Association Between 9p21 Genomic Markers and Heart Disease
A Meta-analysis

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Context  Associations between chromosome 9p21 single-nucleotide polymorphisms (SNPs) and heart disease have been reported and replicated. If testing improves risk assessments using traditional factors, it may provide opportunities to improve public health.

Objectives  To perform a targeted systematic review of published literature for effect size, heterogeneity, publication bias, and strength of evidence and to consider whether testing might provide clinical utility.

Data Sources  Electronic search via HuGE Navigator through January 2009 and review of reference lists from included articles.

Study Selection  English-language articles that tested for 9p21 SNPs with coronary heart/artery disease or myocardial infarction as primary outcomes. Included articles also provided race, numbers of participants, and data to compute an odds ratio (OR). Articles were excluded if reporting only intermediate outcomes (eg, atherosclerosis) or if all participants had existing disease. Twenty-five articles were initially identified and 16 were included. A follow-up search identified 6 additional articles.

Data Extraction  Independent extraction was performed by 2 reviewers and consensus was reached. Credibility of evidence was assessed using published Venice criteria.

Data Synthesis  Forty-seven distinct data sets from the 22 articles were analyzed, including 35,872 cases and 95,837 controls. The summary OR for heart disease among individuals with 2 vs 1 at-risk alleles was 1.25 (95% confidence interval [CI], 1.21-1.29), with low to moderate heterogeneity. Age at disease diagnosis was a significant covariate, with ORs of 1.35 (95% CI, 1.30-1.40) for age 55 years or younger and 1.21 (95% CI, 1.16-1.25) for age 75 years or younger. For a 65-year-old man, the 10-year heart disease risk for 2 vs 1 at-risk alleles would be 13.2% vs 11%. For a 40-year-old woman, the 10-year heart disease risk for 2 vs 1 at-risk alleles would be 2.4% vs 2.0%. Nearly identical but inverse results were found when comparing 1 vs 0 at-risk alleles. Three studies showed net reclassification indexes ranging from −0.1% to 4.8%.

Conclusion  We found a statistically significant association between 9p21 SNPs and heart disease that varied by age at disease onset, but the magnitude of the association was small.

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examined clinical utility. This analysis is part of a targeted systematic review on existing cardiogenomic panels that included 28 genes in addition to the 9p21 SNPs. That review was commissioned by the Evaluation of Genomic Applications

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Clinical Review Section Editor: Mary McGrae McDermott, MD, Contributing Editor. We encourage authors to submit papers for consideration as a Clinical Review. Please contact Mary McGrae McDermott, MD, at mmd608@northwestern.edu.

See also p 631.

CME available online at www.jamaarchivescme.com and questions on p 675.
METHODS

The review team included an experienced consultant to the EWG (G.E.P.) contracted by the Office of Public Health Genomics (OPHG) at the Centers for Disease Control and Prevention, Atlanta, Georgia, an OPHG researcher (S.M.), and a clinical geneticist (L.A.B.). Standard methods for evaluating clinical validity included systematic literature searches, preset inclusion/exclusion criteria, data abstraction, meta-analysis, and grading of studies and cumulative evidence. Expert guidance on literature searches and analytic methods was provided by the Technical Expert Panel. Electronic searches used the HuGE Navigator (version 1.3) with search term (9p21[Text+Mesh]). Previous validations had cross-checked HuGE Navigator and PubMed search results for selected gene-disease associations and found the HuGE Navigator searches equally sensitive but more specific (data available from the author on request). Limiting key questions and truncating search strategies are 2 common methods in rapid reviews that we chose to use. The Web site of the laboratory offers...
ing 9p21 testing was reviewed for references or gray data. Reference lists of included articles were hand searched. Two team members (G.E.P., S.M.) reviewed included articles on clinical validity and extracted the raw data and demographic information into spreadsheets; discrepancies were resolved through discussion.

Included articles were published in English; contained primary outcomes of coronary heart disease (CHD), myocardial infarction (MI), or coronary artery disease (CAD); tested for 9p21 SNPs; reported race and numbers of affected and unaffected participants; and provided the odds ratio (OR) with confidence intervals (CIs) or data suffi-

### Table. Summary of Evidence for 9p21 SNPs and Selected Cardiovascular Outcomes (continued)

<table>
<thead>
<tr>
<th>Source and Data Set</th>
<th>Study Type</th>
<th>Cases/Controls</th>
<th>SNP</th>
<th>OR High</th>
<th>OR Low</th>
<th>Race</th>
<th>Primary Outcome</th>
<th>Age, Mean, y&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Age Cutoff, y&lt;sup&gt;d&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Hiura et al&lt;sup&gt;50&lt;/sup&gt; 2008 Japan</td>
<td>Case-control</td>
<td>586/2432</td>
<td>rs1333049</td>
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<td>0.93</td>
<td>Asian</td>
<td>MI</td>
<td>61</td>
<td>79</td>
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<tr>
<td>Lemmens et al&lt;sup&gt;19&lt;/sup&gt; 2009 Belgium</td>
<td>Case-control</td>
<td>914/809</td>
<td>rs10757278</td>
<td>1.18</td>
<td>0.65</td>
<td>White</td>
<td>CAD</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>McPherson et al&lt;sup&gt;4&lt;/sup&gt; 2007 US ARIC Cohort</td>
<td>Case-control</td>
<td>1037/7743</td>
<td>rs10757274</td>
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<td>54</td>
<td>63&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>CCHS</td>
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<td>80&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>62&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Newton-Cheh et al&lt;sup&gt;53&lt;/sup&gt; 2009 Boston, Massachusetts</td>
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<td>rs10757274</td>
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<td>SCD</td>
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<td>Paynter et al&lt;sup&gt;43&lt;/sup&gt; 2009 ATP III Cohort</td>
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<td>rs10757274</td>
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<td>Peng et al&lt;sup&gt;4&lt;/sup&gt; 2009 China</td>
<td>Case-control</td>
<td>520/560</td>
<td>rs1333049</td>
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<td>0.67</td>
<td>Asian</td>
<td>MI</td>
<td>NR</td>
<td>NR</td>
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<td>Samani et al&lt;sup&gt;51&lt;/sup&gt; 2007 Germany</td>
<td>Case-control</td>
<td>844/1605</td>
<td>rs1333049</td>
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<td>0.68</td>
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<td>MI</td>
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<td>Case-control</td>
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<td>White</td>
<td>MI</td>
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<td>744/1299</td>
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<td>CAD/MI</td>
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<td>NR</td>
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<td>MORGAM</td>
<td>Case-control</td>
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<td>rs1333049</td>
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<td>White</td>
<td>CAD/MI</td>
<td>NR</td>
<td>NR</td>
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<td>Schunkert et al&lt;sup&gt;42&lt;/sup&gt; 2008 AtheroGene</td>
<td>Case-control</td>
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<td>rs1333049</td>
<td>1.27</td>
<td>0.76</td>
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<td>CAD</td>
<td>NR</td>
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<td>GarMIFS II</td>
<td>Case-control</td>
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<td>LMDS</td>
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<td>1.40</td>
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<td>CAD</td>
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<td>78&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>MONICA/KORA</td>
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<td>rs1333049</td>
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<td>MI</td>
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<td>PopGen</td>
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<td>CAD</td>
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<td>55</td>
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<td>PRIME</td>
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<td>UK MI</td>
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<td>756/727</td>
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<td>0.79</td>
<td>White</td>
<td>MI</td>
<td>NR</td>
<td>65</td>
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<tr>
<td>Shen et al&lt;sup&gt;21&lt;/sup&gt; 2008 Italy</td>
<td>Case-control</td>
<td>416/308</td>
<td>rs1075724</td>
<td>1.25</td>
<td>0.80</td>
<td>White</td>
<td>MI</td>
<td>60</td>
<td>75&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Shen et al&lt;sup&gt;22&lt;/sup&gt; 2008 South Korea</td>
<td>Case-control</td>
<td>611/294</td>
<td>rs1075724</td>
<td>1.29</td>
<td>0.78</td>
<td>Asian</td>
<td>CAD</td>
<td>64</td>
<td>79&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Taimud et al&lt;sup&gt;25&lt;/sup&gt; 2008 NPHS II Cohort</td>
<td>Case-control</td>
<td>264/2430</td>
<td>rs1075724</td>
<td>1.11</td>
<td>0.67</td>
<td>White</td>
<td>CHD</td>
<td>64</td>
<td>79</td>
</tr>
<tr>
<td>Zhang et al&lt;sup&gt;23&lt;/sup&gt; 2009 China</td>
<td>Case-control</td>
<td>417/430</td>
<td>rs1075724</td>
<td>1.17</td>
<td>0.61</td>
<td>Asian</td>
<td>MI</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Zhou et al&lt;sup&gt;24&lt;/sup&gt; 2008 China</td>
<td>Case-control</td>
<td>1360/1360</td>
<td>rs2383207</td>
<td>1.38</td>
<td>0.99</td>
<td>Asian</td>
<td>CHD</td>
<td>61</td>
<td>76&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; CHD, coronary heart disease; MI, myocardial infarction; NR, not reported; OR, odds ratio; SCD, sudden cardiac death; SNP, single-nucleotide polymorphism.

<sup>a</sup>Table is restricted to 5 SNPs (rs1333049, rs10757274, rs2891168, and rs10757278) that cover all studies/data sets.

<sup>b</sup>OR high is the odds of disease among those with 2 at-risk alleles vs those with 1 at-risk allele (reference category). OR low is the odds of disease among those with 0 at-risk alleles vs those with 1 at-risk allele (reference category).

<sup>c</sup>The reported mean age at diagnosis for cases.

<sup>d</sup>The reported or estimated age cutoff level for diagnosis. If only the mean and standard deviation were provided, the cutoff level was estimated to be mean age + 1.5 × SD.

<sup>e</sup>Estimated.
cent to compute it. If more than 1 outcome was reported, the best-described phenotype was chosen (eg, MI rather than CAD). The authors’ definition of phenotype was not an exclusion criterion. Excluded articles reported only on stroke, intermediate outcomes (eg, atherosclerosis), or subgroups (eg, patients with diabetes). Several included articles reported consortium results with multiple independent populations. These populations were listed as separate data sets.

Not all researchers use the same 9p21 SNPs, and most articles reported results for multiple SNPs (uniquely identified by their rs number). We extracted data for all SNPs used by at least 2 of the 22 included articles, but we report herein 3 common SNPs (rs1333049, rs10757274, and rs2383207) that were included in all but 3 articles.28-30 These SNPs are in high linkage disequilibrium (D’ = 1.00; r2 > 0.85).28,29,30 The remaining 3 articles used 2 additional SNPs, rs289116820 and rs10757278.18,19 These were also in high linkage disequilibrium.19 One additional SNP (rs2383206) was reported in at least 2 included articles. When possible, we restricted results in each data set to a single race. Information about age at diagnosis and race/ethnicity was also collected.

As previously reported,26,27 individuals with 1 at-risk SNP allele (heterozygotes) were designated as the reference group. Heterozygotes comprise about 50% of the white population. For each data set, the observed genotype frequencies in controls were compared with expected frequencies based on Hardy-Weinberg equilibrium (χ2 test with 2 degrees of freedom). All P values are 2-sided at the P = .05 level.

Summary ORs and corresponding 95% CIs were derived (by reanalysis when possible) and summarized using random-effects modeling weighted by each data set’s total variance (Comprehensive Meta-Analysis, version 2, Biosstat Inc, Englewood, New Jersey).28 Subgroup differences were compared using the Q test for heterogeneity for each covariate separately. A fixed-effects meta-regression was performed for the OR vs age at diagnosis.28 Studies that did not report a value for any covariate were excluded. Publication bias was examined by performing a cumulative effects analysis.28 Wider ranges of these summary ORs indicate potential for publication bias.

Quality of individual studies (levels 1-4) and overall quality of evidence for clinical validity (convincing, adequate, or inadequate) were evaluated with EWG methods,11 consistent with other grading systems.20,21 Assessment of cumulative evidence used a consensus evaluation guideline (Venice criteria) specific to gene-disease association studies22 and focused on amount of evidence, replication of evidence, and protection from

**Figure 2.** 9p21 Single-Nucleotide Polymorphism Markers and Heart Disease, Comparing Individuals With 2 At-Risk Alleles vs Those With 1 At-Risk Allele

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al,55 2009</td>
<td>0.99 (0.76-1.29)</td>
</tr>
<tr>
<td>Ding et al,19 2009</td>
<td>1.42 (1.06-1.89)</td>
</tr>
<tr>
<td>Helgadottir et al,8 2007</td>
<td>1.09 (0.99-1.21)</td>
</tr>
<tr>
<td>Shen et al,21 2008</td>
<td>1.16 (0.97-1.37)</td>
</tr>
<tr>
<td>Samani et al,51 2007</td>
<td>1.22 (0.94-1.58)</td>
</tr>
<tr>
<td>McPherson et al,9 2007</td>
<td>1.04 (0.68-1.60)</td>
</tr>
<tr>
<td>Talmud et al,25 2008</td>
<td>1.29 (1.06-1.57)</td>
</tr>
<tr>
<td>Samani et al,53 2009</td>
<td>1.22 (1.07-1.37)</td>
</tr>
<tr>
<td>Liu et al,7 2009</td>
<td>1.18 (0.94-1.49)</td>
</tr>
<tr>
<td>Smith et al,22 2008</td>
<td>1.25 (1.01-1.55)</td>
</tr>
<tr>
<td>Anderson et al,24 2008</td>
<td>1.26 (0.99-1.61)</td>
</tr>
</tbody>
</table>

The odds ratios (ORs) and 95% confidence intervals (CIs) are shown for the 37 data sets comparing individuals with 2 at-risk alleles vs those with 1 at-risk allele. The consensus (dashed vertical line) and no effect (dotted vertical line) are also shown. Heterogeneity is low.
bias. Cumulative evidence was strong for 3 “A” grades, moderate for “B” grades but no “C” grades, and weak if it received at least 1 “C” grade.

The net reclassification index (NRI) was used as an intermediate measure of potential clinical utility. To compute the NRI, the cases (events) and controls (nonevents) in a population were cross-classified by risk assessment performed on the remaining 33 ORs vs the upper age cutoff level showed a significant association between higher ORs at earlier ages of disease onset (P < .001; slope and intercept of −0.00558 and 0.60881) (Figure 3). The regress OR was 1.35 (95% CI, 1.30-1.40) for an upper age cutoff of 55 years and 1.21 (95% CI, 1.16-1.25) for 75 years; remaining heterogeneity was reduced (Q = 29; I² = 0%; P = .38). Consistent results were found using the mean age at onset (eFigure 2). One way to estimate the OR for all adults is to use the 14 data sets with upper age cutoff levels of greater than 70 years. In this group, the summary OR was 1.19 (95% CI, 1.13-1.25; P < .001), with low heterogeneity (Q = 13; I² = 1%; P = .44).

Comparison of Individuals Having No At-Risk Alleles With Those Having 1 At-Risk Allele

The summary OR was 0.80 (95% CI, 0.77-0.82; P < .001), with moderate

References 8, 9, 18, 19, 43, 46, 49, 53, 54.
heterogeneity (Q=65; I²=29%; P=.04) (Figure 4). No differences in ORs were found between Asians and whites (ORs, 0.81 and 0.79, respectively; P=.79); the SNP used (ORs, 0.82, 0.77, 0.84, 0.78, and 0.70; P=.22); or the outcomes of CAD, CHD, and MI (ORs, 0.79, 0.79, and 0.81; P=.87). Meta-regression again showed a significant slope (P=.001), with lower ORs associated with earlier ages of onset (slope and intercept of 0.00500 and −0.57854) (Figure 5).

The regressed OR was 0.74 (95% CI, 0.71-0.77) for an upper age cutoff of 55 years and 0.82 (95% CI, 0.79-0.85) for 75 years; heterogeneity was lower after fitting the model (Q=40; I²=22%; P=.39). Results were similar when mean age was used (Figure 2). When restricted to the 14 data sets with an upper age cutoff levels of 70 years or higher, the summary OR was 0.83 (95% CI, 0.78-0.89; P<.001). However, heterogeneity was moderate (Q=21; I²=37%; P=.08). With the most discrepant finding removed (OR, 1.16),48 this summary OR became 0.82 (95% CI, 0.79-0.85) and heterogeneity was reduced (Q=13; I²=7%; P=.37).

Several included articles reported the effect size as an allele-specific OR,8,9,21,22,46-49-51,53 where an equivalent “dose” of risk was conferred per allele. That would imply that the reciprocal of our low OR should be similar to the high OR (eg, 1/0.80=1.25; the high OR is 1.25).

Assessment of Evidence for 9p21 and Heart Disease

Three cohort studies (Table) were deemed level I designs and the remaining case-control studies were level 2.11 Based on this and internal validity assessments, the overall quality of evidence for clinical validity was convincing to adequate. After accounting for age at onset, the Venice grading12 was A for amount of evidence (>1000 cases/controls with the least common genotype) and A for replication (low heterogeneity after meta-regression and for the 12 data sets with later ages of onset). Bias required examining phenotype definition, genotyping, population stratification, and selective reporting using the predefined “typical” effect size category (ORs, 1.15-1.80).12 The use of widely agreed-on definitions for CAD, CHD, and MI (eg, CHD defined as requiring coronary artery bypass graft surgery) in the data sets made the likelihood of phenotype bias low or none. Nearly all data sets were tested using commercial or well-described genotyping platforms, making the likelihood of genotyping bias low. Most case-control studies matched on race/ethnicity, and, where possible, we restricted results to a single race. We assigned the likelihood of stratification bias to be low, resulting in an overall protection from bias grade of A.

### Figure 4. 9p21 Single-Nucleotide Polymorphism Markers and Heart Disease, Comparing Individuals With No At-Risk Alleles vs Those With 1 At-Risk Allele

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AtheroGene</td>
<td>0.76 (0.53-1.09)</td>
</tr>
<tr>
<td>GenMFS II</td>
<td>0.90 (0.70-1.15)</td>
</tr>
<tr>
<td>LMDS</td>
<td>0.78 (0.56-1.09)</td>
</tr>
<tr>
<td>MONICA/KORA</td>
<td>0.79 (0.61-1.03)</td>
</tr>
<tr>
<td>PopGen</td>
<td>0.83 (0.67-1.02)</td>
</tr>
<tr>
<td>Prime</td>
<td>0.74 (0.54-1.02)</td>
</tr>
<tr>
<td>UK MII</td>
<td>0.79 (0.61-1.01)</td>
</tr>
<tr>
<td>Shen et al,2008</td>
<td>0.80 (0.65-0.99)</td>
</tr>
<tr>
<td>Shen et al,2008</td>
<td>0.78 (0.64-0.96)</td>
</tr>
<tr>
<td>Talmud et al,2008</td>
<td>0.67 (0.48-0.93)</td>
</tr>
<tr>
<td>Zhang et al,2009</td>
<td>0.61 (0.45-0.84)</td>
</tr>
<tr>
<td>Zhou et al,2008</td>
<td>0.99 (0.76-1.27)</td>
</tr>
</tbody>
</table>

Overall (random effects) 0.80 (0.77-0.82)

Test for heterogeneity: I²=29%; P=.04
CHROMOSOME 9P21 GENOMIC MARKERS AND HEART DISEASE

Figure 5. Meta-regression of 9p21 Single-Nucleotide Polymorphism Markers and Heart Disease, Comparing Individuals With No At-Risk Alleles vs Those With 1 At-Risk Allele

Data sets restricted to early onset heart disease are likely to be smaller in size (since these events are uncommon) and have a larger effect size (Figure 3). This might appear to be positive publication bias. To avoid confounding, each of the high ORs (Table) was divided by the expected OR given that data set’s age at onset (Figure 3). These age-adjusted ORs (median, 1.000) could then be evaluated for publication bias. The cumulative effect size analysis indicated a trivial 4% change from the most precise to the least precise cumulative estimates (0.96 for the 6 largest data sets to 1.00 for all 33 data sets).

The OR associated with an individual’s 9p21 test result can be used to modify heart disease risk based on traditional factors. For example, a 65-year-old man with no other traditional risk factors would have a 10-year heart disease risk of 11%, while a 40-year-old woman with no other risk factors would have a 10-year risk of 2%. If both were to have 2 at-risk 9p21 alleles, risk estimates would increase to about 13.2% (11x1.2) and 2.4% (2x1.2), respectively, compared with an individual with 1 at-risk allele. Having no at-risk alleles would result in reduced risk estimates of 9.2% and 1.7%, respectively, compared with an individual with 1 at-risk allele. Comparing no at-risk alleles with 2 at-risk alleles could modify risk estimates by 1.44-fold.

Net Reclassification

Three studies that included 1721 cases and 34,797 controls also provided information to compute the NRI. Four NRI estimates were made because 1 study reported 2 risk algorithms. For the 4 data sets, the proportions of cases reclassified were 0.5%, 0.7%, 2.5%, and −0.1% (P = .65, .79, .03, and .87), respectively; proportions of controls reclassified were 0.3%, 4.2%, −0.1%, and 0% (P = .36, <.001, .52, and .87), respectively. The corresponding NRIs were 0.8%, 4.9%, 2.5%, and −0.2% (P = .51, .09, .03, and .96), respectively. Details are given in eTable 2.

COMMENT

Based on EWG and Venice criteria, evidence for the association between heart disease and the 9p21 SNP markers has strong credibility. The 9p21 markers have been identified through genome-wide association studies that were not hypothesis-driven and appear independent of traditional risk factors or family history. The pathophysiological mechanism is not yet understood. Risk alleles are more strongly associated with heart disease events in younger persons (OR, 1.35) than with heart disease in general (OR, 1.21). One company offering 9p21 SNP testing and interpretation uses an OR of 1.3 in its clinical reports for “MI at any age” and 1.6 for “MI at a younger age.”

Most data sets are limited to white populations, usually of European descent, so the results for other racial/ethnic groups might differ. In 8 studies among Asians, however, the association appears similar. We did not include data for black populations, but limited evidence suggests a smaller effect. Rather than adjusting ORs for age/sex, we based our OR on raw data when possible, because adjusted ORs appear to be close to raw estimates. For example, 1 article reported per-allele hazard ratios that were 1.14 when unadjusted, 1.15 after adjustment for age, and 1.12 after adjustment for age, blood pressure, lipid measurements, smoking status, diabetes, and antihypertensive use. These differences were not statistically significant. Finally, we removed 2 articles from the meta-analysis for which we could not generate reliable ORs. Both were small (202 cases of CAD/MI and 118 individuals with MI/coronary insufficiency) and inclusion would be unlikely to influence the results reported using larger sample sets.

A test has clinical utility when its results lead to a measurable improvement in health outcomes. Intervention trials to establish the clinical utility of adding 9p21 testing were lacking. There is an expectation that genetic susceptibility information could increase motivation for long-term lifestyle changes (eg, improvement in risk-reducing behaviors, treatment adherence). However, measuring behavioral change is challenging. Communicating genetic information to patients has resulted in encouraging reports of short-term positive effects and has not shown reduced adherence or fatalistic thinking.

Achievement of more accurate risk by adding 9p21 to traditional risk factors could be considered an intermediate measure of clinical utility. The computed NRIs ranged from 0.2% decrease to a 4.9% improvement. The study showing the largest NRI achieved most of the risk reclassification because of reduced risk in individuals without events and, therefore, would have little chance of improving outcomes. The study reporting 2 traditional risk factor models showed that adding 9p21 testing to the Adult Treatment Panel III model showed significant improvement (NRI, 2.5%), while adding testing to the Reynolds Risk Score (RRS) showed no improvement (NRI, −0.2%). One main difference between the 2 models was inclusion of a family history of myocardial infarction in the RRS. None of the 3 studies modified treatment protocols based on addition of 9p21 or exam-
ined long-term health or behavioral outcomes. How best to analyze the effect of adding genomic markers to traditional risk factors (eg, area under the curve, NRI, integrated discrimination improvement) remains an active research area.31-68

The incidence of MI can be reduced by drugs that lower cholesterol/low-density lipoproteins and blood pressure in individuals with risk factors.69 Improved risk assessment might influence decision making about effective interventions and behavioral change. However, only 37% of US physicians reported regular use of a heart disease risk score.70 A systematic review found preliminary evidence that CHD risk scores may translate into modest benefits (eg, increased drug treatment, short-term blood pressure reduction) without clinical harms.71 However, the need for higher-quality evidence on long-term outcomes, and for replication of the results in different clinical settings, was emphasized.72 Other complicating factors may be patient adherence to lipid-lowering medications (about half reach target lipid levels and one-quarter continue long-term drug treatment)72 and access to medical care and medications. Therefore, the clinical utility of adding 9p21 markers to traditional risk factors cannot be assumed, even if risk assessment is improved. One proposal suggests that heart disease may be more effectively prevented by implementing an inexpensive, standardized, multidrug intervention (ie, the polypill) in all persons aged 55 years or older, regardless of individual risk levels.69

In summary, showing that a genetic test has clinical validity does not necessarily lead to improved health. Clinical trials need to demonstrate that use of the test is associated with changes in physician management decisions, patient motivation and long-term behavioral changes, improved health outcomes, and/or reduced costs to the health care system. Using genomic tests to improve existing risk models would likely require the inclusion of many markers like 9p21.73-74 Such risk assessments may be more accurate but may not result in more appropriate treatments until the underlying mechanisms are known. Uncovering these mechanisms may provide insights into new or improved treatments and prevention activities.

Author Contributions: Mr Palomaki had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Palomaki, Bradley.

Acquisition of data: Palomaki, Melillo.

Analysis and interpretation of data: Palomaki, Melillo, Bradly.

Drafting of the manuscript: Palomaki, Melillo, Bradley.

Critical revision of the manuscript for important intellectual content: Palomaki, Melillo, Bradley.

Statistical analysis: Palomaki, Melillo.

Obtained funding: Palomaki.

Administrative, technical, or material support: Palomaki, Bradley.

Study supervision: Palomaki.

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Online-Only Material: Figures 1 and 2 and eTables 1 and 2 are available online at www.jama.com.

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REFERENCES


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