Review Article

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Action of Gene Polymorphism in the Pathogenesis of Periodontal Diseases: A Narrative Review

Abstract:
Presently, it is known that pathogenic bacteria are the key factors for the initiation of periodontal disease, but the host responseand the severity of clinical expression are largely determined by genetic susceptibility and environmental factors. There isevidence that the individual response to the environment and variations in the immune response in periodontitis areassociated with genetic factors. The gene polymorphisms like interleukin-1 beta (IL-1b), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-a) genes and their factors that determine the production of various cytokines which play an important role in the pathophysiology of inflammation andperiodontal diseases. A sequel of this realization is that if the genetic basis of periodontal disease susceptibility can be understood, such information may have diagnostic and therapeutic value.This review focus to upgrade the general practitioners and periodontist about various genetic polymorphisms associated with periodontal diseases to aid in a better approach to the condition in the future.

Key-words: Gene, Polymorphism, Cytokines, Host response, Periodontal disease.

Introduction:

Periodontal disease is the world's second most common oral disease [1].Periodontitis is defined as “an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both[2]. Still, it is believed that bacteria are necessary for the development of periodontitis but in most cases specific microorganisms are not enough to cause the disease[3].While microbial and other environmental factors commence and regulate periodontal disease, individuals respond distinctively to regular environmental challenges, and this distinctive response is determined by the individual's genetic profile. Genes play an important role in the progression of periodontal diseases. The interconnection of genetic mutations and polymorphisms with numerous environmental agents results in harshness of the periodontal disease[4] (Figure 1). Hence, the aim of this review is to describe how gene polymorphism acts on periodontal disease.

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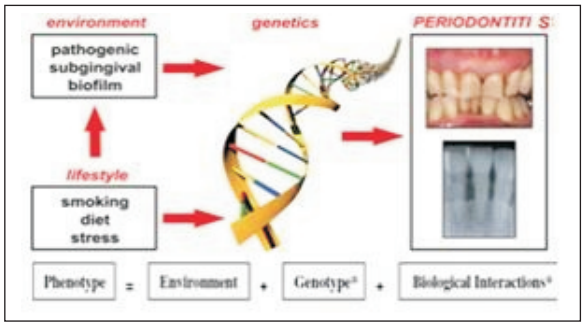

Figure 1: The environmental factors (smoking, diet, etc.), genetic factor (eg. Polymorphisms) and biological interaction (gene-geneand gene-environment) yield the resultant phenotype (periodontitis).

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Definitions:

1. GENE: Gene is the functional and physical unit of hereditary passed from parents to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.[5]

2. ALLELE: An allele is an alternative form of a gene (one member of a pair) that is located at a specific position on a specific chromosome.[5]

3. POLYMORPHISM: Polymorphism refers to the region of genome that varies between individual members of the population in such proportions that the rarest of them cannot be maintained just by recurrent mutation [5].

4. GENETIC POLYMORPHISM: When a specific allele occurs in at least 1% of population, it is said to be a genetic polymorphisms [5].

A brief introduction about Gene:

Gene is the basic unit of hereditary. The human genome can be made up of 25,000-35,000 genes. DNA is known as a chemical substance of a gene. It is made up of two long chains which are twisted around one another to form a double-stranded helix (Figure 2).The subunits of each strand are called nucleotides, and each one contains one of four chemical constituents called bases. There are 3 billion pairs of bases named asadenine (A), thymine (T), guanine (G), and cytosine (C). Adenine (A) added with thymine (T) and guanine (G) with cytosine (C). There are 22 pairs of chromosomes present in human genome, known as autosomes and 2 sex chromosomes [6].

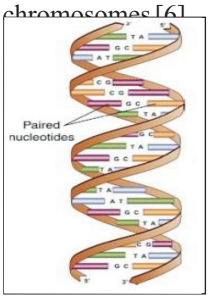

Figure 2: Watson's double helix model of DNA

Sequence of events to determine phenotype from genotype:

The term genotype is used to distinguish one allele, or a combination of alleles, from the others. The genotype of an organism determines its phenotype. Thus, the interactivity of genotype and environment induce the phenotype of the individual [6]. (Figure: 3)

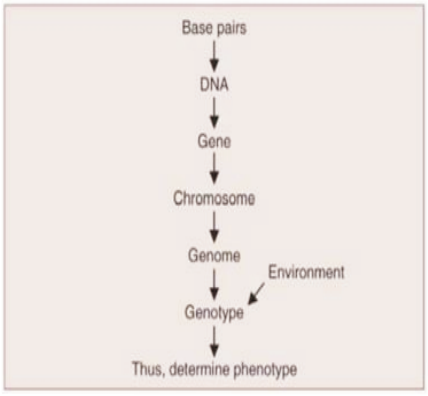

Figure 3: Flow diagram showing basic sequence information of genotype which under the influence of environment determines the phenotype of the individual.

Gene polymorphism:

Gene polymorphisms are located within the genome that vary in sequence among different individuals which causes genetic alterations and modify the function of gene product. Polymorphism in human gene can be found in the following locations [6]. (Figure: 4)

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

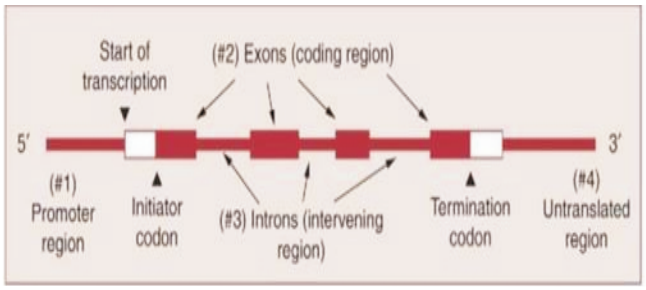

Figure 4: Structure of human gene and sites where polymorphisms occur.

Types of Gene Polymorphism:

There are three types of gene polymorphism:-[6]

1. Change in single base pair at genomic DNA [single nucleotide polymorphisms (SNRs).
2. Simple sequence of repeats of dinucleotide or tri-nucleotide (variable number of tandem repeats or minisatellites).
3. Insertions and deletions of few bases, exons, or entire gene.

Polymorphisms and their relationship to periodontal disease:

Periodontitis is a multifactorial disease. It has complex etiology and genetics is considered as a susceptibility factor for this disease. Genotype polymorphism is one of the most common disease-modifying gene alteration which is responsible for increased susceptibility of the individual to periodontal disease [6].

Classification of Gene Polymorphism:

Gene polymorphism can be classified as follows as shown in (Table 1)[7].

Table-1 Classification of Gene Polymorphism

CYTOKINES AND CHEMOKINE RECEPTOR POLYMORPHISM	METABOLISM RELATED RECEPTOR POLYMORPHISM	ANTIGEN RECOGNITION RELATED POLYMORPHISM	IMMUNORECEPTOR RELATED POLYMORPHISM	MISCELLANEOUS GENE POLYMORPHISM
Interleukins (IL-1,IL-2,IL-4, IL-6, IL-10)	Vitamin D receptor (VDR)	Human leukocyte antigens (HLA).	Fc-Gamma Receptor (FCγR)	Angiotensin converting enzyme (ACE).
Tumor necrosis factor (TNF)	Calprotectin	CD 14 molecule	Cathepsins (CTS-B,-D,-G,-L)	Type 1 collagen
Transforming growth factor-β (TGF –β).	N-acetyl transfererase2 (NAT2)	n-formyl-L-methionyl-L-leucyl-L-phenylalanine	Toll-like receptor (TLR-2,-4)	Endothelial nitric oxide synthase (Eons)
		(Nfmlp)/Formyl peptide receptor (FPR)		
Interleukin enhancing binding factor (ILF)	Matrix metalloproteinases (MMPs)		Prostaglandin family (PTG)	Estrogen receptor -2
IL-6 signal transducer (IL6ST)	Tissue inhibitor of metalloprotein (TIMP-1,-2,-3)		Hydro prostaglandin dehydrogenase (HPGD)	Fibrinogen
Caspase recruitment domain -15	Receptor for advanced glycation end-products (RAGE)		Bactericidal/permeability increasing protein	Glutathione-S- transferase-M1,-T1
Chemokine receptor-5 (CCR5)	Osteoprotegin (OPG), osteopontin(OPN)		Cytotoxic T-lymphocyte antigen-4	Lactoferin
Fas ligand			Human β defensin β 1	Plasminogen activator inhibitor
Lymphotoxin			E-selectin, L-selectin	Tissue plasminogen activator (t-PA)
Regulated on activation Normal T Cell Expressed and Secreted (RANTES)			Intercellular adhesion molecule -1	SO S1 gene
			Mannose binding protein	

Some of the important polymorphisms in relation to periodontal disease are discussed as follows:

1.IL-1 :

Interleukin-1 (IL-1) is a pro-inflammatory cytokine and produced by inflammatory cells such as monocytes, macrophages, and dendritic cells. It plays an important role in thetissue destruction connected with periodontal diseases due to its pro-inflammatory and bone-resorptive properties [8].

2. IL-6:

T-cells producedInterleukin-6 during inflammationwhich is encoded by the IL-6 gene localized on chromosome 7p21. Interleukin-6 is a cytokine that promotes bone resorption. It stimulates and control the osteoclasts. As a result, it plays an important role in the predisposition and progression of periodontal destruction [9].

3. IL-10:

Monocytes/macrophages, dendritic cells, B- lymphocytes (particularly the CD5+ B cells), various subsets of CD4+ and CD8+ T-cells and also human keratinocytes produced IL-10 . IL-10 gene is found on chromosome 1q31-q32, in a cluster with other interleukin genes, including IL-19, IL-20, and IL-24. IL-10 have various effects in immunoregulation and inflammatory action [10].

4. TNF-α:

TNF-ais produced by macrophages. It is a major cytokine in the development of the inflammatory response in periodontitisand could be important for the effectiveness of the immune response as well as degree of clinical results during the anti-inflammatory therapy of the disease[11].

5. Vitamin D receptor gene polymorphism:

Polymerase chain reaction (PCR) and restriction enzyme digestion are commonly used to identify VDR gene polymorphism. [12].Vitamin D receptor gene polymorphism regulates bone mineral density and turnover [13].

6. Calcitonin receptor polymorphism:

Nosaka et al. [14]did a study and revealed that patients with this calcitonin receptor polymorphism were 20 times more likely to suffer from buccal marginal bone loss than patients who were negative calcitonin receptor genotype.

7.Toll-like receptor gene polymorphism:

Toll-like receptors are signal molecules that are required for the cellular response to bacterial cell wall components. Different functional effective polymorphisms of TLR-4gene (Asp 299 Arg 677 Trp; Arg753 Gln) are linked with impaired LPS signal transduction[15].

8. CD 14 gene polymorphism:

The R-allele in the promoter region of CD14 at position -260(-159) increases the transcriptional activity of the gene[16].Patients with severe periodontitis had a higher frequency of the N –allele and the N/N genotype of the CD14-1359 polymorphism.

9. CARD 15 gene polymorphism:

CARD 15 (NOD2) gene causes impaired activation of nuclear factor-κ B, leading in altered transcription of pro-inflammatory cytokine genes and reduced expression of these cytokines. Periodontitis have not been associated with *CARD 15* polymorphisms [17].

10. Cathepsin C gene polymorphism:

Cathepsin C is a lysosomal protease present in neutrophils and macrophages as well as epithelial cells. Hart and co-workers, 2000, discovered and localized a gene on chromosome 11,that causes severe form of pre-pubertal periodontitis in a family of Jordanian descent[18].Other CTS C gene mutation have been associated with the Papillon-Lefevre syndrome, a disease which results in a severe form of pre-pubertal periodontitis[19,20].

11. Matrix metalloproteinase gene polymorphisms:

MMP-1 is an important mediator of connective tissue destruction in periodontal disease. Cao Z *et al*., evaluated the association between the MMP-1 promoter gene polymorphism and chronic periodontitis susceptibility and/or severity in a Chinese population and revealed that severe chronic periodontitis may be linked with a single nucleotide polymorphism in the MMP-1 promoter region of -1607 [21].

Methods of studying genetic variants in periodontal disease:

1. Familial Aggregations:

Familial aggregation of a trait or disease can suggest genetic etiology. It can be caused by shared genes, environmental exposures, and similar socioeconomic factors. There is literature on family aggregation of periodontal diseases, but due to different terminology, classification systems and lack of standardized methods of clinical examination, it is difficult to compare findings directly. Most familial reports are for early-onset periodontitis (EOP) now called as aggressive periodontitis [22].

2. Twin Studies:

Monozygous (MZ) twins are genetically identical and dizygous (DZ) twins have 50% of their genes in common. Differences in disease experienced between MZ twins must be due to environmental factors, and between DZ twins they could arise from both environmental and genetic differences. Twins studies of periodontitis have been limited in scope and generally of small numbers. Most twin studies have studied chronic periodontitis [23].(Figure: 5)

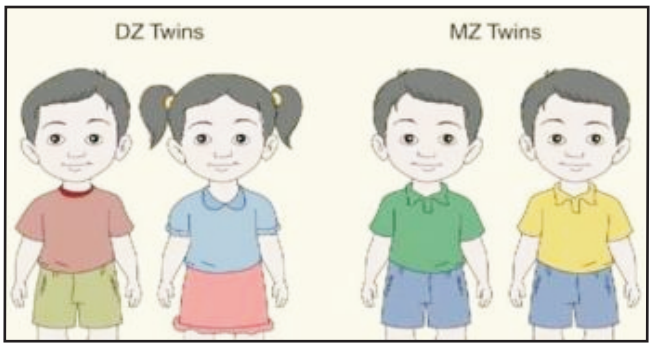

Figure: 5 Effect of environment and gene on the phenotype of dizygotic(DZ) and monozygotic(MZ)twins.

3. Segregation Analysis:

Segregation analysis is a statistical analysis which is used to determine the pattern of transmission of trait or disease within a family. The mode of inheritance of any trait depends on the following:

a. The presence of diseased allele on the autosome or sex chromosome.
b. Whether it is dominant or recessive.
c. Whether it is fully or partially penetrant (Figure:6).
It is used to assess whether the disease is caused by single gene or multiple genes or exposure to the environmental factors [6].

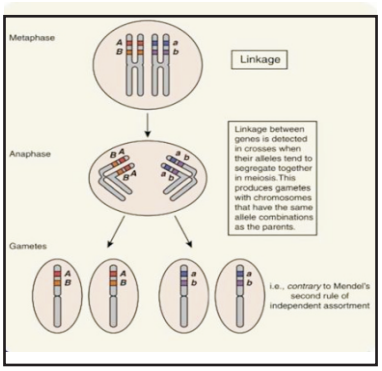

Figure: 6 Diagram showing linkage between the alleles as they segregate together in meiosis.

4. Linkage Analysis:

Linkage analysis is a technique used to localize the gene for a trait to a specific chromosomal location. The fact that genes are located in close proximity to one another on a chromosome. They are transferred from generation to generation as a unit. These genes are said to be "linked" and they violate the Mendelian law of independent assortment (Figure: 6).The disadvantage of this method is that it cannot be recommended for complex diseases [6].

5. Association Analysis:

Genes contributing to common, complex diseases like periodontitis have been proved to be more difficult to isolate. A hypothetical example of the logic in play, in the study of gene polymorphism associations with the disease in periodontitis (condition A), bone is lost (abnormality B) and since bone is removed by osteoclasts, which are influenced by a specific gene (gene C), the association of a known polymorphism (polymorphism D) of gene C periodontal diseases studies [24]

Two types of association analysis are commonly used: Population based and Family based approaches(Figure:7).

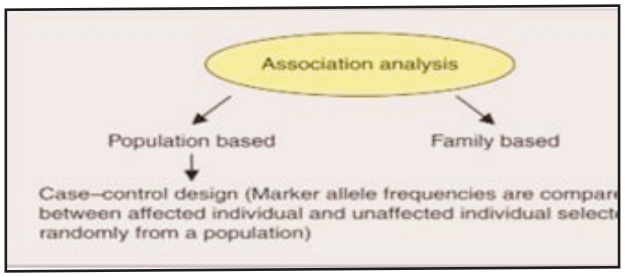

Figure: 7 Association analysis

Significance of genetics in periodontal disease:

Periodontal research has greatly expanded to elucidate therole of genetics in periodontal disease states. As a result,there has been lot of interest in identifying allelic variants ofgenes that can be used to predict periodontal disease risk. Records of genetic polymorphisms related toperiodontal disease are continuously increasing[25](Figure 8). Presently, genetic test kit is available to test the severity of chronic periodontitis and is called periodontal susceptibility test (PST). It determine the presence of specific polymorphisms of the IL-lo' and IL-1~ genes. Aggressive periodontitis is a kind of rapidly progressive form of periodontitis. It is identified by its severity and rapid destruction. It is mainly seen in early age group. Several studies revealed that the high prevalence of aggressive periodontitis occurs among siblings. It has tendency to aggregate in families and proposed that genetic factors is appraised to be important factor for the susceptibility to this disease [6].A study by Deihl et al. found that quantitative measurements of periodontal parameters show significant levels of heritability in aggressive periodontitis patients[4]. In chronic periodontitis the role of genetic component has been evaluated from twin and family studies. The twin model is probably the most effective method to study genetic aspects of periodontal disease [12]. Kornman etal. in 1998, reported that a genetic variation of polymorphism in the genes encoding Interleukin-1a (IL-1a) and IL-1β is linked to a higher risk of a more aggressive form of chronic periodontitis in subjects of Northern European origin[26].

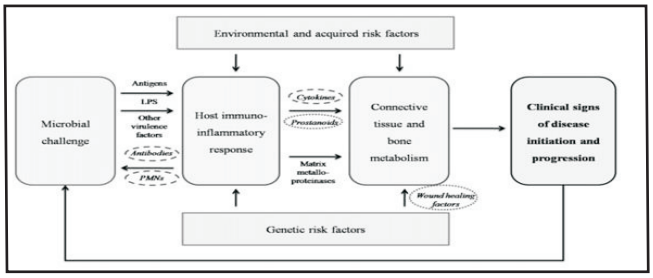

Figure: 8 Genetic factors in Periodontitis and their potential biologic influence.

New achievements of genetics in periodontal diseases:

Many studies have been done to evaluate the genetic basis of periodontal disease. The genetics and evolution of periodontal disease have provided us with useful information for identifying disease markers. Identification of candidate genes and their use as periodontal biomarkers is the possible clinical application of the research done so far in this field.Aberrant genetic pattern is known asepigenetics. Presently, it is a new concept in the field of periodontitis that may be able to explain the missing link between genetics, disease, and environment. It acts through chemical modifications of DNA and proteins which are interconnected with it by preventing the binding of transcription factors through histone modifications (transient) or DNA methylation (stable form). Methylation, histone modification, and RNA interference are the three major methods of epigenetic regulation [6] (Figure: 9).

In future, genome-wide association studiesmay bring to light novel loci susceptible to periodontitis.

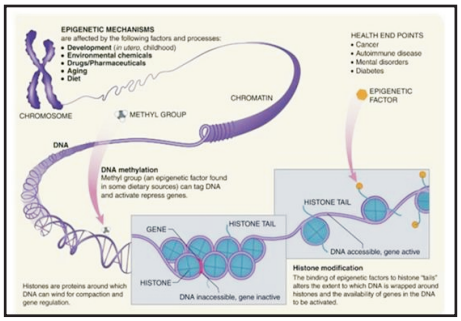

Figure: 9 Diagram showing the mechanism of epigenetics and its effect on health.

Conclusion:

Periodontitis has a multicausal etiology, in which genetic factors play an important role. The Genetic information enables the clinician to direct prevention and cure to individuals who are most susceptible to disease. While, periodontal research focused on studies of microbiological pathogenesis and oral environments. Currently, it is widely accepted that susceptibility to inflammation is also determined by genetics. The role of genetic polymorphisms on periodontal disease may help in modifying our treatment plan to improve periodontal health.

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