

# The Association Between the rs2200733 SNP and Atrial Fibrillation Among Arabs: A Study from Jordan

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**Introduction:** Atrial fibrillation (AFib) is a common disorder featured by an irregular and fast heartbeat. The etiology of AFib is complex and involves genetic and environmental factors. The rs2200733 single nucleotide polymorphism (SNP) is located in close proximity to the promoter of paired-like homeodomain transcription factor 2 (PITX2) which plays a role in heart development.

**Objective:** In this study, the association between the rs2200733 SNP and AFib was examined in the Jordanian population.

**Methods:** The study included 450 subjects (274 controls and 176 patients with AFib). Patients were recruited from King Abdullah University Hospital based on the European Society of Cardiology criteria. The rs2200733 SNP was genotyped using restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR) technique.

**Results:** The mutant T allele of the rs2200733 SNP was common in the studied population with a frequency of 19%. The T allele and CT/TT genotypes were prevalent among patients with AFib compared with the controls ( $P < 0.05$ , OR [CI]: 1.65 [1.12–2.43]). In addition, body mass index, diabetes, and hypertension were found to be associated with AFib risk.

**Conclusion:** The rs2200733 SNP was associated with AFib among Jordanian patients. The mutant T allele of the rs2200733 SNP might increase the risk of AFib.

**Keywords:** atrial fibrillation, rs2200733, PITX2, RFLP, Jordan, Arabs

## Introduction

Atrial fibrillation (AFib) is a common cardiac arrhythmia affects about 1% of the population.<sup>1</sup> This is manifested by irregular and rapid cardiac rhythm with the potential for subsequent development of thromboembolic events.<sup>2</sup> AFib can significantly increase the risk of stroke and heart failure.<sup>3</sup> AFib can be symptomatic as patients may typically experience palpitations and dyspnea, however it can also be asymptomatic and discovered incidentally.<sup>4</sup>

The disease is usually caused by structural problems with the heart. Causes of AFib include coronary artery disease, congenital heart disorders, heart valve disease, high blood pressure, pulmonary diseases, history of heart surgery, and thyroid disorders.<sup>5</sup> AFib is also related to aging, alcoholism, body mass index, diabetes mellitus, and sleep apnea.<sup>6</sup>

The risk of developing AFib can also be influenced by family history. For example, it is estimated that about 30% of all cases of AFib have a history of the condition in their family.<sup>7</sup> Therefore, inherited genetic variations can affect the risk of AFib.<sup>8</sup> Among the proposed variants that increase the risk of AFib is the rs2200733 single nucleotide polymorphism (SNP) located near the promoter of paired-like homeodomain transcription factor 2 (PITX2), thus modulating PITX2 transcription as previously reported.<sup>9,10</sup> PITX2 plays an important embryonic role in left/right asymmetry signaling including heart development. PITX2 is also expressed in cardiac tissue during adulthood where it is involved in atrial ions balance including calcium.<sup>11,12</sup> The rs2200733 SNP has been shown to modulate risk of AFib in several

populations.<sup>13–16</sup> Conversely, the rs2200733 SNP was not associated with AFib risk among a Hispanic/Latino cohort in the USA.<sup>17</sup> Therefore, the association between the rs2200733 SNP and AFib could vary according to the genetic background of the population.

In Arab countries, there is still a need to study the contribution of the rs2200733 SNP to the risk of AFib. Therefore, the current study aimed to examine the association of the rs2200733 SNP with AFib risk in the Jordanian population.

## Methods

### Subjects

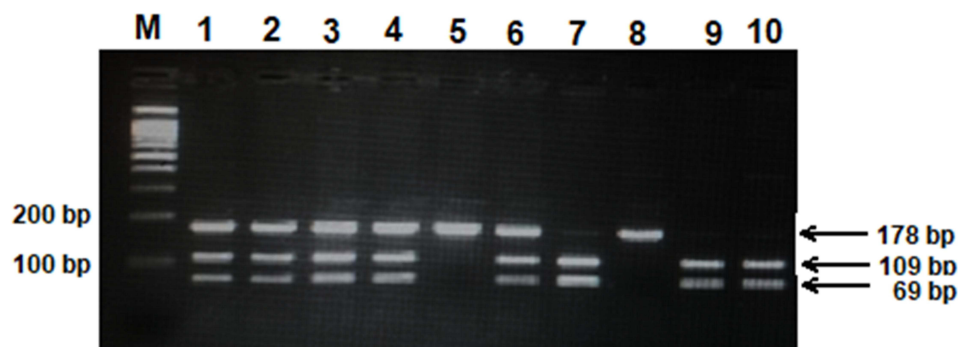
The study is case-control in design and was conducted between April 2022 and May 2024. Subjects with AFib (62.5 ±15.9 years old) were recruited from cardiology out-patient clinics in King Abdullah University Hospital (KAUH), Irbid, Jordan, which is the largest tertiary healthcare provider in northern Jordan and the only center providing percutaneous coronary interventional service, serving approximately 3 million inhabitants. Health controls (without history of AFib, 60.2±12.3 years old) volunteered to be part of the study. Patients with evidence of AFib were selected and invited to participate in the study. AFib was confirmed by a consultant physician (Dr. Abdullah Al-Kasasbeh) according to the European Society of Cardiology diagnostic criteria and based on electrocardiogram data.<sup>18</sup> Patients with defects/disorders of heart structure, congestive heart failure, none-AFib arrhythmias, cancer, autoimmune/blood conditions, liver/renal diseases, and thyroid dysfunction were excluded from the study.<sup>19,20</sup> The study was approved by the Ethics Committee at King-Abdullah University Hospital (KAUH, ID: 213–2022), and was conducted in accordance with the Declaration of Helsinki and its amendments. Informed consent was granted from all subjects before beginning study procedures. This includes access to the clinical records of patients in KAUH. Sociodemographic characteristics such as age, gender, weight, height, smoking status, and family history of atrial fibrillation were obtained using a paper questionnaire.

### Blood Sampling and DNA Extraction

Whole blood in EDTA tubes (3 mL) was obtained from all participants for DNA analysis. Samples were stored at –20°C until use. Blood DNA was isolated using a column-based extraction kit (Qiagen, Düsseldorf, Germany). The integrity of the extracted DNA was assessed using electrophoresis and spectrometric techniques (BioRad-Smart Spec 3000, USA). Isolated DNA was kept at –20°C until used.

### The rs2200733 Genotyping Assay

The rs2200733nSNP was genotyped using PCR as previously described.<sup>19</sup> The PCR primers were forward: “5' TATTCACAGGCTTCCCTCTA3'” and reverse: “5'AATGCTGTGGGAACATAAAC3'”. PCR steps were 95°C for 5min, thirty cycles of 95°C/35sec, 60°C/40sec, and 72°C/40sec, and extension of 72°C/5min. The PCR product (178bp) was exposed to Kzo9I enzyme (cuts at GATC site, Biolabs, USA) at 37°C overnight. The amplified fragment containing the C allele is cleaved by the enzyme to give 109bp and 69bp fragments (Figure 1). The amplified fragment



**Figure 1** Gel electrophoresis image of restriction fragment length polymorphism – polymerase chain reaction (RFLP-PCR) of rs2200733 polymorphism. The amplified PCR product containing rs2200733 polymorphism (178bp) were exposed to Kzo9I restriction enzyme. Digestion of the amplified product with the enzyme produces 109bp and 69bp fragments. Lane M represents a 100bp marker. Lanes 1–4, and 6 represent CT genotype. Lanes 7,9, and 10 represent CC genotype. Lane 5 represents TT genotype.

containing T allele is resistant to the enzyme. DNA fragments were analyzed after enzymatic digestion with 3% agarose and ethidium bromide.

## Statistical Analysis

Sample size calculation was performed using G\*Power 3.1 software with an effect size of 0.25, alpha=0.05 and power of 0.95. The calculated sample size was 164 participants. Continuous variables were assessed using GraphPad program (version 7, USA). The association between genotype frequencies and haplotype frequencies with AFib was conducted using SNPstats program. SNPstats was also used to assess Hardy Weinberg equilibrium for the examined SNP. A p-value of less than 0.05 indicates a significant difference.

## Results

Table 1 shows characteristics of the study subjects. Age (mean  $\pm$  SD) was 60.2 $\pm$ 12.3 for the control group and 62.5 $\pm$ 15.9 for the AFib group (p=0.085). The ratio of men to women and smoking frequency were similar between the two groups (P>0.05). Other parameters (hypertension, family history and diabetes) were more frequent in AFib compared with controls (P<0.01). Moreover, body mass index (BMI) was higher in AFib than controls (P<0.01).

The distribution of rs2200733 SNP genotypes among the study groups is shown in Table 2. The C allele and CC genotype are prevalent among the study subjects (78% and 62%, respectively). The mutant T allele and C/T+TT genotypes were higher among AFib compared to controls (P<0.05, OR [CI]: 1.65 [1.12–2.43]).

Table 3 shows the association between rs2200733 and AFib according to different inheritance models. The results showed an association between rs2200733 and AFib in all inheritance models except the recessive model. The C/T and T/T genotypes increase the risk of AFib by odd ratios of 1.63 to 1.68 (P<0.05). Therefore, the presence of the T allele significantly increased the risk of AFib in the studied population.

Table 4 shows the frequency of the mutant rs2200733 T allele among different world populations. The T allele is common in Chinese and Taiwanese populations (50–60%). However, the mutant T allele is less common in European and Middle Eastern populations (range 10–23%). In the United States, the frequency of the T allele is about 31%. Thus, the T allele frequency spectrum is observed among the world populations.

**Table 1** The Demographic Characteristics of the Participants

Variables	Subcategory	Controls n (%)	Patients n (%)	P-value
<b>Age (mean<math>\pm</math>SD)</b>		60.2 $\pm$ 12.3	62.5 $\pm$ 15.9	0.085
<b>BMI* (kg/m<sup>2</sup>, mean<math>\pm</math>SD)</b>		28.1 $\pm$ 6.0	30.6 $\pm$ 6.2	<0.01
<b>Gender</b>	Men	136 (49.6)	82 (46.6)	0.528
	Women	138 (50.4)	94 (53.4)	
<b>Smoking status</b>	Yes	71 (25.9)	33 (18.2)	0.078
	No	203 (74.1)	143 (81.8)	
<b>Hypertension</b>	Yes	50 (18.2)	123 (69.8)	<0.001
	No	224 (81.8)	53 (30.2)	
<b>Positive-family history</b>	Yes	34 (12.4)	50 (28.4)	<0.001
	No	240 (87.6)	126 (71.6)	
<b>Diabetes mellitus</b>	Yes	39 (14.2)	64 (36.3)	<0.001
	No	235 (85.8)	112 (63.7)	

Abbreviation: \* BMI, Body mass index.

**Table 2** The Distribution of rs2200733 Alleles and Genotypes Among the Study Groups

Allele	All Subjects	Control Group	AFib Group	P value
<b>C (wildtype)</b>	705 (78%)	443 (81%)	262 (74%)	0.022
<b>T (mutant)</b>	195 (22%)	105 (19%)	90 (26%)	
<b>C/C</b>	278 (62%)	182 (66%)	96 (54%)	0.038
<b>C/T</b>	149 (33%)	79 (29%)	70 (40%)	
<b>TT</b>	23 (5%)	13 (5%)	10 (6%)	

**Table 3** The Association Between rs2200733 and Atrial Fibrillation Among the Studied Population

Model	Genotype	Controls n(%)	AFib n(%)	OR (95% CI)*	P-value
<b>Codominant</b>	C/C	182 (66.4%)	96 (54.5%)	1.00	0.039
	C/T	79 (28.8%)	70 (39.8%)	1.68 (1.12–2.52)	
	T/T	13 (4.7%)	10 (5.7%)	1.46 (0.62–3.45)	
<b>Dominant</b>	C/C	182 (66.4%)	96 (54.5%)	1.00	0.012
	C/T-T/T	92 (33.6%)	80 (45.5%)	1.65 (1.12–2.43)	
<b>Recessive</b>	C/C-C/T	261 (95.3%)	166 (94.3%)	1.00	0.66
	T/T	13 (4.7%)	10 (5.7%)	1.21 (0.52–2.82)	
<b>Overdominant</b>	C/C-T/T	195 (71.2%)	106 (60.2%)	1.00	0.017
	C/T	79 (28.8%)	70 (39.8%)	1.63 (1.09–2.43)	

**Abbreviations:** \* OR, odd ratio; CI, confidence interval.

**Table 4** The Frequency of the rs2200733 T Allele in Different World Populations

Population	Frequency (%) of Mutant T Allele	Reference
Jordanian	19	Current
Indian	13.2	Bhanushali et al, <sup>21</sup>
Spanish	15.8	Ferran et al, <sup>22</sup>
Denmark	10.4	Olesen et al, <sup>23</sup>
Italian	15	Anselmi et al, <sup>24</sup>
Polish	12.1	Kiliszek et al, <sup>25</sup>
Taiwanese	60.1	Lee et al, <sup>26</sup>
Chinese	50.5	Han et al, <sup>20</sup>
Uzbek	23.3	Abdullaeva et al, <sup>15</sup>
Greek	17.9	Kalinderi et al, <sup>27</sup>
United States	31.5	Goodloe et al, <sup>28</sup>

## Discussion

In the current study, the rs2200733 was associated with AFib in the Jordanian population. The mutant T allele and the CT and TT genotypes were found to increase the risk of AFib. These findings are consistent with previous reports from other populations. In a genome-wide association study, rs2200733 was found to be associated with AFib in European and Asian populations.<sup>29</sup> The mutant T allele has been reported to increase the risk of AFib by 3 folds in the Indian population.<sup>21</sup> In a Spanish study, the rs2200733 was found to increase the risk of AFib by an odd ratio of 1.87.<sup>22</sup> Similar findings have been reported among Italian, Uzbek, Polish, Chinese, Greek and Taiwanese populations.<sup>20,24–27</sup> Among Danish and US populations, rs2200733 was associated with onset of lone AFib.<sup>23,28,30</sup> The rs2200733 was found to increase the risk of cardioembolic stroke related to AF in Polish subjects.<sup>31</sup> Finally, the rs2200733 has been reported to increase the risk of AFib recurrence after catheter ablation.<sup>32</sup> Conversely, the rs2200733 was not associated with AFib risk among the Hispanic/Latino cohort in the USA.<sup>17</sup>

The clinical significance of the rs2200733 is well documented. In addition to Afib, this variant has been shown to be associated with the incidence of congenital esophageal atresia in the Chinese population,<sup>33</sup> the development of preeclampsia in the Indian population,<sup>34</sup> ischemic stroke in the non-Asian populations,<sup>35</sup> and obstructive sleep apnea in the US population.<sup>36</sup>

The rs2200733 is in close proximity to the PITX2 gene and can modulate gene transcription.<sup>9,10</sup> PITX2 plays a role in left-right anatomical asymmetry, pulmonary cardiomyogenesis, and atrial resting membrane potential.<sup>11,12</sup> PITX2 is also involved in regulating ionic conduction and calcium balance in atrial cardiomyocytes.<sup>37,38</sup> A significant reduction in PITX2 has been reported in patients with sustained AFib.<sup>39</sup> In-silico investigations suggested that Pitx2 insufficiency induced arrhythmia by inductive structural remodeling and the subsequent depolarizations and re-entrant excitation modulation.<sup>40,41</sup>

In the current study, the frequency of the mutant T allele was found to be 19%. This frequency is close to what has been reported in European and Asian countries such as Greece, Italy, Spain, Poland, Uzbekistan, and India.<sup>19,21–25,27</sup> However, higher frequencies (31–60%) have been reported in populations from China, Taiwan, and USA.<sup>20,26–28</sup> Thus, a wide spectrum of mutant T allele frequencies has been observed globally.

In the present study, body mass index, diabetes, and hypertension were reported to be associated with AFib. This finding is consistent with several previous studies.<sup>42–46</sup> In general, obesity negatively impacts cardiovascular hemodynamics and causes structural cardiac remodeling that can cause cardiovascular diseases including AFib.<sup>42</sup> In addition, hypertension is a common risk factor for AFib by inducing atrial structural and electrophysiologic manifestations.<sup>44,45</sup> Similarly, diabetes is linked to AFib by causing structural and electrical remodeling in the myocardium.<sup>46</sup>

A limitation of the study is that the impact of rs2200733 on the expression of PITX2 in subjects was not investigated. In addition, other SNPs affecting the expression of PITX2 such as the rs6843082 SNP have not been investigated. Future studies that address such limitations are highly recommended.

## Conclusion

The rs2200733 is associated with AFib among Jordanian patients. The mutant T allele of the rs2200733 might increase the risk of AFib. In addition, factors such as obesity, diabetes, and hypertension are associated with the development of AFib. Combining the rs2200733 polymorphism with other identified risk factors in a model predicting the occurrence of AFib could identify the at-risk group in Jordan. Finally, future studies linking the rs2200733 polymorphism with the expression of PITX2 in patients could shed light on the mechanisms by which the rs2200733 polymorphism increases the risk of AFib.

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## Disclosure

Authors have nothing to disclose.

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