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Analysis of the relationship between *COMT* polymorphisms and endometriosis susceptibility

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Abstract

This study was aimed to explore the correlation between catechol-O-methyltransferase (*COMT*) gene polymorphisms and endometriosis susceptibility in Chinese Han population.

This case-control study recruited 134 endometriosis patients and 139 healthy individuals. *COMT* gene rs4680, rs2020917, and rs4646312 polymorphisms in the subjects were genotyped by the polymerase chain reaction-restriction fragment length polymorphism method. Association between *COMT* polymorphisms and endometriosis susceptibility was evaluated by χ^2 test and adjusted by Logistic regression. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to present the relative risk of endometriosis.

A allele of rs4680 was distinctly correlated with increased susceptibility of endometriosis (OR = 1.450, 95% CI = 1.012–2.076). However, when adjusted by the confounding factors, these associations become not significant. We failed to find any significant association between rs2020917 and endometriosis risk in the crude results. The adjusted results suggested that rs2020917 TT genotype and T allele were distinctly correlated with enhanced endometriosis risk (TT vs CC: $P = .038$, OR = 2.894, 95% CI = 1.060–7.903; T vs C: $P = .039$, OR = 1.481, 95% CI = 1.021–2.149). Besides, rs4646312 C allele was significantly correlated with endometriosis risk both in the crude ($P = .027$, OR = 1.502, 95% CI = 1.047–2.154) and adjusted ($P = .019$, OR = 1.564, 95% CI = 1.078–2.269) results.

COMT polymorphisms might predict the occurrence of endometriosis.

Abbreviations: 95% CIs = 95% confidence intervals, BMI = body mass index, CHB = Chinese Han in Beijing, COMT = catechol-O-methyltransferase, HWE = Hardy–Weinberg equilibrium, ORs = odds ratios, SNPs = single nucleotide polymorphisms.

Keywords: adjustment, *COMT*, endometriosis, polymorphisms

1. Introduction

Endometriosis is one of the common disease in reproductive age women. Although many endometriosis patients had no significant symptoms, it is mainly characterized by dysmenorrhea and infertility.[1] Recent years, the incidence rate of endometriosis is increased and it shows a younger trend.[2,3] This disease bring high physical and mental wellbeing for the patients and family members.[4,5] There is a popular belief that endometriosis is caused by the activated endometrial cells grows outside the endometrium.[6] The development of endometriosis is similar to the malignant tumors.[7,8] Many hypotheses have been put forward to explain the etiology of it.[9] In spite of the pathogenesis of endometriosis is still unclear, multiple factors have been found contribute to the occurrence and development of endometriosis, including the alteration of the peritoneal microenvironment, disorders of inflammatory response, DNA methylation, lifestyle, and others.[5,9–12] As an estrogen-dependent disease, endometriosis might be regulated by the metabolism of estrogen.[13] Thus any factors contribute to the disorders of estrogen metabolism may be associated with the development of endometriosis.

Catechol-O-methyltransferase (COMT) is one of the key enzymes for estrogen metabolism and widely expressed in different organs. It could inactivate the catechol estrogen via catalyzing the methylation of it.[14,15] The methylated products could inhibit the proliferation of endometrial stromal cells and angiogenesis.[16] Human *COMT* gene is located at chromosome 22q11.21, and encode soluble COMT and membrane-bound COMT 2 isoforms. Alteration of *COMT* expression might cause some disorders. Polymorphisms in *COMT* gene have been found associated with different estrogen-dependent diseases.[17–19] However, the association between *COMT* gene polymorphisms and endometriosis still obscure.

From the 1000 genomes project, we found that the minor allele frequencies of *COMT* gene rs4680 (Val158Met, G1947A), rs4646312, and rs2020917 (−922C>T) single nucleotide polymorphisms (SNPs) were higher than 0.1 in Chinese Han in Beijing (CHB) population. Meanwhile, due to the different distributions of polymorphisms, we analyzed the association

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Table 1

Basic features and environment exposes of the subjects.

Characteristics	Case n = 134 (%)	Control n = 139 (%)	P
Age, years	31.25 ± 7.68	30.96 ± 6.53	.117
BMI, kg/m^2	23.42 ± 3.29	23.43 ± 3.18	.936
Age of menarche, years	13.18 ± 2.00	13.23 ± 2.01	.372
Menstrual cycle, days	29.70 ± 3.82	29.61 ± 3.75	.358
Intrauterine device use	29 (21.64)	25 (17.99)	.448
Oral contraceptive use	35 (26.12)	27 (19.42)	.187
Coffee	58 (43.28)	64 (46.04)	.647
Tea	75 (55.97)	90 (64.75)	.138
Drinking	14 (10.45)	17 (12.23)	.643
Cigarette smoking	16 (11.94)	7 (5.04)	.040
Secondhand smoking	53 (39.55)	34 (24.46)	.007

BMI = body mass index.

between these SNPs and endometriosis susceptibility in present study.

2. Materials and methods

2.1. Case and control population

This study was ratified by the ethic committee of Linyi central hospital. Every participator realized the aim of this study and signed the written informed consent. Cases and controls were matched with each other both in age and body mass index (BMI). Study process was followed the Declaration of Helsinki.

Endometriosis patients were diagnosed by 2 pathologists in Linyi central hospital. Magnetic resonance imaging, B-scan ultrasonography, and pathological examinations were used to diagnose the patients according to the ESHRE guidelines.[20] During the same period, healthy individuals who received the gynecologic examinations and without gynecologic disorders were recruited as the control group. Persons who had the histories of inflammatory disorders, systemic diseases, taking anti-inflammatory medicines at recent 3 months were excluded from this study. All the participants were old than 18 years and belong to Chinese Han population.

2.2. Genotyping method for COMT polymorphisms

After the 12 hours fasting, peripheral blood samples were collected from the antecubital vein of every participant. Blood samples were dealt with EDTA and centrifuged into serum and leukocytes. DNA extraction kit (Tiangen Biotech, Beijing) was used to extract the genomic DNA following the manufacture's instruction.

From 1000 genomes project, *COMT* gene rs4680, rs2020917, and rs4646312 SNPs were with the minor allele frequencies more than 0.1 in CHB population. According to previous studies, these SNPs were genotyped by polymerase chain reaction-restriction fragment length polymorphism method.[21,22]

2.3. Statistical analysis

All of the calculations were performed by the PASW 18.0. Statistical significance was existed when $P < .05$. Continuous variables were presented by mean ± SD. Genotype and allele frequencies were calculated by direct counting. χ^2 test was used to compare the differences of genotype and allele frequencies between case and control groups. Hardy–Weinberg equilibrium (HWE) test was utilized to assess the representativeness of the subjects. Relative risk of endometriosis was addressed by odds ratios (ORs) with 95% confidence intervals (CIs). Age, BMI, age of menarche, menstrual cycle, intrauterine device use, oral contraceptive use, coffee, tea, drinking, cigarette smoking, and secondhand smoking were used as the confounding factors to adjust the association strength via Logistic regression.

3. Results

3.1. Basic features of the subjects

Age, BMI, age of menarche, and menstrual cycle had no significant difference between case and control groups (Table 1, $P > .05$). Meanwhile, intrauterine device use, oral contraceptive use, cigarette smoking, and secondhand smoking were had higher frequencies in endometriosis patients than that in healthy controls. Coffee, tea, and drinking consumption were higher in controls than in cases. But only cigarette smoking and secondhand smoking had a statistically significant difference between these 2 groups (Table 1, $P < .05$).

3.2. Association between COMT polymorphisms and endometriosis susceptibility

Genotype distributions of *COMT* gene rs4680, rs2020917, and rs4646312 polymorphisms were accorded with the HWE test both in case and control groups (Table 2, $P > .05$). It suggested that the study subjects could represent the general population.

GA and AA genotypes of rs4680 SNP had higher frequencies in endometriosis patients than in healthy individuals, but the difference was not significant, indicating these 2 genotypes had no significant association with endometriosis susceptibility (Table 2, $P > .05$). Obviously higher frequency of rs4680 A allele has been discovered in case group ($P = .042$), demonstrated a positive association with the risk of endometriosis (OR = 1.450, 95% CI = 1.012–2.076). For rs2020917 SNP, CT and TT genotypes as well as the T allele were more frequently discovered in endometriosis patients, despite the difference was not significant (Table 2, $P > .05$). We failed to find any significant association between rs2020917 SNP and endometriosis susceptibility. No significant difference of rs4646312 genotypes has been observed between case and control groups ($P > .05$). Distinctly higher rs4646312 C allele in case group demonstrated that this allele was significantly associated with increased susceptibility of endometriosis ($P = .027$, OR = 1.502, 95% CI = 1.047–2.154).

Table 2

Association between *COMT* polymorphisms and endometriosis susceptibility.

Genotype/allele	Case n = 134 (%)	Control n = 139 (%)	*P*	OR (95%CI)	P^*	OR (95% CI) *
rs4680						
GG	55 (41.04)	71 (51.08)	—	—	—	—
GA	59 (44.03)	56 (40.29)	.235	1.360 (0.819–2.259)	.786	1.087 (0.594–1.991)
AA	20 (14.93)	12 (8.63)	.057	2.152 (0.969–4.777)	.066	2.218 (0.948–5.189)
G	169 (63.06)	198 (71.22)				
A	99 (36.94)	80 (27.78)	.042	1.450 (1.012–2.076)	.119	1.345 (0.926–1.954)
P_{HWE}	0.525	0.840				
rs2020917						
CC	54 (40.30)	69 (49.64)	—	—	—	—
CT	65 (48.51)	61 (43.88)	.225	1.362 (0.827–2.242)	.089	1.617 (0.929–2.815)
TT	15 (11.19)	9 (6.47)	.095	2.130 (0.866–5.237)	.038	2.894 (1.060–7.903)
C	173 (64.55)	199 (71.58)				
T	95 (35.45)	79 (28.42)	0.078	1.383 (0.964–1.985)	.039	1.481 (1.021–2.149)
P_{HWE}	0.488	0.354				
rs4646312						
TT	54 (40.30)	73 (52.52)	—	—	—	—
TC	61 (45.52)	54 (38.85)	.317	1.288 (0.784–2.117)	.115	1.611 (0.890–2.915)
CC	19 (14.18)	12 (8.63)	.143	1.806 (0.814–4.007)	.071	2.244 (0.933–5.399)
T	169 (63.06)	200 (71.94)	—	—	—	–
C	99 (36.94)	78 (28.06)	.027	1.502 (1.047–2.154)	.019	1.564 (1.078–2.269)
P_{HWE}	.791	.567				

95% CI = 95% confidence interval, *COMT* = catechol-O-methyltransferase, OR = odds ratio, P_{HWE} = *P* value for Hardy–Weinberg equilibrium test.
* adjusted by age, BMI, and environment expose factors.

3.3. Adjustment for the association

Association between *COMT* polymorphisms and endometriosis susceptibility was adjusted by confounding factors (Table 2). Afterward, we failed to find any significant association between rs4680 SNP and endometriosis risk both in genotypes and alleles ($P > .05$). Besides, TT genotype and T allele of rs2020917 SNP were distinctly correlated with the enhanced risk of endometriosis (TT vs CC: $P = .038$, OR = 2.894, 95% CI = 1.060–7.903; T vs C: $P = 0.039$, OR = 1.481, 95% CI = 1.021–2.149). Meanwhile, the positive association also has been discovered between rs4646312 C allele and endometriosis risk ($P = .019$, OR = 1.564, 95% CI = 1.078–2.269).

4. Discussion

In normal conditions, COMT play an important protective effect for the physiological process through reduce the toxicity of catechol estrogen.[14–16] Previous study found that A allele of rs4680 (Val158Met) SNP was distinctly decreased the enzyme activity of COMT, then lead to the accumulation of endogenous catechol estrogens.[23] Therefore, this SNP might be positively correlated with the risk of estrogen-dependent diseases. Although rs2020917 and rs4646312 SNPs which located in the intron regions of *COMT* gene were obviously correlated with other diseases.[22,24] Polymorphisms in intron region of the gene might moderate the expression of the gene and them participate in different disorders. *COMT* gene rs2020917 and rs4646312 SNPs might play potential role in endometriosis development. However, there was no previous study analyzed the association of them with the endometriosis susceptibility.

In present study, no significant association has been discovered between rs4680 genotypes and endometriosis. Meanwhile, we found a significant association between rs4680 A allele and 1.450 times increased risk of endometriosis. That was accorded with the meta-analysis performed by Tong et al.[19] They suggested that rs4680 was significantly correlated with increased susceptibility of endometriosis both in AA versus GG and A versus G genetic models. In addition, the positive association between them also has been discovered by Juo and colleagues in another Chinese Han population.[25] However, no significant association has been discovered between rs4680 and endometriosis in Australian and Brazilian populations.[26,27] These difference might be caused by the different sample size, ethnicity, or other factors.

TT genotype and T allele of rs2020917 SNP were slightly correlated with enhanced susceptibility of endometriosis. Meanwhile, we failed to find any significant association between rs4646312 genotypes and endometriosis risk. C allele of rs4646312 SNP had obviously higher frequency in endometriosis patients, suggested 1.502 times increased susceptibility for endometriosis. There was no previous study focused on the association of these 2 SNPs with endometriosis susceptibility.

Age, BMI, age of menarche, menstrual cycle, intrauterine device use, oral contraceptive use, coffee, tea, drinking, cigarette smoking, and secondhand smoking were used as confounding factors to adjust the association strength. Then the crude results were altered. Both the genotypes and alleles of rs4680 SNP had no significant association after the adjustment. TT genotype of rs2020917 SNP was significantly associated with 2.894 times increased risk of endometriosis. At the same time, approximately 1.481 times elevated endometriosis risk might be correlated with rs2020917 T allele. No significant correlation was discovered between rs4646312 genotypes and the susceptibility of endometriosis. *COMT* gene rs4646312 C allele was distinctly correlated with 1.564 times increased endometriosis risk. These adjustments might increase the reliablility of current results via included the confounding factors in the analysis.

In conclusion, *COMT* gene polymorphisms act as the risk factor for endometriosis occurrence. This result will help us to select the susceptible population for endometriosis. However, the limitations in this study should not be ignored. First of all, sample size was not large enough to obtain high statistical power. Second, polymorphisms distributions were different in various

regions and ethnicity, but only one ethnicity was analyzed in this study might limit the application rage of the results. Third, a variety of factors involve in the development of endometriosis; however, the interaction analysis between genetic and environmental factors was not detected in this research. Finally, functional analysis for the *COMT* gene polymorphisms and the causality between *COMT* polymorphisms and endometriosis risk were not ascertained in present study. Thus, well-designed studies with enlarged sample size and ethnicity numbers should be carried out in the future. In addition, the causality between *COMT* polymorphisms and endometriosis development should be probed both in vivo and in vitro in the future.

Author contributions

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