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Association of *CYP19* gene SNPs (rs7176005 and rs6493497) with polycystic ovary syndrome susceptibility in Northern Chinese women

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Abstract

Purpose The objective of this study was to elucidate the relationship between two single nucleotide polymorphisms (SNPs) rs7176005 and rs6493497 in *CYP19* gene and the risk of polycystic ovary syndrome (PCOS) in Northern Chinese women.

Methods In this case-control study, a total of 340 women with PCOS and 340 matched healthy controls were recruited. Polymerase chain reaction ligase detection reaction (PCR-LDR) method was used to investigate two SNPs (rs7176005 and rs6493497) in the 5′-flanking region of *CYP19* gene exon 1.

Results We observed a significant association of rs7176005 and rs6493497 with reduced risk of PCOS. Compared with CC genotype, a significant association of CT genotype ($p=0.019$), TT genotype ($p<0.001$) and combined CT+TT genotype ($p<0.001$) with reduced risk of PCOS was observed. The result of linkage disequilibrium analysis showed that these two SNPs are in complete linkage disequilibrium ($r^2=1$). For rs7176005 SNP, compared with CC genotype, CT, TT and CT+TT genotypes reduced the risk of PCOS. The age, BMI-adjusted *OR* were 0.650 (95% *CI* = 0.460–0.917), 0.158 (95% *CI* = 0.066–0.376) and 0.545(95% *CI* = 0.391–0.759), respectively.

Conclusions These findings highlight a significant association between *CYP19* gene polymorphisms and PCOS susceptibility, implying potential protective effects of T and A alleles. Of course, the major limitation of this study is the sample size of the case-control study. Larger cohort studies are needed to confirm these findings and investigate the underlying causes.

Keywords Polycystic ovary syndrome, *CYP19* gene, Single nucleotide polymorphism, Risk, Susceptibility

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Introduction

Polycystic ovary syndrome (PCOS) is a common metabolic disease of endocrine disorder caused by multiple factors in women, with an incidence of 5–10% in women of reproductive age [1–3]. Patients often have hyperandrogenemia and ovarian polycystic characteristics such as hirsutism, acne, obesity [4–6], as well as clinical manifestations such as oligomenorrhea or amenorrhea, infertility, insulin resistance and type 2 diabetes [7–9]. PCOS pathogenesis is complex and multifactorial, involving environmental and genetic factors [10]. Mutations, polymorphisms and differential regulation of genes may be the genetic pathogenesis of PCOS [11].

The *CYP19* gene is located at the 15q21.2 position on the long arm of the chromosome, which is composed of 10 promoters. The *CYP19* gene encodes cytochrome P450 aromatase, a key enzyme in the final step of steroidogenesis, which is a rate-limiting step [12–14]. This enzyme locates in the endoplasmic reticulum and is produced by ovarian granulosa cells. Aromatase converts androgens or C19 steroids (androstenedione and testosterone) produced by ovarian follicle cells into C18 estrogens (estrone and estradiol) [15–16]. Therefore, *CYP19* gene is believed to play an important role in the pathogenesis of PCOS through the production and metabolism of androgens and estrogens. Several studies have shown that the activity of aromatase in PCOS patients is decreased, affecting follicle development [17]. Several single nucleotide polymorphisms (SNPs) of the *CYP19* gene have been reported to be associated with changes in serum androgen concentrations in women, both within and between racial/ethnic groups [18–19]. These studies suggest that alterations in the regulation of this enzyme may be associated with PCOS. Therefore, it is necessary to explore whether the *CYP19* gene plays a critical role in the development of PCOS in Han women.

CYP19 gene contains many genetic variants, among which one SNP (rs2414096) has been the most extensively studied to find the association between gene variant rs2414096 and PCOS. Rs2414096 is an intronic variant located on intron 2, close to exon 3 [14, 20–21]. Therefore, it may not be directly affecting the protein sequence. Instead, aromatase activity is indirectly regulated by changing the conformational site for transcription factor or by changing estrogen levels. Many studies have found an association between this SNP and the risk of developing PCOS. Ma and colleagues identified 88 *CYP19* gene SNPs, including two that affect promoter 1.1, the main promoter in placental tissue that regulates *CYP19* gene expression [19]. Two SNPs (rs6493497 G/A and rs7176005 C/T) are located at 144 bp and 588 bp upstream of exon 1.1 splice site, respectively [22–23]. The polymorphisms of their bases may change the activity of P450 aromatase and lead to differences in gene expression, resulting in differences in individual susceptibility to PCOS. Reporter gene and EMSA analysis showed that the WT sequence at rs7176005 displayed greater DNA-protein binding than did the variant sequence, and showed different transcriptional activities compared with WT sequences. In this paper, we aimed to determine the effect of the *CYP19* gene rs7176005 and rs6493497 SNPs on PCOS risk in Northern Chinese women for the first time.

Materials and methods

Subjects

A convenience sample of 680 women from the Reproductive Medicine Center from June 2023 to June 2024 at the Fourth Hospital of Hebei Medical University was included in the present case–control study. Among them, 340 women diagnosed with PCOS, while the other 340 women were healthy controls.

At least two of the following three criteria were met to be diagnosed with PCOS [24]: (1) Oligomenorrhea or amenorrhea; (2) Clinical manifestations and/or biochemical indicators showed excess androgen, and (3) Polycystic changes in the ovaries (the number of ovary follicles is greater than or equal to 12 and the diameter of the follicles is 2–9 mm, or the volume of the ovary is greater than or equal to 10 ml). Patients should also rule out other reproductive symptoms similar to PCOS, such as Cushing syndrome, hyperprolactinemia, congenital adrenal hyperplasia, thyroid disease and androgen-secreting tumors. Patients who had received hormonal drugs within 3 months were also excluded.

A total of 340 people who participated in physical examination in the Fourth Hospital of Hebei Medical University were randomly selected as the control subjects of this study. All healthy controls had no signs of menstrual dysfunction and a history of at least one successful pregnancy, androgen levels were within normal range, no symptoms of hirsutism, no family history of diabetes, and no polycystic changes in the ovaries found on transvaginal ultrasound.

DNA extraction

Two tubes of venous blood (5 ml each) were collected from fasting individuals on the 2nd to 5th day of menstruation. One of the tubes was treated with sodium citrate and stored in a refrigerator at 4℃. Within a week of blood collection, genomic DNA was extracted by means of protease K (Merck, Darmstadt, Germany) digestion and salting out procedure. And the other was for biochemical analysis. Measurement with a chemiluminescence analyzer (Beckman Kurt, USA) was done for the following hormones: serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2)

and total testosterone (T). The E2/T ratio was used as an index of the aromatase activity.

Genotyping

The genotype of the SNP rs6493497 and rs7176005 were performed by the Shanghai Generay Biotech Co., Ltd. (http://www.generay.com.cn) using the polymerase chain reaction (PCR)/ ligase detection reaction (LDR) method. After the PCR/LDR, the products were analyzed using an ABI 3730 XL DNA sequencer (Applied Biosystems). In order to verify the reliability and accuracy of the genotyping results, 10% of all genotypes on each SNP were randomly selected for sequencing verification.

Statistical analyses

Statistical analyses were carried out by using the SPSS software version 20.0 (SPSS Company, Chicago, Illinois, USA), and $P<0.05$ was considered statistically significant. To compare the observed and expected genotype frequencies in the controls, Hardy Weinberg equilibrium (HWE) analysis was performed by using the χ^2 test. T-test was used to analyze the differences in age, clinical and biochemical features between control and case groups. Data are expressed as means ± SD. The difference of genotype frequency distribution between the control group and the case group was compared with the row-by-list chi-square test. The odds ratio (OR) and 95% confidence interval (CI) adjusted for age and BMI were calculated by unconditional logistic regression method.

Result

Patients characteristics

The clinical characteristics of women with PCOS and the control group are shown in Table 1.

The average age of the healthy controls and PCOS patients was 26.58 ± 3.40 years and 26.40 ± 2.39 years, respectively. The age difference between PCOS patients and healthy controls was not statistically significant ($P=0.426$). There was statistically significant difference in body mass index (BMI) between PCOS patients and healthy controls ($P<0.001$).

The serum concentration of luteinizing hormone, follicle-stimulating hormone, total testosterone, as well as the LH/FSH ratio, the E2/T ratio were statistically significant between healthy controls and PCOS patients ($P<0.05$). There was no significant difference in serum estradiol level between healthy controls and PCOS patients ($P=0.228$).

Table 1 Clinical characteristics of patients with PCOS and healthy controls

Items	Controls(340)	PCOS(340)	t	*P* Value
Age, years	26.58 ± 3.40	26.40 ± 2.39	0.797	0.426
BMI, kg/m^2	22.64 ± 1.48	24.15 ± 2.50	-9.632	< 0.001
LH, mIU/mL	8.47 ± 1.34	10.57 ± 1.46	-19.566	< 0.001
FSH, mIU/mL	5.89 ± 0.95	6.09 ± 0.71	-3.156	0.002
LH/FSH	1.48 ± 0.35	1.76 ± 0.33	-10.671	< 0.001
E2,pg/mL	51.33 ± 8.98	52.32 ± 12.25	-1.207	0.228
T, ng/mL	0.39 ± 0.13	0.53 ± 0.17	-12.036	< 0.001
E2/T	0.15 ± 0.05	0.11 ± 0.03	12.912	< 0.001

BMI, body mass index; LH, luteinizing hormone; FSH, follicle stimulating hormone; LH/FSH, luteinizing hormone/ follicle stimulating hormone ratio; E2, estradiol; T, testosterone; E2/T, estradiol/ testosterone ratio

Association between the CYP19 gene rs7176005 polymorphism and the risk of PCOS

All 340 controls and 340 cases were successfully genotyped by using PCR/LDR method, and the sequencing results of random samples were consistent with the original typing results. The genotype distribution of rs7176005 C/T SNP genotype was consistent with Hardy-Weinberg equilibrium in healthy controls ($\chi^2=1.786$, $P=0.181$). The result of linkage disequilibrium analysis showed that these two SNPs are in complete linkage disequilibrium ($r^2=1$).

We observed a significant association of rs7176005 and rs6493497 with reduced risk of PCOS. Compared with CC genotype, a significant association of CT genotype ($p=0.019$), TT genotype ($p<0.001$) and combined CT + TT genotype ($p<0.001$) with reduced risk of PCOS was observed (Table 2).

The frequencies of C allele and T allele in the controls were 71.3%, 28.7% and 81.8%, 18.2% in the cases, respectively. There was a significant difference in the allele distribution of the rs7176005 polymorphism between the two groups ($p<0.001$) (Table 2).

The women carrying the T allele may have a lower risk of PCOS compared with the women with the C allele ($OR=0.555$, 95%$CI=0.429–0.716$). Genotype frequencies of CC, CT and TT in the controls were 52.4%, 37.9%, 9.7% and 65.6%, 32.4%, 2.0% in the cases, respectively. There was a significant difference in the genotype distribution of this polymorphism between the two groups ($P=0.014$ and $p<0.001$, respectively) (Table 2). Compared with CC genotype, CT, TT and CT + TT genotypes reduced the risk of PCOS. The age, BMI-adjusted *OR* were 0.650 (95% $CI=0.460–0.917$), 0.158 (95% $CI=0.066–0.376$) and 0.545 (95% $CI=0.391–0.759$), respectively.

Discussion

In the present study, we demonstrated an association between the rs7176005 and rs6493497 polymorphisms in the *CYP19* gene and the risk of PCOS development in the Northern Chinese women. The result of linkage disequilibrium analysis showed that these two SNPs are in complete linkage disequilibrium. The result revealed that the T allele is a protective factor for PCOS in women. The women carrying the T allele may have a lower risk

Table 2 Correlation of *CYP19* gene rs7176005 C/T SNP and rs6493497 G/A SNP to susceptibility of PCOS

Locus	Genotype	Control (*n* = 340)	PCOS (*n* = 340)	*P*[a]	OR(95%CI)[b]	*P*[c]	adjusted OR(95%CI)[d]
rs7176005							
	CC	178(52.4)	223(65.6)				
	CT	129(37.9)	110(32.4)	0.019	0.681(0.493–0.939)	0.014	0.650(0.460–0.917)
	TT	33(9.7)	7(2.0)	0.000	0.169(0.073–0.392)	0.000	0.158(0.066–0.376)
	CT + TT	162(47.6)	117(34.4)	0.000	0.576(0.423–0.785)	0.000	0.545(0.391–0.759)
	C allele	485(71.3)	556(81.8)				
	T allele	195(28.7)	124(18.2)	0.000	0.555(0.429–0.716)		
rs6493497							
	GG	178(52.4)	223(65.6)				
	GA	129(37.9)	110(32.4)	0.019	0.681(0.493–0.939)	0.014	0.650(0.460–0.917)
	AA	33(9.7)	7(2.0)	0.000	0.169(0.073–0.392)	0.000	0.158(0.066–0.376)
	GA + AA	162(47.6)	117(34.4)	0.000	0.576(0.423–0.785)	0.000	0.545(0.391–0.759)
	G allele	485(71.3)	556(81.8)				
	A allele	195(28.7)	124(18.2)	0.000	0.555(0.429–0.716)		

p-Value < 0.05 is considered as significant

OR,odds ratio; *CI*,confidence interval

a, Two-sided χ^2 test; b, Unconditional logistic regression models; c, Two-sidedχ^2 test with the adjustment for age, BMI; d, Unconditional logistic regression models with the adjustment for age, BMI

of PCOS compared with the women with the C allele. In other words, compared with CC genotype, CT, TT, and CT + TT genotypes reduced the risk of PCOS. The age, BMI-adjusted *OR* were0.650 (95% *CI* = 0.460–0.917), 0.158 (95% *CI* = 0.066–0.376) and 0.545 (95% *CI* = 0.391–0.759), respectively. To the best of our knowledge, this is the first molecular study to reveal the association between the rs7176005 and rs6493497 polymorphisms and PCOS susceptibility in Northern Chinese women.

CYP19 gene is located on the long arm of chromosome at 15q21.2 position, which encodes the aromatase that played an important role in androgen metabolism [25–26]. Aromatase is able to convert androgens or C19 steroids (androstenedione and testosterone) produced by ovarian follicle cells into C18 estrogens (estrone and estradiol) [27]. So estradiol/testosterone is an important indicator of aromatase activity [28]. Decreased aromatase activity may lead to ovarian hyperandrogenemia and polycystic ovary syndrome. Some studies have shown that when mutations in cytochrome P450 aromatase genes affect their normal activity, the incidence of PCOS is significantly increased. SNP is one of the most common genetic variants in human [22]. It plays an important role in the study of disease gene localization. And it is still one of the main means to search for candidate genes related to the pathogenesis of PCOS [23]. SNPS may affect the binding of genes to transcription factors, promoter activity as well as gene transcription, so different SNPs may have different effects on gene expression, which in turn affect protein expression [29]. Several studies have reported the relationship between *CYP19* gene polymorphism and polycystic ovary syndrome, which focused on the following two polymorphisms [30–31]. The SNP of *CYP19* gene rs2414096, which was located in an intronic region, was significantly associated with decreased aromatase activity, increased estradiol/testosterone ratio (E2/T), hyperandrogen phenotype. It was significantly associated with the occurrence of PCOS in Africa, the United States, China [32], Iran [12], India [33], the Caucasus [34], Iraq [35], and Egypt [15], but was not statistically significant in Japanese [34] and Karnataka [36] patients. In addition, a tetranucleotide repeat polymorphism (TTTA)n of the *CYP19* gene with short alleles inhibit aromatase activity [37–38], resulting in a higher LH/FSH ratio was reported in women with PCOS in hyperandrogenism and its association with elevated testosterone levels. Therefore, different studies have shown that aromatase has a significant correlation in hyperandrogenism and androgen biosynthesis suggested that *CYP19* gene plays a key role as a candidate gene in the development of PCOS.

The two SNPs, one located at 144 bp (rs6493497) and the other located at 588 bp (rs7176005) 5'-upstream of exon 1.1, were in complete linkage disequilibrium. The beginning of transcription is a key stage of gene expression. The structure of gene promoter can affect its affinity with RNA polymerase, thus directly affecting the expression level of related genes. Reporter gene and EMSA analysis of these two closely related SNPs showed that the two SNPs exhibited different DNA protein binding patterns in WT and variant sequences, especially rs7176005. The analysis also showed different transcriptional activities compared with WT sequences [39]. These functional studies provided additional evidence that these SNPs may lead to increased aromatase transcription and thus improved aromatase activity. Based on

the above findings, we designed a case-control study to explore whether these two SNPs located on the *CYP19* gene exon 1 promoter sequence were associated with the risk of PCOS in northern Chinese women. In this study, we demonstrated an association between *CYP19* gene rs7176005 and rs6493497 polymorphisms and the risk of PCOS in northern Chinese women. The result suggested that T and A alleles were protective factors for development of PCOS. Women who carried the T and A alleles had a lower risk of PCOS than those who carried the C and G alleles. By analyzing the reasons, it seems the T allele of rs7176005 and the A allele of rs6493497 of *CYP19* gene may lead to the increase of aromatase transcription, then improve the activity of aromatase, and may promote the conversion process of androgen to estrogen. Thus women who carried the T and A alleles had a lower risk of PCOS.

The frequency of rs7176005 (T) was found in the present study with an incidence of 28.7% which was basically consistent with those reported for the Chinese Han ethnic population [40] and the Korean population [41], by contrast, it was higher in the Tamil population [42] and the South Indian population [43]. All these indicate that differences in genetic background (including ethnic and environmental factors) of the study population may lead to different results, suggesting that we should pay attention to the regional and racial differences of the study population in SNP site-related studies, in order to obtain more reliable and representative results.

Of course, this study also encounters some limitations. The first limitation of this study could be the lower sample size. It only comprised of 340 healthy controls and 340 PCOS patients in all. In further studies, a larger sample set needs to be analyzed to confirm our result. The population homogeneity is another limitation. Both the case group and the healthy control group were Chinese Han population, which ensured the consistency of the genetic background of the study population, but could not highlight the potential impact of ethnic. Multi-ethnic populations should be included in further studies. The lack of data on environmental or lifestyle factors is considered as the third limitation of this study. This prevents our results from highlighting the potential impact of environmental factors. In future studies, we should collect data on lifestyle factors and add them to our analysis.

In conclusion, this study found a strong link between *CYP19* gene polymorphisms and PCOS susceptibility in Northern Chinese women. The protective role of the T and A alleles emphasizes the importance of *CYP19* in PCOS pathogenesis. More research with bigger, multi-ethnic populations and functional validation is needed to validate these relationships and investigate underlying processes.

Abbreviations

SNPs	Single nucleotide polymorphisms
PCOS	Polycystic ovary syndrome
PCR-LDR	Polymerase chain reaction ligase detection reaction

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Not applicable.

Author contributions
Ya-li Hao, Chun-miao Liu and Xi Huang designed and coordinated this study. Ya-li Hao, Chun-miao Liu and Xi Huang performed the experiments and collected and analyzed the data. Ya-li Hao, Chun-miao Liu, Na Wang, Rong-miao Zhou, Ya-nan Wei, Xiao-shuang Bai and Xi Huang wrote, checked and edited the manuscript. Xi Huang provided the funds. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Our study was approved by the Institutional Ethics Committee of the Fourth Hospital of Hebei Medical University, and informed consent was obtained from all enrolled participants before the study was conducted. The study was conducted in accordance with the Declaration of Helsinki.

Human ethics and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Skiba MA, Islam RM, Bell RJ, et al. Understanding variation in prevalence estimates of polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2018;24(6):694–709.
2. Ramezani Tehrani F, Behboudi-Gandevani S, Bidhendi Yarandi R, et al. Prevalence of acne vulgaris among women with polycystic ovary syndrome: a systemic review and meta-analysis. Gynecol Endocrinol. 2021;37(5):392–405.
3. Ma XY, Wang Z, Zhang CM, et al. Association of SNPs in the FK–506 binding protein (FKBP5) gene among Han Chinese women with polycystic ovary syndrome. BMC Med Genomics. 2022;15(1):149.
4. Albaghdadi AJH, Kan FWK. Therapeutic potentials of low-dose tacrolimus for aberrant endometrial features in polycystic ovary syndrome. Int J Mol Sci. 2021;22(6):2872.
5. Zhang FF, Zhang Q, Wang YL, et al. Intergenerational influences between maternal polycystic ovary syndrome and offspring: an updated overview. J Pediatr. 2021;232:272–81.
6. Bi KX, Chen MR, Zhao QR, et al. The shared genetic landscape of polycystic ovary syndrome and breast cancer: convergence on ER + breast cancer but not ER- breast cancer. Breast Cancer Res. 2024;26(1):161.
7. Rojas J, Chavez M, Olivar L, et al. Polycystic ovary syndrome, insulin resistance, and obesity: navigating the pathophysiologic labyrinth. Int J Reprod Med. 2014;1(1):719050.
8. Zou Y, Zhu FF, Fang CY, et al. Identification of potential biomarkers for urine metabolomics of polycystic ovary syndrome based on gas chromatography-mass spectrometry. Chin Med J. 2018;131(8):945–9.

9. Martinez GD, Vidal CS, Palacios I, et al. Effectiveness of probiotics, prebiotics, and synbiotics in managing insulin resistance and hormonal imbalance in women with polycystic ovary syndrome (PCOS): A systematic review of randomized clinical trials. Nutrients. 2024;16(22):3916.
10. Sadeghi HM, Adeli I, Calina D, et al. Polycystic ovary syndrome: A comprehensive review of pathogenesis, management, and drug repurposing. Int J Mol Sci. 2022;23(2):583.
11. Wekker V, van Dammen L, Koning A, et al. Long-term cardiometabolic disease risk in women with PCOS: a systematic review and meta-analysis. Hum Reprod Update. 2020;26:942–60.
12. Mehdizadeh A, Kalantar SM, Sheikhha MH, et al. Association of SNP rs2414096 CYP19 gene with polycystic ovarian syndrome in Iranian women. IJRM. 2017;15:491–6.
13. Chaube R, Sharma S, Joy K. Kisspeptin modulation of nonapeptide and cytochrome P450 aromatase mRNA expression in the brain and ovary of the catfish Heteropneustes fossilis: in vivo and in vitro studies. Fish Physiol Biochem. 2023;49(6):1489–509.
14. Reddy KR, Deepika MLN, Latha KP, et al. Polycystic ovary syndrome: role of aromatase gene variants in South Indian women. Int J Pharm Bio Sci. 2015;6(2):1283–96.
15. Mostafa RA, Al-Sherbeeny MM, Abdelazim IA, et al. Relation between aromatase gene CYP19 variation and hyperandrogenism in polycystic ovary syndrome Egyptian women. J Infertil Reprod Biol. 2016;4:1–5.
16. Chen J, Shen S, Tan Y, et al. The correlation of aromatase activity and obesity in women with or without polycystic ovary syndrome. J Ovarian Res. 2015;8:11.
17. Sowers M, Wilson A, Kardia S, et al. Aromatase gene (CYP 19) polymorphisms and endogenous androgen concentrations in a multiracial/multiethnic, multisite study of women at midlife. Am J Med. 2006;119:23–30.
18. Akhtar M, Wright JN, Lee-Robichaud P. A review of mechanistic studies on aromatase (CYP19) and 17α-hydroxylase-17, 20-lyase (CYP17). J Steroid Biochem Mol Biol. 2011;125:2–12.
19. Ghosh D. Aromatase and steroid sulfatase from human placenta. Methods Enzymol. 2023;689:67–86.
20. Petry CJ, Ong KK, Michelmore KF, et al. Association of aromatase (CYP 19) gene variation with features of hyperandrogenism in two populations of young women. Hum Reprod. 2005;20:1837–43.
21. Maier PS, Spritzer PM. Aromatase gene polymorphism does not influence clinical phenotype and response to oral contraceptive pills in polycystic ovary syndrome women. Gynecol Obstet Invest. 2012;74:136–42.
22. Bulun SE, Sebastian S, Takayama K, et al. The human CYP19 (aromatase P450) gene: update on physiologic roles and genomic organization of promoters. J Steroid Biochem Mol Biol. 2003;86(3–5):219–24.
23. Sebastian S, Bulun SE. A highly complex organization of the regulatory region of the human CYP19 (aromatase) gene revealed by the human genome project. J Clin Endocrinol Metab. 2001;86(10):4600–2.
24. Revised. 2003 consensus. On diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004; 81(1):19–25.
25. Bharathi RV, Swetha S, Neerajaa J, et al. An epidemiological survey: effect of predisposing factors for PCOS in Indian urban and rural population. Middle East Fertil Soc J. 2017;22:313–6.
26. Kaur R, Kaur T, Kaur A. Genetic association study from North India to analyze association of CYP19A1 and CYP17A1 with polycystic ovary syndrome. J Assist Reprod Genet. 2018;35:1123–9.
27. Sowers MR, Wilson AL, Kardia SR, et al. Aromatase gene (CYP19) polymorphisms and endogenous androgen concentrations in a multiracial/multiethnic, multisite study of women at midlife. Am J Med. 2006;119:23–30.
28. Huang X, Wu B, Chen M, et al. Depletion of Exosomal circldlr in follicle fluid derepresses miR-1294 function and inhibits estradiol production via CYP19A1 in polycystic ovary syndrome [J]. Aging. 2020;12(15):15414–35.
29. Wang L, Ellsworth KA, Moon I, et al. Functional genetic polymorphisms in the aromatase gene CYP19 vary the response of breast cancer patients to neoadjuvant therapy with aromatase inhibitors. Cancer Res. 2010;70(1):319–28.
30. Chaudhary H, Patel J, Jain NK, et al. The role of polymorphism in various potential genes on polycystic ovary syndrome susceptibility and pathogenesis. J Ovarian Res. 2021;14(1):125.
31. Castillo-Higuera T, Alarcón-Granados MC, Marin-Suarez J, et al. A comprehensive overview of common polymorphic variants in genes related to polycystic ovary syndrome. REPROD SCI. 2021;28(9):2399–412.
32. Jin JL, Sun J, Ge HJ, et al. Association between CYP19 gene SNP rs2414096 polymorphism and polycystic ovary syndrome in Chinese women. BMC Med Genet. 2009;10:139–43.
33. Ashraf S, Rasool SUA, Nabi M, et al. Impact of rs2414096 polymorphism of CYP19 gene on susceptibility of polycystic ovary syndrome and hyperandrogenism in Kashmiri women [J]. Sci Rep. 2021;11(1):12942.
34. Sowers MR, Wilson AL, Kardia SR, et al. Aromatase gene (CYP 19) polymorphisms and endogenous androgen concentrations in a multiracial/multiethnic, multisite study of women at midlife. Am J Med. 2006;119(9):S23–30.
35. Al-Salihi AR, Hamdan FB, Mutib MT. Effect of CYP19 gene on polycystic ovary syndrome phenotype in Iraqi women. Iraqi J Med Sci. 2015;13(3):272–8.
36. Hegde P, Shetty SS, Shetty PK, et al. Delineating the role of single-nucleotide polymorphism of CYP19 gene on aromatase activity in South Indian women with polycystic ovary syndrome. J Genet Eng Biotechnol. 2023;21(1):87.
37. Leandros Lazaros N, Xita E, Hatzi, et al. CYP19 gene variants affect the assisted reproduction outcome of women with polycystic ovary syndrome. Gynecol Endocrinol. 2013;29(5):478–82.
38. Xu P, Zhang XL, Xie GB, et al. The (TTTA)n polymorphism in intron 4 of CYP19 and the polycystic ovary syndrome risk in a Chinese population. Mol Biol Rep. 2013;40(8):5041–7.
39. Wang L, Ellsworth KA, Moon I, et al. Functional genetic polymorphisms in the aromatase gene CYP19 vary the response of breast cancer patients to neoadjuvant therapy with aromatase inhibitors. CABCER RES. 2010;70(1):319–28.
40. Rui WL, Sheng YY, Hu RM, et al. Association of single nucleotide polymorphisms in the CYP19A1 gene with female pattern hair loss in a Chinese population. Dermatology. 2015;231(3):239–44.
41. LEE SJ, Kim WY, Choi JY, et al. Identification of CYP19A1 single-nucleotide polymorphisms and their haplotype distributions in a Korean population. J Hum Genet. 2010;55(3):189–93.
42. Umamaheswaran G, Kadambari D, Kumar AS, et al. Polymorphic genetic variations of cytochrome P450 19A1 and T-cell leukemia 1A genes in the Tamil population. Volume 39. ENVIRON TOXICOL PHAR; 2015. pp. 102–13. 1.
43. Umamaheswaran G, Dkhar SA, Kalaivani S, et al. Haplotype structures and functional polymorphic variants of the drug target enzyme aromatase (CYP19A1) in South Indian population. MED ONCOL. 2013;30(3):665.

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