Coronary Artery Disease and Its Risk Factors
Leveraging Shared Genetics to Discover Novel Biology

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Coronary artery disease (CAD) is the world-wide leading cause of death not only in high-income countries but also increasingly in developing countries. Although death rates from CAD have decreased in most high- and middle-income countries in the past 2 decades, there are worrying signs of a lessening trend in the United States, and the dramatic increases of world-wide obesity and diabetes mellitus prevalences emphasize the need for improved preventive and therapeutic strategies to battle these major public health problems. Human genetic studies can offer leads toward such improved strategies, both by providing better ways of identifying individuals at increased risk for CAD (risk stratification) and by informing the scientific community about novel biology, pathways, and potential targets for development of the next generation of pharmaceutical drugs.

In this issue of Circulation Research, LeBlanc et al4 have applied an innovative statistical approach to existing large-scale meta-analyses of genome-wide association studies (GWAS) of CAD and risk factors for CAD to enable discovery of novel disease loci. By combining results on association of CAD loci from the Coronary Artery Disease Genome Wide Replication and Meta-Analysis (CARDIoGRAM) plus The Coronary Artery Disease (CAD) Consortium (CARDIoGRAMplusC4D) with results on CAD risk factors from other consortia, they report 67 novel CAD loci, of which 42 were not previously reported using a traditional, unconditional false discovery rate. In addition, they provide eQTL (expression quantitative trait loci) evidence for 32 of these 67 loci, and ingenuity pathway analysis of these associations shows enrichment of pathways involved in inflammation and lipid metabolism. By using this novel approach of combining publically available meta-analyses of GWAS, they show a large extent of shared genetic determinants between these cardiovascular risk factors and CAD. This underlines the shared polygeneticity of these traits and further emphasizes the popularly accepted view that complex traits are determined by a large number of common genetic variants and that many of these variants can be shared between traits that are known to be strongly correlated. In other words, the phenotypic correlations are accompanied by genetic correlations.

Their pathway findings showing an enrichment for pathways known to be central to atherosclerosis pathophysiology, as well as the list of novel loci, supports the robustness of their methodology by providing biologically plausible results. For example, in the list of novel loci, we find nearest genes—not to be taken as conclusive evidence of being the causal genes—that are extensively investigated in relation to coronary heart disease, such as VEGF and HMGCR, as well as genes that have been implicated more recently, such as CXCR4 and NGF.

The authors make the point that components of the metabolic syndrome show a large degree of polygenic overlap with CAD, in particular, low-density lipoprotein-cholesterol. However, low-density lipoprotein-cholesterol is usually not considered to be a part of the metabolic syndrome—not in the original derivation of the concept, or in different efforts to formalize it by World Health Organization and National Cholesterol Education Program. Also, the dyslipidemia that tends to cluster with obesity and insulin resistance is characterized by high triglycerides and low high-density lipoprotein-cholesterol. Nonetheless, low-density lipoprotein-cholesterol is definitely among the most important risk factors for CAD and is a key factor in atherosclerosis development, so it is reasonable to include low-density lipoprotein-cholesterol among the traits investigated for polygenic overlap with CAD.

Perhaps the most interesting feature of this work is the identification of CAD variants that were also associated with type 2 diabetes mellitus. The present study identified 21 novel loci based on conditional analyses of type 2 diabetes mellitus and CAD. The large degree of polygenic overlap between these 2 traits is an important and novel observation because although it should be expected based on phenotypic observations, it stands in stark contrast to what was reported in the original CARDIoGRAMplusC4D article. In that work, no overlap of loci was reported between CAD and type 2 diabetes mellitus.

A plausible reason for this discrepancy is that the analyses in the CARDIoGRAMplusC4D study used a relatively naïve approach where the degree of overlap was determined by the number of genome-wide significant CAD loci that showed an association with type 2 diabetes mellitus (and other traits) at a Bonferroni-corrected threshold. Using that approach, none of the CAD loci were associated with type 2 diabetes mellitus, fasting glucose or insulin, whereas the more advanced approach presented in the current article uncovered a large number of novel CAD by joint analyses with type 2 diabetes mellitus, underlining their shared genetic determinants.
The authors chose to take an unconventional approach with respect to diabetes mellitus, including type 1 diabetes mellitus among the traits that they interrogated. Type 2 diabetes mellitus is the traditional form of the disease that is linked to CAD causality, and it usually presents in middle-aged to elderly individuals as a result of obesity and insulin resistance, whereas type 1 diabetes mellitus is an autoimmune disease presenting in younger age groups. The decision to include type 1 diabetes mellitus among the traits investigated is unlikely to have dramatically altered the outcome of the study, as 10 of the 18 loci with the lowest conditional false discovery rate for this trait also had a significant conditional false discovery rate for another trait investigated; only 8 loci would not have been discovered if the authors had chosen not to include type 1 diabetes mellitus among the traits investigated. Regardless, type 1 diabetes mellitus is undeniably a strong risk factor for CAD, and by investigating the overlap of these 2 traits, the authors were indeed able to report additional loci associated with CAD.

This work highlights the contribution of individual loci to many cardiometabolic traits. Although roughly half of the variants identified were common between CAD and only 1 risk factor trait, the remaining variants were shared between CAD and ≥2 risk traits (Figure). In fact, as many as 13 of the variants were associated with all of the traits examined. For those loci that overlap with just 1 trait, it would seem likely that this trait is actually involved in the causal mechanism (on the causal pathway) responsible for the CAD association. For those variants associated with many traits, it is possible that the variant is related to central processes that mediate signaling through several pathways that are important for risk status. It is also possible that these traits share a correlation with the underlying causal factor and that the traits actually do not represent the causal mechanism per se.

The authors are careful to note that these results should not be interpreted in a causal framework. The fact that there was a large degree of polygenic overlap between CAD and risk factors for CAD does not inform us about the causal role of these risk factors because the statistical modeling applied cannot distinguish between pleiotropy or mediation. To address causality, proper Mendelian randomization methods have to be applied, and indeed, large well-performed such studies have convincingly shown that the associations of high-density lipoprotein-cholesterol and C-reactive protein with CAD are likely to be noncausal. The polygenic overlaps of these traits with CAD reported in the current article should hence be interpreted to be the result of common pathophysiological pathways and/or pleiotropy. The methodology presented in the current article is useful to discover additional loci associated with a trait by leveraging GWAS of other related traits, but cannot be used to address causality.

The authors were not able to estimate the variance explained by the novel loci, but it is unlikely to be dramatic, as each additional common variant typically explains a small fraction of the variance. As such, the present study is not solving the missing heritability problem, but we think that its important contribution instead is the novel loci discovered, and the biology that can be learned from these loci. It should be noted that there is much work remaining before we can reap the benefits of this and other GWAS discovery efforts. For the novel loci reported in the present study, the next step will be to replicate them in an independent study. The authors made a commendable attempt to do so in the Women’s Genome Health Study, which is one of the largest studies that could be used for this purpose at the moment, but still had limited power for replication, even at a nominal significance threshold. It will be important to try to replicate their findings as new large studies, such as the UK Biobank or Million Veteran Program, becomes available. Beyond replicating the novel loci, there is plenty of additional downstream work ahead for the CAD genetics community in following up the novel loci, including establishing the causal genes in the associated loci, and to perform functional studies to disentangle the biological mechanisms leading to CAD. All work ahead of us set aside, the present study provides a novel method to leverage polygenic overlap using existing GWAS data sets and identify a large number of novel genetic loci suggested to be associated with CAD. The authors are to be commended for pushing forward the analysis of complex and complementary data sets, and identifying new and overlapping CAD variant regions with their comprehensive new data analysis approaches.

Sources of Funding
This work was supported by the Knut och Alice Wallenberg Foundation (grant no 2013.0126) to E. Ingelsson, National Institutes of Health grants (U01HL107388, HL109512, and R21HL120757) and a grant from the LeDucq Foundation to T. Quertermous.

Disclosures
None.

References


**Key Words:** Editorials ■ cholesterol, LDL ■ coronary disease ■ diabetes mellitus ■ genetics ■ genome-wide association study
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Circ Res. 2016;118:14-16
doi: 10.1161/CIRCRESAHA.115.307937

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circres.ahajournals.org/content/118/1/14

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