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*Review Article*

# Association of MMP-9 gene polymorphism and ischemic stroke: evidence from a case-control study to a meta-analysis

Xu Liu, Ruixia Zhu, Qu Li, Zhiyi He

*Department of Neurology, First Affiliated Hospital of China Medical University, Shenyang, China*

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**Abstract:** Matrix metalloproteinase 9 (MMP-9) plays an important role in the pathophysiology of inflammation. Several studies have investigated the association between MMP-9 -1562C/T polymorphism and risk of ischemic stroke (IS) where inflammatory process is involved, but the results were inconsistent. Therefore, we first conducted a case-control study to investigate the potential association, and then performed a meta-analysis to further address this issue. A total of 386 patients with IS and 386 unrelated controls were included in the study. Genotyping was performed using polymerase chain reaction-ligation detection reaction method. A meta-analysis was conducted by combining our data with previous relevant studies. In our case-control study, no significant association was found between MMP-9 -1562C/T and IS risk ($P > 0.05$). However, when combined with previous studies, the significant association of MMP-9 -1562C/T with IS risk was observed under allelic (OR = 1.28, 95% CI = 1.06-1.55, $P = 0.01$), homozygous (OR = 2.08, 95% CI = 1.49-2.90, $P < 0.01$), dominant (OR = 1.26, 95% CI = 1.03-1.53, $P = 0.02$) and recessive model (OR = 1.54, 95% CI = 1.08-2.20, $P = 0.02$). Moreover, subgroup analysis by ethnicity detected a significant association in Asian population, but not Caucasian population. In summary, evidence from a case-control study to a meta-analysis indicates that MMP-9 -1562C/T polymorphism likely serves as a potential risk factor for developing IS, especially in Asian population.

**Keywords:** Case-control studies, matrix metalloproteinase 9, meta-analysis, polymorphism, genetic, stroke

## Introduction

Ischemic Stroke (IS) is the leading cause of death and disability worldwide [1]. Traditional factors, such as hypertension and diabetes, account for a significant proportion of IS risk, but much risk still remains uncovered [2, 3]. Evidence from twin and familial aggregation studies indicates that genetic risk factors might contribute to a predisposition to IS [4, 5]. Vascular inflammation is an essential process in the pathogenesis of IS [6, 7]. Therefore, genes involved in inflammatory responses are under investigation to look for genetic variants predisposing to IS.

As a well-known inflammatory mediator, matrix metalloproteinase 9 (MMP-9) belongs to a family of structurally related zinc-binding proteolytic enzymes. MMP-9 is characterized by specialized proteolytic activity against type IV collagen, the major component of the basal lamina around blood vessels [8]. Several experimental studies have reported that MMP-9 may facilitate the migration of vascular smooth muscle cells, infiltration of leucocytes and destabilization of atherosclerotic plaques [9-11]. Moreover, the clinical study has indicated that the increased plasma MMP-9 level may be a predictor of cardiovascular disease risk [12]. The human MMP-9 gene is located on chromosome 20q12-q13 and consists of 13 exons and 12 introns. A functional polymorphic T allele at the -1562 position gave rise to a two fold increase in the promoter activity [13]. The circulating concentrations of MMP-9 from individuals with the T/T or T/C genotypes were statistically higher than those from individuals with the C/C genotype [14, 15].

Therefore, several studies have gradually investigated the potential association between

**Table 1.** Clinical characteristics of study subjects

| | Cases | Control | *P* value |
|---|---|---|---|
| Age | 62.1±9.89 | 61.9±9.84 | 0.83 |
| Male gender, *n* (%) | 267 (69.2) | 265 (68.7) | 0.88 |
| BMI (Kg/m$^2$) | 25.5±3.25 | 25.2±3.15 | 0.20 |
| Hypertension, *n* (%) | 272 (70.5) | 224 (58.0) | <0.01 |
| Diabetes, *n* (%) | 138 (35.8) | 72 (18.7) | <0.01 |
| hyperlipidemia, *n* (%) | 173 (44.8) | 136 (35.2) | <0.01 |
| Smoking, *n* (%) | 134 (34.7) | 70 (18.1) | <0.01 |

BMI-body mass index.

MMP-9 -1562C/T polymorphism and IS risk on different ethnic population. Some studies indicated an association between the MMP-9 -1562C/T and IS [16, 17]. However, these results have not been replicated in other studies [18, 19]. To address the issue, we decided to evaluate the association of MMP-9 -1562C/T with IS risk in a new case-control study, and then performed a comprehensive meta-analysis to derive a more reliable result.

## Material and methods

### *Study participants*

386 IS patients were recruited from Department of neurology, First Affiliated Hospital of China Medical University between September 2011 and December 2012. Eligible patients were defined as those who were first diagnosed with acute ischemic stroke according to neurological examination and radiological imaging. 386 healthy controls were recruited from the health examination department of the Red Cross Hospital, matched by age and sex, without clinical or radiological evidence of stroke and other neurological diseases. This study was approved by the Ethics Committees of both hospitals, and in compliance with the Helsinki Declaration. Written informed consents for the study were obtained from all participants.

### *Genotyping*

Genomic DNA was extracted from EDTA-anticoagulated peripheral blood by a DNA Purification Kit. Genotyping was determined using the polymerase chain reaction-ligation detection reaction (PCR-LDR) method. The PCR primers used were: Forward: TGGGCAGATCACTTGAGTCAGAA; Reverse: GCCCTATTTGGGAAAAACCTGCTA. The PCR cycling program was set at 95°C for 2 min, followed by 11 cycles of 94°C for 20 s, 65°C (decreased 0.5°C per cycle) for 40 s, 72°C for 1.5 min, and then 24 cycles of 94°C for 20 s, 59°C for 30 s, and 72°C for 1.5 min, and a final extension at 72°C for 2 min. The following LDR were performed in a total volume of 10 μL, containing 1 μL 10× ligase reaction buffer, 2 μL PCR product, 0.25 μL Taq DNA ligase, 6 μL double distilled $H_2O$ and 0.4 μL of each probe. LDR probes were composed of two discriminating probes and one common probe. The LDR reactions were cycled as: 38 cycles of 94°C for 60 s and 56°C for 4 min. After the reaction, LDR product was sequenced with ABI3730XL sequencer. Then, the raw data was analyzed by GeneMapper 4.1.

### *Statistical analysis*

Hardy-Weinberg equilibrium (HWE) analysis was assessed by $\chi^2$ test for genotypes in the case and control group. Differences of the distributions of alleles and genotypes between cases and controls were analyzed using $\chi^2$ test. The association of MMP-9 -1562C/T with IS was estimated by computing the odds ratios (OR) and 95% confidence intervals (CI) from logistic regression analysis. All the statistical analyses were performed with SPSS17.0 software. A value of $P < 0.05$ was considered statistically significant.

### *Meta-analysis*

To further investigate the association of MMP-9 -1562C/T polymorphism with IS, a meta-analysis combining published literatures and our current study was conducted. We search various databases including Pubmed, Embase, CNKI (China National Knowledge Infrastructure), Chinese WanFang database up to December 31, 2015. The following terms were used in our search strategies: matrix metalloproteinase/MMP/Gelatinase and stroke/cerebral infarction/brain infarction/cerebrovascular disease and polymorphism/genotype/variant/allele.

The included articles should meet the following criteria: (1) published studies based on case-control design; (2) availability of allele and genotype frequency for calculating ORs and their 95% CIs. The studies were excluded if one of the following existed: (1) not case-control studies, (2) studies without available genotype num-

**Table 2.** Genotype and allele distributions of MMP-9 -1562C/T in patients with ischemic stroke and controls

| | Cases (%) | Control (%) | OR (95% CI) | *P* value | Adjusted OR (95% CI) | *P* value |
|---|---|---|---|---|---|---|
| Genotype | | | | | | |
| CC | 300 (77.7%) | 296 (76.7%) | Reference | | Reference | |
| CT | 79 (20.5%) | 83 (21.5%) | 0.94 (0.66-1.33) | 0.72 | 0.93 (0.65-1.34) | 0.71 |
| TT | 7 (1.8%) | 7 (1.8%) | 0.99 (0.34-2.85) | 0.98 | 1.17 (0.38-3.60) | 0.78 |
| Dominant effect | | | | | | |
| TT+CT vs. CC | 86/300 | 90/296 | 0.94 (0.67-1.32) | 0.73 | 0.95 (0.67-1.35) | 0.78 |
| Recessive effect | | | | | | |
| TT vs. CT+CC | 7/379 | 7/379 | 1.00 (0.35-2.88) | 1.00 | 1.18 (0.39-3.55) | 0.77 |
| Allele | | | | | | |
| C | 679 (88.0%) | 675 (87.4%) | Reference | | | |
| T | 93 (12.0%) | 97 (12.6%) | 0.95 (0.70-1.29) | 0.76 | | |

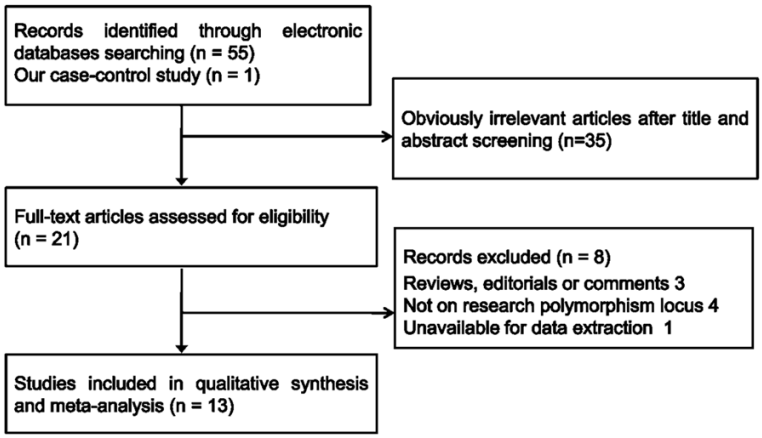


**Figure 1.** Flow diagram of the study selection process.

ber or frequency, (3) animal studies, case reports, abstracts and reviews. For duplicate publications, the one with more complete design or larger sample size was selected. The following information was collected: first author, year of publication, ethnicity, characteristics of cases and controls, distribution of alleles and genotypes in all groups. In order to assess the quality of eligible studies, a set of predetermined criteria, which were initially derived by Thakkinstian et al. [20], were structured as a 16-item list with scores ranging from 0 to 15. As in other meta-analyses [21, 22], studies with scores of ≥ 10 or < 10 were considered high-and low-quality studies, respectively.

Heterogeneity among studies was examined with the $I^2$ statistic and $I^2$ > 50% indicates significant heterogeneity between the studies. If there was heterogeneity in the studies, a pooled OR was calculated by the random effect model; otherwise, the fixed effect model was used. Sensitivity analysis was conducted to assess the effect of each single study on pooled result. Subgroup analysis was performed based on ethnicity. Publication bias was examined by the visual inspection of funnel plot and Egger's regression test. Data were analyzed and processed using Stata 12.0.

## Results

*Our current case-control study*

The characteristics of study participants were provided in **Table 1**. There were no significant differences in age (*P* = 0.83), gender (*P* = 0.88), or body mass index (*P* = 0.20) between patients and controls. However, the prevalence of traditional risk factors for IS, such as hypertension, diabetes mellitus, hyperlipidemia and smoking, in the patients was more frequent than those in the controls (*P* < 0.01).

The genotype and allele frequencies of MMP-9 -1562C/T polymorphism in patients and control subjects were shown in **Table 2**. All genotype distributions in both patients and controls were in the Hardy-Weinberg equilibrium (*P* = 0.50 for patient group, *P* = 0.68 for control group, respectively). As shown in **Table 2**, there was no significant difference in the distribution

**Table 3.** Main characteristics and genotype distribution of included studies

| Author (year) | Ethnicity | Sample size | | Case | | | Control | | | Quality (score) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | case | control | TT | CT | CC | TT | CT | CC | |
| Liu X | Asian | 386 | 386 | 7 | 79 | 300 | 7 | 83 | 296 | High quality (13) |
| Hao YH (2015) | Asian | 317 | 317 | 44 | 59 | 214 | 9 | 66 | 242 | High quality (12) |
| Nie SW (2014) | Asian | 396 | 400 | 29 | 62 | 305 | 21 | 41 | 338 | High quality (10) |
| Yue YH (2014) | Asian | 284 | 226 | 7 | 50 | 227 | 3 | 28 | 195 | High quality (13) |
| Li JY (2013) | Asian | 302 | 308 | 0 | 50 | 252 | 0 | 37 | 271 | High quality (13) |
| Liu D (2011) | Asian | 232 | 235 | 3 | 48 | 181 | 2 | 29 | 204 | High quality (10) |
| Shi N (2011) | Asian | 224 | 112 | 0 | 38 | 186 | 0 | 20 | 92 | High quality (12) |
| Szczudlik P (2010) | Caucasian | 418 | 408 | 14 | 89 | 315 | 6 | 111 | 291 | High quality (13) |
| Zhou J (2009) | Asian | 70 | 60 | 2 | 22 | 46 | 2 | 8 | 50 | Low quality (8) |
| Hou LH (2009) | Asian | 57 | 84 | 1 | 10 | 46 | 0 | 18 | 66 | High quality (11) |
| Zhang L (2008) | Asian | 114 | 80 | 3 | 16 | 95 | 2 | 15 | 63 | High quality (11) |
| Zhou YL (2008) | Asian | 101 | 114 | 0 | 14 | 87 | 2 | 13 | 99 | High quality (12) |
| Montaner J (2003) | Caucasian | 61 | 59 | 0 | 17 | 44 | 0 | 12 | 47 | High quality (10) |

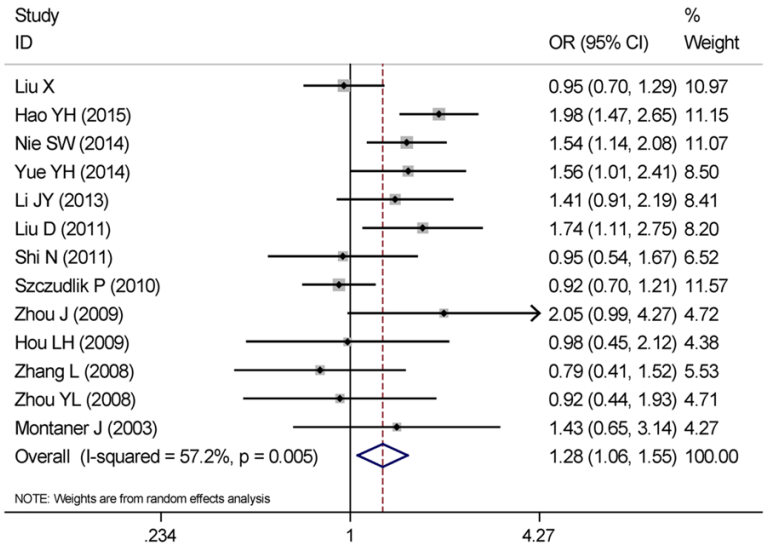


**Figure 2.** Forrest plot on the association between MMP-9 -1562C/T and IS risk for allelic model (T vs. C).

of alleles and genotypes of MMP-9 -1562C/T between IS patients and controls. Furthermore, logistic regression analysis was used to evaluate the association between MMP-9 -1562C/T and IS risk. Logistic regression analysis revealed no association for any genetic model after adjusting for traditional risk factors (TT vs. CC: OR = 1.17, 95% CI = 0.38-3.60, $P$ = 0.78; CT vs. CC: OR = 0.93, 95% CI = 0.65-1.34, $P$ = 0.71; TT + CT vs. CC: OR = 0.95, 95% CI = 0.67-1.35, $P$ = 0.78; TT vs. CT + CC: OR = 1.18, 95% CI = 0.39-3.55, $P$ = 0.77; **Table 2**).

*Meta-analysis*

55 studies were identified by the literature search, among which 13 studies met the inclusion criteria [16-19, 23-30]. A flow diagram schematized the process of selecting and excluding articles with specific reasons, as shown in **Figure 1**. Ethnicity, sample size, quality score and genotype distribution of studies included were summarized in **Table 3**.

The association between MMP-9 -1562C/T polymorphism and IS risk was analyzed in 13 original studies involving 2962 cases and 2789 controls. The analysis on the full data set indicated the significant association of MMP-9 -1562C/T with IS risk under allelic (OR = 1.28, 95% CI = 1.06-1.55, $P$ = 0.01, $I^2$ = 57.2%, **Figure 2**), homozygous (OR = 2.08, 95% CI = 1.49-2.90, $P$ < 0.01, $I^2$ = 30.7%), dominant (OR = 1.26, 95% CI = 1.03-1.53, $P$ = 0.02, $I^2$ = 50.7%) and recessive model (OR = 1.54, 95% CI = 1.08-2.20, $P$ = 0.02, $I^2$ = 26.5%). Moreover, sensitivity analysis showed that no single study qualitatively changed the pooled ORs with corresponding 95% CI under allelic, homozygous, and dominant model, but

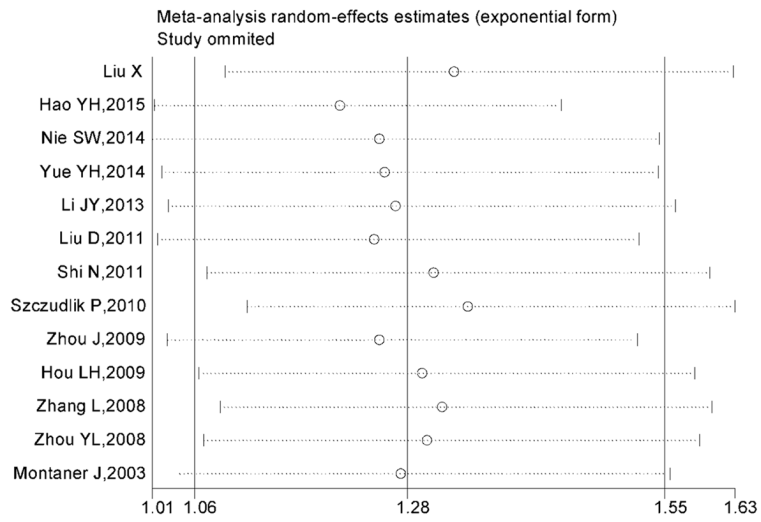


**Figure 3.** Sensitivity analysis for MMP-9 -1562C/T and IS risk in allelic model (T vs. C).

not recessive model (**Figure 3** for allelic model). In the subgroup analysis by ethnicity, similar significant correlation with IS risk was observed in Asian population under allelic, homozygous, heterozygous and dominant model. However, in Caucasian population, the remaining pooled ORs were not significant for any genetic model (**Table 4**).

Visual inspection of funnel plot failed to detect significant bias in all genetic models (**Figure 4** for allelic model). The results were further supported by the analysis of the data with Egger's regression test ($P$ = 0.87 for allelic model, $P$ = 0.49 for homozygous model, $P$ = 0.24 for heterozygous model, $P$ = 0.62 for dominant model, and $P$ = 0.53 for recessive model, respectively).

## Discussion

To investigate the association between MMP-9 -1562C/T polymorphism and IS risk, we performed a case-control study and a comprehensive meta-analysis involving 5751 subjects.

In our case-control study, we found that the allelic and genotypic frequencies of MMP-9 -1562C/T were not associated with CI risk, which was consistent to Polish population as reported by Szczudlik [19]. However, several studies have reported a positive relation between MMP-9 -1562C/T and IS, and findings have been controversial. The difference among research findings can be explained by the following reasons. First, and most importantly, the sample size of the included studies was relatively small. It may be more likely to get false positive or false negative results. Second, the inconsistency might be caused by different allele frequencies across study populations, particularly in different geographical and ethnic groups.

By increasing the sample size, the meta-analysis has the ability to detect small effects in genetic association studies. Therefore, we have performed this comprehensive analysis of thirteen related studies worldwide. In our meta-analysis, we found the significant association of MMP-9 -1562C/T with IS risk in the population worldwide. Subgroup analysis by ethnic group also found MMP-9 -1562C/T was associated with IS in Asian population, but not Caucasian population. In 2014, Wen et al. [31] performed a similar meta-analysis including only 3 studies. Lack of significant association between MMP-9 -1562C/T and IS risk was observed under dominant or recessive model. Subsequently, Fan et al. [32] conducted another meta-analysis involving 6 studies and 2227 subjects. They also found no significant association of MMP-9 -1562C/T with IS risk. The inconsistency of our findings with the other two meta-analyses may be due to sample size. Our current meta-analysis added our own study and another six recent studies, involving 1786 IS patients and 1738 controls. In addition, the most studies in our meta-analysis were considered high quality studies (except for Zhou's study [27]). Moreover, we observed no evidence of publication bias in our meta-analysis by funnel plot or Egger's test. Thus, our meta-analysis might enhance the statistical power and draw a more reliable conclusion.

To our knowledge, this is the latest and largest meta-analysis focused on the association between MMP-9 -1562C/T polymorphism and susceptibility to IS. However, the following limitations should be taken into consideration:

**Table 4.** Summary ORs and 95% CI of MMP-9 -1562C/T polymorphism and ischemic stroke risk

| | N | T vs. C | | TT vs. CC | | CT vs. CC | | TT+CT vs. CC | | TT vs. CT+CC | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | $I^2$ (%) | OR (95% CI) | $I^2$ (%) | OR (95% CI) | $I^2$ (%) | OR (95% CI) | $I^2$ (%) | OR (95% CI) | $I^2$ (%) |
| Total | 13 | 1.28 (1.06-1.55) | 57.2% | 2.08 (1.49-2.90) | 30.7% | 1.19 (0.96-1.47) | 52.3% | 1.26 (1.03-1.53) | 50.7% | 1.54 (1.08-2.20) | 26.5% |
| Ethnicity | | | | | | | | | | | |
| Asian | 11 | 1.34 (1.10-1.64) | 52.0% | 2.07 (1.46-2.95) | 38.7% | 1.25 (1.07-1.45) | 39.9% | 1.34 (1.16-1.55) | 37.2% | 1.42 (0.97-2.07) | 25.6% |
| Caucasian | 2 | 0.96 (0.74-1.25) | 8.6% | 2.16 (0.82-5.68) | NA | 0.95 (0.49-1.84) | 58.3% | 0.88 (0.66-1.17) | 45.3% | 2.65 (0.98-7.15) | NA |

NA - not available.

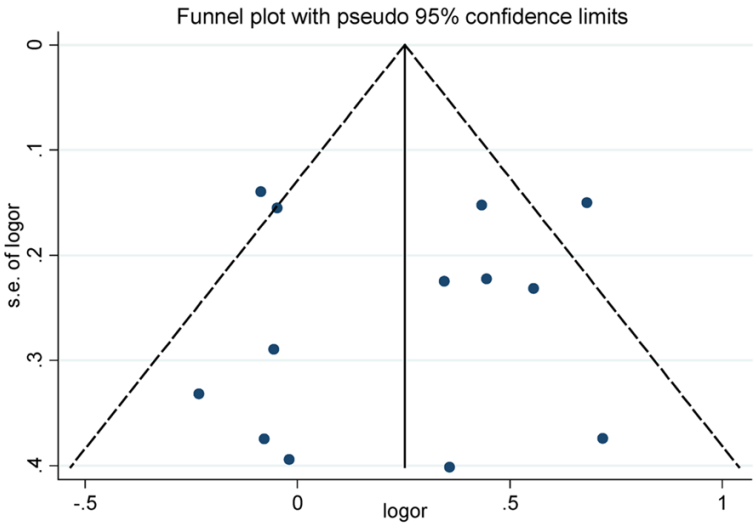


**Figure 4.** Funnel plot analysis to detect publication bias for allelic model (T vs. C).

First, the moderate heterogeneity across studies existed in the following models: T vs. C, TT + CT vs. CC. We performed the subgroup and sensitivity analysis to explain the sources of heterogeneity. Subgroup analysis indicated that ethnicity can explain the part of heterogeneity. When omitting each single study by sequence, we found that no single study was responsible for the heterogeneity of pooled results. Second, the meta-analysis in Caucasian was performed on a small sample size, involving only 479 cases and 467 controls from 2 studies. There was insufficient power to detect significant association with IS risk. Thus, the association of MMP-9 -1562C/T with IS should be elucidated in larger Caucasian cohorts. Third, in our sensitivity analysis, we found that no individual study significantly altered the pooled ORs with corresponding 95% CI under allelic, homozygous, and dominant model, but not recessive model. Hence, the caution is indicated when interpreting the significant association of MMP-9 -1562C/T with IS for the recessive model. Forth, the study results included in this meta-analysis were based on unadjusted analyses. Therefore, a more precise analysis should be adjusted for potentially confounding factors if individual data was available. Last but not least, it has been reported that different genetic variants can predispose to different IS subtypes [33]. Unfortunately, we did not perform stratification analysis according to IS subtypes because of insufficient information in the included studies.

In conclusion, our study suggests that MMP-9 -1562C/T polymorphism is associated with developing IS, with stronger evidence compared with previous case-control studies and meta-analyses. Given the limitations in our case-control study and meta-analysis, the results need to be considered with caution. Well-designed studies with larger sample size and more ethnic groups are required to validate the association of MMP-9 polymorphism and IS in the future.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Zhiyi He, Department of Neurology, First Affiliated Hospital of China Medical University, No. 155 North Nanjing Street, Shenyang 110001, Liaoning Province, China. Fax: +86 24 83282515; E-mail: hezhiyi0301@163.com

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