**EDITORIAL COMMENT**

**Repolarization Recipes for Atrial Fibrillation**

**Beyond Single Channel Variants***

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Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, represents a major health burden to people and health care systems within the Western world (1). Given its increasing prevalence with age, coupled with the aging population, the number of Americans affected is expected to surge from approximately 2.3 million in the year 2000 to nearly 16 million by 2050 (2). Until recently, AF was considered to be a sporadic, nongenetic disorder. However, we and others have shown that lone AF has a substantial genetic basis. Mutations in genes encoding cardiac ion channels, gap junction proteins, and signaling molecules have been reported in isolated cases and small families (3–5).

The advent of the human genome project, HapMap project, and high-throughput genotyping has accelerated our ability to discover the genetic contribution to common variation in human disease. In 2007, a genome-wide association (GWA) study identified 2 common AF susceptibility variants on chromosome 4q25 (6). More recently, 2 additional AF loci on chromosomes 16q22 (7,8) and 1q21 (9) have been identified. It is quite likely, however, that the effects of alleles in many genes and interactions among those gene products contribute to complex diseases such as AF (5). Although GWA studies have identified hundreds of variants associated with common human diseases, and have provided valuable insights into the genetic architecture of complex traits, individually these loci confer relatively small increments in AF risk (odds ratios 1.1 to 2.0) and explain <10% of the heritability of lone AF. This raises the possibility that a combination of variants with intermediate effects may account for a large fraction of the risk for lone AF (10,11).

The development of methods for coupling targeted capture and massively parallel deoxyribonucleic acid sequencing now allows cost-effective determination of all of the coding variation present in an individual genome. Whole exome sequencing is a powerful new approach to identify genes that underlie not only Mendelian disorders but also diseases that do not exhibit simple Mendelian transmission (complex traits). This approach has been utilized successfully to identify variability in protein-coding regions that alter risk for hyperlipidemia (12) and autism (13). In addition, exome sequencing of candidate ion channels genes in patients with idiopathic epilepsy has also demonstrated that rare disease-associated variants in known Mendelian disease genes were also present in a majority of healthy control subjects (14). These data would go against the prevalent dogma that rare variants are always disease causing or disease associated. Furthermore, the importance of evaluating total variant burden in an individual patient is emphasized when estimating the susceptibility to development of a disease.

In contrast to the single candidate gene approach, combinations of common and rare gene variants may play a central role in disease susceptibility (15). Epistasis, namely, gene–gene interaction, is recognized as prevalent in the genetic architecture of many complex traits. Given the inherent difficulty of evaluating multiple combinations of gene variants in vivo or in vitro, the development of in silico methods for modeling these combined effects will be critical when trying to understand and derive meaningful information from genomic data.

Potassium channels play a central role in atrial repolarization, and mutations in genes that encode for the cardiac potassium channels have been associated with AF. In this issue of the *Journal*, Mann et al. (16) evaluated the role of these gene variants in families with AF. They tested the hypothesis that the presence of multiple cardiac potassium ion channel variants may exhibit epistatic effects that contribute to an arrhythmogenic atrial substrate and lead to increased AF susceptibility. Genes encoding the major cardiac potassium channels were resequenced in 80 AF probands. Nonsynonymous variants identified in AF probands were then evaluated in 240 healthy controls. Novel variants were functionally characterized using conventional patch-clamp techniques. Nineteen nonsynonymous variants in 9 potassium channel genes were identified, including 11 rare variants (minor allele frequency <1%). These variants were also present in healthy controls; however, 6 of the 11 rare variants were only present in persons with AF. Overall, rare variants were present in a higher proportion of AF probands than controls, but there was no difference in the number and distribution of common and uncommon var-
Mann et al. (16) have presented convincing data supporting the hypothesis that the presence of rare functional potassium channel variants of varying effect size may contribute to an atrial arrhythmogenic substrate and increase susceptibility to AF. For most of the novel rare variants identified, especially KCN45-G568V and KCNH2-E444K, in vitro analysis revealed a relatively modest effect, suggesting that these rare variants by themselves may not increase the susceptibility to AF, but require the presence of additional variants (rare or common) in combination. Using in silico modeling, the investigators were able to assess the functional consequences of multiple variants and identify how they may combine to substantially modulate atrial repolarization. That is an important step towards a better understanding of the role of multiple genetic variants in AF; however, these results must be interpreted with caution considering the variability of in vivo and in vitro results (18).

**REFERENCES**


**Key Words:** atrial cell modeling ■ familial atrial fibrillation ■ genetics ■ potassium channels.