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Original Article

Association of the *BTNL2* rs9268480 SNP and several environmental factors with serum lipid profiles in the Jing and Han populations

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Abstract: Hyperlipidemia-related mechanisms have been associated with damage to the cardiovascular disease (CVD). Here, we discuss potential explanations for the higher prevalence of hyperlipidemia in the Jing and Han populations. Although genetic and environmental factors are the triggers, the search for the ethnic and gender related factors that explain the increased susceptibility of hyperlipidemia is a promising area for research. Ethnicity and gender differences could be the major confounding variable to prove genetic associations. Despite that, we investigated the ethnic and sex-specific association between the butyrophilin-like 2 gene (*BTNL2*) rs9268480 single nucleotide polymorphism (SNP) and several environmental factors with serum lipid profiles in the Jing and Han populations. Genotypes of the rs9268480 SNP, clinical and biochemical measurements were characterized in a total of 2503 subjects (1148 Jing and 1355 Han). Jing populations had higher serum total cholesterol (TC), triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) levels and lower apolipoprotein (Apo) A1 levels and the ratio of ApoA1 to ApoB than in Han. The frequency of susceptibility alleles of rs9268480 C > T were significantly different between the two populations (20.86% *vs.* 18.16%; $P = 0.016$), and between males and females in Jing (17.18% *vs.* 24.65%; $P < 0.001$) and Han (16.57% *vs.* 19.88%; $P = 0.026$) populations. The minor T allele carriers of *BTNL2* rs9268480 SNP was a risk allele for dyslipidemia, especially higher serum TG levels in ethnic and sexually dimorphic subgroup. These results suggested that the genetic variant of rs9268480 C > T and several environmental factors were associated with hyperlipidemia, and there may be a ethnic- and/or sex-specific association of this SNP.

Keywords: Ethnic and sexual dimorphic association, butyrophilin-like 2 gene (*BTNL2*), single nucleotide polymorphism, lipids, environmental factors

Introduction

Serum lipid and lipoprotein levels [1-3] have proven among the most potent and best substantiated risk for atherosclerosis [4] in cardiovascular diseases (CVD) in particular [5, 6], which leading causes of morbidity and mortality worldwide [7-9]. Several large statin trials and meta-analyses have demonstrated a reduction in low-density lipoprotein cholesterol (LDL-C) and cardiovascular morbidity and mortality [10-15]. Some same statin-trials have also highlighted the significance of residual cardiovascular risk after treatment of LDL-C to target levels. This reflects the complex nature of residual cardiovascular risk. This residual risk is partially due to high triglyceride (TG) despite achievement of LDL-C goals with statin therapy. In subjects with the metabolic syndrome, elevation of plasma TG levels occurs most often in the presence of several environmental factors such as visceral (abdominal) obesity and a diet rich in calories, carbohydrates, and saturated fats [16-18]. Severe elevation of plasma TG levels can result from heritability [19-21]. Although both environmental and genetic factors are the triggers, the search for the ethnic and gender related factors that explain the increased susceptibility of hyperlipidemia is a promising area for research [22-24]. Ethnicity and gender differences could be a major confounding variable to prove genetic associations.

Butyrophilin-like 2 gene (*BTNL2*; Gene ID: 562-44; MIM: 606000; Cytogenetic location: 6p21.-

32; Genomic coordinates (GRCh38):6:32, 393, 338-32, 408, 878), a member of the immunoglobulin gene superfamily with homology to butyrophilin genes (e.g., BTN1A1; 601610) [25]. The BTNL2 protein contains a small hydrophobic sequence that may be a signal peptide, 2 immunoglobulin domains, a 7-amino acid heptad repeat, and 2 more immunoglobulin domains. Unlike other butyrophilins, BTNL2 lacks a C-terminal B30-2 domain. RT-PCR analysis detected BTNL2 expression in mouse skeletal muscle, duodenum, ileum, cecum, ascending colon, descending colon, and appendix. Nguyen *et al.* found that a putative receptor for mouse BTNL2, distinct from Cd28 (186760) and Ctla4 (123890), was expressed on activated B and T cells. BTNL2 appeared to regulate T-cell activation, a finding with implications for the role of BTNL2 in inflammatory autoimmune diseases [26]. Valentonyte *et al.* identified a G-to-A transition at position-1 of a splice donor site (rs2076530) in the BTNL2 gene. The change resulted in the use of an alternative splice site located 4 bp upstream. The loss of 4 bases from the cDNA transcribed from the A allele resulted in a frameshift and a premature stop in the downstream exon. In the corresponding protein product, the 118 C-terminal residues in the nontruncated protein were replaced by 5 different amino acids. The mutant protein lacks the C-terminal IgC domain and transmembrane helix, thereby disrupting localization of the protein [27]. However, the effect of this rs9268480 SNP on lipid profiles was not functionally validated and the mechanism was yet unclear. Furthermore, the reproducibility of this association has not been detected in the Jing and Han populations so far.

China has a majority population of Han ethnicity and 55 officially recognized ethnic minorities [28]. The Jing ethnic group is an isolated minority in the Guangxi Zhuang Autonomous Region, China. The Jing population is the only oceanic ethnic group in China, with a very small population size of 28,199 reported in 2010 [29]. In the early 16th century, the Jing ancestors emigrated from Vietnam to China to first settle on the three islands of Wanwei, Wutou and Shanxin in Dongxing City, where almost all of the Jing population now live [29]. The recent molecular anthropological data showed that Jing has much closer genetic relationship with the other minorities in Guangxi than with the Han nationality [30]. In addition, several previous studies have revealed that the associations of variants in several lipid-related genes and lipid profiles are significantly different between the Jing and Han populations and their gender subgroups [31, 32]. Despite that, we investigated the ethnic and sex-specific association between *BTNL2* rs9268480 mutant and several environmental factors with serum lipid profiles in the Jing and Han populations.

Materials and methods

Ethical approval

The study design was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University. Informed consent was taken from all participants.

Subjects

A total of 2503 subjects including 1148 unrelated subjects of Jing nationality comprising 582 males and 566 females and 1355 unrelated participants of Han nationality including 706 men and 649 women were randomly selected from our previous stratified randomized samples. All of them were rural agricultural and/or fishery workers residing in three islands of Wanwei, Wutou and Shanxin, Dongxing City, Guangxi Zhuang Autonomous Region, People's Republic of China. The age ranged from 15 to 80 years. The mean age of Jing participants was 57.28±13.52 years, whereas that of Han subjects was 56.92±12.95 years. All participants were essentially healthy and had no evidence of diseases related to atherosclerosis, CVD and diabetes. Any participant had a history of taking medications known to affect lipid profiles (lipid-lowering drugs such as statins or fibrates, beta blockers, diuretics, or hormones) was excluded before the blood sample was taken.

Epidemiological survey

The survey was carried out using internationally standardized methods, following a common protocol [33, 34]. Information on demographics, socioeconomic status, and lifestyle factors was collected with standardized questionnaires. The intake of alcohol was quantified as the number of liang (about 50 g) of rice wine,

Table 1. Demographic, clinical and anthropometric parameters and lipid profiles between the Jing and Han populations

Parameter	Jing (n = 1148)	Han (n = 1355)	t (x^2)	P
Male/Female	582/566	706/649	0.492	0.483
Age (year)	57.28±13.52	56.92±12.95	0.680	0.497
Height (cm)	158.17±7.96	157.97±7.98	0.621	0.535
Weight (kg)	58.76±10.15	57.06±9.41	4.340	0.000
Body mass index (kg/m^2)	23.42±3.20	22.83±3.16	4.611	0.000
Waist circumference (cm)	80.42±9.30	77.93±8.72	6.853	0.000
Cigarette smoking [n (%)]				
Non-smoker	933 (81.3)	1028 (75.9)		
< 20 cigarettes/day	55 (4.8)	67 (4.9)		
≥ 20 cigarettes/day	160 (13.9)	260 (19.2)	12.559	0.002
Alcohol consumption [n (%)]				
Non-drinker	884 (77.0)	911 (67.2)		
< 25 g/day	138 (12.0)	98 (7.2)		
≥ 25 g/day	126 (11.0)	346 (25.5)	93.247	0.000
Systolic BP (mmHg)	131.62±21.46	134.68±57.62	-1.701	0.089
Diastolic BP (mmHg)	80.53±10.56	81.39±10.45	-2.036	0.042
Pulse pressure (mmHg)	51.09±17.20	53.29±16.11	-1.279	0.201
Glucose (mmol/L)	6.70±1.75	6.63±1.10	1.262	0.207
Total cholesterol (mmol/L)	5.15±0.91	4.89±0.86	7.391	0.000
Triglyceride (mmol/L)	1.43 (1.13)	1.31 (1.07)	-4.673	0.000
HDL-cholesterol (mmol/L)	1.78±0.53	1.80±0.45	-0.947	0.344
LDL-cholesterol (mmol/L)	2.86±0.43	2.82±0.43	2.168	0.030
Apolipoprotein (Apo) A1 (g/L)	1.31±0.24	1.33±0.20	-3.024	0.003
ApoB (g/L)	1.06±0.25	1.04±0.24	1.737	0.083
ApoA1/ApoB	1.30±0.39	1.35±0.38	-3.000	0.003

BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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 a 5-minute 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 using a portable balance scale. Subjects were weighed in a minimum of clothing with shoes off. Height was measured, to the nearest 0.5 cm, using a stadiometer. From these two measurements body mass index (BMI, kg/m^2) was calculated.

Biochemical measurements

A venous blood sample of 5 mL was obtained from all subjects after at least 12 hours of fasting. A two fifth of the sample (2 mL) was collected into glass tubes and used to determine lipid profiles. The remaining three fifth of the sample (3 mL) was transferred to the tubes contained anticoagulants (4.80 g/L citric acid, 14.70 g/L glucose, and 13.20 g/L tri-sodium citrate) and was used to extract deoxyribonucleic acid (DNA). Measurements of serum total cholesterol (TC), TG, high-density lipoprotein-cholesterol (HDL-C), and LDL-C levels in the samples were performed by 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 apolipoprotein (Apo) A1 and ApoB levels were detected 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 [34, 35].

DNA amplification and genotyping

Genomic DNA was isolated from peripheral blood leukocytes using the phenol-chloroform method [37, 38]. The extracted DNA was stored at 4°C until analysis. Genotyping of the *BTNL2* rs9268480 SNP was performed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). PCR amplification was performed using 5'-GTGGCAGGAGCAGGTATT-3' and 5'-TCGTCAGAGTGGGAGAAG-3' (Sangon, Shanghai, People's Republic of China) as

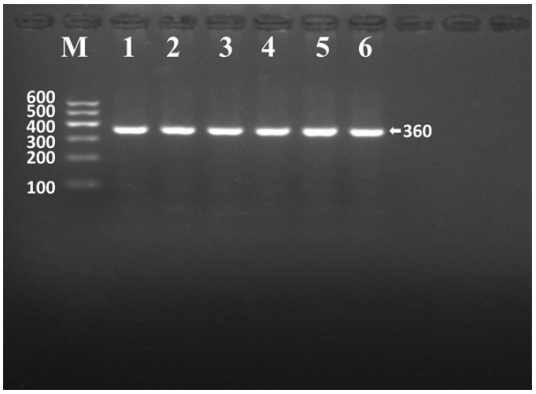

Figure 1. Electrophoresis of PCR products of the samples. Lane M is the 100 bp Marker ladder; Lane 1-6 are samples, the 360-bp bands are the target genes.

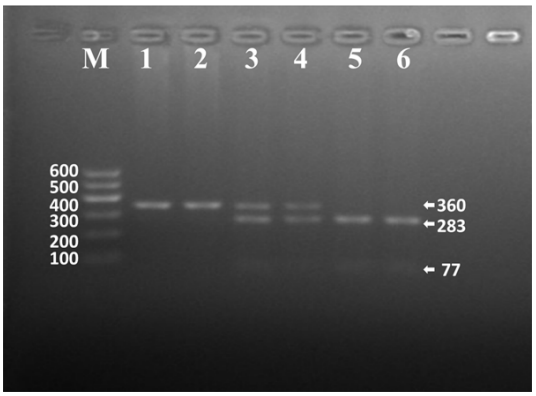

Figure 2. Genotyping of the *BTNL2* rs9268480 SNP. Lane M is the 100 bp Marker Ladder; Lanes 1 and 2, TT genotype (360-bp); Lanes 3 and 4, CT genotype (360-, 283- and 77-bp); and lanes 5 and 6, CC genotype (283- and 77-bp).

the forward and reverse primer pairs; respectively. Each amplification reaction was performed in a total volume of 25 μL, containing 10 × PCR buffer (1.8 mM $MgCl_2$) 2.5 μL, 1 U *Taq* polymerase, 2.5 mmol/L of each dNTP (Tiangen, Beijing, People's Republic of China) 2.0 μL, 20 pmol/L of each primer and 50 ng of genomic DNA, processing started with 95°C for 7 min and followed by 50 s of denaturing at 95°C, 45 s of annealing at 60°C and 1 min of elongation at 72°C for 33 cycles. The amplification was completed by a final extension at 72°C for 7 min. Then 10 U of enzyme *MvaI* was added directly to the PCR products (10 μL) and digested at 37°C overnight. After restriction enzyme digestion of the amplified DNA, genotypes were identified by electrophoresis on 2% ethidium-bromide stained agarose gels and visualizing with ultraviolet illumination. Genotypes were scored by an experienced reader blinded to the epidemiological and lipid results. Six samples (CC, CT and TT genotypes in two; respectively) detected by the PCR-RFLP were also confirmed by direct sequencing. The PCR product was purified by low melting point gel electrophoresis and phenol extraction, and then the DNA sequences were analyzed 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 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. The individuals with TC > 5.17 mmol/L and/or TG > 1.70 mmol/L were defined as hyperlipidemic [39]. Hypertension was diagnosed according to the criteria of 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension [40, 41]. The diagnostic criteria 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 [42].

Statistical analyses

Epidemiological data were recorded on a predesigned form and managed with Excel software. Data analysis was performed using the software SPSS version 19.0 (SPSS Inc., Chicago, Illinois). Quantitative variables were expressed as mean ± standard deviation (serum TG levels were presented as medians and interquartile ranges). Qualitative variables were expressed as percentages. Allele frequency was determined via direct counting, and the standard goodness-of-fit test was used to test the Hardy-Weinberg equilibrium. Difference in genotype distribution between the groups was obtained using the chi-square test. The difference in general characteristics between Jing and Han was tested by the Student's unpaired *t*-test. The association of genotypes and serum lipid parameters was tested by analysis of covariance (ANCOVA). Sex, age, BMI, blood pressure, alcohol consumption, cigarette smok-

Table 2. Comparison of the genotype and allele frequencies of *BTNL2* rs9268480 SNP in the Jing and Han populations [n (%)]

Group	n	Genotype			Allele		HWP
		CC	CT	TT	C	T	
Jing	1148	718 (62.54)	381 (33.19)	49 (4.27)	1817 (79.14)	479 (20.86)	0.863
Han	1355	915 (67.53)	388 (28.63)	52 (3.84)	2218 (81.84)	492 (18.16)	0.180
x^2			6.846		5.827		
P			0.033		0.016		
Jing	1148						
Male	582	404 (69.42)	156 (26.80)	22 (3.78)	964 (82.82)	200 (17.18)	0.161
Female	566	314 (55.48)	225 (39.75)	27 (4.77)	853 (75.35)	279 (24.65)	0.095
x^2			24.069		19.368		
P			0.000		0.000		
Han	1355						
Male	706	498 (70.54)	182 (25.78)	26 (3.68)	1178 (83.43)	234 (16.57)	0.072
Female	649	417 (64.25)	206 (31.74)	26 (4.01)	1040 (80.12)	258 (19.88)	0.929
x^2			6.268		4.970		
P			0.044		0.026		

ing were adjusted for the statistical analysis. Multivariate linear regression analysis with stepwise modeling was performed to evaluate the association of lipid profiles with genotypes (CC = 1, CT = 2 and TT = 3) and several environment factors in the combined population of Jing and Han, Jing, Han, males and females; respectively. A *P* value of less than 0.05 was considered statistically significant.

Results

General characteristics and lipid profiles

The general characteristics and lipid profiles between the Jing and Han populations are summarized in **Table 1**. The values of weight, body mass index, waist circumference, and the levels of TC, TG and LDL-C were higher in Jing than in Han ($P < 0.05$-0.001), whereas the percentage of cigarette smoking, alcohol consumption, the levels of diastolic blood pressure, Apo A1 and the ratio of ApoA1 to Apo B were lower in Jing than in Han ($P < 0.05$-0.001). There were no significant differences in the gender ratio, age structure, height, systolic blood pressure, pulse pressure, blood glucose, HDL-C and Apo B levels between the two ethnic groups ($P > 0.05$ for all).

Results of electrophoresis and genotyping

After the genomic DNA of the samples were amplified by 2% agarose gel electrophoresis, the products of 360 bp nucleotide sequences were found in all samples (**Figure 1**). The genotypes identified were named according to the presence (C allele) or absence (T allele) of the enzyme restriction sites. Thus CC genotype was homozygote for the presence of the sites (bands at 283- and 77-bp). CT genotype was heterozygote for the presence and absence of the site (bands at 360-, 283- and 77-bp), and TT genotype was homozygote for the absence of the site (bands at 360-bp; **Figure 2**). The genotypes of the rs9268480 SNP were followed by the Hardy-Weinberg equilibrium.

Genotypic and allelic frequencies

The genotypic and allelic frequencies of *BTNL2* rs9268480 SNP are shown in **Table 2**. The frequency of susceptibility genotype and allele of rs9268480 (C > T) were significantly different between the two populations (CC, 62.54% *vs.* 67.53%; CT, 33.19% *vs.* 28.63%; TT, 4.27% *vs.* 3.84%; $P = 0.033$; C, 79.14% *vs.* 81.84%; T, 20.86% *vs.* 18.16%; $P = 0.016$) and between males and females in Jing (CC, 69.42% *vs.* 55.48%; CT, 26.80% *vs.* 39.75%; TT, 3.78% *vs.* 4.77%; $P < 0.001$; C, 82.82% *vs.* 75.35%; T, 17.18% *vs.* 24.65%; $P < 0.001$) and Han (CC, 70.54% *vs.* 64.25%; CT, 25.78% *vs.* 31.74%; TT, 3.68% *vs.* 4.01%; $P = 0.044$; C, 83.43% *vs.* 80.12%; T, 16.57% *vs.* 19.88%; $P = 0.026$) populations; respectively.

Results of sequencing

The results were shown as CC, CT and TT genotypes by PCR-RFLP, the CC, CT and TT geno-

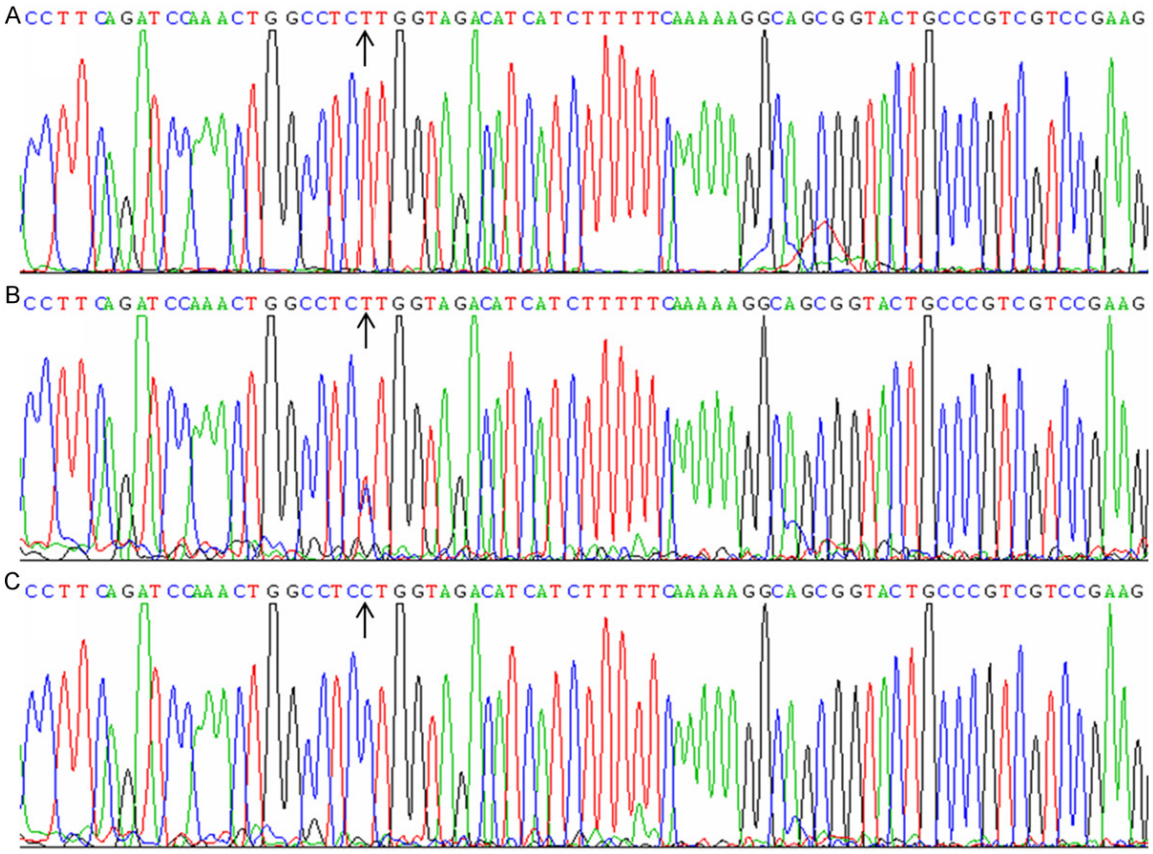

Figure 3. A part of the nucleotide forward sequence of the *BTNL2* rs9268480 SNP. A. TT genotype; B. CT genotype; C. CC genotype.

Table 3. Comparison of the genotypes and lipid profiles in 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	1148							
CC	718	5.10±0.87	1.40 (1.10)	1.81±0.45	2.79±0.44	1.31±0.24	0.99±0.20	1.36±0.41
CT	381	5.21±0.96	1.48 (1.20)	1.79±0.47	2.86±0.42	1.30±0.23	1.06±0.24	1.30±0.39
TT	49	5.30±0.96	1.50 (1.23)	1.71±0.40	2.91±0.40	1.28±0.20	1.06±0.26	1.29±0.38
F		1.919	18.767	1.679	3.661	0.534	1.400	0.267
P		0.147	0.000	0.187	0.026	0.587	0.247	0.766
Han	1355							
CC	915	4.87±0.87	1.29 (1.03)	1.85±0.68	2.85±0.43	1.35±0.20	1.04±0.25	1.35±0.39
CT	388	4.90±0.84	1.39 (1.11)	1.79±0.56	2.87±0.42	1.33±0.20	1.04±0.23	1.35±0.37
TT	52	4.93±0.82	1.43 (1.13)	1.77±0.51	2.92±0.42	1.32±0.20	1.05±0.22	1.30±0.28
F		0.171	16.783	1.422	0.523	0.868	0.135	0.236
P		0.843	0.000	0.242	0.593	0.420	0.874	0.790

types were also confirmed by direct sequencing (**Figure 3**); respectively.

Genotypes and lipid profiles

As shown in **Table 3**, serum TG and LDL-C levels in Jing were different among the genotypes ($P <$ 0.05-0.001). The T allele carriers had higher serum TG and LDL-C levels than the T allele non-carriers. Serum TG levels was different among the genotypes in Han ($P < 0.001$). The T allele carriers had higher serum TG levels than the T allele non-carriers. Subgroup analyses showed that serum TC and TG levels in Jing

Table 4. Comparison of the genotypes and lipid profiles between males and females 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/Male	582							
CC	404	5.05±0.79	1.42 (1.10)	1.78±0.45	2.79±0.37	1.30±0.22	1.02±0.19	1.30±0.43
CT	156	5.20±0.89	1.50 (1.20)	1.78±0.51	2.84±0.39	1.28±0.24	1.06±0.24	1.29±0.36
TT	22	5.55±0.48	1.51 (1.23)	1.69±0.42	2.91±0.21	1.26±0.18	1.07±0.25	1.28±0.41
F		4.088	6.330	0.930	0.779	0.090	0.473	0.024
P		0.017	0.002	0.395	0.460	0.914	0.624	0.976
Jing/Female	566							
CC	314	5.11±0.96	1.32 (1.09)	1.86±0.44	2.79±0.51	1.33±0.27	0.97±0.21	1.41±0.44
CT	225	5.16±0.96	1.40 (1.18)	1.80±0.45	2.88±0.44	1.31±0.22	1.06±0.24	1.31±0.34
TT	27	5.22±1.00	1.42 (1.24)	1.72±0.39	2.91±0.50	1.29±0.22	1.06±0.27	1.30±0.37
F		0.314	9.862	2.429	1.777	0.773	1.504	0.832
P		0.730	0.000	0.089	0.170	0.462	0.223	0.436
Han/Male	706							
CC	498	4.84±0.91	1.27 (0.99)	1.73±0.55	2.83±0.44	1.36±0.22	1.05±0.25	1.35±0.40
CT	182	4.84±0.76	1.38 (1.07)	1.73±0.54	2.89±0.45	1.33±0.20	1.06±0.20	1.33±0.40
TT	26	4.85±0.82	1.43 (1.07)	1.69±0.57	2.91±0.38	1.29±0.14	1.08±0.22	1.22±0.21
F		0.249	8.148	0.051	1.321	0.417	0.053	0.326
P		0.780	0.000	0.950	0.267	0.659	0.949	0.722
Han/Female	649							
CC	417	4.91±0.82	1.31 (1.06)	2.00±0.74	2.83±0.45	1.36±0.24	1.02±0.23	1.38±0.33
CT	206	4.95±0.90	1.43 (1.12)	1.84±0.57	2.86±0.43	1.34±0.19	1.02±0.25	1.37±0.34
TT	26	5.00±0.83	1.47 (1.13)	1.83±0.48	2.95±0.39	1.32±0.20	1.03±0.24	1.35±0.38
F		0.378	7.806	2.624	1.438	1.803	1.169	2.927
P		0.685	0.000	0.073	0.238	0.166	0.311	0.054

males and TG levels in Jing females were different among the genotypes ($P < 0.05$-0.001), the T allele carrier had higher serum TC, TG levels than the T allele non-carriers. Serum TG levels in Hanmales and Han females were different among the genotypes ($P < 0.001$ for each), the T allele carriers had higher serum TG levels than the T allele non-carriers (**Table 4**).

Relative factors for serum lipid parameters

Multiple linear regression analysis showed that serum TC, TG and LDL-C levels in the combined population of Jing and Han; TC, TG and LDL-C levels in Jing; and TG levels in Han were correlated with the genotypes of the *BTNL2* rs9268480 SNP ($P < 0.05$-0.001; **Table 5**). When the correlation of serum lipid parameters and the genotypes was analyzed according to sex, we showed that serum TC and TG levels in Jing males; serum TG, HDL-C and LDL-C levels in Jing females; serum TG levels in Han males; and TG and ApoA1 levels and the ratio of ApoA1 to ApoB in Han females were correlated with the genotypes ($P < 0.05$-0.001; **Table 6**).

Serum lipid parameters were also associated with gender, age, BMI, systolic and diastolic blood pressure, pulse pressure, fasting blood glucose levels, cigarette smoking and alcohol consumption in both ethnic groups or in males and females ($P < 0.05$-0.001; **Tables 5** and **6**).

Discussion

Earlier questions regarding the generalizability of CVD risk and lipid traits to a more heterogeneous populace (i.e., varied populations) have been quelled by the replication of similar risk and lipid profiles and features in contemporary racially and ethnically diverse population surveys. Several reports have suggested that blacks have lower LDL-C concentrations and less hypercholesterolemia than whites. The

Table 5. Correlations between lipid profiles and relative risk factors in the Jing and Han populations

Lipid	Risk factor	B	Std. error	Beta	*t*	*P*
Jing and Han						
TC	Genotype	0.060	0.030	0.038	1.974	0.048
	Ethnic group	-0.255	0.034	-0.143	-7.502	0.000
	Age	0.007	0.001	0.110	5.577	0.000
	Height	-0.009	0.002	-0.085	-4.375	0.000
	Diastolic BP	0.005	0.002	0.057	2.960	0.003
	Glucose	0.127	0.012	0.205	10.640	0.000
TG	Genotype	0.253	0.030	0.151	8.311	0.000
	Gender	-0.150	0.049	-0.079	-3.035	0.002
	Age	-0.009	0.001	-0.123	-5.949	0.000
	Height	-0.026	0.003	-0.217	-7.889	0.000
	Waist circumference	0.042	0.004	0.403	10.617	0.000
	Body mass index	-0.044	0.011	-0.149	-4.080	0.000
	Cigarette smoking	0.270	0.026	0.216	10.282	0.000
	Diastolic BP	0.009	0.002	0.099	5.329	0.000
	Glucose	0.109	0.012	0.165	9.039	0.000
HDL-cholesterol	Ethnic group	-0.081	0.020	-0.081	-4.147	0.000
	Gender	0.102	0.023	0.102	4.476	0.000
	Waist circumference	-0.016	0.001	-0.291	-14.559	0.000
	Cigarette smoking	-0.076	0.015	-0.115	-5.155	0.000
	Alcohol consumption	0.119	0.015	0.189	8.044	0.000
	Diastolic BP	0.003	0.001	0.055	2.830	0.005
LDL-cholesterol	Genotype	0.041	0.015	0.054	2.766	0.006
	Ethnic group	0.038	0.017	0.045	2.281	0.023
	Age	0.003	0.001	0.078	3.863	0.000
	Height	-0.003	0.001	-0.056	-2.816	0.005
	Diastolic BP	0.003	0.001	0.081	4.100	0.000
	Glucose	0.044	0.006	0.147	7.439	0.000
ApoA1	Gender	0.033	0.011	0.075	3.110	0.002
	Weight	-0.003	0.001	-0.116	-3.022	0.003
	Waist circumference	-0.002	0.001	-0.096	-2.621	0.009
	Alcohol consumption	0.062	0.006	0.225	10.116	0.000
	Diastolic BP	0.001	0.000	0.057	2.898	0.004
	Pulse pressure	0.000	0.000	0.041	2.113	0.035
	Glucose	-0.016	0.003	-0.102	-5.243	0.000
ApoB	Age	0.002	0.000	0.104	5.248	0.000
	Height	-0.002	0.001	-0.049	-2.429	0.015
	Waist circumference	0.006	0.001	0.214	10.430	0.000
	Diastolic BP	0.001	0.000	0.052	2.588	0.010
ApoA1/ApoB	Gender	0.073	0.021	0.094	3.434	0.001
	Age	-0.001	0.001	-0.044	-2.094	0.036
	Height	0.003	0.001	0.065	2.452	0.014
	Waist circumference	-0.012	0.001	-0.282	-14.228	0.000
	Alcohol consumption	0.072	0.011	0.148	6.720	0.000
	Glucose	-0.021	0.005	-0.080	-4.118	0.000

CARDIA study identified the prevalence of high LDL-C levels in young adults; LDL-C exceeded 160 mg/dl in 10% and 5% of young black men and women, respectively, compared with 9% and 4% of young white men and women. HDL-C levels were higher in black men than in white men. ApoA1, as known risk factor for CVD, and levels are two- to threefold higher in blacks [43]. In the present study, we showed that Jing population had higher serum TC, TG and LDL-C levels and lower ApoA1 levels and the ratio of ApoA1 to ApoB than in Han. Jing is the only Chinese minority for coastal fisheries, meanwhile is the only sea people in China. In this case, it has a very special lifestyle and dietary habits compared with the other landlocked nationalities. Their marriages were family-arranged in the old days when they sing antiphonal songs to look for the other half. After antiphonal singing, if the boy's into the girl he would kick sand toward her while approaching her. If the girl feel the same she would kick back, which means engagement. While the formal engagement ceremony and wedding they need pork, cake, tea, wine, glutinous rice as gifts. Jing stays endogamy, intermarriage with Han or Zhuang people is seldom happened. Jing people don't get married with someone sharing the same last name, also cross-cousin marriage is

Jing						
TC	Genotype	0.091	0.044	0.058	2.065	0.039
	Gender	0.262	0.064	0.145	4.087	0.000
	Age	0.019	0.002	0.290	9.183	0.000
	Body mass index	0.069	0.014	0.243	4.784	0.000
	Waist circumference	-0.017	0.005	-0.171	-3.260	0.001
	Cigarette smoking	0.103	0.042	0.080	2.422	0.016
	Alcohol consumption	0.153	0.044	0.113	3.503	0.000
	Pulse pressure	-0.008	0.002	-0.147	-4.836	0.000
	Glucose	0.101	0.015	0.195	6.898	0.000
TG	Genotype	0.254	0.041	0.165	6.237	0.000
	Gender	-0.242	0.069	-0.138	-3.508	0.000
	Age	-0.006	0.002	-0.096	-3.113	0.002
	Height	-0.027	0.004	-0.242	-6.172	0.000
	Waist circumference	0.031	0.003	0.330	11.218	0.000
	Cigarette smoking	0.247	0.038	0.198	6.425	0.000
	Diastolic BP	0.008	0.002	0.091	3.300	0.001
	Glucose	0.085	0.013	0.169	6.349	0.000
HDL-cholesterol	Gender	0.162	0.032	0.179	5.064	0.000
	Age	0.003	0.001	0.090	3.012	0.003
	Weight	0.006	0.003	0.126	2.147	0.032
	Waist circumference	-0.022	0.003	-0.452	-8.376	0.000
	Alcohol consumption	0.184	0.021	0.270	8.747	0.000
LDL-cholesterol	Genotype	0.066	0.022	0.089	3.048	0.002
	Age	0.004	0.001	0.135	4.635	0.000
	Diastolic BP	0.003	0.001	0.061	2.102	0.036
	Glucose	0.025	0.007	0.102	3.509	0.000
ApoA1	Weight	-0.004	0.001	-0.190	-6.451	0.000
	Alcohol consumption	0.043	0.010	0.120	4.079	0.000
	Systolic BP	0.001	0.000	0.071	2.436	0.015
	Glucose	-0.018	0.004	-0.132	-4.517	0.000
ApoB	Age	0.003	0.001	0.165	5.788	0.000
	Body mass index	0.016	0.002	0.204	7.138	0.000
ApoA1/ApoB	Age	-0.004	0.001	-0.148	-4.815	0.000
	Waist circumference	-0.011	0.001	-0.272	-9.500	0.000
	Alcohol consumption	0.077	0.017	0.132	4.596	0.000
	Pulse pressure	0.001	0.001	0.063	2.042	0.041
Han						
TC	Height	-0.008	0.003	-0.070	-2.485	0.013
	Cigarette smoking	-0.084	0.030	-0.078	-2.802	0.005
	Systolic BP	0.001	0.000	0.079	2.951	0.003
	Diastolic BP	0.004	0.002	0.053	2.004	0.045
	Glucose	0.218	0.020	0.279	10.773	0.000
TG	Genotype	0.254	0.045	0.141	5.678	0.000
	Age	-0.011	0.002	-0.148	-5.676	0.000
	Weight	-0.025	0.005	-2.234	-5.020	0.000
	Waist circumference	0.045	0.005	0.391	8.626	0.000
	Cigarette smoking	0.286	0.033	0.228	8.694	0.000
	Diastolic BP	0.009	0.002	0.097	3.833	0.000

strictly forbidden. This kind of breeding with exclusive indicates that some hereditary characteristics and genotypes of lipid metabolism-related genes in this population may be different from those in Han people. The Human Project has failed to identify any genotype clearly identifies race and the similarity of the genetic code for all persons is > 99% [44]. Thus, race is poor proxy for genotypes, and exists only as a sociopolitical construct. Ultimately, race and ethnicity are less risk factors and more risk markers, placeholders for more physiologic risks. The continued elucidation of nuances in CVD as a function of varied populations and the discovery of more precise pathophysiologic considerations are appropriate, but discussion of race and ethnicity in medicine must rigorously avoid polarization and the further perpetuation of disparate health care.

The frequency spectrum of *BTNL2* rs9268480 mutation varied significantly among different races/ethnicities. According to the Hap Map data, the minor allele T frequency of the SNP was 17.07% in Peking Chinese, 9.88% in Japanese, 12.50% in Yoruba, 34.07% in European population, 73.3% in Italy. In the current study, we showed that the frequency of susceptibility alleles of rs9268480 C > T were significantly different between the two populations

	Glucose	0.173	0.023	0.191	7.474	0.000
HDL-cholesterol	Gender	0.114	0.034	0.107	3.396	0.001
	Waist circumference	-0.014	0.002	-0.233	-8.684	0.000
	Cigarette smoking	-0.112	0.021	-0.167	-5.279	0.000
	Alcohol consumption	0.095	0.021	0.155	4.599	0.000
	Systolic BP	0.001	0.000	0.056	2.072	0.038
	Diastolic BP	0.004	0.001	0.080	2.918	0.004
	Glucose	-0.032	0.013	-0.066	-2.524	0.012
LDL-cholesterol	Height	-0.006	0.002	-0.120	-4.001	0.000
	Body mass index	-0.021	0.007	-0.158	-2.922	0.004
	Waist circumference	0.010	0.003	0.196	3.579	0.000
	Systolic BP	0.000	0.000	0.054	1.987	0.047
	Diastolic BP	0.004	0.001	0.089	3.264	0.001
	Glucose	0.087	0.010	0.223	8.484	0.000
ApoA1	Weight	-0.005	0.001	-0.225	-8.185	0.000
	Cigarette smoking	-0.015	0.008	-0.061	-1.983	0.048
	Alcohol consumption	0.069	0.007	0.293	9.355	0.000
	Diastolic BP	0.001	0.001	0.072	2.714	0.007
	Glucose	-0.016	0.005	-0.085	-3.253	0.001
ApoB	Gender	-0.030	0.014	-0.063	-2.104	0.036
	Weight	-0.004	0.001	-0.152	-2.862	0.004
	Waist circumference	0.009	0.001	0.325	6.510	0.000
	Diastolic BP	0.002	0.001	0.091	3.396	0.001
	Glucose	0.022	0.006	0.099	3.739	0.000
ApoA1/ApoB	Gender	0.060	0.023	0.079	2.605	0.009
	Waist circumference	-0.012	0.001	-0.285	-10.977	0.000
	Alcohol consumption	0.072	0.013	0.164	5.394	0.000
	Glucose	-0.050	0.009	-0.144	-5.599	0.000

TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo, apolipoprotein; BP, blood pressure.

Table 6. Correlations between lipid profiles and relative risk factors in the males and females of Jing and Han populations

Lipid	Risk factor	B	Std. error	Beta	*t*	*P*
Jing/Male						
TC	Genotype	0.152	0.059	0.102	2.595	0.010
	Age	0.015	0.002	0.255	5.978	0.000
	Body mass index	0.104	0.021	0.388	4.981	0.000
	Waist circumference	-0.028	0.007	-0.329	-4.121	0.000
	Alcohol consumption	0.175	0.040	0.173	4.335	0.000
	Pulse pressure	-0.013	0.002	-0.248	-5.757	0.000
	Glucose	0.080	0.018	0.183	4.529	0.000
TG	Genotype	0.234	0.063	0.134	3.712	0.000
	Age	-0.014	0.003	-0.199	-4.638	0.000
	Height	-0.031	0.006	-0.222	-5.135	0.000
	Waist circumference	0.037	0.004	0.372	9.098	0.000
	Cigarette smoking	0.218	0.043	0.199	5.067	0.000
	Diastolic BP	0.008	0.003	0.087	2.289	0.022
	Glucose	0.107	0.019	0.207	5.711	0.000

(20.86% *vs*. 18.16%; $P = 0.016$) and between males and females in Jing (17.18% *vs*. 24.65%; $P < 0.001$) and Han (16.57% *vs*. 19.88%; $P = 0.026$) populations. The minor T allele carriers of *BTNL2* rs9268480 SNP was a risk allele for dyslipidemia, especially higher serum TG levels in ethnic and sexually dimorphic subgroup. These findings may also partly explain why the prevalence of CVD is higher in females than in males in some ethnic groups.

The relative risk for CVD events associated with elevation of various lipid variables was determined in a nested case-control study from the Nurses' Health Study. Among 32,826 healthy women who provided blood samples at baseline, the multivariable adjusted relative risks (homocysteine and other traditional cardiac risk factors) for the highest quintiles of lipid variables were ApoB (RR, 4.1; 95% CI, 2 to 8.3), LDL-C (RR, 3.1; 95% CI, 1.7 to 5.8), TG (RR, 1.9; 95% CI, 1.0 to 3.9) and low levels of HDL-C (RR, 2.6; 95% CI, 1.4 to 5) [45]. Adverse changes in lipid profiles accompany menopause [46]. Perimenopausal TG levels are the most erratic but follow roughly the same pattern of increase as TC and LDL-C, which increase on average by an absolute 10% from levels at6monthsbeforemenopause. Menopause influences HDL-C less dramatical-

HDL-cholesterol	Age	0.004	0.001	0.123	3.163	0.002
	Body mass index	0.024	0.011	0.160	2.231	0.026
	Waist circumference	-0.024	0.003	-0.512	-7.066	0.000
	Alcohol consumption	0.201	0.021	0.352	9.406	0.000
	Systolic BP	-0.003	0.001	-0.109	-2.753	0.006
LDL-cholesterol	Age	0.003	0.001	0.116	2.599	0.010
	Body mass index	0.042	0.010	0.346	4.244	0.000
	Waist circumference	-0.010	0.003	-0.264	-3.149	0.002
	Alcohol consumption	0.045	0.019	0.098	2.346	0.019
	Pulse pressure	-0.004	0.001	-0.190	-4.244	0.000
	Glucose	0.025	0.008	0.129	3.060	0.002
ApoA1	Height	-0.003	0.001	-0.091	-2.197	0.028
	Waist circumference	-0.005	0.001	-0.222	-5.277	0.000
	Alcohol consumption	0.061	0.011	0.219	5.544	0.000
	Glucose	-0.015	0.005	-0.124	-3.143	0.002
ApoB	Age	0.003	0.001	0.152	3.465	0.001
	Body mass index	0.021	0.003	0.262	6.575	0.000
	Pulse pressure	-0.002	0.001	-0.109	-2.475	0.014
ApoA1/ApoB	Age	-0.003	0.001	-0.088	-2.237	0.026
	Waist circumference	-0.014	0.002	-0.313	-7.927	0.000
	Alcohol consumption	0.096	0.020	0.185	4.691	0.000
Jing/Female						
TC	Age	0.025	0.003	0.318	7.455	0.000
	Weight	0.025	0.008	0.228	3.065	0.002
	Waist circumference	-0.019	0.008	-0.164	-2.277	0.023
	Glucose	0.135	0.024	0.222	5.620	0.000
TG	Genotype	0.243	0.051	0.184	4.751	0.000
	Height	-0.028	0.005	-0.204	-5.059	0.000
	Waist circumference	0.026	0.004	0.291	7.227	0.000
	Cigarette smoking	0.660	0.241	0.107	2.735	0.006
	Glucose	0.059	0.019	0.123	3.144	0.002
HDL-cholesterol	Genotype	-0.062	0.030	-0.082	-2.049	0.041
	Waist circumference	-0.017	0.002	-0.324	-7.893	0.000
	Diastolic BP	0.005	0.002	0.110	2.685	0.007
LDL-cholesterol	Genotype	0.065	0.033	0.079	1.968	0.050
	Age	0.009	0.002	0.230	5.687	0.000
	Glucose	0.043	0.012	0.145	3.587	0.000
ApoA1	Body mass index	-0.008	0.003	-0.105	-2.508	0.012
	Pulse pressure	0.001	0.001	0.095	2.242	0.025
	Glucose	-0.015	0.007	-0.099	-2.323	0.021
ApoB	Age	0.005	0.001	0.230	5.675	0.000
	Body mass index	0.012	0.003	0.162	3.992	0.000
ApoA1/ApoB	Age	-0.05	0.001	-0.162	-3.977	0.000
	Body mass index	-0.023	0.004	-0.213	-5.216	0.000
Han/Male						
TC	Cigarette smoking	-0.091	0.033	-0.097	-2.755	0.006
	Diastolic BP	0.011	0.003	0.130	3.732	0.000
	Pulse pressure	0.001	0.000	0.089	2.556	0.011
	Glucose	0.248	0.027	0.319	9.069	0.000
TG	Genotype	0.273	0.070	0.135	3.884	0.000
	Age	-0.020	0.003	-0.238	-6.109	0.000

ly. HDL-C declines gradually in the two years preceding menopause and then levels off after menopause. The postmenopausal increase in CVD risk may result partly from these lipid alterations.

It is well realized that environmental factors such as dietary patterns, life style, physical inactivity, cigarette smoking and alcohol consumption are all strongly correlated with lipid profiles. In the present study, multivariate linear regression analysis also showed that age, sex, BMI, waist circumference, alcohol consumption, cigarette smoking, and blood pressure were involved in determining serum lipid parameters in both ethnic groups. The values of weight, BMI, waist circumference were higher in Jing than in Han, whereas the percentage of cigarette smoking, alcohol consumption, the levels of diastolic blood pressure were lower in Jing than in Han. These data suggest that the environmental factors also play an important role in determining lipid profiles in our study populations. When talking about diet pattern, rice is Jing people's staple food supplemented with corn, sweet potato, taro and other grains. They prefer glutinous rice and seafood like fish, shrimp, crabs, shellfish and sandworm. Also pigs, chickens and ducks are the main sources of meat. Jing people prefer sweet food such as sweet glutinous

	Weight	-0.036	0.009	-0.288	-4.236	0.000
	Waist circumference	0.057	0.009	0.425	6.495	0.000
	Cigarette smoking	0.233	0.043	0.196	5.409	0.000
	Diastolic BP	0.013	0.004	0.128	3.664	0.000
	Glucose	0.189	0.034	0.191	5.499	0.000
HDL-cholesterol	Waist circumference	-0.018	0.002	-0.271	-7.382	0.000
	Cigarette smoking	-0.106	0.022	-0.182	-4.772	0.000
	Alcohol consumption	0.100	0.022	0.173	4.471	0.000
	Diastolic BP	0.006	0.002	0.122	3.367	0.001
	Pulse pressure	0.001	0.000	0.078	2.175	0.030
LDL-cholesterol	Diastolic BP	0.006	0.001	0.141	3.944	0.000
	Glucose	0.111	0.014	0.289	8.104	0.000
ApoA1	Waist circumference	-0.006	0.001	-0.260	-7.351	0.000
	Cigarette smoking	-0.018	0.008	-0.083	-2.248	0.025
	Alcohol consumption	0.081	0.008	0.368	9.846	0.000
ApoB	Waist circumference	0.006	0.001	0.219	6.083	0.000
	Diastolic BP	0.003	0.001	0.154	4.284	0.000
	Glucose	0.037	0.008	0.173	4.869	0.000
ApoA1/ApoB	Age	0.003	0.001	0.094	2.567	0.010
	Waist circumference	-0.014	0.002	-0.291	-8.112	0.000
	Alcohol consumption	0.079	0.015	0.186	5.208	0.000
	Diastolic BP	-0.003	0.001	-0.083	-2.339	0.020
	Glucose	-0.062	0.013	-0.173	-4.761	0.000
Han/Female						
TC	Height	-0.012	0.005	-0.095	-2.499	0.013
	Glucose	0.201	0.030	0.257	6.776	0.000
TG	Genotype	0.206	0.056	0.135	3.680	0.000
	Weight	-0.021	0.007	-0.223	-3.124	0.002
	Waist circumference	0.041	0.007	0.435	6.116	0.000
	Cigarette smoking	0.404	0.088	0.170	4.568	0.000
	Pulse pressure	-0.006	0.002	-0.103	-2.735	0.006
	Glucose	0.175	0.030	0.219	5.904	0.000
HDL-cholesterol	Waist circumference	-0.010	0.002	-0.178	-4.600	0.000
	Glucose	-0.038	0.019	-0.078	-2.014	0.044
LDL-cholesterol	Age	0.004	0.001	0.101	2.448	0.015
	Height	-0.005	0.003	-0.083	-2.080	0.038
	Glucose	0.064	0.016	0.160	4.054	0.000
ApoA1	Genotype	0.031	0.014	0.086	2.189	0.029
	Body mass index	-0.011	0.002	-0.181	-4.527	0.000
	Alcohol consumption	0.040	0.017	0.088	2.289	0.022
	Diastolic BP	0.002	0.001	0.089	2.228	0.026
	Glucose	-0.022	0.007	-0.117	-2.985	0.003
ApoB	Age	0.003	0.001	0.130	3.306	0.001
	Weight	-0.007	0.002	-0.247	-3.316	0.001
	Waist circumference	0.011	0.002	0.413	5.625	0.001
ApoA1/ApoB	Genotype	0.058	0.024	0.090	2.389	0.017
	Height	0.009	0.002	0.178	4.710	0.000
	Waist circumference	-0.012	0.002	-0.294	-7.683	0.000
	Glucose	-0.044	0.012	-0.131	-3.518	0.000

TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo, apolipoprotein; BP, blood pressure.

rice porridge, mung bean syrup, because they believe sweet food is a symbol for happiness. A kind of fish sauce called nuoc-mam is also popular on Jing people's dinner table, which contains 17 amino acids (8 essential amino acids included of course). Furthermore, the joint effects of different dietary habits and environmental factors probably further modify the association of genetic variations and lipid profiles in our study populations.

Several potential limitations in our study should be considered. First, the number of participants available for MAF of this SNP was not high enough to calculate a strong power as compared with many previous GWAS and replication studies. Second, there are still many unmeasured environmental and genetic factors including omega-3 and/or omega-6 polyunsaturated fatty acids that needed to be considered. Third, the relevance of this finding has to be defined in further high caliber of studies including incorporating the genetic information of this SNP and in vitro functional studies to confirm the impact of a variant on a molecular level.

Conclusions

In conclusion, this study showed that the associations of the *BTNL2* rs9268480 SNP and lipid profiles were different bet-

ween the Jing and Han populations and between males and females in the both ethnic groups. There may be a racial/ethnic- and/or sex-specific association of the *BTNL2* rs9268480 SNP and lipid profiles.

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Disclosure of conflict of interest

The authors have nothing to disclose.

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