Impact of a 4q25 Genetic Variant in Atrial Flutter and on the Risk of Atrial Fibrillation After Cavotricuspid Isthmus Ablation

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Role of a 4q25 Genetic Variant in Atrial Flutter. ***Background:*** **The prediction of atrial fibrillation (AF) following catheter ablation of atrial flutter (Afl) would be helpful to facilitate targeted arrhythmia monitoring and anti-coagulation strategies. A single nucleotide polymorphism, rs2200733, is strongly associated with AF. We sought to characterize the association between rs2200733 and prevalent Afl and to determine if the variant could predict AF after cavotricuspid isthmus ablation.**

Methods and Results: **We performed a genetic association study of 295 patients with Afl and/or AF and 469 controls using multivariable logistic regression. The variant was then assessed as a predictor of incident AF after cavotricuspid isthmus ablation in 87 consecutive typical Afl patients with Cox proportional hazards models. The rs2200733 rare allele was associated with an adjusted 2.06-fold increased odds of isolated Afl (95% CI: 1.13–3.76, P = 0.019) and an adjusted 2.79-fold increased odds of a combined phenotype of AF and Afl (95% CI: 1.81–4.28, P < 0.001). Following catheter ablation for Afl, carrier status of rs2200733 failed to predict an increased risk of AF either among all subjects (adjusted HR: 0.94; 95% CI: 0.58–1.53, P = 0.806) or among those with isolated Afl (adjusted HR: 1.29; 95% CI: 0.51–3.26, P = 0.585).**

Conclusions: **Our study demonstrates that Afl, whether occurring in isolation or along with AF, is associated with the rs2200733 AF risk allele. Genetic carrier status of rs2200733 failed to predict an increased risk of incident or recurrent AF following catheter ablation for Afl. These findings suggest that the causal mechanism associated with rs2200733 is germane to both AF and Afl.** *(J Cardiovasc Electrophysiol, Vol. 25, pp. 271-277, March 2014)*

atrial fibrillation, atrial flutter, catheter ablation, genetics, molecular biology

Introduction

Radiofrequency catheter ablation of the cavotricuspid isthmus is considered curative therapy for typical atrial flutter (Afl).[1] Although recurrence of Afl is rare following successful ablation, the risk of new onset or recurrent atrial fibrillation (AF) is approximately 50% when follow-up is extended beyond 2 years.[2] Despite this markedly elevated risk of AF, no dedicated guidelines exist regarding arrhythmia monitoring and anticoagulation in these subjects.[3] Contemporary practice is frequently restricted to 1 month of anticoagulation following the procedure, which is likely inadequate for a substantial proportion of individuals.[4] This notion was highlighted by a recent study that showed a 6% cumulative incidence of stroke during a mean follow-up of 30 months after ablation for typical Afl.[5] In an effort to improve outcomes in this patient population, there is a critical need to identify features that predict an increased risk of AF after ablation of typical Afl in order to enable targeted administration of anticoagulant therapy to vulnerable individuals.

To date, the sole clinical parameter consistently shown to predict an increased risk of postablation AF has been the presence of AF prior to the ablation procedure.[2,5-10] Although a robust predictor, approximately half of those with isolated flutter (i.e., no known history of AF) will develop AF within 2 years of a successful Afl ablation.[10] Therefore, there is a need to identify additional variables that will better refine our ability to identify at-risk individuals.

Common genetic variations, referred to as single nucleotide polymorphisms (SNPs), have recently been shown to be associated with an increased risk of AF.[11-15] The SNPs with the strongest association with AF are located within the 4q25 locus greater than 100 kilobases away from the nearest

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gene, namely *PITX2*.[11,15] Consistent with the concept of an overlapping pathophysiology between AF and Afl, 2 previous studies involving a small number of Afl patients have suggested that these SNPs may also increase the risk of Afl.[11,16] Interestingly, the rs2200733 SNP within the 4q25 locus is associated with an increased risk of recurrent AF following pulmonary vein isolation.[17,18] Given these observations, we sought to further evaluate the impact of rs2200733 on the risk of Afl and to investigate its ability to predict the risk of recurrent or new onset AF among subjects receiving radiofrequency catheter ablation for typical Afl.

Methods

Study Population

Consecutive consenting patients undergoing procedures at the UCSF Medical Center Cardiac Electrophysiology Laboratory for a history of typical Afl and/or AF were recruited between October 2004 and December 2009. Enrollment into the study required arrhythmia documentation confirmed by a board-certified cardiac electrophysiologist with either 12-lead electrocardiography (ECG) or Holter monitoring. Typical flutter was defined by the 12-lead ECG as previously described, requiring discordant flutter-wave vectors between the inferior leads and V1 and a precordial transition.[19-22] Patients with congenital heart disease were excluded. Participant demographics and medical details were obtained using a study questionnaire and were verified with a subsequent chart review.

Control participants for the study consisted of individuals with no documented history of AF or Afl and were drawn from 3 separate sources: (1) Individuals undergoing procedures for supraventricular tachycardia in the same laboratory with no clinical evidence of Afl or AF; (2) Participants with no known cardiac disease undergoing evaluation at the UCSF Lipid Clinic; and (3) Senior athletes participating in the 2004 Huntsman World Senior Games in St. George, Utah with no prior cardiac history.[23]

All study participants provided informed written consent under protocols that were approved by the University of California, San Francisco Committee on Human Research.

Genetic Analyses

Genomic DNA was extracted from whole blood using the Gentra Puregene Blood Kit (Qiagen Inc., Valencia, CA, USA). Genotyping of rs2200733 and 107 ancestry informative markers was performed using the GoldenGate genotyping platform (Illumina, San Diego, CA, USA) and processed according to the standard protocol using GenomeStudio (Illumina). Principal components analysis of ancestry informative markers was used to generate the principal components ($n = 10$) included as covariates to adjust for potential population stratification.[24]

Atrial Flutter Ablation

A total of 87 patients with Afl underwent treatment with radiofrequency catheter ablation. Invasive electrophysiology studies and cavotricuspid isthmus ablations were performed as described previously.[25] Briefly, a duodecapolar catheter was placed around the tricuspid annulus, a decapolar catheter was inserted into the coronary sinus, and a quadripolar catheter was advanced to the His position. Among the 36 patients in spontaneous Afl at the time of the electrophysiology study, a typical flutter circuit around the tricuspid annulus was confirmed by entrainment mapping. Afl was confirmed in an additional 35 patients following induction of the arrhythmia with atrial burst pacing, while the remaining 16 patients stayed in sinus rhythm for the duration of the procedure. The ablation consisted of a contiguous linear lesion extending from the ventricular aspect of the tricuspid annulus to the inferior vena cava. The procedural endpoint was the presence of bidirectional block across the cavotricuspid isthmus that persisted for a minimum of 30 minutes following the final radiofrequency application.

Outcome of Interest

The primary outcome in the cross-sectional analysis was any history of Afl; a subset of Afl patients without any known history of AF ("isolated Afl") was examined as a secondary outcome. The outcome of interest in the survival analysis was time to incident or recurrent AF. Patients were censored at the first episode of incident or recurrent AF or death, whichever occurred first. Ascertainment of incident or recurrent AF following cavotricuspid isthmus ablation and death was initially performed by review of the electronic medical record. Patients were noted to have incident or recurrent AF based on clinician notes, ECG, or other telemetry monitoring system documentation. Additional telephone follow-up was performed with the patient or provider outside the UCSF medical system in patients with no documentation of AF in the electronic medical record.

Statistical Analysis

Normally distributed continuous variables are presented as means ± standard deviation and were compared using the Student's *t*-test or a 1-way analysis of variance. Comparison of categorical values was performed using the chi-square test. To evaluate for genotyping measurement errors, the genotype distribution of rs2200733 was examined for deviation from Hardy-Weinberg equilibrium among control participants using a Pearson chi-square test. No evidence of genotype measurement error was found ($P = 0.118$).

Logistic regression was used to determine the association between the SNP and prevalent AF and Afl. In order to examine for an influence of age on the association between cases of AF and Afl, subgroup analyses and a formal test of interaction were conducted for individuals less than and greater than or equal to 70 years of age. Time to event analyses using Cox proportional hazards models were employed to evaluate the association of the SNP with incident and/or recurrent AF following Afl ablation. Both analyses utilized an additive genetic model. Separate subgroup analyses were performed for individuals with preexisting AF and isolated Afl. Multivariable logistic and Cox regression analyses were performed to adjust for potential confounding. Covariates added to these models included age, gender, self-reported race, hypertension, diabetes, body mass index (BMI), coronary artery disease, and congestive heart failure. For the adjusted survival curves, categorical covariates were set at 0 and

TABLE 1
Clinical Demographics of Prevalent Cases of Atrial Flutter, Atrial Fibrillation, and Controls

	All Afl[†] n = 122	Isolated AF n = 173	Controls n = 469	P Value[*]
Age (years)	60.8 ± 12.1	58.4 ± 12.0	57.2 ± 15.6	0.037
Male gender	89 (73.0)	128 (74.4)	282 (60.3)	<0.001
White race	87 (71.3)	138 (79.8)	379 (80.8)	0.344
Hypertension	44 (36.1)	63 (36.4)	125 (26.7)	0.005
Diabetes mellitus	17 (13.9)	11 (6.4)	20 (4.3)	0.004
Body mass index	28.5 ± 5.8	29.0 ± 6.4	25.9 ± 4.6	<0.001
Coronary artery disease	17 (13.9)	16 (9.3)	8 (1.71)	<0.001
Congestive heart failure	8 (6.6)	9 (5.2)	3 (0.64)	<0.001
β-blocker	60 (49.2)	85 (49.1)	58 (12.4)	<0.001
ACE inhibitor/ARB	35 (28.7)	36 (20.8)	69 (14.7)	0.001
Non-DHP CCB	16 (13.1)	30 (17.3)	22 (4.7)	<0.001
Type IC AAD	24 (19.7)	41 (23.7)	4 (0.85)	<0.001
Type III AAD	3 (2.5)	13 (7.5)	0 (0)	<0.001
Amiodarone	14 (11.5)	12 (6.9)	1 (0.21)	<0.001

Continuous variables are reported as mean ± standard deviation, categorical values are reported as n (%). [†]Of the 122 subjects with Afl, 43 had isolated Afl; *P-value represents a comparison of cases (All Afl and Isolated AF) with controls.
AAD = anti-arrhythmic drug; AF = atrial fibrillation; Afl = atrial flutter; ARB = angiotensin II receptor blocker; Non-DHP CCB = nondihydropyridine calcium channel blocker.

TABLE 2
Association of rs2200733 with Atrial Flutter and Atrial Fibrillation

Arrhythmia Phenotype	Unadjusted OR (95% CI)	P Value	Adjusted OR[*] (95% CI)	P Value
All Afl n = 122	2.19 (1.61–2.98)	<0.001	2.40 (1.65–3.48)	<0.001
Isolated Afl n = 43	1.82 (1.13–2.92)	0.014	2.06 (1.13–3.76)	0.019
AF + Afl n = 79	2.37 (1.66–3.39)	<0.001	2.79 (1.81–4.28)	<0.001
Isolated AF n = 173	1.60 (1.21–2.10)	0.001	1.88 (1.36–2.58)	<0.001

*Adjusted for age, gender, self-reported race, hypertension, diabetes, body mass index, coronary artery disease, congestive heart failure, and first 10 principal components.
AF = atrial fibrillation; Afl = atrial flutter; CI = confidence interval; OR = odds ratio.

continuous covariates were set at their mean values. Adjustment for population stratification was performed using the first 10 principal components in the adjusted logistic regression models, but not in the Cox regression analyses due to the limited number of outcomes. Two-tailed P-values < 0.05 were considered statistically significant. Statistical analyses were performed using Stata version 12 (College Station, TX, USA).

Results

Patient Characteristics

A total of 295 cases of Afl and/or AF and 469 controls were included. Cases consisted of patients with isolated Afl (n = 43, 14.6%), isolated AF (n = 173, 58.6%), and both Afl and AF (n = 79, 26.8%). Control subjects were recruited from the electrophysiology laboratory (n = 140, 29.8%), the UCSF Lipid Clinic (n = 207, 44.1%), and the 2004 Huntsman World Senior Games (n = 122, 26.0%). The baseline clinical characteristics of the cases and controls are summarized in Table 1. Participants with Afl and isolated AF were older, more often male, and more likely to possess cardiovascular risk factors and comorbidities (Table 1).

Genetic Associations with Prevalent Atrial Fibrillation and Atrial Flutter

Bivariate analysis demonstrated that the presence of the rs2200733 rare allele was associated with a statistically significant 2.19-fold greater odds of Afl relative to controls, which increased to 2.40-fold following adjustment for prespecified covariates (Table 2). Adjusted subgroup analyses revealed that rs2200733 carrier status was associated with a 2.06-fold greater odds of isolated Afl and a 2.79-fold greater odds of a combined phenotype of both AF and Afl (Table 2). Among individuals with Afl less than 70 years of age, genetic carrier status of the SNP was associated with an adjusted 2.58-fold greater odds of the arrhythmia ($P < 0.001$), in comparison with a nonsignificant 1.30-fold increased odds among those 70 years of age or greater ($P = 0.650$). The corresponding test for interaction was not significant ($P = 0.732$). The rs2200733 SNP was associated with a 1.60-fold (unadjusted) and 1.88-fold (adjusted) greater odds of isolated AF relative to control subjects (Table 2). Notably, there was a trend towards a stronger association between the genetic variant and the odds of Afl compared to the odds of isolated AF (adjusted odds ratio [OR]: 1.35; 95% CI: 0.92–2.00, $P = 0.123$).

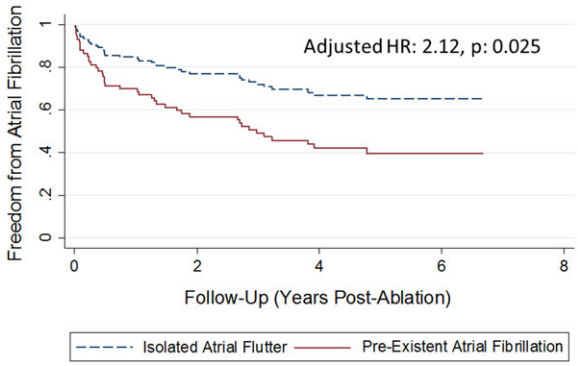

Figure 1. *Adjusted survival curves for the hazard of atrial fibrillation after cavotricuspid isthmus ablation among subjects with isolated atrial flutter and preexistent atrial fibrillation.*

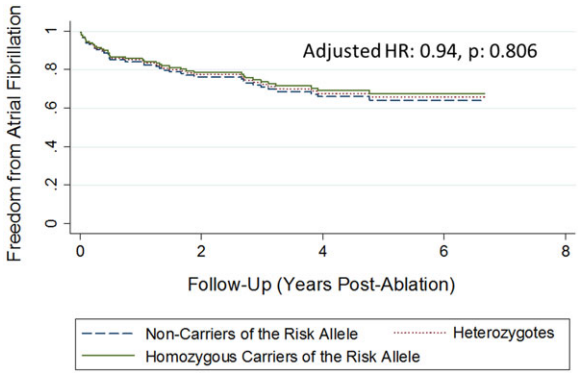

Figure 2. *Adjusted survival curves for the hazard of atrial fibrillation after cavotricuspid isthmus ablation by rs2200733 carrier status.*

Outcomes Following Catheter Ablation for Atrial Flutter

Of the 122 participants with a history of Afl, 87 underwent cavotricuspid isthmus catheter ablation. Bidirectional block was successfully achieved in 82 subjects (94.3%). During a median follow-up period of 2.98 years, 43 subjects (49.4%) were documented to have AF (Fig. 1). Fourteen (35%) isolated Afl patients and 29 (62%) Afl patients with previous evidence of AF had recurrent AF after ablation ($P = 0.018$). Consistent with previous studies, preexistent AF was associated with an increased adjusted hazard of AF following catheter ablation for typical Afl (hazard ratio [HR]: 2.12, 95% CI: 1.10–4.08, $P = 0.025$; Fig. 1).

Association of Genotype with Risk of Atrial Fibrillation Following Ablation

The rs2200733 rare allele frequency among patients that developed AF following catheter ablation was 33.0% in comparison with a rare allele frequency of 32.6% among patients that remained free of AF during the follow-up period ($P = 0.851$). Following adjustment for prespecified covariates using Cox proportional hazards modeling, there was no difference observed in the hazard for developing postablation AF on the basis of genetic carrier status (HR: 0.94; 95% CI: 0.58–1.53, $P = 0.806$; Fig. 2 and Table 3). Subgroup analyses examining subjects with isolated Afl and mixed AF/Afl also revealed no association between postablation AF and the rs2200733 genotype (Table 3).

Discussion

We found a strong association between Afl and the rs2200733 SNP in the largest case control study involving this arrhythmia to date. These findings suggest that the pathophysiology underlying the rs2200733-arrhythmia relationship is common to both AF and Afl. This SNP, previously established as the variant most strongly associated with AF in multiple genome wide association studies,[11-15] fails to predict an increased risk of AF following ablation for Afl.

Our study involving 122 cases of Afl is consistent with the findings from 2 previous studies that suggested an association between Afl and rs2200733.[11,16] The original genome wide association study for AF consisted of cases that were described as AF and/or Afl; however, the precise number of participants with Afl in the overall sample was not specified. A subgroup analysis involving 116 subjects with isolated Afl identified a 2.60-fold increased odds (95% CI: 1.83–3.68, $P = 7.5 \times 10^{-8}$) of the arrhythmia in association with the rs2200733 rare allele.[11] Another Italian study that examined the rs2200733 SNP found significant associations between the SNP and 33 subjects with isolated Afl (OR: 2.38; 95% CI: 1.34–4.22, $P = 0.003$) and 78 subjects with AF/Afl (OR: 2.17; 95% CI: 2.17, $P < 0.001$) relative to prevalent controls.[16]

Our results further reinforce the association between this 4q25 AF risk allele and Afl, particularly given the more rigorous phenotyping utilized in our study. In contrast to previous studies, all cases were diagnosed as typical Afl by board-certified cardiac electrophysiologists and typical Afl was confirmed at the time of invasive electrophysiology study in 71 of the 122 cases. This concept is particularly important given that AF is frequently misdiagnosed as Afl on ECG, which can lead to inaccurate conclusions.[26-28] Our findings

TABLE 3

Association of rs2200733 Genotype and the Risk of AF Following Cavotricuspid Isthmus Ablation for Atrial Flutter

Ablation Subgroups	Unadjusted HR (95% CI)	P Value	Adjusted HR* (95% CI)	P Value
All Subjects n = 87	0.88 (0.54–1.44)	0.603	0.94 (0.58–1.53)	0.806
Isolated AFl n = 40	0.99 (0.41–2.36)	0.974	1.29 (0.51–3.26)	0.585
AF + AFl n = 47	0.84 (0.47–1.51)	0.572	0.94 (0.50–1.76)	0.835

*Adjusted for age, gender, self-reported race, hypertension, diabetes, body mass index, coronary artery disease, and congestive heart failure.
AF = atrial fibrillation; Afl = atrial flutter; CI = confidence interval; HR = hazard ratio.

also suggest that the impact of the SNP may be greater among subjects with earlier onset Afl (age < 70 years), relative to subjects that develop the arrhythmia after 70 years of age. These results align with the notion that heritability may exert a greater role in younger cases, in contrast with later onset forms of the arrhythmia that may be primarily driven by conventional risk factors such as hypertension and heart failure.[29,30] Our findings, however, should be interpreted with caution as we failed to show a significant interaction between age of onset and genetic carrier status, though this may have been secondary to inadequate power.

The association of rs2200733 with the phenotypes of both Afl and AF suggests that this SNP mediates a pathophysiology common to both arrhythmia disorders. Although the functional significance of this SNP remains unclear, multiple lines of evidence have suggested that it influences activity of the *PITX2* gene product.[31-36] The *PITX2* gene encodes for a transcription factor that appears to promote the development of left-right asymmetry within the heart.[31-33] In particular, it has been hypothesized to suppress the development of sinoatrial nodal tissue within the left atrium.[31,33,35] Aberrant development of sinoatrial nodal tissue may lead to inappropriate firing within the left atrium and could potentially contribute to the ectopic foci arising from the pulmonary veins that may be critical for the initiation and maintenance of AF.[37]

Notably, inappropriate triggers from the pulmonary veins are also considered to be critical for initiation of Afl, though this has not been definitively proven.[38] The finding that the 4q25 risk allele also associates with Afl provides further evidence to suggest that the increased risk of AF mediated by rs2200733 is secondary to abnormal triggers as opposed to an arrhythmogenic substrate. Of note, adjacent to *PITX2* within the 4q25 locus is a gene referred to as *ENPEP* that encodes for an aminopeptidase responsible for converting angiotensin II to angiotensin III.[39] Increased levels of angiotensin II have been shown to result in increased atrial fibrosis and may predispose to AF through a substrate-based mechanism leading certain experts to suggest that *ENPEP* may be responsible for the signal at the 4q25 locus.[40] In contrast to AF, whose pathophysiology is felt to be critically dependent upon both pathophysiologic triggers and an abnormal atrial substrate, the arrhythmogenic culprit in Afl is generally attributed to triggers that establish a circuit using conduction boundaries in the right atrium that are part of normal anatomy.[41] Given the nature of the pathophysiologic overlap between AF and Afl, the common association of rs2200733 with both arrhythmias further supports the notion that this SNP may lead to arrhythmogenesis through abnormal ectopic triggers, potentially from the pulmonary veins.

These observations also provide additional support for the hypothesis that the AF signal at the 4q25 locus is mediated through *PITX2* (likely related to triggers) and not *ENPEP* (which might affect atrial substrate). However, it should be noted that additional potential culprits reside within the 4q25 locus, a prominent example being *ANK2* (encoding the ankyrin-2 protein). Loss-of-function *ANK2* mutations have been shown to give rise to a constellation of arrhythmia phenotypes including long-QT syndrome type 4 and AF.[42-44] The additional presence of *ANK2* within the 4q25 locus serves as a reminder that the precise pathophysiology responsible for the association between AF and these noncoding SNPs remains unknown and emphasizes the need for further research in this area.

Limitations

Our study has several limitations. First, our inability to detect an association between genotype and AF following catheter ablation may be secondary to imperfect sensitivity for documenting AF during follow-up. AF is frequently an asymptomatic arrhythmia and our follow-up protocol was mainly reliant on healthcare utilization (clinic visits and hospitalizations) and self-reporting and did not involve rigorous arrhythmia monitoring. Failure to document cases of AF may have potentially led to bias towards the null hypothesis (i.e., an apparent lack of association). This is unlikely as our cumulative incidences of AF are consistent with previous studies reported in the literature and, furthermore, bias would only be introduced in the event that our ability to ascertain the outcome was influenced by genetic carrier status of the patient, which should not be the case. Second, the modest sample size may have limited our ability to detect associations of smaller effects sizes; however, any undetected impact of genotype on the risk of AF following catheter ablation for Afl is unlikely to be of major clinical significance. Finally, the point estimates generally favored a stronger association between the 4q25 variant and Afl than AF and therefore it appears unlikely that the variant would help distinguish the Afl patients at greater risk of AF.

Conclusion

Our study confirms the association between the 4q25 AF rs2200733 risk allele and Afl. Because we found no association between rs2200733 and the risk of AF following catheter ablation for Afl, additional studies will be necessary to further refine our ability to identify the subgroup of individuals that will develop AF despite curative therapy for Afl with cavotricuspid isthmus ablation. Our findings demonstrate that the pathophysiology accounting for the association between rs2200733 and AF is also likely operative in Afl, potentially providing additional insight into the mechanism linking the SNP to both arrhythmias.

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