Int J Clin Exp Med 2017;10(6):8728-8734
www.ijcem.com /ISSN:1940-5901/IJCEM0048154

Review Article

Association between CYP11B2-344T/C gene polymorphism and end-stage renal disease susceptibility: a meta-analysis

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Received December 3, 2016; Accepted March 19, 2017; Epub June 15, 2017; Published June 30, 2017

Abstract: Background: End-stage renal disease (ESRD) is a complex process that may be influenced by many factors, including polymorphismin aldosterone synthase CYP11B2-344T/C (rs1799998) gene. Previous work suggests an association between the CYP11B2-344T/C gene polymorphism and susceptibility to ESRD, but the results have been inconsistent. Methods: PubMed, Embase, Cochrane, Science Direct, and Web of Science were systematically searched to identify relevant studies. A meta analysis was performed to examine the association between CYP11B2 gene polymorphism and susceptibility to ESRD. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Results: Five studies involving 1,329 ESRD cases (965 Asians, 104 Caucasians and 260 mixed) and 1,193 healthy controls (898 Asians, 133 Caucasians and 162 mixed) were included. In overall analysis, the CYP11B2-344T/C gene polymorphism had no association with increased or decreased risk of ESRD. In subgroup analysis, TT genotype was significantly associated with increased risk in Asian population in the recessive comparison (TT vs. TC+CCOR=1.28, 95% CI 1.06-1.54, P=0.01). TC genotype was significantly associated with increased risk in Caucasian population in the Heterozygote comparison (TC vs. CC OR=2.19, 95% CI 1.08-4.44, P=0.03). Conclusions: Our meta analysis indicates that TT genotype of CYP11B2-344T/C gene polymorphism may be a risk factor of ESRD in Asians. Heterozygote TC genotype may be a risk factor of ESRD in Caucasian population. However, these conclusions should be verified in larger, stratified-designed studies.

Keywords: Aldosterone synthase, CYP11B2, end-stage renal disease, gene polymorphism, meta-analysis

Introduction

End-stage renal disease (ESRD) is an increasing problem worldwide and is associated with high morbidity and mortality [1, 2]. Patients with ESRD must receive a kidney transplant or live on dialysis [3]. Some studies suggest that genetic factors play an important role on occurrence and development of ERSD [4-6]. It has been confirmed that renin-angiotensin-aldosterone system (RAAS) has an important influence on the occurrence and development of ESRD [7]. Aldosterone synthase gene has received more and more attention as an important component of RAAS. But whether aldosterone synthase (CYP11B2) polymorphism is related to ESRD is still controversial. There is no meta-analysis so far investigating the association between them. To estimate the overall risk of aldosterone synthase (CYP11B2) polymorphism with ESRD and to quantify the potential between-study heterogeneity, we conducted this comprehensive meta-analysis.

Materials and methods

Search strategy

All clinical and experimental case-control studies were searched from the electronic databases of PubMed, Embase, Cochrane, Science Direct, and Web of Science up to April 13, 2016. No language restrictions were imposed. The search terms used were: end-stage renal disease, ESRD, renal dialysis, dialysis, hemodiafiltration, peritoneal dialysis, kidney transplantation; each of these terms in combination with polymorphism, variation, genotype, genetic or

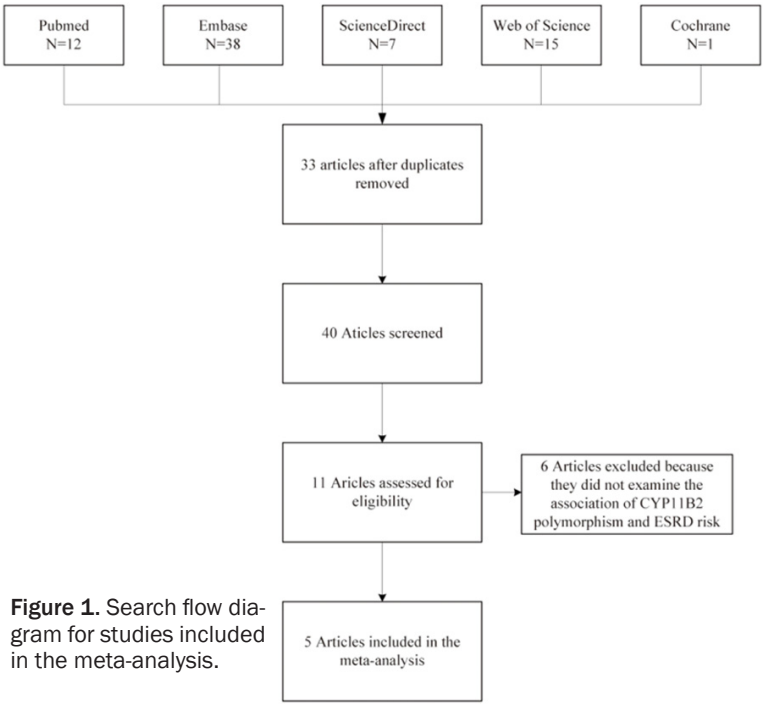

Figure 1. Search flow diagram for studies included in the meta-analysis.

mutation; each of the above terms in combination with *aldosterone synthase* or *CYP11B2*. The Additional reports were identified through references cited in recruited articles.

Inclusion criteria

Studies were included in the meta-analysis if it satisfied the following criteria: (a) it evaluated the association between ESRD and the CYP11B2-344C/T polymorphism; (b) there had to be at least two comparison groups; (c) investigation provided sufficient data for estimating an odds ratio (OR) with a 95% confidence interval (95% CI). If multiple publications of the same data from the same study group, we only recruited the most complete paper into our final analysis.

Exclusion criteria

(a) Review articles and editorials; (b) case reports; (c) preliminary result not on CYP11B2-344T/C gene polymorphism or outcome; (d) investigating the role of CYP11B2 gene expression to disease.

Data extraction and synthesis

Literature searches and identification of eligible study based on the in- and Ex-clusion criteria were carried out by two authors (LZ and XPC) independently. Each of these author sextracted data about the first author's surname, year of publication, country, patient ethnicity, genotyping method, and the number of cases and control. The results were compared and disagreement was resolved by discussion.

Statistical analysis

The unadjusted odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of the association between the CYP11B2 polymorphism and ESRD risk based on the frequencies of allele or genotype incases and controls. The genetic models evaluated for pooled ORs of the polymorphisms were allele comparison (T vs. C), homozygote comparison (TT vs. CC), heterozygote comparison (TC vs. CC), dominant comparison (TC+TT vs. CC) and recessive comparison (TT vs. TC+CC), respectively. Subgroup analysis stratified by ethnicity was also performed. Ethnicity was categorized as Asian, mixed and Caucasian.

All statistical tests for this meta-analysis were performed using Cochrane RevMan5 (Cochrane Collaboration) and Stata 12.0 (StataCorp, College Station, USA). A Q-test was used to assess heterogeneity among studies. I^2>50% indicates the statistical heterogeneity, in this case, the fixed-effect model was used to calculate a pooled OR for each study. Otherwise, the random-effect model was used to calculate pooled OR. The significance of the pooled OR was determined by a Z-test and P<0.05 was considered statistically significant. HWE in the control group was assessed using a web-based program, with P>0.05 considered significant. The meta-analysis was carried out in the light of the PRISMA guidelines as much as possible.

Results

Description of studies

A total of 73 potentially relevant publications published through April 13, 2016 were systematically identified in the PubMed, EMBASE,

Table 1. The characteristics of each study in the meta-analysis

First author year	Country	Ethnicity	Genotyping method	P_{HWE}	Case/ control	No. of case			No. of control		
						CC	CT	TT	CC	CT	TT
Su, 2014	Taiwan	Asian	PCR-RFLP	0.98	647/644	58	205	284	48	256	340
Huang, 2010	China	Asian	PCR-RFLP	0.89	47/120	5	17	25	13	52	55
Lee, 2009	Korea	Asian	PCR-RFLP	0.26	271/134	26	115	130	11	64	59
Lovati, 2001	Switzerland	Mixed	PCR-RFLP	0.95	260/162	59	135	66	35	81	46
Coll, 2003	Spain	Caucasian	Allele-specific PCR	0.06	104/133	16	58	30	32	53	46

Each study was a case-control study, the mean quality score of all studies is 7 stars (Newcastle-Ottawa quality assessment scale). HWE: Hardy-Weinberg equilibrium.

Table 2. Association between CYP11B2-344C/T polymorphism and risk of ESRD nephropathy in overall sample and in sub-racialgroups

Category (study number)	Sample size (case/control)	T vs. C OR (95% CI)	TT vs. TC+CC OR (95% CI)	TC+TT vs. CC OR (95% CI)	TT vs. CC OR (95% CI)	TC vs. CC OR (95% CI)
Overall (5)	1329/1193	1.08 (0.95, 1.22)	1.16 (0.98, 1.36)	0.98 (0.87, 1.26)	0.96 (0.73, 1.27)	0.96 (0.63, 1.46)*
Asian (3)	965/898	1.13 (0.97, 1.31)	1.28 (1.06, 1.54)	0.84 (0.60, 1.17)	0.95 (0.68, 1.35)	0.70 (0.49, 0.99)
Caucasian (1)	104/133	1.09 (0.76, 1.58)	0.77 (0.44, 1.34)	1.89 (0.98, 3.65)	1.30 (0.61, 2.78)	2.19 (1.08, 4.44)
Mixed (1)	260/162	0.91 (0.69, 1.21)	0.86 (0.55, 1.33)	0.95 (0.60, 1.52)	0.84 (0.48, 1.47)	0.97 (0.59, 1.59)

*Significant heterogeneity existing, (χ^2=8.33, I^2=52%), and the random-effects model was chosen to summarize the result. OR: odds ratio; CI: confidence interval.

Science Direct, Cochrane, and Web of Science. Of these, we excluded 33 studies based on review of the titles and abstracts because they did not focus on the association of CYP11B2-344T/C gene polymorphism and ESRD risk. After screened the full text, only five studies [8-12] involving 1,329 cases and 1,193 controls were found to meet the inclusion criteria and included in our meta-analysis (**Figure 1**).

Participants in three studies [8-10] were Asian, while one study [11] was Caucasian, and one study [12] was mixed. Among the five included studies, only one [11] used allele-specific PCR method, while the others [8-10, 12] used polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) genotyping method. The distribution of genotypes among controls showed HWE in all the studies. Detailed characteristics of the five eligible studies are listed in **Table 1**.

Test of heterogeneity

The heterogeneity of CYP11B2-344T/C allelic contrast, homozygote and heterozygote comparison, dominant and recessive genetic models was analyzed for all 5 studies by Q-test and I^2 statistic. Random-effect models were used to analyze the OR for the heterozygote comparison (TC vs. CC, P=0.08, I^2=52%). Fixed-effect models were used to analyze the OR for the other populations.

Quantitative data synthesis

Table 2 shows the summary ORs for the CYP11B2-344T/C gene polymorphism and ESRD risk on the basis of 1,329 cases and 1,193 controls. Calculation of overall OR in the total population showed that CYP11B2-344T/C gene polymorphism was not associated with increased or decreased risk of ESRD based on the allele comparison (OR=1.08, 95% CI=0.95-1.22, P=0.23), homozygote comparison (OR=0.96, 95% CI=0.73-1.27, P=0.79), heterozygote comparison (OR=0.96, 95% CI=0.63-1.46, P=0.84), dominant comparison (OR=0.98, 95% CI=0.77-1.26, P=0.90) and recessive comparison (OR=1.16, 95% CI=0.98-1.36, P=0.08). Given the ethnic differences in the allele frequency of this sequence variant, we evaluated the effect of CYP11B2-344T/C polymorphism in Chinese, mixed and Caucasian populations separately. We also evaluated the summary ORs stratified by different genotyping methods.

Subgroup analysis by ethnicity

Asian population: After stratification for ethnicity, we observed that in the Asian population,

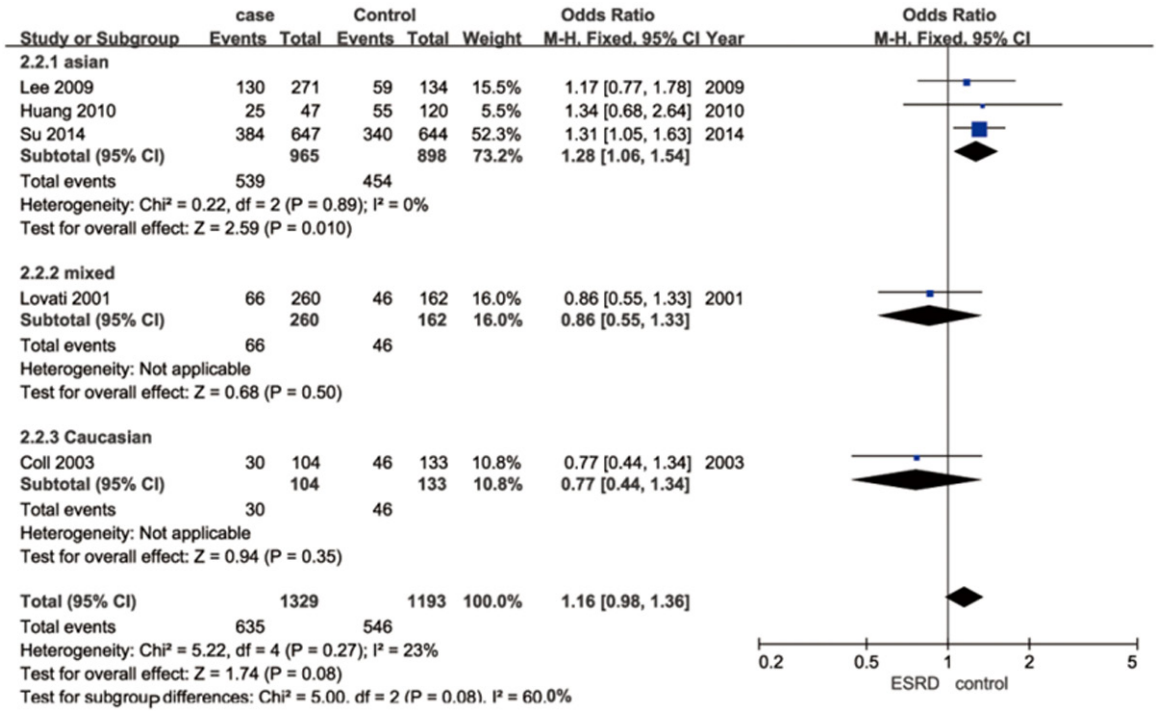

Figure 2. Forest plot for the subgroup analysis for aldosterone synthase CYP11B2 polymorphism and ESRD nephropathy risk for recessive comparison (TT vs. TC+CC). ESRD: end-stage renal disease; M-H: Mantel-Haenszel; CI: confidence interval.

Table 3. Studies included using PCR-RFLP genotyping method (4 studies included 1225 cases and 1060 controls)

Genotype comparison	OR (95% CI)	Z (*P* value)	Heterogeneity of study design			Analysis model
			χ^2	df (*P* value)	I^2	
T vs. C	1.08 (0.94, 1.23)	1.10 (0.27)	1.90	3 (0.59)	0	Fixed
TT vs. TC+CC	1.20 (1.01, 1.43)	2.12 (0.03)	2.90	3 (0.41)	0	Fixed
TC+TT vs. CC	0.88 (0.67, 1.15)*	0.95 (0.34)	0.32	3 (0.96)	0	Fixed
TT vs. CC	0.92 (0.69, 1.24)	0.55 (0.58)	0.30	3 (0.96)	0	Fixed
TC vs. CC	0.78 (0.58, 1.04)	1.71 (0.09)	1.29	3 (0.73)	0	Fixed

*conclusion exchanged after omitted the allele-specific PCR genotyping methodarticle.

TT genotype had significantly increased risk of ESRD in recessive comparison (OR=1.28, 95% CI 1.06-1.54, P=0.01). (**Figure 2**) Significant associations were not detected for comparisons of allele and other genotypes test (**Table 2**).

Caucasian population: Only one study was about Caucasian. The research revealed that, in heterozygote comparison, TC genotype was associated with initiation or progression of ESRD in Caucasian patients. (OR=2.19, 95% CI 1.08-1.54, P=4.44) (**Table 2**).

Mixed population: Analysis of one mixed participants gave results similar to those obtained with the total population (**Table 2**).

Analysis by genotyping method

This analysis was carried out to assess the robustness of the meta-analysis results to diverse genotyping method. Given that one study [11] used allele-specific PCR method, and others [8-10, 12] used the PCR-RFLP method. We excluded the allele-specific PCR study, [11] and the results were not materially altered in every genetic model except for recessive comparison (**Table 3**).

Sensitivity analysis

To evaluate the robustness of the association results, leave-one-out sensitivity analysis was performed by omitting one study at a time and calculating the pooled ORs (**Figure 3** T vs. C). We found the summary ORs remained stable,

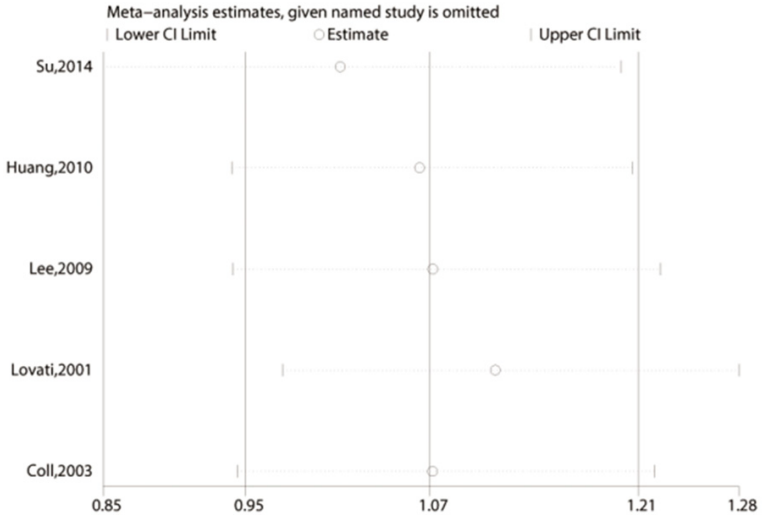

Figure 3. Result of sensitivity analysis. (T vs. C).

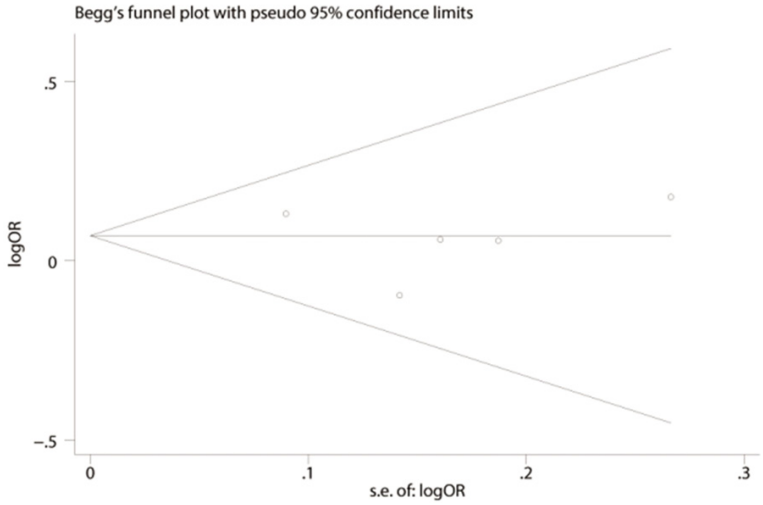

Figure 4. Egger's regression test for publication bias test of the association between aldosterone synthase CYP11B2 polymorphism and ESRD nephropathy risk.

indicating that our results were not driven by any single study.

Publication bias

Both Begg's funnel test and Egger's regression test were performed to assess the publication bias in all comparison. No publication bias was identified. The funnel plots in all genetic models were symmetrical (**Figure 4**, T vs. C).

Discussion

CYP11B2 gene is located on chromosome 8q21-q22, and it encodes a cytochrome P450 enzyme which involved in terminal steps of aldosterone synthesis [13]. Studies have shown that aldosterone synthase -344T/C polymorphism was associated with stroke, essential hypertension, and cardiovascular function [14-16]. Up to now, studies concerning relations between aldosterone synthase -344T/C polymorphism and ESRD still showed controversial conclusions. Su et al. [8] found that T>C (-344) polymorphisms in aldosterone synthase were significantly associated with ESRD susceptibility. Huang et al. [9] showed the -344T/C polymorphism of the aldosterone synthase gene was not associated with ESRD in Asian. So we conducted this meta-analysis to evaluate the association.

As the first meta-analysis focused on the association between aldosterone synthase -344T/C polymorphism and the susceptibility to ESRD, our research included a total of 1,329 cases and 1,193 controls. In overall population, no significant association existed in allele comparison and genotype comparison. Subgroup analyses according to ethnicity were then conducted. A significant increased risk was found in recessive comparison in Asian. That is, TT genotypeis associated with ESRD susceptibility in Asians, but not in allele comparison other genotype comparison. There is only one study was about Caucasian, so we only did descriptive analysis. This research revealed TC genotype in heterozygote comparison is associated with ESRD susceptibility in Caucasian. No significant association existed in Mixed population. The different results between Asians and Caucasians population may be accounted for such ways. Firstly, various genetic and environmental elements in different races may play a crucial role on genephenotypes. Secondly, Caucasus sub-

group has only one research, so may not be able to explain the genotype distribution of aldosterone synthasegene polymorphism in ESRD nephropathy patients.

Patients with different histological subtypes of nephropathy may have different prognoses. Whether genetic risk applies differently to particular histological subtypes is important to understand. Sad to say, this question could not be sufficiently addressed because most included studies did not report detailed genotype data for different histological subtypes. Large, well-designed cohort studies examining the genetic susceptibility of different histological subtypes developed into ESRD are needed.

In this meta-analysis, we conducted sensitivity analysis based on diverse genotyping method. After excluding one allele-specific PCR study, the results were not materially altered in the rest studies except for recessive comparison. The difference conclusion after sensitivity analysis indicates genotyping method may affect the experiment outcome. However, interpreting this result should be cautious, since the number of included studies was quite small and, small sample size may also account for the discrepancy outcome. Besides that, we replaced the fixed effects model for the random effects model to calculate pooled OR, the results were not materially altered.

No publication bias was identified by Egger's regression test. The funnel plots in all the genetic models were symmetrical. But owing to the limited number of included studies, power of these two tests was small. The conclusion needs further support of larger sample size studies.

Some limitations should still be considered when interpreting the results of this meta-analysis. Firstly, our meta-analysis only contained studies in Caucasians and Asians ethnicity. We cannot know the genotype distributions in other ethnic groups. Large, well-designed studies in other populations such as African are warranted to reevaluate these associations. Secondly, small sample size limited further analysis due to shortage of original studies. Thirdly, the heterogeneity existed in the heterozygote comparison (TC vs. CC) should be noted. Genotyping method and sample size might contribute to the heterogeneity.

In conclusion, our meta-analysis suggests that aldosterone synthase -344T/C polymorphism was associated with increased risks of ESRD. However, larger sample size studies conducted in different ethnic populations are required to further confirm our findings in the future.

Disclosure of conflict of interest

None.

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