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Polymorphism of rs1044925 in the acyl-CoA: cholesterol acyltransferase-1 gene and serum lipid levels in the Guangxi Bai Ku Yao and Han populations

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Abstract

Background: The association of rs1044925 polymorphism in the acyl-CoA:cholesterol acyltransferase-1 (ACAT-1) gene and serum lipid profiles is not well known in different ethnic groups. Bai Ku Yao is a special subgroup of the Yao minority in China. The present study was carried out to clarify the association of rs1044925 polymorphism in the ACAT-1 gene and several environmental factors with serum lipid levels in the Guangxi Bai Ku Yao and Han populations.

Methods: A total of 626 subjects of Bai Ku Yao and 624 participants of Han Chinese were randomly selected from our previous stratified randomized cluster samples. Genotyping of rs1044925 polymorphism in the ACAT-1 gene was performed by polymerase chain reaction and restriction fragment length polymorphism combined with gel electrophoresis, and then confirmed by direct sequencing.

Results: The levels of serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), apolipoprotein (Apo) AI and ApoB were lower in Bai Ku Yao than in Han ($P < 0.01$ for all). The frequency of A and C alleles was 79.0% and 21.0% in Bai Ku Yao, and 87.3% and 12.7% in Han ($P < 0.001$); respectively. The frequency of AA, AC and CC genotypes was 63.2%, 31.4% and 5.2% in Bai Ku Yao, and 75.6%, 23.2% and 1.1% in Han ($P < 0.001$); respectively. The levels of TC, LDL-C and ApoB in Bai Ku Yao but not in Han were different between the AA and AC/CC genotypes in females but not in males ($P < 0.05$ for all). The C allele carriers had lower serum TC, LDL-C and ApoB levels as compared with the C allele noncarriers. The levels of TC, LDL-C and ApoB in Bai Ku Yao but not in Han were correlated with genotypes in females but not in males ($P < 0.05$ for all). Serum lipid parameters were also correlated with sex, age, body mass index, alcohol consumption, and blood pressure in both ethnic groups ($P < 0.05-0.001$).

Conclusions: These results suggest that the polymorphism of rs1044925 in the ACAT-1 gene is mainly associated with female serum TC, LDL-C and ApoB levels in the Bai Ku Yao population. The C allele carriers had lower serum TC, LDL-C and ApoB levels than the C allele noncarriers.

Introduction

Coronary artery disease (CAD) is a major health problem and the leading cause of death in many industrialized countries [1,2]. Dyslipidemia such as elevated serum levels of total cholesterol (TC) [3], triglyceride

(TG) [4], low-density lipoprotein cholesterol (LDL-C) [5], and apolipoprotein (Apo) B [6], or low levels of high-density lipoprotein cholesterol (HDL-C) and ApoAI [6-8] is one of the most important modifiable risk factors for CAD in western [9,10] as well as in Asian [11,12] populations. It has been well established that dyslipidemia is a complex trait caused by multiple environmental [13,14] and genetic factors [15-17] and their interactions [18,19]. Family history and twin

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studies have shown that genetic polymorphism could account for 40-60% of the interindividual variation in plasma lipid phenotypes [20-22].

Cholesterol in the body is present in tissues and plasma lipoproteins either as free cholesterol or cholesteryl esters. The esterification of cholesterol in plasma by lecithin: cholesterol acyltransferase (LCAT) plays an important role in the intravascular maturation of lipoproteins, especially HDL. In contrast, intracellular cholesteryl ester synthesis, catalyzed by acyl-CoA:cholesterol acyltransferase (ACAT, E.C.2.3.1.26), also called sterol *o*-acyltransferase (SOAT), serves to store cholesterol in cytosolic droplets and also participates in the hepatic secretion of lipoproteins containing ApoB [23-26]. ACAT has found to be present as two isoforms, ACAT-1 and ACAT-2, with different intracellular localizations, membrane topology in mammalian species, and metabolic function for each enzyme [27-29]. ACAT-1 is ubiquitously expressed in various tissues and cells including adrenal glands, kidney [30-32], and macrophages [33] and is responsible for foam cell formation in macrophages, whereas ACAT-2 is expressed only in intestine and liver [27,28,34] and is in charge of the cholesterol absorption process in intestinal mucosal cells [35]. The first ACAT-1 cDNA was cloned by Chang and colleagues [30] in 1993. ACAT-2 was cloned in 1998 [27,28,34]. The two genes have 47% overall nucleotide identity [30,34] and encode specific ACAT proteins that have 43% amino acid sequence identity and 63% similarity. ACAT activity has been detected in a diverse range of tissues and cell types [36] and is known to play an important role in cell biology and in the pathogenesis of important lipid-related diseases such as atherosclerosis [36] and cholesterol gallstones [37]. For example, ACAT has been shown to play a pivotal functional role in the intestinal absorption of cholesterol, the hepatic secretion of very low-density lipoprotein (VLDL), the biosynthesis of steroid hormones, the production of cholesteryl esters in macrophages (foam cells) in atheroma, and the secretion of biliary cholesterol. From a biochemical and physiological perspective, ACAT is one of the central enzymes regulating plasma and biliary cholesterol concentrations. In several previous studies, two single nucleotide polymorphisms (SNPs) of rs1044925 and -77G > A in the ACAT-1 gene were associated with modifications of serum lipid concentrations [38,39] and with low cerebrospinal fluid levels of cholesterol [40], but one SNP (R526G) in the ACAT-1 gene was not associated with serum lipid parameters [39].

China is a vast and diverse country. There are 56 ethnic groups. Han is the largest ethnic group and Yao is the eleventh largest minority among the 55 minority groups according to the population size. Bai Ku Yao (White-trouser Yao), an isolated branch of the Yao minority, is named so

because all of men wear white knee-length knickerbockers. The population size is about 30000. Because of isolation from the other ethnic groups, the special customs and cultures including their clothing, intra-ethnic marriages, ballad, funeral, bronze drum, spinning top, dietary habits, and corn wine and rum intakes are still completely preserved to the present day. They are currently in a transitional period from the matriarchal society to patriarchal society. In several previous epidemiological studies, we showed that several serum lipid phenotypes were lower in Bai Ku Yao than in Han Chinese from the same region [13,14]. This ethnic difference in serum lipid profiles is still not well known. We hypothesized that some genetic factors may be different between the two ethnic groups. Therefore, the aim of the present study was to detect the association of rs1044925 polymorphism in the ACAT-1 gene and several environmental factors with serum lipid phenotypes in the Guangxi Bai Ku Yao and Han populations.

Materials and methods

Study population

A total of 626 subjects of Bai Ku Yao who reside in Lihu and Baxu villages in Nandan County, Guangxi Zhuang Autonomous Region, People's Republic of China were randomly selected from our previous stratified randomized cluster samples [13,14]. The ages of the subjects ranged from 15 to 80 years, with an average age of 40.25 ± 14.97 years. There were 305 males (48.72%) and 321 females (51.28%). All subjects were rural agricultural workers. The subjects accounted for 2.09% of total Bai Ku Yao population. During the same period, a total of 624 people of Han Chinese who reside in the same villages were also randomly selected from our previous stratified randomized cluster samples [13,14]. The average age of the subjects was 40.71 ± 15.71 years (range 15 to 80). There were 304 men (48.72%) and 320 women (51.28%). All of them were also rural agricultural workers. All study subjects were essentially healthy and had no evidence of any chronic illness, including hepatic, renal, or thyroid. The participants with a history of heart attack or myocardial infarction, stroke, congestive heart failure, diabetes or fasting blood glucose ≥ 7.0 mmol/L determined by glucose meter have been excluded. The participants were not taking medications known to affect serum lipid levels (lipid-lowering drugs such as statins or fibrates, beta-blockers, diuretics, or hormones). The present study was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University. Informed consent was obtained from all subjects after they received a full explanation of the study.

Epidemiological survey

The survey was carried out using internationally standardized methods, following a common protocol [41].

Information on demographics, socioeconomic status, and lifestyle factors was collected with standardized questionnaires. The alcohol information included questions about the number of liangs (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: <25 and \geq 25. Smoking status was categorized into groups of cigarettes per day: <20 and \geq 20. At the physical examination, several anthropometric parameters, such as height, weight, and waist circumference were measured. Sitting blood pressure was measured three times with the use of a mercury sphygmomanometer after the subjects had a 5-minute rest, and the average of the three measurements was used for the level of blood pressure. Systolic blood pressure was determined by the first Korotkoff sound, and diastolic blood pressure by the fifth Korotkoff sound. Body weight, to the nearest 50 grams, was measured using a portable balance scale. Subjects were weighed without shoes and in a minimum of clothing. Height was measured, to the nearest 0.5 cm, using a portable steel measuring device. From these two measurements body mass index (BMI, kg/m^2) was calculated.

Biochemical analysis

A venous blood sample of 8 mL was obtained from all subjects between 8 and 11 AM, after at least 12 hours of fasting, from a forearm vein after venous occlusion for few seconds in a sitting position. A part of the sample (3 mL) was collected into glass tubes and allowed to clot at room temperature, and used to determine serum lipid levels. Another part of the sample (5 mL) was transferred to tubes with anticoagulate solution (4.80 g/L citric acid, 14.70 g/L glucose, and 13.20 g/L tri-sodium citrate) and used to extract DNA. Immediately following clotting serum was separated by centrifugation for 15 minutes at 3000 rpm. The levels of TC, TG, HDL-C, and LDL-C in samples were determined by enzymatic methods with commercially available kits, Tcho-1, TGLH (RANDOX Laboratories Ltd., Ardmore, Diamond Road, Crumlin Co. Antrim, United Kingdom, BT29 4QY), Cholestest N HDL, and Cholestest LDL (Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan); respectively. Serum ApoAI and ApoB levels were detected by the immunoturbidimetric immunoassay using a commercial kit (RANDOX Laboratories Ltd.). All determinations were performed with an autoanalyzer (Type 7170A; Hitachi Ltd., Tokyo, Japan) in the Clinical Science Experiment Center of the First Affiliated Hospital, Guangxi Medical University [13,14].

DNA amplification and genotyping

Genomic DNA was isolated from peripheral blood leukocytes using the phenol-chloroform method [15-19]. The

extracted DNA was stored at 4°C until analysis. Genotyping of the polymorphism of rs1044925 was performed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) [38,42]. PCR amplification was performed using 5'-TATATTAAGGGGATCA-GAAGT-3' and 5'-CCACCTAAAAACATACTACC-3' (Sangon, Shanghai, People's Republic of China) as the forward and reverse primer pairs; respectively. Each amplification reaction was performed using 0.5 μg of genomic DNA in 25 μL of reaction mixture consisting of 0.2 μM of each primer, 200 μM of each deoxynucleotide triphosphate, 2.5 μL of 10 \times PCR buffer (100 mM Tris-HCl, pH 8.3, 500 mM KCl, 20 mM MgCl_2 , 1% Triton), and 1.25 units of *Taq* polymerase. After initial denaturing at 95°C for 5 min, the reaction mixture was subjected to 33 cycles of 45 s denaturation at 95°C, 30 s annealing at 53°C and extension 50 s at 72°C, followed by a final 10 min extension at 72°C. After electrophoresis on a 1.5% agarose gel with 0.5 $\mu\text{g}/\text{mL}$ ethidium bromide, the amplification products were visualized under ultraviolet light. Then 5 U of *RsaI* restriction enzyme was added directly to the PCR products (5 μL) and digested at 37°C overnight. After restriction enzyme digestion of the amplified DNA, genotypes were identified by electrophoresis on 1.5% agarose gels and visualized with ethidium-bromide staining ultraviolet illumination. The genotypes were scored by an experienced reader blinded to the epidemiological data and serum lipid levels. Six samples (AA, AC and CC genotypes in two; respectively) detected by the PCR-RFLP were also confirmed by direct sequencing. The PCR products were purified by low melting point gel electrophoresis and phenol extraction, and then the DNA sequences were analyzed 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 ApoB in our Clinical Science Experiment Center were 3.10-5.17, 0.56-1.70, 0.91-1.81, 2.70-3.20 mmol/L, 1.00-1.78, 0.63-1.14 g/L, and 1.00-2.50; respectively. The individuals with TC > 5.17 mmol/L and/or TG > 1.70 mmol/L were defined as hyperlipidemic [13,14]. Hypertension was diagnosed according to the criteria of 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension [43,44]. 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 [45].

Statistical analyses

Epidemiological data were recorded on a pre-designed form and managed with Excel software. All statistical

analyses were done with the statistical software package SPSS 13.0 (SPSS Inc., Chicago, Illinois). Quantitative variables were expressed as mean \pm standard deviation (serum TG levels were presented as medians and interquartile ranges). Qualitative variables were expressed as percentages. Allele frequency was determined via direct counting, and the standard goodness-of-fit test was used to test the Hardy-Weinberg equilibrium. Difference in genotype distribution between the groups was obtained using the chi-square test. The difference in general characteristics between Bai Ku Yao and Han was tested by the Student's unpaired *t*-test. The association of genotypes and serum lipid parameters was tested by analysis of covariance (ANCOVA). Sex, age, BMI, blood pressure, alcohol consumption, cigarette smoking were adjusted for the statistical analysis. In order to evaluate the association of serum lipid levels with genotypes (AA = 1, AC/CC = 2) and several environment factors, multiple linear regression analysis with stepwise modeling was also performed in the combined population of Bai Ku Yao and Han, Bai Ku Yao, Han, males and females; respectively. A *P* value of less than 0.05 was considered statistically significant.

Results

General characteristics and serum lipid levels

Table 1 gives the general characteristics and serum lipid levels between the Bai Ku Yao and Han populations. The levels of height, weight, BMI, systolic blood pressure, pulse pressure, serum TC, HDL-C, ApoAI, ApoB were lower in Bai Ku Yao than in Han Chinese (*P* < 0.05-0.001), whereas the percentage of subjects who consumed alcohol was higher in Bai Ku Yao than in Han (*P* < 0.001). There was no significant difference in the levels of diastolic blood pressure, serum TG, LDL-C, the ratio of ApoAI to ApoB, age structure, the percentage of subjects who smoked cigarettes, or the ratio of male to female between the two ethnic groups (*P* > 0.05 for all).

Results of electrophoresis and genotyping

After the genomic DNA of the samples was amplified by PCR and imaged by 1.5% agarose gel electrophoresis, the purpose gene of 389 bp nucleotide sequences could be found in all samples (Figure 1). The genotypes identified were named according to the presence or absence of the enzyme restriction sites, when an A to C transversion at rs1044925 locus of the ACAT-1 gene. The presence of the cutting site indicates the C allele, while its absence indicates the A allele (cannot be cut). Thus, the AA genotype is homozygote for the absence of the site (band at 389 bp), AC genotype is heterozygote for the absence and presence of the site (bands at 389-, 279- and 110-bp), and CC genotype is homozygote for

Table 1 The general characteristics and serum lipid levels between Bai Ku Yao and Han Chinese

Parameter	Bai Ku Yao	Han Chinese	<i>t</i> (χ^2)	<i>P</i>
Number	626	624	-	-
Male/female	305/321	304/320	0.000	0.999
Age (years)	40.25 \pm 14.97	40.71 \pm 15.71	-0.523	0.601
Height (cm)	152.69 \pm 7.46	155.41 \pm 8.23	-6.102	0.000
Weight (kg)	51.84 \pm 7.17	54.51 \pm 9.28	-5.703	0.000
Body mass index (kg/m ²)	22.20 \pm 2.38	22.54 \pm 3.22	-2.126	0.034
Systolic blood pressure (mmHg)	119.30 \pm 16.97	121.28 \pm 16.74	-2.077	0.038
Diastolic blood pressure (mmHg)	75.59 \pm 9.53	76.21 \pm 10.61	-1.087	0.277
Pulse pressure (mmHg)	43.71 \pm 12.83	45.09 \pm 11.65	-1.982	0.048
Cigarette smoking [n (%)]				
Nonsmoker	429 (68.5)	448 (71.8)		
< 20 cigarettes/day	90 (14.4)	70 (11.2)		
\geq 20 cigarettes/day	107 (17.1)	106 (17.0)	2.913	0.233
Alcohol consumption [n (%)]				
Nondrinker	334 (53.4)	392 (62.8)		
< 25 g/day	189 (30.2)	160 (25.6)		
\geq 25 g/day	103 (16.5)	72 (11.5)	12.532	0.002
Total cholesterol (mmol/L)	4.34 \pm 0.87	4.74 \pm 1.02	-7.419	0.000
Triglyceride (mmol/L)	1.00 (0.65)	1.01 (0.69)	-0.982	0.326
HDL-C (mmol/L)	1.66 \pm 0.41	1.89 \pm 0.50	-8.790	0.000
LDL-C (mmol/L)	2.56 \pm 0.72	2.63 \pm 0.77	-1.539	0.124
Apolipoprotein (Apo) AI (g/L)	1.31 \pm 0.32	1.42 \pm 0.28	-6.478	0.000
ApoB (g/L)	0.85 \pm 0.22	0.89 \pm 0.22	-3.361	0.001
ApoAI/ApoB	1.66 \pm 0.72	1.69 \pm 0.58	-0.651	0.515

HDL-C, highdensity lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. The value of TG was presented as median (interquartile range). The difference between the two ethnic groups was determined by the Wilcoxon-Mann-Whitney test.

the presence of the site (bands at 279- and 110-bp; Figure 2).

Genotypic and allelic frequencies

The genotypic and allelic frequencies of rs1044925 polymorphism in the ACAT-1 gene are shown in Table 2. The frequency of A and C alleles was 79.0% and 21.0% in Bai Ku Yao, and 87.3% and 12.7% in Han (*P* < 0.001); respectively. The frequency of AA, AC and CC genotypes was 63.2%, 31.4% and 5.2% in Bai Ku Yao, and 75.6%, 23.2% and 1.1% in Han (*P* < 0.001); respectively. There was no significant difference in the genotypic and allelic frequencies between the males and females in both ethnic groups.

Results of sequencing

The results were shown as AA, AC and CC genotypes by PCR-RFLP, the AA, AC and CC genotypes were also confirmed by sequencing (Figure 3); respectively.

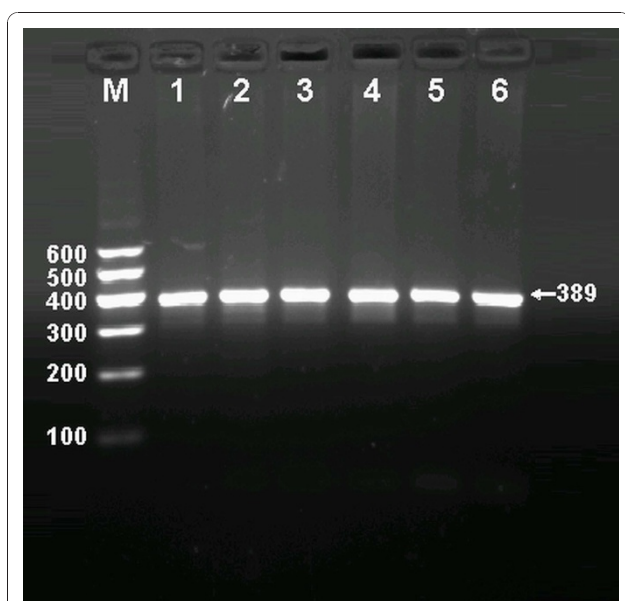


Figure 1 Electrophoresis of PCR products of the samples. Lane M, 100 bp marker ladder; lanes 1-6, samples. The 389 bp bands are the target genes.

Genotypes and serum lipid levels

As shown in Table 3 the levels of TC, LDL-C and ApoB in Bai Ku Yao but not in Han were significant differences between the AA and AC/CC genotypes in females but not in males ($P < 0.05$ for all). The subjects with AC/CC genotype had lower serum TC, LDL-C and ApoB levels than the subjects with AA genotype. There

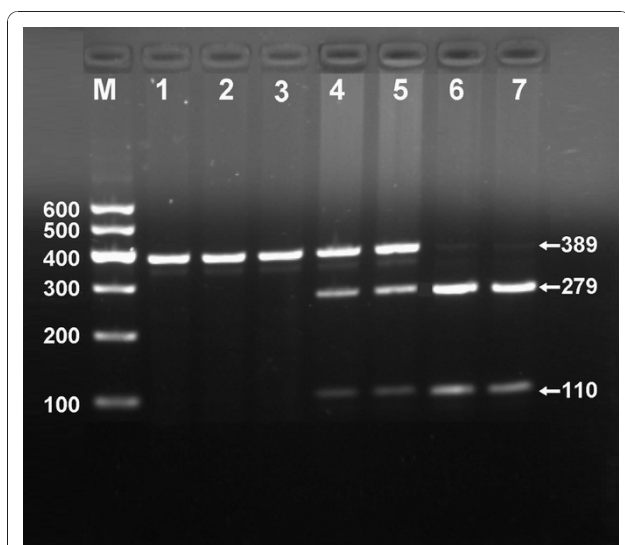


Figure 2 Genotyping of rs1044925 polymorphism in the ACAT-1 gene. Lane M, 100 bp marker ladder; lanes 1-3, AA genotype (389 bp); lanes 4 and 5, AC genotype (389-, 279- and 110-bp); and lanes 6 and 7, CC genotype (279- and 110-bp).

was no significant difference in serum lipid parameters between the AA and AC/CC genotypes in both ethnic groups ($P > 0.05$ for all).

Relative factors for serum lipid parameters

Multiple linear regression analysis showed that the genotypes of rs1044925 polymorphism in the ACAT-1 gene were not correlated with any serum lipid parameters in the combined population of Bai Ku Yao and Han, in the Bai Ku Yao or in the Han population (Table 4). When multiple linear regression analysis was performed in the males and females in both ethnic groups; respectively, we found that the levels of TC, LDL-C and ApoB in Bai Ku Yao but not in Han were correlated with genotypes in females but not in males ($P < 0.05$ for all, Table 5). Serum lipid parameters were also correlated with sex, age, BMI, alcohol consumption, and blood pressure in both ethnic groups (Table 4 and 5).

Discussion

We showed that the levels of serum TC, HDL-C, ApoAI and ApoB were lower in Bai Ku Yao than in Han Chinese. There was no significant difference in the serum levels of TG, LDL-C and the ratio of ApoAI to ApoB between the two ethnic groups. It is well known that dyslipidemia is a multifactorial origin, including hereditary and acquired risk factors. Bai Ku Yao is a special and isolated subgroup of the Yao minority in China. There are about 30000 people of total Bai Ku Yao population who reside in two villages, Lihu and Baxu, Nandan County. Their ancestors began their migration from Hunan and Guizhou Province about Song Dynasty. Both Lihu and Baxu villages are typical infertile mountain area, usually it was called 30 percent soil with 70 percent rock. Thus, their income mostly comes from planting corn and paddy. Strict intra-ethnic marriages have been performed in this ethnic subgroup from time immemorial. Therefore, we believe that some hereditary characteristics and genotypes of lipid metabolism-related genes in this population may be different from those in Han Chinese.

In the present study, we showed that the frequency of C allele of rs1044925 in the ACAT-1 gene was higher in Bai Ku Yao (21.0%) than in Han Chinese (12.7%). The frequency of AC and CC genotypes was also higher in Bai Ku Yao than in Han. In a previous study in northern Han Chinese population, Zhao *et al.* [42] reported that there was no difference in the frequency of C allele between normal controls (9.7%) and Alzheimer's disease patients (9.3%). In another recent study in Han Chinese population, Li *et al.* [38] also found no significant difference in the frequency of C allele between normal controls (13.7%) and endogenous hypertriglyceridemia patients (15.3%). The allele frequency of the R526G

Table 2 The genotypic and allelic frequencies of rs1044925 polymorphism in the ACAT-1 gene between Bai Ku Yao and Han Chinese [n (%)]

Group	n	Genotype			Allele	
		AA	AC	CC	A	C
Bai Ku Yao	626	396 (63.2)	197 (31.4)	33 (5.2)	989 (79.0)	263 (21.0)
Han Chinese	624	472 (75.6)	145 (23.2)	7 (1.1)	1089 (87.3)	159 (12.7)
χ^2	-		31.458		30.436	
<i>P</i>	-		0.000		0.000	
Bai Ku Yao						
Male	305	191 (62.6)	96 (31.5)	18 (5.9)	478 (78.4)	132 (21.6)
Female	321	205 (63.9)	101 (31.5)	15 (4.7)	511 (79.6)	131 (20.4)
χ^2	-		0.486		0.287	
<i>P</i>	-		0.784		0.592	
Han Chinese						
Male	304	223 (73.4)	78 (25.7)	3 (1.0)	524 (86.2)	84 (13.8)
Female	320	249 (77.8)	67 (20.9)	4 (1.3)	565 (88.3)	75 (11.7)
χ^2	-		2.001		1.233	
<i>P</i>	-		0.368		0.267	

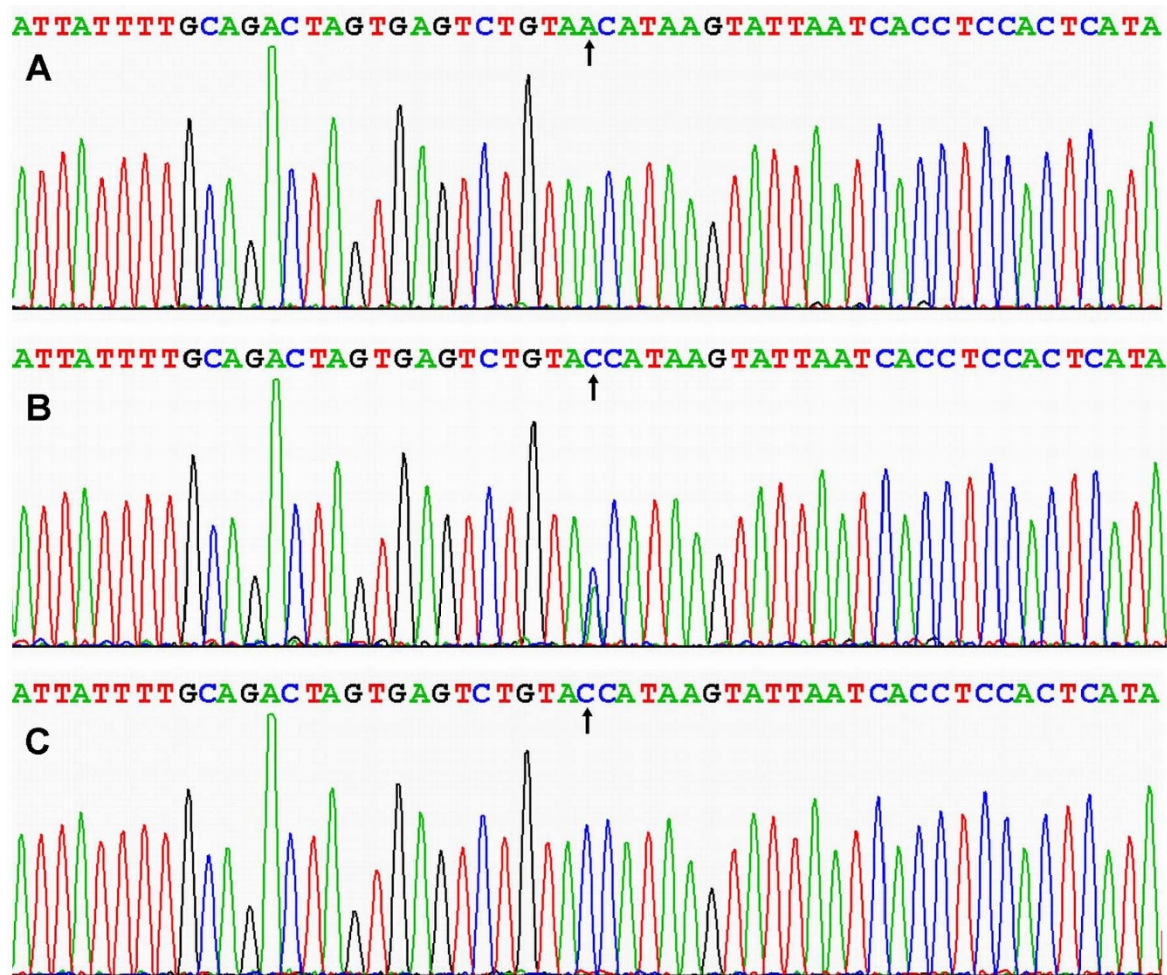


Figure 3 A part of the nucleotide sequence of rs1044925 in the ACAT-1 gene. (A) AA genotype; (B) AC genotype; (C) CC genotype.

Table 3 The genotypes of rs1044925 polymorphism in the ACAT-1 gene and serum lipid levels between Bai Ku Yao and Han Chinese

Genotype	n	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoAI (g/L)	ApoB (g/L)	ApoAI/ApoB
Bai Ku Yao								
AA	396	4.36 ± 0.85	1.02(0.65)	1.67 ± 0.40	2.58 ± 0.70	1.32 ± 0.32	0.85 ± 0.22	1.67 ± 0.71
AC/CC	230	4.29 ± 0.90	0.96(0.66)	1.64 ± 0.41	2.55 ± 0.75	1.29 ± 0.31	0.84 ± 0.22	1.65 ± 0.73
F	-	1.008	0.623	0.811	0.288	1.732	0.871	0.037
P	-	0.316	0.534	0.368	0.591	0.189	0.351	0.847
Male								
AA	191	4.35 ± 0.89	1.16(0.87)	1.72 ± 0.46	2.47 ± 0.72	1.39 ± 0.38	0.82 ± 0.21	1.86 ± 0.87
AC/CC	114	4.38 ± 1.02	1.02(0.74)	1.65 ± 0.46	2.57 ± 0.91	1.32 ± 0.35	0.85 ± 0.25	1.73 ± 0.92
F	-	0.087	0.297	1.728	1.176	2.781	1.100	1.688
P	-	0.768	0.766	0.190	0.279	0.096	0.295	0.195
Female								
AA	205	4.39 ± 0.81	0.94(0.54)	1.64 ± 0.34	2.68 ± 0.66	1.26 ± 0.25	0.89 ± 0.23	1.50 ± 0.45
AC/CC	116	4.19 ± 0.75	0.92(0.54)	1.62 ± 0.34	2.52 ± 0.56	1.24 ± 0.24	0.83 ± 0.19	1.56 ± 0.47
F	-	4.769	0.748	0.108	4.888	0.303	4.866	1.511
P	-	0.030	0.454	0.743	0.028	0.583	0.028	0.220
Han Chinese								
AA	472	4.73 ± 1.03	1.01(0.70)	1.89 ± 0.49	2.64 ± 0.78	1.41 ± 0.27	0.89 ± 0.23	1.69 ± 0.60
AC/CC	152	4.75 ± 1.00	1.00(0.64)	1.90 ± 0.52	2.60 ± 0.74	1.42 ± 0.29	0.89 ± 0.22	1.67 ± 0.50
F	-	0.041	0.307	0.100	0.263	0.164	0.005	0.084
P	-	0.839	0.759	0.751	0.608	0.685	0.946	0.772
Male								
AA	223	4.64 ± 1.05	1.04(0.75)	1.81 ± 0.48	2.59 ± 0.79	1.38 ± 0.28	0.88 ± 0.24	1.69 ± 0.69
AC/CC	81	4.69 ± 1.10	0.98(0.75)	1.84 ± 0.62	2.54 ± 0.81	1.39 ± 0.33	0.88 ± 0.22	1.64 ± 0.47
F	-	0.163	0.872	0.239	0.225	0.128	0.006	0.418
P	-	0.687	0.383	0.625	0.636	0.721	0.94	0.518
Female								
AA	249	4.81 ± 1.00	0.97(0.65)	1.96 ± 0.49	2.68 ± 0.78	1.45 ± 0.26	0.90 ± 0.21	1.69 ± 0.50
AC/CC	71	4.83 ± 0.87	1.07(0.58)	1.95 ± 0.39	2.69 ± 0.65	1.46 ± 0.24	0.91 ± 0.22	1.70 ± 0.53
F	-	0.031	0.344	0.007	0.007	0.017	0.060	0.016
P	-	0.861	0.731	0.935	0.932	0.896	0.806	0.898

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoAI, apolipoprotein AI; ApoB, apolipoprotein B.

variant in the ACAT-1 gene was not different between normolipidemic (67.6%) and hyperlipidemic Japanese subjects (63.3%). There was also no difference in the allele frequency of the -77G > A variant in the ACAT-1 gene between normolipidemic (50.3%) and hyperlipidemic subjects (51.5%) [39]. In the population of central and Southern Europe, however, the frequency of C allele of rs1044925 in the ACAT-1 gene was very high (35.4%) [40]. These results indicate that the prevalence of the C allele variation of rs1044925 in the ACAT-1 gene may have an ethnic specificity.

The association of rs1044925 polymorphism in the ACAT-1 gene and plasma or serum lipid profiles is not well documented. In a previous study in Japanese population, Ohta *et al.* [39] reported that the R526G variant in the ACAT-1 gene did not affect plasma lipid concentrations in subjects studied. However, among hyperlipidemic

subjects, plasma HDL-C and ApoAI concentrations in subjects with -77G > A variant in the ACAT-1 gene were significantly higher than those in subjects without variant. In another recent study in Han Chinese population, Li *et al.* [38] found that control subjects with AA genotype had a higher serum mean concentrations of LDL-C and non-HDL-C when compared with those of C allele carriers (AC and CC genotype carriers), whereas hypertriglyceridemia subjects with AA genotype had a higher HDL-C level compared with those of C allele carriers. In the present study, we showed that the levels of TC, LDL-C and ApoB in Bai Ku Yao but not in Han were significant differences between the AA and AC/CC genotypes in females but not in males. The C allele carriers had lower serum TC, LDL-C and ApoB levels as compared with the C allele noncarriers. The levels of TC, LDL-C and ApoB in Bai Ku Yao but not in Han were also correlated with genotypes in

Table 4 Correlative factors for serum lipid parameters between Bai Ku Yao and Han Chinese

Lipid parameter	Relative factor	Unstandardized coefficient	Std. error	Standardized coefficient	t	P
Bai plus Han						
TC	Body mass index	0.070	0.009	0.204	7.493	0.000
	Ethnic group	0.363	0.051	0.188	7.148	0.000
	Age	0.010	0.002	0.160	5.953	0.000
	Diastolic blood pressure	0.010	0.003	0.109	3.940	0.000
TG	Body mass index	0.070	0.012	0.165	5.742	0.000
	Alcohol consumption	0.185	0.074	0.076	2.478	0.013
	Sex	-0.247	0.074	-0.103	-3.355	0.001
	Diastolic blood pressure	0.008	0.003	0.066	2.286	0.022
HDL-C	Age	0.005	0.001	0.168	6.163	0.000
	Alcohol consumption	0.207	0.028	0.219	7.358	0.000
	Sex	0.127	0.028	0.135	4.566	0.000
	Body mass index	-0.015	0.005	-0.092	-3.334	0.001
	Diastolic blood pressure	0.003	0.001	0.057	2.024	0.043
LDL-C	Ethnic group	0.247	0.025	0.264	9.979	0.000
	Body mass index	0.059	0.007	0.224	8.004	0.000
	Age	0.007	0.001	0.143	5.136	0.000
	Alcohol consumption	-0.177	0.042	-0.117	-4.250	0.000
ApoAI	Diastolic blood pressure	0.005	0.002	0.063	2.187	0.029
	Age	0.004	0.001	0.194	7.110	0.000
	Alcohol consumption	0.143	0.018	0.233	7.849	0.000
	Ethnic group	0.120	0.016	0.198	7.479	0.000
ApoB	Diastolic blood pressure	0.002	0.001	0.069	2.519	0.012
	Sex	-0.037	0.018	-0.061	-2.068	0.039
	Body mass index	0.018	0.002	0.223	8.019	0.000
	Age	0.002	0.000	0.141	5.120	0.000
	Diastolic blood pressure	0.002	0.001	0.100	3.487	0.001
ApoAI/ApoB	Sex	0.032	0.012	0.071	2.613	0.009
	Ethnic group	0.034	0.012	0.076	2.852	0.004
	Alcohol consumption	0.227	0.037	0.172	6.219	0.000
	Body mass index	-0.034	0.006	-0.148	-5.360	0.000
Bai Ku Yao						
TC	Body mass index	0.087	0.014	0.239	6.190	0.000
	Age	0.008	0.002	0.138	3.570	0.000
TG	Alcohol consumption	0.218	0.065	0.155	3.366	0.001
	Body mass index	0.055	0.016	0.137	3.486	0.001
	Sex	-0.229	0.089	-0.119	-2.581	0.010
HDL-C	Alcohol consumption	0.117	0.023	0.198	5.099	0.000
	Age	0.004	0.001	0.152	3.905	0.000
LDL-C	Body mass index	0.077	0.012	0.255	6.587	0.000
	Age	0.006	0.002	0.124	3.215	0.001
	Alcohol consumption	-0.093	0.041	-0.089	-2.278	0.023
ApoAI	Alcohol consumption	0.140	0.018	0.300	7.951	0.000
	Age	0.003	0.001	0.151	3.999	0.000
ApoB	Body mass index	0.023	0.004	0.249	6.458	0.000
	Age	0.002	0.001	0.117	3.036	0.002
ApoAI/ApoB	Alcohol consumption	0.278	0.040	0.266	6.916	0.000
	Body mass index	-0.048	0.012	-0.159	-4.127	0.000
Han Chinese						
TC	Age	0.013	0.002	0.193	5.015	0.000
	Body mass index	0.055	0.012	0.173	4.410	0.000

Table 4: Correlative factors for serum lipid parameters between Bai Ku Yao and Han Chinese (Continued)

	Diastolic blood pressure	0.017	0.004	0.173	4.285	0.000
	Sex	0.161	0.077	0.079	2.098	0.036
TG	Body mass index	0.071	0.018	0.164	4.005	0.000
	Alcohol consumption	0.309	0.090	0.135	3.448	0.001
	Diastolic blood pressure	0.011	0.005	0.084	2.033	0.042
HDL-C	Age	0.006	0.001	0.198	5.022	0.000
	Alcohol consumption	0.170	0.033	0.209	5.129	0.000
	Sex	0.212	0.040	0.213	5.258	0.000
	Body mass index	-0.020	0.006	-0.126	-3.172	0.002
	Diastolic blood pressure	0.005	0.002	0.099	2.429	0.015
LDL-C	Body mass index	0.053	0.009	0.221	5.726	0.000
	Age	0.009	0.002	0.190	4.858	0.000
	Alcohol consumption	-0.135	0.049	-0.107	-2.760	0.006
ApoAI	Age	0.004	0.001	0.251	6.467	0.000
	Alcohol consumption	0.086	0.018	0.189	4.721	0.000
	Sex	0.106	0.022	0.191	4.818	0.000
	Diastolic blood pressure	0.003	0.001	0.103	2.677	0.008
ApoB	Body mass index	0.015	0.003	0.218	5.547	0.000
	Age	0.003	0.001	0.195	5.069	0.000
	Diastolic blood pressure	0.003	0.001	0.119	2.979	0.003
ApoAI/ApoB	Body mass index	-0.027	0.007	-0.152	-3.847	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

Table 5 Correlative factors for serum lipid parameters between males and females in both ethnic groups

Lipid parameter	Relative factor	Unstandardized coefficient	Std. error	Standardized coefficient	t	P
Bai Ku Yao						
Male						
TC	Body mass index	0.138	0.023	0.323	6.017	0.000
	Age	0.009	0.003	0.147	2.739	0.007
TG	Body mass index	0.100	0.031	0.185	3.256	0.001
	Alcohol consumption	0.308	0.153	0.115	2.015	0.045
HDL-C	Age	0.007	0.002	0.229	4.185	0.000
	Alcohol consumption	0.249	0.058	0.237	4.248	0.000
	Body mass index	-0.025	0.012	-0.118	-2.158	0.032
LDL-C	Body mass index	0.119	0.020	0.327	6.023	0.000
ApoAI	Alcohol consumption	0.226	0.046	0.271	4.969	0.000
	Age	0.005	0.001	0.203	3.716	0.000
Apo B	Body mass index	0.032	0.006	0.312	5.709	0.000
ApoAI/ApoB	Alcohol consumption	0.484	0.114	0.239	4.252	0.000
	Body mass index	-0.075	0.023	-0.184	-3.264	0.001
Female						
TC	Body mass index	0.044	0.017	0.139	2.511	0.013
	Genotype	-0.213	0.091	-0.129	-2.333	0.020
TG	Body mass index	0.031	0.014	0.124	2.241	0.026
LDL-C	Systolic blood pressure	0.005	0.002	0.128	2.326	0.021
	Body mass index	0.032	0.014	0.126	2.290	0.023
	Genotype	-0.151	0.072	-0.115	-2.086	0.038
ApoAI	Alcohol consumption	0.070	0.034	0.114	2.061	0.040
	Age	0.002	0.001	0.112	2.030	0.043
ApoB	Body mass index	0.013	0.005	0.152	2.777	0.006
	Systolic blood pressure	0.002	0.001	0.136	2.477	0.014

Table 5: Correlative factors for serum lipid parameters between males and females in both ethnic groups (Continued)

	Genotype	-0.052	0.025	-0.117	-2.128	0.034
ApoA1/ApoB	Diastolic blood pressure	-0.007	0.003	-0.132	-2.381	0.018
Han Chinese						
Male						
TC	Body mass index	0.065	0.018	0.206	3.552	0.000
	Age	0.012	0.004	0.179	3.229	0.001
	Diastolic blood pressure	0.013	0.006	0.138	2.347	0.020
TG	Body mass index	0.138	0.028	0.271	4.892	0.000
	Alcohol consumption	0.308	0.055	0.297	5.587	0.000
HDL-C	Age	0.009	0.002	0.267	4.962	0.000
	Body mass index	-0.022	0.008	-0.145	-2.771	0.006
	Age	0.006	0.003	0.132	2.341	0.020
LDL-C	Alcohol consumption	0.178	0.031	0.303	5.788	0.000
	Age	0.005	0.001	0.268	5.066	0.000
	Diastolic blood pressure	0.003	0.001	0.111	2.133	0.034
ApoA1	Body mass index	0.018	0.004	0.262	4.797	0.000
	Age	0.003	0.001	0.199	3.645	0.000
ApoB	Alcohol consumption	0.183	0.073	0.143	2.515	0.012
	Body mass index	-0.035	0.011	-0.183	-3.123	0.002
	Systolic blood pressure	0.005	0.002	0.119	2.011	0.045
Female						
TC	Diastolic blood pressure	0.020	0.005	0.205	3.715	0.000
	Age	0.013	0.003	0.208	3.863	0.000
	Body mass index	0.045	0.017	0.143	2.662	0.008
TG	Diastolic blood pressure	0.016	0.005	0.160	2.884	0.004
HDL-C	Age	0.005	0.002	0.162	2.921	0.004
LDL-C	Body mass index	0.053	0.013	0.213	3.961	0.000
	Age	0.010	0.003	0.208	3.819	0.000
	Alcohol consumption	-0.319	0.095	-0.176	-3.346	0.001
ApoA1	Diastolic blood pressure	0.009	0.004	0.124	2.242	0.026
	Age	0.004	0.001	0.249	4.588	0.000
	Diastolic blood pressure	0.004	0.001	0.190	3.467	0.001
ApoB	Body mass index	0.014	0.004	0.196	3.654	0.000
	Age	0.003	0.001	0.191	3.559	0.000
	Body mass index	-0.028	0.009	-0.170	-3.076	0.002

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B

females but not in males. These results suggest that the polymorphism of rs1044925 in the ACAT-1 gene is mainly associated with female serum TC, LDL-C and ApoB levels in the Bai Ku Yao population. The reason for this discrepancy between the two ethnic groups is unclear.

Several environmental factors were also found to affect serum lipid levels in this study. Serum lipid parameters were correlated with age, sex, alcohol consumption, BMI, and blood pressure. These data suggest that the environmental factors also play an important role in determining serum lipid levels in our populations [13,14]. The diet and lifestyle were different between the two ethnic groups. Corn was the staple food and rice,

soy, buckwheat, sweet potato, and pumpkin products were the subsidiary foods in Bai Ku Yao. Approximately 90% of the beverages were corn wine and rum. The alcohol content is about 15% (v/v). They are also accustomed to drink hempseed soup and eat hempseed products. In contrast, rice was the staple food and corn, broomcorn, potato, and taro products were the subsidiary foods in Han. About 90% of the beverage was rice wine. The content of alcohol is about 30% (v/v). The staple and subsidiary foods are more favorable for serum lipid profiles in Bai Ku Yao than in Han. Corn contains abundant dietary fiber and plant protein [46]. Consumption of dietary fiber, specifically the soluble

type, such as pectins and guar gum can decrease serum TC levels [47,48]. Corn fiber supplementation in men with hypercholesterolemia resulted in an additional lowering of serum TC, TG, and VLDL-C concentrations. Serum LDL-C and HDL-C concentrations were not significantly altered by corn fiber or wheat fiber supplementation [48]. Plant protein might promote the transportation and excretion of free cholesterol. Dietary soy protein has well-documented beneficial effects on serum lipid concentrations [49,50]. Buckwheat protein product has a potent hypocholesterolemic activity [51,52]. Low to high buckwheat seed and sprout meal can reduce serum TC levels. The high seed and sprout meals can also lower serum TG levels. The levels of serum LDL-C were significantly suppressed by all buckwheat meals. Serum HDL-C levels were increased, however, insignificantly. Nutraceutically more meaningful is that both LDL-C/HDL-C and TC/HDL-C ratios were significantly lowered [52]. Ingestion of 4 g/day caiapo (the extract of the white-skinned sweet potato *Ipomoea batatas*) for 6 weeks has been found to reduce plasma TC, LDL-C [53] and TG levels [54] in type 2 diabetic patients previously treated by diet alone. Adaramoye *et al.* [55] reported that supplemented diets containing 3% and 6% telfairia occidentalis (fluted pumpkin) in rats decreased plasma and postmitochondrial supernatant fraction (PMF) cholesterol levels by 20% and 30% and by 30% and 45%, respectively; decreased the cholesterol-induced increase in plasma and PMF LDL-C levels by 24% and 48% and by 28% and 52%, respectively; and decreased plasma and PMF lipid peroxidation by 24% and 20% and by 42% and 21%, respectively. Dietary hempseed is a rich source of polyunsaturated fatty acids (PUFAs). Hempseed-supplemented diet in animals displayed elevated plasma levels of PUFAs and a prominent enhancement in gamma-linolenic acid levels. When hempseed is added to a cholesterol-enriched diet, cholesterol-induced platelet aggregation returns to control levels [56,57]. This normalization may be partly due to increased levels of plasma gamma-linolenic acid [56]. In addition, several experimental and clinical studies have demonstrated that dietary hempseed or hempseed oil can decrease TC, TG and LDL-C levels [58-60], inhibit lipid peroxidation [61], and reduce atherogenic index [62].

Conclusion

The present study shows that the frequency of C allele of rs1044925 in the ACAT-1 gene was higher in Bai Ku Yao than in Han Chinese. But only the levels of TC, LDL-C and ApoB in Bai Ku Yao but not in Han were different between the AA and AC/CC genotypes in females but not in males. The C allele carriers had lower serum TC, LDL-C and ApoB levels than the C allele noncarriers.

The levels of TC, LDL-C and ApoB in Bai Ku Yao but not in Han were also correlated with genotypes in females but not in males. These results suggest that the polymorphism of rs1044925 in the ACAT-1 gene is mainly associated with female serum TC, LDL-C and ApoB levels in the Bai Ku Yao population.

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Authors' contributions

DFW participated in the design, undertook genotyping, and helped to draft the manuscript. RXY conceived the study, participated in the design, carried out the epidemiological survey, collected the samples, and drafted the manuscript. LHHA, XJH, XLC, LM, QL and TTY collaborated to the genotyping. JZW and SLP carried out the epidemiological survey, collected the samples, and helped to carry out the genotyping. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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