

GENETICS OF PERIODONTAL DISEASES: MOLECULAR PATHWAYS OF INFLAMMATION, FROM SUSCEPTIBILITY GENES TO PRECISION PERIODONTOLOGY

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ABSTRACT

Periodontitis is one of the most prevalent chronic inflammatory diseases affecting humans, involving more than a billion people worldwide and remaining a leading cause of tooth loss. The disease is triggered by a dysbiotic subgingival biofilm. Yet decades of twin, family, and genome-wide studies show that the tempo and severity of tissue destruction depend substantially on the host's inherited and epigenetically modulated inflammatory response. This review synthesises current knowledge of the genetic architecture of periodontitis, moving from the classical candidate-gene era - anchored in interleukin-1 (IL-1) gene-cluster polymorphisms and the Kornman composite genotype - through genome-wide association studies implicating tissue-maintenance genes (SIGLEC5, PLG, ROBO2, ABCA1, PF4, CTSC), to monogenic and syndromic forms such as Papillon-Lefèvre syndrome, leukocyte adhesion deficiency type I, and Down syndrome. We further discuss host-microbiome genetic interactions, DNA methylation, non-coding RNA, and the dual role of bacterial CRISPR-Cas systems as virulence regulators and prospective therapeutics. We appraise the translational trajectory of this knowledge: the limited clinical utility of single-gene susceptibility testing, the promise and constraints of polygenic risk scores, host-modulation therapy, and the first successful gene-therapy trial for a monogenic periodontitis-associated immunodeficiency. A concluding discussion synthesises these findings into practical implications for clinicians and identifies priorities for future research. We argue that periodontal genetic susceptibility should be understood less as simple hyperinflammation and more as an impaired capacity of periodontal tissue to resolve inflammation and repair itself, a reframing with direct implications for precision periodontology.

KEYWORDS: periodontitis; genetic susceptibility; interleukin-1; genome-wide association study; epigenetics; host-modulation therapy

1. INTRODUCTION

Periodontitis is a chronic inflammatory disease of the tooth-supporting tissues that destroys the periodontal ligament and alveolar bone, and it remains the leading cause of tooth loss in adults worldwide [1]. Beyond its local consequences, periodontitis is bidirectionally linked to systemic conditions including type 2 diabetes, cardiovascular disease, and other inflammatory comorbidities, and it imposes a substantial economic burden on health systems [1,2,3]. Global Burden of Disease estimates place the number of prevalent cases of periodontal disease above one billion, with age-standardised incidence and prevalence rates that continue to rise, particularly in low- and middle-income settings [1].

For much of the twentieth century, periodontitis was framed almost exclusively as an infectious disease driven by specific bacteria, most notably *Porphyromonas gingivalis*. This view has been revised: *P. gingivalis* is now understood as a keystone pathogen that, even at low abundance, remodels a symbiotic subgingival community into a dysbiotic one by subverting complement and Toll-like receptor signalling [4,5]. The resulting polymicrobial synergy and dysbiosis model holds that periodontitis arises from a synergistic, dysbiotic microbial community acting on a susceptible host, rather than from any single organism acting alone [6].

The word “susceptible” is doing a great deal of work in that sentence, and it is the subject of this review. Patients with comparable oral hygiene and microbial challenge can present with markedly different rates of attachment and bone loss. Twin and family studies conducted since the 1990s attribute a substantial share of this variability to heritable factors, with heritability estimates for periodontal traits typically falling between 0.3 and 0.5 and rising further for early-onset, aggressive phenotypes [7,8]. Bacteria are necessary but not sufficient: it is the character of the host's immuno-inflammatory response – genetically and epigenetically encoded – that determines whether gingival inflammation remains reversible or progresses to irreversible tissue destruction.

This review synthesises the genetic determinants of the inflammatory response in periodontitis, from the single-gene candidate era to contemporary genome-wide and epigenomic approaches, and examines how far this

knowledge has travelled into clinical practice. We proceed from heritability evidence, through the paradigmatic IL-1 polymorphisms, to genome-wide discovery, monogenic syndromes, host-microbiome interactions, and epigenetic regulation, before addressing genetic testing and host-modulation therapy, and closing with a discussion of clinical and research implications.

2. Periodontitis as a Multifactorial Disease: Evidence for Genetic Predisposition

2.1 Twin and family studies

The classical approach to partitioning genetic from environmental contributions to a complex trait is the twin study, comparing concordance between monozygotic and dizygotic pairs. Early work, including the Minnesota Twin Periodontal Study, found familial aggregation of early-onset and prepubertal periodontitis consistent with a substantial genetic component, while adult chronic periodontitis showed a less clear-cut picture [7]. A subsequent twin study estimated that adult periodontitis heritability approaches 50%, essentially unaltered after adjusting for behavioural covariates including smoking, indicating a biological rather than purely behavioural basis [9]. A large population-based study of Swedish twins (more than 10,000 complete pairs) reinforced that genetic factors make a real contribution to periodontal disease and edentulism risk after adjusting for shared and non-shared environment [10]. The largest and most recent twin analysis to date, using Swedish national dental-register data on almost 12,000 twins, estimated heritability of continuous periodontal traits at 41.5–48.3%, with the highest estimates for tooth loss and pocket-depth progression [8].

A consistent theme is that genetic influence appears strongest in younger patients with rapidly progressing disease and weaker in older adults, among whom cumulative environmental exposure – smoking chief among them – increasingly dominates the phenotype, anticipating the gene-environment interaction discussed in Section 3.1.

2.2 From candidate genes to genome-wide discovery

Twin heritability establishes that genes matter without identifying which genes. The earliest molecular studies pursued a candidate-gene strategy, selecting genes with an a priori biological rationale and testing polymorphisms for association with disease in case-control cohorts. This strategy produced the field's most cited finding, the IL-1 composite genotype (Section 3.1), but also a long tail of underpowered, non-replicating associations typical of candidate-gene epidemiology.

The past decade has been defined by a shift toward hypothesis-free, genome-wide approaches – genome-wide association studies (GWAS) and quantitative trait locus mapping – interrogating hundreds of thousands to millions of variants without prior assumptions [11,12]. Large consortium efforts drawing on the UK Biobank, FinnGen, and GLIDE have confirmed elements of the earlier candidate-gene literature and substantially expanded the list of genome-wide significant loci, several pointing toward biology distinct from classical hyperinflammation (Section 4.1).

3. Classical Genetic Markers of Inflammation: The IL-1 Paradigm

3.1 The IL-1 gene cluster and the composite genotype

Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine in periodontal pathophysiology: it activates matrix metalloproteinases and drives RANKL-mediated osteoclastogenesis, the principal mechanism of alveolar bone resorption in periodontitis [13]. The genes encoding IL-1 α , IL-1 β , and the IL-1 receptor antagonist cluster on chromosome 2q13–q21, close enough that specific allelic combinations are commonly co-inherited. In 1997, Kornman and colleagues reported that a composite genotype – simultaneous carriage of allele 2 at both IL1A(–889) and IL1B(+3954) – was strongly associated with periodontitis severity in 99 non-smoking Caucasian adults [14]. The composite genotype was present in 78% of severe, 26% of moderate, and 16% of mild cases, an odds ratio of approximately 19 for severe versus mild disease (Figure 1) [14]. In a broader dental-practice population, IL-1 genotype-positive, non-smoking or lightly smoking patients carried a three- to five-fold increase in the odds of moderate-to-severe disease [15].

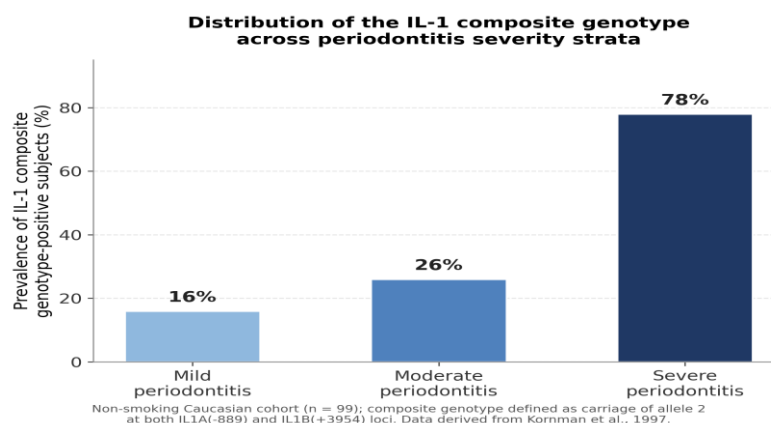


Figure 1. Prevalence of the IL-1 composite genotype (allele 2 at both IL1A(–889) and IL1B(+3954)) across periodontitis severity strata in a non-smoking Caucasian cohort. Data derived from Kornman et al., 1997 [14].

Crucially, the original association was demonstrated specifically in non-smokers; smokers were excluded because tobacco use dominated the phenotype [14]. Later studies made this gene-environment interaction explicit: among more than 1,000 individuals, IL-1 genotype had no discernible effect on risk among non-smokers, while genotype-positive smokers carried substantially higher risk than genotype-negative smokers, with a clear dose-dependent gradient by pack-years [16]. This interaction remains one of the more reproducible findings in periodontal genetics and illustrates that single-gene associations in complex disease are frequently conditional on an environmental co-factor.

Meta-analytic evidence for individual IL1A and IL1B polymorphisms, as opposed to the composite genotype, has been more equivocal: a meta-analysis restricted to adult white populations found only modest, inconsistent associations for IL1A(–889), IL1A(+4845), and IL1B(+3954) considered individually, underscoring that the specific combination – and its interaction with smoking – carries most of the original signal [17].

3.2 Beyond IL-1: TNF- α , IL-6, Fc γ receptors, and VDR

The candidate-gene era extended well beyond IL-1. A 2022 systematic review integrating meta-analyses across twelve cytokine genes and 147 pooled studies found that IL-1, IL-6, and IL-10 polymorphisms showed the most consistent associations with periodontitis risk, while tumour necrosis factor- α (TNF- α , rs1800629) showed smaller, ethnicity-dependent effects, more consistent in Asian than Caucasian cohorts [18]. A complementary review pooling more than 71,000 participants across a similar panel of cytokine and matrix metalloproteinase genes reached comparable conclusions [19]. For IL-6 specifically, the –174G/C promoter polymorphism (rs1800795) has been examined in more than 20 case-control studies and several meta-analyses with inconsistent, sometimes even protective, associations depending on population and periodontitis subtype [20], while functional work in gingival tissue has linked IL-6 receptor genotype directly to local IL-6 expression [21].

Fc γ receptor polymorphisms illustrate the same pattern of ethnicity-dependent heterogeneity: a meta-analysis of FCGR2A, FCGR3A, and FCGR3B variants found the FCGR3A V158 allele and FCGR2A RR/RH genotype associated with periodontitis specifically in Caucasian cohorts, while FCGR3B NA1/NA2 was more specifically linked to aggressive, early-onset disease [22], pointing toward antibody-dependent phagocytic clearance as a further axis of susceptibility. Matrix metalloproteinase gene polymorphisms, notably MMP-3(–1171 5A/6A), have shown similarly modest, population-specific associations in recent meta-analyses [23].

Vitamin D receptor (VDR) polymorphisms (BsmI, TaqI, ApaI, FokI) have been examined even more extensively, motivated by VDR's dual role in bone metabolism and immune regulation. The largest meta-analysis to date, pooling 38 case-control studies, found no overall association between the four polymorphisms and chronic periodontitis, with a significant BsmI signal confined to Caucasian subgroups [24]; a Chinese meta-analysis linked ApaI specifically to reduced risk in northern China [25]. More recent, smaller studies continue this inconsistent pattern, including a 2022 Indonesian study of TaqI [26] and a 2026 Iranian case-control study of all four polymorphisms [27], neither finding significant differences. Taken together, these literatures illustrate a recurring feature of periodontal candidate-gene genetics: effects are real but small, population-specific, and rarely replicate with the consistency required for clinical use (Section 5.1).

3.3 Monogenic and syndromic forms: lessons from extreme phenotypes

While common polymorphisms exert modest, population-level effects, a small number of monogenic and chromosomal disorders cause dramatic, early-onset periodontal destruction and serve as unusually informative natural experiments (Table 1). The 2018 classification of periodontal diseases, which introduced staging and grading for common periodontitis [28,29], explicitly recognises several of these conditions as periodontitis “as a manifestation of systemic disease” [30].

Papillon-Lefèvre syndrome (PLS) is an autosomal recessive disorder caused by loss-of-function mutations in cathepsin C (CTSC), a lysosomal protease expressed in neutrophils and epithelium [31]. CTSC activates neutrophil elastase and proteinase 3, the latter required to generate the antimicrobial peptide LL-37. In PLS, this cascade is broken: cathepsin C activity is essentially absent from neutrophils, and active LL-37 in gingival crevicular fluid and saliva is correspondingly depleted despite severe local inflammation [32,33]. The result is aggressive periodontitis affecting both dentitions from early childhood, frequently causing complete tooth loss before adulthood, alongside palmoplantar hyperkeratosis [32].

Leukocyte adhesion deficiency type I (LAD-I) results from biallelic loss-of-function mutations in ITGB2, encoding CD18, the subunit common to β 2-integrins [34,35]. Neutrophils lacking functional β 2-integrins cannot firmly adhere to inflamed endothelium and fail to extravasate into infected tissue – long assumed to reflect simple absence of neutrophil surveillance. This assumption has been revised: studies in patients and mouse models showed that failed extravasation paradoxically drives a compensatory, IL-17-dominated cytokine cascade that becomes the proximate driver of bone loss, reframing LAD-I periodontitis as a disease of excessive, misdirected inflammation rather than simple deficiency [36]. This has direct clinical significance: in 2025 a multinational phase 1–2 trial showed that lentiviral gene therapy restoring ITGB2 expression in autologous haematopoietic stem cells achieved transplant-free survival and sustained benefit in nine children with severe LAD-I over 24 months, a curative alternative to allogeneic transplantation [35,37].

Down syndrome (trisomy 21) is associated with markedly increased periodontitis prevalence and severity from a young age. A 2025 systematic review comparing inflammatory gene-expression profiles across PLS, LAD-I, and Down syndrome found that Down syndrome-associated periodontitis shows elevated IL-1 β , TNF- α , IL-4, IL-10,

and interferon- γ alongside dysregulated STAT1/STAT3/SOCS3 signalling, consistent with trisomy 21 as a state of chronic interferon-pathway activation arising from triplication of interferon-receptor genes on chromosome 21 [38,39]. Independent work has additionally reported attenuated STAT1 and IRF1 expression in the gingival tissue of Down syndrome patients with periodontitis, and reduced STAT1/STAT3 transcript levels have been reported in periodontitis more broadly, suggesting impaired STAT-mediated resolution of inflammation as a convergent mechanism across genetically distinct severe forms [40].

Table 1. Monogenic and syndromic forms of severe early-onset periodontitis.

Condition	Gene (inheritance)	Core mechanism	Inflammatory / immune signature	Ref.
Papillon–Lefèvre syndrome	CTSC (AR)	Loss of cathepsin C $\rightarrow$ failure to activate neutrophil elastase / proteinase 3 $\rightarrow$ deficient LL-37 generation	Depleted active LL-37 in GCF/saliva despite severe local inflammation	[31,32,33]
Leukocyte adhesion deficiency type I	ITGB2 (AR)	Absent β 2-integrins $\rightarrow$ failure of neutrophil firm adhesion and extravasation	Compensatory, IL-17–driven inflammatory bone loss	[34,35,36]
Down syndrome	Trisomy 21 (chromosomal)	Triplication of interferon-receptor genes $\rightarrow$ chronic interferon-pathway activation	Elevated IL-1 β , TNF- α , IL-4, IL-10, IFN- γ ; dysregulated STAT1/STAT3/SOCS3	[38,39,40]

Note: AR – autosomal recessive; GCF – gingival crevicular fluid.

These three conditions collectively make a point that recurs throughout this review: the common thread linking impaired antimicrobial-peptide processing in PLS, defective neutrophil extravasation with compensatory IL-17 overdrive in LAD-I, and interferon-pathway dysregulation in Down syndrome is not simply “too much inflammation” but a failure of the periodontal tissue’s inflammatory response to resolve appropriately and support repair.

4. New Horizons: GWAS, Host–Microbiome Interactions, and Epigenetics

4.1 Genome-wide association studies and tissue-maintenance genes

The past decade of GWAS has meaningfully broadened periodontitis genetic architecture beyond classical cytokine candidates. Early efforts, including a 2013 study of chronic periodontitis, achieved limited genome-wide significant discovery, reflecting modest effect sizes and phenotypic heterogeneity [41]. Statistical power has since improved through large biobank and consortium efforts. A 2017 GWAS and subsequent meta-analyses identified SIGLEC5 as genome-wide significant for both early-onset, severe periodontitis and more common, later-onset forms, replicated across populations and supported by expression quantitative trait locus data [42,43]. More recent large-scale efforts – the Finnish FinnGen national health-register cohort and a UK Biobank-based GWAS – continue to identify and refine risk loci, while consortia such as GLIDE2 harmonise periodontal phenotype definitions across cohorts to improve replicability [44,45,46,47].

A striking feature of the genes emerging from this hypothesis-free process – SIGLEC5, PLG, ROBO2, ABCA1, PF4, and CTSC among them – is that few are classical inflammatory cytokines; their annotated functions instead cluster around fibrinolysis, extracellular matrix remodelling, cell migration, hemostasis, and epithelial wound repair [11,42]. SIGLEC5, an inhibitory neutrophil receptor, appears at multiple independent risk loci across periodontitis subtypes, and functional work shows that risk variants in its intronic regulatory elements disrupt binding of the transcription factors ERG and MAFB [42]. PLG and CTSC mutations are also found in monogenic forms of early-onset periodontitis (Section 3.3), providing convergent evidence from both common- and rare-variant designs that these genes are functionally important [11].

This evidence supports reframing periodontal genetic susceptibility beyond the “hyperinflammatory host” model dominant in the 1990s and 2000s: a substantial share of the discovered risk architecture impairs the periodontium’s capacity to contain, resolve, and repair chronic microbial challenge – a tissue-maintenance model that sits alongside, rather than in place of, the classical cytokine-centred view (Figure 2) [11].

Table 2. Major genetic loci implicated in periodontitis susceptibility, identified through genome-wide and candidate-gene approaches.

Gene / locus	Chromosomal region & molecular function	Type of evidence	Ref.
IL1A / IL1B (composite genotype)	2q13–q21; IL-1 α / β production	Candidate gene; smoking-dependent effect	[14,16]

TNF- α (rs1800629, –308G/A)	6p21.33; pro-inflammatory cytokine	Candidate-gene meta-analyses; ethnicity-dependent	[19,18]
IL-6 (rs1800795, –174G/C)	7p21.3; pleiotropic cytokine, bone metabolism	Candidate-gene meta-analyses; inconsistent, some protective signals	[20,21]
FCGR2A / FCGR3A / FCGR3B	1q23.3; Fc γ receptors, antibody-mediated phagocytosis	Candidate-gene meta-analysis	[22]
VDR (BsmI/TaqI/ApaI/FokI)	12q13.11; vitamin D signalling, bone & immune regulation	Candidate-gene meta-analyses; inconsistent across ethnicities	[24,27,25]
SIGLEC5	19q13.41; inhibitory neutrophil receptor	GWAS; replicated across cohorts and subtypes	[42,43]
PLG	6q26; fibrinolysis, plasmin generation	GWAS + monogenic prepubertal periodontitis	[11]
ROBO2	3p12.3; epithelial cell migration, wound repair	GWAS + epigenome-wide association study	[11]
ABCA1 / PF4 / PPBP / CXCL5	9q31.1 / 4q13.3; lipid transport, platelet chemokines, hemostasis	GWAS	[11]
CTSC	11q14.1–q14.3; lysosomal cysteine protease	GWAS + monogenic (Papillon-Lefèvre syndrome)	[11,32,31]

Note: GWAS – genome-wide association study.



Figure 2. Conceptual multi-tier model of genetic contribution to periodontitis pathogenesis, integrating monogenic, oligogenic, common polygenic, and epigenetic layers of susceptibility acting on host immuno-inflammatory and tissue-repair pathways.

4.2 Host genetics and the subgingival microbiome

Genetic susceptibility does not act only downstream of microbial colonisation: a growing body of evidence indicates that host genotype also shapes which bacteria establish themselves subgingivally in the first place, a relationship sometimes termed “periodontal infectogenomics” [48]. Early GWAS work specifically targeted subgingival pathogen carriage, rather than clinical disease status, as a phenotype in its own right [49]. A systematic review update found accumulating, though still inconsistent, evidence that host genetic variants – including polymorphisms in IL-1, VDR, and pattern-recognition receptor genes – are associated with the presence and abundance of specific periodontal pathogens, while cautioning that most studies remain underpowered and rarely replicate [50]. A recent study in patients with metabolic syndrome illustrated this approach directly, linking specific single-nucleotide polymorphisms in RUNX2, CAMTA1, and VDR to measures of subgingival microbial diversity and to the relative abundance of individual species, including an association between a VDR variant and *Streptococcus mutans* and between RUNX2 and *P. gingivalis* [51]. These gene-microbiome interactions remain an early-stage but conceptually important extension of the architecture described in Section 4.1, since they suggest that some risk loci act not only on the host inflammatory response but also on the ecological composition of the biofilm that triggers it [48].

4.3 Epigenetic regulation: DNA methylation and non-coding RNA

Genetic sequence variation cannot alone account for the residual variability in periodontitis phenotype among individuals sharing the same GWAS-identified risk alleles, nor for the capacity of environmental exposures such as smoking to modulate risk independently of genotype. Epigenetic mechanisms – heritable, reversible modifications of gene expression that do not alter DNA sequence – offer a plausible bridge between genetic predisposition and environment.

DNA methylation has been the most extensively studied epigenetic mark. An epigenome-wide association study in a UK twin cohort identified differential methylation at specific loci relevant to periodontal traits: signals within or near VDR, IL6ST, TMCO6, IL1RN, CD44, IL1B, WHAMM, and CXCL1 were significant for both gingival bleeding and tooth mobility, and a distinct blood-based signal at cg21245277 (in ZNF804A) was independently associated with gingival bleeding [52]. Tissue-specific work on gingival and oral masticatory mucosa biopsies has further shown that periodontal inflammation and smoking each independently reshape the local methylation landscape. Because methylation changes are, in principle, reversible, several groups have proposed panels of periodontitis-associated methylation marks as diagnostic biomarkers, although the evidence base remains too heterogeneous in gene selection and study design to support clinical adoption at present.

Non-coding RNAs constitute a second, rapidly expanding regulatory layer. Individual microRNAs have shown promising diagnostic accuracy: salivary miR-155 and miR-146a classified periodontitis status with accuracies of 82.6% and 86.1% in non-diabetic and diabetic subgroups respectively [53], with comparable performance reported for miR-199a-3p in gingival crevicular fluid [54] and the miR-181 family across oral biofluids [55]. LncRNAs such as HOTTIP and MIAT regulate periodontal ligament fibroblast and osteogenic gene expression via competitive binding of specific miRNAs, forming competing endogenous RNA networks that connect this biology to the extracellular matrix remodelling pathways described in Section 4.1 [56,57]. As with methylation, the diagnostic promise of individual non-coding RNA biomarkers outpaces cross-cohort validation, and none has yet achieved the reproducibility needed for clinical use.

4.4 CRISPR-Cas: from bacterial virulence regulator to therapeutic tool

An unanticipated contribution to this molecular landscape comes not from the human genome but from the periodontal pathogens themselves. CRISPR-Cas systems – prokaryotic adaptive immune systems that cleave invading viral or plasmid DNA – occur in a substantial proportion of oral bacterial genomes, including numerous *P. gingivalis* strains, and serve functions well beyond antiviral defence: regulating biofilm formation, quorum sensing, gene transfer, nutrient acquisition, and virulence itself [58]. Deletion of the CRISPR-associated nuclease Cas3 in *P. gingivalis* measurably attenuates virulence in experimental models, and non-coding CRISPR spacer arrays lacking any identifiable viral target nonetheless regulate biofilm formation and the host macrophage transcriptional response, revealing a previously unrecognised, immunity-independent physiological role [59].

This dual identity – native regulator of bacterial pathogenicity and programmable nuclease system – has made CRISPR-Cas biology a focus of diagnostic and therapeutic development, distinct from its established role in human gene therapy for monogenic periodontitis-associated conditions (Section 5.3). Proposed applications include sequence-specific antimicrobials that selectively deplete keystone pathogens without the collateral damage of broad-spectrum antibiotics, and anti-CRISPR proteins to re-sensitise resistant strains [58,60]. At present this remains experimental and largely preclinical: engineered CRISPR antimicrobials have shown proof-of-concept efficacy in vitro, but no CRISPR-based periodontal therapeutic has advanced to clinical trial, and delivery and off-target challenges remain unresolved [58,60].

5. From Concept to Practice: Genetic Testing and Host-Modulation Therapy

5.1 Genetic susceptibility testing: promise and limitations

The IL-1 composite genotype finding was rapidly commercialised, giving rise to what remains, more than 25 years later, essentially the only genetic test marketed for periodontal risk assessment (the Periodontal Susceptibility Test and its successors) [14,61]. The premise: identify genotype-positive patients and direct more intensive preventive care toward them. A now-classic critical evaluation, still frequently cited two decades on,

found the relationship between IL-1 genotype and gingival crevicular fluid IL-1 β itself inconsistent across studies, and the test's ability to forecast individual bleeding, attachment loss, or tooth loss ambiguous [61]. Subsequent research has not strengthened this picture: a 2025 dental clinical policy review reached the same conclusion for both IL-1-based tests and newer competitors, finding neither useful for rationing or intensifying preventive care [62].

A comprehensive 2025 narrative review extended this appraisal across the wider candidate-gene literature, concluding that TNF- α (-308) genotyping alone likewise has limited standalone utility, even though the composite IL-1 genotype remains the most consistently replicated association, particularly in European-ancestry populations [63]. The same review is cautiously optimistic about polygenic risk scores aggregating hundreds of GWAS-identified variants and machine-learning models integrating genetic, microbial, and clinical data, while noting these remain investigational [63]. More than a quarter-century after the original finding, genetic risk in periodontitis is best understood as one element within a multifactorial risk assessment, not a standalone, actionable test result.

5.2 Host-modulation therapy: subantimicrobial-dose doxycycline and beyond

If genetic susceptibility operates chiefly by shaping the host's inflammatory and repair response, a logical corollary is to target that response directly – host-modulation therapy. The only agent with regulatory approval for this indication remains subantimicrobial-dose doxycycline (SDD, 20 mg twice daily), developed three decades ago [64]. At this dose, plasma concentrations stay below the antibacterial threshold, yet the drug retains capacity to inhibit matrix metalloproteinases (mainly MMP-8/-9) via cation chelation and suppression of oxidative pro-enzyme activation [64]. A systematic review and meta-analysis of its long-term efficacy found a real but modest additional benefit alongside scaling and root planing, cautioning that early trials carried meaningful risk of bias [65]; more recent, disease-specific trials have reinforced the mechanism, including a 2020 study showing that adjunctive SDD reduces gingival crevicular fluid MMP-9 and MMP-13 in diabetic patients with periodontitis [66]. A comprehensive 2020 update confirmed that, a decade on, SDD remains the only approved agent, while cataloguing investigational alternatives – chemically modified curcumins, resolvins and lipoxins, statins, and bisphosphonates – that still lack the trial evidence required for routine use [67,68]. Among these, specialised pro-resolving mediators such as resolvins and lipoxins are particularly actively investigated: rather than suppressing inflammatory signalling, they promote its active resolution, showing promise in preclinical models but still lacking the clinical trial evidence required for use [68].

5.3 Gene therapy for monogenic periodontitis: a paradigm shift

For the rare monogenic conditions in Section 3.3, the translational trajectory is qualitatively more encouraging. Because LAD-I periodontitis arises from a single, well-characterised gene defect affecting a self-renewing haematopoietic stem cell population, it is amenable to ex vivo lentiviral gene therapy in a way that polygenic susceptibility is not. The 2025 trial discussed above achieved allogeneic-transplant-free survival in all nine treated children at 24 months, together with restoration of neutrophil CD18 expression and markedly reduced infection-related hospitalisation – the clearest proof of concept to date that genetically informed precision medicine can be curative for a periodontitis-associated condition, even though its direct applicability remains confined to this narrow monogenic indication [37]. Whether analogous approaches – for instance, restoration of cathepsin C activity in Papillon-Lefèvre syndrome – will follow remains an open question, but the LAD-I trial establishes that the underlying strategy is feasible.

6. DISCUSSION

Read together, these findings support three conclusions. First, periodontal genetic susceptibility is not adequately captured by “hyperinflammation” alone: the genes implicated by genome-wide discovery (Section 4.1), the gene-microbiome interactions in Section 4.2, and the mechanisms uncovered in monogenic syndromes (Section 3.3) converge on a broader theme of impaired tissue maintenance, microbial ecology, and resolution of inflammation, alongside – not instead of – amplified cytokine signalling. Second, genetic and environmental risk are frequently inseparable rather than additive: the IL-1–smoking interaction (Section 3.1) shows a genotype can be functionally silent in one environmental context and strongly predictive in another, a pattern likely to generalise once adequately powered gene-environment studies are conducted. Third, clinical translation has proceeded unevenly: for common, polygenic periodontitis, decades of candidate-gene and genetic-testing research have yielded only modest, population-specific effects of limited individual value (Section 5.1); for rare monogenic disease, precise molecular diagnosis has already produced a curative gene therapy (Section 5.3).

These conclusions carry direct, if modest, implications for clinical practice today, consistent with contemporary guidance on periodontitis management [69]. Family and early-onset history remains the most accessible clinical proxy for genetic risk: a family history of severe, early periodontal destruction, especially combined with recurrent infections, delayed wound healing, or a known syndromic diagnosis, should prompt consideration of monogenic causes such as Papillon-Lefèvre syndrome or leukocyte adhesion deficiency, for which specific management and, increasingly, curative options exist. For the great majority of patients with common periodontitis, IL-1 or other single-gene genotyping should not be used as a standalone criterion for treatment intensity or maintenance frequency; smoking status, glycaemic control, and clinical and microbial findings, evaluated within current case-definition frameworks [70], remain the more actionable risk factors available at the chairside. Host-modulation

therapy, principally SDD, can reasonably be considered as an adjunct in patients with rapidly progressing or refractory disease, with the understanding that its benefit over mechanical therapy alone is real but modest. Several limitations of the current evidence base deserve emphasis. Much of the candidate-gene and even some GWAS literature remains underpowered relative to the small effect sizes typical of complex-disease genetics, and replication across ancestrally diverse populations is uneven, with European-ancestry cohorts still overrepresented. Diagnostic epigenetic and non-coding RNA biomarkers, while individually promising, have rarely been validated across independent cohorts using harmonised methodology. Finally, the field would benefit from closer integration between the host-genetic and microbial-ecology literatures discussed in Section 4.2, since genetic risk loci that shape biofilm composition, rather than only the inflammatory response to it, remain comparatively understudied.

Two concrete calls to action follow. Clinicians should resist treating a single-gene result as stand-alone justification for altering periodontal care; genetic information earns its place alongside smoking status, glycaemic control, and clinical and microbial assessment, and its main present value lies in flagging the rare monogenic and syndromic presentations described in Section 3.3. Researchers should prioritise adequately powered, prospective, ancestrally diverse cohorts that jointly capture genetic, epigenetic, and microbial data, since retrospective, single-layer designs have repeatedly produced associations that neither replicate nor translate; the FinnGen and UK Biobank efforts described in Section 4.1 offer a template worth extending to non-European populations and to gene-environment interaction analyses.

CONCLUSION

Three decades of research have transformed the genetics of periodontitis from a single candidate-gene finding into a multi-layered field spanning polygenic variation, monogenic extremes, host-microbiome interaction, and epigenetic regulation. Future progress will likely depend on larger, more ancestrally diverse GWAS and biobank cohorts capable of supporting genuinely predictive polygenic risk scores; multi-omic integration of genetic, epigenetic, microbial, and clinical data to capture gene-environment interactions that single-marker analyses cannot; and continued mechanistic dissection of tissue-maintenance genes such as SIGLEC5 and PLG, which may yield host-modulation targets more specific than current broad-spectrum agents. Until then, periodontal genetics remains a field whose scientific maturity exceeds its clinical footprint outside the monogenic extreme – a gap this review has aimed to characterise honestly.

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REFERENCES

1. Hu M, Zhang R, Wang R, Wang Y, Guo J. Global, regional, and national burden of periodontal diseases from 1990 to 2021 and predictions to 2040: an analysis of the global burden of disease study 2021. *Front Oral Health*. 2025 Jul 24;6:1627746. doi: 10.3389/froh.2025.1627746.
2. Genco RJ, Sanz M. Clinical and public health implications of periodontal and systemic diseases: An overview. *Periodontol* 2000. 2020 Jun;83(1):7-13. doi: 10.1111/prd.12344.
3. Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. *Nat Rev Immunol*. 2021 Jul;21(7):426-440. doi: 10.1038/s41577-020-00488-6.
4. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. *Nat Rev Microbiol*. 2012 Oct;10(10):717-25. doi: 10.1038/nrmicro2873.
5. Hajishengallis G, Lamont RJ. Breaking bad: manipulation of the host response by *Porphyromonas gingivalis*. *Eur J Immunol*. 2014 Feb;44(2):328-38. doi: 10.1002/eji.201344202.
6. Hajishengallis G, Lamont RJ. Beyond the red complex and into more complexity: the polymicrobial synergy and dysbiosis (PSD) model of periodontal disease etiology. *Mol Oral Microbiol*. 2012 Dec;27(6):409-19. doi: 10.1111/j.2041-1014.2012.00663.x.
7. Michalowicz BS. Genetic and heritable risk factors in periodontal disease. *J Periodontol*. 1994 May;65(5 Suppl):479-88. doi: 10.1902/jop.1994.65.5s.479.
8. Haworth S, Esberg A, Kuja-Halkola R, Lundberg P, Magnusson PKE, Johansson I. Using national register data to estimate the heritability of periodontitis. *J Clin Periodontol*. 2021 Jun;48(6):756-764. doi: 10.1111/jcpe.13459.

9. Michalowicz BS, Diehl SR, Gunsolley JC, Sparks BS, Brooks CN, Koertge TE, Califano JV, Burmeister JA, Schenkein HA. Evidence of a substantial genetic basis for risk of adult periodontitis. *J Periodontol.* 2000 Nov;71(11):1699-707. doi: 10.1902/jop.2000.71.11.1699.
10. Mucci LA, Björkman L, Douglass CW, Pedersen NL. Environmental and heritable factors in the etiology of oral diseases--a population-based study of Swedish twins. *J Dent Res.* 2005 Sep;84(9):800-5. doi: 10.1177/154405910508400904.
11. Schaefer AS, Nibali L, Zoheir N, Moutsopoulos NM, Loos BG. Genetic risk variants implicate impaired maintenance and repair of periodontal tissues as causal for periodontitis-A synthesis of recent findings. *Periodontol 2000.* 2025 Feb 14;10.1111/prd.12622. doi: 10.1111/prd.12622.
12. Richter GM, Schaefer AS. Genetic Susceptibility to Periodontitis. *J Periodontal Res.* 2025 Jul 11. doi: 10.1111/jre.70002.
13. Kittaka M, Yoshimoto T, Levitan ME, Urata R, Choi RB, Teno Y, Xie Y, Kitase Y, Prideaux M, Dallas SL, Robling AG, Ueki Y. Osteocyte RANKL Drives Bone Resorption in Mouse Ligature-Induced Periodontitis. *J Bone Miner Res.* 2023 Oct;38(10):1521-1540. doi: 10.1002/jbmr.4897.
14. Kornman KS, Crane A, Wang HY, di Giovine FS, Newman MG, Pirk FW, Wilson TG Jr, Higginbottom FL, Duff GW. The interleukin-1 genotype as a severity factor in adult periodontal disease. *J Clin Periodontol.* 1997 Jan;24(1):72-7. doi: 10.1111/j.1600-051x.1997.tb01187.x
15. McDevitt MJ, Wang HY, Knobelmann C, Newman MG, di Giovine FS, Timms J, Duff GW, Kornman KS. Interleukin-1 genetic association with periodontitis in clinical practice. *J Periodontol.* 2000 Feb;71(2):156-63. doi: 10.1902/jop.2000.71.2.156.
16. Meisel P, Schwahn C, Gesch D, Bernhardt O, John U, Kocher T. Dose-effect relation of smoking and the interleukin-1 gene polymorphism in periodontal disease. *J Periodontol.* 2004 Feb;75(2):236-42. doi: 10.1902/jop.2004.75.2.236
17. Yang T, Cheng B, Noble JM, Reitz C, Papapanou PN. Replication of gene polymorphisms associated with periodontitis-related traits in an elderly cohort: the Washington Heights/Inwood Community Aging Project Ancillary Study of Oral Health. *J Clin Periodontol.* 2022 May;49(5):414-427. doi: 10.1111/jcpe.13605.
18. Liu X, Li H. A Systematic Review and Meta-Analysis on Multiple Cytokine Gene Polymorphisms in the Pathogenesis of Periodontitis. *Front Immunol.* 2022 Jan 3;12:713198. doi: 10.3389/fimmu.2021.713198.
19. Ferrara E, D'Albenzio A, Rapone B, Mastrocola F, Murmura G. Genetic polymorphisms associated with periodontitis in Japanese populations: A comprehensive review of pathways, interactions, and clinical implications. *Infect Genet Evol.* 2025 Sep;133:105781. doi: 10.1016/j.meegid.2025.105781.
20. Kriauciunas A, Gedvilaite G, Bruzaite A, Zekonis G, Razukevicius D, Liutkeviciene R. Generalised Periodontitis: Examining TAS2R16 Serum Levels and Common Gene Polymorphisms (rs860170, rs978739, rs1357949). *Biomedicines.* 2024 Jan 30;12(2):319. doi: 10.3390/biomedicines12020319.
21. Mazurek-Mochol M, Bonsmann T, Malinowski D, Serwin K, Czerewaty M, Safranow K, Pawlik A. Interleukin-6 Receptor Gene rs1800795 Polymorphism and Expression of Interleukin-6 in Gingival Tissue in Patients with Periodontitis. *Microorganisms.* 2024 Sep 27;12(10):1954. doi: 10.3390/microorganisms12101954.
22. Brodzikowska A, Górski B. Polymorphisms in Genes Involved in Inflammation and Periodontitis: A Narrative Review. *Biomolecules.* 2022 Apr 7;12(4):552. doi: 10.3390/biom12040552.
23. Hu A, Wang X, Ai L, Liu K, Kong L. Association between matrix metalloproteinase-3 gene polymorphism and susceptibility to chronic periodontitis: A systematic review and meta-analysis. *J Med Biochem.* 2024 Sep 6;43(5):655-663. doi: 10.5937/jomb0-49044.
24. Du F, Liu Z, Qing S. Effect of vitamin D receptor gene polymorphisms on the risk of chronic and aggressive periodontitis: A systematic review and meta-analysis of the Chinese population. *Arch Oral Biol.* 2022 Dec;144:105566. doi: 10.1016/j.archoralbio.2022.105566.
25. Chen Z, Chen G. Interleukin-16 rs4072111 Polymorphism is Associated with the Risk of Peri-Implantitis in the Chinese Population. *Pharmgenomics Pers Med.* 2021 Dec 15;14:1629-1635. doi: 10.2147/PGPM.S336857.
26. Hamrun N, Ruslin M, Marlina E, Oktawati S, Saito T, Yusuf ASH, Ou KL. Profile of vitamin D receptor gene polymorphism TaqI in patients with periodontitis. *Biomed Rep.* 2022 May;16(5):35. doi: 10.3892/br.2022.1518.
27. Kami M, Saghaeian Jazi M, Allahyari M, Fakhari E. Association of Vitamin D Receptor Gene Polymorphisms with Periodontitis. *J Dent (Shiraz).* 2026 Mar 1;27(4):33-42. doi: 10.30476/dentjods.2025.103866.2485.
28. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *J Periodontol.* 2018 Jun;89 Suppl 1:S159-S172. doi: 10.1002/JPER.18-0006. Erratum in: *J Periodontol.* 2018 Dec;89(12):1475. doi: 10.1002/jper.10239.
29. Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, Mealey BL, Papapanou PN, Sanz M, Tonetti MS. A new classification scheme for periodontal and peri-implant diseases and conditions - Introduction and key changes from the 1999 classification. *J Periodontol.* 2018 Jun;89 Suppl 1:S1-S8. doi: 10.1002/JPER.18-0157.
30. Jepsen S, Caton JG, Albandar JM, Bissada NF, Bouchard P, Cortellini P, Demirel K, de Sanctis M, Ercoli C, Fan J, Geurs NC, Hughes FJ, Jin L, Kantarci A, Lalla E, Madianos PN, Matthews D, McGuire MK, Mills MP, Preshaw PM, Reynolds MA, Sculean A, Susin C, West NX, Yamazaki K. Periodontal manifestations of systemic

diseases and developmental and acquired conditions: Consensus report of workgroup 3 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Periodontol*. 2018 Jun;89 Suppl 1:S237-S248. doi: 10.1002/JPER.17-0733.

31. Nagy N, Vályi P, Csoma Z, Sulák A, Tripolszki K, Farkas K, Paschali E, Papp F, Tóth L, Fábos B, Kemény L, Nagy K, Széll M. CTSC and Papillon-Lefèvre syndrome: detection of recurrent mutations in Hungarian patients, a review of published variants and database update. *Mol Genet Genomic Med*. 2014 May;2(3):217-28. doi: 10.1002/mgg3.61.

32. Eick S, Puklo M, Adamowicz K, Kantyka T, Hiemstra P, Stennicke H, Guentsch A, Schacher B, Eickholz P, Potempa J. Lack of cathelicidin processing in Papillon-Lefèvre syndrome patients reveals essential role of LL-37 in periodontal homeostasis. *Orphanet J Rare Dis*. 2014 Sep 27;9:148. doi: 10.1186/s13023-014-0148-y.

33. Sørensen OE, Clemmensen SN, Dahl SL, Østergaard O, Heegaard NH, Glenthøj A, Nielsen FC, Borregaard N. Papillon-Lefèvre syndrome patient reveals species-dependent requirements for neutrophil defenses. *J Clin Invest*. 2014 Oct;124(10):4539-48. doi: 10.1172/JCI76009.

34. Cox DP, Weathers DR. Leukocyte adhesion deficiency type 1: an important consideration in the clinical differential diagnosis of prepubertal periodontitis. A case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2008 Jan;105(1):86-90. doi: 10.1016/j.tripleo.2007.02.026.

35. Justiz Vaillant AA, Ahmad F. Leukocyte Adhesion Deficiency. 2023 Jul 3. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–.

36. Moutsopoulos NM, Konkel J, Sarmadi M, Eskan MA, Wild T, Dutzan N, Abusleme L, Zenobia C, Hosur KB, Abe T, Uzel G, Chen W, Chavakis T, Holland SM, Hajishengallis G. Defective neutrophil recruitment in leukocyte adhesion deficiency type I disease causes local IL-17-driven inflammatory bone loss. *Sci Transl Med*. 2014 Mar 26;6(229):229ra40. doi: 10.1126/scitranslmed.3007696.

37. Booth C, Sevilla J, Almaraz E, Kuo CY, Zubizaray J, Terrazas D, O'Toole G, Chitty-Lopez M, Choi G, Nicoletti E, Long-Boyle J, Fernandes A, Chetty K, De Oliveira S, Banuelos C, Xu-Bayford J, Bastone AL, John-Neek P, Jackson C, Moore TB, Gilmour K, Schambach A, Rothe M, Kasbekar S, Rao GR, Patel K, Shah G, Thrasher AJ, Bueren JA, Schwartz JD, Kohn DB. Lentiviral Gene Therapy for Severe Leukocyte Adhesion Deficiency Type 1. *N Engl J Med*. 2025 May 1;392(17):1698-1709. doi: 10.1056/NEJMoa2407376.

38. Astolfi-Labrador L, Cabezas-Corado Á, Torres-Lagares D, Baus-Domínguez M. Differences in inflammatory genetic profiles in periodontitis associated with genetic and immunological disorders: a systematic review. *Biomedicines*. 2025;13(12):2851. doi:10.3390/biomedicines13122851

39. Villoria GEM, Fischer RG, Tinoco EMB, Meyle J, Loos BG. Periodontal disease: A systemic condition. *Periodontol 2000*. 2024 Oct;96(1):7-19. doi: 10.1111/prd.12616.

40. Gholami L, Movafagh A, Badrlou E, Nazer N, Yari M, Sadeghi G, Mirzajani S, Shadnough M, Sayad A, Ghafouri-Fard S. Altered expression of STAT genes in periodontitis. *Hum Antibodies*. 2021;29(3):209-216. doi: 10.3233/HAB-210444.

41. Divaris K, Monda KL, North KE, Olshan AF, Reynolds LM, Hsueh WC, Lange EM, Moss K, Barros SP, Weyant RJ, Liu Y, Newman AB, Beck JD, Offenbacher S. Exploring the genetic basis of chronic periodontitis: a genome-wide association study. *Hum Mol Genet*. 2013 Jun 1;22(11):2312-24. doi: 10.1093/hmg/ddt065.

42. Munz M, Willenborg C, Richter GM, Jockel-Schneider Y, Graetz C, Staufenbiel I, Wellmann J, Berger K, Krone B, Hoffmann P, van der Velde N, Uitterlinden AG, de Groot LCPGM, Sawalha AH, Direskeneli H, Saruhan-Direskeneli G, Guzeldemir-Akcanat E, Keceli HG, Laudes M, Noack B, Teumer A, Holtfreter B, Kocher T, Eickholz P, Meyle J, Doerfer C, Bruckmann C, Lieb W, Franke A, Schreiber S, Nohutcu RM, Erdmann J, Loos BG, Jepsen S, Dommisch H, Schaefer AS. A genome-wide association study identifies nucleotide variants at SIGLEC5 and DEFA1A3 as risk loci for periodontitis. *Hum Mol Genet*. 2017 Jul 1;26(13):2577-2588. doi: 10.1093/hmg/ddx151. Erratum in: *Hum Mol Genet*. 2018 Mar 1;27(5):941-942. doi: 10.1093/hmg/ddy015.

43. De Almeida SD, Richter GM, de Coö A, Jepsen S, Kapferer-Seebacher I, Dommisch H, Berger K, Laudes M, Lieb W, Loos BG, van der Velde N, van Schoor N, de Groot L; PerioGEN Cohort Group; Blanco J, Carracedo A, Cruz R, Schaefer AS. A genome-wide association study meta-analysis in a European sample of stage III/IV grade C periodontitis patients ≤35 years of age identifies new risk loci. *J Clin Periodontol*. 2024 Apr;51(4):431-440. doi: 10.1111/jcpe.13922.

44. Salminen A, Hyvärinen K, Ritari J, Caetano A, Kambur O, Mäntylä P, Yilmaz M, Sinisalo J; FinnGen; Perola M, Havulinna A, Nibali L, Gürsoy UK, Pussinen PJ. Genetic Loci Associated With Periodontitis: The FinnGen Study Based on National Health Registers. *J Clin Periodontol*. 2025 Sep;52(9):1263-1275. doi: 10.1111/jcpe.14193.

45. Gao C, Iles MM, Bishop DT, Larvin H, Bunce D, Wu B, Luo H, Nibali L, Pavitt S, Wu J, Kang J. Genetic risk factors for periodontitis: a genome-wide association study using UK Biobank data. *Clin Oral Investig*. 2025 Feb 14;29(2):129. doi: 10.1007/s00784-025-06205-8. Erratum in: *Clin Oral Investig*. 2025 Mar 20;29(4):198. doi: 10.1007/s00784-025-06286-5.

46. Divaris K, Haworth S, Shaffer JR, Anttonen V, Beck JD, Furuichi Y, Holtfreter B, Jönsson D, Kocher T, Levy SM, Magnusson PKE, McNeil DW, Michaëlsson K, North KE, Palotie U, Papapanou PN, Pussinen PJ, Porteous D, Reis K, Salminen A, Schaefer AS, Sudo T, Sun YQ, Suominen AL, Tamahara T, Weinberg SM, Lundberg P, Marazita ML, Johansson I. Phenotype Harmonization in the GLIDE2 Oral Health Genomics Consortium. *J Dent Res*. 2022 Oct;101(11):1408-1416. doi: 10.1177/00220345221109775.

47. Kastenbom L, Esberg A, Haworth S. Introduction to genome-wide association studies: Exploring their utility in caries and periodontitis. *Community Dent Health*. 2026 Mar;43(1):25-32. doi: 10.1177/0265539X251381496.
48. Zhang S, Yu N, Arce RM. Periodontal inflammation: Integrating genes and dysbiosis. *Periodontol* 2000. 2020 Feb;82(1):129-142. doi: 10.1111/prd.12267.
49. Divaris K, Monda KL, North KE, Olshan AF, Lange EM, Moss K, Barros SP, Beck JD, Offenbacher S. Genome-wide association study of periodontal pathogen colonization. *J Dent Res*. 2012 Jul;91(7 Suppl):21S-28S. doi: 10.1177/0022034512447951.
50. Zoheir N, Kurushima Y, Lin GH, Nibali L. Periodontal infectogenomics: a systematic review update of associations between host genetic variants and subgingival microbial detection. *Clin Oral Investig*. 2022 Mar;26(3):2209-2221. doi: 10.1007/s00784-021-04233-8.
51. Nibali L, Stephen AS, Allaker RP, Di Pino A, Terranova V, Pisano M, Di Marca S, Ferrara V, Scicali R, Purrello F, Donos N, Regolo M, Malatino L. Associations between Host Genetic Variants and Subgingival Microbiota in Patients with the Metabolic Syndrome. *Int J Mol Sci*. 2023 Nov 23;24(23):16649. doi: 10.3390/ijms242316649.
52. Kurushima Y, Tsai PC, Castillo-Fernandez J, Couto Alves A, El-Sayed Moustafa JS, Le Roy C, Spector TD, Ide M, Hughes FJ, Small KS, Steves CJ, Bell JT. Epigenetic findings in periodontitis in UK twins: a cross-sectional study. *Clin Epigenetics*. 2019 Feb 13;11(1):27. doi: 10.1186/s13148-019-0614-4.
53. Al-Rawi NH, Al-Marzooq F, Al-Nuaimi AS, Hachim MY, Hamoudi R. Salivary microRNA 155, 146a/b and 203: A pilot study for potentially non-invasive diagnostic biomarkers of periodontitis and diabetes mellitus. *PLoS One*. 2020 Aug 5;15(8):e0237004. doi: 10.1371/journal.pone.0237004.
54. Yan K, Zheng Y, Liu J, Li S, Si W. Clinical significance analysis of microRNA-199a-3p in gingival crevicular fluid for patients with chronic periodontitis. *Mol Cell Probes*. 2025 Apr;80:102015. doi: 10.1016/j.mcp.2025.102015.
55. Li Q, Zhu JJ. Expression Levels of miR-181 Family Members in Oral Biofluids as Biomarkers for Periodontitis Severity. *Tohoku J Exp Med*. 2024 Dec 20;264(3):121-130. doi: 10.1620/tjem.2024.J058.
56. Guo J, He Y. LncRNA HOTTIP as a potential biomarker of chronic periodontitis and its role in inflammatory responses. *Odontology*. 2025 Oct;113(4):1678-1688. doi: 10.1007/s10266-025-01094-5.
57. Ren Y, Zheng J, Cao Y, Zhu Y, Ling Z, Zhang Z, Huang M. Diagnostic significance of LncRNA MIAT in periodontitis and the molecular mechanisms influencing periodontal ligament fibroblasts via the miR-204-5p/DKK1 axis. *Arch Oral Biol*. 2024 Dec;168:106066. doi: 10.1016/j.archoralbio.2024.106066.
58. Chopra A, Bhuvanagiri G, Natu K, Chopra A. Role of CRISPR-Cas systems in periodontal disease pathogenesis and potential for periodontal therapy: A review. *Mol Oral Microbiol*. 2025 Feb;40(1):1-16. doi: 10.1111/omi.12483.
59. Solbiati J, Duran-Pinedo A, Godoy Rocha F, Gibson FC 3rd, Frias-Lopez J. Virulence of the Pathogen *Porphyromonas gingivalis* Is Controlled by the CRISPR-Cas Protein Cas3. *mSystems*. 2020 Sep 29;5(5):e00852-20. doi: 10.1128/mSystems.00852-20.
60. Kedlaya MN, Puzhankara L, Prasad R, Raj A. Periodontal Disease Pathogens, Pathogenesis, and Therapeutics: The CRISPR-Cas Effect. *CRISPR J*. 2023 Apr;6(2):90-98. doi: 10.1089/crispr.2022.0094.
61. Greenstein G, Hart TC. Clinical utility of a genetic susceptibility test for severe chronic periodontitis: a critical evaluation. *J Am Dent Assoc*. 2002 Apr;133(4):452-9; quiz 492-3. doi: 10.14219/jada.archive.2002.0203.
62. Pereira NL, Cresci S, Angiolillo DJ, Batchelor W, Capers Q 4th, Cavallari LH, Leifer D, Luzum JA, Roden DM, Stellos K, Turrisi SL, Tuteja S; American Heart Association Professional/Public Education and Publications Committee of the Council on Genomic and Precision Medicine; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Peripheral Vascular Disease; and Stroke Council. *CYP2C19* Genetic Testing for Oral P2Y12 Inhibitor Therapy: A Scientific Statement From the American Heart Association. *Circulation*. 2024 Aug 6;150(6):e129-e150. doi: 10.1161/CIR.0000000000001257.
63. Modafferi C, Grippaudo C, Corvaglia A, Cristi V, Amato M, Rigotti P, Polizzi A, Isola G. Genetic Testing in Periodontitis: A Narrative Review on Current Applications, Limitations, and Future Perspectives. *Genes (Basel)*. 2025 Nov 1;16(11):1308. doi: 10.3390/genes16111308.
64. Golub LM, Lee HM, Greenwald RA, Ryan ME, Sorsa T, Salo T, Giannobile WV. A matrix metalloproteinase inhibitor reduces bone-type collagen degradation fragments and specific collagenases in gingival crevicular fluid during adult periodontitis. *Inflamm Res*. 1997 Aug;46(8):310-9. doi: 10.1007/s000110050193.
65. Sgolastra F, Petrucci A, Gatto R, Giannoni M, Monaco A. Long-term efficacy of subantimicrobial-dose doxycycline as an adjunctive treatment to scaling and root planing: a systematic review and meta-analysis. *J Periodontol*. 2011 Nov;82(11):1570-81. doi: 10.1902/jop.2011.110026.
66. Attia MS, Alblowi JA. Effect of Subantimicrobial Dose Doxycycline Treatment on Gingival Crevicular Fluid Levels of MMP-9 and MMP-13 in Periodontitis Stage 2, Grade B in Subjects with Type 2 Diabetes Mellitus. *J Immunol Res*. 2020 Nov 20;2020:2807259. doi: 10.1155/2020/2807259.
67. Golub LM, Lee HM. Periodontal therapeutics: Current host-modulation agents and future directions. *Periodontol* 2000. 2020 Feb;82(1):186-204. doi: 10.1111/prd.12315.

68. Balta MG, Papathanasiou E, Blix IJ, Van Dyke TE. Host Modulation and Treatment of Periodontal Disease. *J Dent Res*. 2021 Jul;100(8):798-809. doi: 10.1177/0022034521995157.
69. Kwon T, Lamster IB, Levin L. Current Concepts in the Management of Periodontitis. *Int Dent J*. 2021 Dec;71(6):462-476. doi: 10.1111/idj.12630.
70. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, Flemmig TF, Garcia R, Giannobile WV, Graziani F, Greenwell H, Herrera D, Kao RT, Kebschull M, Kinane DF, Kirkwood KL, Kocher T, Kornman KS, Kumar PS, Loos BG, Machtei E, Meng H, Mombelli A, Needleman I, Offenbacher S, Seymour GJ, Teles R, Tonetti MS. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Clin Periodontol*. 2018 Jun;45 Suppl 20:S162-S170. doi: 10.1111/jcpe.12946.