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Common variants predict recurrence after nonfamilial atrial fibrillation ablation in Chinese Han population

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ABSTRACT

Background: Genome-wide association studies (GWAS) have identified several loci associated with atrial fibrillation (AF) and have been reportedly associated with response to catheter ablation for AF in patients of European ancestry; however, associations between susceptibility loci and clinical recurrence of AF after catheter ablation have not been examined in Chinese Han populations. To the personalization of catheter ablation for AF, we examined whether these single nucleotide polymorphisms (SNPs) can predict clinical outcomes after catheter ablation for AF in Chinese Han population.

Methods and results: The association between 8 SNPs and AF was studied in 1418 AF patients and 1424 controls by the unconditional logistic regression analysis. The survival analyses were used to compare AT/AF recurrence differences among 438 AF patients, which were classified by the genotype of rs2200733. rs2200733 and rs6590357 were significantly associated with AF in Chinese Han population. In addition, rs2200733 was associated with clinical recurrence of AF after catheter ablation. In Kaplan–Meier survival analysis, the recurrence-free rates for AF with TT and with TC + CC were 35.5% and 61.9%, respectively ($P = 0.0009$). In multivariate Cox regression analysis, rs2200733 was strong independent risk factor for recurrence.

Conclusion: rs2200733 risk allele at the 4q25 predicted impaired clinical response to catheter ablation for AF in Chinese Han population. Our findings suggested rs2200733 polymorphism may be used as a clinical tool for selection of patients for AF catheter ablation.

1. Introduction

Atrial fibrillation (AF), the most prevalent sustained arrhythmia in clinical practice, affects approximately 0.5% of individuals aged 40–50 years and 5–15% of persons at 80 years [1]. In Chinese population, the incidence of AF is around 0.77%, which is higher in men than women [2]. Percutaneous radiofrequency catheter ablation (RFCA) is widely accepted as an effective treatment for AF and is currently recommended for symptomatic patients that are refractory to antiarrhythmic drug (AAD) therapy. However, the published success rate is highly variable with 20% to 40% of patients [3,4]. To reduce the recurrence rate after catheter ablation, the identification of novel markers to predict an individual's clinical response is a major focus of research.

AF is a heterogeneous arrhythmia at both the clinical and the molecular levels. Many facts indicate that genetic factors may affect AF susceptibility. Over the past decade, GWAS have identified many common genetic variants associated with AF [5–7]. Although common genetic variants have been shown to be associated with AF in population of European ancestry, the relationship between these SNPs and AF in non-European population remains unclear. Furthermore, although multiple factors linked with recurrence have been identified in previous studies, the data regarding the association between genetic variants and recurrence after catheter ablation remain limited. Because common genetic variants are associated with the development of AF, it may hold promise for the personalization of AF catheter ablation, which is guided by genetic variants [8–10]. The goal of this study was two aspects. First, we sought to determine whether the 8 AF-associated SNPs identified in European patients were also associated with AF in Chinese Han patients. These SNPs were rs5063 of NPPA gene; rs4845625 of IL6R gene; rs2200733, rs10033464, and rs3853445 of 4q25 gene; rs6590357 and rs7118824 of KCNJ5 gene; and rs7193343 of ZFHX3 gene. Second, to find the risk markers to predict clinical response to catheter ablation

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in the majority of AF patients, we sought to test the hypothesis that common AF susceptibility alleles conferred an increased risk for recurrence after catheter ablation in AF patients in Chinese Han population.

2. Methods

2.1. Study population

This study was approved by the Institutional Review Board of Shanghai First People's Hospital affiliated to Shanghai Jiao Tong University. All patients provided written informed consent. We enrolled 1418 AF subjects as the AF group (739 men and 679 women; mean age, 63.75 ± 15.93 years), admitted to department of cardiology from July 2011 to August 2013. We also enrolled 1424 healthy subjects as the control group (747 men and 677 women; mean age, 62.80 ± 8.68 years) from our medical examination center in 2012. Both groups came from Shanghai First People's Hospital affiliated to Shanghai Jiao Tong University. AF was diagnosed by electrocardiogram (ECG) or Holter. Exclusion criteria for the case group included one of the following: familial AF, lone AF, recent MI (6 months or less), cardiac surgery (30 days or less), New York Heart Association class III or IV, thyroid dysfunction, renal or lung dysfunction, and AF due to trauma, surgery, or acute medical illness. All subjects in the case group and the control group were less than 80 years old. Transthoracic echocardiography was performed to measure the left atrial and left ventricular diameters and to detect significant valvular disease (defined as moderate to severe valvular regurgitation or stenosis, normal left atrial diameter 19–40 mm, normal left ventricular end-systolic diameter 20–40 mm, left ventricular end diastolic diameter 35–55 mm). We selected 438 paroxysmal and persistent AF patients from 1418 AF group who were treated by RFCA to study their recurrence. The duration of AF in 438 patients was more than 1 year.

2.2. SNP selection and genotyping

We selected SNPs from the top 4 AF-associated genetic loci (4q25 and 16q22) in European patients in previous papers [10]. Multiple factors, including heart dysfunction, atrial electrical remodeling, and inflammation, are linked with recurrence after catheter ablation [11–13]. So we selected these SNPs in NAAP gene, KCNJ5 gene, and IL6R gene to find the risk markers of recurrence after catheter ablation. Some studies reported that rs6590357, rs7118833, and rs5063 were associated with AF in Chinese Han population, which may provide us the clue of the risk markers of recurrence after catheter ablation [14,15]. Genotyping was performed using a previously described approach [16]. A set of commercially synthesized primers (TibMolBiol, Berlin, Germany) was used for polymerase chain reaction (Table 1).

2.3. Catheter ablation

All class I or III antiarrhythmic medications were stopped at least five half-lives before catheter ablation. Patients were anticoagulated with warfarin to maintain an international normalized ratio (INR) of 2–3 for at least 4 weeks prior to the ablation procedure. Transesophageal echocardiography was performed within 3 days before the ablation procedure to exclude left atrial thrombus. 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 catheter ablation.

All patients initially underwent circumferential pulmonary vein (PV) isolation under the guidance of a CARTO mapping system (Biosense Webster). In those patients still with atrial arrhythmias after PV isolation, linear ablation (LA roof, mitral isthmus, cavotricuspid isthmus, etc.) and complex fractionated atrial electrogram ablations were appended, respectively. Electrical or drug cardioversion was attempted when AF termination was not achieved after the above the mentioned Steps. An open irrigated tip catheter (7F Navistar, Biosense Webster; 30 to 35 W; 43 °C) was used for catheter ablation. Heparinized saline (2 U/mL) was infused through the ablation catheter at a pump rate of 2 mL/min during mapping and 17–30 ml/min during radiofrequency delivery.

The end points of persistent or long-lasting AF ablation were the termination of AF and conversion to sinus rhythm, including PV isolation. We confirmed the PV isolation by both entrance and exit block and rechecked it under an isoproterenol infusion before finishing the procedure. For paroxysmal AF, the end points included PV isolation and noninducible atrial arrhythmias lasting for 5 min. Catheter ablation was performed by 1 electrophysiologist (Shao-wen Liu).

2.4. Follow-up

After catheter ablation, all patients received AADs (amiodarone) for 3 months to prevent early recurrence of AF. After 3 months patients without atrial arrhythmia recurrence discontinued ADDs. All patients were followed up in the outpatient clinic for 0 to 48 months after catheter ablation. During this follow-up period, serial 7-day Holter ECG recordings were performed immediately after catheter ablation and at 1, 3, 6, 12, 24, 36, 48 months after catheter ablation. Additional electrocardiograms were obtained when patients' symptoms were suggestive of AF. We defined recurrence of AF as any episode of nonsinus atrial tachyarrhythmia (atrial tachycardia, atrial flutter, or AF [AT/AF]) lasting greater than 30 s that occurred after the 3-month post-ablation blanking period. Patients who experienced a recurrent episode of AT/AF were restarted on an AAD, and if recurrent episodes persisted despite AAD use, the patient was offered repeat ablation. The patients with recurrence after first ablation belonged to the recurrence group in our study.

2.5. Statistical analysis

The statistical analyses were performed with the Stata statistical package (version 10.0; Stata-Corp LP, College Station, TX) and SPSS version 21 (IBM Corp, Armonk, NY). The quantitative variables were presented as the mean ± SD, which are normally distributed and were compared using an unpaired Student's *t*-test. Measured variables were reported as frequencies and were compared using the chi-square test. Hardy–Weinberg Equilibrium (HWE) was tested in the healthy group

Table 1
The primers used for polymerase chain reaction.

SNP ID	Forward primer sequence	Reverse primer sequence	Extended primer sequence
rs5063	ACGTTGGATGCCTTTTACTGGCATTCCAGC	ACGTTGGATGTGAAATCCATCAGGTCTGCG	aCAGAGCTAATCCCATGTACAATGCC
rs4845625	ACGTTGGATGGACATAGCTCGTAAGTGGTG	ACGTTGGATGTTGTCCTTACAGGTCCGATG	AACCAGCATTCCAGTCA
rs2200733	ACGTTGGATGTGGTGGTACTTGGGTTTTG	ACGTTGGATGCCCCAAACTTTCTGGAAAAT	GTACTTGGGTTTTGATTTTGAT
rs10033464	ACGTTGGATGCTGAGGAATTCTAAATGAC	ACGTTGGATGAACTCAGAGCTTGATGAAA	gGCTTGATGAAAGCACTT
rs3853445	ACGTTGGATGGCTCACTGATAAGCCAGTTC	ACGTTGGATGACAACTTACTGCCACATGCC	GCATTTTCTTAGCCAAGATAC
rs6590357	ACGTTGGATGAAGCCACGCCAGCGCTACAT	ACGTTGGATGAAGAGGTCACTCAGGTACCG	atgtTGCACGTTGCACTTGCC
rs7118824	ACGTTGGATGAACGTGGGCTTTGACACGG	ACGTTGGATGAGACATCTCCCAGAAAGGGC	cCACGGGCGACGACCGCCTCTTCCT
rs7193343	ACGTTGGATGAAATGTCGAGTCCTAATGGC	ACGTTGGATGGAGGGGAAAGTTTGAACAGC	GGGGAAAGTTTGAACAGCTTGTTT

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