The 9p21 Myocardial Infarction Risk Allele Increases Risk of Peripheral Artery Disease in Older People

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Background—A common variant at chromosome 9p21 (tagged by the rs1333049 or rs10757278 single-nucleotide polymorphism) is strongly associated with myocardial infarction and major arterial aneurysms. An association with peripheral arterial disease (PAD) was also reported in a sample younger than 75 years, but this disappeared on removal of respondents with a myocardial infarction history, resulting in an odds ratio of 1.09 for PAD (P=0.075). We aimed at estimating the association of this variant with an Ankle-Brachial Index (ABI) and PAD in 3 older populations.

Methods and Results—We used data from the InCHIANTI, Baltimore Longitudinal Study of Aging, and Health, Aging, and Body Composition studies. In 2630 white individuals (mean age, 76.4 years), the C allele at rs1333049 was associated with lower mean ABI measures and with an increased prevalence of PAD. These associations remained after removal of baseline and incident myocardial infarction cases over a 6-year follow-up for both ABI (−0.017 ABI units; 95% CI, −0.03 to −0.01; P=1.3×10−5) and PAD (per allele odds ratio, 1.29; 95% CI, 1.06 to 1.56; P=0.012). These associations also remained after adjustment for known atherosclerosis risk factors, including diabetes mellitus, smoking, hypercholesterolemia, and hypertension.

Conclusions—The C allele at rs1333049 is associated with an increased prevalence of PAD and lower mean ABI. This association was independent of the presence of diagnosed myocardial infarction and atherosclerotic risk factors in 3 older white populations. (Circ Cardiovasc Genet. 2009;2:347-353.)

Key Words: genetics ■ myocardial infarction ■ peripheral vascular disease ■ 9p21 ■ CDKN2a/2b

Recent genome-wide association studies and subsequent replication studies have found consistent associations between a common variant on chromosome 9p21 and myocardial infarction (MI) or coronary artery disease. The nearest genes to this marker are CDKN2b and CDKN2a, which are key regulators of the cell cycle. The possible involvement of these cell cycle control genes in heart disease may be mediated through reduced regrowth of arterial intimal cells, a phenomenon implicated in the development of atherosclerosis. Three independent genome-wide scans have demonstrated that the variant associated with MI is best captured by the single-nucleotide polymorphism (SNP) rs1333049 or its proxy rs10757278 (which are in perfect linkage disequilibrium, r2=1 in HapMap II). Rs10757278 has also been shown to be associated with abdominal aortic aneurysms and intracranial aneurysms, independent of the validated effect on MI. However, similar associations with peripheral arterial disease (PAD) and cardiogenic stroke were no longer significant when subjects with known coronary artery disease were removed, in a study population with age at onset before 70 years for men and before 75 years for women.

Clinical Perspective on p 353

Although a number of atherosclerotic risk factors contribute to PAD and a lower Ankle-Brachial Index (ABI) measure, genetic factors contribute 21% to 48% of the variability of both the continuous ABI level and the presence of PAD, defined using an ABI threshold. Low ABI (the ratio of systolic blood pressure at the ankle divided by that at the brachial artery) is a marker of peripheral arterial narrowing and is used in the definition of PAD. Decreased ABI is a well

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characterized predictor of increased cardiovascular events and all-cause mortality.9–11 In addition, ABI values across the entire range,10,12 including those above the typical PAD threshold of 0.90,13 are implicated in a graded inverse correlation with risk of coronary heart disease, stroke, and preclinical atherosclerosis, suggesting that inclusion of both measures is relevant for the examination of lower-extremity PAD.14

In this study, we aimed at examining further the association of the 9p21 MI SNP (rs1333049) with PAD in older adults, using 3 independent community-dwelling study populations, while accounting for the association of this SNP with MI.

Methods

Study Populations

The InCHIANTI study is a population-based longitudinal study designed to investigate the causes of decline in mobility in older subjects.15 The sample is representative of the population of 2 small towns from the Chianti region in Tuscany, Italy. The study includes 1453 individuals of white European descent ranging in age from 20 to 102 years at baseline, when blood samples were taken. Follow-up measures were collected during 2 waves at 3-year intervals from the baseline interview. For our investigation of the associations with ABI and PAD, only subjects 65 years or older at baseline were included in analyses. Of the 1453 samples in the cohort, 1155 were available, whereas data for those 1266 of black ethnicity, of which 1070 had genotypes and phenotypes, were analyzed separately.

1400 participants, genotype information is available for 1230 participants taking statins were considered to be hypercholesterolemic even if their cholesterol did not exceed this limit.

The Baltimore Longitudinal Study of Aging (BLSA) is a longitudinal study designed as a scientific study of aging. Of the more than 1400 participants, genotype information is available for 1230 participants, aged 17 to 92. The ethnicity of each sample was assessed against the HapMap populations, using the first 2 principal components from an EIGENSTRAT analysis. A strong CEU (CEPH—Utah residents with ancestry from northern and western Europe, http://www.hapmap.org) subset of the population was selected, and following a sex check using the X-chromosome homozygous data to validate the reported gender, 858 samples were available for use within the analysis. Three hundred seventy-two of these remaining participants had ABI measured, of which 257 were 65 years or older.

Phenotypic Measures

The ABI was measured to investigate an association with arterial disease in the lower extremities. ABI was defined as the ratio of systolic blood pressure in the ankle to systolic blood pressure in the arm. In InCHIANTI, systolic blood pressure was measured with a hand-held Doppler stethoscope (Parks Electronics model 41-A, Aloha, Ore) in both posterior tibial arteries and the right brachial artery. The highest pressure at each set was used to calculate the index, and the final ABI was calculated using the lower of the right and left posterior tibial pressures divided by the brachial artery pressure.17 Two follow-up measurements were also taken at 3 and 6 years after the baseline interview, and these were used in assessment of incident PAD.

In Health ABC, ABI was defined as the ratio of blood pressure in the right ankle to the right upper arm and similarly for the left. Two measurements were taken, and a mean was calculated for each leg.18 One follow-up measurement was taken during the fourth year interview and was used to compile incident PAD cases. In BLSA, blood pressure was taken at both right and left arms and ankles, using an automated testing device (Colin VP2000/1000). The minimum value between the left and right legs was used in the analysis. ABI measures were also taken at the fourth year follow-up interview and were used to define incident cases. Those with an ABI measure >1.40 were removed because this is indicative of noncompressible, calcified arteries,14 and although this also carries a risk of mortality,19 inclusion of these individuals could have led to a misclassification of arterial extremity disease. An ABI measure <0.90 in either leg was used to define the presence of PAD because this has been reported to be highly sensitive and specific for defining angiographically documented PAD.20 PAD cases at baseline across all 3 studies were analyzed within the main analysis. Incident PAD was calculated for both studies as those individuals without PAD at baseline who had developed PAD by the follow-up interview(s), as defined by an ABI measure ≤0.9.

Covariates

An MI event was recorded using evidence from questionnaires with the question “Have you ever had an MI?” at baseline for BLSA and InCHIANTI and also “Have you had an MI event since the last interview?” at follow-up interviews for InCHIANTI only. In Health ABC, subjects are asked whether a health professional had ever told them that they had had a heart attack, and their current medications are checked to assess for those compatible with a history of heart disease. At follow-up interviews, participants are asked whether they have been told of a heart attack or hospitalized, and events are adjudicated according to specific algorithms that involve data from hospitalization, such as electrocardiographic findings and enzyme results. Information was combined to record individuals who had had an MI event at baseline or would go on to experience an event in the follow-up period. Smoking exposure and status at baseline in each study were included as 2 covariates: the first recorded as a categorical variable, where 0 was never smoked, 1 was former smoker, and 2 was current smoker and the second as number of pack-years exposure, where 1 pack-year is calculated as 1 pack of cigarettes per day for 1 year from individual self-report data. Diabetes mellitus and hypertension were recorded using self-report questionnaires in InCHIANTI and BLSA, whereas hypercholesterolemia was adjusted for using baseline low-density lipoprotein cholesterol levels, which were calculated using the Friedewald formula.

In Health ABC, those with diabetes at baseline were identified first by report of being told by a health professional that they had diabetes or by the identification of medications specific for diabetes treatment. For hypertension, those who reported hypertension or who were on medications consistent with treatment were considered hypertensive. In addition to total cholesterol ≥240 mg/dL, participants taking statins were considered to be hypercholesterolemic even if their cholesterol did not exceed this limit.

Genotyping

Genotyping of rs1333049 in InCHIANTI and Health ABC was performed in-house, using conventional Taqman probes (Applied Biosystems, Foster City, Calif). Genotyping of its proxy rs4977574 (r²=0.89) in BLSA was performed using the Illumina Infinium HumanHap550 genotyping chip (ver1 and ver3 chips were used). Samples were assessed for minor allele frequency (>1%), genotype success rate (>99%) and HWE (P>0.0001). There were no duplicate errors, and the SNPs were in Hardy-Weinberg equilibrium (P>0.05), within all included studies.

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Statistical Analysis

Logistic regression was used to test for an association of the 3 genotypes in an additive model with PAD. Linear regression was performed to test for a similar association with log-transformed ABI. Meta-analysis was performed using an inverse variance weighting method as implemented using the Stata “metan” command, and heterogeneity was tested using the Q statistic and I² metric.

ABI measures were log-transformed to correct for a modest nonnormal distribution. MI was classified in a binary variable as the presence of a definite or possible MI event. Pack-years smoking exposure was grouped into a dichotomized variable at 20 pack-years because of its highly skewed distribution.

Associations with phenotypes indicative of PAD were adjusted in a 3-tier design. First, we adjusted our analyses for age and sex. Associations were then estimated after participants with definite or possible MI at baseline or within the 6-year follow-up period were removed from the analysis. Finally, we additionally adjusted for known atherosclerotic risk factors: diabetes mellitus, smoking status, hypertension, and hypercholesterolemia, and hypertension.22,23 All analyses were conducted using StataSE 9.0.

Results

Summary statistics of the individual studies are detailed in Table 1. The mean age of genotyped participants ranged from 73.7 to 77.6 years, and an average 49.2% were women across the 3 studies. The prevalence of PAD was 13.3%, 9.4%, and 7.0% for the InCHIANTI, Health ABC, and BLSA studies, respectively, with an average 9.2% of participants with a reported history of MI across the 3 populations.

For the C allele at rs1333049, across the 3 studies, we found a per-allele difference of −0.020 ABI units (95% CI, −0.03 to −0.01; \( P = 1.1 \times 10^{-5} \); Table 2). Similarly, by combining estimates across the 3 studies, we found that each additional copy of the C allele at rs1333049 increased the risk of PAD (odds ratio [OR], 1.34; 95% CI, 1.11 to 1.62; \( P = 0.002 \); Table 2) when compared with the G allele homozygotes.

We next investigated whether the association with PAD was independent of the expected association with history of MI. After removing baseline and incident MI cases (Table 2), rs1333049 remained significantly associated with both a lower ABI (odds ratio [OR], 1.34; 95% CI, 1.11 to 1.62; \( P = 0.002 \); Table 2) when compared with the G allele homozygotes.

These associations remained after adjusting for known atherosclerotic risk factors (Table 2), including the presence of diabetes mellitus, hypercholesterolemia, hypertension, and smoking status.

It has been suggested that because ABI is a blood pressure ratio designed to detect obstruction to flow and that blood flow does not start to drop until an ABI of 0.9, individuals in...
the range of 1.0 to 1.3 may not be informative. To assess the relationship of the variant with the lower ranges of continuous ABI, a sensitivity analysis was performed on those individuals with an ABI \( \leq 1.0 \) (Table 3). The variant was associated with a per C allele change in ABI of \(-0.028\) (95% CI, \(-0.05\) to \(-0.01\); \(P=0.014\)), following adjustment for diagnosed MI and known atherosclerotic risk factors.

In addition, we investigated whether the relationship between PAD and rs1333049 was similar in other ethnic groups, using the black population of Health ABC. Within 1070 subjects, the associations between rs1333049 and both ABI and PAD were nonsignificant (\(β=−0.0006\); 95% CI, \(-0.02\) to \(-0.02\); \(P=0.95\); and OR, 1.06; 95% CI, 0.83 to 1.33; \(P=0.653\), respectively). The association remained nonsignificant when removing MI cases, adjusting for atherosclerotic risk factors, and when restricting analysis to those individuals with an ABI \( \leq 1.0 \).

Finally, the contribution of the variant to incident PAD in InCHIANTI and Health ABC was assessed on 99 and 74 incident cases, respectively. These incident cases had a minor allele frequency of 0.51, which was slightly lower than that of the baseline PAD cases. The association of the C allele at rs1333049 with an increased risk of incident PAD across the 2 white populations did not reach significance (OR, 1.09; 95% CI, 0.87 to 1.38; \(P=0.460\)) in this small subsample. Similarly, the association was nonsignificant in the black population of Health ABC (OR, 0.95; 95% CI, 0.65 to 1.38; \(P=0.787\)).

### Sensitivity Analysis

The associations between ABI and PAD do seem weaker in BLSA than in the other 2 larger studies. However, the 95% CIs around the estimated BLSA effect sizes encompass that of the InCHIANTI and Health ABC estimates, and a formal testing for heterogeneity in the meta-analysis showed no evidence for heterogeneity between the samples for ABI or PAD (\(P=0.287\), \(I^2=20\%\) and \(P=0.278\), \(I^2=22\%\), respectively), leading to the selection of a fixed-effects model (which makes the assumption that the true effect of the risk allele is the same in each study). Huedo-Medina et al.\(^{24}\) reported that heterogeneity statistics, both the \(I^2\) and the Q statistic, suffer from low power when the number of studies included is small. To address the possibility of some heterogeneity between studies, we performed a sensitivity analysis

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**Table 2. Per Risk Allele (C) Linear Regression-Based Associations Between rs1333049 Status and ABI, Plus Logistic Regression-Based Associations With Peripheral Arterial Disease**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Study</th>
<th>Sample, N</th>
<th>( β ) (95% CI)</th>
<th>( P )</th>
<th>( β ) (95% CI)</th>
<th>( P )</th>
<th>( β ) (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI, ABI Units</td>
<td>InChianti</td>
<td>804</td>
<td>(-0.024) ((-0.04) to (-0.005))</td>
<td>0.012</td>
<td>(-0.020) ((-0.04) to (-0.00))</td>
<td>0.036</td>
<td>(-0.019) ((-0.04) to (-0.001))</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>Health ABC</td>
<td>1589</td>
<td>(-0.022) ((-0.03) to (-0.01))</td>
<td>(1.6\times10^{-4})</td>
<td>(-0.020) ((-0.03) to (-0.01))</td>
<td>(8.1\times10^{-4})</td>
<td>(-0.017) ((-0.03) to (-0.006))</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>BLSA‡</td>
<td>257</td>
<td>(-0.002) ((-0.03) to (-0.02))</td>
<td>0.867</td>
<td>0.003 (0.02 to 0.03)</td>
<td>0.842</td>
<td>(-0.007) (0.03 to 0.03)</td>
<td>0.958</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis</td>
<td>2630</td>
<td>(-0.020) ((-0.03) to (-0.01))</td>
<td>(1.1\times10^{-3})</td>
<td>(-0.017) (0.03 to 0.01)</td>
<td>(1.3\times10^{-4})</td>
<td>(-0.016) (0.03 to 0.01)</td>
<td>(1.7\times10^{-4})</td>
</tr>
</tbody>
</table>

**Table 3. Per Risk Allele (C) Linear Regression-Based Associations Between rs1333049 Status and ABI\(\leq1.0\)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Study</th>
<th>Sample, N</th>
<th>( β ) (95% CI)</th>
<th>( P )</th>
<th>( β ) (95% CI)</th>
<th>( P )</th>
<th>( β ) (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI (\leq1.0), ABI Units</td>
<td>InChianti</td>
<td>342</td>
<td>(-0.023) ((-0.05) to (-0.008))</td>
<td>0.151</td>
<td>(-0.017) ((-0.05) to 0.02)</td>
<td>0.297</td>
<td>(-0.019) ((-0.05) to 0.01)</td>
<td>0.248</td>
</tr>
<tr>
<td></td>
<td>Health ABC</td>
<td>306</td>
<td>(-0.051) ((-0.08) to (-0.02))</td>
<td>0.002</td>
<td>(-0.046) ((-0.08) to (-0.02))</td>
<td>0.003</td>
<td>(-0.037) ((-0.07) to (-0.01))</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>BLSA‡</td>
<td>25</td>
<td>(-0.041) ((-0.18) to 0.10)</td>
<td>0.540</td>
<td>(-0.042) ((-0.19) to 0.11)</td>
<td>0.576</td>
<td>(-0.007) ((-0.19) to 0.17)</td>
<td>0.931</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis</td>
<td>673</td>
<td>(-0.037) ((-0.06) to (-0.01))</td>
<td>(4.3\times10^{-4})</td>
<td>(-0.033) ((-0.06) to (-0.01))</td>
<td>0.003</td>
<td>(-0.028) ((-0.05) to (-0.01))</td>
<td>0.014</td>
</tr>
</tbody>
</table>
on both ABI and PAD meta-analyses, using random-effects models, which resulted in only the ABI estimates altered to a small degree ($\beta = -0.019; \text{95\% CI, } -0.03$ to $0.008; P = 2.3 \times 10^{-4}$). Finally, we estimated the effect of rs1333049 on ABI and PAD by following exclusion of the BLSA study, which resulted in very similar effect sizes because of BLSA’s small population size, and thus its relatively small contribution to the meta-analysis. After removal of MI cases from the InCHIANTI and Health ABC samples and adjustment for atherosclerotic risk factors, the rs1333049 C allele remains significantly associated with lower ABI and increased risk of PAD ($\beta = -0.018; \text{95\% CI, } -0.03$ to $0.01; P = 1.5 \times 10^{-4}$; and OR, 1.35; 95% CI, 1.09 to 1.67; $P = 0.007$, respectively).

Alternative approaches to testing whether the reported associations with ABI and PAD were independent of MI diagnosis were considered. These included adding both MI history as a covariate and an interaction term between MI history and genotype into the regression models. Neither adjustment altered the reported estimates (data not shown).

We performed sensitivity tests to check the validity and suitability of the additive model of inheritance. First, we performed a likelihood ratio test of the 1-df additive model against the genotypic 2-df model and found no deviation from additivity in the 3 populations. In addition, we tested both dominant and recessive models of inheritance for the variant against both ABI and PAD and found that neither provided a better model of fit to that of the additive model across the 3 datasets.

**Discussion**

The 9p21 SNP rs1333049 has been shown to be associated with MI and major arterial aneurysms. In a previous study, the relationship between this marker and PAD was also explored, resulting in an association with an odds ratio of 1.14,6 which disappeared when removing those with histories of MI, suggesting a lack of independent effect on the peripheral arterial system. In this study, we examined the association of the rs1333049 polymorphism with peripheral arterial function in older populations. We found that the C allele, present in 49% to 54% of the participants in our meta-analysis, was associated with both a lower ABI and an increased prevalence of PAD. Removing baseline and incident MI cases had very little effect on the association, indicating that the association with PAD is statistically independent of clinical MI in older subjects. In addition, the effect of the C allele of the variant increased when the analysis was restricted to those participants with an ABI $\geq 1.0$.

PAD is a common disease, with an estimated 27 million individuals affected in North America and Europe in 2007.25 Up to 50% of patients experience both coronary artery disease and PAD concomitantly26,27 because atherosclerosis is involved in both conditions. A genome-wide association study of subclinical atherosclerotic measures had previously found no evidence for an association with continuous ABI and the $CDKN2a\alpha2b$ locus, but their analysis was based on 984 young to middle-aged individuals,28 suggesting a lack of power to detect the small effect size expected. By using a sample of 2630 older individuals, we have shown that the rs1333049 variant, known to be associated with MI and major vessel aneurysms, is also associated with a higher prevalence of PAD, independent of diagnosed MI. This is also true for the association with lower ABI values, which suggests an effect on the full range of PAD, including the milder forms that may later progress to more serious disease.29 Unfortunately, the available data do not allow a detailed analysis of the time sequence of onsets of MI and PAD. Future work could focus on this, in sufficiently large cohorts with multiple waves of data.

Our analysis also suggests that rs1333049 can be considered a risk factor for PAD independent of common atherosclerotic risks, such as diabetes mellitus, smoking, hypercholesterolemia, and hypertension. In addition, the C allele increased the risk of PAD in the small number of incident cases from the follow-up ABI measurements of InCHIANTI and Health ABC, although this failed to reach significance.

The rs1333049 SNP is distal to the cyclin-dependent kinase inhibitor genes $CDKN2a$ and $CDKN2b$ locus, which code for p16 and p15, respectively, closely related proteins involved in cell cycle control and cellular senescence. In a range of mice and human tissues, p16 expression increases with age.30,31 Experimental upregulation of p16 in mice promotes aging-related changes in a range of cell types, resulting in cell senescence and decreased tissue regeneration.32–35 Although evidence for the mechanism of action of the 9p21 polymorphism in human MI is limited, it has been suggested that cellular senescence plays a critical role in vascular pathophysiology and atherosclerosis (reviewed in reference 36). Accumulation of vascular senescent cells could lead to a reduction in regeneration and repair capabilities, leading to atherosclerotic damage. Lower levels and poorer quality of circulating endothelial progenitor cells have been reported in preliminary data on patients with PAD,37,38 which are implicated as determinants of subclinical atherosclerosis.39 Although it should be noted that recent work by Samani et al40 has found no association between early atherosclerotic markers in 1295 middle-aged to elderly individuals, there is evidence that the downstream ANRIL locus, which is partially overlapped by the coronary artery disease risk haplotype, is expressed in a number of cells and tissues affected by atherosclerosis,41 suggesting a potential role in heart disease, despite the unknown function of its noncoding RNA transcript.

Furthermore, it is interesting to note that other common (but independent) genetic variants near the p16/p15 locus have been associated with other aging phenotypes, including type II diabetes2,42,43 and impaired physical functioning in elderly individuals.44

In our analysis, we also examined SNP phenotype associations in black origin respondents from the Health ABC study. In this population, rs1333049 SNP was found not to be associated with ABI or PAD in any of the analysis models performed. This is not surprising because the rs1333049 SNP is not associated with MI in this population or in blacks from the ADVANCE study.45 This lack of association may be caused by a different linkage disequilibrium structure in the locus of interest in non-European individuals, making this SNP a poor marker of the biologically relevant locus. In addition, it is possible that the effect size is much smaller in subjects of African descent than that seen in populations of


CLINICAL PERSPECTIVE

A genetic variant at chromosome 9p21 (present in 46% of people of Caucasian origin) is strongly associated with myocardial infarction. Heterozygote carriers are at 28% increased risk. As peripheral arterial disease (PAD) often co-occurs with myocardial infarction, we examined associations between the risk allele and both Ankle-Brachial Index and PAD in 2630 white subjects (mean age, 76.4 years) from 3 cohorts. The relevant risk allele (C allele at rs1333049) was associated with lower mean Ankle-Brachial Index measures and with increased prevalence of PAD (odds ratio per risk allele, 1.34; 95% CI, 1.12 to 1.62; P = 0.002). CC homozygotes may be at 68% increased risk of PAD compared with TT homozygotes. The biological mechanisms involved are believed to relate to endothelial cell repair and, in our analyses, were unrelated to known atherosclerosis risk factors; adjustment for diabetes mellitus, smoking, hypercholesterolemia, and hypertension did not attenuate the association of the risk allele with Ankle-Brachial Index or prevalence of PAD. Our finding adds to the body of evidence implicating the chromosome 9p21 variant in vascular disease.
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