Genetic Variants in Periodontal Health and Disease

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There are estimated to be 25,000–50,000 different kinds of genes in the human genome. Genes can exist in different forms or states. Geneticists refer to the different forms of a gene as allelic variants or alleles. Allelic variants of a gene differ in their nucleotide sequences. When a specific allele occurs in at least 1% of the population, it is said to be a genetic polymorphism. Two or more alleles for a given locus may exist in nature throughout evolution, but may develop at any time. A polymorphic locus is one whose alleles are such that the most common, normal variant (N-allele) among them occurs with 99% frequency in the population. Thus, if a locus is, for example, bi-allelic, the rarer allele (designated R-allele) must occur with a frequency of 41% in the population. In this way, when different alleles of a given gene coexist in the human population, we speak about genetic polymorphisms (Loos et al. 2005).

Polymorphism arises as a result of mutation. The different types of polymorphisms are typically referred to by the type of mutation that created them. The simplest type of polymorphism results from a single base mutation which substitutes one nucleotide for another. The polymorphism at the site harboring such changes has recently been termed a “single nucleotide polymorphism (SNP),” although previously, in some instances, such variation was referred to by the particular methods used to detect it. Digestion of a piece of DNA containing the relevant site with an appropriate restriction enzyme could then distinguish alleles or variants based on the resulting fragment sizes via electrophoresis, and this type of polymorphism was thus referred to as “restriction fragment length polymorphism (RFLP)” (Loos et al. 2005; Schork et al. 2000).

The SNP may have no effects or may have some important biological effects. For example, if a transition has taken place within the coding region of a gene, it may result in an amino acid substitution and therefore an altered protein structure, which may then alter its function. When such mutations have taken place in the promoter region of the gene, it may alter the gene regulation, for example resulting in (completely) inhibited or reduced gene expression or, alternatively, resulting in over-expression of the gene, perhaps with biological consequences. SNPs occur more frequently than any other type of genetic polymorphism; the frequency of SNPs across the human genome is estimated at every 0.3–1 kb (Loos et al. 2005; Schork et al. 2000).

Other types of genetic polymorphisms result from the insertion or deletion of a section of DNA. The most common type of such “insertion:deletion” polymorphism is the existence of variable numbers of repeated base or nucleotide patterns in a genetic region.
Repeated base patterns range in size from several hundreds of base pairs, known as “variable number of tandem repeats” (VNTRs or “minisatellites”), to the more common “microsatellites” consisting of two, three, or four nucleotides repeated some variable number of times. Microsatellites are often referred to as “simple tandem repeats” (STRs). Repeat polymorphisms often result in many alleles or variants (e.g., several different repeat sizes) within the population and are thus considered “highly polymorphic”. This can be extremely useful for population genetic studies since the probability that two individuals from different populations (ethnic groups, diseased vs. number of repeats) can be quite low. The genome-wide frequency estimates for STRs are difficult to come by, though a range of figures of one STR every 3–10 kb seems reasonable (Loos et al. 2005; Schork et al. 2000).

Another type of insertion:deletion polymorphism involves the presence or absence of Alu segments at a genetic location. Alu segments are named according to the restriction enzyme that is used to detect them (e.g., AluI), and contain two sequences of approximately 120–150 bases in length, separated by an A base-rich segment. Insertions of this type occur approximately every 3 kb on average. Large insertion:deletion polymorphism such as Alu insertions is easy to identify and genotype given the large differences in resulting amplified fragments (Loos et al. 2005; Schork et al. 2000).

Kinane and Hart (2003) presented the classic relationship among phenotype, environment, and genotype as follows:

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\text{Phenotype} = \text{Environmental risk factors (smoking status, plaque control, socio-economic status, diabetes, etc.)} + \text{genotype (includes gene–gene interactions)} + \text{genotype } \times \text{environment (that is the interaction between environment and genotype).}
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Genetic polymorphisms are very useful in the genetic studies of the population. After genotyping individuals and assessing genotype frequencies among groups of interest, one can also calculate the frequency of the N-allele and the R-allele among the groups or populations under study. Frequencies of genotypes and alleles may differ between a diseased group and a healthy group. Subsequently, when a given allele is identified to be associated with a disease, functional studies can be started to investigate the possible role of that gene in the etiology and pathogenesis of the disease (Loos et al. 2005).

Evidence for a genetic predisposition to periodontitis comes from four areas of research: (1) the study of inherited diseases and genetic syndromes, (2) family studies, (3) twin studies, and (4) population studies.

### 2.1 Study of Inherited Diseases and Genetic Syndromes

Evidence for the role of specific genes in a disease may be gleaned from the study of inherited conditions or genetic disorders, in which the disease is pathognomonic. A number of monogenic syndromes with accompanying severe periodontal disease have been reported.
in the literature (acatalasia, hypophosphatasia, Chédiak-Higashi syndrome, chronic neutropenia, leukocyte adhesion deficiency, cyclic neutropenia, Ehlers-Danlos syndrome, Papillon-Lefèvre syndrome) (Hodge and Michalowicz 2001).

A commonality of these conditions is that they are inherited as simple Mendelian traits and are usually due to genetic alterations of a single gene locus. The significance of these conditions is that they clearly demonstrate that a genetic mutation at a single locus can impart susceptibility to periodontitis. Additionally, these conditions illustrate that this genetic susceptibility may segregate by different transmission patterns. The fact that the altered proteins function in different structural and immune pathways indicates that genetic modulation of a variety of different genes can affect a variety of different physiological and cellular pathways, imparting susceptibility to pathological consequences in the periodontium in individuals with appropriate microbial challenges. These conditions illustrate that genetic contributions to periodontitis susceptibility are multifaceted and may potentially involve many different gene loci. However, in contrast to non-syndromic forms of periodontitis, these conditions have periodontal disease manifestations as part of a collection of syndromic manifestations. In most cases of aggressive periodontitis, individuals present with clinical manifestations of periodontitis, but do not appear to have any other clinical disease manifestations (Kinane and Hart 2003).

2.2 Family Studies

There is literature reporting familial aggregation of periodontal diseases, but, due to different terminology, classification systems, and lack of standardized methods of clinical examination, it is difficult to compare reports directly. Although periodontal disease nosology has changed many times over the timeframe of these reports, the most familial reports for periodontitis are of the early-onset forms now called aggressive periodontitis (Stabholz et al. 1998). This aggregation within families strongly suggests a genetic predisposition. It must be borne in mind that familial patterns may reflect exposure to common environmental factors within these families. Thus, it is important to consider the shared environmental and behavioral risk factors in any family. These would include education, socio-economic grouping, oral hygiene, possible transmission of bacteria, diseases such as diabetes, and environmental features such as passive smoking, sanitation, etc. Some of these factors, such as lifestyle and behavior and education, may be under genetic control and may influence the standard of oral hygiene. The complex interactions between genes and the environment must also be considered in the evaluation of familial risk for the periodontal diseases (Kinane and Hart 2003).

In chronic periodontitis, the phenotype or disease characteristics do not present significantly until the third decade of life, whereas in the aggressive forms of periodontal disease, the presentation can occur in the first, second, third, and fourth decades. This variability in presentation of significant signs of the disease makes diagnosis difficult, not only in declaring if a patient suffers from the disease but also in detecting patients who do not suffer from the disease, and differentiating between the adult and aggressive forms of periodontitis (Kinane and Hart 2003).
2.3 Twin Studies

Studying phenotypic characteristics of twins is a method of differentiating variations due to environmental and genetic factors. Monozygous twins arise from a single fertilized ovum and are therefore genetically identical and always the same sex. Dizygous twins arise from the fertilization of two separate ova and share, on average, one half of their descendent genes in the same way as siblings do. Any discordance in disease between monozygous twins must be due to environmental factors. Any discordance between dizygous twins could arise from environmental and/or genetic variance. Therefore, the difference in discordance between monozygous and dizygous twins is a measure of the effects of the excess shared genes in monozygous twins, when the environmental influence is constant (Hodge and Michalowicz 2001).

Based on 110 pairs of adult twins, a significant genetic component was identified, suggesting that 38–82% of the population variance for probing depth (PD), attachment loss (AL) and dental plaque may be attributed to genetic factors (Michalowicz et al. 1991). A study by Corey et al. (1993) of self-reported periodontal health among 4,908 pairs of twins found a history of reported periodontal disease in 420 individuals who were members of 116 monozygotic (MZ) and 233 dizygotic (DZ) twin pairs. The mean age at diagnosis in this sample was 31.4 ± 0.7 years and was significantly earlier in females than males (30.1 vs. 33.0 years, P < 0.025). Proband-wise concordance rates were 0.38 for MZ and 0.16 for DZ twins. In a subsequent study on 117 pairs of adult twins (64 MZ and 53 DZ pairs) revealed that approximately half of the variance in disease in the population is attributed to genetic variance. PD, AL, plaque, and gingivitis (GI) were assessed on all teeth by two examiners. Measurements were averaged over all sites, teeth, and examiners. The extent of disease in subjects was defined at four thresholds: the percentage of teeth with AL ≥ 2, AL ≥ 3, PD ≥ 4, or PD ≥ 5 mm. Genetic and environmental variances and heritability were estimated using path models with maximum likelihood estimation techniques. For all clinical measures, MZ twins were more similar than DZ twins. Statistically significant genetic variance was found for both the severity and extent of disease. Adult periodontitis was estimated to have approximately 50% heritability, which was unaltered following adjustments for behavioral variables including smoking. In contrast, while MZ twins were also more similar than DZ twins for GI scores, there was no evidence of heritability for GI after behavioral covariates such as utilization of dental care, and smoking were incorporated into the analyses (Michalowicz et al. 2000).

2.4 Population Studies

Environmental or behavioral risk factors for a disease are often first detected in large epidemiological or population-based studies. In genetic epidemiology, similar approaches can be used to identify genetic risk factors for the disease. The frequencies of polymorphisms
of candidate genes, whose protein products play a role in the inflammatory or immune response, can be compared between cases and controls. A genetic polymorphism is the long-term occurrence in a population of two or more genotypes that could not be maintained by recurrent mutation. A significant difference in the frequency of a specific polymorphism, between a diseased group and a control group, is an evidence that the candidate gene plays some role in determining susceptibility to the disease. An association indicates that either the candidate gene directly affects disease susceptibility or that it is in linkage disequilibrium with (very close to) the disease locus. This method can help to elucidate the pathogenesis of a disease process, identify causal heterogeneity, and ultimately identify individuals most at risk for the disease. In population studies, it is important to clearly define the disease status. Likewise, because of the possibility of racial heterogeneity, it is important to insure that the patient and control groups are racially matched (Hodge and Michalowicz 2001).

References