

## Genetic Basis of Dental Disorders: A Review

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### ABSTRACT

Deciphering the relative roles of heredity and environmental factors ("nature vs. nurture") in the pathogenesis of dental caries and diseases of the periodontium has occupied clinical and basic researchers for decades. Success in the endeavor has come more easily in the case of caries; the complex interactions that occur between host-response mechanisms and mutative microbiologic pathogens in periodontal disease have made elucidation of genetic factors in disease susceptibility more difficult. A critical discussion of the evidence for a hereditary component in caries susceptibility is presented, also from a historical perspective. Recent applications of *in vitro* methods for genetic analyses in periodontal research are also being discussed, with an eye toward a future in which persons who are at risk, i.e., genetically predisposed to periodontal disease may be identified and targeted for interventional strategies. The evidence for the influence of genetics in dental anomalies and malocclusion has also been discussed. The most important conclusion of this review is: while phenotype is inevitably the result of both genetic and environmental factors, there is irrefutable evidence for a significant genetic influence in many genetic and occlusal variables.

**Key Words:** Genetics, malocclusion, periodontal disease, dental caries.

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**G**enetics is the study of genes at all levels from molecules to populations. In dentistry we encounter numerous differences in the dentofacial characteristics of individuals, even among family members. Some children have large teeth; some may have high prevalence of caries, while only some have good occlusions. Is dental health inherited?

The three most common problems in dentistry today remain dental caries, periodontal diseases and malocclusion. While there has always been anecdotal evidence of a genetic basis to each of these problems, for example, "my mother had chalky teeth too" or "he has inherited his father's teeth and his mother's jaws" or "bad gums run in the family". Even within a family some members have a high prevalence of dental caries while others may be caries free. Regardless of abnormal or normal individual states, how do these differences come about? To deal with this question it is necessary to turn to genetics when we examine a specific characteristic or disease in dentistry, we often find it the consequence of two principal factors, genetic and environmental.(1, 2)

Common dental diseases such as dental caries, periodontal disease and malocclusion are mainly influenced by environmental factors. However, even in these diseases the genetics aspects that influence the degree of susceptibility should not be overlooked. A multifactorial etiology for all three conditions has generally been assumed, with both genetic and environmental contributions to observed variability. The paucity of evidence of any clear-cut single gene effects has meant that genetic research in these areas has had little impact up to now on clinical dental practice.(1, 2)

### Genetic aspects affecting a feature or disorder

Several questions need to be answered before a complete understanding can be gained about how genetic factors influence a feature or disorder. These include:

#### Analysis of multifactorial traits

It is important to realize that heritability estimates need to be interpreted with caution as they relate only to the population under study at a particular time, including the prevailing

environmental influences. For this reason it is inappropriate to say for example that ‘tooth size is strongly genetic’ rather one should say that ‘variation’ in tooth size between individuals has a strong genetic component.(3)

Genetic and environmental factors have often been assumed to be independent for the purposes of analysis, but in practice this is unlikely to be case. Three factors that should be considered are assertive mating whereby there is non-random pairing between mates for the trait under investigation, genotype-environment correlation when different possible environments; and genotype-environment interaction in which environmental effects on phenotype differ according to genotype.

### Twin studies

The classical twin approach for separating the effects of nature and nurture involves comparing identical (monozygous) twins and non-identical (dizygous) twin pairs reflect environmental factors whereas differences between dizygous (DZ) pairs are due to both genetic and environmental factors.(4)

### Molecular Approaches

With marked advances in molecular genetic technology in recent years, gene mapping techniques are now providing powerful approaches for locating genes associated with various diseases and disorders.

Positional cloning, also known as reverse genetics, is used to identify the location of the mutant genes on a particular chromosome with the help of polymorphic DNA markers. The first generation of these markers was termed restriction fragment length polymorphisms (RFLPs). RFLPs arise as a result of minor alterations in the DNA sequence on pairs of chromosomes. The DNA, usually obtained from peripheral blood leucocytes, is digested with a restriction enzyme which recognizes particular DNA sequences and cuts at a certain point in the sequence. The resulting DNA fragments are then separated in an agarose gel where the distance they migrate depends upon their size, shorter fragments migrating further than larger fragments over a given period of nylon membrane (Southern blotting) where it can be probed by markers.

The markers are DNA fragments which have been mapped to parts of chromosomes. Because of the variation in cutting sites, in an ideal situation the probe will bind to two different sized fragments of DNA. The probe is labeled using a

radioisotope and appears as one or more bands on an autoradiograph. The different bands are referred to as alleles, and by following the segregation of these alleles with the disease, the position of the gene is established.(2)

### Dental variations as influenced by genetics

The seemingly minor differences in dental traits (e.g., tooth eruption, shape or size) among and within populations can be of great interest and importance to both anthropologists and practicing dentists.

Here, the influences of genetic and environmental factors on dental variation among populations are described. To start with we review several basic principles.

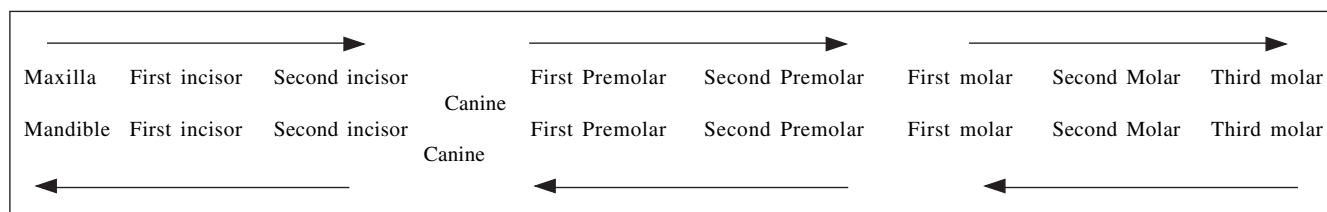
### Basic principles

#### Butler’s field theory

Reference is often made to specific teeth seem to show more variation than others. Much of this descriptive information on dental variation can be simplified if Butler’s field theory is understood.(5) In 1939, Butler, an English paleontologist, proposed that the mammalian dentition can be divided into several developmental fields. Within each field, there is a “key” tooth-one that is more stable developmentally –and on either side of this key tooth, the remaining teeth within the field become progressively less stable. The three fields include those for molars / premolars, incisors, and canines considering each quadrant separately, the molars / premolars field would consist of the first molar as the key tooth, the second the third molars on the distal end of the field, and the first and second premolars on the mesial end. The theory predicts that the third molar and first premolar would be most variable in size and shape. Most clinicians would agree on the third molar but not on the first premolar. Actually the earliest mammals had four premolars and some of the higher primates, including man, have lost the first two, so that the premolars that we refer to as first and second should really be labeled third and fourth. The point is that as Butler’s theory predicted, the premolars farthest from the first molar were the first to be lost in an evolutionary sense and therefore can be considered the least stable.

Adapting Butler’s theory to the human dentition, Dahlberg suggested the following fields and gradients of stability among teeth – the arrows indicate decreasing stability.(6)

With the scheme in mind, it is relatively easy to remember which teeth within a given field will show the greatest variation



in size, shape, eruption, and number. It is also possible to predict which teeth are the most likely to be lost in the course of evolution

### Polygenic inheritance

The second principle which will be useful to remember is that most research data suggest that “normal” variation in the dentition is the result of multiple rather than single genes. By normal variation we mean to exclude the genetic defects or syndromes associated with the dentition. Thus unlike disease such as odontogenesis imperfecta and ectodermal dysplasia which result from the segregation of single genes, the size or shape of the teeth is determined by many genes interacting with each other and the environment.

### Types of dental variations

The common categories used in entropologic studies are crown size, the age of eruption, hypodontia (the congenital absence of teeth), and crown morphology. These four forms of dental variation are interrelated and should not be thought of as being biologically independent of each other.

### Tooth size

Environment plays a major role in the determination of tooth size. This can be seen in the correlations in crown size between siblings or between parents and children. The correlation coefficient, which provide estimate of heritability, range between 0.40 and 0.70, indicating that like most polygenic trait, both the environment and genes are important. The “key” tooth in each morphologic class of teeth has the highest heritability. The more, distal teeth in the same class seem to be more influenced by the environment. This would mean. For example, those genes have a greater effect in determining the size of the first than of the third molar.

Bader reported a relatively strong genetic contribution to the size of the first and second molars (66 %) and what less to the third molar (47 %). (7) The greatest significance, he indicated that the maternal or intrauterine environment is the single largest source of environmental variation in the dentition.

### Tooth eruption

There have only been a few studies of the heritability of tooth eruption but the findings point to multiple genes- much the same as described for tooth size. The effect of environmental on tooth eruption has received considerably more attention. While postnatal environmental factors do not seem to influence tooth eruption, there is increasing evidence that prenatal factors do. Low birth weight child seems to be associated with retarded permanent tooth eruption. Since the weight of a child at birth is determined mainly by the maternal genotype and environment. (Only 19% of birth weight variance can be explained by the Genotype of the child), the relation ship

between birth weight and post natal dental development must result largely from maternal factors. (8)

### Congenitally Missing Teeth

Perhaps the best family study of tooth agenesis was done by Grahnén in 1956. (9) He found that if either parent had one or more congenitally missing teeth, there was an increased likelihood that their children also would be affected. This familial relationship suggests that the genes are important. Most dental anthropologists would probably agree that the absence of teeth in the “normal” individual is a polygenic trait. Several investigators have suggested that tooth agenesis is an example of a ‘quasi-continuous’ trait.

### Tooth morphology

The Cusp of Carabelli and Shovel- shaped incisors are traits of polygenic origin with a discontinuous distribution and can be thought of in much the same way as congenitally absent teeth. That is, they have a quasi-continuous distribution with the complete absence of the trait occurring when a threshold is crossed at the extreme end of the distribution. Studies of mice indicate that changes in maternal environment can influence the morphology of teeth, generally there seems to be a decrease in cusp size and number and an increase in the depth of occlusal pits and fissures. (10)

## Genetics of common dental disorders

### Dental caries

The question of a possible true genetic predisposition toward dental caries has piqued the minds of dental investigators for decades. (11- 17) Excellent reviews of genetic studies of dental caries were published by Finn and Caldwell (1963), and by Zengo and Mandel (1972). (18, 19) Although the pathogenesis of the caries process is rather well understood today, and although it is quite more complex than was believed in the early days of dental research, for the sake of simplification we can presuppose that the caries attack rate in humans is a consequence of at least five distinctly separate traits or attributes: 1. the density or structural integrity of the dental enamel, 2. topical and/or communal water fluoridation, 3. the composition of the secretions of the salivary glands, 4. nutrition and day-to-day dietary habits, and 5. personal and professional oral hygiene. (20) Salivary glands secretion and density and structural integrity of enamel are directly under genetic control.

Klein examined 5,400 individuals who were members of 1,150 different families, and demonstrated that the amount of dental disease (*viz.*, caries, “DMF”) that appeared in the offspring was quantitatively related to that which had been experienced by their parents. (21) He concluded: “... (this) makes it difficult to exclude the view that dental disease susceptibility in children involves strong familial vectors [*sic*] which very likely have a genetic basis, perhaps sex-linked.”

Book and Grahnén adroitly selected the parents and siblings of intellectually normal, middle-class individuals who were highly resistant to dental caries decay free persons. (22) Book and Grahnén could detect no environmental factor that could explain the differences in caries susceptibility between caries-free and caries-prone individuals /parents /siblings. They concluded that “genetic factors play an appreciable part in determining individual resistance against dental caries”.

Horowitz et al brought some clarity to the question of caries susceptibility in their study of human twins. (15,16) They were bothered by the discrepancy between the previous results of studies of adults and juveniles, primarily twin studies, and concluded that “in all probability” a hereditary factor in dental caries experience cannot be readily measured until eruption of the permanent teeth is essentially complete. Introducing the term Caries Experience Rate (CER) into the dental literature, Horowitz et al demonstrated a genetic component of variability in caries incidence in adults who were otherwise in good systemic health, and claimed, therefore, to have found a definitive hereditary factor in susceptibility to caries. (15, 16) Mansbridge examined 232 like-sex twin pairs in schools, and reported that the resemblance in caries experience between monozygous twins was greater than between dizygous twins. (23) These findings were corroborated by Finn and Caldwell, who also detected differences between smooth-surface and pit-and-fissure caries lesions, indicating that the smooth-surface lesion may be under more strict genetic control. (18) Realizing that dental caries is a pathologic entity that results from the interaction of endogenous and exogenous traits, Goodman et al studied 38 like sexed MZ and DZ twin pairs in Michigan in an attempt to relate tooth decay to other factors that might be under genetic control. (28) They reported significant heritability for the presence of several oral microorganisms, including Streptococci, and also for salivary flow rate, salivary pH, and salivary amylase activity. Aside from hereditary factors relating directly to enamel constitution, Goodman and co-workers thus established other genetically influenced factors as operative in caries etiology.

Hans Muhlemann presented a philosophical view when considering the scientific evidence about caries (and periodontal diseases) in humans from the genetic point of view. (25) “Dental caries is a polyfactorial entity. Could caries not therefore also have a polygenic heritability? One gene could influence the resistance of enamel by determining its chemistry or its morphology, another gene could control the composition of saliva, which could influence partly the oral flora; a third gene could determine eating habits; a fourth could influence one’s characteristic personal view of or approach to oral hygiene at home. Given this, is a clean genetic analysis possible in man?”

Boraas and co-workers performed a six-year retrospective

study of a large cohort (N = 97) of adult twins (the mean age was 40.6 yr) who had been raised apart since birth, and a control group of dizygous twins also raised apart. (26) This is a powerful method, because the effects of common environment are eliminated; thus, the intraclass correlation coefficient between monozygous twins becomes a direct measure of heritability. Remarkably, of the 17 orofacial parameters studied, 15 were associated with highly significant within-pair resemblance in monozygous twins reared apart. This study has provided new and convincing evidence for a marked genetic component to dentate status and dental caries experience. It also provides strong support for the earlier studies that had implicated hereditary contributions to tooth size, dental malalignment, occlusion, and tooth morphology.

### Periodontal diseases

While the hereditary basis for susceptibility to dental caries is rather well-founded, the situation *vis-a-vis* chronic inflammatory periodontal disease is considerably less so. This has been due not to any lack of investigative enthusiasm over the past eight decades, but rather to the relative complexity of the disease, continually emerging new knowledge about its pathogenesis, vagaries of clinical diagnosis and statistical quantization, and the profession’s own nomenclature for classifying these diseases, which keeps evolving even today Ranney. (27)

### Periodontal disease associated with genetic or familial conditions

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, possibly inherited, characteristics that affect periodontal disease risk or severity. While such characteristics may be clearly deficient or abnormal in rare conditions, less drastic alterations in structure or function may explain a portion of the inter- individual variability in periodontal health in the general population. Diverse findings from various chromosomal abnormalities, genetically inherited monogenic syndromes, and some rare familial conditions provide substantial support for the role of a single gene or genes of major effect for periodontal disease etiology, rather than a multifactorial concept.

### Aggressive periodontitis

#### Family studies

Evidence for a genetic contribution to individual differences in risk of periodontal disease is clearest for early onset periodontitis. Some of the pioneering initial studies of the mode of inheritance of susceptibility to early onset periodontitis concluded that the increased prevalence in women as well as the lack of father-to-son transmission in families indicated that susceptibility is inherited as an X-linked dominant trait. (28) More extensive analysis of these data has shown that these

two indications of X-linked inheritance are due to the differential ascertainment of women or girls with periodontal disease in families. When the original pedigrees were analyzed redressing for ascertainment bias, they were found to be supportive of autosomal inheritance of EOP. (29) Both autosomal-recessive inheritance and autosomal-dominant inheritance of early-onset periodontitis are supported by existing data. (30- 32) In the largest study to date (100 families), Marazitta and colleagues (1994) found the strongest evidence for an autosomal-dominant susceptibility gene, with 70% penetrance. (32)

Genetic linkage studies have been routinely used to locate disease susceptibility genes in the genome; such studies typically involve detailed genetic and phenotypic studies in families that appear to manifest a genetically inherited disease predisposition. In a large, five-generation family, an autosomal-dominant form of localized juvenile periodontitis was ascertained to be linked to Gc (group-specific component, a vitamin-D-binding protein locus) on the long arm of chromosome 4 (4q).

## Chronic periodontitis

### Twin studies

Twin studies are typically used to detect genetic variance or traits or conditions that are multifactorial. The comparison of the similarity of identical twins with that of fraternal twins is based on the difference in shared genes and the similarity of shared environments, so that a greater degree of similarity for identical twins is evidence for genetic variance.

For the simple model on which estimates of heritability are based, for Mendelian traits one expects the correlation for identical twins to be no more than twice that for fraternal twins; however, this does not always hold for multigenic traits. An even greater difference between the similarity of identical and fraternal twins suggests that a more complex genetic model, gene-environment interaction, or greater shared environment for identical twins, is a better explanation of the observed correlations. A near-equal correlation for identical and fraternal twins suggests that shared environmental factors, and not genes, account for any observed similarities.

Twin similarity for clinical measures of periodontal disease and for potential host risk factors for periodontal disease has recently been assessed. (33, 34) After age and gender effects on each measure were taken into account, the similarities of identical twins reared together, fraternal twins reared together, and identical twins reared apart were compared for attachment loss, pocket probing depth, gingival index, and plaque index. (34) The greater similarity of identical twins, whether reared together or apart, suggested that there is a *genetic contribution* to variation in levels of supragingival plaque and clinical measures of periodontal health. However, the low degree of

similarity in fraternal twins for most measures suggested that the genetic model may not be a straightforward additive model, but may instead be an interaction between genes at one locus (dominance), among genes at more than one locus (epistasis), or between genes and other risk factors.

### Family Studies

Vander Velden and colleagues studied sib ship clustering of periodontal measurements for individuals aged 15-25 years. (35) Sib ship clustering was observed for measurements of plaque, calculus, and attachment loss. Using analysis of covariance, the authors concluded that the clustering of data on attachment loss could be explained by differences in the amounts of dental plaque among sib ships. Because of the age restriction, age effects would have been minimal, but other risk factors for periodontal disease were not considered.

There are several potential difficulties in periodontal disease research: First, genetic heterogeneity in the etiology of adult periodontal disease may make detection of a specific mode of inheritance difficult. This does not pose a great problem if the mode of inheritance for the various genetic susceptibilities is the same (e.g., autosomal-dominant or autosomal-recessive), but it can be a significant problem if the modes of inheritance differ cross families (e.g., autosomal-dominant and autosomal-recessive traits). Second, it may be difficult to determine affected status or to measure periodontal health in some individuals (edentulous family members, adults who may have had early-onset periodontitis rather than adult periodontal disease). Third, there are other factors that affect periodontal disease susceptibility, some of which may be heritable themselves, such as a propensity for tobacco use, or which may cluster in families, such as at-home oral hygiene habits. Although traditional genetic segregation analysis techniques cannot readily take into account specific covariates, extensions of regression techniques that account for the dependency among relatives (regressive models) can simultaneously assess different modes of genetic inheritance and take into account the effects of covariates. (36) Measured genetic factors (e.g., “high-risk” HLA marker) can also be included as risk factors or to assess the interaction between the genetic marker and other periodontal disease risk factors. Apart from Beaty et al (1993), these types of analyses of family data have, to date, not been performed for adult periodontal disease or for periodontal health in adults. (30)

### Malocclusion

Genetic and environmental factors play important role in etiology of malocclusion. While phenotype is inevitable the result of both genetic and environmental factors, there is irrefutable evidence for significant genetic influence in many dental and and occlusal variable. Genetic however varies according to the trait under consideration. The bulk of the

evidence for the heritability of various type of malocclusion arises from family and twin studies .

### Class II division 1

Extensive cephalometric studies have been carried out to determine the heritability of certain craniofacial parameters in class II division 1 malocclusions. These studies have shown that in class II the mandible is significantly more retruded than in class I patients, with the body of mandible smaller and overall mandibular length reduced. These studies also show a higher correlation between the patients and his immediate family and data from random pairings of unrelated siblings, thus supporting the concept of polygenic inheritance for class II division 1 malocclusion.

### Class II division 2

Class II division 2 comprises the unique combination of deep overbite, retroclined incisors , class II skeletal discrepancy , high lip line with strap like activity of the lower lip and active mentalis muscle .Class II division 2 syndrome is a tendency to a forwardly rotating mandibular movement , which contribute to the deep bite, chin prominence , and reduced lower face height. Familial occurrence of class II division 2 has been documented in several published reports including twin and triplet studies conducted by Kloepfel and Markovic; and in family pedigrees from Trauner and Peck S. (38-40) They carried out a clinical and cephalometric study of 114 class II division 2 cases 48 twin pairs and six sets of triplets. Of the monozygotic twin pairs, 100 percent demonstrated concordance for class II division 2 malocclusion, while almost 90 percent of the dizygotic twin pairs were discordant. This is strong evidence as main etiological factor.

### Class III malocclusion

The relative contribution of genetic and environmental factors to class III malocclusion resulting from a skeletal imbalance between the maxillary and mandibular bases may result from excessive mandibular growth, deficiency in maxillary growth, or a combination of both. Various studies have also highlighted the influence of a distinctive cranial base morphology with a more acute cranial base angle and shortened posterior cranial base resulting in a more anteriorly placed glenoid fossa, thus contributing to mandibular prognathism. (41) Familial studies of mandibular prognathism are suggestive of heredity in the etiology of this condition. (42) Various models have been suggested, such as autosomal dominant with incomplete penetrance simple recessive, variable both in expressivity and penetrance with differences in different racial populations. (43, 44)

### Conclusion

The following conclusions can be drawn from this review:

- The 'key' tooth according to Butler's field theory has the highest heritability.

- Multiple genes are responsible for the heritability of tooth eruption.
- Congenital absence of teeth is due to polygenic inheritance.
- Genetic information in the molecular form of RNA is transmitted and odontogenesis is initiated.
- Host genes play a role in the susceptibility of caries.
- Early onset forms of periodontal disease such as juvenile periodontitis and rapidly progressing periodontitis have a genetic component.
- A permanent interaction between genetic and environmental factors, both of a continually altering nature, determine the dentofacial morphology.

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