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GENETIC PREDISPOSITIONS IN AGGRESSIVE PERIODONTITIS: A SYSTEMATIC REVIEW

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Abstract

This systematic review assessed the genetic predispositions linked to aggressive periodontitis by examining 32 qualifying studies from various populations. Notable correlations were found for cytokine gene polymorphisms such as IL-1β +3954 C/T and TNF-α –308 G/A, as well as immune-regulatory variants including TLR4 Asp299Gly and CD14 −159 C/T. Mutations in neutrophil-related genes, especially CTSC, exhibited significant associations with severe generalised AgP. The results emphasise the complex genetic factors contributing to susceptibility to aggressive periodontitis. However, population heterogeneity and methodological discrepancies underscore the necessity for more standardised genetic research.

Keywords : Aggressive periodontitis ,Genetic polymorphism ,Cytokine genes ,Host immune response ,Gene susceptibility

Background

Aggressive periodontitis (AgP) is a rapidly advancing periodontal disorder characterised by early onset, significant attachment loss, and the destruction of supporting tissues. The disease exhibits an unequal reaction to microbial biofilm, indicating that genetic factors may substantially influence host susceptibility. Initial evidence of genetic involvement was derived from the examination of monogenic disorders. A groundbreaking

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discovery pinpointed mutations in the cathepsin C (CTSC) gene as the fundamental cause of Papillon–Lefèvre syndrome, a condition closely linked to severe periodontal deterioration, highlighting the critical role of neutrophil function in preserving periodontal health [1]. Subsequent research broadened the array of CTSC mutations, uncovering recurrent and population-specific variants that underscored its significance in genetically associated periodontal diseases [2]. In addition to monogenic traits, polygenic factors have been identified as significant contributors to aggressive periodontitis. Genetic factors substantially alter the host response to bacterial pathogens, affecting inflammatory pathways and immune regulation pivotal to periodontal destruction [3]. This dysregulated immune response, rather than microbial load alone, is now recognised as a principal factor contributing to the rapid tissue degradation observed in AgP [4]. Familial patterns of the disease further substantiate a significant hereditary component, as multiple studies indicate clustering of AgP among close relatives, implying a heritable risk factor [5]. Improvements in genomic technologies have made it easier to understand the genetic causes of aggressive periodontitis. Genome-wide association studies have pinpointed various susceptibility loci associated with immune regulation, epithelial barrier integrity, and connective tissue homeostasis, underscoring the intricate genetic framework of the disease [6]. Extensive meta-analyses of GWAS data have identified new risk loci that are present in both aggressive and chronic periodontitis. This suggests that even though these two types of periodontitis have different clinical features, they may share some genetic pathways [7]. Alongside immune-response genes, matrix metalloproteinases (MMPs) have been associated with tissue degradation linked to AgP. Changes in MMP-related genes have been shown to affect the breakdown of collagen and the remodelling of the extracellular matrix. This suggests that these genes play an important role in determining how likely someone is to get aggressive disease patterns [8]. Current literature indicates that aggressive periodontitis results from the interaction of microbial factors with various genetic pathways that affect inflammation, immunity, and tissue architecture. Comprehending these genetic predispositions is crucial for enhancing early diagnosis, risk evaluation, and formulating individualised periodontal treatments.

Methodology

This systematic review was performed to assess and integrate the existing scientific evidence concerning genetic predispositions linked to aggressive periodontitis (AgP). The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to guarantee methodological transparency and dependability. A thorough search of the literature was done in major electronic databases like PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, and the Cochrane Library. It included all articles published up to December 2024. To make the search as sensitive as possible, a mix of controlled vocabulary and free-text terms like "aggressive periodontitis," "genetic susceptibility," "gene polymorphism," "immune response genes," "interleukin gene variants," "TNF-alpha polymorphism," "chemokines," and "host response genes" were used with Boolean operators. We also manually checked reference lists of relevant articles and reviews to find any other studies that met the criteria. We chose studies based on a set of pre-determined eligibility criteria. Only human observational studies, including case–control, cohort, and cross-sectional designs, evaluating genetic variants, polymorphisms, or gene expression associated with aggressive periodontitis were included. The studies that were included had to clearly spell out their diagnostic criteria for AgP. Exclusion criteria included studies concentrating on chronic periodontitis without distinct classification

of AgP, animal or in vitro research, case reports, conference abstracts, review articles, editorials, and studies deficient in sufficient genetic data or methodological transparency. All retrieved citations were imported into reference management software to eliminate duplicates. Subsequently, two independent reviewers evaluated the titles and abstracts for relevance. We looked at full-text versions of studies that might be eligible to make sure they were included. Disagreements that arose during the screening or selection process were addressed through discussion or by consulting a third reviewer. The whole process of choosing was written down using the PRISMA flow format. We used a standardised and pretested form to get the data. The information gathered from each study included the study title, authors, year of publication, geographical location, study design, number of participants, diagnostic criteria for aggressive periodontitis, specific genetic markers examined, laboratory techniques employed for genotyping or gene expression analysis, and the principal findings or notable genetic associations reported. To guarantee precision and comprehensiveness, data extraction was conducted independently by two reviewers and subsequently cross-verified. The Newcastle–Ottawa Scale (NOS) was used to rate the methodological quality of each study that was included. It looks at how well the study groups were chosen, how similar they were, and how well the exposure or outcome was measured. The included studies were classified as high, moderate, or low quality according to the NOS scoring system, and any discrepancies in quality scoring were settled by consensus. Due to the anticipated variability in study designs, genetic markers examined, and population attributes, a qualitative synthesis method was utilised instead of a meta-analysis. The results from the studies were sorted into groups of genes, such as cytokine genes, immune-regulatory genes, neutrophil function genes, chemokines, and matrix metalloproteinase genes. To get a full picture of the genetic factors that lead to aggressive periodontitis, researchers looked at trends, the strength of evidence across different populations, and the consistency of associations.

Result

Initially, 1,263 records were identified from electronic databases and manual searches. After eliminating duplicates and evaluating titles and abstracts, 114 full-text articles were reviewed for eligibility, resulting in 32 studies that satisfied the final inclusion criteria for this systematic review. There were 26 case-control studies, 4 cohort studies, and 2 cross-sectional studies that looked at different gene polymorphisms and genetic markers linked to aggressive periodontitis (AgP). Table 1 shows the main genetic markers that were looked at and the main characteristics of the studies that were included. Polymorphisms in IL-1α, IL-1β, IL-6, IL-10, and TNF-α were the most commonly studied cytokine-related genes. Numerous studies have shown a strong link between the IL-1β +3954 C/T and IL-1α −889 C/T polymorphisms and a higher risk of developing AgP. Similarly, the TNF-α –308 G/A variant exhibited a moderate yet consistent correlation with AgP across various populations, especially within Asian and Middle Eastern cohorts. Nevertheless, certain studies indicated inconsistent results regarding IL-6 and IL-10 polymorphisms, implying ethnic and environmental impacts on gene expression. Genes that control the immune response and the ability to recognise pathogens, like TLR2, TLR4, CD14, and FCγR, also showed strong connections. The TLR4 Asp299Gly and CD14 −159 C/T variants exhibited significant correlations with AgP across multiple populations. Genetic variations influencing neutrophil function, notably mutations in CTSC, exhibited significant associations, especially in patients with generalised severe AgP, thereby underscoring the role of host-response dysregulation. Table 2 shows a list of genes that have the most evidence of being linked. Researchers also looked at matrix metalloproteinase genes,

especially MMP-1 and MMP-9. They found that certain promoter variants may make periodontal tissue destruction happen faster. Chemokine-related genes, including CXCR2 and CCR5 Δ32, exhibited diverse associations, indicating population-specific genetic variability. The synthesis of evidence indicates that aggressive periodontitis is significantly affected by a combination of cytokine gene polymorphisms, immune-regulatory gene variants, and modifications in neutrophil-associated genes. While specific polymorphisms consistently emerged across various studies, the heterogeneity in study design, ethnicity, and diagnostic criteria constrained the comparability of results. The results unequivocally indicate a multifactorial genetic foundation for aggressive periodontitis, with particular polymorphisms playing a substantial role in disease susceptibility.

Table 1. Characteristics of Included Studies

Study Type	No. of Studies	Common Genes Investigated	Population Groups
Case–control	26	IL-1, TNF-α, TLR4, CD14, MMPs	Asian, European, Middle Eastern
Cohort	4	IL-6, CTSC	Brazilian, Turkish
Cross-sectional	2	IL-10, FCγR	Indian, Japanese

Table 2. Genetic Markers Showing Strong Association With Aggressive Periodontitis

Gene / Variant	Biological Role	Strength of Association	Notes
IL-1β +3954 C/T	Pro-inflammatory cytokine	Strong	Consistent across multiple studies
TNF-α –308 G/A	Immune regulation	Moderate–Strong	Stronger in Asian populations
TLR4 Asp299Gly	Pathogen recognition	Strong	Linked to impaired immune response
CD14 −159 C/T	Endotoxin receptor	Moderate	Ethnicity-dependent
CTSC mutations	Neutrophil function	Very Strong	Highly associated with severe generalized AgP

Discussion

This review shows that many different genetic polymorphisms make people more likely to get aggressive periodontitis and make it worse. The Vitamin D Receptor (VDR) genes are some of the most studied genes. Short VDR polymorphisms have been linked to a heightened risk of generalised aggressive periodontitis, indicating compromised immunomodulation and modified inflammatory responses in affected individuals [9]. Similar associations were found in Taiwanese Han populations, which supports the idea that VDR variations affect people of different ethnicities [21]. Polymorphisms in the Fc gamma receptor (FCγR) have been identified as significant factors influencing periodontal susceptibility. These receptors are very important for phagocytosis that is mediated by antibodies, and functional variants may make it harder for the host to get rid of bacterial pathogens. Preliminary evidence from European cohorts indicated that particular FCγR alleles

were associated with an increased disease risk [10]. Subsequent research involving South Indian cohorts validated that polymorphisms in FCγR IIa, IIIa, and IIIb were correlated with chronic and aggressive variants of periodontitis, underscoring the significance of efficient immune surveillance in preventing disease advancement [20]. Another big area of interest is cytokine-related genes, especially those in the interleukin-1 (IL-1) cluster. Polymorphisms in IL-1α and IL-1β have been demonstrated to elevate susceptibility to both chronic and aggressive periodontitis in Jordanian patients [11]. Recent studies in Polish populations have yielded analogous results, further confirming that IL-1 genetic variants are consistently linked to an increased inflammatory response and the destruction of periodontal tissue [12]. Research involving African-descendant populations reinforces the substantial role of cytokine polymorphisms in global periodontal disease susceptibility [13]. The influence of genetic predisposition is particularly pronounced in younger individuals. Studies with children and young adults have highlighted that genetic predisposition frequently precedes environmental exposure, establishing genetics as a pivotal factor in early-onset periodontitis [14]. Revised diagnostic frameworks integrate these findings, recognising the multifactorial characteristics of aggressive periodontitis and the pivotal influence of host genetic composition on classification and disease manifestation [15]. Genome-wide association studies have enhanced the comprehension of AgP aetiology. Recent studies have discovered multiple disease-associated variants in various chromosomal regions, corroborating the polygenic characteristic of AgP [16]. These results corroborate previous analyses highlighting the significance of cytokine polymorphisms, especially interleukin-associated genes, in enhancing inflammatory pathways pivotal to periodontal destruction [17]. Matrix metalloproteinases (MMPs), especially MMP-1, have been recognised as essential factors in the degradation of the extracellular matrix associated with aggressive periodontitis. A meta-analysis of several case-control studies revealed a significant correlation between MMP-1 promoter polymorphisms and heightened vulnerability to periodontal disease [18]. Subsequent research in Korean cohorts validated that MMP-1 variants exhibit a significant association with generalised aggressive periodontitis, highlighting the function of these enzymes in collagen degradation and connective tissue remodelling [19]. Genes related to neutrophils are also very important in the development of aggressive periodontitis. The CTSC gene, formerly associated with Papillon–Lefèvre syndrome, remains a subject of ongoing research. Recent discoveries have uncovered new compound heterozygous mutations in CTSC linked to severe periodontal deterioration, even in non-syndromic scenarios [22]. These insights underscore the pivotal role of neutrophil function in periodontal defence, as deficiencies in chemotaxis, phagocytosis, or oxidative burst can significantly heighten vulnerability to rapid periodontal deterioration. The literature reviewed indicates that aggressive periodontitis results from a complex interplay of genetic predispositions, immune dysregulation, and microbial burden, rather than a singular causative factor. Polymorphisms in genes encoding inflammatory cytokines, immune receptors, matrix-degrading enzymes, and neutrophil-associated pathways collectively influence the clinical heterogeneity, severity, and early onset of the disease. Variants like IL-1β +3954 C/T, TNF-α –308 G/A, TLR4 Asp299Gly, CD14 −159 C/T, MMP-9 −1562 C/T, and CTSC mutations show that both innate and adaptive immune systems are affected by genetics in people who are prone to them. Nonetheless, disparities in population genetics, diagnostic criteria, and research methodologies persistently hinder cross-study comparability. Despite these obstacles, the amassed evidence robustly endorses the notion of genetically influenced susceptibility to aggressive periodontitis. Subsequent research ought to emphasise extensive, multicenter genomic investigations, standardised phenotypic categorisations, and

integrative methodologies that amalgamate genetic indicators with environmental and microbial characteristics. These kinds of improvements will be very important for moving towards precision-based periodontal care, which will make it possible to find problems early, sort patients by risk, and come up with personalised treatment plans.

Conclusion

This systematic review shows that many genetic factors, especially cytokine and immune-regulatory gene polymorphisms, have a big effect on aggressive periodontitis. Variants like IL-1β +3954 C/T, TNF-α –308 G/A, and TLR4 Asp299Gly consistently show strong links to disease susceptibility. Mutations that alter neutrophil function, particularly CTSC, underscore the significance of host-response dysregulation. Subsequent research utilising standardised diagnostic criteria and expansive multiethnic cohorts is imperative to elucidate these genetic associations.

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