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Original Article

Association of *BDNF* rs11030104 SNP and serum lipid levels in two Chinese ethnic groups

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Abstract: The correlation between the *BDNF* rs11030104 single nucleotide polymorphism (SNP) and serum lipid levels has been understudied. The present study was conducted to detect the association of the *BDNF* rs11030104 SNP and several environmental factors with serum lipid levels in the Jing and Han nationalities. Genotypes of the *BDNF* rs11030104 SNP in 709 unrelated subjects of Han and 706 unrelated participants of Jing populations were determined by polymerase chain reaction and restriction fragment length polymorphism combined with gel electrophoresis, and further verified by direct sequencing. There was no significant difference in either genotypic or allelic frequencies between the Han and Jing populations. The genotypic and allelic frequencies of the SNP in Jing but not in Han populations were different between male and female subgroups ($P<0.05$ for each). The levels of serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in the Jing population were different among the genotypes, the G allele carriers had lower TC and LDL-C levels than the G allele non-carriers. Subgroup analyses showed that the differences in serum TC and LDL-C levels among the genotypes were observed in the Jing males but not in females. Serum lipid profiles were also significantly associated with some environmental factors in the Han and Jing populations, or in male and female subgroups of the two ethnic groups ($P<0.05$ for all). Our study exhibited a correlation between the *BDNF* rs11030104 SNP and serum TC and LDL-C levels in the Jing males. These results indicate that there may be a racial/ethnic- and/or sex-specific association of the *BDNF* rs11030104 SNP and serum lipid parameters.

Keywords: Brain-derived neurotrophic factor, single nucleotide polymorphism, serum lipid levels

Introduction

Cardiovascular disease (CVD) is a worldwide public health problem. It has become the leading cause of death in the world over past decades [1]. Moreover, world-wide CVD mortality rates are still rising. Dyslipidemia is the main cause of atherosclerosis, which is inextricably linked with the development of CVD [2]. Serum lipid level is an important risk factor not only for atherosclerosis, but also for CVD, and is associated with a considerable increase in morbidity and mortality. Unfavorable lipid profiles such as elevated levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), apolipoprotein (Apo) B, and low levels of high-density lipoprotein cholesterol (HDL-C) and ApoA1, play an important role for atherosclerosis and CVD. Dyslipidemia is demonstrated to result from multiple genetic and environmental factors and their interaction [3]. Especially, some studies in families and twins showed that 40-60% of the inter-individual diversity in serum lipid phenotypes was illustrated by genetic polymorphism [4-6]. So, it is necessary to explore the relationship between the single nucleotide polymorphism (SNP) and serum lipid levels.

In recent years, genome-wide association studies (GWASes) have shown more than 95 loci associated with dyslipidemia [7, 8]. A study

reported the correlation of SNP in the genomic region of Brain-derived neurotrophic factor (*BNDF*, www.ncbi.nlm.nih.gov/gene, Gene ID: 627; Mim: f113505; Location: Chromosomal 11p14.1) and metabolic disorder. *BDNF*-encodes a member of the nerve growth factor family of proteins. It can promote neuronal survival in the adult brain. Expression of this gene is decreased in Alzheimer's, Parkinson's, and Huntington's disease patients. BDNF plays an important role in the regulation of nervous disorders, stress response, and mood disorders [9-11]. Recently, several studies have shown that *BDNF* is associated with body mass index (BMI), obesity, metabolic syndrome, insulin resistance, and diabetes [12-16]. Hyperlipidemia is a main component of metabolic syndrome. But the relationship between the *BDNF* rs11030104 SNP and serum lipid levels and its effect mechanism are still not clear yet. Moreover, it has never been studied in the Chinese populations so far.

China is a multi-ethnic country with 56 ethnic groups. Han nationality is the largest ethnic group and Jing nationality is one of the other 55 ethnic minorities in south part of China with a small population of 28199 (From the sixth national census statistics of China in 2010). Jing nationality mainly lives in Dongxing city of Guangxi, and is the unique coastal living minority in China. The Jing ancestors immigrated from Vietnam to China in the early stage of 16th century, firstly settled in three islands of Wanwei, Wutou and Sanxin in Dongxing city, where are also the main residence of Jing now. They work in the fishing business and have preserved their custom of ethnic inter-marriage. Seafood is a main part of Jing diet, especially fish and shrimp. There are a lot of differences in geographic culture, dietary habits, lifestyle, genetic background, and custom characteristics between the local Han and Jing nationalities. Some previous studies have showed that associations of variants in a few lipid related genes and serum lipid levels are significantly different between the Jing and Han populations and their gender subgroups [17, 18]. However, the association between the *BDNF* rs11030104 SNP and serum lipid levels has not been previously reported in the Jing population so far. Therefore, the present study evaluated the association between the *BDNF* rs11030104 SNP and several environmental factors with serum lipid levels in the Guangxi Han and Jing populations.

Materials and methods

Research subjects

In total, 706 unrelated participants of Jing nationality (360 males, 50.99%; 346 females, 49.01%) and 709 unrelated participants of Han nationality (362 males, 51.06%; 347 females, 48.94%) were randomly selected from our previous stratified randomized samples. All subjects were fishery workers (Jing) and/or rural agricultural (Han) living in Jiangping Down, 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 57.87±13.88 years, while that of Han subjects was 58.71±12.95 years. All participants were essentially healthy and had no evidence of atherosclerosis, CVD, and diabetes. Any participant that had taken medications which affect serum lipid level (lipid-lowering drugs such as statins or fibrates, beta blockers, diuretics, or hormones) was excluded in this study. The study design was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. Written informed consent was acquired from all participants.

Epidemiological survey

The survey was performed by internationally standardized methods, following a common protocol [19]. Information on demographics, socioeconomic status, healthy history, and lifestyle factors was collected with standardized questionnaires. Alcohol consumption was categorized into groups (<25 g/d and ≥25 g/d). Smoking status was categorized into groups of cigarettes per day (<20 cigarettes/d and ≥20 cigarettes/d). In physical examinations, sitting blood pressure was measured three times using a mercury sphygmomanometer after a 5-10 min rest, and the average of three measurements was recorded. Height, weight and waist circumference were measured in physical examination. BMI (kg/m^2) was calculated as weight in kilograms divided by the square of height in meters.

Table 1. The general characteristics and serum lipid levels between Jing and Han Chinese populations

Parameter	Han	Jing	t (χ^2)	P
Number	709	706		
Male/female	362/347	360/346	0.001	0.980
Age (year)	58.71±12.95	57.87±13.88	1.17	0.244
Height (cm)	1.57±7.86	1.58±7.81	-2.184	0.029
Weight (kg)	56.55±9.43	58.69±9.91	-4.134	0.000
Body mass index (kg/m^2)	22.87±3.12	23.45±3.17	-3.419	0.001
Waist circumference (cm)	77.85±8.86	80.31±9.22	-5.075	0.000
Smoking status [n (%)]				
Non-smoker	536 (76.1)	569 (80.7)		
<20 cigarettes/day	66 (9.4)	47 (6.7)		
≥20 cigarettes/day	102 (14.5)	89 (12.6)	5.064	0.079
Alcohol consumption [n (%)]				
Non-drinker	535 (76.0)	601 (80.6)		
<25 g/day	116 (16.5)	80 (13.9)		
≥25 g/day	53 (7.5)	24 (5.5)	21.368	0.000
Systolic BP (mmHg)	132.77±19.15	130.71±21.20	1.913	0.56
Diastolic BP (mmHg)	81.48±10.37	79.98±10.20	2.728	0.006
Pulse pressure (mmHg)	50.66±15.46	51.30±17.86	-0.664	0.507
Glucose (mmol/L)	6.71±1.15	6.82±1.77	-1.333	0.183
Total cholesterol (mmol/L)	4.92±0.87	5.18±0.90	-5.599	0.000
Triglyceride (mmol/L)	1.56±0.91	1.66±0.89	-2.105	0.035
HDL-C (mmol/L)	1.78±0.52	1.78±0.46	-0.176	0.860
LDL-C (mmol/L)	2.86±0.43	2.82±0.42	1.744	0.081
ApoA1 (g/L)	1.32±0.20	1.29±0.23	2.342	0.019
ApoB (g/L)	1.04±0.24	1.05±0.24	-1.185	0.236
ApoA1/ApoB	1.33±0.38	1.28±0.38	2.461	0.014
UA (μmol/L)	304.14±101.95	325.47±96.09	-4.044	0.000
Scr (μmol/L)	89.74±34.26	84.64±74.01	1.660	0.097

BP, Blood pressure; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; UA, Uric Acid; Scr, Serum Creatinine.

Biochemical measurements

Fasting venous blood samples of 5 ml were obtained from all participants. Serum TC, TG, HDL-C, and LDL-C levels were detected by enzymatic methods with commercially available kits. Serum ApoA1 and ApoB levels were measured by the immunoturbidimetric immunoassay using a commercial kit. All determinations were performed with an auto-analyzer in the Clinical Science Experiment Center of the First Affiliated Hospital of Guangxi Medical University. The remaining sample was transferred into 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).

DNA amplification and genotyping

Genomic DNA was isolated from peripheral blood leukocytes using the phenol-chloroform method [20, 21]. The extracted DNA was stored at 4°C until analysis. The genotypes of the *BDNF* rs11030104 were detected by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). PCR amplification was performed using 5'-TCAGCCATGACCAACTTCTTGA-3' as forward and 5'-TGTGATAAAGAGTCATCCGAAGGT-3' as reverse primer pairs (Sangon, Shanghai, China). Each amplification reaction was performed in a total volume of 25 μl, 13.4 μl of 2 × *Taq*PCR Master Mix (constituent: 0.1 U *Taq* polymerase/μL, 500 μM dNTP each and PCR buffer), nuclease-

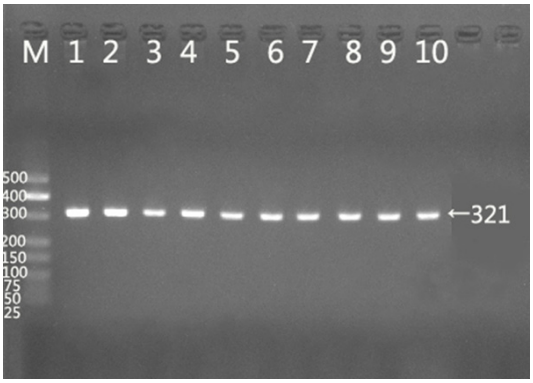

Figure 1. Electrophoresis of PCR products of the *BDNF* rs11030104 polymorphism. Lane M, 25 bp marker ladder; Lanes 1-10, the samples. The 321 bp bands are the PCR products.

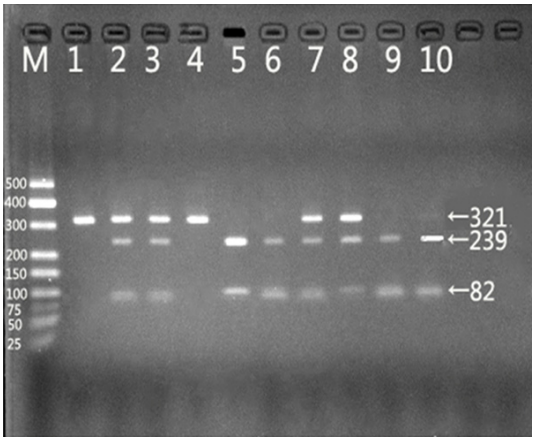

Figure 2. Genotypes of the *BDNF* rs11030104 SNP. Lane M, 25 bp Marker ladder; Lanes 1 and 4, AA genotypes (321 bp); Lanes 2, 3, 7 and 8, AG genotypes (321-, 239- and 82-bp); Lanes 5, 6, 9 and 10, GG genotypes (239- and 82-bp).

free water 10 μl, 0.3 μl each primer (10 pmol/L) and 1 μl genomic DNA, processing started with 94°C for 5 min and followed by 30 s of denaturing at 94°C, 45 s of annealing at 61°C and 30 s of elongation at 72°C for 34 cycles. The amplification was completed with a final extension at 72°C for 8 min. Following electrophoresis on a 2.0% agarose gel with 0.5 μg/mL ethidium bromide, the amplification products were visualized under ultraviolet light. For the restriction digestion, 10 μL of PCR products and 5 U of *Mly*I restriction enzyme were added to each reaction mix (constituent: 2 μL buffer solution and nuclease-free water 7.5 μL), and samples were digested at 37°C water-bath for 30 min. After restriction enzyme digestion of the amplified DNA, genotypes were evaluated by electrophoresis on 2% ethidium-bromide stained agarose gels and visualized by ultraviolet illumination. Genotypes were determined by blinding to the epidemiological and lipid results. Six samples (two samples for AA, AG, and GG genotypes, respectively) performed by PCR-RFLP were also confirmed by direct sequencing. The PCR product was purified by low melting point gel electrophoresis and phenol extraction, and then DNA sequences were analyzed using Bio-systems in Shanghai Sangon Biological Engineering Technology & Services Co., Ltd., China.

Diagnostic criteria

The normal ranges 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. The individuals with TC >5.17 mmol/L and/or TG >1.70 mmol/L were defined as hyperlipidemic [22]. Hypertension was diagnosed depend on the criteria of 1999 World Health Organization-International Society of Hypertension Guide-lines for the management of hypertension [23, 24]. 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 [25].

Statistical analysis

All statistical analyses were performed using SPSS, version 17.0 (SPSS, Chicago, IL, USA). For measurement variables, results were presented as mean ± standard deviation (serum TG levels were presented as medians and interquartile ranges), whereas the qualitative variables were presented as percentages. Allele frequency was confirmed via direct counting, and the standard goodness-of-fit test verified the Hardy-Weinberg equilibrium. The genotype distribution between the two groups was analyzed using a Chi-square test. The difference in general characteristics between Jing and Han was compared by the Student's unpaired *t*-test. The association of genotypes and serum lipid

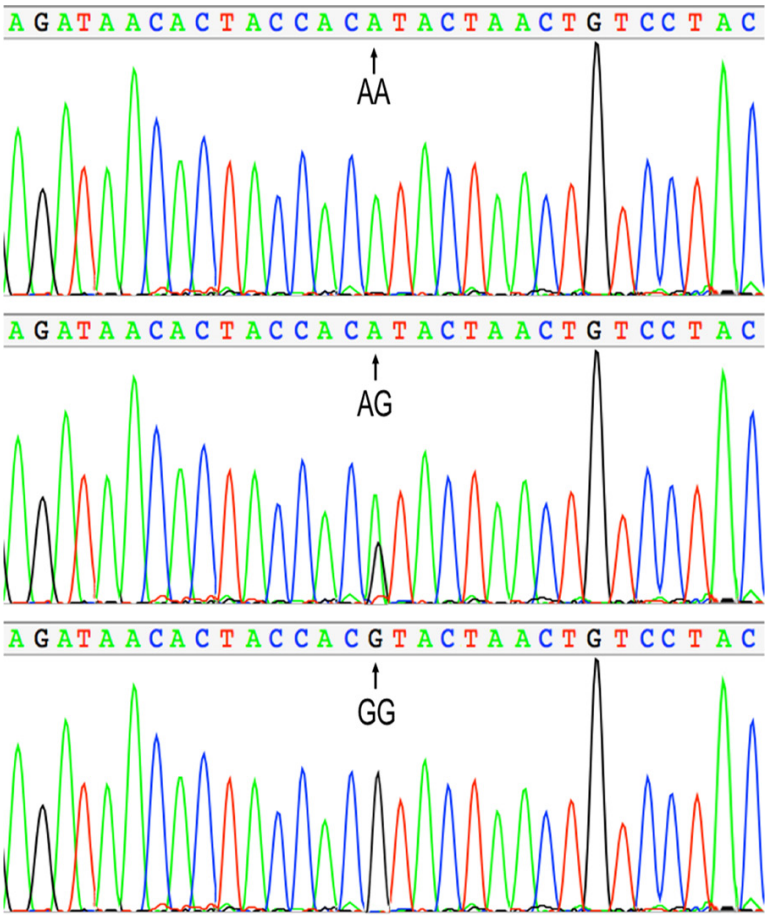

Figure 3. A part of the nucleotide sequences of the *BDNF* rs11030104 SNP by direct sequencing. AA: AA genotype; AG: AG genotypes; GG: GG genotypes.

parameters was evaluated by analysis of covariance (ANCOVA). Sex, age, BMI, blood pressure, alcohol consumption, and cigarette smoking were adjusted for the statistical analyses. Multivariate linear regression analysis with step-wise modeling was performed to determine the association of serum lipid levels with genotypes (AA=1, AG=2 and GG=3) and several environment factors in the combined population of Jing and Han, Jing, Han, males and females, respectively. *P* value <0.05 is considered statistical significance.

Results

Demographic, clinical data and serum lipid levels

The demographic, clinical data, and serum lipid levels of the study populations are summarized in **Table 1**. There was no significant difference in age and gender between the Han and Jing populations. There was significant difference in height, weight, BMI, waist circumference, intake of alcohol, diastolic blood pressure, TC, TG and ApoA1 between the two ethnic groups ($P<0.05$). The levels of height, weight, BMI, waist circumference, TC and TG were higher in Jing than in Han populations, whereas the intake of alcohol, diastolic blood pressure and ApoA1 were lower in Jing than in Han populations ($P<0.05$).

Electrophoresis and genotyping

After the genomic DNA of the samples was amplified by PCR and imaged by agarose gel electrophoresis for the *BDNF* rs11030104 SNP, the electrophoresis of PCR product of 321 bp nucleotide sequences was presented in the samples (**Figure 1**). According to the presence (A allele) or absence (G allele) of the *Apa*I enzyme restriction sites, the genotypes were determined as AA (band at 321-bp), AG (bands at 321-, 239-, and 82-bp) and GG (bands at 239- and 82-bp, **Figure 2**); respectively.

Results of direct sequencing

The results shown as AA, AG and GG genotypes by PCR-RFLP, the AA, AG, and GG genotypes were also verified by direct sequencing (**Figure 3**); respectively.

Genotypic and allelic frequencies

Table 2 shows the genotypic and allelic frequencies of the *BDNF* rs11030104 SNP in the two ethnic groups. The genotypes of the *BDNF* rs11040104 SNP were followed by the Hardy-Weinberg equilibrium ($P>0.05$). The frequencies of A and G alleles were 61.9% and 38.1% in Han, and 59.4% and 40.6% in Jing ($P>0.05$) populations respectively. The frequencies of

Table 2. Comparison of the genotype and allele frequencies of the *BDNF* rs11030104 SNP in the Han and Jing populations [n (%)]

Group	N	Genotype			Allele	
		AA	AG	GG	A	G
Han	709	287 (40.5)	304 (42.9)	118 (16.6)	878 (61.9)	540 (38.1)
Jing	706	268 (38.0)	303 (42.9)	135 (19.1)	839 (59.4)	573 (40.6)
χ^2			1.788		1.852	
P			0.409		0.174	
Han						
Male	362	148 (40.9)	152 (42.0)	62 (17.1)	448 (61.9)	276 (38.1)
Female	347	139 (40.1)	152 (43.8)	56 (16.1)	430 (62.0)	264 (38.0)
χ^2			0.270		0.001	
P			0.874		0.975	
Jing						
Male	360	156 (43.3)	136 (37.8)	68 (18.9)	448 (62.2)	272 (37.8)
Female	346	112 (32.4)	167 (48.3)	67 (19.4)	391 (56.5)	301 (43.5)
χ^2			10.129		4.787	
P			0.006		0.029	

AA, AG and GG genotypes were 40.5%, 42.9% and 16.6% in Han, and 38.0%, 42.9% and 19.1% in Jing ($P>0.05$) population respectively. The genotypic and allelic frequencies of the SNP in Jing but not in the Han population were different between male and female subgroups (**Table 2**, $P<0.05$, respectively).

Genotypes and serum lipid levels

The association between genotypes and serum lipid levels in the two ethnic groups is shown in **Table 3**. The levels of TC and LDL-C in Jing but not in Han subjects were different among the genotypes ($P<0.05$ for each), the G allele carriers had lower TC and LDL-C levels than the G allele non-carriers. Sex-subgroup analysis showed that these results were found in Jing males but not in females (**Table 4**). There were no differences in the remaining serum lipid parameters among the genotypes in both ethnic groups.

Multivariate linear regression analysis showed that the levels of LDL-C were significantly associated with *BDNF* rs11030104 genotypes in both Jing and Han populations ($P<0.05$, **Table 5**). Multivariate regression analysis according to sex showed that serum LDL-C in Jing males, TG in Jing females, and TC and ApoA1 in Han females were associated with the *BDNF* rs11030104 genotypes ($P<0.05$, respectively, **Table 6**). In addition, multiple risk factors such as age, gender, BMI, height, weight, waist circumference, intake of alcohol, smoking, serum creatinine, and blood pressure were also associated with serum lipid levels in both ethnic groups or sex subgroups ($P<0.05$ for all); respectively.

Discussion

In the present study, we adopted a standard design of epidemiological investigation and ensured a good representation of the study population as well as reasonable research methods. The results show that serum TC and TG levels are higher in Jing than in Han populations, whereas ApoA1 levels were lower in Jing than in Han populations. There were no significant differences in the levels of LDL-C, HDL-C, and ApoB. Dyslipidemia is affected by environmental factors, including demographics, diet, alcohol consumption, cigarette smoking, obesity, exercise, hypertension [26] and genetic factors, including lipid-associated gene variants, and their interactions [27]. The differences in serum lipid parameters between the two ethnic groups may be due to genetic diversity, different environmental factors [28] and their interactions [29, 30]. Jing is a special ethnic group in coastal area of China which lives off sea fishing. Seafood is their main business and main diet. Fish solute is the most popular fla-

Table 3. Comparison of the genotypes and serum lipid levels in the Han and Jing 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
Han								
AA	285	4.94±0.87	1.31(0.63)	1.77±0.57	2.80±0.43	1.31±0.20	1.03±0.24	1.33±0.37
AG	302	4.89±0.88	1.35(0.69)	1.81±0.48	2.88±0.45	1.33±0.19	1.05±0.26	1.34±0.40
GG	118	4.92±0.83	1.28(0.66)	1.74±0.52	2.83±0.39	1.31±0.21	1.04±0.21	1.31±0.35
F		0.253	0.271	0.861	0.497	0.907	0.331	0.331
P		0.776	0.873	0.423	0.608	0.404	0.719	0.719
Jing								
AA	268	5.28±0.96	1.45(0.84)	1.78±0.52	2.87±0.43	1.29±0.28	1.07±0.26	1.28±0.39
AG	303	5.20±0.83	1.43(0.64)	1.81±0.43	2.83±0.42	1.29±0.21	1.06±0.23	1.28±0.38
GG	135	4.95±0.89	1.40(0.83)	1.72±0.42	2.75±0.39	1.29±0.19	1.04±0.22	1.30±0.38
F		6.292	0.229	1.940	3.747	0.063	0.743	0.373
P		0.002	0.892	0.144	0.024	0.939	0.476	0.689

TC, Total cholesterol; TG, Triglyceride; HLD-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B.

Table 4. Comparison of the genotypes and serum lipid levels between males and females in the Han and Jing 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
Han/male								
AA	146	4.95±0.88	1.29 (0.57)	1.70±0.56	2.89±0.46	1.33±0.22	1.05±0.25	1.34±0.42
AG	151	4.76±0.87	1.33 (0.71)	1.74±0.51	2.84±0.45	1.32±0.19	1.05±0.25	1.34±0.43
GG	62	4.76±0.77	1.24 (0.92)	1.66±0.55	2.80±0.36	1.30±0.17	1.04±0.18	1.30±0.31
F		2.000	3.426	0.498	1.002	0.395	0.146	0.251
P		0.137	0.180	0.608	0.368	0.674	0.864	0.778
Han/female								
AA	139	4.94±0.85	1.41 (0.67)	1.84±0.57	2.83±0.41	1.28±0.17	1.01±0.23	1.33±0.32
AG	151	5.02±0.88	1.35 (0.67)	1.88±0.44	2.91±0.45	1.34±0.19	1.05±0.26	1.34±0.36
GG	56	5.09±0.87	1.31 (0.41)	1.83±0.47	2.87±0.41	1.32±0.26	1.05±0.24	1.32±0.40
F		0.680	1.986	0.331	1.312	2.545	1.147	0.116
P		0.507	0.370	0.718	0.271	0.080	0.319	0.891
Jing/male								
AA	156	5.25±0.91	1.61 (0.99)	1.75±0.56	2.84±0.39	1.27±0.24	1.05±0.24	1.27±0.39
AG	136	5.12±0.74	1.44 (0.61)	1.74±0.38	2.81±0.34	1.27±0.20	1.06±0.23	1.28±0.44
GG	68	4.89±0.86	1.33 (0.94)	1.66±0.42	2.72±0.37	1.27±0.20	1.06±0.20	1.26±0.39
F		4.382	2.560	0.084	2.880	0.042	0.096	0.050
P		0.013	0.278	0.429	0.047	0.959	0.908	0.951
Jing/female								
AA	112	5.31±1.02	1.34 (0.63)	1.83±0.47	2.90±0.47	1.32±0.32	1.09±0.28	1.27±0.37
AG	167	5.27±0.89	1.40 (0.67)	1.87±0.45	2.83±0.47	1.31±0.21	1.06±0.23	1.29±0.33
GG	67	5.00±0.92	1.46 (0.62)	1.78±0.41	2.78±0.40	1.30±0.19	1.02±0.24	1.35±0.37
F		2.489	2.488	1.117	1.470	0.112	1.817	1.159
P		0.084	0.288	0.328	0.231	0.894	0.164	0.315

TC, Total cholesterol; TG, Triglyceride; HLD-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B.

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

Lipid	Risk factor	B	Std.error	Beta	*t*	*P*
Han and Jing						
TC	Ethnic group	0.255	0.023	0.146	10.867	0.000
	GLU	0.044	0.008	0.077	5.703	0.000
	Height	-0.004	0.002	-0.034	-1.851	0.064
	UA	0.000	0.000	0.048	3.096	0.0002
	Pulse pressure	-0.003	0.001	-0.066	-4.529	0.000
	BMI	0.107	0.029	0.062	3.731	0.000
	Age	0.003	0.001	0.043	2.617	0.009
	Gender	0.73	0.034	0.042	2.149	0.032
TG	UA	0.002	0.000	0.265	8.186	0.000
	Waist circumference	0.019	0.003	0.188	6.696	0.000
	BMI	0.108	0.053	0.103	2.03	0.043
	Gender	0.229	0.072	0.126	3.202	0.001
	Height	-0.016	0.004	-0.14	-3.956	0.000
	Age	-0.007	0.002	-0.105	-3.692	0.000
	GLU	0.061	0.015	0.102	3.956	0.000
	Scr	0.001	0.000	0.079	3.009	0.003
	Cigarette smoking	0.16	0.037	0.126	4.314	0.000
HDL-C	Height	0.007	0.002	0.114	3.783	0.000
	Cigarette smoking	-0.062	0.019	-0.087	-3.235	0.001
	Waist circumference	-0.007	0.001	-0.13	-5.08	0.000
	GLU	-0.015	0.008	-0.044	-1.891	0.059
	Gender	0.181	0.032	0.178	5.604	0.000
	Alcohol consumption	-0.049	0.024	0.053	2.009	0.045
	Scr	0.000	0.000	0.046	1.928	0.054
	Ethnic group	0.044	0.025	0.043	1.785	0.075
LDL-C	Ethnic group	-0.111	0.01	-0.132	-10.815	0.000
	Scr	0.000	0.000	-0.034	-2.672	0.005
	Pulse pressure	0.001	0.000	0.026	2.138	0.033
	Gender	-0.031	0.011	-0.037	-2.933	0.003
ApoA1	BMI	-0.002	0.001	-0.026	-1.868	0.062
	UA	8.38E-05	0.000	-0.04	-2.625	0.002
	Pulse pressure	0.000	0.000	0.026	1.945	0.052
	Alcohol consumption	0.016	0.005	0.042	3.043	0.002
ApoB	Scr	0.000	0.000	0.024	2.441	0.015
	GLU	-0.005	0.002	-0.031	-3.121	0.002
	BMI	0.002	0.001	0.023	2.284	0.023
	Age	0.000	0.000	0.023	2.305	0.021
ApoA1/ApoB	Pulse pressure	0.000	0.000	-0.015	-1.656	0.098
Han						
TC	GLU	0.058	0.013	0.079	4.396	0.000
	Gender	0.068	0.034	0.04	1.99	0.047
	Pulse pressure	-0.002	0.001	-0.038	-2.137	0.033
	Alcohol consumption	-0.071	0.028	-0.051	-2.555	0.011
TG	UA	0.003	0.000	0.302	6.255	0.000
	BMI	0.314	0.051	0.286	6.186	0.000
	Gender	0.417	0.100	0.221	4.178	0.000
	Height	-0.012	0.006	-0.098	-2.1	0.036

	Age	-0.01	0.003	-0.142	-3.669	0.000
	Scr	0.004	0.001	0.164	4.019	0.000
	Waist circumference	0.016	0.004	0.157	4.265	0.000
	SBP	0.018	0.004	0.177	4.853	0.000
	GLU	0.063	0.029	0.078	2.191	0.029
	Cigarette smoking	0.112	0.054	0.088	2.074	0.036
	Alcohol consumption	0.143	0.065	0.093	2.203	0.026
HDL-C	GLU	-0.042	0.016	-0.089	-2.65	0.008
	Waist circumference	-0.005	0.002	-0.083	2.316	0.021
	Gender	0.235	0.054	0.212	4.331	0.000
	Cigarette smoking	-0.089	0.029	-0.118	-3.096	0.002
	Height	0.008	0.003	0.12	2.731	0.007
	UA	0.001	0.000	0.097	2.282	0.023
LDL-C	BMI	0.311	0.011	0.617	28.864	0.000
	Genotype	-0.015	0.008	-0.026	-1.805	0.036
	Cigarette smoking	0.031	0.009	0.053	3.592	0.000
ApoA1	Alcohol consumption	0.018	0.006	0.053	2.84	0.005
ApoB	SBP	0.000	0.000	0.023	1.82	0.069
	Glu	-0.006	0.003	-0.029	-2.265	0.024
	Scr	0.000	0.000	0.047	3.529	0.000
ApoA1/ApoB	Scr	0.000	0.000	0.026	2.151	0.032
Jing						
TC	GLU	0.021	0.009	0.043	2.4	0.017
	Height	-0.008	0.002	-0.072	-3.563	0.000
	Pulse pressure	-0.003	0.001	-0.053	-2.753	0.006
	Cigarette smoking	0.067	0.024	0.054	2.4	0.017
	Age	0.003	0.001	0.46	2.264	0.024
TG	Waist circumference	0.018	0.004	0.188	4.679	0.000
	UA	0.001	0.000	0.147	3.651	0.000
	BMI	0.634	0.084	0.29	7.534	0.000
	GLU	0.074	0.017	0.152	-4.333	0.000
	Height	-0.025	0.005	-0.225	-5.455	0.000
	Age	-0.006	0.002	-0.088	-2.296	0.004
	Cigarette smoking	0.207	0.049	0.163	4.197	0.000
HDL-C	Waist circumference	-0.009	0.002	-0.174	-5.375	0.000
	Height	0.004	0.002	0.075	1.921	0.055
	Alcohol consumption	0.112	0.03	0.115	3.69	0.000
	Gender	0.138	0.034	0.15	4.06	0.000
LDL-C	Alcohol consumption	-0.033	0.015	-0.038	-2.199	0.026
	Genotype	-0.016	0.01	-0.031	-1.852	0.065
	Scr	0.000	0.000	-0.03	-1.761	0.079
ApoA1	BMI	-0.003	0.001	-0.046	-2.345	0.019
	Pulse pressure	0.001	0.000	0.058	2.905	0.004
	Age	0.000	0.000	-0.038	-1.87	0.062
	Glu	-0.004	0.002	-0.032	-1.67	0.095
ApoB	Waist circumference	-0.042	0.01	-0.082	-4.387	0.000
ApoA1/ApoB	Alcohol consumption	0.111	0.033	0.135	30.366	0.001
	Gender	0.064	0.031	0.084	20.098	0.036

TC, Total cholesterol; TG, Triglyceride; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; UA, Uric Acid; Scr, Serum creatinine; GLU, Glucose; BMI, Body mass index; SBP, Systolic pressure.

Table 6. Relationship between serum lipid parameters and relative factors in the males and females of the Han and Jing populations

Lipid	Risk factor	B	Std.error	Beta	t	P
Han/male						
TC	DBP	0.003	0.002	0.037	1.700	0.090
	Age	0.006	0.001	0.087	3.869	0.000
	Scr	-0.002	0.001	-0.083	-3.546	0.000
	Alcohol consumption	-0.062	0.025	-0.054	-2.485	0.013
TG	UA	0.002	0.001	0.204	3.401	0.001
	Age	-0.020	0.004	-0.265	-5.057	0.000
	Alcohol consumption	0.187	0.063	0.135	2.952	0.003
	Scr	0.003	0.001	0.112	2.194	0.029
	Waist circumference	0.013	0.006	0.106	2.264	0.024
HDL-C	DBP	0.005	0.003	0.089	1.893	0.059
	Cigarette smoking	-0.056	0.031	-0.086	-1.807	0.072
LDL-C	DBP	-0.002	0.001	-0.047	-2.351	0.019
	Age	-0.002	0.001	-0.057	-2.979	0.003
	Scr	0.000	0.000	0.036	1.615	0.107
	UA	0.000	0.000	0.038	1.681	0.094
ApoA1	Height	-0.003	0.001	-0.090	-3.306	0.001
	Pulse pressure	0.001	0.000	0.05	1.937	0.054
	Alcohol consumption	0.022	0.008	0.077	2.856	0.005
ApoB	Scr	0.000	0.000	0.057	2.809	0.005
	Waist circumference	0.001	0.001	0.033	1.762	0.079
ApoA1/ApoB	Pulse pressure	-0.001	0.000	-0.041	-2.427	0.000
Han/female						
TC	BMI	0.736	0.054	0.875	3.144	0.000
	GLU	0.093	0.021	0.12	4.337	0.000
	UA	0.001	0.000	0.093	3.438	0.001
	SBP	-0.004	0.001	-0.091	-3.285	0.001
	Genotype	0.062	0.033	0.05	1.887	0.06
TG	UA	0.005	0.001	0.434	8.494	0.000
	Waist circumference	0.009	0.004	0.101	2.081	0.038
HDL-C	Scr	0.003	0.001	0.202	4.964	0.000
	Pulse pressure	-0.002	0.001	-0.075	-1.947	0.053
LDL-C	UA	0.000	0.000	-0.068	-3.377	0.001
	SBP	0.001	0.000	0.059	2.921	0.047
ApoA1	Scr	0.000	0.000	-0.051	-1.743	0.08
	UA	0.000	0.000	-0.088	-3.036	0.003
	Genotype	0.027	0.011	0.129	2.407	0.017
ApoB	Scr	0.000	0.000	0.055	3.112	0.002
	GLU	-0.008	0.004	-0.037	-2.214	0.026
ApoA1/ApoB	UA	0.000	0.000	0.052	20.932	0.004
	BMI	-0.004	0.002	-0.043	-20.408	0.017
	GLU	-0.011	0.005	-0.033	-10.98	0.049
Jing/male						
TC	BMI	0.013	0.007	0.047	1.785	0.075
	Age	0.006	0.002	0.115	3.782	0.000

	Cigarette smoking	0.111	0.026	0.116	4.234	0.000
	Alcohol consumption	0.082	0.035	0.061	2.35	0.019
TG	Waist circumference	0.025	0.006	0.241	4.138	0.000
	Cigarette smoking	0.188	0.061	0.163	3.096	0.002
	GLU	0.097	0.025	0.192	3.875	0.000
	Height	-0.026	0.008	-0.182	-3.122	0.002
	Age	-0.007	0.004	-0.11	-1.793	0.740
	UA	0.001	0.001	0.114	2.242	0.026
HDL-C	Alcohol consumption	0.131	0.03	0.172	4.396	0.000
	Waist circumference	-0.16	0.004	-0.328	-3.626	0.000
	Height	0.054	0.018	0.792	3.025	0.003
	Age	0.004	0.001	0.128	2.974	0.003
	Scr	0.000	0.000	0.078	2.239	0.026
	BMI	0.172	0.063	1.105	2.726	0.007
	Weight	-0.055	0.023	-1.171	-2.346	0.020
LDL-C	Alcohol consumption	-0.035	0.016	-0.058	-2.188	0.029
	Genotype	0.132	0.024	0.168	5.467	0.000
ApoA1	BMI	-0.004	0.002	-0.059	-2.231	0.026
	Pulse pressure	0.001	0.000	0.062	2.57	0.011
ApoB	BMI	0.012	0.003	0.153	3.574	0.000
	Pulse pressure	-0.001	0.000	-0.09	-4.101	0.000
	Age	0.001	0.000	0.059	2.637	0.009
	Alcohol consumption	0.026	0.008	0.069	3.05	0.002
	Waist circumference	-0.003	0.001	-0.118	-2.68	0.008
	Scr	0.000	0.000	0.041	2.06	0.040
ApoA1/ApoB	Pulse pressure	-0.001	0.000	-0.042	-2.467	0.014
Jing/female						
TC	Scr	0.003	0.001	0.093	3.751	0.000
	GLU	0.038	0.001	0.067	2.723	0.007
	Pulse pressure	-0.003	0.001	-0.054	-2.227	0.027
	Waist circumference	-0.005	0.003	-0.042	-1.726	0.085
TG	UA	0.002	0.001	0.18	3.358	0.001
	Cigarette smoking	0.856	0.279	0.151	3.067	0.002
	Genotype	0.117	0.055	0.105	2.124	0.035
	Height	-0.023	0.007	-0.178	-3.235	0.001
	Waist circumference	0.009	0.005	0.101	1.818	0.070
HDL-C	Waist circumference	-0.01	0.002	-0.18	-4.031	0.000
LDL-C	Waist circumference	0.002	0.001	0.044	1.822	0.070
	Scr	-0.001	0.000	-0.078	-3.149	0.002
	Age	0.002	0.001	0.052	2.036	0.043
ApoA1	BMI	0.725	0.025	0.248	2.633	0.000
	Waist circumference	0.886	0.037	0.024	4.062	0.000
ApoB	Pulse pressure	-0.681	0.020	-0.015	-3.296	0.000
ApoA1/ApoB	Waist circumference	-0.202	0.027	-0.807	-4.284	0.000
	Scr	0.038	0.031	0.602	3.063	0.000

TC, Total cholesterol; TG, Triglyceride; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; UA, Uric Acid; Scr, Serum creatinine; GLU, Glucose; BMI, Body mass index; SBP, Systolic pressure; DBP, Diastolic pressure.

voring for each meal, which is made by amarinate small fish. Their marriages are family-arranged but cross-cousin marriage and getting married with someone with the same last name are forbidden. The Jing population preserves their custom of intra-ethnic marriages. So Jing nationality has a special lifestyle, dietary habits, and customs compared with Han and other landlocked nationalities. Moreover, several hereditary characteristics and genotypes of lipid metabolism-related gene in Jing might be different from those in the Han population.

The genotypic and allelic frequencies of the *BDNF* rs11030104 SNP in different racial/ethnic groups are inconsistent. According to the data from International HAP-Map Project, the frequency of A allele was 60.0% in Han Chinese in Beijing, 62.8% in Japanese, 77.0% in European, 99.67 in African. The frequencies of AA, AG, and GG genotypes were 35%, 50% and 15% in Chinese; 44.2%, 37.2%, and 18.6% in Japanese; 58.4%, 37.2%, and 4.4% in European; 99.1%, 0.88%, and 0% in African, respectively. Our study results demonstrated that the frequencies of AA, AG, and GG genotypes were 40.5%, 42.9%, and 16.6% in Han population, and 38.0%, 42.9%, and 19.1% in Jing population and the frequencies of A and G alleles were 61.9% and 38.1% in Han, and 59.4% and 40.6% in Jing populations respectively. These results were slightly different from the data of Beijing, which may be due to different sizes and regions (Northern China *vs*. Southern China). We also found that the genotypic and allelic frequencies of the SNP in the Jing but not in the Han populations was different between males and females, which may be caused by racial and/or gender factors.

BDNF is a member of the neurotrophin family, plays an important role in neurological disorders [31]. BDNF and its high-affinity receptor TrkB are highly expressed in the hypothalamus, where this neurotrophic factor has major regulatory roles in the control of appetite and metabolism [32]. In recent years, several studies have showed that BDNF is also positively correlated with the risk factors of metabolic syndrome [33], BMI and obesity [33-35]. Serum BDNF levels in various physiologic states will likely aid in the assessment and management associated cardiovascular risk [36]. Higher serum BDNF is associated with a decreased risk of CVD and mortality. Mendelian randomization suggests a causal protective role of BDNF in the pathogenesis of CVD. Several studies showed that the *BDNF* rs11030104 SNP was closely associated with BMI level, obesity, and metabolic syndrome [37]. However, there are hardly any studies that exhibit a direct relationship between the *BDNF* rs11030104 SNP and serum lipid levels. Our study showed that the genotypes of *BNDF* rs11030104 SNP were significantly associated with serum TC and LDL-C levels. The G allele carriers had lower TC and LDL-C levels than the G allele non-carriers in the Jing population. Moreover, subgroup analysis presented the G allele carriers had lower TC and LDL-C levels in Jing males. These results show that the association of *BDNF* rs11030104 SNP and serum lipid levels probably has racial/ethnic and/or sex specificity. But, this association needs to be confirmed by further studies with larger sample size.

We also found a gender difference in the association of the *BDNF* rs11030104 SNP and serum lipid levels in the Jing population. Some unknown genetic factors may be involved in affecting this status. In addition, the sample size was possibly not large enough to measure the association of *BDNF* rs11030104 SNP and serum lipid levels in the sex subgroup analyses. Further research should be done to confirm these findings.

It is well known that environmental factors (such as dietary pattern, lifestyle, and physical inactivity) are closely related with serum lipid levels [38-40]. In our study, multivariate linear regression analysis also found that age, gender, BMI, waist circumference, alcohol consumption, cigarette smoking, serum creatinine (Scr) and blood pressure affected serum lipid parameters. These data suggest that environmental factors also play an important role in determining serum lipid levels in our study populations. Jing people like to eat seafood, especially fish. Fish are rich in omrga-3 polyunsaturated fatty acids (N-3PUFA) which have been considered to have a positive effect on serum lipid concentrations. But, previous studies presented the influence of N-3PUFA on key metabolism function, including significant increase in TC, TG, and LDL-C levels and decrease in HDL-C

[41, 42]. Furthermore, several studies show that BMI and alcohol consumption may interact with lipid-related genes to determine serum lipid levels in other populations [43, 44]. Therefore, the effects of dietary pattern, lifestyle, customs, and environmental factors may alter the association of genetic diversities and serum lipid levels in our study populations.

Furthermore, the presence of dyslipidemia was significantly associated with increasing age, male sex, higher BMI, higher blood glucose concentration, higher blood pressure, smoking, high cholesterol diet, and sedentary lifestyle [45, 46]. Our study also showed that age, male, BMI, waist circumference, blood pressure, smoking, and intake of alcohol were associated with serum lipid levels. Moreover, we also found that BMI, waist circumference were higher in Jing than in Han populations. BMI and obesity were already demonstrated to have closely correlation with individual lipid profiles [47, 48]. Waist circumference is also an important index in evaluation of dyslipidemia, waist circumference and BMI are equally useful for monitoring the consequences of obesity [49]. Many studies have shown that smoking and alcohol consumption are major risk factors for atherosclerotic CVD through leading to dyslipidemia [50, 51]. For example, TG increased by 0.15 mmol/L and HDL-C decreased by 0.09 mmol/L with every 20 cigarettes smoked [28]. An another study exhibited TG increased by 5.69 mg/dl, HDL-C decreased by 3.99 mg/dl, and ApoA1 decreased by 8.83 mg/dl with every 30 g intake of alcohol per day [52]. Lifestyle modifications can have similar therapeutic effects with statins. It can effectively control serum lipid levels and reduce the prevalence of CVD [53].

In addition, our study indicates that Scr is significantly associated with several lipid parameters. More and more research has demonstrated that renal dysfunction is associated with dyslipidemia [54-57]. Bowe et al. found that low level of HDL-C was significantly correlated with the prevalence and development of chronic kidney disease (CKD). The level of HDL-C was independently associated with eGFR and the prevalence of low HDL-C level was increasing with reduced grading of eGFR [56]. LDL-C/ApoB and HDL-C/ApoA1 ratios may predict incident of CKD [55].

Our research also has some limitations. First, the cross-sectional study design limits the ability to confirm causality of the relationships observed. Second, we were not able to eliminate the effect of diet during the statistical analysis since the diet intake was self-reported and difficult to classify. Third, there are still some unmeasured environmental and genetic factors which should be considered. Fourth, we only detected serum TC, TG, HDL-C, LDL-C, ApoA1, ApoB levels, and the ratio of ApoA1 to ApoB and measured their relationships with the *BDNF* rs11030104 SNP without comprehensive measurement of the subclasses lipoproteins such as HDL2, HDL3, small dense LDL, and large buoyant LDL. TC, TG, HDL-C and LDL-C are the most important indexes for judging dyslipidemia.

The interaction of gene-gene, gene-environment, and environment-environment on serum lipid levels remain to be confirmed later. Therefore, we propose that these interaction mechanisms and the relationship between *BDNF* rs11030104 SNP and different lipid parameters need to be verified in further depth investigations.

Conclusions

This study shows that *BDNF* rs11030104 SNP is associated with serum TC and LDL-C levels in the Jing males. These results suggest that there may be a racial/ethnic- and/or sex-specific association of the *BDNF* rs11030104 SNP and serum lipid levels in our study populations.

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Disclosure of conflict of interest

None.

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