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Original Article

Lack of association of CYP11B2-344C/T polymorphism with essential hypertension: a meta-analysis

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Abstract: Objective: A meta-analysis was carried out to evaluate the correlation between CYP11B2-344C/T polymorphism and essential hypertension susceptibility. Methods: By retrieving relevant databases and collecting domestic and international literatures about the correlation between CYP11B2-344C/T polymorphism and essential hypertension, the quality of literature were evaluated according to NEWCASTLE-OTTAWA case-control study quality rating scale (NOS). RevMan 5.0 was used to select the best genetic model, analysis the heterogeneity, calculate combined OR and the 95% CI. Results: 8532 subjects were included in this study. Compared with the control group, the OR (95% CI) values of dominant model, recessive model, and additive model were 1.01 (95% CI: 0.81~1.25), 1.03 (95% CI: 0.83~1.19) and 1.10 (95% CI: 0.93-1.29). Conclusion: There is no evidence to confirm that CYP11B2 (-344C/T) polymorphism is associated with susceptibility of essential hypertension.

Keywords: CYP11B2, polymorphism, essential hypertension, meta-analysis

Introduction

Essential hypertension is a complicated disorders resultsing from interaction between genetics and enviromental factors [1-3]. There were two ways of analyzing the correlation between gene polymorphism and essential hypertension. One was calculating the odds ratio (odds ratio, OR) of gene in case and control groups. The other was calculating genotypes of standardized mean difference (standardized mean difference, SMD) between systolic and diastolic blood pressure [4]. CYP11B2 was the hot topic for susceptibility gene of essential hypertension and previous studies suggested that the there was no correlation between gene polymorphism and susceptibility of essential hypertension in Chinese Han people [5-10]. However, the sample size and the results were inconsistent among the previous studies.

In recent years, there were many published papers to further explore the correlation between CYP11B2 gene polymorphism and hypertension [11-15]. In this study, these studies were collected at home and abroad, and evaluated the effect of CYP11B2-344C/T polymorphism on essential hypertension susceptibility by meta-analysis methods.

Materials and methods

Retrieval approaches and strategies

We retrieved PubMed, SCIRUS search engine, CNKI, VIP electronic databases, and collected relevant literatures. The key words were: "essential hypertension" and "CYP11B2" and "polymorphism". We retrieved documents which was eligible retroactively so as not to miss the relevant literatures. Retrieving ended on December 31, 2014.

Inclusion criteria

(1) Studies published at home and abroad or dissertation database contains independent case-control, cohort or status research.

(2) Studies including the analysis between CYP11B2 polymorphism and susceptibility of essential hypertension or blood pressure in Chinese Han people.

(3) Providing detailed genotype data (wild-type, heterozygous mutation, homozygous mutant number were all indispensable in each group).

(4) The results of the most recent posts were included if there were more researches based on the same population.

Table 1. The characteristics of included studies

Authors	Publication Year	Country	Ethnicity	Genotype						Allele				HWE	NOS
				EH patients			Control subjects			EH patients		Control subjects			
				TT	TC	CC	TT	TC	CC	T	C	T	C		
Xue et al.	2009	China	Asian	122	94	29	145	103	29	338	154	393	61	YES	6
Zhang et al.	2003	China	Asian	78	56	2	58	46	6	212	60	162	58	YES	5
Yuan et al.	2002	China	Asian	42	55	11	72	65	9	139	77	209	83	YES	6
Wang et al.	2004	China	Asian	58	41	7	52	42	4	157	55	146	50	YES	6
Sun et al.	2004	China	Asian	63	69	15	53	47	10	195	99	153	67	YES	6
Peng et al.	2010	China	Asian	74	62	12	88	47	6	210	86	223	59	YES	5
Niu et al.	2007	China	Asian	77	84	21	89	84	16	238	126	262	116	YES	8
Hua et al.	2006	China	Asian	114	179	52	70	73	13	407	283	213	99	YES	4
Hu et al.	2003	China	Asian	60	41	7	61	38	4	161	55	160	46	YES	4
Hu et al.	2006	China	Asian	235	152	34	107	81	19	622	220	295	119	YES	6
Gong et al.	2011	China	Asian	102	88	10	108	70	14	292	108	286	98	YES	4
Cheng et al.	2009	China	Asian	118	102	24	23	34	3	338	150	80	40	YES	3
Chen et al.	2011	China	Asian	261	216	33	269	206	35	738	282	744	276	YES	6
Wu et al.	2008	China	Asian	168	133	23	164	121	20	469	179	449	161	YES	7
Gu et al.	2004	China	Asian	237	227	39	236	214	53	701	305	686	320	YES	8
Luo et al.	2011	China	Asian	43	35	17	46	36	18	126	74	128	72	YES	5
Munshi et al.	2010	Idia	Asian	173	179	51	112	195	87	525	281	419	369	YES	8
Sia et al.	2012	China	Asian	268	209	37	91	85	16	745	283	267	117	YES	7

Exclusion criteria

(1) Review articles. (2) The reports repeated the same population. (3) The frequency distribution of gene loci cannot be obtained. (4) Diagnostic criteria were different from other studies. (5) Genotype distribution in the control group did not meet the Hardy-Weinberg (HW) equilibrium.

Classification of case-control studies

The included studies were scored according to NEWCASTLE-OTTAWA case-control study quality rating scale (NOS). The included literatures which scored less than 6 points were classified as Class B literatures.

Quality control of process

Documents were retrieved by two independent researchers, and trade-offs were determined according to the standard; in case of disagreement, another researcher participated to review and make a decision. In first screening, titles and abstracts were read, and literature may meeting the standards were reserved; in secondary screening, full texts of the documents were accurately retained, strictly in accordance with the standard to select qualified literature; for suspicious literature, search and supplementary information before deciding whether to exclude.

Data extraction

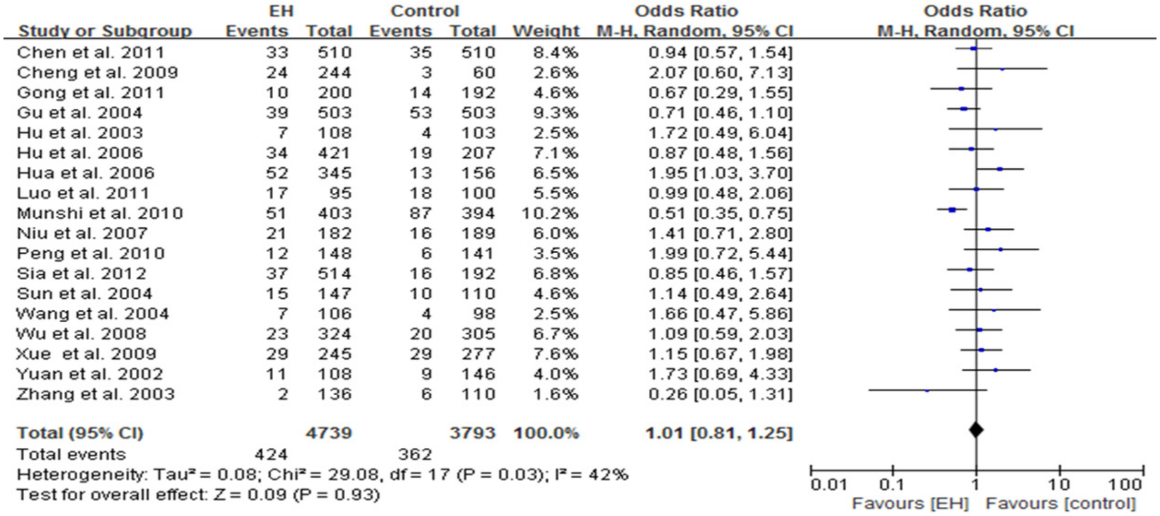
The following information of literature were extracted: title, the first author's name, year of publication, study type, study sample source and population, age, gender, sample size, frequency distribution of gene loci and the mean and standard deviation of genotype corresponding blood pressure.

Statistical analysis

Chi-square test was used to test HW equilibrium of genotypes in each study group, and P <0.05 was deemed as HW disequilibrium. RevMan 5.0 software was used for heterogeneity test; if there was heterogeneity, a random-effects model was used for data consolidation, otherwise a fixed-effects model was used to merge OR values and 95% confidence intervals (95% CI). RevMan 5.0 software was used to draw the forest plot and funnel plot.

Publication bias and sensitivity analysis

We omited one study at a time to perform sensitivity analysis. RevMan software was used to

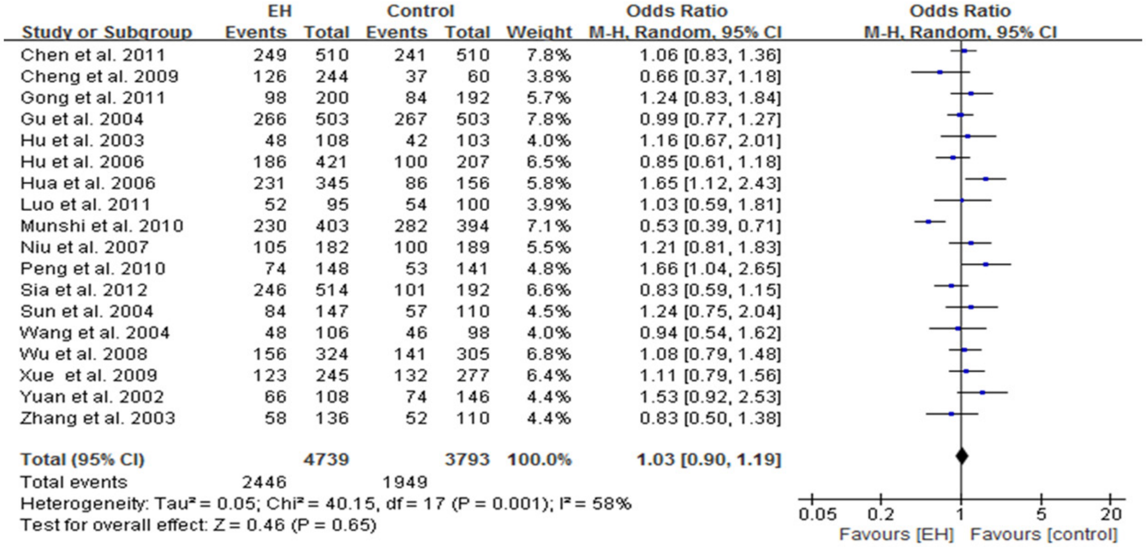


Study or Subgroup	EH Events	EH Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen et al. 2011	33	510	35	510	8.4%	0.94 [0.57, 1.54]
Cheng et al. 2009	24	244	3	60	2.6%	2.07 [0.60, 7.13]
Gong et al. 2011	10	200	14	192	4.6%	0.67 [0.29, 1.55]
Gu et al. 2004	39	503	53	503	9.3%	0.71 [0.46, 1.10]
Hu et al. 2003	7	108	4	103	2.5%	1.72 [0.49, 6.04]
Hu et al. 2006	34	421	19	207	7.1%	0.87 [0.48, 1.56]
Hua et al. 2006	52	345	13	156	6.5%	1.95 [1.03, 3.70]
Luo et al. 2011	17	95	18	100	5.5%	0.99 [0.48, 2.06]
Munshi et al. 2010	51	403	87	394	10.2%	0.51 [0.35, 0.75]
Niu et al. 2007	21	182	16	189	6.0%	1.41 [0.71, 2.80]
Peng et al. 2010	12	148	6	141	3.5%	1.99 [0.72, 5.44]
Sia et al. 2012	37	514	16	192	6.8%	0.85 [0.46, 1.57]
Sun et al. 2004	15	147	10	110	4.6%	1.14 [0.49, 2.64]
Wang et al. 2004	7	106	4	98	2.5%	1.66 [0.47, 5.86]
Wu et al. 2008	23	324	20	305	6.7%	1.09 [0.59, 2.03]
Xue et al. 2009	29	245	29	277	7.6%	1.15 [0.67, 1.98]
Yuan et al. 2002	11	108	9	146	4.0%	1.73 [0.69, 4.33]
Zhang et al. 2003	2	136	6	110	1.6%	0.26 [0.05, 1.31]
Total (95% CI)		**4739**		**3793**	**100.0%**	**1.01 [0.81, 1.25]**
Total events	424		362			

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 29.08$, df = 17 (P = 0.03); $I^2 = 42\%$

Test for overall effect: Z = 0.09 (P = 0.93)

Figure 1. Forest plot of hypertension susceptibility and CYP11B2 -344T/C polymorphism in a dominant model (CC *vs.* CT+TT), 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.



Study or Subgroup	EH Events	EH Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen et al. 2011	249	510	241	510	7.8%	1.06 [0.83, 1.36]
Cheng et al. 2009	126	244	37	60	3.8%	0.66 [0.37, 1.18]
Gong et al. 2011	98	200	84	192	5.7%	1.24 [0.83, 1.84]
Gu et al. 2004	266	503	267	503	7.8%	0.99 [0.77, 1.27]
Hu et al. 2003	48	108	42	103	4.0%	1.16 [0.67, 2.01]
Hu et al. 2006	186	421	100	207	6.5%	0.85 [0.61, 1.18]
Hua et al. 2006	231	345	86	156	5.8%	1.65 [1.12, 2.43]
Luo et al. 2011	52	95	54	100	3.9%	1.03 [0.59, 1.81]
Munshi et al. 2010	230	403	282	394	7.1%	0.53 [0.39, 0.71]
Niu et al. 2007	105	182	100	189	5.5%	1.21 [0.81, 1.83]
Peng et al. 2010	74	148	53	141	4.8%	1.66 [1.04, 2.65]
Sia et al. 2012	246	514	101	192	6.6%	0.83 [0.59, 1.15]
Sun et al. 2004	84	147	57	110	4.5%	1.24 [0.75, 2.04]
Wang et al. 2004	48	106	46	98	4.0%	0.94 [0.54, 1.62]
Wu et al. 2008	156	324	141	305	6.8%	1.08 [0.79, 1.48]
Xue et al. 2009	123	245	132	277	6.4%	1.11 [0.79, 1.56]
Yuan et al. 2002	66	108	74	146	4.4%	1.53 [0.92, 2.53]
Zhang et al. 2003	58	136	52	110	4.4%	0.83 [0.50, 1.38]
Total (95% CI)		**4739**		**3793**	**100.0%**	**1.03 [0.90, 1.19]**
Total events	2446		1949			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 40.15$, df = 17 (P = 0.001); $I^2 = 58\%$

Test for overall effect: Z = 0.46 (P = 0.65)

Figure 2. Forest plot of hypertension susceptibility and CYP11B2 -344T/C polymorphism in a recessive model (CC + CT *vs.* TT), 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.

draw a funnel plot to evaluate publication bias. All *P* values were two-sided test results, and the test level was P <0.05.

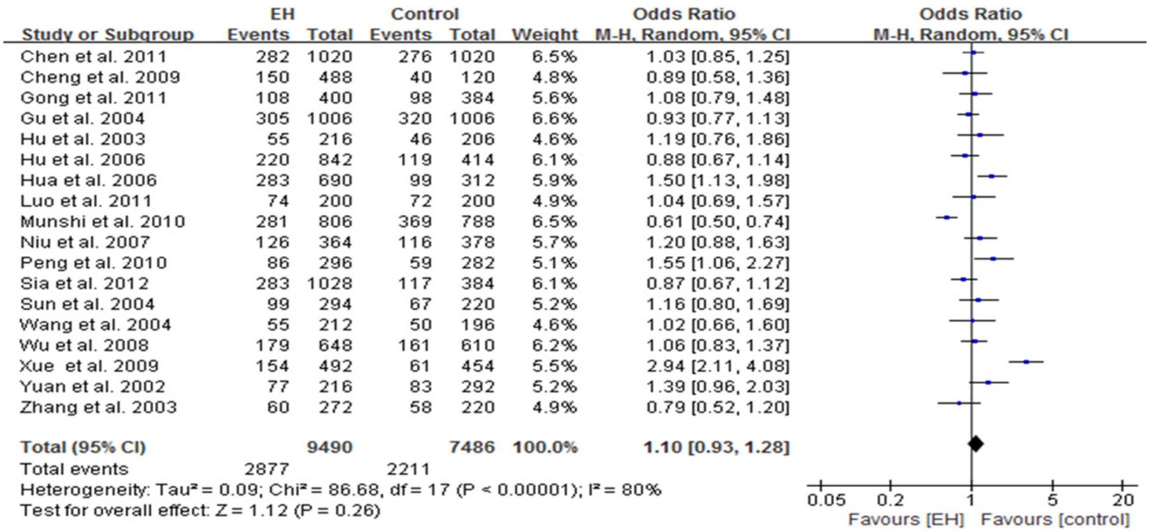
Results

The basic situation of included literature

A total of 18 documents [5-22] were included. Literature on the correlation between CYP11B2 polymorphism and essential hypertension susceptibility contained 4739 cases and 3793 controls (**Table 1**).

Meta-analysis

The distribution of genotype frequencies in control population selected for the study was in line with HW equilibrium; after heterogeneity test, data were merged to determine the best genetic model including dominant model, recessive model, and additive model. Meta-



Study or Subgroup	EH Events	EH Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen et al. 2011	282	1020	276	1020	6.5%	1.03 [0.85, 1.25]
Cheng et al. 2009	150	488	40	120	4.8%	0.89 [0.58, 1.36]
Gong et al. 2011	108	400	98	384	5.6%	1.08 [0.79, 1.48]
Gu et al. 2004	305	1006	320	1006	6.6%	0.93 [0.77, 1.13]
Hu et al. 2003	55	216	46	206	4.6%	1.19 [0.76, 1.86]
Hu et al. 2006	220	842	119	414	6.1%	0.88 [0.67, 1.14]
Hua et al. 2006	283	690	99	312	5.9%	1.50 [1.13, 1.98]
Luo et al. 2011	74	200	72	200	4.9%	1.04 [0.69, 1.57]
Munshi et al. 2010	281	806	369	788	6.5%	0.61 [0.50, 0.74]
Niu et al. 2007	126	364	116	378	5.7%	1.20 [0.88, 1.63]
Peng et al. 2010	86	296	59	282	5.1%	1.55 [1.06, 2.27]
Sia et al. 2012	283	1028	117	384	6.1%	0.87 [0.67, 1.12]
Sun et al. 2004	99	294	67	220	5.2%	1.16 [0.80, 1.69]
Wang et al. 2004	55	212	50	196	4.6%	1.02 [0.66, 1.60]
Wu et al. 2008	179	648	161	610	6.2%	1.06 [0.83, 1.37]
Xue et al. 2009	154	492	61	454	5.5%	2.94 [2.11, 4.08]
Yuan et al. 2002	77	216	83	292	5.2%	1.39 [0.96, 2.03]
Zhang et al. 2003	60	272	58	220	4.9%	0.79 [0.52, 1.20]
Total (95% CI)		**9490**		**7486**	**100.0%**	**1.10 [0.93, 1.28]**
Total events	2877		2211			

Heterogeneity: Tau² = 0.09; Chi² = 86.68, df = 17 (P < 0.00001); I² = 80%

Test for overall effect: Z = 1.12 (P = 0.26)

Figure 3. Forest plot of hypertension susceptibility and CYP11B2 -344T/C polymorphism in an additive model (C *vs.* T), 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.

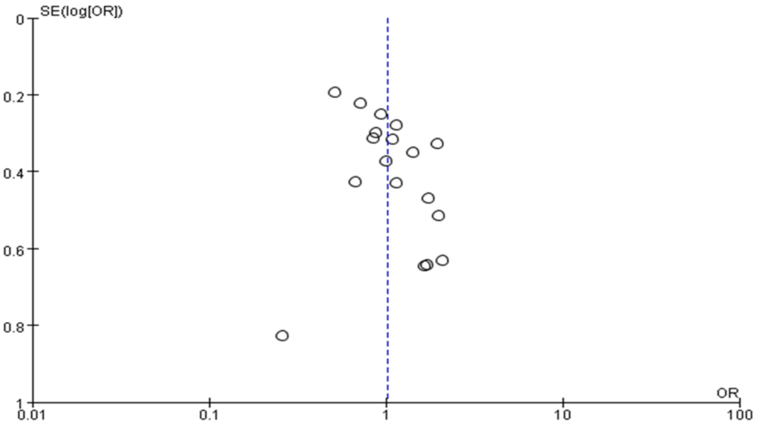


Figure 4. Funnel plot for publication bias test. Each point represents a separate study for the indicated association. Log OR represents the natural logarithm of OR. The vertical line represents the mean effects size.

analysis showed that -344C/T polymorphism was not associated with essential hypertension susceptibility (**Figures 1-3**).

Publication bias and sensitivity analysis

Quality evaluation of 18 literatures based on NOS standard showed that 11 literatures were classified as A and 7 articles were classified as Class B. First of all, the Class B documents were removed and meta-analysis was performed again. The results showed that the effect of the loci on essential hypertension susceptibility had no genetic effects, which was consistent with the previous results. We also omitted one study at a time and did not found significant changes for the OR value, indicating that the meta-analysis results were reliable. Begg's test was used to test publication bias; the results showed that its quantitative Kendall correlation coefficient was not statistically significant (Z = 1.04, P = 0.123). The funnel plot also suggested no publication bias (**Figure 4**).

Discussion

Aldosterone synthase plays an important role in renin-angiotensin-aldosterone system which regulates blood pressure, with the activity of 1lβ- hydroxylase, 18-hydroxylase and 18-oxidase. It is the cytochrome P450 oxidase in mitochondrial; its coding gene CYP11B2 is located on chromosome 8 (8q22). CYP11B2 is the hot spot for essential hypertension susceptibility genes. In this study, 18 studies on the correlation between CYP11B2-344C/T polymorphism and essential hypertension were collected, including a total of 8532 cases; the effect of the variability on primary hypertension susceptibility was studied by meta-analysis. The results show that, CYP11B2 (-344C/T) polymorphism was not associated with hypertension, although aldosterone is an important intermediate link between blood pressure and CYP11B2 (-344C/T) gene. The binding rate of -344C with SF-1 is four times higher than that of -344T, which can promote the synthesis and secretion of aldosterone. In addition to regulating blood pressure by water and salt metabolism, aldosterone also can affect blood pressure levels through the regulation of insulin receptor expression and glucose transporter. Li et al. [23] found that CYP11B2 (-344T/C) C allele can increase aldosterone levels, reduce B cell function and decrease the sensitivity of insulin, may affecting the level of blood pressure. Population-based polymorphism studies of this gene are still controversial; Davies et al. [24] consider that urinary aldosterone level is the intermediate factor between phenotype and genotype; individuals carrying the T allele have high urinary aldosterone content. On the contrary, Pojoga et al. [25] reported that plasma aldosterone levels of hypertension patients with CC genotype were significantly higher than that of patients with TC genotype, which was higher than that of the TT genotype. Meta-analysis of Sookoian et al. [26] showed that the gene polymorphism had no association with systolic and diastolic blood pressure. This study shows that the effect of the loci on susceptibility of essential hypertension has no genetic effects, which is inconsistent with the meta-analysis findings of Cheng and Xu [27]; the former conclusion is that C allele is correlated with the susceptibility of essential hypertension in Chinese population. This study has not yet found the correlation between the gene polymorphism and the susceptibility of essential hypertension. However, in the present study, we did not investigate other factors which will be included in the exploration of essential hypertension susceptibility, such as the linkage disequilibrium between -344C/T and CYP 11B1, they can work together to promote the synthesis of aldosterone, thus increase the risk of essential hypertension susceptibility. Therefore, further studies related to the interaction between genetics and environmental factors should be conducted.

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Disclosure of conflict of interest

None.

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