal estrogens, estrone ( $E_1$ ) and estradiol ( $E_2$ ), undergo oxidative metabolism through hydroxylation, leading to the formation of catechol estrogens. Among catechol estrogens, 2-OH estrogens do not induce tumour (Liehr *et al.*, 1986), whereas 4-OH estrogens have the tumorigenic effects (Liehr *et al.*, 1986). Catechol estrogens can also stimulate prostaglandin synthesis (Kelly and Abel, 1981) in the uterus, which can influence uterine function such as implantation. The enzyme COMT catalyzes O-methylation of catechol estrogens into inactive metabolites (2-methoxyestrone, 2-methoxyestradiol, 4-methoxyestrone and 4-methoxyestradiol). 2-methoxyestradiol actually is a potent inhibitor of tumour cell proliferation (Zhu and Conney, 1998). Therefore, high-activity COMT enzyme may reduce the risk for tumour formation. The *CYP1A1* enzyme is primarily involved in the 2-hydroxylation pathway leading to the formation of 2-OH estrogens, which have no effect on the uterus. The *CYP17* gene is related to catalysis of both 17- $\alpha$ -hydroxylation and 17,20-lyase conversion of 21-carbon steroids to 19-carbon precursors of sex steroids. Accordingly, the *CYP17* genotypes may influence biosynthesis of estrogen. The *CYP1A1* and *CYP17* genes do not have direct effects on the tumorigenic 4-OH estrogens, which may partially explain the lack of association between these two genes and adenomyosis or endometriosis.

An Austrian study of Caucasian women reported no association (OR = 1;  $P = 1.0$ ) between the G/A polymorphism at the *COMT* gene and endometriosis (Wieser *et al.*, 2002). To our knowledge, the above study is the only publicly available report investigating the *COMT* genetic effect on the disease of interest. Our present study is consistent with the finding from the Austrian study. However, among the Asian populations, the frequency of the *COMT* polymorphism is relatively low (the minor allele frequency is 24% in our sample versus approximately 50% in the Caucasians), which may reduce the power to detect a mild genetic effect, if it truly exists.



The *CYP1A1* gene has been studied as a potential susceptibility locus to endometriosis. A study of an UK population did not find an association between the 3801 C/T polymorphism of the *CYP1A1* gene and endometriosis (Hadfield *et al.*, 2001). A recent study where 310 Indian women with endometriosis and 215 controls were analysed showed no evidence of association between endometriosis and the 3801 C/T polymorphism at the *CYP1A1* gene (Babu *et al.*, 2005). However, a Greek study reported that the people carrying the T/T genotype had a reduced risk (Arvanitis *et al.*, 2003) compared with the C allele carriers.

Several studies have investigated the relationship between the *CYP17* gene and endometriosis. A Japanese study reported no relationship between the *CYP17* gene and endometriosis or a mixed group of adenomyosis and leiomyoma (Kado *et al.*, 2002). Although a recent article based on the Taiwanese population reported the *CYP17* gene as a risk marker for endometriosis (Hsieh *et al.*, 2005), the present study cannot replicate their result. Similar to our finding, Asghar *et al.* (2005) failed to show any association between the *CYP17* gene and endometriosis in either the Japanese population or the UK women.

There are strengths and limitations in the present study. The strengths include (i) unlike some studies where adenomyosis was included in endometriosis as one phenotype, we analysed adenomyosis separately, (ii) the study subjects have a relatively homogeneous genetic background and (iii) the selected SNPs are most likely to have functional consequences (Landi *et al.*, 1994; Lachman *et al.*, 1996; Feigelson *et al.*, 1998; Taioli *et al.*, 1999). However, we did not investigate other SNPs of each candidate gene, and thus our results cannot exclude other polymorphisms that may influence the risk for the two diseases. Our moderate sample size may not provide a sufficient power to detect a minor genetic effect. Several estrogen-related genes were not investigated in the present study but will be examined in our subjects in the future. Our controls did not receive invasive tests to exclude the diseases. Therefore, our study may underestimate the genetic risk. If so, the *COMT* genetic effect can be even stronger than reported in this study. Since all our cases underwent surgery, our results may not be applicable to the patients who do not need surgery.

## Conclusion

The present study suggests that the *COMT* gene may play a role to influence the risk for adenomyosis. This present study did not support a pleiotropic effect of the three estrogen-metabolizing genes on both adenomyosis and endometriosis.

## Acknowledgements

This study was partly supported by the NSC grant (NSC 92-2314-B-037-109). The author would like to thank the Statistical Analysis Laboratory, Department of Clinical Research, Kaohsiung Medical University Chung Ho Memorial Hospital, for their help.

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*Submitted on October 12, 2005; resubmitted on January 18, 2006; accepted on January 20, 2006*