Does Atrial Fibrillation Follow Function? 
Ion Channel Mutations and Lone Atrial Fibrillation

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In this issue of Circulation: Arrhythmia and Electrophysiology, Hayashi et al present an interesting study evaluating the role of rare genetic variants in cardiac ion channels in the development of lone atrial fibrillation (AF).

Over the last 10 years, many studies have considered individual candidate genes for AF and identified mutations in a wide range of genes encoding ion channels, signaling molecules, and transcription factors among others. These studies identified mutations in the cardiac sodium channel and accessory subunits, as well as in several potassium channels and gap junction proteins. In aggregate, each of these candidate gene studies has added to an ever-expanding list of putative causative genes for AF. However, when considering the role of a single gene, one is left wondering about the impact of that particular gene in the overall burden of the arrhythmia.

To address this issue, several recent studies have considered panels of candidate AF genes. For example, Weeke et al sequenced 45 candidate genes in 303 patients with lone AF and observed a rare variant in ≈20% of the patients. Similarly, Olesen et al sequenced 14 AF-associated genes in 192 lone AF patients and compared their results to publically available data on 6503 individuals from the Exome Variant Server. They found that lone AF patients carry significantly more novel or rare genetic variants than expected and that the majority of the variants that had been previously functionally evaluated were associated with abnormal channel function.

In this context, Hayashi et al examined 90 Japanese patients with lone AF and 250 healthy controls. They selected a panel of 12 genes previously implicated in AF and performed high-resolution melting curve analyses followed by DNA sequencing to identify potential mutations. The identified mutations were then evaluated in silico to predict the potentially pathogenic effects and in vitro by cellular electrophysiology.

Among the lone AF patients, nearly one third had a family history of AF, confirming the strong genetic basis for this arrhythmia. Seven mutations were identified in 5 ion channel genes (KCN5A, KCNQ1, KCNH2, SCN5A, and SCN1B). In KCN5A, a gene encoding the Kv1.5 or ultrarrapid rectifier current (I_{Kur}), 2 variants were identified that had a gain and loss of channel function, respectively. These findings are in keeping with prior reports linking gain of function and loss of function variants in KCN5A with AF. Two gain of function variants were also identified in the KCNH2 gene encoding the rapid rectifier potassium channel I_{Kr}. These 2 variants resulted in a slower deactivation time course and an increased peak current density. Finally, although one variant was found in KCNQ1, no discernable alteration in channel function was identified.

One loss of function variant was identified in the cardiac sodium channel, SCN5A, that resulted in reduced peak sodium current density and has previously been associated with AF. SCN1B encodes a β-subunit of the sodium channel and harbored a gain-of-function variant that was also predicted as pathogenic. Functional analysis showed that this variant caused an increase of the peak current density and a negative voltage shift to steady-state activation. In contrast, loss of function mutations in SCN1B have also been associated with AF. Interestingly, one of the patients harboring this variant was successfully treated with the sodium channel blocker pilsicainide.

A strength of the work by Hayashi et al is the thorough functional evaluation for each of the identified genetic variants by cellular electrophysiology. Although any in vitro system has inherent limitations, the authors are to be commended for their systematic consideration of every AF-related variant. With variants that have gain, loss, or no overt effect on channel function.
function, their findings highlight how little we understand about the molecular mechanism of this common arrhythmia. In an intriguing aspect of the current work, the authors also illustrate the potential for genotype-directed pharmacological therapy for a subset of AF cases.

A major challenge in the interpretation of this and similar studies resides in the scale of both the number of genes considered and in the sample size. Although the 12 genes were logically selected based on being previously implicated in AF, the role of the rest of the genes in the exome remains unknown. Similarly, with a sample size of 90 cases and 250 controls, the power to conclude that any given gene is definitively related to AF remains limited.

In the end, the study by Hayashi et al serves to nicely demonstrate the complexity in the molecular basis of AF. Ultimately, future large-scale studies with broad coverage of the exome or genome that include thousands of cases and controls will help to clarify the role of these ion channel mutations in AF.

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References

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