Research Paper

Scavenger Receptor Class B Type 1 Gene rs5888 Single Nucleotide Polymorphism and the Risk of Coronary Artery Disease and Ischemic Stroke: A Case-Control Study

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Abstract

Background: Our previous studies have showed that the rs5888 single nucleotide polymorphism (SNP) in Scavenger receptor class B type 1 (*SCARB1*) gene is associated with serum lipid levels in the general Chinese populations. The present study was undertaken to detect the associations between rs5888 SNP and the risk of coronary artery disease (CAD) and ischemic stroke (IS).

Methods: A total of 1,716 unrelated subjects (CAD, 601; IS, 533; and healthy controls, 582) were included in this study. Genotyping of the rs5888 SNP were determined by polymerase chain reaction and restriction fragment length polymorphism.

Results: The genotypic frequencies of *SCARB1* rs5888 SNP were different between CAD patients and controls, the subjects with TT genotype had high risk of CAD (OR = 1.76, *P* = 0.038 for TT *vs.* CC; and OR = 1.75, *P* = 0.036 for TT *vs.* CC/CT). There was no significant association between genotypes and the risk of IS. Further analysis showed that the subjects with TT genotype in the total population had lower levels of high-density lipoprotein cholesterol than the subjects with CC/CT genotypes (*P* < 0.05), the subjects with TT genotype in controls but not in CAD or IS patients had higher levels of serum LDL-C and ApoB than those with CC genotype (*P* < 0.05 for each).

Conclusions: The present study suggests that the *SCARB1* rs5888 SNP influences serum lipid levels, and is associated with the risk of CAD.

Key words: Scavenger receptor class B type 1 gene, Single nucleotide polymorphism, Coronary artery disease, Ischemic stroke, Lipid

Introduction

Among the non-communicable diseases, cardiovascular and circulatory diseases mainly comprising ischemic heart disease (5.2%), hemorrhagic stroke (2.5%), ischemic stroke (IS, 1.6%), and hypertensive heart disease (0.6%), accounted for 11.8% of global DALYs (disability-adjusted life years) [1]. Both coronary artery disease (CAD) and IS shared the common risk factors such as hypertension, diabetes,

dyslipidemia and metabolic syndrome [2], and the common pathophysiology mechanisms: atherosclerosis [3]. Dyslipidemia such as elevated serum levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein (Apo) B, or low levels of high-density lipoprotein cholesterol (HDL-C) and ApoAI is one of the most important modifiable risk factors for CAD [4,5] and IS [6,7]. It is well known that the disorder of lipid metabolism is a complex trait resulted from multiple environmental and genetic factors and their interactions [8,9].

The Scavenger receptor class B type 1 (*SCARB1*), also as known as *SR-BI*, is a HDL receptor which binds HDL-C with high affinity, mediates selective cholesterol uptake of HDL, and plays an important role in reverse cholesterol translation [10]. Previous studies have shown its importance in lipoprotein metabolism and atherosclerosis in mouse models. In targeted deletions of the murine *SR-BI* gene, TC levels were significantly increased in homozygous *SR-BI−/−* mice, and analysis of the lipoprotein profiles by fast protein liquid chromatography showed a significant increase in HDL-C levels and a shift of the HDL particles to a larger size [11,12]. Inversely, lower plasma levels and accelerated clearance of HDL and non-HDL-C were found in *SCARB1* transgenic mice [13]. In LDL receptor-deficient mice, attenuated expression of *SCARB1* was associated with increased LDL-C and accelerated atherosclerosis [14,15]. The association of several variants in the *SCARB1* gene and serum lipid profiles has been reported in diverse populations [16-28]. One of the single nucleotide polymorphisms (SNPs) in the *SCARB1* gene is rs5888 SNP, which was initially found by Acton [17], a "C" to "T" substitution at cDNA position 1050 base position on exon 8. The rs5888 SNP T allele has been associated with increased serum HDL-C levels and decreased risk of atherosclerosis related diseases [24-28]. In our previous studies, however, we found that the rs5888 SNP T allele was associated with decreased HDL-C levels and increased TC, LDL-C and ApoB levels in three Guangxi populations [29,30]. Therefore, the aim of the present study was to determine the associations between rs5888 SNP and the risk of CAD and IS in the Han Chinese.

Materials and methods

Patients and controls

A total of 601 patients with CAD were recruited from hospitalized patients in the First Affiliated Hospital, Guangxi Medical University. Coronary angiography was performed in all enrolled subjects. CAD was defined as significant coronary stenosis ($\geq 50\%$) in at least either one of the three main coronary arteries or their major branches (branch diameter ≥ 2 mm). Subjects with congenital heart disease, cardiomyopathy, valvular disease, autoimmune disease and type I diabetes mellitus were excluded.

A total of 533 patients with IS were also recruited from hospitalized patients in our affiliated hospital. All patients received strict neurological examination and brain magnetic resonance imaging (MRI) scan. IS was diagnosed according to the International Classification of Diseases (9th Revision). The patients with transient ischemic attack (TIA), embolic brain infarction, stroke caused by inflammatory diseases, cardioembolic stroke, autoimmune disease, serious chronic diseases, as well as a past history of CAD have been excluded from the study.

A total of 582 healthy subjects matched by age, gender, and ethnic group (Han Chinese) were also recruited as a control group. The controls were judged to be free of CAD, IS and other diseases by questionnaires, history taking and clinical examination.

All enrolled individuals were Han Chinese from Guangxi, People's Republic of China. A standard questionnaire was used to ascertain the general information and medical history for all participants. The study protocol 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.

Genotyping and biochemical analysis

Venous blood sample was obtained from all subjects after at least 12 hours of fasting. Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood leukocytes using the phenol-chloroform method. Genotyping of the *SCARB1* rs5888 SNP was performed by polymerase chain reaction and restriction fragment length polymorphism [29,30]. The levels of serum TC, TG, HDL-C, and LDL-C in samples were determined by enzymatic methods with commercially available kits. Serum ApoAI and ApoB levels were detected by the immunoturbidimetric immunoassay.

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 [29,30]. Hypertension was diagnosed according to the criteria of 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension [31]. Uncon-

trolled hypertension was defined as a systolic blood pressure of 140 mmHg or higher and a diastolic blood pressure of 90 mmHg or higher. The subjects with systolic blood pressure of only 140 mmHg or higher but a diastolic blood pressure of <90 mmHg were diagnosed as having isolated systolic hypertension. Normal weight, overweight and obesity were defined as a body mass index (BMI) < 24, 24–28, and > 28 kg/m^2; respectively [32].

Statistical analyses

The statistical analyses were carried out using the statistical software package SPSS 13.0 (SPSS Inc., Chicago, Illinois). The standard goodness-of-fit test was used to test the Hardy-Weinberg equilibrium. A chi-square analysis was used to evaluate the difference in genotype distribution and sex ratio between the groups. The general characteristics between patients and controls were 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. Odds ratio (OR) and 95% confidence interval (CI) were calculated using unconditional logistic regression. Meta-analyses were performed using STATA version 12.0 (Stata Corporation, College Station, Texas, USA). A two-tailed P value less than 0.05 was considered statistically significant.

Results

General characteristics and serum lipid levels

The baseline characteristics of the patients and controls are shown in Table 1. The mean age, ratio of males to females, serum LDL-C and ApoB levels, and the percentages of subjects who smoked cigarette were not different between controls and CAD or IS patients (P > 0.05 for all). Compared with the control group, the CAD patients had higher levels of average BMI, pulse pressure and serum TG, and lower levels of diastolic blood pressure, serum TC, HDL-C, ApoAI, ApoAI/ApoB, and the percentages of subjects who consumed alcohol (P < 0.05-0.001). The IS patients had higher levels of average BMI, systolic blood pressure, diastolic blood pressure, pulse pressure and serum TG, and lower levels of serum TC, HDL-C, ApoAI, ApoAI/ApoB, and the percentages of subjects who consumed alcohol (P < 0.05-0.001).

Genotypic and allelic frequencies

The genotypic and allelic frequencies of *SCARB1* rs5888 SNP are presented in Table 2. The genotype distribution was concordant with the Hardy-Weinberg proportions in both patients and controls (P = 0.114 for CAD, P = 0.339 for IS, and P = 0.210 for controls). There was significant difference in the genotypic frequencies between controls and CAD patients (P < 0.05), but not between controls and IS patients (P > 0.05).

SCARB1 rs5888 SNP and the risk of CAD and IS

The subjects with TT genotype were associated with increased risk of CAD (OR = 1.76, 95%CI = 1.03-3.01 for TT *vs.* CC; OR = 1.75, 95%CI = 1.04-2.95 for TT *vs.* CC/CT). There was no significant association between genotypes and the risk of IS (Table 2).

Table 1. General characteristics and serum lipid levels between the controls and patients

Parameter	Control	CAD	IS
Number	582	601	533
Male/female	425/157	444/157	383/150
Age, years	61.48 ± 10.85	62.27 ± 10.55	62.79 ± 12.27
Body mass index, kg/m^2	22.42 ± 2.88	24.00 ± 3.24**	23.34 ± 3.48**
Systolic blood pressure, mmHg	130.89 ± 19.91	133.22 ± 23.41	147.85 ± 22.07**
Diastolic blood pressure, mmHg	82.19 ± 12.57	79.27 ± 14.17**	84.01 ± 12.74*
Pulse pressure, mmHg	49.50 ± 14.67	53.50 ± 18.25**	63.67 ± 17.83**
Cigarette smoking, n (%)	259 (44.5)	282 (46.9)	214 (40.2)
Alcohol consumption, n (%)	263 (45.2)	166 (27.6)**	158 (29.6)**
Total cholesterol, mmol/L	4.93 ± 1.09	4.55 ± 1.22**	4.52 ± 1.15**
Triglyceride, mmol/L	1.40 ± 1.76	1.66 ± 1.12**	1.68 ± 1.40**
HDL-C, mmol/L	1.90 ± 0.50	1.15 ± 0.34**	1.23 ± 0.41**
LDL-C, mmol/L	2.75 ± 0.80	2.72 ± 1.03	2.67 ± 0.90
Apolipoprotein (Apo) AI, g/L	1.41 ± 0.26	1.04 ± 0.54**	1.03 ± 0.26
ApoB, g/L	0.90 ± 0.22	0.91 ± 0.27	0.89 ± 0.25
ApoAI/ApoB	1.66 ± 0.51	1.24 ± 0.0.81**	1.20 ± 0.61**

CAD, coronary artery disease; IS, ischemic stroke; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*P < 0.05 and **P < 0.01, compared with control

Table 2. Genotypic and allelic frequencies, and the risk for CAD and IS

Genotype/ allele	Control, *n* (%)	CAD, *n* (%)	IS , n (%)	CAD		IS	
				OR (95%CI)	*P*	OR (95%CI)	*P*
	n = 582	*n* = 601	*n* = 533				
CC	324 (55.7)	324 (53.9)	290 (54.4)	1		1	
CT	228 (39.2)	224 (37.3)	212 (39.8)	1.02 (0.77-1.34)	0.913	1.04 (0.79-1.38)	0.760
TT	30 (5.2)	53 (8.8)	31 (5.8)	1.76 (1.03-3.01)	0.038	1.25 (0.69-2.26)	0.465
χ^2		6.105	0.328				
P		0.047	0.849				
CC	324 (55.7)	324 (53.9)	290 (54.4)	1		1	
CT/TT	258 (44.3)	277 (46.1)	243 (45.6)	1.10 (0.85-1.43)	0.461	1.07 (0.82-1.40)	0.634
χ^2		0.370	0.179				
P		0.543	0.672				
CC/CT	552 (94.8)	548 (91.2)	502 (94.2)	1		1	
TT	30 (5.2)	53 (8.8)	31 (5.8)	1.75 (1.04-2.95)	0.036	1.23 (0.68-2.19)	0.495
χ^2		6.084	0.235				
P		0.014	0.628				
C	876 (75.3)	872 (72.5)	792 (74.3)	1			
T	288 (24.7)	330 (27.5)	274 (25.7)	1.15 (0.96-1.38)	0.133	1.05 (0.87-1.27)	0.601
χ^2		2.254	0.273				
P		0.133	0.601				

CAD, coronary artery disease; IS, ischemic stroke.

Genotypes and serum lipid levels

As shown in Table 3 and 4, the subjects with TT genotype in the total population had lower serum HDL-C levels than those with CT/CC genotypes (*P* = 0.049). The subjects with TT genotype in controls but not in CAD or IS patients had higher levels of serum LDL-C and ApoB than those with CC genotype (*P* < 0.05; Table 4).

Meta-analysis of the previous association studies

Previous association studies between the *SCARB1* rs5888 SNP and atherosclerosis related diseases are presented in Table 5. We performed a meta-analysis including three studies which had detailed the genotype frequencies. The pooled OR and 95%CI were 0.737 (0.591-0.918) for TT *vs.* CC+CT (*P* = 0.007), and 0.902 (0.764-1.064) for CT+TT *vs.* CC (*P* = 0.222), and 0.919 (0.828-1.019) for T allele *vs.* C allele (*P* = 0.108).

Discussion

The results of several previous association studies between the *SCARB1* rs5888 SNP and atherosclerosis related diseases are not entirely consistent in different ethnic groups (Table 5). Ritsch et al. [26] showed that the T allele of rs5888 SNP was associated with decreased risk of peripheral arterial disease in Austrians. The T allele carriers of the *SCARB1* rs5888 SNP in Tunisan reduced the risk of coronary stenosis and increased serum HDL-C levels [27]. Recently, the TT genotype of the *SCARB1* rs5888 SNP in male Lithuanian aged 65-75 was also shown to decrease the risk of CAD and increase serum HDL-C levels [28]. Two other studies in Korean and Spanish [24,25] did not report the genotype frequencies, but they also showed that the T allele or the T allele carrier was associated with decreased CAD risk. In the present study, however, we showed that the frequency of TT genotype was higher in CAD patients than in controls. The TT genotype was associated with increased risk of CAD than the CC or CC/CT genotype. The TT genotype was also associated with decreased serum HDL-C levels in the total population. Meta-analysis including three previous association studies showed that the TT genotype was associated with decreased risk of CAD. The reasons for the conflicting results between our and previous studies are not well known. One of the possible explanations was different genetic background. According to the data of the International HapMap project, the allelic frequencies of the *SCARB1* rs5888 SNP in diverse racial/ethnic groups are different. The frequencies of C and T alleles were 47.4% and 52.6% in CEU (Utah residents with ancestry from northern and western Europe), 88.1% and 11.9% in YRI (Yoruba in Ibadan, Nigeria), 80.7% and 19.3% in JPT (Japanese in Tokyo, Japan), 75.6% and 24.4% in CHB (Han Chinese in Beijing, China). In addition, the C-T change at exon 8 did not affect its amino acid sequence of the protein. Therefore, the rs5888 SNP might be in linkage disequilibrium (LD) with a functional mutation in the *SCARB1* gene, and the LD pattern at this region is different among populations. Accordingly, it is necessary to further study on the associations of the *SCARB1* rs5888 SNP and atherosclerosis related diseases in different ethnic populations.

Table 3. Effect of the genotypes on serum lipid levels in the combined population

Genotype	TC, mmol/L	TG, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L	ApoAI, g/L	ApoB, g/L	ApoAI/ ApoB
CC, *n* = 938	4.66 ± 1.13	1.59 ± 1.37	1.44 ± 0.57	2.71 ± 0.91	1.17 ± 0.45	0.89 ± 0.24	1.40 ± 0.78
CT, *n* = 664	4.67 ± 1.22	1.55 ± 1.62	1.44 ± 0.52	2.72 ± 0.93	1.16 ± 0.35	0.91 ± 0.25	1.35 ± 0.55
TT, *n* = 114	4.71 ± 1.20	1.58 ± 1.12	1.34 ± 0.47	2.69 ± 0.90	1.16 ± 0.45	0.90 ± 0.24	1.34 ± 0.63
P	0.909	0.856	0.143	0.931	0.969	0.498	0.304
CC/CT, *n* = 1602	4.67 ± 1.17	1.58 ± 1.48	1.44 ± 0.55	2.72 ± 0.92	1.16 ± 0.41	0.90 ± 0.25	1.37 ± 0.69
TT, *n* = 114	4.71 ± 1.20	1.58 ± 1.12	1.34 ± 0.47	2.69 ± 0.90	1.16 ± 0.45	0.90 ± 0.24	1.34 ± 0.63
P	0.680	0.950	0.049	0.794	0.928	0.942	0.563

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

Table 4. Effect of the genotypes on serum LDL-C and ApoB levels in the controls and patients

Genotype	Control		CAD		IS	
	LDL-C, mmol/L	ApoB, g/L	LDL-C, mmol/L	ApoB, g/L	LDL-C, mmol/L	ApoB, g/L
CC	2.70 ± 0.82	0.88 ± 0.22	2.69 ± 0.98	0.88 ± 0.26	2.73 ± 0.92	0.91 ± 0.25
CT	2.76 ± 0.77	0.92 ± 0.21	2.78 ± 1.11	0.94 ± 0.28	2.62 ± 0.86	0.87 ± 0.24
TT	3.11 ± 0.80	0.93 ± 0.21	2.49 ± 1.03	0.88 ± 0.28	2.69 ± 0.92	0.90 ± 0.21
P	0.023	0.040	0.165	0.074	0.457	0.159
CC/CT	2.73 ± 0.80	0.89 ± 0.22	2.73 ± 1.04	0.91 ± 0.27	2.68 ± 0.90	0.90 ± 0.25
TT	3.11 ± 0.80	0.93 ± 0.21	2.49 ± 0.90	0.88 ± 0.28	2.69 ± 0.92	0.90 ± 0.21
P	0.012	0.374	0.115	0.496	0.957	0.995

LDL-C, low-density lipoprotein cholesterol; ApoB, apolipoprotein B.

Table 5. Previous association studies between the *SCARB1* rs5888 SNP and atherosclerosis related diseases

Ethnic/ nation	Locus	Patient/ control	lipid	Disease	CC/CT/TT	Risk	Reference
Austrians	C1050T	354/354	TC, LDL (combined genotype exon1/intron5/exon 8)	Peripheral arterial disease	107/188/59 101/170/83	T ↓ (in females)	[26]
Spanish	C1050T	304/315	Scarb1 expression↑, Cholesteryl ester hydroperoxides ↑	Coronary heart disease	No description	T ↓	[25]
Korean	C1050T	137/124	HDL-C and ApoAI↑ in patients	Coronary artery disease	No description	T ↓	[24]
Tunisian	C1050T	212/104	HDL-C ↑, ApoAI↑	Coronary artery stenosis	105/96/11 34/58/11	T ↓	[27]
Lithuanian	C1050T	468/1976	TT genotype:TC, TG, LDL-C↑ in male, HDL-C↑ in male age 65-74 years	Myocardial infarction	163/233/67 696/944/336	TT↓ (male 65-74 years)	[28]

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoAI, apolipoprotein AI; ↑, increase; ↓, decrease

The association between *SCARB1* rs5888 SNP and serum lipid levels has been described in other several previous studies, which were recently summarized by Stanislovaitiene et al. [28], and also discussed in our recent reports [29,30]. Some studies showed that the *SCARB1* rs5888 SNP T allele was associated with increased serum HDL-C levels [16,18,20,24,27,28] and decreased serum non-HDL-C concentrations [17,20], and therefore has an atheroprotective effect. But other studies found that this SNP T allele has a pro-atherosclerosis serum lipid profile. Tai et al. [23] showed that the exon 8 (rs5888) SNP was associated with increased TC, very-low-density lipoprotein cholesterol (VLDL-C), LDL-C and TG levels in subjects with heterozygous familial hypercholesterolemia. Morabia et al. [18] reported that the subjects with TT genotype had higher levels of TC and LDL-C than the subjects with CC genotype in females. Stanislovaitiene et al. [28] also found that the TT genotype was associated with increased serum TC, TG and LDL-C levels in males. In our previous studies, we observed that the TT genotype was associated with low serum HDL-C and ApoAI levels in the Guangxi Bai Ku Yao, Mulao and Han populations [29,30], and the T allele was associated with increased serum TC, LDL-C, and ApoB levels in Bai Ku Yao females, and increased serum TG and ApoB levels in Han males. In the present study, we showed that the TT genotype was also associated with increased serum LDL-C and ApoB levels in con-

trols.

The relationship between the *SCARB1* gene and serum lipid levels and atherosclerosis is complex and inconsistent. Mice with attenuated expression of *SCARB1* displays elevated concentrations of HDL-C [11]. A study in women with hyperalphalipoproteinemia also showed that the *SCARB1* protein was inversely correlated with HDL-C levels and HDL size [12]. A 11-base pair deletion mutation in the promoter region of the *SCARB1* gene was associated with increased plasma HDL-C levels in Chinese Taiwanese [21], which was consistent with several previous studies [16,18,20,24,27,28]. However, the results of previous association studies between the *SCARB1* rs5888 SNP and atherosclerosis related diseases in human were opposite with those in animal models. *SR-BI* knockout mice in the background of either ApoE or LDL receptor deficiency have been shown to accelerate atherosclerosis and increase LDL-C without significant alterations in HDL-C levels, suggesting that impaired LDL-C clearance may account for the increased atherosclerosis relative to these mice [14,15]. In addition, the *SCARB1* rs5888 SNP was also associated with reduced *SCARB1* protein expression and function *in vitro* [33]. Therefore, the possible mechanism of association between TT genotype of *SCARB1* rs5888 SNP and increased risk of CAD may be related to the reduction in *SCARB1* protein expression resulting the increase in serum LDL-C and ApoB levels.

Study limitations

There are several potential limitations of the present study. Firstly, the drug information was missing in some participants, so interference by drug therapy could not be analyzed or excluded. Secondly, the sample size of our study, especially the number of the subjects with TT genotype was a bit small, which might not have sufficient power to interpret the associations of the rs5888 SNP and the risk of diseases. Therefore large study population with sufficient power required to duplicate these results.

Conclusion

The present study shows that the TT genotype of *SCARB1* rs5888 SNP was higher in CAD patients than in controls; the TT genotype was associated with increased risk of CAD. The levels of serum HDL-C in subjects with TT genotype was lower than those in subjects with CC/CT genotype in the total population, the subjects with TT genotype also associated with increased serum levels of LDL-C and ApoB than those with CC/CT genotype in controls. These suggest that the *SCARB1* rs5888 SNP influences serum lipid levels, and is associated with the risk of CAD.

Competing Interests

The authors have declared that no competing interest exists.

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