Gene 523 (2013) 27–32

Contents lists available at SciVerse ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Interleukin-18 gene polymorphisms and rheumatoid arthritis: A meta-analysis

Jong Dae Ji [a,*], Won Jin Lee [b]

[a] Rheumatology, College of Medicine, Korea University, 126-1, Anam-Dong 5-Ga, Sungbuk-Ku, Seoul 136-705, South Korea
[b] Department of Preventive Medicine, College of Medicine, Korea University, Seoul, South Korea

ARTICLE INFO

Article history:
Accepted 27 March 2013
Available online 13 April 2013

Keywords:
IL-18
Polymorphism
Rheumatoid arthritis
Meta-analysis

ABSTRACT

Interleukin-18 (IL-18) is a member of the IL-1 superfamily that enhances both innate and acquired immune responses. IL-18 is highly expressed in sera, synovial fluids and synovial tissues of patients with RA, and these IL-18 levels are correlated with RA disease activity, indicating an important role of IL-18 in the pathogenesis of RA. Several studies have examined the association of *IL-18* gene polymorphisms with RA, but these studies have shown inconclusive and controversial results. To verify the association between *IL-18* gene polymorphism and susceptibility to RA, we conducted a meta-analysis of all relevant reports cited in MEDLINE/PubMed before October 2012. A meta-analysis on the association between the *IL-18* rs1946518 SNP and RA was performed for 2944 patients with RA and 2377 controls from 7 published studies and a meta-analysis on the association between the *IL-18* rs187238 SNP and RA was performed for 1319 patients with RA and 1211 controls from 5 published studies. In addition, 2 studies involving 1873 RA patients and 1092 controls were considered in the meta-analysis of the association between the *IL-18* rs360722 SNP and RA. No significant association was found between two *IL-18* SNPs (rs1946518 and rs187238) and RA susceptibility in all subjects. In subgroup analysis stratified by ethnicity, there was still no significant association between these two *IL-18* SNPs and RA susceptibility. However, the frequency of the T allele at rs360722 was found to be significantly lower in patients with RA compared with controls, although this finding was based on only 2 studies. The results of our meta-analysis suggest that *IL-18* rs360722 SNP is only associated with RA susceptibility. However, due to only two studies included in our meta-analysis, large-scale well designed studies should be considered in future studies to confirm the exact role of *IL-18* rs360722 SNP in RA susceptibility.

1. Introduction

Rheumatoid arthritis (RA) is a common immune-mediated inflammatory disease characterized by chronic inflammation of synovial joints, which leads to progressive destruction of cartilage and bone. The precise etiology of RA is not completely known, but a large body of studies indicated that proinflammatory cytokines are significantly involved in the pathophysiology of joint inflammation and bone destruction in RA (McInnes and Schett, 2007). It is well known that the imbalance between pro- and anti-inflammatory cytokine activities induces and exacerbates the autoimmune responses, chronic inflammation and tissue destruction in the joints of RA.

Interleukin-18 (IL-18) is a member of the IL-1 superfamily that enhances both innate and acquired immune responses (Dai et al., 2007). IL-18 is produced as pro-IL-18, precursor form, in monocyte/macrophages, dendritic cells, Kupffer cells, keratinocytes, articular chondrocytes, synovial fibroblasts and osteoblasts (Liew et al., 2003). In RA synovium, the expression of IL-18 is associated with that of IL-1β and TNFα and correlates with the acute-phase response, indicating that IL-18 is an important proinflammatory cytokine that drives the local production of IL-1β and TNFα in RA (Joosten et al., 2003). In addition, it was suggested that IL-18 contributes to the development and maintenance of an acquired immune response in RA by promoting differentiation and chemotaxis of T cells (Dai et al., 2007). IL-18 administration exacerbates the development of an erosive, inflammatory arthritis in collagen-induced arthritis (CIA) mice model, and incidence and severity of CIA are reduced in mice lacking IL-18 (Gracie et al., 1999; Wei et al., 2001). All these reports indicate that IL-18 plays an important role in the pathogenesis of RA. Recently, many polymorphisms in the IL-18 gene have been identified. Two single-nucleotide polymorphisms (SNPs) of *IL-18* promoter at positions −607C/A (rs1946518) and −137G/C (rs187238) are found to be associated with transcriptional activity (Giedraitis et al., 2001). Higher promoter activity was observed for the −607C and −137G allele. Therefore, a lot of studies to examine the association of *IL-18* gene polymorphisms with RA had focused on these two polymorphisms, but these studies have shown inconclusive and controversial results (Gracie et al., 2005; Huang et al.,

Abbreviations: IL-18, interleukin-18; RA, rheumatoid arthritis; OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium.

* Corresponding author. Tel.: +82 2 920 5489; fax: +82 2 920 5974.
E-mail address: jjdjmesy@korea.ac.kr (J.D. Ji).

0378-1119/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.gene.2013.03.132

2007; Pawlik et al., 2006; Pawlik et al., 2009; Rueda et al., 2005; Sivalingam et al., 2003; Sugiura et al., 2011; Ying et al., 2011). We performed a meta-analysis on the published studies to clarify whether these two polymorphisms of *IL-18* genes associate with the risk of RA. In addition, two recent studies suggested that *IL-18* gene polymorphism at positions −920C/T (rs360722) may be associated with susceptibility to RA (Pawlik et al., 2009; Sugiura et al., 2011). In addition to two SNPs known to affect transcriptional activity of *IL-18* gene, we also analyzed the association of this polymorphism (rs360722) and the risk of RA.

2. Methods

2.1. Data collection

A search of literature was performed using MEDLINE/PubMed to identify available articles that examined the association between IL-18 polymorphisms and RA published before October 2012. The combination of key words such as "IL-18", "interkeukin-18", "polymorphism" and "Rheumatoid arthritis" were entered as both medical subject heading (MeSH) terms and text words without restriction on the language. We also tried to identify additional studies by hand-searching references of original articles or review articles on this topic.

A study was included in the meta-analysis if it examined the association between *IL-18* SNPs (rs1946518, rs187238 and rs370722) and RA susceptibility and contained available allele and genotype frequency for calculating the odds ratios (ORs) and their 95% confidence intervals (95% CIs). From the literature search we identified 7 publications for meta-analysis on the association between *IL-18* gene polymorphisms and susceptibility to RA. One of the eligible studies contained data on two independent cohorts of Caucasian population (Gracie et al., 2005), and we treated the data of each cohort as a separate study. Therefore, a total of 8 studies of the association between *IL-18* polymorphism and RA were included in the meta-analysis.

2.2. Statistical analyses

Tests for deviation from Hardy–Weinberg equilibrium (HWE) were performed with the De Finetti program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The odds ratios (ORs) and their 95% confidence intervals (95% CIs) associated with the *IL-18* allele or genotype were extracted from the published studies and included in the analysis. Available raw data were used in a 2 × 2 table to calculate the OR and 95% CI as measures of association. Meta-analytic techniques that weighted the logarithm of the OR of each study by a function of its variance were used to calculate a summary estimate. Meta-analyses were performed on the total data set and separately for ethnic groups. Heterogeneity between studies was tested using χ^2-based Q statistics. If the heterogeneity was present ($P < 0.10$), we used random-effects models for calculating summary statistics using the method described by DerSimonian and Laird (1986). Otherwise, the fixed-effects model was used. For assessing potential publication bias, Begg's funnel plots and Egger's test were used (Begg and Mazumdar, 1994; Egger et al., 1997). This statistical test detects whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision. Meta-analysis was performed using the package "metafor" of the R-Project (http://CRAN.R-project.org/package=metafor).

Results

3.1. Characteristics of included studies

Nineteen relevant studies, which investigated about IL-18 and RA, were identified using PubMed. Based on title and abstract details, 9 studies were selected for full-text review (Fig. 1). Due to functional significance for IL-18 production, we performed a meta-analysis on two single-nucleotide polymorphisms (SNPs) (rs1946518 and rs187238).

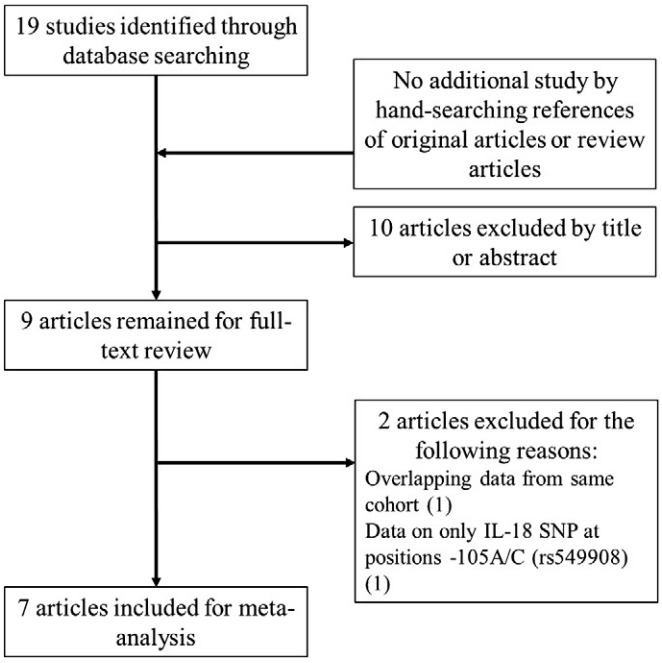

Fig. 1. Flowchart of selection process for meta-analysis.

Additionally, two recent studies suggested that IL-18 gene polymorphism at positions −920C/T (rs360722) may be associated with susceptibility to RA, and this polymorphism (rs360722) was also included for meta-analysis. One study was excluded due to overlapping data from the same cohort and another study was excluded due to data on only *IL-18* SNP at positions −105A/C (rs549908), therefore 7 studies were included in our meta-analysis. One of the eligible studies contained data on two independent cohorts of Caucasian population, and we treated the data of each cohort as a separate study. Thus, a total of 8 separate comparisons were considered in the meta-analysis. Detailed characteristics of each selected study are described in Table 1. A meta-analysis on the association between the *IL-18* rs1946518 SNP and RA was performed for 2944 patients with RA and 2377 controls from 8 studies and a meta-analysis on the association between the *IL-18* rs187238 SNP and RA was performed for 1319 patients with RA and 1211 controls from 6 studies. In addition, 2 studies involving 1873 RA patients and 1092 controls were considered in the meta-analysis of the association between *IL-18* rs360722 SNP and RA. When we stratified the analyses by ethnic group, 4 Caucasian and 4 Asian populations were included in the meta-analysis of the association between *IL-18* rs1946518 SNP and RA. In the meta-analysis of the association between *IL-18* rs187238 SNP and RA, 4 Caucasian and 2 Asian populations were included for stratification by ethnicity.

3.2. Meta-analysis of IL-18 polymorphism and RA susceptibility

A summary of the meta-analyses of the associations between *IL-18* polymorphisms and RA is provided in Table 2. When all 8 studies were pooled into the meta-analysis, no significant association was found between the *IL-18-607* A allele and RA in the overall population (OR 0.87, 95% CI 0.72–1.04) (Fig. 2A). When stratified by ethnicity, no association between *IL-18-607* A allele and RA susceptibility was found in Caucasian or Asian subgroups. Further, when the analysis was restricted to studies in agreement with HWE and to studies genotyped by Allele-specific amplification (ASA), we failed to identify any association between *IL-18-607 A* allele and RA. In addition to analyze the association between *IL-18* rs1946518 SNP and RA in the allelic model (A allele vs. C allele), we also analyze the association between