Two expertly executed papers in this month’s issue of *Circulation: Cardiovascular Genetics* take candidate gene approaches to understanding genetic modification of interesting phenotypes. Kolder et al examine the role of genetic variants shown to associate with QTc interval as modifiers of the autosomal-dominant form of long QT syndrome (LQTS2) caused by mutations in KCNH2. Dauriz et al look at specific genetic variation known to predict type 2 diabetes mellitus (T2D), asking if these same variants predispose to subclinical atherosclerotic disease.

In the case of Dauriz et al, the interesting question is why the predicted association was in fact not observed. After all, T2D is a strong risk factor for the development of cardiac events, as is subclinical atherosclerotic disease. The large sample size and careful phenotyping suggest that the lack of association between T2D genetic risk, as quantified in this study, and subclinical atherosclerotic disease, is correct. What does this lack of association mean? T2D genetic risk was assessed by means of a genetic risk score (GRS) based on 62 T2D loci. The GRS used was essentially the sum of risk alleles at individual loci. But as the authors point out, use of a composite GRS may hide relationships between specific T2D risk alleles and subclinical atherosclerosis.

Use of a composite GRS has a certain appeal. In both the clinic and in the research setting, we like the simplicity of being able to collapse a complicated collection of risk alleles into a single number. But, complex diseases are complex: for most phenotypes driven by a large set of genes and their variants, we do not understand the biological relationship between these genes and variants at a deep level. Given that T2D is such a strong risk factor for cardiovascular disease, it seems counterintuitive that a composite GRS for T2D does not predict subclinical atherosclerosis.

As the authors point out, use of a GRS removes some of the complexities involved. The 62 gene variants used to calculate this GRS explain only a fraction of the T2D risk. And the single nucleotide polymorphism (SNPs) tested at these loci are for the most part unlikely to be the variants causally driving T2D risk. So, although this composite T2D GRS does not predict subclinical atherosclerosis, specific subsets of these genes and variants may well do so. Dissecting this would require even larger data sets.

Before embarking on such an effort, however, it is important to think carefully about phenotypes and their relationships. By focusing on subclinical atherosclerosis, and excluding individuals with overt cardiovascular disease, the authors may be biasing the study in subtle and hard-to-predict ways. If subclinical atherosclerosis lies on a phenotypic spectrum somewhere between no disease and overt cardiovascular disease, then how does choosing a study population from somewhere in the middle of this spectrum bias the analysis? Does such a study design exclude people with precisely those alleles most likely to be common risk factors for T2D and CVD? The answer is not clear, but certainly the observation that the GRS used here does not predict subclinical atherosclerosis does not refute the notion that T2D and CVD share many etiologic factors (genetic as well as nongenetic).

In contrast to the Dauriz et al’s article, Kolder et al look at common genetic factors that may modify a Mendelian form of cardiac disease, Congenital Long QT Syndrome (LQTS) type 2, is caused by heterozygosity for mutations in the voltage-gated potassium channel KCNH2. Like Dauriz et al, Kolder et al examined SNPs in several strong candidate genes, as well as an additional 22 SNPs that had previously been found to modulate QTc interval in the general population. And, like the Dauriz et al’s paper, the specifics of the study design has intentional biases that influence what can and what cannot be detected as QTc modifiers: in this case, individuals with >1 KCNH2 mutations or mutations in a second LQTS gene in addition to KCNH2. Like Dauriz et al, Kolder et al examined SNPs in several strong candidate genes, as well as an additional 22 SNPs that had previously been found to modulate QTc interval in the general population.

The authors also looked at the effect of KCNH2 mutation location on QTc interval and noted some correlations between domains in which mutations localized and QTc length. They also observed an association between 1 KCNQ1 SNP and QTc length. They then how does choosing a study population from somewhere in the middle of this spectrum bias the analysis? Does such a study design exclude people with precisely those alleles most likely to be common risk factors for T2D and CVD? The answer is not clear, but certainly the observation that the GRS used here does not predict subclinical atherosclerosis does not refute the notion that T2D and CVD share many etiologic factors (genetic as well as nongenetic).

The authors also looked at the effect of KCNH2 mutation location on QTc interval and noted some correlations between domains in which mutations localized and QTc length. They also observed an association between 1 KCNQ1 SNP and QTc interval. Of greater interest, Kolder et al investigated SNPs at the NOS1AP locus, previously shown to have large effect on length of QTc interval in the general population. They found that a composite risk score incorporating data from 6 NOS1AP SNPs strongly affected not just QTc interval but event-free survival.

This finding is interesting and somewhat surprising. In general, the effect of highly penetrant mutations, such as those in KCNH2, on phenotype tends to dwarf the effect size of common genetic variants. Common variation in NOS1AP (encoding nitric oxide synthase 1 adaptor protein) presumably alters QTc by different mechanisms than do mutations in channel proteins. The observation that NOS1AP variation...
seems to have a larger effect size on QTc in the setting of a KCNH2 compared with its effect in the general population probably reflects these orthogonal mechanisms.

Both of these studies present interesting and somewhat unexpected findings. Both the studies remind us that gene–gene interactions and their relationship to phenotype are often more complex than expected. What seem to be “obvious” relationships between many common phenotypes still lack clear mechanistic explanations. Both the studies used candidate gene approaches, so were unable to detect new genetic factors responsible for the phenotypes under study. Both the studies relied on precise quantitative assessment of different cardiac phenotypes. We are thus again reminded of the great difficulty in conducting genetic studies that have both the phenotypic precision and the size necessary to power exhaustive dissection of complex traits.

Disclosures

None.

References


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