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The 4q25/*PITX2* SNP rs6817105 and Atrial Fibrillation in Uzbek Patients with Arterial Hypertension

G. M. Radzhabova[1], G. Zh. Abdullaeva[1*], D. V. Zakirova[2], M. T. Pulatova[1], N. Kh. Sherbadalova[1], M. N. Khatamova[1], Z. T. Mashkurova[1], N. N. Ibrokhimov[2], A. A. Abdullaev[2], M. A. Sadulloeva[1]

[1]*Republican Specialized Center of Cardiology*
[2]*Center for Advanced Technologies*
Tashkent, Uzbekistan

Abstract

Background: Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and a major predictor of morbidity and mortality. In recent years, genome-wide association studies (GWAS) have identified common genetic variants associated with a higher risk of AF. The aim of our research was to study the possible association of the 4q25/*PITX2* SNP rs6817105 with the risk of developing AF in patients with arterial hypertension (AH) in the Uzbek population.

***Methods and Results*:** The study included 142 AH (Grades 1-3; ESC/ESH, 2018) patients of Uzbek nationality who were initially diagnosed with paroxysmal form (15[10.6%]), persistent form (43[30.3%]), and permanent form of AF (84[59.1%]). The mean age of these patients was 64.8±10.9 years. AF was verified using ECG Holter monitoring. The control group (n=88) consisted of AH patients without AF with a mean age of 56.5±12.3 years. Echocardiography was carried out according to the recommendations of the American Society of Echocardiography in M- and B-modes. We genotyped SNP rs6817105 (T>C) and examined the relationships among rs6817105 genotype, clinical characteristics, and echocardiographic parameters in AH patients with AF and non-AF AH patients (controls).

In AH patients with AF and AH patients without AF, the 4q25/*PITX2* SNP rs6817105 genotype distribution was as follows: CC=72(50.7%), CT=60(42.3%), TT=10(7.0%) [χ^2=45.690; *P*=0.000], and CC=34(38.6%), CT=37(42.1%), TT=17(19.3%) [χ^2=7.932; *P*=0.019], respectively. The rs6817105 minor C allele frequency was significantly higher in AH patients with AF than in non-AF AH patients (71.8% vs. 59.7%, *P*=0.007). Analysis of the multiplicative model for the rs6817105 SNP showed a significant risk of AF in the carriage of the C allele (OR=1.72, 95% CI: 1.16-2.56, *P*=0.007). The dominant and additive models for the rs6817105 SNP showed a significant risk of AF with the carriage of the CC+CT genotypes (OR=3.16, 95% CI: 1.37-7.27, *P*=0.005) and the homozygous CC genotype (OR=1.63, 95% CI: 0.95-2.81, *P*=0.008), respectively. The allelic distribution showed that the carriage of the C allele was dominant in permanent and persistent AF (110/68.75% vs. 50/31.25% for the T allele [(χ2=22.50, *P*=0.000], and 64(74.42%) vs. 22 (25.58%) for the T allele [χ^2=20.512, *P*=0.000], respectively). Among AH patients with paroxysmal AF, the C allele prevailed to the greatest extent: 20(90.9%) vs. 2(9.1%) for the T allele (χ^2=14.727, *P*=0.000), indicating a significant accumulation of the C allele and CC genotype among patients with paroxysmal AF. In general, in AH patients with AF, carriers of the CC genotype, the left atrial volume index (LAVI) was significantly higher than the carriers of the CT and TT genotypes: 46.8±13.9 ml/m^2 vs. 40.4±13.0 ml/m^2 and 36.1±11.0 ml/m^2, respectively (*P*=0.0083).

Conclusion: The present study is the first molecular genetic study investigating the association of 4q25/*PITX2* SNP rs6817105 in AH patients with AF in the Uzbek population. Our results indicate the rs6817105 minor C allele and CC genotype are associated with the risk of developing AF in AH patients of Uzbek nationality. The highest accumulation of the rs6817105 minor C allele and CC genotype is found in paroxysmal AF. In carriers of the rs6817105 CC genotype, the LAVI was significantly larger than in carriers of the CT and TT genotypes.(**International Journal of Biomedicine. 2023;13(3):72-78.**)

Keywords: atrial fibrillation • rs6817105 • arterial hypertension • left atrial volume index

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Abbreviations

AH, arterial hypertension; **AF**, atrial fibrillation; **BP**, blood pressure; **DBP**, diastolic BP; **GWAS**, genome-wide association studies; **IVST**, interventricular septal thickness; **LVMI**, left ventricular mass index; **LVH**, left ventricular hypertrophy; **LAD**, left atrial dimension; **LAV**, left atrial volume; **LAVI**, left atrial volume index; **LVESD**, left ventricular end-systolic dimension; **LVEDD**, left ventricular end-diastolic systolic dimension; **PWT**, posterior wall thickness; **SBP**, systolic BP; **SNP**, single nucleotide polymorphism.

Introduction

Arterial hypertension (AH) is one of the main factors causing a high risk of cardiovascular complications and mortality. Overall, according to ESH/ESC data for 2018, the prevalence of hypertension is 30%-45% of the general population, with a sharp increase with age. Today, 15%-40% of the adult population suffers from hypertension worldwide, and in people over 65 years of age, hypertension has been detected in 30%-50% of cases. Of patients with hypertension, 76% are at risk of dying within 10 years.[1] The existence of a relationship between high blood pressure (BP) and the risk of developing new-onset atrial fibrillation (AF) has been demonstrated.[2] Experimental evidence suggests that electrical and structural remodeling changes in the hypertensive heart may predispose to AF.[3]

AF is one of the most common cardiac arrhythmias and a major predictor of morbidity and mortality. AF is a polygenic and polyetiological disease. Of no minor importance are racial and ethnic differences in the prevalence of AF in the general population, noted in several studies. Factors that increase the risk of developing AF include age, hypertension, cardiomyopathy, valvular disease, and genetic predisposition. According to the literature, there is a familial form of AF, indicating the importance of genetic factors in the development of AF. Thus, mutations of various genes associated with ion channels have been identified, but it should be noted that such findings are extremely rare.[4]

In recent years, GWAS have identified common genetic variants associated with a higher risk of AF. The first GWAS for AF identified a chromosome 4q25 locus conferring the risk of AF in Icelanders.[5] To date, GWAS have identified ≈140 genetic loci associated with AF,[6] located near genes coding for ion channels, developmental transcription factors, structural remodeling, and cytoskeletal proteins.[7] Among them, variants at 4q25, located upstream of the *PITX2* gene, demonstrate a strong association with AF in European and Japanese populations. GWAS have reported a strong association of the SNP rs6817105 (T>C) on chromosome 4q25 with AF.[8-10]

The paired-related homeobox (*PITX2*) gene is the nearest gene to the 4q25 AF-associated SNPs and is the most likely target for these 4q25 AF susceptibility variants.[11] The *PITX2* gene encoding for the transcription factor PITX2 (paired-like homeodomain transcription factor 2), one of the homeobox transcription factors, is a main player in the regulation of asymmetric organogenesis. The *PITX2*, the closest gene to rs6817105, is a critical mediator of left-side morphogenesis.[12-15] *PITX2* regulates left-right differentiation (including sinoatrial node restriction to the right atrium), and deficiency leads to structural and electrical remodeling of the heart, which may lead to AF through different mechanisms.[7,16] Cardiac expression of *PITX2* is almost exclusively restricted to the left atrium in the normal adult heart.[17] The left atrium and sleeves of the pulmonary vein are potential substrates for AF development, and the pulmonary vein is often the origin of ectopic foci in AF patients.[18]

In mice models, reduced expression of PITX2c during development results in AF inducibility upon stimulation, which implicates a developmental role of this gene in AF susceptibility.[17,19,20] A number of researchers have observed that reduction in PITX2 resulted in potassium and calcium channel gene dysregulation, ultimately leading to a shortening of the atrial action potential, a depolarized resting membrane potential, and a predisposition to AF.[18,20,21]

Tomomori et al.[8] found that the rs6817105 minor C allele frequency (MAF) was significantly higher in AF patients than in non-AF controls (66% vs. 47%, OR 2.12, $P=4.9\times10^{-26}$). Sinus node dysfunction was independently associated with the rs6817105 C allele in these AF patients, and left atrium enlargement was independently associated with the rs6817105 minor C allele in AF patients. The maximum sinus node recovery time (SNRT) and corrected SNRT (CSRT) increased with the number of minor C alleles and were longest in patients with the CC genotype.

Unfortunately, studies on the search for molecular genetic predictors of AF in AH patients in the Uzbek population are rare. Previously, a group of researchers studied only the association of the *ATFB5* SNP rs2200733 with the risk of developing AF in people of Uzbek nationality.[22]

The aim of our research was to study the possible association of the 4q25/*PITX2* SNP rs6817105 with the risk of developing AF in patients with hypertension in the Uzbek population.

Materials and Methods

The study included 142 AH (Grades 1-3; ESC/ESH, 2018) patients of Uzbek nationality who were initially diagnosed with paroxysmal form (15[10.6%]), persistent form (43[30.3%]), and permanent form of AF (84[59.1%]). The mean age of these patients was 64.8±10.9 years. The control group (n=88) consisted of AH patients without AF with a mean age of 56.5±12.3 years. The presence of AF was ruled out based on the history, the absence of symptoms of AF on physical examination, and a normal electrocardiogram at the time of inclusion in the study.

AF was classified as paroxysmal, persistent, and permanent in accordance with the ACC/AHA/ESC guidelines for AF.[23] The diagnosis of AF was based on ECG findings and/or Holter ECG data according to standard diagnostic criteria.[24] AF was verified using ECG Holter monitoring (LABTECH Cardiospy, Hungary).

Office BP was measured using a mercury sphygmomanometer, according to Korotkov's method. BP was measured 3 times, and the means of these measurements were used in the analyses. Echocardiography was carried out according to the recommendations of the American Society of Echocardiography in M- and B-modes[25] using Philips Clearview-350 «Affiniti 30» Ultrasound Machine (the Netherlands). The following parameters were measured and calculated: IVST, PWT, LVEDD, LVESD, LAD, LAVI, and LVM (LVM was calculated using the formula R. Devereux. (1994) LVM was indexed to body surface area (LVMI). LVM was calculated using the formula R. Devereux.[26] Left ventricular hypertrophy (LVH) was defined as LVMI of >95g/m^2 (for women) and >115g/m^2 (for men).[1]

Exclusion criteria were symptomatic hypertension, valvular heart disease, acute coronary syndrome, chronic heart failure (NYHA FC>III), cardiac arrhythmia, history of stroke and myocardial infarction, diabetes, renal impairment, severe co-morbidities, orthostatic hypotension, artificial pacemaker, QT>480 ms, documented, previous episodes of persistent ventricular arrhythmia, WPW syndrome, Brugada syndrome, bradycardia (HR less than 60 bpm), blood clots in the LA, thyroid dysfunction, sinus node dysfunction, SSS, second-third-degree AV block.

To perform genotyping of blood samples for rs6817105 SNP, genomic DNA was isolated from whole blood using the ArtDNA MiniSpin kit (ArtBioTech LLC, BY) according to the manufacturer's standard protocol. The quantity and quality of DNA were determined on a NanoDrop 2000 spectrophotometer (Thermo Scientific™ Wilmington, DE, USA).

PCR was performed on the QuantStudio 5 Dx Real-Time PCR System (Applied Biosystems, USA). The reaction was carried out in a volume of 10µl using the TaqMan® Genotyping Assays kit (Thermo Fisher Scientific, USA) according to the manufacturer's standard protocol. The reaction mixture contained of 10ng genomic DNA, 5µl TaqMan Genotyping Master Mix, 0.5µl TaqMan Genotyping Assays. Sample genotyping results were analyzed using the Thermo Fisher Scientific Design & Analysis 2.6.0 2021 program and entered for primary processing in Microsoft Excel-2019.

Statistical analysis was performed using the statistical software «Statistica» (v10.0, StatSoft, USA). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean± standard deviation (SD) for continuous variables. Multiple comparisons were performed with one-way ANOVA and Tukey HSD post-hoc test. Genetic markers for HWE were tested. One-way table (chi-square goodness-of-fit test) was used to test categorical probabilities when one categorical variable had more than two levels. Four genetic models were analyzed (https://calc.pcr24.ru/index.php): the dominant model, the recessive model, the multiplicative model, and the additive model (the Cochran-Armitage trend test). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A probability value of $P \leq 0.05$ was considered statistically significant.

The study protocol was reviewed and approved by the Ethics Committee of the Republican Specialized Centre of Cardiology. All participants provided written informed consent.

Results

The distribution of polymorphic markers of the 4q25/*PITX2* SNP rs6817105 in AH patients with AF and non-AF AH patients was in HWE (Table1). In AH patients with AF and AH patients without AF, the 4q25/*PITX2* SNP rs6817105 genotype distribution was as follows: CC=72(50.7%), CT=60(42.3%), TT=10(7.0%) [χ^2=45.690; P=0.000], and CC=34(38.6%), CT=37(42.1%), TT=17(19.3%) [χ^2=7.932; P=0.019], respectively. An analysis of the frequency distribution of the rs6817105 alleles showed that the carriage of the C allele was dominant in AH patients with AF (71.8% vs. 28.2% for the T allele; χ^2=78.546, P=0.000), compared to non-AF AH patients (59.7% vs. 40.3% for the T allele; χ^2=6.568, P=0.010). Thus, the rs6817105 minor C allele frequency was significantly higher in AH patients with AF than in non-AF AH patients (71.8% vs. 59.7%, P=0.007).

Table 1.

The distribution of polymorphic markers of the 4q25/PITX2 SNP rs6817105 in AH patients with AF (case) and non-AF AH patients (control).

Genotype	Case	HWE	χ^2	P	Control	HWE	χ^2	P	Allele	Frequency of alleles	
										Case	Control
TT	0.070	0.079			0.193	0.163			T	0.282	0.403
CT	0.423	0.405	0.13	0.72	0.420	0.481	0.74	0.39	C	0.718	0.597
CC	0.507	0.516			0.386	0.356					

Analysis of the multiplicative model for the rs6817105 SNP showed a significant risk of AF in the carriage of the C allele (OR=1.72, 95% CI: 1.16-2.56, P=0.007) (Table 2).

Table 2.

Genetic predisposition to TRH (the genetic models).

Inheritance model	Allele, Genotype	Case	Control	χ^2	P	OR (95%CI)
		n=142	n=88			
Multiplicative model (χ^2 test, df=1)	T	0.282	0.403	7.30	0.007	0.58 (0.39-0.86)
	C	0.718	0.597			1.72 (1.16-2.56)
Additive model ([CATT], xi=[0,1,2], df=1)	TT	0.070	0.193	7.004	0.008	0.32 (0.14-0.73)
	CT	0.423	0.420			1.01 (0.59-1.73)
	CC	0.507	0.386			1.63 (0.95-2.81)
Dominant model (χ^2 test, df=1)	TT	0.070	0193	7.90	0.005	0,32 (0.14-0.73)
	CT+CC	0.930	0.807			3.16 (1.37-7.27)
Recessive model (χ^2 test, df=1)	TT+CT	0.493	0.614	3.18	0.07	0.61 (0,36-1.05)
	CC	0.507	0.386			1.63 (0.95-2.81)

The dominant and additive models for the rs6817105 SNP showed a significant risk of AF with the carriage of the CC+CT genotypes (OR=3.16, 95% CI: 1.37-7.27, *P*=0.005) and the homozygous CC genotype (OR=1.63, 95% CI: 0.95-2.81, *P*=0.008), respectively (Table 2).

Subsequently, the frequency distribution of the rs6817105 genotypes and alleles was analyzed considering the form of AF (Figures 1 and 2).

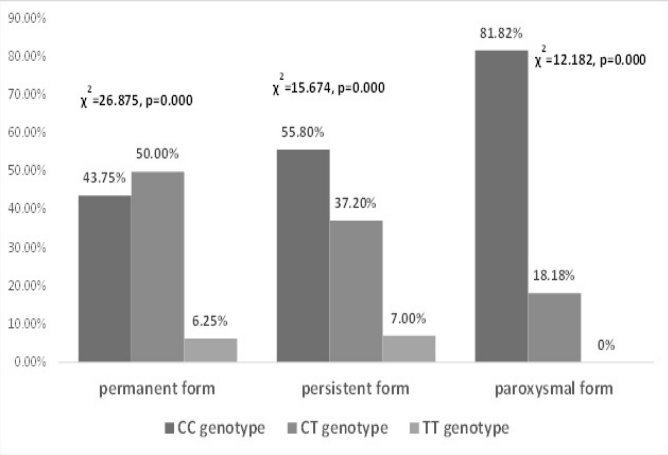

Fig. 1. *Frequency distribution of the 4q25/PITX2 SNP rs6817105 genotypes in AH patients considering the form of AF.*

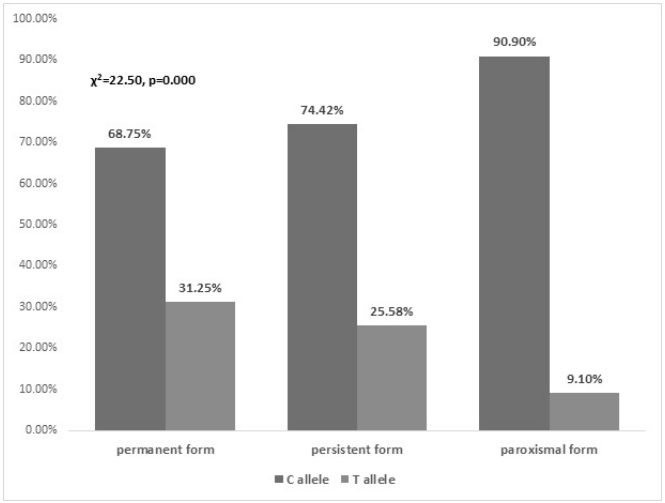

Fig. 2. *Frequency distribution of the 4q25/PITX2 SNP rs6817105 alleles in AH patients considering the form of AF.*

Among AH patients with permanent, persistent, and paroxysmal AF, the genotype distribution was as follows: CC=35(43.75%), CT=40(50%), TT=5(6.25%) (χ^2=26.875, *P*=0.000); CC=24(55.8%), CT=16(37.2%), TT=3(7.0%) (χ^2=15.674, *P*=0.000); CC=9(81.82%), CT=2(18.18%), TT=0 (χ^2=12.182, *P*=0.002), respectively.

The allelic distribution showed that the carriage of the C allele was dominant in permanent and persistent AF (110/68.75% vs. 50/31.25% for the T allele [(χ^2=22.50, *P*=0.000], and 64(74.42%) vs. 22 (25.58%) for the T allele [χ^2=20.512, *P*=0.000], respectively). Among AH patients with paroxysmal AF, the C allele prevailed to the greatest extent: 20(90.9%) vs. 2(9.1%) for the T allele (χ^2=14.727, *P*=0.000), indicating a significant accumulation of the C allele and CC genotype among patients with paroxysmal AF.

We also analyzed the initial clinical data (age, duration of AH, SBP, DBP, LAVI, LVMI) in AH patients with various AF forms, considering the rs6817105 SNP. In general, in AH patients with AF, carriers of the CC genotype, the LAVI was significantly higher than the carriers of the CT and TT genotypes: 46.8±13.9 ml/m^2 vs. 40.4±13.0 ml/m^2 and 36.1±11.0 ml/m^2, respectively (*P*=0.0083) (Table 3). A similar analysis was carried out among AH patients with paroxysmal and persistent AF. These patients were combined into one group (n=54) due to the small size of the presented sample. There were no significant differences in clinical characteristics (age, duration of hypertension, SBP, DBP, IOLR, LVMI) among rs6817105 genotypes in the patient group (Table 4). However, there was a trend toward an increase in the values of LAVI in carriers of the CC genotype.

Table 3.

Clinical characteristics of AH patients with AF considering the 4q25/PITX2 SNP rs6817105 genotypes (n=129).

Variable	Genotype			One-Way ANOVA
	CC (n=69) [1]	CT (n=50) [2]	TT (n=10) [3]	*P*-value
Age, yrs.	64.7±10.2	65.0±10.1	61.7±12.3	0.6483
AH duration, yrs.	12.8±9.1	15.4±10.8	15.3±16.4	0.3780
SBP, mmHg	146.9±25.9	143.4±26.2	147.5±26.0	0.7477
DBP, mmHg	90.4±11.03	88.6±12.9	91.8±14.6	0.6262
LAVI, ml/m^2	46.8±13.9	40.4±13.0	36.1±11.0	0.0083*
LVMI, g/m^2	280.2±104.6	269.6±101.7	230.5±75.8	0.3458

**Tukey HSD post-hoc test: $P_{[1-2]}$=0.0296, $P_{[1-3]}$=0.0507*

A similar analysis was carried out among AH patients with permanent AF (n=75). There were also no significant differences in clinical characteristics (Table 5).

Thus, the results obtained indicate the rs6817105 minor C allele and CC genotype are associated with the risk of developing AF in AH patients of Uzbek nationality. The highest accumulation of the rs6817105 minor C allele and CC genotype is found in paroxysmal AF. In carriers of the rs6817105 CC genotype, the LAVI was significantly larger than in carriers of the CT and TT genotypes.

Table 4.

Clinical characteristics of AH patients with paroxysmal and persistent AF considering the 4q25/PITX2 SNP rs6817105 genotypes (n=54).

Variable	Genotype			One-Way ANOVA
	CC (n=34)	CT (n=15)	TT (n=5)	*P*-value
Age, yrs.	62.2±10.8	61±9.49	53±14.4	0.2152
AH duration, yrs.	11.4±7.4	12.5±9.6	13.8±11.3	0.7989
SBP, mmHg	150.5±25.9	146±28.4	156±28.8	0.7457
DBP, mmHg	92.6±9.6	87.6±16.7	94±15.1	0.3856
LAVI, ml/m^2	37.4±11.8	33.0±9.1	28.9±2.24	0.1578
LVMI, g/m^2	143.0±60.2	128.6±38.9	111.6±25.7	0.3864

Table 5.

Clinical characteristics of AH patients with permanent AF considering the 4q25/PITX2 SNP rs6817105 genotypes (n=75).

Variable	Genotype			One-Way ANOVA
	CC (n=35)	CT (n=35)	TT (n=5)	*P*-value
Age, yrs.	67.2±9.1	66.5±10.1	65.8±7.5	0.9270
AH duration, yrs.	14.3±10.3	16.6±11.1	16.2±19.3	0.6927
SBP, mmHg	143.4±25.7	142.4±25.6	146.0±23.0	0.9533
DBP, mmHg	88.2±12.0	89.0±11.5	91.0±12.4	0.8722
LAVI, ml/m^2	50.4±14.4	48.2±12.0	41.2±12.7	0.3327
LVMI, g/m^2	141.7±44.2	139.0±41.9	131.1±34.1	0.8652

Discussion

The rapid development of scientific technologies has made it possible to identify new cellular and molecular levels of AH pathogenesis. To date, sufficient factual material has been accumulated on the involvement of candidate genes in the development of AH, damage to target organs, and cardiovascular complications. On the one hand, left ventricular myocardial remodeling underlies electrophysiological changes in the heart of a patient with hypertension, triggering cardiac arrhythmias, including AF. On the other hand, the literature presents gene mutations (in particular, *SCN5A*, *KCNQ*, *ATFB5*, *PITX2* gene polymorphisms), which can cause heart rhythm disturbances, including AF. Many loci associated with the development of AF have been identified to date.[27] AF is often promoted by certain combinations of genes, including the genes encoding components of renin-angiotensin-aldosterone and endothelial systems. Detection of left atrial dilatation can provide additional information and is a prerequisite for the diagnosis of diastolic dysfunction. It has been shown that LAVI>34 ml/m^2 is an independent predictor of death, heart failure, AF, and ischemic stroke.

We investigated relationships between 4q25/*PITX2* SNP rs6817105 polymorphic markers and clinical and functional parameters in Uzbek patients with AH and AF. Our results indicate a significantly greater accumulation of the rs6817105 minor C allele and CC genotype among AH patients with AF than among AH patients without AF. In AH patients with AF, carriers of the CC genotype, the LAVI was significantly higher than the carriers of the CT and TT genotypes: 46.8±14.9 ml/m^2 vs. 40.4±13.0 ml/m^2 and 36.5±11.6 ml/m^2, respectively (P=0.020). The multiplicative model for the rs6817105 SNP showed a significant risk of AF in the carriage of the C allele (OR=1.72, 95% CI: 1.16-2.56, P=0.007). The additive and recessive models for the rs6817105 SNP showed a significant risk of AF with the carriage of the homozygous CC genotype (OR=1.63, 95% CI: 0.95-2.81, P=0.008).

In recent years, GWAS have identified common genetic variants associated with a higher risk of AF in populations of European ancestry.[9,28-30] However, ethnic differences exist in the frequency of AF-related SNPs between European and Asian populations.[31,32]

The present study is the first molecular genetic study investigating the association of 4q25/*PITX2* SNP rs6817105 in AH patients with AF in the Uzbek population. Our results regarding the 4q25/PITX2 SNP rs6817105 in AF development are consistent with the previous observations.[8,33-35] We verified that the 4q25/PITX2 SNP rs681710 is associated with AF and showed that a carriage of the minor C allele and CC genotype results in left atrial enlargement.

Conclusions

- Our results indicate the rs6817105 minor C allele and CC genotype are associated with the risk of developing AF in AH patients of Uzbek nationality.
- The highest accumulation of the rs6817105 minor C allele and CC genotype is found in paroxysmal AF.
- In carriers of the rs6817105 CC genotype, the LAVI was significantly larger than in carriers of the CT and TT genotypes.

Competing Interests

The authors declare that they have no competing interests.

References

1. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, et al.; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018

September 1;39(33):3021-3104. doi: 10.1093/eurheartj/ehy339. Erratum in: Eur Heart J. 2019 Feb 1;40(5):475.
2. Van Gelder IC, Crijns HJ, Tieleman RG, Brugemann J, De Kam PJ, Gosselink AT, et al.; Chronic atrial fibrillation. Success of serial cardioversion therapy and safety of oral anticoagulation. Arch Intern Med. 1996 December;156(22):2585-2592. doi: 10.1001/archinte.156.22.2585.
3. Go O, Rosendorff C. Hypertension and atrial fibrillation. Curr Cardiol Rep. 2009 November;11(6):430-435. doi: 10.1007/s11886-009-0062-4.
4. Andalib A, Brugada R, Nattel S. Atrial fibrillation: evidence for genetically determined disease. Curr Opin Cardiol. 2008 May;23(3):176-83. doi: 10.1097/HCO.0b013e3282fa7142.
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 Jul 19;448(7151):353-7. doi: 10.1038/nature06007.
6. Roselli C, Rienstra M, Ellinor PT. Genetics of Atrial Fibrillation in 2020: GWAS, Genome Sequencing, Polygenic Risk, and Beyond. Circ Res. 2020 Jun 19;127(1):21-33. doi: 10.1161/CIRCRESAHA.120.316575
7. Schulz C, Lemoine MD, Mearini G, Koivumäki J, Sani J, Schwedhelm E, et al. *PITX2* Knockout Induces Key Findings of Electrical Remodeling as Seen in Persistent Atrial Fibrillation. Circ Arrhythm Electrophysiol. 2023 Mar;16(3):e011602. doi: 10.1161/CIRCEP.122.011602.
8. Tomomori S, Nakano Y, Ochi H, Onohara Y, Sairaku A, Tokuyama T, et al. Chromosome 4q25 Variant rs6817105 Bring Sinus Node Dysfunction and Left Atrial Enlargement. Sci Rep. 2018 Oct 1;8(1):14565. doi: 10.1038/s41598-018-32453-8.
9. 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 Apr 29;44(6):670-5. doi: 10.1038/ng.2261.
10. Christophersen IE, Rienstra M, Roselli C, Yin X, Geelhoed B, Barnard J, et al.; METASTROKE Consortium of the ISGC; Neurology Working Group of the CHARGE Consortium; Dichgans M, Ingelsson E, Kooperberg C, Melander O, Loos RJF, Laurikka J, et al.; AFGen Consortium. Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation. Nat Genet. 2017 Jun;49(6):946-952. doi: 10.1038/ng.3843. Epub 2017 Apr 17. Erratum in: Nat Genet. 2017 Jul 27;49(8):1286.
11. Aguirre LA, Alonso ME, Badía-Careaga C, Rollán I, Arias C, Fernández-Miñán A, et al. Long-range regulatory interactions at the 4q25 atrial fibrillation risk locus involve PITX2c and ENPEP. BMC Biol. 2015 Apr 17;13:26. doi: 10.1186/s12915-015-0138-0.
12. Shiratori H, Yashiro K, Shen MM, Hamada H. Conserved regulation and role of Pitx2 in situs-specific morphogenesis of visceral organs. Development. 2006 Aug;133(15):3015-25. doi: 10.1242/dev.02470.
13. Lin CR, Kioussi C, O'Connell S, Briata P, Szeto D, Liu F, et al. Pitx2 regulates lung asymmetry, cardiac positioning and pituitary and tooth morphogenesis. Nature. 1999 Sep 16;401(6750):279-82. doi: 10.1038/45803.
14. Franco D, Sedmera D, Lozano-Velasco E. Multiple Roles of Pitx2 in Cardiac Development and Disease. J Cardiovasc Dev Dis. 2017 Oct 11;4(4):16. doi: 10.3390/jcdd4040016.
15. Welsh IC, Thomsen M, Gludish DW, Alfonso-Parra C, Bai Y, Martin JF, Kurpios NA. Integration of left-right Pitx2 transcription and Wnt signaling drives asymmetric gut morphogenesis via Daam2. Dev Cell. 2013 Sep 30;26(6):629-44. doi: 10.1016/j.devcel.2013.07.019.
16. van Ouwerkerk AF, Hall AW, Kadow ZA, Lazarevic S, Reyat JS, Tucker NR, Nadadur RD, Bosada FM, Bianchi V, Ellinor PT, Fabritz L, Martin JF, de Laat W, Kirchhof P, Moskowitz IP, Christoffels VM. Epigenetic and Transcriptional Networks Underlying Atrial Fibrillation. Circ Res. 2020 Jun 19;127(1):34-50. doi: 10.1161/CIRCRESAHA.120.316574. Epub 2020 Jun 18. Erratum in: Circ Res. 2020 Aug 28;127(6):e143-e146.
17. Kirchhof P, Kahr PC, Kaese S, Piccini I, Vokshi I, Scheld HH, et al. PITX2c is expressed in the adult left atrium, and reducing Pitx2c expression promotes atrial fibrillation inducibility and complex changes in gene expression. Circ Cardiovasc Genet. 2011 Apr;4(2):123-33. doi: 10.1161/CIRCGENETICS.110.958058.
18. Syeda F, Kirchhof P, Fabritz L. PITX2-dependent gene regulation in atrial fibrillation and rhythm control. J Physiol. 2017 Jun 15;595(12):4019-4026. doi: 10.1113/JP273123.
19. Wang J, Klysik E, Sood S, Johnson RL, Wehrens XH, Martin JF. Pitx2 prevents susceptibility to atrial arrhythmias by inhibiting left-sided pacemaker specification. Proc Natl Acad Sci U S A. 2010 May 25;107(21):9753-8. doi: 10.1073/pnas.0912585107.
20. Chinchilla A, Daimi H, Lozano-Velasco E, Dominguez JN, Caballero R, Delpón E, et al. PITX2 insufficiency leads to atrial electrical and structural remodeling linked to arrhythmogenesis. Circ Cardiovasc Genet. 2011 Jun;4(3):269-79. doi: 10.1161/CIRCGENETICS.110.958116.
21. Syeda F, Holmes AP, Yu TY, Tull S, Kuhlmann SM, Pavlovic D, et al. PITX2 Modulates Atrial Membrane Potential and the Antiarrhythmic Effects of Sodium-Channel Blockers. J Am Coll Cardiol. 2016 Oct 25;68(17):1881-1894. doi: 10.1016/j.jacc.2016.07.766.
22. Abdullaeva GJ, Abdullaev AA, Kevorkov AG, Abduvalieva GA, Zakirov NU, Kurbanov RD. Interrelation between rs2200733 polymorphism of ATFB5 gene and atrial fibrillation in Uzbek patients. Turk Kardiyol Dern Ars. 2021 July; 49(5):404-409. doi: 10.5543/tkda.2021.08434.
23. 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 Oct 7;37(38):2893-2962. doi: 10.1093/eurheartj/ehw210.
24. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery; Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst A, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010 Oct;31(19):2369-429. doi: 10.1093/eurheartj/ehq278. Epub 2010 Aug 29. Erratum in: Eur Heart J. 2011 May;32(9):1172.
25. Sahn DJ, Demaria A, Kisslo J, Weyman A. Recommendation regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. Circulation. 1978 December;58(6):1072-1083.

***Corresponding author**: Guzal Zh. Abdullaeva, PhD, ScD. Department of Arterial Hypertension, Republican Specialized Center of Cardiology. Tashkent, Uzbekistan. E-mail: guzal-abdullaeva@bk.ru*

doi: 10.1161/01.cir.58.6.1072.
26. Devereux RB, Reichek N. Echocardiographyic determination of left ventricular mass in man. Anatomic validation of the method. Circulation. 1977 April; 55(4):613-618. doi: 10.1161/01.cir.55.4.613.
27. Shul'man VA, Nikulina SYu, Isachenko OO, Aksyutina NV, Romanenko SN, Maksimov VN, et al. [Genetic aspects of atrial fibrillation]. J Arrhythmology. 2006;(46):57-60. [Article in Russian].
28. Kääb S, Darbar D, van Noord C, Dupuis J, Pfeufer A, Newton-Cheh C, et al. Large scale replication and meta-analysis of variants on chromosome 4q25 associated with atrial fibrillation. Eur Heart J. 2009 Apr;30(7):813-9. doi: 10.1093/eurheartj/ehn578.
29. Benjamin EJ, Rice KM, Arking DE, Pfeufer A, van Noord C, Smith AV, et al. Variants in ZFHX3 are associated with atrial fibrillation in individuals of European ancestry. Nat Genet. 2009 Aug;41(8):879-81. doi: 10.1038/ng.416
30. Ellinor PT, Lunetta KL, Glazer NL, Pfeufer A, Alonso A, Chung MK, et al. Common variants in KCNN3 are associated with lone atrial fibrillation. Nat Genet. 2010 Mar;42(3):240-4. doi: 10.1038/ng.537.
31. Li C, Wang F, Yang Y, Fu F, Xu C, Shi L, et al. Significant association of SNP rs2106261 in the ZFHX3 gene with atrial fibrillation in a Chinese Han GeneID population. Hum Genet. 2011 Mar;129(3):239-46. doi: 10.1007/s00439-010-0912-6.
32. Chang SH, Chang SN, Hwang JJ, Chiang FT, Tseng CD, Lee JK, et al. Significant association of rs13376333 in KCNN3 on chromosome 1q21 with atrial fibrillation in a Taiwanese population. Circ J. 2012;76(1):184-8. doi: 10.1253/circj.cj-11-0525.
33. Lee KT, Yeh HY, Tung CP, Chu CS, Cheng KH, Tsai WC, et al. Association of RS2200733 but not RS10033464 on 4q25 with atrial fibrillation based on the recessive model in a Taiwanese population. Cardiology. 2010; 116(3): 151-156. doi: 10.1159/000318172.
34. Ferrán A, Alegret JM, Subirana I, Aragonès G, Lluis-Ganella C, Romero-Menor C, Planas F, Joven J, Elosua R. Association between rs2200733 and rs7193343 genetic variants and atrial fibrillation in a Spanish population, and meta-analysis of previous studies. Rev Esp Cardiol (Engl Ed). 2014 Oct;67(10):822-9. doi: 10.1016/j.rec.2013.12.019.
35. Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, et al. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. Nature. 2008 Dec 18;456(7224):980-4. doi: 10.1038/nature07511.