의학석사 학위논문

Impact of a genetic risk score using common genetic variants on the response to atrial fibrillation catheter ablation

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이 논문을 의학석사 학위논문으로 제출함
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ABSTRACT

Background: Genetic predisposition plays a substantial role in the development and progression of atrial fibrillation (AF). However, the association of AF susceptibility loci with recurrence after catheter ablation has been reported with controversial results. We sought to find out the impact of cumulative genetic risk score (GRS) on response to AF catheter ablation.

Methods: We determined the association between the 20 AF-susceptible single nucleotide polymorphisms (SNPs) and AF recurrence after catheter ablation in 746 patients (74% males; age, 59±11 years; 56% paroxysmal AF).

A GRS was calculated by summing the unweighted numbers of risk alleles of SNPs, which showed at least borderline significant association with AF recurrence. The primary outcome was AF recurrence after a 3-month blanking period. A Cox proportional hazard model was used to identify the association between the GRS and risk of AF recurrence after catheter ablation.

Results: During median 23 months of follow-up, 168 (23%) patients showed clinical recurrence. The GRS was calculated using 5 SNPs (rs1448818, rs2200733, rs6843082, rs6838973 at chromosome 4q25 [PITX2] and rs2106261 at chromosome 16q22 [ZFHX3]), which showed modest

associations with AF recurrence. The GRS was significantly associated with AF recurrence (hazard ratio [HR] per each score, 1.14; 95% confidence interval [CI] 1.04-1.24). Patients with high risks (GRS 6-10) showed HR of 1.50 (95% CI 1.06-2.11), compared to patients with low risk (GRS 0-5).

Conclusion: Our novel GRS using 5 AF-susceptible SNPs strongly associated with AF recurrence after catheter ablation, with patients with a high GRS being at particularly high risk.

Keywords: Arrhythmias; Atrial fibrillation; Genetics; Catheter ablation; Recurrence

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LIST OF ABBREVIATIONS

AF	atrial fibrillation
BMI	body mass index
GRS	genetic risk score
HR	hazard ratio
IVSd	interventricular septal thickness at diastole
LA	left atrium
LVEDD	left ventricular end-diastolic dimension
LVEF	left ventricular ejection fraction
OR	odds ratio
PV	pulmonary vein
SNP	single nucleotide polymorphism

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, affecting 1~2% of the general population worldwide.[1] AF is associated with increased cardiovascular morbidity and mortality, thus imposing a substantial and increasing economic burden on the healthcare system.[2] Since the landmark study by Haissaguerre et al., which revealed the main triggering foci of AF within the pulmonary veins (PVs),[3] advances in catheter ablation of AF have revolutionized the management of this common arrhythmia. The current guidelines recommend that catheter ablation should be considered for patients with symptomatic, antiarrhythmic drug-refractory AF,[4] and catheter ablation is now a widely accepted treatment option in clinical practice.

The reported efficacy of catheter ablation varies depending on the patient characteristics, ablation strategies, and intensity of surveillance. Successful catheter ablation of AF leads to a reduction of the AF burden and improvement in symptoms, but more than 40% of patients experience recurrence during the long-term follow-up, and 20–40% of patients require repeated ablation procedures.[5, 6] Considering the inherent risk of procedure-related adverse events and high cost of the ablation procedure,[7, 8] appropriate selection of candidate patients is as important as technical proficiency to ensure the success of this invasive strategy. Previous studies have reported variable risk factors associated with the clinical response to AF ablation, including patient characteristics, biomarkers, medications, and presence of

structural heart diseases.[9-12] However, our understanding on the mechanism of recurrence and precise prediction of clinical response remains incomplete.

In addition to traditional clinical risk factors, genetic predisposition plays a substantial role in the development and progression of AF. During the past decade, researchers have investigated the genetic basis of AF, and a number of common genetic variants that increase the susceptibility to AF have been discovered.[13-18] To date, however, studies on the utility of such genetic markers to improve the prediction of outcome after AF ablation have shown controversial results, even for the most promising markers at the 4q25 locus.[19-21] Furthermore, many of the candidate AF-related genetic markers have not been studied for their association with the clinical response to catheter ablation. Accordingly, in this study, we sought to perform a comprehensive analysis on the relationship between genetics and outcome of AF ablation by constructing a genetic risk score (GRS) based on common genetic markers known to be associated with AF.

METHODS

Study population

This study was performed in two centers, Seoul National University Hospital and Korea University Medical Center, using an AF ablation cohort comprising patients with available genomic DNA data. Consecutive patients who were admitted and underwent de novo or repeat radiofrequency catheter ablation for symptomatic paroxysmal or persistent AF between June 2008 and March 2015 were enrolled. A detailed medical and personal history of each participant was obtained at the time of admission. Transesophageal and transthoracic echocardiography were performed prior to catheter ablation to exclude the presence of atrial thrombi and to measure the cardiac chamber size, wall thickness, and left ventricular systolic function with standard methods. After the index catheter ablation procedure, the prescription of antiarrhythmic drugs during the blanking period was left to the attending clinician's judgement. Follow-up information was obtained from regular outpatient visits at 1, 3, 6, and 12 months and every 3 to 6 months thereafter, as clinically indicated. Electrocardiograms were performed at every visit, and 24-hour Holter monitoring was performed at 3 and 12 months after the ablation. Supplementary 24-hour Holter monitoring was obtained when recurrence was suspected on the basis of the patient's symptoms.

The primary outcome was the time to recurrence of atrial tachyarrhythmia after AF ablation. Recurrence was defined as any documented episode of AF, atrial flutter, or atrial tachycardia lasting more than 30 seconds after a 3-month blanking period.[22] The study protocol was approved by each

institutional review board, and all subjects provided written informed consent.

Mapping and catheter ablation procedure

Ablation was guided by 3-dimensional electroanatomical mapping using CARTO-3 (Biosense Webster Inc., Diamond Bar, CA, USA) or EnSite Velocity (St. Jude Medical, Sylmar, CA, USA) mapping system. A duo-decapolar Lasso circular mapping catheter was used to guide and map the PVs. Ablation was performed using open irrigation catheters (Celsius or Navistar Thermocool SF, Biosense Webster; Cool Flex, St Jude Medical; 20~35W, 47°C). All patients underwent circumferential PV isolation. Exit and entrance blocks were confirmed after PV isolation. For patients with persistent AF, additional ablation was performed at the roof line, posterior inferior line, anterior line, mitral isthmus line, cavotricuspid line, or regions of complex fractionated electrograms, at the operator's discretion.

Single nucleotide polymorphism (SNP) selection and genotyping

Through a comprehensive screening of previous reports, we selected 20 SNPs from genome-wide association studies in which the robust association between SNPs and incident AF were identified ($P<5x10^{-8}$). [13, 15-18] The selected SNPs are listed in Table 1, along with the risk allele frequencies in our cohort and published effect sizes for incident AF. All SNPs have a reported minor allele frequency of >0.01.

Genomic DNA extraction was performed by standard methods with whole blood samples collected during admission for index catheter ablation. The selected 20 SNPs were genotyped using validated TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA, USA) on the ABI PRISM

7900HT Real-time PCR system according to the supplier's recommendations, and allelic discrimination was calculated with SDS v2.3 software using the same system. The laboratory personnel were blinded to the subjects' clinical characteristics and outcomes of the ablation procedure. All SNPs had a call rate of >99%.

Genetic risk score construction

To construct a GRS model of AF recurrence, the 20 SNPs were separately examined for independent cross-sectional association with AF recurrence using univariable logistic regression analysis. SNPs showing at least borderline significant associations (P<0.1) with AF recurrence were included in the GRS model. Because the association between each AF susceptibility-associated SNP and clinical response to catheter ablation were not previously reported in most cases, the magnitude of genetic effect size of each SNP could not be estimated. Therefore, we applied an additive unweighted model, and the total number of risk alleles each subject carries was summed to calculate the GRS. Previous research has shown that unweighted GRS model gives unbiased prediction of the associations, when there is a lack of relevant data on the individual effects of each genetic variant.[23] Subjects with missing genotype data of the target SNPs included in the final GRS model were excluded from the analysis.

Statistical analysis

Baseline characteristics are presented as mean±SD for continuous variables and as number and percent for categorical variables. A Cox multivariable proportional hazard model was used to identify the association between the

GRS and risk of AF recurrence after catheter ablation. The traditional risk factors used in the adjustment were age, sex, hypertension, persistent (vs. paroxysmal) AF, and left atrium (LA) size, measured by echocardiography. We divided the subjects into 3 subgroups by GRS risk, and the differences in the cumulative AF recurrence rate between the subgroups were calculated by the Kaplan-Meier method and compared by the log-rank test. Comparisons of baseline characteristics of each subgroup were made with independent-samples *t* tests for continuous variables and $\chi 2$ tests for categorical variables. The risks of AF recurrence in the intermediate and high GRS groups were compared with the low GRS group using a Cox multivariable proportional hazard model, adjusted for the same traditional risk factors. All analyses were performed using SPSS Statistics 20.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Study population and AF recurrence

A total of 746 subjects were included. The characteristics of the study population are summarized in Table 2. The median follow-up time was 684 days (interquartile range, 324-1205 days). During the follow-up period, 168 subjects (22.5%) experienced recurrence of atrial tachyarrhythmia. AF accounted for 57.1% of all recurrence events, and atrial flutter or atrial tachycardia accounted for the remainder. The 6- and 12-month recurrence rates were 8.2% and 14.7%, respectively (Table 3).

Target SNP identification for GRS modeling

We evaluated each SNP separately to assess the cross-sectional association between each of the 20 SNPs and recurrence of atrial tachyarrhythmia, and to identify a set of SNPs for joint analysis using our GRS. We assumed that each copy of the risk alleles adds an equal risk effect, and an unweighted additive model was applied in the logistic regression analysis.

Table 4 presents the associations of the individual genetic variants with recurrent AF after catheter ablation. Overall, 6/20 SNPs showed at least borderline association (P<0.1) with recurrence: 5 SNPs at the 4q25 locus (rs1448818, rs6817105, rs2200733, rs6843082, rs6838973) and 1 SNP at the 16q22 locus (rs2106261). Although modest trends were noted, none of these selected SNPs remained significantly associated with recurrence in the multivariable Cox proportional hazard model adjusted for traditional risk factors (Table 5). Of the 6 SNPs, rs6817105 was excluded from the final GRS

model because of its strong linkage disequilibrium (r^2=1.0) with rs2200733, which has been reported as an independent predictor of treatment response after catheter ablation of AF in different populations.[19, 20]

Association between the GRS and AF recurrence

To assess the cumulative effects of genetic variants on AF recurrence, we performed a joint analysis by generating a GRS with the 5 selected SNPs. As we adopted an unweighted additive model, the GRS was calculated by summing the number of risk alleles for each of the 5 selected SNPs, which resulted in a score ranging from 0 to 10. The overall distribution of the GRS is shown in Figure 1. Although the distribution of the GRS between those who experienced recurrence during follow-up and those who remained in sinus rhythm tended to overlap, the mean values of each group significantly differed. The mean GRSs were 6.3±1.7 and 5.7±1.8 in the AF-recurrence and no-recurrence groups, respectively (P<0.001).

Cox regression analysis demonstrated a significant association between the GRS and AF recurrence after adjusting for age, sex, hypertension, type of AF (persistent vs. paroxysmal AF), and LA size (Table 6). The addition of one risk allele was associated with a 13.5% increased risk of recurrence (hazard ratio [HR] 1.135; 95% confidence interval [CI] 1.036-1.244; P=0.006). To illustrate this association further, the subjects were partitioned into 2 groups according to the GRS: the low-risk group (GRS 0–5) and high-risk group (GRS 6–10). The epidemiologic and echocardiographic data of each group are presented in Table 7. Subjects with high-risk GRS profile tended to have a higher prevalence of persistent AF and larger LA. Figure 2 shows Kaplan-Meier curves of the proportions of subjects remaining in sinus rhythm, which

revealed that there was a significant trend toward an increased risk of AF recurrence in the high-risk group (Log-rank test P=0.002). In multivariable analysis, subjects with high GRS had higher risks of AF recurrence (HR 1.496; 95% CI 1.059-2.112; P=0.022) than those with low GRS.

DISCUSSION

In the current study of AF patients of Korean ancestry who had undergone catheter ablation, we sought to demonstrate the influence of 20 well-known AF susceptibility genetic variants on AF recurrence. We found that our GRS, generated from 5 SNPs, was associated with the risk of recurrence of AF after catheter ablation, even after adjusting for known AF recurrence risk factors, including age, type of AF, and LA size. Especially, patients carrying several risk alleles (high-risk group) were found to have a 2.65-fold increased risk of recurrence when compared with those in the lowest risk group.

Since the initial era of familial linkage analysis, numerous genetic variants contributing to the risk of AF have been identified. Recently, genome-wide association studies have revealed multiple loci robustly associated with AF,[13-17] and several investigators have tried to incorporate these genetic data by proposing cumulative GRSs and providing predictive models for reliable assessment of AF risk. Lubitz et al. reported that a GRS comprising 12 SNPs was associated with AF in not only European but also Japanese populations.[20] Another GRS constructed with the top 12 AF-associated SNPs was examined in the Women's Health Study cohort, and the addition of this GRS to a clinical AF risk model improved discrimination and category-less reclassification.[24] A similar GRS constructed from 12 SNPs was significantly associated with incident AF and ischemic stroke in a Swedish population, and modestly, but significantly, improved risk discrimination and reclassification were reported.[25] However, there is currently no study reporting the association between a GRS and AF recurrence after catheter ablation.

In contrast to the previous studies showing the impact of genetic predisposition to AF development, there have been relatively few studies evaluating the correlations of genetic variations and response to AF treatment. Several studies have examined limited number of AF-associated common variants, which were revealed as independent predictors of clinical response to electrical cardioversion and anti-arrhythmic drug therapy.[26, 27] However, the previous evidence of associations between individual genetic variations and the rhythm outcome after catheter ablation of AF is conflicting. Studies conducted in European populations reported positive independent associations between SNPs on chromosome 4q25, one of the most significant AF-associated genetic loci, and increased risk of AF recurrence after catheter ablation.[19, 20, 28] In contrast, we did not find any correlation between AF-susceptibility SNPs and AF recurrence after catheter ablation in our previous study in an Asian population.[21] In the current study, the lack of association between the individual AF-risk SNPs and AF recurrence after catheter ablation was consistent with our previous findings. Nonetheless, our GRS constructed using 5 SNPs was associated with AF recurrence independent of clinical risk factors. The predictive power of individual risk alleles appears small, but combining these risk alleles increased the predictive power, which showed significant association with clinical outcomes. Therefore, our study supports and extends the findings of previous studies that genetic polymorphisms related to AF risk are associated with AF recurrence after catheter ablation.

The clinical implication of our GRS on AF recurrence after catheter ablation includes the identification of high-risk patients before ablation. The operator can change the ablation strategies for these high-risk patients, which may

improve the clinical outcomes. PV antrum isolation is the cornerstone of AF catheter ablation, but some patients recur due to non-PV foci. The DECAF study reported associations of genetic polymorphisms and increased risks of LA scars and non-PV triggers in AF patients.[29] Therefore, tailored ablation strategies could be considered based on the genetic testing results. Future analyses are warranted to determine whether such tailored ablation strategies based on genetic test results will show better outcomes than conventional strategies. Moreover, the GRS can discriminate patients with low risk of AF recurrence after catheter ablation. One recent study reported that the rs2106216 polymorphism (*ZFHX3*) was independently associated with a good response to radiofrequency catheter ablation for longstanding persistent AF.[30]

In the current work, we present the first attempt to study the association between a GRS and risk of AF recurrence after ablation; however, our study has some potential limitations. Our study consists of Korean patients, and hence the current results cannot be generalized to other populations. Further, our panel of genetic variants may be incomplete. As previously described, we adopted common genetic variants obtained from previous genetic association studies that increase the susceptibility to AF, not the risk of recurrence after ablation. Thus far, the relative scarcity of unraveled genetic variants associated with AF recurrence prevents the development of a robust predictive genetic model.

Conclusion

To our knowledge, this is the first study to evaluate whether a cumulative GRS can predict the outcome of AF treatment. Our GRS comprising five known AF-susceptibility SNPs was associated with recurrent AF after catheter ablation in a Korean population. Although this observation may not apply to all populations, it suggests the potential of genetic screening for decision-making in AF management by providing additional information over classic predictors of treatment outcome. Further studies with a complete set of genetic loci associated with AF recurrence in the general population are needed.

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Table 1. Profiles of the 20 Candidate AF-susceptibility SNPs

SNP	Loci	Nearest Gene	AF Associated Risk Allele	Other Allele	Risk Allele Frequency†	Risk‡ Estimates From the Literature	Reference
rs6666258	1q21	KCNN3	C	G	0.980	1.18	16
rs13376333	1q21	KCNN3	T	C	0.019	1.56	15
rs3903239	1q24	PRRX1	G	A	0.609	1.14	16
rs4642101	3p25	CAND2	G	T	0.237	1.10	18
rs1448818	4q25	PITX2	C	A	0.376	1.14	17
rs6817105	4q25	PITX2	C	T	0.696	1.64	16
rs2200733	4q25	PITX2	T	C	0.693	1.72	13
rs4400058	4q25	PITX2	A	G	0.157	1.18	17
rs6843082	4q25	PITX2	G	A	0.863	2.03	15
rs6838973	4q25	PITX2	C	T	0.536	1.21	17
rs13216675	6q22	GJA1	T	C	0.653	1.10	18
rs3807989	7q31	CAV1	G	A	0.712	1.14	16
rs10821415	9q22	C9orf3	A	C	0.293	1.13	16
rs10824026	10q22	SYNPO2L	A	G	0.556	1.17	16
rs12415501	10q24	NEURL	T	C	0.169	1.18	18
rs6490029	12q24	CUX2	A	G	0.725	1.12	18
rs10507248	12q24	TBX5	T	G	0.485	1.11	18
rs1152591	14q23	SYNE2	A	G	0.337	1.13	16
rs7164883	15q24	HCN4	G	A	0.111	1.16	16
rs2106261	16q22	ZFHX3	T	C	0.452	1.24	16

† Risk allele frequency in this study.

‡ Risk of incident AF.

Abbreviations: AF, atrial fibrillation; SNP, single nucleotide polymorphism.

Table 2. Baseline Characteristics of the Study Population

	Total Cohort (N = 746)
Age, y	59.4±10.6
Male sex, %	548 (73.5%)
BMI, kg/m^2	24.8±2.8
Paroxysmal AF, %	420 (56.3%)
Hypertension, %	358 (48.1%)
Diabetes mellitus, %	115 (15.4%)
Heart failure, %	91 (12.2%)
History of stroke, %	38 (5.2%)
Echocardiography	
LA dimension, mm	42.5±6.4
LA volume index, mL/m^2	42.5±15.9
LVEDD, mm	49.3±6.2
IVSd, mm	9.4±1.9
LVEF, %	62.6±8.0

Data are shown as mean±SD or n (%).

Abbreviations: AF, atrial fibrillation; BMI, body mass index; IVSd, interventricular septal thickness at diastole; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction.

Table 3. Clinical Outcomes After Catheter Ablation of AF

	Total Cohort (N = 746)
Median follow-up†, days	684 (324-1205)
Recurrence during blanking period‡	21.4%
6-month recurrence, %	8.2%
12-month recurrence, %	14.7%
Type of recurrence	
AF, %	57.1%
Atrial flutter or atrial tachycardia, %	42.9%

† The follow-up periods are shown as median (interquartile range).

‡ The blanking period is within 90 days after catheter ablation.

Abbreviations: AF, atrial fibrillation.

Table 4. Cross-sectional Association between the 20 AF-susceptibility SNPs and AF Recurrence After Catheter Ablation

SNP	Loci	Nearest Gene	AF Associated Risk Allele	Recurrence[†]		Inclusion in the GRS model
				OR (95% confidence interval)	P-value	
rs6666258	1q21	KCNN3	C	2.579 (0.786-8.465)	0.118	
rs13376333	1q21	KCNN3	T	0.385 (0.115-1.289)	0.122	
rs3903239	1q24	PRRX1	G	1.077 (0.841-1.380)	0.555	
rs4642101[§]	3p25	CAND2	G	0.747 (0.554-1.009)	0.057	
rs1448818	4q25	PITX2	C	1.240 (0.971-1.583)	0.085	Yes
rs6817105[‡]	4q25	PITX2	C	1.405 (1.075-1.837)	0.013	
rs2200733	4q25	PITX2	T	1.430 (1.093-1.871)	0.009	Yes
rs4400058	4q25	PITX2	A	0.816 (0.576-1.155)	0.251	
rs6843082	4q25	PITX2	G	1.438 (0.988-2.092)	0.058	Yes
rs6838973	4q25	PITX2	C	1.269 (0.978-1.648)	0.073	Yes
rs13216675	6q22	GJA1	T	1.010 (0.782-1.305)	0.939	
rs3807989	7q31	CAV1	G	1.010 (0.773-1.318)	0.944	
rs10821415	9q22	C9orf3	A	0.946 (0.720-1.244)	0.691	
rs10824026	10q22	SYNPO2L	A	0.917 (0.723-1.164)	0.477	
rs12415501	10q24	NEURL	T	1.173 (0.859-1.602)	0.314	
rs6490029	12q24	CUX2	A	0.818 (0.626-1.070)	0.142	
rs10507248	12q24	TBX5	T	0.956 (0.754-1.213)	0.713	
rs1152591	14q23	SYNE2	A	0.934 (0.726-1.200)	0.593	
rs7164883	15q24	HCN4	G	1.231 (0.856-1.772)	0.263	
rs2106261	16q22	ZFHX3	T	1.289 (1.007-1.652)	0.044	Yes

The associations were tested with a univariable logistic regression analysis. Additive genetic modeling was used for all SNPs.

† Recurrence includes AF, atrial flutter, or atrial tachycardia.

‡ rs6817105 was excluded from the GRS model because of its strong linkage disequilibrium with rs2200733.

§ rs4642101 was excluded from the GRS model because the known risk allele showed a negative association with recurrence.

Abbreviations: AF, atrial fibrillation; GRS, genetic risk score; OR, odds ratio; and SNP, single nucleotide polymorphism.

Table 5. Multivariable Analysis of the Associations between the Individual SNPs Included in the GRS and AF Recurrence

SNP	Recurrence†	
	Adjusted HR (95% Confidence Interval)	P-value
rs1448818	1.142 (0.918-1.421)	0.234
rs2200733	1.290 (1.004-1.656)	0.046
rs6843082	1.241 (0.876-1.758)	0.224
rs6838973	1.199 (0.951-1.513)	0.126
rs2106261	1.199 (0.960-1.496)	0.109

The associations were tested with a Cox proportional hazards model adjusted for age, sex, hypertension, persistent (vs. paroxysmal) AF, and left atrium size. Additive genetic modeling was used for all SNPs.

† Recurrence includes AF, atrial flutter, or atrial tachycardia.

Abbreviations: AF, atrial fibrillation; GRS, genetic risk score; HR, hazard ratio; SNP, single nucleotide polymorphism.

Table 6. Multivariable association of risk factors with AF recurrence after catheter ablation

Risk factor†	Recurrence‡	
	Adjusted HR (95% Confidence Interval)	P-value
GRS	1.135 (1.036-1.244)	0.006
Age	0.997 (0.981-1.013)	0.677
Male sex	1.201 (0.811-1.779)	0.361
Hypertension	0.757 (0.550-1.042)	0.088
Persistent AF	1.209 (0.875-1.670)	0.249
LA size	1.060 (1.036-1.085)	< 0.001

The associations were tested with a Cox proportional hazards that included all the variables listed in the table. Additive genetic modeling was used for all SNPs.

† Risk for GRS is per allele, age per year, LA size per mm. All other risks are per risk category.

‡ Recurrence was defined as any documented episode of AF, atrial flutter or atrial tachycardia lasting more than 30 seconds after a 3-month blanking period.

Abbreviations: AF, atrial fibrillation; GRS, genetic risk score; HR, hazard ratio; and LA, left atrium.

Table 7. Baseline Characteristics of the Study Population According to the GRS Groups

	GRS Groups		P value
	Low Risk Group (GRS 0~5)	High Risk Group (GRS 6~10)	
No. of subjects	449	297	
Age, y	59.3±10.6	59.4±10.5	0.892
Male sex, %	331 (73.7%)	217 (73.1%)	0.866
BMI, kg/m^2	24.8±2.8	24.8±2.8	0.954
Persistent AF, %	182 (40.5%)	144 (48.5%)	0.035
Hypertension, %	219 (48.9%)	139 (47.0%)	0.653
Diabetes mellitus, %	61 (13.6%)	54 (18.2%)	0.097
Heart failure, %	49 (10.9%)	42 (14.1%)	0.209
History of stroke, %	20 (4.6%)	18 (6.2%)	0.396
Echocardiography			
LA dimension, mm	42.0±6.6	43.2±5.9	0.013
LA volume index, mL/m^2	41.8±16.0	43.5±15.7	0.187
LVEDD, mm	49.3±6.2	49.3±6.1	0.930
IVSd, mm	9.4±1.8	9.4±2.0	0.930
LVEF, %	63.1±8.0	61.9±8.1	0.045
Ablation procedure			
Redo procedure	28 (6.2%)	21 (7.1%)	0.654
Ablation time, min	113.5±44.6	117.8±46.6	0.224

Data are shown as mean±SD or n (%).

Abbreviations: AF, atrial fibrillation; BMI, body mass index; GRS, genetic risk score; IVSd, interventricular septal thickness at diastole; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; RFCA, radiofrequency catheter ablation.

Figure 1. Distribution of the genetic risk score among (A) the total cohort population and (B) subjects who experienced recurrence after atrial fibrillation ablation (black bars) and who remained in sinus rhythm (grey bars).

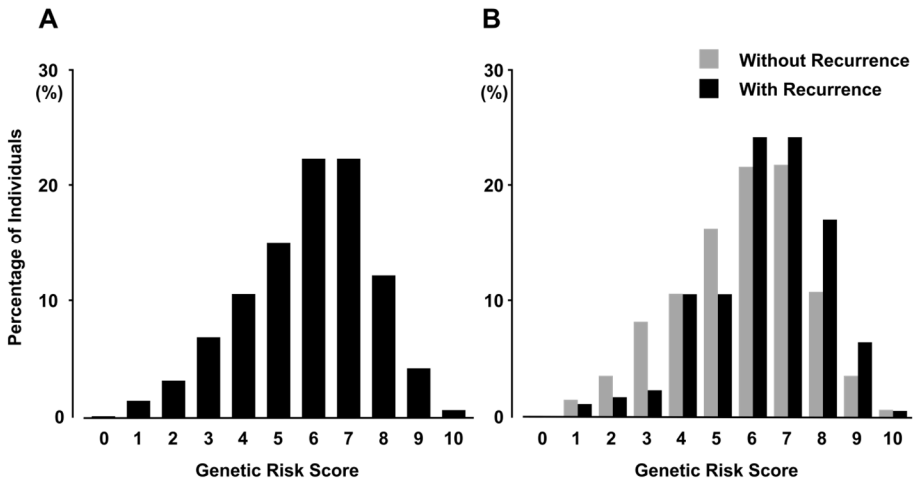
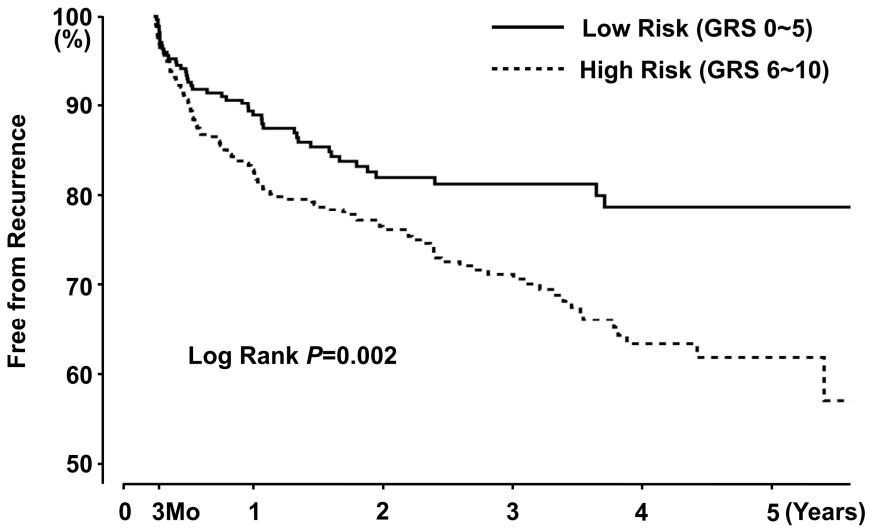


Figure 2. Kaplan-Meier curves depicting the proportion of subjects without recurrence after atrial fibrillation ablation according to risk groups stratified by the genetic risk score (GRS).



Number at Risk						
Low risk	448	327	205	148	74	26
High risk	298	207	136	88	41	10

국문 초록

서론 : 심방세동의 발생과 진행에 유전적 요인이 중요한 역할을 한다는 사실은 잘 알려져 있다. 그러나 심방세동의 발생과 연관된 유전 변이들이 심방세동의 치료법 중 하나인 전극도자절제술을 실시한 후 재발과도 연관이 있는지에 대해서는 잘 알려져 있지 않다. 본 연구에서는 심방세동의 발생과 관련된 유전 변이의 종합적인 영향을 반영할 수 있는 유전변이점수 (genetic risk score)를 구축하고, 유전변이점수와 전극도자절제술 후 재발과의 연관성을 확인하였다.

방법 : 심방세동의 발생과 관련된 것으로 알려진 대표적인 20개의 단일염기다형성 (single nucleotide polymorphism) 을 선정하고, 심방세동으로 전극도자절제술을 실시한 746명의 연구대상자를 대상으로 로지스틱 회귀분석을 수행하여 각각의 단일염기다형성과 심방세동의 재발의 연관성을 조사하였다. 이 개별 분석에서 경계역 이상의 유의성을 보인 단일염기다형성을 선정하고, 각 연구대상자별로 심방세동과 연관된 단일염기다형성의 대립유전자 수를 가중치 없이 합산하여 유전위험점수를 계산하였다. 본 연구의 일차 결과지표는 전극도자절제술 후 심방세동의 재발이며, 시술 직후 일시적으로 발생하는 부정맥을 배제하기 위하여 3개월 동안의 공백기를 설정하였다. 유전변이점수와 전극도자절제술 후 재발과의 연관성은 콕스 비례위험 모형을 통하여 확인하였다.

결과 : 연구대상자의 중앙 추적 경과관찰 기간은 23개월이었으며,

이 기간 동안 168명의 연구대상자가 심방세동의 재발을 경험하였다. 개별 분석에서 5개의 단일염기다형성 (rs1448818, rs2200733, rs6843082, rs6838973, rs2106261) 이 심방세동의 재발과 경계역 이상의 연관성을 보여 유전위험점수 모델에 포함되었다. 이렇게 계산된 유전위험점수는 전극도자절제술 후 심방세동의 재발과 유의한 연관성을 보였으며 (위험비 1.14, 95% 신뢰구간 1.04-1.24), 유전위험점수 6~10점의 고위험군은 0~5점의 저위험군에 비해 1.5배 (95% 신뢰구간 1.06-2.11) 높은 재발 위험을 갖는 것으로 분석되었다.

결론 : 단일염기다형성을 사용하여 계산한 유전위험점수가 심방세동의 전극도자절제술 후 재발을 위험을 예측할 수 있다.

주요어 : 부정맥, 심방세동, 유전학, 전극도자절제술, 재발

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