Cellular & Molecular Biology
Cell. Mol. Biol. 2015; 61 (8): 105-111
Published online December 26, 2015 (http://www.cellmolbiol.com)
Received on July 31, 2015, Accepted on December 21, 2015.
doi : 10.14715/cmb/2015.61.8.17

Associations between interleukin-1 and IL-1 receptor antagonist polymorphisms and susceptibility to rheumatoid arthritis: A meta-analysis

Y. H. Lee[1]✉ and S-C. Bae[2]

[1] Division of Rheumatology, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea
[2] Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea

Corresponding author: Young Ho Lee, MD, PhD, Division of Rheumatology, Department of Internal Medicine Korea University Anam Hospital, Korea University College of Medicine 73, Inchon-ro, Seongbuk-gu, Seoul 136-705, Korea. Email: lyhcgh@korea.ac.kr

Abstract

This study determined whether interleukin-1 (IL-1) polymorphisms are associated with susceptibility to rheumatoid arthritis (RA). A meta-analysis was conducted on the associations between the IL-1A, IL-1B, and IL-1 receptor antagonist (IL-1RN) polymorphisms and RA. A total of 16 studies involving 4,339 RA cases and 3,885 controls were included in the meta-analysis. Meta-analysis of the IL-1B -511 C/T polymorphism revealed an association between the IL-1B -511 T allele and RA in Caucasians (OR = 0.913, 95% CI = 0.840–0.992, p = 0.031), but not in Asians. Ethnicity-specific meta-analysis indicated an association between the TT+TC genotype of the IL-1B 3953 C/T polymorphism and RA in Caucasians (OR = 1.243, 95% CI = 1.008–1.533, p = 0.042) and in Asians (OR = 2.672, 95% CI = 1.662–4.296, $p = 4.9x10^{-6}$). No association was between RA susceptibility and the IL-1A -889 C/T, IL-1A +4845 G/T, and IL-1RN +2018 C/T polymorphisms. This meta-analysis suggests the IL-1B -511 C/T polymorphism is associated with susceptibility to RA in Caucasians, and that the IL-1B +3953 C/T polymorphism is associated with susceptibility to RA in Caucasians and Asians.

Key words: Rheumatoid arthritis, Interleukin-1, Polymorphism, Meta-analysis.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that predominantly involves the synovial joints and affects up to 1% of the world's population. Although the etiology of RA has not been determined, it has been established that RA has a genetic component, and human leukocyte antigen (HLA) class II genes are the most powerful genetic factors identified to date (7). However, this association accounts for only one-third of genetic susceptibility, and associations with non-HLA genes have also been reported (10).

Interleukins (ILs) are cytokines that are secreted by activated macrophages in inflamed synovium and initiate the recruitment of immune cells and inflammation (12). Members of the IL family, interleukin-1α (IL-1A) and interleukin-1β (IL-1B), are pro-inflammatory cytokines that bind to the IL-1 receptor and are involved in signal transduction. Another member of the IL family, IL-1 receptor antagonist (IL-1RN), is a competitive inhibitor that does not activate intracellular signaling when bound to the IL-1 receptor (38); this property allows it to modulate the immune response by inhibiting the activity of IL-1A and IL-1B (6). IL-1A, IL-1B, and IL-1RN are three distinct but closely linked genes located in the 2q13 region of chromosome 2, a region that has been previously identified in genome-wide analyses to be associated with RA (7). A number of polymorphisms within these genes, including the IL-1B -511 C/T (rs16944), IL-1B +3953 C/T (rs1143634), IL-1A -889 C/T (rs1800587), IL-1A +4845 G/T (rs17561), and IL-1RN +2018 C/T (rs419598) polymorphisms, have frequently been investigated to determine their association with RA.

IL-1 polymorphisms have been associated with autoimmune diseases such as systemic lupus erythematosus (37) and ankylosing spondylitis (28). IL-1 levels have previously been shown to be significantly elevated in RA (13), and this elevation is thought to be linked to polymorphisms within IL-1 genes (8). Thus, polymorphisms within IL-1A, IL-1B, and IL-1RN are considered to be potential diagnostic markers of RA based on the functional relevance and linkage chromosomal location. Although a number of attempts have been made to determine the influence of IL-1 polymorphism on RA (1-5,9,18,20,22,25-27,33,34,39,40), the reported results are often contradictory, possibly due to the low statistical powers of individual studies, the genetic heterogeneity among ethnic groups, and/or the clinical variability in disease pathology. In order to overcome these limitations, resolve inconsistencies, and reduce the likelihood of random errors responsible for false-positive or false-negative associations (29,31,32), we performed a meta-analysis of IL-1 genetic diversity to explore whether the IL-1B -511 C/T, IL-1B +3953 C/T, IL-1A -889 C/T, IL-1A +4845 G/T, and IL-1RN +2018 C/T polymorphisms are associated with RA susceptibility.

Methods

Identification of eligible studies and data extraction

A literature search was performed to identify published studies that examined associations between IL-1 polymorphisms and RA. The PUBMED and EMBASE databases were mined (until September 2014) using the keywords "interleukin 1," "IL-1," "polymorphism," "rheumatoid arthritis," and "RA" as Medical Subject Heading (MeSH) components and as text words to identify available articles in which IL-1 polymorphisms were analyzed in RA patients. In general,

bibliographic searches for systematic reviews should include Pubmed, Embase, and the Cochrane Central Register of Controlled Trials. Additional databases are often useful to search. However, Cochrane register did not contain enough data on polymorphisms, and data on polymorphisms can be retrieved from Pubmed and Embase with high precision by using search strategies. Bibliographic searches within the mined studies were performed to identify additional studies not indexed by PUBMED and EMBASE from January 1990 to September 2014. A study was included in the meta-analysis if: (i) it was a case-control study that determined the genetic frequency and distribution of the IL-1B -511 C/T (rs16944), IL-1B +3953 C/T (rs1143634), IL-1A -889 C/T (rs1800587), IL-1A +4845 G/T (rs17561), or IL-1RN +2018 C/T (rs419598) polymorphisms in RA and in normal controls and reviewed by peers or independent scientists with relevant expertise,; (ii) it had original data; and (iii) it provided sufficient data to calculate odds ratios (ORs). No restriction criteria were placed regarding the race or ethnicity of the participants within the study or geographic region in which the study was performed; however, only studies published in English were included. We excluded the following: (1) studies containing overlapping data; (2) studies in which the number of genotypes could not be ascertained; (3) studies from meeting abstracts or unpublished sources; and (4) studies in which family members had been included, as analyses would be confounded by family-wise genetic association through genetic linkage. Data were extracted from the original articles by two independent reviewers. Any discrepancies between the reviewers were resolved by consensus or by a third reviewer. The following information was extracted from each study: author, year of publication, ethnicity and demographics of the study population, number of cases and controls, and the genotype and allele frequencies of each IL-1 polymorphism. Data management resources were used to increase transparency and efficiency.

Evaluation of publication bias

Funnel plots are often used to detect publication sampling bias throughout the literature review. However, due to the limitations of funnel plotting, which require a range of studies of varying sizes involving subjective judgments, we evaluated publication bias using an Egger's linear regression test (15), which measures funnel plot asymmetry using a natural logarithm scale of ORs.

Evaluations of statistical associations

Association analyses were performed for measuring allelic and genotypic frequencies, as well as testing dominant and recessive models of IL-1 genetic diversity. Point estimates of risks, ORs, and 95% confidence intervals (CIs) were estimated for each study. Cochran's Q-statistic was also used to assess within- and between-study variation, and tests of heterogeneity were used to assess the null hypothesis, that all 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 attributed to heterogeneity rather than chance (21). I^2 values of 25, 50, and 75% were nominally considered low, moderate, and high estimates, respectively. The fixed effects model assumes that a genetic factor has a similar effect on RA susceptibility across all studies investigated, and that observed variation among studies were caused by chance alone (16). On the other hand, the random effects model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance (11). When study groups are homogeneous, the two models are similar. However, if this is not the case, the random effects model usually provides wider CIs than the fixed effects model. The random effects model is best used in the presence of significant heterogeneity between studies (11). Statistical manipulations were performed using the Comprehensive Meta-Analysis computer program, Biosta (Englewood, NJ, USA).

Results

Studies included in the meta-analysis

Three hundred and eight studies that investigated the relationship between IL-1 polymorphisms and RA were identified using keyword searches of PUBMED and EMBASE databases and by manual searching. Twenty of these studies were selected for a full-text review based on title and abstract details. Four of the 20 studies were excluded: one due to the presence of additional IL-1 polymorphisms to those proposed in the meta-analysis, one because of duplicate data, and one because no genotypic data was reported. In total, 16 studies met our inclusion criteria (1-5,9,18,20,22,25-27,33,34,39,40), which included 4,339 cases and 3,885 controls (Table 1). Twelve studies examined the IL-1B -511 C/T polymorphism, 10 described the IL-1B +3953 C/T polymorphism, 4 described the IL-1A -889 C/T polymorphism, three IL-1A +4845 G/T polymorphism, and six IL-1RN +2018 C/T polymorphism. These 16 studies described IL-1 polymorphisms from nine European populations, three Asian, one African American, one Arab, one Middle Eastern, and one Latin American population. Data was segregated to enable an ethnicity-specific meta-analysis focused on European and Asian populations. Selected characteristics of these studies with respect to associations between the IL-1 polymorphisms and RA are summarized in Table 1.

Association between IL-1B -511 C/T, and the IL-1B +3953 C/T polymorphisms and RA susceptibility

A summary of associations between IL-1 polymorphisms and RA is provided in Tables 2 and 3. No association was found between the IL-1B -511 C/T polymorphism and RA in the whole population (OR = 0.954, 95% CI = 0.888–1.025, $p = 0.197$) (Table 2). However, stratification by ethnicity revealed an association between the IL-1B -511 T allele and RA in Caucasians (OR = 0.913, 95% CI = 0.840–0.992, $p = 0.031$) but not in Asians (OR = 1.115, 95% CI = 0.888–1.399, $p = 0.349$) (Table 2). The dominant model showed the same pattern as that shown by the IL-1B-511 T allele (Fig. 1, Table 2). Meta-analysis revealed no association between RA and the IL-1B +3953 T allele in any study subjects (OR = 1.189, 95% CI = 0.938–1.507, $p = 0.152$) (Table 2). However, ethnicity-specific meta-analysis showed an association between RA and the IL-1B +3953 T allele in Asians (OR = 2.551, 95% CI = 1.637–3.957, *p*

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

Study (year)	Country	Population	Samples		Studied polymorphism	Findings	Reference
			RA	Control			
Allam (2013)	Algeria	Arab	147	127	IL-1B -511 C/T, IL-1B +3953 C/T	NS	(1)
Trajkov (2009)	Macedonia	Caucasian	84	301	IL-1B -511 C/T, IL-1B +3953 C/T, IL-1A -889 C/T	NS	(39)
Kobayashi (2009)	Japan	Asian	137	108	IL-1B -511 C/T, IL-1B +3953 C/T, IL-1A +4845, G/T, IL-1RN +2018 C/T	IL-1B +3953 C/T (p = 0.03), others (NS)	(27)
Johnsen (2008)	USA	Caucasian	1,277	1,101	IL-1B -511 C/T, IL-1A -889 C/T	IL-1B -511 C/T (NS), IL-1A -889 C/T (p = 0.015)	(25)
Lubbe (2008)	South African	African	136	88	IL-1B -511 C/T, IL-1B +3953 C/T, IL-1RN +2018 C/T	NS	(33)
Harrison (2008)	UK	Caucasian	741	600	IL-1B -511 C/T, IL-1A -889 C/T	NS	(20)
You (2007)	China	Asian	240	227	IL-1B -511 C/T, IL-1B +3953 C/T	IL-1B -511 C/T (NS), IL-1B +3953 C/T (p < 0.001)	(40)
Arman (2006)	Turkey	Middle Eastern	94	104	IL-1B -511 C/T, IL-1B +3953 C/T	IL-1B -511 C/T (p = 0.038)), IL-1B +3953 C/T (p = 0.011)	(2)
Pawlik (2005)	Poland	Caucasian	93	102	IL-1B +3953 C/T	NS	(34)
Camargo (2004)	Colombia	Latin American	172	392	IL-1B -511 C/T, IL-1B +3953 C/T	NS	(4)
Genevay (2002)	Swiss	Caucasian	231	140	IL-1B +3953 C/T, IL-1A +4845 G/T, IL-1RN +2018 C/T	NS	(18)
Kaijzel (2002)	Netherlands	Caucasian	406	245	IL-1B +3953 C/T, IL-1A +4845 G/T, IL-1RN +2018 C/T	IL-1RN +2018 C/T (p = 0.028), others (NS)	(26)
Huang (2001)	Taiwan	Asian	104	50	IL-1B -511 C/T	NS	(22)
Buchs (2001)	France	Caucasian	272	110	IL-1B -511 C/T, IL-1B +3953 C/T, IL-1RN +2018 C/T	NS	(3)
Crilly (2000)	UK	Caucasian	99	66	IL-1B -511 C/T, IL-1A -889 C/T	NS	(9)
Cantagrel (1999)	France	Caucasian	106	124	IL-1B -511 C/T, IL-1B +3953 C/T	NS	(5)

USA, United States of America; UK, United Kingdom; NS, not significant.

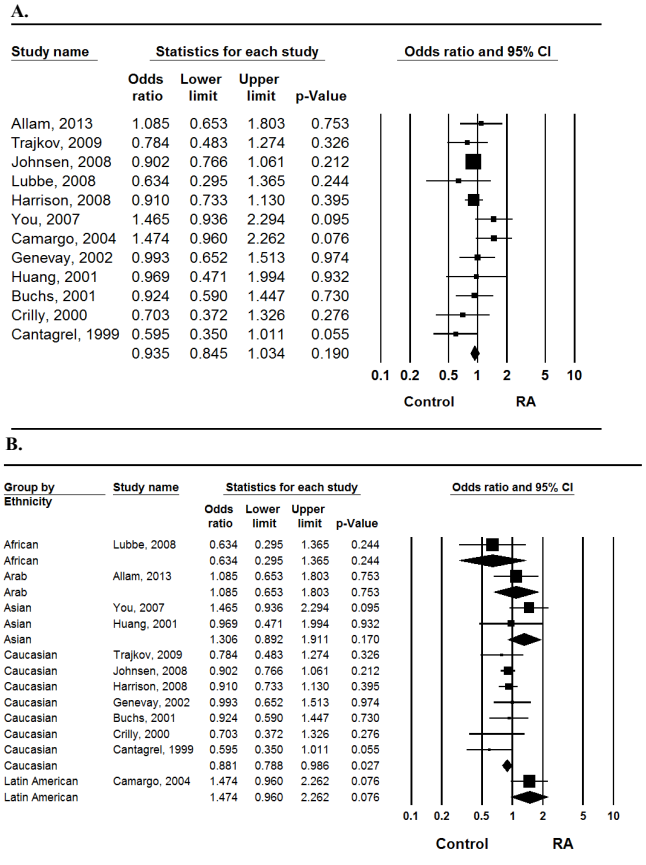

Figure 1. Odds ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data for the association between the TT+TC genotype of the IL-1B -511 C/T (rs16944) polymorphism and rheumatoid arthritis in all study subjects (A) and within each ethnic group (B).

= 3.5×10^{-6}) (Table 2). Stratification by ethnicity indicated an association between the TT+TC genotype of the IL-1B 3953 C/T polymorphism and RA in Caucasians (OR = 1.243, 95% CI = 1.008–1.533, p = 0.042) and in Asians (OR = 2.672, 95% CI = 1.662–4.296, p = 4.9 × 10^{-6}) (Fig. 2, Table 2).

Association between IL-1A -889 C/T, IL-1A +4845 G/T, and IL-1RN +2018 C/T polymorphisms and RA susceptibility

Meta-analysis revealed no association between RA and the IL-1A -889 T allele in any study subjects (OR = 0.911, 95% CI = 0.827–1.003, p = 0.058) (Fig. 3, Table 3). The recessive and dominant models and homozygote contrast failed to reveal an association between the IL-1A- 889 C/T polymorphism and RA (Table 3). Meta-analysis revealed no association between RA and IL-1A +4945 T allele in any study subjects (OR = 1.140, 95% CI = 0.940–1.384, p = 0.184) (Fig. 3, Table 3). The recessive and dominant models and homozygote contrast indicated no association between the IL-1A +4845 G/T polymorphism and RA (Table 3). No association was between RA susceptibility and IL-1RN +2018 C/T polymorphism by meta-analyses (Table 3).

Heterogeneity and publication bias

Analyses of genotype distribution revealed that in two different studies, the control groups for the IL-1B +3953 C/T (4) and IL-1A -889 C/T (39) polymorphisms significantly deviated from the Hardy-Weinberg equilibrium (HWE). Deviation from HWE among controls implies a potential bias during control selection, or ge-

Table 2. Meta-analysis of associations between the IL-1B -511C/T (rs16944) and IL-1B +3953 C/T (rs1143634) polymorphisms and rheumatoid arthritis.

Polymorphism	Test	Population	Number of Studies	Test of association			Test of heterogeneity		
				OR	95% CI	*p* value	Model	*p* value	I^2
IL-1B -511	T vs. C	Overall	12	0.954	0.888-1.025	0.197	F	0.550	0
		Caucasian	7	0.913	0.840-0.992	0.031	F	0.882	0
		Asian	2	1.115	0.888-1.399	0.349	F	0.857	0
	TT vs. TC+CC (Recessive)	Overall	12	0.950	0.829-1.090	0.468	F	0.904	0
		Caucasian	7	0.912	0.767-1.083	0.293	F	0.805	0
		Asian	2	1.031	0.719-1.478	0.867	F	0.568	0
	TT+TC vs. CC (Dominant)	Overall	12	0.935	0.845-1.034	0.190	F	0.238	20.9
		Caucasian	7	0.881	0.788-0.986	0.027	F	0.766	0
		Asian	2	1.306	0.892-1.911	0.170	F	0.340	0
	TT vs. CC	Overall	12	0.941	0.807-1.098	0.441	F	0.541	0
		Caucasian	7	0.853	0.711-1.024	0.088	F	0.868	0
		Asian	2	1.305	0.825-2.063	0.255	F	0.852	0
IL-1B +3953	T vs. C	Overall	10	1.189	0.938-1.507	0.152	R	0.001	69.4
		Caucasian	4	1.163	0.989-1.382	0.086	F	0.380	2.37
		Asian	2	2.551	1.637-3.975	3.5×10^{-6}	F	0.958	0
	TT vs. TC+CC (Recessive)	Overall	10	1.128	0.723-1.762	0.585	R	0.070	44.8
		Caucasian	4	1.043	0.672-1.618	0.852	F	0.404	0
		Asian	2	2.948	0.589-14.75	0.188	NA	NA	NA
	TT+TC vs. CC (Dominant)	Overall	10	1.212	0.942-1.560	0.135	R	0.006	61.0
		Caucasian	4	1.243	1.008-1.533	0.042	F	0	17.8
		Asian	2	2.672	1.662-4.296	4.9×10^{-6}	F	0.955	0
	TT vs. CC	Overall	10	1.180	0.728-1.910	0.502	R	0.041	50.2
		Caucasian	4	1.136	0.727-1.776	0.575	F	0.354	7.74
		Asian	2	3.341	0.666-16.75	0.143	NA	NA	NA

OR, odds ratio; CI, confidence interval; R, Random effects model; F, Fixed effects model.

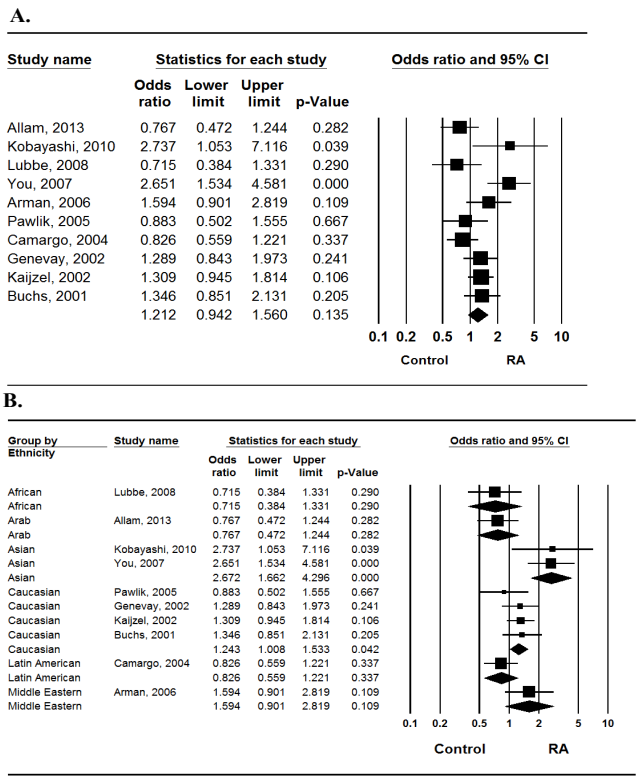

Figure 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data for the association between the TT+TC genotype of the IL-1B 3953 C/T (rs1143634) polymorphism and rheumatoid arthritis in all study subjects (A) and within each ethnic group (B).

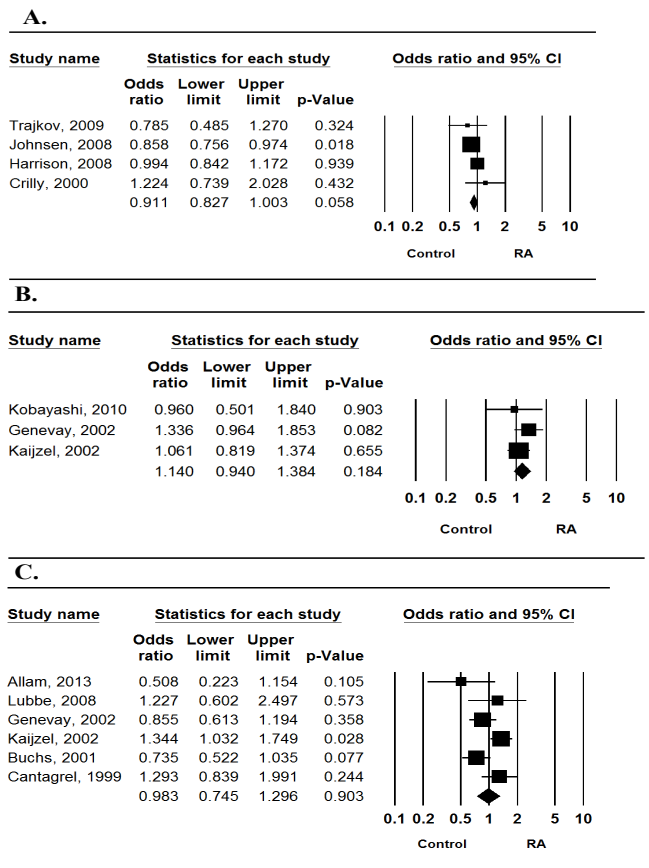

Figure 3. Odds ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data for allelic associations between the IL-1A -889 C/T (rs1800587) (A), IL-1A +4845 G/T (rs17561) (B), and IL-1RN +2018 (rs419598) polymorphisms and rheumatoid arthritis in all study subjects.

notyping errors; however, excluding these studies did not affect the association analysis of either IL-1B +3953 C/T or IL-1A -889 C/T polymorphisms. Between-study heterogeneity was not found in the analyses of IL-1 polymorphisms in the total population or in each ethnic group, except for IL-1B +3953 C/T polymorphism in all study subjects and IL-1RN +2018 C/T polymorphism under the allele contrast and dominant model (Tables 2 and 3). When the studies were stratified by ethnicity, the

Table 3. Meta-analysis of associations between the IL-1A -889 C/T (rs1800587), IL-1A +4845 G/T (rs17561), and IL-1RN +2018 C/T (rs419598) polymorphisms and rheumatoid arthritis.

Polymorphism	Test	Population	Number of Studies	Test of association			Test of heterogeneity		
				OR	95% CI	*p* value	Model	*p* value	I^2
IL-1A -889	T vs. C	Overall	4	0.911	0.827-1.003	0.058	F	0.308	16.5
	TT vs. TC+CC (Recessive)	Overall	4	0.828	0.661-1.037	0.100	F	0.294	19.2
	TT+C vs. CC (Dominant)	Overall	4	0.909	0.803-1.029	0.132	F	0.262	24.8
	TT vs. CC	Overall	4	0.805	0.638-1.016	0.068	F	0.310	16.2
IL-1A +4845	T vs. G	Overall	3	1.140	0.940-1.384	0.184	F	0.478	0
	TT vs. TG+GG (Recessive)	Overall	3	1.025	0.644-1.632	0.916	F	0.171	43.4
	TT+TG vs. GG (Dominant)	Overall	3	1.214	0.952-1.548	0.118	F	0.745	0
	TT vs. GG	Overall	3	1.140	0.706-1.842	0.591	F	0.201	37.6
IL-1RN +2018	C vs. T	Overall	6	0.983	0.745-1.296	0.903	R	0.023	61.5
	CC vs. CT+TT (Recessive)	Overall	6	0.861	0.588-1.260	0.441	F	0.312	158
	CC+CT vs. TT (Dominant)	Overall	6	0.997	0.710-1.400	0.988	R	0.019	63.0
	CC vs. TT	Overall	6	0.900	0.609-1.330	0.595	F	0.232	26.9

OR, odds ratio; CI, confidence interval; R, Random effects model; F, Fixed effects model.

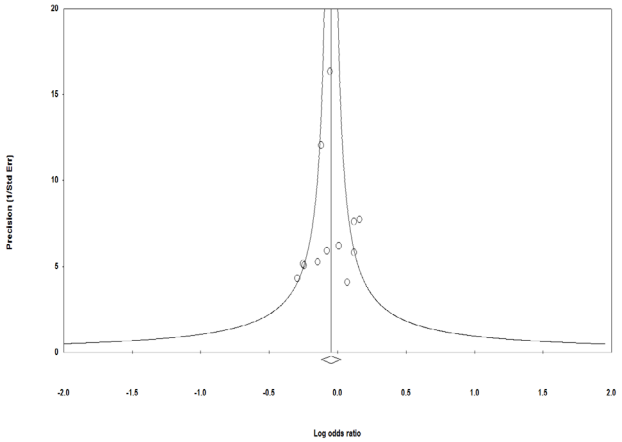

Figure 4. Funnel plot of studies on the allelic association between the IL-1B -511 C/T (rs16944) polymorphism and rheumatoid arthritis in all study subjects (Egger's regression *p*-value = 0.907).

heterogeneity observed in meta-analysis of the IL-1B +3953 C/T polymorphism resolved in each ethnic group (Table 2). An Egger's regression test demonstrated that there was no significant influence of publication bias in this meta-analysis (Egger's regression test, $p > 0.1$) (Fig. 4).

Discussion

IL-1 are a family of potent inflammatory cytokines that play key role in immune regulation (38). RA is characterized by persistent inflammation of the joints with progressive joint destruction. IL-1 stimulates prostaglandin and metalloporoteases that induce bone resorption and joint degradation. Plasma and synovial IL-1 levels have been positively correlated with RA activity and progression of joint damage (13,14). IL-1 receptor blocking has shown beneficial therapeutic efficacy in RA patients (17). In addition, IL-1 gene is located in the RA linkage region (7). Thus, IL-1 is considered to play an important role in RA pathogenesis.

Meta-analyses properly conducted with good methodologies have been published (24,36), and In this meta-analysis, we addressed the association between IL-1 polymorphisms and RA susceptibility. The data from published studies were combined to evaluate genetic associations between RA and the most commonly studied polymorphisms, IL-1B -511 C/T, IL-1B +3953 C/T, IL-1A -889 C/T, IL-1A +4845 G/T, and IL-1RN +2018, of the IL-1 gene. We found significant associations between IL-1B -511 C/T polymorphism and RA in Caucasians and between the IL-1B +3953 C/T polymorphism and RA in both Caucasians and Asians. The associations between IL-1 polymorphisms and the risks of RA observed in this meta-analysis suggest that IL-1 could play a role in RA susceptibility.

The polymorphisms at -511 C/T in the promoter and +3953 C/T in the exon 5 of IL-1B are considered to influence IL-1 expression. Individuals carrying IL-1B -511 allele 2 showed higher levels of IL-1RN (23), and LPS-induced IL-1B production was increased two or three fold by the IL-1B -511 T allele (19). IL-1B +3953 C/T polymorphism has been shown to enhance transcriptional activation of IL-1B, and may be associated with increased plasma levels of IL-1B (35). However, whether the association between RA susceptibility and the polymorphisms of IL-1B -511 C/T and +3953 C/T is due to a causal association or a linkage disequilibrium with the true disease-causing polymorphism remains to be determined.

We have previously identified that the IL-1B +3953 polymorphism was associated with RA in Asians (30). This analysis has been significantly expanded by combining data from all available studies to evaluate the genetic association between IL-1 polymorphisms and RA susceptibility. It is not surprising that the association between IL-1B +3953 polymorphism and RA in Asians described here is in agreement with our previous study. However, this updated meta-analysis revealed that the IL-1B +3953 C/T polymorphism is also associated with susceptibility to RA in Caucasians, and the IL-1B -511 C/T polymorphism is associated with susceptibility to RA in Caucasians.

Our findings do not support an association between the IL-1A -889 C/T, IL-1A +4845 G/T, or IL-1RN +2018 C/T polymorphisms and RA susceptibility. We did not

find an association between the IL-1 polymorphisms and RA susceptibility by the meta-analysis, for any allele using homozygote, recessive, or dominant models in the overall group. However, our results should be interpreted with caution because of the limited number of studies included. The relative importance of the IL-1 polymorphisms during the development of RA may vary between ethnic groups, however, we were unable to perform ethnic-specific meta-analyses on the IL-1A -889 C/T, IL-1A +4845 G/T, or IL-1RN +2018 polymorphisms in each ethnic group due to limited data.

The present study has some limitations that require consideration. First, heterogeneity may have distorted the meta-analysis. However, most heterogeneity was resolved by ethnic-specific subgroup analysis. Second, ethnic-specific meta-analysis included data from Caucasian and Asian patients, and thus, our results are applicable to only these ethnic groups. Third, only a small number of Asian populations were described in the literature and complete genotype data was only available from two Asian studies. Fourth, data were not stratified by factors, including but not limited to rheumatoid factor status, anti-cyclic citrullinated peptide antibody status or clinical or environmental variables, because the studies did not contain enough data.

In conclusion, this meta-analysis suggests that the IL-1B -511 C/T polymorphism is associated with susceptibility to RA in Caucasians, and that the IL-1B +3953 C/T polymorphism is associated with susceptibility to RA in Caucasians and Asians. These findings suggest that IL-1 genes confer susceptibility to RA. Larger scale studies in populations with different ethnicities are now required to explore the broader role these polymorphisms play in the pathogenesis of RA.

Acknowledgements

This study was supported in part by a grant of the Korea Healthcare technology R&D Project, Ministry for Health and Welfare**,** Republic of Korea (HI13C2124).

References

1. Allam, I., Djidjik, R., Ouikhlef, N., Louahchi, S., Raaf, N., Behaz, N., Abdessemed, A., Khaldoun, N., Tahiat, A., Bayou, M., Ladjouze-Rezig, A. and Ghaffor, M., (Interleukin-1 and the interleukin-1 receptor antagonist gene polymorphisms study in patients with rheumatoid arthritis). *Pathol. Biol. (Paris)* 2013, **61**:264-268.

2. Arman, A., Yilmaz, B., Coker, A., Inanc, N. and Direskeneli, H., Interleukin-1 receptor antagonist (IL-1RN) and interleukin-1B gene polymorphisms in Turkish patients with rheumatoid arthritis. *Clin. Exp. Rheumatol.* 2006, **24**:643-648.

3. Buchs, N., di Giovine, F.S., Silvestri, T., Vannier, E., Duff, G.W. and Miossec, P., IL-1B and IL-1Ra gene polymorphisms and disease severity in rheumatoid arthritis: interaction with their plasma levels. *Genes. Immun.* 2001, **2**:222-228.

4. Camargo, J.F., Correa, P.A., Castiblanco, J. and Anaya, J.M., Interleukin-1beta polymorphisms in Colombian patients with autoimmune rheumatic diseases. *Genes. Immun.* 2004, **5**:609-614.

5. Cantagrel, A., Navaux, F., Loubet-Lescoulie, P., Nourhashemi, F., Enault, G., Abbal, M., Constantin, A., Laroche, M. and Mazieres, B., Interleukin-1beta, interleukin-1 receptor antagonist, interleukin-4, and interleukin-10 gene polymorphisms: relationship to occurrence and severity of rheumatoid arthritis. *Arthritis Rheum.* 1999, **42**:1093-1100.

6. Carter, D.B., Deibel, M.R., Jr., Dunn, C.J., Tomich, C.S., Laborde, A.L., Slightom, J.L., Berger, A.E., Bienkowski, M.J., Sun, F.F., McEwan, R.N. and et al., Purification, cloning, expression and biological characterization of an interleukin-1 receptor antagonist protein. *Nature* 1990, **344**:633-638.

7. Choi, S.J., Rho, Y.H., Ji, J.D., Song, G.G. and Lee, Y.H., Genome scan meta-analysis of rheumatoid arthritis. *Rheumatology (Oxford)* 2006, **45**:166-170.

8. Choy, E.H. andPanayi, G.S., Cytokine pathways and joint inflammation in rheumatoid arthritis. *N. Eng.l J. Med.* 2001, **344**:907-916.

9. Crilly, A., Maiden, N., Capell, H.A. and Madhok, R., Predictive value of interleukin 1 gene polymorphisms for surgery. *Ann. Rheum. Dis.* 2000, **59**:695-699.

10. Deighton, C.M., Walker, D.J., Griffiths, I.D. and Roberts, D.F., The contribution of HLA to rheumatoid arthritis. *Clin. Genet*. 1989, **36**:178-182.

11. DerSimonian, R. and Laird, N., Meta-analysis in clinical trials. *Control. Clin. Trials.* 1986, **7**:177-188.

12. Dinarello, C.A., The IL-1 family and inflammatory diseases. *Clin. Exp. Rheumatol.* 2002, **20**:S1-13.

13. Dinarello, C.A. and Wolff, S.M., The role of interleukin-1 in disease. *N. Engl. J. Med.* 1993, **328**:106-113.

14. Eastgate, J.A., Symons, J.A., Wood, N.C., Grinlinton, F.M., di Giovine, F.S. and Duff, G.W., Correlation of plasma interleukin 1 levels with disease activity in rheumatoid arthritis. *Lancet* 1988, **2**:706-709.

15. Egger, M., Davey Smith, G., Schneider, M. and Minder, C., Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997, **315**:629-634.

16. Egger, M., Smith, G.D. and Phillips, A.N., Meta-analysis: principles and procedures. *BMJ* 1997, **315**:1533-1537.

17. Furst, D.E., Anakinra: review of recombinant human interleukin-I receptor antagonist in the treatment of rheumatoid arthritis. *Clin. Ther.* 2004, **26**:1960-1975.

18. Genevay, S., Di Giovine, F.S., Perneger, T.V., Silvestri, T., Stingelin, S., Duff, G. and Guerne, P.A., Association of interleukin-4 and interleukin-1B gene variants with Larsen score progression in rheumatoid arthritis. *Arthritis Rheum.* 2002, **47**:303-309.

19. Hall, S.K., Perregaux, D.G., Gabel, C.A., Woodworth, T., Durham, L.K., Huizinga, T.W., Breedveld, F.C. and Seymour, A.B., Correlation of polymorphic variation in the promoter region of the interleukin-1 beta gene with secretion of interleukin-1 beta protein. *Arthritis Rheum.* 2004, **50**:1976-1983.

20. Harrison, P., Pointon, J.J., Chapman, K., Roddam, A. and Wordsworth, B.P., Interleukin-1 promoter region polymorphism role in rheumatoid arthritis: a meta-analysis of IL-1B-511A/G variant reveals association with rheumatoid arthritis. *Rheumatology (Oxford)* 2008, **47**:1768-1770.

21. Higgins, J.P. and Thompson, S.G., Quantifying heterogeneity in a meta-analysis. *Stat. Med.* 2002, **21**:1539-1558.

22. Huang, C.M., Tsai, F.J., Wu, J.Y. and Wu, M.C., Interleukin-1beta and interleukin-1 receptor antagonist gene polymorphisms in rheumatoid arthritis. *Scand. J. Rheumatol.* 2001, **30**:225-228.

23. Hurme, M. andSanttila, S., IL-1 receptor antagonist (IL-1Ra) plasma levels are co-ordinately regulated by both IL-1Ra and IL-1beta genes. *Eur. J. Immunol.* 1998, **28**:2598-2602.

24. Ji, G., Li, M., Cui, Y. and Wang, J., The relationship of CASP 8 polymorphism and cancer susceptibility: a meta-analysis. *Cellular and molecular biology (Noisy-le-Grand, France)* 2013, **60**:20-28.

25. Johnsen, A.K., Plenge, R.M., Butty, V., Campbell, C., Dieguez-Gonzalez, R., Gomez-Reino, J.J., Shadick, N., Weinblatt, M., Gonzalez, A., Gregersen, P.K., Benoist, C. and Mathis, D., A broad analysis of IL1 polymorphism and rheumatoid arthritis. *Arthritis*

Rheum. 2008, **58**:1947-1957.
26. Kaijzel, E.L., van Dongen, H., Bakker, A.M., Breedveld, F.C., Huizinga, T.W. and Verweij, C.L., Relationship of polymorphisms of the Interleukin-1 gene cluster to occurrence and severity of rheumatoid arthritis. *Tissue Antigens* 2002, **59**:122-126.
27. Kobayashi, T., Murasawa, A., Ito, S., Yamamoto, K., Komatsu, Y., Abe, A., Sumida, T. and Yoshie, H., Cytokine gene polymorphisms associated with rheumatoid arthritis and periodontitis in Japanese adults. *J. Periodontol.* 2009, **80**:792-799.
28. Lea, W.I. and Lee, Y.H., The associations between interleukin-1 polymorphisms and susceptibility to ankylosing spondylitis: A meta-analysis. *Joint Bone Spine* 2012, **79**:370-374.
29. Lee, Y.H., Bae, S.C., Choi, S.J., Ji, J.D. and Song, G.G., Associations between vitamin D receptor polymorphisms and susceptibility to rheumatoid arthritis and systemic lupus erythematosus: a meta-analysis. *Mol. Biol. Rep.* 2011, **38**:3643-3651.
30. Lee, Y.H., Ji, J.D. and Song, G.G., Association between interleukin 1 polymorphisms and rheumatoid arthritis susceptibility: a metaanalysis. *J. Rheumatol.* 2009, **36**:12-15.
31. Lee, Y.H., Rho, Y.H., Choi, S.J., Ji, J.D. and Song, G.G., PADI4 polymorphisms and rheumatoid arthritis susceptibility: a meta-analysis. *Rheumatol. Int.* 2007, **27**:827-833.
32. Lee, Y.H., Woo, J.H., Choi, S.J., Ji, J.D. and Song, G.G., Associations between osteoprotegerin polymorphisms and bone mineral density: a meta-analysis. *Mol. Biol. Rep.* 2010, **37**:227-234.
33. Lubbe, S., Tikly, M., van der Merwe, L., Hodkinson, B. and Ramsay, M., Interleukin-1 receptor antagonist gene polymorphisms are associated with disease severity in Black South Africans with rheumatoid arthritis. *Joint Bone Spine* 2008, **75**:422-425.
34. Pawlik, A., Kurzawski, M., Florczak, M., Gawronska Szklarz, B. and Herczynska, M., IL1beta+3953 exon 5 and IL-2 -330 promoter polymorphisms in patients with rheumatoid arthritis. *Clin. Exp. Rheumatol.* 2005, **23**:159-164.
35. Pociot, F., Molvig, J., Wogensen, L., Worsaae, H. and Nerup, J., A TaqI polymorphism in the human interleukin-1 beta (IL-1 beta) gene correlates with IL-1 beta secretion in vitro. *Eu.r J. Clin. Invest.* 1992, **22**:396-402.
36. Rai, V., Genetic polymorphisms of methylenetetrahydrofolate reductase (MTHFR) gene and susceptibility to depression in Asian population: a systematic meta-analysis. *Cellular and molecular biology (Noisy-le-Grand, France)* 2014, **60**:29.
37. Song, G.G., Kim, J.H., Seo, Y.H., Choi, S.J., Ji, J.D. and Lee, Y.H., Associations between interleukin 1 polymorphisms and susceptibility to systemic lupus erythematosus: a meta-analysis. *Hum. Immunol*. 2014, **75**:105-112.
38. Stylianou, E. and Saklatvala, J., Interleukin-1. *Int. J. Biochem. Cell Biol.* 1998, **30**:1075-1079.
39. Trajkov, D., Mishevska-Perchinkova, S., Karadzova-Stojanoska, A., Petlichkovski, A., Strezova, A. and Spiroski, M., Association of 22 cytokine gene polymorphisms with rheumatoid arthritis in population of ethnic Macedonians. *Clin. Rheumatol.* 2009, **28**:1291-1300.
40. You, C.G., Li, J.F., Xie, X.D., Zhu, Y., Li, P.Q. and Chen, Y.R., Association of interleukin-1 genetic polymorphisms with the risk of rheumatoid arthritis in Chinese population. *Clin. Chem. Lab. Med.* 2007, **45**:968-971.