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Review Article

Association of interleukin-6 -572G/C polymorphism with intracranial aneurysms risk: a meta-analysis

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Abstract: Intracranial aneurysm is mainly caused by the weakening of the arterial wall. The aim of the present article was to determine whether the interleukin-6 (IL-6) gene -572G/C polymorphism is correlated with intracranial aneurysms. The PubMed and Embase databases were retrieved to identify eligible IL-6 gene -572G/C polymorphism studies that examined the susceptibility to intracranial aneurysms risk. Finally, a total of 5 articles with 1068 cases and 3410 controls fulfilled the inclusion criteria and were selected for inclusion in the meta-analysis. The pooled odds ratios (OR) with 95% confidence interval (95% CI) were calculated to examine the associations. The meta-analysis results showed no significant association between IL-6 gene -572G/C polymorphism and intracranial aneurysms risk (GG vs CC: OR=0.98, 95% CI 0.13-7.58; GC vs CC: OR=0.66, 95% CI 0.18-2.42; the dominant model: OR=0.70, 95% CI 0.18-2.76; the recessive model: OR=1.48, 95% CI 0.54-4.08). In the subgroup analysis according to ethnicity, no significant interrelation was found for Caucasians or Asians. In conclusion, the present article suggested that there was no significant association between the IL-6 gene -572G/C polymorphism and intracranial aneurysms risk. Further large-scale studies are required to confirm these results.

Keywords: Intracranial aneurysm, IL-6 gene, genetic variant, meta-analysis

Introduction

Intracranial aneurysms are present in 2%-5% of the general population; Of these, approximately 0.7%-1.9% of cases rupture, causing subarachnoid hemorrhage [1]. With the continued improvement of imaging techniques, there is increased opportunity to detect an asymptomatic aneurysm [2]. The prevention and treatment for intracranial aneurysms has led to increased financial burdens worldwide. Aside from the classical risk factors, such as hypertension, smoking, female sex, and high shear stress that contribute to the pathogenesis of intracranial aneurysms [3, 4], there is evidence that genetic factors may also play an important role in the development of the disorder [5].

Cytokines released by inflammatory cells are critical component of the immune response. Interleukin 6 (IL-6) is one of the most potent proinflammatory cytokines expressed during acute inflammation, inducing and regulating the production of several acute phase proteins. Studies have reported that in patients with intracranial aneurysms, IL-6 worsened the inflammatory response of the hemal wall, leading to the injury of endothelial cells of the hemal wall, the inhibition of collagen expression and increased the hemal wall fragility factors that increase the incidence of intracranial aneurysms [6].

Human IL-6 gene is mapped to chromosome 7p21, and consists of 5 exons and 4 introns and is synthesized as a precursor protein of 232 amino acids [7]. The best characterized genetic variant of IL-6 is a G-to-C substitution at position -572 (-572G/C, rs1800796). Previous studies have shown an association of the -572G/C polymorphism in the IL-6 gene with several diseases, including coronary artery disease and ischemic stroke [8, 9].

In the past decade, several studies have investigated the association between the IL6 gene -572G/C polymorphism and intracranial aneurysms susceptibility. However, these studies have drawn apparently conflicting conclusions. The variation in results could be due partly to

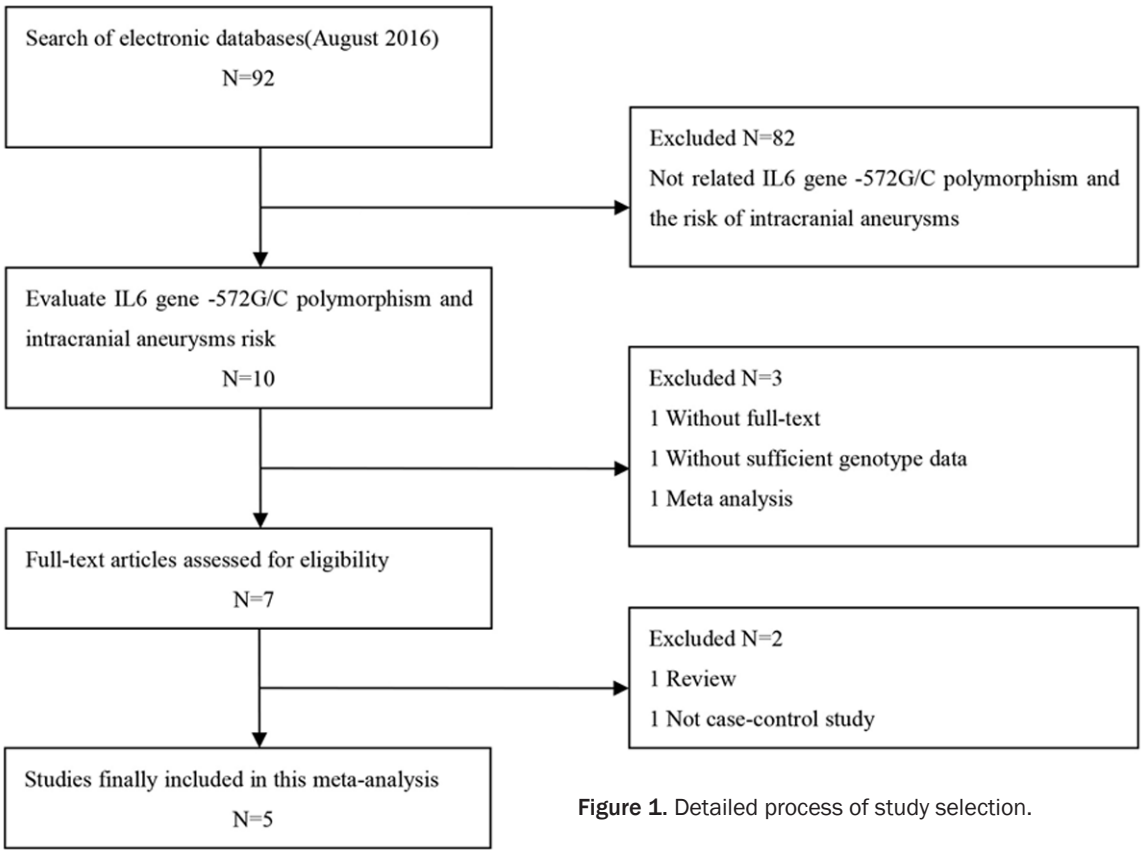

Figure 1. Detailed process of study selection.

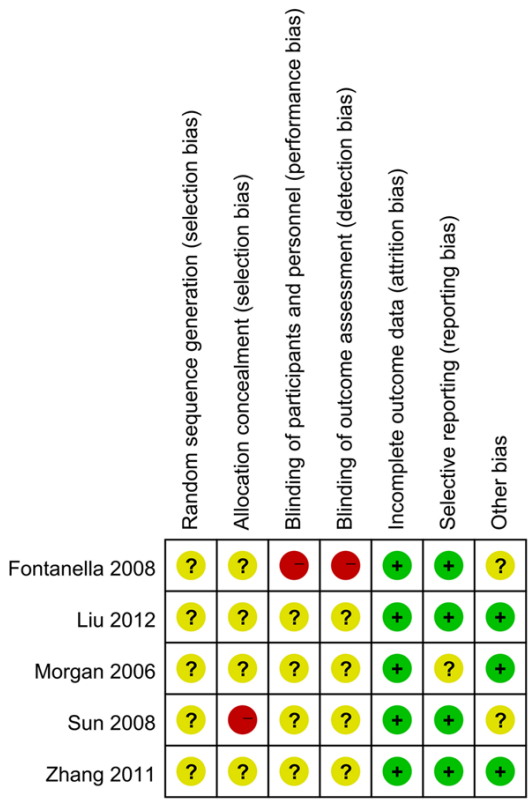

Figure 2. Summary risk of bias assessment.

insufficient power of the studies, a relatively small effect of the polymorphism on intracranial aneurysms risk or false-positive results. In the present study, we investigated whether the -572G/C polymorphism in the IL-6 gene is associated with intracranial aneurysms risk by performing a meta-analysis.

Materials and methods

Literature search

We searched the PubMed and Embase databases for all published articles about the association between the IL-6 gene -572G/C polymorphism and intracranial aneurysms risk (published by August, 2016). The following terms were used as search terms: "intracranial aneurysms", "interleukin-6" or "IL-6", "polymorphism" or "allele" or "genetic variant" or "variants."References of the retrieved articles or reviews on this topic were also manually screened to identify additional relevant eligible studies.

Inclusion and exclusion criteria

For inclusion in the meta-analysis, the articles had to meet the following criteria: (a) provided

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

Study	Year	Area	Race	Design	Cases/ Controls	Genotypes for cases			Genotypes for controls			HWE test
						GG	GC	CC	GG	GC	CC	
Morgan	2006	UK	Caucasians	PCC	91/2612	79	8	4	2359	244	9	0.32
Sun	2008	China	Asians	HCC	240/240	59	130	51	9	82	149	0.58
Fontanella	2008	Italy	Caucasians	HCC	335/156	280	49	6	131	23	2	0.40
Zhang	2011	China	Asians	HCC	182/182	145	32	5	165	16	1	0.38
Liu	2012	China	Asians	HCC	220/220	33	66	121	11	77	132	0.96

HWE, Hardy-Weinberg equilibrium; HCC, hospital-based case-control; PCC, population-based.

Table 2. Summary ORs and 95% CI of IL-6 gene -572G/C polymorphism with intracranial aneurysms risk

Variables	N	Cases/ controls	CC versus GG		CG versus GG		Dominant model		Recessive mode	
			OR (95% CI)	M	OR (95% CI)	M	OR (95% CI)	M	OR (95% CI)	M
Total	5	1068/3410	0.98 (0.13-7.58)	R	0.66 (0.18-2.42)	R	0.70 (0.18-2.76)	R	1.48 (0.54-4.08)	R
Ethnicity										
Caucasian	2	426/2768	2.91 (0.42-19.99)	R	1.34 (0.32-5.55)	R	1.55 (0.37-6.61)	R	2.23 (0.36-13.84)	R
Asians	3	642/642	0.22 (0.02-2.54)	R	0.22 (0.02-2.33)	R	0.22 (0.02-2.55)	R	0.86 (0.58-1.29)	F

N: number; M: model; R: random effects model; F: fixed effects model; CI: confidence interval; OR: odds ratio.

data evaluating the -572G/C polymorphism in the IL-6 gene and intracranial aneurysms risk, (b) used a case-control design, and (c) contained complete information about genotype frequency. The exclusion criteria were as follows: (a) not studying intracranial aneurysms, (b) review articles, (c) reports with incomplete or unusable data, and (d) duplicate publications.

Data extraction

Two authors extracted data from included articles independently and reached a consensus on all the items. For each publication, the following data was extracted: the first author's last name, publication date, country, race of the study participants, numbers of genotyped cases and controls, and the deviation from Hardy-Weinberg Equilibrium (HWE) of the control group.

Quality assessment

The seven studies were assessed qualitatively using tools designed to measure the risk of bias, as recommended by the Cochrane collaboration [10]. A summary of selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias identified in each individual study is presented in **Figure 2**.

Statistical analysis

Quality assessment was performed using Review Manager (version 5.0; The Cochrane Collaboration). All statistical analyses were done using Stata software (version 12.0, Stata Corp LP, College Station, TX, USA). We calculated the odds ratio (OR) and corresponding 95% confidence interval (CI) to evaluate the association between the IL-6 gene -572G/C polymorphism and intracranial aneurysms risk under a homozygote comparison (GG vs CC), a heterozygote comparison (GC vs CC), a dominant model (GG+GC vs CC) and a recessive mode (GG vs GC+CC) between groups. The heterogeneity assumption was assessed using the I^2 test. I^2 ranges between 0 and 100% and represents the proportion of inter-study variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50 and 75% were defined as low, moderate and high estimates, respectively. After confirming a lack of heterogeneity for the selected studies (I^2<50%), the pooled OR was calculated using the fixed effects model (Mantel-Haenszel). Otherwise, the random effects model (DerSimonian and Laird) was selected and applied. Sensitivity analysis was performed through comparison of random effect model values with the values of the fixed effect model to ensure the stability of

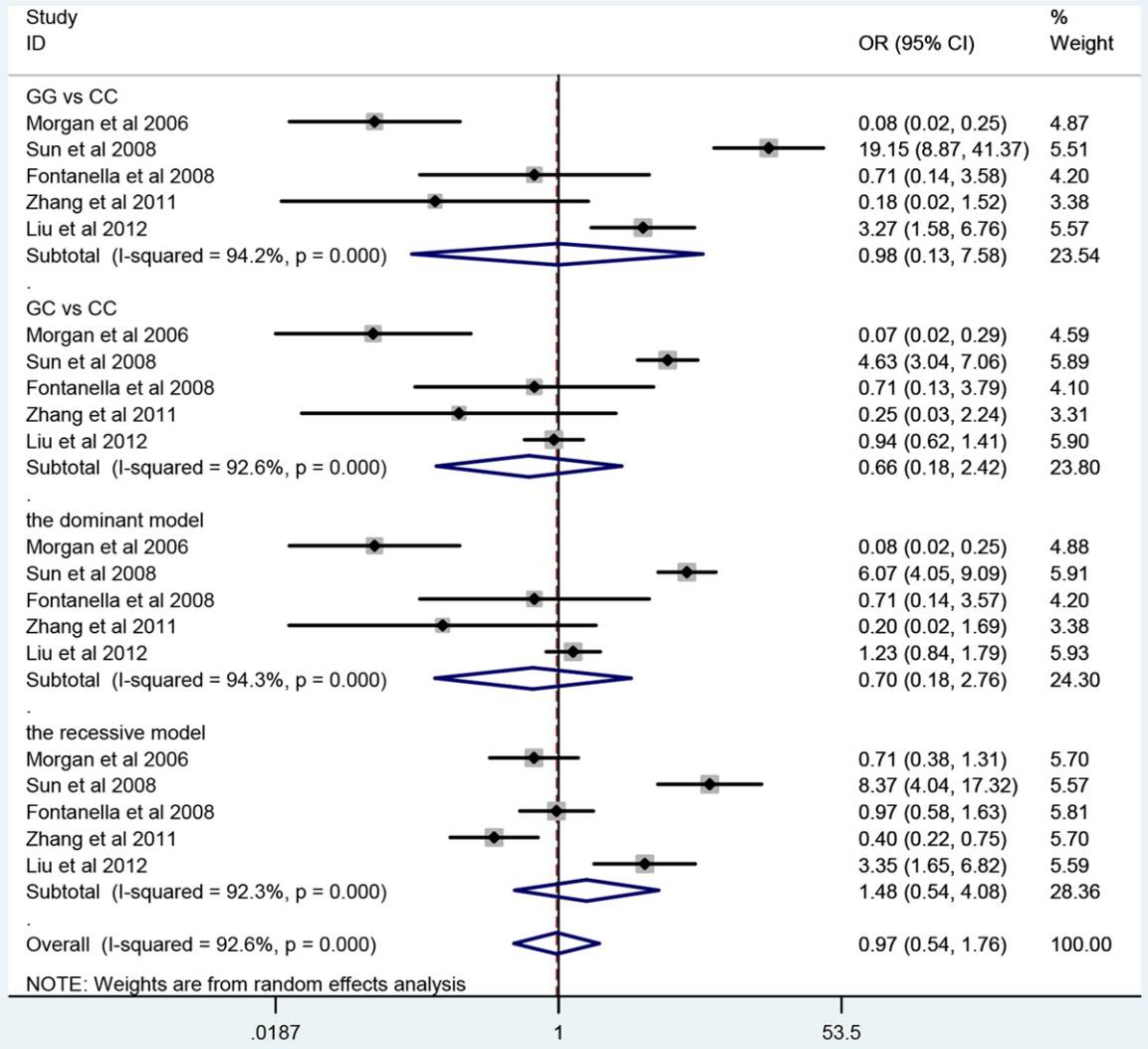

Figure 3. Meta-analysis of the relationship between the -572G/C polymorphism in the IL-6 gene and intracranial aneurysms risk.

the results. Publication bias was performed by plotting a Begg's funnel plot.

Results

Study characteristics

The flow diagram of the literature search is presented in **Figure 1**. A total of 92 potentially relevant articles were systematically identified via the search. Of these 92 studies, 87 were excluded because they did not satisfy the inclusion criteria. The remaining 5 studies with 1068 cases and 3410 controls were included in the meta-analysis [11-15]. All the articles were written in English. The genotype distributions in the control groups for all studies were consistent with HWE. All of the studies had similar eligibility criteria. And the main characteristics of the eligible studies are summarized in **Table 1**. **Figure 2** shows the summary of the risk of bias, and the main study biases may be caused by small sample size, randomization, the procedure for concealing the treatment allocation and blinding.

Quantitative synthesis

Table 2 shows the results of the overall analysis and the subgroup analysis. The analyses of the full data set found no statistical association between the -572G/C polymorphism in the IL-6 gene and intracranial aneurysms risk (**Figure 3**, GG vs CC: OR=0.98, 95% CI 0.13-7.58; GC vs

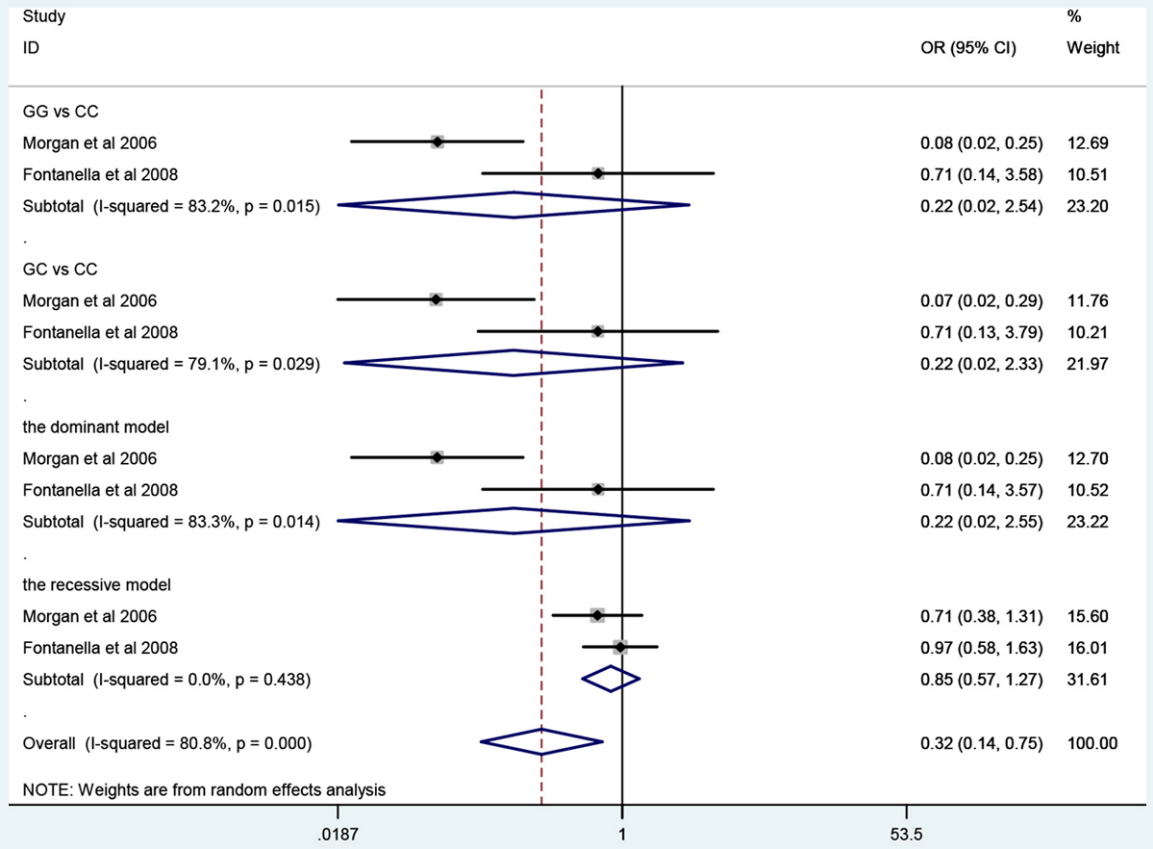

Figure 4. Meta-analysis of the relationship between the -572G/C polymorphism in the IL-6 gene and intracranial aneurysms risk in Caucasians.

CC: OR=0.66, 95% CI 0.18-2.42; the dominant model: OR=0.70, 95% CI 0.18-2.76; the recessive model: OR=1.48, 95% CI 0.54-4.08). The association between the IL6 gene -572G/C polymorphism and intracranial aneurysms risk was additionally investigated by performing stratified analyses based on ethnicity. No significant increased risk was observed in Caucasians and Asians (**Figures 4** and **5**). Sensitivity analyses were conducted by altering the statistic models. No significant alteration in our results was detected, indicating that our conclusions were reasonable and reliable.

Publication bias

Begg's funnel plot was conducted to assess the publication bias of the included studies. The funnel plot was used to measure the asymmetry of the funnel plot (**Figure 6**). Results showed that there was no publication bias.

Discussion

Intracranial aneurysms are balloon-like dilations of the cerebral arteries that affect 2-5% of the population [1]. Intracranial aneurysms have complex pathogenesis development pathways that are influenced by genetic and environmental factors. Epidemiological studies have shown that the main risk factors for intracranial aneurysms include smoking and hypertension. In addition, previous genetic research demonstrated that the pathogenesis of intracranial aneurysms may be related to some specific gene polymorphism, such as in the IL-1β gene [16], TNF-α gene [13], apolipoprotein A gene [17], and the angiotensin converting enzyme gene [18]. Cytokine levels are predictive of coronary aneurysm formation, and IL-6 polymorphisms lead to changes in the inflammatory processes in diseases such as kawasaki disease [19]. IL-6 may also play role in the response to intracranial aneurysms. Previous studies have reported associations between the -572G/C polymorphism in the IL-6 gene and the risk of intracranial aneurysms. Although exhaustive association articles have been undertaken, a definite conclusion has not been reached. Therefore, in our study, we this per-

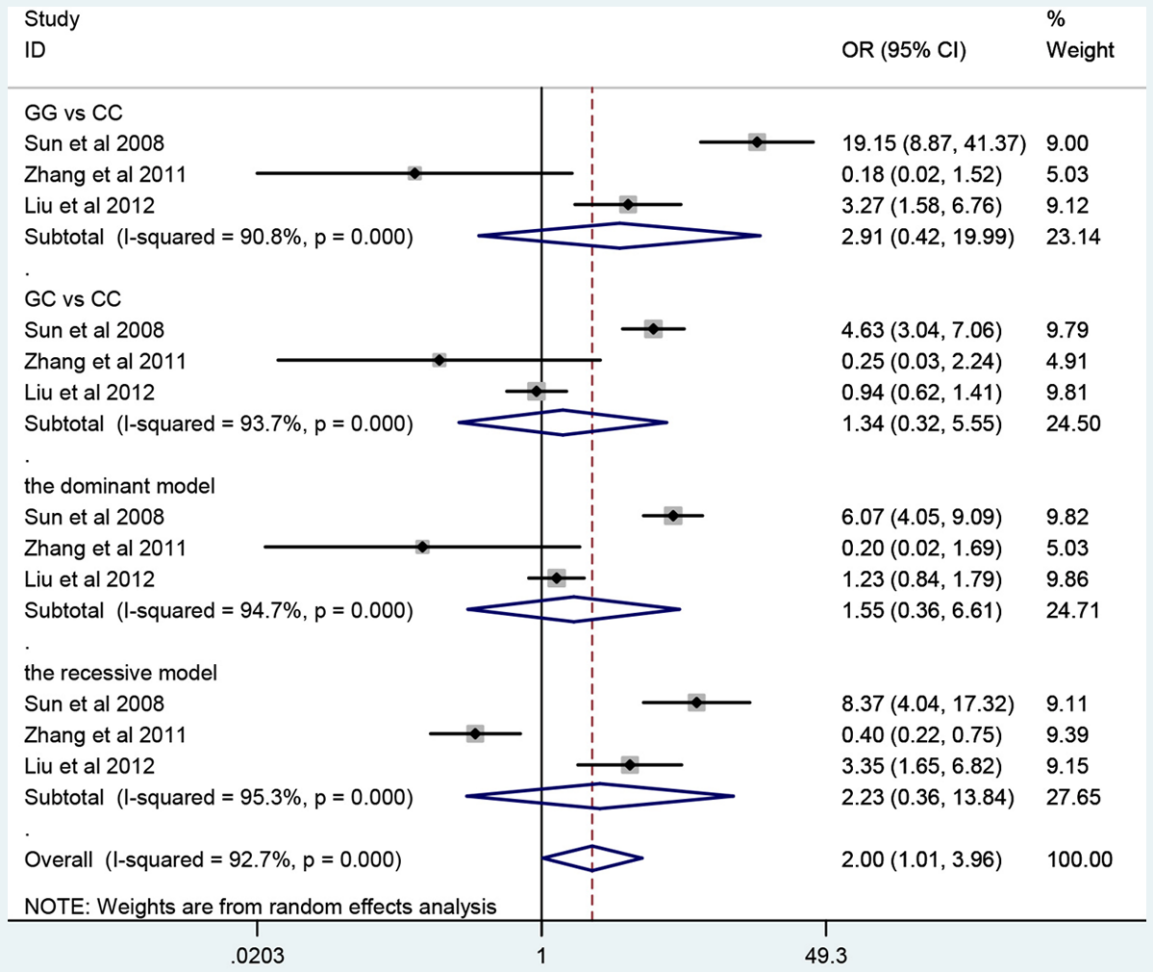

Figure 5. Meta-analysis of the relationship between the -572G/C polymorphism in the IL-6 gene and intracranial aneurysms risk in Asians.

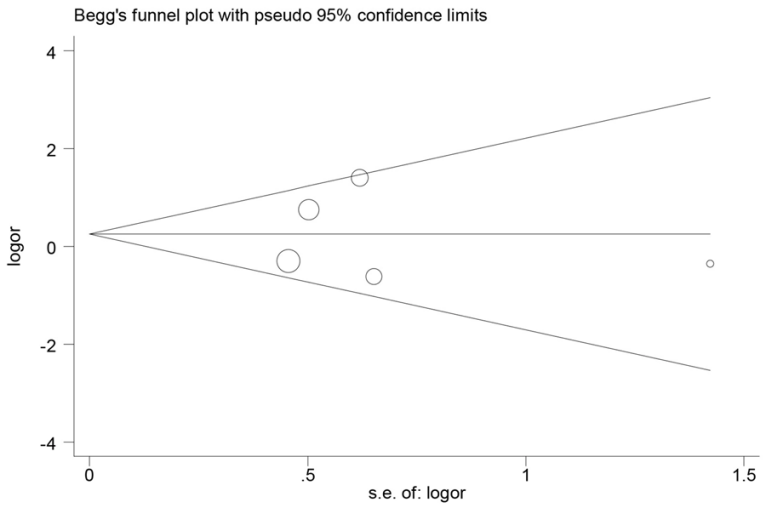

Figure 6. Begg's funnel plot test.

formed the meta-analysis of data from case-controlled studies to investigate whether the -572G/C polymorphism in the IL-6 gene is associated with the occurrence of intracranial aneurysms.

In this study, we included 5 articles that included 4478 subjects. This meta-analysis found an absence of association between the IL-6 gene -572G/C polymorphism and intracranial aneurysms risk. Moreover, a race-based subgroup analysis indicated no significantly increased risk

of intracranial aneurysms in Asians and Caucasians. There are two potential explanations for these results. First, because of the complex nature of intracranial aneurysms, it is unlikely that a single nucleotide polymorphism would be associated with an increased risk of intracranial aneurysms, without a contribution from other polymorphic susceptibility genes. As reported previously, there is strong evidence of linkage disequilibrium between the -174G/C and -572G/C polymorphisms in the IL-6 gene [20], which may synergistically increase the risk of this disease [11]. Second, other factors, such as smoking and hypertension, can also influence the development or the prognosis of intracranial aneurysms. Further studies of gene-gene and gene-environment interactions should be taken into consideration in future studies.

This study has several limitations. First, only published studies in English were included; thus it is possible that some relevant published studies were missed, which may have biased the results. Second, our article was based on unadjusted estimates, without controlling for confounding factors because most studies did not provide these data. Third, we did not evaluate gene-environment interactions due to the lack of sufficient studies. It is possible that specific environmental and lifestyle factors (such as smoking) may alter the associations between gene polymorphisms and intracranial aneurysms risk.

In summary, the present meta-analysis demonstrate that the IL-6 gene -572G/C polymorphism may not contribute to the risk of intracranial aneurysms. Further large-scale studies that examine gene-gene and gene-environment interactions to further investigate an association of the IL-6 gene -572G/C polymorphism to intracranial aneurysm risk.

Disclosure of conflict of interest

None.

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