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Associations between Polymorphisms in the *IL-1* Gene and the Risk of Rheumatoid Arthritis and Systemic Lupus Erythematosus: Evidence from a Meta-Analysis

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Keywords
Rheumatoid arthritis · Systemic lupus erythematosus · *IL-1* · Gene polymorphisms · Meta-analysis

Abstract
Background: Previous studies on polymorphisms in interleukin-1 (*IL-1*) and the risk of rheumatoid arthritis (RA)/systemic lupus erythematosus (SLE) yielded inconsistent results. ***Objectives:*** The authors performed this meta-analysis to more robustly evaluate associations between polymorphisms in the *IL-1* gene and the risk of RA/SLE. ***Methods:*** MEDLINE, Embase, Web of Science, Wanfang, VIP, and CNKI were systematically searched for eligible studies, and 34 relevant studies were finally selected to be eligible for inclusion. ***Results:*** We found that *IL-1A* +4845G/T polymorphism was significantly associated with the risk of RA in the overall population (dominant comparison: $p = 0.02$; overdominant comparison: $p = 0.05$; allele comparison: $p = 0.04$), whereas *IL-1B* +3954C/T polymorphism was significantly associated with the risk of RA in the overall population (overdominant comparison: $p = 0.03$; allele comparison: $p = 0.01$) and Asians (recessive comparison: $p = 0.007$; allele comparison: $p = 0.002$). In addition, we found that *IL-1A* –889C/T polymorphism was significantly associated with the risk of SLE in Caucasians (allele comparison: $p = 0.04$), *IL-1B* –31T/C polymorphism was significantly associated with the risk of SLE in the overall population (recessive comparison: $p = 0.04$), and *IL-1B* –511C/T polymorphism was significantly associated with the risk of SLE in Asians (recessive comparison: $p = 0.01$; allele comparison: $p = 0.03$). ***Conclusions:*** This meta-analysis suggests that *IL-1A* +4845G/T and *IL-1B* +3954C/T polymorphisms may influence the risk of RA, whereas *IL-1A* –889C/T, *IL-1B* –31T/C, and *IL-1B* –511C/T polymorphisms may influence the risk of SLE.

Introduction

Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are two typical autoimmune disorders which feature a proinflammatory immunological status and systemic damage to multiple organs or tissues resulting from severe immunological reactions [1, 2]. The etiologies and pathogenetic mechanisms of RA/SLE are still

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unclear despite previous investigations, but several lines of evidence demonstrate that genetic components are essential for their onset and development. Firstly, the incidence of RA/SLE varies substantially between different ethnic groups [3, 4], and the genetic background is probably one of the major causes of the differences in disease prevalence observed across different ethnic groups. Secondly, previous genetic association studies have also identified and validated numerous genetic loci susceptible of RA/SLE in various populations [5, 6].

Interleukin-1 (IL-1) is a potent proinflammatory Th1 cytokine. It is well established that Th1-related cytokines are crucial for the initiation and development of autoimmune disorders such as RA and SLE [7–10]. Consequently, it is biologically possible that *IL-1* polymorphism may also influence the risk of RA/SLE. Over the last decade, a great number of studies have been conducted to assess the associations between polymorphisms in the *IL-1* gene and RA/SLE, with inconsistent findings. Thus, a meta-analysis was performed by us to more robustly assess the associations between polymorphisms in the *IL-1* gene and the risk of RA/SLE.

Materials and Methods

This meta-analysis was conducted in accordance with the PRISMA guideline [11]. The PRISMA checklist is provided in online supplementary File 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000510641). This meta-analysis was not registered in PROSPERO, but we registered an Open Science Framework account to make this meta-analysis more publicly available (all data sets of this meta-analysis can be accessed at https://osf.io; username: zhulin00111222@163.com; password: zhulin01*).

Literature Search and Inclusion Criteria

MEDLINE, Embase, Web of Science, Wanfang, VIP, and CNKI were systematically searched by the authors using the following keywords: (Interleukin-1 OR Interleukin 1 OR IL-1 OR IL 1) AND (polymorphism OR polymorphic OR variation OR variant OR mutant OR mutation OR SNP OR genotypic OR genotype OR allelic OR allele) AND (Rheumatoid arthritis OR RA OR Systemic lupus erythematosus OR SLE). Moreover, we also manually screened the reference lists of retrieved publications to make up for the potential incompleteness of literature searching from electronic databases. We did not set any restrictions on language of publication or time of publication when conducting literature searching.

The selection criteria of this meta-analysis were as follows: (1) case-control or cohort design; (2) provision of genotypic distributions of *IL-1* polymorphisms in cases with RA/SLE and population-based controls; and (3) the full manuscript with detailed genotypic frequencies of *IL-1* polymorphisms is freely retrievable or buyable. Articles were excluded if one of the following three criteria was satisfied: (1) studies without complete genotypic distribution data on *IL-1* polymorphisms in cases with RA/SLE and population-based controls; (2) narrative or systematic reviews, meta-analyses, or comments; or (3) case series without a control group. If duplicate reports were retrieved from literature searching, we only included the study with the largest sample size for the pooled analyses.

Data Extraction and Quality Assessment

The authors extracted the following data items from eligible studies: (1) last name of the first author; (2) year of publication; (3) country and ethnicity of the study population; (4) the number of cases with RA/SLE and population-based controls; and (5) the genotypic frequencies of *IL-1* polymorphisms in cases with RA/SLE and population-based controls. Hardy-Weinberg equilibrium (HWE) was then tested by using the genotypic frequencies of *IL-1* polymorphisms, and the threshold of deviation from HWE was set at 0.05. The quality of eligible studies was assessed by the Newcastle-Ottawa Scale (NOS) [12], and those with a score of 7–9 were considered to be of good quality. Two authors extracted the data and assessed the quality of eligible publications in parallel. A thorough discussion until reaching a consensus was initiated in case of any discrepancy between the two authors.

Statistical Analyses

All statistical analyses in this meta-analysis were performed with the Cochrane Review Manager software version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK). Associations between *IL-1* gene polymorphisms and the risk of RA/SLE were explored by using odds ratios (ORs) and their 95% confidence intervals (CIs). The statistically significant p value was set at 0.05. The authors used I^2 statistics to estimate heterogeneities among the included studies. The authors used the DerSimonian-Laird method, which is also known as the random-effects model, to pool the results of eligible studies if I^2 was larger than 50%. Otherwise, the authors would use the Mantel-Haenszel method, which is also known as the fixed-effects model, to pool the results of eligible studies. Meanwhile, the authors also conducted subgroup analyses, first by type of disease and then by ethnic group. The stability of integrated results was tested by deleting studies that violated HWE, and then pooling the results of the rest of the eligible studies. Publication bias was evaluated by assessing the symmetry of funnel plots.

Results

Characteristics of the Included Studies

A total of 585 publications were retrieved by the authors using our searching strategy. In all, 61 publications were then selected to be screened for eligibility after excluding 507 unrelated publications and 17 repeated reports. We further excluded 19 reviews and 4 case series, and another 4 publications without complete genotypic distribution data were also excluded by the authors. Ultimately, 34 studies met the inclusion criteria, and these were selected to be included for integrated analyses

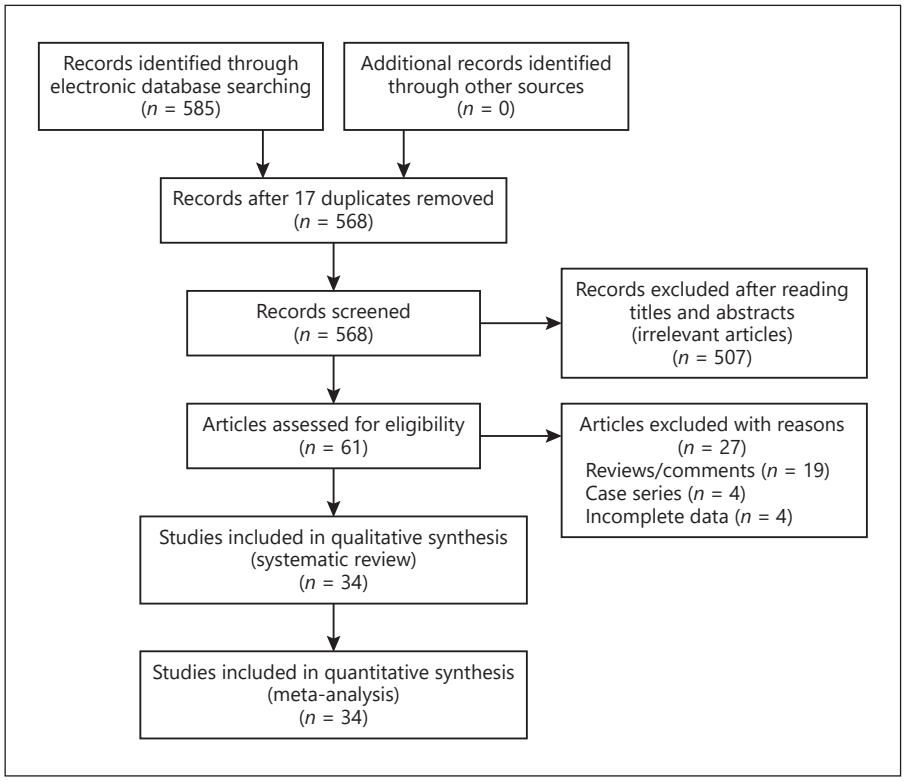

Fig. 1. Flowchart of study selection for this meta-analysis.

(Fig. 1). The data extracted from the eligible studies [21–54] are summarized in Table 1.

IL-1 *Polymorphisms and the Risk of RA*

Five publications assessed the relationship between *IL-1A* –889C/T polymorphism and the risk of RA, 5 publications assessed the relationship between *IL-1A* +4845G/T polymorphism and the risk of RA, 3 publications assessed the relationship between *IL-1B* –31T/C polymorphism and the risk of RA, 17 publications assessed the relationship between *IL-1B* –511C/T polymorphism and the risk of RA, and 17 publications assessed the relationship between *IL-1B* +3953C/T polymorphism and the risk of RA.

The meta-analyses demonstrated that *IL-1A* +4845G/T polymorphism was significantly associated with the risk of RA in the overall population (dominant comparison: OR = 0.79, 95% CI 0.64–0.97, $p = 0.02$; overdominant comparison: OR = 1.24, 95% CI 1.00–1.53, $p = 0.05$; allele comparison: OR = 0.84, 95% CI 0.71–0.99, $p = 0.04$). Moreover, *IL-1B* +3954C/T polymorphism was significantly associated with the risk of RA in the overall population (overdominant comparison: OR = 1.12, 95% CI 1.01–1.25, $p = 0.03$; allele comparison: OR = 0.81, 95% CI 0.68–0.96, $p = 0.01$) and in Asians (recessive comparison: OR = 3.05, 95% CI 1.35–6.88, $p = 0.007$; allele comparison: OR = 0.52, 95% CI 0.34–0.79, $p = 0.002$). Nevertheless, no such positive findings were observed for *IL-1A* –889C/T, *IL-1B* –31T/C, and *IL-1B* –511C/T polymorphisms (Table 2; online suppl. Fig. 1).

IL-1 *Polymorphisms and the Risk of SLE*

Four publications assessed the relationship between *IL-1A* –889C/T polymorphism and the risk of SLE, 2 publications assessed the relationship between *IL-1A* +4845G/T polymorphism and the risk of SLE, 2 publications assessed the relationship between *IL-1B* –31T/C polymorphism and the risk of SLE, 9 publications assessed the relationship between *IL-1B* –511C/T polymorphism and the risk of SLE, and 6 publications assessed the relationship between *IL-1B* +3953C/T polymorphism and the risk of SLE.

The meta-analyses demonstrated that *IL-1A* –889C/T polymorphism was significantly associated with the risk of SLE in Caucasians (allele comparison: OR = 1.21, 95% CI 1.01–1.46, $p = 0.04$), *IL-1B* –31T/C polymorphism was significantly associated with the risk of SLE in the overall population (recessive comparison: OR = 1.64, 95% CI 1.10–2.46, $p = 0.04$), and *IL-1B* –511C/T polymorphism

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

First author [Ref.], year	Country	Ethnicity	Type of disease	Sample size (cases/controls), *n*	Genotype distribution, *n*		*p* value for HWE	NOS score
					cases	controls		
IL-1A –889C/T					CC/CT/TT			
Domínguez-Pérez [21], 2017	Mexico	Mixed	Rheumatoid arthritis	80/80	39/34/7	36/39/5	0.188	7
Johnsen [22], 2008	USA	Mixed	Rheumatoid arthritis	1,283/1,096	687/507/89	546/445/105	0.303	7
McDowell [23], 1995	UK	Caucasian	Rheumatoid arthritis	269/99	108/127/34	51/37/11	0.288	7
Pan [24], 2001	China	Asian	Rheumatoid arthritis	136/102	61/51/24	38/46/18	0.531	7
Zhang [25], 2001	China	Asian	Rheumatoid arthritis	65/60	39/21/5	33/24/3	0.606	7
Parks [26], 2004	USA	Caucasian	Systemic lupus erythematosus	86/202	43/32/11	68/109/25	0.064	7
Parks [26], 2004	USA	African	Systemic lupus erythematosus	144/73	62/57/25	18/43/12	0.112	7
Sánchez [27], 2006	Spain	Caucasian	Systemic lupus erythematosus	417/420	220/164/33	209/166/45	0.168	7
Tahmasebi [28], 2013	Iran	Mixed	Systemic lupus erythematosus	206/209	87/103/16	95/93/21	0.800	7
Ziaee [29], 2014	Iran	Mixed	Systemic lupus erythematosus	59/136	26/25/7	62/62/12	0.527	7
IL-1A +4845G/T					GG/GT/TT			
Domínguez-Pérez [21], 2017	Mexico	Mixed	Rheumatoid arthritis	80/80	39/36/5	47/29/4	0.861	7
Genevay [30], 2002	Switzerland	Caucasian	Rheumatoid arthritis	230/144	105/101/24	76/60/8	0.384	8
Kaijzel [31], 2002	The Netherlands	Caucasian	Rheumatoid arthritis	396/218	194/171/31	117/79/22	0.120	7
Kobayashi [32], 2007	Japan	Asian	Rheumatoid arthritis	86/100	66/19/1	84/15/1	0.721	7
Song [33], 2012	China	Asian	Rheumatoid arthritis	120/100	59/50/11	51/42/7	0.677	7
Kobayashi [32], 2007	Japan	Asian	Systemic lupus erythematosus	71/44	65/6/0	37/7/0	0.566	7
Parks [26], 2004	USA	Caucasian	Systemic lupus erythematosus	86/202	45/27/14	95/83/24	0.375	7
Parks [26], 2004	USA	African	Systemic lupus erythematosus	143/73	96/39/8	54/18/1	0.714	7
IL-1B –31T/C					TT/TC/CC			
Ke [34], 2009	China	Asian	Rheumatoid arthritis	111/120	19/48/44	28/66/26	0.272	7
Kobayashi [35], 2009	Japan	Asian	Rheumatoid arthritis	137/108	27/60/50	26/60/22	0.242	7
You [36], 2013	China	Asian	Rheumatoid arthritis	452/373	121/235/96	106/187/80	0.884	7
Mohammadoo [37], 2016	Iran	Mixed	Systemic lupus erythematosus	163/180	52/87/24	81/85/14	0.196	7
Muraki [38], 2004	Japan	Asian	Systemic lupus erythematosus	102/106	33/41/28	31/52/23	0.892	8
IL-1B –511C/T					CC/CT/TT			
Allam [39], 2013	Algeria	African	Rheumatoid arthritis	147/127	46/66/35	42/60/25	0.669	7
Buchs [40], 2001	France	Caucasian	Rheumatoid arthritis	272/110	119/130/23	46/53/11	0.449	8
Camargo [41], 2004	USA	Mixed	Rheumatoid arthritis	172/392	36/95/41	110/192/90	0.724	8
Cantagrel [42], 1999	France	Caucasian	Rheumatoid arthritis	106/124	50/39/17	43/62/19	0.665	7
Domínguez-Pérez [21], 2017	Mexico	Mixed	Rheumatoid arthritis	80/80	30/39/11	35/34/11	0.555	7
Genevay [30], 2002	Switzerland	Caucasian	Rheumatoid arthritis	231/140	106/99/26	64/61/15	0.935	8
Huang [43], 2001	China	Asian	Rheumatoid arthritis	104/103	23/47/34	24/53/26	0.765	7
Jahid [44], 2018	India	Mixed	Rheumatoid arthritis	187/214	70/92/25	126/74/14	0.487	7
Johnsen [22], 2008	USA	Mixed	Rheumatoid arthritis	1,277/1,101	573/548/156	466/501/134	0.971	7
Lagha [45], 2015	Tunisia	Mixed	Rheumatoid arthritis	104/150	16/67/21	24/112/14	<0.001	7
Pan [24], 2001	China	Asian	Rheumatoid arthritis	136/102	67/44/25	57/30/15	0.003	7
Shafia [46], 2014	India	Mixed	Rheumatoid arthritis	150/200	54/86/10	58/110/32	0.093	7
Song [33], 2012	China	Asian	Rheumatoid arthritis	120/100	56/52/12	45/44/11	0.960	7
Tolusso [47], 2006	Italy	Caucasian	Rheumatoid arthritis	126/178	66/49/11	75/81/22	0.986	8
You [48], 2007	China	Asian	Rheumatoid arthritis	240/227	43/126/71	55/104/68	0.224	7
You [36], 2013	China	Asian	Rheumatoid arthritis	452/373	130/237/85	100/191/82	0.609	7
Zhang [49], 2020	China	Asian	Rheumatoid arthritis	157/155	59/53/45	71/53/31	<0.001	7
Camargo [41], 2004	Colombia	Mixed	Systemic lupus erythematosus	114/392	29/59/26	110/192/90	0.724	7
Huang [50], 2002	Taiwan	Asian	Systemic lupus erythematosus	52/103	14/21/17	26/53/24	0.686	7
Mohammadoo [37], 2016	Iran	Mixed	Systemic lupus erythematosus	163/180	25/87/51	35/92/53	0.662	8
Muraki [38], 2004	Japan	Asian	Systemic lupus erythematosus	103/106	35/46/22	34/49/23	0.501	8
Parks [26], 2004	USA	Caucasian	Systemic lupus erythematosus	86/202	41/36/9	89/87/26	0.515	7
Parks [26], 2004	USA	African	Systemic lupus erythematosus	144/73	48/73/23	25/27/21	0.027	7
Tahmasebi [28], 2013	Iran	Mixed	Systemic lupus erythematosus	207/212	50/121/35	50/133/29	<0.001	7
Tsai [51], 2009	Taiwan	Asian	Systemic lupus erythematosus	95/95	21/36/38	30/41/24	0.194	7
Umare [52], 2018	India	Mixed	Systemic lupus erythematosus	200/201	66/95/39	71/98/32	0.851	7
Ziaee [29], 2014	Iran	Mixed	Systemic lupus erythematosus	58/139	17/24/17	36/82/21	0.022	7
IL-1B +3953C/T					CC/CT/TT			
Allam [39], 2013	Algeria	African	Rheumatoid arthritis	147/127	65/60/22	48/54/25	0.174	7
Buchs [40], 2001	France	Caucasian	Rheumatoid arthritis	273/109	156/102/15	70/34/5	0.739	8
Camargo [41], 2004	USA	Mixed	Rheumatoid arthritis	172/392	122/44/6	262/106/24	0.005	8
Domínguez-Pérez [21], 2017	Mexico	Mixed	Rheumatoid arthritis	80/80	50/22/8	57/22/1	0.483	7
Elshazli [53], 2019	Egypt	Mixed	Rheumatoid arthritis	120/150	96/19/5	117/24/9	<0.001	7
Genevay [30], 2002	Switzerland	Caucasian	Rheumatoid arthritis	230/144	128/86/16	89/48/7	0.872	8
Johnsen [22], 2008	USA	Mixed	Rheumatoid arthritis	1,240/1,096	761/416/63	663/378/55	0.906	7
Kaijzel [31], 2002	The Netherlands	Caucasian	Rheumatoid arthritis	407/245	233/147/27	156/74/15	0.130	7
Kazkaz [54], 2007	France	Caucasian	Rheumatoid arthritis	512/471	NA	NA	NA	7
Kazkaz [54], 2007	Syria	Mixed	Rheumatoid arthritis	156/120	NA	NA	NA	7
Kobayashi [32], 2007	Japan	Asian	Rheumatoid arthritis	86/100	72/14/0	94/6/0	0.757	7
Kobayashi [35], 2009	Japan	Asian	Rheumatoid arthritis	137/108	118/19/0	102/6/0	0.767	7
Shafia [46], 2014	India	Mixed	Rheumatoid arthritis	150/200	41/109/0	64/136/0	<0.001	7
Song [33], 2012	China	Asian	Rheumatoid arthritis	120/100	56/48/16	61/34/5	0.926	7
Tolusso [47], 2006	Italy	Caucasian	Rheumatoid arthritis	126/178	72/49/5	110/58/10	0.524	8
You [48], 2007	China	Asian	Rheumatoid arthritis	235/227	185/44/6	206/19/2	0.050	7
You [36], 2013	China	Asian	Rheumatoid arthritis	452/373	NA	NA	NA	7

Table 1 (continued)

First author [Ref.], year	Country	Ethnicity	Type of disease	Sample size (cases/controls), *n*	Genotype distribution, *n*		*p* value for HWE	NOS score
					cases	controls		
Zhang [25], 2001	China	Asian	Rheumatoid arthritis	65/60	44/17/4	36/23/1	0.209	7
Camargo [41], 2004	Colombia	Mixed	Systemic lupus erythematosus	114/392	89/23/2	262/106/24	0.005	7
Muraki [38], 2004	Japan	Asian	Systemic lupus erythematosus	103/106	93/9/1	98/8/0	0.686	8
Parks [26], 2004	USA	Caucasian	Systemic lupus erythematosus	86/201	49/31/6	121/67/13	0.374	7
Parks [26], 2004	USA	African	Systemic lupus erythematosus	144/72	111/32/1	61/10/1	0.440	7
Tahmasebi [28], 2013	Iran	Mixed	Systemic lupus erythematosus	207/213	112/84/11	102/96/15	0.232	7
Umare [52], 2018	India	Mixed	Systemic lupus erythematosus	200/201	128/66/6	158/40/3	0.798	7
Ziaee [29], 2014	Iran	Mixed	Systemic lupus erythematosus	55/140	34/17/4	70/58/12	0.998	7

HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa Scale; NA, not available.

Table 2. Pooled meta-analysis results of the current study

Polymorphisms	Population	Sample size (cases/controls), *n*	Dominant comparison		Recessive comparison		Overdominant comparison		Allele comparison	
			p value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)
IL-1A –889C/T	RA+SLE	2,745/2,477	0.13	1.16 (0.96–1.40)	0.07	0.84 (0.70–1.01)	0.18	0.87 (0.72–1.06)	**0.008**	**1.12 (1.03–1.22)**
	RA	1,833/1,437	0.13	1.11 (0.97–1.28)	0.12	0.82 (0.65–1.05)	0.53	0.96 (0.83–1.10)	0.06	1.11 (1.00–1.24)
	Asians	201/162	0.20	1.32 (0.86–2.01)	0.79	1.08 (0.59–2.00)	0.14	0.73 (0.47–1.11)	0.41	1.14 (0.83–1.56)
	SLE	912/1,040	0.15	1.28 (0.91–1.80)	0.34	0.87 (0.64–1.17)	0.21	0.79 (0.55–1.14)	0.06	1.14 (0.99–1.31)
	Caucasians	503/622	0.20	1.43 (0.83–2.45)	0.26	0.79 (0.53–1.19)	0.36	0.73 (0.38–1.42)	**0.04**	**1.21 (1.01–1.46)**
IL-1A +4845G/T	RA+SLE	1,212/961	0.07	0.85 (0.71–1.02)	0.19	1.25 (0.89–1.76)	0.27	1.11 (0.92–1.34)	0.05	0.86 (0.75–1.00)
	RA	912/642	**0.02**	**0.79 (0.64–0.97)**	0.56	1.12 (0.76–1.67)	**0.05**	**1.24 (1.00–1.53)**	**0.04**	**0.84 (0.71–0.99)**
	Caucasians	626/362	0.09	0.80 (0.62–1.03)	0.75	1.17 (0.46–2.99)	0.12	1.24 (0.95–1.61)	0.15	0.86 (0.70–1.06)
	SLE	300/319	0.72	0.93 (0.74–1.55)	0.11	1.71 (0.89–3.29)	0.20	0.78 (0.53–1.14)	0.67	0.94 (0.69–1.26)
IL-1B –31T/C	RA+SLE	965/887	0.05	0.81 (0.66–1.00)	**0.02**	**1.64 (1.10–2.46)**	0.32	0.86 (0.64–1.15)	**0.02**	**0.77 (0.62–0.95)**
	RA	700/601	0.22	0.85 (0.66–1.10)	0.11	1.68 (0.89–3.16)	0.25	0.79 (0.52–1.19)	0.09	0.76 (0.55–1.04)
	Asians	700/601	0.22	0.85 (0.66–1.10)	0.11	1.68 (0.89–3.16)	0.25	0.79 (0.52–1.19)	0.09	0.76 (0.55–1.04)
	SLE	265/286	0.50	0.79 (0.40–1.57)	**0.04**	**1.64 (1.03–2.62)**	0.92	0.97 (0.54–1.75)	0.17	0.77 (0.53–1.12)
IL-1B –511C/T	RA+SLE	5,283/5,579	0.62	0.98 (0.90–1.06)	0.13	1.08 (0.98–1.20)	0.64	0.98 (0.91–1.06)	0.19	0.96 (0.91–1.02)
	RA	4,061/3,876	0.45	0.94 (0.80–1.11)	0.45	1.05 (0.93–1.19)	0.93	1.00 (0.91–1.09)	0.36	0.95 (0.84–1.06)
	Asians	1,209/1,060	0.22	0.89 (0.74–1.07)	0.59	1.06 (0.86–1.29)	0.49	1.06 (0.90–1.25)	0.26	0.93 (0.83–1.05)
	Caucasians	735/552	0.06	1.25 (0.99–1.57)	0.58	0.90 (0.63–1.29)	0.12	0.83 (0.66–1.05)	0.09	1.16 (0.98–1.37)
	SLE	1,222/1,703	0.87	0.99 (0.83–1.17)	0.11	1.16 (0.97–1.40)	0.44	0.94 (0.81–1.10)	0.17	0.93 (0.83–1.03)
	Asians	147/198	0.33	0.78 (0.48–1.28)	**0.01**	**1.81 (1.13–2.91)**	0.16	0.73 (0.47–1.13)	**0.03**	**0.71 (0.52–0.96)**
IL-1B +3954C/T	RA+SLE	5,617/5,605	0.09	0.88 (0.77–1.02)	0.83	1.02 (0.84–1.25)	**0.04**	**1.11 (1.01–1.21)**	**0.04**	**0.86 (0.73–1.00)**
	RA	4,708/4,280	0.05	0.86 (0.74–1.00)	0.48	1.08 (0.87–1.36)	**0.03**	**1.12 (1.01–1.25)**	**0.01**	**0.81 (0.68–0.96)**
	Asians	1,095/968	0.06	0.62 (0.37–1.02)	**0.007**	**3.05 (1.35–6.88)**	0.09	1.67 (0.93–3.01)	**0.002**	**0.52 (0.34–0.79)**
	Caucasians	1,548/1,147	**0.03**	**0.84 (0.72–0.98)**	0.65	1.11 (0.72–1.70)	**0.02**	**1.28 (1.04–1.58)**	**0.03**	**0.83 (0.70–0.98)**
	SLE	909/1325	0.89	0.97 (0.65–1.45)	0.35	0.80 (0.51–1.27)	0.75	1.06 (0.75–1.50)	0.93	0.98 (0.70–1.39)

Bold type denotes significance. RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; OR, odds ratio; CI, confidence interval.

was significantly associated with the risk of SLE in Asians (recessive comparison: OR = 1.81, 95% CI 1.13–2.91, p = 0.01; allele comparison: OR = 0.71, 95% CI 0.52–0.96, p = 0.03). Nevertheless, no such positive findings were observed for *IL-1A* +4845G/T and *IL-1B* +3954C/T polymorphisms (Table 2; online suppl. Fig. 1).

Sensitivity Analyses

We examined the stability of the pooled analysis results by deleting studies that violated HEW and then pooling the results of the rest of the studies. The trends for associations remained similar in the sensitivity analyses, which indicates that our pooled analysis results were quite reliable and stable.

Publication Bias

We examined potential publication bias in this meta-analysis by assessing the symmetry of funnel plots. The funnel plots were generally found to be symmetrical, which indicates that our pooled analysis results were unlikely to be severely influenced by publication bias (online suppl. Fig. 2).

Discussion

At present, this meta-analysis is the most comprehensive one regarding associations between gene polymorphisms in *IL-1* and the risk of RA/SLE. The pooled analysis results showed that *IL-1A* +4845G/T polymorphism was significantly associated with the risk of RA in the overall population, whereas *IL-1B* +3954C/T polymorphism was significantly associated with the risk of RA in the overall population and Asians. In addition, we found that *IL-1A* –889C/T polymorphism was significantly associated with the risk of SLE in Caucasians, *IL-1B* –31T/C polymorphism was significantly associated with the risk of SLE in the overall population, and *IL-1B* –511C/T polymorphism was significantly associated with the risk of SLE in Asians.

The following points need to be considered when interpreting our integrated findings. First, based on the results of previous experimental studies, it is rational to speculate that these investigated *IL-1* polymorphisms may alter the mRNA expression level or protein function of IL-1, give rise to a proinflammatory status, and then affect the risk of RA/SLE [13, 14]. Nevertheless, further experimental studies are still warranted to reveal the exact mechanisms underlying the positive associations observed between *IL-1* gene polymorphisms and the risk of RA/SLE in the current meta-analysis.

Second, we initially aimed to study all polymorphic loci of the *IL-1* gene. Nevertheless, we failed to detect sufficient eligible publications to support pooled analyses for other polymorphic loci of the *IL-1* gene, so only five polymorphisms of the *IL-1* gene were covered by the current meta-analysis.

Third, it is worth noting that, previously, Lee and Bae [15] and Wang et al. [16] also tried to investigate associations between *IL-1* gene polymorphisms and RA or SLE through a meta-analysis. Nevertheless, these two previous meta-analyses only included relevant genetic association studies that had been published before 2009. Since our literature search revealed that many related studies were published after 2009, an updated meta-analysis like ours was warranted to get more reliable findings. Consistent with the previous meta-analyses, a significant association with RA was observed for *IL-1B* +3953C/T polymorphism and a significant association with SLE was observed for *IL-1A* –889C/T polymorphism in our pooled analyses. Additionally, we also found that *IL-1A* +4845G/T polymorphism was significantly associated with the risk of RA, whereas *IL-1B* –31T/C and *IL-1B* –511C/T polymorphisms were significantly associated with the risk of SLE, which the previous meta-analyses failed to detect. Besides, we also noticed that Su et al. [17] had previously conducted a meta-analysis to investigate associations between *IL-1A* –889C/T polymorphism and multiple autoimmune disorders, and their findings for RA and SLE are basically identical to our observations, but it should be acknowledged that they only enrolled studies that were published in English, while we did not put any restrictions regarding publication language. Thus, in contrast to their work, two more publications in Chinese were also included by us, which allowed us to perform an additional subgroup analysis for RA in Asians. Considering that our pooled analyses were derived from a greater number of eligible studies, our observations should be considered a valuable supplement to the preexisting literature.

Fourth, considering the proinflammatory nature of IL-1, it would be interesting to explore the associations between *IL-1* polymorphisms and the risk of other types of autoimmune disorders. Nevertheless, due to the paucity of relevant studies, we could not perform such analyses accordingly.

Fifth, for a single genetic association study in which multiple gene polymorphisms were analyzed in a group of study subjects simultaneously, correction of the *p* value should be conducted, since multiple tests were performed on these study subjects at the same time. Given that the investigated polymorphisms may somehow be connected with each other, the possibility of getting false-positive results (type I error) would for sure significantly increase when many gene polymorphisms are studied at the same time, and this is also the reason why in a single genetic association study, the *p* value should be generally set at a much lower level to avoid false-positive results. However, since in this meta-analysis, although several polymorphisms were analyzed by us, different studies were included for different gene polymorphisms, the study subjects for each polymorphism were actually not the same, so that the status of this meta-analysis is somehow different from that of a single genetic association study in which many gene polymorphisms are studied in the exact same population at the same time.

If we used a correction procedure in our meta-analysis, the possibility of getting false-negative results (type II error) would increase to an extremely high level, so correction for multiple testing was not prioritized in this meta-analysis. If we used Bonferroni correction to account for multiple testing and set the *p* value at 0.0125 (0.05/4, since 4 different genetic models were compared for each polymorphism), then the positive associations observed between *IL-1B* –511C/T polymorphism and SLE, as well as

between *IL-1B* +3954C/T polymorphism and RA, would still remain statistically significant in Asians. Nevertheless, the other positive findings observed in this meta-analysis would not withstand this correction for multiple testing.

Our meta-analysis is not without limitations. First, our pooled analysis results are unadjusted. Without access to the raw data from the eligible studies, we could only assess associations between *IL-1* gene polymorphisms and the risk of RA/SLE based on recalculations of the raw genotypic frequencies provided by the eligible literature, and we need to admit that the lack of further adjustment for baseline characteristics such as age and gender may possibly have influenced the reliability of our findings [18]. Second, environmental factors such as food intake, sunshine exposure, and climatic conditions may also influence associations between polymorphisms in the *IL-1* gene and the risk of RA/SLE. However, most of the authors only paid attention to genetic associations in their publications, so it was impossible for us to explore gene-environment interactions in a meta-analysis based on these previous publications [19, 20].

In conclusion, this meta-analysis demonstrates that *IL-1A* +4845G/T polymorphism may influence the risk of RA in the overall population, whereas *IL-1B* +3954C/T polymorphism may influence the risk of RA in the overall population and Asians. Moreover, *IL-1A* –889C/T polymorphism may influence the risk of SLE in Caucasians, *IL-1B* –31T/C polymorphism may influence the risk of SLE in the overall population, and *IL-1B* –511C/T polymorphism may influence the risk of SLE in Asians. If we used Bonferroni correction to further account for multiple testing, then the positive associations observed between *IL-1B* –511C/T polymorphism and SLE, as well as between *IL-1B* +3954C/T polymorphism and RA, would still remain statistically significant in Asians. Nevertheless, the other positive findings observed in this meta-analysis would not withstand this correction for multiple testing. Therefore, further studies with larger sample sizes are still needed to confirm our findings.

Statement of Ethics

This meta-analysis was conducted in accordance with the PRISMA guideline. Ethical approval and informed consent are not applicable to meta-analyses.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Lin Zhu and Peng Chen conceived and designed this meta-analysis and searched the literature. Xuanjing Sun and Shuo Zhang analyzed the data. Lin Zhu and Peng Chen wrote the manuscript. All authors approved the final manuscript as submitted.

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