Genetic, epigenetic and environmental influences on dental development

There is a group of “dental genes” that not only influences the size and shape of teeth but also the expression of missing or extra teeth. In other words, there are both pleiotropic genetic effects operating on the human dentition and spatial and/or temporal variations in local epigenetic events during odontogenesis that lead to distinct phenotypic differences in the dentition, even in genetically identical twin pairs.

Twin models

We agree completely with Professor Carels that studies of twins have contributed greatly to our understanding of the role of genetic and environmental influences on dental development. However, the traditional twin approach involving comparisons between monozygotic (MZ) and dizygotic (DZ) twin pairs requires large samples and is based on assumptions that may not always be valid.

There is a simpler research model involving twins that can also be employed by practising dentists. This model is referred to as the MZ co-twin design and it essentially involves studying pairs of MZ twins who may have different habits, receive different treatments, or differ in expression for one or more features of interest. Because each MZ pair is matched for sex, age and genetic make-up, the co-twins provide an extremely valuable research model. For example, just one pair of MZ twins displaying differences in their dentitions offers a great opportunity to explore the underlying biological processes of tooth formation.

Given that MZ twin pairs almost always share the same genes, any differences observed between the members of an MZ pair are assumed to be due to differences in environmental effects between the co-twins or to the way in which their genes are expressed, that is, epigenetic effects. The MZ pairs described in this article have a very high probability of being genetically identical based on DNA analysis. Furthermore, there is a group of “dental genes” that not only influences the size and shape of teeth but also the expression of missing or extra teeth. In other words, there are both pleiotropic genetic effects operating on the human dentition and spatial and/or temporal variations in local epigenetic events during odontogenesis.

Influences on dental development

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asymmetry. By examining the patterns and degrees of expression of asymmetry between contra-lateral teeth, it is possible to obtain further insights into the roles of genetic, epigenetic and environmental influences on dental development (Khalaf et al., 2005a).

One particularly interesting expression of asymmetry that can be observed in MZ twin pairs is the phenomenon of mirror imaging, where one twin “mirrors” the other for one or more features. Figure 7 shows panoramic radiographs of a pair of MZ male twins, aged 15 years, who show mirror-imaging for hypodontia of the lower second premolars. The left premolar is missing in Twin A (arrowed), whereas the right premolar is missing in Twin B (arrowed). In addition, a developing lower right third molar is evident in Twin A (arrowed) but not in Twin B (arrowed). The biological basis of mirror imaging is still not well understood, although it apparently reflects an underlying alteration in the determination of body symmetry at an early stage of development.

How can the differences between MZ co-twins be explained?

The examples provided in this article and in other studies we have performed support the view that, even though there is a relatively strong genetic basis to missing or extra teeth, the number or position of affected teeth can be influenced by epigenetic factors. The exact nature of these influences is still unclear but they do not need to be due to differences in methylation of DNA or acetylation of histones. Rather, we suggest that they may reflect different responses of odontogenic cells to minor variations in the spatial and temporal expression of local signalling molecules passing between cells during development. In other words, we are proposing that “disturbances” in epigenetic events at the local level during tooth formation can lead to quite major differences in the final appearance of the dentitions of MZ co-twins.

A multi-factorial model linking tooth size and number has been proposed to account for the different patterns of expression of missing and extra, and also large and small teeth observed in males and females (Brook, 1984; Brook et al., 2002; McKeown et al., 2002; Khalaf et al., 2005b). The relatives of individuals with missing or extra teeth have been found to be more likely to also display missing or extra teeth, supporting the concept of an underlying genetic predisposition to hypodontia or supernumerary teeth. We believe that such a multifactorial model, with multiple genetic and environmental influences, provides the best explanation for our observations involving hypodontia and supernumerary teeth in MZ twin pairs. With the superimposition of thresholds on this underlying distribution, it is possible to explain the relationship between tooth size and the presence or absence of teeth. Below a certain threshold for tooth size, missing teeth will occur, and the prevalence of missing teeth is greater in females who have smaller teeth, on average, than males. At the other extreme of the distribution, with increasing tooth size, another threshold is reached above which extra teeth will occur. The prevalence of extra teeth is greater in males who have larger teeth, on average, than females (Fig 8).

Interpreting phenotypic studies in the light of findings at a molecular level

To date, molecular studies in humans have concentrated mainly on locating the genes associated with missing teeth. As Carels has pointed out, mutations in two genes, MSX1 and PAX9, have been shown to be associated with familial cases of severe hypodontia (where many teeth are missing) and the pedigrees have been consistent with an autosomal dominant mode of inheritance albeit showing variations in the number and position of teeth missing. However, there are some 500 genes that appear to be involved in dental development and a number of them could be candidates for missing teeth. Furthermore, the most common clinical presentation relating to missing teeth is hypodontia where only a small number of teeth are missing.

Given that there appears to be a link between the size and shape of teeth, and hypodontia or supernumerary teeth, we propose that there is likely to be a group of “dental genes” that exert pleiotropic effects on all of these dental phenotypes, accounting for their observed co-variation. Just how many genes are involved remains to be seen, but it is possible that it may be a relatively small number. Support for this view is provided by a paper in Nature by researchers from Finland (Kangas et al., 2004) showing that dental characters seem to be non-independent and that increasing the levels of expression of just one gene can lead to increases in cusp number, altered cusp shape and position, development of longitudinal crests on teeth, and increases in tooth number in experimental mice.

Rather than a monogenic mode of inheritance, we believe that a multi-factorial model (with genetic, epigenetic and environmental influences) provides the best explanation for our observations involving hypodontia and supernumerary teeth in MZ twin pairs. Such a model, with superimposed thresholds linking tooth size, morphology and number, enables us to explain why MZ co-twins, who
have the same genotypes, may display different expressions of missing, tapering and microdont incisors. Presumably these MZ twin pairs have a genetic predisposition for hypodontia that places them near the threshold for agenesia, but minor variations in local epigenetic events during odontogenesis may lead to different phenotypic expression between co-twins. A similar explanation may also account for the discordant patterns of missing premolars or supernumerary teeth within MZ co-twins. Presumably, these MZ twin pairs have a genetic make-up that places them near to a threshold for either missing or extra teeth, but variations in local epigenetic events during odontogenesis, probably relating to the spatial arrangement of cells or temporal events, determine on which side of the threshold they fall.

Molenaar’s concept of developmental systems with emergent self-organizing properties is consistent with our current understanding of the molecular basis of tooth development. The various stages of odontogenesis, including initiation, patterning and differentiation, result from a series of epithelial-mesenchymal interactions between oral epithelial and ecto-mesenchymal tissues that are facilitated by the exchange of various signalling molecules. The work of Jernvall and colleagues in Helsinki has shown how the same genes are expressed and the same signalling molecules released in a reiterative fashion to produce each of the cusps of a molar tooth (Jernvall and Jung, 2000). In fact, these genes seem to be highly conserved in an evolutionary sense and once the process of odontogenesis has been initiated, it tends to proceed as a continuous self-organizing process as described by Molenaar and colleagues (Molenaar et al., 1995).

Our studies of intra-coronal dimensions of molar teeth in twins are also consistent with the concept of a dynamically developing crown pattern during odontogenesis, linked to the formation of signalling centres referred to as enamel knots (Townsend et al., 2005). We suggest that variations in dental crown form between species probably result from regulation of a relatively small number of highly conserved genes that control tooth formation in vertebrates, whereas variations observed within a species, for example in humans, probably result from alterations in the timing of interactions between cells during odontogenesis, as well as the positions of cells relative to each other.

Using our broad definition of epigenetics, both of these processes can be considered to be examples of epigenetic control. In the case of variation between species the control is likely to reside at the level of DNA, whereas in variation within a species the epigenetic influences are likely to occur at the local tissue level.

Finding the genes for dental development

Genome-wide association studies (GWAS) are currently being used to identify genes linked to various common diseases, including coronary heart disease, hypertension, diabetes and arthritis. We plan to use a similar approach to identify the key genes involved in dental development.

While the identification of key genes for dental development in humans will undoubtedly be a major step forward, there will still be much work to do. Merely identifying the genes will not necessarily mean that we will be able to explain fully how various dental anomalies arise in individuals. This is where further exploration of epigenetic factors will be essential. Already researchers are beginning to study epigenetic biomarkers in an attempt to explain the reasons for observed differences between MZ twin pairs (Wong et al., 2007). At this stage, the focus is on trying to determine the extent of differences in global genomic DNA methylation levels but it is likely that more specific analyses will be developed soon. Once these approaches are aimed at the level of DNA are refined further, and our understanding of the nature of the epigenetic influences at a local tissue level improves, we should be able to provide a clearer picture of how genetic, epigenetic and environmental factors influence human dental development. With this knowledge, we will be in a better position to consider preventive and therapeutic approaches to many of the common developmental problems affecting the human dentition.