EDITORIAL COMMENT

An Irregularly Irregular Inheritance*

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Atrial fibrillation is the most common arrhythmia syndrome in the U.S., affecting over 3 million people (1,2). Most cases are sporadic, and risk factors include increasing age, hypertension, cardiomyopathies of ischemic or nonischemic origin, and valve diseases that alter atrial structure and electrophysiological function. The morbidity of atrial fibrillation comes from both the rapid irregularly irregular rhythm and blood clots that lead to embolic strokes. Therapeutic options for atrial fibrillation include rate control (beta-blockers, Ca^{2+} channel blockers, digoxin, or atrioventricular node ablation and ventricular pacing) used in conjunction with systemic anticoagulation (warfarin sodium) to prevent strokes, or rhythm control (Class IA, IC, or III antiarrhythmic drugs or surgical and catheter-based ablation). Several randomized, controlled studies comparing rhythm and rate control have not shown a survival advantage for rhythm control (2–4). This may be caused by the limited effectiveness of the currently available drugs in maintaining sinus rhythm and their proarrhythmic risks.

Abnormal focal impulse formation from automaticity and/or triggered activity and multiple-circuit reentry are the major mechanisms responsible for the initiation and maintenance of atrial fibrillation (5). Conditions that shorten action potential duration (APD), shorten the atrial effective refractory period (AERP), or slow conduction velocity promote atrial fibrillation. In addition, the fast heart rate in atrial fibrillation leads to a rapid decrease in APD and AERP, a phenomenon called electrical remodeling that is responsible for the finding that atrial fibrillation begets atrial fibrillation. As such, a large number of genes related to atrial structure and electrical function could theoretically contribute to the arrhythmia.

Atrial fibrillation has an inherited component (6). Using candidate gene and linkage approaches, gain-of-function mutations in K^+ channels have been identified in the rare familial forms of atrial fibrillation alone or in conjunction with other inherited arrhythmia syndromes (7–10). Germ line connexin 40 (Cx40) mutations and somatic Cx40 mutations specific to atrial tissue have also been found in subjects with atrial fibrillation (11). Two additional loci for atrial fibrillation have been identified at chromosome 10q22–24 and 6q14–16 by linkage analysis in large families, but the genes and mutations responsible in these families remain unknown (12,13). In addition, polymorphisms in ion channel (14,15) and non–ion channel genes such as those of the renin-angiotensin-aldosterone system (16) have been associated with either lone atrial fibrillation or atrial fibrillation caused by structural heart disease. Of note, a genome-wide association study in an Icelandic population recently identified an additional locus at 4q25 for the common forms of atrial fibrillation (17). The findings were confirmed in 3 replication cohorts of European descent and in 1 of Chinese descent; the presence of the most predictive single nucleotide polymorphism (rs2200733T, allele frequency 0.1 to 0.2 in Europeans; 0.5 to 0.6 in Chinese) in the linkage disequilibrium (LD) block increased the risk of atrial fibrillation by approximately 1.7, and the association was stronger for younger subjects and for those with atrial flutter. The gene responsible for this association remains unknown.

Many inherited cardiovascular diseases, including cardiomyopathies and atrial fibrillation, are not apparent until relatively advanced ages. This age-dependent penetrance poses a challenge for linkage studies because identification of sufficient living affected individuals for linkage is difficult, many asymptomatic individuals may be gene carriers, and sporadic cases are more common in older individuals. The use of endophenotypes, or hereditary characteristics that are associated with the condition but are not a direct symptom of that condition, may allow earlier identification of affected individuals. For example, the presence of conduction disease has been used to identify individuals with autosomal-dominant forms of dilated cardiomyopathies before the onset of left ventricular dysfunction (18).

In this issue of the *Journal*, Darbar et al. (19) studied a moderate-sized family with lone atrial fibrillation inherited in an autosomal-dominant manner and identified a novel locus at chromosome 5p15. They also showed that an endophenotype, signal-averaged P-wave duration correctly identified carriers of the disease locus and improved the logarithm of the odds score from 3.0 to 3.6. Of note, none of the 5 known genes at that locus had mutations that could explain atrial fibrillation in this family.

To date, only mutations in ion channel genes have been shown to cause familial atrial fibrillation, and the majority of these have been identified by the candidate gene approach. In addition, although 2 other chromosomal loci were deter-

mined for lone atrial fibrillation 4 and 10 years ago, the causative genes have not been found as yet. Several factors make the genetics of atrial fibrillation difficult to study. First, sporadic atrial fibrillation is quite common in older individuals, increasing the phenocopy rate and the potential for misclassification of individuals as affected. Second, the penetrance is age-dependent. Finally, the list of potential candidate genes aside from ion channels is very long. In addition to all genes expressed in the atrium related to structure and electrophysiology, a variety of other genes have been shown to be associated with atrial fibrillation in transgenic mouse models (20,21).

The signal-averaged P-wave duration has been associated with atrial fibrillation in prior studies (20). The current study supports its use for phenotypic characterization of familial atrial fibrillation, especially in young individuals who do not yet show the complete phenotype. Caution is required, however, in the interpretation of the results using this test. Atrial fibrillation is genetically heterogeneous, and there is no guarantee that all families will show similar abnormalities in P-wave duration. In addition, individuals with sporadic atrial fibrillation in a family with inherited fibrillation may also have abnormal P-wave duration, as a result of conditions such as structural heart disease. Thus, although the use of the signal-averaged P-wave duration as an endophenotype may increase the power to identify linkage, it could also increase the likelihood of misclassification of individuals when compared with the use of atrial fibrillation alone in the linkage studies. As such, the use of this and other endophenotypes has the potential to either help or hurt studies aimed at the ultimate identification of the causative gene and mutation.

It is important to search for genes associated with both familial and nonfamilial forms of atrial fibrillation. These genes, mutations, and polymorphisms may point toward novel mechanisms important for the maintenance of coordinated atrial rhythms and suggest new ways to prevent and/or treat the more common forms of this arrhythmia. As the population ages, the prevalence and incidence of atrial fibrillation will continue to increase. The study by Darbar et al. (19) and others like it may help to lessen the impact of this growing source of cardiovascular morbidity and mortality.

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