Review Article

Genetic Aspects of Chronic and Aggressive Periodontitis

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ABSTRACT

Evidence suggests that there is some genetic basis for the periodontal diseases. The molecular abnormality and its genetic inheritance has been established in some cases of generalized aggressive periodontitis. Family studies indicates that this disorder is transmitted by autosomal recessive genes. Recent evidence also suggests that susceptibility to periodontal disease may be related in part to genetically determined immune responsiveness to bacteria. Although specific genetic risk factors have not been identified for the chronic periodontitis, recent studies indicate that there is significant genetic variance in the population. More precise definitions of disease phenotypes will facilitate future genetic epidemiologic studies of the periodontal diseases.

Key words: Gene, Aggressive Periodontitis, Chronic Periodontitis, Polymorphism

INTRODUCTION

Periodontitis is a complex multifactorial disease. Complex human diseases are typical that they mostly have a relatively mild phenotype and are slowly progressing and chronic in nature. The phenotype of the complex diseases is determined by both genetic and the environmental factors that affect the individual. Although pathogenic bacteria and various other environmental factors (e.g., smoking and stress)[(1)] are involved in pathogenesis of periodontitis, genetic factors are proved to be evident in the aetiology of periodontitis. Understanding of the interplay between the host and oral bacteria is a must to the understanding of the pathogenesis of periodontal disease.

The first evidence that genetics plays a role in periodontal disease emerged in the 90's. This new information introduced new concepts such as susceptibility and predisposition to periodontal disease[(2,3)]. A key determinant of whether individuals develop periodontitis appears to be governed by the way they respond to their microflora[(4)]. Therefore, genetic factors modulate how individuals interact with many environmental agents, including biofilm, to determine susceptibility to periodontitis. It's the interplay between genetic and environmental factors, and not the genes alone, which determines the outcome, ie) the periodontal disease. The differential response is influenced by the individual's genetic profile

There are significant clinical and scientific evidences that genetic factors are important determinants of periodontitis susceptibility and progression [(5)]. Support for this statement comes from studies of humans and animals which indicate that genetic factors influence inflammatory and immune responses in general as well as in periodontitis.

Disease modifying genes are responsible for susceptibility to periodontitis. Mendelian principles do not apply to these disease modifying genes, because both heterozygous and homozygous subjects for a given genetic variation in a gene or locus may not necessarily develop the disease. In such a complex and multifactorial disease as periodontitis, other genetic risk factors and behavioural factors must also exist simultaneously to be determinants of an individual's propensity to developing periodontitis[(6)]. Thus, it is possible that periodontitis could be polygenic (gene–gene interactions) and multifactorial (gene–environment–life style interactions such as oral hygiene, smoking, stress and diet)[(7,8)]. This review article focuses on the most studied genetic influences on Chronic and Aggressive Periodontitis.

Polymorphism in Relation to Periodontal Diseases

1. Cytokine gene polymorphisms

IL-1 gene polymorphism

TNF-α gene polymorphism

IL-10 gene polymorphism

2. Receptor and other gene polymorphisms

FCgR gene polymorphisms

FcgRIIa-131 H/R polymorphism

FcgRIIIa-158 F/V polymorphism

FcgRIIIb polymorphism

Cytokine and chemokine receptor gene polymorphisms

Immune receptor gene polymorphism

3. Metabolism - related gene polymorphism

Vitamin D receptor gene polymorphism

Calcitonin receptor gene polymorphism

4. Antigen - recognition related gene polymorphism

HLA gene polymorphism

5. Polymorphisms in the innate immunity receptors

TLR2 and *TLR4* gene polymorphisms

CD 14 gene polymorphism

CARD 15 gene polymorphism

6. Miscellaneous gene polymorphisms

Cytokine Gene Polymorphism

a. *IL-1* gene polymorphism

Kornman et al 1997[9], in Caucasian population reported that *IL-1* composite genotype could be considered a putative severity factor for periodontitis and the "Genotype positive" model was depicted. Diehl et al, 1999[10] showed the *IL-1* gene as a putative susceptibility factor for chronic periodontitis and aggressive periodontitis. Ethnicity also has a role to play in *IL-1* gene polymorphism[11]. Poulsen et al[12] demonstrated that in localized aggressive periodontitis patients, allele 2 of *IL - 1 RN VNTR* was associated. But also, no clear evidence has emerged, and there are currently too many conflicting and negative results. Large cohort studies of homogeneous composition should be initiated in which all of the currently accepted non-genetic (putative) risk factors are included. Multivariate analysis should be employed to estimate relative contributions of all factors[13]. In summary for the global population, polymorphisms in the *IL-1* gene cluster cannot be regarded as (putative) risk factors for Periodontitis or severity of periodontal destruction.

b. *TNF-α* gene polymorphism:

From the studies by Craandijk, 2002 [14] Shapira, 2001 [15] Schulz Machulla 2008 [16], there is no indication that any of the related gene variations are related to susceptibility/ severity of periodontitis. In 2008, Stefan Reichert et al [17] found that *IL - 12 RB2* were significantly higher in aggressive periodontitis patients as compared with healthy controls or chronic periodontitis patients. Investigations into severity of Periodontitis in relation to any of the *TNF- α* gene R -alleles also did not reveal a positive association. Lack of association of *TNF- α* genetic polymorphisms with Periodontitis severity was also reported by others[18]. To summarize, based on the available literature to date, there is only limited data to support associations between any of the reported *TNF- α* gene variations and Periodontitis.

c. *IL-10* gene polymorphism:

IL-10 can stimulate the generation of auto-antibodies[19] which play a role in Periodontitis[20,21]. Functional disturbance in the *IL-10* gene due to genetic polymorphisms could be detrimental to host tissues and could be linked to Periodontal disease susceptibility, with altered *IL-10* production. The *IL-10-1087* polymorphism (N-allele) is more abundant in Periodontitis as particular in non-smokers[22,23]. These observations have led the authors to speculate that the N-allele prevalence in Periodontitis patients may result in higher levels of auto-antibodies, which may lead to increased periodontal destruction.

In summary, a limited number of studies have investigated genetic variations at three positions in the *IL-10* promoter region. For all three positions some significant differences in the allele carriage rates between patients and controls have been reported. Further studies on *IL-10* as candidate gene seems to be justified.

Receptor and Other Gene Polymorphisms

a. *FCgR* gene polymorphism:

FcγR are found on a wide variety of immune cells in the Periodontal tissues[24]. *In* the pathogenesis of Periodontitis, it acts as a bridge between the cellular and humoral branches of the immune system. Microorganisms and bacterial antigens, opsonized with antibody, can be phagocytosed via *FcγR* on neutrophils or internalized via *FcγR* by a variety of antigen presenting cells (APC),

including monocytes, macrophages and B cells. T cells, and natural killer *(NK)* cells may become activated, when *IgG*-opsonized bacteria are bound to these cells via *FcγR*, a variety of cytokines and chemokines may also be released [25]. The leukocyte *FcγR* genes are found on chromosome 1 and encode three main receptor classes: *FcyR1 (CD64), FcγRII (CD32)* and *FcγRIII (CD16)*. These classes are further subdivided into subclasses: *FcγRI a and b, FcγRII a, b and c, and FcγRIII a and b.* To summarize, Polymorphisms in the genes encoding the low affinity receptors may result in variations in antibody binding and phagocytosis and hence susceptibility to periodontitis is documented.

***FcRIIa-131 H/R* polymorphism:**

FcγRIIa-H131 binds *IgG2* immune complexes efficiently, whereas the *FcγRIIa-R131* allotype, cannot mediate, this interaction[26]. The G to T transition polymorphism in the *FcγRIIIa* gene, results in an amino acid 158-valine (V) (N-allele) substitution for 158-phenylalanine (F) (R-allele). Patients with *FcgRIIa-R/R* genotype could be more susceptible for periodontitis due to decreased capacity to phagocyte *IgG2* opsonized Actinobacillus actinomycetemcomitans[27]. But this hypothesis got rejected since Loos et al [28] found that *FcgRIIa-H/H* genotype is higher in aggressive periodontitis subjects than in controls. A recent study by Nicu et al also proved that H/H genotype is associated with more periodontal destruction than H/R or R/R genotype.

***FcgRIIIa-158 F/V* polymorphism:**

The V/V variant is capable of efficient binding of IgG 1, 3, 4 relative to F/F variant in both monocytes and natural killer cells. This substitution was also associated with recurrence of adult periodontitis compared to individuals without recurrence[29]. The *FcγRIIIa-V158* has a higher affinity for *IgGl* and 3 than *FeγRIIIa-F158.* Moreover, *FcγRIIIa-V158* can bind IgG4, while *FcγRIIIa-F158* is unable to do so. A bi-allelic polymorphism in the *FcγIIIb* gene underlies the *FcγRIIIb* neutrophil antigen (NA) 1 or NA2 allotype (the N- or R-allele respectively). This is caused by 4 amino acid substitutions in the Fc-binding region resulting in differences in glycosylation. The NA2 type binds less efficiently human *IgGl* and *IgG3* immune complexes than *FcγRIIIbNA1*[30].

***FcgRIIIb* polymorphism:**

In neutrophils, *FcgRIIIb* exists in two allelic forms, *NA1* and *NA2* as a result of nucleotide substitutions resulting in changes in four aminoacids. *FcgRIIIb-NA1* displays more efficient interaction with *IgG1* and *IgG3* opsonized bacteria compared with *FcgRIIIb-NA2* and was found to be associated with increased resistance to periodontitis in an elderly Japanese population[31]. To summarize, the possibility that genes encoding for *FcgR* are associated with susceptibility and severity of several forms of periodontitis in different ethnic groups seems promising.. However, to date no clear and convincing data are present to definitively assign one or more of the *FcγR* gene polymorphisms as true risk factors for Periodontitis. Further research is recommended in larger group of subjects from different populations[32].

b. Cytokine and Chemokine receptor gene polymorphisms:

Receptors are important constituents of the whole cytokine system. Through these membrane bound or circulating proteins, cell responses to various cytokines are elicited or blocked. The soluble form of *TNF -receptor 2*, which is shed from the cell surface significantly reduced the loss of connective tissue and alveolar bone in experimental periodontitis[33].

c. Immune receptor gene polymorphism:

FMLP receptor polymorphism depressed chemotactic response to *n-formyl-1-methionyl-1-leucyl-1-phenylalanine* peptides has been confirmed in studies done by Van Dyke et al and Serhan CN et al [34].

Metabolism Related Gene Polymorphism

a. *Vitamin D receptor* gene polymorphism:

The 3' portions of the *VDR* gene includes a cluster of linked polymorphisms[35]. The first two sites are in the region of the gene from intron 8 to the 3' untranslated region. A silent mutation within codon 352 of the ninth exon alters the site. *VDR* gene polymorphisms are normally determined by polymerase chain reaction (PCR) and restriction enzyme digestion. The *VDR* gene polymorphisms are commonly present. If these polymorphisms influence the level or function of the *VDR*, they may be pathogenic[36].

Li et al [37] found in his study that *FOKI* polymorphism of vitamin D receptor gene might be associated with generalized aggressive periodontitis in Chinese patients. The carriage of F allele increases the risk of developing generalized aggressive peridontitis. Nibali et al[38] found that *Vitamin D* receptor *Taq - 1 TT* polymorphism was

moderately associated with both the presence and the progression of periodontitis in smokers, while no association was detected in non-smoking individuals.

To summarize, the *VDR* gene affects both bone metabolism and immune functions. Moreover some encouraging results have been found for different ethnic populations.

b. Calcitonin receptor polymorphism:

Nosaka et al[39] have found that patients with this polymorphism were 20 times more likely to suffer buccal marginal bone loss than patients who were calcitonin receptor genotype negative.

ANTIGEN RECOGNITION RELATED GENE POLYMORPHISM

Human leukocyte antigen (HLA) is involved in genetically predetermined humoral response via recognition of foreign antigens. The various alleles associated with disease in Periodontics are: *HLA-DRB1.1501-DQB1.0602* genotype, *HLA-DR4* and its subtypes[40,41]

Polymorphisms in Innate Immunity Receptors

The innate immune response is the first line of defense in infectious diseases. The host is challenged, to detect the pathogen and to mount a rapid defensive response.

a. *TLR2 and TLR4* gene polymorphisms:

The *TLR2 Arg677Trp* and *Arg753Gln* gene polymorphisms have been reported to abrogate the ability of *TLR2* to mediate a Response to bacterial cell wall components[42]. Two common co-segregating polymorphisms of *TLR4, Asp299Gly* and *Thr399Ile*, affect the extracellular domain of the *TLR4* protein leading to an attenuated efficacy of LPS signaling and a reduced, capacity to elicit inflammation[43]. The *TLR4 Asp299Gly* gene polymorphism has been correlated with hypo-responsiveness to inhaled. LPS, sepsis and infections caused by Gram-negative bacteria[44]. One study has attempted to associate these above named *TLR* polymorphisms with Periodontitis[45]. However, despite the perceived importance of these functional. *TLR* polymorphisms, no relation with Periodontitis has been observed[46].

b. *CD 14* gene polymorphism:

The R-allele in the promoter region of *CD14* at position -260 (-159) enhances the transcriptional activity of the gene. Individuals homozygous for the R-allele have increased serum levels of soluble (s) *CD14* and an increased density of *CD14* in monocytes. The *CD 14-260 SNP* has previously been associated of increased risk with myocardial infarction and Crohn's disease.[47] Furthermore, increased serum levels of *CD14* have been associated with Periodontitis. There are contradictory findings from the studies of Holla et al [49] and Yamazaki et al[48] which did not find any association between *CD14* genome polymorphism and chronic periodontitis.

A higher frequency of the N-allele and the *N/N* genotype of the *CD14-1359* polymorphism was found in patients with severe Periodontal disease than in patients with moderate Periodontitis. The importance of this finding requires further study.

c. *CARD 15* gene polymorphism:

The *3020 insC* and *2104 C>T* polymorphisms of the. *CARD 15 (NOD2)* gene leads to impaired activation of nuclear factor-κ B, resulting in altered transcription of pro-inflammatory cytokine genes and reduced expression of these cytokines. These polymorphisms are strongly associated with Crohn's disease. However, to date, these *CARD 15* polymorphisms have not been associated with Periodontitis [50]. No role for the *CARD15 3020insC and 2104 C>T* polymorphism was found for Periodontitis in Caucasians.

Although genes of the innate immunity processes seem good candidates for their association with Periodontitis, investigations have not yielded any strong indications that they might be associated with this condition.

Miscellaneous Gene Polymorphisms

a. *Cathepsin C* gene polymorphism:

Cathepsin C is a proteinase and is expressed in the hyperkeratotic epithelial lesions such as palms, knees and oral keratinized gingiva. Hart et al. identified a gene on chromosome 11 containing the *cathepsin C* gene, responsible for prepubertal periodontitis as well as Papillon - Lefevre syndrome (PLS). All patients with pre-pubertal periodontitis were found to be homozygous for an A-G mutation at gene position *+1040*, resulting in a substitution of the amino acid tyrosine by a cysteine. This gene polymorphism was shown to be functional as there was a diminished activity of *cathepsin C* in PLS. Another study by Noack et al[51] reported two novel gene mutations at positions 947 and 1268, which were associated with these two diseases.

b. MMP gene polymorphism:

Ustun K Alptekin et al[52] examined the association between *MMP-1-1607 1G/2G* polymorphism and chronic periodontitis susceptibility in a Turkish population. The results concluded that there was no significant association between this polymorphism and susceptibility to periodontitis.

c. Polymorphism in smokers:

Cytochrome P450 (CYP) enzymes, CYP1a1 and CYP2E1, are important in the activation of xenobiotics, especially tobacco-derived substances such as polycyclic aromatic hydrocarbon[111] and nitrosamines. Glutathione S-transferase (GST) MI and N-acetyltransferase (NAT1 and NAT2) are involved in detoxification of these associated metabolites. Polymorphism of *CYP1A1* and *CYP2E1* are associated with enhanced catalytic activities of these enzymes. In addition, the null *GSTM1* genotype and mutation in NAT gene result in the inability to efficiently detoxify xenobiotics[53].

It's evident that the slow acetylator genotype of *NAT2* is associated with a higher risk of periodontitis, particularly in smokers[54]. Therefore, polymorphism of other xenobiotics metabolizing enzymes, CYPs and GSTs may also contribute to individual susceptibility to develop periodontitis.

Kocher et al[55] and Meisel et al[56] conducted studies in Caucasian population which demonstrated that the N-acetyl transferase slow phenotype was significantly associated with severity of bone loss. Meisel et al[57] noted that the possible protective effects seen in non-smokers might be due to an allele of *myeloperoxidase* (MPO), which is not obvious in smokers.

d. Other polymorphisms:

Other polymorphisms include *ACE* (Angiotensin converting enzyme), *ER2* (Endothelein receptor 2), *IL* (Interleukin) 2, *IL4, IL6, IFN-GR* (Interferon gamma receptor) 1, *MMP* (Matrix mettaloproteinase)-1, *MMP3, MMP9, MPO* (Myeloperoxidase), *RAGE* (Receptor for advanced glycation end products), *TGF* (Transforming growth factor) *b, TIMP* (Tissue inhibitor of metalloproteinase) 2, *Plasminogen activation, Mannose binding lectin*, Osteoprotegrin and *TNFR* (Tumor necrosis factor receptor) 2 gene polymorphisms. Association between these polymorphisms and periodontal disease is yet to be proved[58].

Summary

THE ROLE OF GENETICS IN CHRONIC PERIODONTITIS: Evidence for the role of genetic component in chronic (adult) periodontitis has been conducted from twin and family studies. The twin model is probably the most powerful method to study genetic aspects of any disease, including periodontal disease. Michalowicz et al [59] evaluated the periodontal conditions (attachment loss, pocket depth, gingival index, and plaque index) of 110 adult twins indicated that between 38% and 82% of the population variance for these measures may be attributed to genetic factors. In a study on 117 adult twin pairs the analysis included the evaluation of the environmental factors like smoking and utilization of dental services. The results showed that chronic (adult) periodontitis was estimated to have approximately 50% heritability, which was unaltered following adjustments for behavioral variables including smoking.

Velden et al [60] studied with a family study design the effect of sibling relationship on the periodontal condition in a group of young Indonesians deprived from regular dental care. The results of the analysis suggest that also in less severe forms of periodontitis there may be a genetic background for the disease. Also epidemiological studies in a Dutch population have suggested that chronic (adult) periodontitis aggregates in families. From both the twin and family studies 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.

Genetic Associations In Aggressive Periodontitis

The genetic association study approach is useful for identifying genetic variants that affect susceptibility to common complex diseases[61]. A leading hypothesis of increased susceptibility to aggressive periodontitis entails deficient host response to periodontal infection, particularly infections with virulent periodontal pathogens. It is now established that genetic factors regulate the innate immune system and that certain genetic polymorphisms may render the immune system defective and unable to successfully fend off assaults by infecting microorganisms. Genetic factors may play a more significant role in the pathogenesis of aggressive periodontitis than in chronic periodontitis, and this may be attributed, to a certain extent, to the significance of the innate immune system in the pathogenesis of this disease. Although local etiological factors are less prevalent in aggressive periodontitis than in chronic periodontitis,

alveolar bone loss and tooth loss are significantly more pronounced in aggressive periodontitis. Periodontal tissue destruction in aggressive periodontitis commences at an early age, shows a rapid rate of progression and has a unique pattern where it affects multiple teeth and occurs bilaterally. In addition, differences in the microbiologic flora or in other environmental factors do not fully explain the variance in the severity and age of onset between these two diseases. In the quest to identify genetic risk markers of aggressive periodontitis, association studies have focused on genetic factors that regulate the immune response[62].

Conclusion

Research on genetic polymorphisms in the recent years has had limited success in unravelling significant and reproducible genetic factors for susceptibility to CP. Taken together the data published so far on gene polymorphisms, some evidence is emerging that polymorphisms in the *IL1, IL6, IL10, VDR, and CD14* genes may be associated with Chronic and Aggressive Periodontitis susceptibility in certain populations. Future studies should apply more strict disease classification, larger study cohorts, adjust for relevant risk factors, and include analysis of multiple genes and polymorphisms. Novel statistical methods may allow a better assessment of multiple genes and polymorphisms within the same pathway and interactions with environmental factors. The possibility to include data from multiple genes and polymorphisms or haplotypes and environmental data, and to model their interactions, will give us a better assessment and pathophysiology.

Identifying genes can result in novel diagnostics for risk, early detection and individualized treatment approaches[63]. Identifying genes that contribute to the pathogenesis of periodontitis can have significant public health, therapeutic and scientific repercussions. Environmental factors involved in the causation of periodontal diseases can be modified or eliminated.

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