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Association between the interleukin-1β C-511T polymorphism and periodontitis: a meta-analysis in the Chinese population

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ABSTRACT. The association between the interleukin-1 beta (*IL-1β*) C-511T (or rs16944) polymorphism and periodontitis remains inconclusive, even though there have been previous studies on this association. To assess the effects of *IL-1β* C-511T variants on the risk of development of periodontitis, a meta-analysis was performed in a single ethnic population. Studies, published up to December 2015, were selected for the meta-analysis from PubMed and Chinese databases. The associations were assessed with pooled OR and 95%CI. This meta-analysis identified 8 studies, including 1276 periodontitis cases and 1558 controls. Overall, a significant association between the *IL-1β* C-511T polymorphism and periodontitis was found in the Chinese population (TT *vs* CC: OR = 1.48, 95%CI = 1.19-1.85; TT + CT *vs* CC: OR = 1.50, 95%CI = 1.25-1.81; T *vs* C: OR = 1.33, 95%CI = 1.06-

1.68). In the subgroup analyses based on geographical area(s), source of controls, and type of periodontitis, significant results were obtained for the association between *IL-1β* C-511T variants and periodontitis. Our meta-analysis indicated that the *IL-1β* C-511T polymorphism may be a genetic susceptibility factor for periodontitis in the Chinese population. This marker could be used to identify Chinese individuals at a high risk for periodontitis.

Key words: Meta-analysis; Interleukin-1 beta; Polymorphism; Periodontitis; Gene; Chinese

INTRODUCTION

Periodontal disease is an infection of the teeth and includes chronic and aggressive forms of the disease (Armitage, 1999). It is a broad and complex inflammatory disease, with a high prevalence of 10-15% (Albandar and Rams, 2002). Periodontitis is a multi-factorial disease, involving both genetic and environmental risk factors. Many researchers have agreed that the susceptibility to periodontal disease is at least partially genetically determined (Seymour, 1991). In recent years, many candidate genes have been identified as potential periodontitis susceptibility loci. Of these genes, an important gene is the interleukin-1 beta (*IL-1β*), which has three polymorphisms based on transitions between C and T at positions +3954/3953 (C→T, rs1143634), -511 (C→T, rs16944), and -31 (T→C, rs1143627) base pairs from the transcription site (Bird et al., 2002; Xu et al., 2013, Yin et al., 2016). The *IL-1β* C-511T single nucleotide polymorphism has been extensively studied. Kornman et al. (1997) conducted the first ever study investigating the relationship between the *IL-1β* C-511T polymorphism and periodontal diseases in a population of European-descent (Kornman et al., 1997). Consequently, many studies have been conducted to attempt to clarify this relationship; however, there has been no definite consensus to date. Differences in results may be owing to the race and clinical heterogeneity of patients, as well as a limitation in the number of patients per study. Meta-analysis is one way to overcome the problems of small sample sizes and inadequate statistical power. To address the association between the *IL-1β* C-511T polymorphism and periodontitis risk further, we performed a meta-analysis of all eligible studies based on Chinese individuals to lessen the influence of different genetic backgrounds. We also performed a subgroup analysis to explore the possible effects of gene-environment interaction on the risk of periodontitis.

MATERIAL AND METHODS

Search strategy and selection criteria

Eligible studies were identified by searching the PubMed and Chinese databases for relevant reports published before December 2015 using the following search terms: periodontitis or periodontal disease, interleukin-1 beta or *IL-1β*, and China or Chinese or Taiwan. No restriction was imposed on the search term language. Furthermore, references cited in the retrieved articles were screened for additional relevant studies.

Inclusion criteria: 1) case-control or cohort studies describing the association of the *IL-1β* C-511T polymorphism with periodontitis, 2) studies that provided information about

the genotypes of cases and controls, 3) Chinese participants. Exclusion criteria: 1) repeated literature, 2) incomplete data, 3) case-only articles, 4) review articles and abstracts, 5) participants with systemic diseases.

Data extraction

We conducted a systematic review and meta-analysis in accordance with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Two authors independently extracted information from all publications that complied with the inclusion criteria. Disagreements were resolved by discussion. First, the titles and abstracts of all identified studies were screened. Full articles were scrutinized if the title and abstract were ambiguous. Data extracted from the selected studies included first author's name, year of publication, type of periodontitis, source of controls, geographical area(s), sample size, and the number of subjects with the *IL-1β* C-511T genotype. Hardy-Weinberg equilibrium (HWE), in controls, was calculated from the corresponding genotype distributions. In this meta-analysis, the quality assessment of individual studies was conducted according to the nine-star Newcastle-Ottawa Scale (Wells et al., 2000).

Statistical analysis

Statistical analysis was conducted using the Stata 10 statistical software package (StataCorp LP, College Station, TX, USA). The chi-square test was used for determining the HWE of genotypes and the heterogeneity of rare allele frequencies in the control groups of each study reviewed. The association of the *IL-1β* C-511T polymorphism with periodontitis risk was estimated by OR with 95%CI. Depending on the results of the heterogeneity test among individual studies, the fixed-effects (Mantel-Haenszel) or random-effects (DerSimonian and Laird) models were selected to summarize the combined OR and their 95%CI. The significance of the pooled OR was determined by a Z-test, and the sensitivity was analyzed by comparing the results of the fixed-effects and random-effects models. The publication bias was assessed using the Begg rank correlation method. In addition to the comparison among all subjects, we also performed stratification analyses by geographical area(s), source of controls, and type of periodontitis. All the P values were two-sided, and a value of less than 0.05 was considered statistically significant.

RESULTS

Description of included studies

Figure 1 illustrates the literature search process in the form of a flow chart. We identified 207 articles that examined the association between the *IL-1β* polymorphisms and the risk of periodontitis from various databases. After screening the titles and abstracts, 196 articles were excluded according to the exclusion criteria described previously. Then, we reviewed all of the remaining full articles (Huang and Zhang, 2004; Zhang et al., 2004; Yang, 2008; Fan, 2009; Zhang, 2009; Li et al., 2004, 2005, 2010; Loo et al., 2012; Hao et al., 2013; Wu et al., 2015). Out of the full articles, two (Li et al., 2005; Hao et al., 2013) were excluded because of duplicate studies and one (Wu et al., 2015) for lack of raw data. Finally, 8 articles

(Huang and Zhang, 2004; Zhang et al., 2004; Yang, 2008; Fan, 2009; Zhang, 2009; Li et al., 2004, 2010; Loo et al., 2012) met the inclusion criteria completely. The publication years of these studies ranged from 2004 to 2012. In total, 1276 periodontitis cases and 1558 controls were included in this meta-analysis. The sources of controls in five studies were population-based. Characteristics of the included studies are summarized in Table 1.
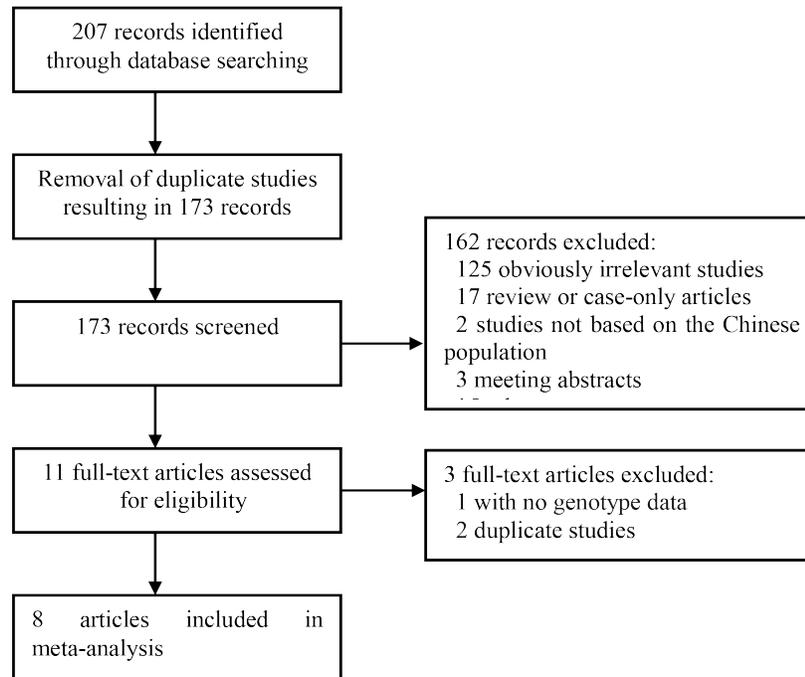

Figure 1. Flow diagram of the literature searching process.

Table 1. Characteristics of studies included in the meta-analysis.

References	Type of periodontitis	Source of controls	Quality score	Geographical area(s)	Number of cases	Number of controls	Cases			Controls			HWE	
							CC	CT	TT	CC	CT	TT	χ^2	P
Li et al. (2004)	AP	PB	8	Beijing	122	95	33	55	34	28	44	23	0.48	0.488
Huang and Zhang (2004)	CP	HB	7	Sichuan	182	89	25	58	99	21	49	19	0.92	0.337
Zhang et al. (2004)	CP	PB	7	Xinjiang	128	130	36	52	40	37	53	40	4.41	0.036
Yang (2008)	CP	PB	6	Xinjiang	44	49	11	20	13	18	21	10	0.70	0.403
Fan (2009)	CP	PB	8	Guangdong	177	139	41	78	58	36	67	36	0.18	0.671
Zhang (2009)	CP	HB	8	Lanzhou	103	126	24	54	25	38	61	27	0.07	0.785
Li et al. (2010)	CP	HB	6	Liaoning	80	80	16	36	28	34	26	20	8.68	0.003
Loo et al. (2012)	CP	PB	8	Sichuan	440	850	61	251	128	179	357	314	16.25	0.000

PB = population-based; HB = hospital-based; CP = chronic periodontitis; AP = aggressive periodontitis; HWE = Hardy-Weinberg equilibrium.

Meta-analysis

Table 2 lists the primary results of our meta-analysis. The combined results showed that *IL-1β* C-511T variants are significantly associated with an increased risk of periodontitis in the Chinese population (for TT *vs* CC: OR = 1.48, 95%CI = 1.19-1.85; for TT + CT *vs* CC:

OR = 1.50, 95%CI = 1.25-1.81; for T *vs* C: OR = 1.33, 95%CI = 1.06-1.68) (Figure 2). In the analysis of controls based on consistency with HWE, we obtained significant results among all the models (T *vs* C, OR = 1.43, 95%CI = 1.06-1.94; TT *vs* CC, OR = 1.78, 95%CI = 1.27-2.48; TT + CT *vs* CC, OR = 1.37, 95%CI = 1.04-1.81; TT *vs* CC + CT, OR = 1.71, 95%CI = 1.02-2.85) (Table 2). In subgroup analyses based on geographical area(s), source of controls, and type of periodontitis, significant results for the association between *IL-1β* C-511T variants and periodontitis were obtained (Table 2). Cumulative analysis further suggested a significant association between the *IL-1β* C-511T polymorphism and the risk of periodontitis in the Chinese population (Figure 3).
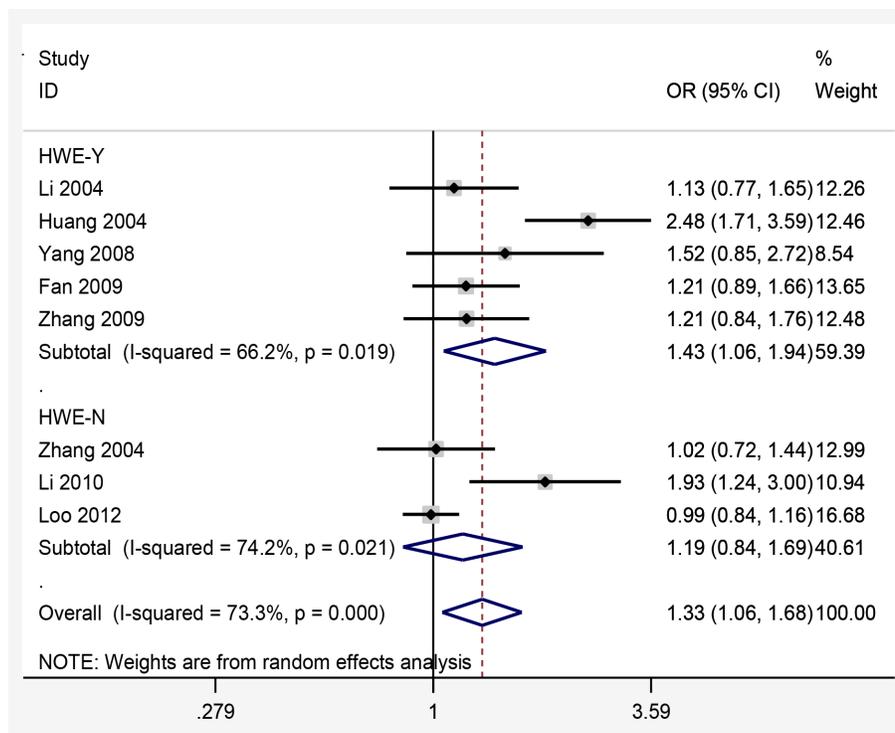

Figure 2. Forest plots of all selected studies on the association between the *IL-1β* C-511T polymorphism and periodontitis risk in the Chinese population (for allele model). HWE: Hardy-Weinberg equilibrium.

Sensitivity analysis and publication bias

In order to compare the differences and evaluate the sensitivity of the analyses, we used both models (the fixed-effects model and random-effects model) to determine the stability of this meta-analysis. All the significant pooled OR did not materially alter, suggesting that the results of this meta-analysis are stable (Table 2). The Begg rank correlation method was performed to assess the publication bias in the allele model. No evidence of publication bias was observed (P = 0.138).
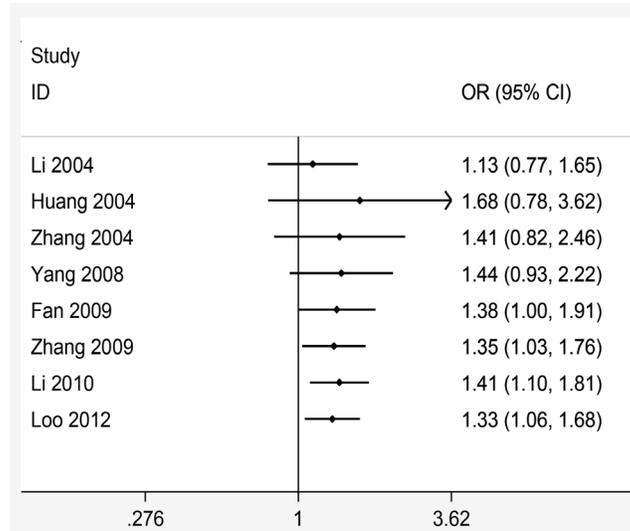
Figure 3. Cumulative analysis of the relationship between the *IL-1β* C-511T polymorphism and periodontitis risk in the Chinese population (for allele model).

Table 2. Association of *IL-1β* C-511T polymorphism with periodontitis susceptibility.

Analysis model		N	ORr (95%CI)	ORf (95%CI)	P_h
T *vs* C	Total analysis	8	1.33 (1.06-1.68)	1.19 (1.07-1.33)	0.000
	In HWE	5	1.43 (1.06-1.94)	1.42 (1.19-1.68)	0.019
	Population-based	5	1.06 (0.93-1.20)	1.06 (0.93-1.20)	0.543
	Hospital-based	3	1.79 (1.16-2.77)	1.77 (1.42-2.22)	0.026
	North China	5	1.27 (1.02-1.59)	1.26 (1.05-1.50)	0.217
	South China	3	1.41 (0.85-2.33)	1.16 (1.01-1.33)	0.000
	CP	7	1.37 (1.05-1.78)	1.20 (1.07-1.34)	0.000
TT *vs* CC	Total analysis	8	1.63 (1.17-2.28)	1.48 (1.19-1.85)	0.054
	In HWE	5	1.84 (1.16-2.91)	1.78 (1.27-2.48)	0.127
	Population-based	5	1.24 (0.97-1.60)	1.24 (0.97-1.60)	0.835
	Hospital-based	3	2.66 (1.39-5.08)	2.59 (1.66-4.05)	0.124
	North China	5	1.51 (1.04-2.20)	1.50 (1.06-2.11)	0.329
	South China	3	1.83 (0.91-3.68)	1.48 (1.11-1.96)	0.010
	CP	7	1.71 (1.17-2.50)	1.51 (1.20-1.90)	0.035
TT *vs* CC + CT	Total analysis	8	1.38 (0.90-2.13)	1.09 (0.93-1.28)	0.000
	In HWE	5	1.71 (1.02-2.85)	1.75 (1.34-2.28)	0.010
	Population-based	5	1.05 (0.74-1.49)	0.89 (0.74-1.07)	0.048
	Hospital-based	3	2.05 (0.91-4.62)	2.18 (1.53-3.09)	0.006
	North China	5	1.24 (0.93-1.65)	1.24 (0.93-1.65)	0.836
	South China	3	1.58 (0.56-4.44)	1.02 (0.84-1.25)	0.000
	CP	7	1.41 (0.86-2.31)	1.08 (0.91-1.28)	0.000
TT + CT *vs* CC	Total analysis	8	1.49 (1.20-1.85)	1.50 (1.25-1.81)	0.290
	In HWE	5	1.38 (1.04-1.81)	1.37 (1.04-1.81)	0.696
	Population-based	5	1.37 (1.10-1.70)	1.38 (1.11-1.71)	0.456
	Hospital-based	3	1.95 (1.29-2.93)	1.93 (1.34-2.80)	0.298
	North China	5	1.45 (1.01-2.10)	1.42 (1.07-1.88)	0.171
	South China	3	1.56 (1.22-2.00)	1.56 (1.22-2.00)	0.397
	CP	7	1.54 (1.22-1.95)	1.55 (1.27-1.88)	0.273

ORr = odds ratio for random-effects model; ORf = odds ratio for fixed-effects model; P_h P = value for heterogeneity test; HWE = Hardy-Weinberg equilibrium; North China included Beijing, Lanzhou, Xinjiang, and Liaoning; South China included Sichuan and Guangdong.

DISCUSSION

Periodontitis is a multifactorial and inflammatory disease that is mainly related to oral hygiene. Convincing evidence has emerged that susceptibility to periodontal disease is partially based on a genetic predisposition to the disease. The relationship between the *IL-1β* C-511T polymorphism and periodontitis risk has attracted the attention of both doctors and researchers. Ever since the first reported study on the association between the *IL-1β* C-511T polymorphism and chronic periodontitis in a population of European-descent (Kornman et al., 1997), many studies have been undertaken to explore this association. However, results of individual studies have been inconclusive. Regional and racial differences are the likely reasons for disparity in the results. Therefore, we performed this meta-analysis to assess the effects of the *IL-1β* C-511T polymorphism on the risk of periodontitis in the Chinese population.

Our meta-analysis included 8 case-control studies with 1276 periodontitis cases and 1558 controls. Results showed a significant association between the *IL-1β* C-511T polymorphism and periodontitis in the overall and subgroup analyses. Controls of two of the cohorts were not in HWE (P < 0.05), including the Loo et al. (2012) cohort, which contributed more than 50% of the controls to the study. We further performed analyses based on consistency of controls with HWE, and the results showed a significant association between the *IL-1β* C-511T polymorphism and periodontitis risk. Cumulative meta-analysis also revealed a trend of an increasingly obvious association between *IL-1β* C-511T variant T and the risk of periodontitis in Chinese individuals as per data accumulated by publication year (Figure 3). The findings from this meta-analysis provide new and strong epidemiological evidence for the association between *IL-1β* C-511T variants and the risk of periodontitis in the Chinese population.

As compared to a previous meta-analysis by Hu et al. (2015), which included only one case-control study based on the Chinese population, our meta-analysis contained more studies using the Chinese population. Furthermore, in another meta-analysis conducted by Zeng et al. (2015), two of the studies (Loo et al., 2012; Hao et al., 2013) potentially involved the same subjects of the Chinese population. The present meta-analysis was strengthened by the exclusion of duplicated studies, and significant results were revealed in the subgroup and overall analyses. The effects of gene-environment interactions with respect to periodontitis risk were determined by subgroup analyses. Additionally, we were able to explore the relationship between the *IL-1β* C-511T polymorphism and the risk of periodontitis without the possible influence of differing genetic backgrounds and living environments on the results. Sensitivity analyses confirmed the reliability and stability of the meta-analysis. Therefore, our results indicated that the *IL-1β* C-511T polymorphism is associated with the susceptibility to periodontitis in individuals from China.

Although our study has strengths such as the investigation of the influence of geographical area(s) and source of control on the association between the *IL-1* C-511T polymorphism and the risk of periodontitis, there are several limitations as well. Firstly, this ethnicity-specific meta-analysis includes data of only Chinese subjects, and thus, our results are applicable to only this ethnic group. Secondly, since this meta-analysis was based primarily on unadjusted effect estimates and CI, confounding factors were not controlled. Thirdly, although we devised a comprehensive search strategy, relatively less number of studies complied with the inclusion criteria.

In conclusion, this meta-analysis indicates that the *IL-1β* C-511T polymorphism is associated with the risk of periodontitis in the Chinese population. Ethnicity seems to play a role in the genetic association of the disease. Since the number of studies analyzed was less, further meta-analyses of larger populations with multiple adjusted variables need to be conducted to achieve robust results and allow for investigation of gene-gene and gene-environment interactions.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

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