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Meta-Analysis

Monocyte chemoattractant protein-1 promoter -2518 polymorphism and susceptibility to vasculitis, rheumatoid arthritis, and multiple sclerosis: A meta-analysis

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Abstract: The purpose of this study was to examine whether the monocyte chemoattractant protein-1 (MCP-1) promoter -2518 A/G polymorphism (rs1024611) is associated with susceptibility to vasculitis, rheumatoid arthritis (RA), or multiple sclerosis (MS). A meta-analysis was conducted on the association between the MCP-1 -2518 A/G polymorphism and vasculitis, RA, and MS. Fourteen studies from 13 articles, including six on vasculitis, five on RA, and three on MS, consisting of 3,038 patients and 3,545 controls were available for the meta-analysis. The meta-analysis revealed no association between the MCP-1 -2518 G allele and vasculitis (odds ratio [OR] = 0.990, 95% confidence interval [CI] = 0.749–1.309, $p = 0.943$). Stratification by ethnicity indicated no association between the G allele of the MCP-1 -2518 A/G polymorphism and vasculitis in Asians and Caucasians. Meta-analysis by vasculitis type revealed an association between the GG+GA genotype of the MCP-1 -2518 A/G polymorphism and Behçet's disease (BD; OR = 1.349, 95% CI = 1.013–1.796, $p = 0.040$). However, sensitivity analysis showed that the association was not statistically significant after removing a study that was conducted in China (OR = 1.030, 95% CI = 0.667–1.590, $p = 0.895$), which indicated that the association was not statistically robust. The meta-analysis revealed no association between the MCP-1 -2518 G allele and RA (OR = 0.986, 95% CI = 0.890–1.093, $p = 0.793$) or MS (OR = 1.281, 95% CI = 0.802–2.046, $p = 0.301$). Our meta-analysis demonstrates that the MCP-1 -2518 A/G polymorphism is not associated with susceptibility to vasculitis, RA, or MS.

Key words: MCP-1, meta-analysis, polymorphism, vasculitis, RA, MS.

Introduction

Vasculitis is a heterogeneous group of disorders characterized by blood vessel inflammation and damage that lead to tissue or organ injury. Behcet's disease (BD) is a chronic inflammatory disease characterized by recurrent oral and genital ulcers, skin lesions and uveitis, and affects all types and sizes of blood vessels. Henoch-Schönlein purpura (HSP), the most common vasculitis of childhood, is a systemic vasculitis involving small vessels and affecting the skin, joints, gastrointestinal tract, and kidneys. Kawasaki disease (KD) is a systemic vasculitis characterized by medium-sized arteries and coronary arthritis, and results in cardiac events, such as, ischemia and myocardial infarction. Rheumatoid arthritis (RA) is a chronic inflammatory disease of predominantly synovial joints that causes significant morbidity and shortens life expectancy (21). Multiple sclerosis (MS) is a demyelinating, inflammatory disease of the central nervous system that affects young adults and shows a relapsing or progressive disease course. Although the etiologies of these autoimmune and inflammatory diseases are not fully understood, interactions between a susceptible genetic background and environmental factors have been suggested (5).

Monocyte chemoattractant protein-1 (MCP-1), known as CC chemokine ligand 2, is a β-chemokine responsible for monocyte and T-lymphocyte recruitment during the acute and chronic phases of inflammation (12). MCP-1 is considered to be responsible for tissue inflammation in autoimmune diseases because of its observed tissue expression in human and experimental autoimmune models (26). Because recruitment of macrophages and monocytes into inflamed areas is a central process in innate immunity, MCP-1 likely plays a key role in disease processes. The MCP-1 gene has been mapped to chromosome 17q11, and the most commonly identified polymorphism is the functional promoter -2518 A/G polymorphism (rs1024611), which affects MCP-1 expression in response to an inflammatory stimulus. The G allele of this polymorphism has been associated with increased interleukin-1-mediated MCP-1 transcription and higher circulating concentrations of MCP-1 protein (25). Previous studies have shown that compared with controls, patients with vasculitis, RA, and MS show increased MCP-1 expression.

Previous association studies on the relationship between the functional MCP-1 -2518 A/G polymorphism and autoimmune and inflammatory diseases including vasculitis, RA, and MS have produced inconsistent results (2-4,10,11,14-18,22,23,27) likely attributable to the sample sizes used, racial/ethnic differences in allele frequencies, or publication bias. Therefore, to overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood that random errors were responsible for false-positive or false-negative associations, we turned to meta-analysis (19,20,24). The aim of the present study was to determine whether

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the functional MCP-1 -2518 A/G polymorphism is associated with susceptibility to vasculitis, RA, or MS.

Materials and Methods

Identification of eligible studies and data extraction

A search of the literature for studies that examined the association between the MCP-1 -2518 A/G polymorphism and vasculitis, RA, and MS was conducted. We used the Pubmed and Embase, Web of Science, and Scopus to identify articles published through April 2015 in which the MCP-1 -2518 A/G polymorphism was identified in patients with vasculitis, RA, or MS and controls. In addition, all references mentioned in the identified articles were reviewed to identify studies not indexed by the electronic databases. The following keywords and subject terms were used in the search: monocyte chemoattractant protein-1, MCP-1, vasculitis, rheumatoid arthritis, and multiple sclerosis. Studies were included in the analysis if they (1) were case-control studies, (2) contained genotype or allele data, (3) included sufficient data to calculate odds ratios (ORs), and (4) included patients diagnosed with vasculitis, RA, or MS based on the respective diagnostic criteria. No restrictions were placed on language, race, ethnicity, or geographic area. We excluded studies (1) that contained overlapping data; (2) in which the number of genotypes could not be ascertained; and (3) in which family members were studied because their analysis was based on linkage considerations. The following information was extracted from each identified study: author, year of publication, ethnicity of the study population, demographics, number of cases and controls, and frequencies of the genotypes and alleles of the MCP-1 -2518 A/G polymorphism.

Evaluation of statistical associations

Meta-analyses were performed using (i) allelic contrast and (ii) recessive, (iii) dominant, and (iv) co-dominant models. Subgroup analyses were performed according to ethnicity and disease type to evaluate ethnicity- and disease-specific effects. Point estimates of risks, ORs, and 95% confidence intervals (CIs) were estimated for each study. Cochran's Q-statistic was used to assess within- and between-study variations and heterogeneities. This heterogeneity test assessed the null hypothesis that all studies evaluated the same effect. I^2 values were used to quantify the effect of heterogeneity. These values range between 0% and 100% and represent the proportion of between-study variability attributable to heterogeneity rather than chance (13). I^2 values of 25%, 50%, and 75% were nominally defined as low, moderate, and high estimates. The fixed effects model assumes that a genetic factor has the same effect on disease susceptibility across all studies investigated and that observed variations between studies are caused by chance alone. The random effects model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance. When study groups are homogeneous, the two models are similar, but if the groups are not homogeneous, the random effects model usually provides wider CIs than the fixed effects model. Furthermore, the random effects model is used in the presence of significant between-study heterogeneity (6). Statistical manipulations were undertaken with the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ, USA). We calculated Cochran's Q-statistic, I^2 values, and did meta-analyses using fixed effects or random effects model with this program. The power of each study was defined as the probability of detecting an association between the polymorphism and autoimmune disease at a level of significance of 0.05, assuming a small effect size (OR = 1.5). Power analysis was performed with the G*Power statistical program (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower). We used goodness-of-fit test using a post-hoc type including a given α error probability, sample size, and effect size.

Evaluation of heterogeneity and publication bias

The chi-square test was used to determine whether the observed genotype frequencies in the controls conformed to Hardy-Weinberg equilibrium (HWE). Sensitivity analysis was performed to assess the influence of individual studies on the pooled OR by omitting each study and to investigate statistically robust results from the meta-analysis. Funnel plots are often used to detect publication bias but require a range of studies of varying sizes and subjective judgments. Therefore, we evaluated publication bias by using Egger's linear regression test (7), which measures funnel plot asymmetry on a natural logarithmic scale of ORs.

Results

Studies included in the meta-analysis

One ninety-nine studies were identified through electronic and manual searches, 15 of which were selected for full-text review based on title and abstract details. Two studies were excluded, because they had data on other MCP-1 polymorphism (there were no data on the MCP-1 -2518 A/G polymorphism) (1,8). Thus, a total of 13 studies met our inclusion criteria (2-4,10,11,14-18,22,23,27). One of these studies contained data on two different groups (2), and we analyzed these data sets independently. Therefore, a total of 14 separate studies were considered in the meta-analysis, which contained a total of 3,038 patients and 3,545 controls in six Caucasian, seven Asian, and one Arab sample population (Table 1, Figure 1). These studies comprised six each on vasculitis, five on RA, and three on MS. Many diseases have been associated with vasculitis, but our literature search found the studies on the MCP-1 -2518 A/G polymorphism only in HSP, BD, and KD among vaducltis diseases, thus only HSP, BD, and KD were included in the analysis of vascultis. All of the studies but three provided genotype data of the MCP-1 -2518 A/G polymorphism (4,10,23). Selected details of the individual studies are summarized in Table 1. The statistical powers of these five studies ranged from 12.4% to 99.5%. Two of the studies had statistical power exceeding 80% (Table 1) (2). The power of each study was the probability of detecting an association of a small effect size (OR = 1.5) between the polymorphism and autoimmune disease at a level of significance of 0.05. For example, Caliz-1, 2013 and Caliz-2, 2013 studies have 86.3% and 99.5% probability to detect an association between the polymorphism and RA, respectively. Although these studies

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

Author [Ref]	Country	Ethnicity	Disease	Numbers		G allele (%)		Association				Power* (%)
				Case	Control	Case	Control	OR	95% CI		*p* value	
Yu, 2015 (27)	Taiwan	Asian	HSP	82	136	47.6	61.8	0.561	0.379	0.831	0.004	31.4
Kim, 2012 (16)	Korea	Asian	BD	132	113	58.0	57.1	1.036	0.724	1.485	0.845	34.6
Hou, 2010 (14)	China	Asian	BD	296	319	56.8	50.9	1.264	1.010	1.583	0.041	69.8
Cho, 2004 (4)	Korea	Asian	BD	104	81	62.0	65.0	0.886	0.578	1.359	0.580	27.4
Chen, 2004 (3)	UK	Caucasian	BD	68	109	30.9	30.7	1.007	0.633	1.601	0.977	26.4
Jibiki, 2001 (15)	Japan	Asian	KD	45	18	66.7	52.8	1.789	0.814	3.933	0.148	12.4
Caliz, 2013a (2)	Spain	Caucasian	RA	458	477	23.3	26.8	0.826	0.670	1.019	0.074	86.3
Caliz, 2013b (2)	Spain	Caucasian	RA	944	1160	26.1	24.6	1.082	0.941	1.244	0.268	99.5
Goldbergova, 2012 (10)	Czech	Caucasian	RA	144	125	26.5	26.3	0.999	0.680	1.468	0.998	37.4
Lee, 2003 (18)	Korea	Asian	RA	117	97	60.7	62.9	0.911	0.616	1.348	0.641	30.9
Gonzalez, 2003 (11)	Spain	Caucasian	RA	141	194	20.2	21.1	0.945	0.647	1.381	0.772	44.8
Namgoong, 2014 (23)	Korea	Asian	MS	79	237	62.7	59.3	1.152	0.795	1.670	0.453	42.7
Messadi, 2010 (22)	Tunisia	Arab	MS	58	74	16.4	19.6	0.804	0.425	1.521	0.502	20.9
Kroner, 2004 (17)	Germany	Caucasian	MS	370	405	40.4	26.8	1.853	1.496	2.295	0.000	79.5

BD: Behçet's disease, CI: confidence interval, HSP: Henoch-Schönlein purpura, KD: Kawasaki disease, MS: multiple sclerosis, OR: odds ratio, RA: rheumatoid arthritis, Ref: reference, UK: United Kingdom., *Power calculations assume α = 0.05 and small effect size (OR = 1.5).

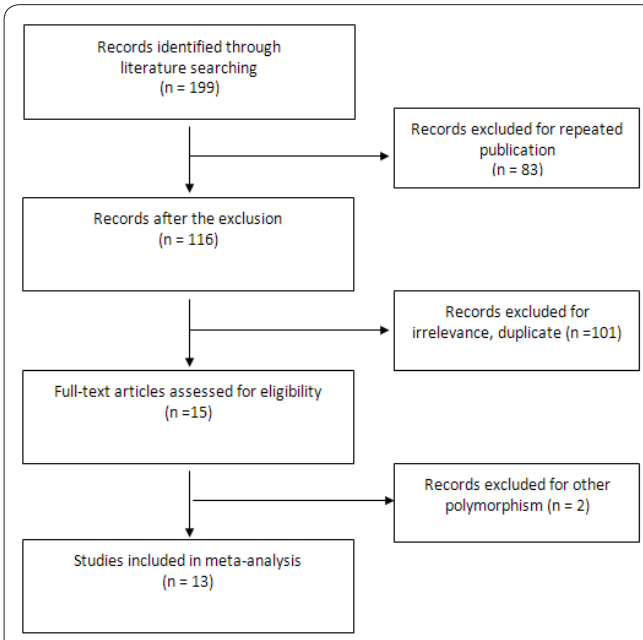

Figure 1. Study flow chart.

have statistical power of 86.3% and 99.5% probability to detect the association, both studies showed no significant associations between MCP-1 -2518 A/G polymorphism and RA (association p-values = 0.074, 0.268).

Frequencies of the G allele of the MCP-1 -2518 A/G polymorphism in different ethnic groups

The mean frequency of the G allele of the MCP-1 -2518 A/G polymorphism was 34.4% among all normal controls, and compared with the other ethnic groups, Arabs had a lower G allele prevalence. Among normal controls, the frequencies of the G allele in the Arab, Caucasian, and Asian populations were 19.6%, 25.5%, and 57.4%, respectively (Table 2).

Meta-analysis of the association between the MCP-1 -2518 A/G polymorphism and vasculitis

A meta-analysis of all vasculitis or BD patients and of each ethnic group was performed and revealed no association between the MCP-1 -2518 G allele and vasculitis (OR = 0.990, 95% CI = 0.749–1.309, $p = 0.943$) (Table 3, Figure 2). Stratification by ethnicity indicated no association between the MCP-1 -2518 G allele and vasculitis in Asians and Caucasians (Table 3). Analysis using the dominant, recessive, and codominant models showed the same G allele pattern (Table 3, Figure 3). Meta-analysis revealed an association between the GG+GA genotype of the MCP-1 -2518 A/G polymorphism and BD (OR = 1.349, 95% CI = 1.013–1.796, $p = 0.040$; see Table 3, Figure 1). However, sensitivity analysis showed that the association was not statistically significant after removing the study by Hou et al. (14) (OR = 1.030, 95% CI = 0.667–1.590, $p = 0.895$), which indicated that the association was not statistically robust. Analysis using the codominant model showed the same pattern (Table 3).

Meta-analysis of the association between the MCP-1 -2518 A/G polymorphism and RA or MS

The meta-analysis revealed no association between the MCP-1 -2518 G allele and RA (OR = 0.986, 95%

Table 2. Prevalence of the G allele of the MCP-1-2518 A/G polymorphism.

Population	No. of studies	Subjects		G allele (%)	
		Case	Control	Case	Control
Caucasian	6	2,125	2,470	27.7	25.5
Asian	7	855	1,001	58.3	57.4
Arab	1	58	74	16.4	19.6
Overall	14	3,038	3,545	36.1	34.4

Table 3. Meta-analysis of associations between the MCP-1-2518 A/G polymorphism and vasculitis.

MCP-1 -2518 polymorphism	Population	No. of studies	Subjects		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	*P* value	Model	*P* value	I^2
G vs. A	Vasculitis	6	727	776	0.990	0.749–1.309	0.943	R	0.011	66.1
	BD	4	600	622	1.121	0.952–1.319	0.171	F	0.450	0
	Asian	5	614	649	0.989	0.708–1.381	0.948	R	0.005	72.8
	Caucasian	1	68	109	1.007	0.633–1.601	0.977	NA	NA	NA
GG vs. GA+AA (recessive)	Vasculitis	5	623	695	0.936	0.617–1.419	0.756	R	0.077	52.4
	BD	3	496	541	1.097	0.832–1.447	0.510	F	0.888	0
	Asian	4	555	586	0.947	0.581–1.543	0.827	R	0.039	64.1
	Caucasian	1	68	109	0.862	0.303–2.450	0.781	NA	NA	NA
GG+GA vs. AA (dominant)	Vasculitis	5	623	695	1.078	0.671–1.732	0.757	R	0.027	63.3
	BD	3	496	541	1.349	1.013–1.796	0.040	F	0.267	24.2
	Asian	4	555	586	1.079	0.575–2.027	0.812	R	0.013	72.1
	Caucasian	1	68	109	1.065	0.581–1.953	0.839	NA	NA	NA
GG vs. AA	Vasculitis	5	623	695	0.992	0.508–1.938	0.981	R	0.008	70.8
	BD	3	496	541	1.358	0.955–1.929	0.088	F	0.443	0
	Asian	4	555	586	1.014	0.451–2.280	0.973	R	0.004	77.8
	Caucasian	1	68	109	0.903	0.305–2.679	0.856	NA	NA	NA
GA vs. AA	Vasculitis	5	623	695	1.219	0.924–1.609	0.162	F	0.144	41.6
	BD	3	496	541	1.362	1.003–1.850	0.048	F	0.271	23.3
	Asian	4	555	586	1.113	0.655–1.894	0.692	R	0.081	55.4
	Caucasian	1	68	109	1.104	0.584–2.088	0.768	NA	NA	NA

BD: Behçet's disease, CI: confidence interval, F: fixed effects model, NA: not available, OR: odds ratio, R: random effects model.

CI = 0.890–1.093, $p = 0.793$) (Table 4, Figure 3). Analysis using the dominant, recessive, and codominant models showed the same G allele pattern (see Table 3, Figure 2). The meta-analysis also revealed no association between the G allele and MS (OR = 1.281, 95% CI = 0.802–2.046, $p = 0.301$) (Table 4, Figure 3), and analysis using the dominant model showed no association between the MCP-1 -2518 A/G polymorphism and MS (Table 4).

Heterogeneity and publication bias

Between-study heterogeneity was found during the meta-analyses of vasculitis and MS (Tables 3, 4). However, no between-study heterogeneity was found during meta-analyses of BD and RA (Tables 3, 4). The distributions of genotypes in normal control groups was not consistent with HWE in one study (14). Deviation from HWE among controls implies genotyping errors or potential bias during control selection. Excluding this study showed that the association between the MCP-1 -2518 A/G polymorphism and BD was not statistically significant. Publication bias results in a disproportionate number of positive studies and poses a problem for meta-analyses. Evidence of publication bias was not found in the meta-analyses of the MCP-1 -2518 A/G polymorphism (Egger's regression test, $p > 0.1$).

Discussion

MCP-1 is a potent chemokine that plays a key role in the recruitment of leukocytes to sites of inflammation (12). The MCP gene has several polymorphisms in its promoter region. In particular, the MCP-1 -2518 A/G polymorphism modifies the degree to which MCP-1 expression is induced by proinflammatory stimuli (25). Moreover, compared with the monocytes of individuals

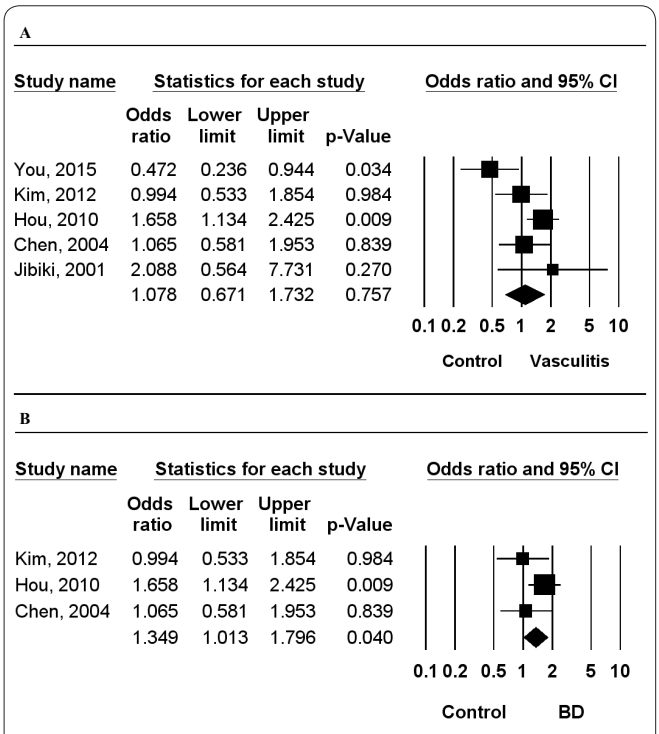

Figure 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data for the association between the MCP-1-2518 A/G polymorphism and vasculitis (A) or BD (B) under the dominant model.

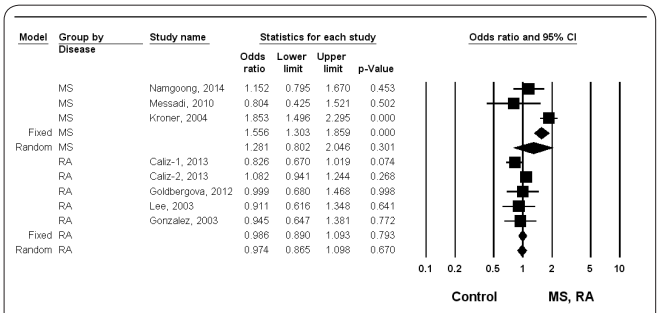

Figure 3. ORs and 95% CIs of individual studies and pooled data for the allelic association between the MCP-1-2518 A/G polymorphism and RA or MS.

with the AA genotype at -2518, those of individuals carrying a G allele produce more MCP-1 protein after treatment with interleukin-1β, thereby possibly increasing inflammatory response (9). The MCP-1 polymorphism is therefore considered a good candidate for causing genetic predisposition to autoimmune diseases.

In this meta-analysis, we combined evidence of associations between the MCP-1 -2518 A/G polymorphism and susceptibility to vasculitis, RA, and MS. The meta-analysis revealed no association between the MCP-1 -2518 A/G polymorphism and vasculitis. However, stratification by vasculitis type showed an association between the GG+GA genotype and BD (OR = 1.349, 95% CI = 1.013–1.796, p = 0.040). However, sensitivity analysis revealed that the association was not statistically significant after the removal of one study from China (OR = 1.030, 95% CI = 0.667–1.590, p = 0.895), which indicated that the association was not statistically robust. The meta-analysis revealed no association between the MCP-1 -2518 A/G polymorphism and RA or MS. However, caution must be used when interpreting our data because the statistical associations observed were rather weak, possibly due to the small sample size, the between-study heterogeneity of the included studies, and a lack of clinical information.

We found no evidence of an association of the MCP-1 -2518 A/G polymorphism with vasculitis, RA, or MS in this meta-analysis. These findings conflict with the results of functional studies conducted on the MCP-1 polymorphism (9). Although it is not uncommon for epidemiologic results to differ from the results of functional studies, in the present case, this disagreement may be attributed to the complexity of vasculitis, RA, and MS, the development of which involves multiple genes, different genetic backgrounds, and various environmental factors. Conversely, because a relatively small number of studies with low statistical power were included in our meta-analysis, we could not rule out the possibility of a type II error (false negative).

The present study had several limitations. First, heterogeneity and confounding factors may have distorted the analysis. Publication bias also may have affected the

Table 4. Meta-analysis of the association between the MCP-1-2518 A/G polymorphism and RA or MS.

Disease	MCP-1 -2518 polymorphism	No. of studies	Subjects		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	*P* value	Model	*P* value	I^2
RA	G vs. A	5	1,804	2,053	0.986	0.890–1.093	0.793	F	0.326	13.8
	GG vs. GA+AA	4	1,660	1,928	0.963	0.760–1.221	0.756	F	0.478	0
	GG+GA vs. AA	4	1,660	1,928	0.989	0.864–1.132	0.869	F	0.141	0
	GG vs. AA	4	1,660	1,928	1.003	0.777–1.294	0.984	F	0.571	0
	GA vs. AA	4	1,660	1,928	0.989	0.857–1.141	0.878	F	0.109	50.3
MS	G vs. A	3	507	716	1.281	0.802–2.046	0.301	R	0.010	78.2
	GG vs. GA+AA	1	370	405	0.959	0.570–1.613	0.874	NA	NA	NA
	GG+GA vs. AA	2	428	479	1.642	0.400–6.742	0.492	R	0.000	92.0
	GG vs. AA	1	370	405	1.942	1.118–3.373	0.019	NA	NA	NA
	GA vs. AA	1	370	405	3.527	2.583–4.817	$<1.0 \times 10^{-8}$	NA	NA	NA

CI: confidence interval, F: fixed effects model, MS: multiple sclerosis, NA: not available, OR: odds ratio, R: random effects model, RA: rheumatoid arthritis.

meta-analysis because studies that produced negative results may have been missed or not published. However, missing studies with negative results would not have changed our conclusions, because such data would have reinforced our observations concerning the lack of an association. Second, the MCP-1 polymorphism may be associated with disease severity as well as susceptibility. However, the small number of available data precluded a meta-analysis of the association between the MCP-1 polymorphism and disease severity. Third, this ethnicity-specific meta-analysis included data from Caucasian and Asian patients, and thus, our results are applicable to only these ethnic groups. The frequency of the MCP-1 -2518 G allele depends on ethnicity; indeed, the prevalence of the MCP-1 -2518 G allele is high in Asians (57.4 %) but relatively low in Caucasians (25.5%). Fourth, the number of studies included in this meta-analysis was small, especially when grouped by ethnicity, RA, and MS. We examined one study of a Caucasian population and five studies of Asian populations in the subgroup analysis by ethnicity, five studies on RA, and three studies on MS. These study numbers may be insufficient to provide conclusive results.

In conclusion, this meta-analysis of published data demonstrates no association between the MCP-1 -2518 A/G polymorphism and vasculitis, RA, or MS. Thus, our findings do not support the hypothesis that the MCP-1 -2518 A/G polymorphism plays a critical role in susceptibility to vasculitis, RA, and MS. Because the frequency of the MCP-1 -2518 A/G polymorphism differs among various ethnic groups, large-scale studies in populations with different ethnicities are needed to explore the relationships between the polymorphisms of the MCP gene and the pathogenesis of vasculitis, RA, and MS.

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