Association between IL-1A (-889C/T) polymorphism and susceptibility of chronic periodontitis: a meta-analysis

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Abstract

Background The purpose of this study was to investigate the association between IL-1A (-889C/T, rs1800587) polymorphism and susceptibility of chronic periodontitis.

Methods A systematic literature search was carried out in the databases updated on July 1, 2019, including PubMed, Embase, Cochrane Library and Web of Science. Through STATA 14.0 software, the association between IL-1A (-889C/T) polymorphism and susceptibility of chronic periodontitis was calculated by pooled odds ratios (ORs) and 95% confidence intervals (CIs). Harbord test was used for the publication bias.

Results The results of overall meta-analysis revealed that IL-1A (-889C/T) polymorphism was associated with the susceptibility of chronic periodontitis among all the genetic models, including allele contrast (T vs. C, OR (95% CI): 1.297 (1.038-1.622), P=0.022), dominant model (TT+CT vs. CC, OR (95% CI): 1.337 (1.015-1.761), P=0.039), recessive model (TT vs. CC+CT, OR (95% CI): 1.453 (1.138-1.856), P=0.003), and codominant model (TT vs. CC, OR (95% CI): 1.555 (1.187-2.038), P=0.001; CT vs. CC, OR (95% CI): 2.559 (1.245-5.260), P=0.011). The results of subgroup analyses indicated that IL-1A (-889C/T) polymorphism was closely related to the susceptibility of chronic periodontitis in African population (T vs. C, OR (95% CI): 1.277 (1.039-1.571), P=0.020; TT+CT vs. CC, OR (95% CI): 1.357 (1.061-1.735), P=0.015; TT vs. CC, OR (95% CI): 1.599 (1.115-2.292), P=0.011), in European population (TT vs. CC+CT, OR (95% CI): 1.645 (1.112-2.435), P=0.013; TT vs. CC, OR (95% CI): 1.639 (1.044-2.574), P=0.032) and in American population (CT vs. CC, OR (95% CI): 6.404 (3.000-13.669), P<0.001).

Conclusions IL-1A (-889C/T) polymorphism is associated with the susceptibility of chronic periodontitis in African, European and American populations according to
the currently available evidence. However, more large-scale, multi-ethnic case-control studies are required to be conducted in future to confirm the role of IL-1A (-889C/T) gene in the occurrence and development of chronic periodontitis.

Background

Periodontal diseases, characterized by an imbalance between subgingival communities and the host immune response, are defined as a dysbiotic condition. They include gingivitis and periodontitis [1]. Gingivitis is regarded as an early form of periodontal diseases, while periodontitis develops with the accumulation of dental plaques, bacterial dysbiosis and periodontal pocket formation, it can result in destruction of connective tissue attachment to the tooth and alveolar bone resorption, ultimately leading to tooth loss [2]. In the United States, the prevalence of gingivitis is 9%-17% in children aged between 3 and 11 years and 47% in the adults [3, 4]. According to the statistics of World Health Organization (WHO), periodontitis occurs in 35%-50% of the world population [5]. In China, the standardized disability-adjusted life years (DALYs) of periodontal diseases had been increased to 25.7 in 2013 from 24.7 in 1990 [6]. In recent years, an increasing number of studies have shown that periodontal diseases may be associated with multiple systemic diseases, such as cardiovascular disease [7, 8], diabetes mellitus [9], head and neck cancer [10] and erectile dysfunction [11]. It is thus very necessary to seek the risk factors for periodontal diseases.

With the development of genetic engineering technology and continuous research on human gene polymorphism, it is gradually recognized that gene polymorphism may be a material basis for the individual difference of periodontal diseases. Gene-related studies have confirmed that chronic periodontitis and aggressive
periodontitis may be two different diseases [12], and interleukin (IL) gene polymorphisms possibly play a pivotal role in the occurrence and progression of chronic periodontitis [13-15]. The genes in IL-1 family have allele polymorphisms which may be related to the susceptibility of chronic periodontitis, in which single nucleotide polymorphism (SNP) -889C/T (rs1800587) in IL-1A gene is researched extensively [16-19]. IL-1A (-889C/T) is an SNP located at the position -889 upstream of translation start, and its polymorphism has a potential functional importance through the regulation on the IL-1 protein production [20].

Until now, a lot of studies have investigated the association between IL-1A (-889C/T) polymorphism and chronic periodontitis, but the results are inconsistent [16-18, 21, 22]. A previous meta-analysis reported that IL-1A (-889C/T) polymorphism was related to the susceptibility of chronic periodontitis, but the included studies were miscellaneous and Hardy-Weinberg equilibrium (HWE) test was not carried out [19]. Herein, an updated meta-analysis was conducted based on the currently available evidence, with the purpose of further clarifying the association between IL-1A (-889C/T) polymorphism and chronic periodontitis.

Materials and Methods

**Literature search**

A systematic literature search was carried out in the databases updated on July 1, 2019, including PubMed, Embase, Cochrane Library and Web of Science. The search terms included “Periodontitis” OR “Periodontal Diseases” AND “Polymorphism” OR “-889C/T” OR “rs1800587” AND “Interleukin” OR “Cytokine”.

**Inclusion and exclusion criteria**
Inclusion criteria: i) case-control studies; ii) patients diagnosed as chronic periodontitis in case group, while healthy people without history of chronic periodontitis in control group; iii) $P$ value of $HWE$ in control group showed no statistical significance; v) studies were published in English.

Exclusion criteria: i) studies with insufficient genotype data; ii) studies unable to extract the effective data; iii) reviews, meta-analyses, letters or editorial articles.

**Data extraction and quality assessment**

The data of the published articles in accordance with inclusion and exclusion criteria were extracted by two authors (XD Feng and JM Liu). The collected information was as follows: the first author, year of publication, ethnicity, country, genotyping method, quality assessment and its score, genotype distribution and frequency, as well as the value of $HWE$ ($p$).

The quality of studies was evaluated by Newcastle-Ottawa Scale with some modifications to match the needs of this meta-analysis [23, 24]. This scoring system primarily depends on the patient selection, comparability of study groups and assessment of outcome to evaluate the quality. The studies with scores <5 were considered low or moderate quality, while those with scores $\geq$ 5 were considered high quality. The quality of studies was assessed independently by two authors (XD Feng and JM Liu).

**Statistical analysis**

STATA 14.0 software (Stata Corporation, College Station, TX, USA) was used in this meta-analysis. $HWE$ was performed with Chi-square test. Association between IL-1A (-889C/T) polymorphism and chronic periodontitis was analyzed with pooled odds
rations (ORs) and 95% confidence intervals (CIs). The heterogeneity of ORs was assessed by $Q$ and $I^2$ test, and $Q > 0.1$ and $I^2 < 50\%$ were regarded as no significant heterogeneity. Random-effect model (with heterogeneity) and fixed-effect model (without heterogeneity) were respectively applied based on the heterogeneity. The sensitivity of all models was analyzed, and Harbord test was used for the publication bias. The value of $P$ less than 0.05 was considered statistically significant.

Results

**Literature search and study characteristics**

A total of 1 109 studies were identified by searching the databases, including PubMed, Embase, Cochrane Library and Web of science. After removing the duplicates, there were 659 studies left. When 57 reviews or meta-analyses, 579 studies irrelevant to IL-1A (-889C/T) and 9 studies not for chronic periodontitis were excluded, there were 14 studies [16-18, 21, 22, 25-33] left, and they were selected for qualitative analysis. The flow diagram describing the study selection process is listed in Figure 1.

Among 14 studies, two studies [25, 30] were found HWE($p$)<0.05, so 12 studies [16-18, 21, 22, 26-29, 31-33] including 1 356 patients with chronic periodontitis and 1 249 controls were finally included in the meta-analysis. The characteristics of included studies are shown in Table 1.

**Overall meta-analysis**

The results of overall meta-analysis revealed that IL-1A (-889C/T) polymorphism was associated with the susceptibility of chronic periodontitis among all the genetic
models, including allele contrast \( [T \text{ vs. } C, \text{ OR (95\% CI)}: 1.297 \ (1.038-1.622), \ P=0.022] \), dominant model \( [TT+CT \text{ vs. } CC, \text{ OR (95\% CI)}: 1.337 \ (1.015-1.761), \ P=0.039] \), recessive model \( [TT \text{ vs. } CC+CT, \text{ OR (95\% CI)}: 1.453 \ (1.138-1.856), \ P=0.003] \), and codominant model \( [TT \text{ vs. } CC, \text{ OR (95\% CI)}: 1.555 \ (1.187-2.038), \ P=0.001; \ CT \text{ vs. } CC, \text{ OR (95\% CI)}: 2.559 \ (1.245-5.260), \ P=0.011] \) (Table 2 and Figure 2a-e).

**Subgroup analysis**

Subgroup analyses were performed further among allele contrast, dominant model, recessive model and codominant model regarding the ethnicity, genotyping method and quality assessment. As shown in Table 2 and Figure 3a-e, IL-1A (-889C/T) polymorphism was closely related to the susceptibility of chronic periodontitis in African population \( [T \text{ vs. } C, \text{ OR (95\% CI)}: 1.277 \ (1.039-1.571), \ P=0.020; \ TT+CT \text{ vs. } CC, \text{ OR (95\% CI)}: 1.357 \ (1.061-1.735), \ P=0.015; \ TT \text{ vs. } CC, \text{ OR (95\% CI)}: 1.599 \ (1.115-2.292), \ P=0.011] \), in European population \( [TT \text{ vs. } CC+CT, \text{ OR (95\% CI)}: 1.645 \ (1.112-2.435), \ P=0.013; \ TT \text{ vs. } CC, \text{ OR (95\% CI)}: 1.639 \ (1.044-2.574), \ P=0.032] \) and in American population \( [CT \text{ vs. } CC, \text{ OR (95\% CI)}: 6.404 \ (3.000-13.669), \ P<0.001] \). An significant correlation was discovered in all genetic models of polymerase chain reaction (PCR) group \( [T \text{ vs. } C, \text{ OR (95\% CI)}: 1.378 \ (1.075-1.767), \ P=0.012; \ TT+CT \text{ vs. } CC, \text{ OR (95\% CI)}: 1.525 \ (1.106-2.102), \ P=0.010; \ TT \text{ vs. } CC+CT, \text{ OR (95\% CI)}: 1.475 \ (1.049-2.074), \ P=0.025; \ TT \text{ vs. } CC, \text{ OR (95\% CI)}: 1.793 \ (1.247-2.577), \ P=0.002; \ CT \text{ vs. } CC, \text{ OR (95\% CI)}: 3.344 \ (1.786-6.262), \ P<0.001] \) and in recessive model of other groups \( [TT \text{ vs. } CC+CT, \text{ OR (95\% CI)}: 1.430 \ (1.006-2.033), \ P=0.046] \) (Table 2).

In terms of the low- and moderate-quality studies, the differences were pronounced
in most genetic models \([T \text{ vs. } C, \text{ OR (95\% CI): } 1.504 (1.175-1.924), P=0.001; TT+CT \text{ vs. } CC, \text{ OR (95\% CI): } 1.620 (1.244-2.108), P<0.001; TT \text{ vs. } CC+CT, \text{ OR (95\% CI): } 1.739 (1.249-2.422), P=0.001; TT \text{ vs. } CC, \text{ OR (95\% CI): } 2.033 (1.381-2.995), P<0.001] \), whereas no significant difference was shown regarding the high-quality studies except for the codominant model \([CT \text{ vs. } CC, \text{ OR (95\% CI): } 3.393(1.529-7.530), P=0.003] \) (Table 2).

**Publication bias**

Harbord test was used for the publication bias, and the \(P\) values were respectively 0.124 in allele contrast, 0.070 in dominant model, 0.879 in recessive model, 0.541 and 0.142 in co-dominant model (TT vs. CC and CT vs. CC). No significant differences were presented among all the models regarding the publication bias.

**Discussion**

Up to now, a great number of studies have investigated the relationship between IL-1A (-889C/T) polymorphism and the susceptibility of chronic periodontitis. Nevertheless, the results of these studies may be incomplete or inconsistent because of relatively fewer sample sizes, which may affect the statistical power. Hence, a comprehensive meta-analysis with the latest findings was carried out to explore the underlying association between IL-1A (-889C/T) polymorphism and the susceptibility of chronic periodontitis. In the present meta-analysis, 12 case-control studies including 1,356 patients with chronic periodontitis and 1,249 controls were finally included, and the results displayed that IL-1A (-889C/T) polymorphism was related to the susceptibility of chronic periodontitis, which might act as a risk variation for chronic periodontitis.
Periodontitis is a bacterial infectious disease modified by various risk factors. IL-1, a pro-inflammatory cytokine, is not only a major regulator of the host responses to microbial infection, but also an important modulator of extracellular matrix catabolism and bone resorption. The variations in IL-1 gene cluster localized on chromosome 2 are reported to have a correlation with the increased susceptibility to severe periodontitis in adults [34]. IL-1A, a member of IL-1 gene family, participates in the establishment of inflammatory lesions in periodontitis [35]. Shirodaria et al. [36] found that IL-1A gene polymorphism is associated with the level of IL-1α in gingival crevicular fluid of teeth with severe periodontal disease, and the level of IL-1α in gingival crevicular fluid in patients carrying IL-1A allele 2 was almost 4 folds than that in negative patients. Additionally, SNPs from the promoter region (regulatory region), such as IL-1A (-889C/T), can make the gene expression changed, which are of great importance to the transcriptional regulation in the coding region [35]. The studies of Majumder et al. [16] and Wagner et al. [26] both indicated that IL-1A (-889C/T) polymorphism was associated with the susceptibility of chronic periodontitis, which was consistent with our results.

In the present meta-analysis, the subgroup meta-analyses were performed regarding the ethnicity, genotyping method and quality assessment. The results showed that IL-1A (-889C/T) polymorphism was related to the increased risk of chronic periodontitis in African, European and American populations. In Yemenis and Indians, a significant association with chronic periodontitis was presented in IL-1A (-889C/T) polymorphism [16, 28]. However, no association was shown in Algerians and Mexicans [17, 22]. This difference might be explained by the ethnic specificity of each population and inter-individual variation in cytokine production. A significant difference was shown in the codominant model (CT vs. CC) of American
population, but only two American studies were included, which might affect the evaluation effect. Therefore, more studies should be conducted in American population to confirm this result. In terms of genotyping methods, the results revealed that PCR technique might be a significative variation in the susceptibility of chronic periodontitis. Moreover, the differences were pronounced in most genetic models regarding the low- and moderate-quality studies, whereas no significant difference was shown regarding the high-quality studies except for the codominant model. In the future, it is expected to carry out more high-quality studies to validate the association between IL-1A (-889C/T) polymorphism and chronic periodontitis.

The strengths of the present meta-analysis were as follows, including: i) the studies from various databases were systematically searched to ensure the retrieved completeness; ii) the study selection, data extraction and quality assessment were all conducted independently by two authors to minimize the errors; iii) no significant publication bias was shown, which made the results more credible. Nevertheless, some limitations were still present in this meta-analysis. For instance, the quality of included studies was common, and the research results were analyzed without adjustment of relevant suspected factors.

To sum up, IL-1A (-889C/T) polymorphism is associated with the susceptibility of chronic periodontitis in African, European and American populations according to the currently available evidence. Nevertheless, more large-scale, multi-ethnic case-control studies are required to be conducted in the future to confirm the role of IL-1A (-889C/T) gene in the occurrence and development of chronic periodontitis.

Abbreviations

WHO: World Health Organization; DALYs: disability-adjusted life years; IL:
interleukin; SNP: single nucleotide polymorphism; HWE: Hardy-Weinberg equilibrium; ORs: odds ratios; CIs: confidence intervals; PCR, polymerase chain reaction

Declarations

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Availability of data and material

All data generated or analyzed during the present study are included in this published article.

Authors’ contributions

XF and JL were responsible for the conception and design of the study. XF and JL contributed to the study retrieval, quality assessment, the data collection and statistical analysis. XF and JL drafted the manuscript and the revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication
Not applicable.

**Ethics approval and consent to participate**

Not applicable.

**References**

1. Michaud DS, Fu Z, Shi J, Chung M. Periodontal disease, tooth loss, and cancer risk. Epidemiol Rev. 2017;39(1):49-58.

2. Abusleme L, Dupuy AK, Dutzan N, Silva N, Burleson JA, Strausbaugh LD, et al. The subgingival microbiome in health and periodontitis and its relationship with community biomass and inflammation. ISME J. 2013;7(5):1016-25.

3. Holm-Pedersen P, Walls A, Ship JA. Textbook of Geriatric Dentistry. Third Edition, Wiley Blackwell; 2015.

4. Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ. Prevalence of periodontitis in adults in the United States: 2009 and 2010. J Dent Res. 2012;91(10):914-20.

5. Petersen PE, Ogawa H. The global burden of periodontal disease: towards integration with chronic disease prevention and control. Periodontol 2000. 2012;60(1):15-39.

6. Zhang Q, Li Z, Wang C, Liu Y, Yang Y, Bussell S, et al. A comparison of DALYs for periodontal disease in China between 1990 and 2013: insights from the 2013 global burden of disease study. BMC Oral Health. 2017;17(1):74.

7. Aarabi G, Zeller T, Seedorf H, Reissmann DR, Heydecke G, Schaefer AS, et al. Genetic susceptibility contributing to periodontal and cardiovascular disease. J Dent Res. 2017;96(6):610-7.
8. Górski B, Górski R. The impact of periodontal treatment on inflammatory markers and cellular parameters associated with atherosclerosis in patients after myocardial infarction. Cent Eur J Immunol.2018;43(4):442-52.

9. Lee CY, Kuan YH, Tsai YF, Tai CJ, Tsai TH, Huang KH. Correlation between diabetes mellitus and periodontitis in Taiwan: A nationwide cohort study. Diabetes Res Clin Pract.2019;150:245-52.

10. Michaud DS, Fu Z, Shi J, Chung M. Periodontal disease, tooth loss and cancer risk. Epidemiol Rev.2017;39(1):49-58.

11. Kellesarian SV, Kellesarian TV, Ros Malignaggi V, Al-Askar M, Ghanem A, Malmstrom H, et al. Association between periodontal disease and erectile dysfunction: a systematic review. Am J Mens Health.2018;12(2):338-46.

12. Shao J, Zhang M, Wu L, Jia XW, Jin YH, Zeng XT. DEF1 rs11362 polymorphism and risk of chronic periodontitis: a meta-analysis of unadjusted and adjusted data. Front Genet. 2019;10:179.

13. Lavu V, Venkatesan V, Venkata Kameswara Subrahmanya Lakkakula B, Venugopal P, Paul SF, Rao SR. Polymorphic regions in the interleukin-1 gene and susceptibility to chronic periodontitis: a genetic association study. Genet Test Mol Biomarkers. 2015;19(4):175-81.

14. Atanasovska-Stojanovska A, Popovska M, Trajkov D, Spiroski M. IL1 cluster gene polymorphisms in Macedonian patients with chronic periodontitis. Bratisl Lek Listy. 2013;114(7):380-5.

15. Hao L, Li JL, Yue Y, Tian Y, Wang M, Loo WT, et al. Application of interleukin-1 genes and proteins to monitor the status of chronic periodontitis. Int J Biol Markers. 2013;28(1):92-9.

16. Majumder P, Panda SK, Ghosh S, Dey SK. Interleukin gene polymorphisms in
chronic periodontitis: A case-control study in the Indian population. Arch Oral Biol. 2019;101:156-64.

17. Boukortt KN, Saidi-Ouahrani N, Boukerzaza B, Ouhaibi-Djellouli H, Hachmaoui K, Benaissa FZ, et al. Association analysis of the IL-1 gene cluster polymorphisms with aggressive and chronic periodontitis in the Algerian population. Arch Oral Biol. 2015;60(10):1463-70.

18. Armingohar Z, Jørgensen JJ, Kristoffersen AK, Schenck K, Dembic Z. Polymorphisms in the interleukin-1 gene locus and chronic periodontitis in patients with atherosclerotic and aortic aneurysmal vascular diseases. Scand J Immunol. 2014;79(5):338-45.

19. da Silva FR, Guimarães-Vasconcelos AC, de-Carvalho-França LF, di-Lenardo D, Rodrigues LS, Barreto-do-Nascimento ML, et al. Relationship between -889 C/T polymorphism in interleukin-1A gene and risk of chronic periodontitis: evidence from a meta-analysis with new published findings. Med Oral Patol Oral Cir Bucal. 2017;22(1):e7-e14.

20. Hall SK, Perregaux DG, Gabel CA, Woodworth T, Durham LK, Huizinga TW, et al. Correlation of polymorphic variation in the promoter region of the interleukin-1 beta gene with secretion of interleukin-1 beta protein. Arthritis Rheum. 2004;50(6): 1976-83.

21. Trevilatto PC, de Souza Pardo AP, Scarel-Caminaga RM, de Brito RB, Alvim-Pereira F, Alvim-Pereira CC, et al. Association of IL1 gene polymorphisms with chronic periodontitis in Brazilians. Arch Oral Biol.2011;56(1):54-62.

22. Domínguez-Pérez RA, Loyola-Rodriguez JP, Abud-Mendoza C, Alpuche-Solis AG, Ayala-Herrera JL, Martinez-Martinez RE. Association of cytokines polymorphisms with chronic periodontitis and rheumatoid arthritis in a Mexican
population. Acta Odontol Scand. 2017;75(4):243-8.

23. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. Lancet. 2001;358(9285):870-5.

24. Athanasiou T1, Al-Ruzzeh S, Kumar P, Crossman MC, Amrani M, Pepper JR, et al. Off-pump myocardial revascularization is associated with less incidence of stroke in elderly patients. Ann Thorac Surg. 2004;77(2):745-53.

25. Brett PM, Zygogianni P, Griffiths GS, Tomaz M, Parkar M, D'Aiuto F, et al. Functional gene polymorphisms in aggressive and chronic periodontitis. J Dent Res. 2005;84(12):1149-53.

26. Wagner J, Kaminski WE, Aslanidis C, Moder D, Hiller KA, Christgau M, et al. Prevalence of OPG and IL-1 gene polymorphisms in chronic periodontitis. J Clin Periodontol. 2007;34(10):823-7.

27. Karasneh JA, Ababneh KT, Taha AH, Al-Abbadi MS, Ollier WE. Investigation of the interleukin-1 gene cluster polymorphisms in Jordanian patients with chronicand aggressive periodontitis. Arch Oral Biol. 2011;56(3):269-76.

28. Al-Hebshi NN, Shamsan AA, Al-Ak'hali MS. Interleukin-1 Two-locus haplotype is strongly associated with severe chronic periodontitis among Yemenis. Mol Biol Int. 2012;2012:231309.

29. Zuccarello D, Bazzato MF, Ferlin A, Pengo M, Frigo AC, Favero G, et al. Role of familiarity versus interleukin-1 genes cluster polymorphisms in chronic periodontitis. Gene. 2014;535(2):286-9.

30. Puri K, Chhokra M, Dodwad V, Puri N. Association of interleukin-1 α (-889) gene polymorphism in patients with generalized aggressive and chronic periodontitis. Dent Res J (Isfahan). 2015;12(1):76-82.
31. Lavu V, Venkatesan V, Venkata Kameswara Subrahmanya Lakkakula B, Venugopal P, Paul SF, Rao SR. Polymorphic regions in the interleukin-1 gene and susceptibility to chronic periodontitis: a genetic association study. Genet Test Mol Biomarkers. 2015;19(4):175-81.

32. Mesa F, Lanza E, García L, Marfil-Alvarez R, Magan-Fernandez A. Polymorphism IL-1RN rs419598 reduces the susceptibility to generalized periodontitis in a population of European descent. PLoS One. 2017;12(10):e0186366.

33. Borilova Linhartova P, Poskerova H, Tomandlova M, Bartova J, Kankova K, Fassmann A, et al. Interleukin-1 gene variability and plasma levels in czech patients with chronic periodontitis and diabetes mellitus. Int J Dent. 2019;2019:6802349.

34. McDevitt MJ, Wang HY, Knobelman C, Newman MG, di Giovine FS, Timms J, et al. Interleukin-1 genetic association with periodontitis in clinical practice. J Periodontol. 2000;71(2):156-63.

35. Barnea TV, Sava A, Gentimir C, Goriuc A, Boişteanu O, Chelaru L, et al. Genetic polymorphisms of TNFA and IL-1A and generalized aggressive periodontitis. Rom J Morphol Embryol. 2015;56(2):459-64.

36. Shirodaria S, Smith J, McKay IJ, Kennett CN, Hughes FJ. Polymorphisms in the IL-1A gene are correlated with levels of interleukin-1alpha protein in gingival crevicular fluid of teeth with severe periodontal disease. J Dent Res.2000;79(11):1864-9.

Figures
### Figure 1

The flow diagram describing the study selection process

| Study | OR (95% CI) | Weight |
|-------|-------------|--------|
| Wagner (2007) | 2.06 (1.34, 3.18) | 0.01 |
| Kornilch (2011) | 1.54 (0.97, 2.09) | 0.02 |
| Velmato (2011) | 0.83 (0.40, 1.68) | 0.09 |
| Al-Helwah (2012) | 1.00 (0.63, 1.60) | 0.04 |
| Amangkar (2014) | 1.48 (0.74, 2.97) | 0.06 |
| Zuccarello (2014) | 1.73 (1.11, 2.69) | 0.02 |
Figure 2

Forest plots for the association between IL-1A (-889C/T) polymorphism and susce|
The image contains a forest plot and two tables from a meta-analysis. The plot represents the results of a meta-analysis comparing different studies across Europe, Africa, and America. The tables list the study IDs, effect sizes (OR with 95% CI), and weights used in the analysis. The notes at the bottom of the plot indicate that the weights are from a random effects analysis.
| Study ID          | OR (95% CI)         | Weight |
|-------------------|---------------------|--------|
| Europe            |                     |        |
| Wagner (2007)     | 1.18 (0.87, 1.59)   | 27.75  |
| Amiri (2014)      | 1.40 (1.14, 1.71)   | 14.24  |
| Zuccarello (2014) | 1.26 (1.09, 1.45)   | 11.91  |
| Mesa (2017)       | 1.22 (1.06, 1.41)   | 9.42   |
| Linhartova (2019) | 1.27 (0.97, 1.66)   | 6.13   |
| Subtotal           | 1.26 (1.09, 1.45)   | 39.34  |
| Africa            |                     |        |
| Karsasneh (2011)  | 1.27 (0.97, 1.66)   | 4.78   |
| Al-Helwah (2012)  | 1.40 (1.14, 1.71)   | 4.78   |
| Boukort (2015)    | 1.22 (1.06, 1.41)   | 3.56   |
| Vani (2015)       | 1.22 (1.06, 1.41)   | 3.56   |
| Majumdar (2019)   | 1.22 (1.06, 1.41)   | 3.56   |
| Subtotal           | 1.22 (1.06, 1.41)   | 11.16  |
| America           |                     |        |
| Treviato (2011)   | 1.27 (0.97, 1.66)   | 2.59   |
| Dominguez-Perez (2017) | 1.29 (0.98, 1.71) | 2.59   |
| Subtotal           | 1.29 (0.98, 1.71)   | 5.17   |
| Overall           | 1.29 (0.98, 1.71)   | 100.00 |
Figure 3

Forest plots for the association between IL-1A (-889C/T) polymorphism and susceptibility to chronic periodontitis.

Supplementary Files

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Table 1.pdf
Table 2.pdf