Role of Genetics in Periodontal Diseases
Masamatti S. S.¹, Kumar A.², Dodwad V.³

Abstract:
Although periodontitis does not follow Mendelian inheritance patterns, evidence is mounting of important hereditary influences. As such, the search for the ‘master gene’, responsible for periodontitis, in an otherwise healthy individual has not been realized. What is evident is that periodontal disease is a consequence of the complex interactions between host factors, genetics, and the environment? Thus, interpretation of genotype status must not be used solely to alter treatment regimens and maintenance schedules. Treatment outcomes will be heavily influenced by environmental and behavioral factors, whether an individual is genetically susceptible to disease or not. Despite major advances in the awareness of genetic risk factors for periodontal disease, we are away from determining the genetic basis of both aggressive and chronic periodontitis. Nevertheless, we must exercise caution and proper scientific method in the pursuit of clinically valid and useful genetic diagnostic tests for chronic and aggressive periodontitis. We must plan our research using plausible biological arguments and carefully avoid the numerous bias and misinterpretation pitfalls inherent in researching genetic associations with disease.

Key words: Genetics, periodontal diseases, polymorphisms.

Introduction:

Periodontal diseases are a heterogeneous group of pathologies that share common clinical signs and symptoms, chiefly inflammation and destruction of the periodontium and represent the main cause of tooth loss in developed countries with increasing prevalence.

Although present in most populations, the risk for periodontal diseases is not uniform for all individuals. In periodontitis, the host-activated inflammatory and immunological cascades, which result in the destruction of connective tissue and bone are under genetic control¹. Thus, it is now evident that there exists a genetic basis for periodontitis.

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Etiological Complexity of Periodontitis:

Environmental Factors

Plaque

Smoking, stress

Specific

Non-

Susceptible

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.

Polymorphism vs. Mutation:

A polymorphism is a genetic variant that appears in at least 1% of a population and arises from mutation. 90% of polymorphisms come from Single Nucleotide Polymorphisms (SNPs) where a single base of one nucleotide is substituted with another. Many Single Nucleotide Polymorphisms that occur in genes, do not change the protein product, but have an effect on the gene product.

Methods of Genetic Analysis:

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[2]. 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[3].
Genetic syndromes predisposing to periodontitis:

A series of genetic syndromes are known to be associated with either premature tooth loss due to periodontitis or a phenotype resembling aggressive periodontitis.

<table>
<thead>
<tr>
<th>Genetic syndromes</th>
<th>Aggressive Periodontitis</th>
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<tbody>
<tr>
<td>Ehlers–Danlos syndrome type 8</td>
<td>Collagen folding defect</td>
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<tr>
<td>Cathepsin C gene on chromosome 11q14-q21</td>
<td>Papillon–Lefèvre syndrome, Haim–Munk syndrome</td>
</tr>
<tr>
<td>Mutations in alkaline phosphatase gene</td>
<td>Hypophosphatasia, Alkaline Phosphatase Deficiency</td>
</tr>
<tr>
<td>LAD1 (Integrin), LAD2 (Selectin) gene defect</td>
<td>Leukocyte Adhesion Deficiency</td>
</tr>
<tr>
<td>OCRL1 gene, X–chromosome</td>
<td>Lowe syndrome</td>
</tr>
</tbody>
</table>

Genotype Polymorphisms in periodontal disease:

Inflammatory and anti-inflammatory cytokines:

A large body of in vitro and in vivo analyses\[^4\] of human tissues as well as studies in animal models strongly support that cytokines play a key role at all stages of the immune response in periodontal disease.

Clinical utility of a genetic susceptibility test for severe chronic periodontitis:

In this regard, a relatively new genetic susceptibility test\[^10\] (Periodontal Susceptibility Test, Interleukin Genetics Inc.) has become commercially available to assess a patient’s risk of developing severe chronic periodontitis.

It detects the simultaneous presence of two interleukin genes - allele 2 at the IL 1 A + 4845 and IL 1 B + 3954 loci. Patients are referred to as being “genotype-positive” if both of these alleles are present.

Additional prospective clinical trials are needed to determine the risk of developing periodontitis or peri-implantitis when allele 2 at the IL1A+4845 and IL1B+3954 loci are present.

Therefore, it is unclear how results of the genetic susceptibility test can be used to alter patients’ periodontal maintenance schedules or to change treatment regimens in periodontally symptomatic or asymptomatic patients.
**Interleukin-1**

IL-1 gene polymorphisms were the first described genetic markers related to periodontal disease in 1997. The three cytokines originally described as the members of the IL-1 family were IL-1α and IL-1β, which have agonist activity, and IL-1Ra, a physiologic antagonist. These functionally similar molecules are encoded on separate genes in the same region of chromosome 2. Two single-nucleotide polymorphisms were identified in IL-1 gene cluster, a C to T transition at position – 889 in the IL-1α and the second at +3954 of IL-1β gene.

**Dental Implants**

Investigations in patients with polymorphisms of IL-1α and IL-1β genes with IL-1β – 511 2/2 genotype exhibited a significantly higher occurrence of marginal bone loss.

**Intrabony defects**

Influence of IL-1 gene polymorphism on clinical and radiographic healing outcomes of GTR therapy did not reveal any statistically significant differences between IL-1+ and IL-1– patients.

<table>
<thead>
<tr>
<th>Interleukin-2</th>
<th>It is established that – 330 (T→G) polymorphism in IL-2 gene is associated with severity and active role in pathogenesis of periodontal disease.</th>
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<tbody>
<tr>
<td>Interleukin –4</td>
<td>Evaluation of IL-4 gene polymorphisms in the intron 2 and in the promoter region (PP +and IP+) showed no association with periodontal disease susceptibility.</td>
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<tr>
<td>Tumor necrosis factor -α</td>
<td>Research to investigate 4 polymorphisms in TNF- α gene which were all transitions from G to A, 3 in the promoter positions: – 376, – 308, – 238 and at position + 489, could not be identified as susceptibility or severity factors in periodontitis.</td>
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<tr>
<td>Interleukin-10</td>
<td>Three single-nucleotide polymorphisms (SNPs) in the IL10 gene at positions – 1087, a G to A substitution, – 819, a C to T substitution and – 592, a C to A substitution have been associated with altered synthesis of IL10.</td>
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<td>HLA Genetics</td>
<td>The MHC genes are the most polymorphic genes present in the genome of every species. Studies suggested that patients with HLA-DRB1<em>1501-DQB1</em>0602 genotype may have accelerated T cell response and increased susceptibility to periodontitis.</td>
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<td>FcγReceptor polymorphisms</td>
<td>When one or several of FcγR-mediated leukocyte functions are less or over efficient due to polymorphisms, it is conceivable that susceptibility for or severity of periodontitis is seen.</td>
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<tr>
<td>Vitamin D receptor (VDR) polymorphisms</td>
<td>Studies demonstrated vitamin D receptor (VDR) gene is localized in chromosome 12 with a cluster of polymorphisms: BsmI, ApaI and TaqI and relationship between TaqI VDR gene polymorphisms and periodontitis.</td>
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<td>Matrix metalloproteinases (MMP) polymorphisms</td>
<td>A single nucleotide polymorphism in the promoter region of -1607 bp of MMP-1 gene a, 5'-GGA-3', instead of 5'-GAT-3' has been found to be associated with increased risk of generalized aggressive periodontitis.</td>
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Conclusion:

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. It should be emphasized, however, that although it is anticipated that high-throughput genetic studies will provide novel biological insights into disease, it is not a replacement for careful hypothesis-driven experiments. 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: