Identification of Atrial Fibrillation Risk Variant RS2200733 In Indian Young Adult Population

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Short Report

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Abstract

Atrial fibrillation (AF) is a common cardiac arrhythmia that affects millions of people. a substantial genetic contribution to AF has been identified by number of studies over the years. The SNP that is often linked with genetic predisposition to AF is rs2200733 located in the intergenic region close to PITX2 gene which is implicated in cardiac structure and function. rs2200733 is commonly observed in major global populations. Our study aimed to establish the prevalence of this important SNP among young healthy adults in order to assess the risk of genetic susceptibility which could culminate into AF later in life. The study identified a substantial frequency of rs2200733 in Indian population at 21%.

Introduction

Atrial fibrillation (AF) is a cardiac arrhythmia that affects millions of individuals globally [1]. It increases the risk of stroke, heart failure and may lead to mortality [2]. Many factors such as advancing age, hypertension, male gender and obesity may increase the risk of AF susceptibility[3] in addition to the presence of strong genetic susceptibility factors [4]. Many studies have reported the association between common genetic variants and the risk of AF [5, 6]. Genome-wide association studies (GWAS) across European and Asian populations [7, 8] have confirmed and validated rs2200733 at 4q25 as a major single nucleotide polymorphism (SNP) linked with AF including the largest meta-analysis of GWAS studies for AF in Europeans, Japanese and African Americans [9]. rs2200733 is also strongly associated with AF recurrence ($p=0.011$), with an OR of 1.715 risk of recurrence associated with T allele [10]. Though the exact mechanism by which the intergenic rs2200733 causes AF is unclear, it has been postulated that it could play a regulatory role for the nearby gene paired-like homeodomain 2 (PITX2)[7] which is known to play an important role in atrial development and differentiation, proliferation and expansion of pulmonary myocardial cells [11, 12]. The aim of the present study is to estimate the prevalence of the important AF-linked SNP rs2200733 in healthy Indian population and hence assess the extent of genetic susceptibility in the general population.

Methods

Subjects

A total of 74 subjects aged between 19-30 years were recruited for the study at Aarupadai Veedu Medical College and Hospital, Puducherry. All participants were healthy without any co-morbidities comprising of north and south Indian ethnicities. There were 40 females and 34 males, the mean (SD) BMI was 25.8 (± 5.6). The study was approved by institutional ethics committee. All subjects provided written informed consent. Two ml of venous blood was collected from the subjects. Genomic DNA was isolated using commercial kit (QIAGEN, Hilden, Germany)

Genotyping

rs2200733 was genotyped using quantitative PCR SNP genotyping assay using separately labeled probe for each of the allele. FAM was used for both alleles requiring two separate reactions for each sample.

Forward primer	GAGTAGTAATTCTGCCTTGGTGGTA
Reverse Primer	GTCCACACCGGTTAGAATCTCA
Probe allele 1 (mutant)	TGGGTTTTGATTTTGATCAGAGA
Probe allele 2 (wild)	CTTGGGTTTTGATTTTGATTAGAGA

Genetic Analysis

Allele and genotype frequencies were estimated by direct gene counting method. Hardy-Weinberg Equilibrium was calculated using Fisher's exact test.

Results And Discussion

The frequency of rs2200733 minor allele T in the study population is 21%. The genotype frequencies were observed at 61.5% (n=48) for homozygous wildtype, 35.8% (n=28) for heterozygotes and 2.5% (n=2) for homozygous mutants. The study shows the presence of the AF risk variant at a substantial frequency suggesting the considerable genetic susceptibility of the general population. An earlier study in Indo-Aryan population identified rs2200733 to be associated with lone AF. However, the frequency of rs2200733 was found at 13% in healthy controls in that population [13]. The present study subjects hail from north and south Indian states, and due to the combination of Indo-Aryan and Indo-Dravidian populations, the results reflect that of the pan-Indian frequency.

The heritability rate for AF has been estimated to be 62% suggesting the significant role played the genetic factors. Both genetic and environmental factors contribute to the pathogenesis of AF. A strong genetic predisposition along with acquired cardiac or systemic diseases culminates in the development of AF [14]. In a study that examined the role of rs2200733 in risk of AF recurrence, the SNP has been suggested to play an important role in the development and differentiation of atria/pulmonary veins (PV). It was also shown that patients harboring TT genotype have a larger right atrium and superior PV. The study also found that carriers of T allele had a larger diameter of superior PVs [10]. rs2200733 is also postulated to regulate its nearest gene PITX2 [15]. This gene has been shown to play an important role in the development of pulmonary vein myocardial sleeve and regulate signaling pathways leading to proarrhythmic changes in the left atrial myocardium and structural remodeling of the intercalated disc which is observed in AF pathophysiology [16, 17]. Many genetic variants identified by GWAS are often found in the intergenic regions which may play a regulatory role in modulating the expression of nearby genes [18]. The intergenic SNP rs2200733 which is widely prevalent across global populations plays a crucial role in AF pathogenesis. The present study did not evaluate the association between the genetic risk variant and AF or consider other potential risk factors. AF being polygenic, future genetic studies of AF in Indian population should consider interrogating rs220733 given its considerable prevalence in

Indians along with other pathogenic SNPs validated by meta-analyses [9, 19]. Developing a panel of highly prevalent risk variants in a population would enable identifying individuals who are genetically predisposed to AF followed up with counselling and advocating life style changes to prevent and lower AF related morbidities later in life.

Statements And Declarations

Competing Interests Authors declare no competing interests

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