Lack of association between interleukin-1 receptor antagonist gene 86-bp VNTR polymorphism and ischemic stroke

A meta-analysis

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Abstract

Objective The results of published studies which examined the association between variable number tandem repeat (VNTR) polymorphism of interleukin-1 receptor antagonist (IL-1RN) and ischemic stroke (IS) are conflicting. Thus, we performed a meta-analysis to examine the potential association between IL-1RN VNTR polymorphism and IS risk.

Methods A systematic literature search of PubMed, Embase, Medline, Web of Science, Cochrane Library, Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure, COVIP, and WANFANG Database identified 10 studies with 2331 cases and 3335 controls. The pooled odds ratio (OR) with 95% confidence interval (95% CI) was calculated to evaluate the strength of the association. Subgroup analysis and meta-regression analysis were used to investigate the potential sources of heterogeneity.

Results In this study, no enough proof was found to prove the association between IL-1RN 86-bp VNTR polymorphism and IS risk with random-effects model in the homozygous model (1/1 vs 2/2, OR = 0.97, 95% CI = 0.50–1.87, P heterogeneity = .00), the heterozygous model (1/2 vs 2/2, OR = 0.64, 95% CI = 0.41–1.01, P heterogeneity = .10), the dominant model (1/1 + 1/2 vs 2/2, OR = 0.85, 95% CI = 0.51–1.42, P heterogeneity = .02), the recessive model (1/1 vs 2/2 + 2/2, OR = 0.69, 95% CI = 0.46–1.03, P heterogeneity = .00), and allelic model (1 vs 2, OR = 1.24, 95% CI = 0.89–1.74, P heterogeneity = .00). A marginally significant negative association was observed between IL-1RN 86-bp VNTR polymorphism and IS risk in the heterozygous model in the fixed-effects model (1/2 vs 2/2, OR = 0.71, 95% CI = 0.53–0.96, P heterogeneity = .10). In subgroup analyses, similar association was found in the group whose control size was lower than 300.

Conclusion In conclusion, our results suggested that there was no sufficient evidence to support the association between IL-1RN 86-bp VNTR polymorphism and IS. Further large epidemiologic studies need to be done to confirm these findings.

Abbreviations: 95% CI = 95% confidence interval, IL-1α = IL-1 alpha, IL-1β = IL-1 beta, IL-1Ra = interleukin-1 receptor antagonist protein, IL-1RN = interleukin-1 receptor antagonist gene, IS = ischemic stroke, OR = odds ratio, VNTR = variable number tandem repeat.

Keywords: interleukin-1 receptor antagonist, ischemic stroke, meta-analysis, variable number tandem repeat

1. Introduction

Stroke is one of the major causes of mortality and most common cause of disability worldwide.[1,2] Approximately 83% of strokes are attributed to ischemic stroke (IS).[3] Etiologically, IS is a multifactorial disease with the combination of several environ-

mental and lifestyle factors. Previous study recommended that the genetic influence was an important tool for determining the risk of developing IS.[4] Recently, a mounting evidence has shown that inflammatory cytokines play a crucial role in the development of IS.[5,6] Weyrich et al reported that chronic low-grade inflammation and activation of the innate immune system are closely involved in the pathogenesis of IS.[7] Inflammatory reactions have been identified in the pathogenesis of cerebral ischemia.[8] So IS has been recognized as an inflammation-related disease.

Interleukin-1 (IL-1) is one of the proinflammatory cytokines produced by monocytes, macrophages and epithelial cells. The IL-1 family consists of the cytokines IL-1 alpha (IL-1α), IL-1 beta (IL-1β), and a specific receptor antagonist (IL-1RN).[9] IL-1 gene complex, mapped on chromosome 2q13-14, including 3 linked genes which encode the secreted glycoproteins, IL-1α, IL-1β, and IL-1RN, respectively.[10] IL-1α and IL-1β are proinflammatory cytokines, while IL-1RN, a 16 to 18 kD protein, is an important counter-inflammatory cytokine by competing with the binding of IL-1 to its receptor. There are a variable number of identical tandem repeats (VNTRs) in intron 2 of the IL-1RN, which contains 86 base pair nucleotide (rs2234663) sequence as repeating element. Five alleles, which are allele 1 (IL-1RN*1) with 4 repeats, allele 2 (IL-1RN*2) with 2 repeats, allele 3 (IL-1RN*3) with 5 repeats, allele 4 (IL-1RN*4) with 3 repeats, and
allele 5 (IL-1RN*5) with 6 repeats, has been identified. Tarlow et al showed that IL-1RN*1 was the most common genotype, and then was the IL-1RN*2. The remaining alleles (IL-1RN*3, IL-1RN*4, and IL-1RN*5) occurred in <1% of the population.\cite{11} Accumulating genetic association studies have investigated the potential association of the IL-1RN VNTR with IS risk. However, the results of these studies remain controversial. The IL-1RN*2 polymorphism has been recognized as a genetic risk factor for atherosclerosis and coronary artery disease, which are closely related with IS.\cite{12,13} Worrall et al confirmed that IL-1RN*2 was associated with IS among Caucasians.\cite{14} However, Balding et al found no significant interaction between IL-1RN VNTR polymorphism frequencies and IS.\cite{15} Here we perform a meta-analysis based on 10 eligible pooled data to further validate the relationship between the IL-1RN VNTR polymorphism and IS susceptibility.

2. Materials and methods

2.1. Literature search

We systematically searched on the databases of PubMed, Embase, Medline, Web of Science, Cochrane Library, Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure (CNKI), CQVIP and WANFANG Database up to February 22, 2018, using the following medical subject headings (MeSH) or search terms: ("stroke" or cerebrovascular disease" or "ischemic stroke" or "brain infarction") and ("polymorphism*" or "variation" or "VNTR" or "variable number tandem repeat") and ("IL-1RN" or "IL-1Ra" or "interleukin 1 receptor antagonist"). The bibliographies of previous similar meta-analyses were also checked for additional relevant publications. We restricted our review to English and Chinese studies, owing to translation difficulties and lack of resources for review. Ethical approval or informed written consent was not applicable in our article because it was a meta-analysis of previously published studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria for studies were as follows: independent case-control studies; studies that evaluated the association between IL-1RN 86-bp VNTR polymorphism and IS susceptibility; studies that provided complete data regarding genotype and allele frequencies. The exclusion criteria were as follows: insufficient data regarding genotypes and allele frequencies; the genotype distribution of the control population did not conform to Hardy–Weinberg equilibrium (HWE), and overlapping publications.

2.3. Data extraction

Three researchers (YY, WW, and LW) extracted information independently including the first author’s name, year of publication, country, source of controls, genotype number and allele number in cases and controls, and HWE in controls. Disagreement was resolved through team discussion.

2.4. Quality assessment

Two researchers (YY and WW) performed independent study quality assessment using the 9-point Newcastle–Ottawa scale (NOS).\cite{16} The quality of each study was assessed based on appropriateness of selection, comparability, and exposure. NOS scores ranged from 0 to 9, and a score of 6 or greater indicate high quality.

2.5. Statistical analysis

The association between IL-1RN 86-bp VNTR polymorphism and IS was compared using the odds ratio (OR) corresponding to a 95% confidence interval (95% CI). Five different comparison models were used as follows: the 1/1 versus the 2/2 genotypes (homozygous model), the 1/1 + 1/2 versus the 2/2 genotypes (dominant model), the 1/2 versus the 2/2 genotypes (heterozygous model), the 1/1 versus the 2/2 + 1/2 genotypes (recessive model), the 1 versus 2 alleles (allele model).

The HWE was tested by Pearson goodness-of-fit Chi-squared test. Two studies were excluded due to not in HWE. Heterogeneity between studies was assessed using P-values for the Q statistic, H statistic, and I^2 values. The heterogeneity was considered significant when P < .05, or H > 1.5, or I^2 > 50%. I^2 was calculated to describe the percentage of variation caused by the heterogeneity: 0% to 25%, no heterogeneity; 25% to 50%, moderate heterogeneity; 50% to 75%, large heterogeneity; and 75% to 100%, extreme heterogeneity.\cite{17,18,19} The selection of a statistical model was based on the question of which model fits the distribution of effect sizes, and takes account of the relevant sources of error. This meta-analysis was performed using a random-effects model, which provided more conservative estimated effects.\cite{20} We also used subgroup analysis based on the region, source of control, control size, and case size. Meta-regression was used to explore reasons for heterogeneity. Sensitivity analyses were performed to assess the stability of the results. We also performed a cumulative meta-analysis to detect the result trends. To test for publication bias, Begg funnel plot and Egger linear regression test were applied.\cite{21} All statistical tests for this meta-analysis were performed with STATA 14.0 software (Version MP 14.0, Stata Corporation, College Station, TX).

3. Results

3.1. Eligible studies and study characteristics

Our literature search initially identified 116 articles by using the prespecified search strategy. Figure 1 showed the process of retrieving eligible studies. After title and abstract evaluation, we were left with 34 selected articles to be assessed by viewing full-text in the end. Three of these were eliminated due to reporting duplicate records, 1 was excluded because it was a meta-analysis and the others were excluded for their irrelevance to our study. Of the remaining 13 publications,\cite{14,18,19,22–31} 2 were eliminated for the unequilibrium of HWE in the control group,\cite{18,19} and 1 was eliminated for not a case-control study.\cite{29} As a result, 10 articles met eligibility criteria for this analysis, which included 3335 controls and 2331 IS patients. One publication included 2 separate case-control studies was considered to be a study when we do the analysis.\cite{14} In term of study design, 7 studies had population-based source of controls,\cite{14,22,23,26–28,31} and 3 had both population-based and hospital-based source of controls.\cite{14,24,25,30} Five studies were designed among Asians,\cite{23,26,27,30,31} and 5 studies non-Asians.\cite{14,22,24,25,28} Two articles were in Chinese\cite{30,31} and other 8 were all in English (Table 1).\cite{14,22–28}

3.2. Meta-analysis results

To evaluate the association between IL-1RN 86-bp VNTR polymorphism and IS risk, we performed both the overall meta-analysis and subgroup meta-analysis based on ethnicity, source of...
Table 1

Studies and data included in this meta-analysis.

| Author                  | Year | Country | Ethnicity | Source of controls | Sample size | Genotype distribution | Allelic frequency (control/case) | Quality score |
|-------------------------|------|---------|-----------|--------------------|-------------|-----------------------|----------------------------------|---------------|
| Rezk and Mohamad        | 2015 | Egypt   | Non-Asian | PB                 | 313         | 82 163 68 93 60 18 327/246 299/96 | 8                  |
| Peddareddygari et al    | 2014 | USA     | Non-Asian | Mixed              | 365         | 181 158 26 250 195 40 520/695 210/275 | 7                  |
| Tong et al              | 2013 | China   | Asian     | PB                 | 100         | 81 16 3 75 21 3 178/171 22/27 | 8                  |
| Tuttolomondo et al      | 2012 | Italy   | Non-Asian | Mixed              | 46          | 23 21 2 46 28 20 67/120 25/68 | 7                  |
| Tong et al              | 2011 | China   | Asian     | PB                 | 457         | 379 76 2 400 54 2 834/854 80/58 | 7                  |
| Gao et al               | 2009 | China   | Asian     | Mixed              | 105         | 84 20 1 72 4 0 188/148 22/4 | 6                  |
| Worrall et al           | 2007 | USA     | Non-Asian | PB                 | 247         | 149 85 13 206 116 33 438/813 136/293 | 8                  |
| Wei et al               | 2005 | China   | Asian     | PB                 | 167         | 135 31 1 139 11 3 301/289 33/17 | 8                  |
| Lee et al               | 2004 | Korea   | Asian     | PB                 | 160         | 153 7 0 129 16 1 313/274 7/18 | 7                  |
| Seripa et al            | 2003 | Italy   | Non-Asian | PB                 | 1335        | 98 511 100 78 13 7 1959/169 711/27 | 7                  |

PB = population based; mixed, both population based and hospital based.
control, control size, and case size. Table 2 showed the main results of the meta-analysis. There are no significant associations in the homozygous model (1/1 vs 2/2, OR = 0.97, 95% CI: 0.50–1.87, \( P_{\text{heterogeneity}} = 0.00 \)), the heterozygous model (1/2 vs 2/2, OR = 0.64, 95% CI: 0.41–1.01, \( P_{\text{heterogeneity}} = 10 \)), and the dominant model (1/1 + 1/2 + 2/2 vs 1/1, \( P_{\text{heterogeneity}} = 0.02 \)), the recessive model (1/2 vs 2/2, OR = 0.85, 95% CI: 0.51–1.42, \( P_{\text{heterogeneity}} = 0.02 \)), the recessive model (1/1 vs 1/2 + 2/2, OR = 1.15, 95% CI: 0.52–2.22, \( P_{\text{heterogeneity}} = 0.00 \)) (Fig. 2).

We further performed subgroup analysis according to the region, source of control, control size, and case size. We still found no association between IL-1RN 86-bp VNTR polymorphism and IS risk in the other 4 models (1/1 vs 2/2, OR = 0.71, 95% CI: 0.33–0.95, \( P_{\text{heterogeneity}} = 10 \)). However, significant heterogeneity was found in the other four genetic models (1/1 vs 2/2, \( P_{\text{heterogeneity}} = 0.00, I^2 = 71.9\% \); 1/1 + 1/2 + 2/2 vs 1/1, \( P_{\text{heterogeneity}} = 0.02, I^2 = 55.1\% \); 1/1 + 1/2 + 2/2 vs 1/1, \( P_{\text{heterogeneity}} = 0.02, I^2 = 85.4\% \); 1 vs 2, \( P_{\text{heterogeneity}} = 0.00, I^2 = 85.7\% \)). The results of the stratified analysis by ethnicity, source of controls, control size, and case size revealed that non-Asian group, population-based control group, and group whose case size lower than 300 were contributed to the heterogeneity. We also conducted meta-regression to assess the extent to which variables explained the heterogeneity. However, the results revealed that the heterogeneity could not be explained by publication year, ethnicity of the population, source of controls, control size, case size, and total size.

### 3.4. Sensitivity analysis and cumulative meta-analysis

Leave-one-out sensitivity analysis was performed to measure the effects of individual research on the meta-analysis results by omitting one study at a time. Then we recalculated the ORs and 95% CIs. Sensitivity analysis revealed that the study of Rezk and Mohamad was the main cause of heterogeneity. When the study was omitted, the heterogeneity had significantly fallen and a negative association between IL-1RN 86-bp VNTR polymorphism and IS risk was found under both the heterozygous model (1/1 vs 2/2, OR = 0.57, 95% CI: 0.40–0.82, \( P_{\text{heterogeneity}} = 0.39, I^2 = 52.2\% \)) and the dominant model (1/1 + 1/2 + 2/2 vs 1/1, OR = 0.72, 95% CI: 0.52–0.99, \( P_{\text{heterogeneity}} = 0.53, I^2 = 0.0\% \)). The cumulative meta-analysis was performed by accumulating the studies sorted by publication year. Under the heterozygote model, the cumulative meta-analysis displays that with the included study accumulated, the OR value showed corresponding increases (Fig. 4). But this trend was not observed in the other 4 models.

### 3.5. Publication bias test results

Begg funnel plot and Egger test were performed to assess the publication bias in the included studies. The results did not show any evidence of publication bias (Fig. 5) (Begg test: \( P = 0.54 \) for dominant model, \( P = 0.47 \) for heterozygous model, \( P = 0.00 \) for dominant model, \( P = 0.86 \) for recessive model, \( P = 0.86 \) for allelic
model, respectively; Egger test: \( P = .49 \) for dominant model, \( P = .25 \) for heterozygous model, \( P = .40 \) for dominant model, \( P = .67 \) for recessive model, \( P = .82 \) for allelic model, respectively).

4. Discussion

The present meta-analysis suggested that no sufficient evidence was found to support the correlation between IL-1RN VNTR polymorphism and IS risk. However, a significantly decreased risks of IS between the IL-1RN 1/2 group and the 2/2 group were observed in the fixed-effects model. After we omitted the study of Rezk and Mohamad, the heterogeneity fell significantly and a similar outcome of statistic association between the IL-1RN 1/2 group and the 2/2 group was found. In addition, the results of our stratified analysis indicated that IL-1RN VNTR polymorphism was associated with decreased risks of IS in homozygous model, heterozygous model, and dominant model in groups whose control size was <300. However, due to the limitation in our study, these results should be interpreted with caution.

Stroke ranks as the second leading cause of death and is reported to be the major cause of permanent disability worldwide. Approximately 87% of stroke patients suffer from IS, which is a complex multifactorial disease with genetic components, environmental triggers, and gene–environment interactions involved in its etiology. \cite{32,33} IL-1 is an important proinflammatory cytokine contribute to the pathophysiology of IS. IL-1Ra, which is a naturally competitive inhibitor of IL-1, inhibits the activity of IL-1 by binding to receptor IL-1R1 and

Figure 2. Forest plot of ischemic stroke risk associated with the interleukin-1 receptor antagonist gene 86-bp variable number tandem-repeat polymorphism (heterozygous comparison). (A) Results in random-effects model. (B) Results in fixed-effects model.
preventing its association for signaling. Several studies have suggested a neuro-protection role of IL-1Ra in IS. In brain ischemia models, peripherally administered rhIL-1ra inhibits brain damage and overexpression of IL-1RN reduces ischemic brain injury. In 2006, Emsley et al reported that compared to the placebo treated acute stroke patients, clinical outcomes at 3 months in the intravenous recombinant human IL-1Ra-treated group were better. The IL-1Ra gene (IL-1RN) contains an 86-bp VNTR polymorphism in intron 2. Homozygotes for allele 2 were found to have more prolonged and more intense inflammatory responses than other genotypes. It is reported that patients with IL-1RN allele 2 had slightly but significantly...
The results of the current meta-analysis suggested that IL-1RN 86-bp VNTR polymorphism is not related to IS. Further studies with larger sample sizes should be performed to confirm these findings.

Author contributions

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