Interleukin-1β (3953/4) C→T polymorphism increases the risk of chronic periodontitis in Asians: evidence from a meta-analysis of 20 case-control studies

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Abstract

Introduction: To investigate the association of the interleukin-1β (IL-1β) (3953/4) C→T polymorphism with chronic periodontitis (CP) in Asians.
Material and methods: Systematic searches of electronic databases and hand searching of references were performed, including PubMed, Embase, the Cochrane Library, and the Chinese National Knowledge Infrastructure (CNKI). Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the associations. Publication bias was tested by Egger's test. Sensitivity analysis was conducted by limiting the meta-analysis studies conforming to Hardy-Weinberg equilibrium (HWE). Data analyses were carried out using RevMan 6.0.
Results: A meta-analysis was performed on 20 published case-control studies, including 1,656 CP cases and 1,498 healthy controls. The pooled OR was 1.60 (95% CI = 1.02–2.52, p = 0.04) for the T allele carriers (TT + CT) compared with CC and 1.60 (95% CI = 1.06–2.42, p = 0.02) for T vs. C. Subgroup analysis by country revealed significant risks of CP among Indians carrying the T allele (TT vs. CC: OR = 3.88, 95% CI = 1.77–8.50, p = 0.0007).
Conclusions: The analysis showed that IL-1β (3953/4) C→T polymorphism probably increases the risk of CP in Asians, and the IL-1β+3954 TT genotype may be associated with a strongly increased risk of CP in Indians, but not in Chinese.

Key words: polymorphism, interleukin-1, chronic periodontitis, meta-analysis, Asians.

Introduction

Periodontal disease is a chronic inflammatory disease of bacterial etiology resulting in loss of the supporting tissues, including formation of periodontal pockets, attachment loss and alveolar bone resorption [1]. It is widely regarded as one of the most common diseases worldwide. According to the International Workshop for Classification of Periodontal Disease, periodontitis can be classified into several categories, including chronic periodontitis (CP), aggressive periodontitis (AgP), and periodontitis as a manifestation of systemic diseases [2]. Chronic periodontitis is relatively common, affecting up to 30% of adults, while 7–13% of the adult population will develop severe forms of destructive periodontal

disease [3]. A study of adults in the United States showed that over 47% of the sample, representing 64.7 million adults, had periodontitis [4]. Although pathogenic microbes are regarded as the primary etiological factor of periodontitis, genetic and environmental factors affect the age of onset, severity, and lifetime risk of developing the disease [5]. Twin studies have suggested that as much as 50% of the risk of periodontitis may be attributed to genetic factors [6].

The interleukin (IL)-1 gene cluster has been mapped to the long arm of chromosome 2 and consists of three genes, IL-1α, IL-1β and IL1-RN, encoding IL-1α, IL-1β and IL-1 receptor antagonist proteins, respectively [7, 8]. Among them, IL-1β is the most pathogenic and potent form. IL-1β has been demonstrated to be a multi-effect mediator of many physiological functions. IL-1β is a proinflammatory cytokine mainly produced by blood monocytes and tissue macrophages and has been implicated in mediating both acute and chronic inflammation [9].

Previous studies revealed that IL-1β (3953/4) C/T polymorphism (rs1143634) was significantly associated with an increased risk of CP especially among Caucasians, indicating that the increased levels of IL-1β in serum were associated with the T allele [10]. Until now, many studies have researched the role of IL-1β (3953/4) C/T polymorphism in CP. Some studies have also indicated that the TT genotype may increase the risk of CP among Asians [11], while subsequent studies found different or even conflicting results [12]. One recent meta-analysis has also been conducted to evaluate the association between IL-1β (3953/4) C/T polymorphism and CP [13]. The study showed that statistically significantly elevated risk was found for Caucasians, but not for Asians, when stratified by ethnicity, based on 15 studies of Asians [13]. It is still obscure whether IL-1β (3953/4) C→T polymorphism is associated with a risk or a protective effect among Asians.

The aim of this study was to assess the overall relationship between the IL-1β (3953/4) C→T polymorphism and CP based on published case-control studies in Asians.

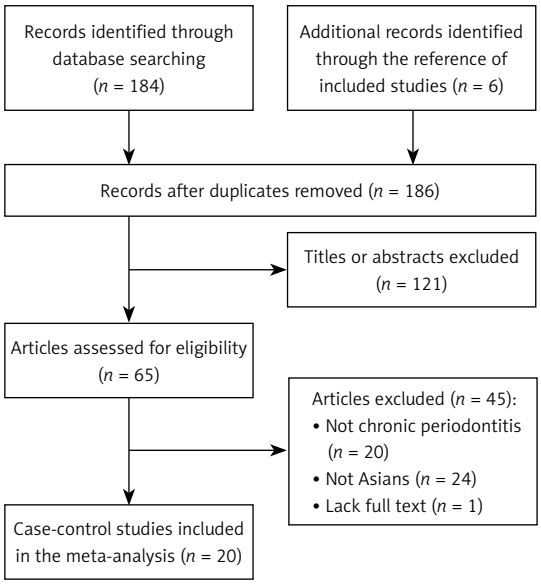

Figure 1. Flow chart from identification of eligible studies for final inclusion

Material and methods

Search strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria [14]. We searched in the following electronic databases: PubMed, Embase, the Cochrane Library, and the Chinese National Knowledge Infrastructure (CNKI) (last search was updated on 15 December 2013) with a combination of the following words: "polymorphism/mutation/variant", "interleukin-1/IL-1/rs1143634", and "chronic periodontitis/CP/adult periodontitis". Other relevant studies were identified by hand-searching the references of included articles identified by the electronic search. Language was limited to English and Chinese. When more than one of the same population was included in several publications, only the most recent or complete study was used in this meta-analysis. Two investigators (Ma and Chu) screened each of the titles, abstracts, and full texts to determine inclusion independently. The results were compared and disagreements were resolved by consensus. Articles reporting an association between IL-1 polymorphisms and periodontitis were identified.

Inclusion and exclusion criteria

Eligible studies included in this meta-analysis had to meet the following criteria: (1) Published case-control studies; (2) Studies on the association between IL-1β (3953/4) C/T polymorphism and chronic periodontitis in Asians; (3) Studies with full text articles; (4) Articles must offer the size of the sample, the distribution of alleles and genotypes, or the information for us to infer the results; (5) If multiple publications reported on the same or overlapping data, the largest or most recent publication was selected. Major exclusion criteria were: (1) No control subjects; (2) With systemic diseases; (3) No usable genotype distribution or allele frequency data. Twenty case-control studies of CP including 1656 patients with CP and 1498 healthy controls were identified (Figure 1).

Data extraction

Information was independently extracted from all eligible studies by two researchers (Ma and

Chu), according to the above-mentioned inclusion and exclusion criteria. Extracted information included: the first author's name, publication date, country/region, subject ethnicity, genotype distribution (cases and controls), genotyping method, and P for Hardy-Weinberg equilibrium (HWE) (a p value less than 0.05 was considered significant). Different ethnicities were categorized as Chinese, Indian, and other Asians.

Quality score assessment

The quality of included studies was assessed independently by the same two investigators using the Newcastle-Ottawa Scale (NOS) [15]. The NOS uses a 'star' rating system to judge quality based on three aspects of the study: selection, comparability, and exposure. Studies with a score of seven stars or more were considered to be of high quality.

Statistical analysis

Crude odds ratios (ORs) with 95% confidence intervals (CIs) were computed to assess the strength of the relationship between the IL-1β (3953/4) C/T polymorphism and CP risk. Pooled ORs were calculated for contrasting alleles (T vs. C), a codominant model (TT vs. CC), and a recessive model (TT vs. CT + CC). Subgroup analysis was conducted for two countries. Heterogeneity assumption was assessed using the χ^2-based Q-test [16]. The pooled OR estimation for each study was calculated using a fixed-effects model (Mantel-Haenszel method) when $p > 0.10$. Otherwise, a random-effects model (DerSimonian and Laird method) was used [17]. In the absence of between-study heterogeneity, the two methods provided identical results. Publication bias was tested by the Egger regression test for funnel-plot asymmetry [18]. Statistical analysis was performed using the software package Review Manager 6.0.

Results

Study characteristics

Twenty case control-studies met the inclusion criteria [11, 12, 19–36]. A total of 1,656 patients with CP and 1,498 healthy controls were includ-

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

Authors (years)	Country	Cases			Controls			Genotyping method	Value of p
		CC	CT	TT	CC	CT	TT		
Duan (2002)	China	23	7	0	90	4	0	PCR	0.83
Zhong (2002)	China	90	38	5	70	17	5	PCR-RFLP	0.01
Lin (2003)	China	89	35	0	148	24	0	PCR	#
Yoshihiko (2003)	Japan	60	4	0	59	5	0	PCR-RFLP	0.75
Anusaksathien (2003)	Thailand	54	0	0	42	1	0	PCR-RFLP	0.94
Huang, Zhang (2004)	China	151	31	0	85	4	0	PCR-RFLP	0.83
Tian (2006)	China	32	4	0	36	0	0	PCR	#
Agrawal (2006)	India	16	49	25	12	15	3	PCR-RFLP	0.59
Han (2009)	China	62	4	0	47	3	0	PCR-RFLP	0.83
Kaarthikeyan (2009)	India	21	9	0	24	6	1	PCR-SSP	0.44
Kobayashi (2009)	Japan	111	6	0	102	6	0	PCR-RFLP	0.77
Shete (2010)	India	40	3	0	75	25	1	PCR-RFLP	0.49
Prakash (2010)	India	38	30	7	39	9	0	PCR	0.47
Karasneh (2011)	Jordan	47	44	9	41	33	6	PCR-RFLP	0.86
Yang (2011)	China	162	34	19	125	62	32	PCR-RFLP	0.00
Ma (2011)	China	55	21	20	77	17	10	PCR-RFLP	0.00
Gayathri (2011)	India	34	16	1	28	24	0	PCR-RFLP	0.03
Al-Hebshi (2012)	Yemen	8	20	12	13	23	4	TaqMan	0.18
Masamatti (2012)	India	14	8	7	22	5	3	PCR-RFLP	0.01
Archana (2012)	India	16	29	0	14	1	0	PCR-RFLP	#

ed in this meta-analysis. Three publications had inadequate information to allow ORs to be calculated for all contrasts [22, 35, 37]. The 20 included studies performed in Asian populations are summarized in Table I. The studies used various genotyping methods, including polymerase chain reaction-restriction fragment length polymorphism, polymerase chain reaction with sequence-specific primers and TaqMan analysis. Five studies were not in agreement with the Hardy-Weinberg equilibrium of the genotype distribution in the controls [11, 12, 20, 32, 36]. Seven studies enrolled Indian subjects [25, 27, 30–32, 35, 36], and eight enrolled Chinese subjects [11, 12, 19, 20, 22, 24, 26, 27]. Two publications had inadequate information to calculate ORs in all contrasts [22, 35].

Overall and subgroup meta-analysis

The main results of this meta-analysis and the ORs for the associations between CP and IL-1β (3953/4) C/T genotype in different regions are shown in Table II. Overall, there was an association between the IL-1β (3953/4) C/T polymorphism and CP risk (for T vs. C: OR = 1.60, 95% CI = 1.06–2.42, $p = 0.02$; for (TT + CT) vs. CC: OR = 1.60, 95% CI = 1.02–2.52, $p = 0.04$) in Asians (Table II, Figure 2). Subgroup analysis by region revealed that the IL-1β (3953/4) C/T polymorphism was also significantly associated with the risk of CP in Indians (for the allele contrast TT vs. CC: OR = 3.88, 95% CI = 1.77–8.50, $p = 0.0007$) (Figure 3), but not in Chinese subjects.

Publication bias

No evidence of publication bias was found in this meta-analysis of the model T vs. C in Asians. As shown in Figure 4, the shapes of the funnel plots did not reveal any visual evidence of obvious asymmetry. This result was also supported by the results of Egger's tests.

Discussion

Interleukin-1 is a key regulator of the host response and a major modulator of extracellular matrix catabolism and bone resorption. Several IL-1 gene single nucleotide polymorphisms (SNPs) have been associated with an increased susceptibility to inflammatory diseases, including periodontitis [38–41]. It has been proven that IL-1β can promote the movement of inflammatory cells from the blood to inflamed tissues, regulate the extracellular matrix and induce other cytokines [42–45], and IL-1β gene polymorphisms were previously reported to be associated with the severity of CP [46, 47].

Previous studies including one recent meta-analysis have revealed that IL-1β (3953/4) C→T polymorphism (rs1143634) was significantly associated with an increased risk of CP especially among Caucasians [13]. A recent meta-analysis showed that statistically significantly elevated risk was found for Caucasians, but not for Asians, when stratified by ethnicity, based on 15 studies of Asians [13]. Some studies suggested that the T

Table II. Results of overall and subgroups analysis of pooled ORs and 95% CIs

Region (*N*)	OR	95% CI	Value of *p*	Model
Asian (20):				
T vs. C	1.60	1.06–2.42	0.02	Random
TT vs. CC	1.86	0.89–3.88	0.10	Random
TT vs. CT + CC	1.46	0.79–2.69	0.23	Random
TT + CT vs. CC	1.60	1.02–2.52	0.04	Random
China (8):				
T vs. C	1.83	0.85–3.94	0.12	Random
TT vs. CC	0.99	0.29–3.37	0.99	Random
TT vs. CT + CC	0.99	0.36–2.74	0.99	Random
TT + CT vs. CC	1.98	0.95–4.14	0.07	Random
India (7):				
T vs. C	1.40	0.68–2.89	0.36	Random
TT vs. CC	3.88	1.77–8.50	0.0007	Fixed
TT vs. CT + CC	1.59	0.76–3.35	0.22	Fixed
TT + CT vs. CC	1.86	0.75–4.65	0.18	Random

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio M-H, random, 95% CI	Year
Duan	7	60	4	188	4.6	6.08 (1.71, 21.55)	2002
Zhong	48	266	27	184	7.2	1.28 (0.77, 2.14)	2002
Anusaksathen	0	108	1	86	1.4	0.26 (0.01, 6.53)	2003
Yoshihiko Soga	40	200	5	128	5.6	6.15 (2.36, 16.04)	2003
Lin	0	0	0	344		Not estimable	2003
Huang, Zhang	31	364	4	178	5.3	4.05 (1,41, 11.66)	2004
Tian	4	72	0	72	1.6	9.53 (0.50, 180.25)	2006
Agrawal	99	180	21	60	6.9	2.27 (1.24, 4.16)	2006
Han	4	132	3	100	3.9	1.01 (0.22, 4.62)	2009
Kobayashi	6	234	6	216	5.0	0.92 (0.29, 2.90)	2009
Kaarthikeyan	9	60	8	62	5.4	1.19 (0.43, 3.32)	2009
Shete	3	86	27	202	4.7	0.23 (0.07, 0.79)	2010
Prakash	44	150	9	96	6.3	4.01 (1.86, 8.68)	2010
Gayathri	18	102	24	104	6.6	0.71 (0.36, 1.41)	2011
Yang	72	430	126	438	7.7	0.50 (0.36, 0.69)	2011
Karasneh	62	200	45	160	7.4	1.15 (0.73, 1.81)	2011
Ma	61	192	37	208	7.4	2.15 (1.36, 3.43)	2011
Archana	0	0	0	0		Not estimable	2012
Al-hebshi	44	80	31	80	6.8	1.93 (1.03, 3.63)	2012
Masamatti	22	58	11	60	6.1	2.72 (1.17, 6.32)	2012
Total (95% CI)		2974		2966	100.0	1.60 (1.06, 2.42)	
Total events	574		389				

Heterogeneity: $\tau^2 = 0.54$, $\chi^2 = 87.71$, $df = 17$ ($p < 0.00001$), $I^2 = 81\%$

Test for overall effect: $Z = 2.25$ ($p = 0.02$)

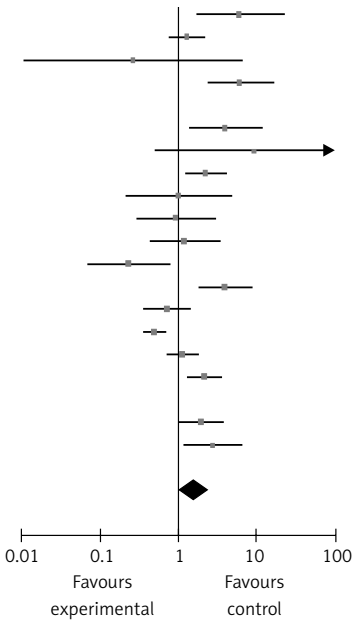

Figure 2. Forest plots of contrasting allelic model (T allele vs. C allele) in Asians

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio M-H, random, 95% CI	Year
Agrawal	25	41	3	15	24.99	6.25 (1.52, 25.66)	2006
Kaarthikeyan	0	21	1	25	19.5	0.38 (0.01, 9.82)	2009
Prakash	7	45	0	39	6.5	15.39 (0.85, 278.83)	2010
Shete	0	40	1	76	14.9	0.62 (0.02, 15.60)	2010
Gayathri	1	35	0	28	7.7	2.48 (0.10, 63.21)	2011
Masamatti	7	21	3	25	26.5	3.67 (0.81, 16.59)	2012
Archana	0	0	0	0		Not estimable	2012
Total (95% CI)		203		208	100.0	3.88 (1.77, 8.50)	
Total events	40		8				

Heterogeneity: $\chi^2 = 4.59$, $df = 5$ ($p = 0.47$), $I^2 = 0\%$

Test for overall effect: $Z = 3.39$ ($p = 0.0007$)

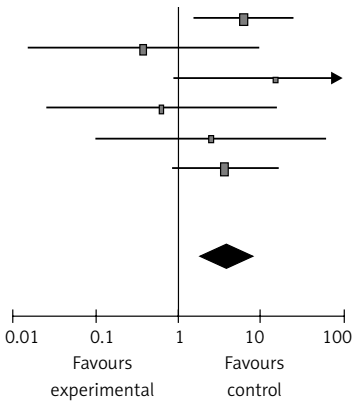

Figure 3. Forest plots of codominant model (TT allele vs. CC allele) in Indians

allele may increase the risk of CP among Asians [11, 12], while Yang also observed an increased frequency of the C allele in Chinese with CP, compared with the control group [11]. Above all, the relationship between the IL-1β (3953/4) C→T polymorphism and CP among Asians is still obscure.

The current meta-analysis investigated the association between the IL-1β (3953/4) C→T polymorphism and CP risk based on 20 case-control studies, mostly performed in Chinese and Indian populations. The results indicated that the T allele increased the risk of CP in Asians (T vs. C: OR = 1.60, 95% CI = 1.06–2.42, $p = 0.02$), in accordance with the results of previous studies. The allelic model suggested that T allele carriers, including T/T and C/T genotypes, were at 1.60-fold increased risk of CP compared with C allele carri-

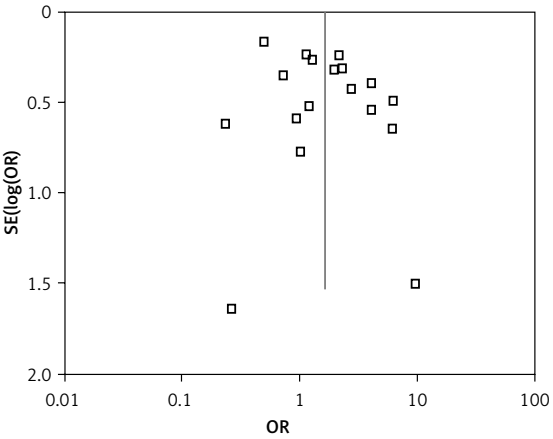

Figure 4. Funnel plots for the assessment of publication bias for the IL-1β (3953/4) C→T polymorphism (T vs. C in Asians)

ers, thus providing evidence for the existence of an association between the IL-1β (3953/4) C→T polymorphism and CP in Asians.

Subgroup analysis by country also identified a significant association between the IL-1β (3953/4) C→T polymorphism and CP risk in Indians, but not in Chinese, indicating possible background genetic and environmental influences (for TT vs. CC: OR = 3.88, 95% CI = 1.77–8.50, p = 0.0007 in Indians).

Chronic periodontitis is a serious and prevalent chronic inflammatory disease in humans, and it is therefore important to clarify its etiology. Environmental factors such as infection by specific bacteria, smoking, and untreated diabetes mellitus are associated with the occurrence of periodontal disease. The development of CP is likely to involve multi-gene interactions. Further stratified analyses and more comprehensive meta-analyses are needed to confirm the real etiological agents of CP in different countries and regions, and among different ethnic groups.

However, our meta-analysis had some limitations. First, ethnicity was the most serious confounding factor affecting the genetic meta-analysis. Although we performed subgroup analysis according to the country, we cannot exclude the fact that some studies did not report the ethnicity of the subjects they investigated, especially in India, which is called a "great museum of human ethnicity". Second, more precise evaluations with adjusted ORs by age, gender, and other environmental factors such as smoking status were not feasible because of a lack of available information. Third, the language of the articles was limited to English and Chinese. Studies in other language were excluded in our study. Finally, studies included in our meta-analysis were limited to those that were published and found in databases including PubMed, Embase, the Cochrane Library, and the CNKI. We did not track unpublished articles such as meeting proceedings to obtain data for analysis. This may have influenced the completeness of the data.

In conclusion, our meta-analysis based on 1,656 CP patients and 1,498 healthy controls showed that IL-1β (3953/4) C→T polymorphism probably increased the risk of CP in Asians, and the IL-1β + 3954 TT genotype may be associated with a strongly increased risk of CP in Indians, but not in Chinese. However, given the limitations of this meta-analysis, we cannot obtain a conclusive result, and the current results should be interpreted with caution.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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