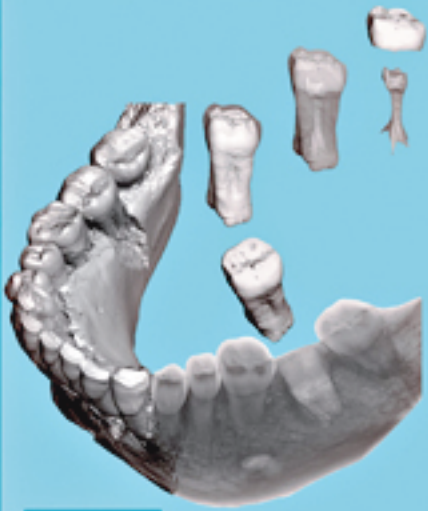
EVOLUTION

Technique and Application in Dental Anthropology

Edited by
Joel D. Irish and Greg C. Nelson



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Technique and Application in Dental Anthropology

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UNIVERSITY PRESS

14 *The quantitative genetic analysis of primate dental variation: history of the approach and prospects for the future*

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14.1 Introduction

From the size and shape of teeth we can learn much about an animal's diet, gain some insight as to how it interacted with its conspecifics and environment, and draw conclusions about its phylogenetic placement. Consequently, primate dental variation has been the focus of an immense amount of research (as evidenced by this volume). These adaptive and phylogenetic scenarios rely on the assumption that variation in the dental phenotype is heritable, or rather, that this variation can be passed on from generation to generation as selection filters through the available phenotypic variance.

In this chapter, we discuss the history of research that tests this hypothesis through quantitative genetic analyses. We will focus attention on analyses of crown morphology with the aim of summarizing what is currently known and unknown about the extent to which dental variation is influenced by genetic factors. And last, we discuss two directions through which quantitative genetics will further enhance our understanding of the evolution of our ancestors and closest relatives.

14.2 Quantitative genetics

> Quantitative genetics is concerned with the inheritance of those differences between individuals that are of degree rather than of kind, quantitative rather than qualitative. These are the individual differences which, as Darwin wrote, "afford materials for natural selection to act on and accumulate . . ." An understanding of the inheritance

Technique and Application in Dental Anthropology ed. Joel D. Irish and Greg C. Nelson
Published by Cambridge University Press.

> of these differences is thus of fundamental significance in the study of evolution and in the application of genetics to animal and plant breeding. (Falconer, 1989, p. 1)

The theories and methods of quantitative genetics extended Gregor Mendel's principles of inheritance – originally adduced from the study of the transmission of qualitative traits – to the analysis of quantitative, or continuously varying, traits in populations. This extension took advantage of theoretical developments in two nascent fields of scientific inquiry: the inheritance of measurements, or biometry, introduced by Francis Galton in the late 1800s, and the genetics of populations, introduced by a number of scientists following the rediscovery of Mendel's work in the early 1900s (Falconer, 1989; Lynch and Walsh, 1998; Provine, 1971). The theoretical basis for quantitative genetics was advanced, coincident with much of inferential statistics, by the early 1920s in the works of Fisher (1918), Haldane (reviewed in 1932), and Wright (1921). Since its formulation, the theory of quantitative genetics primarily has been applied to predicting the genetic properties of populations conditional on the properties of genes, predicting the quantitative outcomes of breeding strategies, and predicting evolutionary change in quantitative traits: conditional, real, or hypothesized genetic properties in agricultural and experimental populations of animals and plants (Falconer, 1989). In the last few decades, it has been extended to the detection, characterization, localization, and identification of genes influencing quantitative variation in traits of basic, evolutionary, and biomedical importance in humans and non-human primates as well (Rogers *et al*., 1999).

At least three general premises are fundamental to much of the quantitative genetics work currently underway. The first is that the inheritance of quantitative differences (and, similarities) is mediated by the Mendelian segregation of genes at many loci. The second premise is the common observation of a greater similarity in measurements for quantitative traits in samples of closely related individuals than in samples of more distantly related individuals. This is explained, in part, by the fact that the former share more genes than the latter. The third premise is that environmental (i.e. non-inherited) factors also contribute to the pattern of observed quantitative differences in traits within a population. Consequently, a common goal of genetic analyses is to assess the relative importance of genotype versus environment to the observed variation in the trait of interest. According to basic quantitative genetic theory, the overall phenotypic, or anatomical variance (σ_P^2) may be decomposed into variance due to the effects of genes (σ_G^2) and variance due to "environment" (σ_E^2), such that:

$$\sigma_P^2 = \sigma_G^2 + \sigma_E^2 \tag{14.1}$$

Given this relationship, an estimate of the *heritability* (h^2), or the proportion of the total phenotypic variance accounted for by genetic effects, is:

$$h^2 = \frac{\sigma_G^2}{\sigma_P^2} \tag{14.2}$$

Dental anthropologists and researchers from other disciplines have employed a variety of quantitative genetic approaches and study designs (sampling and analytical strategies) to determine the relative importance of genes and environmental factors to quantitative variation in dental traits; all of them require quantitative data from samples of related individuals, e.g. twins, sibling pairs, sibships, nuclear families, and extended families, etc. All other things being equal, the greater the number and variety of relative pairs in a sample, the greater the statistical power to detect and estimate the effects of genes and environmental factors on quantitative variation in a trait. This is simply a matter of information available for analysis, i.e. sibships provide more information than sibling pairs, and extended families provide more than nuclear families, etc. However, in quantitative genetics, different research questions/hypotheses may require different study designs, and different study designs may require different analytical approaches (Blangero, 2004). Further, the genealogical structure of anthropologically relevant samples (or of samples typically available to dental anthropologists) can influence the kinds of questions that can be addressed and, consequently, the analytical approaches employed.

We will briefly summarize the history of the use of some of these techniques to address questions of interest to dental anthropologists. Although we categorize these studies into "early," "middle," and "later" years, the reader should realize that the breaks between these categories are somewhat arbitrary.

14.3 The early years (1920s–1950s)

The earliest studies exploring genetic contributions to dental variation utilized twin, sibling, and parent–offspring relationships, and were concerned primarily with patterns of resemblance and inheritance for dental caries and orthodontic disorders (e.g. Bachrach and Young, 1927; Moore and Hughes, 1942). With the exception of studies exploring the susceptibility to dental caries in inbred rat populations (Hunt *et al.*, 1944; Rosen *et al.*, 1961), dental quantitative genetics research in the 1940s and 1950s was dominated by the human monozygotic (MZ) and dizygotic (DZ) twin study model. Investigations of tooth size and occlusion (Lundström, 1948), date of eruption (Hatton, 1955), and molar cusp variation (Ludwig, 1957) from this period established the practice of variance comparison between the two twin types, consistently demonstrating greater

variability for dental traits of DZ twins relative to that of MZ twins. The greater concordance between MZ twins and, in general, the high degree of resemblance between related individuals reported in these studies, provides some of the earliest evidence for genetic inheritance of dental variation and the foundation for all subsequent work.

14.4 The middle years (1950s–1970s)

During the 1950s, 1960s, and 1970s, genetic contributions to dental variation were inferred mainly through studies of inter-populational differences, familial aggregation, and relative pair correlations. Results and observations from the first two classes of study provided circumstantial evidence for heritability, while those from the third category – e.g. comparison of intra-pair variance ratios between twin types, simple measurements of concordance and correlation in twins, the regression and correlation of parents and offspring, and the correlations between full and half siblings – provided improved estimates of the magnitude of the effects of genes on the traits under study. We discuss this research by phenotype, i.e. caries, tooth size, Carabelli's cusp, etc. It is important to note that, as seen in the early years, work from this period focused almost completely on humans. The non-human primate studies by Sirianni and Swindler (1973, 1974) (discussed below) are the few exceptions to this trend.

14.4.1 Caries and occlusion

Our review focuses on crown size and shape; however, it is important to note that quantitative genetic analyses of dental variation continued to demonstrate a genetic contribution to dental caries susceptibility (e.g. Finn and Caldwell, 1963; Horowitz *et al*., 1958b). Assessing the degree to which intra-pair variance in DZ twins exceeded the variance in MZ twins provided a heritability estimate of 0.85 (Goodman *et al*., 1959). However, the observation that both twin types had a higher concordance compared to the controls indicated a significant environmental influence on caries experience (Mansbridge, 1959).

Research on occlusion suggested that despite observed genetic variability, environmental factors are more important among families for traits such as overjet, overbite, molar relationship, crowding, and rotations, and as such, occlusal/dental arch variation has lower heritability estimates than does tooth crown size (Bowden and Goose, 1968; Harris and Smith 1980; Lee and Goose, 1982, but see the latter for contrasting estimation for overjet). This importance of environmental contributions to the phenotypic variance will be addressed in detail later.

14.4.2 Tooth and cusp dimensions

Numerous researchers reported evidence for a genetic contribution to tooth size, i.e. linear measurements of crown mesiodistal and buccolingual lengths. Studies of tooth size incorporating familial relationships in the house mouse (Bader, 1965; Bader and Lehmann, 1965) preceded human research for this trait, introducing the calculation of heritability from coefficients of variance derived from population and sibling comparisons. Numerous human family studies that followed demonstrated that most of the tooth size dimensions could be attributed to additive genetic effects (Bowden and Goose, 1969; El-Nofely and Tawfik, 1995; Goose, 1968; Niswander and Chung, 1965; Townsend and Brown, 1978a, 1978b). Correlations between family members, including twin, sibling, parent–child and cousin, showed a significant genetic basis for crown size, with heritability estimates falling between 0.80 and 0.90 (Garn *et al*., 1968). Data for deciduous teeth from an Aboriginal population agreed with these high estimates of genetic variability in tooth size (Townsend, 1980).

Interestingly though, researchers detected patterned differences in heritability among linear metric phenotypes. A full sib correlation comparison estimated higher heritabilities for labiolingual compared to mesiodistal dimensions in 13 of 16 possible comparisons, suggesting a greater genetic factor for the former set of dimensions (Alvesalo and Tigerstedt, 1974). Additionally, heritability of inter-cuspal distances was found to be less than that for crown diameters of maxillary premolar teeth (Townsend, 1985). Another study found that variation in molar cusp size suggested little difference between MZ and DZ cusp area variance, and hence, a relatively low heritability (Biggerstaff, 1975, 1976). These differences in heritability were thought to possibly represent differing genetic control, with implications for the evolution of the primate dentition.

Multivariate analyses of linear metrics provided additional insight to the genetic contributions to tooth size. Factor analysis demonstrated that three common factors could collectively describe the 56 dimensions of 28 permanent teeth and account for more than one half of total variance of these measurements (Potter *et al*., 1968).

Analyses of size variation in the anterior dentition suggested that genetic control in the various tooth categories differs. In a sibling study that explored the genetic involvement in specific components of occlusion characteristics, the highest degree of correlation was found in incisor width, which suggests stronger genetic involvement for this tooth dimension (Chung and Niswander, 1975). The presence of a genetic component for overall tooth size was indicated in an analysis of variance and concordance in a study of three sets of triplets (Menezes *et al*., 1974). A study of the maxillary and mandibular permanent anterior teeth in MZ and DZ twins demonstrated a greater genetic influence for

the incisors than the canines (Horowitz *et al*., 1958a; Osborne *et al*., 1958). Cross twin analysis also indicated that the anterior dentition might be under genetic control in terms of both general tooth size and adjacent tooth size (Osborne *et al*., 1958). Interestingly, intra-pair variances of mesiodistal crown diameters of deciduous anterior teeth showed high genetic variability in canines and, to a lesser degree, central incisors (Di Salvo *et al*., 1972).

A variety of dental traits other than tooth and cusp dimensions were also explored using quantitative genetic analyses. For example, tooth width of the anterior teeth (Lundström, 1964), mesial ridge counts (although only at a significant level in the maxillary second premolar) (Gilmore, 1968), and intra-alveolar development of the crown and root of permanent mandibular canines, premolars, and first and second molars (Green and Aszkler, 1970).

14.4.3 Morphological traits

The standardization of scoring for morphological traits (Dahlberg, 1956) provided a significant number of dental phenotypes that were also analyzed using quantitative genetic approaches during this time period. Heritability estimates were generally found to be lower for these phenotypes compared to linear metrics. The dichotomization of continuously variable traits inherent in the standardized scoring procedure typically employed in these analyses results in the loss of a significant amount of descriptive power, and therefore may account for these lower heritability estimates.

Carabelli's cusp is perhaps the most "famous" of these morphologies (Figure 14.1), and it was the subject of considerable genetic analysis. Population studies used genetic frequencies of Carabelli's trait to test hereditary models (Turner, 1967) and describe inter-group variation (Scott, 1980). In sibling studies, the frequency of Carabelli's trait in the deciduous and permanent dentition was found to be higher for the siblings of individuals with the character than for siblings from the general population, suggesting some evidence for a genetic basis (Garn *et al*., 1966). Twin research found that concordance of the Carabelli's trait is generally higher in MZ than DZ twins, with heritability estimates as high as 0.91 (Skrinjaric *et al*., 1985). However, this was not a ubiquitous conclusion. A separate study found relatively low MZ concordance, and that concordance sometimes differed enough between antimeres to suggest separate genetic factors for each side of the dentition (Biggerstaff, 1973). Quantitative analysis by tetrachoric correlation of 14 non-metric characters, including Carabelli's trait, also indicated low genetic variability (Mizoguchi, 1977).

Figure 14.1 Top panel shows expression of the cingular remnant Carabelli's cusp on an upper left third molar of a 2.5 million year old hominid from the Omo, Ethiopia (specimen number L 50–2). The bottom panel shows expression of the cingular remnant in the maxillary molar of an extant baboon (*Papio hamadryas*).

Family studies employed in an attempt to establish the mode of inheritance of Carabelli's trait, shoveling of incisors, maxillary molar cusp number, mandibular cusp number, and fissure patterns suggested that these traits are continuous and not discrete; they are, therefore, likely to be inherited in a multifactorial way (Goose and Lee, 1971; Lee and Goose, 1972). However, reducing Carabelli's trait into fewer categories, typically employed by dental anthropologists (Turner *et al*., 1991), resulted in high sibling similarity with values of the coefficient of contingency approximating 0.50 (Garn *et al*., 1966). A separate

analysis of variation in expression of Carabelli's trait in sib pairs reported no correlation, suggesting that it is not due to genetic factors (Alvesalo *et al*., 1975). In addition to Carabelli's cusp, other phenotypes such as shovel form, molar cusp number, and groove pattern were shown to generally have low but positive within-individual correlations with one another, possibly attributable to a general effect of tooth size (Sofaer *et al*., 1972). Also, despite higher MZ values, 100% concordance in MZ twins was rarely reached in an examination of 26 minor variants of the dental crown (Kaul *et al*., 1985). Parent–offspring and sib correlations demonstrated genetic control over the frequency of expression of 20 tooth crown traits (Scott, 1973).

Heritability estimated from parent–offspring correlation showed that about 68% of maxillary incisor shovel shape variation could be explained by additive genetic effects (Blanco and Chakraborty, 1976). A sibship analysis found the frequency of shoveling to be higher among the sibs of affected persons than among randomly sampled sibs from the study population, also showing that the character is heritable (Portin and Alvesalo, 1974).

The genetic contributions to metaconule expression were also explored; estimates of the additive genetic component were found to be 65% for the first molar, but only 15% for the second (Harris and Bailit, 1980).

14.4.4 Asymmetry

Biggerstaff, in his analysis of Carabelli's cusp (1973) and concordance of mandibular molar cusp size between twins (1970), noted that concordance differed enough between antimeres to suggest separate genetic factors for each side of the dentition. This observation and conclusion is remarkable in that it contradicts the bilateral symmetry commonly assumed to be inherent to the dentition (and vertebrate bodies in general).

During the 1950s–1970s considerable research was designed to test whether or not genetic influences could explain dental asymmetry. The results from these studies were mixed. Support for a genetic influence was found when comparing individual teeth and tooth-width sums, although a greater non-genetic influence was observed in the former (Lundström, 1967). An investigation of permanent mandibular first molar and first and second premolars in MZ and DZ twins and non-twins found greater bilateral asymmetry in MZ twins for the seventh cusp of the first molar, but equal asymmetry in MZ and DZ twins for hypoconulid occurrence and premolar cusp number; this suggests a mixed amount of genetic influence (Staley and Green, 1971). Additional work, in which a distinction was made between measurements of discordance, bilateral asymmetry, and

mirror imaging in comparing variance ratios for dimensions of the permanent dentition, showed no sign of a genetic component (Potter and Nance, 1976). A population study of Mexican and Belizean groups found little asymmetry and high correlations between each side of the dentition for a set of discrete dental traits; these findings lead to the conclusion that similar genetic factors may exist for both sides, and that environmental factors may play a significant role in asymmetry (Baume and Crawford, 1980). In a study done to establish dental asymmetry as an indicator of genetic and environmental conditions of human populations, non-significant heritability estimates that ranged between 2–5% suggested a low component of additive genetic variance for fluctuating asymmetry (Bailit *et al*., 1970).

Although genetic factors have not been ruled out in the case of asymmetry, the twin and population data from this period are inconclusive and suggest, if anything, a large environmental influence. For the current status of this debate see Leamy *et al*. (2000, 2005).

14.4.5 Development

During this time, several studies also looked at genetic control of tooth development. Family line analysis (Garn *et al*., 1960) and sibling correlation studies (Garn *et al*., 1965a; Merwin and Harris, 1998) assessed the genetic influence on the tempo of tooth growth and mineralization. Strong genetic control was indicated by a heritability of 0.82 calculated from intra-class correlations between full siblings (Merwin and Harris, 1998).

14.4.6 Sex effects

Sex effects on tooth size were also reported. In comparing the size of the permanent teeth in like- and unlike-sexed siblings, X-chromosomal linkage was suggested by sister–sister correlations that exceeded brother–brother correlations, which in turn exceeded sister–brother correlations (Garn *et al*., 1965b; Lewis and Grainger, 1967). Other sibling correlation studies also suggested genetic control over sexual dimorphism in tooth size (Garn *et al*., 1967). However, several population studies comparing sib correlations for tooth size did not show evidence for the presence of sex-linked genes (Niswander and Chung, 1965; Townsend and Brown, 1978a). Investigations of tooth size inheritance in non-human primates used sib correlations from a captive macaque population to test the hypothesis of X-chromosome mediation, but instead found support for involvement of the Y-chromosome (Sirianni and Swindler, 1973, 1974).

14.4.7 Maternal effects

Both maternal and gestational factors were found to influence crown dimensions. Relatively high mother–offspring correlations were interpreted as a sign of environmental effects associated with the mother (Goose, 1967). Prolonged gestation, high birth weight and length, and maternal hypothyroidism and diabetes were associated with an increase in tooth size, while short gestation, lower birth weight and length, and maternal hypertension were associated with decreased crown dimensions (Garn *et al*., 1980). An analysis of covariance done to determine whether maternal effects influence the development of the permanent dentition showed that dental development is significantly different between families after adjustment for maternal age, birth order, and birth weight (Bailit and Sung, 1968). A cross-fostering experiment between inbred strains of the house mouse that analyzed the prenatal and postnatal maternal environmental effects on molar size variation indicated a non-genetic prenatal factor, as well as strain-specific genetic determinants for the second molar; however, there was little prenatal environment intra-strain influence on the third molar (Tenczar and Bader, 1966).

14.4.8 Dental variation diagnosis of twin zygosity

The high degree of concordance between MZ twins in crown morphology, presence of Carabelli's trait, and molar cusp number proved to be useful for diagnosing zygosity (Townsend *et al*., 1988; Wood and Green, 1969), comparable to that of other phenotypes such as fingerprints and blood grouping (Kraus *et al*., 1959). One twin study showed that concordance comparisons across the entire dentition were able to diagnose zygosity accurately approximately 94% of the time (Lundström, 1963).

14.5 The later years (1970s–1980s)

In the late 1970s, statistical analyses of twin and familial data progressed beyond the simple concordance and correlation techniques employed in the previous decades, as exemplified by the multivariate work by Potter *et al*. (1976). Using this method, within-pair difference covariance matrices were created for each twin type, suggesting that a greater number of genetic factors were influencing mandibular tooth size. In addition to a supposed independence of the mandibular and maxillary dentition, separate factors were indicated for mesiodistal and buccolingual dimensions, in contrast to what appeared to be shared genetic determinants for antimeres (Potter *et al*., 1976, 1978).

The early 1980s saw the introduction of complex segregation analysis into dental genetics, facilitating the identification of genetic and common environmental influences on Carabelli's trait (Kolakowski *et al*., 1980) and tooth dimensions (Kolakowski and Bailit, 1981) from sibling and parent-offspring data. Path analysis was first utilized to investigate the influence of small crown characters on tooth dimension and shoveling (Mizoguchi, 1978). In a later study, path analysis modeling detected environmental variance components responsible for sibling correlation in mesiodistal measurements of the upper left permanent first molar and lateral incisor (Potter *et al*., 1983). A study combining complex segregation analysis of morphological traits and path analysis of tooth size measurements identified roles for both genetic and environmental factors (Nichol, 1990).

In 1979, an attempt to find any association of twin zygosity with tooth size indicated that an important assumption of the twin model, environmental variance equality, had been violated, prompting a refinement of the statistical testing used in later studies (Potter *et al*., 1979). The finding that variances were not necessarily homogenous across twin types suggested the existence of unequal environmental influences, and bias in previous estimates of variance and heritability from studies in which heterogeneity had not been assessed (reviewed in the previous section). Additionally, Potter *et al*.'s (1979) study indicated that among-pair sex differences existed for MZ and DZ mean squares, a confounding factor for variance heterogeneity.

The direct result of this restatement of the twin model and its assumptions was the incorporation of sex differences, mean equality, variance heterogeneity, and environmental equality tests into subsequent studies of occlusal variation using multivariate and principal component analyses to investigate trait interactions. After environmental inequalities and MZ–DZ mean differences were accounted for, an overall average heritability for occlusal traits was estimated as 0.25, reflecting biases that had gone undetected in prior studies of occlusion and the large environmental influence on variance (Corruccini and Potter, 1980). A subsequent analysis of size, asymmetry, and occlusion in the permanent first molar found heritable components for only the lower molars, averaging 0.62 (in contrast to 0.09 for the upper molars) and non-significant genetic components for asymmetry and occlusal discrepancy (although the latter tended to be higher) (Corruccini and Potter, 1981). A general conclusion from the occlusal variance studies from this period indicated a greater environmental than genetic influence on the traits examined (Corruccini and Potter, 1980, 1981; Potter *et al*., 1981).

Investigators of tooth dimension also adopted the refined twin study protocol. A comparison of American and Punjabi MZ and DZ twin pairs yielded an average heritability estimate of 0.73 for tooth size, and when not invalidated by environmental covariance inequality, mesiodistal and buccolingual dimensions

of individual teeth in the Punjabi twin population were used to derive heritability estimates that ranged from 0.26 to 0.72 after correction for variance heterogeneity (Corruccini and Sharma, 1985; Sharma, *et al*., 1985). The size of the maxillary right lateral incisor was found to have a significant heritability estimate of 0.42 (Townsend *et al*., 1986), and heritabilities of mesiodistal tooth dimensions ranged from 0.64 to 0.88, and 0.10 to 0.60 for buccolingual dimensions when calculated using multiple estimation methods (Harzer, 1987). In addition to the more informative narrow-sense heritability estimates provided in these studies, the use of more sophisticated statistical analyses elucidated specific patterns of heritability within the dentition. Summation of dimensions for tooth groups yielded the highest estimates, which was interpreted as an indicator of greater genetic control over tooth groups compared to individual teeth (Harzer, 1987, 1995). Also demonstrated was a general decrease in heritability from anterior to posterior teeth in the upper jaw, a pattern not observed in the mandible (Harzer, 1987, 1995).

14.6 Today (1990s–present)

Following the revisions and elaborations of statistical methods in the 1970s and 1980s, several novel study designs were introduced. A new dimension to dental twin studies was added by the use of twins reared apart in an investigation of caries experience, occlusion, and tooth morphology (Boraas *et al*., 1988). Another original approach to estimating environmental and genetic effects used the offspring of MZ twins and their spouses to perform analyses of variance only possible in half-sib design studies, allowing for detection of common environmental influences, maternal effects, and assortative mating (Potter, 1990).

Studies in the 1990s also introduced the use of statistical software to generate various models representing the genetic and environmental factors involved in the dentition. Once generated, the best fitting model was determined using maximum-likelihood methods and chi-square testing. Using the LISREL software package and PRELIS pre-processor, it was determined that the best model for explaining variation in the Carabelli trait on the permanent maxillary first molar was comprised of additive genetic effects, a general environmental factor, and an environmental component specific to each side; this produced a heritability estimate of 0.94 for the left molar and 0.86 for the right (Townsend and Martin, 1992). More conservative estimates for the Carabelli trait, 0.51 for the right and 0.37 for the left, and for tooth size, 0.60, were calculated after observing possible non-additive genetic effects and overall variance heterogeneity in 11 of 56 variables (Townsend *et al*., 1992).

Multivariate model-fitting analyses (in which progressively more complicated models were fit to data, beginning with a model incorporating unique

environmental influences only, followed by a model including unique environmental and additive genetic factors, and eventually non-additive and common environmental factors) showed that the majority of the variation observed in incisor crown size could be accounted for by unique environmental and additive genetic effects alone (Dempsey *et al*., 1995). Also noted was a general genetic factor influencing all incisors, specific genetic factors for each pair of antimeric teeth, and unique environmental factors specific to each tooth, as well as the entire group of incisors. An average heritability estimate of 0.86 was in agreement with the large amount of additive genetic variance illustrated in this model (Dempsey *et al*., 1995). Using similar statistical analyses, the best fitting model describing variance components of dental maturation in twins was found to incorporate additive genetic, and both unique and common environmental factors. The additive genetic component accounted for 43% of the total variance, while approximately half was attributed to the common environment, a reflection of the twins' shared prenatal, natal and postnatal circumstances of tooth maturation (Pelsmaekers *et al*., 1997).

The more recent quantitative genetic dental research has investigated the covariance structure of dimensions of the deciduous teeth for signs of genotype by environment interaction or directional dominance, and found evidence for neither; the conclusion was that a model incorporating only additive genetic (ranging from 62–91%) and unique environmental components of variance sufficiently explains the total variance in all teeth except for the lower central incisor in females (Hughes *et al*., 2000). When similar methods were applied to crown size of permanent teeth, in the absence of genotype by environmental interaction or assortative mating, a model incorporating additive genetic and unique environmental factors was adequate for all but two teeth: the maxillary left central incisor and right canine, for which introducing non-additive genetic or common environmental factors into the model provided a better fit. The lowest heritability estimates were associated with the mesiodistal length of the maxillary first molar, 0.50–0.60, and the highest with the buccolingual breadth of the maxillary premolars, 0.90, illustrating that no consistent pattern could be assigned to the observed heritabilities (Dempsey and Townsend, 2001). Additive genetic and unique environmental models were also fitted to crown measurements with inter-cuspal dimensions, producing higher heritability estimates for crown size than for inter-cuspal distances (Townsend *et al*., 2003).

14.7 From heritability estimation to redefining the phenotype

All of the quantitative genetics research on primate dental variation to date demonstrates that the size and shape of teeth are influenced significantly by the additive effects of genes. Therefore, the assumptions inherent to the adaptive and

phylogenetic interpretations noted at the beginning of this chapter are merited. However, it is probably clear to the reader at this point that heritability estimates by themselves, once demonstrated, are rather limited in what they can tell us about the genetic architecture of the dentition. Each estimate is specific to the population studied, and given the variety of analytical approaches, direct comparisons of heritability point estimates are somewhat meaningless. Have we hit a brick wall with quantitative genetic approaches? Is this all that we can learn from these types of analyses?

We argue that the answer to both questions is a resounding "no." The future for quantitative genetic analyses of dental variation will witness significant new insights into primate tooth biology primarily through two directions: quantitative trait locus (QTL)/linkage analyses and the estimation of genetic correlations.

14.7.1 Quantitative genetics and "evo-devo"

Advances in developmental genetics over the last 20 years have shown that genes operate through a series of complex spatial and temporal interactions to form the phenotype, and patterned phenotypes often reflect spatial and temporal relationships between functioning genomic regions. For example, the number and morphology of vertebrae in an organism correspond to the patterned expression of members of the *Hox* gene family, a pattern that is highly conserved across vertebrate taxa (Carroll *et al*., 2005; Galis, 1999).

Another example is the paired vertebrate appendages (i.e. limbs) that result from a different cascade of patterned and overlapping *Hox* gene expressions (Carroll *et al*., 2005; Shubin, 2002). Shubin *et al*. (1997) and Shubin (2002) argue that the origin of digits in tetrapods during the Devonian may well correspond to a duplication event of part of the *Hox* gene family to form a third phase of expression during limb development. The fossil record, therefore, provides significant insight into when, and in what types of environments and selective regimes, novel morphologies (such as digits) arose – providing the proverbial "evo" to studies of "devo" (evolutionary developmental genetics).

The dentition provides a similar opportunity to understand morphological evolution from an integrated geno- and phenotypic perspective. Teeth preserve well in the fossil record due to a largely inorganic content that makes them very hard. As is seen in most vertebrate lineages, the mammalian fossil record is dominated by teeth, with many taxa known only by their dentitions. These fossils record information about the evolving genotype as selection operated on the phenotype. A significant barrier, however, is deciphering what these morphological changes represent in terms of the underlying genetics.

Quantitative genetics provides an important opportunity for unlocking this information. Our current understanding of tooth developmental genetics derives almost exclusively from rodent models, and addresses two fundamental questions – how is the overall dental pattern determined (i.e. incisors vs. molars), and how is the morphology of an individual tooth determined. Tooth developmental genetics is beyond the scope of this chapter and we refer the reader to several excellent reviews for more information (Jernvall and Thesleff, 2000; Stock, 2001; Tucker and Sharpe, 2004; Weiss, *et al*., 1998).

As is commonly recognized, the genes necessary to form an organ are not necessarily the same ones that code for its minor phenotypic variation. From the perspective of a mammalian paleontologist, the mechanisms that underlie the variation upon which natural selection typically operates (population level variation) are of more critical concern. One way to obtain genetic information about minor phenotypic variation is to work from the phenotype back toward the genome. Quantitative genetic analyses provide such an approach.

14.7.2 QTL analyses

Gene-mapping techniques have been extremely useful in identifying genes that underlie genetic disorders, such as hemophilia (Lawn, 1985) and cystic fibrosis (Drumm and Collins, 1993). It is now possible to use these same techniques to study the genetic basis of polygenic traits, such as tooth size. There are two techniques that fall under the umbrella of QTL analyses. The first is a candidate gene approach, in which genetic variation at or near a known gene is tested for association with particular phenotypic variants. The second, and perhaps more relevant, approach to this discussion are quantitative trait loci (QTL) analyses, in which individual genes of small phenotypic effect are identified. This latter approach does not require a priori knowledge of gene function, and enables the identification of previously unknown genes that influence the phenotype of interest. Cheverud and Routman (1993) provide a nice overview.

Cheverud, Routman, and colleagues have also performed the majority of published QTL analyses on dental variation to date. By crossing two inbred strains of mice, one large and one small, and comparing the association of genetic marker alleles with morphological variation in the F2 generation, they identified more QTL for molar shape than size, as well as dominance effects for both (Workman *et al*., 2002). This may indicate that the genetic basis for molar size is simpler than that for shape. Additionally, they did not find any differences in the effects of the shape QTL between the three molars, suggesting that these are not distinct developmental structures (Workman *et al*., 2002). A similar study analyzed mandibular size and shape, through which 12 QTL

were identified as significantly influencing size and 25 QTL affecting shape (Klingenberg *et al*., 2001).

14.7.3 Morphological integration and modularity

Aside from providing information about the chromosomal locations of genes that influence mouse molar variation, these analyses also yield information about the inter-relatedness of various teeth. The lack of difference in the associated QTL for the first, second, and third molars indicates that variation in the size and shape of these structures is influenced by the same genetic effects, or rather, that these three molars are affected by complete pleiotropy. Pleiotropy underlies much of the rationale for the concept of morphological integration.

This concept was first introduced by Olson and Miller (1959) and revived by Cheverud (1982, 1989, 1995, 1996; Cheverud *et al*., 1983; Marroig *et al*., 2004). Morphological integration is the idea that phenotypic traits will be tightly correlated when they share a common developmental pathway and/or ultimate function. As such, individual morphological traits can be conceptualized as parts of sets. Identification of these integrated units is based on phenotypic correlations that have been shown to correspond to genetic correlations (Cheverud, 1988; Cheverud *et al*., 1997; Ehrich, *et al*., 2003; Klingenberg *et al*., 2001; Leamy *et al*., 1999; Mezey *et al*., 2000). Quantitative genetic models argue that these heritable patterns of variation may be stable over reasonably long periods of evolutionary time (Lande, 1979, 1980).

Morphological integration is thought to reflect developmental and molecular modularity. Developmental genetics shows that organisms have morphological and developmental modularity that results from modules at the genomic level, such as gene families (Carroll *et al*., 2005; Stern 2000; von Dassow *et al*., 2000; Weiss, 1990), and from modules in embryogenesis (Raff, 1996). This modularity has been defined as "a genotype-phenotypic map in which there are a few pleiotropic effects among characters serving different functions, with pleiotropic effects falling mainly among characters that are part of a single functional complex" (Wagner and Altenberg, 1996, p. 967). This modularity is critical since it enables an organism to be "evolvable" (Wagner and Altenberg, 1996).

Integration is, of course, a matter of degree (Lewontin, 2001; Magwene, 2001). An organism is itself an integrated unit, otherwise it could not function properly. However, it is obvious that an organism is comprised of sub-units that work together to form a whole. Therefore, morphological integration and modularity are hierarchical, though somewhat arbitrary, and can be investigated at multiple levels.

Although the dentition is in a sense its own module, given the hierarchical nature of its development (Bateson, 1892; Stock, 2001), there is also modularity within the dentition. Quantitative genetic analyses, through the estimation of genetic correlations, are further elucidating such modules. This is the level of modularity often thought to be represented by characters in paleontological analyses, especially those at the sub-family level or below (Hlusko, 2004; Peyer, 1968; Swindler, 2002).

14.7.4 Redefining dental phenotypes

We are using quantitative genetic analyses to identify shared genetic effects on the dental variation of a captive pedigreed baboon colony (Hlusko *et al*., 2002, 2004a, 2004b, in press a, in press b; Hlusko and Mahaney, 2003). Our goal is to reveal the genetic architecture that underlies primate dental variation. This is a meticulous process, as we first test for genetic correlations between all possible dental phenotype pairs. When a genetic correlation is estimated, we then test the extent of this correlation – is it 100%, indicating complete pleiotropy? Or is it lower, indicative of incomplete pleiotropy? Through this process, we are identifying phenotypes that represent the same genetic effects, phenotypes that have overlapping, but not identical, genetic effects, and phenotypes that are genetically independent. This knowledge enables the redefinition of the dentition based on the underlying genetic architecture.

For example, we have found complete pleiotropy for antimeres of all phenotypes studied to date, including linear metrics (Hlusko, 2000), morphological traits (Hlusko and Mahaney, 2003), loph/lophid orientation (Hlusko *et al*., 2004b), and 2D areas (Hlusko *et al*., in press b). There is evidence for incomplete pleiotropy between the maxillary and mandibular arches (Hlusko, 2000; Hlusko and Mahaney, 2003). We have also found significant genetic correlations between molar crown size and crown–rump length (body size) (Hlusko *et al*., in press a).

As evidence for genetic correlations improves our understanding of morphological evolution, estimates of no genetic correlation can also be informative, although this must be done with caution. For example, we have performed a quantitative genetic analysis of enamel thickness in baboons as a model for understanding the genetic architecture of this phenotype in other primates, including humans (Hlusko *et al*., 2004b). Hominid paleontologists have emphasized the importance of enamel thickness for decades, starting with "*Ramapithecus*" (Simons and Pilbeam, 1972), and more recently in the identification of newly recovered late Miocene hominids (Andrews, 1995; Brunet *et al*., 2002; Leakey *et al*., 1995; Senut *et al*., 2001; White *et al*., 1995). Genetic

analyses of linear measurements of radial molar enamel thickness in this population of pedigreed baboons indicate that enamel thickness is heritable. However, interestingly, it is not genetically correlated with either sex or tooth size. This result suggests that enamel thickness could evolve rapidly through evolutionary time, tracking dietary shifts, and increasing the likelihood for homoplasy in this character.

We are also using these tests of genetic correlation to redefine the dental phenotype. Although much of this work is still in progress, we have reported results that demonstrate a genetic modularity that does not correspond with developmental modules. The orientation of mesial molar lophids is affected by complete pleiotropy along the tooth row, as is the orientation of the distal lophids. However, the mesial and distal lophids are found to be genetically independent (represented in Figure 14.2). As Workman *et al*. (2002) interpreted the mouse molar series to be indicative of the same genetic factors, baboon molars are similarly reflexive of the same genetic effects. However, the mesial and distal portions of the molar crown are independent of each other in terms of the orientation of the lophids, suggesting a level of modularity that cuts across the developmental module of a tooth.

Another dental phenotype studied in this population of pedigreed baboons also contributes new information about modularity, although the results are more difficult to reconcile with developmental genetics at this point in time. 2D molar cusp area appears to vary taxonomically in primates, although the majority of research to date has focused on extant and extinct hominoids (e.g. Bailey 2004; Corruccini, 1977; Erdbrink 1967; Hills *et al*. 1983; Kondo and Townsend, 2006; Macho, 1994; Sperber, 1974; Suwa *et al*., 1994, 1996; Uchida 1998a, 1998b; Wood and Engleman 1988; Wood *et al*., 1983). We undertook a quantitative genetic analysis of variation in this phenotype in this pedigreed population of baboons (Hlusko *et al*., in press b). Our results show that while variation in cusp size is heritable and sexually dimorphic, there are interesting patterns of genetic correlation between the various cusps. For the first, second, and third mandibular molars the metaconid-hypoconid correlation is consistently estimated as 0.0, whereas the entoconid-protoconid correlation is estimated as 1.0. The other cusp pairs demonstrate incomplete pleiotropy. This diagonal pattern of complete and no genetic correlation counters what we currently know about tooth development and mineralization. We are now collecting data on maxillary molars in baboons and molar cusp area, in general, for mice in an attempt to clarify this conundrum.

Considerably more research is needed to determine whether or not the modularity identified through quantitative genetic analyses of mouse and baboon dental variation is also present in other primates. However, the approach looks promising. A similar analysis of cranial variation in New World monkeys has

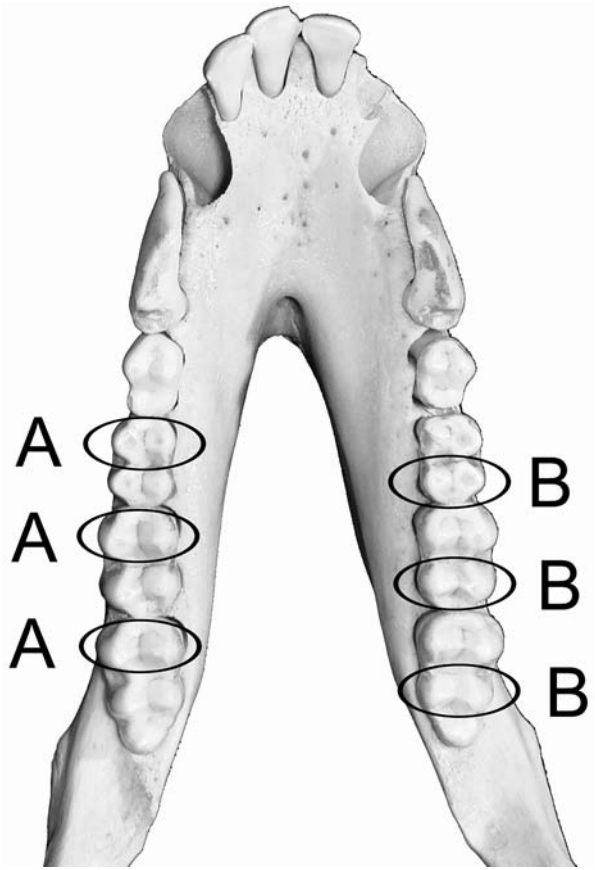

Figure 14.2 Baboon mandible in occlusal view. Quantitative genetic analyses have shown that first, second and third molar mesial lophid orientation (A) along the tooth row is determined by the same genetic effects, as is distal lophid orientation (B). However, the orientations of A and B on the same crown are genetically independent (Hlusko *et al*., 2004a). See text for more details.

found that the genetic architecture appears to be conserved across taxa that diverged 30 million years ago (Marroig and Cheverud, 2005). Given that this cranial study relied on phenotypes with lower heritabilities than those of the dentition, we feel confident that the approach described herein for the dentition will yield informative results. If our initial results are bolstered through further analyses, these newly defined phenotypes will enable us to study dental variation in fossil taxa with a better understanding of what those morphological changes represent in terms of the evolving genotype, enabling us to reconstruct a genetic evolutionary history of the primate dentition (Hlusko, 2004).

14.8 Conclusions

The past 80 years have witnessed a revolution in quantitative genetic approaches to primate dental variation. What started out as a simple question concerning the presence or absence of a genetic contribution to population-level variation has diversified into fairly detailed questions of genetic correlation and gene mapping. Through all of this we have gained tremendous insight to the genetic architecture of primate dental variation. Virtually all tooth size and shape variation is heritable, with most estimates attributing a large portion of the variance to the additive effects of genes. Variation in occlusion, arch shape, and crowding appears to result primarily from non-genetic influences. Dominance, sex, and maternal effects have also been identified. Researchers have found evidence for differing genetic factors for anterior vs. posterior tooth types, and future research estimating genetic correlations promise to refine these propositions. We find two research directions particularly compelling at this point: (1) QTL analyses that are identifying specific chromosomal loci that have phenotypic effects, and (2) estimation of genetic correlations that are elucidating evolutionary modularity. The application of quantitative genetics to dental anthropology may just now be entering its heyday with much promise for the future.

Acknowledgments

MCM and LJH's research cited herein has been supported by the National Science Foundation under Grants No. 0500179 and 0130277. National Institutes of Health, National Center for Research Resources P51 RR013986 supports the Southwest National Primate Research Center. OTR is supported by a Chancellor's Fellowship, University of California Berkeley. SKA is supported in part by a Professional Development International Fellowship from the Wenner-Gren Foundation.

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