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Association between DNA variant sites in the apolipoprotein A5 gene and coronary heart disease in Chinese

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Abstract

The recently discovered apolipoprotein A5 (*APOA5*) gene has been shown to be important in determining plasma triglyceride levels, a major cardiovascular disease risk factor. We searched for possible associations of the *APOA5* gene polymorphisms S19W and −1131T>C with coronary heart disease (CHD) in a Chinese population. A total of 483 Chinese CHD patients and 502 control non-CHD subjects were genotyped by polymerase chain reaction–restriction fragment length polymorphism for these 2 single nucleotide polymorphisms. We found that the minor allele 19W was observed only in CHD patients and not in controls, with allelic frequencies of 0.047 and 0.000, respectively ($P < .000001$), and the minor allele −1131C was significantly higher in CHD patients than in controls (0.391 vs 0.299, $P < .0001$). These results suggest that both the S19W and −1131T>C variations in the *APOA5* gene are associated with the CHD and appear to be 2 genetic risk factors for CHD susceptibility in Chinese. Moreover, we found that triglyceride levels were significantly higher in −1131C carriers than in −1131T subjects of the control group and that high-density–lipoprotein cholesterol was decreased in −1131C carriers among CHD patients.

Keywords: Apolipoprotein A5; Triglycerides; Coronary heart disease; Single nucleotide polymorphisms; Chinese population study

1. Introduction

The apolipoprotein A5 gene (*APOA5*) plays a key role in determining plasma triglyceride (TG) concentrations. In *Apoa5*(−/−) knockout mice, serum TG levels are 4 times higher than those of normal mice, whereas transgenic mice expressing human *APOA5* have TG levels that are only approximately one third of normal [1,2]. Clinical studies have also suggested an important role for *APOA5* in determining plasma TG concentrations. When single nucleotide polymorphisms (SNPs) and their haplotypes across the *APOA5* locus have been studied in human beings, some of SNPs were found to be significantly associated with plasma TG levels in different ethnic populations [3,4]. However, no studies on the possible association of *APOA5* SNPs with coronary heart disease (CHD) in Chinese have been so far reported.

It has become increasingly clear that both genetic and environmental factors contribute to the etiology of CHD. Epidemiological studies have shown that hypertriglyceridemia is a major independent risk factor for CHD [5]. The relationship between elevated plasma TGs and CHD risk has been confirmed by meta-analysis, identifying TG as an independent CHD risk factor [6]. With the discovery of the *APOA5* gene and its association with TG, several common *APOA5* SNPs have been identified [3]. Subsequently, many

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studies in different ethnic groups have demonstrated associations of some of the *APOA5* SNPs with plasma TG and very low-density lipoprotein cholesterol levels [7-13]. Furthermore, 2 haplotypes of the *APOA5* gene, defined by 2 tag SNPs—S19W (GenBank_ID: ss4383597, in the third exon, also reported as 56C>G) and −1131T>C (GenBank_ID: ss3199915, in the promoter, previously reported as SNP3)—are reported to have a significant influence on human plasma TG levels [4].

In the present study, we report an association of *APOA5* SNPs with CHD and the correlation of both the S19>W and −1131T>C mutations with levels of the plasma lipids and lipoproteins in Chinese CHD patients and controls.

2. Materials and methods

2.1. Subjects

Four hundred eighty-three unrelated CHD patients were selected between 2000 and 2004 from the West China Hospital, Sichuan University, for the study by coronary angiography, using the Judkins technique [14]. Individuals having any major coronary artery branch (left anterior descending artery, left circumflex artery, right coronary artery) with at least 1 stenosis of >60% were qualified as CHD patients. In addition, 502 unrelated age- and gender-matched subjects, selected via health screening at the same hospital and free of any clinical or biochemical signs of CHD, were used as controls for the study. None of the patients enrolled in this study was taking hypolipidemic drugs before coronary angiography or measurements of their lipid profiles. The study was approved by the Internal Ethical Review Board of the West China Hospital, Sichuan University, and signed informed-consent forms were obtained from all subjects studied.

2.2. Measurement of lipids and lipoproteins

After an overnight fast, baseline blood samples were collected from all CHD patients and controls. Plasma was separated and used immediately for lipid and lipoprotein analysis. The levels of plasma total cholesterol (TChol), TG, and high- and low-density lipoprotein cholesterol (HDL-C and LDL-C) were measured by an automated chemistry analyzer (Olympus AU5400, Japan) with an enzymatic kit (Roche Diagnostics GmbH).

2.3. DNA preparation, polymerase chain reaction amplification, and genotyping

Genomic DNA was isolated from peripheral blood leukocytes, using the "salting-out" procedure [15], and then stored at 4 °C for use. *APOA5* loci genotyping was performed using the polymerase chain reaction (PCR)–restriction fragment length polymorphism method. The PCR was carried out as described [4]. For amplification of the fragment containing 56C>G (S19W), the primers were as follows: forward, 5′–GGC TCT TCT TTC AGG TGG GTC TCC G-3′; reverse, 5′-GCC TTT CCG TGC CTG GGT GGT-3′. The 157-bp PCR products were digested with 6 U of *Taq*I (MBI Fermentas) for 4 hours at 65 °C. After digestion, the digested products were separated by electrophoresis on a 3% agarose gel stained with ethidium bromide and visualized on an ultraviolet transilluminator. The fragments of 134 and 23 bp represented the Ser-19 allele, and a single uncut product represented the Try-19 allele. The primers for amplification of the fragment containing −1131T>C were as follows: forward, 5′-GGA GCT TGT GAA CGT GTG TAT GAG T-3′; reverse, 5′-CCC CAG GAA CTG GAG CGA AAT T-3′. The PCR products were then directly digested with *Mse*I (New England Biolabs, USA) at 37 °C overnight. When the 154-bp PCR-amplified fragment was digested, it produced fragments of 133 and 21 bp for the −1131T allele, and the single uncut product represented the −1131C allele.

2.4. Statistical analysis

The data of mean and standard deviation are presented as $\bar{\chi} \pm s$ and percentages as %. Because TG levels were not normally distributed, they were logarithmically transformed before the statistical analysis, but untransformed values are presented in the tables. Allele frequencies were determined by counting alleles and calculating sample proportions. Hardy-Weinberg equilibrium was confirmed using the χ^2 test. Differences in lipid and lipoprotein values of the various genotypes were evaluated by 1-way analysis of variance (ANOVA) and the Student-Newman-Keuls SNK test. Differences of genotypic and allelic distribution between patients and controls were analyzed by χ^2 or Fisher exact tests (when appropriate). The odds ratios for CHD were derived from logistic regression analysis. All statistical analyses were carried out with SPSS 11.0 software (SPSS Inc, Chicago, Ill).

3. Results

3.1. General and clinical biochemical characteristics of the patients and controls

The clinical characteristics and plasma lipid levels of the CHD patients and controls are shown in Table 1. As can be

Table 1
General and clinical biochemical characteristics of CHD patients and controls

	CHD patients	Controls	*P*
No. of subjects	483	502	–
Sex (M/F)	285/198	276/226	–
Age (y)	54.2 ± 6.3	54.4 ± 5.8	NS*
BMI (kg/m^2)	25.92 ± 3.24	23.45 ± 2.83	<.01
TG (mmol/L)	1.98 ± 0.88	1.57 ± 0.83	<.01
TChol (mmol/L)	5.51 ± 0.78	5.13 ± 0.80	<.01
HDL-C (mmol/L)	1.13 ± 0.46	1.67 ± 0.83	<.01
LDL-C (mmol/L)	3.21 ± 0.86	3.04 ± 0.92	<.01

M/F indicates male/female; BMI, body mass index.

* NS indicates no significant difference ($P > .05$).

Table 2
Frequencies of alleles and genotypes of APOA5 S19W mutation in CHD patients and controls

Group	Number	Genotype (%)			Allele (%)	
		S/S	S/W	W/W	S	W
CHD	483	439 (90.9)	43 (8.9)	1 (0.2)	921 (95.3)	45 (4.7)
Control	502	502 (100.0)	0 (0.0)	0 (0.0)	1004 (100.0)	0 (0.0)
χ^2			47.87		47.86	
P			.0000001		.000001	

Table 4
Lipid and lipoprotein levels in the different S19W genotypes among CHD patients

Lipids (mmol/L)	Genotype		P
	S/S (n = 439)	S/W + W/W (n = 44)	
TG	1.95 ± 0.87	2.27 ± 0.93	.02
TChol	5.49 ± 0.77	5.67 ± 0.87	.14
HDL-C	1.14 ± 0.45	1.08 ± 0.53	.41
LDL-C	3.20 ± 0.86	3.28 ± 0.84	.56

seen, the values for the body mass index, TG, TChol, and LDL-C were considerable higher in CHD patients than those in controls, but the HDL-C was considerably lower in CHD patients compared with that in controls.

3.2. S19W and −1131T>C mutations in APOA5 are associated with CHD in Chinese

We found that the genotype distributions of both S19W and −1131T>C polymorphisms were in Hardy-Weinberg equilibrium (data not shown). The genotype and allelic frequencies for S19W and −1131T>C in CHD and control groups are shown in Tables 2 and 3, respectively. Among all 502 control subjects, there were no homozygotes or heterozygotes carrying the W-19 (Trp-19) allele; in other words, all controls were homozygous for the S-19 (Ser-19) allele. Among the 483 CHD patients, 43 of Trp-19 heterozygotes and 1 of Trp-19 homozygotes were found. The S/W genotype, W/W genotype, and W-19 allelic frequencies among CHD patients were 8.9%, 0.2%, and 4.7%, respectively, which were very significantly different from that of controls (genotype frequency, $P = .0000001$, $\chi^2 = 47.87$; allelic frequency, $P = .000001$, $\chi^2 = 47.86$).

In Table 3, it was demonstrated that the frequency of the genotypes with the minor allele C (−1131T/C plus −1131C/C) and the frequency of the allele −1131C in the CHD patient group were significantly higher than those of the control group (62.5% vs 51.0% and 39.1% vs 29.9%, $P < .001$, respectively). Because these differences are significant in genotype frequency ($P < .0001$, $\chi^2 = 18.52$) and allelic frequency ($P < .0001$, $\chi^2 = 18.66$), we conclude that the −1131T>C variant is also associated with CHD.

3.3. S19W variant of APOA5 has significant effect on TG levels in CHD patients

Because 19W was found in none of our control subjects, we could not analyze the effect of the S19W variation on plasma lipids among the different genotypes in this group. Among the CHD patients, the carriers of minor allele W had significantly higher TG and lower HDL-C level than the noncarriers (Table 4). It therefore displays that the S19W variation has significant effect on plasma TG in Chinese CHD patients.

3.4. −1131T>C variant of APOA5 displays a significant influence on TG levels in both CHD patients and controls and very significant influence on HDL-C in CHD patients

In both the control and patient groups, the −1131T>C variant showed a significant effect on the plasma TG levels as evidenced by the different TG levels between the subgroups with different genotypes (Tables 5 and 6, respectively). It is also noteworthy that the HDL-C level was decreased in the CHD patient group when the minor allele −1131C is present. Because the difference in HDL-C levels between −1131T/C and −1131C/C patients was not significant, these data suggest that the effect of −1131C allele is dominant.

3.5. −1131T>C variant has stronger effects on fasting TG levels compared with S19W variant in CHD patients

Although both −1131T>C and S19W variations significantly elevated the TG concentrations in CHD patients, −1131T>C variation seems to have stronger TG increasing effect as compared with S19W (T/T vs T/C, $P = .00019$, Table 6; S/S vs S/W +W/W, $P = .02$, Table 4).

Table 3
Genotype and allelic frequencies of APOA5 −1131T>C mutation in CHD patients and controls

Group	Number	Genotype (%)				Allele (%)	
		T/T	T/C	C/C	T/C + C/C	T	C
CHD	483	181 (37.5)	226 (46.8)	76 (15.7)	302 (62.5)	588 (60.9)	378 (39.1)
Control	502	246 (49.0)	212 (42.2)	44 (8.8)	256 (51.0)	704 (70.1)	300 (29.9)
χ^2		18.52			13.33[a]	18.66	
P		<.0001			<.001	<.0001	
OR (95% CI)		–			1.60 (1.24, 2.07)	1.51 (1.25, 1.82)	

OR indicates odds ratio.
[a] Comparison with genotype TT.

Table 5
Lipid and lipoprotein levels in the different −1131T/C genotypes in Chinese controls population

Lipids (mmol/L)	Genotype			P^a	P		
	T/T (n = 246)	T/C (n = 212)	C/C (n = 44)		T/T vs T/C	T/T vs C/C	T/C vs C/C
TG	1.39 ± 0.78	1.74 ± 0.86	1.76 ± 0.90	.0000	.000006	.0049	.8894
TChol	5.03 ± 0.78	5.22 ± 0.82	5.21 ± 0.83	.0321	.0115	.1638	.9415
HDL-C	1.69 ± 0.81	1.67 ± 0.85	1.56 ± 0.87	.6346	.7969	.3331	.4373
LDL-C	3.01 ± 0.89	3.03 ± 0.92	3.26 ± 1.12	.2507	.8135	.1009	.1480

[a] Differences among the 3 −1131T/C genotypes were tested by ANOVA.

Table 6
Lipid and lipoprotein levels in the −1131T/C genotypes among CHD patients

Lipids (mmol/L)	Genotype			P^a	P		
	T/T (n = 181)	T/C (n = 226)	C/C (n = 76)		T/T vs T/C	T/T vs C/C	T/C vs C/C
TG	1.73 ± 0.89	2.06 ± 0.87	2.35 ± 0.92	.0000	.00019	.000001	.0138
TChol	5.52 ± 0.76	5.49 ± 0.78	5.55 ± 0.84	.8288	.6967	.7798	.5699
HDL-C	1.28 ± 0.48	1.04 ± 0.45	1.02 ± 0.44	.0000	.000000	.000065	.7363
LDL-C	3.22 ± 0.83	3.20 ± 0.88	3.21 ± 0.86	.9730	.8154	.9306	.9314

The composite genotypes and their corresponding lipid levels (TG, HDL-C) are presented in Table 7, which also shows a tendency that the composite genotypes can influence on TG and HDL-C levels and a very significant difference of lipid levels between the CHD and control groups.

4. Discussion

In the present investigation, we found that the frequency of the −1131C allele in Chinese population was 0.299, similar to that in Singaporean Chinese (0.294) [13], slightly lower than that in Japanese (0.34) [8], but much greater than that of whites (0.08) [1] or Hispanic Americans (0.16) [3]. This suggests that an ethnic difference exists in the −1131C allelic frequency between white and Asian populations. Furthermore, that the frequency of the Trp-19 minor allele is extremely low in Chinese (0.000 for both Mainland and Singaporean Chinese) [13] compared with that in white, African American, and Hispanic populations (0.071, 0.150, and 0.060, respectively) also supports the suggestion of ethnic difference.

Table 7
Mean genotypic TG and HDL-C levels between CHD and controls

−1131T>C/SW	CHD		Controls		P^a
	n	$\bar{\chi} \pm s$	n	$\bar{\chi} \pm s$	
TG levels					
TT/SS	164	1.71 ± 0.88	246	1.39 ± 0.78	.00013
TC/SS	206	2.03 ± 0.86	212	1.74 ± 0.86	.00063
CC/SS	69	2.29 ± 0.89	44	1.76 ± 0.90	.00266
TT/SW + WW[b]	17	1.90 ± 0.91	–		–
TC/SW	20	2.37 ± 0.89	–		–
CC/SW	7	2.91 ± 1.10	–		–
HDL-C levels					
TT/SS	164	1.29 ± 0.46	246	1.69 ± 0.81	.00000
TC/SS	206	1.05 ± 0.45	212	1.67 ± 0.85	.00000
CC/SS	69	1.02 ± 0.41	44	1.56 ± 0.87	.00002
TT/SW + WW[b]	17	1.18 ± 0.58	–		–
TC/SW	20	1.02 ± 0.45	–		–
CC/SW	7	1.01 ± 0.62	–		–

[a] Analysis between the CHD and controls.
[b] Genotype TT/WW has only 1 subject.

Clinical studies in different populations have shown that some variations in the *APOA5* gene are strongly associated with plasma TG levels, and the −1131T>C and S19W mutations are among those having the most significant effect on TG levels [13,16-19]. It has been noted that hypertriglyceridemic individuals are more likely to carry the −1131C allele than controls (in whites, 0.187 vs 0.085; in Chinese, 0.402 vs 0.265) [9,10]. Recently, there is a report indicating that the Trp-19 minor allele has a significant association with high TG levels in myocardial infarction patients in the Czech Republic [20]. Present studies confirm that the −1131T>C in *APOA5* is associated with elevated TG levels not only in normal control subjects but also in patients with CHD. In the CHD patients, the minor allele of S19W variant is also associated with elevated TG levels.

The possible mechanism by which these 2 variants in the *APOA5* gene alter the lipid biochemistry has not yet been investigated in detail [21-23]. The −1131T>C polymorphism is in the promoter region and is in linkage disequilibrium with another −3A>G variant in the “Kozak” region. The latter could potentially result in a decreased rate of *APOA5* mRNA translation, thereby leading to lower APOA5 plasma levels [21]. The S19W polymorphism of *APOA5* represents a nonconservative change of serine to tryptophan at codon 19. This position is a putative export cleavage site of signal sequence within APOA5; therefore, the amino-acid change at the position could reduce APOA5 secretion across the endoplasmic reticulum, resulting in a decrease in the rate of APOA5 export from the liver. Because APOA5 may act as a brake on the transport of TG-rich

lipoproteins from the liver, the Trp-19 variant would produce lower levels of APOA5 and therefore would increase TG plasma concentrations [3,11].

Recently, Hubacek et al [20] and Szalai et al [24] reported that the frequencies of the −1131C rare allele in coronary artery disease and myocardial infarction are significantly higher than those in their control populations (10.9 vs 5.7%, 7.4 vs 2.0%, respectively). In our study, the frequency of the −1131T>C allele in CHD patient group was significantly higher than that of the controls (0.391 vs 0.299, $P < .0001$, in Table 3). So, it is reasonable to conclude that the −1131T>C variation may not only influence on the TG levels but also is associated with CHD in Chinese population. The Trp-19 allele frequency in our CHD patient group is 0.047 as compared with 0.000 of the control group ($P < .000001$), suggesting that there is also a significant association of the S19W mutation with CHD, and the rare Trp-19 allele which should be extremely scarce in the general Chinese population might be predictive for CHD risk in the Chinese.

In summary, our results indicate that both the −1131T>C and S19W variants in *APOA5* are significantly associated with CHD and contribute to the variation in human plasma TG levels. Whether they could serve as a useful genetic marker for CHD susceptibility in the Chinese population will require further study.

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