Two expertly executed papers in this month’s issue of Circulation: Cardiovascular Genetics take candidate gene approaches to understanding genetic modification of interesting phenotypes.1,2 Kolder et al2 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 al1 look at specific genetic variation known to predict type 2 diabetes mellitus (T2D), asking if these same variants predispose to subclinical atherosclerosis.

In the case of Dauriz et al’s paper,1 the specifics of the study design have 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,1 Kolder et al2 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,1 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 were excluded. Because this study looked only at SNPs with minor allele frequency >10%, rare variants with strong effects that may exist were excluded from possible detection.

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 greatest interest, Kolder et al2 investigated SNPs at the NOS1AP locus, previously shown to have large effect on length of QTc interval in the general population.3 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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Modifiers of Cardiac Phenotypes
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