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The Heritability of Malocclusion: Part 2. The Influence of Genetics in Malocclusion

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Abstract *The relative influence of genetics and environmental factors in the aetiology of malocclusion has been a matter for discussion, debate and controversy in the orthodontic literature. This paper reviews the literature and summarises the evidence for the influence of genetics in dental anomalies and malocclusion. Among the conclusions are that, while phenotype is inevitably the result of both genetic and environmental factors, there is irrefutable evidence for a significant genetic influence in many dental and occlusal variables. The influence of genetics however varies according to the trait under consideration and in general remains poorly understood. More precise research tools and methods are required to improve knowledge and understanding, which in turn is a prerequisite to the appreciation of the potential for genetic and/or environmental manipulation in orthodontic therapy*

Index words: Genetics, Malocclusion.

Introduction

Horowitz *et al*. (1960) studied fraternal and identical adult twin pairs using only linear cephalometric measurements, and he demonstrated highly significant hereditary variations in the anterior cranial base, mandibular body length, lower face height, and total face height. Hunter (1965) also used linear measurements on lateral cephalograms and concluded that there is a stronger genetic component of variability for vertical measurements, rather than for measurements in the anteroposterior dimension.

Fernex *et al*. (1967) found boys to show more similarities to their parents than girls. Facial skeletal structures were more frequently transmitted from mothers to sons than from mothers to daughters. Female twins showed greater concordance in facial features than male twins. While the profile outline coincided most frequently, this was not true of the cranial base and differences increased with age. Hunter *et al*. (1970) found genetic correlation to be strongest between fathers and children, especially in mandibular dimensions. There was a significant relation in facial height between mothers and their offspring. However, the regression equations of parental facial dimensions were of questionable clinical value in predicting adult facial dimensions in offspring. Litton *et al*. (1970) concluded that siblings usually show similar types of malocclusion and examination of older siblings can provide a clue to the need for interception and early treatment of malocclusion.

Harris (1963) recommended that any study of genetic variation using lines and angles requires the use of multivariate analysis in order to identify significant relationships, while Kraus *et al*. (1959) criticized the use of lines and angles to study heredity, and preferred superimposition of bony profiles to illustrate genetic control of craniofacial morphology. Their study involved superimposition of lateral cephalograms of a sample of identical twins and showed that many bony contours are in almost perfect concordance. This applied equally to contours across sutures and to individual bony contours such as the mandible. The latter method had first been described by Curtner (1953) who superimposed lateral cephalograms of children on those of their parents. The superimposed profiles were scored visually and subjectively for concordance or discordance, and close parent–sibling similarities for many craniofacial structures were found. Margolis *et al*. (1968) came to a similar conclusion in a cephalometric study of the parents and siblings of 68 families.

Since there is evidence that these orofacial structures are under genetic control and are significant in craniofacial development they must be considered in the aetiology of malocclusion. It is also well established that many craniofacial abnormalities are not monogenic disorders and are produced by a combination of many genes interacting with the environment, i.e. they are multifactorial. The same is true of malocclusion and the best evidence in establishing the relative contribution of genes and environment in determining certain craniofacial parameters is from familial and twin studies. The following outlines some of the evidence.

The Nature of Malocclusion

Malocclusion may be defined as a significant deviation from what is defined as normal or 'ideal' occlusion (Andrews, 1972). Many components are involved in normal occlusion. The most important are: (a) the size of the maxilla; (b) the size of the mandible, both ramus and body; (c) the factors which determine the relationship between the two skeletal bases, such as cranial base and environmental factors; (d) the arch form; (e) the size and morphology of the teeth; (f) the number of teeth present; and (g) soft tissue morphology and behaviour, lips, tongue, and peri-oral musculature. The term 'normal occlusion' is arbitrary, but is generally accepted to be Class I molar relationship with good alignment of all teeth and represents a situation that occurs in only 30–40 per cent of the population.

There is dental anthropological evidence that population groups that are genetically homogeneous tend to have normal occlusion. In pure racial stocks, such as the Melanesians of the Philippine islands, malocclusion is almost non-existent. However, in heterogeneous popula-

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tions, the incidence of jaw discrepancies and occlusal disharmonies is significantly greater. Stockard (1941) carried out breeding experiments with dogs, and produced gross orofacial deformities and associated malocclusions. He concluded that individual features of the craniofacial complex could be inherited according to Mendelian principles independently of other portions of the skull, and that jaw size and tooth size could be inherited independently, and as genetically dominant traits. These experiments have been severely criticized on the basis that the gene for achondroplasia is likely to have contributed and in the context of inheritance of malocclusions in humans, extrapolation to conclude that racial cross-breeding may explain tooth size/arch size discrepancies is entirely unjustified. Evidence from human family studies and twin studies is considered much more credible. A study by Suarez (1974) examining aetiology of the variation in crown form of the mandibular first premolar indicates that this is determined by a myriad of genes with at least seven different genetic traits had to be taken into account. This points to the much more credible polygenic theory for craniofacial and dental morphogenesis.

Family Studies of Heritability of Dentofacial Phenotypes

The analytical methods in quantitative genetics depend principally on correlations between relatives and on the statistical procedure of analysis of variance. The twin method, where appropriately applied, provides geneticists with one of the most informative techniques available for analysis of complex genetic traits. An alternative method for investigating the role of heredity in determining craniofacial and dental morphology is by familial studies. Heritability in such studies is normally expressed in terms of parent/offspring correlation coefficients or correlation coefficients within sibling pairs, of which twins are a special kind.

The study of craniofacial relationships in twins has provided much useful information concerning the role of heredity in malocclusion. The procedure is based on the underlying principle that observed differences within a pair of monozygotic twins (whose genotype is identical) are due to environment and that differences within a pair of dizygotic twins (who share 50 per cent of their total gene complement) are due to both environment and genotype. A comparison of the observed within-pair differences for twins in the two categories should provide a measure of the degree to which monozygotic twins are more alike than dizygotic twins. The larger this difference between the two twin categories, the greater the genetic effect on variability of the trait. This model implies that zygosity is accurately determined and that environmental effects are equal in the two twin categories. At the present time, accurate zygosity classification is seldom a problem due to the ability to identify the large number of available polymorphic blood group and enzyme markers.

The bulk of the evidence for the heritability of various types of malocclusion arises from family and twin studies.

Class II Division 1 Malocclusion

Extensive cephalometric studies have been carried out to determine the heritability of certain craniofacial parameters in Class II division 1 malocclusions (Harris, 1963, 1975). These investigations have shown that, in the Class II patient, the mandible is significantly more retruded than in Class I patients, with the body of the mandible smaller and overall mandibular length reduced. These studies also showed a higher correlation between the patient and his immediate family than data from random pairings of unrelated siblings, thus supporting the concept of polygenic inheritance for Class II division 1 malocclusions.

Environmental factors can also contribute to the aetiology of Class II division 1 malocclusions. Soft tissues can exert an influence on the position or inclination of upper and lower incisors and the need to achieve lip/tongue contact for an anterior oral seal during swallowing can encourage the lower lip to retrocline the lower incisors and the protruding tongue to procline the uppers, influencing the severity of the overjet. Likewise, digit sucking habits can produce a Class II division 1 incisal relationship, even if the underlying skeletal base relationship is Class I. Lip incompetence also encourages upper incisor proclination by virtue of the imbalance in labial and lingual pressures on the teeth.

Class II Division 2 Malocclusion

Class II division 2 malocclusion is a distinct clinical entity and is a more consistent collection of definable morphometric features occurring simultaneously, i.e. a syndrome than the other malocclusion types put forward by Angle in the early 1900s. Class II division 2 malocclusion 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. This is often accompanied by particular morphometric dental features also, such as a poorly developed cingulum on the upper incisors and a characteristic crown root angulation. Peck *et al*. (1998) also describes characteristic smaller than average teeth when measured mesiodistally, reinforcing a similar observation made by Beresford (1969) and a study by Roberston and Hilton (1965), which found these teeth to be significantly 'thinner' in the labial/lingual dimension. A further feature of the Class II division 2 'syndrome' is a tendency to a forwardly rotating mandibular development, which contributes to the deep bite, chin prominence, and reduced lower face height. This last feature, in turn, has an influence in the position of the lower lip relative to the upper incisors, and an increase in masticatory muscle forces has been reported by Quinn and Yoshikawa (1985). Familial occurrence of Class II division 2 has been documented in several published reports including twin and triplet studies (e.g. Kloeppel, 1953; Markovic, 1992) and in family pedigrees from Korkhaus (1930), Rubbrecht (1930), Trauner (1968) and Peck *et al*. (1998). Markovic (1992) carried out a clinical and cephalometric study of 114 Class II division 2 malocclusions, 48 twin pairs and six sets of triplets. Intra- and interpair comparisons were made to determine concordance/discordance rates for monozygotic and dizygotic twins. Of the monozygotic twin pairs, 100 per cent demonstrated concordance for the Class II division 2 malocclusion, whilst almost 90 per cent of the dizygotic twin pairs were discordant. This is strong evidence for genetics as the main

aetiological factor in the development of Class II division 2 malocclusions.

These studies point to incontestable genetic influence, probably autosomal dominant with incomplete penetrance and variable expressivity. It could also possibly be explained by a polygenic model with a simultaneous expression of a number of genetically determined morphological traits (acting additively), rather than being the effect of a single controlling gene for the entire occlusal malformation. The controversy regarding the aetiology of the Class II division 2 malocclusion arises from a failure to appreciate the synergistic effects of genetics and environment on facial morphology. Ballard (1963), Houston (1975), Mills (1982), and others considered that a high lip line, and a particular lip morphology and behaviour were the main aetiological factors. Graber (1972), Hotz (1974), Meskov (1988), and Markovic (1992) stressed the predominant role of genetic factors in the aetiology of Class II division 2 malocclusions. These views are of course not incompatible if the lower lip morphology, behaviour, and position relative to the upper incisors is considered to be genetically determined or influenced. Aspects of skeletal and muscle morphology are genetically determined and there is some recent experimental evidence from a twin study (Lauweryns *et al*. 1995) indicating strong genetic factors in certain aspects of masticatory muscle behaviour.

Class III Malocclusion

Probably the most famous example of a genetic trait in humans passing through several generations is the pedigree of the so-called Hapsburg jaw. This was the famous mandibular prognathism demonstrated by several generations of the Hungarian/Austrian dual monarchy. Strohmayer (1937) concluded from his detailed pedigree analysis of the Hapsburg family line that the mandibular prognathism was transmitted as an autosomal dominant trait. This could be regarded as an exception and, in itself, does not provide sufficient information to predict the mode of inheritance of mandibular prognathism. Suzuki (1961) studied 1362 persons from 243 Japanese families and noted that, while the index cases had mandibular prognathism, there was a significantly higher incidence of this trait in other members of his family (34·3 per cent) in comparison to families of individuals with normal occlusion (7·5 per cent). Schulze and Weise (1965) also studied mandibular prognathism in monozygotic and dizygotic twins. They reported that concordance in monozygotic twins was six times higher than among dizygotic twins. Both of the above studies report a polygenic hypothesis as the primary cause for mandibular prognathism (Litton *et al*., 1970).

The relative contribution of genetic and environmental factors to Class III has been the subject of a number of previous studies. A Class III malocclusion resulting from a skeletal imbalance between the maxillary and mandibular bases may result from deficiency in maxillary growth, excessive mandibular 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 anterior position of the glenoid fossa, thus contributing to the mandibular prognathism (Ellis and McNamara, 1984; Singh *et al*., 1997).

Familial studies of mandibular prognathism are suggestive of heredity in the aetiology of this condition (Castro, 1928; Downs, 1928; Keeler, 1935; Moore and Hughes, 1942; Gottlieb and Gottlieb, 1954). Various models have been suggested, such as autosomal dominant with incomplete penetrance (Stiles and Luke, 1953), simple recessive (Downs, 1928), variable both in expressivity and penetrance with differences in different racial populations (Kraus *et al*., 1959).

A wide range of environmental factors have also been suggested as contributory to the development of mandibular prognathism. Among these are enlarged tonsils (Angle, 1907), nasal blockage (Davidov *et al*., 1961), congenital anatomic defects (Monteleone and Davigneaud, 1963), hormonal disturbances (Pascoe *et al*., 1960), endocrine imbalances (Downs, 1928), posture (Gold, 1949) and trauma/disease including premature loss of the first permanent molars (Gold, 1949). Litton *et al*. (1970) carried out an analysis of the literature to that date and also analysed a group of probands, siblings and parents with Class III malocclusion, and analysed the results in an effort to determine a possible mode of transmission. Both autosomal dominant and autosomal recessive transmission were ruled out and there was no association with gender since there were equal numbers of males and females. The polygenic multifactorial threshold model put forward by Edwards (1960), however, did fit the data that these authors presented and, accordingly, they proposed a polygenic model with a threshold for expression to explain familial distribution, and the prevalence both within the general population and in siblings of affected persons. They also made the sensible suggestion that different modes of transmission might be operating in different families or different populations.

Soft tissues do not generally play a part in the aetiology of Class III malocclusion, and in fact there is a tendency for lip and tongue pressure to compensate for a skeletal Class III discrepancy by retroclining lower incisors and proclining uppers.

Summary

Polygenic inheritance, by definition, implies that there is scope for environmental modification and many familial and twin studies bear this out. Horowitz *et al*. (1960) studied adult monozygotic and dizygotic twins using lateral skull cephalograms. The statistics derived from their data indicated that there was a highly significant hereditary variation in the anterior cranial base, mandibular body length, and lower face height. In a similar study, Watnick (1972) studied 35 pairs of monozygotic and 35 pairs of dizygotic like-sexed twins using lateral cephalometry. He concluded that the analysis of unit areas within the craniofacial complex represent local growth sites and revealed different modes of control within the same bone. Certain areas, such as the lingual symphysis, lateral surface of the ramus, and frontal curvature of the mandible are predominantly under genetic control. Other areas, such as the antegonial notch, are predominantly affected by environmental factors. This is in line with the conclusions from numerous other studies such as the famous Lundstrom study (1948) and the study by Kraus *et al*. (1959) on six sets of like-sexed triplets. In the latter study 17 skeletal traits from lateral and frontal

cephalograms were studied. Both these studies concluded that although genetic factors appear to govern the basic skeletal form and size, environmental factors in their multitudinous facets have much influence on the bony elements, and both factors combine to achieve the harmonious or disharmonious head and face. The foregoing also provides support for the view of Hughes and Moore (1941) that the mandible and maxilla are under separate genetic control, and that certain portions of individual bones, such as the ramus, body, and symphysis of the mandible are under different genetic and environmental influences.

The simultaneous and synergistic influence of genetics and environment on the development of malocclusion is well illustrated by the Class II division 2 scenario described above. Some workers, such as Graber (1972), Hotz (1974), Meskov (1988) and Markovic (1992) stressed the role of genetic factors in the aetiology of Class II division 2 malocclusions, while others such as Ballard (1963) and Mills (1982) preferred to emphasize the importance of an environmental influence. The truth lies in the interaction between genetics and the environment in the determination of facial and dental morphology.

The literature also provides evidence of a secular trend towards increasing prevalence of malocclusion (Price, 1945; Dixon, 1970; Weiland *et al*., 1996). It is argued that this is proof of an environmental determination of certain types of malocclusion (e.g. Mew, 1981), but this is undoubtedly an over-simplification. The trend towards narrower maxillary arches and greater crowding is compatible with a polygenic multifactorial determination or gene/environment interaction, where certain genetically-determined craniofacial phenotypes will show a greater susceptibility to certain environmental factors. This tendency could be explained, at least in part by the simultaneous increase in interracial mixing which is also a feature of 'westernization'.

Heritability of Local Occlusal Variables

It has been thoroughly documented that measurements of the skeletal craniofacial complex have moderate to high heritablities, while measures of the dento-alveolar portions of the jaws, ie. tooth position and dental relationships are given much less attention in the literature. The popular perception is that because of the adaptability of the dento-alveolar region when subjected to environmental factors, local malocclusions are primarily acquired and would be expected to have low heritabilities. This view is reinforced by evidence that some variables pertaining to the position and occlusion of the teeth have a stronger environmental than hereditary influence (Harris and Smith, 1982). In an analysis of nature versus nurture in malocclusion Lundstrom (1984) concluded that the genetic contribution to anomalies of tooth position and jaw relationship overall is only 40 per cent, with a greater genetic influence on the skeletal pattern than on the dental features.

Evidence from other studies, however, would challenge this view. Lundstrom (1948) studied 50 pairs of monozygotic and 50 pairs of dizygotic twins and concluded that heredity played a significant role in determining, among other factors, width and length of the dental arch, crowding and spacing of the teeth, and degree of overbite. A study by Hu *et al*. (1992) also reported familial similarity in dental archform and tooth position. In a more recent study by King *et al*. (1993) initial treatment records of 104 adolescent sibling pairs, all of whom subsequently received orthodontic treatment, were examined. Heritability estimates for occlusal variations such as rotations, crossbites and displacements, were significantly higher than in a comparable series of adolescents with naturally good occurring occlusions. The explanation offered was that, given genetically-influenced facial types and growth patterns, siblings are likely to respond to environmental factors, e.g. chronic mouth breathing and reduced masticatory stress in similar fashions. The similarity of the sibling pair tooth malpositions and malocclusions may well be because of fundamentally similar craniofacial form, which is genetically determined. They will be diverted to comparable physiological responses leading to the development of similar malocclusions. It is also important to remember that soft tissue morphology and behaviour have a genetic component and they have a significant influence on the dentoalveolar morphology. This concept is described by van der Linden (1966) as the balance between the internal and external functional matrices. For example, in a Class II division 1 malocclusion a short upper lip and low lip level with flaccid lip tone will reduce the external influence and the balance will favour proclination of the upper incisors. On the other hand, a high lip level and more expressive lip behaviour will tend to produce a Class II division 2 incisor relationship. This external matrix is thought to be strongly genetically determined. The internal matrix is determined mainly by tongue posture and behaviour which can be influenced by environmental, as well as a genetic factors.

Genetic Influence on Tooth Number, Size, Morphology, Position, and Eruption

Twin studies have shown that tooth crown dimensions are strongly determined by heredity (Osborne *et al*., 1958). The molecular genetics of tooth morphogenesis with the homeostatic Hox 7 and Hox 8 (now referred to as MSX1 and MSX2) genes being responsible for stability in dental patterning (Mackenzie *et al*., 1992), is confirmation of Butler's field theory (1963). This refers to primate tooth development in evolution with the stability of morphology, eruption pattern and tooth number in the incisor, canine, premolar, and molar domains. As dietary habits in humans adapt from a hunter/gatherer to a defined food culture evolutionary selection pressures are tending to reduce tooth volume, which is manifest in the third molar, second premolar and lateral incisor 'fields'. Hypodontia involving the aforementioned teeth shows a familial tendency and fits the polygenic model (Grahnen, 1956; Gravely and Johnston, 1971), but this evolutionary theory suggests an environmental influence also.

Clinical evidence suggests that congenital absence of teeth and reduction in tooth size are associated, e.g. hypodontia and hypoplasia of maxillary lateral incisors frequently present simultaneously. Numerous pedigrees have been published linking the two characteristics and implying that they are different expressions of the same

disorder. Gruneberg (1965) suggested that a tooth germ must reach a critical size during a particular stage of development or the structure will regress, and Suaraz and Spence (1974) showed that hypodontia and reduction in tooth size are in fact controlled by the same or related gene loci. It is apparent from all the evidence in this respect that tooth size fits the polygenic multi-factorial threshold model.

Supernumerary teeth most frequently seen in the premaxillary region and with a male sex predilection also appears to be genetically determined. Niswander and Sugaku (1963) analysed the data from family studies and have suggested that, like hypodontia, the genetics of the less prevalent condition of supernumerary teeth is under the control of a number of different loci.

The hereditary nature of hypodontia is revealed in familial and twin studies. A study of children with missing teeth found that up to half of their siblings or parents also had missing teeth, while the population prevalence is about 5 per cent (Grahnen, 1956). Markovic (1982) found a high rate of concordance for hypodontia in monozygous twin pairs, while dizygous twin pairs he observed were discordant. These and other previous studies concluded that the mode of transmission could be explained by a single autosomal dominant gene with incomplete penetrance.

Supernumerary Teeth

Brook (1974) reported that the prevalence of supernumerary teeth in British school children is 2·1 per cent in the permanent dentition with a male:female ratio of 2:1. In Hong Kong, however, the prevalence is around 3 per cent with a male:female ratio of 6·5:1 (Davis, 1987). The most common type of supernumerary is a premaxillary conical midline tooth (mesiodens). These are more commonly present in parents and siblings of patients who present, although inheritance does not follow a simple mendalian pattern (Brook, 1984; Mercuri and O'Neill, 1980; Mason and Rule, 1995). Evidence from twins with supernumeraries also supports this theory (Jasmin *et al*., 1993).

Abnormal Tooth Shape

Alvesalo and Portin (1969) provided substantial evidence supporting the view that missing and malformed lateral incisors may well be the result of a common gene defect. Abnormalities in the lateral incisor region varies from peg shaped to microdont to missing teeth, all of which have familial trends, female preponderance, and association with other dental anomalies, such as other missing teeth, ectopic canines, and transposition, suggesting a polygenic aetiology. Aspects of tooth morphology such as the Carabelli trait also seem to be strongly influenced by genes as evidenced by an Australian twin study (Townsend and Martin, 1992).

Ectopic Maxillary Canines

Various studies in the past have indicated a genetic tendency for ectopic maxillary canines (Zilberman *et al*., 1990). Peck *et al*. (1994) concluded that palatally ectopic canines were an inherited trait, being one of the anomalies in a complex of genetically related dental disturbances, often occurring in combination with missing teeth, tooth size reduction, supernumerary teeth, and other ectopically positioned teeth. Previous studies have also shown an association between ectopic maxillary canines and Class II division 2 malocclusion, a genetically-inherited trait (Mossey *et al*., 1994). Peck *et al*. (1997) classified a number of different types of tooth transposition in both maxillary and mandibular arches, with maxillary canine/first premolar class position being the most common. They also provided strong evidence of a significant genetic component in the cause of this most common type of transposition in that there was familial occurrence, bilateral occurrence in a high percentage of cases, female predominance and a difference in different ethnic groups. An increased frequency of associated dental anomalies, tooth agenesis and peg-shaped maxillary lateral incisors were also reported.

Submerged Primary Molars

Primary molar submergence occurs most often in the mandibular arch with a wide variation in the reported general population prevalence, but this would be expected to be less than 10 per cent (Kurol, 1981). The siblings of affected children are likely to also be affected in about 18 per cent of cases, and in monozygous twins there is a high rate of concordance (Helpin and Duncan, 1986) indicating a significant genetic component in the aetiology. A number of other studies provide evidence for genetically determined primary failure of eruption such as those by Kurol (1981), Koyoumdjisky-Kaye and Steigman (1982a,b), and Brady (1990). It is also of interest that a variety of abnormalities are also associated with tooth submergence with a suggestion that this may encompass different manifestations of one syndrome, each manifestation having incomplete penetrance and variable expressivity. Bjerklin *et al*. (1992) and Winter *et al*. (1997) suggested that taurodontism may form part of this syndrome.

Summary

There is considerable evidence suggesting that genes play a significant role in the aetiology of many dental anomalies. Furthermore, a frequency of association of one or more of these dental anomalies coincidentally in the same pedigree suggests some kind of genetically controlled interrelationship. This may add further support to Butler's classic field theory of tooth bud differentiation (Butler, 1939, 1982) and Sperber (1967) speculated that transposition is indicative of faulty field gene function, which would explain why there is an increased occurrence of variations in teeth on either side of transposed teeth. This may also explain the fact that teeth in the critical marginal areas of the dental lamina, lateral incisors, second premolars and third molars are the most vulnerable. The clinical significance of the inheritance of certain dental anomalies is that clinicians should be vigilant in the expectation that the clinical or radiographic detection of one anomaly should alert them to the possibility of other defects in the same individual or other family members. Early diagnosis would enable interceptive paediatric and

orthodontic opportunities in relation to ectopic, missing or malformed teeth,

Practical and Clinical Implications

Skeletal jaw discrepancies and malocclusion of genetic origin can be successfully treated orthodontically, except in extreme cases where surgical intervention is required. This is because it is possible to modify the direction of dentofacial growth using orthodontic appliances and therefore change or forestall morphogenetic abnormalities (Graber, 1969; Harvold *et al*., 1981; Moss and Salentijn, 1997). Orthodontic correction of a malocclusion is in effect altering the phenotypic expression of a particular morphogenetic pattern. The degree to which this can be successfully achieved depends on (a) the relative contribution of each factor to the existing problem, and (b) the extent to which skeletal pattern can be influenced by orthodontic and orthopaedic appliances.

In clinical orthodontics it must be appreciated that each malocclusion occupies its own distinctive slot in the genetic/environmental spectrum and, therefore, the diagnostic goal is to determine the relative contribution of genetics and the environment. The greater the genetic component, the worse the prognosis for a successful outcome by means of orthodontic intervention. The difficulty, of course, is that it is seldom possible to determine the precise contribution from hereditary and environmental factors in a particular case. For example, the simultaneous appearance of proclined maxillary incisors and digit sucking may lead to the assumption that the digit was the sole causative factor, but the effect of the digit may very well be either potentiated or mitigated by other morphological or behavioural features in that particular individual. A similar argument may apply in cases of mouth breathing where the influence of the habit and associated posture is very much dependant on the genetically determined craniofacial morphology on which it is superimposed, and the reason for the habit developing may well be dependant on the morphology in the first place. These senarios are classical examples of the interaction of genotype and environment, and ultimately success of treatment will depend on the ability to ascertain the relative contribution of each.

Every orthodontist believes that it is possible to influence the dento-alveolar regions of the jaws within certain parameters using environmental forces—otherwise orthodontic therapy would be futile. The division in orthodontic opinion arises from the doubt as to whether the skeletal bases can be influenced to any significant effect beyond their genetically-predetermined potential. There is still considerable debate about this as conclusive evidence is lacking in both camps, but what evidence is available from human studies to date tends to support the genetic determination of craniofacial form with a lack of evidence to show any significant long term influence on mandibular or maxillary skeletal bases using orthopaedic appliances. The search for evidence to support the environmental influence on craniofacial growth is not easy and will require randomized clinical trials on longitudinal cohorts of patients treated with various types of appliance using longitudinal growth studies as controls. It is also possible to determine the relative contribution of genes and environment applying genetic modelling and statistical techniques to family and twin data (e.g. Van Cawenberge *et al*., 1996).

If dentofacial structure and malocclusion are primarily genetic, e.g. severe mandibular prognathism or endogenous tongue thrust, then treatment will either be palliative or surgical. The search for a solution would ultimately focus on delineating the responsible genes. Conversely, if components of dentofacial structure and malocclusion have trivial heritabilities, then the search needs to be directed at environmental factors inducing malocclusion during growth and development. The goal would be to identify causes and formulate means of intercepting their negative influences. Such is the case with much of the interceptive orthodontic treatment presently carried out, in which the long-range goal is to permit the face to grow according to its fundamental genetic pattern with minimal obstruction from environmental influences, habit and adverse functional factors. An appropriate dental analogy in environmental manipulation is the reduced caries incidence over the past few decades by introduction of fluoride supplements and public water fluoridation programmes.

The Future

At the present time successful orthodontic interception and treatment of hereditary malocclusion are limited by the extent of our knowledge. Because of (i) lack of research dedicated to this particular problem, e.g. prospective randomized clinical trials, (ii) relatively blunt measuring tools, and (iii) limited knowledge about the genetic mechanisms involved and the precise nature and effects of environmental influences, we are unable to predict with a satisfactory degree of certainty the final manifestation of the growth pattern or the severity of the malocclusion conferred by a particular genotype.

What scientific morphometric evidence can we provide to back up the hypothesis that malocclusion is genetically determined, or to quantify the effect of environmental influences? Since subtle morphological changes are occurring very sensitive techniques and three dimensional models are required to identify these. The limitations of conventional cephalometric analysis are well recognised and more discriminating techniques for craniofacial morphometric analysis have now become available. New techniques such as Procrustes analysis, finite element morphometry, thin plate spline transformations, and Euclidean distance matrix analysis allow computer based morphological analysis of craniofacial configurations that will enable the longitudinal mapping of spatial changes during craniofacial morphogenesis, and from these techniques predictive biomodelling will be possible. Such morphometric computer programmes are being applied to internal craniofacial data obtained derived from lateral and postero-anterior cephalograms (Singh *et al*., 1996), and similar programmes have been or are in the process of being developed for surface data obtained by linear laser scanning (Moss *et al*., 1987) and stereophotogrammetry (Ayoub *et al*., 1996).

On the genetic side the advent of diagnostic techniques in the field of molecular genetics make it possible to identify relevant morphogenes or genetic markers such as those for mandibular prognathism, or to influence the

development of malocclusion, e.g. could crowding be eliminated by selective manipulation of the homeobox gene responsible for initiation of tooth formation and patterning of the dentition? The latter is more of a theoretical concept than a practical proposition, but aspects of orthodontic diagnosis and treatment planning may well take on a completely new meaning as we move into the twenty-first century. Molecular therapeutics is being employed in the field of maxillofacial surgery where knowledge of bone morphogenetic proteins (BMPs) is exploited in therapeutic regeneration in cases of congenital or acquired bone deficiency. It is therefore incumbent on the orthodontic speciality to keep abreast of developments in molecular genetics.

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References

Alvesalo, L. and Portin, P. (1969)
The inheritance patterns of missing, peg-shaped and strongly mesiodistally reduced upper lateral incisors,
Acta Odontological Scandinavica, **27**, 563–575.

Andrews, L. F. (1972)
The six keys to normal occlusion,
American Journal of Orthodontics, **62**, 296–309.

Angle, E. H. (1907)
Treatment of malocclusion of the teeth, 7th edn
S. S. White Manufacturing Company, Philadelphia.

Ayoub, A. F., Moos, K. F. and Wray D. (1996)
Three dimensional reconstruction of the face for Orthognathic Surgical Planning and Evaluation,
Conference presentation at '*Comprehensive management of Craniofacial Asymmetries*' Royal Dental College, University of Aarhus, 23–25 May 1996.

Ballard, C. F. (1963)
Variations of posture and behaviour of the lips and tongue which determine the position of the labial segments; the implications in orthodontics, prosthetics and speech,
Transactions of the European Orthodontic Society, 67–93.

Beresford, J. S. (1969)
Tooth size and class distinction,
Dental Practitioner, **20**, 113–120.

Bjerklin, K., Kurol, J. and Velentin, J. (1992)
Ectopic eruption of maxillary first permanent molars and association with other tooth and developmental disturbances,
European Journal of Orthodontics, **14**, 369–375.

Brady, J. (1990)
Familial primary failure of eruption of permanent teeth,
British Journal of Orthodontics, **17**, 109–113.

Brook, A. H. (1974)
Dental anomalies of number, form and size: their prevalence in British schoolchildren,
Journal of the International Association of Dentistry in Children, **5**, 37–53.

Brook, A. H. (1984)
A unifying aetiological explanation for anomalies of human tooth number and size,
Archives of Oral Biology, **29**, 373–378.

Butler, P. M. (1939)
Studies of the mammalian dentition, differentiation of the post-canine dentition,
Proceedings of the Zoological Society of London, Series B, **109**, 1–39.

Butler, P. M. (1963)
Tooth morphology and primate evolution,
In: *Dental Anthropology, Vol. V, Symposium of the Society for the Study of Human Biology*, (ed. D. Brothwell),
Macmillan Co., New York, pp. 1–14.

Butler, P. M. (1982)
Some problems of the ontogeny of tooth patterns,
In: *Teeth: form, function and evolution* (ed. B. Kurter),
Columbia University Press, New York, pp. 44–51.

Castro, F. M. (1928)
Inherited and causative factors in malocclusion,
Journal of the American Dental Association, **15**, 1250–1260.

Curtner, R. M. (1953)
Predetermination of the adult face,
American Journal of Orthodontics, **39**, 201–217.

Davidov, S., Geseva, N., Donveca, T. and Dehova, L. (1961)
Incidence of prognathism in Bulgaria,
Dental Abstracts, **6**, 240.

Davis, P. J. (1987)
Hypodontia and hyperdontia of permanent teeth in Hong Kong schoolchildren,
Community Dentistry and Oral Epidemiology, **15**, 218–220.

Dixon, G. C. (1970)
The natural history of malocclusion,
Dental Practitioner, **20**, 216–224.

Downs, W. G. (1928)
Studies in the causes of dental anomalies,
Journal of Dental Research, **8**, 267–379.

Edwards, J. H. (1960)
The simulation of Mendelism,
Acta Genetica (Basel), **10**, 63–79.

Ellis, E. and McNamara, J. A., Jr (1984)
Components of adult Class III malocclusion,
Journal of Oral and Maxillofacial Surgery, **42**, 295–305.

Fernex, E., Hauenstein, P. and Roche, M. (1967)
Heredity and craniofacial morphology,
Transactions of the European Orthodontic Society, pp. 239–257.

Gold, J. K. (1949)
A new approach to the treatment of mandibular prognathism,
American Journal of Orthodontics, **35**, 893–912.

Gottlieb, I. and Gottlieb, O. (1954)
Mandibular protrusion in edentulous patients,
Oral Surgery, **7**, 813–821.

Graber, T. M. (1972)
In: *Orthodontics—Principles and Practice* (ed. T. M. Graber) p. 46,
W B Saunders Co, Philadelphia.

Graber, T. M. (1979)
The use of muscle forces by simple orthodontic appliances,
American Journal of Orthodontics, **76**, 1–20.

Grahnen, H. (1956)
Hypodontia in the permanent dentition,
Odontological Revue, **7**, 1100.

Gravely, J. F. and Johnson, D. D. (1971)
Variation in expression of hypodontia in monozygotic twins,
Dental Practitioner, **21**, 212.

Gruneberg, H. (1965)
Genes and genotypes affecting the teeth of the mouse,
Journal of Embryology and Experimental Morphology, **14**, 137–159.

Harris, J. E. (1963)
A multivariate Analysis of the Craniofacial Complex,
School of Dentistry, University of Michigan, Ann Arbor.

Harris, J. E. (1975)
Genetic factors in the growth of the head: inheritance of the craniofacial complex and malocclusion,
Dental Clinics of North America, **19**, 151–160.

Harris, E. F. and Smith, R. J. (1982)
Occlusion and arch size in families: a principal components analysis,
Angle Orthodontist, **52**, 135–143.

Harvold, E. P., Toner, B. S., Vargervik, K. and Chierici, G. (1981)
Primate experiments on oral respiration,
Americal Journal of orthodontics, **79**, 359–372.

Helpin, M. L. and Duncan, W. K. (1986)
Ankylosis in monozygotic twins,
Journal of Dentistry for Children, **53**, 135–139.

Horowitz, S. L., Osborne, R. H. and DeGeorge, F. V. (1960)
A cephalometric study of craniofacial variation in adult twins,
Angle Orthodontist, **30**, 1–5.

Hotz, R. (1974)
Orthodontics in Daily Practice,
Hans Huber Publishers, Bern.

Houston, W. J. B. (1975)
Orthodontic Diagnosis,
John Wright, Bristol.

Hu, J. P., Nakasima, A. and Takayama, Y. (1992)
Familial similarity in dental archtorm and tooth position,
Journal of Craniofacial Genetics and Developmental Biology, **12**, 33–40.

Hughes, B. O. and Moore, G. R. (1941)
Heredity, growth, and the dento-facial complex,
*Angle Orthodontist, **11***, 127–122.

Hunter, W. S. (1965)
A study of the inheritance of craniofacial characteristics as seen in lateral cephalograms of 72 like sexed twins,
European Orthodontic Society Report of Congress, **41**, 59–70.

Hunter, W. S., Ballouch, D. R. and Lamphiear, D. E. (1970)
The heritability of attained growth in the human face,
*American Journal of Orthodontics, **58***, 128–134.

Jasmin, J. R., Jonesco-Benaiche, N. and Muller-Giamarchi, M. (1993)
Supernumerary teeth in twins,
Oral Surgery Oral Medicine Oral Pathology, **76**, 258–259.

Keeler, C. E. (1935)
Heredity in dentistry,
Dental Cosmos, **77**, 1147.

King, L., Harris, E. F. and Tolley, E. A. (1993)
Heritability of cephalometric and occlusal variables as assessed from siblings with overt malocclusions,
American Association of Orthodontics, **104**, 121–131.

Kloeppel, W. (1953)
Deckbiss bei Zwillingen,
Fortschr Kieferorthop, **14(2)**, 130–135.

Korkhaus, G. (1930)
Investigations into the inheritance of orthodontic malformations,
Dental Record, **50**, 271–280.

Koyoumdjisky-Kaye, E. and Steigman, S. (1982a)
Ethnic variability in the prevalence of submerged primary molars,
Journal of Dental Research, **61**, 1401–1404.

Koyoumdjisky-Kaye, E. and Steigman, S. (1982b)
Submerging primary molars in Israeli rural children,
Community Dentistry and Oral Epidemiology, **10**, 204–208.

Kraus, B. S., Wise, W. J. and Frei, R. H. (1959)
Heredity and the craniofacial complex,
American Journal of Orthodontics, **45**, 172–217.

Kurol, J. (1981)
Infraocclusion of primary molars: an epidemiologic and family study,
Community Dentistry and Oral Epidemiology, **9**, 94–102.

Lauweryns, I., Careris, R., Vlientinck, R. and van Steenberghe, D. (1995)
The poststimulus EMG complex: a genetic study in twins,
Journal of Dental Research, **74**, 583.

Litton, S. F., Ackermann, L. V., Issacson, R. and Shapiro, B. L. (1970)
A genetic study of Class III malocclusion,
American Journal of Orthodontics, **58**, 565–577.

Lundstrom, A. (1948)
Tooth Size and Occlusion in Twins, 2nd edn,
S Karger A G, Basel.

Lundstrom, A. (1984)
Nature versus nurture in dentofacial variation,
European Journal of Orthodontics, **6**, 77–91.

MacKenzie, A., Ferguson, M. W. J. and Sharpe, P. T. (1992)
Expression patterns of the homeobox gene, Hox-8, in the mouse embryo suggest a role in specifying tooth initiation and shape,
Development, **115**, 403–420.

Margolis, H. L., Hodge, T. A. and Tanner, J. M. (1968)
Familial similarities in the craniofacial complex,
In: *Oral Facial Genetics* (eds R. E. Stewart and G. H. Prescott); *C V Mosby Company, St Louis, p. 93*.

Markovic, M. D. (1982)
Hypodontia in twins,
Swedish Dental Journal Supplement, **15**, 153–162.

Markovic, M. D. (1992)
At the cross-roads of orofacial genetics,
European Journal of Orthodontics, **14**, 469–481.

Mason, C. and Rule, D. C. (1995)
Midline supernumeraries: a family affair,
Dental Update, **22**, 34–35.

Mercuri, L. G. and O'Neill, R. (1980)
Multiple impacted and supernumerary teeth in sisters,
Oral Surgery Oral Medicine Oral Pathology, **50**, 293.

Meskov, M. (1988)
Morfoloski varijacii na kraniofacijalniot sistem kaj lica so maloklazija klasa II, 2. oddelenie,
Makedonska kniga, Skopje.

Mew, J. (1981)
The aetiology of malocclusions: can the tropic premise assist our understanding,
British Dental Journal, **15**, 296–302.

Mills, J. R. E. (1982)
Principles and Practice of Orthodontics,
Churchill Livingstone, Edinburgh.

Monteleone, L. and Duvigneaud, J. D. (1963)
Prognathism,
Journal of Oral Surgery, **21**, 190–195.

Moore, G. R. and Hughs, B. O. (1942)
Familial factors in diagnosis, treatment and prognosis of dentofacial disturbances,
American Journal of Orthodontics and Oral Surgery, **28**, 603–639.

Moss, M. L. and Salentijn, L. (1997)
Melvin L. Moss and the functional matrix,
Journal of Dental Research, **76(12)**, 1814–1817.

Moss, J. P., Linney, A. D., Grindrod, S. R., Arridge, S. R. and Clifton, J. S. (1987)
Three-dimensional visualisation of the face and skull using computer tomography and laser scanning techniques,
European Journal of Orthodontics, **9**, 247–253.

Moss, M. L. and Salentijn, L. (1969)
The capsular matrix,
American Journal of Orthodontics, **56**, 474–489.

Mossey, P. M., Campbell, H. M. and Luffingham, J. K. (1994)
The palatal canine and the adjacent lateral incisor: a study of a West of Scotland Population,
British Journal of Orthodontics, **21**, 169–174.

Niswander, J. D. and Sugaku, C. (1963)
Congenital anomalies of teeth in Japanese children,
American Journal of Physical Anthropology, **21**, 569–574.

Osborne, R. H., Horowitz, S. L. and DeGeorge, F. V. (1958)
Genetic variations in tooth dimensions; a twin study of permanent anterior teeth,
American Journal of Human Genetics, **10**, 350–359.

Pascoe, J., Hayward, J. R. and Costich, E. R. (1960)
Mandibular prognathism, its etiology and a classification,
Journal of Oral Surgery, **18**, 21–24.

Peck, S., Peck, L. and Kataja, M. (1994)
The palatally displaced canine as a dental anomaly of genetic origin,
Angle Orthodontist, **64**, 249–256.

Peck, S., Peck, L. and Hirsh, G. (1997)
Mandibular lateral incisor—canine transposition in monozygotic twins,
Journal of Dentistry for Children, **64**, 409–413.

Peck, S., Peck, L. and Kataja, M. (1998)
Class II Division 2 malocclusion: a heritable pattern,
Angle Orthodontist, **68**, 9–17.

Price, W. A. (1945)
Nutrition and Physical Degeneration,
Redlands, California. Series of reports produced by the author.

Quinn, R. S. and Yoshikawa, D. K. (1985)
A reassessment of force magnitude in orthodontics,
American Journal of Orthodontics, **88**, 252–260.

Robertson, N. R. E. and Hilton, R. (1965)
Feature of the upper central incisors in Class II, Division 2,
Angle Orthodontist, **35**, 51–53.

Rubbrecht, O. (1930)
Les variations maxillo-faciale sagittales et l'hérédité mendélienne,
Revue Belge Stomat, **27**, 1–24, 61–91, 119–153.

Schulze, C. and Weise, W. (1965)
Zur Vererburg der Progenie,
Fortschr fte Kieferorthop, **26**, 213–229.

Singh, G. D., McNamara, J. A., McGill, J. S. and Lozanoff, S. 91996)
Morphometric analyses of craniofacial morphology in patients with Class III malocclusion,
Clinical Anatomy, **9**, 3.

Singh, G. D., McNamara, J. A. and Lozanoff, S. (1997)
Finite element analysis of the cranial base in subjects with Class III malocclusion,
British Journal of Orthodontics, **24**, 103–112.

Sperber, G. H. (1967)
Genetic mechanisms and anomalies in odontogenesis,
Journal of the Canadian Dental Association, **33**, 433–442.

Stein, K. F., Kelly, T. J. and Wood, E. (1956)
Influence of heredity in the etiology of malocclusion,
American Journal of Orthodontics, **42**, 125–141.

Stiles, K. A. and Luke, J. E. 91953)
The inheritance of malocclusion due to mandibular prognathism,
Journal of Heredity, **44**, 241–245.

Stockhard, C. H. (1941)
The Genetic and Endocrine Basis for Differences in Form and Behaviour,
Wistar Institute of Anatomy and Biology, Philadelphia.

Strohmayer, W. (1937)
Die Vereburg des Hapsburger Familientypus,
Nova Acta Leopoldina, **5**, 219–296.

Stewart, R. E. and Spence, M. A. (1976)
The genetics of common dental diseases,
In: *Oral Facial Genetics* (eds R. E. Stewart and G. H. Prescott),
C V Mosby Co., St Louis, pp. 81–104.

Suarez, B. K. (1974)
The genetics of tooth size in man,
PhD Thesis, University of California at Los Angeles.

Suarez, B. K. and Spence, M. A. (1974)
The genetics of hypodontia,
Journal of Dental Research, **53**, 781–785.

Suzuki, S. (1961)
Studies on the so-called reverse occlusion,
Journal of the Nihon University School of Dentistry, **5**, 51–58.

Townsend, G. C. and Martin, N. G. (1992)
Fitting genetic models to Carabelli trait data in South Australian twins,
Journal of Dental Research, **71**, 403–409.

Trauner, R. 91968)
Leitfaden der praktischen Kieferorthopedie,
Verlag Die Quintessenz, Berlin, pp. 20–21.

Van Cawenberge, N., Carels, C., Loos, R. and Vlietinck (1996)
Genetic modelling of dentofacial data from monozygotic and dizygotic twins,
In: *Proceedings of European Orthodontic Society Meeting*, Brighton, July 1996 (Abstract).

van der Linden, F. P. G. M. (1966)
Genetic and environmental factors in dentofacial morphology,
American Journal of Orthodontics, **52**, 576–583.

Watnick, S. S. (1972)
Inheritance of craniofacial morphology, *Angle Orthodontist*, **42**, 339–351.

Weiland, F., Droschl, H., Bentleon, H. P. and Jonke, E. (1996)
Secular changes in malocclusion in adult males,
In: *Proceedings of European Orthodontic Society Meeting*, Brighton, July 996 (Abstract).

Winter, G. B., Gelbier, M. J. and Goodman, J. R. (1997)
Severe infra-occlusion and failed eruption of deciduous molars associated with eruptive and developmental disturbances in the permanent dentition: a report of 28 selected cases,
British Journal of Orthodontics, **24**, 149–157.

Zilberman, Y., Cohen, B. and Becker, A. (1990)
Familial trends in palatal canines, anomalous lateral incisors, and related phenomena,
European Journal of Orthodontics, **12**, 135–139.