DOI:10.11817/j.issn.1672-7347.2018.06.004
www.csumed.org/xbwk/fileup/PDF/201806594.pdf

Rs17042171 at chromosome 4q25 is associated with atrial fibrillation in the Chinese Han population from the central plains

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ABSTRACT

Objective: To determine the correlations of single nucleotide polymorphisms (SNPs) with atrial fibrillation (AF) in the Chinese Han population from the central plains.

Methods: A total of 168 hospitalized patients, including 56 AF and 112 controls, were recruited in this case-control study. The clinical data were obtained from the medical records. All 5 SNPs, rs337711 in KCNN2, rs11264280 near KCNN3, rs17042171 near PITX2, rs6771157 and rs6795970 in SCN10A, were genotyped using amplification refractory mutation system-polymerase chain reaction or direct sequencing. The χ^2 test was used to compare categorical variables and preliminarily examine correlations between the genotype frequencies and AF. Subsequently, a logistic regression model was constructed to determine the associations between the SNPs and AF based on the above screened results. Odds ratios (ORs) and 95% confidence interval (CI) were calculated to assess the strength of the correlations. Moreover, we downloaded the genotype data from the HapMap Project for linkage disequilibrium analysis of rs17042171.

Results: AF patients were likely to be of older age and longer left atrial diameter and had more coronary artery disease and higher hypertension compared with the control group (P<0.05). Among the 5 SNPs, the frequency distribution of genotype AA for rs17042171 was significantly different between the AF and control groups (P<0.05). After adjusting for several covariates, there was still a high risk ratio in patients with the AA genotype compared with the AC+CC genotype (OR: 5.591, 95%CI 2.176 to 14.365, P-B<0.008). Similarly, stratification analysis on the AA genotype demonstrated significant differences between rs17042171 and persistent AF. However, there were not significant correlations between AF and the control groups for the other

Date of reception: 2018-02-06

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Foundation item: This work was supported by the National Natural Science Foundation of China (U1404833).

4 SNPs (P<0.05).

Conclusion: Rs17042171, near PITX2 on chromosome 4q25, is associated with AF susceptibility in the Chinese Han population from the central plains, suggesting that this SNP can provide a new strategy for clinical diagnosis in AF patients.

KEY WORDS atrial fibrillation; genetics; polymorphism; rs17042171; PITX2

中国中原地区汉族人群染色体4q25上rs17042171与心房颤动有关

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[摘要] 目的：确定中国中原地区汉族人群中单核苷酸多态性位点(SNPs)rs337711，rs11264280，rs17042171，rs6771157和rs6795970与心房颤动(以下简称房颤)的相关性。**方法：**研究共纳入168例患者，包括房颤组(56例)和对照组(112例)。采用突变扩增系统-聚合酶链式反应或直接测序法对上述5个SNPs进行基因分型。构建4种经典遗传模型以确定SNPs与房颤的关联性。**结果：**房颤组与对照组相比具有更大的年龄和左房内径及频发的冠心病和高血压(P<0.05)。rs17042171基因型AA的频率分布在房颤组和对照组间差异有统计学意义(P<0.05)，在校正几个临床因素之后两组间差异仍有统计学意义(OR：5.591，95%CI：2.176~14.365，P-B<0.008)。其他4个SNPs的基因型分布在房颤组和对照组之间差异无统计学意义(P>0.05)。**结论：**染色体4q25区域的rs17042171与中国中原地区汉族人群的房颤易感性相关，该SNP可能为房颤患者临床诊断提供新的策略。

[关键词] 心房颤动；遗传学；多态性；rs17042171；PITX2

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in clinical practice and increases the incidence of various cardiovascular events, especially stroke and heart failure, thereby placing an enormous financial burden on individuals and society[1]. AF can induce a serious atrial electrical activity disorder, which is electrocardiographically characterized by low-amplitude baseline oscillations. The mechanism of the occurrence and maintenance of AF is complicated. The structural remodeling, electrical remodeling, or autonomic nerve remodeling have been observed in atria and the above 3 mechanisms are in reciprocal causation, eventually leading to the occurrence and maintenance of AF[2-4].

Previous studies[5-7] have indicated that AF is associated with various cardiovascular risk factors, such as age, coronary artery disease (CAD), hypertension (HP) and diabetes mellitus (DM). Furthermore, the occurrence of AF has been determined to be associated with genetic factors and clinical factors. Up to one-third of patients carry genetic mutations, which demonstrates that genetic factors could play an important role in the susceptibility of AF. In recent years, genome-wide association studies (GWAS)[8-12] have shown that genetic mutations could increase the risk of AF. The GWAS conducted by Gudbjartsson et al[11] discovered that the SNP rs2200733, located near the PITX2 gene on chromosome 4q25, is strongly associated with AF in European ancestry. Moreover, several follow-up studies[13-14] have replicated the GWAS results in different racial populations, such as the Hong Kong Chinese and Han Chinese populations. Subsequently, Benjamin et al[8] confirmed that the SNP rs2106261 in the gene ZFHX3 significantly increases the risk for developing AF in European population[8]. After that study, Jabbari et al[15] noted that 2 SNPs—rs6590357 and rs7118824 in the gene KCNJ5—are in moderate correlation with Lone AF (LonAF) in Caucasians.

However, the SNPs for AF susceptibility are currently contentious, except for rs2200733[16]. Consequently, it is essential to explore more specific biomarkers that are associated with AF.

By retrieving the literature in National Center for Biotechnology Information (NCBI), we observed that several large-scale Meta-analyses on GWAS identified 4 new susceptibility loci for AF, namely, rs337711 in KCNN2, rs11264280 near KCNN3, rs6771157 and rs6795970 in SCN10A[17-18], and thus the 4 SNPs were selected for our study. Meanwhile, we chose the rs17042171 for the candidate locus, considering that the SNP was rarely reported and located in the chromosome 4q25, a predisposed region for AF.

Taken together, the study was conducted by focusing attention on the above 5 SNPs in the Chinese Han population from the central plains. We first genotyped the variants utilizing an amplification refractory mutation system—polymerase chain reaction (ARMS-PCR) and direct sequencing. Next, the relationship between the clinical indicators and AF was analyzed by χ^2 test. Finally, logistic regression models were constructed to evaluate the associations between SNPs and AF.

1 Materials and methods

1.1 Study population

The study was approved by the Ethical Committee of the Seventh People's Hospital of Zhengzhou. The research was conducted in accordance with the principles of the Helsinki Declaration, and all of the participants received written informed consent.

A total of 168 consecutive hospitalized patients from the Seventh People's Hospital of Zhengzhou were recruited between September 2016 and April 2017 and were randomly allocated into an AF group (n=56) and a control group (n=112). All the patients were of Han Chinese. We classified AF as persistent AF (PerAF, episodes lasting 7 days or more) and paroxysmal AF (ParAF, episodes lasting less than 7 days). AF patients without cardiopulmonary disease, HP or DM, in combination with clinical manifestations and echocardiography (ECG) were defined as LonAF[19]. The inclusion criteria for the AF group were as follows: No discernible P waves, absolutely irregular RR intervals and an episode lasting at least 30 s via 12-lead ECG or 24 h ambulatory ECG[20]. The selection criteria for the control group were no history of AF and no AF shown during hospitalization. Exclusion criteria for the 2 groups included the patients with valvular heart disease, cardiomyopathy, myocarditis, congenital heart disease, hyperthyroidism heart disease and cardiac surgery. General clinical information, such as age, left atrial diameter (LAD), gender, CAD, HP, DM, smoking and alcohol, were obtained from medical files.

1.2 DNA extraction and genotype

Genomic DNA was extracted from EDTA-anticoagulated peripheral blood leukocytes using the Genomic DNA kit (Tiangen Biotech Co Ltd, Beijing, China) according to the manufacturer's protocol and stored at −20 ℃. We used ARMS-PCR to genotype rs17042171, rs6771157 and rs337711. Direct sequencing for rs6795970 and rs11264280 was applied. Primers were designed by primer 5.0 software and listed in Table 1. A 20 μL reaction system was used for PCR amplification, including 10 μL of 2×PCR MIX, 7 μL of sterile water, 2 μL of genomic DNA, and 1 μL of primer. The following PCR conditions were employed: For rs17042171 and rs6795970, 94 ℃ for 4 min, 30 cycles of 94 ℃ for 30 s, 60 ℃ for 30 s, and 72 ℃ for 30 s, and then 72 ℃ for 7 min. For rs6771157, 94 ℃ for 4 min, 30 cycles of 94 ℃ for 30 s, 45 ℃ for 30 s, and 72 ℃ for 30 s, and then 72 ℃ for 7 min. For rs337711, 94 ℃ for 4 min, 30 cycles of 94 ℃ for 30 s, 50 ℃ for 30 s, and 72 ℃ for 30 s, and then 72 ℃ for 7 min. For rs11264280, 94 ℃ for 4 min, 30 cycles of 94 ℃ for 30 s, 52 ℃ for 30 s, and 72 ℃ for 30 s, and then 72 ℃ for 7 min. PCR products were analyzed by agarose gel electrophoresis, one tenth of which were randomly selected for sequencing to ensure the quality of the genotyping of rs17042171, rs6771157, and rs337711.

1.3 Bioinformatics analysis

We downloaded the genotype data file genotypes_chr4_CHB_r24_nr.b36_fwd.txt.gz from the HapMap Project (ftp://ftp.ncbi.nlm.nih.gov/HapMap/genotypes/2008-10_phaseII/) and imported them into Haploview 4.2 for the linkage disequilibrium analysis (LD) of rs17042171. D' is the parameter for normalizing the coefficient of linkage disequilibrium between the 2 loci. R^2, an alternative to D', is also the correlation coefficient between the 2 loci. The above genotype data originated from Chinese Han in Beijing (CHB).

1.4 Statistical analysis

The clinical features of the AF and control groups were compared by χ^2 test. Deviations from Hardy-Weinberg equilibrium expectations in both the AF and control groups were estimated by χ^2 tests or Fisher's exact test. Odds ratios (ORs) were calculated by χ^2 test or logistic regression analysis to evaluate the strength of the correlations between the groups. Co-dominant models were defined by comparing those heterozygous WM (W: wild; M: mutation), those homozygous for the variant allele MM genotypes, and those homozygous for the most frequent allele WW. Dominant models constructed in the study were defined by comparing a combination of WM+WW to the homozygous MM. Recessive models were defined as a combination of MM and WM compared to the variant allele homozygous genotype WW. Additive models were utilized to compare a combination of 2 genotypes 2WW+WM to 2MM+WM[21]. $P<0.05$ was considered statistically significant. In the logistic regression models, the *P*-B (adjusting *P* value for multiple-testing by Bonferroni correction) was calculated as 0.008 according to age, LAD, CAD, HP, rs17042171, and the constant. All of the tests were bilateral, and all of the data were analyzed by IBM SPSS Statistics 19.0.

Table 1 Primer sequences used for genotyping SNPs

SNPs	Primer sequences	Fragment length/bp
rs6771157	M: 5'-CTGAAACTGCGATACCAAG-3'	234
	W: 5'-CTGCAAACTGGATACCAAC-3'	
	C: 5'-CTCAGTAGTCAGGAGAACCC-3'	
rs17042171	M: 5'-GAGGACAGTGGCATAGCATA-3'	384
	W: 5'-GAGGACAGTGGCATAGCATC-3'	
	C: 5'-TTTGGGTTGGTAGTATCATCAG-3'	
rs337711	M: 5'-CATTATCCAATAACTATCGAA-3'	420
	W: 5'-CATTATCCAATAACTATCGAG-3'	
	C: 5'-ATTTCAAAACAGTTTCAGTG-3'	
rs6795970	F: 5'-CACCCTCCAGCCTCTACC-3'	241
	R: 5'-CAGTTGGGACCCTCTCTCA-3'	
rs11264280	F: 5'-TTCTATTGTGTACTGCCG-3'	389
	R: 5'-CTGCTAAGTTTTGGTGTAG-3'	

M: Mutant; W: Wild; C: Common; F: Forward; R: Reverse

2 Results

2.1 Clinical characteristics of patients

In the current study, 35.7% was identified as PerAF, 64.3% as ParAF, and 19.6% as LonAF. There was not significant difference in the distribution of gender, DM, smoking, and alcohol between the AF and control groups ($P>0.05$). The AF patients were characterized by older age, larger LAD, more CAD, and higher HP in the AF group compared with the control group ($P<0.05$, Table 2).

Table 2 Clinical characteristics of the AF and control groups

Variables	AF	Controls	*P*	OR	95%CI
Age/year			0.001		
<56	10	58			
56–66	11	29	0.109	2.200	0.838–5.777
>66	35	25	0.001	8.120	3.488–18.901
LAD/mm			0.001		
<35	24	90			
35–40	10	18	0.108	2.083	0.852–5.097
>40	22	4	0.001	20.625	6.488–65.569
Gender (M/F)	31/25	45/67	0.064	0.542	0.283–1.036

Table 2(Continued)

Variables	AF	Controls	*P*	OR	95%CI
CAD (Yes/No)	25/31	14/98	0.001	5.645	2.617–12.178
HP (Yes/No)	34/22	49/63	0.039	1.987	1.034–3.819
DM (Yes/No)	11/45	15/97	0.294	1.581	0.673–3.715
Smoking (Yes/No)	13/43	18/94	0.263	1.579	0.710–3.512
Alcohol (Yes/No)	5/51	14/98	0.493	0.686	0.234–2.012
ParAF/[No.(%)]	36(64.3)				
PerAF/[No.(%)]	20(35.7)				
LonAF/[No.(%)]	11(19.6)				

M: Male; F: Female

2.2 Linkage analysis of rs17042171 from the online data

Utilizing haploview 4.2, we observed that the minor allele frequencies (MAF) of rs17042171 was 0.42 in CHB. Given that the distance between rs17042171 and rs2200733 was only 1 883 bp, the LD for the 2 SNPs was addressed. The results showed that the values of both D' and R^2 were 1 in CHB (Figure 1).

2.3 Associations betweem the genotype frequencies of five SNPs and AF

The genotype frequencies of 5 SNPs in all the subjects were successfully genotyped and did not deviate from Hardy-Weinberg equilibrium both in the AF and control groups (P>0.05, Table 3). The correlations between rs17042171 and AF based on the 4 standard genetic models (co-dominant, dominant, recessive, and additive) were listed in Table 4, where the recessive model had a minimum P value (0.002). Using multivariate logistic regression models (adjusting factors including age, LAD, CAD, and HP), we observed that patients with the AA genotype were still of the minimum P value, even if which was corrected by the Bonferroni method, compared with those with non-AA in the recessive model (OR: 5.591, 95%CI 2.176 to 14.365, P-B<0.008; Table 5). There was no evidence of associations between the other 4 SNPs and AF (data not shown).

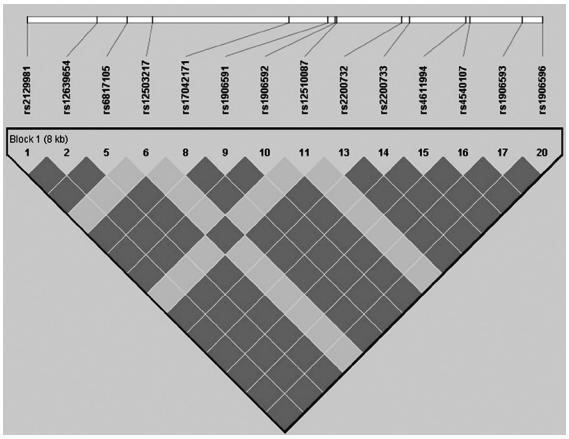

Figure 1 LD plots between rs17042171 and rs2200733 in CHB

Table 3 Genotype frequencies of the 5 SNPs in the AF and control groups

SNPs	Genotypes/ Alleles	AF		Control	
		Frequency/No.	*P**	Frequency/No.	*P**
rs6771157	GG/GC/CC	17/28/11(0.30/0.50/0.20)	1.00	22/63/27(0.20/0.56/0.24)	0.60
	G/C	62/50(0.55/0.45)		108/116(0.48/0.52)	
rs6795970	AA /AG/GG	5/18/33(0.09/0.32/0.59)	0.84	5/28/79(0.04/0.25/0.71)	0.67
	A/G	28/84(0.25/0.75)		38/186(0.17/0.83)	
rs11264280	TT/TC/CC	6/13/37(0.11/0.23/0.66)	0.32	5/34/73(0.05/0.30/0.65)	0.94
	T/C	25/87(0.22/0.78)		45/179(0.20/0.80)	

Table 3(Continued)

SNPs	Genotypes/ Alleles	AF		Control	
		Frequency/No.	*P**	Frequency/No.	*P**
rs337711	AA/AG/GG	2/17/37(0.04/0.30/0.66)	1.00	1/36/75(0.01/0.32/0.67)	0.53
	A/G	21/91(0.19/0.81)		38/186(0.17/0.83)	
rs17042171	AA/AC/CC	23/27/6(0.41/0.48/0.11)	0.92	21/63/28(0.19/0.56/0.25)	0.60
	A/C	73/39(0.65/0.35)		105/119(0.47/0.53)	

**P* value of Hardy-Weinberg equilibrium

Table 4 Associations between the rs17042171 genotypes and AF computed by χ^2 test or Fisher's exact test

Genetic models	Genotypes	Controls	AF	*P*
Co-dominant	CC	28	6	0.005
	AA	21	23	
	AC	63	27	
Dominant	CC	28	6	0.035
	AA+AC	84	50	
Recessive*	AA	21	23	0.002
	CC+AC	91	33	
Additive	2CC+AC	119	39	0.002
	2AA+AC	105	73	

*The genetic model with the smallest *P* value was selected for constructing multivariable logistic regression

Table 5 Associations between rs17042171 genotypes and AF analyzed by multivariable logistic regression

Models	Genotypes	Controls	AF	*P*-B*	OR*	95%CI*
Co-dominant	CC	28	6		1.000	
	AA	21	23	0.005	6.609	1.750–24.958
	AC	63	27	0.722	1.251	0.365–4.279
Dominant	CC	28	6		1.000	
	AA+AC	84	50	0.161	2.250	0.724–6.997
Recessive	CC+AC	91	33		1.000	
	AA	21	23	0.001	5.591	2.176–14.365
Additive	2CC+AC	119	39		1.000	
	2AA+AC	105	73	0.002	2.443	1.372–4.349

* The value after adjusting for age, LAD, CAD, and HP

2.4 Stratification analysis for rs17042171 and AF risk

In the subsequent stratified analysis, we assessed the associations between rs17042171 and AF in the PerAF and ParAF subgroups and selected the recessive model in the PerAF (the minimum *P*=0.010) and the additive model in ParAF (the minimum *P*=0.004) for logistic regression analysis (Table 6). Using multivariate logistic regression models (adjusting factors including age, LAD, CAD, and HP), we observed that patients carrying the AA genotype were still of higher risk of AF in the recessive model (OR: 11.123, 95%CI 2.493 to 49.626, *P*-B<0.008) after Bonferroni correction compared with those with non-AA (Table 7).

Table 6 Associations between the rs17042171 genotypes and AF subgroups analyzed by χ^2 test or Fisher's exact test

Genetic models	Genotypes	Controls	PerAF	*P*	ParAF	*P*
Co-dominant	CC	28	4	0.034	2	0.008
	AA	21	9		14	
	AC	63	7		20	
Dominant	CC	28	4	0.631	2	0.012
	AA+AC	84	16		34	
Recessive*	AA	21	9	0.010	14	0.013
	CC+AC	91	11		22	
Additive*	2CC+AC	119	15	0.072	24	0.004
	2AA+AC	105	25		48	

*The genetic model with the smallest *P* value was selected for constructing multivariable logistic regression

Table 7 Associations between the rs17042171 genotypes and AF subgroups analyzed by multivariable logistic regression

Models	Genotypes	Controls	PerAF	ParAF	*P*-B*	OR*	95%CI*
Recessive	CC+AC	91	11			1.000	
	AA	21	9		0.002	11.123	2.493–49.626
Additive	2CC+AC	119		24		1.000	
	2AA+AC	105		48	0.020	2.145	1.127–4.083

*The value after adjusting for age, LAD, CAD, and HP

3 Discussion

We conducted a case-control study on 56 AF and 112 non-AF patients from the Han Chinese population from the central plains to determine the correlations between the 5 SNPs and AF and found that clinical indices, such as age, LAD, CAD and HP, have impacts on the risk of AF, and among 5 SNPs, only rs17042171 is strongly associated with the risk of AF. Subsequently, the result of a logistic regression demonstrated that the association exists between rs17042171 and AF. Stratification analysis for rs17042171 further comfirmed that the AA genotype is of high risk in the PerAF subgroup.

Previous studies have suggested that AF is associated with age, CAD, and HP. A report[1] showed that the incidence of AF is 0.12%–0.16% in populations less than 49 years old, 3.7%–4.2% in people between 60 and 70 years, and 10%–17% in those aged 80 years or older. As AF progressed from paroxysmal to the persistent or permanent form, the prevalence of CAD increases[6]. A research[5] noted that hypertension could increase the risk of AF by 70% in women and 80% in men. As expected, we observed that AF patients were characteristic of older age, more prevalent CAD, and higher HP in this study. Hypertension could result in AF, reduce contractility and changes in the left atrial structure and function[22-23]. Along with the increase in age, more connective tissue is deposited in the atria and, in turn, causes AF[24-25]. Atrial ischemia caused by CAD could lead to an inconsistent repolarization time of atrial cardiomyocytes[26]. In addition, both HP and CAD could induce the enlargement of the atria, which was validated by larger LAD in AF patients in our study. All of the above factors may affect each other and play important roles in the occurrence and maintenance of AF.

Our findings revealed that the MAF of rs17042171 was 0.47 in the control group, which was similar to 0.42, which was the value from the HaplotypeMap Project in CHB. Furthermore, the MAF in Utah Residents, with Northern and Western European Ancestry was 0.12, which indicated that significant ethnic variations for the allele do exist. For exploring the novel biomarkers, Gudbjartsson et al[11] conducted a GWAS and observed that rs17042171 on 4q25 has a moderate association with AF in European ancestry, and Benjamin et al[8] replicated the above finding in another European population. In our study, we confirmed the association between rs17042171 and AF in the Han Chinese population from the central plains and determined that the OR value of the A to C allele

was 2.44 and the risk rate of the AA to CC+AC genotype was 5.60 after adjusting for age, LAD, CAD, and HP. Stratification analysis for rs17042171 further determined that the AA genotype had a high risk in the PerAF subgroup. Additionally, in the present study, we observed that rs17042171 had a strong LD with rs2200733 (D'=1, R^2=1). The most widely accepted mutation related to AF is rs2200733, which is located near gene PITX2 on 4q25 and is identified in several different populations[11]. In short, the above results indicated that rs17042171 increases the risk of AF in the Han Chinese population from the central plains, similar to rs2200733.

To date, the associations between polymorphisms in the 4q25 region and AF have been extensively studied. One of the reasons that we concerned with SNPs is that the region is adjacent to the gene PITX2[9, 13]. PITX2 encodes a member of the RIEG/PITX homeobox family, which is in the bicoid class of homeodomain proteins. PITX2 has 4 isomers, namely, PITX2A, PITX2B, PITX2C, and PITX2D, of which PITX2C mainly expressed in the heart[27-28]. The expression and function of PITX2 play an important role in directing the development of pulmonary vein sleeves and the conduction system, which are essential substrates associated with the initiation and maintenance of AF[29-30]. Animal experiments showed that PITX2C could directly bind to the sinoatrial node-specific gene SHOX2 to inhibit the expression of SHOX2, which consequently promotes the occurrence of atrial tachyarrhythmia by changing the sinoatrial node impulse. In addition, for PITX2 knockout rats, atrial procedural stimulation is more likely to induce atrial tachyarrhythmias[31]. It is revealed that the ectopic expression of PITX2C could lead to the dysregulation of ion channels and, in turn, give rise to the shortening of an effective atrial refractory period and increases of the atrial conduction rate[32]. PITX2 is approximately 150 kb away from rs17042171 by bioinformatic analysis, suggesting that the gene is expected to become an AF-specific candidate gene and the expression of this gene would be correlated with rs17042171. Therefore, further studies are warranted to determine whether rs17042171 affects the expression of PITX2.

Rs6771157 and rs6795970 are in the gene SCN10A which encodes the Nav 1.8 voltage-gated sodium channel α subunit. Researchers[33-34] have shown that the channel protein is expressed in intracardiac neurons and human cardiomyocytes and plays an important role in the pathogenesis of AF. Rs6771157 and rs6795970 are found to be related to AF[35-36]. Rs11264280 is located near the gene KCNN3, which is the representative gene of small conductance Ca^{2+}-activated K^+ channel 3. KCNN3 is found to be associated with lone AF[10]. Rs337711 is in KCNN2 which encodes a small conductance Ca^{2+}-activated K^+ channel 2 and is known to be involved in the maintenance of atrial cardiac action potential[16]. Rs11264280 and rs337711 are also demonstrated to be correlated with AF[17]. However, there were no significant correlations between the 4 SNPs and AF in any of the co-dominant, dominant, recessive, and additive genetic models in our study. One possible reason is that the sample size of our study was relatively small, compared with that of the large-scale GWAS. The another reason is probably attributed to the genetic diversity, based on different geographical and ethnic backgrounds of the individuals.

In our study, several limitations should be emphasized. On the one hand, the sample size was not sufficiently large compared with the large scale clinical trials. Recruiting more patients for next studies can largely improve the statistical power to further confirm our results and find meaningful biomarkers. On the other hand, all subjects were from the Henan Province of China, and could not completely represent the entire Han Chinese population so that the results of this study may not be extended to other Han Chinese populations. Therefore, multi-center interregional studies are needed to support our findings.

In summary, our study confirms the association between rs17042171 on 4q25 and AF in the Han Chinese population from the central plains and suggests that the SNP can provide a new strategy for clinical diagnosis in AF patients. However, further studies on different populations and functional analyses are warranted to confirm our results.

References

[1] Zoni-Berisso M, Lercari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective[J]. Clinic Epidemiol, 2014, 6: 213-220.

[2] Iwasaki YK, Nishida K, Kato T, et al. Atrial fibrillation pathophysiology: implications for management[J]. Circulation, 2011, 124(20): 2264-2274.

[3] Jayachandran JV, Sih HJ, Winkle W, et al. Atrial fibrillation produced by prolonged rapid atrial pacing is associated with heterogeneous changes in atrial sympathetic innervation[J]. Circulation, 2000, 101(10): 1185-1191.

[4] Van Wagoner DR, Nerbonne JM. Molecular basis of electrical remodeling in atrial fibrillation[J]. J Mol Cell Cardiol, 2000, 32(6): 1101-1117.

[5] Ball J, Carrington MJ, McMurray JJ, et al. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century[J]. Int J Cardiol, 2013, 167(5): 1807-1824.

[6] Chiang CE, Naditch-Brule L, Murin J, et al. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry[J]. Circ Arrhythm Electrophysiol, 2012, 5(4): 632-639.

[7] Nguyen TN, Hilmer SN, Cumming RG. Review of epidemiology and management of atrial fibrillation in developing countries[J]. Int J Cardiol, 2013, 167(6): 2412-2420.

[8] Benjamin EJ, Rice KM, Arking DE, et al. Variants in ZFHX3 are associated with atrial fibrillation in individuals of European ancestry[J]. Nat Genet, 2009, 41(8): 879-881.

[9] Ellinor PT, Lunetta KL, Albert CM, et al. Meta-analysis identifies six new susceptibility loci for atrial fibrillation[J]. Nat Genet, 2012, 44(6): 670-675.

[10] Ellinor PT, Lunetta KL, Glazer NL, et al. Common variants in KCNN3 are associated with lone atrial fibrillation[J]. Nat Genet, 2010, 42(3): 240-244.

[11] Gudbjartsson DF, Arnar DO, Helgadottir A, et al. Variants conferring risk of atrial fibrillation on chromosome 4q25[J]. Nature, 2007, 448(7151): 353-357.

[12] Sinner MF, Tucker NR, Lunetta KL, et al. Integrating genetic, transcriptional, and functional analyses to identify 5 novel genes for atrial fibrillation[J]. Circulation, 2014, 130(15): 1225-1235.

[13] Kaab S, Darbar D, van Noord C, et al. Large scale replication and meta-analysis of variants on chromosome 4q25 associated with atrial fibrillation[J]. Europ Heart J, 2009, 30(7): 813-819.

[14] Shi L, Li C, Wang C, et al. Assessment of association of rs2200733 on chromosome 4q25 with atrial fibrillation and ischemic stroke in a Chinese Han population[J]. Hum Genet, 2009, 126(6): 843-849.

[15] Jabbari J, Olesen MS, Holst AG, et al. Common polymorphisms in KCNJ5 [corrected] are associated with early-onset lone atrial fibrillation in Caucasians[J]. Cardiology, 2011, 118(2): 116-120.

[16] Fatkin D, Santiago CF, Huttner IG, et al. Genetics of atrial fibrillation: State of the art in 2017[J]. Heart Lung Circ, 2017, 26(9): 894-901.

[17] Christophersen IE, Rienstra M, Roselli C, et al. Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation[J]. Nat Genet, 2017, 49(6): 946-952.

[18] Ritchie MD, Denny JC, Zuvich RL, et al. Genome- and phenome-wide analyses of cardiac conduction identifies markers of arrhythmia risk[J]. Circulation, 2013, 127(13): 1377-1385.

[19] January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society[J]. J Am Coll Cardiol, 2014, 64(21): e1-76.

[20] Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS[J]. Europace, 2016, 18(11): 1609-1678.

[21] Sole X, Guino E, Valls J, et al. SNPStats: a web tool for the analysis of association studies[J]. Bioinformatics, 2006, 22(15): 1928-1929.

[22] Go O, Rosendorff C. Hypertension and atrial fibrillation[J]. Curr Cardiol Rep, 2009, 11(6): 430-435.

[23] Kistler PM, Sanders P, Dodic M, et al. Atrial electrical and structural abnormalities in an ovine model of chronic blood pressure elevation after prenatal corticosteroid exposure: implications for development of atrial fibrillation[J]. Europ Heart J, 2006, 27(24): 3045-3056.

[24] Chimenti C, Russo MA, Carpi A, et al. Histological substrate of human atrial fibrillation[J]. Biomed Pharmacother, 2010, 64(3): 177-183.

[25] Nguyen BL, Fishbein MC, Chen LS, et al. Histopathological substrate for chronic atrial fibrillation in humans[J]. Heart Rhythm, 2009, 6(4): 454-460.

[26] Sinno H, Derakhchan K, Libersan D, et al. Atrial ischemia promotes atrial fibrillation in dogs[J]. Circulation, 2003, 107(14): 1930-1936.

[27] Cox CJ, Espinoza HM, McWilliams B, et al. Differential regulation of gene expression by PITX2 isoforms[J]. J Biol Chem, 2002, 277(28): 25001-25010.

[28] Schweickert A, Campione M, Steinbeisser H, et al. Pitx2 isoforms: involvement of Pitx2c but not Pitx2a or Pitx2b in vertebrate left-right asymmetry[J]. Mech Dev, 2000, 90(1): 41-51.

[29] Douglas YL, Jongbloed MR, Deruiter MC et al. Normal and abnormal development of pulmonary veins: state of the art and correlation with clinical entities[J]. Int J Cardiol, 2011, 147(1): 13-24.

[30] Liu C, Liu W, Lu MF, et al. Regulation of left-right asymmetry by thresholds of Pitx2c activity[J]. Development, 2001, 128(11): 2039-2048.

[31] Wang J, Klysik E, Sood S, et al. Pitx2 prevents susceptibility to atrial arrhythmias by inhibiting left-sided pacemaker specification[J]. Proc Natl Acad Sci USA, 2010, 107(21): 9753-9758.

[32] Kirchhof P, Kahr PC, Kaese S, et al. PITX2c is expressed in the adult left atrium, and reducing Pitx2c expression promotes atrial fibrillation inducibility and complex changes in gene expression[J]. Circ Cardiovasc Genet, 2011, 4(2): 123-133.

[33] Facer P, Punjabi PP, Abrari A, et al. Localisation of SCN10A gene product Na(v)1.8 and novel pain-related ion channels in human heart[J]. Int Heart J, 2011, 52(3): 146-152.

[34] Verkerk AO, Remme CA, Schumacher CA, et al. Functional Nav1.8

channels in intracardiac neurons: the link between SCN10A and cardiac electrophysiology[J]. Circ Res, 2012, 111(3): 333-343.

[35] Fang Z, Jiang Y, Wang Y, et al. The rs6771157 C/G polymorphism in SCN10A is associated with the risk of atrial fibrillation in a Chinese Han population[J]. Sci Rep, 2016, 6: 35212.

[36] Jabbari J, Olesen MS, Yuan L, et al. Common and rare variants in SCN10A modulate the risk of atrial fibrillation[J]. Circ Cardiovasc Genet, 2015, 8(1): 64-73.

(Edited by CHEN Liwen)

本文引用：王旭, 聂亚莉, 宁姝威, 师勇, 赵育洁, 牛思泉, 郭成贤, 孟祥光, 袁义强. 中国中原地区汉族人群染色体4q25上rs17042171与心房颤动有关[J]. 中南大学学报(医学版), 2018, 43(6): 594-603. DOI:10.11817/j.issn.1672-7347.2018.06.004

Cite this article as: WANG Xu, NIE Yali, NING Shuwei, SHI Yong, ZHAO Yujie, NIU Siquan, GUO Chengxian, MENG Xiangguang, YUAN Yiqiang. Rs17042171 at chromosome 4q25 is associated with atrial fibrillation in the Chinese Han population from the central plains[J]. Journal of Central South University. Medical Science, 2018, 43(6): 594-603. DOI:10.11817/j.issn.1672-7347.2018.06.004