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Original Article

Gene-Gene Interactions among Pparα/δ/γ Polymorphisms for Apolipoprotein (Apo) A-I/ Apob Ratio in Chinese Han Population

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Abstract

Background: The peroxisome proliferator-activated receptors (PPARs) -α, -δ/β and -γ are the ligand-activated transcription factors involved in the regulation of fatty acid and lipoprotein metabolism, energy balance, cell proliferation and differentiation and atherosclerosis, etc. We investigated the associations of 10 single-nucleotide polymorphisms (SNPs) in PPARs with apolipoprotein (apo) A-I/ apoB ratio in Chinese Han population.

Methods: Overall, 630 subjects (212 males, 418 females) were randomly selected from the Prevention of Metabolic Syndrome and Multiple Metabolic Disorders in Jiangsu Province of China Study Cohort. Population analyzed was as the general population which involved healthy people and individuals with disorders of apoA-I or apoB. 10 SNPs (rs1800206, rs135539, rs4253778, rs2016520, rs9794, rs10865710, rs1805192, rs709158, rs3856806 and rs4684847) were genotyped. Mean difference (*Difference*) and 95% confident interval (*95%CI)* were calculated.

Results: After covariates adjustment, rs1800206-V allele (LV+VV) and rs3856806-T allele (CT+TT) were significantly associated with a decreased apoA-I/ apoB ratio than those wild type carriers, *Difference* (95%CI) were -1.29 (-1.96~-0.62) and -0.8 (-1.42~-0.17), respectively. Rs4253778-C allele was significantly associated with an increased apoA-I/ apoB ratio compared to the wild type carriers (GG), *Difference* (95%CI) was 0.76 (0.04~1.48). Generalized multifactor dimensionality reduction analysis showed that three-to-eight-locus models were significant with apoA-I/ apoB ratio ($P<0.05$). We chose the seven-locus model ($P=0.0010$) as the best GMDR model (cross-validation consistency was 7/10 and testing accuracy was 62.97%).

Conclusion: Our data provided the evidence that PPARs polymorphisms might be involved in regulation of apoA-I/ apoB ratio in independently and/or in an interactive manner.

Keywords: Peroxisome proliferator-activated receptors, Apolipoprotein (apo) A-I/ apoB ratio, Polymorphism, Interaction

Introduction

Cardiovascular diseases (CVD) are the major cause of death in adults in several countries (1). Dyslipidaemia is an important CVD risk factor. Several studies have reported that apolipoprotein B (apoB) in atherogenic particles—mainly low-density lipoprotein cholesterol (LDL-C) (2-4), but also very low-density lipoprotein (VLDL), intermediate density lipoprotein, and lipoprotein (a) (5)—and apolipoprotein A-I (apoA-I) in anti-atherogenic particles, such as high-density lipoprotein cholesterol (HDL-C) types, (6, 7) could improve the prediction of risk of CVD. ApoA-I/ apoB ratio reflected comprehensive changes of apoA-I and apoB, which was superior in predict-

ing risk of CVD events than conventional lipid profile and any other cholesterol ratio, including LDL-C/ HDL-C ratio and non- HDL-C/ HDL-C ratio (8). Previous studies mainly focused on the association of apoA-I/apoB ratio level and atherosclerosis and CVD as well as its predicting effect on atherosclerotic CVD and other disorders of lipid metabolism (6, 7), while the association between genes and the apoA-I/apoB ratio level had not been explained. As studies of twins indicated that genetic factors play a dominant role in determining apoA-I level and apoB level (9-11), we speculated that apoA-I/ apoB ratio may be probably influenced by genetic factors. Either environmental or genetic influence can be determinant on apolipoprotein metabolism, which may affect the risk of developing CVD. Therefore, key metabolism regulators such as the peroxisome proliferator-activated receptors (PPARs) family are candidate genes to investigate genetic predisposition of these complex diseases.

In 1990, the first member of the PPAR isotypes, PPARα was cloned by Issemann and Green, and was named based on its ability to be activated by peroxisome proliferator chemicals (12-14). Soon afterwards, another two homologues of PPARα known as PPARδ and PPARγ were also identified. As members of the nuclear receptor superfamily, PPARs are ligand-activated transcription factors which regulate the expression of genes involved in glucose, fatty acid and lipoprotein metabolism, energy balance, fat cell proliferation and differentiation (15). The hypolipidemic fibrate drugs, mainly via activated PPARα and less activated PPARδ and PPARγ, can lower circulating TG, LDL-C and apoB levels and raise plasma HDL-C and apoA-I levels (16, 17). A number of polymorphisms have been reported in the association of the PPARs isoforms with apoA-I and apoB (18, 19). As can be seen, it is highly possible that PPARα/δ/γ is associated with apoA-I/ apoB ratio. As of now, there is no reports regarding the association of PPARs polymorphisms and apoA-I/ apoB ratio level in Chinese Han population. The present study may provide a basis for further elucidation of the role PPARs played in regulating the apoA-I/ apoB ratio level metabolism.

Therefore, in the present study, we studied a group of 630 adults randomly selected from the Prevention of Metabolic Syndrome and Multiple Metabolic Disorders in Jiangsu Province (PMMJS) of China Study Cohort (20) to investigate the main effects of both single-locus and multi-locus interactions to test the hypothesis that PPARα/δ/γ polymorphisms may contribute to the apoA-I/ apoB ratio level independently and/or through complex interactions.

Materials and Methods

Study populations

Participants were recruited within the framework of the PMMJS cohort population (20), which was initiated from April 1999 to June 2004. A total of 4582 subjects with 5 years follow-up data were obtained between March 2006 and October 2007. 4083 participants (89.11%) completed the supplementary follow-up examination (the baseline characteristics of participants who attended the follow-up examinations were similar to those missing examinations, $P>0.05$). The exclusion criteria for the study included the subjects with a history of stroke/cardiovascular disease (n=36) or diabetes mellitus (n=289) and those with missing data (n=133) or body mass index (BMI) less than 18.5 kg/m^2 (n=27), leaving 3731 eligible participants. The detailed design of this study has been described elsewhere (20). Each subject has an ID. At the October of 2009, we randomly selected 630 subjects (212 males, 418 females) from the remaining 3731 cases by computer-generated random numbers and no individual was related. The subjects who were selected were similar to those who were not selected in terms of gender, age, smoking status, alcohol consumption, family disease history and metabolic variables. Blood samples were collected at baseline from the 630 subjects and analyzed for genotype. The outcome index of this study was follow-up apoA-I/ apoB ratio level. This study was approved by the ethic committee of Soochow University, and all the participants signed an informed consent form at the interview.

Anthropometric measurement and laboratory methods

Data on lifestyle risk factors and demographics of all participants were obtained by using a standard questionnaire administered by trained staff. Body weight, height, and waist circumference (WC) were measured according to standardized procedures, and BMI was calculated as weight in kilograms divided by the square of the height in meters. Blood samples were collected in the morning after at least 8 hours of fasting. All plasma and serum samples were frozen at −80 °C until laboratory testing. Concentrations of apoA-I and apoB were detected by immune turbidimetry and using follow-up apoA-I/ apoB ratio level as outcome. Fasting plasma glucose (FPG) was measured using the oxidase enzymatic method. Concentrations of HDL-C and serum triglyceride (TG) levels were assessed enzymatically by an automatic biochemistry analyzer (Hitachi Inc, Tokyo, Japan) using commercial reagents. All laboratory analyses were performed at the same laboratory. The method of investigation during follow-up was same as those at baseline.

SNP selection, genomic DNA extraction, and genotyping

We selected 10 SNPs within the PPARα/δ/γ gene based on 1) previously reported associations with metabolic abnormalities 2) known heterozygosity and minor allele frequency (MAF) > 0.05 3) selected SNPs in functional areas of the gene fragments, or in the regional which may change the function. Table 1 provides detailed information on the selected SNPs, including their features and allelic variants and the minor allele frequencies.

Genomic DNA from participants was extracted from ethylenediaminetetraacetic acid (EDTA)-treated whole blood, using the DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Two approaches were used to analyze frequent and minor alleles for the 10 SNPs (rs4253778, rs1800206, rs135539, rs2016520, rs9794, rs10865710, rs1805192, rs709158, rs3856806 and rs4684847). Rs4253778 was genotyped by polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP). The restriction enzyme TaqI (TaKaRa, Dalian, China) was used to identify and cut specific sequences, after which PCR was performed with the following primers: forward 5´-ACA ATC ACT CCT TAA ATA TGG TGG -3' and reverse 5´-AAG TAG GGA CAG ACA GGA CCA GTA-3´. A 25-µl PCR mixture included DNA 20ng, 0.5 U DNA polymerase (TaKaRa, Dalian, China), 10×buffer 2.5µl, 10mM dNTP 0.5µl, and 0.5µl forward primer and reverse primer at a concentration of 100µM. PCR conditions were as follows: initial denaturation for 3 minutes at 95°C, the mixture passed through 40 cycles of denaturation for 10 seconds at 95 °C, annealing for 30 seconds at 63 °C, and extension for 30 seconds at 72 °C, and a final extension for 7 minutes at 72 °C. For the other 9 SNPs, ABI Prism 7000 software and an allelic discrimination procedure were used for genotyping with TaqMan fluorescence probe kit (TaKaRa, Dalian, China). The 25-µl reaction mixture included 1.25µl SNP Genotyping Assays (20×), 12.5µl Genotyping Master Mix (2×), and 20ng DNA. The conditions were as follows: initial denaturation for 10 minutes at 95°C, denaturation for 15 seconds at 92°C, and annealing and extension for 90 seconds at 60 °C, for 50 cycles.

Statistical analysis

The Chi-square test (χ^2) was used to examine differences in the categorical data distribution. The clinical characteristics of the continuous variables were described with mean and standard deviation (mean ± SD) and were tested using a two-sample *t*-test or ANOVA. The criterion for statistically significance was set at $P<0.05$ for all tests. A linear regression model was used to examine the association between PPARα/δ/γ mutation and apoA-I/ apoB ratio level, mean differences (*Difference*) and 95% confident interval (95% CI) were calculated. The mean differences were adjusted for potential confounding effects including gender, age, smoking status and alcohol consumption. For quality control purpose, Hardy-Weinberg equilibrium (HWE) test was used to detect genotype typing errors by Fisher's exact test. Linkage disequilibrium (LD) between polymorphisms was estimated

by using SHEsis (available online at http://analysis.bio-x.cn).

Generalized multifactor dimensionality reduction (GMDR) (21) analysis was used to analyze interaction among the 10 SNPs on level of apoA-I/ apoB ratio. To assess each selected interaction, parameters were calculated, including cross-validation consistency, the testing balanced accuracy, and the sign test, to assess each selected interaction. The cross-validation consistency score is a measure of the degree of consistency with which the selected interaction is identified as the best model among all possibilities considered. The testing balanced accuracy is a measure of the degree to which the interaction accurately predicts case-control status with scores between 0.50 (indicating that the model predicts no better than chance) and 1.00 (indicating perfect prediction). Finally, the sign test, or permutation test (providing empirical *P*-values) for prediction accuracy can be used to measure the significance of an identified model. In this study, we analyzed the interaction among 10 SNPs by using a GMDR model that adjusted for gender, age, smoking status and alcohol consumption.

Table 1: Description for the 10 SNPs of PPARα/δ/γ

SNP ID	SNP	Chromosome	Position	Exon/Intron	Nucleotide substitution	MAF*
PPARα						
rs135539	1A>C	22	25949836	Intron_1	A>C	0.228
rs4253778	7G>C	22	26021203	Intron_7	G>C	0.136
rs1800206	L162V	22	26004843	Exon_5	C>G	0.163
PPARδ						
rs2016520	-87T>C	6	35318778	Exon_4	T>C	0.294
rs9794	2806C>G	6	35335795	Exon_9	C>G	0.216
PPARγ						
rs709158	Intron A>G	3	12403176	Intron_2	A>G	0.299
rs10865710	C681G	3	12293198	Exon_A2	C>G	0.328
rs1805192	Pro12Ala	3	12361238	Exon_B	C>G	0.289
rs4684847	Intron C>T	3	12326337	Intron_3	C>G	0.206
rs3856806	C161T	3	12415557	Exon_6	C>T	0.313

MAF, minor allele frequency; SNP, single-nucleotide polymorphism/*MAF in the total group of this study

Results

A total of 630 participants were studied, including 212 males and 418 females. Males were significantly more to reported being a smoker ($P<0.001$) and highly to have alcohol consumption ($P<0.001$) than females. The distributions of FPG, apoA-I, apoB, apoA-I/ apoB ratio and BMI did not significantly differ between males and females ($P>0.05$ for all comparisons). All genotypes were distributed according to the Hardy-Weinberg equilibrium ($P>0.05$). Pairwise LD analysis between SNPs was measured, and D' was less than 0.75 in all cases.

The alleles and genotype frequencies of each SNP are shown in Table 3. There was a significant difference in rs709158 allele distributions between males and females ($P=0.02$) (Table 3). Additionally, the linear regression analysis shows the allelic distributions of the 10 SNPs in subjects versus the level of apoA-I/ apoB ratio (Table 4).

Table 2: General characteristics of the 630 participants separated by gender

Variables	Total	Male	Female	*P**
	(n=630)	(n=212)	(n=418)	
Age(year)	49.781±9.424	50.335±10.064	49.500±9.082	0.294
Smoke n (%)	158(25.1)	130(61.3)	28(6.7)	<0.001
Alcohol n (%)	170(27.0)	132(62.3)	38(9.1)	<0.001
BMI (mmol/L)	23.258±3.131	23.237±2.888	23.268±3.251	0.906
FPG (mmol/L)	4.958±0.670	4.986±0.718	4.943±0.645	0.447
apoA-I (g /L)	1.879±3.686	2.055±6.305	1.790±0.599	0.394
apoB (g/L)	0.814±0.264	0.808±0.264	0.817±0.264	0.699
apoA-I/apoB ratio (g/L)	2.52±3.989	2.648±6.658	2.455±1.251	0.565

Note: Values are means ± SD for age, BMI, FPG apoA-, apoB, apoA/ apoB; BMI: body mass index; TG: triglyceride; FPG: fasting plasma glucose; apoA-I：apolipoprotein A-I; apoB：apolipoprotein B. *P** Values less than 0.05 were considered statistically significant

Table 3: Genotype distribution and allele frequencies of the 10 SNPs in PPARα/δ/γ

SNPs	Genotypes and alleles	Total（n=630）	Male (n=212)	Female (n=418)	*P**
rs135539	AA/AC/CC	384/205/41	128/68/16	256/137/25	0.75
	C(%)	22.8	23.6	22.4	
rs4253778	GG/GC/CC	474/141/15	161/46/5	313/95/10	0.96
	C(%)	13.6	13.2	13.8	
rs1800206	LL/LV/VV	435/185/10	141/67/4	294/118/6	0.6
	V(%)	16.3	17.7	15.6	
rs9794	CC/CG/GG	389/210/31	138/63/11	251/147/20	0.39
	G(%)	21.6	20.0	22.4	
rs2016520	TT/TC/CC	305/279/46	103/91/18	202/188/28	0.69
	C(%)	29.4	30.0	29.2	
rs10865710	CC/CG/GG	289/269/72	83/103/26	206/166/46	0.05
	G(%)	32.8	36.6	30.9	
rs3856806	CC/CT/TT	302/262/66	92/101/19	210/161/47	0.09
	T(%)	31.3	32.8	30.5	
rs709158	AA/AG/GG	307/269/54	87/106/19	220/163/35	0.02
	G(%)	29.9	34.0	27.9	
rs1085192	PP/PA/AA	328/240/62	111/82/19	217/158/43	0.87
	A(%)	28.9	28.3	29.2	
rs4684847	CC/CT/TT	402/197/31	132/71/9	270/126/22	0.63
	T(%)	20.6	21.0	20.3	

*P** Values less than 0.05 were considered statistically significant

After adjustment for gender, age, smoking status and alcohol consumption, it was found that both rs1800206-V allele (LV+VV), and rs3856806-T allele (CT+TT) were significantly associated with a decreased apoA-I/ apoB ratio level than did those wild type carriers, *Difference* (95%CI) values were -1.29 (-1.96~-0.62) and -0.8 (-1.42~-0.17), respectively. Rs4253778-C allele (GC+CC) was significantly associated with an increased apoA-I/ apoB ratio level compared to the wild type carriers (GG), *Difference* (95%CI) values was 0.76 (0.04~1.48). However, other seven SNPs in PPARs did not exhibit any significant association with apoA-I/ apoB ratio level after covariate adjustment (Table 4).

We employed the GMDR analysis to assess the impacts of the interaction among 10 SNPs, after adjustment for covariates including gender, age,

smoking status and alcohol consumption, three-to-eight-locus models were significant with apoA-I/ apoB ratio level (P<0.05). Overall, the seven-locus model (P=0.0010) had the highest level of cross-validation consistency (7/10) and showed a better testing accuracy (62.97%). Therefore, we chose the seven-locus model as the best GMDR model, indicating a potential gene-gene interaction among rs1800206, rs2016520, rs10865710, rs3856806, rs709158, rs1805192 and rs4684847.

Table 4: The association analysis between SNPs in PPARα/δ/γ and apoA-I/ apoB ratio level

SNPs	Genotypes	Total	Male	Female	*Difference* **(*95%CI*)	*P**
	AA	384	128	256	0	
rs135539	AC+CC	246	84	162	-0.63（-1.27~0.01）	0.052
	GG	474	161	313	0	
rs4253778	GC+CC	156	51	105	0.76(0.04~1.48)	0.039
	LL	435	141	294	0	
rs1800206	LV+VV	195	71	124	-1.29(-1.96~-0.62)	0.0002
	CC	389	138	251	0	
rs9794	CG+GG	241	74	167	-0.53(-1.17~0.11)	0.11
	TT	305	103	202	0	
rs2016520	TC+CC	325	109	216	0.30(-0.33~-0.93)	0.35
	CC	289	83	206	0	
rs10865710	CG+GG	341	129	212	0.30(-0.33~-0.93)	0.35
	CC	302	92	210	0	
rs3856806	CT+TT	328	120	208	-0.8(-1.42~-0.17)	0.013
	AA	307	87	220	0	
rs709158	AG+GG	323	125	198	0.12(-0.52~0.75)	0.72
	PP	328	111	217	0	
rs1805192	PA+AA	302	101	201	-0.21(-0.84~-0.42)	0.52
	CC	402	132	270	0	
rs4684847	CT+TT	228	80	148	-0.23(-0.88~0.42)	0.49

: Adjusted for gender, age, smoking status and alcohol consumption./ *P Values less than 0.05 were considered statistically significant.

Table 5: Best gene-gene interaction models, as identified by GMDR

Locus no.	Best combination	Cross-validation consistency	Testing accuracy	*P**
3	rs135539 rs1800206 rs1805192	5/10	0.6680	0.0107
4	rs135539 s1800206 rs3856806 rs1805192	2/10	0.6908	0.0010
5	rs1800206 rs9794 rs10865710 rs3856806 rs1805192	6/10	0.6831	0.0107
6	rs135539 s1800206 rs2016520 rs10865710 rs709158 rs1805192	4/10	0.5921	0.0107
7	rs1800206 rs2016520 rs10865710 rs3856806 rs709158 rs1805192 rs4684847	7/10	0.6297	0.0010
8	rs4253778 rs1800206 rs9794 rs2016520 rs10865710 rs3856806 rs709158 rs1805192	4/10	0.5713	0.01719
9	rs135539 rs4253778 rs1800206 rs2016520 rs10865710 rs3856806 rs709158 rs1805192 rs4684847	5/10	0.5044	0.9453

*P** Values less than 0.05 were considered statistically significant. Adjusted for gender, age, smoking status and alcohol consumption.

Discussion

No gene-gene interaction among these 10 PPARα/δ/γ polymorphisms for apoA-I/ apoB ratio level in Chinese Han population was reported before. After adjusting for gender, age, smoking status and alcohol consumption, our results show important associations of PPARα rs1800206, rs4253778 and PPARγ rs3856806 with apoA-I/ apoB ratio level, and a gene-gene interaction on the level of apoA-I/ apoB ratio level was identified among rs1800206, rs2016520, rs10865710, rs3856806, rs709158, rs1805192 and rs4684847 ($P<0.05$). These findings support the hypothesis that minor gene in single-locus analysis can also contribute to the etiology of apoA-I/ apoB ratio level on account of the existence of gene-gene interaction.

Single-locus analyses showed that after covariate adjustment, the rs1800206 and rs4253778 of PPARα, rs3856806 of PPARγ were significantly associated with apoA-I/ apoB ratio level. Rs1800206 polymorphism in PPARα has been investigated intensively. The frequency of rs1800206-V allele was 16. 0% in the present population, which is similar to the frequency of 14.0% in European population (22) and 10.6% in Canadians (23), lower than the reported frequency of 37.4% in Italian population (24). Current evidence suggests an association between the rs1800206 polymorphism and traits of lipid metabolism, such as apoA-I, apoB, total cholesterol (TC), LDL-C and HDL-C (18, 19). A study conducted by Flavell et al. (25) showed that rs1800206 was involved in regulation of apoA-I and TC. This is in part in agreement with the results obtained by Lacquemant et al. (26), who showed that in Caucasians, TC and apoB concentrations were higher in rs1800206-V allele carriers than that in wild type gene carriers. In our study, rs1800206 was associated with a decreased level of apoA-I/ apoB for the rare V allele. The frequency of rs4253778-C allele in the European population (27) was 18.7%, while 14.0% in the present study which was slightly higher than the Stockholm population (12.4%) (28). Previous studies indicated that rs4253778-C allele of PPARα was significantly associated with lower VLDL and higher HDL-C levels (29). Balcerzyk et al. (30) showed that LDL-C and TG were lower in C-allele carriers of rs42537787 polymorphism compared with non-carriers, suggesting the possibility of a protective effect of this polymorphism on the regulation of lipid metabolism. These findings in part corroborated our finding. In our study, apoA-I/ apoB ratio level existing in rs4253778-C allele carriers was lower than that in wild type gene carriers. In this study slightly higher frequencies of rs3856806-T allele were observed (for T 31.0%) in contrast with Wan et al. (31) study which reports the frequencies as 21.3%. Until now, little is known about the association of the rs3856806 polymorphism with dyslipidaemia. Rhee et al.(32) suggested that subjects with rs3856806-T allele had significantly lower levels of HDL-C and TC than those without T allele. Similar to the previous studies, subjects in the present study showed that higher apoA-I/ apoB ratio level in rs3856806-T allele carriers than that in wild type gene carriers. And all these findings suggest that PPARα/δ/γ polymorphisms might play a central role in regulating the level of apoA-I/ apoB ratio.

In the present study, we investigated gene-gene interaction among PPARα/δ/γ to test the hypothesis that small single gene effects cannot be detected by single-locus studies. Because of the distance among genes, epistasis (33) might exist between adjacent SNPs, so that effects of some minor SNPs to apoA-I/ apoB ratio are covered. For this reason, an interaction analysis of 10 SNPs was needed. In this paper, GMDR analysis was used to assess interaction among the 10 SNPs on apoA-I/ apoB ratio level after covariate adjustment. The results showed that the three-to-eight-locus models were remarkable ($P<0.05$). The seven-locus model, including PPARα (rs1800206), PPARδ (rs2016520), and PPARγ (rs10865710, rs3856806, rs709158, rs1805192, and rs4684847), was determined as optimal model ($P=0.0010$). Skogsberg et al. (34) reported that a noted interactive effect between the PPARα (rs1800206) and PPARδ (rs2016520) on plasma LDL-C and TG. Gu et al. (35) demonstrated an independent and combined association of PPARα (rs1800206),

PPARδ (rs2016520) and PPARγ (rs1805192) and other PPARs polymorphisms with hypertriglyceridemia. Unfortunately, those studies did not investigate a significant interaction between PPARα, PPARδ and PPARγ and apoA-I/ apoB ratio, thus we can not compare our results. The exact biological functions and underlying molecular mechanism of these SNPs on apoA-I/ apoB ratio level need further investigation.

PPARs subtypes are encoded by different genes with similar amino acid sequences, especially the DNA-binding domain and ligand (hormone)-binding domain (LBD). PPARs form heterodimers with the retinoid X receptor and subsequently bind to the specific DNA sequence designated peroxisome proliferator response elements (PPRE) present in the regulatory region of the target genes, which in turn affects the transcription initiation and mRNA abundance of target genes (36). There are potential co-regulation mechanisms of PPARα, PPARδ and PPARγ in effecting lipid metabolism. Activation of PPARα, PPARδ and PPARγ lead to changes in transcription of a large number of genes that regulate lipoprotein metabolism including adenosine triphosphate binding transporter-1(ABCA-1) and lipoprotein lipase (LPL) (15). Changes in transcription of ABCA-1 are thought to enhance the reverse TC transport and increase the apoA-I specific regurgitation of cholesterol while Changes in transcription of LPL are thought to enhance lipolysis of VLDL triglycerides resulting in reducing plasma TG levels and apoB proteasome degradation (1). So we thought that PPAR α/δ/γ may impact apoA-I/ apoB ratio levels by controlling expression of a variety of related factors in apoA-I and apoB metabolic pathways, such as ABCA1 and LPL. However, the exact underlying mechanism still requires further investigation.

One limitation of this study is that these findings might not be generalizable to other populations. Additional, large ethnically matched studies would be necessary to confirm if such interaction is found in non-Chinese Han subjects. Second, only 1 to 5 SNPs per candidate gene were chosen. The selected SNPs might not sufficient to capture most of the genetic information of the candidate gene. Future studies should include more SNPs.

Conclusion

We tested the association between PPARα/δ/γ gene polymorphisms and apoA-I/ apoB ratio level in the Chinese Han population based on single-locus and multi-locus analyses. Our findings support the hypothesis that the SNPs from PPARα/δ/γ polymorphisms may contribute to the level of apoA-I/ apoB ratio independently and/or through complex interactions.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/ or falsification, double publication and/ or submission, redundancy, etc) have been completely observed by the authors.

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Abbreviations footnotes

single-nucleotide polymorphisms (SNPs)
peroxisome proliferator-activated receptor (PPAR)
apolipoprotein (apo)
Cardiovascular diseases (CVD)
apolipoprotein B (apoB)
low-density lipoprotein cholesterol (LDL-C)
very low-density lipoprotein (VLDL)
high-density lipoprotein cholesterol (HDL-C)
apolipoprotein A-I (apoA-I)

body mass index (BMI)
waist circumference (WC)
Fasting plasma glucose (FPG)
triglyceride (TG)
minor allele frequency (MAF)
polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP)
Chi-square test (χ^2)
mean differences (*Difference*)
95% confident interval (*95%CI*)
Hardy-Weinberg equilibrium (HWE)
Linkage disequilibrium (LD)
Generalized multifactor dimensionality reduction (GMDR)
total cholesterol (TC)
ligand (hormone)-binding domain (LBD)
peroxisome proliferator response elements (PPRE)
adenosine triphosphate binding transporter-1(ABCA-1)
lipoprotein lipase (LPL).

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