Informational Paper

Implications of Genetic Technology for the Management of Periodontal Diseases*

Recent technological advances have revolutionized the ability to understand and apply genetic principles to the study of human diseases. These developments may soon alter the management of periodontal diseases. The goal of this informational paper, prepared by the Research, Science and Therapy Committee of the American Academy of Periodontology, is to discuss concepts that are currently emerging in medical genetics, and to describe their potential significance in managing periodontal diseases. *J Periodontol 2005;76:850-857.*

Periodontal diseases are a heterogeneous group of pathologies that share common clinical signs and symptoms, chiefly inflammation and destruction of the periodontium.[1] Although present in most populations, the risk for periodontal diseases is not uniform for all individuals.[2] Approximately 10% to 15% of the general U.S. population develops severe, destructive forms of periodontal diseases.[3,4] While it is believed that bacteria are required to develop periodontitis and that certain microbes may be more prevalent in some types of periodontitis, in most cases specific microorganisms are not sufficient to cause disease.[5-8]

Genomics, the branch of genetics that studies the structure and function of organisms in terms of their DNA sequences, provides powerful means of discovering hereditary factors in disease. Even in the genomic era, however, it is not genes alone but the interplay of genetic and environmental factors that determines phenotype.[9] Genetic factors modulate how individuals interact with many environmental agents. A key determinant of whether individuals develop periodontitis appears to be governed by the way they respond to their microflora. Other behavioral and environmental factors, for example oral hygiene, diet, and cigarette smoking, may also be determinants of an individual's propensity to develop periodontitis.[6,10] In this model of pathogenesis, the emphasis is placed upon the host, with the microbial factor acting as a trigger of the host response. Studies suggest there is a host genetic component of susceptibility for several forms of periodontitis, although except for some syndromic forms of periodontitis, specific genes have either not yet been identified or rigorously demonstrated to have a causal relationship with disease.[11,12]

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APPLYING GENETIC INFORMATION

The concept that heredity is an important determinant of periodontitis susceptibility is not new. Clinical observations, as well as scientific studies, suggest that host heredity may be an important susceptibility factor in developing periodontal diseases.[11,13,14] Current technologies should now allow us to identify the specific genetic, environmental, and behavioral factors that contribute to periodontitis susceptibility.[15] This information should help to improve management of periodontal diseases. To integrate genetic information into clinical care scenarios, it is necessary to identify specific genetic determinants of susceptibility and to evaluate the usefulness of this information in managing periodontitis patients. To effectively do this, it is important to demonstrate the utility of the resulting genetic information as a guide for clinical decision-making.

HERITABLE SUSCEPTIBILITY FOR PERIODONTITIS

Scientific data suggesting host genes are important determinants in periodontal diseases come from multiple sources. Specific animal strains have been noted to show differential susceptibility for periodontitis.[16] In humans, the association of severe periodontitis with a variety of disease conditions clearly demonstrating simple genetic (Mendelian) transmission indicates that genetic mutations of single genes can greatly increase susceptibility to periodontitis.[17] Specific mutations have been identified to define the genetic basis of various syndromic conditions, for example, the cathepsin C gene in Papillon-Lefèvre syndrome,[18] the CHS gene in Chédiak-Higashi syndrome,[19] and the beta-2 integrin chain gene in leukocyte adhesion deficiency type 1.[20] However, these genetic diseases are rare and do not characterize most common forms of periodontitis. Therefore, while understanding rare forms of disease may ex-

pand the understanding of periodontitis, it may not provide specific genetic tests to guide practitioners in managing the majority of patients.[21]

Familial aggregation of severe childhood forms of non-syndromic aggressive periodontitis (formerly referred to as early-onset periodontitis) has been noted in the dental literature.[22-24] Genetically, aggressive periodontitis conditions may be more complex than the simple Mendelian syndromes just mentioned.[25-27] Formal genetic studies (segregation analysis and linkage analysis) indicate that there are multiple different genetic forms of aggressive periodontitis, but it is currently unclear how many genes may be involved in these non-syndromic forms of disease.[14,28-30] While genes of major effect appear etiologic in aggressive periodontitis and some syndromic forms of periodontitis, there is also evidence for smaller contributions by genes that may modify periodontal disease expression.[31-34] Environmental (particularly smoking)[35,36] and microbial agents (virulence factors)[37-39] also modify disease risk and expression. A limiting factor in gene identification for conditions such as aggressive periodontitis is the relative rarity of these conditions and the difficulty of gathering data from families large enough to provide sufficient power to identify disease-related genes.[26,27]

For the more common forms of chronic periodontitis with an older age of onset (formerly referred to as adult periodontitis), evidence for a genetic component for periodontitis susceptibility comes primarily from twin studies.[11,40,41] Exploring periodontal disease in twins suggests that approximately 50% of susceptibility may be due to genetic factors.[11] In contrast to the rarer forms of periodontitis described above, the genetics of the more prevalent chronic forms of periodontitis appear to be complex. There is no evidence of any simple pattern of genetic transmission that would support an etiologic role for a single gene mutation in chronic adult periodontitis. Whether a genetic disease is "simple" or "complex" has important implications for disease-associated gene discovery. It is much more difficult to identify and rigorously demonstrate an etiologic role for a specific gene in a complex genetic disorder.[42,43]

In contrast to simple genetic diseases that may be caused by a single genetic mutation, it is likely that the additive effect of multiple genes is a determinant of disease susceptibility in complex diseases such as chronic periodontitis.[24] Prevailing theoretical models of common, complex genetic diseases suggest that five to 10 different genes may be important determinants of susceptibility. Furthermore, these models suggest that these genes interact with other genes and with environmental factors over a substantial period of time to ultimately influence susceptibility.[44] The genetic factors important in these disease models are not mutations that dramatically change a gene or its product, but rather, they involve more subtle genetic changes that may slightly alter expression or function of a gene product. Because these gene variants (alleles) alter susceptibility for disease, they are referred to as functional variants. Many functional variants occur with a relatively high frequency in the general population. Genetic variants that occur with a population prevalence of greater than 1% are termed genetic "polymorphisms." In contrast to these relatively frequent genetic polymorphisms, genetic mutations are usually rare on a population level, occurring with an allele frequency of much less than 1%. In general terms, gene mutations are rare alleles that dramatically affect the expression or function of a gene product, so that they are deterministic of disease. Genetic mutations underlie most simple genetic diseases. In contrast, complex genetic diseases may result from the combined effect of multiple functional genetic polymorphisms interacting with each other and with environmental factors to such an extent that over time, they modulate disease risk. In this complex disease model, a single functional genetic polymorphism associated with disease (at a population level) is not sufficient to cause disease, and therefore itself is not deterministic of disease. Consequently, such functional polymorphisms may be found in individuals with no evidence of disease and who may not be at great risk for disease. A fundamental characteristic of this genetic model is that such genetic polymorphisms are more frequent in the population than mutations, and the correlation between genetic polymorphisms and disease is generally much weaker than the relationship between a functional mutation and disease phenotype.[41] When studying the genetic basis of a disease, it is important to clarify the genetic model of disease and to apply appropriate statistical tests to determine the degree of association of a specific gene in individuals with disease and also in individuals without disease.

APPLICATION OF GENETIC RESULTS TO CLINICAL PRACTICE

Chronic periodontitis is likely to be a complex genetic disease.[6,24] In one of their twin studies, Michalowicz et al. estimate that about 50% of chronic periodontitis is due to genetic variance.[11] Therefore, there are challenges to developing clinically relevant diagnostic or

screening tests for chronic periodontal diseases, because genetic polymorphisms that contribute to disease susceptibility are individually not deterministic of disease. If there are as many as five to 10 functional genetic polymorphisms that are determinants of chronic periodontitis susceptibility, then any individual gene allele may make only a small (e.g., as little as 5%) contribution to disease susceptibility. Interactions between polymorphic forms of critical genes may act in concert with environmental factors, further complicating the disease model. In such a model, a single gene allele may contribute to susceptibility, but may not make a large enough contribution to disease outcome to provide clinical utility as a genetic test.[44,45]

STATISTICAL ISSUES

There are a number of statistical approaches that have been used to determine the genetic components involved in periodontal diseases. The most appropriate approach depends upon the genetic model of disease. As noted above, family patterns of disease have been analyzed to study aggressive periodontitis and syndromic forms of periodontitis. Twin study designs have been used to investigate adult-onset chronic periodontitis. Such approaches allow tests of hypotheses regarding disease heritability and mode of transmission, but they do not identify the specific genes involved. Gene-mapping approaches are used to identify genes involved in Mendelian single gene disorders or to identify the genes of major effect involved in disorders such as aggressive periodontitis. These approaches rely on the co-segregation of an inherited disorder with alleles at marker genetic loci of known chromosomal location. The statistical methods include both parametric and model-free methods of linkage analysis (such as logarithm of the odds [LOD] scores and identity-by-descent) that can be applied to either extended kindreds or pairs of affected relatives. Positive results from linkage analysis are then evaluated by molecular methods to identify the causal genes.

In contrast to the Mendelian disorders, association methods are more frequently applied to common, complex traits, and may have more power to identify etiologic genes for complex traits than do linkage approaches.[44,46] In association analysis, one compares the allele frequencies of a genetic marker or candidate gene between groups of affected individuals versus controls. Either population- or family-based unaffected controls can be used. If allele frequencies differ significantly between the cases and controls, then a specific allele at the marker or candidate locus is said to be "associated" with the disease at the population level. Genetic linkage between a marker and a disease gene implies that alleles at the marker locus co-segregate with the disease allele "within families." Therefore, the overall population frequencies of the marker need not vary between affected and control groups. When a positive population-level association is found, several interpretations are possible: 1) the associated allele itself is the disease-predisposing allele; 2) the associated allele is in linkage disequilibrium with the actual disease-predisposing locus; 3) the association is due to population stratification; or 4) the association is a sampling or statistical artifact.

GENETIC TESTS FOR PERIODONTITIS

Currently, it is possible to perform genetic testing to identify individuals carrying gene mutations responsible for several syndromic forms of periodontitis including leukocyte adhesion deficiency (LAD) types 1 and 2,[47] Papillon-Lefèvre syndrome,[18] Haim-Munk syndrome,[48] Chédiak-Higashi syndrome,[19] and some forms of Ehlers-Danlos syndrome.[49] To date, there is no evidence that mutations in the genes responsible for these conditions are responsible for the more prevalent forms of aggressive or chronic periodontitis. While there are isolated reports of mutations in aggressive periodontitis patients, these findings have not proven to generalize to patients with these diseases.[50] Genetic testing for mutations of specific genes is not currently utilized for genetic testing for aggressive periodontitis, and the validity of their use for genetic testing for chronic periodontitis is unknown.

Because chronic periodontitis appears to be genetically complex, studies have focused on evaluating a number of genetic variants (polymorphisms) occurring in human genes. A number of genetic polymorphisms have been studied for an association with chronic periodontitis including several interleukin (IL)genes (–1α, –1β, and –4),[51,52] where the most work has been done; the vitamin D receptor;[53] the FcγRIIIb-NA1 gene;[33] the tumor necrosis factor-β gene; and several human leukocyte antigen (HLA) variants.[54]

Genetic testing for complex diseases in the United States is not regulated at the state or federal level with regard to clinical validity and clinical utility. In response to the increasing availability of genetic information that will need to be integrated into clinical settings, a knowledgeable panel of genetic experts, the National Institutes of Health–Department of Energy (NIH-DOE) Working Group on Ethical, Legal, and Social Implications of Human Genome Research,

has offered guidelines for evaluation of prospective genetic tests (accessed December 14, 2004; available at http://www.genome.gov/10001808/). While many genetic polymorphisms have been evaluated and mild associations with disease have been established, none have proven to be strongly predictive as diagnostic or prognostic markers to identify patients within the general population who are at risk. Genotypic information on certain population subgroups, such as young, non-smoking individuals, may provide incremental information of potential clinical utility in the area of diagnosis and/or treatment of periodontitis. In the field of periodontics, most work in evaluating genetic polymorphisms and their relationship to periodontitis has been performed for several interleukin-1 genetic polymorphisms, and these, tests show promise, especially among certain preselected populations, but for reasons stated previously, more genotypic information that identifies additional genomic risk markers would likely provide even better diagnostic and prognostic tools in the future.

COMMERCIALLY AVAILABLE GENETIC SUSCEPTIBILITY TEST FOR SEVERE CHRONIC PERIODONTITIS

Currently, a genetic test† is being marketed for severe chronic periodontitis. It tests for the presence of specific polymorphisms of the IL-1α and IL-1β genes. These are single nucleotide polymorphisms in non-coding regions of these genes. The biological rationale for the test is that an IL-1β allele dosage effect on the secretory capacity of monocytes from diabetic patients was observed after lipopolysaccharide (LPS) stimulation.[55] In clinical studies of periodontitis patients, two of these IL-1 polymorphisms, when found together, have been reported to be associated with a significant increase in the risk for severe generalized periodontitis in non-smokers.[51] The specific periodontitis-associated IL-1 genotype (at nucleotide position +3954) comprises a variant in the IL-1β gene that is reported to be associated with high levels of IL-1 production. In the initial report, the investigators assessed for the simultaneous presence of IL-1α –889 polymorphism (allele "2" at nucleotide position –889 in the IL-1α gene) and IL-1β +3954 polymorphism (allele "2" at nucleotide position +3954 in the IL-1β gene).[51] If this combination of polymorphisms (composite genotype) was present, the patients were referred to as "genotype positive." Subsequently, the test has been modified to assess for the IL-1α +4845 polymorphism because it is technically easier to identify and it is reported to be essentially 100% concordant with the IL-1α –889 locus.[56] In addition, as a result of nomenclature changes in genetic numbering systems, the IL-1β +3954 locus has been renumbered and is now referred to as the IL-1β +3953 locus.[57] The IL-1 beta allele dosage effect reported by Pociot et al.[55] was not verified in a subsequent study that stimulated monocytes from periodontal patients and controls using LPS from various periodontal pathogens.[58] In their initial report, Kornman et al. used a case-control study design to evaluate the association of genes in the interleukin-1 system on periodontal disease.[51] Logistic regression analysis established that smoking was the strongest risk factor and that there was no statistically significant predictive value of other variables when smoking was included in the model.[51] Other investigators have also determined the importance of smoking as a risk factor for periodontitis.[10,35,59] Kornman et al. focused on non-smokers with mild, moderate, or severe periodontitis to evaluate genetic factors.[51] For the total genotype-positive non-smoking group (N = 62), the odds ratio of being associated with severe periodontitis was 6.8 (confidence interval [CI] 1.01-45.62); for the group 40 to 60 years of age (N = 41), the odds ratio was 18.90 (CI 1.04-343.05). The very broad confidence intervals are a consequence of the relatively small sample sizes. Furthermore, given the possible utility of this composite genotype as a screening test for periodontal disease, it is instructive to estimate the sensitivity, specificity, false-positive and -negative rates, as well as the positive and negative predictive values (Table 1). These calculations indicate

Table 1.

Sensitivity and Specificity of the IL-1 "Genotype Positive" Model*

	All Non-Smokers (N = 62)	Non-Smokers, 40-60 Years Old (N = 41)
Odds ratio (CI)	6.8 (1.01-45.62)	18.90 (1.04-343.05)
Sensitivity (%)	74.19	82.93
Specificity (%)	66.67	77.78
False-positive rate (%)	45.45	41.67
False-negative rate (%)	15.00	6.90

* Adapted from Kornman et al.[51]

† Periodontal Susceptibility Test for Severe Periodontitis, Straumann Biologics Division, Waltham, MA.

the overall utility of the test as a screening procedure for the general population. While interesting relationships between specific genetic polymorphisms and periodontitis disease states, as well as responses to treatment, have been reported, the results are equivocal or restricted to specific patient categories, suggesting that further research may provide additional insight into clinical utility.[60-64] Other investigators have also determined the importance of smoking as a risk factor for periodontitis.[10,35,59]

IMPLICATIONS FOR PATIENT MANAGEMENT

Currently more than 10 million single nucleotide polymorphisms (SNPs), which are variations in genomic DNA sequences within DNA, have been identified in the human genome (accessed December 14, 2004; available at http://www.ncbi.nlm.nih.gov/SNP/). These genetic changes occur at a frequency of more than 1% in the human genome. SNPs are the most common genetic alteration found in our hereditary makeup. SNPs are located in coding as well as noncoding regions of genes. While most SNPs are probably not determinants of disease susceptibility and have no known functional consequence, some undoubtedly are. A number of SNPs are likely to be important determinants in disease susceptibility for more common, genetically complex diseases such as chronic periodontitis. Because SNP patterns can be so divergent within the population and periodontal disease traits may also be quite heterogeneous, such tests will require rigorous evaluation before they can be generally utilized as the basis of genetic testing. After verification of the association of one or more genetic polymorphisms with a disease, it will be important to evaluate the utility of the marker to aid patient management. Several studies have evaluated the utility of the commercially available IL-1 genetic susceptibility test to help in patient management, but to date, most studies have been small and results have been mixed.[4,65-69] In general, there have not been any controlled studies of sufficient size to fully evaluate the usefulness of the IL-1 genotype and smoking or other individual characteristics to guide treatment decisions. Thus, although certain studies are encouraging, there is currently an insufficient body of evidence to support a modification of treatment protocols for chronic periodontitis patients based on IL-1 testing (see reference 70 for a more detailed review).

CONCLUSIONS

Emerging data strongly suggest that host genetic factors are important determinants for periodontitis susceptibility. Identification of specific genes responsible for susceptibility may provide the basis for genetic testing that may be helpful in the clinical setting. To identify specific genetic elements of risk, appropriate genetic models of periodontitis must be studied. Approaches such as association analysis will be necessary to uncover the etiologic factors in complex disorders such as periodontal diseases. However, the clinical utility of the results of any such associations will require rigorous application of genetic and statistical principles. Before the endorsement of any such model as a clinical screening tool, the models must be reproducible, biologically plausible and relevant, and of sufficient sensitivity and specificity to warrant application to clinical populations. Currently, only genetic tests for mutations present in certain rare forms of syndromic periodontitis such as Papillon-Lefèvre syndrome, Ehlers-Danlos syndrome, and Chédiak-Higashi syndrome appear to meet these requirements.

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APPENDIX

Allele: Conventional abbreviation for "allelomorph." Refers to the different forms, or DNA sequences, that a gene may have in a population.

False-positive rate: Proportion of controls falsely scored as affected.

False-negative rate: Proportion of cases falsely scored as unaffected.

Genetic polymorphism: A locus in which two or more alleles have gene frequencies greater than 0.01 in a population.

Genetic screening: Large-scale testing of defined populations for a genetic disease or disease-causing gene.

Linkage: A greater association in inheritance of two or more non-allelic genes than is to be expected from independent assortment. Genes are linked because they reside in close proximity on the same chromosome.

Linkage analysis: A method of determining the chromosomal location of a gene of interest.

Linkage disequilibrium: The tendency of specific combinations of alleles at two or more linked loci to occur together on the same chromosome more frequently than would be expected by chance.

Locus (plural, loci): The position that a gene occupies in a chromosome.

LOD (logarithm of the odds) score: Computation performed to evaluate support for/against a linkage hypothesis. Specifically, it is a common logarithm of the ratio of the likelihood of linkage at a specific recombination fraction to the likelihood of no linkage.

Segregation analysis: Method of assessing relative support between various hypothesized inheritance patterns for a trait of interest.

Sensitivity of a genetic test: The proportion of cases that are correctly identified by the genetic test.

Specificity of a genetic test: The proportion of controls that are correctly identified by the genetic test.

Single nucleotide polymorphism (SNP): A small genetic change or variation that can occur within a person's DNA sequence. The genetic code is specified by the four nucleotide "letters" A: adenine; C: cytosine; T: thymine; and G: guanine. SNP variation occurs when a single nucleotide, such as an A, replaces (substitutes for) one of the other three nucleotide letters C, G, or T.