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Association between *IL-1*α rs17561 and *IL-1*β rs1143634 polymorphisms and periodontitis: a meta-analysis

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ABSTRACT. Genetic variations in human interleukin-1 (*IL-1*) genes are known to be involved in inflammatory disorders. The rs17561 and rs1143634 polymorphisms of *IL-1*α and *IL-1*β, respectively, have been increasingly recognized as important regulators in the development of periodontitis. However, the existence of a specific association remains controversial. Therefore, we performed a meta-analysis to explore the relationship between *IL-1* polymorphism and periodontitis risk. Based on our inclusion criteria, six case-control studies were used, involving a total of 336 periodontitis cases and 366 healthy controls. Our meta-analysis results showed that the T allele of *IL-1*α rs17561 is positively associated with periodontitis susceptibility. In addition, carriers of this allele (TC + TT genotypes) demonstrated increased risk of this disease. The *IL-1*β rs1143634 T allele was also positively connected to periodontitis, with TC + TT genotype carriers being significantly more at risk. These results demonstrate that the *IL-1*α rs17561 and *IL-1*β rs1143634 polymorphisms are associated with periodontitis.

Key words: Interleukin-1 gene; Genetic polymorphism; Periodontitis; Meta-analysis

INTRODUCTION

Periodontal disease is viewed as a chronic inflammatory condition, and is provoked by specific pathogenic bacterial consortia in subgingival biofilms (Pihlstrom et al., 2005; Darveau, 2010; Stabholz et al., 2010; Zhang et al., 2011a). Periodontitis is an opportunistic inflammatory disease of the periodontal tissues influenced by environmental and genetic factors (Van Dyke and Sheilesh, 2005). Interleukin-1 (IL-1) proteins, which are associated with tissue destruction due to their proinflammatory and bone-resorptive properties, have been identified in particular as critical determinants of common inflammatory disorders, and their increased levels in gingival crevicular fluid have been correlated with periodontal disease severity (Hou et al., 1995; Goutoudi et al., 2004). In addition, recent studies have indicated that polymorphisms in *IL-1* genes might be associated with greater periodontitis severity (McDevitt et al., 2000). The *IL-1* gene family includes two different but functionally similar members: *IL-1*α and *IL-1*β. Many studies have demonstrated a possible association between the *IL-1*α rs17561 and *IL-1*β rs1143634 polymorphisms and periodontitis susceptibility (Walker et al., 2000). Therefore, we hypothesized that these sequence variants constituted risk factors for this disease. In order to establish a statistically significant relationship, we performed a meta-analysis including the most recent and relevant articles.

MATERIAL AND METHODS

Literature search

We performed an extensive electronic search of the, Cochrane Library, Embase, Web of Science, SpringerLink, and Chinese Biomedical Literature databases to identify relevant studies available as of May 30, 2015. The search terms, including medical subject headings (MeSH), were as follows: ('periodontitis' [MeSH]) and ('*IL-1*α [rs17561]' or '*IL-1*α [-889]') and ('*IL-1*β [rs1143634]' or '*IL-1*β [+3954]') and ('genetic polymorphism' [MeSH]). References in eligible studies or textbooks were also reviewed by manual searching to identify other potentially appropriate studies.

Inclusion and exclusion criteria

The following inclusion criteria were used: studies had to i) consist of a case-control design; ii) focus on the association between *IL-1* rs17561 and rs1143634 polymorphisms and periodontitis; iii) include only patients diagnosed with clinical periodontitis based on symptoms; and iv) be published in English. Articles were excluded if they reported incomplete, unusable, or overlapping data, or if they were meta-analyses, letters, reviews, or editorial articles.

Data extraction

Data from published studies were independently extracted by two reviewers (W.T. Yin and Y.P. Pan) to populate a standardized form with the necessary information, as follows: first author, year of publication, language, study design, source and number of cases and controls, mean age, sample type, clinical symptoms, diagnostic criteria, genotyping method, polymorphism genotype frequency, and evidence of Hardy-Weinberg equilibrium (HWE) in the control group. In cases of conflicting evaluations, an agreement was reached following discussion with a third reviewer (L. Lin).

Quality assessment of included studies

Two reviewers (W.T. Yin and Y.P. Pan) independently assessed the quality of papers according to modified Strengthening the Reporting of Observational Studies in Epidemiology quality score systems (von Elm et al., 2007; Zhang et al., 2011b). Twenty-two quality assessment items were considered in this meta-analysis, with scores ranging from 0 to 44. Those of 0-17.5, 17.5-35, and 35-44 were defined as representing low, moderate, and high quality, respectively. Disagreement was resolved by discussion.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated using Review Manager Version 5.1.6 (provided by the Cochrane Collaboration; http://ims.cochrane.org/revman/download; accessed August 9, 2012). We also quantified the effect of heterogeneity using the I^2 test, which returns a value between 0 and 100%, and represents the proportion of inter-study variability contributed by heterogeneity rather than chance. When $P < 0.05$ or $I^2 > 50\%$ indicated the existence of heterogeneity among studies, the random-effect model was used for meta-analysis. Otherwise, the fixed-effect model was applied. We tested whether genotype frequencies in the control group were in HWE using the chi-square test. In addition, funnel plots were used to detect publication bias, with an asymmetrical plot suggesting its possible presence. All P values were two-sided. To ensure the reliability and accuracy of results, two researchers (W.T. Yin and Y.P. Pan) independently entered data into the statistical programs, obtaining the same results.

RESULTS

Characteristics of included studies

The search strategy retrieved 732 potentially relevant studies. After application of the inclusion criteria, six (Ferreira Jr. et al., 2008; Karasneh et al., 2011; Shibani et al., 2011; Al-hebshi et al., 2012; Masamatti et al., 2012; Cantore et al., 2014) were included in the meta-analysis, with 726 being excluded. A flow chart illustrating the study selection process is shown in Figure 1. The six case-control studies selected included 336 periodontitis cases and 366 healthy controls, and evaluated the relationships between the *IL-1* rs17561 and rs1143634 polymorphisms and periodontitis. These articles were published between 2008 and 2014, and all patients involved fulfilled the periodontitis diagnostic criteria. Control subjects were sourced from healthy populations, and genotype distributions in all control groups were in HWE ($P > 0.05$). All included studies had a quality score >17.5 (moderate-high quality). The characteristics and methodological quality of the included studies are summarized in Table 1.

Association between *IL-1*α gene polymorphism and periodontitis risk

Our meta-analysis findings relating to the association between the *IL-1*α polymorphism and periodontitis risk are summarized in Figure 2. We found that the T allele of rs17561 was positively associated with periodontitis susceptibility (OR = 1.50, 95% CI = 1.11-2.03, P = 0.008). In addition, rs17561 T allele carriers (heterozygous and homozygous T variants, namely TC + TT) also demonstrated greater periodontitis risk (OR = 1.57, 95% CI = 1.03-2.40, P = 0.04) compared to T allele non-carriers (wild-type sequence, namely CC).

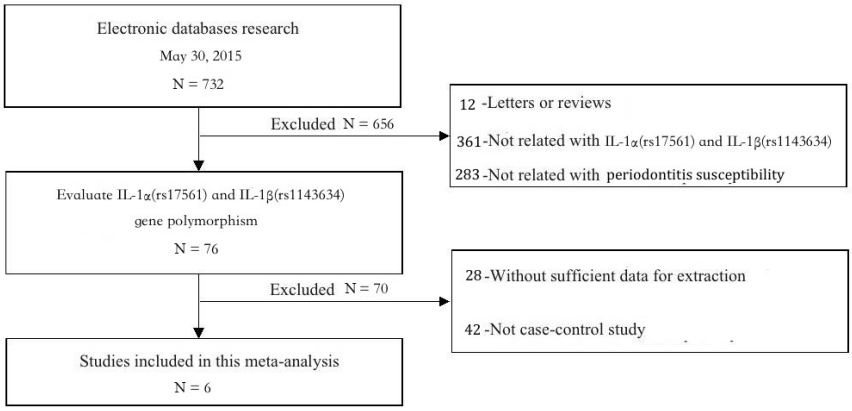

Figure 1. Flow chart describing the study selection process. In this meta-analysis, six studies were selected for qualitative analysis, including 336 periodontitis cases and 366 healthy controls.

Table 1. Characteristics and methodological quality of the included studies.

First author	Year	Cases	Controls	Sample type	Polymorphism	Quality score
Ferreira	2008	117	175	Blood	rs1143634	32
Shibani	2011	32	35	Blood	rs1143634 rs17561	25
Karasneh	2011	100	80	Blood	rs17561	30
Masamatti	2012	30	30	Blood	rs1143634	28
Al-hebshi	2012	40	40	Blood	rs1143634 rs17561	27
Cantore	2014	17	6	Blood	rs1143634 rs17561	22

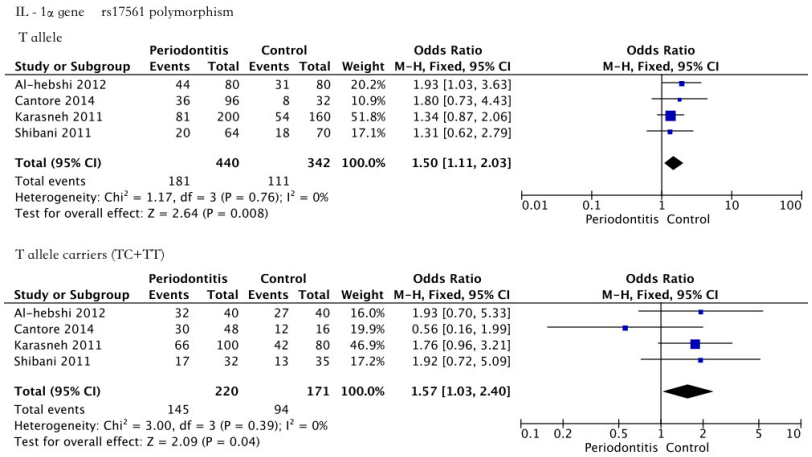

Figure 2. Summary of meta-analysis findings relating to the association between *IL-1α* polymorphisms and periodontitis risk. The T allele of rs17561 demonstrated a positive association with periodontitis susceptibility (OR = 1.50, 95% CI = 1.11-2.03, P = 0.008), as did T allele carriers (TC + TT; OR = 1.57, 95% CI = 1.03-2.40, P = 0.04). OR = odds ratio, CI = confidence interval, d.f. = degrees of freedom.

Association between *IL-1*β gene polymorphism and periodontitis risk

The relationship between the *IL-1*β polymorphism and periodontitis is shown in Figure 3. The T allele of rs1143634 exhibited a significant positive correlation with periodontitis risk (OR = 1.51, 95% CI = 1.14-2.00, P = 0.004), as did carriers of this allele (heterozygous and homozygous T variants, namely TC + TT; OR = 1.53, 95% CI = 1.06-2.21, P = 0.02).

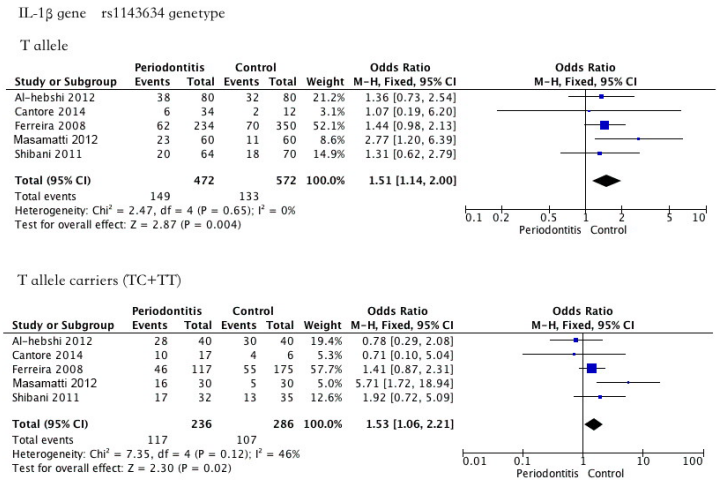

Figure 3. Association between the *IL-1*β rs1143634 polymorphism and periodontitis risk. The T allele showed a significant positive relationship with periodontitis risk (OR = 1.51, 95%CI = 1.14-2.00, P = 0.004), as did T allele carriers (TC + TT; OR = 1.53, 95% CI = 1.06-2.21, P = 0.02). OR = odds ratio, CI = confidence interval, d.f. = degrees of freedom.

Publication bias

Publication bias among the literature included was assessed using funnel plots. These were found to be symmetrical (Figure 4), indicating a lack of publication bias.

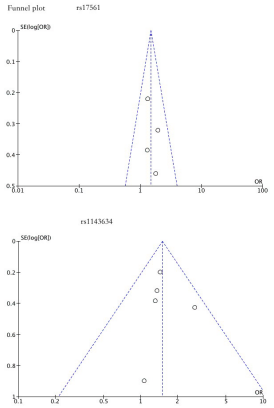

Figure 4. Symmetrical funnel plots of the included studies indicated the absence of publication bias in our meta-analysis. SE = standard error, OR = odds ratio.

DISCUSSION

Periodontitis is an infectious disease involving tissue destruction. In recent years, studies have demonstrated its association with elevated levels of a variety of inflammatory biomarkers. Moreover, genetic variants of some cytokines have been shown to increase susceptibility to this disease.

IL-1 represents a group of proinflammatory cytokines whose activity has been identified as a trigger of inflammatory disorders (Kay and Calabrese, 2004; Bartold et al., 2005; Donath and Shoelson, 2011). Many studies have reported that IL-1 levels are characteristically increased in diseased periodontal tissues, and they are thought to be a critical determinant of periodontitis outcome (Stashenko et al., 1991; Graves and Cochran, 2003; Goutoudi et al., 2004). Kornman et al. (1997) first reported the association between polymorphisms of *IL-1* genes and periodontitis. IL-1α is mainly produced by keratinocytes of the junctional or pocket epithelium, and is a mediator of local inflammation, regulating intracellular events (Dinarello, 2002). In the current study, the *IL-1*α rs17561 polymorphism showed a strong association with periodontitis (Rogers et al., 2002; Wagner et al., 2007; López et al., 2009). However, several other authors have been unable to demonstrate any such relationship (Anusaksathien et al., 2003; Sakellari et al., 2003; Brett et al., 2005; Kobayashi et al., 2007; Ferreira Jr. et al., 2008).

Extracellular IL-1β is primarily produced and released by activated macrophages and fibroblasts (Dinarello, 2002). The *IL-1*β rs1143634 single nucleotide polymorphism is associated with various inflammatory conditions (Pociot et al., 1992; Buchs et al., 2001; Chen et al., 2006), and some investigations have shown the T allele to be a risk factor in the development of severe periodontitis (Kelk et al., 2005; Bodet et al., 2006). However, other researchers have failed to confirm such an association (Kornman et al., 1997; Moreira et al., 2005) and the relevance of *IL-1*β rs1143634 to periodontitis outcome remains controversial (Shapira et al., 2005; Huynh-Ba et al., 2007). Given the interest surrounding these polymorphisms, *IL-1*α rs17561 and *IL-1*β rs1143634 are likely to be the most important sequence variants determining periodontitis pathophysiologic conditions.

In this meta-analysis, we included a total of 336 periodontitis cases and 366 healthy controls from six independent studies. We examined the associations between the rs17561 and rs1143634 polymorphisms and periodontitis risk. As with previous studies, our meta-analysis demonstrated that the T allele of rs17561 in *IL-1*α may increase periodontitis risk. In addition, we identified that rs17561 T allele carriers were positively associated with periodontitis. Moreover, our results showed that the *IL-1*β rs1143634 T allele demonstrated a significant positive correlation with periodontitis risk, while T allele carriers showed a similar relationship. In conclusion, our results showed that the *IL-1*α rs17561 and *IL-1*β rs1143634 polymorphisms are associated with periodontitis, at least in part.

As with other meta-analyses, some limitations of the current study should be addressed. First, the number of eligible studies retrieved was small and the resulting sample size was not large. Second, some relevant studies could not be included in our analysis because of incomplete data. Third, although all cases and controls in each study were well defined using similar inclusion criteria, factors relating to this, such as age, gender, race, might not have been taken into account, potentially influencing our results. Fourth, meta-analysis is a retrospective research method subject to methodological limitations. Most importantly, our meta-analysis was based on unadjusted OR estimates, as not all published studies presented adjusted ORs, or made adjustments based on different confounding variables, such as age, gender, ethnicity, and exposure. Given these complications, additional investigations in this area are needed, and our conclusions should be interpreted cautiously.

In conclusion, this meta-analysis of six case-control studies demonstrated that the *IL-1*α rs17561 and *IL-1*β rs1143634 genetic polymorphisms are involved in the pathogenesis of periodontitis. The T allele and the genotypes in which it is found may be periodontitis risk factors. As few studies have been carried out relating to this particular issue, the current evidence remains limited. Therefore, we emphasize the necessity of conducting large studies of adequate methodological quality, in which the proper control of confounding factors is practiced in order to obtain valid results.

Conflicts of interest

The authors declare no conflict of interest.

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