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ORIGINAL ARTICLE

Association of rs2200733 at 4q25 with early onset of lone atrial fibrillation in young patients

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Abstract

Objective. Genome wide association studies have shown an association between rs2200733 at 4q25 and atrial fibrillation (AF). In this case-control study we investigate the association of rs2200733 and *lone* AF in young patients. *Methods*. We included 196 young patients with lone AF and the first episode before the age of 40 years. We analyzed the single nucleotide polymorphism (SNP) rs2200733 for the lone AF patients and compared them to a control group of 176 age matched healthy individuals. *Results.* No significant differences, in neither genotype distribution, nor minor allele frequencies were found between the lone AF patients and the healthy controls. *Conclusion*. Our results suggest that the rs220733 is not a risk factor for AF in patients with no other cardiovascular disease and with early onset of the arrhythmia.

Key words: *atrial fibrillation, genetics, single nucleotide polymorphisms*

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice. It is caused by disorganized electrical impulses that originate in the atria and pulmonary veins (1), leading to conduction of irregular impulses to the ventricles. It can cause palpitations, fainting, chest pain and even congestive heart failure symptoms and is associated with a significantly increased risk of stroke.

In a recent genome-wide association study by Gudbjartsson et al. (2) on a sample of the Icelandic population, an association was shown between three single nucleotide polymorphisms (SNP) in the 4q25 locus and AF. They included 550 patients with AF and 4476 controls. All three SNPs located in the 4q25 locus (rs2200733, rs2220427 and rs2634073) were within the same single linkage disequilibrium (LD) block. Among the SNPs investigated in the Icelandic study population by Gudbjartsson et al., rs2200733 demonstrated the most robust association ($p = 0.0000000016$). Furthermore, the association between the rs2200733 SNP and AF has been replicated in several studies and in different populations (3,4).

The molecular mechanisms responsible for the increased risk of AF are unknown, but interestingly the closest gene, *PITX2*, is a transcription factor for determining left-right asymmetry (5). *PITX2* has also been shown to be involved in the differentiation of the left atrium and the development of the pulmonary myocardium (6), known to play a role in the development of AF.

In this study we investigated the association of the rs2200733 SNP and AF in a population of patients with *lone* AF and onset of disease before the age 40 years. To our knowledge this association has not previously been investigated in this subgroup of AF patients.

Methods

The study conformed to the principles outlined in the Declaration of Helsinki, and was approved by

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the local ethics committee of Copenhagen and Frederiksberg (No. (KF) 01 313322)). Written informed consent was obtained from patients and healthy volunteers.

A total of 196 patients were included from eight hospitals in the Copenhagen region of Denmark. Patient records from all in- and outpatient activity in the past 10 years with the diagnose code [ICD-10] I48.9 (Atrial fibrillation and flutter) were identified and read. Only lone AF patients with onset of disease before age 40 years were included. No patients had an abnormal echocardiography and 31% had a first-degree relative with a history of AF.

A control population of 176 healthy blood donors was established. Echocardiograph (ECG) and clinical information was collected in order to reduce the possibility of undiagnosed heart disease. All patients and healthy controls were Caucasian.

Genotyping was performed as previously described (7). In brief, the deoxyribonucleic acid (DNA) was extracted from whole blood that had been stored at −20°C using the QIAamp DNA Blood Midi and Maxi kits (Qiagen, Hilden, Germany). The rs220733 SNPs was determined using fluorescence-based real-time PCR (ABI PRISM 7900 Sequence Detection System, Applied Biosystems, CA, USA and a predeveloped assay (Applied Biosystems). An allelic discrimination run was performed allowing for discrimination between the allele composition of each sample.

The genotype distribution of each autosomal polymorphism was compared between subjects with AF and controls by the χ^2 test (3×2) or Fisher's exact test. Allele frequencies were estimated by the gene counting method and analysed with the χ^2 or Fisher's exact test. Logistic regression analysis was used, and odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA). Statistical differences with $p < 0.05$ were considered significant.

Results

No significant differences were found in baseline characteristics between the lone AF patients and the healthy controls. The genotype distributions for lone AF patients and controls were in Hardy-Weinberg equilibrium (data not shown). The genotype distribution for the lone AF patients and controls are presented in Tables I and II. The minor allele frequency for the lone AF patients and controls were respectively, 14.5% and 10.2%. There weren't any significant differences in neither genotype distribution, nor minor allele frequencies between the lone AF patients and the healthy controls.

Table I. Genotype distributions and minor allele frequencies.

	Genotype distributions (%)			
SNP	TT	CT	CC	p-value*
rs220733				
Case	3 (1.5)	50 (25.5)	143 (73.0)	
Control	3 (1.7)	30 (17.1)	143 (81.2)	p = 0.12

Discussion

To the best of our knowledge, this is the first study to explore the association of rs2200733 at 4q25 between patients with early onset lone AF before age 40 years and age matched healthy controls. We do not find an association between AF and rs2200733, as reported by Gudbjartsson et al.

Our aim was to investigate the association between rs2200733 and AF, in a subgroup of patients with no other known cardiac conditions. We excluded patients with structural or ischemic heart disease, hypertension, diabetes or metabolic diseases and patients with abnormal echocardiography. Furthermore we only included patients with the first episode of AF before the age of 40 years. The age-related inclusion criterion is more rigorous than what is usually used when defining lone AF populations (8). So our population is highly selected compared to the GWAS study by Gudbjartsson et al. (2), but also compared to the studies in which the association has been replicated (3,4).

PITX2 is the closest gene to rs2200733 SNP in the 4q25 locus. It is a transcription factor for determining left-right asymmetry (5). *PITX2* has also been shown to be involved in the differentiation of the left atrium and the development of the pulmonary myocardium (6), known to play a role in the development of AF. The fact that an association between rs2200733 and AF cannot be shown in our study, could be the result of our selection of a subgroup of AF patients. A recent study screened the *PITX 2* gene for genetic variants in patients with idiopathic AF. In this comparable and also highly selected cohort no mutations were shown to be associated with AF (9).

We find it very interesting that an association between rs2200733 and early onset of AF could not be shown. The results lead us to speculate whether

Table II. Minor allele distribution, frequency and odds ratio.

Genotype	AF	Controls	OR	95%CI	p-value
CC	143 (73.0)	143 (81.2)			
CT/TT	53 (27.0)	33 (18.8)			
Minor allele frequency (%)	14.3	10.2	1.62	0.98–2.62	0.06

the underlying mechanisms for AF differ in the young patients with AF compared to patients with later onset AF, or AF secondarily to other conditions.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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