Common atrial fibrillation risk alleles at 4q25 predict recurrence after catheter-based atrial fibrillation ablation

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BACKGROUND Common single nucleotide polymorphisms at chromosome 4q25 (rs2200733, rs10033464) are associated with both lone and typical atrial fibrillation (AF). Risk alleles at 4q25 have recently been shown to predict recurrence of AF after ablation in a population of predominately lone AF, but lone AF represents only 5%–30% of AF cases.

OBJECTIVE To test the hypothesis that 4q25 AF risk alleles can predict response to AF ablation in the majority of AF cases.

METHODS Patients enrolled in the Vanderbilt AF Registry underwent 378 catheter-based AF ablations (median age 60 years; 71% men; 89% typical AF) between 2004 and 2011. The primary end point was time to recurrence of any nonsinus atrial tachyarrhythmia (atrial tachycardia, atrial flutter, or AF).

RESULTS Two-hundred atrial tachycardia, atrial flutter, or AF recurrences (53%) were observed. In multivariable analysis, the rs2200733 risk allele predicted a 24% shorter recurrence-free time (survival time ratio 0.76; 95% confidence interval [CI] 0.6–0.95; $P = .016$) compared with wild type. The heterozygous haplotype demonstrated a 21% shorter recurrence-free time (survival time ratio 0.79; 95% CI 0.62–0.99) and the homozygous risk allele carriers a 39% shorter recurrence-free time (survival time ratio 0.61; 95% CI 0.37–1.0; $P = .037$).

CONCLUSIONS Risk alleles at the 4q25 loci predict impaired clinical response to AF ablation in a population of patients with predominately typical AF. Our findings suggest that the rs2200733 polymorphism may hold promise as an objectively measured patient characteristic that can be used as a clinical tool for selecting patients for AF ablation.

KEYWORDS Atrial fibrillation; Ablation; Pulmonary vein isolation; Genetics; 4q25

ABBREVIATIONS **AAD** = antiarrhythmic drug; **AF** = atrial fibrillation; **AT/AF** = atrial tachycardia, atrial flutter, or atrial fibrillation; **BMI** = body mass index; **CI** = confidence interval; **DCCV** = direct current cardioversion; **LA** = left atrial; **PITX2** = paired-like homeodomain transcription factor 2; **PV** = pulmonary vein; **RF** = radiofrequency; **SNP** = single nucleotide polymorphism; **WT** = wild type

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and affects 2–5 million adults in the United States[1] for an annual direct health-care cost of more than 6.5 billion dollars.[2] It is thought that the majority of patients with AF possess a combination of common and rare genetic variants that predispose to its development, which clinically manifests in the presence of acquired cardiac or systemic disease.[3] This is termed "typical" AF and is estimated to represent between 70% to greater than 95% of all AF cases.[4–7] To examine the potential of genetic screening toward addressing the health-care burden imposed by AF, it is necessary to determine the role of common genetic risk markers in modulating response to therapies, such as AF ablation, in patients with typical AF.

Over the last decade, genome-wide association studies have identified many common genetic variants associated with AF.[8–10] The strongest association is mapped to 2 common AF susceptibility single nucleotide polymorphisms (SNPs) on chromosome 4q25. This locus is near the paired-like homeodomain transcription factor 2 (*PITX2*) gene, which regulates development of the pulmonary vein (PV) myocardium and left to right symmetry.[11] Approximately 25% of individuals of European ancestry have been found to carry the 4q25 AF risk allele, and accumulating evidence suggests that these individuals demonstrate impaired clinical response to a variety of AF therapies, including antiarrhythmic drugs (AADs) and catheter-based AF ablation.[12,13] Recently, in a population of predominately lone AF, risk allele

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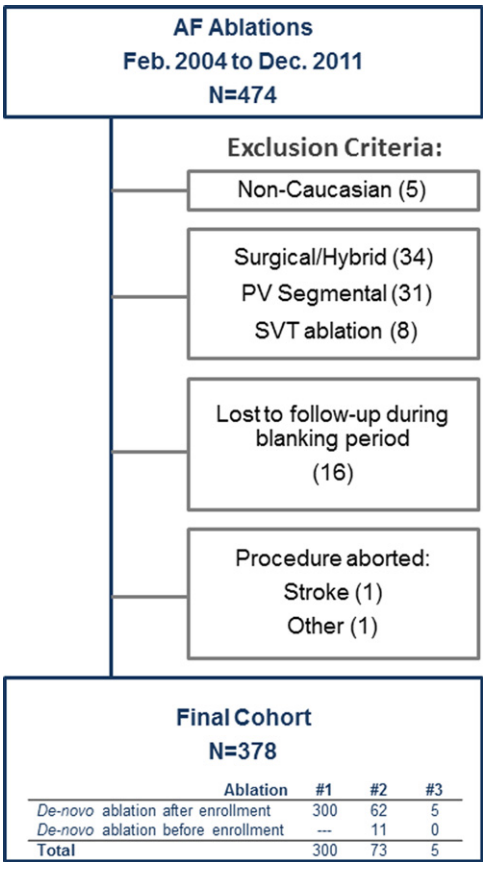

Figure 1 Patient eligibility diagram. AF = atrial fibrillation.

carriers at chromosome 4q25 demonstrated impaired response to catheter ablation.[13] To address the ability of genetic risk markers to predict clinical response to AF ablation in the majority of patients with AF, we sought to test the hypothesis that common AF susceptibility alleles on chromosome 4q25 (rs2200733, rs10033464) conferred an increased risk for AF recurrence after catheter-based ablation in patients with typical AF.

Methods

Study population

Three hundred seventy-two patients enrolled in the Vanderbilt AF Registry underwent 474 catheter-based AF ablations from February 2004 to December 2011 (Figure 1). The Vanderbilt AF Registry is a prospective clinical and genetic database.[14] Eligible ablation records were from Caucasian patients who underwent a de novo or repeat catheter-based AF ablation and were followed up for at least 3 months. Records from de novo segmental PV isolation procedures, surgical AF ablation, and hybrid catheter/surgical ablations were excluded. In addition, patients lost to follow-up prior to the end of the 3-month blanking period, and ablations aborted owing to intraoperative complications were excluded.

Clinical evaluation

Patient characteristics and procedural details were entered into a central database.[15] A detailed medical history was obtained through patient questioning and examination of medical records, and a physical examination was performed. Lone AF was defined as AF occurring in the absence of cardiac or systemic disease in patients younger than 66 years. Typical AF was defined as patients with nonlone AF. Paroxysmal AF was defined as episodes lasting less than 7 days and terminating spontaneously. Nonparoxysmal AF was defined as AF episodes lasting greater than 7 days and/or requiring termination with pharmacologic or direct current cardioversion (DCCV). Total number of lifetime DCCV prior to ablation and number of lifetime AAD trials were recorded based on the patient's report. Body mass index (BMI) was calculated by weight in kilograms divided by height in meters squared. Measurements of left atrial (LA) size and left ventricular ejection fraction were obtained from preablation cardiac magnetic resonance imaging or transthoracic echocardiogram.

Catheter ablation

All patients received general anesthesia during the ablation. Vascular access was obtained from the right and/or left femoral veins with or without right internal jugular veins according to operator preference for coronary sinus cannulation. All ablations were performed by using biplane fluoroscopy. LA access was obtained by using transseptal puncture under anteroposterior and left anterior oblique fluoroscopic views with assistance from intracardiac echocardiogram.

Standard periprocedural anticoagulation strategies were used. In cases where preprocedure therapeutic international normalized ratio for at least 1 month was not documented, a transesophageal echocardiogram was performed prior to the ablation to document the absence of LA thrombus. Postprocedure, heparin or low-molecular-weight heparin was resumed after sheath removal and hemostasis and continued until therapeutic oral anticoagulation was achieved. Anticoagulation with warfarin or dabigatran was continued for at least 3 months after ablation.

All de novo ablations consisted of circumferential PV antral isolation confirmed by entrance block, with additional linear ablation and ablation of non-PV foci based on operator discretion. Wide-area circumferential antral ablation was performed with use of a 3-dimensional electroanatomic mapping system and placement of contiguous lesions 5–15 mm from the PV ostia with testing for entrance and exit blocks. Prior to 2009, ablation was performed by using an 8Fr 5-mm-tip temperature-controlled radiofrequency (RF) catheter, with RF energy applied at temperatures of 55–60°C and a maximum power of 50 W for 30–45 seconds at each site. Since 2009, an 8-Fr 3.5-mm open irrigated-tip power-controlled ablation catheter was used with a maximum power of 25 W on the posterior wall and 30–35 W on the anterior wall and roof. Entrance and exit blocks were tested by using high-output pacing with isoproterenol and/or adenosine administration, directing additional lesions as necessary to achieve complete bidirectional electrical isolation of all PVs.

Repeat catheter ablation was performed for patients who experienced a recurrent atrial tachyarrhythmia after the 3-month