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REVIEW ARTICLE

Genetics and Aggressive Periodontal Disease: An Update Review

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ABSTRACT

Periodontitis is an inflammatory condition of supporting tissues of teeth, for which several risk and susceptibility factors are proposed. Periodontal disease results when balance between host factors and etiologic agents is disrupted. Bacteria have a primary role in the initiation of periodontal disease, and a range of host related factors influence the clinical presentation and rate of progression of disease. Genetic variations that modify immunological reactions identify the disease susceptibility in various individuals. Many studies have proved the effect of various single or composite nucleotide polymorphisms to susceptibility, progression or severity of periodontal diseases. Despite these studies, association between periodontal disease and candidate genes is still not clear. The reports of familial nature of chronic periodontitis are less frequent as compared to aggressive periodontitis. The striking familial aggregation of trait in aggressive periodontitis is consistent with significant genetic etiology. In this paper, an attempt has been made to summarize recent views on various genes involved in the pathogenesis and progression of aggressive periodontal disease. Data were identified by searches of the Medline, and Pubmed. Articles published in English were selected, and most up-to-date or relevant references were chosen.

Keywords: Aggressive periodontal disease, candidate gene, familial aggregation, genetic, periodontitis, polymorphism.

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INTRODUCTION

Periodontitis is a multifactorial disease for which several risk and susceptibility factors are proposed. Bacteria have a primary role in the initiation of periodontal disease, and a range of host related factors influence the clinical presentation and rate of progression of disease(1).

Most genetic, environmental factors and immune functions are characterized by complex interactions that involve the interaction of the amount of gene products. Host susceptibility may be defined in terms of genetic variation; hence a relatively recent focus on periodontology has been to quantify genetic risks and identify specific gene variants that determine disease susceptibility(2).The practical ability to apply genetic information to disease paradigm is transforming our approach to diagnosis and treatment of periodontal diseases. The genetic basis of periodontitis has also been elucidated. Reports of genetic polymorphisms associated with periodontal disease are increasing in recent years.There are reports in the literature on familial aggregation of periodontal diseases, but it is difficult to compare them. Although periodontal disease terminology has changed many times over the years, most familial reports of early onset forms of periodontitis are now referred to as Aggressive Periodontitis(3). Reports of familial nature of chronic form of periodontitis are less frequent but the aggregation within families is consistent with a genetic predisposition.

The striking familial aggregation of trait in Aggressive Periodontitis is consistent with a significant genetic etiology. A gene of major effect in Aggressive Periodontitis appears to be etiologically complex and heterogenous. Characterization of a specific genetic component in the etiology of Aggressive Periodontitis requires mere formal genetic analysis. Hence the aim of this paper is to discuss the important genetic variants which contribute to etiology/pro-

gression of Aggressive Periodontal disease.

AGGRESSIVE PERIODONTAL DISEASE

Aggressive Periodontitis (AP) is a group of periodontal diseases characterized by localized or generalized loss of alveolar bone usually affecting individuals under 30 years of age(4).

Several genes have been found to be associated with Aggressive Periodontitis. The familial nature of Aggressive Periodontitis has led to speculation that a major gene defect is responsible for its transmission but such a gene that is generalized to the population has not been found yet. However like Chronic Periodontitis, several genetic polymorphisms are associated with disease risk(5) (Table 1).

In 1986, Boughman *et al* reported that a major gene located on chromosome 4q was responsible for autosomal dominant transmission of Localised Aggressive Periodontitis in an extended family that also exhibited Dentinogenesis Imperfecta(6).

SEGREGATION ANALYSIS

Aggressive Periodontitis aggregates in families. Several research groups have used segregation analyses to determine the likely mode of inheritance for aggressive periodontal disease(2).Segregation analysis evaluates the relative support for different transmission models to determine which model can account for observed segregation of a trait through families. By sequentially comparing models to each other, segregation analysis identifies the model that best accounts for the observed transmission of a trait in a given population. Geneticists generally apply segregation analysis to determine whether a disease transmission appears to fit a Mendelian or other mode of genetic transmission. Segregation analyses have low power to resolve heterogeneity. It cannot differentiate between genetic effects and unmeasured environmental cause of the disease, such as transmission of pathogenic organism within families(3). This analysis support the hypothesis that genetic factors play a role in Aggressive Periodontitis and a few loci, each with relatively small effects contribute to Aggressive Periodontitis, with or without interaction with environmental factor(7). Various forms of AP have been observed in same family and found to occur sequentially in the same individual(8).

Melnick *et al* (1976) proposed X-linked inheritance because of the preponderance of female probands but the fact that women are more likely to seek dental care than men can be the reason for this bias(9).The autosomal dominant mode was favored in African American and Caucasian families in contrast of Finnish population where an autosomal recessive mode of inheritance was favored(10).

Schenkein (1994) proposed a model of inheritance that distinguishes between etiologies of localized and generalized Aggressive Periodontitis and allows for family clustering. He theorized that Aggressive Periodontal disease and IgG2 responsiveness to bacterial lipopolysaccharide (LPS) segregate independently as dominant and codominant trait. Subjects with 2 copies of high IgG2 response allele with one Aggressive Periodontal disease allele would develop less widespread disease than in subjects with only one copy of IgG2 allele(11).

LINKAGE STUDIES

Linkage analysis is a technique used to localize the gene for a trait to a specific chromosomal location. Genetic linkage studies are based on the fact that the alleles at syntenic gene loci in close proximity on the same chromosome tend to be passed together from generation to generation (i.e. segregate) as a unit. Such genes are said to be "linked", and violate Mendel's law of independent assortment. Linkage is often used as a first step to determine the approximate location of gene of interest, permitting subsequent studies to identify the mutation responsible for a disease trait. Linkage studies have been particularly effective in identifying the genetic basis of simple Mendelian trait. A limiting factor in the traditional application of linkage to complex diseases is that complex diseases are due to combined effect of 'multiple gene of minor effect'(2).

Boughman *et al* (1986) first reported linkage between Aggressive Periodontitis and a specific chromosomal region (4q11-13) near the gene for Dentinogenesis Imperfecta(6).

Scott *et al* (1999) reported in linkage analysis that IL-1 genetic variation contributes an important influence on disease risk(12). Liy *et al* (2005) reported linkage of Localised Aggressive Periodontitis to a marker on chromosome 1(1q25)(13).

ASSOCIATION STUDIES

Allelic association refers to a situation in which frequency of an allele is significantly increased or decreased in a particular disease. Association studies compare a population of affected individuals with control population. They can be performed as case control studies that include unrelated affected individuals and matched controls, or as family based studies that compare frequencies of allele transmitted or not transmitted to the affected children(2).

Study design is a critical factor in association studies. Linkage analysis requires consistent segregation across generations in families, which is not always apparent and it also requires large sample size than association studies(14). In contrast, association studies, if large enough can be sensitive

Table 1: Genes associated with Aggressive Periodontitis risk

Polymorphism	Gene
● IL-1A(+4845)IL-1B(+3954)	IL-1 gene
● IL-4 promoter and introns polymorphism	Il-4 gene
● FcãRIIIb-NA2 allele FcãRIIIa-158F	Fc receptor gene polymorphism
● Gc locus chromosome 4q	Unknown
● FMLP receptor	N-FMLP polymorphism
● VDR polymorphism	Vit-D receptor polymorphism

Table 2: Relation between genetic polymorphism and aggressive periodontal disease

Candidate gene	Population	Findings	
HLA-DR4	10 RPP patients,	High frequency reported in rapidly progressive periodontitis patients(17).	Katz et al (1987)
HLA-A9, B-15	26(11 localized and 15 generalized EOP)	Found to be significantly elevated(18).	Shapira et al (1994)
HLA-DQB1	24 Japanese patients	Plays a crucial role in pathogenesis of AP(19).	Ohyama et al (1996)
HLA-A2 and B-5	Meta analysis of 12 case control studies on Caucasians	Potential protective factors against periodontitis(20).	Stein et al (2008)
IL-1á, IL-1â	135 Caucasian subjects	A strong association between IL-1á gene at position -889 and AP(21).	Kornman et al (1997)
	36 patients in Chilean population	Positive association was found between Aggressive Periodontitis and presence of IL-1â+3954 allele 2 polymorphism(4).	Quappe et al (2004)
	10 year study on 20 EOP patients with progressive disease	Higher prevalence of composite IL-1 genotype was detected(22)	Kratka Z et al (2007)
	Caucasians	IL-1 gene cluster not associated with AP (23).	Feibig A et al (2008)
IL-4	58 Gen AP patients and 51 healthy controls	Association between IL-4-590 T/T, IL-4-34T/T genotype and AP(24).	Gonzales JR et al (2007)
	47 EOP patients with their siblings	Prevalent production of IL-4 and lower levels of IFN-ã and Th2 cells, probably B cells & their products play an important role in disease pathogenesis(25).	Bartova et al (2000)
IL-6	In a meta-analysis of 6 case control studies (1093 cases and 574 controls)	IL-6-174G allele increased the risk of aggressive periodontitis and IL-6-572 C/G polymorphism is associated with pathogenesis(26).	Shao M et al (2009)
	A case control association study (224 cases and 231 controls) in Caucasians	A link between IL-6-1363,-1480 polymorphism and LAP susceptibility(27).	Nibali et al (2008)
IL-10	CP (n = 27) and AP (n = 32) controls (n = 34)	IL-10 promoter polymorphism at positions -1082G>A, -819C>T, -590C>A showed that haplotype ATA known as low IL-10 producer is a putative risk indicator for Generalized AP(28).	Reichert S et al (2008)
FMLP receptor	African Americans (30 subjects and 33 controls) and Turks (75 subjects and 63 controls)	FPR 348T>C polymorphisms was significantly higher in African American subjects with no effect on Turkish population(29).	Maney P et al(2009)
	African American subjects (37 cases and 38 controls)	Homozygous 348T genotypeis associated with increased risk of developing AP(30).	Maney P et al (2009)
TLR-4	In a meta-analysis of 7 studies (744 CP cases & 855 controls) and 4 studies (295 AP cases and 456 controls)	TLR-4 399 lle (TLR-4+1196C>T) polymorphism showed a protective effect against AP in contrast to CP(31).	Otzurk A(2009)
FcγRIIa,	Thirty-one GAP and 49 periodontally healthy Brazilian subjects	FcγRIIIb-NA2 allele and FcγRIIIb-NA2/NA2 genotype and composite genotype FcãRIIIb-NA2/NA2 plus FcγRIIa-H/H131 may be associated with Generalized AP(32).	RC Desouza (2006)
FcγRIIIb	224 cases and 231 control	FcγRIIIb polymorphism may predispose to AP through a modulation of neutrophil superoxide production(33).	Nibali L et al (2006)
	42 generalized EOP , 52 adult periodontitis, and 55 control	VDR, FcãRIIIb composite genotype may be associated with susceptibility to Generalized EOP(34).	Yoshihara et al (2001)
TNF-α	14 cases and 13 controls	High levels of TNF-á and low levels of IL-4 in generalized AP(35).	Bastos et al (2009)

enough to detect genes with very modest effects in adjunct to linkage analysis(15). Aggressive periodontitis offers advantage for these type of studies as there are fewer problems with diagnosis, variable phenotype and age of onset.

The progression of gingivitis to established periodontal diseases is of primary clinical importance and elucidation of the immunopathogenesis is central to our understanding. In the early stages of inflammation, proinflammatory cytokines secreted by inflammatory cells will predominate. Cytokine genes play a very significant role in orchestrating the immune response. The inflammatory immune response and aggressive periodontitis appears to be genetically determined(16). Various studies have been done to know the role of HLA gene, cytokine gene and receptor gene polymorphism. All of these studies have shown the relationship of aggressive periodontitis susceptibility with genetic polymorphism (Table 2).

Despite the large number of studies showing relationship between genetic polymorphism and Aggressive Periodontitis susceptibility, few studies have proved that Aggressive Periodontitis may not be associated with genetic polymorphism. Walker *et al* found that IL-1â allele at +3953 position provides little diagnostic or predictive information for Localised Juvenile Periodontitis(36). In a cross-sectional study of Caucasians (European origin) with 56 Generalized early onset periodontitis patients and 56 healthy controls, a lack of association between IL-1 polymorphism and Gen EOP was observed and no significant differences was found whether smoking was included as a covariate or not(37). In an association study on 111 patients with aggressive periodontitis and 80 periodontally healthy controls, it was concluded that functionally relevant IL-18 and TLR-4 gene mutations have no significant effect on AP susceptibility alone or in combination(38). Early and aggressive periodontitis is a consistent feature in several inherited or genetic disorders which demonstrate the variety of ways in which gene mutations can affect the risk of Aggressive Periodontitis (Table 3).

CLINICAL IMPLICATION OF GENETIC INFORMATION

With the knowledge of genetic profile of susceptible individual, prognosis and diagnosis of a disease can be made. Environmental risk factors play a major role in activation of involved genes to be modified.

A profile of genetic polymorphism haplotypes or other heritable units found to be associated with aggressive periodontitis could be performed at some point prior to the typical circumpubertal age of onset of disease. Clinical periodontal assessments of siblings of aggressive periodontitis probands can be done to ensure early diagnosis of disease.

Gene therapy approaches can be utilized as preventive measures. In cases where a high genetic likelihood of disease exists, aggressive steps could be taken at a time prior to typical disease to remove these environmental factors that cause the disease(5).

After preventive measures, assays for gene expression could be administered during recall visits to detect subclinical disease prior to overt tissue destruction. If disease activity is detected with gene expression, proper measures to eliminate environmental factors should be taken.

CONCLUSION

Periodontitis is a complex genetic disease which occurs when allelic variants of multiple genes act synergistically with environmental and bacterial factors to increase or decrease the likelihood of developing a disease. Identification of specific genes and genetic variants aids in diagnosis and treatment of aggressive periodontal disease.

Table 3: Genetic and inherited disorders associated with Aggressive Periodontitis

Disorder	Protein or tissue defect
Leukocyte adhesion deficiency type I	CD 18(â-2 integrin of LFA-leukocyte function associated antigen molecule)
Leukocyte adhesion deficiency type II	CD 15(neutrophil ligand for E and P selectins); inborn errors in fucose metabolism(chromosome 21)
Acatalasia	Catalase enzyme
Chronic and cyclic neutropenia	Unknown
Chediak higashi syndrome	Abnormal transport of vesicles to and from neutrophil lysozyme caused by mutations in lysosomal trafficking regulator gene (LYST)
Ehler danlos syndrome (EDS)	Type III collagen for EDS type IV, unknown for EDS type VIII
Papillon lefevre syndromeHaim munk syndrome	Cathepsin C(dipeptidyl aminopeptidase) (CTSC gene) (chromosome 11)
Hypophosphatasia	Tissue non specific alkaline phosphatase
Trisomy 21	Multiple, vertical trisomic regions atleast 5Mb(megabase) long
Pre pubertal periodontitis (non-syndromic)	Cathepsin-C
Kindler syndrome	Defect in actin-extracellular matrix linkage caused by loss of function in KIND-1

LFA - leukocyte function-associated antigen; Mb - Megabase; KIND-1 - Gene associated with Kindler syndrome

Human genome project allows accurate diagnosis and risk assessment of numerous conditions. Such genetic information would be invaluable in therapeutic interventions but for utilization of genetic polymorphism knowledge, large studies are needed in future to know the target genes and well defined risk factors. This will guide the clinician to determine and confirm any susceptible or resistant genes which will lead to more accurate diagnosis of periodontal disease as well as well improved prognostic processes to develop novel therapies.

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