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When Cogs and Gears Fail- Role of Genetics in Periodontal Diseases

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Abstract:

Microbiological & environmental factors reportedly either initiate or modulate the course of periodontal diseases. But the response to these factors especially environmental is dependent on the patient's genome. Thus variations in genetic factors are implicated in periodontal diseases. Several study designs have been structured to establish the extent of the impact of genetic factors in the causation as well as modulation of the course of periodontal diseases. There are several mechanisms which cause alteration of the genetic factors leading to periodontal pathology. Most notable among them are polymorphisms of several genetic factors such as interleukin-1, tumour necrosis factor gene etc. But the exploration of the "master gene" responsible for periodontal disease in an otherwise healthy individual still continues. No doubt evidence till date suggests that periodontal disease is a complex multifactorial interaction but it is actually the genes which hold the key to unearthing hidden answers as they are truly the cogs and gears of our system.

Key words: Genetic factor, Genetic study, Periodontal disease

INTRODUCTION

We all know that cogs and gears are the smallest functional unit of machines. Our body is a highly complex machine and genes and genetic factors are our cogs and gears. Just as even if the smallest of cogs and gears have problems then the whole machine may start functioning inefficiently or may completely stop working. In the same way faults in genes and genetic factors can give rise to a myriad variety of diseases.

Periodontitis is a multifactorial disease. Although microbiological and environmental factors are reported to either initiate or modulate periodontitis. It is seen that because of the difference in the response to environmental factor is due to patient's genome.

Thus it can be said that variation in genetics is one of the key factor in the development of periodontal diseases [1,2].

GENETIC STUDY DESIGNS

Various techniques have been used to establish the genetic aspect of the disease. Certain techniques are general, while others allow accurate identification of genetic variations which cause or favours the occurrence of the disease.

Role of genetics and its effects in various diseases including periodontitis have been assessed using following techniques

1. Familial aggregation
2. Twin studies.
3. Segregation analysis.
4. Association studies.
5. Linkage analysis
6. International HapMap project.

Familial aggregation

It is the first step in the study of a potential genetic characteristic. Its aim is to identify new disease genes. Familial aggregation is the affinity for disease to bunching in families. Here the study unit involves comparing the case with the family history [3] .

No way there is control for individual or environmental risk factors for each relative, which might have influence the genetic aspect. This is the biggest drawback of this type of study.

The possibility of a positive family history of disease rises with age and the number of relatives involved [3] which makes imprecise this aspect.

Thus, shared genes, environmental exposures and similar socioeconomic influences may result in familial aggregation. Large number of formal genetic researches are needed to support this part of genetic factor but until recently the research tools to track these reports were deficient [4].

Twin studies [3]

The study unit comprises of reared together monozygotic & dizygotic twins.

For binary traits a genetic trait is concluded if the positive concordance rate or percentage of twin pairs in which both twins are affected. The monozygotic twins are affected more compared to dizygotic twins. For continuous measures such as pocket depth and clinical attachment level) twin pair similarities are assessed using intra class co-relation. These co-relations reflect the difference among twin pairs relative to the variation within pairs.

The very large number of raised together twins are required for the evaluation of heritability with accuracy.

Segregation Analyses

Its aim is to determine whether the pattern of disease occurrence in families fits a particular type of inheritance. Segregation analyses are typically used in aggressive periodontitis case studies as it clusters in families[5] . Such clustering suggests that the disease has a genetic basis because family members can share deleterious components of their environment as well. In aggressive periodontitis both dominant & recessive modes of inheritance patterns have been proved. Despite inconsistent conclusions regarding their mode of inheritance, these analyses regularly have sustained the role of a prime gene as one of the etiological factor of aggressive periodontitis

The main drawback of segregation analyses is that it does not certainly offer the true model. Segregation analyses are considered only as good models tested since its just comparison of two models. If main assumptions of the model tested becomes incorrect can leads to the limitation in the results.

Linkage Analysis

The localization of the gene for a trait to a specific chromosomal location is the prime aim of this type of analysis. Genetic linkage researches are based on the facts that alleles at gene loci in close vicinity on the same chromosome tend to be passed together from one generation to other generation (i.e. segregate), as a unit. Therefore to prove the genetic basis for a disease linkage can used.

To decide the approximate position of a gene of interest linkage analysis can be done, allowing successive studies to identify the mutation responsible for a disease trait. Simple Mendelian traits can be used to recognize the genetic basis using linkage studies. Where mutation of a single gene can cause a disease. Linkage studies of complex genetic traits have not been as successful for a several reasons [6].

A limiting factor in the traditional use of linkage to complex diseases is that complex diseases are due the combined effect of multiple genes of minor effect. When multiple genes each pay a small amount to the disease phenotype, traditional parametric linkage studies are much less powerful.

In the absence of specific genetic models, the etiology of complex diseases is often conceptualized as due to multiple factors, which in turn interacts with additional environmental factors to produce an actual disease state.

Thus, linkage analyses may not be a useful strategy to detect modifier genes or genes that exert small effects – precisely those genes which might be operating in chronic periodontitis.

Association studies [3]

Its aim is to find more common genetic variations which are greatly prevalent in the general population.

Association studies are similar to case-control studies except that the disease associated "exposures" that one seeks to identify are variant alleles of genes. In practice, frequencies of variant alleles among affected individuals are compared to unaffected individuals.

There is no functional role played by the associated allelic polymorphism in causing disease, but the polymorphism is in close physical proximity to the gene may contribute to susceptibility.

CLINICAL IMPLICATION OF GENETIC STUDIES

The role of host genes as an etiology and pathogenesis of the periodontal diseases is in budding stage. Genetic tests may demonstrate useful tool in identifying patients who are most likely to develop disease, suffer from recurrent disease, or suffer tooth loss as a result of disease. The useful of any screening tool, has to be evaluated in diverse populations. The complex nature of the periodontal diseases, suggests that any genetic test will be useful. Knowledge of specific genetic risk factors could enable clinicians to direct environmentally based prevention and treatments to individuals who are most susceptible to disease. At present, however, the efficacy of specific preventive and treatment strategies in susceptible patients has yet to be clearly recognized.

MECHANISMS OF GENETIC ALTERATIONS

Single nucleotide polymorphisms

Single nucleotide polymorphisms happen as a solitary base-match site in the human genome each 100–1,000 base sets with individual variation.

Not all single nucleotide polymorphisms result in an unmistakable phenotype, while others are obvious clinically.

Cytokine polymorphisms

Differences in the expression of cytokines, especially pro-inflammatory cytokines, are of great interest in periodontal research.

Cytokines, such as (IL)-1 and tumor necrosis factor (TNF) have critical roles in hard tissue destruction has been made to explain the relationship of single nucleotide polymorphisms between persistent population. Among one of the more focused hereditary relationship with periodontal illness is that of the IL-1 genotype. This hereditary marker includes two polymorphism of the IL-1 quality group on chromosome 2[7].

In people, IL-1b has been recognized as a key cytokine required in destruction of extracellular framework and resorption of bone

Recent investigations regarding the correlation between IL-1 genotype status and gingival crevice fluid (GCF) levels of IL-1a and IL-1b have provided evidence of a genetic influence on the levels of these inflammatory mediators in GCF A reduction in IL- 1b concentration in GCF was seen for periodontitis associated genotype patients after treatment[8].

It is apparent from these findings that while IL-1 genotype status may influence the susceptibility and expression of periodontal disease for many patients, no one individual fits into the universal 'genotype box' as yet some other undetermined genetic factors may also influence periodontal outcomes.

Fc, FMLP Receptor Polymorphisms

The Fc portion of an antibody is responsible for binding to receptors present on immune cells independent of the

antigen-binding, Fab portion. These cellular Fc receptors, especially IgG Fc receptors designated FcγRs. They are found on cells capable of binding the Fc portion of IgG antibody. They play an important in the phagocytosis, antibody- dependent cell-mediated cytotoxicity, endocytosis, enhancement of antigen presentation, and the release of inflammatory mediators[9].

FcγRs are currently classified into FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16) each containing isoforms within each class that affect cellular distribution and binding affinity to IgG subclasses[9] .Polymorphisms in the genes encoding the low affinity receptors FcγRIIa, FcγRIIb, FcγRIIIa, and FcγRIIIb may result in variations in antibody binding and phagocytosis and hence susceptibility to periodontitis.

The existence of several FcγR polymorphisms of periodontal relevance has been documented and appears to be involved in microbial clearance. Depressed chemotactic response to FMLPs in localized aggressive periodontitis (LAP) patients has been confirmed by several investigators[10]. The authors suggest that the presence of the single nucleotide polymorphisms may play a role in decreased chemotactic activity seen in some patients with LAP.

HLA Genetics

Human leukocyte antigens (HLA) are involved in genetically predetermined humoral immune response via recognition of foreign antigens.

The MHC genes are the most polymorphic genes present in the genome of every species analyzed. MHC molecules play a central role in immune responses to protein antigens and in autoimmunity. In periodontics, research has focused on identifying alleles associated with disease.

GENETIC FACTORS IN THE PATHOGENESIS OF PERIODONTAL DISEASES

The following are the putative genetic risk factors for susceptibility to periodontal diseases

1. IL1 gene cluster
2. The TNF gene
3. The FcγRIIa and b genes
4. The FcγRIIIa and FcγRIIIb genes
5. The VDR gene
6. Pattern recognition receptors gene
7. The MMP1 gene

The IL1 gene cluster [11]

Interleukin-1 (IL1) is a potent pro-inflammatory mediator that is primarily released by monocytes, macrophages and dendritic cells. The genes encoding the proteins IL1a, IL1b and interleukin receptor antagonist (RA) are located in close proximity in the IL1 gene cluster at chromosome position 2q13-21. IL1A-889 (in linkage disequilibrium with +4845, IL1B-511 (in linkage disequilibrium), IL1B +3954 (also referred to as +3953) and IL1RN VNTR (variable number of tandem repeats, in linkage disequilibrium with +2018) are studied in periodontal research.

The IL1A gene

There is considerable variation in the carriage rate of the IL1A-889 (+4845) R allele. This highlights that the carriage rate of genetic polymorphisms may vary among ethnic populations. Therefore, probable positive associations among a genetic polymorphism and disease within one population cannot be certainly be generalized to other populations.

The IL1B gene

An association was found among the R /R genotype and aggressive periodontitis (P = 0.012). This research was carried out in large cohort (‡100 individuals) Caucasian aggressive periodontitis patients[12] .

The IL1RN Receptor Antagonist gene

Inconsistent outcomes have been stated in IL1RN VNTR (+2018) gene polymorphism. The R allele carriage rate ranged from 6 and 50%. This has been associated as a single genetic risk factor with aggressive periodontitis and chronic periodontitis. The IL1RN R allele has been stated to have a link with periodontitis susceptibility in non-smokers in combination with IL1A-889 and IL1B +3954[13].

TNF- gene

It is one of the potent pro-inflammatory cytokine which possesses a widespread action immunoregulatory functions.

The location of TNF gene is on chromosome position 6p21. The SNPs that have been studied for the TNF gene are mostly in the promoter region and in the first intron of the coding region.

TNF gene variations and periodontitis susceptibility has been supported by very limited amount of data

The IL10 gene

An anti-inflammatory cytokine which has effect on pro-inflammatory immune response of monocytes and macrophages is Interleukin-10 (IL10.) It is produced by monocytes, macrophages and T cells. The regulation of IL1 and TNF-α is done by IL10 gene.

The gene encoding IL10 is located at chromosome position 1q31-32, in a cluster with closely related interleukin genes, including IL19, IL20 and IL24.

The IL4 gene

Pleiotropic cytokine is Interleukin-4 (IL4). The sources are T helper 2 cell, B lymphocytes. Macrophage function has been down regulated by IL4. On chromosome position 5q31.1 is the l gene for IL4 is located.

There is no confirmation for an association among single SNPs of IL4 and chronic periodontitis. The relationship between aggressive periodontitis and IL4 gene polymorphisms has not been supported by large cohort studies.

The IL6 gene

Interleukin-6 (IL6) has been identified by various functions. Different cell types release IL-6, and its secretion levels are determined by the cell type and the nature of the stimulus[14]. The IL6 gene is placed at chromosome position 7p21. The serum levels of circulating IL6, and influence IL6 expression is affected by IL6 polymorphism. The plasma levels of IL6 is raised by N allele carriers.

The FcγR genes

1. The FcγRIIa and b genes
2. The FcγRIIIa and FcγRIIIb genes

For the host defense against bacteria leukocyte receptors for the constant (Fc) part of immunoglobulin (FcγR) link cellular and humoral parts of the immune system are considered critical. In the periodontal tissues on various immune cells FcyRs are detected. They are probably play a vital role in the pathogenesis of periodontitis. Microorganisms and bacterial antigens, opsonized with antibody, are phagocytosed via FcγR on neutrophils or internalized via FcγR by a variety of antigen-presenting cells such as T cells and natural killer cells. A variety of cytokines and chemokines may also be released.

The chromosome 1 is the location for FcyR genes and encode three main receptor classes: FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16). These classes are further sub-divided into sub-classes FcγRIa and b, FcγRIIa, b and c, and FcγRIIIa and b.

The FcγRIIa and b genes

The FcγRIIa polymorphisms and periodontitis relationship has been studied in several researches. But no association has been found between periodontitis (aggressive periodontitis or chronic periodontitis) and FcγRIIa polymorphisms.

The FcγRIIIa and FcγRIIIb genes

A limited number of data supports the association between FcγR polymorphisms and periodontitis (chronic periodontitis, and aggressive periodontitis). At present no large-scale convincing epidemiological data are available, to check whether the FcγR gene polymorphisms are risk factors for periodontitis.

The VDR gene

Along with regulation of various biological processes the vitamin D receptor (VDR) regulates bone metabolism as well as immune response to microbial infections. The chromosome position 12q12–q14 is the location of human VDR gene. There is a possible that the vitamin D receptor (VDR) and its genetic polymorphisms can play a vital role in periodontitis susceptibility since alveolar bone resorption and bacterial deposition. The VDR polymorphisms at Restriction Fragment Length Polymorphism (RFLP) positions TaqI, BsmI, FokI and ApaI in relation to aggressive periodontitis and chronic periodontitis have been identified in several investigations. Among them TaqI polymorphism being the most studied polymorphism. Though most of the studies on the TaqI SNP of the VDR gene have found associations with chronic periodontitis, but not always completely.

Due its effect on bone metabolism and immune functions the VDR gene is an interesting candidate gene for association with periodontitis. Future researches should focus on these aspect to confirm the current preliminary data.

Pattern Recognition Receptor Genes

Polymorphisms in the:

- CD14
- TLR2 and TLR4 genes

Polymorphisms in the CD14 gene

The gene for CD14 is located at chromosome position 5q21-23. Increased serum levels of soluble CD14 have been associated with periodontitis[15].

Conflicting results have been found with CD14-260 polymorphism and chronic periodontitis association. No association has been noted with aggressive periodontitis[16].

Polymorphisms in the TLR2 and TLR4 genes

The TLR2 and TLR4 genes map to chromosome locations 4q32 and 9q32-33, respectively. Limited studies have been able to find an association between the TLR4 +299 and +399 N / N genotypes and aggressive periodontitis, R /R genotypes and chronic periodontitis[17,18]. In a Japanese population, TLR4 +3725 polymorphism was found to be associated with chronic periodontitis when nine additional SNPs in TLR2 and TLR4 genes were studied [19].

Current investigations have not yielded strong evidence supporting this direction of research with periodontal disease.

The MMP1 gene

In events like embryonic development, morphogenesis, angiogenesis and tissue repair, excessive breakdown of connective tissues in inflammatory disorders such as periodontitis matrix metalloproteinases (MMPs) is considered to play an important role. In inflamed periodontal tissues different types of MMPs have been identified[20]. The abundant protein components of the periodontal extracellular matrix like type I, II and III collagens have been cleaved by MMP-1. The MMP1 gene is based at chromosome position 11q22, and is expressed in various cells. Polymorphisms in the promoter region of the MMP1 gene have been studied vastly [21].

FUTURE OF GENETIC STUDIES IN PERIODONTOLOGY

Due to its multifactorial nature researches should focus studies which will examine the role of important environmental and genetic factors simultaneously as an etiology for the progression of periodontal disease. Given the large numbers of genes in the human genome and bacteria in the oral cavity, it is likely that genes and the environment interact in important way but yet unrecognized the exact mechanism involved in this.

Large number of markers required to identify the risk alleles for genomic influence in the disease. Single-nucleotide polymorphisms (SNPs) are likely to be valuable tools in this search. SNPs are single-nucleotide base-pair substitutions that occur frequently (i.e., about every 1000 base pairs) throughout the genome. The amino acid sequences of proteins has been altered by few SNPs. However, SNPs are useful in epidemiological view since they represent variation in the population.

Only limited number of polymorphisms have been consistently associated with a periodontal disease have been identified. Furthermore, the number of subjects or families studied has been relatively small, and the risk attributable to any one allele or genotype has not been estimated precisely. Before any nucleotide sequence variant is touted as a risk marker for periodontitis, the gene it affects should have some established or biologically plausible role in the pathogenesis of the disease, and its association with periodontitis should be confirmed in independent populations. Given the vast number of annotated variants in the human genome, the potentially

large number of false-positive results could lead to clinicians and researchers alike to become disillusioned with the potential clinical utility of such tests.

CONCLUSION

The search for the 'master gene' responsible for periodontitis in an otherwise healthy individual is still continuing. The multifactorial nature of the disease makes the investigations more challenging and demanding. The evidence till the date suggests that periodontal disease occurs as complex interactions among host factors, genetics, and the environment.

Thus, along with interpretation of genotype status other factors also must be used in the treatment regime and for maintenance schedules. Future researches should focus on finding out the confirmed etiologies and their exact role in the disease development and progression. Genetics studies may play major role in solving this aspect.

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