

## Original Article

# The association study on renalase polymorphism and hypertension: a meta-analysis

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**Abstract:** Hypertension is considered a multi-factorial disease since its development is affected by both genetic and environmental factors. Intensive efforts have been focused on identifying gene(s) related to hypertension. Renalase is a recently discovered protein that expressed in kidney, heart, liver, and brain that metabolizes catecholamines, regulation of blood pressure in humans and animals. A common missense polymorphism in the flavin-adenine dinucleotide-binding domain of human renalase (Glu37Asp) has recently been described. But the reported results are not always consistent. In this meta-analysis, we examined the association between (Glu37Asp) polymorphism (rs2296545) in renalase gene and risk of hypertension. Through a systematic literature search for publications between 2007 and 2014, we summarized the data from 4 studies on polymorphism (rs2296545) in renalase gene and risk of hypertension. We did not find any association of rs2296545 with risk of hypertension in dominant model (OR=0.64; 95% CI: 0.41-1.00), recessive model (OR=1.29, 95% CI: 0.95-1.75), co-dominant model (OR=1.38, 95% CI: 0.92-2.08), and allelic model (OR=1.19; 95% CI: 0.96-1.47). The results of the present study indicated that the renalase genetic polymorphism was not associated with risk of hypertension.

**Keywords:** Renalase gene, polymorphism, hypertension, meta-analysis

## Introduction

Hypertension is not only a chronic disease but a major risk factor for various diseases. Increased blood pressure is considered to be a major risk factor for cardiovascular diseases, stroke and end-stage renal disease [1]. The etiology and pathogenesis of hypertension are likely to comprise a multifactorial disorder resulting from inheritance of several susceptibility genes, as well as multiple environmental determinants [2, 3]. Epidemiological studies have suggested that the genetic factors contributed to blood pressure variation ranging from 30% to 50% within a population [4]. Some studies showed that a number of genes have been identified as having strong associations with the risk of hypertension or high blood pressure [5].

Renalase (gene name RNLS) is a novel, newly discovered monoamine oxidase enzyme discovered by Xu et al in 2005. They found that Renalase was secreted by the kidney and

metabolizes circulating catecholamines, Renalase activity is markedly augmented by an increase in plasma catecholamines, suggesting that renalase plays a role in degrading circulating catecholamines and regulates blood pressure and cardiac function [6, 7]. Basic research reviewed that reduction in renalase contributes to the occurrence of hypertension [7, 8]. Whose genes may contain sequence variations contributing to the inherited tendency for hypertension. Studies revealed that renalase is related to primary hypertension [9, 10].

It is likely that renalase is associated with hypertension and related disease. A common missense polymorphism in the flavin-adenine dinucleotide-binding domain of human renalase (Glu37Asp) has recently been described which is showed an association with hypertension, type 2 diabetes, Coronary Heart Disease and inducible ischemia [10-13]. But in Fava study [14], at variance with previous reports, found no association with hypertension related traits in a well-powered sample of middle-aged men and women participating.

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In view of the conflicting evidence and controversy, we conducted a meta-analysis on the published data to evaluate the association between the rs2296545 polymorphism and hypertension.

### Methods

#### *Search strategy*

In this report, we tested the hypothesis by performing a meta-analysis that the inter-individual susceptibility to hypertension is associated with genetic variation in renalase gene. We summarized reported case-control studies on rs2296545 SNP. Because a single study may have been underpowered in detecting the effect of low penetrance genes, a quantitative synthesis of accumulated data from published studies may enhance statistical power to detect the association between genetic polymorphisms and hypertension. A comprehensive literature search was independently performed by two investigators for all potential studies related to rs2296545 polymorphisms and EH published until January 2015 from PubMed, EMBASE, CBM (Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), VIP (Chinese) Database and Wanfang (Chinese) Database. Only studies in English and Chinese were selected. The following key words: (“renalase” or “rs2296545” or “Glu37Asp”) and (“polymorphism” or “variation” or “mutations”) and (“hypertension” or “essential hypertension” or “blood pressure” or “high blood pressure”) or relevant Chinese technical terms were used to search for relevant studies. In total, 7 records were identified as relevant to our initial search. Of the 7 studies, 1 studie examined the rs2296545 polymorphism with Chronic Kidney Disease, 1 study was conducted in cohort study, while 1 study only examined the rs2296545 polymorphism with ischemic stroke.

#### *Inclusion and exclusion criteria*

Eligible studies must meet the following inclusion criteria: (1) exploration of associations between renalase polymorphisms (rs2296545) and EH; (2) case-control studies; (3) focus on genotype frequencies of renalase rs2296545 polymorphism (4) hypertension was defined as systolic blood pressure (SBP)  $\geq 140$  mmHg and/ or diastolic blood pressure (DBP)  $\geq 90$  mmHg or

treatment with anti-hypertensive medication; (5) using healthy individuals as controls. The exclusion criteria were as follows: (1) a review, case report, editorial, or comment; (2) a duplicated study; (3) preliminary results that do not include renalase polymorphisms (rs2296545) or outcome; and (4) animal models researchers.

#### *Data extraction*

Date, name of the first author, year of publication, origin of country, ethnicity of the participants, sources of controls, diagnostic criteria for EH, numbers of cases and controls, and distribution of genotypes in the case and control groups. Disagreements were resolved by consensus.

#### *Statistical analysis*

Heterogeneity was assessed using Cochran's Q statistic and  $I^2$  method. The strength of the association between the enalase gene rs2296545 polymorphism risk was assessed by crude ORs with 95% confidence intervals (CIs), which comprised the following models: allele contrast (C versus G); dominant(GG versus CC + CG); and recessive (CG + CC versus CC); Codominant model(CC versus GG). Taking possible between-study heterogeneity into consideration,  $I^2$  statistics were used to estimate the degree of heterogeneity among the studies.  $I^2 > 50\%$  indicated an obvious between-study heterogeneity [20], and OR (95% CI) was calculated by the random effects model; Otherwise, the fixed-effect model (Mantel-Haenszel method) was adopted. Publication bias was detected by several methods. Asymmetry of the funnel plot indicated the possible publication bias. All statistical analyses were conducted using Stata 9.0 (Stata Corporation, College Station, TX).

### Results

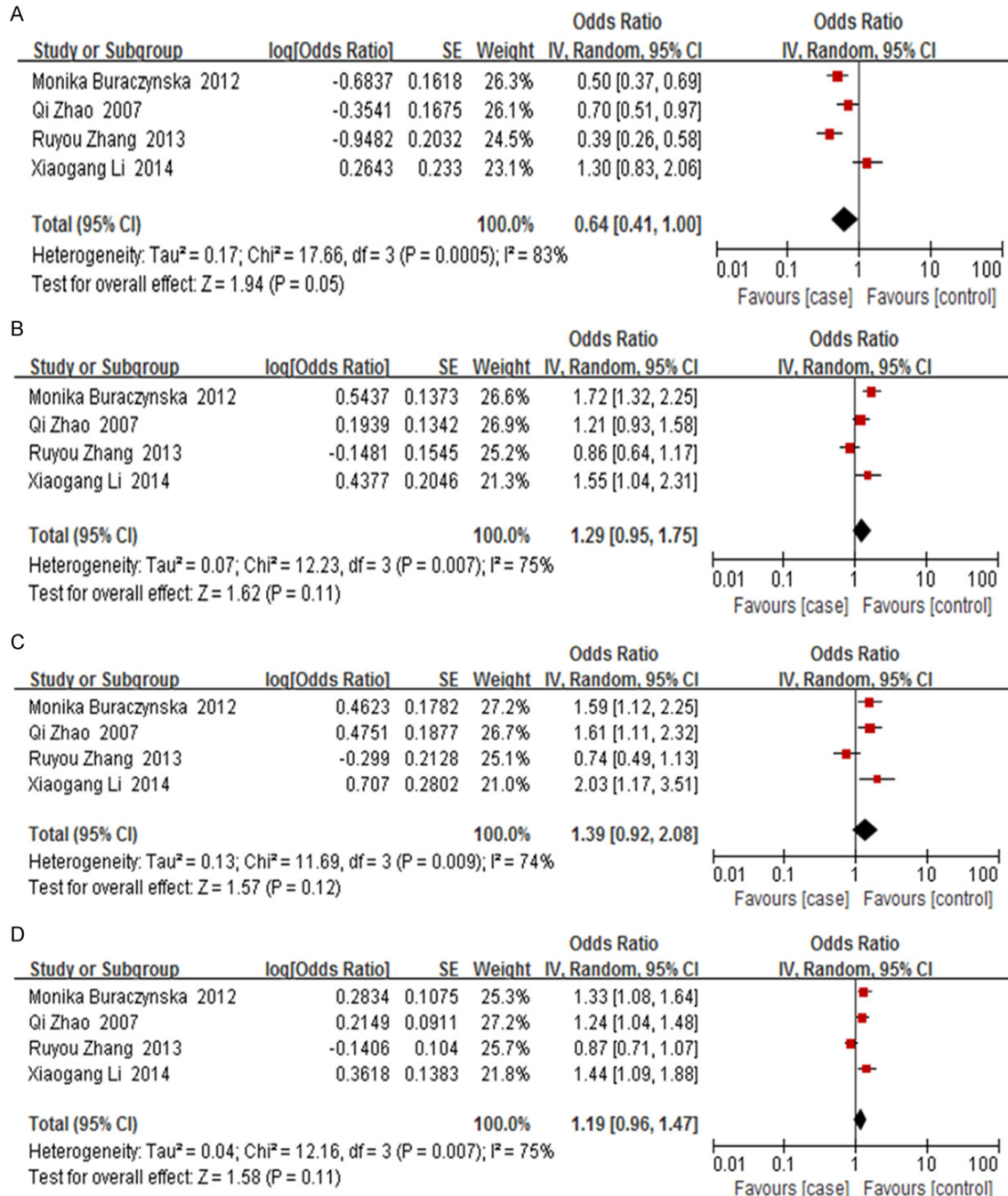
#### *Quantitative synthesis*

*Renalase rs2296545 polymorphism and EH:* A total of seven relevant studies (the studied include 2493 cases and 2205 controls) were selected to assessed the association between Renalase gene rs2296545 polymorphism and EH between the year 2007 to 2014. Four articles were written in English and no article was

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**Table 1.** Characteristics of case-control studies on Renalase rs2296545 polymorphism and hypertension risk included in the meta-analysis

First author	Year	Country	Racial/descent	Source of controls	N		Genotype distribution						Genotyping methods
					Case	Control	Case			Control			
							CC	GG	CG	CC	GG	CG	
Ruyou Zhang	2013	China	Asian	Hospital control	507	503	98	60	149	174	79	241	PCR-RFLP
Qi Zhao	2007	China	Asian	Population control	503	490	182	74	247	156	102	232	PCR-RFLP
Xiaogang Li	2014	China	Asian	Hospital control	802	812	78	31	93	67	54	111	PCR-RFLP
Monika Buraczynska	2012	Poland	Caucasians	Population control	681	400	265	136	280	108	88	204	PCR-RFLP



**Figure 1.** Forest plot of hypertension and rs2296545 polymorphism. A: Dominant model; B: Recessive model; C: Co-dominant model; D: Allelic model.

written in Chinese. Of all these articles, three were in Asian populations and 1 was in Caucasian populations. The baseline characteristics of the participants are shown in **Table 1**.

### *Meta-analysis*

In general, the overall results showed that Renalase gene rs2296545 polymorphism was not associated with EH in the meta-analysis of four genotype models. We did not find any association of rs2296545 with risk of hypertension in dominant model (OR=0.64; 95% CI: 0.41-1.00), recessive model (OR=1.29, 95% CI: 0.95-1.75), co-dominant model (OR=1.38, 95% CI: 0.92-2.08), and allelic model (OR=1.19; 95% CI: 0.96-1.47). The results of the present study indicated that the renalase genetic polymorphism was not associated with risk of hypertension (**Figure 1**).

### *Publication bias*

Funnel plot and Egger's test were performed to estimate to value the publication bias of the studies. The shapes of the funnel plots in all genetic models did not show any asymmetrical evidence. **Figure 2** shows the shapes of the funnel plots of four genetic model, which was used in the studies to examine the populations.

### **Discussion**

In the present study, we found that the renalase genetic polymorphism was not associated with risk of hypertension. This is the first study to clarify the relation between renalase gene polymorphism and hypertension.

Hypertension as the most common chronic disease is a multifactorial disease, which is one of important cardiovascular and cerebrovascular diseases risk predictors and closely related to the CHD and brain stroke [15, 16]. Recent years, the candidate gene for hypertension has been a special focus of attention, and the genetic susceptibility to hypertension had been studied so far [17-19].

Renalase (gene name RNLS) is an amine oxidase that responsible for metabolizing catecholamines, which is expressed in kidney, heart, liver, and brain. The renalase protein

consists of a secretory signal peptide, a flavin adenine dinucleotide-binding region, and an amine oxidase domain. The RNLS gene has a common missense polymorphism, rs2296545 C→G, resulting in a substitute from aspartic acid to glutamic acid (Asp37Glu) at codon 37, which is closely near C terminus of a deduced FAD-binding site of the renalase protein. This missense polymorphism might affect the function of the gene product. Renalase is involved in the regulation of salt and water excretion to influence blood pressure and cardiac function. People who possess the C allele were reported to be associated with an increased risk for the development of essential hypertension.

To date, several studies have investigated the association between rs2296545 polymorphisms and the risk of EH among different ethnic populations. Li et al [12] reported the frequency of allele C of rs2296545 in hypertensive patients was significantly higher than that in healthy controls (P=0.009, OR=1.436, 95% CI 1.095-1.883). Zhao et al [10] observed that the rs2296545 C allele were significantly higher in the cases than in the controls (both P values < 0.0001); Buraczynska M [13] found that the C allele of rs2296545 SNP was associated with hypertension (P < 0.01). Zhang et al [11] discovered that the recessive model showed a strong association of rs2296545 with ischemic stroke patients in hypertension subgroups (OR=1.927, 95% CI=1.012-3.669, P=0.046). But in Fava's study [14] the Renalase Asp37Glu polymorphism was not found to be associated with hypertension. Rs2296545 C>G genotype [OR: 0.988 (95% CI: 0.911-1.072, P=0.77) for the additive genetic model; 0.971 (0.843-1.118, P=0.68) for the autosomal recessive model and 0.994 (0.877-1.127, P=0.93) for the autosomal dominant model. This is a study in a Swedish urban-based cohort, including more than 5,000 subjects. Li et al [20] found that in the stroke patient the levels of rs2296545 did not reach statistical significance.

However, although several previous studies indicated that rs2296545 was associated with hypertension risk, we did not find any association of rs2296545 polymorphism with hypertension in all genetic models, which indicated that there is no association between renalase gene and hypertension. Meta-analysis is a powerful tool for pooling data from different studies

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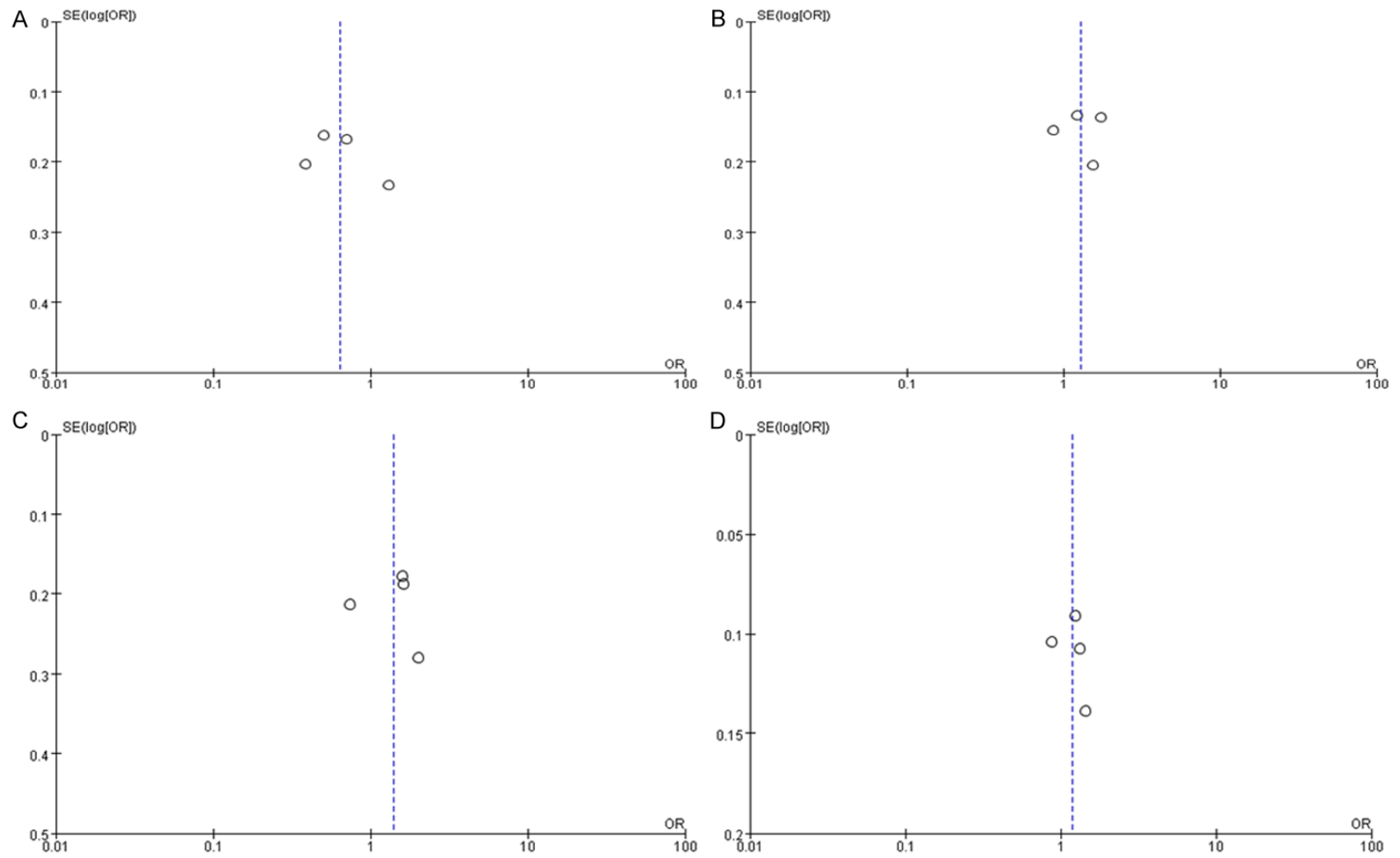


Figure 2. Funnel plot for publication bias tests. A: Dominant model; B: Recessive model; C: Co-dominant model; D: Allelic model.

to strengthen the statistical power. In the present study, we enrolled 2493 hypertension patients and 2205 control subjects. The sample size is large enough and the conclusion is credible.

The strengths of this meta-analysis include access to the individual participant data records from all population studies to date which met our entry criteria, resulting in a large sample size. We thus feel that publication bias is highly unlikely to be present in our review and meta-analysis.

A number of limitations deserve mention. On the one hand, we only enrolled the studies published in English. There may be several publications written in non-English that were not included in the present study. On the other hand, we only pooled the univariate analysis in the present study for most of the included studies did not report the multivariate analysis results.

In conclusion, the present study indicated that the renalase genetic polymorphism was not associated with risk of hypertension.

### Disclosure of conflict of interest

None.

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