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Statistical Genetics of Molar Cusp Patterning in Pedigreed Baboons: Implications for Primate Dental Development and Evolution+

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ABSTRACT Gene expression and knock-out studies provide considerable information about the genetic mechanisms required for tooth organogenesis. Quantitative genetic studies of normal phenotypic variation are complementary to these developmental studies and may help elucidate the genes and mechanisms that contribute to the normal population-level phenotypic variation upon which selection acts. Here we present the first quantitative genetic analysis of molar cusp positioning in mammals. We analyzed quantitative measures of molar cusp position in a captive pedigreed baboon breeding colony housed at the Southwest National Primate Research Center in San Antonio, Texas. Our results reveal complete pleiotropy between antimeric pairs of traits – i.e., they are influenced by the same gene or suite of genes. Mandibular morphological homologues in the molar series also exhibit complete pleiotropy. In contrast, morphological homologues in maxillary molar series appear to be influenced by partial, incomplete pleiotropic effects. Variation in the mandibular mesial and distal molar loph orientation on the same molar crown is estimated to be genetically independent, whereas the maxillary molar mesial and distal loph orientation is estimated to have partially overlapping genetic affects. The differences between the maxillary and mandibular molar patterning, and the degree of genetic independence found between lophs on the same molar crown, may be indicative of previously unrecognized levels of modularity in the primate dentition. *J. Exp. Zool. (Mol. Dev. Evol.) 302B:268–283, 2004.*

INTRODUCTION

Developmental research over the last 15 years has changed the way we think about morphological evolution (Raff, '96). For example, knowledge of the genetics underlying limb development elucidates the origins and evolution of the tetrapod limb (Shubin, 2002; Tickle, 2002; Shubin, et al., '97). The combination of fossil and genetic data also sheds light on the radiation of metazoans and their body plans in the Cambrian 'explosion' (Raff, '96). Similarly, as our understanding of the mechanisms underlying dental development improves, so does our appreciation for how evolution of these processes may have produced the tooth morphologies recorded in the fossil record (Keränen et al., '98; Weiss et al., '98; Jernvall, 2000; Jernvall et al., 2000; Stock, 2001).

There are two fundamental research directions concerning the development of the mammalian dentition, and advances have been made towards our understanding of both, primarily through gene expression and knock-out studies of mice (Maas and Bei, '97; Weiss et al., '98; Jernvall and Thesleff, 2000; Stock, 2001). The aim of the first major direction is to decipher the mechanisms that determine tooth row patterning; i.e., how incisors are produced in one region of the mouth and molars in another, with canines and premolars in between. This overall dental patterning may be the result of a combinatorial genetic code, much like is seen for *Hox* genes and the vertebral column (Kessel and Gruss, '91; Condie and Capecchi, '93).

However, *Hox* genes are not expressed in the tissues from which the dentition develops, so they

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do not seem to regulate the patterning of the dentition. Rather, several other homeobox genes from the *Barx*, *Dlx*, and *Msx* families have been implicated in an *odontogenetic code* (Sharpe, '95; Thomas and Sharpe, '98; Tucker and Sharpe, '99). A different model has also been proposed based on the concept of *reaction-diffusion* or Bateson-Turing processes (Turing, '52; Kieser, '84; Jernvall, '95; Jernvall et al., '98; Weiss et al., '98). In this model, *morphogens* interact in differential wave-like patterns to produce spatial variation in chemical reactions, such as inhibition, production, autocatalysis, etc. Cells respond to these spatial morphogenetic variations, resulting in spatially patterned morphology, such as in pigmentation, mineralization, location of scales or feathers, etc. Though there is experimental and syndromic evidence supporting the combinatorial code model (Vastardis et al., '96; Thomas et al., '97; Ferguson et al., '98; Vanden Boogaard et al., 2000), these results can also be interpreted in terms of threshold models that comply with the reaction-diffusion model (Thesleff, '96; Stock, 2001). Some patterns of population morphological variation have also been interpreted to better fit this latter model (Jernvall, 2000).

The second major direction within dental developmental research focuses on the formation of individual teeth and the mechanism(s) that determine the number, size, shape, and placement of cusps (Jernvall and Thesleff, 2000; Stock, 2001). By mouse embryonic day 13.5 (E13.5) tooth buds have formed as outgrowths of the dental lamina, a thickened band of epithelial tissue, possibly specified by antagonistic fibroblast growth factor (FGF) and bone morphogenetic protein (BMP) signaling (Fig. 1). The tooth bud invaginates into the mesenchyme as the inductive potential shifts from the epithelium to the mesenchyme. The epithelial tissue then enfolds a mass of mesenchyme forming a cap-like structure, initiating what is known as the cap stage.

At this point in odontogenesis, a condensation of non-proliferating epithelial cells forms at the tip of the tooth bud. This condensation, known as an enamel knot, does not proliferate, expresses many of the same signaling molecules as other embryonic signaling centers, and is surrounded by rapidly dividing epithelial cells (Jernvall et al., '98; Thesleff et al., 2001). The initiation of the enamel knot may be a critical moment in morphogenesis, as it potentially indicates the start of the molecular cascades that determine species-specific cusp patterns (Keränen et al., '98; Jernvall et al., 2000).

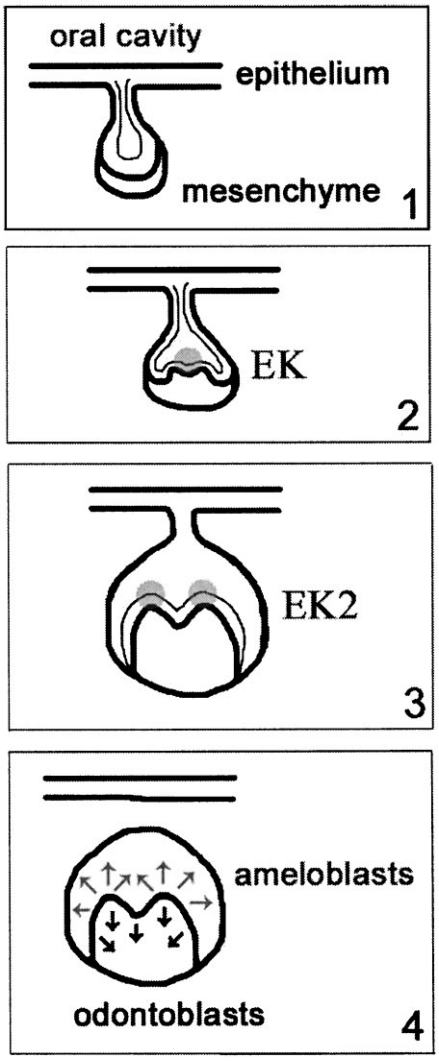

Fig. 1. Representation of the early stages of mammalian tooth development. **Panel 1**: embryonic day 13.5 (E13.5), the bud stage; **Panel 2**: E14.5, cap stage, primary enamel knot (EK) shown in gray; **Panel 3**: formation of secondary EKs, shown in gray; **Panel 4**: E16, bell stage when mineralization starts. See text for more details.

In mice, the enamel knot grows distally from the mesial aspect of the tooth bud into a bullet-shaped structure (Jernvall et al., '94) that then undergoes apoptosis in reverse order from its original growth; i.e. the most distal region dies off first (Vaahtokari et al., '96).

This primary enamel knot gives rise to secondary enamel knots (E15). These secondary enamel knots are located at what becomes the tip of each cusp and express virtually all the same known regulatory genes as the primary enamel knot, except for *BMP2* (Jernvall, 2000). Additionally, no differences in homeobox gene expression have

been found between the various cusps (Zhao et al., 2000b). Therefore, the secondary enamel knots appear to be identical in terms of their molecular signaling, suggesting that the patterning of cusp positions may be the product of an overall dynamic program. Consequently, pleiotropy among cusps is assumed to be high (Jernvall and Jung, 2000).

The next stage of odontogenesis is the bell stage (E16) during which enamel-forming ameloblasts derive from the epithelium and the mesenchyme gives rise to odontoblasts that form dentine. With the start of mineralization, bunodont molar crown morphology is largely determined and is finalized at the time of eruption. Teeth do not continue to grow after this point because the enamel-forming cells are external to the crown and are shed at eruption. Only wear and breakage alter crown morphology after this point.

Species-specific cusp arrangements first appear with the development of the secondary enamel knots (Keränen et al., '98; Jernvall and Thesleff, 2000; Jernvall, et al., 2000). Keränen et al. ('98) and Jernvall et al. (2000) studied the expression patterns of numerous regulatory genes in two rodent species, mouse and vole. These two species are similar in size, gestation time, and dental pattern. However, mice have roughly parallel and low-crowned mandibular molar cusps, whereas voles have asymmetrical and continuously growing high-crowned cusps. Despite the morphological differences in their teeth and an evolutionary divergence 20–25 million years ago (Nikoletopoulos et al., '92), they are found to have similar molecular cascades throughout tooth organogenesis. This further demonstrates the conserved nature of dental developmental mechanisms, as is also seen in such phylogenetically distant and morphologically dissimilar taxa as mice and humans (Davideau et al., '99).

Species differences do appear just prior to the formation of the secondary enamel knots. Morphological differences between mouse and vole secondary enamel knots were closely correlated with immediately preceding *Fgf4*, *Shh*, *Lef1*, and *p21* spatial expression patterns (Jernvall et al., 2000). Therefore all four genes appear to be involved in cusp patterning, though the interactions between these signaling pathways are currently unknown (Jernvall, et al., 2000).

It is widely recognized that the mechanisms required to make an organ are not necessarily the same mechanisms that result in its normal population level variation. As selection operates on populations, knowledge of the mechanisms that produce normal variation is needed in order to reconstruct an integrated geno- and phenotypic evolutionary history (Jernvall, 2000). The mouse/vole study represents a critical break-though in understanding molar morphological variation and evolution in terms of underlying variation in gene expression (Polly, 2000), and draws attention to *Fgf4*, *Shh*, *Lef1*, and *p21* and their regulators as potential candidate genes for determining population level molar morphological variation.

A mouse and human genetic mutation bolster this interpretation. *Tabby* mice and humans with X-linked anhidrotic (hypohidrotic) ectodermal dysplasia share a genetic mutation of the syntenic ectodysplasin A gene (*Eda*) on the X chromosome that causes buccal/labial and lingual molar cusps to be compressed or fused along with other epithelial disorders (Ferguson et al., '97; Srivastava et al., '97). Pipsa et al. ('99) found that *Tabby* molars cultured in vitro with FGF4 and –10 have partially corrected cusp development. A more recent study (Gaide and Schneider, 2003) demonstrated that *Tabby* mouse embryos treated with a recombinant form of EDA1 in utero have an almost completely and permantly rescued phenotype. Further research is needed to discern the relationship between *Eda* and *Fgf4* and *–10* and their potential role(s) in determining molar cusp positioning.

If *Fgf4*, *Shh*, *Lef1*, and *p21* and/or the mechanisms that regulate them underlie population level variation in cusp patterning, then the patterning cascade interpreted from their expression suggests significant pleiotropy between molar cusps, and that distal cusp pairs are essentially genetic reiterations of the first cusp pair. Both morphological (Marshall and Butler, '66; Van Valen, '94; Jernvall and Jung, 2000) and developmental studies provide evidence that characters of occluding teeth may also result from the same developmental process. Here we test these two hypotheses (hypothesis 1: mesial and distal cusp pair orientations results from significant pleiotropy; hypothesis 2: maxillary and mandibular inter-arch cusp pair orientations result from significant pleiotropy) using modern quantitative genetic analyses of dental variation from a captive pedigreed breeding colony of baboons.

At first, our chosen approach to the dissection of the genetic architecture for dental developmental variation may seem to be in direct contrast to more established approaches of molecular developmental biology and genetics; however, they actually are complementary. While the latter

investigate directly the effects and/or expression of known candidate loci on, respectively, target traits or in target tissues in developing organisms, we utilize quantitative genetic approaches to statistically detect and measure the effects of initially unidentified genes on phenotypic variation in fully differentiated traits in adults. Once detected, available extensions to these statistical genetic approaches allow us to localize the genetic effects to specific chromosomal regions.

These approaches are derived entirely from the classical genetics description of the phenotypic variance in a trait (σ_P^2) as an additive function of the genetic (σ_G^2) and environmental (σ_E^2) variances, such that, in its simplest form $\sigma_P^2 = \sigma_G^2 + \sigma_E^2$. Classical quantitative genetics theory describes the phenotypic covariance among relatives for a trait similarly, and its methods allow us to take advantage of the fact that the degree of genetic and phenotypic similarity between any relative pair is proportional to their kinship (Falconer, '89; Lynch and Walsh, '98) to detect and quantify the relative contributions of genes and environmental factors – including random, unmeasured factors – to this covariance (Almasy and Blangero, '98).

Additionally, multivariate extensions to this approach allow us to detect shared or correlated genetic and non-genetic effects between different phenotypes, such as different dental crown dimensions or morphologies (Almasy and Blangero, '98). Genetic correlations are indicative of pleiotropy – i.e., the effect of a gene or suite of genes on variation in more than one phenotype. Because we hypothesize that patterns of pleiotropy between dental trait pairs in adults may represent the results of coordinated developmental processes, we used multivariate variance decomposition methods to analyze data on such trait pairs in a pedigreed population of non-human primates.

We find that a significant proportion of the phenotypic variance in molar loph orientation does result from the additive effects of genes. The results of bivariate quantitative genetic analyses suggest that antimeric, morphologically homologous characters across the dental arcade and between teeth along the mandibular tooth row result from complete pleiotropy (additive genetic correlation of one), whereas variation in maxillary morphological homologous cusp pairs is influenced by incomplete pleiotropy. In contrast, traits on the same tooth crown are partially (maxillary) or completely (mandibular) genetically independent. These results necessitate that the proposed hypotheses of patterning mechanisms be modified as we progress in our understanding of the genetic and developmental mechanisms that contribute to primate dental variation and evolution.

MATERIALS AND METHODS

The baboon population

The world's largest captive, pedigreed breeding colony of baboons ($>3{,}000$) is housed at the Southwest National Primate Research Center (SNPRC) at the Southwest Foundation for Biomedical Research in San Antonio, Texas. The colony is maintained in pedigrees (with all matings controlled) and genetic marker maps have been constructed using data obtain from $\sim 1{,}000$ of the animals, making this colony unique and important for the quantitative genetic analysis of normal phenotypic variation in primates (Rogers et al., '99).

Data for this study were collected from high resolution plaster dental casts of 630 pedigreed baboons, *Papio hamadryas*. The sample has a female to male sex ratio approximating 2:1 with individuals ranging in age from 4.6 to 30 years. The protocol for collecting the dental casts is outlined in detail elsewhere (Hlusko et al., 2002). The Institutional Animal Care and Use Committee, in accordance with the established guidelines (National Research Council, '96), approved all procedures related to the treatment of the baboons during the conduct of this study.

The computer package PEDSYS (Dyke, '96) was used for all pedigree data management and preparation. The animals from which data were collected are distributed across eleven extended pedigrees. 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. 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.

Data collection protocol

Digital photographs were taken of high-resolution plaster replicas of each molar using a protocol described elsewhere (Hlusko et al., 2002). All data used in this analysis were collected from these photographs. Measurements were not collected from broken or unusually worn molars. Because of

differential wear and breakage, not all molars from all individuals could be used in the study. Consequently, from our overall sample of 630 individuals, the sample sizes for each phenotype ranged between 168–455.

Cusp position was assessed for all maxillary and mandibular molars via the orientation of the mesial and distal lophs relative to an approximate mesiodistal axis of the molar. We established this relationship via angle measurements (Fig. 2). A reference line was drawn as a tangent connecting the lingual-most points on the occlusal view of the tooth crown for mandibular molars and the two buccal/labial-most points on the crown edge for maxillary molars. Using Optimas© we measured the mesial angle of the mesial and distal lophs relative to this reference line. Measurements were taken three times and averaged.

When developing the measurement protocol our goal was to document cusp pair orientation. Ideally this measurement would be independent of crown size, however orientations not influenced by size proved to be more problematic to replicate. The most replicable of the methods tried was to orient the cusp pairs off of the most vertical side of the molar crown, as this was the least affected by wear (the lingual side of the mandibular molar and the buccal/labial side of the maxillary molar). Therefore, our angle measurements by necessity include a bias due to molar width. The ramifications of this bias will be discussed later.

Linear measurements of mesiodistal length and buccolingual width of each loph were collected from the same digital images, also using Optimas.

Analytical methods

Statistical genetic analyses were conducted by means of a maximum likelihood based variance decomposition approach implemented in the computer package SOLAR (Almasy and Blangero, '98). Accordingly, the phenotypic covariance for each trait within a pedigree in this study is modeled as $\Omega = 2\Phi\sigma_G^2 + \sigma_E^2$, 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 also are additive, such that $\sigma_P^2 = \sigma_G^2 + \sigma_E^2$, we estimated heritability, or the proportion of the phenotypic variance attributable to additive genetic effects, as $h^2 = \sigma_G^2/\sigma_P^2$. Phenotypic variance attributable to non-genetic factors is estimated as $e^2 = 1 - h^2$. Additionally, we estimated the mean effects of sex, age, mesiodistal length, and mesial and distal buccolingual width of the crown on the loph angles recorded for each molar studied.

Using extensions to univariate genetic analysis that encompass the multivariate state (Hopper and Mathews, '82; Lange and Boehnke, '83;

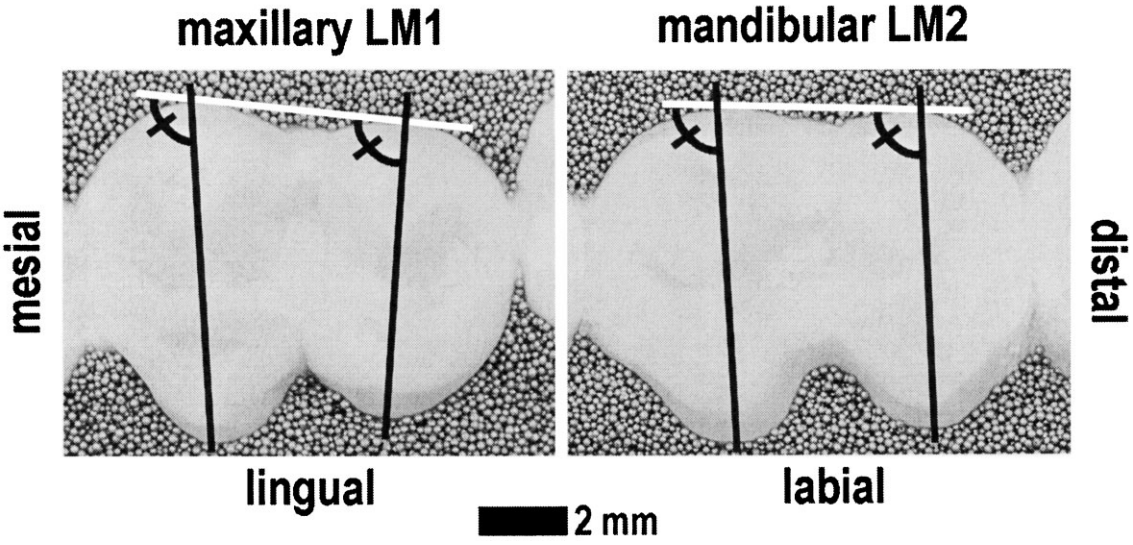

Fig. 2. Occlusal views of a maxillary left first molar and mandibular left second molar showing the protocol for collecting angle of loph orientation. The white line represents the mesiodistal reference line. The black lines were drawn between the buccal/labial and lingual most points of the lophs. The angle of the black line relative to the reference line was used as the quantification of loph orientation. See text for further explanation.

Boehnke et al., '87), we followed an approach described in detail elsewhere (Mahaney et al., '95) to model 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. From this model, we obtained the phenotypic variance-covariance matrix from which we partitioned the additive genetic and random environmental variance-covariance matrices, given the relationships (kinship coefficients) observed in the pedigree. From these two variance-covariance matrices, we estimated the additive genetic correlation, ρ_G, and the environmental correlation, ρ_E, between trait pairs. Respectively, these correlations 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 trait.

The genetic and environmental components of the phenotypic correlation matrix are additive, like those of the corresponding variance-covariance matrix, so we could use the maximum likelihood estimates of the additive genetic and environmental correlations to obtain the total phenotypic correlation between two traits, ρ_P, as

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

We conducted a series of bivariate quantitative genetic analyses of all loph angle-related trait pairs using multivariate extensions to the basic variance decomposition methods implemented in SOLAR (Almasy and Blangero, '98). These analyses were subsumed into two categories: analyses of trait pairs on two antimeric teeth within the same dental arch and analyses of serial trait pairs on the same side of the same arch. We used this approach to obtain simultaneous maximum likelihood estimates of the phenotypic means (μ), phenotypic standard deviations (σ), heritabilities (h^2), and the mean effects of covariates on all traits, as well as the genetic and environmental correlations between them.

Significance of the maximum likelihood estimates for heritability and other parameters was assessed by means of likelihood ratio tests. Twice the difference of the maximum likelihoods of a general model (in which all parameters were estimated) and a restricted model (in which the value of a parameter to be tested was held constant at some value, usually zero), were compared. This difference is distributed asymptotically approximately as either a $\frac{1}{2}{:}\frac{1}{2}$ mixture of χ^2 and a point mass at zero, for tests of parameters like h^2 for which a value of zero in a restricted model is at a boundary of the parameter space, or as a χ^2 variate for tests of covariates for which zero is not a boundary value (Hopper and Mathews, '82). In both cases degrees of freedom is equal to the difference in the number of estimated parameters in the two models (Boehnke et al., '87). However, in tests of parameters like h^2, whose values may be fixed at a boundary of their parameter space in the null model, the appropriate significance level is obtained by halving the P-value (Boehnke et al., '87).

For bivariate models in which genetic correlations are found to be significantly greater than zero and indicative of pleiotropy, additional tests are performed to compare the likelihood of a model in which the value of the genetic correlation is fixed at 1.00 or zero to that of the unrestricted model in which the value of the genetic correlation is estimated. A significant difference between the likelihoods of the restricted and polygenic models suggests incomplete pleiotropy; i.e., not all of the additive genetic variance in the two traits is due to the effects of the same gene or genes.

Individuals sampled in pedigrees are not all independent of one another and statistical tests that do not account for patterns of kinship within the sample may yield misleading significance estimates. The effect of kinship on independence within a pedigree may be appreciated by comparing the original N to an estimate of the effective sample size as $n_{es} = \hat{\sigma}^2/2\,\mathrm{var}(\hat{\sigma})$, where $\hat{\sigma}^2$ is the estimated residual phenotypic variance of the quantitative trait from our maximized, unrestricted quantitative genetic model (as described in Blangero et al., '92).

RESULTS

Quantitative genetic analyses of 18 of the 24 angle phenotypes yield significant heritability estimates (Table 1a, b), demonstrating that a significant proportion of the population variance in loph orientation results from additive genetic effects. Total h^2 estimates center around 0.29, meaning that, on average, 29% of the total phenotypic variance in these traits is attributable to the additive effects of genes. The mean proportion of the total phenotypic variance in these traits attributable to covariates is 0.24. On average, the

TABLE IA. Quantitative genetic analyses of individual maxillary loph angle phenotypes[1]: summary statistics, maximum likelihood parameter estimates, and covariate effects summaries

	RM^1 ma	RM^1 da	RM^2 ma	RM^2 da	RM^2 ma	RM^3 da	LM^1 ma	LM^1 da	LM^2 ma	LM^2 da	LM^3 ma	LM^3 da
Mean	96.11	92.73	97.06	92.64	100.19	93.96	96.10	93.18	97.86	93.97	100.35	94.01
Variance	8.51	9.55	11.27	8.75	17.86	18.29	6.28	6.65	11.72	10.69	160.29	17.43
Low value	86.28	77.81	85.33	81.30	81.59	81.76	87.64	77.89	82.54	76.65	90.58	82.38
High value	105.82	100.61	107.83	101.03	112.78	106.31	102.66	102.02	107.37	103.58	112.89	105.21
n	308	308	436	436	197	168	344	330	434	434	241	252
n_{es}	265.8	264.7	310.4	266.5			175.8	296.4	302.7	307.9		
p-value	<0.001	<0.01	<0.001	<0.001	ns	ns	<0.001	<0.001	<0.001	<0.001	ns	ns
Total h^2	0.327	0.244	0.216	0.223			0.318	0.308	0.273	0.300		
Total c^2	0.244	0.248	0.394	0.335			0.260	0.234	0.344	0.257		
Total e^2	0.429	0.508	0.390	0.442			0.422	0.458	0.383	0.443		
Residual h^2	0.432	0.324	0.356	0.336			0.429	0.402	0.416	0.404		
±SE	±0.174	±0.141	±0.099	±0.109			±0.137	±0.142	±0.109	±0.123		
β length		↓		↓								
β mes width	↑↑↑	↑↑↑	↑↑↑	↑↑↑			↑↑↑	↑↑↑	↑↑↑	↑↑↑		
β dist width	↓↓↓	↓↓↓	↓↓↓	↓↓↓			↓↓↓	↓↓↓	↓↓↓	↓↓↓		
β age		↓↓		↓								
β sex		↓	↓	↓↓↓				↓↓↓		↓↓		
β age^2	↓	↓	↓	↓				↓				
β age*sex		↓	↓	↓				↓				

[1]Arrows indicate direction of covariate effect (↑=positive, ↓=less than 1 or negative). Number of arrows indicates the significance level of the covariate listed in the left-hand column in the polygenic model: ↑↑↑ *p*-value <0.001; ↑↑ *p*-value <0.01; ↑ *p*-value <0.1. Total c^2=amount of phenotypic variance attributable to covariates. Total h^2=(Residual h^2)(1−Total c^2). Total e^2=[1−(Total c^2+Total h^2)]. n=original sample size; n_{es}=effective sample size, see text for explanation.

TABLE IB. Quantitative genetic analyses of individual mandibular loph angle phenotypes[1]: summary statistics, maximum likelihood parameter estimates, and covariate effects summaries

	RM_1 ma	RM_1 da	RM_2 ma	RM_2 da	RM_3 ma	RM_3 da	LM_1 ma	LM_1 da	LM_2 ma	LM_2 da	LM_3 ma	LM_3 da
Mean	83.82	86.22	83.38	84.54	80.30	820.44	83.00	85.16	82.81	83.86	81.87	84.10
Variance	6.83	6.21	5.33	7.03	7.74	10.06	7.67	6.86	6.51	7.56	6.88	8.126
Low value	76.23	79.28	76.80	75.33	70.42	70.67	75.19	75.88	73.60	77.13	74.03	73.77
High value	90.64	92.09	89.82	92.33	90.15	101.00	93.06	91.76	89.99	91.89	89.43	92.31
N	227	227	337	344	436	436	259	274	332	333	424	424
n_{es}	197.4	172.0	310.4	301.5		243.8		244.4	300.8	303.8	181.5	255.2
p-value	<0.001	<0.001	<0.01	<0.001	ns	<0.001	ns	<0.01	<0.01	<0.001	<0.01	<0.001
Total h^2	0.343	0.591	0.166	0.282		0.236		0.207	0.202	0.299	0.243	0.402
Total c^2	0.177	0.132	0.336	0.306		0.273		0.144	0.194	0.178	0.140	0.107
Total e^2	0.480	0.277	0.498	0.412		0.491		0.649	0.604	0.523	0.617	0.491
Residual h^2	0.417	0.681	0.25	0.406		0.325		0.242	0.250	0.364	0.283	0.450
±SE	±0.183	±0.179	±0.144	±0.133		±0.117		±0.137	±0.133	±0.122	±0.124	±0.111
β length												
β mes width	↓↓↓	↓↓↓	↓↓↓	↓↓↓		↓↓↓		↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓
β dist width	↑↑↑	↑↑↑	↑↑↑	↑↑↑		↑↑↑		↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑
β age			↓						↓			
β sex	↓↓											↓
β age^2												
β age*sex												

[1]Arrows indicate direction of covariate effect (↑=positive, ↓=less than 1 or negative). Number of arrows indicates the significance level of the covariate listed in the left-hand column in the polygenic model: ↑↑↑ *p*-value <0.001; ↑↑ *p*-value <0.01; ↑ *p*-value <0.1. Total c^2=amount of phenotypic variance attributable to covariates. Total h^2=(Residual h^2) (1−Total c^2). Total e^2=[1−(Total c^2+Total h^2)]. *n*=original sample size; n_{es}=effective sample size, see text for explanation.

proportion of the variance remaining to be explained – i.e., the residual ''environmental'' variance due to the effects of unmeasured environmental factors, measurement error, dominance affects, and environmental variance, is approximately 0.47. Our models do not show significant

differences in these relative proportions between the maxillary and mandibular loph orientations/angles.

Likelihood ratio tests of the models for the individual angle phenotypes identify several significant covariates. In our maximized models, mesial and distal loph buccolingual widths contribute significantly to loph angle variation. For the mandibular molars, mesial buccolingual width has a negative mean effect, and distal buccolingual width has a positive mean effect on loph angle. The maxillary molars show the opposite relationship: mesial buccolingual width has a positive effect, whereas distal buccolingual width has a negative effect. In comparison, the mean effects of other covariates (mesiodistal length, age, sex, age^2, and age*sex) are usually not significant or appear to contribute little to loph angle. Due to the fact that dental crown development ceases following emergence of a tooth into the oral cavity, age in these analyses acts as a proxy for wear. Significant age-related effects are detected in some of our analyses, but not consistently.

The results of our bivariate quantitative genetic analyses are presented in Table 2. Antimeric analyses estimate the genetic and environmental correlations between loph angles on opposite sides of the same dental arch, for example the RM_1 versus LM_1 mesial angle. Of the eight bivariate analyses in this category, seven of the genetic correlations are either estimated to equal one or are not significantly different from one. The eighth is estimated to be 0.79. The non-genetic

TABLE 2. Bivariate statistical genetic analyses: Maximum-likelihood estimates (MLE) of genetic and environmental correlations[1]

			Correlations		Significance, P(Hypothesis)			
	Phenotype pairs	N	ρ_G	ρ_E	$\rho_G=0$	$\lvert\rho_G\rvert = 1$	$\rho_E=0$	$\lvert\rho_E\rvert = 1$
	RM_1da–LM_1da	215	0.793	0.112	0.0070	0.1300	0.7200	0.0300
	RM_2ma – LM_2ma	296	1.000	0.306	0.0200	–	0.0500	<0.0001
	RM_2da–LM_2da	296	0.985	0.283	0.0008	0.9200	0.0800	<0.0001
Antimeres	RM_3da–LM_3da	380	0.757	0.055	0.0076	0.2980	0.6636	<0.0001
	RM^1ma – LM^1ma	288	1.000	−0.689	<0.0001	–	0.0850	0.6800
	RM^2ma–LM^2ma	454	0.900	0.171	<0.0001	0.3337	0.1554	0.0002
	RM^1da–LM^1da	288	1.000	0.172	0.0004	–	0.2900	0.0004
	RM^2da–LM^2da	454	0.952	−0.066	<0.0001	0.6064	0.6806	<0.0001
	RM_1ma – RM_2ma	270	1.000	0.0117	0.0100	–	0.9400	<0.0001
	RM_1da–RM_2da	208	1.000	−0.228	0.0010	–	0.3600	0.1000
	RM_2da–RM_3da	375	0.639	0.111	0.0305	0.03867	0.4596	<0.0001
Serial–between teeth	LM_1da–LM_2da	270	0.774	0.254	0.0100	0.5700	0.1200	0.0003
	LM_2ma–LM_3ma	384	1.000	0.194	0.0229	–	0.1470	0.0004
	LM_2da–LM_3da	384	0.849	0.009	0.0027	0.4367	0.9489	<0.0001
	RM^1ma–RM^2ma	377	0.409	0.199	0.0890	0.0020	0.1726	<0.0001
	RM^1da–RM^2da	377	0.610	0.103	0.0121	0.0085	0.5044	<0.0001
	LM^1ma–LM^2ma	402	0.279	0.092	0.2209	<0.0001	0.5711	<0.0001
	LM^1da–LM^2da	402	0.453	0.130	0.0868	0.0022	0.4315	<0.0001
	RM_1ma–RM_1da	220	−0.083	0.479	0.7828	0.0036	0.0655	0.1166
	RM_2ma–RM_2da	337	0.407	0.460	0.2400	0.0200	0.0050	<0.0001
	LM_2ma – LM_2da	325	0.225	0.480	0.5139	0.0100	0.0020	<0.0001
Serial – same tooth	LM_3ma – LM_3da	424	0.427	0.438	0.1112	0.0037	0.0026	<0.0001
	RM^1ma–RM^1da	305	0.351	0.349	0.3000	0.0010	0.1200	0.0010
	RM^2ma–RM^2da	455	0.353	0.656	0.0690	<0.0001	<0.0001	<0.0001
	LM^1ma–LM^1da	324	0.067	0.451	0.8400	0.0010	0.0200	0.0005
	LM^2ma–LM^2da	434	0.745	0.536	0.0001	<0.0001	0.0005	<0.0001

[1]MLE: maximum likelihood estimate.
P(Hypothesis): probability of the hypothesis (indicated in columns below) being true given the available pedigreed data.
ma=mesial loph angle.
da=distal loph angle.
mw=mesial loph buccolingual width.
dw=distal loph buccolingual width.

correlations are low or not significantly different from zero. The analyses of R&LM^2 mesial angles and R&LM^2 distal angles yield negative ρ_E correlations. Further analyses are needed to determine if these negative estimates are statistically anomalous.

The serial analyses were performed on two types of comparisons. The first is between morphologically homologous traits on teeth along the same tooth row, such as the RM_1 and RM_2 mesial angles. Ten comparisons were possible from these data sets. All six mandibular pairs are estimated to have high genetic correlations, five of which are not significantly different from one. None of the non-genetic correlations were found to be significantly different from zero.

All four of the maxillary, serial, between-teeth comparisons return lower ρ_G estimates. All are significantly different from one; three are also significantly different from zero. The ρ_E estimates are all low and not significantly different from zero.

The second component to the serial analyses is the relationship between the mesial and distal loph angles on the same molar crown. We performed these analyses on the eight molars for which both loph angles were found to have significant heritability estimates. For the mandibular molars, the genetic correlations between mesial and distal loph angle variance on the same molar crown are not significantly different from zero. For both maxilla and mandible, all but one of the non-genetic correlations are estimated to be between zero and one. In contrast, the maxillary molar same tooth ρ_G are all significantly different from one, and half are also significant from zero.

Inter-arch bivariate analyses were also performed (results not shown). However, paired sample sizes are small and analytical results are inconclusive.

DISCUSSION

Heritability estimates

We find that a significant proportion of loph angle variance in this population is due to the additive effects of genes. Understanding additive genetic contributions to phenotypic variance is critical to evolutionary studies, as well as to animal and plant breeders, because these effects reflect how strongly the trait will respond to selection, both natural and artificial (Falconer, '89; Lynch and Walsh, '98; Hartl and Jones, 2001). Studies of variation between synchronic and diachronic primate populations show that cusp proportions, number, and position do vary in significant ways (Frisch, '63; Swindler et al., '67; Swindler and Orlosky '74;). The results presented here demonstrate that the inherent assumption of these authors, that changes in such phenotypes could reflect either an adaptive response to selection or result from processes such as drift, is tenable (i.e., their assumptions imply an underlying additive genetic component).

Genetic and covariate effects

Though it is important to establish this additive genetic foundation for morphological studies, the detection and characterization of a significant genetic component for loph angle variation is of considerably more interest than the actual heritability point estimates themselves. Quantitative genetic analytical approaches, such as the one employed here, enable us to estimate the relative contributions of various covariates and non-genetic factors to the population variance in loph angle (Almasy and Blangero, '98). This may allow us some additional insights into genetic and environmental sources of variation in developmental mechanisms underlying dental phenotypic variation, more than was possible in many previous odontological heritability analyses (e.g., Alvesalo and Tigerstedt, '74; Sirianni and Swindler, '75; Townsend and Brown, '78; Potter et al., '83). Additionally, it may facilitate the generation of hypotheses concerning the developmental mechanisms themselves.

Our models indicate that a large portion, approximately 50%, of the variance is attributable to non-genetic or ''environmental'' effects. This component of the variance includes factors such as unidentified covariate effects, dominance, measurement error, etc.

Not all of the potential covariates screened in these analyses were found to be significant. The significant covariates include sex and age to minimal extents, and predominantly molar crown width measurements. These account for approximately 20% of the phenotypic variance.

Sex of the individual is found to be significant in seven of the 18 polygenic models. Age and variants of age by sex interactions are also significant in seven of the models, though the significance level of these contributions is minimal for six of these. Due to tooth development and mineralization, growth is halted at eruption and molar morphology

is only altered by wear and breakage from that point on. As noted previously, we did not include broken or unusually worn molars in these analyses. Therefore, age acts as a proxy for normal occlusal wear in these models. Future analyses using established wear stages as a covariate will enable us to confirm this relationship. For now however, we interpret the minimal significance of the mean effect of age to indicate that wear does not contribute substantively to the variance in these measures in this population of animals. We conclude similarly for sex. This latter observation accords well with studies of morphological variation at the population level; where cusp number, positioning, and proportion are not sexually dimorphic (Frisch, '63; Swindler '67; Swindler and Orlosky, '74; Uchida, et al., '98).

The most significant and consistent covariate effect across these 11 analyses involves the width measurements. This probably results from the interdependence between loph orientation and loph width inherent in our measurement protocol. Specific molar cusp positioning has not been extensively studied in human and primate odontology. However, the few relevant studies suggest that the covariance identified in our analyses may be suspect. Peretz and Smith ('93) and Peretz et al. ('97, '98) performed a series of analyses on the relationship between size and shape in deciduous fourth premolars (deciduous second molars) versus permanent first molars. They find strong correlations between various size measurements, and strong correlations between various shape-oriented variables, but not between these two categories (Peretz and Smith, '93; Peretz et al., '98). This suggests ''that the two processes develop in an independent pattern and rate'' (Peretz et al., '98:533). Cusps do appear to shift position when early and late stages of crown mineralization are compared (Peretz et al., '97, '98). The combination of these results suggests that cusp positioning may be genetically independent of crown size, though as cusps develop the process of mineralization does ultimately influence cusp positioning (Polly, '98). Likewise, the opposite influence of loph width on loph angle in maxillary versus mandibular molars may be an artifact of our measurement protocol, as we estimated loph position relative to the most vertical side of the molar crown (lingual for mandibular molars and buccal/labial for maxillary molars), the orientation of which is influenced by loph width.

We tested an alternate protocol that corrects for this bias by using the mesiodistal axis of the tooth as the line from which the angles are estimated. In analyses applying this protocol to data for two mandibular molars, width accounts for less than 1% of the overall phenotypic variance. However, maximum likelihood estimates of heritabilities and correlations (from the bivariate analyses) closely approximated those obtained using the first protocol described earlier in this paper (data not shown). Therefore, while the detected mean effects of tooth width on cusp position measures may be artifacts of our reported measurement protocol, their inclusion in our models does not substantively affect the results and conclusions presented in this paper.

Pleiotropy

In theory, there are two possible causes of genetic correlation (see e.g., Bulmer, '74; Lynch and Walsh '98): pleiotropy and gametic phase disequilibrium, including linkage disequilibrium; however, we feel that the latter is unlikely to explain the genetic correlations estimated in this study. Given the age and non-inbred nature of the pedigreed baboon population from which we obtained our data, we posit that gametic phase disequilibrium – i.e., non-random association between genotypes at different, unlinked loci – is not particularly extensive. Additionally, the relationship between linkage disequilibrium (LD) and genetic distance (on the same chromosome) in these baboons seems similar to that observed for non-inbred human populations (e.g., Jorde et al., '94; Abecasis et al., 2001): i.e., LD is only moderate between 50 kb and 500 kb and inconsistently manifested at distances beyond these two boundaries. Further, we envision molar cusp patterns to be complex phenotypes whose variation is due to the effects of multiple genes at multiple loci, multiple developmental environmental factors, and multiple interactions between the two. Therefore, we believe that is it is unlikely that evidence for complete pleiotropy – i.e., a situation wherein all the additive genetic variance in two traits appears due to the effects of the same gene(s) – would actually result from multiple cases of nearly total gametic phase disequilibrium at multiple, different loci throughout the genome.

Antimeric pleiotropy

Odontological studies in both humans and nonhuman primates have long been based on the assumption that right and left antimeres are genetic and developmental equivalents, typically

relying on only one side of the dentition to represent the whole (Scott and Turner, '97). Bilateral fluctuating dental asymmetry is generally assumed to result from disturbances to, or noise in, the developmental process (e.g., Perzigian, '77; Keiser, '92), as may be caused by illness, pre- and/or postnatal trauma, or other stresses such as malnourishment. Fluctuating asymmetry is not typically thought to result from genetic patterning. Consequently, we anticipated and found that bivariate analyses of traits on antimeres performed in this study yield genetic correlations of one. The non-genetic, or environmental correlations are greater than zero but still low. This suggests that the nongenetic effects influencing loph angles on opposite sides of the same dental arch in this healthy baboon population overlap to some degree, but are largely independent.

Serial genetic correlations

Our results also indicate that in this population 100% of the genetic effects determining loph angle variation in the mandibular molars are shared between serial morphological homologues, such that the genetic determinants of variation in mandibular first molar mesial angle are identical to those of the second molar mesial angle. Serial morphological homologues on the maxillary molars also have a high genetic correlation, although this is estimated to be significantly different from one. This high degree of pleiotropy accords with predictions from morphological studies (Van Valen, '94) that find high levels of phenotypic correlation.

In contrast, the non-genetic correlation between serial morphological homologues is low or zero. This again suggests that non-genetic perturbations to the patterning process are essentially independent, and possibly, if not probably, the result of the offset between molars in mineralization and eruption times (Phillips-Conroy and Jolly, '88; Kahumbu and Eley, '91).

Comparisons between traits on the same crown return surprisingly different results from the serial comparisons between molar crowns. All mesial and distal loph genetic correlations are found to be significantly different from one. In the mandibular molars, this correlation is not significantly different from zero, whereas in the maxillary molars it is. Therefore, for mandibular molars, the genetic effects determining variation in the mesial loph appear to be independent of those that determine variation in the distal loph. Maxillary molar mesial and distal loph orientation appears to results from incomplete pleiotropy.

The mandibular estimates in particular stand in contrast to the hypothesis that pleiotropy would be high within crowns. Developmental studies suggest considerable pleiotropy between mesial and distal loph orientation, and there may well be such pleiotropy at more fundamental stages of development. However, in this baboon population the genetic effects that determine population level variation in loph angles on the same molar are independent to varying degrees.

Although the genetic correlation for loph angle variation on the same molar crown is low or zero, there is a significant nongenetic correlation. Therefore, the nongenetic influences are shared to a certain degree. This probably results from the close timing and spatial positioning of these traits during tooth organogenesis. The developmental picture that can be drawn from these results suggests that non-genetic effects rapidly become independent of each other as the phenotypes become more distant, in terms of both ontogenetic time and space.

Bateson (1894) recognized similarities in patterns of serially homologous structures and likened these to Chladni figures, frequency interference in wave patterns. Butler ('39, '56) specifically addressed such patterns in the dentition, proposing that classes of teeth derive from one 'type.' Variation of tooth shape within each class may result from identical tooth primordia reacting to morphogens. In this scenario, known as the *field theory*, ultimate tooth shape is determined by extrinsic factors.

The *clone theory*, proposed by Osborn ('78), contrasts with the field theory in that each tooth in a class is produced by the replication of the original type or polar tooth (M1 for the molar field), and morphology is predetermined by intrinsic factors. The concept of dental fields has been explored primarily through studies of morphological variation and correlation (e.g., Dahlberg, '45; Van Valen, '61; Lombardi, '75; Henderson and Greene, '75), though information from human genetic disorders has also been examined (Line, 2001). However, none of these studies is particularly conclusive and scenarios can be drawn from most of this research to support both theories. Neither of these two models has yet to be reconciled with either the

odontogenetic or *reaction-diffusion* dental patterning mechanisms described previously.

Our estimates of the genetic correlation between mesial and distal loph variation are relevant to the debate between the field and clone theories. If tooth primordial cusp positioning were determined via extrinsic morphogens, then considerable pleiotropy would be expected not only between teeth, but between structures on the same tooth crown. Here we find that mesial loph variation between molars along the tooth row is determined by complete pleiotropy, as is distal loph variation. However mesial and distal loph variation on the same crown appears to be genetically independent in mandibular molars and partially independent in maxillary molars. We interpret these data to mean that minor molar morphological variation may not be extrinsically influenced by genes once tooth primordia are established. Rather, our results suggest that minor variation in cusp position is determined intrinsically. It remains to be determined if tooth buds themselves are initated via an odontogenetic code or a reaction-diffusion process.

The concept of morphological integration was first introduced by Olson and Miller ('58), was revived by Cheverud and colleagues (Cheverud, '82; Cheverud et al., '83), and has received considerable attention and refining since (Magwene, 2001; Stock, 2001; VonDassow and Munro, '99). This is the concept 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. Several approaches have been employed to identify these sets, from phenotypic statistical correlations (Olson and Miller, '58), quantitative genetics (Cheverud, '96), and neontological ontogeny (Shubin and Wake, '96).

As Cheverud and colleagues have demonstrated (Cheverud, '96; Leamy et al., '99; Workman et al., 2002), quantitative genetic analyses provide a means through which to identify morphological integration and ultimately correlate morphologically integrated sets with QTL effects. Quantitative genetic analyses are preferable to tests of phenotypic correlation (when possible) because genetic and nongenetic correlations can be estimated separately. Our investigation of dental variation in this pedigreed baboon colony is yielding information about morphological integration in the primate dentition, providing further evidence of hierarchical modularity in the dentition (Stock, 2001).

The evidence for pleiotropic effects in the baboon dentition presented here may be indicative of modularity different from what previously has been proposed. Based on gene expression data, Jernvall et al. (2000) propose that the patterning mechanism for the mesial loph in mandibular molars is duplicated to create the more distal cusp pairs or lophs on the same tooth crown. This implies that variation in the mesial cusp pair will be repeated/copied in the subsequent pairs, and accords with the concept that morphological metamerism results from the duplication of a patterning mechanism (Weiss, '90). Jernvall et al. (2000) propose two fundamental mechanisms to molar crown patterning. The first is the repetition of the mesial pair of cusps and the second is control over the length of the molar crown that ultimately determines the number of repeated cusp pairs.

Based on our quantitative genetic analysis of baboon dental variation, we suggest that there is modularity that integrates features from different molars independently of other parts of the molar crown. We infer that mesial molar lophs comprise one module and distal lophs another (Fig. 3). This is a modification of Jernvall et al.'s (2000) hypothesis. Building on Van Valen's ('70) concept of prepatterns, we suggest that the molar prepattern may have more than one cusp pair, the original pair and a duplicated set. The original and repeated segments may share the same fundamental genetic determinants, such as are identified in the gene expression studies of mouse and vole molars (Keränen et al., '98; Jernvall et al., 2000). However, the duplicated segments are then

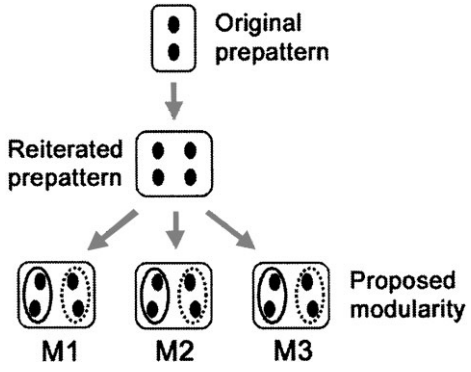

Fig. 3. Diagram showing possible new level of modularity in molar development, indicated with dotted lines. See ''serial genetic correlations'' section in discussion.

free to vary independently following the concept of metameric variation (Bateson 1894; Weiss '90).

If this prepattern provides the foundation for all molars, then the genetic mechanisms determining variation in the mesial lophs will all be shared and the genetic mechanisms causing variation in the distal lophs will also all be shared. However, the two lophs may have developed independent genetic determinants for minor morphological variation. This independence may have been expected given the developmental delay in mesial and distal loph formation. There are examples of normal adult phenotypic variation being determined very early in development making this hypothesis reasonable (Richardson, '99). We cannot speculate at this time whether such a mechanism would be morphostatic or morphodynamic (Salazar-Cuidad et al., 2003).

Relationship between maxillary and mandibular molars

Morphological studies of synchronic and diachronic populations also suggest that the maxillary and mandibular dentitions probably result from the pleiotropic effects of many of the same genes; and this is logical given the strong selection for proper occlusion (Marshall and Butler, '66; Van Valen, '94). Olson and Miller ('58) studied morphological integration in the postcanine dentition of the South American monkey *Aotus trivirgatus* and found differences in patterns of correlation between linear size measures of upper and lower teeth, where length and width were more strongly correlated in maxillary molars compared to mandibular molars. Their results suggest the presence of pleiotropic effects and a complex relationship between the upper and lower jaws. A study of bat molar cusp development found that during all stages of odontogenesis maxillary and mandibular molar cusps would properly occlude if they were placed into articulation (Marshall and Butler, '66).

Though our knowledge of the early development of the dentition is continually increasing (Thesleff and Sharpe, '95; Stock et al., '97; Weiss et al., '98; Peters and Balling, '99; Zhao et al., 2000a), we still do not know what genetic processes enable the maxillary and mandibular arches to arrive at such similar morphologies but still retain the ability to evolve independently. Early in development, the first arch of the embryo gives rise to the right and left mandibular arches that grow distally from the body and join at midline to form the mandibular symphysis. The maxillary arch forms from both the first arch and the frontonasal mass. The maxillary incisors derive from the frontonasal tissue whereas the maxillary canines, premolars, and molars derive from the first arch processes. Focusing solely on the non-incisal teeth, there are several feasible processes that determine tooth row patterning (Weiss et al., '98). Gene expression studies to date have been unable to provide clear evidence as to which, if any, of these models is potentially correct.

Our bivariate analyses of inter-arch loph orientation are underpowered and therefore provide no conclusive evidence at this time. However, the observed differences and similarities between the two sets of intra-arch bivariate analyses demonstrate that the genetic architectures of the maxilla and mandible are similar but not identical. This is reminiscent of inter-arch analyses performed for two other morphological characters from this same pedigreed baboon population, the interconulus and interconulid. These are ancillary cusps on the side of molar crowns whose degree of expression is influenced by incomplete pleiotropy (Hlusko and Mahaney, 2003).

Future research

Narrow-sense heritability estimates, the estimates of the proportion of the phenotypic variance due to the additive effects of genes, have implications for finding genes for traits like loph orientation. Statistical power to detect and localize quantitative trait loci (QTLs) influencing variation in loph orientation, or any other quantitative trait, is largely a function of the QTL-specific heritability—i.e., the proportion of the variance in the trait attributable to the effect of the QTL—for which the heritability estimate described in this report provides the upper bound. Demonstrating that variation in loph angle is significantly heritable is prerequisite to searching for the genes responsible for that heritable component. A whole genome linkage map is available for this population of baboons (Rogers et al., 2000) and the majority of animals for which we have loph angle measurements are genotyped at the marker loci that comprise this map. We are currently undertaking a QTL analysis of these loph orientation data to test the hypothesis that one of the four genes identified in Jernvall et al.'s (2000) study influence normal population-level variation in this baboon colony.

SUMMARY

This quantitative genetic analysis of baboon dental variation provides three new insights into the mechanisms that underlie normal variation in loph orientation. First we find that maxillary and mandibular molar loph orientation is determined by similar proportions of additive genetic effects and nongenetic effects.

Second, we find that variation in mandibular molar serial repeats of morphologically homologous traits is also determined by identical genetic affects. However, the same comparisons in the maxillary molars indicate incomplete pleiotropy. We also find that variation in the orientation of different lophs on the same crown is genetically independent in mandibular molars but exhibits partial pleiotropy in maxillary molars. This latter result contrasts with the high pleiotropy we anticipated given previous gene expression studies. We interpret this genetic independence to possibly result from a previously unidentified level of modularity in the dentition. One module is comprised of all mesial molar lophs in an arch and another, of all the distal molar lophs. This may result from a duplication event in a putative molar prepattern.

Third, our bivariate analyses demonstrate that the intra-arch genetic relationships between lophs differ in the maxillary molars compared to the mandibular molars. Therefore, somewhat different genetic architectures appear to pattern the maxillary and mandibular dental arcades.

Given the conserved nature of developmental pathways, it is possible that the mechanisms underlying normal dental phenotypic variation in this captive baboon breeding colony may also underlie variation in other primate populations, both past and present. Therefore, these results may be applicable to the study of a wide range of extant and extinct mammalian taxa.

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