Genetics : An Insight to Periodontal Disease

1Dr. Bushra .K Quazi - M.D.S, 2Dr. M. L. Bhongade – M.D.S, 3Dr Pranav S Patil -M.D.S, 4Dr Priti Charde –M.D.S ,

Corresponding Author: Dr. Bushra .K Quazi

Abstract: Periodontal disease is a complex infectious disease resulting from interplay of bacterial infection and host response to bacterial challenge, and the disease is modified by environmental, acquired risk factors and genetic susceptibility. Molecular and Epidemiological studies of the oral microbial flora suggest that, microbial factors responsible for periodontal disease, alone cannot predict the presence or severity of the disease. Therefore, in high-risk patient groups, host susceptibility factors might play an important role in the etiology and progression of periodontal disease. Recently, host susceptibility factors, such as immune response factors, systemic disease state, and other environmental factors like smoking, have been found to be important contributors to the periodontal disease. Hence, periodontitis as a whole may represent a lifelong account of complex interactions between our genetic, our behavioral, and our environmental factors. This article, provides an overview of the most relevant literature, presenting the main concepts and insights of the strategies that have been emerging to better diagnose and treat periodontal disease based on biomarker analysis and host modulation.

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I. Introduction

Periodontitis can be defined as a chronic infectious disease of the tooth supporting tissues. The bacterial infection, resulting in inflammation of periodontal tissues, lead to further destruction by an inflammatory process. Meanwhile, teeth lose their ligamentous support to the alveolar bone leading to bone resorption, mobility and ultimately are lost as the disease progresses.1 Earlier, periodontitis was thought to be environmental in origin. However, later, it was recognized that environmental factors alone were only responsible for a part of the variability of disease in the population. Periodontal disease does not appear to be a single disease with variations in clinical symptoms but a group of diseases with overlapping symptomatology. The nature of periodontal diseases may be multifactorial. It will be quite important to consider known risk factors for periodontal disease when studying familial clustering or possible genetic mechanisms, because many risk factors for periodontal disease tend to cluster in families through genetic or culture mechanism. It will be important to identify candidate genes that may be the basis for genetic susceptibility to periodontal disease. Genes that may affect immune response to oral bacteria are the most obvious and learning more about traits that predispose to disease, such as tissue response characteristics, may provide additional clues about possible candidate genes. Identification of such genes could enable clinicians better to identify high-risk individuals for targeted prevention and treatment. In the majority of cases, the development of periodontitis in an individual depends probably on the collective presence of a number of environmental risk factors in conjunction with a number of susceptibility factors at a given time points during life. At present, the specific genetic susceptibility factors and genetic risk determinants remains largely unknown.2 This article, provides an overview of the most relevant literature, presenting the main concepts and insights of the strategies that have been emerging to better diagnose and treat periodontal disease based on biomarker analysis and host modulation on the basis of a genetic insight.

Periodontal disease

There are two major forms of periodontal disease: chronic and aggressive periodontitis. Although very prevalent, periodontal diseases are not evenly distributed across all populations, and only a small percentage, 10% to 15%, develop severe, destructive forms of periodontal diseases.3 This differential expression for periodontitis is consistent with heritable elements of susceptibility.4 Periodontal disease destruction is initiated by a bacterial challenge that triggers a susceptible host immune response. The host's response to infection depends on the nature and virulence of the pathogen, and on the bacterial species involved; some species may be more prevalent in some types of periodontitis. However, in most cases, specific microorganisms are not sufficient to cause disease. This finding indicates that environmental factors (subgingival biofilm) and genetic factors could influence the modulation of the disease activity.5-10

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Many periodontitis-related and some peri-implantitis-related genetic factors have been investigated. Disease-modifying genes are responsible for susceptibility to periodontitis. Mendelian principles do not apply to these disease-modifying genes, because both heterozygous and homozygous subjects for a given genetic variation in a gene or locus may not necessarily develop the disease. In such a complex and multifactorial disease as periodontitis, other genetic risk factors and behavioral factors must also exist simultaneously to be determinants of an individual's propensity to developing periodontitis. With this in mind, several authors have been looking into the possibility that periodontitis could be polygenic (gene–gene interactions) and multifactorial (gene–environment–life style interactions such as oral hygiene, smoking, stress and diet).

Genetic Susceptibility To Periodontitis
Genetics of both humans and pathogens and the genetic interaction between them are involved in both Periodontics and Medicine. There is increasing awareness of the destructive processes involved in periodontitis which are host-derived. These host modulated inflammatory processes leading to destruction of periodontal tissues are of great interest in research field. The information contained within the human genome can potentially lead to a better understanding of the mechanisms that modulate the host response through the production of inflammatory mediators and provide potential therapeutic targets for successful periodontal regeneration. The gene interacts directly or indirectly through its protein product with many other genes in coordinated networks, that result in striking variations in signs and symptoms among different patients with the same disease. The study and search for periodontitis-susceptibility alleles and genetic variations is complicated because: (1) Multiple causes may exist for the same disease (etiologic heterogeneity) and (2) Variations in genetic mechanisms may lead to the same clinical outcomes (genetic heterogeneity).

Genetic Variance:
Except for identical twins, we each have slightly different versions of the 30,000-40,000 genes in our cells. There are about four amino acid sequence differences per gene between any two people, which may consist of larger insertions or deletions of several base pairs. They explain why some people are more or less susceptible to an illness. Genes exist in different forms or states called Allelic variants or alleles, which differ in their nucleotide sequences and rare alleles are called mutants. When a specific allele occurs in at least 1% of the population, it is said to be a Genetic polymorphism and are considered normal variants in the population.

Evidence for the role of genetic variants in periodontitis:
Since all forms of periodontitis are associated with bacterial infections, defining the relative roles of genes and environmental factors in these complex diseases is a challenge. In case of chronic periodontitis, studies of adult twins indicate that a substantial proportion of the population variance for periodontal measures—such as pocket depth, attachment loss, and bone loss may be attributable to heritable factors. Aggressive periodontitis is often familial, and the likelihood of inheriting aggressive periodontitis is high, as family studies indicate.

Genetic approaches in the study of periodontal diseases
The approaches used in the study of periodontal diseases are:
1. Family and population studies: segregation Analysis.
2. Molecular epidemiology.
3. Twin studies.
4. Linkage Studies.
5. Association of periodontitis susceptibility with inherited disorder.
6. Association studies.
-Association with known genetic markers
-Modifying genes – serum IgG
7. Recombinant DNA technology

Genetic Disorders Associated With Gingivae And Periodontium
The genetic disorders have been grouped according to the resultant protein or biochemical defect(s); the alleles that undergo mutation may affect the function of phagocytic immune cells or the epithelium, connective tissue, or the teeth themselves. The defect in specific gene or tissue responsible for the condition has been identified for some disorders but some are yet to be identified.

Hereditary gingival fibromatosis: It is an autosomal dominant form of gingival overgrowth, found to be associated with a mutation in the SOS (Son of sevenless-1) gene. There is a frame-shift, creating a truncated protein that destroys a vital portion of the protein due to mutation.

Connective tissue metabolism Defects: It includes the disorders which alter the connective tissue matrices, their resident cells, or both that may significantly affect the tissues of the periodontium. As such, many
periodontal defects may be associated with genetic disorders such as the mucopolysaccharidoses, affecting glycosaminoglycans metabolism, mannosidosis, affecting the metabolism of glycoproteins and Ehlers-Danlos syndrome, which alters collagen synthesis.

**Skin disorders:** A number of skin disorders have been studied to have a periodontal component. For example, *Papillon-Lefèvre syndrome (PLS)* is a rare autosomal recessive disorder and is characterized by hyperkeratosis of the palms and soles, aggressive periodontitis, typically occurring in childhood. A large amount of periodontal destruction in this condition results in premature exfoliation of deciduous teeth and the permanent dentition often follows a similar fate. The mutations in the cathepsin C gene, located on chromosome 11 (11q14-q21) is believed to be responsible for PLS. It has been observed that Cathepsin C has an important role in degrading proteins and activating proenzymes in immune and inflammatory cells.

**Metabolic disorders:** *Acatasemia* is an autosomal recessive disease characterized by inability to produce catalase and hence break down hydrogen peroxide, which is a by-product of normal cell activity. The hydrogen peroxide being toxic, produces superoxide radicals that leads to tissue destruction. The periodontal tissues, where severe gingival necrosis and marked bone loss has occurred in this condition are common occurrences.

**Hypophosphatasia** being a rare disorder, is caused by mutations in the tissue non-specific alkaline phosphatase gene (lp36.1-p34) that lead to alterations in bone metabolism. It is associated with cementum hypoplasia and early periodontal disease with bone loss and tooth loss. There is premature loss of the primary teeth and occasionally the permanent teeth.

**Leukocyte function Defects:** The response of leukocytes in the periodontal milieu is important to the outcome of the Periodontal disease process. Therefore, diminished numbers of leukocytes or decreased leukocyte function by any process can lead to severe periodontal breakdown. The *neutropenias* include a family of disorders of which severe periodontal disease is a common feature.

**Chediak-Higashi syndrome** is a genetic disorder characterized by abnormal neutrophil function and is associated with severe early-onset periodontitis. It appears to have a strong pattern of familial distribution leading to impaired leukocyte adhesion.

**Chromosomal abnormalities:** *Trisomy 21 (Down syndrome)* is a chromosomal defect in which there are associated periodontal problems. It is associated with both early onset and adult type of periodontitis. A genetic contribution to the periodontal condition is noted and individuals are likely to have poor oral hygiene compared with unaffected individuals. Impaired neutrophil function is one of the most likely contributory factors to the increased level of periodontitis.

**Gene Polymorphisms In Periodontal Health And Disease**

Human gene Polymorphisms occur at one or more of the following sites: (1) 5'-flanking region or promoter region; (2) The gene coding regions or the exon; (3) The intron(s) or the gene intervening regions; (4) The 3'-untranslated region. The single nucleotide polymorphism is the most common form of polymorphisms, which is a change in a single base pair in the genomic DNA.

**Cytokine Gene Polymorphisms**

**A. IL-1 Gene Polymorphisms:** Specific polymorphism of the IL-1 gene has been reported by many investigators that have a positive association with periodontitis. However, interaction between the IL-1 genetic polymorphism and environmental factors such as smoking is still not clear. Smokers with IL-1 gene polymorphisms may be at an increased risk of developing periodontitis.

**B. Tumor Necrosis Factor-α (TNF-α) Gene Polymorphisms:** TNF-α is one of the most important widely studied cytokines in periodontitis in terms of polymorphisms and its association with periodontitis. Polymorphisms have been reported in the promoter region of the TNF-α gene at positions -238 (G to A) and -308 (G to A). High promoter activity and enhanced TNF-α production has been associated with -308 A allele.

**C. IL-10 Gene Polymorphism:** IL-10 is located in a cluster along with related interleukin genes, including IL-19, IL-20 and IL-24 on chromosome 1. IL-10 plays a role in the regulation of activities of pro-inflammatory cytokines such as IL-1, IL-2 TNF-α, IL-8. Aggressive periodontitis has been found to be associated with IL-10 gene polymorphisms.

**Hla genetics:**

The human leukocyte antigen (HLA) complex plays an important role in immune responses and may be involved in antigen recognition of periodontal pathogens. HLA class II molecules commonly have been studied on immune cells including lymphocytes and macrophages. They are responsible for interaction between T and B lymphocytes and production of high affinity IgG antibodies. The expression of various HLA antigens has been studied by several investigators in patients with different forms of periodontitis. Polymorphisms of HLA-
DR molecules in patients with periodontitis and significant association between several DRB1 alleles and the disease has been investigated.\textsuperscript{15}

3. Immuno-Receptors (FcγR Gene) Polymorphisms: Periodontitis and the association of immuno-receptors has been well studied. Receptors for the Fc domain of IgG (Fc gamma R, FcγR) provide a critical link between specific humoral responses and the cellular branch of the immune system.\textsuperscript{17} FcγRs are categorized as a family of receptors, expressed on leukocytes, that bind IgG antibodies and immune complexes. In humans, FcγRs are expressed on natural killer cells, macrophages, T lymphocytes, monocytes, and mast cells. The interaction between FcγRs and IgG triggers a variety of biological responses, phagocytosis, endocytosis, antibody-dependent cellular cytotoxicity, release of inflammatory mediators, and enhancement of antigen presentation. Majority of reports indicate that polymorphisms of FcγR gene tend to be associated with both aggressive and chronic forms of periodontitis. These alleles may be in linkage disequilibrium with a gene causing periodontitis, although it still remains unclear whether the outcome of periodontitis is associated with the functional defect of FcγRs.\textsuperscript{18}

4. Matrix Metalloproteinases (Mmp’s) Polymorphism: Matrix metalloproteinases are enzymes chiefly involved in periodontal connective tissue destruction. Despite this, there are very few reports concerning polymorphisms of genes for matrix metalloproteinases and periodontitis. Due to the limited number of studies carried out to date, it is difficult to relate single nucleotide polymorphisms of matrix metalloproteinase genes with periodontitis.\textsuperscript{19}

5. Structural Molecules (Cathepsin C): Aggressive periodontitis in prepubertal children is often associated with genetic disorders such as Papillon–Lefèvre syndrome. This syndrome is associated with mutations in the cathepsin C gene. Whether the pathogenetic role of cathepsin C gene variants also relates to types of periodontitis other than syndrome-associated periodontitis remains to be confirmed.\textsuperscript{15}

Gene Polymorphisms In Chronic (Adult) Periodontitis A study by Holla et al examined a series of polymorphisms in genes contained within the human leukocyte antigen (HLA) Class III region, including genes for TNF-β, angiotensin-converting enzyme, and endothelin-1, and found that various combinations of genotypes were associated with chronic periodontitis. It is noteworthy that many investigators have also studied relationships between periodontitis and HLA Class I and Class II antigens. However, definitive relationships have not been found to date, although several associations have been suggested.\textsuperscript{20} A polymorphism in the gene coding for an Fc receptor (CD16), FcγRIIIb, was shown to be associated with increased disease recurrence in a Japanese patient cohort. This polymorphism affects the function of polymorphonuclear neutrophils and influences their ability to utilize antibodies efficiently as opsonins; thus, this polymorphism could play a role in the patients’ ability to deal with bacterial infections. Additionally, a polymorphism in the N-acetyl transferase gene (NAT-2) has been demonstrated to have an association with periodontitis risk. This polymorphism codes for the ‘slow acetylator’ phenotype, which is known to be a risk factor for other smoking-related diseases, in particular, cancer susceptibility.\textsuperscript{21}

Gene Polymorphisms In Aggressive (Early Onset) Periodontitis Analogous to chronic periodontitis, polymorphisms in the IL-1 gene complex have been found to be associated with aggressive periodontitis. The alternative alleles imparting risk for chronic periodontitis were found to be associated with aggressive periodontitis. Also, the FcγRIIIb polymorphism in the Japanese population was found to be associated with risk for generalized aggressive (early onset) periodontitis.\textsuperscript{22} Polymorphisms in the promoter and intron regions of the gene coding for the cytokine IL-4 have been reported to be associated with early onset periodontitis. This cytokine is important in stimulating production of B lymphocytes and the consequent production of immunoglobulin G (IgG) and IgE antibodies, as well as in the differentiation of T cells. It also inhibits macrophage inflammatory responses such as IL-1 production. Polymorphisms present in the vitamin D receptor (VDR) gene, which have been correlated with both bone mineral density and bone turnover rate, were reported to be associated with localized aggressive periodontitis (but not generalized aggressive periodontitis).\textsuperscript{23} Gwinn et al reported a single nucleotide polymorphism in the gene coding for the IMLP receptor in localized aggressive periodontitis patients. This polymorphism, located in the ligand-binding region of this receptor, could explain the defective chemotaxis observed in many such patients. Finally, in 1986, Boughman et al reported that a major gene located on chromosome 4q was responsible for autosomal dominant transmission of localized aggressive periodontitis in an extended family that also exhibited dentinogenesis imperfect.\textsuperscript{24}
Host Modulation As A Treatment Strategy

The understanding of inflammation and its resolution has opened the door to the study of new periodontal treatment strategies, as more is learned about the role of the host response. Recent research has examined the inflammatory and resolution cascade in greater detail, while looking at endogenous and exogenous mediators that can be utilized to modulate the host. In this regard, new drugs warrant a new strategy for pharmacologic agents that may have beneficial effects in periodontal disease treatment. In the near future, periodontal gene therapy will be a reality for clinicians. An improved understanding of periodontal biology, coupled with current advances in scaffolding matrices, has introduced novel treatments that use cell and gene therapy to enhance periodontal tissue reconstruction and its biomechanical integration. Cell and gene delivery technologies have the potential to overcome limitations associated with existing periodontal therapies, and may provide a new direction in sustainable inflammation control, as well as more predictable results.

Problems With Genetic Susceptibility Tests
- The data demonstrate either cross-sectional or retrospective associations, not prospective data of the disease.
- The polymorphisms utilized in this test have been evaluated only in certain populations, not in all.
- The tests have limited sensitivity and specificity.
- The genes in question determine a relatively small, but significant, component of the overall risk of the disease.

Problems In Research
- Whatever be the cause of the disease, symptoms are the same.
- In majority of the cases, periodontitis is influenced by environmental risk factors, rather than solely by genetic factors.
- It is difficult to find out the recombination fraction.
- Genetic studies in relation to periodontitis are hampered by population heterogeneity and differences in patient selection and diagnostic criteria.
- Valid comparison between different studies is not possible because of the different definitions that have been used for cases of chronic and localized and generalized aggressive forms of periodontitis.

Future Of Genetic Studies In Periodontology

Prognostic tests: Clinicians tend to view the application of prognostic knowledge in the context of currently available therapeutic approaches, that is, they are accustomed to treating periodontal disease after it has occurred and try to predict whether there will be recurrent disease in the future. They could predict the initiation of disease before it occurs that ultimately will be linked to knowledge of the environmental factors that could initiate the inappropriate activation of genes that are problematic. Such tests would also be useful if they could be used to predict the ultimate success of a variety of therapies.

Diagnostic tests: The currently immutable genetic susceptibility profile for an individual can be used to develop assays of the patient’s variable gene expression profile at any given time. This would require identification of the baseline ‘activity’ of susceptibility genes in subjects with no disease and the change in activity that occurs during and as a result of initiation or progression of disease. It is conceivable that, should such tests be administered at an opportune time, subclinical disease could be detected and appropriate environmental or genetic therapies could be administered.

Gene therapy: It is a technology of introducing foreign genetic material into a patient for correcting its genomic defect. Genetic surgeons can now go deep into the cells and fix those defective genes with a new scalpel—a virus. The inherent benefit of this therapy is to permanently cure the physiological dysfunction by repairing the genetic defect.

II. Conclusion

Periodontitis is multifactorial, and researchers need to examine the role of important environmental and genetic factors simultaneously that contribute to the same. Given the large numbers of genes in the human genome and bacteria in the oral cavity, genes and the environment interact in important but as-yet unrecognized ways to alter disease risk. Until additional new knowledge emerges, one must accept the likelihood that no specific periodontal disease susceptibility resides in the genetic control of one or more aspects of the host response. As such, the high susceptibility genes responsible for periodontitis have not yet been recognized and further research is needed in this regard. The increasing knowledge of functional polymorphisms will highlight new therapeutic approaches to treat diseases and will allow the targeting of new and existing therapies to those patients who will derive the most benefit without the risk of serious side effects. Rather, it is essential to combine genetic studies with carefully conducted pre-clinical and clinical experiments to extract the true value of high-throughput genetics-based research.
References


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