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Original Article

KCNA5 gene polymorphism associate with idiopathic atrial fibrillation

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Abstract: Objective: To investigate the correlation between KCNA5 single nucleotide polymorphism (SNP) and idiopathic atrial fibrillation (IAF). Methods: A case-control study was conducted, including 282 cases of IAF patients and 300 cases of age and sex-matched normal controls; gene sequencing method was used to detect the distribution of KCNA5 SNP (rs3741930 and rs1056468) in the two groups. The IAF patients were divided into two groups based on the different genotypes of rs1056468 and rs3741930; differences in clinical parameters between the two groups of patients were compared. Results: For rs3741930, the CC, CT and TT genotype frequencies in the IAF group were 16.7%, 50.0%, and 33.3% respectively; C allele frequency in IAF group was 41.7%; in the normal control group, those were 10.0%, 49.3%, 40.7% and 34.7% respectively; CC genotype frequency and C allele frequency in IAF group were significantly higher compared with the control group (P=0.019, P=0.014). For rs1056468, the AA, AT and TT genotype frequencies in the IAF group were 44.3%, 48.6%, and 7.1% respectively; in 300 cases of normal controls, those were 38.7%, 50.7%, and 10.6% respectively; A allele frequency in IAF group was 68.6 %, and it was 64.0% in normal controls. There were no significant differences in genotype and allele frequencies between control and IAF groups (P>0.05). In IAF group, among different genotypes of rs1741930 and rs1056468, there were no significant differences in age, SBP, DBP, HR, LAD and LVEF (P>0.05). While the BMI in CC and CC+TT groups of rs3741930 locus were 26.9±2.3 Kg/m^2 and 24.8±2.5 Kg/m^2 respectively. There were statistical differences between the two groups (P=0.019). BMI in AA and AA+TT groups of rs1056468 locus were 24.9±2.7 Kg/m^2 and 26.4±2.4 Kg/m^2 respectively; There was statistically significant significance between the two groups (P=0.014). Conclusion: The single nucleotide polymorphism rs3741930 locus in KCNA5 gene was related to the risk of IAF; the population carrying C allele was more susceptible to IAF; the polymorphic loci, rs3741930 and rs1056468, were correlated with the BMI of IAF patients.

Keywords: Idiopathic atrial fibrillation, KCNA5, SNPs

Introduction

Atrial Fibrillation (AF) is a common clinical tachyarrhythmia. According to the AF guideline proposed by European Society of Cardiology (ESC) in 2010 [1], the prevalence of AF in general population is 1-2%; ZHOU et al [2] found that in the Chinese population, the incidence of AF is around 0.77%, which is higher in men than women; the incidence was positively correlated with age, and in elderly population older than 80 years, the incidence rate is up to 7.5%.

The advanced age, male gender, hypertension, obesity, coronary heart disease, myocardial infarction, valvular heart disease and hyperthyroidism were the traditional risk factors for AF [3-6]. However, there are some younger AF patients who have not these traditional risk factors such as structural heart disease, high blood pressure, valvular heart disease, hyperthyroidism and myocardial infarction. This kind of AF is named idiopathic atrial fibrillation (IAF) [7]. IAF patients often have a familial aggregation, and its pathogenesis may be related to genetic factors [8].

Framingham study showed that if there is at least one parent with AF, the risk of AF in offspring will significantly increase (OR=1.85, 95% CI 1.12-3.06, P=0.02). If the first-onset-age of farther (mother) was younger than 75 years, the

risk will be higher (OR=3.23, 95% CI: 1.87-5.58, P<0.001) [9]. Arnar et al [10] reported that, when there were AF patients in parents and siblings, the relative risk of AF was 1.77. And when the AF onset-age of parents and siblings was younger than 60 years, the relative risk increased to 4.67 times, which is similar to Framingham study. In 2009, a Danish researcher found [11] that the probability of simultaneous AF in identical twins (n=356) was significantly higher than that in fraternal twins (n=781) (22.0% *vs.* 11.6%, P<0.0001).

In subsequent studies, Chinese scholar Chen [12] conducted a microsatellite and genome-wide association study for a Chinese familial atrial fibrillation (FAF) family in 2003, and found that KCNQ1 gene mutation was related with AF generation and maintenance; the gene encodes a subunit of slow delayed rectifier potassium current (Iks) channel in cardiomyocytes. By sequencing they found that the adenine nucleotide in the 418 locus of the gene was replaced by guanine nucleotide (A>G), leading to the replacement of 140th Serine by Glycine (S140G) in the encoded Iks channel protein. The mutation was only found in patients with AF in this family, and none of the mutation was screened in a wider range of healthy control population. Further research found that this mutation can enhance Iks potassium current, shorten action potential duration and effective refractory phase of atrial myocytes, and easy the atrium reentry to induce AF. Yang et al [13] found that in 2004, KCNE2 mutations located in the 21 q22.1 region of human chromosome 21 were associated with AF; the gene encodes the β subunit of slow delayed rectifier potassium current (Iks) channel in cardiac myocytes; its mechanism of inducing AF is similar to S140G. Otway et al [14] found that in 2005, KCNQI R14C missense mutation was related with AF. R14C mutation in this gene can increase Iks channel current under hypotonic state, and faster the activation speed, and slow deactivation rate. The results confirmed that other factors could interact with genetic mutations to co-induce AF.

Since Brugada [15] found the first AF locus 10q22-q24 region in 1997, so far more than ten disease-causing gene mutations which can induce the IAF and FAF have been found, such as KCNJ2, KCNH2, ABCC9, KCNN3, NPPA, KCNQI, KCNSA, and CYP11B [16-22]. Speeding delayed rectifier potassium current (IKur) is a potassium ion channel current only existing in atrial myocytes, playing an important role in the repolarization and action potential duration of atrial myocytes; its molecular basis is Kv 1.5 potassium channel; KCNA5 gene encodes the pore section of the channel; KCNA5 genetic mutation can cause changes in Ikur, thereby inducing IAF. Therefore, this study selected IAF patients as subjects to explore the correlation between KCNA5 gene single nucleotide polymorphism (SNP) and the IAF.

Subjects and methods

Subjects

In this study, 282 patients with IAF admitted in the First Hospital of Hebei Medical University and the Second Hospital of Hebei Medical University were collected from May 2008 to November 2014.

Inclusion criteria

The included patients must meet to 1) ECG suggesting AF; 2) AF signs existing: the intensity of first heart sound varied, absolutely irregular heartbeat, and pulse shortage; 3) presence of AF symptoms with palpitation, shortness of breath, or irregular heartbeat, etc. or without related symptoms.

Exclusion criteria

The patients will be excluded from this study if meet to the following factors: 1) with coronary heart disease, cardiomyopathy, pericarditis, hypertension, hyperthyroidism, structural heart disease and other traditional risk factors and 2) age of onset >60 years.

All included patients underwent comprehensive and systemic medical history review and physical examination, and the electrocardiogram, echocardiogram, blood count, blood chemistry and other laboratory examinations were carried out. 300 cases of age and sex-matched healthy individuals were identified as the control group. In both case and control groups, 5 ml peripheral blood from each patient were drawn into anticoagulant tubes containing EDTA, and placed in -80°C refrigerator for DNA extraction. The study was approved by the ethic committee of Tongji Hospital, and all patients and controls have signed the informed consent.

Table 1. Distribution of genotype and allele frequency of rs3741930 in IAF and control group

SNPs		IAF group (n=282)	Control group (n=300)	*P* value	OR (95% CI)
rs371930					
Genotype	CC	47 (16.7%)	30 (10.0%)	0.019	1.800 (1.102~2.938)
	CT	141 (50.0%)	148 (49.3%)	0.813	1.027 (0.741~1.422)
	TT	94 (33.3%)	122 (40.7%)	0.068	0.729 (0.520~1.023)
Allele	C	235 (41.7%)	208 (34.7%)	0.014	1.346 (1.062~1.706)
	T	329 (58.3%)	392 (65.3%)		

OR: Odds ratio, CI: Credible intervals.

Table 2. Distribution of genotype and allele frequency of rs3741930 in IAF and control group

SNPs		IAF group (n=282)	Control group (n=300)	*P* value	OR (95% CI)
rs1065486					
Genotype	AA	125 (44.3%)	116 (38.7%)	0.166	1.263 (0.907~1.357)
	AT	137 (48.6%)	152 (50.7%)	0.615	0.920 (0.664~1.274)
	TT	20 (7.1%)	32 (10.6%)	0.133	0.639 (0.356~1.126)
Allele	A	387 (68.6%)	384 (64.0%)	0.095	1.229 (0.964~1.569)
	T	177 (31.4%)	216 (36.0%)		

OR: Odds ratio, CI: Credible intervals.

Methods

Polymorphic loci selection: KCNA5 gene is located on the 12p13 region of human chromosome 12 [23, 24]. We selected two SNPs (rs3741930 and rs1056468) according to human genome database on HapMap (http://hapmap.ncbi.nlm.nih.gov//). rs3741930 (C>T) is located in 5 'Untranslated Region (5'-UTR) and rs1056468 (A>T) is located in 3' Untranslated Regions (3'-UTR).

Genomic DNA extraction: Genomic DNA from the whole blood cells was extracted using a QIAamp Blood kit (Qiagen, Hilden, Germany), following the manufacturer's instructions. DNA concentration and purity of each sample were measured by ultraviolet spectrophotometer (Eppendorf, Hamburg, Germany). DNA samples were routinely stored at -20°C.

Genotyping: Analysis of rs3741930 and rs1056468 were performed using TaqMan SNP genotyping assay allelic discrimination method (Applied Biosystems) as previously described [25, 26]. The average genotype completeness was 98% for the patient and control subject samples. The accuracy was >99% according to duplicate genotyping of 10% of all samples.

Statistical analysis: All data were processed using SPSS 17.0 statistical software (SPSS, Chicago, IL, USA). Hardy-Weinberg equilibrium (HWE) were analyzed using χ^2 test; and the frequency distributions of KCNA5 SNPs in the IAF and control groups were compared using χ^2 test. In order to assess the impact of KCNA5 SNPs on IAF progression, the patients were divided into two groups (wild-type and mutant-type) based on different genotypes; the significant differences in clinical indicators were analyzed between the two groups of patients. χ^2 test was used to compare percentages and ratios; t test was used to compare the mean index. $P \leq 0.05$ was considered significant.

Results

Characteristics of participants

IAF patients included 221 males and 61 females which were in line with the typically high incidence of AF in males. The mean age was 46.12±9.11 years (from 18 years old to 60 years old). In normal control group, there were 226 males and 74 females; the mean age was 47.12±8.43 years (ranging from 30 years old to 60 years old). There was no significant difference between the two groups both in age and sex ($P>0.05$).

Genotype and allele frequency distribution of rs3741930

As shown in **Table 1**, the genotypes distribution of rs3741930 both in IAF group and control group were in line with H-WE. The CC, CT and TT genotype frequencies in the IAF group were 16.7%, 50.0%, and 33.3% respectively; C allele

Table 3. The characteristics of included participants among different genotypes

Indices	rs3741930			rs1056468		
	CC	CT+TT	*P* values	AA	AT+TT	*P* values
Age (Year)	46.6±6.4	46.7±7.1	0.443	46. 8±7.4	47.1±7.0	0.490
BMI (Kg/m^2)	26.9±2.3	24.8±2.5	0.019	24.9±2.7	26.4±2.4	0.014
SBP (mmHg)	122.1±11.3	118.1±12.3	0.305	118.3±11.8	121.4±12.4	0.132
DBP (mmHg)	79.6±7.4	77.4±8.3	0.110	76.0±9.4	76.5±7.8	0.440
HR (BPM)	78.1±13.5	78.4±17.1	0.876	79.9±20.1	77.1±16.3	0.763
LAD (mm)	35.4±7.5	34.5±5.1	0.409	33.4±3.9	34.2±5.1	0.069
EF (%)	62.1±5.1	63.4±5.3	0.160	64.2±5.3	63.1±6.0	0.201

LAD: Left atrial diameter; BMI: Body Mass Index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Hear Rate; EF: Ejection fraction.

frequency in IAF group was 41.7%; in the normal control group, those were 10.0%, 49.3%, 40.7% and 34.7% respectively; CC genotype frequency and C allele frequency in IAF group were significantly higher compared with the control group (P=0.019, P=0.014).

Genotype and allele frequency distribution of KCNA5 rs1056468

As shown in **Table 2**, rs1056468 genotypes frequency distribution was also in line with H-WE. The AA, AT and TT genotype frequencies in the IAF group were 44.3%, 48.6%, and 7.1% respectively; in 300 cases of normal controls, those were 38.7%, 50.7%, and 10.6% respectively; A allele frequency in IAF group was 68.6 %, and it was 64.0% in normal controls. There were no significant differences in genotype and allele frequencies between control and IAF groups (P>0.05).

Comparisons of clinical data among different genotypes in IAF group

The relationships among various clinical parameters in patients with different genotypes of rs3741930 and rs1056468 were analyzed respectively (**Table 3**). The results showed that for the two loci, there was no significant correlation among age, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), left atrium diameter (LAD), left ventricular ejection fraction (LVEF) and other clinical indicators (P>0.05). While the BMI in CC and CC+TT groups of rs3741930 locus were 26.9±2.3 Kg/m^2 and 24.8±2.5 Kg/m^2 respectively. There were statistical differences between the two groups (P=0.019). BMI in AA and AA+TT groups of rs1056468 locus were 24.9±2.7 Kg/m^2 and 26.4±2.4 Kg/m^2 respectively; There was statistically significant significance between the two groups (P=0.014).

Discussion

In the present study, we found the single nucleotide polymorphism rs3741930 locus in KCNA5 gene was related to the risk of IAF; the population carrying C allele was more susceptible to IAF; the polymorphic loci, rs3741930 and rs1056468, were correlated with the BMI of IAF patients.

With advanced progression in molecular genetics, the researchers found that IAF may be a "molecular channel disease" [27]. While further studies found that KCNA5 mutations were closely associated with IAF [28, 29]. In 1993, Phromchotikul et al [30], used multiple-region correlation analysis to position four molecular markers of KCNA5 gene. KCNA5 gene-encoded Kv1.5 potassium channel is a subtype of Kvl potassium channel. The channel consists of αand β subunits; four identical αsubunits form a homologous tetramer, forming the pore region and voltage-sensitive area of Kv1.5 channel complex. Each α subunit contains six transmembrane protein molecule areas (S1 to S6), respectively, constituting the subjects of voltage-gated channels, N and C-terminal subunit. β play a supporting role, maintaining the stability of Kvl.5 channel as a chaperone together with associated membrane protein [31].

KCNA5 gene is specifically expressed in atrial myocytes, coding the pore region of Kv1.5 potassium channel; the channel is the molecular basis of Ikur, playing an important role in action potential duration and effective refrac-

tory period of atrial muscle [32]. It helps stabilize cardiac cell electrophysiological activity in sympathetic nervous excitements, and it is down-regulated during AF [33, 34]. In 2006, Olson et al [28] conducted the KCNA5 gene screening in 154 cases of American IAF patients. It had been found in one patient with early-onset FAF that Kv1.5 channel function-loss caused by E375X mutation was an important factor to induce IAF, and it had been confirmed in animal models. Then Yang et al [29] have found that function-loss mutations in T527M, A576V, and E610K of KCNA5 gene can reduce IKur current, thereby inducing IAF.

At present, some studies have shown that mutations of SNP loci located on KCNA5 gene may affect the function and expression of Kv1.5 channel [35]. In order to determine whether KCNA5 gene SNP is associated with IAF in Chinese population, this study included 282 cases of IAF patients and 300 cases of age and sex-matched healthy individuals to compare their KCNA5 gene SNP distribution s. The results show that SNP rs3741930 of KCNA5 gene was correlated with IAF, and C allele frequency was significantly higher compared with control group. This is the first report by far on the correlation between KCNA5 gene SNP rs3741930 and IAF in Chinese population. Rs3741930 is located in the 5'-UTR region of KCNA5 gene, involved in composing some splicing enhancer sequences. The single nucleotide polymorphism C>T of this locus might affect the expression of KCNA5 gene, and impair the structure and function of human atrial myocyte Kv1.5 potassium ion channel, resulting in changes in Ikur current, the action potential duration and effective refractory phase, and thus leading to AF susceptibility.

In addition, we also found there were significant differences in BMI between IAF patients with rs3741930 or rs1056468 locus mutation and those without gene mutations. Sascha Dublin et al [36] conducted a study on 425 new-onset AF patients and 707 normal individuals and found that with each unit increase in BMI, the probability of occurrence of AF will be increased by 3%; the occurrence and development of AF had a significant association with BMI. Up to date, there is no literature reporting the correlation between KCNA5 gene and BMI; the specific mechanism is unclear and needs further study.

In conclusion, we found that the SNP rs3741930 of KCNA5 gene was related with IAF pathogenesis; patients carrying C allele were more susceptible to IAF. Meanwhile both rs3741930 and rs1056468 were associated with the BMI of IAF patients. However, our results should be confirmed by large-sample and multi-center studies in future.

Disclosure of conflict of interest

None.

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