Coronary artery disease (CAD) is a multistaged process leading to a wide spectrum of pathoanatomic and clinical presentations. Given the diversity of underlying mechanisms, it is reasonable to involve distinct genetic modifiers along the cascade of events. Yet, molecular genetic association studies usually admix patients with stable and acute presentation, stenotic and ectatic forms of CAD, as well as proximal, distal or bifurcational lesions. In this issue of Circulation: Cardiovascular Genetics, Kitsios et al address this issue by analyzing the impact of phenotype heterogeneity on the strength of association at previously identified risk loci for CAD. Perhaps surprisingly, the authors found little evidence for a contribution of phenotype definition to between-study heterogeneity of association signals at already known genomic CAD loci.

This meta-analysis clustered 965 individual studies into 3 groups: those involving patients with (1) acute coronary syndromes (ie, myocardial infarction [MI] and unstable angina), (2) angiographically diagnosed CAD, or (3) “broadly defined” CAD. The later group included association studies that combined patients with MI, revascularization procedures (angioplasty or bypass surgery), positive exercise test findings, symptomatic angina, history of hospitalization for CAD-related diagnoses, or fatal CAD at autopsy. The CAD polymorphisms analyzed represented 22 CAD loci including firmly established ones such as 9p21, apolipoprotein E, and lipoprotein lipase. The bottom line of this comprehensive study is that none of the variants analyzed revealed a consistent change in odds ratio, allele frequency, or significance level related to a particular phenotypic subgroup.

Although the meta-analysis was carefully designed and executed, Kitsios et al rightfully point to inherent limitations of such investigation. Indeed, rearrangement of studies within a meta-analysis does not overcome lack of phenotypic precision in individual studies, as there was major overlap between different CAD presentations in most of them (eg, angiographically defined patients with 3-vessel disease presenting with acute MI occurred in each of the 3 groups selected by Kitsios et al). Thus, lack of individual patient-level data may have blurred the overall picture. Moreover, despite large numbers of cases and control subjects enrolled, this analysis had limited power for discrimination of genetic effects on distinct subphenotypes of CAD.

Nevertheless, there are several key messages from this study that may be grouped into technical notes for conduction of association studies and others for further in-depth analysis of known CAD loci. First, given that none of the subphenotypes tested by Kitsios et al outperformed in this analysis, the totality of evidence should be examined for discovery of new CAD loci. In fact, subgroup analyses have reduced power, and the vast majority of loci identified thus far appear to affect angiographic evidence of CAD and risk of MI in a similar fashion. Second, once a locus has been established, subgroup analysis may point to a specific mechanism. In fact, Reilly et al recently demonstrated that the ABO locus appears to have a predominant effect on MI risk, whereas ADAMTS7 predominantly affects the development of atherosclerosis. Similar observations have been made before at the 9p21 locus, which appears to precipitate predominantly vascular disease.

Third, the fact that hardly any of the loci tested by Kitsios et al discriminated between angiographic evidence of CAD and the risk of MI suggests that the vast majority of genetic variants discovered thus far enhance the probability of the development of CAD in the first place. As a consequence, the risk allele increases the probability of subsequent acute events. In other words, the relative risk increase associated with a given risk allele being similar for the 2 phenotypes suggests that the extension of CAD appears to affect the risk of MI in a linear fashion.

The lack of discrimination between specific clinically defined phenotypes based on genetic risk variants, observed in the study of Kitsios et al, also brings to attention how poor such clinical categorization reflects the biology of the disease. Indeed, lack of discrimination does not imply that the underlying genetically induced mechanisms act arbitrarily; rather, the common trunk of a lifetime disease, as diagnosed in a patient, falls short to discriminate different pathways leading to its clinical manifestation. Therefore, improved phenotype definition will be of critical importance for a better mechanistic understanding of the development of CAD and MI generally and its genetic roots specifically. Indeed, imprecision in phenotyping not only represents a significant challenge to genetic discovery but also limits clinical translation of genetic findings into preventive and therapeutic measures.

As another example for genetic diversity in CAD, we have previously demonstrated distinct heritable patterns of angiographic CAD in MI families. Subphenotypes of CAD with particularly strong heritability and familial clustering were left main disease, CAD with ectatic lesions, and CAD with calcified coronary lesions. It will be necessary to pool large numbers of individual patients with in-depth phenotyping to
uncover the underlying specific genetic factors leading to such phenotypes of CAD.

Taken together, to achieve future progress in the genetics of CAD and to eventually close the gap of missing heritability, it will be crucial to sharpen phenotype definitions. A list of such subphenotypes of CAD warranting distinct genetic analysis is suggested in the Table. The list also acknowledges the limited clinical tools for mechanistic discrimination of different etiologies in the development of CAD. Therefore, other means of phenotypic characterization, including transcriptomic, proteomic, or epigenomic profiling of atherosclerotic lesions, may be warranted. Any meticulous phenotype definition in CAD will be particularly important for identification of rare variants through whole genome sequencing studies. In summary, phenotyping quality and genotyping quantity will determine the future success of genetic association studies for CAD.

Disclosures
None.

References


Table. Subphenotypes of CAD With Potentially Distinct Genetic Etiology

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Frequency</th>
<th>Heritability (h2)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>0.75</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Plaque rupture/plaque erosion</td>
<td>?</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Left main disease/proximal manifestation</td>
<td>10% to 30%</td>
<td>0.47</td>
<td>7</td>
</tr>
<tr>
<td>Diffuse/focal CAD</td>
<td>40%</td>
<td>0.41</td>
<td>7</td>
</tr>
<tr>
<td>CAD with ectatic lesions/coronary aneurysms</td>
<td>5%</td>
<td>0.54</td>
<td>7</td>
</tr>
<tr>
<td>Coronary calcification</td>
<td>15%</td>
<td>0.51</td>
<td>7</td>
</tr>
<tr>
<td>In-stent restenosis</td>
<td>?</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>
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Patrick Diemert and Heribert Schunkert

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