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Association of apolipoprotein A5 gene polymorphisms and serum lipid levels

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KEYWORDS
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Abstract *Background and aims:* Apolipoprotein (APO) A5 gene polymorphisms have been associated with increased plasma triglyceride (TG), but the results are inconsistent. The present study was undertaken to detect the *APOA5* gene polymorphisms and their associations with lipid profiles in the Guangxi Hei Yi Zhuang and Han populations.
Methods and results: Genotyping of the APOA5 −1131T>C, c.553G>T and c.457G>A was performed in 490 subjects of Hei Yi Zhuang and 540 participants of Han Chinese aged 15–89 years. The −1131C allele frequency was higher in high total cholesterol (TC) than in normal TC subgroups in both the ethnic groups ($P < 0.05$). The c.553T allele frequency was higher in high TG than in normal TG subgroups ($P < 0.01$), in high APOB than in normal APOB subgroups in Hei Yi Zhuang ($P < 0.05$), or in females than in males in Han ($P < 0.01$). The c.457A allele frequency in Han was higher in high TG than in normal TG subgroups, in low APOA1 than in normal APOA1 subgroups, in males than in females, or in normal APOB than in high APOB subgroups ($P < 0.05$–0.01). The levels of TC, low-density lipoprotein cholesterol and APOB in Hei Yi Zhuang were correlated with −1131T>C genotype or allele, and the levels of TG were associated with c.553G>T genotype ($P < 0.05$). The levels of TG, APOA1 and APOB in Han were

Abbreviations: CAD, coronary artery disease; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; APO, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; SNPs, single-nucleotide polymorphisms; BMI, body mass index; DNA, deoxyribonucleic acid; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; LD, linkage disequilibrium.

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correlated with c.457G>A genotype or allele, and the levels of TC were associated with −1131T>C allele ($P < 0.05$).
Conclusions: The differences in the lipid profiles between the two ethnic groups might partly result from different *APOA5* gene−environmental interactions.

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in both industrialised and developing countries. Dyslipidaemia, 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 cholesterol (HDL-C) [5], is a major risk factor for CAD. It is well-documented that dyslipidaemia results from complex interactions between genetic and environmental factors [6]. The genetic factors could account for 40−80% of the interindividual variation in the blood lipid phenotypes [7].

APOA5 is a secreted protein present in human serum and is associated with specific lipoprotein particles. It was detectable in very low-density lipoprotein, HDL and chylomicrons. Serum APOA5 is very low compared with other apolipoproteins [8]. The gene of APOA5 was originally identified by experiments looking for new open reading frames in the *APOA1−APOC3−APOA4* gene cluster, which is located on human chromosome 11q23 [9]. It has been reported that the human *APOA5* transgenic mouse has significantly decreased TG and the *APOA5* gene knockout mouse has significantly increased plasma TG concentrations as compared with wild-type mice [10]. The adenovirus-mediated overexpression of *APOA5* was associated with markedly decreased (−70%) serum TG levels [11]. At least 36 single-nucleotide polymorphisms (SNPs) have been identified in the *APOA5* gene (http://www.ncbi.nlm.nih.gov/SNP/). The minor alleles of several common SNPs in the human *APOA5* gene locus have been reported to be significantly associated with both increased plasma TG levels in several populations [12−19], and the risk of CAD [20−23]. But the results have not always been consistent among different ethnicities [24,25].

There are 56 ethnic groups in China. Han is the largest ethnic group, and Zhuang is the largest minority. Zhuang can be classified into 43 ethnic subgroups according to the differences in habitats and languages. Hei Yi Zhuang is a special subgroup of the Zhuang minority. The population size is 51,655. Because of isolation from the other ethnic groups, the special customs and cultures including their clothing, intra-ethnic marriage, diet and lifestyle are still completely conserved to the present day. We have previously found that there were significant differences in serum lipid profiles between the two ethnic groups [26]. We hypothesise that some genetic factors may be responsible for this discrepancy. Therefore, the aim of the present study was to detect the *APOA5* −1131T>C (rs662799), c.553G>T (rs2075291) and c.457G>A (rs3135505) polymorphisms and their associations with lipid profiles in the Guangxi Hei Yi Zhuang and Han populations.

Methods

Study populations

A total of 490 unrelated subjects of Hei Yi Zhuang were surveyed by a stratified randomised cluster sampling. The age of the subjects ranged from 15 to 80 years, with an average age of 44.49 ± 18.85 years. There were 230 males (46.9%) and 260 females (53.1%). The subjects were peasants. During the same period, a total of 540 subjects of Han Chinese who reside in the same county were also surveyed by the same method. The average age of the subjects was 43.22 ± 16.52 years (range 15−89 years). There were 262 males (48.5%) and 278 females (51.5%). They were also peasants. The study subjects had no evidence of diseases related to atherosclerosis. 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.

Epidemiological survey

The survey was carried out using internationally standardised methods. Information on demographics, socioeconomic status and lifestyle was collected with standardised questionnaires. Smoking status was categorised into subgroups of cigarettes per day: <20 and ≥20. Alcohol consumption was categorised into subgroups of grams of alcohol per day: ≤25 and >25. The physical examination included blood pressure [27], body height and body weight, and body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Laboratory investigations

Venous blood sample (8 mL) was drawn from a forearm vein. A part of the sample (3 mL) was collected into a glass tube and used to determine serum lipid levels. Another part of the sample (5 mL) was transferred into a tube with anticoagulate solution and used to extract deoxyribonucleic acid (DNA). The levels of TC, TG, HDL-C and LDL-C in the samples were determined by enzymatic methods with commercially available kits. Serum APOA1 and APOB levels were assessed by the immunoturbidimetric immunoassay [26].

DNA preparation and genotyping

Genomic DNA was isolated from peripheral blood leucocytes using the phenol−chloroform method. Genotyping