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ORIGINAL ARTICLE

Association of TaqIB Polymorphism in the Cholesteryl Ester Transfer Protein Gene With Serum Lipid Levels in the Guangxi Hei Yi Zhuang and Han Populations

Zhou Yijiang, MSc,*† Yin Ruixing, MD,* Li Yiyang, MD,* Deng Yaju, MSc,* Pan Shangling, MD,‡ Lin Weixiong, MSc,§ and Yang Dezhai, MSc§

ABSTRACT

Background: Cholesteryl ester transfer protein (CETP) plays an important role in lipoprotein metabolism. The present study was undertaken to compare the difference in the *CETP Taq*IB gene polymorphism and its association with serum lipid levels between the Guangxi Hei Yi Zhuang and Han populations.

Methods: A total of 758 subjects of Hei Yi Zhuang and 778 participants of Han Chinese were surveyed. Genotyping of the *CETP Taq*IB was performed using polymerase chain reaction and restriction fragment length polymorphism and then confirmed using direct sequencing.

Results: The genotypic and allelic frequencies were significant differences between smokers and nonsmokers, or between hypertensives and normotensives in Hei Yi Zhuang, and between drinkers and nondrinkers in Han. The levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein AI in Hei Yi Zhuang but not in Han were higher in B2B2 genotype than in B1B1 genotype ($P < 0.01$ for each). Higher HDL-C levels in Hei Yi Zhuang were found only in females, nondrinkers, nonsmokers, subjects with a body mass index of 24 kg/m^2 or lesser, or normotensives in B2B2 genotype. Higher HDL-C levels in Han were found only in females in B2B2 genotype and in subjects with a body mass index of 24 kg/m^2 or lesser or normotensives in B1B2 genotype. The levels of HDL-C in B1B1 and B1B2 individuals in both ethnic groups were higher in drinkers than in nondrinkers.

Conclusions: There were significant differences in the interactions between the *CETP Taq*IB genotypes and several environmental factors in the Hei Yi Zhuang and Han populations. The polymorphism predicted differences in HDL-C and ApoAI in the Hei Yi Zhuang but not in the Han Chinese, even after adjustment for confounding variables. This means that the gene may not be truly involved in regulation of high-density lipoprotein metabolism or that there is an ethnic-specific effect.

Key Words: lipids, apolipoproteins, cholesteryl ester transfer protein, gene, polymorphism

INTRODUCTION

Coronary artery disease (CAD) is a major cause of morbidity and mortality in the industrialized nations and is of growing concern in developing countries. Dyslipidemia such as high levels of plasma total cholesterol (TC),[1] triglycerides (TGs),[2] low-density lipoprotein cholesterol (LDL-C),[3] apolipoprotein (Apo) B,[4] and low levels of high-density lipoprotein (HDL) cholesterol[5] are correlated with the development and progression of atherosclerosis and a higher incidence of CAD.[6] Cumulative evidences show that every 1 mg/dL decrease in HDL cholesterol (HDL-C) causes a 3% to 4% increase in CAD.[5] It has been reported that more than 50% of the variation in HDL-C levels in humans is genetically determined.[7] It has been suggested that plasma cholesteryl ester transfer protein (CETP) facilitates the transfer of cholesteryl ester from HDL to apoB-containing lipoproteins, such as very low-density lipoprotein, intermediate-density lipoprotein, and low-density lipoprotein, thus regulating the blood plasma HDL-C levels.[8–10]

The *CETP* gene located on chromosome 16q12-21 adjacent to the lecithin-cholesterol acyltransferase gene consists of 16 exons and 15 introns and spans a region of approximately 25 kb.[11,12] Cholesteryl ester transfer protein is

From the *Department of Cardiology, Institute of Cardiovascular Diseases, the First Affiliated Hospital; †Department of Cardiology, Guangxi Provincial Corps Hospital, Chinese People's Armed Police Forces; ‡Department of Pathophysiology, School of Premedical Sciences; and §Department of Molecular Biology, Medical Scientific Research Center, Guangxi Medical University, Nanning, Guangxi, People's Republic of China.

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Reprints: Yin Ruixing, MD, Department of Cardiology, Institute of Cardiovascular Diseases, the First Affiliated Hospital, Guangxi Medical University, 22 Shuangyong Road, Nanning 530021, Guangxi, People's Republic of China. E-mail: yinruixing@yahoo.com.cn.

expressed primarily in liver, spleen, and adipose tissue. In addition, lower levels of CETP have also been detected in the small intestine, adrenal gland, heart, kidney, or skeletal muscle.[9,11] Several rare mutations that result in the absence of detectable CETP mass and/or activity have been reported at the *CETP* gene locus. In humans, CETP deficiency is characterized by the presence of increased concentrations of large cholesteryl ester–enriched HDL particles in the plasma and, often, reduced concentrations of LDL-C.[13]

Several common mutations, or polymorphisms, have been identified at the *CETP* gene, such as I405V, D442G, I14A, A373P, R451Q, promoter polymorphism (–629A/C, –1337C/T and –971G/A), and so on.[14–18] It is difficult to establish a consensus about the relationship between the common single nucleotide polymorphisms in the human *CETP* gene and CETP mass and activity, HDL-C levels, and CAD. One of the common variants is *Taq*IB, a silent base change affecting the 277th nucleotide in the first intron of the *CETP* gene.[11] The B2 allele (absence of the *Taq*I restriction site) has been found to be associated with raised plasma HDL-C levels and reduced plasma CETP mass and CAD risk[19–24] but not all studies.[25–28] It has been suggested that this association may be population specific[28,29] and influenced by environmental factors, such as alcohol consumption, cigarette smoking, and body mass index (BMI).[30–34]

There are 56 ethnic groups in China. Han is the largest group, and Zhuang is the largest minority. Geographically and linguistically, Zhuang can be classified into 43 ethnic subgroups, among which, Hei Yi (means black worship and black dressing) Zhuang is considered to be the most conservative subgroup. The population size of Hei Yi Zhuang is approximately 52,000. Because of isolation from the other ethnic groups, the special customs and cultures including their clothing, intra-ethnic marriages, and alcohol consumption are still completely conserved to the present day. We have previously reported that the serum levels of TC, TG, LDL-C, and ApoB in Hei Yi Zhuang were significantly lower than those in Han Chinese, whereas the levels of HDL-C and the ratio of ApoAI to ApoB in Hei Yi Zhuang were significantly higher than those in Han from the same region.[35–37] We hypothesize that some genetic factors may be involved in determining the serum lipid concentrations in these populations.[38–40] Therefore, the aim of the present study was to determine the polymorphism of the *CETP* gene and its association with serum lipid levels in the Guangxi Hei Yi Zhuang and Han populations.

■ METHODS

Subjects

A total of 758 subjects of Hei Yi Zhuang residing in 7 villages in Napo County, Guangxi Zhuang Autonomous Region, were surveyed by a stratified randomized cluster sampling. The age of the subjects ranged from 15 to 70 years, with an average age of 42.45 ± 16.43 years. There were 380 men and 378 women. All of the subjects were peasants. At the same time, a total of 778 subjects of Han Chinese residing in 9 villages in Napo County were also surveyed by the same method. The average age of the subjects was 40.28 ± 15.16 years (range, 15–70 years). There were 390 men and 388 women. All of them were also peasants. All study subjects were essentially healthy and had no evidence of diseases related to atherosclerosis, CAD, and diabetes. None of them had been treated with β-adrenergic blocking agents and lipid-lowering drugs such as statins or fibrates. 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, after a common protocol.[41] Information on demography and lifestyle factors was collected with standardized questionnaires. Smoking status was categorized into groups of cigarettes per day: less than 20 and 20 or greater. Alcohol consumption was categorized into groups of grams of alcohol per day: less than 25 and 25 or greater. The physical examination included blood pressure, body height, body weight, waist circumference, and the like, and BMI was calculated as weight (kilograms) divided by height (meters) squared. Sitting blood pressure was measured 3 times with the use of a mercury sphygmomanometer after the subject rest of 5 minutes, and the average of the 3 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.

Measurements of Lipids and Apolipoproteins

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. Three milliliters was collected into glass tubes and used to determine serum lipids, and the remaining 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 trisodium citrate) and used to extract DNA. The levels of TC, TG, HDL-C, and LDL-C in samples were determined by enzymatic methods with commercially available kits, Tcho-1, TG-LH (Randox Laboratories Ltd, Crumlin, Antrim, United Kingdom), Cholestest N HDL, and Cholestest LDL (Daiichi Pure Chemicals Co, Ltd., Tokyo, Japan), respectively. Serum ApoAI and ApoB levels were assessed

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.

Genotyping of the CETP TaqIB

Genomic DNA was isolated from peripheral blood leukocytes by standard methods.[42] Genotyping of the *CETP Taq*IB was performed as described by Fumeron et al.[30] A 535–base pair (bp) fragment in intron 1 of the *CETP* gene was amplified by polymerase chain reaction (PCR), with use of the following oligonucleotide primers: F-5′-CACTAGCCCAGAGAGAGGAGTGCC-3′ and R-5′-CTGAGCCCAGCCGCACACTAA-3′ (Institute of Biochemistry and Cell Biology, Shanghai Institute for Advanced Studies, Chinese Academy of Sciences, Shanghai, China). Polymerase chain reaction was performed in a volume of 25 μL containing 200 ng of genomic DNA, with 1.5 mM Mg^{2+}, 2.5 mM of each dNTP (Tiangen, Beijing, China), 3.125 μM (0.5μL) of each primer, and 1 U of DNA polymerase. For the amplification, initial denaturation at 94°C for 4 minutes was followed by 30 cycles of denaturation at 94°C for 30 seconds, annealing at 61°C for 30 seconds, and extension at 72°C for 45 seconds, with final extension at 72°C for 5 minutes. Polymerase chain reaction products (8 μL) were digested with *Taq*I (0.2 U) restriction endonuclease (Takara Biotechnology [DaLina] Co, LTD, China) at 64°C for 4 hours, and the fragments were separated by electrophoresis in a 2% agarose gel for 60 minutes at 80 V. The target DNA fragments were 174 and 361 bp for the B1 allele and 535 bp for the undigested B2 allele. The genotypes were identified and named according to the presence or absence of the enzyme restriction sites. B1B2 genotype is heterozygote for the presence and absence of the site (bands at 535, 361, and 174 bp), B1B1 genotype is homozygote for the presence of the site (bands at 361and 174 bp), and B2B2 genotype is homozygote for the absence of the site (band at 535 bp) (Fig. 1). Six samples (B1B1, B1B2, and B2B2 genotypes in 2, respectively) detected by the PCR–restriction fragment length polymorphism methods were also confirmed by direct sequencing. The PCR product was purified by low melting point gel electrophoresis and phenol extraction and, then, were analyzed in Generay Biotech (Shanghai) Co, Ltd, China.

Diagnostic Criteria

The normal values of serum TC, TG, HDL-C, LDL-C, ApoAI, and ApoB in our Clinical Science Experiment Center were 3.10 to 5.17, 0.56 to 1.70, 0.91 to 1.81, 1.70 to 3.20 mM, 1.00 to 1.76, and 0.63 to 1.14 g/L, respectively. The individuals with TC of greater than 5.17 mM and/or TG of greater than 1.70 mM were defined as hyperlipidemic.[36,37] 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 Coorperative Meta-analysis Group of China Obesity Task Force. Normal weight, overweight, and obesity were defined as a BMI of less than 24, 24 to 28, and greater than 28 kg/m^2, respectively.[45]

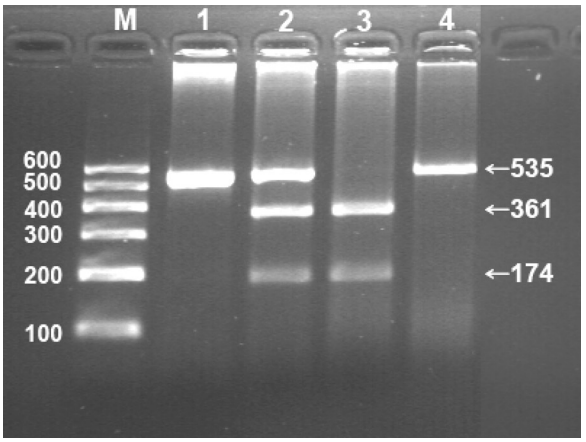

FIGURE 1. Genotyping of PCR products of the samples. Lane M, 100 bp marker ladder; lanes 1 and 4, B2B2 genotype (535 bp); lane 2, B1B2 genotype (535, 361, and 174 bp); and lane 3, B1B1 genotype (361 and 174 bp).

Statistical Analysis

Hardy-Weinberg equilibria and linkage equilibrium were calculated. Levels of the quantitative variables are presented as mean ± SD. The difference of general characteristics between Hei Yi Zhuang and Han was tested by the Student unpaired *t* test. The statistical significance of differences of frequencies between groups was compared by the χ^2 test. The association of *CETP Taq*IB genotypes with lipid variables was tested by analysis of covariance. The sex, age, BMI, alcohol consumption, cigarette smoking, and blood pressure were adjusted for the statistical analyses. To evaluate the association of serum lipid levels with sex (men, 0; women, 1), age (year), cigarette smoking (nonsmokers, n = 0; <20 cigarettes per day, n = 1; ≥20 cigarettes per day, n = 2), alcohol consumption (nondrinkers, n = 0; <25 g/d, n = 1; ≥25 g/d, n = 2), BMI (kilograms per square meter), blood pressure (millimeters of mercury), unconditional logistic regression analysis with forward stepwise modeling was also performed in combined population of Hei Yi Zhuang and Han, Hei Yi Zhuang, and Han; respectively. All statistical analyses were done with the statistical software package SPSS 13.0 (SPSS Inc, Chicago, IL). A *P* value of less than 0.05 was considered significant.

■ RESULTS

General Characteristics and Serum Lipid Levels

Table 1 gives the general characteristics and serum lipid levels of the subjects. The levels of systolic blood pressure and pulse pressure, the prevalence of hypertension, and the percentages of subjects who consumed alcohol were significantly higher in Hei Yi Zhuang than in Han ($P < 0.01$ for all). Body mass index and the levels of TC, TG, LDL-C, and ApoB were significantly lower in Hei Yi Zhuang than in Han ($P < 0.01$ for all), whereas the levels of HDL-C and the ratio of ApoAI to ApoB were significantly higher in Hei Yi Zhuang than in Han ($P < 0.01$ for each). There were no significant differences in ApoAI levels between the 2 ethnic groups ($P > 0.05$). There were also no significant differences in the age structure, the percentages of subjects who smoked cigarettes, the ratio of male to female, or diastolic blood pressure levels between the 2 ethnic groups ($P > 0.05$).

Genotypic and Allelic Frequencies

The frequencies of the B1 and B2 alleles were 65.2% and 34.8% in Hei Yi Zhuang and 63.2% and 36.8% in Han ($P > 0.05$), respectively. The frequencies of the B1B1, B1B2, and B2B2 genotypes were 43%, 44.3%, and 12.7% in Hei Yi Zhuang and 41.7%, 45.1%, and 13.3% in Han ($P > 0.05$; Table 2), respectively. There were significant differences in the genotypic and allelic frequencies between smokers and nonsmokers or between hypertensives and normotensives in Hei Yi Zhuang and between drinkers and nondrinkers in Han. The genotypic frequencies were also different between the subjects with a BMI of greater than 24 kg/m^2 and those with a BMI of 24 kg/m^2 or lesser in Han. The B1B1, B1B2, and B2B2 genotypes determined by PCR–restriction fragment length polymorphism method were able to be confirmed by sequencing (Fig. 2).

Interactions Between the Genotypes and Several Factors on Serum HDL-C Levels

The interactions between the *CETP Taq*IB genotypes and sex, alcohol consumption, cigarette smoking, BMI, and blood pressure on serum HDL-C levels are shown in Table 3. In the Hei Yi Zhuang population, higher serum HDL-C levels were found in women, nondrinkers, nonsmokers, subjects with a BMI of 24 kg/m^2 or lesser, or normotensives in B2B2 genotype. The levels of HDL-C in B1B1 and B1B2 genotypes were higher in drinkers than in nondrinkers.

In the Han population, higher serum HDL-C levels were found in women in B2B2 genotype and in subjects with a BMI of 24 kg/m^2 or lesser, or normotensives in B1B2 genotype. The levels of HDL-C in B1B1 and B1B2 genotypes were higher in drinkers than in nondrinkers, whereas the levels of HDL-C in B1B2 genotype were lower in subjects with a BMI of 24 kg/m^2 or greater than in those with a BMI of 24 kg/m^2 or lesser.

Genotypes and Serum Lipid Levels

Multiple analysis with covariates such as age, BMI, blood pressure, alcohol use, smoking, and sex revealed that the levels of HDL-C and ApoAI in Hei Yi Zhuang but not in Han were higher in B2B2 genotype than in

TABLE 1. Comparison of the General Characteristics and Serum Lipid Levels Between the Hei Yi Zhuang and Han Populations

Parameters	*Hei Yi Zhuang (n = 758)*	*Han Chinese (n = 778)*	*t (χ^2)*	*P*
Sex, male/female	380/378	390/388	0.000	0.999
Age, yrs	42.45 ± 16.43	40.28 ± 15.16	1.850	0.065
BMI, kg/m^2	21.16 ± 2.23	22.43 ± 2.63	7.220	0.000
Systolic blood pressure, mm Hg	126.11 ± 17.60	122.38 ± 15.61	4.407	0.000
Diastolic blood pressure, mm Hg	77.32 ± 11.04	77.18 ± 9.96	0.270	0.788
Pulse pressure, mm Hg	48.79 ± 13.56	45.23 ± 10.86	5.683	0.000
Hypertension, n (%)	170 (22.4)	94 (12.1)	28.869	0.000
Cigarette smoking, n (%)				
Nonsmoker	502 (66.2)	546 (70.2)		
<20 cigarettes/d	138 (18.2)	108 (13.9)		
≥20 cigarettes/d	118 (15.6)	124 (15.9)	5.395	0.067
Alcohol consumption, n (%)				
Nondrinker	342 (45.1)	438 (56.3)		
<25 g/d	316 (41.7)	278 (35.7)		
≥25 g/d	100 (13.2)	62 (8)	22.903	0.000
TC, mM	4.50 ± 1.02	4.77 ± 1.08	5.050	0.000
TGs, mM	0.87 (0.45)	0.99 (0.57)	6.200	0.000
HDL-C, mM	2.08 ± 0.48	1.96 ± 0.44	5.074	0.000
LDL-C, mM	2.35 ± 1.49	2.57 ± 0.73	3.715	0.000
Apo AI, g/L	1.43 ± 0.15	1.42 ± 0.15	0.665	0.506
ApoB, g/L	0.87 ± 0.21	0.96 ± 0.21	8.443	0.000
ApoAI/ApoB	1.76 ± 0.63	1.55 ± 0.35	8.062	0.000

TABLE 2. Allele and Genotype Frequencies Among the Subgroups of the Hei Yi Zhuang and Han Populations (n [%])

		Genotypes				*Alleles*		
Groups	***n***	***B1B1***	***B1B2***	***B2B2***	***P***	***B1***	***B2***	***P***
Hei Yi Zhuang	758	326 (43)	336 (44.3)	96 (12.7)		988 (65.2)	528 (34.8)	
Han Chinese	778	314 (41.7)	356 (45.1)	108 (13.3)	0.536	984 (63.2)	572 (36.8)	0.264
Hei Yi Zhuang								
Males	380	158 (41.6)	178 (46.8)	44 (11.6)		494 (65)	266 (35)	
Females	378	168 (44.4)	158 (41.8)	52 (13.8)	0.340	494 (65.3)	262 (34.7)	0.888
Nondrinkers	342	154 (45.0)	142 (41.5)	46 (13.5)		450 (65.8)	234 (34.2)	
Drinkers	416	172 (41.3)	194 (46.6)	50 (12.0)	0.367	538 (64.7)	294 (35.3)	0.647
Nonsmokers	502	232 (46.2)	208 (41.4)	62 (12.4)		672 (66.9)	332 (33.1)	
Smokers	256	94 (36.7)*	128 (50.0)*	34 (13.3)	0.039	316 (61.7)	196 (38.3)	0.044
BMI, ≤24 kg/m^2	674	290 (43.0)	298 (44.2)	86 (12.8)		878 (65.1)	470 (34.9)	
BMI, >24 kg/m^2	84	36 (42.9)	38 (45.2)	10 (11.9)	0.970	110 (65.5)	58 (34.5)	0.930
Normotensives	588	272 (46.3)	238 (40.5)	78 (13.3)		782 (66.5)	394 (33.5)	
Hypertensives	170	54 (31.8)‡	98 (57.6)‡	18 (10.6)	0.000	206 (60.6)	134 (39.4)	0.044
Han Chinese								
Males	390	162 (41.5)	170 (43.6)	58 (14.9)		494 (63.3)	286 (36.7)	
Females	388	152 (39.2)	186 (47.9)	50 (12.9)	0.444	490 (63.1)	286 (36.9)	0.938
Nondrinkers	438	164 (37.4)	200 (45.7)	74 (16.9)		528 (60.3)	348 (39.7)	
Drinkers	340	150 (44.1)	156 (45.9)	34 (10.0)†	0.013	456 (67.1)	224 (32.9)	0.006
Nonsmokers	546	214 (39.2)	262 (48.0)	70 (12.8)		690 (63.2)	402 (36.8)	
Smokers	232	100 (43.1)	94 (40.5)	38 (16.4)	0.130	294 (63.4)	170 (36.6)	0.948
BMI, ≤24 kg/m^2	610	256 (42.0)	260 (42.6)	94 (15.4)		772 (63.3)	448 (36.7)	
BMI, >24 kg/m^2	168	58 (34.5)	96 (57.1)‡	14 (8.3)*	0.002	212 (63.1)	124 (36.9)	0.951
Normotensives	684	278 (40.6)	316 (46.2)	90 (13.2)		872 (63.7)	496 (36.3)	
Hypertensives	94	36 (40.4)	40 (45.8)	18 (13.9)	0.288	112 (59.6)	76 (40.4)	0.266

*$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$ in comparison with male subjects, nondrinkers, nonsmokers, those with BMI of 24 kg/m^2 or lesser, or normotensives of the same ethnic group.

B1B1 genotype ($P < 0.01$ for each). There were no significant differences in TC, TG, LDL-C, and ApoB levels and the ratio of ApoAI to ApoB between the B1B1, B1B2, and B2B2 genotypes in Hei Yi Zhuang and in Han ($P > 0.05$ for all; Table 4).

Correlative Factors of Serum Lipid Levels

Multivariate logistic regression analysis also showed that the levels of HDL-C, LDL-C, and ApoAI were correlated with age, sex, alcohol consumption, and cigarette smoking ($P < 0.05$-0.01). Total cholesterol and ApoB levels were correlated with age, BMI, and ethnic group ($P < 0.01$ for all). Triglyceride and LDL-C levels were correlated with BMI and cigarette smoking ($P < 0.01$ for all). High-density lipoprotein cholesterol and ApoB levels were correlated with ethnic group and sex ($P < 0.05$–0.01) in the combined population of Hei Yi Zhuang and Han (Table 5).

■ DISCUSSION

The present study shows that serum levels of TC, TG, LDL-C, and ApoB in Hei Yi Zhuang were significantly lower than those in Han, whereas the levels of HDL-C and the ratio of ApoAI to ApoB in Hei Yi Zhuang were significantly higher than those in Han. There were no significant differences in ApoAI levels between the 2 ethnic groups. These findings are in accordance with those of our previous reports in a large population.[35–37] Hei Yi Zhuang is a special subgroup of the Zhuang minority in China. Strict intra-ethnic marriages have been performed from time immemorial in this ethnic subgroup. Namely, only both man and woman are Hei Yi Zhuang can marry and cannot intermarry with the other subgroups of Zhuang or other ethnic groups.[36,37] Therefore, we are confident that some genetic factors may be involved in determining the serum lipid profiles in this population.

In the present study, we found that there were no significant differences in the allelic and genotypic frequencies of *CETP Taq*IB between the 2 ethnic groups. The frequency of B2 allele was 34.8% in Hei Yi Zhuang, and 36.8% in Han, which is quite similar to the results in Vietnamese (34%) and Koreans (36%)[46,47] but lower than that in white populations (40%–64%), the Chinese in Taiwan (42.83%), and Japanese (43%).[20,48,49] In the current study, however, we found that there were significant differences in the genotypic and allelic frequencies in several subgroups between the 2 ethnic groups. Significant differences in the genotypic and allelic frequencies were found between the smokers and nonsmokers or between hypertensives and normotensives in Hei Yi Zhuang and between drinkers and nondrinkers in Han. The genotypic frequencies in Han were also found to

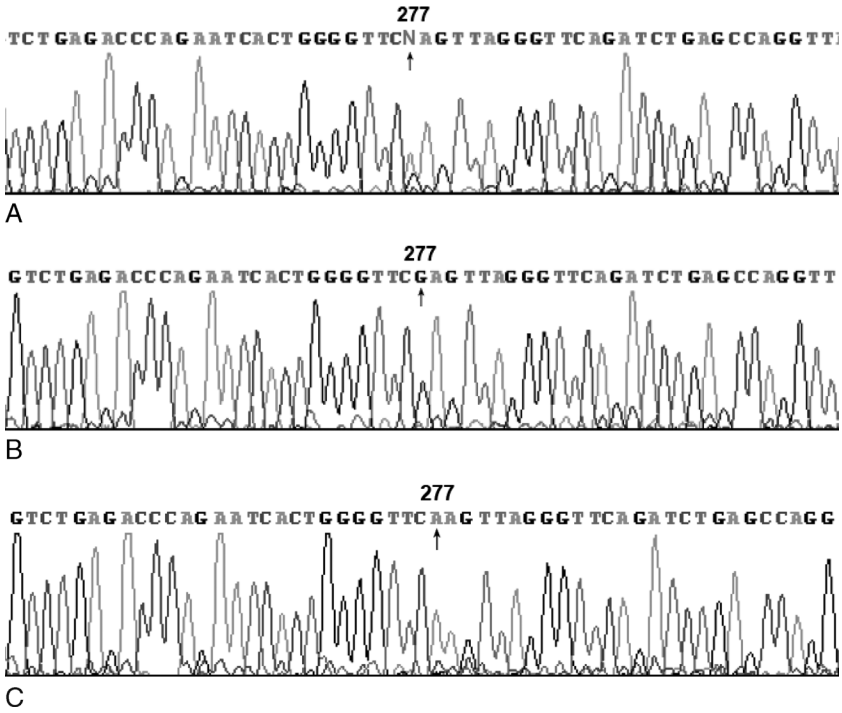

FIGURE 2. A part of the nucleotide sequence in the first intron of the *CETP* gene. B1B2 genotype (A), B1B1 genotype (B), and B2B2 genotype (C).

be different between the subjects with a BMI of greater than 24 kg/m^2 and those with a BMI of 24 kg/m^2 or lesser.

The polymorphism of the *CETP Taq*IB has been suggested to be a major cause of genetically determined variation in plasma HDL-C levels. In the present study, we found that the levels of HDL-C and ApoAI in Hei Yi Zhuang but not in Han were higher in B2B2 genotype than in B1B1 genotype. These findings are in agreement with those in several previous studies[22–24,46,50,51] but not in others.[25–27] The reason for this discrepancy between the 2 ethnic groups is not yet known. Given the reported associations of the *Taq*IB polymorphism with CETP mass and/or activity and serum lipid levels, the most plausible explanation is that this polymorphism is in linkage disequilibrium with some functional promoters in the regulatory region of the *CETP* gene. Frisdal et al.[18] demonstrated that these 3 functional *CETP* promoter polymorphisms (−1337C/T, −629A/C, and −971G/A) can interact together to determine the overall activity of the *CETP* gene and, thus, contribute significantly to variation in plasma CETP mass concentration. Evidence exists that the consequences of CETP activity may depend on the metabolic setting, particularly on TG levels.[52] The fact that carriers of B1 allele versus B2 allele had lower HDL-C and ApoAI indicates that B1 allele compared with B2 allele has fewer HDL particles, with each carrying less cholesterol. A biologically plausible explanation for such an association could be that carriers of B2 allele induce lower CETP activity, transferring fewer cholesteryl esters out of HDL particles.

In addition to the genetic factors, several studies have shown the possible interaction between some environmental factors (sex, alcohol consumption, cigarette smoking, and BMI) or ethnic differences and the *Taq*IB polymorphism on plasma HDL-C levels. In Italian and Greek migrants to Australia, Mitchell et al.[29] found associations between the *Taq*IB polymorphism in all Greek samples but not in the Italian samples. This research suggests that associations between the *CETP* gene and lipid phenotypes may be population specific. The effect of B2 allele on plasma HDL-C was absent in nondrinkers[53] or in subjects drinking less than 25 g/d of alcohol but increased commensurably with higher values of alcohol consumption.[30] High-density lipoprotein cholesterol levels in Turks may be modulated by an interaction between the *CETP Taq*IB polymorphism and smoking, as well as an interaction with hypertriglyceridemia and BMI.[54] Park et al.[55] reported that B1B1 homozygote of the *CETP Taq*IB polymorphism is associated with low HDL-C levels in female subjects and nonsmoking male subjects. Smoking interferes with the activity of plasma enzymes involved in HDL metabolism, namely CETP, lecithin cholesterol acyltransferase, lipoprotein lipase, hepatic lipase, and phospholipid. The circulating levels of HDL may be dependent in part on the relative activity of these

TABLE 3. Interactions Between the CETP *Taq*IB Genotypes and Sex, Alcohol Consumption, Cigarette Smoking, BMI, and Blood Pressure on HDL-C Levels

	HDL-C, mM				
Groups	***B1B1***	***B1B2***	***B2B2***	***F***	***P***
Hei Yi Zhuang					
Males	1.99 ± 0.49	2.14 ± 0.60	2.09 ± 0.33	1.470	0.231
Females	2.04 ± 0.37	2.07 ± 0.46	2.27 ± 0.41**††‡‡	6.191	0.002
Nondrinkers	1.94 ± 0.38	2.02 ± 0.50	2.21 ± 0.43**†	6.400	0.002
Drinkers	2.09 ± 0.47‡‡‡	2.17 ± 0.56‡‡	2.16 ± 0.34	0.621	0.538
Nonsmokers	2.04 ± 0.42	2.08 ± 0.49	2.26 ± 0.41**††	6.061	0.003
Smokers	1.96 ± 0.45	2.16 ± 0.60	2.05 ± 0.30‡‡	0.965	0.382
BMI, ≤24 kg/m^2	2.01 ± 0.43	2.12 ± 0.55	2.17 ± 0.40**	5.282	0.005
BMI, >24 kg/m^2	2.06 ± 0.45	2.02 ± 0.41	2.29 ± 0.22	1.233	0.297
Normotensives	2.01 ± 0.43	2.08 ± 0.50	2.20 ± 0.40**†	6.038	0.003
Hypertensives	2.06 ± 0.45	2.19 ± 0.62	2.10 ± 0.30	0.668	0.514
Han Chinese					
Males	1.93 ± 0.46	1.97 ± 0.46*¶	1.97 ± 0.47§	0.407	0.666
Females	1.92 ± 0.45¶	2.00 ± 0.39	2.06 ± 0.42§	3.252	0.040
Nondrinkers	1.85 ± 0.44	1.91 ± 0.37§	1.92 ± 0.38¶	2.610	0.075
Drinkers	2.01 ± 0.46‡‡‡	2.08 ± 0.47‡‡‡	2.09 ± 0.60	0.143	0.867
Nonsmokers	1.91 ± 0.43¶	1.99 ± 0.39§	1.99 ± 0.39¶	2.705	0.068
Smokers	1.97 ± 0.49	1.98 ± 0.50§	1.96 ± 0.55	0.608	0.545
BMI, ≤24 kg/m^2	1.92 ± 0.43¶	2.030.43**§	1.99 ± 0.45¶	6.445	0.002
BMI, >24 kg/m^2	1.98 ± 0.54	1.86 ± 0.38‡‡‡§	1.86 ± 0.46§	1.428	0.243
Normotensives	1.92 ± 0.44§	1.99 ± 0.43*§	1.97 ± 0.47¶	3.515	0.030
Hypertensives	2.01 ± 0.54	1.97 ± 0.42§	2.02 ± 0.31	0.831	0.439

Analysis of covariance with adjustment for age, sex, alcohol consumption, cigarette smoking, and blood pressure were performed in this table.
*$P < 0.05$ and **$P < 0.01$ in comparison with B1B1 genotype of the same subgroup.
$^{\dagger}P < 0.05$ and $^{\dagger\dagger}P < 0.01$ in comparison with B1B2 genotype of the same subgroup.
$^{\ddagger}P < 0.05$, $^{\ddagger\ddagger}P < 0.01$, and $^{\ddagger\ddagger\ddagger}P < 0.001$ in comparison with male subjects, nondrinkers, nonsmokers, those with BMI of 24 kg/m^2 or lesser, or normotensives of the same ethnic group.
$^{\S}P < 0.05$ and $^{\P}P < 0.01$ in comparison with the same subgroup of Hei Yi Zhuang.

enzymes. Smoking seems to impede the HDL-raising effect of the *Taq*IB2 allele.[56] Vohl and colleagues[34] reported that raising effect of the B2 allele on plasma HDL-C concentrations was blunted in the presence of a BMI of 27 kg/m^2 or greater. In the present study, we also found that the interactions between the *CETP Taq*IB genotypes and sex, alcohol consumption, cigarette smoking, BMI, and blood pressure on serum HDL-C levels were different between the Hei Yi Zhuang and Han populations. Higher HDL-C levels in Hei Yi Zhuang were found only in female subjects, nondrinkers, nonsmokers, subjects with a BMI of 24 kg/m^2 or lesser, or normotensives in B2B2 genotype, whereas higher HDL-C levels in Han were found only in female subjects in B2B2 genotype and in subjects with a BMI of 24 kg/m^2 or lesser or normotensives in B1B2 genotype. The levels of HDL-C in B1B1 and B1B2 individuals in both ethnic groups were higher in drinkers than in nondrinkers. The effect of different kinds of wine on the *CETP Taq*IB genotypes and serum HDL-C levels is not well known. In the present study, 90% of the wine drunk by Hei Yi Zhuang was corn wine and rum, in

TABLE 4. Comparison of the Lipid and Apo Levels Among the Genotypes Between Hei Yi Zhuang and Han

Groups	***Genotypes***	***n***	***TC, mM***	***TG, mM***	***HDL-C, mM***	***LDL-C, mM***	***ApoAI, g/L***	***ApoB, g/L***	***ApoAI/ApoB***
Hei Yi	B1B1	326	4.46 ± 1.17	0.89 (0.42)	2.10 ± 0.43	2.43 ± 2.13	1.41 ± 0.16	0.87 ± 0.21	1.76 ± 0.79
Zhuang	B1B2	336	4.52 ± 0.86	0.85 (0.44)	2.11 ± 0.53	2.28 ± 0.65	1.43 ± 0.13	0.86 ± 0.20	1.76 ± 0.51
	B2B2	96	4.58 ± 0.92	0.93 ± 0.42	2.18 ± 0.39*	2.30 ± 0.71	1.45 ± 0.10*	0.87 ± 0.20	1.74 ± 0.37
F	—	—	0.662	3.427	5.650	0.931	4.766	0.095	0.022
P	—	—	0.516	0.180	0.004	0.395	0.009	0.910	0.978
Han Chinese	B1B1	314	4.81 ± 1.22	1.14 ± 0.60	1.93 ± 0.45	2.60 ± 0.75	1.41 ± 0.17	0.96 ± 0.21	1.52 ± 0.33
	B1B2	356	4.78 ± 0.99	0.99 (0.69)	1.97 ± 0.42	2.60 ± 0.75	1.41 ± 0.13	0.96 ± 0.22	1.55 ± 0.37
	B2B2	108	4.65 ± 0.92	1.31 ± 1.29	1.98 ± 0.45	2.44 ± 0.60	1.43 ± 0.14	0.93 ± 0.16	1.58 ± 0.31
F	—	—	0.896	0.323	1.569	2.036	1.812	1.274	1.018
P	—	—	0.408	0.851	0.209	0.131	0.164	0.280	0.362

Analysis of covariance with adjustment for age, sex, alcohol consumption, cigarette smoking, and blood pressure were performed in this table.
*$P < 0.05$ in comparison with B1B1 genotype.

TABLE 5. Correlative Factors for the Lipid Parameters Between Hei Yi Zhuang and Han

Lipids	*Relative Factors*	*Regression Coefficient*	*SE*	*SRC*	*t*	*P*
Hei plus Han						
TC	Age	0.014	0.001	0.252	10.559	0.000
	BMI	0.082	0.009	0.222	9.308	0.000
TG	Alcohol consumption	0.166	0.040	0.104	4.158	0.000
	BMI	0.032	0.010	0.083	3.327	0.001
HDL-C	Age	0.003	0.001	0.110	4.407	0.000
	Alcohol consumption	0.145	0.021	0.182	6.776	0.000
	Cigarette smoking	−0.060	0.018	−0.089	−3.352	0.001
	BMI	−0.011	0.005	−0.058	−2.350	0.019
	Genotype	−0.065	0.028	−0.057	−2.301	0.022
LDL-C	Age	0.009	0.001	0.230	9.638	0.000
	Alcohol consumption	−0.166	0.028	−0.144	−6.023	0.000
	BMI	0.072	0.006	0.263	11.154	0.000
ApoAI	Age	0.002	0.000	0.201	8.174	0.000
	Alcohol consumption	0.043	0.006	0.190	6.949	0.000
	Sex	−0.029	0.001	−0.102	−3.370	0.001
	BMI	0.003	0.006	0.053	2.193	0.028
	Cigarette smoking	−0.011	0.006	−0.059	−1.989	0.047
ApoB	Age	0.003	0.000	0.281	11.979	0.000
	Alcohol consumption	−0.038	0.008	−0.109	−4.653	0.000
	BMI	0.024	0.002	0.288	12.469	0.000
Hei Yi Zhuang						
TC	Sex	−0.226	0.073	−0.131	−3.464	0.000
TG	Cigarette smoking	0.174	0.076	0.083	2.280	0.023
HDL-C	Genotype	0.085	0.025	0.119	3.425	0.001
	Alcohol consumption	0.150	0.026	0.216	5.732	0.000
	Cigarette smoking	−0.078	0.025	−0.132	−3.146	0.002
LDL-C	BMI	0.119	0.024	0.178	4.971	0.000
	Alcohol consumption	−0.377	0.082	−0.176	−4.627	0.000
	Cigarette smoking	0.190	0.077	0.094	2.475	0.014
ApoAI	Genotype	0.024	0.008	0.112	3.196	0.001
	BMI	0.007	0.002	0.107	3.034	0.002
	Sex	−0.028	0.012	−0.097	−2.302	0.022
	Alcohol consumption	0.049	0.008	0.234	5.939	0.000
	Cigarette smoking	−0.027	0.008	−0.134	−3.291	0.001
ApoB	BMI	0.012	0.003	0.134	3.716	0.000
	Alcohol consumption	−0.029	0.012	−0.099	−2.495	0.013
	Sex	−0.045	0.016	−0.111	−2.816	0.005
Han Chinese						
TC	BMI	0.116	0.014	0.283	8.333	0.000
	Alcohol consumption	0.266	0.057	0.158	4.640	0.000
TG	BMI	0.104	0.021	0.175	5.003	0.000
	Alcohol consumption	0.406	0.086	0.165	4.728	0.000
HDL-C	BMI	−0.013	0.006	−0.080	−2.250	0.025
	Genotype	0.046	0.023	0.072	2.053	0.040
	Sex	−0.090	0.032	−0.102	−2.777	0.006
	Alcohol consumption	0.145	0.026	0.210	5.650	0.000
LDL-C	BMI	0.076	0.010	0.273	7.901	0.000
ApoAI	Genotype	0.019	0.008	0.087	2.493	0.013
	Sex	−0.042	0.011	−0.141	−3.900	0.000
	Alcohol consumption	0.062	0.008	0.264	7.269	0.000
ApoB	BMI	0.024	0.003	0.305	8.929	0.000
	Alcohol consumption	0.032	0.011	0.097	2.845	0.005

SRC indicates standardized regression coefficient.

which the alcohol content is lower. On the contrary, a great deal of the wine drunk by Han is rice wine, in which the alcohol content is higher.

In the present study, we also found that many confounding factors affect serum lipid levels. The levels of HDL-C, LDL-C, and ApoAI were correlated with age, sex, alcohol consumption, and cigarette smoking. Total cholesterol and ApoB levels were correlated with age, BMI, and ethnic group. Triglyceride and LDL-C levels were correlated with BMI and cigarette smoking.

High-density lipoprotein cholesterol and ApoB levels were correlated with ethnic group and sex in the combined population of Hei Yi Zhuang and Han. These findings suggest that the environmental factors also play an important role in determining the lipid levels in these population. Differences in the lipid levels between the 2 ethnic groups may mainly result from different dietary patterns and lifestyle factors. The great majority of Hei Yi Zhuang people reside in the mountainous areas. Corn gruel or tortillas was the staple food all year around. Corn contains abundant dietary fiber and high-quality plant protein.[57] Consumption of dietary fiber, specifically soluble fiber such as pectins and guar gum, can result in a decrease in serum cholesterol levels in healthy and hyperlipidemic subjects.[58] Plant protein might raise serum levels of HDL-C and promote the transportation and excretion of free cholesterol. Although Han takes rice as the staple food mostly. The standard of living in Han is higher than that in Hei Yi Zhuang. The intake of animal fat is more than that in Hei Yi Zhuang, and the BMI is also significantly higher than those in Hei Yi Zhuang.[36,37] It has been widely accepted that high-fat diets, particularly those that contain large quantities of saturated fatty acids, raise blood cholesterol concentrations and predispose individuals to cardiovascular disease.[59] It is widely recognized that regular physical activity is associated with an increase in plasma HDL-C levels.[60,61] In previous study, however, we showed that there was no significant difference in physical activity level between both ethnic groups.[37] Furthermore, considerable heterogeneity in the responsiveness of plasma HDL-C levels to exercise training has been reported.[62,63] For instance, in the Health, Risk Factors, Exercise Training and Genetics Family Study, marked interindividual variability was found in the HDL-C response to a fully standardized endurance training program.[64] Thus, the difference in the serum HDL-C levels between the 2 ethnic groups may not be related to the physical activity level.

■ CONCLUSIONS

In conclusion, the current study shows that there were significant differences in the interactions between the *CETP Taq*IB genotypes and several environmental factors in the Hei Yi Zhuang and Han populations. The levels of HDL-C and ApoAI in Hei Yi Zhuang but not in Han were higher in B2B2 genotype than in B1B1 genotype. The B1 carriers in both ethnic groups benefited more from alcohol consumption than B2 carriers in increasing serum HDL-C levels. The differences in serum lipid levels between the 2 ethnic groups might result from different interactions between environmental and genetic factors.

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