Guidance of medical therapy on the basis of genetic carrier status, termed pharmacogenomics, has been increasingly used with success in other fields of medicine.1,2 Despite relatively modest results thus far,3,4 gene-guided therapy holds great promise in cardiac electrophysiology owing to the importance of genetics in atrial fibrillation (AF) and the more rare inherited arrhythmia syndromes. In the context of AF, genetic factors play a critical role in modulating the risk of the arrhythmia in both rare families with Mendelian patterns of AF inheritance and the general population.5,6 Insights gleaned from genetic discoveries among rare families with Mendelian inheritance patterns have highlighted substantial individual heterogeneity in the pathophysiology governing AF, suggesting the presence of subphenotypes of the arrhythmia.7 This phenomenon not only likely accounts for the variable response to therapy among patients with similar clinical phenotypes, but also suggests that greater efficacy might be achieved if specific therapies were appropriately targeted to particular mechanistic subphenotypes.

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A personalized approach to therapy targeting the culprit pathophysiology in an individual patient carries the promise of optimizing outcomes, whereas concomitantly minimizing adverse events. Genome-wide association studies have identified multiple single-nucleotide polymorphisms (SNPs), a type of common genetic variant, associated with an increased risk of AF.8 The mechanism through which these SNPs affect AF predisposition is unclear, owing partly to their presence in noncoding areas of the genome with no known effect on protein expression or function. Although the biological role of these SNPs remains elusive, this does not preclude evaluating their influence on treatment outcomes.

Catheter ablation is highly effective as a rhythm control strategy, however, upwards of 30% to 40% derive limited to no benefit, even among ideal candidates with paroxysmal AF.9 Given this invasive procedure associated with significant cost and the potential for serious adverse events, including cardiac tamponade, stroke, and death, targeting its use to those poised to experience desirable clinical outcomes is advantageous to patients, physicians, and healthcare systems.10 Multiple clinical variables have been shown to be predictive of procedural success, however, outcomes may still vary substantially among patients with similar clinical phenotypes.11 Prior work has suggested that genetic carrier status of the SNP most strongly linked with AF, rs2200733 residing within the 4q25 locus, was associated with an increased risk of AF recurrence, highlighting a potential role for an ablatogenomic approach to catheter ablation.12,13 In other words, perhaps patient genotype can help guide the decision to perform an ablation or not or potentially be used to identify an optimal ablation technique.

In this issue of the journal, Shoemaker et al14 seek to determine the impact of 4 SNPs associated with AF, including 2 within the 4q25 locus, on the success of catheter ablation for the arrhythmia. They conducted a meta-analysis of data from 3 centers that involved 991 participants undergoing their first catheter ablation for either paroxysmal or persistent AF. Pulmonary vein isolation was performed using wide area circumferential ablation, whereas empirical linear lesions were performed at the discretion of the operator. Postprocedural arrhythmia monitoring was performed with clinic visits and ECGs at 3, 6, and 12 months. Two of the sites also performed ambulatory monitoring at these time points, whereas additional screening for AF at the third site was at the discretion of the treating physician.

The primary end point of the study, the presence of any atrial tachyarrhythmia during the subsequent 12 months excluding an initial 3-month blanking period, was experienced by 42% of study participants. On combined multivariate analysis, the presence of the AF-associated rs2200733 risk allele within the 4q25 locus was associated with a statistically significant 1.3-fold increased hazard of the primary end point, whereas nonsignificant associations were observed for the remaining 3 SNPs. When the end point was restricted to AF recurrence alone, there was discordance among the centers about the impact of the SNP. Although the direction of association was consistent with an increased hazard of AF in 2 of the 3 centers, it trended toward a protective effect in the third (adjusted hazard ratio, 0.4; \(P=0.111\)). A separate meta-analysis was not performed for these findings.

The present report, given its relatively large size and multicenter design, serves to reinforce previous findings that the presence of the 4q25 SNP (rs2200733) is associated with an increased risk of atrial tachyarrhythmias after AF catheter ablation. Validity of the results is further enhanced by consistency across the 3 centers with respect to the patient population being studied (restricted to those undergoing their first catheter ablation), the procedure and its targeted end point of pulmonary vein isolation, and follow-up for AF detection (clinic visits and ECGs at 3, 6, and 12 months). The consistent direction of association between the SNP and the risk of atrial tachyarrhythmias across all 3 cohorts serves to further bolster the strength of the finding.
Although clinical practice patterns were similar among the 3 sites, there were some notable differences. The additional placement of empirical left atrial linear lesions, at the discretion of the operator, ranged from 19% to 44% among the centers, whereas the use of antiarrhythmic drugs and ambulatory monitoring for asymptomatic AF recurrence during the follow-up period was also variable. Despite these differences, they are unlikely to have introduced bias given that none would be anticipated to be related to genetic carrier status and hence do not reflect true confounders in the association being evaluated.

The discordant direction of association observed within 1 of the cohorts when the outcome was restricted to AF recurrence rather than any atrial tachyarrhythmia is notable. Although this may have occurred secondary to chance, especially given the relatively small number of individuals from this center (87), a differential impact of the SNP on AF recurrence versus other atrial tachyarrhythmias should be clarified in future studies. Another intriguing issue that remains to be explored is the possibility that the SNP exerts a differential impact in patients with paroxysmal and persistent AF. Although paroxysmal AF is generally considered to be driven by pathological triggers, most often from the pulmonary veins, persistent AF is felt to be more dependent on abnormal atrial substrate. Given their contrasting pathophysologies, the effect of the SNP may be different in these alternative forms of the arrhythmia.

As the investigators highlighted, the findings from their study have the potential to affect clinical practice, particularly given the magnitude of impact of the SNP on arrhythmia recurrence (a 30% increase) and the prevalence of the SNP in the general population (≈30%). The impact of the SNP on postablation arrhythmia recurrence is greater than routinely measured clinical features, such as left atrial size,15 which raises the question: should patients undergo routine genotyping for this SNP before AF ablation? As mentioned by the authors, knowledge of SNP carrier status may allow physicians to better predict procedural success when counseling patients and could potentially lead to alternative strategies being pursued. It should be noted, however, that genetic carriers of a 4q25 SNP have also been reported to be more refractory to antiarrhythmic medications and hence a clear treatment algorithm would predict procedural success when counseling patients and hence anticipate related to genetic carrier status and hence do not reflect true confounders in the association being evaluated.

It is notable that the rs2200733 SNP conferring an increased risk of arrhythmia recurrence after ablation seems to conflict with the current theory accounting for its predisposition to AF. Although uncertainty remains, it has been hypothesized that this SNP exists within an enhancer/repressor element that influences expression of PITX2. PITX2 encodes a transcription factor reported to influence development of the pulmonary vein sleeves and inhibit left-sided sinoatrial node development.17-19 On the basis of these findings, investigators have hypothesized that the rs2200733 SNP, through reduced expression of PITX2, may predispose to AF via the development of pathological triggers from the pulmonary veins.19 Identification of ectopic beats from the pulmonary veins capable of inducing AF provided the rationale for their electric isolation from the left atrium with catheter ablation20 and hence rs2200733 genetic carriers would be anticipated to experience superior, rather than inferior, outcomes. The discordant findings from this study seem to highlight our limited understanding of the mechanistic impact of this SNP on AF risk, emphasizing an ongoing need for future work.

In summary, the study by Shoemaker et al14 reinforces previous evidence documenting an association between the rs2200733 SNP and an increased risk of atrial tachyarrhythmias after catheter ablation for AF. The magnitude of impact of the SNP on procedural success, coupled with its high prevalence in the general population, highlights its potential clinical utility, providing an impetus for routine genotyping before catheter ablation. This study represents an important step forward, however many questions still remain, including the ongoing mystery accounting for why SNPs within the 4q25 locus increase the risk of AF. For example, perhaps the mechanisms underlying AF in the patients carrying a particular allele (or alleles of the other known AF-associated SNPs) are those that benefit most from a particular ablation strategy, whether it be extra lines, targeting of vagal inputs, or more extensive substrate modification. Deeper insight into this phenomenon may therefore facilitate the development of novel treatment approaches for AF and serve to unlock the potential of the burgeoning field of ablatogenomics.

Disclosures

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References


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