Systematic Review and Meta-Analysis

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Association between gene variants and the recurrence of atrial fibrillation

An updated meta-analysis

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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 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* = .014; CT vs CC: OR [CI] = 0.759 [0.614–0.937], *P* = .01; TT vs CT + CC: OR [CI] = 2.308 [1.440–3.700], *P* = .001). The association was significant under rs10033464 genetic model (TT vs GG: OR [CI] = 1.517 [1.165–1.976], *P* = .002).

Conclusions: Rs13376333 on chromosome 1q21 (in *KCNN3*), rs7193343 and rs2106261 on chromosome 16q22 (in *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 *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.

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

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting millions of individuals worldwide.[1] AF increases the incidence of ischemic stroke, heart failure, and mortality.[2] The susceptibility factors of AF such as smoking, sex, obesity, and hypertension have been identified in some publications.[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.[6–11] During the past decade, AF ablation was a common therapy for AF.[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.[13] Several pieces of research were involved in the association between variants and AF recurrence.[3,4,14–18] The hottest variants involved in the recurrence of AF were rs2200733 (g.111710169C > T) and rs10033464 (g.111720761T > G) on chromosome 4q25 (near *PITX2*), rs13376333 (g.154841877C > T) on chromosome 1q21 (in *KCNN3*), rs7193343 (g.72995261T > C), and rs2106261 (g.45915G > A) on chromosome 16q22 (in *ZFHX3*).[3,4,14–17] However, the limited small samples, different ethnicity, and procedural follow-up brought the confusing final conclusion. As a result, current information cannot support the use of gene variants-guide individual management strategies.

There were a few meta-analyses involved in the limited sample size and variants on AF recurrence, which did not use updated data.[17,19] Therefore, it is necessary to carry out an updated meta-analysis to draw a more accurate conclusion. We combined all available data and derived a more precise and comprehensive assessment to update this systematic review and meta-analysis in order to find out the reliable associations of the recurrence of AF.

Editor: Ovidiu Constantin Baltatu.

The study was supported by grants from the National Natural Science Foundation of China (No. 81503166, 81603208) and Hunan Provincial Natural Science Foundation of China (2018JJ3718).

All authors have no competing interests to disclose.

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Medicine (2019) 98:23(e15953)

Received: 29 June 2018 / Received in final form: 10 February 2019 / Accepted: 15 May 2019

http://dx.doi.org/10.1097/MD.0000000000015953

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 I^2 test were used in heterogeneity assessment. Fixed effect model was used if $P>.05$ or $I^2<50\%$, 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

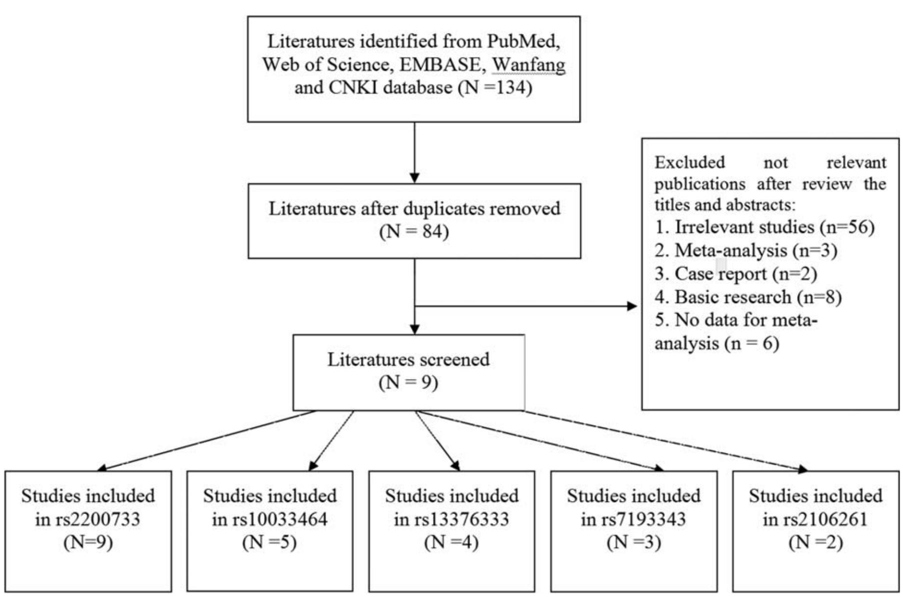

Figure 1. Procedure of article selection.

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	63.20%	383	rs2200733; rs10033464
Marek Kiliszek[4]	2016			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[3]	2015	Korean	Asian	8	57.5±10.9	74.60%	1068	rs2200733; rs13376333; rs2106261
Shoemaker MB[15]	2015	Germany	Caucasian	7	61 (54–67)	71%	146	rs2200733; rs10033464; rs13376333; rs7193343
Parvez B[30]	2013			7	65±11	77%	208	rs2200733; rs10033464; rs13376333; rs7193343
Benjamin Shoemaker M[21]	2013	USA	Caucasian	8	60 (52–66)	71%	311	rs2200733
Husser D[16]	2010	Germany	Caucasian	7	56±12	78%	195	rs2200733; rs10033464

QS=quality score.

between variants and AF recurrence in articles were 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], $P=.014$; CT vs CC: OR [CI]=0.759 [0.614–0.937], $P=.01$; TT vs CT + CC: OR [CI]=2.308 [1.440–3.700], $P=.001$) (Fig. 2). There was no significant association in CT + TT versus CC genetic model (OR [CI]=1.325 [0.983–1.787], $P=.065$). 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], $P=.002$) (Fig. 3). There was no significant association in genetic model (GT + TT vs GG: OR [CI]=1.228 [0.826–1.826], $P=.31$). 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], $P=.022$).

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], $P=.221$; CT + TT vs CC: OR [CI]=1.084 [0.747–1.573], $P=.671$). We also

Table 2

Association between variants and AF recurrence in literatures.

Rs number	Author	Year	CC	CT	TT	CT + TT versus CC	TT versus CT + CC
rs2200733	Zhao LQ	2017	Reference	0.634 (0.388–1.037)	1.818 (1.081–3.059)		
	Hu YF	2016	Reference		1.23 (0.87–1.76)		
	MarekKiliszek	2016	Reference		1.42 (0.97–2.08)	1.16 (0.69–1.95)	3.30 (1.46–7.46)
	Chen F	2016	Reference		1.694 (1.092–2.627)	1.499 (0.787–2.854)	3.524 (1.516–8.913)
	Eue-Keun Choi	2015	Reference		1.01 (0.80–1.26)		
	Shoemaker MB	2015	Reference			1.3 (1.1–1.6)	
	Parvez B	2013	Reference		2.41 (1.45–4.00)	2.01 (1.20–3.36)	
	Benjamin	2013	Reference	0.79 (0.62–0.99)	0.61 (0.37–1.0)	0.76 (0.6–0.95)	
	Husser D (1)	2010	Reference		1.461 (0.952–2.243)	1.768 (0.984–3.177)	1.419 (0.558–3.608)
	Husser D (2)	2010	Reference		1.356 (0.777–2.356)	1.812 (0.835–3.931)	0.925 (0.245–3.49)
Rs number	Author	Year	GG	GT	TT	GT + TT versus GG	TT versus GT + GG
rs10033464	Hu YF	2016	Reference		1.71 (1.05–2.80)		
	Marek Kiliszek	2016	Reference		1.06 (0.61–1.86)	1.00 (0.54–1.84)	2.90 (0.26–32.48)
	Shoemaker MB	2015	Reference			0.8 (0.6–1.1)	
	Parvez B	2013	Reference		1.30 (0.65–2.59)	1.30 (0.65–2.59)	
	Husser D (1)	2010	Reference		1.653 (0.923–2.96)	1.706 (0.924–3.15)	
	Husser D (2)	2010	Reference		2.227 (1.078–4.6)	2.288 (1.048–4.997)	
Rs number	Author	Year	CC	CT	TT	CT + TT versus CC	TT versus CT + CC
rs13376333	Marek Kiliszek	2016	Reference		1.02 (0.69–1.49)	0.75 (0.414–1.28)	1.91 (0.89–4.10)
	Eue-Keun Choi	2015	Reference		0.72 (0.38–1.36)		
	Shoemaker MB	2015	Reference		1.1 (0.9–1.4)		
	Parvez B	2013	Reference		1.47 (0.99–2.18)	1.44 (0.88–2.37)	
Rs number	Author	Year	CC	CT	TT	CT + TT versus CC	TT versus CT + CC
rs7193343	Marek Kiliszek	2016	Reference		0.86 (0.55–1.34)	0.91 (0.52–1.58)	0.57 (0.17–1.87)
	Shoemaker MB	2015	Reference		0.9 (0.7–1.1)		
	Parvez B	2013	Reference		1.45 (0.96–2.17)	1.57 (0.96–2.57)	
Rs number	Author	Year	GG	GA	AA	GA + AA versus GG	AA versus GA + GG
rs2106261	Chen F	2016	Reference		0.851 (0.567–1.277)	0.800 (0.212–3.019)	3.599 (0.720–17.989)
	Eue-Keun Choi	2015	Reference		0.86 (0.71–1.04)		

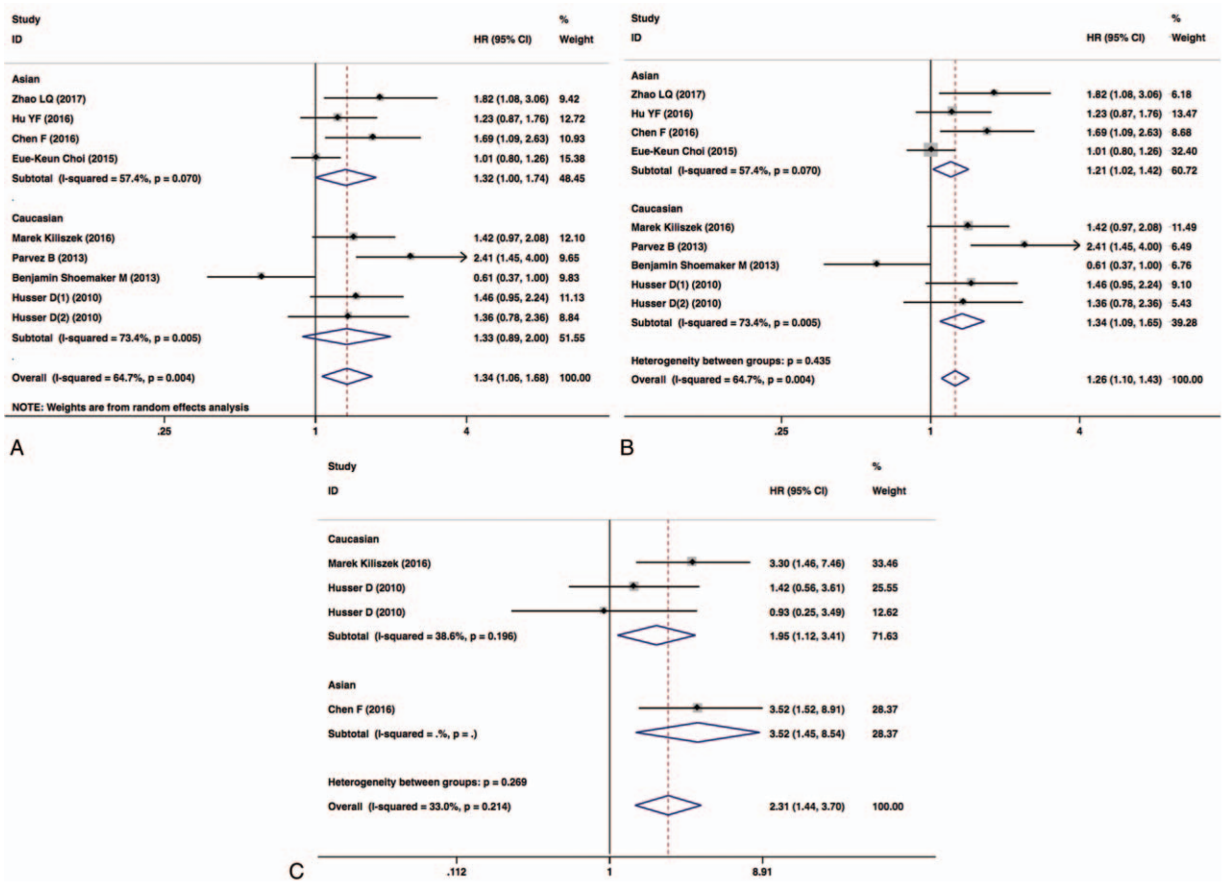

Figure 2. Forest plots of HR in the risk of AF recurrence by rs2200733. (a) TT versus CC with random effect model; (b) TT versus CC with fixed effect model; (c) TT versus CT + CC with fixed effect model. HRs (and its 95% CI) stratified by ethnicity. AF = atrial fibrillation, CI = confidence interval, HR = hazard ratio.

Table 3

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

Genetic comparisons	No. of studies	Study groups	Test of association			Model	Test of heterogeneity				Begger	Egger
			OR/HR (95% CI)	Z	P-value		$\chi2$	P-value	I^2 (%)	Tau-squared		
rs2200733	9											
CT versus CC	2	All	**0.759 (0.614–0.937)**	**2.56**	**.01**	F	0.63	.428	0	–	0.317	–
TT versus CC	8	All	**1.336 (1.061–1.683)**	**2.46**	**.014**	R	22.67	.004	64.70%	0.0767	1.98	0.08
			1.257 (1.105–1.431)	**3.47**	**.001**	F						
	4	Asian	1.318 (0.996–1.745)	1.93	.054	R	7.05	.07	57.40%	0.0457		
	4	Caucasian	1.330 (0.887–1.996)	1.38	.167	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	73.50%	0.1027	0.652	0.132
	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%	–	0.497	0.261
	1	Caucasian	**1.952 (1.118–3.408)**	**2.35**	**.019**	F	3.26	.196	38.60%	–		
rs10033464	5											
TT versus GG	4	All	**1.517 (1.165–1.976)**	3.09	**.002**	F	3.17	.53	0	–	0.327	0.296
	3	Caucasian	**1.445 (1.056–1.978)**	2.3	**.022**	F	2.85	.416	0	–		
GT + TT versus GG	4	All (Caucasian)	1.228 (0.826–1.826)	1.02	.31	R	9.71	.046	58.80%	0.1149	1.71	0.2
rs13376333	4											
TT versus CC	4	All	1.109 (0.939–1.310)	1.22	.221	F	3.91	.272	23.20%	–	1	0.813
	3	Caucasian	1.145 (0.964–1.360)	1.54	.123	F	2.01	.366	0.60%	–		
CT + TT versus CC	2	All (Caucasian)	1.084 (0.747–1.573)	0.43	.671	F	2.9	.089	65.50%	–	0.317	–
rs7193343	3											
TT versus GG	3	All (Caucasian)	0.981 (0.819–1.175)	0.21	.835	F	4.42	.11	54.80%	–	0.117	0.429
CT + TT versus CC	2	All (Caucasian)	1.141 (0.787–1.653)	0.7	.486	F	3.74	.053	73.20%	–	0.317	–
rs2106261	2											
AA versus GG	2	All (Asian)	0.858 (0.722–1.020)	1.73	.083	F	0	.963	0.00%	–	0.317	–

CI = confidence interval, HR = hazard ratio, OR = odds ratio.

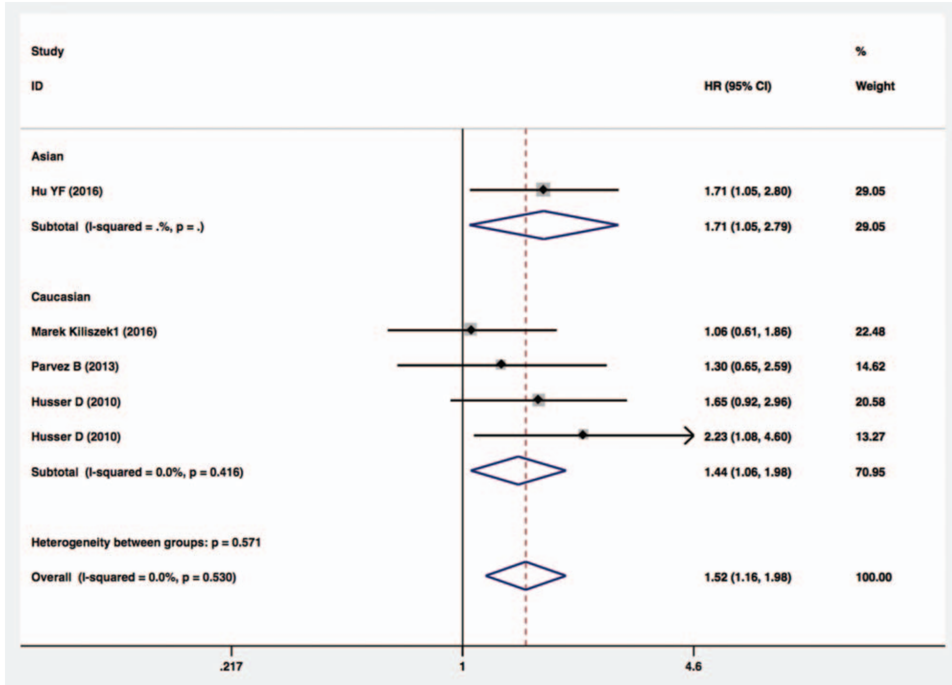

Figure 3. Forest plots of HR in the risk of AF recurrence by rs10033464 TT versus GG with fixed effect model. HRs (and its 95% CI) stratified by ethnicity. AF = atrial fibrillation, CI = confidence interval, HR = hazard ratio.

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*).[24] Previous GWAS studies found the variants near *PITX2* were associated with the risk of AF.[7,9–11] 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 of the gene *PITX2*.[11] Nielsen et al also found variant upstream of the gene *PITX2* were associated with the risk of AF.[22] Lee and Low et al found the susceptibility loci of Korean and Japanese AF was also included

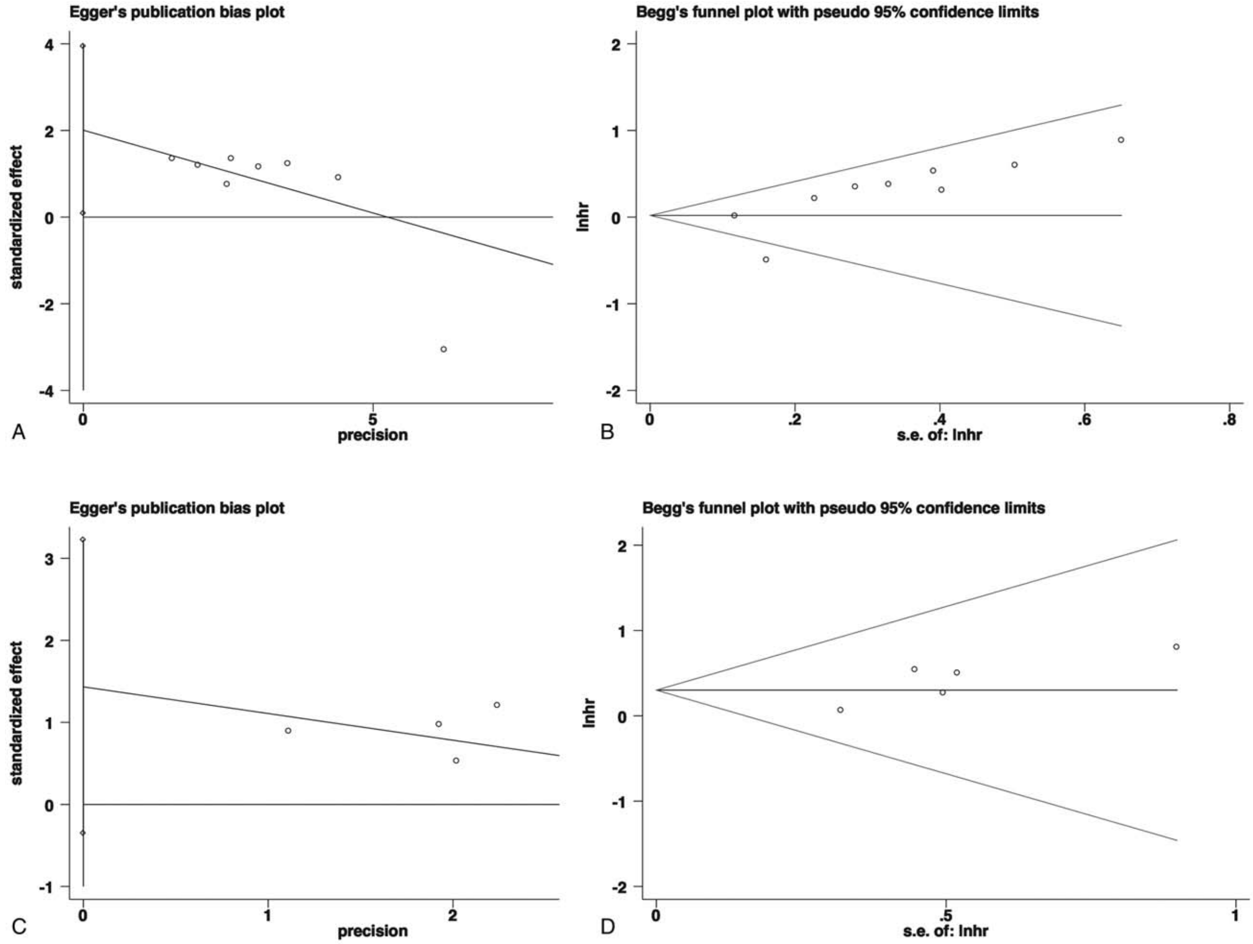

Figure 4. Begg and Egger bias plot for publication bias test in the enrolled studies on the association between AF recurrence and variants under genetic models. (a) Egger bias plot in rs2200733plot in TT versus CC model. (b) Begg bias plot in rs2200733 under TT versus CC model. (c) Egger bias plot in rs10033464 under TT versus GG model. (d) Begg bias plot in rs10033464 under TT versus GG model. AF = atrial fibrillation, HR = hazard ratios, SE = standard error.

4q25/PITX2.[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.[26,27] Rs2200733 encodes regulatory elements that modulate the expression of *PITX2*.[28]

Our meta-analysis results were consistent with previous meta-analysis, which only focused on rs2200733and rs10033464 and AF recurrence.[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.[29] ZFHX3 protein is a regulatory factor for STAT3-mediated inflammatory process.[30] *ZFHX3* knockdown in atrial myocytes dysregulated calcium homeostasis and increased atrial arrhythmogenesis, ultimately contributing to AF occurrence.[31] Studies found rs13376333, rs7193343, and rs2106261 increased risk of AF[32–34] and some studies also involved in their relationship on AF recurrence.[3,4,23,35] 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 $P>.05$ 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.[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.[38,39] Second-generation cryoballoon is effective for treatment of paroxysmal and persistent AF.[40] Incidence of pulmonary vein reconnections during the chronic phase is substantially lower when compared to radiofrequency ablation according to studies.[39,41] Arrhythmia recurrence during the blanking period, presence of cardiomyopathy and pulmonary vein abnormality were independent predictors of AF recurrence.[42] 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.

Author contributions

Conceptualization: Yun-Dai Chen, Jian Qu.
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Methodology: Ya-Nan Wang.
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Supervision: Yun-Dai Chen.
Writing – original draft: Tao Jiang, Jian Qu.
Writing – review and editing: Tao Jiang, Ya-Nan Wang, Qiang Qu, Yun-Dai Chen, Ting-Ting Qi, Jian Qu.

References

[1] Zulkifly H, Lip GYH, Lane DA. Epidemiology of atrial fibrillation. Int J Clin Pract 2018;72:e13070.
[2] Caplan LR. Atrial fibrillation, past and future: from a stroke non-entity to an over-targeted cause. Cerebrovasc Dis 2018;45:149–53.
[3] Choi EK, Park JH, Lee JY, et al. Korean atrial fibrillation (AF) network: genetic variants for af do not predict ablation success. J Am Heart Assoc 2015;4:e002046.
[4] Kiliszek M, Kozluk E, Franaszczyk M, et al. The 4q25, 1q21, and 16q22 polymorphisms and recurrence of atrial fibrillation after pulmonary vein isolation. Arch Med Sci 2016;12:38–44.
[5] Zhu W, Yuan P, Shen Y, et al. Association of smoking with the risk of incident atrial fibrillation: a meta-analysis of prospective studies. Int J Cardiol 2016;218:259–66.
[6] Husser D, Buttner P, Stubner D, et al. PR interval associated genes, atrial remodeling and rhythm outcome of catheter ablation of atrial fibrillation-a gene-based analysis of GWAS data. Front Genet 2017; 8:224.
[7] Nielsen JB, Fritsche LG, Zhou W, et al. Genome-wide study of atrial fibrillation identifies seven risk loci and highlights biological pathways and regulatory elements involved in cardiac development. Am J Hum Genet 2018;102:103–15.
[8] Weng LC, Lunetta KL, Muller-Nurasyid M, et al. Genetic interactions with age, sex, body mass index, and hypertension in relation to atrial fibrillation: the AFGen consortium. Sci Rep 2017;7:11303.
[9] Lee JY, Kim TH, Yang PS, et al. Korean atrial fibrillation network genome-wide association study for early-onset atrial fibrillation identifies novel susceptibility loci. Eur Heart J 2017;38:2586–94.
[10] Low SK, Takahashi A, Ebana Y, et al. Identification of six new genetic loci associated with atrial fibrillation in the Japanese population. Nat Genet 2017;49:953–8.
[11] Roselli C, Chaffin MD, Weng LC, et al. Multi-ethnic genome-wide association study for atrial fibrillation. Nat Genet 2018;50:1225–33.
[12] Rosati F, Muneretto C, Merati E, et al. Epicardial, biatrial ablation with integrated uni-bipolar radiofrequency technology in stand-alone persistent atrial fibrillation. Innovations (Phila) 2018;13:114–9.
[13] Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2013;61:e6–75.
[14] Zhao LQ, Zhang GB, Wen ZJ, et al. Common variants predict recurrence after nonfamilial atrial fibrillation ablation in Chinese Han population. Int J Cardiol 2017;227:360–6.
[15] Hu YF, Wang HH, Yeh HI, et al. Association of single nucleotide polymorphisms with atrial fibrillation and the outcome after catheter ablation. Acta Cardiol Sin 2016;32:523–31.
[16] Chen F, Yang Y, Zhang R, et al. Polymorphism rs2200733 at chromosome 4q25 is associated with atrial fibrillation recurrence after radiofrequency catheter ablation in the Chinese Han population. Am J Transl Res 2016;8:688–97.
[17] Shoemaker MB, Bollmann A, Lubitz SA, et al. Common genetic variants and response to atrial fibrillation ablation. Circ Arrhythm Electrophysiol 2015;8:296–302.
[18] Husser D, Adams V, Piorkowski C, et al. Chromosome 4q25 variants and atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol 2010;55:747–53.
[19] He J, Zhu W, Yu Y, et al. Variant rs2200733 and rs10033464 on chromosome 4q25 are associated with increased risk of atrial fibrillation after catheter ablation: evidence from a meta-analysis. Cardiol J 2018;25:628–38.
[20] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[21] Camm AJ, et al. European Heart Rhythm Association; European Association for Cardio-Thoracic SurgeryGuidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369–429.
[22] Kobza R, Hindricks G, Tanner H, et al. Late recurrent arrhythmias after ablation of atrial fibrillation: incidence, mechanisms, and treatment. Heart Rhythm 2004;1:676–83.
[23] Benjamin Shoemaker M, Muhammad R, Parvez B, et al. Common atrial fibrillation risk alleles at 4q25 predict recurrence after catheter-based atrial fibrillation ablation. Heart Rhythm 2013;10:394–400.
[24] Gudbjartsson DF, Arnar DO, Helgadottir A, et al. Variants conferring risk of atrial fibrillation on chromosome 4q25. Nature 2007;448:353–7.
[25] Gudbjartsson DF, Holm H, Gretarsdottir S, et al. A sequence variant in ZFHX3 on 16q22 associates with atrial fibrillation and ischemic stroke. Nat Genet 2009;41:876–8.
[26] Kirchhof P, Kahr PC, Kaese S, et al. PITX2c is expressed in the adult left atrium, and reducing Pitx2c expression promotes atrial fibrillation inducibility and complex changes in gene expression. Circ Cardiovasc Genet 2011;4:123–33.
[27] Chinchilla A, Daimi H, Lozano-Velasco E, et al. PITX2 insufficiency leads to atrial electrical and structural remodeling linked to arrhythmogenesis. Circ Cardiovasc Genet 2011;4:269–79.
[28] Tao Y, Zhang M, Li L, et al. Pitx2, an atrial fibrillation predisposition gene, directly regulates ion transport and intercalated disc genes. Circ Cardiovasc Genet 2014;7:23–32.
[29] Ellinor PT, Lunetta KL, Glazer NL, et al. Common variants in KCNN3 are associated with lone atrial fibrillation. Nat Genet 2010;42:240–4.
[30] Nojiri S, Joh T, Miura Y, et al. ATBF1 enhances the suppression of STAT3 signaling by interaction with PIAS3. Biochem Biophys Res Commun 2004;314:97–103.

[31] Kao YH, Hsu JC, Chen YC, et al. ZFHX3 knockdown increases arrhythmogenesis and dysregulates calcium homeostasis in HL-1 atrial myocytes. Int J Cardiol 2016;210:85–92.
[32] Yao JL, Zhou YF, Yang XJ, et al. KCNN3 SNP rs13376333 on chromosome 1q21 confers increased risk of atrial fibrillation. Int Heart J 2015;56:511–5.
[33] Zhai C, Cong H, Liu Y, et al. Rs7193343 polymorphism in zinc finger homeobox 3 (ZFHX3) gene and atrial fibrillation: an updated meta-analysis of 10 case-control comparisons. BMC Cardiovasc Disord 2015;15:58.
[34] Li C, Wang F, Yang Y, 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.
[35] Parvez B, Shoemaker MB, Muhammad R, et al. Common genetic polymorphism at 4q25 locus predicts atrial fibrillation recurrence after successful cardioversion. Heart Rhythm 2013;10:849–55.
[36] Darby AE. Recurrent atrial fibrillation after catheter ablation: considerations for repeat ablation and strategies to optimize success. J Atr Fibrillation 2016;9:1427.
[37] Cai L, Yin Y, Ling Z, et al. Predictors of late recurrence of atrial fibrillation after catheter ablation. Int J Cardiol 2013;164:82–7.
[38] Miyazaki S, Ebana Y, Liu L, et al. Chromosome 4q25 variants and recurrence after second-generation cryoballoon ablation in patients with paroxysmal atrial fibrillation. Int J Cardiol 2017;244:151–7.
[39] Reddy VY, Sediva L, Petru J, et al. Durability of pulmonary vein isolation with cryoballoon ablation: results from the sustained pv isolation with arctic front advance (SUPIR) study. J Cardiovasc Electrophysiol 2015;26:493–500.
[40] Yalin K, Lyan E, Abdin A, et al. Second-generation cryoballoon for pulmonary vein isolation in patients with pulmonary vein abnormality: safety, efficacy and lessons from re-ablation procedures. Int J Cardiol 2018;272:142–8.
[41] Cappato R, Negroni S, Pecora D, et al. Prospective assessment of late conduction recurrence across radiofrequency lesions producing electrical disconnection at the pulmonary vein ostium in patients with atrial fibrillation. Circulation 2003;108:1599–604.
[42] Yalin K, Abdin A, Lyan E, et al. Safety and efficacy of persistent atrial fibrillation ablation using the second-generation cryoballoon. Clin Res Cardiol 2018;107:570–7.