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# Good responders to catheter ablation for long-standing persistent atrial fibrillation: Clinical and genetic characteristics

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ABSTRACT

*Background:* Radiofrequency catheter ablation (RFCA) for long-standing persistent atrial fibrillation (L-PeAF) is challenging and has a relatively high recurrence rate. We explored clinical and genetic characteristics associated with being good responders (no early or clinical recurrence within 12 months in the absence of anti-arrhythmic drugs) to RFCA among patients with L-PeAF.
*Methods:* Of 1319 patients in the Yonsei AF Ablation Cohort, this study included 141 consecutive patients with L-PeAF (80.9% male, age 57.8 ± 9.7 years) who were followed >12 months after RFCA.
*Results:* During 25 (19–35) months follow-up, the recurrence rate was 39%, and 38 patients (27%) were categorized as good responders, those had a shorter AF duration ($p = 0.010$), and smaller left atrial (LA) size ($p = 0.033$) than others. The *rs2106216* (16q22/*ZFHX3*) genetic polymorphism was independently associated with being a good responder in multivariate analysis (adjusted OR = 2.70, 95% CI 1.41–5.14, $p = 0.003$), after adjusting for LA size and AF duration. The *rs2106261* had predictive value for clinical recurrence of AF after RFCA among patients with an AF duration 12–65 months (log rank, $p = 0.025$).
*Conclusions:* Despite a relatively high recurrence rate after RFCA for L-PeAF, patients with a shorter AF duration and smaller LA size showed a more favorable outcome. The *rs2106216* polymorphism (*ZFHX3*) was independently associated with being good responders to RFCA for L-PeAF, especially with AF duration 12–65 months.


## Introduction

Radiofrequency catheter ablation (RFCA) is an effective rhythm control strategy for patients with atrial fibrillation (AF), and it has become a standard procedure for anti-arrhythmic drug (AAD) resistant AF in current guidelines for AF management [1]. The main target of AF catheter ablation is the pulmonary vein (PV) antrum, and complete durable circumferential PV isolation (CPVI) is a cornerstone of this procedure [2]. However, RFCA is still challenging in patients with persistent AF (PeAF) or long-standing persistent AF (L-PeAF) [3]. Because of a substantially high recurrence rate, catheter ablation for L-PeAF is considered to be insufficient with CPVI alone [4]. To overcome this limitation, various ablation strategies have been attempted, including additional linear ablation, complex fractionate atrial electrogram (CFAE) guided ablation, right atrial (RA) ablation, non-PV foci ablation, or rotor ablation, etc. Despite the various ablation strategies for L-PeAF, the success rates of single procedures have ranged between 20% and 60% [3]. With 1.3–2.3 times of multiple procedures, long-term AF control rate is 72–79% with or without AAD [5]. Although RFCA for L-PeAF significantly reduces AF burden, this procedure still has limitations, even when performed with current technology at world-class, experienced institutions. Therefore, we sought to identify patient factors predicting favorable success rates, and hypothesized that better patient selection criteria may improve clinical outcomes, reduce unnecessary cardiac tissue damage, or avoid unnecessary ablation procedures and reduce medical costs and procedure-related complications. Recently, there were several reports for the

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relationship between genetic polymorphism and clinical outcome of AF ablation [6–9]. Although there are significant ethnic differences [10], genetic polymorphism can be utilized as an innate biomarker to identify good responders for AF catheter ablation. The purposes of this study were to evaluate long-term clinical outcomes of L-PeAF after linear ablation, and to explore clinical predictors representing atrial remodeling and genetic factors associated with AF recurrence after RFCA for L-PeAF.

## Materials and methods

### *Patient selection and definition of "good responder"*

This study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Yonsei University Health System and registered at Clinicaltrials.gov (registration number: NCT02138625). All patients provided written informed consent. Among the 1319 patients in the Yonsei AF Ablation Cohort, 421 patients had non-paroxysmal AF, and we included 330 consecutive patients with L-PeAF who were enrolled between March 2009 and November 2013. We defined AF duration based on electrocardiographic (ECG) documents, not on the presence of symptoms alone. Each patient underwent RFCA for symptomatic AF that was refractory to pharmacologic management. Exclusion criteria included the following: (1) follow-up duration less than 12 months ($n = 134$), (2) valvular heart disease with a grade higher than 2 ($n = 9$), (3) structural heart disease other than left ventricular hypertrophy ($n = 8$), (4) previous RFCA or cardiac surgery ($n = 11$), or (5) no available genetic data for the six single nucleotide polymorphisms (SNPs) previously documented to be associated with AF in genome-wide association studies (GWAS, $n = 27$). A total of 141 patients with L-PeAF were included in this study. We defined the "good responders" as those patients without an early or clinical recurrence of AF at least for 12 months after RFCA, in the absence of AAD treatment.

### *Measurement of left atrial size and volume*

Both transthoracic and transesophageal echocardiography, and 3D cardiac computed tomography (CT; 64 Channel, Light Speed Volume CT, Philips, Brilliance 63, Amsterdam, Netherlands) were performed in all patients to determine whether they had combined structural heart disease or a left atrial (LA) thrombus. LA size and volume index were measured using transthoracic echocardiography in all patients. The 3D spiral CT images were analyzed on an image processing workstation (Aquarius, Terarecon Inc., Foster City, CA, USA). For the regional volumetric analyses, each LA image was subdivided according to embryological origin as follows: anterior LA, venous LA, and LA appendage.

### *Electrophysiologic mapping and radiofrequency ablation*

All AADs were discontinued for at least five half-lives prior to RFCA, and amiodarone was stopped for more than 4 weeks. Anticoagulation was maintained before the procedure. For patients taking novel oral anticoagulants, we stopped these medications for 24 h before RFCA and switched them to subcutaneous injection of low molecular weight heparin. A 3D electroanatomical map (NavX, St. Jude Medical Inc., Minnetonka, MN, USA; CARTO3, Johnson & Johnson Inc., Diamond Bar, CA, USA) was generated using a circular PV mapping catheter (Lasso; Biosense-Webster Inc., Diamond Bar, CA, USA). NavX or CARTO system-generated 3D geometry of the LA and PVs was merged with the corresponding 3D spiral CT images. RFCA (25–35 W, 47 °C, irrigation flow rate of 20–35 mL/min, 30 s of radiofrequency energy delivery at each ablation point, Stockert generator, Biosense Webster) was performed using an open irrigated-tip catheter (Celsius, Biosense-Webster Inc.; Coolflex, St. Jude Medical Inc., St. Paul, MN, USA), with guidance from the 3D electroanatomic mapping (NavX system, St. Jude Medical Inc.). After CPVI, we added a roof line, a posterior-inferior line, an anterior line, and a cavo-tricuspid isthmus line as a standard lesion set. Additional ablations of the superior vena cava (15.6%), non-PV foci (12.0%), or complex fractionated electrograms (18.4%) were conducted at the operator's decision.

We generated 3D-voltage maps in 96 patients after CPVI by obtaining contact bipolar electrograms from 350 to 500 points on the LA endocardium during atrial pacing with a pacing cycle length of 500 ms. Bipolar electrograms were filtered at 32–300 Hz. Color-coded voltage maps were generated by recording bipolar electrograms and measuring peak-to-peak voltage as previously described [11]. If frequently recurring AF still persisted after 3 attempts of cardioversion, no further efforts were made to generate a LA voltage map.

### *Post-ablation management and follow-up*

Among 141 patients, 35 patients (24.8%) kept anti-arrhythmic medication before AF recurrence because of high chance of recurrence with frequent atrial premature beats or short runs of non-sustained atrial tachycardia, and were not included in good responders. Other patients including good responders were followed in the absence of anti-arrhythmic medications after RFCA. Patients visited the outpatient clinic regularly at 1, 3, 6, and 12 months after the procedure, and every 6 months thereafter or whenever symptoms reoccurred after RFCA. ECG was performed during every visit and 24- or 48-h Holter monitoring and/or event recording was performed at 3 and 6 months, and every 6 months thereafter in accordance with the 2012 HRS/EHRA/ECAS Expert Consensus Statement Guidelines [2]. In addition, whenever patients reported palpitations, Holter or event monitor recordings were obtained and evaluated for the possible recurrence of the arrhythmia. We defined recurrence of AF as any episode of AF or atrial tachycardia lasting for 30 s or longer [12]. Any documentation of AF recurrence after the 3-month blanking period was classified as a clinical recurrence [12].

### *Genotyping*

We evaluated top six SNPs that have previously proven to be associated with AF in a European ancestry database and an Asian population [13–15]: *rs2200733* and *PITX2* (*rs6843082* and *rs17042171*) on chromosome 4q25, *ZFHX3* (*rs7193343* and *rs2106261*) on chromosome 16q22, and *KCNN3* (*rs13376333*) on chromosome 1q21. We used whole blood samples for the DNA extraction and genetic analyses. The forementioned genetic polymorphisms were analyzed using validated TaqMan assays (Applied Biosystems, Life Technologies, Carlsbad, CA, USA). The polymerase chain reaction products were 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 mM $MgCl_2$, 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 greater than 99%.

For validation study, genomic DNA was extracted from peripheral blood monocytes by standard protocol (QuickGene DNA whole blood kit L, Kurabo, Osaka, Japan) using same patient's blood. Affymetrix Genome-Wide Human SNP Array 6.0 chip (Affymetrix, Inc., Santa Clara, CA, USA) was used to genotype 137 patients according to Affymetrix's protocol. Four patients were not genotyped due to the lack of genomic DNA. There was no

exclusion individual with low call rate (<95%), gender mismatch, sample duplication, or contamination. The following quality control criteria were applied to assure the data quality for each SNPs: (i) minor allele frequency (MAF) ≥ 5%, (ii) genotype call rate ≥ 90%. The final amounts of SNPs included for final association were 609,900 for Affymetrix SNP Array 6.0.

### *Statistical analysis*

Normally distributed continuous variables were expressed as mean ± standard deviations. Statistical significance was assessed using Student *t*-tests, $\chi^2$ tests, or Fisher's exact tests. Continuous variables that were not normally distributed are reported as median values (25–75 percentile range) and compared using the Mann–Whitney test. Logistic regression analysis was used, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using an additive genetic model. Multivariate binary logistic regression was performed to identify independent predictors of good responder with a $p$-value < 0.05/6 to control the type 1 error. Kaplan–Meier analysis was used to evaluate AF-free survival after catheter ablation.

For validation of our results, we selected SNPs genotyped by GWAS in a region of ~100 kb containing *rs2106261*. And a total of 52 SNPS nearby rs2106261 were analyzed by logistic regression and each SNP was modeled using an additive model adjusted by age, sex, AF duration, and LA dimension. Statistical analyses were performed using SPSS (Version 23; IBM, Armonk, NY, USA) and PLINK (Ver 1.07).

## Results

### *Clinical characteristics of good responders*

Among the 141 patients with L-PeAF who underwent RFCA and were followed up longer than 12 months (80.9% male and 57.9 ± 9.7 years old), 38 patients (27%) were classified as good responders (Table 1). Compared to patients who recurred within 12 months or were treated with AADs, good responders had significantly shorter history of AF ($p$ = 0.010), and smaller LA diameter ($p$ = 0.033) measured by echocardiogram. As shown in Table 2, there were no significant differences in procedure time, ablation lesion set, or complication rate between good responders and other patients. The ablation time was shorter in the good responder group ($p$ = 0.037). During the 25 (19–35) months of follow-up, the overall clinical recurrence rate of AF was 39% (10.5% in good responders vs. 49.5% in others, log rank $p < 0.001$; Fig. 1A). Even in the good responder group, clinical recurrences were also noted during the follow-up period but after 12 months post-RFCA.

### *The* rs2106261 *(16q22/*ZFHX3*) genetic polymorphism is associated with good responders*

We genotyped the six SNPs associated with AF based on previous GWAS (Table 3) [13,14]. The *rs2106216* genetic polymorphism was significantly associated with good responders in additive model ($p$ = 0.008). In multivariate logistic regression analysis, a short AF duration (stratified by quartiles, OR 0.58, 95% CI 0.39–0.85, $p$ = 0.005) and small LA dimension (OR 0.92, 95% CI 0.85–0.99, $p$ = 0.040) were independently associated with being a good responder to L-PeAF ablation (Table 4). The *rs2106216* genetic polymorphism was also significantly associated with being a good responder in an additive model after adjusting for age, gender, AF duration, and LA dimension (OR 2.70, 95% CI 1.41–5.14, $p$ = 0.003; Fig. 2). However, the other five SNPs were not associated with being a good responder.

In this study, mean LA voltage was significantly lower for the *rs2106261* GG genotype than for the others ($p$ = 0.030, $n$ = 96 analyzable LA voltage maps; Supplementary Table 1 and Supplementary Figure). Among 55 patients with clinical recurrence, we conducted a second ablation in 13 patients who were resistant to AAD. The number of patients with GG, GA, and AA

**Table 1**
Patient characteristics.

| | All ($n$ = 141) | Good responders ($n$ = 38) | Others ($n$ = 103) | $p$-value |
|---|---|---|---|---|
| Age, years | 57.9 ± 9.7 | 55.8 ± 9.6 | 58.6 ± 9.7 | 0.132 |
| Male, $n$ (%) | 114 (80.9) | 31 (81.6) | 83 (80.6) | >0.999 |
| BSA, $m^2$ | 1.86 ± 0.16 | 1.86 ± 0.16 | 1.86 ± 0.16 | 0.840 |
| BMI, $kg/m^2$ | 25.4 ± 2.7 | 25.5 ± 2.7 | 25.4 ± 2.7 | 0.911 |
| AF duration, month[a] | 64.8 (32.4–110.3) | 47.9 (21.3–78.0) | 69.3 (44.7–118.6) | 0.010 |
| $CHADS_2$ score | 0.96 ± 1.00 | 0.89 ± 1.09 | 0.98 ± 0.98 | 0.655 |
| Congestive heart failure, $n$ (%) | 4 (2.8) | 1 (2.6) | 3 (2.9) | >0.999 |
| Hypertension, $n$ (%) | 71 (50.4) | 15 (39.5) | 56 (54.4) | 0.132 |
| Age > 75years, $n$ (%) | 5 (3.5) | 0 (0.0) | 5 (4.9) | 0.324 |
| Diabetes mellitus, $n$ (%) | 21 (15.0) | 6 (15.8) | 15 (14.7) | >0.999 |
| Stroke, $n$ (%) | 13 (9.2) | 5 (13.2) | 8 (7.8) | 0.336 |
| TIA, $n$ (%) | 5 (3.5) | 1 (2.6) | 4 (3.9) | >0.999 |
| Follow-up duration, month[a] | 25 (19–35) | 29 (20–36) | 24 (19–35) | 0.504 |
| Echocardiographic finding | | | | |
| LA size, mm | 45.2 ± 5.5 | 43.6 ± 5.3 | 45.8 ± 5.4 | 0.033 |
| LA volume index, $mL/mm^2$ | 42.4 ± 11.6 | 40.0 ± 10.3 | 43.3 ± 12.0 | 0.144 |
| Ejection fraction, % | 61.7 ± 8.1 | 61.3 ± 6.4 | 61.9 ± 8.6 | 0.704 |
| E/Em | 10.3 ± 3.7 | 9.8 ± 3.5 | 10.5 ± 3.7 | 0.336 |
| LVMI | 95.8 ± 22.7 | 99.1 ± 21.1 | 94.8 ± 23.2 | 0.395 |
| 3D-CT finding | | | | |
| LA volume, mL | 151.6 ± 42.7 | 139.1 ± 41.4 | 155.7 ± 42.5 | 0.068 |
| LA volume/BSA, $mL/mm^2$ | 81.7 ± 22.5 | 74.8 ± 23.0 | 84.0 ± 22.0 | 0.055 |
| Anterior LA/BSA, $mL/mm^2$ | 50.3 ± 15.4 | 46.3 ± 16.1 | 51.6 ± 15.0 | 0.105 |
| Posterior LA/BSA, $mL/mm^2$ | 25.0 ± 8.5 | 23.1 ± 7.3 | 25.6 ± 8.8 | 0.171 |
| LA appendage/BSA, $mL/mm^2$ | 6.5 ± 2.9 | 5.5 ± 2.3 | 6.8 ± 3.0 | 0.041 |

Data are mean ± standard deviation unless otherwise indicated.
[a] Mann–Whitney test, median (25th–75th percentile).
*Abbreviations*: 3D-CT, three-dimensional computed tomography; AF, atrial fibrillation; BMI, body mass index; BSA, body surface area; CHADS, congestive heart failure, hypertension, age >75, diabetes mellitus, and prior stroke or transient ischemic attack; LA, left atrium; LVMI, left ventricular mass index; TIA, transient ischemic attack.

**Table 2**
Comparisons of procedures, complications, and medications between the good responder group and others group.

| | All ($n$ = 141) | Good responders ($n$ = 38), | Others ($n$ = 103) | $p$-value |
|---|---|---|---|---|
| Ablation time (s)[a] | 6376 (5071–7278) | 5638 (4869–6813) | 6548 (5265–7326) | **0.037** |
| Procedure time (min)[a] | 209 (186–239) | 199 (181–230) | 211 (191–245) | 0.079 |
| Additional ablations | | | | |
| Superior vena cava, $n$ (%) | 22 (15.6) | 4 (10.5) | 18 (17.4) | 0.435 |
| Non-PV foci, $n$ (%) | 17 (12.0) | 3 (8.0) | 14 (13.6) | 0.559 |
| CFAE ablation, $n$ (%) | 26 (18.4) | 5 (13.2) | 21 (20.4) | 0.462 |
| Complication, $n$ (%) | | | | |
| Hemopericardium | 6 (4.3) | 1 (2.6) | 5 (4.9) | >0.999 |
| Groin complication | 1 (0.7) | 1 (2.6) | 0 (0.0) | 0.265 |
| Pericarditis | 1 (0.7) | 0 (0.0) | 1 (1.0) | >0.999 |
| Postablation medication, $n$ (%) | | | | |
| ACEI/ARB | 45 (32.1) | 9 (23.7) | 36 (35.3) | 0.226 |
| β-blocker | 35 (25.0) | 5 (13.2) | 30 (29.4) | 0.051 |
| Statin | 31 (22.1) | 7 (18.4) | 24 (23.5) | 0.649 |
| Post-procedure AAD | 35 (24.8) | 0 (0.0) | 35 (34.3) | **<0.001** |
| Early recurrence, $n$ (%) | 62 (44) | 0 (0.0) | 62 (60.2) | **<0.001** |
| Clinical recurrence, $n$ (%) | 55 (39) | 4 (10.5) | 51 (49.5) | **<0.001** |

Significant $p$-value are in bold.
[a] Mann–Whitney test, median (25th–75th percentile).
AAD, anti-arrhythmic drug; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CFAE, complex fractionate atrial electrogram; PV, pulmonary vein.

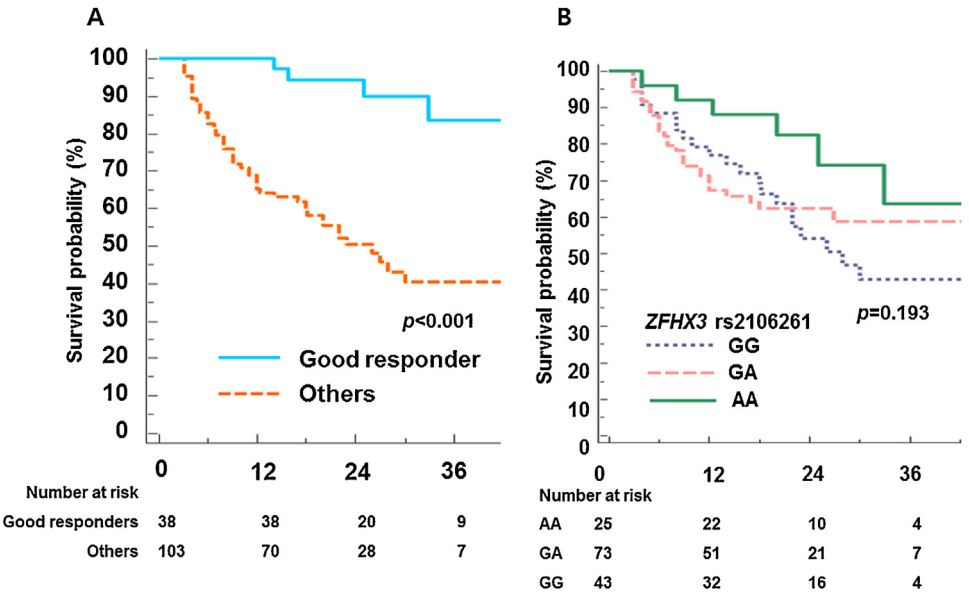


**Fig. 1.** Atrial fibrillation-free survival after radiofrequency catheter ablation. (A) Good responders vs. other patients and (B) patients with the *rs2106261* (*ZFHX3*) polymorphism.

genotypes of *rs2106261* were three (23.1%), nine (69.2%), and one (7.7%), respectively. The mean numbers of reconnected PV were 0.7 ± 0.6, 0.9 ± 1.4, and 0 per patient; the rates of non-PV triggers were 33.3%, 22.2%, and 0% in GG, GA, and AA genotypes, respectively. Nevertheless, we were unable to demonstrate a statistical difference in repeat procedural mapping in accordance with genetic differences, because of the limited number of patients (Supplement Table 2).

### *Validation of the* rs2106216 *genetic polymorphism and good responders*

Because ablation strategies for L-PeAF are different in each institute, we conducted replication genetic study with same patient population, but different genetic methods (target SNP assay vs. genome-wide association study). Among 52 SNPs nearby *rs2106216*, four variants (*rs9940520*, *rs879324*, *rs16971447*, and *rs7193343*) were associated with the AF in multivariate analysis ($p < 0.05$). Especially, *rs879324*, nearby *rs2106216*, was significantly associated with being a good responder with a same minor allele (A) and similar effect size (OR 1.99, 95% CI 1.11–3.58, $p = 0.022$; Supplementary Table 3).

### *The* rs2106216 *genetic polymorphism and AF recurrence*

Although *rs2106261* was independently associated with being a good responder to L-PeAF ablation, it was not a predictor for AF recurrence in an additive model (log rank, $p = 0.193$, Fig. 1B). Subgroup analysis showed that the *rs2106261* polymorphism exhibited a borderline association with favorable clinical outcome in patients with L-PeAF <65 months duration (median value, log rank, $p = 0.025$, Fig. 3A), but not in those with an AF duration ≥65 months (Fig. 3B).

**Table 3**
Genotyping of six single nucleotide polymorphisms from four atrial fibrillation-associated loci and frequency of good responders in 141 patients with long-standing atrial fibrillation.

| Nearest gene | SNP | Chromosome | Position | Minor allele | MAF | Genotype | Good responders *n* (%) | Others *n* (%) | *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| | *rs2200733* | 4 | 110789013 | *C* | 0.245 | TT | 22 (27.8) | 57 (72.2) | 0.636 |
| | | | | | | CT | 15 (27.3) | 40 (72.7) | |
| | | | | | | CC | 1 (14.3) | 6 (85.7) | |
| *PITX2* | *rs6843082* | 4 | 110796911 | *A* | 0.099 | GG | 33 (28.2) | 84 (71.8) | 0.615 |
| | | | | | | AG | 5 (20.8) | 19 (79.2) | |
| | | | | | | AA | – | – | |
| *PITX2* | *rs17042171* | 4 | 110787131 | *C* | 0.202 | AA | 22 (27.8) | 57 (72.2) | 0.636 |
| | | | | | | CA | 15 (27.3) | 40 (72.7) | |
| | | | | | | CC | 1 (14.3) | 6 (85.7) | |
| *ZFHX3* | *rs2106261* | 16 | 73017721 | *A* | 0.508 | GG | 8 (18.6) | 35 (81.4) | **0.008** |
| | | | | | | GA | 17 (23.3) | 56 (76.7) | |
| | | | | | | AA | 13 (52.0) | 12 (48.0) | |
| *ZFHX3* | *rs7193343* | 16 | 72995261 | *G* | 0.393 | AA | 19 (31.1) | 42 (68.9) | 0.318 |
| | | | | | | GA | 16 (24.6) | 49 (75.4) | |
| | | | | | | GG | 3 (20.0) | 12 (80.0) | |
| *KCNN3* | *rs13376333* | 1 | 154841877 | *T* | 0.025 | CC | 37 (27.4) | 98 (72.6) | 0.683 |
| | | | | | | CT | 1 (16.7) | 5 (83.3) | |
| | | | | | | TT | – | – | |

Significant *p*-value are in bold.
*Abbreviations*: MAF, minor allele frequency; SNP, single nucleotide polymorphism.

**Table 4**
Logistic regression analysis of clinical and genetic factors associated with being a good responder to catheter ablation for L-PeAF.

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p*-value | Adjusted OR | 95% CI | *p*-value |
| Age, years | 0.97 | 0.93–1.01 | 0.134 | 0.98 | 0.94–1.03 | 0.427 |
| Male | 1.07 | 0.41–2.78 | 0.894 | 0.94 | 0.32–2.8 | 0.936 |
| AF duration, quartiles | 0.60 | 0.42–0.86 | **0.006** | 0.58 | 0.39–0.85 | **0.005** |
| LA size, mm | 0.93 | 0.86–0.99 | **0.035** | 0.92 | 0.85–0.99 | **0.040** |
| Gene/SNP | | | | | | |
| *rs2200733_C* | 0.85 | 0.45–1.60 | 0.609 | | | |
| *PITX2/rs6843082_A* | 0.67 | 0.23–1.9 | 0.461 | | | |
| *PITX2/rs17042171_C* | 0.85 | 0.45–1.61 | 0.609 | | | |
| *ZFHX3/rs2106261_A* | 2.19 | 1.23–3.89 | **0.008** | 2.70 | 1.41–5.14 | **0.003** |
| *ZFHX3/rs7193343_G* | 0.73 | 0.41–1.32 | 0.300 | | | |
| *KCNN3/rs13376333_T* | 0.53 | 0.06–4.69 | 0.568 | | | |

Significant *p*-value are in bold.
*Abbreviations*: AF, atrial fibrillation; CI, confidence interval; LA, left atrium; OR, odds ratio; SNP, single nucleotide polymorphism.

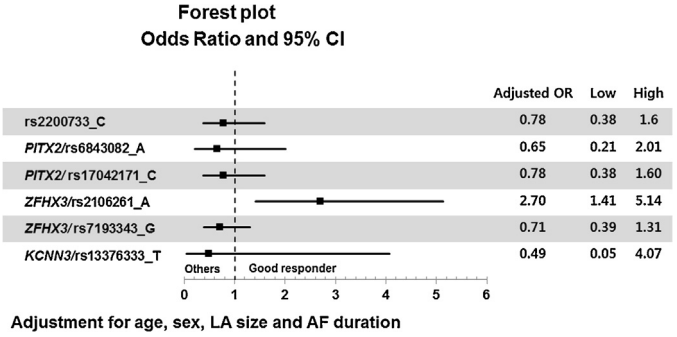


**Fig. 2.** Forest plot of six single nucleotide polymorphisms for good responders. OR, odds ratio; CI, confidence interval; LA, left atrial; AF, atrial fibrillation.

## Discussion

In this study, we examined the clinical and genetic background related to being a good responder to L-PeAF ablation. "Good responder" was defined as no early and clinical recurrence within 12 months after RFCA, in the absence of AAD therapy. Despite the relatively high recurrence rate after RFCA for L-PeAF, patients with a shorter duration of AF and smaller LA size were more likely to be good responders. The *rs2106216* polymorphism of the *ZFHX3* gene on chromosome 16q22 was independently associated with being good responders, and it was specifically associated with a lower AF recurrence rate among patients with an AF duration of 12–65 months. However, some good responders had recurrent AF after 12 months post-RFCA for L-PeAF.

### *Definition of L-PeAF and LA remodeling*

Outcomes after ablation for L-PeAF are relatively poor and characterized by frequent failure, because of significantly advanced electrical and structural remodeling that occurs in these patients [16,17]. It has been reported that a longer duration of AF [18] and more advanced LA remodeling [19] are associated with a higher likelihood of recurrence after RFCA, and the results of our current study of patients with L-PeAF are consistent with these reports. However, there are several issues regarding the definition of L-PeAF in the patients who underwent RFCA. As demonstrated in the CRYSTAL AF [20] and EMBRACE trials [21], a substantial proportion of AF is asymptomatic. Therefore, L-PeAF duration of more than 1 year determined by symptoms alone may not be accurate; therefore, we defined L-PeAF based on ECG documentation in this study. Nevertheless, an ECG-based definition of L-PeAF may underestimate the frequency of L-PeAF. Some patients with

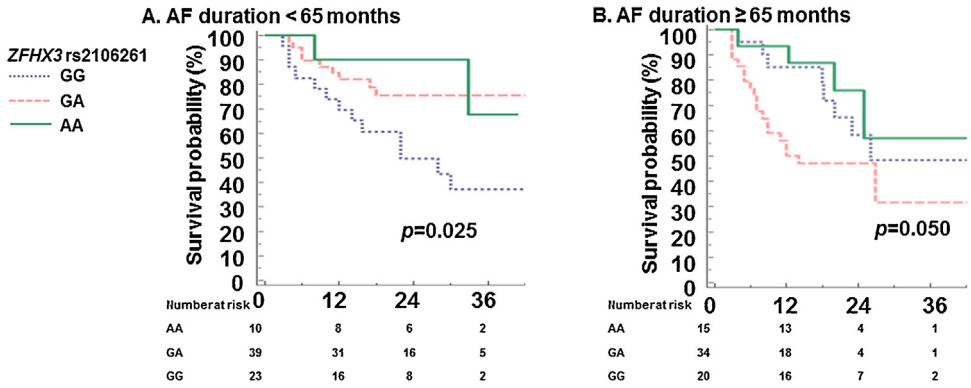


**Fig. 3.** Kaplan–Meier curves for atrial fibrillation (AF)-free survival depending on additive model of presence of the rs2106261 (*ZFHX3*) polymorphism. (A) Patient group with AF duration between 12 and 65 months and (B) patient group with AF duration longer than 65 months.

L-PeAF change to paroxysmal AF after receiving AAD therapy; they may be classified as paroxysmal AF in some institutions and as PeAF in others depending on the operator's decision. In this study, we designated only those patients who exhibited AF continuously for more than 1 year as fulfilling the definition of L-PeAF.

*Ablation strategy for L-PeAF*

RFCA remains challenging with substantial recurrence rates in patients with L-PeAF [3]. It has been generally accepted that CPVI alone is not sufficient for the treatment of L-PeAF [4]. Linear ablation, CFAE-guided ablation, RA ablation, non-PV foci ablation, rotor ablation, or multiple procedures may improve the clinical outcome of RFCA for L-PeAF [5]. Most of the current ablation strategies for L-PeAF reduce AF burden by substrate modification, but this is accompanied by extensive atrial scarring and the risk of collateral damages. The DECAAF study showed poor clinical outcomes after AF ablation in patients with extensive atrial scarring [22]. Therefore, we tried to maintain a consistent linear ablation design in this study, but incomplete conduction block and triggers associated with AF recurrence remained.

*Genetic and patient factors and ablation outcome*

Because we conducted this study in a relatively homogeneous group of patients with L-PeAF and utilized a consistent ablation strategy, we sought to identify patient factors associated with a high success rate. Consistent with the previous reports, a shorter duration of AF [18] and a less remodeled LA [19] were associated with being a good responder to L-PeAF ablation. We also found that the *rs2106216 (ZFHX3)* genetic polymorphism on chromosome 16q22 was an independent predictor for being a good responder after catheter ablation in patients with L-PeAF. AF is well known to be affected by genetic factors, and a parental history of AF increases the risk of AF by 1.4–1.9 times [23]. Over the last few years, several common genetic variants have been demonstrated to be associated with AF in GWAS performed in European ancestry [14] and the Chinese Han GeneID cohort [13]. Some reports have suggested that these genetic polymorphisms are associated with an increased risk of AF recurrence after RFCA [6–9,24]. However, there are ethnic differences in the frequency of these SNPs and their association with clinical phenotypes [10,13]. Recently, we evaluated the relationship between common AF-related SNPs and AF recurrence after catheter ablation in 1068 Korean patients (4.6% male, $57.5 \pm 10.9$ years old, 67.9% paroxysmal AF). Therein, reported genetic variants, including *rs2200733*, which has prognostic value in individuals of European descent, failed to predict ablation success [10]. Therefore, differences in ethnicity, patient characteristics, or ablation technique should be considered, and we do not think that a single genetic variant can determine all outcomes of a procedure for all people. In this study, we found a clear association between being a good responder to L-PeAF ablation and one of the AF-related SNPs. The *rs2106261* is located within the intron of ZFHX3, a transcription factor that is supposed to be related to JAK/STAT signaling cascade [13] by interacting with protein inhibitor of activated STAT 3 (PIAS3) [25] and regulates myogenic and neuronal differentiation [26]. STATs have been shown to mediate the inflammatory process as major downstream mediators of many different signaling pathways. Therefore, this cascade can be associated with AF susceptibility by contributing to electrical and structural remodeling of the atrium with inflammatory changes [27]. Although Magnani et al. failed to identify an association between *rs2106216* and LA structure in the Framingham Heart Study [28], mean LA voltage was significantly affected by *rs2106261* genotype in this study. The mechanism for its relationship to good responders to RFCA remains to be explored.

*Study limitations*

This was a single-center observational study and data were obtained from a cohort registry that included a highly selective group of patients referred to our institution for AF catheter ablation. The number of patients is small and ethnicity is limited to Korean population, so that genetic evaluation may not be generalized to other races and ethnicities. We conducted genetic validation study with the same patient population, but different genetic methods (target SNP assay vs. genome-wide association study). It was because ablation strategies for L-PeAF are different in each institute, and we could not find an appropriate independent cohort for replication study.

## Conclusion

Despite a relatively high recurrence rate after RFCA for L-PeAF, patients with a shorter duration of AF and smaller LA size showed favorable outcomes. The *rs2106216* genetic polymorphism was independently associated with being a good responder to RFCA for L-PeAF.

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## Authors' contribution

JKP, JYL, ESS, and HNP analyzed genetic data and had substantial contributions to research design, or the acquisition, analysis, or interpretation of data. PSY, THK, JBP, and JSU helped to draft the manuscript. BYJ and MHL drafted the paper or revised it critically. All authors read and approved the final manuscript.

## Conflict of interest

The authors declare that there is no conflict of interest.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.jjcc.2016.04.017.

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