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Genetics in Periodontics: A Review

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Abstract: ***Periodontal diseases are complex diseases with multifactorial etiology. While microbial and other environmental factors initiate and modulate periodontal disease, individuals respond differently to common environmental challenges, This differential host response is influenced by the individual's genetic makeup. Susceptibility to periodontal disease and the severity of the disease results from the interactions of genetic mutations and polymorphisms. This review presents various genetic factors and methods used to delineate the various periodontal diseases and genetic associations. There is a need to design studies that examine the role of important environmental and genetic factors simultaneously.***

Keywords: genetics, aggressive periodontitis, chronic periodontitis, periodontics, Periodontal diseases, multifactorial etiology

1. Introduction

Periodontitis**,** a complex disease characterized by gingival inflammation and alveolar bone resorption, [1]was traditionally, thought to be strictly of environmental origin. Later, it was realized that just a part of the inconsistency of disease in the population could be described by the environmental factors alone.[2] In a classic study by Löe et al, [3] it was found that from among people with poor oral hygiene who had no access to dental care, some developed disease at a high rate while others had mild to no disease. This difference was then attributed other factors including differences in susceptibility of host to disease. Due to susceptibility being directly related to genetics of the individual, it is now a topic of emphasis in periodontology. Elaboration of the genetic foundation of periodontitis is imperative for a better understanding of disease etiology, proper classification and diagnosis and customized treatment planning[2]

Types of Genetic Diseases[4]
Based on the pattern of transmission, genetic diseases are divided into two broad groups.

Simple mendelian diseases are relatively rare (<0.1%) types of diseases which follow a classic Mendelian mode of inheritance (autosomal dominant, autosomal recessive or X-linked). In most cases, genetic alterations at a single gene locus are the major factor responsible for the phenotype of the diseases. Examples include papillon–lefe`vre syndrome, cleidocranial dysplasia, amelogenesis imperfecta and crouzon syndrome.

Complex genetic diseases are relatively common (prevalence of greater than 1%) type of diseases that do not follow a simple pattern of familial transmission. These result from interaction of alleles at multiple different gene loci and environmental factors are etiologically important for the development of these diseases.

Polymorphism Vs. Mutation

Mutations are individual genetic changes causing the disease which are result of a genetic alteration altering protein's function. These are rare and are present in less than 0.1% of the population.[4]

Genetic polymorphisms are alleles occurring in at least 1% of the population and are considered to be normal variants in the population.[4]

Single nucleotide polymorphisms (SNPs) are commonly occurring (1 in 1000 base pairs) single-nucleotide base-pair substitutions.[4]

Methods of Genetic Analyses
A variety of techniques are used by geneticists to demonstrate the genetic basis of disease. **Table 1**[5] summarizes the important features of the techniques

Table 1

Candidate gene approach	A gene-mapping approach that tests if or not one allele of a gene occurs more frequently in patients with the disease than in individuals without the disease. Also known as association analyses, these methods identify the genes associated with the disease. Candidate genes are chosen on the basis of their presumed function. .
Case– control studies	These are the studies in which the genetic makeup is compared between cases, i.e., individuals having the disease and controls, i.e., individuals having the disease. The populations need to be matched carefully for such comparisons.
Twin studies	These include comparisons of traits including diseases in monozygotic and dizygotic, or both types of twins to determine cause of variation in the trait among members of a population. The cause may be genetic variation in inherited DNA sequences or environmental exposures of the subjects or a combination of both.
Familial aggregation and relative risk	The degree of clustering of genes within the family can be assessed by comparing the number of disease cases in patients' family to the disease risk in the general population. This approach can be difficult as family members have many genes in common. Also, there is a sharing of a common environment in aspects such as diet, nutrition, smoking, infectious organisms and shared socioeconomic factors.
Segregation analyses	It is the statistical analyses of the patterns of transmission of a disease in families to assess the likelihood of the disease being caused by a single gene with dominant or recessive inheritance, by multiple genes, or by variation in exposure to risk factors. It cannot differentiate between genetic effects and environmental grounds of disease. Also, it is not aimed to

	find a specific gene that is responsible for a trait.
Linkage analysis	These are the studies grounded on the fact that genes located close to each other on the chromosome have a tendency to be inherited together as a unit. As such, these genes are said to be "linked. " These initially require the use of expensive DNA markers and hence are only applied after a strong evidence of a genetic basis for a trait has been found by segregation analyses or family aggregation. This approach has little power for detection, whereas association analysis methods may still be quite powerful.
Genome wide analyses	A genome-wide association study (GWAS) has the aim of identifying genetic associations related to a trait or disease of interest by investigating genetic variation across the entire genome simultaneously. It is the Human Genome Project completed in in 2003 and the development of technologies enabling the assaying of more than half a million single nucleotide polymorphisms that have made GWAS possible.

Evidence for the Role of Genetic Variants In Periodontitis

The genetic makeup of an individual is a vital factor affecting their systemic or host response-related risk. The interactions between genes and environment are complex and are difficult to quantify, but are important while considering the risk for the periodontal diseases.

Aetiologic heterogeneity, i.e., existence of multiple causes of same disease and **genetic heterogeneity,** i.e., same clinical endpoint of different genetic mechanisms are the factors complicating the search for periodontitis-susceptibility alleles.

Syndromic Forms of Periodontitis

Severe periodontitis appears as clinical manifestation of various monogenic syndromes whose gene mutation and biochemical defect is known. These are inherited as simple Mendelian traits as there is genetic alteration of a single gene locus. This implies that a genetic mutation at a single locus can render individuals susceptible to periodontitis.

Aggressive Periodontal (AP) Diseases

The risk for aggressive periodontitis seems to be heritable to a large extent. Aggressive periodontitis is a constantclinical finding of several genetic disorders. **Hypophosphatasia** is a rare disorder caused by mutations in the tissue-nonspecific alkaline phosphatase gene causing deficiency in alkaline phosphatase activity resulting in features such as abnormal bone mineralization, skeletal anomalies, and cementum hypoplasia. Both autosomal dominant forms and recessive forms have been reported. Data from Baab et al[6] also suggests that hypophosphatasia might be considered in the etiology of some forms of aggressive periodontitis. **Papillon-Lefèvre syndrome (PLS)** is caused by mutations in the cathepsin C gene, which is located on chromosome 11 (11q14-q21). The periodontal destruction in PLS patients has been found to be arrested by elimination of Aggregatibacter actinomycetem comitans suggesting that aggressive periodontitis in PLS is the consequence of a bacterial infection in a host with high susceptibility rather than any genetic mutation. Other genetic disorders associated with aggressive periodontitis are neutropenia, genetic agranulocytosis, Cohen's syndrome and Ehlers–Danlos syndrome.

Segregation analyses

Despite variable outcomes regarding the mode of inheritance, segregation analyses have suggested the major role of a gene in the etiology of aggressive periodontitis. Clustering of aggressive periodontitis in families suggests but does not prove the genetic basis of disease as because family members share harmful components of their environment as well.

Linkage studies

Boughman et al. (1986) [7] first reported linkage between and specific region on chromosome. He reported segregation between aggressive periodontitis and dentinogenesis imperfecta. However, Hart (1993) [8] denied the possibility of any such occurrence. To date, a gene of major effect for aggressive periodontitis has not been identified.

Association studies

The human leukocyte antigens (HLA) have been considered as candidate genetic risk markers for AP disease. HLA-A9 and B15 are the two antigens found to be consistently associated with AP diseases. The risk of disease in subjects with HLA-A9 or B15 is about 1.5 to 3.5 times greater. The HLA-A2 antigen, appears to be less prevalent in patients with aggressive periodontitis than in controls, suggesting it to be protective.

Chronic Periodontitis

Correlations within families (e. g., sibling, parent-offspring) were used to estimate genetic and environmental variances for periodontitis among various racial groups in Hawaii. Similarities within families were found to be caused by shared cultures and family environments and not shared genes. **Beaty et al** reported similar results in a sample comprised mostly of African Americans.

Twin studies

Michalowicz et al.[9] studied dizygous twins reared apart (dizygous-A) and reared together (dizygous-T) and monozygous twins reared apart (monozygous-A) and reared together (monozygous-T). The mean probing depth and clinical attachment level scores were found to vary less for monozygousT than for dizygous-T twin pairs, further supporting the role of genetics in this disease. It was concluded that genetics plays a role in susceptibility to periodontal disease. In another study of 117 adult twin pairs, **Michalowicz and coworkers**[10] estimated genetic and environmental variances and heritability for gingivitis and chronic periodontitis. The basis for the heritability of periodontitis was found to be biological and not behavioral. In adults, however, neither host genes nor early family environments appear to have a significant influence on the presence of periodontal bacteria in subgingival plaque. It can thus be concluded that although host genes may influence initial bacterial colonization of the oral cavity, the effect does not persist into adulthood.

2. Association Studies

Kornman et al.[11] reported that a "composite" IL-1 genotype, consisting of at least one copy of the rarer allele at both an IL-1α and IL-1β loci, was associated with severe periodontitis in Northern European adults. **Galbraith et al.**[12] found no association between CP and TNF-α polymorphisms, although one genotype was correlated with elevated TNF-α production by oral PMNs in patients with advanced disease. Similarly, **Engebretson et al**[13] reported a difference in the amount of IL-1 in the gingival crevicular fluid of patients with periodontitis who were positive for the composite IL-1 genotype. A more recent study found the IL-1 genotype to be associated with disease in smokers but not nonsmokers. Thus, although smoking and the IL-1 genotype appear to interact to affect risk for periodontitis, the nature and direction of this interaction are poorly understood. The IL-1 composite, which has been associated with chronic disease does not appear to increase the risk for aggressive periodontitis.

Clinical Implications of Genetic Studies

Genetic tests may prove useful in early identification of patients who are most likely to develop disease, suffer from recurrent disease, or suffer tooth loss as a result of disease. Knowledge of specific genetic risk factors could enable direct environmental based prevention and treatments of disease in susceptible individuals. New treatment strategies can be developed to directly counter the deleterious effects of risk alleles.

Interleukin-1 Composite Genotype in Periodontitis

Reports on this composite genotype have been mixed and it can be concluded that it appears irrelevant in aggressive periodontitis but may be in linkage disequilibrium with the gene contributing susceptibility to chronic periodontitis. It may be part of several involved in the genetic risk for chronic periodontitis;

3. Conclusion

Simple or Mendelian genetic traits generally occur when a single gene defect disrupts the normal function of a protein sufficiently to cause a disease or syndrome. Complex genetic diseases occur when allelic variants of multiple different genes act synergistically with environmental factors to increase or decrease the likelihood of developing a disease. While there have been dramatic successes in identification of mutations responsible for rare syndromic forms of periodontitis, few genetic polymorphisms reported for more complex genetic forms of periodontitis have been demonstrated to be clinically valid or to have clinical utility. A review of genetic associations reported for more common forms of periodontitis reveals that we are still some way from determining the genetic basis of either aggressive or chronic periodontitis.

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