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Original Article

Association of the SLC39A8 rs971752 polymorphism and serum lipid levels in the Jing and Han populations

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Abstract: The association of the rs971752 single nucleotide polymorphism (SNP) in the solute carrier family 39 member 8 gene (*SLC39A8*) and serum lipid profiles has not previously been studied in the Chinese population. The present study aimed to detect the association of the *SLC39A8* rs971752 SNP and several environmental factors with serum lipid levels in the Jing and Han populations. Genotyping of the *SLC39A8* rs971752 SNP was performed in 741 unrelated subjects of Jing nationality and 742 participants of Han nationality using polymerase chain reaction and restriction fragment length polymorphism, and then confirmed by direct sequencing. The frequencies of the G allele (12.7% *vs*. 9.6%, $P < 0.01$) and AG genotype (23.3% *vs*. 16.5%, $P < 0.01$) were higher in Han than in Jing nationalities. The G allele carriers in Jing but not in Han had higher serum triglyceride (TG) and lower total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels than the G allele non-carriers ($P < 0.05$-0.01). Subgroup analyses showed that the G allele carriers had higher TG levels in Jing females; and lower TC, HDL-C and LDL-C levels in Jing males than the G allele non-carriers ($P \leq 0.01$ for all). Serum lipid parameters were also correlated with several environmental factors in Jing and Han populations. These findings suggest that the association between the *SLC39A8* rs971752 SNP and serum lipid levels might have ethnic- and/or sex-specificity.

Keywords: Lipids, sex-specific association, solute carrier family 39 member 8 (SLC39A8), single nucleotide polymorphism, environmental factors

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the word. It is also the major disease burden in the developing countries [1-3]. According to the World Health Organization, 29% of deaths caused by CAD and myocardial infarction worldwide [4]. It is well-known that dyslipidemia associated with high levels of low-density lipoprotein cholesterol (LDL-C) [5], total cholesterol (TC) [6], triglyceride (TG) [7], apolipoprotein (Apo) B [8], and/or low levels of high-density lipoprotein cholesterol (HDL-C) [9] and ApoA1 [8] is one of the most important risk factors for CAD [5]. Therefore, blood lipid control has become an important approach for CAD prevention [10]. Dyslipidemia is a complex multi-factorial disease resulted from the interaction of genetic variations and environmental factors [11, 12]. A population-based, longitudinal Chinese twin study showed that genetic and environmental factors contributed to individual variations in lipid levels [13]. In addition, a number of studies have shown that environmental factors including diet, lifestyle and physiological parameters, can affect the regulation of lipid metabolism [14-16].

Recently, genome wide association studies (GWASs) have reported more than 95 loci associated with serum lipid levels [17], some of the loci are the novel genes associated with circulating lipid levels [18]. The solute carrier family 39 (zinc transporter) member 8 gene (*SLC39A8*; also known asZIP8; CDG2N; PP3105; BIGM103; LZT-Hs6) on chromosome 4q24 (http://www.ncbi.nlm.nih.gov/gene/64116) is one of the novel identified locus. It encodes a member of the SLC39 family of solute-carrier genes, which show structural characteristics of zinc transporters. The encoded protein has been shown to functions in the cellular import of zinc at the

onset of inflammation, and its expression is induced by tumor necrosis factor-α [19, 20]. Many epidemiological studies suggest that exposure to metals such as Cd and Pb may play a role in the development of hypertension by various complex mechanisms and ZIP8 transporter encoded by expression of the *SLC39A8* plays an important role in the uptake of cadmium, iron and manganese and other metal in mammalian cells [21-23]. GWASs of large datasets from human populations have suggested that single nucleotide polymorphisms (SNPs) in the *SLC39A8* were associated with type 2 diabetes risk [24-26], body mass index (BMI)/obesity [27], activation of plasminogen [28], CAD risk [18], and schizophrenia [29]. One of the SNPs, rs13107325, located in exon 8 of the *SLC39A8* and caused a change in amino acid from alanine to threonine has been associated the changes of serum lipid levels, the T allele (frequency 8%) is associated with lower circulating levels of HDL-C [18]. Furthermore, Verdugo *et al*. reported that the *SLC39A8* directly connected to formation of atherosclerosis, but this effect of the SNP on plaques was not completely mediated by HDL-C. It may also play an important role by intracellular transport of cadmium, a toxic heavy metal and carcinogen [30]. Recently, a comprehensive meta-analysis of the GWASs suggested that a missense variant of the *SLC39A8* rs13107325 (4q22-q24) was associated with HDL-C, BMI, adiponectin, systolic blood pressure, diastolic blood pressure and waist circumference [31]. However, the effect of another SNP of rs971752 on serum lipid levels has not been validated previously in the general populations.

China is a multiethnic country with 56 ethnic groups. Han nationality is the largest ethnic groups and Jing nationality is one of the smallest minorities with population of 28199 according to the six national census statistics of China in 2010. 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 ethnic group emigrated from Vietnam to China and first settled on the three abovementioned lands. Jing is the only minority for coastal fisheries in China. Therefore, it is different in the customs, diet structure, lifestyle and genetic background between the Jing and the 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 Jing and Han populations [32-34]. The reason for these differences between the two ethnic groups is not entirely clear. To the best of our knowledge, the association between the *SLC39A8* rs971752 SNP and serum lipid profiles has not been previously reported. Therefore, the present study aimed to explore the association of the *SLC39A8* rs971752 SNP and several environmental factors with serum lipid levels in the Jing and Han populations.

Materials and methods

Study population

This study included 741 unrelated subjects of Jing nationality and 742 unrelated participants of Han nationality who live in the same regions. They were randomly selected from our previous stratified randomized samples. All of the participants were rural agricultural (Han) and/or fishery (Jing) workers from Jiangping Down, Dongxing City, Guangxi Zhuang Autonomous Region, People's Republic of China. The subjects of Han were composed of 370 (49.4%) males and 372 (50.1%) females, with a mean age of 56.66±12.89 years. The participants of Jing were composed of 368 (49.7%) males and 373 (50.3%) females, with a mean age of 56.50±13.31 years. The age of the participants ranged from 15 to 80 years. All study subjects were essentially healthy and had never been diagnosed with cardiovascular disease such as CAD, stroke, hyper- or hypo-thyroids, chronic renal disease, and diabetes. They did not take medications known to affect serum lipid levels (such as statins or fibrates, beta-blockers, diuretics, or hormones). The study design was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University. Informed consent was obtained from all participants.

Epidemiological survey

The epidemiological data were obtained using internationally standardized methods, following a common protocol [35]. The characteristics of demography, socioeconomic status, and lifestyle factors were collected with standardized questionnaires. The information of alcohol intake included questions about the number of

liang (~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. In the physical examination, several parameters 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. BMI (kg/m^2) was calculated by height and weight measurement.

Biochemical measurements

A venous blood sample of 5 mL was obtained from all participants in a fasting state. A part of the sample (2 mL) was collected into glass tubes and used to measure serum lipid levels. Another part of the sample (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 TC, TG, HDL-C, and 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 quantified 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 the Clinical Science Experiment Center of the First Affiliated Hospital, Guangxi Medical University. Fasting blood glucose was determined with a glucose meter (Accu-Chek; F. Hoffman-La Roche AG, Basel, Switzerland) [36].

DNA amplification and genotyping

Genomic DNA was isolated from peripheral blood leukocytes using the phenol-chloroform method [34, 37]. The extracted DNA was stored at -20°C until analysis. Genotyping of the *SLC39A8* rs971752 SNP was performed by polymerase chain reaction (PCR) and restriction fragment length polymorphism (PCR-RFLP). PCR amplification was performed using 5'-GGCAAGTGTCTTCCTGGTTC-3' as the forward and 5'-TCCCCTTAACTGGCTTTCCT-3' (Sangon, Shanghai, People's Republic of China) as reversed primer pair. Each amplification reaction was performed in a total volume of 25 μL, containing 2 μL of genomic DNA, 1 *μ*l of each primer (10 pmol/l), 12.5 *μ*l 2 × *Taq* PCR Master mix (including 20 mM Tris-HCl, pH 8.3, 100 mM KCl, 3 mM $MgCl_2$, 0.1 U *Taq* polymerase/*μ*l, 500 *μ*M dNTP each) and 8.5 *μ*l double-distilled H_2O (DNase/RNase-free). The processing started with pre-denaturing at 95°C for 5 min and followed by denaturing at 94°C for 45 s, annealing at 56°C for 45 s and 40 s of extension at 72°C for 30 cycles. The amplification was completed by a final extension at 72°C for 7 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 μl of amplified DNA; 9 μl of nuclease-free water and 1 μl of 10 × buffer solution; and 5 units of *Xba*I restriction enzyme in a total volume of 15 μl digested at 37°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 ratio of

Table 1. Comparison of demographic, lifestyle characteristics and serum lipid levels between the Jing and Han populations

Parameter	Jing	Han	t (χ^2)	P
Number	741	742		
Male/female	368/373	370/372	0.006	0.938
Age (year)	56.50±13.31	56.66±12.89	-0.237	0.813
Height (cm)	158.13±8.04	157.40±7.92	1.757	0.079
Weight (kg)	58.97±10.22	56.27±9.38	5.258	0.000
Body mass index (kg/m^2)	23.50±3.19	22.66±3.08	5.126	0.000
Waist circumference (cm)	80.47±9.16	77.37±8.68	6.637	0.000
Cigarette smoking [n (%)]				
Non-smoker	617 (83.3)	606 (81.7)		
≤ 20 cigarettes/day	31 (4.2)	34 (4.6)	0.652	0.722
> 20 cigarettes/day	93 (12.6)	102 (13.7)		
Alcohol consumption [n (%)]				
Non-drinker	638 (86.1)	598 (80.6)		
≤ 25 g/day	50 (6.7)	33 (4.4)	25.288	0.000
> 25 g/day	53 (7.2)	111 (15.0)		
Systolic blood pressure (mmHg)	131.47±21.58	133.57±55.36	-0.957	0.339
Diastolic blood pressure (mmHg)	80.24±10.31	80.50±10.11	-0.489	0.625
Pulse pressure (mmHg)	51.23±17.64	52.93±53.89	-0.810	0.418
Glucose (mmol/L)	6.87±1.64	6.59±1.05	3.936	0.000
Total cholesterol (mmol/L)	5.10±0.90	4.89±0.88	4.588	0.000
Triglyceride (mmol/L)	1.43 (0.76)	1.32 (0.65)	-4.272	0.000
HDL-C (mmol/L)	1.77±0.45	1.79±0.50	-1.060	0.290
LDL-C (mmol/L)	2.81±0.43	2.85±0.44	-1.822	0.069
Apolipoprotein (Apo) A1 (g/L)	1.28±0.22	1.32±0.20	-3.741	0.000
ApoB (g/L)	1.04±0.23	1.04±0.25	-0.010	0.992
ApoA1/ApoB	1.30±0.38	1.34±0.38	-2.340	0.019

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. The quantitative variables were presented as mean ± standard deviation and their difference between the groups was determined by the *t*-test. 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. The difference in percentages of cigarette smoking and alcohol consumption between the groups was determined by Chi-square test.

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 [38]. The individuals with TC > 5.17 mmol/L and/or TG > 1.70 mmol/L were defined as hyperlipidemic [34]. Hypertension was diagnosed according to the criteria of 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension [39]. The criteria of judgment of overweight and obesity were 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 [40].

Statistical analysis

The quantitative variables were presented as mean ± standard deviation, except serum TG levels were presented as medians and interquartile ranges. 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. 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 between specific genotypes and serum lipid parameters. Sex,

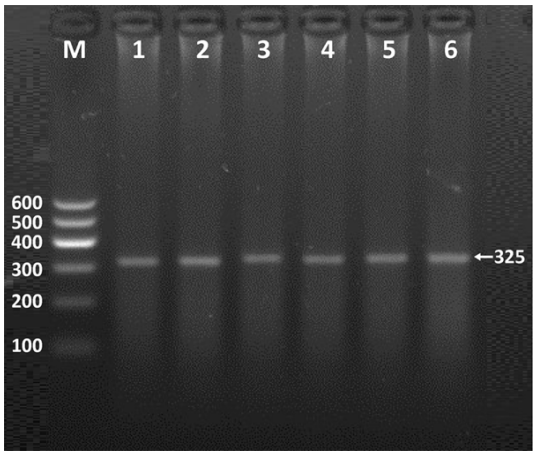

Figure 1. Electrophoresis of PCR products of the *SLC39A8* rs971752 polymorphism. Lane M is 100 bp marker ladder; lanes 1-6 are samples. The 325 bp bands are the PCR products.

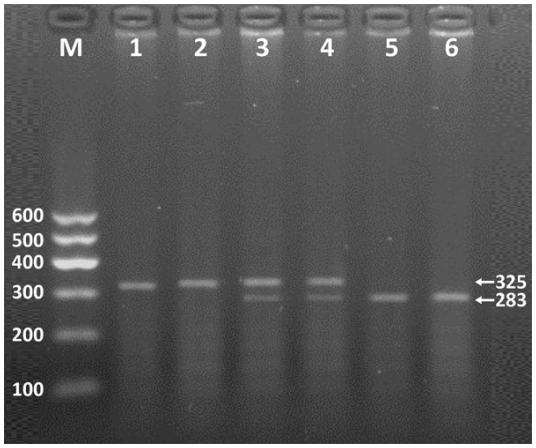

Figure 2. Genotyping of the *SLC39A8* rs971752 SNP. Lane M, 100 bp Marker Ladder; lanes 1 and 2, GG genotype (325-bp); lanes 3 and 4, AG genotype (325-, 283- and 42-bp); and lanes 5 and 6, AA genotype (283- and 42-bp). The 42-bp segment is not visible in the gel owing to its fast migratory speed.

age, alcohol consumption, blood pressure, BMI, cigarette smoking were adjusted for the statistical analysis. Multivariate linear regression analysis with stepwise modeling was performed to determine the association of serum lipid levels with genotypes (AA = 1, AG = 2 and GG = 3; or AA = 1, AG/GG = 2) and several environment factors 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 the statistical analyses were done with the statistical software package SPSS17.0 (SPSS Inc., Chicago, Illinois).

Results

General characteristics and serum lipid levels

The comparison of general characteristics and serum lipid levels between the Han and Jing populations is summarized in **Table 1**. The levels of ApoA1, the ratio of ApoA1 to ApoB and the percentages of alcohol consumption were higher in Han than in Jing ($P < 0.05$), whereas the values of body weight, BMI, waist circumference, blood glucose, TC, TG were lower in Han than in Jing ($P < 0.001$ for each). There were no significant differences in the gender ratio, age structure, the percentage of cigarette smoking, and systolic blood pressure, diastolic blood pressure, body height, pulse pressure, serum HDL-C, LDL-C and ApoB levels between the two ethnic groups ($P > 0.05$ for all).

Results of electrophoresis and genotyping

After the genomic DNA of the samples was amplified by PCR and imaged by 2.0% agarose gel electrophoresis. The products of 325-bp nucleotide sequences could be discovered in all samples (**Figure 1**). The genotypes identified were labeled according to the presence (A allele) or absence (G allele) of the enzyme restriction sites. Thus, the GG genotype was homozygous for the absence of the site (band at 325 bp), the AG genotype was heterozygous for the absence and presence of the site (bands at 325-, 283- and 42-bp) and the AA genotype was homozygous for the presence of the site (bands at 283- and 42-bp; **Figure 2**). The 42-bp segment is not visible in the gel owing to its fast migratory speed.

Results of sequencing

The results were separated into AA, AG and GG genotypes by PCR-RFLP and the genotypes were further confirmed by the backward sequencing (**Figure 3**).

Genotypic and allelic frequencies

The genotypic and allelic frequencies of the *SLC39A8* rs971752 SNP are summarized in **Table 2**. The genotypic distribution in both Jing and Han was conformed to the Hardy-Weinberg equilibrium (HWE, $P > 0.05$ for each). The frequency of *SLC39A8* rs971752G allele was higher in Han than in Jing (12.7% vs. 9.6%, $P < 0.01$). The frequencies of AA, AG and GG geno-

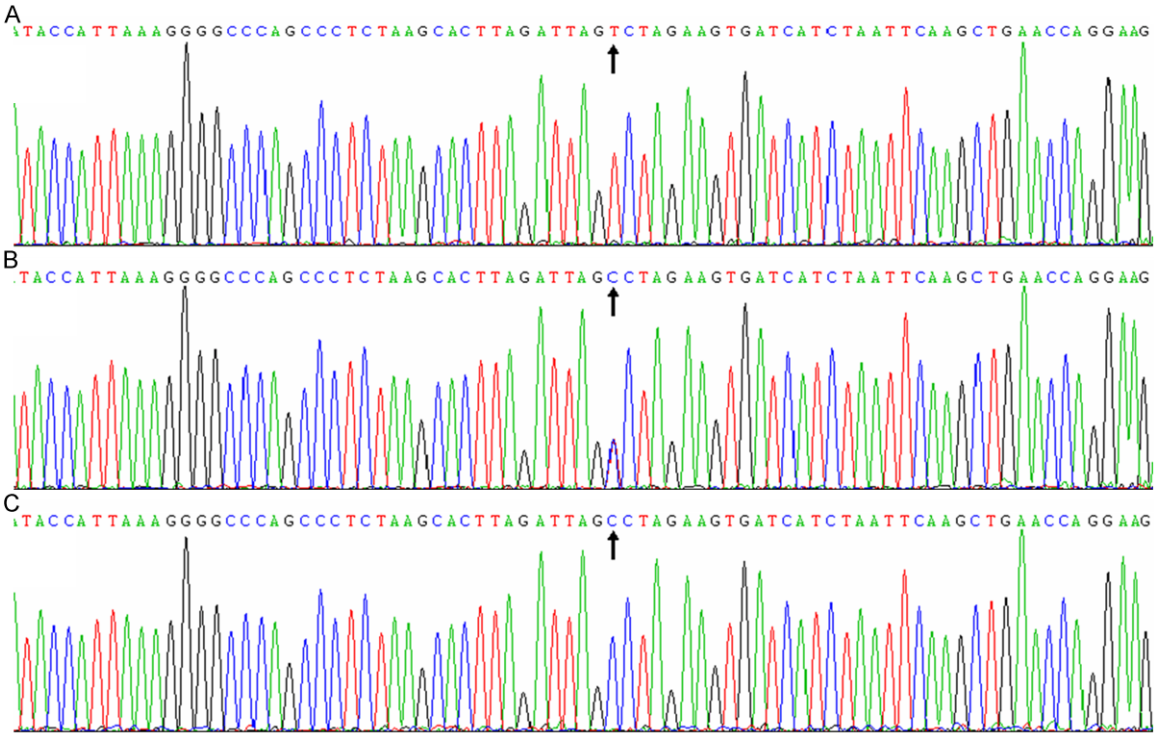

Figure 3. A part of the nucleotide sequences of the *SLC39A8* rs971752 SNP by backward sequencing. A. AA genotype; B. AG genotype; and C. GG genotype.

Table 2. Comparison of the genotype and allele frequencies of SLC39A8 rs971752 SNP between the Han and Jing populations [n (%)]

Group	N	Genotype			Allele		HWE (*P*)
		AA	AG	GG	A	G	
Jing	741	609 (82.2)	122 (16.5)	10 (1.3)	1340 (90.4)	142 (9.6)	0.175
Han	742	561 (75.6)	173 (23.3)	8 (1.1)	1295 (87.3)	189 (12.7)	0.183
x^2	-		11.008			7.441	
P	-		0.004			0.006	
Jing							
Male	368	300 (81.5)	64 (17.4)	4 (1.1)	664 (90.2)	72 (9.8)	0.778
Female	373	309 (82.8)	58 (15.5)	6 (1.6)	676 (90.6)	70 (9.4)	0.098
x^2	-		0.794			0.068	
P	-		0.672			0.794	
Han							
Man	370	267 (72.2)	100 (27.0)	3 (0.8)	634 (85.7)	106 (14.3)	0.052
Female	372	294 (79.0)	73 (19.6)	5 (1.3)	661 (88.8)	83 (11.2)	0.846
x^2	-		6.008			3.351	
P	-		0.050			0.067	

HWE, Hardy-Weinberg equilibrium.

types were 82.2%, 16.5% and 1.3% in Jing, and 75.6%, 23.3% and 1.1% in Han ($P < 0.01$); respectively. There was no significant difference in the genotypic and allelic frequencies between males and females in the both ethnic groups ($P > 0.05$ for all).

Genotypes and serum lipid levels

Tables 3 and **4** describe the association between genotypes and serum lipid levels. Serum TC, TG, HDL-C and LDL-C levels in Jing were different between the AA and AG/GG gen-

Table 3. Comparison of the genotypes and serum lipid levels in the Han and Jing 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	609	5.13±0.90	1.41 (0.73)	1.80±0.45	2.83±0.44	1.29±0.20	1.04±0.23	1.31±0.38
AG/GG	132	4.97±0.89	1.59 (0.75)	1.64±0.43	2.75±0.38	1.26±0.30	1.04±0.23	1.27±0.40
F	-	7.111	-2.728	11.698	4.933	0.323	0.005	0.287
P	-	0.008	0.006	0.001	0.027	0.570	0.946	0.592
Han								
AA	561	4.91±0.86	1.33 (0.62)	1.79±0.53	2.86±0.43	1.33±0.20	1.04±0.25	1.35±0.39
AG/GG	181	4.84±0.92	1.27 (0.82)	1.81±0.43	2.86±0.48	1.31±0.20	1.04±0.26	1.33±0.38
F	-	1.036	-0.651	0.047	0.003	2.432	0.000	0.454
P	-	0.309	0.515	0.828	0.955	0.119	0.999	0.501

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 Wilcoxon-Mann-Whitney test.

Table 4. Comparison between the SLC39A8 rs971752 genotypes and serum levels in males and females of the Jing and Han populations

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	300	5.11±0.81	1.46 (0.85)	1.76±0.48	2.83±0.37	1.27±0.20	1.04±0.21	1.28±0.40
AG/GG	68	4.88±0.84	1.62 (0.86)	1.53±0.35	2.72±0.34	1.21±0.22	1.04±0.21	1.23±0.41
F	-	7.131	-1.386	10.722	6.807	3.194	0.301	0.306
P	-	0.008	0.166	0.001	0.009	0.075	0.583	0.580
Jing/Female								
AA	309	5.15±0.98	1.35 (0.57)	1.84±0.42	2.83±0.49	1.30±0.19	1.03±0.24	1.33±0.37
AG/GG	64	5.08±0.93	1.55 (0.58)	1.76±0.47	2.97±0.41	1.32±0.36	1.05±0.25	1.31±0.39
F	-	2.134	-2.576	2.379	1.145	0.817	0.048	0.000
P	-	0.145	0.010	0.124	0.285	0.367	0.827	0.993
Han/Male								
AA	267	4.82±0.85	1.33 (0.67)	1.70±0.57	2.85±0.43	1.32±0.20	1.05±0.24	1.34±0.42
AG/GG	103	4.81±0.82	1.29 (0.86)	1.78±0.42	2.85±0.42	1.30±0.20	1.04±0.20	1.30±0.31
F	-	0.272	-0.337	0.312	0.125	2.185	0.212	0.863
P	-	0.602	0.736	0.577	0.724	0.140	0.646	0.353
Han/Female								
AA	294	4.99±0.86	1.33 (0.59)	1.87±0.46	2.86±0.43	1.33±0.20	1.04±0.25	1.35±0.36
AG/GG	78	4.89±1.04	1.27 (0.76)	1.84±0.43	2.88±0.56	1.32±0.20	1.04±0.31	1.38±0.46
F	-	1.004	-0.480	0.752	0.006	0.432	0.000	0.347
P	-	0.317	0.631	0.387	0.937	0.511	1.000	0.556

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 values of TG were presented as median (interquartile range), and the difference between the TT and TC/CC genotypes was determined by the Wilcoxon-Mann-Whitney test.

otypes ($P < 0.05$-0.01). The G allele carriers had higher TG levels, and lower serum TC, HDL-C and LDL-C levels than the G allele non-carriers. Subgroup analyses showed that serum levels of TC, HDL-C and LDL-C in Jing males and TG levels in Jing females were different between the AA and AG/GG genotypes ($P < 0.05$ for all), the G allele carriers had higher serum TG levels

Table 5. Relationship between serum lipid parameters and relative factors in the Han and Jing populations

Lipid parameter	Relative factor	B	Std. error	Beta	*t*	*P*
Jing and Han						
TC	Glucose	0.134	0.017	0.209	8.084	0.000
	Height	-0.008	0.004	-0.072	-1.958	0.050
	Ethnic group	-0.154	0.046	-0.086	-3.375	0.001
	Age	0.008	0.002	0.113	3.925	0.000
	Waist circumference	0.006	0.003	0.057	2.152	0.032
	Cigarette smoking	0.099	0.037	0.077	2.662	0.008
	Gender	0.145	0.066	0.081	3.179	0.029
	Genotype	-0.110	0.055	-0.050	-2.004	0.045
TG	Waist circumference	0.039	0.005	0.402	8.058	0.000
	Cigarette smoking	0.258	0.035	0.204	7.355	0.000
	Glucose	0.102	0.016	0.161	6.505	0.000
	Height	-0.024	0.004	-0.217	-5.697	0.000
	Diastolic blood pressure	0.008	0.002	0.093	3.734	0.000
	Age	-0.007	0.002	-0.101	-3.615	0.000
	Body mass index	-0.036	0.013	-0.130	-2.711	0.007
	Gender	-0.128	0.063	-0.073	-2.035	0.042
HDL-C	Waist circumference	-0.016	0.001	-0.298	-11.525	0.000
	Alcohol consumption	0.143	0.021	0.194	6.937	0.000
	Gender	0.208	0.036	0.217	5.813	0.000
	Cigarette smoking	-0.060	0.020	-0.087	-2.958	0.003
	Height	0.007	0.002	0.112	3.124	0.002
	Age	0.003	0.001	0.069	2.483	0.013
LDL-C	Glucose	0.039	0.008	0.126	4.732	0.000
	Age	0.003	0.001	0.080	3.029	0.002
	Diastolic blood pressure	0.003	0.001	0.066	2.560	0.011
	Ethnic group	0.054	0.023	0.063	2.413	0.016
ApoA1	Weight	-0.006	0.001	-0.265	-8.400	0.000
	Alcohol consumption	0.063	0.009	0.195	7.062	0.000
	Glucose	-0.010	0.004	-0.066	-2.592	0.010
	Gender	0.050	0.014	0.118	3.454	0.001
	Height	0.003	0.001	0.108	2.857	0.004
	Systolic blood pressure	0.000	0.000	0.051	2.007	0.045
ApoB	Waist circumference	0.006	0.001	0.224	8.454	0.000
	Age	0.002	0.000	0.087	3.345	0.001
	Height	-0.002	0.001	-0.061	-2.249	0.025
ApoA1/ApoB	Waist circumference	-0.013	0.001	-0.299	-11.424	0.000
	Alcohol consumption	0.070	0.016	0.117	4.291	0.000
	Glucose	-0.019	0.007	-0.067	-2.645	0.008
	Gender	0.097	0.026	0.126	3.709	0.000
	Height	0.005	0.002	0.100	2.974	0.003
Jing						
TC	Glucose	0.108	0.019	0.198	5.566	0.000
	Age	0.018	0.003	0.263	6.496	0.000
	Cigarette smoking	0.269	0.053	0.203	5.075	0.000
	Gender	0.331	0.071	0.185	4.649	0.000
	Pulse pressure	-0.006	0.002	-0.123	-3.135	0.002
	Genotype	-0.213	0.081	-0.092	-2.631	0.009
	Body mass index	0.025	0.010	0.088	2.501	0.013

TG	Waist circumference	0.033	0.004	0.346	9.524	0.000
	Cigarette smoking	0.346	0.048	0.264	7.250	0.000
	Height	-0.019	0.004	-0.172	-4.472	0.000
	Glucose	0.064	0.018	0.119	3.490	0.001
HDL-C	Waist circumference	-0.017	0.002	-0.343	-9.985	0.000
	Alcohol consumption	0.171	0.030	0.208	5.738	0.000
	Gender	0.130	0.033	0.143	3.941	0.000
	Genotype	-0.125	0.040	-0.106	-3.138	0.002
LDL-C	Age	0.005	0.001	0.152	3.948	0.000
	Cigarette smoking	0.097	0.026	0.155	3.722	0.000
	Gender	0.098	0.035	0.115	2.768	0.006
	Glucose	0.024	0.010	0.094	2.535	0.011
	Genotype	-0.085	0.040	-0.077	-2.110	0.035
ApoA1	Weight	-0.005	0.001	-0.242	-6.671	0.000
	Alcohol consumption	0.041	0.015	0.102	2.818	0.005
	Glucose	-0.011	0.005	-0.079	-2.192	0.029
ApoB	Waist circumference	0.005	0.001	0.190	5.228	0.000
	Age	0.002	0.001	0.105	2.902	0.004
ApoA1/ApoB	Waist circumference	-0.007	0.003	-0.175	-2.757	0.006
	Alcohol consumption	0.079	0.025	0.112	3.146	0.002
	Age	-0.003	0.001	-0.120	-3.264	0.001
	Weight	-0.006	0.002	-0.150	-2.321	0.021
Han						
TC	Glucose	0.118	0.029	0.228	6.403	0.000
	Systolic blood pressure	0.001	0.001	0.079	2.190	0.029
	Waist circumference	0.030	0.006	0.296	4.841	0.000
	Weight	-0.029	0.006	-0.315	-5.154	0.000
	Diastolic blood pressure	0.007	0.003	0.077	2.091	0.037
TG	Waist circumference	0.039	0.006	0.395	6.386	0.000
	Glucose	0.173	0.029	0.212	5.949	0.000
	Cigarette smoking	0.216	0.044	0.177	4.863	0.000
	Diastolic blood pressure	0.011	0.003	0.123	3.473	0.001
	Weight	-0.020	0.006	-0.223	-3.473	0.001
	Age	-0.007	0.002	-0.097	-2.652	0.008
HDL-C	Cigarette smoking	-0.140	0.030	-0.197	-4.668	0.000
	Alcohol consumption	0.154	0.030	0.222	5.200	0.000
	Diastolic blood pressure	0.005	0.002	0.094	2.633	0.009
	Waist circumference	-0.014	0.002	-0.240	-6.649	0.000
	Gender	0.134	0.042	0.133	3.196	0,001
LDL-C	Glucose	0.084	0.015	0.202	5.566	0.000
	Diastolic blood pressure	0.005	0.002	0.116	3.182	0.002
ApoA1	Alcohol consumption	0.064	0.010	0.232	6.266	0.000
	Weight	-0.005	0.001	-0.212	-5.732	0.000
ApoB	Waist circumference	0.013	0.002	0.465	6.902	0.000
	Weight	-0.009	0.002	-0.325	-4.423	0.000
	Diastolic blood pressure	0.003	0.001	0.108	2.952	0.003
	Gender	-0.047	0.021	-0.095	-2.242	0.025
ApoA1 /ApoB	Waist circumference	-0.012	0.002	-0.279	-7.790	0.000
	Glucose	-0.039	0.013	-0.106	-2.988	0.003
	Alcohol consumption	0.047	0.019	0.089	2.482	0.013

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.

in Jing females, and lower serum TC, HDL-C and LDL-C levels in Jing males than the G allele non-carriers.

Relative factors for serum lipid parameters

As shown in **Tables 5** and **6**, multiple linear regression analysis showed that serum TC levels in the combined population of Han and Jing; and TC, HDL-C, LDL-C levels in Jing but not in Han were correlated with the genotypes of the *SLC39A8* rs971752 SNP ($P < 0.05$). When the correlation of serum lipid parameters and the genotypes was performed according to sex subgroups, we revealed that serum TC; HDL-C and LDL-C levels in Jing males but not in females were correlated with the genotypes ($P < 0.05$). Serum lipid parameters were also correlated with several environmental factors such as age, gender, height, weight, BMI, waist circumference, alcohol consumption, cigarette smoking, blood pressure and blood glucose in both ethnic groups ($P < 0.05$-0.001).

Discussion

In the current study, we showed that serum lipid profiles were significantly different between Han and Jing ethnic groups. The levels of TC and TG were higher but ApoA1 and the ratio of ApoA1 to ApoB were lower in Jing than in Han ($P < 0.05$ for all). There were no significant differences in the levels of HDL-C, LDL-C and ApoB between the two ethnic groups. A significant difference in the *SLC39A8* rs971752 genotype and allele frequencies was noted between the two ethnic groups. The frequencies of AA, AG and GG genotypes were 82.2%, 16.5% and 1.3% in Jing, and 75.6%, 23.3% and 1.1% in Han ($P < 0.01$); respectively. The minor G allele frequency in Jing and Han was 9.6% and 12.7% respectively which was lower than those of Chinese Han Beijing (14.3%) reported in international haplotype map (HapMap) project. This difference may be caused by different sample sizes and regions. According to the Hap Map data, the minor allele G frequency of the rs971752 SNP was 13.7% in European population, 10.5% in Japanese, 17.3% in Yoruba, 20.0% in Mexican and 17.2% in Italy. This study recognized that genotype and allele frequencies of *SLC39A8* rs971752 SNP may have a racial/ethnic difference.

The genetic background between the Jing and Han populations is different. The ancestors of the Jing ethnic group emigrated from Vietnam to China and settled on the three lands of Wanwei, Wutou and Shanxin, Dongxing City, Guangxi, China. 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 research, we showed that serum TC, TG, HDL-C and LDL-C levels in Jing but not in Han were different between the AA and AG/GG genotypes ($P < 0.05$-0.01). The G allele carriers had higher TG levels, and lower TC, HDL-C and LDL-C levels than the G allele non-carriers. Subgroup analyses showed that serum levels of TC, HDL-C and LDL-C in Jing males and TG levels in Jing females were different between the AA and AG/GG genotypes ($P < 0.05$ for all); the G allele carriers had higher serum TG levels in Jing females, and lower serum TC, HDL-C and LDL-C levels in Jing males than the G allele non-carriers. These findings indicated that the association of *SLC39A8* rs971752 SNP and serum lipid levels is inconsistent between the two ethnic groups. There may be a sex-specific association of the rs971752 SNP and serum lipid parameters in the Jing population. The direct relationship between the rs971752 SNP and serum lipid levels has not been reported previously. A meta-analysis of the GWAS suggested that the *SLC39A8* rs13107325 SNP was associated with HDL-C, BMI, adiponectin, systolic blood pressure, diastolic blood pressure and waist circumference [31]. To the best of our knowledge, this study is the first report of the association between the rs971752 SNP and serum lipid levels. Therefore, these results need to be further confirmed in larger sample size and in different ethnic groups.

In the present study, multivariate linear regression analysis also showed that age, sex, weight,

Table 6. Relative risk factors for serum lipid parameters in the males and females of the Han and Jing populations

Lipid	Risk factor	B	Std. error	Beta	*t*	*P*
Jing/male						
TC	Cigarette smoking	0.201	0.051	0.215	3.930	0.000
	Age	0.015	0.003	0.259	4.267	0.000
	Glucose	0.082	0.024	0.178	3.403	0.001
	Pulse pressure	-0.009	0.003	-0.194	-3.335	0.001
	Genotype	-0.249	0.101	-0.121	-2.450	0.015
	Body mass index	0.077	0.026	0.292	2.969	0.003
	Alcohol consumption	0.145	0.058	0.129	2.512	0.012
	Waist circumference	-0.018	0.008	-0.210	-2.069	0.039
TG	Waist circumference	0.039	0.005	0.380	7.429	0.000
	Cigarette smoking	0.243	0.058	0.210	4.175	0.000
	Height	-0.036	0.008	-0.242	-4.458	0.000
	Age	-0.016	0.004	-0.228	-4.125	0.000
	Glucose	0.106	0.028	0.187	3.820	0.000
HDL-C	Waist circumference	-0.018	0.002	-0.363	-7.632	0.000
	Alcohol consumption	0.175	0.031	0.271	5.714	0.000
	Genotype	-0.175	0.056	-0.147	-3.111	0.002
LDL-C	Cigarette smoking	0.070	0.022	0.167	3.196	0.002
	Genotype	-0.112	0.048	-0.121	-2.320	0.021
ApoA1	Waist circumference	-0.007	0.001	-0.347	-7.026	0.000
	Alcohol consumption	0.059	0.014	0.206	4.164	0.000
ApoB	Weight	0.006	0.001	0.268	5.240	0.000
ApoA1/ApoB	Weight	-0.015	0.002	-0.382	-7.527	0.000
	Alcohol consumption	0.076	0.027	0.137	2.794	0.005
	Age	-0.003	0.001	-0.120	-2.364	0.019
Jing/female						
TC	Glucose	0.154	0.032	0.241	4.901	0.000
	Age	0.018	0.004	0.230	4.675	0.000
TG	Waist circumference	0.026	0.004	0.300	6.038	0.000
	Height	-0.028	0.006	-0.223	-4.462	0.000
	Cigarette smoking	1.176	0.314	0.183	3.745	0.000
HDL-C	Waist circumference	-0.017	0.003	-0.340	-6.700	0.000
	Diastolic blood pressure	0.005	0.002	0.103	2.042	0.042
LDL-C	Age	0.008	0.002	0.214	4.242	0.000
	Glucose	0.046	0.016	0.145	2.864	0.004
ApoA1	Body mass index	-0.010	0.004	-0.145	-2.821	0.005
ApoB	Age	0.004	0.001	0.191	3.790	0.000
	Body mass index	0.012	0.004	0.157	3.118	0.002
ApoA1/ApoB	Body mass index	-0.024	0.006	-0.214	-4.260	0.000
	Age	-0.004	0.002	-0.145	-2.876	0.004
Han/male						
TC	Glucose	0.201	0.038	0.264	5.323	0.000
	Diastolic blood pressure	0.011	0.004	0.136	2.697	0.007
	Systolic blood pressure	0.001	0.001	0.107	2.115	0.035
TG	Diastolic blood pressure	0.020	0.005	0.207	4.245	0.000
	Glucose	0.232	0.043	0.264	5.365	0.000

	Cigarette smoking	0.199	0.054	0.182	3.661	0.000
	Waist circumference	0.044	0.011	0.373	4.187	0.000
	Age	-0.013	0.004	-0.174	-3.245	0.001
	Weight	-0.028	0.011	-0.247	-2.658	0.008
HDL-C	Waist circumference	-0.016	0.003	-0.248	-4.861	0.000
	Alcohol consumption	0.152	0.032	0.256	4.744	0.000
	Cigarette smoking	-0.142	0.032	-0.233	-4.402	0.000
	Diastolic blood pressure	0.007	0.003	0.130	2.569	0.011
LDL-C	Glucose	0.088	0.020	0.227	4.503	0.000
	Diastolic blood pressure	0.007	0.002	0.159	3.156	0.002
ApoA1	Alcohol consumption	0.075	0.011	0.340	6.911	0.000
	Waist circumference	-0.005	0.001	-0.211	-4.286	0.000
ApoB	Waist circumference	0.006	0.001	0.210	4.080	0.000
	Diastolic blood pressure	0.003	0.001	0.129	2.503	0.013
	Glucose	0.023	0.011	0.110	2.187	0.029
ApoA1/ApoB	Waist circumference	-0.014	0.002	-0.284	-5.613	0.000
	Alcohol consumption	0.068	0.022	0.156	3.091	0.002
Han/female						
TC	Glucose	0.233	0.046	0.262	5.126	0.000
TG	Waist circumference	0.024	0.004	0.295	5.916	0.000
	Glucose	0.116	0.036	0.159	3.189	0.002
HDL-C	Body mass index	-0.037	0.007	-0.262	-5.128	0.000
LDL-C	Glucose	0.089	0.023	0.197	3.841	0.000
	Height	-0.010	0.004	-0.140	-2.733	0.007
ApoA1	Body mass index	-0.012	0.003	-0.195	-3.756	0.000
ApoB	Waist circumference	0.017	0.003	0.580	5.755	0.000
	Weight	-0.012	0.003	-0.410	-4.013	0.000
	Age	0.003	0.001	0.122	2.339	0.020
ApoA1/ApoB	Height	0.016	0.003	0.261	5.252	0.000
	Waist circumference	-0.013	0.002	-0.318	-6.373	0.000
	Glucose	-0.049	0.018	-0.130	-2.659	0.008

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.

waist circumference, alcohol consumption, and cigarette smoking were involved in determining serum lipid parameters in males and females of both Jing and Han populations. These data suggest that the environmental factors also play an important role in determining serum lipid levels in our study populations. There are significant differences in the customs, dietary patterns, lifestyle and physical activity between the Jing and Han populations. Jing nationality is the only minority for coastal fisheries in China. They live in an isolated environment and have different dietary habits. Although rice is the staple food in the both ethnic groups, the people of Jing prefer glutinous rice and seafood like fish, shrimp, crabs, shellfish and sandworm. A kind of fish sauce, "nuoc-mam" (Vietnamese language), is a typical Jing food, which contains 17 amino acids [34]. The habits of chewing betel nut are also common in Jing females. Jing people generally like to eat sweet food such as sweet glutinous rice porridge, mung bean syrup, sweet vermicelli soup or sweet potato soup. They believe that sweet food embodies their hopes and yearnings for a good life because sugar is sweet. Some studies suggest that high-sugar diets induced glucose intolerance, increased fasting blood lipids and glucose and associated with body weight gain [41, 42]. So the preference of dessert may be related to the higher body weight, BMI and glucose level in Jing than in Han people. Garcia-Palmieri *et al*.

stated that diet and relative weight could account for at most 6% of the variability in serum cholesterol levels, with up to 2.5% of the variability due diet alone [43]. In particular, for every 1-kg decrease in body weight, TG decreased by 0.011 mmol/L and HDL-C increased by 0.011 mmol/L and for every 1% decrease in energy consumed as dietary saturated fatty acid, TC decreased by 0.056 mmol/L and LDL-C by 0.05 mmol/L [44]. In comparison, the main sources of meat in the local Han population are pigs, chickens and ducks. They also like to use animal oil to cook foods and eat fat meat, animal offal, brain ridge and pith which contain abundant saturated fatty acid. 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 cardiovascular disease [32-34].

In the current study, we also found that the percentages of alcohol consumption were higher in Han than in Jing nationalities ($P < 0.001$). Many epidemiological studies reported that low-to-moderate of alcohol consumption has been consistently associated with reduced CAD risk that is generally attributed to the beneficial effects of alcohol on lipids [45]. A meta-analysis stated that 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 [46]. However, negative effect with heavy drinking also needs to be honored. The study showed that heavy alcohol consumption is toxic for the cardiovascular system, increasing the incidence of total and cardiovascular mortality, CAD, peripheral artery disease, heart failure, stroke, hypertension, dyslipidemia, and diabetes mellitus [47]. In addition, the results of exposure to different dietary habits and environmental factors probably further modify the association of genetic variations and serum lipid levels in our study populations.

There are some potential limitations in the current study. First, this study is the first report of the association between the *SLC39A8* rs971752 SNP and serum lipid levels. Therefore, further studies with larger samples are needed to replicate our discoveries in other populations. Second, lifestyle, diet pattern and physical activities are important factors for lipid regulation. But the cross-sectional study design make us were not able to control the effect during the statistical analysis due to they were self-reported and difficult to classify. Third, although we discovered significant association of the *SLC39A8* rs971752 SNP and serum lipid levels, there are still numerous unmeasured genetic and environmental factors and their interactions. Finally, we recognized the limited power to provide an understanding of full impact of the *SLC39A8* rs971752 SNP on lipid metabolism.

In conclusion, the present study showed that the genotypic and allelic frequencies of the *SLC39A8* rs971752 SNP were different between the Jing and Han populations. The association of the *SLC39A8* rs971752 SNP and serum lipid levels was found in the Jing but not in the Han populations. The G allele carriers had higher serum TG levels in Jing females and lower TC, HDL-C and LDL-C levels in Jing males than the G allele non-carriers. These findings suggest that the association between the *SLC39A8* rs971752 SNP and serum lipid levels might have ethnic- and/or sex-specificity.

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Disclosure of conflict of interest

None.

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