Original Article
Yonsei Med J 2020 May;61(5):391-399
https://doi.org/10.3349/ymj.2020.61.5.391
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

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

Liming Hu*, Bingyang Li*, Xin Liao, and Junxia Yan

Department of Epidemiology and Health Statistics, XiangYa School of Public Health, Central South University, Changsha, China.

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-1α*, *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-1α* 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.[7] 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-

Received: February 11, 2020 **Accepted:** March 20, 2020
Corresponding author: Junxia Yan, PhD, Department of Epidemiology and Health Statistics, XiangYa School of Public Health, Central South University, Shang Mayuanling, KaiFu District, Changsha 410078, China.
Tel: 86-0731-84805465, Fax: 86-0731-84805454, E-mail: 20457456@qq.com

*Liming Hu and Bingyang Li contributed equally to this work.
•The authors have no potential conflicts of interest to disclose.

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,[10] and several studies have investigated the possible associations between polymorphisms of inflammatory cytokine genes and risk of IA, although with inconsistent results.[11-14] 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.[15] Quality assessment of studies was conducted based on the Strengthening the Reporting of Genetic Association Studies statement.[16]

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*", "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	TS=("intracranial aneurysm*") OR TS=("cerebral aneurysm*") OR TS=("subarachnoid hemorrhage*") Databases=WOS, BCI, KJD, RSCI, SCIELO Timespan=All years Search language=Auto	40547
2	TS=("inflammatory cytokine*") OR TS=("interleukin*") OR TS=("IL") OR TS=("tumor necrosis factor*") OR TS=("TNF*") Databases=WOS, BCI, KJD, RSCI, SCIELO Timespan=All years Search language=Auto	761024
3	#2 AND #1 Databases=WOS, BCI, KJD, RSCI, SCIELO Timespan=All years Search language=Auto	840
4	#3 NOT TS=(animal) Databases=WOS, BCI, KJD, RSCI, SCIELO Timespan=All years Search language=Auto	170
5	#4 NOT (TS="case report") Databases=WOS, BCI, KJD, RSCI, SCIELO Timespan=All years Search language=Auto	167
6	#5 NOT (TS=review) Databases=WOS, BCI, KJD, RSCI, SCIELO Timespan=All years Search language=Auto	132
PubMed		
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

https://doi.org/10.3349/ymj.2020.61.5.391

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,

Table 2. Characteristics of Studies Included in the Meta-Analysis of Inflammatory Cytokine Gene Polymorphisms

Gene	SNPs	Author and reference	Year	Country	Sample size		Mean age (yr)		Male (n, %)		Genotype*		Allele (M/m)†		OR (95% CI)		NOS	HWE
					Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Dominant model	Allelic model		
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	45/21	109/53	0.79 (0.34–1.82)	0.96 (0.52–1.77)	6	0.00
	G>A	Sathyan, et al.[17]	2015	India	220	250	51.2±11.4	-	123 (55.91)	-	185/41/0	192/51/1	411/41	435/53	0.82 (0.52–1.29)	0.82 (0.53–1.26)	6	0.21
		Fontanella, et al.[14]	2007	Italy	171	144	54.1±14.0	53.4±14.2	56 (32.75)	70 (48.61)	136/30/5	92/50/2	302/40	234/54	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	301/137	344/142	0.95 (0.66–1.37)	0.91 (0.68–1.20)	6	0.25
	C>T	Fontanella, et al.[18]	2010	Italy	215	155	55.0±14.5	53.7±14.0	74 (34.42)	50 (32.26)	82/110/23	63/80/12	274/156	206/104	1.11 (0.73–1.69)	1.13 (0.83–1.53)	7	0.05
IL-1β	rs16944	Sathyan, et al.[17]	2015	India	220	250	51.2±11.4	-	123 (55.91)	-	84/101/38	90/115/39	269/177	295/193	0.97 (0.66–1.41)	0.99 (0.76–1.29)	6	0.82
	C>T	Fontanella, et al.[18]	2010	Italy	215	155	55.0±14.5	53.7±14.0	74 (34.42)	50 (32.26)	94/88/33	64/68/23	276/154	196/114	0.91 (0.60–1.38)	0.96 (0.71–1.30)	7	0.48
		Slowik, et al.[19]	2006	Poland	231	231	49.9±12.7	50.4±12.4	99 (42.86)	99 (42.86)	100/99/32	111/106/14	299/163	328/134	1.21 (0.84–1.75)	1.33 (1.01–1.76)	7	0.08
IL6	rs1800795	Sathyan, et al.[17]	2015	India	220	250	51.2±11.4	-	123 (55.91)	-	144/63/8	153/80/11	351/79	386/102	0.83 (0.56–1.22)	0.85 (0.61–1.18)	6	0.90
	G>C	Bayri, et al.[12]	2015	Turkey	120	120	-	-	-	-	72/36/12	66/42/12	180/60	174/66	0.81 (0.49–1.36)	0.88 (0.59–1.32)	6	0.18
		Pera, et al.[20]	2012	Poland	276	581	50.5±12.7	56.0±17.7	120 (43.48)	274 (47.16)	82/138/56	186/275/120	302/250	647/515	1.11 (0.82–1.52)	1.04 (0.85–1.28)	6	0.32
		Fontanella, et al.[21]	2008	Italy	179	156	53.7±14.1	53.7±14.0	58 (32.40)	50 (32.05)	78/86/15	66/71/19	242/116	203/109	0.95 (0.62–1.47)	0.89 (0.65–1.23)	8	0.99
		Morgan, et al.[11]	2006	UK	91	2720	55 (24–80)	56 (49–64)	36 (40.0)	2720 (100)	40/40/6	867/1358/495	120/52	3092/2348	0.54 (0.35–0.83)	0.57 (0.41–0.79)	6	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	240/200	273/215	1.42 (0.95–2.13)	0.95 (0.73–1.23)	6	0.23
	G>C	Bayri, et al.[12]	2015	Turkey	120	120	-	-	-	-	94/24/2	83/33/4	212/28	199/41	0.62 (0.35–1.11)	0.64 (0.38–1.08)	6	0.75
		Liu, et al.[22]	2012	China	220	220	47.4±11.3	45.6±10.7	95 (43.18)	103 (46.82)	33/66/121	11/77/132	132/308	99/341	0.30 (0.15–0.61)	0.68 (0.50–0.92)	7	0.96
		Zhang, et al.[23]	2011	China	182	182	36.0±4.2	33.0±4.5	103 (56.59)	95 (52.20)	145/32/5	165/16/1	322/42	346/18	2.48 (1.34–4.59)	2.51 (1.41–4.45)	6	0.38
		Fontanella, et al.[21]	2008	Italy	179	156	53.7±14.1	53.7±14.0	58 (32.40)	50 (32.05)	149/26/4	131/23/2	324/34	285/27	1.06 (0.59–1.89)	1.11 (0.65–1.88)	8	0.40
		Sun, et al.[24]	2008	China	240	240	45.2±11.7	41.8±9.0	104 (43.33)	116 (48.33)	59/130/51	9/82/149	248/232	100/380	0.12 (0.06–0.25)	0.25 (0.19–0.33)	6	0.58
		Morgan, et al.[11]	2006	UK	91	2720	55 (24–80)	56 (49–64)	36 (40.0)	2720 (100)	79/8/4	2359/244/9	166/16	4962/262	1.42 (0.76–2.64)	1.83 (1.08–3.10)	6	0.32
IL-12B	rs3212227	Sathyan, et al.[17]	2015	India	220	250	51.2±11.4	-	123 (55.91)	-	88/96/36	83/115/31	272/168	281/177	0.85 (0.58–1.25)	0.98 (0.75–1.28)	6	0.37
	A>C	Li, et al.[25]	2012	China	164	258	53.1±13.1	50.0±8.9	60 (36.59)	108 (41.86)	29/100/35	80/136/42	158/170	296/220	2.09 (1.29–3.38)	1.45 (1.10–1.91)	6	0.21

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.

https://doi.org/10.3349/ymj.2020.61.5.391

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.

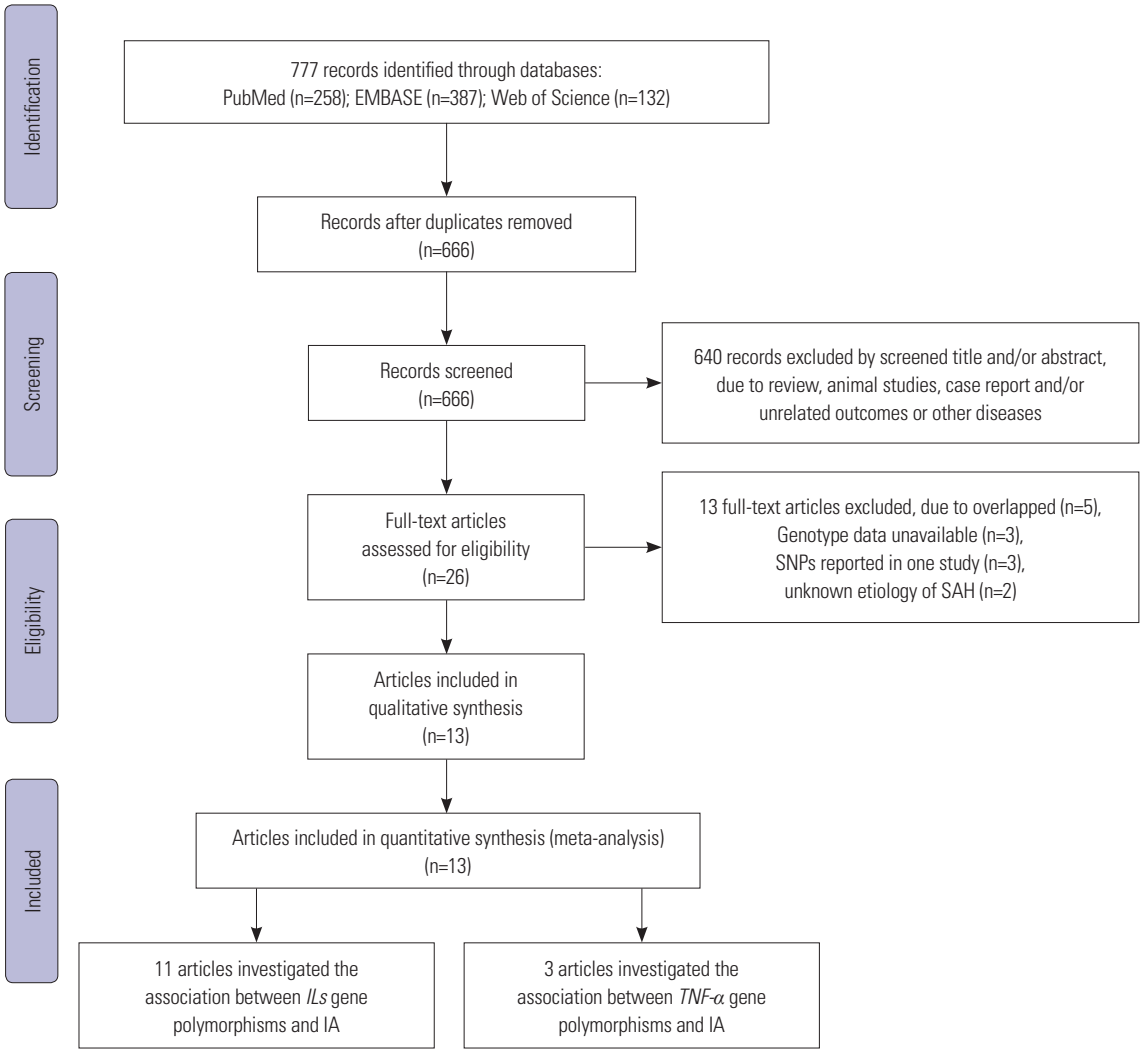

Fig. 1. PRISMA flow diagram of study selection process. SNPs, single nucleotide polymorphisms, SAH, subarachnoid hemorrhage; IA, intracranial aneurysm.

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)	I^2 (%)	P_Q	P_Z	OR (95% CI)	I^2 (%)	P_Q	P_Z
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)	46.4	0.113	0.126	0.84 (0.69–1.04)*	56.8	0.055	0.114
IL6 rs1800796	7	1252/3888	0.75 (0.38–1.51)*	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; I^2, Higgins I^2 statistic; P_Q, value for Q test; P_Z value for Z test; OR, odds ratio; CI, confidence interval.
*ORs were calculated in random-effect model.

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.[17,18] 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.

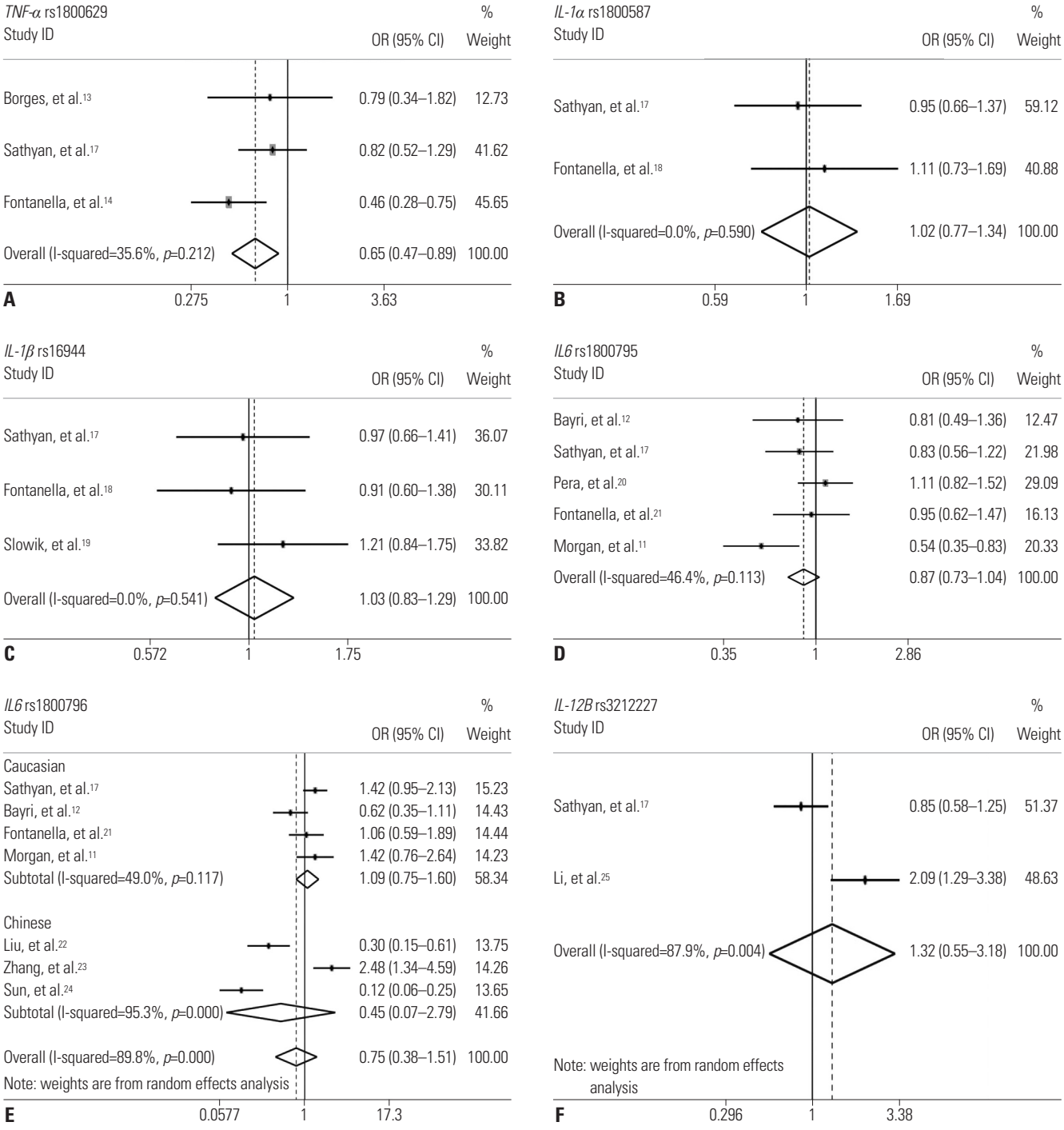

Fig. 2. Forest plots for the associations of inflammatory cytokine gene polymorphisms with IA risk in a dominant model. (A) Forest plot of *TNF-α* rs1800629 and IA risk in the dominant model. (B) Forest plot of *IL-1α* rs1800587 and IA risk in the dominant model. (C) Forest plot of *IL-1β* rs16944 and IA risk in the dominant model. (D) Forest plot of *IL6* rs1800795 and IA risk in the dominant model. (E) Forest plot of *IL6* 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.

https://doi.org/10.3349/ymj.2020.61.5.391

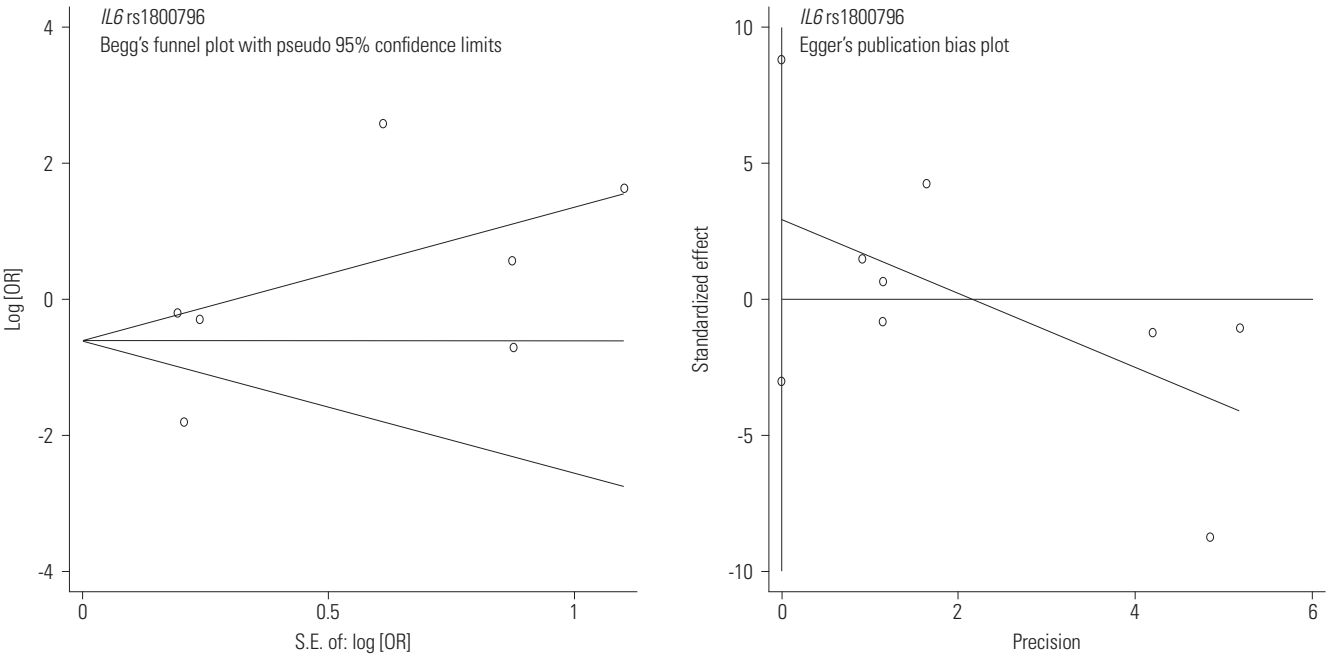

Fig. 3. Begg's funnel plots and Egger's plots for the association of rs1800796 with IA risk in a dominant model. IA, intracranial aneurysm; OR, odds ratio.

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:[28] it can activate proteolytic enzymes that destroy endothelial cells.[13] *TNF-α* has been shown to be associated with the occurrence of many diseases, including inflammatory diseases.[31] 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.[32] 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.[33] 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.[34] Studies have shown that *IL1* is involved in many processes, including inflammation, immune regulation, and neurodegeneration.[9] *IL1* 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.[35] 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.[17] 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).[36,37] 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.[21] Previous studies have reported that *IL6* gene polymorphisms are associated with the onset and progression of cerebral hemorrhage.[38] 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.[39] 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.[23] conducted in Chinese; sex distributions differed in other studies from the study of Morgan, et al.[11] conducted in Caucasians. In addition, the genotype distributions of *IL6* rs1800796 in Sun,

et al.[24] and Liu, et al.[22] 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.[40] Study had shown that *IL-12B* rs3212227 polymorphism is associated with susceptibility to IA.[25] However, a meta-analysis of *IL-12B* rs3212227 polymorphism and IA risk reported no association.[17] 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.

ACKNOWLEDGEMENTS

This work was supported by grants from the National Nature Science Foundation of China to J.Y (No. 81502881).

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 final manuscript: all authors.

ORCID iDs

Liming Hu https://orcid.org/0000-0002-0166-8585
Bingyang Li https://orcid.org/0000-0003-0138-773X
Xin Liao https://orcid.org/0000-0002-9640-8638
Junxia Yan https://orcid.org/0000-0001-6067-1613

REFERENCES

1. Brown RD Jr, Broderick JP. Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening. Lancet Neurol 2014;13:393-404.
2. Zhou S, Gan-Or Z, Ambalavanan A, Lai D, Xie P, Bourassa CV, et al. Genome-wide association analysis identifies new candidate risk loci for familial intracranial aneurysm in the French-Canadian population. Sci Rep 2018;8:4356.
3. Liu H, Mao P, Xie C, Xie W, Wang M, Jiang H. Apolipoprotein E polymorphism and the risk of intracranial aneurysms in a Chinese population. BMC Neurol 2016;16:14.
4. Connolly ES Jr, Choudhri TF, Mack WJ, Mocco J, Spinks TJ, Slosberg J, et al. Influence of smoking, hypertension, and sex on the phenotypic expression of familial intracranial aneurysms in siblings. Neurosurgery 2001;48:64-8.
5. Caranci F, Briganti F, Cirillo L, Leonardi M, Muto M. Epidemiology and genetics of intracranial aneurysms. Eur J Radiol 2013;82:1598-605.
6. Zhou S, Dion PA, Rouleau GA. Genetics of intracranial aneurysms. Stroke 2018;49:780-7.
7. Meng H, Wang Z, Hoi Y, Gao L, Metaxa E, Swartz DD, et al. Complex hemodynamics at the apex of an arterial bifurcation induces vascular remodeling resembling cerebral aneurysm initiation. Stroke 2007;38:1924-31.
8. Kataoka H. Molecular mechanisms of the formation and progression of intracranial aneurysms. Neurol Med Chir (Tokyo) 2015;55:214-29.
9. Rothwell NJ, Luheshi GN. Interleukin 1 in the brain: biology, pathology and therapeutic target. Trends Neurosci 2000;23:618-25.
10. Ali MS, Starke RM, Jabbour PM, Tjoumakaris SI, Gonzalez LF, Rosenwasser RH, et al. TNF-α induces phenotypic modulation in cerebral vascular smooth muscle cells: implications for cerebral aneurysm pathology. J Cereb Blood Flow Metab 2013;33:1564-73.
11. Morgan L, Cooper J, Montgomery H, Kitchen N, Humphries SE. The interleukin-6 gene -174G>C and -572G>C promoter polymorphisms are related to cerebral aneurysms. J Neurol Neurosurg Psychiatry 2006;77:915-7.
12. Bayri Y, Taskin E, Ulus A, Bayrakli F, Altun A, Bagci H. Lack of association between interleukin 6 gene promoter polymorphisms and aneurysmal subarachnoid hemorrhage in Turkish population. J Neurol Sci-Turk 2015;32:288-92.
13. Borges FSA, Freitas RS, Morais RM, Funghetto SS, Nóbrega OT, Ferreira LB, et al. TNFA gene in Brazilian patients with hemorrhagic stroke or cerebral aneurysm. J Bras Patol Med Lab 2018;54:164-9.

https://doi.org/10.3349/ymj.2020.61.5.391

14. Fontanella M, Rainero I, Gallone S, Rubino E, Fenoglio P, Valfrè W, et al. Tumor necrosis factor-alpha gene and cerebral aneurysms. Neurosurgery 2007;60:668-72.
15. Minelli C, Thompson JR, Abrams KR, Thakkinstian A, Attia J. The quality of meta-analyses of genetic association studies: a review with recommendations. Am J Epidemiol 2009;170:1333-43.
16. Little J, Higgins JP, Ioannidis JP, Moher D, Gagnon F, von Elm E, et al. Strengthening the reporting of genetic association studies (STREGA): an extension of the STROBE statement. Eur J Epidemiol 2009; 24:37-55.
17. Sathyan S, Koshy LV, Srinivas L, Easwer HV, Premkumar S, Nair S, et al. Pathogenesis of intracranial aneurysm is mediated by proinflammatory cytokine TNFA and IFNG and through stochastic regulation of IL10 and TGFB1 by comorbid factors. J Neuroinflammation 2015;12:135.
18. Fontanella M, Rainero I, Gallone S, Rubino E, Fornaro R, Fenoglio P, et al. Interleukin-1 cluster gene polymorphisms and aneurysmal subarachnoid hemorrhage. Neurosurgery 2010;66:1058-62.
19. Slowik A, Borratynska A, Turaj W, Pera J, Dziedzic T, Wloch D, et al. Interleukin 1beta-511 C/T polymorphism and risk of aneurysmal subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 2006;77:279-80.
20. Pera J, Dziedzic T, Adamski M, Jagiella J, Krupa M, Moskala M, et al. Interleukin 6-174G>C polymorphism and risk of aneurysmal subarachnoid hemorrhage: case-control study and meta-analysis. Acta Neurol Scand 2012;125:111-5.
21. Fontanella M, Rainero I, Gallone S, Rubino E, Fenoglio P, Valfrè W, et al. Interleukin 6 gene polymorphisms are not associated with aneurysmal subarachnoid haemorrhage in an Italian population. J Neurol Neurosurg Psychiatry 2008;79:471-3.
22. Liu Y, Sun J, Wu C, Cao X, He M, You C. The interleukin-6-572G/C gene polymorphism and the risk of intracranial aneurysms in a Chinese population. Genet Test Mol Biomarkers 2012;16:822-6.
23. Zhang G, Tu Y, Feng W, Huang L, Li M, Qi S. Association of interleukin-6-572G/C gene polymorphisms in the Cantonese population with intracranial aneurysms. J Neurol Sci 2011;306:94-7.
24. Sun H, Zhang D, Zhao J. The interleukin-6 gene -572G>C promoter polymorphism is related to intracranial aneurysms in Chinese Han nationality. Neurosci Lett 2008;440:1-3.
25. Li LJ, Pan XM, Sima X, Li ZH, Zhang LS, Sun H, et al. Interactions of interleukin-12A and interleukin-12B polymorphisms on the risk of intracranial aneurysm. Mol Biol Rep 2012;39:11217-23.
26. Hu J, Luo J, Wang H, Wang C, Sun X, Li A, et al. Association of TNF-α-3959T/C gene polymorphisms in the Chinese population with intracranial aneurysms. J Mol Neurosci 2017;63:349-54.
27. Yan J, Hitomi T, Takenaka K, Kato M, Kobayashi H, Okuda H, et al. Genetic study of intracranial aneurysms. Stroke 2015;46:620-6.
28. Low SK, Zembutsu H, Takahashi A, Kamatani N, Cha PC, Hosono N, et al. Impact of LIMK1, MMP2 and TNF-α variations for intracranial aneurysm in Japanese population. J Hum Genet 2011;56: 211-6.
29. Wu P, Wu A, Wang Y. Correlation of tumor necrosis factor receptor superfamily 13B variation with sporadic intracranial aneurysm and clinical characteristics in Han Chinese populations. Neural Regen Res 2010;5:236-40.
30. Inoue K, Mineharu Y, Inoue S, Yamada S, Matsuda F, Nozaki K, et al. Search on chromosome 17 centromere reveals TNFRSF13B as a susceptibility gene for intracranial aneurysm: a preliminary study. Circulation 2006;113:2002-10.
31. Bradley JR. TNF-mediated inflammatory disease. J Pathol 2008; 214:149-60.
32. Starke RM, Chalouhi N, Jabbour PM, Tjoumakaris SI, Gonzalez LF, Rosenwasser RH, et al. Critical role of TNF-α in cerebral aneurysm formation and progression to rupture. J Neuroinflammation 2014;11:77.
33. Wang Y, Emeto TI, Lee J, Marshman L, Moran C, Seto SW, et al. Mouse models of intracranial aneurysm. Brain Pathol 2015;25: 237-47.
34. Nicklin MJH, Weith A, Duff GW. A physical map of the region encompassing the human interleukin-1α, interleukin-1β, and interleukin-1 receptor antagonist genes. Genomics 1994;19:382-4.
35. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol Rev 2018;281:8-27.
36. Johnston WF, Salmon M, Pope NH, Meher A, Su G, Stone ML, et al. Inhibition of interleukin-1β decreases aneurysm formation and progression in a novel model of thoracic aortic aneurysms. Circulation 2014;130(11 Suppl 1):S51-9.
37. Meher AK, Spinosa M, Davis JP, Pope N, Laubach VE, Su G, et al. Novel role of IL (interleukin)-1β in neutrophil extracellular trap formation and abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol 2018;38:843-53.
38. Pawlikowska L, Tran MN, Achrol AS, McCulloch CE, Ha C, Lind DL, et al. Polymorphisms in genes involved in inflammatory and angiogenic pathways and the risk of hemorrhagic presentation of brain arteriovenous malformations. Stroke 2004;35:2294-300.
39. Zheng S, Su A, Sun H, You C. The association between interleukin-6 gene polymorphisms and intracranial aneurysms: a meta-analysis. Hum Immunol 2013;74:1679-83.
40. Wolf SF, Temple PA, Kobayashi M, Young D, Dicig M, Lowe L, et al. Cloning of cDNA for natural killer cell stimulatory factor, a heterodimeric cytokine with multiple biologic effects on T and natural killer cells. J Immunol 1991;146:3074-81.