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Review Article

Relationship between *ADIPOQ* polymorphisms and polycystic ovary syndrome: a meta-analysis involving 6,735 subjects

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Abstract: To address the relationship of *ADIPOQ* T45G and G276T polymorphisms with polycystic ovary syndrome (PCOS), a meta-analysis was performed in this report. An extensive literature search, selection of eligible publications and extract relevant data were carried out. Sixteen eligible papers with a total number of 2,456 PCOS patients and 4,279 controls met the major including criteria in the pooled analysis on the correlation between *ADIPOQ* polymorphisms and PCOS. We used crude odds ratios (ORs) with 95% confidence intervals (CIs) to evaluate the strength of relationship. The results demonstrated that there was no evidence for the correlation between *ADIPOQ* T45G and PCOS even in the subgroup analyses. However, *ADIPOQ* G276T polymorphism conferred the decreased risk to PCOS in two genetic models: T vs. G (OR, 0.88; 95% CI, 0.78-1.00; *P*=0.047) and TT+GT vs. GG (OR, 0.80; 95% CI, 0.70-0.93; *P*=0.003). In a subgroup analysis by ethnicity, the similar findings were also found among Asians in two genetic models: TT vs. GG (OR, 0.55; 95% CI, 0.39-0.78; *P*=0.001) and TT+GT vs. GG (OR, 0.71; 95% CI, 0.56-0.89; *P*=0.003). In a subgroup analysis by diagnosis criteria of PCOS, we found that *ADIPOQ* G276T polymorphism was associated with the decreased risk of PCOS among European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine criteria (ESHRE/ASRM) in three genetic models: T vs. G (OR, 0.80; 95% CI, 0.66-0.99; *P*=0.036), TT vs. GG (OR, 0.60; 95% CI, 0.40-0.91; *P*=0.015) and TT+GT vs. GG (OR, 0.71; 95% CI, 0.59-0.85; *P*<0.001). In summary, our results suggest that *ADIPOQ* G276T polymorphism was associated with the decreased risk of PCOS, especially in Asians and ESHRE/ASRM of PCOS subgroups.

Keywords: Polymorphism, *ADIPOQ*, polycystic ovary syndrome, susceptibility, meta-analysis

Introduction

Polycystic ovary syndrome (PCOS), one of the leading diseases of female infertility, is a heterogeneous endocrine/metabolic disorder and a major reason for anovulatory infertility, which affects about 5-10% of women in reproductive age [1, 2]. Characteristics of PCOS are polycystic ovary (PCO), chronic anovulation, hyperandrogenism and metabolic syndrome (e.g. insulin resistance, obesity, and type 2 diabetes et al.) [3]. The etiology and pathogenesis of PCOS are very complicated and have been unknown clearly. Some investigations suggested that a number of genetic and environmental factors might contribute to the susceptibility of PCOS. Identification of these genetic variants and environmental factors may enrich our view on the complex etiology and pathogenesis of PCOS.

Results of many epidemiologic studies indicated that many genetic variants, which involving steroidogenesis, oxidative stress, insulin resistance, metabolic syndrome and adipocytokine, may affect the predisposition to PCOS. Adiponectin is a versatile adipocytokine which is encoded by *ADIPOQ* gene (adipocyte C1q and

collagen domain containing). It serves as a modulator in anti-inflammatory action, energy metabolism and insulin sensitivity [4]. The circulating adiponectin promotes glucose uptake and fatty acid oxidation [5]. It was reported that hypoadiponectinemia confer the increased risk to cardiovascular disease, obesity, and type 2 diabetes (DM2) [6, 7]. Recently, several studies focused on the vital role of adipocytokine in the pathogenesis of PCOS [8-10].

The *ADIPOQ* is located on 3q27, including 3 exons and 2 introns. It is expressed and secreted mainly by white adipose tissue and acts as an important regulator in metabolic processes such as insulin sensitivity, glucose regulation and fatty acid catabolism etc [4, 11]. In addition, *ADIPOQ* variants were suggested to be correlated with the expression level of serum adiponectin [12], and wherefore these functional variants could influence the susceptibility of PCOS. Nowadays, approximately 4,014 single nucleotide polymorphisms (SNPs) in *ADIPOQ* gene have been identified (http://www.ncbi.nlm.nih.gov/SNP). Among them, two SNPs [*ADIPOQ* T45G (rs2241766), *ADIPOQ* G276T (rs1501299)] have been extensively studied for their potential role in the susceptibility of many endocrine/metabolic disorder. Of late, a number of case-control studies indicated that *ADIPOQ* T45G and G276T polymorphisms might involve in the development of PCOS [13-27]; however, the results remain conflicting rather than conclusive. With respect to *ADIPOQ* T45G polymorphism, two meta-analyses identified that individuals carrying G alleles were associated with the increased risk of PCOS [28, 29]. With respect to *ADIPOQ* G276T polymorphism, three meta-analyses on this issue have suggested that *ADIPOQ* G276T polymorphism decreased the risk of PCOS [28-30]. However, these studies failed to enroll the latest larger sample study by Pau *et al.* [19] and other eligible investigations [13, 18, 31, 32], which might make their determinations questionable. To obtain a comprehensive evaluation of the association between *ADIPOQ* polymorphisms and PCOS risk, we conducted an updated meta-analysis of all eligible studies relating the *ADIPOQ* T45G and G276T polymorphisms for the susceptibility of PCOS.

Materials and methods

Search strategy

We first searched literatures from PubMed and EMBASE databases (the last search updated to June 27, 2016) by using the following searching words related to *ADIPOQ* polymorphisms and PCOS: (PCOS or polycystic ovary syndrome) and (polymorphism or SNP or variant) and (adiponectin or ADIPOQ or apM1 or ACDC). The potential publications in reference as well as 'related articles' of PubMed option were also searched. Studies with insufficient data were excluded. If there were duplication or overlapping data, the studies with the largest sample size were eligible for the final analysis.

Inclusion and exclusion criteria

In our analysis, studies were included according to the criteria as follows: (a) case-control studies focused on the relationship of *ADIPOQ* polymorphisms with PCOS risk; (b) PCOS patients should be diagnosed with National Institute of Health criteria (NIH) or European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine criteria (ESHRE/ASRM) [30]; (c) sufficient data (the frequencies of alleles or genotypes) should provided to calculate the odds ratios (ORs) with 95% confidence intervals (95% CIs). Accordingly, studies with insufficient data, not case-control design, reviews and meta-analysis were excluded.

Data extraction

The following data from eligible studies were independently collected by two authors (X. Li and Y. Chen): the first author's name, year of publication, country, ethnicity of participants, diagnosis criteria of PCOS (NIH or ESHRE/ASRM), selection criteria of control, sample size, genotyping method as well as allele and genotype frequencies. In case of conflicting evaluations, the third author (W. Tang) was consulted to resolve these disagreements.

Statistical analysis

The relationships between *ADIPOQ* polymorphisms and the risk of PCOS were assessed by crude ORs and their 95% CIs under the following four genetic models: allele comparing, homozygous model, recessive model and dominant model. An online Goodness-of-fit chi-square test (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) was performed to determine the deviation from HWE in controls and a $P<0.05$ was considered significant. We used Chi square-based Q-test to assess the heterogeneity in our pooled-analysis. The fixed-effects model (the

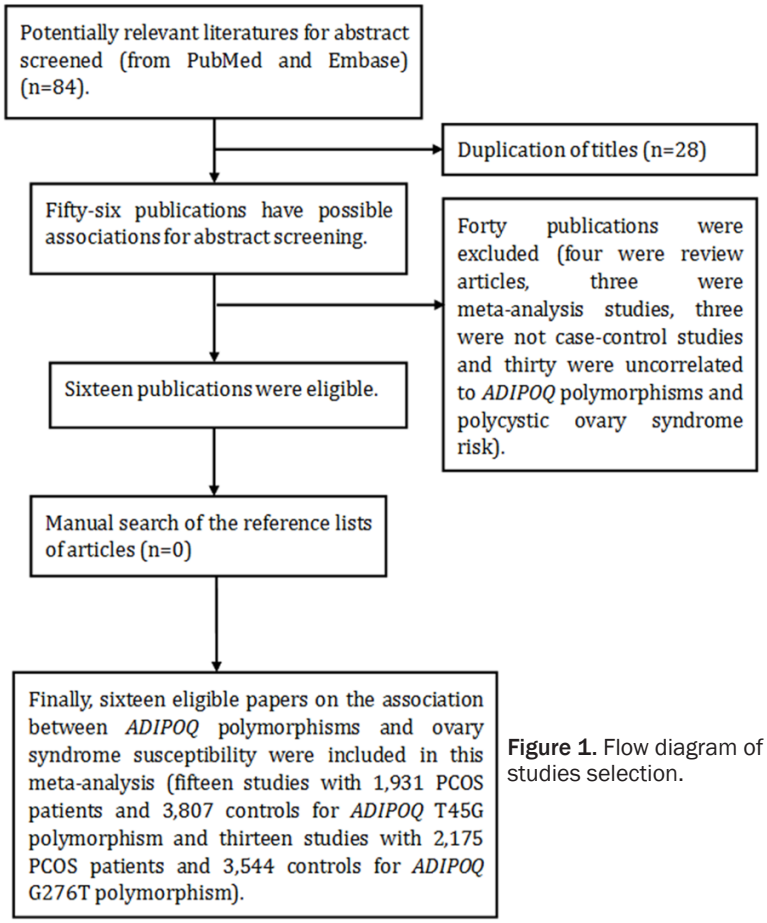

Figure 1. Flow diagram of studies selection.

Mantel-Haenszel method) was used when studies were low heterogeneity ($P \geq 0.10$ for the Q test) [33]; otherwise, significant heterogeneity confirmed in studies ($P<0.10$ for the Q test), random-effects model (the DerSimonian and Laird method) was harnessed [34]. We also conducted subgroup analyses according to HWE, ethnicity and diagnosis criteria of PCOS. The potential publication bias among the studies was also determined by Begg's funnel plot and the Egger' linear regression test [35], and a $P<0.1$ was considered statistically significant. Begg's funnel plot symmetry was identified by visual inspection. Sensitivity of our findings was checked by one-way sensitivity method [excluding each individual study and re-calculating the pooled estimates (ORs and their corresponding 95% CIs) to assess the effect of each study on the overall results]. All data were calculated by using STATA 12.0 software (Stata Corporation, College Station, TX). A $P<0.05$ (two-sided) was considered as significant.

Results

Characteristics

A total of eighty-four publications were retrieved through the primary searching. The literature screening process was shown in **Figure 1**. Finally, there were sixteen eligible papers included in our final analysis [13-27]. Five studies conducted in Asians [13-17], ten studies conducted in Caucasians [18-26, 36] and one study conducted in mixed population [32]. Of these articles, seven studies adopted NIH diagnosis criteria of PCOS [18-20, 22, 23, 26, 36] and nine studies adopted ESHRE/ASRM diagnosis criteria of PCOS [13-17, 21, 24, 25, 32]. The characteristics of the included studies [13-27] are shown in **Table 1**. The distribution of *ADIPOQ* T45G, G276T variants as well as alleles in our analysis islisted in **Tables 2** and **3**.

Quantitative synthesis

Overall, there were sixteen eligible publications with 2,456 PCOS patients and 4,279 controls met the major inclusion criteria [13-27]. For *ADIPOQ* T45G polymorphism, there were 1,931 PCOS patients and 3,807 controls included in fifteen studies met the inclusion criteria [13-18, 20-27, 36]. For *ADIPOQ* G276T polymorphism, thirteen studies with 2,175 PCOS patients and 3,544 controls were eligible for data collection [13-20, 22, 23, 25, 32, 36].

Overall, *ADIPOQ* T45G polymorphism was not associated with the risk of PCOS (**Table 4** and **Figure 2**). In subgroup analyses by ethnicity and diagnosis criteria of PCOS, the similarly negative results were not also found (**Table 4**).

However, *ADIPOQ* G276T polymorphism was associated with the decreased risk of PCOS in two genetic models: T vs. G (OR, 0.88; 95% CI, 0.78-1.00; $P=0.047$) and TT+GT vs. GG (OR,

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

Study	Year	Country	Ethnicity	Number of cases	Number of controls	PCOS	Control	Genotype method	Polymorphism
Nambiar et al.	2016	India	Asians	282	200	ESHRE/ASRM	Healthy women without menstrual irregularities, reproductive concerns or hormonal abnormalities	PCR-RFLP	T45G, G276T
Zhang et al.	2015	China	Asians	207	192	ESHRE/ASRM	Infertility females without history of PCOS	DNA-sequence	T45G, G277T
Ramezani Tehrani et al.	2013	Iran	Caucasians	186	156	NIH	Healthy non hirsute normo-ovulatory women	PCR-RFLP	T45G, G276T
Radavelli-Bagatini et al.	2013	Brazil	mixed	80	1500	ESHRE/ASRM	Non-hirsute women with regular cycles	PCR-RFLP	T45G, G277T
Pau et al.	2013	USA	Caucasians	525	472	NIH	Normal menstrual cycles, no hyperandrogenism	MALDI-TOF MS	G276T
Li et al.	2011	Korea	Asians	144	159	ESHRE/ASRM	No hyperandrogenism, PCO or oligo-, amenorrhea	PCR-RFLP	T45G, G276T
Ranjzad et al.	2011	Iran	Caucasians	181	181	NIH	Normal menstrual cycles, no hyperandrogenism	PCR-RFLP	T45G, G276T
Demirci et al.	2010	Turkey	Caucasians	96	93	ESHRE/ASRM	Normal menstrual cycles without history of PCOS or diabetes mellitus	PCR	T45G
Yoshihara et al.	2009	Japan	Asians	59	97	ESHRE/ASRM	Female volunteers without any of the three PCOS criteria (JSOG, 2007)	TaqMan	T45G, G276T
Zhang et al.	2008	China	Asians	120	120	ESHRE/ASRM	Normal menstrual cycles without history of PCOS	PCR	T45G, G276T
Escobar-Morreale et al.	2006	Spain	Caucasians	76	40	NIH	Female volunteers and consecutive patients for dietary treatment of obesity	PCR-RFLP	T45G, G277T
Xita et al.	2005	Greece	Caucasians	100	140	NIH	Healthy normal weight women with regular menstrual cycles and no signs of hyperandrogenism	PCR	T45G, G278T
Haap et al.	2005	Germany	Caucasians	53	542	ESHRE/ASRM	Healthy non-diabetic women with regular menses and without hyperandrogenaemia	PCR	T45G
Heinonen et al.	2005	Finland	Caucasians	143	245	ESHRE/ASRM	115 hospital-based controls with normal menstrual cycles, normal ovaries and no hyperandrogenism and 130 non-diabetic subjects	SNaPshot	T45G, G278T
Panidis et al.	2004	Germany	Caucasians	132	100	NIH	Female volunteers with normal menstrual cycles, no hyperandrogenism	PCR	T45G
San Millan et al.	2004	Spain	Caucasians	72	42	NIH	Females with normal menstrual cycles, no hyperandrogenism, no history of infertility	PCR-RFLP	T45G, G278T

NIH: National Institute of Health criteria; ESHRE/ASRM: EuropeanSociety for Human Reproduction and Embryology/American Society for Reproductive Medicine criteria; PCOS: polycystic ovary syndrome; PCO: polycystic ovary; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; MALDI-TOF MS: Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry; PCR: polymerase chain reaction.

Table 2. Distribution of *ADIPOQ* T45G polymorphism genotypes and alleles

Study	Year	Case			Control			Case		Control		HWE
		GG	GT	TT	GG	GT	TT	G	T	G	T	
Nambiar et al.	2016	9	60	213	4	40	156	78	486	48	352	Yes
Zhang et al.	2015	17	84	106	19	75	98	118	296	113	271	Yes
Ramezani Tehrani et al.	2013	2	42	142	4	46	106	46	326	54	258	Yes
Radavelli-Bagatini et al.	2013	1	19	60	39	268	1193	21	139	346	2654	No
Li et al.	2011	6	59	79	3	84	72	71	217	90	228	No
Ranjzad et al.	2011	3	34	144	6	54	121	40	322	66	296	Yes
Demirci et al.	2010	6	20	70	3	16	74	32	160	22	164	Yes
Yoshihara et al.	2009	5	23	31	15	29	53	33	85	59	135	No
Zhang et al.	2008	9	54	57	4	42	74	72	168	50	190	Yes
Escobar-Morreale et al.	2006	1	20	55	1	13	26	22	130	15	65	Yes
Xita et al.	2005	0	23	77	4	30	106	23	177	38	242	Yes
Haap et al.	2005	7	8	38	16	112	414	22	84	144	940	No
Heinonen et al.	2005	1	17	125	1	22	222	19	267	24	466	Yes
Panidis et al.	2004	7	33	92	2	17	81	47	217	21	179	Yes
San Millan et al.	2004	2	22	48	1	12	29	26	118	14	70	Yes

HWE: Hardy-Weinberg equilibrium.

Table 3. Distribution of *ADIPOQ* G276T polymorphism genotypes and alleles

Study	Year	Case			Control			Case		Control		HWE
		GG	GT	TT	GG	GT	TT	T	G	T	G	
Nambiar et al.	2016	23	94	165	15	86	99	424	140	284	116	Yes
Zhang et al.	2015	119	78	10	92	75	22	98	316	119	259	Yes
Ramezani Tehrani et al.	2013	92	76	18	77	71	8	112	260	87	225	Yes
Radavelli-Bagatini et al.	2013	42	27	11	670	672	158	49	111	988	2012	Yes
Pau et al.	2013	N/A	N/A	N/A	N/A	N/A	N/A	288	762	288	656	Yes
Li et al.	2011	61	73	10	48	87	24	93	195	135	183	Yes
Ranjzad et al.	2011	92	77	12	91	79	11	101	261	101	261	Yes
Yoshihara et al.	2009	34	17	8	58	24	15	33	85	54	140	No
Zhang et al.	2008	56	46	18	41	50	29	82	158	108	132	Yes
Escobar-Morreale et al.	2006	30	39	7	15	21	4	53	99	29	51	Yes
Xita et al.	2005	39	49	12	52	73	15	73	127	103	177	Yes
Heinonen et al.	2005	77	58	8	110	110	25	74	212	160	330	Yes
San Millan et al.	2004	28	34	10	18	20	4	54	90	28	56	Yes

HWE: Hardy-Weinberg. N/A: not available.

0.80; 95% CI, 0.70-0.93; *P*=0.003) (**Table 5** and **Figure 3**). In a subgroup analysis by ethnicity, the decreased risk of PCOS was also found among Asians in two genetic models: TT vs. GG (OR, 0.55; 95% CI, 0.39-0.78; *P*=0.001) and TT+GT vs. GG (OR, 0.71; 95% CI, 0.56-0.89; *P*=0.003) (**Table 5**). In a subgroup analysis by diagnosis criteria of PCOS, we found that *ADIPOQ* G276T polymorphism was associated with the decreased risk of PCOS among ESHRE/ASRM in three genetic models: T vs. G (OR, 0.80; 95% CI, 0.66-0.99; *P*=0.036), TT vs. GG (OR, 0.60; 95% CI, 0.40-0.91; *P*=0.015) and TT+GT vs. GG (OR, 0.71; 95% CI, 0.59-0.85; *P*<0.001) (**Table 5**).

Tests for publication bias

We used Begg's funnel plot test and Egger's test to assess publication bias of literatures on PCOS. As shown in **Figures 4** and **5**, no evidence of bias was found in all genetic models (*ADIPOQ* T45G polymorphism: G vs. T: Begg's

Table 4. Meta-analysis of the *ADIPOQ* T45G polymorphism and polycystic ovary syndrome

	No. of study	Alleliccomparison			Homozygote comparison			Dominantcomparison			Recessive comparison		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)
Overall	15	1.05 (0.87-1.26)	0.602	0.005	1.23 (0.76-1.98)	0.403	0.066	1.04 (0.85-1.26)	0.722	0.022	1.21 (0.75-1.95)	0.425	0.063
HWE													
Yes	11	1.04 (0.82-1.32)	0.736	0.005	1.08 (0.73-1.61)	0.696	0.326	1.04 (0.81-1.34)	0.732	0.014	1.05 (0.71-1.56)	0.805	0.508
No	4	1.03 (0.82-1.29)	0.788	0.118	1.39 (0.42-4.61)	0.657	0.017	0.99 (0.75-1.30)	0.915	0.226	1.40 (0.38-5.13)	0.612	0.006
Ethnicity													
Asians	5	1.05 (0.88-1.24)	0.598	0.135	1.13 (0.72-1.76)	0.596	0.255	1.07 (0.79-1.44)	0.662	0.099	1.07 (0.69-1.65)	0.761	0.225
Caucasians	9	1.04 (0.76-1.43)	0.799	0.002	1.21 (0.52-2.80)	0.657	0.044	0.99 (0.73-1.35)	0.958	0.028	1.25 (0.56-2.82)	0.588	0.057
Mixed	1	1.16 (0.72-1.86)	0.541	-	0.51 (0.07-3.77)	0.510	-	1.30 (0.77-2.18)	0.331	-	0.47 (0.06-3.50)	0.464	-
Diagnosis criteria of PCOS													
ESHRE/ASRM	9	1.13 (0.98-1.31)	0.085	0.164	1.53 (0.88-2.66)	0.131	0.079	1.14 (0.96-1.35)	0.146	0.300	1.48 (0.83-2.64)	0.181	0.045
NIH	6	0.86 (0.60-1.23)	0.406	0.023	0.69 (0.35-1.39)	0.303	0.345	0.85 (0.58-1.25)	0.418	0.037	0.71 (0.35-1.43)	0.343	0.454

HWE: Hardy-Weinberg equilibrium; NIH: National Institute of Health criteria; ESHRE/ASRM: EuropeanSociety for Human Reproduction and Embryology/American Society for Reproductive Medicine criteria; PCOS: polycystic ovary syndrome.

Table 5. Meta-analysis of the *ADIPOQ* G276T polymorphism and polycystic ovary syndrome

	No. of study	Alleliccomparison			Homozygote comparison			Dominantcomparison			Recessive comparison		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)
Overall	13	0.88 (0.78-1.00)	0.047	0.061	0.78 (0.56-1.09)	0.144	0.048	0.80 (0.70-0.93)	0.003	0.696	0.89 (0.64-1.24)	0.504	0.013
HWE													
Yes	12	0.88 (0.77-1.00)	0.048	0.045	0.77 (0.54-1.11)	0.160	0.032	0.79 (0.68-0.92)	0.002	0.696	0.90 (0.63-1.27)	0.542	0.008
No	1	1.01 (0.60-1.68)	0.980	-	0.91 (0.35-2.37)	0.846	-	1.09 (0.57-2.11)	0.790	-	0.86 (0.34-2.17)	0.745	-
Ethnicity													
Asians	5	0.80 (0.60-1.08)	0.144	0.008	0.55 (0.39-0.78)	0.001	0.102	0.71 (0.56-0.89)	0.003	0.516	0.67 (0.37-1.23)	0.193	0.002
Caucasians	7	0.92 (0.81-1.04)	0.163	0.524	1.01 (0.69-1.47)	0.974	0.323	0.91 (0.74-1.11)	0.339	0.808	1.07 (0.74-1.54)	0.723	0.381
Mixed	1	0.90 (0.64-1.27)	0.545	-	1.11 (0.56-2.21)	0.764	-	0.73 (0.47-1.15)	0.172	-	1.35 (0.70-2.61)	0.366	-
Diagnosis criteria of PCOS													
ESHRE/ASRM	9	0.80 (0.66-0.99)	0.036	0.024	0.60 (0.40-0.91)	0.015	0.078	0.71 (0.59-0.85)	<0.001	0.773	0.73 (0.46-1.16)	0.177	0.003
NIH	6	0.95 (0.84-1.09)	0.489	0.752	1.28 (0.82-1.99)	0.274	0.834	0.98 (0.78-1.24)	0.892	0.990	1.32 (0.86-2.01)	0.200	0.820

HWE: Hardy-Weinberg equilibrium; NIH: National Institute of Health criteria; ESHRE/ASRM: EuropeanSociety for Human Reproduction and Embryology/American Society for Reproductive Medicine criteria; PCOS: polycystic ovary syndrome.

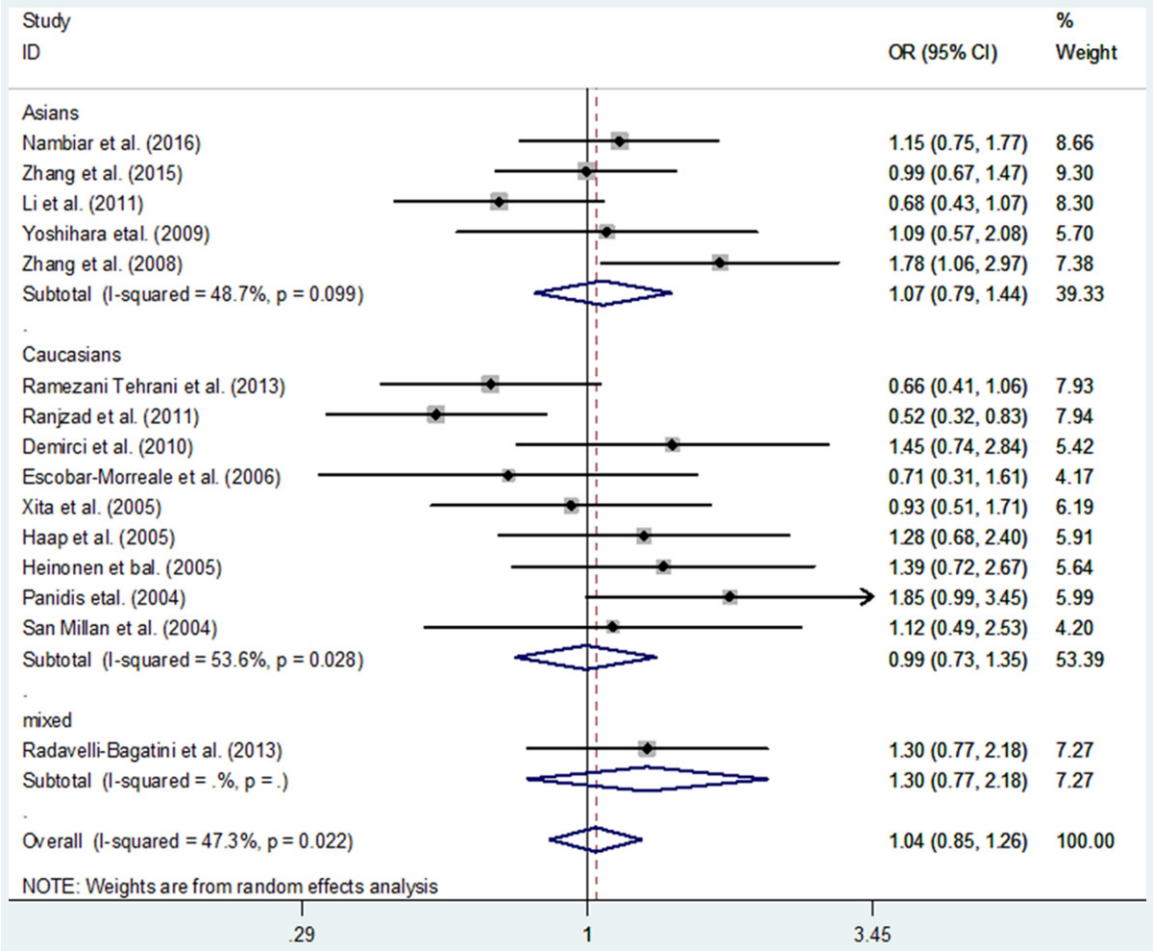

Figure 2. Meta-analysis with a random-effects model in the different race for the association between *ADIPOQ* T45G polymorphism and polycystic ovary syndrome risk (the dominant genetic model).

test *P*=0.843, Egger's test *P*=0.408; GG vs. TT: Begg's test *P*=0.553, Egger's test *P*=0.470; GG+TG vs. TT: Begg's test *P*=0.428, Egger's test *P*=0.296 and GG vs. TG+TT: Begg's test *P*=0.553, Egger's test *P*=0.532; *ADIPOQ* G276T polymorphism: T vs. G: Begg's test *P*=0.855, Egger's test *P*=0.703; TT vs. GG: Begg's test *P*=0.631, Egger's test *P*=0.517; TT+GT vs. GG: Begg's test *P*=0.631, Egger's test *P*=0.226 and TT vs. GT+GG: Begg's test *P*=0.837, Egger's test *P*=0.291).

Tests for sensitivity analyses

To evaluate the effect of an individual investigation on the overall findings of meta-analysis, we omitted one study in turn, and the exclusion of anyone did not materially change the final decision of our study, suggesting the robustness of our findings (**Figures 6** and **7**, data not shown).

Tests for heterogeneity

The results of Q-test statistics were listed in **Tables 4** and **5**. Significant heterogeneity across studies was identified in overall meta-analyses for both *ADIPOQ* T45G and G276T polymorphisms. We explored some potential sources of the heterogeneity, including ethnicity and diagnosis criteria of PCOS. The results demonstrated that Caucasians and ESHRE/ASRM subgroups may contribute to source of heterogeneity for *ADIPOQ* T45G polymorphism, while Asians and HIN subgroups may contribute to source of heterogeneity for *ADIPOQ* G276T polymorphism.

Discussion

Large sample sizes epidemiological investigations of predisposition SNPs could enrich our

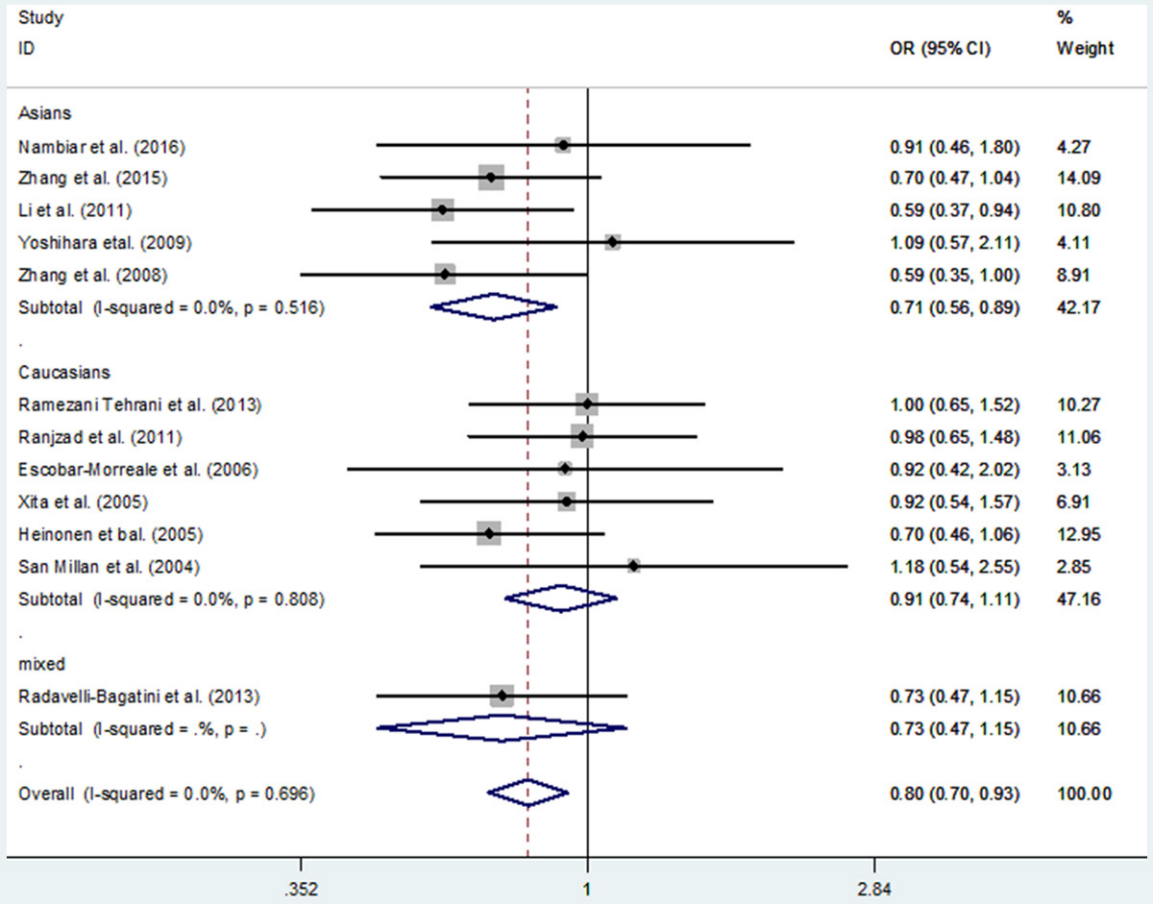

Figure 3. Meta-analysis for the association between *ADIPOQ* G276T polymorphism and polycystic ovary syndrome risk in different race (the dominant genetic model; fixed-effects model).

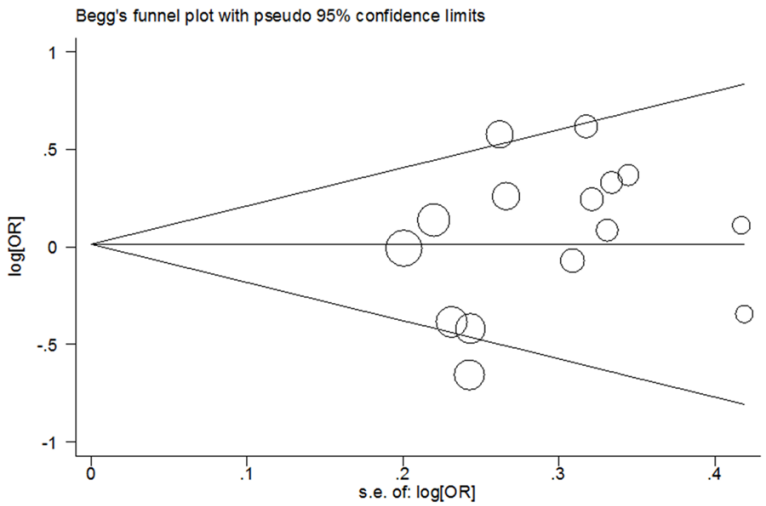

Figure 4. Begg's funnel plot of meta-analysis for the association between *ADIPOQ* T45G polymorphism and the risk of polycystic ovary syndrome.

insight into the association between complex human diseases and candidate genes. The involvement of adiponectin in anti-inflammatory action, energy metabolism and insulin sensitivity may underlie the mechanism responsible for the relationship of *ADIPOQ* genotype with PCOS susceptibility. So far, many studies on the molecular epidemiology had focused on the correlation of *ADIPOQ* polymorphism with the risk of PCOS, but the findings remain controversial. With respect to *ADIPOQ* polymorphisms, several pooled analyses with small sample sizes on this issue have suggested that *ADIPOQ* polymorphisms might affect the risk of PCOS [28-30]. However, these studies failed to enroll the latest larger sample study by Pau *et al.* [19]

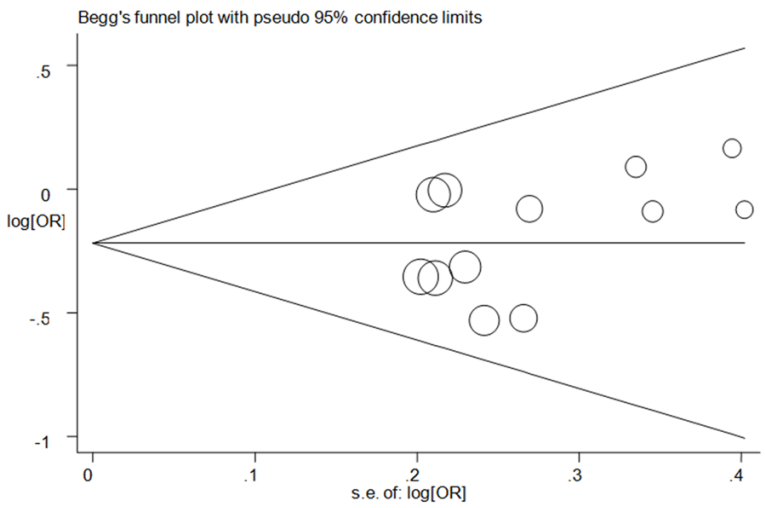

Figure 5. Begg's funnel plot of meta-analysis for the association between *ADIPOQ* G276T polymorphism and the risk of polycystic ovary syndrome.

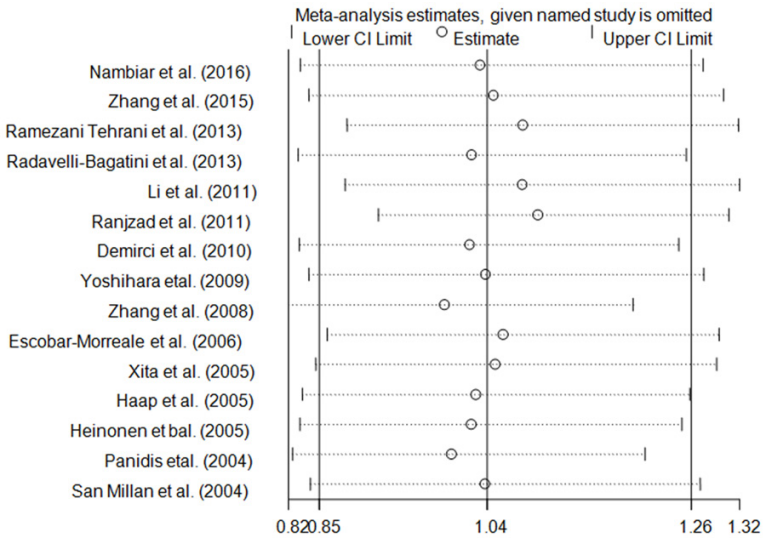

Figure 6. Analysis of the influence of the dominant genetic model in the overall polycystic ovary syndrome meta-analysis for *ADIPOQ* T45G polymorphism.

and other eligible investigations [13, 18, 31, 32], which might limit the power to obtain a comprehensive assessment. Our updated meta-analysis is the most comprehensive analysis explored these two functional polymorphisms (T45G, G276T) in *ADIPOQ* gene and their association to susceptibility for PCOS. Its strength of the potential association was based on the sufficient published data to identify significant differences. In total, this updated meta-analysis enrolled sixteen studies for PCOS which provided 2,456 PCOS patients and 4,279 controls [13-27].

For ADIPOQ 45T/G polymorphism, as shown in **Table 1**, fifteen case-control studies which focused on the relationship of this polymorphism with PCOS susceptibility were included in the present analysis. Several investigations have reported positive signals of *ADIPOQ* gene 45T/G polymorphism with the development of PCOS [17, 24, 26]; contrastingly, a case-control study showed that *ADIPOQ* 45T/G polymorphism decreased the risk of PCOS [20]. However, the other eleven studies suggested no significant correlation between the *ADIPOQ* 45T/G polymorphism and PCOS risk [13-16, 18, 21-23, 25, 32, 36]. In total, as illustrated in overall results among 1,931 PCOS patients and 3,807 controls, there was no significant correlation, even in different diagnosis criteria (NIH and ESHRE/ASRM) or different populations. Our results were similar to the findings of a recent meta-analysis [30], while were inconsistent with other pooled-analysis [28, 29]. The controversial assessments between these meta-analyses may be due to the following possible reasons. Firstly, the genetic profiles were variational indifferent populations. Indeed, in our study, the minor allele frequency (MAF) of the controls was higher in Asians (0.306) than in Caucasians (0.149). Secondly, in the previous meta-analyses, the number of studies and the subjects of included investigations among Asians were limited. Finally, studies conducted in Asians were lesser, which may have insufficient power to detect a real influence in PCOS risk.

In this updated meta-analysis, the combined evidence showed that *ADIPOQ* G276T polymorphism was a protective factor for PCOS in two genetic models: T vs. G (OR, 0.88; 95% CI, 0.78-

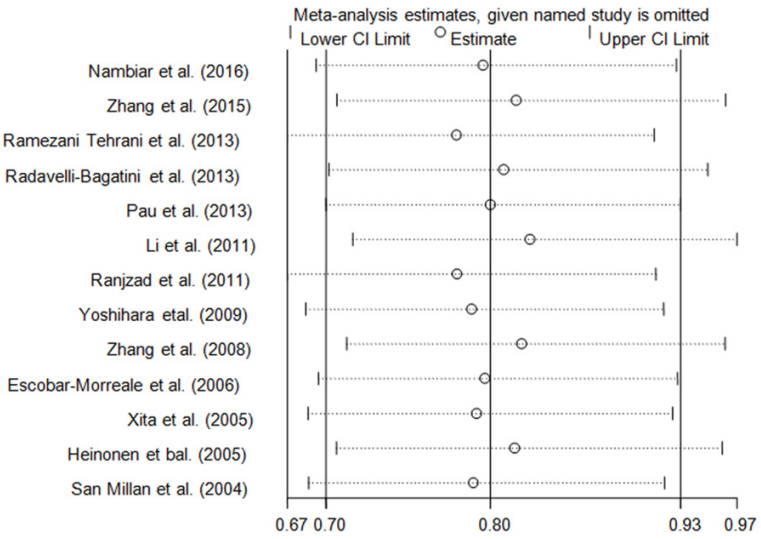

Figure 7. Analysis of the influence of the dominant genetic model in the overall polycystic ovary syndrome meta-analysis for *ADIPOQ* G276T polymorphism.

1.00; *P*=0.047) and TT+GT vs. GG (OR, 0.80; 95% CI, 0.70-0.93; *P*=0.003). In a subgroup analysis by race, the similar results were also found in Asians (**Table 5**). The results of our present meta-analysis were consistent with several previous meta-analyses which reported that *ADIPOQ* G276T polymorphism conferred the decreased risk on PCOS [28-30]. Some studies demonstrated that hypoadiponectinemia was associated with insulin resistance and might be associated with complex human diseases, such as cardiovascular disease, obesity, and type 2 diabetes (DM2) [6, 7]. Adiponectin acts as a modulator and may exert its protective effect on PCOS by anti-inflammatory action and promoting insulin sensitivity [4]. Of late, the potential role of adiponectin in PCOS has been identified by a meta-analysis. In that study, the low level of adiponectin in PCOS patients compared with the similar body mass index (BMI) non-PCOS controls was confirmed [37]. Results of the present meta-analysis indicated the influence of *ADIPOQ* G276T polymorphism and diversity in different ethnicities to the risk of PCOS. In addition, we found that *ADIPOQ* G276T polymorphism decreased the risk of PCOS, suggesting the presence of the T allele, which had higher serum adiponectin concentration [38], might be a protective factor for PCOS.

In our analysis, severalinvestigations deviated from the HWE in controls (**Tables 2** and **3**). When we excluded or enrolled these studies, as shown in **Tables 4** and **5**, the relationship between *ADIPOQ* polymorphisms and PCOS risk were similar, suggesting the robustness of our findings.

Similar to other meta-analyses, some limitations of this pooled analysis should be acknowledged. Firstly, the eligible articles are not many and number of the subjects was relatively limited. In addition, the relationship of *ADIPOQ* polymorphisms with PCOS risk was determined by crude ORs and their CIs. For lack of the some characteristic data, such as serum and rogen concentration, insulin resistance and BMI *et al*., a detailed analysis was not performed. Thirdly, the controls in the eligible investigations were not unified, which were selected from healthy volunteers and some were non-PCOS patients. Finally, heterogeneity between the included studies for both *ADIPOQ* T45G and G276T polymorphisms was found in our study. Our results should be interpreted with cautions.

In conclusion, the results indicate that *ADIPOQ* G276T polymorphism is associated with the decreased susceptibility of PCOS, especially in Asians and ESHRE/ASRM subgroups. In addition, for practical reasons, future studies with well-matched controls may further evaluate the potential gene-gene and gene-environmental interactions in this relationship.

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Disclosure of conflict of interest

None.

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References

[1] Brassard M, AinMelk Y and Baillargeon JP. Basic infertility including polycystic ovary syndrome. Med Clin North Am 2008; 92: 1163-1192, xi.

[2] Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES and Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004; 89: 2745-2749.

[3] Moran LJ, Misso ML, Wild RA and Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2010; 16: 347-363.

[4] Brochu-Gaudreau K, Rehfeldt C, Blouin R, Bordignon V, Murphy BD and Palin MF. Adiponectin action from head to toe. Endocrine 2010; 37: 11-32.

[5] Bruce CR, Mertz VA, Heigenhauser GJ and Dyck DJ. The stimulatory effect of globular adiponectin on insulin-stimulated glucose uptake and fatty acid oxidation is impaired in skeletal muscle from obese subjects. Diabetes 2005; 54: 3154-3160.

[6] Stumvoll M, Tschritter O, Fritsche A, Staiger H, Renn W, Weisser M, Machicao F and Haring H. Association of the T-G polymorphism in adiponectin (exon 2) with obesity and insulin sensitivity: interaction with family history of type 2 diabetes. Diabetes 2002; 51: 37-41.

[7] Duncan BB, Schmidt MI, Pankow JS, Bang H, Couper D, Ballantyne CM, Hoogeveen RC and Heiss G. Adiponectin and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes 2004; 53: 2473-2478.

[8] Manneras-Holm L, Leonhardt H, Kullberg J, Jennische E, Oden A, Holm G, Hellstrom M, Lonn L, Olivecrona G, Stener-Victorin E and Lonn M. Adipose tissue has aberrant morphology and function in PCOS: enlarged adipocytes and low serum adiponectin, but not circulating sex steroids, are strongly associated with insulin resistance. J Clin Endocrinol Metab 2011; 96: E304-311.

[9] Artimani T, Saidijam M, Aflatoonian R, Ashrafi M, Amiri I, Yavangi M, SoleimaniAsl S, Shabab N, Karimi J and Mehdizadeh M. Downregulation of adiponectin system in granulosa cells and low levels of HMW adiponectin in PCOS. J Assist Reprod Genet 2016; 33: 101-110.

[10] Katsikis I, Mouslech T, Kourtis A, Panidis D and Georgopoulos NA. Oligo-ovulation or anovulation and hyperandrogenemia contribute to the decreased serum adiponectin levels in normal-weight women with PCOS with obesity and insulin resistance. Fertil Steril 2009; 91: e3; author reply e4.

[11] Diez JJ and Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol 2003; 148: 293-300.

[12] Pollin TI, Tanner K, O'Connell J R, Ott SH, Damcott CM, Shuldiner AR, McLenithan JC and Mitchell BD. Linkage of plasma adiponectin levels to 3q27 explained by association with variation in the APM1 gene. Diabetes 2005; 54: 268-274.

[13] Nambiar V, Vijesh VV, Lakshmanan P, Sukumaran S and Suganthi R. Association of adiponectin and resistin gene polymorphisms in South Indian women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2016; 200: 82-88.

[14] Zhang W, Wu X, Ding M, Yu X, Liu G and Shi Y. Case-control based study between polymorphisms in the adiponectin gene and polycystic ovary syndrome. Chin J Obstet Gynecol 2015; 50: 825-829.

[15] Li L, Yun JH, Lee JH, Song S, Choi BC and Baek KH. Association study of +45G15G(T/G) and +276(G/T) polymorphisms in the adiponectin gene in patients with polycystic ovary syndrome. Int J Mol Med 2011; 27: 283-287.

[16] Yoshihara K, Yahata T, Kashima K, Mikami T and Tanaka K. Association of single nucleotide polymorphisms in adiponectin and its receptor genes with polycystic ovary syndrome. J Reprod Med 2009; 54: 669-674.

[17] Zhang N, Shi YH, Hao CF, Gu HF, Li Y, Zhao YR, Wang LC and Chen ZJ. Association of +45G15G(T/G) and +276(G/T) polymorphisms in the ADIPOQ gene with polycystic ovary syndrome among Han Chinese women. Eur J Endocrinol 2008; 158: 255-260.

[18] Ramezani Tehrani F, Daneshpour M, Hashemi S, Zarkesh M and Azizi F. Relationship between polymorphism of insulin receptor gene, and adiponectin gene with PCOS. Iran J Reprod Med 2013; 11: 185-194.

[19] Pau C, Saxena R and Welt CK. Evaluating reported candidate gene associations with polycystic ovary syndrome. Fertil Steril 2013; 99: 1774-1778.

[20] Ranjzad F, Mahmoudi T, Irani Shemirani A, Mahban A, Nikzamir A, Vahedi M, Ashrafi M and Gourabi H. A common variant in the adiponectin gene and polycystic ovary syndrome risk. Mol Biol Rep 2012; 39: 2313-2319.

[21] Demirci H, Yilmaz M, Ergun MA, Yurtcu E, Bukan N and Ayvaz G. Frequency of adiponectin gene polymorphisms in polycystic ovary syndrome and the association with serum adiponectin, androgen levels, insulin resistance and clinical parameters. Gynecol Endocrinol 2010; 26: 348-355.

[22] Escobar-Morreale HF, Villuendas G, Botella-Carretero JI, Alvarez-Blasco F, Sanchon R, Luque-Ramirez M and San Millan JL. Adiponectin and resistin in PCOS: a clinical, biochemical and molecular genetic study. Hum Reprod 2006; 21: 2257-2265.

[23] Xita N, Georgiou I, Chatzikyriakidou A, Vounatsou M, Papassotiriou GP, Papassotiriou I and Tsatsoulis A. Effect of adiponectin gene polymorphisms on circulating adiponectin and insulin resistance indexes in women with polycystic ovary syndrome. Clin Chem 2005; 51: 416-423.

[24] Haap M, Machicao F, Stefan N, Thamer C, Tschritter O, Schnuck F, Wallwiener D, Stumvoll M, Haring HU and Fritsche A. Genetic determinants of insulin action in polycystic ovary syndrome. Exp Clin Endocrinol Diabetes 2005; 113: 275-281.

[25] Heinonen S, Korhonen S, Helisalmi S, Koivunen R, Tapanainen J, Hippelainen M and Laakso M. Associations between two single nucleotide polymorphisms in the adiponectin gene and polycystic ovary syndrome. Gynecol Endocrinol 2005; 21: 165-169.

[26] Panidis D, Kourtis A, Kukuvitis A, Farmakiotis D, Xita N, Georgiou I and Tsatsoulis A. Association of the T45G polymorphism in exon 2 of the adiponectin gene with polycystic ovary syndrome: role of Delta4-androstenedione. Hum Reprod 2004; 19: 1728-1733.

[27] Radavelli-Bagatini S, de Oliveira IO, Ramos RB, Santos BR, Wagner MS, Lecke SB, Gigante DP, Horta BL and Spritzer PM. Haplotype TGTG from SNP 45T/G and 276G/T of the adiponectin gene contributes to risk of polycystic ovary syndrome. J Endocrinol Invest 2013; 36: 497-502.

[28] Gao L, Zhang Y, Cui Y, Jiang Y, Wang X and Liu J. Association of the T45G and G276T polymorphisms in the adiponectin gene with PCOS: a meta-analysis. Gynecol Endocrinol 2012; 28: 106-110.

[29] Xian L, He W, Pang F and Hu Y. ADIPOQ gene polymorphisms and susceptibility to polycystic ovary syndrome: a HuGE survey and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2012; 161: 117-124.

[30] Jia H, Yu L, Guo X, Gao W and Jiang Z. Associations of adiponectin gene polymorphisms with polycystic ovary syndrome: a meta-analysis. Endocrine 2012; 42: 299-306.

[31] Zhang W, Wu X, Ding M, Yu X, Liu G and Shi Y. [Case-control based study between polymorphisms in the adiponectin gene and polycystic ovary syndrome]. Zhonghua Fu Chan Ke Za Zhi 2015; 50: 825-829.

[32] Radavelli-Bagatini S, de Oliveira IO, Ramos RB, Santos BR, Wagner MS, Lecke SB, Gigante DP, Horta BL and Spritzer PM. Haplotype TGTG from SNP 45T/G and 276G/T of the adiponectin gene contributes to risk of polycystic ovary syndrome. J Endocrinol Invest 2013; 36: 497-502.

[33] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.

[34] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

[35] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

[36] San Millan JL, Corton M, Villuendas G, Sancho J, Peral B and Escobar-Morreale HF. Association of the polycystic ovary syndrome with genomic variants related to insulin resistance, type 2 diabetes mellitus, and obesity. J Clin Endocrinol Metab 2004; 89: 2640-2646.

[37] Toulis KA, Goulis DG, Farmakiotis D, Georgopoulos NA, Katsikis I, Tarlatzis BC, Papadimas I and Panidis D. Adiponectin levels in women with polycystic ovary syndrome: a systematic review and a meta-analysis. Hum Reprod Update 2009; 15: 297-307.

[38] Li P, Jiang R, Li L, Liu C, Yang F and Qiu Y. Correlation of serum adiponectin and adiponectin gene polymorphism with metabolic syndrome in Chinese adolescents. Eur J Clin Nutr 2015; 69: 62-67.