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Meta-Analysis

Intercellular adhesion molecule-1 polymorphisms, K469E and G261R and susceptibility to vasculitis and rheumatoid arthritis: a meta-analysis

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Abstract: The aim of this study was to determine whether intercellular adhesion molecule-1 (ICAM-1) polymorphisms are associated with susceptibility to vasculitis or rheumatoid arthritis (RA). Meta-analyses were performed to assess the associations between K469E and G241R polymorphisms of ICAM-1 and vasculitis or RA. A total of 12 studies on 1,368 patients and 1,922 controls, which comprised 8 vasculitis studies and 4 RA studies, were included in the meta-analysis. We found no significant association between vasculitis and K469E E allele among the various subjects (OR = 1.238, 95% CI = 0.9781–1.566, $p = 0.076$). However, an association between vasculitis and K469E polymorphism was observed under homozygote contrast (OR = 1.443, 95% CI = 1.084–1.920, $p = 0.012$). Stratification by ethnicity and vasculitis type showed no association between vasculitis and 1 K469E polymorphism under heterozygote contrast. In addition, the meta-analysis revealed a significant association between the ICAM-1 G241R R allele and Behcet's disease (BD) (OR = 3.261, 95% CI = 1.653–6.434, $p = 0.001$), but not giant cell arteritis. Moreover, the meta-analysis indicated an association between RA and the R allele and RR+ RG genotype of the ICAM-1 G241R polymorphism (OR = 2.014, 95% CI = 1.215–3.339, $p = 0.007$; OR = 2.394, 95% CI = 1.354–4.235, $p = 0.003$). This meta-analysis suggests that the K469E polymorphism is associated with susceptibility to vasculitis, and that the G241R polymorphism is associated with susceptibility to BD and RA.

Key words: Vasculitis,rheumatoid arthritis, ICAM-1, polymorphism, meta-analysis.

Introduction

Vasculitis is a heterogeneous group of disorders characterized by inflammation and damage to the blood vessels, leading to tissue or organ injury (1). Rheumatoid arthritis (RA) is a chronic inflammatory disease that predominantly involves the synovial joints. RA causes significant morbidity, shortens life expectancy, and affects up to 1% of adults worldwide (2). Although the etiologies of vasculitis and RA remain to be fully elucidated, some researchers have suggested that these diseases occur under conditions of specific interactions between a susceptible genetic background and environmental factors.

The process through which leukocytes adhere to endothelial cells is a key step in their migration to inflammation, and the interaction of leucocytes with the vascular endothelium is mediated by adhesion molecules. The intercellular adhesion molecule (ICAM-1), a member of the immunoglobulin (Ig) superfamily, is a single-stranded glycoprotein expressed on vascular endothelial cells, fibroblasts, macrophages, antigen presenting cells, and activated lymphocytes (3). ICAM-1 plays a key role in the transendothelial migration of neutrophils, as well as in T-cell activation during inflammation. It also controls the migration of leukocytes into tissues during inflammation, via adhesion to lymphocyte functional-associated antigen-1 (LFA-1) and macrophage-1 antigen (MAC-1), which are expressed on leukocytes (4).

The ICAM-1 gene, which is located on chromosome 19p13.2-13.3, consists of 7 exons and 6 introns. ICAM-1 polymorphisms include 2 coding region polymorphisms—lysine (K) or glutamine (E) at codon 469 on exon 6 (rs5498), and glycine (G) or arginine (R) at codon 241 on exon 4 (rs1799969); these two polymorphisms have been studied extensively for their role in vasculitis and RA (5). The ICAM-1 K469E and G241R polymorphisms are located within the first and third Ig-like domains, and they act as LFA-1- and Mac-1-binding domains, respectively. There is evidence has that these polymorphisms play important roles during leukocyte transmigration (6, 7).

Some reports have shown that ICAM-1 polymorphisms are associated with vasculitis and RA, whereas others have presented contradictory findings (4, 8-18). The reasons for these disparities may be small sample sizes, low statistical power, and/or clinical heterogeneity (19). Therefore, to overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood that random errors are responsible for false-positive or false-negative associations, we conducted a meta-analysis (20-23). The aim of the present study was to determine whether K469E and G241R polymorphisms of ICAM-1 are associated with susceptibility to vasculitis and RA by performing a meta-analysis.

Methods

Identification of eligible studies and data extraction

We performed a literature search for studies that examined associations between ICAM-1 polymorphisms and vasculitis or RA, using the MEDLINE and

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EMBASE citation databases to identify the studies that analyzed ICAM-1 polymorphisms in patients with vasculitis or RA. Combinations of keywords such as "intercellular adhesion molecule-1," "ICAM-1," "polymorphism," "vasculitis," and "rheumatoid arthritis" were entered as Medical Subject Headings (MeSH) or key words. References in the identified studies were also further investigated to search for additional studies that were not indexed by MEDLINE and EMBASE. Genetic association studies that determined the distributions of the K469E and/or G241R genotypes of ICAM-1 in vasculitis or RA and normal controls were also eligible for inclusion. The inclusion criteria used were as follows: (1) case control study design; (2) original data; and (3) sufficient genotype data to calculate odds ratios (ORs). No language restriction was applied. Exclusion criteria were as follows: (1) overlapping data; (2) inability to ascertain the number of null and wild genotypes; and (3) family members studied, because the analysis was based on linkage considerations. Data were extracted from the original studies by two independent researchers. Any discrepancy between the reviewers was resolved by consensus or by consultation with a third researcher. The following information was extracted from each study: author, year of publication, ethnicity of the study population, demographics, and numbers of cases and controls for each of the K469E and G241R genotypes of ICAM-1. Allele frequencies were determined from the corresponding genotype distributions.

Evaluation of publication bias

Funnel plots are often used to detect publication bias. However, funnel plotting has some limitations in that it requires a broad range of studies of varying sample sizes and involves subjective judgments; therefore, we evaluated the publication bias using Egger's linear regression test (24), which measures funnel plot asymmetry using a natural logarithm scale of ORs.

Evaluation of statistical associations

We performed the meta-analysis using (1) allelic contrast and (2) homozygote contrast techniques, and (3) recessive and (4) dominant models. A chi-squared test was used to determine whether the observed genotype frequencies conformed to the Hardy–Weinberg (H-W) equilibrium. Subgroup analyses were performed by ethnicity and vasculitis type to evaluate ethnic- and disease-specific effects. Point estimates of risk, ORs, and 95% confidence intervals (CI) were estimated for each study. In addition, within- and between-study variation or heterogeneities were analyzed using Cochran's Q-statistic, which assesses the null hypothesis under the condition that all the studies evaluated the same effect. The effect of heterogeneity was quantified using I^2, which ranges from 0% to 100% and represents the proportion of between-study variability that can be attributed to heterogeneity rather than chance (25). I^2 values of 25%, 50%, and 75% were nominally assigned as low, moderate, and high estimates, respectively. The fixed effects model assumes that genetic factors exert similar effects on disease susceptibility across all studies investigated, and that the observed variations between studies are caused by chance alone (26). The random effects model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance (27). When study groups are homogeneous, the fixed and random effects models produce similar results, and when this is not the case, the random effects model usually provides wider CIs than does the fixed effects model. Thus, the random effects model is used when there is significant between-study heterogeneity (27). We performed statistical manipulations using the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ, USA).

Results

Studies included in the meta-analysis

A total of 92 studies were identified by electronic and manual literature search, and of these, 15 were selected for full-text review on the basis of the title and abstract details retrieved. Three reports were excluded, because one report lacked genotype data, another was a review, and the third one referred to a different disease. Thus, 12 studies, including eight studies on vasculitis and four on RA, were included in the meta-analysis (4, 8-18) (Figure 1). In total, these studies contained data from 1,368 patients and 1,922 controls, including 812 patients and 1,242 controls for vasculitis, and 556 patients and 680 controls for RA. The 12 studies described four European, three Arab, and one Asian populations that were examined for vasculitis associations, and two Asian, one European, and one Latin American populations examined for RA associations (Table 1). The vasculitis studies comprised five studies on Behcet's disease (BD), two on giant cell arteritis (GCA), and one on Henoch-Schonlein purpura (Table 1). Thus, ethnic-specific meta-analysis was conducted for the European, Arab, and Asian populations, and disease-specific meta-analysis was conducted for BD, GCA, and RA. Selected characteristics of these studies are summarized in Table 1.

Meta-analysis of relationships between the K469E and G241R polymorphisms and vasculitis

The meta-analysis revealed no association between vasculitis and the ICAM-1 K469E E allele among the subjects examined (OR = 1.238, 95% CI = 0.9781–

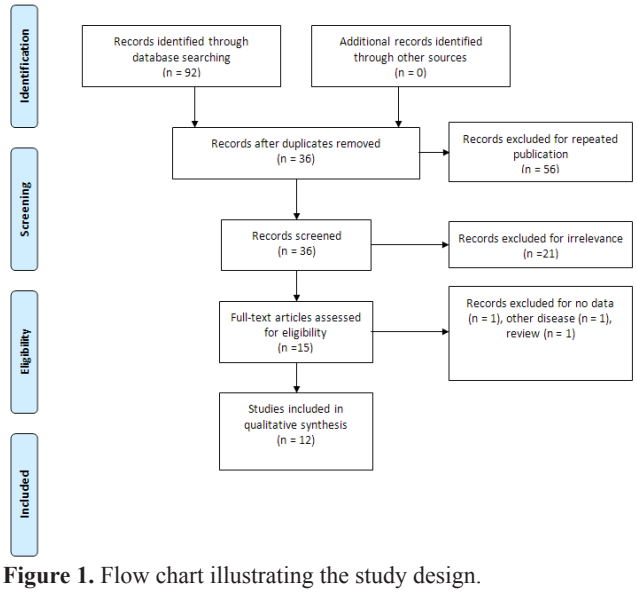

Figure 1. Flow chart illustrating the study design.

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

Author (Ref)	Country	Ethnicity	Disease	Subjects		Polymorphisms studied	Association findings
				Case	Control		
Dhifallah, 2010 (14)	Tunisia	Arab	BD	135	157	ICAM-1 K469E	NS
Chmaisse, 2006 (8)	Lebanon	Arab	BD	39	32	K469E	K469E ($p < 0.01$)
Kim, 2003 (9)	Korea	Asian	BD	197	248	K469E	K469E ($p = 0.004$)
Amoli-1, 2001 (10)	Spain	European	GCA	57	117	K469E, G241R	NS
Boiardi, 2001 (11)	Italy	European	BD	74	228	K469E, G241R	K469E (NS), G241R ($p = 0.0001$)
Amoli-2, 2001 (12)	Spain	European	HSP	50	129	K469E, G241R	NS
Salvarani, 2000 (13)	Italy	European	GCA	177	228	K469E, G241R	K469E (NS), G241R ($p = 0.000001$)
Verity, 2000 (4)	Jordan	Arab	BD	83	103	K469E, G241R	K469E ($p = 0.046$), G241R (NS)
Yuan, 2011 (15)	China	Asian	RA	275	254	K469E	NS
Navarro, 2009 (16)	Mexico	Latin American	RA	60	60	G241R	G241R ($p = 0.040$)
Lee, 2004 (17)	Korea	Asian	RA	143	138	K469E	K469E ($p = 0.0029$)
Macchioni, 2000 (18)	Italy	European	RA	78	228	K469E, G241R	K469E (NS), G241R ($p = 0.039$)

Ref: reference, BD, Behcet's disease; GCA, giant cell arteritis; HSP, Henoch-Schonlein purpura; OR, odds ratio; CI, confidence interval; NS, not significant.

Table 2. Meta-analysis of the associations between the ICAM-1 K469E and G241R polymorphisms and vasculitis.

A

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	*p*-value	Model	*p*-value	I^2
K469E E vs. K	Overall	8	1.238	0.978–1.566	0.076	R	0.005	65.4
	HWE	6	1.316	0.991–1.884	0.057	R	0.004	70.9
	European	4	1.068	0.889–1.284	0.484	F	0.605	0
	Arab	3	1.612	0.759–3.425	0.214	R	0.001	85.5
	BD	5	1.364	0.937–1.987	0.105	R	0.002	77.0
	GCA	2	1.118	0.882–1.418	0.357	F	0.223	32.7
EE vs. EK + KK (recessive)	Overall	8	1.351	1.051–1.736	0.019	F	0.724	0
	HWE	6	1.335	0.974-1.830	0.072	F	0.487	0
	European	4	1.333	0.955-1.860	0.091	F	0.859	0
	Arab	3	1.140	0.687-1.862	0.611	F	0.289	19.5
	BD	5	1.365	0.978-1.905	0.067	F	0.447	0
	GCA	2	1.449	0.946-2.221	0.089	F	0.843	0
EE + EK vs. KK(dominant)	Overall	8	1.338	0.904–1.980	0.145	R	0.001	71.7
	HWE	6	1.633	1.803–2.660	0.049	R	0.003	71.7
	European	4	0.941	0.701–1.264	0.688	F	0.359	6.89
	Arab	3	1.960	0.661–5.814	0.225	R	0.001	86.6
	BD	5	1.525	0.867–2.684	0.143	R	0.001	79.6
	GCA	2	1.160	0.516–2.609	0.719	R	0.085	66.1
EE vs. KK	Overall	8	1.443	1.084–1.920	0.012	F	0.170	32.3
	HWE	6	1.649	1.152–2.359	0.006	F	0.114	43.6
	European	4	1.244	0.837–1.848	0.281	F	0.589	0
	Arab	3	1.709	0.591–4.941	0.322	R	0.059	64.5
	BD	5	1.583	0.906–2.764	0.107	R	0.085	51.0
	GCA	2	1.392	0.832-2.330	0.207	F	0.233	29.7

OR, odds ratio; *CI*, confidence interval; *R*, random effects model; *F*, fixed effects model; *HWE*, Hardy-Weinberg equilibrium.

B

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	*p*-value	Model	*p*-value	I^2
G241R R vs. G	Overall	5	1.977	0.920–4.251	0.081	R	0.003	75.4
	European	4	2.201	0.965–5.007	0.060	R	0.002	79.8
	BD	2	3.261	1.653–6.434	0.001	F	0.106	61.6
	GCA	2	2.523	0.715–8.898	0.150	R	0.009	85.2
RR vs. RG + GG (recessive)	Overall	5	1.957	0.591–6.476	0.272	F	0.312	16.0
	European	4	2.517	0.693–9.142	0.161	F	0.295	19.0
	BD	2	2.350	0.341–16.19	0.386	F	0.182	43.7
	GCA	2	2.671	0.459–15.53	0.274	F	0.154	50.7
RR + RG vs. GG (dominant)	Overall	5	2.266	1.106–4.641	0.025	R	0.015	67.7
	European	4	2.400	1.094–5.263	0.029	R	0.008	74.6
	BD	2	3.551	1.696–7.435	0.001	F	0.265	19.6
	GCA	2	2.806	0.871–9.038	0.084	R	0.024	80.3
RR vs. GG	Overall	5	2.176	0.657–7.209	0.203	F	0.264	23.5
	European	4	2.842	0.782–10.33	0.113	F	0.257	25.8
	BD	2	2.588	0.375–17.86	0.335	F	0.163	48.7
	GCA	2	3.102	0.532–18.07	0.208	F	0.141	53.9

OR, odds ratio; *CI*, confidence interval; *R*, random effects model; *F*, fixed effects model.

1.566, $p = 0.076$; Table 2). Stratification by ethnicity indicated no association between the ICAM-1 K469E E allele and vasculitis in European and Arab populations (OR = 1.068, 95% CI = 0.889–1.284, $p = 0.484$; OR = 1.612, 95% CI = 0.759–3.425, $p = 0.214$; Table 2). A subgroup meta-analysis stratified by vasculitis type showed no association between BD, GCA, and the ICAM-1 K469E E allele (Table 2). However, meta-analysis indicated an association between vasculitis and the ICAM-1 K469E polymorphism under homozygote contrast (OR = 1.443, 95% CI = 1.084–1.920, $p = 0.012$) (Table 2, Figure 2). However, stratification by ethnicity and vasculitis type showed no association between vasculitis and the ICAM-1 K469E polymorphism under heterozygote contrast (Table 2). In addition, the meta-analysis revealed no association between vasculitis and the ICAM-1 G241R polymorphism in the overall group as well as in the European population (Table 2). However, disease-specific meta-analysis showed an association between the ICAM-1 G241R polymorphism and BD (OR = 3.261, 95% CI = 1.653–6.434, $p = 0.001$), but not GCA (OR = 2.523, 95% CI = 0.715–8.898, $p = 0.150$), as determined using the allelic or dominant model, respectively (Table 2, Figure 3).

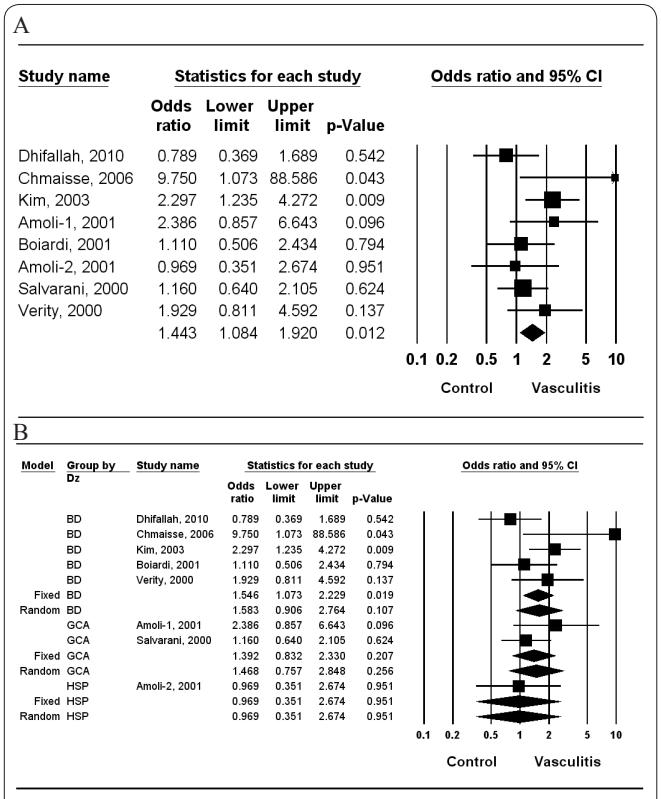

Figure 2. ORs and 95% CIs of individual studies and pooled data for associations of the EE vs. KK genotype between the ICAM-1 K469E polymorphism and vasculitis in overall group (A) and each type of vasculitis (B).

Meta-analysis of the relationships between K469E and G241R polymorphisms and RA

The meta-analysis indicated no association between RA and the ICAM-1 K469 polymorphism in the overall and European groups (Table 3). No association was found between RA and the ICAM-1 G241R polymorphism using the allelic contrast, recessive, or dominant model, or by homozygote contrast in Asians (Table 3). However, a significant association between RA and the ICAM-1 G241R R allele was observed among the study subjects (OR = 2.014, 95% CI = 1.215–3.339, $p = 0.007$; Table 3). The ICAM-1 G241R RR+ RG genotype showed the same association pattern as the R allele in the overall group (OR = 2.394, 95% CI = 1.354–4.235, $p = 0.003$; Table 3, Figure 4). Any potential association between the ICAM-1 G241R polymorphism and RA

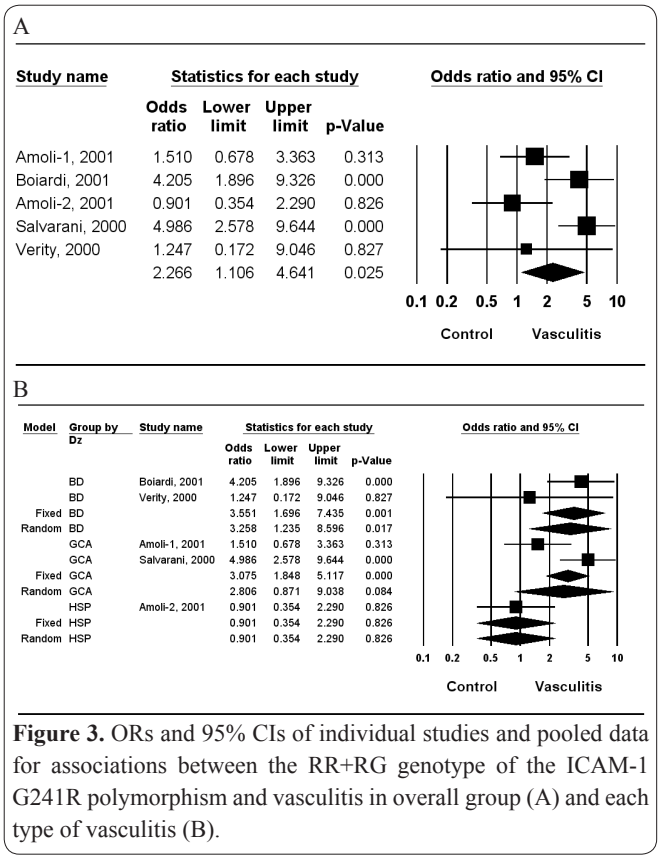

Figure 3. ORs and 95% CIs of individual studies and pooled data for associations between the RR+RG genotype of the ICAM-1 G241R polymorphism and vasculitis in overall group (A) and each type of vasculitis (B).

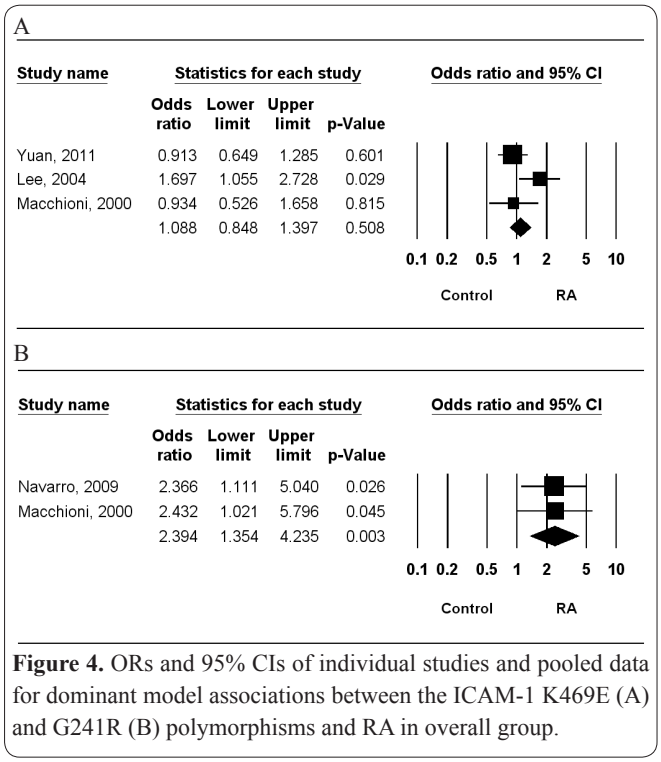

Figure 4. ORs and 95% CIs of individual studies and pooled data for dominant model associations between the ICAM-1 K469E (A) and G241R (B) polymorphisms and RA in overall group.

Table 3. Meta-analysis of the associations between the ICAM-1 K469E and G241R polymorphisms and RA.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	*p*-value	Model	*p*-value	I^2
K469E E vs. K	Overall	3	1.152	0.796–1.667	0.454	R	0.023	73.4
	Asian	2	1.260	0.711–2.234	0.428	R	0.010	84.8
EE vs. EK + KK (recessive)	Overall	3	1.416	0.721–2.783	0.313	R	0.091	58.2
	Asian	2	1.741	0.668–4.541	0.257	R	0.077	67.9
EE + EK vs. KK(dominant)	Overall	3	1.121	0.751–1.674	0.576	R	0.098	56.9
	Asian	2	10216	0.664–2.229	0.526	R	0.038	76.8
EE vs. KK	Overall	3	1.464	0.647–3.311	0.360	R	0.047	67.3
	Asian	2	1.844	0.572–5.947	0.306	R	0.037	76.9
G241R R vs. G	Overall	2	2.014	1.215–3.339	0.007	F	0.834	0
RR vs. RG + GG (recessive)	Overall	2	1.365	0.279–6.675	0.701	F	0.878	0
RR + RG vs. GG (dominant)	Overall	2	2.394	1.354–4.235	0.003	F	0.963	0
RR vs. GG	Overall	2	1.755	0.354–8.706	0.491	F	0.717	0

OR, odds ratio; *CI*, confidence interval; *R*, random effects model; *F,* fixed effects model.

could not be investigated in all ethnic groups because of the limited data available regarding ICAM-1 G241R polymorphisms in RA patients.

Heterogeneity and publication bias

Meta-analysis of the association between G241R polymorphism and RA did not uncover any between-study heterogeneity. However, some heterogeneities were found in the meta-analyses of the ICAM polymorphisms, while subgroup analysis showed resolved heterogeneity in the meta-analysis of the European population and BD (Tables 2 and 3). The distribution of the *ICAM-1* polymorphism genotypes in the control groups were consistent with the HWE in 9 of the 12 studies. Deviation from the HWE among controls suggests the possibility of bias during control selection or genotyping errors. When we excluded these three studies, the overall results of EE vs. KK of the ICAM-1 K469E polymorphism in vasculitis remained significant (OR = 1.649, 95% CI = 1.152-2.359, $p = 0.006$) (Table 2). However, it was difficult to correlate the funnel plot that is usually used to detect publication bias, likely due to the fact that the number of studies included in the analysis was relatively small. Moreover, the Egger's regression test showed no evidence of publication bias (Egger's regression test *p*-values > 0.1).

Discussion

In this meta-analysis, we combined data from published studies to evaluate genetic associations between vasculitis and RA and the most commonly studied polymorphisms of the ICAM-1 gene, namely K469E and G241R polymorphisms. Our meta-analysis demonstrated an association between K469E polymorphism and vasculitis, but not RA. Furthermore, the meta-analysis indicated an association between G241R polymorphism and vasculitis in Europeans, BD, and RA. Thus, our data suggest that the ICAM-1 K469E polymorphism plays a role in the susceptibility to vasculitis, and G241R polymorphism plays a role in vasculitis in Europeans, BD, and RA. Nevertheless, our data must be interpreted with caution, because the statistical associations observed in this meta-analysis are rather weak, considering the small sample size, between-study heterogeneity of the included studies, and particularly, the lack of clinical information.

BD is a chronic inflammatory disease characterized by recurrent oral and genital ulcers, skin lesions, and uveitis (28). This disease affects all types and sizes of blood vessels, joints, central nervous system, lungs, and the gastrointestinal system. Vasculitis and thrombosis are prominent features of BD, and endothelial dysfunction is considered to play an important role in the pathogenesis of vasculitis in BD (28). The synovium of RA is characterized by inflammation and the infiltration of T cells, plasma cells, and macrophages. ICAM-1 is involved in the regulation of inflammation, and the activation of synoviocytes is partly dependent on the interaction between ICAM-1 and integrins, LFA-1 and MAC-1 (29). Moreover, serum levels of ICAM-1 (sICAM-1) were found to be significantly elevated in patients with BD or RA (14, 16).

ICAM-1 plays a role as a mediator of inflammation that modulates the recruitment, adhesion, and migration of leukocytes to the inflammation site. The functional significance of the ICAM-1 K469E and G241R polymorphisms is currently unclear. These polymorphisms are reported to be associated with sICAM-1 levels (30), and G241R polymorphism is located in the region of the functionally important domain III of ICAM-1, which includes the binding site for the leukocyte integrin, Mac-1 (6, 7). Thus, these two polymorphisms may modify the activity of ICAM-1, resulting in alternative activation of inflammation. It is likely that the ICAM-1 polymorphisms play a role in the susceptibility to vasculitis, BD, and RA.

The present study has some limitations that require consideration. First, heterogeneity and confounding factors may have distorted the analysis. Some heterogeneity remained even in subgroup analysis according to study quality including HWE, ethnicity, and disease type, suggesting other factors such as diversity in clinical and methodological aspects may affect the heterogeneity. Furthermore, publication bias could also have adversely affected the analysis, because studies that produced negative results may not have been published or may have been missed during our literature search. Second, an ethnicity-specific analysis using European and Asian population study data was performed in the meta-analysis of the ICAM-1 K469E polymorphism, and thus, our results are applicable only to these specific ethnic groups. In addition, the relative importance of the ICAM-1 G241R polymorphism during the development of vasculitis and RA might be dependent on ethnicity. In particular, the frequency of the G241R R allele is known to be dependent on ethnicity. In fact, the prevalence of the G241R R allele is relatively high among Europeans (up to 18%), but is relatively uncommon or even rare in other ethnic groups such as Japanese and Arab populations (11). In the present study, we performed an ethnicity-specific meta-analysis of the ICAM-1 G241R polymorphism only in the European group, and thus, our results are applicable only to this ethnic group. Third, haplotype analysis could have been a more powerful analytical tool and provided more information than the single polymorphism analysis. Unfortunately, it was not possible to conduct a meta-analysis of haplotypes due to inadequate haplotype data. Lastly, the degree of vasculitis is very different in each case of the disease, and it was unclear how such degree of variation was implicated in each case. The data on vasculitis and RA were not stratified by autoantibody status or clinical variables such as disease severity or activity. The limited amount of data available did not allow us to perform meta-analyses on these potential associations.

In conclusion, this meta-analysis demonstrates that the ICAM-1 K469E polymorphism is associated with susceptibility to vasculitis under the heterozygote model, and the ICAM-1 G241R polymorphism is associated with vasculitis in Europeans, BD, and RA. Our findings suggest that further large-scale studies in different ethnic populations are required to explore the role of ICAM-1 polymorphisms in the pathogeneses of vasculitis and RA.

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References

1. Bloch DA, Michel BA, Hunder GG, McShane DJ, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. Arthritis Rheum. 1990;33(8):1068-73.

2. Harris ED, Jr. Rheumatoid arthritis. Pathophysiology and implications for therapy. N Engl J Med. 1990;322(18):1277-89.

3. Staunton DE, Marlin SD, Stratowa C, Dustin ML, Springer TA**.** Primary structure of ICAM-1 demonstrates interaction between members of the immunoglobulin and integrin supergene families. Cell. 1988;52(6):925-33.

4. Verity DH, Vaughan RW, Kondeatis E, Madanat W, Zureikat H, Fayyad F, et al. Intercellular adhesion molecule-1 gene polymorphisms in Behcet's disease. Eur J Immunogenet. 2000;27(2):73-6.

5. Vora DK, Rosenbloom CL, Beaudet AL, Cottingham RW**.** Polymorphisms and linkage analysis for ICAM-1 and the selectin gene cluster. Genomics. 1994;21(3):473-7.

6. Verity DH, Wallace GR, Seed PT, Kanawati CA, Ayesh I, Holland-Gladwish J, et al. Soluble adhesion molecules in Behcet's disease. Ocul Immunol Inflamm. 1998;6(2):81-92.

7. Springer TA**.** Traffic signals on endothelium for lymphocyte recirculation and leukocyte emigration. Annu Rev Physiol. 1995;57:827-72.

8. Chmaisse HN, Fakhoury HA, Salti NN, Makki RF. The ICAM-1 469 T/C gene polymorphism but not 241 G/A is associated with Behcets disease in the Lebanese population. Saudi Med J. 2006;27(5):604-7.
9. Kim EH, Mok JW, Bang DS, Lee ES, Lee SN, Park KS. Intercellular adhesion molecule-1 polymorphisms in Korean patients with Behcet s disease. J Korean Med Sci. 2003;18(3):415-8.
10. Amoli MM, Shelley E, Mattey DL, Garcia-Porrua C, Thomson W, Hajeer AH, et al. Lack of association between intercellular adhesion molecule-1 gene polymorphisms and giant cell arteritis. J Rheumatol. 2001;28(7):1600-4.
11. Boiardi L, Salvarani C, Casali B, Olivieri I, Ciancio G, Cantini F, et al. Intercellular adhesion molecule-1 gene polymorphisms in Behcet's Disease. J Rheumatol. 2001;28(6):1283-7.
12. Amoli MM, Mattey DL, Calvino MC, Garcia-Porrua C, Thomson W, Hajeer AH, et al. Polymorphism at codon 469 of the intercellular adhesion molecule-1 locus is associated with protection against severe gastrointestinal complications in Henoch-Schonlein purpura. J Rheumatol. 2001;28(5):1014-8.
13. Salvarani C, Casali B, Boiardi L, Ranzi A, Macchioni P, Nicoli D, et al. Intercellular adhesion molecule 1 gene polymorphisms in polymyalgia rheumatica/giant cell arteritis: association with disease risk and severity. J Rheumatol. 2000;27(5):1215-21.
14. Ben Dhifallah I, Karray EF, Sassi F, Hamzaoui K. Intercellular adhesion molecule 1 K469E gene polymorphism is associated with presence of skin lesions in Tunisian Behcet's disease patients. Tissue Antigens. 2010;75(1):74-8.
15. Yuan ZL, Zhang XX, Shen B, Zhu M, Xu W, Li J, et al. [No association of K469E polymorphism of intercellular adhesion molecule-1 with rheumatoid arthritis]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2011;28(1):69-72.
16. Navarro-Hernandez RE, Oregon-Romero E, Vazquez-Del Mercado M, Rangel-Villalobos H, Palafox-Sanchez CA, Munoz-Valle JF. Expression of ICAM1 and VCAM1 serum levels in rheumatoid arthritis clinical activity. Association with genetic polymorphisms. Dis Markers. 2009;26(3):119-26.
17. Lee EB, Kim JY, Kim EH, Nam JH, Park KS, Song YW. Intercellular adhesion molecule-1 polymorphisms in Korean patients with rheumatoid arthritis. Tissue Antigens. 2004;64(4):473-7.
18. Macchioni P, Boiardi L, Casali B, Nicoli D, Farnetti E, Salvarani C. Intercellular adhesion molecule 1 (ICAM-1) gene polymorphisms in Italian patients with rheumatoid arthritis. Clin Exp Rheumatol. 2000;18(5):553-8.
19. Lee YH. Meta-analysis of genetic association studies. Ann Lab Med. 2015;35(3):283-7.
20. Lee YH, Harley JB, Nath SK. Meta-analysis of TNF-alpha promoter -308 A/G polymorphism and SLE susceptibility. Eur J Hum Genet. 2006;14(3):364-71.
21. Lee YH, Rho YH, Choi SJ, Ji JD, Song GG. Association of TNF-alpha -308 G/A polymorphism with responsiveness to TNF-alpha-blockers in rheumatoid arthritis: a meta-analysis. Rheumatol Int. 2006;27(2):157-61.
22. Lee YH, Rho YH, Choi SJ, Ji JD, Song GG, Nath SK, et al. The PTPN22 C1858T functional polymorphism and autoimmune diseases--a meta-analysis. Rheumatology (Oxford). 2007;46(1):49-56.
23. Lee Y, Bae S. Association between functional CD24 polymorphisms and susceptibility to autoimmune diseases: A meta-analysis. Cell. Mol. Biol. 2014;61(8):97-104.
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
25. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
26. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ. 1997;315(7121):1533-7.
27. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.
28. Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. N Engl J Med. 1999;341(17):1284-91.
29. Mojcik CF, Shevach EM. Adhesion molecules: a rheumatologic perspective. Arthritis Rheum. 1997;40(6):991-1004.
30. Ponthieux A, Lambert D, Herbeth B, Droesch S, Pfister M, Visvikis S. Association between Gly241Arg ICAM-1 gene polymorphism and serum sICAM-1 concentration in the Stanislas cohort. Eur J Hum Genet. 2003;11(9):679-86.