



# Association between the interleukin-1 $\beta$ gene -511C/T polymorphism and ischemic stroke: an updated meta-analysis

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**ABSTRACT.** Numerous studies have investigated the relationship between the interleukin-1 $\beta$  gene (*IL1B*) -511C/T polymorphism and ischemic stroke (IS) risk. However, the results are inconsistent. We performed this meta-analysis of all available case-control studies that evaluated the relationship between the *IL1B* -511C/T polymorphism and IS. Studies were retrieved from the PubMed and Embase databases. Statistical analyses were conducted using the STATA 11.0 software. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were applied to determine the strength of association. Nine studies comprising a total of 2072 patients and 2173 controls were included. No significant variation in IS risk was detected in any of the genetic models (CC vs TT: OR = 0.78, 95%CI = 0.48-1.27; CT vs TT: OR = 0.83, 95%CI = 0.62-1.10; dominant model: OR = 0.79, 95%CI = 0.55-1.15; recessive model: OR = 0.90, 95%CI = 0.66-1.24). Taking into account the effects of race, further subgroup analyses were performed and our results showed no association between the *IL1B* gene -511C/T polymorphism and IS in either Asians or Caucasians. No publication

bias was found in our study. In conclusion, the *IL1B* gene -511C/T polymorphism might not be associated with IS risk.

**Key words:** -511C/T polymorphism; Ischemic stroke; Interleukin-1 $\beta$

## INTRODUCTION

According to the global data, stroke is the second most common cause of death and a major cause of disability, and ischemic stroke (IS) accounts for about 85-90% of all types of stroke (Bonita et al., 2004). Despite extensive investigation, the causes of IS are not yet fully understood. Previous studies have identified smoking behavior, diabetes, hypertension, high body mass index, and lack of physical exercise as the common risk factors that contribute to IS (O'Donnell et al., 2010). In addition, strong evidence from genetic association studies indicates that genetic factors also play a key role in the pathogenesis of IS (Sharma, 1996).

Inflammation plays a vital role in the development and progression of IS, and is one of its most important causative factors (Chamorro, 2004). Interleukin-1 (IL-1) is considered an important mediator of inflammation, and it occurs in two forms: IL-1 $\alpha$  and IL-1 $\beta$  (Dinarello, 1996). The gene that encodes IL-1 $\beta$  (*IL1B*) has the chromosomal locus 2q13-21, and is located in the 70-110 kb region; it includes seven exons and six introns. Recently, a C/T base substitution in the promoter region (position -511) of the *IL1B* gene has been identified (-511C/T; National Center for Biotechnology Information (NCBI) ID: rs16944). A previous study has shown that individuals with the TT genotype secrete significantly more IL-1 $\beta$  than those with the TC genotype, who in turn secrete significantly more than those with the CC genotype (Pociot et al., 1992).

In the past decade, numerous case-control studies have assessed the interrelationship between the *IL1B* -511C/T polymorphism and IS risk. However, the conclusions are controversial. This may be due to insufficient power, false-positive results, or the small effect of the polymorphism on IS susceptibility (Attia et al., 2003). To draw a more reliable conclusion and further explore the associations between the *IL1B* gene -511C/T polymorphism and IS risk, we performed the present meta-analysis, which included all the relevant published papers.

## MATERIAL AND METHODS

### Selection of studies

We carried out an on-line retrieval from PubMed and Embase databases, covering all available papers published before 2015, and using the following terms: "cerebral infarction" or "ischemic stroke," "interleukin-1" or "-511C/T", and "polymorphism" or "variant". The retrieval was performed without applying any restrictions on language or article type.

### Inclusion and exclusion criteria

Titles were scanned first, then abstracts were read, and ultimately full articles were reviewed. We imposed the following inclusion criteria: 1) all studies must have been conducted to evaluate the interrelationship between the *IL1B* gene -511C/T polymorphism and the risk of IS; 2) sufficient data must have been provided to calculate the odds ratios (ORs) and 95%

confidence intervals (95% CIs); and 3) the studies must have described the sources of cases and controls. The exclusion criteria were as follows: 1) abstracts or reviews; 2) genotype frequency not provided; and 3) duplicated publications.

## Data extraction

Data were independently abstracted by two reviewers (W. Yan and Z.Y. Chen) using a standard data-collection method according to the inclusion criteria. The following data, which are clearly listed in Table 1, were collected from each study: the name of the first author, the year of publication, the country of origin of the sample, the nationality, the number of patients and controls, and gene polymorphisms and evidence of agreement with the Hardy-Weinberg equilibrium (HWE). Different ethnicities were divided into European and Asian groups.

**Table 1.** Characteristics of the studies included for meta-analysis.

| Study included    | Year | Area   | Race       | Cases/Controls | Genotypes of cases |     |     | Genotypes of controls |     |     | HWE test |
|-------------------|------|--------|------------|----------------|--------------------|-----|-----|-----------------------|-----|-----|----------|
|                   |      |        |            |                | CC                 | CT  | TT  | CC                    | CT  | TT  |          |
| Seripa et al.     | 2003 | Italy  | Caucasians | 101/110        | 41                 | 47  | 13  | 39                    | 58  | 13  | 0.22     |
| Dziedzic et al.   | 2005 | Poland | Caucasians | 221/219        | 99                 | 94  | 28  | 103                   | 100 | 16  | 0.21     |
| Rubattu et al.    | 2005 | Poland | Caucasians | 115/180        | 47                 | 51  | 17  | 79                    | 83  | 18  | 0.57     |
| Iacoviello et al. | 2005 | Poland | Caucasians | 134/134        | 66                 | 59  | 9   | 52                    | 61  | 21  | 0.70     |
| Lai et al.        | 2006 | China  | Asians     | 112/95         | 25                 | 55  | 32  | 30                    | 46  | 19  | 0.86     |
| Zee et al.        | 2008 | USA    | Caucasians | 258/258        | 113                | 123 | 22  | 111                   | 120 | 27  | 0.52     |
| Li et al.         | 2010 | China  | Asians     | 371/371        | 93                 | 170 | 108 | 101                   | 178 | 92  | 0.44     |
| Zhang et al.      | 2013 | China  | Asians     | 440/486        | 119                | 226 | 95  | 108                   | 261 | 117 | 0.10     |
| Rezk et al.       | 2014 | Egypt  | Caucasians | 320/320        | 125                | 145 | 50  | 206                   | 101 | 13  | 0.89     |

HWE = Hardy-Weinberg equilibrium.

## Statistical analysis

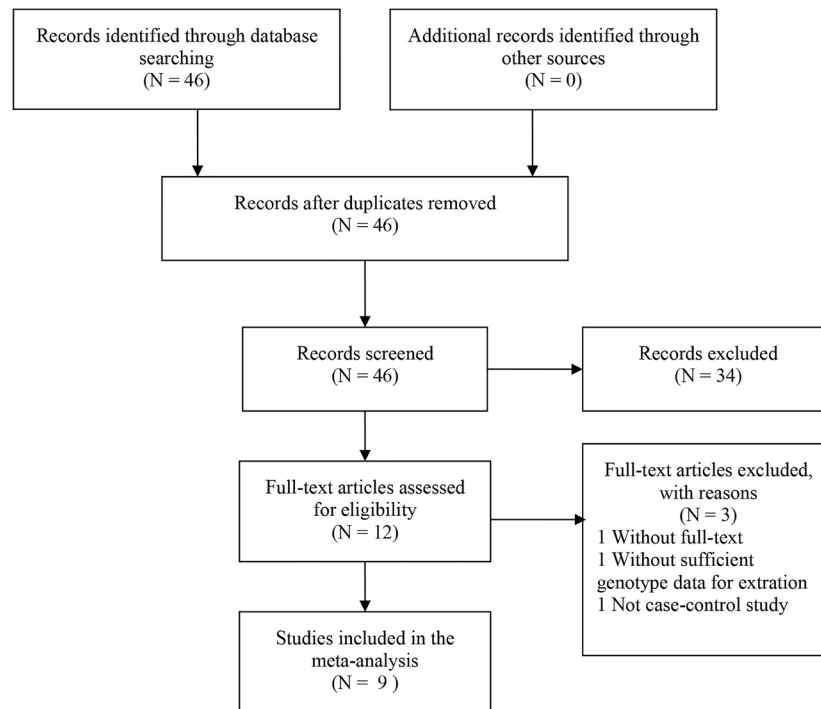
In this meta-analysis, all statistical data were analyzed using STATA software (version 11.0; Stata Corporation, College Station, TX) with two-sided P values. ORs with 95% CIs were used to assess the relationship between the *IL1B* gene -511C/T polymorphism and IS risk. The pooled ORs were calculated for a homozygote comparison (CC vs TT), a heterozygote comparison (CT vs TT), a dominant model (CC+CT vs TT), and a recessive model (CC vs CT+TT). We quantified the effect of heterogeneity using the  $I^2$  test. In cases where an  $I^2 < 50\%$  indicated heterogeneity across studies, the fixed-effects model was used for meta-analysis; otherwise, the random-effects model was used. Subgroup analysis based on race was used to explain diversity among the different studies. Sensitivity analysis was performed by comparing the random-effects model values with those of the fixed-effects model. Publication bias was investigated by Begg's and Egger's linear regression tests ( $P < 0.05$  was considered statistically significant publication bias).

## RESULTS

### Study characteristics

As a result of the search and screening, 46 papers were retrieved using the databases mentioned above, of which 9 papers were included in this meta-analysis and 37 studies were

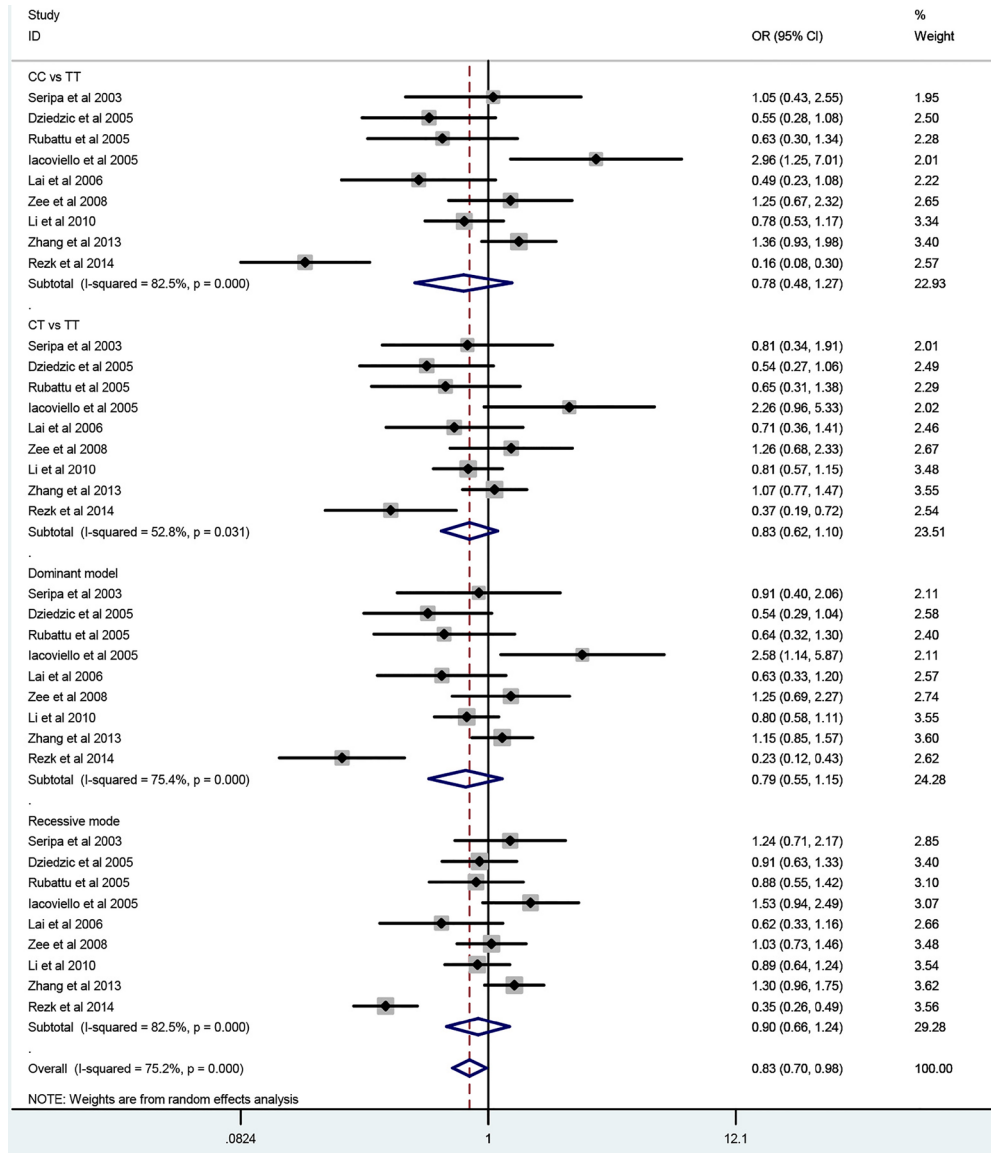
excluded (Seripa et al., 2003; Dziedzic et al., 2005; Iacoviello et al., 2005; Rubattu et al., 2005; Lai et al., 2006; Zee et al., 2008; Li et al., 2010; Zhang et al., 2013). Figure 1 depicts the selection process. All included studies were case-control studies that evaluated the relationship between the *IL1B* gene -511C/T polymorphism and IS risk. All included studies were published between 2003 and 2014, and were written in English. The genotype distributions among the controls of all included studies were in agreement with the HWE test ( $P > 0.05$ ). The study characteristics are presented in Table 1.



**Figure 1.** Flow chart showing the detailed steps for eligible study selection.

## Meta-analysis

The combined results of the *IL1B* gene -511C/T polymorphism and IS risk analysis are summarized in Figure 2 and Table 2. The meta-analysis results showed no significant association between the *IL1B* gene -511C/T polymorphism and susceptibility to IS (CC vs TT: OR = 0.78, 95%CI = 0.48-1.27; CT vs TT: OR = 0.83, 95%CI = 0.62-1.10; dominant model: OR = 0.79, 95%CI = 0.55-1.15; recessive model: OR = 0.90, 95%CI = 0.66-1.24). To explore the sources of heterogeneity, we performed further race-related analyses. Similarly, there were no significant relationships in the race-related subgroup analyses, and significant heterogeneity in most of the comparison models still existed. Table 2 shows the detailed results. Sensitivity analyses were conducted by altering the statistical models. Ultimately, no material alteration was detected, indicating that our results were valid and reliable.



**Figure 2.** Forest plots showing absence of association between the *IL1B* gene -511C/T polymorphism and risk of ischemic stroke (IS) in the overall population.

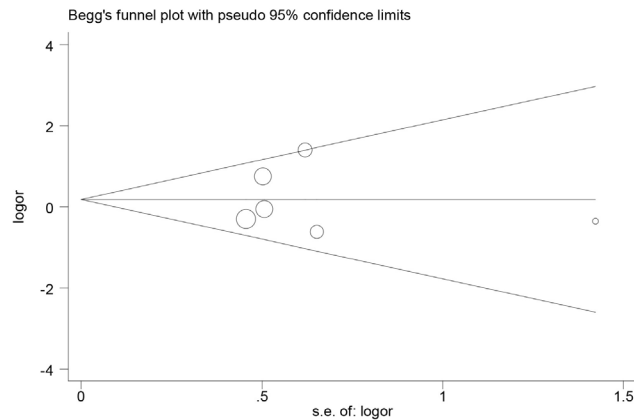
**Table 2.** Summary of different comparative results.

| Variables  | N | CC vs TT         |                |      | CT vs TT         |                |      | Dominant model   |                |      | Recessive mode   |                |      |
|------------|---|------------------|----------------|------|------------------|----------------|------|------------------|----------------|------|------------------|----------------|------|
|            |   | OR (95%CI)       | I <sup>2</sup> | P    | OR (95%CI)       | I <sup>2</sup> | P    | OR (95%CI)       | I <sup>2</sup> | P    | OR (95%CI)       | I <sup>2</sup> | P    |
| Total      | 9 | 0.78 (0.48-1.27) | 82.5%          | 0.00 | 0.83 (0.62-1.10) | 52.8%          | 0.03 | 0.79 (0.55-1.15) | 75.4%          | 0.00 | 0.90 (0.66-1.24) | 82.5%          | 0.00 |
| Ethnicity  |   |                  |                |      |                  |                |      |                  |                |      |                  |                |      |
| Caucasians | 6 | 0.76 (0.34-1.68) | 86.0%          | 0.00 | 0.80 (0.48-1.32) | 65.2%          | 0.01 | 0.77 (0.48-1.32) | 81.1%          | 0.00 | 0.89 (0.57-1.41) | 86.4%          | 0.00 |
| Asians     | 3 | 0.87 (0.52-1.47) | 71.7%          | 0.03 | 0.91 (0.73-1.14) | 0.0%           | 0.40 | 0.89 (0.65-1.23) | 50.9%          | 0.13 | 0.96 (0.66-1.40) | 63.8%          | 0.06 |

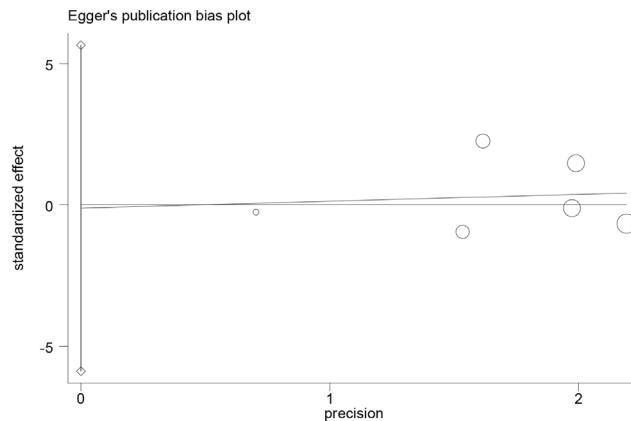
N = number; I<sup>2</sup> = inconsistency index; OR = odds ratio; CI = confidence interval.

## Publication bias

Literature publication bias was assessed by Begg's and Egger's tests. No obvious visual asymmetry was observed (Figure 3 and Figure 4). The results described above indicate that there was no publication bias, and that the results of our study are credible.



**Figure 3.** Begg's funnel plot for publication bias test.



**Figure 4.** Egger's funnel plot for publication bias test.

## DISCUSSION

Stroke is a complicated disease caused by environmental and genetic factors (Meschia et al., 2011; Jin et al., 2015). Previous studies have indicated that inflammatory cytokines and genetic polymorphisms in the genes encoding inflammatory mediators play a key role in the pathogenesis of IS (Hollegaard and Bidwell, 2006). In addition, high levels of IL-1 are secreted after ischemia, which exacerbates infarction severity by increasing the production and infiltration of neutrophils during IS (McColl et al., 2007). To date, many studies have

evaluated the relationship between the *IL1B* gene -511C/T polymorphism and IS risk. Previous meta-analyses have indicated that *IL1B* -511C/T is not associated with IS risk (Ye et al., 2012). With the benefit of more published literature, we conducted this meta-analysis to explore the association between the *IL1B* -511C/T polymorphism and IS risk.

Our study quantitatively assessed the association between the *IL1B* -511C/T polymorphism and susceptibility to IS. Ultimately, nine studies were included comprising 2072 patients and 2173 controls, and the results revealed no significant interrelationship between the *IL1B* gene -511C/T polymorphism and IS risk in the overall population. Furthermore, we performed a race-related analysis, and the results revealed that the *IL1B* gene -511C/T polymorphism is not associated with increased or decreased risk of IS in either the Caucasian and Asian populations. There are several potential explanations for the negative results described above. First, the negative results may be partly due to the heterogeneity of the included studies. Heterogeneity may result from variations in genetic background and environmental risk factors across populations, or differences in study design. Second, the potential influence of the *IL1B* gene -511C/T polymorphism may be affected by gene-gene and gene-environment interrelationships, which were not tested in the present study owing to the lack of relevant data from the original studies. Third, only literature published in English was included in this meta-analysis, so we may have missed potentially relevant studies published in other languages. In conclusion, our meta-analysis indicates that the *IL1B* -511C/T polymorphism is not associated with the risk of IS.

## Conflicts of interest

The authors declare no conflict of interest.

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