Association of rs17042171 with chromosome 4q25 with atrial fibrillation in Chinese Han populations

Liyan Zhao, Xin-Guang Chen, Yaowu Liu, Zhen Fang, Fengxiang Zhang

Section of Pacing and Electrophysiology, Division of Cardiology, the First Affiliated Hospital of Nanjing Medical University; Nanjing-*China*

ABSTRACT

Objective: A recent genome-wide association study (GWAS) identified a susceptibility single nucleotide polymorphism (SNP), rs17042171 on 4q25 for atrial fibrillation (AF). The aim of the present study was to investigate whether this association between rs17042171 and AF also exists in Chinese Han populations.

Methods: It was a case-control study. We enrolled a total of 1,593 Chinese Han origin individuals in the study, including 597 AF patients and 996 AF-free controls. Genotyping was performed using the TaqMan allelic discrimination Assay. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in logistic regression models.

Results: There was strongly significant difference between AF patients and control subjects regarding rs17042171 assumption of additive model (OR=2.20, 95% CI: 1.88-2.57, $p=2.00 \times 10^{-22}$), dominant model (OR=2.99; 95% CI: 2.19-4.09; $p=6.47 \times 10^{-12}$) and a recessive (OR=2.75; 95% CI: 2.21-3.43; $p=1.30 \times 10^{-19}$). In the stratification analysis based on age, gender, hypertension, diabetes and coronary artery disease, there was no significant difference of the associations for rs17042171 among the subgroups.

Conclusion: Our results indicated that rs17042171 confers an increased risk of AF in Chinese Han Populations and expanded the association to non-European ancestry populations for the first time. *(Anatol J Cardiol 2016; 16: 165-9)*

Keywords: atrial fibrillation, genetics, single nucleotide polymorphism, rs17042171

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice. Independent of preexisting diseases, AF can increase both cardiovascular mortality and morbidity (1-3). Arrhythmia has become an important public health problem because of its association with significantly increased risks of stroke, heart failure, and death (4). Recently, radiofrequency catheter ablation has been developed as an aggressive management of AF. Moreover, morphological and electrophysiological alterations that develop and maintain AF have been studied extensively (5). However, the limited effectiveness of the management and the high recurrence rate of catheter ablation indicate that the mechanism of AF is still not fully understood. There is a growing body of studies demonstrating that genetic factors play an important role in the pathogenesis of AF (6), especially in patients with lone AF (7). Scientific studies conducted in the last decade described an increased risk in offspring of patients with AF (8, 9). Moreover, the first genome-wide association study (GWAS) of AF identified some noncoding single-nucleotide polymorphisms (SNPs) located on chromosome 4q25 that are associated with an increased AF risk (10). Till date, several follow-up studies have replicated these GWAS results in populations with different racial backgrounds (11-14). However, it is worth noting that there were some drastic differences in individuals of different populations. The frequency of the risk allele T of SNP rs2200733 in the European population deviates greatly from that in the Chinese population and SNP rs2200733 is a more common genetic risk factor in the Chinese population (12-15). These results suggest that the common AF is a complex disease resulting from the interaction among multiple genes, environmental factors, and gene-environment interactions (16, 17).

Then, Benjamin et al. (18) performed an independent GWAS and revealed variants in the *ZFHX3* gene on chromosome 4q25 that are associated with AF in various individuals of European ancestry and identified a new locus for AF on chromosome 4q25 (rs17042171, OR=2.46, $p=6.9\times10^{-51}$), which was approximately 150 kb telomeric to the transcription factor gene *PITX2*. Accordingly,

Address for Correspondence: Fengxiang Zhang, MD, PhD, Section of Pacing and Electrophysiology, Division of Cardiology, the First Affiliated Hospital of Nanjing Medical University, 300, Guangzhou Road, Nanjing-*China*
Phone: 86-25-8371-7168 E-mail: njzfx6@njmu.edu.cn

Accepted Date: 12.03.2015 **Available Online Date:** 24.04.2015

DOI:10.5152/akd.2015.5999

we conducted a large-scale case-control association study in 597 AF patients and 996 non-AF controls in Chinese Han populations to investigate or replicate whether the rs17042171 confers a risk of AF in a non-European ancestry cohort.

Methods

Study subjects

For this study, cases were selected from patients enrolled in our cardiovascular ward or had visited our cardiovascular clinic who had self-reported ethnic Han origin. The study recruited 597 consecutive patients with AF formed the case group. The diagnostic criterion of AF was made by expert cardiologists and according to ACC/AHA/ESC 2006 guidelines for the management of patients with AF (19). Physical examinations were performed by either a 12-lead electrocardiogram (ECG) or by Holter ECG recordings. On the ECG, AF is characterized by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing, associated with an irregular, frequently rapid ventricular response. According to clinical characteristics, AF can be classified into paroxysmal AF (episodes that generally last 7 days or less), persistent AF (episodes that sustain beyond 7 days), and permanent AF (ongoing long-term episodes, in which cardioversion has failed or has not been attempted). AF patients who are under 60 years of age without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension, were considered as lone AF. Patients with other types of cardiac arrhythmias, cardiomyopathies, and valvular disease were excluded from this study. We acquired relevant information such as age; gender; and history of hypertension, diabetes, coronary artery disease (CAD), and hyperthyroidism from the medical records. The remaining 996 patients were assigned to control group on the basis of the ECG or no history of AF. Similar to the cases, the controls were selected without consideration of the presence or absence of hypertension, diabetes, coronary artery disease, and hyperthyroidism. The study protocol was approved by local Ethics Committees and all participants signed consent forms.

DNA isolation and genotyping

Blood samples were drawn from study participants and genomic DNA was extracted from EDTA-preserved whole blood, using the standard phenol-chloroform method (20). The SNP was genotyped using the TaqMan allelic discrimination Assay (Applied Biosystems, Inc., USA). Genotyping was performed in 25 μL of standard PCR volume containing 1 μL of LC Green dye, 5 pmoL of each primer, 25 ng of genomic DNA, 2.5 μL of 10× PCR buffer with 1.5 mmoL/L $MgCl_2$, 5 mmoL deoxynucleotide triphosphates, and 1 U of Taq polymerase.

Statistical analysis

SNP rs17042171 genotypes were tested for Hardy-Weinberg equilibrium among controls using PLINK v1.05. Continuous variables were presented as mean and standard deviation (SD); normality tests (Kolmogorov-Smirnov) were used. Categorical variables compared using the χ^2 test. The χ^2 test was used to determine deviations of the genotype distribution between two groups. The Hardy-Weinberg equilibrium of the genotype distribution of polymorphisms in the case and control groups was determined using the χ^2 test. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated when we used logistic regression to adjust for covariant factors, including age; gender; and presence or absence of hypertension, diabetes, coronary artery disease, or hyperthyroidism, to assess the strength of the relationship of the genotype distribution of SNPs between the AF and control groups. The results have statistical significance if $p<0.05$ or the range of 95% CI did not include unity. All statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA).

Table 1. Clinical characteristics of the study population

	AF (n=597)	Control (n=996)	*P*
Male gender, n (%)	397 (66.5)	674 (67.7)	0.630
Age* (Mean±SD)	58.37±11.46	58.9±10.21	0.428
Paroxysmal AF, n (%)	383 (64.2)	NA	-
Persistent AF, n (%)	196 (32.8)	NA	-
Permanent AF, n (%)	18 (3.0)	NA	-
Lone AF, n (%)	71 (11.9)	NA	-
Hypertension, n (%)	260 (43.6)	267 (26.8)	6.18×10^{-12}
CAD, n (%)	53 (8.0)	28 (5.1)	0.019
Diabetes, n (%)	48 (8.9)	51 (2.8)	9.55×10^{-8}

*Age was defined as the age at the sample collection. Data are presented as mean ± standard deviation or number (percentage); AF - atrial fibrillation; CAD - coronary artery disease; NA - not available; SD - standard deviation

Results

Characteristics of study patients

We performed genetic analysis in 597 patients with AF vs. 996 control subjects to detect the association between SNP rs17042171 and the risk of AF in the Chinese Han population. The general and clinical characteristics of the AF patients and controls are summarized in Table 1. The average age for AF cases and controls was 58.37±11.46 and 58.99±10.21 years, respectively. There were no significant differences between AF patients and control subjects regarding age and gender (p=0.428 and p=0.630, respectively). Among the AF group, 64.2% patients were paroxysmal AF, 32.8% were persistent, and permanent AF accounted for 11.9%. The hypertensive patients in the AF and control groups amounted to 260 and 267, respectively, and 48 had CAD. In the AF group, 53 patients had diabetes. Common cardiovascular risk factors for AF, including hypertension, coronary artery disease, and diabetes, were more prevalent in the AF group than in the control group ($p=6.18\times10^{-12}$, p=0.019, and $p=9.55\times10^{-8}$, respectively).

Table 2. Genotype distribution and allelic analysis of the association of rs17042171 with AF

Phenotype	CC, n (%)	AC, n (%)	AA, n (%)	*P*	Frequency (A/C)	*P*	OR (95% CI)
AF	58 (9.7)	242 (40.6)	296 (49.7)	7.57×10^{-24}	0.70/0.30	5.15×10^{-26}	2.25 (1.93–2.62)
Control	245 (24.6)	488 (49.0)	263 (26.4)		0.51/0.49		

A - adenine; AF - atrial fibrillation; C - cytosine; CI - confidence interval; OR - odds ratio. Genotyping calling rate: 99.9%

Table 3. Genotypic analysis of SNP rs17042171 with AF under three genetic models

SNP	Genotype	Adjusted OR* (95% CI)	*P**	*P***
rs17042171	AA	2.18 (1.84-2.58)	2.72×10^{-19}	0.823
	AC	2.07 (1.49-2.88)	2.76×10^{-12}	
	CC	1.00		
	Dominant model	2.99 (2.19-4.09)	6.47×10^{-12}	
	Recessive model	2.75 (2.21-3.43)	1.30×10^{-19}	
	Additive model	2.20 (1.88-2.57)	2.00×10^{-22}	

*Obtained in logistic regression models with adjustment for gender, age, hypertension, diabetes, coronary artery disease, and hyperthyroidism; ***P* for Hardy–Weinberg equilibrium test. A - adenine; AF - atrial fibrillation; C - cytosine; CI - confidence interval; OR - odds ratio

Hardy-Weinberg equilibrium of the genotype distribution of polymorphisms

The distribution of genotypes for SNP rs17042171 was not significantly deviated from Hardy-Weinberg equilibrium in the control group (p=0.823).

Genotypic association of rs1704217 with AF

The allele and genotype associations in patients with AF and control subjects are shown in Table 2. The distributions of the SNP rs17042171 genotype was significantly different between the AF group and the controls ($p=7.57\times10^{-24}$). The SNP rs17042171 AA genotype was found was more in the AF group than in the control group (9.7% vs. 24.6%, $p=7.57\times10^{-24}$). We found a significant allelic association between SNP rs1704217 and AF. The frequency of the allele A of SNP rs17042171 was 0.70 compared with 0.30 in the unaffected controls (OR=2.25, 95% CI: 1.93-2.62, $p=5.15\times10^{-26}$).

Adjusting for gender, age, hypertension, diabetes, coronary artery disease, and hyperthyroidism, logistic regression analysis of SNP revealed that patients with the AA genotype were at a higher risk (2. 8-fold) of developing AF than those with the CC genotype (OR=2.18, 95% CI: 1.84-2.58, $p=2.72\times10^{-19}$). Patients with the heterozygous genotype (AC) were 2.07 times more likely to develop AF (OR=2.07, 95% CI: 1.49-2.88; $p=2.76\times10^{-12}$). To test the association between rs17042171 and AF, genotypic frequencies under three genetic models (dominant, recessive, and additive) were also applied. Indeed, rs17042171 was strongly associated with the AF assumption of additive model (OR=2.20, 95% CI: 1.88-2.57, $p=2.00\times10^{-22}$), dominant model (OR=2.99; 95% CI: 2.19-4.09; $p=6.47\times10^{-12}$), and recessive model (OR=2.75; 95% CI: 2.21-3.43; $p=1.30\times10^{-19}$) (Table 3).

To further validate the associations of the significance, stratified analysis was also performed for rs17042171 on the basis of age and gender and hypertension, diabetes, or CAD. As shown in Table 4, risk effects were also observed between subgroups stratified by age, gender, hypertension, and CAD. When the cohort was divided into different age groups, the OR in AF cases diagnosed over 59 years of age was slightly higher than that in AF cases under 59 years of age (2.52 vs. 1.93), but the difference was not significant (p for heterogeneity was 0.104). The association between rs17042171and AF was significant in the AF group without diabetes but not in the AF group with diabetes (Table 4).

Discussion

We conducted a case-control association study of 597 subjects with AF vs. 996 controls for SNP rs1704217 on chromosome 4 locus. Consistent with previous studies (OR=2.46, $p=6.9\times10^{-51}$) (18), our results indicated that rs17042171 confers an increased risk of AF in Chinese Han populations (OR=2.20, $p=2.00\times10^{-22}$).

In the present control subjects, the frequency of the A allele of SNP rs17042171 was approximately 51%, which is comparable to that reported in the NCBI dbSNP database, ranging from 42% to 54% in other Asian ethnicities, but much more than that in European-descent populations (the allelic frequency is 0.115). In the study on European ancestry AF subjects by Benjamin et al. (18), the allele frequency of the allele A of SNP rs17042171 was approximately 16%, much lower than that of 70% in the present AF subjects of Chinese Han populations. Although the cause and significance of the apparent higher frequency of the allele C of SNP rs1704217 are uncertain, it may account for the different estimated risks in the two populations.

The limited success of various therapies for AF and differences between the individual treatment effects suggested that the pathogenesis of AF is multifactorial (21). Subsequently, data that have emerged from independent studies strongly support the notion that genetic variants are associated with AF risk, including ion channel genes (6, 11). A genome-wide association study has been instrumental in the identification of common

Table 4. Stratification analysis for the association between rs17042171 and AF risk

Variables	Case, n	Control, n	Adjusted OR* (95% CI)	*P**	*P***
SNP	rs17042171 (AA/AC/CC)				
Age					
≤59	33/117/157	111/221/146	1.93 (1.55-2.40)	3.74×10^{-9}	0.104
>59	25/125/139	134/267/117	2.52 (1.99-3.19)	1.91×10^{-14}	
Gender					
Male	43/154/199	167/329/178	2.14 (1.77-2.59)	6.24×10^{-15}	0.653
Female	15/88/97	78/159/85	2.32 (1.72-3.11)	2.48×10^{-8}	
Hypertension					
Yes	21/105/134	66/139/62	2.68 (2.03-3.53)	2.64×10^{-12}	0.075
No	37/137/162	179/349/201	1.97 (1.62-2.40)	9.81×10^{-12}	
CAD					
Yes	3/21/23	11/30/10	3.15 (1.42-6.99)	0.005	0.358
No	55/221/273	234/458/253	2.15 (1.82-2.53)	1.65×10^{-9}	
Diabetes					
Yes	4/24/25	7/14/7	2.32 (0.96-5.60)	0.062	0.900
No	54/218/271	238/474/256	2.19 (1.86-2.58)	5.47×10^{-21}	

*Associations were evaluated using logistic regression with adjustment for gender, age, hypertension, diabetes mellitus, coronary artery disease, and hyperthyroidism; ***P* for heterogeneity test using the chi-square-based Q test. A - adenine; AF - atrial fibrillation; C - cytosine; CAD - coronary artery disease; CI - confidence interval; n - number of genotypes. OR - odds ratio; SNP - single nucleotide polymorphism

variants on 4q25, 16q22, and 1q21 for the nonfamilial AF (22) and a strong association between variants on chromosome 4q25 and AF was identified in three populations of European descent and a Chinese population from Hong Kong (10). The most popular and widely accepted hypothesis suggests the close proximity of these variants on 4q25 to the *PITX2* (paired-like homeodomain transcription factor 2), known to be critical in the embryonic development of the cardiac conduction system and pulmonary venous myocardium, which is a major source of ectopic activity related to the initiation and maintenance of AF (23). Previous studies revealed that reducing *PITX2c* expression can promote atrial fibrillation inducibility and the mutant *PITX2c* is associated with significantly reduced transcriptional activity (24-26). By examining GWAS data for AF, Benjamin et al. (18) replicated the previously reported association with chromosome 4q25 variants and identified a new locus rs17042171 on chromosome 4 locus, which was approximately 150 kb telomeric to *PITX2* ($p=6.9\times10^{-51}$). Rs17042171 may be expected to exert influence on the transcriptional activity of *PITX2c*. Further studies are warranted to evaluate the precise mechanism by which rs1704217 regulates AF risk.

Study limitations

This study has several limitations. One limitation is that this is the first time that SNP rs17042171 was found to be associated with AF in the Chinese Han population; therefore, further investigation should be conducted in other independent Chinese Han populations. Second, the mean age of the AF patients was 58.37±11.46 years, which was lesser than that of typical AF in the community. Moreover, our findings suggested rs17042171 is an AF-susceptibility SNP; however, its role in AF was rarely examined.

Conclusion

In summary, to the best of our knowledge, this is the first study to investigate whether rs17042171 confers a highly significant risk of AF in the Chinese Han population. The results expand the association of SNPrs17042171 with AF previously identified in a cohort of European descent to a non-European ancestry population.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Funding: This work was supported by grants from the National Natural Science Foundation of China (Grant no. 81470456, 81170160), by National "Twelfth Five-Year" Plan for Science & Technology Support (Grant no. 2011BAI11B13), by "A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions," by the Six Peak Talents Foundation of Jiangsu Province (Grant no. 2011-WS-071), and by the Program for Development of Innovative Research Team in the First Affiliated Hospital of Nanjing Medical University (Grant no. IRT-004).

References

1. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: The Framingham study. N Engl J Med 1982; 306: 1018-22. [CrossRef]

2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham heart study. Circulation 1998; 98: 946-52. [CrossRef]
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The anticoagulation and risk factors in atrial fibrillation (ATRIA) study. JAMA 2001; 285: 2370-5. [CrossRef]
4. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002; 113: 359-64. [CrossRef]
5. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: A translational appraisal. Physiol Rev 2011; 91: 265-325. [CrossRef]
6. Tsai CT, Lai LP, Hwang JJ, Lin JL, Chiang FT. Molecular genetics of atrial fibrillation. J Am Coll Cardiol 2008; 52: 241-50. [CrossRef]
7. Marcus GM, Smith LM, Vittinghoff E, Tseng ZH, Badhwar N, Lee BK, et al. A first-degree family history in lone atrial fibrillation patients. Heart Rhythm 2008; 5: 826-30. [CrossRef]
8. Fox CS, Parise H, D'Agostino RB Sr, Lloyd-Jones DM, Vasan RS, Wang TJ, et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA 2004; 291: 2851-5. [CrossRef]
9. Arnar DO, Thorvaldsson S, Manolio TA, Thorgeirsson G, Kristjansson K, Hakonarson H, et al. Familial aggregation of atrial fibrillation in Iceland. Eur Heart J 2006; 27: 708-12. [CrossRef]
10. Gudbjartsson DF, Arnar DO, Helgadottir A, Gretarsdottir S, Holm H, Sigurdsson A, et al. Variants conferring risk of atrial fibrillation on chromosome 4q25. Nature 2007; 448: 353-7. [CrossRef]
11. Kaab S, Darbar D, van Noord C, Dupuis J, Pfeufer A, Newton-Cheh C, et al. Large scale replication and meta-analysis of variants on chromosome 4q25 associated with atrial fibrillation. Eur Heart J 2009; 30: 813-9. [CrossRef]
12. Shi L, Li C, Wang C, Xia Y, Wu G, Wang F, et al. Assessment of association of rs2200733 on chromosome 4q25 with atrial fibrillation and ischemic stroke in a Chinese han population. Hum Genet 2009; 126: 843-9. [CrossRef]
13. Lee KT, Yeh HY, Tung CP, Chu CS, Cheng KH, Tsai WC, et al. Association of rs2200733 but not rs10033464 on 4q25 with atrial fibrillation based on the recessive model in a Taiwanese population. Cardiology 2010; 116: 151-6. [CrossRef]
14. Mohanty S, Santangeli P, Bai R, Di Biase L, Mohanty P, Pump A, et al. Variant rs2200733 on chromosome 4q25 confers increased risk of atrial fibrillation: Evidence from a meta-analysis. J Cardiovasc Electrophysiol 2013; 24: 155-61. [CrossRef]
15. Li C, Wang F, Yang Y, Fu F, Xu C, Shi L, et al. Significant association of snp rs2106261 in the zfhx3 gene with atrial fibrillation in a Chinese Han Geneid population. Hum Genet 2011; 129: 239-46. [CrossRef]
16. Ruo B, Capra AM, Jensvold NG, Go AS. Racial variation in the prevalence of atrial fibrillation among patients with heart failure: The epidemiology, practice, outcomes, and costs of heart failure (EPOCH) study. J Am Coll Cardiol 2004; 43: 429-35. [CrossRef]
17. Benjamin EJ, Chen PS, Bild DE, Mascette AM, Albert CM, Alonso A, et al. Prevention of atrial fibrillation: Report from a national heart, lung, and blood institute workshop. Circulation 2009; 119: 606-18. [CrossRef]
18. Benjamin EJ, Rice KM, Arking DE, Pfeufer A, van Noord C, Smith AV, et al. Variants in zfhx3 are associated with atrial fibrillation in individuals of european ancestry. Nat Genet 2009; 41: 879-81.
19. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: Full text: A report of the american college of cardiology/american heart association task force on practice guidelines and the european society of cardiology committee for practice guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace 2006; 8: 651-45. [CrossRef]
20. Albarino CG, Romanowski V. Phenol extraction revisited: A rapid method for the isolation and preservation of human genomic DNA from whole blood. Mol Cell Probes 1994; 8: 423-7. [CrossRef]
21. Kourliouros A, Savelieva I, Kiotsekoglou A, Jahangiri M, Camm J. Current concepts in the pathogenesis of atrial fibrillation. Am Heart J 2009; 157: 243-52. [CrossRef]
22. Liu X, Wang F, Knight AC, Zhao J, Xiao J. Common variants for atrial fibrillation: Results from genome-wide association studies. Hum Genet 2012; 131: 33-9. [CrossRef]
23. Douglas YL, Jongbloed MR, Deruiter MC, Gittenberger-de Groot AC. Normal and abnormal development of pulmonary veins: State of the art and correlation with clinical entities. Int J Cardiol 2011; 147: 13-24. [CrossRef]
24. Wang J, Klysik E, Sood S, Johnson RL, Wehrens XH, Martin JF. Pitx2 prevents susceptibility to atrial arrhythmias by inhibiting left-sided pacemaker specification. Proc Natl Acad Sci U S A 2010; 107: 9753-8.
25. Chinchilla A, Daimi H, Lozano-Velasco E, Dominguez JN, Caballero R, Delpon E, et al. Pitx2 insufficiency leads to atrial electrical and structural remodeling linked to arrhythmogenesis. Circ Cardiovasc Genet 2011; 4: 269-79. [CrossRef]
26. Wang J, Zhang DF, Sun YM, Yang YQ. A novel pitx2c loss-of-function mutation associated with familial atrial fibrillation. Eur J Med Genet 2014; 57: 25-31. [CrossRef]