Effect of *Cholesteryl Ester Transfer Protein* Gene TaqIB Polymorphism on the Risk of Ischemic Stroke: A Meta-Analysis

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Background: The association between cholesteryl ester transfer protein (CETP) TaqIB polymorphism and ischemic stroke (IS) risk has generated conflicting results. To investigate whether the TaqIB polymorphism of the *CETP* gene was associated with the risk of IS, a meta-analysis was performed. *Methods:* Studies were retrieved by searching PubMed, Web of Science, the Chinese National Knowledge Infrastructure, the Chinese Wanfang Database, and the Chinese VIP Database before January 16, 2017. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to assess the association. Depending on the heterogeneity the fixed-effects model or the random-effects model was used. *Results:* A total of 6 case-control studies were identified with 1494 cases and 1370 controls. Overall, an association of CETP TaqIB polymorphism with IS was found in the 4 genetic models (B2B2 versus B1B1: OR = .63, 95% CI = .51-.79, $P < .001$; B1B2 + B2B2 versus B1B1: OR = .75, 95% CI = .64-.87, $P < .001$; B2B2 versus B1B2 + B1B1: OR = .70, 95% CI = .57-.85, $P < .001$; B2 versus B1: OR = .78, 95% CI = .70-.87, $P < .001$). In the subgroup analysis by ethnicity, similar risks were also observed in Asian population. *Conclusions:* This meta-analysis indicates that CETP TaqIB polymorphism is associated with IS risk, and the B2 allele is a protective factor for IS. **Key Words:** Ischemic stroke—CETP—polymorphism—meta-analysis.

Introduction

Stroke is a brain-vascular disease that is the major cause of death among people over 60 years and the second cause of death among those between 15 and 59 years old; thus, stroke has become a leading cause of death or disability in the world.[1,2] Approximately 5.5 million of patients have died from stroke-related factors and 5 million of them suffer from permanent disability, which has a direct impact not only on themselves, but also on their families and society.[3] Stroke is an acute loss of neurologic function caused by damaged brain tissue with 2 primary types: ischemic and hemorrhagic. Ischemic stroke (IS) is caused by arterial occlusion so that the flow of the cerebral blood is restricted; hemorrhagic stroke is caused by the rupture or leak in the cerebral vasculature.[4] Among the strokes, 87% of them are ischemic, which is by far the most common stroke.[4] Stroke is recognized as a complex multifactorial and polygenic disease, originating from a wide number of gene–environment and gene–gene interactions.[5] Environmental factors such as smoking, hypertension, dyslipidemia, diabetes mellitus, polycythemia, obesity, age, gender, and race may contribute to the development of IS.[6] Recently, several genes have been linked to the risk of IS such as *interleukin-1* (*IL-1*) gene,[7] *MTHFR* gene,[8] *APOE* gene,[9] and *TNF-α* gene,[10] but the contribution of susceptibility genes to IS is still obscure.

The *cholesteryl ester transfer protein* (*CETP*) gene is located on chromosome 16q21 that encodes the key plasma protein and mediates the transfer of esterified cholesterol from

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high-density lipoprotein (HDL) to apolipoprotein B-containing particles in exchange for triglycerides.[11,12] This gene has found many single-nucleotide polymorphisms, but the TaqIB (rs708272) that is located in nucleotide 277 of intron 1 is the most extensively studied.[13] It is reported that TaqIB is related to the risk of coronary artery disease,[14] type 2 diabetes mellitus,[15] longevity,[16] metabolic syndrome,[17] and myocardial infarction.[18]

So far, a number of studies have evaluated the association between TaqIB variant and IS risk, but the results are inconsistent. So we conducted this meta-analysis to assess the correlation.

Methods

Literature Search Strategy

A comprehensive search strategy proceeded using electronic databases, including PubMed, Web of Science, the Chinese National Knowledge Infrastructure, the Chinese Wanfang Database, and the Chinese VIP Database, and studies up to January 16, 2017 were searched for by using the following terms: ("'cholesteryl ester transfer protein'" or "'CETP'") AND ("polymorphism" or "polymorphisms" or "variant" or "variants" or "genotype" or "SNP") AND ("stroke" or "ischemic stroke" or "cerebral infarction" or "brain infarction" or "cerebrovascular disease"). In addition, we searched the references to identify other potential articles.

Inclusion and Exclusion Criteria

The studies were eligible for inclusion if they met the following criteria: (1) the relationship between the TaqIB polymorphism and IS risk is evaluated; (2) studies are based on case-control design; and (3) there is sufficient information to calculate the gene frequencies in 2 groups. Studies were excluded if one of the following existed: (1) case reports, reviews, lectures, editorials, or correspondence letters; (2) only recently published studies were ultimately selected if there were duplicated studies.

Data Extraction and Quality Assessment

Data were independently extracted by 2 reviewers with the standard protocol. Potential disagreements were resolved by discussion. To facilitate a general understanding of the eligible studies, in addition to genotype and allele data, investigators also extracted the first author's name, publication year, country of origin, ethnicity, genotyping method, Hardy–Weinberg equilibrium (HWE) of genotype of controls. The Newcastle–Ottawa Scale was used for assessing the quality of included studies.[19] The Newcastle–Ottawa Scale scores ranged between 0 and 9.

Statistical Analysis

Data management and statistical analyses were completed with the STATA software (version 14.0; Stata Corp, College Station, TX). Crude odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were used to assess the strength of the association between gene polymorphisms and IS susceptibility. The pooled ORs were performed for the homozygote model (B2B2 versus B1B1), dominant model (B1B2 + B2B2 versus B1B1), recessive model (B2B2 versus B1B2 +B1B1), and allele model (B2 versus B1). The heterogeneity among the results was tested by the I^2 statistic and was considered statistically significant at I^2 greater than 50%.[20,21] The fixed-effects model was used if there was no heterogeneity; otherwise, we used the random-effects model.[22,23] The distribution of the genotypes in the control population was measured for HWE using a goodness-of-fit chi-square test. Subgroup analyses based on the ethnicity were conducted. Publication bias was tested by Begg's and Egger's test.[24,25] Sensitivity analyses were performed by omitting 1 study each time to reflect the effect of the study on the pooled OR. When the *P* value of Egger's and Begg's test was less than .05, statistically significant publication bias might exist.

Results

Study Selection and Characteristics

In the light of our search criteria, there were 110 papers found to be relevant to the search words. Then, according to our inclusion and exclusion criteria, a total of 6 studies including 1494 cases and 1370 controls were brought into our final meta-analysis.[26-31] A detailed flow diagram of literature retrieval is shown in Figure 1. Of these studies, 4 studies were performed in Asian populations, 2 in Europeans. The main characteristics of eligible studies are shown in Table 1.

Quantitative Data Synthesis

The main results of this meta-analysis are summarized in Table 2. Overall, the CETP TaqIB polymorphism was associated with the risk of IS in the 4 genetic models (B2B2 versus B1B1: OR = .63, 95% CI = .51-.79, Fig 2; B1B2 + B2B2 versus B1B1: OR = .75, 95% CI = .64-.87, Fig 3; B2B2 versus B1B2 + B1B1: OR = .70, 95% CI = .57-.85, Fig 4; B2 versus B1: OR = .78, 95% CI = .70-.87, Fig 5).

After the studies where the genotype distribution in controls was not within HWE were excluded from the meta-analysis, the overall association between the CETP TaqIB polymorphism and IS was unchanged (Table 2).

To clarify the difference in ethnicity, subgroup analyses based on population group was performed in our study. In Asians, the results were similar with the total population. However, the results were inconsistent in