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AGT M235T polymorphisms and ischemic stroke risk: A meta-analysis

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ABSTRACT

Recently, the association between AGT M235T polymorphism and ischemic stroke (IS) has attracted widespread attention, and many investigations have been performed. However, the results were inconsistent. Therefore, we performed a meta-analysis to further evaluate the association between M235T and IS. All of the relevant studies were identified from PubMed, EMBASE, Chinese National Knowledge Infrastructure database (CNKI), Chinese Biological Medical Literature database (CBM), Chinese Wanfang and Chongqing VIP database up to January 2013. Statistical analyses were conducted with STATA software version 11.1. Odds ratios with 95% confidence interval were applied to evaluate the strength of the association. We performed the cumulative meta-analysis to assess the tendency of pooled OR over time. Heterogeneity was evaluated by *Q*-test and the I^2 statistic. The funnel plots and Egger's regression test were used to assess the publication bias. A significant association between AGT M235T polymorphism and IS was found under the dominant model (OR = 1.368, 95% CI = 1.070–1.749), recessive model (OR = 1.66, 95% CI = 1.310–2.103), over-dominant model (OR = 1.285, 95% CI = 1.085–1.523), co-dominant model (OR = 1.574, 95% CI = 1.276–1.942) and allele model (OR = 1.447, 95% CI = 1.207–1.735). Besides the Caucasian and the population-based controls, significant association could be found in the subgroup analysis of Asian and hospital-based controls. Results from cumulative analysis showed a tendency of significant association of this polymorphism with IS. However, the opposite trend was observed among Caucasians. Results from our meta-analysis indicated that the AGT M235T polymorphism might be a risk factor for IS among Asians, but not for Caucasians. More studies are required to further confirm our findings.

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1. Introduction

Stroke is a common cerebrovascular disorder and has been one of the leading causes of death and disability worldwide [1]. It has been reported by the World Health Organization (WHO) that a total of 6.15 million individuals die from stroke every year throughout the world [2], and about 15 million people suffer from ischemic stroke (IS) every year, of which 5 million were dead and 5 million became permanently disabled [3]. In china, over seven million people were estimated to be diagnosed with cerebrovascular disease, and IS accounted for 70% of the patients [4]. Accounting for over half of the stroke cases, ischemic stroke is one of the most common diseases that are associated closely with genes, the environment and their interactions [5–7].

The human AGT gene is located on chromosome 1q42–43 [8], and it encodes angiotensinogen, which is one of the components of the renin-angiotensin-aldosterone system (RAAS) [9]. Angiotensinogen is a circulating substrate, which is converted to angiotensin I by renin, and subsequently forms angiotensin II via angiotensin I-converting enzyme [10]. Angiotensin II is responsible for the regulation of systemic blood pressure, salt and water homeostasis and the maintenance of vascular tone, as well as increasing the levels of vasopressin and adrenocorticotropic hormone in the central nervous system [9]. Thus, it is speculated that the AGT gene is involved in the pathogenesis of stroke, mainly by affecting blood pressure.

The association between the M235T polymorphism (rs699) within the AGT gene and the risk of IS has attracted widespread attention, and a large number of investigations have been performed in recent years, but these studies presented inconsistent results. Sethi et al. [11] and Lalouschek et al. [12] observed no association between AGT M235T polymorphism and the increased susceptibility to IS. However, Tiret et al. [13] and Yamakawa-Kobayashi et al. [14] supported that the AGT M235T polymorphism was associated with the risk of IS. With a larger sample size, meta-analysis provides a good method for synthesizing data from individual studies on the same topic. To date, two meta-analyses of the association between AGT M235T polymorphism and IS have been conducted [11,15]. A meta-analysis by Wang et al. [15] with a sample size of 10,720

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demonstrated a significant association between AGT M235T polymorphism and the risk of IS among the Han Chinese population. However, a meta-analysis by Sethi et al. [11] with 8898 subjects failed to replicate the same result among Caucasians. Whether a relatively small sample size or differences among different ethnic populations that account for the controversial results remains unknown. Therefore, we performed a meta-analysis with a sample size of 16,030 to evaluate the association between AGT M235T polymorphism and the susceptibility of IS among overall individuals, in which we also investigated whether ethnicity and sources of controls could affect the association.

2. Materials and methods

2.1. Literature search and selection

All of the relevant studies were identified from PubMed, EMBASE, Chinese National Knowledge Infrastructure database (CNKI), Chinese Biological Medical Literature database (CBM), Chinese Wanfang and Chongqing VIP database with the following the search terms or their adjusted combinations: "angiotensinogen," "AGT M235T," "mutation," "variant," "polymorphism," "stroke," "brain infarction," "cerebral infraction" and "cerebrovascular disease" up to January 2013. We also hand-searched all cited references to find additional eligible studies. The language was limited to Chinese and English. We e-mailed authors for actual concrete data that were not presented in the article.

2.2. Selection criteria

Studies selected in this meta-analysis should conform to following criteria: (1) studies relate the AGT M235T polymorphism to susceptibility to ischemic stroke; (2) clear diagnosis for ischemic stroke; (3) applied case–control studies; (4) full-text articles; and (5) actual data for estimating an odds ratio (OR) with 95% confidence interval (CI). We excluded studies for (1) no original genotype data, (2) duplicate publications and (3) the study not conforming to the Hardy–Weinberg equilibrium (HWE).

2.3. Data extraction

Two investigators (Qin and Wei) screened the titles, abstracts and full text and extracted the data according to selection criteria independently. Other authors were consulted when two authors could not come to a conclusion. Any disagreements were resolved by consensus. We extracted the following data from each included study in a unified form: first author's name, time of publication, country, ethnicity of the study population, numbers of cases and controls, diagnostic criteria, genotyping methods, source of control groups and the distribution of genotypes and alleles between cases and controls.

2.4. Statistical analysis

Statistical analyses were conducted with STATA software version 11.1. We used χ^2 test to check the HWE for the genotype distribution of controls. Five genetic models selected in our study are as follows: dominant model (TT + MT vs. MM), recessive model (MT + MM vs. TT), over-dominant model (TT + MM vs. MT), co-dominant model (TT vs. MT) and allelic model (T vs. M). The OR and the 95% CI values were calculated to measure the strength of genetic interaction for the AGT M235T polymorphism with ischemic stroke. Heterogeneity between studies was computed by Q-test and I^2 statistics. We used a fixed-effects model when there was pool heterogeneity ($I^2 < 50\%, p > 0.05$); otherwise, the random-effects model was adopted. Subgroup analyses were carried out by ethnicity and source of controls for further heterogeneity explosion. Sensitivity analysis was adopted to examine the effect of excluding each study. The cumulative meta-analysis was performed to show the trend in the estimated risk effect. We used funnel plots and Egger's regression test to assess potential publication bias.

3. Results

3.1. Selection process

By searching with the keywords in the database of PubMed (58), EMBASE (113), CBM (33), CNKI (178), Chinese Wan Fang (51) and Chongqing VIP (44), a total of 477 articles were identified. Titles and abstracts of the publications generated by these searches were reviewed, and 25 potentially relevant studies were deemed suitable for further eligibility. After reviewing the full text, eight studies were excluded. Among them, five studies were duplicate publications and two articles was excluded owing to a lack of original genotype data. Also, one study did not follow HWE. Finally, seventeen articles [11,12,16–30] were enrolled in the meta-analysis on the association of the AGT M235T polymorphism with the risk of ischemic stroke.

3.2. Study characteristics

The final 17 studies included a total of 16,030 subjects, which consisted of 3842 IS patients and 12,188 controls. Table 1 shows the identified studies and their main characteristics, respectively. Among these studies, twelve were about Asian [16–26,29] and five were about Caucasian [11,12,27,28,30] populations. Ten studies [11,19–22,24,25,28,29] had hospital-based populations as controls, while seven [12,16–18,24,27,29]were based on the healthy population. The patients with ischemic stroke in seven [12,16,17,22,26,28,29] studies were confirmed by computed tomography (CT) and/or magnetic resonance imaging (MRI). Among those studies, patients in three studies [16,17,28] were also diagnosed according to the clinical symptoms of stroke. The diagnostic criteria applied in the eligible studies were as follows: the National Institute for Neurological Disorders and Stroke [29], the WHO International Classification of Diseases [11], the Chinese Medical Association Second National Conference on Cerebrovascular Disease 3rd Revised Diagnostic Criteria [24], the 3rd National Conference on Diagnostic Criteria for Cerebrovascular Disease [18], the Cardiovascular Health Study [27], the 4th National Conference on Diagnostic Criteria for Cerebrovascular Disease [19–21,23,25] and The Acute Stroke Treatment Criteria (TOAST) [30]. PCR-based genotyping methods were used for the determination of genetic polymorphism in sixteen articles. However, the genotyping methods in the study by Brenner et al. [28] were not mentioned. In addition, Table 2 shows the distribution of the AGT gene M235T genotypes and alleles between cases and controls and the p value for HWE. Genotype distributions in the controls of all studies were in agreement with HWE.

3.3. Quantitative synthesis

As shown in Table 3 and Fig. 1, the AGT (M235T) polymorphism was significantly associated with ischemic stroke in all genetic comparison models (dominant model: OR = 1.368, 95% CI = 1.070–1.749, $I^2 = 72.2$, $p = 0.000$; recessive model: OR = 1.66, 95% CI = 1.310–2.103, $I^2 = 75.8$, $p = 0.000$; over-dominant model: OR = 1.285, 95% CI = 1.085–1.523, $I^2 = 64.5$, $p = 0.000$; co-dominant model: OR = 1.574, 95% CI = 1.276–1.942, $I^2 = 64.6$, $p = 0.000$; allele model: OR = 1.447, 95% CI = 1.207–1.735, $I^2 = 84.2$, $p = 0.000$).

Subgroups were further investigated by ethnicity to observe the effect of the AGT M235T polymorphism on the risk of ischemic stroke. Significant associations were observed in the subgroup analysis by ethnicity among Asians (dominant model: OR = 1.762, 95% CI = 1.296–2.395, $I^2 = 18.4$, $p = 0.263$; recessive model: OR = 2.035, 95% CI = 1.665–2.487, $I^2 = 19.5$, $p = 0.253$; over-dominant model:

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