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Ion channel mutations in AF: Signal or noise?

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Since the initial report of a gain of function mutation in KCNQ1 in a single family with atrial fibrillation (AF) and prolonged QT interval¹, multiple sequence variants in a variety of ion channels have been reported in subjects with AF. Missense variants in several potassium channels¹⁻⁸, and in the sodium channel⁹⁻¹³ have been identified both in individuals, and occasionally in larger extended kindreds with more rigorous genetic support. In addition, somatic myocardial mutations in connexin 40, a gap junction subunit have been reported in a series of atrial biopsies obtained from subjects with lone AF.

Despite these data, the role of ion channel mutations in AF remains uncertain. For the vast majority of the sequence variants identified to date, there are few genetic data to substantiate a causal role in the arrhythmia. Even for the reported gain of function mutations in KCNQ1 where the genetic data are more robust, there is discordance between the available *in vitro* data and observed effects on atrial and ventricular electrophysiology. Understanding the allele specific and regional expression of this imprinted gene, and modeling the specific disease alleles *in vivo* may shed light on these discrepancies, but to date the precise mechanism by which AF and QT prolongation coexist is unclear. *In vitro* data for other ion channel variants have not yet identified a unifying physiologic mechanism, which may reflect the multiple possible etiologies of this common disease, but may also raise questions about the pathophysiologic role of these variants in AF.

The *in vitro* data obtained in heterologous expression systems may not reflect *in vivo* physiology where many other accessory proteins, local membrane composition and significant redundancy all may modify the final phenotype. In addition, apparent mutations may have no effect in the context of homeostatic influences of other physiologic pathways. Human genetics offers many examples of profound *in vitro* effects that fail to translate into an *in vivo* phenotype. The absence of robust genetic support in humans or in animal models is compounded by other circumstantial evidence. Ion channel gene mutations, if causal in AF, are responsible for only a small fraction of disease. Resequencing studies of each of the

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ion channel genes implicated to date have identified only a handful of putative mutations, which even if they were all causal would represent less than 2% of all AF (Figure 1). This is in contrast to a more widely accepted ion channelopathy such as long QT syndrome in which at least 75% of subjects have a mutation in one of five ion channel proteins. Furthermore, it is important to note that in most studies of AF the control populations have not been subjected to parallel resequencing, so that similar rare variants with modest functional consequences that may well exist in normal individuals have not been revealed. Novel sequencing technologies will allow cost effective and comprehensive resequencing of subjects and controls in the near future.

It is in this context that Ravn and colleagues report in this issue of *Heart Rhythm*¹⁴, a series of 158 patients with AF was screened for mutations in KCNE5 where they identified one variant, L65F, in a highly conserved region of the protein. KCNE5 or MiRP4 is a beta-subunit that interacts with KCNQ1 or the alpha/pore-forming subunit of the potassium channel complex and leads to a suppression of the I_{Ks} current. Expression of the L65F variant in combination with KCNQ1 results in a failure of the normal inhibition of the I_{Ks} current or a gain of function of I_{Ks} . Importantly, the authors demonstrate that this gain of function of I_{Ks} is dominant and would be anticipated to lead to a shortening of the atrial action potential duration and a predisposition to AF. While the study is limited by the lack of additional family members that would permit stringent genetic support, the potential shared mechanism with well-validated KCNQ1 mutations strongly suggests the L65F variant plays a role in the AF seen in this family.

Ultimately, several different strategies will converge to help resolve the true role of ion channel gene mutations in AF. Novel third generation sequencing technologies will allow large-scale studies in subjects and controls. Genome wide association studies will define the common small effect alleles contributing to atrial arrhythmias¹⁵. *In vivo* modeling of some of the putative AF alleles may resolve questions on the net effects on atrial and ventricular electrophysiology, though this will likely require the use of organisms other than the mouse. Emerging technologies will uncover subclinical endophenotypes for AF, facilitating genetic studies of informative families with Mendelian AF. The identification of the causal genes at several loci and the evaluation of these genes in large series of less selected AF subjects will define new pathways predisposing to the arrhythmia. Importantly the known loci do not contain any obvious ion channel genes, suggesting that distinctive mechanisms are responsible for such AF. Overlap with known loci for cardiomyopathy exists, and the relationship between AF and heart failure is likely to be much more fundamental than simple elevation of atrial pressure. As investigators explore the links between these novel AF genes and emerging macromolecular complexes regulating ion channel conductance and downstream signaling, the mechanistic role of ion channels in AF will be established.

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Figure 1. Ion channel mutations are rare in atrial fibrillation

Compilation from the literature of the total number of subjects with AF screened for each gene versus total number of mutations identified in these genes. Note: Only mutations in subjects with AF are illustrated. Some series of patients were selected cases of familial AF. Figure based on references: ^{2-10, 16}, but it is anticipated that similar studies are underway at other centers. Since not all subjects have been screened for every gene, it is not possible to determine the precise frequency of these mutations.