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Genetic and environmental influences on human dental variation: A critical evaluation of studies involving twins☆

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ABSTRACT

Utilising data derived from twins and their families, different approaches can be applied to study genetic and environmental influences on human dental variation. The different methods have advantages and limitations and special features of the twinning process are important to consider. Model-fitting approaches have shown that different combinations of additive genetic variance (A), non-additive genetic variance (D), common environmental variance (C), and unique environmental variance (E) contribute to phenotypic variation within the dentition, reflecting different ontogenetic and phylogenetic influences. Epigenetic factors are also proposed as important in explaining differences in the dentitions of monozygotic co-twins. Heritability estimates are high for most tooth size variables, for Carabelli trait and for dental arch dimensions, moderate for intercuspal distances, and low for some occlusal traits. In addition to estimating the contributions of unmeasured genetic and environmental influences to phenotypic variation, structural equation models can also be used to test the effects of measured genetic and environmental factors. Whole-genome linkage analysis, association analysis of putative candidate genes, and whole genome association approaches, now offer exciting opportunities to locate key genes involved in human dental development.

1. The classical twin model and its assumptions

Monozygotic (MZ) co-twins share the same genes, whereas dizygotic (DZ) co-twins on average share only half of their genes. Therefore, by assuming that both types of twins have been sampled from the same gene pool and that similar environmental factors act upon them, one can estimate the relative contributions of genetic and environmental influences to observed variation in different features or traits. The calculation of heritability estimates provides a means of quantifying the extent of the genetic contribution to phenotypic variation, with proportions ranging theoretically from 0 to 1. Various formulae can be utilised to calculate estimates of heritability for both quantitative and categorical data, and their standard errors, although few early twin studies provided such estimates. Two types of heritability can be distinguished: 'narrow-sense' heritability refers to the contribution of additive genetic

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variance to observed phenotypic variance, whereas 'broad-sense' heritability refers to the total contribution of genetic factors (additive and non-additive) to the observed variation. Additive effects represent the sum of parental genes influencing the offspring's trait, whereas non-additive effects encompass the effects of genetic dominance and gene–gene interaction.

There are several assumptions that underlie the classical twin approach and these were not tested fully in many of the early studies. Furthermore, it has often been overlooked that heritability is a population concept, referring to the proportion of genetic variation within a given population at a particular time. The concept should not be applied to a single individual but, rather, to a group of individuals.[1] In addition, as Smith and Bailit[2] have pointed out, "contrary to popular opinion, the extent to which genes determine a trait has no relationship whatsoever with the success of environmental intervention".

Kang et al.[3] and Christian[4] have outlined some of the assumptions that are implicit in using the classical twin model to partition variance into genetic and environmental components. The mean values for the trait under investigation should not differ between zygosity groups. Total variance within zygosities should also be equal for the model to hold, as heterogeneity of total variance suggests that environmental factors are not equal for MZ and DZ twins. Environmental covariances should also be equal, with heritability estimates being inflated if environmental covariance is greater in MZ twins than DZ twins. All of these assumptions should be tested statistically prior to calculating genetic and environmental contributions to phenotypic variance. Interestingly, Harris[5] has recently noted heterogeneity in total variances for human odontometric data derived from twins, with DZ twins showing significantly larger within-pair values than MZ twins, leading him to question whether twins are representative of the broader population.

2. Criticisms of the twin model

A major issue of concern in many previous studies of twins has been the accuracy of zygosity determination. Although comparisons of physical appearance can provide a reasonably reliable means of determining zygosity, errors can occur and these may influence subsequent analyses. The use of blood groups, as well as serum and enzyme polymorphisms, improved the ability to assign zygosities to twins. More recently, the use of highly polymorphic regions of DNA derived from blood or buccal cells has proved to be accurate and reliable.[6]

One of the main criticisms of the classical twin model has been based on the assertion that MZ co-twins are likely to share more similar environments post-natally than DZ co-twins, so greater similarities between them compared with DZ co-twins may partly reflect more similar environments rather than more similar genetic constitutions. While this can be an important issue with some behavioural phenotypes, it is less likely to be a major factor in studies of dental morphology, although nutritional similarities could possibly affect dental development.

Another consideration is the possibility of an interaction between genetic and environmental influences. The classical twin model tends to assume that these two influences operate independently, hence the often-used phrase 'nature versus nurture'. This is seldom the situation and there is frequent interaction between genetic and environmental factors.

A further criticism of the classical twin model has been whether it is reasonable to extrapolate the findings from twin studies to a general population containing many singletons, given the special nature of the twinning event, twin pregnancies and births, and the upbringing of twins. The nature of the phenotype under investigation is important when attempting to assess the importance of these factors. However, there are some who question whether this is an appropriate assumption, even for dental variables.[5,7]

3. Special features of the twinning process

The twinning process itself and the circumstances surrounding the birth of twins and their peri-natal development is special. Twinning has been associated with a high peri-natal mortality rate[8] and MZ twins display a higher prevalence of congenital abnormalities, many of which appear to be related to failure of bilateral structures to fuse properly during development.[9] Although some claim that the potentially harmful effects of twin gestation have been exaggerated,[10] a large percentage of twins may not develop past 16 weeks post-conception, leading some researchers to refer to a 'vanishing twin' syndrome.[11]

Apart from an apparently higher prevalence of peri-natal mortality and morbidity amongst twins, there is another special feature of the twinning process that frequently has been overlooked. MZ twin pairs most often share a common placenta and chorion (around 60–70%), but there are around 20–30% of MZ co-twins who have separate placentas and chorions. Di-chorionic twins are thought to have separated at an early stage of development, probably in the first 5 days post-conception whereas mono-chorionic twins are thought to have separated at a later stage, around six to 9 days post-conception. In around 30% of mono-chorionic MZ twins, there can be arterio–venous anastomoses that can lead to marked differences in physical development. Few studies of dental features in twins have taken account of chorion type, although Burris and Harris[12,13] have provided evidence that chorion type can affect permanent tooth dimensions. These researchers have suggested that previous estimates of heritabilities for dental traits, where these types of effects have not been considered, are likely to have been biased. In a recent study involving Australian twins, it was found that intrapair variances for tooth-size data in mono-chorionic twin pairs generally exceeded those for di-chorionic pairs, indicating that the prenatal environment of twins may have an effect on their developing dentitions.[14]

The fascinating phenomenon of mirror-imaging, where one member of a twin pair 'mirrors' the other for one or more features, is well known to most people. However, most of the studies of mirror-imaging in twins have been retrospective reports based on small sample sizes rather than being well-planned prospective studies. To ensure that findings are not purely due to chance, a suite of study variables needs to be defined, measurements and observations made, error studies