Association between gene variants and the recurrence of atrial fibrillation
An updated meta-analysis

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1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting millions of individuals worldwide.\textsuperscript{[1] AF increases the incidence of ischemic stroke, heart failure, and mortality.\textsuperscript{[2] The susceptibility factors of AF such as smoking, sex, obesity, and hypertension have been identified in some publications.\textsuperscript{[3–5]} AF has a heritable component and common or rare variants associated with AF have been identified in genome-wide association studies (GWAS) with a large population.\textsuperscript{[6–11]} During the past decade, AF ablation was a common therapy for AF.\textsuperscript{[12]} Despite the identification of these AF-associated variants, the factors regarding the association between variants and AF recurrence remain limited.

Recurrence of AF following catheter-based pulmonary veins isolation approaches up to 30% after 1 year later.\textsuperscript{[13]} Several pieces of research were involved in the association between variants and AF recurrence.\textsuperscript{[3,4,14–18]} The hottest variants involved in the recurrence of AF were rs2200733 (g.111710169C \(\rightarrow\) T) and rs10033464 (g.111720761T \(\rightarrow\) G) on chromosome 4q25 (near \(\text{PITX2}\)), rs13376333 (g.154841877C \(\rightarrow\) G) on chromosome 1q21 (in \(\text{KCNN3}\)), rs17193343 and rs2106261 on chromosome 16q22 (in \(\text{ZFHX3}\)) were not associated with AF recurrence in our meta-analysis. In total, our meta-analysis found that rs2200733 and rs10033464 on chromosome 4q25 (near \(\text{PITX2}\)) were associated with the risk of AF recurrence.

Abbreviations: AF = atrial fibrillation, CI = confidence interval, GWAS = genome-wide association studies, HR = hazard ratio, OR = odds ratio, variants

Keywords: rs10033464, rs2200733, the recurrence of atrial fibrillation, variants

Abstract
Background: Studies showed the controversial results about the effect of common genetic polymorphisms on the atrial fibrillation (AF) recurrence. We performed the systematic review and meta-analysis to qualify the association between common genetic polymorphisms and AF recurrence.

Methods: Articles were systematically retrieved from PubMed, Web of Science, EMBASE, Wanfang, and CNKI database and 9 studies including 3204 patients were enrolled in our meta-analysis.

Results: Results showed that the associations were significant under rs2200733 3 genetic models (TT vs CC: odds ratio [OR] [confidence interval [CI]] = 1.336 [1.061–1.683], \(P=0.014\); CT vs CC: OR [CI] = 0.759 [0.614–0.937], \(P=0.01\); TT vs CT + CC: OR [CI] = 2.308 [1.440–3.700], \(P=0.001\). The association was significant under rs10033464 genetic model (TT vs GG: OR [CI] = 1.517 [1.165–1.976], \(P=0.002\).

Conclusions: Rs13376333 on chromosome 1q21 (in \(\text{KCNN3}\)), rs7193343 and rs2106261 on chromosome 16q22 (in \(\text{ZFHX3}\)) were not associated with AF recurrence in our meta-analysis. In total, our meta-analysis found that rs2200733 and rs10033464 on chromosome 4q25 (near \(\text{PITX2}\)) were associated with the risk of AF recurrence.

Conflict of Interest: All authors have no competing interests to disclose.

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2. Materials and methods

2.1. Articles selection

We searched articles from PubMed, Web of Science, EMBASE, Wanfang, and CNKI database published before 29 March 2018. The searching keywords were “Atrial fibrillation,” “AF,” “recurrence,” “genetics,” “polymorphisms or variants,” and “SNP.” Dr Jian Qu and Dr Tao Jiang reviewed all relevant articles to collect potential eligible articles.

2.2. Inclusion and exclusion criteria

We screened the titles and abstracts to identify the potential eligible articles, and then full-text review was performed to get the detailed data.

The inclusion criteria were as follows:
1. cohort or case-control study;
2. AF patients;
3. genetic information about the AF patients;
4. has the data about the risk for AF recurrence with 95% confidence interval (CI).

Studies were excluded if they had the following criteria:
1. a review, case report or abstract having no data;
2. no variants information or had no clinical indicators;
3. involved just in animals or cells.

2.3. Data extraction and quality assessment

Dr Tao Jiang and Dr Yun-Dai Chen independently extracted data including authors’ names, year, ethnicities (Asian and Caucasian), sample size, and genotyping methods. The quality assessment was evaluated separately by 2 investigators (Dr Qiang Qu and Dr Ya-Nan Wang) using the Newcastle-Ottawa scale method.[20] Because this is a meta-analysis whose data is from other articles, we did not get the Ethics Approval/Institutional Review Board.

2.4. Statistical analyses

Stata 12.0 software (Stata Corp, College Station, TX) was used in all statistical analyses. Odds ratio (OR) or hazard ratio (HR) and their 95% CI were used in the association between variants and AF recurrence. Pooled HRs were performed for several different genetic models. Cochran Q test and I² test were used in heterogeneity assessment. Fixed effect model was used if P > .05 or I² < 50%, otherwise, a random model was chosen. Z-test was used in the significance of the pooled HRs. Publication bias was calculated by the Egger test and Begg test. Statistical significance was accepted when P < .05. The different comparison models in genetics were described as follows: For mutation (T > C), additive model: homozygous for mutation versus homozygous for mutation (CC vs TT); recessive model: homozygous for mutation versus heterozygous plus nonmutation carriers (CC vs CT + TT); dominant model: mutation carriers versus nonmutation carriers (CC + CT vs TT); co-dominant model: heterozygous versus all homozygous (CT vs CC + TT).

3. Results

3.1. Characteristics of articles

According to the search strategy and exclusion criteria, we enrolled 84 publications and excluded 56 irrelevant studies, 3 meta-analyses, 2 case reports, 8 basic research, and 6 publications having no data for meta-analysis, then 9 publications were enrolled for pooling HRs of meta-analysis. The CONSORT diagram is shown in Figure 1.

The characteristics of publications including the first author’s name, publishing year, country, ethnicity, the method of detecting polymorphisms, quality score, and the number of patients were shown in Table 1. The ORs or HRs of association

![Figure 1. Procedure of article selection.](Image)
between variants and AF recurrence in articles shown in Table 2.

### 3.2. Association between rs2200733/rs10033464 and AF recurrence

There were 9 articles including 3204 patients enrolled for rs2200733. The associations were significant under 3 genetic models (TT vs CC: OR [CI]=1.336 [1.061–1.683], P=0.014; CT vs CC: OR [CI]=0.759 [0.614–0.937], P=0.01; TT vs CT + CC: OR [CI]=2.308 [1.440–3.700], P=0.001) (Fig. 2). There was no significant association in CT + TT versus CC genetic model (OR [CI]=1.323 [0.983–1.787], P=0.65). Moreover, we also carried out the ethnic-subgroup analysis and found no significance under any genetic models in Asian or Caucasian population (Table 3).

There were 4 articles including 1170 patients enrolled for rs10033464. The association was significant under genetic model (TT vs GG: OR [CI]=1.517 [1.165–1.976], P=0.002) (Fig. 3). There was no significant association in genetic model (GT + TT vs GG: OR [CI]=1.228 [0.826–1.826], P=0.31). We also carried out the ethnic-subgroup analysis and found significance under genetic model in Caucasian population (TT vs GG: OR [CI]=1.445 [1.056–1.978], P=0.022).

### 3.3. Association between rs13376333 and AF recurrence

There were 4 articles including 1660 patients enrolled for rs13376333. The associations were not significant under genetic model (TT vs CC: OR [CI]=1.109 [0.939–1.310], P=0.221; CT + TT vs CC: OR [CI]=1.084 [0.747–1.573], P=0.671). We also

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### Table 1

**Characteristics of enrolled literatures.**

| Author            | Year | Country  | Ethnicity | QS       | Age     | Male | Patients' number | Genes                                      |
|-------------------|------|----------|-----------|----------|---------|------|------------------|--------------------------------------------|
| Zhao LQ[12]       | 2017 | China    | Asian     | 8        | 63.75±15.93 | 39%  | 438             | rs2200733                                  |
| Hu YF[13]         | 2016 | China    | Asian     | 8        | 61.9±14.0  | 62.0% | 383             | rs2200733; rs10033464                      |
| Marek Kiliszek[4] | 2016 | China    | Asian     | 8        | 55 (47–61) | 67%  | 238             | rs2200733; rs10033464; rs13376333; rs7193343 |
| Chen F[14]        | 2016 | China    | Asian     | 8        | 59.41±10.90| 74%  | 217             | rs2200733; rs2106261                      |
| Eue-Keun Choi[15] | 2015 | Korea    | Asian     | 8        | 57.5±10.9  | 74.60%| 1068            | rs2200733; rs13376333; rs2106261           |
| Shoemaker MB[16]  | 2015 | Germany  | Caucasian | 7        | 61 (54–67) | 71%  | 146             | rs2200733; rs10033464; rs13376333; rs7193343 |
| Parvez B[17]      | 2013 | USA      | Caucasian | 7        | 65±11     | 77%  | 208             | rs2200733; rs10033464; rs13376333; rs7193343 |
| Benjamin Shoemaker MB[18] | 2013 | USA      | Caucasian | 7        | 65 (52–66) | 71%  | 311             | rs2200733                                 |
| Hu YF[19]         | 2016 | China    | Asian     | 8        | 56±12     | 76%  | 195             | rs2200733; rs10033464                     |

**Table 2**

**Association between variants and AF recurrence in literatures.**

| Rs number | Author          | Year | Country | Ethnicity | Genes                                      |
|-----------|-----------------|------|---------|-----------|--------------------------------------------|
| rs2200733 | Zhao LQ         | 2017 | Reference | CC        | TT + TT versus CC                         |
| rs10033464| Hu YF[13]       | 2016 | Reference | CC        | TT versus CT + GG                         |
| rs13376333| Marek Kiliszek  | 2016 | Reference | CC        | TT + CT versus CC                         |
| rs7193343 | Chen F[14]      | 2016 | Reference | CC        | TT + CT versus CC                         |
| rs2106261 | Eue-Keun Choi   | 2015 | Reference | CC        | TT + CT versus CC                         |
Figure 2. Forest plots of HR in the risk of AF recurrence by rs2200733. (a) TT versus CC with random effect model; (b) TT versus CC with fixed effect model; (c) TT versus CT + CC with fixed effect model. HRs (and its 95% CI) stratified by ethnicity. AF = atrial fibrillation, CI = confidence interval, HR = hazard ratio.

Table 3
Meta-analysis of the association between variants and AF recurrence.

| Genetic comparisons      | No. of studies | Study groups | OR/HR (95% CI) | Z   | P-value | Test of heterogeneity | P-value | Tau-squared | Begger | Egger |
|--------------------------|----------------|--------------|----------------|-----|---------|------------------------|---------|-------------|--------|-------|
| rs2200733                | 9              | All          | 0.759 (0.614–0.937) | 2.56 | .01     | F                       | 0.63    | .428        | 0      | –     |
| CT versus CC             | 2              | All          | 1.336 (1.061–1.683) | 2.46 | .014    | R                       | 22.67   | .004        | 64.70% | 0.0767 |
|                          | 4              | Asian        | 1.257 (1.105–1.431) | 3.47  | .001    | F                       | 7.05    | .07         | 57.40% | 0.0457 |
|                          | 4              | Caucasian    | 1.318 (0.996–1.745) | 1.93  | .054    | R                       | 15.01   | .005        | 73.40% | 0.1555 |
| CT + TT versus CC        | 6              | All          | 1.325 (0.983–1.787) | 1.85  | .065    | R                       | 22.68   | .001        | 73.30% | 0.1027 |
|                          | 5              | Caucasian    | 1.311 (0.944–1.820) | 1.62  | .106    | R                       | 22.04   | .001        | 77.30% | 0.1133 |
| TT versus CT + CC        | 2              | All          | 2.308 (1.440–3.700) | 3.47  | .001    | F                       | 4.48    | .214        | 33%    | .497   |
|                          | 1              | Caucasian    | 1.952 (1.118–3.408) | 2.35  | .019    | F                       | 3.26    | .196        | 38.60% | –      |
| rs10033464               | 5              | All          | 1.517 (1.165–1.976) | 3.09  | .002    | F                       | 3.17    | .53         | 0      | .327   |
| TT versus GG             | 4              | All          | 1.445 (1.056–1.978) | 2.3   | .022    | F                       | 2.85    | .416        | 0      | –      |
|                          | 3              | Caucasian    | 1.228 (0.826–1.826) | 1.02  | .31     | R                       | 9.71    | .046        | 58.80% | 0.1149 |
| GT + TT versus GG        | 4              | All          | 1.109 (0.939–1.310) | 1.22  | .221    | F                       | 3.91    | .272        | 23.20% | 1      |
| rs13376333               | 4              | All          | 1.145 (0.964–1.360) | 1.54  | .123    | F                       | 2.01    | .366        | 0.60%  | –      |
| TT versus CC             | 4              | All (Caucasian) | 1.084 (0.747–1.573) | 0.43  | .671    | F                       | 2.9     | .089        | 65.50% | 0.317  |
| rs7193343                | 3              | All (Caucasian) | 0.981 (0.819–1.175) | 0.21  | .835    | F                       | 4.42    | .11         | 54.80% | 0.117  |
| TT versus GG             | 3              | All (Caucasian) | 1.141 (0.787–1.653) | 0.7   | .468    | F                       | 3.74    | .053        | 73.20% | –      |
| rs2106261                | 2              | All (Caucasian) | 0.858 (0.722–1.032) | 1.73  | .083    | F                       | 0.963   | 0.0100     | 0.00%  | –      |

CI = confidence interval, HR = hazard ratio, OR = odds ratio.
carried out the ethnic-subgroup analysis and found no significance under genetic model in Caucasian population (TT vs CC: OR [CI] = 1.145 [0.964–1.360], P = .123).

3.4. Association between rs7193343/rs2106261 and AF recurrence

There were 3 articles including 592 patients enrolled for rs7193343. The associations were not significant under genetic models (TT vs GG: OR [CI] = 0.981 [0.819–1.175], P = .835; CT + TT vs CC: OR [CI] = 1.141 [0.787–1.653], P = .486).

There were 2 articles including 1285 patients enrolled for rs2106261. The associations were not significant under genetic model (AA vs GG: OR [CI] = 0.858 [0.722–1.020], P = .083).

3.5. Publication bias and sensitivity analysis

No publication bias was identified by the Egger test and Begg test under any genetic models (Table 3 and Fig. 4). Sensitivity analysis results showed that changing the effect models had no significant effects on the pooled HRs and the final strength of the association (Table 3).

4. Discussion

This meta-analysis enrolled 9 publications to pool the HRs of associations between rs2200733 and rs10033464 on chromosome 4q25 (near PITX2), rs13376333 on chromosome 1q21 (in KCNN3), rs7193343 and rs2106261 on chromosome 16q22 (in ZFHX3), and AF recurrence. Results showed that rs2200733 TT genotypic patients were more likely to occur AF recurrence compared with CC genotypic patients (OR=1.336 [1.061–1.683], P = .014) or patients carrying C allele (OR=2.308 [1.440–3.700], P = .001). Rs10033464 TT genotypic patients were more likely to occur AF recurrence compared with GG genotypic patients (OR=1.517 [1.165–1.976], P = .002). Rs13376333 on chromosome 1q21 (in KCNN3), rs7193343 and rs2106261 on chromosome 16q22 (in ZFHX3) were not associated with AF recurrence in our meta-analysis.

AF is the most prevalent sustained arrhythmia in clinical practice and happened in 5% to 15% of persons at 80 years.[21] Percutaneous radiofrequency catheter ablation was a useful treatment method for AF although success rate is highly variable from 20% to 40% of patients.[22] Evidence showed that common genetic variants are associated with the development of AF.[6,23] Therefore, genetic variants may influence the personalization of AF catheter ablation. GWAS have identified chromosome 4q25 (rs2200733) and 16q22 (rs7193343) associated with AF.[24,25] Recently, some studies focused on the association between genetic variants and AF recurrence. However, their results were not accordant.[3,4,14–17] In our meta-analysis, we found that rs2200733 and rs10033464 on chromosome 4q25 were associated with AF recurrence. However, the mechanisms of how these variants affect the recurrence remained elusive. Rs2200733 and rs10033464 are located in an intergenic region of chromosome 4q25 upstream from the nearest gene, paired-like homeodomain 2 (PITX2). Previous GWAS studies found the variants near PITX2 were associated with the risk of AF.[7–11] Roselli et al conducted the largest meta-analysis of GWAS studies for AF to date, and they also found the region most significantly associated with AF in Europeans, Japanese, and African Americans was on chromosome 4q25, upstream from the gene PITX2.[11] Nielsen et al also found variant upstream of the gene PITX2 was associated with the risk of AF.[21] Lee and Low et al found the susceptibility loci of Korean and Japanese AF was also included...
4q25/PITX2.\textsuperscript{9,10} PITX2 plays an important role in the development of the pulmonary vein myocardial sleeve, regulation of signaling pathways that result in proarrhythmic changes in the left atrial myocardium, and structural remodeling of the intercalated disc as seen in human AF.\textsuperscript{26,27} Rs2200733 encodes regulatory elements that modulate the expression of PITX2.\textsuperscript{28}

Our meta-analysis results were consistent with previous meta-analysis, which only focused on rs2200733 and rs10033464 and AF recurrence.\textsuperscript{19} Previous meta-analysis only enrolled 6 publications involved in rs2200733 and 3 publications involved in rs10033464. And it found both 2 variants were associated with AF recurrence. Here, we updated the articles and enrolled 9 publications involved in rs2200733 and 4 publications involved in rs10033464, which have more precise and confidential data to draw the conclusion. Moreover, we also investigated other variants including rs13376333 on chromosome 1q21 (in KCNN3), rs7193343 and rs2106261 on chromosome 16q22 (in ZFHX3), although the results were negative. KCNN3 encodes a member of a family of calcium-activated potassium channels involved in atrial repolarization.\textsuperscript{29} ZFHX3 protein is a regulatory factor for STAT3-mediated inflammatory process.\textsuperscript{30} ZFHX3 knockout in atrial myocytes dysregulated calcium homeostasis and increased atrial arrhythmogenesis, ultimately contributing to AF occurrence.\textsuperscript{31} Studies found rs13376333, rs7193343, and rs2106261 increased risk of AF\textsuperscript{32–34} and some studies also involved in their relationship on AF recurrence.\textsuperscript{13,4,23,35} Therefore, we also pooled the HRs of rs13376333, rs7193343, and rs2106261 variants on AF recurrence. We found no association between these variants and AF recurrence under any genetic models.

Publication bias and heterogeneity are 2 major problems in meta-analysis. We used the Egger test and Begg test to analyze publication bias. We found no publication bias in any pooling analysis. We also used the Cochran \(Q\) test and \(I^2\) test in heterogeneity assessment. Fixed effect model was used if \(P > 0.05\) or \(I^2 < 50\%\), otherwise, a random model was chosen. We just found the heterogeneity in rs2200733 TT versus CC model and changing the effect models had no significant effects on the pooled HRs and the final strength of the association (Table 3).

Previous multivariate logistic regression analysis showed the risk factors of AF recurrence after catheter ablation includes hypertension, obesity, metabolic syndrome, left atrial dilatation, sleep-disordered breathing, and longstanding persistent AF.\textsuperscript{36,37} Adding rs2200733 and rs10033464 to the list of the risk of AF recurrence may help physicians predict outcomes, reduce patients and physicians' frustration and create the most efficacious strategy for AF. With the rapidly decreasing cost of genomic sequencing and development of sequencing method, precision
medicine guided by gene testing will bring better treatment to patients. Some clinical parameters could be related to genetic aspects of recurrence. Studies found that ablation energy type may influence the recurrence probability of AF. Second-generation cryoballoon is effective for treatment of paroxysmal and persistent AF. Incidence of pulmonary vein reconnections during the chronic phase is substantially lower when compared to radiofrequency ablation according to studies. Arrhythmia recurrence during the blanking period, presence of cardiomyopathy and pulmonary vein abnormality were independent predictors of AF recurrence. Whether these clinical parameters influence AF recurrence need further large-scale sample investigations and mechanism experiments. There were some limitations in our meta-analysis. First, there were limited articles and small sample size. Second, variability and accuracy of AF monitoring after ablation limited the interpretation of data. Third, the single or limited variants, not the GWAS data may also bring some false positive results. Fourth, not only genetic factor but also other factors such as sex distributions may also influence the recurrence of AF. Therefore, further large sample-size, more candidate variants and more factors involved in studies are needed in the future. In total, our meta-analysis found that rs2200733 and rs10033464 on chromosome 4q25 (near PITX2) were associated with the risk of AF recurrence; rs13376333 on chromosome 1q21 (in KCNN3), rs7193343 and rs2106261 on chromosome 16q22 (in ZFHX3) were not associated with the recurrence of AF.

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