

Korean atrial fibrillation network genome-wide association study for early-onset atrial fibrillation identifies novel susceptibility loci

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Aims	Some genetic susceptibility loci for atrial fibrillation (AF) identified by genome-wide association studies (GWAS) in a European database showed ethnic differences in the Asian population. We explored novel AF susceptibility variants for patients with early-onset AF (≤60 years old) among Korean patients who underwent AF catheter ablation.
Methods and results	A genome-wide association study (GWAS) was conducted with 672 cases (\leq 60 years old, Yonsei AF Ablation cohort) and 3700 controls (Korea Genome Epidemiology Study). Association analysis was performed under an additive model of logistic regression, and replication study was conducted with 200 independent cases of Korean AF Network and 1812 controls. Five previously proven genetic loci (1q24/PRRX1, 4q25/PITX2, 10q24/NEURL, 12q24/TBX5, and 16q22/ZFHX3) were validated. Two novel genetic loci associated with early-onset AF were found on chromosomes 1q32.1/PPFIA4 (rs11579055, $P = 6.84 \times 10^{-10}$) and 4q34.1/HAND2 (rs8180252, $P = 1.49 \times 10^{-11}$) and replicated in an additional independent sample of the Korean AF Network. The identified loci implicate candidate genes that encode proteins related to cell-to-cell connection, hypoxic status, or long non-coding RNA.
Conclusion	Two novel genetic loci for early-onset AF were identified in Korean patients who underwent catheter ablation. One of the novel susceptibility loci on chromosome 4 has strong associations with previously proven gene in a European ancestry database.
Keywords	Genome-wide association study • Atrial fibrillation • Single nucleotide polymorphism

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice, and it is associated with increased morbidity and mortality.¹ Atrial fibrillation is predominantly a disease of the elderly. Well-established risk factors for AF include hypertension, diabetes mellitus, obesity, and structural heart disease, all of which are

associated with advancing age.² However, subjects without clear precipitating factors for AF may present with AF at a relatively young age with familial clustering.³ Recent studies have shown genetic susceptibility in the development of AF with significantly increased risk of AF for family members of patients with lone AF.^{4,5} Arnar *et al.*⁶ also reported a five-fold increased risk of incident AF in first-degree relatives of patients diagnosed with AF before the age of 60.

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Genome-wide association studies (GWAS) have recently been used to assess the genetic basis of many diseases. The first GWAS for AF identified a chromosome 4q25 locus conferring the risk of AF in Icelanders.⁷ A recent GWAS, mostly performed in populations of European ancestry, identified approximately 14 common genetic susceptibility loci for AF.^{8–12} However, ethnic differences exist between Europeans and other populations,^{13,14} and the impacts of these loci on AF in Asian populations remain to be elucidated. Although several studies have replicated these identified loci in Asian populations, some studies showed weak or no association with AF due to different allele frequencies and linkage disequilibrium (LD) patterns compared with European ancestry.^{10,15,16}

The purposes of this study were to: (1) examine previously identified loci from European ancestry in the Korean population and (2) identify novel variants of AF susceptibility loci in Korean patients with early-onset (≤ 60 years of age) AF who underwent AF catheter ablation using two-stage GWAS.

Methods

Study design and subjects

A GWAS was performed in two stages, as displayed in *Figure 1*. Stage 1 consisted of 672 cases of early-onset AF (\leq 60 years old) who underwent radiofrequency catheter ablation (RFCA) and 3700 controls free of AF from a large urban cohort. Stage 2 consisted of 200 cases of early-onset AF (\leq 60 years old) and 1812 controls free of AF from a large community cohort. The Institutional Review Board of Human Research for each institution approved the study protocol, and written informed consent was obtained from all subjects. A detailed description is available in the see Supplementary material online.



Figure I Study flowchart showing the two-staged genome-wide association study (GWAS). AF, atrial fibrillation; GWAS, genome-wide association study; MAF, minor allele frequency.

Genotyping and validation study for SNP selection

Details of genotyping, imputation methods, and validation study for SNP selection are available in the see Supplementary material online.

Analysis of expression quantitative trait loci (eQTL) and implicated genes

Expression quantitative trait loci analyses were performed using the publicly available Genotype-Tissue Expression Portal (GTEx) of the Broad Institute of Harvard and MIT (GTex, Broad Institute, Boston, MA, USA; http://www.gtexportal.org/home/, 23 June 2016). Further description is available in the see Supplementary material online.

Statistical analyses

Details of statistical analyses are available in the data see Supplementary material online.

Results

Baseline characteristics and early-onset AF susceptibility loci in the Korean population

Table 1 summarizes the patient characteristics in this case-control study and replication study. Among 672 patients who underwent RFCA (81.0% male and 50.5 ± 7.8 years old), 482 patients (71.7%) were categorized as having paroxysmal AF. The prevalence of hypertension, coronary artery disease, and stroke in the case group was higher than that of controls (P < 0.001, respectively). In the replication set, the mean age of cases was 50.0 ± 8.2 , while in the control group it was 60.7 ± 6.6 . The prevalence of coronary artery disease (P < 0.001) was higher in cases than in controls, while the prevalence of diabetes (P < 0.001) was lower in cases than in controls.

A total of 14 genetic loci known to be associated with AF in the European ancestry database were compared using GWAS of early onset AF in Koreans (*Table 2*). Among these 14 previously defined genetic polymorphisms, five genetic loci were reproducibly associated with Korean early-onset AF with statistical significance: 1q24/PRRX1 rs3903239, 4q25/PITX2 rs17042171, 10q24/NEURL rs6584554, 12q24/TBX5 rs883079, and 16q22/ZFHX3 rs2106261 (based on Bonferroni correction; P < 0.05/14 = 0.0036). The most significant association was shown in 4q25/PITX2 rs17042171 [odds ratio (OR) 0.41; 95% confidence interval (CI) 0.36–0.46, $P = 1.80 \times 0^{-43}$], followed by 16q22/ZHFX rs2106261 (OR 2.09; 95% CI 1.85–2.85, $P = 1.79 \times 10^{-33}$, *Table 2*). Of note, the association of 10q24/NEURL rs6584554 is similar to the magnitude and direction of previous findings in a Japanese population (OR 1.50; 95% CI 1.28–1.75, $P = 5.03 \times 10^{-7}$).

Two novel genetic loci associated with early-onset AF

A total of 642 422 SNPs genotyped on the Affymetrix Genome-Wide Human SNP Array 6.0 chip in 672 AF patients and 3700 controls was analysed following a data-cleaning procedure. As shown in the Manhattan plot of GWAS results (*Figure 2*), 4 loci were associated with early onset AF with $P < 5 \times 10^{-8}$ in the discovery stage. While two loci were previously identified (4q25/*PITX2* and 16q22/*ZFHX3*), two novel loci in chromosome 1q32.1/*PPFIA4* and chromosome

B aseline characteristics	Discovery		Replication	
	Case (n = 672)	Control (n = 3700)	Case (n = 200)	Control (<i>n</i> = 1812)
Age, year	50.5 ± 7.8	53.1±8.3*	50.0 ± 8.2	$60.7 \pm 6.6^{*}$
Male sex, %	546 (81.0)	1649 (44.6)*	156 (78.0)	859 (47.3)*
PAF, %	482 (71.7)	_	99 (49.5)	_
Body mass index, kg/m ²	25.1 ± 3.0	24.0 ± 2.9*	24.9 ± 2.9	24.7 ± 3.3
Hypertension, %	237 (35.3)	691 (18.7)*	66 (33.0)	597 (32.9)
Diabetes, %	51 (7.6)	249 (6.7)	15 (7.5)	656 (36.1)*
Coronary artery disease, %	56 (8.3)	106 (2.9)*	21 (10.5)	43 (2.4)*
Stroke, %	47 (7.0)	56 (1.5)*	7 (3.5)	60 (3.3)
CHADS ₂ Score	0.93 ± 1.1	_	0.61 ± 0.7	$0.77 \pm 0.9*$
Echocardiography				
LA size (mm)	41.0 ± 6.4	_	41.9 ± 7.4	_
LV ejection fraction (%)	62.3 ± 8.8		59.7 ± 10.6	

Table I	Characteristics	of discovery and	l replication stud	y subjects
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Data are shown as mean \pm SD or n (%).

LA, left atrium; LV, left ventricle; PAF, paroxysmal atrial fibrillation.

*P-values <0.05.

4q34.1/HAND2 were significantly associated with Korean early onset AF. A total of 12 SNPs clustered in those two genetic loci had statistically strong associations (based on *P*-value < 5×10^{-8} , *Table 3*). Figure 3 shows signal plots for the two strong loci 1q32.1/PPFIA4 rs11579055 ($P = 6.84 \times 10^{-10}$) and 4q34.1/rs8180252 ($P = 1.49 \times 10^{-11}$) using imputation analyses, and we found that additional SNPs could be highly correlated with top significant SNPs.

Using an independent replication set consisting of 200 cases and 1812 controls, the 12 SNPs showing strong association with Korean early onset AF in the discovery study were tested. Two genetic loci, rs11579055 in chromosome 1q32.1/PPFIA4 (P = 0.044) and rs8180252 in 4q34.1/HANDS2 (P = 0.011), were significantly associated with AF disease risk in the replication stage (*Table 3*). In the combined data set, the loci at chromosome 1q32.1 (rs3737883, rs6694477, and rs6670637) and 4q34.1 (rs8180252 and rs2067518) showed significant associations ($P < 5.0 \times 10^{-8}$, *Table 3*). For haplotype analyses, all significant SNPs genotyped at 1q32.1 (50 kb region containing rs11579055 and rs3737883) and 4q34.1 (50 kb region containing rs4615152 and rs8180252) were included in high LD block (see Supplementary material online, *Figure S1*).

Because there were age and gender mismatches in both discovery and replication group, propensity score matching was conducted. The four genetic variants in novel genetic loci (*rs11579055*, *rs3737883*, *rs4615152*, and *rs8180252*) were consistently associated with Korean early onset AF (see Supplementary material online, *Table S1*). Controls in the replication cohort had a higher prevalence of diabetes and a lower prevalence of coronary artery disease. To adjust for these factors using a multivariate logistic regression model, we included age, sex, diabetic mellitus, coronary artery disease, and hypertension as covariates, while maintaining a consistent effect size. We observed that the top SNP (*rs11579055*) was no longer significant in this analysis, whereas the significance for variants located in chromosome 4 had even stronger significance than the unadjusted state (see Supplementary material online, *Table S2*). The allele frequencies of the recessive genetic model were compared between case and control groups in see Supplementary material online, *Table S3*, and we observed that genetic variants at two novel loci (4q34.1/HAND2 and 1q32.1/PPFIA4) were consistently associated with AF risk in the recessive genetic model (see Supplementary material online, *Table S4*).

Expression quantitative trait loci mapping of novel genetic loci

The influence of novel susceptibility signals on expression of candidate genes was assessed by investigating eQTLs. By accessing the publicly available GTEx, several significant associations between novel susceptibility genetic variants and gene expression were found. The AF risk allele of the top SNP at 1q32.1, rs11579055, was significantly associated with a higher expression of PPFIA4 in whole blood $(P = 1.4 \times 10^{-10})$. Four other AF risk alleles of SNPs at the same locus also had a significant eQTL association with PPFIA4 in whole blood (rs3737883, $P = 2.1 \times 10^{-10}$; rs6694477, $P = 1.4 \times 10^{-7}$; rs6670637, $P = 1.2 \times 10^{-7}$; and rs10920559, $P = 1.4 \times 10^{-7}$). PPFIA4 encodes a protein named liprin- α 4. Liprin- α 4 is involved in cell-to-cell junctions and can be up-regulated by hypoxia-inducible factor- 1α in hypoxic states. Among SNPs associated with AF at 4q34, rs8180252 was located close to HAND2 and had a significant eQTL association with non-coding RNA (IncRNA) RP11-161D15.1 in the left ventricle of the heart ($P = 1.7 \times 10^{-6}$). HAND2 is a cardiac transcription factor related to heart repair and development, but the function of RP11-161D15.1 is not yet clearly defined.

Discussion

Main findings

In this study, a two-stage GWAS was performed using 672 patients with early-onset AF (\leq 60 years of age) who underwent AF ablation

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Table 2

Chromosome	SNP	Position	Closest			Europ	oean meta-G	SWAS	Korean GW	AS					
			gene	Coded allele	Allele frequency (%)	RR	(95%CI)	Meta P-value	SNP ^b	Position	Coded allele	Allele frequency (%)	QR	(95%CI)	P-value
F	rs6666258	154841792	KCNN3	U	29.9	1.18	(1.13–1.23)	2.0×10^{-14}	rs6666258	154814268	υ	1.8	0.96	(0.62–1.51)	0.87
~	rs3903239	170600176	PRRX1	U	44.7	1.14	(1.10–1.18)	9.1×10^{-11}	rs3903239	170569317	U	54.3	1.41	(1.24–1.60)	1.25×10^{-7}
m	rs4642101	12800724	CAND2	U	65.0	1.10	(1.06–1.14)	$9.8 imes 10^{-9}$	rs4642101	12842223	U	24.9	1.09	(0.95–1.25)	0.24
4	rs6817105	110784612	PITX2	υ	13.1	1.64	(1.55–1.73)	1.8×10^{-74}	rs6817105	111705768	υ	52.5	2.43	(2.12–2.78)	5.01×10^{-38}
6	rs13216675	122131183	GJA1	μ	0.69	1.10	(1.06–1.14)	$2.2 imes 10^{-8}$	rs13216675	122452329	⊢	64.1	1.10	(0.97–1.26)	0.14
7	rs3807989	116546187	CAV1	∢	40.4	0.88	(0.84–0.91)	9.6×10^{-11}	rs3807989	116186241	∢	33.7	0.80	(0.70–0.92)	0.013
6	rs10821415	94951177	C9orf3	∢	42.4	1.13	(1.08–1.18)	$7.9 imes 10^{-9}$	rs10821415	97713459	∢	26.9	1.07	(0.93–1.23)	0.33
10	rs6584555 ^a	103539854	NEURL1	υ	12.0	1.32	(1.26-1.39)	2.0×10^{-25}	rs6584555	105299611	υ	12.6	1.58	(1.33–1.88)	2.77×10^{-7}
10	rs10824026	73661450	SYNPO2L	U	15.8	0.85	(0.81–0.90)	$1.7 imes 10^{-8}$	rs10824026	75421208	ט	43.8	1.00	(0.88–1.13)	0.99
12	rs10507248	11439288	TBX5	μ	73.0	1.12	(1.08–1.16)	5.7×10^{-11}	rs10507248	114797093	⊢	43.2	1.19	(1.05–1.35)	0.006
12	rs6490029 ^a	111260653	CUX2	∢	64.0	1.12	(1.08–1.16)	$3.9 imes 10^{-9}$	rs6490029	111698457	∢	75.1	1.11	(0.96–1.29)	0.15
14	rs1152591	64214130	SYNE2	∢	47.6	1.13	(1.09–1.18)	6.2×10^{-10}	rs1152591	64680848	∢	32.3	1.11	(0.97–1.27)	0.12
15	rs7164883	73359833	HCN4	ט	16.0	1.16	(1.10–1.22)	$1.3 imes 10^{-8}$	rs7164883	73652174	ט	8.4	1.05	(0.83–1.32)	0.70
16	rs2106261	73051620	ZFHX3	F	17.6	1.24	(1.17–1.30)	3.2×10^{-16}	rs2106261	73051620	F	34.8	2.08	(1.83–2.36)	3.32×10^{-30}
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Significance level was set as P < 0.005/14 after Bonferroni correction (Bold P-value). Cl, confidence interval: SNP, single nucleotide polymorphism. ^alapanese study. ^bImputed SNPs.



Figure 2 Manhattan plot of GWAS results. Among four loci that showed associations with early onset AF with $P < 5 \times 10^{-8}$ in the discovery stage, two novel loci in chromosome 1q32.1/*PPFIA4* and chromosome 4q34.1/*HAND2* show significant associations with Korean early-onset AF.

and 3700 controls in stage 1, and 200 subjects with early-onset AF and 1812 controls from a large community cohort in stage 2. Five out of 14 known AF susceptibility loci identified in patients with European ancestry were reproducibly associated with AF risk in the Korean population. Two novel loci located at 1q32 [*PPFIA4*] and 4q34 [*HANDS2*] were identified as new AF susceptibility loci associated with early onset AF in the Korean population.

Replication of atrial fibrillation associated genetic loci and early onset atrial fibrillation in the Korean population

Five of the 14 known AF susceptibility loci previously discovered in subjects with European ancestry^{8-10,12} had significant associations with early onset AF in patients of the Korean AF Network. Significant and replicated associations were found in rs6817105 at 4q25 [PITX2] and rs2106261 at 16q22 [ZFHX3], consistent with other GWAS in Non-European populations.^{7,10,13} This suggests a shared genetic basis for the pathophysiology of AF between European and Korean populations. The KCNN3 gene at 1q21, one of the strongest AF risk genetic loci associated with shortened action potential duration (APD),¹⁷ showed no significant association, with a rare minor allele frequency of 1.8% in this Korean population. This is consistent with previous studies in Asian populations.^{13,16} Also, the frequency of HCN4 variants in the Korean population is relatively low (5.1%), compared with that in Europeans. The rs6584554 at 10q24/NEURL, which was also identified in a Japanese population, and rs3807989 at 7q31/CAV1, which was replicated in a Chinese population, were relevant in the Korean population. These results indicate that there are ethnic differences in the genetic basis of AF, with considerable genomic variants conferring AF risk.

Potential mechanisms of early-onset atrial fibrillation related genes

Atrial fibrillation is an age-dependent progressive disease and nonwhite populations have lower AF prevalence than patients of European descent in individuals older than 65 years of age.¹⁸ Early-onset AF present in populations with a lack of predisposing conditions for AF may indicate a significant underlying genetic etiology. Recently, Ma et al. reported that TBX5 gene gain-of-function mutations contribute to early-onset AF.¹⁹ The TBX5 gene has a critical role in cardiac development. It reduces fibrosis and improves cardiac function by reprogramming non-myocytes²⁰ while increasing conduction heterogeneity by up-regulating connexin-40 expression.¹⁹ Similarly, HAND2, the closest gene to the novel AF variant (rs8180252) in the Korean early onset AF population, is also reported as a cardiac transcription factor related to heart repair. HAND2 reprograms non-myocytes, and its overexpression can facilitate regenerative cardiomyocyte proliferation with reprogramming of cardiac fibroblasts into functional cardiac-like myocytes.²⁰

A second novel genetic locus associated with early onset AF was identified on chromosome 1q32 (*rs11579055*) in *PPFIA4*, which encodes a member of the liprin (LAR: leucocyte antigen related, protein-tyrosine phosphatase-interacting protein) protein family.²¹ The evolutionarily conserved proteins of the liprin family play key roles in synapse maturation and regulation. Liprin proteins regulate the disassembly of focal cell adhesion to aid cell-matrix interactions.²² Although liprin is also present in the heart, association between *PPFIA4* and cardiac disease has not yet been reported.

Clinical implication of genetic studies

Although estimates of AF heritability have been reported as up to 60%,⁵ no genetic test is indicated for AF. This is because only a small portion of its mechanism has been defined and none of the known genes have been reported to account for \geq 5% of AF pathogenesis. Some recent studies have demonstrated the positive effect of AF risk

CHR	SNP	Closest	Position	R ²	Risk	Discove	гy				Replica	tion				Combin	ed		
		gene			allele	(Case n	= 672/C	Control	n = 37(00)	(Case n	= 200/4	Control	n = 18'	12)	(Case n	= 872/Co	ontrol n =	: 5512)
						RAF	N	95% C	_	Ра	RAF	N	95% C	_	Pa	OR	95% CI		P ^a
-	rs11579055	PPFIA4	203031315	0.96	U	0.67	1.55	1.35	1.79	6.84E-10	0.69	1.31	1.01	1.31	4.40E-02	1.48	1.30	1.68	2.29E-09
~	rs3737883	PPFIA4	203034906	Ref	∢	0.68	1.58	1.37	1.81	2.85E-10	0.69	1.29	0.99	1.29	5.90E-02	1.48	1.31	1.68	1.49E-09
-	rs6694477	PPFIA4	203035365	0.55	∢	0.79	1.70	1.44	2.02	7.64E-10	0.80	1.21	0.89	1.21	2.19E-01	1.52	1.31	1.77	3.17E-08
-	rs6670637	PPFIA4	203035551	0.55	U	0.79	1.69	1.43	2.01	1.23E-09	0.79	1.21	06.0	1.21	2.09E-01	1.52	1.31	1.77	4.08E-08
-	rs10920559	PPFIA4	203035693	0.55	υ	0.79	1.70	1.43	2.01	8.56E-10	0.79	1.21	06.0	1.21	2.20E-01	1.52	1.31	1.77	2.69E-08
4	rs4615152	HAND2	174599459	Ref	υ	0.42	1.59	1.40	1.80	3.05E-13	0.42	1.22	0.99	1.22	6.70E-02	1.51	1.35	1.68	1.43E-12
4	rs10024812	HAND2	174604286	0.51	∢	0.54	1.46	1.29	1.66	4.16E-09	0.54	1.18	0.93	1.18	1.64E-01	1.36	1.22	1.54	8.29E-08
4	rs13132889	HAND2	174609693	0.43	⊢	0.54	1.44	1.27	1.63	2.14E-08	0.54	1.20	0.94	1.20	1.39E-01	1.36	1.21	1.52	1.36E-07
4	rs12507756	HAND2	174609772	0.43	⊢	0.54	1.45	1.28	1.65	7.45E-09	0.54	1.20	0.95	1.20	1.31E-01	1.36	1.22	1.54	7.90E-08
4	rs2067518	HAND2	174612666	0.43	A	0.54	1.45	1.28	1.65	6.47E-09	0.54	1.21	0.96	1.21	1.15E-01	1.36	1.22	1.54	6.75E-08
4	rs7680060	HAND2	174616061	0.43	⊢	0.53	1.46	1.29	1.66	4.52E-09	0.53	1.16	0.92	1.16	2.13E-01	1.35	1.21	1.52	2.04E-07
4	rs8180252	HAND2	174618863	0.56	A	0.32	1.56	1.37	1.77	1.49E-11	0.32	1.38	1.08	1.38	1.10E-02	1.51	1.34	1.68	1.57E-11
R2 based CHR, chr ^a Adjustec	on 1000G CHE omosome; OR, 1 by age and sex.	8 + JPT (Ref, tc odds ratio; Cl	pp significant SN , confidence inte	IP in D erval; F	iscovery). (AF, risk all	ele frequenc	×												



Figure 3 Regional plots of new variants that reached genome-wide significance. (A–B) Regional plots of log P-values for the two replicated loci. Results (–log P) are shown for the association of directly genotyped and imputed SNPs for a 400-kb region centred on replicated lead SNP, reported AF genome-wide association studies (GWAS) in Korean (purple squared). Genotyped SNPs are represented as square, while imputed SNPs are marked by circles. Marks (rs number) indicate replicated and top significant SNPs among two loci. The recombination rates estimated from 1000 Genomes project's Han Chinese and Japanese samples are plotted in blue.



loci in predicting cardioversion, catheter ablation, and antiarrhythmic medication responses.^{23–25} Although pre-defined genetic variants did not predict AF ablation success in the Korean AF Network,¹⁶ rs2106261 at 6q22 ZFHX3 predicted a good response to AF ablation among a sub-group with longstanding persistent AF.²⁶ Future studies directed at determining the role of AF risk alleles in predicting the progression of AF substrate, defining types of AF, and finding a potential target for pharmacological treatment of AF are warranted. Despite recent advances in genetics, it is still challenging to investigate the mechanism through which these genetic variants influence AF risk. Genome-wide association studies identified chromosome loci of common variants increasing AF risk, their closest gene, and their potential mechanisms are summarized in *Figure 4*.

Limitations

There are several potential limitations of our study. First, although we tried to find functions of novel SNPs by investigating eQTLs with accessing the publicly available GTEx, the specific functions of the two novel genetic loci in the pathophysiology of early onset AF are not fully elucidated. The identification of two novel SNPs is still insufficient to assume causality, but may represent just proxy associations suggesting existing unexplained molecular pathways. Therefore, potential genetic interactions using biological analysis are required to interpret these findings. Deep sequencing and fine mapping to identify causal variants are necessary to confirm these findings. Second, this study included a highly selected group of patients (60 years old and younger) who were referred for AF catheter ablation. This select patient population represents symptomatic anti-arrhythmic drug resistant early onset AF; as such, it is more susceptible to an active catheter ablation with a corresponding higher success rate. Third, the study findings may not be generalized to other cohorts with different ethnicities and races. In addition, comparison of the Caucasian (CEU), African (AFR), Han Chinese (CHB), and Japanese (JPT) data from the 1000 Genomes Project Phase 3 revealed notable ethnic differences in allele frequencies in the risk allele (see Supplementary material online, Table S5). Especially, at chromosome 4, the major risk allele frequencies of six SNPs (rs4615152, rs10024812, rs13132889, rs12507756, rs2067518, and rs7680060) were much higher in a population of European ancestry than in an Asian population (MAFs ranging from 0.79 to 0.99 in CEU). These substantial differences in inter-ethnic MAF results indicated different associations in individuals of different descent, resulting in insufficient power to identify the observed variants in other ancestries. Although there were significant associations between novel SNP rs11579055 in 1q32.1 and European database proven loci in 1q21 (rs13376333, KCNN3; OR 4.77, 95% CI 2.40~9.50, $P = 9.0 \times 10^{-6}$), and between novel rs8180252 in 4q34 and previously proven loci in 4q25 (rs4611994 proxy to PITX2 rs2200733; OR 12.9, 95% CI 7.33-22.68, $P = 7.3 \times 10^{-19}$) using gene-gene interaction analysis in discovery set (see Supplementary material online, Table S6), there was no association between our novel variant on chromosome 1 (rs11579055) and previously identified variant (rs13376333) in replication cohorts, probably due to an underpowered sample size and differences in MAF between populations.

Conclusions

Two novel genetic loci for early-onset AF were identified in Korean patients who underwent catheter ablation. One of the novel susceptibility loci on chromosome 4 has strong associations with previously proven gene in a European ancestry database.

Supplementary material

Supplementary material is available at European Heart Journal online.

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