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 rations (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 ≥ 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 *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] (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 *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].

An significant correlation was discovered in all genetic models of polymerase chain reaction (PCR) group [T *vs*. C, OR (95% CI): 1.378 (1.075-1.767), *P*=0.012; TT+CT *vs.* CC, OR (95% CI): 1.525 (1.106-2.102), *P*=0.010; TT *vs*. CC+CT, OR (95% CI): 1.475 (1.049-2.074), *P*=0.025; TT *vs.* CC, OR (95% CI): 1.793 (1.247-2.577), *P*=0.002; CT *vs.* CC, OR (95% CI): 3.344 (1.786-6.262), *P*<0.001] and in recessive model of other groups [TT *vs*. CC+CT, 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 *vs*. C, OR (95% CI): 1.504 (1.175-1.924), *P*=0.001; TT+CT *vs.* CC, OR (95% CI): 1.620 (1.244-2.108), *P*<0.001; TT *vs*. CC+CT, OR (95% CI): 1.739 (1.249-2.422), *P*=0.001; TT *vs.* CC, 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 *vs.* CC, 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 rations; 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.

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Figures

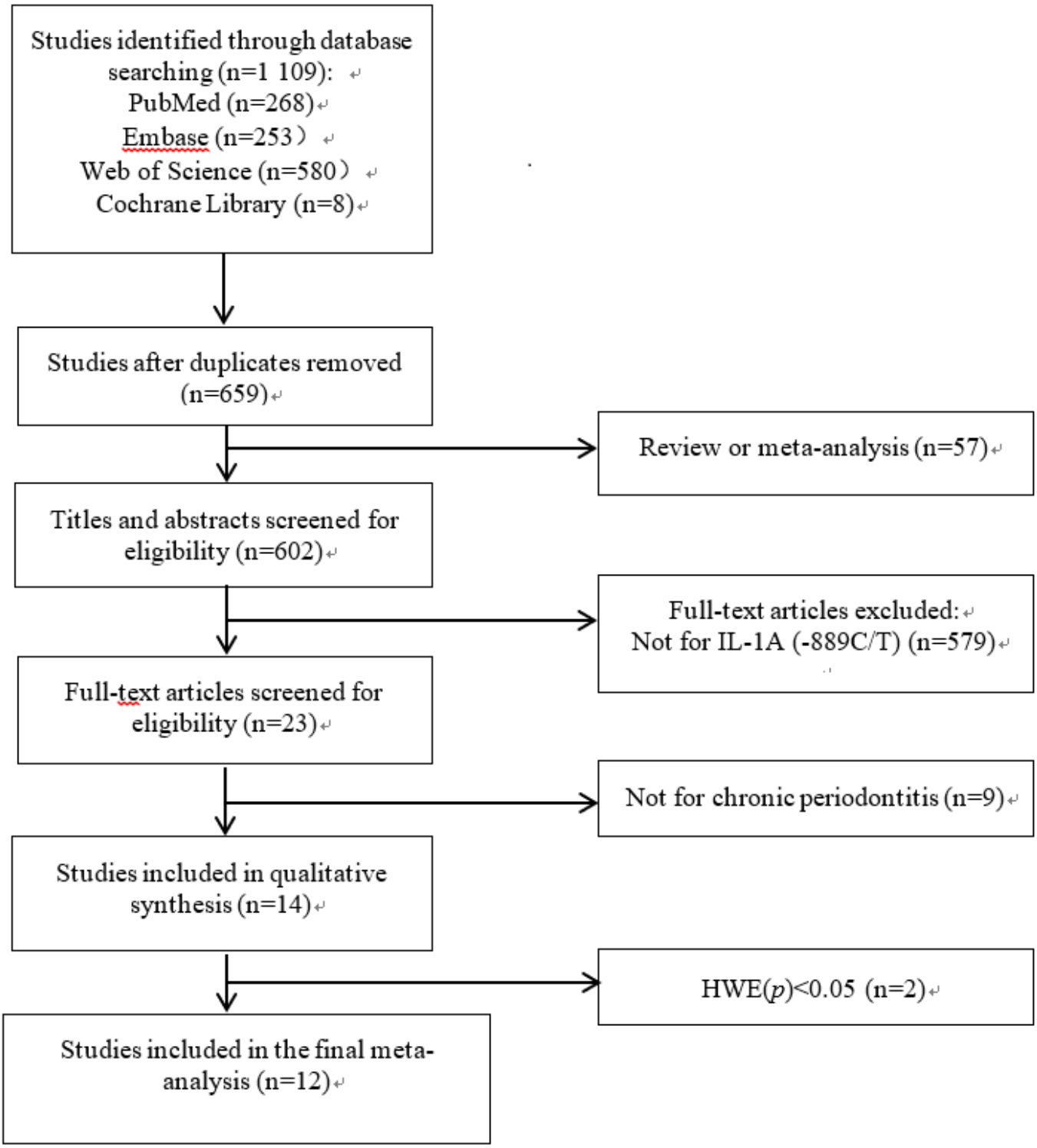

Figure 1

The flow diagram describing the study selection process

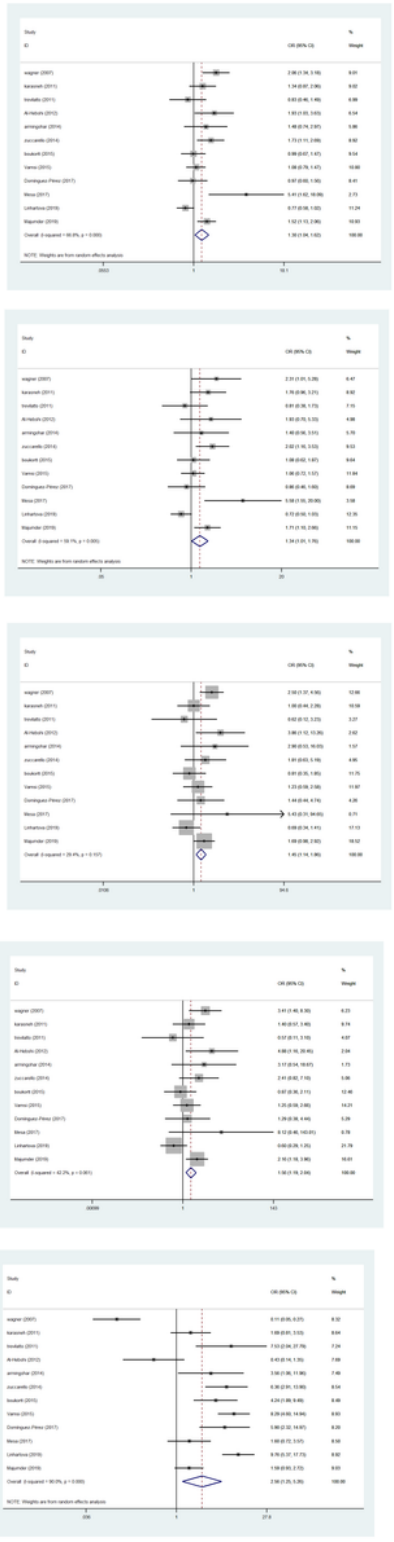

Figure 2

Forest plots for the association between IL-1A (-889C/T) polymorphism and susceptibility of chronic periodontitis among all the genetic models, including: (a) allele contrast (T vs. C), (b) dominant model (TT+CT vs. CC), (c) recessive model (TT vs. CC+CT), (d) codominant model (TT vs. CC) and (e) codominant model (CT vs. CC).

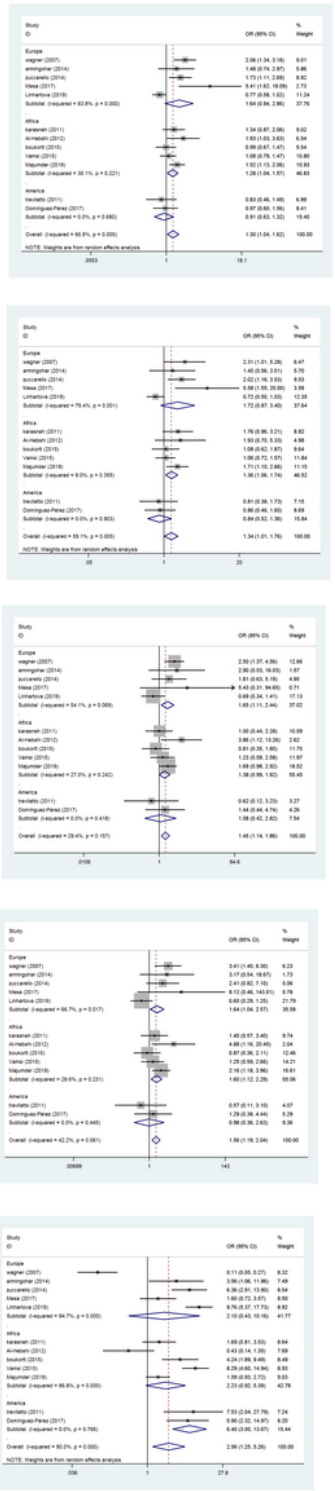

Figure 3

Forest plots for the association between IL-1A (-889C/T) polymorphism and susceptibility of chronic periodontitis in multiple ethnicities, including: (a) allele contrast (T vs. C), (b) dominant model (TT+CT vs. CC), (c) recessive model (TT vs. CC+CT), (d) codominant model (TT vs. CC) and (e) codominant model (CT vs. CC).

Supplementary Files

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