Review Article

Role of Genetics in Periodontal Disease

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Abstract

Periodontitis is a multifactorial disease affecting the tooth-supporting tissues. It is associated with an interplay between bacteria, host response, and environmental factors. As you see family history in Aggressive Periodontitis, we can suggest the role of genetics in the pathogenesis of periodontal disease. It is proved that genetic factors impair the immunoinflammatory response. Identifying the specific gene will help prevent disease progression. The aim of the present review is to focus on the role of genetics in periodontal disease.

Keywords: Genetic studies,Genetics inflammation,Periodontitis,Polymorphism.

Introduction

Periodontitis is a multifactorial disease affecting tooth-supporting tissues, resulting in attachment loss and bone loss. The progression of periodontitis depends on plaque biofilm present in the gingival sulcus, and specific bacteria form other risk factors. Environmental factors, such as smoking, systemic factors, and genetic factors, also have a role in disease progression. Current research on risk factors focuses on genes of immunoregulatory molecules, such as cytokines, chemokines, membrane surface receptors, and antigen recognition proteins.[1]

Cytokines such as interleukins (IL-1A, IL-1B, IL-6, and IL-10, among others), surface receptors such as the Fcγ family, and cyclooxygenase-2 and matrix metalloproteinase (MMP) are considered main factors in the progression of periodontitis. They cause recruitment, differentiation, activation of B lymphocytes, formation of inflammatory infiltrate, and stimulation of the osteoclasts. Any polymorphisms in these molecules influence the risk of developing the disease.

Host immunity is regulated by many determinants which are intrinsic and acquired, including the genetic susceptibility of the host. Chronic inflammatory diseases are associated with many disease-associated genetic variants (single nucleotide polymorphisms).[2-4] Epigenetic modifications of DNA can be inherited and can be intrinsic. Age, microbiota, diet, systemic conditions (e.g., obesity, diabetes, osteoporosis, and depression), environmental factors (e.g., pollution), as well as modifiable risk and lifestyle factors, such as smoking, stress, and alcohol intake, can induce epigenetic changes.[5].

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The major epigenetic modifications are DNA methylation, and histone modification involving acetyl, methyl, and phosphate groups, leading to alteration in the normal molecular structure of DNA and remodeling of chromatin. In chronic inflammatory diseases, epigenetic mechanisms, such as single nucleotide polymorphisms, contribute to gene expression and function, altered immune function, and the magnitude of the inflammatory responses. Periodontitis is not uniform throughout life. There will be a burst of disease activity followed by a quiescent period. Homeostasis changes, where aging, epigenetic modifications, and comorbidities alter the immune function of the host.

Host Response in Periodontitis

Hyperresponsive immune function is the main component in the pathogenesis of periodontitis. Excessive inflammatory reactions lead to dysbiotic changes, concomitant with periodontal tissue destruction and alveolar bone loss. Polymorphonuclear neutrophils (PMN) contribute to destruction in periodontitis. Their hyperfunction is seen in aggressive periodontitis. Hyperactive neutrophils contribute to bone destruction by stimulating osteoclastic activity when they are close to the alveolar bone. Neutrophils are involved

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in the chemotactic recruitment of Th17 cells, which mediate and direct the activity of osteoclasts, which in turn cause bone loss.[6]

In severe, early-onset forms of periodontitis, neutrophils are hyperactive. Decreased neutrophil chemotaxis and calcium uptake seem to be a comorbidity associated with hyperactive neutrophils. Aberrations in phagocytosis, respiratory burst, and intracellular killing have been reported. Certain mutations cause a rare form of periodontitis. Papillon–Lefèvre syndrome, lazy leukocyte syndrome, leukocyte adhesion defect syndrome, and other congenital diseases are considered special forms of periodontitis where specific neutrophil functions are altered or absent.[7] Decreased production of immunoglobulins is another factor affecting the immune system.

Syndromes and Periodontitis

These syndromes result in alteration in immune system which further enhance susceptibility of individual to gingival inflammation, clinical attachment loss and bone loss. Neutrophils form the first line of defense in periodontitis. Any abnormality in the action of neutrophils aggravates the periodontal disease. In LAD, lazy leukocyte syndrome, and Down syndrome, we can see abnormalities in the actions of neutrophils. Several genetic and acquired conditions are associated with gingival enlargement, gingival bleeding, gingival fibromatosis, alveolar bone, and tooth loss.

Genetics and Periodontal Disease

In periodontitis, different individuals exhibit a varied response to microbial and environmental factors due to the complex interplay between the host immune system composition of the microbiome and external influence, which in turn depends on genetic profile. Genes have a clear role in the progression of periodontal diseases. The severity of the periodontal disease results from the interaction between genetic mutations and polymorphisms with environmental agents. The human genome is made of 23 pairs of chromosomes which are located in the cell nucleus and a small chromosome in the mitochondria. It comprises 3 billion DNA base pairs. Gene is a specific unit on a chromosome that has a special effect on the phenotype of an organism. Phenotypes are the traits that can be detected through observation .Genes play significant role in determining phenotype, environmental factors can influence its expression. Whereas genotype refers to an organism's genetic makeup, which is the actual DNA sequence at a specific location in the genome.

Genetic Basis of the Disease

Genetic variance and environment are the key determinants of phenotypic differences between individuals. Genetic diseases are mainly classified into two groups, "Simple" Mendelian and "complex" diseases. Simple Mendelian disorders are caused by a mutation in a single gene. For ex certain diseases like Diabetes,hypertension ,cancer are not caused solely due to genetic factors there might be other environmental factors like lifestyle, habits influencing the pathogenesis of the disease. Diseases that follow predictable and generally simple patterns of transmission are called "Mendelian" conditions. Mendelian diseases follow a classic Mendelian mode of inheritance, such as autosomal-dominant, autosomal-recessive, X-linked dominant, or X-linked recessive and mitochondrial. Complex traits are the result of the interaction of alleles at multiple different loci. One disease-causing allele is not sufficient to cause disease.

Methods of Genetic Analyses

Familial aggregation

Familial aggregation of a trait or disease can suggest genetic etiology. To determine the evidence for genetic factors in the familial aggregation of a trait, more formal genetic studies are needed.

Segregation analysis

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

Twin studies

Phenotypic characteristics are studied primarily of monozygotic (MZ) twins, which is a method of differentiating variations caused by environmental and genetic factors. MZ twins are genetically identical and always the same sex. Therefore, any discordance in disease between twins must be due to environmental factors. Any discordance between dizygotic (DZ) twins could arise from environmental and/or genetic variance. Therefore, any difference in the discordance between MZ and DZ twins is a measure of the effects of the excessively shared genes in MZ twins when the environmental influence is constant.[8-10]

Michalowicz *et al*.[11] studied that dizygous twins reared apart (raised in different environments) (dizygous-A) and reared together (raised in common environment) (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 in dizygous-T twin pairs, supporting the role of genetics in this disease. They concluded that genetics have a significant role in susceptibility to periodontal disease.

In another study of 117 adult twin pairs, Michalowicz *et al*.[8] estimated genetic and environmental variances and heritability for gingivitis and chronic periodontitis. Heritability of periodontitis was found to be biological and not behavioral in adults. It means presence of microorganisms in oral cavity is not influenced by host genes and socio economic status of the person. They concluded that although host genes may

influence initial bacterial colonization of the oral cavity, the effect does not persist into adulthood.

Family studies

Familial aggregation of severe non-syndromic aggressive periodontitis is not an unusual finding. There are syndromic forms of aggressive periodontitis. Formal genetic studies (segregation analysis and linkage analysis) indicate that there are different genetic forms of aggressive periodontitis, but it is not clear how many genes might be involved in these non-syndromic forms of the disease. This family aggregation (which means multiple family members have the same disease) strongly suggests a genetic predisposition to periodontal disease. We have to consider the shared environmental and risk behavior in any family. These factors include parent modeling, family conflicts, education, socioeconomic status, unhealthy lifestyle, oral hygiene, the transmission of bacteria, systemic diseases such as diabetes, and environmental features such as passive smoking, sanitation, etc. Therefore, the interplay between environment and genes must also be considered in the evaluation of familial risk for periodontal diseases. We have to develop strategies for prevention and treatment modalities.

Association studies

Kornman *et al*.[12] 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. They said specific genetic variation in the IL-1 gene is strongly associated with severe periodontitis. Galbraith *et al*.[13] found no association between CP and tumor necrosis factor-alpha (TNF-α) polymorphisms, although one genotype was correlated with elevated levels of TNF-α production by oral PMNs in patients with advanced periodontal disease. A recent study found the IL-1 genotype to be associated with disease in smokers but not non-smokers. Thus, although smoking and the IL-1 genotype appear to affect the risk for periodontitis, the interaction is poorly understood.

Population studies

Behavioral or environmental factors for disease are often identified in large population-based studies. The frequencies of polymorphisms of candidate genes are compared between cases and control. A clear difference is found in the frequency of a specific gene polymorphism between a diseased group and a control group. It is evident that the candidate gene plays some role in determining susceptibility to the disease. In this way, causal heterogeneity of disease and individuals at more risk for the disease can be identified.

Polymorphism in Relation to Periodontal Diseases

Extensive research has been done on cellular and molecular levels, especially on IL-1, IL-4, IL-6, TNF-α, Vitamin-D receptor, Fc-gamma receptor, IL-10, and MMP. Studies analyzed the genetic association of IL-1 with periodontitis in clinical practice. The studies said that the composite IL-1 genotype is significantly associated with the severity of periodontitis in both chronic and aggressive periodontitis. It also confirmed that both IL1 genotype and smoking history provide objective risk factors in periodontal disease. However, variation has been found between the different ethnic groups of IL-1 on periodontitis. Armitage *et al*.[14] concluded that the prevalence of both IL-1A and IL-1B polymorphism was lower in Chinese people than in Europeans.

An interaction between IL-1 positive genotype and age, smoking, and *Porphyromonas gingivalis* suggests that the IL-1 genotype is a contributory but non-essential risk factor in the progression of periodontal disease in this population. Diehl *et al*. investigated the relationship between IL-1 genetic polymorphisms and early-onset periodontitis.[15] In their study, they selected 28 African–American families and seven Caucasian–American families with two or more affected members. IL-1A and IL-1B polymorphism were in strong disequilibrium with each other in the Caucasian race but not in African–Americans. It means that these genetic variants tend to be inherited together, suggesting a possible association between polymorphisms and the disease. Their study results showed aggressive periodontitis as a complex, oligogenic (trait influenced by a small no of genes) disorder, with IL-1 genetic variation acting as an important but not exclusive influence on disease risk.

Papapanou *et al*. analyzed an IL-1 gene polymorphism and periodontal disease in a case–control study. No relation was found between genotype-positive and subgingival microbial profiles. Genotype-positive patients revealed overall reduced serum antibody levels and specific titers against selected bacteria. Thus, the composite genotype failed to distinguish between periodontitis patients and controls but correlated in patients with the severity of disease and antibody responses to periodontal microbiota.[16]

Genetics Test for Diagnosis and Therapeutic Treatment

Genetic counseling

Genetic counseling is defined as a communication process involved in human problems associated with the occurrence and recurrence of a genetic disorder in a family.

The following are the steps in genetic counseling:

1. Family history, clinical examination, and investigation
2. These are specialized tests that may be essential to arrive at the final diagnosis: chromosomal analysis, enzyme assay, metabolite measurements, and DNA analysis
3. Disease management.

Genetic Test for Periodontitis

Genetic tests assess individuals' chances of developing the disease but are not definite predictors. Many tests target genes involved in inflammatory response as chronic inflammation plays a role in the development and progression of periodontitis

for ex-testing for variation in IL-1 and IL-B genes involved in the production of IL-1, a key inflammatory cytokine. The specific combination of these gene variants is associated with increased susceptibility to severe chronic periodontitis. More research continues to find the interplay between genetics, environment, and periodontitis and to identify biomarkers to develop treatment strategies.

Human genome project

It is an international scientific research project that mapped and sequenced the entire human genome with the goal of identifying a large number of disease-causing genes.

Candidate gene approach

Focuses on genes involved in immune response and inflammation. It is a tool for exploring genetic risk factors in periodontitis.

Syndrome diagnosis

Syndrome brings up structural and functional changes in patients. Various computerized databases, namely, pictures of selected syndromes and undiagnosed malformations and the London dysmorphology database, greatly helped with diagnostic approaches that give detailed descriptions of syndromes.[17]

Clinical Implications of Genetic Studies

Genetic studies help in identifying the persons who are likely to develop disease at an early stage. New treatment strategies can be developed to counteract the adverse effects of risk alleles.

Future perspectives

The future of genetics and periodontal disease research lies in personalized approaches, focusing on individual genetic profiles to understand susceptibility, predict disease progression, and develop treatment strategies. This includes developing genetic screening tests to identify individuals at higher risk, understanding how genetic variations influence the immune response to periodontal pathogens, and exploring epigenetic factors that can modify the gene expression and contribute to the disease.

Conclusion

Despite extensive research in genetics, the causative gene polymorphisms of periodontitis and their pathophysiological effect are still very controversial. Association studies have limited power to detect rare genetic risk factors. Current dental treatments do not employ knowledge of genetic factors for treatment. There is utmost need for incorporating genetic knowledge on regular basis at teaching level which will improve the treatment outcome.

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