Gene Variants in *TNF-α* and *HLA* in Phenotypes of Chronic and Aggressive Periodontitis: A Systematic Review *

Variantes génicas en *TNF-α* y *HLA* en fenotipos de periodontitis crónica y agresiva: una revisión sistemática

Variantes genéticas em *TNF-α* e *HLA* em fenótipos de periodontite crônica e agressiva: uma revisão sistemática

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DOI : https://doi.org/10.11144/Javeriana.uo44.gvth
Submission Date: 30 August 2024
Acceptance Date: 20 May 2025
Publication Date: 24 November 2025

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ABSTRACT

Background: Periodontitis is an infectious disease that affects the supporting tissues of the tooth. It is usually chronic and can have an aggressive course. *TNF-α* is a cytokine associated with disease progression. Its gene is located near the *HLA* genes on chromosome 6. Some haplotype variants may be associated with susceptibility. **Purpose**: To present a systematic analysis of the literature on variants in the *HLA* and *TNF-α* genes associated with chronic and aggressive periodontitis phenotypes (the most frequently reported in the literature), and their possible linkage disequilibrium. **Methods**: A search for articles was conducted in databases. Inclusion and exclusion criteria were applied, and the risk of bias was assessed. The independent variable was the genetic variant reported in each publication. The dependent variable was periodontal health status. To explore linkage disequilibrium, multiple associations between variants were reviewed. **Results**: Thirty-eight case-control studies were included. In chronic and aggressive periodontitis, *TNF-α* variants associated with increased susceptibility were reported. *HLA* class I and II genotypes and haplotypes were also described with higher frequency in the evaluated groups. **Conclusions**: No reports of haplotype association between *TNF-α* and *HLA* polymorphisms were identified. However, SNVs at positions -308, -1031, -863, and -857 of *TNF-α* have been associated with periodontal disease and increased aggressiveness. In *HLA* class I and II, the findings remain heterogeneous, and consistently associated variants have not been defined.
Keywords: dentistry; disease susceptibility; genetic polymorphism; haplotype; human leukocyte antigen; periodontitis; tumor necrosis factor alpha

RESUMEN

Antecedentes: La periodontitis es una enfermedad infecciosa que compromete los tejidos de soporte del diente. Suele ser crónica y puede tener un curso agresivo. El *TNF-α* es una citocina relacionada con la progresión de la enfermedad. Su gen se

ubica cerca de los genes *HLA* en el cromosoma 6. Algunas variantes en haplotipo podrían asociarse con susceptibilidad. **Objetivo:** Presentar un análisis sistemático de la literatura sobre variantes en los genes *HLA* y *TNF-α* asociadas con fenotipos de periodontitis crónica y agresiva (los más reportados en la literatura), y su posible desequilibrio de ligamiento. **Métodos:** Se realizó una búsqueda de artículos en bases de datos. Se aplicaron criterios de inclusión y exclusión y se evaluó el riesgo de sesgo. La variable independiente fue la variante genética reportada en cada publicación. La variable dependiente fue el estado de salud periodontal. Para explorar el desequilibrio de ligamiento se revisaron asociaciones múltiples entre variantes. **Resultados:** Se incluyeron 38 estudios de casos y controles. En periodontitis crónica y agresiva se reportaron variantes de *TNF-α* relacionadas con mayor susceptibilidad. También se describieron genotipos y haplotipos de *HLA* clase I y II con mayor frecuencia en los grupos evaluados. **Conclusiones:** No se identificaron reportes de asociación en haplotipo entre polimorfismos de *TNF-α* y *HLA*. Sin embargo, los SNV en las posiciones -308, -1031, -863 y -857 de *TNF-α* se han asociado con enfermedad periodontal y con mayor agresividad. En *HLA* clase I y II, los hallazgos siguen siendo heterogéneos y no se han definido variantes asociadas de forma consistente.
Palabras clave: antígeno leucocitario humano; factor de necrosis tumoral alfa; haplotipo; odontología; periodontitis; polimorfismo genético; susceptibilidad a la enfermedad

RESUMO

Antecedentes: A periodontite é uma doença infecciosa que afeta os tecidos de suporte dos dentes. Geralmente é crônica e pode ter um curso agressivo. O *TNF-α* é uma citocina associada à progressão da doença. Seu gene está localizado próximo aos genes *HLA* no cromossomo 6. Algumas variantes de haplótipos podem estar associadas à suscetibilidade. **Objetivo**: Apresentar uma revisão sistemática da literatura sobre variantes nos genes *HLA* e *TNF-α* associadas aos fenótipos de periodontite crônica e agressiva (os mais frequentemente relatados na literatura) e seu potencial desequilíbrio de ligação. **Métodos**: Foi realizada uma busca de artigos em bases de dados. Critérios de inclusão e exclusão foram aplicados e o risco de viés foi avaliado. A variável independente foi a variante genética relatada em cada publicação. A variável dependente foi o estado de saúde periodontal. Múltiplas associações entre variantes foram revisadas para explorar o desequilíbrio de ligação. **Resultados**: Trinta e oito estudos de caso-controle foram incluídos. Em periodontite crônica e agressiva, foram relatadas variantes do *TNF-α* associadas ao aumento da suscetibilidade. Os genótipos e haplótipos de *HLA* de classe I e II também foram descritos como mais frequentes nos grupos avaliados. **Conclusões**: Não foram identificados relatos de associação de haplótipos entre *TNF-α* e polimorfismos de *HLA*. No entanto, variantes de nucleotídeo único (SNVs) nas posições -308, -1031, -863 e -857 do *TNF-α* foram associadas à doença periodontal e ao aumento da agressividade. Para *HLA* de classe I e II, os achados permanecem heterogêneos e nenhuma variante consistentemente associada foi identificada.
Palavras-chave: antígeno leucocitário humano; fator de necrose tumoral alfa; haplótipo; odontologia; periodontite; polimorfismo genético; suscetibilidade a doenças

INTRODUCTION

Periodontitis is a chronic infectious disease that affects the tooth-supporting tissues. It is characterized by inflammation and progressive destruction of these tissues (1). More than 40 types of gingival diseases have been described whether associated with dental plaque or not, as well as destructive periodontal diseases. These include stage III and IV periodontitis, previously referred to before 2017 as chronic and aggressive periodontitis. This document will maintain that terminology because most of the cited publications use the previous denominations (2). The diagnosis of these forms of periodontitis is established in patients with probing depths ≥ 5 mm and gingival inflammation. The distinction between them is based on specific clinical features, including age of onset, rate of progression, patterns of tissue destruction, and the relationship between the amount of bacterial plaque and calculus (3). Periodontal disease pathogenesis is complex and multifactorial. It involves genetic factors, pathogenic bacterial agents, and the host immunoinflammatory response, as well as environmental risk factors such as smoking, poorly controlled diabetes, and vitamin D deficiency (4).

Periodontitis develops when dental plaque, composed of bacterial components such as lipopolysaccharides (LPS), peptidoglycans, lipoteichoic acids, proteases, and toxins (5), accumulates at the gingival margin (6). This accumulation activates the host immune response and leads to the release of inflammatory mediators such as prostaglandin E2 (PGE2), various interleukins (i.e., IL-1β, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17, IL-23, and IL-22), tumor necrosis factor α (*TNF-α*), and proteolytic

enzymes. Among these enzymes, matrix metalloproteinases (MMPs) are particularly prominent (5).

In its initial phase (gingivitis), a marked inflammatory infiltrate is observed in the connective tissue, characterized by an abundance of polymorphonuclear cells (PMNs) and macrophages (7). Through a cascade of events, mast cells are activated and release vasoactive amines and additional *TNF-α*. This increases vascular permeability and the expression of adhesion molecules. Simultaneously, PMNs release lysosomal enzymes that degrade gingival tissue and destroy approximately 60% to 70% of the collagen at the lesion site. However, at this stage the alveolar bone remains intact, which allows tissue repair and remodeling without irreversible damage (5).

However, in individuals with genetic predisposition or exposure to environmental factors such as smoking or stress, inflammation may persist chronically. This promotes the interaction between antigen-presenting cells and naïve T lymphocytes and induces their differentiation into effector subsets, including T helper Th1, Th2, Th9, and Th17 cells, follicular helper T cells (Tfh), and regulatory T cells (Treg) (7).

Th1 cells are characterized by secreting cytokines such as interferon gamma (IFN-γ), IL-2, and *TNF-α*, which promote cell-mediated immune responses. In contrast, Th2 cells are associated with humoral immunity and mainly produce IL-4, IL-5, IL-6, IL-10, and IL-13 and, in some contexts, TGF-β. Th17 cells, in turn, play a key role in inflammation and release IL-17, IL-22, IL-6, and *TNF-α*. This stimulates the synthesis of pro-inflammatory mediators such as PGE2, IL-1β, and *TNF-α*. These mediators then induce bone resorption through osteoclast activation, a process extensively studied in inflammatory diseases (5). Studies such as that by Moutsopoulos *et al*. have shown that Th17-derived IL-17 amplifies this osteoclastic effect by stimulating expression of receptor activator of nuclear factor κB ligand (RANKL), a critical regulator of osteoclast differentiation and activity (8). Finally, Treg cells differentiate in TGF-β–rich microenvironments and exert immunosuppressive functions by secreting IL-10 and TGF-β, thereby modulating exaggerated immune responses (5).

TNF-α plays a critical role in the pathogenesis of periodontitis. It induces apoptosis in gingival fibroblasts and epithelial cells in a manner dependent on concentration and microenvironment. It also inhibits extracellular matrix synthesis in fibroblasts, which compromises the integrity of the oral epithelial barrier and facilitates disease onset. In addition, *TNF-α* promotes bone resorption by stimulating RANKL expression in epithelial and gingival cells, T lymphocytes, and osteoblasts. It activates osteoclast differentiation and function (9).

On the other hand, the gene encoding *TNF-α* in humans is located on the short arm of chromosome 6 (6p21), within the major histocompatibility complex (MHC). This complex is divided into three classes: *HLA* class I (*HLA*-A, *HLA*-B, *HLA*-C genes), *HLA* class II (*HLA*-DP, *HLA*-DQ, *HLA*-DR genes), and *HLA* class III, where the *TNF-α* gene is located. The class III region is flanked by the *HLA* class I and II gene clusters, separated by an approximate distance of 2,000 kilobases (kb). This proximity favors inheritance of these genes as a block within a haplotype. This phenomenon is known as linkage disequilibrium and hinders their independent segregation during meiosis (10). Studies such as that by Kumar *et al*. have linked this disequilibrium to genetically based inflammatory diseases (11). In patients from northern India with type 1 diabetes, they found that single-nucleotide variants (SNVs) at positions -308 G/A and -238 G/A in the non-translated 5'UTR region of the *TNF-α* gene are inherited together with specific *HLA*-A-B-DR-DQ haplotypes, suggesting genetic co-selection. These findings support the hypothesis that the interaction between MHC genetic variants and *TNF-α* dysregulation may contribute to multifactorial diseases with an inflammatory component, such as periodontitis. In this context, overproduction of this cytokine exacerbates tissue and bone destruction (5).

Stage IV periodontitis is characterized by marked genetic susceptibility, particularly associated with variants in genes involved in the immune response. Pioneering studies in the early 2000s identified polymorphisms in the IL-1, IL-10, and FcgR genes as potential risk factors for periodontitis development (1). More recently, patients with this condition have been reported to show a positive association with certain *HLA-A* system alleles, including specific haplotypes. Conversely, an inverse correlation with *HLA-A2* and *HLA-B5* has been described, suggesting a modulatory role of the major histocompatibility

complex in pathogenesis (12).

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Given the genomic proximity between the *TNF-α* locus and the *HLA* region, analyzing genetic variants in both loci could reveal new susceptibility mechanisms for periodontitis phenotypes type III and IV. In addition, investigating linkage disequilibrium between *TNF-α* and *HLA* would help determine whether their joint inheritance contributes to disease predisposition or progression.

In this context, this systematic review aimed to synthesize the available scientific evidence on genetic variants in the *HLA and TNF-α* systems associated with type III and IV periodontitis, as well as on the potential interaction and linkage disequilibrium between these loci. The ultimate goal is to update the theoretical framework on the genetic determinants of these clinical entities and to provide perspectives for future diagnostic strategies and personalized management.

MATERIALS AND METHODS

Study Search and Selection Strategy

A systematic search was conducted in PubMed, Wiley Online Library, and Web of Science (1993-2023) using MeSH terms combined with Boolean operators (AND/OR). Human studies and original articles were prioritized. The selection of a 30-year interval was justified by the limited evidence available on *HLA/TNF-α* genetic variants and periodontitis. The methodology followed the PRISMA 2020 guidelines for systematic reviews (13).

Inclusion and Exclusion Criteria

Studies assessing periodontal disease according to the Armitage (1999) criteria, classified as chronic or aggressive, were included because this terminology was the most frequently used in the reviewed publications (14). Analyses of genetic variants in *HLA, TNF-α*, or the MHC region using validated genotyping methods, such as PCR, sequencing, or microarrays, were also included. Articles in languages other than English or Spanish were excluded, as were systematic reviews, meta-analyses, animal studies, case reports, or case series with fewer than 50 participants. Studies on apical periodontitis, peri-implantitis, or systemic comorbidities such as diabetes or HIV were also excluded.

Article Selection Process

Two independent reviewers conducted screening in three phases: 1) duplicate removal and title/abstract screening; 2) full-text assessment to verify methodological criteria, with discrepancies resolved by consensus or by a third reviewer; and 3) quality and risk-of-bias assessment. The Newcastle–Ottawa Scale, adapted for genetic studies, was applied across three domains: selection (representativeness of cases/controls and phenotype definition), comparability (adjustment for confounders such as age, smoking, and oral hygiene), and exposure (validity of the genotyping method and blinding during analysis).

Data Analysis and Synthesis in the Studies

The association between polymorphisms and periodontitis should have been assessed using odds ratios (OR) or relative risks (RR), with 95% confidence intervals. For dichotomous variables, such as the presence or absence of a variant and disease status, chi-square tests or Fisher's exact test should have been applied as appropriate; a p value < 0.05 set as the threshold for statistical significance; and OR/RR > 1 interpreted as a positive association (increased risk), whereas OR/RR < 1 was interpreted as a negative association (potential protective effect).

Findings were stratified by periodontal phenotype: Chronic periodontitis versus aggressive periodontitis, which is justified above based on the availability of studies. Regarding the genetic locus, data were stratified focusing on specific variants in *HLA* (classes I and II) and in *TNF-α*, including -308G/A and -238G/A. Findings were also stratified by linkage disequilibrium (LD), with emphasis on MHC haplotypes showing joint inheritance. Results were presented using comparative tables (Tables 1 and 2) and a narrative analysis. Where applicable, methodological heterogeneity was highlighted.

TABLE 1
Articles Excluded After Full Text Review

Title of article excluded	Reason for the exclusion
Searches for the genes associated with periodontitis with gene polymorphisms	Review, article in Mandarin
TNF-α gene promoter polymorphisms contribute to periodontitis susceptibility: evidence from 46 studies	Meta-analysis
Epithelial expression of *HLA* class II antigens and Fc gamma receptors in patients with adult periodontitis	The 1999 classification was not used
Heterogeneity of host immunological risk factors in patients with aggressive periodontitis	The 1999 classification was not used
Variations in inflammatory genes are associated with periodontitis	The overall assessment did not focus on polymorphisms of interest
Association between genetic risk score and periodontitis onset and progression: a pilot study	The overall assessment did not focus on polymorphisms of interest
Are there common human leucocyte antigen associations in juvenile idiopathic arthritis and periodontitis?	Relationship with systemic disease
Immunoregulatory gene polymorphisms in Japanese women with preterm births and periodontitis	Relationship with systemic disease
The -308 polymorphism in the promoter region of the tumor necrosis factor-alpha (TNF-alpha) gene and ex vivo lipopolysaccharide-induced TNF-alpha expression in patients with aggressive periodontitis and/or type 1 diabetes mellitus	Relationship with systemic disease (diabetes)
Gene polymorphisms in periodontitis and hypodontia: methodological basis of investigations	Relationship with systemic disease
The influence of interleukin gene polymorphism on expression of interleukin-1beta and tumor necrosis factor-alpha in periodontal tissue and gingival crevicular fluid	Only cytokine levels were evaluated
Clinical relevance of cytokines gene polymorphisms and protein levels in gingival cervical fluid from chronic periodontitis	Only cytokine levels were evaluated, not polymorphisms

patients	
Study on the correlation of cytokine gene polymorphism with chronic periodontitis	TNF or *HLA* I/II were not evaluated.
Association of LTA gene haploblock with periodontal disease in Italian adults	TNF or *HLA* I/II were not evaluated
Chronic periodontitis and immunity, towards the implementation of a personalized medicine: a translational research on gene single nucleotide polymorphisms (SNPs) linked to chronic oral dysbiosis in 96 Caucasian patients	Only IL-10 was evaluated
Polymorphisms of pro-inflammatory cytokine genes and the risk for acute suppurative or chronic nonsuppurative apical periodontitis in a Colombian population	Periapical periodontitis was evaluated
Tumor necrosis factor-alpha -308G/A single nucleotide polymorphism and red-complex periodontopathogens are independently associated with increased levels of tumor necrosis factor-alpha in diseased periodontal tissues	Microorganisms

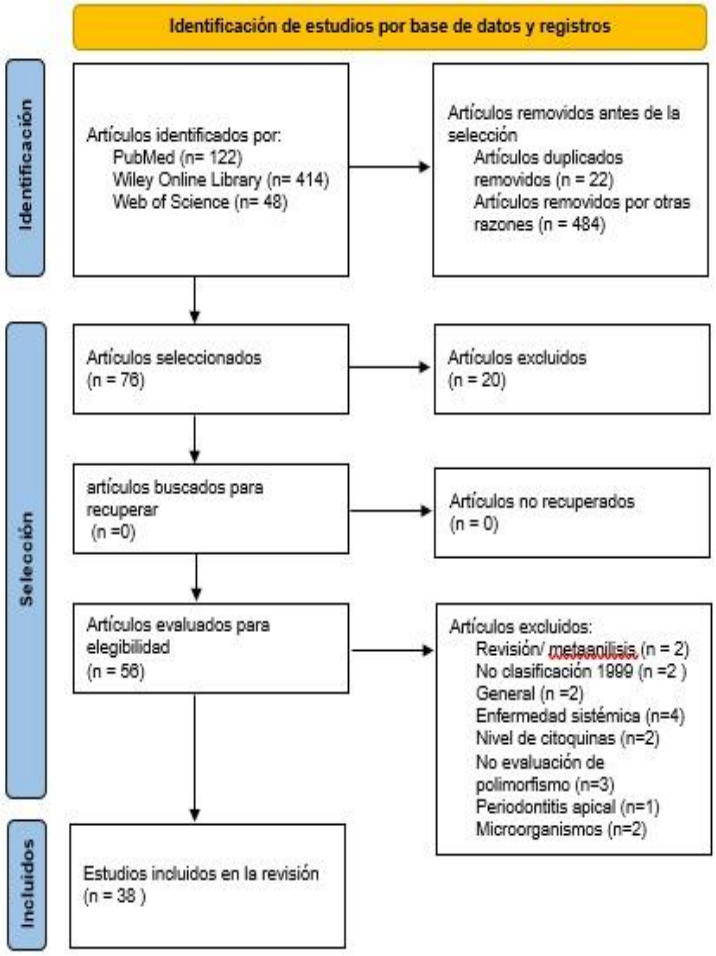


FIGURE 1
Flowchart of the selection of articles from the databases

TABLE 2
Articles where *TNF-α* polymorphisms were evaluated. CP: chronic periodontitis. AgP: aggressive periodontitis

Authors	Population	Study Type	Sample	Evaluated SNP(s)	Methodology	OR (95% CI)/ RR	Hardy-Weinberg Equilibrium	Conclusion
Brett, *et al.,* 2005 (15)	Caucasian	Case-control	51 AgP patients; 57 CP patients; 100 controls.	IL-1A: -889; IL-1B: -511 and +3953; IL-6: -174; IL10: -627 and -1082; Vitamin D receptor (VDR) Taq I gene; *TNF-α*: -308; TLR-4: -299 and -399.	10 ml of blood. Genotyping analysis: PCR-RFLP	Not reported for TNF	Not reported	There are shared and unique genetic associations in chronic and aggressive periodontitis.
Craandijk, *et al.,*2002 (16)	Dutch	Case-control	90 CP patients.	*TNF-α* -376, -308, -238 and +489	Venous blood. Genotyping by PCR.	Not reported	Criteria for Hardy-Weinberg equilibrium were met.	Genetic polymorphisms in the *TNF-α* gene at positions -376, -308, -238 and +489 could not be identified as susceptibility or severity factors in periodontitis, regardless of the patients' smoking status.
Darvishi, *et al*., 2016 (17)	Iranian	Case-control	54 controls; 31 AgP patients.	*TNF-α* -1031	DNA extraction from blood cells. Genotyping PCR-CTPP.	Not reported	Not reported	There was no significant association between *TNF-α* gene polymorphisms (promoter -1031 T/C) and the risk of generalized aggressive periodontitis disease.
Panova, *et al*., 2015 (18)	Bulgarian	Case-control	• 30 CP patients; • 10 controls.	*TNF-α* (G-308A), IL-6 (G-174C), IL-6 (G-597A) and LT-α (A+252G)	Total genomic DNA extracted from buccal epithelial cells; PCR.	Not reported	Not reported	Evaluation of IL-6 (G-597A), IL6 (G-174C) and *TNF-α* (G-308A) revealed the GG genotype was moderately associated with chronic periodontitis in Bulgarian individuals.
Galbraith, *et al.,* 1999 (19)	Caucasian	Case-control	20 patients with plaque-associated gingivitis without attachment loss; 20 patients with CP	IL-1β +3953 and *TNF-α* -308	Oral PMNs: mouthwash. PMNs: peripheral venous blood. Genotyping by PCR.	OR=10.20 (1.12, 90.9)	Not reported	The frequency of the *TNF-α* 308 allele 1 was significantly higher in patients with advanced disease compared to those with plaque-associated gingivitis.
Laine, *et al*., 2013 (20)	Caucasian	Case-control	155 controls, 230 CP patients.	• IL-1A -889; IL-1B -31 and +3954; IL-1RN +2018; IL-10 -1082 and -819; CD14 -260; LTA +252 and +368; TNF -308, -857 and -863.	Periodontal pocket samples processed for anaerobic culture within 6 h of sampling. SNP detection: PCR (TaqMan).	Not reported for SNP	11 SNPs were in Hardy-Weinberg equilibrium in the control group.	The simultaneous presence of *T. forsythia*, *P. gingivalis* and *A. actinomycetemcomitans*, and SNPs TNF -857 and IL-1A -889 as discriminators between periodontitis and periodontal health.

Babel, *et al*., 2006 (21)	Caucasian	Case-control	122 CP patients, 114 Controls.	IL-10: -1082; *TNF-α*: -308; TGF-β1: (codons 10 and 25); IL-6: -174; IFN-γ: +874	Epithelial oral cells by swab. PCR.	Not reported	Genotype distribution met Hardy-Weinberg criteria.	The single nucleotide polymorphisms IL-6 -174 and TGF-β1 (codon 25) are associated with susceptibility to chronic periodontitis in the studied population.
Folwaczny, *et al*., 2004 (22)	Caucasian	Case-control	81 CP patients; 80 controls.	*TNF-α*: -308 G/A	Peripheral venous blood samples. Genotyping of polymorphism by PCR.	Not reported	Not reported	The present study revealed no association between the *TNF-α* -308 gene polymorphism and periodontal disease.
Gurol, *et al.*, 2011 (23)	Turkish	Case-control	22 CP patients; 34 healthy controls.	IL-10 (-1082 A/G and -819 C/T); *TNF-α* (-308 A/G)	DNA isolation from oral swabs. DNA genotyping by amplification refractory mutation system (ARMS-PCR).	Not reported	Not reported	Found no significant association of IL-10 or *TNF-α* genes in susceptibility to the development of chronic periodontitis or implant failure.
Loo, *et al*., 2012 (24)	Chinese	Case-control	850 controls; 440 CP patients.	• IL-1α; IL-1β; IL-6; IFN-γ; IL-10; *TNF-α*; IL-4.	Peripheral blood; Genomic DNA extracted from blood samples following QIAamp DNA Blood Mini Kit protocols; PCR.	G/G OR = 3.716 (1.943 - 7.104)	Not reported	Patients with the G allele have twice the risk of contracting the disease. The risk of having moderate or severe chronic periodontitis is almost four times higher than for people with A/A and A/G genotypes.
Ianni, *et al*., 2013 (25)	Italian	Case-control	• 58 generalized CP patients; • 19 localized CP patients; 452 controls.	SNPs in the promoter regions of the VEGF (−2578 C/A), ACT (−51 G/T), HMG-CR (−911 C/A), and IL-6 (−174 G/C) genes. SNPs in IL-1β (−511 C/T), IL-10 (−1082 G/A), IFN-γ (+874 T/A), and *TNF-α* (−308 G/A).	Epithelial cell samples from the oral cavity via buccal swabs. SNP detection: PCR.	OR = 2.463 (1.094-5.548) "Triple SNP carriers": OR = 7.375 (3.973-13.68)	Not reported	*TNF-α*: the percentage of GG genotype at *TNF-α* -308 was higher in periodontitis patients; "triple SNP carriers" (concomitant presence of the *VEGF C* allele, the *IL-10 A* allele, and the *TNF-α GG* genotype) were more frequent in periodontitis patients.
Costa, *et al*. 2010 (26)	Brazilian	Case-control	17 moderate CP patients; 21 severe CP patients; 27 controls.	IL-6: -174 G/C; *TNF-α*: -308 G/A	Total DNA isolated from peripheral blood leukocytes. Genotype determination by PCR.	Not reported	Not reported	The *TNF-α* gene polymorphism may not be involved in the progression of chronic periodontitis in the elderly Brazilian female population.
Menezes & Colombo, 2008 (27)	Brazilian	Case-control	51 controls; 74 CP patients; 38 AgP patients.	*TNF-α* -308 (G/A)	Mouthwash samples. Genotyping by PCR.	CP OR=0.616 (0.34-1.11); AgP OR=0.596 (0.29-1.23)	Allele distribution was assumed to be in Hardy-Weinberg equilibrium.	The data suggest that the *TNF-α* -308 G/A polymorphism is not associated with periodontitis in this Brazilian population.

Jia & Wu. 2013 (28)	Chinese	Case-control	180 CP patients; 180 AgP patients; 180 controls.	*TNF-α* (1031T/C, 857C/T, 308G/A and 238G/A)	10 ml blood sample. PCR-RFLP. PCR products checked on a 1% agarose gel.	OR = 2.36, 95% CI = 1.03, 5.43	$\chi 2$ test was used to test deviation of genotype frequencies.	Our data demonstrated that the *TNF-α* 1031CC genotype was a risk factor for CP, and that the *TNF-α* 308AA genotype was a risk factor for AgP.
Lavu, *et al*., 2017 (29)	Indian	Case-control	40 controls; 41 CP patients.	IL1B: +3954C/T and IL1B -511G/A; *TNF-α* -1031T/C and *TNF-α* -863C/A.	Five microliters of gingival crevicular fluid, analysis performed using FCAP software. Genotyping: peripheral blood, TaqMan.	Not reported	Not reported	The results of this study revealed the presence of higher levels of IL-1β and *TNF-α* in subjects with periodontitis and genetic control of IL-1β levels in our Indian samples.
Lavu, *et al*., 2016 (30)	Indian	Case-control	176 controls; 177 CP patients.	FCGR2A (131 His/Arg); FCGR2B (232Ile/Thr); *TNF-α* -1031T/C and -863C/A.	Peripheral blood. Genotyping by PCR.	*TNF-α* -1031 OR=154.29 (0.219-108915.0); *TNF-α* -863 OR=0.372 (0.003-45.15)	*TNF-α* -1031 controls=0.328 CP=0.320; *TNF-α* -863 controls=<0.001 CP=0.011	The SNPs are not associated with susceptibility to chronic periodontitis in the selected South Indian cohort.
Soga, *et al*,. 2003 (31)	Japanese	Case-control	64 CP patients; 64 controls.	*TNF-α* 1031T/C, 863C/A, 857C/T, 308G/A, 238G/A; IL-1β 511T/C, 31C/T, +3953C/T	SNP detection: PCR-RFLP.	OR=2.52 (1.23–5.18)	Not reported	*TNF-α* 1031, 863 and 857 associated with severe adult periodontitis.
Yücel, *et al*., 2015 (32)	Turkish	Case-control	38 AgP patients, 29 CP patients, 26 controls.	*TNF-α* -308	Peripheral venous blood for DNA extraction, PCR-RFLP. Crevicular fluid samples for TNF measurement by ELISA.	Not reported	Genotypic frequencies were in agreement with Hardy-Weinberg equilibrium (P> 0.01 for all analyses).	Association between the frequency of the *TNF-α* (-308) allele 2 (nucleotide A) and aggressive periodontitis patients with clinical attachment level greater than 4 mm in the studied population.
Trevilatto , *et al*., 2002 (33)	Brazilian	Case-control	The 2-generation family consisted of 14 people: 8 women and 6 men.	IL-1α (-889), IL-1β (-511), IL-1β (+3953), *TNF-α* (-308) and IL-RN (intron 2) genes	Microbiological samples from subgingival plaque of affected sites. Paper points in periodontal pockets used subsequently for PCR analysis.	Not reported	Not reported	Current microbiological and genetic parameters were not relevant for predicting susceptibility to periodontitis in this family.
Ebadian, *et al*., 2013 (34)	Iranian	Case-control	58 AgP patients; 60 controls.	Interleukin-1 beta (IL-1β) +3954 C/T and tumor necrosis factor alpha (*TNF-α*) -308 G/A.	Blood samples, genotyped by PCR-RFLP.	Not reported	Allele and genotype frequencies were in Hardy-Weinberg equilibrium.	Role of *IL-1β* +3954 and *TNF-α* -308 polymorphisms, separately, as determinants of AgP risk in the Iranian population.

Shapira, *et al.,* 2001 (35)	Israeli	Case-control	A total of 64 individuals were typed in 11 nuclear families. 21 were parents, 43 their children over 11 years old	*TNF-α*: -308	Blood sample, genotyped by PCR.	Not reported	Not reported	The present results could not demonstrate any link between EOP and genetic polymorphism at position -308 of the *TNF-α* promoter region.
Endo, *et al*., 2001 (36)	Japanese	Case-control	46 AgP patients; 104 healthy patients.	*TNF-α* 5' UTR: -1031, -863 (C/A), -309 (G/A) and -238 (G/A)	Genomic DNA from peripheral blood. Genotyping by PCR-SSOP.	Not reported	$\chi 2$ test with 1 degree of freedom.	Genotypic and allelic frequencies at positions -1031C and -863A are increased in patients with aggressive periodontal disease compared to healthy patients; while the frequency at position -857T is decreased.
Barnea, *et al*., 2015 (37)	Romanian	Case-control	*TNF-α* polymorphism: 22 AgP, 10 controls; IL-1A polymorphism: 66 AgP, 31 controls.	C > T (-857) for the *TNF-α* gene; C >T (-889) for the IL1A gene.	Saliva samples. Genotype determination by RT-PCR.	Not reported	Not reported	The data suggest that *TNF-α* (-857) C/T and IL-1A (-889) C/T polymorphisms are not associated with susceptibility to AgP.
Schulz, *et al*., 2008 (38)	Caucasian	Case-control	54 CP patients; 69 AgP patients; 52 controls.	*TNF-α*: -308G-A and -238G-A	Microbial samples collected from the deepest pocket with a paper point. Venous blood, CTS-PCR-SSP.	OR 1.02 (1.02-1.03)	Genotype distributions of the polymorphisms were tested according to Hardy-Weinberg equilibrium.	Although *TNF-α* genetic background could be shown to be associated with subgingival colonization by P. intermedia, there is no evidence that it is an independent risk factor for periodontitis in multivariate models.
Sakellari, et *al*., 2006 (39)	Greek	Case-control	56 CP patients; 46 AgP patients; 90 controls.	IL1A +3954; IL1B +4845; TNFA -308; COL1A1 Sp1	Fingerstick blood via lancet puncture. Genotyping by PCR.	Not reported	$\chi 2$ test, df=1, p=>0.05	These polymorphisms cannot discriminate between periodontitis (chronic or aggressive) and non-periodontitis cases.
Ho, *et al*., 2015 (40)	Taiwanese	Case-control	90 AgP patients; 369 CP patients; 161 controls.	*TNF-α* -308 and LT-α +252	Genomic DNA extracted from peripheral blood leukocytes. Genotyping by PCR.	Not reported for TNF	p= 0.23	Suggests that LT-α +252 and *TNF-α* -308 genetic polymorphisms are not a risk factor for AgP or CP.
Moreira, *et al*., 2009 (41)	Brazilian	Case-control	55 AgP patients; 67 CP patients; 43 controls.	IL-10 (-1082) and *TNF-α* (-889)	Epithelial cells by oral swab. PCR-RFLP.	Not reported	Study groups tested for Hardy-Weinberg equilibrium by comparing expected with observed genotype frequencies	The investigated IL10 and *TNF-α* gene promoter polymorphisms are not associated with different clinical forms of periodontitis or with disease severity in the Brazilian population.

Kim, *et al*., 2020 (42)	Korean	Case-control	135 controls, 387 generalized CP patients and 26 AgP patients.	IL-1α +4845 G/T; IL-1β +3954 C/T; *TNF-α* −863 C/A.	Genomic DNA extracted from mouthwash samples. Polymorphism detection by PCR.	OR= 11.7 (1.72-154.5)	Evaluated by a chi-square test for each SNP between controls and cases separately.	Genetic variations of IL-1β +3954 and *TNF-α* -863 are associated with increased risk of periodontitis in Koreans.
Majumder, *et al*., 2018 (43)	Indian	Case-control	• 40 AgP patients; • 157 CP patients; • 200 controls.	Various *TNF-α*: -238G/A, -308 G/A, -857C/T, -863C/A and -1031 T/C.	Peripheral blood. Genotyping by PCR.	A/A OR = 3.06 (1.42–6.59) and G/A OR= 2.98 (1.896–4.696); T-1031C CP OR=2.81 (1.633–4.8); AgP OR=3.02 (1.391–6.57).	P>0.001, $\chi 2<10.83$	The findings suggest that the *TNF-α* gene (-308G/A) polymorphism is associated with chronic and aggressive periodontitis, while *TNF-α* gene -857C/T and -1031T/C are associated only with increased susceptibility to chronic periodontitis.
Fassmann, *et al*., 2003 (44)	Czech	Case-control	35 moderate CP patients; 97 severe CP patients; 114 controls.	*TNF-α* G-308A and LT-α A+252G	Genomic DNA isolated from peripheral blood leukocytes. Genotyped by PCR.	Not reported for TNF	Chi-square was used to test for deviation of genotype distribution from Hardy-Weinberg equilibrium.	Combined genotypes composed of *TNF-α* and LT-α gene polymorphisms may influence susceptibility to chronic periodontitis.
Donati, *et al*., 2005 (45)	Caucasian	Case-control	60 CP patients; 39 controls.	CD14: C-159T; IL-4RA: Q551R and V75I; *TNF-α*: -308.	Peripheral blood by venipuncture. Genotyped by restriction endonuclease mapping.	Not reported	All genetic markers were in Hardy-Weinberg equilibrium.	It is suggested that the CD14 -159 gene polymorphism is associated with chronic periodontitis in Caucasian subjects of Northern European origin.
Galbraith, 1998 (46)	Caucasian	Case-control	10 patients with early CP; 10 patients with moderate CP and 12 patients with advanced CP; 32 controls	*TNF-α* -308,*TNF-α* -238 and TNF-ß + 252	Mononuclear cells were separated from heparinized venous blood by density centrifugation. The genotypes of PCr restriction fragment length polymorphisms	Not reported	Not reported	Although the TNF gene type appears to be associated with genetic susceptibility to adult periodontitis, it may be a marker of susceptibility to severe disease.

RESULTS

Selection and Characteristics of Studies

The systematic review included 38 case-control studies, and the study selection summary is presented in Figure 1. The initial search across three databases identified 584 records, of which 22 duplicates were removed. After applying the predefined eligibility criteria, 484 articles were excluded, leaving 78 for preliminary assessment. Subsequently, 20 studies were excluded due to inadequate methodology. The remaining 58 underwent full-text assessment, and an additional 20 were excluded because of irrelevant content, as detailed in Table 1.

Thematic and Population Distribution

Of the 38 included articles, 31 analyzed *TNF-α*: 14 in chronic periodontitis, 10 in combined chronic/aggressive periodontitis, 6 in aggressive periodontitis, and 1 in gingivitis/chronic periodontitis. Also, 7 studies evaluated *HLA*: 1 in chronic periodontitis, 3 in combined chronic/aggressive periodontitis, and 3 in aggressive periodontitis. Details of these results are presented in Tables 2 and 3. The total sample comprised 7,247 patients, predominantly Caucasian (56.3%), followed by Asian (28.1%), Middle Eastern (12.5%), and Latin American populations (3.1%).

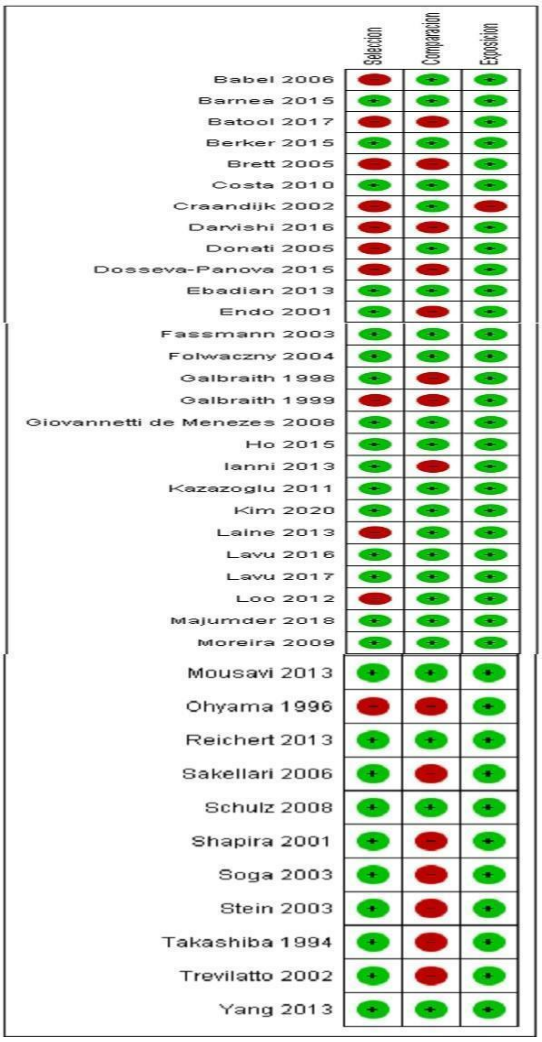
Bias Risk Assessment

The methodological quality and risk-of-bias assessment for the 38 articles is presented schematically in Figure 2. The domain with the highest risk of bias was comparability (74.5%), attributable to the lack of control for confounding factors in 68% of the studies. This was followed by the selection domain (63.2%), mainly due to failure to report: a) clinical history of controls (41%), and b) geographic recruitment criteria (34%). Seven articles (15-19,47,48) showed high risk in two categories simultaneously (18% of the total). Although all three assessed domains exceeded 50% relative risk of bias, the overall evidence was classified as moderately reliable because 82% of studies showed low risk in at least two key domains.

TABLE 3
Articles evaluating *HLA* (I and/or II) polymorphisms, chronic (CP), and aggressive periodontitis (AgP)

Author	Population	Study Type	Sample	Evaluated SNP(s)	Methodology	OR (95% CI) / RR	Hardy-Weinberg Equilibrium	Conclusion
Al-Ghurabi, *et al*., 2017 (47)	Iraqi	Case-control	40 CP patients; 40 controls.	*HLA*-DQB1	Blood sample; *HLA*-DQ genotyping performed by PCR-SSO.	*HLA*-DQB1*05:02 (OR= 4.11, 95% CI 1.04 - 16.30, p=0.04)	Not recorded	Correlation between the *HLA-DQB1* locus and the occurrence of periodontitis in Iraq, supporting *DQB1*05:02 as a predisposing allele for this disease.
Ohyama, *et al*. 1996 (48)	Japanese	Case-control	24 AgP patients; 47 controls.	*HLA* class II (DRB1, DQA1 and DQB1)	Genomic DNA isolated from peripheral mononuclear cells. Genotyping PCR-RFLP.	DRB1*1403 RR=3.53; DQA1*0101 RR=2.82	Not recorded	Could not detect a strong link between *HLA* class II alleles.
Stein, *et al*.,2003 (49)	Caucasian	Case-control	50 AgP patients; 102 CP patients; 102 controls.	*HLA*	Anticoagulated blood samples; separated from peripheral blood by density gradient centrifugation; typed by standard NIH microlymphocytotoxicity test; PCR-SSP.	*HLA*-A*68/69 (A28): Cw*07 RR:3.77, p=0.031; *HLA*-B*18 RR=15.11 p=0.034; *HLA*-Cw*08 RR=13.81, p=0.014	Not recorded	Susceptibility/resistance to both aggressive and chronic periodontitis may be influenced by particular combinations of *HLA* markers.
Reichert, *et al*. 2013 (50)	Caucasian	Case-control	• 85 AgP patients; • 71 CP patients; 88 controls.	*HLA*	Subgingival scraping for identification of periodontopathogens. Genomic DNA preparation from blood and *HLA* typing by PCR.	*HLA*-DQB1*0302 (OR = 0.428) and *HLA*-DRB1*04; DRB4*; DQB1*0302 (OR= 0.403, 95% CI 0.164-0.944)	Not recorded	Negative association for periodontal disease; decreased frequencies of *HLA*-A*02; B*57, *HLA*-DQB1*0302 and *HLA*-DRB1*04; DRB4*; DQB1*0302 were found. Also found negative association of *HLA*-DRB1*04, *HLA*-DQB1*0302 and *HLA*-DRB1*04; DRB4*; DQB1*0302 with subgingival colonization of *A. actinomycetemcomitans.*
Takashiba, *et al*., 1994 (51)	Japanese	Case-control	70 AgP patients; 26 controls.	*HLA* II	*HLA* serological typing was performed by complement-dependent microcytotoxicity method using the Terasaki DRw tray.	Not recorded	Not recorded	Intronic genetic variations may be useful as genetic markers for a subpopulation of early-onset periodontitis.

Jazi, *et al*., 2013 (52)	Iranian	Case-control	50 AgP patients; 130 controls.	*HLA* class II	Peripheral blood samples; *HLA* typing performed using PCR.	*HLA*-DRB1*13:01 and *HLA*-DQB1*06:03 (p=0.006; OR=0.20, 95% CI: 0.05–0.7); *HLA*-DRB1*04:01 / *HLA*-DQA1*03:01 / *HLA*-DQB1*03:02 (p=0.01, OR=2.56, 95% CI: 1.18–5.55); *HLA*-DRB1*16:01 / *HLA*-DQA1*01:03 / *HLA*-DQB1*05:01 (p=0.05, OR=5.38, 95% CI: 0.83–42.96)	Not recorded	DQ loci are associated with protection and susceptibility to aggressive periodontitis.



a)

b)

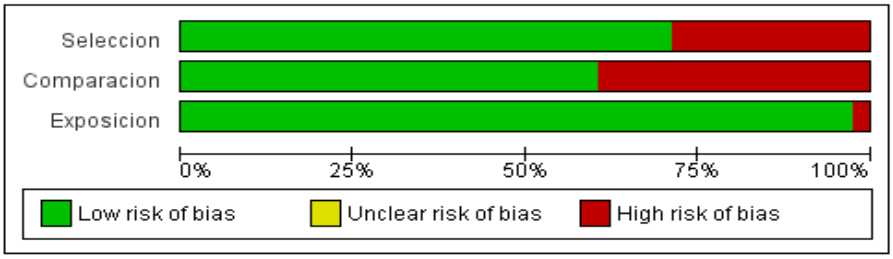


FIGURE 2

Bias risk analysis. a) Parameters evaluated: Selection, comparison, and exposure of each article individually. b) Overall bias results: green indicates low risk; yellow, unclear risk; and red, high risk

TNF-α Variants and Chronic Periodontitis

The relationship between SNVs in the *TNF-α* gene and chronic periodontitis has been extensively investigated. However, findings have been heterogeneous, reflecting the complex interplay among genetic, microbiological, and population factors.

Summary of Key Findings in Different Populations

Polymorphism -308 G/A (rs1800629)

Studies without significant association: in European populations (German and Swedish), studies with sample sizes ranging from 60 to 200 participants found no significant differences in the frequency of the -308 allele between periodontitis patients and controls (Babel, *et al.* (21) Donati, *et al*. (45) Folwaczny, *et al*. (22). In Brazil, investigations with small cohorts (n = 17–71) also found no association for this SNV, even after stratification by disease severity (26,27,33,41).

Association in specific contexts: a German study identified a higher frequency of the *G* allele in patients with advanced periodontitis compared with gingivitis (95% vs. 65%; p = 0.044) (19). In a Chinese population (440 cases vs. 850 controls), the *G* allele was associated with an approximately twofold increase in risk (57% vs. 34%; OR = 2.0), and the G/G genotype increased the risk of moderate/severe periodontitis fourfold (p < 0.001) (24). In Italians (77 cases vs. 452 controls), the G/G genotype was more frequent among patients (p = 0.025), particularly when combined with *VEGF* and *IL-10 SNVs* (p = 0.0001) (25).

-857 (rs1799724) Polymorphisms and Microbial Synergy

Laine's study highlighted that the combination of the *TNF-α* -857 SNV with the presence of *Tannerella forsythia* (*T. forsythia*), *Porphyromonas gingivalis* (*P. gingivalis*), and *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) could discriminate between periodontal health and disease (20).

-1031 (rs1799964) and -863 (rs1800630) Polymorphisms

In China, the -1031 C/C genotype was associated with an increased risk of periodontitis (p = 0.004) (28). In India, although *TNF-α* levels were higher in patients, no association was found between *TNF-α* expression and these *SNVs* (29,30,43). In a Japanese population, carriers of at least one variant allele (-1031C, -863A, -857T) showed greater susceptibility to severe periodontitis (p = 0.012) (31,36).

TNF-α Variants and Aggressive Periodontitis

Studies without significant association:

- In Turkey, a study including 38 patients with aggressive periodontitis, 29 with chronic periodontitis, and 26 controls found no significant differences across groups for the *G*-308 allele. However, the *A*-308 allele was more prevalent in aggressive periodontitis (26.3%), and a significant correlation was observed with clinical attachment loss (p = 0.04) (32).
- In Brazil, an analysis of a family carrying the *G*-308 allele described a specific clinical and microbiological profile. However, this finding was not associated with increased susceptibility to the disease (33).
- In Iran, a study conducted in the country's north, including 118 patients and 60 controls, found no association between the *IL-1β* +3954 and *TNF-α* -308 polymorphisms and periodontitis (34).
- In Israel, evaluation of the -308 G/A polymorphism in 64 individuals from 11 families found no association with aggressive periodontitis (35).

Findings with positive correlation:

- In China, in a study with 180 participants per group (aggressive periodontitis, chronic periodontitis, and controls), the -308 G/A polymorphism was associated with an increased risk of aggressive periodontitis ($p = 0.03$) (28).
- In Japan, a study including 46 patients and 104 controls found higher frequencies of the -1031C and -863A genotypes in patients, although these differences did not reach statistical significance. In contrast, the -857T variant showed a lower frequency (36).

Contradictory results depending on the population:

- In Romania, the -857 polymorphism was not associated with susceptibility in 67 Romanian patients (37). Similarly, in 31 Iranian patients, the -1031 (T/C) variant also showed no relationship with the disease (17).
- In South Korea, in a study including 387 patients with chronic periodontitis, 26 with aggressive periodontitis, and 135 controls, the *TNF-α* −863 C/A and A/A genotypes were associated with an increased risk of periodontitis compared with C/C ($p = 0.028$) after adjustment for confounding factors (42).

Consistencies in specific populations: studies in Caucasian (15,38), Greek (39), and Taiwanese populations (40) agreed on the absence of an association between the -308 polymorphism and disease. Similarly, in Brazil, the *TNF-α* -889 SNV showed no association with either chronic or aggressive periodontitis (41).

HLA Polymorphisms and their Association with Periodontal Disease

MHC Class I and Periodontal Disease

MHC class I genes include classical (*HLA-A*, *HLA-B*, and *HLA-C*) and non-classical (*HLA-E*, *HLA-F*, and *HLA-G*) loci. These glycoproteins are expressed on most nucleated cells and participate in presenting peptides derived from intracellular pathogens. After these proteins are degraded in the cytosol, peptide fragments bind to MHC-I molecules and are displayed on the cell surface. This enables cytotoxic T lymphocytes to recognize the MHC–peptide complex and destroy the infected cell (53).

In German populations, some studies identified a lower frequency of the *HLA-A02* and *HLA-A*03 alleles in patients with aggressive periodontitis ($p = 0.040$). In chronic periodontitis, a significant reduction in the heterozygous *HLA-A01*/*A*03 genotype was observed compared with controls ($p = 0.032$) (49). An analysis including 85 patients with aggressive periodontitis, 71 with chronic periodontitis, and 88 controls showed decreased frequencies of *HLA-A02* and *HLA-B*57. However, after adjustment for factors such as age, plaque index, and smoking, only *HLA-B*57* retained a non-significant trend ($p = 0.086$) (50).

MHC Class II and Periodontal Disease

MHC class II molecules (*HLA*-DR, *HLA*-DQ, and *HLA*-DP) are exclusively expressed on antigen-presenting cells, such as macrophages and dendritic cells. These cells capture extracellular pathogens, process their peptides within lysosomes, and present them via MHC-II to helper T lymphocytes. This

process activates immune responses, particularly humoral immunity (50).

In Japan, one study found no overall association between *HLA* class II polymorphisms and aggressive periodontitis. However, it identified an atypical site in *HLA*-DQB1 in 35% of patients (7/20) compared with 7.5% of controls (3/40) ($p = 0.002$), suggesting a potential susceptibility marker (51).

In Iran, a study including 50 patients with aggressive periodontitis and 130 controls identified positive associations with *HLA*-DRB104:01 ($p = 0.04$), *HLA*-DQA103:01 ($p = 0.01$), *HLA*-DQB103:02 ($p = 0.04$), and *HLA*-DQB103:05 ($p = 0.05$), and a protective association with *HLA*-DQB106:03 ($p = 0.006$). In the haplotype analysis, DRB104:01/DQA103:01/DQB103:02 was more frequent among patients ($p = 0.01$), as was DRB116:01/DQA101:03/DQB1*05:01 ($p = 0.05$) (52).

In a Caucasian population, aggressive periodontitis showed higher frequencies of homozygotes for *HLA*-DRB115, *HLA*-DRB551, and *HLA*-DQB106, with relative risks (RR) of 3.48, 3.49, and 2.65, respectively. Among heterozygotes, *HLA*-DQB106 and *HLA*-DQB10303 were notable ($p = 0.039$). In chronic periodontitis, a lower frequency of homozygotes for *HLA*-DRB1blank was reported (49). In addition, reduced frequencies of *HLA*-DQB10302 (OR = 0.428) and the *HLA*-DRB104:*HLA*-DRB4*:*HLA*-DQB1*0302 haplotype (OR = 0.403; 95% CI: 0.164–0.944) were reported in both forms of periodontitis. A negative association between these alleles and colonization by *A. actinomycetemcomitans* was also described ($p = 0.030$) (50).

In Iraq, the *HLA-DQB1*05:02* allele showed a significantly higher frequency in patients with chronic periodontitis ($n = 40$) compared with controls ($n = 40$) ($p = 0.04$). This finding supports its potential role as a susceptibility marker in this population (47).

Ligation Imbalance and its Relationship with Periodontal Disease

In India, a study including 40 patients with aggressive periodontitis, 157 with chronic periodontitis, and 200 controls identified significant associations between *TNF-α* gene polymorphisms and both forms of periodontitis. The A/A genotype of the -308G/A polymorphism was associated with chronic and aggressive periodontitis ($p = 0.002$). The G/A genotype at the same locus showed a stronger association with both disease forms ($p = 0.0001$). The T-1031C variant was exclusively associated with increased susceptibility to chronic periodontitis ($p < 0.0001$). In addition, linkage disequilibrium was observed between the G-238A and G-308A polymorphisms in patients with aggressive periodontitis, and between G-308A and T-1031C in patients with chronic periodontitis (43).

In Czechia, analysis of *TNF-α* and *LT-α* variants in 132 patients with chronic periodontitis and 114 controls showed that certain genotypic combinations increase disease risk under a Monte Carlo statistical model. Specifically, *TNF-α* G/A + *LT-α* 1/1 was associated with higher risk ($p = 0.0043$), as was *TNF-α* G/G + *LT-α* 1/1 ($p = 0.0043$). These findings suggest a synergistic effect between pro-inflammatory cytokine variants in the pathogenesis of chronic periodontitis (44).

HLA Haplotypes in Caucasian Population

In linkage disequilibrium–based studies, *HLA* haplotypes associated with susceptibility or protection in periodontal disease have been identified. In aggressive periodontitis, a higher frequency of the *HLA-A68/69* (A28):Cw07 (RR = 3.77; $p = 0.031$) and *HLA-B18* (RR = 15.11; $p = 0.034$) haplotypes was reported. In healthy controls, a significant reduction of the *HLA-B14/Cw*08* haplotype was observed (RR = 13.81; $p = 0.014$), suggesting a potential protective effect. In addition, linkage disequilibrium between polymorphisms in inflammatory genes, such as *TNF-α* and *LT-α*, and specific *HLA* haplotypes may play a relevant role in susceptibility to aggressive and chronic forms of periodontitis. These patterns vary across populations, highlighting the influence of genetic and ethnic diversity on disease predisposition (43).

DISCUSSION

Periodontal disease, with a multifactorial etiology, has a complex genetic component that interacts with microbial and environmental factors. This discussion integrates the available evidence on genetic polymorphisms, population heterogeneity, and immunoinflammatory mechanisms. It also highlights the main advances and limitations of current research.

Genetic Susceptibility and Disease Progression

The *G* allele of the *TNF-α -308* polymorphism appears to function as a marker of disease progression rather than disease onset, as it has been reported more frequently in advanced periodontitis than in gingivitis (19). This interpretation helps explain the inconsistency of studies seeking a direct causal relationship in chronic or aggressive forms (24,25) and suggests that susceptibility depends on interactions among multiple genetic variants (28,31,42). In addition to -308, other loci such as -1031, -889, -863, and +489 have been associated with chronic periodontitis in specific populations (24,28,38). However, ethnic heterogeneity modulates these findings. In Iran (16), Brazil (41), and Romania (37), these associations have not been replicated, highlighting the influence of environmental factors and ancestry.

A critical finding is the synergy between genetic variants and pathogenic microbiota. The coexistence of the *TNF-α* -857 SNV, the *IL-1* -889 SNV, and colonization by *T. forsythia*, *P. gingivalis*, and *A. actinomycetemcomitans* increases periodontitis risk (54). *P. gingivalis* (K1/K2 serotypes) induces a dysregulated pro-inflammatory response with overproduction of IL-1β, IL-6, and RANKL. This promotes bone resorption and may suppress bone formation (55-57). This mechanism reinforces that pathogenesis does not rely on a single factor, but on the convergence of genetic susceptibility, microbial dysbiosis, and an exacerbated immune response.

Ethnic Influence and Latin American Reality

In Asian populations, greater genetic homogeneity may facilitate the identification of more consistent associations, whereas in Latin America—where admixture results in high genetic diversity—findings tend to be discordant. In Colombia, the IV National Oral Health Study—ENSAB IV reported that 61.8% of the population has periodontitis, with moderate disease predominating (43.46%) (58). Despite this high prevalence, local studies have not confirmed an association between *TNF-α* -308 and the disease (59), although variants such as -1031 and -308 have been linked to Chagas cardiomyopathy (60). These findings underscore the need for studies that integrate population genetics, the microbiome, and socio-environmental factors to design more personalized preventive and management strategies.

Role of the *HLA* System: Antigen Presentation and Protection

Genes within the MHC (*HLA*) modulate the immune response to periodontal pathogens. In a German population, the *HLA-A02* and *HLA-B57* alleles have shown a potential protective effect, possibly due to less efficient antigen presentation to CD8+ T lymphocytes, which could dampen inflammatory pathways linked to osteoclast activation (49,50). For MHC class II, *HLA-DRB104* and *HLA-DQB10302* were negatively associated with colonization by *A. actinomycetemcomitans* (50), a key pathogen in aggressive periodontitis. In Colombia, the most frequent haplotypes (i.e., *A24-B35* and *B35-DRB104*) (61-63) partially overlap with alleles described as protective, suggesting that studying them could provide insight into local resistance mechanisms.

Gene-Microbiota Interaction: Epitope Affinity and Linkage Disequilibrium

HLA polymorphisms influence binding affinity to epitopes from periodontal pathogens. For example, *P. gingivalis* and *A. actinomycetemcomitans* carry antigens that may elicit exaggerated antibody responses in genetically susceptible hosts (64). In addition, linkage disequilibrium between *TNF-α* and *LT-α* (the *TNF-β* gene in MHC class III) suggests that interactions among inflammatory genes may amplify risk (44). This supports investigating complete haplotypes rather than isolated variants.

CONCLUSIONS

Periodontitis is a polygenic, multifactorial disorder in which the dynamic interplay among genetic variants—particularly in *TNF-α* (such as -308, -1031, -863, and -857) and *HLA* system genes—microbial dysbiosis (i.e., *P. gingivalis* and *A. actinomycetemcomitans*), and environmental factors such as oral hygiene habits and smoking determines both disease onset and progression. Although no single *HLA* class I or II polymorphism has shown a conclusive association with chronic or aggressive forms, a potential protective role has been reported for alleles such as *HLA-A02* and *HLA-B*57 in Caucasian populations, as well as a negative association of *HLA-DRB104* and *HLA-DQB1*0302 with colonization by pathogens linked to more aggressive disease patterns.

Linkage disequilibrium among inflammatory genes, such as *TNF-α* and *LT-α* in MHC class III, suggests that susceptibility may depend more on specific haplotypes than on isolated variants. For example, combinations such as *TNF-α G-238A/G-308A* in aggressive periodontitis and *TNF-α/LT-α* or *TNF-α G-308A/T-1031C* in chronic forms highlight the importance of studying synergistic gene–gene interactions. Nevertheless, a critical gap remains: the lack of studies assessing combined *TNF-α/HLA* haplotypes and their relationship to the disease.

Advancing toward personalized periodontal medicine requires overcoming current methodological limitations, such as the predominance of cross-sectional studies and heterogeneity in diagnostic criteria, through longitudinal approaches that capture disease progression, haplotype analyses in genetically diverse populations such as those in Latin America—where admixture may mask or modulate genetic associations—and multidisciplinary integration of genomic, microbiological, and clinical data to identify predictive biomarkers.

In summary, although current evidence reinforces the polygenic nature of periodontitis, the lack of consensus in findings—particularly regarding the *HLA* system—highlights the need for studies designed to elucidate not only individual variants but also gene networks and their interaction with the environment. Only then can preventive and therapeutic strategies be developed that are aligned with the ethnic and biological complexity of each population.

RECOMMENDATIONS

Most included studies were cross-sectional, primarily case-control designs, which limits assessment of disease progression. In addition, methodological heterogeneity—such as non-standardized criteria for selecting controls or lack of adjustment for smoking and diabetes—reduces comparability across studies. Therefore, future research should prioritize:

- Longitudinal designs to capture disease dynamics.
- Haplotype analysis in mixed-race populations, integrating genomic, microbiological, and clinical data.
- Functional studies that explore how gene variants affect immune pathways (e.g., RANK/RANKL) or microbial colonization.
- Studies of the same nature using the current classification of periodontal diseases.

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* Original research.

***How to cite this article*:** Romero-Fonseca AZ, Sir-Mendoza F, Rey-Buitrago M. Gene Variants in *TNF-α* and *HLA* in Phenotypes of Chronic and Aggressive Periodontitis: A Systematic Review. Univ Odontol. 2025; 44. https://doi.org/10.11144/Javeriana.uo44.gvth