Association between Lipoprotein Lipase Polymorphism and the Risk of Stroke: A Meta-analysis

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Background: Several studies have studied the relationship between lipoprotein lipase (LPL) *Hind*III gene polymorphism and stroke susceptibility. However, the conclusions remain controversial. To clarify the association of *LPL* gene *Hind*III polymorphism and stroke susceptibility, we therefore conducted a comprehensive meta-analysis. *Materials and Methods:* The PubMed, Web of Science, EMBASE, and Google Scholar databases were systemically searched to indentify available studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated under the allelic, dominant, homozygous, heterozygous, and recessive models. The data were analyzed by using Stata 12.0 (StataCorp, College Station, TX). *Results:* Ten studies were enrolled, including a total of 2122 cases and 2235 controls. The overall results showed that LPL *Hind*III variants were associated with a decreased risk of stroke (G versus T: OR = .78, 95% CI = .70-.87, $P < .001$; GG + TG versus TT: OR = .76, 95% CI = .67-.87, $P < .001$; GG versus TT: OR = .69, 95% CI = .53-.90, $P = .006$; TG versus TT: OR = .78, 95% CI = .68-.90, $P < .001$; GG versus TG + TT: OR = .74, 95% CI = .57-.95, $P = .02$). Stratified analysis by ethnicity (Asian and non-Asian) indicated that LPL *Hind*III variants were associated with a decreased risk of stroke in the Asian population, but not in the non-Asian population. In the subgroup analysis by stroke subtype, the results suggested that LPL *Hind*III variants contributed to a decrease in both ischemic stroke and hemorrhagic stroke risks. *Conclusion:* Our meta-analysis suggested that LPL *Hind*III variants were associated with a decreased risk of stroke in the Asian population, but not in the non-Asian population. **Key Words:** Lipoprotein lipase—meta-analysis—polymorphism—stroke.

Introduction

Stroke is the second most common cause of morbidity and mortality worldwide.[1] There are strong pieces of evidences that environmental and genetic factors contribute to the risk of stroke.[2-7] Previous studies have shown that lipoprotein lipase (LPL) anomalies are correlated with hyperlipidemia, stroke, atherosclerosis, coronary heart disease, cancer, chronic kidney disease, and diabetes.[8-11] Recently, we have noted that *Hind*III variants in the *LPL* gene could influence the susceptibility to stroke.[12]

Studies on LPL produced by cells of the vascular wall, especially macrophages, have found that additional actions of this enzyme play a vital role in the promotion of foam cell formation and atherosclerosis.[13] Moreover, overexpression of LPL may cause insulin resistance (IR) syndrome,[14] which is associated with essential hypertension.[15] The human *LPL* gene, located on chromosome 8p22, spans approximately 35 kb and contains 10 exons, which encodes a mature of 448 amino acids.[16] *Hind*III is the most commonly studied polymorphism of the *LPL* gene. *Hind*III polymorphism located on intron 8 of the *LPL* gene has been reported to

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be associated with elevated triglyceride (TG) levels[17,18] and low high-density lipoprotein cholesterol (HDL-c) levels.[19,20] The more common T allele is related to a lower LPL activity compared with the G allele.[21] Therefore, the *Hind*III T allele may be associated with atherogenesis.

Currently, several case–control studies have investigated the relationship between LPL *Hind*III polymorphism and stroke in different populations. However, the results are controversial. Shimo-Nakanishi et al[12] firstly found that *Hind*III variants were associated with a reduced risk of stroke in the Japanese population. Subsequent case–control studies have shown inconsistent results: 4 studies support the protective effect of *Hind*III variants,[22-25] whereas 5 other studies report negative results.[26-30] Those inconsistent results may be attributed to the differences in sample size and ethnicity. We have therefore conducted a meta-analysis to gain more reliable results about the associations between *LPL* gene *Hind*III variants and the susceptibility to stroke.

Materials and Methods

Literature Search

Two investigators (T. He and J. Wang) searched the Web of Science, PubMed, EMBASE, and Google Scholar databases up to December 30, 2016, using the combinations of the following items: ("lipoprotein lipase" or "LPL") and ("cerebral infarction" or "stroke" or "brain infarction" or "cerebrovascular disease") and ("single nucleotide polymorphism" or "SNP" or "genetics" or "variant" or "polymorphism"). All literature searches were restricted to full texts written in English. We also manually searched the reference lists of relevant articles to obtain the other available publications.

Inclusion and Exclusion Criteria

The selected studies had to match the following inclusion criteria: (1) case–control or cohort study; (2) study evaluating the association between *LPL* gene *Hind*III polymorphism and the risk of stroke; (3) provision of sufficient genotype distributions of cases and controls to calculate the odds ratio (OR) and the 95% confidence interval (CI); (4) full-text publications; (5) inclusion of only those articles published in English in our meta-analysis; and (6) genotype distributions of the controls were in Hardy–Weinberg equilibrium. Moreover, case reports, reviews, abstracts or meta-analyses, animal studies, studies that do not have a case–control or a cohort design, and irrelevant articles were all excluded.

Data Extraction

Two investigators (T. He and J. Wang) independently extracted the information. Any disagreements were resolved by discussion between the 2 investigators. The following information was extracted from the selected studies: first author, year of publication, country, ethnicity, sample sizes of cases and controls, genotype number, age, gender, genotyping method, and Hardy–Weinberg equilibrium.

Statistical Analysis

The association between LPL *Hind*III polymorphism and stroke susceptibility was assessed from selected studies using ORs and 95% CIs. In this meta-analysis, 5 genetic models, such as allelic (G versus T), dominant (GG + TG versus TT), homozygous (GG versus TT), heterozygous (TG versus TT), and recessive (GG versus TG + TT) models, were analyzed for *Hind*III polymorphism. Heterogeneity was evaluated by I^2 statistics,[31,32] and I^2 values higher than 50% indicated that significant heterogeneity (no heterogeneity: $I^2 < 25\%$, moderate heterogeneity: $I^2 = 25\%$-50%) exist.[33] If significant heterogeneity existed, the random-effect model was used; otherwise the fixed model was adopted.[34] The potential publication bias was checked by a visual inspection of a funnel plot and the *P* value of Begg's test. The asymmetric plot and the *P* value of Begg's test below .05 were considered a significant publication bias.[35] To assess the stability of the results, a sensitivity analysis was conducted by omitting each individual study in turn from the all selected studies and reanalyzing the remainder. All statistical tests were carried out using Stata 12.0 (StataCorp, College Station, TX).

Results

Characteristics of the Selected Studies

Figure 1 graphically describes the flowchart of the selection process of identifying available articles. Totally, 10 studies with 2122 cases and 2235 controls were included in our meta-analysis.[12,22-30] Of those studies, 4 studies were performed in China,[23-25,27] 1 in Japan,[12] 1 in India,[22] 1 in Russia,[26] 1 in Mexico,[28] 1 in Sweden,[29] and 1 in Columbia.[30] In terms of ethnicity, 6 studies were carried out in the Asian population,[12,22-25,27] and the other 4 studies focused on the non-Asian population.[26,28-30] With respect to stroke subtypes, 3 studies focused on hemorrhagic stroke (HS),[23-25] and 7 studies focused on ischemic stroke (IS).[12,22,26-30] The primary characteristics and the genotype distributions of LPL *Hind*III polymorphism in the selected studies are listed in Table 1.

Association between LPL Hind*III Polymorphism and Stroke Susceptibility*

The relationship between LPL *Hind*III polymorphism and stroke susceptibility was analyzed in 10 independent studies. In the overall analysis, the results indicated that LPL *Hind*III variants were associated with a decreased risk of stroke (G versus T: OR = .78, 95% CI = .70-.87,