Association Between Interleukin 1 Polymorphisms and Rheumatoid Arthritis Susceptibility: A Metaanalysis

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ABSTRACT. ***Objective.*** To determine whether interleukin 1 (IL-1) polymorphisms confer susceptibility to rheumatoid arthritis (RA).

Methods. We conducted metaanalyses on associations between IL-1 polymorphisms and RA susceptibility, using fixed or random effects models.

Results. A total of 18 separate comparisons were made using 10 European, 7 Asian, and 1 Latin American population samples. Metaanalysis of the *IL-1B+3954* CC genotype revealed an association with RA in all subjects (odds ratio = 0.776, 95% confidence interval = 0.609–0.988, p = 0.040). In Asians, an association between *IL-1B+3954* and RA was identified. In contrast, no association was found between the *IL-1B+3954* polymorphism and RA susceptibility in European populations. Metaanalyses of the *IL-1B-511* and *IL-1RN VNTR* polymorphisms identified no association between these polymorphisms and RA.

Conclusion. Our metaanalysis shows that the *IL-1B+3954* polymorphism was associated with the development of RA, but only in Asians. (First Release Nov 1 2008; J Rheumatol 2009;36:12–15; doi:10.3899/jrheum.080450)

Key Indexing Terms:
INTERLEUKIN 1 GENETIC POLYMORPHISM RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease that predominantly involves synovial joints, and affects up to 1% of adults worldwide. Although the etiology of RA is not fully understood, it has a genetic component.

Interleukin 1 (IL-1) is secreted by activated macrophages in inflamed synovium and initiates the recruitment of immune cells and inflammation. Studies have revealed that 2 single-nucleotide polymorphisms (SNP) at positions –511 and +3954 of the *IL-1B* gene and a variable number of tandem repeats (VNTR) in the second intron of IL-1 receptor antagonist (IL-1RA) are associated with increased risk of autoimmune disease development. *IL-1* polymorphisms have been reported to be associated with RA susceptibility in some studies, showing mixed results[1-17]. The aim of our study was to determine whether *IL-1* polymorphisms confer susceptibility to RA, and to identify the polymorphisms concerned.

MATERIALS AND METHODS

Identification of eligible studies and data extraction. We searched for studies that examined the associations between IL-1 polymorphisms and RA. The Medline citation index was used to identify articles in which IL-1 polymorphisms were analyzed in patients with RA (up to March 2008). In addition, combinations of key words, such as "Interleukin 1," "IL-1," "polymorphism," "rheumatoid arthritis," and "RA" were entered as both Medical Subject Heading (MeSH) and text words. References in the studies identified were also investigated to identify additional studies not indexed by Medline. Genetic association studies that determined the distributions of IL-1 genotypes in RA cases and controls were eligible for inclusion.

Evaluations of statistical associations. We assessed within- and between-study variations and heterogeneities using Cochran's Q-statistics and I^2 values. We evaluated publication bias using Egger's linear regression test. Statistical manipulations were undertaken using a Comprehensive Meta-Analysis computer program (Biostat, Englewood, NJ, USA).

RESULTS

Studies included in the metaanalysis. We identified 63 studies by electronic and manual searches and 19 were selected for full text review based on titles and abstracts. Two studies were excluded due to no extractable data, and data on only one *IL-1A* intron 6 polymorphism, respectively. A total of 17 relevant studies met the study inclusion criteria[1-17]. One of the eligible studies contained data on 2 different RA groups, and these were treated separately. Therefore, a total of 18 separate studies were considered on 10 European, 7 Asian, and 1 Latin American population samples (Table 1).

Due to the limited number of studies on some polymorphisms, 3 types of metaanalyses were performed on the *IL-1B-511 (rs16944)*, *IL-1B+3954 (rs1143634)*, and *IL-1RN VNTR* polymorphisms (Table 1). Some studies did not give complete genotype data (Table 2), so there was a difference in study numbers in different genetic models.

Metaanalysis of the IL-1B-511 polymorphism and RA sus-

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

Study	Country (Ethnicity)	Numbers, RA/Controls	*IL-1* Polymorphism(s)	Major Findings for Association
Kobayashi[1]	Japan (A)	100/100	IL-1A+4845, IL-1B+3954, IL-RN+2018	IL-1B+3954 (association p = 0.03)
You[2]	China (A)	240/227	IL-1B-511, IL-1B+3954, IL-1RN VNTR	IL-1B+3954 C/T (p < 0.001), IL-1RN 2 allele (p = 0.028)
Arman[3]	Turkey (A)	94/104	IL-1B-511, IL-1B+3954, IL-1RN VNTR	IL-1B-511 C/T (p = 0.038), IL-1B+3954 T/T (p = 0.028), T allele (p = 0.011)
Kazkaz 1[4]	France (E)	512/471	IL-1B+3954, IL-1RN+2018	NS
Kazkaz 2[4]	Syria (A)	156/120	IL-1B+3954, IL-1RN+2018	NS
Tolusso[5]	Italy (E)	126/178	IL-1B-511, IL-1B+3954, IL-1RN VNTR	NS
Grover[6]	India (A)	107/111	IL-1RN VNTR	NS
Pawlik[7]	Poland (E)	93/102	IL-1B+3954	NS
Camargo[8]	Colombia (LA)	172/392	IL-1B-511, IL-1B+3954	NS
Lee[9]	Korea (A)	138/127	IL-1RN VNTR	2 allele: OR 0.34 (p = 0.024)
Martinez[10]	Spain (E)	229/371	IL-1RN VNTR	NS
Genevay[11]	UK (E)	233/148	IL-1A+4845, IL-1B-511, IL-1B+3954, IL-1RN+2016	NS
Kaijzel[12]	Netherlands (E)	407/245	IL-1A+4845, IL-1B-511, IL-1B+3954, IL-1RN+2016	NS
Cvetkovic[13]	Sweden (E)	154/202	IL-1RN VNTR	NS
Huang[14]	Taiwan (A)	104/103	IL-1B-511, IL-1B+3954, IL-1RN VNTR	NS
Buchs[15]	France (E)	272/110	IL-1B-511	NS
Cantagrel[6]	France (E)	106/110	IL-1B-511, IL-1B+3954, IL-1RN VNTR	NS
Perrier[17]	France (E)	43/100	IL-1RN VNTR	NS

E: European; A: Asian; LA: Latin American; UK: United Kingdom; NS: not significant.

Table 2. Meta analysis of *IL-1B-511* and *IL-1B+3954* polymorphisms and RA association.

Polymorphism	Population	No. of Studies	Test of Association OR	95% CI	p	Test of Heterogeneity Model	Q	p	I^2
IL-1B-511	Overall	8	1.046	0.934–1.172	0.436	F	9.40	0.225	25.5
C vs T	Asian*	3	1.037	0.857–1.253	0.711	F	3.19	0.202	37.4
	European	4	1.158	0.975–1.374	0.094	F	2.33	0.505	0
CC vs CT+TT	Overall	8	1.136	0.865–1.492	0.357	R	17.8	0.013	60.8
(Recessive)	Asian*	3	1.201	0.631–2.285	0.576	R	8.52	0.014	76.5
	European	4	1.251	0.994–1.575	0.056	F	3.26	0.353	8.02
CC+CT vs TT	Overall	8	1.019	0.829–1.252	0.859	F	1.58	0.979	0
(Dominant)	Asian	3	0.955	0.729–1.359	0.977	F	0.29	0.863	0
	European	4	1.105	0.770–1.586	0.589	F	0.98	0.806	0
CC vs TT	Overall	8	1.007	0.792–1.282	0.952	F	6.22	0.514	0
	Asian*	3	0.962	0.656–1.412	0.844	F	2.00	0.367	0.30
	European	4	1.260	0.859–1.846	0.237	F	1.27	0.735	0
IL-1B+3954	Overall	10	0.798	0.628–1.015	0.066	R	25.5	0.002	64.8
C vs T	Asian*	4	0.489	0.357–0.669	< 0.001	F	5.2	0.151	43.3
	European	5	0.869	0.740–1.020	0.086	F	3.22	0.521	0
CC vs CT+TT	Overall	10	0.776	0.609–0.988	0.040	R	18.8	0.027	52.1
(Recessive)	Asian*	4	0.496	0.346–0.710	≤ 0.001	F	6.08	0.108	50.6
	European	5	0.832	0.677–1.001	0.051	F	1.49	0.827	0
CC+CT vs TT	Overall	8	0.836	0.507–1.380	0.484	R	13.7	0.055	49.2
(Dominant)	Asian*	2	0.286	0.118–0.691	0.005	F	0.06	0.804	0
	European	5	0.933	0.620–1.404	0.741	F	5.06	0.281	21.0
CC vs TT	Overall	8	0.789	0.470–1.325	0.370	R	14.3	0.046	51.1
	Asian*	2	0.263	0.108–0.645	0.003	F	0.03	0.852	0
	European	5	0.867	0.572–1.314	0.501	F	5.00	0.287	20.0
CT vs TT	Overall	8	0.938	0.685–1.412	0.926	F	10.0	0.184	30.5
	Asian*	2	0.404	0.158–1.033	0.058	F	0.81	0.365	0
	European	5	1.660	0.635–4.341	0.301	F	0.30	0.10	0

* Some studies did not give complete genotype data. F: fixed effect model; R: random effect model.

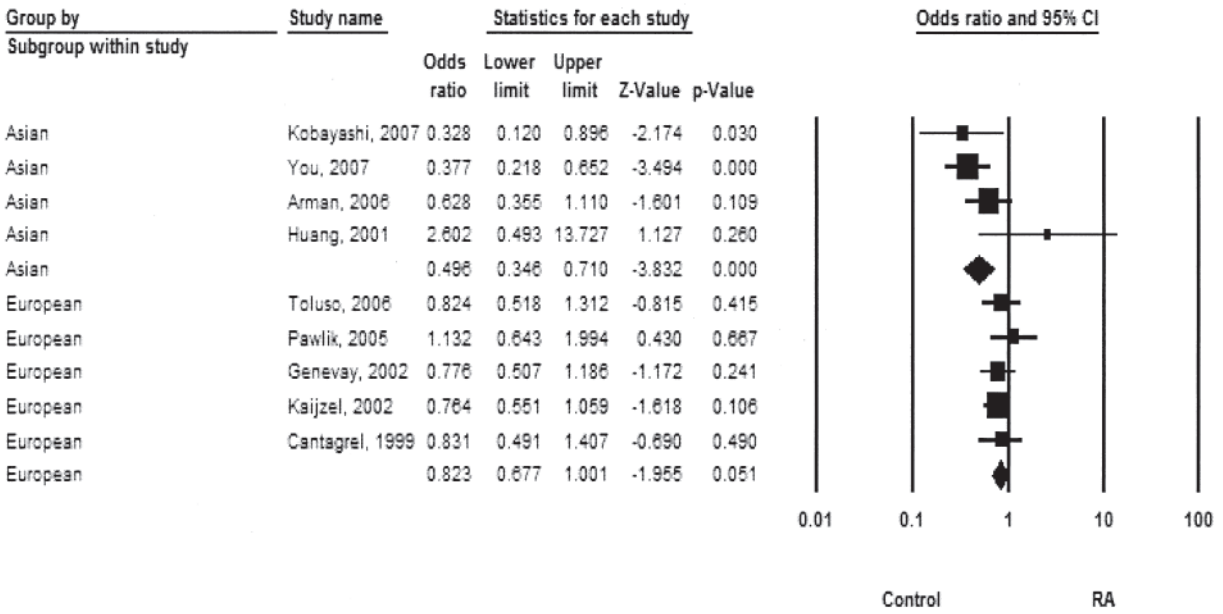

Figure 1. Odds ratios and 95% confidence intervals of individual studies and pooled data for the *IL-1B+3954* CC and CT+TT genotypes (recessive model) for susceptibility to RA in Asians and Europeans.

ceptibility. Metaanalysis identified no association between RA and *IL-1B-511* C allele in the overall population (OR 1.046, 95% CI 0.934–1.172, p = 0.436; Table 2). Further, stratification by ethnicity failed to identify any association between this polymorphism and RA in the European or Asian groups (Table 2).

Metaanalysis of the IL-1B+3954 polymorphism and RA susceptibility. Metaanalysis revealed a significantly greater association between the CC genotype and the risk of developing RA than between the CT+TT genotype and RA (OR 0.776, 95% CI 0.609–0.988, p = 0.040), but with between-study heterogeneity (p = 0.027; Table 2). In Asians, an associational difference was found between the CC genotype and the CT+TT genotype (OR 0.496, 95% CI 0.346–0.710, p < 0.001; Figure 1). A measure consisting of the ratio of log OR_{CT} versus log OR_{CC} was 0.67, which suggests a codominant mode of action. However, in Europeans, no association was found between the *IL-1B+3954* polymorphism and RA susceptibility.

Metaanalysis of the IL-1RN VNTR versus RA association. No association was found between RA susceptibility and *IL-1RN VNTR* by metaanalyses.

DISCUSSION

Our findings do not support associations between the *IL-1B-511* and *IL-1RN VNTR* polymorphisms and RA susceptibility. Further, although heterogeneity was found among studies, no association was found between the *IL-1B-511* or *IL-1RN VNTR* polymorphisms and RA susceptibility. In contrast, metaanalysis of the *IL-1B+3954* polymorphism revealed that the CC genotype was more associated with the risk of developing RA than the CT+TT genotype. In particular, in Asians, an association between the CC genotype and RA was observed, but this was not evident in Europeans. These findings suggest that the *IL-1B+3954* polymorphism is associated with development of RA in Asians but not in Europeans. However, in the European populations, recessive and allele contrast analyses showed that the *IL-1B+3954* polymorphism tended to be associated with RA susceptibility, and thus the possibility that the *IL-1B+3954* polymorphism plays a role in the pathogenesis of RA in Europeans cannot be ruled out.

Our study has some limitations that should be considered. First, heterogeneity and small sample size may have distorted the metaanalysis, but most heterogeneity was resolved by ethnic-specific subgroup analysis. Second, ethnic-specific metaanalysis included data from European and Asian patients, and thus our results are applicable only to these ethnic groups. Third, there was only a handful of studies in Asian populations and complete genotype data were not available from 2 Asian studies.

This metaanalysis of published data identified that the *IL-1B+3954* polymorphism was associated with RA in Asians.

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