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GENETICS AND PERIODONTAL DISEASE: GENETIC EVIDENCE AND DIAGNOSTIC ADVANCES—A NARRATIVE REVIEW

Dental Science

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ABSTRACT

Periodontitis is a multifactorial inflammatory disease shaped by microbial, environmental, and host factors, with genetic susceptibility influencing both onset and progression. Genetic testing methods such as single-nucleotide polymorphism analysis and genome-wide association studies have been explored to estimate individual risk and treatment response, but their routine use in clinical periodontics remains limited. Relevant recent studies were identified through PubMed, Scopus, and Google Scholar for this narrative review. Polymorphisms in genes related to IL-1, IL-6, TNF-α, immune regulation, and bone metabolism have been associated with periodontitis. However, inconsistent study designs, population stratification, and gene–environment interactions limit clinical applicability. Emerging approaches such as polygenic risk scores and machine learning may improve prediction in the future. A better understanding of genetic susceptibility may support precision dentistry and personalized periodontal care, although important challenges remain before genetic testing becomes a routine diagnostic tool.

KEYWORDS

Periodontitis; Genetics; Polymorphism; Oral Microbiome; Genetic Testing; Precision Dentistry.

INTRODUCTION

Periodontitis is a chronic inflammatory disease characterized by attachment loss, pocket formation, and alveolar bone destruction. Disease expression reflects interactions between microbial challenge and host response, with genetic susceptibility influencing bacterial recognition, inflammation, neutrophil function, and bone remodeling (Modafferi et al., 2025; Wankhede et al., 2017).

Hereditary influences were first suggested by familial aggregation, twin studies, and candidate-gene research. Twin studies demonstrated a genetic contribution to probing depth, attachment loss, and gingival inflammation, while candidate-gene studies highlighted IL1A, IL1B, TNFA, IL6, and IL10 polymorphisms, particularly the IL-1 genotype, as contributors to periodontal susceptibility (Hart, 1996; Michalowicz et al., 2000; Kornman et al., 1997; McDevitt et al., 2000; Gore et al., 1998; Laine et al., 2001).

EVIDENCE OF THE ROLE OF GENETICS IN PERIODONTITIS

Evidence for genetic involvement in periodontitis comes from familial, twin, candidate-gene, and genome-wide studies. Familial clustering and twin studies indicate substantial heritability and explain differing disease outcomes despite similar environmental exposures (Kinane & Hart, 2003; Yoshie et al., 2007).

Candidate-gene studies focused mainly on inflammatory mediators, especially the IL-1 cluster. The IL1A and IL1B polymorphisms were associated with greater disease severity in selected populations, supporting the role of pro-inflammatory genetic variation in susceptibility (Loos et al., 2015; Schork et al., 2000). More recent genome-wide studies identified loci such as GLT6D1, SIGLEC5, and DEFA1A3, suggesting that periodontitis is a polygenic disease involving innate immunity and antimicrobial defense (Brookes, 1999). Polygenic risk models may eventually improve prediction, but their clinical use remains limited because of incomplete validation and ancestry bias (McCarthy et al., 2008; Visscher et al., 2017)

EVIDENCE OF THE ROLE OF GENETICS IN AGGRESSIVE PERIODONTITIS

Aggressive periodontitis appears to have a stronger hereditary component than many other periodontal phenotypes and is best understood as a polygenic host-response disorder rather than a single-gene disease. Candidate-gene studies have implicated IL1A, IL1B, TNFA, IL6, IL10, VDR, Fcγ receptor genes, and MMPs, which influence inflammation, neutrophil function, and connective-tissue breakdown. Among these, the IL-1 and TNF-α pathways are most studied because of their role in inflammatory amplification and tissue destruction (Schaefer et al., 2010).

HLA markers are also important in aggressive periodontitis. Studies have reported associations of HLA-A9 and HLA-B15 with generalized early-onset disease, while HLA-A10 may be protective. Later reports and meta-analysis suggested that HLA-A9 and HLA-B15 are susceptibility factors, whereas HLA-A2 and HLA-B5 may be protective in some populations, although the overall HLA association remains heterogeneous and ancestry-dependent (Nibali et al., 2014)

ROLE OF HOST GENETICS IN ORAL MICROBIOME DYSBIOSIS

Host genetics influences the oral microbiome by modifying innate immune recognition, inflammatory response, epithelial barrier function, and antimicrobial defense. Variants in genes such as IL1A, IL1B, TNFA, IL10, VDR, TLR4, and CD14 can create an environment that favors pathogenic species like *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, and *Aggregatibacter actinomycetemcomitans*, leading to dysbiosis rather than simple plaque accumulation (Hajishengallis & Chavakis, 2021).

These gene–microbe interactions are important because host polymorphisms affect not only inflammation but also bacterial selection and virulence. For example, CD14 and TLR4 variants may alter lipopolysaccharide recognition, while VDR, IL-1, and TNF-α polymorphisms can increase cytokine production and tissue breakdown, further supporting growth of pathogenic anaerobes. Thus, periodontal dysbiosis is a genetically modified ecological shift (Hajishengallis, 2022; Lu et al., 2020).

GENETIC POLYMORPHISM IN GINGIVITIS

Gingivitis is a reversible inflammatory condition of the gingiva, but it is important because it reflects early host susceptibility before attachment loss begins. Genetic studies show that some individuals are more prone to persistent gingival inflammation, making gingivitis a useful phenotype for studying early immune responses (Chen et al., 2012).

Among the genes studied, the vitamin D receptor (VDR) gene is one of the most important. VDR polymorphisms such as TaqI, FokI, BsmI, and ApaI have been linked to gingivitis and periodontitis, with VDR

TaqI (rs731236) showing significant association in some pediatric cohorts, while other variants have shown inconsistent or no association (Barbosa et al., 2020; Izakovicova Holla et al., 2017).

Table 1. Major polymorphisms reported in gingivitis and periodontitis

Gene/variant	Main biological role	Reported association	Interpretation
VDR TaqI (rs731236)	Vitamin D signaling, immune modulation	Associated with gingivitis in some cohorts	Variant-specific and population-dependent
TNF-α −308G/A	Pro-inflammatory cytokine	A allele may be protective	Heterogeneous effects
IL1A/IL1B	Pro-inflammatory cytokines	Stronger evidence in periodontitis	More established in tissue destruction
IL6 promoter variants	Acute-phase response	Associated with periodontitis in some populations	Mixed evidence
MMP-9 −1562C/T	Matrix degradation	Linked more clearly to periodontitis	Tissue destruction marker

GENETIC POLYMORPHISM IN PERIODONTITIS

The strongest genetic associations in periodontitis are in inflammatory and immune-regulatory pathways. The IL-1 gene cluster is the most studied and has been linked to disease severity in selected populations, likely because IL-1 amplifies inflammation, recruits neutrophils, and promotes tissue breakdown (Lu et al., 2020).

TNFA promoter variants such as −308 G>A, IL6, and IL10 polymorphisms may also influence inflammatory balance and tissue injury, although effects are usually modest and inconsistent. Innate immune receptors including TLR2, TLR4, and CD14 affect microbial recognition, while RANKL/OPG pathways regulate the transition from inflammation to bone loss (Bartosova et al., 2020; Brown, 2018). GWAS have expanded the field by identifying loci such as GLT6D1, SIGLEC5, DEFA1A3, and others, supporting the view that periodontitis is polygenic and biologically heterogeneous. Population differences and phenotype selection remain major challenges, and some authors suggest chronic gingivitis as a better comparison group than healthy controls (Alberts et al., 2015; Lodish et al., 2021).

DIFFERENT TOOLS AND TECHNIQUES FOR GENETIC TESTING

Polymerase chain reaction (PCR) and quantitative PCR

PCR remains the foundation of molecular testing. It amplifies selected DNA sequences through repeated cycles of denaturation, annealing, and extension. In periodontics, PCR is used to detect polymorphisms in genes such as IL-1, IL-6, and TNF-α, and to amplify bacterial DNA for pathogen detection. Real-time PCR and qPCR add quantification and are useful for measuring gene expression or bacterial load. Their strengths are sensitivity, speed, and low DNA requirement. Their main limitation is that they require prior knowledge of the target sequence (Brown, 2018; Lodish et al., 2021).

SNP genotyping assays

SNP genotyping is widely used because many periodontal markers are known single-base variants. Common methods include TaqMan assays, PCR-RFLP, ARMS-PCR, and MALDI-TOF mass spectrometry. These methods are efficient for known polymorphisms in IL-1, IL-6, IL-10, TNFA, VDR, CD14, and TLR genes. They are highly useful in association studies, but they cannot identify novel variants (Alberts et al., 2015; Strachan & Read, 2018).

DNA sequencing: Sanger and next-generation sequencing

Sanger sequencing remains useful for validating known variants and small-scale studies because of its high accuracy. Next-generation sequencing enables parallel analysis of millions of DNA fragments, facilitating discovery of rare and novel variants through targeted panels, whole-exome, or whole-genome sequencing. Limitations include cost, bioinformatic demands, and interpretation of variants of uncertain significance (Mardis, 2017).

HapMap and genome-wide association studies

The International HapMap Project made large-scale genetic studies more efficient by cataloguing common SNPs and haplotypes across populations. This reduced the number of markers required for disease association studies and supported the development of GWAS (International HapMap Consortium, 2003, 2005). GWAS scan the whole genome without preselecting candidate genes and have identified loci such as GLT6D1, SIGLEC5, DEFA1A3, EFCAB4B, LAMA2, ARHGAP18, HAS2/HAS2-AS1, RP11-61G19.1, and HIST1H3L. GWAS is powerful but requires large cohorts and explains only a fraction of heritability (Collins et al., 1998; International HapMap Consortium, 2003).

Microarray analysis and transcriptomic profiling

Microarrays allow simultaneous evaluation of thousands of genes and have been used to compare diseased and healthy gingival tissues. Their limitation is that they only assess known sequences and are less sensitive than sequencing-based approaches. Serial analysis of gene expression also contributed to the development of transcriptomics in oral disease (Strachan & Read, 2018).

Fluorescence in situ hybridization (FISH)

FISH is a cytogenetic technique that localizes specific DNA sequences on chromosomes. It is useful for detecting large-scale structural abnormalities such as deletions, duplications, and translocations, but it has limited resolution for single-base changes (International HapMap Consortium, 2005).

MLPA

Multiplex ligation-dependent probe amplification detects copy number variation across multiple targets in a single reaction. It may be useful for dosage changes in immune-related genes and is efficient for multiplex testing, although it is still relatively specialized (Liehr, 2017).

CRISPR-based diagnostics and emerging tests

CRISPR-based diagnostics using Cas12 and Cas13 are promising because they offer rapid, sensitive nucleic acid detection and may eventually support chairside genetic or microbial screening. These platforms are still emerging but represent an important future direction (Mardis, 2017).

Polygenic risk scores and machine learning

Polygenic risk scores aggregate the effects of many small variants into a single estimate of genetic risk. In periodontitis, they may eventually help identify high-risk individuals, especially when combined with smoking, diabetes, and oral hygiene data. Machine learning approaches may further improve prediction by integrating genetic, microbiome, and clinical variables. Both approaches are promising but still require validation in large, diverse cohorts (McCarthy et al., 2008; Schaefer et al., 2010).

Table 2. Comparative overview of major genetic testing techniques

Technique	Main target	Best use	Strength	Limitation
PCR/qPCR	Known DNA or RNA	SNP detection, expression analysis, pathogen detection	Fast, sensitive, inexpensive	Limited to known targets
Microarray	Thousands of probes	Expression profiling	High-throughput	Lower sensitivity
GWAS	Genome-wide variants	Susceptibility mapping	Unbiased discovery	Requires very large cohorts
FISH	Chromosomal loci	Structural abnormalities	Visual localization	Low base-pair resolution
MLPA	Copy number changes	CNV detection	Multiplex and efficient	Specialized use
CRISPR diagnostics	Nucleic acids	Rapid emerging detection	Sensitive and portable	Still developing

FUTURE PERSPECTIVE AND LIMITATIONS

The future of periodontal genetics lies in precision dentistry, integrating polygenic risk scores, microbiome profiles, inflammatory biomarkers, and clinical data to improve risk assessment and early

detection (Nibali et al., 2014; Schaefer et al., 2010).

CONCLUSION

Periodontitis is influenced by microbial factors, host response, and genetic susceptibility. Family, twin, candidate-gene, and GWAS studies confirm a hereditary component, with genes such as IL-1, TNF-α, IL-6, IL-10, VDR, CD14, TLR4, and loci including GLT6D1, SIGLEC5, and DEFA1A3 implicated in disease risk. Gingivitis also shows genetic influence (Barbosa et al., 2020).

Despite advances in genetic testing, routine clinical application remains limited. Future risk assessment will likely combine genetics, microbiology, biomarkers, and clinical findings (International HapMap Consortium, 2003; Liehr, 2017). Overall, periodontal genetics improves understanding of disease susceptibility and may support personalized periodontal care.

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