Int J Clin Exp Med 2015;8(10):17418-17429
www.ijcem.com /ISSN:1940-5901/IJCEM0014639

Original Article

Peroxisome proliferator-activated receptor gamma rs1801282 C>G polymorphism is associated with polycystic ovary syndrome susceptibility: a meta-analysis involving 7,069 subjects

Sheng Zhang[1*], Yafeng Wang[2*], Heping Jiang[3*], Chao Liu[4], Bin Sun[4], Shuchen Chen[5], Mingqiang Kang[5], Weifeng Tang[4,5]

[1]Department of General Surgery, Changzhou No. 3 People's Hospital, Changzhou, Jiangsu Province, China; [2]Department of Cardiology, The People's Hospital of Xishuangbanna Dai Autonomous Prefecture, Jinghong, Yunnan Province, China; [3]Emergency Department, Affiliated Jintan People's Hospital of Jiangsu University, Jintan, China; [4]Department of Cardiothoracic Surgery, Affiliated People's Hospital of Jiangsu University, Zhenjiang, Jiangsu Province, China; [5]Department of Thoracic Surgery, The Union Clinical Medical College of Fujian Medical University, Fuzhou, Fujian Province, China. [*]Equal contributors.

Received August 17, 2015; Accepted October 6, 2015; Epub October 15, 2015; Published October 30, 2015

Abstract: In the *peroxisome proliferator-activated receptor gamma* (*PPARG*) gene, a polymorphism (rs1801282 C>G), has been shown to change an amino acid residue and then results in alternation of *PPARG* function. A number of studies have explored the relationship between *PPARG* rs1801282 C>G variants and polycystic ovary syndrome (PCOS) risk, but yielding inconsistent findings, especially in Asian population. This study aimed to assess the role of *PPARG* rs1801282 C>G polymorphism in susceptibility to PCOS. Databases of Pubmed, Embase and China National Knowledge Internet (CNKI) were searched until August 2, 2015. The association of PPARG 1801282 C>G polymorphism with PCOS risk was evaluated by crude odds ratios (ORs) with their 95% confidence intervals (CIs). Finally, there were twenty-three studies involving 3,458 PCOS cases and 3,611 controls included in our pooled analysis. Significant associations were identified between PPARG rs1801282 C>G variants and decreased PCOS risk in three genetic comparison models (OR, 0.78; 95% CI, 0.69-0.89; P < 0.001 for G *vs.* C; OR, 0.77; 95% CI, 0.68-0.89; P < 0.001 for GG+CG *vs.* CC and OR, 0.79; 95% CI, 0.68-0.91; P = 0.001 for CG *vs.* CC). In a subgroup analysis by race, significant correlation was also observed between PPARG rs1801282 C>G variants and decreased PCOS risk in three genetic models: G *vs.* C (OR, 0.83; 95% CI, 0.71-0.97; P = 0.019) and GG+CG vs. CC (OR, 0.83; 95% CI, 0.70-0.99; P = 0.033) among Caucasians and in one genetic models: G *vs.* C (OR, 0.72; 95% CI, 0.59-0.88; P = 0.001) among Asians. In summary, our results demonstrate that PPARG rs1801282 C>G polymorphism may be a protective factor for PCOS.

Keywords: Polycystic ovary syndrome, polymorphism, peroxisome proliferator-activated receptor gamma, meta-analysis

Introduction

Polycystic ovary syndrome (PCOS) is characterized by exaggerated production of androgens, ovulatory dysfunction and abnormalities in ovarian morphology, which affects about 5%-10% of women of reproductive age and is a leading cause of infertility [1, 2]. PCOS is a common disease which is attributed to a handful of genetic and environmental risk factors. Various PCOS phenotypes may probably result from the interaction between a number of predisposing genomic mutations, each exerting only minor functions and strong environmental influences [3]. Of late, many candidate genes, such as *insulin receptor substrate-1/2, follicle stimulating hormone receptor* and *insulin receptor*, have been identified to contribute to PCOS risk [4-8].

Accumulating evidences demonstrate that impaired glucose tolerance, insulin resistance (IR)

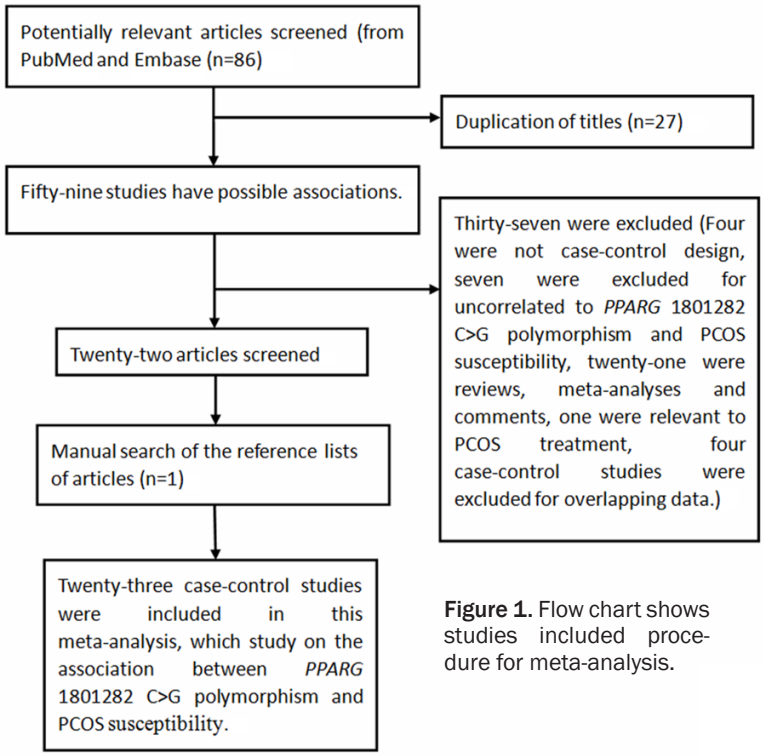

Figure 1. Flow chart shows studies included procedure for meta-analysis.

and type 2 diabetes mellitus (T2DM) are correlated with the development of PCOS [9-11]. Peroxisome proliferator-activated receptor gamma (PPARG), a known nuclear hormone receptor, regulates intracellular insulin-signaling events and controls adipocyte differentiation, lipid and glucose homeostasis. Prior studies have therefore explored the hypothesis that the mutation of *PPARG* gene involves in the development and progression of PCOS. Some single nucleotide polymorphisms (SNPs) of *PPARG* gene are deemed to influence the activity of PPARG. *PPARG* gene is polymorphic, and many SNPs have been identified, such as the rs1801282, rs4135247, rs3856806, rs1175543, rs2938395 and rs709158 polymorphisms, etc. Among these SNPs, the *PPARG* rs1801282 C>G polymorphism are the most widely studied for the relationship with PCOS susceptibility.

Recently, mounting studies have focused on the relationship of PPARG rs1801282 C>G polymorphism with PCOS. In several previous study, PPARG rs1801282 C>G polymorphism was correlated with decreased risk of PCOS [12, 13]; however, an association between this SNP and the increased susceptibility of PCOS was found in another study [14]. Several meta-analyses suggested that PPARG rs1801282 C>G polymorphism was correlated with the decreased susceptibility of PCOS, especially in Caucasians [15, 16]; however, in these studies, the included studies were seldom conducted in Asians populations. Now, more studies have focused on the association between PPARG rs1801282 C>G polymorphism and the risk of PCOS in Asians; nevertheless, the result remains inconclusive. Therefore, an updated meta-analysis was conducted to further clarify the role of the PPARG polymorphisms in PCOS risk.

Materials and methods

Search strategy

We extensively searched literatures from PubMed, Embase and China National Knowledge Internet (CNKI) databases (published up to August 2, 2015) using the following words 'Peroxisome proliferator-activated receptor gamma', 'PPARG' 'PPARγ', 'polymorphism', 'SNP', 'variant', 'polycystic ovary syndrome', 'PCOS'. The relevant publications in the references were also manually scanned. If there were overlapping data, only the latest investigation with the larger subjects was recruited.

Inclusion and exclusion criteria

In the current analysis, all publications included had to meet the following criteria: (a) designed as a case-control or a cohort study; (b) assessed the relationship of PPARG rs1801282 C>G polymorphism with PCOS risk; (c) the available frequencies of genotypes or alleles must be provided. The major reasons for exclusion-were: (a) incomplete data; (b) overlapping data; (c) only relevant to PCOS treatment; (d) review, editorial, comment, meta-analysis or letter.

Data extraction

In a uniform table, three reviewers (S. Zhang, Y. Wang and H. Jiang) independently extracted the relevant data from all included studies. The

Table 1. Characteristics of the included studies

Study	Year	Country	Ethnicity	Sample size	Genotype method
Baldani et al.	2014	Croatia	Caucasians	151/179	TaqMan
Yang et al.	2013	China	Asians	120/118	RFLP
Shaikh et al.	2013	Indian	Asians	450/300	Direct sequencing
Hemimi et al.	2013	USA	Caucasians	50/96	RFLP
Dasgupta et al.	2012	Indian	Asians	250/299	PCR
Bidzińska-Speichert et al.	2011	Poland	Caucasians	54/51	RFLP
Christopoulos et al.	2010	Greece	Caucasians	183/148	RFLP
San-Millán et al.	2010	Spain	Caucasians	161/113	RFLP
Chae et al.	2009	Korea	Asians	184/256	RT-PCR
Xita et al.	2009	Greece	Caucasians	180/140	RFLP
Gu et al.	2009	Korea	Asians	238/125	RFLP
Koika et al.	2009	Greece	Caucasians	156/56	RFLP
Zheng et al.	2008	China	Asians	150/135	RFLP
Knebel et al.	2008	German	Caucasians	21/120	RFLP
Antoine et al.	2007	USA	Caucasians	285/187	TaqMan
Guzman et al.	2007	Chile	Caucasians	50/75	RFLP
Yilmaz et al.	2006	Turkey	Caucasians	100/100	RFLP
Wang et al.	2006	China	Asians	201/147	RFLP
Haap et al.	2005	German	Caucasians	57/567	PCR
Hahn et al.	2005	German	Caucasians	102/104	RFLP
Tok et al.	2005	Turkey	Caucasians	60/60	PCR
Oroi et al.	2004	Italy	Caucasians	120/120	RFLP
Korhonen et al.	2003	Finland	Caucasians	135/115	SSCP

RT-PCR: real-time PCR; RFLP: restriction fragment length polymorphism; SSCP: single strand conformation polymorphism.

following characteristics were extracted: (a) first author, (b) year of publication, (c) country of study, (d) ethnicity, (e) the allele and genotype frequencies, (f) genotyping method, (g) sample size and (H) the evidence of HWE in controls. If disputes generated, they were solved by consulting the third author (W. Tang).

Statistical analysis

In our study, the pooled odds ratios (ORs) with their 95% confidence intervals (CIs) were measured for dominant model, recessive model, heterozygote comparison, homozygote comparison and allelic comparison. A stratified analysis was performed by ethnicity. Heterogeneity among the included studies was evaluated by using a χ^2-test-based Q statistic test. The value of $P < 0.1$ was considered as a substantial heterogeneity across the publications, then the data were pooled by using the random-effects model (DerSimonian and Laird) [17]; otherwise, the fixed-effects model was harnessed (Mantel-Haenszel) [18]. Sensitivity analysis was conducted to check the stability of this meta-analysis. Potential publication bias was assessed by a funnel plots and Egger's linear regression test [19]. A $P < 0.1$ was considered as statistical significance. The distribution of the genotypes in controls was tested for Hardy-Weinberg equilibrium (HWE) using a web-based χ^2 test program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Data analysis was conducted with STATA 12.0 software package (Stata Corp LP, College Station, Texas).

Results

Study characteristics

As summarized in **Figure 1**, a total of eighty-six potentially relevant publications were retrieved based on the search words from PubMed, Embase and CNKI databases. Finally, there were twenty-three publications [12-14, 20-39] involving 3,458 PCOS cases and 3,611 controls included in our analysis. In additional, all subjects were female. As for subjects in these

Table 2. Distribution of *PPARG* rs1801282 C>G polymorphism genotypes and alleles

Study	Year	Case			Control			Case		Control		HWE
		CC	CG	GG	CC	CG	GG	G	C	G	C	
Baldani et al.	2014	106	43	2	129	47	3	47	255	53	305	Yes
Yang et al.	2013	111	9	0	101	17	0	9	231	17	219	Yes
Shaikh et al.	2013	381	65	4	219	79	2	73	827	83	517	Yes
Hemimi et al.	2013	43	7	0	74	22	0	7	93	22	170	Yes
Dasgupta et al.	2012	197	36	10	211	53	17	56	430	87	475	No
Bidzińska-Speichert et al.	2011	35	13	6	30	15	6	25	83	27	75	Yes
Christopoulos et al.	2010	166	14	3	131	15	2	20	346	19	277	Yes
San-Millán et al.	2010	141	20	0	92	21	0	20	302	21	205	Yes
Chae et al.	2009	171	11	2	230	23	3	15	353	29	483	No
Xita et al.	2009	150	30	0	122	17	1	30	330	19	261	Yes
Gu et al.	2009	222	16	0	125	0	0	16	460	0	250	No
Koika et al.	2009	136	19	1	48	6	2	21	291	10	102	No
Zheng et al.	2008	140	10	0	127	8	0	10	290	8	262	Yes
Knebel et al.	2008	17	4	0	99	19	2	4	38	23	217	Yes
Antoine et al.	2007	213	52	2	134	29	5	56	478	39	297	No
Guzman et al.	2007	42	7	1	59	14	2	9	91	18	132	Yes
Yilmaz et al.	2006	85	15	0	78	22	0	15	185	22	178	Yes
Wang et al.	2006	183	18	0	136	10	1	18	384	12	282	Yes
Haap et al.	2005	43	9	1	407	133	6	11	95	145	947	Yes
Hahn et al.	2005	79	22	1	80	24	0	24	180	24	184	Yes
Tok et al.	2005	54	6	0	47	13	0	6	114	13	107	Yes
Oroi et al.	2004	113	7	0	115	5	0	7	233	5	235	Yes
Korhonen et al.	2003	104	28	3	76	34	5	34	236	44	186	Yes

HWE: Hardy-Weinberg equilibrium.

studies, sixteen studies focused on Caucasians [13, 20-34] and seven studies focused on Asians [12, 14, 35-39]. As for HWE test, eighteen studies conformed to HWE [13, 22-34, 37-39], while five studies deviated from the HWE [14, 20, 21, 35, 36]. Characteristics of the included studies and distribution of the PPARG rs1801282 C>G variants as well as alleles are listed in **Tables 1** and **2**, respectively.

Association between PPARG rs1801282 C>G polymorphism and the risk of pcos

A total of 3,458 PCOS cases and 3,611 controls from twenty-three eligible studies were relevant to the relationship between PPARG rs1801282 C>G polymorphism and PCOS risk. In overall meta-analysis, significantly decreased PCOS risk was associated with PPARG rs1801282 C>G variants in three genetic models: G vs. C (OR, 0.78; 95% CI, 0.69-0.89; P < 0.001), GG+CG vs. CC (OR, 0.77; 95% CI, 0.68-0.89; P < 0.001) and CG vs. CC (OR, 0.79; 95% CI, 0.68-0.91; P = 0.001) (**Table 3**). Additionally, in a subgroup analysis by ethnicity, a significantly decreased PCOS risk was also identified among Caucasians in three genetic models: G vs. C (OR, 0.83; 95% CI, 0.71-0.97; P = 0.019) and GG+CG vs. CC (OR, 0.83; 95% CI, 0.70-0.99; P = 0.033) (**Table 3**; **Figures 2** and **3**) and among Asians in one genetic model: G vs. C (OR, 0.72; 95% CI, 0.59-0.88; P = 0.001) (**Table 3**; **Figure 2**).

Publication bias and non-parametric 'trim-and-fill'

Funnel plots and the Egger's linear regression test were conducted to measure potential publication bias among literatures [19]. A slight publication bias was identified in some genetic comparison models (G vs. C: Begg's test P = 0.635, Egger's test P = 0.084; GG vs. CC: Begg's test P = 0.767, Egger's test P = 0.925; GG+CG vs. CC: Begg's test P = 0.492, Egger's test P = 0.081; GG vs. CG+CC: Begg's test P =

Table 3. Meta-Analysis of *PPARG* rs1801282 C>G polymorphism with polycystic ovary syndrome risk

	No. of study	G vs. C			GG vs. CC			GG+CG vs. CC			GG vs. CG+CC			CG vs. CC		
		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)	OR (95% CI)	P	P (Q-test)
Total	23	0.78 (0.69-0.89)	< 0.001	0.458	0.66 (0.43-1.02)	0.060	0.962	0.77 (0.68-0.89)	< 0.001	0.229	0.70 (0.46-1.07)	0.098	0.947	0.79 (0.68-0.91)	0.001	0.122
Ethnicity																
Asians	7	0.72 (0.59-0.88)	0.001	0.112	0.69 (0.36-1.32)	0.264	0.834	0.73 (0.50-1.06)	0.102	0.051	0.74 (0.39-1.41)	0.353	0.788	0.75 (0.49-1.13)	0.165	0.032
Caucasians	16	0.83 (0.71-0.97)	0.019	0.842	0.64 (0.37-1.14)	0.128	0.871	0.83 (0.70-0.99)	0.033	0.720	0.67 (0.38-1.18)	0.167	0.849	0.85 (0.71-1.01)	0.071	0.595
HWE																
Yes	18	0.76 (0.66-0.88)	< 0.001	0.493	0.81 (0.46-1.45)	0.481	0.980	0.74 (0.63-0.86)	< 0.001	0.288	0.87 (0.49-1.54)	0.623	0.977	0.73 (0.62-0.86)	< 0.001	0.206
No	5	0.84 (0.66-1.06)	0.134	0.217	0.52 (0.27-0.99)	0.047	0.557	0.89 (0.69-1.16)	0.392	0.163	0.54 (0.29-1.02)	0.059	0.508	0.97 (0.73-1.29)	0.854	0.121

HWE: Hardy-Weinberg equilibrium. Bold values are statistically significant (P < 0.05).

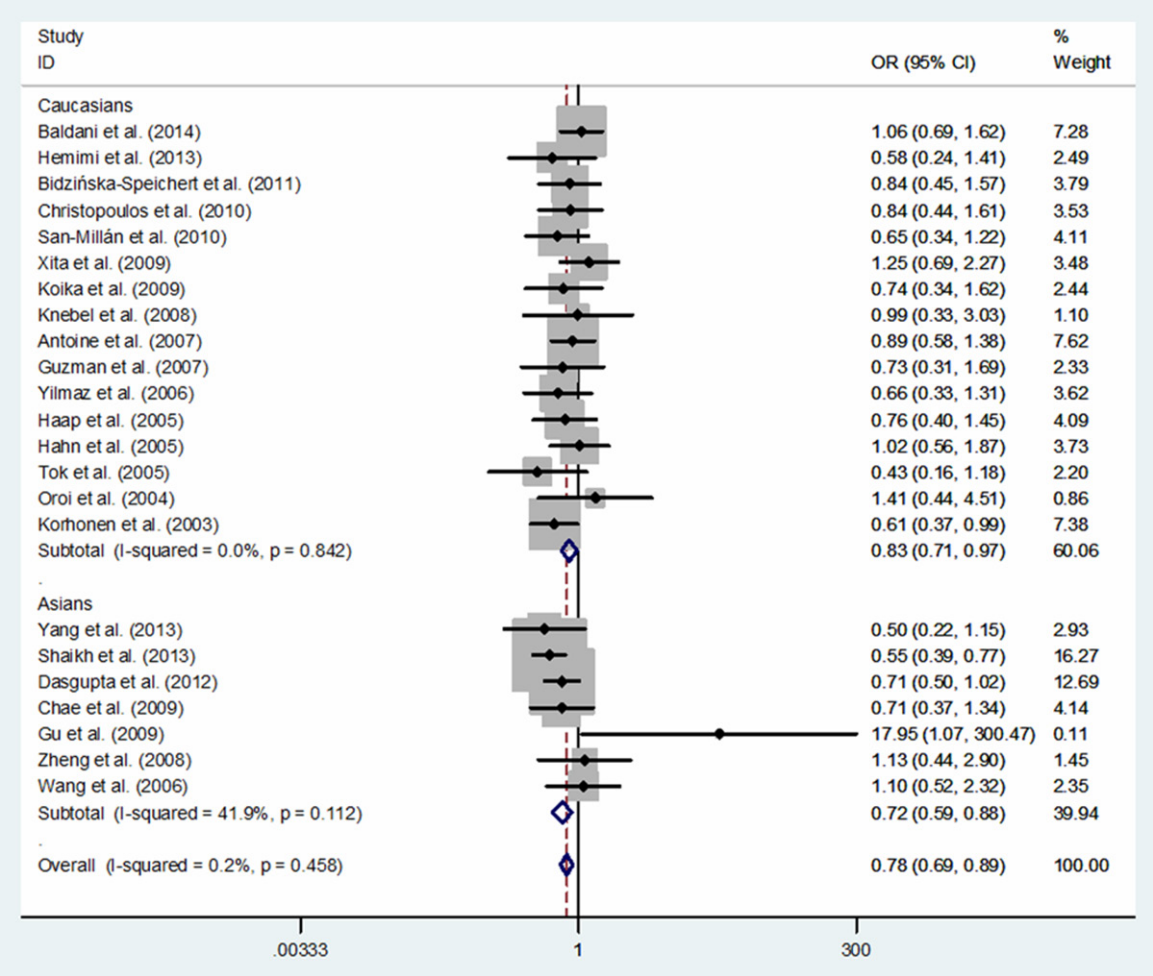

Figure 2. Forest plot of PCOS risk associated with *PPARG* rs1801282 C>G polymorphism for the G vs. C (fixed effects model).

0.843, Egger's test P = 0.961; CG vs. CC: Begg's test P = 0.369, Egger's test P = 0.090; **Figure 4**). Thus, non-parametric 'trim-and-fill' method was used to calculate the adjusted ORs and CIs. The results also suggested that PPARG rs1801282 C>G variants may be a protective factor for PCOS risk (G vs. C: adjusted pooled OR = 0.76, 95% CI: 0.67-0.86, P < 0.001; GG vs. CC: adjusted pooled OR = 0.67, 95% CI: 0.43-1.04, P = 0.073; GG+CG vs. CC: adjusted pooled OR = 0.74, 95% CI: 0.65-0.85, P < 0.001; GG vs. CG+CC: adjusted pooled OR = 0.71, 95% CI: 0.46-1.09, P = 0.119; CG vs. CC: adjusted pooled OR = 0.713, 95% CI: 0.622-0.818, P < 0.001; **Figure 5**).

Sensitivity analyses

One-way sensitivity analysis was harnessed to check the stability of our findings. The results demonstrated that there were not significantly altered when anyone was omitted at a time, attesting the robustness of our findings (**Figure 6**).

Tests for heterogeneity

Heterogeneity across studies was listed in **Table 3**. There was no significant heterogeneity in five genetic models, suggesting the robustness of our findings.

Discussion

PCOS is a common cause of infertility, which affects 6-10% of reproductive-aged women [40]. The etiology of PCOS is very complex and was not completely understood. PCOS is characterized by hyperandrogenism, peripheral IR, glucose-stimulated hyperinsulinemia, abnormalities of energy expenditure and dyslipidemia and chronic anovulation [41-43]. Addi-

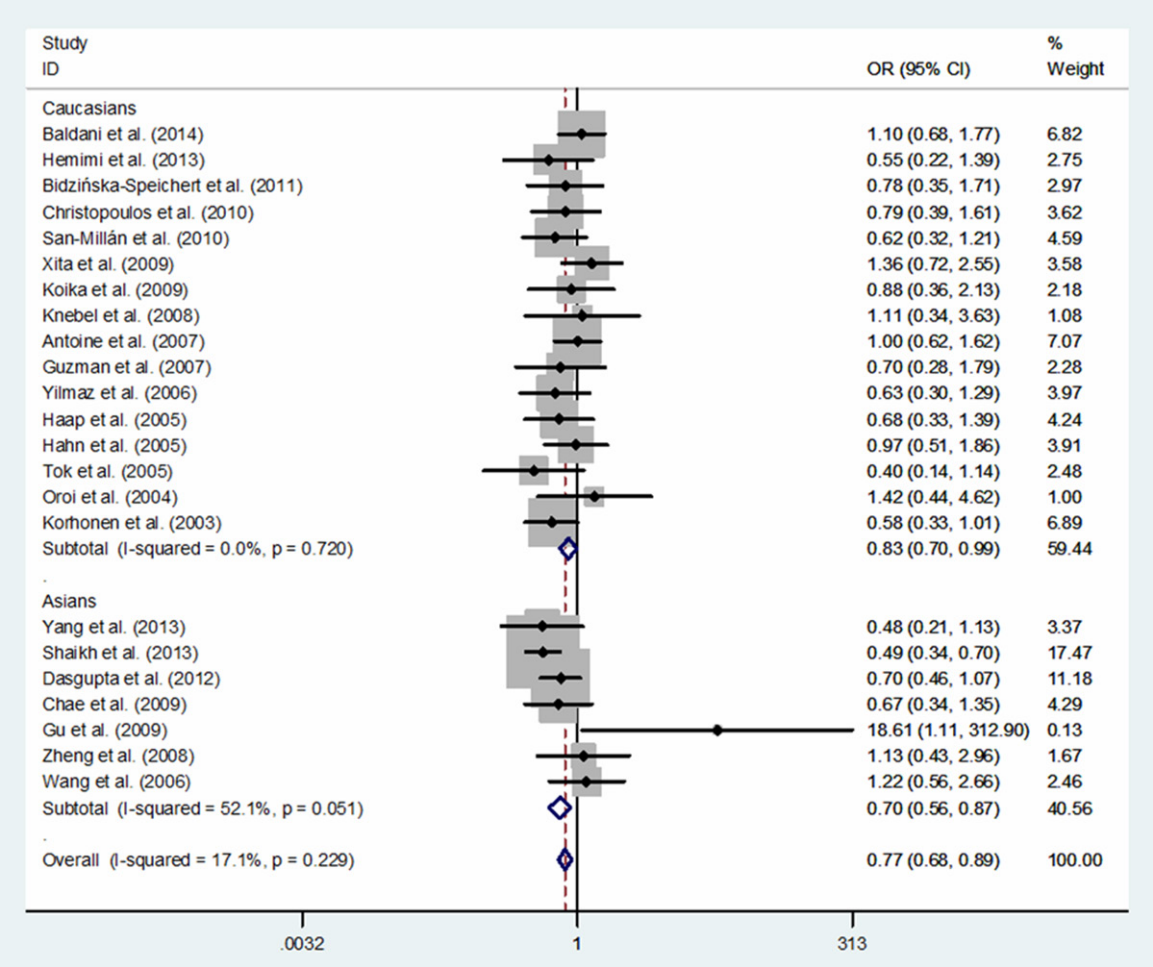

Figure 3. Forest plot of PCOS risk associated with *PPARG* rs1801282 C>G polymorphism for the GG+CG vs. CC (fixed effects model).

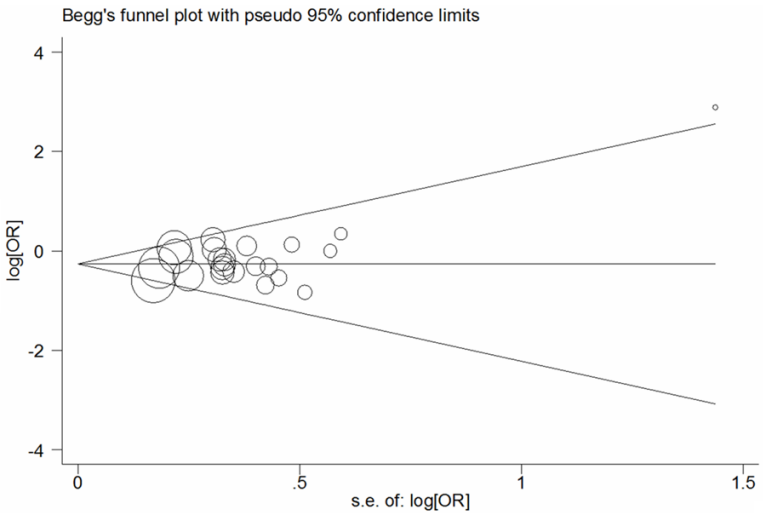

Figure 4. Begg's funnel plot analysis of *PPARG* rs1801282 C>G polymorphism with PCOS risk for the G vs. C (fixed-effects model).

tionally, a higher risk of developing impaired glucose tolerance at a relatively younger age and probably T2DM later in life is found in PCOS cases [44, 45]. It is also reported that PCOS patients accompanied with significant IR in a few classic insulin target tissues, including adipocytes and skeletal muscle [46]. In view of these primary findings, the PPARG rs1801282 C>G polymorphism have been extensively studied for the relationship with PCOS susceptibility. Results of previous meta-analyses demonstrated that the PPARG rs1801282 G

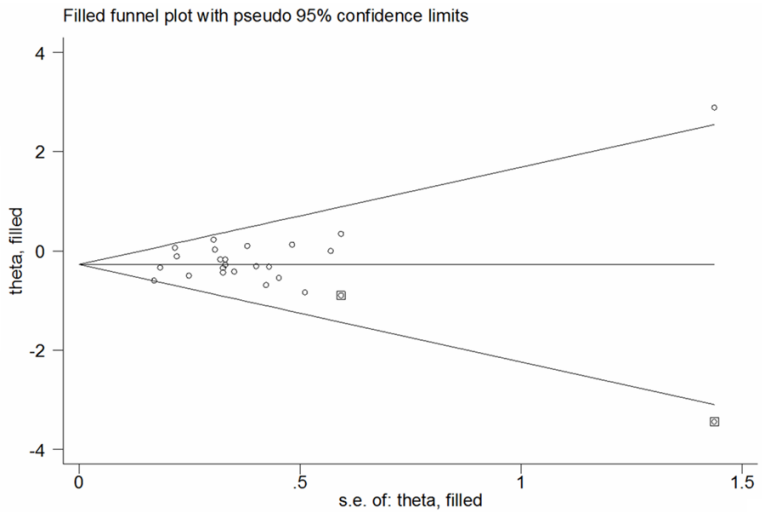

Figure 5. Filled funnel plot of *PPARG* rs1801282 C>G polymorphism with PCOS risk for the G vs. C (fixed-effects model).

allele modified the risk of PCOS in Caucasians [15, 16]. Recently, more case-control studies were conducted on the association of PPARG rs1801282 C>G polymorphism with PCOS susceptibility; however, the results were inconclusive, especially in Asian population. In this study, we summarized data for 3,458 PCOS cases and 3,611 controls from twenty-three included studies and attempted to examine the risk of PPARG rs1801282 C>G variants to PCOS by an updated meta-analysis. Our findings suggested that PPARG rs1801282 G allele might significantly decrease the risk of PCOS in both Caucasians and Asians.

PPARG, a nuclear hormone receptor, recognizes and binds to the certain PPARG response elements, then regulates the target genes in their promoter region. PPARG plays a vital role in insulin sensitization, lipogenesis, glucose homeostasis, inflammatory cytokine production and cell differentiation [47]. The PPARG rs1801282 C>G variant, a common polymorphism in exon 2 of PPARG gene, encodes a Pro→Ala substitution (Pro12Ala) [48]. As demonstrated in a previous study, the missense substitution of PPARG Pro12Ala could cause less transcriptional activation of target genes in vitro [49], it may presumably affect the risk of PCOS. In combination with this pooled analysis, our findings suggested that PPARG rs1801282 C>G polymorphism may decreased the risk of PCOS, probably through changing binding capacity for PPARG response elements, and then promoting anti-proliferative, pro-differentiation and pro-apoptotic properties. In our study, five studies deviated from the HWE, which showed the presence of population stratification and/or genotyping errors [14, 20, 21, 35, 36]. When we omitted these studies, the relationship between PPARG rs1801282 C>G polymorphism and PCOS was also significant with respect to the three genetic models (OR, 0.76; 95% CI, 0.66-0.88; $P < 0.001$ for G vs. C; OR, 0.74; 95% CI, 0.63-0.86; $P < 0.001$ for GG+CG vs. CC and OR, 0.73; 95% CI, 0.62-0.86; $P < 0.001$ for CG vs. CC; **Table 3**), attesting the robustness of our findings.

Some merits should be mentioned in our study. First of all, the sample sizes of our study were larger than several previous studies [15, 16, 50]. Secondly, for the first time, we highlighted PPARG rs1801282 G allele decreased the susceptibility of PCOS in Asians. Finally, in current study, there was no significant heterogeneity in all genetic models, suggesting the robustness of our findings. But, some limitations need to be acknowledged. Only published studies were included in our pooled analysis, certain bias may inevitably exist. Moreover, in this study, most of publications were conducted mainly in Caucasians. Only seven studies focused on Asians, which limited the power to measure a real influence. Hence, large-scale studies in Asian populations are needed. Furthermore, due to lack of sufficient information, further evaluation of potential interactions, such as age, family history, and body mass index, was not carried out. In consideration of the complex etiology of PCOS, these factors should not be ignored. Finally, the correlation of other important SNPs of *PPARG* gene (e.g., rs4135247, rs1175543, rs709158, rs3856806 and rs2938395) with PCOS was seldom studied, these SNPs were not considered in current study.

In summary, our findings highlight that PPARG rs1801282 C>G variants are correlated with a decreased risk of PCOS in both Caucasians

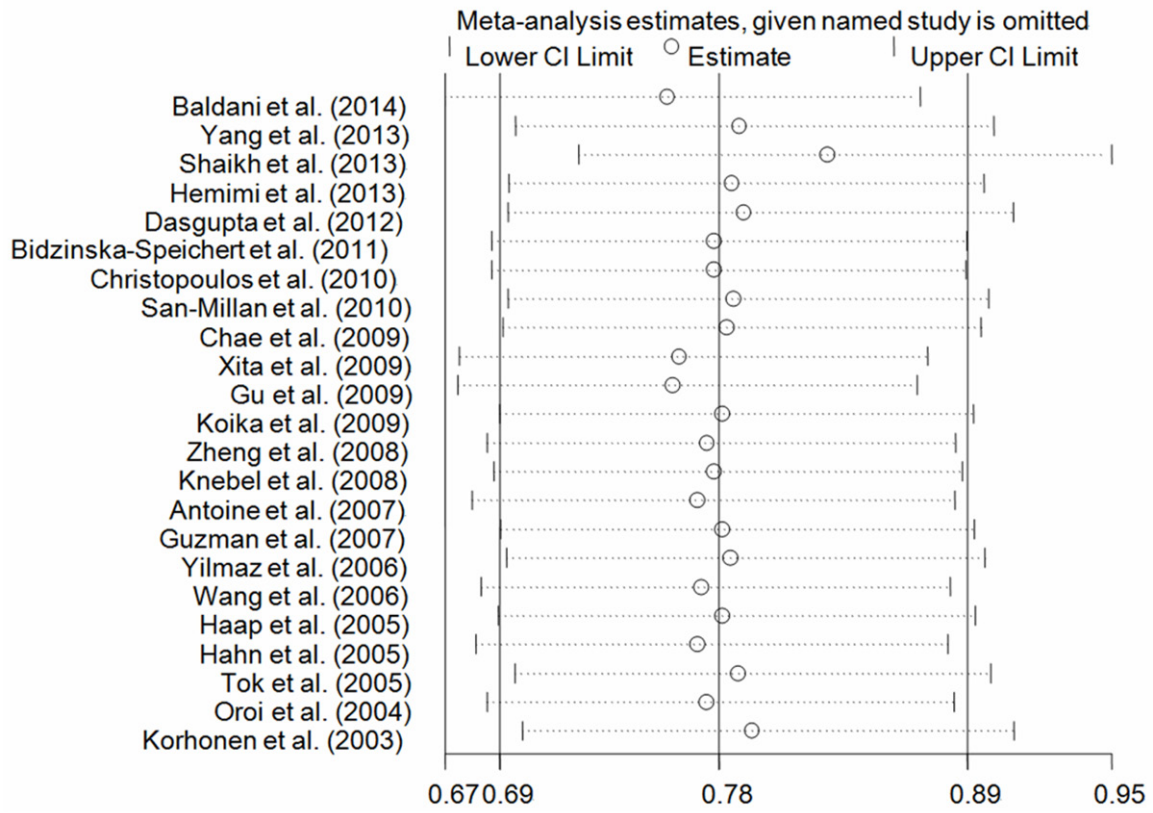

Figure 6. One-way sensitivity analysis of *PPARG* rs1801282 C>G polymorphism with PCOS risk for the G vs. C (fixed-effects model).

and Asians. In the future, larger and well-designed epidemiological studies are definitely demanded to further confirm our findings.

Acknowledgements

This study was supported in part by Jiangsu University Clinical Medicine Science and Technology Development Fund (JLY20140012), National Natural Science Foundation of China (81472332, 81341006), Fujian Province Natural Science Foundation (2013J01126, 2013-J05116), Fujian Medical University professor fund (JS12008), The Fund of Union Hospital (2015TC-1-048 and 2015TC-2-004) and Fujian Province Science and Technology Programmed Fund (2012Y0030).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Weifeng Tang, Department of Cardiothoracic Surgery, Affiliated People's Hospital of Jiangsu University, Zhenjiang 212000, China. E-mail: twf001001@126.com; Dr. Sheng Zhang, Department of General Surgery, Changzhou No. 3 People's Hospital, Changzhou 213000, China. E-mail: 13601507172@163.com

References

[1] Ehrmann DA. Polycystic ovary syndrome. N Engl J Med 2005; 352: 1223-1236.

[2] Pasquali R and Gambineri A. Polycystic ovary syndrome: a multifaceted disease from adolescence to adult age. Ann N Y Acad Sci 2006; 1092: 158-174.

[3] Diamanti-Kandarakis E and Piperi C. Genetics of polycystic ovary syndrome: searching for the way out of the labyrinth. Hum Reprod Update 2005; 11: 631-643.

[4] Diamanti-Kandarakis E and Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev 2012; 33: 981-1030.

[5] Villuendas G, Botella-Carretero JI, Roldan B, Sancho J, Escobar-Morreale HF and San Millan JL. Polymorphisms in the insulin receptor substrate-1 (IRS-1) gene and the insulin receptor substrate-2 (IRS-2) gene influence glucose ho-

meostasis and body mass index in women with polycystic ovary syndrome and non-hyperandrogenic controls. Hum Reprod 2005; 20: 3184-3191.

[6] Saxena R, Georgopoulos NA, Braaten TJ, Bjonnes AC, Koika V, Panidis D and Welt CK. Han Chinese polycystic ovary syndrome risk variants in women of European ancestry: relationship to FSH levels and glucose tolerance. Hum Reprod 2015; 30: 1454-1459.

[7] Wu S, Divall S, Nwaopara A, Radovick S, Wondisford F, Ko C and Wolfe A. Obesity-induced infertility and hyperandrogenism are corrected by deletion of the insulin receptor in the ovarian theca cell. Diabetes 2014; 63: 1270-1282.

[8] Li M, Youngren JF, Dunaif A, Goldfine ID, Maddux BA, Zhang BB and Evans JL. Decreased insulin receptor (IR) autophosphorylation in fibroblasts from patients with PCOS: effects of serine kinase inhibitors and IR activators. J Clin Endocrinol Metab 2002; 87: 4088-4093.

[9] Legro RS, Kunselman AR, Dodson WC and Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999; 84: 165-169.

[10] Greenwood EA, Pasch LA, Shinkai K, Cedars MI and Huddleston HG. Putative role for insulin resistance in depression risk in polycystic ovary syndrome. Fertil Steril 2015; 104: 707-714. e1.

[11] Chen L, Xu WM and Zhang D. Association of abdominal obesity, insulin resistance, and oxidative stress in adipose tissue in women with polycystic ovary syndrome. Fertil Steril 2014; 102: 1167-1174.e1164.

[12] Shaikh N, Mukherjee A, Shah N, Meherji P and Mukherjee S. Peroxisome proliferator activated receptor gamma gene variants influence susceptibility and insulin related traits in Indian women with polycystic ovary syndrome. J Assist Reprod Genet 2013; 30: 913-921.

[13] Korhonen S, Heinonen S, Hiltunen M, Helisalmi S, Hippelainen M, Koivunen R, Tapanainen JS and Laakso M. Polymorphism in the peroxisome proliferator-activated receptor-gamma gene in women with polycystic ovary syndrome. Hum Reprod 2003; 18: 540-543.

[14] Gu BH and Baek KH. Pro12Ala and His447His polymorphisms of PPAR-gamma are associated with polycystic ovary syndrome. Reprod Biomed Online 2009; 18: 644-650.

[15] Zhang H, Bi Y, Hu C, Lu W and Zhu D. Association between the Pro12Ala polymorphism of PPAR-gamma gene and the polycystic ovary syndrome: a meta-analysis of case-control studies. Gene 2012; 503: 12-17.

[16] He J, Wang L, Liu J, Liu F and Li X. A meta-analysis on the association between PPAR-gamma Pro12Ala polymorphism and polycystic ovary syndrome. J Assist Reprod Genet 2012; 29: 669-677.

[17] Hua Z, Li D, Xiang G, Xu F, Jie G, Fu Z, Jie Z, Da P and Li D. PD-1 polymorphisms are associated with sporadic breast cancer in Chinese Han population of Northeast China. Breast Cancer Res Treat 2011; 129: 195-201.

[18] Bayram S, Akkiz H, Ulger Y, Bekar A, Akgollu E and Yildirim S. Lack of an association of programmed cell death-1 PD1.3 polymorphism with risk of hepatocellular carcinoma susceptibility in Turkish population: a case-control study. Gene 2012; 511: 308-313.

[19] 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.

[20] Antoine HJ, Pall M, Trader BC, Chen YD, Azziz R and Goodarzi MO. Genetic variants in peroxisome proliferator-activated receptor gamma influence insulin resistance and testosterone levels in normal women, but not those with polycystic ovary syndrome. Fertil Steril 2007; 87: 862-869.

[21] Koika V, Marioli DJ, Saltamavros AD, Vervita V, Koufogiannis KD, Adonakis G, Decavalas G and Georgopoulos NA. Association of the Pro12Ala polymorphism in peroxisome proliferator-activated receptor gamma2 with decreased basic metabolic rate in women with polycystic ovary syndrome. Eur J Endocrinol 2009; 161: 317-322.

[22] Baldani DP, Skrgatic L, Cerne JZ, Ferk P, Simunic V and Gersak K. Association of Pro12Ala polymorphism with insulin sensitivity and body mass index in patients with polycystic ovary syndrome. Biomed Rep 2014; 2: 199-206.

[23] Bidzinska-Speichert B, Lenarcik A, Tworowska-Bardzinska U, Slezak R, Bednarek-Tupikowska G, Milewicz A and Krepula K. Pro12Ala PPAR gamma2 gene polymorphism in women with polycystic ovary syndrome. Ginekol Pol 2011; 82: 426-429.

[24] Hemimi N.S.E. SIA, Alshawa H.H.A. Association of genetic polymorphism of peroxisome proliferator-activated receptor-gamma gene and polycystic ovary syndrome. FASEB J 2013; 27.

[25] Christopoulos P, Mastorakos G, Gazouli M, Deligeoroglou E, Katsikis I, Diamanti-Kandarakis E, Panidis D and Creatsas G. Peroxisome proliferator-activated receptor-gamma and -delta polymorphisms in women

with polycystic ovary syndrome. Ann N Y Acad Sci 2010; 1205: 185-191.
[26] San-Millan JL and Escobar-Morreale HF. The role of genetic variation in peroxisome proliferator-activated receptors in the polycystic ovary syndrome (PCOS): an original case-control study followed by systematic review and meta-analysis of existing evidence. Clin Endocrinol (Oxf) 2010; 72: 383-392.
[27] Xita N, Lazaros L, Georgiou I and Tsatsoulis A. The Pro12Ala polymorphism of the PPAR-gamma gene is not associated with the polycystic ovary syndrome. Hormones (Athens) 2009; 8: 267-272.
[28] Knebel B, Janssen OE, Hahn S, Jacob S, Gleich J, Kotzka J, Muller-Wieland D. Increased low grade inflammatory serum markers in patients with polycystic ovary syndrome (PCOS) and their relationship to PPARγ gene variants. Expe Clin Endocrinol Diabetes 2008; 116: 6.
[29] Guzman N, Erices L, Valdes P, Salazar L. A common 34C>G variant at the peroxisome proliferator-activated receptor-2 gene in Chilean women with polycystic ovary syndrome and controls. International Journal of Morphology 2007; 25: 7.
[30] Yilmaz M, Ergun MA, Karakoc A, Yurtcu E, Cakir N and Arslan M. Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma gene in women with polycystic ovary syndrome. Gynecol Endocrinol 2006; 22: 336-342.
[31] 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.
[32] Hahn S, Fingerhut A, Khomtsiv U, Khomtsiv L, Tan S, Quadbeck B, Herrmann BL, Knebel B, Muller-Wieland D, Mann K and Janssen OE. The peroxisome proliferator activated receptor gamma Pro12Ala polymorphism is associated with a lower hirsutism score and increased insulin sensitivity in women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 2005; 62: 573-579.
[33] Tok EC, Aktas A, Ertunc D, Erdal EM and Dilek S. Evaluation of glucose metabolism and reproductive hormones in polycystic ovary syndrome on the basis of peroxisome proliferator-activated receptor (PPAR)-gamma2 Pro12Ala genotype. Hum Reprod 2005; 20: 1590-1595.
[34] Orio F Jr, Palomba S, Cascella T, Di Biase S, Labella D, Russo T, Savastano S, Zullo F, Colao A, Vettor R and Lombardi G. Lack of an association between peroxisome proliferator-activated receptor-gamma gene Pro12Ala polymorphism and adiponectin levels in the polycystic ovary syndrome. J Clin Endocrinol Metab 2004; 89: 5110-5115.
[35] Chae SJ, Kim JJ, Choi YM, Kim JM, Cho YM and Moon SY. Peroxisome proliferator-activated receptor-gamma and its coactivator-1alpha gene polymorphisms in Korean women with polycystic ovary syndrome. Gynecol Obstet Invest 2010; 70: 1-7.
[36] Dasgupta S, Sirisha P, Neelaveni K, Anuradha K, Sudhakar G and Reddy BM. Polymorphisms in the IRS-1 and PPAR-gamma genes and their association with polycystic ovary syndrome among South Indian women. Gene 2012; 503: 140-146.
[37] Yang J, Gong H, Liu W and Tao T. The association of Pro12Ala polymorphism in the peroxisome proliferator-activated receptor-gamma2 gene with the metabolic characteristics in Chinese women with polycystic ovary syndrome. Int J Clin Exp Pathol 2013; 6: 1894-1902.
[38] Zheng J. BH. Peroxisome proliferator-activated receptor-γ2 gene pro12Ala polymorphisms cannot predict ovarian reproductive function through rosiglitazone in women with polycystic ovarian syndrome. Journal of Xi'an Jiaotong University (Medical Sciences) 2008; 29: 4.
[39] Wang Y, Wu X, Cao Y, Yi L, Fan H and Chen J. Polymorphisms of the peroxisome proliferator-activated receptor-gamma and its coactivator-1alpha genes in Chinese women with polycystic ovary syndrome. Fertil Steril 2006; 85: 1536-1540.
[40] Diamanti-Kandarakis E, Kouli CR, Bergiele AT, Filandra FA, Tsianateli TC, Spina GG, Zapanti ED and Bartzis MI. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. J Clin Endocrinol Metab 1999; 84: 4006-4011.
[41] Franks S, Gharani N, Waterworth D, Batty S, White D, Williamson R and McCarthy M. The genetic basis of polycystic ovary syndrome. Hum Reprod 1997; 12: 2641-2648.
[42] Tan BK, Heutling D, Chen J, Farhatullah S, Adya R, Keay SD, Kennedy CR, Lehnert H and Randeva HS. Metformin decreases the adipokine vaspin in overweight women with polycystic ovary syndrome concomitant with improvement in insulin sensitivity and a decrease in insulin resistance. Diabetes 2008; 57: 1501-1507.
[43] Vigil P, Contreras P, Alvarado JL, Godoy A, Salgado AM and Cortes ME. Evidence of subpopulations with different levels of insulin resistance in women with polycystic ovary syndrome. Hum Reprod 2007; 22: 2974-2980.
[44] Celik C, Abali R, Bastu E, Tasdemir N, Tasdemir UG and Gul A. Assessment of impaired glucose tolerance prevalence with hemoglobin A(1)c

and oral glucose tolerance test in 252 Turkish women with polycystic ovary syndrome: a prospective, controlled study. Hum Reprod 2013; 28: 1062-1068.

[45] Trakakis E, Basios G, Peppa M, Simeonidis G, Labos G, Creatsa M, Misailidou M, Boutati E, Vaggopoulos V, Panagopoulos P, Dimitriades G and Kassanos D. The prevalence of glucose metabolism abnormalities in Greek women with polycystic ovary syndrome. Gynecol Endocrinol 2012; 28: 867-870.

[46] Venkatesan AM, Dunaif A and Corbould A. Insulin resistance in polycystic ovary syndrome: progress and paradoxes. Recent Prog Horm Res 2001; 56: 295-308.

[47] He W. PPARgamma2 polymorphism and human health. PPAR Res 2009; 2009: 849538.

[48] Yen CJ, Beamer BA, Negri C, Silver K, Brown KA, Yarnall DP, Burns DK, Roth J and Shuldiner AR. Molecular scanning of the human peroxisome proliferator activated receptor gamma (hPPAR gamma) gene in diabetic Caucasians: identification of a Pro12Ala PPAR gamma 2 missense mutation. Biochem Biophys Res Commun 1997; 241: 270-274.

[49] Masugi J, Tamori Y, Mori H, Koike T and Kasuga M. Inhibitory effect of a proline-to-alanine substitution at codon 12 of peroxisome proliferator-activated receptor-gamma 2 on thiazolidinedione-induced adipogenesis. Biochem Biophys Res Commun 2000; 268: 178-182.

[50] Tang ST, Wang CJ, Tang HQ, Peng WJ, Wang YM and Zhang Q. Association of Pro12Ala polymorphism in peroxisome proliferator-activated receptor gamma with polycystic ovary syndrome: a meta-analysis. Mol Biol Rep 2012; 39: 9649-9660.