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Original Article

Relationships between CYP11B2 -344C/T gene polymorphism and coronary artery disease: a meta-analysis

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Abstract: Objective and Background: The CYP11B2 gene has been suggested to play an important role in the pathogenesis of coronary artery disease (CAD). However, the results have been inconsistent. In this study, we performed a meta-analysis to clarify the association of the CYP11B2 -344C/T variant with CAD. Methods: A literature search of PubMed, Embase, Web of Science, CNKI and WanFang databases was conducted on articles published. The odds ratios with 95% confidence intervals were calculated. Heterogeneity analyses were performed using Q statistic. Tests for publication bias were also performed and biased studies should be removed from subsequent analyses. Results: A total of 7 case-control studies with a total of 2905 CAD patients and 5543 controls were included. There was no statistical evidence of association between CYP11B2 -344C/T polymorphism and CAD in all genetic models (allele model: OR 1.03, 95% CI 0.95-1.10, P = 0.49; dominant model: OR 1.13, 95% CI 0.77-1.66, P=0.54; recessive model: OR 1.02, 95% CI 0.92-1.14, P = 0.69; additive model: OR 1.03, 95% CI 0.89-1.21, P = 0.68, respectively). The pooled ORs were not substantially altered after the exclusion of one study in the control group that deviated from Hardy-Weinberg equilibrium. Conclusion: The present meta-analysis suggested that CYP11B2 -344C/T polymorphism was not contributed to CAD.

Keywords: Angiotensin-converting enzyme gene, CYP11B2, coronary artery disease, polymorphisms, meta-analysis

Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality, therefore, much effort has been focused on identifying risk factors and devising strategies to ameliorate their effects [1]. Given that atherosclerosis and CAD are multi-genetic disease, the focus should be on the combined effects of multiple susceptibility genes [2] that interact with demographic, lifestyle, and external factors (environmental or non-genetic risk factors) [3]. The renin-angiotensin aldosterone system (RAAS) is a well-described hormone system that regulates blood pressure and salt/water homeostasis. RAAS dysfunction contributes to functional and structural perturbations that occur in atherosclerosis formation [4]. Aldosterone is one of the main effectors of the renin-angiotensin system [5]. Aldosterone synthase (CYP11B2), which may influence plasma aldosterone levels, has been reported to strongly influence left ventricular diameters and mass in young adults and arterial stiffness in essential hypertensive patients [6], is sensible to the effects of angiotensin II (ATII), catalyses the final step of aldosterone biosyntesis in adrenal glomerulosa. Because of the various physiologic effects of ATII, including vasoconstriction, promotion of vascular smooth muscle cells growth and increase of extracellular collagen matrix synthesis, genetic variation of the level of each RAAS component could probably affect a wide variety of clinical phenotypes [7].

The enzyme aldosterone synthase is encoded by the CYP11B2 gene, in which a thymidine to cytosine substitution variant (-344T>C) has

been described in the promoter region of the gene [8]. It has been reported that, the binding of a steroidogenic transcription factor (SF-1) is elevated four-folds in vitro, whilst circulating aldosterone levels, arterial stiffness, left ventricular mass and dimensions in vivo are increased in all C-allele carriers [8-11]. Thus this polymorphism could influence arterial diastolic dysfunction and ventricular remodelling evolution [12]. However the exact relationship between the CYP11B2 -344C/T polymorphism and susceptibility to CAD is not entirely established. Therefore, we performed a meta-analysis of all eligible studies to derive a more precise estimation of the association between the CYP11B2 -344C/T polymorphism and CAD.

Method

Ethical standards

This is a meta-analysis and no ethnical issue is required.

Search strategy

Literature searches were performed to identify all relevant and published case-control studies focused on the relation of polymorphisms of CYP11B2 gene with CAD. Without any language restrictions, we searched electronic databases (PubMed, Embase, Web of Science, CNKI and WanFang) updated on April 15, 2015, using "Angiotensin-converting enzyme gene", "CYP11B2", "T-344C", "coronary artery disease", and "polymorphisms" as key words. We also reviewed the bibliographies of all selection articles to identify additional relevant studies.

Publications selection

Two reviewers (Ting-Ting Wu and Yun Zhou) independently screened titles and abstracts of all studies for relevancy. Disagreements were resolved by a third opinion (Dilare Adi).

Inclusion and exclusion criteria

Criteria for inclusion were as follows: (1) A validated diagnosis of CAD. (2) Clinical case-control study focused on genetic polymorphisms of CYP11B2 with CAD. (3) Useful data including genotype number or frequency given. (4) Studies written in English and Chinese with full-text. (5) Studies that conform to the Hardy-Weinberg equilibrium (HWE).

The exclusion criteria were: (1) Studies without available genotype number or frequency, (2) Animal studies, reviews, case reports, and abstracts. (3) Studies do not conform to the Hardy-Weinberg equilibrium. For the studies with the same or overlapping data by the same authors, the most recent or largest population was selected.

Data extraction

Data were drawn out according to a standard protocol. The extracted data comprised the following items: first author's name, publication year, study region, ethnicity, study design, quality score, *p* value for HWE, number of genotypes, matching criteria and total number of cases and controls.

Sensitivity analysis

The association between the CYP11B2 -344C/T variant and CAD was estimated by calculating pooled OR and 95% CI under an allelic model, a dominant model, a recessive and an additive model. The significance of pooled OR was determined by Z test ($P<0.05$ was considered statistically significant). Heterogeneity between studies was tested using the Q statistic. Heterogeneity was considered statistically significant if $P<0.10$. Heterogeneity was quantified using the I^2 metric, which was independent of the number of studies in the meta-analysis ($I^2<25\%$ no heterogeneity; I^2 = 25-50% moderate heterogeneity; and $I^2>50\%$ large or extreme heterogeneity). Funnel plot and Egger's test were performed to assess the publication bias in the literature. Data analysis was performed using Revman 5.0 (The Cochrane Collabor-ation).

Results

Study selection

Based on our search criteria, we identified 697 potentially relevant articles. By scanning the titles and the abstracts we excluded 646 articles. 51 peer-reviewed articles were retrieved for full text evaluation, 43 studies were excluded for the following reasons: 14 lacking any of our requisite data and 27 not related to CAD or myocardial infarction, 3 were not case-control studies. Finally, 7 case-control studies [1, 6-8, 13-15] with a total of 2905 CAD patients and 5543 controls fulfilling all inclusion criteria

Table 1. Baseline characteristics of the all included studies in the meta-analysis

First author	Year	Region	Study design	Quality score	*P* value for HWE	Ethnicity	Sample size		Genotypes distribution (case/control)					Sex (male)		Age (years)	
							Case	Control	TT	CT	CC	T	C	Case	Control	Case	Control
Aarno Hautanen	1999	Finland	Case-control	8	0.55	Caucasian	141	270	31/78	74/132	36/60	136/288	146/252	100%	100%	48.2	47.5
Christian Hengstenberg	2000	German	Case-control	7	0.98	Caucasian	606	1675	187/517	299/826	120/332	673/1860	539/1490	88%	49.2%	50.7±0.6	<60
Samita Pate	2000	UK	Case-control	7	0.18	Caucasian	542	500	168/154	281/237	93/109	617/545	467/455	68.2%	61.6%	61.8±9.8	58.6±11.3
J.R. Paynea	2004	UK	Case-control	6	0.06	Caucasian	187	2303	52/701	105/1121	30/481	209/2523	165/2083	100%	100%	56.4±3.5	56.0±3.4
Erica Franco	2007	Italy	Case-control	7	0.06	Caucasian	201	201	59/69	87/97	55/35	205/235	197/167	90.5%	Matched	40±4	Matched
En-Zhi Jia	2012	China	Case-control	7	0.2	Asian	720	360	394/174	268/154	58/32	1056/502	384/218	80%	64.6%	63.07±10.63	59.57±10.06
Avshesh Mishra	2012	India	Case-control	7	0.22	Asian	508	234	190/77	252/124	66/33	632/278	384/190	86.4%	79.9%	56.04 ±9.42	54.18 ± 8.47

Table 2. Meta-analysis of the relationship between genetic polymorphism of CYP11B2 gene with coronary artery disease

	T vs.C (Allelic model)			TT vs. CC+TC (Recessive model)			TT+TC vs. CC (Dominant model)			TT vs. CC (Additive model)		
	OR	95% CI	P for z test	OR	95% CI	P for z test	OR	95% CI	P for z test	OR	95% CI	P for z test
AarnoHautane	0.82	0.61-1.09	0.16	0.69	0.43-1.12	0.13	0.83	0.52-1.34	0.45	0.66	0.37-1.19	0.17
Avshesh Mishra	1.12	0.90-1.41	0.30	1.22	0.88-169	0.24	1.10	0.70-1.72	0.68	1.23	0.75-2.02	0.41
Christian	1.00	0.88-1.14	1.00	1.00	0.82-1.22	1.00	1.00	0.79-1.26	0.99	1.00	0.77-1.31	1.00
En-Zhi Jia	1.19	0.98-1.45	0.08	1.29	1.00-1.66	0.05	1.11	0.71-1.75	0.64	1.25	0.78-1.99	0.35
Erica Franco	0.74	0.56-0.98	0.03	0.79	0.52-1.21	0.28	0.56	0.35-0.90	0.02	0.54	0.31-0.94	0.03
J.R. Paynea	1.05	0.85-1.29	0.68	0.88	0.63-1.23	0.45	1.17	0.78-1.75	0.45	1.19	0.75-1.89	0.46
Samita Pate	1.10	0.93-1.31	0.27	1.01	0.78-1.3	0.95	3.24	2.22-4.72	<0.00001	1.28	0.9-1.82	0.17
Total	1.03	0.95-1.10	0.49	1.02	0.92-1.14	0.69	1.13	0.77-1.66	0.54	1.03	0.89-1.21	0.68

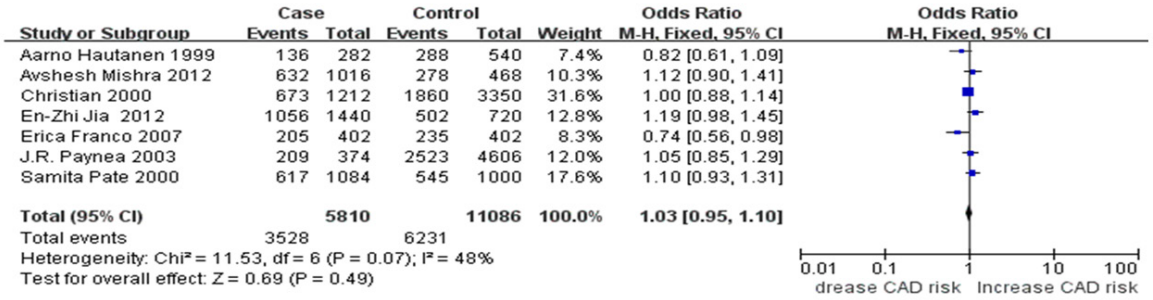

Figure 1. Forest plot of CAD and CYP11B2 -344C/T genetic polymorphism in an allelic model, the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

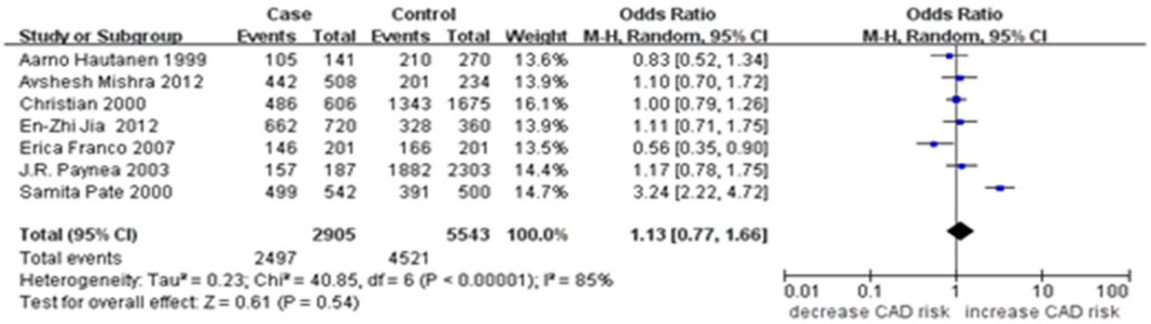

Figure 2. Forest plot of CAD and CYP11B2 -344C/T genetic polymorphism in a dominant model, the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

were included in this meta-analysis. The characteristics of 7 studies included in the meta-analysis are summarized in **Table 1**.

Quantitative synthesis

Random and fixed effects models were used to calculate the pooled ORs in all genetic models. Overall, the combined results showed no significant association between the CYP11B2 -344C/T polymorphism and CAD for all genetic models. (allelic model: OR = 1.03, 95% CI = 0.95-1.10; dominant model: OR = 1.13, 95% CI = 0.77-1.66; additive model: OR = 1.03, 95% CI = 0.89-1.21; and recessive model: OR = 1.02, 95% CI =0.92-1.14) (**Table 2** and **Figures 1**-**4**).

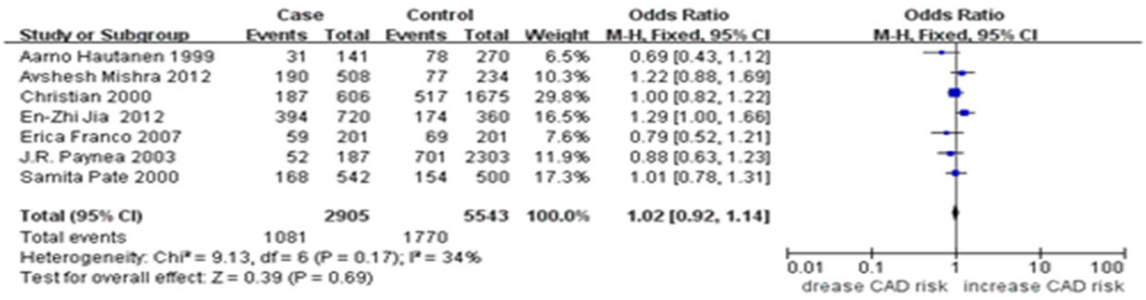

Figure 3. Forest plot of CAD and CYP11B2 -344C/T genetic polymorphism in a recessive model, the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

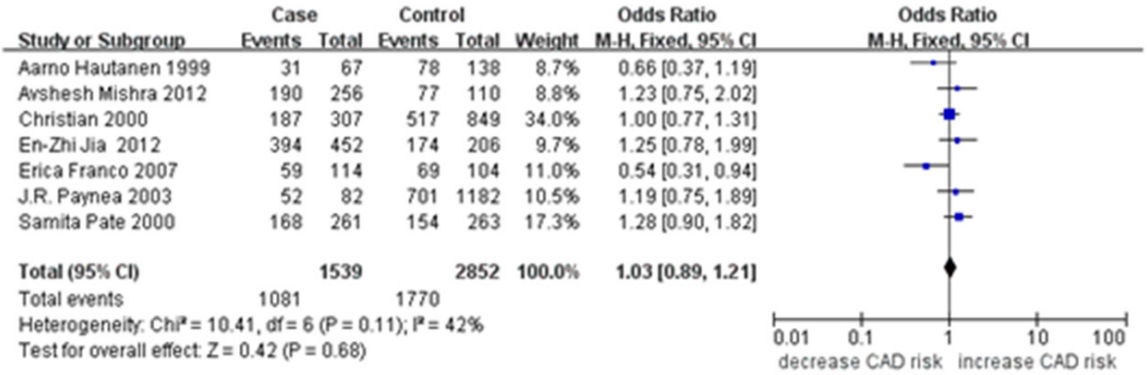

Figure 4. Forest plot of CAD and CYP11B2 -344C/T genetic polymorphism in a additive model, the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

On subgroup analysis by ethnicity of study population, no evidence of association was also found in all genetic models in Caucasians. For none-Asians, the combined ORs and 95% CIs were (allelic model: OR = 0.99, 95% CI = 0.90-1.07, P = 0.73; additive model: OR = 0.99, 95% CI = 0.83-1.17, P = 0.88; dominant model OR = 1.13, 95% CI = 0.66-1.93, P = 0.65 and recessive model: OR = 0.93, 95% CI = 0.82-1.06, P = 0.30). Significant association was found in some model between the -344T>C polymorphism and CAD risk in Asians (allelic model: OR = 1.16, 95% CI = 1.00-1.35, P = 0.05; recessive model: OR = 1.26, 95% CI = 1.03-1.54, P = 0.02). However, no significant association in dominant model OR = 1.11, 95% CI = 0.80-1.52, P = 0.53 and additive model: OR = 1.24, 95% CI = 0.88-1.74, P = 0.21) (**Table 3**).

Publication bias

As shown in **Figure 5**, the publication bias of the individual studies was evaluated using the funnel plot. No visual publication bias was found in the funnel plot for CYP11B2 -344C/T gene polymorphism and coronary artery disease.

Discussion

The renin-angiotensin-aldosterone system (RAAS) plays an important role in cardiovascular homeostasis and diseases of the cardiovascular system [16]. The enzyme aldosterone synthase is the key rate-limiting enzyme in the final step of aldosterone synthesis [17]. Therefore, the CYB11B2 gene expression level is the key factor to regulate aldosterone secretion [18]. Neal suggested that both LV hypertrophy and decreased baroreflex sensitivity are well-established predictors of morbidity and mortality from MI, raising the possibility that the -344C/T polymorphism may represent an independent cardiovascular risk factor [19]. Previous studies have suggested the -344C/T polymorphism (rs1799998) in the associated with the risk of

Table 3. Subgroup analysis of CYP11B2 -344C/T polymorphism and CAD in all genetic models

Caterory	Allelic model		P for I^2	Dominant model		P for I^2	Recessive model		P for I^2	Additive model		P for I^2
	OR (95% CI)	I^2 (%)		OR (95% CI)	I^2 (%)		OR (95% CI)	I^2 (%)		OR (95% CI)	I^2 (%)	
Ethnicity												
Asians	1.16 (1.00-1.35)	0	0.69	1.11 (0.80-1.52)	0	0.97	1.26 (1.03-1.54)	0	0.78	1.24 (0.88-1.74)	0	0.97
non-Asians	0.99 (0.90-1.07)	48	0.1	1.13 (0.66-1.93)	90	<0.0001	0.93 (0.82-1.06)	0	0.57	0.94 (0.71-1.24)	56	0.06

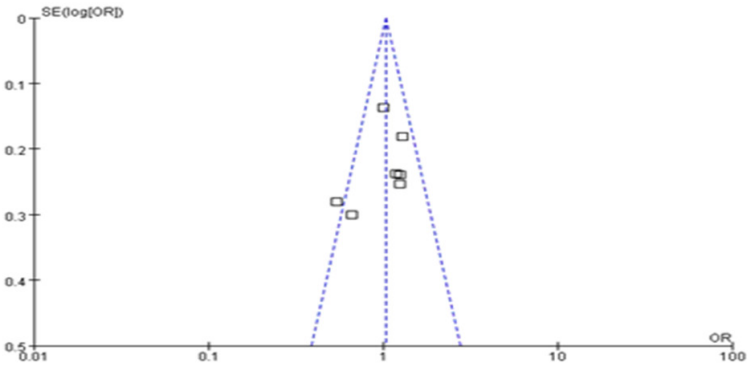

Figure 5. Funnel plot for publication bias tests. Each point represents a separate study for the indicated association. Log or represents natural logarithm of OR. Vertical line represents the mean effects size.

coronary heart disease [12, 14]. Aarno Hautanen find that smoking and dyslipidemia are more potent risk factors for non-fatal MI in males who have the -344C/T allele of CYP11B2 [1]. Sharma also find the CYP11B2 -344C>T polymorphism has been associated with the progression of atherosclerotic plaque size in the carotid artery [20]. However, other studies have failed to confirm such an association [6-8, 15, 21-24].

Therefore, we conducted a meta-analysis on all published eligible studies via collecting summary statistics on the association of between CYP11B2 and CAD. Present meta-analysis reveals a negative correlation between CYP11B2 genetic polymorphisms and increased risk for CAD under all of the genetic model (allele model: OR 1.03, 95% CI 0.95-1.10, P = 0.49; dominant model: OR 1.13, 95% CI 0.77-1.66, P = 0.54; recessive model: OR 1.02, 95% CI 0.92-1.14, P = 0.69; additive model: OR 1.03, 95% CI 0.89-1.21, P = 0.68). On subgroup analysis by ethnicity of study population, no evidence of association was also found in all genetic models in Caucasians. However, in Asians in some models, -344T>C polymorphism in the CYP11B2 gene might be associated with CAD.

Current Meta-analysis admittedly harbors some limitations. Firstly, the studies included for the analysis were small (n = 7). Large-scale studies on the association between CAD and CYP11B2 -344C/T gene polymorphism were still relatively inadequate. Secondly, the CYP11B2 expression level was influenced not only by the CYP11B2 344C/T gene polymorphism, but also by other genetic and environmental factors such as sympathetic nerve activation, inflammation state etc. Thirdly, heterogeneity might exist, due to the diverse study designs, ethnic differences, sample sizes, genotyping methods and other risk factors such as age, body mass index, and premeditation in the individual studies not well matched yet. Lastly, publication bias might also exist in our Meta analyses since studies with negative results are harder to get accepted than those with positive findings.

In conclusion, due to the limitations above, the present meta-analysis provides evidence that CYP11B2 -344C/T polymorphism was not associated with genetic susceptibility of CAD based on the current published studies. It might be associated with susceptibility to CAD in Asians in some model. However, further studies with larger sample sizes are needed to be conducted to obtain a more representative statistical analysis, due to the limitations mentioned above.

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Disclosure of conflict of interest

None.

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