Association of SNP Rs6903956 on Chromosome 6p24.1 with Angiographical Characteristics of Coronary Atherosclerosis in a Chinese Population

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Abstract

Objective: To explore the association between rs6903956 and severity of coronary artery disease (CAD) in a Chinese population.

Methods: A cohort of 1075 consecutive patients who underwent coronary arteriography for suspected or known coronary atherosclerosis was enrolled in our study. Coronary atherosclerosis severity was defined by Gensini’s Score System and counts of diseased vessels.

Results: Gensini score frequencies and counts of diseased vessels differed among GG, AG, AA genotype groups at the rs6903956 locus (p = 0.025 for Gensini score frequencies vs. p = 0.024 for counts of diseased vessels, respectively). A univariate logistic regression analysis revealed that the genotype distribution of this SNP was associated significantly with angiographical characteristics of coronary atherosclerosis risk (p = 0.030, odds ratio (OR) = 1.444, 95% confidence interval (CI) = 1.036–2.013 for AG vs. GG; p = 0.021, OR = 5.896, 95% CI = 1.299–26.750 for AA vs. GG and p = 0.007, OR = 1.564, 95% CI = 1.132–2.162 for combined (AG+AA) vs. GG). A multivariate logistic regression analysis indicated that the genotype distribution of the rs6903956 polymorphism be associated significantly with the angiographical characteristics of coronary atherosclerosis risk (p = 0.004, OR = 1.578, 95% CI = 1.155–2.154 for GG vs. AG vs. AA; p = 0.013, OR = 1.541, 95% CI = 1.097–2.163 for GG vs. GA+ AA). A stratification analysis revealed that male subjects and smoking subjects had a higher frequency of the rs6903956 heterozygous mutant among higher Gensini score subjects than among lower Gensini score subjects (p = 0.023, OR = 1.579, 95% CI = 1.064–2.344 for male subgroup; p = 0.005, OR = 2.075, 95% CI = 1.249–3.448 for smoking subgroup).

Conclusions: Allele A is a risk factor for CAD and the G-to-A allele substitution may underlie the association between rs6903956 and CAD.

Introduction

Coronary artery disease (CAD) is predicted to be the most common cause of death globally, including in China, by 2020, when the 10 leading causes of disability-adjusted life-years (in descending order) are projected to be ischaemic heart disease [1], in addition to lifestyle and environmental factors, which are major aetiologic determinants, multiple combinations of gene–gene and gene–environment interactions play a key role in the development of CAD [2–3]. Although the heritability of CAD is estimated to be 40 to 60%, the mechanism of genetic is still little known [4]. A number of genomic regions, variants in candidate genes, and risk factors were implicated in increasing the susceptibility of CAD [5]. However, most of the variants and genes have not been established consistently. The most robust genetic risk variant for CAD was identified on chromosome 9p21.3 by genome-wide association studies (GWAS) [6]. Recently, the first GWAS for CAD in a Chinese Han population had identified rs6903956, which is in C6orf105 on chromosome 6p24.1, to be significantly associated with susceptibility to CAD [7].

However, the true causative of rs6903956 to CAD is unknown. Despite its limitations, coronary arteriography remains to be the golden standard for documenting the extent and severity of CAD. Our research seek to test the hypothesis that 6p24.1 locus promote atherosclerosis by examining the relationship between rs6903956 genotype and angiographical severity in Chinese population who underwent coronary arteriography.
Materials and Methods

Study population
Over a span of three year, from January 2004 to December 2006, we selected a total of 1,075 consecutive subjects (803 men and 272 women) who underwent coronary angiography for suspected or known coronary atherosclerosis at the First Affiliated Hospital of Nanjing Medical University (Nanjing, China). Patients with a history of hyperlipidemia, cerebrovascular disease, peripheral arterial disease, infectious processes within the 2 weeks preceding catheterization heart failure (Killip Class≥2 after acute myocardial infarction), or severe hepatic or renal disease were excluded. Written informed consent was obtained from all enrolled participants and this study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University.

Biochemical analysis
Twelve-hour fasting blood samples were collected from all enrolled subjects. All measurements were conducted at the clinical laboratory in the First Affiliated Hospital of Nanjing Medical University. Total cholesterol (TCH, mmol/L), triglyceride (TG, mmol/L), fasting high-density lipoprotein-cholesterol (HDL-C, mmol/L), fasting low-density lipoprotein-cholesterol (LDL-C, mmol/L), blood urea nitrogen (BUN, mmol/L) and creatinine (CR, μmol/L) levels were determined by enzymatic procedures on an automated autoanalyzer (AU 2700 Olympus, First Chemical Ltd, Tokyo, Japan).

Coronary angiography
Coronary angiography was carried out according to the Judkins technique, and images of the right and left coronary trees were obtained with routine standardized projections and recorded on Kodak 3-mm cinefilm (New York) at a rate of 30 frames per second. All coronary angiograms were evaluated by two experienced cardiologists who were blinded to the laboratory results of the patients. The severity of each lesion was assessed by quantitative coronary angiography.

Scoring of coronary angiogram
Coronary angiograms were scored according to vessel score and Gensini’s score. Vessel score was defined as the number of vessels with significant stenosis (≤50% of lumen diameter patency). Scores ranged from 0 to 3, depending on the number of vessels involved. In Gensini’s scoring system [8], angiographic stenosis in the range of 0%–25% was scored as 1 point, stenosis in the range of 25%–50% was scored as 2 points, 50%–75% was scored as 4 points, 75%–90% was scored as 8 points, 90%–99% was scored as 16 points, and total occlusion was scored as 32 points. Each stenosed segment was then weighted from 0.5 to 5, depending on the functional significance of the area supplied by that segment. These scores were multiplied by the coefficient defined for each coronary artery and segment, and the results were then summed. According to this system, a substantial reduction in lumen diameter was assigned a higher score than a distal lesion.

Anthropometric measurements
Anthropometric measurements were taken while the patients were barefoot and donned an examining gown. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m²). Blood pressure was measured in the bare right arm with the participant seated. Three readings were obtained for each participant, and the mean was recorded for each patient.

Cigarette smoking and alcohol intake
Cigarette smoking (number of cigarettes per day) and alcohol (amount per week) intake were assessed by means of standardized questionnaire. For smoking, patients were classified as non-smokers (never having smoked) or smokers (including former and current smoking). Patients who smoked ≥1 cigarette per day during preceding year were classified as current smokers. For alcohol use, patients were classified as non-drinkers (never having consumed alcohols) or drinkers (including former and current drinking). Patients who consumed at least 50 g per week of alcoholic beverages were regarded as current drinkers.

Hypertension and diabetes mellitus
Patients were defined as having hypertension if they had been previously diagnosed with hypertension and took antihypertensive drugs or if their blood pressure levels were ≥140 mmHg in systole or ≥90 mmHg in diastole. Patients were defined as having diabetes mellitus if they had been previously diagnosed with diabetes mellitus and had received oral hypoglycemic agents or insulin therapy, if their fasting blood sugar (FBS) levels were above 126 mg/dl, or their postprandial 2 h blood glucose (PP2hr glucose) levels were above 200 mg/dl [9].

Family history of coronary artery disease
All participants completed a detailed self-administered family history questionnaire. The following information was collected and analyzed for all first-degree (parents, siblings, and offspring) family members, including current age or age at death, history of heart attack, age at heart attack, and whether or not hospitalized for a heart attack [10].

Single nucleotide polymorphism (SNP) genotyping
Genomic DNA was extracted from the patients’ peripheral blood leukocytes by a common salting-out procedure using peripheral blood samples anticoagulated with ethylenediaminetetraacetic acid (EDTA). SNP genotyping was performed using the 5’ nucleotide discrimination assay (Taqman Assays, Applied Biosystems, and Foster City, CA, USA) on an ABI PRISM 7900HT Sequence Detection System. The quality of SNP genotyping was verified by direct DNA sequence analysis of 1075 samples.

Statistical analysis
Data were analyzed using Statistics Package for Social Sciences software (SPSS, version 16.0; Chicago, IL, USA). Patients were classified into two groups according to their Gensini scores using the median as a cutoff point: ≥22 for the low score group and <22 for the low score group. Genotypes were tested for Hardy-Weinberg equilibrium among all participants using a χ² test with one degree of freedom. Variables were tested for normality with Kolmogorov-Smirnov statistics. Data of BMI were normally distributed and therefore presented in the form of mean ± SD, whereas skewed data, including AGE, SBP, DBP, TCH, TG, HDL-C, LDL-C, BUN, CR and Gensini’s score were expressed as medians and interquartile ranges. Differences in selected demographic continuous variables among groups were evaluated by using one-way analysis of variance (ANOVA) or the Kruskal-Wallis H test. Categorical variables, namely sex, smoking status, alcohol consumption status, hypertension status, diabetes status and family history of CHD were compared among the genotypes of rs6903956 using a χ²-test. Variables of counts of diseased vessel were compared among the genotypes of rs6903956 using a χ²-test for linear-by-linear association. A binary logistic regression procedure was used for association analyses of Gensini score-
related phenotypes, association of rs6903956 genotype variants and angiographical characteristics of coronary atherosclerosis risk were estimated by computing the OR and their 95% CI without/ with adjustments for age, sex, BMI, and other confounding risk factors. The genotype data were further stratified by age, sex, BMI, and smoking subgroups. Differences were considered to be significant if the null hypothesis could be rejected with >95% confidence. All \( p \) values are two-tailed.

**Power calculation**

Power calculation was performed using the NCSS/PASS Dawson edition software (Kaysville, UT) for Windows XP. A logistic regression of a binary response variable (Y) on a binary independent variable (X) with a sample size of 1075 observations (of which 50% are in the group \( X = 0 \) and 50% are in the group \( X = 1 \)) achieves 78% power at a 0.05 significance level to detect a change in \( \text{Prob} (Y = 1) \) from the baseline value of 0.138 to 0.200. This change corresponds to an OR of 1.564.

**Results**

**Genetic characteristics of the study cohort**

A total of 1075 ethnic Han Chinese participants were genotyped for the rs6903956 SNP and included in this study. The clinical characteristics of the population according to genotype are summarized in Table 1. The rs6903956 genotype groups did not differ significantly in their demographics, biochemical laboratory test result, family history, or lifestyle habits. However, Gensini score did differ significantly among the rs6903956 genotypes \( (p=0.025) \).

The observed genotypic frequencies were consistent with Hardy-Weinberg equilibrium (Table 2, \( p=0.124 \)) with a risk allele frequency of 0.09 (observed frequency of allele A).

**Genotype distribution of rs6903956 polymorphisms in subjects grouped by diseased vessel count**

The distribution of rs6903956 polymorphism genotypes within the diseased vessel score subgroups are presented by Table 3. Coronary angiography revealed coronary heart disease in 716/1075 patients, including 264 patients who had a single vessel diseases affected, 192 who had 2 vessel diseases affected and 260 who had 3 vessel diseases affected. As reported in Table 3, we observed a dose-dependent influence of the genotype of the human rs6903956 polymorphisms on the response to the vessel score (\( \chi^2 \) test for linear-by-linear association; \( P=0.024 \) for GG vs. AG and \( P=0.042 \) for GG vs. AG+AA, respectively).

**Table 1. Patient characteristics by rs6903956 genotype.**

| Variables                  | Rs6903956 genotype | Statistical parameter | \( P \)-value |
|----------------------------|---------------------|-----------------------|--------------|
|                            | GG                  | AG                    | AA           |
| AGE (years)                | 63.00(54.00–70.00)  | 62.00(53.00–69.25)    | 64.00(60.00–69.00) | 0.231 | 0.891 |
| SBP (mmHg)                 | 130(120–145)        | 130(120–140)          | 130(120–140) | 0.274 | 0.872 |
| DBP (mmHg)                 | 80(70.00–85.00)     | 80(70.00–88.50)       | 80(70.00–90.00) | 0.567 | 0.753 |
| BMI (kg/m\(^2\))          | 24.98±3.07          | 24.85±3.11            | 24.06±3.01   | 0.626 | 0.535 |
| CH (mmol/L)                | 4.08(3.47–4.59)     | 4.13(3.63–4.70)       | 3.68(3.44–4.81) | 2.162 | 0.139 |
| TG (mmol/L)                | 1.42(1.00–2.00)     | 1.31(0.94–2.00)       | 1.19(0.84–1.45) | 7.890 | 0.019 |
| HDL-C (mmol/L)             | 0.98(0.85–1.16)     | 1.02(0.86–1.18)       | 0.99(0.78–1.27) | 0.869 | 0.648 |
| LDL-C (mmol/L)             | 2.37(1.89–2.85)     | 2.44(2.02–3.05)       | 2.37(2.06–3.00) | 4.300 | 0.116 |
| BUN (mmol/L)               | 5.32(4.35–6.51)     | 5.31(4.37–6.24)       | 4.51(4.15–4.91) | 4.449 | 0.108 |
| CR (mmol/L)                | 73(61–87)           | 75(62–92)             | 64(55–78)    | 1.716 | 0.424 |
| Gensini score              | 20.00(13.71–21.45)  | 20.00(13.71–21.45)    | 20.00(13.71–21.45) | 7.403 | 0.025 |
| Sex(male/female)           | 663/230             | 130/39                | 10/3         | 0.574 | 0.750 |
| Smoking status (Yes/No)    | 413/480             | 91/78                 | 5/8          | 3.707 | 0.157 |
| Alcohol consumption (Yes/No) | 192/701            | 36/133                | 3/10         | 0.023 | 0.989 |
| Hypertension status (Yes/No) | 584/308           | 112/57                | 8/5          | 0.338 | 0.987 |
| Diabetes status (Yes/No)   | 155/738             | 23/146                | 0/13         | 4.056 | 0.132 |
| Family history of CHD (Yes/No) | 103/790           | 27/14                 | 2/11         | 2.721 | 0.257 |

Data shown in the table: Systolic blood pressure (SBP, mmHg), Diastolic blood pressure (DBP, mmHg), Body mass index (BMI, kg/m\(^2\)), Total cholesterol (CH, mmol/L), triglyceride (TG, mmol/L), fasting high-density lipoprotein-cholesterol (HDL-C, mmol/L), fasting low-density lipoprotein-cholesterol (LDL-C, mmol/L), Blood urea nitrogen (BUN, mmol/L), Creatinine (CR, µmol/L) and CHD (coronary heart disease).

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that it is well established that CAD, a complex multifactorial disease, is the one of the most common causes of death in China. Atherosclerosis is the most common cause of mortality and morbidity of CAD [11]. We all know that CAD is associated with hypertension, obesity, low HDL-C levels and diabetes mellitus (DM) [12–16]. Hence, identification the pathogenesis of genetic factor for CAD is of extreme importance.

The present study examined the association between angiographical characteristics of coronary atherosclerosis and the rs6903956 polymorphism in an ethnic Han Chinese population. In a cohort of 1,075 consecutive patients (803 men and 272 women) who underwent coronary arteriography for suspected or known coronary atherosclerosis, we found that severity of the coronary atherosclerosis estimated by Gensini score and diseased vessel counts both differed in relation to rs6903956 genotype. However, the traditional risk factors of CAD (ie age, blood pressure, total cholesterol, triglyceride levels, etc.) did not differ among the three rs6903956 genotypes.

In the first GWAS for CAD in an ethnic Han Chinese population, Dandona et al. identified rs6903956 on chromosome 6p24.1 as being significantly associated with susceptibility to CAD [6], although the exact mechanism underlying the relationship between rs6903956 and CAD is still unclear, coronary arteriography remains the golden standard for CAD.

Our present study was conducted to evaluate the association between the angiographical characteristics of coronary atherosclerosis and the rs6903956 polymorphism in the Chinese population. In our study, the Gensini score system was used to define the degree of severity of coronary atherosclerosis estimated by Gensini score and diseased vessel counts both differed in relation to rs6903956 genotype. However, the traditional risk factors of CAD (ie age, blood pressure, total cholesterol, triglyceride levels, etc.) did not differ among the three rs6903956 genotypes.

### Discussion

The present study evaluated the association between angiographical characteristics of coronary atherosclerosis and the rs6903956 polymorphism in an ethnic Han Chinese population. In a cohort of 1,075 consecutive patients (803 men and 272 women) who underwent coronary arteriography for suspected or known coronary atherosclerosis, we found that severity of the coronary atherosclerosis estimated by Gensini score and diseased vessel counts both differed in relation to rs6903956 genotype. However, the traditional risk factors of CAD (ie age, blood pressure, total cholesterol, triglyceride levels, etc.) did not differ among the three rs6903956 genotypes.

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| Genotype | Diseased vessel score | linear-by-linear $\chi^2$ value | $P$-value |
|----------|-----------------------|-------------------------------|-----------|
|          | 0                     | 1                             | 2         | 3         | 5.074 | 0.024 |
| Rs6903956, n (%) |                       |                               |           |           |       |       |
| GG       | 307(85.5)             | 222(84.1)                     | 157(81.8) | 207(79.6) |       |       |
| AG       | 50(13.9)              | 38(14.4)                      | 34(17.7)  | 47(18.1)  |       |       |
| AA       | 2(0.6)                | 4(1.5)                        | 1(0.5)    | 6(2.3)    |       |       |
| Rs6903695, n (%) |                       |                               |           |           | 4.116 | 0.042 |
| GG       | 307(85.5)             | 222(84.1)                     | 157(81.8) | 207(79.6) |       |       |
| AG+GG    | 52(14.5)              | 42(15.9)                      | 35(18.2)  | 53(20.4)  |       |       |


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### Table 2. Hardy-Weinberg equilibrium test for rs6903956 genotype frequencies among all patients (N = 1075).

| comparator | Rs6903956 genotype | Allele |
|------------|---------------------|--------|
|            | GG n (%)            | AG n (%)| AA n (%)| G n (%) | A n (%) |
| Observed frequencies | 893(83.07) | 169(15.72) | 13(1.21) | 1955(90.93) | 195(9.07) |
| Expected frequencies | 888.84   | 177.32   | 8.84    |           |          |

$\chi^2 = \sum (observed frequencies - expected frequencies)^2/expected frequencies = 2.363$, df = 1, $P = 0.124$, rs6903956 genotype information was available for 1075 patients.


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### Table 3. Genotype distribution of the human rs6903956 polymorphisms in subjects grouped by the vessel score.

| Genotype | Diseased vessel score | linear-by-linear $\chi^2$ value | $P$-value |
|----------|-----------------------|-------------------------------|-----------|
|          | 0                     | 1                             | 2         | 3         | 5.074 | 0.024 |
| Rs6903956, n (%) |                       |                               |           |           |       |       |
| GG       | 307(85.5)             | 222(84.1)                     | 157(81.8) | 207(79.6) |       |       |
| AG       | 50(13.9)              | 38(14.4)                      | 34(17.7)  | 47(18.1)  |       |       |
| AA       | 2(0.6)                | 4(1.5)                        | 1(0.5)    | 6(2.3)    |       |       |
| Rs6903695, n (%) |                       |                               |           |           | 4.116 | 0.042 |
| GG       | 307(85.5)             | 222(84.1)                     | 157(81.8) | 207(79.6) |       |       |
| AG+GG    | 52(14.5)              | 42(15.9)                      | 35(18.2)  | 53(20.4)  |       |       |


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This is the first study, however, to explore the association between rs6903956 genotype and severity of the coronary atherosclerosis as defined by Gensini scores system. Considering that one-third of all cigarettes are smoked in China [17], advanced age, alcohol consumption, high BMI, and male gender are all traditional risk factors to CAD, so our study included a deeper analysis of the relationship between rs6903956 genotype and the risk of higher Gensini score stratified by age, sex, BMI, smoking, and drinking status. We found that being a smoker or being male was associated with an increased likelihood of being in the higher Gensini score group. This relationship with smoking fits well with previous research showing that the number of cigarettes smoked was an independent risk factor for mortality in subjects with atherosclerosis in Chinese population [18]. Maleness has previously been associated with risk of coronary artery disease in subjects of European ancestry [19]. Interestingly, several traditional risk factors for CAD, such as being older than 60 years of age, being a drinker, and having a BMI $\geq 24$ kg/m$^2$, were not found to be significantly associated with a higher Gensini score in our study. The lack of positive associations for these factors could have been due to the effects being too weak to be confirmed in the present sample size or our enrolled patients not adequately representing the general population.

In addition to the rs6903956 SNP examined here, another SNP, rs499818, which is located in the same chromosomal region 6p24.1, has been demonstrated to be associated with coronary heart disease. A community-based genome-wide association study of major cardiovascular disease outcomes was conducted, 1345 Framingham Heart Study participants from the largest 310 pedigrees were recruited in the study, and, 70,987 qualifying SNPs (Affymetrix 100 K GeneChip) were analyzed. The results demonstrated that the rs499818 was associated with the major cardiovascular outcomes ($p = 6.6 \times 10^{-6}$) [20]. In the PAGE study, another GWAS identified several SNPs associated with incident coronary heart disease, the rs499818 SNP to be associated with the incidence of CAD in white American participants. ($P = 0.0002$, Cox proportional hazards model with additive mode of inheritance adjusted for age, sex, and ancestry as

| Genotype | Gensini score | OR (95% CI) | P-value |
|----------|--------------|-------------|---------|
| Rs6903956, n (%) | | | |
| GG | 462(86.2) | 431(80.0) | 1 |
| AG | 72(13.4) | 97(18.0) | 1.444(1.036–2.013) | 0.030 |
| AA | 2(0.4) | 11(2.0) | 5.896(1.299–26.750) | 0.021 |
| Rs6903695, n (%) | | | |
| GG | 462(86.2) | 431(80.0) | 1 |
| AG + GG | 74(13.8) | 108(20.0) | 1.564(1.132–2.162) | 0.007 |

**Table 4.** Association of the rs6903956 genotypes with the angiographical characteristics of coronary atherosclerosis using univariate logistic analyse.

| Genotype | Gensini score | OR (95% CI) | P-value |
|----------|--------------|-------------|---------|
| Rs6903956 | | | |
| GG/AG/AA | (462/72/2) | (431/97/1) | 1.578(1.155–2.154) | 0.004 |
| Sex(Male/Female) | (364/172) | (439/100) | 0.657(0.472–0.914) | 0.013 |
| Age | 61(52~68) | 66(57~71) | 1.046(1.033–1.059) | 0.000 |
| Smoking status(Yes/no) | (202/334) | (307/232) | 2.138(1.602–2.855) | 0.000 |
| Rs6903956 | | | |
| GG/(AG+AA) | (462/74) | (431/108) | 1.541(1.097–2.163) | 0.013 |
| Sex(Male/Female) | (364/172) | (439/100) | 0.656(0.472–0.914) | 0.013 |
| Age | 61(52~68) | 66(57~71) | 1.046(1.033–1.059) | 0.000 |
| Smoking status(Yes/no) | (202/334) | (307/232) | 2.134(1.599–2.848) | 0.000 |

**Table 5.** Association of the risk factors with the angiographical characteristics of coronary atherosclerosis using multivariate Logistic regression analyse.

OR: odds ratio.
CI: confidence internal.
Group 1: the lower ($\leq 22$) Gensini score group.
Group 2: the higher ($\geq 22$) Gensini score group.

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Table 6. The risk assessment of rs6903956 genotype to the coronary atherosclerosis.

| Variables                  | Rs6903956 genotype | Adjusted OR(95%CI) | P-value |
|----------------------------|--------------------|--------------------|---------|
|                            | Genotype           | GS = 0–21.9 Group 1(%) | GS = 22 Group 2(%) |
| Age (years)                |                    |                    |         |
| <60                        | GG                 | 211(50.7)          | 135(32.5) | 1 |
|                            | AG                 | 33(7.9)            | 34(8.2)  | 0.268(0.022–3.223) | 0.300 |
|                            | AA                 | 1(0.2)             | 2(0.5)   | 0.423(0.034–5.278) | 0.504 |
|                            | AG+AA              | 34(8.2)            | 36(8.7)  | 1.633(0.962–2.772) | 0.069 |
| >= 60                      | GG                 | 251(38.1)          | 296(44.9) | 1 |
|                            | AG                 | 39(5.9)            | 63(9.6)  | 1.385(0.887–2.162) | 0.152 |
|                            | AA                 | 1(0.2)             | 9(1.4)   | 7.680(0.946–62.377) | 0.056 |
|                            | AG+AA              | 40(6.1)            | 72(10.9) | 1.541(0.999–2.376) | 0.051 |
| BMI(kg/m²)                 |                    |                    |         |
| <24                        | GG                 | 157(39.4)          | 170(42.7) | 1 |
|                            | AG                 | 25(6.3)            | 39(9.8)  | 1.584(0.890–2.891) | 0.118 |
|                            | AA                 | 1(0.3)             | 6(1.5)   | 5.341(2.628–10.471) | 0.125 |
|                            | AG+AA              | 26(6.5)            | 45(11.3) | 1.749(1.003–3.051) | 0.049 |
| >= 24                      | GG                 | 301(45.2)          | 253(38.3) | 1 |
|                            | AG                 | 47(7.1)            | 58(8.7)  | 1.424(0.927–2.188) | 0.107 |
|                            | AA                 | 1(0.2)             | 4(0.6)   | 5.347(0.555–51.487) | 0.147 |
|                            | AG+AA              | 48(7.2)            | 62(9.3)  | 1.498(0.982–2.284) | 0.061 |
| Sex(male/female)           |                    |                    |         |
| Male                       | GG                 | 315(39.2)          | 348(43.3) | 1 |
|                            | AG                 | 49(6.1)            | 81(10.1) | 1.579(1.064–2.344) | 0.023 |
|                            | AA                 | 0(0)               | 10(1.2)  | —                   | —       |
|                            | AG+AA              | 49(6.1)            | 91(11.3) | 1.753(1.189–2.586) | 0.005 |
| Female                     | GG                 | 147(50.4)          | 83(30.5) | 1 |
|                            | AG                 | 23(8.5)            | 16(5.9)  | 1.122(0.550–2.291) | 0.752 |
|                            | AA                 | 2(0.7)             | 1(0.4)   | 0.814(0.068–9.684) | 0.870 |
|                            | AG+AA              | 25(9.2)            | 17(6.2)  | 1.098(0.549–2.196) | 0.792 |
| Smoking status             |                    |                    |         |
| No                         | GG                 | 285(50.4)          | 195(34.5) | 1 |
|                            | AG                 | 47(8.3)            | 31(5.5)  | 0.975(0.585–1.625) | 0.922 |
|                            | AA                 | 20(4.0)            | 6(1.1)   | 3.688(0.669–20.335) | 0.134 |
|                            | AG+AA              | 49(8.7)            | 37(6.5)  | 1.087(0.667–1.772) | 0.738 |
| Yes                        | GG                 | 177(34.8)          | 236(46.4) | 1 |
|                            | AG                 | 25(4.9)            | 66(13)   | 2.075(1.249–3.448) | 0.005 |
|                            | AA                 | 0(0)               | 5(1)     | —                   | —       |
|                            | AG+AA              | 25(4.9)            | 71(13.9) | 2.233(1.350–3.694) | 0.002 |
| Drinking status            |                    |                    |         |
| No                         | GG                 | 366(43.4)          | 335(39.7) | 1 |
|                            | AG                 | 59(7.8)            | 74(8.8)  | 1.424(0.965–2.103) | 0.075 |
|                            | AA                 | 20(2.4)            | 8(0.9)   | 3.790(0.743–19.349) | 0.019 |
|                            | AG+AA              | 61(7.2)            | 82(9.7)  | 1.504(1.028–2.199) | 0.036 |
| Yes                        | GG                 | 96(41.6)           | 96(41.6) | 1 |
|                            | AG                 | 13(5.6)            | 23(10.0) | 1.755(0.836–3.685) | 0.137 |
|                            | AA                 | 0(0)               | 3(1.3)   | —                   | —       |
|                            | AG+AA              | 13(5.6)            | 26(11.3) | 1.990(0.961–4.120) | 0.064 |

Adjusted for age, sex, BMI in a binary logistic regression for each stratum, data are shown as numbers (percentages are given in parentheses).

GS: Gensini score, Group 1 (N = 536), Group 2 (N = 539).

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needed) [21], although rs499818 and rs6903956 are located in the same chromosomal region 6p24.1, the distance between them was observed to be greater than 1 M. Future studies are need to determine the linkage disequilibrium between these two SNPs and to further examine whether these SNPs are indeed a causal variant or just a marker/tagger.

**Conclusion**

In conclusion, the present findings demonstrating that the A allele of the rs6903956 SNP confers greater risk of CAD, and a G-to-A allele substitution may underlie the relationship between rs6903956 and CAD. Although the exact biological mechanism of this association remains to be explored, our study provides credible evidence that the rs6903956 polymorphism may contribute to the etiology of the severity of coronary atherosclerosis and plays an important role in the atherosclerotic process in the Chinese population. Further studies are needed to interpret SNP rs6903956 on coronary atherosclerosis susceptibility.

**Author Contributions**

Conceived and designed the experiments: EZJ. Performed the experiments: CYG YG LL. Analyzed the data: WZM ZJY. Contributed reagents/materials/analysis tools: CJL LSW KJC. Wrote the paper: CYG. Collected data: WZM ZJY.

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