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# The association between interleukin-6 polymorphisms and rheumatoid arthritis: a meta-analysis

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**Abstract**
*Objective* The aim of this study was to determine whether the functional interleukin-6 (IL-6) promoter −174 G/C and −572 G/C polymorphisms confer susceptibility to rheumatoid arthritis (RA) in ethnically different populations.
*Methods* Meta-analysis was conducted on the associations between these IL-6 polymorphisms and RA.
*Results* A total of nine studies involving 3,851 subjects (RA 2,053 and controls 1,798) were considered in this study and ethnicity-specific meta-analysis was performed on European subjects. In all study subjects, meta-analysis revealed a trend toward to an association between RA and the IL-6 −174 G allele (odds ratio [OR] = 0.699, 95 % confidence interval [CI] = 0.463–1.054, $p = 0.088$). Stratification by ethnicity indicated a significant association between RA and the IL-6 −174 G/C polymorphism in Europeans using the dominant (OR = 0.329, 95 % CI = 0.155–0.699, $p = 0.004$) and recessive (OR = 0.823, 95 % CI = 0.679–0.997, $p = 0.047$) models. Meta-analysis of the IL-6 −572 G/C polymorphism showed no association between RA and the IL-6 −572 G allele in all study subjects (OR = 1.641, 95 % CI = 0.613–4.397, $p = 0.324$).
*Conclusions* This meta-analysis shows that the IL-6 −174 G/C polymorphism may confer susceptibility to RA in Europeans.

**Keywords** Interleukin-6 · Polymorphism · Rheumatoid arthritis · Meta-analysis

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## Introduction

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 remains unknown, a genetic component has been established by twin and family studies, in which it was estimated to contribute as much as 60 % to RA susceptibility. Furthermore, human leukocyte antigen (HLA) class II molecules have been shown to be strongly associated with RA, and genome-wide association studies and family studies suggest that this association accounts for one-third of genetic susceptibility and that non-HLA genes are also involved [1, 2].

Interleukin-6 (IL-6) is a multifunctional cytokine involved in the inflammatory response and in the modulation of immune responses, including B-cell and T-cell differentiation. IL-6 is a B-cell differentiation cytokine that induces the final maturation of activated B cells into immunoglobulin-secreting plasma cells [3], and is overexpressed in the affected tissues of RA patients [4]. A humanized antihuman IL-6 receptor monoclonal antibody, tocilizumab, is designed to block IL-6 signaling and is used as an effective therapeutic agent for RA involving IL-6 overproduction [5]. Furthermore, IL-6 overproduction in RA may be due to polymorphisms in regions with regulatory functions. The *IL-6* gene is located on chromosome

7p21, and of the several known polymorphisms in its promoter region, two polymorphisms, namely –174 G/C and −572 G/C, are known to be associated with IL-6 production [6]. Several studies have examined the potential contributions made by IL-6 polymorphisms to RA susceptibility [7–15], but these studies have produced diverse results.

Individual studies based on small sample sizes have insufficient statistical power to detect positive associations and are incapable of demonstrating the absence of an association. Furthermore, the low statistical powers of individual studies could explain the contradictory published results. On the other hand, meta-analysis integrates previous research, and increases statistical power and resolution by pooling the results of independent analyses [16–18]. In the present study, we explored whether the −174 G/C and −572 G/C polymorphisms of *IL-6* promoter contribute to RA susceptibility, using a meta-analysis approach.

## Materials and methods

### Identification of eligible studies and data extraction

A literature search was conducted for studies that examined associations between IL-6 polymorphisms and RA. The MEDLINE citation index was used to identify articles in which an IL-6 polymorphism was examined in RA patients and controls (up to October 2011). In addition, all references mentioned in identified articles were reviewed to identify additional studies not indexed by MEDLINE. The following key words and subject terms were searched: "interleukin-6," "IL-6," "rheumatoid arthritis", and "RA." The following information was extracted: author, year of publication, ethnicity of the study population, demographics, numbers of cases and controls, and genotype and allele frequency information.

### Evaluation of publication bias

Funnel plots are used to detect publication bias, but they require a range of studies of varying sizes and subjective judgments, and thus we evaluated publication bias using Egger's linear regression test [19], which measures funnel plot asymmetry on a natural logarithm scale of odds ratios (ORs).

### Evaluation of statistical associations

We performed meta-analyses using (1) allelic contrast (G vs. C), (2) homozygote contrast (GG vs. CC), (3) recessive (GG vs. GC + CC), and (4) dominant models (GG + GC vs. CC). Allele frequencies of the IL-6 polymorphisms in respective studies were determined using the allele counting method. The chi-squared test was used to determine whether the observed genotype frequencies in controls conformed to the Hardy–Weinberg (H–W) equilibrium.

Point estimates of risks, ORs, and 95 % confidence intervals (CIs) were determined for each study. Cochran's $Q$-statistic was used to assess within- and between-study variations and heterogeneities [20]. The heterogeneity test was used to assess the probability of the null hypothesis that all studies were evaluating the same effect. When the significant $Q$-statistic ($p < 0.10$) indicated heterogeneity across studies, the random effects model was used for the meta-analysis, but when heterogeneity was not indicated across studies, the fixed effects model was used. Fixed effects assume that genetic factors have similar effects on RA susceptibility across all studies and that observed variations between studies are caused by chance alone [20]. The random effects model assumes that different studies show substantial diversity, and assesses both within-study sampling errors and between-study variances [21]. The random effects model is used in the presence of significant between-study heterogeneity. We quantified the effect of heterogeneity by using a recently developed measure, namely, $I^2 = 100\% \times (Q - df)/Q$ [22]. $I^2$ ranges between 0 and 100 % and represents the proportion of inter-study variability attributable to heterogeneity rather than chance. $I^2$ values of 25, 50, and 75 % were defined as low, moderate, and high estimates, respectively. Statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ, USA).

## Results

### Studies included in the meta-analysis

Sixty-one studies were identified after electronic and manual searches and 12 were selected for a full-text review based on title and abstract details [7–15, 23–25]. Three of these 13 studies were then excluded because they contained no extractable data [10, 23–25]. The remaining nine studies addressed the IL-6 polymorphism and RA and met the study inclusion criteria [7–15]. These studies involved in total 3,851 subjects (RA 2,053 and controls 1,798) and comprised seven European, one Asian, and one Turkish population (Table 1). Given the populations available, ethnicity-specific meta-analysis was performed only on the European population. Six studies examined the IL-6 −174 G/C polymorphism, two the IL-6 −572 G/C polymorphism, and one −597G/A, 565G/A, −622G/A, the AT-rich mini satellite in the 3′ flanking region, and the *Msp*I and

**Table 1** Characteristics of the individual studies included in the systematic review and meta-analysis

| Studies | Country | Population | Numbers | | Polymorphisms studied | Findings (polymorphisms associated with RA) |
|---|---|---|---|---|---|---|
| | | | RA | Control | | |
| Arman et al. [7] | Turkey | Turkish | 425 | 247 | −174 G/C, −572 G/C,−597 G/A | NS |
| Palomino-Morales et al. [8] | Spain | European | 311 | 226 | −174 G/C | NS |
| Trajkov et al. [9] | Macedonia | European | 401 | 379 | −174 G/C, 565 G/A | NS |
| Panoulas et al. [10] | United Kingdom | European | 422 | 383 | −174 G/C | NS |
| Huang et al. [11] | China | Asian | 120 | 168 | −174 G/C, −572 G/C | −174 G/C ($p < 0.001$)<br>−572 G/C ($p < 0.001$) |
| Pawlik et al. [12] | Poland | European | 98 | 105 | −174 G/C | NS |
| Martinez et al. [13] | Spain | European | 157 | 163 | −622 G/A | NS |
| Crilly et al. [14] | United Kingdom | European | 95 | 55 | AT-rich minisatellite in 3′ flanking region | NS |
| Fugger et al. [15] | Denmark | European | 24 | 72 | *Msp*I and *Bgl*II RFLP | NS |

*RA* rheumatoid arthritis, *NS* not significant, *RFLP* restriction fragment length polymorphism

**Table 2** Meta-analysis of the association between the IL-6 promoter −174 G/C polymorphism and RA

| Polymorphism | Population | No. of studies | Test of association | | | Test of heterogeneity | | |
|---|---|---|---|---|---|---|---|---|
| | | | OR | 95 % CI | *p* value | Model | $I^2$ | *p* value |
| G versus C allele | Overall | 6 | 0.699 | 0.463–1.054 | 0.088 | R | 89.7 | 0.000 |
| | European | 4 | 0.975 | 0.849–1.121 | 0.724 | F | 41.5 | 0.162 |
| | Asian | 1 | 0.074 | 0.022–0.248 | $<1.0 \times 10^{-8}$ | NA | NA | NA |
| | Turkish | 1 | 0.460 | 0.636–0.583 | $7.4 \times 10^{-5}$ | NA | NA | NA |
| GG + GC versus CC | Overall | 6 | 0.345 | 0.169–0.705 | 0.004 | R | 86.7 | 0.000 |
| (dominant) | European | 4 | 0.329 | 0.155–0.699 | 0.004 | R | 86.5 | 0.000 |
| | Asian | 1 | 0.028 | 0.002–0.484 | 0.014 | NA | NA | NA |
| | Turkish | 1 | 0.770 | 0.457–1.296 | 0.326 | NA | NA | NA |
| GG versus GC + CC | Overall | 6 | 0.702 | 0.480–1.027 | 0.068 | R | 77.6 | 0.000 |
| (recessive) | European | 4 | 0.823 | 0.679–0.997 | 0.047 | F | 0 | 0.658 |
| | Asian | 1 | 0.048 | 0.014–0.161 | $8.6 \times 10^{-7}$ | NA | NA | NA |
| | Turkish | 1 | 0.820 | 0.597–1.126 | 0.219 | NA | NA | NA |
| GG versus CC | Overall | 6 | 0.580 | 0.329–1.021 | 0.059 | R | 76.8 | 0.001 |
| | European | 4 | 0.781 | 0.590–1.034 | 0.084 | F | 30.4 | 0.229 |
| | Asian | 1 | 0.176 | 0.007–4.372 | 0.289 | NA | NA | NA |
| | Turkish | 1 | 0.242 | 0.149–0.393 | $9.5 \times 10^{-6}$ | NA | NA | NA |

*IL-6* interleukin-6, *RA* rheumatoid arthritis, *OR* odds ratio, *CI* confidence interval, *F* fixed model, *R* random model, *NA* not available

*Bgl*II restriction fragment length polymorphisms (RFLPs). Selected characteristics of these studies are summarized in Table 1. Meta-analysis was performed on the association between the above-mentioned polymorphisms and RA when there were at least two relevant studies.

## Meta-analysis of the IL-6 −174 G/C polymorphism and RA susceptibility

A summary of meta-analyses findings concerning the association between the IL-6 −174 G/C polymorphism and RA is provided in Table 2. Six studies examined the IL-6 −174 G/C polymorphism. In all study subjects, meta-analysis revealed a trend toward to an association between RA and the IL-6 −174 G allele (OR = 0.699, 95 % CI = 0.463–1.054, $p = 0.088$) (Fig. 1; Table 2). Stratification by ethnicity indicated no association between the IL-6 −174 G allele and RA in Europeans (OR = 0.975, 95 % CI = 0.849–1.121, $p = 0.724$) (Table 2). However, a significant association was found between RA and the IL-6 −174 G/C polymorphism in Europeans using the dominant (OR = 0.329, 95 % CI = 0.155–0.699,

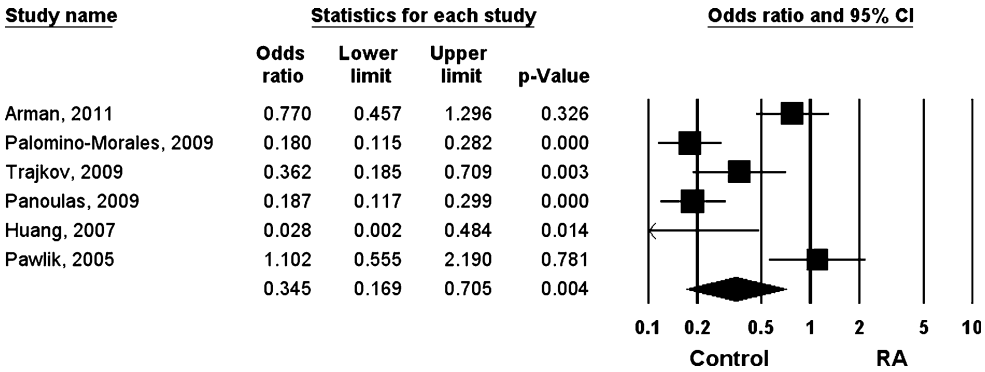


**Fig. 1** ORs and 95 % CIs of individual studies and pooled data for the association between the GG + GC of the IL-6 promoter −174 G/C polymorphism and RA in all study subjects

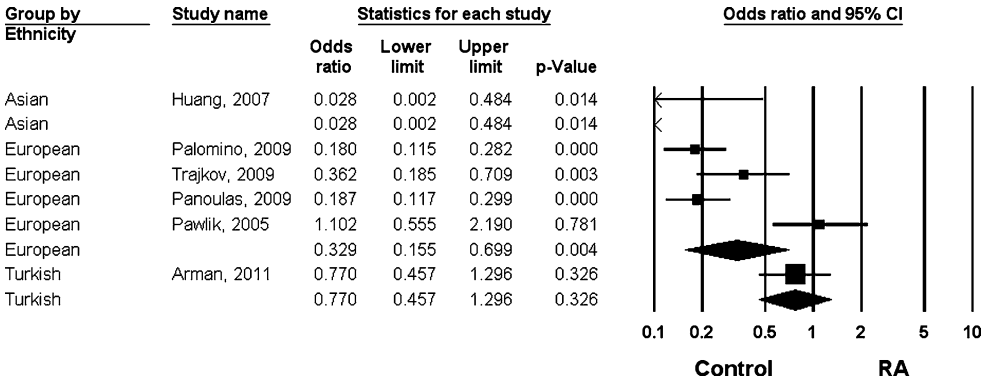


**Fig. 2** ORs and 95 % CIs of individual studies and pooled data for the association between the GG + GC of the IL-6 promoter −174 G/C polymorphism and RA in each ethnic group

$p = 0.004$) and recessive (OR = 0.823, 95 % CI = 0.679–0.997, $p = 0.047$) models, and the additive model revealed a trend toward to an association between RA and the IL-6 −174 G/C polymorphism (Fig. 2; Table 2). Furthermore, the single Asian and Turkish studies showed a significant association between RA and the IL-6 −174 G allele (Table 2).

### Meta-analysis of the IL-6 −572 G/C polymorphism and RA susceptibility

Two studies examined the IL-6 −572 G/C polymorphism. Meta-analysis of the IL-6 −572 G/C polymorphism showed no association between RA and the IL-6 −572 G allele in all study subjects (OR = 1.641, 95 % CI = 0.613–4.397, $p = 0.324$) (Table 3). However, the single Asian study revealed a significant association between the IL-6 −174 G/C polymorphism and RA by allelic contrast and the recessive model (Fig. 3; Table 3).

### Association between other IL-6 polymorphisms and RA susceptibility

One study only examined each of the following: −597 G/A, 565 G/A, −622 G/A, the AT-rich minisatellite in the 3′ flanking region, and the *Msp*I and *Bgl*II RFLPs. However, none of these IL-6 polymorphisms were found to be associated with RA.

### Heterogeneity and publication bias

The distributions of genotypes of the IL-6 polymorphisms in control groups were consistent with the H–W equilibrium, except for the IL-6 −174 G/C polymorphism in the study performed by Arman et al. [7], which could imply bias in terms of control selection or genotyping errors. However, when we excluded this study, the overall results were not substantially affected. Some between-study heterogeneity was found during the meta-analyses, but no evidence of heterogeneity was found for the IL-6 −174 G/C polymorphism in Europeans. Publication bias causes a disproportionate number of positive studies, and poses a problem for meta-analyses. Funnel plots, which are usually used to detect publication bias, were difficult to correlate, presumably because of the small number of studies included. However, Egger's regression test showed no evidence of publication bias in this meta-analysis of IL-6 polymorphisms in any of the studies included (Egger's regression test $p$ values >0.1).

## Discussion

Previous studies of IL-6 polymorphisms in RA have produced controversial results [7–15], which is not surprising because discordant results are common among genetic studies of complex diseases. Possible explanations for

**Table 3** Meta-analysis of the association between the IL-6 promoter −572 G/C polymorphism and RA

| Polymorphism | Population | No. of studies | Test of association | | | Test of heterogeneity | | |
|---|---|---|---|---|---|---|---|---|
| | | | OR | 95 % CI | *p* value | Model | $I^2$ | *p* value |
| G versus C allele | Overall | 2 | 1.641 | 0.613–4.397 | 0.324 | R | 90.3 | 0.001 |
| | Asian | 1 | 2.758 | 1.673–4.547 | $7.0 \times 10^{-5}$ | NA | NA | NA |
| | Iranian | 1 | 1.008 | 0.706–1.440 | 0.963 | NA | NA | NA |
| GG + GC versus CC | Overall | 2 | 0.739 | 0.055–9.952 | 0.820 | R | 79.6 | 0.027 |
| (dominant) | Asian | 1 | 2.432 | 0.773–7.652 | 0.129 | NA | NA | NA |
| | Iranian | 1 | 0.169 | 0.021–1.326 | 0.091 | NA | NA | NA |
| GG versus GC + CC | Overall | 2 | 1.838 | 0.653–5.169 | 0.249 | R | 88.6 | 0.003 |
| (recessive) | Asian | 1 | 3.189 | 1.784–5.703 | $9.1 \times 10^{-5}$ | NA | NA | NA |
| | Iranian | 1 | 1.109 | 0.754–1.632 | 0.600 | NA | NA | NA |
| GG versus CC | Overall | 2 | 0.898 | 0.060–13.41 | 0.938 | R | 80.9 | 0.022 |
| | Asian | 1 | 3.126 | 0.986–9.907 | 0.053 | NA | NA | NA |
| | Iranian | 1 | 0.195 | 0.025–1.553 | 0.123 | NA | NA | NA |

*IL-6* interleukin-6, *RA* rheumatoid arthritis, *OR* odds ratio, *CI* confidence interval, *F* fixed model, *R* random model, *NA* not available

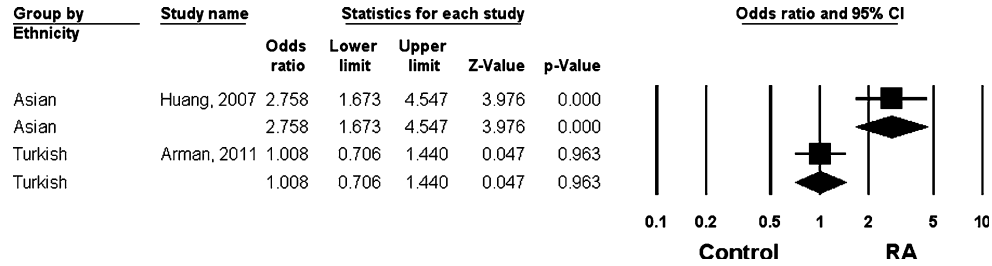


**Fig. 3** ORs and 95 % CIs of individual studies and pooled data for the association between the G allele of the IL-6 promoter −572 G/C polymorphism and RA in each ethnic group

controversial results include clinical heterogeneity, ethnic differences, real genetic heterogeneity, and small sample sizes. Meta-analysis provides a useful means of analyzing inconsistent results because it increases sample size, and thus statistical power [18, 26, 27]. Accordingly, in the present study, because of the inconsistent results published on relationships between IL-6 polymorphisms and RA, we utilized meta-analysis to clarify associations.

In this meta-analysis, we found an association between RA and the IL-6 −174 G/C polymorphism and RA in Europeans using the dominant and recessive models. Furthermore, the single Asian study included also revealed a significant association between the IL-6 −174 G/C polymorphism and RA. Regarding the IL-6 −572 G/C polymorphism, no association was found with RA in all study subjects, but ethnicity-specific analysis showed that the single Asian study revealed an association between RA and the IL-6 −572 G/C polymorphism. On the other hand, in the single Iranian study no association was found between the IL-6 −174 G/C polymorphism and RA.

HLA class II genes, including HLA-DRB1, are the most powerful genetic factors of RA identified to date. However, this association accounts for only one-third of the genetic susceptibility and non-HLA genes such as protein tyrosine phosphatase nonreceptor 22 (*PTPN22*) or cytotoxic T-lymphocyte associated antigen-4 (*CTLA-4*) are also involved [16, 28]. *IL-6*, located on chromosome 7p21, has been suggested as a candidate gene for RA because IL-6 has proinflammatory activities and induces secretion of acute phase proteins, stimulates T cells, B cells, and synoviocytes, resulting in damage to cartilage and bone in RA. However, small number of studies of IL-6 polymorphisms has been carried out in RA compared to HLA-DRB1, *PTPN22*, or *CTLA-4*. IL-6 is regulated mainly at the transcriptional level by regulatory elements in the 5′ flanking region of the gene [29], and in this region, the −174 G/C and −572 G/C polymorphisms are important regulators of transcription [30]. For example, a luciferase reporter vector assay showed that the −174 G construct was expressed significantly more than the corresponding −174 C construct [6], and in the same study, the G allele was found to be associated with higher levels of plasma IL-6 in healthy adults. The IL-6 −572 G/C polymorphism lies near a potential glucocorticoid receptor element at positions −557 to −552 [31]. Furthermore, the −572 G/C polymorphism has been reported to influence levels of circulating C-reactive protein and bone resorption markers in postmenopausal women, and to be associated with several diseases, such as systemic lupus erythematosus and Hashimoto's thyroiditis [32].

Regarding ethnic differences and IL-6 −174 G/C polymorphism frequencies, the inter-ethnic frequency of the minor allele −174 C has been found to vary enormously; for example, the frequency of this allele has been reported to be low in Afro-Caribbeans (5 %) but high in Europeans (>50 %) [33]. This finding suggests that associations between RA and the IL-6 −174 G/C polymorphism are differentially dependent on the frequencies of its genotypes in different ethnic groups [34].

The present study has some limitations that should be considered. First, publication bias, heterogeneity, and confounding factors may have distorted the analysis. Second, our ethnicity-specific meta-analysis of the −174 G/C polymorphism included only data from Europeans, and thus our results are applicable only to this ethnic group. Furthermore, only a small number of studies were conducted on Europeans, which may mean that our investigation was underpowered. Third, a study by Palomino-Morales showed that RA patients homozygous for the IL-6 −174 G/G genotype had more severe endothelial dysfunction than those carrying the IL-6 −174 G/C or IL6 −174 C/C genotypes, thus suggesting that the IL-6 −174 gene polymorphism participates in the development of subclinical atherosclerosis in patients with RA [8]. Furthermore, an investigation of associations between IL-6 polymorphisms and RA activity and clinical features would have been interesting [35], but was not possible due to limited data. Fourth, we were unable to conduct meta-analysis on *IL-6* susceptibility haplotypes due to limited data.

In conclusion, this meta-analysis demonstrates that the IL-6 −174 G/C polymorphism may confer susceptibility to RA in Europeans, and that the IL-6 −572 G/C polymorphism may not be associated with susceptibility to RA. Since the allelic frequencies of genes often differ substantially between ethnicities, this analysis demonstrates that further studies are required to determine whether polymorphisms of IL-6 contribute to RA susceptibility in different ethnic groups.

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**Conflict of interest** The authors have no financial and non-financial conflicts of interest to declare.

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