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Original Article

Sex-specific association of the *PLA2G6* rs2760114 and serum lipid-related phenotypes in two Chinese ethnic groups

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Abstract: Little is known about the association of the phospholipase A2 group VI gene (*PLA2G6*) rs2760114 mutation and serum lipid phenotypes in the south Chinese populations. This study aimed to detect the association of the *PLA2G6* rs2760114 mutation and several environmental factors with serum lipid phenotypes between males and females in the Jing and Han populations. Genotyping of the *PLA2G6* rs2760114 mutation was performed in 785 Jing subjects and 844 Han participants using polymerase chain reaction and restriction fragment length polymorphism. The genotype and allele frequencies were significantly different between Jing and Han populations (GG, 64.46% *vs*. 70.02%; CT, 30.32% *vs*. 26.18%; and TT, 5.22% *vs*. 3.80%; $P = 0.045$; C, 79.62% *vs*. 83.12%; T, 20.38% *vs*. 16.88%; $P = 0.010$). The levels of triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), apolipoprotein (Apo) A1, ApoB and the ratio of ApoA1 to ApoB in Jing; TG and the ratio of ApoA1 to ApoB in Han; TG and ApoB in Jing males; TG and ApoA1 in Jing females; total cholesterol (TC), TG and low-density lipoprotein cholesterol (LDL-C) in Han males; and TG and ApoA1 in Han females were different among the CC, CT and TT genotypes. These finding suggest that the association of the *PLA2G6* rs2760114 mutation and serum lipid phenotypes might have an ethnic- and/or sex-specificity.

Keywords: Phospholipase A2 group VI (PLA2G6), rs2760114, serum lipid phenotypes, sex-specific association, environmental factors

Introduction

Cardiovascular disease (CVD) is the major global cause of morbidity and mortality [1]. It is a well-established association between dyslipidemia and an increased risk of CVD [2]. There is increasing evidence that sex and gender differences are important in epidemiology, pathophysiology, treatment, and outcomes in dyslipidemia [3]. The relative risk of CVD in subjects with high plasma triglyceride (TG) levels is higher in women than in men [4]. It has also reported that regulating serum TG and high-density lipoprotein cholesterol (HDL-C) level is more essential in women than in men [5]. Women have been shown to have less well-controlled low-density lipoprotein cholesterol (LDL-C) levels than men and to be less likely to have received lipid-lowering medications even though their risk of developing coronary artery disease (CAD) is similar to that of men with dyslipidemia [6-8]. To achieve the greatest possible reduction in CVD risk, antihyperlipidemic treatment strategies should also be aimed at reducing elevated serum lipid levels in women.

Recently, several genome-wide association studies (GWASs) have reported the association of many mutations near the phospholipase A2 group VI gene (*PLA2G6*; Gene ID: 8398; MIM: 603604; formerly known as GVI; PLA2; INAD1; NBIA2; iPLA2; NBIA2A; NBIA2B; PARK14; PNPLA9; CaI-PLA2; IPLA2-VIA and iPLA2beta, located on Chromosome 22q13.1 NC_0000-22.11 38111495...38192109; exon count: 29) and serum lipid phenotypes [9, 10] through the biological function of the A2 phospholipase, a class of enzyme that catalyzes the release of fatty acids from phospholipids [11]. The gene encoded protein may play a role in phospholipid remodeling, arachidonic acid release, leukotriene and prostaglandin synthesis, fas-mediated apoptosis, and transmembrane ion flux in glucose-stimulated B-cells. Several transcript vari-

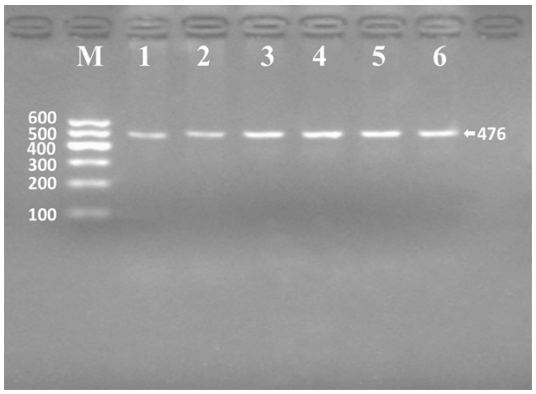

Figure 1. Electrophoresis of PCR products of the *PLA2G6* rs2760114 mutation. Lane M, 100-bp marker ladder; lanes 1-6, 476-bp band of PCR products.

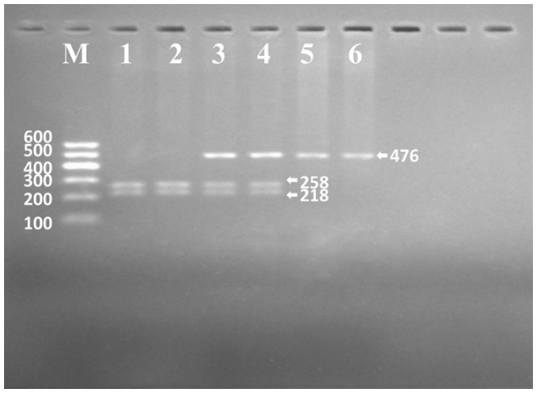

Figure 2. Electrophoresis of genotyping of the *PLA2G6* rs2760114 mutation. Lane M, 100-bp marker ladder; lanes 1 and 2, TT genotype (258- and 218-bp); lanes 3 and 4, CT genotype (476-, 258- and 218-bp); and lanes 5 and 6, CC genotype (476-bp).

ants encoding multiple isoforms have been described, but the full-length nature of only three of them have been determined to date (http://www-ncbi-nlm-nih-gov.ezp-prod1.hul.harvard.edu/gene/8398).

As one of China's 55 minority groups, Jing is an oceanian ethnic minority come from Vietnam and continue to speak the Vietnamese language and persist in fishing for a living until today, with a population of 22,517 (in 2000 the fifth national census statistics of China). Among 56 nationalities in China, the Han is the biggest one. Compared with Han populations, Jing population is a relatively conservative and isolated minority, and preserves their custom of intra-ethnic marriages. Thus, their genetic background may be less heterogeneous within the population [12, 13].

Materials and methods

Ethical considerations

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University. Written informed consent for all the participants was obtained as per the guidelines.

Subjects

Two groups of study populations including 785 unrelated participants (387 males, 49.3% and 398 females, 50.7%) of Jing and 844 unrelated subjects (418 males, 49.5% and 426 females, 50.5%) of Han were randomly selected from our previous stratified randomized samples [14]. All participants were agricultural workers (Han) or fishermen (Jing) from Dongxing City, Guangxi Zhuang Autonomous Region, People's Republic of China. The participants' age ranged from 18-80 years with the mean age of 54.88±12.45 years in Jing and 52.99±8.82 years in Han; respectively. The age distribution and gender ratio matched between the two populations. The participants were not taking medications known to affect serum lipid levels (lipid lowering drugs such as statins or fibrates, beta-blockers, diuretics, or hormones). They did not show any signs of CVD from their health questionnaires, clinical examinations.

Epidemiological survey

The epidemiological survey was carried out using internationally standardized methods, following a common protocol [15]. Information on demographics and exposure factors was collected with standardized questionnaires. Alcohol consumption was categorized into subgroups of grams of alcohol per day: 0, ≤ 25 and > 25. Cigarette smoking was categorized into subgroups of cigarettes per day: 0, ≤ 20 and > 20. Several parameters including height, weight, body mass index (BMI), waist circumference, blood pressure and fasting blood glucose were measured using methods described in our previous studies [12-16].

Analyses of serum lipid phenotypes

Blood samples were drawn from all subjects after an overnight fast. Sera were separated immediately and stored at -20°C. Serum lipid levels were measured. The levels of total cho-

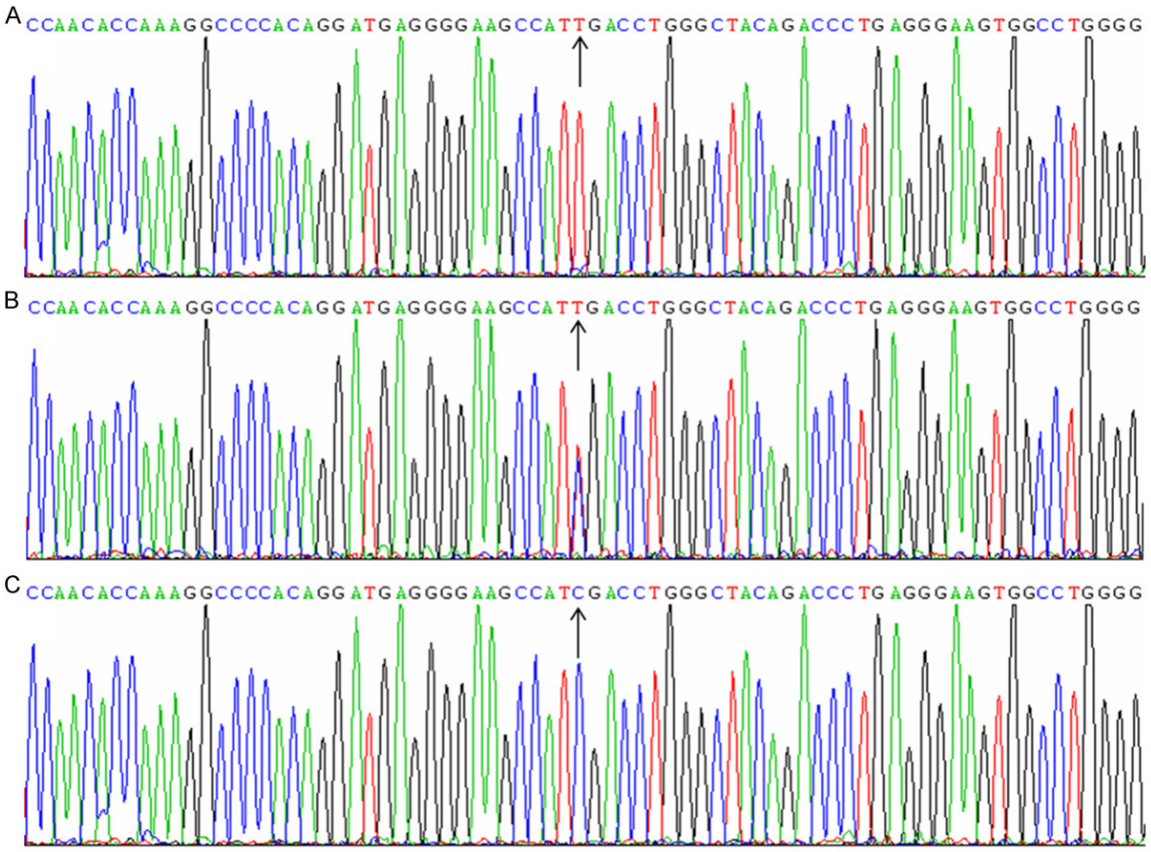

Figure 3. A part of the nucleotide sequences of the *PLA2G6* rs2760114 mutation by direct sequencing. (A) TT genotype; (B) CT genotype; (C) CC genotype.

lesterol (TC), TG, HDL-C and LDL-C in the samples were determined by enzymatic methods with commercially available kits. Serum apolipoprotein (Apo) A1 and ApoB levels were assessed by the immuneturbidimetric immunoassay.

Diagnostic criteria

The normal values of serum TC, TG, HDL-C, LDL-C, ApoA1 and ApoB levels, and the ratio of ApoA1 to ApoB in our Clinical Science Experiment Center were 3.10-5.17, 0.56-1.70, 1.16-1.42, 2.70-3.10 mmol/L, 1.20-1.60, 0.80-1.05 g/L, and 1.00-2.50; respectively [16].

Isolation of DNA

Genomic DNA was extracted from EDTA whole blood sample using a spin column method according to the protocol (QIAamp Blood Kit; Qiagen GmbH, Hilden, Germany). DNA was stored at -20°C till the time of use.

Genetic polymorphism detection

Genotyping of the *PLA2G6* rs2760114 mutation was performed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). PCR amplification (**Figure 1**) was carried out with forward primer 5'-GGGATTACAGGGTGAGCG-3' and reverse primer 5'-AGGCCAACAAGGTGAAGAAA-3'. After initial denaturing at 95°C for 5 min, the reaction mixture was subjected to 33 cycles of 45 s denaturation at 95°C, 30 s annealing at 65°C and extension 60 s at 72°C, followed by a final 10 min extension at 72°C. After restriction enzyme (*Taq*I [C]) digestion of the amplified DNA, the genotypes were identified by electrophoresis on 2% agarose gels and visualized with ethidium-bromide staining ultraviolet illumination. Three genotypes were detected: CC genotype (476-bp), CT genotype (476-, 258- and 218-bp) and TT genotype (258- and 218-bp; **Figure 2**). Six samples (each genotype in two; respectively) detected by the PCR-RFLP were also con-

Table 1. Anthropometric and biochemical characteristics of the participants

Parameter	Jing (n = 785)		Han (n = 844)	
	Male	Female	Male	Female
Number [n (%)]	387 (49.3)	398 (50.7)	418 (49.5)	426 (50.5)
Age (years)	54.88±12.45	52.99±8.82	54.21±13.24	53.32±10.41
Height (cm)	162.62±6.16	155.40±6.28[c]	162.51±5.77	153.51±6.68[c]
Weight (kg)	62.20±9.17	56.11±8.22[c]	60.33±8.31	54.50±9.26[c]
Body mass index (kg/m^2)	23.52±3.26	23.21±2.97	22.82±2.72	23.10±3.52
Waist circumference (cm)	81.47±9.34	78.60±8.15[c]	78.57±7.69	77.77±9.93
Cigarette smoking [n (%)]				
Nonsmoker	253 (65.4)	367 (92.2)	226 (54.1)	420 (98.6)
≤ 20 cigarettes/day	34 (8.8)	4 (1.0)	34 (8.1)	0 (0)
> 20 cigarettes/day	100 (25.8)	27 (6.8)[c]	158 (37.8)	6 (1.4)
Alcohol consumption [n (%)]				
Nondrinker	244 (63.0)	367 (92.2)	176 (42.1)	412 (96.7)
≤ 25 g/day	67 (17.3)	11 (2.8)	52 (12.4)	2 (0.5)
> 25 g/day	76 (19.6)	20 (5.0)[c]	190 (45.5)	12 (2.8)
Systolic blood pressure (mmHg)	129.68±18.56	129.10±18.21	131.21±17.00	130.94±18.37
Diastolic blood pressure (mmHg)	81.13±10.58	80.50±9.88	81.19±9.33	81.32±10.01
Pulse pressure (mmHg)	48.55±14.59	48.59±14.87	50.02±13.86	49.62±15.00
Blood glucose (mmol/L)	6.58±1.52	6.51±1.09	6.58±1.07	6.53±0.94
Total cholesterol (mmol/L)	5.12±0.98	5.11±0.85	4.92±0.84	4.73±0.77[b]
Triglyceride (mmol/L)	1.44 (1.16)	1.37 (1.14)	1.27 (1.04)	1.26 (1.03)
HDL-cholesterol (mmol/L)	1.71±0.53	1.85±0.43[c]	1.73±0.43	1.86±0.44[c]
LDL-cholesterol (mmol/L)	2.86±0.39	2.84±0.41	2.89±0.47	2.78±0.38[c]
Apoliprotein (Apo) A1 (g/L)	1.31±0.24	1.32±0.21	1.32±0.21	1.33±0.20
ApoB (g/L)	1.07±0.26	1.05±0.25	1.05±0.24	1.03±0.24
ApoA1/ApoB	1.30±0.41	1.32±0.11	1.34±0.43	1.35±0.34

HDL-C: high-density lipoprotein; LDL-C, low-density lipoprotein; Apo: apolipoprotein. [a]P < 0.001; [b]P < 0.01; [c]P < 0.05 in comparison with males from the same ethnic group.

firmed by direct sequencing. The PCR products were purified by low melting point gel electrophoresis and phenol extraction, and then the DNA sequences were analyzed using an ABI Prism 3100 (Applied Biosystems) in Shanghai Sangon Biological Engineering Technology & Services Co., Ltd., People's Republic of China (**Figure 3**).

Statistical analyses

Descriptive parameters are presented as mean ± SD (serum TG levels were presented as medians and interquartile ranges) and Categorical variables were presented using frequency counts. Comparisons between groups of means were compared by the Student's unpaired *t*-test. Chi-square test (χ^2) was used to compare categorical variables between the groups. Genotype frequencies in Jing and Han were tested for Hardy-Weinberg equilibrium, and any deviation between the observed and expected frequencies was tested for significance using the χ^2 test. The association between genotypes and serum lipid parameters was performed using analysis of covariance (ANCOVA). Age, gender, BMI, waist circumference, smoking, and alcohol consumption were adjusted for the statistical analysis. Multivariable linear regression analyses with stepwise modeling were used to determine the correlation between genotypes (CC = 1, CT = 2, TT = 3) or alleles (the T allele non-carrier = 1, the T allele carrier = 2) and several environmental factors with serum lipid phenotypes in subgroups. Two sided *P* value < 0.05 was considered statistically significant. All data were evaluated using SPSS version 21.0 (SPSS Inc., Chicago, Illinois) of windows 10.

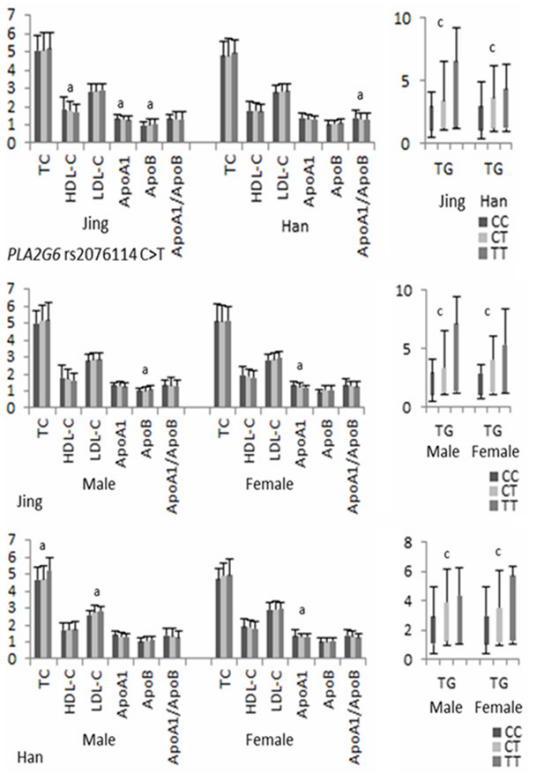

Figure 4. Lipid-associated phenotypes according to genotypes for the two ethnic groups and sex-/gender-subgroups. [a]P < 0.001; [b]P < 0.01; [c]P < 0.05 in comparison with males from the same ethnic group.

Results

General and biochemical characteristics of the participants

Table 1 compares the general characteristics and serum lipid phenotypes between males and females in Jing and Han populations. The values of height, weight and serum HDL-C levels were significant different between men and women in the two populations ($P < 0.001$ for all). The values of waist circumference, the percentages of subjects who smoked cigarettes and the percentages of participants who consumed alcohol were different between males and females in Jing ($P < 0.001$ for all). The levels of serum TC and LDL-C were different between males and females in Han ($P < 0.01$ for each).

Genotypic and allelic frequencies

As shown in **Table 2**, the genotype frequency of *PLA2G6* rs2760114 mutation agrees with the Hardy-Weinberg equilibrium in the two populations ($P > 0.05$ for each). The genotype and allele frequencies of *PLA2G6* rs2760114 mutation were significantly different between Jing and Han populations (GG, 64.46% *vs*. 70.02%; CT, 30.32% *vs*. 26.18%; TT, 5.22% *vs*. 3.80%; $P = 0.045$; C, 79.62% *vs*. 83.12%; T, 20.38% *vs*. 16.88%; $P = 0.010$). There were no significant differences among genotype and/or allele frequencies of *PLA2G6* rs2760114 mutation in gender-subgroups in the two populations ($P > 0.05$ for all; **Table 3**).

Genotypes and serum lipid phenotypes

Figure 4 describes serum levels of TG, HDL-C, ApoA1, ApoB and the ratio of ApoA1 to ApoB in Jing; TG and the ratio of ApoA1 to ApoB in Han; TG and ApoB in Jing males; TG and ApoA1 in Jing females; TC, TG and LDL-C in Han males; and TG and ApoA1 in Han females were different between CC, CT and TT genotypes ($P < 0.05$-0.001).

Risk factors for serum lipid phenotypes

Several environmental factors such as age, gender, weight, waist circumference, alcohol consumption, and cigarette smoking and traditional cardiovascular risk factors such as BMI, fasting blood glucose and blood pressure levels were also correlated with serum lipid phenotypes in males and females of the two populations ($P < 0.05$-0.001; **Tables 4** and **5**).

Discussion

In the present study, we demonstrate that the values of serum lipid phenotypes were significantly different between males and females in both Jing and Han populations. As expected, the level of serum HDL-C was lower in men than women in the two populations. The levels of serum TC and LDL-C in Han were higher in males than females. The genotype and allele frequencies of *PLA2G6* rs2760114 mutation were significantly different between Jing and Han populations. However, there were no significant differences among genotype and/or allele frequencies of *PLA2G6* rs2760114 mutation in gender-subgroups in the two populations. Serum levels of TG, HDL-C, ApoA1, ApoB and the ratio of ApoA1 to ApoB in Jing; TG and the ratio of ApoA1 to ApoB in Han; TG and ApoB in Jing males; TG and ApoA1 in Jing females; TC,

Table 2. Genotypic and allelic frequencies between the two populations

SNP	Genotype/Allele	Jing (n = 785)	Han (n = 844)	X^2	*P*-value
PLA2G6	CC	506 (64.46)	591 (70.02)		
rs2076114	CT	238 (30.32)	221 (26.18)		
	TT	41 (5.22)	32 (3.80)	6.197	0.045
	HWE(P)	0.065	0.051		
	C	1250 (79.62)	1403 (83.12)		
	T	320 (20.38)	285 (16.88)	6.583	0.010

HWE, Hardy-Weinberg equilibrium.

Table 3. Genotypic and allelic frequencies in gender subgroups

Group	n	Genotype			Allele		HWE(P)
		CC	CT	TT	C	T	
Jing	785						
Male	387	249 (64.34)	117 (30.23)	21 (5.43)	615 (79.46)	159 (20.54)	0.146
Female	398	257 (64.32)	121 (30.15)	20 (5.53)	635 (79.77)	161 (20.23)	0.118
x^2			0.064		0.024		
P			0.969		0.876		
Han	844						
Male	418	292 (69.86)	110 (26.32)	16 (3.82)	694 (83.01)	142 (16.99)	0.172
Female	426	299 (70.19)	111 (26.06)	16 (3.76)	709 (83.22)	143 (16.78)	0.165
x^2			0.012		0.012		
P			0.994		0.912		

HWE, Hardy-Weinberg equilibrium.

Table 4. Risk factors for serum lipid-related phenotypes in the two populations

Lipid-associated phenotype	Risk factor	B	Std. error	Beta	t	P
Jing						
TC	Age	0.014	0.003	0.170	4.852	0.000
	Body mass index	0.088	0.017	0.298	5.076	0.000
	Waist circumference	-0.021	0.006	-0.199	-3.398	0.001
	Pulse pressure	-0.007	0.002	-0.116	-3.305	0.001
	Glucose	0.193	0.023	0.277	8.241	0.000
TG	Genotype	0.461	0.045	0.321	10.225	0.000
	Height	-0.016	0.004	-0.135	-3.816	0.000
	Waist circumference	0.029	0.003	0.310	9.193	0.000
	Cigarette smoking	0.177	0.039	0.157	4.521	0.000
	Diastolic blood pressure	0.005	0.003	0.064	1.975	0.049
	Glucose	0.062	0.020	0.097	3.093	0.002
HDL-C	Gender	0.090	0.039	0.092	2.287	0.022
	Height	-0.008	0.003	-0.111	-2.716	0.007
	Systolic blood pressure	0.003	0.001	0.130	3.643	0.000
	Glucose	0.027	0.013	0.074	2.116	0.035
LDL-C	Waist circumference	-0.006	0.002	-0.131	-3.708	0.000
ApoA1	Genotype	-0.032	0.013	-0.084	-2.374	0.018
	Waist circumference	-0.003	0.001	-0.130	-3.673	0.000
	Alcohol consumption	0.039	0.012	0.119	3.351	0.001
ApoB	Genotype	-0.037	0.015	-0.085	-2.507	0.012
	Age	0.003	0.001	0.135	3.978	0.000

	Body Mass Index	0.022	0.003	0.276	8.182	0.000
	Glucose	0.016	0007	0.083	2.453	0.014
ApoA1/ApoB	Age	-0.003	0.001	-0.097	-2.830	0.005
	Body Mass Index	-0.034	0.004	-0.274	-8.050	0.000
	Glucose	-0.026	0.010	-0.087	-2.544	0.011
Han						
TC	Gender	0.193	0.053	0.119	3.618	0.000
	Waist circumference	0.007	0.003	0.078	2.344	0.019
	Glucose	0.220	0.026	0.274	8.306	0.000
TG	Genotype	0.298	0.041	0.226	7.197	0.000
	Age	-0.008	0.002	-0.131	-3.954	0.000
	Weight	-0.014	0.005	-0.179	-2.982	0.003
	Waist circumference	0.034	0.005	0.419	7.109	0.000
	Cigarette smoking	0.145	0.030	0.160	4.770	0.000
	Diastolic blood pressure	0.007	0.002	0.088	2.761	0.006
	Glucose	0.075	0.023	0.105	3.232	0.001
HDL-C	Gender	0.134	0.030	0.153	4.469	0.000
LDL-C	Gender	0.178	0.034	0.208	5.165	0.000
	Age	0.006	0.001	0.155	3.978	0.000
	Body Mass Index	-0.011	0.005	-0.079	-2.303	0.022
	Cigarette smoking	0.052	0.022	0.096	2.364	0.018
	Systolic blood pressure	0.002	0.001	0.079	2.091	0.037
ApoA1	Gender	0.078	0.019	0.194	4.065	0.000
	Age	0.002	0.001	0.115	2.970	0.003
	Height	0.004	0.001	0.144	3.045	0.002
	Weight	-0.005	0.001	-0.234	-6.061	0.000
	Cigarette smoking	-0.025	0.010	-0.099	-2.380	0.018
	Alcohol consumption	0.093	0.010	0.395	9.332	0.000
	Pulse pressure	-0.002	0.001	-0.120	-3.358	0.001
ApoB	Waist circumference	0.006	0.001	0.238	7.120	0.000
	Systolic blood pressure	0.001	0.000	0.089	2.566	0.010
	Glucose	0.020	0.008	0.082	2.377	0.018
ApoA1/ApoB	Gender	0.186	0.035	0.239	5.258	0.000
	Age	0.007	0.001	0.211	5.641	0.000
	Height	0.009	0.002	0.181	4.267	0.000
	Waist circumference	-0.013	0.001	-0.305	-9.293	0.000
	Alcohol consumption	0.089	0.018	0.196	5.007	0.000
	Pulse pressure	-0.004	0.001	-0.143	-4.021	0.000
	Glucose	-0.047	0.013	-0.121	-3.591	0.000

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoA1/ApoB, the ratio of apolipoprotein A1 to apolipoprotein B; B, unstandardized coefficient; Beta, standardized coefficient.

Table 5. Risk factors for serum lipid-related phenotypes in gender subgroups between two Chinese ethnic groups

Lipid-associated phenotype	Risk factor	B	Std. error	Beta	t	P
Jing/Male						
TC	Age	0.012	0.004	0.182	3.456	0.001
	Body mass index	0.107	0.024	0.412	4.528	0.000
	Waist circumference	-0.020	0.008	-0.216	-2.328	0.020

	Cigarette smoking	0.105	0.051	0.108	2.063	0.040
	Alcohol consumption	0.173	0.052	0.163	3.304	0.001
	Pulse pressure	-0.012	0.003	-0.027	-4.078	0.000
	Glucose	0.130	0.027	0.234	4.884	0.000
TG	Genotype	0.463	0.066	0.309	6.992	0.000
	Age	-0.010	0.003	-0.145	-3.058	0.002
	Weight	-0.018	0.009	-0.185	-1.966	0.050
	Waist circumference	0.043	0.009	0.454	4.700	0.000
	Cigarette smoking	0.131	0.050	0.128	2.641	0.009
	Diastolic blood pressure	0.011	0.004	0.126	2.750	0.006
	Glucose	0.071	0.026	0.121	2.740	0.006
HDL-C	Height	-0.011	0.004	-0.125	-2.450	0.015
	Systolic blood pressure	0.006	0.001	0.209	4.078	0.000
LDL-C	Age	-0.005	0.002	-0.153	-2.857	0.005
	Cigarette smoking	-0.059	0.025	-0.126	-2.332	0.020
	Diastolic blood pressure	-0.004	0.002	-0.114	-2.238	0.026
ApoA1	Weight	-0.009	0.003	-0.360	-3.600	0.000
	Body mass index	0.017	0.007	0.233	2.331	0.020
	Alcohol consumption	0.041	0.015	0.136	2.707	0.007
ApoB	Genotype	-0.056	0.020	-0.128	-2.724	0.007
	Waist circumference	0.010	0.001	0.368	7.770	0.000
	Alcohol consumption	-0.031	0.015	-0.097	-2.048	0.041
ApoA1/ApoB	Waist circumference	-0.017	0.002	-0.374	-7.890	0.000
	Alcohol consumption	0.067	0.024	0.130	2.745	0.006
Jing/Female						
TC	Age	0.025	0.005	0.227	4.979	0.000
	Cigarette smoking	-0.333	0.086	-0.173	-3.857	0.000
	Glucose	0.308	0.041	0.341	7.511	0.000
TG	Genotype	0.440	0.061	0.323	7.241	0.000
	Age	0.008	0.004	0.088	1.916	0.056
	Weight	-0.029	0.010	-0.298	-3.020	0.003
	Body Mass Index	0.094	0.025	0.353	3.731	0.000
	Waist circumference	0.021	0.008	0.211	2.630	0.009
	Cigarette smoking	0.314	0.090	0.202	3.509	0.001
	Alcohol consumption	-0.324	0.095	-0.188	-3.414	0.001
LDL-C	Age	0.007	0.002	0.160	3.252	0.001
	Waist circumference	-0.008	0.002	-0.166	-3.392	0.001
ApoA1	Genotype	-0.046	0.018	-0.130	-2.619	0.009
	Waist circumference	-0.003	0.001	-0.127	-2.586	0.010
	Alcohol consumption	0.058	0.022	0.128	2.589	0.010
ApoB	Age	0.006	0.001	0.206	4.195	0.000
	Body Mass Index	0.019	0.004	0.223	4.630	0.000
	Glucose	0.023	0.011	0.099	2.035	0.043
ApoA1/ApoB	Age	-0.008	0.002	-0.185	-3.780	0.000
	Body Mass Index	-0.028	0.006	-0.228	-4.744	0.000
	Glucose	-0.046	0.016	-0.136	-2.805	0.005
Han/Male						
TC	Waist circumference	0.020	0.005	0.196	4.246	0.000
	Systolic blood pressure	0.008	0.002	0.186	3.893	0.000
	Glucose	0.130	0.034	0.180	3.823	0.000

TG	Genotype	0.254	0.056	0.197	4.525	0.000
	Age	-0.013	0.003	-0.235	-4.750	0.000
	Body Mass Index	-0.055	0.020	-0.211	-2.762	0.006
	Waist circumference	0.037	0.007	0.400	5.212	0.000
	Systolic blood pressure	0.008	0.002	0.192	4.109	0.000
	Cigarette smoking	0.121	0.035	0.161	3.489	0.001
LDL-C	Body Mass Index	-0.014	0.007	-0.102	-2.090	0.037
	Pulse pressure	0.003	0.001	0.114	2.334	0.020
ApoA1	Weight	-0.005	0.001	-0.194	-4.328	0.000
	Cigarette smoking	-0.029	0.010	-0.133	-2.814	0.005
	Alcohol consumption	0.091	0.010	0.415	8.716	0.000
ApoB	Age	-0.004	0.001	-0.209	-4.300	0.000
	Waist circumference	0.010	0.001	0.299	6.642	0.000
	Systolic blood pressure	0.003	0.001	0.224	4.623	0.000
	Glucose	0.028	0.011	0.123	2.621	0.009
ApoA1/ApoB	Age	0.010	0.002	0.312	6.584	0.000
	Waist circumference	-0.017	0.002	-0.309	-7.067	0.000
	Alcohol consumption	0.112	0.020	0.243	5.551	0.000
	Systolic blood pressure	-0.006	0.001	-0.236	-5.009	0.000
	Glucose	-0.047	0.018	-0.118	-2.591	0.010
Han/Female						
TC	Weight	-0.031	0.009	-0.345	-3.626	0.000
	Waist circumference	0.023	0.008	0.271	2.847	0.005
	Glucose	0.306	0.041	0.345	7.523	0.000
TG	Genotype	0.296	0.060	0.218	4.947	0.000
	Height	-0.015	0.005	-0.135	-3.049	0.002
	Waist circumference	0.025	0.003	0.330	7.319	0.000
	Glucose	0.115	0.034	0.147	3.345	0.001
LDL-C	Age	0.011	0.002	0.249	5.250	0.000
ApoA1	Body Mass Index	-0.012	0.003	-0.215	-4.544	0.000
	Alcohol consumption	0.084	0.027	0.147	3.106	0.002
ApoB	Height	-0.012	0.002	-0.328	-6.124	0.000
	Body Mass Index	-0.020	0.007	-0.310	-3.078	0.002
	Waist circumference	0.012	0.002	0.507	4.966	0.000
	Glucose	0.025	0.012	0.102	2.177	0.030
ApoA1/ApoB	Height	0.097	0.016	1.874	5.928	0.000
	Weight	-0.120	0.024	-3.247	-5.092	0.000
	Body Mass Index	0.275	0.054	2.837	5.103	0.000
	Waist circumference	-0.007	0.004	-0.212	-2.073	0.039
	Cigarette smoking	-0.213	0.089	-0.147	-2.402	0.017
	Alcohol consumption	0.192	0.063	0.190	3.055	0.002
	Glucose	-0.059	0.016	-0.161	-3.660	0.000

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoA1/ApoB, the ratio of apolipoprotein A1 to apolipoprotein B; B, unstandardized coefficient; Beta, standardized coefficient.

TG and LDL-C in Han males; and TG and ApoA1 in Han females were different among the genotypes. These findings suggest that the association of the *PLA2G6* rs2760114 mutation and serum lipid phenotypes might have an ethnic-specificity. But it can't deny the sex-specific association of the *PLA2G6* rs2760114 mutation and serum lipid phenotypes. Because sev-

eral environmental factors such as age, gender, weight, waist circumference, alcohol consumption, and cigarette smoking and traditional cardiovascular risk factors such as BMI, fasting blood glucose and blood pressure levels were also correlated with serum lipid parameters in males and females of the two populations according our present results.

PLA2G6 is modulated by n-3 PUFA supplementation, since it was differentially expressed in peripheral blood mononuclear cells (PBMCs) after supplementation [17]. PLA2G6 was shown to be influenced by n-3 PUFA supplementation since its gene product is a secreted enzyme whose activity is associated with CAD biomarkers. In a previous study [18], five SNPs (rs5750546, rs132989, rs133016, rs2235346 and rs2284060) of the *PLA2G6* influenced TG levels independently of the supplementation. In addition, genotypes × n-3 PUFA supplementation interaction was observed for the five SNPs as previously mentioned [19, 20]. These SNPs and the interaction considerably contributed to explain inter-individual variability in plasma TG levels after n-3 PUFA supplementation.

A previous study reported that genotype-phenotype association of the rs132984 was associated with TG levels (P = 0.022, empirical P = 0.044) [21]. Another study demonstrated that fatty acid metabolism-related *PLA2G6* SNPs (rs4821737, rs2076370 and rs4821767) as contributing factors play a crucial role of biological processes of metabolism-related disease [22].

Little is known about the association of the *PLA2G6* rs2760114 mutation and serum lipid phenotypes in the south Chinese population. Our data showed that it might be due to the differences in genetic backgrounds, dietary habits, and environmental factors between the two ethnic populations and/or simply due to the low power of this study. It is well accepted that ethnic differences in serum lipid levels were partly due to the differences in the dietary intakes [23]. Diet alone could account for up to 2.5% of the variability on serum lipid levels [24-28]. Therefore, it is possible that the difference in dietary habit between Jing and Han ethnic groups partly contribute variability in the effect of *PLA2G6* rs2760114 mutation on serum lipid phenotypes.

To the best of our knowledge, this study is the first report about the sex-specific association of the *PLA2G6* rs2760114 mutation and serum lipid phenotypes. Therefore, further studies with larger sample size are still needed to confirm this association. In addition, several environmental factors were also correlated with serum lipid levels in males and females of both Jing and Han populations. In the current study, the general characteristics and the values of serum lipid phenotypes in the Jing and Han populations had significantly different between males and females. For every 1-kg decrease in body weight, TG decreased by 0.011 mmol/L and HDL-C increased by 0.011 mmol/L [29]. In this study, the percentages of subjects who smoked cigarettes and consumed alcohol were significantly higher in males than in females. Rimm *et al*. documented that consuming of 30 g of ethanol per day increased the concentrations of HDL-C by 3.99 mg/dl, ApoA1 by 8.82 mg/dl, and TG by 5.69 mg/dl [30]. Therefore, the results of exposure to different environmental factors may further modify the effect of genetic variation on serum lipid levels in our study populations.

There are some potential limitations in our study. First, it is undeniable that this study has insufficient power to produce a robust conclusion; therefore, such a small-scale study needs to replicate in independent cohorts. Second, the cross-sectional study design limits the ability to determine any causality of the relationships observed. Third, the impact of diet, such as including TFA, SFA, PUFA (including n-3 PUFA and n-6 PUFA) and MUFA was not evaluated in this study. It is possible that part of the relationship observed in this study may be partly influenced by the effect of dietary intake.

Conclusion

The genotype and allele frequencies were significantly different between Jing and Han populations. The subjects with TT genotype in Jing (higher TG and ApoB, lower HDL-C and ApoA1), Han (higher TG, lower the ratio of ApoA1 to ApoB), Jing males (higher TG and ApoB), Jing females (higher TG, lower ApoA1), Han males (higher TC, TG and LDL-C), and Han females (higher TG, lower ApoA1) have different serum lipid levels compared with other genotypes. These findings suggest that the association

between the *PLA2G6* rs2760114 and serum lipid phenotypes might have an ethnic- and/or sex-specificity.

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Disclosure of conflict of interest

None.

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