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Genetic polymorphisms in periodontal disease

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Abstract

Periodontitis is a multifactorial disease occurs due to complex interaction between pathogenic bacteria and host response. Genes and environment plays a very important role and therefore, genetic factors are considered to be predisposing factor for the periodontal disease. The genetic polymorphisms influence the immune function and bone metabolism which are related to cause periodontitis. Only by carefully studying the genetics of a disease in populations we can hope to begin to unearth the complex interaction between genes and environment that underlie individual differences in disease susceptibility. So, to resolve, genetic susceptibility associated with periodontitis should be identified which might help to improve the diagnostic and treatment strategies.

Keywords: periodontal disease, genes, polymorphisms, SNPs

1. Introduction

Periodontitis is defined as “an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms^[1]. According to the world health organization report, severe periodontitis leads to loss of tooth about 5%-15%^[2,3]. So it is considered among the prevalent and important global health problems in terms of quality of life. Although the cause of the disease is a bacterial biofilm, the onset and progression are influenced by the number of risk factors including smoking, stress, diet, and environmental factors. aside from this, genes also can be liable for condition to periodontal disease.

Genetics is a branch of biology concerned with the study of genes, genetic variation, and heredity in organisms^[3]. Genes play a role in the predisposition and progression of periodontal disease. The involvement of periodontal tissues has been witnessed in number of genetic disorders. The role of genetics in the periodontal condition is directly related to genetic factors, condition, or syndrome. Completion of the human genome has great implications for both medicine and dentistry. Genetic factors play an important role in human diseases. Many human diseases are influenced by heritable alteration in the structure and function of genes^[6,7].

Genes undergo alteration in transcript level of protein function, this is biologically called as mutation. Many studies revealed that gene polymorphism influences immune function and the connective tissue or bone metabolism as related to periodontal pathogenesis. Additional support for a genetic contribution for periodontitis emerged recently for the identification of certain genetic polymorphism that correlates with immune response phenotypes found in certain periodontitis patients. It is hoped that identifying these specific genes which causes periodontal disease susceptible to have diagnostic and therapeutic value^[6].

2. Genetics in Periodontitis

Periodontitis is an inflammatory condition of the periodontium which affects the gingival, periodontal ligament, cementum, and alveolar bone.

Genetic variance and environmental exposures are the key determinants of phenotypic differences between individuals. There are extreme scenarios where either an environmental agent or a genetic factor alone can result in the pathology of periodontitis.

Environmental exposures can have an overwhelming and pathologic effect on any individual, regardless of his/her genetic make-up. Geneticists have traditionally divided genetic diseases into two broad groups, "Simple" Mendelian diseases and "complex" diseases. The distinction between these broad groups is based on the pattern of transmission of the disease, which reflects how genes contribute to each disease [8].

2.1. Simple Mendelian Diseases

Diseases that follow predictable and generally simple patterns of transmission have been called "Mendelian" conditions. The name reflects the fact that these diseases occur in simple patterns in families, and in most cases, a single gene locus is the major determinant of the clinical disease phenotype. These diseases follow a classic Mendelian mode of inheritance (autosomal dominant, autosomal-recessive, or X-linked) [3].

2.2. Complex Genetic Diseases

Genetically complex diseases differ from Simple Mendelian diseases in several important ways. Genetically complex diseases are much more prevalent and usually occur with a frequency of greater than 1% of the population. Complex diseases do not typically follow a simple pattern of familial distribution or transmission. In contrast to the single-gene cause of "simple traits", these "complex traits" are the result of the interaction of multiple different gene loci. Unlike simple genetic traits, which are often due to rare mutations at a single gene locus, the genetic variants that are etiologically important for most complex genetic diseases are common in the population and occur in unaffected as well as affected individuals. Also, in contrast to mutations that can eliminate a gene product or change the protein product of a gene so significantly that it acts to disrupt other biological processes, the individual genetic variants that are important in complex diseases are much less disruptive and usually work within the normal range of the function [3].

3. Polymorphism Vs Mutation

A major difference in the genetic basis for Simple Mendelian diseases and complex genetic diseases is the number of genes involved and the contribution of each gene to the overall disease phenotype. In Mendelian disease, alteration of a single gene locus can result in a mutation that has a major physiological impact and therefore may be considered to be deterministic of the disease.

Environmental factors as well as allelic variance at other genes may act as modifiers and contribute to the variable clinical expression of a disease or trait (Chanock and Wacholder, 2002).

In contrast, the genetic alterations that contribute to complex diseases are individuals of much smaller effect. The types of genetic variants that contribute to complex diseases are generally called "genetic polymorphisms" because, in contrast to mutations, they are prevalent in the population. In contrast to mutations that have been causally linked with Mendelian diseases, genetic polymorphisms that are associated with complex diseases are often not directly causally linked, but rather specific alleles are reported to be found more frequently in diseased individuals than in non-affected controls.

There is no one-to-one correlation of the presence of a specific genetic allele and the occurrence of disease. It is important to understand that disease alleles reported to be

associated with a disease are also found in unaffected individuals, and some individuals with the disease do not have the specific disease-associated allele. Thus, the presence of a disease-associated allele in an individual is not diagnostic for a disease.

Gene polymorphisms are locations within the genome that vary in sequence between individuals and are very prevalent, affecting at least 1% of the population. Polymorphisms of human genes occur at one or more of the following sites,

- The promoter or 5'-flanking region
- The exon(s) or the gene coding regions
- The intron(s) or the gene intervening regions
- The 3'-untranslated region

The most common form of polymorphisms is the single nucleotide polymorphism, which is a change in a single base pair (bp) in the genomic DNA. Single nucleotide polymorphisms can affect gene function.

4. Single Nucleotide Polymorphisms (SNPS) In Inflammatory Diseases

Inflammation is a complex process that develops following initial tissue trauma and is completed with the induction of tissue repair. The innate immune system plays an important role to the initiate, progress, and containment of the inflammatory response. Hence, genetic variations that disrupt innate immune sensing of tissue injury could explain individual differences in the ability of the immune system to respond to tissue injury, the diversity of the clinical presentation of inflammation, and the response to current medical treatment. Such genetic variations may identify patients at high risk for the development of abnormal inflammatory responses.

Genotype polymorphisms have also been associated with disease diagnosis, severity, and presence of subgingival bacteria. A polymorphism that is associated with periodontal disease are.,

1. Cytokine Gene Polymorphisms

- IL-1,2,4,6,10 gene polymorphism
- TNF- α gene polymorphism

2. Receptor and Other Gene Polymorphisms

- FC γ R gene polymorphisms
 - Fc γ RIIa-131 H/R polymorphism
 - Fc γ RIIIa-158 F/V polymorphism
 - Fc γ RIIIb polymorphism
- Cytokine and chemokine receptor gene polymorphisms
- Immune receptor gene polymorphism
 - FMLP receptor gene polymorphism

3. Metabolism – Related Gene Polymorphism

- Vitamin D receptor gene polymorphism
- Calcitonin receptor gene polymorphism

4. Antigen – Recognition Related Gene Polymorphism:

- HLA gene polymorphism

5. Polymorphisms in the Innate Immunity Receptors

- TLR2 and TLR4 gene polymorphisms
- CD 14 gene polymorphism
- CARD 15 gene polymorphism

6. Miscellaneous Gene Polymorphisms

- Angiotensin-converting enzyme (ACE)

- Type I Collagen
- Plasminogen activator inhibitor
- Tissue plasminogen activator (t- PA)

4.1. Interleukin-1 Gene Polymorphisms

Interleukin-1 (IL-1) is a pro-inflammatory cytokine and has important roles in bony destruction and inflammatory response, and the attempts have made in an association with single nucleotide polymorphisms. To date, IL-1 family of cytokines comprises at least 11 members, they include Interleukin-1 Alpha, Interleukin-1 Beta, Interleukin-1 receptor antagonist (IL-1 RN, IL-36 Ra, IL-38), molecules with agonist activity (IL-18, IL-33, IL-1 α , IL-1 β , IL-33, IL-36a, IL-36b, IL-36g) and an anti-inflammatory cytokine (IL-37)².

The IL-1 cytokines are made by a variety of cells and it stimulates monocytes, macrophages, and epithelial cells. These molecules are encoded on separate genes in the region of chromosome 2. Interleukin-1 is a critical element of immune responses in health and disease. If the levels of IL-1 is low, they are beneficial in host responses to infection, and elevated levels can be detrimental and that the margin between beneficial effects of these cytokines and pathologic effects are very small. This data relates, circulating levels of IL-1 to disease severity in conditions associates with dysregulated inflammatory responses^[3, 8].

The study done by Kornman *et al.* has reported that IL-1 gene polymorphism has association with periodontitis in Caucasian population and he concluded that IL-1 composite genotype could be considered a putative severity factor for periodontitis in Caucasians.

Diehl *et al.* stated that the association of IL-1 gene cluster and aggressive periodontitis, but it is different from the previous ones. He concluded by stating that IL-1 gene cluster acts as putative susceptibility factor for periodontitis.

Anne Havemose - Poulsen *et al.* has demonstrate that in localized aggressive periodontitis patients, allele 2 of IL - 1 RN VNTR was associated with significantly higher levels of IL - 1 α , 6, 10 and TNF - α , whereas allele 2 of IL - 1 β +3954 was associated with significantly lower levels of the same cytokine.

Moreira PR Costa *et al.* evaluated the association of IL - 1A (-889) gene polymorphism in Brazilian individuals with different clinical forms and severity of periodontitis and demonstrated a significant association between the two.

4.2. Other Cytokines

The IL-2 gene is located in chromosome 4q26-q27. IL-2 has an essential role in anti-tumor immunity. IL-2 has showed some initial response towards association with severity in aggressive periodontitis^{3,9}.

The gene for IL-4 is found in chromosome 5q31.1. A study was conducted among African-American-Brazilian population and there found no significant difference in the frequency of IL-4 gene polymorphisms between control and periodontitis group⁹.

In 1988 Bowcock *et al.* has demonstrated the IL-6 gene found to be localized in chromosome 7q21. Irwin and Myrillas in 1998 described that IL-6 has been thought to play a crucial role in the pathogenesis of periodontal disease, especially in bone loss. IL-6 is at higher levels in inflamed tissue, GCF, and plasma of periodontitis patients. However, there is a significant reduction in serum IL-6 was observed after periodontal therapy¹⁰.

IL-10 is an anti-inflammatory cytokine and was originally described as "cytokine synthesis inhibitory factor" because of

its important inhibitory role. This gene is located on chromosome 1q31-32. IL-10 plays a role in periodontitis by inhibiting the synthesis of pro-inflammatory cytokines like IL-1, IL-2, IL-6, and IL-8, tumor necrosis factor α , interferon γ , and stimulating protective antibody production. Berglundh *et al.* in 2003 described IL10 -1087 polymorphism shown that the G-allele is more abundant in periodontitis, in particular in non-smokers. G-allele prevalence in periodontitis patients may result in higher levels of auto-antibodies and lead to increased levels of periodontal destruction^[3].

TNF- α referred to as Cachectin, which is a protein said by Beutler and Cerami, 1986. TNF- α is a key inflammatory mediator in periodontal disease and shares the cellular activity with IL-1 β . It plays a role in immune responses, increases neutrophil activity, and mediates cell and tissue turnover by inducing MMP secretion. Craandijk *et al.*, found no significant association between a different series of four TNF- α gene polymorphisms and periodontitis patients^[3, 23].

4.3. Fc Gamma Receptor Polymorphisms

Fc gamma receptors (Fc γ R) recognized as key players in immune defense mechanisms against foreign cells and pathogens. Fc γ R is glycoproteins that are part of the immunoglobulin superfamily expressed on leukocytes. These receptors have a major role in antigen recognition during an immune response. They serve as a link between humoral and cell-mediated immune systems, but also between innate and adaptive immune responses.

To date, four classes of Fc γ Rs they are; Fc γ RI (CD64), Fc γ RII (CD32) A/B/C, Fc γ RIII (CD16) A/B and Fc γ RIV have been described with different affinities and isotype binding patterns^[25].

Fc γ R induces leukocyte functions like phagocytosis, cytotoxicity, cytokine production, degranulation, antigen presentation, and regulation of antibody production upon crosslinking. Fc γ R is encoded by eight genes on the long arm of chromosome 1. In humans, all three Fc γ R groups present genetically determined polymorphism. In contrast to Fc γ RI, that exhibits high affinity towards monomeric IgG, Fc γ RII, and Fc γ RIII are capable of binding effectively only aggregated, multimeric IgG that is bound to an antigen.

Fc γ polymorphism may result in variations in immune response and, thereby, might confer risk to many diseases including periodontitis said by Sugita *et al.* 1999, Loos *et al.* 2003, Nares 2003.

Fc γ R on leukocytes in effect link cellular and humoral branches of the immune system, they can be considered to be an essential component of the host-defense mechanism against bacteria. Therefore, any alteration in Fc γ R expression and function would alter host immune responses against periodontal pathogens and hence susceptibility to periodontal diseases.

Several studies investigated Fc γ and reported that Fc γ RIIa H/H genotype seemed to be suffering more on bone loss when compared to H/R or R/R genotype periodontitis and PMNs showed higher reactivity in response to periodontopathogenic bacteria. Fc γ RIIIb is the predominant Fc γ R on neutrophils, which are present at a high level in GCF and subjacent to the apical part of the pocket epithelium^[3].

4.4. Human Leukocyte Antigen (HLA) Polymorphisms

HLA also called a major histocompatibility complex (MHC). They are involved in the genetically predetermined humoral immune response through the recognition of foreign antigens. The HLA complex plays an important role in immune

responsiveness and may involve in antigen recognition of periodontal pathogens. The human major histocompatibility complex lies on the short arm of chromosome 6. HLA genes are highly pleomorphic, that is they have many different alleles allowing them to an adaptive immune system.

HLAs are Susceptible to periodontal disease and has been demonstrated in genetic predisposition by Hart and Kornman in 1997, Michalowicz *et al.* 2000. Recognition of antigen peptides and their presentation to T cells is crucial for an effective antigen-specific immune response towards periodontal pathogens and underlies genetic control. Because antigen presentation to and thereby activation of T cells is restricted by the MHC, the polymorphism of the human MHC molecules can directly affect the binding capability of antigen peptides and thus the antigen-specific T-cell response. Hence, this polymorphism could provide important susceptibility or resistance factors for periodontitis.

4.5. CD 14 Gene Polymorphisms

CD14 is a glycoprotein. The gene for the CD14 receptor is on chromosome 5 (region q23–21), consists of two exons, and encodes a protein of 375 amino acids. They localized on the cell surfaces of myeloid cells, functions as a pattern recognition receptor for various bacterial products, like LPS. They expressed on neutrophils, monocytes/macrophages, and fibroblasts, all of which are present in periodontitis lesions.

CD14 interacts with bacterial LPS, which shows the high affinity towards systemically circulating LPS-binding protein. The signal transduction of the LPS/LBP (LPS-binding protein)/CD14 ternary complex on effector cells is then transferred via the toll-like receptor (TLR)4/MD-2. Upon stimulation, the TLR4/MD-2 complex leads to the activation of innate host defense mechanisms through the nuclear factor- κ B pathway and the release of pro-inflammatory cytokines.

So many studies have undergone on this polymorphism and researchers had concluded that there is association between CD14 polymorphisms and periodontitis. Recently, Tervonen *et al.* in 2007 showed that the extent of periodontal disease was higher in subjects with the T-containing genotype (TT and CT) of CD14 -260C > T and the GG genotype of IL-6 -174C > G when compared to the extent in the rest of the group. The above two composite genotypes are seen in severely affected periodontal disease. We conclude that the CD14 -260 polymorphism may be associated with Chronic Periodontitis.

4.6. Toll-Like Receptor Gene Polymorphisms:

Toll-like receptors are signal molecules essential for the cellular response to bacterial cell wall components¹¹.

Several studies have attempted to associate the TLR polymorphisms with periodontitis, but controversial results were obtained. Brett *et al.* in 2005 found that the TLR-4 (-399) gene polymorphism showed a statistically significant difference was between total subjects with periodontal disease (aggressive/chronic) and controls. Fukusaki *et al.* in 2007 revealed that the frequency of the C/C genotype in TLR4 3725G > C polymorphism was significantly higher in both the moderate and the severe periodontitis patient group than in the control group.

4.7. Transforming Growth Factor - β 1 (Tnf- β 1) Gene Polymorphism

Transforming growth factor - β 1 (TGF- β 1) is a multifunctional cytokine that regulates cell growth, differentiation, and matrix. TGF - β is secreted by platelets,

macrophages, and lymphocytes and induces fibrosis in a variety of tissues. It regulates connective tissue formation and remodeling in both soft and mineralized connective tissues. It has potent immunosuppressive activity and down-regulates the transcription of other pro-inflammatory cytokines. The gene is encoded on chromosome 19q13.1^[12].

TGF- β 1 gene polymorphisms have been associated with risk for systemic diseases including cardiovascular diseases and rheumatoid arthritis which are related to periodontitis. In previous studies shown that Cytokines gene polymorphisms play an important role in the pathogenesis of periodontal diseases. Skaleric *et al.* found elevated TGF- β 1 levels in gingival crevicular fluid samples from sites with deeper periodontal pockets^[3, 12].

4.8. Card15/Nod2 Gene Polymorphisms

Nucleotide-binding oligomerization domain (NOD) receptors, including NOD1, NOD2, and ICE protease activating factor (IPAF) are cytoplasmic receptors for recognition of microbial products. These receptors either detect organisms that enter the cytoplasm of the cell like the intracellular bacterium *Shigella flexneri* or detect products that released or transported into the cytoplasm by processes such as phagocytosis and degradation of microbes.

The NOD2 protein encoded by the CARD15 gene is located on chromosome 16.

The 3020insC and 2104 C > T polymorphisms of the CARD15 (NOD2) gene lead to impaired activation of nuclear factor- κ B, resulting in altered transcription of proinflammatory cytokine genes and reduced expression of these cytokines. Thus it found a great association with periodontitis^[13].

4.9. N-Formyl-L-Methionyl-L-Leucyl-L-Phenylalanine (Fmlp) Receptor Polymorphisms:

Human neutrophils play a key role in host defense against bacterial infections. Neutrophils are activated by the bacterial formyl peptide N-formyl-l-methionyl-l-leucyl-l-phenylalanine (FMLP). FMLP binds to a specific formyl peptide receptor (FPR). These receptors are seven-transmembrane pertussis toxin-sensitive G protein-coupled receptors. Ligand binding to FPR activates some downstream effector enzymes including phospholipase C, catalyzing the cleavage of phosphatidylinositol 4,5-biphosphate into secondary messenger's inositol 1,4,5-triphosphate and diacylglycerol leading to calcium mobilization and activation of protein kinase C. These signaling events triggers morphological and biochemical alterations including polarization of the actin cytoskeleton, activation of various integrins, and directed migration. FPR signaling also initiates the production of superoxide and arachidonic acid metabolites and induces degranulation. These events allow phagocytic leukocytes to locate, sequester, and destroy invading microorganisms^[3].

FPR located on human chromosome 19q13.3. Localized aggressive periodontitis is a disease characterized by rapid loss of alveolar bone in teeth of otherwise healthy patients. Neutrophils from patients with localized aggressive periodontitis have been shown to exhibit diminished chemotaxis and low levels of FPR surface expression.

4.10. Matrix Metalloproteinase Polymorphisms

Matrix metalloproteinases (MMPs) are a large family of calcium-dependent zinc-containing endopeptidases, which are responsible for the tissue remodeling and degradation of the extracellular matrix (ECM)^[1, 22].

Several investigators have evaluated in the recent years the relationship between polymorphisms of genes for MMPs and periodontitis owing that it is difficult to relate single-nucleotide polymorphisms of MMP genes with periodontitis.

4.11. Cathepsin - C Polymorphisms

Cathepsin C (CTSC) also known as dipeptidyl peptidase I is a lysosomal exo-cytosine protease belonging to the peptidase C1 family. Cathepsin C gene consists of seven exons and is located on chromosome 11q14-q21. It acts as a central coordinator for the activation of many serine proteases in immune or inflammatory cells [3].

Noack *et al.* in 2008 analyzed the carrier frequency of cathepsin C genotype that the missense variant p.I453V was significantly increased in persons with the disease compared to healthy control individuals. Cathepsin C activity in leukocytes from individuals harboring this variant was significantly reduced and no influence of promoter variants was found on mRNA expression. It was concluded that Cathepsin C gene variants contribute to increased susceptibility in generalized aggressive periodontitis.

4.12. Vitamin D Receptor Gene Polymorphisms

Vitamin D receptor gene polymorphism has regulatory effects on bone mineral density and bone turnover. Hennig *et al.*, suggested that genotype of TaqI VDR gene might be a risk indicator for susceptibility to EOP [14].

4.13. Rank/Osteoprotegrin Gene Polymorphisms

RANKL and its receptor RANK have been implicated in increased rates of bone resorption in periodontal disease. Key mediators of osteoclast differentiation and activation involve receptor activator of nuclear factor- κ B (RANK), RANK ligand (RANKL), and osteoprotegrin (OPG). An association analysis with allelotypes showed that SNPs identified in the RANK/RANKL/OPG genes have no significant association with AgP in the Japanese Population [15].

4.14. Plasminogen Activator Gene Polymorphisms

The fibrinolytic system also called the plasminogen-activating system plays an important role in controlling proteolytic events in the extracellular matrix. This system is also involved in fibrinolysis in balancing the coagulation of blood as well as in cell migration and tissue remodeling [16].

Two types of PA that are encoded with different genes and therefore immunologically distinguishable were identified by Collen in 1999 are

- a) The tissues/blood vessel-type activator.
- b) urokinase-type activator.

Their activities are regulated by specific inhibitors called plasminogen activator inhibitor-1 (PAI-1) and PAI-2. The presence of the PA system was previously demonstrated in high levels in inflamed gingival tissues and gingival crevicular fluid (GCF) of periodontitis patients and thereby plays a key role in local inflammatory reactions in gingival tissues. The destructive potential of the PAs plays an important role in the spread of inflammatory reactions and thereby could contribute to the initiation and progression of periodontal disease. It was demonstrated that elevated plasma PAI-1 activity is related to the reduced fibrinolytic activity in individuals with cardiovascular disease [16].

5. Conclusion

Periodontal disease is a multi-factorial disease. Genes are

important for those factors. Although several studies associate various candidate genes to periodontitis, to date there is not much clarity in genetic susceptibility to the disease since its multitude etiological factor. Present knowledge suggests that genetic polymorphism is associated with the pathogenesis of the periodontal disease. Genetic factors along with environmental factors are strongly associated with the development and progression of periodontal disease. Identification of specific gene and genetic variants, aids in diagnosis and treatment of aggressive periodontitis. Future research should focus on the multitude of genes, their interactions, and epigenetic regulation during different stages of periodontal disease pathogenesis is required to fully understand the molecular mechanisms behind the etiopathogenesis of periodontitis.

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