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Angiotensinogen gene polymorphism and ischemic stroke in East Asians

A meta-analysis☆

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Abstract

OBJECTIVE: To investigate the association between angiotensinogen gene M235T polymorphism and ischemic stroke in East Asians.

DATA RETRIEVAL: A computer-based online search was conducted in PubMed, Google scholar, China National Knowledge Infrastructure database between January 1990 and April 2012 for relevant studies. The key words were angiotensinogen or AGT, polymorphism or genetic and ischemic stroke or cerebral infarction.

SELECTION CRITERIA: Case-controlled studies addressing the correlation between angiotensinogen gene M235T polymorphism and ischemic stroke in East Asians were included. The distribution of genotypes in the included studies was tested for Hardy-Weinberg equilibrium. Quality evaluation of the included studies was conducted by two physicians. Statistical analyses were carried out using Stata 12.0 software for meta-analysis. Heterogeneity tests, sensitivity analysis and publication bias were also conducted.

MAIN OUTCOME MEASURES: The association between angiotensinogen gene M235T polymorphism and ischemic stroke risk in East Asians was assessed.

RESULTS: Six relevant studies involving 891 patients with ischemic stroke and 727 controls were included in this meta-analysis. Results showed that there was a significant association between angiotensinogen gene M235T polymorphism and the risk of ischemic stroke in East Asians (T *vs*. M: odds ratio (*OR*) = 1.54, 95% confidence interval (*CI*) = 1.10–2.16; TT *vs*. MM: *OR* = 2.24, 95%*CI* = 1.37–3.66; TT *vs*. MT: *OR* = 1.76, 95%*CI* = 1.41–2.20; MM + MT *vs*. TT: *OR* = 0.57, 95%*CI* = 0.46–0.70). Sensitivity analysis confirmed that the study results were stable and reliable, with no publication bias.

CONCLUSION: The angiotensinogen gene M235T polymorphism is associated with ischemic stroke in East Asians, and the TT genotype and T allele are risk factors for ischemic stroke.

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Key Words

neural regeneration; brain injury; cerebrovascular disease; angiotensinogen; ischemic stroke; risk factor; meta-analysis; East Asians; genetic polymorphism; cerebral infarction; grants-supported paper; neuroregeneration

Research Highlights

(1) The association between angiotensinogen gene M235T polymorphism with ischemic stroke remains controversial, and no related meta-analysis in East Asians has been published.
(2) High-quality genetic polymorphism studies addressing the association between angiotensinogen gene M235T polymorphism and ischemic stroke in East Asians were summarized, and a quantitative

meta-analysis was performed using Stata 12.0 software. All the retrieved papers underwent sensitivity analysis for heterogeneity and publication bias, to ensure the reliability of the results.
(3) The meta-analysis showed that angiotensinogen gene M235T polymorphism is a risk factor for ischemic stroke in East Asians.

INTRODUCTION

Ischemic stroke is a complex disease of multiple etiologies and major clinical manifestations[1]. It is a major cause of death and disability worldwide. In the United States, it is estimated that there are 795 000 incident cases per year resulting in 134 000 deaths annually[2]. Over the past few years, a variety of risk factors have been identified to contribute to ischemic stroke, including hypertension, diabetes mellitus and hyperlipidemia[3-4]. In addition, epidemiological and animal-based studies provide strong evidence that genetic factors are important in the pathogenesis of ischemic stroke[5-6]. Growing evidence suggests that the activation of the renin-angiotensin system plays a key role in vascular inflammation, generation of reactive oxygen species and production of proinflammatory cytokines that are closely associated with cardiovascular disease and stroke[7-8]. Angiotensinogen is a component of the renin-angiotensin system. Angiotensinogen gene M235T polymorphism (a methionine to threonine amino acid substitution at codon 235 designated the M and T alleles) may elevate the serum level of angiotensinogen[9], thus causing hypertension, coronary heart disease, atrial fibrillation and heart failure[10-25]. Existing studies have demonstrated an association between M235T polymorphism and ischemic stroke[26-27]. However, the published findings are still controversial[28]. A search on the PubMed database identified a comprehensive genetic meta-analysis which found no association of M235T polymorphism with ischemic stroke risk in East Asians. In this study, we performed a meta-analysis to further investigate whether M235T polymorphism is associated with the risk of ischemic stroke in East Asians.

DATA SOURCES AND METHODOLOGY

Data retrieval

Two investigators (Jinsong Huang and Rong Zeng) independently identified relevant papers. Disagreements were discussed and a consensus was reached on all items. Computerized databases of PubMed, Google Scholar, and the China National Knowledge Infrastructure from January 1990 to April 2012 were searched using the following key words: angiotensinogen or AGT, polymorphism or genetic, and ischemic stroke or cerebral infarction. No limitations were applied for language and foreign language papers were translated. Full texts of all papers were obtained for analyses. References were scrutinized for other relevant studies.

Inclusion and exclusion criteria

Studies included in this meta-analysis met the following inclusion criteria: (1) published case-control studies pertaining to angiotensinogen gene M235T polymorphism and ischemic stroke in East Asians; (2) genotype frequencies in both cases and controls were available; (3) ischemic stroke was confirmed using CT or MRI; and (4) for multiple repeated studies, those recently published or with a large sample size were preferred. Exclusion criteria were: (1) original data were not available for the control group; (2) duplicate studies; (3) a review of the literature; and (4) raw data which did not provide adequate information.

Quality evaluation and data extraction

Two reviewers (Jinsong Huang and Rong Zeng) independently extracted the data and information from each eligible publication. The extracted information included the main authors, year of publication, location, race, total numbers in the case group and control group, and allele and genotype information for cases and controls. The allele frequency and Hardy-Weinberg equilibrium were obtained either directly from the articles or indirectly by calculation from the genotype distributions. The quality of the included literature was evaluated based on the genetic association and the guidelines for meta-analysis proposed by Little *et al* [29], as follows: (1) efficiency of the genotyping identification method; (2) data of the included subjects; (3) a mixed and stratified population; (4) statistical analysis. The maximum score of the evaluation scale was 26 points, a score of 1 to 8 was poor, 9 to 18 was moderate, and 19 to 26 was good.

Outcome measures

Genotype and allele distributions in the angiotensinogen gene M235T locus in cases and controls were analyzed.

Statistical analysis

The distribution of genotypes in the included studies was

tested for Hardy-Weinberg equilibrium (significance set at $P < 0.10$). The association between angiotensinogen gene M235T polymorphism and ischemic stroke risk was estimated by the odds ratio (*OR*) with 95% confidence interval (*CI*) for an allele comparison (T *vs*. M), a homozygote comparison (TT *vs*. MM), a heterozygote comparison (TT *vs*. MT), a dominant model (MM + MT *vs*. TT) and a recessive model (TT + MT *vs*. MM). The *Q*-test and I^2 quantitative analysis were performed to evaluate heterogeneities. If no heterogeneity was found among the studies ($P > 0.10$ or $I^2 < 50\%$), the pooled *OR* was estimated by the fixed effects model (Mantel-Haenszel method)[30], otherwise the random effects (DerSimonian and Laird method) model was used[31]. Sensitivity analysis was performed by comparing random effect model values with fixed effect model values to ensure the stability of the results. Begg's test[32] was used to measure publication bias. Analyses were performed using Stata 12.0 software (StataCorp, College Station, TX, USA). All *P* values were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Data retrieval results

A total of 734 documents were screened and twelve publications were identified which emphasized angiotensinogen gene M235T polymorphism and ischemic stroke. Two studies in Caucasians were removed, one duplicated publication was excluded, and three studies were also removed because they included other diseases (Figure 1). In the six included studies[26-28, 33-35], there were 891 patients in the ischemic stroke group, and 727 control subjects in the control group.

Baseline analysis and quality evaluation

The six included studies were all case-control studies with a population of Chinese in three studies[26, 33, 35], Korean in two studies[27-28] and Japanese in one study[34]. The characteristics of the populations in the included studies are shown in Table 1. Among the six case-control studies, four used population-based controls[26, 33-35] and two used hospital-based controls[27-28]. One study used gene chip technology for genotyping[34], and the others used restriction fragment length polymorphism-PCR with a restriction enzyme (*Tht*lll I). The quality of the included literature was evaluated in accordance with the genetic association study and meta-analysis guidelines proposed by Little *et al* [29]. The six studies were assessed as medium quality, scoring 12–18 points.

Meta-analysis results

Table 2 lists the main results of this meta-analysis. Overall, M235T polymorphism was associated with ischemic stroke risk in East Asians (T *vs*. M: *OR* = 1.34, 95%*CI* = 0.82–2.19, I^2 = 83.9%, $P_{heterogeneity}$ = 0.00; TT *vs*. MM: *OR* = 2.24, 95%*CI* = 1.37–3.66, I^2 = 0.0%, $P_{heterogeneity}$ = 0.67; TT *vs*. MT: *OR* = 1.76, 95%*CI* = 1.41–2.20, I^2 = 0.0%, $P_{heterogeneity}$ = 0.74; Dominant model: *OR* = 0.57, 95%*CI* = 0.46–0.70, I^2 = 0.0%, $P_{heterogeneity}$ = 0.61; Recessive model: *OR* = 4.25, 95%*CI* = 0.95–19.04, I^2 = 89.1%, $P_{heterogeneity}$ = 0.00; Figures 2–6). The genotype distributions among the controls of all studies were not consistent with Hardy-Weinberg equilibrium except for one study by Zhang *et al* [26] ($P = 0.77$).

Sensitivity analysis results

To compare differences and evaluate the sensitivity of the meta-analysis, we conducted a sensitivity analysis to evaluate the stability of the meta-analysis. Sensitivity analysis was performed by comparing the results of fixed and random effect models, and the results was not altered, suggesting the data in this meta-analysis were relatively stable and credible (Table 2).

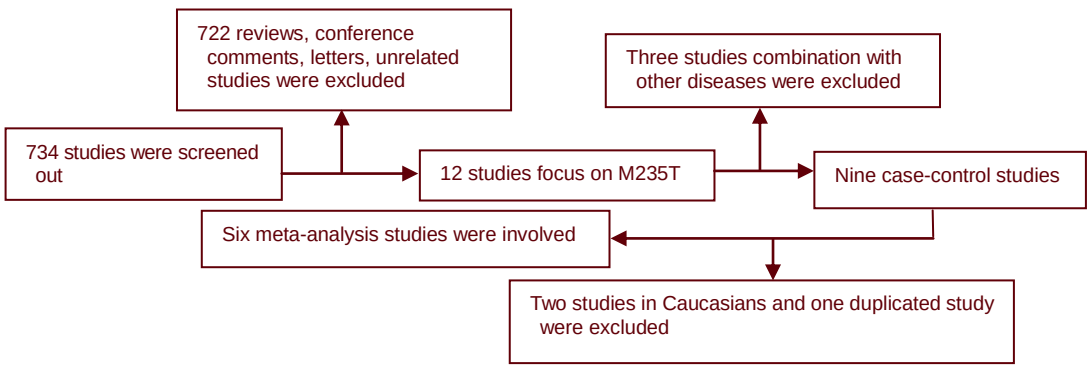

Figure 1 Flow diagram of study searching and selection process.

Table 1 Characteristics of the included studies for meta-analysis

Study	Year	Area	Race	Cases/controls	Allele for cases		Allele for controls		Genotypes for cases			Genotypes for controls		
					M	T	M	T	MM	MT	TT	MM	MT	TT
Zhang *et al* [26]	2001	China	Asian	75/48	33	137	38	58	6	21	48	8	22	18
Jea *et al* [28]	2001	Korea	Asian	100/100	38	162	46	154	2	33	65	0	41	59
Um *et al* [27]	2003	Korea	Asian	365/319	88	642	118	520	3	82	280	5	108	206
Liu *et al* [33]	2004	China	Asian	90/90	26	154	40	140	3	20	67	8	24	58
Nakase *et al* [34]	2007	Japan	Asian	147/94	58	236	22	166	16	15	102	19	15	60
Cui *et al* [35]	2008	China	Asian	114/76	41	187	43	109	2	37	75	3	37	36

Table 2 Summary odds ratio (*OR*) and 95% confidence interval (*CI*) of the included studies for meta-analysis

Genetic model	Type of model	Test of heterogeneity		Test of association		Test of publication bias		Sensitivity analysis	
		I^2 (%)	*P*	*OR*	95%*CI*	*z*	*P*	*OR*	95%*CI*
T *vs*. M	Random	83.9	0.00	1.34	0.82–2.19	1.13	0.26	1.41	1.17–1.69
TT *vs*. MM	Fixed	0.0	0.67	2.24	1.37–3.66	0.75	0.45	2.33	1.41–3.86
TT *vs*. MT	Fixed	0.0	0.74	1.76	1.41–2.20	0.75	0.45	1.76	1.41–2.21
Dominant model	Fixed	0.0	0.61	0.57	0.46–0.70	1.50	0.13	0.57	0.46–0.70
Recessive model	Random	89.1	0.00	4.25	0.95–19.04	0.38	0.71	9.34	6.31–13.81

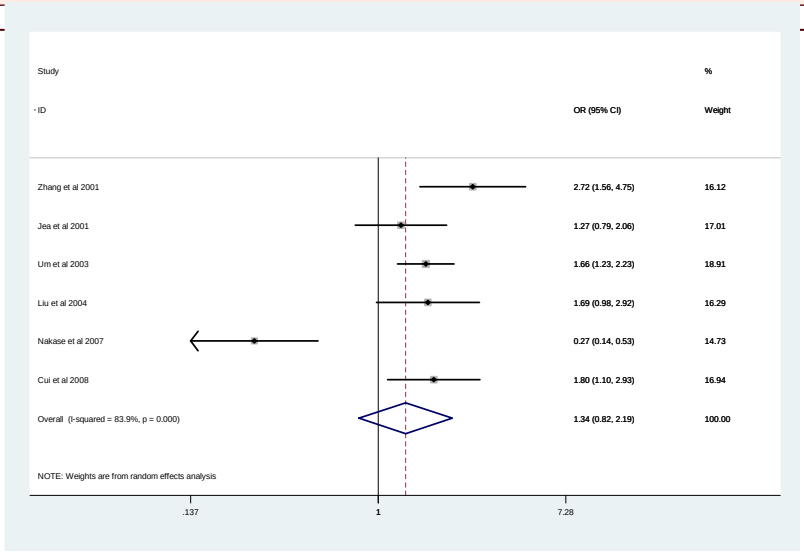

Figure 2 Association of M235T polymorphism with the risk for ischemic stroke in East Asians (T *vs*. M).

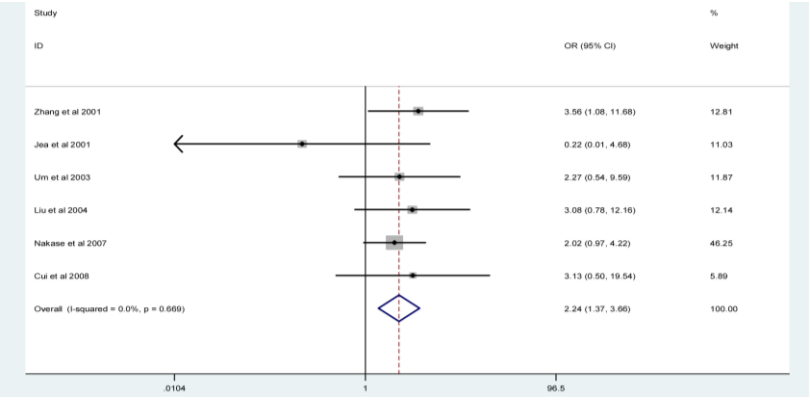

Figure 3 Association of M235T polymorphism with the risk for ischemic stroke in East Asians (TT *vs*. MM).

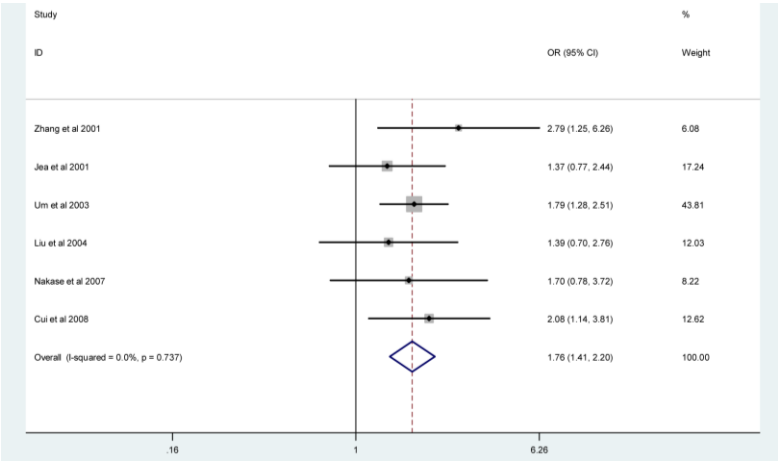

Figure 4 Association of M235T polymorphism with the risk for ischemic stroke in East Asians (TT *vs*. MT).

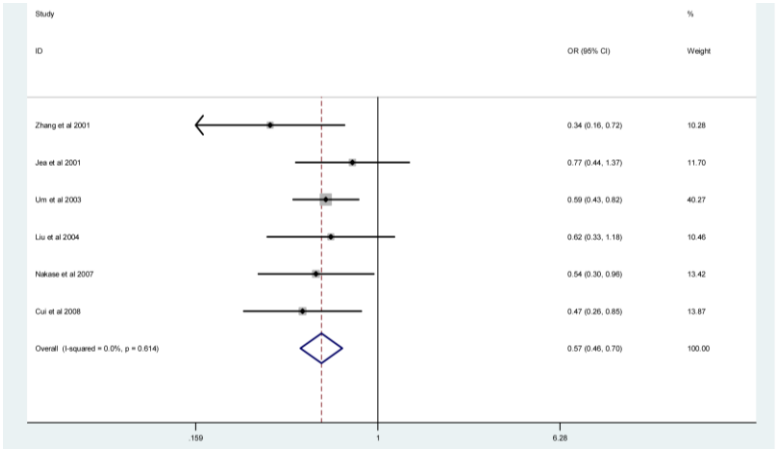

Figure 5 Association of M235T polymorphism with the risk for ischemic stroke in East Asians (dominant model: MM + MT *vs*. TT).

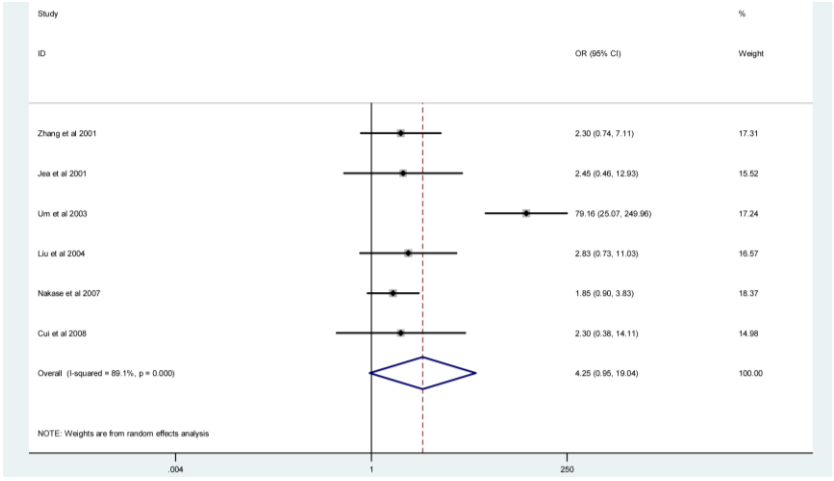

Figure 6 Association of M235T polymorphism with the risk for ischemic stroke in East Asians (recessive model: TT + MT *vs*. MM).

Publication bias results

Publication bias in the included papers was assessed by Begg's funnel plot (Table 2, Figure 7). Results showed that there was no publication bias ($P > 0.05$).

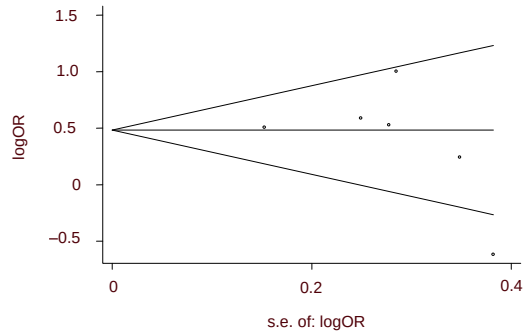

Figure 7 Begg's funnel plot of the comparison of T *vs*. M to determine publication bias.

The results showed that there was no publication bias.

DISCUSSION

Although angiotensinogen gene M235T polymorphism is involved in blood pressure regulation and cardiovascular disease, its contribution to ischemic stroke remains controversial. Barley *et al* [36] were the first to investigate the association between M235T polymorphism and ischemic stroke in Caucasians, and they did not found any significant association between M235T polymorphism and ischemic stroke risk. Subsequently, several studies, but not all, have confirmed a relationship between M235T polymorphism and susceptibility to ischemic stroke. The current meta-analysis was performed to obtain a more adequate result by combining comparable studies, and increasing the sample size and statistical power. The present meta-analysis demonstrated a significant relationship between angiotensinogen gene M235T polymorphism and ischemic stroke. This meta-analysis provides evidence that the T allele and TT genotype are genetic risk factors for ischemic stroke in East Asians. Ethnic differences in genetic backgrounds and the environment in which study populations lived may explain previous discrepancies in the association of M235T polymorphism with ischemic stroke[37-42].

The mechanism underlying the association between angiotensinogen gene M235T polymorphism and ischemic stroke risk is still unclear. M235T polymorphism has been associated with elevated levels of angiotensinogen, with 235TT homozygotes having 10–20% more plasma angiotensinogen than 235MM individuals[43-44]. Angiotensinogen interacts with renin to produce angiotensin II. Angiotensin II triggers vascular cell apoptosis and contributes to vascular remodeling in the ischemia-reperfusion process[45], thus rendering the vasculature more vulnerable to adverse cerebrovascular remodeling after ischemic stroke. In addition, stroke is multifactorial in nature, and multiple candidate gene variants play a synergistic role in determining the overall risk[46]. The haplotypes of angiotensinogen 174T/235M/-6A, angiotensinogen 174T/235T/-6G, angiotensinogen 174T/235T/-6A and angiotensinogen 174M/235T/-6A can synergistically increase the risk of ischemic stroke[47].

Some limitations of this meta-analysis should be considered when interpreting the results. First, the results may be affected by additional confounding factors, such as gender and age, but gender-related and age-related subgroup analysis could not be investigated because of incomplete data. Second, the random effects model was used in this meta-analysis and the results must be interpreted with caution. Additionally, there may be other eligible studies that were not published and indexed by electronic databases[48-50].

In conclusion, despite the above-mentioned limitations, this meta-analysis suggests that M235T polymorphism is a risk factor for ischemic stroke in East Asians. Further evaluation of the influence of gene polymorphism on ischemic stroke will require well-designed studies with large sample sizes.

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Author contributions: Jinsong Huang and Sheng Wang participated in the study concept, design and wrote the manuscript. Jinsong Huang, Rong Zeng, and Limin Lei were responsible for data integration and analysis. All authors approved the final version of the manuscript.

Conflicts of interest: None declared.

Author statements: The manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application/funding source disputations.

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