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Genetics in Periodontics

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Periodontal disease does not appear to be a single disease with variations in clinical symptoms but a group of diseases with overlapping symptomatology. The nature of periodontal diseases may be multifactorial. It will be quite important to consider known risk factors for periodontal disease when studying familial clustering or possible genetic mechanisms, because many risk factors for periodontal disease tend to cluster in families through genetic or culture mechanism. It will be important to identify candidate genes that may be the basis for genetic susceptibility to periodontal disease. Genes that may affect immune response to oral bacteria are the most obvious and learning more about traits that predispose to disease, such as tissue response characteristics, may provide additional clues about possible candidate genes. Identification of such genes could enable clinicians better to identify high-risk individuals for targeted prevention and treatment. In the majority of cases, the development of periodontitis in an individual depends probably on the collective presence of a number of environmental risk factors in conjunction with a number of susceptibility factors at a given time point during life. The more susceptibility factors an individual has inherited, the greater the genetic predisposition and the higher the chance for early development of periodontitis. With the increasing knowledge of major and modifying disease genes it is conceivable that a number of genetic tests will be developed. Database was collected using Medline, Cochrane Datbase of systemic reviews, DARE. Database was collected from last 25 yrs to latest keeping in mind all the changes and new evidences which have evolved during this time. Key concept was kept in mind and synonym terms were searched using MeSH headings by running a preliminary search and

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noting the terms used in the titles and abstracts as well as the subject headings to make the search more sensitive. Search was made more specific by following the inclusion and exclusion criteria for selecting articles like only those relevant articles were searched which offered knowledge and evidence relating to both periodontitis and genetics. Only articles discussing genetics in general were excluded.

Keywords: Gene; periodontitis; individual susceptibility; host response; risk factors; polymorphisms.

ABBREVIATIONS

MZ - Monozygous
DZ - Dizygous
IgG - Immnoglobulin G
JP - Juvenile Periodontitis
CTC C - Cathepsin C
MHC - Major Histocompatibility complex
IL- 1 - Interleukin -1
TNF - α - Tumour necrosis factor- alpha
GJP - Generalized Juvenile Periodontitis

1. INTRODUCTION

Periodontal diseases are multifactorial and in general no single etiologic agent that totally accounts for the pathologic alterations can be found. Initiation and progression of periodontal infections are clearly modified by local and systemic conditions called risk factors. Systemic factors recently have been identified by large epidemiologic studies using multifactorial statistical analyses to correct for confounding or associated risk factors.

Recent studies also point to several potentially important periodontal potential risk indicators. These include stress and coping behaviors and osteopenia associated with estrogen deficiency. There are also background determinants associated with periodontal disease including gender, age hereditary factors. Experience or exposures shared by family members also effect these risk factors for periodontal disease.

When considering genetic influences on periodontal disease or periodontal measures, it is important to consider genetic factors in a broad sense – to measure adequately and include risk factors that may have a genetic component or cluster in families for non-genetic reasons.

Johnson et al. [1] recognized that poor oral hygiene alone cannot account for severe destructive periodontal disease and, that certain individuals are at relatively high risk of periodontal destructions and the risk is partly under genetic control. Most studies of genetic risk factors for periodontal disease have focused on the early onset form of disease, which include prepubertal, Juvenile (localized and generalized) and rapidly progressing periodontitis.

In Klein [2] reviewed the periodontal status of several families and concluded that susceptibility and immunity to caries and periodontal disease are probably heritable. Whereas 'Gorlin' et al. [3] concluded in their study, that the genetic factors in periodontal disease are extremely complex and the isolation of these factors is extremely difficult.

By examining associations between periodontal disease and specific medical conditions or syndromes, and learning about the underlying causes of those associations, it is possible to discover specific, possible inherited, characteristic's that affect periodontal risk or severity. Studies of association between periodontal disease and known genetic market have provided limited support for a genetic contribution to disease susceptibility.

Periodontal pathology had been demonstrated in a number of inherited disorders. Risk factors for periodontitis are environmental, behavioral or biologic as confirmed by temporal sequence.

The recent publication of the architecture of the human genome and its implication for understanding both human biology and disease susceptibility raises the question of how such knowledge both currently influences and ultimately will change our approach to the management of disease [4].

Even before the publication of the sequence of human genome, methods for management of periodontal diseases that capitalize on the understanding of associations between genetic variants and clinical severity were proposed. In view of the fact that clinicians are already being encouraged to take advantage of new knowledge regarding the contribution of genetic susceptibility factors to periodontitis, it is appropriate to review the current status of the field and attempt to forecast the direction in which the application of future knowledge is likely to go.

Delgado and Calderon [5] have suggested that actalasia, the enzyme deficiency is associated with periodontal destruction. Whereas Eastman and Bixler [6] and Fung [7] have concluded that there may be almost a total lack of cementum and normally attached periodontal fibers leading to poor support and premature loss of tooth in hypophosphatasia. Peterson and Marsh [8] have stated that a relationship between alpha-1 antitrypsin deficiency and periodontal disease had been suggested for chronic periodontitis. Certain leukocyte defects appear to confirm particular susceptibility to periodontal disease. Genetic studies like Segregation analysis, Linkage studies, Genetic heterogeniety, Twin studies, and Association studies are based for analyzing the genetic risk factors for the periodontal disease.

The study of genetic risk factors in periodontology is in its infancy. An ultimate goal of genetic research is to identify and locate genes responsible for a particular disease. More precise definitions of disease phenotypes based on clinical, immunologic and bacteriologic criteria are needed. Thereafter, identification of specific host genetic risk factors could enable clinicians to institute more intensive preventive measures aimed at modifying the environments of those most at risk for periodontitis.

In this article an attempt is made to discuss genetic influences in periodontal disease.

2. REVIEW

2.1 Etiological Complexity of Periodontal Disease [4]

Few clinicians or investigators would dispute the assertion that bacteria are to be only associated with the various forms of periodontitis, but that they are primary etiological agents of these diseases. Overlying this fundamental etiological construct exist other etiological modifiers of risk for disease that interact with the bacterial infections that are not completely understood. Cigarette smoking, as an example, is now regarded to be a major modifier of risk for periodontitis. Other modifiers of risk for periodontitis, such as diabetes and stress are also thought to combine with the microbial agents to enhance disease.

The environmental etiological agents of periodontitis each define relatively complex pathways whereby they can initiate, propagate, or modify disease. For example, current dogma describes the ability of bacteria to induce gingival inflammation and periodontitis by producing toxins and inducing host immune reactions. Indeed, there is sufficient reason to believe that the severity of disease can be significantly modified by nonbacterial factors which might not, on their own, be etiological agents [4].

2.2 Individual Susceptibility to Periodontitis [4]

Despite the fact that environmental factors appear to provide sufficient disease-provoking factors, the fact remains that not everyone appears to be equally susceptible to periodontal disease. One might assume, for example, that people raised in the same house, with similar oral hygiene and smoking habits, and sharing similar bacterial loads and composition, should also share the same phenotype with regard to periodontal disease expression. We know that this is not the case. Rather there is individual susceptibility to periodontitis even when these known etiological factors are taken into account.

The hypothesis that genetic factors account for this observation has been formally tested by comparing disease characteristics in monozygous (identical, MZ) and dizygous (fraternal, DZ) twins.

Calculations from the measurement of large numbers of adult twins indicate that about 50% of the variance in attachment loss is due to the influence of heredity. This considerable contribution of genes to the expression of periodontal disease traits provides an additional layer of complexity to the etiology of periodontitis.

2.2.1 Genetic approaches in the study of periodontal diseases

The approaches used in the study of periodontal diseases are:

1. Family and population studies: segregation Analysis.
2. Molecular epidemiology.
3. Twin studies.
4. Linkage Studies.
5. Association of periodontitis susceptibility with inherited disorder.
6. Association studies.
   -Association with known genetic markers
   -Modifying genes – serum IgG.
7. Recombinant DNA technology

2.2.2 Recent study

In genetic epidemiology, a genome wide association study (GWA study, or GWAS), also known a whole genome association study (WGA study, or WGAS) or common-variant association study (CVAS), is an examination of many common genetic variants in different individuals to see if any variant is associated with a trait. GWASs typically focus on associations between single nucleotide pleomorphisms (SNPs) and traits like major diseases. These studies normally compare the DNA of two groups of participants: people with the disease (cases) and similar people without (controls). This approach is known as phenotype-first, in which the participants are classified first by their clinical manifestations.

2.3 Evidence for the Role of Genetics in Periodontitis

2.3.1 Heritability of aggressive periodontitis (Early onset periodontitis) [4]

As an epidemiological survey in the United States showed that the prevalence of Juvenile Periodontitis varies between 0.16 and 2.49% (Loe & Brown 1991), the high prevalence of JP in these families suggests a genetic background for the disease. The largest JP family study included 227 probands with aggressive periodontitis [9].

2.3.2 Heritability of Chronic Periodontitis (Adult Periodontities) [4]

Vander Velden et al. (1993) studied the effect of sibling relationship on the periodontal condition in a group of young Indonesians deprived of regular dental care. The study population included 23 family units consisting of three or more siblings. In all, 78 subjects aged 15-25 years were studied. The mean interproximal amount of loss of attachment in this population was 0.29 mm. The individual mean ranged from 0 to 1.27 mm. In 33% of the subjects, ≥ 1sites with a probing depth of 5 mm or more in conjunction with 2 mm loss of attachment were present. The results of the analysis showed a significant siblingship effect for plaque, calculus, loss of attachment, spirochetes on the tongue and in the pocket, P. *gingivalis* on the gingiva and in the saliva and P. *intermedia* in the saliva. However, the microbiological parameters which showed a significant siblingship effect were not significantly correlated with attachment loss. These findings suggest that also in less severe forms of periodontitis there may be a genetic background for the disease [10].

2.4 The Twin Model

Largest twin study included 4908 twin pairs of which, on the basis of questionnaire data, 349 (116 MZ and 233 DZ) pairs reported a history of periodontal disease in one or both pair members [11]. Michalowicz et al. [12] and co-workers evaluated the periodontal condition (attachment loss, pocket depth, gingival index and plaque index) of 110 adult twins with a mean age of 40 years ranging from 16 to 70 years. Therefore it can be concluded that the basis for familial aggregation of periodontitis appears not bacterial/ environmental/behavioral in nature; rather, genetics seem to form the basis for the familial aggregation of periodontitis.

3. A MAJOR DISEASE GENE ASSOCIATED WITH PERIODONTITIS [10]

To date, genetic studies in relation to periodontitis have revealed only one major disease gene that follows the principles of Mendel.

Through an internal marriage event in a family of Jordanian descent, Hart et al. (2000) and co-workers have identified and localized a gene on chromosome 11 that is responsible for a severe form of prepubertal periodontitis. Starting with four affected children from generation IV of two families, a disease causing R-allele of the cathepsin C (CTS C) gene was discovered.

Cathepsin C is a proteinase which is found in neutrophils and lymphocytes as well as epithelial cells. Affected children, but not their brothers and sisters, were homozygous for an A to G transition polymorphism at gene position + 1040. This resulted in a substitution of the amino acid tyrosine by a cysteine. This polymorphism was shown to be functional as there was a decreased cathepsin C activity. Interestingly, other mutations in the CTS C gene have been identified and have been linked to the Papillon-Lefevre syndrome, a disease which is also associated with a severe form of prepubertal periodontitis.

Table 1. Genes associated with periodontal health [4]

Polymorphism	Gene
HLA-A28 and HLA-B5	HLA haplotype
FcγRIIIb-NA1	Fc receptor polymorphism

4. MODIFYING DISEASE GENES IN RELATION TO PERIODONTITIS [10]

In addition, modifying disease genes contribute to susceptibility and severity of periodontitis.

Table 2. Genes associated with chronic (adult) periodontitis risk [4]

Polymorphism	Gene
IL-1A (+4845) and IL-1B (+3954)	IL-1 gene
TNF-α-308 allele 1	TNF-α gene
TNF-β NcoI, ET-1 gene, and ACE gene insertion/deletion polymorphism	Lymphotoxin alpha (TNF-β), ET-1 and ACE genes
FcγRIIIb-NA2 allotype	Fc receptor polymorphism
NAT2	N-acetyltransferase polymorphism

Table 3. Genes associated with aggressive (early onset) periodontitis risk [4]

Polymorphism	Gene	Disease association
IL-1A (=4845) and IL-1B (-3954)	IL-1 gene	Early onset periodontitis
IL-4 promoter and intron polymorphisms	IL-4 gene	Early onset periodontitis
FcγRIIIb-NA2 allele (and possibly FcγRIIIa-158F)	Fc receptor gene polymorphisms	Early onset periodontitis or generalized early onset periodontitis
Gc locus chrom 4q	Unknown	Early onset periodontitis or localized juvenile periodontitis
fMLP receptor	N-formyl peptide receptor polymorphisms	Early onset periodontitis or localized juvenile periodontitis
VDR gene	Vitamin D receptor polymorphism	Early onset periodontitis or localized juvenile periodontitis

Table 4.Genes associated with systemic conditions [4]

Genetic defect	Disease	Phenotype
Collagen folding defect	Ehlers-Danlos syndrome type 8	Early onset periodontitis or localized juvenile periodontitis
CTSC gene on chromosome 11q14-q21	Papillon-Lefevre syndrome, Haim-monk syndrome	Prepubertal periodontitis
Multiple possible mutations in alkaline phosphatase gene	Hypophosphatasia, alkaline phosphatase deficiency	Prepubertal periodontitis
LAD1 (integrin), LAD2 (selectin) gene defect	Leukocyte adhesion deficiency	Prepubertal periodontitis
OCRL1 gene, x-chromosome	Lowe syndrome	Prepubertal periodontitis (atypical finding)

4.1 Cytokine Gene Polymorphisms [10]

There are several arguments why the genes encoding for interleukin-1 (IL-1) and tumor necrosis factor-a (TNF-a) seem good candidates for genetic studies in relation to periodontitis [13]:

1. There is evidence to suggest that IL-1 and TNF-a play important roles in the pathogenesis of periodontitis. IL-1α and IL-1β and TNF-α are potent immunologic mediators with pro inflammatory properties. Moreover, IL-1 and TNF- α have the capacity to increase bone resorption and can regulate fibroblast cell proliferation, both from gingival and periodontal ligament origin.
2. Genetically determined, inter-individual differences have been observed for the IL-1 and TNF-α production by peripheral blood mononuclear cells or oral leukocytes, isolated from individuals with and without periodontitis. It is conceivable that these differences in IL-1 and TNF- α production and secretion play a role as susceptibility and/ or severity factors.
3. Some IL-1 and TNF- α alleles have been suggested as potential genetic markers for disease. For example, IL-1 polymorphisms have been associated with inflammatory bowel disease, Sjogren syndrome and psoriasis. TNF- α gene polymorphisms have been associated with (chronic) inflammatory and infectious disease processes, including leishmaniasis, alopecia areata, meningococcal disease, leprosy and cerebral malaria.

4.2 1L-1 Gene Polymorphisms [10]

The genes encoding IL-1 α and IL1-~ are located in close proximity in the IL-1 gene cluster on chromosome 2. The combined presence of the R-allele of the IL-1 α gene at nucleotide position -889 (IL-1a-889T) and the R-allele of IL-1 ~ gene at nucleotide position +3953 (IL-1 ~+3953'I) was associated with *severity* of periodontitis in non-smoking Caucasian patients.

Summary of studies investigating the IL-1 compostie genotype in relation to periodontitis.

It is important to note that the above studies were carried out in Caucasians. Therefore, the IL-1 composite geno type can be considered a putative severity factor for periodontitis in Caucasians.

4.3 TNF-A Gene Polymorphisms [10]

The TNF-a gene is located on chromosome 6 within the major histocompatibility complex (MHC) gene cluster. Several studies have investigated genetic polymorphisms in the TNF-a gene as putative susceptibility and severity factors in relation to periodontitis. The genetic polymorphisms are mainly G to A transitions. TNF-a gene polymorphisms in relation to aggressive periodontitis were also investigated, but the TNF¬a-308 R-allele was found not to be associated with aggressive periodontitis. Based on the literature to date on TNF-α genetics in relation to periodontitis, there is no indication that any of the reported gene variations are related to the susceptibility or severity of periodontitis.

Table 5. Cross sectional studies

Study	Patients (n)	Controls (n)	Putative susceptibility	Putative severity
Kornman et al. 1997	99		Not tested	+
Gore et al. 1998	32	32	-	Not tested
Walker et al. 2000	37	37	-	Not tested
Armitage et al. 2000	300		-	-
Mc Devitt et al. 2000	90		Not tested	+
Hodge et al. 2001	56	56	-	Not tested
Papanano et al. 2001	132	73	-	+
Laine et al. 2001	105	53		Not tested

Table 6. Longitudinal studies

Study	Patients (n)	Susceptibility	Severity
McGuire and Nunn 1999	42	Not tested	+
Ehmke et al. 1999	33	Not tested	-
De Santisand Zucchelli 2000	40	Not tested	+
Cattabriga et al. 2001	60	Not tested	-
Cullinan et al. 2001	295	Trend	+

4.4 IL-1O Gene Polymorphisms [10]

IL-lO is located on chromosome 1, in a cluster with closely related interleukin genes, including IL-19, IL-20 and IL-24. IL-lO plays a role in the regulation of pro-inflammatory cytokines such as IL-l and TNF-a. Functional disturbance in IL-IO due to genetic polymorphisms could be detrimental to host tissues and could be linked to periodontal disease susceptibility. IL-lO gene polymorphisms have been investigated in relation to aggressive periodontitis; 79 Caucasian patients from West Scotland with GJP were included and matched with a control population [14].

5. DISCUSSION

The nature of periodontal diseases may be multifactorial. Currently, based on a model of susceptibility to periodontal disease in which the genotype of the patient-centered. The disease (phenotype), however, is also dependent on the presence of microbiological risk factors, lifestyle factors, and the interaction between these factors and the genes. Even large number of candidate genes has been studied in relation to most parodontitis. The investigated candidate genes encode proteins that play a role in the innate system. However there seems that some variants of candidate genes (genetic polymorphisms) are in the *IL1* and -gencluster in the *Fc* γ *R* genes possible with periodontal disease [15]. It will be important to identify candidate genes that may be the basis for genetic susceptibility to periodontal disease.

With the increasing knowledge of major and modifying disease genes it is conceivable that a number of genetic tests will be developed. These tests could be used to diagnose the degree of genetic predisposition at an early age when periodontitis has not yet developed, e.g. children of parents suffering from periodontitis. The results of recent studies including genome-wide association study of CP that was carried out in a cohort of 4504 European Americans (EA) participating in the Atherosclerosis Risk in Communities (ARIC) Study showed no genome-wide significant association signals for CP; however, suggestive evidence of association (P < 5 3 1026) for six loci, including NIN, NPY, WNT5A for severe CP and NCR2, EMR1, 10p15 for moderate CP. Analysis indicated significant enrichment of nervous system signaling, cellular immune response and cytokine signaling pathways. A significant interaction of NUAK1 (rs11112872, interaction P 5 2.9 3 1029) with smoking in ARIC was not replicated in Health ABC, although estimates of heritable variance in severe CP explained by all single nucleotide polymorphisms increased from 18 to 52% with the inclusion of a genome-wide interaction term with smoking. These genome-wide association results provide information on multiple candidate regions and pathways for interrogation in future genetic studies of CP [16].

NOD proteins are part of innate immunity mechanisms. They play a role in epithelial barrier functions and inflammatory responses to bacteria. Various studies have been conducted investigating relationship between Single nucleotide polymorphisms (SNPs) in the NOD1 gene and aggressive periodontitis but no significant relationship has been found between them [17]. In periodontitis, increased platelet response to oral bacteria is paralleled by increased formation of platelet-leukocyte complexes with elevated capacity for bacterial clearance. Certain studies have shown that activated platelets and leukocytes might contribute to increased atherothrombotic activity. [18,19]. There is growing evidence that polymorphisms in the IL1, IL6, IL10, vitamin D receptor, and CD14 genes may be associated with CP in certain populations. [20] Certain studies investigating the influence of genetic polymorphisms and bacteria on chronic periodontitis. Thus, modern bioinformatics tools are valuable in modelling the multifactorial and complex nature of periodontitis [21].

6. CONCLUSION

Genetic studies in period ontology are complicated by the difficulty of defining specific disease categories. Nonetheless, advances in molecular genetics. Such as the identification of highly polymeric markers and polymerares chain reaction technology have improved the capability for conducting more complete linkage analysis.

Finally, at last until additional new knowledge emerges, one must accept the likehood that no specific periodontal disease susceptibility resides in the genetic control of one or more aspects of the host response.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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