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Common Genetic Variants and Response to Atrial Fibrillation Ablation

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Abstract

Background—Common single nucleotide polymorphisms (SNPs) at chromosomes 4q25 (rs2200733, rs10033464 near *PITX2*), 1q21 (rs13376333 in *KCNN3*), and 16q22 (rs7193343 in *ZFHX3*) have consistently been associated with the risk of atrial fibrillation (AF). Single-center studies have shown that 4q25 risk alleles predict recurrence of AF after catheter ablation of AF. Here, we performed a meta-analysis to test the hypothesis that these 4 AF susceptibility SNPs modulate response to AF ablation.

Methods and Results—Patients underwent de novo AF ablation between 2008 and 2012 at Vanderbilt University, the Heart Center Leipzig, and Massachusetts General Hospital. The primary outcome was 12-month recurrence, defined as an episode of AF, atrial flutter, or atrial tachycardia lasting >30 seconds after a 3-month blanking period. Multivariable analysis of the individual cohorts using a Cox proportional hazards model was performed. Summary statistics from the 3 centers were analyzed using fixed effects meta-analysis. A total of 991 patients were included (Vanderbilt University, 245; Heart Center Leipzig, 659; and Massachusetts General Hospital, 87). The overall single procedure 12-month recurrence rate was 42%. The overall risk allele frequency for these SNPs ranged from 12% to 35%. Using a dominant genetic model, the 4q25 SNP, rs2200733, predicted a 1.4-fold increased risk of recurrence (adjusted hazard ratio, 1.3

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Disclosures

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[95% confidence intervals, 1.1–1.6]; *P*=0.011). The remaining SNPs, rs10033464 (4q25), rs13376333 (1q21), and rs7193343 (16q22) were not significantly associated with recurrence.

Conclusions—Among the 3 genetic loci most strongly associated with AF, the chromosome 4q25 SNP rs2200733 is significantly associated with recurrence of atrial arrhythmias after catheter ablation for AF.

Keywords

ablation techniques; atrial fibrillation; genomics

Atrial fibrillation (AF) affects ≈25% of adults >40 years of age and ≈50% had mild to disabling symptoms when in AF.[1] During the past decade, AF ablation has emerged as a common therapy for AF.[2] In many cases, AF ablation is an effective means to improve symptoms in patients who have failed antiarrhythmic drug therapy; however, the published success rate is highly variable with 20% to −40% of patients requiring a second procedure at an average cost of >$50 000 each.[3,4]

To reduce the recurrence rate after AF ablation, the identification of novel markers to predict an individual's clinical response is a major focus of research. Emerging data suggest that common genetic variants associated with the development of AF may hold promise for the personalization of AF ablation. Single-center studies have examined an AF susceptibility allele at the chromosome 4q25 locus that is present in one-third of patients and found it may predict up to 4-fold higher risk of AF recurrence after ablation.[5,6] Here, we sought to perform a meta-analysis to test the hypothesis that common genetic variants (single nucleotide polymorphisms [SNPs]) at the top 3 AF susceptibility loci (4q25, 1q21, and 16q22) predict recurrence of atrial arrhythmias after AF ablation.

Methods

Study Cohorts

A total of 3 centers with AF ablation cohorts and available genotype data were included: Vanderbilt University (VU), the Heart Center Leipzig (HCL), and Massachusetts General Hospital (MGH). Investigators from these centers agreed to uniform subject eligibility criteria. To restrict our analysis to ablations performed using more current AF ablation approaches, only subjects undergoing de novo catheter-based AF ablation since 2008 were included. Using these eligibility criteria, 87% (572/659) of subjects from the HCL cohort and 16% (38/245) from the VU cohort represent individuals not included in previous reports examining an association between 4q25 risk alleles and AF ablation outcome. No subjects from the MGH cohort have been previously reported. No previous reports from any of the centers have examined SNPs from the other AF risk loci at 1q21 and 16q22. Subjects with paroxysmal and persistent AF were included. Subjects were defined as having paroxysmal AF if they had no history of episodes lasting >7 days or requiring the use of electric or pharmacological cardioversion.

The technical approach to AF ablation was comparable between all 3 centers. In brief, AF ablation was performed under propofol sedation (HCL) or general anesthesia (VU and

MGH) with continuous invasive monitoring of blood pressure and oxygen saturation. A 3-dimensional mapping system (Carto 3, Biosense-Webser, Inc, Diamond Bar, CA; or NavX-Ensite v.7.0, Endocardial Solutions, Inc, St. Paul, MN) was used for nonfluoroscopic catheter navigation, computed tomographic or magnetic resonance image integration, and tagging of ablation sites. Transseptal access was obtained using fluoroscopy (HCL) +/− intracardiac or transesophageal echocardiographic guidance (VU and MGH). An irrigated-tip ablation catheter was used. Circumferential left atrial (LA) ablation lines were placed around the antrum of the ipsilateral pulmonary veins (PVs). Demonstration of PV isolation was a major procedural end point at all centers. PV potentials were recorded using a circular mapping catheter placed in each PV to test for the absence of signals conducting into the PVs during LA pacing (entrance block) or conducting into the LA from the PVs during PV pacing (exit block). Additional ablation was performed until PV isolation was achieved. Empirical linear lesions to the LA roof, basal posterior wall, and mitral isthmus, and ablation of complex fractionated electrograms were performed based on operator discretion. Anticoagulation with heparin was used in an attempt to maintain an activated clotting time >300 seconds during LA access.

Given the observational design of our study, the practice pattern for use of antiarrhythmic drugs (AADs) after ablation differed between centers. At VU, AADs were routinely restarted immediately after the ablation and were discontinued at the 1- or 3-month follow-up appointment in patients who had experienced no recurrence of atrial tachycardia (AT)/AF. At HCL, subjects routinely had AADs discontinued before their ablation and were not restarted after the ablation. At MGH, AAD use was prescribed after the ablation procedure at the discretion of the treating physician. The primary outcome was recurrence defined according to standards established by the Heart Rhythm Society, European Heart Rhythm Association, and the European Cardiac Arrhythmia Society as any episode of AF, AT, or atrial flutter lasting >30 seconds and occurring after a 3-month blanking period.[4] All centers performed routine clinical follow-up at 3, 6, and 12 months including a 12-lead ECG at that time. Postablation monitoring to assess asymptomatic recurrence was performed at all centers. At VU and HCL, monitors were routinely placed at 3, 6, and 12 months (48-hour continuous monitor, or 7- to 21-day auto-triggered event monitor). At MGH, monitoring for asymptomatic recurrence was performed according to a schedule determined by the individual provider. All centers obtained additional monitoring in response to symptoms suggestive of recurrence.

The Institutional Review Board from each center approved the study procedures. Written informed consent was obtained from all study subjects, including the consent to use DNA for genetic analysis.

Genotyping

Genomic DNA was extracted from whole blood samples using standard techniques. In the VU samples, genotyping for rs2200733 C>T, rs10033464 G>T, rs13376333 C>T, and rs7193343 C>T was performed using TaqMan (Applied Biosystems, Foster City, CA), a plate-based, 1-step reaction that identifies the SNP allele during polymerase chain reaction amplification.[7] Samples that failed the initial genotyping with TaqMan were resequenced

using Sanger sequencing methods. In the HCL samples, real-time polymerase chain reaction using fluorescence resonance energy transfer followed by the analysis of the melting curve was applied. Allele-specific, commercially synthesized primers and fluorescent probes were used (TibMolBiol, Berlin, Germany). In the MGH samples, genotyping was performed using the Illumina HumanExome BeadChip version 1.0 (Illumina Inc, San Diego, CA). In all the cohorts, genotyping was performed by laboratory personnel blinded to ablation outcome, and clinical research staff were blinded to genotype.

Statistical Analysis

The common AF susceptibility SNPs were tested for Hardy–Weinberg equilibrium using a χ^2 test and $P<0.01$ cutoff. The primary analysis was performed using dominant genetic modeling (assumes that either 1 or 2 copies of the risk allele confers an equivalent risk), and the reference genotype for each SNP was homozygous for the ancestral (wild-type) allele. The primary outcome was time to recurrence >12 months. The primary analysis consisted of 4 independent models testing the ability of each SNP (rs2200733, rs10033464, rs13376333, and rs7193343) to predict recurrence and adjusted for other clinical covariates. Correction for multiple hypothesis testing was performed using a Bonferroni adjustment such that the α threshold to be interpreted as statistically significant in our primary analysis was reduced to $P\leq0.0125$ (=0.05/4). Multivariable analysis was performed using a Cox proportional hazards model. Clinical covariates were prespecified based on an expected relationship to the primary outcome (recurrence of all atrial arrhythmias) and all covariates were included in the final model. To avoid overfitting our final model, the number of covariates was selected to allow 1 *df* per 10 recurrence events. Accordingly, covariates included in the VU and HCL cohorts included age, sex, body mass index, paroxysmal AF (yes/no), hypertension, LA diameter, and left ventricular ejection fraction. Because of sample size limitations, the MGH cohort was adjusted for age and sex. Assumptions of the Cox proportional hazards model were met in all 3 cohorts such that: 1) censoring was noninformative and 2) proportional hazards were examined using log–log plots that demonstrated parallel, proportionally separated curves. All secondary analyses were prespecified. We first tested for an association between all 4 SNPs (in separate models) and the primary end point of atrial tachyarrhythmia recurrence adjusting for the clinical covariates included in our primary analysis. Given AT and atrial flutter after AF ablation is widely considered an iatrogenic rhythm amenable to repeat ablation, we then performed a secondary analysis that evaluated recurrence defined only as a qualifying episode of AF (not AT or atrial flutter). Subjects who experienced recurrence only in the form of AT or atrial flutter were included in the analysis as nonevents. Finally, a post hoc analysis was performed to explore whether an association existed between empirical linear ablation and recurrence that may provide insight into between-center differences in recurrence rates. The primary and secondary analyses were performed separately in each cohort using Cox proportional hazards multivariable regression models, and summary statistics were submitted for inverse-variance–weighted fixed effects meta-analysis.[8,9] In addition to our primary analysis, we assessed the effect of heterogeneity between centers using a random-effects meta-analysis. All analyses were performed using a combination of R version 3.0 and SPSS version 21 (IBM Corp, Armonk, NY). Meta-analysis was performed using the METAL software package.[10]

Results

A total of 991 subjects were included in the study (VU, 245; HCL, 659; MGH, 87). There were no deaths in any of the cohorts. No patients were lost to follow-up in the MGH or HCL cohorts. Five patients were lost to follow-up in the VU cohort (5/245=0.02). Complete baseline characteristics are listed in Table 1. The 3 cohorts were similar in age. Study subjects were predominately men, which is consistent with worldwide trends for AF ablation. Compared with the VU and HCL cohorts, the MGH cohort included a higher proportion of male patients, lower proportion with hypertension, and higher proportion with paroxysmal AF. Given only 3 subjects were of non-European Ancestry (0.3%, 3/991), they were not excluded from the analysis. The 12-month recurrence rate ranged from 36% to 60% (Table 2), with an overall rate of 42%. AF accounted for the majority of recurrences and ranged from 62% (MGH) to 86% (VU).

The minor allele frequencies are presented in Table 3. For all 4 SNPs, the minor allele represents the AF susceptibility allele. Overall, the proportion of subjects who carried an AF susceptibility (risk) allele was 34% for rs13376333 (1q21), 25% for rs2200733 (4q25), 12% for rs10033464 (4q25), and 22% for rs7193343 (16q22). The overall call rate for the 4 SNPs tested was 96.4%. All SNPs were found to be in Hardy–Weinberg equilibrium.

Results of the univariate analysis for recurrence during the 90-day blanking period and 12-month follow-up are presented in Tables I and II in the Data Supplement. In univariate analysis, the chromosome 4q25 risk allele (rs2200733) predicted a 60% increased risk of recurrence of atrial arrhythmias during the 90-day blanking period (combined odds ratio [OR], 1.6 [95% confidence interval [CI], 1.2–2.1]; $P<0.001$; Table I in the Data Supplement), and a 20% increased risk of recurrence at 12 months (combined OR, 1.2 [95% CI 1.0–1.5]; $P=0.026$; Table II in the Data Supplement). The remaining SNPs were not significantly associated with recurrence in univariate analysis (Table II in the Data Supplement). In multivariable analysis using a dominant genetic model, the presence of a chromosome 4q25 risk allele (rs2200733) predicted a 30% increased risk of recurrence of atrial arrhythmias at 12 months (combined Adj. HR, 1.3 [95% CI, 1.1–1.6]; $P=0.011$]; Table 4 and Figure). The results of the multivariable analysis of the individual cohorts are presented in Table 5. The remaining SNPs did not significantly predict recurrence. The association between rs2200733 and AF recurrence persisted when accounting for the heterogeneity between centers using a random-effects meta-analysis (OR, 1.36 [95% CI, 1.01–1.98]; $P=0.045$). The absolute 12-month recurrence rate in patients with a risk allele at rs2200733 compared with patients without was 67% versus 55% (VU), 38% versus 37% (HCL), and 49% versus 37% (MGH).

A secondary analysis was performed to examine whether the strength of the association between AF susceptibility alleles and recurrence was stronger when restricted to only those subjects who experienced an AF recurrence (rather than atrial flutter or tachycardia). Results for each cohort are presented in Table III in the Data Supplement, which demonstrates a significant association between AF recurrence and rs2200733 in the VU cohort (Adj. HR, 1.7 [95% CI, 1.1–2.7]; $P=0.015$), and nonsignificant associations in the HCL cohort (OR, 1.3 [95% CI, 0.9–2.0]; $P=0.167$) and MGH (Adj. HR, 0.4 [95% CI, 0.1–1.2]; $P=0.111$)

cohorts. Finally, the post hoc analysis detected a discordant effect between empirical linear ablation and recurrence, which did not reach statistical significance in any of the cohorts (VU: HR, 0.7 [95% CI, 0.5–1.2]; *P*=0.18; HCL: HR, 1.3 [95% CI, 1.0–1.8]; *P*=0.07; MGH: HR, 1.0 [95% CI, 0.4–2.4]; *P*=0.95).

Discussion

In this study, we demonstrated that a common AF risk allele (rs2200733) at the chromosome 4q25 locus (near *PITX2*) is associated with recurrence of atrial arrhythmias in a large cohort of patients who underwent catheter ablation for AF. The presence of a risk allele conferred an increased risk of atrial tachyarrhythmia recurrence of 30% when adjusted for other clinically relevant covariates. Common SNPs at the other top 2 AF susceptibility loci (1q21 and 16q22) were not found to be associated with recurrence of atrial arrhythmias. The identification of common genetic variants that modulate the response to ablation therapy may represent an important step toward the personalization of AF therapy by identifying those subjects most likely to benefit from this invasive therapy.

Originally discovered by genome wide association studies to be associated with development of AF, the rs2200733 SNP is located in an intergenic region of chromosome 4q25 upstream from the nearest gene, paired-like homeodomain 2 (*PITX2*).[11] Subsequently, it was found in experimental models that the transcription factor Pitx2c (encoded by *PITX2)* plays a critical role in (1) development of the PV myocardial sleeve, (2) regulation of signaling pathways that result in proarrhythmic changes in the LA myocardium such as enhanced automaticity and shortening of atrial refractoriness, and (3) structural remodeling of the intercalated disc as seen in human AF.[12–15] It is thought that rs2200733 encodes regulatory elements that modulate the expression of *PITX2*. A potential explanation for our findings could relate to *PITX2*-mediated alterations in the PV myocardial sleeve and LA electrophysiology that affect response to PV isolation.

Clinical Implications

The findings of our study represent important progress toward the goal of personalizing AF treatments with the identification of rs2200733 as a modulator of response to AF ablation. Given AF ablation is an invasive procedure associated with significant cost, unavoidable surgical risk, and frequent need for multiple procedures, there is a critical need for improved strategies to guide (1) patient selection between ablative versus nonablative options and (2) the personalization of targets for ablation. Research in animal models suggests the 4q25 risk locus may promote the existence of non-PV AF sources. If confirmed by future studies, novel ablative approaches, such as the mapping and ablation of focal sources of AF, may provide an effective therapeutic alternative to PVI.[16] Alternatively, genetic susceptibility information may help identify patients in whom specific triggers, such as non-PV foci, play a predominant role in AF genesis and who may benefit from adjunctive ablation.

In general, a challenge to the implementation of personalized medicine is identification of genetic variants that are both common and confer a clinically meaningful effect size. The rs2200733 AF risk allele is present in ≈30% of the general population and depending on the number of risk alleles can confer up to a 2-fold increased risk of recurrence of atrial

arrhythmias after ablation. Furthermore, we found the effect of rs2200733 is independent of other established predictors of recurrence including LA size and persistent AF demonstrating its incremental benefit in predicting an individual's risk of recurrence. As medicine advances toward more personalized approaches, patient choice should continue to be recognized as an important element for which improved risk prediction will permit more accurate patient counseling in the choice to undergo ablative therapy for AF. A future direction of this work is to determine the ability of common genetic markers, such as rs2200733 to improve the prediction of AF recurrence when added to existing clinical prediction models.

Limitations

This is an observational study; as such, unavoidable differences exist between centers and operators that introduce some variability. The size of the cohorts was significantly different between centers (MGH, N=87; VU, N=245; HCL, N=659), and notable differences existed in the proportion of female patients, and those with hypertension, coronary artery disease, and persistent AF (all lower in the MGH cohort). Furthermore, the use of empirical linear ablation was more common in the MGH cohort, and differences existed in postablation rhythm monitoring and the 12-month recurrence rate. Although these differences may favor the generalizability of our findings, they likely diminished the strength of our observed association. These differences may also have contributed to the lack of an association between rs2200733 and 12-month atrial tachyarrhythmia recurrence in the HCL sample (Adj. HR, 1.2 [95% CI, 0.9–1.6]; *P*=0.203; Table 4). Interestingly, rs2200733 was strongly associated with early recurrence of AF during the 90-day blanking period (combined OR 1.6 [1.2–2.1] *P*=0.000; Table I in the Data Supplement), which is known to be associated with future recurrence of AF.[5] To formally account for the heterogeneity between centers observed for the association between rs2200733 and recurrence, we performed a random effects meta-analysis which resulted in results consistent with our primary analysis (OR, 1.4; *P*=0.046). To explore whether the difference observed between centers in AF recurrence rate was related to the use of empirical LA linear ablation, we performed a post hoc analysis including linear ablation (yes/no) as a covariate. This was found to be nonsignificant; however, that analysis may be subject to the limitations of meta-analysis. It should also be noted that the data reported for recurrence during the blanking period (<90 days) is limited by the lack of systematic ambulatory monitoring for asymptomatic recurrence and substantial practice differences between centers in the use of AADs during the blanking period.

Although genotype–phenotype association studies using a candidate gene approach are prone to false-positive and false-negative associations, several factors support the validity of our results. First, the SNPs we selected have a well-established association with the development of AF, and it is therefore a logical extension of this work to examine their association with response to AF therapies. Second, we selected SNPs from the 3 genetic loci most strongly associated with AF. Finally, we corrected for multiple testing and adjusted our models for numerous clinically relevant confounders and covariates. It is possible that an association exists between the other SNPs and AF recurrence but was not detected because of limitations in the length of follow-up and sample size. Furthermore, the association

between rs2200733 and AF recurrence may relate to the fact that it has the strongest association with AF. Therefore, AF recurrence related to electric gaps in ablation lines, rather than non-PV AF sources, would be most readily detected in association with rs2200733, but also exist for the other SNPs that we were underpowered to detect. Finally, given symptomatic recurrence is more likely to be detected, the possibility that rs2200733 risk allele carriers experience a higher burden of symptomatic AF would be an explanation for our findings that we were unable to assess.

Conclusions

In this meta-analysis, a common genetic variant at chromosome 4q25 (rs2200733) that is present in ≈30% of individuals was found to predict recurrence of atrial arrhythmias after catheter ablation of AF. This AF susceptibility allele is believed to modulate a nearby gene, *PITX2*. Downregulation of *PITX2* has been found to promote proarrhythmic electric and structural changes in the LA substrate, as well as inhibit development of the PV myocardial sleeve—the key source of ectopic triggers targeted by PV isolation. Further work to understand the mechanism by which rs2200733 and *PITX2* contribute to AF pathogenesis may explain the variation in clinical response between patients and lead to personalized approaches for ablative therapy of AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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WHAT IS KNOWN

- The original 3 common genetic variants associated with atrial fibrillation exist at the chromosome 1q21, 4q25, and 16q22 loci.
- The single nucleotide polymorphism rs2200733 at 4q25 has the strongest association with atrial fibrillation and risk alleles at rs2200733 have previously been shown to be associated with earlier recurrence of atrial fibrillation after catheter-based pulmonary vein isolation.

WHAT THE STUDY ADDS

- In this study, we analyzed atrial fibrillation ablation outcome data from 3 centers and found that single nucleotide polymorphisms at the 4q25 locus predict earlier recurrence of atrial fibrillation, but not single nucleotide polymorphisms at the 1q21 and 16q22 loci.
- This finding provides further support that variants at the 4q25 locus modulate response to pulmonary vein isolation.

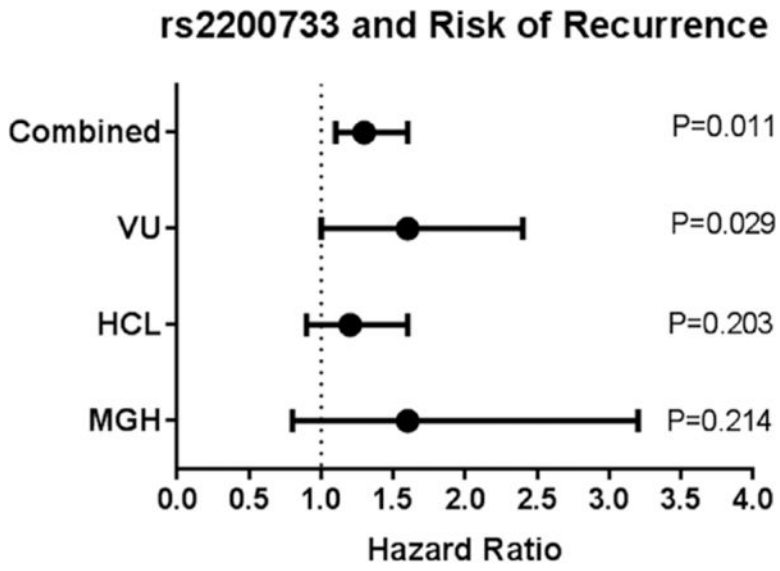

Figure.

The association between risk alleles at rs2200733 (4q25) and time to recurrence of atrial fibrillation (AF), atrial tachycardia, or atrial flutter. Values displayed are the results of the multivariable Cox proportional hazards model (adjusted effect size and 95% confidence intervals) for the individual cohorts and the combined meta-analysis. Dominant genetic modeling is used for all single nucleotide polymorphisms. The Vanderbilt University (VU) and Heart Center Leipzig (HCL) models are adjusted for age, sex, paroxysmal AF status, hypertension, body mass index, left atrial diameter, and left ventricular ejection fraction. The Massachusetts General Hospital (MGH) model is adjusted for age and sex.

Table 1

Study Subject Characteristics (N=991)

	VU	HCL	MGH
No. of subjects	245	659	87
Age, y	61 (54–67)	60 (53–67)	57 (51–64)
Women, %	29	33	18
Body mass index, kg/m^2	30 (26–35)	28 (26–31)	29 (26–32)
Hypertension, %	66	78	46
Paroxysmal AF, %	48	59	87
Coronary artery disease, %	16	12	2
Left atrial size, mm	39 (35–45)	42 (39–46)	40 (36–45)
Left ventricular ejection fraction	60 (55–69)	60 (55–65)	60 (55–65)
Left atrial linear ablation, %	19	36	44

Continuous data expressed as median with interquartile range. Left atrial linear ablation includes the addition of roof, inferior (floor), and mitral isthmus ablation lines to standard pulmonary vein isolation. AF indicates atrial fibrillation; HCL, Heart Center Leipzig; MGH, Massachusetts General Hospital; and VU, Vanderbilt University.

Table 2

Clinical Outcome After Atrial Fibrillation Ablation

	VU	HCL	MGH
Blanking period (<90 d) recurrence, %	47	54	45
6-Mo recurrence, %	38	28	21
12-Mo recurrence, %	60	36	42
Time to recurrence, d	133 (102–189)	90 (90–180)	330 (172–365)
Type of recurrence			
Atrial fibrillation, %	86	73	62
Atrial flutter or atrial tachycardia only, %	14	27	38

Time to recurrence expressed as median with interquartile range. Blanking period is <90 days after date of ablation. HCL indicates Heart Center Leipzig; MGH, Massachusetts General Hospital; and VU, Vanderbilt University.

Table 3

Atrial Fibrillation Susceptibility Alleles

				Copies of Risk Allele, %								
				VU			HCL			MGH		
SNP	**Chromosome Locus**	**Nearest Gene**	**Major/Minor Allele***	**0**	**1**	**2**	**0**	**1**	**2**	**0**	**1**	**2**
rs13376333	1q21	*KCNN3*	C/T	42	46	12	42	46	12	46	49	5
rs2200733	4q25	*PITX2*	C/T	58	35	7	56	36	8	60	37	3
rs10033464	4q25	*PITX2*	G/T	79	19	2	77	22	1	72	28	0
rs7193343	16q22	*ZFHX3*	C/T	58	39	3	61	35	4	58	38	5

HCL indicates Heart Center Leipzig; MGH, Massachusetts General Hospital; SNP, single nucleotide polymorphism; and VU, Vanderbilt University.

* The minor allele is the risk allele for all the SNPs.

Table 4

Multivariable Analysis: Risk of Recurrence According to Risk Allele Status

			Combined		VU		HCL		MGH	
SNP	**Locus**	**Risk Allele**	**Adj. HR**	***P* Value**	**Adj. HR**	***P* Value**	**Adj. HR**	***P* Value**	**Adj. HR**	***P* Value**
rs13376333	1q21	T	1.1 (0.9–1.4)	0.208	1.4 (0.9–2.1)	0.115	1.1 (0.9–1.5)	0.377	0.7 (0.4–1.5)	0.384
rs2200733	4q25	T	1.3 (1.1–1.6)	0.011	1.6 (1.0–2.4)	0.029	1.2 (0.9–1.6)	0.203	1.6 (0.8–3.2)	0.214
rs10033464	4q25	T	0.8 (0.6–1.1)	0.155	0.6 (0.4–1.1)	0.101	0.9 (0.7–1.3)	0.605	0.7 (0.3–1.7)	0.466
rs7193343	16q22	T	0.9 (0.7–1.1)	0.345	1.4 (0.9–2.1)	0.143	0.8 (0.6–1.0)	0.070	0.7 (0.3–1.4)	0.281

Recurrence includes AF, atrial flutter, or atrial tachycardia. Dominant genetic modeling is used for all SNPs. VU and HCL models are adjusted for age, sex, paroxysmal AF status, hypertension, BMI, LA diameter, and LVEF. The MGH model is adjusted for age and sex. The reference genotype is CC for rs2200733, rs7193343, and rs13376333. The reference genotype is GG for rs10033464. AF indicates atrial fibrillation; BMI, body mass index; HCL, Heart Center Leipzig; HR, hazard ratio; LA, left atrial; LVEF, left ventricular ejection fraction; MGH, Massachusetts General Hospital; SNP, single nucleotide polymorphism; and VU, Vanderbilt University.

Table 5

Results of Multivariable Analysis for rs2200733 and Atrial Tachyarrhythmia Recurrence

	VU		HCL		MGH	
SNP	**Adj. HR**	***P* Value**	**Adj. HR**	***P* Value**	**Adj. HR**	***P* Value**
rs2200733 (≥1 risk allele)	1.58 (1.05–2.38)	0.029	1.19 (0.91–1.56)	0.203	1.57 (0.77–3.17)	0.214
Age	0.99 (0.97–1.02)	0.597	1.01 (0.99–1.03)	0.181	1.01 (0.97–1.05)	0.667
Women	1.82 (1.15–2.88)	0.010	0.95 (0.69–1.31)	0.753	1.05 (0.42–2.63)	0.921
Paroxysmal AF	0.75 (0.48–1.19)	0.222	0.68 (0.51–0.91)	0.008	…	…
Hypertension	1.05 (0.67–1.67)	0.827	0.88 (0.62–1.24)	0.460	…	…
BMI (per 5 kg/m^2)	0.78 (0.64–0.97)	0.023	1.01 (0.85–1.20)	0.905	…	…
LA diameter (per 5 mm)	1.19 (1.02–1.39)	0.025	1.12 (0.99–1.25)	0.067	…	…
LVEF (per 10%)	0.81 (0.67–0.99)	0.034	0.97 (0.83–1.12)	0.664	…	…

Recurrence includes AF, atrial flutter, or atrial tachycardia. Regression analysis was performed using a Cox Proportional Hazards model. Dominant genetic modeling is used for all SNPs. VU and HCL models are adjusted for age, sex paroxysmal AF status, hypertension, BMI, LA diameter, and LVEF. Because of sample size limitations, the MGH model is adjusted for age and sex. The reference genotype is CC for rs2200733. AF indicates atrial fibrillation; BMI, body mass index; HCL, Heart Center Leipzig; HR, hazard ratio; LA, left atrial; LVEF, left ventricular ejection fraction; MGH, Massachusetts General Hospital; SNP, single nucleotide polymorphism; and VU, Vanderbilt University.