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ORIGINAL ARTICLE

Associations of adiponectin gene polymorphisms with polycystic ovary syndrome: a meta-analysis

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Abstract Adiponectin gene polymorphisms have been implicated in polycystic ovary syndrome (PCOS) development. However, results from previous studies were inconsistent and inconclusive. To shed some light on the relationship of two adiponectin gene polymorphisms, T45G and G276T, with PCOS, we conducted the current meta-analysis. PubMed was used for searching all eligible studies up to September 30, 2011. Odds ratio (OR) with the corresponding 95% confidence interval (CI) was adopted to evaluate the strength of the associations. In total, ten case–control studies involving 2,821 participants were included in the meta-analysis. Results showed that the T45G polymorphism was not associated with PCOS for allelic contrast (OR = 1.10, 95%CI: 0.83–1.44, $P = 0.514$), with evidence of large heterogeneity ($P_{\text{heterogeneity}} = 0.002$). Concerning G276T polymorphism, the results showed that the T allele was related to a reduced risk of PCOS compared with the G allele under allelic genetic model (OR = 0.81, 95%CI: 0.70–0.93, $P = 0.003$), and no significant heterogeneity ($P_{\text{heterogeneity}} = 0.268$) was revealed. Similar results were observed under additive, dominant and recessive genetic models for both of these two polymorphisms. No publication bias was detected. Our results suggested that the T45G polymorphism of adiponectin gene was not significantly associated with PCOS, while the G276T polymorphism was related to a decreased risk of PCOS.

Keywords Adiponectin · Polycystic ovary syndrome · Polymorphisms · Meta-analysis

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine/metabolic disorder which affects 5–10% of women of fertile age. It is considered to be the most common reason for anovulatory infertility [1]. Besides the principal features of hyperandrogenism, chronic anovulation and polycystic ovary (PCO), PCOS is frequently associated with components of metabolic syndrome such as insulin resistance, obesity, and type 2 diabetes (T2D) [2, 3]. Although the pathogenesis of PCOS is still unknown, previous studies suggested that interaction between multiple genetic and environmental factors contribute to the development of PCOS [4–6]. Therefore, identification of susceptibility genes may not only improve our understanding of the etiology of PCOS, but also perfect the current prevention and therapy strategies.

Adiponectin is a multifunctional adipocytokine that is secreted mainly by white adipose tissue and plays a pivotal role in modulating insulin sensitivity and energy metabolism [7]. It has been reported that serum adiponectin levels were decreased in patients with T2D, obesity, and insulin

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resistance [8, 9]. Furthermore, molecular epidemiologic studies suggested that variants in adiponectin gene were implicated in the etiopathogenesis of the above-mentioned disorders [10, 11]. Considering the metabolic features of PCOS, it is reasonable to hypothesize that adiponectin is a potential functional candidate for PCOS.

The adiponectin gene is encoded by *ADIPOQ* (adipocyte C1q and collagen domain containing), also named as adipose most abundant gene transcript1 (*apM1*) and adipocyte C1q and collagen domain-containing (*ACDC*). The gene is located at chromosome 3q27, including 3 exons and 2 introns. Recently, multiple polymorphisms of adiponectin gene have been identified [12]. Among them, two polymorphisms T45G (rs2241766) with a T>G transition in exon 2 and G276T (rs1501299) with a G>T transition in intron 2 attracted the most attention. These two single-nucleotide polymorphisms (SNPs) were suggested to be associated with altered serum concentration of adiponectin [13]. Until recently, a number of studies have investigated the associations between these two polymorphisms and PCOS risk. However, results of these studies were conflicting rather than conclusive. The lack of consistency among these studies might be due to small sample size, ethnic difference, diversity of selection criteria for both cases and controls, and other limitations in study design. To shed some light on the relationship between these two polymorphisms and PCOS, we performed the current meta-analysis.

Methods

Search strategy

We performed an exhaustive search from PubMed up to September 30, 2011 for all eligible publications on the association between adiponectin polymorphisms and polycystic ovary syndrome. Search terms were used as follows: "adiponectin or *ADIPOQ* or *apM1* or *ACDC*", and "PCOS", and "polymorphisms or polymorphism". We also manually searched all reference lists of the relevant articles for additional papers. Language was limited to English.

All eligible studies met with the following criteria: 1) was case–control design investigating the associations of adiponectin gene polymorphisms, T45G and/or G276T, with PCOS; 2) provided genotype distribution information both in cases and controls, or provided odds ratio (OR) with 95% confidence interval (95%CI) (or sufficient data that allowed us to calculate these). For overlapping data, the most complete or recent study was included. Cases were confined to PCOS patients with at least two of three criteria of hyperandrogenism, polycystic ovaries and oligo-, or anovulation defined according to the NIH and the ESHRE/ASRM Rotterdam consensus criteria [14, 15]. Controls were subjects without PCOS. No sample size limitation was applied.

Data extraction

Two authors (Hongxia Jia and Lili Yu) independently extracted and tabulated the relevant information by using a pre-defined data extraction sheet. Consensus was reached on all items. For each selected study, we extracted the following data: first author's name, publication year, ethnicity and country of the study population, selection criteria and general clinical characteristics (age, body mass index (BMI), matching information, etc.) of cases and controls, genotyping methods, genotype and allele distribution information, and number of cases and controls.

Quality score assessment

The same two reviewers independently assessed the quality of individual studies based on the predefined scale for quality assessment (Table 1), which was modified according to the scoring systems by Sun [16] and Thakkinstian et al. [17]. Briefly, the scores were based on both traditional and genetic epidemiological considerations. Total scores ranged from 0 to 15, with the higher the better. Discrepancies were settled by discussion and re-evaluating the same items together.

Statistical analysis

Pooled OR with 95%CI was used to evaluate the strength of the associations of adiponectin gene polymorphisms with PCOS. When zero events occurred, we treated this problem by adding 0.5 to all the 2×2 cells of the contingency table to calculate the study-specific OR just as implemented in Stata software [18]. Primarily, we examined the association of T45G polymorphism with PCOS for allelic contrast (G vs. T). Secondly, we adopted another three genotypic contrasts: additive genetic model (GG vs. TT), dominant genetic model (GG + TG vs. TT) and recessive genetic model (GG vs. TG + TT). The same genetic comparison pattern was also applied to analyze G276T polymorphism. Furthermore, we conducted subgroup analyses by stratifying ethnicity into Caucasians and East Asians separately. A Z test was used to determine the significance of the pooled OR, and P value < 0.05 was considered significant. Hardy–Weinberg equilibrium (HWE) in controls of all included studies was tested with exact test using an online HWE calculator (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) and significant cutoff was set at 0.05. Studies with controls not in HWE were subjected to sensitivity analyses (i.e. re-performed the meta-analysis by

Table 1 Criteria for quality assessment

Criteria	Scores
Representativeness of cases	
Consecutive/randomly selected from case population with clearly defined sampling frame.	2
Consecutive/randomly selected from case population without clearly defined sampling frame or with extensive inclusion/exclusion criteria.	1
No method of selection described.	0
Representativeness of controls	
Controls were consecutive/randomly drawn from the same sampling frame (ward/community) as cases.	3
Controls were consecutive/randomly drawn from health examination population or healthy volunteers.	2
Controls were consecutive/randomly drawn from patients without PCOS history.	1
Not described.	0
Ascertainment of cases	
Clearly described objective criteria for diagnosis of cases.	2
Diagnosis of cases by patient self-report or by patient history.	1
Not described.	0
Ascertainment of controls	
Controls were tested to screen out PCOSs.	2
Controls were subjects who did not report PCOSs or no objective testing.	1
Not described.	0
Genotyping examination	
Genotyping done with equal ways in cases and control under "blinded" condition and in replicates.	2
Genotyping done with equal ways in cases and control under "blinded" condition or in replicates.	1
Not mentioned.	0
Hardy–Weinberg equilibrium	
Hardy–Weinberg equilibrium in control group.	2
Hardy–Weinberg disequilibrium in control group.	1
No checking for Hardy–Weinberg equilibrium.	0
Association assessment	
Assess association between genotypes and PCOSs with appropriate statistics and adjustment for confounders	2
Assess association between genotypes and PCOSs with appropriate statistics without adjustment for confounders.	1
Inappropriate statistics used.	0

excluding studies with controls not in HWE) as suggested by Zintzaras and Lau [19].

Heterogeneity among studies was assessed with a Chi-square based Q statistic test, and a $P < 0.10$ was taken as evidence of potential heterogeneity. A random effects model was used if there was significant heterogeneity among studies. Otherwise, a fixed effects model was adopted. To evaluate the influence of individual studies on the overall association, sensitivity analysis was also conducted by omitting one study at a time and re-analyzing the association for the remaining studies. Publication bias was accessed by the Egger's regression test. P value < 0.10 was considered as evidence of possible publication bias. All the statistical analyses were performed using Stata 11.0 software (Stata Corporation, College Station, TX, USA). All P values were two-sided.

Results

Data summary

The primary literature search yielded 15 papers. After further scrutiny, 13 potential relevant papers were identified. Of these papers, three papers were excluded for the following reasons: one paper investigated other polymorphism, one paper was not case–control design, one paper might include overlapping data with another study, and the recent one was selected [20]. One study that adopted the JSOG 2007 (the Japan Society of Obstetrics and Gynecology) criteria simultaneously met with the ESHRE/ASRM Rotterdam consensus criteria and was considered eligible to be included in our meta-analysis [21]. Finally, a total of ten papers were eventually included in our meta-analysis [20–29]. The general characteristics of the selected studies are shown in Table 2. All the included studies consistently fulfilled the NIH criteria and/or the ESHRE/ASRM Rotterdam consensus criteria. Controls were predominantly healthy subjects with regular menstrual cycles and without signs of hyperandrogenism. These ten papers all evaluated the association of T45G polymorphism with PCOS, while only seven of them were about G276T association [20, 21, 24, 25, 27–29]. Three studies were conducted in East Asian populations [21, 25, 29], and the others were in Caucasians. The sample size of individual studies ranged from 116 to 595. Quality scores were from 7 to 13. Genotype distribution in controls was conformed to HWE in all studies, except for three studies concerning T45G and one study concerning G276T [21, 23, 25]. Polymerase chain reaction-restriction fragment-length polymorphism (PCR–RFLP), SNaPshot, Taqman and direct sequencing were adopted as genotyping methods. Among all the studies, only one study mentioned quality control to validate the genotyping result [27].

Association of the T45G polymorphism with PCOS

A total of ten studies concerning the T45G polymorphism included 2, 821 individuals (1,104 cases and 1,717 controls). The pooled frequency of G allele was 17 and 15% for cases and controls, respectively. For cases, the prevalence of the TT, TG, and GG genotypes was 70, 26 and 4%,

Table 2 General characteristics of the selected studies in the meta-analysis

Author (reference)	Year	Country	Ethnicity	PCOS	Control	SNPs	Cases			Controls			P_{HWE} controls	Quality scores
							GG	GT	TT	GG	GT	TT		
Zhang et al. [29]	2008	China	East Asian	ESHRE/ASRM	Non-PCOS subjects	T45G	9	54	57	4	42	74	0.78	7
						G276T	56	46	18	41	50	29	0.10	
Li et al. [25]	2011	Korea	East Asian	ESHRE/ASRM	No HA, PCO or oligo-, amenorrhea	T45G	6	59	79	3	84	72	0.00007	10
						G276T	61	73	10	48	87	24	0.15	
Yoshihara et al. [21]	2009	Japan	East Asian	ESHRE/ASRM	No HA, PCO or oligo-, anovulation	T45G	5	23	31	15	29	53	0.007	9
						G276T	34	17	8	58	24	15	0.00026	
Ranjzad et al. [27]	2011	Iran	Caucasian	NIH	Normal menstrual cycles, no CHA	T45G	3	34	144	6	54	121	1.00	13
						G276T	92	77	12	91	79	11	0.35	
Escobar-Morreale et al. [20]	2006	Spain	Caucasian	NIH	No hyperandrogenic disorders	T45G	1	20	55	1	13	26	1.00	9
						G276T	30	39	7	15	21	4	0.51	
Xita et al. [28]	2005	Greece	Caucasian	NIH	Regular menstrual cycles, no HA	T45G	0	23	77	4	30	106	0.28	9
						G276T	39	49	12	52	73	15	0.20	
Panidis et al. [26]	2004	Greece	Caucasian	NIH	Regular menses, no HA	T45G	7	33	92	2	17	81	0.28	10
Heinonen et al. [24]	2005	Finland	Caucasian	ESHRE/ASRM	$N = 115$, no CHA normal ovaries, regular cycles, proven fertile; $N = 130$, non-diabetic subjects	T45G	1	17	125	1	22	222	0.45	9
						G276T	77	58	8	110	110	25	0.88	
Demirci et al. [22]	2010	Turkey	Caucasian	ESHRE/ASRM	Regular cycles, no HA or PCO	T45G	6	20	70	3	16	74	0.11	8
Haap et al.[23]	2005	Germany	Caucasian	ESHRE/ASRM	Regular menses, no HA	T45G	7	8	38	16	112	414	0.02	12

NIH National Institute of Health criteria, oligo-ovulation together with clinical and/or biochemical signs of hyperandrogenism and exclusion of other etiologies, *ESHRE/ASRM* European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine criteria, oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, polycystic ovaries (at least two out of three) and exclusion of other etiologies, *HA* hyperandrogenism, *CHA* clinical hyperandrogenism, *PCOS* polycystic ovary syndrome, *PCO* polycystic ovary, *SNPs* single nucleotide polymorphisms, P_{HWE} *P* value for HWE test, *N* number

respectively. For controls, the prevalence of the TT, TG and GG genotypes was 72, 25 and 3%, respectively. Expect for three studies suggesting an at-risk effect of G allele [23, 26, 29] and one study presenting the opposite result with the T allele as the risk one [27], all the others did not produce significant results. The overall analysis for evaluating the association of T45G polymorphism with PCOS under allelic model showed that there was large heterogeneity between these ten studies ($P_{\text{heterogeneity}} = 0.002$) (Table 3), and the random effects pooled OR was not significant: OR = 1.10, 95%CI: 0.83–1.44, $P = 0.514$ (Table 3). Ethnicity was not significantly responsible for the heterogeneity. Subgroup analyses stratified by ethnicity also yielded negative results in East Asian and Caucasian populations with large heterogeneity between studies (Table 3). No significant association was found for other genotypic contrasts either (Table 3).

Sensitivity analyses evaluating the influence of single studies on overall risk estimate by omitting one study in each turn did not materially altered the overall effect size, with a range from OR = 1.04 (95%CI 0.78–1.38) to OR = 1.19 (95%CI 0.94–1.52), and excluding studies not in HWE did not significantly change the results either (Table 3). No publication bias was revealed for allelic contrast (G vs. T) by the Egger's regression test ($P = 0.502$).

Association of the G276T polymorphism with PCOS

In total, seven studies with 823 cases and 982 controls concentrated on the G276T polymorphism. The pooled frequency of T allele was 31% and 35% for cases and controls, respectively. For cases, the prevalence of TT, TG and GG genotypes was 9, 44 and 47%, respectively. And For controls, the prevalence of the TT, TG and GG genotypes was 13, 45 and 42%, respectively. Except for four studies reporting non-significant association, the other three all favored the protective effect of T allele [24, 25, 29]. The analysis for evaluating the association of G276T polymorphism with PCOS for allelic contrast showed that there was no significant heterogeneity among all the studies ($P_{\text{heterogeneity}} = 0.268$) (Table 3), and the fixed effects pooled OR was significant: OR = 0.81, 95%CI: 0.70–0.93, $P = 0.003$ (Table 3). Subgroup analyses showed that significant association was detected in East Asian populations using fixed effects model: OR = 0.70, 95%CI: 0.56–0.87, $P = 0.002$, with no evidence of significant heterogeneity ($P_{\text{heterogeneity}} = 0.295$) (Table 3). For Caucasians, no significant association (OR = 0.89, 95%CI: 0.74–1.07, $P = 0.212$) or heterogeneity ($P_{\text{heterogeneity}} = 0.482$) was observed (Table 3). The other genotypic contrasts produced the similar results as that of allelic contrast for overall and subgroup analyses (Table 3).

Sensitivity analyses evaluating the influence of single studies on overall risk estimate by omitting one study in each turn did not materially altered the overall effect size, with a range from OR = 0.76 (95%CI 0.65–0.90) to OR = 0.84 (95%CI 0.72–0.99), and excluding the study not in HWE did not significantly change the results either (Table 3). No publication bias was revealed for allelic contrast (T vs. G) by the Egger's regression test ($P = 0.416$).

Discussion

The current meta-analysis including ten case–control studies was in an effort to clarify the relationship between adiponectin gene polymorphisms and PCOS susceptibility. The overall results indicated that the G276T polymorphism exerted a protective effect on PCOS, while T45G polymorphism showed no significant association. Although obvious heterogeneity was detected for T45G association, sensitivity analyses did not materially altered the overall and subgroup results for both polymorphisms under different genetic models, indicating that the results were stable and reliable.

In further subgroup analyses stratified by ethnicity, we found that G276T polymorphism was significantly related to a reduced risk of PCOS in East Asians, but not in Caucasians. The conflicting results between these two populations might be due to the following reasons. First, the genetic profiles of these two populations were different. Indeed, the T allele frequencies of the controls were higher in East Asians (39%) than in Caucasians (32%). Second, selection criteria might play an important role in affecting the results of genetic association studies. For example, women with PCOS were more obese (mean BMI ranging from 26.8 to 29.5 kg/m^2) in studies involving Caucasians than those (mean BMI ranging from 23.22 to 25.68 kg/m^2) in studies concerning East Asians. Interestingly, a recent meta-analysis conducted by Yu et al. [30] showed that the T allele of G276T conferred to an increased risk of obesity which is opposite to our findings with PCOS. If it is the case, it could be presumed that the protective effects exerted by G276T polymorphism on PCOS might be attenuated in Caucasians. Last, it should be noticed that the observed ethnic differences might be due to chance considering the relatively small sample size involved in the subgroup analyses. As for T45G polymorphism, no significant associations with PCOS were observed in both populations.

Although the direct biological role of adiponectin involved in the pathogenesis of PCOS is unclear, it is now hypothesized that adiponectin may exert its effect on PCOS by modulating insulin sensitivity. The notion has been confirmed by a recent meta-analysis which indicated that

Table 3 Summary risk estimates for the associations between adiponectin gene polymorphisms, T45G and G276T and PCOS

Polymorphisms	*N*	Allele[b]			Dominant model[c]			Recessive model[d]			Additive model[e]		
		OR (95%CI)	*P*	P_h	OR (95%CI)	*P*	P_h	OR (95%CI)	***P***	P_h	OR (95%CI)	*P*	P_h
T45G													
All	10	1.10 (0.83–1.44)[a]	0.514	0.002	1.07 (0.79–1.43)[a]	0.675	0.008	1.45 (0.74–2.83)[a]	0.281	0.040	1.46 (0.75–2.86)[a]	0.264	0.045
All in HWE	7	1.11 (0.76–1.62)[a]	0.579	0.002	1.12 (0.75–1.68)[a]	0.570	0.006	1.26 (0.71–2.26)	0.432	0.367	1.32 (0.74–2.36)	0.346	0.218
Caucasians	7	1.11 (0.76–1.63)[a]	0.577	0.003	1.06 (0.73–1.53)[a]	0.764	0.024	1.47 (0.58–3.74)[a]	0.417	0.058	1.43 (0.55–3.73)[a]	0.463	0.047
Caucasians in HWE	6	1.03 (0.68–1.56)[a]	0.881	0.007	1.03 (0.67–1.58)[a]	0.898	0.016	1.02 (0.52–2.01)	0.952	0.371	1.02 (0.52–2.00)	0.953	0.268
East Asians	3	1.06 (0.69–1.64)[a]	0.782	0.042	1.09 (0.60–1.98)[a]	0.787	0.023	1.22 (0.61–2.44)	0.581	0.106	1.32 (0.65–2.69)	0.445	0.134
G276T													
All	7	**0.81 (0.70–0.93)**	**0.003**	0.268	**0.78 (0.65–0.95)**	**0.011**	0.489	**0.69 (0.50–0.94)**	**0.018**	0.484	**0.62 (0.45–0.86)**	**0.004**	0.283
All in HWE	6	**0.79 (0.68–0.92)**	**0.002**	0.234	**0.76 (0.62–0.93)**	**0.006**	0.501	**0.67 (0.48–0.93)**	**0.016**	0.385	**0.59 (0.42–0.83)**	**0.003**	0.239
Caucasians	4	0.89 (0.74–1.07)	0.212	0.482	0.86 (0.67–1.09)	0.208	0.695	0.86 (0.55–1.33)	0.489	0.531	0.79 (0.50-1.25)	0.321	0.462
East Asians	3	**0.70 (0.56–0.87)**	**0.002**	0.295	**0.68 (0.50–0.92)**	**0.013**	0.268	**0.56 (0.36–0.86)**	**0.009**	0.511	**0.48 (0.30–0.77)**	**0.002**	0.279
East Asians in HWE	2	**0.64 (0.50–0.82)**	**0.000**	0.940	**0.59 (0.42–0.84)**	**0.003**	0.982	**0.56 (0.36–0.86)**	**0.005**	0.592	**0.39 (0.23–0.68)**	**0.001**	0.558

P_h *P* value of *Q* test for heterogeneity test, *N* number of studies, *PCOS* polycystic ovary syndrome, *HWE* Hardy–Weinberg equilibrium, *OR* odds ratio, *95%CI* 95% confidence interval

[a] The ORs and 95%CIs were calculated using random effects model, others were using fixed effects model

[b] For T45G G vs. T; For G276T T vs. G

[c] For T45G GG and TG vs. TT; For G276T TT and TG vs. GG

[d] For T45G GG vs. TG and TT; For G276T TT vs. TG and GG

[e] For T45G GG vs. TT; For G276T TT vs. GG

Statistically significant ORs with 95%CIs and *P* values of < 0.05 are indicated in bold numbers

adiponectin level was lower in PCOS women compared with their normal counterparts with similar BMI, and the lower concentration of adiponectin was associated with insulin resistance [31]. In our included studies, three studies evaluated the genetic effects of G276T polymorphism on adiponectin levels and insulin resistance [21, 28, 29]. Except for one study observing non-significant associations between G allele carriers of G276T and increased risks of hyperinsulinemia and elevated HOMA-IR (homeostatic model assessment for insulin resistance) [21], the other two studies both statistically confirmed the above-mentioned associations. In addition, they found that the G carriers were related with decreased serum adiponectin levels, which is independent of age, BMI and insulin concentration [28, 29]. However, concerning T45G polymorphism, the results were rather contradictory. For example, Xita et al. [28] found that the TG genotype was significantly associated with hyperinsulinemia compared with TT genotype in Greeks. And similar trends were observed by Demirci et al. [22] for G carriers of T45G with increased fasting insulin level and HOMR-IR in Turkishes. Nevertheless, the other two studies produced the opposite results indicating the T allele as the risk one in women with PCOS [21, 23]. For data limitation and various variables adopted by different studies, we were not able to quantitatively evaluate all these associations. However, a recent meta-analysis conducted by Menzaghi et al. [32] observed that G276T, but not T45G, was significantly related to insulin resistance and altered adiponectin level, which further supported our findings that G276T, rather than T45G, was associated with PCOS risk.

Limitations of our study should be noticed. First, heterogeneity between studies for T45G association was unsatisfactorily explained although we conducted subgroup analyses and sensitivity analyses to find the source. The heterogeneity might be due to various reasons, including the heterogeneous features of PCOS, variations in genotyping methods, sample size and other study design. Second, our search database was limited to PubMed and the language was confined to English, which might introduce possible publication bias. However, the Egger's regression test did not revealed any publication bias. Third, the quality of the included studies was relatively low. Three out of ten studies included in our meta-analysis showed significant deviation from HWE in controls which might reflect problems in study design and conduct such as genotyping errors, population stratification, selection bias of controls and small sample size. However, after excluding the studies with control not in HWE from overall and subgroup analyses under all genetic models for both polymorphisms, the corresponding results were not significantly altered. Fourth, for data limitation, we were not able to conduct further subgroup analyses, such as according to serum androgen level. A previous study observed that the GG and GT genotypes of T45G polymorphism were more prevalent in PCOS women with relatively higher Δ_4-androstenedione levels compared with healthy controls, and suggested that there might be an interaction between adiponectin and steroid synthesis or action in PCOS [26]. Last but not the least, since PCOS not only affects reproductive system, but also is frequently associated with metabolic derangements, such as obesity, insulin resistance, T2D and dislipidemia, including subjects afflicted by these disorders in cases and/or control groups or not might influence the effect estimation. Further studies involving more homogeneous populations should be warranted to address the independent or the interaction effects of adiponectin polymorphisms with those factors.

Despite the limitations, our meta-analysis has some important advantages. First, our study has significantly increased statistical power compared with individual studies, which might lead to a more precise estimation. Second, we adopted allelic, additive, dominant and recessive genetic models to investigate the genetic effect of adiponectin polymorphisms on PCOS, which made our analysis more comprehensive and valid.

In conclusion, our meta-analysis supported an association between the G276T polymorphism of adiponectin gene and PCOS, which indicated that adiponectin might play a role in the etiology of PCOS. However, considering that the conclusion was based on relatively small samples, larger well-designed studies are required to verify our findings. In addition, the biological role of adiponectin and its genetic variations in the pathogenesis of PCOS needs further research. The interactions between gene–gene and gene-environment should also be evaluated in future studies.

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Conflict of interest The authors declare that they have no conflict of interest.

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