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ORIGINAL RESEARCH

Association Between *TCF21* Gene Polymorphism with the Incidence of Paroxysmal Atrial Fibrillation and the Efficacy of Radiofrequency Ablation for Patients with Paroxysmal Atrial Fibrillation

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Purpose: Atrial fibrillation (AF) is the most common sustained arrhythmia with a high rate of recurrence after catheter ablation. The gene encoding transcription factor 21 (*TCF21*) has been linked to coronary artery disease risk by human genome-wide association studies in multiple racial ethnic groups. However, the association of *TCF21* with AF remains unclear.

Patients and Methods: Circulating leukocytes in patients with paroxysmal AF (PAF) and 92 age-matched controls without a history of cardiovascular disease, AF and other arrhythmias were collected. A total of 224 PAF patients receiving radiofrequency ablation had an 18-month scheduled follow-up study for recurrence of AF. Three single-nucleotide polymorphisms (SNPs) of *TCF21* (*rs2327429, rs2327433* and *rs12190287*) were genotyped by PCR, and serum levels of *TCF21* were measured by ELISA.

Results: More males and smokers were observed in the PAF group compared with controls. C allele of *rs2327429*, G allele and GG genotype of *rs12190287* were markedly associated with the increased onset of PAF. The levels of serum TCF21 were significantly higher in PAF group than those in control group (1.96 ± 0.85 vs 0.86 ± 0.49 ng/mL, $P<0.001$). Based on logistic regression analysis, we confirmed that risk allele at *rs12190287* and serum TCF21 concentration were independently correlated with the incidence of PAF. Furthermore, GG genotype of *rs12190287* enhanced the susceptibility of AF recurrence after ablation.

Conclusion: G allele and GG genotype of *rs12190287* in *TCF21* and elevated TCF21 concentration are significantly associated with the onset of PAF and recurrence after ablation.

Keywords: transcription factor 21, paroxysmal atrial fibrillation, single-nucleotide polymorphism, radiofrequency ablation

Introduction

Atrial fibrillation (AF) is the most common human arrhythmia, which affects approximately 3% of adults.[1,2] Its prevalence increases with age and currently become one of the most global health burdens in the elderly population.[3,4] AF presence affects patient's quality of life and increases the risk of stroke and heart failure.[2,5] AF was regarded as a progressive disease and categorized as paroxysmal, persistent and permanent AF. More than 33% of the patients with paroxysmal AF (PAF) develop to persistent AF within 10 years.[2] Apart from electrical remodeling, atrial fibrosis and structural remodeling are considered to be associated with the initiation and maintenance of AF.[6] Since trigger from pulmonary veins is a common trigger of AF, pulmonary vein isolation with radiofrequency ablation (RFA) is the mainstay of AF control, especially for drug-refractory PAF patients.[7] However, a meta-analysis reported that only 30% to 85% patients could successfully maintain sinus rhythm after RFA with a median of 12 months.[8] Hence, there is an urgent need for a better understanding of the pathogenesis of AF.

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Numerous studies demonstrated that AF has a substantial genetic basis.[9,10] Despite risk factors including sex, aging, smoking and comorbidities contribute to the AF risk, a family history of AF also confers a high AF risk.[3] Population-based genome-wide association studies (GWAS) among familial studies shed light on the genetic mutations and polymorphisms associated with AF, such as *KCNQ1, SCN5A, GATA4*, etc.[11] Nevertheless, more novel biomarkers are still needed for the risk stratification of AF recurrence, which enables better patient's selection for RFA and post-intervention monitoring.

Transcription factor 21 (*TCF21*) is a member of the basic helix-loop-helix transcription factor family, and plays a vital role in cell fate and differentiation.[12] In murine models, *Tcf21* is required for phenotypic modulation of smooth muscle cells in atherosclerotic tissues and promotes a fibroblast phenotype in these cells.[13] Likewise, TCF21 is essential for the formation of resident cardiac fibroblasts. Mice deficient in *Tcf21* failed to produce cardiac fibroblasts and suppress cardiac repair.[14] Human GWAS indicated that single nucleotide polymorphism (SNP) *rs12190287* located in the 3′ untranslated region (3′-UTR) of *TCF21* was associated with coronary artery disease risk in multiple racial ethnic groups.[15–17] Furthermore, *TCF21 rs12190287* polymorphisms also conferred predisposition to ventricular septal defects in a Chinese population.[18] Genetic variants could contribute to the AF pathology by affecting the expression and function of proteins responsible for various cellular activities. Therefore, given the marked effect of TCF21 in cardiovascular diseases, we hypothesized that TCF21 may play an important role in the AF pathogenesis. In the present study, we aimed to investigate the association of *TCF21* SNPs with AF patients after RFA in a Chinese population.

Materials and Methods

Study Design

This study was an observational study of 224 PAF patients and 92 age-matched controls from our institution. Patients over 18 years of age with documented symptomatic PAF were eligible for enrollments if they were refractory to at least one class I to IV antiarrhythmic drug. PAF was defined as AF that terminated spontaneously or with intervention within 7 days of onset according to the diagnostic criteria of guidelines.[19] The mean duration of PAF before ablation was 9.32 months. All patients were administrated with warfarin or new oral anticoagulants for at least 1 month before RFA. Transesophageal echocardiography was performed within 48 hours before operation to exclude left atrial thrombus. Exclusion criteria included 1) malignant tumor; 2) severe liver dysfunction defined by an increase in alanine amino-transferase (ALT) levels 5 times the upper limit of normal[20]; 3) severe renal dysfunction defined by estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2; 4) hematologic disorders including leukemia, lymphoma, myelodysplastic syndrome and severe anemia (hemoglobin <60 g/L), and history of cerebral infarction or ischemia within 6 months; 5) myocarditis or cardiomyopathies or heart failure; 6) reversible AF caused by cardiopulmonary surgery, cardiac surgery; 7) left atria diameter (LAD) >60mm. The control subjects without a history of cardiovascular diseases, including coronary artery disease, valvular disease, cardiomyopathy and congenital heart disease, were recruited. Of note, the controls were documented with normal electrocardiogram and had no history of AF or any other cardiac arrhythmias.

RFA performed by well-experienced cardiologists. Briefly, the electrical isolation of the circumferential pulmonary vein lesions was conducted under the guidance of CARTO system (Biosense Webster, USA). Additional ablation lines of the left atrium roof were implemented in less than 5% patients as necessary. The endpoint of RFA was the absence or dissociation of potentials between the pulmonary vein and left atrium.[21]

This study was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College and complied with the Declaration of Helsinki. Written informed consent was obtained from each subject.

Social and Clinical Parameters

Social information was obtained from the subjects, including sex, age, smoking habits, history of diabetes and hypertension. The P wave duration and PR intervals from electrocardiograms under sinus rhythm were collected in all enrollments. The LAD, left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (EF) were measured by transthoracic ultrasonic testing. Venous blood samples were

obtained in subjects after overnight fast. Plasma creatinine were assayed by standard methods in the Department of Laboratory Medicine of the First Affiliated Hospital of Bengbu Medical College.

SNPs Selection and DNA Genotyping

All peripheral blood samples were taken in the morning with patients fasting from midnight onward before RFA. According to linkage disequilibrium via Haploview and previous studies, we selected three reported SNPs in *TCF21* (*rs2327429 T>C, rs2327433 A>G* and *rs12190287 C>G*).[18,22] Circulating leukocytes in patients with 224 PAF patients and 92 controls were collected for DNA extraction by phenol chloroform. We performed genotyping with the selected SNPs in the samples with TaqMan allelic discrimination via ABI 7900HT (Applied Biosystems, Foster City, CA, USA). The TaqMan assay kits and probes were obtained from Applied Biosystems. All data were analyzed via ABI Prism SDS software version 2.3.

Measurement of Serum TCF21

The serum levels of TCF21 were measured by enzyme-linked immunosorbent assay (ELISA) using commercially available reagent (catalog XPEH1455, Xpressbio, USA), according to the manufacturer's instruction.

Follow-Up Study

All participants were monitored with ECGs and holter by qualified physicians during hospital stay. AF patients underwent RFA procedure were followed up with clinic visits every 2–3 months for 18 months, or earlier if symptoms were consistent. And, 24-hour holter and 12-lead ECG were preformed to determine the recurrence of AF, defined as any recording of AF on 12-lead ECG or an episode >30 seconds on 24-hour holter after 3-month post-ablation blanking period.

Statistical Analysis

Data were expressed as mean ± standard deviation or numbers with the percentage in parentheses. Differences between PAF patients and control subjects were analyzed by the Student's *t*-test and chi-squared test, respectively. Multivariate logistic regressions were conducted to detect the independent determinants of PAF onset and recurrence. AF-free survival in PAF patients among different genotypes were analyzed by Log rank test. SPSS19.0 software was used for statistical analysis. $P<0.05$ was considered statistically significant.

Results

Characteristics of the Study Participants

Clinical characteristics of participants are presented in Table 1. All PAF patients received RFA therapy. Compared with control subjects, PAF patients had more male (73.2% vs 44.6%, $P < 0.01$) and more smokers (29.9% vs 16.3%, $P = 0.01$). There were no significant differences in other factors between PAF patients and control subjects, such as age, diabetes, hypertension, LAD, LVESD, LVEDD, EF and plasma creatinine (all $P > 0.05$).

Rs12190287 and Serum Concentration of TCF21 Associated with the Risk of PAF Onset

Based on previous findings, we selected three *TCF21* polymorphisms (*rs2327429, rs2327433, rs12190287*) reported to be associated with the incidence of human diseases in Chinese population and investigated these SNPs in our studies.[18,22,23] Table 2 shows genotype and allele frequencies of the selected 3 SNPs in *TCF21* and serum concentration of TCF21 in PAF patients and control subjects. *Rs2327429* (CC genotype and C allele) and *rs12190287* (CG/GG genotype and G allele) had different frequencies between PAF patients and control subjects (*rs2327429* CC vs TT, $P = 0.031$; C vs T allele, $P = 0.032$; *rs12190287* CG vs CC, $P = 0.020$; GG vs CC, $P = 0.030$; G vs C allele, $P = 0.005$). We also found that *rs12190287* genotype had similar frequencies between female and male groups ($P = 0.622$). Furthermore,

Table 1 Clinical Characteristics of Individuals with and without Paroxysmal Atrial Fibrillation

	Control (n=92)	PAF (n=224)	p-value
Age, years	62.8 ± 13.9	64.0 ± 10.5	0.41
Male	41 (44.6)	164 (73.2)	<0.01
Smoking	15 (16.3)	67 (29.9)	0.01
Diabetes	25 (27.2)	42 (18.8)	0.10
Hypertension	56 (60.9)	151 (67.4)	0.27
LAD, mm	40.2 ± 4.9	40.8 ± 5.5	0.33
LVESD, mm	47.9 ± 6.5	47.3 ± 5.2	0.44
LVEDD, mm	31.7 ± 6.8	31.0 ± 5.5	0.34
EF, %	59.8 ± 7.8	57.5 ± 10.9	0.07
Creatinine, μmol/L	88.3 ± 42.8	78.6 ± 27.0	0.21

Note: Data are expressed as mean ± standard deviation.
Abbreviations: EF, ejection fraction; LAD, left atrial diameter; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; PAF, paroxysmal atrial fibrillation.

Table 2 Association of TCF21 Polymorphism and Concentration with the Incidence of Paroxysmal Atrial Fibrillation

	Control (n=92)	PAF (n=224)	p-value
rs2327429			
TT	31 (33.7)	102 (45.5)	
CT	40 (43.5)	89 (39.7)	CT vs TT 0.167
CC	21 (22.8)	33 (14.7)	CC vs TT 0.031
Allele T	106 (56.4)	293 (65.4)	C vs T 0.032
C	82 (43.6)	155 (34.6)	
rs2327433			
AA	28 (30.4)	97 (43.3)	
AG	37 (40.2)	67 (29.9)	AG vs AA 0.028
GG	27 (30.4)	60 (26.8)	GG vs AA 0.158
Allele A	93 (50.5)	261 (58.3)	G vs A 0.076
G	91 (49.5)	187 (41.7)	
rs12190287			
CC	50 (54.3)	84 (37.5)	
CG	28 (30.4)	90 (40.2)	CG vs CC 0.020
GG	14 (15.2)	50 (22.3)	GG vs CC 0.030
Allele C	128 (69.6)	258 (57.6)	G vs C 0.005
G	56 (30.4)	190 (42.4)	
TCF21 (ng/mL)	0.86 ± 0.49	1.96 ± 0.85	<0.001

Abbreviations: PAF, paroxysmal atrial fibrillation; TCF21, transcription factor 21.

the levels of serum TCF21 were also significantly higher in the PAF group than those in the control group (1.96 ± 0.85 vs 0.86 ± 0.49 ng/mL, $P < 0.001$).

Importantly, only G allele at *rs12190287* significantly increased TCF21 serum concentration ($P < 0.05$), but no difference in TCF21 concentration among genotypes of *rs2327429* and *rs2327433* ($P = 0.558$; $P = 0.510$, respectively) (Figure 1). Moreover, multivariate logistic regression analysis together with conventional risk factors (age, sex, smoking, diabetes and hypertension) validated that the onset of PAF was significantly associated with *rs12190287* (adjusted odds ratio 2.732, $P = 0.036$) and serum concentration of TCF21 >1.63 ng/mL (adjusted odds ratio 5.824, $P < 0.001$, Table 3).

Association of rs12190287 Genotype with Electrical and Structural Parameters

To further investigate the association of *rs12190287* with electrical and structural parameters, we analyzed these parameters (including P wave duration, PR intervals, LAD, LVESD, LVEDD and EF) in different genotypes at

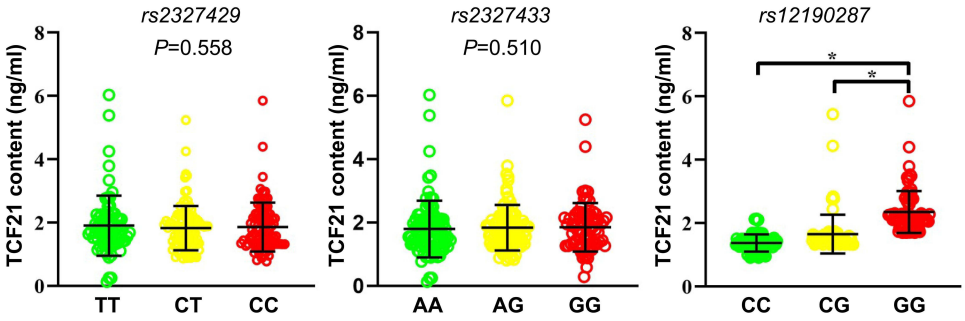

Figure 1 Association between *TCF21* gene polymorphism and serum TCF21 concentration. Serum concentration of TCF21 among different genotypes of *rs2327429, rs2327433* and *rs12190287* was measured by ELISA. * P<0.05. TCF21 = transcription factor 21.

rs12190287 and found that there were no significant differences between *rs12190287* genotype and cardiac function parameters (all $P > 0.05$, Table 4).

Rs12190287 and Serum Concentration of TCF21 Associated with PAF Recurrence

With a follow-up time of 18 months, the total PAF recurrence rate in our study was 19.6%. There was no statistical significance in recurrent rate between female and male PAF patients ($P = 0.546$). Multivariate logistic analysis with adjustment for conventional risk factors demonstrated that GG genotype of *rs12190287* significantly enhanced the susceptibility of PAF recurrence after RFA (adjusted odds ratio 1.659, $P = 0.032$, Table 5). Further, Log rank test was performed to investigate the association of PAF recurrence among different genotypes at *rs12190287*, and results indicated that GG genotype at *rs12190287* dramatically reduced the freedom rate of PAF recurrence ($P = 0.023$, Figure 2). Interestingly, we found that serum concentration of TCF21 greatly declined after 18 months of follow-up in non-recurrent group (1.93 ± 0.84 vs 1.51 ± 0.78 ng/mL, $P < 0.001$), while TCF21 levels slightly elevated in recurrent group without statistical significance (2.04 ± 0.91 vs 2.09 ± 0.88 ng/mL, $P = 0.334$).

Discussion

In the present study, we first reported that a novel SNP *rs12190287* (G allele) in *TCF21* and serum TCF21 concentration were independently correlated with the incidence of PAF. Moreover, GG genotype of *rs12190287* enhanced the susceptibility of PAF recurrence after RFA during a follow-up time of 18 months.

AF, the most common cardiac arrhythmia in clinical practice, represents a major cause of mortality and morbidity, mainly due to embolic events and heart failure.[24,25] Since it is a disorganized tachyarrhythmia with irregular atrial activity initiated by ectopic foci from around or inside the pulmonary veins, pulmonary vein isolation with catheter ablation is already widely used in the past few decades and associated with high rates of AF freedom in PAF patients.[24]

Table 3 Multivariate Regression Analysis of Independent Determinants of PAF

	Exp(B)	95% CI	p-value
Age (> 65 yrs)	0.777	(0.415, 1.457)	0.432
Male	0.218	(0.115, 0.412)	<0.001
Smoking	2.688	(1.250, 5.781)	0.011
Hypertension	1.631	(0.856, 3.109)	0.137
Diabetes	0.541	(0.266, 1.098)	0.089
rs2327429	0.666	(0.443, 1.003)	0.052
rs2327433	0.731	(0.500, 1.070)	0.107
rs12190287	2.732	(1.863, 3.059)	0.036
TCF21 (>1.63 ng/mL)	5.824	(3.397, 8.703)	<0.001

Note: Exp(B): adjusted odds ratio.
Abbreviations: CI, confidence interval; PAF, paroxysmal atrial fibrillation.

Table 4 Association of rs12190287 Genotype with Electrical and Structural Parameters

	rs12190287			p-value
	CC (n=134)	CG (n=118)	GG (n=64)	
P wave duration, s	0.097 ± 0.019	0.096 ± 0.018	0.100 ± 0.021	0.386
PR intervals, s	0.147 ± 0.020	0.146 ± 0.019	0.150 ± 0.021	0.386
LAD, mm	41.19 ± 5.70	39.94 ± 5.05	40.72 ± 5.13	0.173
LVESD, mm	47.08 ± 5.59	47.84 ± 5.75	47.91 ± 5.31	0.473
LVEDD, mm	30.61 ± 5.54	31.94 ± 6.49	31.17 ± 5.33	0.196
EF, %	58.04 ± 10.04	57.64 ± 10.63	59.58 ± 9.49	0.485

Abbreviations: EF, ejection fraction; LAD, left atrial diameter; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter.

Table 5 Logistic Analysis of Determinants for PAF Recurrence

	Exp(B)	95% CI	p-value
Age (> 65 years)	0.637	(0.304, 1.333)	0.231
Male	1.121	(0.524, 2.398)	0.769
Smoking	0.489	(0.220, 1.084)	0.078
Hypertension	1.052	(0.519, 2.132)	0.889
Diabetes	0.691	(0.278, 1.716)	0.426
rs2327429	0.932	(0.573, 1.514)	0.775
rs2327433	0.836	(0.558, 1.254)	0.387
rs12190287	1.659	(1.044, 2.637)	0.032
TCF21 (>1.63 ng/mL)	1.510	(0.760, 3.001)	0.240

Note: Exp(B): adjusted odds ratio.
Abbreviations: CI, confidence interval; PAF, paroxysmal atrial fibrillation.

Indeed, a significant recurrence rate was observed after RFA at nearly 30% after first intervention and 20% after two or more interventions.[25] Accumulating evidence indicated that genetic alterations affected AF incidence and recurrence.[26] GWAS is widely used to identify common SNPs during the development of AF, such as *rs6666258* of *KCNN3-PMVK, rs6817105* of *PITX2* and *rs3903239* of *PRRX1*, etc.[27,28] Despite there is a limitation on the usefulness of just one SNP as a predictor of AF onset/recurrence, adding it to our already established risk factors could be helpful for a prognostic risk stratification in PAF patients before performing procedures. In our study, for the first time, we found that *rs12190287* of *TCF21* was strongly associated with PAF onset and recurrence.

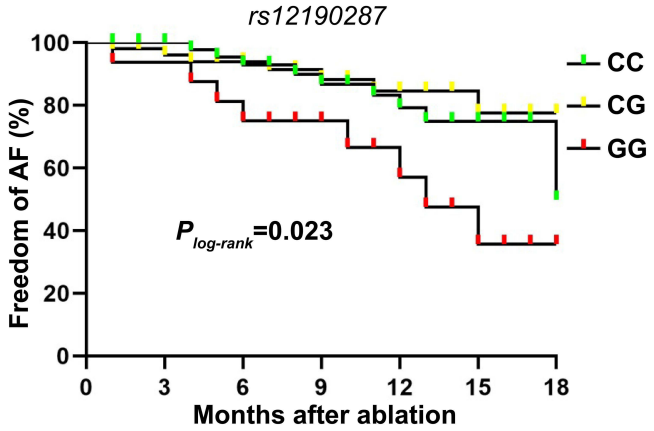

Figure 2 Freedom of atrial fibrillation in patients after radiofrequency ablation. Freedom rate of AF recurrence among different genotypes of *rs12190287* in AF patients receiving radiofrequency ablation was compared by Log rank test (Mantel–Cox).

Recently, *TCF21* was identified as a tumor suppressor gene in several types of cancer.[22,29,30] Besides that, TCF21 expression was also strongly associated with SMC phenotypic modulation in diseased human coronary arteries by single-cell analysis.[15] Nagao et al[13] revealed that SMC-derived TCF1 suppressed SMC differentiation via inhibition of Myocardin-SRF pathway. On the other hand, TCF21 was essential for the formation of resident cardiac fibroblasts, even deficiency of *Tcf21* failing to the production and transition of cardiac fibroblasts in mice.[14] Moore-Morris et al[31] found that resident cardiac fibroblasts derived from epicardial population, expressing TCF21, mediated pressure overload-induced cardiac fibrosis. As a consequence, excessive extracellular matrix deposition and cardiac fibrosis exacerbated AF and triggered the recurrence of AF after RFA.[32] Emerging evidence demonstrated that *TCF21* polymorphism plays an important role in cancer,[22,23] coronary artery diseases[16,17] and ventricular septal defects.[18] For instance, the CG and GG genotypes of *rs12190287* predict elevated risk of osteosarcoma[23] and conferred genetic susceptibility to VSDs in a Chinese population.[18] Herein, we provided the first data on the association between *TCF21* polymorphism and PAF onset/recurrence. We extracted DNA from circulating leukocytes of PAF patients and control subjects to analyze *TCF21* gene polymorphisms. Subsequently, we investigate whether the three SNP candidates were related to the PAF risk and recurrence. Fortunately, we discovered that *rs12190287* G allele was significantly associated with a higher risk of PAF onset and recurrence.

It is well known that SNPs in genes may affect gene expression through different mechanisms depending on their locations. Gao et al[22] reported that *rs12190287* C allele had a lower transcription activity than G allele, possibly owing to miRNA-mediated regulation of gene expression influenced by the functional genetic variants in 3' UTR region. Consistently, we found that C allele at *rs12190287* had a lower serum concentration of TCF21 than G allele, suggesting an important role of *rs12190287* in PAF onset and recurrence. Further studies on TCF21 were warranted to elucidate the function of *TCF21 rs12190287* during the AF pathogenesis.

The findings of the present study need to be interpreted within its limitations. First and foremost, the distribution of *rs12190287* genotype fluctuated in Chinese population among different studies.[18,22,23] It could be partly explained by the fact that the definition of control group may affect the frequencies of *rs12190287* among different studies. Although the controls in our study were free of AF and other arrhythmias, some concomitant diseases in control individuals may be underestimated. Second, the sample size was not large enough and inherent selection bias was unavoidable, because all participants were selected from our hospital in a Chinese population. The findings should be further validated in the future through population-based cohorts in different races. Last, *TCF21* polymorphisms might be affected by environmental factors or lifestyle.[23,33]

Conclusions

Taken together, *TCF21 rs12190287* polymorphism can regulate TCF21 expression, and the G allele and GG genotype of *rs12190287* were associated with PAF onset and recurrence. These findings indicated that *TCF21 rs12190287* polymorphism may serve as a potential marker for genetic susceptibility to PAF onset and recurrence after catheter ablation in a Chinese population.

Abbreviations

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; RFA, radiofrequency ablation; SNP, single-nucleotide polymorphism; TCF21, transcription factor 21.

Data Sharing Statement

The raw data could be available upon reasonable request to the corresponding author.

Ethics Approval and Informed Consent

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College. A written informed consent was obtained from all participants.

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Disclosure

The authors report no conflicts of interest in this work.

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