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ORIGINAL ARTICLE

Genetic Susceptibility for Atrial Fibrillation in Patients Undergoing Atrial Fibrillation Ablation

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BACKGROUND: Ablation is a widely used therapy for atrial fibrillation (AF); however, arrhythmia recurrence and repeat procedures are common. Studies examining surrogate markers of genetic susceptibility to AF, such as family history and individual AF susceptibility alleles, suggest these may be associated with recurrence outcomes. Accordingly, the aim of this study was to test the association between AF genetic susceptibility and recurrence after ablation using a comprehensive polygenic risk score for AF.

METHODS: Ten centers from the AF Genetics Consortium identified patients who had undergone de novo AF ablation. AF genetic susceptibility was measured using a previously described polygenic risk score (N=929 single-nucleotide polymorphisms) and tested for an association with clinical characteristics and time-to-recurrence with a 3 month blanking period. Recurrence was defined as >30 seconds of AF, atrial flutter, or atrial tachycardia. Multivariable analysis adjusted for age, sex, height, body mass index, persistent AF, hypertension, coronary disease, left atrial size, left ventricular ejection fraction, and year of ablation.

RESULTS: Four thousand two hundred seventy-six patients were eligible for analysis of baseline characteristics and 3259 for recurrence outcomes. The overall arrhythmia recurrence rate between 3 and 12 months was 44% (1443/3259). Patients with higher AF genetic susceptibility were younger ($P<0.001$) and had fewer clinical risk factors for AF ($P=0.001$). Persistent AF (hazard ratio [HR], 1.39 [95% CI, 1.22–1.58]; $P<0.001$), left atrial size (per cm: HR, 1.32 [95% CI, 1.19–1.46]; $P<0.001$), and left ventricular ejection fraction (per 10%: HR, 0.88 [95% CI, 0.80–0.97]; $P=0.008$) were associated with increased risk of recurrence. In univariate analysis, higher AF genetic susceptibility trended towards a higher risk of recurrence (HR, 1.08 [95% CI, 0.99–1.18]; $P=0.07$), which became less significant in multivariable analysis (HR, 1.06 [95% CI, 0.98–1.15]; $P=0.13$).

CONCLUSIONS: Higher AF genetic susceptibility was associated with younger age and fewer clinical risk factors but not recurrence. Arrhythmia recurrence after AF ablation may represent a genetically different phenotype compared to AF susceptibility.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: atrial fibrillation ■ genetic variation ■ genetics ■ phenotype ■ pulmonary veins

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WHAT IS KNOWN?

- Family history of atrial fibrillation (AF) and individual common genetic variants associated with AF (eg, chromosome 4q25 single-nucleotide polymorphisms) are associated with arrhythmia recurrence after catheter-based ablation for AF.
- Polygenic risk scores can combine the effect of hundreds to thousands of common genetic variants (single-nucleotide polymorphisms) to measure overall genetic susceptibility to AF.

WHAT THE STUDY ADDS?

- Patients with higher genetic susceptibility for AF are younger and have fewer clinical risk factors for AF.
- Genetic susceptibility for AF based on common genetic variation is not significantly associated with arrhythmia recurrence after ablation.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
BMI	body mass index
CAD	coronary artery disease
GWAS	genome-wide association study
HCN-4	hyperpolarization cyclic nucleotide-gated potassium channel 4
HR	hazard ratio
LA	left atrial
LVEF	left ventricular ejection fraction
SNP	single-nucleotide polymorphism

Atrial fibrillation (AF) is a common disease with a lifetime risk now estimated to be as high as 37%.[1] The mechanistic heterogeneity contributing to the prevalence of AF is underscored by the diverse clinical and genetic factors associated with the disease.[2] Genome-wide association studies (GWAS) have highlighted the polygenic nature of AF predisposition and have demonstrated how scores comprising many genetic variants can be used to estimate an individual's overall genetic susceptibility to AF.[3–8]

AF ablation focused on pulmonary vein isolation (with or without additional ablation targets) is a commonly used treatment for symptomatic AF. Recent data estimate the recurrence rate after AF ablation is ≈35% at 1-year and at least 15% of patients undergo a second procedure.[9,10] A major knowledge gap is how to select patients who will respond favorably to AF ablation. Current practice already incorporates clinical factors into the considerations for ablation (eg, AF persistence), but the ability of genetic factors to predict AF recurrence remains incompletely defined.[11] Evidence to suggest that recurrence after AF ablation is genetically mediated is based on its association with a family history of AF (a genetic surrogate) and reported associations between individual AF susceptibility alleles and recurrence (eg, single-nucleotide polymorphisms [SNPs] at chromosome 4q25).[12–15] Taken together, these data provide the basis for the overarching goal of this study, which was to define the association between genetic susceptibly to AF and arrhythmia recurrence following AF ablation. To do so, 10 centers contributed clinical data from patients who underwent first-time AF ablation and had genotype data available to calculate a previously described polygenic AF risk score used to measure AF genetic susceptibility.[6] The primary analysis tested for an association between the polygenic AF risk score and arrhythmia recurrence between 3 and 12 months with multivariable adjustment for patient-specific clinical and technical factors. Given potential differences between centers in their patient populations, ablation technique, and recurrence monitoring, results were analyzed separately for each center and combined using meta-analysis.

METHODS

Data Sharing Policy

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participating Cohorts

The AF Genetics Consortium is an international, multicenter working group comprised of prospective cohort studies and observational prospective and retrospective registries with a focus on AF genetics research. The participating studies were approved by their institutional review boards, and all participants underwent written informed consent. Ten centers contributed to the current AF Ablation substudy (Notes in the Data Supplement). Eligible participants underwent first-time catheter-based ablation for AF (radiofrequency or cryoenergy), were clinically followed for at least 12 months after ablation, had available genotype data, and were of European ancestry.

Clinical Characteristics

Age, height, and body mass index (BMI) were recorded at the time of AF ablation. Persistent AF was defined as a history of an AF episode ≥7 days in duration and a history of direct current or pharmacological cardioversion.[16] A history of hypertension and coronary artery disease (CAD) was recorded if the diagnosis occurred before the day of ablation. Hypertension and CAD were defined as present if the diagnosis was listed in the past medical history. CAD included both obstructive and nonobstructive disease. Left atrial (LA) size and left ventricular ejection fraction (LVEF) were recorded from the most recent measurement before ablation and included measurements from transthoracic echocardiogram, cardiac magnetic resonance imaging, or cardiac computed tomography. LA size was recorded as the anterior-posterior dimension. Reported LVEF values greater than 55% were truncated to 55% for analysis.

Catheter-Based AF Ablation and Recurrence Monitoring

AF ablation was performed using methods and protocols according to the clinical standards of each participating center (Table I in the Data Supplement). All patients underwent pulmonary vein isolation. Additional ablation lesions were performed at the discretion of the operator. All patients were monitored during the follow-up period for asymptomatic recurrence using ambulatory monitors, or, if present, implanted devices (pacemakers, implantable cardioverter defibrillators, loop recorders). According to established standards for reporting arrhythmia recurrence for AF ablation research, the definition for recurrence was any episode of AF, atrial flutter, or atrial tachycardia lasting at least 30 seconds and occurring after a 90-day blanking period.[11]

The AF Susceptibility Score

Genetic susceptibility to AF was measured with a polygenic risk score using methods previously described.[1,6] The genotyping array used by each center is reported in Table II in the Data Supplement. Standard quality control steps were undertaken. GWAS quality control included checking for sex concordance, genotyping efficiency at the subject (>98%) and SNP level (>98%), relatedness between samples (Z0 ≥0.8), Mendelian errors, and concordance between duplicates. Imputation was performed using the Haplotype Reference Consortium panel revision 1.1.[17] Preimputation quality control included alignment to the Haplotype Reference Consortium reference panel (McCarthy Group Tools, https://www.well.ox.ac.uk/~wrayner/tools/), which filters palindromic SNPs, SNPs with allele frequencies significantly deviating from the Haplotype Reference Consortium reference frequency, and SNPs not mapping to known Haplotype Reference Consortium positions. Given differences in the imputation quality between different genotyping platforms used by the centers, the final polygenic risk score was comprised of 929 SNPs that were common to all the centers and were directly genotyped or had an imputation INFO score >0.3 (Table III in the Data Supplement). We refer to this polygenic risk score as the AF susceptibility score. The AF susceptibility score was calculated as the weighted sum of the AF risk alleles. For each SNP included in the AF susceptibility score, the risk allele is listed in Weng et al,[1] and the weight is equal to the β coefficient for its association with AF in the GWAS from Christophersen et al.[3] The AF susceptibility score was standardized by zero centering and dividing by the SD of each center's AF genetic susceptibility score. The distribution of the genetic risk score for each cohort is presented in Figure I in the Data Supplement. To present the association between baseline clinical characteristics and genetic susceptibility, individual-level data for the AF susceptibility score was pooled across cohorts and divided into quintiles to define cutoffs for assigning participants into the bottom quintile 1 (Q1) to the top quintile (Q5). To investigate the potential for a different polygenic AF risk score derived from the results of another recent AF GWAS to yield different results, a second polygenic risk score was created using 97 SNPs that met the genome-wide significance threshold of $P<5\times10^{-8}$ from the report by Roselli et al.[4] This polygenic score is referred to here as the limited AF susceptibility score.

Statistical Analysis

Continuous variables were reported as the median and interquartile range and categorical variables as the frequency and percentage. Overall baseline clinical characteristics are presented along with results stratified according to the AF genetic susceptibility class. Differences between clinical characteristics and AF genetic susceptibility class were compared using the Kruskal-Wallis H test or χ^2 test. To further explore the association between AF genetic susceptibility and risk factors that have age-related penetrance, hypertension, CAD, persistent AF, BMI, and obesity (≥30 kg/m²) were analyzed using a multivariable regression model with adjustment for age at ablation (logistic regression models: hypertension, CAD, persistent AF, and obesity; linear regression model: BMI). To examine the combined effect of multiple clinical risk factors, clinical risk factors for AF were defined as age >60 years, BMI >30 kg/m², CAD, and LVEF <50%. Low clinical risk burden was defined as zero risk factors, moderate clinical risk burden was 1 risk factor, and high clinical risk burden was defined as greater than or equal to 2 risk factors. A multinomial logistic regression was used to test the association between clinical risk burden (low, moderate, and high) as the dependent variable and the AF susceptibility score (continuous) as the determinant of interest. The primary analysis tested the association between time to arrhythmia recurrence and AF genetic susceptibility using a Cox proportional hazards model. The AF susceptibility score was included as a continuous variable. Both the univariate and multivariable models included adjustment for 3 principal components of ancestry, which is a method to use ancestry informative markers from a genome-wide array to account for the modest genetic variation that remains within a given ancestral population.[18] Covariates in the multivariable model were prespecified and included age at ablation (per 10 years), sex, height (per 10 cm), BMI (per 5 kg/m²), persistent AF (yes/no), hypertension (yes/no), CAD (yes/no), LA size (per cm), LVEF (per 10%), and year of ablation. As a secondary analysis to demonstrate the association between AF recurrence and individual SNPs that comprise the AF susceptibility score, a separate multivariable model (using the same covariates as the primary analysis) was performed. To address the potential for differences between centers related to clinical phenotyping and/or genotyping batch effects, each center was analyzed separately, and the results were meta-analyzed using inverse variance weighted random-effects meta-analysis. Between-center heterogeneity was assessed by calculating I^2. A secondary analysis was performed by replacing the AF susceptibility score with the limited AF susceptibility score in the univariate and multivariable Cox proportional hazards models described above. Statistical and genetic analyses were performed using R version 3.5.1, PLINK version 1.9,[19] and METAL version 2011-03-25.[20] Figures were generated using GraphPad Prism version 5.04 (GraphPad Software, Inc, La Jolla, CA).

RESULTS

AF Genetic Susceptibility and Clinical Characteristics

Among 4267 individuals across the 10 centers included in the analysis of baseline characteristics, the median age at ablation was 61 years (interquartile range, 53–68) and 30% were women (Table, Table IV in the Data Supplement). Clinical characteristics were stratified according to AF genetic susceptibility class. Individuals in the top AF genetic susceptibility class were younger at the time of ablation (median age 58 years [interquartile range, 51–67]) compared with those in the bottom AF genetic susceptibility class (63 years [interquartile range, 54–69]; P<0.001) and were less likely to have LV systolic dysfunction (EF<50%) compared with the bottom class (12% versus 18%, P=0.01). When adjusted for age, none of the other baseline characteristics examined (eg, hypertension, CAD, persistent AF, BMI, or obesity (BMI≥30 kg/m²) were significantly associated with AF genetic susceptibility class.

In multinomial regression, odds of having a low clinical risk burden was increased 15% per SD increase in the AF susceptibility score (odds ratio, 1.15 [95% CI, 1.06–1.25]; P=0.001) compared with a moderate clinical risk burden (Figure 1). However, there was no statistically significant association between high clinical risk burden and AF genetic susceptibility (OR, 0.95 [95% CI, 0.88–1.03]; P=0.21).

AF Genetic Susceptibility and Arrhythmia Recurrence

Centers eligible for inclusion in the primary recurrence analyses had time-to-recurrence data available and at least 100 cases of arrhythmia recurrence with time-to-recurrence data. This resulted in a total of 3259 individuals from 8 centers that were eligible for analysis and 1017 that were excluded. The overall arrhythmia recurrence rate between 3 and 12 months was 44% (1443/3259). There was no difference in the overall rate of recurrence between AF genetic susceptibility classes (Tables V and VI in the Data Supplement). In the primary analysis using a univariate model, there was a nonstatistically significant trend towards higher risk of recurrence with increasing AF genetic susceptibility (hazard ratio [HR], 1.08 [95% CI, 0.99–1.18], P=0.07; Table VII in the Data Supplement). With the multivariable adjustment, the association between the AF susceptibility score and time-to-recurrence became less significant (HR, 1.06 [95% CI, 0.98–1.15]; P=0.13; Figure 2; Table VII in the Data Supplement). Factors that significantly associated with time-to-recurrence in the multivariable analysis included persistent AF (HR, 1.39 [95% CI, 1.22–1.58]; P<0.001), LA size (per cm: HR, 1.32 [95% CI, 1.19–1.46]; P<0.001), and LVEF (per 10%: HR, 0.88 [95% CI, 0.80–0.97]; P=0.008). Results from the univariate and multivariable analyses are presented for each cohort in Figure 3 and Tables VIII and IX in the Data Supplement. There was low to moderate heterogeneity between cohorts for the association between the AF susceptibility score and recurrence as indicated by an I^2 statistic of 34%. Next, the limited AF susceptibility score was examined. Thirty-four percent of individuals had no change in AF genetic susceptibility class when using the limited AF susceptibility score compared with the comprehensive AF susceptibility score, and 49% changed by ±1 class. Overall, results using the limited AF susceptibility score were similar to those obtained using the comprehensive AF susceptibility score. There was no association between the limited AF susceptibility score and time-to-recurrence in univariate (HR, 1.01 [95% CI, 0.93–1.09]; P=0.83) or multivariable analysis (HR, 1.01 [95% CI, 0.95–1.07]; P=0.83).

Table. Baseline Characteristics Stratified by AF Genetic Susceptibility Class Derived From the AF Susceptibility Score

		AF Genetic Susceptibility Class (Quintiles)					
	Total	Q1 (Bottom)	Q2	Q3	Q4	Q5 (Top)	P Value
No. of subjects, N	4267	767	763	825	891	1021	NA
AF genetic susceptibility score (SD*)	NA	−1.2 (−1.5 to −1.0)	−0.5 (−0.7 to −0.4)	−0.1 (−0.2 to 0.1)	0.5 (0.3 to 0.7)	1.3 (1.0 to 1.8)	NA
Age at AF ablation, y	61 (53 to 68)	63 (54 to 69)	62 (55 to 68)	62 (54 to 68)	60 (53 to 68)	58 (51 to 67)	<0.001
Female gender (yes)	30%	29%	29%	30%	29%	30%	0.97
Height, cm	178 (170 to 183)	178 (170 to 184)	178 (169 to 185)	178 (170 to 183)	178 (170 to 183)	178 (170 to 183)	0.66
BMI, kg/m²	28 (25 to 32)	28 (25 to 32)	29 (25 to 33)	28 (25 to 33)	29 (26 to 32)	28 (25 to 32)	0.04
Obese (BMI ≥30 kg/m²; yes)	35%	36%	42%	36%	40%	35%	0.03
Persistent AF (yes)	40%	43%	38%	43%	43%	43%	0.63
Hypertension (yes)	58%	61%	61%	63%	62%	60%	0.73
Coronary artery disease (yes)	13%	14%	17%	14%	14%	14%	0.52
Left atrial size, cm	4.2 (3.7 to 4.7)	4.2 (3.7 to 4.7)	4.1 (3.7 to 4.7)	4.2 (3.7 to 4.6)	4.2 (3.7 to 4.7)	4.1 (3.6 to 4.6)	0.68
LVEF (<50%)	14%	18%	12%	12%	13%	12%	0.01

P value for the difference between quintiles was calculated using the Kruskal-Wallis H test for continuous variables or the χ^2 test for categorical variables. AF indicates atrial fibrillation; BMI, body mass index; IQR, interquartile range; LVEF, left ventricular ejection fraction; and NA, not applicable.

*SD, the median and IQR is presented for the standardized AF Genetic Susceptibility Score.

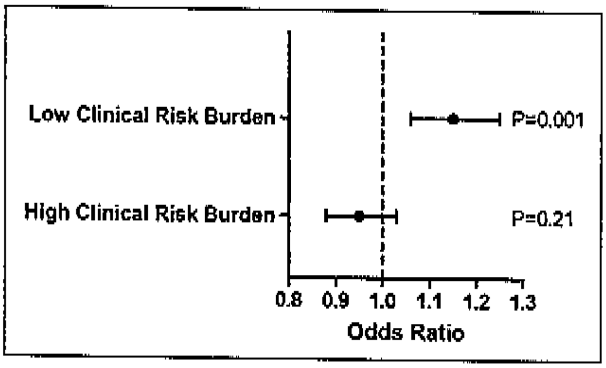

Figure 1. Higher atrial fibrillation (AF) genetic susceptibility is associated with increased odds of a low clinical risk factor burden but not associated with a high clinical risk factor burden.

Results of a multinomial regression. Clinical risk factors were age >60 y, body mass index (BMI) >30 kg/m², coronary artery disease (yes/no), and left ventricular ejection fraction (LVEF) <50%. Low clinical risk burden was defined as zero risk factors, and high clinical risk burden was defined as greater than or equal to 2 risk factors.

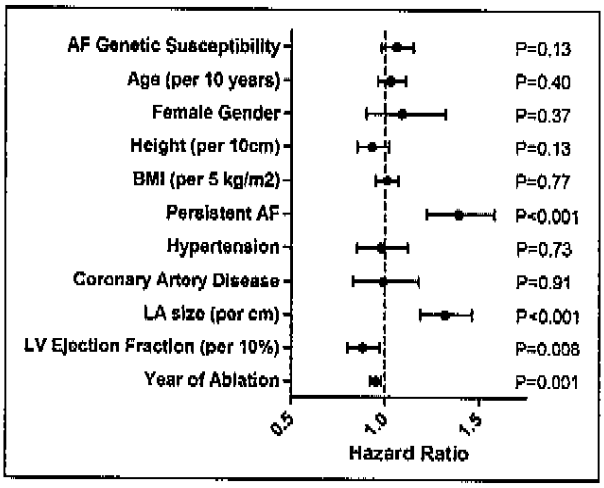

Figure 2. Results of a multivariable Cox proportional hazards model testing the association between atrial fibrillation (AF) genetic susceptibility and time to arrhythmia recurrence following AF ablation.

The comprehensive AF genetic susceptibility score (N=929 single-nucleotide polymorphisms) was expressed as a continuous variable, and adjustment was made for all the covariates listed in the figure.

Association Between Individual AF Susceptibility Alleles and Arrhythmia Recurrence

The association between the 929 individual SNPs that comprise the AF susceptibility score and time to arrhythmia recurrence were tested using separate multivariable models for each SNP. Overall, 53 SNPs (6%; 53/929) had a *P* value for association with recurrence <0.05. Among the 53 SNPs, 40 SNPs (75%, 40/53) were in the direction of increased risk of arrhythmia recurrence and 13 SNPs (25%, 13/53) in the direction of decreased risk of recurrence (Figure 4). A quantile-quantile (Q-Q) plot is presented in Figure II in the Data Supplement. Among notable individual loci for whom the AF risk allele was associated with an increased risk of recurrence were previously reported associations at the 4q25 locus near the gene *PITX2* (*P*=0.03–0.005),[12,14,15] and the 1q21 locus near the gene *IL6R* (*P*=0.0009–0.002),[21,22] along with a variant at the 2q31 locus near the gene *TTN* (*P*=0.01) and the 15q24 locus near the gene *HCN4* (*P*=0.047). At the 10q24 locus near the gene *NEURL1* (*P*=0.02–0.04), the AF risk allele was associated with a decreased risk of recurrence.

DISCUSSION

Genetic studies have defined a core set of common DNA variants associated with AF susceptibility across patient subgroups. Nevertheless, AF is a clinically and mechanistically heterogeneous disorder, so defining subgroups of AF based on clinical and genetic features may identify individuals with shared AF mechanisms and provide the opportunity to advance therapies such as AF ablation towards a more targeted approach. Accordingly, our study sought to define the contribution of AF genetic susceptibility to ablation outcomes. We found that higher genetic susceptibility to AF was associated with younger age at ablation, less systolic dysfunction, and an overall lower clinical risk burden. However, in contrast to the potential relevance of these clinical risk factors to ablation outcomes, AF genetic susceptibility was not statistically significantly associated with arrhythmia recurrence after ablation. This is an unexpected result based on previous smaller studies suggesting AF genetic susceptibility would be associated with AF recurrence based on its association with family history of AF, and previously reported associations between individual AF susceptibility alleles and recurrence.[12–15]

A possible explanation is suggested by the association between individual AF susceptibility alleles and arrhythmia recurrence. Among SNPs that were significantly associated with recurrence (*P*<0.05), the AF susceptibility allele increased risk of recurrence in the majority (75%) of SNPs but in 25% of SNPs the AF susceptibility allele decreased risk (Figure 4). The net effect was to reduce the overall association between comprehensive measures of AF genetic susceptibility and recurrence after ablation resulting in an overall trend in the direction of increased risk but not reaching significance.

Contribution to the Existing Literature

Prior studies have reported the associations between a family history of AF and baseline clinical characteristics.[13,23] Consistent with the results of these studies, we found individuals with higher AF genetic susceptibility were more likely to develop AF when younger, and with a lower clinical risk profile. Conversely, AF genetic susceptibility was not associated with a high clinical risk profile.

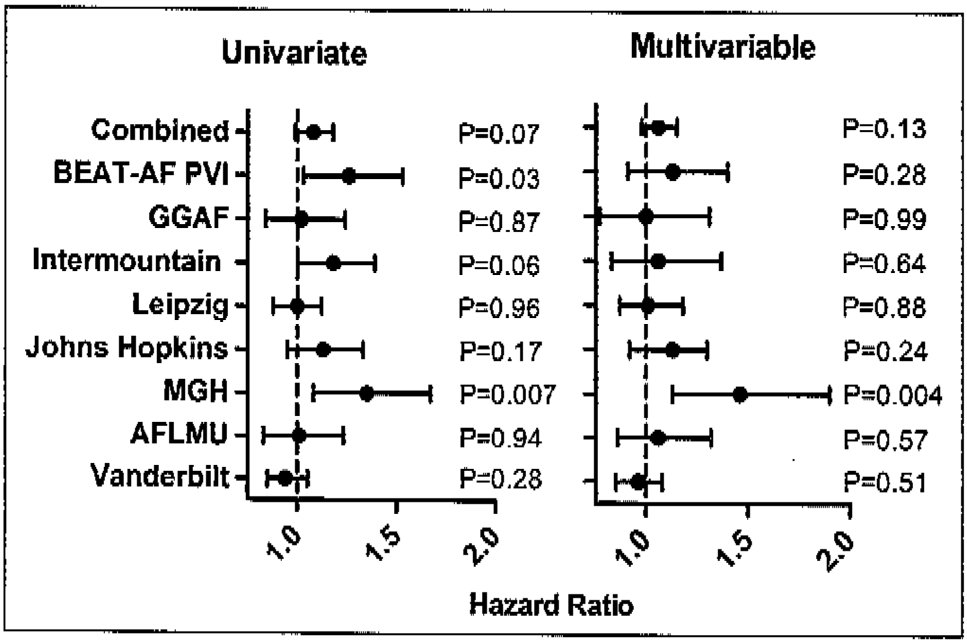

Figure 3. The association between the atrial fibrillation (AF) genetic susceptibility score and arrhythmia recurrence in univariate and multivariable modeling.

Displayed are results for each cohort and the combined meta-analyzed result. Analysis was performed using a Cox proportional hazards model. Multivariable adjustment was made for age, sex, height, body mass index (BMI), persistent AF, hypertension, coronary artery disease (CAD), left atrial (LA) size, left ventricular ejection fraction (LVEF), and year of ablation. GGAF indicates Groningen Genetics of Atrial Fibrillation.

These findings suggest that genetic susceptibility contributes to the risk of developing AF in younger patients with fewer comorbidities but in older and sicker patients AF can develop without a significant genetic contribution.

Prior research by our group and others using a candidate SNP approach has reported the association between individual AF susceptibility alleles and recurrence after ablation.[12,14,15] Most notable has been the association between recurrence and variants at the top AF susceptibility locus, chromosome 4q25 near the gene *PITX2*. This association has been detected in cohorts of European Ancestry but not detected when tested in cohorts of Asian-ancestry.[24] In our present dataset, AF susceptibility alleles at the 4q25/*PITX2* locus conferred an increased risk of recurrence after AF ablation (Figure 4, *P*=0.005–0.03 for 4q25/*PITX2* SNPs). Experimental data have suggested many potential mechanisms for this association including differences in the pulmonary vein myocardial sleeve, LA myocyte automaticity, and impaired response to oxidative stress and inflammation.[25–28] Another previously reported genetic association with recurrence after ablation are common variants within *IL6R*, the gene encoding the receptor for interleukin-6. Interleukin is a known regulator of inflammation, which is a well-recognized mechanism for recurrence of AF after ablation.[29–31] Other notable but to the best of our knowledge not previously reported associations with recurrence included SNPs within *TTN* and *HCN4*. *TTN* is the gene encoding the sarcomeric protein titin in which rare variants are a major cause of dilated cardiomyopathy and have recently been shown to be associated with AF, especially in the young.[32] *HCN4* encodes the pore-forming α-subunit of the cardiac funny channel, which regulates the rate of phase 4 depolarization and serves as the cardiac pacemaker current. Dysfunctional HCN (hyperpolarization cyclic nucleotide-gated potassium channel)-4 channels have been linked to ectopic atrial pacemaker activity.[33] Among SNPs associated with a decreased rate of recurrence were those near the gene *NEURL1*. *NEURL1* was first identified as an AF associated gene in 2014 and then later by GWAS in 2017.[3,34] Potential mechanisms by which *NEURL1* activity associates with AF pathogenesis are suggested by experiments where downregulation of the *NEURL* ortholog in zebrafish lengthened atrial action potential duration, as well as an in-vitro interaction between *PITX2* and *NEURL*.[34]

Strengths and Limitations

This study used observational data collection and is, therefore, limited by variability in the study population, phenotyping, ablation procedure, and follow-up which may introduce the potential for bias and heterogeneity. However, the primary determinant of the study was genetic data, to which the clinical and research teams were blinded at the time of ablation, follow-up, and data collection thereby reducing the potential for bias. The sample size of our study was large relative to prior studies investigating AF ablation outcomes. Our study was multicenter and measured the overall association between AF genetic susceptibility and recurrence

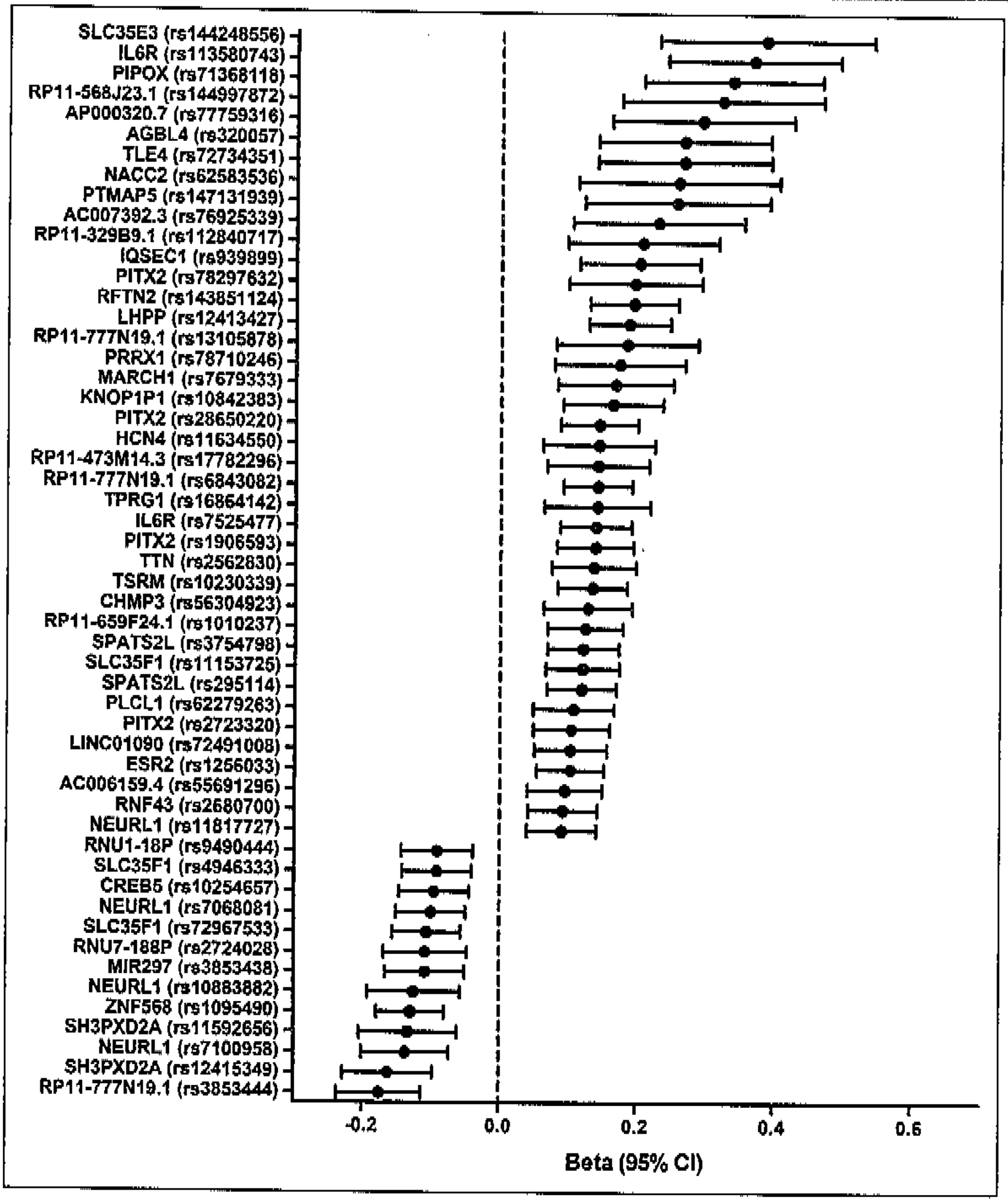

Figure 4. The association between individual atrial fibrillation (AF) susceptibility alleles and arrhythmia recurrence after ablation (displayed are single-nucleotide polymorphisms [SNPs] with $P<0.05$).
Each SNP was expressed using an additive genetic model and individually tested for an association with time to arrhythmia recurrence using a multivariable Cox proportional hazards model with adjustment for age, gender, height, body mass index (BMI), persistent AF, hypertension, coronary artery disease (CAD), left atrial (LA) size, left ventricular ejection fraction (LVEF), and year of ablation.

outcomes across a wide variety of centers and operators which increases the generalizability of our findings. Outcome data on repeat ablations, antiarrhythmic drug use following ablation, and cardioversions were not available across all centers and not available to report. The polygenic AF susceptibility scores used to estimate genetic risk for AF were derived from the results of GWAS in individuals of European ancestry, and our study cohort was, therefore, restricted to this population. The generalizability of the results of this study to other racial and ethnic populations is unknown. This highlights the need for GWAS of AF in other ancestral populations and also further research into the racial disparity in utilization of AF ablation.

Conclusions

AF genetic susceptibility measured by a polygenic AF susceptibility risk score refines the clinical profile of patients undergoing ablation and identifies patients with high genetic susceptibility for AF as younger and with less clinical risk factors for AF. Despite the importance of these clinical associations, AF genetic susceptibility was not found to be significantly associated with arrhythmia recurrence outcomes. Identifying common genetic variants specifically associated with arrhythmia recurrence after AF ablation is a logical next step in this work because these data suggest recurrence may represent a genetically different phenotype.

ARTICLE INFORMATION

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