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A comprehensive meta-analysis of the association between three *IL1B* polymorphisms and rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is an immune-mediated chronic inflammatory disease that causes huge destruction to human body. *IL1B* encodes key mediator IL-1*β* protein, which plays an important role in the pathogenesis of inflammatory syndromes. The aim of this study was to evaluate the association between *IL1B* polymorphisms and RA. A meta-analysis was performed on the association between three *IL1B* polymorphisms (*IL1B*-31: rs1143627; *IL1B*-511: rs16944; *IL1B* + 3954: rs1143634) and RA. A trend of significant association was observed between *IL1B* + 3954 and RA (*p* = 0.06, odd ratio (OR) = 1.19, 95% confidential interval (CI) = 1.00 - 1.42). A significant association was found in Europeans under the dominant model between *IL1B*-511T and RA (*p* = 0.03, OR = 0.89, 95% CI = 0.81 - 0.99). Our meta-analysis indicated that *IL1B* − 511-T played a protective role against RA in Europeans, and that *IL1B* + 3954-T had the potential to increase the risk of RA. Future large-scale studies should be considered to confirm the association between *IL1B* polymorphisms and RA.

KEYWORDS

Rheumatoid Arthritis; Meta-Analysis; Polymorphism; *IL1B*-511; Dominant Model

1. INTRODUCTION

Rheumatoid arthritis (RA) is an immune-mediated chronic inflammatory disease [1] that can lead to low bone mineral density [2], depression [3], obstructive lung disease [4] and Cardiovascular diseases [5], causing huge destruction to human body. Twin studies estimated that heritability of RA liability was up to 60% [6]. Family-based studies demonstrated that genetic factors played a more important role in the development of RA than environmental factors did [7,8].

IL1B encodes IL-1*β* that is one of the distinct polypeptides molecules of IL-1, a key mediator in the pathogenesis of inflammatory syndromes such as RA [9]. *IL1B* is 7020 bp in length and contains 826 polymorphisms according to the NCBI dbSNP database. Among them, *IL1B*-31 [10-14], *IL1B*-511 [9-11,14-26] and *IL1B* + 3954 [9-11,14,16-23,25-29] are the most studied in the association with RA.

Inconsistent results exist in the current association between *IL1B* variants and RA. For *IL1B*-31, there were 1 study with significant association result in European population [10] and 4 studies with non-significant association results in European [11-13] and Asian populations [14]. For *IL1B*-511, there were 3 significant comparisons in European population [10, 21, 24] and 13 non-significant comparisons in European [9,11,15,16,18,19, 22,26], Asian [14,17,23], Latin American [20] and African [25] populations. For *IL1B*+3954, there were 3 significant comparisons in European [21] and Asian [23,29] populations and 15 non-significant comparisons in European [9-11,16,18,19,21,22,26-28], Asian [14,17], and African populations [25].

Discrepancy among the association studies might be due to the different ethnic background, inefficient sample size [30], or the uncorrected physiological status among

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the association studies [31]. Meta-analysis is often used to enhance statistical power and to draw a more convincing conclusion by pooling up the research data from individual association study [32]. The goals of our meta-analyses were to find out the causes of the above inconsistent findings among various case-control association studies, and to evaluate the contribution of *IL1B* polymorphisms to RA.

2. MATERIALS AND METHODS

2.1. Data Collection

A systematic literature searching was performed in PubMed/MEDLINE without language restriction, using the keywords "rheumatoid arthritis *IL1B*association" and "rheumatoid arthritis *IL1B* polymorphism" to identify available articles. We also checked Chinese databases (WanFang, WeiPu and CNKI) using the same keywords. The inclusion criteria of the literatures for the meta-analyses comprise the following items: (1) It was an original case-control study with an assessment of the association between *IL1B* polymorphisms and RA risk in humans; (2) It contains sufficient information to infer the odd ratios (ORs) and 95% confidential intervals (95% CI); (3) Genotype distribution of each polymorphism in controls met Hardy-Weinberg equilibrium (HWE). All of the association studies between *IL1B* polymorphisms and RA were fully considered and carefully selected in July 2013. We extracted or calculated the following information from each study: Genetic locus, first author's name, year of publication, ethnicity, numbers of cases and controls, control source, HWE for controls, the result of individual studies about the association of *IL1B* − 31, *IL1B* − 511 and *IL1B* + 3954 with RA and power analysis for each of the involved studies.

2.2. Statistical Analysis

Arlequin program was used to test HWE [33]. Power and Sample Size Calculation program was applied to calculate the power of each study [34]. Review Manager 5 was used for the meta-analysis [35]. Statistical heterogeneity was tested using Cochran's Q statistic and I^2 test [36] to decide the type of analysis to be used in the meta-analysis. For the studies with minimal to moderate heterogeneity (I^2 < 50%), the fixed-effect model would be used for the meta-analysis. For the studies with significant heterogeneity (I^2 > = 50%), the random-effect model would be used. Funnel plots are also drawn to observe the potential publication bias.

3. RESULT

3.1. Data Collection

As shown in **Figure 1**, 10 relevant studies were involved

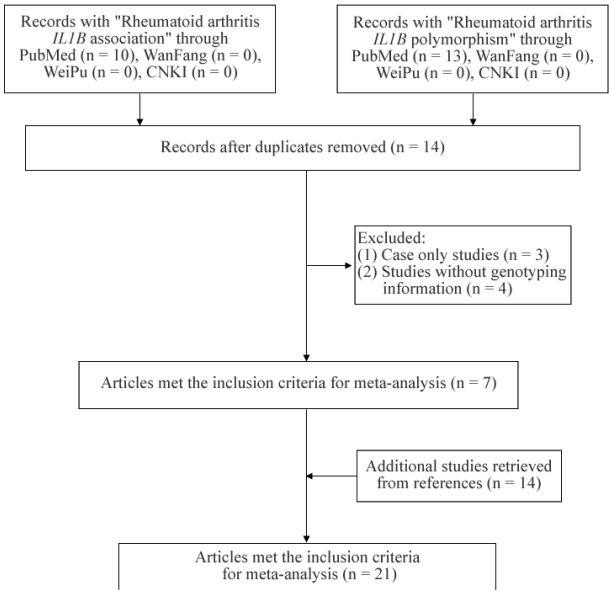

Figure 1. Flowchart of selection process for meta-analyses.

using Pubmed through the keywords "Rheumatoid arthritis *IL1B* association", and 13 relevant studies were involved through the words "Rheumatoid arthritis *IL1B* polymorphism". No relative study was found in Chinese databases (WanFang, WeiPu and CNKI). Among the 23 retrieved articles, we excluded 9 duplicates, 4 case-only studies [37-40], and 3 studies [41-43] for a lack of allele or genotype information. In addition, 14 additional studies [9,15-24,27-29] were retrieved from the references. Finally, a total of 21 studies [9-29] were included in our meta-analysis. The distribution of genotype in the controls met HWE (p > 0.05) in all comparisons except for one [20] with significant deviation from HWE in controls (p < 0.05) (**Table 1**). At last, there were 2214 RA patients and 2466 controls among 5 comparisons for the meta-analysis of *IL1B*-31 (rs1143627), 4491 RA patients and 4006 controls among 16 comparisons for the meta-analysis of *IL1B*-511 (rs16944) in 7 studies, and 4338 RA patients and 3742 compared controls among 16 comparisons for the meta-analysis of *IL1B* + 3954 (rs1143634) (**Table 2**).

3.2. Meta-Analyses of Three Polymorphisms and RA Risk

As showed in **Table 2**, among the overall analysis, a trend of significant association was observed between *IL1B* + 3954-T and RA (p = 0.06, OR = 1.19, 95% CI = 1.00 - 1.42, **Figure 2**, **Table 2**). And there was a significant heterogeneity for *IL1B* + 3954-T (p = 0.0003, I^2 = 65%, **Figure 2**, **Table 2**). A further subgroup meta-analysis under the dominant model identified a significant association of *IL1B*-511-T and RA (p = 0.03, OR = 0.89, 95% CI = 081 - 0.99, **Figure 2**, **Table 2**). No publication

Table 1. Characteristics of studies in the meta-analyses of *IL1B* − 31, *IL1B* − 511 and *IL1B* + 3954 polymorphisms with RA.

First author	Year	Ethnicity	Cases/Controls	Control source	HWE	Result*	Power
IL1B-31							
Stephanie K	2004	Mix*	25/31	Population	NA	S	0.076
Alyssa K	2008	Europeans	1237/1093	NARAC	YES	NS	0.850
Konenkov VI	2010	Europeans	125/513	Population	NA	NS	0.248
Marieke E	2011	Europeans	375/456	Hospital	YES	NS	0.243
Chong-ge Y	2013	Asians	452/373	Hospital	YES	NS	0.452
IL1B-511							
Alian G	1999	Europeans	106/124	Hospital	YES	NS	0.161
Anne C	2000	Europeans	66/99	Population	YES	NS	0.123
N Buchs	2001	Europeans	272/110	Population	YES	NS	0.190
Chung-Ming H	2001	Asians	104/103	Population	YES	NS	0.152
E.L. Kaijzel	2002	Europeans	302/209	Hospital	YES	NS	0.251
Stephana G	2002	Europeans	231/140	Hospital	YES	NS	0.205
JF Camargo	2004	Europeans	172/392	Population	YES	NS	0.076
Stephanie K	2004	Mix*	25/31	Population	NA	S	0.291
A. Arman	2006	Europeans	94/104	Population	YES	S	0.133
Barbara T	2006	Europeans	126/178	Population	YES	NS	0.189
Chong-ge Y	2007	Asians	240/227	Hospital	YES	NS	0.283
Alyssa K	2008	Europeans	1277/1101	NARAC	YES	NS	0.856
P. Harrison	2008	Europeans	741/600	Population	YES	S	0.149
Steven L	2008	Africans	136/88	Hospital	YES	NS	0.613
I. Allam	2013	Europeans	147/127	Population	YES	NS	0.453
Chong-ge Y	2013	Asians	452/373	Hospital	YES	NS	0.185
IL1B+3954							
Alian G	1999	Europeans	107/128	Hospital	YES	NS	0.131
Chung-Ming H	2001	Asians	104/103	Population	YES	NS	0.060
N Buchs	2001	Europeans	273/109	Population	YES	NS	0.147
E.L. Kaijzel	2002	Europeans	319/245	Hospital	YES	NS	0.243
Stephana G	2002	Europeans	273/109	Hospital	YES	NS	0.171
JF Camargo	2004	Europeans	172/392	Population	NO	NS	NA
Stephanie K	2004	Mix*	25/31	Population	NA	NS	0.068
A. Pawlik	2005	Europeans	93/102	Population	YES	NS	0.131
Barbara T	2006	Europeans	126/178	Population	YES	NS	0.158
A. Arman	2006	Europeans	94/104	Population	YES	S	0.116
Leyla K1	2006	Europeans	156/120	Population	NA	NS	NA
Leyla K2	2006	Europeans	512/471	Population	NA	NS	NA
Chong-ge Y	2007	Asians	235/227	Hospital	YES	S	0.096
Tetsuo K	2007	Asians	96/100	Population	YES	S	0.062
Steven L	2008	Africans	129/84	Hospital	YES	NS	0.101
Alyssa K	2008	Europeans	1240/1096	NARAC	YES	NS	0.755
I. Allam	2013	Europeans	147/127	Population	YES	NS	0.183
Chong-ge Y	2013	Asians	452/373	Hospital	YES	NS	0.140

30 Europeans, 1 African; NARAC, North American Rheumatoid Arthritis Consortium; HWE, Hardy-Weinberg equilibrium; Result, The association between IL1B gene and PD; NS, No significant; S, Significant; NA: Not applicable.

Table 2. Meta-analyses of the *IL1B* − 31, *IL1B* − 511 and *IL1B* + 3954 polymorphisms with RA.

Genetic locus	Genetic model	Ethnicity	Stages*	Cases/Controls	OR (95% CI)	*P* value	I²	Power
IL1B − 31	Overall (C vs T)	Overall	5	2214/2466	0.96 (0.88 - 1.05)	0.38	0.00%	0.990
	Dominant (CC/CT vs TT)	Overall	3	2064/1922	0.96 (0.84 - 1.09)	0.50	0.00%	0.976
	Recessive (CC vs CT/TT)	Overall	3	2064/1922	0.99 (0.82 - 1.18)	0.88	0.00%	0.833
	Additive (CC vs TT)	Overall	3	1120/1028	0.97 (0.80 - 1.18)	0.78	0.00%	0.833
IL1B − 511	Overall (T vs C)	Overall	16	4491/4006	0.95 (0.89 - 1.01)	0.13	12.00%	1.000
		Europeans	11	3387/2823	0.93 (0.87 - 1.01)	0.08	0.00%	0.998
		Asians	3	796/703	0.96 (0.83 - 1.11)	0.56	14.00%	0.701
		Africans	1	272/176	0.78 (0.53 - 1.15)	0.22	NA	0.238
		Colombia	1	302/209	1.02 (0.77 - 1.35)	0.87	NA	0.291
	Dominant (TT/TC vs CC)	Overall	15	4466/3975	0.93 (0.85 - 1.01)	0.09	35.00%	1.000
		Europeans	10	3362/2792	0.89 (0.81 - 0.99)	**0.03**	**15.00%**	**0.999**
		Asians	3	796/703	1.00 (0.68 - 1.46)	0.98	56.00%	0.567
		Africans	1	136/88	0.63 (0.29 - 1.36)	0.24	NA	0.141
		Colombia	1	172/392	1.47 (0.96 - 2.26)	0.08	NA	0.229
	Recessive (TT vs TC/CC)	Overall	15	4466/3975	0.94 (0.83 - 1.06)	0.29	0.00%	0.994
		Europeans	10	3362/2792	0.96 (0.82 - 1.13)	0.63	0.00%	0.924
		Asians	3	796/703	0.87 (0.69 - 1.11)	0.27	0.00%	0.593
		Africans	1	136/88	0.77 (0.44 - 1.35)	0.36	NA	0.254
		Colombia	1	172/392	1.05 (0.69 - 1.60)	0.82	NA	0.236
	Additive (TT vs CC)	Overall	15	2446/2129	0.92 (0.80 - 1.06)	0.24	0.00%	0.994
		Europeans	10	1915/1530	0.90 (0.76 - 1.06)	0.21	0.00%	0.924
		Asians	3	386/355	0.93 (0.69 - 1.24)	0.62	29.00%	0.593
		Africans	1	68/44	0.57 (0.25 - 1.33)	0.20	NA	0.254
		Colombia	1	77/200	1.39 (0.82 - 2.36)	0.22	NA	0.236
IL1B + 3954	Overall (T vs C)	Overall	15	3670/3151	1.19 (1.00 - 1.42)	**0.06**	65.00%	0.988
		Europeans	10	2561/2162	1.06 (0.97 - 1.17)	0.20	43.00%	0.937
		Asians	4	887/803	1.59 (0.66 - 3.83)	0.30	84.00%	0.214
		Africans	1	129/84	0.86 (0.49 - 1.48)	0.58	NA	0.101
	Dominant (TT/TC vs CC)	Overall	16	4313/3711	1.15 (0.97 - 1.36)	0.12	57.00%	1.000
		Europeans	11	3297/2824	1.06 (0.95 - 1.17)	0.30	0.00%	0.999
		Asians	4	887/803	1.64 (0.64 - 4.18)	0.30	84.00%	0.353
		Africans	1	129/84	0.72 (0.38 - 1.33)	0.29	NA	0.134
	Recessive (TT vs TC/CC)	Overall	14	3645/3120	1.11 (0.88 - 1.40)	0.38	32.00%	0.626
		Europeans	9	2629/2223	1.06 (0.84 - 1.34)	0.61	34.00%	0.610
		Asians	4	887/803	2.95 (0.59 - 14.76)	0.19	NA	0.058
		Africans	1	129/84	3.35 (0.38 - 29.16)	0.27	NA	0.051
	Additive (TT vs CC)	Overall	14	2580/2268	1.13 (0.90 - 1.43)	0.30	37.00%	0.626
		Europeans	9	1704/1477	1.08 (0.85 - 1.38)	0.51	39.00%	0.610
		Asians	4	772/731	3.34 (0.67 - 16.76)	0.14	NA	0.058
		Africans	1	104/60	2.98 (0.34 - 26.13)	0.32	NA	0.051

Stages*: Amount of Stages; NA: Not applicable.

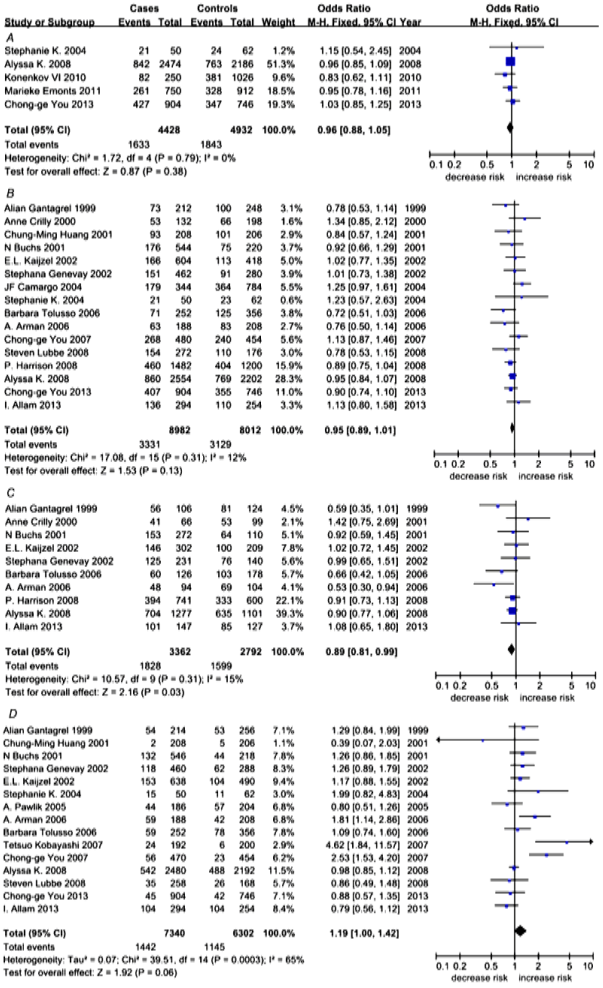

Figure 2. Forest plots of the three SNPs with RA. A) Forest plot of *IL1B* − 31 in overall analysis; B) Forest plot of *IL1B* − 511 in overall analysis; C) Forest plot of Dominant model of *IL1B* − 511 in Europeans; D) Forest plot of *IL1B* + 3954 in overall analysis.

bias was found for the meta-analyses of the three SNPs (**Figure 3**).

4. DISCUSSION

In the current meta-analyses, we summarized the associations of three *IL1B* variants with RA from 21 studies (22 stages) among 5888 cases and 5760 controls. Our results showed a trend of association between *IL1B* + 3954-T and RA (**Table 2** and **Figure 2**) and a significant association under the dominant model between *IL1B*-511-T and RA in Europeans (**Table 2** and **Figure 2**).

Single nucleotide polymorphisms (SNPs) occur in a high frequency in the human genome, which may affect the function of genes [44]. *IL1B* + 3954 in the exon 5 and *IL1B* − 511 in the promoter are two key polymorphisms of *IL1B* that play an important role in inflammatory diseases [9]. Previous studies proved that *IL1B*-511-T in-

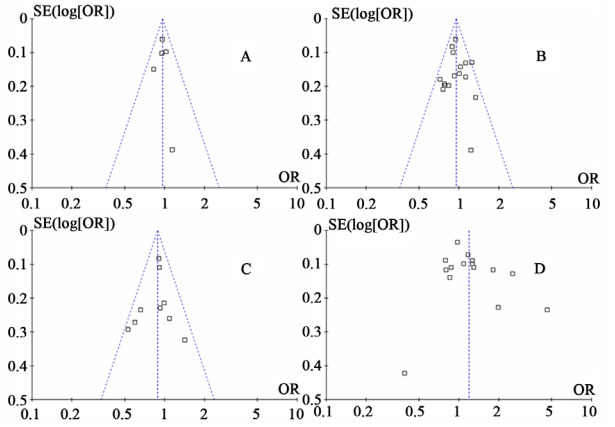

Figure 3. Funnel plots of three SNPs with RA. A) Funnel plot of *IL1B* − 31 in overall analysis; B) Funnel plot of *IL1B* − 511 in overall analysis; C) Funnel plot of Dominant model of *IL1B* − 511 in Europeans; D) Funnel plot of *IL1B* + 3954 in overall analysis.

creased LPS-induced IL-1β production by 2 - 3 folds and showed higher levels of IL-1Ra [45]. Different conclusions were shown for *IL1B* + 3954-T. Some researches indicated that it might increase plasma levels of IL-1β [10,46], but some others found it had no influence or reduced IL-1 levels [16,20,47]. *IL1B* − 511 and *IL1B* + 3954 showed a wide association with diseases like gastric cancer [48,49], breast cancer [50], aspirin-tolerant asthma [51], left ventricular systolic dysfunction [52], hip osteoarthritis [53] and RA [10,21-24,29].

Several other RA association studies observed dominant effect among a handful of SNPs such as −607A/C polymorphism of *IL*-18 gene [54], −670A/G polymorphism of *FAS* gene [55], rs1343151 and rs10489629 of *IL*-23*R* gene [56] and −173G/C polymorphism *MIF* gene [57]. The significant association of *IL1B*-511-T polymorphism under the dominant model may provide a new hint in the pathogenesis of RA.

Significant heterogeneity showed in the overall analysis (I^2 = 65%, **Table 2**) and dominant model (I^2 = 57%, **Table 2**) of *IL1B* + 3954. A subgroup study by ethnicity (**Table 2**) showed that significant heterogeneity was only found in Asians (I^2 = 56% in dominant model of *IL1B* − 511 in Europeans, I^2 = 84% in overall analysis and dominant model of *IL1B* + 3954 in Europeans). Frequency of *IL1B*-511-C and in Asians (Hapmap-HCB) is 0.547 that is lower to 0.642 in Europeans (Hapmap-CEU). And the allele frequency of *IL1B*+3954-C and in Asians (Hapmap-HCB) is 0.988 that is much higher to 0.792 in Europeans (Hapmap-CEU). A further analysis of the two polymorphisms showed a non-significant ethnic difference between Asians and Europeans (*IL1B* − 511: Fst = 0.0094; *IL1B* + 3954: Fst = 0.0988). A further power analysis suggested there was a lack of power for the subgroup meta-analysis in Asians (power = 0.701 in *IL1B*-

511, power = 0.214 in *IL1B* + 3954, **Table 2**), suggesting that the non-significant association in Asians might be due to the small sample size in the existing case-control association studies in Asian population. In contrast, the power in the meta-analysis in European populations for *IL1B* − 511 and *IL1B* + 3954 polymorphisms are 0.998 and 0.937 (**Table 2**).

Compared with the previous two meta-analysis studies [24,58] about the polymorphisms of *IL1B* and RA, our meta-analyses included 13 and 8 more case-control studies than the studies by P. Harrison *et al*. [24] and Young LEE *et al*. [58], respectively. Our research showed that *IL1B* − 511 was significantly associated with RA in Europeans under the dominant model, and a trend association of *IL1B* + 3954 with RA. Moreover, our study grouped Turkish population into Caucasians instead of Asians in the subgroup meta-analysis according to the fact that the ancestors of major Turkish population were from Europe [59-61]. We performed HWE test for the controls in all the involved studies, and excluded one [20] that was included in previous meta-analysis [58]. With an enhanced power and stricter selection criteria, our meta-analyses produced a more reliable conclusion than the previous meta-analysis studies.

However, our study presented several limitations that needed to be carefully considered. Firstly, there are only a limited number of associations in non-Caucasian populations. A lack of power in the non-Caucasian studies suggested that non-significant results in Asians and other population needed to be taken with caution. Future studies with larger samples size are required to establish the association of *IL1B* polymorphisms with RA. Secondly, RA is a complex disease that different physiological status of RA may exist in the cases. All the existing case-control studies didn't perform a stratified analysis by the RA disease stage. This may partially explain the discrepancies in the current case-control studies. Thirdly, genetic heterogeneity may exist in *IL1B* since there are 826 known *IL1B* polymorphisms. Our meta-analyses only focused on three *IL1B* SNPs that might not fully represent the overall contribution of *IL1B* variations. Other *IL1B* polymorphisms needed to be analyzed for their contribution to RA in the future. Fourthly, the positive findings of current study might not reach a very precise statistical significance by the certain extent multiple testing in our analyses.

In conclusion, our meta-analysis observed a trend association of *IL1B* + 3954-T with RA and a significant association under the dominant model between *IL1B* − 511-T and RA in Europeans. Further researches are required to confirm our findings and to discover the underlying mechanisms of other polymorphisms of *IL1B* that might contribute to the risk of RA.

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