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A comprehensive meta-analysis on relationship between *CYP11B2* rs1799998 polymorphism and atrial fibrillation

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ABSTRACT

Background: The correlation between *CYP11B2* rs1799998 polymorphism and atrial fibrillation (AF) was analyzed by several studies, but the results of these studies were inconsistent. Thus, we performed this study to obtain a more conclusive result on relationship between *CYP11B2* rs1799998 polymorphism and AF.
Methods: Eligible studies were searched in PubMed, Medline and Embase. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the strength of correlation.
Results: A total of 12 studies with 5466 participants were analyzed. We found that *CYP11B2* rs1799998 polymorphism was significantly associated with AF in overall population under recessive genetic model with FEM ($P = 0.005$, OR = 1.29, 95%CI 1.08–1.54), but no positive results were detected in overall analyses with REMs. Further subgroup analyses revealed that *CYP11B2* rs1799998 polymorphism was significantly correlated with AF in East Asians, but not in West Asians. Furthermore, significant associations between rs1799998 polymorphism and AF were observed in subjects with essential hypertension (EH) and heart failure (HF). No any other positive results were found in overall and subgroup analyses.
Conclusions: Overall, our meta-analysis suggested that rs1799998 polymorphism may serve as a potential biological marker of AF in East Asians and subjects with EH or HF.

Introduction

Atrial fibrillation (AF) is the most common type of tachyarrhythmia, with an estimated prevalence of 1–2% in general population [1]. Previous studies showed that AF is associated with a significantly elevated risk of stroke and sudden cardiac death [2]. Moreover, this disorder often co-exists with other cardiovascular diseases like hypertension (HTN), heart failure (HF) and coronary artery disease (CAD), which worsens the prognosis of patients [3]. To date, the exact pathogenic mechanism of AF is still largely unclear. Nevertheless, a lot of evidences support that genetic factors substantially contribute to its occurrence and development. First, family clustering of AF was not uncommon, and positive family history in first-degree relatives was proved to be a strong independent risk factor of developing AF [4]. Second, various genetic variants were found to be correlated with an increased risk of AF by previous epidemiological studies [5,6]. In summary, these findings jointly indicated that genetic predisposition to AF is crucial for its development.

The renin-angiotensin-aldosterone system (RAAS) regulates volume homeostasis, sodium-potassium exchange and cardiac remodeling, and its dysfunction is closely related to the development of multiple cardiovascular diseases including arrhythmia [7,8]. Aldosterone synthase (CYP11B2) is the key enzyme for synthesis of aldosterone, an important component of RAAS. Previous experimental studies demonstrated that the mutant allele of *CYP11B2* rs1799998 polymorphism was associated with elevated gene expression level and increased ~~synthetic~~ enzymatic activity [9,10]. Therefore, it is speculated that this polymorphism may be involved the pathogenesis of various cardiovascular diseases [11,12]. To date, several studies already explored the relationship between *CYP11B2* rs1799998 polymorphism and AF. But the results of these studies were conflicting. Thus, we conducted this meta-analysis to obtain a more conclusive result.

Materials and methods

Literature search and inclusion criteria

This meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [13]. Potentially related articles published prior to October 2018 were searched in Pubmed, Medline and Embase using the following key words: “atrial fibrillation”, “AF”, “aldosterone synthase”, “CYP11B2”, “polymorphism”, “variant”, “mutation”, “genotype” and “allele”. The reference lists of all

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retrieved publications were also screened to identify other potentially relevant articles.

To test the research hypothesis of this meta-analysis, included studies should meet the following criteria: (1) retrospective case-control study on correlation between *CYP11B2* rs1799998 polymorphism and the likelihood of AF; (2) provide adequate data to calculate odds ratios (ORs) and 95% confidence intervals (CIs); (3) full text available. Studies were excluded if one of the following criteria was fulfilled: (1) not relevant to *CYP11B2* rs1799998 polymorphism and AF; (2) family based association studies; (3) case reports or case series; (4) abstracts, reviews, comments, letters and conference presentations. For duplicate reports, only the study with the largest sample size was enrolled. No language restrictions were imposed in this meta-analysis.

Data extraction and quality assessment

The following data were extracted from all included studies: (1) name of first author; (2) year of publication; (3) country and ethnicity of participants; (4) the number of cases and controls; and (5) the genotypic distribution of *CYP11B2* rs1799998 polymorphism in cases and controls. The probability value (*P* value) of Hardy-Weinberg equilibrium (HWE) test was also calculated.

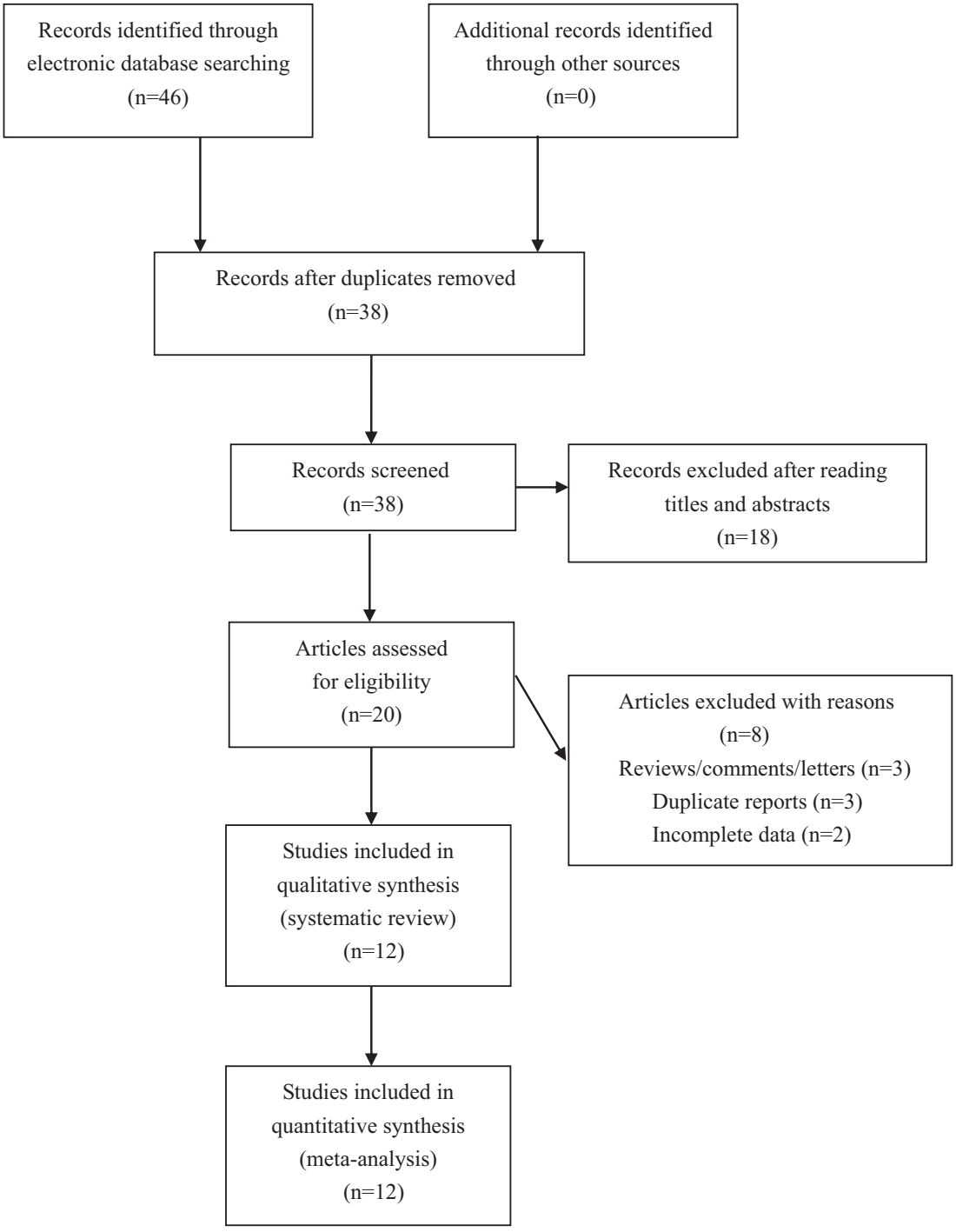

Fig. 1. Flowchart of study selection for the present study.

The Newcastle-Ottawa scale (NOS) was employed to assess the quality of eligible studies from three aspects: (1) selection of cases and controls; (2) comparability between cases and controls; and (3) exposure in cases and controls [14]. The NOS has a score range of zero to nine, and studies with a score of more than seven were thought to be of high quality.

Two reviewers conducted data extraction and quality assessment independently. When necessary, the reviewers wrote to the corresponding authors for extra information or raw data. Any disagreement between two reviewers was solved by discussion until a consensus was reached.

Statistical analysis

All statistical analyses in the present study were conducted with Review Manager Version 5.3.3 (The Cochrane Collaboration, Software Update, Oxford, United Kingdom). ORs and 95% CIs were used to assess potential association of *CYP11B2* rs1799998 polymorphism with the likelihood of AF in all genetic models, and a *P* value of 0.05 or less was considered to be statistically significant. Between-study heterogeneities were evaluated with Q test and I^2 statistic. If *P* value of Q test was <0.1 or I^2 was >50%, the between-study heterogeneity was considered to be obvious. Subgroup analyses by ethnicity of participants and source of controls were subsequently conducted to obtain more specific results. Overall and subgroup analyses were performed with both fixed-effect models (FEMs) and random-effect models (REMs). Sensitivity analyses were carried out to test the stability of the results. Funnel plots were applied to evaluate possible publication bias.

Results

Characteristics of included studies

The literature search identified 46 potentially relevant articles. After excluding irrelevant and duplicate articles by reading titles and abstracts, 20 articles were retrieved for further evaluation. Another 8 articles were subsequently excluded after reading the full text (animal studies and in vivo studies). Finally, a total of 12 studies containing 2110 cases and 3356 controls that met the inclusion criteria of our meta-analysis were included (see Fig. 1). The NOS score of eligible articles ranged from 7 to 8, which suggested that all included studies were of relatively high quality. Characteristics of included studies were summarized in Table 1.

Overall and subgroup analyses

A total of 5466 participants were analyzed. We found that *CYP11B2* rs1799998 polymorphism was significantly associated with AF in overall population under recessive genetic model with FEM ($P = 0.005$, OR = 1.29, 95%CI 1.08–1.54), but no positive results were detected in overall analyses with REMs. Further subgroup analyses revealed that *CYP11B2* rs1799998 polymorphism was significantly correlated with AF in East Asians, but not in West Asians. Furthermore, significant associations between rs1799998 polymorphism and AF were observed in subjects with essential hypertension (EH) and heart failure (HF). No any other positive results were found in overall and subgroup analyses (see Table 2).

Sensitivity analyses

Sensitivity analyses were carried out to examine the stability of meta-analysis results by eliminating studies that deviated from HWE. No changes of results were observed in any comparisons, which indicated that our findings were statistically reliable.

Publication biases

Potential publication biases in the current study were evaluated with funnel plots. No obvious asymmetry of funnel plots was observed in any comparisons, which suggested that our findings were unlikely to be influenced by severe publication bias.

Discussion

To the best of our knowledge, this is so far the most comprehensive meta-analysis on correlation between *CYP11B2* polymorphism and AF. Pooled analyses indicated that *CYP11B2* rs1799998 polymorphism was significantly correlated with AF in East Asians, but not in West Asians. Moreover, when we stratified data by source of controls, we noticed that significant associations between rs1799998 polymorphism and AF were only existed in subjects with EH and HF. The stability of synthetic results was subsequently evaluated in sensitivity analyses, and no changes of results were observed in any comparisons, which indicated that our findings were quite statistically reliable. As for evaluation of heterogeneities, obvious between-study heterogeneities were detected in all comparisons. But in further stratified analyses, a great reduction of heterogeneity was found in the West Asian, EH and HF subgroups, which suggested that differences in ethnic background and

Table 1
The characteristics of included studies for *CYP11B2* rs1799998 polymorphism and AF.

First author, year	Country	Ethnicity	Sample size (Case/control)	Source of controls	Genotype distribution		*p* Value for HWE	NOS score
					Cases	controls		
Amir 2008	Israel	West Asian	63/270	Healthy controls	25/25/13	64/152/54	0.036	8
Bress 2013	USA	African	37/157	Heart failure	22/10/5	109/46/2	0.238	7
Hu 2010	China	East Asian	59/77	Heart failure	24/30/5	48/24/5	0.409	7
Hu 2011	China	East Asian	115/123	Healthy controls	56/48/11	77/41/5	0.875	8
Huang 2009	China	East Asian	97/529	Essential hypertension	44/43/10	266/223/40	0.471	7
Jin 2012	China	East Asian	202/200	Essential hypertension	75/78/49	68/105/27	0.174	7
Lei 2013	China	East Asian	150/150	Healthy controls	68/75/7	90/56/4	0.169	8
Sun 2011	China	East Asian	310/310	Essential hypertension	130/157/23	150/138/22	0.196	7
Wang 2011	China	East Asian	405/398	Essential hypertension	150/156/99	136/208/54	0.067	7
Zhang 2009	China	East Asian	120/120	Healthy controls	56/59/5	75/43/2	0.131	8
Zhang 2012	China	East Asian	193/297	Healthy controls	97/77/19	139/122/36	0.254	8
Liu 2015	China	East Asian	203/418	Healthy controls	104/90/9	130/223/65	0.056	8
Liu 2015	China	West Asian	156/307	Healthy controls	50/86/20	116/158/33	0.053	8

Abbreviations: AF, Atrial fibrillation; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa scale; NA, Not available.
Rating criteria of NOS: Selection: 1, is the case definition adequate? (if some independent validation was required, one point); 2, representativeness of the cases (if yes, one point); 3, selection of controls (if they were from community controls, one point); 4, definition of controls (if they had no history and new occurrence, one point). Comparability: comparability of cases and controls on the basis of design or analysis: 1, ethnicity (if yes, one point); 2, age (if yes, one point). Exposure: 1, ascertainment of exposure (if in reliable method, one point); 2, same method of ascertainment for cases and controls (if yes, one point); 3, non-response rate (if they were the same between cases and controls, one point).

Table 2
Results of overall and subgroup analyses for *CYP11B2* rs1799998 polymorphism and AF.

Population	Sample size	Dominant comparison	Recessive comparison	Additive comparison	Allele comparison
		P value OR (95%CI) I^2 statistic	*P* value OR (95%CI) I^2 statistic	*P* value OR (95%CI) I^2 statistic	*P* value OR (95%CI) I^2 statistic
Overall (FEM)	2110/3356	0.55 0.97 (0.86–1.08) 80%	**0.005 1.29 (1.08–1.54)** 71%	0.24 0.93 (0.83–1.05) 77%	0.08 0.93 (0.85–1.01) 81%
Overall (REM)	2110/3356	0.41 0.89 (0.68–1.17) 80%	0.13 1.35 (0.92–1.98) 71%	0.95 1.01 (0.79–1.29) 77%	0.14 0.86 (0.70–1.05) 81%
East Asian (FEM)	1854/2622	0.54 0.96 (0.85–1.09) 82%	**0.01 1.28 (1.05–1.56)** 74%	0.35 0.94 (0.83–1.07) 80%	0.11 0.93 (0.85–1.02) 83%
East Asian (REM)	1854/2622	0.33 0.86 (0.63–1.17) 82%	0.31 1.27 (0.80–2.00) 74%	0.67 1.06 (0.80–1.42) 80%	0.19 0.85 (0.67–1.08) 83%
West Asian (FEM)	219/577	0.71 1.07 (0.77–1.48) 87%	0.57 1.14 (0.73–1.78) 0%	0.45 0.89 (0.65–1.21) 82%	0.98 1.00 (0.79–1.25) 73%
West Asian (REM)	219/577	0.65 1.25 (0.47–3.35) 87%	0.57 1.14 (0.73–1.78) 0%	0.56 0.79 (0.35–1.76) 82%	0.83 1.05 (0.66–1.68) 73%
Healthy controls (FEM)	1000/1685	0.68 1.03 (0.88–1.22) 88%	0.21 0.84 (0.63–1.10) 70%	0.74 1.03 (0.88–1.21) 72%	0.38 1.06 (0.93–1.19) 88%
Healthy controls (REM)	1000/1685	0.87 0.96 (0.60–1.54) 88%	0.94 1.02 (0.58–1.80) 70%	0.69 1.07 (0.78–1.46) 72%	0.77 0.95 (0.66–1.36) 88%
Essential hypertension (FEM)	1014/1437	0.65 0.96 (0.81–1.14) 31%	<**0.001 1.76 (1.37–2.26)** 29%	**0.009 0.80 (0.67–0.95)** 84%	**0.01 0.85 (0.75–0.96)** 0%
Essential hypertension (REM)	1014/1437	0.69 0.96 (0.77–1.18) 31%	<**0.001 1.70 (1.24–2.32)** 29%	0.37 0.82 (0.53–1.27) 84%	**0.01 0.85 (0.75–0.96)** 0%
Heart failure (FEM)	96/234	**0.008 0.51 (0.31–0.84)** 0%	**0.03 2.87 (1.09–7.58)** 76%	0.11 1.51 (0.90–2.53) 66%	**0.002 0.53 (0.36–0.80)** 0%
Heart failure (REM)	96/234	**0.009 0.51 (0.31–0.85)** 0%	0.23 3.75 (0.43–32.52) 76%	0.42 1.46 (0.58–3.66) 66%	**0.002 0.53 (0.36–0.80)** 0%

Abbreviations: AF, Atrial fibrillation; OR, Odds ratio; CI, Confidence interval; NA, Not available.
The values in bold represent there is statistically significant differences between cases and controls.

co-morbidity conditions could partially explain the observed heterogeneities between studies.

There are several points that need to be addressed about the current study. First, it is noteworthy that Li et al. [15] and Fu et al. [16] also analyzed the potential correlation between *CYP11B2* polymorphism and AF by conducting a meta-analysis (Li et al., 1054 cases and 1704 controls; Fu et al., 1629 cases and 2284 controls), and they found that *CYP11B2* polymorphism was associated with AF in all genetic comparisons. Considering that our findings were based on more eligible studies and the sample size of the present analysis was significantly larger than that of previous studies, maybe the results of the current study were more convincing. However, considering that the results of these three meta-analyses were partially conflicting, further studies with larger sample size, especially in Caucasians are still warranted to confirm our findings. Second, Takeuchi et al. [17] found that *CYP11B2* polymorphism could result in altered blood pressure, while Vasan et al. [18] found that *CYP11B2* polymorphism was correlated with variation in left ventricular diastolic dimensions, and these findings suggested that *CYP11B2* polymorphism may influence cardiac remodeling, a vital pathogenic process of AF, EH and HF. Since AF, EH and HF are closely related, future meta-analyses should also investigate the potential association of *CYP11B2* polymorphism with EH and HF.

As with all meta-analysis, this study certainly has some limitations. First, our results were based on unadjusted estimations due to lack of raw data, and failure to conduct further adjusted analyses for age, gender and co-morbidity conditions may impact the reliability of our findings [19]. Second, obvious heterogeneities were detected in certain subgroup comparisons, which indicated that the inconsistent results of included studies could not be fully explained by differences in ethnic background and co-morbidity conditions, and other unmeasured characteristics of participants may also partially attribute to between-study heterogeneities [20]. Third, association between *CYP11B2* rs1799998 polymorphism and AF may also be influenced by gene-gene and gene-environmental interactions. However, the majority of studies did not consider these potential interactions, which impeded us to perform relevant analyses accordingly [21]. Fourth, only retrospective case-control studies were included in this meta-analysis, and thus direct causal relation between *CYP11B2* rs1799998 polymorphism and AF could not be established. Taken these limitations into consideration, the results of the current study should be interpreted with caution.

To overcome limitations of the current meta-analysis, we hope that up-coming genetic association studies could provide more baseline characteristics of study participants, and if possible, present their raw data in supplementary files. Additionally, interactions between genetic and environmental factors should be investigated when exploring pathogenic mechanisms of complex diseases like AF.

Conclusions

Overall, our meta-analysis suggested that rs1799998 polymorphism may serve as a potential biological marker for AF in East Asians and subjects with EH or HF. However, further well-designed studies with larger sample size are warranted to confirm our findings. Moreover, future investigations also need to explore potential roles of other CYP11B2 polymorphisms in the development of AF.

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Disclosure statement

The authors declare that they have no conflict of interest.

Statement of ethics

The authors have no ethical conflicts to disclose.

Authors' contributions

Xiaoxu Wang and Qiulai Li conceived of the study, participated in its design. Xiaoxu Wang and Yingzheng Li conducted the systematic literature review. Yingzheng Li performed data analyses. Xiaoxu Wang drafted the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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