

## Periodontal disease: a genetic perspective\*

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**Abstract:** Periodontitis is a multifactorial disease that causes tooth loss. The complex pathogenesis of periodontitis implies the involvement of a susceptible host and a bacterial challenge. Many studies have provided a valuable contribution to understanding the genetic basis of periodontal disease, but the specific candidate genes of susceptibility are still unknown. In fact, genome-wide studies and screening of single-nucleotide polymorphisms have yielded new genetic information without a definitive solution for the management of periodontal disease. In this manuscript, we provide 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.

**Descriptors:** Periodontitis; Genetic Predisposition to Disease; Diagnosis; Risk Factors.

### Introduction

The aim of this manuscript was to publish the content of the presentation on “Periodontal Disease: a genetic perspective.” A review of the genetic background factors related to periodontal disease and the potential applications of this accumulated knowledge in the diagnosis and treatment of periodontal disease are included.

Currently, researchers and clinicians are seeking genetic evidence to explain the differences in susceptibility to periodontal disease, in the rate of clinical attachment loss and in the severity of bone loss observed in periodontal patients. New data would help understand the pathogenesis of periodontal disease, and would directly impact the treatment options and prognosis. Additionally, any compelling information could help develop new diagnostic tools and therapy strategies for prevention, host modulation and treatment of the disease.

### Periodontal disease

There are two major forms of periodontal disease: chronic and aggressive periodontitis. Briefly, periodontitis is a chronic and multifactorial polymicrobial infection initiated by the presence of bacteria, which accumulates in the gingival crevice region. Periodontopathogenic bacteria cause gingival inflammation, which may lead to the destruction of the periodontal ligament and the adjacent supporting bone, resulting in tooth loss.<sup>1-4</sup>

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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.<sup>5</sup> This differential expression for periodontitis is consistent with heritable elements of susceptibility.<sup>6-9</sup>

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.<sup>1,3,5,8,10</sup>

Many periodontitis-related and some peri-implantitis-related genetic factors have been investigated.<sup>11-13</sup> 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.<sup>14</sup> 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).<sup>14,15</sup>

### **Evidence of the genetic component in periodontal disease**

The first evidence that genetics plays a role in periodontal disease emerged in the 90s. This new information introduced new concepts such as susceptibility and predisposition to periodontal disease.<sup>8,16</sup>

A key determinant of whether individuals develop periodontitis appears to be governed by the way they respond to their microflora. Therefore, genetic factors modulate how individuals interact with many environmental agents, including biofilm, to

determine susceptibility to periodontitis. The interplay of genetic and environmental factors, and not the genes alone, determines the outcome. Bearing in mind this intrinsic characteristic, lifestyle factors pave the way to developing the disease.<sup>5,14</sup>

## **Genetic background**

### **Mutations**

Specific mutations have been identified as defining the genetic basis of various syndromic conditions, for example, the cathepsin-C gene in Papillon-Lefèvre syndrome, the CHS gene in Chédiak-Higashi syndrome, and the beta-2 integrin chain gene in leukocyte adhesion deficiency type 1. The association of severe periodontitis with syndromic conditions demonstrating simple genetic (Mendelian) transmission indicates that genetic mutations of single genes can greatly increase susceptibility to periodontitis in these patients.<sup>5,8</sup> However, these genetic diseases are rare and do not characterize the most common forms of periodontitis.<sup>5</sup>

While genes of major effect appear etiologic in aggressive periodontitis and some syndromic forms of periodontitis, there is also evidence of smaller contributions by genes that may modify periodontal disease expression.<sup>9</sup> Other important factors, such as environmental (particularly smoking) and microbial agents (virulence factors), also modify disease risk and expression.<sup>3-5,17</sup>

### **Polymorphism**

The major genetic factors in complex disease models are not single mutations that dramatically change a gene or its product, but rather, those that involve more subtle genetic changes that may slightly alter the expression or function of a gene product. Because these gene variants (alleles) alter susceptibility to disease, they are referred to as functional variants.<sup>3,5</sup> Many functional variants occur with a relatively high frequency in the general population. When a specific allele occurs in at least 1% of the population, it is said to be a genetic polymorphism.<sup>15</sup> More than 10 million single nucleotide polymorphisms (SNPs) have been identified in the human genome.<sup>5</sup>

Polymorphism arises as a result of mutation. The

different types of polymorphisms are typically referred to by the type of mutation that created them. The simplest type of polymorphism results from a single base mutation which substitutes one nucleotide for another, and has recently been termed as a single nucleotide polymorphism (SNP). Other types of polymorphism are restriction fragment length polymorphism (RFLP) and simple tandem repeats (STRs), consisting of relevant allele or nucleotide repetition.<sup>3,15,18</sup>

Genetic polymorphisms are very useful in genetic studies of the population. Frequencies of genotypes and alleles may differ between a diseased group and a healthy group. Subsequently, when a given allele is identified as associated with a disease, functional studies may be conducted to investigate the possible role of that gene in the etiology and pathogenesis of the disease.<sup>14,15,19</sup>

A number of SNPs are likely to be important determinants in disease susceptibility for the more common, genetically complex diseases such as chronic periodontitis.<sup>11,13</sup> In this model, a single functional genetic polymorphism associated with disease (at a population level) is not sufficient to cause disease, and is therefore not deterministic of disease in itself. Consequently, such a functional polymorphism may be found in individuals who have no evidence of disease and who may not be at great risk for disease. A fundamental characteristic of this genetic model is that such genetic polymorphisms are more frequent in the population than are mutations, and the correlation between genetic polymorphisms and disease is generally much weaker than the relationship between a functional mutation and a disease phenotype.<sup>5,15,20</sup>

## Epigenetics

Epigenetics is described as the study of changes in patterns of gene expression, which do not involve changes in the DNA sequence. Epigenetic events act through chemical modifications of DNA and its associated proteins by blocking the binding of transcription factors through histone modifications (considered more transient) or DNA methylation (stable form of gene regulation).<sup>1,21</sup>

Studies evaluating the methylation pattern of cy-

tokine genes may have relevance for inflammatory diseases in which the expression of some cytokines is altered, such as in periodontal disease.<sup>1</sup> Preliminary findings suggested that the IL-6 gene is hypomethylated in tissues of individuals with periodontal disease, compared to control samples, suggesting an overexpression of this cytokine in inflamed tissues.<sup>1</sup> Additionally, the overexpression of IL-6 might exert an epigenetic influence. These findings are important since IL-6 is a key cytokine involved in bone resorption, and has been detected in high levels in individuals with severe periodontitis.<sup>1,22</sup>

Interestingly, it is speculated that persistent inflammation and bacterial infection may also cause DNA methylation, which inactivates suppressors of cytokine signaling and contributes to exaggerated cytokine signaling.<sup>1,23</sup>

## Studies designed to investigate heritability

The studies that show evidence of genetic predisposition to periodontitis can be grouped into four areas of research based on the statistical approaches to determine genetic components, genetic model and study design:<sup>5</sup>

- (i) the study of inherited diseases and genetic syndromes,
- (ii) family studies,
- (iii) twin studies, and
- (iv) population studies.

For example, family patterns of disease have been analyzed in order to study aggressive periodontitis and syndromic forms of periodontitis. Twin study designs have been used to investigate chronic periodontitis. Such approaches allow tests of hypotheses to be conducted regarding disease heritability and mode of transmission, but they do not identify the specific genes involved.<sup>5,24,25</sup>

## Study of inherited diseases and genetic syndromes

Gene-mapping approaches are used to identify genes involved in Mendelian single gene disorders or to identify the genes of major effect involved in dis-

orders such as aggressive periodontitis. These studies can also demonstrate the role of specific genes.<sup>5,25</sup>

Some monogenic syndromes are associated with severe periodontal disease (acatalasia, hypophosphatasia, Chédiak-Higashi syndrome, chronic neutropenia, leukocyte adhesion deficiency, cyclic neutropenia, Ehlers-Danlos syndrome and Papillon-Lefèvre syndrome).<sup>26-28</sup> These conditions share the same genetic principle: they are inherited as simple Mendelian traits and are usually caused by genetic alterations of a single gene locus. The significance of these conditions is that they clearly demonstrate that a genetic mutation at a single locus can impart susceptibility to periodontitis.<sup>25</sup>

However, in contrast to non-syndromic forms of periodontitis, these conditions have periodontal disease manifestations as part of a collection of syndromic manifestations. In most cases of non-syndromic aggressive periodontitis, individuals present with clinical manifestations of periodontitis, but do not appear to have any other clinical disease manifestations.<sup>3,26,27</sup>

### Family studies

Familial aggregation of severe non-syndromic aggressive periodontitis is not an unusual finding. Genetically speaking, aggressive periodontitis conditions may be more complex than the simple Mendelian syndromes. Formal genetic studies (segregation analysis and linkage analysis) indicate that there are multiple different genetic forms of aggressive periodontitis, but it is currently unclear how many genes may be involved in these non-syndromic forms of disease.<sup>5,25,29,30</sup>

This aggregation within families strongly suggests a genetic predisposition.<sup>29</sup> It is important to mention that familial patterns may also indicate exposure to common environmental factors within these families. Thus, it is important to consider the shared environmental and behavioral risk factors in any family. These would include education, socioeconomic grouping, oral hygiene, possible transmission of bacteria, diseases such as diabetes, and environmental features such as passive smoking, sanitation etc. Therefore, the complex interactions between genes and the environment must also

be considered in the evaluation of familial risk for periodontal diseases.<sup>3</sup> In chronic periodontitis, the phenotype or disease characteristics do not present significantly until the third decade of life, thus adding other confounding factors.<sup>3,4,19</sup>

### Twin studies

Studying phenotypic characteristics, primarily of monozygotic twins, is a method of differentiating variations due to environmental and genetic factors. Monozygotic twins are genetically identical and always the same sex. Therefore, any discordance in disease between twins must be due to environmental factors.<sup>8,26</sup> Any discordance between dizygotic twins could arise from environmental and/or genetic variance. Therefore, the difference in the discordance between monozygotic (MZ) and dizygotic (DZ) twins is a measure of the effects of the excess shared genes in monozygotic twins, when the environmental influence is constant.<sup>17,26,31</sup>

In a study based on 110 pairs of adult twins, a significant genetic component was identified. Authors suggest that 38–82% of the population variance for probing depth (PD), attachment loss (AL) and dental plaque may be attributed to genetic factors.<sup>32</sup> A subsequent study on 117 pairs of adult twins (64 MZ and 53 DZ pairs) revealed that approximately half of the variance in disease in the population is attributed to genetic variance. For all clinical measures, MZ twins were more similar than DZ twins.<sup>17,33</sup>

### Population studies

Environmental or behavioral risk factors for a disease are often first detected in large epidemiological or population-based studies. The frequencies of polymorphisms of candidate genes, whose protein products play a role in the inflammatory or immune response, can be compared between cases and controls. A significant difference in the frequency of a specific polymorphism, between a diseased group and a control group, is evidence that the candidate gene plays some role in determining susceptibility to the disease. This method can help elucidate the pathogenesis of a disease process, identify causal heterogeneity, and ultimately identify individuals

most at risk for the disease.<sup>4,14,26</sup>

There is no evidence of any simple pattern of genetic transmission that would support an etiologic role for a single gene mutation in chronic periodontitis. Whether a genetic disease is “simple” or “complex” has important implications for disease-associated gene discovery. It is much more difficult to identify and rigorously demonstrate an etiologic role for a specific gene in a complex genetic disorder. In contrast to simple genetic diseases that may be caused by a single genetic mutation, it is likely that the additive effect of multiple genes is a determinant of disease susceptibility in complex diseases such as chronic periodontitis.<sup>3,5,26</sup>

## **Applications of genetic knowledge to periodontal disease**

At least 50% of periodontitis susceptibility is credited to heredity or genetic factors.<sup>17</sup> Clinical observations, as well as scientific studies, have shown that the heredity of a host response pattern may be an important susceptibility factor in developing periodontal diseases.<sup>6,17,24,30</sup>

Additional information from new technologies, such as micro-arrays and DNA-sequencing, should contribute to the identification of specific genetic, environmental, and behavioral factors that influence periodontitis susceptibility.<sup>34</sup> In order to apply these potential new discoveries to improving the management of periodontal disease, we must not only be able to identify genetic determinants, but also learn how to safely control or modulate the host response by inducing a desired immune response, or even blocking the progression of the disease by shutting down activating factors of bone resorption.<sup>2,35,36</sup>

## **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.<sup>37,38</sup> 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.<sup>37</sup>

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.<sup>2,39,40</sup>

## **Genetic test for periodontal disease**

Chronic periodontitis is likely to be a complex genetic disease. Therefore, there are challenges to developing clinically relevant diagnostic or screening tests for chronic periodontal diseases, because genetic polymorphisms that contribute to disease susceptibility are individually not deterministic of disease.<sup>5,11</sup> Single genes may contribute to susceptibility, but since we have many interactions at the gene-gene and the gene-environmental levels, the real contribution to disease outcome might not be decisive.<sup>5,14</sup>

Although it is possible to perform genetic testing for several syndromic forms of periodontitis, there is no evidence that mutations in the genes responsible for these conditions are responsible for the more prevalent forms of non-syndromic aggressive or chronic periodontitis.<sup>5</sup>

Because chronic periodontitis appears to be genetically complex, studies have focused on evaluating polymorphisms instead. A number of genetic polymorphisms have been studied for their association with chronic periodontitis, including several interleukin (IL) genes; the vitamin D receptor; the FcγRIIb-NA1 gene; the tumor necrosis factor-β gene; and several human leukocyte antigen (HLA) variants.<sup>3,5,11-13,15,18,41</sup> However, none have proven to be strongly predictive as diagnostic or prognostic markers to identify patients within the general population who are at risk, hampered by population

heterogeneity and different disease criteria.<sup>5,15</sup>

### Diagnosis of periodontal disease activity

The comprehensive study by Demmer *et al.* published in 2008 analyzed the whole genome to show the differential gene expression of healthy and diseased periodontal sites. They found thousands of up- or down-regulated genes in disease compared to health, including apoptosis, antimicrobial response, antigen presentation, regulation of metabolic process, signal transduction, and angiogenesis.<sup>42</sup> Although the pathogenesis of periodontitis and its episodic nature are well understood, the application of this information in diagnostic tests is still limited. Alternatively, the understanding of the genetics and progression of periodontal disease has provided valuable information for the identification of disease markers.<sup>10,38,43</sup>

Currently, the detection of disease biomarkers in saliva has proved a very promising diagnostic tool to screen oral and systemic health. Therefore, the monitoring of the qualitative changes in the com-

position of these biomarkers may have a diagnostic value, by identifying patients with enhanced disease susceptibility and associated systemic conditions, identifying sites with active disease, predicting sites that will have active disease in the future and/or serving as surrogate end points for monitoring the effectiveness of therapy.<sup>10,22,43</sup>

### Conclusion

With the new available technologies and the fast growing body of related knowledge, the prospects are very promising. The genetic basis of periodontal disease is moving from experimental evidence to a more consistent translation effect on diagnosis and development of new strategies to modulate the host.

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