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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.[1] Although death rates from CAD have decreased in most high- and middle-income countries in the past two decades, there are worrying signs of a lessening trend in the U.S.,[2] and the dramatic increases of world-wide obesity[3] and diabetes[1] prevalences emphasizes the need for improved preventive and therapeutic strategies to battle these major public health problems. Human genetic studies can offer leads towards 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 and colleagues 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.[4] By combining results on association of CAD loci from the CARDIoGRAMplusC4D consortium[5] 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 (FDR). In addition, they provide eQTL 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

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Conflicts of interest

None.

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 evidence of being the causal genes – that are extensively investigated in relation to coronary heart disease, such as *VEGF*[6] and *HMGCR*,[7] as well as genes that have been implicated more recently, such as *CXCR4*[8] and *NGF*.[9]

The authors make the point that components of the metabolic syndrome show a large degree of polygenic overlap with CAD, in particular LDL cholesterol. However, LDL cholesterol is usually not considered to be a part of the metabolic syndrome – not in the original derivation of the concept,[10] or in different efforts to formalize it by WHO[11] and NCEP[12]. Also, the dyslipidemia that tends to cluster with obesity and insulin resistance is characterized by high triglycerides and low HDL cholesterol. Nonetheless, LDL 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 LDL 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. The present study identified 21 novel loci based on conditional analyses of type 2 diabetes and CAD. The large degree of polygenic overlap between these two traits is an important and novel observation, since although it should be expected based on phenotypic observations, it stands in stark contrast to what was reported in the original CARDIoGRAMplusC4D paper. In that work, no overlap of loci was reported between CAD and type 2 diabetes.[5] A plausible reason for this discrepancy is that the analyses in the CARDIoGRAMplusC4D study used a relatively naive 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 (and other traits) at a Bonferroni-corrected threshold. Using that approach, none of the CAD loci were associated with type 2 diabetes, fasting glucose or insulin, while the more advanced approach presented in the current paper uncovered a large number of novel CAD by joint analyses with type 2 diabetes, underlining their shared genetic determinants.

The authors chose to take an unconventional approach with respect to diabetes, including type 1 diabetes among the traits that they interrogated. While type 2 diabetes is the traditional form of the disease that is linked to CAD causality, it usually presents in middle-aged to elderly individuals as a result of obesity and insulin resistance while type 1 diabetes is an autoimmune disease presenting in younger age groups, and is not traditionally considered a common risk factor for CAD. The decision to include type 1 diabetes among the traits investigated is unlikely to have dramatically altered the outcome of the study, as ten out of the 18 loci with the lowest conditional FDR for this trait also had a significant

conditional FDR for another trait investigated; only eight loci would not have been discovered if the authors had chosen not to include type 1 diabetes among the traits investigated. Regardless, type 1 diabetes is undeniably a strong risk factor for CAD, and by investigating the overlap of these two traits, the authors were indeed able to report additional loci associated with CAD.

This work highlights the contribution of individual loci to a number of cardiometabolic traits. While roughly half of the variants identified were common between CAD and only one risk factor trait, the remaining variants were shared between CAD and two or more 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 one 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 a number of traits, it is possible that the variant is related to central processes that mediate signaling through a number of 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, since the statistical modelling 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 HDL cholesterol[13] and CRP[14] with CAD are likely to be non-causal. The polygenic overlaps of these traits with CAD reported in the current paper should hence be interpreted to be the result of common pathophysiological pathways and/or pleiotropy. The methodology presented in the current paper 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 very small fraction of the variance. As such, the present study is not solving “the missing heritability problem”, but we believe 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,[15] 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 datasets 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 datasets, and identifying new and overlapping CAD variant regions with their comprehensive new data analysis approaches.

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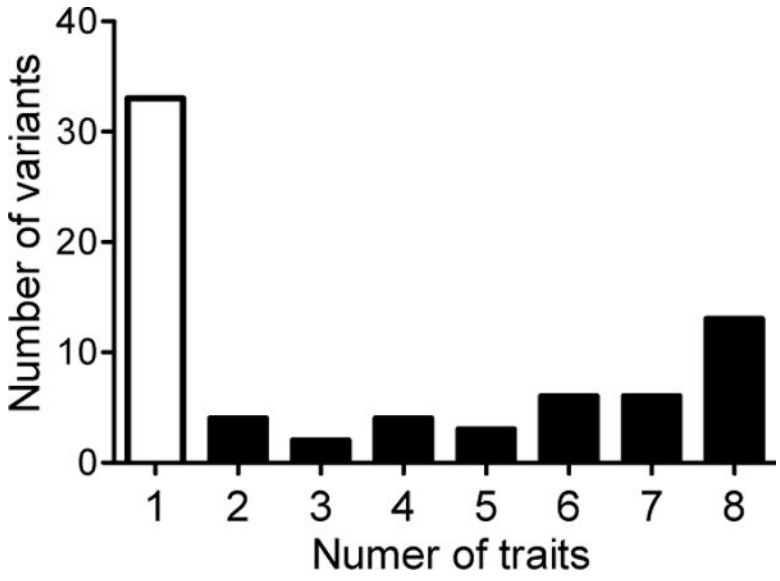

Figure.

The number of associated variants at FDR<0.01 were tabulated and graphed as a function of the total number of traits with evidence of a shared association with CAD.