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Science Section

The Heritability of Malocclusion: Part 1—Genetics, Principles and Terminology

P. A. MOSSEY, B.D.S., PH.D., D.ORTH., M.ORTH., F.D.S., F.F.D.

Unit of Dental and Oral Health, Dundee Dental School, Park Place, Dundee DD1 4HR, UK

Abstract: *The relative contribution of genes and the environment to the aetiology of malocclusion has been a matter of controversy throughout the twentieth century. Genetic mechanisms are clearly predominant during embryonic craniofacial morphogenesis, but environment is also thought to influence dentofacial morphology postnatally, particularly during facial growth. Orthodontic and orthopaedic techniques are used in the treatment of malocclusion and other dentofacial deformities, but with limited effectiveness. The key to the determination of the aetiology of malocclusion, and its treatability lies in the ability to differentiate the effect of genes and environment on the craniofacial skeleton in a particular individual. Our ability to do this is limited by our lack of knowledge on the genetic mechanisms that control facial growth and lack of scientific evidence for the influence of environmental factors on human craniofacial morphogenesis.*

Index words: Craniofacial Growth, Environment, Genetics, Malocclusion, Orthodontic Treatment.

Refereed Paper

Genetics, Principles and Terminology

Genotype and Phenotype

The science of genetics is concerned with the inheritance of traits, whether normal or abnormal, and with the interaction of genes and the environment. This latter concept is of particular relevance to medical genetics, since the effects of genes can be modified by the environment.

Consideration of the heritability of a particular feature or trait requires a consideration of the relationship between genotype and phenotype. Genotype is defined as the genetic constitution of an individual, and may refer to specified gene loci or to all loci in general. An individual's phenotype is the final product of a combination of genetic and environmental influences. Phenotype may refer to a specified character or to all the observable characteristics of the individual. The proportion of the phenotypic variance attributable to the genotype is referred to as heritability.

Genetic variation in man may be observed at two levels. In specific traits individual genotypes are readily identified and differences are qualitative (discrete), for example, the ABO blood antigen system. Gene frequencies can be estimated and the Mendelian type of analysis can be applied. In continuous traits such as height, weight, or tooth size differences are characterized quantitatively between individuals. These quantitative traits in man are more elusive to study because they are determined by the alleles of many gene loci and, therefore, the Mendelian type of analysis is not appropriate. They are further modified by environmental conditions which obscure the genetic picture. If the genetic variation of a particular phenotypic trait is dependent on the simultaneous segregation of many genes and affected by environment it is referred to as being subject to multifactorial inheritance. Genetic differences caused by the segregation of many genes is referred to as

polygenic variation and the genes concerned are referred to as polygenes. These genes are, of course, subject to the same laws of transmission and have the same general properties as the single genes involved in qualitative traits, but segregation of genes is translated into genetic variations seen in continuous traits through polygenes.

Different types of genetic 'product' can be thought of as being different distances from the fundamental level of gene activity. Enzymes, for instance, are almost direct products of gene action and, in most cases where genetic variation of enzyme structure has been demonstrated, it has been shown that a single locus is responsible for the structure of a single enzyme. The structure and, consequently, the activity of an enzyme is therefore usually simply and directly related to allele substitutions at a single locus. Morphological characters, on the other hand, such as the numerous dimensions used to describe the shape of the face and jaws, are furthest removed from the fundamental genetic level and are the end results of a vast complexity of interacting, hierarchical, biochemical, and developmental processes. Each gene is therefore likely to influence many morphological characters so that a deleterious mutation, although producing a unitary effect at the molecular level, almost always results in a syndrome of morphological abnormalities. When a gene is known to affect a number of different characters in this way its action is said to be pleiotropic. A reverse hierarchy also exists, making each morphological character dependent on many different genes.

Modes of Inheritance

Population genetics deals with the study of the mode of inheritance of traits and the distribution of genes in populations.

All chromosomes exist in pairs so our cells contain two

copies of each gene, which may be alike or may differ in their substructure and their product. Different forms of genes at the same locus or position on the chromosome are called alleles. If both copies of the gene are identical, the individual is described as homozygous, while if they differ, the term used is heterozygous.

The exception to the rule that cells contain pairs of chromosomes applies to the gametes, sperm and ovum, which contain only single representatives of each pair or chromosomes, and therefore, of each pair of genes. When the two gametes join at fertilization, the new individual produced again has paired genes, one from the father and one from the mother. If a trait or disease manifests itself when the affected person carries only one copy of the gene responsible, along with one normal allele, the mode of inheritance of the trait is called dominant (Figure 1a). If two copies of the defective gene are required for expression of the trait, the mode of inheritance is called recessive (Figure 1b).

The special case of genes carried on the X chromosome produces yet different pedigrees. Since male-to-male transmission is impossible and since females do not express the disease when they carry only one copy of the disease gene (since it is modified by the homologous X chromosome), the usual pedigree consists of an affected male with clinically normal parents and children, but with affected brothers, maternal uncles, and other maternal male relatives (Figure 1c). This mode of inheritance is described as X-linked recessive.

It has been long appreciated that many normal traits, such as height, intelligence, and birth weight, have a significant genetic component, as do a number of common diseases, such as diabetes mellitus, schizophrenia, hypertension, and cleft lip and palate. However, the pattern of inheritance of these traits does not follow the simple modes just described. Mathematical analysis of many of these has led to the conclusion that they follow the rules of polygenic inheritance, that is, are determined by a constellation of several genes, some derived from each parent.

The determination of heritability for polygenic or multifactorial characters is difficult, as a feature of continuous variation is that different individuals may occupy the same position on the continuous scale for different reasons. Using mandibular length as an example, micrognathia can occur in chromosomal disorders, such as Turner's Syndrome, in monogenic disorders such as Treacher Collins Syndrome or Sticklers Syndrome, or due to an intra-uterine environmental problem, such as foetal alcohol syndrome. Combined with this the concept of aetiological heterogeneity encompasses the principle of the same gene defect producing different phenotypic anomalies, and syndromes can be due to defective gene activity in different cells. Conversely, different gene defects or combinations of defective genes can produce a similar phenotypic abnormality. Genetic lethality or reduced reproductive fitness can also complicate the diagnostic picture and genomic imprinting can result in a gene defect 'skipping' a generation. These complexities serve to hamper progress in the understanding of polygenic or multifactorial disorders such as orofacial clefting.

Multifactorial inheritance. In contrast to single-gene inheritance, either autosomal or sex-linked, the pedigree

pattern does not afford a diagnosis of multifactorial inheritance. In multifactorial traits, the trait is determined by the interaction of a number of genes at different loci, each with a small, but additive effect, together with environmental factors (i.e. the genes are rendering the individual unduly susceptible to the environmental agents). Many congenital malformations and common diseases of adult life are inherited as multifactorial traits and these are categorized as either continuous or discontinuous.

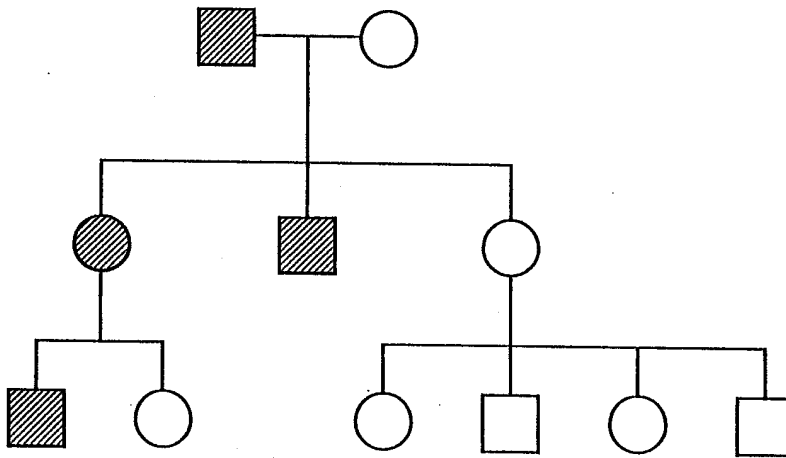
Discontinuous multifactorial traits. This describes traits determined by multiple gene loci which are present or absent depending on the number or nature of the genetic, and/or environmental factors acting. When present these traits can vary continuously. The accepted explanation of discontinuous multifactorial variation rests on the assumption that there is an underlying scale of continuous variation of liability to develop the condition resulting from a combination of all the genetic and environmental influences involved. The condition is present only when the liability exceeds a critical threshold value, and the greater the level of liability beyond the threshold the more severe the disease.

More than 20 discontinuous multifactorial traits have been described in humans. Cleft lip and palate is a congenital malformation inherited as a multifactorial trait. In the mildest form the lip alone is unilaterally cleft, whereas in the most severe form the lip is bilaterally cleft and the palatal cleft is complete. The parents of a cleft lip and palate proband are often unaffected, and there may be no family history of cleft lip and palate, but by producing an affected child the parents are deemed to have some underactive genes for lip and palate formation. However, the parents must have sufficient normally active genes to have normally formed lips and palates. Only when the balance exceeds a certain threshold will the malformation occur, and the further the threshold is exceeded, the greater the extent of the malformation. For parents (first-degree relatives) of an affected child the liability curve is shifted to the right (see Figure 2), and so we would expect to find an increased frequency of this malformation amongst parents and other first-degree relatives. With each further degree of relationship the liability curve moves back a step towards the general population position, with a corresponding reduction in the incidence.

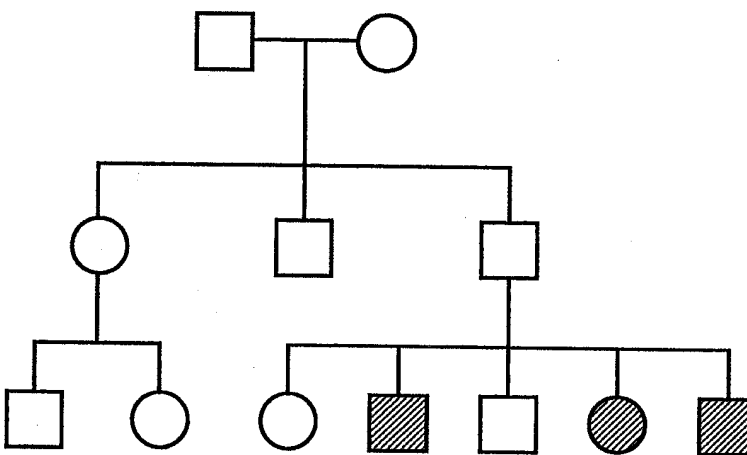
The more severe the malformation in the affected child, the more the parents' liability curve is shifted to the right and the higher the incidence in relatives. Thus, 5% of first-degree relatives are affected if the clefting is bilateral and complete, whereas only 2% are affected if unilateral and incomplete.

Some multifactorial traits show an unequal sex ratio. The incidence is increased in the relatives of affected males, but is even more increased in the relatives of affected females. This indicates that for this malformation the female threshold is higher than the male threshold. The parents of an affected female therefore reveal themselves to have a higher proportion of underactive genes, a more displaced liability curve and, hence, they would be at greater risk of having further affected or more severely affected children (especially if male).

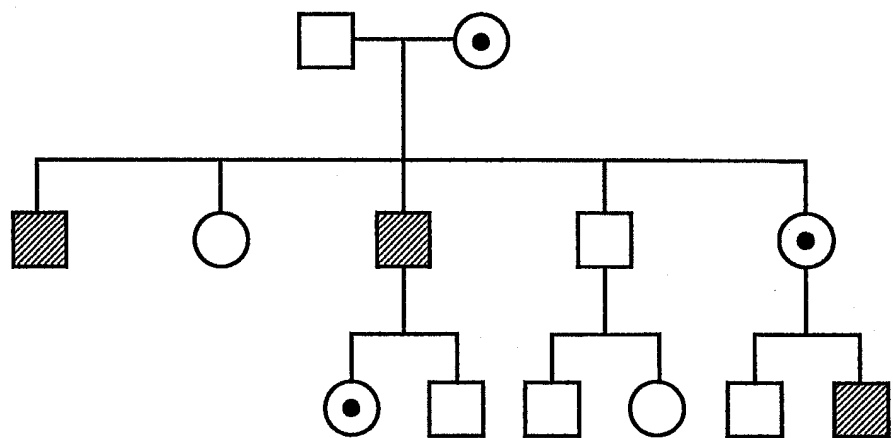
In the analysis of a discontinuous trait it is first necessary to show that the incidence in members of affected families



(a) Autosomal dominant pedigree.



(b) Autosomal recessive pedigree.



(c) X-linked recessive pedigree.

FIG. 1

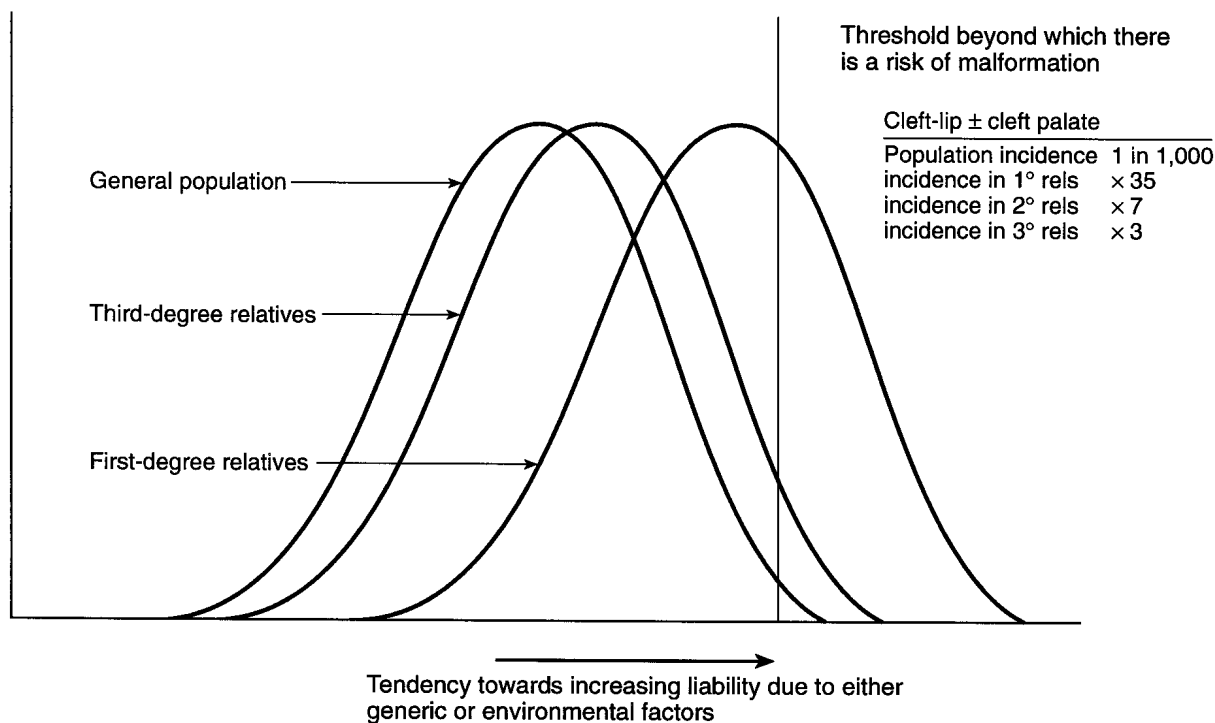


FIG. 2 Multifactorial threshold model.

is increased above the general population incidence. If the incidence is not increased the condition is probably non-genetic. If it is increased, the pedigree pattern is examined for evidence of single-gene inheritance. If multifactorial inheritance is then suspected, studies of twin concordance and family correlation are necessary.

Continuous multifactorial traits. Many normal human characteristics are determined as continuous multifactorial traits. These traits by definition have a continuously graded distribution. Thus, for height there is a range from the very tall to the markedly short with the mean of 169 ± 6.5 cm in English males (Connor and Ferguson Smith, 1993). The majority of individuals are centred around the mean. Such distribution is characteristic of a continuous multifactorial trait. It is important to put malocclusion in context in this regard—malocclusion should be regarded not as abnormal or as a disease, but as a variation of occlusion in a continuous multi-factorial trait. Orthodontists may try to impose a threshold according to treatment need or complexity of mechanical treatment, but this is superimposed on an infinite range of biological variation.

Aetiologic heterogeneity. Both continuous and discontinuous variation have a multifactorial basis so that different patients are not necessarily affected for the same reasons. Thus, although for the majority of CL(P) patients no single cause can be identified, the malformation can be found in chromosomal disorders for example the Wolf-Hirschhorn syndrome and trisomy 13 (Patau's syndrome), in monogenic disorders such as the Van der Woude and popliteal pterygium syndromes. It may also be associated with environmental teratogens such as alcohol, cigarette

smoke and anticonvulsant drugs. Furthermore, there is evidence for genotype-environment interaction in orofacial clefting, with certain major genes conferring susceptibility to particular teratogenic agents (Hwang *et al.*, 1995; Shaw *et al.*, 1996).

Population Genetics

Since each chromosome carries hundreds or thousands of genes in a linear order, and there is intra-species specificity in the gene order, i.e. the same chromosomes contain the same genes, chromosome maps can be constructed. This enables studies of genetic linkage and association—usually done by studying the coinheritance of specific alleles of two or more genes within families. Linkage refers to the closeness of two genes in any of their allelic forms on the same chromosome. The term association is used when a specific allele of a gene is associated with a particular condition more frequently than by chance (e.g. alleles of the *TGF α* gene and clefting), and may imply something about the physiological function of the product of that allele.

Two more terms commonly used in population genetics are penetrance and expressivity. Penetrance is a statistical term and indicates the proportion of individuals carrying a certain gene who can be detected. As our ability to detect the expression of a gene improves, the penetrance increases. Expressivity refers to the degree of expression of a gene in an individual. For example, full expressivity for osteogenesis imperfecta would include fragile bones, dentinogenesis imperfecta, blue sclerae, and deafness. The presence of one or two of these findings comprises partial expressivity, while the absence of all four occasionally found in carriers of this gene, is zero expressivity.

Population genetics is also concerned with the distribution of genes in the human population. The frequency of various alleles, normal or abnormal, may vary from group to group. The information required to make a decision about the inheritance of a disease can only be obtained through a complete family history with attention to all the factors mentioned above. It is, however, important to appreciate that positive findings in the family history does not eliminate the possibility of an inherited disease, since new mutations, decreased penetrance, or undetected heterozygosity of the parents often mask genetic factors.

Twin studies. Twins are concordant if they both show a discontinuous trait and discordant if only one shows the trait. As twins usually share a similar family environment it may be difficult to separate the relative extent of environmental (nurture) and genetic contributions (nature) to a multifactorial trait (Emery and Mueller, 1992).

Monozygotic twins have identical genotypes (with some rare exceptions, see below), whereas dizygotic twins are only as alike as siblings. If a condition has no genetic component, for example due to chance or trauma, concordance rates would be expected to be similar for both types of twins. For a single-gene trait or a chromosomal disorder the monozygotic concordance rate will be 100%, whereas the dizygotic rate will be less than this and equal to the rate in siblings. For discontinuous multifactorial traits with both genetic and environmental contributions, the rate in monozygotic twins, although less than 100%, will exceed the rate in dizygotic twins.

In cleft studies, the monozygotic twin concordance rate for CL(P) and for CP is 35 and 26 per cent, respectively, and for dizygotic twins 5 and 6 per cent, respectively (Connor and Ferguson-Smith, 1993). This reflects the heritability of the condition: the higher the monozygotic concordance, the more important the genetic contribution, and so the higher the heritability.

Genetic Mutation

Although gene alleles are usually transmitted unaltered from one generation to the next, rare events occur that cause changes within them. These events are called mutations and an allele that has undergone such a change is transmitted in its new mutant form. If it occurs during gametogenesis the mutant allele will appear in a gamete and, consequently, in cells throughout the body of any resulting individual. If it occurs after fertilization, as a somatic mutation, only a proportion of cells will be affected.

Mutations of DNA are broadly divisible into length mutations with gain or loss of genetic material, and point mutations with alteration of the genetic code, but no gain or loss of genetic material.

Large deletions remove many adjacent genes (contiguous gene disorders) and these should be suspected if a boy has several X-linked disorders or if a patient with a single-gene disorder has unexplained mental retardation and/or other congenital malformations. In a point mutation a single nucleotide base is replaced by a different nucleotide base [*transitions* of purine to purine or pyrimidine to pyrimidine adenine (A)–guanine (G) or thymine (T)–cytosine (C);

transversions if purine to pyrimidine or vice versa, G–C or A–T]. Most point mutations are spontaneous and unexplained, but certain factors, such as mutagenic chemicals and ionizing radiation, can increase the spontaneous mutation rate. In the absence of such agents, the mutation rate is in the order of one base pair substitution for every billion base pairs replicated.

There are four main groups of chemicals which cause DNA mutations: base analogues which mimic standard bases, but pair improperly (e.g. 5-bromouracil); alkylating agents which add alkyl groups to bases and so hamper correct pairing (e.g. nitrogen mustard or ethyl methane-sulphonate); intercalating agents which intercalate with DNA and distort its structure (e.g. deamination by hydroxylamine). As a rule, these mutagens produce point mutations, and the number produced is a function of the concentration of the chemical and duration of exposure. In contrast X-rays rarely cause point mutations, but lead to chromosomal breakage. Ultraviolet light can cause several different types of mutation.

The majority of mutations are likely to cause reduced fitness, a reduced ability of the resulting zygote to contribute progeny to the next generation. In this way, harmful genes tend to be eliminated from the population so that only the more favourable new variants remain. This is natural selection and is responsible for sorting out the best genes for a particular environment. Nevertheless, because mutation occurs at every generation, disadvantageous alleles are always being produced. A balance between the production of disadvantageous alleles through mutation and their elimination by selection results in a permanent presence of harmful alleles in the population, albeit at a low frequency. It is these alleles that are responsible for inherited disease or susceptibility to disease.

Recent Advances in Genetics and Molecular Biology

Craniofacial development in the embryo. Recent advances in molecular biology and in human genetics have had a considerable influence in the understanding of orofacial genetics. The Orthodontic speciality is faced with the evidence that genetic factors play a predominant role in the aetiology of malocclusion (Markovic, 1992). This is backed up by population studies, especially family and twin studies (Lundstrom, 1954; Schulze and Weise, 1965; Johnston and Hunter, 1989). However, these studies have also occasionally revealed remarkable differences between parents and children, between siblings and even between members of monozygotic twin pairs (Stewart and Spence, 1976), emphasizing the significant role of environmental factors in the development of occlusion.

Some insight into the genetic mechanisms involved in craniofacial morphogenesis at the molecular level in the embryo assists our appreciation of the role of genetics, not only in the aetiology of craniofacial abnormalities, but also in the regulation of maxillary, mandibular, and tooth morphology.

Facial development in the embryo is demarcated by the appearance of the pre-chordal plate (the cranial end of the embryo) on the fourteenth day of development. One of the most unusual features of vertebrate facial development is the origin of the facial mesenchyme which arises from

neural crest cells. Unusually, they disrupt the ectodermal-mesodermal junction and migrate into the underlying tissue as ectomesenchymal cells. Migration and division of neural crest cells are extremely important in facial development. During their migration they undergo a number of interactions with the extra-cellular matrix, and with adjacent epithelia to determine the nature and patterning of the neural, skeletal and connective tissue structures they will form. Among the derivatives of the cephalic neural crest cells are the maxilla, mandible, zygomatic, nasal bones, and bones of the cranial vault.

Although the cessation of neural crest cell migration and the factors that cause neural crest cells to localize in particular regions are not yet completely understood, their migration into the branchial arches occurs in a highly regulated manner. This process is presumed to be under the control of genes known as homeobox genes, which endow neural crest cells (NCC) with a positional identity, which mediates aspects of craniofacial morphogenesis and patterning.

The role of cell adhesion molecules. Cell adhesion molecules such as cadherins, integrins, immunoglobulins, and proteoglycans are glycoproteins on the external surface of the cell membranes, and are thought to be important in embryogenesis, particularly organ formation. In craniofacial development the precise positioning of the neural crest cells in the branchial arches may involve changes in expression of cell adhesion molecules are expressed and down regulated in neural crest cells during their pre-migratory and migratory stages. The down regulation of molecules such as the cadherins could alter the attachment of cells to one another allowing them to migrate (Baldwin *et al.*, 1996; Kerrigan *et al.*, 1998). At a somewhat later stage, the cell adhesion molecule, syndecan, is expressed as the palatal shelves elevate from vertical to horizontal, and expression decreases during fusion (Fitchett *et al.*, 1990). It is thought that these changes in expression are due to epithelial mesenchymal interactions, and during the medial edge epithelium breakdown at the time of palatal shelf fusion there is an increased expression of N-cadherin. This may be instrumental in the transformation of epithelium to its different phenotypes (nasal and oral) and into mesenchyme. Epithelial mesenchymal interaction during the bud and cap stages of tooth follicle formation is also thought to be dependent on the action of cell adhesion molecules, especially syndecan (Bernfield *et al.*, 1993).

The role of homeobox genes. Homeobox genes are genes which are highly conserved throughout evolution of diverse organisms and are now known to play a role in patterning the embryonic development. As such, they are likely to be fundamental in evolution of the specialised body parts of many animal species and the differences between different organisms can be explained by the different modes of action of the homeobox genes. These can also be regarded as master genes of the head and face controlling patterning, induction, programmed cell death, and epithelial mesenchymal interaction during development of the craniofacial complex.

Those of particular interest in craniofacial development include the Hox group, Msx1 and Msx2 (muscle segment),

Dlx (distalless), Otx (orthodental), Gsc (gooseoid), and Shh (sonic hedgehog). The proteins encoded by these homeobox genes are transcription factors which control the transcription of RNA from the DNA template within the cell nucleus. Transcription factors can switch genes on and off by activating or repressing gene expression, and therefore control other genes producing a co-ordinated cascade of molecular events which, in turn, control patterning and morphogenesis (Thesleff, 1995). At a cellular level this control is expressed through two main groups of regulatory proteins, the **growth factor** family and the **steroid/ thyroid/ retinoic acid** super family (Evans, 1988). These regulatory molecules in the mesenchyme such as fibroblast growth factor (FGF), epidermal growth factor (EGF), transforming growth factor alpha (TGF α), transforming growth factor beta (TGF β), and bone morphogenetic proteins (BMPs) are the vehicles through which homeobox gene information is expressed in the co-ordination of cell migration and subsequent cell interactions that regulate growth (Johnston and Bronsky, 1995). By this means different parts of the DNA are activated in different cells regulating the different proteins, enzymes, etc., produced by different tissues and organs. These mechanisms will hold the key to understanding disease and dysmorphology, and are the subject of intensive research in craniofacial biology. Some examples relevant to craniofacial development serve to illustrate how this is providing new insights.

Molecular genetics in oral and craniofacial dysmorphology. Molecular genetics studies using animal models for human malformations enables elucidation of pathogenetic mechanisms. For example, mice with retinoic acid syndrome (RAS) have illustrated major neural crest cell involvement (Sulik *et al.*, 1988) and in similar human syndromes such as hemifacial microsomia neural crest involvement is implicated. Later administration of retinoic acid in mice in excessive doses kills ganglionic placodal cells and leads to a malformation complex virtually identical to the Treacher Collins syndrome.

Craniosynostosis, premature closure of cranial sutures, is a common birth defect in humans, occurring in approximately 1:2500 live births (Cohen, 1993) and premature suture closure has also been found to have its origins in neural crest cell disorders. Through molecular genetics the mechanisms which underlie craniosynostosis are beginning to be unravelled. Considerable progress in elucidating the developmental origin and morphogenesis of a craniofacial skeleton has been made through pioneering studies by Noden (1991) and by Couly and colleagues (1993).

Mutations in fibroblast growth factor (FGF) receptor genes are known to affect suture development in mice and humans, and such mutations have been found to occur in Apert, Crouzon and Pfeiffer syndromes (Wilkie, 1997). In suture formation the FGF is thought to provide a signal from the dura mater preventing cells from undergoing premature ossification at presumptive sutures (Opperman *et al.*, 1995), and the FGF receptor mutation disrupts these progenitor osteoblast cells to differentiate and causes fusion to occur prematurely. Also, mutations in two transcription factors, MSX2 and TWIST, cause Boston type craniosynostosis and Saethre-Chotzen syndrome respectively (Jabs *et al.*, 1993; Howard *et al.*, 1997, el Ghouzzi *et al.*, 1997).

Other examples of autosomal dominant craniofacial abnormalities are cleidocranial dysplasia and Treacher Collins syndrome. In cleidocranial dysplasia mutations have been found in the core binding factor 1 gene (CBFA1). This results in defects in the membranous bones of the cranial vault and clavicles due to deficiencies in signalling between the periosteum and chondrocytes essential for endochondral bone formation (Mundlos *et al.*, 1997). The Treacher Collins syndrome locus has been mapped to the long arm of chromosome 5 (Dixon, 1996) and numerous mutations spread throughout the gene affecting the production of the treacle protein can produce the anomaly. Hypoplastic mandible and zygomatic bones, cleft palate, and conductive deafness are features and although the genetic defects have been (mapped) identified, the pathogenesis of these disorders remains unknown.

Molecular genetics in dental development. The first sign of tooth development is a local thickening of oral epithelium, which subsequently invaginates into neural crest-derived mesenchyme and forms a tooth bud. Subsequent epithelial folding and rapid cell proliferation result in first the cap, and then the bell stage of tooth morphogenesis. During the bell stage, the dentine producing odontoblasts and enamel secreting ameloblasts differentiate. Tooth development, like the development of all epithelial appendages, is regulated by inductive tissue interactions between the epithelium and mesenchyme (Thesleff, 1995).

There is now increasing evidence that a number of different mesenchymal molecules and their receptors act as mediators of the epithelial-mesenchymal interactions during tooth development. Of the bone morphogenetic proteins, BMP2, 4, and 7 mRNAs shift between the epithelium and mesenchyme in the regulation of tooth morphogenesis (Aberg *et al.*, 1997). The fibroblast growth factor (FGF) family have also been localized in epithelial and mesenchymal components of the tooth by immunohistochemistry (Cam *et al.*, 1992); and in dental mesenchyme tooth development and shape is regulated by FGF8 and FGF9 via downstream factors MSX1 and PAX9 (Kettunen and Thesleff, 1998).

Control of tooth development. Homeobox genes have particular implications in tooth development and, therefore, on Orthodontics. Muscle specific homeobox genes *Msx-1* and *Msx-2* appear to be involved in epithelial-mesenchymal interactions, and are implicated in craniofacial development, and in particular in the initiation, developmental position (*Msx-1*) and further development (*Msx-2*) of the tooth buds (MacKenzie *et al.*, 1991; Jowett *et al.*, 1993). Further evidence of the role of *Msx1* comes from gene knock-out experiments which results in disruption of tooth morphogenesis among other defects (Satokata and Maas, 1994). *Pax9* is also transcription factor necessary for tooth morphogenesis (Neubuser *et al.*, 1997). Bone morphogenetic proteins (BMPs) are members of the growth factor family (TGF β) and they function in many aspects of craniofacial development with tissue specific functions. BMPs have been found to have multiple roles not only in bone morphogenesis, (BMP 5 for example induces endochondral osteogenesis *in vivo*), but BMP 7 appears to induce dentinogenesis (Thesleff, 1995).

Disorders in tooth morphogenesis. Advances in the field of molecular genetics have made great progress in the understanding of a number of dental anomalies with a genetic component.

Amelogenesis imperfecta (AI): this is a group of genetically heterogeneous disorders affecting enamel formation. It is clinically heterogeneous in that hypoplastic, hypocalcified and hypomaturational forms have been described (Witkop, 1988); and genetically heterogeneous with families exhibiting autosomal dominant, autosomal recessive and X-linked inheritance (Witkop, 1988; Crawford and Aldred, 1992; Franco *et al.*, 1995). Also, the prevalence appears to vary quite significantly between 1:14,000 (Witkop and Rao, 1971) and 1:700 (Backman and Holm, 1986). In humans, two amelogenes, *AMGX* and *AMGY*, have been cloned and mapped to the X and Y chromosomes, respectively (Lau *et al.*, 1989) and in 1997 MacDougall *et al.* mapped the ameloblastin gene within the critical region for autosomal dominant AI at chromosome 4q21. It is likely, however, that mutations in several genes may be involved in the aetiology of different forms of autosomally inherited AI.

Dentinogenesis imperfecta (DI): this is autosomal dominant and occurs in approximately 1:8000 live births. It presents with brownish discolouration of the teeth, crowns susceptible to rapid attrition, fragile roots and pulp chamber obliteration due to abnormal continuous production of dentine matrix (Shields, 1973). DI also presents a number of sub-types, one of which is coupled with osteogenesis imperfecta in which there is an alteration in type 1 collagen genes. Most patients with this type of dentinogenesis imperfecta have mutations and deletions for amino acid substitutions in genes which encode for sub-units of type 1 collagen (Bonadio *et al.*, 1990; Ganguly *et al.*, 1991; Nicholls *et al.*, 1996). The structural defects in the collagen type 1 molecules affects the extra cellular matrix formation, resulting in the pathogenesis of DI.

Hypodontia: muscle specific homeobox gene (*MSX1*) is strongly expressed in the dental mesenchyme throughout the bud, cap and bell stages of odontogenesis (Mackenzie *et al.*, 1992). Satokata and Maas (1994) found that mice with the *Msx1* gene knocked out had amongst other defects, complete failure of tooth development at the E13.5 bud stage. More recently, Vastardis *et al.* (1996) demonstrated that a mutation in *MSX*, the human counterpart of murine *msx1*, caused familial tooth agenesis, and genetic linkage analysis of a family with autosomal dominant agenesis of second premolars and third molars identified a locus on chromosome 4p as the site of the *MSX1* gene.

Ectodermal dysplasia (EDA): hypohidrotic ectodermal dysplasia is a heterogeneous disorder with many clinically distinct types, and is characterized by the triad of hypotrichosis (sparse hair), hypohydrosis (lack of sweat glands), and hypodontia (reduced number of teeth). The hypodontia in EDA varies from a few missing teeth to complete anodontia; and tooth shape abnormality and tooth size can also be affected (Kere *et al.*, 1996; Thesleff, 1996). Kere and his colleagues (1996) identified the gene responsible for X-linked EDA, and it was found to be expressed in keratinocytes, hair follicles, sweat glands, and in other adult and foetal tissues.

A recent initiative by Yamada *et al.* (1998) entitled 'The Oral and Craniofacial Genome Project' seeks to set up

collaborative laboratory research projects on human and mouse embryonic tissue. The objective is to build up cDNA libraries with a view to discovering the genes for normal and abnormal oral and craniofacial development.

In summary, two major groups of regulatory proteins including mesenchymal growth factors, bone morphogenetic proteins and the steroid/thyroid/retinoid group are the vehicles through which homeobox gene information is expressed. Their temporal and spatial distribution in the facial structures is being gradually elucidated. Poorly coordinated control of form and size of structures (e.g. teeth and jaws), by regulatory genes should do much to explain the frequent mismatches found in dentofacial deformities and indeed in malocclusions. In the search for 'candidate genes' involved in maxillary or mandibular dysmorphogenesis, polymorphisms in the homeobox genes and the genes for the molecules that they regulate will be prime targets.

The Role of Epigenetic Factors

The orthodontic profession seems preoccupied with the problem of demonstrating the relative importance of genetics versus environment in the aetiology of malocclusion rather than understanding their interaction. A crucial objective in studying a multifactorial trait in man is to contemplate the effect of genotype/environment interaction. The effect of a particular environmental factor on phenotype will vary depending on the genetic background because of the influence of the latter on the response.

It is generally accepted that the basic form of a part of the neurocranium and splanchnocranium is determined genetically in the cartilagenous precursor during embryonic development. However, the form and size of the brain determine the morphology of the membranous cranial bones and regulate the further building up of the neurocranium. Likewise, with facial morphology the basic form of the mandibular body, and the location and morphology of the nasal capsule, which gives rise to the pyriform apertures are genetically determined in the chondrocranium. The form and size of the teeth are also principally genetically determined. Growth and the final morphology of the dentofacial structures is undoubtedly influenced by environmental factors, a classical case of gene/environment interaction. The influence of genetic determination on dentofacial morphology does not imply that the genetic information is located solely in the bones, but also in the neurological, muscular and neuromuscular fields, which have an indirect influence on the skeleton. There is no doubt that certain neuromuscular patterning are innate and are under direct genetic influence, and this, in turn, influences muscular posture and behaviour. Mastication, facial expression, speech, and swallowing are examples of neuromuscular patterns, and although there can be conscious control of these activities, there is no basis to suggest that these patterns can be changed permanently or altered to an unconscious level.

Genetic determination and regulation are responsible for the morphogenesis of an individual during embryonic development. There is ample evidence to indicate that hereditary dentofacial characteristics can be influenced during post-natal development by general environmental factors ranging from climate, nutrition, and lifestyle to oral

dental pressure habits, muscle malformation, and Orthodontic treatment. The influence of environmental factors on the retardation of general somatic growth is apparent in chronic illness, prolonged starvation, and situations of excessive stress (Tanner, 1965). Although each of the facial bones has a genetically predetermined size and growth potential (van der Linden, 1966), these bones are also influenced by related functional muscle attachments and oronasopharyngeal function which Moss and Salentijn (1969a,b) refers to collectively as the 'functional matrix'. It is important to realize that the functional matrix encompasses neuromuscular activity which is influenced by genetics, as well as environmentally-influenced behavioural and postural adaptations. It would, therefore, be erroneous to believe that craniofacial size and shape are entirely determined either by genetics or by environmental factors, but by the complex interaction of both and every malocclusion will occupy a unique slot on the gene/environment spectrum. This will have a direct bearing on the more important issue from an orthodontic viewpoint, which is the determination of the extent to which a particular malocclusion can be influenced by therapeutic environmental intervention, i.e. the prognosis for orthodontic correction. This issue is addressed in Part 2.

Goodman and Gorland (1970) observed a low tongue position in mandibular prognathism and a raised lingual dorsum in mandibular retrognathia. Salzmann (1972) highlighted the familial nature of tongue thrusting, jaw posturing and orofacial soft tissue mannerisms, and the similarity of the resulting occlusions or malocclusions. A recent twin study by Lauweryns (1995) to investigate the genetic contribution to a specific craniofacial neuromuscular component, i.e. masseter muscle reflex latency and peak latency concluded that these are under strong genetic control. This provides further evidence for the view that genetic control of craniofacial morphogenesis may reside in the soft tissues. Another aspect of the influence of soft tissues on the position and occlusion of the teeth, was highlighted by Solow (1980), namely the dento-alveolar compensatory mechanism. Since soft tissue morphology is considered to be primarily genetically determined, but soft tissue behaviour influenced by both genetic and environmental factors the resulting occlusal modifications are of multifactorial aetiology.

A further concept very relevant to the aetiology of malocclusion is that of dento-alveolar disproportion. Inheriting large teeth in a small jaws is a distinct possibility as bone is a mesodermal structure, while tooth enamel is of ectodermal origin. Genetically, most people will develop the normal human dentition of 32 permanent teeth and the implication of functional matrices is that it should be possible to expand the arches to accommodate all 32 teeth in all individuals. If this is not possible, then there must be a genetic aetiology for dentoalveolar disproportion. It is unreasonable to attribute the deficiency in size of the skeletal or dento-alveolar elements in such cases to lack of orofacial nasal pharyngeal function, at least until such claims have been substantiated by scientific evidence. Cases of extreme mandibular prognathism and disproportionately large noses, for example, cannot be explained by functional variation.

The question of whether environment or genetics exerts the greater influence in the aetiology of malocclusion has

been a matter of debate since the origin of orthodontics. As far back as 1891, Kingsley was unequivocal in his views in describing inheritance as a major factor in producing malocclusion. Edward H. Angle (1907), in one of his many papers, was equally adamant in his belief that malocclusions arise from local causes. This dichotomy is an unhelpful framework in which to consider the phenomenon of malocclusion and elements from both schools of thought can be carefully reconciled, even at the level of each individual orthodontic case scenario.

Studies on asymmetry of traits provide further evidence for environmental influence even during embryonic developmental processes. There are distinct differences between right and left sides in the developing embryo as evidenced, for example, by the contents of the thorax, and the marked differences in function between right and left cerebral hemispheres. Bilateral traits, such as size of teeth on contra-lateral sides of the arch, are however assumed to be under identical genetic control, i.e. are determined by the same genes. If this were true than the phenotypic expression of the trait on the contra-lateral side should be a function of identical developmental processes. Failure of the two sides to develop identically will reflect an underlying genetic instability referred to as developmental noise or interference encountered by the genes during ontogeny, which affects the attempts to render the same developmental message bilaterally.

In 1967, Adams and Niswander reported a significant increase in dental and dermatoglyphic asymmetry within individuals who also manifested cleft lip and palate. The authors postulated that polygenic systems normally buffer developmental processes against adverse environmental effects. However, substitution of deleterious genes caused the level of buffering to be lowered beyond the point where environmental disturbances may be compensated and a developmental defect results. Thus, in cleft lip and palate, for which a polygenic basis has been suggested, the developmental instability is manifested as asymmetry in the dermatoglyphic and dental patterns. In general, therefore, somatic asymmetry is a phenotypic manifestation of developmental noise attributable to environmental disturbances during tooth development.

Summary

Considering the embryogenesis of craniofacial form, development is genetically determined through neural crest cell migration and through this the expression of homeobox gene information. Epithelial-mesenchymal interaction during the process of craniofacial patterning, induction and programmed cell death is mediated by two groups of regulatory molecules, the growth factor and the steroid/thyroid/retinoic acid superfamilies. In polygenic multifactorial systems there is an additional factor, environmental modification. Such is the nature of the aetiology of many craniofacial malformations and of malocclusion.

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