

## Original Article

# Sex-specific association of the peptidase D gene rs731839 polymorphism and serum lipid levels in the Mulao and Han populations

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**Abstract:** Little is known about the association of peptidase D (PEPD) gene rs731839 single nucleotide polymorphism (SNP) and serum lipid profiles in the Chinese population. The objective of the present study was to detect the association of the *PEPD* rs731839 SNP and serum lipid levels in the Mulao and Han populations. Genotyping of the *PEPD* rs731839 SNP was performed in 751 subjects of Mulao and 762 subjects of Han using polymerase chain reaction and restriction fragment length polymorphism and then confirmed by direct sequencing. The A allele carriers had higher serum high-density lipoprotein cholesterol (HDL-C), apolipoprotein (Apo) AI levels and lower triglyceride (TG) levels in Mulao; and higher HDL-C, low-density lipoprotein cholesterol (LDL-C) and ApoAI levels in Han than the A allele non-carriers. Subgroup analyses showed that the A allele carriers had higher HDL-C, ApoAI levels and lower TG levels in Mulao males but not in females; higher total cholesterol (TC), HDL-C, LDL-C and ApoAI levels in Han males; and higher TG, HDL-C and ApoAI levels in Han females than the A allele non-carriers. Serum lipid parameters were also correlated with several environmental factors in Mulao and Han populations, or in males and females in both ethnic groups. The association of the *PEPD* rs731839 SNP and serum lipid levels was different between the Mulao and Han populations, and between males and females in the both ethnic groups. There may be an ethnic- and/or sex-specific association of the *PEPD* rs731839 SNP and serum lipid levels in our study populations.

**Keywords:** Lipids, sex-specific association, peptidase D (PEPD) gene, single nucleotide polymorphism, environmental factors

## Introduction

The prevalence of cardiovascular disease (CVD), which contributes to approximately 30% of deaths worldwide over several decades, continues to rise surely in both developing and developed countries [1, 2]. It is well established that dyslipidemia is a major risk factor for CVD among several conventional risk factors such as older age, positive family history, diabetes mellitus, obesity, hypertension, tobacco use, and unhealthy diet [3-5]. Dyslipidemia in the forms of hypertriglyceridemia, hypercholesterolemia, and low high-density lipoprotein cholesterol (HDL-C) has been widely accepted as a result of complex interactions between genetic and environmental factors [6, 7]. Approximately

43-83% of the variability in serum lipid levels is attributable to genetic factors from twin and family-based studies [8-10]. The discovery of common genetic variants related to lipid traits including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and HDL-C may provide new insights into target preventive intervention which is a key to reduce the global burden of CVD.

Meanwhile, gender differences are reported in the regulation of lipid metabolism for many years [11]. However, the reasons for these differences concerned with gender remain unclear. It seems to be the result of a complex network of gene expression or sexual hormones in sexually dimorphic manner [12]. Thus, the focus on sex-specific

association between single nucleotide polymorphisms (SNPs) and serum lipid levels may also inspire a new way for individualized treatment.

Since 2006, candidate gene studies as well as genome-wide association studies (GWASs) have screened out many causative genes associated with dyslipidemia [13-15]. Likewise, it has reported that the identified common variants associated with blood lipids, can account for ~10-12% of total trait variations [13]. A newly GWAS conducted in European-ancestry population for lipid traits has identified several new loci associated with TG and HDL-C levels, peptidase D (PEPD) gene included [15]. *PEPD*, located at chromosome 19q13, encodes a member of the peptidase family [16]. Human peptidase, responsible for hydrolyzing dipeptides with proline or hydroxyproline at the carboxyl terminus, plays a crucial role in collagen turnover, which is the essential content in atherosclerotic plaque [17, 18]. A recent GWAS about insulin resistance has mentioned that the *PEPD* rs731839 SNP was associated with adiponectin levels (an adipocyte-secreted protein correlated with HDL-C concentration, TG levels, and other cardiovascular risks) and it was likely to have a role in adipokine biology supported by eQTL data in adipose tissue [19]. A meta-analysis including 7827 East Asians also revealed that a locus (rs889140) in *PEPD* associated with adiponectin [20]. In addition, another meta-analysis stated that the rs3786897 SNP in an intron of *PEPD* was highly associated with mRNA expression levels of *PEPD* in the adipose tissue of 776 individuals of European ancestry ( $P_{eQTL} = 2.14 \times 10^{-8}$ ) [21]. Moreover, increasing evidence suggested that *PEPD* variants were significantly associated with type 2 diabetes [21-23]. However, to our best knowledge, the biological function of the *PEPD* rs731839 on serum lipid metabolism remains unclear at this time. Importantly, the genetic variation has different magnitudes of effect in the different ethnicities but until now no GWAS has comprehensively investigated the genetic determinants of serum lipid levels in Chinese populations. Therefore, it would be attractive to characterize the relationship between the rs731839 SNP and serum lipid levels in Chinese populations.

China is a multiethnic country with Han as the majority nationality and 55 ethnic minorities.

Mulao nationality is a distinctive ethnic group with population of 207,352 according to the fifth national census statistics of China in 2000. Ninety percent of them settled in the Luocheng Mulao Autonomous County, Guangxi Zhuang Autonomous Region, People's Republic of China. The history and culture of this minority radiated with eternal light in ancient Chinese culture, may trace to ancient Baiyue tribe in south China in the Jin Dynasty (AD265-420). A previous study has showed that the genetic relationship between Mulao nationality and other minorities in Guangxi was much closer than that between Mulao and Han or Uighur nationality [24]. The population resident in Guangxi has various lifestyles and environments which may lead to the effect of genetic variation to be further modified. Since different lifestyles and customs inherited in Mulao population, it tends to be more genetically isolated. Therefore, we believed that the Mulao nationality has become a meaningful group for population genetic analysis. However, no previous research has been demonstrated the association between the *PEPD* rs731839 SNP and serum lipid levels in this population. Thus, the present study was aiming to detect and get insight into the association of rs731839 SNP and several environmental factors with serum lipid traits in the Guangxi Mulao and Han populations.

## Materials and methods

### Study population

Participants in the present study included 751 subjects of Mulao and 762 subjects of Han Chinese who were randomly selected from our previous stratified randomized samples [25, 26]. All of them were rural agricultural workers lived in Luocheng Mulao Autonomous County, Guangxi Zhuang Autonomous Region, People's Republic of China. The Mulao comprised 372 (49.5%) males and 379 (50.5%) females, aged from 17 to 89 years, with a mean age of  $53.45 \pm 15.03$  years. The subjects of Han consisted of 371 (48.7%) males and 391 (51.3%) females, aged from 15 to 87 years, with a mean age of  $53.35 \pm 15.19$  years. The subjects had no evidence of any chronic illness, including hepatic, renal, or thyroid diseases and did not take medications known to affect serum lipid levels (lipid-lowering drugs such as statins or fibrates, beta-blockers, diuretics, or hormones). The par-

ticipants with diseases related to atherosclerosis, CVD, and stroke were excluded from the analyses. Ethical approval for this study was obtained from the Ethics Committee of the First Affiliated Hospital Guangxi Medical University. All participants signed informed consent forms in accordance with ethics guidelines regarding the study.

#### *Epidemiological survey*

The survey was carried out using internationally standardized methods [27]. All participants underwent anthropometric measurements by trained personnel of health care centers including height, weight, and waist circumference. Information on demographics, socioeconomic status, and lifestyle factors was collected with standardized questionnaires. The alcohol information included questions about the number of *liang* (about 50 g) of rice wine, corn wine, rum, beer, or liquor consumed during the preceding 12 months. Alcohol consumption was categorized into groups of grams of alcohol per day:  $\leq 25$  and  $> 25$ . Smoking status was divided into groups of cigarettes per day:  $\leq 20$  and  $> 20$ . Sitting blood pressure was measured three times with the use of a mercury sphygmomanometer after the subjects had a 5-minute rest, and the average of the three measurements was used for the level of blood pressure. Systolic blood pressure (SBP) was determined by the first Korotkoff sound, and diastolic blood pressure (DBP) was determined by the fifth Korotkoff sound. Body weight, to the nearest 50 grams, was measured by using a portable balance scale. Subjects were weighed without shoes and minimum of clothing. Height was measured, to the nearest 0.5 cm, using a portable measuring device. Body mass index (BMI) was calculated as  $\text{weight}/\text{height}^2$  ( $\text{kg}/\text{m}^2$ ).

#### *Laboratory methods*

Blood samples were collected from individuals after a 12-hour fast. Biochemical parameters including serum TC, TG, HDL-C, and LDL-C in the samples were measured by standard 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) AI and ApoB concentrations were quantified by the immunoturbidimetric immunoassay using a

commercial kit (RANDOX Laboratories Ltd.) [28]. Fasting blood glucose was determined by glucose meter.

#### *DNA preparation and genotyping*

Genomic DNA was isolated from peripheral blood leukocytes by standard phenol/chloroform method [25]. The extracted DNA was stored at  $-20^\circ\text{C}$  until analysis. Genotyping of the rs731839 SNP was performed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). The following primers were used for the amplification: a forward primer, 5'-TCCAGGGCAGCCAGATTA-3' and a reverse primer, 5'-GGTAAGGACGGAGCAGTAGG-3' (Sangon, Shanghai, People's Republic of China). Each 25  $\mu\text{L}$  PCR reaction mixture contained 100 ng (1.8  $\mu\text{L}$ ) of genomic DNA, 0.60  $\mu\text{L}$  of each primer (10  $\mu\text{mol}/\text{L}$ ), 12.5  $\mu\text{L}$   $2 \times \text{Taq PCR MasterMix}$  (constituent: 0.1 U *Taq* polymerase/ $\mu\text{L}$ , 500  $\mu\text{M}$  dNTP each, 20 mM Tris-HCl, pH 8.3, 100 mM KCl, 3 mM  $\text{MgCl}_2$ , and stabilizers), and 9.5  $\mu\text{L}$  nuclease-free water. Cycling was carried out on the thermal cycler with initial denaturation at  $94^\circ\text{C}$  for 5 min, followed by 30 cycles of denaturation phase at  $94^\circ\text{C}$  for 35 s, annealing at  $54.5^\circ\text{C}$  for 45 s, and extension at  $72^\circ\text{C}$  for 35 s with a final extension of 6 min at  $72^\circ\text{C}$ . After electrophoresis on a 2.0% agarose gel with 0.5  $\mu\text{g}/\text{mL}$  ethidium-bromide, the amplification products were visualized under ultraviolet light. A 5  $\mu\text{L}$  aliquot of the PCR product mixtures was completely digested using 2U of *Bsp1407I* restriction enzyme (Fermentas Inc., ON, Canada) at  $37^\circ\text{C}$  overnight. Digestion products were visualized through ethidium bromide staining after electrophoresis in 2.0% agarose gels. Genotypes were scored by an experienced reader blinded to epidemiological data and serum lipid levels. Six samples (each genotype in two; respectively) detected by the PCR-RFLP were also confirmed by direct sequencing. The PCR products were purified by low melting point gel electrophoresis and phenol extraction, and then the DNA sequences were analyzed using an ABI Prism 3100 (Applied Biosystems) in Shanghai Sangon Biological Engineering Technology & Services Co., Ltd., People's Republic of China.

#### *Diagnostic criteria*

The normal values of serum TC, TG, HDL-C, LDL-C, ApoAI, ApoB levels and the ratio of ApoAI to

**Table 1.** Comparison of demography, lifestyle and serum lipid levels between the Mulao and Han populations

Parameter	Mulao	Han	T ( $\chi^2$ )	P
Number	751	762		
Male/female	372/379	371/391	0.108	0.742
Age (years)	53.45 ± 15.03	53.35 ± 15.19	0.120	0.905
Height (cm)	155.64 ± 8.18	154.93 ± 7.78	1.723	0.085
Weight (kg)	52.83 ± 9.09	53.91 ± 8.83	-2.343	0.019
Body mass index (kg/m <sup>2</sup> )	21.75 ± 2.96	22.44 ± 3.30	-4.277	0.000
Waist circumference (cm)	74.87 ± 8.51	75.58 ± 7.93	-1.687	0.092
Cigarette smoking [n (%)]				
Nonsmoker	537 (71.5)	515 (67.6)		
≤ 20 cigarettes/day	173 (23.0)	217 (28.5)	7.049	0.029
> 20 cigarettes/day	41 (5.5)	30 (3.9)		
Alcohol consumption [n (%)]				
Nondrinker	545 (72.5)	577 (75.7)		
≤ 25 g/day	80 (10.7)	81 (10.6)	2.943	0.230
> 25 g/day	126 (16.8)	104 (13.6)		
Systolic blood pressure (mmHg)	130.09 ± 22.02	130.93 ± 19.28	-0.693	0.488
Diastolic blood pressure (mmHg)	81.31 ± 11.84	82.87 ± 11.12	-2.635	0.008
Pulse pressure (mmHg)	48.88 ± 16.28	48.06 ± 14.78	0.023	0.306
Blood glucose (mmol/L)	6.05 ± 1.61	6.05 ± 1.68	-1.415	0.157
Total cholesterol (mmol/L)	4.97 ± 1.16	5.06 ± 1.15	-1.546	0.122
Triglyceride (mmol/L)	1.09 (0.80)	1.08 (0.85)	1.006	0.314
HDL-C (mmol/L)	1.73 ± 0.43	1.74 ± 0.58	-0.149	0.881
LDL-C (mmol/L)	2.93 ± 0.88	2.91 ± 0.90	0.464	0.642
Apolipoprotein (Apo) AI (g/L)	1.31 ± 0.40	1.34 ± 0.27	-1.824	0.068
ApoB (g/L)	1.00 ± 0.59	0.87 ± 0.21	5.658	0.000
ApoAI/ApoB	1.57 ± 0.77	1.63 ± 0.69	-1.860	0.063

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoAI, apolipoprotein AI; ApoB, apolipoprotein B. The quantitative variables were presented as mean ± standard deviation and their difference between the groups was determined by the t-test. The values of triglyceride were presented as median (interquartile range), and their difference between the groups was determined by the Wilcoxon-Mann-Whitney test. The difference in percentage of cigarette smoking and alcohol consumption between the groups was determined by Chi-square-test.

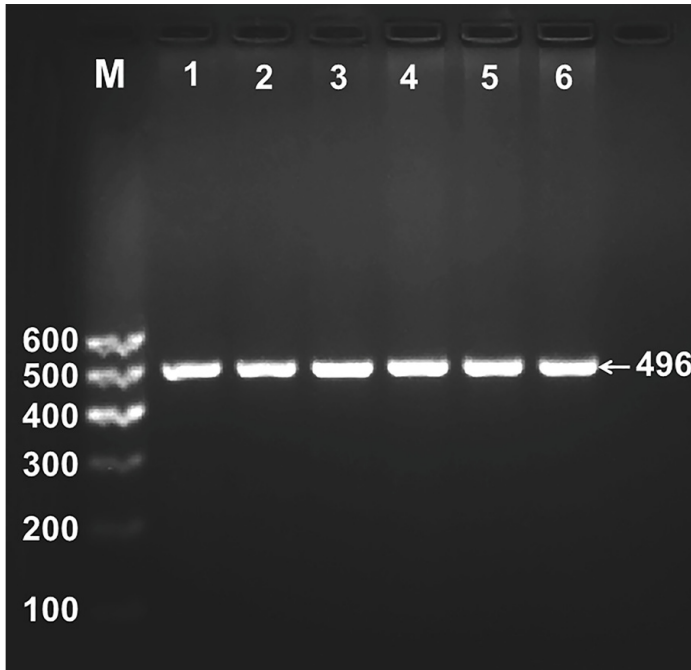
ApoB in our Clinical Science Experiment Center were 3.10-5.17, 0.56-1.70, 1.16-1.42, 2.70-3.10 mmol/L, 1.20-1.60, 0.80-1.05 g/L, and 1.00-2.50; respectively. Hyperlipidemia was defined as TC > 5.17 mmol/L, and/or TG > 1.70 mmol/L [26]. According to the criteria of 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension, hypertension was defined as an average SBP ≥ 140 mmHg, and/or an average DBP ≥ 90 mmHg in at least two separate measurements, and/or self-reported current treatment for hypertension with antihypertensive medication [29]. Normal weight,

overweight and obesity were defined as a BMI < 24, 24-28, > 28 kg/m<sup>2</sup>; respectively [30].

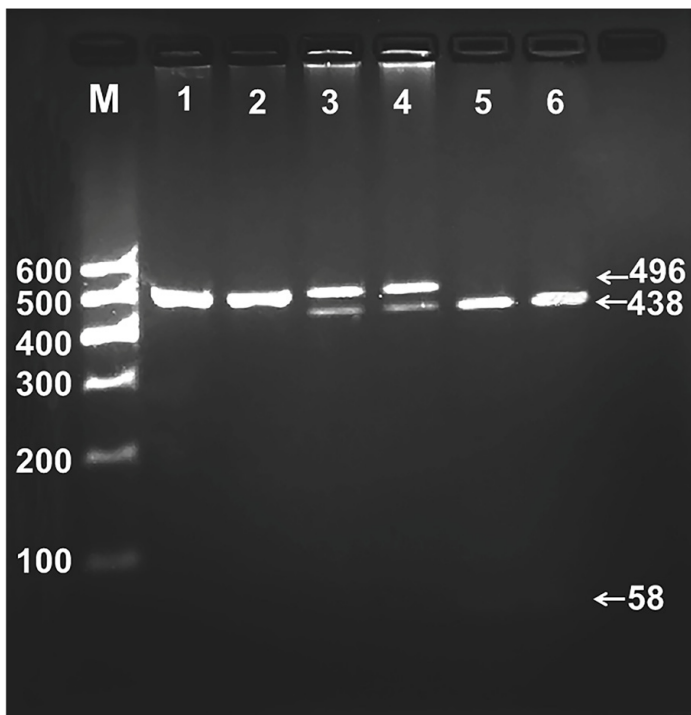
#### Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (serum TG levels were presented as medians and interquartile ranges). Qualitative variables were expressed as raw count and percentages. The Student's unpaired t-test was performed to estimate the difference in general characteristics between Mulao and Han. Allele frequency was determined via direct counting, and the Hardy-Weinberg equilibrium was verified with the standard goodness-of-fit test. Difference in genotype distribution between the groups was obtained using the chi-square test. The association of genotypes and serum lipid parameters

was tested by analysis of covariance (ANOVA). Multiple linear regression analyses were performed to assess the association of serum lipid levels with genotypes (GG = 1, GA = 2, AA = 3; or GG = 1, GA/AA = 2) and several environment factors. Age, sex, height, weight, BMI, waist circumference, blood pressure, alcohol consumption, cigarette smoking, and blood glucose were adjusted for both ANOVA and multiple linear regression analyses. A two-tailed P value less than 0.05 was considered statistically significant. All the statistical analyses were done with the statistical software package SPSS16.0 (SPSS Inc., Chicago, Illinois).



**Figure 1.** Electrophoresis of PCR products of the samples. Lane M, 100 bp marker ladder; lanes 1-6, samples. The 496 bp bands are the target genes.



**Figure 2.** Genotyping of the rs731839 SNP. Lane M, 100 bp marker ladder; lane 1 and 2, GG genotype (496 bp); lanes 3 and 4, GA genotype (496-, 438- and 58-bp); and lanes 5 and 6, AA genotype (438-bp). The 58 bp fragment was invisible in the gel owing to its fast migration speed.

## Results

### Population characteristics

The baseline characteristics and serum lipid levels of the Mulao and Han populations are presented in **Table 1**. The values of body weight, BMI and DBP were lower in Mulao than in Han ( $P < 0.05-0.001$ ), whereas the levels of ApoB and the percentages of individuals who smoked cigarettes were higher in Mulao than in Han ( $P < 0.05$ ). Gender subgroups showed that males had higher values of general characteristic parameters (height, weight, waist circumference, BMI, DBP, glucose, the percentages of subjects consuming alcohol and the percentages of individuals who smoked cigarettes) than females in both ethnic groups. Males had higher TG, ApoB levels and lower the ratio of ApoA1 to ApoB than females in both ethnic groups ( $P < 0.05$ ). Lower HDL-C and higher TC levels were noted in Han males (**Table S1**).

### Results of electrophoresis and genotyping

After the genomic DNA of the samples was amplified by PCR and imaged by 2.0% agarose gel electrophoresis, the purpose gene of 496 bp nucleotide sequences could be found in all samples (**Figure 1**). The genotypes identified were named according to the presence (A allele) or absence (G allele) of the enzyme restriction sites. Thus, GG genotype is homozygote for the absence of the site (bands at 496 bp), GA genotype is heterozygote for the absence and presence of the site (bands at 496-, 438- and 58-bp), and the AA genotype is homozygote for the presence of the site (bands at 438- and 58-bp; **Figure 2**). The GG, GA and AA genotypes detected by PCR-RFLP were also confirmed by direct sequencing with an accordance of 100%.

### Genotypic and allelic frequencies

As shown in **Table 2**, the distribution of genotypes in both Mulao and Han

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**Table 2.** Comparison of the genotypic and allelic frequencies between the Mulao and Han populations [n (%)]

Group	n	Genotype			Allele		HWE (P value)
		GG	GA	AA	G	A	
Mulao	751	315 (41.9)	329 (43.8)	107 (14.3)	959 (63.8)	543 (36.2)	0.162
Han	762	304 (39.9)	357 (46.9)	101 (13.2)	965 (63.3)	559 (36.7)	0.813
$\chi^2$	-	1.432			0.091		
P	-	0.489			0.763		
Mulao							
Male	372	160 (43.0)	171 (46.0)	41 (11.0)	491 (66.0)	253 (34.0)	0.641
Female	379	155 (40.9)	158 (41.7)	66 (17.4)	468 (61.7)	290 (38.3)	0.052
$\chi^2$	-	6.321			2.943		
P	-	0.042			0.086		
Han							
Male	371	149 (40.2)	174 (46.9)	48 (12.9)	472 (63.6)	270 (36.4)	0.801
Female	391	155 (39.6)	183 (46.8)	53 (13.6)	493 (63.0)	289 (37.0)	0.930
$\chi^2$	-	0.068			0.053		
P	-	0.967			0.818		

HWE, Hardy-Weinberg equilibrium; difference in genotype or allele distribution between the groups was tested by the Chi-square test; the standard goodness-of-fit test was used to test the Hardy-Weinberg equilibrium.

**Table 3.** Comparison of serum lipid levels among the genotypes in the Mulao and Han populations

Genotype	n	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoA1 (g/L)	ApoB (g/L)	ApoA1/ ApoB
Mulao								
GG	315	5.00 ± 1.23	1.21 (0.81)	1.68 ± 0.42	2.96 ± 0.93	1.26 ± 0.43	1.00 ± 0.62	1.52 ± 0.87
GA	329	4.98 ± 1.13	1.03 (0.74)	1.76 ± 0.44	2.95 ± 0.86	1.34 ± 0.38	1.00 ± 0.60	1.58 ± 0.70
AA	107	4.85 ± 1.00	0.97 (0.64)	1.79 ± 0.44	2.79 ± 0.75	1.35 ± 0.34	0.96 ± 0.54	1.63 ± 0.61
F	-	0.272	13.005	3.512	0.714	4.170	0.119	0.151
P	-	0.762	0.005	0.030	0.490	0.016	0.887	0.860
Han								
GG	304	4.94 ± 1.20	1.01 (0.93)	1.66 ± 0.41	2.76 ± 0.94	1.31 ± 0.28	0.85 ± 0.23	1.63 ± 0.54
GA	357	5.13 ± 1.17	1.11 (0.84)	1.71 ± 0.49	2.95 ± 0.83	1.34 ± 0.25	0.88 ± 0.20	1.60 ± 0.44
AA	101	5.22 ± 0.86	1.15 (0.80)	2.04 ± 0.41	3.02 ± 0.80	1.43 ± 0.30	0.87 ± 0.16	1.69 ± 0.50
F	-	1.564	3.447	16.093	3.845	6.318	0.234	0.741
P	-	0.210	0.178	0.000	0.022	0.002	0.791	0.477
Mulao/male								
GG	160	5.08 ± 0.92	1.32 (0.97)	1.66 ± 0.37	2.95 ± 0.79	1.25 ± 0.45	1.06 ± 0.68	1.38 ± 0.65
GA	171	5.01 ± 1.15	1.07 (0.98)	1.77 ± 0.46	2.93 ± 0.85	1.37 ± 0.40	1.09 ± 0.70	1.54 ± 0.71
AA	41	5.07 ± 1.04	0.98 (1.00)	1.86 ± 0.49	2.87 ± 0.71	1.40 ± 0.40	1.00 ± 0.55	1.61 ± 0.58
F	-	0.073	12.371	3.759	0.039	3.779	0.514	2.591
P	-	0.930	0.002	0.024	0.962	0.024	0.599	0.076
Mulao/female								
GG	155	4.92 ± 1.49	1.13 (0.64)	1.70 ± 0.46	2.98 ± 1.07	1.27 ± 0.42	0.94 ± 0.53	1.66 ± 1.03
GA	158	4.97 ± 1.12	1.00 (0.74)	1.74 ± 0.41	2.97 ± 0.88	1.32 ± 0.36	0.92 ± 0.45	1.63 ± 0.70
AA	66	4.72 ± 0.96	0.95 (0.60)	1.74 ± 0.40	2.74 ± 0.75	1.31 ± 0.29	0.94 ± 0.53	1.66 ± 0.63
F	-	0.714	3.702	0.605	0.703	0.559	0.013	0.713
P	-	0.490	0.157	0.546	0.496	0.572	0.987	0.491
Han/male								
GG	149	4.96 ± 0.95	1.14 (1.08)	1.62 ± 0.36	2.81 ± 0.77	1.34 ± 0.27	0.91 ± 0.24	1.59 ± 0.57
GA	174	5.16 ± 0.86	1.22 (0.99)	1.67 ± 0.43	2.97 ± 0.83	1.35 ± 0.26	0.92 ± 0.19	1.51 ± 0.38

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AA	48	5.43 ± 0.78	1.32 (0.83)	1.92 ± 0.50	3.13 ± 0.72	1.52 ± 0.39	0.91 ± 0.14	1.73 ± 0.55
F	-	6.537	0.037	7.127	10.995	4.661	0.710	2.020
P	-	0.002	0.982	0.001	0.000	0.010	0.492	0.134
Han/female								
GG	155	4.83 ± 1.22	0.95 (0.69)	1.69 ± 0.47	2.85 ± 1.08	1.27 ± 0.37	0.81 ± 0.23	1.67 ± 0.52
GA	183	4.94 ± 1.03	1.02 (0.68)	1.75 ± 0.39	2.93 ± 0.82	1.33 ± 0.38	0.83 ± 0.20	1.69 ± 0.48
AA	53	5.03 ± 0.89	1.05 (1.02)	2.14 ± 1.51	2.92 ± 0.87	1.34 ± 0.41	0.85 ± 0.17	1.65 ± 0.45
F	-	0.229	7.980	7.841	0.387	3.695	0.910	2.415
P	-	0.795	0.019	0.000	0.680	0.026	0.404	0.091

TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoAI, Apo lipoprotein AI; ApoB, Apo lipoprotein B. The association of genotypes and serum lipid parameters was tested by analysis of covariance (co-variables include sex, age, BMI, blood pressure, alcohol consumption, cigarette smoking and blood glucose). The value of TG was presented as median (interquartile range), and their difference among the genotypes was determined by the Wilcoxon-Mann-Whitney test.

satisfied the Hardy-Weinberg equilibrium. The frequencies of G and A alleles were 63.8% and 36.2% in Mulao; and 63.3% and 36.7% in Han ( $P > 0.05$ ); respectively. The frequencies of GG, GA and AA genotypes were 41.9%, 43.8% and 14.3% in Mulao; and 39.9%, 46.9% and 13.2% in Han ( $P > 0.05$ ); respectively. The genotypic frequencies were different between Mulao males and females ( $P < 0.05$ ).

### Genotypes and serum lipid levels

**Table 3** presents the association between the genotypes and serum lipid levels. The levels of TG, HDL-C and ApoAI in Mulao were different among the GG, GA and AA genotypes ( $P < 0.05-0.001$ ); the A allele carriers had higher HDL-C, ApoAI levels and lower TG levels than the A allele non-carriers. The levels of HDL-C, LDL-C and ApoAI in Han were also different among the genotypes ( $P < 0.05-0.001$ ); the A allele carriers had higher HDL-C, LDL-C and ApoAI levels than the A allele non-carriers. In the subgroup analyses, the A allele carriers in Mulao males but not in females had higher HDL-C, ApoAI levels and lower TG levels than the A allele non-carriers ( $P < 0.05-0.01$ ). The A allele carriers had higher HDL-C and ApoAI levels in both Han males and females; higher TC, LDL-C levels in Han males; and higher TG levels in Han females than the A allele non-carriers ( $P < 0.05$  for all).

### Risk factors for lipid parameters

Multiple linear regression analyses showed that serum HDL-C and ApoAI levels in Mulao and Han; TG, HDL-C and ApoAI levels in Mulao; and HDL-C, LDL-C, ApoAI levels in Han were correlated with genotypes ( $P < 0.05-0.001$ ; **Table**

**4**). As shown in **Table 5**, subgroup analyses showed that the levels of TG, HDL-C and ApoAI in Mulao males; TC, HDL-C, LDL-C and ApoAI in Han males; and TG, HDL-C, and ApoAI in Han females were correlated with genotypes ( $P < 0.05-0.001$ ). Serum lipid parameters were also correlated with several environmental factors such as age, gender, height, weight, BMI, waist circumference, alcohol consumption, cigarette smoking, blood pressure and blood glucose in both ethnic groups ( $P < 0.05-0.001$ ; **Tables 4 and 5**).

### Discussion

It has been well documented that modification of the conventional risk factors for CVD such as dyslipidemia can lead to 30-40% reduction in mortality and morbidity [31, 32]. Thus, genetic predisposition associated with serum lipid levels should be a prerequisite for comprehensive prevention of CVD. Recently, large numbers of candidate genes were claimed to be related to dyslipidemia by GWAS mainly in European population and replicating these results in independent populations have generally been necessary.

Mulao nationality has unique lifestyle, dietary habits, and strict intra-ethnic marriages which have been performed in this population from time immemorial. Traditionally, they prefer to marry to relatives of maternal side (mother's brother's daughter) in childhood. Divorce and remarriage were permitted, with little restriction. The two generation household is the most common unit of residence. Households are under the control of the father and divided when the sons marry, with only the youngest son remaining with the parents. Therefore,

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**Table 4.** Relative risk factors for serum lipid parameters in the Mulao and Han populations

Lipid parameter	Risk factor	Unstandardized coefficient	Standard error	Standardized coefficient	t	P
Han/Mulao						
TC	Age	0.008	0.002	0.102	3.768	0.000
	Waist circumference	0.023	0.004	0.163	6.087	0.000
	Alcohol consumption	0.115	0.046	0.073	2.481	0.013
	Diastolic blood pressure	0.009	0.003	0.086	3.172	0.002
	Cigarette smoking	0.219	0.061	0.107	3.612	0.000
TG	Waist circumference	0.047	0.006	0.196	7.652	0.000
	Cigarette smoking	0.608	0.085	0.174	7.116	0.000
	Blood glucose	0.164	0.031	0.136	5.375	0.000
	Diastolic blood pressure	0.019	0.005	0.109	4.169	0.000
	Age	-0.010	0.003	-0.078	-3.018	0.003
HDL-C	Ethnic group	0.286	0.097	0.072	2.934	0.003
	Waist circumference	-0.006	0.002	-0.093	-2.402	0.016
	Alcohol consumption	0.103	0.018	0.148	5.608	0.000
	Genotype	0.103	0.019	0.136	5.392	0.000
LDL-C	Weight	-0.009	0.002	-0.151	-3.876	0.000
	Body mass index	0.047	0.010	0.165	4.809	0.000
	Age	0.009	0.001	0.152	6.063	0.000
	Alcohol consumption	-0.091	0.031	-0.075	-2.953	0.003
	Waist circumference	0.009	0.004	0.087	2.506	0.012
ApoAI	Ethnic group	0.039	0.017	0.057	2.272	0.023
	Weight	-0.005	0.001	-0.122	-4.649	0.000
	Genotype	0.055	0.013	0.108	4.308	0.000
	Alcohol consumption	0.114	0.012	0.243	9.242	0.000
	Pulse pressure	0.001	0.001	0.055	2.197	0.028
ApoB	Ethnic group	-0.130	0.023	-0.144	-5.737	0.000
	Gender	-0.079	0.023	-0.087	-3.375	0.001
	Waist circumference	0.008	0.001	0.138	5.339	0.000
	Pulse pressure	0.003	0.001	0.111	4.372	0.000
	Blood glucose	0.024	0.007	0.086	3.388	0.001
ApoAI/ApoB	Ethnic group	0.079	0.032	0.062	2.478	0.013
	Gender	0.252	0.045	0.197	5.643	0.000
	Waist circumference	-0.018	0.002	-0.237	-9.130	0.000
	Blood glucose	-0.037	0.010	-0.095	-3.797	0.000
	Alcohol consumption	0.136	0.026	0.155	5.315	0.000
	Height	0.009	0.003	0.109	3.469	0.001
Mulao						
TC	Age	0.009	0.003	0.115	3.200	0.001
	Body mass index	0.058	0.014	0.148	4.098	0.000
	Cigarette smoking	0.148	0.072	0.073	2.039	0.042
TG	Waist circumference	0.024	0.006	0.208	4.117	0.000
	Weight	0.012	0.006	0.108	2.125	0.034
	Genotype	-0.145	0.070	-0.073	-2.088	0.037
HDL-C	Body mass index	-0.038	0.005	-0.258	-7.450	0.000
	Alcohol consumption	0.142	0.024	0.250	6.016	0.000
	Gender	0.100	0.036	0.116	2.795	0.005



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	Genotype	0.058	0.022	0.092	2.658	0.008
	Age	0.002	0.001	0.079	2.287	0.022
LDL-C	Body mass index	0.046	0.010	0.170	4.610	0.000
	Age	0.007	0.002	0.110	3.081	0.002
ApoAI	Alcohol consumption	0.090	0.019	0.171	4.708	0.000
	Waist circumference	-0.005	0.002	-0.104	-2.827	0.005
	Genotype	0.049	0.021	0.083	2.283	0.023
ApoB	Waist circumference	0.006	0.003	0.087	2.378	0.018
	Pulse pressure	0.006	0.001	0.162	4.500	0.000
	Gender	-0.223	0.052	-0.188	-4.275	0.000
	Alcohol consumption	-0.099	0.034	-0.127	-2.948	0.003
ApoAI/ApoB	Waist circumference	-0.017	0.003	-0.192	-5.341	0.000
	Blood glucose	-0.055	0.017	-0.115	-3.212	0.001
Han						
TC	Age	0.012	0.003	0.155	4.256	0.000
	Waist circumference	0.023	0.005	0.160	4.426	0.000
	Diastolic blood pressure	0.015	0.004	0.145	3.833	0.008
	Alcohol consumption	0.248	0.058	0.151	4.274	0.000
TG	Waist circumference	0.108	0.018	0.326	5.956	0.000
	Blood glucose	0.301	0.055	0.192	5.438	0.000
	Cigarette smoking	1.266	0.164	0.270	7.712	0.000
	Age	-0.027	0.007	-0.156	-4.171	0.000
	Diastolic blood pressure	0.037	0.009	0.157	4.291	0.000
HDL-C	Genotype	0.158	0.031	0.183	5.060	0.000
	Waist circumference	-0.011	0.003	-0.143	-3.973	0.000
LDL-C	Body mass index	0.062	0.009	0.236	6.799	0.000
	Age	0.013	0.002	0.216	6.225	0.000
	Genotype	0.135	0.045	0.104	2.973	0.003
	Cigarette smoking	-0.222	0.055	-0.142	-4.065	0.000
ApoAI	Alcohol consumption	0.130	0.016	0.333	8.249	0.000
	Weight	-0.006	0.001	0.209	-5.840	0.000
	Genotype	0.050	0.014	0.123	3.584	0.000
	Cigarette smoking	0.045	0.020	0.092	2.312	0.021
ApoB	Waist circumference	0.010	0.001	0.369	10.812	0.000
	Blood glucose	0.021	0.004	0.167	5.133	0.000
	Systolic blood pressure	0.001	0.000	0.134	3.994	0.000
	Alcohol consumption	0.046	0.010	0.153	4.451	0.000
	Height	-0.003	0.001	-0.124	-3.572	0.000
ApoAI/ApoB	Body mass index	-0.030	0.007	-0.209	-4.595	0.000
	Diastolic blood pressure	-0.005	0.002	-0.125	-3.558	0.000
	Waist circumference	-0.008	0.003	-0.140	-2.948	0.003
	Gender	0.118	0.038	0.123	3.074	0.002
	Alcohol consumption	0.137	0.027	0.200	5.117	0.000
	Blood glucose	-0.033	0.010	-0.117	-3.415	0.001

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoAI, Apolipoprotein AI; ApoB, Apolipoprotein B. The correlative factors were determined by multivariable linear regression analysis with stepwise modeling.

Mulao population is considered to share the same ethnic ancestry and possess the same

genetic background. Moreover, we surmised that the hereditary characteristic and some lip-

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**Table 5.** Relative risk factors for serum lipid parameters in males and females of the Mulao and Han populations

Lipid parameter	Risk factor	Unstandardized coefficient	Standard error	Standardized coefficient	t	P
Mulao/male						
TC	Body mass index	0.048	0.018	0.135	2.598	0.010
TG	Waist circumference	0.040	0.007	0.308	6.171	0.000
	Genotype	-0.274	0.114	-0.120	-2.399	0.017
HDL-C	Alcohol consumption	0.278	0.092	0.152	3.017	0.003
	Weight	-0.017	0.002	-0.326	-6.905	0.000
	Alcohol consumption	0.146	0.023	0.294	6.264	0.000
	Pulse pressure	0.003	0.001	0.117	2.446	0.015
	Genotype	0.067	0.031	0.103	2.165	0.031
LDL-C	Blood glucose	-0.028	0.011	-0.115	-2.412	0.016
	Body mass index	0.045	0.014	0.164	3.185	0.002
	Alcohol consumption	0.124	0.024	0.256	5.081	0.000
ApoAI	Blood glucose	-0.030	0.012	-0.130	-2.589	0.010
	Genotype	0.069	0.032	0.107	2.126	0.034
	Diastolic blood pressure	-0.004	0.002	0.126	-2.476	0.014
ApoB	Pulse pressure	0.012	0.002	0.267	5.093	0.000
	Alcohol consumption	-0.111	0.039	-0.144	-2.845	0.005
	Age	-0.005	0.002	-0.117	-2.251	0.025
ApoAI/ApoB	Alcohol consumption	0.179	0.039	0.232	4.581	0.000
	Waist circumference	-0.012	0.004	-0.160	-3.137	0.000
	Blood glucose	0.040	0.019	-0.108	-2.149	0.032
	Systolic blood pressure	-0.004	0.002	-0.112	-2.146	0.032
Mulao/female						
TC	Age	0.015	0.004	0.181	3.600	0.000
	Body mass index	0.060	0.021	0.140	2.796	0.005
TG	Body mass index	0.065	0.014	0.238	4.741	0.000
HDL-C	Body mass index	-0.035	0.007	-0.240	-4.787	0.000
LDL-C	Age	0.013	0.003	0.211	4.289	0.000
	Body mass index	0.067	0.016	0.208	4.222	0.000
ApoB	Waist circumference	0.012	0.003	0.193	3.856	0.000
	Blood glucose	0.045	0.018	0.125	2.457	0.014
	Age	0.004	0.002	0.111	2.197	0.029
ApoAI/ApoB	Waist circumference	-0.020	0.005	-0.186	-3.736	0.000
	Age	-0.010	0.003	-0.184	-3.697	0.018
Han/male						
TC	Diastolic blood pressure	0.032	0.005	0.306	6.205	0.000
	Alcohol consumption	0.216	0.070	0.152	3.085	0.002
	Genotype	0.214	0.087	0.121	2.450	0.015
	Blood glucose	0.087	0.033	0.131	2.646	0.009
TG	Waist circumference	0.171	0.036	0.382	4.721	0.000
	Diastolic blood pressure	0.060	0.016	0.193	3.807	0.000
	Weight	-0.104	0.033	-0.252	-3.151	0.002
	Blood glucose	0.393	0.101	0.198	3.873	0.000
HDL-C	Age	-0.031	0.012	-0.132	-2.548	0.011
	Genotype	0.100	0.031	0.159	3.232	0.001
	Alcohol consumption	0.114	0.025	0.225	4.553	0.000

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	Age	0.003	0.001	0.124	2.396	0.017
	Blood glucose	-0.039	0.012	-0.163	-3.214	0.001
	Weight	-0.011	0.002	-0.231	-4.641	0.000
LDL-C	Genotype	0.198	0.064	0.155	3.084	0.002
	Body mass index	0.051	0.012	0.213	4.243	0.000
	Cigarette smoking	-0.359	0.072	-0.252	-4.967	0.000
ApoAI	Alcohol consumption	0.132	0.017	0.381	7.816	0.000
	Weight	-0.007	0.002	-0.203	-4.321	0.000
	Genotype	0.050	0.020	0.115	2.443	0.015
	Cigarette smoking	0.057	0.024	0.119	2.415	0.016
ApoB	Diastolic blood pressure	0.004	0.001	0.212	4.404	0.000
	Waist circumference	0.009	0.001	0.327	6.580	0.000
	Blood glucose	0.018	0.005	0.156	3.324	0.001
	Height	-0.004	0.001	-0.149	-3.123	0.002
	Alcohol consumption	0.034	0.011	0.139	3.016	0.003
ApoAI/ApoB	Waist circumference	-0.009	0.004	-0.151	-2.503	0.013
	Alcohol consumption	0.123	0.028	0.213	4.487	0.000
	Pulse pressure	0.004	0.001	0.135	2.819	0.005
	Blood glucose	-0.028	0.013	-0.102	-2.118	0.035
Han/female						
TC	Age	0.026	0.003	0.355	7.430	0.000
	Alcohol consumption	-0.621	0.238	-0.127	-2.607	0.010
	Body mass index	0.086	0.018	0.232	4.834	0.000
TG	Waist circumference	0.041	0.007	0.289	6.034	0.000
	Genotype	0.157	0.074	0.101	2.124	0.034
	Blood glucose	0.153	0.032	0.228	4.770	0.000
HDL-C	Genotype	0.190	0.053	0.183	3.576	0.000
LDL-C	Age	0.020	0.003	0.322	6.611	0.000
	Waist circumference	0.017	0.009	0.136	1.851	0.065
	Body mass index	0.048	0.023	0.150	2.039	0.042
	Alcohol consumption	-0.597	0.210	-0.142	-2.840	0.005
ApoB	Pulse pressure	0.002	0.001	0.148	3.093	0.002
	Waist circumference	0.010	0.001	0.349	7.662	0.000
	Blood glucose	0.024	0.006	0.180	3.866	0.000
	Height	-0.006	0.002	-0.161	-3.459	0.001
ApoAI	Age	0.003	0.001	0.156	2.698	0.007
	Diastolic blood pressure	-0.004	0.001	-0.183	-3.289	0.001
	Genotype	0.059	0.026	0.113	2.222	0.027
	Cigarette smoking	0.187	0.072	0.135	2.578	0.010
ApoAI/ApoB	Waist circumference	-0.015	0.003	-0.241	-4.921	0.000
	Cigarette smoking	0.393	0.122	0.153	3.208	0.001
	Height	0.010	0.004	0.125	2.554	0.011
	Systolic blood pressure	-0.005	0.001	-0.194	-3.863	0.000

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoAI, Apolipoprotein AI; ApoB, Apolipoprotein B. The correlative factors were determined by multivariable linear regression analysis with stepwise modeling.

id-related gene polymorphisms in the Mulao population may be different from those in Han nationality.

The genotypic and allelic frequencies of *PEPD* rs731839 SNP in diverse racial/ethnic groups are poorly understood. According to the

HapMap data, the frequency of A allele of rs731839 SNP was 42.7% in Han Chinese from Beijing, 49.1% in Japanese, 35.6% in Indian. However, it was more than 50% in non-Asian populations, e.g. 65.9% in European, 65.3% in Italy, 62.3% in African and 57.8% in Mexican. In the present study, we showed that the A allele frequency of rs731839 SNP was 36.2% in Mulao and 36.7% in Han ( $P > 0.05$ ), which was lower than that in the Beijing Chinese samples. This difference may be caused by different sample sizes and regions (Beijing vs. Guangxi). The genotypic frequencies were different between Mulao males and females, but not between Han males and females. Serum lipid profiles were also significantly different between males and females in both ethnic groups. These results suggested that the prevalence of A allele of *PEPD* rs731839 SNP may have gender specificity in the Mulao population.

There were hardly any previous studies presented the direct relationship between the rs731839 SNP and lipid levels in humans except a newly GWAS which showed that the rs731839 SNP was significant associated with HDL-C and TG concentrations ( $P = 3 \times 10^{-9}$  in both) in the population of European descent. Our present study showed that the A allele carriers had higher HDL-C, ApoAI and lower TG levels in Mulao males but not in females; higher HDL-C, ApoAI, TC, LDL-C levels in Han males; and higher HDL-C, ApoAI and TG levels in Han females than the A allele non-carriers. These findings indicated that the association of *PEPD* rs731839 SNP and serum lipid levels may have racial/ethnic and/or sex specificity. As far as we know, our study is the first replication of GWAS signals (studied in European) about the association of *PEPD* rs731839 SNP with lipid levels in Chinese population. Therefore, further studies with larger sample size are still needed to confirm this association.

The influence of sex on the development of dyslipidemia is well established although the molecular basis in lipid metabolism is poorly understood. Females were tended to have more favorable serum lipid profiles than males, with lower levels of TG, TC and LDL-C, and higher HDL-C levels [33, 34]. It is commonly thought that sex hormones are important for sexual dimorphism in the serum lipid profile. However, some researchers recently reported that the effects of progestogens and androgens can

explain only a small part of the differences and it is likely that an underlying mechanism is differential gene regulation or genotype-sex interaction in males and females [12, 35]. The role of sex as a potential modifier of the effects of genetic variation on lipids was seldom reported in the identification of common variants associated with blood lipids [36]. Thus, sex-specific genetic associations between SNPs and serum lipid levels may lead to studying common preventive approach and treatment strategy for dyslipidemia. The present study is the first attempt to report the sex-specific association of the *PEPD* rs731839 SNP. Hence, the consistent effects across racial/ethnic groups with larger sample size should be added to support the findings reported here.

In the present study, we also noted that several environmental factors such as age, height, weight, waist circumference, BMI, blood pressure, alcohol consumption, cigarette smoking, and blood glucose were also correlated with serum lipid levels in both Mulao and Han, or males and females in both ethnic groups. These data suggest that the environmental factors also play a not-so-trivial role in determining serum lipid levels in our study populations. The people of Mulao live in an isolated environment and have different dietary habits. They have partiality for cold foods along with acidic and spicy dishes, local bean soy sauce, pickled vegetables, and animal offals which contain abundant saturated fatty acids (SFA). Accumulating evidence suggested that unhealthy diet is a strong, modifiable risk factor for dyslipidemia and CVD and it is believe that diet modification is a key strategy for prevention and regression of CVD [37, 38]. A meta-analysis revealed that every 1% alteration in total energy from SFA will lead to a change in TG of 1.9 mg/dl; LDL-C of 1.8 mg/dl and HDL-C of 0.3 mg/dl [39]. In the current study, we also found that the percentages of subjects who consumed alcohol and smoked cigarettes were significantly higher in males than females in both ethnic groups. Light-to-moderate volumes of alcohol consumption has been consistently associated with reduced cardiovascular risk in many epidemiological studies. The beneficial effects have attributed to the increase in HDL-C and ApoAI levels caused by alcohol consumption [40]. Koppes *et al.* stated that a 10-g/day difference in alcohol consumption was positively related with a 0.05-mmol/L difference in HDL-C levels [41]. In

contrast, the harmful effects of heavy drinking were equally documented. Alcohol was found to be an independent predictor of increased TG levels with the alcohol intake of 60 g/day increasing the TG levels by about 0.19 mg/dl/g of alcohol consumed [42]. In addition, many studies reported that cigarette smoking could account for the variability on serum lipid levels independently. Srinivasa *et al.* observed decreased levels of HDL-C and increased levels of TC, LDL-C and TG in smokers as compared to those in non-smokers [43]. Moreover, a meta-analysis based on 7,256 subjects concluded that smoking increased TG by 0.15 mmol/L, and decreased HDL-C by 0.09 mmol/L with every 20 cigarettes smoked [44]. Therefore, the joint effects of different dietary habits, lifestyles, and environmental factors may further modify the effect of genetic variation on serum lipid levels in our study populations.

There are several strengths in our study. First of all, the study is an epidemiological investigation of Mulao and Han populations in Guangxi and the special ethnic minority may be a useful subgroup for population genetic studies. Secondly, the number of subjects in our study is moderate, the statistical power is relatively reliable. Besides, the *PEPD* rs731839 SNP is the first reported lipid-related locus in the latest GWAS and the present study will provide the basis for further studies with ethnically diverse populations. Meanwhile, several potential limitations in our study should be recognized. First, this is the first time to report the sex-specific association of the *PEPD* rs731839 SNP and no previous evidence to support our findings. Hence, further studies with larger samples are needed to replicate our findings in other populations. Second, lifestyles including diet pattern, physical activities are important factors for lipid regulation. It is possible that part of the relationship observed in this study may be partly attributed to the effect of dietary intake and physical activities. But the cross-sectional study design limits the ability to determine these effects due to they were self-reported and difficult to classify. Third, although we observe significant association of the rs731839 SNP and serum lipid levels, the unmeasured interactions of gene-gene, gene-environment, and environment-environment on serum lipid levels are remained to be determined. Furthermore, the impact of sex hormones was not evaluated in both males and females of the two

ethnic groups respectively due to the relatively small samples. Lastly, we must recognize the limited power to provide an understanding of full impact of the *PEPD* rs731839 SNP on lipid metabolism since there are none of published documents involved in this aspect directly. The association of the *PEPD* rs731839 SNP and serum lipid levels should be detected in further investigations.

In conclusion, an association between the *PEPD* rs731839 SNP and serum lipid levels was detected in the both Mulao and Han populations, but these associated trends of the SNP and serum lipid parameters are different between the two ethnic groups, or between males and females. Our findings suggest that the association between *PEPD* rs731839 SNP and serum lipid levels might have ethnic- and/or sex-specificity.

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#### Disclosure of conflict of interest

None.

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**Table S1.** Comparison of demographic, lifestyle characteristics and serum lipid levels between males and females of the Mulao and Han populations

Parameter	Mulao (n = 751)		Han (n = 762)	
	males	females	males	females
Number [n (%)]	372 (49.5)	379 (50.5)	371 (48.7)	391 (51.3)
Age (years)	53.65 ± 14.71	53.25 ± 15.36	54.06 ± 15.3	52.69 ± 15.07
Height (cm)	160.98 ± 6.03	150.39 ± 6.42 <sup>a</sup>	159.44 ± 7.05	150.66 ± 5.78 <sup>a</sup>
Weight (kg)	56.97 ± 8.60	48.77 ± 7.62 <sup>a</sup>	58.05 ± 8.58	49.98 ± 7.10 <sup>a</sup>
Body mass index (kg/m <sup>2</sup> )	21.96 ± 2.95	21.54 ± 2.96 <sup>a</sup>	22.88 ± 3.56	22.03 ± 2.98 <sup>a</sup>
Waist circumference (cm)	76.86 ± 8.68	72.91 ± 7.88 <sup>a</sup>	77.57 ± 7.90	73.69 ± 7.50 <sup>a</sup>
Cigarette smoking [n (%)]				
Nonsmoker	161 (43.3)	376 (99.2)	137 (36.9)	378 (96.7)
≤ 20 cigarettes/day	170 (45.7)	3 (0.8) <sup>a</sup>	204 (55.0)	13 (3.3) <sup>a</sup>
> 20 cigarettes/day	41 (11.0)	0 (0.0)	30 (8.1)	0 (0.0)
Alcohol consumption [n (%)]				
Nondrinker	171 (46.0)	375 (98.9)	193 (52.0)	384 (98.2)
≤ 25 g/day	79 (21.2)	1 (0.3) <sup>a</sup>	78 (21.0)	3 (0.8) <sup>a</sup>
> 25 g/day	122 (32.8)	3 (0.8)	100 (27.0)	4 (1.0)
Systolic blood pressure (mmHg)	130.39 ± 21.30	129.99 ± 22.74	135.95 ± 18.73	126.16 ± 18.60 <sup>a</sup>
Diastolic blood pressure (mmHg)	82.65 ± 12.31	80.00 ± 11.22 <sup>a</sup>	84.53 ± 11.21	81.30 ± 10.81 <sup>a</sup>
Pulse pressure (mmHg)	47.74 ± 15.51	49.99 ± 16.95	51.43 ± 15.75	44.87 ± 13.04 <sup>a</sup>
Glucose (mmol/L)	6.19 ± 1.82	5.91 ± 1.38 <sup>a</sup>	6.13 ± 1.80	5.98 ± 1.56 <sup>a</sup>
Total cholesterol (mmol/L)	5.04 ± 1.04	4.91 ± 1.26	5.23 ± 1.18	4.90 ± 1.09 <sup>a</sup>
Triglyceride (mmol/L)	1.15 (0.95)	1.03 (0.68) <sup>a</sup>	1.15 (0.95)	1.03 (0.68) <sup>a</sup>
HDL-C (mmol/L)	1.73 ± 0.43	1.73 ± 0.43	1.68 ± 0.42	1.78 ± 0.69 <sup>c</sup>
LDL-C (mmol/L)	2.92 ± 0.81	2.93 ± 0.95	2.93 ± 0.86	2.90 ± 0.95
Apolipoprotein (Apo) AI (g/L)	1.32 ± 0.42	1.30 ± 0.38	1.31 ± 0.29	1.37 ± 0.26
ApoB (g/L)	1.07 ± 0.67	0.93 ± 0.51 <sup>a</sup>	0.91 ± 0.20	0.82 ± 0.20 <sup>a</sup>
ApoAI/ApoB	1.48 ± 0.67	1.65 ± 0.84 <sup>a</sup>	1.57 ± 0.49	1.67 ± 0.49 <sup>b</sup>

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. The quantitative variables were presented as mean ± standard deviation and their difference between the groups was determined by the t-test. The values of triglyceride were presented as median (interquartile range), and their difference between the groups was determined by the Wilcoxon-Mann-Whitney test. The difference in percentage of cigarette smoking and alcohol consumption between the groups was determined by  $\chi^2$ -test. <sup>a</sup>P < 0.001 in comparison with males from the same ethnic group. <sup>b</sup>P < 0.01 in comparison with males from the same ethnic group. <sup>c</sup>P < 0.05 in comparison with males from the same ethnic group.