Association of Interleukin 1B -511C/T polymorphism with Osteoarthritis, Juvenile Idiopathic Arthritis and Rheumatoid Arthritis susceptibility: a meta-analysis

Research Article

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Summary

Background: A number of studies have been conducted to investigate the different types of inflammatory arthritis potential association with the IL-1B -511C/T polymorphism. However, results were inconsistent. We performed this meta-analysis to estimate the association between -511C/T polymorphism and osteoarthritis (OA), juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA).

Methods: Electronic search of PubMed and CNKI was conducted to select studies. Studies containing available genotype frequencies of -511C/T were chosen, and pooled odds ratio (OR) with 95% confidence interval (CI) was used to assess the association.

Results: The final meta-analysis included 17 published studies including 1447 OA cases and 1171 controls, 234 JIA cases and 313 controls, 3524 RA cases and 3111 controls separately. The results suggested that the variant genotype was associated with RA in the total population (additive model: OR 0.925, 95% CI (0.860~0.995), P = 0.035). However, the association was not significant between this polymorphism and OA (additive model: OR=1.067, 95% CI: 0.937~1.214, p= 0.328; dominant model: OR =0.930, 95% CI: 0.706~1.225, p=0.606) or JIA in the total population (additive model: OR=1.067, 95% CI: 0.821~1.338, p= 0.626; dominant model: OR =1.269, 95% CI: 0.843~1.909, p=0.254), The stratification by ethnicity failed to identify any association between this polymorphism and OA, JIA, RA in Asian, Caucasian or African groups.

Conclusion: This meta-analysis suggests that the allele T of IL-1B -511C/T polymorphism is associated with decreased risk of RA in all ethnicities including Caucasian, Asian and African.
I. Introduction

Arthritis is a chronic inflammatory disease that predominantly involves the synovial joints. Due to the different symptoms and diagnostic criteria there are different types of arthritis. Osteoarthritis (OA) is the most frequent joint pathology associated with health problems for middle aged and older people. It is a debilitating, chronic, progressive, and impact on a society regarding medical, social, and economic issues (1). Juvenile idiopathic arthritis (JIA) is a multifactorial autoimmune disease that cause of chronic arthritis in children. It is a heterogeneous disease with seven mutually exclusive categories, and its pathogenesis is complex with both genetic and environmental factors (2). Rheumatoid arthritis (RA) is a systemic autoimmune disease, characterized by chronic inflammation of multiple joints and synovial inflammation. As the disease progresses, irreversible joint damage may lead to loss of function disability of joints (3).

Over the past decade, members of the Interleukin 1 (IL-1) family have been identified, and their important roles in innate and adaptive immune responses have been revealed. IL-1 family has IL-1A, IL-1B and IL-1RN genes which respectively code for IL-1α, IL-1β and IL-1 receptor antagonist (IL-1Ra) in about 430 kb area located on chromosome 2q13-21 (4). IL-1α and IL-1β can activate the release of other pro-inflammatory cytokines such as TNF and IL-6, and induce a Th17 bias in the cellular adaptive response (5). Much interest has been generated regarding the processing and release of bioactive IL-1β since the discovery of an entire group of disorders called autoinflammatory syndromes that specifically respond to the blockade of the IL-1 receptor with the IL-1 receptor antagonist (IL-1Ra), or with neutralization of IL-1β by the monoclonal anti-IL-1β antibodies. These syndromes are characterized by attacks of sterile inflammation of joints, serositis, fever, and skin lesions (6). In addition, IL-1 is a major monocyte derived pro-inflammatory cytokine that mediates tissue damage and cartilage loss in chronic arthritis (7). Chondrocytes are known to respond to IL-1β by decreasing the synthesis of matrix components and increasing the synthesis of matrix metalloproteinases (MMPs). MMPs can degrade extracellular matrix components in articular cartilage (8).

While the IL-1B is well known pro-inflammatory cytokine gene and relates with the autoinflammatory syndromes of sterile inflammation of joints. OA, JIA and RA are associated with synovial inflammation and joint destruction. Besides sex, age, nutritional status, and other factors, genetic polymorphism may be an important factor for different responses of humans to inflammation and infection. Wen, A. found that -511T with -31C in the IL-1B promoter haplotype can decrease the LPS induced protein secretion, they assumed IL-1B promoter influences the expression and transcriptional activity of the IL-1B gene and regulate the expression of IL-1B gene after LPS exposure (9). So The polymorphism in IL-1B gene can be associated with arthritis and affect severity or susceptibility. The important single nucleotide polymorphisms (SNP) at -511C/T (rs16944) in the promoter region of IL-1B has been reported associated with JIA, RA and OA in human (10, 11, 12, 13). However, the results were inconsistent. Therefore, we conducted a meta-analysis to assess the effect of the -511C/T polymorphism on the risk of JIA, RA and OA.

II. Materials and methods

2.1 Publication search

We performed an exhaustive search on articles that studied the association of IL-1B -511C/T polymorphism with JIA, RA and OA. The computer-based searches in the PubMed database using IL-1B, -511, JIA, RA and OA as the key words (the last search update was on July 7, 2013). There is no limit on human race or language of the search. In addition, we search in Chinese with China National Knowledge Infrastructure (CNKI) database using the same keywords to find the studies in Chinese. Case-control studies containing available genotype frequencies of -511C/T were chosen. Additional studies were identified by a manual search of the references of original studies. When more than one of the same or overlapping population by same authors were found, only the most recent or complete study was used for this meta-analysis.

2.2 Statistic analysis

For control group of each study, the observed genotype frequencies of the IL-1B codon -511C/T polymorphism were assessed for Hardy–Weinberg equilibrium using the χ² test. The strength of association between -511C/T polymorphism of IL-1B gene and JIA, RA and OA was accessed by calculating crude ORs (odds ratios) with 95% CIs (confidence intervals). The pooled ORs were performed for additive genetic model (T vs. C), dominant model TT + CT vs. CC) and recessive model (TT vs. CT + CC), respectively. Heterogeneity assumption was checked by a χ² based Q-test. A significant Q-statistic (P<0.05) indicated heterogeneity across studies. The summary OR estimate of each study was calculated by the fixed-effects model if there was not significant heterogeneity. Otherwise, the random-effects model was employed (24, 25). The potential for publication bias was examined by a Begg's test (funnel plot method) and Egger's linear regression test (P<0.05 considered representative of statistical significance) (26). All statistical analyses were performed with Stata software (version 9.0; Stata Corporation, College Station, TX).

2.3 Result

Eligible studies

We identified 17 case–control studies on 12 Caucasian, 4 Asian, 1 African population samples research the association between IL-1B -511C/T polymorphism and JIA, RA and OA, including 1447 OA cases and 1171 controls, 234 JIA cases and 313 controls, 3524 RA cases and 3111 controls separately.
The distribution of genotypes in the controls of all the studies was in agreement with Hardy–Weinberg equilibrium, except two studies (1,11).

**Meta-analysis**

The results of the association between the IL-1B -511C/T polymorphism and OA, JIA, RA and the heterogeneity test were shown in Table 2 (Figure 1). Meta-analysis identify an association between the -511C/T polymorphism and RA in the total population (additive model: OR 0.925, 95% CI (0.860–0.995), P = 0.035)). Furthermore, stratification by ethnicity failed to identify any association between this polymorphism and OA, JIA, RA in Asian, Caucasian or African groups.

**Publication bias**

Funnel plot, Egger’s test and the Begg’s test were done to estimate the publication bias of literatures. The results of the Egger’s and the Begg’s test showed the publication bias in the OA group (P=0.013), (P=0.042), but there is no evidence of publication bias in RA group (Table 2).

<table>
<thead>
<tr>
<th>Arthritis type</th>
<th>Author</th>
<th>Country</th>
<th>Design</th>
<th>Year</th>
<th>Ethnicity</th>
<th>Case</th>
<th>Control</th>
<th>P^a</th>
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^a: p value for Hardy–Weinberg equilibrium in control group.
HCC hospital-based case-control study
PCC population-based case-control study

**Table 1:** The distribution of the IL-1B -511C/T variant for cases and controls
Table 2: ORs and 95% CI for OA, JIA, RA and the IL-1B -511C/T polymorphism under different genetic models.
**Discussion**

It was thought that OA, JIA and RA are the results of a combination of environmental factors and the accumulation of genetic variation. The genetic susceptibility to arthritis may be attributed to the SNP of major genetic pathways including cytokine secretion patterns, pro-inflammatory affect. Some studies have attempted to discover a possible association between the IL-1B -511C/T polymorphism and the risk of human arthritis [1, 2, 9-12, 14-17, 19-23, 27]. A significant association between this polymorphism and OA has been shown in Caucasian[20] and Chinese[13], as well as the association showed on RA in Caucasian and African [9, 19, 27]. On the contrary, the other studies did not demonstrate any significant difference in the prevalence of the IL-1B -511C/T genotype between OA[11, 21], JIA patients[2, 12, 16], and RA[10, 11, 16, 17, 22, 23].

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**Figure 1:** Forest plot of ORs of RA T allele when compared to the C allele (Additive model). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.
Our meta-analysis reveal a significant association between the -511C/T polymorphism and RA in additive model in the total population (additive model: OR 0.925, 95% CI (0.860-0.995), P = 0.035), that is the T allele can decrease the risk of RA. Significant ethnic difference was not found in the polymorphism. Genevay S. has reported that-511 minor T allele carriers show lower joint destruction progression after 20 years in Swiss RA patients (14). Arman A. has reported that the CT genotype of -511 can have a protective effect for RA in Turkish, they assumed that the genotype CT of -511 can influence the IL-1B gene expression in a negative way by inhibiting transcription factors’ binding. Whereas the CC genotype promoter and activate gene expression positively. Thus higher levels of IL-1β might be produced and might affect the course of RA (19).

IL-1 is crucial for the development of collagen-induced arthritis (CIA) in mice, mainly because it can drive TH17 cell differentiation, enhance IL-17 production and mediate joint destruction and many autoimmune or chronic inflammatory diseases (28). The processing and release of bioactive IL-1β relate to autoinflammatory syndromes (29). There are three mechanisms leading to the processing of pro-IL-1β into active fragments, caspase-1 activation, neutrophil-derived serine proteases and pathogen-released enzymes can process and activate IL-1β, these processes have important effects during inflammation and infection (6). Following the release of active cytokines from the cell, the actions of IL-1β can be blocked by two physiological mechanisms. First, IL-1 receptor antagonist (IL-1Ra) binds tightly to IL-1R1, thereby blocking binding of IL-1α and IL-1β (29). Second, another IL-1-binding protein, called IL-1R type II (IL-1R2), has an extracellular region that is similar to IL-1R1 but has a short cytoplasmic domain that cannot signal, therefore it acts as a decoy receptor (30). Adjust of IL-1β become an important component of RA management. IL-1Ra is a naturally occurring, acute-phase, anti-inflammatory protein (31), and its recombinant human form named Anakinra (Kineret; Amgen/Biovitrum). It is a specific inhibitor of IL-1 by blocking the binding of IL-1 to type I receptors. However, the therapeutic use of Anakinra in rheumatoid arthritis has yielded disappointing results, with fewer patients benefiting and higher disease scores than inhibitors of TNF or biologics (32). Initially it was thought this poor response might be due to the short in vivo half-life of IL-1Ra, but more recent clinical trials of longer-lived IL-1-blocking agents have not shown greater success. The differences between the observations in mouse models of arthritis and in patients with rheumatoid arthritis highlight the fact that these models have poor predictive value for clinical trial results (33). In the systemic onset form of JIA (SO-JIA), however, IL-1 has an important role, and treatment with Anakinra is highly beneficial in many, but not all, cases (34).

In conclusion, from the point of view that pro-inflammatory cytokines take an important role in the occurrence and development of rheumatic inflammation. The potent and pathologic effects of IL-1 in RA which our finding in the meta consensus with. This meta-analysis suggests the T allele of -511C/T polymorphism may be associated with the risk of RA. Meta-analysis maximizes the sample size, increase statistical power. But future well designed large studies might be necessary to validate this association in different populations incorporated with environmental factors in the susceptibility of OA, JIA and RA.

Arthritis is a complex and multifactorial process. The genetic factors in the etiology of arthritis are still relatively unknown. Large genetic screenings can be useful for elucidating the molecular pathogenesis of arthritis.

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Conflict of Interest: None

References:


Havemose-Poulsen, A., Sorensen, L. K., Bendtz, K., and Holmstrup, P. (2007) Polymorphisms within the IL-1 gene cluster: effects on cytokine profiles in peripheral blood and whole blood cell cultures of patients with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis, *J Periodontol* 78, 475-492.


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rheumatology 24, 365-371.