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Genetic Relationship to Periodontal Disease: A Review

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ABSTRACT

Periodontal disease is the most widespread and prevalent disease in the world which involves complex interactions between plaque microorganism and host immune system resulting in the loss of periodontal structures surrounding the tooth. Till recently the disease was thought to be caused by environmental factors, but now research is pointing to genetic causes of many of these diseases. Researchers are trying to identify the genetic mutations or polymorphism in respect to the various aspects of immunity. This article is a review of the monogenic disorders are caused by mutation of single gene and referred to as single gene disorders and polygenic alterations at multiple areas of the genes, each with a small contribution and is called polymorphism, that are influenced by environmental and behavioral factors.

Key words: Genetic mutation, Genetic polymorphism, Monogenic disorders, Polygenic disorders, Periodontitis, gene defect, Inheritance, syndromes.

INTRODUCTION

Periodontal disease is the most widespread and prevalent disease in the world which involves complex interactions between plaque microorganism and host immune system resulting in the loss of periodontal structures surrounding the tooth. Most of these diseases are chronic, but a small percentage of the people develop rapidly progressing irreversible destruction of the periodontal tissues. A wide variety of risk factors have been implicated for the manifestation and progression of the disease including microbial plaque, tooth associated factors, systemic and genetic factors, social, behavioral and environmental factors. The disease has remained an enigma and the prediction and predilection of the disease has always been a problem.

Until recently, periodontitis was thought to be determined by environmental factors alone. It is a common observation that although people are exposed to the same conditions only some people develop aggressive forms of the disease while some others suffers from mild or no disease. This suggeststhat the individual's susceptibility to the disease and perhaps a genetic basis for the susceptibility.

Genetic factors influence the inflammatory and immune response of periodontitis. As immune system plays an important role in the pathogenesis of the disease, researchers have been trying to identify the genetic mutations or polymorphism in respect to the various aspects of immunity. The effects of these genetic variations may be minor or insignificant or very significant and severe.[1]

Monogenic disorders

Genetic diseases have been broadly classified into two groups: simple Mendelian diseases and complex disease[1]. The simple mendelian disease or monogenic disorders are caused by mutation of single gene and referred to as single gene disorders. These may be of autosomal recessive or dominant type of

inheritance. Severe periodontitis is part of the clinical manifestation of several monogenetic gene mutations with the syndromes having biochemical defects[1]. The significance of these conditions is that the genetic mutation occurs at a single locus and is sufficient to produce the clinical phenotype to cause the disease. The impact of the gene is same in all families. The genetic alteration is associated with a disease phenotype and there is no compensatory mechanism to overcome the effects of the genetic defect. Such a genetic alteration is termed 'mutation' as in the case of Mendelian diseases.[2]

Complex genetic diseases (Polygenic disorders)

This is more prevalent than monogenic disorders occurring in more than 1% of the population. They are a result of genetic alterations at multiple areas of the genes and are influenced by environmental and behavioral factors. These qualitative trait disorders are regulated by several genes, associated with variations in multiple genes, each with a small contribution and is called polymorphisms. When a specific allele occurs, in at least 1% of the population, it is said to be genetic polymorphism. 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.[3]

In contrast to Mendelian inheritance these genetic polymorphisms are not directly linked to the disease but specific alleles are reported more frequently in the diseased individuals than non-affected individuals.[1]The results are evident only when two different genetic alterations coexist.The resulting complex periodontal diseases are mostly mild phenotype and chronic, slowly progressive in nature.[3] Variations in a number of genes encoding different proteins result in a genetic predisposition to a clinical phenotype. Thereare no Mendelian inheritance patterns and gene mutations are not present. Environment and life-style are major contributors to the pathogenesis of complex diseases.

The progression of periodontal disease is governed by host response which is influenced by the genetic makeup. Genetic deficiencies or variations can increase the likelihood of periodontal disease.A gene may be considered as a causative or modifying factor in periodontitis if the physiological process determined by the genes has been associated with the presence or severity of disease.[4]Clinical and scientific data from a variety of sources suggest that the genetic variants are major determinants of syndromic and non-syndromic periodontitis.

Various syndromes, which have periodontal disease manifestations as part of syndromic manifestations are Papillon Lefevre syndrome, Chediak-Higashi syndrome, Ehler-Danlos syndrome, cyclic neutropenia, and leukocyte adhesion deficiency, Hereditary gingival fibromatosis is found to be associated with a mutation in the SOS (Son of Sevenless) gene.[1,5] The significance of these conditions is that they clearly demonstrate that a genetic mutation at a single locus can impart susceptibility to periodontitis.

Currently, little is known about which genes may be involved in periodontitis as disease modifying genes. Several immune response traits have been associated with clinical forms of periodontitis and some of these factors the underlying genetic determinants are known. Although it is unlikely that polymorphisms in all these genetic determinants impart differential susceptibility to periodontal disease, it is reasonable to expect that multiple genes will be found to be important and that knowledge of these may permit determination of individual susceptibility. The key will be able to identify the genetic factors that are important enough to impart significant clinical risk.

The technological advances in the human genome projects have changed the understanding of diseases, prediction of risk factors and its treatment based on genomic approach to target molecular pathways of disrupting the disease process. The genomic studies leads to the understanding of the mechanisms modulating the inflammatory process and the knowledge of the complement of genes should be possible to identify

Genetic disorders and their periodontal manifestations

Disorders/ syndromes	Inheritance	Gene/ Defect	Functions of normal gene	Type of periodontal disease
Severe congenital neutropenia Type 1	AD	Neutrophil elastase gene (ELA2)-19p13.36	The products of elastase gene degrade membrane protein A of bacterial cell wall.6	Early age periodontitis similar to Pre pubertal periodontitis.6,8
Severe congenital neutropenia Type II	AD	Growth factor independent gene (GFI 1) 1p226	GFI 1 gene function to replace ELA26	Early age periodontitis6
Severe congenital neutropenia Type III	AR	HCLS1 associated protein X1 (HAX1)-1q21.36	Controls development of neutrophils	Early age periodontitis6
Severe congenital neutropenia	AD	Granulocyte colony stimulating factor gene(G-CSF)-17q11.2-q126,10	Stimulation of granulocyte activity.	Early age periodontitis.6
Leukocyte adhesion deficiency (LAD) syndrome type I	AR	Integrin B2 (ITGB2)-21q22.37,9,11	Leucocyte chain adhesion molecule CD 18. Adhesion & Chemotaxis7	Homozygous form manifest generalized aggressive periodontitis, hetezygous may have pre-pubertal status.7
LAD syndrome type II	AR	Solute carrier family 35 member C1 (SLC35C1)11p11.27,8,16	Secrete guanosine 5'-diphosphate, fructose transporter 17,8	Severe periodontitis
Chediak- Higashi syndrome (CHS)	AR	Lysosomal trafficking regulator gene (LYST)-1q42.1-q42.26,7,14	Transport of vesicles to and from the neutrophil lysosyme9,11	Early onset and premature loss of teeth in both dentitions.
Papillion -Lefevere syndrome (PLS)	AR	Cathepsin C gene-11q14-q216,14,17	Degrading proteins and activation proenzymes in immune cells.6	Early onset and premature loss of teeth in both dentition.
Hiam-Munk syndrome	AR	Cathepsin C- CTSC 602365- on chromosome 11q14.6.7,14	Degrading proteins and activation proenzymes in immune cells.6	Aggressive Periodontitis

Ehlers-Danlos syndrome (EDS) type IV	AD	Type III collagen gene (COL 3A1-2q316,7,18	Synthesis of type III collagen	Early onset periodontitis
EDS tppe VIII	AD	Ehler-Danlos syndrome8 (EDS 8) 12p136,7,18	Unknown. Defect in collagen ?	Early onset periodontitis
Phosphatasia	AD/AR	Alkaline phosphatase liver/Bone/ kidney (ALPL)-1p36.1-p3412,13,15	Maintains normal level of alkaline phosphatase	Aggressive periodontitis. Premature loss of primary teeth.
Kindler syndrome	AR	Kindlin 1(KIND 1)-20p136,19	Abnormality in basement membrane,: cell to contact	Aggressive periodontitis in primary and permanent dentition.
Infantile genetic agranulocytosis	AR	ELANE (Formerly ELA2) gene on chromosome 19p13.36,7,8	Deficiency of LL-37, Neutrophil elastase deficiency, a peptide antibiotic present in neutrophils..	Aggressive periodontitis
Cohen syndrome	AR	8q22 gene VPS13B commonly called COH16,11	Deficiency of functional VPS13B protein.	Early adult periodontitis.
Hyper IgE Job's syndrome (HIE)	AR	7q216,12,16	Marked elevation of IgE	Opportunistic infections, periodontitis and oral ulcerations.

the metabolic pathways involved in periodontal destruction and regeneration.

There a paradigm shift in understanding periodontal disease and there is more emphasis on host genetic and other non-microbial environmental factors. The characteristic feature of periodontitis is that, whatever be the cause, the symptoms are deepening of periodontal pocket, loss of attachment, and alveolar bone loss. It is the likelihood of the overlapping clinical phenotypes existing between different forms of periodontitis. The development of periodontitis depends on the environmental risk factors and the genetic factors inherited or present at that point of time. The increased number of the genetic factors inherited, the greater the genetic predisposition and higher chances of developing early onset periodontal disease.

CONCLUSION

Despite the advances made in the genetic search, we still have not determined the genetic basis of aggressive and chronic periodontitis. No major mutations which could cause periodontitis in otherwise healthy individuals have been identified. The studies have failed to quantify the magnitude of the contribution of a particular disease associated allele to disease risk. Even among studies with subjects of same ethnic background no consistent results have been obtained.

The table summarizes candidate gene polymorphisms investigated in relation to periodontitis.

Interleukin 1 (IL-1á and IL-1â)	IL-1á -889 and IL- â+3954 2q13. These functionally similar molecules are encoded on separate genes in the same chromosome 2. Frequency of allele 2 of the IL-1B +3953 SNP was significantly increased in patients with advanced periodontitis. Studies in both chronic and aggressive periodontitis showed mixed results[6,7,20,21,24].
Interleukin 2 (IL2)	IL-2 -350 (T-G) SNP might be associated with severity in aggressive periodontitis[7,23].
Interleukin 4 (IL4)	No difference was found in the frequency of IL-4 gene polymorphisms between control and periodontitis group in African–American-Brazilian population[7,24].
Interleukin 6 (IL6)	IL-6 in intron 2 and in the promoter region (PP- and IP-) gene polymorphisms in chronic periodontitis suggested that -572 G/C polymorphisms of IL-6 gene might be one of the protective factors associated with lower susceptibility to chronic periodontitis[7,23.25]
Interleukin 10 (IL10)	IL-10 promoter polymorphisms at position -824 and other at -597 in chromosome 1, on aggressive and chronic periodontitis found no association between the genes for the cytokine and aggressive periodontitis while IL-10 1087 was susceptible to periodontitis[7,26,27]..
Interleukin 18 (IL18)	Six different IL-18 gene polymorphism (-656, -607, -137, +113, +127, and codon 35/3) were studied and none of the polymorphisms were associated with destructive periodontal disease[7,20,22].
Tumor necrosis factor (TNF-á)	Research to investigate 4 polymorphism in TNF-á gene transitions from G to A, 3 in the promoter positions:-376, -308, -238, and at +489 could not be identified as susceptible or severity factors[6,7.20,21].
	Immunoreceptor related Polymorphism
Fc gamma receptor (FcãR)	The Fc-gamma receptor is the receptor present on phagocytes, which binds to IgG..There are three main classes of FcR: FcãRI (CD 64), FcãR II (CD 32), FcãR III (CD 16) in chromosome 1. FcãR IIIa and FcãR IIIb, is associated with chronic periodontitis. FcãR IIIb has a NA1-NA2 polymorphism. NA1 is a more efficient opsono-phagocytic agent than NA2[6,28].
Toll-like receptors (TLR-2,-4) gene polymorphism	Signal molecules essential for the cellular response to bacterial cell wall components.TLR 2exhibits polymorphism (Arg to Thr at 677, Arg to Gly at 753) losing their ability to respond to cell wall components. Polymorphism of TLR4 (Asp 299 Arg 677 Trp; Arg753 Gln) have been associated with impaired LPS signal transduction. Their relationship has still not been established[6,7,29].
CD14 gene polymorphism	The R-allele in the promoter region of CD14 at position -260(-159) enhances the transcriptional activity of the gene. Studies with Caucasian subjects investigated the CD14-260 polymorphism in chronic periodontitiswith no significant associations.A higher frequency of the N –allele and the N/N genotype of CD14-1359 polymorphism was found in patients in severe periodontitis[6,7].
Card 15 gene polymorphisms	The 3020insC and 2104 C >T polymorphisms of the CARD15 (NOD2) gene leads to impaired activation of nuclear factor-kappa B, resulting in altered transcription of pro inflammatory cytokine genes and reduced expression of these cytokines. However no role for CARD 15 found in Caucasians[6].

Polymorphism of RANK gene	RANKL and its receptor RANK have been reported to cause increased bone resorption in periodontal disease through osteoclast differentiation and activation of nuclear factor-êB (RANK), RANK ligand (RANKL), and osteoprotegrin (OPG). Association studies show no significant association of the SNPs with AgP in Japanese population[6,7].
Vitamin D receptor gene polymorphism	Vitamin D receptor gene polymorphism has regulation on bone density and turnover. Studies have suggested genotype of TaqI VDR gene might be the risk indicator for susceptibility to periodontal disease[1,30].
N-formyl peptide receptor polymorphism	The affinity of FMLP receptor (FPR1) of phagocytic cells interact with FMLP receptors of Bacterial cells resulting in chemotaxis, degranulation and superoxide production which are distupted in aggressive periodontitis. Polymorphisms at nt329T-C (codon 110 phenylalanine-serine), and at nt378C-G (codon 126 cysteine-tryptophan) in the 583 bp interval of the FMLP receptor gene found to significantly associated in Agp phenotype in Afro- American patients[6,7].
	Antigen- Antibody gene polymorphisms
Class II Human leukocyte antigens (HLA antigens)	HLA are genetically predetermined humoral immune response through the recognition of foreign antigens. Studies have suggested that patients with the HLA-DRB1 1501-DQB1 0602 genotype may have an accelerated T cell response and an increased susceptibility to periodontitis[1,31].
Immunoglobulin g2 variations	IgG molecules carry genetically determined variations in the gamma heavy chains, termed Gm allotypes. Rapidly progressing periodontitis patients positive for G2mshow elevated antibodies[7].
	Polymorphisms in genes encoding enzymes
Cathepsin C gene polymorphism	Cathepsin C is a lysosomal protease in neutrophils and macrophages identified in chromosome 11, responsible fro pre-pubertal periodontitis[6,7].
Matrix metallo proteinase gene polymorphisms	MMP-1 is an important mediator of connective tissue destruction in periodontal disease. A single nucleotide polymorphism in the MMP-1 promoter region of -1607 bp may be associated with severe chronic periodontitis[1,6].
Polymorphisms in cyclogenase -2 gene	PGE_2 is an important mediator of tissue destruction, catalysed by COX-2. A single nucleotide polymorphism of COX-2 in the chromosome 9q32-33 has been shown to alter the expression of the COX-2 gene and polymorphism of -765G to C is associated with e decreased risk for periodontitis[6,7,8].
Polymorphisms in genes encoding myeloperoxidase (MPO) and N-acetyl transferace (NAT-2)	A SNP 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. Anassociation between bone loss in periodontal disease and polymorphism of NAT2 have been reported[6,8].
Polymorphisms in genes encoding vasoactive enzymes	The study of genotypes between diseased and healthy showed the presence of lymphotoxin-á (TNF-â), angiotensin- converting enzyme and endothelin-1(ET-1) polymorphism with regard to three-locus combination[7,8].

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