

Correlation between CYP11B2 polymorphism and the risk of preeclampsia

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Abstract

Background: Many studies have evaluated the association between aldosterone synthase (CYP11B2) C-344T polymorphism and preeclampsia (PE) susceptibility, however, the results from different studies are inconsistent.

Objective: The study aimed to derive a more precise estimation of this association.

Methods: We searched PubMed, Embase, Chinese National Knowledge Infrastructure, China Biological Medicine, and Wanfang Database. The association was evaluated by calculating the odds ratios (ORs) with the corresponding 95% confidence intervals (CIs).

Results: Seven case-control studies with a total of 720 cases and 766 controls were eligible to be included in this meta-analysis. Overall, there was no significant association between CYP11B2 C-344T polymorphism and PE (for the allele model T vs. C: OR=0.78, 95%CI 0.60-1.01, $p=0.06$; for the codominant model CT vs. CC: OR=1.08, 95%CI 0.80-1.46, $p=0.63$; for the dominant model TT + CT vs. CC: OR=0.91, 95%CI 0.68-1.20, $p=0.49$). Similar results were obtained in sensitivity analysis.

Conclusion: In summary, the present meta-analysis suggests that CYP11B2 C-344T polymorphism may not be associated with genetic susceptibility of PE, but the association remains indeterminate due to the insufficient evidence.

Abbreviations: CIs = confidence intervals, CYP11B2 = aldosterone synthase, EOPE = early onset preeclampsia, HWE = Hardy-Weinberg equilibrium, LOPE = late onset preeclampsia, ORs = odds ratios, PE = preeclampsia, RAAS = renin-angiotensin-aldosterone system.

Keywords: CYP11B2, meta-analysis, polymorphism, preeclampsia, rs1799998

1. Introduction

Preeclampsia (PE) is a serious complication of pregnancy and remains to be a major cause of mortality of mothers, fetuses, and newborns around the world, and it is usually characterized by

hypertension (>140/90 mmHg) and proteinuria (>300 mg/24 hours) developed after 20 weeks of gestation.^[1,2] Although previous literature reports a series of risk factors for PE, including immunologic factors, coagulation disorders, nutritional factors, and also oxidative stress, the exact pathogenesis of PE is still unknown.^[3-7] Importantly, renin-angiotensin-aldosterone system (RAAS) has long been thought to play a key role in the pathogenesis of PE, especially in blood pressure regulation and the regulation of electrolyte balance.^[8] The genetic polymorphisms in RAAS may be related to the development of PE.

The gene of “cytochrome P450, family 11, subfamily B, polypeptide 2” is called aldosterone synthase (CYP11B2, rs1799998) gene.^[9] The CYP11B2 gene encodes the aldosterone synthase enzyme, which participates in the synthesis of aldosterone. The primary regulation of aldosterone synthesis is via the RAAS, which is responsive to the state of the electrolyte balance and plasma volume. The C-344T polymorphism in the CYP11B2 promoter region was also reported to be associated with hypertension.^[10-13] Although hypertension is one of the major clinical components of PE, many studies have investigated the association between CYP11B2 C-344T polymorphism and PE risk.^[14-20] However, these studies showed inconsistent results. The existing evidence needs to be reviewed systematically and impartially to draw an accurate conclusion of the association between CYP11B2 C-344T polymorphism and PE.

2. Material and methods

2.1. Identification and eligibility of relevant studies

We retrieved the relevant papers that had been published in English or Chinese through PubMed, Embase, Chinese National

Editor: Surinder Kumar.

This study was supported by the Medical Research Projects of Foshan Municipal Health Bureau (NO.20200352) and the Foshan Science and Technology Innovation Project (NO.1920001001440).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Wang Y, Zhou M, Deng X, Ma Y, Jiang D. Correlation between CYP11B2 polymorphism and the risk of preeclampsia. *Medicine* 2020;99:48(e23322).

Received: 7 June 2020 / Received in final form: 18 September 2020 / Accepted: 21 October 2020

<http://dx.doi.org/10.1097/MD.00000000000023322>

Knowledge Infrastructure, China Biological Medicine, and Wanfang Databases (up to February 2020). The initial search terms included aldosterone synthase, CYP11B2, rs1799998, preeclampsia, and PE.

2.2. Inclusion and exclusion criteria

The studies included in this meta-analysis must be a case-control study which used PE genotype model. On the contrary, studies without control, abstract, review, comment, no usable genotype frequency data, and duplicate publication are excluded.

2.3. Data extraction

All potentially relevant data including first author, year of publication, country of study, ethnicity, and numbers of genotyped cases and controls were extracted by 2 investigators independently (YW and XD). Disagreements were resolved by discussion among the authors.

2.4. Ethical approval

All data in this meta-analysis were extracted from the previous published studies, no ethical approval or patient consent was required.

2.5. Statistical analysis

Data analysis was performed using the software Review Manager 5.1 software (Cochrane Collaboration, Oxford, UK) STATA 12.0 software (STATA, USA). Odds ratio (ORs) with 95% confidence intervals (CIs) for genotypes and alleles were used to assess the strength of association between CYP11B2 C-344T polymorphism and PE risk. The allele model (T vs C), codominant model (CT vs CC), and dominant model (TT + CT vs CC) were performed respectively. The Z test was used to assess the significance of the pooled ORs, and $P \leq .05$ was considered as statistically significant. The effect of heterogeneity is also measured using a quantitative measure, $I^2 = 100\% \times (Q - df) / Q$. According to the heterogeneity, the fixed effects or random effects model would be used to calculate the ORs with 95% CIs. If there was a statistical difference in terms of heterogeneity ($P_Q < .10$, $I^2 > 50\%$), the random effects model was used to calculate the pooled ORs. Otherwise, fixed effects model was used. The Hardy-Weinberg equilibrium (HWE) was determined in the control group. Sensitivity analyses were also performed by excluding studies in which the genotype frequencies significantly deviated from the HWE. Publication bias among the included studies was investigated by Begg test and Egger test.

3. Results

3.1. Characteristics of published studies

According to the inclusion and exclusion criteria, a total of 104 potentially relevant studies were retrieved after a comprehensive search. After skimming the title, abstract, and reviewing the full text, 97 studies were excluded due to duplicated studies and irrelevant articles (Fig. 1). Eventually, 7 studies were identified to be eligible studies.^[14–20] The main characteristics of the eligible studies are presented in Table 1. Out of the 7 studies, 6 of 7 studies were published in English^[15–20] and 1 study was

published in Chinese.^[14] Among all the eligible publications, the subjects in 5 included studies were of Caucasian,^[15–17,19,20] one of Asian,^[14] and the other one of black.^[18] The genotype distributions of all studies in the control groups conformed to the HWE equilibrium except for 2 studies.^[18,19]

3.2. Meta-analysis results

The combined results based on 7 studies showed that there is no statistically significant association between CYP11B2 C-344T polymorphism and PE (for the allele model T vs C: OR=0.78, 95%CI 0.60–1.01, $P=.06$; for the codominant model CT vs CC: OR=1.08, 95%CI 0.80–1.46, $P=.63$; for the dominant model TT + CT vs CC: OR=0.91, 95%CI 0.68–1.20, $P=.49$) (Table 2, Supplemental Digital Content [Figures S1–S3, <http://links.lww.com/MD/F297>, <http://links.lww.com/MD/F298>, <http://links.lww.com/MD/F299>]).

3.3. Sensitivity analysis

Sensitivity analysis was performed by excluding studies in which the genotype frequencies significantly deviated from the HWE. A consistent result was obtained when the sensitivity analysis was used to evaluate the association between CYP11B2 C-344T polymorphism and PE susceptibility (data are not shown).

3.4. Publication bias

Begg test and Egger test were performed to assess the publication bias. The results of Begg test and Egger test were shown in Table 2. These results did not show any evidence of publication bias in all genetic models.

4. Discussion

PE is the most common of pregnancy complications, and the risk of developing PE is between 2% and 8% worldwide and it can rise to 10% in developing countries.^[21,22] Although the etiology of PE is still far from being understood, it has been generally accepted that PE pathogenesis is involved in RAAS responses. Therefore, the discovery of genes in RAAS that may affect the risk of development of PE may help to understand the pathophysiology and offer therapeutic targets for these conditions. Inconsistent results are observed in previous studies when it comes to the relationship between CYP11B2 C-344T and the risk of PE. In particular, several studies show that CYP11B2 C-344T polymorphism is associated with PE development in Polish, Iranian, and South African populations but not in Turkish and Brazilian populations.^[15–20] Moreover, CYP11B2 C-344T polymorphism is an independent risk factor for early-onset preeclampsia (EOPE) in Chinese and Romanian pregnancy,^[14,19] but not in late-onset preeclampsia (LOPE). Due to the relatively small sample size and different populations, these studies showed inconsistent results. To gain a better understanding, we conducted a meta-analysis by analyzing the above studies.

In this meta-analysis, 7 eligible case-control studies including 720 cases and 776 controls were analyzed. The pooled results indicated that there was no significant association between CYP11B2 C-344T polymorphism and PE risk in all genetic models. In the HWE test, we found that genotype distributions of all studies in the control groups conformed to the HWE equilibrium except for the 2 studies reported by Aung et al^[18]

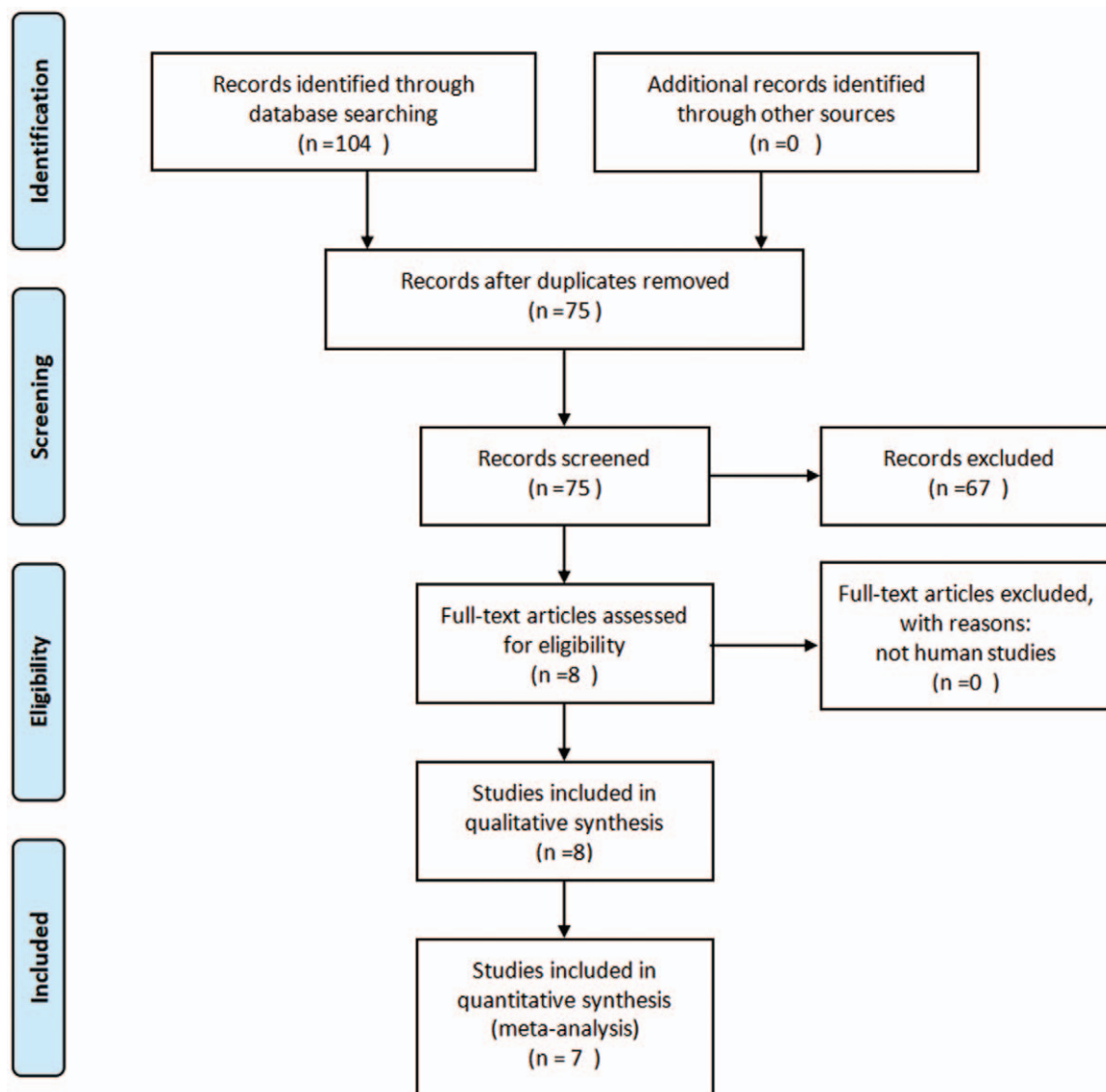


Figure 1. Flow diagram of the meta-analysis literature search results.

and Procopciuc et al.^[19] However, the association was not significant change when excluded the study.

Meta-analysis is usually used to combine comparative studies to enlarge the sample size and statistical power to obtain a more

obvious conclusion. However, there are some factors including different genetic backgrounds of subjects and publication bias, which may affect the results. In this study, no publication bias was identified by either Begg test or Egger test. The result

Table 1
The characteristics of the included studies in this meta-analysis.

Study	Area	Ethnicity	No. of cases	No. of controls	Cases CC CT TT	Controls CC CT TT	HWE (control) P
Yue et al, 2005	China	Asian	43	44	6 20 17	5 17 22	.54
Percin et al, 2006	Turkey	Caucasian	143	147	35 74 34	34 70 43	.59
Vasconcelos et al, 2009	Brazil	Caucasian	70	118	8 38 24	17 51 50	.49
Bogacz et al, 2016	Poland	Caucasian	59	106	14 26 19	28 53 25	.99
Aung et al, 2018	South Africa	Black	201	129	9 67 125	5 24 100	.03
Procopciuc et al, 2019	Romania	Caucasian	87	129	22 27 38	13 34 82	.003
Nezhad et al, 2020	Iran	Caucasian	117	103	26 76 15	28 54 21	.59

HWE=Hardy-Weinberg equilibrium.

Table 2
Meta-analysis of CYP11B2 C-344T polymorphism and risk of PE.

Genetic comparison	Begg test(z, p)	Egger test(t, p)	I ² (%)	Fixed model		Random model	
				OR [95% CI]	P _{OR}	OR [95% CI]	P _{OR}
T vs C	0.00, 1.000	-0.28, 0.793	61	0.79 [0.67, 0.92]	.003	0.78 [0.60, 1.01]	.06
CT vs. CC	0.00, 1.000	-0.07, 0.946	0	1.08 [0.80, 1.46]	.63	1.08 [0.80, 1.47]	.61
TT + CT vs. CC	0.90, 0.368	-0.30, 0.779	36	0.91 [0.68, 1.20]	.49	0.90 [0.62, 1.30]	.56

CI=confidence interval, OR=odds ratio.

suggested that the selection of publication was an unlikely source of bias in this meta-analysis. Due to limited data in Asian and black populations, we can not perform a subgroup analysis of ethnicity to evaluate the effect of different genetic backgrounds.

Because this meta-analysis had several limitations, the results should be interpreted with caution. Firstly, our research only focuses on English and Chinese literature, which might bias the result. Secondly, due to limited data, we did not carry out subgroup analysis to other factors, such as ethnicity, the type of PE, and lifestyle, which might contribute to the development of PE. Moreover, the study may be influenced by gene–environment interactions and intergenic interactions.

In conclusion, our study suggested that CYP11B2 C-344T polymorphism may not be associated with genetic susceptibility of PE based on the current published studies. However, more studies with large sample sizes, gene–gene, gene–environment interactions and well-designs are needed to confirm these findings.

Author contributions

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