www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 30), pp: 48996-49004

Research Paper

Comprehensive analysis of interleukin-8 gene polymorphisms and periodontitis susceptibility

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Keywords: *interleukin-8, periodontitis, periodontal diseases, meta-analysis, polymorphism*

Received: *February 14, 2017* ***Accepted:*** *March 09, 2017* ***Published:*** *April 07, 2017*

ABSTRACT

Background: Associations between interleukin-8 (IL-8) gene polymorphisms and periodontitis susceptibility have been investigated in many published studies, but the conclusions are still inconsistent. Therefore, we performed this systematic review and meta-analysis to review which polymorphisms have been researched and to obtain a precise result of the same polymorphism from different studies.

Results: Finally 10 publications involving 1938 patients and 1569 controls were yielded, including 12 polymorphisms. Six studies investigated rs4073 polymorphism; two focused on rs2227306 and rs2227307; two referred to rs2227532 and T-738A; one detected rs2230054, rs1126579 and rs1126580; one inspected A2767T, $T_1$1722T_2 and C1633T, and one for rs2234671 polymorphism. Of them, IL-8 C1633T and rs1126580 polymorphisms showed positive association while the other ten polymorphisms revealed negative results.

Materials and methods: A comprehensive literature search from PubMed, Web of Science, and Chinese National Knowledge Infrastructure was conducted for all potentially relevant studies published before January 2, 2017. Two authors selected the studies and extracted data. The pooled analysis was conducted using the RevMan 5.1 software if a polymorphism was reported by two or more studies.

Conclusions: Based on current evidence, the IL-8 rs4073, A2767T, $T_1$1722T_2, rs2234671, rs2230054, rs1126579, rs2227306, rs2227307, rs2227532, and T-738A polymorphisms were not associated with periodontitis susceptibility; the IL-8 C1633T and rs1126580 polymorphisms were associated with increased risk of periodontitis.

INTRODUCTION

Interleukin (IL) plays an important role in mediating immune and inflammatory responses, and periodontitis is known as a chronic infectious disease. Hence, the genes and their variants (polymorphisms) of IL may be the important determinants of pathogenesis of periodontitis [1]. There are a large number of publications reporting the association between IL gene polymorphisms and periodontitis, some related meta-analyses have been performed for IL-1 polymorphisms [2–6], IL-4 polymorphisms [7], IL-6 polymorphisms [8], IL-10 polymorphisms [9–10], and IL-18 polymorphisms [11]. IL-8 gene is a component of IL genes with more than ten polymorphisms [12]. Numerous studies exploring the association between IL-8 gene polymorphisms and periodontitis have been published, but the results of previous studies of same polymorphism were inconsistent. Yang et al. [13] in 2016 performed a meta-analysis to investigate the effect of rs4073 (A251T/T-353A) on periodontitis susceptibility and found a positive association. The meta-analysis by Chen et al. [14] in 2015 focused on the rs4073 (A251T/T-353A) and rs2227532 (T-845C) polymorphisms which also revealed a positive association. Obviously, many other polymorphisms of IL-8 gene has not been explored, so we performed this analysis

for further assessing the relationship between all IL-8 gene polymorphisms and periodontitis; additionally, we also reviewed which polymorphisms have been investigated. The present study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15–16].

RESULTS

Study characteristics

The initial search identified 61 publications and finally 10 articles [17–26] were included in the systematic review and meta-analysis. The literature retrieval and selection are shown in Figure 1.

The characteristics and relevant data of the included studies are shown in Table 1 and Table 2. All studies were case-control studies involving 12 polymorphisms: rs4073 (A251T/T-353A), A2767T, $T_1$1722T_2, C1633T, rs2234671, rs2230054 (C785T), rs1126579 (T1208C), rs1126580 (G1440A), rs2227306 (C781T), rs2227307 (G396T), rs2227532 (T-845C), and T-738A. Eight studies focused on chronic periodontitis (CP) [17-21, 24-26]; contained CP and agreessive periodontitis (AgP) [22], and one only referred to AgP [23]. There were a total of 1938 patients and 1569 controls.

rs4073 polymorphism

Six studies [17, 22, 24–27] reported the correlation between rs4073 (A251T/T-353A) polymorphism and periodontitis. The meta-analysis based on random effect model indicated no significant association between them [T vs. A: odds ratio (OR) = 0.75, 95% confidence interval (CI) = 0.51–1.11, Figure 2; TA+TT vs. AA: OR = 0.70, 95%CI = 0.33-1.48, Figure 3)]. The funnel plot was symmetrical (Figure 4).

A2767T polymorphism

One study [22] on A2767T polymorphism reported that it was not associated with periodontitis risk (T vs. A: OR = 1.12, 95%CI = 0.79–1.580, p = 0.52; TA+TT vs. AA: OR = 1.38, 95% CI = 0.59–3.25, p = 0.46).

rs2227306 polymorphism

Meta-analysis of two studies [21–22] showed there was no significant association between rs2227306 (C781T) polymorphism and periodontitis risk. The specific results were presented in Table 3.

$T_1$1722T_2 polymorphism

One study [22] detecting the relationship between the $T_1$1722T_2 polymorphism and periodontitis susceptibility suggested that there was no significant association between them (T_2 vs. T_1: OR = 17.04, 95%CI = 0.91–317.97, p = 0.06; T_2T_1+T_2T_2 vs. T_1T_1: OR = 17.35, 95%CI = 0.93-325.33, p = 0.06).

rs2227307 polymorphism

Table 3 showed the results of rs2227307 (G396T) polymorphism and periodontitis risk, and the meta-analysis of two studies [21–22] indicated non-significant association.

C1633T polymorphism

The results from one study [22] on C1633T polymorphism indicated that this was an increased risk of periodontitis (T vs. C: OR = 1.89, 95%CI = 1.33–2.69, p < 0.01; TC+TT vs. CC: OR = 3.19, 95%CI = 1.85–5.51, p < 0.01).

rs2234671 polymorphism

One study [20] involving rs2234671 polymorphism showed it was not related to periodontitis risk (C vs. G: OR = 1.10, 95%CI = 0.67–1.79, p = 0.71; CG+CC vs. GG: OR = 1.12, 95%CI = 0.66–1.90, p = 0.68).

rs2227532 polymorphism

Two studies [18, 25] reported the data for rs2227532 (T-845C) polymorphism, and the meta-analysis displayed this polymorphism was had no significant impact on periodontitis (Table 3).

T-738A polymorphism

The T-738A polymorphism was evaluated by two studies [18, 25] and the pooled results uncovered there was non-significant association of T-738A polymorphism with periodontitis (Table 3).

rs2230054 polymorphism

The rs2230054 (C785T) polymorphism was assessed in one study [19] which revealed non-significant association between this polymorphism and periodontitis (T vs. C: OR = 1.02, 95%CI = 0.79–1.32, p = 0.86; TC+TT vs. CC: OR = 1.08, 95%CI = 0.55–2.12, p = 0.82).

rs1126579 polymorphism

The rs1126579 (T1208C) polymorphism was reported by one study [19]. The results indicated that this polymorphism was not implicated in periodontitis (C vs. T: OR = 1.06, 95%CI = 0.82–1.37, p = 0.64; CT+CC vs. TT: OR = 0.84, 95%CI = 0.47–1.51, p = 0.56).

Table 1: Characteristics of included studies

Reference	Country (ethnicity)	Type	Polymorphism	Smoking status	Source of control	Genotyping method	HWE
Kim 2009	Brazil (Brazilian)	CP	rs4073 (A251T/T-353A)	Mixed	Healthy	PCR-SSP	Yes
Kim 2010	Brazil (Brazilian)	CP	rs2227532 (T-845C), T-738A	Mixed	Healthy	PCR–RFLP	Yes
Viana 2010	Brazil (Brazilian)	CP	rs2230054 (C785T), rs1126579 (T1208C), rs1126580 (G1440A)	Mixed	Healthy	PCR-SSP	Yes
Andia 2011	Brazil (Brazilian)	CP	rs4073 (A251T)	No	Healthy	PCR	Yes
Scarel-Caminaga 2011	Brazil (Brazilian)	CP	rs2227306 (C781T), rs2227307 (G396T)	Mixed	Healthy	PCR–RFLP	Yes
Scarel-Caminaga 2011	Brazil (Brazilian)	CP	rs2234671	Mixed	Healthy	PCR-SSP	Yes
Houshmand 2012	Iran (Caucasian)	CP and AgP	rs4073 (A251T), A2767T, C781T, T11722T2, G396T, C1633T	NA	Healthy	PCR	Yes
Andia 2013	Brazil (Brazilian)	AgP	rs4073 (A251T)	No	Healthy	PCR	Yes
Khosropanah 2013	Iran (Caucasian)	CP	rs4073 (A251T)	No	Healthy	PCR	Yes
Sippert 2013	Brazil (Brazilian)	CP	rs4073 (T-353A), rs2227532 (T-845C), T-738A	Mixed	Healthy	PCR–RFLP	Yes

AgP, aggressive periodontitis; CP, chronic periodontitis; HWE, Hardy Weinberg equilibrium; Mixed, included smokers and non-smokers; NA, not available; PCR-SSP, polymerase chain reaction- single strand polymorphism; PCR-RFLP, PCR-restriction fragment length polymorphism.

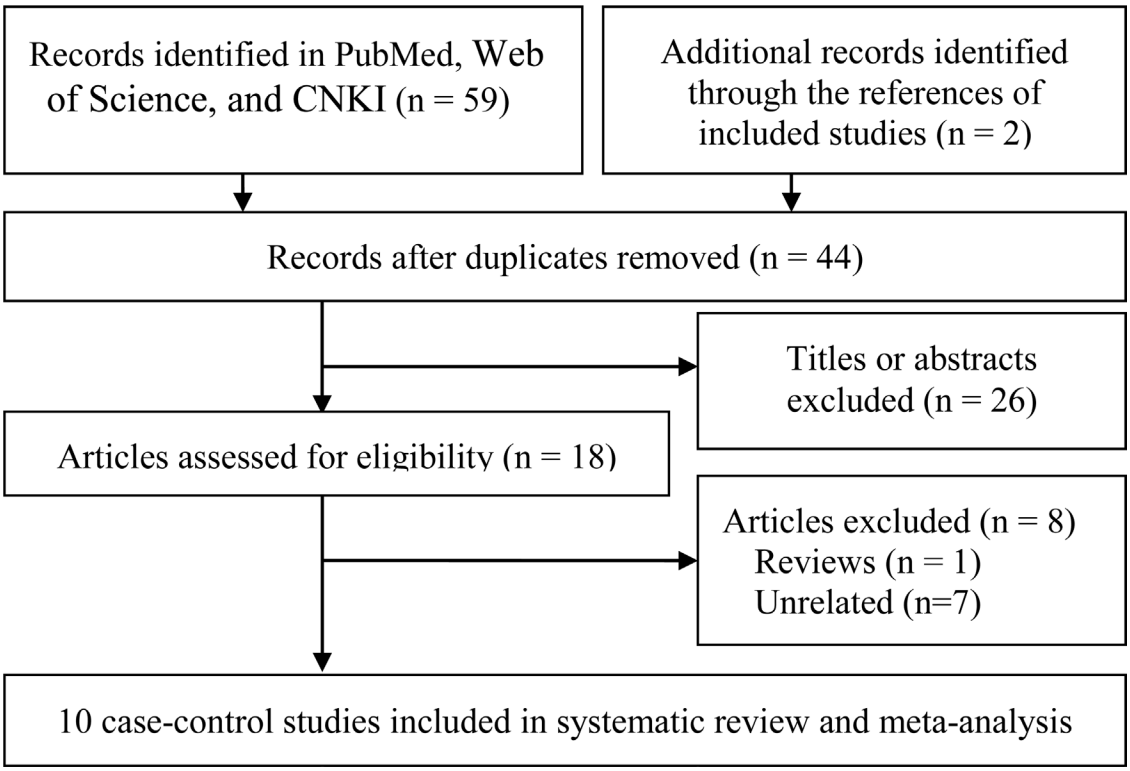

Figure 1: Study selection flow chart.

Table 2: The data of included studies

Polymorphism	Type	Case/Control			
rs4073 (A251T/T-353A)					
		AA	TA	TT	N
Andia 2011	CP	21/13	135/57	25/38	181/108
Andia 2013	AgP	11/13	50/57	15/38	76/108
Houshmand 2012	CP and AgP	40/10	55/120	12/69	107/199
Sippert 2013	CP	34/53	62/92	28/42	124/187
Khosropanah 2013	CP	41/12	101/17	85/11	227/40
Kim 2009	CP	56/36	146/120	66/64	268/220
A2767T					
		AA	AT	TT	N
Houshmand 2012	CP and AgP	8/20	59/110	40/69	107/199
rs2227306 (C781T)					
		CC	CT	TT	N
Houshmand 2012	CP and AgP	42/70	63/129	2/0	107/199
Scarel-Caminaga 2011	CP	141/105	112/96	17/22	270/223
T11722T2					
		T1T1	T1T2	T2T2	N
Houshmand 2012	CP and AgP	103/199	4/0	0/0	107/199
rs2227307 (G396T)					
		GG	GT	TT	N
Houshmand 2012	CP and AgP	28/10	55/120	24/69	107/199
Scarel-Caminaga 2011	CP	36/29	120/125	114/69	270/223
C1633T					
		CC	CT	TT	N
Houshmand 2012	CP and AgP	22/90	21/0	64/109	107/199
rs2234671					
		GG	GC	CC	N
Scarel-Caminaga 2011	CP	161/164	31/28	3/3	195/195
rs2227532 (T-845C)					
		TT	TC	CC	N
Sippert 2013	CP	117/183	6/4	1/0	124/187
Kim 2010	CP	137/127	80/55	1/0	218/182
T-738A					
		TT	TA	AA	N
Sippert 2013	CP	123/186	1/1	0/0	124/187
Kim 2010		61/59	155/122	2/1	218/182
rs2230054 (C785T)					
		CC	CT	TT	N
Viana 2010	CP	20/17	244/193	8/5	272/215
rs1126579 (T1208C)					
		TT	TC	CC	N
Viana 2010	CP	31/21	198/170	43/24	272/215
rs1126580 (G1440A)					
		GG	GA	AA	N
Viana 2010	CP	13/32	194/119	65/64	272/215

AgP, aggressive periodontitis; CP, chronic periodontitis; N, sample size.

Table 3: Results of meta-analysis of IL-8 gene rs4037, rs2227306, rs2227307, rs2227532 and T-738A polymorphisms

Polymorphism	Genetic model	No.	Heterogeneity		Effect model	Meta-analysis	
			I^2(%)	p^h		OR (95% CI)	p
rs4073 (A251T/T-353A)	T vs. A	6	87	< 0.01	Random	0.75 (0.51–1.11)	0.15
	TA + TT vs. AA	6	88	< 0.01	Random	0.70 (0.33–1.48)	0.35
rs2227306 (C781T)	T vs. C	2	97	< 0.01	Random	0.44 (0.10–1.99)	0.29
	TC + TT vs. CC	2	0	0.92	Fixed	0.82 (0.62–1.10)	0.18
rs2227307 (G396T)	T vs. G	2	94	< 0.01	Random	0.90 (0.73–1.10)	0.31
	TG + TT vs. GG	2	94	< 0.01	Random	0.39 (0.06–2.44)	0.31
rs2227532 (T-845C)	C vs. T	2	44	0.18	Fixed	1.41 (0.99–2.01)	0.06
	CT+CC vs. TT	2	6	0.3	Fixed	1.47 (0.99–2.18)	0.06
T-738A	A vs. T	2	0	0.83	Fixed	1.11 (0.83–1.49)	0.46
	AT + AA vs. TT	2	0	0.89	Fixed	1.24 (0.81–1.89)	0.32

No., number of studies; CI, confidence interval; OR, odds ratio.

rs1126580 polymorphism

The results from one study [19] demonstrated that rs1126580 (G1440A) polymorphism might be associated with the increased risk of periodontitis (AG+AA vs. GG: OR = 3.48, 95%CI = 1.78–6.82, $p < 0.01$).

DISCUSSION

IL-8 gene located on chromosome 4q12-21 contains four exons and three introns which possesses many functional polymorphisms [12, 28]. Published meta-analyses indicate that IL-8 gene polymorphisms are associated with some diseases, such as gastric cancer [29], oral cancer [30], and peptic ulcer disease [31]. The first study assessing IL-8 rs4037 polymorphism and periodontitis was published by Kim et al. [17] in 2011. Our systematic review and meta-analysis included 10 publications involving 3507 individuals, investigating the correlations between 12 polymorphisms of IL-8 gene and periodontitis. The results showed that the IL-8 rs4073 (A251T/T-353A), A2767T, $T_1$1722T_2, rs2234671, rs2230054 (C785T), rs1126579 (T1208C), rs2227306 (C781T), rs2227307 (G396T), rs2227532 (T-845C), and T-738A polymorphisms were not significantly related to periodontitis susceptibility; however, there was a significant difference in the IL-8 C1633T and rs1126580 (G1440A) polymorphisms between the periodontitis patients and healthy control groups.

Compared with published two meta-analyses [13–14] on this topic, the major strength of our study is that it is the first comprehensive meta-analysis on IL-8 gene polymorphisms and periodontitis risk. We believe it gives a useful summary of current data regarding the relationship between IL-8 gene polymorphisms and periodontitis risk, and provides improved clinical clarity to obtain a solid evidence base for the diagnosis and treatment of periodontitis. As to the included studies, sample size for each polymorphism was very small, so the relevant researches are suggested to be conducted in the future. Since there are more than 15 polymorphisms of IL-8 gene have been characterized [29], the association between additional polymorphisms and risk of periodontitis should be investigated. The AgP and CP are

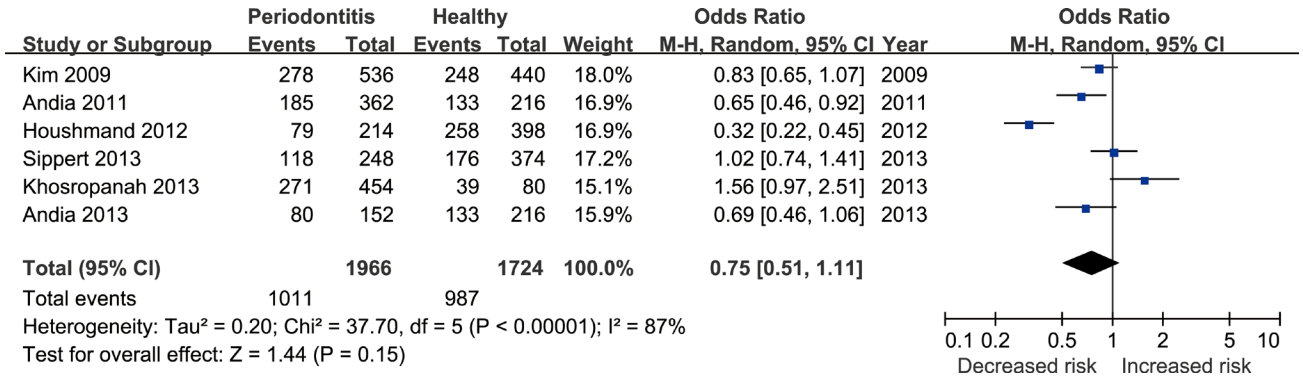

Figure 2: Forest plot for the T vs. A genetic model in IL-8 rs4073 polymorphism.

two different types of periodontitis and the former type is considered as a genetically inherited disease [2, 32]. Hence, the further studies should report the data for CP and AgP separately.

The major limitation of our study was the numbers of included studies and sample size. Of these 12 polymorphisms, only IL-8 rs4073 polymorphism was involved in 6 studies while the others referred to one or two studies. Correspondingly, the sample size for each polymorphism was relatively small, which restrained the confidence of current results. Moreover, the subgroup analyses based on difference between ethnicity, smoking status, type of periodontitis, or other factors couldn't be conducted to investigate the source of heterogeneity, which might bias the results. Because of the limited numbers of included studies, we only assessed the publication bias of those investigating the IL-8 rs4073 polymorphism. Secondly, systematic review and meta-analysis is an observational study which was restricted by the quality of primary studies [6, 16, 33–35]. Although we had conducted a more comprehensive search, our study could not escape from this limitation. Lastly, our results were based on unadjusted data and the original data were sufficient, hence the evaluation of the effects of the gene - gene or gene - environment interactions was neglected. These limitations mentioned above might affect our final conclusions.

In conclusion, our meta-analysis suggests that the IL-8 rs4073, A2767T, $T_1$1722T_2, rs2234671, rs2230054, rs1126579, rs2227306, rs2227307, rs2227532, and T-738A polymorphisms are not associated with periodontitis while the IL-8 C1633T and rs1126580 polymorphisms may elevate the susceptibility of periodontitis based on the currently available evidences. However, for considering that the studies included in our meta-analysis were based on small numbers, the current results should be treated with caution, and the results may change with the larger sample size in future. Due to these limitations, more well designed, studies with larger sample size, and adjusted risk factors are required to further validate our results.

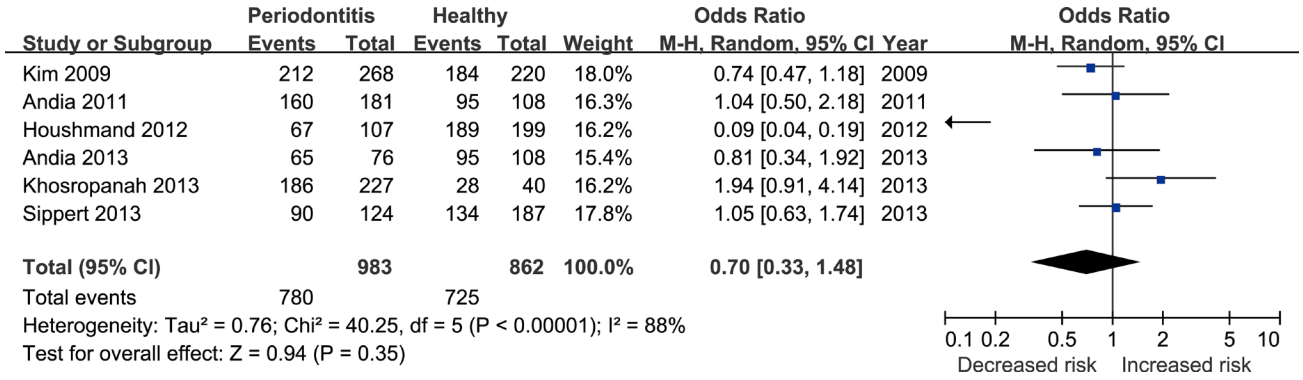

Figure 3: Forest plot for the TA+TT vs. AA genetic model in IL-8 rs4073 polymorphism.

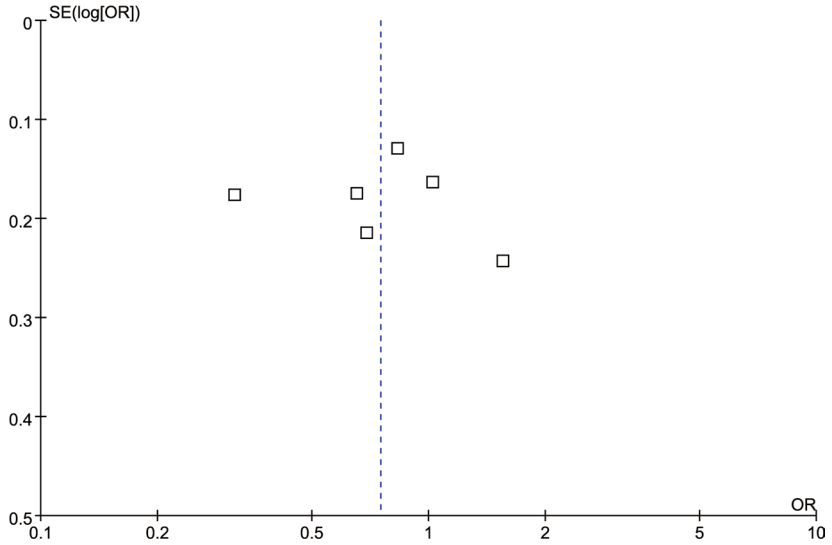

Figure 4: Funnel plot for the T vs. A genetic model in IL-8 rs4073 polymorphism.

MATERIALS AND METHODS

Eligible criteria

We included the studies which met all of the following criteria: (1) the patients were clearly diagnosed as periodontitis (CP and/or AgP) and the controls were periodontitis-free or periodontal healthy; (2) at least one of the IL-8 polymorphisms and periodontitis susceptibility were evaluated, using a case-control or cohort study design; (3) the studies reported full data for necessary genotypes in each group or contained sufficient data to calculate them. If the same institute published two or more publications, we treated them as independent ones and chose the more comprehensive one.

Search strategy

A comprehensive literature search was performed in PubMed, Web of Science, and Chinese National Knowledge Infrastructure (CNKI) up to January 2, 2017. The following key words were used: IL-8, interleukin-8, interleukin 8, periodontal disease, periodontitis, variant, and polymorphism. Moreover, all listed references of included studies and recently reviews were retrieved for any additional relevant studies. No language restriction was applied in the search process.

Data extraction

Study selection and data extraction were performed by two authors and any discrepancy was resolved by discussion. The following data were extracted from each included study: surname of first author, year of publication, study design, country and ethnicity of study population, demographics, periodontitis type, smoking status, number of cases and controls, polymorphism, genotype distribution, source of controls, genotyping method, and Hardy-Weinberg equilibrium (HWE) for controls.

Data analysis

The OR and its 95% CI were calculated to estimate the relationship between the IL-8 polymorphisms and periodontitis risk. All studies used a allele genetic model and a dominant genetic model [5]. If a polymorphism was reported in two or more studies, a meta-analysis was conducted. Heterogeneity was assessed using the Cochran's Q statistic and I^2 statistic [15, 36], with values of $P \geq 0.1$ and $I^2 < 50\%$ indicating acceptable heterogeneity. If no significant heterogeneity existed, the fixed effect model was used; otherwise, the random-effects model was used. If the number of included studies was available, we conducted subgroup analyses on the ethnicity, smoking status, and periodontitis type. Publication bias was assessed by funnel plot [37]. All analyses were performed using RevMan 5.1 software [38–39].

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

GRANT SUPPORT

This research was supported (in part) by the Foundation of Evidence-based Medicine Nursery Fund of Taihe Hospital (EBM2013028 and EBM2014007), without commercial or not-for-profit sectors. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study. We also wish to thank relevant editors and peer-reviewers for their hard work and suggestions.

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