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Genetic Risk Scores for Atrial Fibrillation: Do they Improve Risk Estimation?

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Atrial fibrillation (AF) is the most common clinical arrhythmia and its hazards of heart failure, stroke, and death pose a growing dilemma for the future of health care across the globe. Over the last several decades, two major challenges have been identified in the management of AF. First, the ability to identify patients with occult or asymptomatic AF, who are at heightened risk for arterial embolism. Second, the development of efficacious treatments for patients with persistent AF in whom multiple mechanisms are most likely operant. Despite widespread adoption of catheter ablation for AF its prevalence is still expected to increase two-fold by 2050 in the United States.[1] Increased recognition that focusing on the later stages of AF may render therapies less effective has made diagnosis of AF earlier in a patient's disease course a more desirable goal as clinical response to treatments may be more successful in the long term.[2] Current established risk factors for AF include age, gender, hypertension, diabetes, obesity, heart failure, obstructive sleep apnea, and metabolic syndrome.[3]

Our realization that genetics play a significant role in the development of AF has driven the impetus to characterize the genetic architecture of this complex disease. While the majority of cases of AF in the general population are sporadic, at least 15% of these patients develop AF at a young age, in the absence of other recognized risk factors.[4, 5] Among these sporadic cases of AF, epidemiological studies have observed that the odds of developing AF are increased three to five-fold depending on the age of onset of AF in a parent.[4, 6] We and others have used linkage analyses approaches to identify several genes and loci linked with Mendelian forms of early-onset AF.[3] In 2003, the first AF gene (*KCNQ1*), encoding the cardiac potassium channel (I_{Ks}), was identified.[7] Mayo Clinic investigators identified the first non-ion channel atrial gene, natriuretic peptide precursor A (*NPPA*), encoding atrial natriuretic peptide (ANP) that was linked with familial AF.[8] The identification of *KCNQ1* as AF-causing led to the screening of other potassium and cardiac ion channels as candidate genes. One study showed that AF was only present when a *KCNQ1* mutation (R14C) occurred in the presence of left atrial dilatation.[9] These findings and our data showing that the risk of developing AF is increased when both common and rare AF risk alleles are present support a "two-hit" hypothesis.[10]

During the last decade, genome-wide association studies (GWAS) have identified 14 genetic loci associated with AF in European and Asian ancestry groups.[3] The most significant locus

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is in a region near the gene encoding the transcription factor PITX2. Compared to rare disease-causing mutations, the effect sizes of common risk alleles for AF have been small to modest (odds ratio [OR] 1.1–1.7), limiting our ability to predict AF when considering a single common risk allele alone. While Lubitz et al.[11] showed that a genetic risk score comprised of 12 genetic markers was associated with an estimated five-fold gradient in AF risk the number of individuals that carry multiple AF susceptibility single nucleotide polymorphisms (SNPs) is small. However, the risk of developing AF increases substantially (OR 12–26) when a rare variant combines with a common one such as susceptibility variants in the 4q25 locus.[12] Nonetheless, in the general population, AF mutations with strong effects are very rare.

A limitation of GWAS studies is the possibility that a genotype-phenotype association represents a chance finding or an artifact due to uncontrolled biases, thus replication studies in different populations are crucial for validating associations and their generalizability. The earliest and largest GWAS tested patients of mainly European descent and identified common risk alleles believed to alter cardiopulmonary development, expression of cardiac ion channels and transcription of cell signaling molecules. Although the overall prevalence of AF is lower in patients of non-European background, there does appear to be overlapping of genetic susceptibility to AF between individuals of European and non-European descent. [11, 13]

To explore the role of AF susceptibility loci and prediction of risk, a number of genetic risk scores (GRS) have been proposed.[11, 14, 15] In this issue of the journal, Liu et al.[16] genotyped 5461 patients of Japanese ancestry for 11 AF-susceptibility SNPs and calculated a weighted GRS based on number of risk alleles per patient. They also assessed the ability of the GRS to predict AF. In the study, six SNPs: rs593479 (1q24), rs1906617 (4q25), rs11773845 (7q31), rs6584555 (10q25), rs6490029 (12q24), and rs12932445 (16q22) were associated with AF. However, five of the AF-susceptibility loci derived from prior GWAS of cohorts of European decent did not reach genome-wide significance. Thus far this is the largest replication study conducted in a cohort of Japanese ancestry. Patients with a high total number of risk alleles (9–12) tended to develop AF at a younger age when compared to those with a low number of risk alleles (1–4). GRS analysis showed a 4.38-fold difference (95% confidence interval [CI]: 3.69–5.19) in AF risk between patients with scores in the top and bottom quartiles of the GRS with receiver operating characteristic analysis showing an area under the curve (ROC) of 0.641 (95% CI: 0.628–0.653, P<0.0001).

The novel finding of the study was that age of onset of AF was influenced by the weighted GRS in the cohort.[16] Patients who carried a high total number of risk alleles (9–12) had a younger median age of onset of AF (58 years, 95% CI: 55–60 years) than patients with a low total number (1–4) (63 years, 95% CI: 61–64 years; P = 0.0015). This equated to over four-fold difference in risk of AF between individuals with scores in the top and bottom quartiles of the GRS. While it is unclear if the GRS using these six SNPs would still be as useful for predicting age of onset in a younger set of patients (which may limit its clinical usefulness), the report is still the first to show age of onset of AF is modulated by the number of risk alleles carried by an individual.

The clinical utility of GRS for AF would be supported if studies clearly demonstrate an improvement in risk estimation over and above that achieved by traditional clinical risk factors. In the Liu et al.[16] study failure to compare the AUC derived from clinical data alone with the AUC derived from both the clinical and genetic data is a major limitation. This is mainly related to being underpowered to evaluate a difference if both clinical and genetic variables were included in the model. Other limitations of the study include using only six SNPs in the GRS; it is possible that inclusion of additional AF risk alleles could have improved discriminatory ability. Using a hospital-based cohort with onset of AF occurring relatively late in the patient population is another limitation of the study. While this study was not able to assess the incremental value of the GRS, other studies have not shown clear benefit or utility to adding AF susceptibility SNPs to risk models derived from clinical variables.[17, 18] One recent study showed that AF genetic risk is associated with incident AF beyond the effects observed for established clinical risk factors.[19] Despite a 28–67% increased risk of AF among patients in the highest versus the lowest quartile of the GRS, which is comparable to the magnitude of risk conferred by traditional clinical AF risk factors, the magnitudes of risk associated with genetic risk improved discrimination only minimally beyond clinical factors. A more intriguing finding of the Lubitz et al.[19] study raises the possibility that a GRS for AF may serve as a surrogate marker for AF-related cardioembolic stroke and asymptomatic AF. However, this study was performed primarily in patients of European descent and it remains unclear if the same holds true for other ethnic races.

In summary, Liu et al. validated AF risk loci identified in Europeans and a prior GWAS in Japanese, demonstrated a graded relative risk for AF conditioned on the number of AF risk alleles, and showed that the age of onset of AF in Japanese patients is modulated by common AF-associated SNPs. Genetic studies of AF have not only provided important insights into underlying mechanisms and identified novel therapeutic targets but also ushered in an era of a more mechanism-based approach to the treatment of AF. Studies to date have shown only small improvements in discrimination of AF risk using GRS. However, with advances in next generation sequencing increasingly uncovering the contribution of common genetic variation in susceptibility to the arrhythmia, future studies will likely demonstrate net improvements in AF discrimination; thus allowing genetic risk profiling for AF to be incorporated into routine clinical decision-making.[20]

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