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RESEARCH ARTICLE

GENETIC BACKGROUND IN INITIATION, PROGRESSION AND TREATMENT OF PERIODONTAL DISEASES – A REVIEW

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Abstract

Periodontitis is a complex chronic inflammatory disease that results in the loss of connective tissue and alveolar bone support of the teeth. With increase in knowledge, the etiology of periodontal diseases is becoming more complex. A pathogenic micro flora is the causative agent for the initiation of periodontitis, which is often promoted by a poor oral hygiene and smoking, which both contribute strongly to the disease risk. Apart from the environmental factors, formal genetic studies have demonstrated the genetic basis of periodontitis and indicated that about half of the population variance in chronic periodontitis can be attributed to genetic factors. Thus it is now widely accepted that these differences among individuals who are at risk for the development of most diseases have a substantial inherited component. This complex combination of variables determines if and when a disease affects the person, how fast and how severely symptoms of the disease progress. Not only the initiation and progression of the disease, genetics also determines how the person responds to different treatments in terms of both side effects and the success of alternative therapies as pharmacogenomics which helps in individualizing the treatment.

Introduction:-

Periodontal diseases are a series of complex, distinct, pathologic entities caused by the interaction of bacterial plaque and the host. This interaction results in destruction of the supporting alveolar bone and connective tissue. Although bacterial plaque has been implicated as the primary etiological agent in most forms of periodontal disease, there are local and systemic factors which may modify both microbial and host components. Local factors may favor plaque accumulation and maturation, while systemic factors may modulate the host's protective response.[1] Factors in the environment interact with each person's genetic predisposition to determine his or her health outcomes due to which individuals with similar local factors are not responding similarly. The complex combination of variables also determines if and when a disease affects the person, how fast and how severely symptoms of the disease progress, and how the person responds to different treatments in terms of both side effects and the success of alternative therapies.[2]

Principles of human genetics:-

Genome is the whole of genetic information of an organism found in the nucleus of Eukaryotes. Each and every cell of a human contains genome within the nucleus. It is explained by chromosomes which are of 23 pairs in number, where 22 pairs are of autosomes (somatic) and 1 pair of sex chromosome (either XX or XY). DNA is a Deoxyribose

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Nucleic Acid formed by nucleotides Purines and Pyramidines. The relationship between nucleotide sequence and aminoacid sequence is known as Genetic code. Triplet of nucleotides forms a codon which represents an aminoacid.

Gene is a linear polymer of DNA which codes for protein and is the basic physical and functional unit of heredity. Gene expression is the formation of proteins by decoding the codons which carry out functions of the cells. It is done by:

1. Transcription
2. Translation
3. Post translation modifications

Gene expression is regulated by various factors like transcription factors, repressors, co-activators and co-repressors.

Replication of DNA:-

Genetic information is transmitted to daughter cells under two circumstances

1. Mitosis- in somatic cells
2. Meiosis- in germ cells forming gametes

Crossing over occurs during meiosis between maternal and paternal sister chromatids which is responsible for tremendous diversity and forming genetically unique gamete.

Mutations:-

It is a structural change in genomic DNA which can be transmitted from a cell to its daughter cells. All organisms undergo spontaneous mutations as a result of normal cellular function or random interactions with the environment. Typically present in less than 0.1% of population. Occur during gene expression or segregation crossing over.

Polymorphism:-

Allele is a variant form of a gene. The coexistence of multiple alleles at a locus is called "Genetic polymorphism". 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 (Fig:1):

a. The promoter or 5'-flanking region;
b. The exon(s) or the gene coding regions;
c. The intron(s) or the gene intervening regions;
d. The 3'-untranslated region

i. If the polymorphism occurs in the promoter or intron (regulatory regions) regions, the protein production may be increased or decreased which affect the disease phenotype.[3]
ii. If the polymorphism occur in the exon region (gene expression region), the change in protein produced may be affected. Thus change in cellular function may affect the disease phenotype.[3]

Common genetic polymorphisms may change the function of a protein, but usually the change is relatively minor. These differences in physiological functioning of different proteins can be enhanced by certain environmental exposures. Certain polymorphisms may increase or decrease a person's risk for a disease phenotype.

Genetic Diseases:-

These variations in normal function of a gene and mutations cause diseases called Genetic diseases. Based on the pattern of transmission of disease, they are divided into two broad groups: Monogenetic diseases and Complex diseases.[4]

Monogenetic diseases (Fig.2)	Complex diseases (Fig.3)
• Alteration of a single gene locus that has a major physiological impact. • There is no redundancy or compensation in the particular biological system. • Major disease gene • Follow predictable and generally simple patterns of transmission called Mendelian conditions.	• Multiple different gene alleles and biologic interactions can contribute to a complex disease state. • Have many compensatory and redundant aspects. • Disease modifying genes. • Doesn't follow Mendelian conditions.

Role Of Genetics In Periodontitis:-

In the last decades, epidemiologic studies as well as longitudinal clinical studies have shown that the presence of bacteria does not invariably induce periodontal attachment loss, but that host factors are also required for periodontitis. The concept of "high- risk groups" was added to the pathogenesis model, and was one of the factors that developed the hypothesis that periodontitis may have a genetic background.[5] Trott and Cross in 1966 in a study stated that certain individuals are more at risk for periodontitis than others. Their study resulted in each age category; the percentage of teeth lost due to periodontal disease is always higher than the percentages of patients who lost teeth due to periodontal disease. It implies relatively many teeth are lost in relatively few patients.[6] Thus relatively small proportion of population is at risk for developing severe forms of periodontitis but not everybody is equally susceptible to periodontitis.

Various studies used for genetic analysis to evaluate susceptibility to periodontitis which include Candidate gene approach, case- control studies, familial aggregation and relative risk, twin studies, linkage analysis, segregation analysis, Genome wide analysis. But the search for periodontitis-susceptibility alleles is complicated because:

1. Multiple causes may exist for the same disease
2. Different genetic mechanisms may lead to same clinical end point.

PeriodntitisAs A Monogenetic Disease:-

Among various genetic disorders which involve mutations of single gene or larger chromosomal regions, those affect the immune system like number and function of neutrophils lead to periodontal destruction[9] – monogenetic disease.[10]

1. Papillon – Lefevre Syndrome: Inherited condition with autosomal recessive pattern. Caused by mutations in the cathepsin C (CTSC) gene. Cathepsin C activity is essential for activation of neutrophil enzymes responsible for phagocytosis. Effects on periodontium include early inflammatory changes and bone loss.[11] Exfoliation of both primary and permanent teeth.
2. Chediak-Higashi syndrome: Rare familial disorder transmitted by autosomal recessive trait. It affects the production of organelles found in almost every cell. Neutrophils contain abnormal giant lysosomes that fuse with the phagosome but the ability to release their contents is impaired. Granulocyte ingestion of bacteria appears to be normal but abnormalities of degranulation and defective intracellular bactericidal activity have been reported. Thus there is increased susceptibility to periodontitis.
3. Leukocyte Adhesion deficiency: It is diagnosed at birth. Many children with the syndrome do not survive. It is the inability to produce or failure to normally express an important cell surface interinβ2 subunit (CD18) or absence of CD15 on leukocytes where adhesion or rolling of leukocytes to vessel wall at the site of infection is impaired. Effects on periodontium include extremely acute inflammation and proliferation of gingival tissues with rapid destruction of bone.[16,17] Absence of neutrophils in the gingival tissues.
4. Down syndrome: It is characterized by poor PMN chemotaxis, phagocytosis and intracellular killing affecting the prevalence of periodontal disease in Down syndrome is high almost 100% in patients younger than 30 years. Periodontal destruction is characterized by deep periodontal pockets associated with substantial plaque accumulation and moderate gingivitis. Moderate gingival recession may also be seen.
5. Ehlers–Danlos syndrome refers to a collection of connective tissue disorders characterized by defective collagen synthesis and related to an increased susceptibility to periodontitis and are inherited in an autosomal dominant manner.
6. Cohen's syndrome is another autosomal recessive syndrome and is characterized by mental retardation, obesity, dysmorphia, and neutropenia. Individuals with Cohen's syndrome show more frequent and extensive alveolar bone loss than do age, sex and mental ability-matched controls.
7. Infantile genetic agranulocytosis, a rare autosomal recessive disease where polymorphonuclear leukocyte numbers are very low has been associated with aggressive periodontitis.
8. Hypophosphatasia: It is a rare disorder caused by mutations in the tissue-nonspecific alkaline phosphatase gene. Mutations leading to deficiency in alkaline phosphatase activity result in abnormal bone mineralization, skeletal anomalies, and cementum hypoplasia. The condition leads to the premature loss of the primary teeth and occasionally the permanent teeth.
9. Weary–Kindler syndrome: Aggressive periodontitis has been reported in Weary–Kindler syndrome where abnormalities of the epidermal keratinocytes occur.

Periodontitis As A Complex Disease:-
The complex traits are the result of the interaction of alleles at multiple different gene loci and with the environmental factors.
Common features of complex human diseases.

1. They present mostly a relatively mild phenotype.
2. Slowly progressive and chronic inn nature.
3. It may affect various biological pathways leading to similar clinical phenomena.
4. Associated with variations in multiple genes each having a small overall contribution and relative risk for the disease process.
5. They are influenced by environmental factors (gene-environmental interactions) (Fig.4).

Thus complex diseases are typically polygenic i.e., multiple genes each play a limited role (low penetrance genes). The disease genes in complex diseases are therefore called as "Disease modifying genes". They are also influenced by environmental factors (gene- environmental interactions).

Periodontitis is considered to be a "complex disease". For periodontitis atleast 10 and possibly as many as 20 disease-modifying genes may be involved.[30] However, it is important to realize that the number and types of disease-modifying genes for the same condition may not be equal for different forms of periodontitis and different ethnic populations. Polymorphisms of multiple genes combined with environmental factors within the body leads to susceptibility to a disease. As immune system plays a crucial role in the pathogenesis of periodontitis, researchers have concentrated on the identification of genetic polymorphisms in several aspects of host immunity which play a role in severity of periodontal disease.

HLA (Human Leukocyte Antigen):-
One genetic marker that has been frequently associated with Early Onset Periodontitis is the HLA, which plays an important role in regulating and mediating immune processes. Sofaer (1990) compiled and analyzed data from a number of studies and concluded that the strongest negative associations with EOP are with HLA-A2 and that, subjects with HLA-A9 or HLA-B15 may have an increased risk for LJP.[31]

Immunoglobulin G2 (IgG2):-
It has been postulated that IgG subclass responses are closely associated with IgGallotypes. IgG2 response to certain periodontal pathogens observes individual variability, suggesting a genetic component that makes some individuals more prone to a specific form of periodontal disease.[32]

Cytokine gene polymorphisms:-
Pro-inflammatory and anti-inflammatory cytokines have a role in regulating the inflammatory response. Gene-disease associations are concentrated on polymorphisms of genes that have some role in the inflammatory response.

IL-1, TNF-α and PGE_2 Polymorphism:-
Kornman et al. (1997) showed that polymorphisms in the IL-1 gene cluster are correlated with the severity of adult periodontal disease.[33]The cytokine IL-1 is a major modulator of bone resorption and extracellular matrix catabolism. One of the main sources of IL-1 are the macrophages, that produce IL-1, TNF-αand PGE_2 due to LPS stimuli .[34,35] LPS is bound by a plasma protein, the Lipopolysaccharide binding protein (LBP).[36] The binding of this LPS-LPB complex to the macrophages is mediated by a specific membrane receptor, CD14.[36] Subsequently the macrophages enhance the production of cytokines which can be diminished by blocking the CD14 receptor by a specific antibody.[37] Furthermore, blockage of the activity of IL-1β (and TNF-α) was found to slow down the progression of experimental periodontitis in primates.[38]

IL-6 Polymorphism:-
IL-6 is another pro-inflammatory mediator and plays a role in B-cell differentiation and T-cell proliferation. It also stimulates haematopoiesis and accelerates bone resorption.[39] High levels of IL-6 in biological fluids and blood has been determined in infections and chronic inflammatory diseases. It is suggested to be involved in genetic susceptibility to inflammatory diseases.[40]

IL-10 Polymorphism:-
Anti-inflammatory cytokine, IL-10 have a role in controlling the inflammatory response. SNPs in the IL-10 gene have been associated with altered synthesis of IL-10 in response to inflammatory stimuli that could be detrimental to host tissues and could be linked to periodontal disease susceptibility.[41,42]

IL-4 Polymorphism:-
IL-4 is a potent down regulator of macrophage function inhibiting the secretion of PGE2 and cytokines by macrophages. Furthermore IL-4 can also down-regulate the CD14 receptor and is also found to induce apoptosis in monocytes. This led to the hypothesis that the absence of IL-4 triggers periodontal disease.[43]An association between the IL-4 polymorphism and AgP is found by Gonzales *et al*. 2007.[44]

MMP-8 (-779) gene polymorphisms:-
Matrix metalloproteinase (MMP)-8 is a protease that degrades numerous extracellular molecules and has been implicated in the pathogenesis of periodontitis. Polymorphism in the MMP-8 (MMP-8 -779 C<T polymorphism) could affect the susceptibility to disease.[45]

Receptor Gene Polymorphisms:-
Many cell surface receptors respond to host derived or external ligands and affect the physiologic events during inflammation. This group includes receptors to cytokines, Immunoglobulin receptors and pattern recognition receptors.

Fcγ Receptor Gene Polymorphism:-
Three main classes of FcγRs on human leukocytes, two of which (FcγRII [CD32] andFcγRIII [CD16]) are constitutively expressed on neutrophils, have been identified. Studies defining the structural features of the family of FcγRs revealed the existence of multiple isoforms within each class. A defined polymorphism for FcγRIIa has been described and shown to influence the binding of human IgG subclasses. This polymorphism has been associated with EOP and with phagocytic function of neutrophils in conjunction with more severe periodontitis in adults.

Vitamin D receptor (VDR) gene polymorphisms:-
Mediators of bone metabolism play a role in the pathophysiology of periodontitis. Genetic polymorphisms in genes encoding for mediators linked to factors affecting bone mineral density, Vit D receptor, have been related to disorders of bone metabolism. Along with bone metabolism Vit D and its receptor play a role in phagocytosis by monocytes and affect monocyte differentiation thus affecting susceptibility to periodontitis.[47,48]

GENOME WIDE ASSOCIATION STUDIES:-
Most of the genetic association studies which were designed for the elucidation of the genetic risk factors of periodontitis focused on a range of various candidate genes selected for their roles in the immune system, tissue destructive processes, or various metabolism mechanisms.[9] For reasons similar to those described for other complex diseases in the pre- GWAS era, despite many efforts in the field of genetic association studies, the genetic risk factors of periodontitis and their pathophysiologic effects had largely remained controversial.

Except for *IL- 10*, this study showed no strong association between the tested genes and their regulatory regions with periodontitis, and the authors suggested that the positive associations with periodontitis that had previously been reported for these genes were most likely caused by type I errors. Some genes can still be considered as true genetic susceptibility factors for periodontitis if evidence for this is replicated in repeated independent, reasonably large case–control populations.

***ANRIL*:-**
The best- replicated evidence for conferring risk of periodontitis to date has been for the gene ANRIL ("antisense non- coding RNA in the INK4 locus"). This gene encodes a large antisense non- protein coding RNA molecule found with aggressive periodontitis[49,50] and chronic periodontitis

***CAMTA1/VAMP3*:-**
VAMP3 (vesicle- associated membrane protein 3; chromosome 1), plays a role in phagocytosis, where it mediates, for example, the delivery of TNF- α to the cell surface.[52] Located 2 kb upstream of VAMP3 is the extremely large gene CAMTA1 (calmodulin- binding activator 1), spanning >1 Mb. In a GWAS on periodontal pathogen

colonization, a large stretch of the CAMTA1/VAMP3 region was reported to be strongly associated with increased quantities of pathogenic oral bacteria[53] and alsoidentified several SNP located at this pathogen- associated region to be significantly associated with aggressive periodontitis.

***GLT6D1*:-**
Another risk gene of aggressive periodontitis, GLT6D1 was identified in the first GWAS on periodontitis.[55] It encodes an unknown protein belonging to a family of proteins that is characterized by a glycosyltransferase domain- 1. GLT6D1 was found to be predominantly expressed in the gingiva and T cells. Sequencing and subsequent molecular biologic characterization of the main associated genetic polymorphisms suggest an impaired GATA3- transcription factor binding site as the causative variant for increased disease risk.

***COX- 2*:-**
The metabolic protein COX- 2 converts arachidonic acid into prostaglandin E2 (PGE2) which is a group of key inflammatory mediators of the immune response to infection and is partly responsible for the resorption of the alveolar bone in the course of periodontal pathogenesis. COX- 2 (located on chromosome 1 at 1q24- 25) expression is specifically induced by cytokines and specific COX- 2 expression has been reported for gingival tissues in periodontitis. COX- 2 was subjected to various candidate–SNP association studies for different complex diseases, and polymorphisms within the COX- 2 gene were related to increased susceptibility to various inflammatory diseases.

***NPY*:-**
NPY (neuropeptide Y) has immunomodulatory effects that are thought to alter the pro- inflammatory T- helper type 1 (Th1)- to- anti- inflammatory T- helper type 2 (Th2) balance. Binding of NPY to Y1 receptors on a variety of immune cells is thought to be responsible for promoting the anti- inflammatory Th2 response. Accordingly, the presence of NPY Y1 receptors was verified in human gingival tissue and of NPY in human gingival crevicular fluid (GCF), with significantly higher NPY levels in GCF in healthy compared with periodontitis- affected sites.[57] A GWAS first described an association with severe chronic periodontitis downstream of the coding region of *NPY* (chromosome 7) in a large sample of European–American individuals.[58] A second GWAS that systematically analyzed gene–sex interactions in German cases of aggressive periodontitis, where *NPY* was associated with aggressive periodontitis.[59]

Epigenetic Signatures:-
Epigenetics can be defined as the structural (mitotically or meiotically) heritable or reversible adaptation of chromosomal regions so as to register, signal or perpetuate altered gene activity states,[60] which refers to changes in gene expression that do not involve a change in the DNA nucleotide sequence, but encompass an array of post translational modifications. In this context, the low concordance rates in MZ twins, who do not always show the same disease susceptibility, also raised the possibility of epigenetic differences arising during early development as well as with aging.[61] Accordingly, it has been reported that young twins have similar amounts of DNA methylation, whereas older twins differ considerably in the amounts and patterns of this modification.[62] It is a subject of speculation whether the amounts and patterns of epigenetic alterations could give rise to the divergent disease predispositions of some MZ twins.

It has been speculated that epigenetic modifications can play a role in periodontitis. However, only a very few studies on epigenetic effects have been performed to date.[63,64] Large- scale systematic studies of periodontitis- associated epigenetic variation will surely elucidate the role of epigenetic changes in the pathophysiology of periodontitis in the future.

Pharmacogenomics:-
Pharmacogenomics is the application of genomics technology to the discovery and development of drugs,[65] genetic factors may contribute to the effectiveness and safety of a drug. If individuals differ with regard to their susceptibility to disease and especially if underlying the superficial signs and symptoms of a disease there really are etiologically distinct subtypes of disease pathogenesis, then the traditional medical model of “one size fits all” will not be optimal. Sometimes concerns about severe side effects that limit the use of a therapy rather than differences in efficacy and risk of side effects can also be genetically determined.

If clinicians are not aware of the relationships between these genotypes and treatment success or side effects, it would appear that neither treatment is consistently effective. As the benefits of individualized or personalized treatments that are optimally matched to the genome of each patient have been demonstrated for cancer and increasing numbers of other human diseases, interest has grown in applying this approach to dentistry.[66]

Figure Legends:-

Fig.1:-

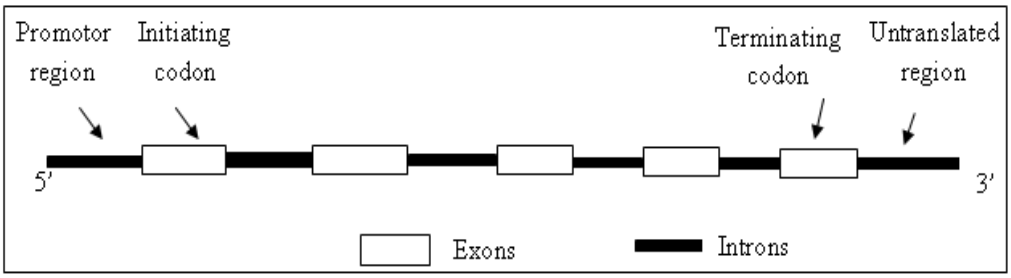


Fig.2:-
Mendelian or monogenic

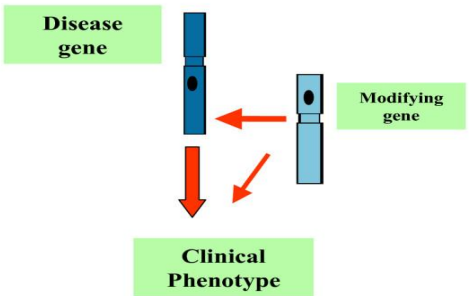


Fig.3:-
Complex or multifactorial

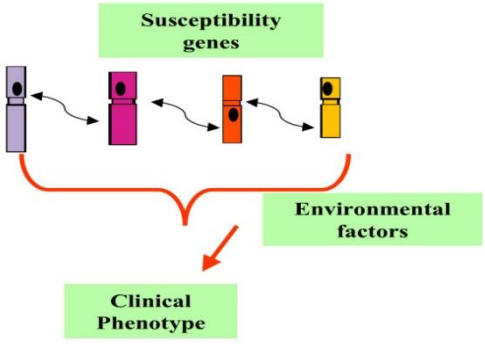
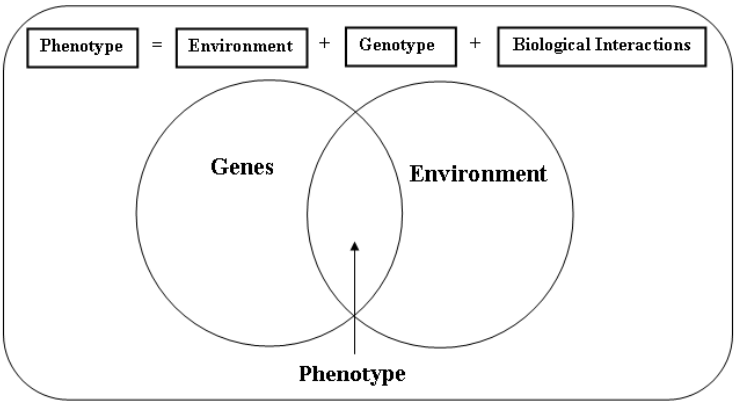


Fig.4:-



Conclusion:-

It is apparent that the causative agents like periodontal pathogens act on tissues that possess inborn potentials of reaction. Therefore, the contribution of hereditary factors in general must be considered in their relationship to other etiological agents which act on the organism to produce the diseased state i.e., when a disease affects the person, how fast and how severely symptoms of the disease progress.Unfortunately, with very few exceptions, association studies of periodontitis have been very inadequately powered to detect genetic variation with modest effects on disease risk or progression (i.e., sample sizes that are much too small). In addition, inconsistency with regard to the methods used to classify subjects as periodontal cases versus controls or to quantitatively measure disease severity and extent greatly limit our ability to draw sound conclusions by comparing results reported in different studies.But they do not explain the complete heritability of periodontitis, and many more other genes, genetic elements, and variants are yet to be discovered.

Advances in genetics not only determines the initiation and progression of the disease, also determines how the person responds to different treatments in terms of both side effects and the success of alternative therapies studied as pharmacogenomics which helps in individualising the treatment.

References:-

1. Caton, J. G., & Quinones, C. R. (1991). Etiology of periodontal diseases. *Current opinion in dentistry*, *1*(1), 17-28.
2. Freires, I. D. A., Alves, L. A., & Castro, R. D. D. (2012). Pharmacogenomics and dental practice: Clinical implications and current researches. *Odontol. clín.-cient*, *11*(2), 97-101.
3. Takashiba, S., &Naruishi, K. (2006). Gene polymorphisms in periodontal health and disease. *Periodontology 2000*, *40*(1), 94-106.
4. Thorn, G. W., & Harrison, T. R. (1977). *Harrison's principles of internal medicine*. McGraw-Hill Companies.
5. Wilton, J. M. A., Griffiths, G. S., Curtis, M. A., Maiden, M. F. J., Gillett, I. R., Wilson, D. T., & Johnson, N. W. (1988). Detection of high- risk groups and individuals for periodontal diseases. *Journal of clinical Periodontology*, *15*(6), 339-346.
6. Trott, J. R., & Cross, H. G. (1966). An analysis of the principle reasons for tooth extractions in 1813 patients in Manitoba. *The Dental practitioner and dental record*, *17*(1), 20.
7. Hirschfeld, L., & Wasserman, B. (1978). A long-term survey of tooth loss in 600 treated periodontal patients. *Journal of periodontology*, *49*(5), 225-237.
8. McFallJr, W. T. (1982). Tooth loss in 100 treated patients with periodontal disease: a long-term study. *Journal of Periodontology*, *53*(9), 539-549.
9. Loos, B. G., John, R. P., &Laine, M. L. (2005). Identification of genetic risk factors for periodontitis and possible mechanisms of action. *Journal of clinical periodontology*, *32*(s6), 159-179.
10. Kinane, D. F., & Hart, T. C. (2003). Genes and gene polymorphisms associated with periodontal disease. *Critical Reviews in Oral Biology & Medicine*, *14*(6), 430-449.
11. Noack, B., Görgens, H., Hempel, U., Fanghänel, J., Hoffmann, T., Ziegler, A., &Schackert, H. K. (2008). Cathepsin C gene variants in aggressive periodontitis. *Journal of dental research*, *87*(10), 958-963.

12. Hart, T. C., Hart, P. S., Michalec, M. D., Zhang, Y., Firatli, E., Van Dyke, T. E., ...&Soskolne, W. A. (2000). Haim-Munk syndrome and Papillon-Lefevre syndrome are allelic mutations in cathepsin C. *Journal of medical genetics*, *37*(2), 88-94.
13. Zhang, Y., Hart, P. S., Moretti, A. J., Bouwsma, O. J., Fisher, E. M., Dudlicek, L., ... & Hart, T. C. (2002). Biochemical and mutational analyses of the cathepsin c gene (CTSC) in three North American families with PapillonLefèvre syndrome. *Human mutation*, *20*(1), 75-75.
14. Tempel, T. R., Kimball, H. R., Kakenashi, S., & Amen, C. R. (1971). Host factors in periodontal disease: periodontal manifestations of Chediak-Higashi Syndrome. *Journal of periodontal research*, (10), 26-27.
15. Lavine, W. S., Page, R. C., & Padgett, G. A. (1976). Host Response in Chronic Periodontal Disease: V. The Dental and Periodontal Status of Mink and Mice Affected by Chediak-Higashi Syndrome. *Journal of periodontology*, *47*(11), 621-635.
16. Waldrop, T. C., Anderson, D. C., Hallmon, W. W., Schmalstieg, F. C., & Jacobs, R. L. (1987). Periodontal Manifestations of the Heritable Mac-1, LFA-1, Deficiency Syndrome* Clinical, Histopathologic and Molecular Characteristics. *Journal of periodontology*, *58*(6), 400-416.
17. Page, R. C., Beatty, P., & Waldrop, T. C. (1987). Molecular basis for the functional abnormality in neutrophils from patients with generalized prepubertal periodontitis. *Journal of periodontal research*, *22*(3), 182-183.
18. Izumi, Y., Sugiyama, S., Shinozuka, O., Yamazaki, T., Ohyama, T., & Ishikawa, I. (1989). Defective neutrophil chemotaxis in Down's syndrome patients and its relationship to periodontal destruction. *Journal of periodontology*, *60*(5), 238-242.
19. Hart, T. C., Stabholz, A., Meyle, J., Shapira, L., Van Dyke, T. E., Cutler, C. W., &Soskolne, W. A. (1997). Genetic studies of syndromes with severe periodontitis and palmoplantar hyperkeratosis. *Journal of periodontal research*, *32*(1), 81-89.
20. Linch, D. C., & Acton, C. H. C. (1979). Ehlers-Danlos syndrome presenting with juvenile destructive periodontitis. *BRIT DENT J*, *147*(4), 95-96.
21. Alaluusua, S., Asikainen, S., & Lai, C. H. (1991). Intrafamilial transmission of Actinobacillusactinomycetemcomitans. *Journal of periodontology*, *62*(3), 207-210.
22. Sağlam, F., Atamer, T., Onan, U., Soydinç, M., &Kiraç, K. (1995). Infantile genetic agranulocytosis (Kostmann type). A case report. *Journal of periodontology*, *66*(9), 808-810.
23. Baab, D. A., Page, R. C., Ebersole, J. L., Williams, B. L., & Scott, C. R. (1986). Laboratory studies of a family manifesting premature exfoliation of deciduous teeth. *Journal of clinical periodontology*, *13*(7), 677-683.
24. Beumer, J., Trowbridge, H. O., Silverman, S., & Eisenberg, E. (1973). Childhood hypophosphatasia and the premature loss of teeth: A clinical and laboratory study of seven cases. *Oral Surgery, Oral Medicine, Oral Pathology*, *35*(5), 631-640.
25. Casson, M. H. (1969). Oral manifestations of primary hypophosphatasia. A case report. *British dental journal*, *127*(12), 561-566.
26. Wiebe, C. B., Silver, J. G., &Larjava, H. S. (1996). Early-onset periodontitis associated with Weary-Kindler syndrome: a case report. *Journal of periodontology*, *67*(10), 1004-1010.
27. Risch, N. J. (2000). Searching for genetic determinants in the new millennium. *Nature*, *405*(6788), 847-856.
28. Hart, T. C., Marazita, M. L., & Wright, J. T. (2000). The impact of molecular genetics on oral health paradigms. *Critical Reviews in Oral Biology & Medicine*, *11*(1), 26-56.
29. Kinane, D. F., Shiba, H., & Hart, T. C. (2005). The genetic basis of periodontitis. *Periodontology 2000*, *39*(1), 91-117.
30. Lindhe, J. (1983). *Textbook of clinical periodontology*. WB Saunders Company.
31. Sofaer, J. A. (1990). Genetic approaches in the study of periodontal diseases. *Journal of clinical periodontology*, *17*(7), 401-408.
32. Choi, J. I., Ha, M.H., Kim, J.H. & Kim, S.J. (1996) Immunoglobulin allotypes and immunoglobulin G subclass responses to Actinobacillusactinomycetemcomitans and Porphyromonasgingivalis in early-onset periodontitis. *Infection and Immunity* 64, 4226–4230.
33. Kornman, K. S., Crane, A., Wang, H.Y., di Giovine, F.S., Newman, M.G., Pirk, F.W., Wilson, T.G., Jr., Higginbottom, F.L. & Duff, G.W. (1997) The interleukin-1 genotype as a severity factor in adult periodontal disease. *Journal of Clinical Periodontology* 24, 72–77.
34. Honig, J., Rordorf Adam, C., Siegmund, C., Wiedemann, W. &Erard, F. (1989) Increased interleukin-1 beta (IL-1 beta) concentration in gingival tissue from periodontitis patients. *Journal of Periodontal Research* 24, 362–367.

35. Heasman, P. A., Collins, J.G. &Offenbacher, S. (1993) Changes in crevicular fluid levels of interleukin-1 beta, leukotriene B4, prostaglandin E2, thromboxane B2 and tumour necrosis factor alpha in experimental gingivitis in humans. *Journal of Periodontal Research* 28, 241–247.
36. Wright, S. D., Ramos, R.A., Tobias, P.S., Ulevitch, R.J. &Mathison, J.C. (1990) CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. *Science* 249, 1431–1433.
37. Couturier, C., Haeffner-Cavailon, N., Caroff,M. &Kazuchkine, M.D. (1991) Binding sites for endotoxins and lipopolysaccharides on human monocytes. *Journal of Immunology* 147, 1899–1904.
38. Graves, D. T., & Cochran, D. (2003). The contribution of interleukin-1 and tumor necrosis factor to periodontal tissue destruction. *Journal of periodontology*, *74*(3), 391-401.
39. Ishimi, Y. O. S. H. I. K. O., Miyaura, C. H. I. S. A. T. O., Jin, C. H., Akatsu, T., Abe, E. T. S. U. K. O., Nakamura, Y. U. I. C. H. I., ... & Hirano, T. (1990). IL-6 is produced by osteoblasts and induces bone resorption. *The Journal of Immunology*, *145*(10), 3297-3303.
40. Fishman, D., Faulds, G., Jeffery, R., Mohamed-Ali, V., Yudkin, J. S., Humphries, S., & Woo, P. (1998). The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *Journal of Clinical Investigation*, *102*(7), 1369.
41. Scarel- Caminaga, R. M., Trevilatto, P. C., Souza, A. P., Brito, R. B., Camargo, L. E., & Line, S. R. (2004). Interleukin 10 gene promoter polymorphisms are associated with chronic periodontitis. *Journal of Clinical Periodontology*, *31*(6), 443-448.
42. Berglundh, T., Donati, M., Hahn- Zoric, M., Hanson, L. Å., &Padyukov, L. (2003). Association of the− 1087 IL 10 gene polymorphism with severe chronic periodontitis in Swedish Caucasians. *Journal of clinical periodontology*, *30*(3), 249-254.
43. Shapira, L., Van Dyke, T. E., & Hart, T. C. (1992). A localized absence of interleukin-4 triggers periodontal disease activity: a novel hypothesis. *Medical hypotheses*, *39*(4), 319-322.
44. Gonzales, J. R., Mann, M., Stelzig, J., Bödeker, R. H., &Meyle, J. (2007). Single- nucleotide polymorphisms in the IL- 4 and IL- 13 promoter region in aggressive periodontitis. *Journal of clinical periodontology*, *34*(6), 473-479.
45. Chou, Y. H., Ho, Y. P., Lin, Y. C., Hu, K. F., Yang, Y. H., Ho, K. Y., ... & Tsai, C. C. (2011). MMP- 8- 799 C> T genetic polymorphism is associated with the susceptibility to chronic and aggressive periodontitis in Taiwanese. *Journal of clinical periodontology*, *38*(12), 1078-1084.
46. Wilson, M. E., & Kalmar, J. R. (1996). FcγRIIa (CD32): A potential marker defining susceptibility to localized juvenile periodontitis. *Journal of Periodontology*, *67*(3s), 323-331.
47. Hennig, B. J., Parkhill, J. M., Chapple, L. L., Heasman, P. A., & Taylor, J. J. (1999). Association of a vitamin D receptor gene polymorphism with localized early-onset periodontal diseases. *Journal of periodontology*, *70*(9), 1032-1038.
48. de Brito Junior, R. B., Scarel-Caminaga, R. M., Trevilatto, P. C., Souza, A. P., & Barros, S. P. (2004). Polymorphisms in the vitamin D receptor gene are associated with periodontal disease. *Journal of periodontology*, *75*(8), 1090-1095.
49. Schafer, A.S., Richter, G.M., Groessner- Schreiber, B. *et al.* (2009). Identification of a shared genetic susceptibility locus for coronary heart disease and periodontitis. *PLoS Genetics* **5**,e1000378.
50. Schafer, A.S., Bochenek, G., Manke, T. *et al.* (2013). Validation of reported genetic risk factors for periodontitis in a large- scale replication study. *Clinical Periodontology* 40, 563–572.
51. Schafer, A.S., Richter, G.M., Dommisch, H. *et al.* (2011). CDKN2BAS is associated with periodontitis in different European populations and is activated by bacterial infection. *Journal of Medical Genetics* 48, 38–47.
52. Murray, R.Z., Kay, J.G., Sangermani, D.G. & Stow, J.L. (2005). A role for the phagosome in cytokine secretion. *Science* 310,1492–1495.
53. Divaris, K., Monda, K.L., North, K.E. *et al.* (2012). Genome- wide association study of periodontal pathogen colonization. *Journal of Dental Research* 91, S21–28.
54. Bochenek, G., Hasler, R., El Mokhtari, N.E. *et al.*. (2013). The large non- coding RNA ANRIL, which is associated with atherosclerosis, periodontitis and several forms of cancer, regulates ADIPOR1, VAMP3 and C11ORF10. *Human Molecular Genetics* 22, 4516–4527.
55. Schafer, A.S., Richter, G.M., Nothnagel, M. *et al.* (2010b). A genome- wide association study identifies GLT6D1 as a susceptibility locus for periodontitis. *Human Molecular Genetics* 19, 553–562.
56. Schafer, A.S., Richter, G.M., Nothnagel, M. *et al.* (2010a). COX- 2 is associated with periodontitis in Europeans. *Journal of Dental Research* 89, 384–388.
57. Lundy, F.T., El Karim, I.A. & Linden, G.J. (2009) Neuropeptide Y (NPY) and NPY Y1 receptor in periodontal health and disease. *Archives of Oral Biolgy*54, 258–262.

58. Divaris, K., Monda, K.L., North, K.E. *et al.* (2013). Exploring the genetic basis of chronic periodontitis: a genome- wide association study. *Human Molecular Genetics* 22, 2312–2324
59. Freitag- Wolf, S., Dommisch, H., Graetz, C., Jockel- Schneider, Y., Harks, I., Staufenbiel, I., ...&Gieger, C. (2014). Genome- wide exploration identifies sex- specific genetic effects of alleles upstream NPY to increase the risk of severe periodontitis in men. *Journal of clinical periodontology*, *41*(12), 1115-1121.
60. Bird, A. (2007). Perceptions of epigenetics. *Nature* 447, 396–398.
61. Wong, A. H., Gottesman, I. I., &Petronis, A. (2005). Phenotypic differences in genetically identical organisms: the epigenetic perspective. *Human molecular genetics*, *14*(suppl 1), R11-R18.
62. Fraga, M.F., Ballestar, E., Paz, M.F. *et al.* (2005). Epigenetic differences arise during the lifetime of monozygotic twins. *Proceedings of the National Academy of Sciences of the United States if America* 102, 10604–10609.
63. Loo, W.T., Jin, L., Cheung, M.N., Wang, M. & Chow, L.W. (2010). Epigenetic change in E- cadherin and COX- 2 to predict chronic periodontitis. *Journal of Translational Medicine* 8, 110.
64. Zhang, S., Barros, S.P., Niculescu, M.D. *et al.* (2010). Alteration of PTGS2 promoter methylation in chronic periodontitis.*Journal of Dental Research* 89, 133–137.
65. Rothstein, M. A., & Epps, P. G. (2001). Ethical and legal implications of pharmacogenomics. *Nature Reviews Genetics*, *2*(3), 228-231.
66. Freires, I. D. A., Alves, L. A., & Castro, R. D. D. (2012). Pharmacogenomics and dental practice: Clinical implications and current researches. *Odontol. clín.-cient*, *11*(2), 97-101.