Dissecting the Genetic Basis of the ECG as a Means of Understanding Mechanisms of Arrhythmia

Rafik Tadros, MD, PhD; Ruben Coronel, MD, PhD; Connie R. Bezzina, PhD

The surface ECG records the electrical potential of the heart at the surface of the body as the electrical impulse travels throughout the heart with each heartbeat. The P wave represents depolarization of the atria, which spreads from the sinoatrial node toward the atrioventricular node and from the right to the left atrium. The PR interval reflects the time the electrical impulse takes to travel from the sinus node through the atrioventricular node. The QRS complex represents the rapid depolarization of the ventricles, and the T wave represents the repolarization of the ventricles.

The ECG is one of the most accessible and valuable diagnostic tests. It informs about the presence of cardiac chamber enlargement/hypertrophy, conduction disturbance, arrhythmia, myocardial infarction/ischemia, and even provides indications for electrolyte imbalance or drug intoxication. Since about a decade, researchers have turned to the ECG as a tool to dissect the genetic basis of cardiac electrical function with the idea that the biological processes that underlie or impinge on the different parameters of the ECG are mediators (intermediate phenotypes, endophenotypes) of arrhythmia risk. This concept, which in itself is clearly intuitive, is supported by population-based studies that demonstrated that ECG parameters are associated with risk of arrhythmia or sudden cardiac death. The approach is furthermore rationalized by the fact that ECG parameters have been shown to have a heritable component (reviewed in reference). The first ECG parameter that was studied in this way by the genome-wide association study (GWAS) approach was the QT interval; in fact the QT interval was one of the first traits to be studied at the outset of the GWAS era 10 years ago. Facilitated by the availability of large cohorts with ECG recordings and the ability to measure ECG parameters reproducibly in an automated fashion, GWAS has since been applied to several ECG parameters in increasingly larger cohorts of individuals primarily of European descent with >150 loci being identified as modulators of these traits.

In the current issue of Circulation: Cardiovascular Genetics, Christophersen et al report findings from a GWAS that they conducted on parameters related to the P wave in 44,456 individuals originating from 12 cohort studies. These parameters were namely P wave duration, so far understudied by GWAS, and P wave terminal force, studied by GWAS for the first time. Concordant with the intermediate phenotype paradigm, and the relationship between these parameters and atrial electrophysiology and risk for atrial fibrillation (AF), these investigators posited that elucidating genetic variants related to these parameters will help in understanding atrial electrophysiology and possibly uncover genetic determinants and mechanisms of AF. The authors further postulate that this may in turn allow identification of new therapeutic targets for AF. They report 15 loci that include loci previously identified for P wave duration or the related PR interval, as well as novel loci. As expected for common variants, the effect size associated with each of the identified variants is small, and also when considered in aggregate, the variants explain only a small percentage of the population variance of these traits. Loci identified by GWAS are not directly informative with respect to the gene underlying the effect or the underlying mechanism; in an effort to provide clues on the causal gene at the identified loci, the authors conducted expression quantitative trait locus analysis, relating the associating single nucleotide polymorphisms (SNPs) to gene expression in left atrial tissue and other tissues from the Genotype-Tissue Expression consortium.

The validity of the intermediate phenotype approach to dissecting complex arrhythmias, such as AF, is underscored by the fact that genetic loci that were identified by GWAS as modulators of the P wave have also been related to AF susceptibility. For example, the SCN10A locus that was shown to be associated with P wave duration in the current study has also been robustly associated with AF. Yet, although this framework is attractive, the complex relationship between P wave-derived markers and AF complicates the process of relating the identified genetic variants to mechanisms of AF. This is, in part, related to the multifactorial nature of the arrhythmia. Atrial fibrillation occurs predominantly in the aged, where atrial dilatation secondary to various acquired cardiac diseases (such as hypertension, cardiomyopathy, ischemic heart disease, or valvular heart disease) may also contribute. Moreover, the arrhythmia occurrence is strongly modulated by the action of the autonomic nervous system.

The mechanisms of AF are multiple. AF is thought to arise from the myocardial sleeves of the pulmonary veins from where a focal mechanism based on automaticity or triggered
activity may maintain the arrhythmia. Pulmonary vein isolation of the atrium prevents AF recurrence. On the other hand, aging-induced fibrosis of the atrial myocardium may provide an arrhythmogenic substrate for reentrant arrhythmias. Electrophysiological remodeling brought about by AF itself may lead to perpetuation of the arrhythmia. A short atrial action potential facilitates both mechanisms, whereas slow conduction is a prerequisite for reentry. Thus, although some genes at the loci described by Christophersen et al. such as SCN5A and TBX5, can be easily placed within this framework by virtue of their recognized role in mediating cardiac conduction, it is not surprising that for others their possible role is difficult to gather. However, one could argue that the latter may be the most interesting because they may uncover yet-unknown mechanisms.

In Discussion in the Data Supplement section, the authors speculate about the potential roles of the genes closest to the most significant variant at the identified loci. Although one must here acknowledge the caveats associated with connecting associating SNPs to genes in the region, primarily because the effector genes may be located at considerable distances and an SNP located in a particular gene may in fact act through effects on a neighboring gene, in our view, this is a very, if not the most, interesting part of their article. As mentioned above, the SCN5A and TBX5 genes are of obvious importance, and the pleiotropy observed for SNPs in these genes (with SNPs being associated with multiple ECG conduction parameters and arrhythmia phenotypes) underscores their relevance for conduction in different compartments of the heart.

The authors speculate that the involvement of KCND3 in modulating P wave terminal force can be explained by downregulation of the encoded K_\text{v}4.3 channel underlying the transient outward potassium current I_o, leading to a prolongation of the action potential duration. A prolongation of the action potential may lead to early afterdepolarizations, triggered activity, and arrhythmias with a focal origin. Conversely, an increased K_\text{v}4.3 expression would shorten the atrial action potential and promote re-entrant arrhythmias like AF. Therefore, an increased K_\text{v}4.3 and a subsequent shortening of the atrial action potential are another plausible explanation for the relationship between the genetic markers, the P wave, and AF suggested by the study of Christophersen et al.

In the absence of a strong candidate gene within a given locus, the identification of the likely causal gene for downstream functional studies is at present a laborious endeavor. As for most GWAS loci, those identified in this study most likely act by means of effects on gene expression dosage through causal variant(s) within regulatory regions. The identification of the underlying genetic mechanism and the gene(s) through which they act thus necessitates an understanding of the gene regulatory landscape in the relevant tissue. The application of next-generation sequencing–based technologies, such as chromatin immunoprecipitation sequencing (which combines chromatin immunoprecipitation with massively parallel DNA sequencing to identify transcription factor–binding sites), self-transcribing active regulatory region sequencing (which is capable of identifying enhancer regions), and chromosome conformation capture (such as Hi-C which inform us of the 3-dimensional topology of DNA and point to promoter–enhancer interactions), in cardiac tissue is expected to empower these efforts. Expression quantitative trait locus analysis that is also being increasingly applied in human heart and as implemented by Christophersen et al. will help in prioritizing genes at loci and in inferring the direction of effect. Other transcriptomic approaches, such as coexpression analysis as recently implemented by us in a functional follow up study of a locus identified for Brugada syndrome, may also provide functional hypotheses to be tested experimentally.

The progress being made in recent years in dissecting genetic factors contributing to AF, both by means of genetic studies in large cohorts of AF and by the intermediate phenotype approach, is remarkable. With their large collaborative study on P wave indices as intermediate phenotypes, Christophersen et al. have made another important contribution along a journey that will eventually lead us through the maze of AF.

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Disclosures
None.

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