Association of Chromosome 9p21.3 with Disease Location, Including the Number of Diseased Vessels, but not with Greater Burden of Coronary Disease

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Abstract

Introduction: Single nucleotide polymorphisms (SNPs) at chromosome 9p21.3 do not influence myocardial infarction, but their role in coronary artery disease (CAD) progression, burden, and outcomes is controversial. This study evaluated whether rs1333049 impacts CAD burden.

Methods: Non-diabetic CAD patients enrolled in the Intermountain Heart Collaborative Study (N=1,757) were evaluated for association of rs1333049 with the Duke CAD Index (primary endpoint) and other CAD measures. Multivariable regression adjusted for potential confounders. Statistical significance of secondary endpoints was corrected for multiple comparisons.

Results: No association of rs1333049 with Duke CAD Index was found for 0, 1, and 2 C alleles: 42.4 ± 16.1, 44.0 ± 17.4, 47.4 ± 17.6, respectively (p-trend=0.12, adjusted p-trend=0.11). It also did not predict the number of CAD lesions (adjusted p-trend=0.11) or the maximum CAD stenosis (adjusted p-trend=0.89). The SNP did predict the number of major vessels with proximal or left main lesions (0.56 ± 0.69, 0.62 ± 0.74, and 0.71 ± 0.77 for 0, 1, and 2 C alleles, respectively; adjusted p-trend=0.0056) and another location parameter: the number of major vessels with at least one significant stenosis (p-trend=0.0017). Rs1333049 was not associated with future events, but association with CAD presence was confirmed (p-trend=0.0001).

Conclusion: Rs1333049 was not associated with CAD burden, lesion number or severity, or cardiovascular events. The SNP did strongly predict CAD presence and was associated with lesion location. These findings reaffirm that a primary role of 9p21.3 may be related to the presence of CAD rather than the clinical severity of obstructive lesions. Because follow-up angiography was not systematically performed, CAD progression could not be evaluated.

Keywords: Genetic association ; Genetic variation; Coronary heart disease; CAD progression; CAD burden

Introduction

Coronary artery disease (CAD) is the leading cause of mortality in low- and high-income countries, [1] and a core set of environmental and lifestyle factors influence CAD risk [2]. A genetic component in CAD has long been known, [3] which was strengthened by contemporary family- [4,5] and population-based studies [6-8]. A 58 kilobase region on chromosome 9p21.3 was shown in 2007 to contain common single nucleotide polymorphisms (SNPs) that are associated with CAD risk [6-8]. These SNPs are located at CDKN2BAS, an antisense noncoding RNA (i.e., ANRIL) [9]. Deletion of an orthologous region in a murine model showed a higher mortality rate during both development and adult life than normal mice [10]. That mortality risk was linked to primary cultures of smooth muscle cells having markedly increased proliferation, which may indicate decreased expression of Cdkn1a and Cdkn2b (products of the two closest genes), [10] or may indicate ANRIL regulation of some unknown gene or pathway [11].

In humans, 9p21.3 SNPs are associated with various complex, overlapping coronary heart disease (CHD) phenotypes [6-8,12-16]. CHD is a complex disease that may evolve through several distinct stages, including disease initiation, progression to obstructive lesions, and (for some but not all patients) acute coronary syndrome precipitation, each of which may involve distinct pathophysiological mechanisms [15]. A refined understanding of the role of 9p21.3 in CHD requires an analysis of its impact on each of these stages.
including CAD severity, extent, and location, requires prospective testing. We hypothesized that rs1333049 is associated with the Duke CAD Index, a measure of the burden of CAD based on the number, severity, and location of all coronary lesions [22].

Materials and Methods

Objectives

The primary study objective was to assess the association of the 9p21.3 rs1333049 SNP in patients with the burden of CAD as measured by the Duke CAD Index in non-diabetic patients with an early onset of angiographically-defined CAD. Other objectives included: to analyze the significance of 9p21.3 sequence variation on CAD extent and to evaluate the 9p21.3 association with CHD events. Analyses were also performed: 1) among diabetic patients and 2) by including patients free from clinical CAD together with the CAD patients.

Study population

Patients ≥ 18 years of age were enrolled if they underwent coronary angiography within the Utah-based Intermountain Healthcare system and provided written, informed consent to participate in the prospective, observational cardiac catheterization registry of the Intermountain Heart Collaborative Study. Patients were excluded from the study if they were of non-Caucasian ancestry, did not undergo coronary angiography during their catheterization procedure, or the genotyping for rs1333049 was unsuccessful. The study protocol was approved by the Intermountain Healthcare Institutional Review Board.

Attending cardiologists blinded to genotype provided lesion characteristics, including location and degree of stenosis. Patients were categorized as free of CAD (i.e., no lesions or only mild luminal irregularities), moderate CAD (i.e., most severe lesion 10%-<70% stenosis), or significant CAD (i.e., ≥1 lesion of ≥70% stenosis and Duke CAD Index ≥19). For the primary analyses, only patients with significant CAD and free from diabetes were evaluated. Diabetes was defined as fasting blood glucose >125 mg/dL or use of anti-diabetic medication. Due to the limited number of patients with other ancestral histories, only Caucasians were evaluated.

The primary endpoint was the Duke CAD Index, a measure that assesses the overall burden (extent and severity) of CAD [22]. The study sample included male patients ≥60 years of age and females ≥65 years who were genotyped for a candidate gene study or a validation of a genome-wide association study [20,23]. Secondary endpoints were the total number of lesions, the maximum lesion stenosis, and lesion locations (a total of 8 secondary endpoints) [24].

Tertiary endpoints included the number of major vessels with ≥1 clinically-significant lesion and, to compare to the analysis of Dandona et al. [16] the genotypic distribution in 3-vessel disease was evaluated against the combination of 1- plus 2-vessel disease, along with CHD event endpoints that included survival (i.e., free from all-cause death), MI, MI-free survival, readmission for heart failure (HF), and stroke. Deaths were determined from hospital records, health department records, and US Social Security records, and patients not listed as deceased were considered to be alive. Other events were queried by ICD-9 code and clinical laboratory data from electronic medical records. Non-diabetic patients free from clinically-significant CAD (with mild CAD or no CAD) were evaluated in tertiary analyses to validate that 9p21.3 is a strong differentiator of the presence of CAD. Diabetic patients were evaluated for tertiary comparison to validate that 9p21.3 is less risk-discriminating in this subpopulation [16] and other comparisons evaluated endpoints in substrata defined by other cardiac risk factors.

Study variables

Demographic, health history, and vital signs at entry were obtained from physician and hospital records to adjust SNP associations by multivariable regression. These included age, sex, body mass index (BMI), hypertension history, hyperlipidemia, diabetes, smoking, and family history of early CHD. BMI was defined as patient weight (kg) divided by the square of the height (m²), measured at the index angiography. Hypertension was reported if the systolic blood pressure was ≥140 mm Hg, the diastolic blood pressure ≥90 mm Hg, or if there was use of anti-hypertensive drugs. Hyperlipidemia was defined as a total cholesterol level ≥200 mg/dL, a low-density lipoprotein level ≥130 mg/dL, or use of cholesterol-lowering medication. Smoking included active or previous (>10 pack-years) tobacco use. Family history of early CHD was self-reported when first-degree relatives had experienced cardiovascular death, MI, or coronary revascularization at age ≤65 years.

For Cox regression, covariables included MI history and stroke history—both defined by ICD-9 codes from electronic medical records. Renal failure was physician-reported for creatinine >2.0 mg/dL or prior clinical diagnosis. HF was defined as left ventricular ejection fraction (determined by ventriculography or echocardiography) ≤40% or a normal ejection fraction with a clinical diagnosis. Patient presentation at the index admission (i.e., stable or non-anginal status, unstable angina, and acute MI), number of diseased vessels (i.e., 1, 2, or 3), the type of intervention at baseline (i.e., medical only, percutaneous coronary intervention, or bypass surgery), and discharge medications (i.e., statins, beta-blockers, ACE inhibitors, diuretics) were also included.

Rs1333049 was genotyped using the Sequenom iPLEX MassARRAY platform (Sequenom Inc., San Diego, CA).

Statistical considerations

For baseline characteristics, variables are summarized as means ± standard deviations (SD) for continuous variables and proportions for discrete variables. Comparisons across genotypes used an additive genetic model in analysis of variance for continuous variables or by the chi-square test for discrete variables.

The primary analysis of the association of rs1333049 with CAD Index utilized analysis of variance. Multivariable adjustments were made for age, sex, BMI, hypertension, hyperlipidemia, smoking, and family history of early CHD. The same methods were used for the number of CAD lesions, the maximum stenosis, and the number of major vessels with proximal and left main (LM) lesions. Analyses for 3-vessel CAD vs. 1+2-vessel CAD and for individual lesion locations (i.e., ostial, LM, proximal right coronary [RCA], proximal left anterior descending [LAD], or proximal left circumflex [LCx]), the Armitage test of trend in a 3x2 chi-square test was used, with multivariable adjustments made in logistic regression. For SNP associations with 3- vs. 2- vs. 1-vessel CAD, the test of trend in a 3x3 chi-square test was used.

For CHD events, Cox regression was employed for univariable and multivariable analyses of rs1333049 in association with all-cause mortality, MI, death/MI, HF readmission, and stroke. Multivariable adjustments were made for age, sex, BMI, hypertension, hyperlipidemia, smoking, family history of early CHD, MI history, stroke history, presentation, number of diseased coronary arteries, baseline intervention, and discharge medications.
A power calculation was performed to determine whether the current study could reasonably be expected to replicate prior findings by Dandona and colleagues [16]. Using the present study’s CAD patient sample size (N=1,757) and Dandona’s effect sizes [16], it was found that this study had >99% power to detect a difference for 3-vessel vs. 1+2-vessel disease, assuming a two-sided test and α=0.05. An estimate was also made for the power to detect by-genotype differences in the CAD Index using this study’s CAD patient sample size and previously published secondary endpoint data [16], which showed that this study had >99% power to detect a genotype difference for CAD Index.

A probability value of 0.05 or less was accepted as statistically significant for the primary CAD Index endpoint, with secondary analyses requiring Bonferroni correction for nine tests (one primary and eight secondary) at p≤0.0056. Tertiary analyses were either confirmatory of findings from other studies (requiring p<0.05 for validation) or new results that are hypothesis-generating. All statistical calculations were made using SPSS v15.0 (SPSS, Chicago, IL).

Results

Baseline characteristics

Among non-diabetic CAD patients, age averaged 55 ± 8 years and 22% were female. Baseline characteristics were similar across the rs1333049 genotypes (Table 1).

CAD Index

Association of rs1333049 with the primary Duke CAD Index endpoint was not significant in univariable evaluation for GG, GC, and CC genotypes (p-trend=0.12). This result remained after multivariable analysis (p-trend=0.11). Some potential effect of the SNP on CAD burden was seen qualitatively (Figure 1), with average CAD Index ranging from 42 for GG to 47 for CC genotype (Table 2).

Compared by rs1333049 genotype, the total number of CAD lesions (regardless of location) had p-trend=0.042 in univariable analysis, which did not achieve the multiple comparisons corrected threshold for significance (p ≤ 0.0056) of secondary endpoints and had p>0.05 in multivariable analysis (Table 2). The average most severe stenosis was not different across genotype categories in univariable (p-trend=0.44) or multivariable analyses (Table 2). The location of CAD lesions had trends across genotypes for the proximal RCA (Table 2), but not other proximal or ostial sites (although statistical power may be a problem). Combining all of the location measures as a total count of vessels with proximal or LM lesions had significantly higher averages for variant C allele carriers (p-trend=0.0023), and this remained after adjustment (Table 2).

Number of diseased vessels

The number (i.e., 1, 2, or 3) of significantly-diseased coronary vessels differed by rs1333049 genotype (p-trend=0.0017, Table 3). Comparing 3-vessel CAD to the combination of 1+2-vessel disease yielded p-trend=0.00033 in univariable analysis (multivariable: p-trend=0.00031, OR=1.37 per C allele, 95% confidence interval [CI]=1.15, 1.63).

Additional analyses

Subanalysis of the association of rs1333049 genotypes with CAD Index among strata defined by the number of diseased vessels showed that no differences existed. Among genotypes GG, GC, and CC, respectively, CAD Index averaged 69.4 ± 8.9, 70.2 ± 8.3, 69.7 ± 9.2 for 3-vessel CAD (n=349, p-trend=0.93), 47.8 ± 9.9, 48.1 ± 12.5, 47.0 ± 9.4 for 2-vessel CAD (n=471, p-trend=0.57), and 31.7 ± 7.1, 31.8 ± 8.0, 31.3 ± 7.0 for 1-vessel disease (n=937, p-trend=0.57).

Survival

Across rs1333049 genotypes, a paradoxical trend toward better survival was observed (adjusted p-trend=0.08, HR=0.86 per C allele, CI=0.73, 1.02). No differences were found for incident MI (p-trend=0.75, HR=0.98 per C allele), MI-free survival (p-trend=0.38, HR=0.95 per C allele), HF readmission (p-trend=0.23, HR=0.85 per C allele), or stroke (p-trend=0.86, HR=1.03 per C allele). Among only patients with a baseline MI, rs1333049 did not predict survival (p-trend=0.12, HR=1.25 per C allele), incident MI (p-trend=0.84, HR=0.98 per C allele), or MI-free survival (p-trend=0.55, HR=1.06 per C allele).
Addition of 0-vessel disease

In contrast to the CAD-only analyses above, when patients with 0-vessel disease (n=1,606) were included in the analysis (total N=3,363), mean CAD Index achieved very high significance: 20.5 ± 23.9, 22.2 ± 24.8, and 27.1 ± 26.0 for GG, GC, and CC, respectively (p-trend=6.6 x 10^-6, adjusted p-trend=1.7 x 10^-5). Similarly, when considering the number of diseased vessels, the association was substantially strengthened when 0-vessel (mild/no-CAD) patients were included (p-trend=9.0 x 10^-5, Table 3). Further evaluation of CAD endpoints showed that the strongest differences were between the presence and absence of CAD (Table 4).

Other populations

Further analyses were performed in diabetics with CAD (Supplemental Results and Table S1) and substrata defined by other cardiovascular risk factors (Supplemental Results, Table S2, Table S3).

Discussion

In contrast to an earlier report [16], the 9p21.3 variant rs1333049, a strong and widely-replicated predictor of the presence of obstructive CAD, did not predict disease burden/severity (as measured by the Duke CAD Index) in non-diabetic patients with early, angiographically-defined CAD. It also did not predict the number of clinically-significant CAD lesions or the lesion maximum stenosis.

Two CAD lesion location findings were significant, though, after multiple comparisons correction. The number of coronary vessels measures how many major vessels have at least one clinically-significant lesion and this was statistically different across rs1333049 genotypes after correction for multiple comparisons. This finding validates the presence of the small genotype difference noted in a prior report [16], although the number of diseased vessels was reported previously to not be heritable [24]. Secondly, the sum of proximal and LM lesions differed across genotypes after correction for multiple comparisons, an intriguing and potentially important finding. Both LM disease and proximal disease were shown previously to be heritable [24].

In evaluating the association of rs1333049 with the presence of CAD, the C allele was replicated as a strong predictor of CAD, as expected [8]. Thus this study reafirms a major impact of 9p21.3 on clinical CAD prevalence. Together, this study’s findings suggest that the major 9p21.3 impact is in promoting the presence of atherosclerotic lesions and possibly the location, but not CAD burden or severity since the CAD Index, number of lesions, and maximum stenosis were not predicted by rs1333049.

While not elucidating underlying biological mechanisms of 9p21.3-related risk, these observations nevertheless can suggest and limit the mechanistic possibilities. Some have suggested that 9p21.3 influences CAD progression [16,25], although those studies did not measure the change in lesions over time. While progression is one possible explanation of the association of 9p21.3 with the number of diseased vessels [16,25], the data instead may have arisen due to other mechanisms. For example, the 9p21.3 association with number of diseased vessels but lack of association with the number of lesions may indicate that 9p21.3 acts independently on each coronary vessel, resulting in a greater spread of lesions across the major arteries. This is reasonable since a coronary lesion in one vessel occurs independently of what is occurring in the other major vessels.

Some of the debate regarding whether an association of 9p21.3 with 3-vessel disease indicates CAD burden may arise because of the heterogeneity of the CAD measure being studied. The number of diseased vessels is counted as 1, 2, or 3 major arteries with significant disease, encapsulating data from within each artery in a relatively simple but robust measure of disease burden that applies well clinically for cardiovascular event risk prediction. Comparison across patients who have 3-vessel disease (or 1- or 2-vessel disease), though, shows that the metric of the “number of diseased vessels” is all-inclusive, including the patient with a total of 3 simple focal proximal lesions (one in each of the 3 arteries), the patient with more than a dozen diffuse clinically-

### Table 2: Average Duke CAD Index (mean ± SD) and the means or proportions of its component CAD burden measures by rs1333049 among non-diabetics with CAD (N=1,757).

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>0 variants</th>
<th>1 variant</th>
<th>2 variants</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DukeCAD Index</td>
<td>42.4 ± 16.1</td>
<td>44.0 ± 17.4</td>
<td>47.4 ± 17.6</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Secondary: CAD Index Components</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Lesions</td>
<td>2.5 ± 1.9</td>
<td>2.7 ± 2.1</td>
<td>2.8 ± 2.0</td>
<td>0.11</td>
</tr>
<tr>
<td>Maximum Stenosis</td>
<td>95.2 ± 7.5</td>
<td>95.3 ± 7.6</td>
<td>95.6 ± 7.2</td>
<td>0.89</td>
</tr>
<tr>
<td>Number of Proximal+LM Lesions</td>
<td>0.56 ± 0.69</td>
<td>0.62 ± 0.74</td>
<td>0.71 ± 0.77</td>
<td>0.0055†</td>
</tr>
<tr>
<td>Ostial Lesions</td>
<td>2.50%</td>
<td>4.20%</td>
<td>4.50%</td>
<td>0.17</td>
</tr>
<tr>
<td>Left Main Lesions</td>
<td>2.00%</td>
<td>4.00%</td>
<td>3.90%</td>
<td>0.18</td>
</tr>
<tr>
<td>Proximal RCA Lesions</td>
<td>25.10%</td>
<td>24.70%</td>
<td>32.30%</td>
<td>0.01</td>
</tr>
<tr>
<td>Proximal LAD Lesions</td>
<td>21.40%</td>
<td>25.70%</td>
<td>24.30%</td>
<td>0.37</td>
</tr>
<tr>
<td>Proximal LCx Lesions</td>
<td>7.30%</td>
<td>8.00%</td>
<td>10.40%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Adjusted in analysis of variance or logistic regression for age, sex, BMI, hypertension, hyperlipidemia, smoking, and family history of early CHD; †Secondary endpoint significant after correction for multiple comparisons (p ≤ 0.0056 / 0.05 / 9 tests).

### Table 3: Genotype distributions for non-diabetic patients among CAD patients stratified by 3-, 2-, and 1-vessel CAD and among all CAD and no-CAD patients by 3-, 2-, 1-, and 0-vessel disease.

<table>
<thead>
<tr>
<th>Comparision</th>
<th>Adjusted* OR (95% CI)</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD (1-, 2-, and 3-vessel)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs. mild/no-CAD (0-vessel)</td>
<td>1.28 (1.12, 1.46)</td>
<td>2.4 x 10^-5</td>
</tr>
<tr>
<td>vs. no-CAD†</td>
<td>1.26 (1.11, 1.44)</td>
<td>5.1 x 10^-5</td>
</tr>
<tr>
<td>3-vessel CAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs. 2-vessel CAD</td>
<td>1.32 (1.08, 1.61)</td>
<td>0.006</td>
</tr>
<tr>
<td>vs. 1-vessel CAD</td>
<td>1.38 (1.15, 1.65)</td>
<td>4.5 x 10^-5</td>
</tr>
<tr>
<td>vs. 0-vessel CAD (mild/no)</td>
<td>1.68 (1.36, 2.06)</td>
<td>9.5 x 10^-7</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, BMI, hypertension, hyperlipidemia, smoking, and family history of early CHD; †Mild CAD (n=152) was excluded from this analysis.

### Table 4: Comparison of odds ratios per risk-associated C allele at rs1333049 for non-diabetics by CAD status and by number of diseased vessels.

<table>
<thead>
<tr>
<th>Comparison Adjusted* OR (95% CI)</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-vessel CAD (mild/no)</td>
<td></td>
</tr>
<tr>
<td>vs. mild/no-CAD (0-vessel)</td>
<td>1.28 (1.12, 1.46)</td>
</tr>
<tr>
<td>vs. no-CAD†</td>
<td>1.26 (1.11, 1.44)</td>
</tr>
<tr>
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</tr>
</tbody>
</table>
significant lesions spread throughout the coronary tree, and everything in between. In an attempt to evaluate the issues underlying the number of diseased vessels, the present study found that the number of lesions, the clinical severity of lesions, and the burden of lesions (CAD Index) were not associated with 9p21.3.

Connecting 9p21.3 to CAD progression requires information about the pre-disease state so that the change over time can be measured [26]. Unfortunately, due to the clinical indications for CAD diagnosis, risks associated with coronary imaging, and the differential treatment plans used as standard care when patients have more vs. less severe CAD, it is not possible to identify an unbiased human population in which to study the natural history of CAD progression [27], thus some claims that 9p21 predicts CAD progression are erroneous [16,25]. Certainly the pathophysiological implications of the 9p21.3 locus require further study.

For event-free survival, the literature is less clear on the impact of 9p21.3. One prior study indicated no association with mortality [19], whereas the GRACE registry recently reported an increased risk of recurrent MI and death/MI among patients carrying a 9p21.3 variant after an acute coronary syndrome [28]. In the present study, a trend to lower risk of mortality was predicted by rs1333049 (similar to the protective effect of the risk allele for MI noted in an earlier study [17]). The findings herein of a 9p21.3 association with CAD onset but not with subsequently higher mortality risk is supported by other recent literature reports [19,29].

When analysis was restricted to patients with baseline MI, as per the GRACE study [28], the risk of mortality was 28-29% higher per C allele in both the initial and replication samples, which was non-significant but may indicate a hypothesis for further investigation. However, the GRACE report abandoned the de facto additive genetic model in favor of a dominant model and still lost statistical significance after multivariable adjustment [28]. Further, the GRACE model did not adjust for CAD severity or number of diseased vessels and may, thus, have been confounded. Similar concerns exist for a study of mortality following bypass surgery, including the use of a recessive genetic model instead of the additive model. Additional evaluations of post-MI 9p21.3-associations with survival are required.

Limitations

This study may be limited by the various challenges associated with observational cohort designs, including unmeasured confounding variables. Statistical adjustments were made, however, for the common predictors of CAD and, further, studies of 9p21 have shown that genetic variants such as rs1333049 are not associated with other cardiac risk factors, thus confounding issues are unlikely to have biased the study. Physician selection of which patients will undergo coronary angiography is another potential observational limitation, thus these results may not apply to the general population. Finally, the exclusion of non-Caucasians may limit the generalizability of the results; therefore further evaluation of this study’s hypotheses and findings is indicated for other racial groups.

Conclusion

Using a large population idealized for the study of the common CAD phenotype (i.e., early-onset disease in non-diabetics) and a preferred genotype (rs1333049) [16], this study found no association of 9p21.3 with CAD burden, lesion number or severity, or cardiovascular events. The study did reconfirm a strong association of 9p21.3 variation with CAD presence and, despite conservative correction for multiple comparisons, associations of rs1333049 with the location of CAD lesions was found, both for proximal + LM location (which are heritable [24]) and for location of at least one significant CAD lesion in a greater number of major coronary vessels. Subgroup analyses suggested some potential associations, but these should be prospectively tested. These findings reaffirm that the primary role of 9p21.3 may be related to the presence of CAD rather than the clinical severity of obstructive lesions. These results provide little information about the progression of CAD since only single measurements were made, although further longitudinal study of the role of 9p21.3 in CAD progression from one time to another within the same patient is indicated.

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References


