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Ethnic and Geographic Differences in the Association between Angiotensin II Type 1 Receptor A1166C Polymorphism and Essential Hypertension in China: A Meta-Analysis

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INTRODUCTION

Review question / Objective This study aimed to investigate the association between angiotensin II type 1 receptor (AT1R) A1166C gene polymorphism and the susceptibility to essential hypertension (EH) in China.

Condition being studied Essential hypertension (EH) shows clear familial aggregation, with genetic factors accounting for approximately 40% of its incidence. To date, several genes have been confirmed to be associated with EH. The renin–angiotensin system is one of the mechanisms underlying hypertension, and its main component, angiotensin II, exerts a pressor effect through the angiotensin II type 1 receptor (AT1R). The AT1R gene is located on the long arm of chromosome 3 (3q21–25) and plays a key role in mediating the biological effects of angiotensin II. More than 20 single-nucleotide polymorphisms (SNPs) have been identified in this gene, with A1166C (rs5186 A > C) being the most extensively studied. It has been reported that the A1166C mutation is associated with early-onset EH.
Due to the influence of factors such as race, ethnicity and region, the relationship between AT1R A1166C gene polymorphism and hypertension in the Chinese population remains controversial.

METHODS

Participant or population Participants were Chinese patients diagnosed with EH and without diabetes, myocardial infarction, cerebrovascular accidents or other serious diseases, and healthy individuals in the control group.

Intervention Not applicable.

Comparator Not applicable.

Study designs to be included This paper systematically collects relevant literature and uses meta-analysis to explore the association between AT1R A1166C gene polymorphism and susceptibility to EH.

Eligibility criteria The inclusion criteria were as follows: 1) research type was a case–control or cross-sectional study; 2) participants were Chinese patients diagnosed with EH and without diabetes, myocardial infarction, cerebrovascular accidents or other serious diseases, and healthy individuals in the control group; 3) diagnostic criteria for hypertension was systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, based on office blood pressure measurements following national or WHO/ISH guidelines [10] (office measurements were taken after at least 5 minutes of quiet rest, with the cuff positioned 2–3 cm above the elbow, and blood pressure was measured twice with a 1–2 minute interval; a third measurement was taken if the difference between the first two exceeded 5 mmHg; none of the studies used ambulatory or home blood pressure monitoring); and 4) research content was the association between AT1R A1166C gene polymorphism and EH.
The exclusion criteria were as follows: 1) deviation from Hardy–Weinberg equilibrium (HWE) in genotype and allele frequencies; 2) secondary hypertension cases; 3) incomplete or unavailable original data; 4) duplicate publications; and 5) animal experiments, reviews, case reports, comments or non-original research.

Information sources Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses instruction manual, five English-language databases – PubMed, the Cochrane Library, Embase, Web of Science and the National Library of Medicine – were systematically searched. Four Chinese-language databases were also searched: the China National Knowledge Infrastructure database, Wanfang Database, China Biomedical Literature Database and Weipu Chinese Science and Technology Journal Full-text Database.

Main outcome(s) The number of A1166C genotypes in the case and control groups is shown in Table 1. The cumulative percentages of AA and AC/CC genotype in the case group were 84.81% and 14.60%, respectively, whereas in the control group, they were 84.88% and 15.12%, respectively. The average proportion of the C allele in the case group was 9.50%, and in the control group, it was 8.42%.

Quality assessment / Risk of bias analysis The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the included case–control studies. The evaluation covered three aspects: 1) selection; 2) comparability; and 3) exposure or outcome. The total score of the scale was 9 points, with each item scoring 1 point. Studies scoring <5 were classified as low quality, and those scoring ≥5 were classified as high quality. Studies with a NOS score <5 were not included in the meta-analysis [11].
The methodological quality of the included cross-sectional studies was assessed using the 11-item criteria recommended by the Agency for Healthcare Research and Quality (AHRQ). Each item was answered with 'yes', 'no', 'unclear' or 'not applicable' to evaluate potential risks of bias across key domains, including source of information, participant selection criteria, definition of time period, consecutive inclusion, blinding of assessors for subjective components, quality assurance assessments, handling of exclusions, assessment and control of confounding, management of missing data, response rates and follow-up completeness (if applicable). The overall quality of each study was interpreted based on the comprehensive evaluation of these criteria.

Strategy of data synthesis Meta-analysis was performed using RevMan 5.3 software and STATA 16.0 (StataCorp LLC, College Station, TX, USA). The odds ratio (OR) was used as the effect index for count data, and the weighted mean difference was used for measurement data. Each effect size was expressed as a point estimate with a 95% confidence interval (CI). Heterogeneity among the included studies was assessed using Cochran's Q test and the I^2 statistic. The fixed-effects model (Mantel–Haenszel method) was applied when heterogeneity was low (I^2 0.1). When significant heterogeneity was observed ($I^2 \geq 50\%$ or $P \leq 0.1$), the random-effects model (DerSimonian–Laird method) was used. To assess the robustness of the results and explore potential sources of heterogeneity, sensitivity analysis was conducted using the leave-one-out method in Stata 16.0, whereby one study was removed at a time to observe the stability of the combined effect size. In addition, meta-regression analyses were performed to explore possible sources of heterogeneity by incorporating covariates such as age group, region and study design. The significance level for the meta-analysis was set at $\alpha = 0.05$.

Subgroup analysis The AC/CC (vs AA) genotype and C (vs A) allele were stratified according to ethnic and regional characteristics. The results are

shown in Table 2. Subgroup analysis of the AC/CC (vs AA) genotype and C (vs A) allele was performed according to different ethnic groups (Han, Yi, Kazakh, Tibetan). The results showed that there was a statistically significant difference in the AC/CC genotype between ethnic groups compared with the AA genotype (Z = 2.07, P = 0.04) (Supplementary Figure 7). The correlation between the AC/CC genotype and EH was statistically significant in Han and Yi populations (OR = 1.56, 95% CI: 1.09–2.24, P = 0.02; OR = 1.80, 95% CI: 1.02–3.19, P = 0.04). Compared with the A allele, the difference in the C allele between ethnic groups was also statistically significant (Z = 2.94, P = 0.003) (Supplementary Figure 8). The correlation between the C allele and EH in the Han and Yi populations was statistically significant (OR = 1.58, 95% CI: 1.11–2.24, P = 0.01; OR = 1.84, 95% CI: 1.01–3.34, P = 0.05).

A subgroup analysis of the AC/CC (vs AA) genotype and C (vs A) allele was also performed in different regions (southeast/east, southwest, north/northwest). The results showed that, compared with the AA genotype, the difference in AC/CC genotype distribution across regions was statistically significant (Z = 2.53, P = 0.01) (Supplementary Figure 9). However, no significant correlation between the AC/CC genotype and EH was found within individual regions. Compared with the A allele, the regional difference in the C allele was statistically significant (Z = 2.83, P = 0.005) (Supplementary Figure 10). The correlation between the C allele and EH in the north/northwest region was also significant (OR = 1.37, 95% CI: 1.02–1.83, P = 0.04).

Sensitivity analysis To assess the robustness of the results and explore potential sources of heterogeneity, sensitivity analysis was conducted using the leave-one-out method in Stata 16.0, whereby one study was removed at a time to observe the stability of the combined effectsize.

Country(ies) involved China.

Keywords angiotensin II type 1 receptor A1166C gene polymorphism; essential hypertension; susceptibility.

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