Polymorphisms of Inflammatory Cytokine Genes and Risk for Intracranial Aneurysm: A Systematic Review and Meta-Analysis

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**Purpose:** Inflammatory cytokines are thought to be involved in the pathogenesis of intracranial aneurysm (IA), although results among studies in the literature are inconsistent. This article sought to review studies on the associations among polymorphisms in inflammatory cytokine genes and IA risk and to provide recommendations for future research.

**Materials and Methods:** A systematic search of PubMed, Embase, and Web of Science was conducted up to August 4, 2019. The associations between polymorphisms of inflammatory cytokine genes and IA risk were estimated by pooled odds ratios (ORs) and 95% confidence intervals (CIs). Subgroup analyses were performed according to race. Qualitative systematic review was conducted for variants that were studied in only one study. All analyses were performed using STATA 12.0.

**Results:** 13 studies investigating the associations between polymorphisms in five inflammatory cytokine genes (TNF-α, IL-1a, IL-1β, IL6, and IL-12B) and IA were reviewed. Combined results showed that the A allele of TNF-α rs1800629 polymorphism has a protective effect against IA (dominant model: OR=0.65, 95% CI=0.47–0.89, p=0.007). No associations were identified between polymorphisms in IL-1a rs1800587, IL-1β rs16944, IL6 rs1800795 and rs1800796, or IL-12B rs3212227 and IA risk.

**Conclusion:** This review demonstrated an association between TNF-α rs1800629 polymorphism and IA in Caucasians, illustrating the potentially important role of genes involved in inflammation in IA.

**Key Words:** Intracranial aneurysm, inflammatory cytokines, polymorphism, meta-analysis

**INTRODUCTION**

Intracranial aneurysm (IA) is characterized by abnormal dilation or expansion of the intracranial arteries. The prevalence of IA is appropriately 3.2% in the adult population.1 The rupture of IA can lead to subarachnoid hemorrhage (SAH), a devastating neurological condition with high morbidity and mortality.2,3 Despite great research efforts, the pathophysiology of IA is not fully understood, the prognosis of ruptured IA remains poor, and methods with which to predict, prevent, and manage IA are limited.

Many studies have indicated that, in addition to known environmental risk factors of smoking, excessive drinking, and hypertension,4,5 inflammation is also involved in the etiology of IA.6 Studies have shown that local infiltration of inflammatory cells can lead to thinning and weakening of the walls of intracranial arteries, making them susceptible to IA. Tumor necrosis factors (TNFs) and interleukins (ILs) are important components of inflammatory cytokines. TNF-α is the earliest and most important inflammatory mediator in the inflammatory process: it can activate neutrophils and lymphocytes, increase the permeability of vascular endothelial cells, regulate the metabolic activity of other tissues, and promote the synthesis and release of other cytokines.8 ILs play important roles in the maturation, activation, proliferation, and immune regulation of immune cells, and participate in a variety of physiological and pathological reactions of the body.9 Growing evidence indi-
cates that inflammatory cytokines may be associated with the occurrence of IA, possibly through the phenotypic regulation of cerebral smooth muscle cells or systemic inflammation, and several studies have investigated the possible associations between polymorphisms of inflammatory cytokine genes and risk of IA, although with inconsistent results. The lack of reproducibility of association studies is probably due to population heterogeneity or small sample sizes with inadequate statistical power. Considering the insufficient evidence and inconclusive results about the genetic variants of inflammatory cytokine genes associated with IA risk, a systematic review and meta-analysis is important and necessary to assess the associations. The aims of this study were to overview the associations between polymorphisms in inflammatory cytokine genes and risk of IA and to provide reference for future study.

MATERIALS AND METHODS

This study was conducted in accordance with the recommendations to improve the quality of meta-analyses of genetic association studies and followed the Human Genome Epidemiology Network guidelines. Quality assessment of studies was conducted based on the Strengthening the Reporting of Genetic Association Studies statement.

Literature search strategy

Electronic databases (PubMed, Embase, and Web of Science) were used to search for articles on human association studies between polymorphisms of inflammatory cytokine genes and risk of IA that had been published up to August 4, 2019. The keywords “intracranial aneurysm” or “cerebral aneurysm” or “subarachnoid hemorrhage” or “inflammatory cytokine” or “interleukin” or “IL” or “tumor necrosis factor” or “TNF” were used in “and” combinations (Table 1). The search was limited

| Table 1. Literature Search Strategy |
|-----------------------------------|
| **Web of Science**                |
| 1. Search ((intracranial aneurysm*) OR cerebral aneurysm*) OR subarachnoid hemorrhage*) 49444 |
| 2. Search ((inflammatory cytokine*) OR interleukin*) OR tumor necrosis factor*) OR TNF*) 759468 |
| 3. 1 AND 2 759 |
| 4. Filters: Humans 414 |
| 5. (#4) NOT case report 339 |
| 6. (#5) NOT review 258 |
| **Embase**                       |
| 1. (“intracranial aneurysm” OR “cerebral aneurysm” OR “subarachnoid hemorrhage”) AND [embase]/lim 54462 |
| 2. “inflammatory cytokine” OR “interleukin” OR “tumor necrosis factor” OR “TNF”) AND [embase]/lim 831026 |
| 3. #1 AND #2 936 |
| 4. #3 AND [humans]/lim AND [embase]/lim 597 |
| 5. #4 NOT ‘case report’/exp AND [embase]/lim 569 |
| 6. #5 NOT ‘review’/exp AND [embase]/lim 387 |
to English-language publications. The reference lists of included articles were checked for additional studies.

Selection criteria
We included studies assessing associations of inflammatory cytokine gene polymorphisms with proven IA (ruptured or unruptured IA diagnosed by computed tomography angiography or magnetic resonance angiography or digital subtraction angiography or confirmed during intracranial surgery). The inclusion criteria were as follows: 1) case-control studies investigating the associations between at least one genetic variant of an inflammatory cytokine gene and risk of IA; 2) sufficient information was available to calculate odds ratios (ORs) and 95% confidence intervals (CIs). The exclusion criteria included other genetic disorders with IA, reviews, comments, meeting abstracts, animal models, case reports, and unknown etiology of SAH. When duplication or overlapping data occurred, only the largest research was included. Gene polymorphisms included in meta-analysis need to be evaluated in at least two publications, and for variants studied just in one study, a systematic review was performed.

Data extraction and quality assessment
Data from the included studies were extracted by two authors (LH and BL) independently, and disagreements were resolved by consensus with another author (XL). The following variables were retrieved from the included studies: first author, year of publication, country, sex, mean age, sample size, numbers or frequencies of genotypes and alleles, and Hardy-Weinberg equilibrium (HWE) status. HWE was obtained either from the article or by calculating genotype distributions. The Newcastle-Ottawa quality assessment scale (NOS) was used to evaluate the quality of studies in this meta-analysis. Studies with NOS scores ≥6 were considered to be of high quality.

Statistical analysis
Statistical analyses were performed using STATA 12.0 software (Stata Corporation, College Station, TX, USA). Chi-square was used to compare the frequencies of genotypes and alleles between case and control groups. With the rarity of homozygous variants and the generally small study sizes, the risk estimates for the recessive model were unstable, and thus, this study only presented the results of dominant and allele models. In this meta-analysis, pooled ORs and corresponding 95% CIs were estimated using a fixed-effect model or random-effect model. Heterogeneity was assessed using the Cochran Q test and corresponding $p$-values and $I^2$. Variables with values of $p<0.05$ or $I^2>50\%$ was considered as having significant heterogeneity, for which the random-effect model was used. Otherwise, the fixed-effect model was used. In addition, considering that the distribution of genotypes can differ between different populations, subgroup analyses were performed based on race. Publication bias was assessed by visualization of funnel plots from the Begg’s rank correlation method and Egger’s regression asymmetry. $p<0.05$ was considered statistically significant.

RESULTS

Characteristics of the available studies
A total of 777 articles were identified through the initial search, and no article was identified through the relevant references check. Upon screening for duplication and eligibility, data from 13 studies were extracted and finally included in this meta-analysis. In these studies, 3 articles investigated the associations between TNF-α rs1800629 polymorphism and risk of IA;13,14,17 11 articles investigated the associations between IL gene (IL-1α, IL-1β, IL6, and IL-12B) polymorphisms and risk of IA.11,12,17-25 Detailed characteristics of the included studies are summarized in Table 2. A detailed flow chart of study selection is presented in Fig. 1.

Associations between inflammatory cytokine gene polymorphisms and risk of IA
In total, 13 studies investigating the associations of polymorphisms in five inflammatory cytokine genes (TNF-α, IL-1α, IL-1β, IL6, and IL-12B) with the risk of IA were involved. The pooled results showed a significant association between TNF-α rs1800629 polymorphism and IA in dominant and allelic models (dominant model: OR=0.65, 95% CI=0.47–0.89, $p=0.007$; allelic model: OR=0.74, 95% CI=0.56–0.97, $p=0.030$) (Table 3). No association was found between IL-1α rs1800587, IL-1β rs16944, IL6 rs1800795 or rs1800796, and IL-12B rs3212227 and risk of IA ($p>0.05$). In addition, race-based subgroup analyses showed that IL6 rs1800796 was not associated with IA in either Chinese (3 studies) or Caucasian (4 studies) individuals (Table 3, Fig. 2). Interstudy heterogeneity was found in IL6 rs1800796 and IL-12B rs3212227 (Table 3). For IL6 rs1800796, 4 studies found statistically significant differences, whereas the other 3 did not. One study found that IL-12B was not related to IA, while another found that its polymorphism was a risk factor for IA. As the association between rs1800796 and IA was investigated by 7 studies, we used Begg’s funnel plot and the Egger’s test to assess publication bias. In the dominant model, no significant publication bias was observed (Fig. 3).

Systematic review of other inflammatory cytokine gene polymorphisms and risk of IA
In addition to the inflammatory cytokine gene polymorphisms mentioned above, there were various other polymorphisms in TNF and IL genes that were studied in Chinese, Japanese, and Indian populations.17,18,25-30 The studies reported significant associations between TNF-α rs361525 and rs1799964 polymorphisms and IA in Indian and Chinese individuals, respectively. Additional research showed that IL-11RA and TNFRSF13B polymorphisms were associated with IA in a Japanese cohort.
| Gene | SNPs | Author and reference | Year | Country | Sample size | Mean age (yr) | Male (n, %) | Genotype<sup>*</sup> | Allele (M/m)<sup>†</sup> | OR (95% CI) | NOS | HWE |
|------|------|----------------------|------|---------|-------------|--------------|------------|----------------|----------------|----------------|-----|-----|
| TNF-α | rs1800629 | Borges, et al.13 | 2018 | Brazil | 33 | 81 | 54.0±9.0 | 52.0±6.0 | - | 38 (46.91) | 21/3/9 | 47/15/19 | 0.79 (0.34–1.82) | 0.96 (0.52–1.77) | 6 | 0.00 |
|      |      | Sathyan, et al.17 | 2015 | India | 220 | 250 | 51.2±11.4 | - | 123 (55.91) | - | 185/41/0 | 192/51/1 | 0.82 (0.52–1.29) | 0.82 (0.53–1.26) | 6 | 0.21 |
|      |      | Fontanella, et al.16 | 2007 | Italy | 171 | 144 | 51.4±14.0 | 53.4±14.2 | 56 (32.75) | 70 (48.61) | 136/30/5 | 92/50/2 | 0.46 (0.28–0.75) | 0.57 (0.37–0.89) | 7 | 0.09 |
| IL-1α | rs1800587 | Sathyan, et al.17 | 2015 | India | 220 | 250 | 51.2±11.4 | - | 123 (55.91) | - | 109/83/27 | 118/108/17 | 0.95 (0.66–1.37) | 0.91 (0.69–1.20) | 6 | 0.25 |
|      |      | Fontanella, et al.16 | 2010 | Italy | 215 | 155 | 55.0±14.5 | 53.7±14.0 | 74 (34.42) | 50 (32.28) | 82/110/23 | 63/80/12 | 1.11 (0.73–1.69) | 1.13 (0.83–1.53) | 7 | 0.05 |
|      |      | Sathyan, et al.18 | 2015 | India | 220 | 250 | 51.2±11.4 | - | 123 (55.91) | - | 84/101/38 | 90/115/39 | 0.97 (0.66–1.41) | 0.99 (0.76–1.29) | 6 | 0.82 |
| IL-1β | rs18044 | Sathyan, et al.17 | 2015 | India | 220 | 250 | 51.2±11.4 | - | 123 (55.91) | - | 94/88/33 | 64/68/23 | 0.91 (0.59–1.43) | 0.65 (0.49–0.88) | 7 | 0.48 |
|      |      | Khandelwal, et al.19 | 2006 | India | 220 | 250 | 51.2±11.4 | - | 123 (55.91) | - | 118/108/17 | 123/110/11 | 1.11 (0.73–1.69) | 1.13 (0.83–1.53) | 7 | 0.05 |
| IL-6 | rs1800795 | Sathyan, et al.17 | 2015 | India | 220 | 250 | 51.2±11.4 | - | 123 (55.91) | - | 114/63/8 | 153/80/11 | 0.83 (0.56–1.22) | 0.85 (0.61–1.18) | 6 | 0.90 |
|      |      | Morgan, et al.11 | 2006 | UK | 91 | 2720 | 55 (24–80) | 56 (49–64) | 36 (40.0) | 37 (42.1) | 2720/2324 | 200/100 | 0.54 (0.35–0.83) | 0.57 (0.41–0.79) | 7 | 0.36 |
| IL6 | rs1800796 | Sathyan, et al.17 | 2015 | India | 220 | 250 | 51.2±11.4 | - | 123 (55.91) | - | 57/126/37 | 81/111/52 | 1.42 (0.95–2.13) | 0.95 (0.73–1.23) | 6 | 0.23 |
|      |      | Morgan, et al.11 | 2006 | UK | 91 | 2720 | 55 (24–80) | 56 (49–64) | 36 (40.0) | 37 (42.1) | 220/240 | 220/240 | 0.54 (0.35–0.83) | 0.57 (0.41–0.79) | 7 | 0.36 |
| IL-6 | rs1800796 | Sathyan, et al.17 | 2015 | India | 220 | 250 | 51.2±11.4 | - | 123 (55.91) | - | 57/126/37 | 81/111/52 | 1.42 (0.95–2.13) | 0.95 (0.73–1.23) | 6 | 0.23 |
|      |      | Morgan, et al.11 | 2006 | UK | 91 | 2720 | 55 (24–80) | 56 (49–64) | 36 (40.0) | 37 (42.1) | 220/240 | 220/240 | 0.54 (0.35–0.83) | 0.57 (0.41–0.79) | 7 | 0.36 |
| IL-12B | rs3212227 | Sathyan, et al.17 | 2015 | India | 220 | 250 | 51.2±11.4 | - | 123 (55.91) | - | 88/86/36 | 83/115/31 | 0.85 (0.58–1.25) | 0.98 (0.75–1.28) | 6 | 0.37 |
|      |      | Morgan, et al.11 | 2006 | UK | 91 | 2720 | 55 (24–80) | 56 (49–64) | 36 (40.0) | 37 (42.1) | 220/240 | 220/240 | 0.54 (0.35–0.83) | 0.57 (0.41–0.79) | 7 | 0.36 |
|  
|      |      | Morgan, et al.11 | 2006 | UK | 91 | 2720 | 55 (24–80) | 56 (49–64) | 36 (40.0) | 37 (42.1) | 220/240 | 220/240 | 0.54 (0.35–0.83) | 0.57 (0.41–0.79) | 7 | 0.36 |

SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; =, not available; NOS, Newcastle-Ottawa quality assessment scale; HWE, Hardy-Weinberg equilibrium. *Genotype presented as wild type/heterozygous/homozygous, †M/m, major/minor allele.
illustrating the potential roles of these genes in IA (Supplementary Table 1, only online). However, as these polymorphisms were discussed only in a single study or the genotype frequencies could not be obtained, no definite conclusions could be drawn in this review, and more studies are needed to clarify whether these associations can be detected in different populations of larger sample sizes.

**Fig. 1.** PRISMA flow diagram of study selection process. SNPs, single nucleotide polymorphisms, SAH, subarachnoid hemorrhage; IA, intracranial aneurysm.

**Table 3.** Main Results of the Pooled ORs in Meta-Analysis of the Associations between Inflammatory Cytokine Gene Polymorphisms and Intracranial Aneurysm

| Gene SNPs     | N  | Sample size (case/control) | Dominant model | Allelic model |
|---------------|----|----------------------------|----------------|--------------|
|               |    |                           | OR (95% CI)    | P (%)        | Pz            | OR (95% CI)    | P (%)        | Pz            |
| **TNF-α rs1800629** | 3  | 424/475                    | 0.65 (0.47–0.89) | 36.5 | 0.212 | 0.007 | 0.74 (0.56–0.97) | 7.7 | 0.338 | 0.030 |
| **IL-1α rs1800587** | 2  | 435/405                    | 1.02 (0.77–1.34) | 0.0 | 0.590 | 0.903 | 1.11 (0.91–1.37) | 0.0 | 0.916 | 0.307 |
| **IL-1β rs16944** | 3  | 666/636                    | 1.03 (0.83–1.29) | 0.0 | 0.541 | 0.786 | 1.09 (0.93–1.28) | 35.2 | 0.214 | 0.282 |
| **IL6 rs1800795** | 5  | 886/3827                   | 0.87 (0.73–1.04) | 48.4 | 0.113 | 0.126 | 0.84 (0.69–1.04)* | 56.8 | 0.065 | 0.114 |
| **IL6 rs1800796** | 7  | 1252/3888                  | 0.75 (0.58–1.15)* | 89.8 | <0.001 | 0.422 | 0.91 (0.51–1.62)* | 93.8 | <0.001 | 0.735 |
| **IL6 rs1800796 subgroup analysis** | | | | | | | | | |
| Chinese       | 3  | 642/642                    | 0.45 (0.07–2.79)* | 95.3 | <0.001 | 0.390 | 0.73 (0.24–2.23)* | 96.6 | <0.001 | 0.579 |
| Caucasian     | 4  | 610/3246                   | 1.13 (0.87–1.46) | 49.0 | 0.117 | 0.376 | 1.08 (0.75–1.54)* | 61.3 | 0.052 | 0.684 |
| **IL-12B rs3212227** | 2  | 384/508                    | 1.32 (0.55–3.18)* | 87.9 | 0.004 | 0.537 | 1.19 (0.81–1.74)* | 74.3 | 0.048 | 0.373 |

SNPs, single nucleotide polymorphisms; N, number of studies; P, Higgins P statistic; Pz, value for Q test; OR, odds ratio; CI, confidence interval.

*ORs were calculated in random-effect model.

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DISCUSSION

IA comprises a multifactorial disease related to genetic and environmental factors. While evidence indicates that inflammation may play an important role in injury to the intracranial artery wall, research on associations of inflammatory cytokines and IA risk has proven inconsistent. In this meta-analysis, we quantitatively evaluated the associations of inflammatory cytokine gene polymorphisms with IA risk. The pooled results showed that TNF-α rs1800629 polymorphism is associated with IA, suggesting that inflammatory cytokines, especially TNF-α, are associated with IA.

**Fig. 2.** Forest plots for the associations of inflammatory cytokine gene polymorphisms with IA risk in a dominant model. (A) Forest plot of TNF-α rs1800629 and IA risk in the dominant model. (B) Forest plot of IL-1α rs1800587 and IA risk in the dominant model. (C) Forest plot of IL-1β rs16944 and IA risk in the dominant model. (D) Forest plot of IL-6 rs1800795 and IA risk in the dominant model. (E) Forest plot of IL-6 rs1800796 and IA risk in the dominant model. (F) Forest plot of IL-12B rs3212227 and IA in the dominant model. IA, intracranial aneurysm; OR, odds ratio; CI, confidence interval.
TNF-α is located at chromosome 6p21.3 and is a powerful pro-inflammatory cytokine that plays a key role in initiating and regulating the cascade events of the inflammatory response. It can activate proteolytic enzymes that destroy endothelial cells. TNF-α has been shown to be associated with the occurrence of many diseases, including inflammatory diseases. In this article, we found that TNF-α rs1800629 played a protective role of IA in dominant and allelic models, indicating that TNF-α may be important in IA. Interestingly, animal study has revealed that TNF-α knockout and TNF-α inhibition can significantly reduce the occurrence and rupture of IA. Increased TNF-α protein can promote inflammation and subsequent apoptosis in vessels, thereby weakening vessel walls, destroying the integrity thereof, and increasing the risk of IA. However, few studies have investigated the mechanism of TNF-α polymorphism in relation to IA. It is not clear whether rs1800629 polymorphism can affect the occurrence of IA by regulating the expression levels of TNF-α, because in the studies that are available, participants did not undergo measurement of TNF-α levels for the mutant and wild-type allele. Moreover, only 3 original studies have investigated the association between this polymorphism and IA, and a discrepancy was observed between the pooled results and the original data. Due to the small sample sizes and potential population heterogeneity, no definite conclusions could be drawn, and more studies are needed to clarify whether the association can be detected in different populations of larger sample sizes.

IL1 is located at the long arm of human chromosome 2 and consists of three types: IL-1α, IL-1β, and IL-1Ra, which have pleiotropic actions in the central nervous system. Studies have shown that IL1 is involved in many processes, including inflammation, immune regulation, and neurodegeneration. IL6 is primarily related to congenital immunity, and imbalance in its activity has been found to be associated with genetic modification or mutations related to auto-inflammatory diseases. In this study, we were unable to document an association for IL-1α rs1800587 and IL-1β rs16944 with IA. This was consistent with a previous meta-analysis. Meanwhile, studies have indicated that IL-1β induces infiltration of neutrophils, macrophages, and other immune cells associated with the formation of thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm (AAA). Whether there is genic overlap among IA, TAA, and AAA and whether the mechanism of IL-1’s effect on IA is consistent with AAA and TAA still need to be studied.

IL6 is located at the short arm of chromosome 7 and encodes a 184 amino acid glycosylated protein, which has two biallelic polymorphisms in its promoter region. Previous studies have reported that IL6 gene polymorphisms are associated with the onset and progression of cerebral hemorrhage. In this study, we conducted meta-analysis and subgroup analyses based on race to study the associations between IL6 rs1800795 and rs1800796 polymorphisms and IA, but found no associations. However, in conflict with these results, Zheng, et al. conducted a meta-analysis with 6 studies prior to 2013 using fixed-effect model and concluded that IL6 promoter polymorphisms (rs1800795 and rs1800796) are associated with IA. Due to high heterogeneity between the studies, we chose a random-effect model, which may account for the difference in results. Heterogeneity between studies may stem from different basic data for the subjects included in the studies: for example, age distributions differed in other studies from the study of Zhang, et al. conducted in Chinese; sex distributions differed in other studies from the study of Morgan, et al. conducted in Caucasians. In addition, the genotype distributions of IL6 rs1800796 in Sun, 4
et al. and Liu et al. opposed those of other studies conducted in China, which may be the source of heterogeneity and may explain the opposite direction of their ORs. Considering the potential difference in genetic background and allelic frequency distributions among different populations, it is necessary to study the correlation between IL6 gene polymorphisms and IA risk in different countries and races.

*IL12B*, located at chromosome 5q33.3, is a cytokine with extensive biological activity and encodes a subunit of IL12. Study had shown that *IL-12B* rs3212227 polymorphism is associated with susceptibility to IA. However, a meta-analysis of *IL-12B* rs3212227 polymorphism and IA risk reported no association. Consistent with the results of the latter study, we recorded no association between *IL-12B* rs3212227 polymorphism and IA in different models. As fewer studies were incorporated in this meta-analysis and as the distributions of sex and allelic frequencies were different in these two studies, the results may be biased, such that further studies are needed.

Some limitations of this study should be considered. First, this research was conducted at the study level, due to the limited information on individuals, and we could not adjust the results for possible confounding factors. Also, ecological bias was unavoidable. Second, the analysis was limited to articles published in English, excluding other languages and databases, and selection bias cannot be ruled out (Supplementary Table 2, only online). Third, there are not many relevant studies at present, and no definite conclusions can be drawn. More research is needed to confirm the association. Despite these limitations, in this article, we have collected and analyzed all available data from original studies on inflammatory cytokine genes and IA so far, and compared with a single study, this study increases the efficiency and credibility of results. As a polygenic hereditary disease, larger sample sizes with high-quality studies are needed to confirm the associations of polymorphisms in inflammatory cytokine genes with the risk of IA.

In conclusion, this review showed that *TNF-α* rs1800629 polymorphism is associated with IA in Caucasians, providing direction for future laboratory and clinical research. Identifying these risk factors can help with identifying individuals at high risk of IA, increasing the likelihood of early therapeutic intervention to improve prognosis. However, as different environmental or genetic factors may lead to IA, more data from multi-center studies conducted in different ethnic populations are still needed to clarify the pathophysiological mechanisms of inflammatory cytokine gene polymorphisms in relation to IA.

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AUTHOR CONTRIBUTIONS

Data curation: Liming Hu and Bingyang Li. Funding acquisition: Junxia Yan. Methodology: Liming Hu and Xin Liao. Project administration: Junxia Yan. Software: Liming Hu and Xin Liao. Supervision: Xin Liao. Validation: Junxia Yan. Writing—original draft: Liming Hu. Writing—review & editing: Bingyang Li and Junxia Yan. Approval of the final manuscript: all authors.

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