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Original Article

Influence of rs1746048 SNPs on clinical manifestations and incidence of acute myocardial infarction in Guangxi Han population

Fan Wang[1*], Wei Wang[2#], Shouming Qin[3#], Quanfang Chen[3*], Zhou Huang[2], Dongling Huang[2], Tian Li[2], Jun Li[1], Zhongyi Sun[1], Xuefeng Liu[1], Xiangtao Zeng[1], Zong Ning[2], Yuanli Liao[2]

[1]Graduate School, Guangxi Medical University, Nanning, Guangxi, People's Republic of China; [2]Department of Emergency, [3]Institute of Respiratory Disease, The First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, People's Republic of China. [*]Equal contributors and co-first authors. [#]Equal contributors.

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Abstract: A relationship of the *CXCL12* gene rs1746048 SNPs with AMI has been reported in American, European, Caucasian, and Pakistani populations. However, little is known about this association in the Guangxi Han population. In this study, we detect associations between rs1746048 SNPs and susceptibility, risk factors, clinical characteristics, and gene-environment interactions for AMI. 300 AMI patients and 300 healthy controls of Chinese Han were enrolled. Genotyping of rs1746048 SNPs was performed using polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) and then confirmed by direct sequencing. Significant differences in both genotypic and allelic frequencies of rs1746048 SNPs between AMI and the control group were not detected ($P > 0.05$ for each). The frequency of CC genotypes of rs1746048 SNPs was the highest in the 2 h < DT ≤ 6 h subgroup ($P < 0.05$). The frequencies of the CT genotype and the T allele were significantly higher in the severe complications subgroup of AMI ($P < 0.05$). There were interactions between the subjects with rs1746048 SNPs and smoking or alcohol consumption ($P < 0.017$ for each). Rs1746048 SNPs were not correlated with the risk of AMI in present study. For the first time, we discovered that the CC genotype of the rs1746048 SNPs was significantly correlated with DT of AMI; the frequencies of the CT genotype and the minor T allele were positively correlated with the severe complications of AMI. Also, the interaction between the rs1746048 SNPs and smoking or alcohol appears to increase the risk of AMI exposure.

Keywords: Acute myocardial infarction (AMI), single nucleotide polymorphism (SNPs), risk factor, clinical feature, gene-environment interaction

Introduction

Coronary heart disease (CHD) is one of the leading causes of death and loss of disability-adjusted life years in both developed and developing countries [1]. In China, the World Health Organization estimated that more than 700,000 people die from CHD each year [2]. Acute myocardial infarction (AMI), characterized by dangerous pathogenic conditions and high fatality, is the most serious clinical manifestation and a major cause of death [3]. With the development and adaptation of genetic sequencing technology, single nucleotide polymorphisms (SNPs) have been to a new generation of molecular genetic markers and have identified many genetic lociassociated with disease susceptibility. In addition, genome-wide association studies (GWAS) have focused on genomic factors contributing to the development of CHD and AMI recently [4-7]. For example, the upregulation of chemokine (C-X-C motif) ligand 12 (*CXCL12*) genes can promote *CXCL12* migration and improve the ischemia of anoxic myocardial cells subsequently [8]. The association of *CXCL12* rs1746048 SNPs with AMI have been reported in American [9], European [10], Caucasian [11], and Pakistani [12] populations. However, little was known about this association in Chinese Han population, especially in population from Guangxi province. Therefore, the present study was undertaken to evaluate

whether the rs1746048 SNPs and its interaction with environmental factors was related to the susceptibility to, risk factors for, and clinical characteristics of AMI in this population.

Materials and methods

Study population

A total of 300 AMI patients and 300 healthy subjects who were matched for age, lifestyle, and socioeconomic status, all in Guangxi province, People's Republic of China, were enrolled in the study from January 1, 2012 to December 31, 2016. The AMI patients were comprised of 228 (76.0%) males and 72 (24.0%) females, ranging in age from 33 to 84 years, with a mean age of 61.67 ± 10.43 years. The healthy control subjects consisted of 210 (70.0%) males and 90 (30.0%) females, ranging in age from 34 to 83 years, with a mean age of 58.49 ± 10.54 years. The present study was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University, Guangxi province, People's Republic of China. Informed consent was obtained from all participants after they received a full explanation of the study.

Subgroups

To evaluate the relationship between rs1746048 SNPs and clinical characteristics, the 300 cases comprising the AMI group were subdivided as follows. (1) They were subdivided into two subgroups: those with typical symptoms (n = 78) and those with atypical symptoms (n = 222). (2) They were subdivided into four subgroups according to diagnosis time (DT): DT ≤ 2 h (n = 40), 2 h < DT ≤ 6 h (n = 119), 6 h < DT ≤ 12 h (n = 116), and DT > 12 h (n = 25). (3) They were subdivided into six subgroups according to infarction location: extensive anterior wall (n = 141), inferior wall (n = 97), anteroseptal wall (n = 18), lateral wall (n = 7), right ventricle (n = 13), and multivessel lesion (n = 24). (4) They were divided into two subgroups according to whether or not serious complications developed: no serious complications (n = 275) and serious complications (n = 25).

Epidemiological survey

Information on demographics, socioeconomic status, and lifestyle factors was collected using standardized questionnaires. Information on alcohol consumption included questions about the number of Liangs (about 50 g) of rice wine, corn wine, rum, beer, or liquor consumed during the preceding 12 months. Alcohol consumption was categorized into groups according to grams of alcohol consumed per day: ≤ 250 g and > 250 g. Smoking status was categorized into groups according to cigarettes smoked per day: ≤ 20 and > 20. Height, weight, and waist circumference were manually measured under the supervision of two people. Sitting blood pressure was measured using a mercury sphygmomanometer on three separated intervals after the subjects had a 15-minute rest, and the average of the three measurements was used for the level of blood pressure. Body mass index (BMI) was calculated as weight in kg divided by the square of height in meters (kg/m^2).

Biochemical analysis

The survey was carried out using internationally standardized methods [13]. Serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatine kinase-MB (CK-MB), and cardiac troponin I (cTnI) levels were obtained from samples analyzed by the biochemical laboratory of the First Affiliated Hospital, Guangxi Medical University, Guangxi province, China.

DNA amplification and genotyping

Genomic DNA was extracted from peripheral blood leukocytes using the phenol-chloroform method [14]. The extracted DNA was stored at 4°C for future analysis. Genotyping of the rs1746048 SNPs was performed using the pair of primers: sense primer 5'-CAGTTTATAGCCCCACTCACA-3', anti-sense primer 5'-AGTCAAACACCTCTTTAGCGT-3' (Sangon, Shanghai, People's Republic of China). Each 20.0 μL PCR reaction mixture consisted of 1.0 μL of genomic DNA, 1.0 μL of each primer (10 pmol/L), 10.0 μL of 2 × *Taq* PCR Mastermix (20 mM Tris-HCl, pH 8.3, 100 mM KCl, 3 mM $MgCl_2$, 0.1 U *Taq* polymerase/μL, 500 μM dNTP each), and 7.0 μL of ddH_2O (DNase/RNase-free). The reaction mixture was subjected to denaturation at 95°C for 5 min, followed by 35 cycles at 95°C for 30 s, 63°C for 30 s, 72°C for 30 s, then a final extension at 72°C for 7 min. Then the amplification products, in 5 mL, were digested

Table 1. General characteristics and serum lipid levels between AMI and control group

Parameter	AMI group	Control group	t (X^2)	P
Number	300	300	-	-
Male/female	228/72	210/90	2.740	0.098
Age (years)	61.67 ± 10.43	58.49 ± 10.54	3.712	< 0.001
Body mass index (kg/m^2)	23.76 ± 3.11	22.66 ± 3.15	4.296	< 0.001
Cigarette smoking (n %)	-	-	69.924	< 0.001
Nonsmoker	156 (52.00)	225 (75.00)	-	-
≤ 20 cigarettes/day	61 (20.33)	65 (21.67)	-	-
> 20 cigarettes/day	83 (27.67)	10 (3.33)	-	-
Alcohol consumption [n (%)]	-	-	42.887	< 0.001
Nondrinker	226 (75.33)	240 (80.00)	-	-
≤ 25 g/day	26 (8.67)	54 (18.00)	-	-
> 25 g/day	48 (16.00)	6 (2.00)	-	-
Total cholesterol (mmol/L)	5.20 ± 0.95	4.97 ± 1.05	2.775	0.006
Triglycerides (mmol/L)	1.66 ± 1.13	1.45 ± 1.11	2.217	0.027
LDL-C (mmol/L)	3.71 ± 0.92	2.89 ± 0.87	11.241	< 0.001
HDL-C (mmol/L)	1.08 ± 0.26	1.36 ± 0.25	-13.176	< 0.001

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

using 5 U of *BsrI* restriction enzyme (New England Biolabs, Inc, Beverly, MA, USA) at 37°C overnight. After restriction enzyme digestion of the amplified DNA, genotypes were identified by electrophoresis on 2% agarose gels and visualized with ethidium-bromide staining ultraviolet illumination. Genotypes were scored by an experienced reader blinded to epidemiological data and serum lipid levels. Six samples (genotypes: 2 CC, 2 CT, and 2 TT) that were positive by PCR-RFLP were also confirmed by direct sequencing. The PCR products were purified by low melting point gel electrophoresis and phenol extraction, and then the DNA sequences were analyzed in Shanghai Sangon Biological Engineering Technology & Services Co., Ltd., People's Republic of China.

Diagnostic criteria

The diagnostic criteria and study protocol followed the guidelines of the European Resuscitation Council [15-17]. Inclusion in the study required a diagnosis of ST-segment elevation myocardial infarction (STEMI), defined as follows: a 12-lead electrocardiogram showing ST-segment elevation of 1 mm or greater in at least two contiguous leads; prolonged chest discomfort typical of myocardial ischemia; cardiac biomarkers, and creatine kinase-MB (CK-MB) or troponin (or both) elevated to more than twice the upper limit of normal laboratory reference values; coronary artery radiography confirmation. Ventricular fibrillation (VF) was defined on the basis of the following atypical electrocardiogram patterns: chaotic irregular deflections of varying amplitude; no identifiable P waves, QRS complexes, or T waves; and heart rate between 150 and 500 beats/min. Shock is described as systolic blood pressure < 90 mm Hg; high heart rate (> 120 beats/min); skin pale and clammy; and confusion. Heart failure (HF) diagnosis was determined on the basis of brain natriuretic peptide (BNP) and heart ultrasound. The normal values of serum TC, TG, HDL-C, LDL-C, CK-MB, and cTnI in our Clinical Science Experiment Center were 3.10-5.17 mmol/L, 0.56-1.70 mmol/L, 0.91-1.81 mmol/L, 2.70-3.20 mmol/L, 0-25 μ/L, and 0-0.014 ng/mL, respectively. Hypertension was diagnosed according to the criteria of the 2003 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension [18]. Normal weight, overweight, and obesity were defined as BMI 19-24, BMI 25-28 or > 28 kg/m^2 respectively [19].

Statistical analyses

The Hardy-Weinberg equilibrium (HWE) test was applied to confirm the independent segregation of the alleles. Qualitative variables were expressed as raw count and percentage. Mean ± SD was used for the presentation of quantitative variables. Genotypic and allelic frequencies were calculated by direct counting. Pearson's χ^2 test was used to evaluate the difference in genotype distribution and sex ratio between the groups. The difference in general characteristics between the AMI group and the control group was evaluated by the Student's unpaired *t*-test. Unconditional binary logistic regression

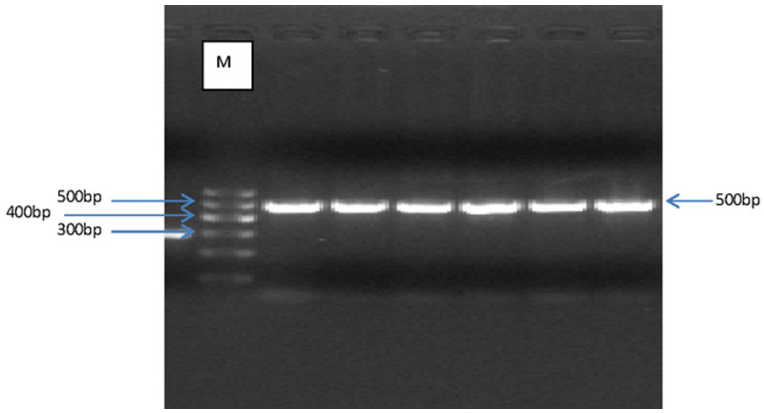

Figure 1. Electrophoresis of rs1746048 SNPs PCR products in the CXCL12 gene. Lane M is the 100 bp marker ladder; Lanes 1-6 are samples, the 500 bp bands are the target genes.

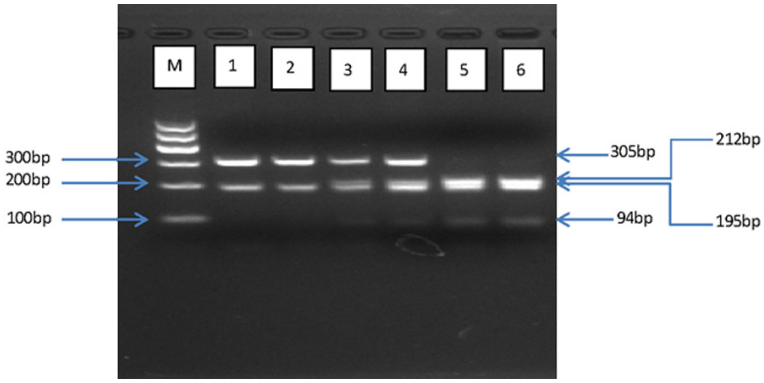

Figure 2. Genotyping of rs1746048 SNPs polymorphism in the *CXCL12* gene. Lane M is the 100 bp marker ladder; lanes 1 and 2, CC genotype (195 and 305 bp); lanes 3 and 4, CT genotype (195, 305, 212, and 94 bp); and lanes 5 and 6, TT genotype (195, 212 and 94 bp).

was used to assess the risk factors and gene-environment interaction in AMI. Sex, age, BMI, alcohol consumption, and cigarette smoking were adjusted for the statistical analysis. Two-sided $P < 0.05$ was considered significant. When we estimated the interactions between rs1746048 SNPs and BMI, cigarette smoking and alcohol consumption, a value of $P < 0.017$ (corresponding to $P < 0.05$ after adjusting for 3 independent tests by the Bonferroni correction) were considered significant. Odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) were also calculated. All statistical analyses were carried out using the statistical software package SPSS 22.0 (SPSS Inc., Chicago, Illinois, USA).

Results

General characteristics and serum lipid levels

Comparison of generalized features can be found in **Table 1**. The values of mean age (61.67 ± 10.43 *vs.* 58.49 ± 10.54) and BMI (23.76 ± 3.11 *vs.* 22.66 ± 3.15) were higher in the AMI group than in the control group. The numbers (percentages) of subjects who smoked and consumed alcohol were 144 (48.00%) and 74 (24.67%) in the AMI group, respectively, and 75 (25.00%) and 60 (20.00%) in the control group, respectively. Significantly more subjects in the AMI group smoked and consumed alcohol than in the control group ($P < 0.001$ for each). There was no significant difference in sex ratio between the two groups ($P > 0.05$).

Comparisons of lipid levels are also shown in **Table 1**. The levels of TC, TG and LDL-C were 5.20 ± 0.95 mmol/L, 1.66 ± 1.13 mmol/L and 3.71 ± 0.92 mmol/L in the AMI group, respectively, and 4.97 ± 1.05 mmol/L, 1.45 ± 1.11 mmol/L and 2.89 ± 0.87 mmol/L in the control group, respectively. The levels of serum TC, TG and LDL-C in the AMI group were higher than those in the control group ($P < 0.05$ for each). The serum HDL-C level in the AMI group was lower than in the normal group (1.08 ± 0.26 mmol/L vs. 1.36 ± 0.25 mmol/L, $P < 0.001$).

Electrophoresis, genotyping, and sequencing

Amplification of genomic DNA yielded PCR products of 500 bp (**Figure 1**). The genotypes identified were named according to the presence (C allele) or absence (T allele) of the enzyme restriction sites. Thus, the CC genotype is a homozygote for the absence of the site (bands at 195 and 305 bp, lanes 1 and 2;

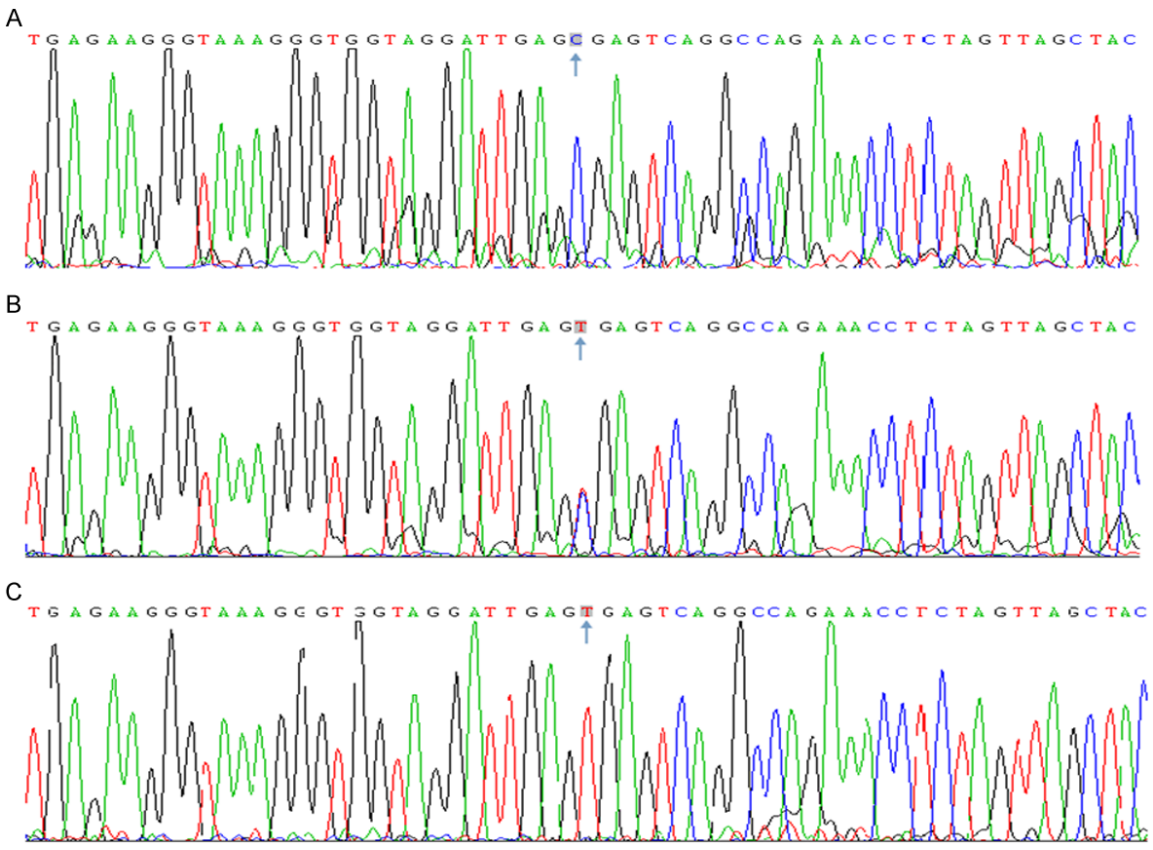

Figure 3. A part of rs1746048 SNPs nucleotide sequence in the *CXCL12* gene. A: CC genotype; B: CT genotype; C: TT genotype.

Figure 2). The CT genotype is a heterozygote for the absence and presence of the site (bands at 195, 305, 212, and 94 bp, lanes 3 and 4; **Figure 2**). The TT genotype is a homozygote for the presence of the site (bands at 195, 212 and 94 bp; lanes 5 and 6, **Figure 2**). The genotypes of CC, CT, and TT detected by the PCR-RFLP were also confirmed by sequencing (**Figure 3**).

Genotypic and allelic frequencies

The genotypic and allelic frequencies of rs1746048 SNPs are shown in **Table 2**. The CC genotype and C allele frequency, respectively, were 55.67% and 77.33% in the AMI group, which were higher than those in the control group, 50.00% and 75.00%. The frequencies of the CT and TT genotypes and the T allele were 44.33%, and 22.67%, respectively, in the AMI group, which were lower than the 50.00%, and 25.00% seen in the control group. There were no statistically significant differences in both genotypic and allelic frequencies between the AMI and control groups ($P > 0.05$ for each).

Risk factors for AMI

As shown in **Table 3**, non-conditional binary logistic regression analysis showed that diabetes, high blood pressure, age, smoking and sex were strongly associated with AMI risk, with OR values of 69.214, 9.080, 4.775, 4.674, and 2.235 respectively. In contrast, HDL-C was negatively correlated with the risk of AMI, with an OR value of 0.052 ($P < 0.05$ for each). However, no significant differences were seen between AMI and control groups in terms of correlation of BMI, TC, TG, rs1746048 SNPs, alcohol consumption, and LDL-C with the risk of AMI ($P > 0.05$ for each).

Frequencies of rs1746048 and clinical characteristics

The genotypic frequency of rs1746048 SNPs in the CC genotype was the highest in the 2 h < DT

Table 2. The distribution difference of rs1746048 genotype and allele frequency between AMI and control group

Parameter	AMI group [n (%)]	Control group [n (%)]	X^2	P
Number (n = 600)	300 (50.00)	300 (50.00)	-	-
Genotypes	-	-	5.340	0.069
CC	167 (55.67)	150 (50.00)	-	-
CT+TT	133 (44.33)	150 (50.00)	-	-
Allele	-	-	0.900	0.343
C	464 (77.33)	450 (75.00)	-	-
T	136 (22.67)	150 (25.00)	-	-

Table 3. The risk factor analysis of AMI

Parameter	B	SE	Wald	Sig	Exp (B)/OR
Diabetes	4.237	1.155	13.461	< 0.001	69.214
High blood pressure	2.206	0.362	37.086	< 0.001	9.080
Age	1.563	0.327	22.828	< 0.001	4.775
Smoking	1.542	0.250	38.038	< 0.001	4.674
Sex	0.854	0.357	5.085	0.024	2.235
HDL-C	-2.953	0.724	16.639	< 0.001	0.052
BMI	0.662	0.330	4.029	0.180	1.938
TC	0.989	0.530	3.488	0.248	2.689
TG	0.380	0.345	1.216	0.270	1.462
Rs1746048	0.269	0.283	0.902	0.342	1.309
Alcohol consumption	0.192	0.258	0.554	0.457	1.313
LDL-C	0.184	0.553	0.110	0.740	1.202

TC, total cholesterol; HDL-C; high-density lipoprotein cholesterol; BMI, body mass index; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol.

≤ 6 h subgroup (61.34%), significantly higher than those of the other subgroups ($P < 0.05$). In addition, the frequencies of the CT genotype and the T allele were 68.00%, and 38.00%, respectively, in the severe complications subgroup, which were significantly higher than the 41.09%, and 21.27% seen in non-severe complications subgroup ($P < 0.05$). There were no significant differences in the genotypic and allelic frequencies of rs1746048 SNPs between the controls and the AMI subgroups, including subgroups divided according to typical symptoms and infarction location ($P > 0.05$ for each) (**Table 4A-D**).

Interaction between rs1746048 SNPs and BMI, smoking, or alcohol consumption

In **Table 5**, there were significant interactions between rs1746048 SNPs and smoking or alcohol consumption ($P < 0.017$ for each). The subjects who smoked < 20 cigarettes/day or who smoked ≥ 20 cigarettes/day carrying the CC genotype subgroup had an increased risk for AMI of 1076.2% and 840.0%. The subjects who consumed < 250 g/day or ≥ 250 g/day of alcohol and who also had the CC genotype subgroup were at a 1421.1% or 2400.0% increased risk for AMI. The subjects who smoked < 20 cigarettes/day or who smoked ≥ 20 cigarettes/day carrying the T allele had an increased risk for AMI of 1375.7% and 958.9%. The subjects who consumed < 250 g/day or ≥ 250 g/day of alcohol and who also had the T allele were at a 750.0% or 1800.0% increased risk for AMI. No interaction was seen between rs1746048 SNPs and BMI that affected AMI risk ($P > 0.017$ for each).

Discussion

Throughout the world, CHD and AMI are the leading causes of mortality [20]. AMI is caused when plaque that has built up in the walls of coronary arteries erodes or ruptures, leading to transient, partial, or complete arterial occlusion. AMI is a complicated condition brought about by multiple genetic and environmental factors as well as their interactions [21, 22]. Rs1746048 SNPs has been identified as a risk variant for CHD and AMI by genome-wide association studies (GWAS) [11, 23]. In this study, we have replicated the association between rs1746048 SNPs and susceptibility, risk factors, clinical characteristics of AMI in Guangxi Han people.

In the current study, rs1746048 SNPs were not correlated with the risk of AMI, which is the same with the result of Shahid et al. [12] research but different from the result of a MOOSE-compliant meta-analysis by Chen et al. [24]. This might be a power issue as the GWAS SNPs have been studied with thousands of samples. The ethnicity may also be another factor as the linkage disequilibrium (LD) differ in different ethnicities and genetic factors also

Table 4A. Comparison of genotype and allele of rs1746048 among different diagnosis time

Parameter	Groups [n (%)]				X^2	*P*
	DT ≤ 2 h	2 h < DT ≤ 6 h	6 h < DT ≤ 12 h	DT > 12 h		
Number (n = 300)	40 (13.33)	119 (39.67)	116 (38.67)	25 (8.33)	-	-
Genotype	-	-	-	-	16.638	0.034
CC	21 (52.50)	73 (61.34)	60 (51.72)	13 (52.0)	-	-
CT	18 (45.00)	45 (37.82)	56 (48.28)	11 (44.00)	-	-
TT	1 (2.50)	1 (0.84)	0 (0.00)	1 (4.00)	-	-
Allele	-	-	-	-	2.009	0.571
C	60 (75.00)	191 (80.2)	176 (75.87)	37 (74.00)	-	-
T	20 (25.00)	47 (19.75)	56 (24.13)	13 (26.00)	-	-

DT, diagnosis time (time until diagnosis).

Table 4B. Comparison of genotype and allele between severe complications group and non-severe complications group

Parameter	Groups [n (%)]		X^2	*P*
	Non-complications	Complications		
Number (n = 300)	275 (91.67)	25 (8.3)	-	-
Genotype	-	-	10.370	0.006
CC	160 (58.18)	7 (28.00)	-	-
CT	113 (41.09)	17 (68.00)	-	-
TT	2 (0.73)	1 (4.00)	-	-
Allele	-	-	7.316	0.007
C	433 (78.73)	31 (62.00)	-	-
T	117 (21.27)	19 (38.00)	-	-

Table 4C. Comparison of genotype and allele between typical symptom group and non-typical symptom group

Parameter	Groups [n (%)]		X^2	*P*
	Typical symptom	Non-typical symptom		
Number (n = 300)	78 (26.00)	222 (74.00)	-	-
Genotype	-	-	0.460	0.795
CC	41 (52.56)	126 (56.76)	-	-
CT	36 (46.15)	94 (42.34)	-	-
TT	1 (1.28)	2 (0.90)	-	-
Allele	-	-	0.344	0.557
C	118 (75.64)	346 (77.93)	-	-
T	38 (24.36)	98 (22.07)	-	-

interact with that of the environmental factors. Another reason may be that our study population was more homogenous than the CHD population. All cases in our study had a validated history of AMI. At present, it is unknown whether rs1746048 SNPs will be helpful in the early diagnosis of AMI. However, our study presents the first discovery that the CC genotype of the rs1746048 SNPs was significantly correlated with 2 h < DT ≤ 6 h of AMI and the frequencies of the CT genotype and the T allele were positively correlated with the severe complications subgroup of AMI. The relevant mechanism underlying this phenomenon is not known, but it is possible that related gene regulation affects the stability of atherosclerotic plaques. Rs1746048 SNPs [odds ratio (OR) for MI 1.17, *P*-value 38.1 × 1029], a highly replicated SNPs, map to a region on chr10q11 at 44.2 Mb, which is 80 kb downstream proximal to the *CXCL12* gene [25-27]. There are two isoforms of CXCL12, a (also called isoform-1) and b (also called isoform-2), which predominate in the adult human, with the majority in most adult tissues being isoform a [28]. CXCL12 is an inflammatory chemokine which extensively participates in cellular processes about angiogenesis, cell signaling, hematopoiesis [29], and a plausible biological candidate for the GWAS signal as it plays a role in recruiting leucocytes in response to vascular injuries, which has been implicated in atherosclerosis in rodent models [30, 31]. CXCL12 holds a direct contribution to the process of atherosclerosis, and is highly expressed in human atherosclerotic plaque [25] within

Table 4D. Comparison of genotype and allele between among different infarct sites

Parameter	Groups [n (%)]						X^2	P
	Extensive anterior	Inferior	Anteroseptal	Lateral	Right ventricular	Multivessel lesion		
Number (n = 300)	141 (47.00)	97 (32.33)	18 (6.00)	7 (2.33)	13 (4.33)	24 (8.00)	-	-
Genotype	-	-	-	-	-	-	4.245	0.936
CC	74 (52.48)	55 (56.70)	11 (61.11)	4 (57.14)	6 (46.15)	17 (70.83)	-	-
CT	65 (46.10)	41 (42.27)	7 (3.89)	3 (42.86)	7 (53.85)	7 (29.17)	-	-
TT	2 (1.42)	1 (1.03)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	-	-
Allele	-	-	-	-	-	-	2.833	0.726
C	213 (75.53)	151 (77.84)	29 (80.56)	11 (78.57)	19 (73.08)	41 (85.42)	-	-
T	69 (24.47)	43 (22.16)	7 (19.44)	3 (21.43)	7 (26.92)	7 (14.58)	-	-

Table 5. Interaction between genotypes of Rs1746048 and environment factors on the impact of AMI

Genotypes	Environment factor	B	SE	Wald	Sig	Exp (B)/OR	95.0% CI for OR	
							Lower	Upper
-	BMI (Kg/m^2)	-	-	-	-	-	-	-
CC	19-24	-	-	3.012	0.083	-	-	-
CC	≥ 24	0.598	0.267	5.011	0.175	1.818	1.077	3.068
CT+TT	19-24	-	-	0.520	0.471	-	-	-
CT+TT	≥ 24	0.621	0.260	5.683	0.119	1.861	1.117	3.100
-	Smoking (n/d)	-	-	-	-	-	-	-
CC	0	-	-	26.746	< 0.001	-	-	-
CC	0-20	2.376	0.459	26.743	< 0.001	10.762	4.373	26.486
CC	≥ 20	2.128	0.502	18.003	< 0.001	8.400	3.143	22.451
CT+TT	0	-	-	23.398	< 0.001	-	-	-
CT+TT	0-20	2.622	0.545	23.112	< 0.001	13.757	4.724	40.056
CT+TT	≥ 20	2.261	0.584	14.980	< 0.001	9.589	3.052	30.124
-	Alcohol (g/d)	-	-	-	-	-	-	-
CC	0	-	-	15.567	< 0.001	-	-	-
CC	0-250	2.654	0.747	12.626	< 0.001	14.211	3.287	61.428
CC	≥ 250	3.178	0.805	15.567	< 0.001	24.000	4.950	116.371
CT+TT	0	-	-	17.138	< 0.001	-	-	-
CT+TT	0-250	2.015	0.627	10.318	0.007	7.500	2.194	25.644
CT+TT	≥ 250	2.890	0.704	16.865	< 0.001	18.000	4.531	71.511

BMI, body mass index; n/d, number of cigarettes smoked per day; g/d, grams of alcohol consumed per day.

endothelial cells and smooth muscle cells [32]. Recent study showed that CXCL12 have enhanced expression on platelets, and platelet-bound CXCL12 correlated with the degree of systemic platelet activation [33]. The CXCL12 protein has been associated with activated platelets and plaque stabilization [34, 35]. Its protein product is directly involved in trafficking of leucocytes that are involved in the development and complications of atherosclerosis. It is also expressed in cells directly relevant to atherogenesis [36], such as leucocytes, platelets [25], endothelial cells, and smooth muscle cells [26]. Platelet-mediated inflammation may make contribution to the process of atherosclerosis [37]. Continuous cytokines and matrix proteases secreted by cells within the plaque may also play a role in the thinning of the stability-providing fibrous cap after the formation of plaque [38]. A recent report showed plasma CXCL12 levels to be modulated in human CHD [39], and the other study reported that there was an association of rs1746048 SNPs with increased carotid intimal-medial thickness [10]. Moreover, CXCL12 also participates in the cell trafficking of monocytes, macrophages, and endothelial

progenitor cells [40], which are the key components in the pathogenesis of atherosclerosis. These data suggest a relationship between CXCL12 and human CHD; however, whether CXCL12 actions are atheroprotective or atherogenic in humans remain uncertain.

In the present study, we also assessed the association between rs1746048 SNPs and several environmental factors. The data indicate that the interaction between rs1746048 SNPs and smoking or alcohol may result in an increased risk of AMI. Diabetes, high blood pressure, age, smoking and sex were all risk factors for AMI, while HDL-C was negatively correlated with AMI risk. AMI is a multifactorial disease with a complex pathogenesis, in which lifestyle, individual genetic background and environmental risk factors are involved [1]. Well-known risk factors for AMI include obesity, smoking, excessive alcohol intake, lack of exercise, high blood pressure, poor diet, diabetes, and high blood cholesterol [41-44]. However, little is known about the combined genetic influence of rs1746048 SNPs together with environmental factors. At the same time, telomere shortening may be a risk factor for AMI. Some studies have found telomere shortening to be related to the pathogenesis of atherosclerosis and acute vascular syndromes [45, 46] and the other studies have suggested that short telomere length is associated with an increased risk of myocardial infarction [47, 48]. Telomeres are specialized DNA-protein structures at the ends of all chromosomes, which preserve chromosome stability and integrity. In normal cells, the DNA replication machinery is unable to completely duplicate the telomeric DNA, and thus telomeres are shortened after each cell division [49]. Telomere length is highly variable at birth and decreases with age [50]. Previous studies have demonstrated an association between telomere length, health, and longevity [51]. Shorter leukocyte telomeres have been measured in AMI cases and offspring of AMI cases [52, 53]. Apart from this, it has been confirmed that lifestyle is one of the strongest predictors of CHD risk, and that this increase in risk may stem from effects on telomere length [54]. For example, a sedentary lifestyle may accelerate the aging process [55]. Various cardiovascular risk factors, such as smoking, sex, and obesity, can be related to regulation of telomere length [56, 57]. Smoking has been associated with shorter telomeres in normal-weight as well as in lean and obese women [58], while greater physical activity in leisure time has been associated with longer telomeres in healthy twins [55]. In addition, telomere shortening has been demonstrated in patients with hypertension and diabetes [59, 60]. Some previous studies have shown that subjects with impaired glucose tolerance and type II diabetes have shorter telomeres than controls [61]. Another study demonstrated that men with lower vitamin C intake are more likely to suffer from AMI [62]. Several environmental factors have been documented to influence biological mechanisms, but relatively little is known about gene-environmental effects. Further studies are essential.

Conclusions

In conclusion, the studied samples were within Hardy Weinberg equilibrium, but rs1746048 SNPs were not correlated with the risk of AMI in present study. However, for the first time, the data in the our study demonstrated that the CC genotype of the rs1746048 SNPs was significantly correlated with early diagnosis (2 h < DT ≤ 6 h) of AMI. The frequencies of the CT genotype and the T allele were positively correlated with the severe complications subgroup of AMI. Also, the interaction between rs1746048 SNPs and smoking or alcohol appears to increase the risk of AMI. Finally, it was verified again that diabetes, high blood pressure, age, smoking and sex were risk factors for AMI, while HDL-C was negatively correlated with AMI risk.

Limitations

In our study, there were several potential limitations. First, the total number of patients in the study was small, which restricted the statistical power of our findings. Second, the early diagnosis time of AMI lacked objectivity and supporting materials. In addition, SNP-SNP interactions associated with AMI were not examined in our study. Finally, the study did not include any data regarding the mechanism of association between the gene and AMI.

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Disclosure of conflict of interest

None.

Address correspondence to: Wei Wang, Department of Emergency, The First Affiliated Hospital, Guangxi Medical University, 6 Shuangyong Road, Nanning 530021, Guangxi, People's Republic of China. E-mail: weiwanggx@163.com; Shouming Qin, Institute of Respiratory Disease, The First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, People's Republic of China. E-mail: qinshouming2008@126.com

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