Review Article

Role of Genetic in Periodontal Disease

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Abstract

Genetics is the study and understanding of the phenomena of heredity and variation. A large number of genes are associated with many systemic conditions. Periodontitis is inflammatory condition of periodontium. Periodontium consists of gingiva, periodontal ligament, cementum, and alveolar bone. It is considered being a multifactorial disease. Studies of animals and humans support the concept that a large number of genes' factor may be associated with periodontitis and clearly play a role in the predisposition and progression of periodontal diseases. It has been proven that genetic factors impair inflammatory and immune responses during periodontal diseases. Research on identifying specific genes causing periodontitis may improve and prevent the disease progression. The aim of this article is to focus on genetic risk factors and its influence for the various forms of periodontal disease.

Keywords: *Aggressive, chronic, genetic, gingivitis, periodontitis, polymorphism, single nucleotide, syndrome*

Introduction

Periodontitis is a complex disease. It is one of the most common oral diseases and is characterized by gingival inflammation and alveolar bone resorption.[1] According to the World Health Organization report, severe periodontitis can lead to tooth loss in 5%–15% of most world populations. Hence, it can be considered among the prevalent and important global health problem in terms of quality of life.

Periodontitis is initiated by microorganisms and perhaps viruses in the subgingival biofilm and further affected by lifestyle factors such as smoking, stress, diet, and environment. It can also be influenced by acquired systemic diseases which reduce or hamper an optimal host response. Apart from this, some modifying disease genes can also be responsible for susceptibility to periodontitis. Aggressive periodontitis is inherited as Mendelian traits, and they are good models to identify genetic risk factors in periodontitis.[2] However other genetic risk factors, i.e., gene–gene interactions, gene-environmental, and environment–gene-life style interaction also need to be present simultaneously for the phenotype to develop in periodontal disease.[3,4]

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Gingivitis and Periodontitis

Oral cavity is a mirror of human body. More than 800 different bacterial species are found in oral cavity.[4-6] W. D. Miller was one of the important individuals who worked greatly on oral microbiology. In 1890, he published a book titled *Microorganisms of the Human Mouth*.[7] Specific group of microorganism or specific microorganism leads to the destruction of periodontium by synthesizing products such as collagenase, hyaluronidase, protease, and endotoxin that causes damage to epithelium, connective tissue, and to intercellular constituents. These products initiate the inflammatory process and activate monocytes/macrophages which produce substances such as prostaglandin E_2, interferon, tumor necrosis factor (TNF), and interleukin (IL)-1.

Inflammatory process transforms the healthy gingiva into gingivitis and the severity of the gingivitis further affected by smoking, lifestyle, stress, diet, genetic

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makeup of the individual, and host–response and if any underlying systemic diseases which can lead to increase in progression of periodontitis.[8] Risk factors for periodontal diseases include microbiologic factors, immunologic factors, environmental factors, and genetic factor.

Gingivitis is the inflammation of gingiva. Gingivitis is a reversible condition whereas periodontitis is irreversible condition, in which along with inflammation of gingiva, destruction of tooth-supporting structure occurs. Not all cases of gingivitis become periodontitis; however, other cases go through a brief phase of gingivitis and rapidly develop into periodontitis that means periodontitis is always preceded by gingivitis but not all cases of gingivitis progress to periodontitis.

Aggressive Periodontitis and Chronic Periodontitis

Periodontitis is an inflammatory condition of the periodontium which affects gingiva, periodontal ligament, cementum, and alveolar bone. Periodontitis is further classified into chronic periodontitis and aggressive periodontitis.

Aggressive periodontitis differs from the chronic periodontitis by the rapid rate of disease progression seen in an otherwise healthy individual, absence of large accumulations of plaque and calculus, and family history suggestive of a genetic trait in aggressive periodontitis.[9] Chronic Periodontitis is as an infectious disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment loss, and bone loss.[10] It is the most common form of periodontitis. Chronic periodontitis is more prevalent in adults but can occur in children too. Amount of destruction consistent with the subgingival calculus, variable microbial pattern, and possibly modified by and/or associated with the systemic diseases. Untreated chronic periodontitis may lead gingival inflammation, pocket formation, clinical attachment loss, resorption of alveolar bone, and occasional suppuration which are consider to be a clinical sign of chronic periodontitis.

Role of Genetics in Etiopathogenesis of Periodontal Diseases

Periodontal disease is a polymicrobial in origin which is highly governed by host response, environmental factors, and genetic factors. Scientists had done the research to find the role of genes and pattern of inheritance in periodontal disease. There are chromosome regions that potentially harbor susceptibility genes for periodontal diseases.

Among chronic and aggressive periodontitis, aggressive periodontitis showed genetic predisposition in the affected person. Various investigators conducted a familial study based on the hypothesis that it is inherited. Saxén concluded that the juvenile periodontitis (aggressive periodontitis) is inherited in an autosomal recessive mode.[11] Shapira *et al*. showed family pedigree is consistent with an autosomal dominant mode of transmission in aggressive periodontitis.[12] Michalowicz *et al*. analyzed periodontal finding which included probing depth, clinical attachment level, and plaque score in 110 adult twins who were both reared together and reared apart. A significant genetic component was identified for gingivitis, probing depth, attachment loss, and plaque score.[13] Heritability studies indicate that 38%–82% of population variance for these periodontal measures of disease may be attributed to a genetic factor, whereas there is general agreement that bacteria are important in pathogenesis of periodontal disease. Approximately half of variance in disease in the population is attributed to genetic variance, the basis for heritability of periodontitis appears to be biological not behavioral in nature.[14]

Method of Genetic Analyses in Periodontics

Methods that are generally used to find the mode of inheritance in periodontitis is done by familial aggregation, twin studies, segregation analysis, linkage analysis, and association studies. There have been many clinical reports suggesting a familial aggregation of periodontitis, but until recently, the research tools to pursue these reports were lacking.[15]

Polymorphism

Human shares 99.9% of their genetic information. The 0.1% differs from one person to the other. There are a number of differences in the DNA sequences of two individuals and not all differences in the DNA sequences cause disease; such differences are known as polymorphism. Polymorphism differs from the mutation in such way that mutation causes the heritable alteration or change in the genetic material. Single nucleotide polymorphisms are variations of single base pairs spread all over the genome.[16]

Polymorphism in Relation to Periodontal Diseases

Research on new methods for investigation of disease condition at molecular level put the light to the study interaction between host and parasite. In periodontal disease, researcher has done worked on

cellular and molecular level, especially on IL-1,[17-19] IL-4,[20] IL-6,[21-23] TNF-α,[24-26] Vitamin-D receptor,[27-29] Fc-gamma receptor,[30-32] IL-10,[33,34] and matrix metalloproteinase.[35-39]

Studies had analyzed IL1 genetic association with periodontitis in clinical practice. The studies demonstrated that composite IL-1 genotype is significantly associated with severity of periodontitis both in chronic and aggressive periodontitis. It also confirmed that both IL1 genotyping and smoking history provide objective risk factors for periodontal disease.[40-43] However, there is variation has been found between the different ethnic groups of IL-1 on periodontitis. Armitage *et al*. concluded that prevalence of both IL-1A and IL-1B polymorphism dramatically lower in Chinese than Europeans.[44]

An interaction of IL-1 positive genotype with age, smoking, and *Porphyromonas gingivalis* which suggests that IL1 genotype is a contributory but nonessential risk factor for periodontal disease progression in this population.[45] Diehl *et al*. analyzed linkage disequilibrium of IL-1 genetic polymorphism with aggressive periodontitis. 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 Caucasians but not in African-Americans. Results showed that aggressive periodontitis as a complex, oligogenic disorder, with IL-1 genetic variation contributing an important but not exclusive influence on disease risk.[46]

Papapanou *et al*. analyzed a IL-1 gene polymorphism and periodontal disease in a case–control study. No relation between genotype positive and subgingival microbial profile was observed. Genotype positive patients revealed both overall lower serum antibody level and specific titers against selected bacteria. Thus, 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.[47]

Syndromes and Periodontitis

Periodontitis has a common and interlink relation with syndromes which may or may not be present with syndromes but when present, syndromes bring up structural and functional changes on periodontium. Syndromes such as Chèdiak–Higashi syndrome,[48] lazy leukocyte syndrome,[48,49] leukocyte adhesion deficiency (LAD),[48] Papillon-Lefèvre syndrome,[48] and Down syndrome[49] showed the features of periodontitis. Neutrophil is the first line of defence in periodontitis. Abnormality in the action of neutrophil aggregates periodontal disease condition. Conditions such as LAD, lazy leukocytes, Down syndrome in which abnormality in the action of neutrophil are seen. Some of syndromes are associated with gingival enlargement, gingival bleeding, gingival fibromatosis, periodontitis, alveolar bone loss, and tooth loss.[50]

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. This process involves the expertise of a trained counselor to guide individuals, family to the medical facts related to diagnosis, prognosis, and management of a disorder, the role of heredity in genetic disorder, the probable impact on the other members of the family, and preventive measures for further recurrence of such disorders in the family.[51]

Steps in genetic counseling:[52]

a. Family history
   - To construct and analysis pedigree
b. Clinical Examination
c. Investigation*
   - Chromosomal analysis
   - Enzyme assays
   - Metabolite measurements
   - DNA analysis.

*These are specialized tests which may be essential to arrive at the final diagnosis

d. Disease managements.

Genetic tests for periodontitis

At present, it is possible to perform genetic testing to identify individuals carrying gene mutations responsible for several syndromic forms of periodontitis including LAD types 1 and 2, Papillon-Lefèvre syndrome, Haim-Munk syndrome, Chédiak-Higashi syndrome, and some forms of Ehlers-Danlos syndrome. To date, there is no evidence that mutations in the genes responsible for these conditions are responsible for the more prevalent forms of aggressive or chronic periodontitis. Genetic testing for mutations of specific genes is not currently utilized for genetic testing for aggressive periodontitis and chronic periodontitis is unknown. In the field of periodontics, most work in evaluating genetic polymorphisms and their relationship to periodontitis has been performed for several IL-1 genetic polymorphisms, and these tests show promise, especially among certain preselected populations, but for reasons stated previously, more genotypic information that identifies additional genomic risk markers would likely provide even better diagnostic and prognostic tools in the future.[53]

Human Genome project

It is an international scientific research project with the goal of determining identification of a large number of disease-causing genes. It opened the floodgate of DNA diagnostic tests which have found a firm place in clinical management of various diseases by way of genetic counselling, carrier detection, and presymptomatic.[51]

Candidate gene approach

Gene mapping is a test which is used to find whether one allele of a gene occurs more often in patients with the disease than in participant without a disease. Gene, i.e., candidate gene is chosen on the basis of their presumed or known function.[54]

Syndrome diagnosis

Syndrome brings up structural and functional changes in patients. Most of time, it is very difficult to do accurate diagnosis. Various computerized database, namely, Pictures of Selected Syndromes and Undiagnosed Malformation and London Dysmorphology Database greatly helped for diagnostic approaches which give detailed descriptions of syndromes.[52]

Clinical Importance of Genetic Information in Diagnosis and Treatment

Genetics is the study and understanding of variation and heredity in organism. Dentists and Periodontist should be able to take the advantage of available genetic knowledge to improved patient care. Clinical findings such as pocket depth, clinical attachment level, and clinicians experience give the warning sign of present condition; on the other hand, genetics knowledge and its role in periodontal disease will provide the likelihood of disease initiation before it occur. In cases of aggressive periodontitis, genetic counseling will help to draw a pedigree chart which can help to establish the mode of inheritance in family of patient. Once the mode of inheritance is established, we can predict the susceptible member for aggressive periodontitis and thus treatment can be started.

Periodontitis is generally associated with syndromes. Syndromes can be diagnosis on the basis of clinical finding, genetic counseling, and investigation such as karyotyping and polymerase chain reaction. Syndromes such as lazy leukocyte syndrome,[48,49] LAD,[48] Papillon-Lefèvre syndrome,[48] and Down syndrome,[49] in which abnormality in neutrophils action and function occur. In such cases, patient education and motivation along with parents counseling, regular dental check, and proper follow-up after nonsurgical and surgical treatment should be maintained.

Conclusion

Despite tremendous efforts and published papers in the field of genetic association with periodontitis over the past decade, the causative gene polymorphisms of periodontitis and their pathophysiological effect are still very controversial. Association studies have limited power to detect the rare genetic risk factors. Knowledge of the hereditary influence of disease is not a new finding, and it seems that the oral cavity is not excluded from genetic factors. Genes do not work in a vacuum, nor does it appear that one gene is responsible for this disease. At present, current dental treatment and/or periodontal treatment does not commonly use the available knowledge of genetic factor for treatment. There will be need of a proper approach (protocol) for patient treatment which will incorporate genetic knowledge on a regular basis.

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Conflicts of interest

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