

Association Between Apical Periodontitis and TNF- α -308 G>A Gene Polymorphism: A Systematic Review and Meta-Analysis

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Currently, investigations have focused on the identification of Single Nucleotide Polymorphisms (SNP) involved in host response and its ability to generate an immunity deficiency. The aim of this study was to perform a systematic review (SR) and meta-analysis to evaluate the association between TNF- α -308 G>A polymorphism and apical periodontitis (AP) phenotypes. A broad search for studies was conducted. The following databases were used: PubMed, Scopus, Web of Science, and VHL (Medline, SciELO, Ibecs, and Lilacs). The MeSH terms "Periapical Periodontitis," "Periapical Abscess," "Polymorphism, Genetic," and "Polymorphism, Single Nucleotide" were used. MeSH synonyms, related terms, and free terms were included. Clinical investigations of individuals with different AP phenotypes in permanent teeth were selected. After application of the eligibility criteria, selected studies were qualified by assessing their methodological quality. A fixed effect model was used for the meta-analysis. The initial search identified 71 references. After excluding duplicate abstracts, 33 were selected. From these, two were eligible for quality assessment and were classified as being of moderate evidence. The included studies did not demonstrate association between AP and TNF- α -308 G>A SNP. However, the meta-analysis demonstrated an association between the genotype distribution and AP phenotype (OR= 0.49; confidence interval= 0.25, 0.96; p=0.04). The role of TNF- α -308 G>A SNP in AP phenotypes is debatable. Further studies are needed to confirm and understand the underlying mechanisms of the identified association.

Introduction

Apical periodontitis (AP) is generally a sequel of a root canal system infection, but even though microbial factors play a main role in the etiology of AP, the presence of lymphocytes, macrophages and neutrophils in periapical lesions indicates that the immune system is also involved in the process of pathogenesis (1,2). The main immunological constituents of periapical lesions are represented by macrophages and type 1 T helper cells (Th1). Consequently, cytokines such as tumor necrosis factor alpha (TNF- α) and interleukins (1a, 1b, 6, 8 and 12p40) probably take part in the development of AP. TNF- α has been reported in human AP and root canal exudate, which reinforces the hypothesis that this cytokine is involved in pulp and periapical pathogenesis, including the concomitant bone loss (1-7).

The TNF- α gene is located in the short arm of chromosome 6, in the class III region of the major histocompatibility complex (MHC), and consists of four exons and three introns (8). A Single Nucleotide Polymorphism (SNP) at the -308 position of the promoter region has been described in which there is a base substitution of guanine (G) by an adenine base (A) (9). Among the various SNPs of TNF- α , the -308 G>A polymorphism has been shown to directly

affect the expression of TNF- α . The A allele was related to higher production of TNF- α in vitro (10) and seven-fold more transcriptional activity in vivo (9,11). TNF has many biological activities, has a direct cytotoxic effect and a general debilitating effect in chronic disease and plays an important role in immune response, causing severe damage to the host when the balance between pro- and anti-inflammatory cytokines is broken.

AP is a multifactorial disease and although the infection of the root canal system by pathogens is the main factor in the pathogenesis, other aspects also need to be taken into consideration. Host risk factors such as age, gender, smoking, socioeconomic factors, certain systemic diseases and genetic profile are being studied (12-14). In this way, several investigations have focused on the identification of SNPs involved with the host response and its ability to generate a deficient immune system (12,15-19). Some of these investigations have focused on the TNF- α -308 G>A polymorphism and its association with AP. Therefore, we carried out a systematic review and meta-analysis to evaluate the association between AP phenotypes and TNF- α -308 G>A polymorphism.

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Material and Methods

This systematic review was registered in the PROSPERO database (<http://www.crd.york.ac.uk/PROSPERO/>), CRD42016035688, and was conducted following the PRISMA Statements (www.prismastatement.org) (20). The protocol for this systematic review was developed based on criteria adopted from published recommendations on the assessment of the quality of genetic association studies (21–23).

Focused Question

The present systematic review was conducted in order to answer the following focused question: "Is there an association between TNF- α -308 G>A polymorphism and AP phenotype in the permanent teeth of humans?" The question was developed by using the patient population, exposition, comparison and outcome (PECO) framework.

Eligibility Criteria

Studies that evaluate the TNF- α -308 G>A polymorphism in patients with acute AP and chronic AP in permanent teeth were included. Only studies that performed the diagnosis of AP through clinical and radiographic examinations were considered. Case reports, review studies, book chapters, theses, guidelines, cell culture laboratory studies, and animal studies were not included.

Literature Search Strategy

An electronic search was conducted in PubMed, Scopus, Web of Science (WOS), and Virtual Health Library (VHL) (Lilacs, Ibecs, Mediline, Scielo) databases through March 15, 2016, without year and language restrictions. The MeSH (Medical Subject Headings) terms (www.nlm.nih.gov/mesh/meshhome.html) used in the search were "Periapical

Periodontitis," "Periapical Abscess," "Polymorphism, Genetic," and "Polymorphism, Single Nucleotide." Furthermore, we included MeSH synonyms, related terms, and free terms (Table 1). The Boolean operators "AND" and "OR" were applied to combine the keywords. The searches were complemented by screening the references of selected studies to find any study that did not appear in the database search.

Study Selection

Initially, two of the authors selected the studies by title and abstracts according to the previously described search strategy. To evaluate agreement between authors, 10% of the publications were randomly selected, had their classification compared, and then a Kappa statistic of 0.97 was determined. Only studies that matched inclusion criteria were accepted. Studies appearing in more than one database were considered only once. In those cases in which the abstract and the title were not clear, the study was fully read in order to minimize the possibility of disregarding important studies. Subsequently, the full texts of all potentially eligible studies were accessed and the inclusion and exclusion criteria were applied again. Any disagreement was discussed and solved by consensus or discussion with a third author.

Quality Assessment

The authors adapted a 10-point scoring sheet used by Clark and Baudouin (21) which was based on criteria from published recommendations on the assessment of the quality of genetic association studies. Each quality criterion was assessed as present (yes, score of 1 point) and absent or undetermined (no, score of 0 points). One author initially scored all of the papers. In any paper where the author felt uncertainty about assigning an individual score, the

Table 1. Search strategy

PubMed	#1 ("Periapical Periodontitis" [MeSH Terms] OR "Periapical Periodontitis" [Title/Abstract] OR "Periapical Abscess" [MeSH Terms] OR "Periapical Abscess" [Title/Abstract] OR "apical periodontitis" [Title/Abstract]) #2 ("Polymorphism, Genetic" [MeSH Terms] OR "Polymorphism, Genetic" [Title/Abstract] OR "Polymorphism, Single Nucleotide" [MeSH Terms] OR "Polymorphism, Single Nucleotide" [Title/Abstract] OR "Polymorphism" [Title/Abstract] OR "SNP"[Title/Abstract]) #1 and #2
Scopus	#1 (TITLE-ABS-KEY (periapical periodontitis) OR TITLE-ABS-KEY (periapical abscess) OR TITLE-ABS-KEY (apical periodontitis)) #2 (TITLE-ABS-KEY (polymorphism, genetic) OR TITLE-ABS-KEY (polymorphism, single nucleotide) OR TITLE-ABS-KEY (polymorphism) OR TITLE-ABS-KEY (snp)) #1 and #2
WOS	#1 TS=("Periapical Periodontitis" OR "Periapical Abscess" OR "apical periodontitis") #2 TS=("polymorphism, genetic" OR "polymorphism, single nucleotide" OR "polymorphism" OR "snp") #1 and #2
VHL	(tw:(polymorphism genetic OR polymorphism single nucleotide OR polymorphism OR snp)) AND (tw:(Periapical Periodontitis OR Periapical Abscess OR apical periodontitis))

second author independently scored the paper and then consensus was reached for the final score. Agreement was good (standard deviation of the difference in scores was 0.3). A final quality score was obtained by summation of each component giving a range of 0-10 for each study. Based on the score, the studies were classified into three categories: i) high methodological quality: presenting 8 or more criteria; ii) moderate methodological quality: presenting 5-7 criteria; iii) low methodological quality: presenting 4 or fewer of the evaluated criteria. Considering the methodological quality, the studies were also classified as having high, moderate and low evidence.

Data Extraction

Data extraction were conducted independently by two reviewers (A.G.S. and P.A.C.) by completely reading the articles and considering the categories and variables. The data from the included studies were compiled and organized according to: 1 - the first author of the paper and publication year; 2 - population studied and ethnicity; 3 - SNP; 4 - sample size per condition; 5 - matching criteria; 6 - molecular biology technique (PCR- polymerase chain reaction; RFLP- restriction fragment length polymorphism; SSCP- single strain conformation polymorphism, and amplification by HRM - high resolution melting); 7 - statistical analyzes (HWE); 8 - TNF- α -308 G>A polymorphism results; 9- other results; 10 - observations and limitations.

Meta-analysis

For the meta-analysis, the odds ratio (OR) and 95% confidence interval (CI) were estimated and used to evaluate the strength of the association between AP phenotypes and TNF- α -308 G>A polymorphism for both genotype and allele distribution. The pooled ORs were calculated for the genotypic recessive model (GG vs. AG+AA) and for the allelic model (G vs. A).

A fixed effect model was used for the meta-analysis. OR and 95% CI values were estimated for each study using the Cochran-Mantel-Haenszel test. The I² was used to assess statistical heterogeneity between studies where I² values of 25%, 50%, and 75% indicated low, medium and high heterogeneity, respectively (24). Meta-analysis calculation and Forest Plots creation were performed with RevMan 5.3.

Results

Characteristics of the Studies

Figure 1 presents a flowchart of the systematic review process. Initially, 71 studies were identified through their abstracts in the following electronic databases: 19 studies from PubMed, 24 from Web of Science, 22 from Scopus and six from BVS. After disregarding the duplicated studies, 33 remained. Of these, 25 studies were excluded after reading

the title and abstract due to obvious irrelevance towards the proposed theme; one study was excluded since it was a systematic review; five studies were excluded as they assessed associations between other genes and AP (e.g. CD14, TLR4, MMP2, MMP3, MMP9, MMP13, MMP14, TIMP2, IL-1, Fc γ RIIIa, IL1- β);. Finally, two studies met the inclusion criteria, De Sá et al. (25) and Amaya et al. (26), and were included in the qualitative assessment (Table 2). Regarding this aspect, Amaya et al.(26) failed in the control group criteria due to a smaller control group than case group. Both studies did not report blinding and power calculation criteria. They also did not discuss if the studies were corrected for the possibility of a false-positive (type I) error. Consequently, these studies were classified as being of moderate evidence.

Other SNPs besides TNF- α were also evaluated: CD14, IL1B, IL6, IL10, IL8/CXCL8, and IL12B. Table 3 shows the data extraction from the selected studies. Amaya et al.(26) and De Sá et al.(25) compared acute AP to chronic AP with the same description for the pathologies and similar methodologies.

Meta-Analysis Results

Data from the included studies were compared through the meta-analysis. Figure 2 presents the Forest Plots for the genotype and allele distributions. An association was observed (OR= 0.49; confidence interval= 0.25, 0.96; p=0.04) for genotype distribution (Figure 2A). Figure 2B presents the Forest Plot for the allele distribution; only a borderline association was observed (OR= 0.59; confidence interval= 0.32, 1.08; p=0.08).

The heterogeneity among the studies was low, I²=0%.

Table 2. Methodological scoring protocol based on quality assessment for selected studies.

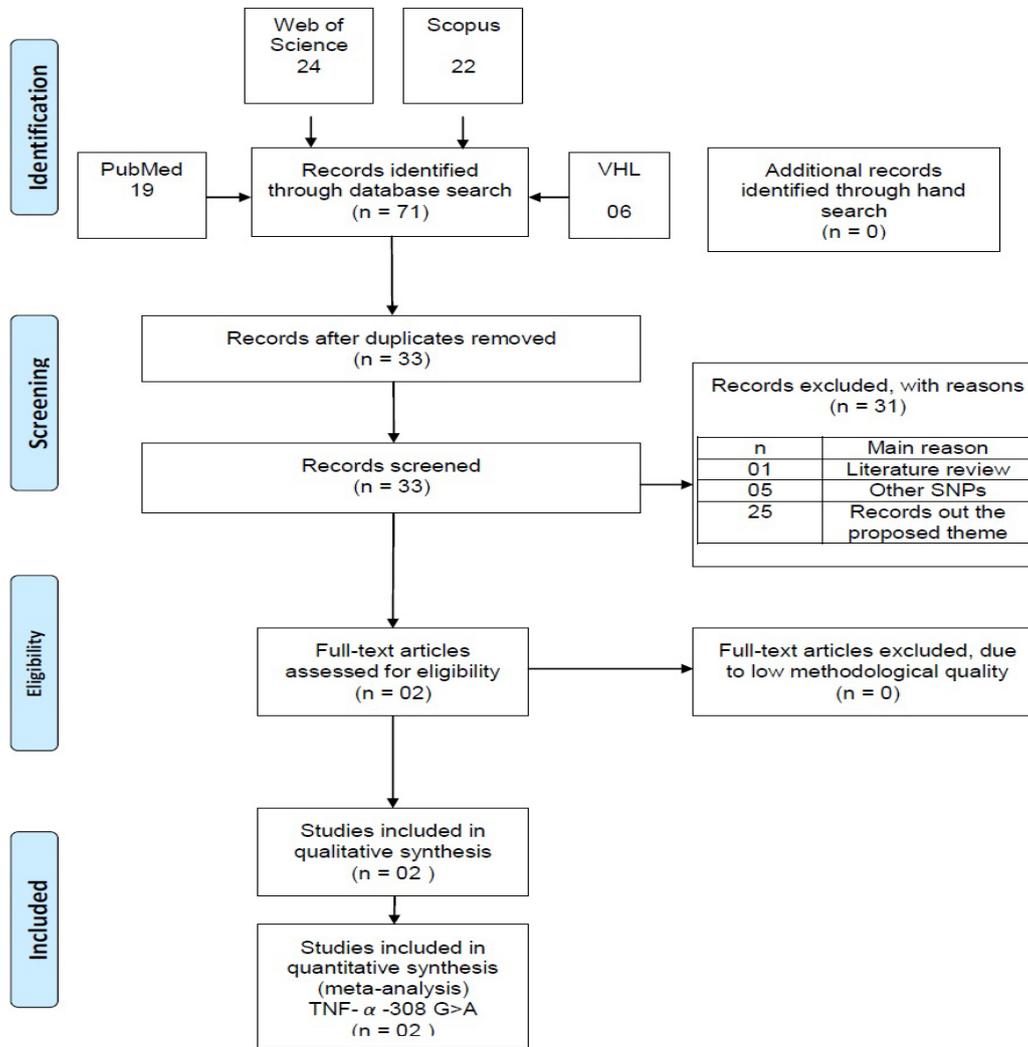
Criteria evaluated	Studies	
	De Sá et al. (25)	Amaya et al. (26)
Control group	1	0
Hardy-Weinberg equilibrium	1	1
Case group	1	1
Primer	1	1
Reproducibility	1	1
Blinding	0	0
Power calculation	0	0
Statistics	1	1
Corrected statistics	0	0
Independent replication	0	1
Score	6	6
Evidence	Moderate	Moderate

*For the quantification of criteria: «1» means present, and «0» absent.

Table 3. Data extraction of included studies

Year/ Author	Population / Ethnicity	SNP	Sample size per phenotype	Matching criteria	Molecular biology technique	HWE	TNF- α -308 G>A results	Other results	Observations and limitations
Amaya et al. (26)	Bucaramanga City, Colombia Mixed	TNF- α -308 G>A *and IL-1 β , IL-8, IL-12B	63 ASAP (cases) 57 CNAP (controls)	Age, sex	PCR-RFLP	Tested	No significant difference was observed for TNF- α -308 G>A between groups (p>0.05).	Significant differences in the distribution of IL8/CXCL8 and IL8/CXCL were observed.	It is not clear if cases and controls were matched. Power calculation was not provided. Correction for type I error was not discussed.
De Sá et al. (25)	Belo Horizonte, Brazil Mixed	TNF- α -308 G>A *and IL-1 β , IL-6, IL-10, CD14	45 SDA (cases) 53 AIPL (controls)	Age, sex	PCR-RFLP	Tested	No significant difference was observed for TNF- α -308 G>A between groups (p>0.05).	Significant statistical differences were not observed for any polymorphism (p>0.05). The multivariate analysis demonstrated an association for IL6.	Power calculation was not provided. Correction for type I error was not discussed.

Abbreviations: ASAP = Acute Suppurative Apical Periodontitis; CNAP = Chronic Nonsuppurative Apical Periodontitis; SDA = symptomatic dental abscesses; AIPL = asymptomatic inflammatory periapical lesions; PL= periapical lesions; PCR-RFLP = Polymerase Chain Reaction- restriction fragment length polymorphisms method; SNP = Single Nucleotide Polymorphisms. *These SNPs were not considered in the present study.



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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: Prisma 2009 Flow Diagram. (From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org).

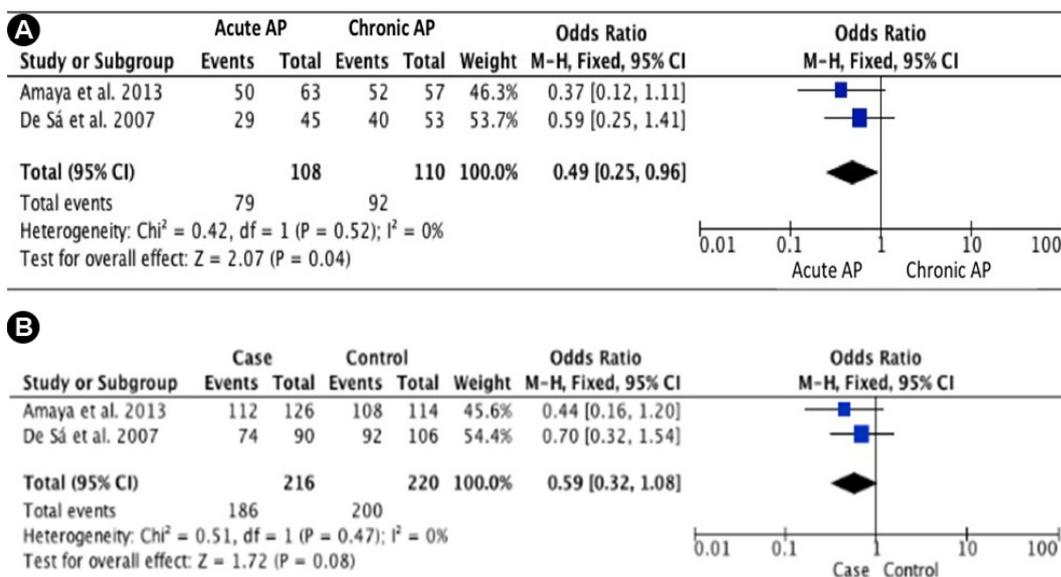


Figure 2. Odds ratios and forest plots. A. Genotype distribution; B. Allele distribution.

Discussion

Several studies have focused on the identification of SNPs with the capacity to affect the host response through a compromised immunity. It is already known that the production of cytokine and cell receptors can vary among individuals and this variance can be explained partially by genetic polymorphisms, like the TNF- α -308 G>A (9,27,28). Mei et al. (6) reported that TNF- α genes are highly expressed in developing periapical lesions in rats, which supports the hypothesis that this cytokine can be involved in AP. Our study aimed to verify if there is an association between TNF- α -308 G>A polymorphism with AP phenotype in humans.

De Sá et al. (25) did not find statistical association between AP and the studied polymorphism in TNF- α . However, the authors reported an inverse correlation between TNF- α SNP and acute AP in cases where the GG genotype (low rate of TNF- α transcription) was predominant. At the same time, it was observed that the AA genotype (high rate of transcription) was associated with chronic AP. This inverse correlation led the authors to speculate that the genetic variant (allele A) could express a protector phenotype against acute AP and suggested that, although it was not relevant to symptomatic AP, it could play an important role in chronic AP. They still hypothesized that it could be in linkage disequilibrium with some genes involved in the immunomodulatory mechanisms. We think that besides the hypothesis of linkage disequilibrium, there is the possibility of a sampling artifact due to the small size or population stratification that occurs when cases and controls differ in ethnic background and disease risk, since De Sá et al. (25) did not establish ethnicity because of the hazards of judging Brazilians by color, race, and geographical origin.

Amaya et al. (26) did not find statistical association between AP and the studied polymorphism in TNF- α . However, they evaluated the association by combining polymorphisms: IL1 β +3954 C, IL12 β +1188 A, TNF- α -308 G>A and IL-8/CXCL8 -251 A. They hypothesized that alleles could act together as a protective factor in the development of acute AP, but not of chronic AP. As limitations of the study, the small sample size and differences in allele frequency amongst the studied populations could explain some failures to find association with individual alleles.

Both selected studies presented similar methodologies, reporting the same description for the acute phenotype (case group) and chronic phenotype (control group) despite different nomenclatures for the pathologies, which is understandable due to a great variety of classifications for AP with different terminologies in the literature (29). Hence, it was possible to develop a meta-analysis, but some limitations need to be taken into consideration. Small sample

size, diversity in ethnicity, possibility of misclassification of cases and controls, and failing the correct statistics criteria, as seen in the quality assessment, lead us to interpret the results with restraint. The effects of these limitations are unknown and could have resulted in some false results. Studies of genetic association with apical periodontitis are just beginning to become popular and the development of acceptable specific criteria for the determination of the validity of these reports involving AP and SNPs would be very welcome in order to actually identify genetic markers that could direct the clinical treatment of patients at higher risk of the disease. Furthermore, the replication of these studies should be incentivized.

Although the studies were not able to report an association between the genetic polymorphism in TNF- α and AP, our meta-analysis clearly suggested that the TNF- α -308 G>A polymorphism is involved in the difference between acute and chronic AP. Meta-analysis is a useful statistical tool to pool data from individual studies, increasing the statistical power and precision of effect estimates. Although the number of minimum studies to perform a meta-analysis is largely discussed in the literature, the authors agree with Valentine et al. (30) and believe that two articles are sufficient, because all other synthesis techniques are less transparent and/or less likely to be valid. The meta-analysis performed for the genotype distribution demonstrated a statistical significance in which the GG genotype was more common in chronic AP and AA plus AG is more common in acute AP.

The changes caused by SNPs in the gene expression or in its product can lead to individuals with a certain genotype having a higher susceptibility to a particular disease with a greater degree of severity (31). The AA genotype in the TNF- α -308 G>A polymorphism has been significantly associated with increased production of TNF- α and, in some cases, with increased morbidity and mortality in sepsis, malaria, chronic obstructive pulmonary disease, leishmaniasis, systemic lupus erythematosus, autoimmune type 1 hepatitis, and other diseases mediated by the immune system (32). This allele also seems to be involved in the development of inflammatory and degenerative diseases, like rheumatoid arthritis (33), systemic lupus erythematosus (34), and rheumatic fever (35).

Although our study supports the hypothesis that this genetic polymorphism is involved in AP phenotype, only a borderline association was found for genotype evaluation and could represent a false-positive. Further studies should be conducted to confirm or refuse our borderline association and to evaluate the underlying mechanisms of the identified association.

The meta-analysis demonstrated that the genotype distribution was different among AP phenotypes; however,

there was no statistical difference for allele distribution among the groups.

Resumo

Atualmente as investigações têm focado na identificação de Polimorfismos de Núcleo Único (SNP) envolvidos na resposta do hospedeiro e sua capacidade de gerar uma deficiência de imunidade. O objetivo deste estudo foi realizar uma revisão sistemática (RS) e uma meta-análise para avaliar a associação entre o polimorfismo do gene TNF- α (-308 G> A) e os fenótipos de periodontite apical (PA). Esta RS foi registrada na base de dados PROSPERO, CRD42016035688, e foi conduzida seguindo o método PRISMA. Foi realizada uma ampla pesquisa de estudos. Foram utilizadas as seguintes bases de dados: PubMed, Scopus, Web of Science e BVS (Medline, SciELO, Ibecs e Lilacs). Foram utilizados os seguintes descritores (MeSH) "Periapical Periodontitis," "Periapical Abscess," "Polymorphism, Genetic," and "Polymorphism, Single Nucleotide". Sinônimos, termos relacionados e termos livres foram incluídos. Foram selecionadas investigações clínicas de indivíduos com diferentes fenótipos de PA em dentes permanentes. Após a aplicação dos critérios de elegibilidade, os estudos selecionados foram classificados através da avaliação da qualidade metodológica. Foi utilizado um modelo de efeito fixo para a metanálise. A pesquisa inicial identificou 71 referências. Após a exclusão de resumos duplicados, 33 foram selecionados. Destes, dois eram elegíveis para a avaliação da qualidade e foram classificados como sendo de evidência moderada. Os estudos incluídos não demonstraram associação entre PA e o TNF- α -308 G>A. No entanto, a metanálise demonstrou associação entre a distribuição do genótipo e os fenótipos da PA (OR = 0,49, intervalo de confiança=0,25, 0,96; p=0,04). O papel do TNF- α -308 G>A em fenótipos da PA é discutível. São necessários mais estudos para confirmar e compreender os mecanismos subjacentes à associação identificada.

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