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Review Article

Periodontal disease and genetics an overview and lineage

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ABSTRACT

Periodontal diseases are a heterogeneous group of pathologies. It is believed that bacteria are required to develop periodontitis. While microbial and other environmental factors initiate and modulate periodontal disease, individuals respond differently to common environmental challenges, and this differential response is influenced by the individual's genetic profile. Genes clearly play a role in the predisposition to and progression of periodontal diseases. Susceptibility to periodontal disease and the severity of the disease results from the interactions of genetic mutations and polymorphisms. This is my brief review of various genetic factors and methods used to delineate the various periodontal diseases and genetic associations.Their affects on the disease phenotype, morphology and outcome.

Conclusion: Periodontitis is clearly multifactorial, and researchers need to design studies that examine the role of important environmental and genetic factors simultaneously. Given the large no. of genes in human genome and bacteria in the oral cavity, it is likely that genes and environment interact in important but as-yet un-recognized ways to alter disease risk. Most importantly, identifying specific genetic risk factors may be academically appealing but is of little use unless it leads to improvements in the prevention or treatment of disease.

1. Introduction

Periodontal diseases are a heterogeneous group of pathologies. It is believed that bacteria are required to develop periodontitis. While microbial and other environmental factors initiate and modulate periodontal disease, individuals respond differently to common environmental challenges, and this differential response is influenced by the individual's genetic profile. Genes clearly play a role in the predisposition to and progression of periodontal diseases. Susceptibility to periodontal disease and the severity of the disease results from the interactions of genetic mutations and polymorphisms with numerous environmental agents.

1.1. Definition and terminologies

1. *Genetics:* The branch of biology concerned with the study of heredity and variation in organisms.[1] The term first proposed by British biologist William Bateson in 1905. Human genome consist of more than 3 billion pairs of bases contained in 22 pairs of chromosomes termed Autosomes and two sex chromosomes.
2. *Genome:* The entire hereditary information of an organism
3. *Chromosome:* A nuclear structure that contains genetic information
4. *Gene:* The basic unit of heredity that occupies specific position on a chromosome and has specific effect on phenotype of the organism

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5. *Phenotype:* The observable characteristics displayed by an organism
6. *Genotype:* The genetic composition of an organism
7. *Exons:* protein coding region of DNA
8. *Introns:* A DNA region within a gene that is not translated into protein
9. *Loci:* Specific locations on chromosomes
10. *Alleles:* Variations in the nucleotide sequence at a locus .Diseases with etiologies that include both genetic and environmental factors are referred to as multifactorial.[2]

At a given locus, an individual is considered homozygous if the alleles are identical or heterozygous if alleles are different. Trait and disease might be caused by a single gene (monogenic), several genes (oligogenic), or many genes (polygenic). The term genetic marker refers to any gene or nucleotide sequence that can be mapped to a specific location or region on a chromosome.

Environmental factors generally play a minor role in determining the phenotype. In contrast, genes involved in complex multifactorial disease are called susceptibility genes. Penetrance refers to the probability that a particular phenotype will result from a genotype.

Functions of DNA include Protein synthesis,Transmission of genetic information in genes from one generation to other.

1.2. Genetic disease paradigms

1. Genetic variances
2. Genetic basis of disease
3. Simple Mendelian Diseases
4. Complex genetic diseases
5. Polymorphism vs mutation

1.3. Genetic variances

There are estimated to be 25,000–50,000[3] different genes in the human genome. Genes can exist in different forms or states (alleles). Allelic variants of a gene differ in their nucleotide sequences. When a specific allele occurs in at least 1% of the population, it is said to be a genetic polymorphism. When nucleotide changes are very rare and not present in many it is called mutation

1.4. Genetic basis of disease

Genetic variance and environmental exposures are the key determinants to phenotypic differences between individuals. However, for many diseases, human populations show differential disease susceptibilities, and the basis for this differential susceptibility may have a genetic or both a genetic and an environmental component. Geneticists have traditionally divided genetic diseases into two broad groups, "Simple" Mendelian diseases and "complex" diseases. Distinction is based on the pattern of transmission of disease which reflects the manner in which genes contribute to each disease.

1.5. Simple mendelian diseases

Diseases that follow predictable and generally simple patterns of transmission have been called "Mendelian" conditions. The name reflects the fact that these diseases occur in simple patterns in families, and in most cases a single gene locus is the major determinant of the clinical disease phenotype. These diseases follow a classic Mendelian mode of inheritance: Autosomal-dominant, Autosomal-recessive, or X-linked.

Complex genetic diseases-Genetically complex diseases are much more prevalent (>1% of population). Do not follow a simple pattern of familial distribution or transmission. Complex traits are result of interaction of alleles at multiple different loci. Presence of one disease causing allele is not sufficient to cause disease. Alleles reported[4] to be associated with a disease are also found in unaffected individuals and some individuals with disease who do not have the allele. Polymorphism vs mutation.

1.6. Methods of genetic analyses

1.6.1. Familial aggregation

Familial aggregation of a trait or disease can suggest genetic etiology. But, it may result from shared genes, environmental exposures, and similar socio-economic influences. To determine the evidence for genetic factors in familial aggregation of a trait, more formal genetic studies are required.

1.6.2. Twin studies

Estimates influence of genetic and environmental factors on complex diseases. Classic twin study reared together monozygotic and dizygotic twins were compared to estimate effects of shared genes. This include “Concordance” — similarities in disease experience and “Discordance” — differences in disease experience. Studying disease presentation in twins is useful for differentiating the variations due to environment from those due to genetic factors and for estimating the amount of heredity in a phenotype.

1.6.3. Segregation analyses

Genes are passed from parents to children in a predictable manner, and genes segregate in families. Pattern of transmission of disease through generation is studied in different families using segregation analyses. Segregation analyses evaluates the relative support for different transmission models to determine which can account for the observed segregation of a trait through families. Comparing models to each other segregation analyses identifies the

model that best account for observed transmission of a trait in given population. Geneticists generally apply segregation analyses to determine if trait transmission appears to fit a Mendelian or other mode of genetic transmission. Can assess whether the disease gene is autosomal or sex linked, recessive or dominant, complex or multilocus. But it Cannot distinguish between genetic & environmental influences and Does not provide information about specific genes

1.6.4. Linkage analysis

It is a technique used to localize the gene for a trait to a specific chromosomal location. These studies are based on the fact that genes are located close to each other on chromosome tend to be inherited together as a unit. These genes are tended to be linked. Difficulty with linkage analyses is that many diseases are not caused by a single gene of major effect , but multiple genes of minor effect. Effective in identifying genetic basis of simple Mendelian traits

1.6.5. Association studies

Genes[5] contributing to common, complex diseases such as periodontitis which has proved to be more difficult to isolate are studied by association studies. Several genetic loci interact with each other to produce an underlying susceptibility, which in turn interacts with additional environmental factors to produce an actual disease state. These studies are used as an alternative to linkage analysis for locating the disease susceptibility genes. Two types of association analysis are commonly used in genetic studies: Population-based and Family-based approaches. Population-based approach utilizes a standard case-control design, in which marker allele frequencies are compared between cases (affected individuals) and controls (either unaffected individuals or individuals randomly chosen from the population). Genetic and inherited disorders associated with aggressive periodontitis. The mutant allele affect the function of phagocytic immune cells or structure of epithelia, connective tissue or teeth themselves,

1.7. Hypophosphatasia

Characterized by mutations in tissue non-specific alkaline phosphatase gene. Mutations lead to deficiency in alkaline phosphatase activity leading to abnormal bone mineralization, skeletal abnormalities and cementum hypoplasia. Autosomal dominant and recessive forms reported ,The Infantile form — fatal, milder forms in children and adults leading to Premature loss of primary teeth and occasionally permanent teeth

1.8. Papillon lefevre syndrome

Autosomal recessive disorder characterized by palmoplantar hyperkeratosis and aggressive periodontitis, Primary and secondary dentition affected. Caused by mutation in cathepsin C gene. Cathepsin C is a cysteine protease expressed at high levels in epithelium and PMNS. It Play a role in degrading proteins and activating proenzymes in immune and inflammatory cells

1.9. Acatalasia

Is a condition affecting the production of catalase which is important in removing hydrogen peroxide generated during normal cell metabolism, hence results in tissue destruction due to superoxide radical generation. These patients are known to exhibit features of gingival necrosis and alveolar bone destruction.

1.10. Leukocyte defects

Polymorphonuclear[6] neutrophils form the first line of host defence. Defects in the quality and/or quantity of leukocytes could lead to increased susceptibility to infectious agents. Aggressive periodontitis is said to of common occurrence in neutropenia. Moreover, there are various forms of neutropenias which are familial in nature, and are transmitted via the autosomal dominant mode.

1.11. Chediack-higashi syndrome

Is a genetically transmitted disorder and is characteristically associated with aggressive periodontitis. Affects phagocytosis and chemotaxis which, if deficient, might predispose to severe periodontal destruction.

1.12. Leukocyte adhesion deficiency

Occurs in two forms, leukocyte adhesion deficiency syndrome type 1 and leukocyte adhesion deficiency syndrome type2 Autosomal recessive traits. Circulating leukocytes have reduced or defective surface receptors and do not adhere to vascular endothelial cells; thus they do not accumulate in sites of inflammation where they are needed. Generalized form of aggressive periodontitis seen.

1.13. Connective tissue disorders

Ehlers Danlos syndrome- types IV, VII and IX have all been associated with an early onset form of periodontitis. Other CT disorders include mucopolysaccharidoses, mannosidosis and familial fibromatoses and shown to be associated with gingival overgrowth.

1.14. Chromosomal disorders

The best recognized chromosome defect which has a periodontal component is trisomy 21 or Down's syndrome. Both early onset and adult periodontitis have been noted in these individuals.

Genetic study design for aggressive periodontitis includes Segregation analyses, Linkage studies, Association studies.

1.15. Segregation analyses for aggressive periodontitis

Aggressive periodontitis (AP) aggregates in families. Few segregation analysis conducted with AP — showed disparate results. But genetic basis not proven — family members can share same environmental factors. Marazita (1994)[7] considered localized and generalized forms of AP as variants of same disorder and both forms frequently seen in same family. He concluded that autosomal dominant mode was favored in African American and caucasian families. Saxen in 1984 — autosomal recessive mode of inheritance in finnish populations. Hodge in 2000 indicated either autosomal-dominant or x-linked-dominant inheritance in north European caucasian family. De carvalho in 2009 — genetic factors play a role in aggressive periodontitis and few loci, each with relatively small effects, contribute to aggressive periodontitis, with or without interaction with environmental factors. Errors due to Difficulty in correctly diagnosing older individuals, Variable clinical appearance of disease etiologic and genetic heterogeneity of these diseases.

1.16. Genetic etiologies of LAP and GAP

AP disease and IgG2 responsiveness to bacterial LPS (Schenkein 1994)

1. Subjects with 1 AP disease allele + 2 copies of IgG2 response allele — LAP
2. Subjects with 1 AP disease allele + 1 copy of IgG2 response allele — GAP (Their IgG2 response to LPS less robust)

Confounding effects of race and smoking on IgG2 levels and disease needs to considered with more rigorous testing.

1.17. Linkage studies

AP and chromosome 4-Boughman et al. (1986) were the first to report linkage between AP and specific chromosomal region. He studied an extended family in which AP was found to cosegregate with dentinogenesis imperfecta. Hart (1993) — AP does not typically co segregate with DGI

AP and HLA (Human Leucocyte Antigen)-Saxen and Koskimies (1984) finnish families –AP was linked to HLA region (chromosome 1- (1q25) region containing putative LAP locus spans over 25 million base pairs) Association studies with HLA polymorphism, IL polymorphism and others.

1.17.1. With HLA polymorphism

Few consistent[7,8] results of case control studies of HLA associated with AP. Reasons being due to False positive findings, Differences in racial or ethnic make up of study group, Differences in clinical criteria used to define patients group, True genetic heterogeneity. Kaslick, Terasaki in 1975- HLA A2 — less prevelant in AP — protective.

1.17.2. Class I HLA and AP

Two antigens consistently associated with AP are HLA — A9 and B15 Sofaer in 1990 — risk of AP in subjects with HLA — A9 and B15 is 1.5 – 3.5 times greater than those without these antigens. Thomas et al. — 2006 in case control study showed association of HLA — A9 and B15 alleles with AP in Indian population.

1.17.3. Class II HLA and AP

Rotter 1992- class II DR 4 antigen — associated with type I DM (insulin dependent)- increased risk for diabetes related complications including periodontitis. Katz et al. — DR4 antigen more prevalent in diabetic patients with AP than in controls. Dyer et al. suggested HLA D antigen may mediate association between Periodontal disease and type I DM.

1.17.4. With IL polymorphism

In humans, genes encoding IL 1 and its receptor antagonist are clustered on long arm of chromosome 2. Hart in 1997 — single nucleotide base pair substitution in IL 1β coding region (IL $1\beta^{+3954}$)has been associated with four fold increase in IL 1β production. Walker in 2000 found high risk IL 1β allele is common in African Americans and are at high risk for AP than Caucasians. Tachi in 2001 — Polymorphisms in vitamin D receptor may be associated with AP. Tai in 2002 — Polymorphisms in IL 1 receptor antagonist genes may be associated with AP. Gwinn in 1999- mutations in N-formyl-1-methionyl -1-leucyl-1-phenyl alanine(FMLP) receptor gene have been associated with AP. Hans in 2011 found gene polymorphism of Fc γ receptor (Neutrophil Ig G receptor) in south Indian population with GAP.

1.18. Genetic study design for chronic periodontitis

1.18.1. Twin studies

1940 Noack — periodontal conditions of identical twins were similar. Michalowicz in 1994 studied Minnesota group both reared together and reared apart and concluded — heritable component to chronic periodontitis (CP) exists. MZ reared apart and reared together had same severity of disease. Corey in 1993 in a questionnaire survey of thousand adult twin pairs — heritable component of periodontitis. Concordance rate for disease was greater in MZ twins than DZ twins. Draw back : assessment method is questionable (twins not aware of their periodontal condition). These findings suggest that host genes may influence initial bacterial colonization of oral cavity and not persist to adulthood.

1.18.2. Association studies

Role of HLA in determining risk for chronic periodontitis is poorly understood. HLA B5 antigen seen in adult resistant to disease. Kornman et al. in 1997 reported composite IL 1 genotype (IL 1α and IL 1β) associated with severe periodontitis. Gore et al. in 1998 found rare IL 1β allele prevalent in patients with advanced CP than composite genotype.

Galbraith et al. in 1998 found no association between CP and TNF α polymorphisms Saudi et al. in 2011- allele genotype and composite genotype effects of IL α^{+4845} and IL $1\beta^{+3954}$ polymorphism for CP in Indian population. Chilida et al in 2010 association between IL 6 polymorphism and periodontitis in Indian population. Problems associated with genetic studies.

Exposures such as smoking[9] or systemic disease modifiers have large influences on expression of phenotype thus interfere with results. There are methodological problems also associated with these studies, eg — deciding the study design. Bias against publishing negative results has impact on literature available on subject. Studies fail to report sensitivity and specificity of their tests to describe associates environmental aspects. Problems arise with the number of cases and controls may be insufficient, Racial and ethnic influence on genes, Not sure whether controls are truly susceptible. Allele may not be always be active and may need environment or other gene to be active

Human genome project. Scientific research project with the goal of determining the sequence of chemical base pairs which make up human DNA, and of identifying and mapping all of the genes of the human genome from both a physical and functional standpoint. Completed in 2003.

1.19. Genome wide analyses

Genome wide association study investigates genetic variation across entire genome simultaneously to identify genetic associations related to trait or disease of interest. Identify genetic contribution to common diseases. Require large number of clinical sample size.

1.20. Clinical implications of genetic studies

Genetic tests useful for identifying patients who[10] are likely to develop disease or suffer from recurrent disease. Genetic testing to determine risk for complex disease is common. Genetic risk if known can help clinician in environment based prevention and treatment to patient susceptible to periodontal disease. The outcome of treatment will become more predictable and maintenance schedule can be varied according to genetic risk factor of patient.

1.21. Periodontal susceptibility test

Genetic susceptibility test is the first and only genetic test that analyze two IL 1 genes for variations that identify an individual[11] predisposition for overexpression of inflammation and risk for periodontal disease. Samples are collected using a soft brush inside the cheek which is then sent to lab for testing. Sample assessed for IL 1 composite genotype , presence makes test positive. Future of genetic studies in periodontology. GWAS — large number of markers required. So search for risk allele must focus on candidate gene region — SNP. Si ngle Nucleotide Polymorphisms[12] (SNP) — single nucleotide base pair substitutions occur frequently through out genome. SNP useful as they represent variation in population.

2. Conclusion

Periodontitis is clearly multi factorial, and researchers need to design studies that examine the role of important environmental and genetic factors simultaneously. Given the large no. of genes in human[10] genome and bacteria in the oral cavity, it is likely that genes and environment interact in important but as-yet un-recognized ways to alter disease risk. Most importantly, identifying specific genetic risk factors may be academically appealing but is of little use unless it leads to improvements in the prevention or treatment of disease.

3. Source of Funding

None.

4. Conflict of Interest

None.

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