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ORIGINAL ARTICLE

Association of interleukin-6 promoter polymorphism with rheumatoid arthritis: a meta-analysis with trial sequential analysis

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Abstract

Objectives The association of interleukin-6 (IL-6) -174G/C (rs1800795) and IL-6 -572G/C (rs1800796) single-nucleotide polymorphism (SNP) with the risk of acquiring rheumatoid arthritis (RA) was inconsistent among previous studies. This paper aims to investigate the association between IL-6 promoter polymorphism with RA in different ethnics.

Methods Relevant studies were searched using Medline and Google Search engines; STATA software was used to perform the meta-analysis. Pooled odds ratios (OR) were calculated to estimate the potential genetic associations. Subgroup analysis and sensitivity analysis were applied to explore the sources of heterogeneity. Lastly, we used TSA (trial sequential analysis) software to verify the reliability of meta-analysis results.

Results A total of 18 studies were included, involving 8116 subjects (3820 RA patients and 4296 controls). We found a tendency to associate RA with the IL-6 -174G/C allele in Asians (C vs G: OR = 4.56, 95% CI = 1.85–11.23; $P < 0.001$); with IL-6 -572G/C genotype or allele frequencies, there was no statistical differences between RA patients and controls ($P > 0.05$). TSA results indicate that the current meta-analysis can draw conclusions.

Conclusions IL-6-174G/C gene polymorphism were associated with increased risk of RA in Asians, but not in Caucasians. There was no association between IL-6 -572G/C gene polymorphism and the risk of RA.

Key Points

- *Although the association between interleukin-6 (IL-6) promoter polymorphism and rheumatic arthritis (RA) has been discussed in the previous meta-analysis, their conclusions are inconsistent.*
- *In this study, trial sequential analysis (TSA) was introduced into the meta-analysis, and the following two important conclusions were confirmed: (1) IL-6-174G/C gene polymorphism was associated with increased risk of RA in Asians, but not in Caucasians. (2) There was no association between IL-6 -572G/C gene polymorphism and the risk of RA.*

Keywords IL-6 · Meta-analysis · Polymorphism · Rheumatic arthritis · TSA

Introduction

Rheumatoid arthritis (RA) is a common and complex systemic autoimmune disease characterized by the chronic inflammatory synovitis and destructive changes in the bone; its multiple organ feature can lead to severe disability and even death [1]. Although the exact immunopathogenesis of arthritic inflammation is unclear, immunological dysregulation by inflammatory cytokines have been shown to play important roles in the occurrence and progression of RA [2, 3]. There was evidence that synovial cells, infiltrated monocytes/macrophages, and lymphocytes in synovial tissues of RA patients can produce a large number of cytokines and inflammatory mediators by means of

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autocrine or paracrine and participate in the pathogenic process of RA [4]. Interleukin-6 (IL-6) is one of these pro-inflammatory cytokines; the levels of IL-6 and soluble IL-6 receptor (sIL6R) in serum and synovial fluid of RA patients were significantly higher than those of healthy subjects [5, 6].

IL-6 comes from a wide range of sources and can be produced by various types of lymphoid and non-lymphoid cells. IL-6 gene is located in region 1 of the short arm of chromosome 7, with a total length of 5 kb, consisting of 5 exons and 4 introns, showing genetic polymorphism [7]. Recently, it has been shown that -174G/C (rs1800795) and -572G/C (rs1800796) polymorphisms of IL-6 promoter affect the expression of IL-6 [8–11]. However, these positive associations have not been consistently replicated. For example, two studies conducted in India about IL-6-174G/C failed to detect any association with RA [12, 13]. Besides, multiple studies also reported no difference in distribution between alleles and genotypes in RA patients and controls [14–19]. Interestingly, almost all studies from China have shown that C alleles could increase the susceptibility to RA [20–24], but You et al. did not find this conclusion [8]. On the other hand, Zhuang et al. proposed that G allele of IL-6 -572G/C may have protective effect against RA [25]; however, other studies have not drawn that conclusion [10, 14, 26]. These discrepancies could be due to the effects of genotyping method differences, publication bias, ethnic differences, and small sample size. In our study, we performed a meta-analysis to overcome the limitations of individual studies and resolve disagreements in their results.

In epidemiological studies, the size of the sample has a decisive effect on the reliability of research conclusions. As a statistical method of calculating the combined effects of multiple research subjects, a meta-analysis not only expands the sample size but also enhances the accuracy and robustness of the results. However, meta-analyses are constantly updated as new studies continue to be included. There is evidence that $P < 0.05$ is repeatedly used for statistical difference test; the probability of type I errors (false positives) is between 10 and 30% [27–29]. To minimize the increased risk of repetitive hypothesis testing due to inclusion of new research, trial sequential analysis (TSA) was introduced into this meta-analysis. With this meta-analysis, we aimed to determine the overall association of IL-6 gene rs1800795 and rs1800796 polymorphism with RA risk and to assess whether the association varies by ethnicity. We also searched the GWAS database to verify the robustness of the results.

Materials and methods

Search strategy

We performed a comprehensive search in Web of Science, Chinese Biomedical Database (CBM), Chinese National Knowledge Infrastructure (CNKI), and PubMed, using the following keywords: interleukin-6, IL-6, rheumatoid arthritis, gene, polymorphisms, and promoter. In addition, eligible publications in the bibliography list of relevant papers were evaluated. Final retrieval will take place in July 2020, without language or date constraints.

Inclusion and exclusion criteria

Included studies must meet all the following criteria: (1) case–control studies about IL-6 polymorphisms and RA in human beings; (2) sufficient genotype data presented to calculate the odds ratios (ORs) and 95% confidence intervals (CIs); and (3) full text in English or Chinese available. The exclusion criteria were as follows: (1) not a case–control design; (2) genotype frequency not reported; and (3) abstracts and reviews.

Data extraction and quality assessment

Relevant data were evaluated carefully and independently by two reviewers (Ming Shao and Huimin Xie), and disagreement was resolved with another author (Faming Pan). The relevant data were extracted: first author, publication year, country of the study population, the number of case–control samples, genotyping method, study site, genotype, and allele frequencies in each case–control study. The probability value (p value) of Hardy–Weinberg equilibrium (HWE) was also calculated. The quality of the included studies was assessed based on the Newcastle–Ottawa Scale (NOS) by two reviewers independently [30].

Statistical analyses

For included articles, the HWE of genotypes in the controls was evaluated using the Pearson chi-square test. The role of allele C in the risk of RA was targeted. Thus, an analysis was made using allelic model (C versus G), homozygote model (CC versus GG), heterozygote model (GC versus GG), dominant model (GC + CC versus GG), and recessive model (CC versus GC + GG). Between-study heterogeneities were evaluated with I^2 statistic. When $P < 0.1$ or $I^2 > 50\%$, a high level of heterogeneity between studies was envisaged and random-effect model was adopted. Otherwise, analyses would be conducted with fixed-effect models (Mantel- Haenszel method). We also conducted subgroup analyses by ethnicity of participants. The effect of IL-6 -174G/C and IL-6 -572G/C on the risk of RA was measured by P value, odds ratio (OR), and 95% confidence interval (CI). $P < 0.05$ was seen as statistically significant. Ethnicity was independently determined by the two authors based on historical data combined with the original study area. Meanwhile, sensitivity

analysis was conducted by repeating analysis after omitting one study each time to estimate the effect of studies quality on the final result. Publication bias was measured using Begg's test and Egger's tests. All statistical analyses were carried out using STATA software (STATA 11.0, StataCorp, College Station, TX, USA).

Trial sequential analysis

Due to the increased risk of random errors and repeated significance tests, meta-analysis may be affected by type I errors. Trial sequential analysis (TSA) was a useful tool to verify the reliability of the results from meta-analysis by estimating the required information size (RIS) (sample size of included studies) and calculating the threshold for statistical significance. The red curves represent the O'Brien-Fleming boundary and futility boundary. The blue line represents the cumulative Z-curve. RIS represents required information size. If the Z-curve crossed RIS line, the result of meta-analysis would be conclusive. Moreover, if the Z-curve crossed the O'Brien-Fleming boundary or futility boundary, the conclusions could also be made even before it crossed the RIS. However, if the cumulative *Z* value does not cross the O'Brien-Fleming boundary or futility boundary or the RIS threshold, it means the sample size is not sufficient [31], and more studies are needed to confirm the result. TSA would be conducted in allelic model in our study. Our study set the relative ratio reduction (RRR) to 20%, the first type of error $\alpha = 0.05$, the second type of error $\beta = 0.2$, and control event proportion was an average of each included study to evaluate RIS. TSA was conducted on TSA version 0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen) [32].

Results

Characteristics of the included studies

The selection process of literature retrieval is shown in Fig. 1. To put it simply, we found 2713 references through electronic databases and other channels, and 2598 references were not associated with cytokine polymorphism in terms of titles and abstracts. Of the remaining 115 studies, 90 were excluded for not performing the IL-6 promoter polymorphisms. After full text evaluation, we excluded 7 articles for

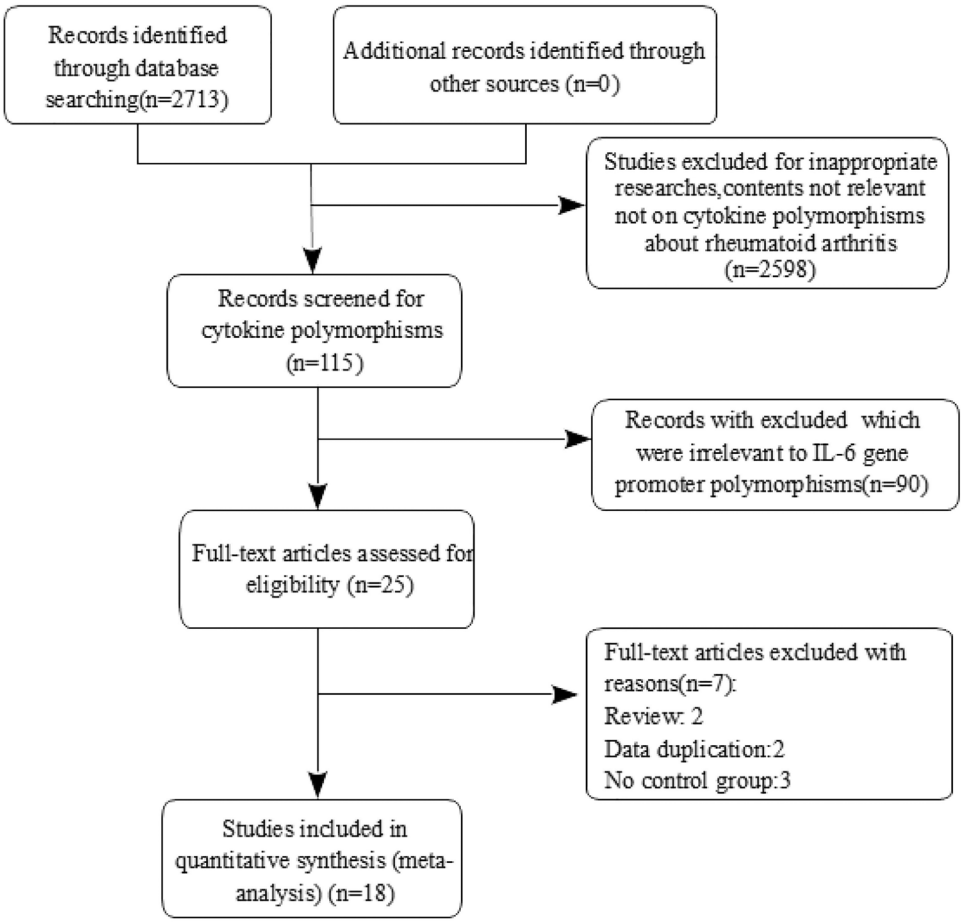

Fig. 1 Flowchart of study selection

Table 1 Characteristics of studies included in the meta-analysis

First author	Year	Country	Ethnicity	Case	Control	Genotyping method	Study site	NOS score	P_{HWE} for control	Major allele frequencies (%)	
Ad'hiah et al. [26]	2018	Iraq	Caucasian	51	45	RT-qPCR	rs1800796	8	$P<0.05$	IL-6-174G	IL-6-572G
Dar et al. [13]	2017	India	Asian	34	80	PCR-SSP	rs1800795	8	0.385		2.60
Wielioska et al. [10]	2016	Poland	Caucasian	130	112	TaqMan probe	rs1800795	8	0.701	84.21	
Amr et al. [14]	2016	Egypt	Caucasian	99	99	PCR-SSP	rs1800795;rs1800796	8	0.598; 0.847	56.38	
Li et al. [22]	2014	China	Asian	752	798	PCR–RFLP	rs1800795	7	$P<0.05$	77.53	62.12
Li et al. [23]	2014	China	Asian	256	311	TaqMan probe	rs1800795;rs1800796	8	$P<0.05$; 0.932	94.58	
Shafia et al. [12]	2014	India	Asian	150	200	PCR–RFLP	rs1800795	8	0.233	98.39	34.50
Zavaleta-Muñiz et al. [9]	2013	Mexico	Caucasian	137	102	PCR–RFLP	rs1800795;rs1800796	6	0.575; 0.362	96.71	
You et al. [8]	2013	China	Asian	452	373	PCR-HRM	rs1800795;rs1800796	7	0.672; 0.753	88.28	76.78
Arman et al. [11]	2012	Turkey	Caucasian	178	247	PCR–RFLP	rs1800795;rs1800796	8	$P<0.05$; 0.059	97.76	31.01
Emonts et al. [15]	2011	The Netherlands	Caucasian	376	463	PCR–RFLP	rs1800795	8	0.570	72.47	88.94
Panoulas et al. [16]	2009	UK	Caucasian	383	422	PCR–RFLP	rs1800795	7	0.385	59.19	
Li et al. [21]	2009	China	Asian	60	84	PCR-SSP	rs1800795;rs1800796	8	0.912; 0.848	94.79	
Lu et al. [24]	2009	China	Asian	148	120	PCR-SSP	rs1800795;rs1800796	8	0.927; 0.126	94.22	82.99
Trajkov et al. [17]	2009	Macedonia	Caucasian	85	301	PCR–SSP	rs1800795	7	0.492	68.31	15.30
Palomino-Morales et al. [18]	2009	Spain	Caucasian	311	266	TaqMan probe	rs1800795	7	0.305	64.99	
Huang et al. [20]	2007	China	Asian	120	168	PCR-SSP	rs1800795;rs1800796	8	0.907; 0.052	95.31	17.19
Pawlik et al. [19]	2005	Poland	Caucasian	98	105	PCR–RFLP	rs1800795	7	0.279;	52.46	

HWE, Hardy–Weinberg equilibrium

the following reasons: 3 were not case–control studies, 2 were review articles, and 2 were repeated data sets. Finally, 18 studies met the inclusion criteria including 3820 cases and 4296 controls. Table 1 showed the main characteristics of included studies. These 18 studies were conducted in 11 countries (number of studies): China (6); India (2); Iraq (1); Poland (2); Mexico (1); Turkey (1); the Netherlands (1); the UK (1); Macedonia (1); Egypt (1); and Spain (1). There were 4 studies in which the genotype distribution of the control group did not conform to HWE ($P < 0.05$) [10, 22, 23, 26]. The NOS results showed that these studies had scores ranging from 6 to 8, with an average score of 7.56. Therefore, the methodological quality of the selected studies is generally reliable. Table 1 shows that the inter-ethnic frequency of the major allele -174G has been found to vary enormously.

Meta-analysis results

The association and heterogeneity test results between IL-6 promoter polymorphism and RA are shown in Table 2. Overall, a significant association of IL-6 -174G/C polymorphism with an increased risk of RA was observed in the allelic model (C vs G: OR = 1.83, 95% CI = 1.31–2.54; $P < 0.001$), heterozygote model (GC vs GG: OR = 1.83, 95% CI = 1.20–2.79; $P = 0.005$), and dominant model (CC + GC vs GG: OR = 2.23, 95% CI = 1.51–3.29; $P < 0.001$), but not in the homozygote recessive models. The relationship between IL-6 -174G/C SNP and RA risk was also analysed by subgroup analysis of ethnic stratification. The result of the subgroup analysis was very interesting. In Caucasians, none of the models showed a significant association between IL-6 -174G /C polymorphism and RA risk. In contrast, IL-6 rs1800795 was significantly associated with increased RA risk in Asians. The pooled OR and 95% CI for the various genetic models were: allelic (C vs G: OR = 4.56, 95% CI = 1.85–11.23, $P = 0.001$); homozygous (CC vs GG: OR = 5.09, 95% CI = 2.35–11.04, $P < 0.001$); heterozygous (GC vs GG: OR = 4.59, 95% CI = 1.71–12.31, $P = 0.001$); dominant (GC + CC vs GG: OR = 5.27, 95% CI = 1.96–14.11, $P < 0.001$); and recessive (CC versus GC + GG: OR = 4.06, 95%CI = 1.94–8.481, $P < 0.001$). There was no statistical difference in IL-6 -572G/C polymorphism between cases and controls (Fig. 2).

TSA

To assess the risk of random errors, we performed a sequential analysis of the trials. The red vertical bars represent the amount of information required (sample size). Figure 3A and Fig. 3B showed that the cumulative Z-curve crossed the traditional boundary and the O'Brien-Fleming boundary, and Fig. 3C showed crossed the futility boundary and the RIS, suggesting there was no need for more evidence to establish an additional study of rs1800795 in RA. For IL-6 rs1800796, TSA studies showed that although the Z-curve did not cross the traditional boundary, it crossed the invalid boundary, indicating that this result would not change after more studies were included (Fig. 4). Perhaps there is really no correlation between RS1800796 polymorphism and RA.

Heterogeneity and publication bias diagnostics

We found significant heterogeneity in the interleukin-6 promoter polymorphism and RA-related information. Due to the large heterogeneity among studies, a single study included in the meta-analysis was omitted continuously, and the source was found through sensitivity analysis (Supplementary Fig. 1). Although we did not find the possible source of heterogeneity through sensitivity analysis, we searched the GWAS catalog (https://www.ebi.ac.uk/gwas/). It is a pity that rs1800795 was not found, but the results of GWAS on rs1800796 were consistent with our results (Supplementary Fig. 2). The findings indicated that no individual study influenced the overall. Begg's and Egger's tests did not suggest significant publication bias ($P > 0.05$).

Discussion

RA is a systemic autoimmune disease with progressive and destructive osteoarthropathy, and its pathogenesis is complex and unclear. Previous studies of IL-6 promoter polymorphism in RA have yielded controversial results, which is not surprising as inconsistent results are common in genetic studies of complex diseases. The most likely explanations are true genetic heterogeneity, ethnic differences, clinical heterogeneity, and small sample size. As a method, meta-analysis can obtain reliable results by expanding the sample size. However, previous meta-analysis results on the correlation between IL-6 promoter polymorphisms and RA were inconsistent [13, 33–35]. Therefore, it is useful to adopt a new method to help prove the stability of meta-analysis results. Compared with the previous meta-analysis of this topic, our study introduced the TSA method for the first time, which further proved the reliability of the current meta-analysis results. As a multifunctional cytokine, IL-6 is involved in inflammatory and immune responses. IL-6 is located on chromosome 7p21, and the expression of IL-6 can be regulated at the transcriptional level by -174G/C and -572G/C at the 5′ end [11, 36]. IL-6 promotes the proliferation and secretion of T and B lymphocytes and causes inflammatory secretion in the acute stage, leading to cartilage and bone damage in RA patients [37]. Regarding IL-6 -174G/C gene polymorphism, our meta-analysis revealed that C alleles was associated with RA risk (Fig. 2A) and increased the

Table 2 Meta-analysis results for the association between IL-6 promoter polymorphism and RA susceptibility

Model		No. of comparisons	Test of association					Test of heterogeneity			P^a	P^b
			OR	95% CI	*Z*	*P*	Model	Q	*P*	I^2 (%)		
-174G/C												
Overall	C vs G	17	**1.83**	**1.31, 2.54**	**3.56**	**< 0.001**	R	164.28	< 0.001	90.3	0.072	0.381
	CC vs GG	17	1.38	0.92, 2.06	1.56	0.118	R	36.82	0.001	59.3	0.607	0.597
	GC vs GG	17	**1.83**	**1.20, 2.79**	**2.80**	**0.005**	R	140.33	< 0.001	88.6	0.300	0.054
	CC + GC vs GG	17	**2.23**	**1.51, 3.29**	**4.05**	**< 0.001**	R	124.79	< 0.001	87.2	0.473	0.055
	CC vs GC + GG	17	1.23	1.03, 1.47	2.24	0.025	F	29.86	0.019	46.4	0.811	0.907
Caucasian	C vs G	8	1.10	0.88, 1.38	0.84	0.401	R	34.32	< 0.001	78.8	0.386	0.163
	CC vs GG	8	1.11	0.77, 1.60	0.57	0.570	R	18.18	0.011	61.5	0.653	0.356
	GC vs GG	8	1.02	0.75, 1.40	0.14	0.888	R	28.67	< 0.001	75.6	0.386	0.072
	CC + GC vs GG	8	1.38	1.04, 1.83	2.21	0.027	R	24.72	0.001	71.7	0.266	0.156
	CC vs GC + GG	8	1.14	0.85, 1.53	0.90	0.367	F	14.12	0.049	50.4	0.986	0.272
Asian	C vs G	8	**4.56**	**1.85, 11.23**	**3.30**	**0.001**	R	66.15	< 0.001	89.4	0.536	0.365
	CC vs GG	8	**5.09**	**2.35, 11.04**	**4.12**	**< 0.001**	F	7.72	0.260	22.2	0.764	0.777
	GC vs GG	8	**4.59**	**1.71, 12.31**	**3.03**	**0.002**	R	60.50	< 0.001	88.4	0.711	0.327
	CC + GC vs GG	8	**5.27**	**1.96, 14.11**	**3.30**	**< 0.001**	R	63.02	< 0.001	88.9	0.711	0.273
	CC vs GC + GG	8	**4.06**	**1.94, 8.48**	**3.72**	**< 0.001**	F	8.46	0.294	17.2	0.536	0.635
Mixed	C vs G	1	0.99	0.57, 1.74	0.03	0.977						
	CC vs GG	1	0.38	0.03, 4.24	0.79	0.436						
	GC vs GG	1	1.13	0.60, 2.14	0.38	0.702						
	CC + GC vs GG	1	1.17	0.62, 2.20	0.49	0.627						
	CC vs GC + GG	1	0.37	0.03, 4.11	0.81	0.417						
-572G/C												
Overall	C vs G	9	1.23	0.90, 1.68	1.27	0.203	R	39.85	< 0.001	79.9	0.164	0.120
	CC vs GG	9	1.40	1.04, 1.89	2.24	0.025	F	11.62	0.169	31.1	0.843	0.057
	GC vs GG	9	1.15	0.92, 1.43	1.23	0.220	F	12.07	0.098	42.0	1.000	0.000
	CC + GC vs GG	9	1.21	0.85, 1.71	1.05	0.293	R	17.54	0.025	54.4	0.164	0.493
	CC vs GC + GG	9	1.39	0.87, 2.20	1.38	0.168	R	29.08	< 0.001	72.5	0.321	0.064
Caucasian	C vs G	3	1.08	0.66, 1.77	0.30	0.762	F	3.90	0.143	48.7	0.912	0.138
	CC vs GG	3	0.79	0.14, 4.50	0.27	0.789	F	4.23	0.125	43.8	0.312	0.158
	GC vs GG	3	1.33	0.91, 1.95	1.45	0.146	F	0.32	0.571	0.0	0.326	0.065
	CC + GC vs GG	3	1.25	0.86, 1.81	1.16	0.244	F	1.49	0.475	0.0	0.721	0.587
	CC vs GC + GG	3	0.78	0.24, 2.49	0.43	0.669	F	5.41	0.132	42.7	0.092	0.235
Asian	C vs G	5	1.30	0.80, 2.11	1.05	0.292	R	35.69	< 0.001	88.8	0.806	0.819
	CC vs GG	5	1.46	1.06, 2.01	2.30	0.022	F	7.25	0.123	44.8	0.806	0.985
	GC vs GG	5	0.88	0.49, 1.59	0.42	0.675	R	10.57	0.032	62.1	0.806	0.337
	CC + GC vs GG	5	1.16	0.60, 2.27	0.44	0.661	R	15.92	0.003	74.9	0.221	0.958
	CC vs GC + GG	5	1.58	0.93, 2.69	1.70	0.089	R	23.36	< 0.001	82.9	1.000	0.619
Mixed	C vs G	1	1.24	0.80, 1.91	0.96	0.339						
	CC vs GG	1	1.40	0.32, 6.08	0.45	0.656						
	GC vs GG	1	1.31	0.77, 2.34	1.00	0.316						
	CC + GC vs GG	1	1.32	0.78, 2.22	1.04	0.296						
	CC vs GC + GG	1	1.18	0.90, 1.56	1.20	0.231						

RA rheumatoid arthritis; *CI* confidence interval; *No.* number of studies; *OR* odds ratio; P^a Begg's test; P^b Egger's test; *R* random-effects model; *F* fixed-effects model; boldface indicates statistical significance

susceptibility of RA in the study. When the analysis was stratified by ethnicity, we found a statistically significant relationship between rs1800795 and the increased RA risk in the Asian population under all genetic models, but not in Caucasians. As far as we know, the inter-ethnic frequency of the minor allele -174C has been found to vary

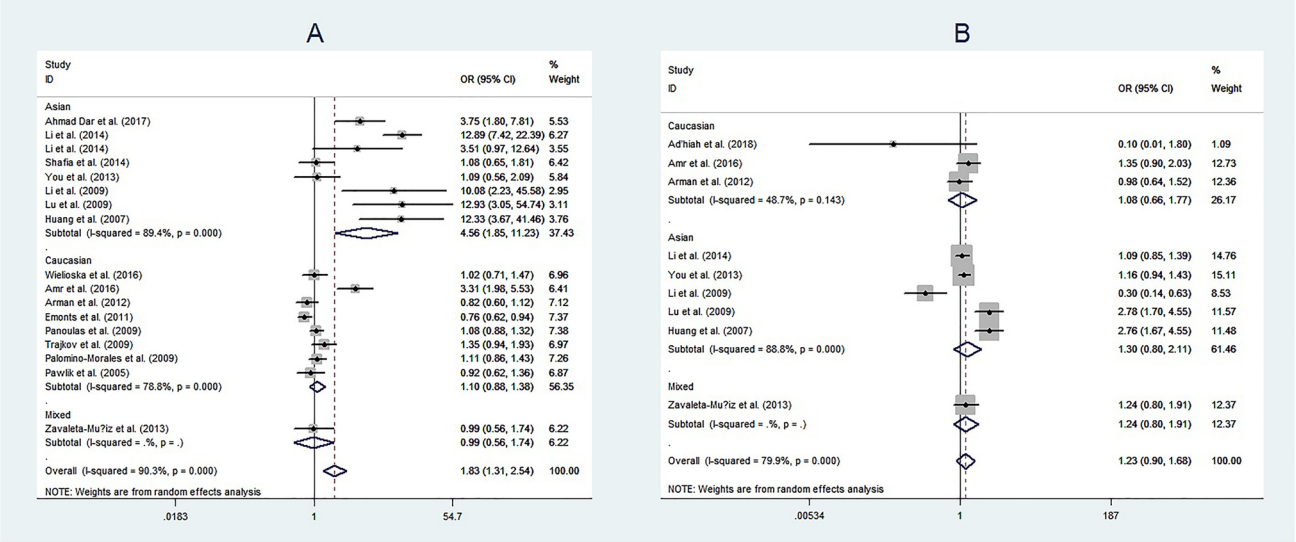

Fig. 2 The association between IL-6 promoter polymorphism and RA susceptibility in allele model: **A** rs1800795; **B** rs1800796

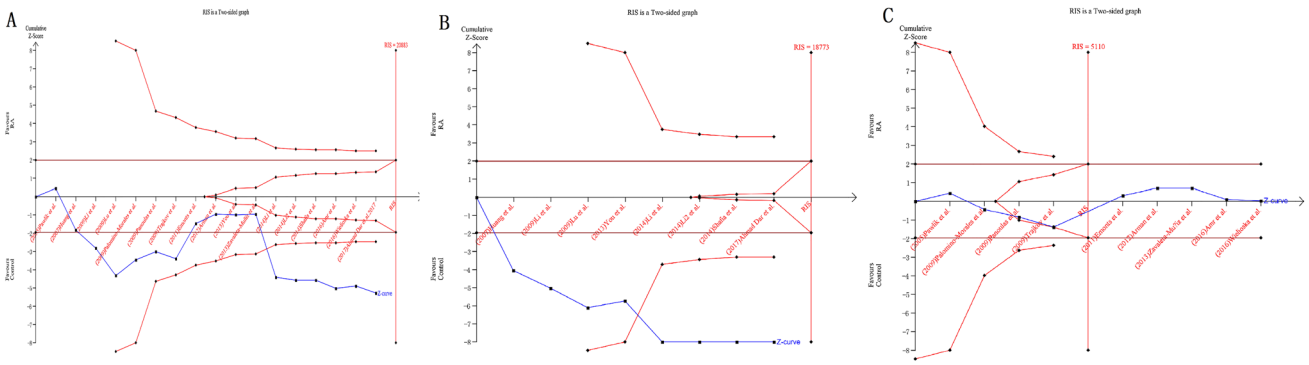

Fig. 3 TSA of the analysis on the association between IL-6–174 G/C polymorphism and the risk of RA under allele model: **A** Overall; **B** Asians; **C** Caucasians

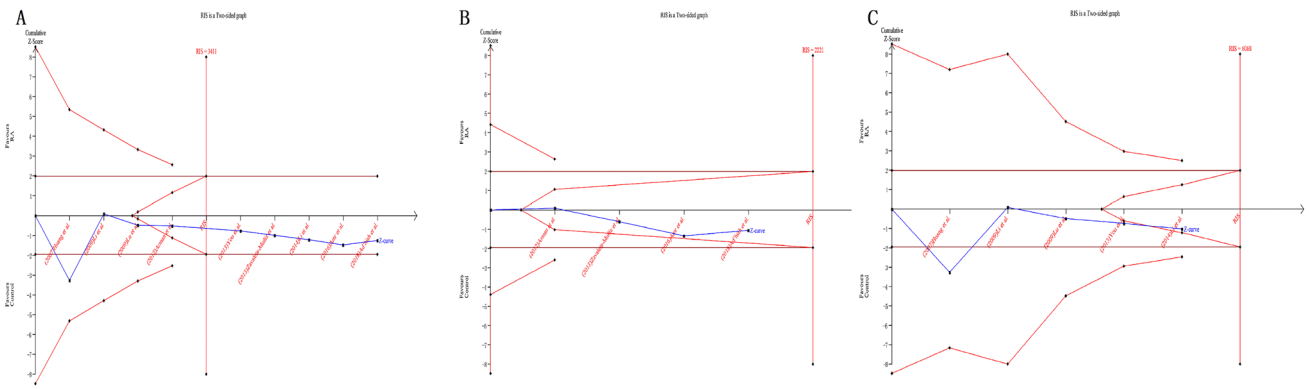

Fig. 4 TSA of the analysis on the association between IL-6–572 G/C polymorphism and the risk of RA under allele model: **A** Overall; **B** Caucasians; **C** Asians

enormously. The frequency of this allele has been reported to be higher in Europeans (50%), but lower in the Afro-Caribbeans (5%) [38]. There is growing evidence that some ethnically specific polymorphisms are functional, suggesting that they may play an important role in disease susceptibility. Thus, this finding suggests that the association between RA and IL-6 -174G/C polymorphism varies among ethnic groups due to the frequency of their genotypes [39]. In addition, the regional differences between Europe and Asia could be a consequence of referral bias with more severe patients being referred to hospitals. The meta-analysis results of Dar et al. also reached a consistent conclusion [13], but the meta-analysis results of Lee et al. showed that the IL-6 -174G/C polymorphism may confer susceptibility to RA in Caucasians [33]. In our study, TSA analysis results show that the Z-curve intersects the TSA boundary, indicating that the current study has been able to draw reliable conclusions.

With respect to IL-6 -572G/C gene polymorphism, our study identified that no significant differences were observed in the genotypes and alleles frequencies (Fig. 2B) between RA and controls. According to the TSA results, we believe that there is no correlation between rs1800796 alleles and RA. However, the meta-analysis of Zhang et al. showed that the IL-6 -572G/C gene polymorphism was associated with the risk of RA [34]. This is obviously contrary to the conclusion of our meta-analysis. In addition, the results of the two existing meta-analyses were consistent with our conclusion [33, 35]. On the other hand, although there may be different definitions of ethnicity, the results of Pacheco-Soto et al. support our conclusions [40]. Besides, all studies have shown no association between the IL-6 -572G/C gene polymorphism and RA susceptibility in Caucasians [9, 10, 14, 26]. However, Huang et al. and Lu et al. found that the rs1800796 C allele increased the risk of RA in Asians [20, 24]. Therefore, we believe that there is no correlation between IL-6 -572G/C gene polymorphism and RA in Caucasians, and there is no need to conduct redundant research in the future. TSA has shown that the results of the current study can be concluded. The results of the GWAS study were consistent [41].

However, there are some limitations to our study. First, the subgroup analysis was based on ethnicity, not other variables. There has been a lot of debate about the definition of ethnicity, so that might affect the analysis. In addition, it is well known that certain gene frequencies vary in disease duration, age, disease activity, and so on. Second, this meta-analysis found significant heterogeneity between studies, and possible causes of heterogeneity, such as lifestyle and environmental exposure, were not examined, which may have distorted the analysis. Third, although TSA can effectively support the conclusions in our meta-analysis, TSA will increase the risk of false negative (type II error) while strictly controlling false positive error (type I error). In other words, IL-6 -572G/C gene polymorphism may influence the RA susceptibility, but there is no such relationship in our analysis.

Conclusion

In conclusion, this meta-analysis suggests that IL-6 -174G/C gene polymorphism were associated with increased risk of rheumatic arthritis in Asians, but not in Caucasians. There was no correlation between IL-6 -572G/C gene polymorphism and the risk of RA.

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Declarations

Ethics approval We have sought approval from the biomedical ethics committee of Anhui Medical University.

Conflict of interest Ming Shao, Huimin Xie, Hui Yang, Wei Xu, Yuting Chen, Xing Gao, Shiyang Guan, Shengqian Xu, Zongwen Shuai and Faming Pan declare that they have no conflict of interest.

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