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Genetic Markers Linked to Aggressive Periodontitis in Young Adults: A Case-Control Study

Dr. Mahesh D R[1*], Dr. Kathiravan Saminathan[2], Dr. Saloni Verma[3], Dr. Mohammad Aamir[4], Dr. Kanimozhi[5], Dr. Ankur Singh[6]

[1*]Professor, Department of Oral Medicine and Radiology, Dayananda Sagar College of Dental Sciences, Shavigemalleshwara Hills, K S Layout, Bangalore, Karnataka, India

[2]MDS, Assistant Professor, Department of Conservative Dentistry and Endodontics, Government Dental College and Hospital, Cuddalore, Tamil Nadu, India

[3]Department of Oral Pathology and Microbiology, King George's Medical University, Lucknow, Uttar Pradesh, India

[4]Reader, Department of Periodontology, Babu Banarasi Das College of Dental Sciences, BBD University, Lucknow, Uttar Pradesh, India

[5]Senior Lecturer, Department of Oral Medicine & Radiology, Sri Venkateshwaraa Dental College, Puducherry, India

[6]Professor, Department of Oral Medicine and Radiology, Narsinhbhai Patel Dental College and Hospital, Faculty of Dental Sciences, Sankalchand Patel University, Visnagar, Gujarat, India

***Corresponding Author:**

Dr. Mahesh D R, Professor, Department of Oral Medicine and Radiology, Dayananda Sagar College of Dental Sciences, Shavigemalleshwara Hills, K S Layout, Bangalore, Karnataka, India

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KEYWORDS

Aggressive periodontitis, genetic polymorphism, IL-1B, TNF-α, IL-10, cytokines, case-control study, young adults.

ABSTRACT:

Aim:

This study aimed to evaluate the association between selected genetic polymorphisms and the risk of developing aggressive periodontitis in young adults, focusing on cytokine and matrix metalloproteinase gene variants that influence host inflammatory response.

Methodology:

A total of 120 participants aged 18–35 years were enrolled, including 60 patients with generalized aggressive periodontitis and 60 periodontally healthy controls. Genomic DNA was extracted from venous blood samples, and polymorphisms in IL-1A (+4845), IL-1B (+3954), IL-6 (−174 G/C), IL-10 (−1082 A/G), TNF-α (−308 G/A), and MMP-8 (−799 C/T) genes were analyzed using PCR-RFLP. Clinical parameters were recorded, and statistical analysis was performed using chi-square and logistic regression tests to identify associations and risk estimates.

Result:

Significant associations were observed for IL-1B (+3954 T), IL-6 (−174 C), and TNF-α (−308 A) polymorphisms, which were more frequent among patients with aggressive periodontitis ($p < 0.05$). The IL-10 (−1082 G) genotype was more prevalent in healthy controls, indicating a potential protective role. Logistic regression confirmed IL-1B (+3954 T) and TNF-α (−308 A) as independent predictors of disease susceptibility after adjusting for smoking and oral hygiene status.

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Conclusion:

Pro-inflammatory cytokine gene polymorphisms, particularly IL-1B (+3954 T) and TNF-α (−308 A), are significantly associated with increased susceptibility to aggressive periodontitis in young adults, while IL-10 (−1082 G) may confer protective effects. Genetic screening may aid in identifying high-risk individuals for early preventive intervention.

Background

Aggressive periodontitis is a distinct form of periodontal disease characterized by rapid attachment loss and bone destruction that typically affects systemically healthy young adults. Unlike chronic periodontitis, its pathogenesis involves a complex interplay of microbial challenge, host immune response, and genetic predisposition. Recent research has increasingly focused on identifying genetic markers that contribute to individual susceptibility, particularly those related to pro-inflammatory cytokines and tissue-degrading enzymes (1). Interleukin-1 (IL-1) has emerged as one of the most extensively studied cytokines due to its potent role in mediating inflammation and bone resorption in periodontal tissues. Quappe et al. (1) reported a significant association between IL-1 gene polymorphisms and the severity of aggressive periodontitis, suggesting that genetic variations in IL-1 may influence the intensity of host response to bacterial challenge.Genetic variability in cytokine genes such as interleukin-1 can modulate the balance between pro-inflammatory and anti-inflammatory pathways, altering the progression of periodontal tissue destruction (2). Brodzikowska et al. demonstrated that specific IL-1 genotypes are more prevalent in periodontitis patients, reinforcing the hypothesis that cytokine gene polymorphisms contribute to differential susceptibility. Moreover, polymorphisms in interleukin-6 (IL-6) and interleukin-10 (IL-10) have also been implicated in modifying host response patterns. Toker et al. (3) found significant differences in IL-6 and IL-10 gene variants between aggressive and chronic periodontitis, indicating that these cytokines may play distinct roles in disease expression depending on genetic makeup.Scapoli et al. (4) provided further evidence that IL-6 and IL-10 polymorphisms act as genetic susceptibility factors for periodontal disease, emphasizing the dual role of these cytokines in both inflammatory regulation and tissue repair. Beyond cytokines, other genetic components such as matrix metalloproteinases (MMPs) are also critical to periodontal tissue breakdown. Borilova Linhartova et al. (5) demonstrated a link between interleukin gene variability and the presence of specific periodontal pathogens, suggesting a gene–bacteria interaction that may exacerbate tissue destruction in aggressive forms. Similarly, Emingil et al. (6) identified associations between MMP-8 and TIMP-1 gene polymorphisms and disease severity, highlighting how imbalances in extracellular matrix turnover can contribute to disease progression. Complementary findings by Li et al. (7) further established that MMP genetic variants are linked with heightened risk of periodontitis, confirming the importance of these enzymes in connective tissue degradation. Collectively, these studies underline the multifactorial nature of aggressive periodontitis and point toward a genetic foundation that modulates inflammatory response, microbial colonization, and tissue remodeling processes.

Methodology

The present case-control study was designed to investigate the association between specific genetic markers and susceptibility to aggressive periodontitis in young adults. A total of 120 participants aged 18 to 35 years were enrolled, comprising 60 patients diagnosed with generalized aggressive periodontitis and 60 periodontally healthy controls matched for age and gender. All participants were selected from the outpatient department of periodontology at a university dental hospital. The diagnosis of aggressive periodontitis was established based on clinical attachment loss, probing pocket depth, and radiographic evidence of alveolar bone destruction in at least three permanent teeth other than first molars and incisors, according to the 1999 American Academy of Periodontology classification. Healthy controls exhibited no clinical signs of attachment loss, bleeding on probing, or radiographic bone loss.Venous blood samples were collected from each participant under aseptic conditions and stored at −20°C until DNA extraction. Genomic DNA was isolated using a standard

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phenol-chloroform extraction method and quantified spectrophotometrically. Polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) analysis was performed to detect polymorphisms in candidate genes, including interleukin-1 (IL-1A +4845 and IL-1B +3954), interleukin-6 (−174G/C), interleukin-10 (−1082A/G), tumor necrosis factor-alpha (−308G/A), and matrix metalloproteinase-8 (−799C/T). PCR amplification was carried out using specific primers for each locus under optimized conditions, and products were visualized on 2% agarose gel stained with ethidium bromide. Genotype frequencies were determined by direct counting, and the distribution of alleles between case and control groups was compared.Clinical periodontal parameters, including probing depth, clinical attachment level, plaque index, and bleeding on probing, were recorded at six sites per tooth by a calibrated examiner to ensure consistency. Data were analyzed using SPSS software (version 25.0; IBM Corp., USA). Chi-square and Fisher's exact tests were applied to evaluate differences in genotype and allele frequencies between groups, and odds ratios with 95% confidence intervals were calculated to assess the strength of association. Hardy–Weinberg equilibrium was verified for each polymorphism. A p-value of less than 0.05 was considered statistically significant. The study protocol was reviewed and approved by the Institutional Ethics Committee, and informed consent was obtained from all participants prior to inclusion.

Result

A total of 120 subjects were included in the final analysis, consisting of 60 individuals diagnosed with generalized aggressive periodontitis and 60 periodontally healthy controls. The mean age of the case group was 27.3 ± 4.1 years, and that of the control group was 26.8 ± 3.9 years, with no significant difference in gender distribution between the groups ($p > 0.05$). Clinical parameters such as probing pocket depth and clinical attachment loss were significantly higher in the case group ($p < 0.001$), confirming the clinical distinction between cases and controls.Genotypic analysis revealed distinct differences in the distribution of certain alleles between groups. The frequency of the IL-1B (+3954 T) and IL-6 (−174 C) alleles was significantly elevated in patients with aggressive periodontitis compared to healthy subjects ($p = 0.002$ and $p = 0.01$, respectively). Similarly, carriers of the TNF-α (−308 A) allele showed an increased risk of disease with an odds ratio of 2.76 (95% CI: 1.23–6.19). The IL-10 (−1082 G) genotype was found to be more prevalent in healthy controls, suggesting a possible protective role. No significant association was detected for the MMP-8 (−799 C/T) polymorphism.Multivariate logistic regression confirmed IL-1B (+3954 T) and TNF-α (−308 A) as independent predictors of susceptibility to aggressive periodontitis after adjusting for smoking and oral hygiene status. The genotype distributions for all loci were in Hardy–Weinberg equilibrium. These findings indicate that pro-inflammatory cytokine gene polymorphisms play a crucial role in the early onset and progression of aggressive periodontitis in genetically predisposed young adults.

Table 1. Distribution of genotypes and alleles among aggressive periodontitis patients and controls

Gene polymorphism	Genotype	Cases (n=60)	Controls (n=60)	p-value	Odds Ratio (95% CI)
IL-1A (+4845)	TT	18 (30%)	10 (16.7%)	0.09	1.98 (0.88–4.47)
IL-1B (+3954)	TT	22 (36.7%)	8 (13.3%)	**0.002**	**3.78 (1.56–9.12)**
IL-6 (−174 G/C)	CC	25 (41.7%)	12 (20%)	**0.01**	**2.84 (1.27–6.33)**
IL-10 (−1082 A/G)	GG	9 (15%)	20 (33.3%)	**0.03**	**0.36 (0.15–0.89)**
TNF-α (−308 G/A)	AA	16 (26.7%)	6 (10%)	**0.01**	**2.76 (1.23–6.19)**

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Gene polymorphism	Genotype	Cases (n=60)	Controls (n=60)	p-value	Odds Ratio (95% CI)
MMP-8 (−799 C/T)	TT	14 (23.3%)	12 (20%)	0.66	1.22 (0.52–2.86)

Table 2. Logistic regression analysis identifying independent predictors of aggressive periodontitis

Genetic marker	β coefficient	Standard error	Odds Ratio	95% CI	p-value
IL-1B (+3954 T)	1.43	0.45	4.19	1.72–10.19	**0.002**
TNF-α (−308 A)	0.97	0.38	2.63	1.25–5.51	**0.01**
IL-6 (−174 C)	0.69	0.34	1.99	0.98–4.04	0.06
IL-10 (−1082 G)	−0.83	0.39	0.44	0.20–0.96	**0.04**
Smoking	0.51	0.32	1.67	0.89–3.14	0.10
Plaque index	0.18	0.11	1.20	0.96–1.50	0.12

The analysis demonstrates that IL-1B (+3954 T) and TNF-α (−308 A) polymorphisms significantly increase susceptibility to aggressive periodontitis, whereas IL-10 (−1082 G) may confer protection. These findings highlight the influence of inflammatory cytokine gene variants on host response and disease progression in young adults with aggressive periodontitis.

Discussion

The findings of the present study reinforce the growing body of evidence suggesting that genetic polymorphisms significantly influence susceptibility to aggressive periodontitis. Several gene families have been implicated in modulating inflammatory responses, collagen degradation, and tissue remodeling, which are fundamental to the pathophysiology of periodontal breakdown. Among these, matrix metalloproteinases (MMPs) and their inhibitors play an essential role in extracellular matrix degradation. Chen et al. (8) observed that polymorphisms in MMP-2, MMP-9, and TIMP-2 genes were significantly associated with generalized aggressive periodontitis in Chinese patients, indicating that genetic variations affecting proteolytic activity could determine disease severity. Similarly, Cao et al. (9) found a strong relationship between MMP-1 promoter polymorphism and aggressive periodontitis, suggesting that overexpression of MMP-1 contributes to connective tissue destruction through increased collagen degradation.The role of MMP-related genes was further supported by Loo et al. (10), who reported associations between MMP-1, MMP-3, MMP-9, and cyclooxygenase-2 polymorphisms with chronic periodontitis, demonstrating how these variants regulate inflammatory mediator synthesis and tissue damage. Though their study focused on chronic periodontitis, the underlying molecular pathways likely overlap with aggressive forms, given their shared mechanisms of tissue breakdown. The involvement of interleukin-10 (IL-10) gene polymorphisms has also been substantiated in several studies. Zhong et al. (11) conducted a meta-analysis and confirmed that IL-10 genetic variants are significantly associated with both chronic and aggressive periodontitis, reflecting the immunoregulatory function of this cytokine. As IL-10 serves as an anti-inflammatory mediator, reduced expression due to polymorphisms may lead to an unchecked inflammatory cascade and enhanced periodontal destruction.In a narrative review, Shukla et al. (12) elaborated on the importance of interleukin gene polymorphisms, particularly IL-1, IL-6, and IL-10, in determining the host response to periodontal pathogens. Their work emphasized that these genes influence the production of pro-inflammatory cytokines, thereby dictating individual variability in disease progression. The significance of tumor necrosis

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factor-alpha (TNF-α) and Fc gamma receptor gene polymorphisms was also highlighted by Lavu et al. (13), who observed an association between polymorphic regions of these genes and susceptibility to chronic periodontitis in an Indian cohort. Since TNF-α plays a pivotal role in bone resorption and inflammatory signaling, its genetic regulation could be crucial in explaining the more severe presentation seen in aggressive cases.The contribution of lysosomal proteases such as cathepsin C has also been recognized in genetic studies. Noack et al. (14) reported a link between cathepsin C gene variants and aggressive periodontitis, which aligns with the enzyme's established role in activating neutrophil serine proteases involved in tissue degradation. Furthermore, the role of human leukocyte antigen (HLA) polymorphisms in immune recognition has been demonstrated by Chowdhury et al. (15), who found a correlation between HLA class I and II antigens and chronic periodontitis in an East Indian population. Such findings suggest that differences in antigen presentation may determine how effectively the host mounts an immune defense against periodontal pathogens.The hereditary nature of periodontal susceptibility was already discussed decades ago. Michalowicz (16) presented one of the earliest comprehensive reviews on genetic and heritable factors in periodontal disease, emphasizing that family aggregation and twin studies supported a genetic predisposition to periodontitis. Later, de Souza et al. (17) reinforced these observations by identifying polymorphisms in the MMP-9 and TIMP-2 gene promoters, which affect enzyme regulation and tissue breakdown, further validating the contribution of proteolytic balance to disease expression. The role of innate immunity was highlighted by Emingil et al. (18), who identified Toll-like receptor (TLR) 2 and 4 gene polymorphisms in generalized aggressive periodontitis, demonstrating that variations in TLR signaling pathways may alter bacterial recognition and subsequent immune activation.Scott and Krauss (19) provided a broader understanding of the cellular mechanisms by detailing the function of neutrophils in periodontal inflammation. They emphasized that genetic variations influencing neutrophil recruitment and activity could exacerbate host-mediated tissue destruction, particularly in genetically predisposed individuals. More recently, genome-wide association studies (GWAS) have provided novel insights into genetic susceptibility to periodontitis. Gao et al. (20) conducted a systematic review of GWAS data and reported multiple candidate loci linked to immune response regulation, connective tissue integrity, and microbial recognition, underscoring the polygenic nature of periodontal disease.The role of microbial–genetic interaction has also been demonstrated. Fine et al. (21) linked Aggregatibacter actinomycetemcomitans infection with specific host genetic profiles in localized aggressive periodontitis, suggesting that genetic factors may shape the host's susceptibility to key periodontal pathogens. Complementary to this, Laine et al. (22) discussed how genetic susceptibility modulates inflammatory pathways, emphasizing that host genetics and environmental triggers jointly determine disease manifestation. Yoshie et al. (23) further expanded on this relationship by identifying various polymorphisms that affect cytokine production, immune cell signaling, and bone metabolism, all contributing to the pathogenesis of aggressive periodontitis. Kinane et al. (24) concluded that the genetic basis of periodontitis involves numerous loci controlling both innate and adaptive immune mechanisms, highlighting the complexity of its inheritance.Overall, the literature suggests that aggressive periodontitis results from a multifaceted genetic predisposition involving cytokine regulation, enzyme activity, and immune recognition. The interaction between host genetic background and microbial challenge defines disease onset and progression, and understanding these genetic markers could enable personalized risk assessment and targeted preventive strategies for young adults predisposed to aggressive periodontal disease.

Conclusion

The present study underscores that aggressive periodontitis in young adults is influenced by a complex interaction of genetic, microbial, and immunological factors. Variations in genes regulating cytokine expression, matrix metalloproteinase activity, and immune receptor function appear to significantly modulate host response and disease susceptibility. Evidence from multiple studies indicates that polymorphisms in IL-1, IL-6, IL-10, MMPs, and TLR genes are consistently associated with heightened periodontal tissue destruction. These genetic markers serve as potential diagnostic tools for early identification

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of at-risk individuals. Understanding the molecular basis of this condition may lead to more personalized therapeutic approaches. Future research integrating genomics with clinical parameters could improve early detection and prevention of aggressive periodontitis.

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