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Associations between interleukin 18 gene polymorphisms and susceptibility to vasculitis: A meta-analysis

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Abstract. Interleukin 18 (IL18), a pro-inflammatory cytokine, affects the development and progress of vasculitis. The production, expression, and function of this cytokine are affected by polymorphisms of promoter region of the *IL18* gene. In this study, a meta-analysis of the associations between several *IL18* polymorphisms and susceptibility to vasculitis was performed. Published literature from PubMed and Embase were retrieved. In total, nine studies comprising 1006 patients with vasculitis and 1499 controls combined, and the investigating the rs187238, rs194618, and rs360719 polymorphisms of the promoter region of the *IL18* gene, were included in the meta-analysis. Pooled odds ratios (OR) and 95% confidence intervals (CI) were estimated with fixed-effects model or random-effects model. The recessive model of the rs194618 polymorphism was found to be significantly associated with a high susceptibility to vasculitis (OR = 1.54, 95% CI = 1.02–2.33, $P = 0.04$), especially in the Mongoloid race, where the *A* allele of rs194618 was associated with a low risk of the disease (OR = 0.77, 95% CI = 0.62–0.95, $P = 0.01$). By contrast, the rs187238 and rs360719 polymorphisms were not associated with this inflammatory condition. This meta-analysis showed that some *IL18* polymorphisms are associated with susceptibility to vasculitis. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 203-211)*

Key words: Vasculitis, Interleukin 18, Polymorphism, Meta-analysis

Introduction

Vasculitis is a heterogeneous disease that causes inflammation of the blood vessel walls and damage to the skin and other organ systems. It is classified into large vessel (e.g., Takayasu's disease and giant cell arteritis), medium vessel (e.g., Kawasaki disease), and small vessel vasculitis type (e.g., antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and immune complex vasculitis) depending on the size of the blood vessels affected, with Behçet's disease and Cogan's syndrome being included among the various types (1). Several cytokines and chemokines play a major role in the development and progression of vasculitis, although there are differences depending on the type of blood vessel affected (2, 3). The gene

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polymorphisms of these cytokines, including interleukin (IL) 1, IL6, and IL10, are also associated with susceptibility to vasculitis (1, 4, 5).

IL18, a member of the IL1 superfamily, is biologically and structurally related to IL1β, mediates the T-helper 1 (Th1)-polarized immune response, and promotes inflammation by enhancing the production of tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and granulocyte-monocyte colony-stimulating factor (6, 7). IL-18 is associated with various diseases, including infections, inflammations, autoimmune diseases, and cardiovascular diseases (8, 9). Previous studies have shown that vasculitis is also associated with IL18, where serum levels of this cytokine were elevated in Behçet's disease and ANCA-associated vasculitis, which was associated with kidney involvement (10, 11). Polymorphisms of the *IL18* gene have been shown to be associated with elevated IL18 levels (12). The *IL18* gene is located on chromosome 11q22.2-22.3, and various polymorphisms in the promoter resion of this gene are associated with autoimmune diseases (13). Among the polymorphisms of *IL18*, those at positions rs187238 (-137 G/C) and rs194618 (-607 C/A) have been studied the most (14-16). Nonetheless, there are some published studies on polymorphisms at other positions, such as rs549908 (+105 A/C), rs1946519 (-656 T/G), and rs360719 (-1297 T/C) (17-19).

Although published studies on the association between *IL18* polymorphisms and vasculitis are available, the types of vasculitis and promoter regions analyzed were different, and the results were different as well (6, 7, 20-27). In this present study, we performed a meta-analysis to investigate the associations between several polymorphisms of the *IL18* gene (rs187238, rs194618, and rs360719) and susceptibility to vasculitis.

Methods

Databases and literature sources

A literature search was performed for studies examining the association between *IL18* gene polymorphisms and vasculitis using the PubMed and Embase databases (up to January 2020). The following keywords and subject terms were used interleukin 18, IL18, polymorphism, variant, mutation, genotype, haplotype, vasculitis, arteritis, Takayasu, giant cell, Kawasaki, polyarteritis, polyangiitis, eosinophilic granulomatosis, purpura, Wegener, Churg-Strauss, Behcet, and ANCA. Additional studies not found in PubMed or Embase were manually obtained using citied references from included studies. No restrictions were placed on race, language, ethnicity, or geographical area.

Selection criteria and data extraction

The inclusion criteria for this meta-analysis were case-control studies that determined the distributions of the *IL18* gene polymorphisms and vasculitis, detailed data for both the case and control groups, and any other data from which the desired numbers could be calculated. Two or more studies of polymorphisms at the same position in the *IL18* promoter region were included. Studies were excluded on the basis of the following criteria: those that contained overlapping data; studies in which the number of null and wild genotypes or alleles could not be ascertained; and investigations that were review articles or contained only abstracts. We extracted the author, year of publication, country of the study subjects, number of cases and controls, Hardy–Weinberg equilibrium (HWE) *P* value, and the allele and genotype frequencies of the *IL18* polymorphism from each study. This meta-analysis was reported on according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines.

Statistical analysis

The allele counting method was used to determine the allele frequencies in the *IL18* promoter region. The meta-analysis was performed using Cochrane Collaboration RevMan 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The HWE *P*-value was estimated using Pearson's chi-squared test. The odds ratio (OR) and 95% confidence interval (CI) were used to determine whether there was evidence of an association between the respective *IL18* polymorphisms and susceptibility to vasculitis. The meta-analysis was also based on allele contrast and dominant, recessive, and homozygote models. The heterogeneity of the included studies was estimated

using Cochran's Q test and I^2 statistics. When the Q test was significant ($P < 0.05$) or $I^2 > 50\%$, the random-effects model was used; otherwise, the fixed effects model was used (28). Forest plots were drawn to visualize the overall effects. To overcome the heterogeneity observed in the meta-analysis, subgroup analysis by race and vasculitis type was performed. Funnel plots were generated and visually inspected for asymmetry to determine if there was any publication bias.

Results

Studies included in the meta-analysis

In total, nine studies (comprising 1006 patients with vasculitis and 1499 controls combined) were included in this meta-analysis. A flow chart detailing the inclusion and exclusion processes is shown in Figure 1. With regard to the promoter region of the *IL18* gene, there were nine studies on rs187238, eight studies on rs1946518, and three studies on rs360719. In terms of the races of the subjects studied, six studies were on Caucasians and three studies were on the Mongoloid race. With regard to the vasculitis type, there were six studies on Behçet's disease and one study each on giant cell arteritis, Kawasaki disease, and Henoch–Schönlein purpura. Additionally, a subgroup analysis was performed on Behçet's disease. Details of the *IL18* polymorphism studies are summarized in Table 1.

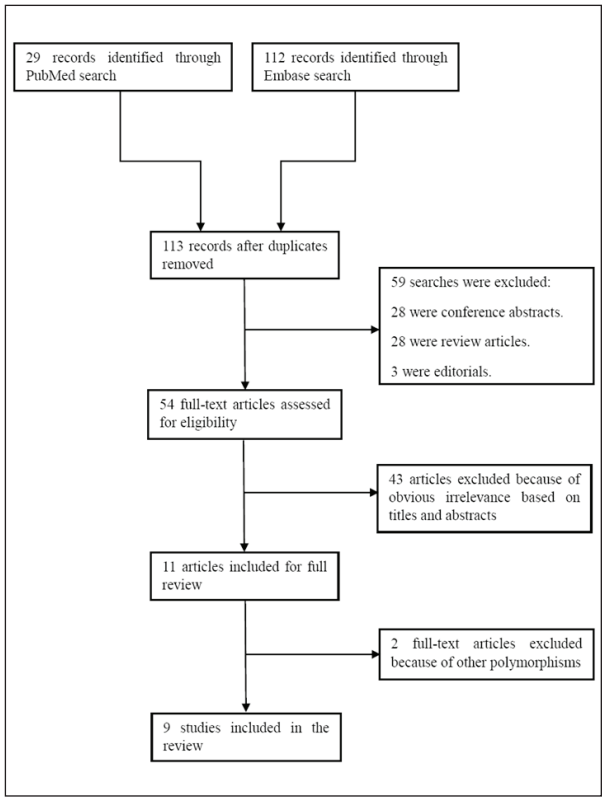

Fig. 1. Flow chart of the application of inclusion/exclusion criteria

Meta-analysis of associations between the IL18 polymorphisms and overall vasculitis

In the meta-analysis of associations between the rs187238 and rs360719 polymorphisms and vasculitis, both polymorphisms were found to be not significantly associated with the allele contrast and all genotypes. In the case of the rs194618 polymorphism, the recessive model was found to be significantly associated with susceptibility to overall vasculitis (OR = 1.54, 95% CI = 1.02–2.33, $P = 0.04$; Figure 2A), but not the allele contrast and other genotypes (Table 2).

In the subgroup analysis by race, both the rs187238 and rs194618 polymorphisms in Caucasians were not found to be significantly associated with susceptibility to vasculitis. In the Mongoloid race, rs187238 was also not significantly associated with susceptibility to vasculitis, whereas the *A* allele of rs194618 tended to be protective against the condition (OR = 0.77, 95% CI = 0.62–0.95, $P = 0.01$), with the recessive model showing a tendency to increase the susceptibility risk (OR = 1.99, 95% CI = 1.37–2.88, $P = 0.0003$; Table 3 and Figure 2B).

Meta-analysis of associations between the IL18 polymorphisms and Behçet's disease

A subgroup analysis of the associations of the rs187238 and rs194618 polymorphisms with Behçet's disease was performed (Table 4). There was no significant association found between susceptibility to Behçet's disease and the allele contrast and all genotype models of the rs187238 polymorphism. By contrast, for the rs194618 polymorphism, only the recessive model was found to be significantly associated with susceptibility to this disease (OR = 2.17, 95% CI = 1.54–3.06, $P = 0.04$; Figure 2C).

Table 1. Characteristics of the individual studies included in the meta-analysis

First author	Year	Country	Race	Disease	Promoter region	Number of cases	Number of controls	HWE *P*-value
Hazzaa	2014	Egypt	Caucasian	Behçet's disease	rs187238, rs1946518	80	80	0.590, 0.650
Vaccarino	2013	Italy	Caucasian	Behçet's disease	rs187238	32	128	0.560
Htoon	2011	Turkey	Caucasian	Behçet's disease	rs187238, rs1946518, rs360721	153	243	NA
Torres	2010	Spain	Caucasian	IgA vasculitis	rs187238, rs1946518, rs360722	62	200	0.101, 0.047, 0.344
Palomino-Morales	2010	Spain	Caucasian	Giant cell arteritis	rs187238, rs1946518, rs360723	212	403	0.221, 0.013, 0.346
Keskin	2009	Turkey	Caucasian	Behçet's disease	rs187238, rs1946518	123	101	0.001, 0.820
Hsueh	2008	Taiwan	Mongoloid	Kawasaki disease	rs187238, rs1946518	143	136	0.780, 0.267
Lee	2006	Korea	Mongoloid	Behçet's disease	rs187238, rs1946518	103	103	0.225, 0.934
Jang	2005	Korea	Mongoloid	Behçet's disease	rs187238, rs1946518	98	105	0.028, 0.000

HWE, Hardy–Weinberg equilibrium; NA, not applicable

Heterogeneity and publication bias

The genotypes of the control groups of two studies on the rs187238 polymorphism and of three studies on the rs194618 polymorphism were not in HWE. One study did not show HWE in all three promoter polymorphisms (Table 1). In the meta-analysis of the rs187238 polymorphism, the fixed-effects model was used because there was no significant heterogeneity found. By contrast, significant heterogeneity was found in the allele contrast and dominant model in the meta-analysis of the rs194618 polymorphism, and in the all genotype models in the analysis of the rs360719 polymorphism (Table 2).

Funnel plots were drawn for the meta-analyses of the rs187238 and 194618 polymorphisms to identify publication bias. The plots were generally symmetrical, with four on the left and five on the right in the plot for the rs187238 polymorphism, and five on the left and three on the right in the plot of the rs194618 polymorphisms (Figure 3).

Discussion

IL18 acts mainly as a pro-inflammatory cytokine, inducing IFN-γ. It stimulates Th1 cytokines, promotes the differentiation and immune response of Th1 cells, and up-regulates other cytokines such as TNF-α and IL1β (29). Being structurally similar to IL1, IL18 is related to this cytokine superfamily through their sharing of common signaling pathway. IL1 is also primarily a pro-inflammatory cytokine and is involved in the development of inflammation in various diseases. Single-nucleotide polymorphisms (SNPs), which are common in humans, are associated with the susceptibility and therapeutic responses to a variety of diseases (6). *IL1* polymorphisms have been found to be significantly associated with vasculitis, including Behçet's disease (4), and a previous meta-analysis showed that Behçet's disease was associated with *IL18* rs1946518 polymorphisms. Although vasculitis is a heterogeneous disease, polymorphisms of genes encoding inflammatory cytokines such as IL10, have been reported to be associated with overall vasculitis (5). Our present meta-analysis showed

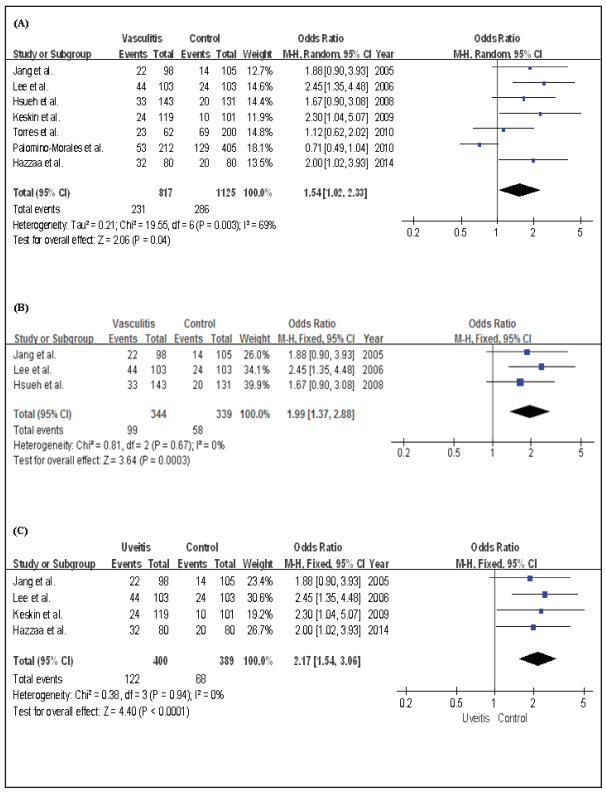

Fig. 2. Odd ratio (OR) and 95% confidence interval (CI) of individual studies and pooled data for determined of the association between the recessive model of the *IL18* rs194618 polymorphism and susceptibility to vasculitis. (A) Overall vasculitis. (B) Mongoloid race. (C) Behçet's disease. *IL18*, interleukin 18 gene.

a significant association between vasculitis and the *IL18* rs1946518 polymorphism, with the recessive model having a protective effect on the development of the disease, including Behçet's disease. However, the rs187238 and rs360719 polymorphisms were not associated with susceptibility to vasculitis. Although the *IL18* rs1946518 polymorphism is known to be associated with vascular diseases (e.g., coronary artery disease) and other diseases (e.g., cancer, asthma and tuberculosis), the relationships between the polymorphisms of the different promoter regions and each d,isease were different (17, 30-33). These results suggest that SNPs of the *IL18* gene affect the inflammatory process but act differently for each disease. Various factors, such as race and the environment, are related to SNPs.

Vasculitis chronically inflames the blood vessels through an autoimmune process, during which T-cell functional abnormalities occur (34). In particular, an imbalance between Th1 and Th2 cells occurs in vasculitis, and genetic variants of the Th1 and Th2 cytokines are closely related to the susceptibility to this inflammatory condition (21). The Th1 cytokine is representative of IL12 and IL18. SNPs of *IL18* are suggested to play a role in the development of vasculitis by affecting the imbalance between Th1 and Th2 cells. In addition to this Th cell imbalance,

Table 2. Meta-analysis of associations between the *IL18* polymorphisms and overall vasculitis

	Test of association			Test of heterogeneity		
	OR	**95% CI**	***P***	**Model**	***P***	***I²* (%)**
rs187238						
C vs. G	0.98	0.85–1.13	0.79	F	0.13	36
Dominant model	1.20	0.84–1.73	0.32	F	0.41	0
Recessive model	1.02	0.83–1.24	0.85	F	0.09	43
CC vs. GG	0.90	0.54–1.48	0.67	F	0.18	34
rs194618						
A vs. C	0.89	0.68–1.15	0.36	R	<0.0001	78
Dominant model	1.05	0.83–1.33	0.69	F	0.08	50
Recessive model	1.54	1.02–2.33	0.04	R	0.003	69
AA vs. CC	0.75	0.44–1.28	0.28	R	0.007	69
rs360719						
C vs. T	1.18	0.86–1.62	0.29	R	0.10	56
Dominant model	1.15	0.12–10.65	0.90	R	0.11	61
Recessive model	0.79	0.45–1.41	0.43	R	0.08	66
CC vs. TT	0.92	0.08–10.93	0.95	R	0.08	67

OR, Odds ratio; CI, confidence interval; R, random-effects model; F, fixed-effects model.

Table 3. Meta-analysis of associations between the *IL18* rs194618 polymorphism and overall vasculitis according to race

	Test of association			Test of heterogeneity		
	OR	**95% CI**	***P***	**Model**	***P***	***I²* (%)**
Caucasian						
A vs. C	0.96	0.67–1.38	0.85	R	0.0002	82
Dominant model	1.12	0.64–1.95	0.70	R	0.03	67
Recessive model	1.30	0.73–2.30	0.37	R	0.010	74
AA vs. CC	0.74	0.31–1.78	0.51	R	0.002	80
Mongoloid						
A vs. C	0.77	0.62–0.95	0.01	F	0.34	9
Dominant model	1.10	0.74–1.64	0.63	F	0.39	0
Recessive model	1.99	1.37–2.88	0.0003	F	0.67	0
AA vs. CC	0.71	0.44–1.13	0.15	F	0.89	0

OR, Odds ratio; CI, confidence interval; R, random-effects model; F, fixed-effects model.

Table 4. Meta-analysis of associations between the *IL18* polymorphisms and Behçet's disease

	Test of association			Test of heterogeneity		
	OR	**95% CI**	***P***	**Model**	***P***	***I²* (%)**
rs187238						
C vs. G	0.97	0.80–1.18	0.78	F	0.28	20
Dominant model	1.31	0.59–2.87	0.51	F	0.27	24
Recessive model	1.11	0.83–1.46	0.49	F	0.28	21
CC vs. GG	0.71	0.31–1.60	0.41	F	0.28	22
rs194618						
A vs. C	0.89	0.68–1.15	0.36	R	<0.0001	78
Dominant model	1.05	0.83–1.33	0.69	F	0.08	50
Recessive model	2.17	1.54–3.06	0.04	R	0.003	69
AA vs. CC	0.75	0.44–1.28	0.28	R	0.007	69

OR, Odds ratio; CI, confidence interval; R, random-effects model; F, fixed-effects model.

distortions in the Th17 response and functional defects of regulatory T cells play roles in the pathogenesis of vasculitis, where cytokines such as IL4, IL17, IL10, and IL21 are involved in the immune response (34). In addition, our meta-analysis included mainly Behçet's disease, an inflammatory disorder that has been shown by a previous meta-analysis to be associated with *IL12B* polymorphisms aside from *IL18* polymorphisms. Because these various genes are involved in the susceptibility to vasculitis, gene–gene interactions should be considered. Environmental and genetic factors are also associated with susceptibility to vasculitis, with smoking, ultraviolet light and silica reportedly increasing the susceptibility risk

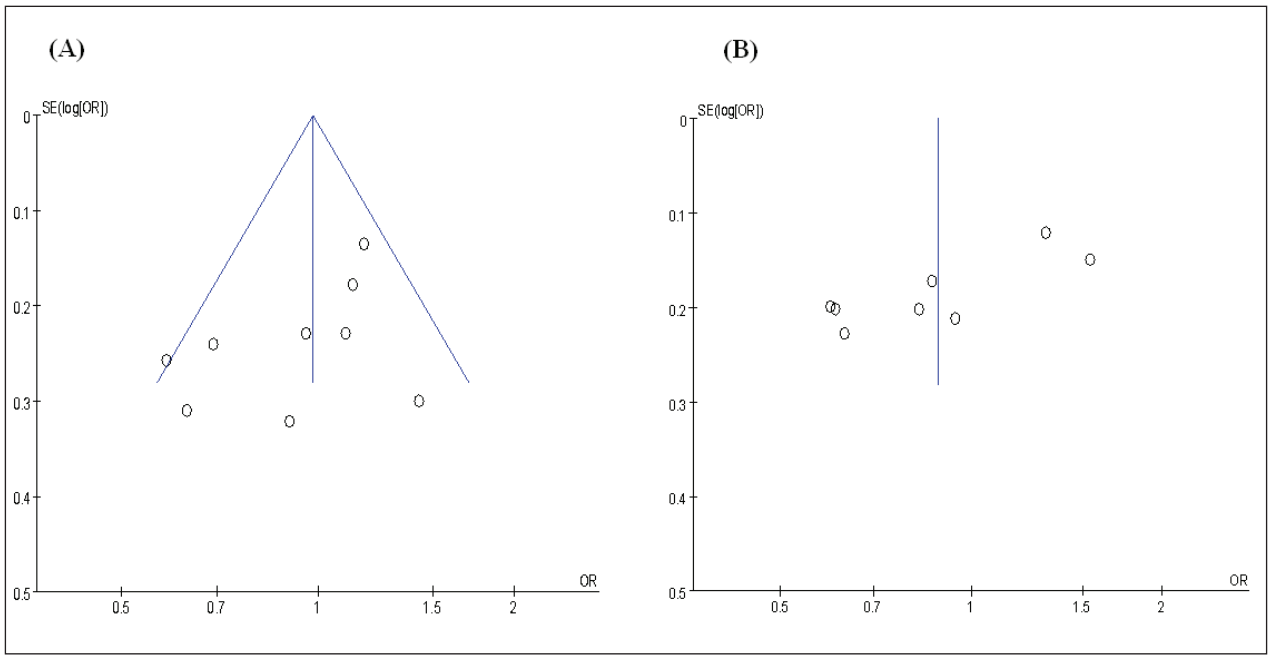

Fig. 3. Funnel plots for studies on *IL18* polymorphisms and susceptibility to vasculitis. (A) rs187238. (B) rs194618. *IL18*, interleukin 18 gene.

(35, 36); therefore, gene–environmental interactions should also be considered.

The effect of SNPs on diseases depends on the race of the patients. In this meta-analysis, *IL18* rs194618 polymorphisms were associated with the Mongoloid race, but not with Caucasians. The prevalence of each type of vasculitis was also different by geographical area, with that of giant cell arteritis being high in Scandinavians, that of Kawasaki disease being high in North-East Asians, that of IgA vasculitis being high in Britons and Spaniards, and that of Behçet's disease being high in Turks and Middle Eastern individuals (37). The difference in prevalence among different geographical areas can be influenced by both race and environmental factors, with Caucasians being distributed mainly throughout Europe, Northern Africa, and West Asia, whereas the Mongoloid race is distributed throughout East Asia and includes Native Americans. The differences between race-related SNPs and the susceptibility to diseases are important for identifying disease risk factors in each group and in planning health services.

This study is the first meta-analysis of the associations between vasculitis and *IL18* polymorphisms. However, the study had some limitations. First, vasculitis is a heterogeneous disease with multiple types being classified according to the size of the affected blood vessels. The clinical manifestations for each disease type and the therapeutic drug requirements are also different (38). Giant cell arteritis responds well to steroids and shows an effective response to tocilizumab; Kawasaki disease is mainly treated with aspirin and intravenous immunoglobulins; IgA vasculitis has no standard treatment; and Behçet's disease is treated with methotrexate or azathioprine, with TNF-α being used in special cases (38-40). However, vasculitis is commonly accompanied by skin lesions, and the damage and weakening of the blood vessel wall have a common effect in destroying the vessel functions (41, 42). In addition, subgroup analysis was performed on Behçet's disease, which belongs to various vessel vasculitis types. Second, there was heterogeneity in the studies included in the meta-analysis. Although most of the studies were consistent with HWE, some either did not display or were not consistent with HWE (Table 1). In addition, because some genotype models had heterogeneity, the random-effects model had to be used in

the meta-analysis (Tables 2, 3, and 4). However, we did conduct a subgroup analysis according to races for an analysis of heterogeneity, and confirmed differences between the Caucasian and the Mongoloid races in this regard. Third, aside from the disease susceptibility, these *IL18* polymorphisms may also be associated with the disease severity and treatment response; however, we did not perform a meta-analysis to determine this association. Finally, publication bias could not be completely excluded (Figure 3).

In conclusion, this meta-analysis showed that the *IL18* rs194618 polymorphism was significantly associated with susceptibility to vasculitis, especially Behçet's disease. According to race differences, this polymorphism was significantly associated with susceptibility to vasculitis in the Mongoloid race, but not in the Caucasians. However, owing to the small sample size and heterogeneity of the studies included in the meta-analysis, further studies are required.

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