





Atrial Fibrillation Susceptibility Alleles on Chromosome 4q25 Modulate Response to Catheter Ablation

Dawood Darbar, MBChB, MD, FACC

Divisions of Cardiovascular Medicine and Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville, TN.

Introduction

In the last five years, increasing evidence has emerged for a genetic predisposition to atrial fibrillation (AF). Framingham Heart Study investigators observed that the odds of developing AF were three times higher for individuals with at least one parent in whom AF was diagnosed before the age of 75 than in those without a parental history of AF.¹ Similarly, in a large group of Icelanders, the risk of developing AF was increased nearly five-fold if one parent was affected before the age of 60.² Furthermore, single rare genetic variants thought to be responsible for familial AF have been identified.³ Multiple genetic loci and mutations in ion channels,⁴ gap junction proteins,⁵ and signaling molecules⁶ 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).

Genome-wide association studies have been made possible by advances in genotyping technology that allow investigators to assay hundreds of thousands of single nucleotide polymorphisms (SNPs) spread over the entire human genome. In the first GWAS of AF, a strong association was discovered between AF and a haplotype block on chromosome 4q25.7 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. The SNP most strongly associated with AF, rs2200733, conferred a 1.71 fold increased odds of AF (P =6.1 x 10-41) while the other SNP, rs10033464, conferred a 1.42 fold increased odds of AF (P = 3.1 x10-11). Although the mechanism for this observed association remains unknown, both variants are adjacent to the PITX2 gene, which is critical for cardiac development. In knockout mice, pitx2c has been implicated in the formation of the extension of left atrial myocardium into the pulmonary veins^{8,9}; since abnormal automaticity in this region is now implicated as a common driver for many forms of AF,¹⁰ PITX2 is an obvious candidate gene. We worked with others to replicate this association in a study of four large populations,¹¹ and showed that the association also holds in post-cardiac surgery AF,¹² a setting thought to be related to inflammation.

In a recent study published in the Journal of the American College of Cardiology, Husser et al.¹³ examined whether the AF-susceptibility alleles on chromosome 4q25 were associated with AF recurrence after catheter ablation. The study included 195 consecutive patients with drug-resis-

Corresponding Address : Dawood Darbar, MD, Division of Cardiovascular Medicine, Vanderbilt University School of Medicine, 2215B Garland Avenue, Room 1285A MRB IV, Nashville.

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tant paroxysmal or persistent AF who underwent left atrial ablation with isolation of the pulmonary veins. Recurrence of AF was detected by performing 7-day Holter recordings, immediately after the procedure and at 3 and 6 months. In 37% of the patients, AF recurred within 7 days and late recurrence (between 3 and 6 months) was observed in 21% of the patients. Surprisingly, none of the clinical and baseline echocardiographic characteristics that have previously been associated with AF recurrence (e.g., advanced age, left atrial enlargement) were associated with AF recurrence. In contrast, the presence of either of the common polymorphisms (rs2200733 and rs10033464) on chromosome 4q25 was associated with in creased risk of both early and late AF recurrence. The study by Husser et al.¹³ is the first study to introduce the concept of common genetic variants modulating response to catheter ablation for AF. The ability to risk stratify individuals based on pre-procedural characteristics is highly desirable as the procedure is not only expensive but also associated with significant morbidity and mortality. Determining whether patients are at increased risk for both early and late recurrence of AF based on the presence of AF-susceptibility alleles would be an important first step towards 'personalizing therapy' for individual patients. However, it should be appreciated that many putative factors (e.g., type of AF, clinical characteristics, biomarkers, presence of structural heart disease and concomitant medications) have been associated with AF recurrence after ablation. Although the study has many strengths including the prospective design, consecutive series, and the rigorous assessment for recurrent AF with Holter monitoring, the findings will need to replicated in larger and more diverse populations. Furthermore, the additive role of genetic variants in risk stratification of patients undergoing pulmonary vein ablation will need to be determined. Another important issue raised by the study relates to potential mechanisms of AF recurrence after radiofrequency catheter ablation. The study strongly suggests that both early and late AF recurrence share a common genetic link. Although it is now accepted that early and late recurrence of AF are interrelated, an improved understanding of how these genetic variants increase AF susceptibility may not only provide valuable insight into AF mechanisms in general but also specific mechanisms underlying AF recurrence after catheter ablation. The study by Husser et al.¹³ also reinforces the importance of including a genetic component to the next generation of large AF trials such as CABANA (Catheter Ablation Versus Antiarrhythmic Drug for Atrial Fibrillation). Importantly, the CABANA trial steering committee recently approved the creation of CABANAgene: a resource that will accumulate DNA samples from CABANA subjects to enable subsequent genotype-phenotype studies. Some examples of issues that CABANAgene could address include predictors of response to antiarrhythmic or rate control drug therapies; predictors of response to warfarin therapy; predictors of response to ablation therapy and clinical and genetic approaches to defining AF subtypes. Although common polymorphisms on chromosome 4q25 appear to modulate response to catheter ablation, two additional AF susceptibility loci on chromosomes 16q22 and 1q21 have recently been identified.^{14, 15} The role of these variants in determining response to ablation will also need to be determined. Ultimately, however, there is an urgent need to develop a robust clinical risk algorithm for AF which may include genetic variants. Such an algorithm would be invaluable not only in guiding catheter ablation therapy but also improving clinical outcomes in patients with AF.

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