Original research

Association Of The Interleukin-6 -174G>C Polymorphism With Osteoarthritis Risk: a Meta-Analysis of 3,814 Cases and 3,876 Controls

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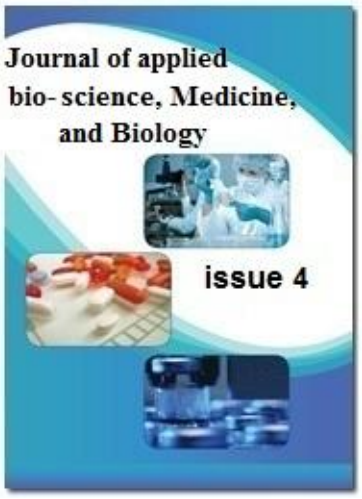

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ABSTRACT

Background: Osteoarthritis (OA) multifactorial joint disease with strong genetic and occupational components. Many studies have reported the association of Interleukin-6 (IL-6) -174G>C polymorphism on the risk of OA risk, but the results remained controversial. The aim of this meta-analysis was to more systematically summarize the association between IL-6 -174 G>C polymorphism and OA.

Methods: Eligible articles were identified by search of databases including PubMed, Embase, ISI Web of Knowledge and Google scholar up to December 2016. Data were extracted by two independent authors and pooled odds ratio (OR) with 95% confidence interval (CI) was calculated.

Results: A total of 10 eligible publications were included in the meta-analysis including 3,814 cases and 3,876 controls. Overall pooled analysis suggest a not significant association between IL-6 -174G>C polymorphism and OA risk under Allelic comparison (C vs. G: OR=3.50, 95% CI = 1.49-8.24, p= 0.004) and dominant comparison (CC+GC vs. GG; OR= 1.25, 95% CI = 1.00-1.55, p= 0.04). Among them, 8 studies of Caucasian population and 2 studies of Asian population were included.

Conclusion: The present meta-analysis suggests that IL-6 -174G>C polymorphism is associated with an increased OA risk. However, future large studies with gene-gene and gene-environment interactions are needed to validate these findings.

Keywords Osteoarthritis**,** Interleukin-6, IL-6 -174 G>C, polymorphism, meta-analysis.

Introduction

Osteoarthritis (OA) is a common joint disease that most often affects middle-age to elderly people (1,2). OA is progresses gradually and worsens over time. It was estimated that OA is the 10th leading cause of non-fatal burden in the world in 1990, accounting for 2.8% of total YLD, around the same percentage as schizophrenia and congenital anomalies (3). According with worldwide estimates 9.6% of men and 18.0% of women aged over 60 years has symptomatic osteoarthritis (4). OA is characterized by structural changes to the joint, such as loss of cartilage, meniscal damage, osteophyte formation, and inflammation (5). There is currently no cure for OA, but treatments exist that slow the progression and improve quality of life with the disease (6).

Interleukin-6 (IL-6), as a pleiotropic cytokine of 23.7 kDa, is one of the important inflammatory cytokines and regulates the inflammatory response, which secreted by cells from the immune system, cardiovascular components, and adipose tissue (8,9). The IL-6 gene is located at chromosome 7p21 and contains 6 exons with a 1.3-kb coding sequence and there are several common polymorphisms at the 50 flanking region of the promoter region including -598A/G, -597G/A, -572 C>G, and -174 G>C (10,11). It has been reported that the IL-6 -174G>C polymorphism, which is designated as rs1800795 as well, is a G-to-C transition mutation, is associated with the transcription activity of IL-6 gene (12).

Several number of studies have been performed to figure out whether there is an association between -174 G>C polymorphism and OA risk (13-19), but the results are controversial. This may be due to the inadequate sample sizes, patient selection, and ethnicity of the populations studied. Additionally, a single study may be insufficient for detecting the potential small effect of the polymorphism on OA. Therefore, to overcome the limitations of individual studies and resolve the inconsistencies, we performed this meta-analysis on all eligible case-control studies to estimate the effect the IL-6 -174G>C polymorphism on the risk of OA.

Material and methods

Identification of relevant studies

Relevant publications were identified with a literature search using terms “Osteoarthritis” OR “OA” and ‘‘Interleukin 6’’ OR ‘‘IL-6,’’ ‘‘-174 G>C ’’ OR ‘‘rs1800796,’’ ‘‘polymorphism’’ OR ‘‘SNPs’’ OR “variant” OR “genetic susceptibility” in the PubMed, Web of Science, Google Scholar database up to the December 2016. The research was limited to English language publications. Additional studies were identified by a manual search of the references of original studies and unpublished data were not considered.

Inclusion Criteria

The studies were eligible for this meta-analysis on condition that they satisfied the inclusion criteria as follows: (1) evaluation of the association between IL-6 -174G/C polymorphism and OA; (2) case-control or cohort studies; (3) available the genotypes data in detail to estimate an odds ratio (OR) with 95 % confidence interval (CI). Studies were excluded if one of the following existed:

1) it was not a case-control genetic study, 2) duplicated reports, 3) no useful data were reported, and 4) other *IL-6* polymorphisms other than -174G>C were investigated.

Data extraction

Two independent investigators extracted the information from all eligible publications using standard data extraction according to the inclusion criteria listed above forms including first author's name, publication year, country of origin, ethnicity of the study population, number of cases and controls, genotype frequencies for cases and controls, Hardy-Weinberg equilibrium (HWE). Different ethnicities were categorized as Caucasians, Asians, and Africans. We did not define any minimum number of patients to include in the meta-analysis. Disagreements were resolved by discussion between the two authors or through consultation with a third investigator.

Statistical methods

The strength of association between the IL-6 -174G>C polymorphism and risk of OA was assessed by OR with 95 % CI values under allelic comparison (C *vs* G), homozygote comparison (GG *vs* CC), heterozygote comparison (GG *vs* GC), dominant (CC+GC *vs* GG), and recessive (GG+GC *vs* CC) model comparisons. Heterogeneity assumption was examined by the Cochran's Q-test. The heterogeneity between studies was assessed using the Cochran's Q statistic and I^2 test. P<0.1 and I^2 exceeding 50% indicated substantial heterogeneity across studies, then a random-effects model was chosen to perform meta-analysis (20); otherwise, a random effects model was selected (the DerSimonian and Laird method) (21). Hardy-Weinberg equilibrium (HWE) was checked in the control groups by Pearson's $\chi 2$ test. If P value > 0.05, the genotype distribution of control population conformed to HWE (22). To explore the source of the heterogeneity and to evaluate ethnicity-specific effects, subgroup analyses performed for IL-10 polymorphisms were investigated in a sufficient number of studies. In addition, one-way sensitivity analysis was also used to assess the stability of the results by omitting one of the studies each time. Publication bias was assessed by Begg's funnel plots, and Egger's test was used as a test for small study effects (23,24). All the statistical analyses were performed by comprehensive meta-analysis (CMA) V2.0 software (Biostat, USA). Two-sided P values < 0.05 were considered statistically significant.

Results

Studies included in the meta analysis

A total of 25 articles were identified by electronic and manual searching and selected 6 of these for a full-text review based on title and abstract details. After the full-text review, 13 of these articles were excluded because they were review articles, had no data, or reported duplicate data (Fig. 1). Finally, a total of 10 case-control studies (13-19) met our inclusion criteria, including 3,814 cases and 3,876 controls. Among them, 8 studies of Caucasian population and 2 studies of Asian population were included. The countries of these studies included UK, Germany, Finland, Italy,

Estonia, China, and Thailand. The genotypes in control group for 1 study was not consistent with HWE ($P < 0.05$).

Results of meta-analysis

The random effects model was chosen to synthesize the data from the allelic model, heterozygote, and dominant comparisons. Overall pooled analysis suggest a not significant association between IL-6 -174G>C polymorphism and OA risk under Allelic comparison (C vs. G: OR=3.50, 95% CI = 1.49-8.24, p= 0.004; Fig. 2A) and dominant comparison (CC+GC vs. GG; OR= 1.25, 95% CI = 1.00-1.55, p= 0.04; Fig. 2B). However, there was not a significant association between IL-6 -174G>C polymorphism and OA risk under homozygous comparison (GG vs. AA: OR=1.15, 95% CI = 0.97-1.36, p= 0.10), heterozygous comparison (GA vs. AA: OR= 1.20, 95% CI = 0.98-1.46, p = 0.06), and recessive comparison (GG vs. GA+ AA: OR= 1.12, 95% CI = 0.96-1.30, p= 0.13; Fig. 2C) (Table 1).

Sensitivity analysis

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs. The results suggested that no individual study significantly affected the pooled ORs. Sensitivity analysis was performed after excluding HWE-violating studies, and the corresponding pooled ORs were not materially altered, indicating that our results are statistically robust (not shown).

Publication bias

Begg's funnel plot and Egger's test were carried out to evaluate the publication bias among the selected studies to the meta analysis. The shape of the funnel plot did not show obvious publication bias for IL-6 -174G>C polymorphism in Allelic comparison (C vs. G: $P_{Begg's}$= 0.15 and $P_{Egger's}$= 0.92; Fig. 3A), heterozygous comparison (GA vs. AA: C vs. G: $P_{Begg's}$= 0.05 and $P_{Egger's}$= 0.08), homozygous comparison (GG vs. AA: C vs. G: $P_{Begg's}$= 0.34 and $P_{Egger's}$= 0.68), dominant comparison (CC+GC vs. GG; $P_{Begg's}$= 0.07 and $P_{Egger's}$= 0.25; Fig. 3B) and recessive comparison (GG vs. GA+ AA: C vs. G: $P_{Begg's}$= 0.60 and $P_{Egger's}$= 0.65).

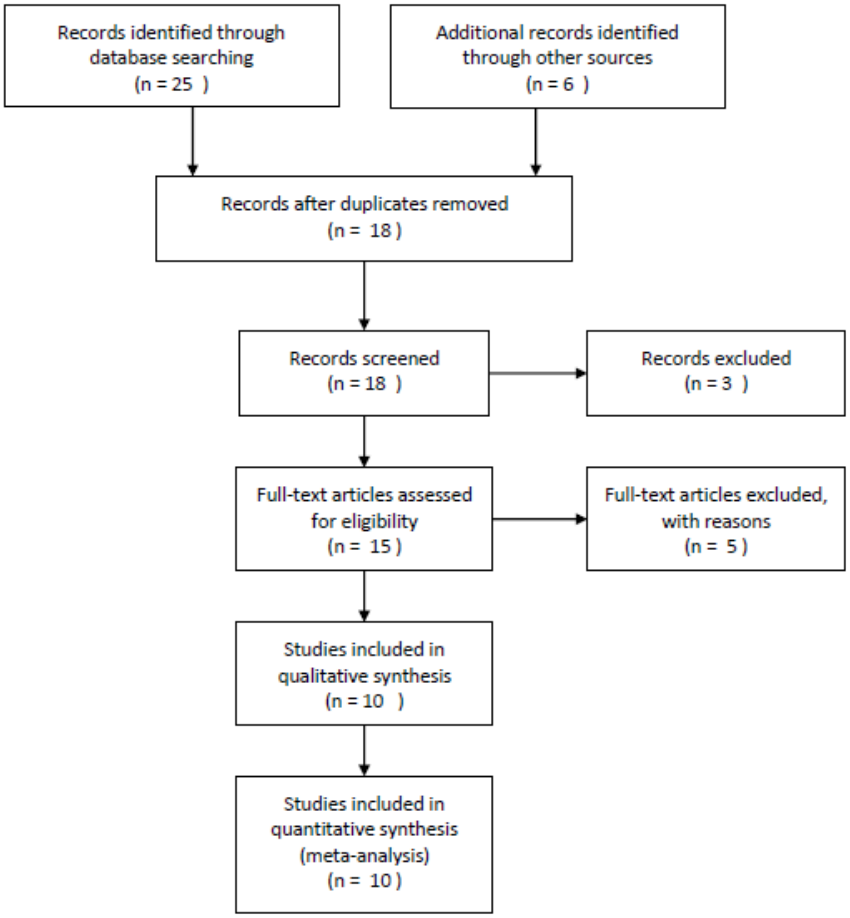

Fig. 1. PRISMA flow diagram for inclusion of the studies to the meta analysis.

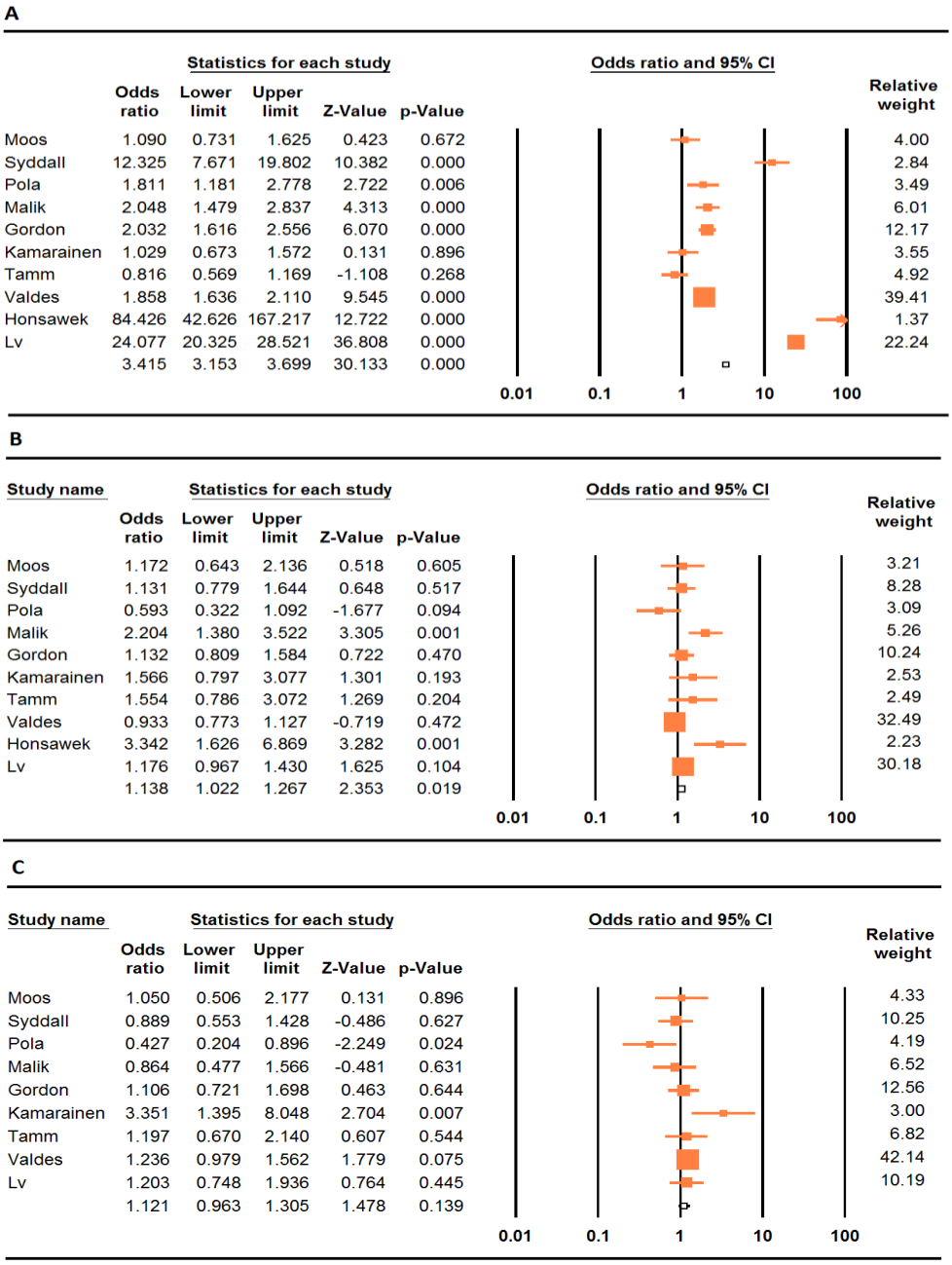

Fig. 2. Forest plots (Random effect) showed significant association between IL-6 -174G>C polymorphism and risk of OA risk. **A:** allelic comparison (C *vs* G), **B:** dominant (CC+GC *vs* GG), and **C:** recessive (GG+GC *vs* CC) model comparisons.

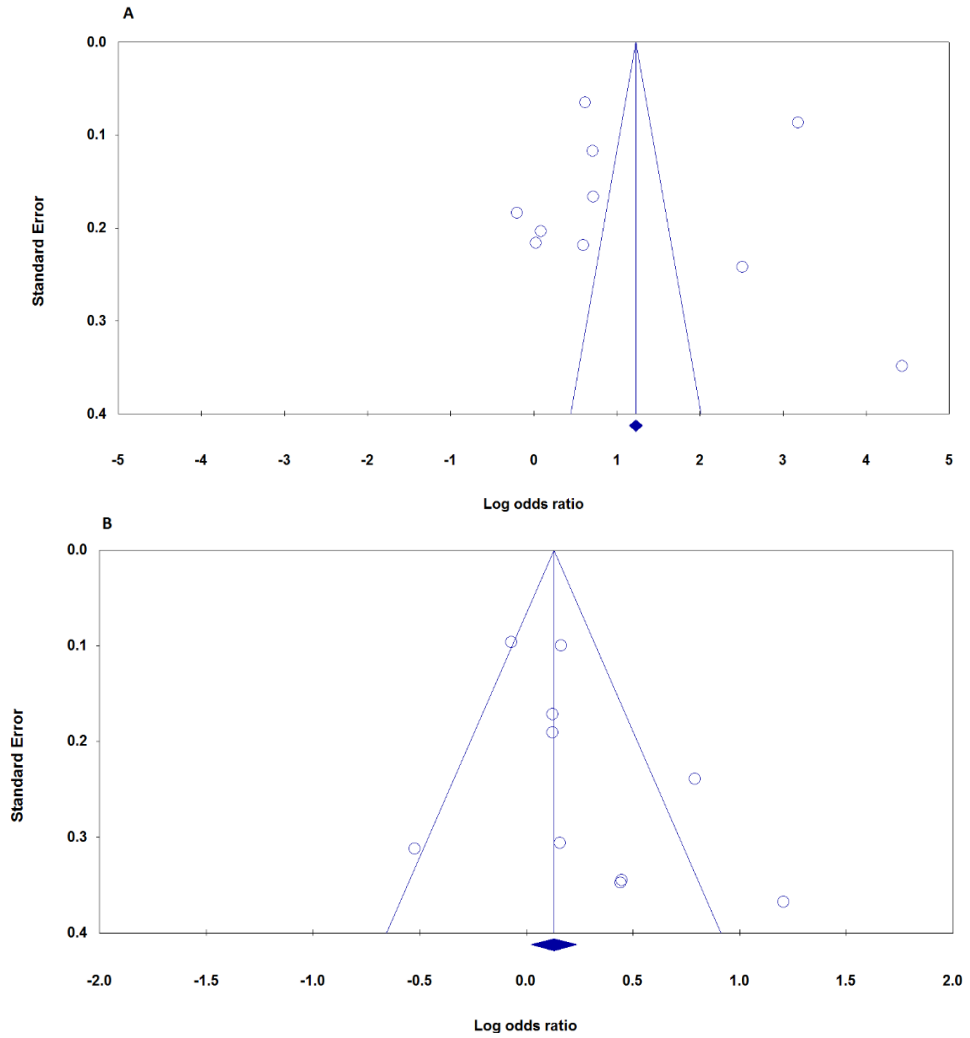

Fig. 3. Funnel plot for studies of the association of IL-6 -174G>C polymorphism and risk of OA risk. **A:** Allelic comparison (C *vs* G) and **B:** dominant (CC+GC *vs* GG).

Discussion

The present meta-analysis we performed to get a more precise assessment of the association between IL-6 -174G>C polymorphism and OA risk. Ten publications with a total of 3,814 cases and 3,876 controls were finally included into the met analysis. Overall, there was obvious association between IL-6 -174G>C polymorphism and OA risk under allelic comparison (C vs. G: OR=3.50, 95% CI = 1.49-8.24, p= 0.004) and dominant comparison (CC+GC vs. GG; OR= 1.25, 95% CI = 1.00-1.55, p= 0.04). Compared with the previous meta-analysis [], this present study was focused only on association between IL-6 -174G>C polymorphisms and KOA. Our meta-analysis results were different from a previous meta-analysis, which revealed that no significant association between IL-6 -174G>C polymorphism and OA (28). Several reasons may explain for the difference. It seems the inclusion and exclusion criteria were different.

Between-study heterogeneity is common in meta-analysis for genetic association studies (29). In the current meta-analysis fixed-effects or random-effects models were used based on heterogeneity testing. According to the previous reports several factors could be the sources of heterogeneity between-study such as ethnicity, gender, sample selection, source of controls, age, sample size, environmental exposures etc. However, in this meta-analysis subgroup analysis, which aim to reduce heterogeneity not available due insufficient size of studies.

Similar to other meta-analyses, our study also bears some limitations. First, the number of studies and the number of subjects in the studies included in the current meta-analysis were small and had not sufficient statistical power to detect the association between IL-6 -174G>C polymorphism and risk of OA. Therefore, more studies with larger sample size are required. Second, the effect of gene-gene and gene-environment interactions was not considered in this meta-analysis. Second, the results were based on unadjusted ORs, while a more precise estimation should take into account the effect of multiple factors such as ethnicity, age and gender distribution on the association. Third, most of the publications in this meta-analysis were from Caucasian populations mostly of UK populations; hence, our results are only applicable to Europe population. Therefore, more studies containing the full range of possible ethnic differences are needed to avoid selection bias. Finally, nowadays several genes were identified to associate with OA. Thus, the possible gene–gene and gene–environment interactions may play central roles in the OA development and need further confirmation in future studies.

In conclusion, our meta-analysis suggested that the IL-6 -174G>C polymorphism and risk of OA risk. However, the results should be interpreted with caution because of the publication bias. Moreover, further studies with large sample size, especially in subgroup analysis, should be done to confirm these findings.

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