Common Variants in 22 Loci Are Associated with QRS Duration and Cardiac Ventricular Conduction

Sotoodehnia et al

Sotoodehnia et al investigated the role of common genetic variations (single nucleotide polymorphisms; SNPs) in determining QRS duration. The authors performed a meta-analysis of 14 genome-wide association studies of QRS duration in a total of 40 407 individuals (after adjustment for clinical variables) using a cut off of $P=5\times10^{-8}$. The discovery phase was followed by a validation study consisting of 7170 newly genotyped European individuals. The most significant association has been identified in a region of chromosome 3 corresponding to the gene SCN10A encoding for the Nav1.8 voltage gated sodium channel, thus confirming results of two previous genome-wide association studies that investigated the genetic component of heritability of QRS. The study also included an experimental section that complemented the molecular results and elegantly demonstrated that SCN10A is expressed in ventricular tissue and in Purkinje fibers of mice. The bench study also showed that pharmacologic blockade of Nav1.8 delays intraventricular conduction, thus confirming that Nav1.8 is involved in the conduction system.

This study is important because it demonstrates, in a very large cohort, the effect of several common DNA variations in the modulation of electrophysiologic properties of the heart (Figure 1). The large size of the study and its confirmatory nature implicate genes such as Nav1.5 and Nav1.8 (two sodium channels expressed in the heart) in the control of cardiac conduction. The study also highlights the importance of calcium-controlling proteins in impulse propagation in the heart showing association of QRS duration and loci that include the following genes: 1) calsequestrin that acts as a calcium buffer in the sarcoplasmic reticulum; 2) phospholamban that regulates calcium uptake by sarcoplasmic reticulum Ca$^{2+}$ ATPase (SERCA2a); 3) protein kinase Ca implicated in regulation of phosphorylation of phospholamban; and 4) striatin, a Ca$^{2+}$-calmodulin binding protein that directly binds to caveolin proteins.

Among the genes associated with QRS duration, there are genes coding for a few TFs, such as HAND1, 3 TBXs, NFIA, and KLF12. Unfortunately, so far, there is no biologically plausible explanation for their effect on cardiac conduction based on current knowledge. Time will tell whether this reflects the shortcomings of the existing knowledge and the superiority of a nonbiased genetic approach or whether the association will turn out not to be real.

Cardiac electrophysiology has achieved major results in the understanding of electrical properties of the heart in animal preparations, but it has always faced the difficulty of dissecting the electrical component of the human heart. The functional characterization of human myocytes is extremely difficult, as cells do not grow in vitro; they rapidly dedifferentiate, and the availability of human samples is mainly restricted to sick hearts or to the few donors’ hearts that are not used in transplants. Investigations, such as the study by Sotoodehnia et al, help fill in this gap, increasing our understanding of the electrical activity in the human heart. Beside identifying loci that modulate the duration of QRS, the study highlights genes included in the region of association that are also likely to contribute to electrical propagation in human hearts.

Interestingly, the data show that a variety of genes concur to influence intraventricular conduction, and they also demonstrate that several genes identified in the present study in association with QRS duration have previously been linked to other ECG parameters. Overall, these observations support the view that these genes exert multiple effects, whether direct or indirect, on different targets, the so-called pleotropic effect (from the Greek “multiple” and “changes”). We learn from Sotoodehnia et al that there is a large overlapping of the effect of genes on the different electrocardiographic parameters. As shown by the authors, genes that modulate cardiac conduction (PR and QRS intervals on the ECG) also influence repolarization (QT interval). Interestingly, the genes that affect PR and QRS do so in the same direction as expected, whereas genes that influence both QRS and QT exert a predominant mildly discordant influence. Because this is at variance with what happens in clinical settings, there is no clear explanation for the observation. This complexity leads to the evidence that, as would be expected, it is not possible to pinpoint a single common DNA variant as being responsible for the control of a specific electrical parameter (in other words, there is not an SNP that profoundly modulates PR or QRS). In a teleological perspective, we could say that having a large number of SNPs that modulate a single ECG interval provides a larger “safety factor” as multiple concomitant “minor alleles” are required to induce a clinically relevant abnormality.

The negative side of this molecular Yin and Yang is that there is not a single polymorphism that has a strong effect on QRS duration to recommend its use to predict the propensity of carriers to develop specific human diseases. Even the
strongest hit of the study, SCN10A, is not able to explain a substantial proportion of QRS variation to allow its use in clinical practice. As the authors report, it takes 20 SNPs to explain approximately 6% of the observed variance in QRS duration.

Despite, at present, the polygenic nature of genetic regulation of cardiac electricity prevents clinical applications of the observations made in this study, it is reasonable to anticipate that when genome sequencing will become faster and cheaper and will enter clinical medicine, bioinformatics will allow development of risk prediction schemes able to integrate the molecular complexity of polygenic regulation of biologic parameters into clinically applicable risk stratification metrics.

References
Genetic Determinants of Cardiac (Electric) Conduction
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