Genetic variants associated with atrial fibrillationand long-term recurrence after catheter ablation for atrial fibrillation in Turkish patients

Taner Ulus*, Muhammet Dural*, Pelin Meşe*, Furkan Yetmiş*, Kadir Uğur Mert*, Bülent Görenek*, Oğuz Çilingir**, Ebru Erzurumluoğlu Gökalp**, Serap Arslan**, Sevilhan Artan**, Özlem Aykaç***, Ertuğrul Çolak****, Hikmet Yorgun[1], Uğur Canpolat[1], Kudret Aytemir[1]

Departments of *Cardiology, and **Medical Genetics, ***Neurology, ****Biostatistics, Faculty of Medicine, Eskişehir Osmangazi University; Eskişehir-*Turkey*
[1]Department of Cardiology, Faculty of Medicine, Hacettepe University; Ankara-*Turkey*

Abstract

Objective: Genome-wide association studies have revealed that single nucleotide polymorphisms (SNPs) are associated with atrial fibrillation (AF) and can predict AF recurrence after catheter ablation in different populations. However, there exists no such data for the Turkish population. We aimed to investigate whether 11 SNPs in the *PITX2, ZFHX3, EPHX2, CAV1, TBX5, TGF-1*, and *SCN10A* were related to AF and whether these SNPs can predict long-term atrial tachyarrhythmia (ATa) recurrence after pulmonary vein isolation (PVI) for AF in Turkish patients.
Methods: A total of 245 consecutive patients with non-valvular AF (44.9% men, mean age: 60.2±13.2 years, 65.3% paroxysmal AF) and 50 age- and sex-matched controls were included in this analysis. The clinical features and genetic variants were compared between the 2 groups. Of the 245 patients, 128 who underwent PVI with second-generation cryoballoon were further examined for long-term recurrence after the procedure.
Results: Four SNPs in *PITX2* were significantly associated with AF (rs10033464_T: OR 3.29, 95%CI: 1.38–7.82, p=0.007; rs6838973_T: OR 3.06, 95% CI 1.36–6.87, p=0.007; rs3853445_C: OR 2.84, 95%CI: 1.27–6.36, p=0.011; rs17570669_T: OR 4.03, 95% CI: 1.71–9.51, p=0.001). Among these patients who underwent PVI, one locus in *CAV1* (rs3807989_G: OR 4.50, 95% CI 1.04–19.31, p=0.043) and early recurrence (OR: 8.06, 95% CI: 2.12–30.55, p=0.002) predicted long-term AF recurrence after catheter ablation.
Conclusion: Significant associations exists between 4 SNPs in *PITX2* and AF (rs10033464, rs6838973, rs3853445, and rs17570669) in Turkish patients. In addition, 1 genetic variant in *CAV1* (rs3807989) and early recurrence can predict long-term ATa recurrence after catheter ablation.
Keywords: atrial fibrillation, single nucleotide polymorphisms, catheter ablation

Cite this article as: *Ulus T, Dural M, Meşe P, Yetmiş F, Mert KU, Görenek B, et al. Genetic variants associated with atrial fibrillation and long-term recurrence after catheter ablation for atrial fibrillation in Turkish patients. Anatol J Cardiol 2021; 25: 129-38.*

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice. Recent studies have reported that the lifetime risk of having AF is 37% (1). Advanced age, systemic hypertension, heart failure (HF), and other structural heart diseases are important risk factors for the development of AF. In addition, AF has also been encountered in individuals who do not possess any of the abovementioned classical risk factors. Catheter ablation is an effective treatment option for restoring and maintaining the sinus rhythm in patients with symptomatic paroxysmal or persistent AF (2). Despite technological advances, recurrence can occur up to 40% after a single procedure and up to 25% after multiple procedures (3). Individuals with AF in any 1 of their parents develop AF by 3-fold more frequency (4). These findings suggest that genetic factors play an important role in the pathogenesis of AF.

Genome-wide association studies (GWAS) have allowed the identification of several AF-related genes that encode transcription factors, ion channel proteins, myocyte, and cytoskel-

Address for correspondence: Dr. Taner Ulus, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Eskişehir-*Türkiye*
Phone: +90 222 239 29 79 E-mail: tanerulusbuca@gmail.com
Accepted Date: 14.09.2020 **Available Online Date:** 03.01.2021

DOI:10.14744/AnatolJCardiol.2020.44082

Anatol J Cardiol 2021; 25: 129-38
DOI:10.14744/AnatolJCardiol.2020.44082

HIGHLIGHTS

- Genetic variants may be associated with AF and the success of catheter ablation for AF in Turkish patients.
- Four single nucleotide polymorphisms (SNPs) in PITX2 gene are strongly associated with AF.
- One SNP in CAV1 gene may predict long-term atrial tachyarrhythmia recurrence after catheter ablation for AF.

etal proteins. Single nucleotide polymorphisms (SNPs) in the *pituitary homeobox 2 (PITX2),* the zinc finger homeobox 3 (ZFHX3), *KCNN3, caveolin-1 (CAV1), T-box 5 (TBX5),* and SCN10A have been shown to be associated with AF in the Western and Asian populations (5-9). Several past studies have demonstrated that SNPs in the *PITX2, ZFHX3, soluble epoxide hydrolase 2 (EPHX2), and transforming growth factor beta-1 (TGF-ß1)* are associated with the success of catheter ablation for AF management (10-14), while others have not shown such a relationship (8,15). In a large-scale study, racial differences have also been shown to be a risk factor for AF in patients without any existing cardiovascular comorbidities (16). This finding suggests that genetic factors for AF development differ among communities. However, there is a paucity of data regarding genetic predictors related to AF in a Turkish population. In the light of these data, we investigated whether 11 SNPs in the *PITX2, ZFHX3, EPHX2, CAV1, TBX5, TGF-ß1*, and *SCN10A* are related to AF occurrence and whether these SNPs can predict long-term recurrence of AF after catheter ablation in a Turkish population.

Methods

Study population

In this prospective study, 245 consecutive patients with paroxysmal or persistent AF and 50 age- and sex-matched controls of age >18 years attending the Eskişehir Osmangazi University and Hacettepe University Hospitals between June 2016 and January 2019 were enrolled. A subgroup analysis was performed to determine the predictors of atrial tachyarrhythmia (ATa) recurrence in 128 patients who underwent catheter ablation for PVI using second-generation cryoballoon (CB2). The flow chart of the study protocol is illustrated in Figure 1. The conditions of paroxysmal and persistent AF (2) and HF with reduced left ventricular ejection fraction (LVEF) (17) were defined in accordance with the recent guidelines on the same. Alcohol intake was defined as up to 1 drink/day for women and up to 2 drinks/day for men (18). In all patients, transthoracic echocardiography was performed to evaluate the LVEF, valvular pathology, and the internal dimensions in accordance with the recommended guidelines (19). The exclusion criteria for the study were the presence of severe valvular disease, severe left atrial (LA) enlargement (≥55 mm), pre-procedural significant coronary artery disease or acute coronary syndrome, cardiac surgery within the previous 3 months, reversible causes of AF

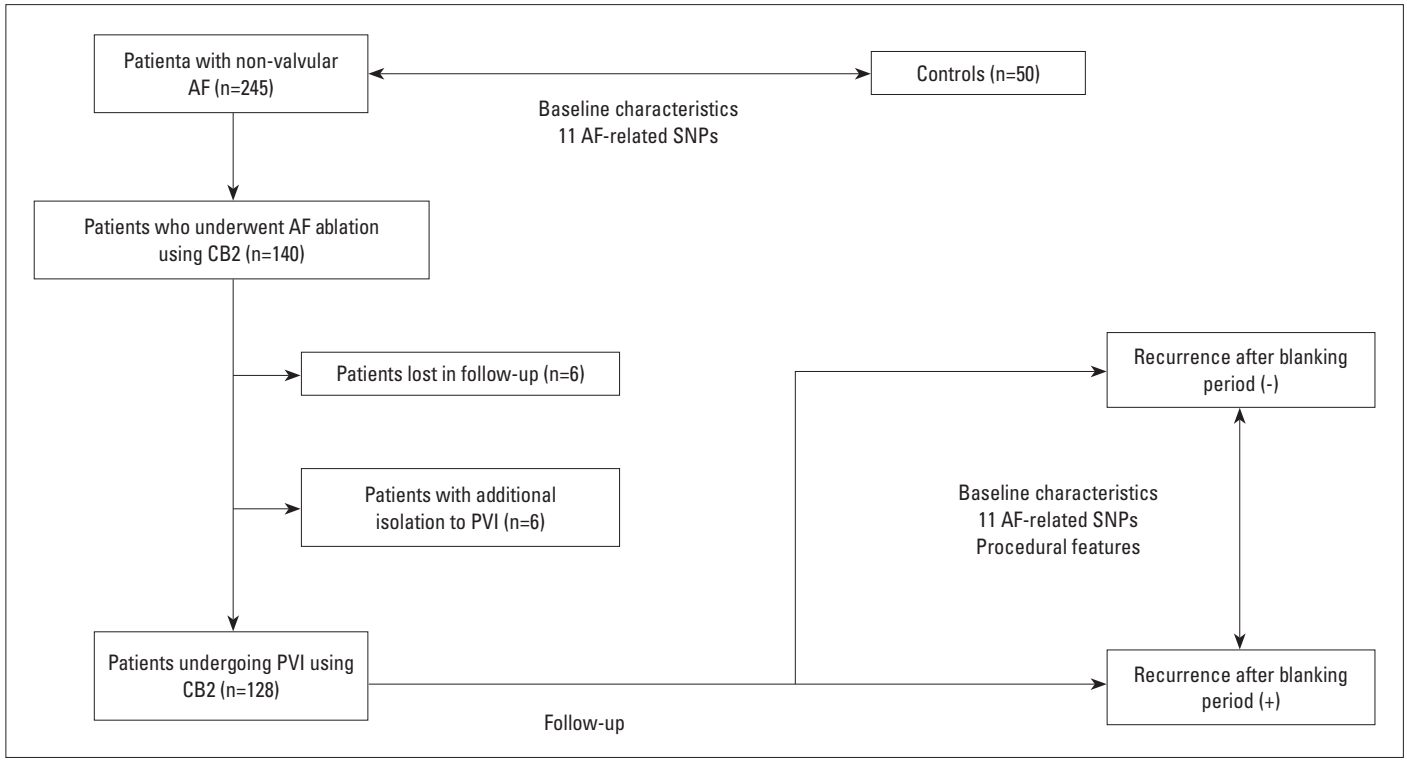

Figure 1. Flow chart of the study
AF - atrial fibrillation, CB2 - second-generation cryoballoon, PVI - pulmonary vein isolation, SNP - single nucleotide polymorphism

such as active hyperthyroidism, severe disease with life expectancy of <1 year, or pregnancy. All patients accepted genetic testing and provided a written informed consent. The study was approved by the Institutional Local Ethics Committee. The study protocol complied with the guidelines of the Declaration of Helsinki.

Genotyping

We selected 11 SNPs (Table 1) that were associated with AF in other world communities (3-13). We genotyped all participants for these SNPs. Genomic DNA was extracted from the whole blood of patients by using a DNA extraction kit (QIAamp DNA Blood Mini Kit, Qiagen Inc., Valencia, CA, USA), according to the manufacturer's recommendations. SNPs in PITX2, ZFHX3, EPHX2, CAV1, TBX5, TGF-1, and SCN10A were studied by using the SnapShot technique. SnapShot reactions were undertaken as recommended by the manufacturer. Electrophoresis of amplified PCR products related to these polymorphism regions was performed on the ABI 3130 Genetic Analyzer, and the data were analyzed by using the GeneMapper 4.0 Software (Applied Biosystems, Life Technologies, CA, USA).

Catheter ablation

All antiarrhythmic drugs were discontinued for at least 5 half-lives prior to the procedure. Transesophageal echocardiography was performed in all patients who underwent catheter ablation to assess the interatrial septum and eliminate the presence of thrombus in the LA or LA appendage within 24 h before starting the procedure. The procedure was performed under conscious sedation obtained with dexmedetomidine or midazolam and fentanyl boluses. The PVI using CB2 was performed as described previously (18). Briefly, a 6-F decapolar catheter (St. Jude Medical) was inserted into the coronary sinus (CS) and a 6-F pigtail catheter (Alvision™) was inserted into the aortic root. A single trans-septal (TS) puncture was performed from the right femoral vein using a TS needle (BRK-1™; St. Jude Medical) and an 8.5-F TS sheath (SL0; St. Jude Medical) was inserted into the LA. The TS sheath was replaced with a 15-F steerable sheath (FlexCath Advance, Medtronic Inc., Minneapolis, MN, USA) over the wire. After LA access, intravenous unfractionated heparin was administered at a dose of 100 U/kg, followed by administration of repeated boluses to maintain the activated clotting time of 300–350 sn.

Table 1. Genotype frequency

Chr band	Nearest gene	SNP	Genotype frequency					
			AF (–) (n, %)	AF (+) (n, %)	AF (–) (n, %)	AF (+) (n, %)	AF (–) (n, %)	AF (+) (n, %)
4q25	PITX2	rs2200733	CC 24 (48.0)	CC 142 (58.0)	CT 18 (36.0)	CT 80 (32.7)	TT 8 (16.0)	TT 23 (9.4)
4q25	PITX2	rs10033464	GG 24 (48.0)	GG 48 (19.6)	GT 26 (52.0)	GT 158 (64.5)	TT 0 (0)	TT 39 (15.9)
4q25	PITX2	rs6838973	CC 33 (66.0)	CC 101 (41.2)	CT 13 (26.0)	CT 131 (53.5)	TT 4 (8.0)	TT 13 (5.3)
4q25	PITX2	rs3853445	TT 29 (58.0)	TT 54 (22.0)	TC 14 (28.0)	TC 127 (51.8)	CC 7 (14.0)	CC 64 (26.1)
4q25	PITX2	rs17570669	AA 33 (66.0)	AA 58 (23.7)	AT 13 (26.0)	AT 93 (38.0)	TT 4 (8.0)	TT 94 (38.4)
16q22	ZFHX3	rs2106261	CC 15 (30.0)	CC 39 (15.9)	CT 24 (48.0)	CT 176 (71.8)	TT 11 (22.0)	TT 30 (12.2)
8p21	EPHX2	rs751141	GG 41 (82.0)	GG 156 (63.7)	GA 9 (18.0)	GA 76 (31.0)	AA 0 (0)	AA 13 (5.3)
7q31	CAV1	rs3807989	AA 26 (52.0)	AA 59 (24.1)	AG 24 (48.0)	AG 147 (60.0)	GG 0 (0)	GG 39 (15.9)
12q24	TBX5	rs10507248	GG 18 (36.0)	GG 76 (31.0)	GT 29 (58.0)	GT 130 (53.1)	TT 3 (6.0)	TT 39 (15.9)
19q13	TGF-1	rs1800469	GG 13 (26.0)	GG 49 (20.0)	GA 37 (74.0)	GA 91 (37.1)	AA 0 (0)	AA 105 (42.9)
3q22	SCN10A	rs6795970	AA 23 (46.0)	AA 125 (51.0)	AG 20 (40.0)	AG 78 (31.8)	GG 7 (14.0)	GG 42 (37.1)

AF - atrial fibrillation, Chr - chromosome, SNP - single nucleotide polymorphism

Anatol J Cardiol 2021; 25: 129-38
DOI:10.14744/AnatolJCardiol.2020.44082

A second-generation 28-mm CB2 catheter (Arctic Front Advance™, Medtronic) was used for PVI. A spiral inner-balloon mapping catheter (Achieve AdvanceTM mapping catheter 20-mm, Medtronic) was used to display the PV signals. Following the insertion of the spiral catheter into the PV, the CB2 catheter was positioned in the PV antrum region. The complete occlusion of the PV ostium was verified by the administration of 50% diluted contrast medium. A 180–240 s freezing cycle was applied for each targeted PV. If the PV potentials did not disappear within 60 s after starting to freeze or if early PV reconnection occurred, bonus freezing was applied. While freezing the right-sided PVs, the decapolar catheter was placed in the superior vena cava to avoid the occurrence of phrenic nerve paralysis. The phrenic nerve stimulation was performed with a 1500–2000-ms cycle and 12–15-mA output and monitored by intermittent fluoroscopy and direct palpation of the right hemi-diaphragmatic jump. Acute procedural success was defined as the elimination or dissociation of all visible PV potentials. The PVI was confirmed by CS and the spiral catheter stimulations.

Post-procedural management and follow-up

The transthoracic echocardiography was repeated immediately after the procedure to exclude the presence of pericardial effusion. Oral anticoagulation was started on the day after the procedure unless pericardial effusion was detected, and it was continued for at least 3 months thereafter. Antiarrhythmic drugs were continued for 3 months after the procedure. All patients were followed-up for at least 18–24 h with continuous electrocardiography monitoring after the procedure. Any ATa episode (such as AF, atrial flutter, or atrial tachycardia) that lasted for at least 30 s was defined as recurrence. Early recurrence was defined as recurrence within a 3-month blanking period (18). The patients were followed-up with physical examination and 24-h Holter recording at the outpatient clinics at the 3th, 6th, and 12th months and at every 1 year thereafter. If the patients experienced symptoms related to ATa recurrence or procedural complications, they were evaluated earlier.

Statistical analysis

Continuous data were expressed as the mean±standard deviation for normally distributed variables or as the median [25th, 75th percentiles] for non-normally distributed variables, and then compared using Student's t-test or Mann-Whitney U test, respectively. Categorical variables were compared using the Chi-square test. The effects of genotypes were analyzed under dominant (wild type vs. heterozygous and homozygous variant), additive (wild type vs. heterozygous variant vs. homozygous variant), and recessive (homozygous variant vs. heterozygous variant and wild type) models, as previously described (11).

Logistic regression analysis was used to determine the relationship of genotypes with AF in 3 different models, and the odds ratios (ORs) and their 95% confidence intervals (CIs) were accordingly calculated. Variables with p<0.05 were included in the binary logistic regression analysis to identify factors showing a significant relationship with AF. Our study showed >97% power in determining the relationship of AF with major alleles in rs10033464, rs6838973, rs3853445, and rs17570669. In addition, multiple Cox regression analyses were performed to evaluate the relationship between genetic variants and ATa recurrence after the blanking period on the patient subgroup who underwent PVI, and their ORs and 95% CIs were accordingly calculated. Multiple Cox regression model was used to test the independent associations of clinical variables and genetic factors with long-term ATa recurrence after ablation. Kaplan-Meier analysis was used to determine the relationships between significant genetic variants and recurrence.

Statistical analyses were performed using the SPSS statistical software (IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp., USA). A two-tailed p<0.05 was considered statistically significant.

Results

Clinical features

The median CHA2DS2-VASc score was 2.00 (1.00–3.00), while the median AF duration was 25.00 (18.00–36.00) months in the AF group. In addition, 160 patients (65.3%) showed paroxysmal AF and 85 patients (34.7%) showed persistent AF in the AF group. There were 20 HF patients (8.2%) with reduced LVEF value in the AF group, while there were no such individuals in the control group. There was no difference between the AF group and the control group in terms of age, sex, and the body mass index. The history of hypertension was longer in the AF group than in the control group, although the difference was not statistically significant (58.8% vs. 44.0, p=0.055). The estimated glomerular filtration rate (84.37±23.53 vs. 92.46±24.00, p=0.028) and LVEF [60.00 (60.00–65.00) vs. 64.00 (60.00–65.00), p<0.001] were lower while the LA diameter was greater [40.00 (37.00–44.00) vs. 36.00 (34.00–38.00), p<0.001] in the AF patients than in the controls. The baseline characteristics of the patients are presented in Table 2.

Relationships among AF, clinical features, and genetic variants

We analyzed 11 SNPs by using the Snapshot technique to identify the associated SNPs in a Turkish AF population. The genotype frequencies of the study population are presented in Table 1. In the dominant and additive models, rs10033464 (p<0.001 and p=0.001), rs6838973 (p=0.002 and p=0.001, respectively), rs3853445 (p<0.001 and p<0.001, respectively), rs17570669 variants (p<0.001 and p<0.001, respectively) in *PITX2*, rs2106261 variant in *ZFHX3* (p=0.021 and p=0.006, respectively), rs751141 variant in *EPHX2* (p=0.015 and p=0.043, respectively), and rs3807989 variant in *CAV1* (p<0.001 and p=0.002, respectively) were significantly associated with AF. In the recessive model, rs17570669 variant in *PITX2* was significantly associated with AF (p<0.001). Relationships between 11 SNPs and AF in the univariate analysis are presented in Table 3.

Table 2. Baseline characteristics of the study population

Parameter	Controls (n=50)	AF (n=245)	*P*
Age (years)	58.50 (52.75-67.00)	62.00 (53.00-70.00)	0.250
Sex (male) (n, %)	20 (40.0)	110 (44.9)	0.525
BMI (kg/m^2)	27.21 (24.87-29.75)	27.60 (25.71-30.47)	0.472
Hypertension (n, %)	22 (44.0)	144 (58.8)	0.055
Diabetes mellitus (n, %)	7 (14.0)	56 (22.9)	0.164
Coronary artery disease (n, %)	5 (10.0)	38 (15.5)	0.314
Current smoking (n, %)	5 (10.0)	27 (11.0)	0.833
Alcohol intake (n, %)	2 (4.0)	6 (2.4)	0.627
Hemoglobin (g/dL)	14.01±1.39	13.59±1.60	0.087
eGFR (mL/min/1.73 m^2)	92.46±24.00	84.37±23.53	**0.028**
LA dimeter (mm)	36.00 (34.00-38.00)	40.00 (37.00-44.00)	**<0.001**
LVEF (%)	64.00 (60.00-65.00)	60.00 (60.00-65.00)	**<0.001**

AF - atrial fibrillation, BMI - body mass index, eGFR - estimated glomerular filtration rate, LA - left atrium, LVEF - left ventricular ejection fraction

The results of binary logistic regression analyses revealed associations among AF, SNPs, and clinical features (Table 4). Four variants at the PITX2 locus were significantly associated with AF (rs10033464_T: OR 3.29, 95% CI: 1.38–7.82, p=0.007; rs6838973_T: OR 3.06, 95% CI 1.36–6.87, p=0.007; rs3853445_C: OR 2.84, 95% CI: 1.27–6.36, p=0.011; rs17570669_T: OR 4.03, 95% CI: 1.71–9.51, p=0.001) in the dominant model. In addition, the LA diameter was significantly associated with AF (OR: 1.16, 95% CI: 1.06–1.27, p=0.001).

Procedural features and complications in patients undergoing catheter ablation

The mean age of 128 patients undergoing PVI was 56.71±10.85, 59 (46.1%) of them were men, 96 (75.0%) had paroxysmal AF, 15 (11.7%) had coronary artery disease, and 8 (6.3%) had systolic HF. A total of 478 PVs including 32 left common trunk and 2 right common trunks were detected. Overall, 474 of PVs (99.1%) were isolated successfully. The total procedural and fluoroscopic times were 72.00 (60.00–90.00) min and 13.50 (4.00–19.00) min, respectively. The median freezing application was 2.0 (1.0–2.7) for the left superior PV, 2.0 (1.0–2.0) for the left inferior PV, 2.0 (1.0–2.0) for the right superior PV, 1.0 (1.0–2.0) for the right inferior PV, 2.0 (2.0–3.0) for the left common trunk, and 1.5 (0.7–1.7) for the right common trunk.

No case of procedure-related death, stroke/transient ischemic attack, or PV stenosis occurred. Access site complications were observed in 6 (4.7%) patients. Among these, 4 cases (3.1%) were of inguinal hematoma, 1 (0.8%) of retroperitoneal hematoma, and another 1 (0.8%) of femoral arteriovenous fistula. The patient with

Table 3. Relationship between 11 SNPs and AF in univariate analysis

SNP	Reference allele	AF related allele	Dominant model		Additive model		Recessive model	
			OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
rs2200733	C	T	0.67 (0.36-1.23)	0.197	0.75 (0.38-1.46)	0.402	0.54 (0.22-1.29)	0.170
rs10033464	G	T	3.78 (2.00-7.17)	**<0.001**	3.03 (1.59-5.77)	**0.001**	Not analyzed	
rs6838973	C	T	2.76 (1.46-5.23)	**0.002**	3.29 (1.64-6.57)	**0.001**	0.64 (0.20-2.06)	0.460
rs3853445	T	C	4.88 (2.58-9.24)	**<0.001**	4.87 (2.38-9.93)	**<0.001**	2.17 (0.93-5.07)	0.073
rs17570669	A	T	6.25 (3.25-12.05)	**<0.001**	13.37 (4.50-39.69)	**<0.001**	7.15 (2.49-20.53)	**<0.001**
rs2106261	C	T	2.26 (1.13-4.53)	**0.021**	2.82 (1.35-5.86)	**0.006**	0.49 (0.22-1.06)	0.073
rs751141	G	A	2.59 (1.20-5.59)	**0.015**	2.21 (1.02-4.80)	**0.043**	Not analyzed	
rs3807989	A	G	3.41 (1.82-6.39)	**<0.001**	2.69 (1.43-5.07)	**0.002**	Not analyzed	
rs10507248	G	T	1.25 (0.66-2.36)	0.492	3.07 (0.85-11.09)	0.086	2.96 (0.87-10.00)	0.080
rs1800469	G	A	1.40 (0.69-2.84)	0.344	0.65 (0.31-1.34)	0.246	Not analyzed	
rs6795970	A	G	0.81 (0.44-1.50)	0.518	1.53 (0.60-3.93)	0.369	1.27 (0.53-3.01)	0.587

AF - atrial fibrillation, CI - confidence interval, OR - odds ratio, SNP - single nucleotide polymorphism

Anatol J Cardiol 2021; 25: 129-38
DOI:10.14744/AnatolJCardiol.2020.44082

Table 4. Binary logistic regression analysis of clinical features and SNPs associated with AF

Risk factor	Beta	OR (95% CI)	*P*
Hypertension	-0.092	0.91 (0.39-2.13)	0.831
eGFR (mL/min/1.73 m²)	-0.004	0.99 (0.97-1.01)	0.696
LA dimeter (mm)	0.150	**1.16 (1.06-1.27)**	**0.001**
LVEF (%)	-0.109	0.89 (0.79-1.00)	0.061
rs10033464_T	1.193	**3.29 (1.38-7.82)**	**0.007**
rs6838973_T	1.119	**3.06 (1.36-6.87)**	**0.007**
rs3853445_C	1.046	**2.84 (1.27-6.36)**	**0.011**
rs17570669_T	1.396	**4.03 (1.71-9.51)**	**0.001**
rs2106261_T	-0.329	0.71 (0.28-1.79)	0.479
rs751141_A	0.587	1.79 (0.69-4.63)	0.224
rs3807989_G	0.711	2.03 (0.92-4.46)	0.076

AF - atrial fibrillation, eGFR - estimated glomerular filtration rate, LA - left atrium, LVEF - left ventricular ejection fraction, SNP - single nucleotide polymorphism

femoral arteriovenous fistula underwent surgical repair, while other access site complications resolved with medical therapy. One patient (0.8%) developed cardiac tamponade requiring pericardiocentesis and another one (0.8%) developed phrenic nerve palsy. Phrenic nerve injury developed at 30 s in this patient, at which time the temperature was –45°C. Phrenic nerve paralysis continued at 12 months after the procedure in this patient.

Follow-up of patients undergoing catheter ablation

Patients undergoing PVI were followed-up for 30.50 (21.25–41.00) months. Early recurrence was noted in 12 patients (9.3%). Meanwhile, 8 of the patients returned to sinus rhythm spontaneously, sinus rhythm was achieved with electrical cardioversion in 3 patients and pharmacological cardioversion in 1 patient. Among the 46 patients (35.1%) who developed ATa recurrence, 19 (41.3%) were followed-up medically, 24 (52.1%) underwent RF catheter ablation, and 3 (6.5%) underwent catheter ablation via CB2. The third procedure was performed in 3 of the redo-ablation patients by using the RF technique. The mean number of procedures was 1.23±0.47. ATa-free survival was 78.9% after multiple ablations (101 of 128 patients).

Clinical outcomes of patients undergoing catheter ablation

The clinical, demographic, and procedural characteristics of patients who underwent catheter ablation according to the presence of long-term recurrence are given in Table 5.

Table 5. Patient characteristics of those without and with ATa recurrence after the blanking period

	Recurrence (–) (n=82)	Recurrence (+) (n=46)	*P*
Age (years)	58.00 (48.00–62.25)	60.00 (52.75–64.25)	0.323
Sex (Male)	40 (48.8)	19 (41.3)	0.416
BMI (kg/m²)	27.52 (25.71–29.01)	28.03 (26.40–32.22)	0.058
Hypertension (n, %)	39 (47.6)	31 (67.4)	**0.031**
Diabetes mellitus (n, %)	15 (18.3)	10 (21.7)	0.637
Coronary artery disease (n, %)	11 (13.4)	4 (8.7)	0.426
HF with reduced LVEF (n, %)	5 (6.1)	3 (6.5)	1.000
Current smoking (n, %)	15 (18.3)	6 (13.0)	0.442
Alcohol intake (n, %)	3 (3.7)	2 (4.3)	1.000
CHA2DS2-VASc score	1.50 (1.00–2.25)	2.00 (1.00–3.00)	0.338
AF duration (months)	24.00 (18.00–28.00)	30.00 (24.00–36.25)	**<0.001**
Persistent AF (n, %)	18 (22.0)	14 (30.4)	0.288
Hemoglobin (g/dL)	13.47±1.44	13.67±1.65	0.475
eGFR (mL/min/1.73 m²)	90.22±19.43	87.01±18.56	0.364
LA diameter (mm)	38.00 (36.00–40.00)	42.00 (36.75–45.00)	**0.009**
LVEF (%)	60.00 (60.00–65.00)	61.50 (60.00–65.00)	0.362
PV anatomy			
Common trunk PV (n, %)	17 (20.7)	16 (34.8)	0.081
Accessory PV (n, %)	12 (14.6)	9 (19.6)	0.470
Procedure time (min)	75.00 (60.00–90.00)	65.50 (54.00–86.25)	0.123
Fluoroscopy time (min)	14.00 (8.00–19.25)	12.50 (3.00–17.00)	0.110
Early recurrence (n, %)	4 (4.9)	8 (17.4)	**0.027**
Follow-up (months)	27.00 (19.75–40.25)	33.00 (23.75–43.25)	0.108

AF - atrial fibrillation, ATa - atrial tachyarrhythmia, BMI - body mass index, eGFR - estimated glomerular filtration rate, HF - heart failure, LA - left atrium, LVEF - left ventricular ejection fraction, PV - pulmonary vein

Hypertension was more frequent (67.4% vs. 47.6%, p=0.031) and early recurrence was higher [17.4% vs 2.4, p=0.004] in patients with long-term recurrence as compared to that in those without long-term recurrence. Persistent AF was more frequent in those with recurrence than in those without it (30.4% vs. 22.0%), although the difference was not statistically significant (p=0.288). AF duration was longer [30.00 (24.00–36.25) vs. 24.00 (18.00–28.00), p<0.001] and the LA diameter was greater [42.00 (36.75–45.00) vs. 38.00 (36.00–40.00), p=0.009] in patients with long-term recurrence than in those without it.

No significant difference was noted between patients without and with long-term recurrence with regard to the total procedure time, fluoroscopy time, and PV anatomy (p>0.05) (Table 5). In addition, the freezing numbers were similar between patients without and with long-term recurrence for the left superior PV (p=0.099), left inferior PV (p=0.713), right superior PV (p=0.142), right inferior PV (p=0.202), and left common trunk (p=0.684).

The relationships between 11 SNPs and ATa recurrence after the blanking period in univariate analysis are presented in Table 6. In the additive model, rs3853445 variant in *PITX2* was significantly associated with recurrence after the blanking period (p=0.014). In the dominant and additive models, the rs751141 variant in *EPHX2* (p=0.032 and p=0.016) and the rs3807989 variant in *CAV1* (p=0.044 and p=0.038) were significantly associated with long-term recurrence. The results of multiple Cox regression analysis for the relationships among AF, SNPs, and clinical features are depicted in Table 7. One variant in *CAV1* (rs3807989_G: OR 4.50, 95%CI 1.04–19.31, p=0.043) in the additive model and early recurrence (OR: 8.06, 95%CI: 2.12–30.55, p=0.002) predicted long-term ATa recurrence after catheter ablation. The Ata-free survival was significantly lower in patients with the AG genotype (heterozygous haplotype) [34.00 (30.00–38.00) months] than in those with the AA genotype (wild-type) [43.00 (38.00–48.00) months] (long-rank p=0.028) (Fig. 2).

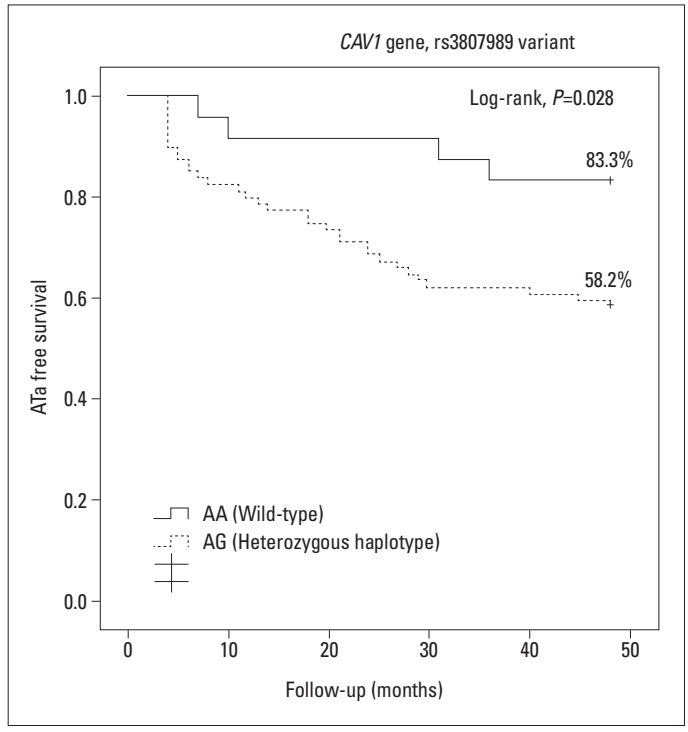

Figure 2. Kaplan-Meier curve illustrating the relationship between ATa-free survival after the blanking period and the risk allele of rs3807989 in *CAV1* [83.3% in wild-type (AA) vs. 58.2% in heterozygous haplotype (AG), log-rank *P*=0.028]
ATa - atrial tachyarrhythmia

Table 6. Genotype distribution of the studied SNPs among subjects subdivided according to ATa recurrence after the blanking period

SNP	Recurrence (–)* (%)	Recurrence (+)* (%)	Dominant model		Additive model		Recessive model	
			OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
rs2200733	47.6/36.6/15.9	34.8/43.5/21.7	1.65 (0.90–3.03)	0.104	1.63 (0.84–3.16)	0.141	1.27 (0.63–2.57)	0.492
rs10033464	19.5/72.0/8.5	21.7/69.6/8.7	0.96 (0.47–1.94)	0.917	0.95 (0.46–1.94)	0.896	1.13 (0.40–3.15)	0.816
rs6838973	40.2/50.0/9.8	30.4/58.7/10.9	1.35 (0.27–2.53)	0.349	1.36 (0.71–2.60)	0.342	0.98 (0.38–2.48)	0.965
rs3853445	36.6/34.1/29.3	21.7/60.9/17.4	1.88 (0.93–3.80)	0.076	2.47 (1.19–5.09)	**0.014**	0.57 (0.26–1.23)	0.154
rs17570669	40.2/32.9/26.8	34.8/34.8/30.4	1.31 (0.71–2.40)	0.380	1.30 (0.65–2.60)	0.459	1.14 (0.61–2.14)	0.671
rs2106261	24.4/72.0/3.7	19.6/71.7/8.7	1.38 (0.66–2.86)	0.384	2.83 (0.86–9.28)	0.085	2.04 (0.73–5.71)	0.173
rs751141	79.3/18.3/2.4	60.9/39.1/0	1.91 (1.05–3.46)	**0.032**	2.07 (1.14–3.75)	**0.016**	Not analyzed	
rs3807989	24.4/56.1/19.5	8.7/71.7/19.6	2.87 (1.03–8.01)	**0.044**	3.00 (1.06–8.48)	**0.038**	1.01 (0.48–2.09)	0.980
rs10507248	18.3/53.7/28.0	23.9/52.2/23.9	0.78 (0.39–1.54)	0.487	0.80 (0.39–1.63)	0.543	0.87 (0.44–1.73)	0.708
rs1800469	28.0/52.4/19.5	32.6/50.0/17.4	1.09 (0.59–2.03)	0.768	0.92 (0.48–1.77)	0.821	0.91 (0.42–1.96)	0.826
rs6795970	51.2/17.1/31.7	39.1/30.4/30.4	1.41 (0.78–2.55)	0.253	1.78 (0.88–3.59)	0.104	0.93 (0.50–1.76)	0.844

*: Wild type/polymorphic heterozygous allele/polymorphic homozygous allele. ATa - atrial tachyarrhythmia; MAF - minor allele frequency; SNP - single nucleotide polymorphism

Anatol J Cardiol 2021; 25: 129-38
DOI:10.14744/AnatolJCardiol.2020.44082

Table 7. Parameters predicting long-term ATa recurrence after catheter ablation for AF using multiple Cox regression analysis

	Univariate			Multivariate		
	Beta	**OR (95% CI)**	***P***	**Beta**	**OR (95% CI)**	***P***
Hypertension (n, %)	0.66	1.93 (1.04–3.58)	**0.036**	–0.21	0.81 (0.36–1.78)	0.601
Persistent AF	0.30	1.35 (0.72–2.54)	0.338	0.80	2.23 (0.96–5.14)	0.059
AF duration (months)	0.02	1.02 (1.01–1.03)	**0.001**	0.01	1.00 (0.99–1.02)	0.435
LA diameter (mm)	0.09	1.10 (1.03–1.17)	**0.002**	0.07	1.07 (0.98–1.17)	0.101
Early recurrence (n, %)	1.30	3.69 (1.71–7.98)	**0.001**	2.08	8.06 (2.12–30.55)	**0.002**
SNP						
rs3853445_C	0.90	2.47 (1.19–5.09)	**0.014**	0.56	1.76 (0.64–4.79)	0.267
rs751141_A	0.72	2.07 (1.14–3.75)	**0.016**	0.21	1.24 (0.53–2.87)	0.616
rs3807989_G	1.10	3.00 (1.06–8.48)	**0.038**	1.50	4.50 (1.04–19.31)	**0.043**

AF - atrial fibrillation, ATa - atrial tachyarrhythmia, CI - confidence interval, LA - left atrium, OR - odds ratio, SNP - single nucleotide polymorphism

Discussion

In this prospective, multicenter study, we examined the relationship of 11 SNPs found to be associated with AF occurrence in the Western and Asian populations with AF and ATa recurrence after catheter ablation for AF in a Turkish population. According to our study: 1) there are 4 risk alleles in *PITX2* (namely, rs10033464, rs6838973, rs3853445, and rs17570669) that are significantly associated with AF. 2) The risk allele rs3807989 in *CAV1* is predictive for long-term ATa recurrence after catheter ablation by CB2 for AF. 3) Early recurrence is significantly associated with long-term recurrence after catheter ablation for AF.

Genetic variants on chromosome 4q25

GWAS have demonstrated that AF is a polygenic condition (20). Such studies have identified the common genetic variants associated with AF, called the SNPs. Genetic variants are most commonly associated with AF among the Europeans, Asians, and African-Americans, where the SNPs occur on chromosome 4q25/*PITX2* (5-9, 21). The PITX2 is a homeodomain transcription factor that plays an important role in the right-left asymmetrical development of the heart, the suppression of the sinus node formation in the LA, and the formation of the PV myocardial sleeves (22). Our results are compatible with the data from other communities. We found that 4 SNPs (rs10033464, rs6838973, rs3853445, and rs17570669) on chromosome 4q25/*PITX2* were significantly associated with AF in the Turkish population. Our findings once again highlight the importance of PV sleeves in the AF development.

Other genetic variants

We found that rs2106261 locus in *ZFHX3*, rs3807989 locus in *CAV1*, and rs751141 locus in *EPHX2* was associated with AF in univariate analysis, although rs2106261, rs751141, and rs3807989 are not independent predictors of AF in binary logistic regression analysis. Moreover, we did not find any associations between rs10507248 at *TBX5*, rs6795970 at *SCN10A*, and rs1800469 at *TGF-ß1* and AF.

Clinical conditions associated with AF

AF is the one of the most common causes of stroke, with left ventricular systolic dysfunction recorded in 20–30% of all AF patients. The LA enlargement is another condition related to AF (2). We found that the AF group has less LVEF, less eGFR, and greater LA diameter. These findings are compatible with those reported in the literature (2). The impaired kidney function in the AF group can be explained by more HT and HF history. Of these parameters, only LA diameter had a significant relationship with AF.

Genetic variants and recurrence after catheter ablation

We found that the rs3807989 SNP in *CAV1* predicted the long-term recurrence after catheter ablation. Other SNPs were not significantly associated with long-term recurrence. *CAV-1* encodes for caveolin-1 (*CAV-1*) (23). CAV-1 is the basic structural component of caveolae, which is composed of 50–100-nm plasma membrane vesicles, and is involved in cell signaling (24). CAV-1 is expressed in atrial cardiomyocytes (25) and plays an important role in the regulation of ionic currents by affecting the functions of ion channels such as Kir2.1, KCNH2, HCN4, Nav1.8, and Nav1.5 (26-30). In addition, CAV-1 is an inhibitor of the TGF-ß1 signaling pathway, which plays an important role in atrial fibrosis (31). The SNP rs3807989 is located in the second intron of CAV-1 (23). The major G allele of rs3807989 decreases the CAV-1 expression (loss of function) (32). As a result, the Na and K ion channel currents and the TGF-ß1 expression are affected; these changes are believed to increase the risk of developing AF (23, 32). Our findings may indicate the importance of cardiac ion channels and atrial fibrosis in the development of long-term recurrence after catheter ablation for AF.

In addition, our results highlight the importance of early recurrence after catheter ablation as a long-term recurrence predictor, which is consistent with the reports of previous studies (10, 18). The patients who developed recurrence after catheter ablation had a history of hypertension, greater LA diameter, and longer AF duration. Although statistically significant at the border, BMI was higher in patients who developed recurrence. These abovementioned factors may be attributed to the fact that other SNPs were not found to be predictive for long-term recurrence after catheter ablation in our study. Finally, the procedural characteristics such as freezing number per PV, PV anatomy, total procedural time, and fluoroscopy time were not associated with long-term ATa recurrence after catheter ablation. These findings may indicate that genetic factors are important in the development of recurrence after catheter ablation.

In our study, we conducted a standard procedure involving PVI with CB2 in all patients. In the study of Miyazaki et al. (10), additional ablation was performed with 8-mm conventional cryocatheter if PVI was not achieved 3 times after freezing. In the studies of Choi et al. (8) and Husser et al. (11, 12), additional linear lesions were created in patients with persistent AF. Kiliszek et al. (15) reported the isolation of vena cava superior. In these studies, the application of different ablation strategies may have affected the study outcomes. In addition, in our study, the follow-up period of patients was longer than that reported by several other past studies on this subject (median ßduration: 30.5 months). For instance, this period was 6 months in the study of Husser et al. (11).

The reports of the abovementioned studies demonstrate that several variants in genes encoding transcription factors and ion channel proteins are associated with AF and recurrence after catheter ablation. In these studies, genetic variants associated with AF differed according to the ethnic status/race. In our study, PITX2 associated with AF is a transcription factor, while CAV1 associated with long-term recurrence after catheter ablation is an ion channel protein. These findings can be used to identify individuals in whom the measurements such as blood pressure control and weight control can be applied more strictly to reduce the frequency of AF development. These features may also help define individuals who are most likely to benefit from PVI.

Study limitations

This study comprised 2 centers from Turkey, but does not represent the entire Turkish population. The study has a nonrandomized prospective design. However, all patients were included in the study consecutively to overcome any possible selection bias. The low frequency of the genetic variant in the study population may explain the absence of the relationships mentioned above. Finally, as recurrences were assessed by 24-h Holter monitoring, asymptomatic nonsustained ATa episodes may have been overlooked.

Conclusion

SNPs in genes encoding transcription factors and ion channel proteins may be associated with AF and ATa recurrence after catheter ablation for AF in Turkish populations. Four genetic variants in *PITX2* are strongly associated with AF. One genetic variant in *CAV1* may predict long-term ATa recurrence after catheter ablation.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – T.U., M.D., P.M., F.Y., K.U.M., B.G., O.Ç., E.E.G., S.Arslan, S.Artan, Ö.A., E.Ç., H.Y., U.C., K.A.; Design – T.U., M.D., P.M., F.Y., K.U.M., B.G., O.Ç., E.E.G., S.Arslan, S.Artan, Ö.A., E.Ç., H.Y., U.C., K.A.; Supervision – T.U., M.D., P.M., F.Y., K.U.M., B.G., O.Ç., E.E.G., S.Arslan, S.Artan, Ö.A., E.Ç., H.Y., U.C., K.A.; Fundings – T.U., M.D., P.M., F.Y., K.U.M., B.G., O.Ç., E.E.G., S.Arslan, S.Artan, Ö.A., E.Ç., H.Y., U.C., K.A.; Materials – T.U., M.D., P.M., F.Y., K.U.M., B.G., O.Ç., E.E.G., S.Arslan, S.Artan, Ö.A., E.Ç., H.Y., U.C., K.A.; Data collection &/or processing – T.U., M.D., P.M., F.Y., K.U.M., B.G., O.Ç., E.E.G., S.Arslan, S.Artan, Ö.A., E.Ç., H.Y., U.C., K.A.; Analysis &/or interpretation – T.U., M.D., P.M., F.Y., K.U.M., B.G., O.Ç., E.E.G., S.Arslan, S.Artan, Ö.A., E.Ç., H.Y., U.C., K.A.; Literature search – T.U., M.D., P.M., F.Y., K.U.M., B.G., O.Ç., E.E.G., S.Arslan, S.Artan, Ö.A., E.Ç., H.Y., U.C., K.A.; Writing – T.U., M.D., P.M., F.Y., K.U.M., B.G., O.Ç., E.E.G., S.Arslan, S.Artan, Ö.A., E.Ç., H.Y., U.C., K.A.; Critical review – T.U., M.D., P.M., F.Y., K.U.M., B.G., O.Ç., E.E.G., S.Arslan, S.Artan, Ö.A., E.Ç., H.Y., U.C., K.A.

References

1. Weng LC, Preis SR, Hulme OL, Larson MG, Choi SH, Wang B, et al. Genetic Predisposition, Clinical Risk Factor Burden, and Lifetime Risk of Atrial Fibrillation. Circulation 2018; 137: 1027–38.
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS Eur Heart J 2016; 37: 2893–962.
3. Luik A, Kunzmann K, Hörmann P, Schmidt K, Radzewitz A, Bramlage P, et al. Cryoballoon vs. open irrigated radiofrequency ablation for paroxysmal atrial fibrillation: long-term FreezeAF outcomes. BMC Cardiovasc Disord 2017; 17: 135.
4. Fox CS, Parise H, D'Agostino RB Sr, Lloyd-Jones DM, Vasan RS, Wang TJ, et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA 2004; 291: 2851–5.
5. Gudbjartsson DF, Arnar DO, Helgadottir A, Gretarsdottir S, Holm H, Sigurdsson A, et al. Variants conferring risk of atrial fibrillation on chromosome 4q25. Nature 2007; 448: 353–7.
6. Mohanty S, Santangeli P, Bai R, Di Biase L, Mohanty P, Pump A, et al. Variant rs2200733 on chromosome 4q25 confers increased risk of atrial fibrillation: evidence from a meta-analysis. J Cardiovasc Electrophysiol 2013; 24: 155–61.
7. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, et al. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. Nat Genet 2012; 44: 670–5.

Anatol J Cardiol 2021; 25: 129-38
DOI:10.14744/AnatolJCardiol.2020.44082

8. Choi EK, Park JH, Lee JY, Nam CM, Hwang MK, Uhm JS, et al. Korean Atrial Fibrillation (AF) Network: Genetic Variants for AF Do Not Predict Ablation Success. J Am Heart Assoc 2015;4:e002046.
9. Liu L, Ebana Y, Nitta JI, Takahashi Y, Miyazaki S, Tanaka T, et al. Genetic Variants Associated With Susceptibility to Atrial Fibrillation in a Japanese Population. Can J Cardiol 2017; 33: 443–9.
10. Miyazaki S, Ebana Y, Liu L, Nakamura H, Hachiya H, Taniguchi H, et al. Chromosome 4q25 variants and recurrence after second-generation cryoballoon ablation in patients with paroxysmal atrial fibrillation. Int J Cardiol 2017; 244: 151–7.
11. Husser D, Adams V, Piorkowski C, Hindricks G, Bollmann A. Chromosome 4q25 variants and atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol 2010; 55: 747–53.
12. Husser D, Büttner P, Ueberham L, Dinov B, Sommer P, Arya A, et al. Association of atrial fibrillation susceptibility genes, atrial fibrillation phenotypes and response to catheter ablation: a gene-based analysis of GWAS data. J Transl Med 2017; 15: 71: 1–6.
13. Wutzler A, Kestler C, Perrot A, Loehr L, Huemer M, Parwani AS, et al. Variations in the human soluble epoxide hydrolase gene and recurrence of atrial fibrillation after catheter ablation. Int J Cardiol 2013; 168: 3647–51.
14. Cao H, Zhou Q, Lan R, Røe OD, Chen X, Chen Y, et al. A functional polymorphism C-509T in TGFß-1 promoter contributes to susceptibility and prognosis of lone atrial fibrillation in Chinese population. PLoS One 2014; 9: e112912.
15. Kiliszek M, Kozluk E, Franaszczyk M, Lodzinski P, Piatkowska A, Ploski R, et al. The 4q25, 1q21, and 16q22 polymorphisms and recurrence of atrial fibrillation after pulmonary vein isolation. Arch Med Sci 2016; 12: 38–44.
16. Dewland TA, Olgin JE, Vittinghoff E, Marcus GM. Incident atrial fibrillation among Asians, Hispanics, blacks, and whites. Circulation 2013; 128: 2470–7.
17. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129–200.
18. Canpolat U, Kocyigit D, Yalcin MU, Coteli C, Sener YZ, Oksul M, et al. Long-term outcomes of pulmonary vein isolation using second-generation cryoballoon during atrial fibrillation ablation. Pacing Clin Electrophysiol 2019; 42: 910–21.
19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015; 28: 1–39.
20. Bapat A, Anderson CD, Ellinor PT, Lubitz SA. Genomic basis of atrial fibrillation. Heart 2018; 104: 201–6.
21. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM, et al. Multi-ethnic genome-wide association study for atrial fibrillation. Nat Genet 2018; 50: 1225–33.
22. Feghaly J, Zakka P, London B, MacRae CA, Refaat MM. Genetics of Atrial Fibrillation. J Am Heart Assoc 2018; 7: e009884.
23. Jia W, Qi X, Li Q. Association Between Rs3807989 Polymorphism in Caveolin-1 (CAV1) Gene and Atrial Fibrillation: A Meta-Analysis. Med Sci Monit 2016; 22: 3961–6.
24. Razani B, Woodman SE, Lisanti MP. Caveolae: from cell biology to animal physiology. Pharmacol Rev 2002; 54: 431-67.
25. Cho WJ, Chow AK, Schulz R, Daniel EE. Caveolin-1 exists and may function in cardiomyocytes. Can J Physiol Pharmacol 2010; 88: 73-6.
26. Ambrosini E, Sicca F, Brignone MS, D'Adamo MC, Napolitano C, Servettini I, et al. Genetically induced dysfunctions of Kir2.1 channels: implications for short QT3 syndrome and autism-epilepsy phenotype. Hum Mol Genet 2014; 23: 4875–86.
27. Lin J, Lin S, Choy PC, Shen X, Deng C, Kuang S, et al. The regulation of the cardiac potassium channel (HERG) by caveolin-1. Biochem Cell Biol 2008; 86: 405–15.
28. Barbuti A, Scavone A, Mazzocchi N, Terragni B, Baruscotti M, Difrancesco D. A caveolin-binding domain in the HCN4 channels mediates functional interaction with caveolin proteins. J Mol Cell Cardiol 2012; 53: 187–95.
29. Ohman E, Nilsson A, Madeira A, Sjögren B, Andrén PE, Svenningsson P. Use of surface plasmon resonance coupled with mass spectrometry reveals an interaction between the voltage-gated sodium channel type X alpha-subunit and caveolin-1. J Proteome Res 2008; 7: 5333–8.
30. Brisson L, Driffort V, Benoist L, Poet M, Counillon L, Antelmi E, et al. NaV1.5 Na^+ channels allosterically regulate the NHE-1 exchanger and promote the activity of breast cancer cell invadopodia. J Cell Sci 2013; 126: 4835–42.
31. Yi SL, Liu XJ, Zhong JQ, Zhang Y. Role of caveolin-1 in atrial fibrillation as an anti-fibrotic signaling molecule in human atrial fibroblasts. PLoS One 2014; 9: e85144.
32. Chen S, Wang X, Wang J, Zhao Y, Wang D, Tan C, et al. Genomic variant in CAV1 increases susceptibility to coronary artery disease and myocardial infarction. Atherosclerosis 2016; 246: 148–56.