ORIGINAL RESEARCH

Korean Atrial Fibrillation (AF) Network: Genetic Variants for AF Do Not Predict Ablation Success

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***Background*—**Genomewide association studies 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 top susceptibility loci and AF recurrence after ablation have not been examined in Asian populations. We examined whether the top single nucleotide polymorphisms (SNPs) at chromosomes 4q25 (*PITX2*), 16q22 (*ZFHX3*), and 1q21 (*KCNN3*) were associated with AF in a Korean population and whether these SNPs were associated with clinical outcomes after catheter ablation for AF.

***Methods and Results*—**We determined the association between 4 SNPs and AF in 1068 AF patients who underwent catheter ablation (74.6% male, aged 57.5±10.9 years, 67.9% paroxysmal AF) and 1068 age- and sex-matched controls. The SNPs at the *PITX2* and *ZFHX3* loci, but not the *KCNN3* locus, were significantly associated with AF (*PITX2*/rs6843082_G: odds ratio 3.41, 95% CI 2.55 to 4.55, $P=1.32\times10^{-16}$; *PITX2*/rs2200733_T: odds ratio 2.05, 95% CI 1.66 to 2.53, $P=2.20\times10^{-11}$; *ZFHX3*/rs2106261_A: odds ratio 2.33, 95% CI 1.87 to 2.91, $P=3.75\times10^{-14}$; *KCNN3*/rs13376333_T: odds ratio 1.74, 95% CI 0.93 to 3.25, $P=0.085$). Among those patients who underwent catheter ablation for AF, none of the top AF-associated SNPs were associated with long-term clinical recurrence of AF after catheter ablation.

***Conclusions*—**SNPs at the *PITX2* and *ZFHX3* loci were strongly associated with AF in Korean patients. In contrast to prior reports, none of the 4 top AF-susceptibility SNPs predicted clinical recurrence after catheter ablation. **(*J Am Heart Assoc*. 2015;4: e002046 doi: 10.1161/JAHA.115.002046)**

Key Words: atrial fibrillation • catheter ablation • genetic polymorphism • phenotype • recurrence

Atrial fibrillation (AF) is the most commonly found sustained arrhythmia, with a lifetime risk of 25%.[1] Risk factors include advancing age, hypertension, structural heart disease, and congestive heart failure, yet a subset of younger persons develop AF in the absence of established risk factors. Genetic factors play an important role in the pathogenesis of AF. Parental history of AF increases risk of AF by 1.4 to 1.9 times.[2,3] Familial cases of AF underscore a genetic basis for disease,[4] and research has implicated mutations and polymorphisms in the development of AF.[5]

Recently, several common genetic variants have been shown to be associated with AF in genomewide association studies performed in populations of European ancestry[6–10]; however, ethnic differences exist in the frequency of AF-related single nucleotide polymorphisms (SNPs) between European and Asian populations,[11,12] and thus the relationship between these SNPs and AF in non-European populations remains unclear. Furthermore, despite the identification of these AF-associated loci, data regarding the association between variants at these loci and clinical outcomes remain limited. Some reports suggested that these variants were associated with an increased risk of AF recurrence after a radiofrequency catheter ablation (RFCA),[13–15] a common therapy in symptomatic patients with lone AF. These reports, however, were conducted in patients of European ancestry, and the associations between

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/4/8/e002046/suppl/DC1

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genetic variants and responses to RFCA in other ancestral groups remain unclear.

The goal of the current study was 2-fold. First, we sought to determine whether the top 4 AF SNPs identified in European patients were also associated with AF in Korean patients. These SNPs reside on chromosomes 4q25 (*PITX2* locus), 16q22 (*ZFHX3* locus), and 1q21 (*KCNN3* locus). Second, we examined whether these AF SNPs were associated with AF recurrence after RFCA.

Methods

Patient Inclusion

The study protocol was approved by the institutional review board of Severance Cardiovascular Hospital, Yonsei University Health System, and adhered to the Declaration of Helsinki. This study is registered at ClinicalTrials.gov (identifier NCT02138695). All 2136 subjects (1068 with AF patients and 1068 with age- and sex-matched control subjects) provided written informed consent. All AF patients who underwent RFCA were included in the Yonsei AF Ablation Cohort registry. The exclusion criteria of this study were as follows: (1) permanent AF refractory to electrical cardioversion, (2) AF with valvular disease, (3) structural heart disease other than left ventricular hypertrophy, and (4) prior AF ablation. Age- and sex-matched control DNA was obtained from the Korea Centers for Disease Control and Prevention, National Biobank of Korea (KOBB-2012-00).[16,17] All control subjects had a 12-lead electrocardiogram to exclude the presence of AF.

SNP Selection and Genotyping

We evaluated selected SNPs from the top 3 AF-associated genetic loci in European patients from the meta-analysis of genomewide association studies reported by Ellinor and colleagues in 2012 and in other previous papers.[6,10,18] Specifically, we selected the top variant or a proxy SNP at each locus. For the locus at *PITX2*, the top SNP reported was rs6817105,[6] and the SNP rs2200733 is a perfect proxy for this SNP (r^2=1.0). Because SNP rs6843082 has also been reported to be strongly associated with AF[10] and is in only modest linkage disequilibrium with rs6817105, we included this SNP in our analyses (r^2=0.434). For the locus at *ZFHX3* on chromosome 16q22, the top SNP selected was rs2106261. At the *KCNN3* locus on chromosome 1q21, the top SNP reported was rs6666258,[6] and we selected a perfect proxy for genotyping: SNP rs13376333 (r^2=1.0).

We used whole blood samples for DNA extraction and genetic analyses. The SNPs were genotyped using validated TaqMan assays (Applied Biosystems, Life Technologies). Polymerase chain reaction product was amplified using 0.9 μm each of the forward and reverse primers, 0.2 μm each of the fluoresce in amidite and VIC minor groove binder sequence–specific probes, 3 ng DNA, 5.0 mmol/L $MgCl_2$, and 1× TaqMan Universal PCR Master Mix containing AmpliTaq gold DNA polymerase in a 5.5-μL reaction volume. All SNPs had a call rate of >99%.

Radiofrequency Catheter Ablation

During the procedure, intracardiac electrograms were recorded using a Prucka CardioLab electrophysiology system (General Electric Health Care System Inc). Ablation was guided by 3-dimensional electroanatomical mapping (NavX system; St. Jude Medical Inc). An open irrigation 3.5-mm-tip deflectable catheter (Celsius, Johnson & Johnson Inc; Cool Flex, St. Jude Medical Inc; 30 to 35 W; 47°C) was used for RFCA (Stockert generator; Biosense Webster Inc). All patients initially underwent circumferential pulmonary vein (PV) isolation and cavotricuspid isthmus ablation. For patients with persistent AF, we added a roof line, posterior inferior line, and anterior line[19] as a standard lesion set. At the operator's discretion, additional ablations were delivered to the superior vena cava, non-PV foci, or regions of complex fractionated electrograms. We confirmed the PV isolation by both entrance and exit block and rechecked it under an isoproterenol infusion before finishing the procedure. In addition, we attempted to reinduce AF by isoproterenol infusion with rapid atrial pacing before finishing the procedure. The end point of our procedure was defined as no immediate recurrence of AF after cardioversion while receiving an isoproterenol infusion (5 to 10 μg/min). If there was immediate recurrence of AF after cardioversion, we then ablated these non-PV foci.

Postablation Management and Follow-up

Patients were seen in the outpatient clinic at 1, 3, 6, and 12 months and then every 6 months thereafter or whenever symptoms occurred after RFCA. An electrocardiogram was performed on every visit. A 24- or 48-hour Holter recording and/or event recorder was obtained at the 3- and 6-month visits as well as every 6 months afterward in accordance with the 2012 Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society expert consensus statement guidelines.[20] Whenever patients reported symptoms of palpitations, Holter monitor or event monitor recordings were obtained and evaluated for possible arrhythmia recurrences. We defined recurrence of AF as any episode of AF or atrial tachycardia of at least 30 seconds in duration.[21] Early recurrence was defined as having a documented AF electrocardiogram within 3 months after ablation. Clinical recurrence was defined as (1) any documented

Table 1. Baseline Characteristics of the Study Population

	AF (n=1068)	Controls (n=1068)
Age, y	57.5±10.9	57.5±11.5
Male sex, %	74.6	74.6
PAF, %	67.9	—
Body mass index, kg/m^{2†}	24.7±3.2	23.6±3.1*
Hypertension	510 (47.8)	19 (1.8%)*
Diabetes mellitus	139 (13.0)	14 (1.3%)*
Congestive heart failure	70 (6.6)	1 (0.1%)*
Stroke	106 (9.9)	0 (0%)*
Coronary artery disease	136 (12.7)	0 (0%)*
$CHADS_2$ score	0.95±1.09	—
Echocardiography		
LA dimension, mm	41.6±6.5	—
LA volume index	35.0±12.3	
LVEF, %	63.1±9.0	—
E/Em	9.7±5.1	—
LVEDD, mm	49.3±6.6	—
LVESD, mm	33.2±5.8	—
LVMI, g/m^2	75.3±41.2	—
Early recurrence, %	28.5	—
Clinical recurrence, %	19.0	—

Data are shown as mean±SD or n (%), except as noted. AF (n=1068) and control (n=1068). For the $CHADS_2$ score, 1 point is given for congestive heart failure, hypertension, age >75 years, and diabetes mellitus; 2 points are given for previous stroke and transient ischemic attack. AF indicates atrial fibrillation; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVMI, left ventricular mass index; PAF, paroxysmal atrial fibrillation.
*P<0.001 compared with AF.
†16% of body mass index in controls are missing.

recurrence of AF after 3 months[21] or (2) the initiation of an antiarrhythmic medication for AF.

Statistical Analyses

Odds ratios (ORs) were calculated using logistic regression with an additive genetic model. In case-only analysis, multiple parameters including clinical features and echocardiography parameters were compared depending on genotype distribution. Univariate analysis was performed for continuous variables using the t test and for nominal variables using the chi-square test. The log-rank test with Bonferroni correction for multiplicity of comparisons was applied to control the type 1 error. Multivariable Cox regression analyses were conducted to evaluate the associations between genetic variants and AF recurrence, with adjustment for age, sex, left atrium size, AF subtype (persistent AF), and early recurrence (≤3 months). Cases and controls were matched using the variables age and sex to reduce confounding effects. Conditional logistic regression models were used to assess the association between each SNP and AF risk to take matching situation into account. Potential confounding factors that were statistically significant at P<0.05 in the univariate analysis were included in the final analysis. ORs and 95% CIs were estimated using conditional logistic regression analysis with adjustments for potential confounding factors, body mass index, hypertension, diabetic mellitus, and congestive heart failure. Additional analyses were performed in 4 different subgroups. All statistical analyses were performed using SPSS version 19.0 (IBM Corp).

Results

Baseline characteristics of the study population are summarized in Table 1. We studied 1068 patients who underwent an AF ablation and 1068 controls who were matched on the basis of age and sex. The mean age of our study population was 57.5±11.2 years, and 74.6% of participants were male. As expected, the AF group had a higher prevalence of hypertension, diabetes mellitus, congestive heart failure, stroke, and coronary artery disease than the control group. To exclude the possible confounding effects caused by the imbalance of disease prevalence between cases and controls, we sequentially performed subgroup analyses excluding patients with the following risk factors: (1) hypertension; (2) diabetes mellitus; (3) congestive heart failure; and (4) strokes,

Table 2. Association Between AF and SNPs From 3 Known AF Loci

Nearest Gene	SNP	Chr	Position	Minor Allele/Major Allele	MAF	AF Associated Allele	OR	95% CI	P Value*
PITX2	rs6843082	4	111937516	*A/G*	0.204	G	3.41	2.55 to 4.55	1.32×10^{-16}
PITX2	rs2200733	4	111929618	*C/T*	0.394	T	2.05	1.66 to 2.53	2.20×10^{-11}
ZFHX3	rs2106261	16	71609121	*A/G*	0.395	A	2.33	1.87 to 2.91	3.75×10^{-14}
KCNN3	rs13376333	1	153080977	*T/C*	0.019	T	1.74	0.93 to 3.25	0.085

AF indicates atrial fibrillation; Chr, chromosome; MAF, minor allele frequency; OR, odds ratio; SNPs, single nucleotide polymorphisms.
*P value was calculated by using conditional logistic regression after adjusting for body mass index, hypertension, diabetes mellitus, and congestive heart failure.

Table 3. Comparisons of Phenotypes and Clinical Outcomes According to SNPs From 3 Known AF Loci

	rs6843082 (*PITX2*)			rs2200733 (*PITX2*)			rs2106261 (*ZFHX3*)			rs13376333 (*KCNN3*)		
	AA (n=17)	GA (n=215)	GG (n=836)	CC (n=84)	CT (n=447)	TT (n=527)	GG (n=297)	GA (n=520)	AA (n=251)	CC (n=1020)	CT (n=48)	TT (n=0)
Age, y	50.8±15.3	59.0±11.1*	57.2±10.7	56.7±12.7	58.1±10.7	57.1±10.8	58.2±11.8	57.6±10.5	56.4±10.7	57.5±11.0	56.2±9.4	—
Male sex, %	58.8	71.2	75.8	71.4	72.0	77.2	72.4	75.6	75.3	74.4	79.2	—
PAF, %	70.6	67.4	67.9	70.2	66.7	68.3	64.3	67.9	72.1	67.5	77.1	—
Body mass index, kg/m^2	26.0±3.5	24.6±2.8	24.9±2.8	24.8±2.8	24.7±2.9	25.0±2.7	24.7±2.8	24.8±2.8	24.9±2.6	24.8±2.8	25.5±2.5	—
$CHADS_2$ score	0.88±0.78	1.06±1.14	0.93±1.08	0.95±1.04	0.95±1.10	0.97±1.09	0.98±1.10	0.97±1.12	0.88±1.01	0.96±1.09	0.73±0.94	—
Hypertension	9 (52.9%)	108 (50.2%)	393 (47.0%)	44 (52.4%)	202 (45.2%)	261 (49.5%)	147 (49.5%)	256 (49.2%)	107 (42.6%)	493 (48.3%)	17 (35.4%)	—
Diabetes mellitus	0 (0%)	26 (12.1%)	113 (13.5%)	6 (7.1%)	62 (13.9%)	71 (13.5%)	31 (10.4%)	75 (14.4%)	33 (13.1%)	134 (13.1%)	5 (10.4%)	—
Congestive heart failure	2 (11.8%)	21 (9.8%)	47 (5.6%)	7 (8.3%)	31 (6.9%)	32 (6.1%)	20 (6.7%)	34 (6.5%)	16 (6.4%)	67 (6.6%)	3 (6.3%)	—
Stroke	2 (11.8%)	24 (11.2%)	80 (9.6%)	6 (7.1%)	43 (9.6%)	56 (10.6%)	29 (9.8%)	52 (10.0%)	25 (10.0%)	101 (9.9%)	5 (10.4%)	—
Coronary artery disease	1 (5.9%)	28 (13.0%)	107 (12.8%)	8 (9.5%)	67 (15.0%)	60 (11.4%)	35 (11.8%)	69 (13.3%)	32 (12.7%)	130 (12.7%)	6 (12.5%)	—
Echocardiography												
LA dimension, mm	40.2±7.1	41.6±6.5	41.7±6.0	41.1±6.6	41.5±6.1	41.9±6.0	41.4±6.3	41.8±6.4	41.0±5.7	41.7±6.1	41.5±5.8	—
LA volume index	38.3±18.9	35.5±13.1	35.0±11.9	34.4±12.5	35.2±12.6	34.9±11.9	35.2±12.4	35.5±12.5	33.7±11.5	35.1±12.3	32.8±10.6	
LVEF, %	62.8±11.3	63.4±8.2	63.3±8.3	62.8±9.0	63.5±8.5	63.1±8.1	64.0±7.6	63.5±8.0	62.7±9.0	63.3±8.4	62.7±7.7	—
E/Em	9.8±3.4	10.8±5.4	10.3±4.3	10.5±4.4	10.5±4.9	10.3±4.2	9.8±3.8	10.7±4.4	9.5±3.4	10.4±4.6	9.9±3.5	—
LVEDD, mm	50.1±3.7	49.8±4.6	49.9±4.2	50.7±4.7	49.6±4.5	50.0±4.1	49.6±4.3	49.9±4.3	50.0±4.6	49.8±4.3	50.4±4.7	—
LVESD, mm	33.8±4.7	33.8±5.1	33.6±4.6	34.4±5.1	33.4±4.7	33.7±4.6	33.3±4.6	33.5±4.4	33.8±5.0	33.6±4.7	34.1±4.9	—
LVMI, g/m^2	93.4±16.8	95.9±22.8	92.3±20.9	97.3±24.3	92.8±20.3	92.8±21.7	93.5±23.0	93.8±20.2	91.3±20.4	93.3±21.4	67.4±18.4	—
Early recurrence, %	0	28.8	28.9	25.0	28.2	29.4	29.6	28.1	27.9	27.6	45.8	—

$CHADS_2$ score, 1 point is given for cardiac heart failure, hypertension, age >75 years, and diabetes mellitus; 2 points are given for previous stroke and transient ischemic attack. AF indicates atrial fibrillation; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVMI, left ventricular mass index; PAF, paroxysmal atrial fibrillation; SNPs, single nucleotide polymorphisms.
*p<0.05 compared between AA and GA.

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coronary artery disease, and congestive heart failure simultaneously. All subgroup analyses were performed by using multivariable logistic regression, adjusting for age, sex, body mass index, hypertension, diabetic mellitus, and congestive heart failure, as appropriate, and the results were consistent (Table S1).

PITX2 and *ZFHX3* Were Strongly Associated With AF in Korean Patients

We found that 2 of the 3 known AF-associated loci were strongly associated with AF in Korean patients (Table 2). Two variants at the *PITX2* locus and 1 at the *ZFHX3* locus were significantly associated with AF (rs6843082_G: OR 3.41, 95% CI 2.55 to 4.55, $P=1.32\times10^{-16}$; rs2200733_T: OR 2.05, 95% CI 1.66 to 2.53, $P=2.20\times10^{-11}$; rs2106261_A: OR 2.33, 95% CI 1.87 to 2.91, $P=3.75\times10^{-14}$) In contrast, genetic variants at the *KCNN3* locus were not associated with AF in Korean patients (rs13376333_T: OR 1.74, 95% CI 0.93 to 3.25, $P=0.085$). Interestingly, the frequency of the AF risk allele at this locus (rs13376333_T) was very low in the Korean population, at only 1.9% compared with 29.5% in European patients.[10]

Relationship Between AF-Risk SNPs and Baseline Clinical Characteristics of Patients Undergoing AF Ablation

Next we sought to determine whether any baseline differences existed in an extensive set of clinical and echocardiographic parameters based on AF genotype (Table 3). Among the 1068 AF ablation patients, the only notable difference was that carriers of the AF-associated risk allele for SNP rs6843082 on chromosome 4q25 were younger (50.8±15.3 versus 59.0±11.1, $P=0.005$).

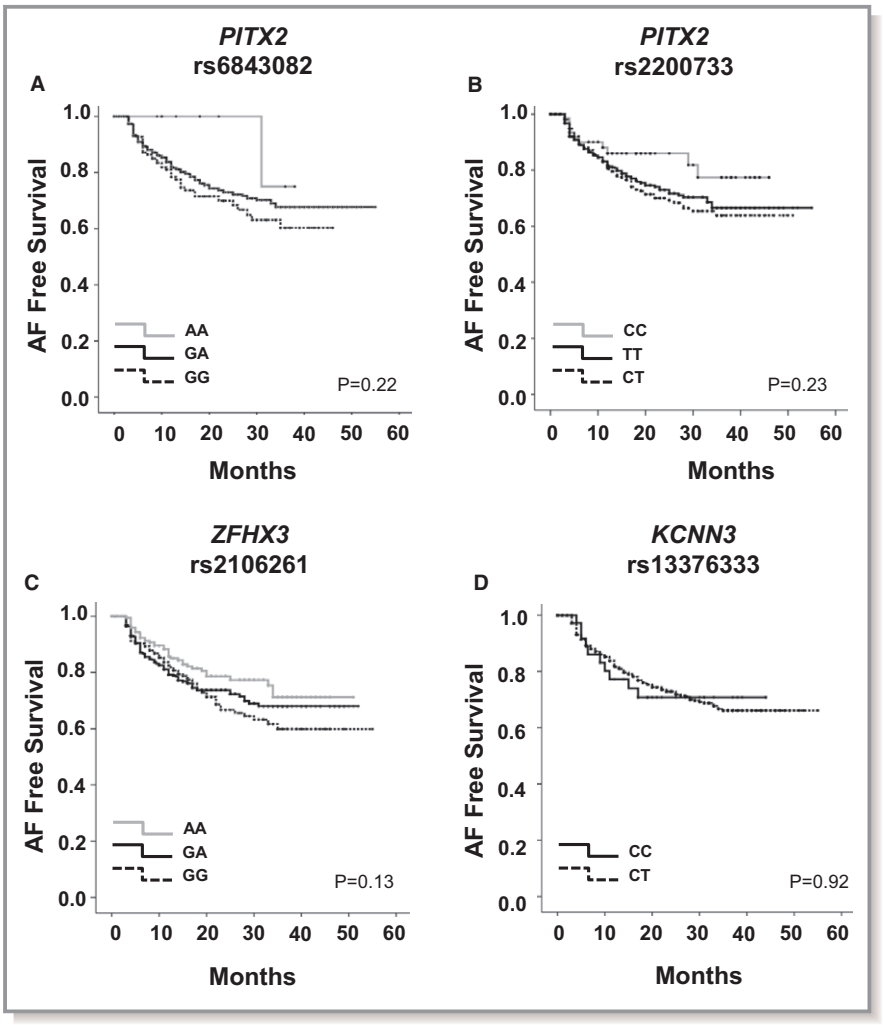

Figure. Kaplan–Meier curve showing relationship among recurrence and risk alleles of rs6843082 in *PITX2* (A), rs2200733 in *PITX2* (B), rs2106261 in *ZFHX3* (C), and rs13376333 in *KCNN3* (D). AF indicates atrial fibrillation.

Table 4. Association Between Candidate Genes (SNPs) and Clinical Recurrence of AF Using Cox Regression Model

	Adjusted*		
Gene/SNP	HR	95% CI	*P* Value
PITX2/rs6843082_G	0.84	0.61 to 1.15	0.280
PITX2/rs2200733_T	1.01	0.80 to 1.26	0.963
ZFHX3/rs2106261_A	0.86	0.71 to 1.04	0.128
KCNN3/rs13376333_T	0.72	0.38 to 1.36	0.308

AF indicates atrial fibrillation; HR, hazard ratio; SNPs, single nucleotide polymorphisms. *Adjusted for sex, age, left atrium size, AF subtype (persistent AF), and early recurrence (≤3 months).

Relationship Between AF Genotype and Outcomes After AF Ablation

After ablation, 304 patients (28.5%) had early recurrence during the 3-month blanking period. We did not observe any significant associations between AF-risk SNPs and early AF recurrence. During 18.3±13.9 months (range 0 to 55 months) of follow-up, 203 patients (19.0%) had a clinical recurrence >3 months from RFCA. Figure displays the freedom from AF recurrence for each of the 4 SNPs. None of the 4 SNPs were associated with a long-term clinical recurrence after RFCA (Table 4).

Discussion

In a well-characterized cohort of >1000 Korean patients with nonvalvular AF, we observed that 2 of the 3 main AF susceptibility signals discovered in European patients (chromosomes 4q25 [*PITX2*] and 16q22 [*ZFHX3*]) were similarly associated with AF, supporting a shared genetic basis for AF that transcends ancestry. Second, and in contrast to prior reports,[13,14] we did not observe any significant associations between these top 4 AF susceptibility loci and AF recurrence following catheter ablation.

Interestingly, the AF risk allele at 1q21 was not associated with AF; however, the frequency of this variant in the Korean population was rare. Large-scale genomewide association studies showed the association of SNPs in *PITX2, ZFHX3*, and *KCNN3* with AF in patients of European ancestry, and the results were replicated in a Japanese study.[6] In Table 5, we summarized the published results of these 4 AF variants in patients of Asian descent. We noted that most published studies were smaller and studied only 1 or 2 of the top AF variants. Although SNPs at *PITX2* and *ZFHX3* were consistently associated with AF, there was less consistency among the studies at the *KCNN3* locus. The lack of replication of the association at the *KCNN3* locus may be due to the rarity of this risk allele among those of Asian descent. In Korean patients, the risk allele was quite rare, with a minor

Table 5. Summary of Association Results for the 3 AF Loci

Ethnicity	European[6]	Japanese[6]	Hong Kong[9]	Chinese[11]	Taiwanese[12]	Hong Kong[22]	Chinese[23]	Chinese[24]	Korean
Total Number (AF Patients)	59 133 (6707)	4193 (843)	3048 (285)	2097 (650)	428 (214)	3169 (333)	1234 (383)	1593 (597)	2136 (1068)
PITX2									
OR	1.64	1.84				1.42	1.81		3.06
95% CI	1.55 to 1.73	1.59 to 2.13				1.16 to 1.73	1.21 to 3.20		2.59 to 3.61
P value	1.8×10^{-74}	3.7×10^{-17}				0.00064	3.7×10^{-11}		4.3×10^{-14}
SNP	rs6817105	rs2634073				rs2200733	rs2200733		rs6843082
ZFHX3									
OR	1.24	0.8	1.05	1.32				1.71	2.03
95% CI	1.17 to 1.30	0.71 to 0.91	0.87 to 1.26	1.15 to 1.51				1.46 to 2.00	1.79 to 2.31
P value	3.2×10^{-16}	6.8×10^{-4}	0.63	1.97×10^{-4}				1.9×10^{-11}	5.3×10^{-14}
SNP	rs2106261	rs12932445	rs7193343	rs2106261				rs2106261	rs2106261
KCNN3									
OR	1.18	1.46		1.24	3.02				1.38
95% CI	1.13 to 1.23	0.85 to 2.51		0.88 to 1.75	1.54 to 6.29				0.89 to 2.14
P value	2.0×10^{-14}	0.17		0.333	<0.001				0.152
SNP	rs6666258	rs7514452		rs13376333	rs13376333				rs13376333

AF indicates atrial fibrillation; OR, odds ratio; SNP, single nucleotide polymorphism.

Table 6. Summary of AF Genetic Studies Related to AF Catheter Ablation

	N	Age	Male	PAF	Race	End Point		SNP	Closest Gene	Late Recurrence of AF	
						Early Recurrence of AF	Late Recurrence of AF			HR (95% CI)	*P* Value
Husser[14]	195	56±12	73%	78%	European	Within 7 days	Between 3 and 6 months	rs10033464_T	*PITX2*	2.82 (1.29 to 6.15)*	0.009
								rs2200733_T	*PITX2*	2.46 (1.06 to 5.69)*	0.036
Shoemaker[13]	311	60 (52 to 66)	72%	47%	European	N/A	After the 3-month postablation blanking period	rs2200733_T	*PITX2*	0.76 (0.6 to 0.95)†	0.016
								rs10033464_T	*PITX2*	N/A	0.97‡
Current study	1068	58±11	75%	68%	Asian	Within the 3-month postablation period	After the 3-month postablation blanking period	rs6843082_G	*PITX2*	0.84 (0.61 to 1.15)	0.280
								rs2200733_T	*PITX2*	1.01 (0.80 to 1.26)	0.963
								rs2106261_T	*ZFHX3*	0.86 (0.71 to 1.04)	0.128

AF indicates atrial fibrillation; HR, hazard ratio; N/A, not available due to lack of data in published paper[13]; PAF, paroxysmal atrial fibrillation; SNP, single nucleotide polymorphism.
*Odds ratio.
†Survival time ratio.
‡Log-rank test.

allele frequency of only 1.9%. Similarly, in Japanese and Chinese studies, this variant had a minor allele frequency of 1.5% and 4%, respectively. In contrast, European and Taiwanese populations had high prevalence of the AF risk allele (29.6% and 8.6%, respectively). Our findings highlight the variability in this *KCNN3* AF risk allele, even among those of Asian descent. Our results also demonstrate the need for large-scale genetic studies in specific Asian subgroups to identify this and other regions uniquely associated with AF.

The first identification of common genetic variants dates to 2007, yet data on the clinical utility of these variants remains relatively limited.[25] Investigators have examined the risk of AF after cardioversion,[26] the initiation of antiarrhythmic medication,[27] and PV isolation ablation procedures.[13,14] In our study of >1000 Korean patients who underwent PV ablation, we did not observe any significant associations between the AF risk alleles on chromosomes 4q25, 16q22, or 1q21 and recurrent AF after catheter ablation. Our findings are in contrast to the recent observations in 2 studies of patients with Europeans ancestry (Table 6).[13,14] Many potential causes could underlie the discordant results observed between Asian and European populations. First, our results may point to a specific racial difference in the associations between AF genetic data and clinical recurrence after RFCA. It is possible that the genetic variants that we considered in Korean patients are only proxies rather than the truly causative SNPs at these loci. Second, because our study is nearly 3 times larger than the prior studies, it is possible that the findings in European patients reflected a relatively smaller sample size. Finally, the differences may also be due to technical variability of RFCA, surveillance for AF, or the length of the follow-up period among the studies. Ultimately, further large-scale multicenter studies will help resolve each of these issues.

Strengths of our study include the largest cohort of patients of Asian descent described to date, a well-characterized ablation population with detailed phenotypic data, and a standardized clinical protocol for follow-up after ablation. Our study was also subject to a number of potential limitations. First, we excluded patients with significant structural heart disease. Second, because we studied a Korean population, our results may not be generalizable to other races and ethnicities. This observational study included a highly selected group of patients referred for Yonsei AF Ablation Cohort; therefore, the results cannot be generalized to the entire AF population or to other ethnicities. The lack of association of the polymorphism to the recurrence of AF after ablation might be related to the low frequency of the variant in the selected population, a small effect of polymorphisms, heterogeneity of the population with varying underlying substrate, variable ablative techniques used, and follow-up, despite the relatively consistent protocols for inclusion, ablation, and follow-up.

Conclusions

Genetic variants at the *PITX2* and *ZFHX3* loci were strongly associated with AF among Korean patients, whereas there

was no association at the *KCNN3* locus. The clinical outcomes after a catheter ablation for AF could not be predicted by genetic variants in Korean patients.

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Disclosures

None.

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