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Original Article

Association between the *GPAM* rs1129555 SNP and serum lipid profiles in the Maonan and Han populations

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Abstract: The glycerol-3-phosphate acyltransferase mitochondrial gene (*GPAM*) variant has been associated with serum lipid levels in the Eurpean ancestry, but little is known about such association in Chinese populations. The aim of the present study was to investigate the relationship between the *GPAM* rs1129555 single nucleotide polymorphism (SNP) and several environment factors with blood lipid profiles in the Guangxi Maonan and Han populations. A total of 720 individuals of Maonan nationality and 780 participants of Han nationality were randomly selected from our previous stratified randomized samples. Genotyping of the rs1129555 SNP was carried out using the polymerase chain reaction-restriction fragment length polymorphism technique, and then confirmed by direct sequencing. The frequencies of C and T alleles were 72.85% and 27.15% in Maonan, and 65.19% and 34.81% in Han ($P < 0.001$); respectively. The frequencies of CC, CT, and TT genotypes were 51.53%, 42.36%, and 5.97% in Maonan, and 43.08%, 44.23%, and 12.69% in Han populations ($P < 0.001$). The T allele carriers had higher serum triglyceride (TG) in Han and higher low-density lipoprotein cholesterol (LDL-C) in both Maonan and Han than the T allele non-carriers ($P < 0.05$-0.01). Gender subgroup analyses showed that the T allele carriers had higher TG levels in Han males ($P < 0.05$) and higher LDL-C levels in Maonan males but not in famales ($P < 0.01$). Serum lipid parameters were also associated with several environmental factors ($P < 0.05$-0.001). These findings suggest that racial/ethnic- and/or gender-specific association occurs between the *GPAM* rs1129555 variant and serum lipid parameters in our study populations.

Keywords: Glycerol-3-phosphate acyltransferase mitochondrial, single nucleotide polymorphism, lipids, environmental factor

Introduction

Cornary heart disease (CHD) has been the largest threat to public health in developed contries [1]. CHD and its sequelae (angina, myocardial infarction, cardiac revascularization or transplantation) affect more than 16 million Americans and untold numbers of people world-wide [2]. In China, the CHD prevalence and mortality rate have been increasing in recent decades [3]. It is generally accepted that CHD is a multifactorial disease [4]. Reduction of known risk factors for CHD such as hyperlipidemia, hypertension, diabetes, heavy alcohol consumption, and smoking has been assessed in multiple clinical trials and is associated with 30% to 40% less clinical events such as myocardial infarction and chronic heart failure [5]. Dyslipidemia, particularly hypertriglyceridemia, hypercholesterolemia and low high-density lipoprotein cholesterol (HDL-C), is well-described independent predictor for atherosclerosis and CHD [6]. Low-density lipoprotein cholesterol (LDL-C) has been considered to be the major lipid risk factor and main target of lipid-lowering therapy in most national guidelines [7, 8]. Lipid disorder is a common result that is determined by age, gender, genetic, ethnicity, environmental factors and their interactions [9]. Family studies based on twins suggest that in different populations, genetic factors contribute to about half of the variation in serum lipid profiles [10]. Although it has been estimated that up to 41% of interindividual variability may be determined by genetic factors [11], the genetic architecture of dyslipidemia and CHD remains largely undefined. Genome-wide association studies (GWASs) have identified that the common variants at loci together can explain about 10-12% of the variations in each

lipid trait and rare variants with large individual effects may also contribute to the heritability of lipid traits [12]. Gentic variants with small effects can point to pathways and therapeutic targets that enable clinically-important changes in blood lipids. Therefore, understanding of the association of SNP and serum lipid levels may become a new approach for preventing and treatment of CHD.

In recent years, a multitude of new gene loci associated with blood lipid levels have been discovered by GWAS, the glycerol-3-phosphate acyltransferase mitochondrial gene (*GPAM*; also knows as: GPAT, GPAT1; Gene ID: 57678, HGNC ID: 24805, chromosomal location: 10q25.2) is one of the potential candidate genes that play an important role in serum lipid metabolism [13]. *GPAM*, is a member of protein family (pfam) 01553 family of glycerolipid acyltransferases, located in the outer mitochondrial membrane. *GPAM* is most highly expressed in liver and adipose tissue, but is also present in many other tissues including brain, kidney, heart, and adrenal gland. Liver is a major organ of regulating lipid metabolism, knockout and overexpression studies suggest that *GPAM* isoforms play a critical role in the development of hepatic steatosis and that steatosis initiated by overexpression of *GPAM* result in fatty liver, obesity, insulin resistance, and hyperlipidemia [14, 15]. Gain-of-function and loss-of-function studies highlight the importance of *GPAM* in *de novo* triglyceride (TG) synthesis. The pathway of TG biosynthesis is remarkable for the number of enzymes that catalyze each step. For example, four independent *GPAM* isoforms, each encoded by a separate gene, catalyze the synthesis of lysophosphatidic acid from glycerol-3-phosphate and long-chain acyl-CoA. Coleman et al. showed that the esterification of glycerol-3-phosphate with a long-chain acyl-CoA was the initial step in the synthesis of phospholipids and TG [16]. Plasmid- and adenovirus-mediated overexpression of *GPAM* in Chinese hamster ovary and HEK293 cells and in primary rat hepatocytes increases TG content and [^{14}C]oleate incorporation into TG 3- to 4-fold, whereas hepatic TG content variably affects very-low-density lipoprotein (VLDL) secretion [17, 18]. More recently, research of human populations has showed that genetic polymorphsims in *GPAM* are significantly associated with plasma tatol cholesterol (TC) and LDL-C levels [13, 19-21]. But the reproducibility and repeatability of this association has not been performed in Chinese populations. Genetic variation is known to have different magnitudes of effect in the different ethnic groups. Therefore, it may be acctractive to characterize the association between the rs1129555 variation and serum lipid levels in the Chinese populations.

China is a multiethnic country, with a culture of different ethnic groups having different content and features. The Han population accounts for the majority of the total population of our country. Maonan, on the other hand, is one of the minorities with a population of 107,166 according to the China's fifth national census in 2000. They are mainly distributed in the Shangnan, Zhongnan, and Xianan townships of Huanjiang Maonan Autonomous County in Guangxi Zhuang Autonomous Region, which is situated in Southwestern China. The Maonan ethnic group has various lifestyles and different eating habits which may result in the effect of hereditary variation to be further modified. Several previous studies have showed that the genetic relationship between Maonan nationality and other minorities in Guangxi [22] was much closer than that between Maonan and Han nationalities [23]. Furthermore, they have their tradition of ethnic endogamy and consanguineous marriage to cousins of maternal side, suggesting that the genetic background of Maonan nationality may be less heterogeneous within the population. Taken together, we believed that the Maonan nationality has become a useful group for population genetic studies. Thus, the present study was to detect the association of the rs1129555 SNP and serum lipid levels in the Maonan and Han populations.

Materials and methods

Subjects

A total of 780 unrelated participants of Han (306 males, 39.23% and 474 females, 60.77%) and 720 unrelated subjects of Maonan (291 males, 40.42% and 429 females, 59.58%) were randomly selected from our previous stratified randomized samples [24]. All participants were agricultural workers living in Huanjiang Maonan Autonomous Region, Guangxi Zhuang Autonomous Region, People's Republic of China. The age of the participants ranged from 25 to 80 years, with a mean age of 55.90±13.54 years in Han and 57.07±15.02

years in Maonan ($P > 0.05$), respectively. All study subjects were essentially healthy with no history of cardiovascular disease such as CHD and stroke, diabetes, hyper-or hypo-thyroids, and chronic renal disease. We excluded the subjects who had a history of taking medications known to affect serum lipid levels (lipid-lowering drugs such as statins or fibrates, beta blockers, diuretics, or hormones) before the blood sample was drawn. The present study was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University (No. Lunshen-2014-KY-Guoji-001, Mar. 7, 2014). Informed consent was taken from all participants.

Epidemiological survey

The survey was carried out using internationally standardized methods, following a common protocol [25]. Information on demographics, socioeconomic status, and lifestyle factors was collected with standardized questionnaires. Alcohol consumption was categorized into groups of grams of alcohol per day: 0 (non-drinker), < 25 and ≥ 25. Smoking status was categorized into groups of cigarettes per day: 0 (non-smoker), < 20 and ≥ 20. Several parameters such as blood pressure, height, weight, waist circumference, and body mass index (BMI) were measured or calculated. The methods of measuring above parameters were referred to previous studies [26].

Biochemical measurements

A fasting venous blood sample of 5 mL was drawn from the participants. A part of the sample (2 mL) was collected into glass tubes and used to determine serum lipid levels, and another part (3 mL) was shifted to tubes with 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). Measurements of serum TC, TG, 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 measured by the immunoturbidimetric immunoassay using a commercial kit (RANDOX Laboratories Ltd.). All determinations were performed with an auto-analyzer (Type 7170A; Hitachi Ltd., Tokyo, Japan) in the Clinical Science Experiment Center of the First Affiliated Hospital, Guangxi Medical University [27].

DNA amplification and genotyping

Genomic DNA of the samples was extracted from peripheral blood leucocytes according to the phenol-chloroform method [28]. The extracted DNA was stored at 4°C until analysis. Genotyping of the *GPAM* rs1129555 SNP was performed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). PCR amplification was performed using 5'-AGAGAGGAGGGAAGTTGTGCA-3' and 5'-TAACCCAGCATTGCCCAAAC-3' (Sangon, Shanghai, People's Republic of China) as the forward and reverse primer pairs, respectively. Each 25 μL PCR reaction mixture consisted of 2.0 μL genomic DNA, 1.0 μL each primer (10 μmol/L), 12.5 μL of 2 × *Taq* PCR Master mix (constituent: 0.1 U *Taq* polymerase/μL, 500 μM dNTP each and PCR buffer.), and 8.5 μL of ddH_2O (DNase/RNase-free). PCR was performed with an initialization step of 95°C for 5 min, followed by 30 s denaturing at 95°C, 30 s of annealing at 58°C and 30 s of elongation at 72°C for 33 cycles. The amplification was completed by a final extension at 72°C for 7 min. Following electrophoresis on a 2.0% agarose gel with 0.5 μg/mL ethidium bromide, the amplification products were visualized under ultraviolet light. Subsequently, each restriction enzyme reaction was performed with 5.0 μL amplified DNA, 8.8 μL nuclease-free water, 1.0 μL of 10 × buffer solution and 0.2 μL *BstMA*I restriction enzyme in a total volume of 15 μL digested at 55°C overnight. After restriction enzyme digestion of the amplified DNA, genotypes were identified by electrophoresis on 2% ethidium-bromide stained agarose gels and visualized with UV illumination. Genotypes were scored by an experienced reader blinded to the epidemiological and serum lipid results. Six samples (CC, CT, and TT genotypes in two; respectively) detected by the PCR-RFLP were also confirmed by direct sequencing with 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, ApoB levels and the ApoA1/ApoB ratio in our Clinical Science Experiment Center were 3.10-5.17, 0.56-1.70, 1.16-1.42, 2.70-

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

Parameter	Han	Maonan	t (x^2)	P
Number	780	720		
Male/female	306/474	291/429	0.220	0.639
Age (years)	55.90±13.54	57.07±15.02	-1.578	0.115
Height (cm)	154.25±7.90	153.87±8.05	0.908	0.364
Weight (kg)	53.40±9.18	53.17±10.72	0.443	0.658
Body mass index (kg/m^2)	22.39±3.25	22.34±3.63	0.325	0.745
Waist circumference (cm)	75.53±8.14	76.60±9.25	-2.360	0.018
Smoking status [*n* (%)]				
Non-smoker	593 (76.03)	538 (74.72)		
≤ 20 cigarettes/day	166 (21.28)	142 (19.72)		
> 20 cigarettes/day	21 (2.69)	40 (5.56)	8.076	0.018
Alcohol consumption [*n* (%)]				
Non-drinker	625 (80.13)	511 (70.97)		
≤ 25 g/day	83 (10.64)	110 (15.28)		
> 25 g/day	72 (9.23)	99 (13.75)	17.108	0.000
Systolic blood pressure (mmHg)	130.37±19.43	135.57±23.80	-4.589	0.000
Diastolic blood pressure (mmHg)	82.01±11.51	83.20±12.44	-1.911	0.056
Pulse pressure (mmHg)	48.36±15.73	52.37±17.44	-4.639	0.000
Glucose (mmol/L)	6.29±1.96	6.19±1.43	1.133	0.257
Total cholesterol (mmol/L)	5.00±1.02	4.99±0.94	0.156	0.876
Triglyceride (mmol/L)	1.14 (0.51)	1.28 (0.52)	-3.917	0.000
HDL-C (mmol/L)	1.70±0.46	1.58±0.39	5.128	0.000
LDL-C (mmol/L)	2.87±0.75	2.93±0.66	-1.552	0.121
ApoA1 (g/L)	1.33±0.23	1.36±0.21	-3.101	0.002
ApoB (g/L)	0.86±0.20	0.88±0.18	-1.665	0.096
ApoA1/ApoB	1.63±0.53	1.62±0.44	0.282	0.778

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo, apolipoprotein. 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.

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 hyperlipidaemic [29]. Hypertension diagnosis standard is according to the cirteria of 1999 and 2003 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension [30]. 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.

Statistical analyses

Statistical analyses were performed with the statistical software package SPSS 22.0 (SPSS Inc., Chicago, Illinois). Quantitative variables were presented as mean ± standard deviation (serum TG levels were presented as median and interquartile ranges). Allele frequency was determined via direct counting, and the Hardy-Weinberg equilibrium was verified with the standard goodness-of-fit test. The genotype distribution between the two ethnic groups was analyzed by the Chi-square test. General characteristics between two ethnic groups were compared by the Student's unpaired *t*-test. Association between genotypes and serum lipid parameters was tested by covariance analysis (ANCOVA). Gender, age, BMI, blood pressure, alcohol consumption, and cigarette smoking were adjusted for the statistical analysis. Multivariate linear regression analyses with stepwise modeling were used to determine the correlation between the genotypes (CC = 1, CT = 2, TT = 3) and several environmental factors with serum lipid levels in males and females of Han and Maonan populations. Two-sided P values < 0.05 were considered statistically significant.

Results

General characteristics and serum lipid levels

Table 1 shows the general characteristics and serum lipid parameters between the Han and Maonan populations. The levels of serum HDL-C and ApoA1 were higher in Han than in Maonan (P < 0.01), whereas the percentages of cigarette smoking, alcohol consumption, and the levels of systolic blood pressure, pulse pressure, body waist circumference, serum TG

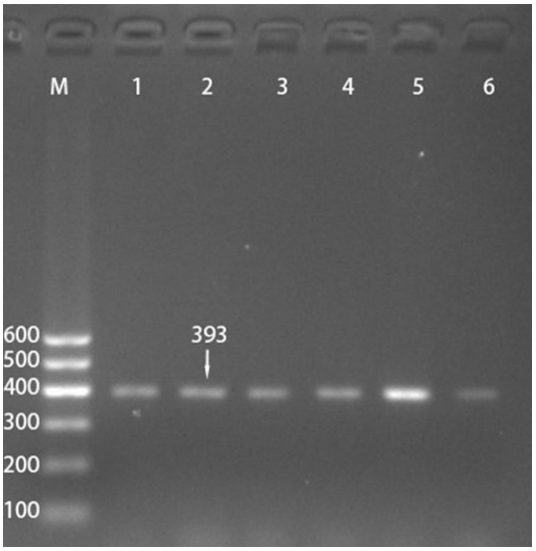

Figure 1. Electrophoresis of polymerase chain reaction products of the samples. Lane M is the 100 bp marker ladder; lanes 1-6 are samples, the 393 bp bands are the target genes.

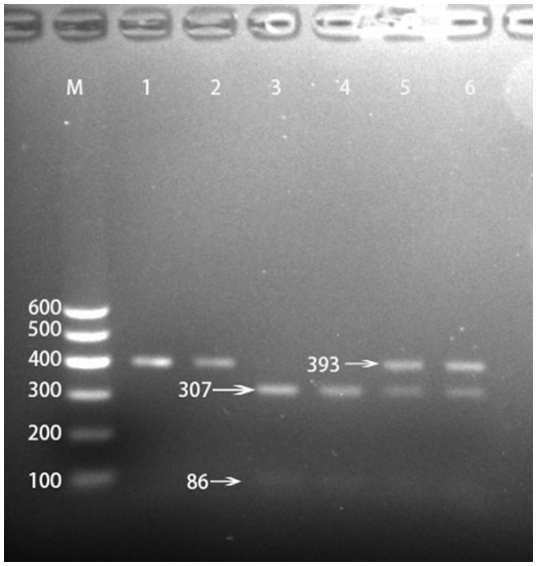

Figure 2. Genotyping of the *GPAM* rs1129555 SNP. Lane M, 100 bp marker ladder; lanes 1 and 2, TT genotype (393-bp); lanes 3 and 4, CC genotype (307- and 86-bp); and lanes 5 and 6, CT genotype (393-, 307- and 86-bp).

were lower in Han than in Maonan ($P < 0.05$-0.001). There were no significant differences in the gender ratio, age structure, height, weight, BMI, diastolic blood pressure, glucose, serum TC, LDL-C, ApoB levels and the ratio of ApoA1 to ApoB between the two ethnic groups ($P > 0.05$ for all).

Results of electrophoresis and genotyping

After the genomic DNA of the samples was amplified using PCR and visualized with 2% agarose gel electrophoresis, the products of 393 bp nucleotide sequences were observed in all samples (**Figure 1**). The genotypes identified were termed according to the presence (C allele) or absence (T allele) of the enzyme restriction sites. Thus, the CC genotype is homozygous for the presence of the site (bands at 307- and 86-bp), the CT genotype is heterozygous for the presence and absence of the site (bands at 393-, 307- and 86-bp) and the TT genotype is homozygous for the absence of the site (bands at 393 bp; **Figure 2**). The CC, CT and TT genotypes detected by PCR-RFLP were also confirmed by direct sequencing (**Figure 3**), respectively.

Genotypic and allelic frequencies

The genotypic and allelic frequencies of the *GPAM* rs1129555 SNP are shown in **Table 2**. The genotype and allele frequencies were significantly different between the Han and Maonan populations (CC, 43.08% *vs*. 51.53%; CT, 44.23% *vs*. 42.36%; TT, 12.69% *vs*. 5.97%; $P = 0.000$; C, 65.19% *vs*. 72.85%; T, 34.81% *vs*. 27.15%; $P = 0.000$). Gender subgroup analysis showed that there were no differences in the genotypic and allele frequencies between males and females in the two ethnic groups ($P > 0.05$ for each).

Genotypes and serum lipid levels

Tables 3 and **4** describe the association between genotypes and serum lipid levels. Serum LDL-C levels were different among the three genotypes in both ethnic groups ($P < 0.05$). Serum TG levels were different among the three genotypes in Han but not in Maonan ($P < 0.05$), the T allele carriers had higher TG and LDL-C levels than the T allele non-carriers ($P < 0.05$). Gender subgroup analysis showed that the TG levels in Han males and LDL-C levels in Maonan males were associated with the genotypes ($P <$ 0.05-0.01).

Relative factors for serum lipid parameters

The risk factors for serum lipid parameters in Maonan and Han are shown in **Tables 5** and **6**. Multiple linear regression analysis showed

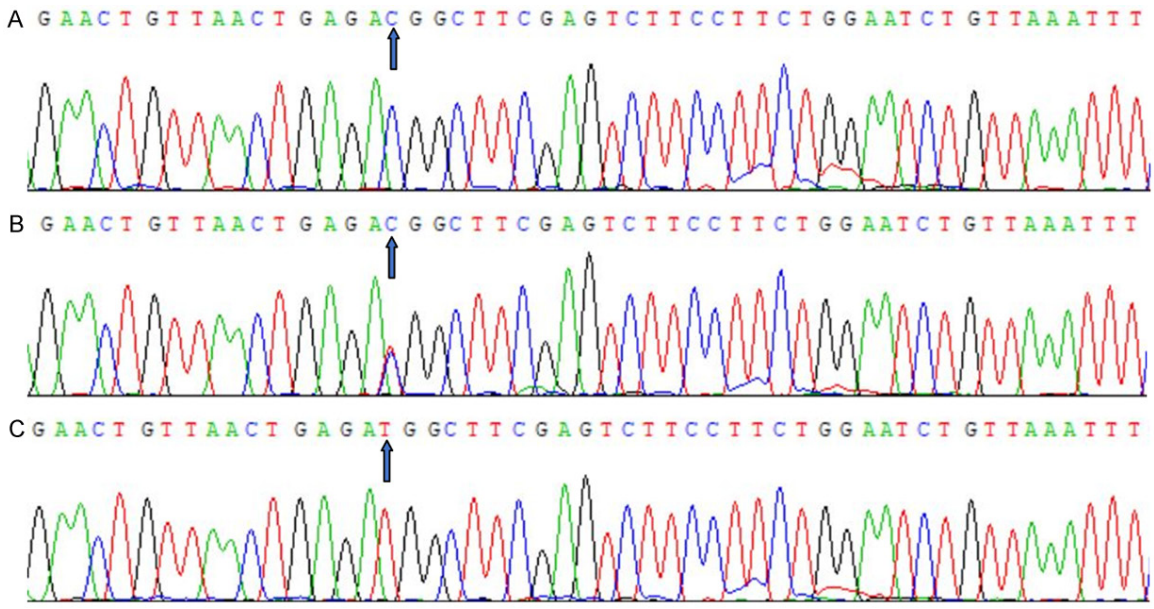

Figure 3. Nucleotide sequence of the *GPAM* rs1129555 SNP. A. CC genotype; B. CT genotype; C. TT genotype.

Table 2. Comparison of the genotype and allele frequencies of *GPAM* rs1129555 SNP in the Han and Maonan populations [*n* (%)]

Group	*n*	Genotype			Allele	
		CC	CT	TT	C	T
Han	780	336 (43.08)	345 (44.23)	99 (12.69)	1017 (65.19)	543 (34.81)
Maonan	720	372 (51.53)	305 (42.36)	43 (5.97)	1049 (72.85)	391 (27.15)
x^2			23.836		20.465	
P			0.000		0.000	
Han						
Male	306	138 (45.10)	125 (40.85)	43 (14.05)	404 (65.52)	211 (34.48)
Female	474	198 (41.77)	220 (46.41)	56 (11.81)	616 (64.98)	332 (35.02)
x^2			2.513		0.048	
P			0.285		0.826	
Maonan						
Male	291	158 (54.30)	115 (39.52)	18 (6.19)	431 (74.05)	151 (25.95)
Female	429	214 (49.89)	190 (44.29)	25 (5.83)	618 (72.03)	240 (27.97)
x^2			1.525		0.720	
P			0.467		0.396	

that serum LDL-C levels in both Maonan and Han populations; TG, LDL-C, in Han and LDL-C levels in Maonan were correlated with the genotypes of the *GPAM* rs1129555 SNP ($P < 0.05$-0.01; **Table 5**). As shown in **Table 6**, when the correlation between serum lipid parameters and the genotypes was analyzed according to gender, the TG levels were assocated with genotypes in Han males and serum LDL-C levels in Maonan males were correlated with the genotypes ($P < 0.05$-0.01 for all; **Table 6**). Blood lipid phenotypes were also correlated with several environmental factors such as age, gender, weight, waist circumference, alcohol consumption, and cigarette smoking, and traditional cardiovascular risk factors such as BMI, fasting blood glucose, and blood pressure levels in males and females of both ethnics ($P < 0.05$-0.001; **Tables 5** and **6**).

Discussion

China has experienced a considerable increase in the prevalence of CHD over the past years [31]. Disorders of lipid metabolism plays an important role in the pathogenesis and development of atherosclerosis and CHD. It is widely accepted that genetic variants and interactions with environmental factors have a great impact on serum lipid levels. Numerous studies have

Table 3. Comparison of the genotype and serum lipid levels in the Han and Maonan 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								
CC	335	4.85±1.17	1.03 (0.29)	1.76±0.74	2.71±0.75	1.35±0.23	0.85±0.24	1.72±0.77
CT	345	5.00±1.01	1.10 (0.45)	1.71±0.42	2.87±0.77	1.34±0.24	0.85±0.19	1.65±0.47
TT	99	5.04±0.98	1.16 (0.61)	1.66±0.39	2.93±0.73	1.31±0.22	0.88±0.20	1.58±0.50
F		1.376	7.786	1.905	3.274	1.938	1.510	2.908
P		0.253	0.020	0.150	0.038	0.145	0.221	0.055
Maonan								
CC	372	4.76±1.05	1.16 (0.41)	1.64±0.31	2.75±0.62	1.39±0.19	0.84±0.17	1.70±0.40
CT	305	5.00±0.96	1.28 (0.54)	1.60±0.39	2.87±0.71	1.37±0.22	0.89±0.19	1.64±0.49
TT	43	5.01±0.91	1.25 (0.52)	1.56±0.38	2.99±0.62	1.35±0.20	0.88±0.18	1.60±0.39
F		1.421	3.303	1.191	4.308	1.589	1.043	1.546
P		0.242	0.192	0.305	0.014	0.205	0.353	0.214

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoA1/ApoB, the ratio of apolipoprotein A1 to apolipoprotein B. The value of TG was presented as median (interquartile range). The difference between the genotypes was determined by the Kruskal-Wallis test.

indicated that ~40-60% of variation in serum lipid profiles was genetically determined [11]. The Han nationality is the largest ethnic group and widely live in 2/3 regions of China, whereas the Maonan nationality is a peculiar mountainous minority in Guangxi. Maonan people mainly engage in agriculture and are good at raising beef cattle and preparing the bamboo hat. Special geographical and folk customs formed a cooking culture with distinct characteristics. Corn and rice are the main food for them and sweet potatoes, pumpkin, and sorghum are an important supplement. In addition, the individuals of Maonan nationality are more inclined to eat pickles, sauerkraut and spicy and sour dishes. Maonan nationality preserves their custom of ethnic intermarriages, with parents arranging marriages being common. They have their culture of consanguineous marriage to cousins of maternal side, intermarriage with Han or Zhuang people seldom occurs. In summary, owing to their unique diet habits, lifestyle, and endogamy customs, we speculate that the hereditary characteristics of lipid metabolism-realted genes in Maonan ethnic group may be different from those in Han Chinese.

The genotypic and allelic frequencies of the rs1129555 SNP in diverse ethnic groups are significantly different, which can be found on the International HapMap project data-base. The frequencies of C and T alleles were 70.34% and 34.81% in European; 74.17% and 31.71% in Yoruba; 80% and 20% in Japanese; 68.29% and 31.71% in Chinese Han in Beijing. In the present study, we showed that the frequencies of C and T alleles were 72.85% and 27.15% in Maonan, and 65.19% and 34.81% in Han ($P < 0.001$), which were in close proximity to those of Chinese Han Beijing; the T allele frequency of the rs1129555 SNP was lower in Maonan than in Han. The distribution of TT and CT genotypes was also different in two ethnic groups ($P < 0.001$). Gender subgroup analysis showed that there were no conspicuous differences in the genotypic and allelic frequencies between males and females in the Maonan and Han populations. These findings suggest that the genotype and allele frequencies of the rs1129555 SNP in *GPAM* may exhibit a racial/ethnic specificity.

Several previous GWASs reported that genetic polymorphism in *GPAM* was significantly associated with plasma lipid levels. A study of common and rare lipid-associated risk loci has indentified that the *GPAM* rs1129555 SNP is associated with serum LDL-C concentrations in European population [19]. A meta-analysis of the mechanisms and genetic determinant regulating human lipid disease showed that the minor allele of the rs1129555 SNP was related with higher blood LDL-C and TC levels [32]. In the current study, we found that the rs1129555

Table 4. Comparison of the genotypes and serum lipid levels between males and females in the Han and Maonan 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
Han/male								
CC	138	5.00±1.32	1.03 (0.29)	1.74±0.44	2.79±0.81	1.36±0.26	0.92±0.27	1.58±0.45
CT	125	5.09±0.95	1.12 (0.56)	1.67±0.45	2.88±0.75	1.35±0.28	0.88±0.20	1.60±0.46
TT	43	5.16±0.96	1.32 (0.79)	1.59±0.37	2.96±0.68	1.30±0.24	0.91±0.19	1.49±0.45
F		0.421	8.685	2.756	0.993	1.940	0.859	2.177
P		0.657	0.013	0.065	0.372	0.145	0.425	0.115
Han/female								
CC	198	4.73±1.05	1.02 (0.34)	1.78±0.92	2.64±0.70	1.34±0.19	0.80±0.20	1.82±0.94
CT	220	4.94±1.03	1.09 (0.44)	1.73±0.40	2.85±0.79	1.33±0.22	0.83±0.18	1.68±0.47
TT	56	4.97±0.99	1.11 (0.47)	1.72±0.40	2.90±0.76	1.32±0.21	0.85±0.21	1.65±0.52
F		1.179	2.054	0.305	2.511	0.350	1.375	1.998
P		0.308	0.358	0.737	0.082	0.705	0.254	0.137
Maonan/male								
CC	158	4.69±0.90	1.15 (0.28)	1.61±0.31	2.71±0.58	1.34±0.21	0.80±0.16	1.73±0.39
CT	115	4.98±0.95	1.25 (0.76)	1.53±0.38	2.76±0.68	1.36±0.24	0.89±0.21	1.63±0.61
TT	18	4.99±0.89	1.38 (0.57)	1.55±0.43	2.99±0.58	1.33±0.19	0.89±0.17	1.56±0.38
F		0.908	1.917	0.339	5.463	0.448	2.132	1.458
P		0.405	0.384	0.713	0.005	0.639	0.120	0.234
Maonan/female								
CC	214	4.81±1.16	1.16 (0.49)	1.67±0.31	2.78±0.66	1.42±0.18	0.87±0.18	1.69±0.42
CT	190	5.01±0.97	1.20 (0.47)	1.64±0.40	2.94±0.71	1.38±0.20	0.88±0.19	1.64±0.40
TT	25	5.03±0.92	1.26 (0.39)	1.57±0.35	2.98±0.64	1.36±0.20	0.87±0.18	1.63±0.39
F		0.585	2.818	2.042	1.125	1.356	0.156	0.277
P		0.557	0.244	0.131	0.326	0.259	0.855	0.758

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoA1/ApoB, the ratio of apolipoprotein A1 to apolipoprotein B. The value of TG was presented as median (interquartile range). The difference between the genotypes was determined by the Kruskal-Wallis test.

SNP was significant associated with multiple serum lipid parameters in the Maonan and Han populaitons. The T allele carriers had higher TG in Han and higher LDL-C in both ethnic groups than the T allele non-carriers. Gender subgroup analyses showed that the T allele carriers had higher TG levels in Han males and higher LDL-C levels in Maonan males but not in famales in both ethnics. These experimental results indicate that the association between the *GPAM* 1129555 SNP and serum lipid levels may have racial/ethnic and/or sex specificity. *GPAM* has been considered to be the rate-limiting step in the pathway of glycerolipid synthesis and to regulate fatty acid flux through the pathway, which plays a key role in lipid biosynthesis. Animal models and *in vitro* studies showed that *GPAM* is upregulated transcriptionally by sterol regulatory element-binding protein-1c (SREBP-1c) and downregulated acutely by AMP-activated protein kinase, consistent with a role in TG synthesis [33]. Combined with our experimental results, we speculate that the *GPAM* rs1129555 mutation may act in the rate-limiting step of glycerolipid synthesis and bring about the cascade of events in dyslipidemia. However, the biogical role and function of the rs1129555 SNP in lipid metabolism need to be further investigation.

The influence extents of genetic and environmental factors on serum lipid levels remain a controversial issue, but several environmental factors such as low-carbohydrate and high-fat dietary patterns, obesity, hypertension, diabetes and unhealthy lifestyle have been associated with serum lipid levels [34]. In the present study, multivariate linear regression analysis

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

Lipid	Risk factor	B	Std.error	Beta	*t*	*P*
Han and Maonan						
TC	Waist circumference	0.019	0.005	0.165	3.903	0.000
	Diastolic blood pressure	0.008	0.002	0.093	3.438	0.001
	Glucose	0.042	0.015	0.072	2.735	0.006
TG	Alocohol consumption	0.164	0.075	0.065	2.185	0.029
	Cigarette smoking	0.428	0.101	0.134	4.247	0.000
	Distolic blood pressure	0.010	0.003	0.079	3.021	0.003
	Waist cirumference	0.041	0.007	0.230	5.637	0.000
	Glucose	0.096	0.023	0.106	4.164	0.000
HDL-C	Ethnic group	-0.099	0.0262	-0.114	-4.488	0.000
	Gender	0.131	0.034	0.148	3.809	0.000
	Cigarette smoking	0.075	0.028	0.084	2.635	0.009
	Alocohol consumption	0.089	0.021	0.128	4.210	0.000
	Waist circumference	-0.008	0.002	-0.159	-3.843	0.000
LDL-C	Waist circumference	0.012	0.003	0.150	3.533	0.000
	Genotype	0.011	0.004	0.124	3.296	0.001
	Distolic blood pressure	0.004	0.002	0.065	2.393	0.017
	Glucose	0.022	0.011	0.053	1.980	0.048
ApoA1	Alcohol consumption	0.076	0.011	0.217	7.077	0.000
	Ethnic group	0.036	0.011	0.081	3.161	0.002
	Cigarette smoking	0.069	0.014	0.154	4.784	0.000
	Gender	0.087	0.018	0.193	4.940	0.000
ApoB	Waist circumference	0.005	0.001	0.229	5.617	0.000
	Glucose	0.010	0.003	0.094	3.661	0.000
	Age	0.001	0.000	0.107	3.639	0.000
	Distolic blood pressure	0.001	0.000	0.061	2.346	0.019
ApoA1/ApoB	Gender	0.182	0.038	0.182	4.769	0.000
	Age	-0.004	0.001	-0.130	-4.398	0.000
	Alcohol consumption	0.097	0.023	0.124	4.141	0.000
	Cigarette smoking	0.105	0.031	0.105	3.330	0.001
	Height	0.018	0.007	0.287	2.396	0.017
	Weight	-0.022	0.010	-0.440	-2.157	0.023
	Waist circumference	-0.010	0.002	-0.185	-4.532	0.000
	Glucose	-0.015	0.007	-0.052	-2.056	0.040
Han						
TC	Waist circumference	0.002	0.008	0.178	2.898	0004
	Glucose	0.071	0.019	0.136	3.750	0.000
	Distolic blood pressure	0.012	0.003	0.139	3.810	0.000
TG	Age	-0.014	0.005	-0.109	-2.726	0.007
	Cigarette smoking	0.471	0.152	0.135	3.098	0.002
	Waist circumference	0.057	0.013	0.269	4.423	0.000
	Glucose	0.105	0.032	0.119	3.327	0.001
	Genotype	0.354	0.154	0.103	2.297	0.022
HDL-C	Gender	0.139	0.052	0.145	2.658	0.008
	Cigarette smoking	0.113	0.042	0.121	2.708	0.007
	Alcohol consumption	0.087	0.032	0.117	2.715	0.007

LDL-C	Gender	-0.214	0.085	-0.138	-2.523	0.012
	Glucose	0.041	0.014	0.107	2.895	0.004
	Genotype	0.016	0.008	0.118	2.001	0.046
ApoA1	Gender	0.064	0.025	0.133	2.514	0.012
	Age	-0.002	0.001	-0.116	-2.903	0.004
	Cigarette smoking	0.093	0.020	0.201	4.616	0.000
	Alcohol consumption	0.092	0.016	0.246	5.897	0.000
	Weight	-0.014	0.007	-0.554	-2.074	0.038
ApoB	Gender	-0.059	0.022	-0.143	-2.696	0.007
	Waist circumference	0.004	0.002	0.168	2.779	0.006
	Glucose	0.015	0.004	0.143	4.207	0.000
ApoA1/ApoB	Gender	0.229	0.058	0.209	3.934	0.000
	Age	-0.006	0.002	-0.143	-3.583	0.000
	Cigarette smoking	0.151	0.047	0.141	3.252	0.001
	Alcohol consumption	0.091	0.036	0.106	2.525	0.012
Maonan						
TC	Age	0.007	0.004	0.108	2.008	0.045
	Waist circumference	0.023	0.007	0.203	3.041	0.002
TG	Waist circumference	0.030	0.006	0.299	4.764	0.000
HDL-C	Gender	0.148	0.048	0.174	3.112	0.002
	Height	0.019	0.009	0.407	2.159	0.031
	Waist circumference	-0.006	0.003	-0.146	-2.251	0.025
LDL-C	Waist circumference	0.019	0.005	0.246	3.731	0.000
	Genotype	0.020	0.005	0.260	3.970	0.000
ApoA1	Gender	0.094	0.027	0.202	3.519	0.000
ApoB	Age	0.002	0.001	0.154	3.037	0.003
	Waist circumference	0.007	0.001	0.360	5.698	0.000
ApoA1/ApoB	Waist circumference	-0.015	0.003	-0.350	-5.546	0.000

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

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

Lipid	Risk factor	B	Std. error	Beta	*t*	*P*
Han/male						
TC	Waist circumference	0.027	0.012	0.226	2.216	0.027
TG	Genotype	0.554	0.225	0.142	2.421	0.016
	Age	-0.027	0.012	-0.163	-2.333	0.020
	Cigarette smoking	0.460	0.226	0.120	2.036	0.043
	Waist circumference	0.090	0.028	0.322	3.214	0.001
	Glucose	0.177	0.083	0.127	2.138	0.033
HDL-C	Cigarette smoking	0.094	0.040	0.137	2.349	0.019
	Alcohol consumption	0.086	0.030	0.167	2.856	0.005
LDL-C	Age	-0.008	0.004	-0.158	-2.188	0.030
	Cigarette smoking	-0.189	0.073	-0.158	-2.558	0.010
ApoA1	Cigarette smoking	0.080	0.024	0.189	3.381	0.001
	Alcohol consumption	0.095	0.018	0.296	5.297	0.000

showed that serum lipid parameters were correlated to age, gender, weight, waist circumference, BMI, blood pressure, fasting blood glucose levels, alcohol consumption, and cigarette smoking in both ethnic groups. These results suggest that environmental factors and their interactions with a hereditary component also play a critical role in determining serum lipid levels in our study populations. Moreover, the percentages of subjects who con-

	Weight	-0.021	0.010	-0.748	-2.190	0.029
ApoB	Diastolic blood pressure	0.003	0.001	0.173	2.627	0.009
	Glucose	0.018	0.007	0.149	2.475	0.014
ApoA1/ApoB	Cigarette smoking	0.118	0.043	0.157	2.760	0.006
	Alcohol consumption	0.098	0.032	0.171	3.018	0.003
Han/female						
TC	Glucose	0.078	0.022	0.162	3.563	0.000
TG	Waist circumference	0.029	0.012	0.186	2.359	0.019
	Diastolic blood pressure	0.015	0.005	0.138	2.879	0.004
	Glucose	0.075	0.025	0.136	2.955	0.003
HDL-C	Waist circumference	-0.009	0.003	-0.145	-3.031	0.003
LDL-C	Age	0.010	0.003	0.176	3,231	0.001
	Glucose	0.039	0.017	0.108	2.352	0.019
ApoA1	Age	-0.003	0.001	-0.163	-2.939	0.003
	Cigarette smoking	0.197	0.061	0.157	3.211	0.011
	Body mass index	-0.084	0.036	-1.174	-2.330	0.020
	Height	-0.022	0.010	-0.641	-2.109	0.035
ApoB	Age	0.002	0.001	0.165	3.105	0.002
	Cigarette smoking	-0.122	0.054	-0.106	-2.273	0.023
	Glucose	0.012	0.004	0.135	3.010	0.003
ApoA1/ApoB	Age	-0.010	0.002	-0.235	-4.369	0.000
	Cigarette smoking	0.555	0.158	0.166	3.504	0.001
Maonan/male						
TC	Height	-0.125	0.062	-0.917	-2.010	0.045
	Weight	0.179	0.083	1.983	2.144	0.033
TG	Alcohol consumption	0.272	0.136	0.117	2.044	0.046
	Waist circumference	0.044	0.021	0.216	2.130	0.034
	Glucose	0.214	0.073	0.166	2.920	0.004
HDL-C	Waist circumference	-0.017	0.004	-0.395	-3.856	0.000
	Alcohol consumption	0.115	0.030	0.230	3.896	0.000
LDL-C	Alcohol consumption	-0.098	0.049	-0.123	-1.985	0.048
	Genotype	0.120	0.029	0.243	4.100	0.000
ApoA1	Waist circumference	-0.005	0.002	-0.231	-2.206	0.028
	Alcohol consumption	0.074	0.016	0.286	4.749	0.000
ApoB	Weight	0.037	0.016	1.805	2.083	0.038
	Age	0.002	0.001	0.158	2.248	0.025
	Glucose	0.019	0.007	0.145	2.620	0.009
ApoA1/ApoB	Waist circumference	-0.012	0.005	-0.227	-2.246	0.026
Maonan/female						
TC	Age	0.011	0.004	0.162	2.771	0.006
	Waist circumference	0.023	0.008	0.186	2.739	0.006
TG	Waist circumference	0.028	0.006	0.316	4.944	0.000
HDL-C	Height	0.022	0.011	0.305	2.033	0.043
	Waist circumference	-0.006	0.003	-0.139	-2.072	0.039
LDL-C	Age	0.007	0.003	0.154	2.680	0.008
	Waist circumference	0.018	0.005	0.226	3.381	0.001
ApoA1	Waist circumference	-0.003	0.002	-0.146	-2.146	0.032
ApoB	Age	0.003	0.001	0.209	3.793	0.000
	Waist circumference	0.008	0.001	0.354	5.528	0.000

sumed alcohol and smoked cigarettes were higher in Maonan than in Han. Moderate alcohol intake has been showed to reduce cardiovascular events, and the beneficial effects of alcohol on CHD have been ascribed to the increase in HDL-C and ApoA1 levels [35]. Long-term alcohol abuse can cause liver damage, hypertriglyceridemia, hypertension and serious cardiovascular lesions. In a previous meta-analysis, 30 g of alcohol daily was associated with a plasma TG increase of 5.69 mg/dl, wheres alcohol intake of 60 g/day increased the TG levels by about 0.19 mg/dL per 1 gram of alcohol consumed [36]. The influence of alcohol on blood lipid metabolism seems to be different among males and famales. A previous study of Turks found that the levels of LDL-C as well as ApoB and TG were increased in male drinkers, while females had decreased TG and no change in LDL-C or ApoB with alcohol [37]. Another research study indicated that the effects of alcohol consumptionon on LDL-C levels appear to vary by specific patient types or patterns of alcohol intake, and sex as well as genetic variants [38]. Smoking has been strongly implicated as a risk factor for dyslipidemia, arteriosclerosis, chronic obstructive pulmonary disease, and lung cancer. Cigarettes contain a large number of

	Pulse pressure	0.002	0.001	0.187	3.716	0.000
ApoA1/ApoB	Age	-0.004	0.001	-0.139	-2.497	0.013
	Waist circumference	-0.016	0.003	-0.350	-5.436	0.000
	Systolic blood pressure	-0.003	0.001	-0.175	-2.616	0.009

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

oxidants and many adverse effects of smoking result from oxidative damage to cirtical biologic substances. A related study indicated that oxidation of LDL by cigarette smoking may contribute a causative link between cigarette smoking and atherogenesis [39]. Additionally, according to the results of a meta analysis based on 7,256 subjects, smoking increased TG by 13 mg/dl (0.15 mmol/L) and decreased HDL-C by 3.5 mg/dl (0.09 mmol/L) with every 20 cigarettes smoked [40]. It is well accepted that dietary patterns are strongly related with serum lipid profiles and the prevalence of dyslipidemia. The people of Maonan nationality like to eat cold foods along with acidic and spicy dishes, so acidic meat and pickled vegetables are among their most popular dishes, which contain abundant sodium salt. This preference of high-carbohydrates and salt diet may be related to the higher TG, LDL-C levels, and waist circumference in Maonan than in Han populations. Numerous studies have indentified that dietary intake of saturated and trans-fat raises blood cholesterol concentrations and CVD risk [41, 42]. Diet and relative weight could account for up to 6% of the variability in serum cholesterol levels and 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 [43]. To summarize, the mutual effects of different eating habits, lifestyles, and environmental factors probably further modify the association of genetic variations and serum lipid levels in our study populations.

Limitations

There are several potential limitations in our study. First, the sample size is relatively small compared to many GWASs and replication studies, further studies with larger sample sizes are needed to confirm our results. Second, we were not able to alleviate the effect of diet and several environmental factors during the statistical analysis. Third, although we have detected effects of *GPAM* rs1129555 SNP on serum lipid levels in our study, there are still many lipid-related SNPs and the interaction of SNP-SNP and/or SNP-environmental factors. Thus, further studies on biological functions of the rs1129555 variation and interactions of gene-environment are necessary.

Conclusions

In conclusion, the genotype and allele frequencies of the rs1129555 SNP were significantly different between the Han and Maonan populations. The minor T allele carriers have more unfavorable serum lipid profiles than the T allele non-carriers in both ethnic groups. These findings suggest that the association between the *GPAM* rs1129555 variant and serum lipid levels might have racial/ethnic- and/or sex- specificity.

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Disclosure of conflict of interest

None.

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References

[1] Roberts R, Stewart AF. Genes and coronary artery disease: where are we? J Am Coll Cardiol 2012; 60: 1715-1721.

[2] Dorn GW, Cresci S. Genome-wide association studies of coronary artery disease and heart failure: where are we going. Pharmacogenomics 2009; 10: 213-223.

[3] Ye X, Peng L, Kan H, Wang W, Geng F, Mu Z, Zhou J, Yang D. Acute effects of particulate air pollution on the incidence of coronary heart

disease in Shanghai, China. PLoS One 2016; 11: e0151119.
[4] Wang Y, Du F, Zhao H, Yu X, Liu J, Xiao Y, Lu C, Li X, Wang Y, Wang B, Niu W. Synergistic association between two alcohol metabolism relevant genes and coronary artery disease among Chinese hypertensive patients. PLoS One 2014; 9: e103161.
[5] Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2004; 326: 1419.
[6] Qian DF, Fan GL, Chen P, He DC, Fan JD, Feng C, Zhu PG, Zhou ZH, Liao YH. Risk factors for hyperuricemia in active and retired employees underwent physical examination. Zhonghua Xin Xue Guan Bing Za Zhi 2013; 41: 60-64.
[7] Vaverkova H. LDL-C or apoB as the best target for reducing coronary heart disease: should apoB be implemented into clinical practice. Clin Lipidol 2011; 6: 35-48.
[8] Graham I, Dan A, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, Backer GD, Ebrahim S, Gjelsvik B. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice. Eur Heart J 2007; 28: 2375-2414.
[9] Ordovás JM, Robertson R, Cléirigh EN. Gene-gene and gene-environment interactions defining lipid-related traits. Curr Opin Lipidol 2011; 22: 129-136.
[10] Pilia G, Chen WM, Scuteri A, Orrú M, Albai G, Dei M, Lai S, Usala G, Lai M, Loi P. Heritability of cardiovascular and personality traits in 6,148 Sardinians. PLoS Genet 2006; 2: e132.
[11] Draisma HH, Reijmers TH, Meulman JJ, van der Greef J, Hankemeier T, Boomsma DI. Hierarchical clustering analysis of blood plasma lipidomics profiles from mono- and dizygotic twin families. Eur J Hum Genet 2013; 21: 95-101.
[12] Kathiresan S, Willer CJ, Peloso GM, Demissie S, Musunuru K, Schadt EE, Kaplan L, Bennett D, Li Y, Tanaka T, Voight BF, Bonnycastle LL, Jackson AU, Crawford G, Surti A, Guiducci C, Burtt NP, Parish S, Clarke R, Zelenika D, Kubalanza KA, Morken MA, Scott LJ, Stringham HM, Galan P, Swift AJ, Kuusisto J, Bergman RN, Sundvall J, Laakso M, Ferrucci L, Scheet P, Sanna S, Uda M, Yang Q, Lunetta KL, Dupuis J, de Bakker PI, O'Donnell CJ, Chambers JC, Kooner JS, Hercberg S, Meneton P, Lakatta EG, Scuteri A, Schlessinger D, Tuomilehto J, Collins FS, Groop L, Altshuler D, Collins R, Lathrop GM, Melander O, Salomaa V, Peltonen L, Orho-Melander M, Ordovas JM, Boehnke M, Abecasis GR, MohIke KL, Cupples LA. Common variants at 30 loci contribute to polygenic dyslipidemia. Nat Genet 2009; 41: 56-65.
[13] Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin CY, Jin GM, Jin KY, Lee JY, Park T, Kim K, Sim X, Twee-Hee OR, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua ZJ, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, König IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees HG, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Döring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA, Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. Nature 2010; 466: 707-713.

[14] Gimeno RE, Cao J. Thematic review series: glycerolipids. Mammalian glycerol-3-phosphate acyltransferases: new genes for an old activity. J Lipid Res 2008; 49: 2079-88.
[15] Karlsson E, Wang SQ, Coleman R, Beck M. Glycerol-3-phosphate acyltransferase 1 is essential for the immune response to infection with coxsackievirus B3 in mice. J Nutr 2009; 139: 779-783.
[16] Coleman RA, Lee DP. Enzymes of triacylglycerol synthesis and their regulation. Prog Lipid Res 2004; 43: 134-176.
[17] Igal RA, Wang S, Gonzalez-Baró M, Coleman RA. Mitochondrial glycerol phosphate acyltransferase directs the incorporation of exogenous fatty acids into triacylglycerol. J Biol Chem 2001; 276: 42205-42212.
[18] Lewin TM, Wang S, Nagle CA, Van Horn CG, Coleman RA. Mitochondrial glycerol-3-phosphate acyltransferase-1 directs the metabolic fate of exogenous fatty acids in hepatocytes. Am J Physiol Endocrinol Metab 2005; 288: E835.
[19] Johansen CT, Wang J, Lanktree MB, McIntyre AD, Ban MR, Martins RA, Kennedy BA, Hassell RG, Visser ME, Schwartz SM, Voight BF, Elosua R, Salomaa V, O'Donnell CJ, Dallinga-Thie GM, Anand SS, Yusuf S, Huff MW, Kathiresan S, Cao H, Hegele RA. An increased burden of common and rare lipid-associated risk alleles contributes to the phenotypic spectrum of hypertriglyceridemia. Arterioscler Thromb Vasc Biol 2011; 31: 1916-1926.
[20] Tikkanen E, Tuovinen T, Widén E, Lehtimäki T, Viikari J, Kähönen M, Peltonen L, Raitakari OT, Ripatti S. Association of known loci with lipid levels among children and prediction of dyslipidemia in adults. Circ Cardiovasc Genet 2011; 4: 673-80.
[21] Qi Q, Liang L, Doria A, Hu FB, Qi L. Genetic predisposition to dyslipidemia and type 2 diabetes risk in two prospective cohorts. Diabetes 2012; 61: 745-752.
[22] Deng Q, Lin X, Gong J, Zhou L, Li S, Deng X, Luo G, Xie X. Genetic relationships among four minorities in Guangxi revealed by analysis of 15 STRs. J Genet Genomics 2007; 34: 1072-1079.
[23] Wang Y, Aung LHH, Tan JY, Yin RX, Hu XJ, Long XJ, Wu DF, Miao L, Yang DZ, Pan SL. Prevalence of dyslipidemia and its risk factors in the Chinese Maonan and Han populations. International Journal of Clinical & Experimental Medicine 2016.
[24] Lin QZ, Yin RX, Guo T, Wu J, Sun JQ, Shen SW, Shi GY, Wu JZ, Liu CW, Pan SL. Association of the ST3GAL4 rs11220462 polymorphism and serum lipid levels in the Mulao and Han populations. Lipids Health Dis 2014; 13: 123-123.
[25] An epidemiological study of cardiovascular and cardiopulmonary disease risk factors in four populations in the People's Republic of China. Baseline report from the P.R.C.-U.S.A. collaborative study. People's Republic of China--United states cardiovascular and cardiopulmonary epidemiology research group. Circulation 1992; 85: 1083-1096.
[26] Guo T, Yin RX, Li H, Wang YM, Wu JZ, Yang DZ. Association of the Trp316Ser variant (rs1801690) near the apolipoprotein H (beta-2glycoprotein-I) gene and serum lipid levels. Int J Clin Exp Pathol 2015; 8: 7291-7304
[27] Miao L, Yin RX, Wu JZ, Yang S, Lin WX, Pan SL. The SRGAP2 SNPs, their haplotypes and G × E interactions on serum lipid traits. Sci Rep 2017; 7: 11626.
[28] Tao G, Yin RX, Yuan B, Nie RJ, Xia C, Pan SL. Association of the SPT2 chromatin protein domain containing 1 gene rs17579600 polymorphism and serum lipid traits. Int J Clin Exp Pathol 2015; 8: 12995-13010.
[29] Ramazauskiene V, Petkeviciene J, Klumbiene J, Kriaucioniene V, Sakytė E. Diet and serum lipids: changes over socio-economic transition period in Lithuanian rural population. BMC Public Health 2011; 11: 447.
[30] Whitworth JA. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003; 21: 1983-1992.
[31] Joanne F, Huo Y, Ji L, Zhao D, Dylan B, Meng HJ, Susan S, Hu D. Unique and varied contributions of traditional CVD risk factors: a systematic literature review of CAD risk factors in China. Clin Med Insights Cardiol 2013; 7: 59-86.
[32] Calandra S, Tarugi P, Speedy HE, Dean AF, Bertolini S, Shoulders CC. Mechanisms and genetic determinants regulating sterol absorption,circulating LDL levels, and sterol elimination: implications for classificationand disease risk. J Lipid Res 2011; 52: 1885-926.
[33] Ehara T, Kamei Y, Takahashi M, Yuan X, Kanai S, Tamura E, Tanaka M, Yamazaki T, Miura S, Ezaki O, Suganami T, Okano M, Ogawa Y. Role of DNA methylation in the regulation of lipogenic glycerol-3-phosphate acyltransferase 1 gene expression in the mouse neonatal liver. Diabetes 2012; 61: 2442-2450.
[34] Ruixing Y, Qiming F, Dezhai Y, Shuquan L, Weixiong L, Shangling P, Hai W, Yongzhong Y, Feng H, Shuming Q. Comparison of demography, diet, lifestyle, and serum lipid levels between the Guangxi Bai Ku Yao and Han populations. J Lipid Res 2007; 48: 2673-81.
[35] Matsumoto C, Miedema MD, Ofman P, Gaziano JM, Sesso HD. An expanding knowledge of the mechanisms and effects of alcohol consump-

tion on cardiovascular disease. J Cardiopulm Rehabil Prev 2014; 34: 159-71.
[36] Perissinotto E, Buja A, Maggi S, Enzi G, Manzato E, Scafato E, Mastrangelo G, Frigo AC, Coin A, Crepaldi G, Sergi G; ILSA Working Group. Alcohol consumption and cardiovascular risk factors in older lifelong wine drinkers: the Italian longitudinal study on aging. Nutr Metab Cardiovasc Dis 2010; 20: 647-655.
[37] Onat A, Hergenc G, Dursunoglu D, Ordu S, Can G, Bulur S, Yüksel H. Associations of alcohol consumption with blood pressure, lipoproteins, and subclinical inflammation among Turks. Alcohol 2008; 42: 593-601.
[38] Brinton EA. Effects of ethanol intake on lipoproteins and atherosclerosis. Curr Opin Lipidol 2010; 21: 346-51
[39] Morrow JD, Frei B, Longmire AW, Gaziano JM, Lynch SM, Shyr Y, Strauss WE, Oates JA, Roberts LJ 2nd. Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers. Smoking as a cause of oxidative damage. N Engl J Med 1995; 332: 1198-203.
[40] Rao CS, Subash YE. The effect of chronic tobacco smoking and chewing on the lipid profile. J Clin Diagn Res 2013; 7: 31-34.
[41] Valente EA, Sheehy ME, Avila JJ, Gutierres JA, Delmonico MJ, Lofgren IE. The effect of the addition of resistance training to a dietary education intervention on apolipoproteins and diet quality in overweight and obese older adults. Clin Interv Aging 2011; 6: 235-241.
[42] Solá R, Fitó M, Estruch R, Salas-Salvadó J, Corella D, de La Torre R, Muñoz MA, López-Sabater Mdel C, Martínez-González MA, Arós F, Ruiz-Gutierrez V, Fiol M, Casals E, Wärnberg J, Buil-Cosiales P, Ros E, Konstantinidou V, Lapetra J, Serra-Majem L, Covas MI. Effect of a traditional Mediterranean diet on apolipoproteins B, A-I, and their ratio: a randomized, controlled trial. Atherosclerosis 2011; 218: 174-80.
[43] Bermudez OI, Velez-Carrasco W, Schaefer EJ, Tucker KL. Dietary and plasma lipid, lipoprotein, and apolipoprotein profiles among elderly Hispanics and non-Hispanics and their association with diabetes. Am J Clin Nutr 2002; 76: 1214-1221.