Chapter

# Genetics and Periodontal Disease: An Explicit Insight

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## Abstract

A branch of Biology which deals with the science of hereditary influences on living organisms is termed as Genetics. There has been a broad study related to hereditary influence on human tissue linking to health and disease conditions. A vital role is played by genetics in the proper functioning, adaptive repair, regeneration and remodelling of hard and soft tissue. A major segment of genes are related to periodontal disease. Periodontal disease, being multifactorial in origin is directly or indirectly known to be caused by genetic factors also. A study on human and animals validates the concept that genetics could have influenced periodontal disorders and also plays a key role in the predisposition and progressiveness of the condition. The role played by genetics to damage the inflammatory and immune response system of the host tissues during periodontal conditions has been proved and this section will give a clear insight on the influence of genetics in this condition.

**Keywords:** Genetics, Periodontal disease, Hereditary influence, Polymorphism, Syndromes, Genetic study design

## 1. Introduction

A distinct approach is required for periodontal pathologies that produces lesions within the tooth- supporting tissues, once associated with risk factors which are complementary to systemic diseases [1]. Bacterial plaque is the prime aetiology of periodontal diseases, accelerating tissue damage. However, the role of plaque is debated when the vulnerability to periodontal diseases persist despite regular conditions. According to the majority of researchers' perspective, periodontal disease cannot occur in the absence of plaque and tartar, and also suggests that a systematic predisposition merely progresses the tissue destruction caused by microbial flora. On the other hand, few authors claim that there is no concrete evidence establishing cause-effect relationship between the nonspecific bacterial plaque and severity of tooth supporting tissue injury [2].

The host immune response system, the integrity of the tissues, humoral and cellular immunity, and certain endocrine and nutritional factors are the major factors for the development and progression of periodontal disease. Multitude of other factors are also related to periodontal diseases including age, intraoral sites that are more prone to infection and specific microbial agents such as Captosinofaga, Actinomyces naeslundi and Actinobacillus actinomycetemcomitans [2]. Apart from the host immune response system, these factors also add on

to the vulnerability to periodontal disease, presenting simple to complex signs. Furthermore, the presence of associated metabolic disorders would also lead to periodontal damage [2].

Genetic elements play a vital role in influencing the inflammatory and immune response of the periodontal disease. Due to the key role played by the immune system in the pathophysiology of the disease, research is directed to identify the genetic mutation or polymorphism related to the various aspect of immunity. The result of these genetic variations might be minor or unimportant or very important and severe based on its effect and infectivity [3]. Genetic diseases are broadly classified into two entities: Simple Mendelian Disorders and Complex Genetics Disorders. Simple Mendelian Disorders are otherwise known as monogenic or single-gene disorders since they are caused by alterations of a single gene, acquired through autosomal recessive or dominant type of inheritance. Several monogenic gene disorders with biochemical defects present with severe periodontitis as one of their clinical manifestations. In these conditions, genetic alteration occurs at a single locus, producing the clinical phenotype which is responsible to cause the disease. Such a genetic alteration, that is associated with a disease phenotype in all families and there is no alternative mechanism to overcome the impact of the genetic defect, is termed as mutation [4].

Complex genetic diseases prevail in more than 1% of the population and are known to be more dominant than Simple Mendelian disorders. Being affected by environmental and lifestyle factors, complex genetic diseases occur as a result of genetic variations at multiple areas of the genes. Alterations in multiple genes, with each contributing a little to these complex genetic diseases, are called polymorphisms. Specific allele occurring in at least 1% of the population is known as genetic polymorphism. Single base mutation that replaces one nucleotide for another is said to be the simplest type of polymorphism and is termed as a single nucleotide polymorphism (SNP). Restriction fragment length polymorphism (RFLP) and simple tandem repeats (STRs), comprising of nucleotide or allele repetition are other types of polymorphism [5]. These genetic polymorphisms are not directly associated with the disease as in monogenetic disorders, however, specific alleles are found with greater incidence in the affected individuals than healthy individuals. The results prove to be true only when two different genetic variations coexist. Complex periodontal disorders are chronic, slowly progressive and are mostly of mild phenotype [5].

Variations in numerous genes encoding different proteins result in a genetic predisposition to a clinical phenotype. Environment and lifestyle play a significant role in impacting the development of complex diseases. Host response influenced by the genetic makeup is responsible for the progression of periodontal disease. Genetic defects or alterations can raise the incidence of periodontal disease. If the physiological process elicited by the gene is related to the occurrence and severity of disease, that specific gene is considered as a contributory element in periodontal disease [6]. Literature evidence reports that the genetic variants play a major role in the aetiology of syndromic and non-syndromic periodontitis.

## 1.1 Terminologies

### *1.1.1 Allele*

One of two or more alternate forms of a gene or marker at a particular locus on a chromosome. (A glossary of relevant genetic terms –Dialogues in clinical neuroscience) [7].

*1.1.1.1 Chromosomes*

A thread-like, gene-carrying bodies in the nucleus of a cell. Chromosomes are composed primarily of DNA and protein. They are visible only under magnification during certain stages of cell division. Humans have 46 chromosomes in each somatic cell and 23 in each sex cell. (Basic principles of Genetics -Glossary of terms) [8].

*1.1.1.2 Genes*

Units of inheritance usually occurring at specific locations, or loci, on a chromosome. Physically, a gene is a sequence of DNA bases that specify the order of amino acids in an entire protein or, in some cases, a portion of a protein. A gene may be made up of hundreds of thousands of DNA bases. Genes are responsible for the hereditary traits in plants and animals. (Basic principles of Genetics -Glossary of terms) [8].

*1.1.1.3 Genetics*

The study of gene structure and action and the patterns of inheritance of traits from parent to offspring. Genetic mechanisms are the underlying foundation for evolutionary change. Genetics is the branch of science that deals with the inheritance of biological characteristics. (Basic principles of Genetics -Glossary of terms) [8].

*1.1.1.4 Genotype*

The genetic makeup of an individual. Genotype can refer to an organism's entire genetic makeup or the alleles at a particular locus. (Basic principles of Genetics -Glossary of terms) [8].

*1.1.1.5 Monozygotic twins*

Identical twins. Twins that come from the same zygote are essentially the same genetically. Differences between monozygotic twins later in life are virtually always the result of environmental influences rather than genetic inheritance. Fraternal twins may look similar but are not genetically identical. (Basic principles of Genetics -Glossary of terms) [8].

*1.1.1.6 Dizygotic twins*

Nonidentical twins that arise when two different eggs are fertilised by two different sperm; also called fraternal twins. (Glossary. Nature) [9].

*1.1.1.7 Mutation*

An alteration of genetic material such that a new variation is produced. For instance, a trait that has only one allele (A) can mutate to a new form (a). This is the only mechanism of evolution that can produce new alleles of a gene. (Basic principles of Genetics -Glossary of terms) [8].

*1.1.1.8 Phenotype*

The observable or detectable characteristics of an individual organism--the detectable expression of a genotype. (Basic principles of Genetics -Glossary of terms) [8].

*1.1.1.9 Epigenetics*

Heritable changes to DNA structure that do not alter the underlying DNA sequence, eg, DNA methylation.

*1.1.1.10 Polymorphism (genetic)*

The existence within a population of two or more genotypes, the rarest of which exceeds some arbitrarily low frequency (say, 1 percent); more rarely, the existence of phenotypic variation within a population, whether or not genetically based. (Glossary. Nature) [9].

*1.1.1.11 Single nucleotide polymorphism (SNP)*

Heritable polymorphism resulting from a single base pair change. SNPs generally have only two alleles.

*1.1.1.12 Linkage*

In genetics, refers to how two genes that are nearby to one another on the same chromosome are often inherited together (Glossary. Nature) [9].

*1.1.1.13 Linkage disequilibrium*

Describes the state of two genotypes at different loci being dependent, showing a correlation; does not require gene linkage (Glossary. Nature) [9].

*1.1.1.14 Linkage equilibrium*

The association of two alleles at two or more loci at the frequency predicted by their individual frequencies (Glossary. Nature) [9].

*1.1.1.15 Segregational analysis*

The process of fitting formal genetic models to data on expressed disease characteristics (phenotype) in biological family members in order to determine the most likely mode of inheritance for the trait or disease under study. (NCI"s Dictionary of Genetic terms) [10].

*1.1.1.16 Histone modification*

A histone modification is a covalent post-translational modification (PTM) to histone proteins which includes methylation, phosphorylation, acetylation, ubiquitylation, and sumoylation. The PTMs made to histones can impact gene expression by altering chromatin structure or recruiting histone modifiers. (What is epigenetics).

*1.1.1.17 Linkage analysis*

Study aimed at establishing linkage between genes. Today linkage analysis serves as a way of gene-hunting and genetic testing (Webster's New World medical dictionary) [11].

*1.1.1.18 Concordance*

The amount of similarity in phenotype between a set of individuals. May be used to refer to the presence of the same trait in both members of a pair of twins. (Molecular biology -Glossary) [12].

*1.1.1.19 Discordance*

Typically means that a similar trait is not shared between twin members [12].

## 2. Methodology

An electronic bibliographic search was carried out in three databases namely Pubmed central, Google Scholar, Ebsco, focusing on genetic studies related to periodontics. Books on genetics and periodontics were additionally referred for writing the book review.

## 3. Genetic study designs

The studies that show evidence of genetic predisposition to periodontitis can be grouped into four areas of research based on the statistical approaches to determine genetic components and genetic model [13].

i. Family studies.

ii. Segregation analysis.

iii. Twin studies.

iv. Population studies.

v. Linkage studies.

vi. Association studies.

### 3.1 Family studies

Hereditary combination of a trait or disorder will recommend genetic aetiology. Hereditary patterns may additionally indicate exposure to common environmental factors within these families. Familial aggregation could result from shared genes, shared environmental exposures and behavioural risk factors like education, socio economic grouping, oral hygiene, possible transmission of bacteria, diseases like polygenic disorder, passive smoking, exposure to pollutants and sanitation. Therefore, the complex interactions between genes and also the surroundings should even be thought-about in the analysis of familial risk for periodontic diseases [14].

### 3.2 Segregation analysis

They are used to study the inheritance of disease within the families. Genes are passed from parents to kids in an exceedingly foreseeable manner, and typically segregate in families as foretold by Mendel's laws [15]. Pattern of transmission of disease through generations is analysed in several families and compared with those expected under different models of inheritance to choose the best fitting model.

In this way, segregation analysis helps to identify the best model that simulates the ascertained transmission of a trait in a given population by sequential comparison with all the available models. Segregation analysis is applied by geneticists to determine whether a trait transmission belongs to Mendelian mode of genetic transmission [16].

The pattern by which disease is transmitted across generations depends on whether or not disease alleles:

- Lie on autosome/sex chromosomes.
- Dominant or Recessive.
- Fully or partially penetrant.

Genetic characteristics involving mode of transmission (e.g. autosomal, X-linked, dominant, recessive, complex, multi-locus, or random environmental), penetrance, phenocopy rates and frequencies for disease and non-disease alleles are some of the characteristics assessed in the various models. Phenotype of individual will be determined by the dominant allele. The recessive allele can be inherited only if it is located at both loci on homologous chromosomes. Penetrance refers to the possibility that a particular phenotype will rise from a genotype. Partially penetrant explains that only few individuals who inherit the disease alleles will be affected. The power of segregation analysis was dependent upon the size of population to study the observed pattern of disease.

*3.2.1 Advantages*

Segregation analysis helps to assess whether the disease gene is autosomal or sex linked, recessive or dominant.

*3.2.2 Limitations*

1. Minimal power to resolve heterogeneity (Multiple causes)
2. Cannot distinguish between genetic and environmental influences
3. Mode of inheritance among older individuals was difficult to carry out
4. Does not find or aim to find a specific gene responsible for a trait.

**3.3 Twin studies**

Twin studies are commonly used to study the influence of genetic and environmental factors on the complex diseases like periodontitis with multifactorial aetiology. Studying phenotypic traits of twins is a method of differentiating variations due to environmental and genetic factors [17]. Sir Francis Galton in 1875 was the first scientist to use this concept. The subject of interest in twin studies can be monozygotic or dizygotic twins.

Monozygotic twins ascend from single fertilised ovum and are therefore genetically identical and always the same sex. Dizygous twins arise from the fertilisation of two separate ovum and share one half of their descendent genes in the same way as siblings do. Concordance refers to the degree of similarity between twins in one or more characteristics whereas discordance refers to the degree of dissimilarity between twins in one or more characteristics.

Only environmental factors might account for any discordance in disease between monozygotic twins [18, 19]. Environmental and genetic variation might account for any discordance in disease between dizygotic twins. Presuming that the environmental influence is constant, the effects of excess shared genes in monozygotic twins measures the difference in discordance between monozygotic (MZ) and dizygotic (DZ) twins [20, 21].

For binary traits (present or absent), a genetic effect is inferred if the positive concordance rate, or percentage of twin pairs in which both twins are affected, is greater for MZ than DZ twins.

There are two types of twin studies:

i. Classic twin study- Monozygotic and dizygotic twins are reared together and compared.

ii. Study in which monozygotic twins are reared apart- This study shows the effects of shared genes without the confounding effects of a common family environment. Any similarities between both of them will be attributed to their shared genes and dissimilarities will be because of environmental factors.

Heritability, which refers to the proportion of phenotypic variation attributed to genetic variation, can be evaluated efficiently by twin data. 50% heritability clearly states that half of phenotypic variance in the population is attributed to genetic variance and it does not imply that a child of an affected parent has a 50% chance of inheriting the disease.

It was proposed that 38–82% of the population variance for probing depth (PD), attachment loss (AL) and dental plaque may be attributed to genetic factors in a study involving 110 pairs of adult twins [22]. A successive study on 64 monozygotic and 53 dizygotic pairs of adult twins disclosed the fact that genetic variance contributes to almost half of the variance in disease pattern in the population. From the results of the study, it was concluded that MZ twins were more alike than DZ twins for all clinical parameters [23].

Therefore, the difference in concordance between MZ and DZ twins for a specific phenotype could be used to evaluate the relative contribution of genes (heredity) and environmental factors to a disease and analysing disease presentation in twins is an essential first step in this process. Though twin studies overcame the drawbacks of segregation analysis, few such studies have been conducted because of the inadequacy of such twins.

### 3.4 Population studies

Environmental or behavioural risk factors for a disease are usually first detected in significant epidemiological or population-based studies. A genetic polymorphism is the long-time manifestation in a population of two or more genotypes that could not be maintained by frequent mutation.

The frequencies of polymorphisms of candidate genes can be compared between diseased individuals and controls [4]. It can be proved that the candidate gene determines the vulnerability to disease when there is a clear cut difference in the frequency of a specific polymorphism, between a case group and a control group. In this way, pathogenesis, causal heterogeneity of disease process and individuals most at risk for the disease can be interpreted well [24, 25].

In chronic periodontitis, no evidence of any simple pattern of genetic transmission that would support an etiologic role for a single gene mutation is demonstrated. In contrast to simple genetic diseases that may be caused by a single genetic

mutation, the additive effect of multiple genes is a determinant of disease susceptibility in complex diseases such as chronic periodontitis [14].

### 3.5 Linkage studies

Linkage analysis is a technique used to map the gene responsible for a trait to a specific position on a chromosome. These studies are based on the information that genes that are located closely on the same chromosome incline to have inherited together as a unit. Such genes are said to be linked and defy Mendel's law of independent assortment.

The distance between two allele at different loci will determine whether they will recombine. This is termed as recombination or crossover event. There is 50% chance that any two maternal or paternal alleles will recombine and be transmitted together to an offspring. However, alleles at nearby loci are linked and they tend to segregate together.

Linkage study necessitates use of very expensive DNA markers which was acceptable only after learning strong evidence of a genetic basis for a trait using segregation analysis or family aggregation analysis. By identifying the genetic markers that are associated with the disease causing alleles, the researchers can modify the location of a disease allele. Inheritance of a disease can be established if the distance between marker and disease allele is within 20–30 centimo grams (cM). In humans, 1 cM represents approximately 1 million nucleotide bases.

In this way, segregation of a trait in a manner consistent with linkage to a known genetic marker can be tested. Once the linkage is detected, the gene responsible for the trait can be placed in the vicinity of the linked genetic polymorphism since the exact chromosomal location of the genetic marker is known. Hence the genetic basis of disease is proved by linkage. Linkage is usually used as an initial step to identify the approximate location of a gene of interest, allowing the successive studies to determine the mutation responsible for a disease trait.

Linkage studies usually start by identifying markers (Single Nucleotide Polymorphisms) on a section of chromosome and then narrowing down the region until the gene of interest is found. DNA markers that are located proximal to a disease gene will be inclined to be inherited together with the disease gene. The closer a marker is to the disease gene, the closer the linkage and the more likely it is that they will be inherited together.

Linkage studies use sets of families, containing multiple affected individuals. Genotypes are determined for affected and unaffected family members, and complex statistical models are used to decide whether marker allele and disease co-segregate in the families under a given inheritance model.

Linkage is calculated using a LOD (Logarithm of odds) score. It is described as the ratio of probability that the disease and the marker loci are linked rather than unlinked. Supporting linkage gives a LOD score of +3 (1000:1) whereas, absence of linkage denotes a score of −2. Boughman et al. was first to assess the linkage between dentinogenesis imperfecta and aggressive periodontitis [26].

Marker linked to disease allele within a family may not be linked with disease in the population, which implies that same marker allele need not be transmitted with the disease allele in all affected families. However, Allelic associations (which is discussed below) occur when the same marker allele is linked to disease in multiple families.

#### *3.5.1 Drawbacks*

- Linkage studies have been successful only in identifying the genetic basis of simple Mendelian traits, where mutation of a single gene can cause a disease.

Nevertheless, Linkage studies of complex diseases are not successful since complex diseases are due to the combined effect of multiple genes of minor effect and each gene contribute a small amount to the disease phenotype [27, 28].

- It has extremely low statistical power for diseases in which there is extensive heterogeneity among different families that have different combinations of vulnerable genes and environmental exposures.

### 3.6 Association studies

Associations indicate that the presence of an allele confers risk for disease within a specific environment. Allele association helps to identify whether the frequency of an allele is considerably increased or decreased in a particular disease. The difference between association studies and genetic linkage is that association studies compare a population of affected individuals with control population whereas, the latter is demonstrable only in families or siblings.

Therefore, Association studies involve candidate gene approach, a gene mapping approach that tests whether one allele of a gene appears more frequently in patients with disease than in subjects without the disease. Candidate genes are selected based on their reasonable role in disease process such as producing a protein that is important in disease pathogenesis.

Linkage disequilibrium is a term used when the same marker allele is linked with disease in multiple families. Frequency of allele at a given locus is compared between patients with disease and healthy subjects to test this association. Biologic link between the disease and an allele cannot be confirmed through association. Association might result due to few environmental factors causing both the marker and the disease to rise in the population, or due to a difference in the racial or ethnic makeup of the cases and controls, or from chance alone [29]. True linkage disequilibrium refers to a situation when marker and disease allele are placed close to each other on chromosomes and the chances of disease are more.

On the whole, this population-based approach compares marker allele frequencies between affected and unaffected individuals, using a standard case–control design. When a positive association is found, few interpretations are made: [30].

- Associated allele is considered as the disease-predisposing allele.
- Associated allele is in linkage disequilibrium with the exact disease-predisposing locus.
- Association arise out of population stratification.
- Association is a sampling, or statistical, artefact.

Numerous case control studies are reported in which genotype frequencies of an inherited DNA variant for a group of periodontitis cases are statistically compared to periodontally healthy control subjects. If the genotype frequencies vary so much that the results are very unlikely to occur by coincidence, it is assumed that the genotype is more common in cases than controls and is associated with high disease risk.

#### *3.6.1 Advantages*

Association studies are beneficial for discovery of inherited genetic variation important for a wide range of complex diseases including diabetes, cardiovascular diseases, metabolic disorders, obesity and mental illness.

### 3.6.2 Disadvantages

- Alleles that can be used to predict disease in one population may not be useful in other populations or even in the same population when exposed to extremely different environments. In the presence of pathogens, individuals with the low response allele develop disease. On the other hand, no relationship may exist between the disease and this allele in populations where the particular bacteria is absent.
- Low power to evaluate small genetic effects
- Small presentation of actual causal or rare variants
- Non-consideration of prior mechanistic or biological information [31]

## 3.7 Evidence for the role of genetic variants in periodontitis

The above mentioned studies demonstrate that different genetic loci are capable of causing the disease in dominant and recessive ways [32]. Few of the genes responsible are autosomal whereas others are X-linked. These factors account for the different observed modes of transmission (**Tables 1–4**).

| Author | Study | Results |
|---|---|---|
| Melnick et al., 1976 [32] | Mode of inheritance for Aggressive Periodontitis among Caucasians and African-Americans | X linked inheritance-preponderance of female probands |
| Saxen, 1984 [33] | Mode of inheritance for Aggressive Periodontitis among Finnish population | Autosomal recessive mode of inheritance |
| Marazita et al., 1994 [34] | Largest US study among African-Americans to evaluate the mode of inheritance for aggressive periodontitis | Autosomal Dominant mode with penetrance of about 80% |
| Schenkein, 1994 [35] | Subjects with one AP disease allele and two copies of the high IgG2 response allele develops Localised Aggressive periodontitis<br>Subjects with one AP disease allele and one copy of high IgG2 response allele develops widespread disease since their IgG2 response to LPS would be less robust. | Aggressive Periodontitis disease and IgG2 responsiveness to bacterial LPS segregate independently as dominant and codominant trails |

**Table 1.**
*Segregation analysis.*

| Author | Study | Results |
|---|---|---|
| Corey et al., 1992 [36] | Questionnaire survey for several thousand adult twin pairs about the history of periodontal disease | Concordance rate was greater in MZ twins than DZ twins. |
| Michalowicz 1991 [22] | Independent twin studies at Minnesota and Virginia in which the relative contribution of environmental and host genetic factors to clinical measures of periodontal disease were examined | Significant heritable component for gingivitis, PD, CAL, plaque. 38–82% of the population variance for these periodontal measures of disease may be attributed to genetic factors. |

**Table 2.**
*Twin studies.*

| Author | Study | Results |
|---|---|---|
| Boughman et al.,1986 [26] | First to report linkage of Localised Aggressive Periodontitis and a specific chromosomal region. | Aggressive periodontitis segregates with Dentinogenesis imperfecta. Localised to long arm of chromosome 4 near the gene for dentinogenesis imperfecta |
| Li Y et al., 2004 [37] | Study conducted on 4 families with Localised Aggressive Periodontitis | Aggressive Periodontitis has been linked to a marker on choromosome 1(1q25) with LOD-3.48. |
| Tabeta K et al., 2009 [38] | Linkage disequilibrium block analysis- SNPs and Microsatellites in chromosome 19 | A single microsatellite marker allele 17 of 1902 G31 on chromosome 19- associated with severe chronic periodontitis |

**Table 3.**
*Linkage studies.*

| Author | Study | Results |
|---|---|---|
| Korman et al., 1997 [39] | Composite IL-1 genotype consisting atleast one copy of the rare allele at both an IL- 1 α and IL -1β loci was associated with severe periodontitis in North European adults. | Association-18.9<br>Genotype positive nonsmokers were 6.8 times likely to have severe periodontal disease. |
| Gore et al., 1998 [40] | Study conducted to analyse composite genotype in Caucasians | More rare IL-1β sites were in linkage disequilibrium,ie, IL-1 β allele was found to be more prevalent in chronic periodontitis than the composite genotype. |
| Kobayashi et al., 1997 [41] | Tested association between neutrophil IgG receptor FcγR polymorphisms and Chronic periodontitis in a Japanese population | Association was found with FcγRIII-NA2 allele and it was more prevalent in those with recurrent disease. |
| Engebretson et al., 1999 [42] | Study conducted on periodontitis patients who were positive for composite IL-1 genotype in US population | Elevated levels of IL-1β in GCF |
| Galbraith et al., 1998 [43] | TNF genotypes were determined in 32 Caucasian patients with chronic periodontitis and 32 orally healthy matched controls, and correlated with TNF- alpha production by oral polymorphonuclear leukocytes | No association between Chronic Periodontitis and TNF- α polymerisation |
| Sofaer et al., 1990 [44] | Study conducted on patients with Aggressive periodontitis (AP) | HLA A-9 and B15 antigens were constantly associated with AP. The risk of disease was 1.5 to 3.5 times greater than those lacking these antigen |
| Terazaki et al., 1975 [45] | Study conducted on patients with Aggressive periodontitis (AP) | HLA- A2 antigen appears to be less prevalent in patients with AP than controls suggesting a protective role |
| Katz et al., 1987 [46] | Study conducted on patients with Chronic and Aggressive periodontitis (AP) | MHC class II DR4 antigen were at increased risk of type of DM 1 related complications including periodontitis<br>DR4 antigen was more prevalent in patients with AP disease than controls |

**Table 4.**
*Association studies.*

## 4. Genetic polymorphisms and periodontal disease

A polymorphism is a form of genetic variant that appears in at least 1% of a population and evolves from mutation. 90% of polymorphisms come from Single Nucleotide Polymorphisms (SNPs) where a single base of one nucleotide is replaced with another. In majority of SNP that occur in genes, the protein produced remains unaffected, but have an effect on the gene product. Since all forms of periodontal disorders are linked with bacterial infections, outlining the relative roles of genes and environmental factors in these complex disorders is a challenge [47]. In case of chronic periodontitis, studies on twin adults imply that a sizable proportion of the population variance for periodontal measures such as pocket depth, attachment loss, and bone loss might be endorsed to genetics. Early onset periodontitis is often genetic, and the likelihood of inheriting periodontitis is high, as indicated by genetic studies [48].

A large part of in vitro and in vivo analyses [49] of human tissues as well as studies in animals strongly confirms that cytokines play a key role at all stages of the immune response in periodontal disorder. The various genetic polymorphisms associated with periodontal diseases are shown in (**Figure 1**).

### 4.1 Inflammatory and anti-inflammatory cytokines

#### *4.1.1 Interleukin-1*

IL-1 gene polymorphisms were the first described genetic markers related to periodontal disease in 1997 [10]. The three cytokines originally defined as the members of the IL-1 family were IL-1α and IL-1β, are the major agonistic molecules, whereas IL-1Ra, a biological antagonist. These functionally similar molecules are encoded on separate genes in the same region of chromosome 2. SNP's were found in IL-1 gene cluster, a C to T transition at nucleotide: 889 in the IL-1α and the second at +3954 of IL-1β gene. Occurrence of allele 2 of the IL-1B +3953 SNP was significantly increased in patients with advanced periodontal disorder [50–54].

*Dental Implants:* Investigations in individuals with polymorphisms of IL-1α and IL-1β genes with IL-1β – 511 2/2 genotype showed evidence of a substantially higher incidents of marginal bone loss [55].

*Intrabony defects*: Impact of IL-1 gene polymorphism on clinical and radiographic healing results in patients treated with Guided Tissue Regeneration (GTR) therapy [56] did not reveal any statistical variations between IL-1 + and IL-1 – patients.

#### *4.1.2 Interleukin-2*

It is established that – 330 (T → G) polymorphism in IL-2 gene is related to acute and vital role in pathogenesis of periodontitis [57].

#### *4.1.3 Interleukin-4*

Study of IL-4 gene polymorphisms in the intron 2 and in the promoter positions (PP+ and IP+) showed no link with periodontal disease exposure.

#### *4.1.4 Interleukin 6*

IL-6 in intron 2 and in the promoter positions (PP- and IP) gene polymorphisms in chronic periodontitis suggested that –572 G/C polymorphisms of IL-6 gene may be one of the protecting factors connected with lower susceptibility to chronic periodontal disease [50–53].

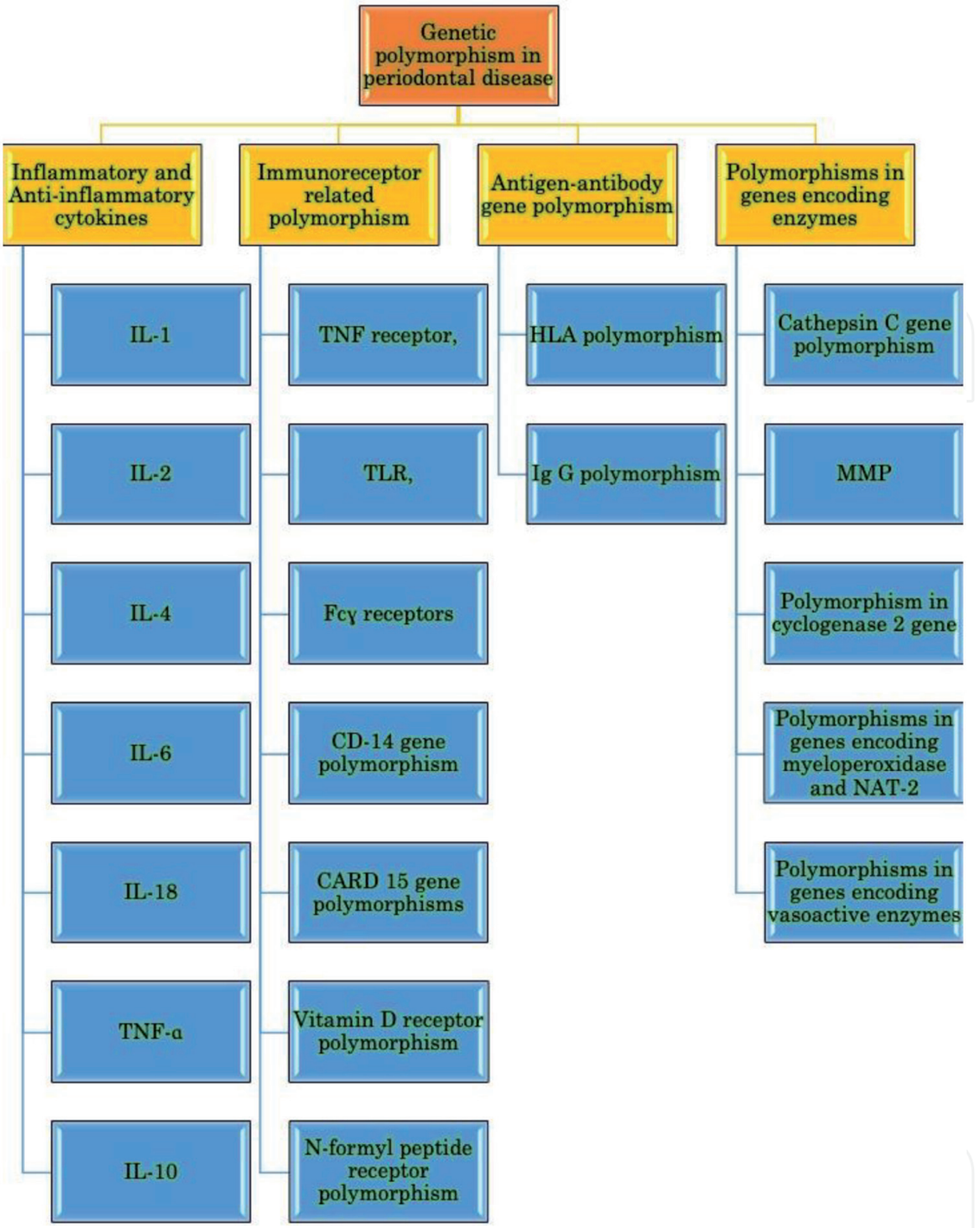


**Figure 1.**
*Flowchart showing the various genetic polymorphisms associated with periodontal disease.*

### *4.1.5 Tumour necrosis factor-α*

Study to explore 4 polymorphisms in TNF- α gene which are all transitions from G to A, 3 in the promoter positions: – 376, – 308, – 238 and at position +489, failed to be identified as susceptibility or severity factors in periodontitis.

### *4.1.6 Interleukin-10*

Three SNPs in the promoter regions of IL10 genes, a G to A transition, at position – 1087, C to T transition at 819, and a C to A transition at 592 have been linked with altered synthesis of IL10.

*4.1.7 Interleukin 18*

Six different IL-18 gene polymorphism (−656, −607, −137, +113, +127, and codon 35/3) were investigated and none of the polymorphisms were linked to destructive periodontal disease [38, 44].

## 4.2 Immunoreceptor related polymorphism

*4.2.1 Fcγ receptor polymorphisms*

The phagocytes harbour the Fc-gamma receptor which attaches to IgG. There are three broad classes of FcR: FcãRI (CD 64), FcãR II (CD 32), FcãR III (CD 16) in chromosome 1. Of which FcãR IIIa and FcãR IIIb, is found to be frequently associated with chronic periodontitis. FcãR IIIb has a NA1-NA2 polymorphism. NA1 is a more efficient opsono-phagocytic agent than NA2 [58].

When one or several of FcγR-mediated leukocyte functions are less or over efficient due to polymorphisms, it is likely that vulnerability or severity of periodontal disease is seen [46, 47].

*4.2.2 Toll-like receptors (TLR-2,-4) gene polymorphism*

These are signal molecules essential for the cellular response to bacterial cell wall components. TLR 2 exhibits polymorphism (Arg to Thr at 677, Arg to Gly at 753) which alters their ability to respond to cell wall components. Polymorphism of TLR4 (Asp 299 Arg 677 Trp; Arg753 Gln) have been known to be linked with impaired Lipopolysaccharide (LPS) signal transduction. Their relationship has still not been established [48].

*4.2.3 CD14 gene polymorphism*

The transcriptional activity of the CD 14 gene is enhanced by the presence of R-allele in the promoter region at position −260(−159). Research in Caucasian population revealed CD14–260 polymorphism in chronic periodontitis with no major link. A higher frequency of the N –allele and the N/N genotype of CD14–1359 polymorphism were observed in patients with aggressive periodontitis and in subjects with severe periodontal disorder [37, 41].

*4.2.4 CARD 15 gene polymorphisms*

The 3020insC and 2104 C > T polymorphisms seen in CARD15 (NOD2) gene results in decreased stimulation of nuclear factor-kappa B, thereby leads to alteration in the gene expression of pro inflammatory cytokine genes and diminished production of cytokines. However there has been no further established role for CARD 15 from studies in Caucasians [52].

*4.2.5 Polymorphism of RANK gene*

RANKL and its receptor RANK are the key elements reported to cause increased bone resorption in periodontal disease through osteoclast differentiation and activation of nuclear factor-B (RANK), RANK ligand (RANKL), and osteoprotegrin (OPG). Association studies show no significant link of the SNPs with AgP in Japanese population.

#### *4.2.6 N-formyl peptide receptor polymorphism*

FMLP receptor has a high affinity variant (FPR1) which binds with FMLP receptors of microbial cells triggering chemotaxis, degranulation and superoxide production which are found to be disrupted in genetically modified periodontitis. Polymorphisms were noted at the nt329T-C (codon 110 phenylalanine-serine), and at the nt378C-G (codon 126 cysteine-tryptophan) in the 583 bp interval of FMLP receptor gene. Coincidentally this is found to be significantly linked to the Agp phenotype in Afro-American patients [17, 18].

#### *4.2.7 Vitamin D receptor (VDR) polymorphisms*

Vitamin D receptor gene polymorphism has influence on bone mineral density and turnover. Studies proved vitamin D receptor (VDR) gene is localised in chromosome 12 with a group of polymorphisms: BsmI, ApaI and TaqI and relationship between TaqI VDR gene polymorphisms and periodontitis.

### 4.3 Antigen–antibody gene polymorphism

#### *4.3.1 HLA genetics*

The MHC genes are the most polymorphic genes present in the genome of every living organism. Research implied that patients with HLA-DRB1*1501-DQB1*0602 genotype may have accelerated T cell response and are thereby prone to periodontitis.

#### *4.3.2 Immunoglobulin g2 variations*

IgG molecules constitute genetically strong variants in the gamma heavy chains, termed Gm allotypes. Patients with rapidly progressing periodontitis with positive Gm shows higher antibodies [54].

### 4.4 Polymorphism in genes encoding enzymes

#### *4.4.1 Cathepsin C gene polymorphism*

Cathepsin C is a lysosomal protease in neutrophils and macrophages identified in chromosome 11, responsible for periodontal disease in young children termed as prepubertal periodontitis [51, 52].

#### *4.4.2 Matrix metalloproteinases (MMP) polymorphisms*

MMP-1 is an important mediator of connective tissue destruction in periodontal disease. A single nucleotide polymorphism in the promoter position of - 1607 bp of MMP-1 gene a, 5′-GGA-3′, instead of 5′-GAT-3′ has been identified to be linked with higher threat of generalised aggressive periodontitis [58].

#### *4.4.3 Polymorphisms in cyclogenase −2 gene*

PGE2 is a significant mediator of tissue destruction, catalysed by COX-2. A SNP of COX-2 in the chromosome 9q32–33. This modifies the expression of the COX-2 gene and polymorphism of -765G to C is linked with lesser risk for periodontitis.

*4.4.4 Polymorphisms in genes encoding myeloperoxidase (MPO) and N-acetyl transferase (NAT-2)*

A SNP in the promoter position of −1607 bp of MMP-1 gene a, 5′-GGA-3′, instead of 5′-GAT-3′ has been learned to be connected with increased risk of generalised aggressive periodontitis. A link between bone density loss in periodontal disease and polymorphism of NAT2 have been reported [59].

*4.4.5 Polymorphisms in genes encoding vasoactive enzymes*

The study of genotypes between affected and healthy showed the presence of lymphotoxin-á (TNF-â), angiotensin- converting enzyme and endothelin-1(ET-1) polymorphism with link to three-locus combination [41, 60].

## 5. Periodontal diseases as a manifestation of systemic genetic disorders

Certain systemic disorders predispose the patient's susceptibility to acquire periodontal disease, which may present clinically in a chronic or an aggressive form. The *involved pathogenesis includes* modifications in the immune, endocrine and connective tissue status of the individual. These changes eventually result in the occurrence of syndromes with periodontal disease either as a primary manifestation or by aggravating a pre-existing condition associated with the presence of local factors. The alterations in the immune system may be noted at cellular and/or humoral level. Lymphocytes play a pivotal role in driving the immune response, and a defect or absence of one or more lineages may result in fatal conditions like leukaemia or Acquired immune-deficiency syndrome [61]. Neutrophil defects in turn may be of a qualitative (altered chemotaxis and phagocytosis) or quantitative nature (neutropenia, agranulocytosis), and both predispose to rapid and severe periodontal destruction.

A high susceptibilty to develop periodontitis has been associated with conditions such as Down syndrome (trisomy 21), Chediak-Higashi syndrome and Papillon-Lefèvre syndrome. These subjects present with an increased incidence of infections with a plausibility owing to a diminished expression of surface glycoproteins required for bacterial adhesion [62]. Other connective tissue disorders, also induce an elevation to periodontal inflammation mostly linked with plaque and in some cases an overstated response relatively disproportionate to the amount of microbial plaque present.

### 5.1 Unleashing the underlying mechanism

Inorder to understand the pathogenesis of Genetic diseases, they have been broadly classified as,

a. Connective tissue deformities: eg Marfan syndrome, Ehler-Danlos syndrome.

b. Immune related alterations: eg severe congenital neutropenia (SCN) or infantile genetic agranulocytosis or Kostmann syndrome (IGA), Chediak-Higiashi syndrome, Down syndrome, Papillon-Lefèvre syndrome, hyperimmunoglobulinemia E syndrome [61].

## 5.2 Systemic and periodontal manifestations of common genetic disorders

### *5.2.1 Connective tissue deformities*

#### *5.2.1.1 Marfan syndrome*

Mutation of a gene encoding for fibril-1 present in chromosome 15 marks a defect in the synthesis of a glycoprotein forming part of the connective tissue matrix. This causes defects in a series of locations such as the ocular lens suspensory ligament, blood vessel walls and, apparently, the periodontal ligament [62].

Periodontal manifestations:

The mode of periodontal pathogenesis in these syndromes can be understood by connective tissue modifications which generates increased vulnerability to periodontal inflammation and bone resorption. Despite the co-existence of a similar background alteration, the manifestations of periodontal disease vary in their presentation in each of the syndromes. For instance, Marfan syndrome exhibit both chronic and severe form of disease with patterns of horizontal and vertical bone resorption, in accordance to the presence of bacterial plaque. However, tooth mobility has been shown to be a sequel to periodontitis, and is not endorsed to the primary condition of the syndrome [62, 63].

#### *5.2.1.2 Ehler-Danlos syndrome*

Ehlers-Danlos syndrome (EDS) comprises a group of genetic diseases involving the connective tissue characterised by mutations in the genes responsible for the collagen biosynthesis. The clinical expressions of EDS include increased tissue fragility, hypermobility of joints, and hyperextensibility of skin [64].

Periodontal manifestations

In EDS, periodontal disease can be linked with syndromes type I, VII, III, or IV. Type I EDS has *increased predisposition to periodontal disease, whereas type VIII manifests as early onset periodontitis, with premature loss of permanent teeth, fragility of the mucosa leading to bleeding gums and oral mucosa The postulated mechanism is a defect in type III collagen, amounting to a total of periodontal junction. Moreover, a relationship has been found to Fusobacterium nucleatum, which could be isolated from the active affected sites* [65].

### *5.2.2 Immune related conditions*

The immune conditions contemplated in the above classification are all primary immune deficiencies caused by a decrease in neutrophil presence, or by modifications in the functions of these cells – as in the above cited syndromes. These conditions predispose patients to bacterial and fungal infections in childhood, because the decrease in neutrophil presence alters the host defence capacity. Additionally, a drop is seen in the production of granulocyte colony stimulating factors [66, 67]. Let us discuss some significant disorders.

#### *5.2.2.1 Chediak-Higiashi syndrome*

Chediak-Higiashi syndrome is supplemented by leukocyte modification, basically limited to the lysosomes, which destroy melanosomes producing oculocutaneous albinism. Affected patients also present mental retardation, and neutropenia additionally may also be observed – with altered LA.

*5.2.2.2 Down syndrome*

Down syndrome or trisomy 21 results because of chromosomal abnormality that causes peculiar physical changes, with co-existing mental retardation and other systemic alterations. The immune changes described in Down syndrome are linked to function of WBCs, responsible for the defensive mechanisms in periodontal tissues [68, 69].

*5.2.2.3 Papillon-Lefèvre syndrome*

Papillon-Lefèvre syndrome is classically manifested as palmoplantar erythematous hyperkeratosis along with periodontal disease. The proposed mechanism is linked to a mutation of the gene encoding for cathepsin C, which generates a lysosomal protein implicated to modify the host immune response, inflammatory response and extracellular matrix function with significant changes in the palmar, plantar and gingival epithelium [64]. Hyperimmunoglobulinemia E (HE) consists of an increase in serum immunoglobulin E (IgE). This in turn leads to a series of systematic variations with involvement of the skin, facial malformations and increased vulnerability to staphylococcal infections [70, 71].

**5.3 Periodontal manifestations of immune related disorders**

In neutrophil disorders, the notable reduction in the amount of neutrophils tends to disregulate the host defence capacity, causing periodontal disease to manifest at a younger age. Gingival inflammation, aggressive periodontal tissue destruction, edema, pocket formation and tooth mobility are common presentations. This clinical representation is much similar to prepuberal or rapidly progressive periodontitis with premature loss of the deciduous teeth [66, 68, 72].

*5.3.1 Chediak-Higiashi syndrome*

Chediak-Higiashi syndrome manifests as early occurrence of periodontitis with premature exfoliation of both dentitions. The bone resorption patterns may be local or generalised, and are linked to associated inflammation. The disorder is associated with anaerobic flora, due to the amble presence of purulent processes. The abundant presence of spirochetes in the locations with inflammation and high proteolytic activity, which facilitates bacterial adherence further explains the pathosis. Adding to this, the co-existence of lysosomal modifications and defective chemotaxis in neutrophils gives rise to very rapidly progressing periodontitis that inclines to be recurrent and is refractory to antibiotic treatment [68].

*5.3.2 Down syndrome*

Down syndrome is characterised by aggressive and generalised periodontitis, with subsequent damage of the supporting tissues and loss of teeth at an early age. Eight percent of Down syndrome children suffer periodontal lesions by 12 years of age [73]. The rate of occurence of periodontal disease in this population ranges from 60–100% in young adults under 30 years of age [70]. The co existence of immune deficiency, inadequate control of bacterial plaque, deficient masticatory function, early ageing and alterations in dental anatomy (short roots) predispose or aggravate the progression of periodontal disease [74, 75].

In patients with higher level of mental retardation, difficulties are observed with relation to oral hygiene maintenance. Oral health care needs to be emphasised

| Syndrome | Mode of inheritance | Defect | Function of normal gene | Oral & periodontal manifestation |
|---|---|---|---|---|
| Severe congenital neutropenia type 1 | Autosomal dominant | Neutrophil elastase gene (ela2)- 19p13.36 | The products of elastase gene degrade membrane protein a of bacterial cell wall. | Early age periodontitis similar to pre pubertal periodontitis |
| Severe congenital neutropenia type ii | Autosomal dominant | Growth factor independent gene (GFi 1) 1p226 GFi 1 gene | Function to replace ela2 | Early age periodontitis6 |
| Severe congenital neutropenia type iii | Autosomal recessive | Ar hcls1 associated protein x1 (hax1)- 1q21.36 | Controls development of neutrophils | Early age periodontitis6 |
| Hiam-munk syndrome | Autosomal recessive | Cathepsin c- ctsc 602365- on chromosome 11q14.6.7,14 | Degrading proteins and activation proenzymes in immune cells. | aggressive periodontitis |
| Phosphatasia | Autosomal dominant or recessive | Alkaline phosphatase liver/bone/ kidney (alpl)-1p36.1-p3412,13,15 | Maintains normal level of alkaline phosphatase aggressive periodontitis | Premature loss of primary teeth Aggressive periodontitis |
| Kindler syndrome | Autosomal recessive | Kindlin 1(kind 1)- 20p136,19 | Normal basement membrane, cell to contact | Aggressive periodontitis in primary and permanent dentition. |
| Infantile genetic agranulocytosis | Autosomal recessive | Elane (formerly ela2) gene on chromosome 19p13.36,7,8 deficiency of ll-37, | Synthesis of neutrophil elastase, a peptide antibiotic present in neutrophils | Aggressive periodontitis |
| Hyper ige job's syndrome (hie) | Autosomal. recessive | 7q216,12,16 | Regulation of IgE | Opportunistic infections, periodontitis and oral ulcerations |
| Familial and cyclic neutropenia | Autosomal dominant | Elane mutation | Regulating the number of circulating neutrophils | Oral ulcers, Gingival inflammation, Severe periodontitis |
| Down syndrome | Autosomal dominant | Trisomy chromosome 21 | Normal chemotaxis and phagocytosis | Gingivitis, Necrotizing ulcerative gingivitis, Severe periodontitis, Tooth mobility |

| Syndrome | Mode of inheritance | Defect | Function of normal gene | Oral & periodontal manifestation |
|---|---|---|---|---|
| Leukocyte adhesion deficiency syndrome | Autosomal. recessive | Integrin b2 (itgb2)- 21q22.37,9,11 | Adhesion receptors of the white blood cells and phagocytosis | *Type 1*: severe gingival inflammation, Rapidly progressive periodontitis, *Type 2:* chronic severe periodontitis |
| Papillon-lefèvre syndrome | Autosomal recessive | Cathepsin c gene11q14-q216,14,17 mutation of gene encoding for cathepsin-c, | Neutrophil function | Aggressive periodontitis, Premature loss of teeth |
| Chédiak-higashi syndrome | Autosomal recessive | Mutation in lyst gene Lysosomal trafficking regulator gene (lyst)-1q42.1-q42.26,7,14 | Transport of vesicles to and from the neutrophil lysosyme9,11 | Oral ulcerations, Severe gingivitis Early-onset periodontitis |
| Histiocytosis syndromes | Unknown | Abnormal proliferation of bone marrow-derived histiocytes | — | Periodontitis, Alveolar bone loss replaced by soft tissue, Oral ulceration, Premature loss of teeth |
| Glycogen storage disease | Autosomal recessive | *Type 1b:* deficiency of glucose-6-phosphate translocase | Regulation of glycogen breakdown | Oral ulcers, Hyperplastic gingiva, Periodontal infections, Prolonged bleeding |
| Severe congenital neutropenia | Autosomal dominant | Elane and hax1 mutations | Maintainance of circulating neutrophil | Gingival inflammation, Increased probing depth, Severe alveolar bone loss in both dentitions |
| Cohen syndrome | Autosomal recessive | Mutation in the vps13b gene | Functional vps13b protein. | Early adult periodontitis |
| Ehlers-danlos syndrome (type iv and viii) | Autosomal dominant | *Type iv:* mutation in *type iii* collagen *Type viii:* mutation in chromosome 12p13 | Synthesis of type iii collagen | Severe periodontitis Prolonged bleeding Delayed healing |

**Table 5.**
*Comprehensive tabulation of genetic disorders and their periodontal manifestations [44, 61, 62].*

in order to avoid the accumulation of plaque leading to initiation of the disease [76–78]. The presence of defective neutrophil chemotaxis, leads to progressive periodontitis as observed in juvenile periodontitis. Concurrently, it has been reported that the B cells,T cells, and monocytes, also illustrate functional defects. The periodontal destruction is directly proportional to the degree of alteration in

functional chemotaxis. The mechanism mounting for the dysfunction is attributed to a decrease in the number of cell surface receptors, and diminished levels of zinc and some vitamins in serum [70].

*5.3.3 Papillon-Lefèvre syndrome*

Papillon-Lefèvre syndrome presents as aggressive periodontal inflammation with the premature loss of both primary and permanent dentitions. The underlying mechanism involved are due to immune modifications apart from alterations in the gingival tissues along with the notable presence of *Actinobacillus actinomycetem-comitans* [72].

*5.3.4 Hyperimmunoglobulinemia E syndrome*

Hyperimmunoglobulinemia E syndrome manifests with overhiked susceptibility to infections and thus contributing to the development of periodontitis. The process involved here is thought to be associated with a deficient host cellular and humoral immune response, comprising of an inadequate neutrophil chemotaxis secondary to alteration in the regulation of T cell cytokines. The rapid spike in circulating IgE leads to a reduced production of gamma-interferon, which intervenenes with anti-inflammatory and bone resorption-inhibiting processes. Thereby, the heightened inflammatory and resorptive phenomena noted in these patients, gives rise to early and advanced periodontitis. This disorder is associated with abundance of pathogenic microflora (*P. gingivalis, T. denticola, E. corrodens*) that results in severe periodontal damage in adults and in children [73]. The syndromes, mode of inheritance, function of responsible gene and periodontal manifestations are given in **Table 5**.

## 6. Future perspectives

At least 50% of periodontitis vulnerability is attributed to heredity or genetic factors [20]. Clinical observations and scientific studies have demonstrated that the heredity of a host response pattern may be an important susceptibility factor in developing periodontal diseases [20, 79, 80]. Added information from new technologies, such as micro-arrays and DNA-sequencing, lead to the identification of specific genetic, environmental, and behavioural factors that influence periodontitis susceptibility [81].

In order to enhance the therapeutic management of periodontal disease, we must not only be able to identify genetic determinants, but also learn to modify, control or modulate the host response either by stimulating a desired immune response, or by decreasing the activating factors of bone resorption,both of which hinders the progression of the disease by [82–84].

## 7. Concluding remarks

At present, the clinical application of the effect of genetics in periodontics is minimal. Despite several researches revealing association of candidate gene polymorphisms with periodontal disease, lacunae lies owing to co-existence of multiple etiotrophic factors and the plausible role of epigenetics in the periodontal disease severity. Future research shall be directed towards multiple genes, their interactions and role of epigenetics in modifying the periodontal etiopathogenesis.

## Conflict of interest

The authors declare no conflict of interest.





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