Original Article

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Association between the *MVK* rs2287218 SNP and the risk of coronary heart disease and ischemic stroke: A case-control study

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Summary **The association between the mevalonate kinase gene (*MVK*) single nucleotide polymorphism (SNP) and serum lipid levels has been detected in several previous genome-wide association studies, but the results are inconsistent. In addition, it is still unclear whether the loci indentified exert the similar effect on the susceptibility of coronary heart disease (CHD) or ischemic stroke (IS). Therefore, the present study was undertaken to detect the association between the *MVK* rs2287218 SNP and serum lipid levels, the susceptibility of CHD and IS in a Southern Chinese Han population. The genotypes of the SNP in 1764 unrelated subjects (CHD, 583; IS, 555; and healthy controls, 626) were determined by the Snapshot technology. The genotypic and allelic frequencies were different between CHD and control subjects ($P \leq 0.013$ for each), or between IS and control groups ($P < 0.01$ for each). The T allele carriers had an increased risk of CHD and IS (CHD: OR = 1.674, 95% CI = 1.25-2.25, $P = 0.001$ for CT/TT *vs.* CC genotypes; OR = 1.595, 95% CI = 1.23-2.07, $P < 0.001$ for T *vs.* C alleles; IS: OR = 1.890, 95% CI = 1.36-2.47, $P = 0.001$ for CT/TT *vs.* CC genotypes; OR = 1.829, 95% CI = 1.38-2.42, $P < 0.001$ for T *vs.* C alleles). The T allele carriers in healthy controls had lower serum high-density lipoprotein cholesterol (HDL-C) levels than the T allele non-carriers ($P = 0.013$). These findings suggest that the *MVK* rs2287218 SNP is likely to increase the risk of CHD and IS by decreasing serum HDL-C levels in our study populations.**

Keywords: Coronary heart disease, ischemic stroke, mevalonate kinase gene, rs2287218, single nucleotide polymorphism, serum lipid levels

1. Introduction

Among the non-communicable disease, cardiovascular and circulatory disease primarily made up by ischemic heart disease (5.2%), hemorrhagic stroke (2.5%), ischemic stroke (IS, 1.6%), and hypertensive heart (0.6%), accounted of 11.8% of global disability-adjusted life years (DALYS) (*1*). More than 2.5 and 1 million persons suffered from the stroke and heart attack, resulting in more than 2 million deaths each year in China (*2*). The location of coronary heart disease (CHD) and IS was different, but they may share the common risk factors such as hypertension, dyslipidemia and metabolic syndrome (*3*), and the same pathophysiological basis: atherosclerosis (*4*). Dyslipidemia such as low concentration of high-density lipoprotein cholesterol (HDL-C), high levels of low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and triglyceride (TG) was one of the most important risk factors for CHD (*5,6*) and IS (*7,8*). It is well-known that the disorder of lipid metabolism is a complex characteristic, resulted from multiple environmental and genetic factors and their interactions (*9,10*). Twins and family studies indicated that disorder of lipid metabolism was influenced by genetic and environmental factors, which might contribute to the individual discrepancy in the serum lipid profiles (*11*).

Previous genome-wide association studies (GWASes) have found the association of several novel loci in the mevalonate kinase gene (*MVK*, also as: *MK*; *LRBP*; *MVLK*; *POROK3*) and serum lipid levels

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(*12,13*). The *MVK* was located at chromosome 12q24 (*12,13*) and encoded the mevalonate kinase (MVK) (*14*). MVK was a key early enzyme in isoprenoid and sterol synthesis metabolism, which implicated to affect HDL-C levels (*12,15*). Mutations in the *MVK* gave rise to hyperimmunoglobulinemia D syndrome (HIDS), in which low HDL-C levels could be found (*16*), in accordance with the latest GWAS findings (*12,13*). Several novel loci in *MVK* were confirmed to be associated with serum HDL-C levels (*17-19*) and an increased risk of CHD and IS (*19*). But no significant association between the *MVK* rs2287218 SNP and serum lipid levels was conducted by Sun *et al*. in a Northern Chinese Han population (*20*). To our knowledge, the genetic evidence on the associations between the *MVK* rs2287218 SNP and serum lipid levels, and the susceptibility of CHD or IS in a Southern Chinese Han population has not been reported previously. Therefore, the present study was undertaken to detect the association between the *MVK* rs2287218 SNP and serum lipid levels, and the susceptibility of CHD and IS in a Southern Chinese Han population.

2. Materials and Methods

2.1. *Study patients*

A total of 1138 patients with CHD (n = 583) and IS (n = 555) were recruited from the First Affiliated Hospital, Guangxi Medical University. The age of these patients ranged from 23 to 87 years with a mean age of 62.26 ± 10.51 years in CHD and 62.85 ± 12.32 years in IS. All of enrolled CHD patients were evaluated by coronary angiography. The coronary angiograms were analyzed by two experienced interventional cardiologist. CHD was defined as severe coronary stenosis (≥ 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 and type 1 diabetes mellitus (T1DM) were excluded in the study. All of enrolled IS patients received a strict neurological examination and brain magnetic resonance imaging. The diagnosis of IS was according to the International Classification of Diseases (9th Revision). Patients with a transient ischemic attack, embolic brain infarction, stroke caused by inflammatory disease, or serious chronic diseases were excluded from the study. The CHD patients who had a past history of IS, or the IS cases who had a past history of CHD were also excluded from the study (*21*).

2.2. *Controls*

A control group of 626 subjects matched by age, gender, and nationality was also included in the study. They were randomly selected from the healthy adults who underwent periodical check-up at our hospital during the same period when CHD and IS patients recruited. The average age of the participants was 61.95 ± 10.01 years. They were free from CHD and IS at time of history taking, clinical, biochemical, and image examinations such as 64-slice computed tomographic coronary angiography. Information on demography, medical history and lifestyle was collected with standardized questionnaires. This study design was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University (No. Lunshen 2009-Guike-018). Informed consent was obtained from all participants before the study.

2.3. *Biochemical measurements*

A fasting venous blood sample of 5 ml was obtained from the participants. A part of the sample (2 mL) was collected into glass tubes and used to determine serum lipid levels. Another part of the sample (3 mL) was transferred to tubes with anticoagulants (4.80 g/L citric acid, 14.70 g/L glucose and 13.20 g/L tri-sodium citrate) and used to extract deoxyribonucleic acid (DNA). Measurements of serum TC, TG, HDL-C, and LDL-C levels in the samples were performed by enzymatic methods with commercially available kits (RANDOX Laboratories Ltd., Ardmore, Diamond Road, and Crumlin Co. Antrim, United Kingdom, BT29 4QY; Daiichi Pure Chemicals Co, Ltd., Tokyo, Japan). Serum apolipoprotein (Apo) A1 and ApoB levels were detected by the immunoturbidimetric immunoassay using a commercial kit (RANDOX Laboratories Ltd.). All determinations were performed with an auto-analyzer (Type 7170A; Hitachi Ltd., Tokyo, Japan) in the Clinical Science Experiment Center of the First Affiliated Hospital, Guangxi Medical University (*22*).

2.4. *Genotyping*

Genomic DNA was extracted from peripheral blood leukocytes using the phenol-chloroform method. Genotyping of the *MVK* rs2287218 SNP was performed by the Snapshot technology platform in the Center for Human Genetics Research, Shanghai Genesky Bio-Tech Co. Ltd., China (*23*). The restriction enzyme for the *MVK* rs2287218 SNP was SAP (Promega) and Exonucleasel (Epicentre). The sense and antisense primers were 5'-CTGCGGGAGAGTCACGTTTCAC-3' and 5'-GAGGGACACTGGCCAGGTAAGG-3', respectively.

2.5. *Diagnostic criteria*

The normal values of serum TC, TG, HDL-C, LDL-C, ApoA1, ApoB levels and the ApoA1/ApoB ratio 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 (*24*). The individuals with TC > 5.17 mmol/L and/or TG

> 1.70 mmol/L were defined as hyperlipidemic (*25*). LDL-C ≥ 3.20 mmol/L was defined as high low-density lipoproteinemia (*26*). Hypertension was diagnosed according to the 1999 and 2003 criteria of the World Health Organization-International Society of Hypertension Guidelines for the management of hypertension (*27*). 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 body mass index (BMI) < 24, 24-28 and > 28 kg/m^2, respectively (*28*).

2.6. *Statistical analyses*

The statistical analyses were performed with the statistical software package SPSS 21.0 (SPSS Inc., Chicago, Illinois). The quantitative variables were presented as mean ± standard deviation (serum TG levels were presented as medians and interquartile ranges). Allelic frequency was determined via direct counting, and the Hardy-Weinberg equilibrium was verified with the standard goodness-of-fit test. The sex ratio and genotypic distribution between the two groups were analyzed by the chi-square test. General characteristics between patients and controls were compared by the Student's unpaired *t*-test. The association between genotypes and serum lipid parameters was tested by covariance analysis (ANCOVA). Unconditional logistic regression was used to assess the correlation between the risk of CHD or IS and genotypes. Gender, age, BMI, blood pressure, alcohol consumption and cigarette smoking were adjusted for the statistical analysis. Odds ratio (OR) and 95% confidence interval (CI) were calculated by using unconditional logistic regression. Results were considered to be statistically significant if two-sided *P* value was less than 0.05.

3. Results

3.1. *Clinical characteristics of the subjects*

The clinical characteristics of the subjects are described in Table 1. The male to female ratio, mean age, serum LDL-C and ApoB levels were not different between the control and experimental groups ($P > 0.05$ for all). As compared with the CHD and IS patients, the control subjects had higher serum TC, HDL-C, ApoA1 levels and the ApoA1/ApoB ratio ($P < 0.05$). The body height, weight, average BMI, systolic blood pressure, pulse pressure, the prevalence of hypertension, TG levels and the percentages of subjects who smoked cigarettes and did not drink alcohol were lower in the control than in CHD and IS groups ($P < 0.05$). In addition, the control subjects had lower diastolic blood pressure levels than the IS patients ($P < 0.01$).

Table 1. Comparison of the clinical characteristics and serum lipid levels between the controls and patients

Parameter	Control	CHD	IS	P_{CHD}	P_{IS}
Number	626	583	555	-	-
Male/female	457/169	431/152	401/154	0.716	0.773
Age (years)	61.95 ± 10.01	62.26 ± 10.51	62.85 ± 12.32	0.599	0.175
Height (cm)	155.04 ± 7.87	164.15 ± 6.83	163.74 ± 7.14	0.000	0.000
Weight (kg)	54.51 ± 9.04	64.57 ± 10.60	62.96 ± 11.11	0.000	0.000
Body mass index (kg/m^2)	22.60 ± 2.81	23.89 ± 3.21	23.42 ± 3.49	0.000	0.000
Cigarette smoking [*n* (%)]					
Non-smoking	382 (61.0)	328 (56.2)	324 (58.4)		
≤ 20 cigarettes per day	189 (30.2)	99 (17.0)	162 (29.1)		
> 20 cigarettes per day	55 (8.8)	156 (26.8)	69 (12.4)	0.000	0.124
Alcohol consumption [*n* (%)]					
Non-drinker	354 (56.6)	449 (77.0)	400 (72.1)		
≤ 25 g per day	200 (31.9)	81 (13.9)	122 (22.0)		
> 25 g per day	72 (11.5)	53 (9.1)	33 (5.9)	0.000	0.000
SBP (mmHg)	128.00 ± 19.60	133.03 ± 23.21	147.72 ± 22.03	0.000	0.000
DBP (mmHg)	80.49 ± 11.35	79.17 ± 14.17	83.78 ± 12.90	0.077	0.000
Pulse pressure (mmHg)	47.52 ± 14.73	53.85 ±17.50	63.94 ± 17.80	0.000	0.000
Total cholesterol (mmol/L)	4.90 ± 1.02	4.53 ± 1.18	4.52 ± 1.13	0.000	0.000
Triglycerid (mmol/L)	1.01 (0.66)	1.36 (0.94)	1.37 (0.91)	0.000	0.000
HDL-C (mmol/L)	1.92 ± 0.50	1.14 ± 0.34	1.23 ± 0.40	0.000	0.000
LDL-C (mmol/L)	2.73 ± 0.78	2.71 ± 0.99	2.68 ± 0.89	0.701	0.349
ApoA1 (g/L)	1.41 ± 0.27	1.04 ± 0.52	1.02 ± 0.22	0.000	0.000
ApoB (g/L)	0.90 ± 0.21	0.91 ± 0.27	0.89 ± 0.24	0.779	0.450
ApoA1/ApoB	1.65 ± 0.52	1.38 ± 2.45	1.25 ± 0.58	0.011	0.000
Hypertension [*n* (%)]	210 (33.5)	419 (71.9)	379 (68.3)	0.000	0.000

CHD, coronary heart disease; IS, ischemic stroke; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoA1/ApoB, the ratio of apolipoprotein A1 to apolipoprotein B; SBP, systolic blood pressure; DBP, diastolic blood pressure. P_{CHD}: CHD *vs*. control; P_{IS}: IS *vs*. control. The value of triglyceride was presented as median (interquartile range); the difference among the genotypes was determined by the Wilcoxon-Mann-Whitney test. The remaining characteristics between patients and controls were tested by the Student's unpaired-test.

3.2. *Genotypic and allelic frequencies*

The genotypic and allelic frequencies of the rs2287218 SNP are presented in Figure 1. The genotypic and allelic frequencies were different between the CHD/IS and control groups ($P < 0.05$). The C and T allele frequencies were 88.7% and 11.3% in controls, 84.8% and 15.2% in CHD, and 84.1% and 15.9% in IS patients; respectively. The CC, CT and TT genotype frequencies were 78.4%, 20.6% and 1.0% in controls; 72.0%, 25.6% and 2.4% in CHD; and 71.0%, 26.1% and 2.9% in IS patients; respectively. The genotypic distribution was in accordance with the Hardy-Weinberg equilibrium in the three groups ($P > 0.05$).

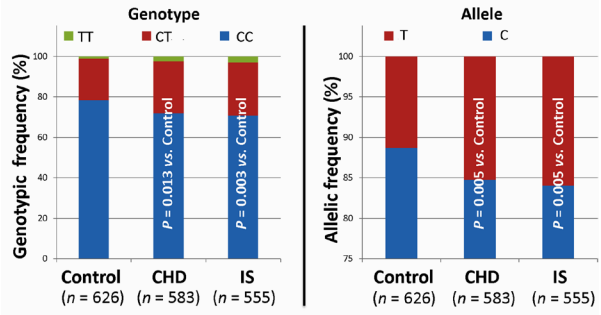

Figure 1. Genotypic and allelic frequencies of the *MVK* rs2287218 SNP in controls, coronary heart disease (CHD) and ischemic stroke (IS) patients. The genotypic and allelic distribution in the three groups was analyzed by the chi-square test.

3.3. *The rs2287218 SNP and the risk of CHD or IS*

The T allele carriers had an increased risk of CHD and IS (CHD: OR = 1.674, 95% CI = 1.25-2.25, $P = 0.001$ for CT/TT *vs*. CC genotypes; OR = 1.595, 95% CI = 1.23-2.07, $P < 0.001$ for T *vs*. C alleles; IS: OR = 1.890, 95% CI = 1.36-2.47, $P = 0.001$ for CT/TT *vs*. CC genotypes; OR = 1.829, 95% CI = 1.38-2.42, $P < 0.001$ for T *vs*. C alleles) after adjusting for age, gender, BMI, smoking status, alcohol consumption and hypertension.

3.4. *Gene-environment interactions on the risk of CHD or IS*

Stratified analysis showed that an increased risk of CHD and IS was found in subjects with CT/TT genotypes, especially in those who belonged to one of the following categories: females, elder (> 60 years), low BMI (< 24 kg/m^2), nonsmokers and nondrinkers (Table 2).

3.5. *Related risk factors for CHD and IS*

As shown in Table 3, multivariate logistic analysis showed that the incidence of CHD and IS was positively correlated with smoking, high BMI (≥ 24 kg/m^2), hypertension and CT/TT genotypes, whereas it was negatively associated with alcohol consumption. There was also a positive association between the incidence of CHD and hyperlipidemia, but not between the incidence of IS and hyperlipidemia.

Table 2. The *MVK* rs2287218 SNP and the risk of CHD and IS according to gender, age, body mass index, smoking status and alcohol consumption

Factor	Genotype	OR (95%CI)$_{CHD}$	P_{CHD}	P_I	OR (95%CI)$_{IS}$	P_{IS}	P_I
Gender	CC	1			1		
Male	CT + TT	1.332 (0.943-1.880)	0.104		1.324 (0.927-1.890)	0.123	
	CC	1		0.000	1		0.000
Female	CT + TT	8.002 (3.397-18.852)	0.000		6.366 (2.691-15.060)	0.000	
Age	CC	1			1		
≤ 60 years	CT + TT	1.505 (0.928-2.442)	0.097		1.643 (0.991-2.725)	0.054	
	CC	1		0.161	1		0.121
> 60 years	CT + TT	1.917 (1.304-2.818)	0.001		1.848 (1.221-2.797)	0.004	
BMI	CC	1			1		
< 24 kg/m^2	CT + TT	1.656 (1.130-2.426)	0.010		2.048 (1.387-3.025)	0.000	
	CC	1		0.584	1		0.678
≥ 24 kg/m^2	CT + TT	1.006 (0.97-1.10)	0.028		1.469 (0.857-2.518)	0.162	
Smoking	CC	1			1		
Nonsmoking	CT + TT	2.844 (1.869-4.327)	0.000		3.092 (1.969-4.854)	0.000	
	CC	1		0.000	1		0.000
Smoking	CT + TT	1.235 (0.704-2.165)	0.462		0.916 (0.581-1.446)	0.708	
Drinking	CC	1			1		
Nondrinking	CT + TT	2.578 (1.753-3.791)	0.000		3.068 (1.995-4.719)	0.000	
	CC	1		0.000	1		0.000
Drinking	CT + TT	0.945 (0.473-1.889)	0.873		0.759 (0.457-1.262)	0.288	

OR and 95% CI were obtained from unconditional logistic regression model after adjusting for age, gender, body mass index, smoking status, alcohol consumption, hypertension. P_I, the value of interaction between the SNP and factors

Table 3. Related risk factors for CHD and IS

Factor	OR (95%CI)$_{CHD}$	P_{CHD}	OR (95%CI)$_{IS}$	P_{IS}
Nonsmoking	1		1	
Smoking	1.586 (1.186-2.121)	0.003	1.468 (1.075-2.004)	0.016
Nondrinking	1		1	
Drinking	0.214 (0.156-0.295)	0.000	0.388 (0.281-0.535)	0.000
BMI < 24 kg/m^2	1		1	
BMI ≥ 24 kg/m^2	2.260 (1.739-2.937)	0.000	1.622 (1.213-2.167)	0.001
rs2287218CC	1		1	
rs2287218CT/TT	1.658 (1.232-2.231)	0.001	1.890 (1.378-2.592)	0.000
Normotensive	1		1	
Hypertension	4.298 (3.046-6.066)	0.000	1.709 (1.239-2.358)	0.001
Normal blood lipids	1		1	
Hyperlipidemia	1.833 (1.411-2.383)	0.000	0.804 (0.575-1.123)	0.201

OR and 95% CI were obtained from unconditional logistic regression model after adjusting for age, gender, body mass index (BMI), smoking status, alcohol consumption, hypertension.

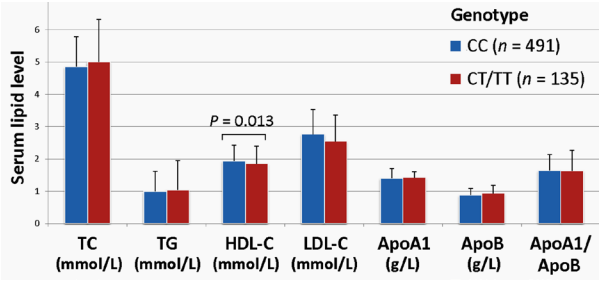

Figure 2. Association between the *MVK* rs2287218 SNP and serum lipid levels in the controls. TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoA1/ApoB, the ratio of apolipoprotein A1 to apolipoprotein B. The value of TG was presented as median (interquartile range), and the difference between the genotypes was determined by the Wilcoxon-Mann-Whitney test. The association between genotypes and the remaining serum lipid parameters was tested by analysis of covariance (ANCOVA).

3.6. *Genotypes and serum lipid levels*

As shown in Figure 2, the subjects with CT/TT genotypes in control group had lower serum HDL-C levels than those with CC genotype ($P = 0.013$). There was no difference in the remaining lipid parameters between the CT/TT and CC genotypes ($P > 0.05$ for all).

4. Discussion

A considerable amount of literatures showed that blood lipid metabolism was closely related to the occurrence and development of atherosclerosis and cardiovascular disease (CVD) (*29,30*). As a significant monitoring indicator of CVD, dyslipidemia is a complex and multifactorial disease, resulting from multiple environmental factors, including age, sex, obesity, abnormal glucose, hypertension, lifestyle and daily exercise (*31,32*), genetic factors, and their interactions (*33,34*). The SNP was the most abundant genetic variation in the human genome, which was manifested in the substitution mutation of a single base. SNP could be used to explain the individual phenotypic discrepancy and the susceptibility of different groups and individuals to some diseases. So, to identify the gene mutations regulating the serum lipid profiles and increasing the risk of CHD or IS has received considerable critical attentions, especially in the development of new markers for risk stratification assessment, diagnosis, treatment and prognosis of CVD.

The principal finding of the present study was a significant association between the *MVK* rs2287218 SNP and serum HDL-C levels in a Southern Chinese Han population. The subjects with CT/TT genotypes in healthy controls had lower serum HDL-C levels than the subjects with CC genotype ($P = 0.013$). Recent GWASes have found that several novel loci in *MVK* could influence HDL-C concentrations (*12,13*). The subjects with GG genotype (the major homozygote) of the *MVK* S52N had lower HDL-C levels than the subjects with AA genotype (*17*). The associations between the *MVK* rs2338104 SNP and HDL-C levels were definitive ($P < 0.001$) and consistent (*18,35*). In addition, the *MVK* rs3759387AA genotype had lower HDL-C levels than the rs3759387AC/CC genotypes (*19*). Furthermore, *MVK* (i85G→T and S52NG→A) had low HDL-C levels linked to dietary habit, especially in carbohydrates intakes (*17*). These studies suggested that the *MVK* rs2287218 SNP, as a member of *MVK*, may be linked to HDL-C levels. In the present study, our results in accordance with the latest GWAS findings (*12,13*) may be reasonable. But Sun *et al*. showed that there was no significant association between the *MVK* rs2287218 SNP and serum lipid levels in a Northern Chinese Han population (*20*). The precise reason for these conflicting results was unknown. Because blood lipid metabolism genes were multilocus and multivariate, the locations and properties of different populations may be diverse. The relationships between the same genetic frequency and serum lipid levels may not be the same in different ethnic groups or geographic

areas (*36*). On one hand, in addition to sample size and different statistical methods, they were different in exposed environments. It was reported that serum lipid levels and the prevalence of dyslipidemia were influenced by multiple environmental factors, such as dietary habit (*37*), lifestyle (*38*), daily exercise (*39*). Junyent *et al*. found that *MVK* (i85G→T and S52NG→A) had low HDL-C levels linked to dietary habit, especially in carbohydrates intakes (*17*). On the other hand, their genetic background was not similar, which may contribute to the discrepancies between our and the other studies in different populations. In the present study, we showed that the *MVK* rs2287218T allele frequency was 14.0% in the Guangxi Han population. According to the International 1000 Genomes data-base (*https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/*), the *MVK* rs2287218T allele frequency was 10.7% in Han Chinese in Beijing, China (CHB); 13.9% in Japanese in Tokyo, Japan (JPT); 21.9% in African Carribbeans in Barbados (ACB); 17.2% in Americans of African ancestry in SW USA (ASW); and 17.2% in Mexican ancestry from Los Angeies USA (MXL). These results showed that the prevalence of the *MVK* rs2287218T allele was higher in North American or in European than in Asian. The minor allele frequency of the *MVK* rs2287218 SNP was also different between Southern and Northern Chinese populations. These findings revealed that the *MVK* rs2287218 SNP has a racial/ethnic and geographic specificity.

The MVK exists in a wide range of organisms from bacteria to human and is a key early enzyme in isoprenoid and sterol synthesis metabolism (*12,15*). The *MVK* was modified by sterol-responsive element-blinding protein 2 (SREBP2) by sharing a promoter, which was a transcription factor that played a vital role in controlling cholesterol homeostasis (*40*). Moreover, it was also reported that *MVK* took part in metabolic pathways and had an effect on HDL-C metabolism in the previous study. *MVK* mutations, especially in homozygosity, or the *MVK* deficiency caused hyperimmunoglobu-linemia D syndrome (HIDS), in which the basic symptoms were recurrent episodes of fever and high concentrations of immunoglobulin (Ig) D and A in blood (*16*). When the patients suffered from HIDS, low HDL-C levels could be found, in accordance with the latest GWAS findings (*12,13*). In some previous studies, the increased immunoglobulin containing IgD and IgA contributed to the low levels of HDL-C (*41,42*). It was likely that the immunoglobulin synthesis took a lot of nutrients, such as albumin and cholesterol, resulting in decreased HDL-C levels. It was worth mentioning that the statins were reported to be applied in the treatment of HIDS by inhibiting the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and the pro-inflammatory cytokines (*43*). These results indicated that the *MVK* rs2287218 SNP could influence serum HDL-C levels. However, the precise mechanism of *MVK* on serum lipid metabolism remains to be explored.

Another important finding in the current study was that the *MVK* rs2287218 SNP was strongly associated with the risk of CHD and IS in the Guangxi Han population. The frequencies of the TT/CT genotypes and T allele were associated with an increased risk of CHD and IS after adjusting for potential confounding factors. Multivariate analysis showed that the known factors, such as cigarette smoking, high BMI (≥ 24 kg/m^2), hypertension, hyperlipidemia and the TT/CT genotypes were dependently associated with CHD. Meanwhile, the occurrence of IS was positively correlated with cigarette, high BMI, hypertension and the TT/CT genotypes. Both CHD and IS were negatively correlated with the *MVK* rs2287218 CC genotype and alcohol consumption. We also found that the drinkers, especially moderate alcohol, had a lower risk of CVD than non-drinkers (*44*). The effects of alcohol on lipid metabolism, especially the HDL-C-elevating effects (*45*), were considered to greatly promote the cardio-protective action of alcohol (*46*). In the stratified analysis, the increased risk of CHD and IS in subjects with the CT and TT genotypes was mainly observed in females, age > 60 years, BMI < 24 kg/m^2, nonsmokers and nondrinkers. Significant interactions between the *MVK* rs2287218 SNP and environmental factors on the risk of CHD or IS were observed in those of females, nonsmokers and nondrinkers. The subjects with CT/TT genotypes of the *MVK* rs2287218 SNP contributed to the increased risk of CHD and IS. A previous study confirmed that the *MVK* rs3759387 AC/CC genotypes interacted with some environmental exposures (such as males, elder), resulting in increasing the risk of CHD and IS (*19*), which suggested gene-environment interactions contributed to higher risk of CHD and IS. It was reported that the *MVK* variants displayed low HDL-C levels and an activity decline of the MVK. The high levels of HDL-C could regulate moncytes proliferation and activation, changing the composition of the myeloid cell lineage, which was thought to generate beneficial anti-inflammatory and athero-protective effects to prevent CVD (*47,48*). In addition, the activity of the MVK played a key role in controlling cholesterol homeostasis (*13*) and HDL-C metabolism. Elimination of the MVK activity caused low HDL-C levels in HIDS and increased atherosclerosis. It has been demonstrated that the abnormal blood lipid metabolism is closely related to the occurrence and development of atherosclerosis and CVD (*29,30*). Therefore, the *MVK* rs2287218 SNP was likely to increase the risk of CHD and IS by reducing serum HDL-C levels without anti-inflammatory and athero-protective effects. Besides, the frequencies of genotype

and allele were statistically significant between the CHD or IS and control groups. The frequency of the *MVK* rs2287218T allele was higher in the CHD (15.2%) and IS (15.9%) patients than in the controls (11.3%, $P = 0.005$). According to the International 1000 Genomes data-base, the frequency of the *MVK* rs2287218T allele was diverse in different racial groups and geographic areas. We also showed that the frequencies of TT/CT genotypes were higher in the CHD (28.0%) and IS (29.0%) patients than in the controls (21.6%, $P \leq 0.01$ for each). In addition, a previous study indicated that the *MVK* expression levels were different in some tissues (*49*). These findings suggested that the *MVK* rs2287218 SNP may be a susceptibility to CHD and IS. It was likely to increase the risk of CHD and IS by decreasing the serum HDL-C levels. However, large genetic association studies or meta-analyses are necessary to further explore these associations between them.

The present study had several potential limitations. Firstly, the number of involved patients was relatively small compared to many previous GWASs and replication studies. Therefore, further studies with larger sample sizes are needed to confirm our findings. Secondly, a number of patients with CHD or IS took anti-atherosclerotic drugs, such as statins, angiotensin-converting enzyme inhibitors, beta blockers, and aspirin when they were enrolled in the study, whereas the controls did not take any medicine. The levels of TC and LDL-C were lower in the patients with CHD or IS than in the healthy controls. However, the drug information was missing for some IS and CHD patients. Finally, only one *MVK* SNP was studied in this study. The interaction of the *MVK* SNP-SNP on serum lipid profiles and the susceptibility of CHD and IS was not observed. Therefore, the observed associations need further replications to avoid spurious associations.

5. Conclusion

The *MVK* rs2287218 SNP was associated with serum HDL-C levels and the susceptibility of CHD and IS in a Southern Chinese Han population. The T allele carriers had an increased risk of CHD and IS. The T allele carriers in healthy controls had lower serum HDL-C levels than the T allele non-carriers. These findings suggest that the *MVK* rs2287218 SNP is likely to increase the risk of CHD and IS by decreasing serum HDL-C levels.

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