ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Genetic Polymorphism on Chromosome 4q25 (rs17570669) May Predict Recurrence After Successful Electrical Cardioversion in Patients with Persistent Atrial Fibrillation

Kromozom 4q25 (Rs17570669) Üzerindeki Genetik Polimorfizm Dirençli Atriyal Fibrilasyon Hastalarında Başarılı Elektriksel Kardiyoversiyon Sonrası Nüksü Belirleyebilir

ABSTRACT

Objective: Direct current electrical cardioversion (DCCV) is an effective rhythm-control option for patients with atrial fibrillation (AF). Despite initial success, a high recurrence rate remains a significant challenge. There is limited data on the genetic predictors of AF recurrence following successful DCCV. In this study, we aimed to evaluate whether 11 single nucleotide polymorphisms (SNPs) previously associated with AF are also linked to recurrence after DCCV in the Turkish population.

Methods: Seventy-five patients with persistent AF, who achieved stable sinus rhythm following DCCV, were included in the study. The patients were prospectively monitored for the onset of AF recurrence. Clinical characteristics and SNPs were analyzed and compared between patients who experienced recurrence and those who did not.

Results: The average age of the patients was 61.9 ± 11.5, and 33 (44%) were female. Over an average follow-up period of 17.0 (11.0-25.0) months, AF recurrence was observed in 38 patients (50.7%). A SNP in the *PITX2* gene (rs17570669) (OR: 9.00, 95% Confidence Interval (CI): 1.28-63.02) and another in the *ZFHX3* gene (rs2106261) (OR: 8.96, 95% CI: 1.03-77.66) were notably associated with AF recurrence in the additive model (P = 0.027 and 0.047, respectively). Multivariate Cox regression analysis revealed that the rs17570669 SNP was the sole independent predictor of AF recurrence (Hazard Ratio (HR): 3.59, 95% CI: 1.05-12.21, P = 0.040).

Conclusion: The SNP in the paired-like homeodomain 2 (*PITX2*) gene (rs17570669) emerges as an independent predictor for AF recurrence after successful electrical cardioversion.

Keywords: Atrial fibrillation, electrical cardioversion, single nucleotide polymorphism

ÖZET

Amaç: Doğrudan akım elektriksel kardiyoversiyon (DAKV), atriyal fibrilasyon (AF) hastalarında etkin bir ritim kontrol seçeneğidir. Başlangıç başarısına rağmen, yüksek bir nüks oranı önemli bir problemdir. Başarılı DAKV sonrası AF nüksünün genetik belirteçleri ile ilgili yeterli veri yoktur. Bu çalışmada, daha önce AF ile ilişkili olduğu gösterilen 11 tek nükleotid polimorfizminin (TNP) Türk toplumunda DAKV sonrası nüks ile ilişkili olup olmadığını değerlendirmeyi amaçladık.

Yöntem: DAKV sonrası stabil sinüs ritmine ulaşan dirençli AF'li 75 hasta çalışmaya dahil edildi. Hastalar AF nüksü gelişimi açısından prospektif olarak takip edildi. Nüksü olan ve olmayanlar arasında klinik özellikler ve TNP'ler karşılaştırıldı.

Bulgular: Hastaların yaş ortalaması 61,9 ± 11,5 olup, 33'ü (%44) kadındı. Ortalama 17,0 (11,0-25,0) aylık takipte 38 hastada (%50,7) AF nüksü gelişti. Aditif modelde *PITX2* genindeki bir TNP (rs17570669) (OR = 9,00, %95 GA: 1,28-63,02) ve *ZFHX3* genindeki bir TNP (rs2106261) (OR = 8,96, %95 GA = 1,03-77,66) AF ile anlamlı şekilde ilişkiliydi (sırasıyla P = 0,027 ve 0,047). Çok değişkenli Cox regresyon analizi, rs17570669 TNP'sinin AF nüksü için tek bağımsız belirleyici olduğunu gösterdi (HR = 3,59, %95 GA = 1,05-12,21, P = 0,040).

Sonuç: *PITX2* genindeki bir TNP (rs17570669), başarılı elektriksel kardiyoversiyon sonrası AF nüksünün bağımsız belirleyicisidir.

Anahtar Kelimeler: Atriyal fibrilasyon, elektriksel kardiyoversiyon, tek nükleotid polimorfizmi

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

Taner Ulus[1]
İlkin Aliyev[1]
Serap Arslan[2]
Oğuz Çilingir[3]
Ertuğrul Çolak[4]

[1]*Department of Cardiology, Eskişehir Osmangazi University, Eskişehir, Türkiye*
[2]*Department of Medical Genetics, Karabük University, Karabük, Türkiye*
[3]*Department of Medical Genetics, Eskişehir Osmangazi University, Eskişehir, Türkiye*
[4]*Department of Biostatistics, Eskişehir Osmangazi University, Eskişehir, Türkiye*

Corresponding author:
Taner Ulus
✉ tanerulusbuca@gmail.com

Received: March 20, 2023
Accepted: April 19, 2023

Cite this article as: Ulus T, Aliyev İ, Arslan S, Çilingir O, Çolak E. Genetic polymorphism on chromosome 4q25 (rs17570669) may predict recurrence after successful electrical cardioversion in patients with persistent atrial fibrillation. *Turk Kardiyol Dern Ars.* 2023;51(8):550-556.

DOI:10.5543/tkda.2023.37679

Atrial fibrillation (AF) is the most common arrhythmia, affecting approximately 1.5-2% of the general population.[1] It is linked to symptoms such as palpitations, breathlessness, fatigue, angina pectoris, and syncope. Furthermore, AF can lead to heart failure (HF), stroke, cognitive decline, and increased mortality.[2] Direct current electrical cardioversion (DCCV) is an effective rhythm-control option when sinus rhythm is not achieved spontaneously.[2] While there is a high initial success rate of 68-98%, the maintenance rate of sinus rhythm drops to around 50% one month after DCCV, with most patients experiencing AF recurrence within a year after successful DCCV.[1,3,4] Several factors have been identified as being associated with AF recurrence after DCCV, including older age, female gender, AF persisting for longer than six months, chronic obstructive pulmonary disease, renal impairment, HF, and an enlarged left atrium (LA) volume index (LAVI).[1,2,4]

Genetic polymorphisms have also been identified as factors related to AF. Previous studies have demonstrated that single nucleotide polymorphisms (SNPs) on chromosomes 3p22 in the Sodium Voltage-Gated Channel Alpha Subunit 10 (*SCN10A*) gene, 4q25 in the paired-related homeobox gene (*PITX2*), 7q31 in the Caveolin 1 (*CAV1*) gene, 12q24 in the T-Box Transcription Factor 5 (*TBX5*) gene, 16q22 in the Zinc Finger Homeobox 3 (*ZFHX3*) gene, and 19q13 in the transforming growth factor-β1 (*TGF-β1*) gene are linked with AF.[5-10] Other studies indicated that *SNPs* in the *PITX2* gene and *ZFHX3* genes, and on chromosome 8q21 in the Epoxide Hydrolase 2 (*EPHX2*) gene, relate to recurrence after catheter ablation for AF.[11-13] Previously, we discovered that 4 SNPs in the *PITX2* gene were significantly associated with AF (rs10033464, rs6838973, rs3853445, and rs17570669), and a single SNP in the *CAV1* gene (rs3807989) served as an independent predictor for recurrence after AF ablation.[14]

There is insufficient data regarding the genetic predictors of AF recurrence after successful DCCV. Only one study has shown that a SNP in the *PITX2* gene (rs2200733) is an independent predictor of AF recurrence following DCCV.[15] Based on this information, we sought to determine whether 11 SNPs, previously associated with AF, also relate to AF recurrence after successful DCCV in Turkish patients. These SNPs include one in the *SCN10A* gene (rs6795970), five in the *PITX2* gene (rs2200733, rs10033464, rs6838973, rs3853445, and rs17570669), one in the *CAV1* gene (rs3807989), one in the EPHX2 gene (rs751141), one in the *TBX5* gene (rs10507248), one in the *ZFHX3* gene (rs2106261), and one in the *TGF-β1* gene (rs1800469).

ABBREVIATIONS

AF	Atrial Fibrillation
CI	Confidence İnterval
DCCV	Direct Current Electrical Cardioversion
ECG	Electrocardiogram
HF	Heart Failure
HR	Hazard Ratio
IV	Intravenous
LA	Left Atrium
LAVI	Left Atrium Volume Index
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
OR	Odds Ratio
PITX2	Paired-Related Homeobox Gene
SNP	Single Nucleotide Polymorphism
TGF-β1	Transforming Growth Factor-β1

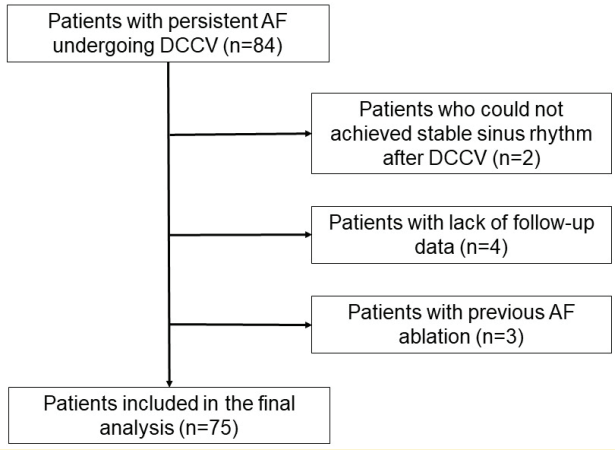

Figure 1. Flow chart of the study.

Materials and Methods

We prospectively enrolled 84 patients with persistent AF who underwent DCCV at Eskişehir Osmangazi University between February 2021 and September 2022. The definition of persistent AF adhered to the current guidelines.[2] We excluded patients who did not achieve a stable sinus rhythm after DCCV, those with incomplete follow-up data, previous AF ablation, severe heart valve disease or prosthetic heart valve, acute coronary syndrome/stroke or cardiac surgery within the last three months, abnormal thyroid function, or an acute infection. As a result, 75 patients were included in the final analysis. A flow chart of the study is provided in Figure 1.

Baseline clinical characteristics, medication use, and laboratory measurements, including hemoglobin levels and estimated glomerular filtration rate, were documented for all patients prior to cardioversion. Two-dimensional echocardiography was conducted to assess the left ventricular (LV) ejection fraction (EF), LAVI, LV mass index, and to rule out severe valvular disease. All echocardiographic assessment were carried out before cardioversion by two experienced echocardiographers who were blind to the clinical data of the patients, following current guidelines.[16] Transesophageal echocardiography was executed for all patients before the procedure to ensure the absence of a LA thrombus. The Ethics Committee of Eskişehir Osmangazi University approved the study (Approval Number: 45, Date: 04.02.2021). The study complied with the Declaration of Helsinki.

Electrical Cardioversion

The DCCV procedures were conducted in the coronary care unit on fasting patients, as described previously.[2,17,18] Blood pressure and oximetry monitoring were routinely monitored during the procedure. Electrical cardioversion was synchronized with the R-wave on the electrocardiogram (ECG). Conscious sedation was administered using intravenous (IV) midazolam for all patients. The anode was positioned in the right parasternal region, and the cathode was placed on the left lateral chest wall along the mid-axillary line. A biphasic defibrillator (Nihon Kohden Corporation, Tokyo, Japan) was utilized, delivering 200-joule energy for the initial shock. If the first shock did not succeed, two additional shocks of 200 joules were given at one-minute intervals. If a stable sinus rhythm was established 10 minutes after the procedure, the DCCV was deemed successful. All patients began

IV amiodarone therapy 24 hours prior to the cardioversion, and oral amiodarone treatment continued for a minimum of three months after cardioversion.

Follow-Up

All patients were monitored at our outpatient clinic at 1, 3, 6, and 12 months, and subsequently on an annual basis after the successful cardioversion. Alongside a physical examination and a 12-lead ECG, a 24-hour ambulatory Holter ECG was performed on all patients, irrespective of symptom presence. An AF episode lasting longer than 30 seconds and documented via ECG was categorized as an AF recurrence.

Genotyping

Genotyping procedures were consistent with those previously described.[14] Genomic Deoxyribonucleic Acid (DNA) was extracted from the patients' whole blood using a DNA extraction kit (QIAamp DNA Blood Mini Kit, Qiagen Inc., Valencia, CA, USA), following the manufacturer's instructions. The 11 SNPs mentioned above were analyzed using the SnapShot technique. Electrophoresis of amplified Polymerase Chain Reaction (PCR) products related to these polymorphic regions was conducted on the ABI 3130 Genetic Analyzer, and the data were analyzed using GeneMapper 4 Software (Applied Biosystems, Life Technologies, CA, USA).

Statistical Analysis

Continuous variables were presented as mean ± standard deviation for normally distributed variables and as median (interquartile ranges) for non-normally distributed ones. Comparisons between continuous variables were made using the independent Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed ones. Categorical variables were presented as numbers (percentages) and compared using the chi-square test. The effects of genotypes were evaluated with 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.[14]

Logistic regression analysis was used to determine the relationship between AF recurrence and genotypes in three different models, and the odds ratio (OR) and 95% confidence intervals (CI) were calculated. Our study had a 92% power to determine the relationship between AF recurrence after DCCV and SNPs. Cox regression analysis was used to identify predictors of AF recurrence after DCCV, and the hazard ratio (HR) and 95% CI were calculated. Variables with a p-value of <0.10 in the univariate analysis were included in the multivariate analysis to identify independent predictors of AF recurrence. A Kaplan-Meier curve was used to illustrate AF recurrence-free survival. Statistical analyses were carried out using the IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp., USA). A p-value of <0.05 was considered statistically significant.

Results

The average age of the patients was 61.9 ± 11.5, and 33 (44%) were female. None of the patients experienced complications related to DCCV. Over an average follow-up of 17.0 (11.0-25.0) months, AF recurrence was observed in 38 patients (50.7%). The proportion of females was higher (55.3% vs. 32.4%), and the AF duration before DCCV was more extended [9.2 (5.5-11.6) vs. 5.0 (2.7-11.0) months], and the LAVI was greater [43.6 ± 8.8 vs.

Table 1. Clinical Characteristic Features of the Patients According to AF Recurrence After Successful Electrical Cardioversion

	AF recurrence (-) (n=37)	AF recurrence (+) (n = 38)	*P*
Age (years)	60.4 ± 12.8	63.3 ± 10.0	0.279
Female sex	12 (32.4)	21 (55.3)	0.046
BMI (kg/m^2)	27.7 (26.2-31.9)	28.6 (26.6-33.0)	0.203
Hipertension (n,%)	23 (62.2)	27 (71.1)	0.414
Diabetes mellitus (n,%)	10 (27.0)	6 (15.8)	0.235
CAD (n,%)	7 (18.9)	7 (18.4)	0.956
HF with reduced LV EF (n,%)	12 (32.4)	9 (23.7)	0.399
COPD (n,%)	6 (16.2)	3 (7.9)	0.309
CHA_2DS_2VASc score	3.0 (1.0-4.0)	2.0 (2.0-3.2)	0.807
Smoking (n,%)	12 (32.4)	8 (21.1)	0.265
Alcohol (n,%)	0 (0)	2 (5.3)	0.493
Beta blocker (n,%)	35 (94.6)	33 (89.2)	0.674
ACEI/ARB (n,%)	21 (56.8)	22 (57.9)	0.921
Spironolactone (n,%)	11 (29.7)	7 (18.4)	0.252
Amiodarone (n,%)	23 (62.2)	18 (47.4)	0.242
AF duration (months)	5.0 (2.7-11.0)	9.2 (5.5-11.6)	0.029
Follow-up duration (months)	14.0 (9.5-24.0)	20.0 (11.7-28.0)	0.124
Hemoglobin (g/dl)	14.3 ± 1.8	13.7 ± 1.8	0.144
eGFR (ml/dk/1,73 m^2)	80.0 (59.5-90.0)	74.2 (59.7- 90.0)	0.491
LV EF (%)	55.0 (40.0-60.0)	60.0 (44.7-62.0)	0.300
LAVI (ml/m^2)	38.2 ± 12.9	43.6 ± 8.8	0.036

ACEI, Angiotensin converting enzyme inhibitor; AF, Atrial fibrillation; ARB, Angiotensin receptor blocker; BMI, Body mass index; CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; eGFR, Estimated glomerular filtration rate; HF, Heart failure; LAVI, Left atrium volume index; LVEF, Left ventricular ejection fraction.

38.2 ± 12.9 (ml/m^2)] in patients with AF recurrence than in those without (P = 0.046, P = 0.029, and P = 0.036, respectively). The baseline clinical characteristics of the patients, categorized by AF recurrence after electrical cardioversion, are detailed in Table 1.

Genotypic Features

The genetic variant frequencies of the 11 SNPs in the study population are shown in Table 2. A SNP in the *PITX2* gene (rs17570669) had a significant association with AF recurrence in the additive model (OR = 9.00, 95% CI = 1.28-63.02, P = 0.027). A SNP in the *ZFHX3* gene (rs2106261) was significantly linked to AF recurrence in both the additive (OR = 8.96, 95% CI = 1.03-77.66, P = 0.047) and dominant (OR = 8.63, 95% CI = 1.01-74.01, P = 0.049) models. The logistic regression analysis results that show the associations between the 11 SNPs and AF recurrence are provided in Table 3.

Follow-Up

Catheter ablation for AF was conducted on 25 (65.7%) of the 38 patients who had AF recurrence after DCCV. The remaining

Table 2. Genetic Variant Frequencies of 11 SNPs in the Study Population According to AF Recurrence

			Wild type		Heterozygous variant		Homozygous variant	
Chromosome band	Nearest gene	SNP	Recurrence (-) n (%)	Recurrence (+) n (%)	Recurrence (-) n (%)	Recurrence (+) n (%)	Recurrence (-) n (%)	Recurrence (+) n (%)
4q25	PITX2	rs2200733	CC 9 (24.3)	CC 7 (18.4)	CT 24 (64.9)	CT 29 (76.3)	TT 4 (10.8)	TT 2 (5.3)
4q25	PITX2	rs10033464	GG 4 (10.8)	GG 5 (13.2)	GT 27 (73.0)	GT 29 (76.3)	TT 6 (16.2)	TT 4 (10.5)
4q25	PITX2	rs6838973	CC 7 (18.9)	CC 9 (23.7)	CT 29 (78.4)	CT 26 (68.4)	TT 1 (2.7)	TT 3 (7.9)
4q25	PITX2	rs3853445	TT 4 (10.8)	TT 5 (13.2)	TC 31 (83.8)	TC 32 (84.2)	CC 2 (5.4)	CC 1 (2.6)
4q25	PITX2	rs17570669	AA 9 (24.3)	AA 4 (10.5)	AT 26 (70.3)	AT 26 (68.4)	TT 2 (5.4)	TT 8 (21.1)
16q22	ZFHX3	rs2106261	CC 7 (18.9)	CC 1 (2.6)	CT 25 (67.6)	CT 32 (84.2)	TT 5 (13.5)	TT 5 (13.2)
8q21	EPHX2	rs751141	GG 12 (32.4)	GG 18 (47.4)	GA 25 (67.6)	GA 19 (50.0)	AA 0 (0)	AA 1 (2.6)
7q31	CAV1	rs3807989	AA 8 (21.6)	AA 3 (7.9)	AG 25 (67.6)	AG 27 (71.1)	GG 4 (10.8)	GG 8 (21.1)
12q24	TBX5	rs10507248	GG 5 (13.5)	GG 8 (21.1)	GT 22 (59.5)	GT 26 (68.4)	TT 10 (27.0)	TT 4 (10.5)
19q13	TGF-1	rs1800469	GG 3 (8.1)	GG 3 (7.9)	GA 27 (73.0)	GA 28 (73.7)	AA 7 (18.9)	AA 7 (18.4)
3q22	SCN10A	rs6795970	AA 6 (16.2)	AA 10 (26.3)	AG 26 (70.3)	AG 22 (57.9)	GG 5 (13.5)	GG 6 (15.8)

AF, Atrial fibrillation; SNP, Single nucleotide polymorphism.

Table 3. Genotype Distribution of the Studied SNPs Among Subjects According to AF Recurrence After Successful Electrical Cardioversion

			Dominant model		Additive model		Recessive model	
SNP	AF recurrence (-) (%)*	AF recurrence (+) (%)*	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
rs2200733	24.3/ 64.9/ 10.8	18.4/ 76.3/ 5.3	1.42 (0.4-4.3)	0.534	1.55 (0.5-4.8)	0.443	0.46 (0.1-2.7)	0.385
rs10033464	10.8/ 73.0/ 16.2	13.2/ 76.3/ 10.5	0.80 (0.2-3.2)	0.755	0.85 (0.2-3.5)	0.834	0.60 (0.1-2.3)	0.472
rs6838973	18.9/ 78.4/ 2.7	23.7/ 68.4/ 7.9	0.75 (0.2-2.3)	0.615	2.33 (0.2-27.5)	0.501	3.08 (0.3-31.1)	0.339
rs3853445	10.8/ 83.8/ 5.4	13.2/ 84.2/ 2.6	0.80 (0.2-3.2)	0.755	0.40 (0.0-6.2)	0.512	0.47 (0.0-5.4)	0.548
rs17570669	24.3/ 70.3/ 5.4	10.5/ 68.4/ 21.1	1.09 (0.9-1.2)	0.124	9.00 (1.3-63.0)	0.027	4.66 (0.9- 23.7)	0.063
rs2106261	18.9/ 67.6/ 13.5	2.6/ 84.2/ 13.2	8.63 (1.0-74.1)	0,049	8.96 (1.0-77.7)	0.047	0.97 (0.2 -3.7)	0.964
rs751141	32.4/ 67.6/ 0	47.4/ 50.0/ 2.6	0.53 (0.2-1.3)	0.189	0.50 (0.2-1.3)	0.158	Not analyzed	
rs3807989	21.6/ 67.6/ 10.8	7.9/ 71.1/ 21.1	3.21 (0.8-13.2)	0.105	5.33 (0.9-31.9)	0.067	2.20 (0.6 -8.0)	0.234
rs10507248	13.5/ 59.5/ 27.0	21.1/ 68.4/ 10.5	0.58 (0.2-2.0)	0.392	0.25 (0.5-1.2)	0.092	0.31 (0.9 -1.1)	0.076
rs1800469	8.1/ 73.0/ 18.9	7.9/ 73.7/ 18.4	1.02 (0.2-5.5)	0.973	1.03 (0.2-5.6)	0.966	0.96 (0.3-3.1)	0.956
rs6795970	16.2/ 70.3/ 13.5	26.3/ 57.9/ 15.8	0.54 (0.2-1.7)	0.290	0.50 (0.1-1.6)	0.252	1.20 (0.3-4.3)	0.781

AF, Atrial fibrillation; CI, Confidence interval; OR, Odds ratio; SNP, Single nucleotide polymorphism.

Table 4. Cox Regression Analysis Showing the Relationship Between Clinical Characteristics, SNPs, and AF Recurrence After Successful Electrical Cardioversion

	Univariate			Multivariate		
	Beta	**HR (95% CI)**	***P***	**Beta**	**HR (95% CI)**	***P***
Female gender	0.691	1.99 (1.05-3.79)	0.035	0.595	1.81 (0.94-3.47)	0.073
AF duration	0.028	1.02 (0.97-1.08)	0.313			
BMI	0.042	1.04 (0.98-1.10)	0.140			
LAVI	0.023	1.02 (0.99-1.05)	0.089	0.016	1.01 (0.98-1.04)	0.241
rs2106261 SNP	1.632	5.11 (0.69-37.50)	0.108			
rs17570669 SNP	1.427	4.16 (1.22-14.11)	0.022	1.280	3.59 (1.05-12.21)	0.040

AF, Atrial fibrillation; BMI, Body mass index; CI, Confidence interval; HR, Hazard ratio; LAVI, Left atrium volume index; SNP, Single nucleotide polymorphism.

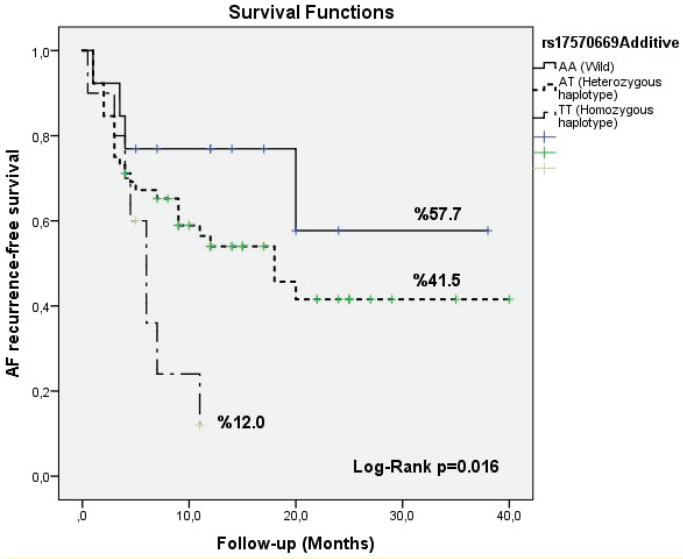

Figure 2. Kaplan-Meier curve: The SNP in the rs17570669 locus in the additive model and AF recurrence-free survival after successful electrical cardioversion. AF: Atrial fibrillation, SNP: Single nucleotide polymorphism.

patients, either asymptomatic or those who declined AF ablation, were medically managed. During the follow-up period, six patients passed away. The causes of death were cardiac-related in two patients (linked with HF), and non-cardiac for four patients (two due to COVID-19 infection, one from acute renal failure, and one from sepsis).

Predictors of AF Recurrence After Successful Electrical Cardioversion

Cox regression analysis showing the relationship between clinical characteristics, SNPs, and AF recurrence after DCCV is given in Table 4. Female gender (HR = 1.99, 95% CI = 1.05-3.79) and the rs17570669 SNP (HR = 4.16, 95% CI = 1.22-14.11) were associated with AF recurrence after cardioversion in the univariate analysis (P = 0.035 and P = 0.022, respectively). Multivariate analysis demonstrated that the rs17570669 SNP was the only independent predictor of AF recurrence (HR = 3.59, 95% CI = 1.05-12.21, P = 0.040). A Kaplan-Meier survival curve showed that the percentages of AF recurrence-free survival after DCCV were significantly different between wild type, heterozygous variant, and homozygous variant for the rs17570669 SNP (57.7% for wild type, 41.5% for heterozygous variant, 12.0% for homozygous variant, log-rank P = 0.016) (Figure 2).

Discussion

In our study, we aimed to investigate whether 11 SNPs, previously shown to be associated with AF, were predictive of AF recurrence in patients who underwent successful DCCV for persistent AF. The main findings of the study are as follows: 1) Female gender, pre-procedural AF duration, and pre-procedural LAVI were associated with the development of AF recurrence after DCCV. 2) AF recurrence was more common in patients with the rs17570669 SNP in the *PITX2* gene and the rs2106261 SNP in the *ZFHX3* gene in the additive model. 3) In the Cox proportional regression model, both female gender and the rs17570669 SNP were associated with the development of AF recurrence during follow-up, but the rs17570669 SNP was the only independent predictor for AF recurrence in the multivariate analysis.

Although electrical cardioversion is an effective method for maintaining sinus rhythm in patients with AF, a high recurrence rate remainsa significant concern. Recurrence after DCCV has been shown to be associated with increased mortality in AF patients.[19] Identifying factors associated with AF recurrence in patients undergoing DCCV pre-procedurally is crucial for appropriate patient selection, improving prognosis, and enhancing monitoring after electrical cardioversion.[1]

In recent years, numerous studies have aimed to uncover the relationship between SNPs and the pathogenesis of AF and recurrence after catheter ablation for AF.[12,14,20] The literature offers limited data on the association between genetic markers and AF recurrence after DCCV. Only one study has delved into this relationship.[15] This study had significant limitations: it explored only three SNPs, had a relatively short follow-up period of 12 months, and did not use Holter ECG to detect AF recurrence.[15] In contrast, our study investigated the association of 11 SNPs with AF recurrence after DCCV in the Turkish population. Patients were monitored for a longer duration (average of 17 months), and routine Holter ECGs were utilized during checks. We discovered that the rs17570669 SNP in the *PITX2* gene emerged as an independent predictor for AF recurrence after successful DCCV. Additionally, we found that the rs2106261 SNP in the *ZFHX3* gene, while not an independent determinant, was correlated with AF recurrence.

The *PITX2* gene, while instrumental in augmentiing nodal tissue expression in the right atrium, actively inhibits nodal tissue development and fosters the growth of myocardial tissues in the LA and pulmonary veins.[21,22] Studies indicate that the *PITX2* gene critically influences the regulation of pathways linked to ion channels, cell-cell binding, and beta-adrenergic stimulation through microRNAs.[23] Subsequent analysis revealed that whether upregulated or downregulated, the *PITX2* gene plays an active role in the pathogenesis of AF, causing structural and electrical remodeling as well as affecting calcium handling.[24] Additionally, the *PITX2* gene regulates the expression of other genes, such as *ZFHX3*, which can contribute to the development of AF by influencing the inflammatory process.[21] The results of our study align with the aforementioned findings, further emphasizing the role of the *PITX2* gene in the pathogenesis of AF.

In our study, we found that the female gender was a determinant for AF recurrence after cardioversion, although it was not an independent predictor. Women tend to be referred to rhythm control treatments later, and risk factors associated with AF recurrence, such as advanced age, hypertension, heart valve disease, and thyroid disease, are more common in women at the time of cardioversion.[1] These factors may account for the observed association between female gender and AF recurrence after DCCV in our study. Previous studies have demonstrated that the length of AF duration before cardioversion and the enlarged LA dimensions can lead to atrial remodeling and are linked to AF recurrence after DCCV.[1,4] In line with these findings, our study also identified a correlation between pre-procedural AF duration and LAVI and AF recurrence after cardioversion, even though they were not independent predictors.

If genetic analysis can be performed on patients undergoing electrical cardioversion, and if individuals with SNPs in the *PITX2* and *ZFHX3* genes are identified, several interventions might be considered. These could include a closer follow-up for potential AF recurrence, stricter control of reversible risk factors (such as hypertension and obstructive sleep apnea), and earlier referral to treatments with a lower likelihood of recurrence, like AF ablation. Nevertheless, more research is necessary before these findings can be integrated into clinical practice.

Our study also had some limitations. It was a single-center study, and the patient sample was relatively small. Despite this, our study possessed adequate statistical power to discern the roles of genetic markers in AF recurrence following successful DCCV. We evaluated AF recurrence using a 12-channel surface ECG and 24-hour Holter monitoring. No extended ECG monitoring was undertaken, which may mean that certain asymptomatic AF recurrences went undetected.

Conclusion

A SNP in the PITX2 gene (rs17570669) emerges as an independent predictor for AF recurrence after successul electrical cardioversion. If this SNP is identified through genotyping before cardioversion, affected patients may benefit from closer monitoring, stricter management of reversible risk factors, and perhaps an earlier consideration for catheter ablation for AF. Moreover, female patients should be observed more meticulously for potential AF recurrence after DCCV. However, further studies are required before these findings become standard in clinical practice.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Eskişehir Osmangazi University (Approval Number: 45, Date: 04.02.2021).

Informed Consent: Written informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – T.U., İ.A., O.Ç.; Design – T.U., S.A., O.Ç.; Supervision – T.U., İ.A., S.A., E.Ç.; Resource – T.U., İ.A., S.A.; Materials – S.A., O.Ç.; Data Collection and/or Processing - T.U., İ.A., S.A.; Analysis and/or Interpretation – T.U., O.Ç., E.Ç.; Literature Review – T.U., İ.A.; Writing – T.U., İ.A., O.Ç.; Critical Review – T.U., İ.A., S.A., O.Ç., E.Ç.

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study received no financial support.

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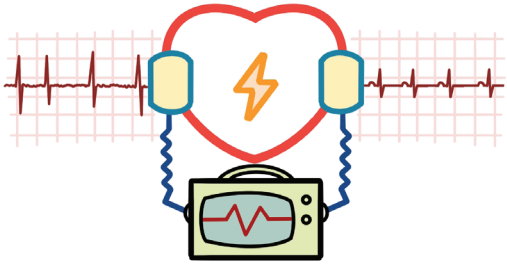
Genetic Polymorphism on Chromosome 4q25 (rs17570669) May Predict Recurrence After Successful Electrical Cardioversion in Patients with Persistent Atrial Fibrillation

75 pts w/ Persistant AF who achieved SR following DCCV



- **The average age of the patients was 61.9 ± 11.5.**
- **AF recurrence was observed in 38 patients.**
- **The 11 SNPs were analyzed using the SnapShot technique.**

- **The rs17570669 SNP was the sole independent predictor of AF recurrence**
  (HR: 3.59, 95% CI: 1.05-12.21, P = 0.040).

The SNP in the paired-like homeodomain 2 (PITX2) gene (rs17570669) emerges as an independent predictor for AF recurrence after successful electrical cardioversion.

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