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Association between rs1800795 polymorphisms in the interleukin-6 gene and vasculitis: A meta-analysis

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Abstract. Interleukin (IL)-6 is associated with the development and progression of vasculitis, and inhibitors of this cytokine are used to treat this disease. Polymorphisms of the promoter region of *IL-6* are associated with the production and expression of IL-6. The aim of this study was to perform a meta-analysis of eligible studies to derive a precise estimate of the association between *IL6* polymorphisms and susceptibility to vasculitis. A meta-analysis was conducted to identify the associations between *IL6* rs1800795 (-174 G/C) polymorphisms and vasculitis. A total of 13 studies involving 1,294 vasculitis patients and 1,594 controls were considered in the meta-analysis. There were significant associations between *IL6* rs1800795 polymorphisms and vasculitis in allele contrast, dominant genetic model, and heterozygote vs. dominant homozygote comparison (OR 0.80, 95% CI 0.67-0.94, *P* =0.009 and OR 0.76, 95% CI 0.63-0.92, *P* =0.005, respectively). In subgroup analysis based on subtype, there were significant associations between *IL6* polymorphisms and susceptibility in large and medium vessel vasculitis, but not in small and variable vessel vasculitis. The GC genotype of *IL6* rs1800795 was suggested by the analyses to be related to low prevalence of vasculitis, especially for large and medium vessels. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36 (4): 302-310)*

Key words: vasculitis, interleukin-6, polymorphism, meta-analysis

Introduction

Vasculitis is a heterogeneous disease that causes inflammation of the blood vessel wall and damage to systemic organ. Vasculitis is divided into large (Takayasu arteritis and giant cell arteritis), medium (polyarteritis nodosa and Kawasaki disease), and small vessel vasculitis (antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis and immune complex vasculitis), depending on the size of the invading vessels, while Behçet's disease and Cogan's syndrome are classified as various vessel vasculitis (1). The clinical and pathological features are variable and depend on the site and type of affected blood vessels. The cause of vasculitis is unknown, but the prevailing hypothesis is that vasculitis is initiated by an environmental agent in genetically predisposed individuals (2).

Interleukin (IL)-6 is a pleiotropic cytokine that regulates immune function and is associated with various cancers, infectious diseases, as well as autoimmune diseases (3). IL-6 is thought to act as a

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mediator between damaged vascular wall tissues and immune cells, and it is known to polarize naive T cells into Th17 cells. IL-6 levels are increased in vasculitis and IL-6 blockers were effective in the treatment of vasculitis of large-medium vessels (4). Genetic variants, particularly in the promoter region of genes, can alter gene function and expression of *IL6*. The IL-6 gene is located on chromosome 7p21 and has three promoter variants (rs1800795, rs1800796, and rs1800797) (5). The polymorphism of rs1800795 (-174 G/C) consists of a single nucleotide change from G to C at position -174 in the promoter region and is associated with increased serum IL-6 protein levels (6). The *IL6* rs1800795 polymorphism is associated not only with autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, but also with obesity and atherosclerosis (5-8).

Previous genetic studies have shown conflicting results: *IL6* variants are either strongly associated or not associated with vasculitis diseases, such as Behçet's disease, Kawasaki disease, Takayasu arteritis, and giant cell arteritis, in different ethnic groups. The reasons for these disparities may be small sample sizes, low statistical power, and/or clinical heterogeneity. The aim of this study was to investigate the genetic association between *IL6* rs1800795 polymorphisms and susceptibility to disease in patients with vasculitis using a meta-analysis.

Methods

Identification of eligible studies and data extraction

A search was performed for studies that examined associations between *IL6* polymorphisms and vasculitis. Genetic association studies that determined the distributions of the *IL6* rs1800795 polymorphisms in vasculitis and in normal controls were included. The literature was searched using the PubMed and Embase databases to identify available articles in which *IL6* polymorphisms were analyzed in vasculitis patients (up to January 2019). We listed combinations of key words and subject terms, such as "interleukin-6," "IL-6," "polymorphism," "vasculitis," "arteritis," "Takayasu," "giant cell arteritis," "Kawasaki," "polyarteritis nodosa," "Wegener," "microscopic polyangiitis," "eosinophilic granulomatosis," "Churg-Strauss," "ANCA," and "Behçet." References from the identified studies were also investigated to identify additional studies not indexed by PubMed and Embase. The following information was extracted from each study: author, year of publication, ethnicity of the study population, demographics, number of cases and controls, Hardy-Weinberg equilibrium (HWE) *P* value, and the allele and genotype frequencies of the *IL6* rs1800795 polymorphisms.

Inclusion and exclusion criteria

Studies in this meta-analysis included the following a: 1) case-control studies that determined the distributions of *IL6* rs1800795 polymorphisms and susceptibility to vasculitis, and 2) detailed data reported for case and control groups, or alternatively results that could be calculated from the data provided. Studies were excluded based on the following: 1) overlapping data, 2) inability to determine the number of null and wild genotypes or alleles, and 3) review articles or abstracts-only publications. No restrictions were placed on race, language, ethnicity, or geographic area.

Statistical associations

Allele frequencies of genetic polymorphisms were determined by the allele counting method. The Chi-squared test was used to detect if the controls in each study conformed to HWE. The associations between the -174 G/C alleles and vasculitis were estimated by evaluating odds ratio (OR) and 95% confidence interval (CI). We performed meta-analyses using the 1) allelic contrast (C vs. G), 2) recessive (CC vs. GC+GG), and 3) dominant (CC+GC vs. GG) models, and 4) heterozygote vs. dominant homozygote (GC vs. GG), 5) heterozygote vs. recessive homozygote (GC vs. CC), and 6) homozygote comparison (CC vs. GG). Subgroup analyses were performed by ethnicity and vasculitis type to evaluate ethnic- and disease-specific effects. Inter-study heterogeneity was assessed by Cochran Q test and I^2 statistics (*P* value <0.10 and $I^2 \geq 50$ was regarded as statistically significant heterogeneity). If no significance between study heterogeneity was detected, a fixed-effects model was used. Otherwise, a random-effect model was used. Forest plots were drawn to visualize the overall effect. Meta-analysis was performed using Review Manager Software, version 5.3.

Publication bias

A funnel plot was used to analyze publication bias in a meta-analysis.

Results

Literature search

Twenty-one studies that investigated the relationship between *IL6* polymorphisms and vasculitis were identified using PubMed and Embase. Eight studies were excluded for reasons such as another *IL6* polymorphism, or the lack of suitable controls. Thus, 13 studies met the inclusion criteria (Figure 1) (9-21).

Main characteristics of the included studies

A total of 13 studies were included, comprising 1,294 vasculitis cases and 1,594 control subjects. There were 6 studies on Middle-Eastern populations, 4 on Caucasian populations, and 3 on Asian populations. Among the vasculitis cases, Behçet's disease (5 studies), Kawasaki disease (2 studies), Takayasu arteritis (2 studies), giant cell arteritis (2 studies), granulomatosis with polyangiitis (1 study), and IgA vasculitis (1 study) were included in the present study. Other types of vasculitis were excluded because of a lack of case-control studies. Details of the *IL6* polymorphism studies are summarized in Table 1.

Meta-analysis of relationships between IL6 rs1800795 polymorphisms and overall vasculitis

Meta-analysis of rs1800795 polymorphisms revealed significant association between overall vasculitis and the C allele (OR 0.87, 95% CI 0.76-0.99, P =0.03; Figure 2). A significant association was also found between overall vasculitis and rs1800795 polymorphism using a dominant model and heterozygote vs. dominant homozygote comparison (OR 0.80,

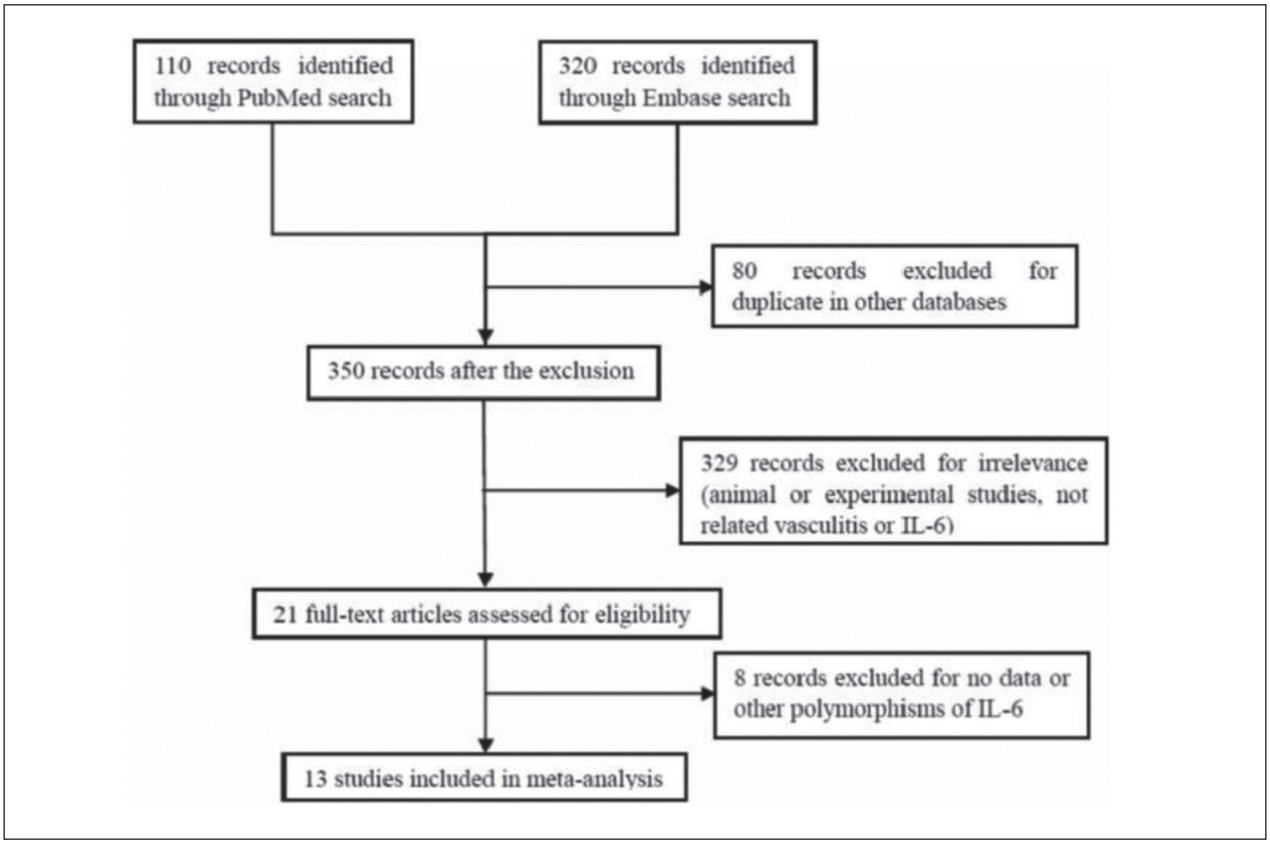

Fig. 1. Flow chart of inclusion/exclusion criteria

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

Study	Population		Numbers		Disease	HWE
First author (year)	Country	Ethnicity	Case	Control		*P* value
Danda (2017) (9)	India	Asian	120	119	Takayasu arteritis	0.362
Saruhan-Direskeneli (2016) (16)	Turkey	Middle Eastern	94	108	Takayasu arteritis	0.451
Salvarani (2005) (18)	Italy	Caucasian	126	112	Giant cell arteritis	0.801
Gonzalez-Gay (2002) (20)	Spain	Caucasian	62	124	Giant cell arteritis	0.753
Assari (2018) (8)	Iran	Middle Eastern	55	139	Kawasaki disease	0.000
Weng (2010) (13)	Taiwan	Asian	211	221	Kawasaki disease	0.892
Zhou (2004) (19)	USA	Caucasian	117	123	Granulomatosis with polyangiitis	0.406
Talaat (2014) (10)	Egypt	Middle Eastern	87	97	Behçet's disease	0.232
Hamzaoui (2014) (11)	Iran	Middle Eastern	43	43	Behçet's disease	0.561
Amirzargar (2010) (12)	Iran	Middle Eastern	147	139	Behçet's disease	0.000
Dilek (2009) (14)	Turkey	Middle Eastern	97	122	Behçet's disease	0.091
Chang (2005) (17)	Korea	Asian	89	123	Behçet's disease	0.000
Amoli(2007) (15)	Spain	Caucasian	46	124	IgA vasculitis	0.451

HWE: Hardy Weinberg Equilibrium; USA: United States of America; NA: not applicable

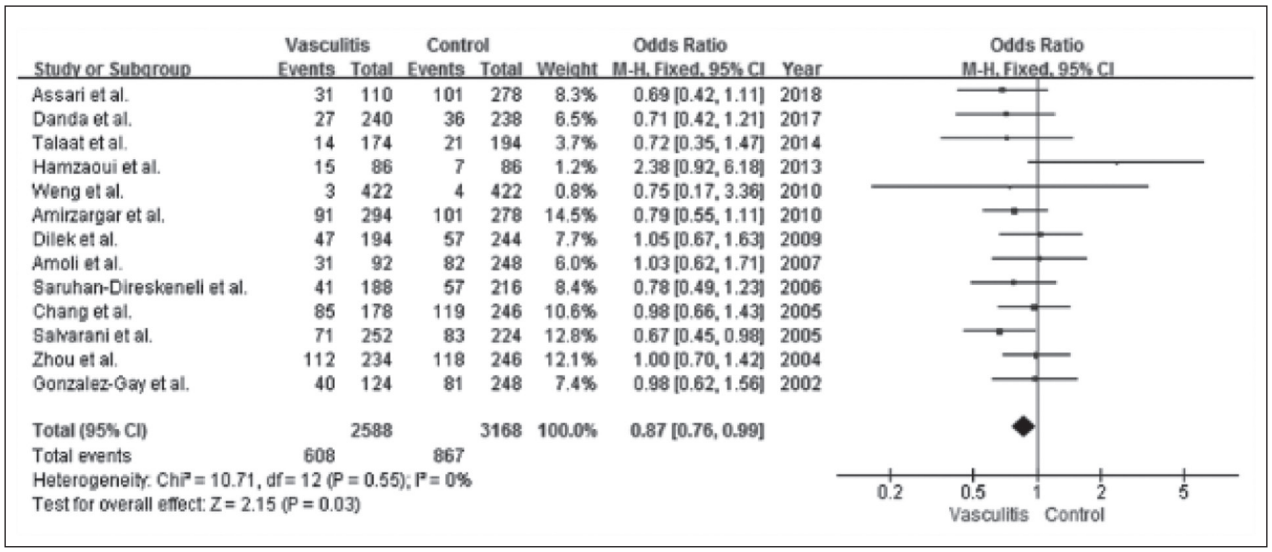

Fig. 2. OR and 95% CI of individual studies and pooled data for the association between C allele of *IL6* rs18007954 and vasculitis in all study subjects

95% CI 0.67-0.94, *P* =0.009 and OR 0.76, 95% CI 0.63-0.92, *P* =0.005, respectively). There was no significant relationship between other genetic models and vasculitis.

Meta-analysis of relationships between IL6 rs1800795 polymorphisms and vasculitis in the different ethnicity groups

This study included three ethnic groups. The first group is Middle Eastern, which included Iranian, Turkish, and Egyptian populations. People of Spanish, Italian, and American heritage were included in the Caucasian group. The third group, i.e., the Asian group, included Indian, Taiwanese, and Korean populations. We performed ethnicity-specific meta-analysis of the Middle Eastern, Caucasian, and Asian populations. *P* values for allele comparisons in the Middle Eastern, Caucasian and Asian population were 0.10, 0.26, and 0.37, respectively, with no significant association between *IL6* rs1800795 polymorphism and vasculitis. There were no significant associations among all genetic models of *IL6* rs1800795 and vasculitis in the different ethnicities.

Meta-analysis of relationships between IL6 rs1800795 polymorphisms and vasculitis subgroups

According to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC2012) (1), subgroup analysis was performed by dividing vasculitis into large, medium, small, and variable vessel vasculitis. In large vessel vasculitis, meta-analysis of *IL6* rs1800795 polymorphisms revealed significant associations between the disease and the C allele (OR 0.77, 95% CI 0.61-0.96, *P* =0.02). A significant association was also found between large vessel vasculitis and this polymorphism using a dominant model and heterozygote vs. dominant homozygote comparison (OR 0.70, 95% CI 0.52-1.93, *P* =0.01 and OR 0.69, 95% CI 0.51-0.93, *P* =0.01, respectively; Figure 3). In medium vessel vasculitis, there were significant associations between the dominant model and heterozygote vs. dominant homozygote comparison of *IL6* rs1800795 and disease (OR 0.49, 95% CI 0.25-0.88, *P* =0.02 and OR 0.46, 95% CI 0.25-0.85, *P* =0.01, respectively; Table 2). In small and variable vessel vasculitis, there were no associations between allele contrast and genetic models of *IL6* rs1800795 and diseases.

Heterogeneity and publication bias

Fixed effect models were used because there was no significant heterogeneity in allele contrast and the genetic models of *IL6* rs1800795 polymorphism and overall vasculitis. However, in the subgroup analysis conducted for sensitivity analysis, some random effect models were used because of the heterogeneity in several gene models (Table 2). The genotype of the control groups of 10 studies were in HWE, but those of three studies were not in HWE (9, 13, 18).

Funnel plots were drawn for meta-analyses of *IL6* polymorphisms that included more than 10 studies to identify publication bias. Funnel plots were generally symmetrical, with 7 on the left and 6 on the right (Figure 4).

Discussion

IL-6 is a pleiotropic cytokine that is mainly increased during inflammation. Serum IL-6 levels are increased in Takayasu arteritis and giant cell arteritis, and IL-6 is an important molecule in the pathophysiology of the inflammation process of Takayasu arteritis and giant cell arteritis (22). IL-6 plays a role as a biomarker of intravenous immunoglobulin treatment for Kawasaki disease in non-responders (23), and inhibitors of IL-6 are effective in the treatment of Takayasu arteritis and giant cell arteritis (22). Most of the studies on the association of *IL6* with vasculitis were focused on large vessels; however, in granulomatosis with polyangiitis and microscopic polyangiitis, the serum levels of IL-6 were elevated, the expression of IL-6 was increased upon biopsy, and treatment with tocilizumab, an IL-6 receptor inhibitor, was effective (24). Although tocilizumab has been reported to be effective in Behçet's disease-related uveitis (25), studies of IL-6 treatment against small or various vessel vasculitis are still lacking.

The polymorphism of the promoter region of *IL6* has been implicated in the production and expression of IL-6. In this study, we performed a meta-analysis of the association between *IL6* rs1800795 polymorphisms in the *IL6* promotor region and vasculitis, and the C allele and GC genotype were all

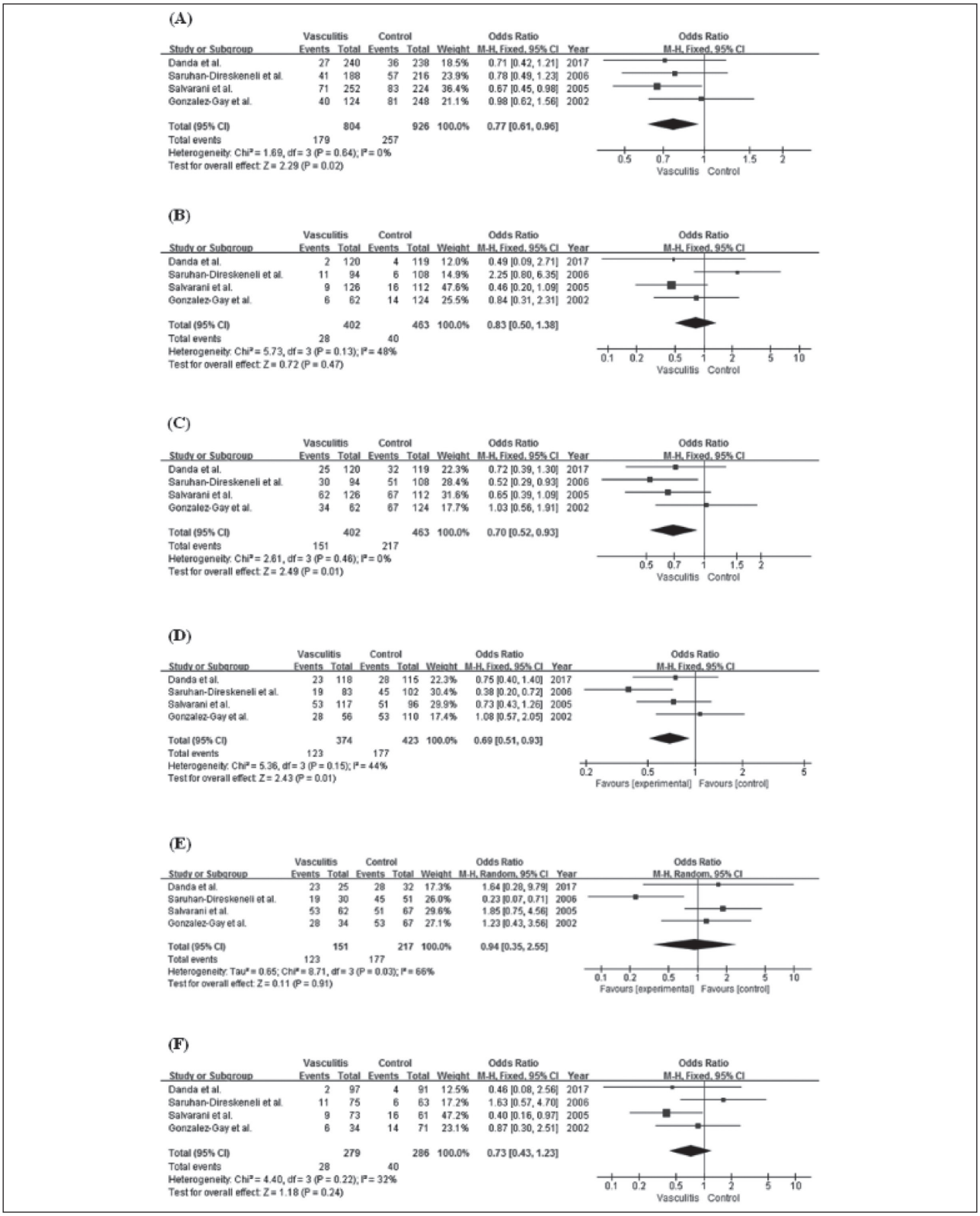

Fig. 3. OR and 95% CI of individual studies and pooled data for the association between *IL6* rs1800795 polymorphisms and large vessel vasculitis. **(A)** allelic contrast, **(B)** recessive and **(C)** dominant model, and **(D)** heterozygote vs. dominant homozygote, **(E)** heterozygote vs. recessive homozygote, and **(F)** homozygote comparison

Table 2. Meta-analysis of associations between the *IL6* rs1800795 polymorphisms and vasculitis according to category

	Test of association			Test of heterogeneity		
	OR	95% CI	*P*	Model	*P*	I^2(%)
Large vessel						
C vs. G	0.77	0.61-0.96	0.02	F	0.64	0
CC vs. GC+GG	0.83	0.50-1.38	0.47	F	0.13	48
CC+GC vs. GG	0.70	0.52-0.93	0.01	F	0.46	0
GC vs. GG	0.69	0.51-0.93	0.01	F	0.15	44
GC vs. CC	0.94	0.35-2.55	0.91	R	0.03	66
CC vs. GG	0.73	0.43-1.23	0.24	F	0.22	32
Medium vessel						
C vs. G	0.69	0.44-1.10	0.12	F	0.92	0
CC vs. GC+GG	1.95	0.42-9.00	0.39	NA	NA	NA
CC+GC vs. GG	0.49	0.27-0.88	0.02	F	0.54	0
GC vs. GG	0.46	0.25-0.85	0.01	F	0.46	0
GC vs. CC	0.36	0.08-1.71	0.20	NA	NA	NA
CC vs. GG	1.17	0.24-5.63	0.85	NA	NA	NA
Small vessel						
C vs. G	1.01	0.75-1.35	0.96	F	0.92	0
CC vs. GC+GG	0.96	0.56-1.65	0.89	F	0.99	0
CC+GC vs. GG	1.04	0.67-1.62	0.85	F	0.92	0
GC vs. GG	1.05	0.61-1.80	0.86	F	0.94	0
GC vs. CC	1.16	0.54-2.53	0.70	F	0.88	0
CC vs. GG	0.99	0.53-1.86	0.98	F	0.98	0
Variable vessel						
C vs. G	0.94	0.76-1.15	0.53	F	0.24	27
CC vs. GC+GG	1.03	0.23-4.55	0.97	R	0.08	68
CC+GC vs. GG	1.00	0.62-1.61	0.99	R	0.06	59
GC vs. GG	0.96	0.52-1.74	0.88	R	0.01	68
GC vs. CC	2.76	0.93-8.16	0.07	F	0.89	0
CC vs. GG	0.88	0.39-2.02	0.77	F	0.28	15

OR: odds ratio; CI: confidence interval; R: random effects model; F: fixed effects model; NA: not applicable

associated with a low prevalence of vasculitis. IL-6 is also associated with acute vascular events, and the GG genotype of rs1800795 in *IL6* has been found to be associated with the severity of acute vascular disease (26). In addition, the C allele of rs1800795 was associated with low prevalence of rheumatoid arthritis, psoriasis, systemic lupus erythematosus, febrile seizures, tuberculosis, and sepsis (27-32). However, the C allele was associated with high susceptibility to Grave's disease (33), and there was no association

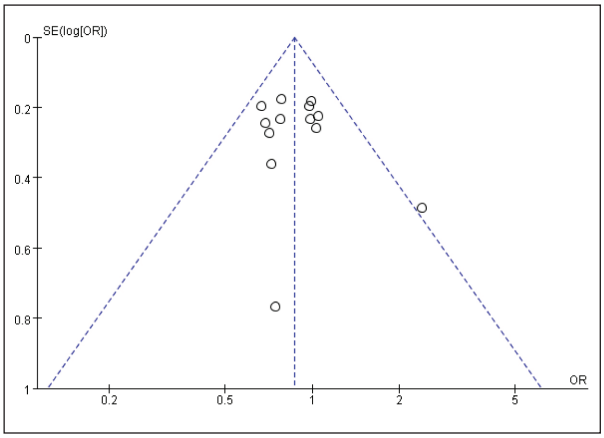

Fig. 4. Funnel plots for *IL6* rs1800795 and susceptibility of vasculitis

between *IL6* rs1800795 polymorphism and susceptibility to osteoarthritis or obesity (34, 35). IL-6 stimulates the production of most acute-phase proteins, including C-reactive protein (CRP) (36), and the C allele of rs1800795 may play a protective role in most autoimmune diseases and infectious diseases in which CRP can be elevated. In addition, there was no association between the rs1800795 polymorphism and the level of circulating IL-6 with health (37), and the relationship between the genotypes of the *IL6* promoter region and the expression of IL-6 is complex and varies depending on the producing cell type (21); thus, the role of the polymorphisms may differ in each disease.

In subgroup analysis, large and medium vessel vasculitis showed similar results. The C allele was associated with a lower prevalence of vasculitis, but no significant difference was found in homozygote comparisons. Considering that the dominant homozygote was associated with a higher prevalence of vasculitis when compared with heterozygotes and heterozygotes + recessive homozygotes, the association may be due to the difference between heterozygote and dominant homozygote. It is suggested that the GC genotype results in a lower risk of vasculitis compared with the GG genotype, particularly for large and medium vessels. There were no genetic models associated with small and variable vessel vasculitis. In the case of small vessel vasculitis, there were only two studies of granulomatosis with polyangiitis from ANCA-associated vasculitis and IgA vasculitis from immune complex vasculitis, suggesting heterogeneity and bias. Variable vessel vasculitis was included only in studies in Behçet's disease, which is a heterogeneous disease, and other genetic backgrounds such as *human leukocyte antigen (HLA)-B51* may be more closely related.

There was no association between *IL6* polymorphisms and vasculitis in sub-analyses based on ethnicity. This is likely because of the heterogeneity of vasculitis in each ethnic group. In case of the Middle Eastern populations, four studies on Behçet's disease, which did not show any association with *IL6* polymorphisms, one on Takayasu arteritis, and one on Kawasaki disease were included. In the case of the Caucasian populations, two studies on giant cell arteritis, one on granulomatosis with polyangiitis, and one on IgA vasculitis were included. In the case of the Asian populations, one study each on Takayasu arteritis, Kawasaki disease, and Behçet's disease was included. However, the prevalence and presentations of vasculitis varies by race and ethnicity, and epigenetics differ based on the type of vasculitis; thus, further studies are needed (2, 38, 39).

This is the first meta-analysis of the association between *IL6* rs1800795 polymorphisms and vasculitis, but there are some limitations. First, vasculitis is a heterogeneous disease with multiple types. However, subgroup analysis was performed by classifying vasculitis according to CHCC2012. Second, not all studies in this meta-analysis were consistent with HWE, possibly leading to heterogeneity of the meta-analysis. Although heterogeneities were prevalent, a test of heterogeneity showed no significant heterogeneity in the meta-analysis including overall vasculitis, and the fixed-effect model was used in all genetic models. Third, the distinction of ethnicity was unclear in countries with mixed ethnicities such as in India and the United States of America. Lastly, *IL6* polymorphisms may be associated with disease severity as well as susceptibility, but we did not perform a meta-analysis for this association.

In conclusion, this meta-analysis detected significant associations between *IL6* rs1800795 polymorphisms and susceptibility to vasculitis, especially for large and medium vessels. The C allele and GC genotype exert protective effects against vasculitis. However, owing to the heterogeneity of vasculitis, large-scale studies involving various ethnicities and subtypes of vasculitis are necessary.

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