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EDITOR'S FORUM

Gene-guided therapy for catheter-ablation of atrial fibrillation: are we there yet?

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In the last decade, increasing evidence has emerged for a genetic predisposition to atrial fibrillation (AF). In 2003, Mayo Clinic investigators showed that 15 % of patients with lone AF had a positive family history of the condition [1]. Subsequent epidemiological studies observed that the odds of developing AF increased three to five-fold depending on the age of onset of AF in a parent [2, 3]. Furthermore, numerous genes associated with AF have been identified using positional cloning and linkage analyses, candidate gene and exome-sequencing approaches [4]. In 2003, the first gene (*KCNQ1*) encoding the delayed cardiac rectifier potassium channel (I_{Ks}) was linked with familial AF. [5] Mutations encoding cardiac ion channels (Na^+, K^+ and Ca^{2+}), gap junction proteins (connexins) and signaling molecules (nucleoporin 155 [*NUP155*], natriuretic peptide precursor A [*NPPA*]) have been described in Mendelian forms of AF. However, the extent to which genetic factors contribute to the more common forms of AF remained unclear until the advent of genome-wide association studies (GWAS).

While many patients with AF have known risk factors, e.g., hypertension, the majority of the patients in the general population with those risk factors do not develop AF. Thus, one concept proposed is that common genetic variants increase susceptibility to AF in some individuals with other identifiable risk factors—a basis for the "two-hit" hypothesis [4]. Recent advances in next generation sequencing have now made it possible to assay hundreds of thousands of single nucleotide polymorphisms (SNPs) spread across the entire human genome. In 2007, the first GWAS of AF identified a strong association between AF and a haplotype block on chromosome (chr) 4q25 [6]. Within this locus, two non-coding SNPs were independently associated with AF, and these findings were replicated in two populations of European descent and one of Asian descent [6]. Although the mechanism for this observed association still remains unclear, the locus is adjacent to the paired-like homeodomain transcription factor 2 (*PITX2*) which is important for pulmonary vein (PV) development [7]. This association has been independently replicated, and we also showed that the association also holds in post-cardiac surgery AF. [8] Two additional loci on chr16q22 [9] and chr1q21 [10] were identified, and a meta-analysis of AF GWAS in 2012, not only validated these three SNPs but also identified and replicated six additional novel AF susceptibility alleles [11]. More recently, the AFGen Consortium has identified five more novel AF loci [12].

Although GWAS have identified common SNPs associated with AF and provided insights into underlying genetic mechanisms, recent studies suggest that these risk alleles may also identify genetic subtypes of AF with differential response to therapy [4]. A 2012 study examined whether symptomatic response to antiarrhythmic drug (AAD) therapy is modulated by the three common AF susceptibility loci on chr4q25 (near *PITX2*), 16q22 (in *ZFXH3*), and 1q21 (in *KCNN3*) in 478 (discovery cohort) and 198 (validation cohort), age- and gender-matched European Caucasian patients [13]. Successful response to rhythm control therapy was defined as maintenance of the same AAD for a minimum of 6 months with ≥75 % reduction in AF symptoms. While clinical variables such as age, hypertension, and lone AF failed to predict maintenance of sinus rhythm, rs10033464 (chr4q25) SNP did predict successful rhythm control in patients with typical AF carrying the wild-type (WT) allele with an odds ratio of 4.7 (95 % CI 1.83 to 12, $P<0.001$). We and others [14] also

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showed that the same AF locus predicted a 24 % shorter recurrence-free time from AF than did the presence of the WT SNP after AF ablation [15], and this association was more recently confirmed in a meta-analysis [16]. A chr4q25 SNP also independently predicted AF recurrence after restoration of sinus rhythm after electrical cardioversion [17]. Contrarily, a recently published study of patients of solely Asian descent did not demonstrate a significant correlation between SNPs at commonly associated AF loci and AF recurrence following catheter ablation seen in other reports [18]. Though supported only by the findings of a single study, additional data to ascertain whether the predictive value of susceptibility loci for AF treatment response are truly ethnic/race-dependent are needed. Collectively, the overall data supports the concept that the chr4q25 locus not only increases susceptibility to AF but also modulates response to AADs, catheter ablation of AF, and electrical cardioversion identifying a sub-group of patients in whom a more mechanism-based approach to therapy should be considered.

In this issue of the journal, Mohanty et al. examined the association between common AF risk SNPs and non-pulmonary vein (PV) triggers and prevalence of left atrial scar in 371 patients undergoing catheter ablation for AF [19]. Their main findings were that a common SNP at the chr16q22 locus (in *ZFHX3*) was associated with a high risk for both non-PV triggers and atrial scar formation; a chr4q25 (near *PITX2*) SNP was inversely associated with both phenotypes; an SNP near the Na^+ channel gene *SCN10A* was inversely associated with non-PV triggers, and seven out of 16 SNPs were associated with atrial fibrosis. The authors must be congratulated on exploring for the first time the association between 16 known AF risk SNPs and non-PV triggers as well as the severity of atrial scarring in patients with both paroxysmal and non-paroxysmal AF. While the findings are fascinating and novel, more importantly, they not only improve our understanding of the underlying pathophysiology of AF but may also direct ablation therapy to mechanistic sub-types of AF.

A major finding of the study is the link between a chr16q22 SNP (in *ZFHX3*) (rs7193343) and the risk of both non-PV triggers and atrial scar formation. It is increasingly appreciated that atrial fibrosis not only plays a prominent role in the pathogenesis of AF but may also be a plausible link between genetic variants and AF risk [20]. While the transcription factor zinc finger homeobox 3 (encoded by *ZFHX3*) is a tumor suppressor-suppressor gene, it associates with another transcription factor (runt-related transcription factor 3 [RUNX3]) and both translocate to the nucleus in response to transforming growth factor (TGF)–β signaling, an important mediator of fibrosis [21, 22]. It is therefore not surprising that the chr16q22 locus is linked with both left atrial scarring (and by extension fibrosis) and non-PV triggers.

The other take-home message from this study is that a chr4q25 SNP (near *PITX2*) (rs6843082) was inversely associated with both non-PV triggers and left atrial scarring. This association may have been predicted based on the fact that *PITX2c* encodes a transcription factor that is important for suppression of sino-atrial node formation on the left, left-right patterning in the atria, and PV development during embryogenesis. While Chinchilla et al. showed that homozygous $Pitx2c^{-/-}$ mice had enlarged cardiac chambers with increased expression of collagen precursor genes in the atria [23], the heterozygous $Pitx2c^{+/-}$ mouse had structurally normal hearts with little or no evidence of atrial fibrosis supporting the hypothesis that chr4q25 SNP regulation of *Pitx2c* leads to atrial electrical remodeling especially in patients with paroxysmal AF. However, it is interesting that another chr4q25 SNP (rs1448817) when combined with the chr16q22 SNP was associated with a combined odds ratio (OR) of 1.9 for non-PV triggers suggesting that there is an increased risk for non-PV triggers in patients having both SNPs as compared to those harboring either variant.

The study also raises a number of provocative questions. It is unclear why the investigators did not test the association between non-PV triggers and LA scarring and 2 chr4q25 SNPs that have most commonly associated with AF, i.e., rs2200733 and rs10033464 [6]. Another question relates to analysis of scar burden as a categorical variable rather than a continuous (by percentage) one which would have provided additional power. The study also raises the question why different chr4q25 SNPs have discordant associations with non-PV triggers: rs1448817 was associated with a high risk for non-PV triggers whereas rs6843082 was negatively associated with this phenotype. Possible explanations for this discordant effect include the chr4q25 locus being complex and harboring at least four different haplotype blocks that have been associated with AF susceptibility not all of which necessarily trigger AF from the PVs [24, 25]; different cis- and trans-acting regulatory elements; and gene-gene interaction as was recently demonstrated between *ZFHX3* and *PITX2c* SNPs [26]. Another explanation that should be considered relates to the study being under-powered to test for gene-gene interactions.

In summary, the study by Mohanty et al. [19] is hypothesis-generating, and additional studies in larger cohorts of patients are needed to confirm their findings. However, this study does provide important insights into the underlying mechanisms by which common AF risk SNPs not only increase susceptibility to the arrhythmia but also subtype AF. More importantly, Mohanty et al. have contributed to the "burgeoning field of ablatogenomics" [27] and paved the way for a trial of a gene-guided approach to catheter ablation of AF that targets the underlying mechanism.

Compliance with ethical standards

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