Exploring the Genetic Basis of Periodontal Diseases–A Review.

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ABSTRACT

The periodontal disease is initiated by microbial plaque, which accumulates in the gingival crevice & induces an inflammatory response. This inflammation leads to chronic gingivitis, which is reversible & may later progress as periodontitis, by destruction of bone & other tooth-supporting structures. Although present in most of the population, the risk for periodontal disease is not uniform for all individuals. About 10-15% of the population develops severe destruction of the periodontal structures leading to early loss of the tooth. This inflammatory response leading to periodontal destruction is assumed to have a genetic basis. It is now recognized that poor oral hygiene alone cannot account for severe destructive periodontal disease, that certain individuals are at relatively high risk of periodontal destruction and that the risk is partly under genetic control. The microbial causation of the inflammatory periodontal disease is well established. There are however other elements that influence the inflammatory and immune response both locally and systemically. These include systemic disease such as diabetes and environmental factors such as smoking and possibly stress. The effectiveness of an individual's immune response may influence the extent of periodontal destruction. The role of genetic factors in the causation of peridontitis is worthy of in depth discussion.

Keywords: Aggressive Periodontitis, Genetics, Gene polymorphism, Hereditary Gingival Fibromatosis, Periodontitis.

INTRODUCTION

Genetics is the study of the inheritance, or heredity of living things. It is a wide ranging science that explores the transmission of biological properties (traits) from parent to off spring. Many human diseases are influenced by heritable alterations in the structure or function of genes. Many human diseases have a complex pathogenesis. They may arise due to many unfavourable conditions like: Environmental factor, Genetic abnormality acting alone or combination of both. The genetic origin of a disease is either partly or entirely due to abnormalities within the genetic code

Periodontitis is an inflammatory condition that attributes to be the main cause of tooth loss.[1]. Periodontitis is defined as "an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both.[2] A risk factor is defined as any characteristic, behavior or exposure with an association to a particular disease. The relationship need not necessarily be causal in nature.

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This risk factor increases the chances of occurrence of the disease and the absence of the same reduces the chances.[3] Risk factors are modifiable; in contrast risk determinants like genetic factors, age, gender, socioeconomic status, and stress are non-modifiable. The microbial and environmental factors are attributed to trigger and initiate the periodontal disease [Figure 1].[4,5,6] Loe et al[7] showed that people with poor oral hygiene status, developed the disease in a faster rate in contrast others showed little or no disease. This difference is due to the genetic variation among the individuals. Identifying the genes and their polymorphism can help in modern diagnostics for risk assessment, early detection of the disease with a streamlined treatment approach. Thus proper information about genetic polymorphism will be a guide to the understanding of the periodontal disease.

GENE POLYMORPHISM IN PERIODONTAL DISEASES

Immune system plays a vital role in pathogenesis of periodontitis. In particular genetic variations in immune mediators such as cytokines are used as target for susceptibility factor as IL-1 and TNF - α plays an important role in periodontitis.

IL-1 Gene Polymorphisms: Kornman et al[8] in their study reported polymorphism for the IL-1 genes in relation to periodontitis. The gene encoding for IL-α and IL-β are located close to the IL-1 gene cluster on chromosome 2.

They found that the combined presence of R–allele of IL α gene at nucleotide position -889 and the R–allele of IL–1 β gene at nucleotide position +3953 was associated with severity of periodontitis in non-smoking Caucasian patients.
Now, several longitudinal and cross sectional studies have been performed which help us to assess whether a given genotype can be considered of true susceptibility and /or severity factor.

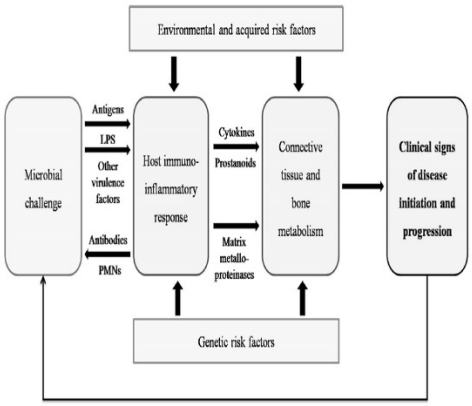

Figure 1: Model for pathogenesis of human periodontal diseases.

IL–10 gene polymorphism: IL–10 is located on chromosome 1, in a cluster with closely related interleukin genes, including Il-19, IL-20 and IL-24. IL-10 plays a role in the regulation of proinflammatory cytokines such as IL–1 and TNF-α. Functional disturbances in IL–10, due to genetic polymorphism could be detrimental to host tissues and could be linked to periodontal disease susceptibility

TNF-α gene polymorphisms: The TNF–α gene is located on chromosome 6 within the major histocompatibility complex (MHC) gene cluster. Several studies have investigated genetic polymorphism in TNF–α gene as putative susceptibility and severity factors in relation to periodontitis. The genetic polymorphism is mainly G to A transition.

FcɣR Gene polymorphisms: It is the polymorphism of the receptors for the Fc fragment of immunoglobulin IgG formed as FcɣR gene polymorphism.[9] FcɣR are found on leukocytes from both the myeloid and lymphoid lineages. The FcɣR links the humoral part of the host defence with the cellular aspects of the immune system. The genes for the FcɣR are found on the long arm (q) of the chromosome 1, and encode for three main classes of FcR: FcyR I, II and III. The FcɣR II is the most widely distributed of IgG receptor molecules, expressed by all granulocytes. It has been shown that structural and functional differences in FcyRIIa are due to genetic polymorphism.[10]

Loos BG,[11] in his study on polymorphism on Fcy gene reports that, Wilson and Kalmer speculated that the FcyRIIa–R–allele might be associated for aggressive periodontitis due to reduced capacity to phagocytoze IgG2 opsonized Aggregatibacter actinomycetemcomitans. The FcyRIIIa N–allele is proposed as a putative susceptibility factor for periodontitis.

EARLY ONSET PERIODONTITIS

Early onset Periodontitis are a heterogeneous group of diseases sharing several characteristics including severe periodontal destruction and early age onset.[12] Schenkein and Van Dyke[13] stated that this group of diseases includes prepubertal periodontitis, juvenile periodontitis (localized EOP) and rapidly progressive periodontitis, where the affected individuals are systematically healthy with significant periodontal destruction.
Page et al[4] was the first to define prepubertal periodontitis in children as a distinct clinical entity affecting the attachment apparatus of primary dentition. They classified prepubertal periodontitis (EOP) into localized and generalised forms, where the generalized form is an oral manifestation of leukocyte adhesion deficiency syndrome. Although periodonto-pathogenic bacteria are primary etiologic agents in the disease process familiar aggregation of the affected individuals suggests genetic factors also play a role in the initiation and progression of the disease.
Various genetic studies of EOP suggest the pattern of disease transmission to be consistent with Mendelian inheritance of a disease of major gene, which means that one (or) more genes of major effort could account for the observed familial pattern of EOP. Such a genetically transmitted genotype could predispose these individuals to a periodontitis phenotype when they are exposed to certain bacteria.
The host response in case of early onset periodontitis may not be constant to all individuals and may be determined by the genotype of the patient. As a result, the intensity for developing periodontitis may differ, reflecting both their environmental and host risk factors. The degree of increased disease risk in genetically susceptible individuals is dependent on the relationship between genotype and exposure. Different strains of the same bacteria manifest different virulence factors. Microbial virulence factors are important in the initiation and progression of periodontal disease and differ from individual to individual depending upon their specific genetic predisposition.

AGGRESSIVE PERIODONTITIS

Unlike the chronic periodontitis, the specific polymorphisms associated with Aggressive periodontitis (AgP) are still obscure. AgP may occur probably due to a major gene locus which is transmitted in an autosomal-dominant manner with reduced penetrance. As the gene responsible for AGP is partially penetrant, in the phenotypic expression of the AGP trait, the environmental factors (such as smoking, bacterial plaque) may play a large role in allowing the phenotype to be present clinically.

Hart et al (1993) & Boughman (1986)[12], found that at least one gene locus responsible for AGP was located on Chromosome 4. Takashiba et al (1999)[14] investigated that polymorphism of HLA.DR gene with DRB1 allele to be significantly associated with AgP.

GENETIC BASIS OF GINGIVAL ENLARGEMENT

In addition to inflammation induced and drug induced gingival enlargement, pronounced gingival enlargement, also occurs in a genetic form called Hereditary Gingival Fibromatosis (HGF).[15].It is characterized by slowly progressive benign enlargement of gingival tissues. The most common forms of non syndromic hereditary gingival fibromatosis are inherited as autosomal dominant trait. The underlying cause is mutation at the gene locus present at chromosome 2p21-22. Gross 1856[16] reported the first case and since then increasing efforts have been made to understand the genetic, molecular and cellular basis of the gingival enlargement of HGF patients, which is impaired by the intense clinical, genetic and biologic heterogeneity of the disease. Three different loci have been associated with the isolated form of HGF: two mapping to chromosome 2 (GINGF on 2p21-22 and GINGF3 on 2p22.3-p23.3), which do not overlap, and one mapping to chromosome 5 (GINGF2 on 5q13-q22).

Drug-induced gingival overgrowth has been seen in patients following intake of phenytoin, cyclosporine or nifedipine. Phenytoin, cyclosporine and nifedipine are all metabolized by the hepatic cytochrome P450 enzymes. Cytochrome P450 genes exhibit considerable polymorphism, which results in interindividual variation in drug levels.[17].

SYNDROMATIC ASSOCIATION OF PERIODONTITIS

Down's Syndrome: Patterson. D[18] in his study on "Molecular genetic analysis of Down's syndrome reported that John Langdon (1866) was the first to describe this genetic disorder. Down's John syndrome results from Trisomy of chromosome 21 caused by non-disjunction during oogenesis (the critical region being the β chain, β 2 gene region of chromosome 21). It is the most frequently occurring genetic disorder with the frequency of approximately 1 in 700 live births.

Orally they have a typical class III occlusion with anterior open bite, a large tongue and lack of lip seal. Studies of Cohen .et al (1961) and Johnson and Young (1963)[19], showed that the affected individuals frequently manifest an aggressive form of periodontal disease affecting both the primary and permanent dentition which may lead to early exfoliation of teeth.

The periodontal destruction is characterized by formation of deep periodontal pockets associated with heavy plaque accumulation and intense gingival inflammation. Periodontal destruction is most severe among the lower anteriors and they have short conical roots followed by upper incisor and first molars and the deciduous molars, premolars and canines. The most common clinical presentation is mobility of lower incisors with radiographic evidence of advanced alveolar bone loss.

It has been shown that individuals with Trisomy 21 are more susceptible to periodontal disease relative to normal aged matched control group and other mentally impaired patients. The prevalence of periodontal disease in downs syndrome patients was shown to be 90-100% Kisling and Krebs (1963).[20]

Papillon Lefevre Syndrome: Shabina Sachdeva, Namita Kalra, in their case report on Papillon-Lefèvre Syndrome,[21] reported that, Papillon and Lefevre (1924) originally described this syndrome. It is an autosomal recessive inherited disease characterized by a diffuse palmar-plantor keratosis and premature loss of deciduous and permanent dentitions, cranical calcification, increased susceptibility to infection and severe early onset periodontitis. It has been classified as type IV Ectodermal dysplasia. {Mutation of Cathepsin C gene, which is important for host response and maintenance of epithelial integrity, is responsible for this condition}.

Lesions associated with this disease begin to manifest at 2- 4 years of age and affects the primary and permanent dentition. The primary teeth are affected from the second year are prematurely exfoliated by the sixth year and are lost in the order of the eruption.

The tissues then heal and the permanent teeth erupt early. A similar destructive rapidly progressive periodontal affect these teeth and results in progressive bone loss and exfoliation. The clinical sign resemble those of an advanced adult periodontitis with severe gingival inflammation.

The prognosis of the teeth is very poor and most subjects are edentulous by the age of 16 years.

Cyclic Neutropenia: Cyclic neutropenia disease of unknown aetiology characterized by 15 to 35 day cyclic fluctuation in formed elements of blood (characterized by a regular 7-day period of depression in the number of neutrophils, occurring every 21 days)[22]. Affected individuals experience recurrent fever and malaise, oral ulceration and skin infection and episodes of life threatening infections.
Oral manifestations include oral mucosal ulceration, severe gingivitis and periodontitis.[23].The defect present is the mutation in neutrophil elastase gene. It was also reported that it can affect both the primary and permanent dentition. The periodontal destruction is usually more severe if the cyclic Neutropenia starts in infancy and childhood.

Chediak-Higashi Syndrome: It is a rare autosomal recessive inherited disease caused by a lysosomal defect leading to anamolies of blood cells and neutrophilic destruction.[24] The features of this syndrome include, albinism (pigmentation of hair and eyes) with photophobia and nystagmus and frequent pyogenic infections and febrile illness. This disease gives rise to very severe gingivitis and periodontitis and premature loss of primary and permanent teeth.[25]

Leukocyte Adhesion Deficiency: Leukocyte adhesion deficiency (LAD) is used to denote a heterogenous group of rare disorders characterized by abnormal leukocyte function and decreased cellular adhesion. Clinically these patients present with recurrent, necrotic and non-bacterial infections generally involving the skin and sub cutaneous tissues, middle ear and the oropharynx. The affected individuals have delayed separation of the umbilical cord and defective neutrophil mobility. One of the most dramatic findings in LAD is severe periodontal disease [26]. Periodontal findings include rapid bone loss leading to exfoliation of teeth; gingival clefting and recession associated with fiery red gingival, profuse bleeding and signs of generalized destruction. Periodontal destruction arises immediately after the eruption of primary teeth. Extremely acute inflammation and proliferation of the gingival tissues with rapid destruction of the bone are seen. Two forms of LAD have been described:
Type I LAD is an autosomal disorder (localized chromosome 21q 22.3) characterized by the inability of the individuals express the β2 subunit (CD 18) common to the leukocyte intergrins LFA - 1, Mac-1 and P150/95.
Type II LAD there appears to be a selectin-ligand deficiency (the leukocytes do not express sialo-lewis x or gp150-lewis x) referred to as leukocyte adhesion deficiency[27], in which neutrophils rolling does not increase in response to inflammation. Individuals with this deficiency suffer from recurrent bacterial infection, neutrophilia (20,000 to 70,000 neutrophils per mm3.) and severe early onset periodontitis.

Ehlers Danlos Syndrome (EDS): It is an inherited condition affecting the connective tissue and is a disorder in collagen. Ten variants of this condition have been described. The mode of inheritance of four types is autosomal dominant (Type I, II, III &VIII) and three types are autosomal recessive (IV, VI and VII) and other three types are X-linked (V, IX, X).
The precise nature of the defect is unknown but in Type IV the defect in collagen is due to reduced lysyl hydroxylation of the molecules, also in Type IV there is deficiency in the synthesis structure and secretion of Type III collagen and a deficiency of the enzyme procollagen peptidase. It is characterized by hyper extensibility of the joints, increased fragility and stretchability of the skin, bleeding tendencies skeletal deformities, ocular fragility and rupture of instestines or arteries. The underlying genetic defect in collagen synthesis seen in EDS types IV, VII and IX appear to increase susceptibility for rapid progressive periodontal destructions. The oral mucosa, gingival tissues, periodontium, teeth and T.M.joints are affected.[28] The oral mucosa is fragile and is susceptible to bruising. The gingival tissues bleed easily after brushing and post extraction haemorrhage may be a problem.[29].

Hypophosphatasia: It is a rare familiar disease with an autosomal recessive mode of inheritance characterized by incomplete bone mineralization, characterized by low levels of serum, liver, kidney and bone alkaline phosphatase, and elevated levels of phosphoethanolamine in serum and urine. Affected individuals of hypophosphatasia, typically show premature exfoliation of teeth, craniostenosis, microcephaly, bone defects, osteogenesis defects and neurological seizures. It is due to defect in alkaline phosphatase gene leading to defective cementum formation and early exfoliation.[30] It can be diagnosed from samples of the gingival crevicular fluid.

DIAGNOSIS OF GENETIC DISEASES

Diagnosis of genetic diseases requires examination of genetic material (i.e. Chromosome and gene). Hence the general methods employed are: A) Cytogenetic analysis, B) Molecular analysis.
Parental Chromosome Analysis: It should be offered to all patients who are at risk of

cytogenetically abnormal progeny. It can be performed on cells obtained by amniocentesis, as chronic villus, biopsy or as umbilical cord blood.

Postnatal Chromosome Analysis: Performed in peripheral blood lymphocytes.

Direct Gene Diagnosis: Mainly depends on the detection of an important qualitative change in DNA. Methods employed are: a) Allele specific oligonucleotides Hybridization, b) Polymerization Chain Reaction Analysis (PCR).

Southern Blot Analysis: When the full mutation cannot be detected by PCR Analysis, because the effective segment of DNA is too large for conventional PCR (e.g. in fragile X Syndrome).

Northern blot Analysis: Newly developed approaches include microassays and DNA sequencing.

Other methods of detection of mutation and other chromosome disorders are:

SSCP: Single strand conformational polymorphism

DGGF: Denaturation gradient gel Electrophoresis

OSH: Oligonucleotides specific hybridization

RFLP: RNAase cleavage restriction fragment length polymorphism.

INDIRECT GENE DIAGNOSIS

Direct gene diagnosis is possible only if the mutant gene and its normal counterpart have been identified and cloned and their nucleotide sequences are known. In a large number of genetic diseases, information about the gene sequence is lacking. Therefore, alternative strategies are applied to track the mutant gene on the basis of its linkage to detectable genetic marker. The success of such strategies depends on the ability to distinguish the chromosome that carries the mutation from its normal homologous counterpart. This is accomplished by exploiting the naturally occurring variations or polymorphisms in DNA sequences in different phenotypic and genotypic variants.

The strategies that come under the indirect gene diagnosis are:

Segregation Analyses: The pattern in which a disease is transmitted across generations depends on whether the disease allele lie as autosome or sex chromosome whether they are dominant or recessive and whether they are fully or partially penetrant. Generally, a dominant allele determines the phenotype in a heterozygote with another recessive allele. A recessive allele determines the phenotype only when present in both the loci on the homologous chromosomes [31]. Penetrance refers to the probability that a particular phenotype will result from a genotype. Partially penetrants means that only fraction of individuals who inherit the disease allele will be affected.

In segregation analysis, the observed pattern of disease in families is compared with pattern expected under various models of inheritance. The strategically power of this design depends on the number and composition of the families and the heterogenecity of the disease. Heterogeneity means that there are different causes of disease among the families. Generally, segregation analyses have a low power to resolve heterogenecity. Segregation analysis also cannot distinguish between genetic effects and unmeasured environmental causes of diseases.

Twin Studies: The relative effect of genetic and environmental factors on complex diseases can be estimated using twin data.[32] In classical twin study, reared together monozygotic and dizygotic twins are compared to estimate the effects of shared genes. Monozygotic (MZ) twins are genetically identical, whereas dizygotic (DZ) twins share on an average 50% of these genes by descent. For binary traits (present or absent) a genetic effect is inferred if the positive concordance rate or percentage of twins in which both twins are affected, is greater for MZ than DZ twins. Typically twin data are used to estimate heritability, which is proportional of phenotypic variations attributed to genetic variation.[33] A Heritability estimate of 50% means that one half of the variance in population is due to genetic variance. Heritability can also be estimated from MZ twins who are separated at birth and raised apart. Although studies of concordance in twins do not provide information about the specific gene involved in a trait, they can provide estimate of the effect of heredity versus environment. They also describe the impact of genes on specific populations exposed to a particular range of environment.

LINKAGE AND ASSOCIATION STUDIES

These studies are used to map disease alleles to specific regions on chromosome.[34] Genetic linkage refers to the fact that genes are physically connected or linked, to one another along the chromosome. Two fundamental principles of linkage are:

When two genes are close together on the chromosome, they are usually transmitted together, unless a recombination process separates them. The odds of a cross over, or recombination event, between two linked genes are proportional to the distance between them.

One can assess whether certain marker alleles co-segregate with the disease. Markers that are closest to the disease genes are less likely to undergo recombination events and therefore receive higher linkage score. Linkage is expressed as a LOD (Logarithm of odds) score the ratio of probability that the disease and the marker loci are linked rather than unlinked. LOD score of +3 (1000:1) are generally accepted as supporting linkage, whereas a

score of -2 is consistent with the absence of linkage.

ASSOCIATION STUDIES

Allele association refers to a situation in which the frequency of an allele is significantly increased or decreased in a particular disease while genetic linkage is demonstrable in families or siblings, association studies compare a population of affected individuals with control population. They can be performed as case control studies that include correlated affected individuals and matched controls, on as family based studies that compare the frequencies of alleles transmitted or not transmitted to the affected children. Association studies[35] are particularly useful for identifying susceptibility genes in complex diseases. When alleles at two loci occur more frequently than would be predicted (based on known allele frequencies and recombination fractions) they are said to be in linkage disequilibrium.

CONCLUSION

Oral microbes are the primary etiological agents in inflammatory periodontal diseases, but the consequences of microbial challenge are dependent upon the genetic background of the host. Data from various epidemiological studies of periodontitis suggest that the host response to the microbial challenge is variable. Modulated factors and a large part of this variance are determined at genetic level.

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