

# Meta-Analysis of Risk Association between Interleukin-17A Gene Polymorphism and Chronic Periodontitis

## Abstract

The association of genetic polymorphisms with periodontitis has been studied extensively. The interleukin-7 (IL-17) is a group of cytokines, which comprises six different molecules (IL-17A, B, C, D, E, and F). Among this, IL-17A is the most commonly understood cytokine, and its polymorphism plays a critical role in inflammatory diseases and periodontal inflammation. The present study was aimed at pooling the data available for meta-analysis and to evaluate whether IL-17A (rs2275913) polymorphism is associated with the susceptibility of chronic periodontitis.

**Keywords:** Chronic periodontitis, ethnicity, interleukin-17A gene, interleukin-17A polymorphism

## Introduction

Periodontitis is a multifactorial disease that affects the supporting structures of teeth, resulting in partial or complete loss of teeth.<sup>[1]</sup> The microbial organisms present in the plaque and calculus are the most common etiological factors for the initiation of periodontal disease (PD) in particular sites.<sup>[2]</sup> Other factors such as environmental, anatomical factors, systemic diseases, and genetic background also play a vital role in PDs.<sup>[3]</sup> The genetic factors that are associated with periodontitis may alter the immunoregulatory mechanism which could modify the pathogenesis of periodontitis.

The association of genetic polymorphisms with periodontitis has been studied extensively.<sup>[4-7]</sup> The interleukin-17 (IL-17) is a group of cytokine which comprises six different molecules (IL-17A, B, C, D, E, and F).<sup>[8-10]</sup> Among these, IL-17A and F are the most commonly understood cytokine, which plays a critical role in periodontal inflammation. These types of cytokines are released from CD4 + T-helper cells and involved in the central role of inflammation and autoimmune diseases.<sup>[11]</sup> IL-17A is an initiator of the inflammatory process that induces the fibroblast, macrophages, endothelial, and epithelial cells to produce the proinflammatory mediators.<sup>[12]</sup> T-cells produce IL-17 that

activates many signaling events of innate cytokines such as tumor necrosis factor  $\alpha$  and IL-1  $\beta$ , and thus, it is considered as an important bridging molecule between the adaptive and innate immunity.<sup>[13]</sup> IL-17 also induces the expression of receptor activator of nuclear factor kappa-B ligand on osteoblasts and stimulates the differentiation and activation of osteoclasts, which can influence the bone resorption mediated by this cells.<sup>[14-17]</sup> Many studies have demonstrated the presence of IL-17 in periodontal tissues, gingival crevicular fluid, saliva, and plasma of patients with PD.<sup>[18-20]</sup>

The two variations of gene polymorphism (rs2275913 and rs763780) from IL-17 family have been found to be commonly involved in systemic and PDs.<sup>[21-24]</sup> The IL-17 polymorphism is also associated with inflammatory diseases such as rheumatoid arthritis, periodontitis, and inflammatory bowel diseases.<sup>[25]</sup> The individual studies have evaluated and showed the association between IL-17A and F gene polymorphism and the risk of periodontitis. In contrast to this, few studies were evaluated in patients with aggressive and chronic periodontitis based on the population distribution, smoking, nonsmoking status and stated that there was no significant association between the polymorphism (rs2275913 and rs763780) in IL-17A and F genes both in chronic/aggressive periodontitis patients.<sup>[26]</sup>

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Nevertheless, the association of these genetic variations had influenced the molecular expression of IL-17 in PDs. Similarly, the IL-17A polymorphism was highly associated with chronic and aggressive periodontitis when compared with IL-17F polymorphism.<sup>[27]</sup> The variability of results between different studies of IL-17A polymorphism and periodontitis could be the reason which led to the search for a new literature of IL-17A polymorphism in chronic periodontitis. Therefore, the present study is aimed at pooling the data available for meta-analysis and to evaluate whether IL-17A (rs2275913) polymorphism is associated with the susceptibility of chronic periodontitis.

### Eligibility Criteria

Articles evaluating the association of IL-17A polymorphism with chronic periodontitis were included in this meta-analysis based on the recommended Preferred Reporting Items for Systemic Reviews and Meta-analysis Statement.<sup>[27]</sup> (1) The inclusion criteria were selected in the concept of P-Patient, problem or population, I-Intervention, C-Comparison, control, O-Outcome (PICO). (2) Articles compared the IL-17A polymorphism with or without chronic periodontitis. (3) Studies included were either case control or cohort design. (4) The articles included were based on population studies. (5) Diagnosis of the chronic periodontitis was confirmed through the clinical features and radiographic finding. (6) Studies also include IL-17A genotypic and allelic evaluation in chronic periodontitis. The exclusion criteria are as follows: (1) nonhuman studies, abstract only, reviews or letters, and mechanism studies; (2) family-based design or sibling pair studies; (3) studies with a lack of information; and (4) unpublished articles.

### Literature Search

The primary studies that would have met the inclusion criteria were included in this meta-analysis. This sensitive research has been done to retrieve the association between rs2275913 polymorphism in the IL-17A gene with chronic periodontitis articles by trained informed specialists. It gives the unbiased selection of studies based on the search results. We have included the sources which contain the appropriate database and electronic sources such as index journals and conferences to identify published reports. In addition to database searching, we evaluated the reports of eligible studies such as checking references in existing reviews, citation searching, and hand searching. We have also included free-text terms in the title and abstract and any suitable subject indexing in MeSH or Emtree. The following keywords are used: IL-17A, or IL-17A, IL-17A, polymorphism genetic variation or rs2275913 polymorphism, or-197A/G polymorphism and periodontitis or PDs or chronic periodontitis [Figure 1]. There was a language restriction in the search strategy included in this meta-analysis which published before February 2019.

### Data Collection

Two investigators were involved in this initial appraisal phase and done the review process independently. The rigorous data collection was done at the protocol stage using the structured data collection. The synthesis and the interpretation data were collected with numerical and structured from six literatures. The articles were selected based on a standard protocol, and the data were collected from the published literatures if they met the following criteria: Original data, study assessed the association of IL-17A rs2275913 and the susceptibility to PDs, comparison between patients with chronic periodontitis and controls. The rs2275913 polymorphism was evaluated with genomic and allelic type frequencies according to the Hardy-Weinberg Equilibrium (HWE). We have collected the data for this analysis based on authors, publication data, country, ethnicity, and sample size, as shown in Table 1. The quality of each study included in this analysis was assessed by using the periodontal genetic association studies proposed by Nibali (<10 score was excluded).<sup>[28]</sup>

### Risk of Bias Assessment

Before the start of study each and everyone involved in this assessment has been trained to use of the proper method of assessment tools. Two authors independently assessed and allotted six literatures for the final assessment with discussion. We have used ROBIS assessment tool to assess the bias for different statistical results found within the study.<sup>[29]</sup> The assessment of articles in phase 1 was based on ROBIS, and then, we have matched target questions with meta-analysis review questions (diagnostic test). When the risk of bias assessment details was compared with guideline documents, the whole analysis got the result of “partial match” among the literatures. In the second phase of assessment, we evaluated the bias by using four domains of ROBIS and identified the stage in which the bias was introduced in the review process (whether in study eligibility criteria, Identification of studies, data collection and finding). Finally, we found the answer of “probably yes” through the signaling questions. This depicted that our overall review had low levels of bias during the evaluation. We have made a transparent discussion among the authors completing assessments independently.

### Statistical analysis

The statistical analysis of the data was calculated with the roman version 5.3 and STATA, version 11.0 (Stata Corp., Collage Station, TX, USA) the crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to measure the strength of the association between IL-17A rs2275913 and chronic periodontitis. The significance of the pooled OR was measured by using of  $I^2$ -test, and  $P < 0.05$  was statistically significant. The pooled ORs of IL-17A rs2275913 polymorphism and risk of chronic periodontitis with smokers were evaluated for

**Table 1: Characteristic of studies included in the quantitative meta-analysis**

Author	Year	Country	Ethnicity	Study design Case control/cohort study	Sample size	Age
Correa	2012	Brazil	Mixed	Case control	30/30	40.5/45.5
Saraiva	2013	Brazil	Mixed	Case control	85/72	49/31
Zacaris	2015	Brazil	Mixed	Case control	140/173	47.1/45.6
Boriliva	2016	Czech republic	Caucasian	Case control	244/154	52.5/45.6
Chaudhari	2016	Indian	Asian	Case control	35/35	21.3/data not available
Vahabi	2018	Iranian	Asian	Case control	99/75	40.28/31.67

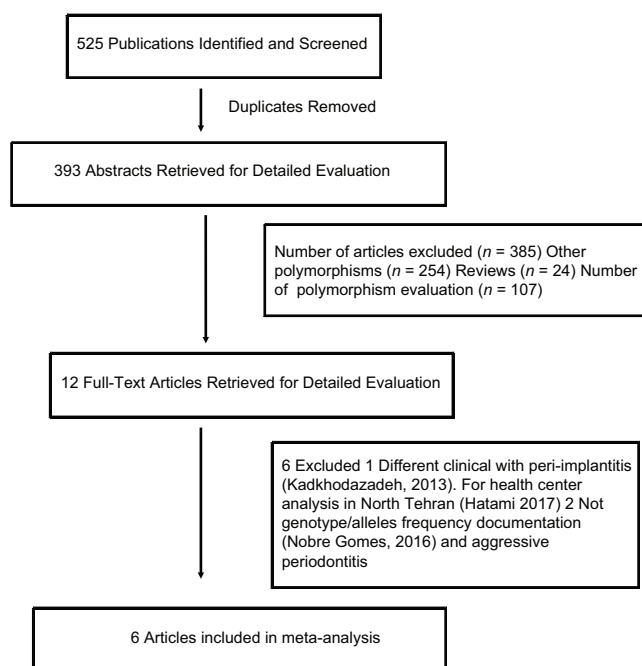
the codominant model (GA vs. GG and AA vs. GG), the dominant model (GA + AA vs. GG), and recessive model (GA + GG vs. AA) and also assessed for the allelic contrast (A vs. G). The forest plot graph was shown to assess the overall association between the IL-17A rs2275913 polymorphism and risk for chronic periodontitis. The heterogeneity of the studies had been calculated by using Cochran's Q test and  $I^2$  assessment (defined as the ratio of overall variation that existed among study variants). In this study,  $P < 0.10$  and  $I^2$  value higher than 50% considered as significant heterogeneity. The random-effect model was used when there is a presence of significant heterogeneity if not present the fixed effect model was selected. Beggers and Eggers, mean regression analysis was applied for publication bias when the  $P < 0.10$ .

## Results

### Study characteristics

In this current meta-analysis, a total of six articles were analyzed. This quantitative analysis included 1172 cases (633 patients diagnosed with chronic periodontitis and 539 patients were controls). Two articles have evaluated both forms of periodontitis.

Chronic periodontitis and aggressive periodontitis and four articles have evaluated the chronic periodontitis with IL-17A polymorphism. Among them, three articles have been analyzed in smokers and non-smokers; none of the studies have stratified the patients by gender. Three articles were composed and studied in a mixed population more specifically in the Brazilian populations. The retrieved articles composed for this meta-analysis were in agreement with HWE.<sup>[30]</sup> The results showed no significant association between the mutant allele with the risk of chronic periodontitis, as shown in Figure 1. The random-effects statistical model was used for the OR calculation due to the high heterogeneity ( $I^2 = 86\%$ ,  $df = 5$  [ $P > 0.00001$ ], overall effect  $Z = 1.07$  [ $P = 0.28$ ]). In mixed population and smoking status, there was a nonsignificant association between the rs2275913 polymorphism in IL-17A and chronic periodontitis in mutant allelic evaluation ( $P = 0.60$ ). The IL-17A polymorphism and periodontitis in all allelic and genotypic evaluations, as well as in a stratified analysis by population and smoking status are shown in Tables 2 and 3.



**Figure 1: Selection process of the included publications**

However, the overall disparity between the groups for the AA versus GG and GA + AA versus GG genotypes as well as that of the GA + GG versus AA were not associated with the risk of periodontitis ( $P > 0.05$ ). Figure 2 showed the forest plot of the risk of chronic periodontitis related to IL-17A 2275913 polymorphism. The fixed effect statistical model was used for the OR calculation. Our pooled evidence showed that none of the IL-17A rs2275913 comparison was associated with the risk of periodontitis and codominant, dominant, and recessive models ( $P > 0.05$ ).

### Heterogeneity and sensitivity analysis

There were significant heterogeneities in the information of IL-17A rs 2275913 variations. Because of major heterogeneity across studies, individual studies included in this metaanalysis were omitted consecutively to find out the change of pooled ORs qualitatively. The finding indicated that no individual study influenced the overall OR values for rs2275913 variation [Table 4]. The Beggs and Egger test was done to assess the publication bias. The funnel plot validating results also presented and showed in Figure 3 with no asymmetry.

## Discussion

The meta-analysis was carried out to find the association of IL-17A polymorphism with chronic periodontitis. In this analysis, we have retrieved six studies (case-control) which included IL-17A polymorphism with chronic periodontitis in different populations. When considering the forest plot analysis, evaluation of rs 2275913 polymorphism

in the IL-17A gene and chronic periodontitis showed no significant association between mutant allele with the risk of chronic periodontitis, as shown in Figure 1 (OR 1.40, 95% CI 0.76, 2.59,  $P = 2.59$ ). When compared with the previous meta-analysis, cumulative results showed that the possible association for three studies found and the remaining three studies showed no significant association, as given in Figure 1. However, there was some differences in the forest plot graph that consists of no significant association, even though increased  $P$  value ( $P = 0.28$ ) when compared with the previous studies ( $P = 0.21$ ). Distribution in the forest plot graph showed that two studies are significantly associated with IL-17A polymorphism with chronic periodontitis (CP) on the right side of the graph and three studies had a borderline association and only one study with no association on the left side of the graph.

In this analysis, there was substantial heterogeneity (86%) in the forest plot graph. Because two or more subgroups of studies presented in the data of Saraiva *et al.*<sup>[31]</sup> and Borilova *et al.*<sup>[32]</sup> which have a different true effect. Our study also used a random-effects model, and there was no exact way to handle studies with small numbers when assuming random effects.  $I^2$  value was also depended on the strength of evidence for heterogeneity. The power of the test depends on the six studies included, the total information available, and the distribution of weights among the different studies. We have shown that the value of the study increases with the total information available rather than the number of studies. The data used in our study were unadjusted which generally recognized as the high potential of bias due to confounding factors. It also included the unadjusted OR from six studies without considering heterogeneity due to covariate adjustment. Even though the risk of bias involving in some individual studies, the results altogether showed no association of IL-17A polymorphism with the risk of chronic periodontitis ( $I^2 = 86\%$ ,  $df = 5$  ( $P > 0.00001$ ), overall effect  $Z = 1.07$  ( $P = 0.28$ ) [Figure 2].

IL-17A rs 2275913 G/A polymorphism were analyzed by using codominant, dominant, and recessive models. When considering the allelic variants, A versus G showed no significant association with  $P$  value of 0.6249. In genotypic variations, GA versus GG consists of a protective factor

**Table 2: Meta-analysis of association between interleukin-17A rs2275913 polymorphism and chronic periodontitis (allelic and genotypic comparisons)**

Genotypes/ alleles	Polymorphism	Test of association	
		$P$	OR (95% CI)
<b>Smokers</b>			
Alleles	A versus G	0.73	0.84 (0.48-1.895)
Codominant	GA versus GG	0.84	0.895 (0.198-5.015)
	AA versus GG	0.89	1.09 (0.315-4.983)
Dominant	GA+AA versus GG	0.54	0.85 (0.501-1.254)
Recessive	AA versus GA+GG	0.87	0.95 (0.454-2.052)
<b>Mixed population</b>			
Alleles	A versus G	0.58	0.852 (0.435-1.783)
Codominant	GA versus GG	0.75	1.581 (0.905-2.932)
	AA versus GG	0.78	0.653 (0.198-1.192)
Dominant	GA+AA versus GG	0.45	0.839 (0.532-1.35)
Recessive	AA versus GA+GG	0.201	1.453 (0.79-3.001)

OR: Odds ratio; CI: Confidence interval

**Table 3: Association of interleukin-17A polymorphism and chronic periodontitis (allele and genotype frequency)**

	Allele frequency		Genotype frequency			HWE ( $P$ )
	G	A	GG	GA	AA	
Correa	P 21	P 39	P 6	P 9	P 15	P 0.06
	C 40	C 20	C 18	C 4	C 8	C 0.00
Saraiva	P 126	P 30	P 49	P 28	P 1	P 0.1501
	C 88	C 36	C 31	C 26	C 5	C 0.045
Zacaris	P 189	P 43	P 75	P 39	P 2	P 0.21
	C 88	C 36	C 31	C 26	C 5	C 0.48
Boriliva	P 327	P 161	P 115	P 97	P 32	P 0.11
	C 201	C 107	C 65	C 71	C 18	C 0.83
Chaudhari	P 48	P 22	P 7	P 8	P 20	P 0.063
	C 21	C 49	C 23	C 3	C 9	C 0.184
Vahabi	P 97	P 18	P 0	P 16	P 81	P 0.421
	C 75	C 11	C 2	C 11	C 64	C 0.210

HWE: Hardy-Weinberg Equilibrium

**Table 4: Association of interleukin-17A polymorphism and chronic periodontitis by using codominant, dominant, and recessive models**

Genotypes/ alleles	Number of studies	Polymorphism	Test of association		Test of heterogeneity	
			$P$	OR (95% CI)	$P$	$I^2$ (%)
Alleles		A versus G	0.6249	0.9561 (0.7987-1.145)	0.001	86.7
Codominant		GA versus GG	0.001	0.5007 (0.3866-0.6484)	0.001	75.9
		AA versus GG	0.001	1.997 (1.542-2.586)	0.005	82.8
Dominant	6	GA+AA versus GG	0.001	1.778 (1.406-2.247)	0.001	86.4
Recessive		AA versus GA+GG	0.001	1.778 (1.406-2.247)	0.001	79.4

OR: Odds ratio; CI: Confidence interval

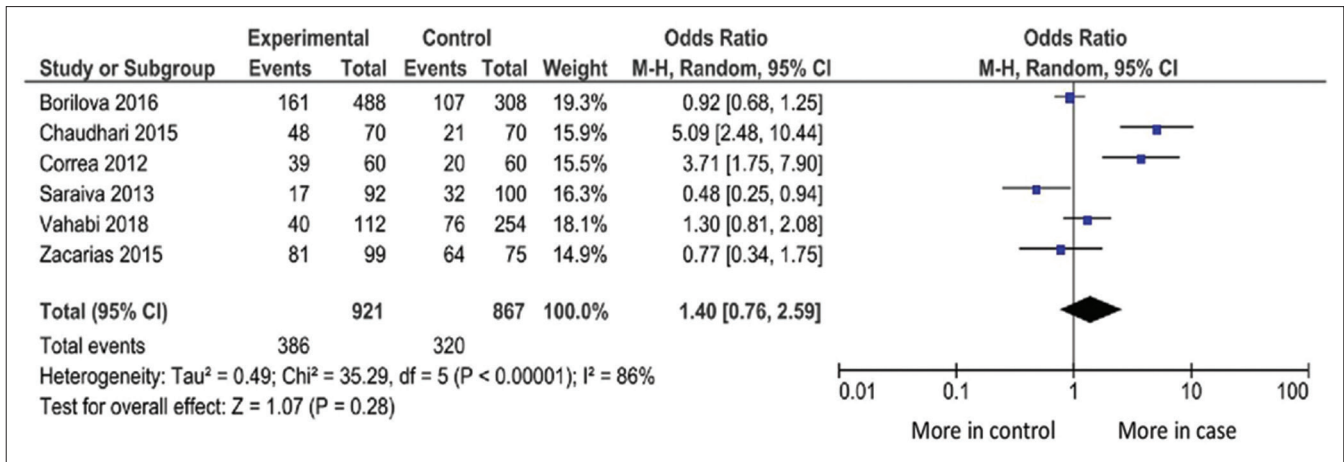


Figure 2: Forest plot of comparison of mutant allele versus wild type allele in rs2275913 polymorphism and chronic periodontitis

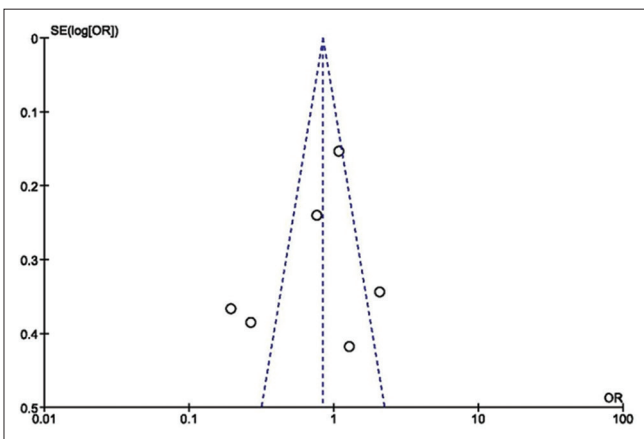


Figure 3: A funnel plot for publication bias in allelic evaluation in rs2275913 polymorphism and chronic periodontitis

against CP and all other genetic models (AA vs. GG, GA + AA vs. GG, AA vs. GA + GG) had causative factors against CP, as shown in Table 4. The study was done by Saraiva *et al.* also demonstrated the similar findings of increased frequency of A allele polymorphism in the IL-17A gene in the Brazilian population.<sup>[31]</sup> Zacarias *et al.* have shown that rs 2275913 AA genotype and A allele were associated with susceptibility to CP in a Brazilian population.<sup>[33]</sup> In contrast to our findings, Corrêa *et al.* indicated that rs2275913 AA genotype and A allele were a protective factor against CP in the Brazilian population.<sup>[34]</sup>

Considering the ethnicity of subjects, there was an important variable that differs between different ethnic groups. The mixed population of current meta-analysis with allelic (A vs. G,  $P = 0.58$ , OR = 0.852, CI = 0.435–1.783) and genotypes (AA vs. GG, GA vs. GG) variation found to be no differences ( $P = 0.78$ , OR = 0.653, CI = 0.198–1.192 and  $P = 0.75$ , OR = 1.581, CI = 0.905–2.932, respectively) [Table 2] when compared with previous meta-analysis.<sup>[25]</sup> The Brazilian population has been described, with a high degree of admixture from Amerindians, African, and or European ancestors.<sup>[31]</sup> Hence,

only a few studies were included in this meta-analysis with pooled OR calculation showed limitation, although the results were accurate by the use of fixed-effect model. The highlight of this analysis was the evaluation of heterogeneity and sensitive analysis across the studies and found no individual study has an influence on the overall OR values for rs2275913 variation.

When dealing with methodological/experimental bias, some differences in the periodontal examinations, diagnosis, and severity of diseases were completely not available in the literature. The association of chronic periodontitis and smoking seems to be an important confounding variable, and consequently, the inclusion of smoking and nonsmoking participants can be an additional source of variation. Considering primary studies, three studies included individuals with mixed smoking status, and remaining, three studies selected nonsmoking individuals.<sup>[32,35-38]</sup> The rs2275913 polymorphism in IL-17A with smoking factors evidenced that nonsignificant association with CP when considering of allelic (A vs. G,  $P = 0.73$ , OR = 0.84, CI = 0.48-1.895) and genotypic variations (GA vs. GG, AA vs. GG,  $P = 0.84$ , OR = 0.895, CI = 0.198-5.015 and  $P = 0.89$ , OR = 1.09, CI = 0.315–4.983, respectively) [Table 2]. These results were supported and agreed with the previous study done by Souto *et al.* which showed a negative correlation between cigarettes smoked per day and IL-17A level in gingival sample tissues from the smokers of CP.<sup>[39]</sup>

There are several limitations of the current meta-analysis which includes first, limited number of studies which could be the reason for no significant association found in the pooled OR calculations. Second, the study information in this literature was based on unadjusted analysis and thus we were unable to determine the risk of PDs when considering environmental elements, age, family background, lifestyle or additional risk factors that could be have possible effects on pooled results. Third, the small numbers that were evaluated in the chronic form of periodontitis in this

meta-analysis leads to the improper publication bias for rs2275913 polymorphism. Fourth, for the subgroup analysis of ethnicity, the number of each subgroup was very small, and there was not enough statistical power to explore the real association. Fifth, this meta-analysis has done by using the data in published literature, but some important data could be present in the unpublished studies being unable to be included. Sixth, we have not done the protocol registration at the NHIS webpage based on the Cochrane review before the start of the review process.

The results obtained from this study showed no association of IL-17A polymorphism with CP susceptibility. This meta-analysis with six articles in 633 patients diagnosed with CP, 539 control patients; totally, 1172 participants showed a no significant association between the rs 2275913 polymorphism in the IL-17 A with the risk of CP. The results also showed no significance in mixed population and smokers of chronic periodontitis based on allelic evaluation as well as in genomic comparisons. Further studies should assess the association of IL-17A polymorphism in larger samples with different populations by using precise genetic analysis for future perfectives.

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#### Conflicts of interest

There are no conflicts of interest.

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