Systematic Review and Meta-Analysis

Medicine®

OPEN

Association between peroxisome proliferator-activated receptor-alpha, delta, and gamma polymorphisms and risk of coronary heart disease

A case–control study and meta-analysis

Yufeng Qian, MD[a], Peiwei Li, MD[b], Jinjie Zhang, MD[b], Yu Shi, PhD[c], Kun Chen, PhD[b], Jun Yang, PhD[d], Yihua Wu, PhD[b,*], Xianhua Ye, MD[a,*]

Abstract

Objectives: Risk of coronary heart disease (CHD) has been suggested to be associated with polymorphisms of peroxisome proliferator-activated receptors (PPARs), while the results were controversial. We aimed to systematically assess the association between PPAR polymorphisms and CHD risk.

Methods: A case–control study with 446 subjects was conducted to evaluate the association between CHD risk and C161T polymorphism, which was of our special interest as this polymorphism showed different effects on risks of CHD and acute coronary syndrome (ACS). Meta-analyses were conducted to assess all PPAR polymorphisms. Either a fixed- or a random-effects model was adopted to estimate overall odds ratios (ORs).

Results: In the case–control study, *T* allele carriers of C161T polymorphism were not significantly associated with CHD risk (Odds ratio (OR) = 0.74, 95% confidence interval (CI) 0.47–1.15, $P = 0.19$), while *T* allele carriers showed higher risk of ACS (OR = 1.63, 95% CI 1.00–2.65, $P = 0.048$). The meta-analysis indicated that compared with *CC* homozygous, *T* allele carriers had lower CHD risk (OR = 0.69, 95% CI 0.59–0.82, $P < 0.001$) but higher ACS risk (OR = 1.43, 95% CI 1.09–1.87, $P = 0.010$). Three other polymorphisms were also found to be significantly associated with CHD risk under dominant model: PPAR-alpha intron 7G/C polymorphism (*CC+GC* vs *GG*, OR 1.42, 95% CI 1.13–1.78, $P = 0.003$), L162V polymorphism (*VV+LV* vs *LL*, OR 0.74, 95% CI 0.56–0.97, $P = 0.031$), and PPAR-delta +294T/C polymorphism (*CC+TC* vs *TT*, OR 1.51, 95% CI 1.12–2.05, $P = 0.007$).

Conclusions: The results suggested that PPAR-alpha intron 7G/C and L162V, PPAR-delta +294T/C and PPAR-gamma C161T polymorphisms could affect CHD susceptibility, and C161T polymorphism might have different effects on CHD and ACS.

Abbreviations: ACS = acute coronary syndrome, CHD = coronary heart disease, CI = confidence interval, HWE = Hardy–Weinberg equilibrium, IHD = ischemic heart disease, MAF = minor allele frequency, MI = myocardial infarction, OR = odds ratio, PCR = polymerase chain reaction, PPARA = PPAR alpha, PPARD = PPAR delta, PPARG = PPAR gamma, PPARs = peroxisome proliferator-activated receptors, T2DM = type 2 diabetes mellitus.

Keywords: coronary heart disease, meta-analysis, PPAR polymorphisms, risk factor

Editor: Shizhang Ling.

YQ and PL are co-first authors.

Authors' contribution: XY, YW, and JY contributed to conception and design of the study; PL and YQ contributed to conception, design, and conduct of the case–control study and edited the manuscript; JZ contributed to conduct of the case–control study and statistical analysis; YS and KC contributed to the data acquisition, analysis, and interpretation of the data.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] *Department of Cardiology, Hangzhou First People's Hospital,* [b] *Department of Epidemiology and Health Statistics, Zhejiang University School of Public Health,* [c] *State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine,* [d] *Department of Toxicology, Hangzhou Normal University School of Public Health, Hangzhou, China.*

[*] *Correspondence: Yihua Wu, Department of Epidemiology and Health Statistics, School of Public Health, Zhejiang University, 886 Yuhangtang Road, 310058 Hangzhou, China (e-mail: georgewuer@126.com); Xianhua Ye, Department of Cardiology, Hangzhou First People's Hospital, No. 261 Huansha Road, 310000 Hangzhou, China (e-mail: doctoryexianhua@163.com).*

Medicine (2016) 95:32(e4299)

Received: 19 January 2016 / Received in final form: 16 May 2016 / Accepted: 24 June 2016

http://dx.doi.org/10.1097/MD.0000000000004299

1. Introduction

Progression of atherosclerosis plays a critical role in the development of coronary heart disease (CHD), and is influenced by multiple genetic and environmental factors.[1] Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear transcription factors that regulate lipid and carbohydrate metabolism. Three subgroups have been identified: PPAR alpha (PPARA), PPAR delta (PPARD), and PPAR gamma (PPARG).[2] PPARs can alter metabolism by binding to specific elements in the promoter region of target genes.[3] In addition to the influence on lipid and glucose metabolism, PPARs also have many other functions. For instance, PPARG plays an important role in the suppression of inflammation, free radical generation, and smooth muscle cell growth.[4–6] Besides, PPARG was found to be expressed in atherosclerotic lesions and macrophage foam cells, suggesting that PPARG may influence atherosclerogenic processes.[4,7,8]

In recent years, there is growing interest in the link between PPAR polymorphisms and CHD risk, including PPARA intron 7G/C, PPARD +294T/C, PPARG P12A, and C161T (the general description of these polymorphisms are shown inFig. 1).[9–12] However, the current results are inconsistent and no concrete conclusion can be drawn regarding the relationship between PPAR polymorphisms and CHD risk. The previous meta-analyses on the association between PPAR polymorphisms and CHD risk evaluated PPARG polymorphisms but not PPARA and PPARD polymorphisms. Besides, the results of these meta-analyses were inconsistent.[13–16] For example, Xu et al[13] found no significant association between C161T polymorphism and CHD susceptibility, while another meta-analysis indicated that C161T polymorphism was statistically associated with CHD risk among Chinese.[14] We found that for C161T polymorphism, all the studies reported that *T* allele was negatively associated with CHD risk.[10,12,17–20] On the other hand, only 2 studies investigating acute coronary syndrome (ACS) indicated a non-significant positive association between C161T polymorphism and ACS risk (*CT*+*TT* vs *CC*, OR = 1.45, 95% CI 0.91–2.32 for Evangelisti et al[21]; OR = 1.25, 95% CI 0.79–1.98 for Chao et al[22]). To further clarify this issue, we conducted a case–control study to further assess the possible different role of C161T polymorphism between CHD and ACS risk. Besides, a meta-analysis was also applied to evaluate all PPAR polymorphisms.

2. Methods

This case–control study and meta-analysis was designed, conducted, and reported according to STROBE, MOOSE, and PRISMA statements.[23–25]

2.1. Case–control study

2.1.1. Study subjects. We enrolled 281 consecutive CHD patients in this study, including 137 ACS patients. All subjects were documented by angiography and were recruited from May 2011 to June 2012 at Department of Cardiology, The First People's Hospital of Hangzhou. CHD was defined as at least one stenosis of >50% diagnosed in a major coronary artery. Diagnosis of ACS was established according to American College of Cardiology Foundation/American Heart Association.[26] A total of 165 healthy subjects were recruited in this study as controls.

2.1.2. Ethics statement. This study was approved by Ethics Committee of The First People's Hospital of Hangzhou (IRB approval number: HUM00081230), and all participants were given and signed the written informed consent form.

2.1.3. Genotyping. Genomic DNA was extracted from peripheral lymphocytes using a whole blood DNA isolation kit (TIANamp Genomic DNA kit, Tiangen, China). Genotyping of the C161T polymorphism at exon 6 of the *PPAR-gamma* gene was performed by polymerase chain reaction (PCR), PCR kit was provided by TAKARA, Japan. The forward primer was 5′-CAA GAC AAC CTG CTA CAA GC-3′ and reverse primer was 5′-TCC TTG TAG ATC TCC TGC AG-3′. The amplification was performed in a 20 μL volume containing 100 ng DNA, 20 pmol of

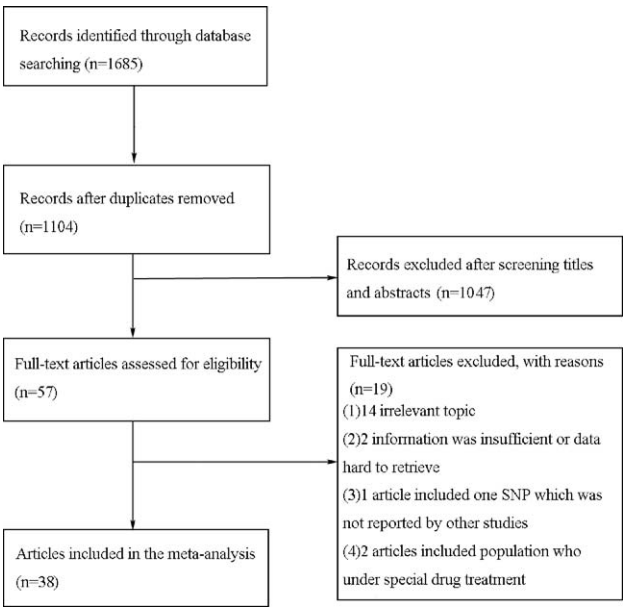

Figure 1. Meta-analysis of PPARD+294T/C polymorphism. PPARD = peroxisome proliferator-activated receptor delta.

each primer, 1.5 mmol/L $MgCl_2$, 50 mmol/L KCl, 25 μmol/L dNTP, and 1 Unit Taq polymerase. Samples were subjected to denaturing at 95°C for 5 minutes followed by 30 cycles of 95°C for 30 seconds, 58°C for 1 minute, 72°C for 1 minute. The final thermal cycle was at 72°C for 5 minutes. All PCR products were sent to sequencing for results.

2.1.4. Statistical analyses. The data were analyzed using the SPSS software (Version 13.0; SPSS, Chicago, IL). Since the number of the *TT* homozygous patients was small, allelic variants were dichotomized into *T* carriers (*TT* and *CT*) and *CC* homozygous. The statistical significance was defined as $P < 0.05$.

2.1.5. Meta-analysis. Ethics review board approval was not required for the meta-analysis process, since no animal experiment or direct human trial was conducted in this section.

2.2. Literature search and selection criteria

PUBMED and EMBASE (up to October 2015) were searched to identify eligible studies using key words relating to CHD disease ("coronary heart disease" OR "coronary artery disease" OR "myocardial infarction (MI)" OR "acute coronary syndrome" OR "ischemic heart disease (IHD)" OR "cardiovascular disease" OR "CHD" OR "CAD" OR "MI" OR "ACS" OR "IHD"), PPAR ("peroxisome proliferator-activated receptor" OR "PPAR" OR "PPAR alpha" OR "PPAR delta" OR "PPAR gamma"), and polymorphism ("polymorphism" OR "variant" OR "SNP" OR "mutation"). References of relevant articles were also scanned for potentially missing studies. Titles and abstracts were scanned and then full papers were reviewed. Articles published in English and Chinese were retrieved. The retrieved studies were carefully examined to exclude potential duplicates or overlapping data.

Articles were included if they met all the following criteria: study should evaluate the association between PPAR polymorphism and cardiovascular diseases, including CHD, MI, ACS, and other IHD; odds ratio (OR) estimates and their 95% confidence intervals (95% CI) were given or sufficient data were available to calculate these numbers; and each polymorphism should be analyzed by at least 2 studies.

Our original case–control study met all the inclusion criteria and would also be included in the meta-analysis.

2.3. Data extraction

Two reviewers (Drs YQ and PL) independently extracted study characteristics using standardized forms, and the following information was extracted from each study: first author, year of publication, country, study design, phenotype (disease), genotype of cases and controls, consistency of genotype frequencies with Hardy–Weinberg equilibrium (HWE). Discrepancies were resolved by a third investigator. The minor allele frequency (MAF) was calculated using the extracted genotype.

2.4. Statistical analysis

Dominant genetic model was adopted to pool ORs of PPAR polymorphisms first, as dominant genetic model was applied in most of the studies included. Then recessive and additive models were also applied. The significance of the pooled OR was determined by Z test ($P < 0.05$ was considered to be significant). The extent of heterogeneity across studies was checked using the χ^2 test and I^2 test (I^2 test quantifies the proportion of total variation across studies due to heterogeneity rather than chance); $P \leq 0.10$ in combination with $I^2 > 50\%$ indicates significant heterogeneity. The OR was pooled by applying a fixed-effects model or a random-effects model according to heterogeneity. When $P > 0.10$, OR of each study was pooled by the fixed-effects model, otherwise the random-effects model was applied. Subgroup analyses were adopted to assess C161T and P12A polymorphisms as they were evaluated by sufficient studies. Funnel plots were constructed and Begg and Egger tests were used to assess publication bias, and $P \leq 0.10$ was considered to be significant. All analyses were conducted using the Stata software (version 11.0; StataCorp, College Station, TX).

Table 1

Basic characteristics of participants in the case–control study.

Variables	CHD (n = 281)	ACS (n = 137)	Control (n = 165)
Age	56.2 ± 10.8	57.3 ± 11.5[#]	55.4 ± 15.3
Men	163 (58)	82 (60)	90 (55)
Smoker	142 (51)[*]	75 (55)[#]	72 (44)
Hypertension	192 (68)[*]	98 (71)[#]	52 (31)
Diabetes	98 (35)[*]	51 (37)[#]	25 (15)
Total cholesterol (mmol/L)	4.9 ± 0.9[*]	5.1 ± 0.7[#]	4.3 ± 0.8
LDL cholesterol (mmol/L)	2.5 ± 0.8[*]	2.6 ± 0.6[#]	2.1 ± 1.0
HDL cholesterol (mmol/L)	1.5 ± 0.5	1.4 ± 0.4	1.6 ± 0.5
Triglycerides (mmol/L)	2.8 ± 2.3[*]	2.6 ± 1.7[#]	1.7 ± 0.8

All continuous variables are expressed in means ± standard deviation (SD) while categorical variables are in number with percentage.

ACS = acute coronary syndrome, BMI = body mass index, CHD = coronary heart disease, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

[*] Indicates $P < 0.05$ when the CHD group was compared with the control group.

[#] Indicates $P < 0.05$ when the ACS group was compared with the control group.

3. Results

3.1. Case–control study

The basic characteristics of the cases and controls are shown in Table 1. The mean age was 57.3 ± 11.5 years in ACS group and was higher than control group ($P < 0.05$), while no significant difference was found in mean ages in CHD group and control group. No statistical difference in sex was found in case groups (CHD group and ACS group) and control group. As expected, both CHD group and ACS group had a higher prevalence of smoking habit, hypertension, diabetes, and higher levels of total-cholesterol, LDL-cholesterol, and triglycerides. We did not found significant difference in HDL-cholesterol level between case groups and control group.

The genotype distributions and allele frequencies of C161T polymorphism in cases and controls are shown in Table 2. Genotype frequencies in control group were in HWE ($P = 0.53$). Compared with *CC* homozygous, *T* allele carriers (*CT*+*TT*) were found to increase ACS risk (OR = 1.63, 95% CI 1.00–2.65, $P = 0.048$), while no significant association between C161T polymorphism and CHD risk was found (OR = 0.74, 95% CI 0.47–1.15, $P = 0.19$).

3.2. The Meta-analysis

A total of 38 eligible articles (comprising 40 studies) were finally extracted from databases and our own case–control study was also included for the meta-analysis.[9–12,17–22,27–54] The selection

Table 2

C161T polymorphism genotype distributions and allele frequencies in cases and controls.

Groups	n	Genotypes (%)				Alleles	
		CC	*CT*	*TT*	*CT+TT*	*C*	*T*
ACS	137	85 (62.04)	48 (35.04)	4 (2.92)	52 (37.96)*	79.56	20.44#
CHD	281	220 (78.29)	55 (19.57)	6 (2.14)	61 (21.71)	88.08	11.92
Controls	165	120 (72.73)	43 (26.06)	2 (1.21)	45 (27.27)	85.76	14.24

ACS = acute coronary syndrome, CHD = coronary heart disease.

* $P = 0.048$, indicating a higher *CT+TT* frequency in ACS group compared with controls.

$P = 0.044$, indicating a higher *T* frequency in ACS group than controls.

process is detailed in Fig. 2. The characteristics of the included studies were presented in Supplementary Table 1, http://links.lww.com/MD/B201. Among the 38 articles, 18 articles evaluated PPARG P12A polymorphism, and risk of CHD; 8 articles investigated PPARG C161T polymorphism; 5 articles reported PPARD +294T/C polymorphism; 4 articles assessed PPARA intron 7G/C polymorphism; and the number of studies assessing PPARA L162V, PPARG −681C/G, −689C/T, and C1431T was 5, 3, 3, and 5, respectively. All studies followed HWE, except 1 study assessing intron 7G/C polymorphism.[11]

3.3. Association between PPARG C161T polymorphism and CHD risk

Seven studies (including our own study) containing 3089 participants (1921 cases and 1168 controls) evaluated the association between C161T polymorphism and risk of CHD. The pooled OR was 0.69 (95% CI 0.59–0.82, $P < 0.001$) under dominant model (*CT+TT* vs *CC*), indicating a significant association between C161T polymorphism and CHD risk (Fig. 3A). No significant heterogeneity was found ($I^2 = 0\%$, $P = 0.635$) (Fig. 3A).

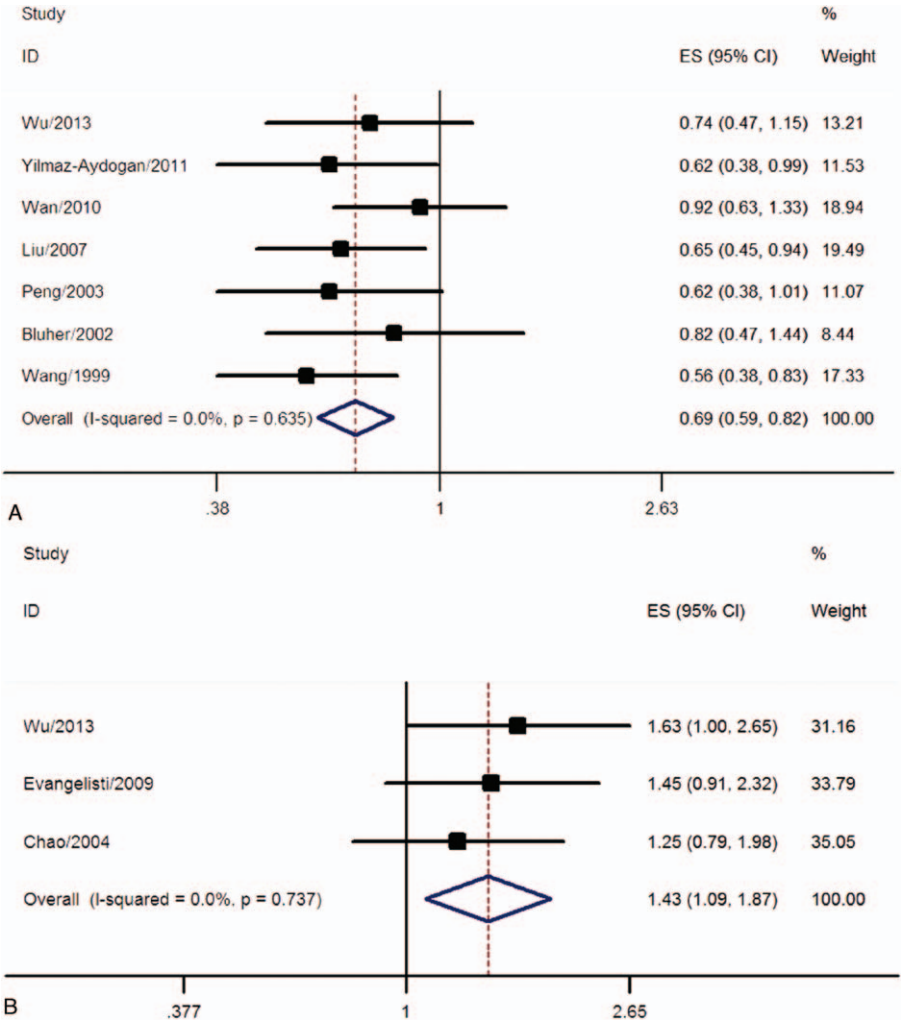

Figure 2. Flow diagram of study selection process.

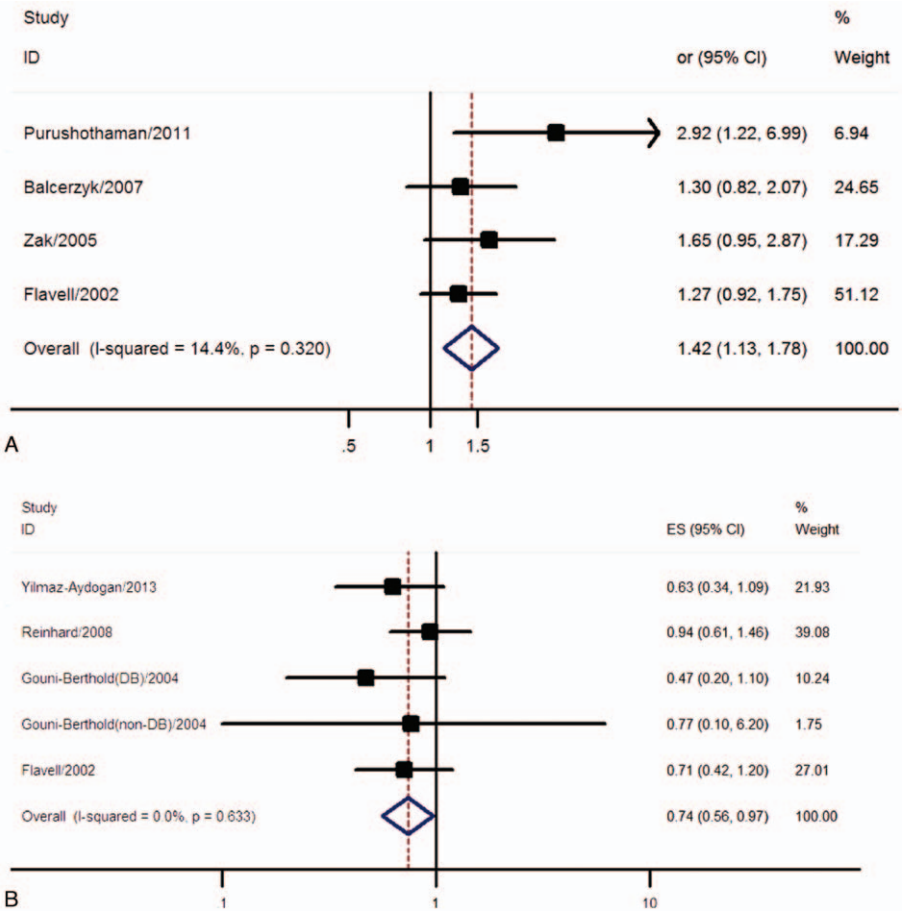

Figure 3. Meta-analysis of PPARG C161T polymorphism. (A) Forest plot of the association between C161T polymorphism and coronary heart disease (CHD) risk. (B) Forest plot of the association between C161T polymorphism and acute coronary syndrome (ACS) risk. PPARG = peroxisome proliferator-activated receptor gamma.

Three studies (including our own study) with 1091 participants (485 cases and 606 controls) assessed association between C161T polymorphism and ACS risk. Compared with *CC* homozygous, *T* allele carriers showed significantly higher ACS risk (OR = 1.43, 95% CI 1.09–1.87, $P = 0.010$) without significant heterogeneity ($I^2 = 0\%$, $P = 0.737$) (Fig. 3B).

For all the nine studies (including our own study) focused on the association between C161T polymorphism and CHD risk (including ACS), 3878 participants (2269 cases and 1609 controls) were included. An inverse association was found between *T* allele and CHD risk (pooled OR = 0.80, 95% CI 0.64–0.99, $P = 0.041$) (Table 3). Results of subgroup analyses are shown in Table 4.

Table 3

Association between PPAR polymorphisms and CHD risk under dominant model.

PPAR gene	Polymorphism	Comparison	Studies included	Cases/controls	I^2 (%)	*P* value for heterogeneity	OR (95% CI)	*P*
PPARA	Intron 7G/C[#]	*CC+GC* vs *GG*	4	608/2815	14.4	0.320	1.42 (1.13–1.78)	0.003
	L162V	*VV+LV* vs *LL*	5	NR	0	0.633	0.74 (0.56–0.97)	0.031
PPARD	+294T/C	*CC+TC* vs *TT*	5	1301/1873	63.8	0.026	1.51 (1.12–2.05)	0.007
	C161T	*TT+CT* vs *CC*	9	2269/1609	53.0	0.030	0.80 (0.64–0.99)	0.041
	P12A	*AA+PA* vs *PP*	20	8668/13,912	52.9	0.004	0.97 (0.86–1.09)	0.625
PPARG	−681C/G	*GG+CG* vs *CC*	3	1625/1395	0	0.732	0.97 (0.83–1.12)	0.657
	−689C/T	*TT+CT* vs *CC*	3	1488/1960	62.9	0.068	1.10 (0.78–1.54)	0.597
	C1431T	*TT+CT* vs *CC*	5	2290/2410	84.3	<0.001	1.17 (0.77–1.76)	0.461

CHD = coronary heart disease, CI = confidence interval, NR = not reported, OR = odds ratio, PPAR = peroxisome proliferator-activated receptor, PPARA = PPAR alpha, PPARD = PPAR delta, PPARG = PPAR gamma.

[#] The data of intron 7G/C polymorphism above was based on meta-analysis of all 4 studies assessing intron 7G/C polymorphism. After exclusion of the study not in Hardy–Weinberg equilibrium, the pooled OR was 1.59 (95% CI 1.14–2.20, $P = 0.006$).

Table 4

Subgroup analysis results of C161T and P12A polymorphisms.

Groups	C161T polymorphism					P12A polymorphism				
	No. of studies	Participants	I^2 (%)	OR (95% CI)	*P*	No. of studies	Participants	I^2 (%)	OR (95% CI)	*P*
Overall	9	3878	53.0	0.80 (0.64–0.99)	0.041	20	22,530	52.9	0.97 (0.86–1.09)	0.625
Ethnicity										
Caucasian	4	1816	71.2	0.79 (0.51–1.23)	0.304	18	20,848	49.4	0.94 (0.83–1.06)	0.287
Asian	5	2062	38.9	0.80 (0.67–0.97)	0.022	2	1682	31.4	1.40 (1.02–1.91)	0.035
Study design										
Retrospective	9	3878	53.0	0.80 (0.64–0.99)	0.041	13	11,944	55.6	0.96 (0.81–1.13)	0.632
Prospective	0	–	–	–	–	7	10,586	55.0	0.99 (0.82–1.19)	0.882
Phenotype										
CHD	7	3089	0	0.69 (0.59–0.82)	<0.001	10	8181	12.3	1.01 (0.89–1.14)	0.890
ACS/MI	3	1091	0	1.43 (1.09–1.87)	0.010	10	14,349	71.2	0.91 (0.75–1.11)	0.352

ACS = acute coronary syndrome, CHD = coronary heart disease, MI = myocardial infarction, OR = odds ratio.

3.4. Association between PPARA intron 7G/C, L162V, and PPARD +294T/C polymorphisms and CHD risk

A total of 4 studies assessed intron 7G/C polymorphism, while L162V polymorphism was evaluated by 4 articles including 5 studies. Under dominant model, patients with *C* allele had a significantly higher risk of CHD (*CC*+*GC* vs *GG*, OR = 1.42, 95% CI 1.13–1.78, *P* = 0.003) (Fig. 4A), while an inverse association between *V* allele in L162V polymorphism and CHD risk was suggested (*VV*+*LV* vs *LL*, OR = 0.74, 95% CI 0.56–0.97, *P* = 0.031) (Fig. 4B).

For +294T/C polymorphism, 5 studies including 1301 cases and 1873 controls were included, and the pooled analysis indicated a significant association with CHD risk (*CC*+*TC* vs *TT*, OR = 1.51, 95% CI 1.12–2.05, *P* = 0.007) (Fig. 1).

3.5. Other PPAR polymorphisms and CHD risk

We also assessed the association between PPARG P12A, −681C/G, −689C/T, and C1431T polymorphisms and CHD risk. No significant association with CHD risk was found under dominant model, as shown in Table 3 and Supplementary Figure 1, http://links.lww.com/MD/B201.

Results of recessive and additive models for all the PPARA, PPARD, and PPARG polymorphisms are shown in Supplementary Table 2, http://links.lww.com/MD/B201. No Publication bias was observed in the meta-analyses.

4. Discussion

Progression of atherosclerosis is the main reason of CHD, and is influenced by numerous factors such as high plasma LDL-C concentration, blood glucose level, inflammation, and oxidant stress.[1] Meanwhile, many of the above factors have been proven to be closely related to PPAR polymorphisms.[4,5,7] Thus, much attention has been paid to evaluate the link between PPAR polymorphisms and CHD risk. We conducted a case–control study to evaluate the association between C161T polymorphism and CHD risk, indicating that C161T polymorphism was not significantly associated with total CHD risk but *T* allele carriers showed higher ACS risk. In the meta-analysis, a total of 40 studies were included and 8 polymorphisms in PPARA, PPARD,

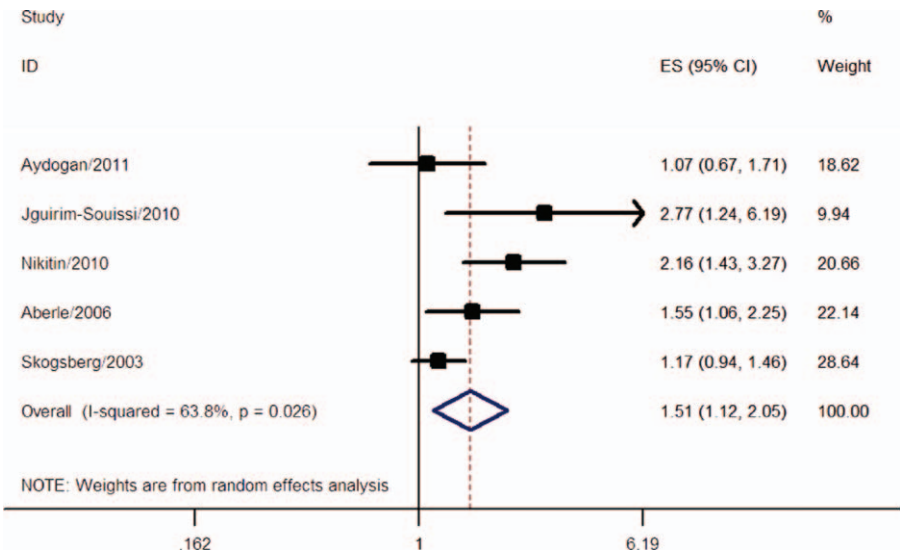

Figure 4. Meta-analysis of PPARA intron 7G/C and L162V polymorphisms. (A) Forest plot of the association between intron 7G/C polymorphism and CHD risk. (B) Forest plot of the association between L162V polymorphism and CHD risk. PPARA = peroxisome proliferator-activated receptor alpha.

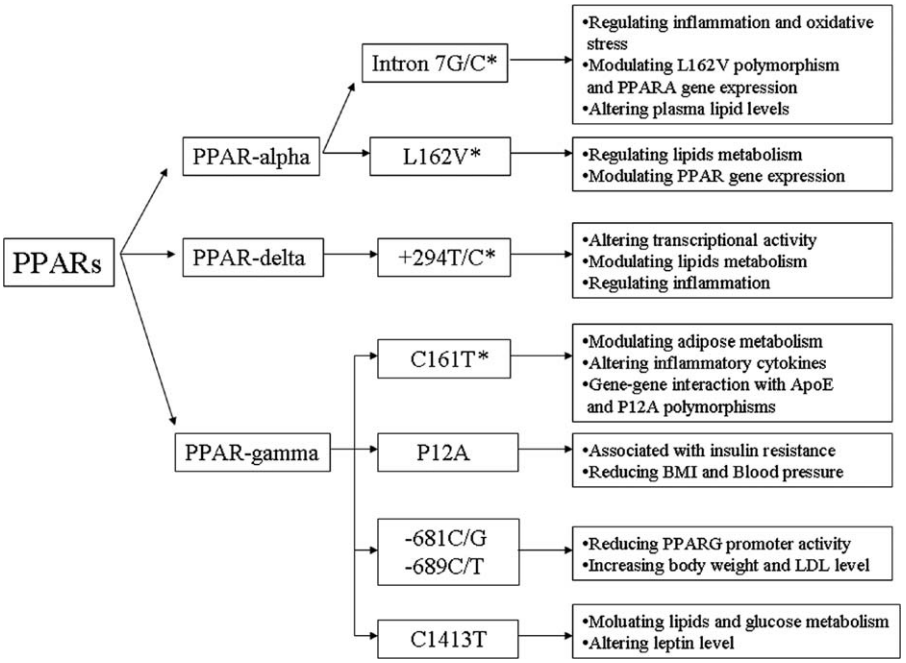

Figure 5. General descriptions of PPAR polymorphisms. BMI = body mass index, PPAR = peroxisome proliferator-activated receptor. * Stands for polymorphisms significantly associated with risk of coronary heart disease (CHD).

and PPARG were assessed, as shown in Fig. 5. The meta-analysis results of C161T polymorphism indicated *T* allele carriers had lower CHD risk but higher ACS risk. Moreover, PPARA intron 7G/C, L162V, and PPARD +294T/C polymorphisms also affected CHD susceptibility.

When only ACS was assessed, both our case–control study and the meta-analysis indicated a statistically positive association with C161T polymorphism. Interestingly, the meta-analysis of C161T polymorphism showed an inverse association with total CHD risk. The results might indicate that C161T polymorphism has different effects on stable CHD and ACS. The association between C161T polymorphism and CHD risk might involve multiple mechanisms. First, C161T polymorphism might influence CHD risk by modulating adipose metabolism in CHD patients with diabetes. Wan et al[20] reported that *T* allele carriers had significantly lower triglyceride levels than *CC* homozygote carriers in CAD patients with type 2 diabetes mellitus (T2DM). Second, C161T polymorphism might influence CHD risk by altering inflammatory cytokines. *CC* homozygotes seemed to have higher MMP-9 and TNF-α levels compared with *T* allele, which may partially explain why *CC* homozygotes are more susceptible to CHD.[17] However, the *161T* allele was also associated with an increased plasma leptin level, which is a marker of inflammation and might be involved in the genesis of acute myocardial infarction.[55–57] Third, it was found that for gene–gene interaction between C161T polymorphism and apolipoprotein E (ApoE), compared with *CT* carriers, *CC* homozygotes accentuated the cholesterol difference between apoE4 carriers and non-apoE4 carriers.[18] Interaction between C161T polymorphism and P12A polymorphism was also reported, and it has been shown that in diabetic CHD patients, serum triglyceride and VLDL-C levels increased in the order of P12P-CC<P12P-CT<P12A-CC<P12A-CT, suggesting the favorable effects of P12P genotype in lowering triglyceride level.[19] There are 3 kinds of mRNAs produced by PPARG gene transcription, namely PPARG1, PPARG2, and PPARG3.[58] C161T polymorphism occurs in all 3 mRNAs, the effects of this polymorphism might be diverse, and C161T polymorphism might have both pro- and anti-atherosclerotic effects.[18] This may partially explain the different effects of *T* allele on ACS and non-ACS CHD patients. However, it should be noted that ACS and non-ACS CHD patients are not quite distinguishable and the non-ACS patients may have an ACS attack in their later lives. So the results should be interpreted cautiously, and more studies, especially prospective studies with long follow-up time, are warranted to further validate this phenomenon. Besides, the underlying molecular mechanisms remain unclear and are warranted to be investigated.

Several studies also indicated the relationship between C161T polymorphism and severity of CHD. Wang et al[10] reported a frequency of *T* allele carriers (*CT*+*TT*) of 21.3% for CHD patients with 1 diseased vessel, 28.1% for patients with 2 diseased vessels, and 31.8% for those with 3 diseased vessels ($P = 0.004$), suggesting that CHD in patients with *T* allele tends to be more severe. Besides, Wan et al[20] indicated that *T* allele carriers were at a higher risk of severe stenosis in CHD plus type 2 diabetes mellitus patients, indicating diabetes might modulate the effects of C161T polymorphism on CHD severity. However, there were no significant association between PPARG C1431T, P12A polymorphisms and number of diseased vessels in CHD patients.[29,42] Moreover, ACS includes unstable ST or non-ST elevation MI and unstable angina, which are quite different from each other. Thus, it would be interesting and important to include factors such as the cardiac enzymes, left ventricular systolic function, and Killip class in the future analysis.

Three other polymorphisms, PPARA intron 7G/C, L162V, and PPARD +294T/C, also showed significant associations with CHD risk. Our study did not support a significant association between PPARG P12A, −681C/G, −689C/T, and C1431T polymorphism and CHD risk. Interestingly, in the subgroup

analysis of P12A polymorphism, we found that in Asian populations, P12A polymorphism was shown to be associated with CHD susceptibility (as shown in Table 4). However, only 2 studies evaluated P12A polymorphism in Asian populations, thus this conclusion should be considered carefully.

Several meta-analyses assessed the association between PPARG polymorphisms and CHD risk and only C161T, P12A, C1431T polymorphisms were evaluated,[13–16] while the current study is the first meta-analysis evaluating PPARA intron 7G/C, L162V, and PPARD +294T/C. A total of 8 polymorphisms were assessed and 4 of them were found to be significantly associated with CHD risk. For C161T polymorphism, results of previous meta-analyses were inconsistent: Xu et al[13] found no significant association between C161T polymorphism and CHD risk, Wu et al[14] indicated C161T polymorphism was only associated with CHD risk among Chinese and *T* allele was associated with reduced CHD risk. Another study reported that *T* allele of C161T polymorphism was associated with increased CHD risk (*CT*+*TT* vs *CC*, pooled OR = 1.182, 95% CI 1.023–1.341), but most of the studies included reported an opposite trend, furthermore, we found that one study included in that meta-analysis actually assessed C1431T polymorphism (not C161T) which leads to the ambiguous results. Our study adds additional evidence of the effect size of the C161T polymorphism on CHD and ACS risk, and found that C161T polymorphism might have different effects on CHD and ACS susceptibility. No publication bias was found in this study, and subgroup analyses were performed to assess the role of some polymorphisms in special populations or under certain conditions.

The current analysis also has several limitations. First, most of the included studies were from Asia, Europe, and USA, so the conclusions may not be true for other ethnic groups. Second, significant interstudy heterogeneity was found and could not be completely explained when assessing some polymorphisms. Third, gene–gene interaction and gene–environment interaction were not assessed because of insufficient data, though they were important in the genesis of CHD.

To conclude, our study supported that PPARA intron 7G/C and L162V, PPARD +294T/C, and PPARG C161T polymorphisms could affect the susceptibility to CHD, and C161T polymorphism might have different effects on CHD and ACS. The current study provided further insight into the etiology of CHD, and might be helpful to identify those with higher risk of CHD. Larger and well-designed studies of different ethnic populations are warranted to confirm our findings.

References

[1] Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115–26.

[2] Berger J, Moller DE. The mechanisms of action of PPARs. Annu Rev Med 2002;53:409–35.

[3] Blaschke F, Takata Y, Caglayan E, et al. Obesity, peroxisome proliferator-activated receptor, and atherosclerosis in type 2 diabetes. Arterioscler Thromb Vasc Biol 2006;26:28–40.

[4] Duval C, Chinetti G, Trottein F, et al. The role of PPARs in atherosclerosis. Trends Mol Med 2002;8:422–30.

[5] Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685–95.

[6] Balakumar P, Rose M, Singh M. PPAR ligands: are they potential agents for cardiovascular disorders? Pharmacology 2007;80:1–0.

[7] Zaman AG, Helft G, Worthley SG, et al. The role of plaque rupture and thrombosis in coronary artery disease. Atherosclerosis 2000; 149:251–66.

[8] Marx N, Sukhova G, Murphy C, et al. Macrophages in human atheroma contain PPARgamma: differentiation-dependent peroxisomal proliferator-activated receptor gamma (PPARgamma) expression and reduction of MMP-9 activity through PPARgamma activation in mononuclear phagocytes in vitro. Am J Pathol 1998;153:17–23.

[9] Skogsberg J, McMahon AD, Karpe F, et al. Peroxisome proliferator activated receptor delta genotype in relation to cardiovascular risk factors and risk of coronary heart disease in hypercholesterolaemic men. J Intern Med 2003;254:597–604.

[10] Wang XL, Oosterhof J, Duarte N. Peroxisome proliferator-activated receptor gamma C161T polymorphism and coronary artery disease. Cardiovasc Res 1999;44:588–94.

[11] Flavell DM, Jamshidi Y, Hawe E, et al. Peroxisome proliferator-activated receptor alpha gene variants influence progression of coronary atherosclerosis and risk of coronary artery disease. Circulation 2002;105:1440–5.

[12] Bluher M, Klemm T, Gerike T, et al. Lack of association between peroxisome proliferator-activated receptor-gamma-2 gene variants and the occurrence of coronary heart disease in patients with diabetes mellitus. Eur J Endocrinol 2002;146:545–51.

[13] Xu W, Xu J, Sun B, et al. The effect of PPARG gene polymorphisms on the risk of coronary heart disease: a meta-analysis. Mol Biol Rep 2013;40:875–84.

[14] Wu Z, Lou Y, Jin W, et al. The C161T polymorphism in the peroxisome proliferator-activated receptor gamma gene (PPARgamma) is associated with risk of coronary artery disease: a meta-analysis. Mol Biol Rep 2013;40:3101–12.

[15] Wu Z, Lou Y, Jin W, et al. The Pro12Ala polymorphism in the peroxisome proliferator-activated receptor gamma-2 gene (PPARgamma2) is associated with increased risk of coronary artery disease: a meta-analysis. PLoS One 2012;7:e53105.

[16] Ding S, Liu L, Zhuge QC, et al. The meta-analysis of the association of PPARG P12A, C161T polymorphism and coronary heart disease. Wien Klin Wochenschr 2012;124:671–7.

[17] Liu Y, Yuan Z, Liu Y, et al. PPARgamma gene C161T substitution is associated with reduced risk of coronary artery disease and decreased proinflammatory cytokine expression. Am Heart J 2007;154:718–24.

[18] Peng DQ, Zhao SP, Nie S, et al. Gene-gene interaction of PPARgamma and ApoE affects coronary heart disease risk. Int J Cardiol 2003;92:257–63.

[19] Yilmaz H, Kurnaz O, Kurt O, et al. Effects of the PPARG P12A and C161T gene variants on serum lipids in coronary heart disease patients with and without Type 2 diabetes. Mol Cell Biochem 2011;358:355–63.

[20] Wan J, Xiong S, Chao S, et al. PPARgamma gene C161T substitution alters lipid profile in Chinese patients with coronary artery disease and type 2 diabetes mellitus. Cardiovasc Diabetol 2010;9:13.

[21] Evangelisti L, Attanasio M, Lucarini L, et al. PPARgamma promoter polymorphisms and acute coronary syndrome. Atherosclerosis 2009;205:186–91.

[22] Chao TH, Li YH, Chen JH, et al. The 161TT genotype in the exon 6 of the peroxisome-proliferator-activated receptor gamma gene is associated with premature acute myocardial infarction and increased lipid peroxidation in habitual heavy smokers. Clin Sci 2004;107:461–6.

[23] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

[24] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.

[25] STROBE statement—checklist of items that should be included in reports of observational studies (STROBE initiative). Int J Public Health 2008;53:3–4.

[26] Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2002;40:1366–74.

[27] Purushothaman S, Ajitkumar VK, Renuka R. Association of PPARalpha intron 7 polymorphism with coronary artery disease: a cross-sectional study. ISRN Cardiol 2011;1:21–5.

[28] Yilmaz-Aydogan H, Kucukhuseyin O, Kurnaz O, et al. Investigation of polymorphic variants of PPARD and APOE genes in Turkish coronary heart disease patients. DNA Cell Biol 2012;31:867–75.

[29] Zhou X, Chen J, Xu W. Association between C1431T polymorphism in peroxisome proliferator-activated receptor-gamma gene and coronary artery disease in Chinese Han population. Mol Biol Rep 2012;39: 1863–8.
[30] Aydogan HY, Kucukhuseyin O, Tekeli A, et al. Associations of receptor for advanced glycation end products -374T/A and Gly82 Ser and peroxisome proliferator-activated receptor gamma Pro12Ala polymorphisms in Turkish coronary artery disease patients. Genet Test Mol Biomarkers 2012;16:134–7.
[31] Jguirim I, Jelassi A, Hrira Y, et al. +294T/C polymorphism in the PPAR-delta gene is associated with risk of coronary artery disease in normolipidemic Tunisians. Genet Mol Res 2010;9:1326–33.
[32] Nikitin AG, Chistiakov DA, Minushkina LO, et al. Association of the CYBA, PPARGC1A, PPARG3, and PPARD gene variants with coronary artery disease and metabolic risk factors of coronary atherosclerosis in a Russian population. Heart Vessels 2010;25:229–36.
[33] Ashok M, Veera NG, Kanthimathi S, et al. Associations for lipoprotein lipase and peroxisome proliferator-activated receptor-gamma gene and coronary artery disease in an Indian population. Arch Med Res 2010;41:19–25.
[34] Galgani A, Valdes A, Erlich HA, et al. Homozygosity for the Ala allele of the PPARgamma2 Pro12Ala polymorphism is associated with reduced risk of coronary artery disease. Dis Markers 2000;29:259–64.
[35] Vogel U, Segel S, Dethlefsen C, et al. PPARgamma Pro12Ala polymorphism and risk of acute coronary syndrome in a prospective study of Danes. BMC Med Genet 2009;10:52.
[36] Dallongeville J, Iribarren C, Ferrieres J, et al. Peroxisome proliferator-activated receptor gamma polymorphisms and coronary heart disease. PPAR Res 2009;2009:543746.
[37] Reinhard W, Stark K, Sedlacek K, et al. Association between PPARalpha gene polymorphisms and myocardial infarction. Clin Sci 2008;115: 301–8.
[38] Li JP, Cheng LX, He MA, et al. Study on the association of -689C/T polymorphism in the PPARgamma2 promoter with myocardial infarction. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2008;25:19–22.
[39] Za MH, Vander YT, Grobbee DE, et al. Peroxisome proliferator-activated receptor gamma-2 P12A polymorphism and risk of acute myocardial infarction, coronary heart disease and ischemic stroke: a case-cohort study and meta-analyses. Vasc Health Risk Manag 2008;4:427–36.
[40] Balcerzyk A, Zak I, Krauze J. Synergistic effect between polymorphisms of PPARA and ABCA1 genes on the premature coronary artery disease. Acta Cardiol 2007;62:233–8.
[41] Ruiz EA, Kraft P, Campos H. Ala12 variant of the peroxisome proliferator-activated receptor-gamma gene (PPARG) is associated with higher polyunsaturated fat in adipose tissue and attenuates the protective effect of polyunsaturated fat intake on the risk of myocardial infarction. Am J Clin Nutr 2007;86:1238–42.
[42] Rhee EJ, Kwon CH, Lee WY, et al. No association of Pro12Ala polymorphism of PPAR-gamma gene with coronary artery disease in Korean subjects. Circ J 2007;71:338–42.
[43] Aberle J, Hopfer I, Beil FU, et al. Association of the T+294C polymorphism in PPAR delta with low HDL cholesterol and coronary heart disease risk in women. Int J Med Sci 2006;3:108–11.
[44] Li L, Cheng LX, Nsenga R, et al. Association between Pro12Ala polymorphism of peroxisome proliferator-activated receptor-gamma 2 and myocardial infarction in the Chinese Han population. Clin Cardiol 2006;29:300–4.
[45] Zak I, Balcerzyk A, Sarecka B, et al. Contemporaneous carrier-state of two or three "proatherosclerotic" variants of APOE, ICAM1, PPARA and PAI-1 genes differentiate CAD patients from healthy individuals. Clin Chim Acta 2005;362:110–8.
[46] Pischon T, Pai JK, Manson JE, et al. Peroxisome proliferator-activated receptor-gamma2 P12A polymorphism and risk of coronary heart disease in US men and women. Arterioscler Thromb Vasc Biol 2005;25:1654–8.
[47] Gouni I, Giannakidou E, Muller D, et al. Association between the PPARalpha L162V polymorphism, plasma lipoprotein levels, and atherosclerotic disease in patients with diabetes mellitus type 2 and in nondiabetic controls. Am Heart J 2004;147:1117–24.
[48] Tobin MD, Braund PS, Burton PR, et al. Genotypes and haplotypes predisposing to myocardial infarction: a multilocus case-control study. Eur Heart J 2004;25:459–67.
[49] Doney AS, Fischer B, Leese G, et al. Cardiovascular risk in type 2 diabetes is associated with variation at the PPARG locus: a Go-DARTS study. Arterioscler Thromb Vasc Biol 2004;24:2403–7.
[50] Ridker PM, Cook NR, Cheng S, et al. Alanine for proline substitution in the peroxisome proliferator-activated receptor gamma-2 (PPARG2) gene and the risk of incident myocardial infarction. Arterioscler Thromb Vasc Biol 2003;23:859–63.
[51] Vos HL, Doggen C, Rosendaal FR. Effect of the PPAR gamma2 Pro12Ala polymorphism on the risk of myocardial infarction. Blood 2000;96:62–72.
[52] Oladi M, Nohtani M, Avan A, et al. Impact of the C1431T Polymorphism of the Peroxisome Proliferator Activated Receptor-Gamma (PPAR-gamma) Gene on Fasted Serum Lipid Levels in Patients with Coronary Artery Disease. Ann Nutr Metab 2015; 66:149–54.
[53] Youssef SM, Mohamed N, Afef S, et al. A Pro 12 Ala substitution in the PPARgamma2 polymorphism may decrease the number of diseased vessels and the severity of angiographic coronary artery. Coron Artery Dis 2013;24:347–51.
[54] Yilmaz H, Kurnaz O, Kucukhuseyin O, et al. Different effects of PPARA, PPARG and ApoE SNPs on serum lipids in patients with coronary heart disease based on the presence of diabetes. Gene 2013;523:20–6.
[55] Meirhaeghe A, Fajas L, Helbecque N, et al. A genetic polymorphism of the peroxisome proliferator-activated receptor gamma gene influences plasma leptin levels in obese humans. Hum Mol Genet 1998;7:435–40.
[56] Loffreda S, Yang SQ, Lin HZ, et al. Leptin regulates proinflammatory immune responses. Faseb J 1998;12:57–65.
[57] Soderberg S, Ahren B, Jansson JH, et al. Leptin is associated with increased risk of myocardial infarction. J Intern Med 1999; 246:409–18.
[58] Zhu Y, Qi C, Korenberg JR, et al. Structural organization of mouse peroxisome proliferator-activated receptor gamma (mPPAR gamma) gene: alternative promoter use and different splicing yield two mPPAR gamma isoforms. Proc Natl Acad Sci 1995;92:7921–5.