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Original Article

Interleukin-1β rs1143634 polymorphism and aggressive periodontitis susceptibility: a meta-analysis

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Abstract: Multiple studies had focused on the association between interleukin-1 (IL-1) rs1143634 polymorphism and aggressive periodontitis (AgP) susceptibility, but the results remained inconclusive. Therefore, this meta-analysis was conducted to explore its role in the development of AgP. PubMed and Embase databases were searched up to April 15, 2014. After study selection and data extraction form eligible studies, meta-analysis was performed. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the association. All the analysis was performed using Comprehensive Meta-Analysis software. Finally a total of 25 case-control studies were included. The pooled results showed non-association between AgP susceptibility and IL-1 rs1143634 polymorphism [for T vs. C: OR = 0.99, 95% CI = 0.79-1.23; for TT vs. CC: OR = 1.14, 95% CI = 0.78-1.66; for CT vs. CC: OR = 0.97, 95% CI = 0.70-1.36; for (CT + TT) vs. CC: OR = 1.02, 95% CI = 0.76-1.37; for TT vs. (CT + CC): OR = 1.22, 95% CI = 0.85-1.75]. Subgroup analyses remain did not find any association. No publication bias was detected. Hence, our meta-analysis showed that IL-1β rs1143634 polymorphism is not linked to AgP susceptibility, regardless of ethnicity.

Keywords: Interleukin-1, periodontitis, aggressive periodontitis, polymorphism, meta-analysis

Introduction

There are 200 possible connections between systemic diseases and periodontal disease have been highlighted by the American dental association in 2006 [1], such as chronic obstructive pulmonary diseases [2], head and neck cancer [3], cardiovascular diseases [4], diabetes [5]. Therefore, seek the risk factor of periodontal disease and prevent them is an important and interesting work for overall health. Periodontal disease is divided into two major forms, namely, chronic periodontitis (CP) and aggressive periodontitis (AgP) [6]. CP is widely regarded as one of the most common diseases with a prevalence of 10-15% [7] whereas AgP is less prevalent than CP. However, AgP shows more rapid attachment loss and bone destruction than CP [8]. Both CP and AgP were believed as multifactor diseases [9], environmental and genetic factors combines play a role to make individuals affected [10]. However, the susceptibility is not always the same to CP and AgP for the same genetic polymorphism, sometimes is linked to CP but not linked to AgP [11-13].

Interleukin-1 (IL-1) is considered to be one of the most active stimulators of osteoclastic activity and contributed to periodontal disease development [14]. The IL-1 gene family locates on chromosome 2q13-14 and encodes three proteins: IL-1α (alpha), IL-1β (beta), and IL-1RN (receptor antagonist); of them, IL-1β is believed as the most potent and pathogenic form [15, 16]. The IL-1β gene is highly polymorphic and three polymorphisms that base on transitions between C and T at positions -511 (C→T, rs16944), -31 (T→C, rs1143627), and +3954/3953 (C→T, rs1143634) base pairs from the transcriptional site have been widely researched [16, 17]. The IL-1β rs1143634 is a

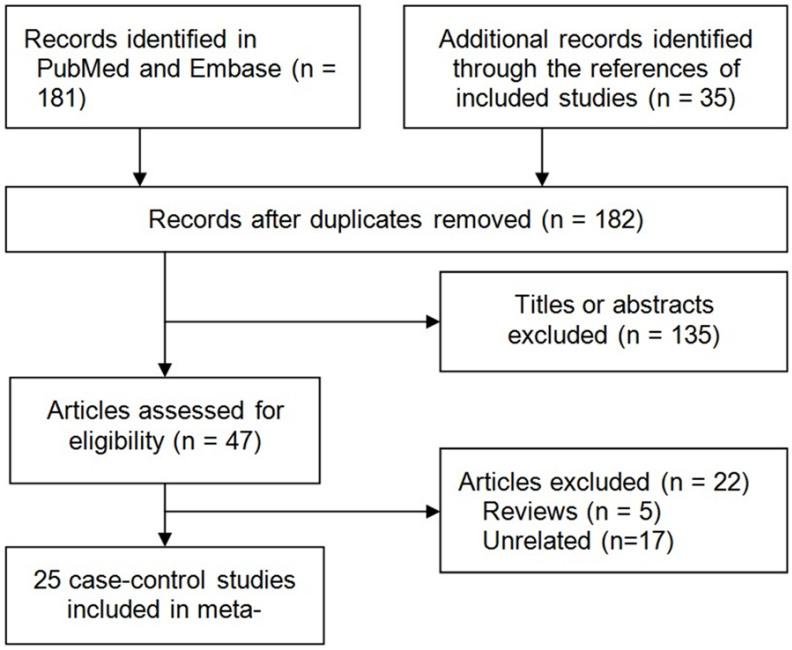

Figure 1. Flow chart from identification of eligible studies to final inclusion.

synonymous single nucleotide polymorphism and locates in exon 5, a published meta-analysis indicated that IL-1β rs1143634 polymorphism was associated with increased risk of CP [18]. For CP and AgP are different types of periodontal disease and the results of numerous epidemiological studies that investigated the association between IL-1β rs1143634 polymorphism and AgP were inconsistent, we conducted this meta-analysis for deriving a more precise estimation of the association between IL-1β rs1143634 polymorphism and AgP.

Materials and methods

We following the recommended Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (File S1) [19] to report this meta-analysis.

Eligibility criteria

The study was included if it met all the following criteria: (1) the design was a case-control study, (2) the topic was evaluated the association between IL-1β rs1143634 polymorphism and AgP susceptibility, (3) the AgP patient was not company with other systematic diseases and the control was healthy individuals or periodontitis-free; (4) reported odds ratios (ORs) and its 95% confidence intervals (CIs) or/and the number of genotypes in both case and control group, or the reported data can calculate them.

Search strategy

The PubMed and Embase databases were comprehensively searched using the search terms [(polymorphism OR mutation OR variant) AND (interleukin-1 OR IL-1) AND (periodontal disease OR periodontitis)] up to April 15, 2014. For each identified study, additional studies were manually searched from its references.

Data extraction

Two authors independently selected studies according to the criteria listed above and then extracted data from all eligible studies. The first author's name, publication year, country of origin and ethnicity, source of control, genotyping method, number of cases and controls and genotype frequency, ORs and its 95% CIs, and HWE (Hardy Weinberg Equilibrium) for controls were gathered from each study. All disagreements were resolved by asking a third author.

Data analysis

First, the heterogeneity among included studies was detected using I^2 statistics [20]. The value of $I^2 \leq 40\%$ was considered no substantive heterogeneity existed and we used the fixed effect model to pool the data; otherwise, the random-effects model was used [21]. The ORs and corresponding 95% CIs was used for estimating the association between IL-1β rs1143634 polymorphism and AgP using the five genetic models: allele comparison (T vs. C), homozygote comparison (TT vs. CC), heterozygote comparison (CT vs. CC), dominant model (TT + CT vs. CC), and recessive model (CC + CT vs. TT). The subgroups analysis based on the ethnicity, source of controls, and the HWE for controls were conducted to explore the potential source of heterogeneity among studies and test the effects of study characteristics on the

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

Reference	Country (Ethnicity)	Sample size (case/control)	Source of control	Genotype method	HWE (*P* value)
Walker 2000	USA (African-American)	37/104	PB	PCR	0.89
Parkhill 2000	UK (Caucasian)	70/72	Mixed	PCR	< 0.05
Hodge 2001	UK (Caucasian)	56/56	HB	PCR	0.34
Duan 2002	China (Asian)	20/94	HB	PCR-RFLP	0.83
Rogers 2002	Australia (Caucasian)	21/60	PB	PCR	0.21
Tai 2002	Japan (Asian)	47/97	HB	PCR	0.63
Anusaksathien 2003	Thailand (Asian)	26/43	HB	PCR	0.94
Gonzales 2003	Germany (Caucasian)	44/47	PB	PCR	0.13
Li 2004	China (Asian)	122/95	Mixed	PCR-RFLP	0.92
Quappe 2004	Chile (Caucasian)	36/75	HB	PCR	0.07
Moreira 2005	Brazil (Mixed)	31/46	PB	PCR	0.31
Brett 2005	UK (Caucasian)	50/103	PB	PCR	0.39
Scapoli 2005	Italy (Caucasian)	40/96	PB	PCR	0.99
Sakellari 2006	Greece (Caucasian)	46/90	Mixed	PCR	0.73
Havemose-Poulsen 2007	Denmark (Caucasian)	45/25	HB	PCR-RFLP	0.27
Guzeldemir 2008	Turkey (Caucasian)	31/31	PB	PCR	< 0.05
Karasneh 2011	Jordan (Caucasian)	80/80	PB	PCR	0.86
Schulz 2011	Germany (Caucasian)	85/88	PB	PCR-SSP	0.88
Shibani 2011	Syria (Caucasian)	32/35	PB	PCR	< 0.05
Masamatti 2012	India (Asian)	30/30	HB	PCR	< 0.05
Ebadian 2013	Iran (Iran)	53/48	HB	PCR-RFLP	0.95
Ayazi 2013	Iran (Iran)	26/26	HB	PCR-RFLP	0.09
Yücel 2013	Turkey (Caucasian)	56/47	PB	PCR-RFLP	< 0.05
Fiebig 2008*	Germany and Netherlands (Caucasian)	415/874	PB	TaqMan	0.58
Scapoli 2010*	Italy (Caucasian)	95/121	PB	MassARRAY	> 0.05

HWE: Hardy Weinberg Equilibrium; Mixed: hospital and population based; PB: population based; HB, hospital based; *, OR and its 95% CI for T vs. C; PCR: polymerase chain reaction; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism.

overall estimation. Sensitivity analysis was applied by excluding each single study every time to explore the robust of pooled results. The publication bias was detected by funnel plot and the Egger linear regression test [22]. All the analysis was performed using the Comprehensive Meta-Analysis software, version 2.2 (Biostat, Englewood, New Jersey) [23], and all the *p* values were two-sided.

Results

Study section and characteristic

The primary search yielded 216 publications and finally 25 case-control studies involving 1594 AgP patients and 2483 healthy controls were included [24-48]. **Figure 1** shows the study selection process.

Of these studies, 16 studies were concerned about Caucasian origin [24, 26, 28, 31, 33, 34, 36-44, 48], 7 were Asian origin [27, 29, 30, 32, 45-47], one was African-American origin [25], and one was Brazil (Mixed) origin [35]. The controls of five studies were out of HWE [24, 40, 44, 45, 48]. Two studies reported ORs and 95% CIs for the allele comparison (T vs. C) [39, 41]. **Table 1** shows the main characteristics of identified studies.

Meta-analysis

Table 2 presents the results of overall and subgroup analyses. All the genetic models provided evidence that there was no association between the IL-1β rs1143634 polymorphism and AgP susceptibility in overall populations [for T vs. C: OR = 0.99, 95% CI = 0.79-1.23, I^2 = 62.22%, **Figure 2**; for TT vs. CC: OR = 1.14, 95%

Table 2. Results of overall and subgroups analyses of pooled ORs and 95% CIs

Genetic model	Subgroup	Number of studies	OR (95% CI)	I^2 (%)
T vs. C	Overall	25	0.99 (0.79-1.23)	62.2
	Caucasian	16	0.89 (0.72-1.09)	52.92
	Asian	7	1.99 (0.84-4.69)	73.63
	Other ethnic	2	0.67 (0.34-1.31)	0
	HWE (yes)	20	1.02 (0.82-1.27)	51.3
	HWE (no)	5	0.83 (0.38-1.82)	83.19
	HB	9	1.53 (0.89-2.64)	65.78
	PB	13	0.82 (0.64-1.06)	57.02
	Mixed	3	1.02 (0.53-1.96)	57.81
TT vs. CC	Overall	23	1.14 (0.78-1.66)	35.7
	Caucasian	14	0.99 (0.65-1.51)	31.23
	Asian	7	1.58 (0.35-6.62)	56.26
	Other ethnic	2	0.81 (0.03-20.41)	0
	HWE (yes)	18	1.26 (0.82-1.94)	23.2
	HWE (no)	5	0.58 (0.16-2.11)	61.03
	HB	9	1.48 (0.77-2.86)	38.86
	PB	11	0.70 (0.32-1.56)	50.29
	Mixed	3	1.42 (0.53-3.76)	0
CT vs. CC	Overall	23	0.97 (0.70-1.36)	59.1
	Caucasian	14	0.87 (0.60-1.26)	57.75
	Asian	7	1.57 (0.63-3.91)	64.84
	Other ethnic	2	0.66 (0.32-1.36)	0
	HWE (yes)	18	0.89 (0.71-1.11)	39
	HWE (no)	5	0.98 (0.26-3.77)	84.49
	HB	9	1.43 (0.77-2.66)	58.68
	PB	11	0.79 (0.52-1.21)	51.96
	Mixed	3	0.81 (0.33-2.02)	65.39
(CT + TT) vs. CC	Overall	23	1.02 (0.76-1.37)	55.1
	Caucasian	14	0.90 (0.66-1.23)	50.66
	Asian	7	1.97 (0.85-4.53)	63.16
	Other ethnic	2	0.65 (0.31-1.33)	0
	HWE (yes)	18	0.94 (0.76-1.16)	35.9
	HWE (no)	5	0.89 (0.29-2.75)	82.18
	HB	9	1.56 (0.90-2.73)	54.51
	PB	11	0.83 (0.58-1.19)	47.83
	Mixed	3	0.90 (0.37-2.22)	66.87
TT vs. (CT + CC)	Overall	23	1.22 (0.85-1.75)	35.2
	Caucasian	14	1.11 (0.75-1.63)	16.14
	Asian	7	1.11 (0.13-9.92)	70.43
	Other ethnic	2	0.92 (0.04-23.08)	0
	HWE (yes)	18	1.42 (0.93-2.17)	37.6
	HWE (no)	5	0.80 (0.40-1.61)	20.27
	HB	9	1.03 (0.27-3.88)	59.09
	PB	11	1.04 (0.66-1.65)	36.77
	Mixed	3	1.74 (0.67-4.52)	0

HWE: Hardy Weinberg Equilibrium; Mixed: hospital and population based; PB: population based; HB: hospital based.

CI = 0.78-1.66, I^2 = 35.68%; for CT vs. CC: OR = 0.97, 95% CI = 0.70-1.36, I^2 = 59.13%; for (CT + TT) vs. CC: OR = 1.02, 95% CI = 0.76-1.37, I^2 = 55.14%; for TT vs. (CT + CC): OR = 1.22, 95% CI = 0.85-1.75, I^2 = 35.18%, respectively]. In the subgroup analysis for ethnicity, source of controls, and HWE, we remain did not find any association. Sensitivity analysis showed that the conclusions remained similar when any single study was deleted each time (**Figure 3**).

Publication bias

Egger's test showed that there was no bias in the T vs. C genetic model (P = 0.16), CT vs. CC (P = 0.58), (CT + TT) vs. CC (P = 0.37), or the TT vs. (CT + CC) (P = 0.09); but that bias was evident in the TT vs. CC (P = 0.03) model.

Discussion

To date, numerous studies evaluated the association between IL-1β rs1143634 polymorphism and AgP risk have been published, but the results were inconsistent. Moreover, the credibility of results from a single case-control study is limited due to relative small sample size. Meta-analysis has the benefit to overcome this limitation by increasing the sample size [49, 50] and is being widely used in genetic association studies [11, 12, 21, 51-54]. Therefore, we performed this meta-analysis to assess the association between IL-1β rs1143634 polymorphism and AgP risk based on pooled results. Of all included studies, two studies showed a significantly increased risk [27, 46], two studies showed a significantly decreased risk [36, 40], and the other 19 studies showed non-significant association; however, the results of present meta-analysis based on these 25 case-control studies obtained a negative association (**Figure 2**). The sensitivity analysis also proved

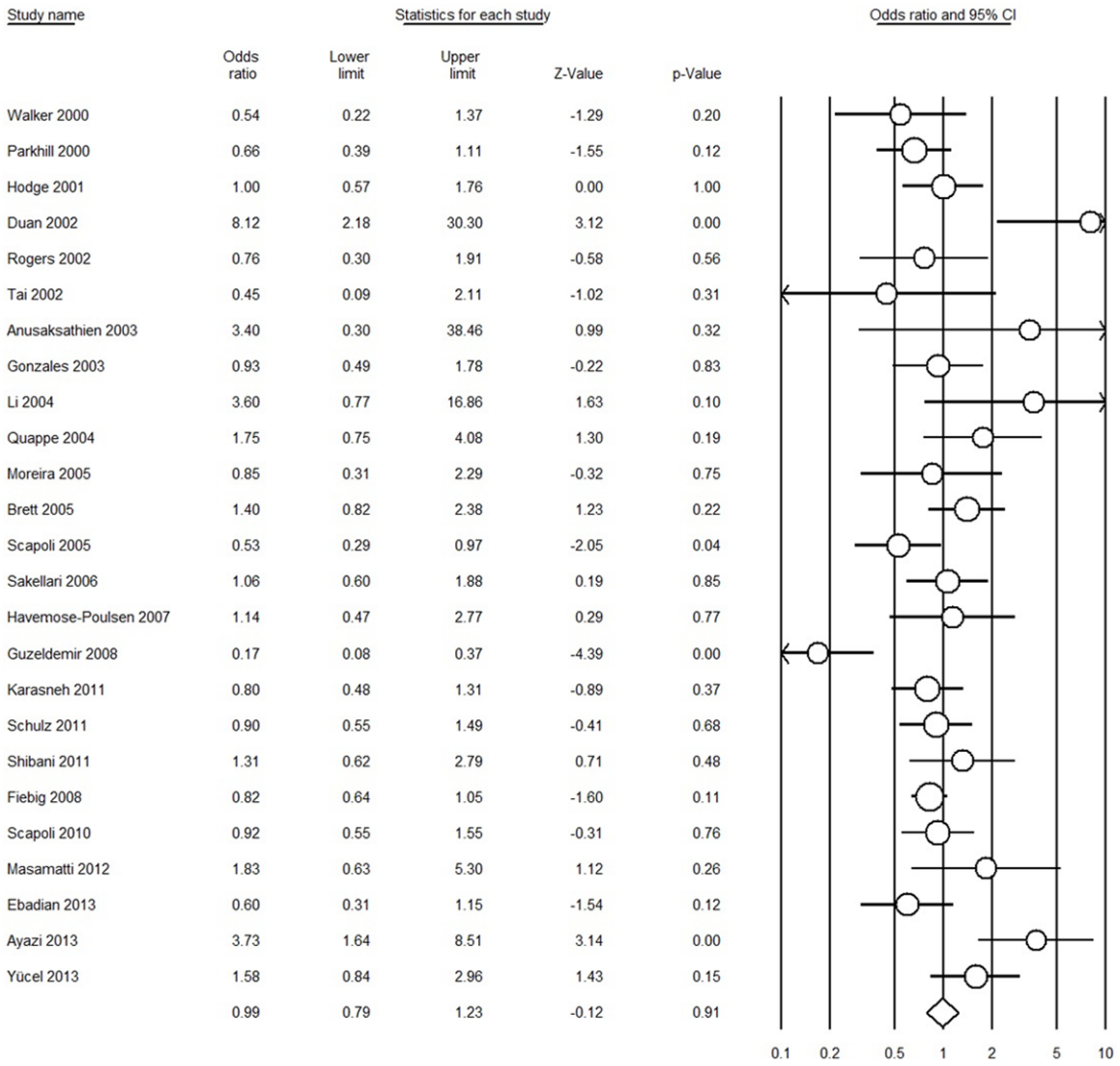

Figure 2. Forest plot for T vs. C comparison (random-effect model).

that the overall results were not influenced by any single study. To make a comprehensive analysis between IL-1β rs1143634 polymorphism and AgP, we also conducted subgroup analyses according to the ethnicity, source of controls, and the HWE for controls. All the results were same with overall analysis (**Table 2**), indicating the genetic backgrounds and the environment they lived in did not play a role.

IL-1β is the secreted form of IL gene and can promote the movement of inflammatory cells from the blood to inflamed tissues and regulate the extracellular matrix and induce other cytokines [55, 56]. Higher levels of IL-1β in gingival crevicular fluid were detected in the patients who with periodontal disease [57, 58]. It suggested that IL-1β rs1143634 polymorphism might influence the levels of IL-1β and that was associated with periodontal disease. The published meta-analysis of Deng et al in 2013 suggested that IL-1β rs1143634 polymorphism is associated with CP [18]; however, our meta-analysis indicated IL-1β rs1143634 polymorphism is not associated with AgP. The reason maybe AgP is more like a genetically inherited disease [59] and the IL-1 gene is not belonged to the specify genes. For some scholars considered that AgP and CP shared some susceptibility genes, but not in all [60, 61]; hence, our result also provided further evidence that AgP was different from CP in some aspects.

Some limitations should be demonstrated in our meta-analysis. First, the sample size is still

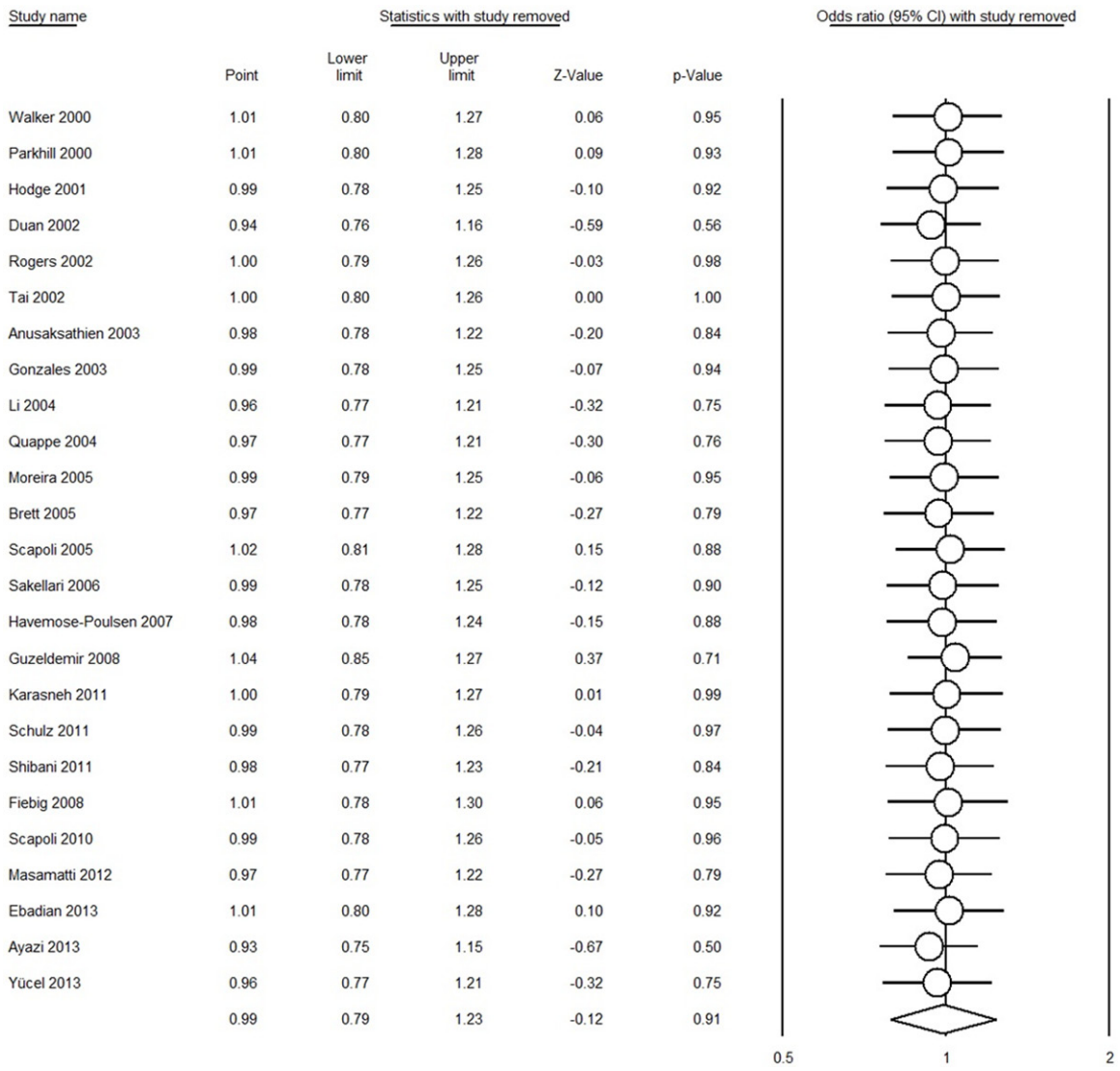

Figure 3. Sensitivity analysis by detecting any single study each time in T vs. C comparison (random-effect model).

large enough. Although we comprehensively searched relevant articles, however, due to the less prevalent of AgP, it is different to obtain large sample size. For lacking of accurate prevalence of AgP, we could not estimate the optimal sample size in this topic. Second, heterogeneity is a potential problem that may affect the interpretation of the results. Obviously, substantial heterogeneity existed of all the genetic models in our meta-analysis. The heterogeneity might due to the diversity in study design, sample size, inclusion and exclusion criteria, demographic background, etc; however, the heterogeneity of our meta-analysis could not be interpreted by ethnicity or source/HWE of controls. Third, due to the limited of right to use databases and languages, studies included in our meta-analysis were limited to English and Chinese published articles. Moreover, we did not track the unpublished articles. Although four genetic models indicated no publication bias existed, we could not ignore that publication bias may have distorted our results. Fourth, for smoking is the classical risk factors of periodontal disease [62], data were not stratified by gender, smoking, or other environmental variables because of insufficient data. Hence, we could not perform subgroup analysis based on adjusted information due to the limited data.

In summary, our meta-analysis suggested that IL-1β rs1143634 polymorphism does not con-

tribute to the risk of AgP, and there is no genetic or ethnic background. In addition, there was no statistical evidence of publication bias among studies and the sensitivity analysis showed the overall results are stable, indicating that the pooled results may be unbiased. However, further studies are suggested to conduct multiple variables adjustment in order to explore the gene-gene, gene-environmental interactions.

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Disclosure of conflict of interest

None.

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