

REVIEW

CYP17 T/C (rs74357) gene polymorphism contributes to polycystic ovary syndrome susceptibility: evidence from a meta-analysis

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Abstract

The cytochrome P450 family 17 (CYP17) is associated with hyperandrogenism in women, and the association between CYP17 gene polymorphism and the risk of polycystic ovary syndrome (PCOS) is not definitive. In order to determine whether the CYP17 T/C (rs74357) gene polymorphism is an exposure risk for PCOS, a comprehensive meta-analysis summarizing 19 studies was performed. The pooled odds ratio (OR) and the corresponding 95% CI were measured under five genetic models, and the stratified analyses by ethnicity, Hardy–Weinberg equilibrium, testosterone levels and BMI in controls were carried out to identify the causes of substantial heterogeneity. The overall results validated that the CYP17 T/C (rs74357) gene polymorphism was significantly associated with PCOS risk in four genetic models. Moreover, the outcomes of subgroup analysis by ethnicity indicated that the frequencies of the C allele of CYP17 T/C (rs74357) polymorphism were markedly higher in women from Asia than in Caucasians (T vs C: OR 0.85, 95% CI = 0.74–0.99, $P < 0.05$). Therefore, these findings suggested that the CYP17 T/C (rs74357) gene polymorphism played an indispensable part in increasing the susceptibility of PCOS when carrying the C allele, which proposed that the polymorphism of the CYP17 gene may be a predictive factor for the risk of PCOS or an important pathway in PCOS-associated metabolic and hormonal dysregulation.

Key Words

- ▶ meta-analysis
- ▶ polycystic ovary syndrome
- ▶ gene polymorphism
- ▶ CYP17

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Introduction

Polycystic ovary syndrome (PCOS), characterized by oligo-ovulation, hyperandrogenism and polycystic ovarian morphology (1), is a heterogeneous endocrine metabolic disorder among which 3–10% of women in reproductive age had been affected (2). Hyperandrogenism is regarded as the common characteristic of PCOS, accompanied by luteinizing hormone (LH) hypersecretion, follicle-stimulating hormone (FSH) (3) reduction and insulin resistance (IR). To date, the pathophysiology of hyperandrogenism in PCOS has not been defined even though enormous researches had been performed in this field, which is included as a key point in the diagnostic program. Genetic and environmental factors were recommended by researchers as important contributions to our understanding of PCOS pathogenesis (4).

It is well known that increased androgen was primarily secreted from theca cells in PCOS (5, 6, 7). A number of studies have reported that the level of androgen in PCOS was augmented with which compared normal women by isolation and cultivation of theca cells (8, 9). The excess biosynthesis of androgen in PCOS was attributed to the enhanced expression of steroid-17- α -hydroxylase/17,20 lyase (CYP17A1 gene) in theca cells (10).

The cytochrome P450 family 17 (CYP17), which encodes the activity of enzyme 17- α -hydroxylase and 17,20 lyase, is characterized as the crucial enzymes on the pathway of androgen biosynthesis (11). In humans, it is coded by CYP17A1 (CYP17 subfamily A member 1) gene which is located at chromosome 10q24.32 (12). The

expression of CYP17 could be mainly discovered in the adrenal gland, Leydig cells and theca cells (13). Thus far, a great deal of interest has been shown in single nucleotide polymorphisms (SNPs) in CYP17 gene, a substitution of thymine (T) with cytosine (C) at the 34th bp upstream from the translation initiation point in the promoter region of CYP17 (rs 743572) (14), which hypothesized that additional Sp-1 transcription-binding site was produced and genotyped. Subsequently, the expression of CYP17 was enhanced (15).

More than 100 candidate genes about PCOS associated with metabolism, hormones and inflammation have been explored in numerous researches (16). Genetic trend was identified as the primary etiology, and genome-wide association study (GWAS) widely used in PCOS facilitated us to recognize the pathogenesis in PCOS. The GWAS conducted by Chen on Han Chinese populations had determined the candidate gene loci: DENND1A, RAB5B, INSR, FSHR, LHCGR, YAP1, C9orf3, HMG2, SUMO1P1, SUOX, TOX3 and THADA (17, 18). Afterward, three new risk variants (near PLGRKT, ZBTB16 and MAPRE1) related to PCOS on European women were demonstrated by Day *et al.* in 2018 (19). Polymorphisms of CYP17 T/C gene have been proved to result in increased synthesis of androgen and a higher risk of the development of several diseases, such as breast cancer (20), prostate cancer (21) and endometriosis (22) *et al.*, which was genotyped in the different studies. Taking into account the disorders of androgen metabolism, CYP17 SNPs have been explained to be involved in various pathophysiological diseases.

The genes related to hyperandrogenism such as CYP11A1, CYP17A, CYP19, HSD17B5 and HSD17B6 are considered to be potential candidate genes of PCOS. The polymorphism of CYP17 gene had a connection to the risk of PCOS which was discovered in quite a few studies (20, 22, 23). However, as we know that data from GWAS researches in PCOS on CYP17 polymorphism have not been reported yet and that the current study could be a contribution to the scientific literature. Therefore, our present study was designed to characterize better the association between the CYP17 T/C gene polymorphism and the susceptibility of PCOS.

Materials and methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (24). As this was a meta-analysis, ethical approval was not required.

Search strategy

All the available literatures were identified from the following electronic databases: PubMed, Embase, Web of Science, Scopus, Cochrane, and Google Scholar, WanFang Database (Chinese Ministry of Science & Technology), the Chinese National Knowledge Infrastructure Databases and Chinese Biomedical Database. Studies were searched using the search strategy shown in Fig. 1, from their inception date to November 16, 2020, without restriction on language. The following keywords and combinations were applied: 'polycystic ovary syndrome or PCOS', 'cytochrome p450-c17 α -hydroxylase or CYP17', 'gene polymorphism'. Besides, the references of the literature were manually screened to identify additional eligible studies.

Study selection

Eligible studies were involved if they met the following criteria: (i) the study used case-control design; (ii) the correlation between CYP17 T/C gene polymorphism and PCOS was explored in the study; (iii) raw genotype data for each study could be collected; (iv) the diagnosis of PCOS was based on the NICHD standard or the Rotterdam ESHRE/ASRM standard (25).

Studies were excluded from this review if insufficient data (e.g. allele was incomplete) or duplicate data were reported. Studies without a control group were also excluded. When more than one paper was investigated on the same research group, studies without the most recent publication date or the most extensive sample were excluded.

Data extraction

The literature was screened by two reviewers (Mei Xu and Min Qian), and the data were extracted from all eligible articles separately. Discrepancies were resolved by consensus and arbitration with a third author (Xingyan Liu) if necessary. The following data were collected from included studies: general characteristics (first author, publication year, ethnicity and country), study groups (sample sizes, genotyping method and frequencies of different genotype) and outcome measurement data (serum testosterone levels in total and different genotype, BMI). Furthermore, the Hardy-Weinberg equilibrium (HWE) test was also calculated manually. The characteristics of studies are summarized in Table 1.

Quality assessment

The overall quality of identified articles was evaluated by two reviewers separately (Xingyan Liu and Lindong Yang) in

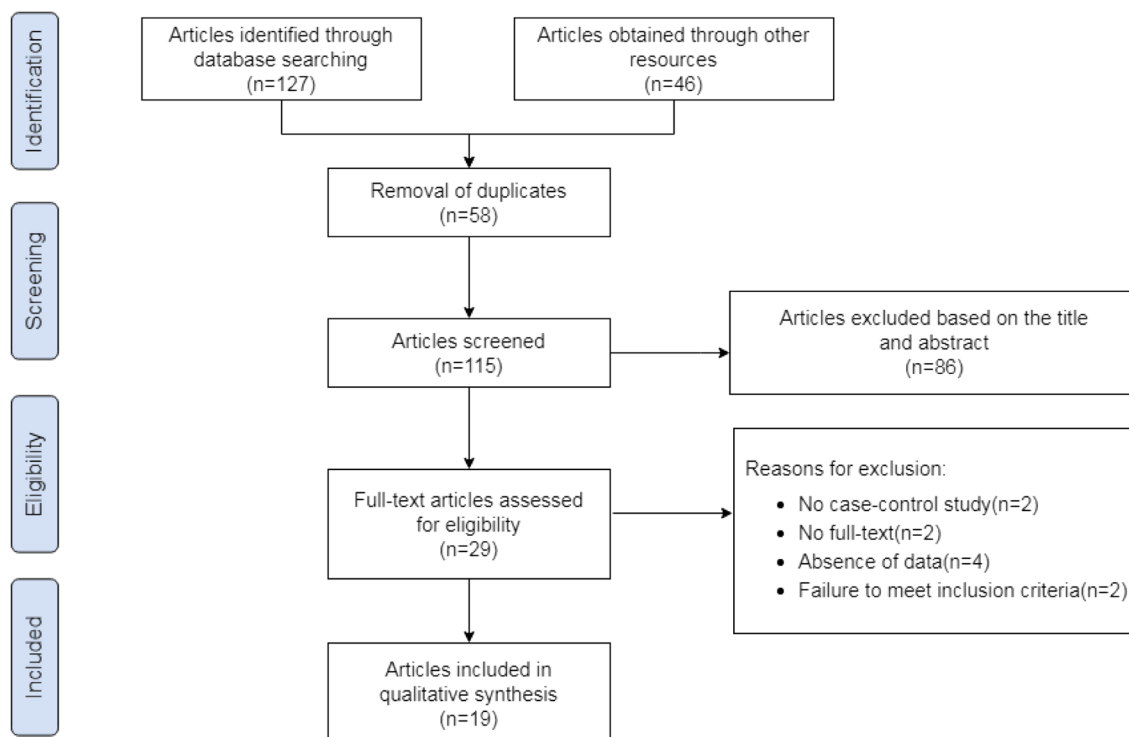


Figure 1
Flowchart for selection of studies.

accordance with the Newcastle Ottawa Quality Assessment Scale (NOS) for case–control studies, in which a star system was used to allow a semi-quantitative assessment for study quality. The NOS was ranged from zero (the worst) to nine stars (the best) in terms of studies’ quality.

Statistical analysis

First of all, HWE was calculated by the chi-square test in the genotype frequencies of controls, from which a *P* value <0.05 was considered as significant departure. Then the pooled odds ratio (OR) and the corresponding 95% CI were measured to assess the strength of association between CYP17 T/C gene polymorphism and PCOS risk under four genetic models: the allele model (T vs C), the co-dominant model (TT vs CC, TC vs CC, TT vs TC), the dominant model (TT vs TC+CC) and the recessive model (CC vs TC+TT). The significance of ORs was estimated by the Z-test and *P*-value. *P* < 0.05 was considered to be indicative of statistically significant. Besides, both the Cochran’s Q test and the *I*² statistic, which expressed the proportion of variation in this review, were assessed for heterogeneity across studies. A *P*-value <0.1 from the Q-test and *I*² > 50% indicated the presence of significant heterogeneity among researches, which the

random-effects model was allowed to apply. Otherwise, the fixed-effects model was appropriate. In order to identify the causes of substantial heterogeneity, the stratified analyses by ethnicity, HWE in controls, BMI and testosterone levels were carried out. In addition, sensitivity analyses in which excluded one study at a time were undertaken to assess the stability of the pooled effect. Begg’s funnel plot and Egger’s test were examined to assess the potential publication bias statistically. All analyses were generated by using STATA 15 (StataCorp, College Station, TX, USA).

Results

Description of literature

A total of 115 articles were obtained from the original search after the exclusion of duplicates. The examination of the title and abstract performed on these articles led to the removal of 86 studies and 29 continued to detailed assessment. After screening the full text of these publications, 10 articles were excluded for not meeting the inclusion criteria. Ultimately, 19 eligible case–control studies (23, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43) were included in this review in Fig. 1.

Table 1 Characteristics of studies included in the meta-analysis.

Author (year)	Country	Ethnicity	Case number	Control number	Genotype distribution						Genotype methods	P for HWE
					PCOS			Control				
					TT	TC	CC	TT	TC	CC		
Cao (1999)	China	Asian	56	30	17	17	22	8	14	8	PCR-RFLP	0.72
Diamanti-Kandarakis (1999)	Greece	Caucasian	50	50	17	29	4	22	28	0	PCR-RFLP	0.01
Marszalek(2001)	Poland	Caucasian	55	56	17	27	11	20	29	7	PCR-RFLP	0.48
KahsarMiller (2004)	America	Caucasian	259	161	79	142	38	50	94	17	PCR-RFLP	0.01
Tan (2005)	China	Asian	118	106	12	66	40	21	55	30	PCR-RFLP	0.64
Luo (2007)	China	Asian	74	27	6	29	39	5	14	8	PCR-RFLP	0.80
Ding (2007)	China	Asian	329	275	55	145	129	30	151	94	PCR-RFLP	0.01
Park (2008)	Korea	Asian	133	99	40	61	32	25	41	33	Taqman	0.10
Li (2008)	China	Asian	61	45	11	32	18	14	18	13	PCR-RFLP	0.18
Echiburú (2008)	Chile	Caucasian	159	93	59	81	19	43	36	14	PCR-RFLP	0.17
Pusalkar (2009)	India	Asian	100	100	44	42	14	62	30	8	PCR-SSCP	0.13
Unsal (2009)	Turkey	Caucasian	44	50	15	19	10	20	24	6	PCR-RFLP	0.77
Liu (2011)	China	Asian	55	50	19	23	13	17	22	11	PCR-RFLP	0.45
Zhao (2011)	China	Asian	177	159	18	100	59	32	81	46	PCR-RFLP	0.74
Li (2015)	China	Asian	318	306	158	139	21	137	141	28	PCR-RFLP	0.33
Banerjee (2016)	India	Asian	75	73	20	33	22	18	35	20	PCR-RFLP	0.73
Wu (2017)	China	Asian	260	237	90	109	61	81	104	52	PCR-RFLP	0.09
Kaur (2018)	India	Asian	250	250	107	118	25	146	94	10	PCR-RFLP	0.28
Ashraf (2020)	India	Asian	394	306	115	209	70	108	156	42	PCR-RFLP	0.23

HWE, Hardy-Weinberg equilibrium in controls; PCOS, polycystic ovary syndrome; RFLP, restriction fragment length polymorphism.

A total of 2967 PCOS patients diagnosed by the Rotterdam or NIH criteria and 2473 non-PCOS participants were involved in our analysis. Fourteen articles were conducted in Asian populations (China, Korea and India), while five articles were carried out in Caucasian populations (Turkey, Chile, Poland, the United States and Greece). Characteristics of included studies are presented in [Table 1](#).

Quality of included reviews

The NOS employed for case-control studies to evaluate the quality of reviews ranged from 2 to 9 stars, which corresponded to low scores of 7 and high scores of 8–9. The NOS quality scores were shown in Supplementary Table 1 (see section on [supplementary materials](#) given at the end of this article).

Quantitative analysis

For the overall analysis, our meta-analysis revealed significant association between the CYP17 T/C gene polymorphism and the susceptibility of PCOS in four genetic models: the allele model: (T vs C) ([Fig. 2A](#)) OR=0.86, 95% CI=0.76–0.97; the dominant model (TC+CC vs TT) ([Fig. 2F](#)): OR=1.24, 95% CI=1.02–1.62); the recessive model (TC+TT vs CC) ([Fig. 2E](#)): OR=0.81, 95% CI=0.69–0.96; the co-dominant model: (TT vs CC) ([Fig. 2B](#)): OR=0.72, 95% CI=0.56, 0.94; (TC vs CC) ([Fig. 2D](#)): OR=0.84, 95% CI=0.72–0.99. Stratified analysis was conducted to determine the sources of heterogeneity, which showed that neither ethnicity nor HWE contributed to the observed heterogeneity (Supplementary Figure 1). Nevertheless, the outcome of subgroup analysis by ethnicity indicated that the frequencies of CC genotype and the C allele of the CYP17 T/C polymorphism were markedly higher in women from Asia than in Caucasians (T vs C: OR 0.85, 95% CI=0.74–0.99; TC vs CC: OR 0.85, 95% CI=0.73–1.00; TC+TT vs CC: OR 0.83, 95% CI=0.69–0.99), while no significant connections were discovered in the Caucasian population under all genetic models in [Table 2](#). Additionally, the effect of the CYP17 polymorphism on testosterone levels was also analyzed, shown in [Table 3](#). There was a statistically significant difference in PCOS co-dominant model (TC vs CC: SMD=−0.21, 95% CI=−0.34, −0.07), whereas no difference was observed in the others of PCOS. In contrast, significant differences were existed among various genotypes and BMI, which indicated that the risk of CYP17 genotype in PCOS was robustly associated with BMI.

Publication bias and sensitivity analyses

Two models were discovered publication bias on the skewed funnel plot (TC+TT vs CC: Begg's test $P=0.025$, Egger's test $P=0.108$; TT vs CC: Egger's test $P=0.041$, Begg's test $P=0.069$) ([Table 3](#)). Studies reporting a positive association in the recessive model (TC+TT vs CC) seem to be over-represented, while smaller studies reporting negative association may be lost in the published papers. However, no significant result in the homozygous model (TT vs CC: OR=0.72, 95% CI=0.56, 0.94) indicated that TT homozygote had no connection with PCOS risk compared with the CC homozygote, suggesting the assumption was indefinite. Begg's funnel plots were negative for publication bias ($P > 0.05$), which was near to symmetry demonstrating no evidence of publication bias under the other models ([Fig. 3E](#) and [F](#)). Neither was in Egger's bias test. (TT vs TC: Begg's test $P=0.726$, Egger's test $P=0.547$; T vs C: Begg's test $P=0.294$, Egger's test $P=0.353$; TC+CC vs TT: Begg's test $P=0.363$, Egger's test $P=0.332$) ([Table 2](#)). The sensitivity analysis suggested that no significant influence was yielded on the overall results, which implied the effect of individual study on the overall analysis estimate was stable (Supplementary Figures 2, 3 and 4).

Discussion

Principal findings of the study

Altogether, the higher frequencies of the CC genotype were strongly correlated with women in PCOS than controls, which indicated that the CC genotype and the C allele of the CYP17 T/C (rs74357) gene polymorphism increase PCOS susceptibility. Likewise, the significant correlation of CYP17 polymorphism with BMI, especially in the CC genotype, suggested that the CYP17 T/C (rs74357) polymorphism may be influenced by obesity. Furthermore, the pooled OR in the study by ethnicity indicated that the apparently enhanced frequencies of the CC genotype and C allele occurred only in Asians but not in Caucasians. However, no significant relationship could be discovered among stratified analyses by HWE and testosterone levels. The overall results suggest that not only the gene polymorphism of CYP17 but also obesity could be potential factors to the pathogenesis of PCOS.

PCOS is considered a heterogeneous endocrine syndrome with various genetic, metabolic and environmental abnormalities. Inheritable tendencies have been identified as pathogenesis of PCOS by performed multiple studies during the past two decades. With the

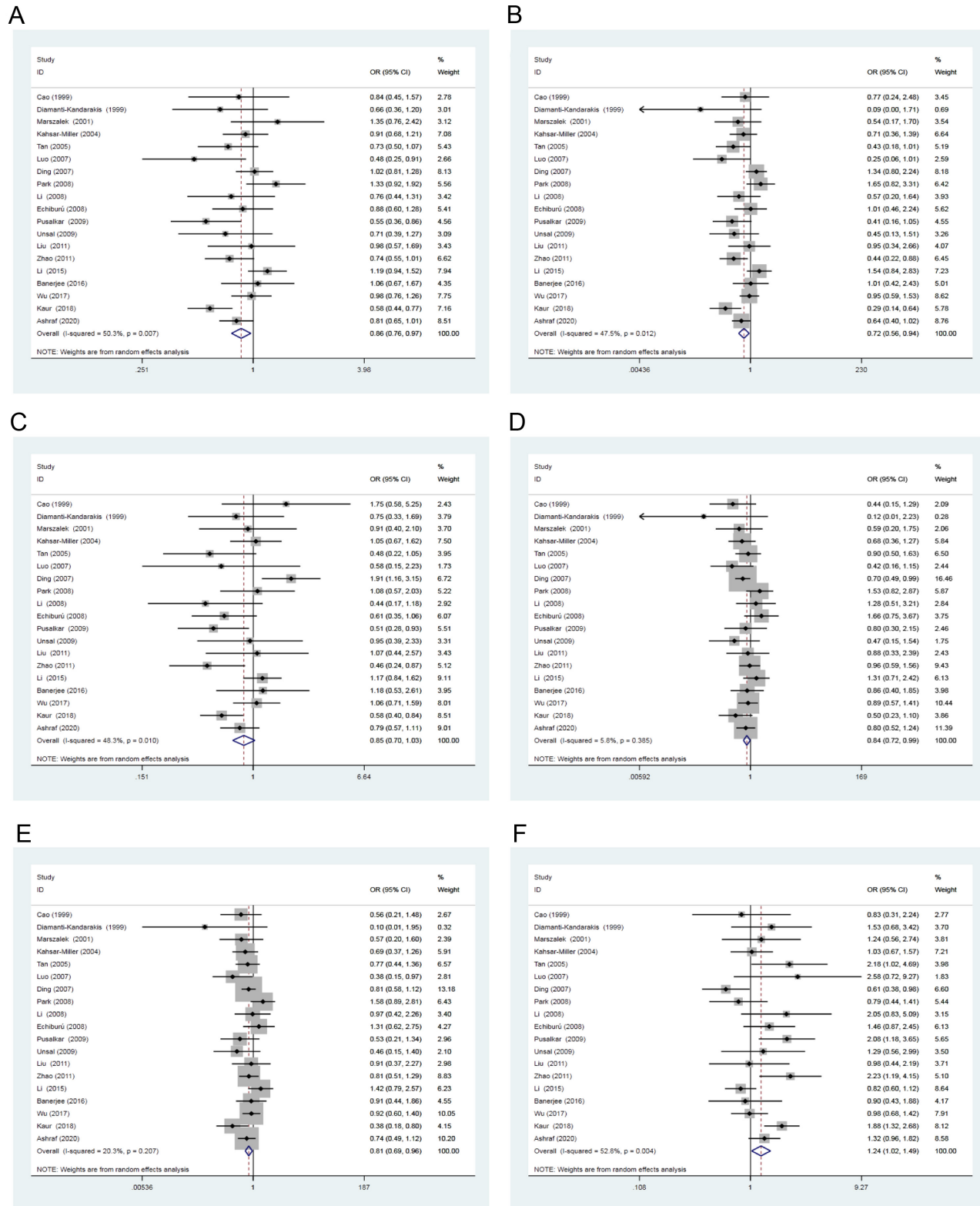


Figure 2 Forest plots of ORs with 95% CIs for the association between CYP17 T/C polymorphism and PCOS. (A) The allele model (T vs C). (B, C and D) the co-dominant model (TT vs CC, TT vs TC, TC vs CC), (E) the recessive model (TT + TC vs CC) and (F) the dominant model (TC + CC vs TT).

Table 2 Meta-analysis of the CYP 17 gene polymorphism on PCOS risk.

Variables	Total	Ethnicity		HWE in controls		Publication bias	
		Asian	Caucasian	Yes	No	Egger's test	Begg's test
Number	19	14	5	16	3		
Allele model (T vs C)							
OR (95% CI)	0.86 (0.76, 0.97)	0.85 (0.74, 0.99)	0.89 (0.73, 1.07)	0.85 (0.74, 0.98)	0.94 (0.79, 1.12)		
P-value	0.014 ^a	0.033 ^a	0.21	0.025 ^a	0.487	0.353	0.294
Co-dominant model							
TT vs CC							
OR (95% CI)	0.72 (0.56, 0.94)	0.74 (0.54, 1.00)	0.68 (0.44, 1.05)	0.70 (0.53, 0.92)	0.85 (0.56, 0.94)		
P-value	0.32	0.053	0.085	0.01 ^a	0.691	0.041 ^a	0.069
TT vs TC							
OR (95% CI)	0.85 (0.70, 1.03)	0.85 (0.67, 1.09)	0.85 (0.64, 1.13)	0.79 (0.65, 0.95)	1.21 (0.73, 2.01)		
P-value	0.098	0.198	0.268	0.015 ^a	0.467	0.547	0.726
TC vs CC							
OR (95% CI)	0.84 (0.72, 0.99)	0.85 (0.73, 1.00)	0.75 (0.42, 1.32)	0.90 (0.76, 1.07)	0.68 (0.50, 0.92)		
P-value	0.034 ^a	0.049 ^a	0.314	0.237	0.013 ^a	0.329	0.142
Recessive model (TC + TT vs CC)							
OR (95% CI)	0.81 (0.69, 0.96)	0.83 (0.69, 0.99)	0.72 (0.45, 1.15)	0.82 (0.68, 1.00)	0.76 (0.57, 1.02)		
P-value	0.014 ^a	0.04 ^a	0.165	0.053	0.068	0.108	0.025 ^a
Dominant model (TC + CC vs TT)							
OR (95% CI)	1.24 (1.02, 1.62)	1.23 (0.97, 1.58)	1.23 (0.94, 1.62)	1.31 (1.07, 1.60)	0.92 (0.57, 1.48)		
P-value	0.029 ^a	0.093	0.127	0.008 ^a	0.733	0.332	0.363

^aSignificant; $P < 0.05$ = significant; $P > 0.05$ = non-significant.

HWE, Hardy-Weinberg equilibrium; OR, odds ratio.

advance of technologies in genotype, more than 100 PCOS-susceptible genes have been validated and several of these have determined a significant relationship with PCOS (44). However, the limitation of these researches was a lack of large sample size and conducted on different populations. While a breakthrough was made through numerous explorations, the above problems could be eliminated perfectly by GWAS which provides a benefit for uncovering the associations between genetic variations and diseases.

It represented a significant milestone for PCOS genetics that candidate loci on Han Chinese populations were recognized: DENND1A, RAB5B, INSR, FSHR, LHCGR, YAP1, C9orf3, HMG2, SUMO1P1, SUOX, TOX3 and THADA (18). McAllister discovered DENND1A.V2, a splice variant of PCOS candidate locus, enhanced CYP17A1 and CYP11A1 gene expression in theca cells and induced the cells to synthesize more androgen (45). Meanwhile, the transcriptional activation of CYP17A1 and CYP11A1 in

Table 3 The association of CYP 17 polymorphism with PCOS according to testosterone and BMI.

	Testosterone		BMI	
PCOS				
Co-dominant model				
TT vs CC	-0.16 (-0.71, 0.39)	0.57	-0.83 (-1.07, -0.58)	<0.0001 ^a
TT vs TC	-0.21 (-0.34, -0.07)	0.002 ^a	-0.19 (-0.36, -0.03)	0.02 ^a
TC vs CC	-0.01 (-0.14, 0.12)	0.88	-0.61 (-0.84, -0.38)	<0.0001 ^a
Recessive model				
TC + TT vs CC	-0.04 (-0.46, 0.39)	0.87	-0.72 (-0.93, -0.50)	<0.0001 ^a
Dominant model				
TC + CC vs TT	0.14 (-0.13, 0.40)	0.32	0.33 (0.18, 0.49)	<0.0001 ^a
PCOS vs control				
Total	1.73 (1.15, 2.31)	<0.0001 ^a	0.58 (0.42, 0.73)	<0.0001 ^a
TT	0.87 (0.35, 1.38)	0.0004 ^a	-1.37 (-1.67, -1.07)	<0.0001 ^a
TC	1.09 (0.95, 1.23)	<0.0001 ^a	-0.81 (-1.06, -0.55)	<0.0001 ^a
CC	1.03 (0.13, 1.94)	0.003 ^a	-0.32 (-0.66, 0.02)	0.06
Total	1.73 (1.15, 2.31)	<0.0001 ^a	0.58 (0.42, 0.73)	<0.0001 ^a

^aSignificant; $P < 0.05$ = significant; $P > 0.05$ = non-significant.

SMD, Std. mean difference.

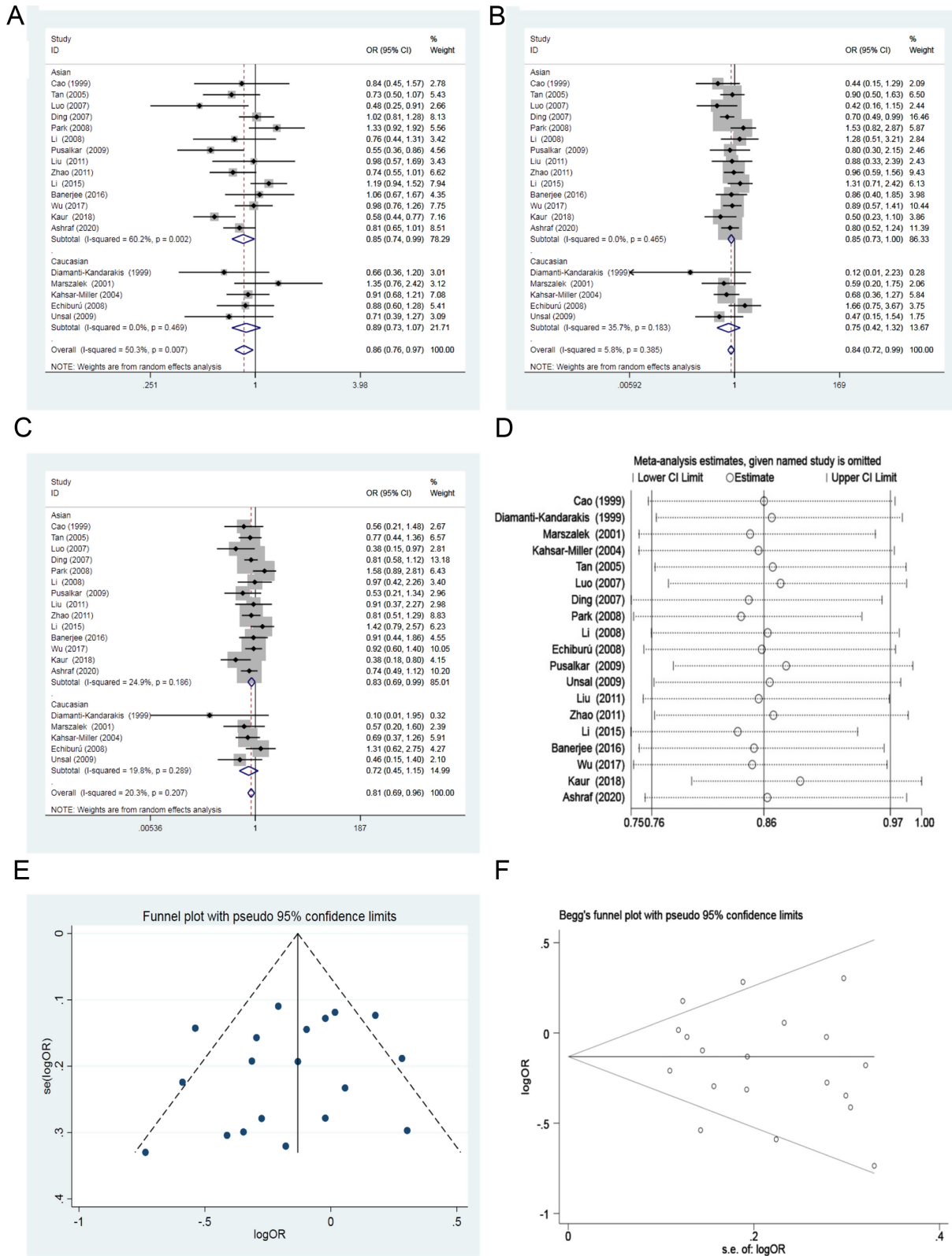


Figure 3

Statistical analysis for CYP17 T/C polymorphism and risk for PCOS. (A) Subgroup analysis in the allele model (T vs C). (B) Subgroup analysis in the co-dominant model (TC vs CC). (C) Subgroup analysis in the recessive model (TT + TC vs CC). (D) Sensitivity analysis in the allele model (T vs C). (E and F) Funnel plot and Begg's funnel plot with pseudo 95% confidence limits for publication bias test in the allele model (T vs C).

the signaling pathway of DENND1A.V2 was facilitated by RAB5B, another PCOS candidate locus. All of these investigations suggested that CYP17A1 was contained in a steroidogenic signaling cascade and resulted in augmented androgen production. Although researches about the function of CYP17 on PCOS from GWAS have not been conducted, polymorphisms of CYP17 T/C gene have been proved to result in a higher risk of breast cancer (20), prostate cancer (21) and endometriosis (22).

To the best of our knowledge, CYP17 encodes the enzyme 17- α -hydroxylase/17,20 lyase (P45017 α), which is a rate-limiting enzyme in androgen synthesis. Diamanti-Kandarakis (27) was the first to propose that CYP17 T/C gene polymorphism could be responsible for the dysregulation of gene CYP17 expression, which aggravated hyperandrogenemia of PCOS, which was later supported by Pusalkar (39), who described a strong association of CYP17 T/C gene polymorphism with PCOS. In the current study, more frequencies of the polymorphic C allele and CC genotype were discovered in women with PCOS than in controls, which supported the hypothesis that the significance of the association was found to be more significant compared with controls. Contradictory observations, however, were made in previous studies (23, 27, 30) where the authors failed to observe any difference in genotype and allele frequencies of the CYP17 T/C gene polymorphism between PCOS and controls.

Consistent with some but not all former studies, stratified analyses by ethnicity were conducted. Our findings demonstrated that the C allele of the CYP17 T/C gene polymorphism was markedly augmented in women from Asia for PCOS according to the allele, recessive, dominant and co-dominant models. This finding is analogous with the study done by Park (38) showing higher expression in the recessive model of CYP17 genotype among PCOS compared with control subjects in a Korean population. However, null associations were observed in Caucasians by Marszalek (37), Echiburú (27) and Ushasi Banerjee (28). Consequently, whether the significant relationship existed in Caucasian women could not be assessed owing to the small number of women in this category, which remains unknown and needs further examination.

CYP17 T/C polymorphism has been respectively discovered to associate with hyperandrogenism and IR in Caucasian women (27, 33). Chen had identified insulin receptor (INSR), a strong PCOS candidate locus, played a crucial role in PCOS etiology via IR and metabolic syndrome-related pathways in Chinese women (17). However, no significant correlation was detected between CYP17T/C polymorphism and IR in Thai PCOS women

(46). Thus, it is conceivable that mutations in the INSR gene, like DENND1A gene, possibly converge to upregulate CYP17 expression and androgen biosynthesis through downstream signaling cascades associated with insulin metabolism. Besides, theca cells from PCOS women overexpressed steroidogenic enzymes, particularly CYP17 gene, which explained the steroidogenic disorder of functional ovarian hyperandrogenism in PCOS women (4). Yan Lu considered that the significant role of CYP17 played in glucose metabolic disturbance was mediated by the co-gonadotrophic effects of insulin (47). Consistent with the recent research outcome, the increased BMI associated with CC genotype in our finding provides speculation that CYP17 may affect obesity through a metabolic disorder-related pathway.

Up to now, quantities of researches on the correlation between CYP17 T/C gene polymorphism and PCOS risk have been carried out. In the previous meta-analysis conducted by Li (48), no connection was discovered between the CYP17 T/C gene polymorphism and PCOS risk in ten case-control studies and some subgroup analyses (by ethnicity and country). Considering the tiny sample size, the discrepancy between the previous analysis and our systemic review was understandable.

Strengths and limitations

The primary strength of this meta-analysis is the comprehensive search strategy. So far, no preliminary analysis on this issue, which included a larger number of studies in our database than those of previous studies investigating the role of CYP17 T/C gene polymorphism in PCOS, has been as excellent or comprehensive. Moreover, the systematic quality assessment in accordance with the NOS for the quality of study which guaranteed the accuracy and dependability of the conclusions demonstrated that the overall study quality was reasonable. In addition, the sensitivity analysis which was performed to discover influential studies is crucial because these influential studies could lead to reverse results.

However, this review is not without limitations. First, although participants were geographically diverse, more than half of them were categorized as Asian. As shown in the stratified analysis by ethnicity, only five articles were included in the Caucasian population. The meta-analysis conclusions might be attenuated on account of the inadequate sample sizes. Therefore, further studies are warranted to ascertain whether significant connections exist in Caucasians. Secondly, statistically significant heterogeneity was found in the majority of models except

for the recessive model. Unfortunately, conceivable reasons for heterogeneity, such as ethnicity, country, year, HWE in controls, and genotyping methods, could not explain the source of any significant difference by meta-analysis, and we speculated that the discrepancy was caused by gray literature and/or unavailable studies. Thirdly, there was a potential publication bias in the recessive model (TC+TT vs CC) and the co-dominant model (TT vs CC) due to unpublished articles while such a bias could not be assessed in the other models as only studies in English or Chinese included. Last but not least since some of the included women showed the presence of Rotterdam criteria I and III, they were diagnosed with PCOS with normal androgen. However, these people were not categorized into the subgroup to discuss the influence of normal androgen levels. So the hypothesis that PCOS women with normal androgens would be affected by the CYP17 polymorphism could not be confirmed, which provides new directions for future research.

Conclusion

Excess activity of this CYP17 enzyme has been presumed to contribute to increased androgen biosynthesis and secretion in PCOS (49). We hypothesized that CYP17 T/C gene polymorphism was causally correlated with PCOS and the subsequent change of metabolic disorder in PCOS, which indicates the CYP17 T/C gene polymorphism may be potential pharmaceutical targets in fertility treatment and gynecology. In that case, a CYP17 antagonist would be recommended for the prevention of PCOS, as well as for improving symptoms of hyperandrogenemia. The current findings suggest that gene polymorphisms influence the expression and production of CYP17, and the CYP17 T/C (rs74357) gene polymorphism plays an essential role in increasing the susceptibility of PCOS when carrying the C allele. Close attention should be paid to the diversity of ethnicity because evidence of a relationship in Caucasians was lacking. Despite the convincing connection of CYP17 gene polymorphism to PCOS, the extent to which CYP17 gene polymorphism contributes to metabolic dysfunction in PCOS is unidentified and requires further investigation.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-21-0327>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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