

## ORIGINAL ARTICLE

# The research of ion channel-related gene polymorphisms with atrial fibrillation in the Chinese Han population

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**Funding information**

This work was supported by the National Natural Science Foundation of China (No. 81470550), the Science and Technology Planning Project of Xi'an (No. SF1508(1)), and the Science and Technology Research and Development Program of Shaanxi Province of China (No. 2015SF025).

**Abstract**

**Background:** Atrial fibrillation (AF) is one of the common arrhythmia in clinics. Its incidence is high among the elderly. This study aimed to identify a possible connection between ion channel-related gene polymorphisms and the risk of AF.

**Methods:** A total of 381 patients with coronary heart disease were recruited. Based on complete cardiac examination, the patients were divided into two subgroups: 185 patients with AF and 196 patients without AF. An association analysis was performed using 13 genotyped SNPs. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated by conditional logistic regression.

**Results:** In our research, we found that *KCNE2* rs8134775 was associated with a decreased AF risk in the allele model (OR = 0.70; 95% CI: 0.50–0.97;  $p = 0.034$ ). Genetic model analysis shown that the minor allele T of *GJA5* rs35594137 was associated with a decreased AF risk under the recessive model (OR = 0.40; 95% CI: 0.19–0.86;  $p = 0.018$ ) and the minor allele G of *KCNJ2* rs8079702 was associated with an increased AF risk in the recessive model (OR = 2.31; 95% CI: 1.20–4.42;  $p = 0.012$ ).

**Conclusions:** Our results suggest that *KCNE2*, *KCNJ2*, and *GJA5* influence the development of AF.

**KEYWORDS**

atrial fibrillation (AF), case–control study, single nucleotide polymorphism (SNP)

## 1 | INTRODUCTION

Atrial fibrillation (AF) is one of the common arrhythmia in clinics and its prevalence is increasing gradually due to aging populations (Luo et al., 2018). The incidence is more than 5% in the elderly over 65 years, and 10% in those over 75 years. Atrial fibrillation is also a main cause of heart failure and stroke (Hu & Sun, 2008; Roberts & Gollob, 2010). About 20% of stroke patients are hospitalized with AF detected by electrocardiogram, another 7–8% of patients have

paroxysmal or persistent AF during hospitalization (Jauch et al., 2013). However, since the mechanisms of AF has not elucidated clearly, many difficulties remain in the clinical treatment of AF (Luo et al., 2018). Therefore, in order to take early prevention measures and reduce the disease burden of AF, it is an imperative need to identify genetic contributors to AF risk through epidemiological studies.

Previous studies have shown that first-degree relatives of AF patients were 1.77- to 4.67-fold more likely to have AF than the general population, and parental AF increases approximately

three times the future risk of developing AF in offspring (Arnar et al., 2006; Fox et al., 2004). These facts indicate that genetic factors play a key role in the pathogenesis of AF. Over the past years, lots of genetic studies of AF were performed and some single nucleotide polymorphisms (SNPs) of different genes associated with an increased AF risk have been identified in the general population. For example, one research shows that three predominant genomic regions (1q21, 4q25, and 16q22) associated with increased AF risk in African Americans (Delaney et al., 2012), and the other research identified six new genetic loci associated with AF in the Japanese population (Low et al., 2017). Ion channel-related genes have also been found to play an important role in the development of AF.

The studies found that somatic and germline mutations within the coding regions of human Cx40 gene (GJA5) have been linked to AF patients and families (Gollob et al., 2006). Miao et al. (2017) found that the KCNE4 (rs12621643) was an independent risk factor for AF among both Uyghurs and Hans. Wu et al. (2017) found that rs6795970 genotypes in SCN10A are independently associated with AF recurrence in Chinese Han patients who undergo a catheter ablation. Li, Shen, Yao, Liang, and Huang (2015) found that the rs1805127\*G allele of KCNE1, and the rs2283228\*C and rs1057128\*A alleles on KCNQ1 are risk factors for AF, while the rs1805120\*T allele on KCNH2 may serve as a protective factor for AF. The findings of Jabbari et al. (2011) indicate that rs6590357 and rs7118824 in KCNJ5 are associated with early-onset lone AF in Caucasians. Tian, Liu, Wang, Zheng, and Li (2015) found that the SNP rs3741930 locus in KCNA5 gene was related to the risk of IAF; the population carrying C allele was more susceptible to IAF. Yang et al. (2004) found that KCNE2 R27C is a gain-of-function mutation associated with the initiation and/or maintenance of AF. Xia et al. (2005) reported that KCNJ2 gene V93I mutation may play a role in initiating and/or maintaining AF by increasing the activity of the inward rectifier K(+) channel. Therefore, these ion channel-related genes were associated with AF.

Therefore, we selected 13 ion channel-related gene SNPs, according to the minor allele frequencies (MAF) greater than 5% in the global population from the 1000 Genomes Project, to assess their potential to affect AF risk. Our study shed light on the association between candidate SNPs and AF risk in Chinese Han population.

## 2 | MATERIAL AND METHODS

### 2.1 | Editorial Policies and Ethical Considerations

The protocols for this study were approved by the Ethical Committee of the First Hospital of Xi'an, complied with the World Medical Association Declaration of Helsinki. After fully explaining the details of our study, all participants

signed informed consents. Then, approximately 5-ml venous blood was collected from each subject.

### 2.2 | Study Population

We recruited 381 patients with coronary heart disease in First Hospital of Xi'an. All patients underwent a complete cardiac examination. Based on this, the patients with coronary heart disease were divided into two subgroups: 185 patients with AF and 196 patients without atrial fibrillation (NAF). This case-control study was performed within 185 unrelated AF patients (91 female and 94 male) and 196 unrelated NAF controls (92 female and 104 male). Demographic and clinical data including white blood cell (WBC), lymphocyte ratio (LYMPH), neutrophil ratio (NEUT), red blood cell (RBC), hemoglobin (HGB), platelet, urea, creatinine (Cr), uric acid (UA), cystatin-C (Cys-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting glucose (FPG), postprandial glucose (PPG), triacylglycerol (TG), total cholesterol (TC), apolipoproteins A1 (Apo A1), high-density lipoprotein (HDL), lipoprotein a (Lpa), low-density lipoprotein (LDL), thyroid-stimulating hormone (TSH), total serum triiodinitrogolic acid (TT3), free thyroxine (TT4), free triiodothyronine (FT3), free thyroxine (FT4), thyroxine-binding globulin (TBG), and glycosylated hemoglobin (HbA1c) were recorded for each study participant.

### 2.3 | SNP selection and genotyping

We selected 13 ion channel-related genes SNPs for analysis in this study. Minor allele frequencies of all SNPs were greater than 5% in the global population from the 1000 Genomes Project. We extracted genomic DNA from whole peripheral blood using a GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Co. Ltd. Xi'an City, China) according to the manufacturer's protocol, then the concentration of DNA was measured by NanoDrop 2000C (Thermo Scientific, Waltham, Massachusetts, USA). Agena Bioscience's MassARRAY Assay Design 3.0 software was used to design the multiplexed SNP MassEXTEND assay, and SNP genotyping was performed using the Agena Bioscience's MassARRAY RS1000 recommended by the manufacturer. Agena Typer 4.0 software was used to perform data management and analyses.

### 2.4 | Statistical analysis

All continuous data are presented as the mean  $\pm$  SD. Pearson's chi-squared test and Student's *t* test were used to compare the distribution of categorical variables and continuous variables, respectively. The lower frequency alleles were coded as the minor allele. A Fisher's exact test was used to assess the variation in each SNP frequency from the Hardy-Weinberg

equilibrium (HWE) in the control subjects. Differences in SNP genotype distribution between cases and controls were compared by the chi-squared test (Adamec, 1964). All two-sided  $p$  values less than 0.05 were considered statistically significant. Associations between the SNPs and the risk of AF were tested using various genetic models (genotype, dominant, recessive, and additive). These genetic models were performed using PLINK 1.07 software (<http://www.cog-genomics.org/plink2>) to estimate ORs for SNP main effects (Purcell et al., 2007). ORs and 95% CIs were determined by conditional logistic regression with adjustments for age and gender (Bland & Altman, 2000).

### 3 | RESULTS

A total of 381 patients with coronary heart disease were recruited, including 185 AF patients and 196 controls in our study. The distributions of age and gender of the cases and controls were presented in Table 1. The average ages were 77.26 ( $\pm$  9.56) years for AF patients and 70.90 ( $\pm$  7.72) years for controls (NAF). The clinical and biochemical characteristics of all study participants are summarized in Table 1. The mean of LYMPH, NEUT, erythrocyte (RBC), HGB, platelet, urea, Cr, UA, PPG, TG, HDL, and FT4 were significantly different between AF and controls.

Chromosomal position, alleles, and HWE test results for all the 13 SNPs are presented in Table 2. All of the SNPs displayed significant deviation from HWE among controls ( $p > 0.05$ ). In the allele model, the “C” allele of rs8134775 near *KCNE2* was significantly associated with a 0.70-fold decreased AF risk at a 5% level (OR = 0.70; 95% CI: 0.50–0.97;  $p = 0.034$ ).

Comparisons of the SNP genotypes and the risk of AF are presented in Table 3. We identified two significant SNP genotypes associated with the risk of AF. *GJA5* rs35594137 was associated with a decreased AF risk both in the recessive model (OR = 0.40; 95% CI: 0.19–0.86;  $p = 0.018$ ) and in the genotype model (OR = 0.41; 95% CI: 0.19–0.91;  $p = 0.029$ ). *KCNJ2* rs8079702 was also associated with an increased AF risk under the recessive (OR = 2.31; 95% CI: 1.20–4.42;  $p = 0.012$ ) and genotype models (OR = 2.40; 95% CI: 1.19–4.86;  $p = 0.015$ ).

### 4 | DISCUSSION

In this case–control study, we investigated the association between ion channel-related gene polymorphisms and the risk of AF in Chinese Han population. We genotyped 13 SNPs and found three SNPs (rs8134775 near *KCNE2*, rs8079702 near *KCNJ2*, and rs35594137 in *GJA5*) were associated with AF risk in the Chinese Han population.

**TABLE 1** Characteristics of cases and controls in this study

Variable	AF	NAF	$p$ value
$N$	185	196	
Gender			0.660
Male	94	104	
Female	91	92	
Age (year)	77.26 $\pm$ 9.56	70.90 $\pm$ 7.72	0.000*
WBC ( $10^9/L$ )	6.11 $\pm$ 2.16	6.44 $\pm$ 1.75	0.104
LYMPH (%)	1.28 $\pm$ 0.65	3.20 $\pm$ 7.05	0.000*
NEUT (%)	4.27 $\pm$ 1.99	13.13 $\pm$ 54.87	0.026*
RBC ( $10^{12}/L$ )	4.02 $\pm$ 0.75	4.24 $\pm$ 0.55	0.001*
HGB (g/l)	124.18 $\pm$ 22.79	130.91 $\pm$ 15.64	0.001*
Platelet ( $10^9/L$ )	168.56 $\pm$ 89.53	188.20 $\pm$ 64.13	0.015*
Urea (mmol/L)	6.73 $\pm$ 3.38	5.88 $\pm$ 2.37	0.006*
Cr ( $\mu$ mol/L)	89.64 $\pm$ 27.09	84.33 $\pm$ 19.98	0.034*
UA ( $\mu$ mol/L)	340.31 $\pm$ 122.87	313.38 $\pm$ 96.16	0.020*
Cys-C (mg/L)	1.19 $\pm$ 0.48	1.06 $\pm$ 1.87	0.357
ALT (U/L)	22.21 $\pm$ 19.23	20.55 $\pm$ 11.75	0.320
AST (U/L)	27.38 $\pm$ 22.54	24.67 $\pm$ 22.72	0.252
FPG (mmol/L)	5.63 $\pm$ 1.94	6.04 $\pm$ 3.41	0.168
PPG (mmol/L)	6.83 $\pm$ 1.91	9.10 $\pm$ 2.82	0.000*
TG (mmol/L)	1.16 $\pm$ 0.83	1.33 $\pm$ 0.61	0.031*
TC (mmol/L)	3.64 $\pm$ 0.92	5.87 $\pm$ 25.74	0.252
Apo A1(g/L)	1.13 $\pm$ 0.25	1.31 $\pm$ 1.94	0.217
HDL (mmol/L)	1.22 $\pm$ 0.33	1.14 $\pm$ 0.29	0.017*
Lpa (mg/L)	216.37 $\pm$ 201.63	260.55 $\pm$ 239.59	0.061
LDL (mmol/L)	2.12 $\pm$ 0.76	2.82 $\pm$ 4.74	0.053
TSH (mU/L)	3.21 $\pm$ 3.20	4.75 $\pm$ 11.82	0.169
T3 (ng/mL)	1.49 $\pm$ 1.38	1.65 $\pm$ 0.32	0.178
T4 (ng/mL)	92.94 $\pm$ 25.10	97.03 $\pm$ 18.66	0.141
FT3 (pg/mL)	4.41 $\pm$ 5.99	4.43 $\pm$ 0.61	0.903
FT4 (pg/mL)	16.87 $\pm$ 3.32	15.93 $\pm$ 2.74	0.013*
TBG (IU/mL)	20.79 $\pm$ 46.40	19.59 $\pm$ 76.31	0.911
HbA1c (%)	7.23 $\pm$ 1.07	6.74 $\pm$ 1.07	0.067

Abbreviations: ALT, alanine aminotransferase; Apo A1, apolipoproteins A1; AST, aspartate aminotransferase; Cr, creatinine; Cys-C, cystatin-C; FPG, fasting glucose; FT3, free triiodothyronine; FT4, free thyroxine; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HGB, hemoglobin; Lpa, lipoprotein a; LDL, low-density lipoprotein; LYMPH, lymphocyte ratio; NEUT, neutrophil ratio; PPG, postprandial glucose; RBC, red blood cell; TBG, thyroxine-binding globulin; TC, total cholesterol; TG, triacylglycerol; TSH, thyroid-stimulating hormone; TT3, total serum triiodonitrogolic acid; TT4, free thyroxine; UA, uric acid; WBC, white blood cell.

\* $p < 0.05$  indicates statistical significance.

The *KCNE2* gene resides on chromosome 21 at the band 21q22.11 and contains two exons. *KCNE2* is a ubiquitously expressed potassium channel  $\beta$  subunit associated with cardiac arrhythmia, atherosclerosis, and myocardial infarction

**TABLE 2** Basic information on the candidate SNPs

SNP	Gene	Chromosome	Position	Alleles A/B	dbSNP func annot	MAF		HWE <i>p</i> value	Allele model	
						case	control		ORs (95%CI)	<i>p</i> value
rs10465885	GJA5	1	147,760,632	T/C	Intronic	0.476	0.459	0.774	1.07 (0.80–1.42)	0.648
rs35594137	GJA5	1	147,773,393	T/C	/	0.300	0.342	0.342	0.83 (0.61–1.12)	0.217
rs12621643	KCNE4	2	223,053,265	T/G	Missense	0.303	0.339	0.750	0.85 (0.62–1.15)	0.280
rs10428132	SCN10A	3	38,736,063	T/G	Intronic	0.205	0.237	0.239	0.83 (0.59–1.17)	0.290
rs1805120	KCNH2	7	150,952,443	G/A	Synonymous	0.332	0.334	0.423	0.99 (0.73–1.34)	0.959
rs1057128	KCNQ1	11	2,776,007	A/G	Synonymous	0.311	0.296	0.390	1.07 (0.79–1.46)	0.655
rs2283228	KCNQ1	11	2,828,300	C/A	Intronic	0.380	0.367	0.168	1.06 (0.79–1.42)	0.709
rs6590357	KCNJ5	11	128,911,444	T/C	Synonymous	0.127	0.128	0.527	1.00 (0.65–1.52)	0.983
rs3741930	KCNA5	12	5,043,981	C/T	5'-UTR	0.368	0.406	0.377	0.85 (0.64–1.14)	0.281
rs8079702	KCNJ2	17	70,194,685	G/A	/	0.416	0.355	0.280	1.30 (0.97–1.74)	0.081
rs8134775	KCNE2	21	34,219,525	C/T	/	0.219	0.286	0.727	0.70 (0.50–0.97)	0.034*
rs754467	KCNE2	21	34,292,662	G/A	/	0.527	0.500	0.886	1.11 (0.84–1.48)	0.456
rs9984281	KCNE2	21	34,369,557	G/A	Intronic	0.189	0.219	0.297	0.83 (0.58–1.18)	0.302

Abbreviations: 95% CI, 95% confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; SNP, single nucleotide polymorphism.

\**p* < 0.05 indicates statistical significance.

**TABLE 3** Ion channel-related gene polymorphisms and the risk of AF based on the results of logistic regression model analysis

SNP	Model	Genotype	Cases	Controls	ORs (95% CI)	p value
GJA5 rs35594137	Genotype	CC	86	88	1	
		CT	87	82	1.08 (0.68–1.69)	0.754
		TT	12	26	0.41 (0.19–0.91)	0.029*
	Dominant	CC	86	88	1	
		TT + CT	99	108	0.91 (0.59–1.40)	0.663
	Recessive	CC + CT	173	170	1	
		TT	12	26	0.40 (0.19–0.85)	0.018*
Additive	/	/	/	0.79 (0.56–1.10)	0.152	
KCNJ2 rs8079702	Genotype	AA	64	78	1	
		AG	88	97	1.07 (0.67–1.72)	0.770
		GG	33	21	2.40 (1.19–4.86)	0.015*
	Dominant	AA	64	78	1	
		GG + AG	121	118	1.27 (0.81–1.98)	0.294
	Recessive	AA + AG	152	175	1	
		GGs	33	21	2.31 (1.20–4.42)	0.012*
Additive	/	/	/	1.40 (1.02–1.94)	0.040*	

Note: p values were calculated by unconditional logistic regression analysis with adjustments for gender and age.

\*p < 0.05 indicates statistical significance.

(MI) in human populations. Previous studies have provided evidence that mutations in *KCNE2* cause familial AF (Yang et al., 2004). Besides, the *KCNE2* gene is also associated with other diseases. For example, *KCNE2* deletion will impair insulin secretion and cause type 2 diabetes mellitus (Lee et al., 2017). Two *KCNE2* gene-pairs (*KCNE2* and *API5*, and *KCNE2* and *PRPF3*) were correlated with gastric cancer prognosis after 5-fluorouracil chemotherapy (Abbott & Roepke, 2016). The SNP rs8134775, located near *KCNE2*, was significantly associated with a 0.70-fold decreased AF risk in our study. Through the function prediction of rs8134775 (<http://pubs.broadinstitute.org/mammals/haploreg/haploreg.php>) (Ward & Kellis, 2012), the mutation at rs8134775 may affect the binding of *KCNE2* gene to CEBPB protein. It has been found that CEBPB plays a transcriptional regulatory role in the recognition and binding of target gene regulatory regions, and is involved in cell proliferation, differentiation, immune response and tumor formation (Ramji & Foka, 2002).

As part of this study, rs8079702 “G” allele was most consistently associated with AF and exhibited an increased risk for AF. The SNP rs8079702 located 15 kb downstream of *KCNJ2* (Pillas et al., 2010). The *KCNJ2* gene encodes the inward rectifying potassium channel Kir2.1, commonly expressed in brain, skeletal and cardiac muscle (Zaritsky, Eckman, Wellman, Nelson, & Schwarz, 2000). Mutations in the *KCNJ2* gene have been associated with Andersen–Tawil syndrome (ATS), short QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT) (Plaster et

al., 2001; Priori et al., 2005; Tester et al., 2006). The SNP rs8079702, in proximity to potassium channel gene *KCNJ2*, exhibited decreased longitudinal QTc variance (Mints, Zippunikov, Khurram, Calkins, & Nazarian, 2014). Besides, it has been shown that associated with the timing of first tooth eruption and the number of teeth at one year of age were genotyped in Japanese and Korean populations (Yamaguchi et al., 2014). The mutation at rs8079702 may affect the binding of *KCNJ2* gene to CEBPB protein by the Bioinformatics prediction (<http://pubs.broadinstitute.org/mammals/haploreg/haploreg.php>) (Ward & Kellis, 2012). It has been found that CEBPB plays a transcriptional regulatory role in the recognition and binding of target gene regulatory regions, and is involved in cell proliferation, differentiation, immune response and tumor formation (Ramji & Foka, 2002).

The gene *GJA5* encodes the gap-junction protein Cx40, which is specific for the atria. Together with Cx43, it is responsible for the electrical coupling of the atrial cardiomyocytes. Mutations in the connexin genes have previously been associated with AF (Christophersen et al., 2013). Mutations in *GJA5* have been linked to AF (Sun, Hills, Ye, Tong, & Bai, 2013). The rs35594137 in *GJA5* was identified to be associated with AF risk in our research. Through the function prediction of rs8134775 (<http://pubs.broadinstitute.org/mammals/haploreg/haploreg.php>) (Ward & Kellis, 2012), the mutation at rs35594137 may affect the binding of *GJA5* gene to EGR1 protein. Gene-EGR1 was continuously differentially expressed among the three kinds of samples (permanent AF, sinus rhythm (SR), and human

left ventricular non-failing myocardium (LV)) (Zhang, Liu, Hu, & Song, 2015). The early growth response transcription factor Egr-1 controls cell-specific responses to proliferation, differentiation, and apoptosis (Wang et al., 2014). Therefore, these findings indicate that *GJA5* may play a critical role in the probability of AF development. Further studies are required to confirm our result.

Although this study identified four SNPs associated with AF susceptibility after adjusted by age and gender, some potential deficiencies should be considered. First, our sample size was quite small (185 cases and 196 controls), which might cause false-positive results. Second, only considering the variations in age and gender during our analysis, we could not statistically analyze other variables like lifestyle and family history due to lack of these data from both cases and controls. Therefore, the findings must be verified in studies with larger sample sizes. Besides, more comprehensive and in-depth analyses are also required.

## 5 | CONCLUSIONS

In conclusion, we have identified three SNPs (rs8134775 near *KCNE2*, rs8079702 near *KCNJ2*, and rs35594137 in *GJA5*) associated with risk of AF in Chinese Han population, which may provide more data for screening of AF in Chinese Han population and shed light on the candidate SNPs for the further study on occurrence mechanism of AF.

## ACKNOWLEDGMENTS

XL contributed to the major part in writing the manuscript. YL and HZ collected and analyzed the patient data. TY searched and analyzed literature. ZZ did data interpretation. CY did study designed. All authors read and approved the final manuscript. We are grateful to all people who participated in the study. We would also like to thank the clinicians and other hospital staff who contributed to the data collection for this study.

## CONFLICT OF INTERESTS

The authors declare that they have no competing interests and manuscript is approved by all authors for publication.

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**How to cite this article:** Liu X, Li Y, Zhang H, Ji Y, Zhao Z, Wang C. The research of ion channel-related gene polymorphisms with atrial fibrillation in the Chinese Han population. *Mol Genet Genomic Med*. 2019;7:e835. <https://doi.org/10.1002/mgg3.835>