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Strategies for risk analysis and disease classification in atrial fibrillation

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Editorial Comment

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia, impacting 30 million people worldwide, with three million people in the United States (U.S.) alone. Notably, this number is expected to increase to > ten million Americans by 2050.^{1–4} AF results in an increased risk for morbidity, as well as mortality, with patients having a five-fold increase in risk of stroke and a 1.5–1.9 fold overall increase risk of mortality, after adjusting for other risk factors.^{5–9}

AF risk is multi-factorial, with a common risk factor for AF being increased age. For example, the prevalence of AF increases from 4% in individuals >60 years of age to 10% in individuals over 80 years.² In addition to age, other risk factors for AF include cardiac (sinus node dysfunction, valvular heart disease, cardiomyopathy) and non-cardiac (diabetes) phenotypes, as well as environmental factors.^{2–4} Furthermore, while not generally considered an inherited arrhythmia, there is now significant data to support the role of genetics in AF.^{10, 11} Considering the broad interplay between various risk factors and genetic tendencies that contribute to AF, as well as heterogeneity of disease pathways (electrical, inflammation, fibrosis), it is not surprising that the efficacy of AF treatment strategies is variable.^{12–14}

Given the global impact of AF, an enhanced understanding of disease pathophysiology is essential for improved diagnostics and therapies. As in many forms of cardiovascular disease, findings from rare familial forms of AF have provided critical clues to our understanding of common acquired forms of this complex disease. While first reports suggesting the heritability of AF trace back nearly 75 years¹⁵, seminal work from the

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Framingham Heart Study reported that ~one-third of individuals with AF had at least one parent with the disease.¹⁶ Subsequent work from Lubitz and colleagues further illustrated that individuals with a first-degree relative with AF displayed a multivariable-adjusted hazard ratio for AF of 1.4.¹⁷ Additional evidence supporting the heritability of AF ranges from risk association studies in twins to examination of large population cohorts.^{11, 18–20}

Familial AF has aided our understanding of disease pathogenesis. For example, the link between electrical dysfunction and AF was clearly illustrated by studies in linking a “gain-of-function” variant in the gene encoding the alpha-subunit of the cardiac I_{Ks} potassium channel (*KCNQ1*).²¹ Subsequent studies have identified multiple forms of congenital AF linked with variants in cardiac ion channels^{22, 23}, gap junction molecules²⁴, cytoskeletal proteins^{25, 26}, and molecules that regulate cardiac transcriptional programming.²⁷

While useful in describing critical cellular pathways underlying AF pathobiology, congenital forms of AF are relatively rare. Thus, genetic screening for familial AF in the clinic has had limited application. However, advances in sequencing platforms and a decade of data from Genome Wide Association Studies (GWAS) have pushed forward the potential of utilizing genetic variation to predict AF risk, treatments, and outcomes. For AF, GWAS has linked AF risk in multiple large populations with single nucleotide polymorphisms (SNPs) located at 4q25.¹⁰ In fact, data from these studies illustrate both the power and limitations of GWAS data. On one hand, 4q25 AF SNPs are common across populations and therefore may have widespread clinical application for defining AF susceptibility. However, on the other hand, the 4q25 AF SNPs are found in a non-coding region located ~150 kilobases from any known gene.¹⁰ Thus, similar to other SNPs linked with AF, while clear beacons for disease risk, until recently these variants have not necessarily generated explicit data on disease mechanisms, clinical outcomes, or therapeutic strategies. However, recent GWAS data have provided important clues for disease mechanisms and outcomes. An elegant example of GWAS to identify potentially new AF therapeutic approaches was a study that identified intronic variants in the gene encoding the small conductance SK3 potassium channel (*KCNN3*) in AF patients.²⁸ In only 6 years since this study was published, work on multiple pre-clinical models has illustrated the exciting potential of SK channel regulation for modulation of the atrial action potential in disease.^{29, 30} In addition to defining mechanisms, studies support the potential use of GWAS markers to predict AF outcomes. For example, a common 4q25 SNP has now been linked with response to anti-arrhythmogenic treatments as well as an independent indicator of recurrence of AF following cardioversion.^{31–33} Similar methodologies have utilized multiple genetic markers to assess potential risk for stroke associated with AF.³⁴ In summary, advancements in genetic platforms and screening have transformed our ability to correlate specific AF disease signatures and outcomes with combinations of variants at the population level. However, few past studies have combined approaches to dissect directly the relationship of common AF disease SNPs with AF tissue pathobiology.

While electrical dysfunction is widely linked to arrhythmogenic triggers, other hallmark features of human AF are inflammation and fibrosis. It is known that inflammation and fibrosis are highly associated with AF, both in patients with organic heart disease and those with lone AF.³⁵ In fact, studies in AF patients have revealed that the extent of fibrosis may

be predictive of AF recurrence post-ablation, regardless of comorbidities.³⁶ In this issue of *Journal of Cardiovascular Electrophysiology*, Roberts and colleagues expand on the above described approaches³⁷ to pose an important question: is there a way to correlate genetic risk with histopathology of AF, and moreover, is there a role for the evaluation of risk SNPs in further characterizing inflammation and fibrotic mechanisms of the disease?³⁸ The group selected ten previously identified SNPs based on disease-specific prevalence and SNP relationship with genes implicated in AF etiology. Following detailed analysis of inflammation and fibrosis in the left atrial appendage of 177 patients with AF, and correlation with the patient's corresponding SNP, it was found that only one, rs71664883, had a statistically significant association.³⁷ More specifically, this SNP was associated with reduced left atrial inflammation. The rs71664883 SNP is located in *HCN4*, and is presumed to impact the function of atrial I_f that regulates diastolic depolarization. Although it is possible that dysfunction of the I_f may promote atrial remodeling over time, it is reasonable that the phenotype of AF in patients harboring this SNP is founded in electrical disturbances or "triggers", rather than being predominantly driven by disruptions in substrate or tissue inflammation.

Roberts and colleagues posed a thoughtful integrative approach to the current understanding of genetic causality of disease risk.³⁷ Moreover, they address an important variable in understanding response to treatment that addresses the risk profile of a patient; specifically the genetic risk profile and its relation to the fibrosis/inflammation that serve as perpetuating substrates for disease. Given our current abilities with genetic analysis and classification of large data sets, it is feasible, particularly with the ability to utilize whole exome sequencing data (versus evaluation of select genes), that genetic analysis may inform clinical treatment if we efficiently (and cost-effectively) correlate variant "signatures" with specific disease sub-classifications.

There are two factors to discuss related to the current study. First, while the population studied was one of the largest of its type, it may take additional power to reveal small, yet significant, correlations between inflammation, fibrosis, and AF risk. For example, in the recent work from Tada and colleagues, genetic (12 SNPs) and clinical data from 27,471 individuals were analyzed to link AF with increased risk of stroke.³⁴ It is also likely that in a complex disease such as AF, comorbidities such as diabetes, congestive heart failure, coronary artery disease, and hypertension may impact tissue/inflammatory signatures thus confounding the discovery of additional correlations. Second, as was addressed by the authors, the local histological environment of the left atrial appendage may differ from other regions of the atria impacted by remodeling. Highly implicated areas of arrhythmogenesis in AF include the pulmonary vein orifices and the right atrial lateral wall. Limitations of studying these particular areas of tissue *in vivo* are difficult to overcome, and will require further investigation into alternative study strategies.

As illustrated by Robert and colleagues, and reviewed recently by Ellinor and colleagues, the scientific community has never been more suited to begin correlating genetic data in patient populations with disease risk.¹⁰ Public-access databases are now available to cross-reference variants with described phenotypes and set the groundwork for such genetic analysis. Importantly, analysis of large data sets will require seamless integration of electronic

medical records (ECGs, family history, pathology, imaging) with genetic databases, a potentially impactful effort that requires computational biology, data analytics, and engineering that remains to be fully tapped. In the future, independent laboratories and consortia will continue to improve our ability to collect, catalog, and sort the genomic/phenomic profile of individual patients. In light of these advancements as they relate to AF risk, it is imperative that we begin to formulate ways to use genetic data to stratify patients into risk categories for paroxysmal, persistent, and permanent AF.

In addition to genetic profiling, potential areas of further risk stratification in real-time may exist in various biomarkers and new imaging techniques. In coronary artery disease, it is well established that elevated troponins are an indicator of myocardial infarction and cardiomyocyte injury.³⁹ Just as myocardial infarction is governed by hypoxemic injury of tissue, AF is driven in part by inflammation and is further exacerbated by AF itself. In light of this, it is reasonable to hypothesize that there may exist markers for inflammation specific to the atria, that can be detected in the presence of disease development, possibly prior to the onset of arrhythmogenesis, and used to inform interventions.

In summary, while precise cellular and electrical mechanisms of AF are still being discovered, the characterization of phenotypes early in disease may serve as a vital area for advancing new and potentially patient-specific disease therapies. Techniques that involve genetic risk profiling, biomarkers, and imaging all serve to describe different levels of this complex disease. Furthermore, these methods will be useful in informing clinicians as to targeted therapies and treatment strategies for patients thus reducing the morbidity and mortality associated with AF across the world.

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