2. Of mice and monkeys: Quantitative genetic analyses of size variation along the dental arcade

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Abstract

We present preliminary results from quantitative genetic analyses of tooth size variation in two outbred pedigreed populations, baboons and mice. These analyses were designed to test the dental field theory as proposed by Butler (1939), that there are three fields within the dentition: incisor, canine, and molar. Specifically we estimated the genetic correlation between pairs of linear size measurements. Results from the baboon analyses suggest that there may also be a premolar field that is only partially independent of the molar field proposed by Butler (1939). Analyses of the mouse data indicate that for mice, size variation in the incisors appears to be genetically independent of molar size. If the field theory is correct, future analyses on incisor data for the baboons will return similar results of genetic independence. Circumstantial evidence from the fossil record suggests that there will be at least some degree of independence between the anterior and postcanine dentitions of primates.

Introduction

Huxley and de Beer (1934) were among the first embryologists to formalize the concept of the gradient-field in relation to the development of the animal body plan. They defined it as:

"... a region throughout which some agency is at work in a co-ordinated way, resulting in the establishment of an equilibrium within the area of the field.

S.E. Bailey and J.-J. Hublin (Eds.), Dental Perspectives on Human Evolution, 237–245.

A quantitative alteration in the intensity of operations of the agency in any one part of the field will alter the equilibrium as a whole. A field is thus a unitary system, which can be altered or deformed as a whole; it is not a mosaic in which single portions can be removed or substituted by other without exerting any effect on the rest of the system." (1934: 276).

In 1939, Butler evoked this concept to explain the dental pattern of mammals, i.e., the number and morphology of incisors, canines, premolars, and molars. In his morphogenic field theory of dental development, Butler suggests that each tooth primordium is equivalently pluripotent, possessing the potential to develop into any type of tooth in the dentition. Determination of the ultimate form of each tooth is a function of the tooth primordium's exposure to morphogens and the nature and concentration of these morphogen(s), both of which are related to the tooth placode's location within a developmental field. Butler infers that morphogenic fields are distinct: each perfused with a characteristic combination of morphogens and, consequently, one should be able to identify different morphogenic fields within a dental arch based on tooth morphology. By this logic, Butler identifies three distinct dental morphogenic fields in the mammalian dentition: the molar, canine, and incisor fields. In this scheme, incisor size and shape would be developmentally independent of molar size and shape; however, because premolars are within the molar field, the development of their size and shape is correlated with that of molars but independent of incisors, for example (Butler, 1939).

The last 15 years have seen a dramatic increase in our understanding of the genetic mechanisms needed to form teeth and pattern the overall dentition, primarily in rodent models. From this work we know that the patterning of the mouse dentition, or dental formula, first appears histologically at embryonic day 11 (E11) when a region of the mouse oral epithelium thickens to form the dental lamina (for more details see Weiss et al., 1998; Jernvall and Thesleff, 2000; Stock, 2001; Tucker and Sharpe, 2004).

At this dental lamina stage of development, tooth position and fate is induced by the oral epithelium. The dental pattern, or formula that is already determined by this stage of development has been hypothesized to result from one of two possible mechanisms. The first is an odontogenetic combinatorial code (Cobourne and Sharpe, 2003). This is similar in concept to the *Hox* gene patterning of the vertebral column, although *Hox* genes are not expressed in tooth development and therefore do not similarly regulate dental patterning (James et al., 2002). Other regulatory genes including members of the *Barx, Dlx, Msx*, and *Pitx* gene families have been implicated (Cobourne and Sharpe, 2003). Restricted expression of two members of the *Dlx* family to the more caudal region of the developing branchial arch may be important for determining the maxillary versus mandibular jaws (Depew et al., 2002).

The second dental patterning mechanism proposed is that of a reaction diffusion process. Weiss et al. (1998) attribute the periodicity of the dentition to quantitative interactions of diffusible signaling factors. This idea is based on Savart's and Chladni's nineteenth century recognition that different wave lengths mechanically interact to form different interference patterns, easily visualized as patterns formed by sound waves moving through powder on violin plates (see Weiss et al., 1998 for more details). Bateson (1894) applied this concept to serially homologous traits, such as the dentition, and coined the term "meristic variation". Alan Turing (1952) later proposed that chemical interactions could similarly result in wave-like patterns as substances, or morphogens, interact in a *reaction diffusion* process.

To date, there have been no convincing data that refute or support the validity of either of these models. We have not yet been able to successfully test these hypotheses partly

because of the derived and reduced dentition of the model animal used in gene expression studies: mice. Mice lack deciduous dentitions, permanent premolars and canines. Therefore, only two tooth types are present – molars in the distal region of the jaw and incisors in the anterior region with a large diastema in between – and consequently, hypotheses about the molecular mechanisms that pattern the dental arcade remain relatively untestable.

Butler's (1939) concept of morphogenic fields is relevant today, as it provides an alternative to the two molecularly-driven hypotheses, or rather it is a combination of the two models. Here, we propose a method through which Butler's morphogenic field hypothesis can be tested using quantitative genetic analyses. Specifically, Butler's model predicts that genetic correlations will be higher within fields than between them. We present preliminary results from two sets of quantitative genetic analyses of tooth size variation, one on a pedigreed population of baboons, and the other a pedigreed population of mice.

Material and Methods

Study Population – Papio hamadryas

Mesiodistal length and mesial buccolingual widths of all maxillary molars and premolars were collected from dental casts made for 630 baboons. These animals are part of a captive, pedigreed breeding colony of baboons, *Papio hamadryas,* housed at the Southwest National Primate Research Center (SNPRC) in San Antonio, Texas. Taxonomy follows Jolly (1993). The colony is maintained in pedigrees with all mating opportunities controlled.

Genetic management of the colony was started over 20 years ago and allows for data collection from non-inbred animals. All non-founder animals in this study resulted from matings that were random with respect to dental, skeletal, and developmental phenotype. The female to male sex ratio is approximately 2:1. The animals from which data were collected are distributed across eleven extended pedigrees that are 3–5 generations deep. The mean number of animals with data per pedigree was 44, and these individuals typically occupied the lower two or three generations of each pedigree.

The Institutional Animal Care and Use Committee, in accordance with the established guidelines. (National Research Council, 1996), approved all procedures related to the treatment of the baboons during the conduct of this study.

Study Population – Mus sp.

Length of the maxillary first molar, incisor, and molar (M^{1-3}) row were collected for 222 individuals that are part of a large pedigreed collection of skeletonized mice made by Richard D. Sage between 1977 and 2002, currently housed at the University of California Berkeley's Museum of Vertebrate Zoology.

This collection is unusual in that it is outbred and founded with at least 7 species of wild-caught *Mus* rather than inbred, homozygous lab strains. The collection is quite diverse at the subgeneric and species levels. Three of the four subgenera are represented: *Coelomys* (shrew mice), *Mus* (house and rice field mice), and *Nannomys* (African pygmy mice). Taxonomy follows Nowak (1991). Table 1 summarizes the taxonomic composition.

These mice are from stocks of wild mice collected in the 1970s by R.D. Sage and his colleagues. The number of founders for each species ranges between 2 and 16. Taxonomy became difficult as various species were crossed, and therefore the designations shown in Table 1 represent the best estimation of each individual's closest taxonomic affinity based on ancestry from the founders.

In total, pedigree data for 299 mice were used to reconstruct the pedigrees, although

Table 1. Taxonomic composition of the Mus sample used in these quantitative genetic analyses

Subgenus	*Species*	*Total # of individuals*
Coelomys	*pahari*	11
Mus ($n = 196$)	*caroli*	23
	cervicolor	92
	cooki	51
	musculus	23
	spicilegus	7
Nannomys	*minuotoides*	4
Hybrids	–	11
	TOTAL	222

dental phenotype data were only collected for 222 animals. Of the 299, 155 are female and 144 are male. For analytical purposes the pedigrees were divided by litter, with approximately 47 pedigrees for each analysis, and an average of 6 individuals per pedigree.

Analytical Methods

All pedigree data management and preparation was facilitated through use of the computer package PEDSYS (Dyke, 1996). Statistical genetic analyses were performed using a maximum likelihood based variance decomposition approach implemented in the computer package SOLAR (Almasy and Blangero, 1998). The phenotypic covariance for each trait within a pedigree is modeled as

$$\Omega = 2\Phi\sigma_G^2 + I\sigma_E^2 \qquad (1)$$

where Φ is a matrix of kinship coefficients for all relative pairs in a pedigree, σ_G^2 is the additive genetic variance, I is an identity matrix (composed of ones along the diagonal and zeros for all off diagonal elements), and σ_E^2 is the environmental variance. Because the components of the phenotypic variance are additive, such that

$$\sigma_P^2 = \sigma_G^2 + \sigma_E^2 \qquad (2)$$

we estimated heritability, or the proportion of the phenotypic variance attributable to additive genetic effects, as

$$h^2 = \frac{\sigma_G^2}{\sigma_P^2} \qquad (3)$$

Phenotypic variance attributable to nongenetic factors is estimated as $e^2 = 1 - h^2$.

Using extensions to univariate genetic analyses that encompass the multivariate state (Hopper and Mathews, 1982; Lange and Boehnke, 1983; Boehnke et al., 1987), we modeled the multivariate phenotype of an individual as a linear function of the measurements on the individual's traits, the means of these traits in the population, the covariates and their regression coefficients, plus the additive genetic values and random environmental deviations, as well as the genetic and environmental correlations between them (for more detailed explanation see Mahaney et al., 1995). We obtained these two correlations from additive genetic and random environmental variance-covariance matrices. Respectively, the additive genetic correlation (ρ_G) and the environmental correlation (ρ_E) are estimates of the additive effects of shared genes (i.e., pleiotropy) and shared environmental (i.e., unmeasured and nongenetic) factors on the variance in a pair of traits. Because the genetic and environmental components of the phenotypic correlation matrix are additive, like those of the corresponding variance-covariance matrix, we use the maximum likelihood estimates of these two correlations to calculate a total phenotypic correlation between two traits, ρ_P, in a way that accommodates the nonindependence between data obtained from relatives as

$$\rho_P = \sqrt{h_1^2}\sqrt{h_2^2}\ \ \rho_G + \sqrt{(1-h_1^2)}\sqrt{(1-h_2^2)}\ \rho_E. \qquad (4)$$

Significance of the maximum likelihood estimates for heritability and other parameters was assessed by means of likelihood ratio tests (see Hlusko et al., 2004a, b for details).

Results

Papio hamadryas

Analyses of the baboon maxillary length and width data (Table 2) show that the shared genetic affects between premolar measurements are not significantly different from models constraining the genetic correlation to one. The same degree of shared genetic affects is found when data from pairs of first, second, and third molars are analyzed. However, when premolars are compared to molars, the shared genetic affects are estimated to be between 0.63 and 0.50, and significantly different from models constraining the genetic correlations to one (complete pleiotropy) or zero (no pleiotropy).

Mus sp.

Estimates of the shared genetic affects for the mouse data are presented in Table 3. The genetic correlation between incisor and first molar length is not significantly different from the model in which we constrain this correlation to zero. Our analysis of the mesiodistal length of the incisor compared to the overall mesiodistal length of the molar series also returns a genetic correlation not significantly different from zero. However, when the length

*Table 2. Results from bivariate quantitative genetic analyses of the length and widths of baboon maxillary premolars and molars**

Lengths	$h^2_{mesial\ tooth}$	$h^2_{distal\ tooth}$	*n*	ρ_G	$P(\rho_G = 0)$	$P(\lvert\rho_G\rvert = 1)$
RP^3:RP^4	0.26	0.73	403	0.98	<0.0001	0.46
RP^4:RM^1	0.72	0.66	537	0.63	<0.0001	<0.0001
RM^1:RM^2	0.69	0.71	547	0.99	<0.0001	0.40
RM^2:RM^3	0.79	0.31	541	0.95	0.0003	0.39
RM^1:RM^3	0.66	0.42	495	0.65	0.01	0.05
Widths	$h^2_{mesial\ tooth}$	$h^2_{distal\ tooth}$	n	ρ_G	$P(\rho_G = 0)$	$P(\lvert\rho_G\rvert = 1)$
RP^3:RP^4	0.64	0.66	423	1	<0.0001	na
RP^4:RM^1	0.61	0.65	536	0.50	0.006	<0.0001
RM^1:RM^2	0.66	0.59	543	0.85	<0.0001	0.0007
RM^2:RM^3	0.57	0.48	552	0.90	<0.0001	0.10
RM^1:RM^3	0.72	0.54	535	0.78	<0.0001	0.003

* h^2 = residual heritability; L = left, R = right; superscript # = maxillary tooth row position; P = premolar; M = molar; length = mesiodistal diameter; width = crown width (mesial buccolingual diameter)

*Table 3. Results from the bivariate quantitative genetic analyses of the length of mice incisors and molars**

Lengths	$h^2_{mesial\ tooth}$	$h^2_{distal\ tooth}$	*n*	ρ_G	$P(\rho_G = 0)$	$P(\lvert\rho_G\rvert = 1)$
I^1:M^1	0.32	0.42	214	0.25	0.32	0.0009
I^1:M^{1-3}	0.32	0.38	214	0.22	0.24	0.00008
M^1:M^{1-3}	0.42	0.38	214	0.93	<0.0001	0.16

* h^2 = residual heritability; L = left, R = right; superscript # = maxillary tooth row position; I = incisor; M = molar; length = mesiodistal diameter

of the first molar is compared to the entire molar row length, the shared genetic affects are estimated as not significantly different from the model in which we constrain the genetic correlation to one.

Discussion

In this paper we present preliminary results from quantitative genetic analyses of dental size variation in an outbred pedigreed population of baboons and an outbred pedigreed population of mice. As is often the case with exploratory research, the results presented here beg more questions than they answer. But in so doing, they demonstrate the potential usefulness of such a comparative approach for refining hypotheses about the genes responsible for the mechanisms that pattern the mammalian dentition.

Before discussing these results, we first address the potential caveats inherent to the analyses presented here. Genetic correlations can result from either pleiotropy or gametic phase disequilibrium between genes affecting different traits. In the case of pleiotropy, the same gene or set of genes influences variation in more than one phenotype. In the case of gametic phase disequilibrium, alleles at two or more loci with similar effects on more than one trait exhibit non-random association (Lynch and Walsh, 1998). The degree of gametic phase disequilibrium is a function of a population's genetic history and demography: e.g., it will be lower in outbred populations with many unrelated founders as recombination exerts its effects each generation, higher in populations undergoing rapid expansion from a small number of founders and those resulting from recent admixture. Given a conducive set of population characteristics, the likelihood of genetic correlation between two traits being due to gametic phase disequilibrium is higher for simple traits, with monogenic (or nearly so) inheritance. However, if variation in a pair of traits is attributable to the effects of multiple alleles at multiple loci – as well as to the effects of multiple environmental factors and interactions between them – gametic phase disequilibrium is not likely to be a major contributor to the genetic correlation (Lynch and Walsh, 1998).

Therefore, we are cautiously confident that significant additive genetic correlations estimated in our analyses of data on pairs of complex, multifactorial dental measures from our non-inbred, extended pedigrees of baboons are primarily indicative of pleiotropy rather than gametic phase disequilibrium. Ongoing and planned whole genome screens and linkage disequilibrium analyses in this population will help confirm this. However, we have less confidence concerning the unambiguous interpretation of significant genetic correlations estimated in our analyses of data from the first and second generation hybrids of mouse species. We are currently investigating whether or not a model of linkage disequilibrium or pleiotropy better fits with the genetic correlations found for these mouse data. These analytical tests are beyond the scope of this chapter and will be published elsewhere in the near future. In this paper, we will focus on the lack of a genetic correlation rather than the presence, a result that is of more relevance to the discussion of Butler's field theory (1939).

One hypothesis derived from the field theory is that the incisor field would be genetically independent of the molar field (Butler, 1939). This indeed is what we find in our analyses of the mouse data. The mesiodistal length of the maxillary incisor appears to be genetically independent of the mesiodistal length of both the first molar and the entire length of the molar row.

The second hypothesis inherent to Butler's theory is that variation in the premolars and molars would be due to the effects of the same gene or genes. That is, they would exhibit genetic correlations because

their development, occurring in the same morphogenic field (the molar field), is influenced by the same morphogens whose molecular and biochemical characteristics and concentrations are influenced by the same gene(s). The results of some of our analyses of data for the maxillary postcanine teeth in these pedigreed baboons do accord with this prediction in that size variation in the premolars is influenced by overlapping but not identical genetic affects as is size variation in the molars.

However, not all of our analyses of data from the baboon produce results consistent with Butler's theory. If there are only three dental fields (incisor, canine, and molar), then the degree of genetic correlation among the premolars and molars would be similar since they are part of the same molar field. This is not what we find. Rather, the shared genetic affects are greatest within tooth classes (premolars versus molars) and reduced but not independent between classes. Therefore, these preliminary analyses suggest that there may be a fourth dental morphogenetic field that corresponds to the premolars.

Dahlberg applied the field theory to his study of the human dentition (1945). He proposed different fields depending on which phenotype or trait was under consideration. For example, he argued that *form* was divided into four fields: incisors, canine, premolars, and molars. However, Dahlberg's focus on only one extant species (*Homo sapiens*), led him to state that, "They [a particular set of teeth] are, as a rule, either all small, all large or at some stage in between . . ." (1945: 688). Therefore, he proposed that size was uniformly influenced across the dentition. Our results suggest that Dahlberg's concept of four dental fields for form, rather than just three as proposed by Butler (1939), may also apply to size variation.

The genetic relationships between the tooth classes may also be variable, with some teeth more genetically independent of others. For example, incisors may be relatively more genetically independent from molars than are premolars. A key test that remains is to analyze incisor data for the baboons. This work is underway.

In the meantime, suggestive evidence lends support to the hypothesis that the genetic independence we see between mouse incisors and molars may be similarly found in primates. Across primate taxa, the most variable aspect of the dentition is the incisor region. There are numerous dramatic variations in the incisors relative to the rest of the dentition, for example, within the hominids *Australopithecus boisei* has reduced anterior teeth relative to those of *A. garhi* (Asfaw et al., 1999), in the Old World monkeys *Theropithecus oswaldi leakeyi* has a reduced anterior dentition relative to its phyletic ancestor *Theropithecus oswaldi darti* (Leakey, 1993), lemurs (the tooth comb), Oligocene primates from Egypt (*Parapithecus*' extreme reduction of the maxillary incisors and loss of the mandibular incisors), and last but not least, *Daubentonia*'s extremely derived large robust continuously growing rodent-like incisors.

Of course these evolutionary trends may result from different selective forces operating on the anterior and posterior aspects of the dentition. However, the key question that underlies all of evolutionary biology does not concern adaptation or even phylogeny, but rather "what are the characters upon which the process of evolution occurs?" Character definition is in many ways the most fundamental question to be addressed in evolutionary biology (Lewontin, 2001). Does the incisor region represent a character distinct from the postcanine dentition? Are the premolars and molars correlated but not distinct characters? In this paper we present two sets of quantitative genetic analyses of dental variation that are part of an endeavor to better understand the mammalian dental phenotype from the perspective of the genetic

architecture, and thereby to identify the phenotypic characters upon which selection operates.

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