Effects of *apoC1* genotypes on the hormonal levels, metabolic profile and PAF-AH activity in Chinese women with polycystic ovary syndrome

Renjiao Zhang¹, Qingqing Liu¹, Hongwei Liu², Huai Bai¹, Yujin Zhang², Linbo Guan¹ and Ping Fan¹*

**Abstract**

**Background:** Elevated serum levels of apolipoprotein (apo) C1 may be an early protein marker of metabolic abnormality in women with polycystic ovary syndrome (PCOS). It is not clear, however, whether there are any relationships between the *apoC1* rs4420638A/G and -317deletion (H1)/insertion (H2) polymorphisms and PCOS. We investigated the relationship between these two variants and the risk of PCOS, evaluated the genotypic effects on clinical, hormonal and metabolic indexes and plasma platelet-activating factor acetylhydrolase (PAF-AH) activity, and defined the association of *apoC1* gene variants with *apoE* ε2/ε3/ε4 polymorphisms.

**Methods:** This is a cross-sectional study of 877 women with PCOS and 761 controls. The *apoC1* rs4420638A/G genotype was determined by a Taqman real-time PCR allelic discrimination assay. The *apoC1* -317H1/H2 and *apoE* ε2/ε3/ε4 genotypes were measured using PCR and restriction fragment length polymorphism analysis. The clinical, hormonal and metabolic parameters and PAF-AH activity were measured.

**Results:** The frequencies of *apoC1* rs4420638A/G and -317H1/H2 genotypes and alleles were similar between PCOS and control groups (P > 0.05). However, the rs4420638 G allele was related to increased serum luteinizing hormone, cholesterol and apoB levels, and the ratio of apoB to apoA1 (P < 0.05), and the -317H1H1 genotype was associated with a higher acne grade score and a higher ratio of apoB-PAF-AH to H-PAF-AH activity (P < 0.05) in patients with PCOS. We also demonstrated that the *apoC1* rs4420638A/G and -317H1/H2 gene variants existed in moderate to reasonably high linkage disequilibrium with *apoE* ε2/ε3/ε4 polymorphisms in Chinese women.

**Conclusion:** The *apoC1* rs4420638A/G and -317H1/H2 gene variants might be involved in endocrine abnormalities of reproductive axis, metabolic abnormalities and chronic inflammation in PCOS, although no association was observed between the *apoC1* genetic variants and the risk of PCOS in Chinese women.

**Keywords:** *apoC1*, Gene polymorphism, Lipoprotein, PAF-AH activity, *apoE*, Polycystic ovary syndrome

**Background**

Polycystic ovary syndrome (PCOS) is a common heterogeneous female endocrine metabolic disorder affecting 4–18% of reproductive-aged women [1, 2]. In addition to reproductive disorders, PCOS is often associated with long-term cardiovascular health risks, including obesity, visceral obesity, insulin resistance, hyperinsulinemia, dyslipidemia, increased oxidative stress, chronic low-grade inflammation, endothelial dysfunction, vascular preclinical abnormalities, elevated risks of metabolic syndrome, impaired glucose tolerance, type 2 diabetes, and future cardiovascular diseases [2–7]. The etiology of PCOS remains obscure, but studies have suggested that PCOS appears to have a complex, multifactorial etiology resulting from the interactions between genetic, environmental and intrauterine factors [8, 9].

*Correspondence: fanping15@sccu.edu.cn
1Laboratory of Genetic Disease and Perinatal Medicine, Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, People’s Republic of China
Full list of author information is available at the end of the article

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Apolipoprotein (apo) C1 is a constituent of high-density lipoprotein (HDL) and triglyceride-rich lipoproteins and plays an important role in the regulation of lipoprotein metabolism and serum lipid levels. ApoC1 affects catabolism and clearance of apoB-containing lipoproteins by inhibiting lipoprotein lipase (LPL), liver-specific low density lipoprotein (LDL) receptor (LDLR) and LDLR-related protein (LRP) [10–12]. This elevates serum levels of cholesterol and triglycerides (TG) in human apoC1–transgenic mice [10–12].

The human apoE–apoC1–apoC4–apoC2 gene cluster is located on chromosome 19. Several genome-wide association studies have demonstrated that the rs4420638 A → G variant of the apoC1 gene, located in the non-coding region, is associated with increased serum total cholesterol (TC) and LDL-C levels [13–15], plasma glucose concentration [16] and platelet-activating factor acetylhydrolase (PAF-AH) activity [17]. Furthermore, the rs4420638 A → G variant is associated with elevated risks of metabolic syndrome, type 2 diabetes, and coronary heart disease [14, 16, 17]. However, the mechanism by which the apoC1 rs4420638A/G variant influences plasma lipid levels and increases the risks of diseases is unclear. A 4-bp CGTT deletion (H1)/insertion (H2) polymorphism (rs11568822) at the −317 site in the apoC1 promoter region has been reported to affect apoC1 gene expression [18, 19] and is related to the risks of late-onset Alzheimer’s disease [20] and type III hyperlipoproteinemia [21]. In addition, the rs4420638A/G and -317H1/H2 polymorphisms of the apoC1 gene have been reported to exist in linkage disequilibrium with apoE e2/e3/e4 polymorphisms but exhibit a different degree of linkage disequilibrium in populations of different races [19, 22].

The elevated serum apoC1 levels in patients with PCOS, even PCOS patients with normal weight or normolipemic indexes, suggest that apoC1 may be an early protein marker of metabolic abnormality in these patients [23]. However, to date, little information is available regarding the possible connection between the apoC1 rs4420638A/G and -317H1/H2 polymorphisms and PCOS and the degree of linkage disequilibrium between these variants and apoE e2/e3/e4 polymorphisms in Chinese women. In the present study, we investigated the relationship between the rs4420638A/G and -317H1/H2 polymorphisms of the apoC1 gene and the risk of PCOS, evaluated the effects of the genotypes on clinical and metabolic indexes and PAF-AH activity and defined the association of apoC1 gene variations with apoE allele status in southwest Chinese women with or without PCOS using relatively large sample sizes.

**Methods**

**Study subjects**

Women with or without PCOS aged 17 to 40 years were recruited from 2006 to 2015 from the Outpatient Clinic of Reproductive Endocrinology at West China Second University Hospital. For the genetic association study of apoC1 and apoE polymorphisms, we included 877 patients and 761 controls. For association studies between apoC1 genotypes and hormonal levels, metabolic parameters, and PAF-AH activity, the subjects were excluded if they met one of the following criteria: [i] taking medication known to affect the metabolism of carbohydrates, lipids, or hormones within 3 months before the study; [ii] being pregnant or in the luteal phase; and [iii] smoking. Finally, 575 patients and 506 controls were included in the metabolism-related study. In addition, PAF-AH activity was measured in 281 patients and 277 controls of the metabolic analysis groups.

Each patient with PCOS met the revised 2003 Rotterdam ESHRE/ASRM consensus criteria [24]. Oligo-ovulation or anovulation (OA) was assessed as oligomenorrhea (i.e., fewer than eight cycles per year). Clinical or biochemical hyperandrogenism (HA) was assessed by three measures: hirsutism with a modified Ferriman–Gallwey (F-G) score of more than 6, clinical presence of obvious acne and/or total testosterone (TT) level ≥ 2.60 nmol/L [3, 4, 25]. Polycystic ovaries (PCOs) were confirmed if there were 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (> 10 mL) by ultrasonic examination. The diagnosis of PCOS was based on a patient having two of these three findings with HA as an essential condition for women aged < 20 years [2] and exclusion of other etiologies such as androgen-secreting tumors, congenital adrenal hyperplasias, and Cushing syndrome. All the controls were clinically healthy women who had regular menstrual cycles (between 21 and 35 days), exhibited normal circulating androgen levels, did not show hirsutism or obvious acne on physical examination, and had normal ovarian morphology as determined by ultrasound.

None of the subjects had clinically evident acute or chronic diseases, such as infection, tumors, cardiovascular disease, thyroid dysfunction, endometriosis, hyperprolactinemia, hypogonadotropic hypogonadism or premature ovarian insufficiency.

Clinical and anthropometrical parameters, including waist circumference, waist-to-hip ratio, body mass index (BMI, kg/m²), systolic and diastolic blood pressure (SBP and DBP), the degree of hirsutism and acne, and ultrasound ovarian volume [26] were measured or assessed in all subjects.

Blood samples were obtained in the morning after overnight fasting on day 3–10 of the menstrual cycle from regularly menstruating women or at random from women with OA. Samples were placed on ice immediately and centrifuged at 1500×g for 15 min at 4 °C within 2 h. Plasma and serum samples were stored at −80 °C. Blood cells were stored at 4 °C.
Genotype analysis
Genomic DNA was isolated from peripheral blood leukocytes of the subjects [27, 28]. For the apoC1 rs4420638 genotype, a 101-bp fragment was amplified and detected by a Taqman real-time PCR allelic discrimination assay using the forward primer, 5’TCTACGCTTACAATTTGTCATGTA-TATGC-3’, the reverse primer, 5’GTCTGGGCTCTAAAGAAACACAGAAAAGG-3’ and the wild-type probe, HEX-CCTTTCTATGTTGGCTAGTA-TAMRA and the mutant probe, FAM-CACCTTTCCTTGTTGGTGT-TAMRA. The 151-bp wild-type (A) or mutant (G) DNA fragments of the apoC1 gene were used as positive controls. The primers, probes and positive controls were designed and synthesized by the Genecore Biotech Co. Ltd., Shanghai, China. For the -317H1/H2 genotype, the 221-bp (H1, CGTT deletion) and 225-bp (H2, CGTT insertion) fragments were amplified using the forward primer: 5’TTTGGAGCTCGGTCTT-GAGACAGGAA-3’ and the reverse primer 5’-HXTCAAGGCTACAAG-3’ [29]. The -317H1/H2 PCR products were digested with HpaI (Thermo) and analyzed by electrophoresis on a 3.0% agarose gel and visualized by staining with Genecolour fluorescent dye. The enzyme digestion resulted in 159- and 66-bp fragments for the -317H2 allele and a non-digested 221-bp fragment for the -317H1 allele. ApoE ε2/ε3/ε4 polymorphisms (rs429358 and rs7412) were measured as described previously [30]. For quality control, more than 30% of DNA samples were genotyped again by a different operator.

Analysis of PAF-AH activity, hormonal markers and metabolic markers
Serum luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E2), TT, triglyceride (TG), total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), apoA1, apoB, plasma glucose and insulin concentrations, plasma PAF-AH, apoB-containing lipoprotein-associated PAF-AH (apoB-PAF-AH) and HDL-associated PAF-AH (H-PAF-AH) activity were measured as previously described [4, 31, 32]. Additionally, the atherogenic index (AI) and the homeostatic model assessment of insulin resistance (HOMA index) were assessed as previously described [4, 31]. The intra- and inter-assay coefficients of variation for all measurements were less than 5 and 10%, respectively.

Statistical analysis
Data were presented as the mean ± standard deviation (SD). Differences in variables were evaluated by an independent sample t-test between PCOS and control subjects. Variables with asymmetric distribution were evaluated by a Mann-Whitney U test. A chi-square analysis was used to determine allele or genotype frequencies and to test deviations in the genotype distribution from Hardy-Weinberg equilibrium between patients and controls. An analysis of covariance (ANCOVA) or a two-way analysis of variance (ANOVA) was used to estimate the differences in clinical parameters, hormonal levels, metabolic profile and PAF-AH activity between the two groups or genotype subgroups after correction for differences in age and BMI. A P-value of < 0.05 was considered to be statistically significant. All statistical analyses were performed using the Statistical Program for Social Sciences (SPSS) 13.0 for Windows (Chicago, IL, USA).

The analysis of linkage disequilibrium between different genetic polymorphic loci was performed by the SHEsis online software at http://analysis.bio-x.cn/myAnalysis.php.

Results
Clinical and biochemical characteristics of the study population
Because mean age and BMI were different between the PCOS and the control groups (Table 1), differences that could bias comparisons of other clinical parameters, the hormonal and metabolic indexes and PAF-AH activity between the two groups were adjusted for the difference in age and BMI in the following analysis.

As shown in Table 1, BMI, waist circumference, waist-to-hip ratio, F-G score, acne grade score, and average ovarian volume were significantly increased, and age was significantly decreased in the PCOS group compared with the control group.

TT and LH levels, the ratio of LH to FSH, fasting insulin concentration, HOMA index, TG, TC, LDL-C, non-HDL-C and apoB levels, AI, the ratio of apoB to apoA1, and the ratio of apoB-PAF-AH to H-PAF-AH were significantly increased, whereas FSH and HDL-C levels and H-PAF-AH activity were significantly reduced in the PCOS group compared with the control group (Table 2).

Distribution of the apoC1 rs4420638A/G and -317H1/H2 genotypes and alleles
Genotypic distributions of apoC1 rs4420638A/G and -317H1/H2 were in Hardy-Weinberg equilibrium in the PCOS and control groups. No significant differences were observed in the frequencies of the apoC1 rs4420638A/G and -317H1/H2 genotypes and alleles between PCOS and control groups (P > 0.05, Table 3). The degree of linkage disequilibrium (LD) among the apoE ε2/ε3/ε4, and the apoC1 rs4420638A/G and -317H1/H2 genetic polymorphisms was analyzed in patients with PCOS and the controls, with all found to be in moderate to reasonably high LD with each other: apoC1–317H1/H2 loci and apoE ε2/ε3/ε4 loci (D’ = 0.970, r² = 0.702), apoC1–317H1/H2 loci and rs4420638A/G loci (D’ = 0.910, r² = 0.455), and apoC1 rs4420638A/G loci and apoE ε2/ε3/ε4 loci (D’ = 0.758, r² = 0.397).

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### Table 1  Clinical characteristics of PCOS patients and controls

|                      | Controls (n = 761) | PCOS (n = 877) | P       | P^a     |
|----------------------|-------------------|----------------|---------|---------|
| Age (years)          | 28.19 ± 4.14      | 24.66 ± 3.95   | < 0.001 |         |
| BMI (kg/m²)          | 21.18 ± 2.95      | 22.79 ± 4.04   | < 0.001 |         |
| Waist circumference (cm) | 73.63 ± 8.23   | 78.74 ± 11.17  | < 0.001 | < 0.001|
| Waist-to-hip ratio   | 0.82 ± 0.06       | 0.85 ± 0.07    | < 0.001 | < 0.001|
| F-G score            | 0.22 ± 0.71       | 1.68 ± 2.03    | < 0.001 | < 0.001|
| Acne grade score     | 0.09 ± 0.29       | 0.60 ± 0.90    | < 0.001 | < 0.001|
| SBP (mmHg)           | 113.20 ± 11.72    | 114.09 ± 10.62 | 0.110   | 0.743   |
| DBP (mmHg)           | 73.87 ± 9.25      | 75.51 ± 8.92   | < 0.001 | 0.089   |
| Ovarian volume (ml)  | 7.53 ± 2.84       | 9.90 ± 4.09    | < 0.001 | < 0.001|

Values are presented as the mean ± SD

P^a All comparisons were corrected for differences in age and BMI between the two groups except the parameters of age and BMI

### Table 2  Hormonal levels, metabolic profile and PAF-AH activity in PCOS patients and controls

|                      | Controls (n = 506) | PCOS (n = 575) | P       | P^a     |
|----------------------|-------------------|----------------|---------|---------|
| Age (years)          | 27.96 ± 4.19      | 24.66 ± 3.96   | < 0.001 |         |
| BMI (kg/m²)          | 21.10 ± 2.91      | 23.10 ± 4.26   | < 0.001 |         |
| Hormonal levels      |                   |                |         |         |
| E2 (pmol/L)          | 333.95 ± 351.36   | 284.06 ± 271.26| 0.014   | 0.373   |
| TT (nmol/L)          | 1.54 ± 0.54       | 2.42 ± 0.77    | < 0.001 | < 0.001|
| LH (IU/L)            | 8.72 ± 11.33      | 13.89 ± 10.91  | < 0.001 | < 0.001|
| FSH (IU/L)           | 6.67 ± 2.98       | 5.99 ± 2.23    | < 0.001 | 0.015   |
| LH/FSH               | 1.30 ± 1.32       | 2.35 ± 1.26    | < 0.001 | < 0.001|
| Metabolic profile    |                   |                |         |         |
| Fasting Ins (pmol/L) | 66.98 ± 36.74     | 106.08 ± 74.24 | < 0.001 | < 0.001|
| Fasting Glu (mmol/L) | 5.30 ± 0.73       | 5.37 ± 0.77    | 0.010   | 0.515   |
| HOMA-IR              | 2.34 ± 1.90       | 3.79 ± 3.19    | < 0.001 | 0.006   |
| TG (mmol/L)          | 1.04 ± 0.90       | 1.42 ± 1.36    | < 0.001 | < 0.001|
| TC (mmol/L)          | 4.25 ± 0.70       | 4.41 ± 0.81    | < 0.001 | < 0.001|
| HDL-C (mmol/L)       | 1.51 ± 0.32       | 1.38 ± 0.35    | < 0.001 | 0.006   |
| LDL-C (mmol/L)       | 2.35 ± 0.61       | 2.55 ± 0.76    | < 0.001 | < 0.001|
| non-HDL-C (mmol/L)   | 2.73 ± 0.64       | 3.02 ± 0.81    | < 0.001 | < 0.001|
| AI                   | 1.90 ± 0.68       | 2.37 ± 1.02    | < 0.001 | < 0.001|
| ApoA1 (g/L)          | 1.45 ± 0.21       | 1.42 ± 0.21    | 0.005   | 0.725   |
| ApoB (g/L)           | 0.75 ± 0.17       | 0.82 ± 0.20    | < 0.001 | < 0.001|
| ApoB/apoA1           | 0.53 ± 0.14       | 0.60 ± 0.18    | < 0.001 | < 0.001|
| PAF-AH activity^a    |                   |                |         |         |
| Plasma PAF-AH (nmol/min/ml) | 48.39 ± 10.81 | 47.44 ± 12.94 | 0.344   | 0.722   |
| H-PAF-AH (nmol/min/ml) | 5.14 ± 1.51   | 4.67 ± 1.91    | 0.001   | 0.031   |
| ApoB-PAF-AH (nmol/min/ml) | 43.25 ± 9.96 | 42.77 ± 11.89 | 0.604   | 0.967   |
| ApoB-PAF-AH/H-PAF-AH  | 8.86 ± 2.48      | 10.04 ± 3.89   | < 0.001 | < 0.001|

Values are presented as the mean ± SD

P^a All comparisons of parameters were corrected for differences in age and BMI between the two groups except the parameters of age and BMI

^a Control (n = 277), PCOS (n = 281)
Table 3 Frequencies of the apoC1 genotype and allele in PCOS patients compared with controls

| Genotype | Controls (n = 761) | PCOS (n = 877) | X² | P |
|----------|-------------------|----------------|----|---|
| rs4420638 |                   |                |    |   |
| AA       | 483 (63.5%)       | 570 (65.0%)    |    |   |
| AG       | 245 (32.2%)       | 269 (30.7%)    |    |   |
| GG       | 33 (4.3%)         | 38 (4.3%)      | 0.448 | 0.799 |

Allele frequency

| Allele | Controls (n = 761) | PCOS (n = 877) | X² | P |
|--------|--------------------|----------------|----|---|
| -317   | 0.796              | 0.803          |    |   |
| H2     | 0.204              | 0.197          | 0.297 | 0.586 |
| rs4420638 | 0.875          | 0.883          |    |   |
| G      | 0.125              | 0.117          | 0.419 | 0.518 |

Genotype data are presented as the number (%) of patients or controls.

Effects of the apoC1 rs4420638A/G and -317H1/H2 genetic variants on clinical, hormonal and metabolic parameters and PAF-AH activity

Because the sample sizes of the rs4420638GG or -317H2H2 homozygotes were too small, we combined them into the heterozygous subgroups.

As shown in Table 4, compared with AA homozygotes, G allele carriers (AG + GG) of the rs4420638 polymorphism had significantly higher apoB levels and a higher ratio of apoB to apoA1 in patients with PCOS or the controls (P < 0.05). Patients with the G allele had higher serum LH, TC, LDL-C and non-HDL-C levels (P < 0.05), and tended to have a reduced waist-to-height ratio, DBP and fasting insulin levels (P < 0.100) and an increased ratio of LH to FSH (P = 0.074) compared with patients with the AA genotype. The controls with the G allele had higher fasting insulin and glucose concentrations, HOMA indexes, AI, plasma PAF-AH and apoB-PAF-AH activity (P < 0.05), and tended to have increased LDL-C and non-HDL-C levels (P < 0.080) and decreased HDL-C concentrations (P < 0.070) than the controls with the AA genotype.

Compared with patients with the H1H1 genotype, patients with the H2 allele (H1H2 + H2H2) in -317H1/H2 polymorphism had lower acne grade score and the ratio of apoB-PAF-AH to H-PAF-AH (P < 0.05). The controls with the H2 allele had lower TC and LDL-C levels (P < 0.05), and tended to have increased waist-to-height ratio and HOMA index (P < 0.09) and reduced non-HDL-C and apoB levels (P < 0.09) than the controls with the H1H1 genotype (Table 5).

Additionally, patients with the respective AA and AG + GG genotypes of the rs4420638 polymorphism or the respective H1H1 and H1H2+ H2H2 genotypes of the -317H1/H2 polymorphism were more obese and had a higher F-G score, acne grade score and average ovarian volume, and more adverse hormonal, glucose and lipid metabolic profiles compared with the corresponding control subgroups. Patients with the AA or H1H1 genotype had a decreased H-PAF-AH activity and an increased ratio of apoB-PAF-AH to H-PAF-AH compared with the corresponding AA or H1H1 control subgroups (P < 0.05, Tables 4 and 5).

ApoC1 rs4420638A/G and -317H1/H2 allele status by apoE ε2/ε3/ε4 alleles

The associations of apoC1 allele status with apoE ε2/ε3/ε4 allele status were observed in patients with PCOS and controls, as shown in Tables 6. A strong association of the apoC1 H2 allele with the apoE ε2 or apoE ε4 allele and of the apoC1 rs4420638 G allele with the apoε4 allele was revealed in patients with PCOS and controls. Of the apoE ε2 alleles evaluated, 273 (100%) were associated with apoC1 H2 alleles. Of the 319 apoE ε4 alleles, 303 (95%) were H2 alleles or rs4420638 G alleles and only 16 (5%) were H1 alleles or rs4420638 A alleles. In contrast, the apoE ε3 allele was strongly associated with the apoC1 H1 or rs4420638 A alleles. Of the 2684 apoε3 alleles, 2604 (97%) were H1 alleles and 2594 (96.6%) were rs4420638 A alleles; however, only 80 (3%) were H2 alleles and 90 (3.4%) were rs4420638 G alleles. Nevertheless, these differences were not statistically significant for patients with PCOS versus the controls (P > 0.05, Table 6).

Discussion

In this study, we show that apoC1 rs4420638A/G and -317H1/H2 genetic polymorphisms are not associated with a risk of PCOS in Chinese women. However, compared with patients carrying the AA genotype, patients carrying the G allele (AG + GG) of the rs4420638 polymorphism had significantly higher LH, TC, LDL-C, non-HDL-C and apoB levels, and a higher ratio of apoB to apoA1, and tended to have an increased ratio of LH to FSH. This suggests that this polymorphism may potentially be linked to endocrine abnormalities of the reproductive axis and dyslipidemia in the patients. In addition, we found a higher acne grade score and an increased ratio of apoB-PAF-AH to H-PAF-AH activity in patients carrying the H1H1 genotype of the -317H1/H2 polymorphism compared with patients carrying the H2 allele. This suggests that the -317H1/H2 genetic polymorphism is associated with systemic chronic inflammation in these patients. Furthermore, we demonstrated that the rs4420638A/G or -317H1/H2 polymorphisms of the apoC1 gene exist in moderate to reasonably high linkage disequilibrium with apoE ε2/ε3/ε4 polymorphisms.

Several studies have found that the rs4420638A/G polymorphism in the apoC1 gene is associated with
serum lipid levels, chronic inflammation and disease risk. The G allele of rs4420638 is associated with a higher level of TC, LDL-C, TG and PAF-AH activity, abdominal obesity, and increased risk of type 2 diabetes and coronary heart disease [13–17]. On the other hand, the G allele is associated with lower serum C-reactive protein (CRP) levels [13]. In this study, we found that the G allele carriers were associated with not only increased serum LDL-C levels but also elevated serum non-HDL-C and apoB levels, and the ratio of apoB to apoA1 than the AA homozygotes in patients with PCOS or the controls. Because apoB and the apoB/apoA-I ratio

| Table 4 Clinical characteristics, hormonal levels, metabolic profile and PAF-AH activity of the apoC1 rs4420638 genotypes in PCOS patients and controls |
|---------------------------------|-----------------|-----------------|
| Controls                        | PCOS            |
| AA (n = 379)                    | AA (n = 435)    | AG + GG (n = 121 + 6) | AG + GG (n = 134 + 6) |
| Age (yr)                        | 28.18 ± 4.10    | 27.28 ± 4.41   | 24.68 ± 4.01   | 24.60 ± 3.81 |
| BMI (kg/m²)                     | 21.17 ± 2.96    | 20.88 ± 2.74   | 23.24 ± 4.32   | 22.68 ± 4.03 |
| Waist circumference (cm)        | 73.41 ± 8.21    | 73.36 ± 8.36   | 80.13 ± 11.67  | 77.96 ± 11.22 |
| Waist-to-hip ratio              | 0.81 ± 0.06     | 0.82 ± 0.06    | 0.86 ± 0.07    | 0.84 ± 0.07  |
| F-G score                       | 0.22 ± 0.69     | 0.26 ± 0.82    | 1.73 ± 2.07    | 1.71 ± 2.08  |
| Acne grade score                | 0.10 ± 0.30     | 0.08 ± 0.27    | 0.66 ± 0.94    | 0.53 ± 0.86  |
| SBP (mmHg)                      | 131.42 ± 11.55  | 112.98 ± 11.84 | 114.89 ± 10.42 | 113.78 ± 11.65 |
| DBP (mmHg)                      | 73.97 ± 8.88    | 73.40 ± 8.75   | 76.35 ± 9.08   | 74.70 ± 8.99 |
| Ovarian volume (ml)             | 7.88 ± 2.76     | 7.47 ± 3.24    | 10.22 ± 3.92   | 9.95 ± 4.63  |
| Hormonal levels                 |                |                |                |
| E2 (pmol/L)                     | 322.08 ± 341.61 | 367.37 ± 376.94 | 281.07 ± 279.42 | 293.07 ± 245.85 |
| TT (nmol/L)                     | 1.54 ± 0.54     | 1.53 ± 0.56    | 2.41 ± 0.77    | 2.45 ± 0.77  |
| LH (IU/L)                       | 8.53 ± 10.38    | 9.28 ± 13.76   | 13.24 ± 8.57   | 15.85 ± 15.91 |
| FSH (IU/L)                      | 6.59 ± 2.84     | 6.89 ± 3.34    | 5.95 ± 2.27    | 6.12 ± 2.11  |
| LH/FSH                          | 1.31 ± 1.24     | 1.29 ± 1.54    | 2.28 ± 1.18    | 2.58 ± 1.45  |
| Metabolic profile               |                |                |                |
| Fasting Ins (pmol/L)            | 64.87 ± 32.78   | 73.28 ± 46.17a | 109.10 ± 77.82a | 96.60 ± 60.96a |
| Fasting Glu (mmol/L)            | 5.26 ± 0.46     | 5.42 ± 1.22a   | 5.38 ± 0.71a   | 5.36 ± 0.93a |
| HOMA-IR                         | 2.22 ± 1.22     | 2.73 ± 3.13a   | 3.89 ± 3.31a   | 3.46 ± 2.80a |
| TG (mmol/L)                     | 1.02 ± 0.93     | 1.08 ± 0.76    | 1.46 ± 1.50a   | 1.29 ± 0.73a |
| TC (mmol/L)                     | 4.22 ± 0.71     | 4.31 ± 0.66    | 4.35 ± 0.80a   | 4.57 ± 0.82a |
| HDL-C (mmol/L)                  | 1.52 ± 0.32     | 1.48 ± 0.29    | 1.37 ± 0.34a   | 1.42 ± 0.36a |
| LDL-C (mmol/L)                  | 2.32 ± 0.61     | 2.44 ± 0.60    | 2.51 ± 0.75a   | 2.66 ± 0.77a |
| non-HDL-C (mmol/L)              | 2.70 ± 0.63     | 2.83 ± 0.65    | 2.98 ± 0.81a   | 3.14 ± 0.78a |
| AI                              | 1.87 ± 0.65     | 2.02 ± 0.74a   | 2.37 ± 1.05a   | 2.37 ± 0.91a |
| ApoA1 (g/L)                     | 1.46 ± 0.22     | 1.44 ± 0.18    | 1.41 ± 0.21a   | 1.43 ± 0.22a |
| ApoB (g/L)                      | 0.74 ± 0.17     | 0.78 ± 0.17a   | 0.81 ± 0.20a   | 0.85 ± 0.20a |
| ApoB/apoA1                      | 0.52 ± 0.14     | 0.55 ± 0.16a   | 0.59 ± 0.18a   | 0.61 ± 0.19a |
| PAF-AH activityd                |                |                |                |
| Plasma PAF-AH (nmol/min/ml)     | 47.80 ± 10.91   | 50.08 ± 10.39a | 47.54 ± 12.27b| 47.05 ± 15.17 |
| H-PAF-AH (nmol/min/ml)          | 5.09 ± 1.51     | 5.30 ± 1.52    | 4.64 ± 1.89b   | 4.77 ± 2.01  |
| ApoB-PAF-AH (nmol/min/ml)       | 42.74 ± 10.09   | 44.78 ± 9.50a  | 42.91 ± 11.34  | 42.28 ± 13.74 |
| ApoB-PAF-AH/H-PAF-AH            | 8.85 ± 2.61     | 8.88 ± 2.09    | 10.91 ± 4.17a  | 9.48 ± 2.60  |

Values are presented as the mean ± SD
Comparisons of all parameters were corrected for differences in age and BMI between the two subgroups except the parameters of age and BMI

*P < 0.05, compared with AA genotype subgroup in controls
**P < 0.05, compared with AG + GG genotype subgroup in controls
***P < 0.05, compared with AA genotype subgroup in PCOS patients

Controls: AA (n = 207), AG + GG (n = 67 + 3); PCOS: AA (n = 219), AA + AG (n = 60 + 2)
have been reported to be better predictors of cardiovascular diseases than traditional lipid measurements [4, 33], our results provide further evidence that the A → G variant of rs4420638 in the apoC1 gene is associated with cardiovascular disease risk. We also demonstrated that the controls with the G allele had higher fasting insulin and glucose concentrations, HOMA indexes, plasma PAF-AH and apoB-PAF-AH activity than the AA homozygotic controls. Additionally, patients carrying the G allele tended to have a reduced waist-to-hip ratio than the AA homozygotic patients. Consistent with our findings, Avery et al. demonstrated that the rs4420638A/G

| Table 5 Clinical characteristics, hormonal levels, metabolic profile and PAF-AH activity of the apoC1–317H1/H2 genotypes in PCOS patients and controls |
|---------------------------------|---------------------------------|---------------------------------|
|                                | Controls                        | PCOS                            |
|                                | H1H1 (n = 318)                  | H1H1 (n = 370)                  |
|                                | H1H2 + H2H2 (n = 163 + 25)      | H1H2 + H2H2 (n = 177 + 28)      |
| Age (yr)                        | 28.17 ± 4.17                    | 24.68 ± 4.03± b                 |
|                                |                                 | 24.63 ± 3.84± b                 |
| BMI (kg/m²)                     | 21.18 ± 2.95                    | 22.94 ± 4.23± b                 |
|                                |                                 | 23.41 ± 4.29± b                 |
| Waist circumference (cm)        | 73.36 ± 7.96                    | 79.35 ± 11.36± b                |
|                                |                                 | 80.06 ± 12.02± b                |
| Waist-to-hip ratio              | 0.81 ± 0.06                     | 0.85 ± 0.07± b                  |
|                                |                                 | 0.85 ± 0.08± b                  |
| F-G score                       | 0.25 ± 0.76                     | 1.77 ± 2.06± b                  |
|                                |                                 | 1.63 ± 2.10± b                  |
| Acne grade score                | 0.11 ± 0.31                     | 0.68 ± 0.96± a, b               |
|                                |                                 | 0.52 ± 0.86± a, c               |
| SBP (mmHg)                      | 113.32 ± 11.26                  | 114.36 ± 10.43± a               |
|                                |                                 | 115.08 ± 11.27                  |
| DBP (mmHg)                      | 73.81 ± 8.89                    | 76.27 ± 9.08± b                 |
|                                |                                 | 75.38 ± 9.06                    |
| Ovarian volume (ml)             | 7.80 ± 2.86                     | 10.15 ± 3.90± b                 |
|                                |                                 | 10.15 ± 4.32± b                 |
| Hormonal levels                 |                                 |                                 |
| E2 (pmol/L)                     | 324.35 ± 341.91                 | 283.87 ± 285.58                 |
|                                |                                 | 284.41 ± 244.71                 |
| TT (nmol/L)                     | 1.55 ± 0.53                     | 2.41 ± 0.77± b                  |
|                                |                                 | 2.43 ± 0.77± b                  |
| LH (IU/L)                       | 8.80 ± 11.33                    | 13.65 ± 9.01± a, b              |
|                                |                                 | 14.33 ± 13.68± b                |
| FSH (IU/L)                      | 6.64 ± 3.02                     | 5.94 ± 1.89± b                  |
|                                |                                 | 6.08 ± 2.74± a, b               |
| LH/FSH                          | 1.32 ± 1.26                     | 2.32 ± 1.20± b                  |
|                                |                                 | 2.42 ± 1.36± b                  |
| Metabolic profile               |                                 |                                 |
| Fasting Ins (pmol/L)            | 65.53 ± 34.31                   | 105.28 ± 75.66± b               |
|                                |                                 | 107.54 ± 71.75± b               |
| Fasting Glu (mmol/L)            | 5.27 ± 0.44                     | 5.39 ± 0.84± d                  |
|                                |                                 | 5.35 ± 0.62                     |
| HOMA-IR                         | 2.24 ± 1.27                     | 3.80 ± 3.40± b                  |
|                                |                                 | 3.77 ± 2.79± b                  |
| TG (mmol/L)                     | 1.03 ± 1.00                     | 1.41 ± 1.47± a, b               |
|                                |                                 | 1.45 ± 1.13± b                  |
| TC (mmol/L)                     | 4.30 ± 0.68                     | 4.41 ± 0.81± a, b               |
|                                |                                 | 4.39 ± 0.82± b                  |
| HDL-C (mmol/L)                  | 1.52 ± 0.32                     | 1.39 ± 0.34± b                  |
|                                |                                 | 1.37 ± 0.35± a                  |
| LDL-C (mmol/L)                  | 2.41 ± 0.57                     | 2.57 ± 0.76± a, b               |
|                                |                                 | 2.51 ± 0.77± b                  |
| non-HDL-C (mmol/L)              | 2.78 ± 0.60                     | 3.03 ± 0.82± b                  |
|                                |                                 | 3.02 ± 0.80± b                  |
| AI                              | 1.92 ± 0.65                     | 2.37 ± 1.03± b                  |
|                                |                                 | 2.37 ± 1.00± b                  |
| ApoA1 (g/L)                     | 1.46 ± 0.22                     | 1.42 ± 0.21± a                  |
|                                |                                 | 1.41 ± 0.22± b                  |
| ApoB (g/L)                      | 0.76 ± 0.15                     | 0.83 ± 0.21± a, b               |
|                                |                                 | 0.81 ± 0.20± b                  |
| ApoB/apoA1                      | 0.53 ± 0.13                     | 0.60 ± 0.18± b                  |
|                                |                                 | 0.59 ± 0.18± b                  |
| PAF-AH activityd                |                                 |                                 |
| Plasma PAF-AH (nmol/min/ml)     | 49.20 ± 10.27                   | 48.01 ± 12.50                   |
|                                |                                 | 46.39 ± 13.71                   |
| H-PAF-AH (nmol/min/ml)          | 5.12 ± 1.46                     | 4.61 ± 1.98± b                  |
|                                |                                 | 4.76 ± 1.80                     |
| ApoB-PAF-AH (nmol/min/ml)       | 44.08 ± 9.40                    | 43.39 ± 11.49                   |
|                                |                                 | 41.63 ± 12.56                   |
| ApoB-PAF-AH/H-PAF-AH            | 9.07 ± 2.59                     | 10.42 ± 4.37± b                 |
|                                |                                 | 9.33 ± 2.69                     |

Values are presented as the mean ± SD
Comparisons of all parameters were corrected for differences in age and BMI
a P < 0.05, compared with AA genotype subgroup in controls
b P < 0.05, compared with H1H2 + H2H2 genotype subgroup in controls
c P < 0.05, compared with AA genotype subgroup in PCOS patients
d Controls: H1H1 (n = 165), H1H2 + H2H2 (n = 97 + 15); PCOS: H1H1 (n = 182), H1H2 + H2H2 (n = 86 + 13)
polymorphism of the apoC1 gene was associated with elevated plasma glucose, atherogenic dyslipidemia, vascular inflammation, and central obesity in individuals of European descent [34]. Grallert et al. reported that the \( A \rightarrow G \) variant of \( rs4420638 \) was associated with increased plasma PAF-AH activity [17]. Furthermore, in this study, we demonstrated that the \( apoC1 \) \( rs4420638 \) \( G \) allele exist in strong linkage disequilibrium with the \( apoE \) \( e4 \) allele, which may partially explain the effect of the \( rs4420638 \) \( G \) allele on lipoprotein metabolism and disease risk. The \( apoE \) \( e4 \) allele was associated not only with higher serum TC and LDL-C levels but also with higher oxidative stress, a more pro-inflammatory state and increased risk of cardiovascular disease and late-onset Alzheimer’s disease [30, 35]. For the first time, our findings, Xu et al. reported that the \( H2 \) allele was associated with lower ratio of apoB-PAF-AH to H-PAF-AH and acne grade score in patients with PCOS. Furthermore, the \( H2 \) allele decreased or tended to decrease TC, LDL-C, non-HDL-C and apoB levels, but tended to increase waist-to-hip ratio and HOMA index in the controls. We also determined that the \( apoC1 \) \( H2 \) allele has complete linkage disequilibrium with the \( apoE \) \( e2 \) allele, and to a lesser extent, the \( apoE \) \( e4 \) allele in Chinese women. Consistent with our findings, Xu et al. reported that the \( H2 \) allele was associated with a decrease or tending decrease in apoB and LDL-C levels compared with \( H1H1 \) homoygotes in African-Americans with the \( apoE \) \( e3/e3 \) genotype but not the \( apoE \) \( e3/e4 \) genotype [19]. Similar to apoE2, modest levels of apoC1 expression may decrease hepatic secretion of VLDL and apoB and produce lower LDL levels due to decreased partitioning of dietary lipids to the liver, relating to delayed remnant clearance, especially in the \( apoE \) \( e2 \) and \( apoE \) \( e3 \) contexts; however, higher apoC1 levels may increase plasma lipid levels via decreased remnant clearance [19]. Expression of apoC1 is upregulated and serum apoC1 levels are higher in patients with PCOS compared with the controls [23]. This may be one of the reasons why serum lipid profiles in the \( apoC1 \) \( –317H1/H2 \) polymorphism are different between patients and controls. Plasma PAF-AH specifically hydrolyzes and inactivates PAF and PAF-like oxidized phospholipids that are potent pro-inflammatory mediators [36]. Given that H-PAF-AH, an antioxidant enzyme of HDL, plays anti-inflammatory role and apoB-PAF-AH is associated with inflammation, it has recently been suggested that an increased ratio of apoB-PAF-AH to H-

### Table 6 ApoC1/apoE haplotypes in patients with PCOS and controls

| ApoE controls/cases | ApoC1–317 | ApoC1 rs4420638 |
|---------------------|-----------|-----------------|
|                     | H1        | H2             | A        |
|                     |           | P              | G        | P       |
| e2                  |           |                |          |         |
| Controls            | 0         | 131 (100%)     | 131 (100%)| 0       |
| PCOS                | 0         | 142 (100%)     | 139 (97.9%)| 3 (2.1%)| 0.094 |
| Total               | 0         | 273 (100%)     | 270 (98.9%)| 3 (1.1%)|
| e3                  |           |                |          |         |
| Controls            | 1203 (96.7%) | 41 (3.3%)   | 1194 (96.0%)| 50 (4.0%)|
| PCOS                | 1401 (97.3%)| 39 (2.7%)     | 1400 (97.2%)| 40 (2.8%)| 0.075 |
| Total               | 2604 (97.0%)| 80 (3.0%)     | 2594 (96.6%)| 90 (3.4%)|
| e4                  |           |                |          |         |
| Controls            | 8 (5.4%)  | 139 (94.6%)    | 7 (4.8%)  | 140 (95.2%)|
| PCOS                | 8 (4.7%)  | 164 (95.3%)    | 9 (5.2%)  | 163 (94.8%)| 0.848 |
| Total               | 16 (5.0%) | 303 (95.0%)    | 16 (5.0%) | 303 (95.0%)|

Haplotype data are presented as the number (%) of patients or controls.
PAF-AH might be a marker for chronic inflammation [31, 32, 36, 37]. These results suggest that the H1 allele might relate to increased systemic chronic inflammation in patients with PCOS.

In addition, our study also showed that the A → G variant and the CGTT insertion (H2) allele of apoC1 appeared to have a greater impact on metabolic profile in the controls relative to in patients with PCOS (Tables 4 and 5). It has been demonstrated that in addition to genetic variations, other factors such as obesity, insulin resistance, etc., also have a significant impact on metabolic profile [4, 5, 38]. Since patients with PCOS are more obese and have a more severe insulin resistance compared with the controls in this study (Tables 1, 2, 4 and 5), it is possible that the effects of apoC1 genetic variations on metabolic profile may be disturbed or weakened by these factors in patients. Further research is needed to clarify this issue.

In particular, the allele frequencies for apoC1 and apoE genetic variants differ among ethnic groups, and these variants exhibit an ethnically distinct linkage disequilibrium pattern [19, 20, 30]. For example, the frequency of the apoC1 H2 allele combined with apoE ε2, ε3 and ε4 is 0.95, 0.02 and 0.85, respectively, in European-Americans; 1.00, 0.08 and 0.55, respectively, in African-Americans [19]; and 1.00, 0.03 and 0.95, respectively, in Chinese women. Therefore, it is possible that the relationships between the apoC1 and apoE genetic polymorphisms and lipoprotein levels or diseases may differ among ethnic groups.

We should point out that this study has some limitations. Firstly, given the low frequency of homozygosity of minor alleles rs4420638GG and -317H2H2, we could not analyze them in the form of subgroups. A larger sample size of patients and controls are needed to properly evaluate dose-dependent genotype characteristics. Second, due to insufficient sampling, we did not measure plasma and lipoprotein-associated PAF-AH activity in some subjects, which might influence the statistical power of these parameters. Third, we could not determine plasma apoC1 concentrations due to plasma or serum sample inadequacy. Further study to detect apoC1 levels may help provide clues to the mechanisms responsible for the genetic association with PCOS.

**Conclusion**

The present study demonstrates that apoC1 rs4420638A/G and -317H1/H2 genetic polymorphisms are not associated with the risk of PCOS in Chinese women. However, the apoC1 rs4420638A → G variation may potentially be linked to elevated serum LH levels, a relatively high ratio of LH to FSH, and an adverse lipid metabolic profile; and the -317 H1H1 genotype is associated with increased the ratio of apoB-PAF-AH to H-PAF-AH activity and the acne grade score in the patients with PCOS. Additionally, this study also indicates that apoC1 rs4420638A/G and -317H1/H2 genetic variations are associated with an adverse glucose and lipid metabolic profile and the rs4420638G allele increases plasma PAF-AH and apoB-PAF-AH activity in the control women. These results suggest that apoC1 rs4420638A/G and -317H1/H2 genetic variants are related to metabolic abnormalities and chronic inflammation in patients and controls, while the rs4420638A/G polymorphism might be involved in endocrine abnormalities of reproductive axis in patients.

**Abbreviations**

A: Atherogenic index; apoA1: Apolipoprotein A1; apoB: Apolipoprotein B; apoB-PAF-AH: apoB-containing lipoprotein-associated platelet activating factor acetylhydrolase; apoE: Apolipoprotein E; BMI: Body mass index; DBP: Diastolic blood pressure; E2: Estradiol; F-G score: Ferriman–Gallwey score; FSH: Follicle stimulating hormone; Glu: Glucose; HOMA-C: High-density lipoprotein cholesterol; HOMA index: Homeostatic model assessment of insulin resistance; H-PAF-AH: HDL-associated PAF-AH; Ins: Insulin; LDL-C: Low-density lipoprotein cholesterol; LH: Luteinizing hormone; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglycerides; TT: Total testosterone

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**Availability of data and materials**

Please contact author for data requests.

**Authors’ contributions**

PF conceived and designed the experiments. RZ, QL and YZ performed the experiments. LG helped with the experiments. HL was responsible for patient screening. PF, RZ and HB analyzed the data and wrote the paper. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

All of the participants provided their informed consent, and the study was approved by the Institutional Review Board of the West China Second University Hospital, Sichuan University (2014–014 to PF).

**Consent for publication**

Not applicable.

**Competing interests**

All authors declare that they have no competing interests.

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**Author details**

1Laboratory of Genetic Disease and Perinatal Medicine, Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, People’s Republic of China. 2Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, People’s Republic of China.
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