The HindIII and PvuII polymorphisms of lipoprotein lipase (LPL) gene reduce the risk of ischemic stroke (IS)

A meta-analysis

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Abstract

Background: Lipoprotein lipase (LPL) polymorphisms were suggested to be the risk factor for ischemic stroke (IS). However, controversial results were obtained. Our objective was to investigate the association of LPL polymorphisms at Ser447Ter, HindIII (+/−), and PvuII (+/−) with IS risk.

Methods: Literatures search were carried out on databases: PubMed, Web of science, the Cochrane database of system reviews, Chinese National Knowledge Infrastructure, and Embase. Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated to detect the relationship between LPL polymorphisms and the risk of IS.

Results: No significant association was detected between LPL Ser447Ter and IS in allelic, dominant, or recessive models (P > .05). Significant lower frequencies of allelic and dominant models of LPL HindIII (+/−) and PvuII (+/−) in cases were detected (HindIII (+/−): allelic model: P = .0002, OR[95%CI] = 0.80 [0.71, 0.90]; dominant model: P = .003, OR[95%CI] = 0.80 [0.69, 0.92]; PvuII (+/−): allelic model: P < .0001, OR[95%CI] = 0.75 [0.65–0.86]; dominant model: P = .02, OR[95%CI] = 0.67 [0.48–0.93]). And the recessive model of PvuII (+/−) was significantly associated with the IS risk (P = .01, OR[95%CI] = 0.71 [0.55–0.93]). Subgroup analysis stratified by ethnicity showed that the frequencies of allelic, dominant, and recessive models of HindIII (+/−), as well as dominant model of PvuII (+/−) were significant lower in Asian cases (HindIII (+/−): allelic model: P < .0001, OR[95%CI] = 0.69 [0.59, 0.79]; dominant model: P < .0001, OR[95%CI] = 0.69 [0.58, 0.83]; recessive model: P = .008, OR[95%CI] = 0.66 [0.51–0.84]), but not in Caucasian cases (P > .05). In addition, the frequencies of allelic and recessive models of PvuII (+/−) significantly decreased in Caucasian cases (P < .05).

Conclusion: the HindIII (+/−) and PvuII (+/−), but not the Ser447Ter might be the protective factors for IS.

Abbreviations: CI = confidence interval, IS = ischemic stroke, LPL = lipoprotein lipase, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: cerebral infarction, ischemic stroke, lipoprotein lipase, meta-analysis

1. Introduction

Ischemic stroke (IS) is one of the major causes of morbidity and mortality in adults over the world[11–4] Various factors including hypertension, lipid metabolism imbalance, diabetes, smoking, diet, obesity, insufficient physical activity, hemostatic disturbances, inflammation, and genetic factors were associated with increased IS risk.[11–14] Notably, hypertension was considered to be the most powerful, prevalent, and treatable risk factor for IS.[12,13] Both systolic blood pressure and diastolic blood pressure are independently related to stroke incidence. However, this factor could not completely explain the development of this disease. Recently, amount of specific gene variants refer to lipid metabolism were also reported to be susceptible risk factors for the development of IS.[14–16] which indicate the genetic factor might play an important role in IS risk.

Lipoprotein lipase (LPL) is an enzyme that plays a key role in lipoprotein metabolism.[17] The human LPL gene is located on chromosome 8p22, encodes a 448 amino acid protein.[18] Increasing number of studies has suggested LPL gene variants might contribute to the risk of IS.[19,20] And the most common polymorphisms that associated with IS risk should be the Ser447Ter, HindIII (+/−), and PvuII (+/−).[21,22] Shimo-Nakaniishi et al[23] and Jiang et al[24] have reported LPL Ser447Ter polymorphism was associated with the risk for IS. However, Velázquez Pereira et al found no association between LPL Ser447Ter polymorphism and IS.[22] For HindIII (+/−), several studies have shown significant association between HindIII (+/−) and IS.[15,24] However, no association was reported by Huang et al and Xu et al.[27,28] As for PvuII (+/−), Xu et al have suggested that PvuII (+/−) polymorphism was associated with lipid profile and IS.[28] However, other 2 studies reported no genetic association between PvuII (+/−) and IS.[29,30]

Due to the inconsistent and inconclusive results in the individual studies, we aim to get a more precise and
comprehensive estimation of the association between the LPL Ser447Ter, HindIII (+/-), and PvuII (+/-) polymorphisms and IS risk using meta-analysis.

2. Methods

2.1. Identification of relevant studies

Meta-analysis and systematic review of published literature was performed adhering to PRISMA 2009 guidelines. No Ethical Committee approval was necessary for this meta-analysis. A comprehensive literature search throughout PubMed, Web of Science, the Cochrane database of system reviews, Chinese National Knowledge Infrastructure, and Embase was confirmed to retrieve the genetic association studies of LPL gene polymorphisms and IS using following search terms: lipoprotein lipase, LPL, and cerebral infarction, CI, brain infarction, BI, cerebral stroke, ischemic stroke, IS, stroke, and “polymorphism,” “variant,” “mutation,” “single nucleotide polymorphism (SNP),” and “gene variation” before September 01, 2017. No language was limited.

2.2. Inclusion/exclusion criteria

Inclusion criteria: case–control or retrospective study designed; available data for genotype frequencies in cases and controls; and the frequency of allele in control group should be in Hardy–Weinberg equilibrium.

Exclusion criteria: Replicated studies, abstracts, letters, or reviews; and publications against to the inclusion criteria.

2.3. Data extraction

The data and information of each eligible publication was extracted by 2 reviewers (LMC and QL) independently. The following information from each study was extracted: first author, year of publication, ethnicity, numbers of cases and controls, mean age, gender, body mass index, hypertension, smoking, diabetes, systolic blood pressure, diastolic blood pressure, triglycerides, total cholesterol, high-density lipoprotein, low-density lipoprotein in cases and controls, and SNPs in each study. Disagreements were resolved by discussion.

2.4. Quality assessment

The study quality was assessed independently by LMC and XC by the following aspects: group selection, comparability, and assessment of outcome or exposure. The quality of each included article was assessed according to the Newcastle–Ottawa Scale. Any discrepancies in the assessment were resolved by discussion.

2.5. Statistical analysis

The Stata software (version 12.0; Stata Corp LP, College Station, TX) and Revman software (version 5.1; The Nordic Cochrane Centre, Copenhagen, Denmark) were used in meta-analysis. Combined odds ratio (OR) and 95% confidence intervals (CIs) were used to access the associations between LPL polymorphisms and IS risk. The statistical significance of the pooled ORs under different genetic models (allelic, recessive, and dominant models) were determined by Z-test and considered significant when \( P < .05 \). A test of heterogeneity was conducted using Cochran Q test and Higgins I-squared statistic. Significant heterogeneity among studies was defined as \( I^2 > 50\% \). And a random effect model was used. Otherwise the fixed effect model was applied \( (I^2 < 50\%) \). The effects of individual study on pooled results and the stability of results were assessed by sensitivity analysis. Begg and Egger test were used to assessed the publication bias.

3. Results

3.1. Study characteristics

After screening the database, a total of 629 records were identified. And 20 of additional records were also identified through cross screening. After reviewing the titles, abstracts, and full-texts, removing duplicated and irrelevant records, 23 eligible articles were included in the present study \( (22,23,27,30,37) \) (Fig. 1). Four studies were excluded for no available data \( (33,34,35,36) \). And, 2 studies reported the association between 3 LPL polymorphisms and IS \( (23,28) \). Four articles reported the association between 2 LPL polymorphisms and IS \( (22,27,30,37) \). For there were 2 different populations in the study conducted by Yue et al \( (37) \), we treated each group as an individual studies. Finally, a total of 19 studies were enrolled in present study. Among them, 14 studies with 2515 cases and 3324 controls were included for LPL Ser447Ter \( (22,24,28,37–45) \). Ten studies with 2109 cases and 2081 controls were included for LPL for HindIII (+/-) \( (22,23,25,28,30,37,46) \). And 6 studies with 786 cases and 896 controls were included for LPL PvuII (+/-) \( (22,23,27–30) \). The studies involved and their main characteristics were shown in Table 1. And the Newcastle–Ottawa Scale quality assessment of these included studies is provided in Table 2. All the included studies were of relatively high-quality (assessment score \( \geq 6 \)).

Figure 1. PRISMA flow chart of studies inclusion and exclusion.
| First author Year | Ethnicity | Case/control | Gender (M/F) (E/C) | Age (E/C) | Hypertension (Yes/No) (E/C) | Smoking (Yes/No) (E/C) | BMI (kg/m²) (E/C) | Diabetes (Yes/No) (E/C) |
|-------------------|-----------|--------------|-------------------|-----------|-----------------------------|------------------------|-------------------|------------------------|
| Baum 2006         | Chinese   | 246/336      | 134/112:152/184   | 70.7 ± 12.1:70.5 ± 5.9 | 162/58:202/134          | 108/183:126/210       | NA                | 75/171:59/277        |
| Fidani 2005       | Greece    | 98/100       | 50/48:53/47       | 75.8 ± 9.7:72.7 ± 6.1 | NA                        | NA                     | NA                | NA                     |
| Guan 2006         | Chinese   | 166/72       | NA                | 68.7 ± 12.6:65.5 ± 4.6 | NA                        | NA                     | NA                | NA                     |
| Hu 2012           | Chinese   | 206/203      | 123/63:110/90     | 67.6 ± 12.15:66.1 ± 4.7 | 159/51:80/123           | 105/10:73/124         | 23.6 ± 2.2:23.60 ± 3.3 | 55/151:10/193        |
| Jiang 2015        | Chinese   | 150/160      | 86/64:85/73       | 69.1 ± 12.6:59.1 ± 1.2 | NA                        | NA                     | NA                | NA                     |
| Liu 2008          | Chinese   | 63/62        | 48/15:44/18       | 59.3 ± 12.6:55.5 ± 1.4 | NA                        | NA                     | NA                | NA                     |
| Morrison 2002     | Americans | 218/964      | 113/100:540/397   | 56.0 ± 0.45:39.0 ± 0.1 | NA                        | 38/180:20/938         | NA                | 35/183:9/955          |
| Myllykangas 2001  | Finland   | 119/133      | 18/101:25/108     | 89.2 ± 4.88:88.2 ± 2.9 | 28/91:36/97             | 2.9 ± 0.6:3.0 ± 0.7  | 31.9:18.8          |
| Nakashishi, 2001  | Japanese  | 177/177      | 124/53:114/63     | 62.2 ± 10.8:60.2 ± 9.1 | NA                        | NA                     | NA                | 49/128:24/153         |
| Pereira 2016      | Colombian | 133/269      | 75/68:133/96      | 69.3 ± 6.4:66.6 ± 3.1  | NA                        | NA                     | NA                | NA                     |
| Zhao 2003         | Chinese   | 90/117       | 53/43:73/44       | 64 ± 11.6:61.7 ± 8.3   | 55/41:26/61             | 23.7 ± 3.5:22.7 ± 2.4 | 20/76:21/15        |
| Xu 2008           | Chinese   | 185/186      | 102/84:118/67     | 60.8 ± 12.1:61.5:18 ± 10.1 | 148 ± 7.9:22 ± 0.3   | 21.1:212:123/218     | 23.9 ± 4.1:24 ± 3.3 | NA                     |
| Jiang 1996        | Swedish   | 128/35       | NA                | NA                | NA                        | NA                     | NA                | NA                     |
| Munshi 2012       | Indian    | 525/500      | 374/151:357/143   | 49.3 ± 17.3:49.0 ± 16.7 | 302/72:151:349         | 233/292:161/339       | NA                | 237/286:143/357       |
| Song 1999         | Korean    | 96/98        | 59/57:68/73       | 63.4 ± 10.9:93 ± 16.4 | NA                        | NA                     | NA                | NA                     |
| Parfenov 2007     | Russian   | 107/101      | 69/38:61/40       | 58.4 ± 11.5:57.6 ± 11.6 | NA                        | NA                     | NA                | NA                     |
| Coja-Espiritu 2016| Mexican   | 100/120      | 46/54:59/70       | 67.9 ± 12.5:61.6 ± 9.7 | 49.51:69/51             | 27.9 ± 5.0:29 ± 5.7  | 47/53:89/31         |
| Lin 2006          | Chinese   | 67/81        | NA                | NA                | NA                        | NA                     | NA                | NA                     |

**Table 1**

Main characteristic of the studies for polymorphisms included in meta-analysis.
3.2. Meta-analysis results

Significant associations were detected between LPL HindIII (+/−) in allelic and dominant models (allelic model: \( P = .0002 \), OR [95%CI] = 0.80 [0.69, 0.92]); PvuII (+/−) in allelic, dominant and recessive models (allelic model: \( P < .0001 \), OR[95%CI] = 0.75 [0.65–0.86]; dominant model: \( P = .02 \), OR[95%CI] = 0.67[0.48–0.93]; recessive model: \( P = .01 \), OR[95%CI] = 0.71[0.55–0.93]), and IS (Table 3, Figs. 2 and 3). No association was detected between LPL Ser447Ter in allelic, dominant or recessive models, as well as LPL HindIII (+/−) in recessive model and IS (\( P > .05 \)) (Table 3).

Subgroup analysis stratified by ethnicity showed that the frequencies of allelic, dominant, and recessive models of LPL HindIII (+/−) were significant lower in Asian cases (allelic model: \( P < .00001 \), OR[95%CI] = 0.69 [0.59, 0.79]); dominant model: \( P = .003 \), OR[95%CI] = 0.80 [0.69, 0.92]; recessive model: \( P = .005 \), OR[95%CI] = 0.66 [0.50, 0.89]), but not in Caucasian cases (\( P > .05 \)). However, significant association was observed in allelic model of PvuII (+/−) in both Asian and Caucasian populations (Asian: \( P < .00001 \), OR[95%CI] = 0.66[0.50–0.76]; Caucasian: \( P = .01 \), OR[95%CI] = 0.75 [0.59, 0.94]). And the distribution of dominant model of PvuII (+/−) was significantly decreased in cases than that in controls in Asian (\( P = .0008 \), OR [95%CI] = 0.66 [0.51–0.84]), but not in Caucasian (\( P > .05 \)). Furthermore, significant difference between the distribution of recessive model of PvuII (+/−) in cases and controls was detected in Caucasian (\( P = .02 \), OR[95%CI] = 0.63 [0.43–0.93]), but not in Asian (\( P > .05 \)) (Table 3).

3.3. Heterogeneity

The heterogeneity between the studies about all genetic models of LPL Ser447Ter, allelic, and dominant models of HindIII (+/−), as
well as dominant model of PvuII (+/−) were observed. Therefore subgroup analyses were essential. Significant heterogeneities existed in allelic, dominant, and recessive models of LPL Ser447Ter in Asian subgroup when stratified by ethnicity. The heterogeneity in this polymorphism was contributed mainly by Jiang et al, Xu et al, and Zhao et al. Removal of these studies from meta-analysis gave 0% to 43% heterogeneities ($P > 0.05$). As for HindIII (+/−) and PvuII (+/−), the heterogeneities in these 2 polymorphisms were contributed mainly by Song et al. Removal of this study from meta-analysis gave 0% to 47% heterogeneities ($P > 0.05$).

3.4. Sensitivity analysis
Sensitivity analysis which excluded the influence of a single study on the overall risk estimate by excluding 1 study at a time was confirmed. The ORs were not significantly altered in each SNP (Fig. 5).

3.5. Publication bias
We performed the Begg and Egger tests to evaluate the publication bias. None of the funnel plots explored the evidence of publication bias (Fig. 6). The $P$ value and Z value for Egger and
Begg test were shown in Table 4 separately. No obvious publication bias was observed for LPL Ser447Ter, HindIII (+/−) and PvuII (+/−), and IS.

4. Discussion
In the present meta-analysis study, we found that the LPL HindIII (+/−) and PvuII (+/−), but not the Ser447Ter, might significantly reduce the risk of IS. Multiple gene variants have been identified to be susceptible factors for IS in both familiar and sporadic cases.[47,48] Several variants of the LPL gene have been found and reported to underlie changes in plasma lipoprotein levels and to be important cardiovascular risk factors.[21,22] The Ser447Ter, 1 mutation of LPL gene, may result in beneficial lipid profile. Recently, a meta-analysis with 13 studies was performed to investigate the relationship of LPL Ser447Ter and IS.[49] LPL Ter447 variant was shown to be associated with a significantly reduced risk for IS both in Caucasian and East-Asian populations.[49,50] In our meta-analysis, we included 14 studies, partly different from previous meta-analysis, with 2515 cases and 3324 controls, for IS analysis. Different from the previous results, we failed to detect the significant association between LPL Ser447Ter and IS. Furthermore, we also demonstrated no risk of IS for allele, recessive, and dominant models both in Caucasian and Asian populations.

In contrast to Ser447Ter variant, HindIII (+/−) has the protective effect on IS. The HindIII (+/−) polymorphism could lead to a substitution of thymine (T) to guanine (G), which was suggested to affect the transcription or translation of the LPL gene.[27] Huang et al.[27] firstly investigated the genetic association between HindIII (+/−) variant and stroke, and obtained negative results. This result was followed by Song et al.[30] Velásquez Pereira et al.[22] and Xu et al.[28] Although negative results were
observed in individual study, our study confirmed this variant in allelic and dominant models were associated with a significant reduction of the IS risk especially in Asian population, which was similar with the results reported in latest publication by He et al.\[51\] Notable, we included 2 more studies[30,37] and found that the recessive model of HindIII (+/-/C0) might not be the susceptible factor of IS, which was partly different from that reported by He et al.\[51\] In addition, we excluded 3 studies[52–54] that included in study conducted by He et al on the association between the HindIII (+/-) and hemorrhagic stroke (HS) risk for the present meta-analysis mainly focused on the association between HindIII (+/-) and IS risk. Recent studies suggested that

Figure 4. Forest plots of odds ratios for the association between LPL HindIII (+/-) and IS. (A) Allelic model; (B) dominant model; and (C) recessive model. IS = ischemic stroke, LPL = lipoprotein lipase.

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total Weight | Odds Ratio M-H | Random. 95% CI |
|-------------------|---------------------|----------------|--------------|--------------|----------------|----------------|
| Baum 2006         | 50                  | 492            | 542          | 66           | 0.90           | 0.90–0.91      |
| Fidani 2005       | 22                  | 196            | 218          | 45           | 0.84           | 0.83–0.85      |
| Guan 2006         | 9                   | 332            | 341          | 56           | 0.82           | 0.80–0.85      |
| Hu 2012           | 34                  | 412            | 446          | 86           | 0.81           | 0.80–0.82      |
| Jiang 2015        | 27                  | 300            | 327          | 59           | 0.72           | 0.71–0.74      |
| Liu 2008          | 11                  | 126            | 137          | 26           | 0.70           | 0.69–0.72      |
| Nakanishi 2001    | 36                  | 354            | 390          | 78           | 0.67           | 0.66–0.69      |
| Pereira 2016      | 24                  | 266            | 290          | 58           | 0.63           | 0.62–0.65      |
| Xu 2008           | 28                  | 370            | 398          | 79           | 0.61           | 0.60–0.63      |
| Zhao 2003         | 50                  | 192            | 242          | 48           | 0.46           | 0.45–0.48      |

Total (95% CI) 2072 events, 100% 0.88 [0.85–0.91]

Heterogeneity: Tau^2 = 0.37; Chi^2 = 53.78, df = 9 (P < 0.00001); I^2 = 83%

Test for overall effect: Z = 0.61 (P = 0.54)

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HS and IS were 2 different subtype of stroke.\cite{55,56} However, most studies have not distinguished IS from HS. The pathogenesis and proportion of IS and HS were suggested to be partly different from each other.\cite{57,58} Thus, we did not take the association between HindIII (+/−) and IS into account. And this indicated the protective effect for HindIII (+/−) polymorphism in IS in Asian population might be reliable. Several reasons accounted for this incontinency in Asian and Caucasian populations. First, different gene background in Caucasian and Asian populations may lead to the inconsistent association between LPL HindIII and stroke.
Second, limited studies with small sample size were included in Caucasian subgroup, which may reduce the adequate power to detect the real correlation.

The PvuII (+/-) polymorphism is located in intron 6 and has been reported to be associated with coronary heart disease in patients with type 2 diabetes in Chinese, Caucasian (United States), and Brazilian. Previous study suggested that the Pvu (+/-) mutation might lead to significant change in levels of plasma triglycerides and high-density lipoprotein-c, which indicate the Pvu (+/-) mutation may influence the plasma

Figure 6. Funnel plot of publication bias for the association between LPL Ser447Ter, HindIII (+/-) and PvuII (+/-), and IS. (A) Ser447Ter; (B) HindIII (+/-); and (C) PvuII (+/-). IS=Ischemic stroke, LPL=Lipoprotein lipase.
LPL activity, and then play a role in the pathogenesis of stroke. However, the effect of PvuII (+/-) mutation in IS was controversial. Huang et al firstly reported no significant relationship between PvuII (+/-) polymorphism and IS in Swedish. Similar results were obtained in Korean, Japanese, Chinese, and Colombian. However, Xu et al showed discouraging results. Our combined analysis demonstrated that the dominant model of PvuII (+/-) was significantly related to the IS risk in Asian. And the recessive model of PvuII (+/-) was significantly related to IS risk in Caucasian. Relatively small numbers of studies were enrolled in subgroups may explain these inconsistency. Thus, to confirm these results, larger number of case-control design studies with sufficient cohorts is necessary.

Significant heterogeneities were observed in Asian subgroup in allelic, dominant, and recessive models when stratified by ethnicity. The following reasons might result in these heterogeneities. Firstly, there was relatively small sample size in most of these studies that conducted in Asian population. Second, different control source, genotyping methods, and phenotypes were applied in individual studies. Limitations need be mentioned. First, the number of study and subject included in present meta-analysis were relatively small. Only 2 or 3 eligible study was included in Caucasian subgroup, which may be lack of sufficient power to detect slight association. Second, uncorrected estimates were used in the present meta-analysis. It would be better to take potential contributory factors including gender, age, environmental factors, and other lifestyle factors such as diabetes, smoking, diet, and obesity into account in further precise analysis. Third, significant heterogeneity existed in studies, which may due to the different source of control, genetic backgrounds, and environmental factors. Fourth, we included studies only in Asian and Caucasian populations. The results may need be further accessed in multiple ethnicity groups.

5. Conclusion

The LPL HindIII (+/-) and PvuII (+/-), but not Ser447Ter may contribute to the susceptibility to IS. To confirm these results, more case-control designed studies with larger sample size of subject, and multiple ethnicities are necessary.

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