Four SNPs on Chromosome 9p21 in a South Korean Population Implicate a Genetic Locus That Confers High Cross-Race Risk for Development of Coronary Artery Disease

Gong-Qing Shen, Lin Li, Shaoqi Rao, Kalil G. Abdullah, Ji Min Ban, Bok-Soo Lee, Jeong Euy Park, Qing K. Wang

Objective—Recent genome-wide association studies have identified 4 SNPs on chromosome 9p21 associated with CAD (rs10757274 and rs2383206) and myocardial infarction (MI: rs2383207 and rs10757278) in White populations in Northern Europe and North America. We aimed to determine whether this locus confers significant susceptibility to CAD in a South Korean population, and thus cross-race susceptibility to CAD.

Methods and Results—We performed a case-control association study with 611 unrelated CAD patients and 294 normal controls from South Korea. Allelic associations of SNPs and SNP haplotypes with CAD were evaluated. Multivariate logistic regression analysis was used to adjust effects of clinical covariates. We found that 4 SNPs on chromosome 9p21 were associated with susceptibility to CAD in a South Korean population. The association remained significant after adjusting for significant clinical covariates ($P_{\text{adj}} = 0.001$ to 0.024). We identified one risk haplotype (GGGG; $P_{\text{adj}} = 0.017$) and one protective haplotype (AAAA; $P_{\text{adj}} = 0.007$) for development of CAD. Further analysis suggested that the SNPs probably confer susceptibility to CAD in a dominance model (covariates-adjusted $P_{\text{adj}} = 0.001$ to 0.024; OR = 2.37 to 1.54). This represents the first study that expands association of these 9p21 SNPs with CAD beyond White populations.

Conclusion—Chromosome 9p21 is an important susceptibility locus that confers high cross-race risk for development of CAD. (Arterioscler Thromb Vasc Biol. 2008;28:360-365)

Key Words: coronary artery disease □ myocardial infarction □ single nucleotide polymorphism □ association study □ Asian population

Coronary artery disease (CAD), including its acute complication of myocardial infarction (MI), is the leading cause of mortality worldwide.1 CAD is a complex trait which is assumed to be caused by both genetic and environmental factors as well as their interaction with each other.2-4 Genetic factors have been defined as an important risk contributor for the pathogenesis of CAD and MI,2,5 but the responsible molecular and genetic determinants remain largely unidentified. Genome-wide SNP association studies are a recently developed strategy for identifying genetic factors for common, complex disease traits.5 Very recently, independent genome-wide SNP association studies identified 4 SNPs on chromosome 9p21 that were associated with CAD and MI in several White cohorts.6,7 McPherson et al reported 2 susceptibility SNPs (rs10757274 and rs2383206) that were located within 20 kb of each other on chromosome 9p21 and were associated with CAD in a Canadian population and 5 other

White cohorts,6 and Helgadottir et al described an association between MI and 2 SNPs (rs2383207 and rs10757278) located in the same 9p21 region in an Icelandic population and replicated the finding in 4 White cohorts.7 Later, the same genetic locus was also identified by a genome-wide association study involving 1926 cases and 3000 controls from a British population,8 and was then replicated in a German population.9 Very interestingly, the 4 most recent independent population-based case-control studies also identified several SNPs on chromosome 9p21 that were significantly associated with diabetes or related disorders among Whites in England,10 Finland,11 and Sweden.12 To date, all studies conducted have found associations between these SNPs and CAD, but only in populations of mainly Northern European descent.

As the fast pace of genomics research continues to identify susceptibility loci, it becomes apparent that many indepen-
dent studies are often needed to unequivocally establish a valid genotype-phenotype association across diversities of human populations before their considerations as clinical markers for disease. It is essential that independent replication studies conform to certain standards to ensure proper refutation or acceptance of identified loci. This requirement is particularly salient and time impressive for a small to medium-size genotype-phenotype relationship, such as the association between the 4 SNPs on chromosome 9p21 and CAD/MI. Therefore, we carried out a case-control association study in a Korean population to determine whether the association of chromosome 9p21 SNPs with CAD can expand beyond the White populations already confirmed and to establish the credibility of this locus-specific contribution to the development of CAD within an Asian population.

Methods

Study Subjects
We carried out a case-control association study involving 611 unrelated cases (63.7±10.1 years old) that were randomly selected from patients admitted to the Samsung Medical Center (Seoul, South Korea) with a diagnosis of CAD. Koreans represent one of the world’s most ethnically and genetically homogeneous populations and are ideal for case-control association studies. As such, all subjects in this study were of the same ethnicity (Korean). The diagnostic criteria for CAD are as described previously and include >70% luminal narrowing in at least one vessel by coronary angiography, percutaneous coronary angioplasty, coronary artery bypass graft, and MI. The diagnosis of MI was based on typical chest pain of >30 minutes duration, characteristic electrocardiographic patterns of acute MI, and significant elevation of cardiac enzymes such as creatine kinase myocardial band “CK-MB”. For the control group, 294 volunteers (60.1±11.0 years old) were selected from individuals who were admitted to Samsung Medical Center for evaluation by coronary angiography for reasons other than CAD, mainly valvular heart disease, but were found to have no detectable stenosis. Thus, the controls were in general good health and determined to have no CAD. Blood was drawn after an overnight fast but within 48 hours of admission to the hospital and before coronary angiography or percutaneous coronary intervention. Fasting concentrations of total cholesterol, triglyceride, and blood sugar were measured at the Department of Laboratory Medicine at Samsung Medical Center. Hypertension was defined as systolic blood pressure of >140 mm Hg or diastolic blood pressure >90 mm Hg, and diabetes was defined as ongoing therapy of diabetes or a fasting blood sugar of >126 mg/dL. The clinical characteristics of both CAD cases and healthy controls are shown in Table 1. The local institutional review board is on human subject research approved this study, and written informed consent was obtained from all participants. The investigation conformed to the principles outlined in the Declaration of Helsinki.

Genotyping of SNPs
Human genomic DNA was isolated from blood using the DNA Isolation Kit for Mammalian Blood (Roche Diagnostics). The ABI PRISM 7900HT Sequence Detection System was used to perform SNP genotyping using the 5’ nucleotide allelic discrimination assay (TaqMan Assay). The TaqMan Assay kit (Assays-on-Demand) was purchased from ABI (Applied Biosystems). It included the forward target-specific polymerase chain reaction (PCR) primer, the reverse primer, and the TaqMan MGB probes labeled with 2 special dyes, DFMAM and VIC. Genotyping was performed in a 5-μL volume containing 2.5 μL of TaqMan Universal PCR Master Mix, 0.125 μL of 40× TaqMan MGB Assay Mix, and 25 ng of genomic DNA. Automatic allele calling with the default settings (95%) was carried out by ABI PRISM 7900HT data collection and analysis software version 2.1. The quality for SNP genotyping was assured by independently replicating the genotyping and allelic calls of 64 randomly selected samples and by direct DNA sequence analysis of 24 samples. The results of quality control were 100% in agreement with the initial genotyping results. In addition, all the DNA samples for cases and controls were run in the same batches.

Statistical Analysis
A statistical power analysis was performed using a free program for power and sample size computations for a case-control design. Allelic association of a SNP with a binary disease trait was assessed using Pearson 2×2 contingency table Chi-square test implemented using SAS Ver 9.00 (SAS Institute Inc) or Haploview version 3.0 (http://www.broad.mit.edu/mpg/haploview/). Odds ratios and 95% confidence intervals were estimated using SAS Ver 9.00. Multivariate logistic regression analysis was performed using SAS Ver 9.00 to test relations between the SNPs and CAD accounting to the significant covariates previously described (gender, age, hypertension, and diabetes). Empirical probability values were also calculated using 100 000 Monte Carlo simulations by the CLUMP program (http://www.mds.qmw.ac.uk/statgen/dcurtis/software.html). Haplotypes were estimated using the PHASE software (www.stat.washington.edu/stephens/software.html). Haplotype data were then subject to permutation analysis with 100 000 Monte Carlo simulations using Haploview software. All 4 SNPs were tested for Hardy-Weinberg equilibrium among the CAD patients and normal controls using a Chi-square test with one degree of freedom. Because all 4 SNPs are in the same block and highly correlated (for details, see Results), we used pointwise statistical significance (eg, P≤0.05) as the approximated multiple-tests-corrected significance criterion based on the principle of the Bonferroni method.

Results

Power Analysis
Before implementation of this study, we performed a statistical power analysis using the PS program to verify whether the recruited samples could provide adequate power in identifying the association between the modest-effect-size SNPs and CAD, provided that the chromosome 9p21 locus confers the same size of risk for development of CAD in the South Korea population as in Whites. Under the population parameter settings of the effect size of odd ratios of 1.25 and the allelic frequency of 0.45 derived from the previous studies, our samples with 611 well-characterized CAD cases and 294 healthy controls with evidenced lack of CAD can provide a statistical power of 97% and 91% at the nominal Type I error rate of 0.05 and 0.01, respectively. The

Table 1. Clinical Characteristics of CAD Patients and Normal Controls in a South Korean Population

<table>
<thead>
<tr>
<th>Items</th>
<th>Case (n=611)</th>
<th>Control (n=294)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F</td>
<td>433/178</td>
<td>171/123</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, yr†</td>
<td>63.7±10.1</td>
<td>60.1±11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>26.1</td>
<td>24.2</td>
<td>0.66</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>24.4±3.4</td>
<td>24.3±4.1</td>
<td>0.77</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>55.4</td>
<td>40.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>30.8</td>
<td>17.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>175.5±44.9</td>
<td>172.1±41.6</td>
<td>0.43</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>150.9±92.6</td>
<td>147.2±82.7</td>
<td>0.70</td>
</tr>
</tbody>
</table>

*Data are shown as mean±SD or percentage. †Age, age-at-onset for cases and age-at-examination for controls. ‡Continuous data were tested using 2-tailed Student t test and categorical data were tested using a Chi-square test (with df=1) for difference between case (patient) and control (normal) groups.
power analysis indicates that our South Korean sample size is sufficient for identifying the chromosome 9p21 CAD locus.

Association Between the Four SNPs on 9p21 and CAD
Before statistical analysis, we compared our genotyping data for control subjects with data for East Asians (Chinese or Japanese) estimated by the HapMap project. The allelic and genotypic distributions for the 3 cohorts were remarkably similar, indicating that our Korean control subjects were representative Asians of that region. All SNPs did not deviate significantly (P>0.3) from the Hardy-Weinberg equilibrium (Table 2).

We carried out a standard allelic association analysis for all 4 SNPs and found significant association with the CAD phenotype (all P-obs [nominal probability value]=0.011; OR=1.29 to 1.32; Table 2). To account for the interference of potential confounding factors with assessment of the relations between the SNPs and CAD, we performed a multivariate logistic regression analysis. Higher significance (the probability value. Again, empirical probability values were calculated using 100 000 Monte Carlo simulations.

Considering these results, this study provided solid evidence that the SNPs on chromosome 9p21 are associated with CAD in a South Korean population.

Identification of Two Haplotypes Associated With CAD in the South Korean Population
An extended SNP haplotype analysis was conducted to provide some insights into the relation between the SNP patterns and CAD that is beyond what single point SNP analysis can reveal. As the 4 SNPs were highly correlated as shown in Figure 1, each haplotype was thus treated as a single variant (all the remaining haplotypes were collapsed into the alternative allele) to test its association with the disease trait. As shown in Table 3, the 2 most common haplotypes, GGGG and AAAA, showed strong associations with CAD. Haplotype GGGG conferred a significant risk effect (P-obs=0.017; P-emp=0.019; OR=1.28; 95% CI=1.04 to 1.56), whereas the AAAA haplotype conferred protection of CAD (P-obs=0.007; P-emp=0.007; OR=0.75; 95% CI=0.60 to 0.92).

Genotypic Association Analysis Suggest That the Putative Genetic Model Involved in Development of CAD Is Dominant
To further investigate how each of the SNP alleles and haplotypes interacted in conferring genetic risks to CAD, we further conducted genotypic association analysis assuming 3 common genetic models (dominant, recessive, and additive inheritance). The results for the 4 SNPs and derived haplotypes (considering 2 most common ones as alternative alleles) consistently showed that the SNPs either directly exerted an effect or the linked functional gene impacted the disease trait in a dominant model (without adjustment for covariates, P=0.0011 to 0.015; after adjustment for significant covariates of gender, age, hypertension, and diabetes, P=0.001 to 0.024) or less likely additive model (without adjustment for covariates, P=0.010 to 0.013; after adjustment for covariates, P=0.009 to 0.037; Table 4).

Discussion
The recruited Korean CAD case and control samples used in this study were carefully ascertained and have also been used in several studies of molecular determinants or genetic factors for this disorder. In addition to the strict criteria used

![Figure](http://atvb.ahajournals.org/)

**Figure.** Analysis of linkage disequilibrium (LD) patterns between 4 SNPs, rs10757274, rs2383206, rs2383207, and rs10757278, were derived from the genotyping data from the Korean CAD (A) and healthy control (B) populations, respectively. The pairwise correlation between the SNPs was measured as D* and shown (×100) in each diamond.
for defining the CAD phenotype and the normal phenotype (for detail, see14), all CAD patients and non-CAD controls were verified to be genetically unrelated by examining their familial relationships.

We have taken significant steps to assure that our study conforms to the standards outlined by the NCI-NHGRI Working Group on Replication in Association Studies for establishing positive replication.13 Although our study aims to replicate the association between CAD and chromosome 9p21, it is the first of its kind to attempt to establish the association in a cohort of non-European descent.6–12 Thus, our study emerges as a novel finding in an East Asian population, which provides new evidence that implicates the chromosome 9p21 locus as an impressive locus or hotspot that harbors one or more causal genes that confer high cross-race risk for development of CAD.

It is interesting to note that in 2004 we reported a suggestive linkage of marker SNP9558 on chromosome 9p21 to MI.19 We performed a genome-wide linkage scan with 428 multiplex GeneQuest families, each of which had at least 2 affected sibs with CAD and MI. Model-free linkage analysis using SAGE20 revealed that the linkage with SNP9558 achieved the threshold for suggestive linkage (pP = 3.13; LOD = 2.2). The single point and multipoint pP values were 4.28 and 3.68, respectively (Table 2 in Wang et al19).

**Table 3. Assessment of Association Between SNP Haplotypes With CAD in a South Korean Population**

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Control (%)</th>
<th>Case (%)</th>
<th>OR (95% CI)*</th>
<th>P-obs†</th>
<th>P-emp‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>GGGG</td>
<td>42.2</td>
<td>48.1</td>
<td>1.28 (1.04–1.56)</td>
<td>0.017</td>
<td>0.019</td>
</tr>
<tr>
<td>AAAA</td>
<td>35.3</td>
<td>29.2</td>
<td>0.75 (0.60–0.92)</td>
<td>0.007</td>
<td>0.007</td>
</tr>
<tr>
<td>AAGA</td>
<td>16.8</td>
<td>15.9</td>
<td>0.93 (0.71–1.22)</td>
<td>0.612</td>
<td>0.633</td>
</tr>
<tr>
<td>AAGG</td>
<td>2.5</td>
<td>2.8</td>
<td>1.16 (0.62–2.17)</td>
<td>0.651</td>
<td>0.754</td>
</tr>
<tr>
<td>GAGA</td>
<td>1.1</td>
<td>1.3</td>
<td>1.27 (0.49–3.26)</td>
<td>0.619</td>
<td>0.657</td>
</tr>
<tr>
<td>AGGA</td>
<td>1.0</td>
<td>1.1</td>
<td>1.33 (0.48–3.72)</td>
<td>0.583</td>
<td>0.634</td>
</tr>
</tbody>
</table>

*OR, odds ratio. CI, confidence interval. †P-obs, uncorrected P value. ‡P-emp, permutation P value calculated using 100 000 Monte Carlo simulations.

**Table 4. Assessment of Association Between Four SNPs on Chromosome 9p21 With CAD Under Different Genetic Models in a South Korean Population**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Model</th>
<th>Without Adjustment*</th>
<th>With Adjustment†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P</td>
<td>OR (95% CI)‡</td>
</tr>
<tr>
<td>Single SNP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs10757274</td>
<td>Dominant</td>
<td>0.001</td>
<td>1.67 (1.2–2.3)</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>0.381</td>
<td>1.16 (0.8–1.6)</td>
</tr>
<tr>
<td></td>
<td>Additive</td>
<td>0.011</td>
<td>1.30 (1.1–1.6)</td>
</tr>
<tr>
<td>rs2383206</td>
<td>Dominant</td>
<td>0.011</td>
<td>1.50 (1.1–2.0)</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>0.104</td>
<td>1.33 (0.9–1.9)</td>
</tr>
<tr>
<td></td>
<td>Additive</td>
<td>0.010</td>
<td>1.30 (1.1–1.6)</td>
</tr>
<tr>
<td>rs2383207</td>
<td>Dominant</td>
<td>0.001</td>
<td>2.15 (1.3–3.4)</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>0.136</td>
<td>1.24 (0.9–1.6)</td>
</tr>
<tr>
<td></td>
<td>Additive</td>
<td>0.010</td>
<td>1.34 (1.1–1.7)</td>
</tr>
<tr>
<td>rs10757278</td>
<td>Dominant</td>
<td>0.015</td>
<td>1.48 (1.1–2.0)</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>0.090</td>
<td>1.33 (1.0–1.9)</td>
</tr>
<tr>
<td></td>
<td>Additive</td>
<td>0.012</td>
<td>1.29 (1.1–1.6)</td>
</tr>
</tbody>
</table>

Haplotype

| GGGG vs AAAA | Dominant | 0.002 | 2.20 (1.4–3.6) | 0.007 | 1.90 (1.2–3.0) |
|             | Recessive | 0.257 | 1.25 (0.9–1.8) | 0.711 | 1.93 (0.9–3.8) |
|             | Additive  | 0.013 | 1.40 (1.1–1.8) | 0.010 | 3.10 (1.3–7.3) |

*P values were obtained from logistic regression modeling where the predictor is coded with the No. of risk alleles, but without any other covariates. †P values were obtained from logistic regression modeling after adjustment for gender, age, hypertension, and diabetes. ‡OR, odds ratio, CI, confidence interval.
positive SNPs, rs10757274, rs2383206, rs2383207, and rs10757278. Future studies will focus on identification of the specific susceptibility gene(s) for CAD and MI at this locus.

We are confident that our findings of cross-race susceptibility are valid for several reasons: (1) 4 SNPs in one strong linkage disequilibrium block all showed significant allelic association with CAD in the Korean population; (2) both risk and protective haplotypes were identified and found to be associated with CAD in the Korean population; (3) the association remained valid even after adjustment for other significant risk factors for CAD (age, gender, hypertension, and diabetes); (4) dominant inheritance is the most likely allelic interaction model when comparing different genetic models based on either genotypic or haplotypic data, indicating that the SNPs may be linked to a disease gene whose one copy is sufficient to increase disease susceptibility.

The frequencies of risk alleles (G) for 3 of the 4 SNPs, rs10757274, rs2383206, and rs10757278, in the White control populations were similar to that in the Korean control population, 0.45 to 0.49, 0.47 to 0.52, and 0.43 to 0.48 versus 0.44, 0.44, and 0.46, respectively. The risk allele (G) frequency for rs2383207 was higher in the Korean population than in the White populations, 0.65 versus 0.46 to 0.54. Despite the difference, all 4 SNPs showed positive allelic association with CAD in the Korean population with similar odds ratios (1.32 for rs2383207 versus 1.29 to 1.30 for the other 3 SNPs; Table 2). The LD structure was not analyzed in the previous reports, thus we were unable to compare the LD structure in the Korean population to those in the White populations studied by others. Genotypic associations were analyzed in the study by McPherson et al. and positive associations were detected with SNPs rs10757274, rs2383206, and rs10757278, respectively. Despite the difference, all 4 SNPs showed positive allelic association with CAD in the Korean population with similar odds ratios (1.32 for rs2383207 versus 1.29 to 1.30 for the other 3 SNPs; Table 2). The LD structure was not analyzed in the previous reports, thus we were unable to compare the LD structure in the Korean population to those in the White populations studied by others. Genotypic associations were analyzed in the study by McPherson et al. and positive associations were detected with SNPs rs10757274, rs2383206, and rs10757278, respectively. Despite the difference, all 4 SNPs showed positive allelic association with CAD in the Korean population with similar odds ratios (1.32 for rs2383207 versus 1.29 to 1.30 for the other 3 SNPs; Table 2). The LD structure was not analyzed in the previous reports, thus we were unable to compare the LD structure in the Korean population to those in the White populations studied by others. Genotypic associations were analyzed in the study by McPherson et al. and positive associations were detected with SNPs rs10757274, rs2383206, and rs10757278, respectively. Despite the difference, all 4 SNPs showed positive allelic association with CAD in the Korean population with similar odds ratios (1.32 for rs2383207 versus 1.29 to 1.30 for the other 3 SNPs; Table 2). The LD structure was not analyzed in the previous reports, thus we were unable to compare the LD structure in the Korean population to those in the White populations studied by others. Genotypic associations were analyzed in the study by McPherson et al. and positive associations were detected with SNPs rs10757274, rs2383206, and rs10757278, respectively.

We should recognize the limitations of this study or any single human genetic study because of the sample size that is often fixed, and the genetic complexities of the studied disease (eg, involvement of multiple small to modest size effects of genes, polygenic and environmental backgrounds). As such, the genetic parameter estimates (odd ratios, risk allelic or genotypic frequencies) for the Korean population may be biased and not reach the adequate precision for population genetic studies or clinical use. However, based on the consistent risk estimates of the SNPs from the previous studies and the current one, in addition to stringent analysis that included haplotype and model-based significance, we are confident that the risk estimation we report is valid.

In conclusion, this study replicates the association of 4 SNPs on the susceptibility locus 9p21 previously identified in multiple cohorts of European descent and provides the first evidence of a cross-race susceptibility to CAD in this promising region.

**Sources of Funding**

This work was supported by National Institutes of Health grant P50 HL077107, China National 863 Scientific Program Project 2006AA02Z476, an American Heart Association Established Investigator award (to Q.K.W.), and the Cleveland Clinic Lerner College of Medicine (to K.G.A.), and the Korea Science and Engineering Foundation Grant R01-2005-000-10275-0 (to J.E.P.).

**Disclosures**

None.

**References**

8. Wellcome Trust Case-Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447:661–678.


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Arterioscler Thromb Vasc Biol. 2008;28:360-365; originally published online November 29, 2007;
doi: 10.1161/ATVBAHA.107.157248

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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