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Original Article

Association of the *CMIP* rs2925979 polymorphism and several environmental factors with serum lipid levels in the Chinese Jing and Han populations

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Abstract: The c-Maf inducing protein gene (*CMIP*) rs2925979 single nucleotide polymorphism (SNP) has been associated with serum high-density lipoprotein cholesterol (HDL-C) levels in the individuals of European ancestry in a previous genome-wide association study, but the reproducibility of this association has not been detected in the other populations. The aim of the present study was to explore the association of the *CMIP* rs2925979 SNP and several environmental factors with serum lipid levels in the Chinese Jing and Han populations. Genotyping of the *CMIP* rs2925979 SNP in 552 unrelated subjects of Jing ethnic group and 632 participants of Han nationality was performed by polymerase chain reaction and restriction fragment length polymorphism, and then confirmed by direct sequencing. Serum total cholesterol (TC) and triglyceride levels were higher in Jing than in Han ($P < 0.01$ for each). The genotypic and allelic frequencies of the SNP were not different between the Jing and Han populations, but the genotypic frequencies of the SNP in Han but not in Jing were different between males and females (18.9%, 52.8% and 28.3% *vs*. 18.5%, 43.4% and 38.0%; respectively, $P = 0.028$). Serum HDL-C levels in the Jing population were different among the genotypes ($P = 0.048$), the G allele carriers had higher HDL-C levels than the G allele non-carriers. Serum TC levels in the Han population were different among the genotypes ($P = 0.007$), the G allele carriers had lower TC levels than the G allele non-carriers, subgroup analyses showed that this finding was restricted to Han females but not Han males. Multivariate linear regression analyses revealed that serum HDL-C and apolipoprotein (Apo) B levels in the combined population of Jing and Han, and serum HDL-C levels and the ApoA1/ApoB ratio in Jing were correlated with genotypes ($P < 0.05$ for all). Serum lipid phenotypes were also correlated with several environmental factors in the Jing and Han populations, or in males and females of the both ethnic groups ($P < 0.05$-0.001). These findings suggest that there may be an ethnic- and/or sex-specific association of the *CMIP* rs2925979 SNP and serum lipid levels in our study populations.

Keywords: Lipids, sex-specific association, c-Maf inducing protein (*CMIP*), single nucleotide polymorphism, environmental factors

Introduction

Dyslipidemia is one of the most important and modifiable risk factors for cardiovascular disease (CVD) in both developed and developing countries [1-3]. A recent cross-sectional study in the general population aged > 18 years in China showed that the overall prevalence of dyslipidemia was 34.0% (35.1% in urban and 26.3% in rural areas). The prevalence of dyslipidemia was significantly higher in males than in females (41.9% *vs*. 32.5%; $P < 0.001$) [4]. Dyslipidemia is believed to be caused by various environmental [5-7] and genetic [8-10] factors, and their interactions [11-13]. Data from family-based and twin studies have revealed that genetic polymorphism could account for 43-83% of the interindividual variation in plasma lipid phenotypes [14-16].

A number of single nucleotide polymorphisms (SNPs) associated with serum lipid levels have been identified in the previous genome-wide association studies (GWASes) in different populations [17-22]. Some loci contribute not only to normal variation in lipid traits but also to

extreme lipid phenotypes and impact lipid traits in three non-European populations (East Asians, South Asians, and African Americans) [22]. These GWASes have also discovered a large number of novel loci that impact serum lipid phenotypes [17, 18, 21, 22]. One of these newly identified SNPs is the rs2925979 SNP within the c-Maf inducing protein gene (*CMIP*). This gene encodes a c-Maf inducing protein that plays a role in T-cell signaling pathway. Alternatively spliced transcript variants encoding different isoforms have been described for this gene [23, 24]. The rs2925979 is an A > G single-nucleotide variation on human chromosome 16q23.2. It has been associated with serum adiponectin levels [25, 26]. Adiponectin is an adipocyte-secreted protein and blood adiponectin levels are positively associated with high-density lipoprotein cholesterol (HDL-C) concentration and negatively correlated with the risk of type 2 diabetes, glucose, insulin, insulin resistance, triglyceride (TG) and anthropometric measures of obesity [27-30]. In addition, the *CMIP* rs2925979 SNP in a previous GWAS has been associated with serum HDL-C levels in the individuals of European ancestry [22, 31]. But the reproducibility of this association has not been detected in the other populations.

There are 56 ethnic groups in China. Han nationality is the largest ethnic group and Jing nationality is one of the smallest minorities with population of 28199 in 2010 [32]. Most of them live in the three islands of Wanwei, Wutou and Shanxin, Dongxing City, Guangxi Zhuang Autonomous Region, People's Republic of China. About 1511, the ancestors of the Jing nationality emigrated from Vietnam to China and first settled on the three above-mentioned lands. Jing is the only minority for coastal fisheries in China. The customs, diet structure, lifestyle and genetic background are different between the Jing and local Han populations. Our previous studies showed that the serum lipid profiles, the prevalence of hyperlipidemia, and several lipid-related SNPs were different between the two ethnic groups [33-36]. We hypothesized that there may be significant differences in some lipid-related SNPs and environmental factors between the two ethnic groups. Therefore, the aim of the present study was to detect the association of the *CMIP* rs2925979 SNP and several environmental factors with serum lipid profiles in the Chinese Jing and Han populations.

Materials and methods

Study population

The present study randomly selected 552 unrelated subjects of Jing nationality and 632 participants of Han nationality from our previous stratified randomized samples [33-36]. All of the participants were rural fishery (Jing) and/or agricultural (Han) workers from Jiangping Down, Dongxing City, Guangxi Zhuang Autonomous Region, People's Republic of China. The Jing subjects included 226 (40.9%) males and 326 (59.1%) females, and age ranged from 30 to 88 years, with a mean age of 57.25± 13.34 years. The Han participants were composed of 269 (42.6%) males and 363 (57.4%) females, and age ranged from 27 to 92 years, with a mean age of 57.96±13.07 years. All study subjects were essentially healthy and had never been diagnosed with CVD such as coronary heart disease, stroke, hyper- or hypothyroids, chronic renal disease, and diabetes. They did not take drugs known to affect serum lipid levels (such as statins or fibrates, beta-blockers, diuretics, or hormones). The investigations were carried out following the rules of the Declaration of Helsinki of 1975 (http://www.wma.net/en/30publications/10policies/b3/), revised in 2008. The study design was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University (No: Lunshen-2011-KY-Guoji-001; Mar. 7, 2011). Informed consent was obtained from all participants.

Epidemiological survey

The epidemiological survey was performed using internationally standardized methods [32, 33]. The data of demography, socioeconomic status, and lifestyle factors were collected with standardized questionnaires. The information of alcohol intake included questions about the number of liangs (~50 g) of rice wine, corn wine, rum, beer or liquor consumed during the preceding 12 months. Alcohol consumption was categorized into groups of grams of alcohol per day: ≤ 25 and > 25. Smoking status was categorized into groups of cigarettes per day: ≤ 20 and > 20. General physical examination was performed, and several parameters

Table 1. Epidemiological characteristics and serum lipid levels between the Jing and Han populations

Parameter	Jing	Han	t (χ^2)	P
Number	552	632		
Male/female	226/326	269/363	0.318	0.573
Age (year)	57.25±13.34	57.96±13.07	0.925	0.355
Height (cm)	157.06±7.77	156.48±8.05	-1.258	0.209
Weight (kg)	57.77±10.11	55.88±9.60	-3.271	0.001
Body mass index (kg/m^2)	23.35±3.29	22.82±3.42	-2.681	0.007
Waist circumference (cm)	79.83±9.16	77.49±8.97	-4.411	0.000
Cigarette smoking [n (%)]				
Non-smoker	474 (85.9)	527 (83.4)		
≤ 20 cigarettes/day	59 (10.7)	79 (12.5)	1.395	0.498
> 20 cigarettes/day	19 (3.4)	26 (4.1)		
Alcohol consumption [n (%)]				
Non-drinker	486 (88.0)	523 (82.8)		
≤ 25 g/day	52 (9.4)	74 (11.7)	8.833	0.012
> 25 g/day	14 (2.6)	35 (5.5)		
Systolic blood pressure (mmHg)	131.48±21.30	133.99±44.34	1.209	0.227
Diastolic blood pressure (mmHg)	80.21±10.26	81.16±10.26	1.589	0.112
Pulse pressure (mmHg)	51.28±17.08	52.83±42.65	0.800	0.424
Glucose (mmol/L)	6.65±1.52	6.64±1.07	-0.095	0.925
Total cholesterol (mmol/L)	5.13±0.93	4.93±0.87	-3.909	0.000
Triglyceride (mmol/L)	1.42 (0.64)	1.32 (0.63)	-3.188	0.001
HDL-C (mmol/L)	1.79±0.45	1.79±0.50	-0.224	0.823
LDL-C (mmol/L)	2.82±0.45	2.87±0.44	1.735	0.083
Apolipoprotein (Apo) A1 (g/L)	1.31±0.23	1.32±0.20	0.997	0.319
ApoB (g/L)	1.06±0.25	1.04±0.25	-1.026	0.305
ApoA1/ApoB	1.30±0.38	1.33±0.37	1.491	0.136

HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol. The value of triglyceride was presented as median (interquartile range), the difference between the two ethnic groups was determined by the Wilcoxon-Mann-Whitney test.

such as height, weight, and waist circumference were measured. Sitting blood pressure was measured three times with the use of a mercury sphygmomanometer after the subject for a 5-minute of rest and the average of the three measurements was recorded. Systolic blood pressure was determined by the first Korotkoff sound, and diastolic blood pressure by the fifth Korotkoff sound. Body weight, to the nearest 50 grams, was measured by using a portable balance scale. Subjects were weighed in a minimum of clothing and without shoes. Height was measured, to the nearest 0.5 cm, using a stadiometer. Body mass index (BMI, kg/m^2) was calculated from the height and weight measurements [32, 33].

Biochemical measurements

A venous blood sample of 5 mL was drawn from an antecubital vein in all participants after an overnight fast. A part of the sample (2 mL) was collected into glass tubes and used to measure serum lipid and apolipoprotein (Apo) levels, another part (3 mL) was stored in the tubes contained anticoagulants (4.80 g/L citric acid, 14.70 g/L glucose, and 13.20 g/L tri-sodium citrate) and used to extract deoxyribonucleic acid (DNA). The levels of serum total cholesterol (TC), TG, HDL-C, and low-density lipoprotein cholesterol (LDL-C) in the samples were measured using enzymatic methods with commercially available kits (RANDOX Laboratories Ltd., Ardmore, Diamond Road, Crumlin Co. Antrim, United Kingdom, BT29 4QY; Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan). Serum ApoA1 and ApoB levels were determined by the immunoturbidimetric immunoassay using a commercial kit (RANDOX Laboratories Ltd.). All determinations were performed with an autoanalyzer (Type 7170A; Hitachi Ltd., Tokyo, Japan) in

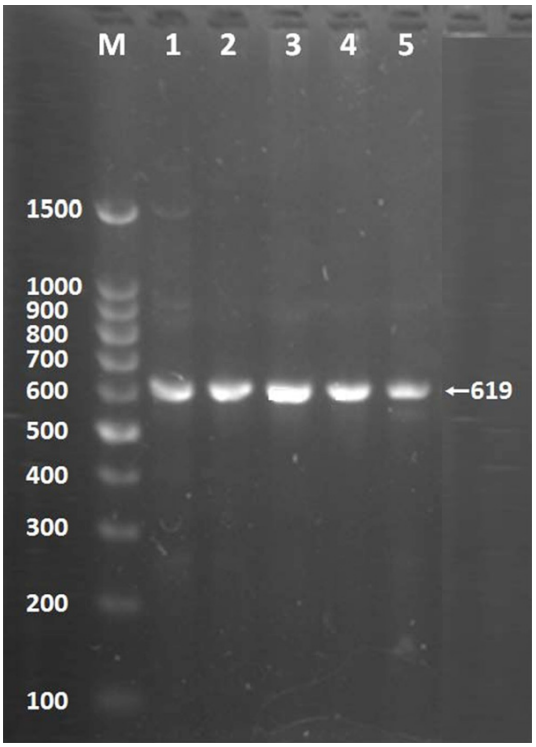

Figure 1. Electrophoresis of the PCR products of the *CMIP* rs2925979 polymorphism. Lane M, 100 bp marker ladder; lanes 1-5, the samples. The 619 bp bands are the PCR products.

the Clinical Science Experiment Center of the First Affiliated Hospital, Guangxi Medical University. Fasting blood glucose was determined using a glucose meter (Accu-Chek; F. Hoffman-La Roche AG, Basel, Switzerland) at the epidemiological investigation site [32, 33].

DNA amplification and genotyping

Genomic DNA was isolated from peripheral blood leukocytes using the phenol-chloroform method [34-36]. The extracted DNA was stored at -20°C until analysis. Genotypes of the *CMIP* rs2925979 SNP was determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism (PCR-RFLP). PCR amplification was performed using 5'-CAAGGAGCCCGATACAATGC-3' as the forward and 5'-CTCTGTCCTTCCCTTCCTCC-3' (Sangon, Shanghai, People's Republic of China) as reversed primer pair. Each amplification reaction was performed in a total volume of 20 μL, containing 1.0 μl of genomic DNA, 1.0 μl of each primer (10 pmol/l), 10.0 μl 2 × *Taq* PCR Mastermix (including 20 mM Tris-HCl, pH 8.3, 100 mM KCl, 3 mM $MgCl_2$, 0.1 U *Taq* polymerase/μl, 500 μM dNTP each) and 7.0 μl double-distilled H_2O (DNase/RNase-free). The processing started with pre-denaturing at 94°C for 5 min and followed by denaturing at 94°C for 45 s, annealing at 55°C for 30 s and 45s of extension at 72°C for 33 cycles. The amplification was completed by a final extension at 72°C for 10 min. After electrophoresis on a 2.0% agarose gel with 0.5 μg/ml ethidium bromide, the amplified products were visualized under ultraviolet light. Then each restriction enzyme reaction was performed with 5.0 μl of amplified DNA; 9.0 μl of nuclease-free water and 1.0 μl of 10 × buffer solution; and 1.0 μl of *Apa*I restriction enzyme in a total volume of 15 μl digested at 30°C overnight. After restriction enzyme digestion of the amplified DNA, the digestive products were separated by electrophoresis on 2% agrose gel. The length of each digested DNA fragment was determined by comparing migration of a sample with that of standard DNA marker. Genotypes were scored by an experienced reader blinded to the epidemiological and serum lipid results. Six samples (AA, AG and GG genotypes in two; respectively) detected by the PCR-RFLP were also confirmed 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.

Diagnostic criteria

The normal values of serum TC, TG, HDL-C, LDL-C, ApoA1 and ApoB levels, and the ApoA1/ApoB ratio 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 [33]. The individuals with TC > 5.17 mmol/L and/or TG > 1.70 mmol/L were defined as hyperlipidemic [33]. Hypertension was diagnosed according to the criteria of 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension [32]. The diagnosis of type 2 diabetes was according to the World Health Organization diagnostic criteria: (1) Fasting glucose ≥ 7.0 mmol/L; (2) 2 h postprandial glucose ≥ 11.1 mmol/L; or (3) self-reported history of a physi-

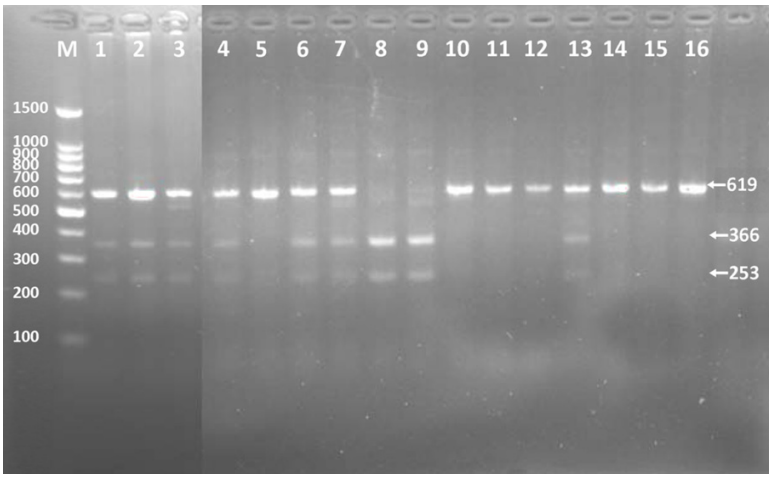

Figure 2. Genotyping of the *CMIP* rs2925979 SNP. Lane M, 100 bp Marker Ladder; lanes 1-4, 6, 7 and 13, AG genotype (253-, 366- and 619-bp); lanes 5, 10-12 and 14-16, AA genotype (619 bp); and lanes 8 and 9, GG genotype (253- and 366-bp).

cian diagnosis of diabetes or use of anti-diabetic drugs [37, 38]. The criteria of overweight and obesity were judged according to the Cooperative Meta-analysis Group of China Obesity Task Force. Normal weight, overweight and obesity were defined as a BMI < 24, 24-28, and > 28 kg/m^2; respectively [39, 40].

Statistical analyses

The quantitative variables were presented as mean ± standard deviation (serum TG levels were presented as medians and interquartile ranges). The epidemiological characteristics between the Jing and Han populations were compared by Student's unpaired *t*-test. Analysis of covariance (ANCOVA) was used to test the association among the genotypes and serum lipid parameters. Sex, age, BMI, blood pressure, blood glucose, alcohol consumption, and cigarette smoking were adjusted for the statistical analysis. Qualitative variables were expressed as percentages. Allele frequency was calculated by direct counting, and the standard goodness-of-fit test was used to test the Hardy-Weinberg equilibrium. The genotype distribution between the two groups was determined by the chi-square test. Multivariate linear regression analysis was performed to determine the association of the *CMIP* rs2925979 genotypes (AA = 1, AG = 2 and GG = 3) and several environment factors with serum lipid levels in the combined population of Jing and Han, Jing, Han, males and females; respectively. Two sided *P* value < 0.05 was considered statistically significant. All of the statistical analyses were done with the statistical software package SPSS17.0 (SPSS Inc., Chicago, Illinois).

Results

Epidemiological characteristics and serum lipid profiles

The epidemiological characteristics and serum lipid profiles of the subjects are summarized in **Table 1**. The mean values of weight, BMI, waist circumference, serum TC and TG were significantly higher in Jing than in Han, whereas the percentages of alcohol consumption were lower in Jing than in Han (*P* < 0.05-0.001). There were no significant differences in the sex ratio, age structure, body height, blood pressure, blood glucose, serum HDL-C, LDL-C, ApoA1 and ApoB levels, the ratio of ApoA1 to ApoB, and the percentage of cigarette smoking between the two ethnic groups (*P* > 0.05 for all). In addition, there were also significant differences in the dietary patterns between the two ethnic groups. Fish and shrimp are the daily dishes of the Jing people. The Jing people especially women are accustomed to chew betel nut (Areca catechu L.). In contrast, the intake of animal (pig) fat was more in Han than in Jing nationalities. The Han people also like to eat animal offals which contain abundant saturated fatty acid.

PCR products and genotypes

The PCR products and genotypes of the *CMIP* rs2925979 SNP are shown in **Figures 1** and **2**. After the genomic DNA of the samples was amplified by PCR and imaged by 2.0% agarose gel electrophoresis. The products of 619 bp nucleotide sequences could be seen in the samples (**Figure 1**). The genotypes identified were labeled according to the presence (G allele) or absence (A allele) of the enzyme restriction sites. Thus, the AA genotype was homozygous for the absence of the site (band

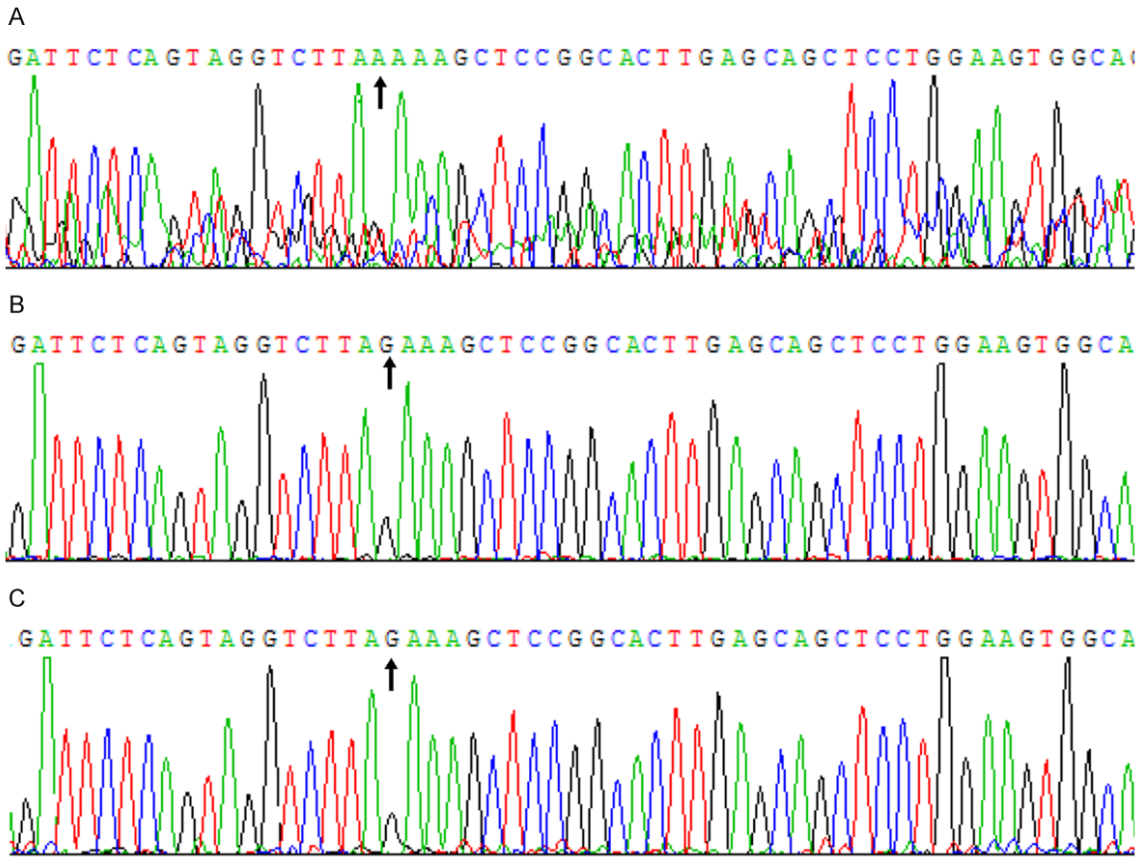

Figure 3. A part of the nucleotide sequences of the *CMIP* rs2925979 SNP by direct sequencing. A, AA genotype; B, AG genotype; and C, GG genotype.

at 619 bp), the AG genotype was heterozygous for the absence and presence of the site (bands at 253-, 366- and 619-bp) and the GG genotype was homozygous for the presence of the site (bands at 253- and 366-bp; **Figure 2**).

Sequence analysis

The nucleotide sequences of the *CMIP* rs2925979 AA, AG and GG genotypes identified by PCR-RFLP were also confirmed by direct sequencing (**Figure 3**).

Genotypic distribution

The genotypic and allelic frequencies of the *CMIP* rs2925979 SNP are summarized in **Table 2**. The frequencies of A and G alleles were 43.4% and 56.6% in Jing; and 42.4% and 57.6% in Han ($P > 0.05$); respectively. The frequencies of AA, AG and GG genotypes were 18.8%, 49.1% and 32.1% in Jing, and 18.7%, 47.4% and 33.9% in Han ($P > 0.05$); respectively. The genotypic distribution of the *CMIP* rs2925979 SNP was followed by the Hardy-Weinberg equilibrium. The AA, AG and GG genotypic frequencies of the SNP in Han but not in Jing were different between males and females (18.9%, 52.8% and 28.3% *vs.* 18.5%, 43.4% and 38.0%; respectively, $P = 0.028$). There was no significant difference in the allelic frequencies between males and females in the both ethnic groups ($P > 0.05$ for each).

Genotypes and serum lipid levels

The associations of the *CMIP* rs2925979 genotypes and serum lipid levels are described in **Tables 3** and **4**. Serum HDL-C levels in the Jing population were different among the genotypes ($P = 0.048$), the G allele carriers had higher HDL-C levels than the G allele non-carriers. Serum TC levels in the Han population were different among the genotypes ($P = 0.007$), the G allele carriers had lower TC levels than the G allele non-carriers. Subgroup analyses accord-

Table 2. Genotype and allele frequencies of the *CMIP* rs2925979 SNP between the Han and Jing populations [n (%)]

Group	N	Genotype			Allele		P_{HWE}
		AA	AG	GG	A	G	
Jing	552	104 (18.8)	271 (49.1)	177 (32.1)	479 (43.4)	625 (56.6)	0.988
Han	632	118 (18.7)	300 (47.4)	214 (33.9)	536 (42.4)	728 (57.6)	0.478
x^2		0.454			0.232		
P		0.797			0.630		
Jing							
Male	226	45 (19.9)	107 (47.4)	74 (32.7)	187 (43.6)	255 (56.4)	0.576
Female	326	59 (18.1)	164 (50.3)	103 (31.6)	282 (43.3)	370 (56.7)	0.654
x^2		0.526			0.012		
P		0.769			0.913		
Han							
Male	269	51 (18.9)	142 (52.8)	76 (28.3)	244 (45.4)	294 (54.6)	0.287
Female	363	67 (18.5)	158 (43.5)	138 (38.0)	292 (40.2)	434 (59.8)	0.071
x^2		7.163			3.333		
P		0.028			0.068		

P_{HWE}, *P* value of the Hardy-Weinberg equilibrium (HWE).

Table 3. Genotypes of the *CMIP* rs2925979 SNP and serum lipid levels in the Jing and Han populations

Ethnic/ Genotype	N	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoA1 (g/L)	ApoB (g/L)	ApoA1/ ApoB
Jing								
AA	104	5.13±0.90	1.43 (0.61)	1.74±0.43	2.84±0.48	1.30±0.21	1.09±0.24	1.25±0.32
AG	271	5.13±0.93	1.41 (0.78)	1.84±0.45	2.80±0.44	1.31±0.25	1.04±0.25	1.33±0.40
GG	177	5.19±0.99	1.44 (0.83)	1.78±0.48	2.85±0.43	1.30±0.21	1.05±0.24	1.30±0.40
F	-	0.450	0.222	3.057	0.709	0.313	1.451	2.189
P	-	0.638	0.895	0.048	0.493	0.732	0.235	0.113
Han								
AA	118	5.09±0.83	1.38 (0.78)	1.77±0.51	2.92±0.42	1.34±0.21	1.07±0.29	1.34±0.42
AG	300	4.95±0.89	1.31 (0.67)	1.83±0.47	2.87±0.45	1.33±0.19	1.04±0.23	1.34±0.36
GG	214	4.74±0.81	1.31 (0.57)	1.74±0.51	2.81±0.42	1.30±0.19	1.05±0.25	1.30±0.37
F	-	5.035	1.472	0.982	1.900	0.768	0.824	0.546
P	-	0.007	0.479	0.375	0.150	0.465	0.439	0.579

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. The value of TG was presented as median (interquartile range). The difference between the genotypes was determined by the Kruskal-Wallis test.

ing to sex showed that serum TC levels in Han females were different among the genotypes ($P = 0.032$), the G allele carriers had lower TC levels than the G allele non-carriers.

Risk factors for serum lipid parameters

The risk factors for serum lipid parameters are shown in **Tables 5** and **6**. Multiple linear regression analysis showed that serum HDL-C and ApoB levels in the combined population of Jing and Han, and serum HDL-C levels and the ApoA1/ApoB ratio in Jing were correlated with genotypes ($P < 0.05$ for all). We also showed that serum lipid phenotypes were correlated with several environmental factors such as sex, age, height, weight, BMI, cigarette smoking, alcohol consumption, blood glucose, and

Table 4. *CMIP* rs2925979 genotypes and serum lipid levels in males and females of both ethnic groups

Sex/ Genotype	N	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoA1 (g/L)	ApoB (g/L)	ApoA1/ ApoB
Jing/Male								
AA	45	4.93±0.72	1.44 (0.69)	1.69±0.42	2.78±0.35	1.31±0.23	1.08±0.20	1.25±0.30
AG	107	5.17±0.85	1.50 (1.11)	1.80±0.50	2.80±0.37	1.27±0.22	1.04±0.23	1.30±0.42
GG	74	5.13±0.86	1.44 (0.90)	1.67±0.42	2.86±0.40	1.27±0.20	1.09±0.28	1.29±0.54
F	-	1.839	3.086	1.348	1.053	0.374	0.781	0.645
P	-	0.162	0.214	0.262	0.351	0.689	0.459	0.526
Jing/Female								
AA	59	5.28±0.98	1.43 (0.70)	1.78±0.43	2.89±0.56	1.30±0.20	1.09±0.27	1.25±0.33
AG	164	5.11±0.98	1.40 (0.62)	1.86±0.42	2.80±0.47	1.34±0.27	1.04±0.26	1.35±0.39
GG	103	5.22±1.06	1.45 (0.75)	1.84±0.51	2.84±0.46	1.31±0.22	1.03±0.22	1.31±0.28
F	-	0.643	2.838	1.372	0.702	0.979	0.941	1.893
P	-	0.526	0.242	0.255	0.496	0.377	0.391	0.152
Han/Male								
AA	51	4.92±0.74	1.28 (0.94)	1.75±0.50	2.92±0.40	1.33±0.21	1.11±0.26	1.28±0.42
AG	142	4.90±0.0.87	1.27 (0.73)	1.76±0.47	2.89±0.44	1.32±0.20	1.05±0.22	1.31±0.37
GG	76	4.68±0.89	1.33 (0.68)	1.62±0.61	2.74±0.41	1.28±0.20	1.03±0.24	1.31±0.35
F	-	1.725	0.501	0.754	2.690	0.440	2.352	1.253
P	-	0.180	0.778	0.472	0.070	0.645	0.097	0.287
Han/Female								
AA	67	5.20±0.87	1.41 (0.60)	1.80±0.52	2.92±0.44	1.35±0.21	1.05±0.30	1.38±0.41
AG	158	4.98±0.91	1.32 (0.65)	1.88±0.45	2.86±0.46	1.33±0.19	1.02±0.24	1.36±0.35
GG	138	4.80±0.72	1.28 (0.54)	1.84±0.37	2.86±0.43	1.31±0.19	1.08±0.26	1.29±0.39
F	-	3.469	2.963	0.235	0.439	1.216	0.682	1.697
P	-	0.032	0.227	0.791	0.645	0.298	0.506	0.185

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. The value of TG was presented as median (interquartile range). The difference between the genotypes was determined by the Kruskal-Wallis test.

blood pressure in the Jing and Han populations, or in males and females of the both ethnic groups ($P < 0.05$-0.001).

Discussion

The results of the present study showed that the serum lipid profiles were different between the Jing and Han populations. The levels of serum TC and TG were significantly higher in Jing than in Han. There were no significant differences in the HDL-C, LDL-C, ApoA1 and ApoB levels, and the ApoA1/ApoB ratio between the two ethnic groups. Multiple linear regression analyses also showed that serum lipid parameters were correlated with the *CMIP* rs2925979 genotypes and several environmental factors such as sex, age, height, weight, BMI, cigarette smoking, alcohol consumption, blood glucose, and blood pressure in the Jing and Han populations, or in males and females of the both ethnic groups ($P < 0.05$-0.001). These differences in serum lipid profiles between the two ethnic groups may result from the combined effects of different dietary habits, life style and genetic background.

Although Jing and Han reside in the same region, there was significant difference in their customs, dietary habits, life style and genetic background [32-36]. Jing ethnic group is the only minority for coastal fisheries in China. The Jing people live in a subtropical area with plenty of rainfall and rich mineral resources. The Beibu Gulf to its south is an ideal fishing ground. There were more than 700 species of fish, over 200 are of great economic value and high yields. Pearls, sea horses and sea otters which

Table 5. The risk factors for serum lipid parameters in the Jing and Han populations

Lipid parameter	Risk factor	B	Std.error	Beta	*t*	*P*
Jing and Han						
TC	Glucose	0.152	0.020	0.219	7.603	0.000
	Age	0.008	0.002	0.114	3.851	0.000
	Ethnic group	0.217	0.052	0.120	4.202	0.000
	Height	-0.010	0.003	-0.084	-2.845	0.005
TG	Waist circumference	0.028	0.003	0.308	10.774	0.000
	Glucose	0.110	0.018	0.169	6.139	0.000
	Cigarette smoking	0.377	0.052	0.215	7.260	0.000
	Height	-0.014	0.003	-0.133	-4.358	0.000
HDL-C	Waist circumference	-0.013	0.001	-0.262	-9.171	0.000
	Gender	0.118	0.032	0.123	3.667	0.000
	Alcohol consumption	0.162	0.032	0.166	5.027	0.000
	Genotype	-0.039	0.016	-0.069	-2.419	0.016
	Cigarette smoking	-0.076	0.033	-0.078	-2.312	0.021
LDL-C	Glucose	0.046	0.010	0.135	4.558	0.000
	Age	0.003	0.001	0.087	2.835	0.005
	Diastolic blood pressure	0.004	0.001	0.086	2.925	0.004
	Height	-0.003	0.002	-0.061	-2.038	0.042
ApoA1	Weight	-0.005	0.001	-0.212	-7.183	0.000
	Alcohol consumption	0.069	0.013	0.154	5.232	0.000
	Glucose	-0.012	0.005	-0.072	-2.486	0.013
ApoB	Body mass index	0.013	0.002	0.168	5.641	0.000
	Age	0.003	0.001	0.140	4.780	0.000
	Genotype	0.020	0.009	0.066	2.282	0.023
	Diastolic blood pressure	0.002	0.001	0.066	2.208	0.027
ApoA1/ApoB	Body mass index	-0.017	0.006	-0.148	-2.866	0.004
	Age	-0.003	0.001	-0.103	-3.569	0.000
	Alcohol consumption	0.091	0.025	0.116	3.629	0.000
	Gender	0.063	0.025	0.082	2.562	0.011
	Waist circumference	-0.005	0.002	-0.119	-2.284	0.023
Jing						
TC	Age	0.017	0.003	0.241	5.342	0.000
	Glucose	0.126	0.026	0.206	4.939	0.000
	Pulse pressure	-0.009	0.002	-0.160	-3.624	0.000
	Height	-0.011	0.006	-0.094	-1.892	0.059
	Body mass index	0.062	0.021	0.220	2.910	0.004
	Alcohol consumption	0.225	0.097	0.100	2.307	0.021
	Waist circumference	-0.016	0.008	-0.161	-2.033	0.043
TG	Waist circumference	0.033	0.004	0.352	8.382	0.000
	Glucose	0.111	0.023	0.196	4.914	0.000
	Cigarette smoking	0.387	0.080	0.207	4.836	0.000
	Height	-0.019	0.005	-0.171	-3.828	0.000
HDL-C	Waist circumference	-0.017	0.002	-0.345	-8.536	0.000
	Alcohol consumption	0.247	0.048	0.225	5.184	0.000
	Gender	0.127	0.040	0.137	3.165	0.002
	Genotype	-0.051	0.021	-0.099	-2.461	0.014
LDL-C	Age	0.006	0.001	0.165	3.838	0.000
	Glucose	0.032	0.013	0.109	2.532	0.012

ApoA1	Weight	-0.005	0.001	-0.230	-5.343	0.000
	Alcohol consumption	0.062	0.025	0.108	2.526	0.012
	Glucose	-0.014	0.007	-0.093	-2.185	0.029
ApoB	Age	0.004	0.001	0.198	4.661	0.000
	Body mass index	0.013	0.003	.178	4.183	0.000
ApoA1/ApoB	Body mass index	-0.028	0.005	-0.243	-5.765	0.000
	Age	-0.004	0.001	-0.140	-3.309	0.001
	Genotype	-0.039	0.018	-0.088	-2.092	0.037
Han						
TC	Glucose	0.246	0.032	0.304	7.793	0.000
TG	Waist circumference	0.037	0.006	0.399	5.840	0.000
	Cigarette smoking	0.379	0.068	0.227	5.590	0.000
	Glucose	0.107	0.030	0.138	3.569	0.000
	Weight	-0.017	0.006	-0.194	-2.785	0.006
HDL-C	Weight	-0.011	0.002	-0.227	-5.565	0.000
	Diastolic blood pressure	0.004	0.002	0.081	1.987	0.047
LDL-C	Glucose	0.081	0.016	0.198	4.959	0.000
	Diastolic blood pressure	0.005	0.002	0.112	2.801	0.005
ApoA1	Alcohol consumption	0.073	0.015	0.196	4.784	0.000
	Weight	-0.004	0.001	-0.187	-4.566	0.000
ApoB	Waist circumference	0.008	0.002	0.302	4.460	0.000
	Diastolic blood pressure	0.003	0.001	0.128	3.169	0.002
	Glucose	0.021	0.009	0.089	2.233	0.026
	Weight	-0.004	0.002	-0.137	-2.009	0.045
ApoA1/ApoB	Waist circumference	-0.010	0.002	-0.246	-6.087	0.000
	Glucose	-0.038	0.014	-0.109	-2.765	0.006
	Diastolic blood pressure	-0.003	0.001	-0.094	-2.364	0.018
	Alcohol consumption	0.086	0.031	0.122	2.757	0.006
	Gender	0.135	0.041	0.180	3.278	0.001
	Height	0.006	0.002	0.127	2.424	0.016

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.

grow in abundance are prized for their medicinal value. Seawater from the Beibu Gulf is good for salt making. The main crops include rice, sweet potato, peanut, taro and millet, and subtropical fruits like papaya, banana and longan. Jing nationality has become one of the most affluent ethnic groups in China. Rice is the staple food and sweet potatoes, corn, taro, dog tail millet, and duck-foot millet are the subsidiary foods for the Jing people. Both fish and shrimp are the daily dishes of the Jing people. Fish sauce is a favorite condiment for them. Deep-sea fishes such as sardines, herring and salmon are rich in omega-3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). A number of studies have indicated that the supplementation of EPA and DHA lowered TG levels, which is accomplished by decreasing the production of hepatic TG and increasing the clearance of plasma TG [41-43]. AMR101 is an omega-3 fatty acid agent containing ≥ 96% pure icosapent-ethyl, the ethyl ester of eicosapentaenoic acid. In the ANCHOR study [43], AMR101 4 and 2 g/day significantly decreased TG levels by 21.5% ($P < 0.0001$) and 10.1% ($P = 0.0005$), respectively, and non-HDL-C by 13.6% ($P < 0.0001$) and 5.5% ($P = 0.0054$), respectively. AMR101 4 g/day produced greater TG and non-HDL-C decreases in patients with higher-efficacy statin regimens and greater TG decreases in patients with higher baseline TG levels. AMR101 4 g/day decreased LDL-C by 6.2% ($P = 0.0067$) and decreased ApoB (9.3%),

Table 6. The risk factors for serum lipid phenotypes in males and females of both ethnic groups

Lipid phenotype	Risk factor	B	Std.error	Beta	*t*	*P*
Jing/Male						
TC	Age	0.012	0.004	0.205	2.668	0.008
	Pulse pressure	-0.014	0.004	-0.270	-3.770	0.000
	Glucose	0.080	0.031	0.172	2.575	0.011
	Alcohol consumption	0.206	0.092	0.148	2.237	0.026
	Height	-0.020	0.009	-0.166	-2.227	0.027
TG	Waist circumference	0.042	0.006	0.430	6.631	0.000
	Glucose	0.129	0.033	0.236	3.865	0.000
	Cigarette smoking	0.257	0.096	0.173	2.691	0.008
	Height	-0.036	0.010	-0.258	-3.655	0.000
	Age	-0.013	0.005	-0.198	-2.834	0.005
HDL-C	Waist circumference	-0.019	0.003	-0.403	-6.597	0.000
	Alcohol consumption	0.269	0.048	0.339	5.552	0.000
ApoA1	Waist circumference	-0.007	0.001	-0.313	-4.806	0.000
	Alcohol consumption	0.085	0.024	0.231	3.585	0.000
	Glucose	-0.016	0.008	-0.131	-2.031	0.044
ApoB	Body mass index	0.015	0.005	0.207	3.031	0.003
ApoA1/ApoB	Waist circumference	-0.012	0.003	-0.291	-4.401	0.000
	Alcohol consumption	0.147	0.046	0.209	3.158	0.002
Jing/Female						
TC	Age	0.023	0.004	0.289	5.261	0.000
	Glucose	0.180	0.040	0.243	4.557	0.000
	Pulse pressure	-0.007	0.003	-0.120	-2.156	0.032
TG	Cigarette smoking	4.830	0.698	0.345	6.916	0.000
	Waist circumference	0.025	0.005	0.281	5.464	0.000
	Height	-0.020	0.007	-0.148	-2.891	0.004
	Glucose	0.075	0.029	0.128	2.552	0.011
HDL-C	Waist circumference	-0.015	0.003	-0.288	-5.367	0.000
	Cigarette smoking	-0.894	0.418	-0.115	-2.139	0.033
LDL-C	Age	0.009	0.002	0.236	4.351	0.000
	Glucose	0.052	0.020	0.141	2.604	0.010
ApoA1	Weight	-0.004	0.001	-0.153	-2.756	0.006
ApoB	Age	0.005	0.001	0.255	4.698	0.000
	Body mass index	0.012	0.004	0.160	2.956	0.003
ApoA1/ApoB	Body mass index	-0.024	0.006	-0.228	-4.239	0.000
	Age	-0.006	0.002	-0.198	-3.675	0.000
	Genotype	-0.045	0.022	-0.108	-2.014	0.045
Han/Male						
TC	Glucose	0.306	0.047	0.379	6.571	0.000
	Diastolic blood pressure	0.011	0.005	0.134	2.319	0.021
TG	Cigarette smoking	0.410	0.084	0.288	4.890	0.000
	Waist circumference	0.028	0.007	0.242	4.141	0.000
	Glucose	0.140	0.053	0.157	2.665	0.008
HDL-C	Waist circumference	-0.020	0.004	-0.321	-5.248	0.000
	Diastolic blood pressure	0.007	0.003	0.132	2.183	0.030
	Alcohol consumption	0.149	0.047	0.205	3.135	0.002
	Cigarette smoking	-0.136	0.050	-0.177	-2.725	0.007
LDL-C	Glucose	0.125	0.024	0.309	5.218	0.000

	Diastolic blood pressure	0.006	0.002	0.133	2.240	0.026
ApoA1	Alcohol consumption	0.090	0.017	0.318	5.371	0.000
	Waist circumference	-0.005	0.001	-0.221	-3.742	0.000
ApoB	Waist circumference	0.005	0.002	0.189	3.120	0.002
	Glucose	0.042	0.013	0.191	3.216	0.001
	Diastolic blood pressure	0.004	0.001	0.168	2.763	0.006
ApoA1/ApoB	Waist circumference	-0.011	0.003	-0.256	-4.232	0.000
	Glucose	-0.050	0.021	-0.142	-2.414	0.017
	Alcohol consumption	0.076	0.031	0.145	2.428	0.016
	Diastolic blood pressure	-0.005	0.002	-0.145	-2.404	0.017
Han/Female						
TC	Glucose	0.182	0.042	0.225	4.307	0.000
	Alcohol consumption	-1.516	0.490	-0.161	-3.092	0.002
TG	Waist circumference	0.021	0.004	0.267	5.182	0.000
	Glucose	0.096	0.035	0.141	2.746	0.006
HDL-C	Body mass index	-0.020	0.007	-0.156	-2.932	0.004
LDL-C	Alcohol consumption	-1.046	0.253	-0.218	-4.140	0.000
	Age	0.005	0.002	0.145	2.748	0.006
ApoA1	Body mass index	-0.008	0.003	-0.141	-2.632	0.009
ApoB	Waist circumference	0.007	0.001	0.246	4.776	0.000
	Height	-0.007	0.002	-0.172	-3.118	0.002
	Alcohol consumption	-0.500	0.141	-0.180	-3.542	0.000
	Age	0.003	0.001	0.127	2.331	0.020
ApoA1/ApoB	Body mass index	0.110	0.060	1.026	1.828	0.068
	Alcohol consumption	1.004	0.198	0.251	5.060	0.000
	Age	-0.004	0.002	-0.140	-2.639	0.009
	Height	0.049	0.018	0.831	2.648	0.008
	Weight	-0.060	0.026	-1.441	-2.300	0.022

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.

TC (12.0%), very-low-density lipoprotein cholesterol (24.4%), lipoprotein-associated phospholipase A_2 (19.0%), and high-sensitivity C-reactive protein (22.0%) versus placebo ($P < 0.001$ for all comparisons). In addition, the Jing people especially women are accustomed to chew betel nut (Areca catechu L.). Its seeds contain a variety of alkaloids. Jeon et al. [44] have showed that the supplementation of the Areca catechu L. extracts I and II in male rats for 6 days significantly lowered the concentrations of plasma cholesterol by 13.4% and 11.7% and plasma triglycerides by 35.0% and 36.9%, respectively, compared with the pre-experimental values. In contrast, the Han people like to eat fat meat (pig), they also like to use animal oil to cook foods and eat animal offal, brain ridge and pith which contain abundant saturated fatty acid. For nearly 50 years it has been widely accepted that high-fat diets, particularly those that contain large quantities of saturated fatty acids, raise blood cholesterol concentrations and predispose individuals to CVD [45]. Moreover, these high calorie diets that contain high saturated fatty acid, high fat and high cholesterol may stimulate the synthesis of blood cholesterol and elevate blood lipid concentrations.

Although the sex ratio in this study was not significantly different between the two ethnic groups, the percentage of the females was high in the both nationalities (Jing, 59.1% and Han, 57.4%). Sex differences in serum lipid profiles have already been familiar for the people, but the exact molecular mechanisms are not yet fully understood. A large number of epidemiological and clinical studies have found that the

females seem to have a more favorable serum lipid profile, showing lower serum TC, TG and LDL-C levels, and higher serum HDL-C levels [46]. In the past, the reason for sex differences in serum lipid levels was considered to be associated with different sex hormone levels, but some recent studies show that the effect of estrogen and progesterone on the serum lipid regulation is actually minimal. It may be associated with genetic variation or gene-gender interaction [47, 48].

The associations of lifestyle factors and serum lipid levels have been extensively studied. Many epidemiological surveys found that light and moderate volumes of alcohol consumption were inversely associated with cardiovascular mortality [49]. A 10-g/day difference in alcohol consumption was positively related with a 0.05 mmol/L (1.9 mg/dl) difference in HDL-C in both cross-sectional ($P = 0.004$), and longitudinal ($P < 0.0001$) analyses. This relationship did not differ for men and women or for the consumption of beer, wine or distilled spirits [50]. Cigarette smoking remains the most important cause of the preventable morbidity and the early mortality. There was a significant increase in TC and LDL-C in tobacco users, as compared to non tobacco users [51]. A meta-analysis showed that smoking increased TG by 13 mg/dl (0.15 mmol/L) and decreased HDL-C by 3.5 mg/dl (0.09 mmol/L) with every 20 cigarettes smoked according to the regression equation [52]. In the present study, we showed that the percentages of alcohol consumption were lower in Jing than in Han ($P < 0.05$). There were no significant differences in the percentage of cigarette smoking between the two ethnic groups. The effects of different kinds of wine and cigarettes on serum lipid profiles are not well known.

The relationship between obesity and dyslipidemia has been clearly documented. The typical dyslipidemia of obesity consists of increased TG and free fatty acids (FFA), decreased HDL-C with HDL dysfunction and normal or slightly increased LDL-C with increased small dense LDL. The concentrations of plasma ApoB are also often increased, partly due to the hepatic overproduction of ApoB-containing lipoproteins [53-55]. In the present study, we found that the average levels of body weight, BMI, waist circumference, serum TC and TG were higher in Jing than in Han. Hypertriglyceridemia in obesity may be the major cause of the other lipid abnormalities since it will lead to delayed clearance of the TG-rich lipoproteins [56] and formation of small dense LDL [56, 57]. Lipolysis of TG-rich lipoproteins is further impaired in obesity by reduced mRNA expression levels of lipoprotein lipase (LPL) in adipose tissue [58] and reduced LPL activity in skeletal muscle [59]. Hypertriglyceridemia further induces an increased exchange of cholesterol esters and TG between VLDL and HDL and LDL by cholesterylester-transfer-protein. In addition, hepatic lipase removes TG and phospholipids from LDL for the final formation of TG-depleted small dense LDL.

The genetic background between the Jing and Han populations is different. The ancestors of the Jings emigrated from Vietnam to China in the early 16th century and first settled on the three uninhabited lands (Wanwei, Wutou and Shanxin). Jing people have a unique marriage customs and their marriages were arranged by parents in the old days. Now, most of them can free love and sing antiphonal songs to look for the other half. Jing stays ethnic intermarriage and intermarriage with Han or Zhuang people is seldom happened. Jing people can't get married with the one sharing the same last name, and cross-cousin marriage is also strictly prohibited. As a consequence, it should be obvious that the hereditary characteristics and genotypes of lipid metabolism-related genes in this population may be different from those in Han nationality. In the current study, we showed that the genotypic and allelic frequencies of the *CMIP* rs2925979 SNP were not different between the Jing and Han populations, but the genotypic frequencies of the SNP in Han but not in Jing were different between males and females (18.9%, 52.8% and 28.3% *vs*. 18.5%, 43.4% and 38.0%; respectively, $P = 0.028$). Serum HDL-C levels in the Jing population were different among the genotypes ($P = 0.048$), the G allele carriers had higher HDL-C levels than the G allele non-carriers. Serum TC levels in the Han population were different among the genotypes ($P = 0.007$), the G allele carriers had lower TC levels than the G allele non-carriers, subgroup analyses showed that this finding was restricted to Han females but not Han males. Multivariate linear regression analyses revealed that serum HDL-C and ApoB levels in

the combined population of Jing and Han, and serum HDL-C levels and the ApoA1/ApoB ratio in Jing were correlated with genotypes ($P < 0.05$ for all). These findings suggest that there may be an ethnic- and/or sex-specific association of the *CMIP* rs2925979 SNP and serum lipid levels in our study populations. In a previous GWAS, the *CMIP* rs2925979 SNP has been associated with serum HDL-C levels in the individuals of European ancestry [22], but the reproducibility of this association has not been detected in the other populations. To the best of our knowledge, this study is the first report of the association between the *CMIP* rs2925979 SNP and serum lipid levels. Therefore, these results need to be further confirmed in larger sample size and in different ethnic groups.

Limitations

This study has several potential limitations. First, the sample size is a bit small, and the sex ratio in both groups did not meet the 1:1. The male subjects were 226 (40.9%) in Jing and 269 (42.6%) in Han. It has been postulated that an adequate analysis of this kind research requires a sample of at least 600 subjects [60]. Therefore, further studies with larger samples are needed to replicate our findings in the other populations. Second, diet pattern and physical activities are important factors for lipid metabolism. But the intake of macronutrients and overall physical activity were not calculated and analyzed in this study. Finally, it is well-known that serum lipid levels are regulated by multiple environmental and genetic factors, and their interactions. Although we have detected the association of the *CMIP* rs2925979 SNP and several environmental factors with serum lipid levels in this study, there are still many unmeasured environmental and genetic factors and their interactions.

Conclusions

The results of the present study showed that the genotypic frequencies of the *CMIP* rs2925979 SNP in Han but not in Jing were different between males and females. Serum HDL-C levels in Jing and TC levels in Han females were different among the genotypes, the G allele carriers had higher HDL-C and lower TC levels than the G allele non-carriers. These results suggest that the association of the *CMIP* rs2925979 SNP and serum lipid phenotypes might have ethnic- and/or sex-specificity.

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Disclosure of conflict of interest

None.

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