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Genetic Correlations Between Mandibular Molar Cusp Areas in Baboons

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ABSTRACT Primate evolutionary studies rely significantly on dental variation given the large role that teeth play in how an organism interacts with its environment (animal and plant) and conspecifics. Variation in cusp size has been shown to vary among primate taxa, although most studies to date focused on extant and extinct hominoids. Here we test the assumed hypothesis that a significant proportion of this variation in baboons is due to the additive effects of genes. We perform quantitative genetic analyses on variation in two-dimensional (2-D) mandibular molar cusp size in a captive pedigreed breeding population of baboons (*Papio hamadryas*) from the Southwest National Primate Research Center. These analyses show that variation in cusp size is heritable and sexually dimorphic. Additionally, we tested for genetic correlations between cusps on the same crown, between morphological homologues along the tooth row, and between cusp area and crown buccolingual width. We find that four of the six cusp pairs on the first molar have a genetic correlation of one, save for the metaconid–hypoconid and entoconid–hypoconid, which are not statistically different from zero. The second and third molars have lower genetic correlations, although the metaconid–hypoconid correlation is similarly estimated at zero and the entoconid–protoconid correlation is estimated to be one. This cross pattern of genetic and no genetic correlation does not immediately accord with the known pattern of development and/or calcification. We propose two explanative hypotheses. Am J Phys Anthropol 132:445–454, 2007.

Dental variation plays a critical role in reconstructing the phylogenetic relationships, diet, and ethology of numerous primate taxa (Rose et al., 1981; Ungar, 2004; Seiffert et al., 2005). This is particularly evident in paleontological research, where teeth are often the most abundant or only known anatomy of an extinct taxon. With advances in computer technology, researchers are starting to study variation in dental phenotypes that are relatively complicated to quantify, i.e. anatomical features that are non-linear. One of these non-linear phenotypes that has proven to vary significantly is the two-dimensional (2-D) occlusal area of molar cusps, also called the basal cusp area (Erdbrink, 1965, 1967; Sperber, 1974; Corruccini, 1977; Wood and Abbott, 1981; Hills et al., 1983; Wood et al., 1983; Wood and Engelman, 1988; Suwa, 1990; Reid et al., 1991; Wood and Xu, 1991; Macho and Moggi-Cecchi, 1992; Macho, 1994; Suwa et al., 1994; Suwa, 1996; Suwa et al., 1996; Uchida, 1996, 1998a,b; Kondo and Yamada, 2003; Bailey, 2004; Bailey et al., 2004; Kondo et al., 2005; Kondo and Townsend, 2006).

Early studies of molar cusp area analyzed data collected as polyhedrons constructed from X,Y landmarks from photographs (Biggerstaff, 1969, 1976) or measured photographs with a planimeter (Erdbrink, 1965, 1967; Hills et al., 1983; Wood et al., 1983; Wood and Engleman, 1988; Reid et al., 1991; Macho, 1994). Other studies employed cusp diameter as a proxy for cusp size (Sperber, 1974; Corruccini, 1977; Kondo and Yamada, 2003; Kondo et al., 2005). More recent studies digitized negatives (Uchida, 1996, 1998a,b), employed digital tablets (Suwa, 1990; Wood and Xu, 1991; Macho and Moggi Cecchi, 1992; Suwa et al., 1994, 1996; Suwa, 1996), or used digital photography and image-analysis software programs to measure 2-D basal cusp area (Bailey, 2004; Bailey et al., 2004; Kondo and Townsend, 2006). 3-D studies of cuspal area have also been conducted (Kanazawa et al., 1983; Kanazawa et al., 1984; Mayhall and Kanazawa, 1989; Mayhall and Alvesalo, 1992; M'Kirera and Ungar, 2003; Ungar and M'Kirera, 2003; Ulhaas et al., 2004; Ungar, 2004). Although the data collection process has grown easier as technology has improved, the results from earlier 2-D studies have been largely validated and expanded on by more recent projects.

To date, neontological research has focused primarily on hominoids, assessing basal cusp size within and between humans, chimpanzees and gorillas. Erdbrink, (1965, 1967) reported negative correlations between human mandibular molar cusp areas such that the more distal and lingual cusps are relatively smaller. However, Hills et al. (1983) found that human mandibular molar cusp areas have only a weak, if any, allometric relationship with crown area. In contrast, maxillary molar cusp areas do appear to be allo-

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metric with crown size—the decrease in human maxillary molars from anterior to posterior is primarily a function of the reduction of the distal components of the crown (Macho, 1994).

Gorillas and chimpanzees are not reported to have an allometric relationship between crown size and cusp size (Hills et al., 1983), although a relative shift in trigonid–talonid relative size is a critical distinction between the lesser and great ape mandibular molar crown morphologies (Corruccini, 1977).

Researchers have also found differences in cusp area variance across primate taxa. Uchida (1996) noted that *Papio* molar cusps have greater variability than do great ape cusps, attributing this to differing levels of sexual dimorphism, although cusp areas are sexually dimorphic in *Gorilla* and *Pongo* (Uchida, 1998a,b, respectively). Human molar cusps also show evidence of sexual size dimorphism, but the degree of dimorphism varies depending on the cusp (Kondo and Townsend, 2006), which accords somewhat with an earlier study reporting a minimal level of sexual dimorphism in human molar cusp size (Biggerstaff, 1976). Variance also appears to increase in the later forming cusps such that the primary cusp, the paracone is the least variable in the maxillary first molar (Kondo and Townsend, 2006).

Paleontological research indicates that relative basal cusp areas also differentiate extinct taxa. Uchida (1996) reported that mandibular first molars (M_1s) of *Proconsul africanus* have relatively larger hypoconulids and entoconids and relatively smaller metaconids and hypoconids compared to those of *P. major*. A lack of variation in basal cusp area has been evoked to argue against the presence of more than one taxon in the large assemblage of teeth from Lufeng, China (Wood and Xu, 1991).

Plio-Pleistocene hominid basal cusp area has been the most intensively investigated to date (Sperber, 1974; Wood et al., 1983; Wood and Engleman, 1988; Suwa et al., 1994; Suwa et al., 1996; Bailey, 2004). Wood et al. (1983) noted that the mandibular molars of the robust species of *Australopithecus* ("*Paranthropus*") tend to have relatively smaller mesial cusps and larger distal cusps compared to other hominids. Later studies show that although the mesial cusps are smaller in the megadont species, the expanded talonid is largely due to the enlargement of different distal cusps in *A. boisei* and *A. robustus*, the entoconid or the hypoconid (Suwa et al., 1994). This may reflect either developmental sample bias, epigenetic factors, or that talonid expansion is convergent in these species (Suwa et al., 1994).

Bailey (2004) also found that a negative correlation between the trigon and talon differentiate Neandertal from modern human maxillary molars, with the hypocone and metacone primarily accounting for these differences. Corruccini (1977) also reported mesial/distal proportional differences in the mandibular molars of hominoids, driven primarily by the metaconid in the trigonid and the entoconid in the talonid.

Variation in basal area between cusps clearly contributes to taxonomic variation. Given that the nature and magnitude of the genetic contribution(s) to the phenotypic variance in a trait influence to a large extent the response of that trait to selection (Fisher, 1930; Lynch and Walsh, 1998), understanding the genetic architecture of population-level variation in molar cusp area would facilitate our interpretation of its evolutionary significance.

It has long been recognized that offspring tend to resemble their parents, and that this tendency can be exploited in animal and plant breeding. Darwin applied this understanding to his development of the concept of natural selection (1859). By incorporating advances in inferential statistics to Gregor Mendel's principles of inheritance and Francis Galton's biometry, biologists developed the following well-known equation to describe the relationship between the inheritance of variation and selection,

$$R = h^2 S$$

where S is the selection differential (the difference in population mean before and after selection in a single generation), R is the response to selection in the following generation (Falconer, 1989) and h^2 is the heritability of the trait of interest. The additive genetic variance of the phenotype is a critical element in understanding how a trait will respond to selective pressure. Genetic variance has since become instrumental in studies of "evolvability" (Houle, 1992), with heritability estimation being one of the more common parameters for comparative studies (Lande, 1976, 1979; but see also Hansen et al., 2003).

To date, there have been very few studies elucidating the genetics of molar cusp area. From a study of basal cusp area in 199 pairs of same sex-twins in which co-twin and cross-twin correlations were compared, Biggerstaff (1976) concluded that the genetic component to variation in this trait was relatively low. More recent reports of human genetic diseases indicate that there is a genetic contribution to molar cusp area variation. Mayhall and Alvesalo (1992) considered the specific molar morphology of 45,XO human females (individuals lacking a second sex chromosome who are therefore phenotypically female). Affected individuals have smaller molar crowns overall, although the distal cusps are relatively smaller compared to 46,XX females (Mayhall and Alvesalo, 1992). Individuals with Down syndrome also have cuspal differences in their maxillary molars (Peretz et al., 1996).

In light of the importance of molar cusp area to primate odontological evolution and the dearth of knowledge regarding the genetic architecture of this variation, we undertook a quantitative genetic analysis of variation in mandibular molar cusp basal area in a captive pedigreed population of baboons housed at the Southwest National Primate Research Center in San Antonio, Texas. Specifically, our aims were: 1) to estimate the heritability of this variation; 2) to estimate genetic correlations between cusps on the same molar crown and along the tooth row; and lastly 3) to test for genetic correlations between variation in molar cusp area and crown mesiodistal width.

MATERIALS

Data were collected from a large captive, pedigreed breeding colony of baboons, *Papio hamadryas*, housed at the Southwest National Primate Research Center (SNPRC) in San Antonio, Texas, following protocols in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996). The colony is maintained in pedigrees (all familial relationships known) with all matings controlled and a female to male sex ratio approximating 2:1.

Genetic management of the colony, initiated over 20 years ago, 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. Genetic marker maps have been constructed using data obtained from approximately 1,000 individuals (Rogers et al., 2000; Cox et al., 2006).

All pedigree data management and preparation was conducted using the computer package PEDSYS (Dyke, 1996). 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, most recent two or three generations of each pedigree.

Odontometric data were collected from high resolution plaster dental casts of 627 pedigreed genotyped baboons. Dental casts were collected following a protocol described in detail elsewhere (Hlusko et al., 2002).

2-D areas of each tooth crown and cusp were measured from these digital photographs using Image Pro Plus 5.1© software. Area data were only collected from the left mandibular tooth row. Each image was calibrated using the program's calibration function and a millimeter scale that was present in every photograph. Image Pro Plus 5.1© enables users to outline a 2-D shape using the mouse and cursor, and a measuring function then calculates the area within the designated shape.

Cusp areas were not taken from broken or unusually worn cusps. Sample sizes ranged from 198 to 510 out of an overall sample of 627.

Cusps were defined as in Figure 1, following Suwa et al. (1994), but with modifications to account for the differences between baboon and hominid molar morphology. The fissures of each molar were used to define the interior edges of individual cusps. Intercusp enamel areas such as the mesial and distal enamel shelves, buccal enamel shelves between the protoconid and entoconid, lingual enamel shelves existing between the metaconid and entoconid, and the middle fovea were not included, which differs from the method of Suwa et al. (1994) and Wood et al. (1983). When fissures delineating a cusp were obliterated by wear, that cusp was excluded from measurement. On the M_3s, crown and hypoconulid cusp areas would not be taken if obscured by the gumline. This practice lead to rather small sample sizes for the M_3 phenotypes.

Two of the authors collected these data (LH and ND). Interobserver and intraobserver error was assessed for a combination of first, second, and third molars. Measurement error never exceeded 8% for interobserver or 5% for intraobserver error (Table 1). This does not differ greatly from the error reported by other researchers for these types of data (Bailey et al., 2004).

Mesial and distal buccolingual widths were also analyzed. Details on how these data were collected are available in Hlusko et al. (2002).

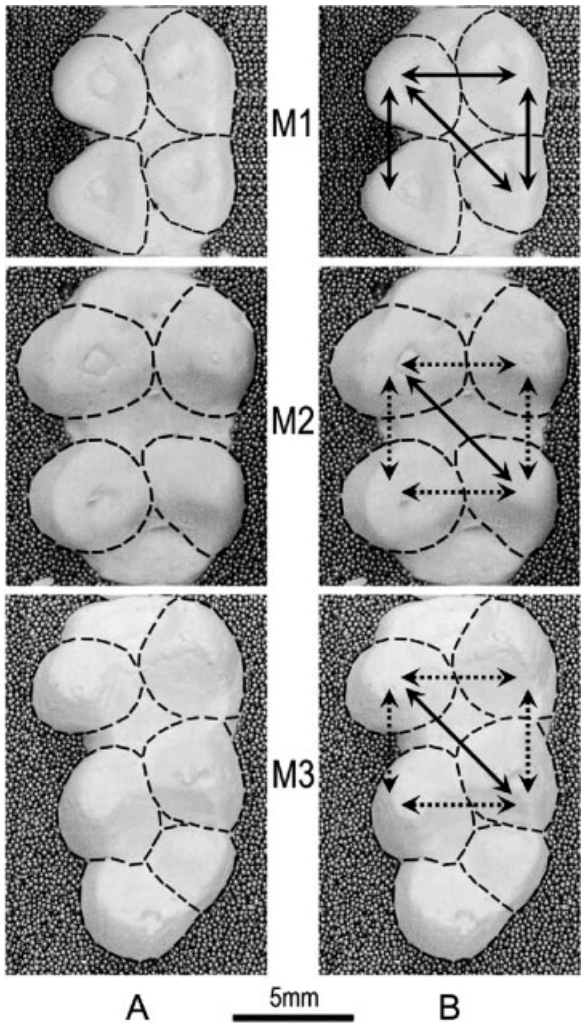

Fig. 1. Mesial is to the top and lingual to the right. **A**. This figure shows how the cusps were defined for the data collection protocol. See text for more details. **B**. Schematic of the genetic correlations between cusps on the same molar crown. The solid arrows indicate a genetic correlation that is not significantly different from one. The dotted arrows indicate partial correlations and incomplete pleiotropy. The cut-off point for significance in this figure was at the 0.05 level. Note the lack of a correlation between the metaconid and hypoconid on all three molars.

METHODS

Statistical genetic analyses were performed using a maximum likelihood based variance decomposition approach implemented in the computer package SOLAR 2.1.2 (Almasy and Blangero, 1998). The phenotypic covariance for each trait within a pedigree was modeled as $\Omega = 2\Phi\sigma^2_G + I\sigma^2_E$, where Φ is a matrix of kinship coefficients for all relative pairs in a pedigree, σ^2_G 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^2_E is the environmental variance. Because the components of the phenotypic variance are additive, such that $\sigma^2_P = \sigma^2_G + \sigma^2_E$, we estimated heritability as $h^2 = \sigma^2_G/\sigma^2_P$. Phenotypic variance attributable to non-genetic factors is calculated as $e^2 = 1 - h^2$. We estimated the mean effects of sex and age on the 2-D area recorded for each molar and each molar cusp. Covariates found to be significant in the univariate analyses were also included in the bivariate analyses. We used likelihood ratio tests to compare the likelihoods of models in which the value of each one of these covariates was constrained to be zero to that of the general model in which all covariate effects were estimated. For the purposes of these analyses, $P \leq 0.10$ indicated a significant mean effect of the covariate.

Using extensions to univariate genetic analyses that encompass the multivariate state (Hopper and Mathews,

TABLE I. Inter- and Intra-observer measurement error for the SNPRC baboon basal cusp area data

	Protoconid area	Metaconid area	Entoconid area	Hypoconid area
Inter-observer error ($n = 19$)				
Avg. difference	1.33	1.25	0.86	1.21
Avg. measurement	17.52	18.36	15.79	16.48
Percent error	7.6	6.8	5.5	7.3
Intra-observer error ($n = 10$)				
Percent error	1.63	4.60	3.01	1.96

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. This approach is described in detail elsewhere (Mahaney et al., 1995). The phenotypic covariance in this multivariate extension is modeled as $\Omega = G \otimes 2\Phi + E \otimes I$, where G and E, respectively are the genetic and environmental variance–covariance matrices among traits and $\otimes$ is the Kronecker product operator. From these two variance–covariance matrices, we estimated the additive genetic correlation, ρ_G, and the environmental correlation, ρ_E, between trait pairs. 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, respectively.

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

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

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) is distributed asymptotically approximately as either a [1/2]:[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, 1982). In both cases, degrees of freedom is equal to the difference in the number of estimated parameters in the two models (Boehnke et al., 1987). 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., 1987).

For bivariate models in which genetic correlations are found to be significantly greater than zero, 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.

RESULTS

Analyses for 12 of the 13 cusp area phenotypes yielded significant heritability estimates (Table 2), demonstrating that a significant amount of phenotypic variance in molar cusp size in this population is due to the additive effects of genes. Total h^2 estimates indicate that 15–42% of the phenotypic variance can be attributed to additive genetic effects.

The M_3 protoconid area has a leptokurtic distribution (1.89), making further analyses with this phenotype questionable. We present the results from these analyses with this caveat in mind. The M_3 hypoconulid area is not found to be significantly heritable, arguably an artifact of the rather small sample size ($n = 198$).

Covariate effects account for 16–34% of the total phenotypic variance. Sex is the only consistently significant covariate indicating that cusp area is sexually dimorphic, where males are larger than females.

Age and age-by-sex effects are found for 7 of the phenotypes. In these analyses, age serves as a proxy for wear since enamel formation stops at eruption. This indicates that wear introduced a systematic measurement error for 7 of the phenotypes. However this does not appear to significantly raise the covariate variance relative to the other cusps, and therefore does not appear to contribute significantly to the total phenotypic variance or negatively affect these results.

Our first set of bivariate analyses tested for genetic and environmental correlations between all possible cusp area pairs within an individual molar (Table 3). Statistical significance levels are biologically arbitrary and serve only as a cut-off point chosen by the researcher. Several of our likelihood ratio tests yielded P-values that are significant at $P < 0.05$ but not at $P < 0.01$. We generally apply a significance criterion of $P < 0.01$ unless otherwise noted.

For the M_1, four of the six genetic correlations are high and not significantly different from one. The genetic correlation for the remaining two pairs is lower. The metaconid–hypoconid ($\rho_G = 0.359$) is not significantly different from zero but it is significantly different from one. The entoconid–hypoconid ($\rho_G = 0.604$) is significantly different from zero but arguably different from one, $P(\rho_G = 1) = 0.015$. The standard errors for these estimates are high.

The bivariate analyses yielded similar genetic correlations for the M_2 and M_3 cusp pairs. For the M_2, these genetic correlations are lower than are those found for the M_1, with the lowest two correlations similarly being

TABLE 2. Descriptive statistics and heritability estimates for SNPRC baboon mandibular molar cusp areas[a]

	M_1 ma	M_1 ea	M_1 pa	M_1 ha	M_2 ma	M_2 ea	M_2 pa	M_2 ha	M_3 ma	M_3 ea	M_3 pa	M_3 ha	M_3 hla
Mean	14.57	13.27	15.66	15.32	21.62	16.91	21.33	19.79	23.45	18.30	22.38*	21.59	17.28
Variance	4.13	2.45	3.42	3.20	7.64	3.36	5.65	5.37	8.72	5.43	7.39	5.97	16.02
Low value	8.27	7.69	8.47	9.00	11.00	10.26	12.83	11.65	12.67	9.31	12.55	12.62	4.45
High value	21.00	20.00	22.00	22.40	29.44	23.07	29.51	26.48	32.12	25.41	30.66	27.61	28.51
CV	13.95	11.81	11.81	11.68	12.78	10.84	11.14	11.71	12.59	12.74	12.14	11.31	23.16
n	340	346	338	356	498	475	479	480	406	382	405	392	198
h^2 residual ±	0.448 ±	0.290 ±	0.248 ±	0.276 ±	0.500 ±	0.386 ±	0.193 ±	0.572 ±	0.585 ±	0.435 ±	0.283 ±	0.334 ±	0.033 ±
SE	0.139	0.144	0.124	0.140	0.108	0.116	0.108	0.119	0.120	0.131	0.111	0.114	0.138
P-value	<0.001	<0.01	<0.01	<0.01	<0.001	<0.001	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	ns
Total h^2	0.378	0.228	0.185	0.233	0.369	0.288	0.150	0.418	0.387	0.324	0.213	0.237	0.028
e^2	0.466	0.558	0.560	0.611	0.368	0.458	0.627	0.312	0.275	0.421	0.540	0.471	0.822
c^2	0.157	0.213	0.255	0.156	0.263	0.254	0.223	0.270	0.337	0.256	0.247	0.292	0.151
β age	ns	ns	ns	ns	ns	<0.1	<0.01	<0.1	ns	ns	<0.1	ns	ns
β age^2	ns	ns	<0.1	ns	ns	ns	ns	ns	ns	ns	<0.1	<0.1	ns
β sex	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
β age*sex	ns	ns	ns	ns	ns	<0.1	<0.1	<0.1	ns	ns	ns	ns	ns
β age^{2}sex	ns	ns	ns	ns	ns	ns	ns	ns	ns	<0.1	<0.1	<0.1	ns

[a] ma = metaconid area; ea = entoconid area; pa = protoconid area; ha = hypoconid area; hla = hypoconulid area; ns = not significant.
Asterisk (*) denotes a high residual kurtosis (1.89); 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)]; Coefficient of variation (CV) = [standard deviation * 100]/mean; measurements are in mm^2.

the metaconid–hypoconid and entoconid–hypoconid. As for the M_1, the metaconid–entoconid correlation is also significantly different from zero, whereas the entoconid–hypoconid [$P(\rho_G = 0) = 0.04$] is arguable, and the metaconid–hypoconid [$P(\rho_G = 0) = 0.28$] is not significantly different from zero.

The M_3 results mirror those found for the M_1 and M_2. The genetic correlations are lower than those estimated for the M_1. The metaconid–hypoconid pair is particularly low and not significantly different from zero. The entoconid–protoconid pair is the highest, and not significantly different from one.

Our second set of bivariate analyses focused on serial analyses of cusp morphological homologues along the molar row (Table 3). Genetic correlations for all homologue pairs were generally high, significantly different from zero, and not statistically different from one. The exceptions to this are for the M_1 and M_3 comparisons of entoconid, protoconid, and hypoconid, which returned large standard errors and consequently statistically inconclusive results.

Lastly, cusp area and buccolingual width were compared: the mesial cusps were compared with the mesial width and the distal cusps with distal width (Table 4). The buccal cusps yielded higher genetic correlations than did the lingual cusps, and all the correlations between cusps and widths were found to be significantly different from one. Likelihood ratio tests indicate that the ρ_G estimate for hypoconid area – distal width ($\rho_G = 0.882$) is significantly different ($P = 0.01$) from that for the lingual cusp. The ρ_G estimate for protoconid area – mesial width ($\rho_G = 0.717$) is only suggestively different ($P = 0.07$) from that estimate for the lingual cusp ($\rho_G = 0.481$).

DISCUSSION

Variation in molar cusp size is heritable in this population of captive pedigreed baboons. Although not unexpected, this is an important first step to understanding the genetic architecture of cusp area, as only variation that is heritable can respond to selective pressure (Fisher, 1930; Lynch and Walsh, 1998).

The second aim of this project was to identify the genetic interrelatedness of cusps on the same tooth as well as serially along the molar row. We first address the question of genetic correlations between cusps on the same crown.

Genetic correlations between traits can result from either pleiotropy or gametic phase disequilibrium (Lynch and Walsh, 1998). The degree of gametic phase disequilibrium (or linkage disequilibrium, LD) 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 LD 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, LD is not likely to be a major contributor to the genetic correlation (Lande, 1980; Lynch and Walsh, 1998). Therefore, we are cautiously confident that significant additive genetic correlations esti-

TABLE 3. Bivariate statistical genetic analyses: Maximum-likelihood estimates (MLE) of genetic and environmental correlations[a]

	Phenotype pairs	*N*	Correlations (MLEs)		Significance of correlations P(Hypothesis)	
			ρ_G (se)	ρ_E	$\rho_G = 0$	$\lvert\rho_G\rvert = 1$
M_1	ma–ea	346	0.836 (0.145)	0.549	0.0046	0.1063
	ma–pa	350	0.915 (0.093)	−0.353	<0.0001	0.1442
	ma–ha	356	0.359 (0.270)	−0.089	0.2229	0.0049
	ea–pa	354	0.934 (0.122)	0.011	0.0004	0.2805
	ea–ha	356	0.604 (0.246)	0.157	0.0725	0.0146
	pa–ha	356	0.838 (0.163)	0.592	0.0175	0.1144
M_2	ma–ea	503	0.616 (0.116)	0.593	0.0007	<0.0001
	ma–pa	507	0.489 (0.185)	0.039	0.0250	0.0005
	ma–ha	508	0.160 (0.169)	0.003	0.3581	<0.0001
	ea–pa	504	0.806 (0.132)	0.052	0.0001	0.0317
	ea–ha	504	0.428 (0.156)	0.010	0.0152	<0.0001
	pa–ha	502	0.802 (0.084)	0.624	<0.0001	0.0005
M_3	ma–ea	410	0.535 (0.145)	0.4420	0.0065	<0.0001
	ma–pa	421	0.458 (0.175)	−0.056	0.0198	<0.0001
	ma–ha	421	0.141 (0.211)	0.065	0.5121	<0.0001
	ea–pa	423	0.910 (–)	−0.156	<0.0001	0.2817
	ea–ha	417	0.580 (0.201)	0.099	0.0149	0.0057
	pa–ha	423	0.675 (0.148)	0.647	0.0026	0.0011
Metaconid	M_1–M_2	519	1.000 (–)	0.154	<0.0001	–
	M_1–M_3	490	0.884 (0.081)	0.251	<0.0001	0.0236
	M_2–M_3	543	0.897 (0.060)	0.335	<0.0001	0.0107
Entoconid	M_1–M_2	518	0.760 (0.206)	0.444	0.0095	0.1195
	M_1–M_3	492	0.542 (0.252)	0.218	0.0532	0.0375
	M_2–M_3	546	0.935 (0.079)	0.124	<0.0001	0.1655
Protoconid	M_1–M_2	522	0.567 (0.237)	0.316	0.0776	0.0059
	M_1–M_3	506	0.481 (0.278)	−0.007	0.1003	0.0303
	M_2–M_3	548	1.000 (–)	0.161	<0.0001	–
Hypoconid	M_1–M_2	524	0.777 (0.165)	0.225	0.0018	0.0383
	M_1–M_3	503	0.691 (0.360)	−0.033	0.0728	0.1638
	M_2–M_3	546	0.951 (0.111)	0.007	<0.0001	0.3138

[a] P(Hypothesis): probability of the hypothesis indicated in the columns below being true given the available pedigreed data; se = standard error; ma = metaconid area; ea = entaconid area; pa = protoconid area; hypoconid area; M_1 = first mandibular molar.

TABLE 4. Bivariate statistical genetic analyses between cusp area and widths for M_2: Maximum-likelihood estimates (MLE) of genetic and environmental correlations[a]

Phenotype pairs	*N*	Correlations (MLEs)		Significance P(Hypothesis)	
		ρ_G	ρ_E	$\rho_G = 0$	$\lvert\rho_G\rvert = 1$
pa–mw	534	0.717	0.731	0.0051	0.0045
ma–mw	534	0.481	0.503	0.0242	<0.0001
ha–dw	532	0.882	0.750	<0.0001	0.0001
ea–dw	528	0.612	0.531	0.0185	0.0008

[a] pa = protoconid area; ma = metaconid area; ha = hypoconid area; ea = entoconid area; mw = mesial buccolingual width; dw = distal buccolingual width; P(Hypothesis): probability of the hypothesis (indicated in columns below) being true given the available pedigreed data.

mated in our analyses on pairs of complex, multifactorial dental measures from our non-inbred, extended baboon pedigrees are primarily indicative of pleiotropy rather than LD. Ongoing and planned whole genome screens and LD analyses in this population will help confirm this.

The sequence of cusp calcification in the mandibular molars of baboons is usually protoconid → metaconid → hypoconid → entoconid (Swindler et al., 1968; Swindler, 1985). This sequence of calcification is the same for macaques, humans, chimpanzees, and gorillas (Kraus and Jordan, 1965; Oka and Kraus, 1969; Swindler, 1985). Macaque protoconids and hypoconids start calcification very close in time (Swindler and Gavan, 1962) and the second cusp to calcify varies between the metaconid and hypoconid (Swindler and McCoy, 1965). During molar cusp coalescence in cercopithecoids, a buccolingual crest forms uniting the two mesial and two distal cusps prior to circumferential calcification (Swindler and Gavan, 1962; Swindler and McCoy, 1965). This coalescence patterns differs from humans and howler monkeys (Tarrant and Swindler, 1972; Swindler, 1985).

It would be reasonable to hypothesize that cusps temporally adjacent to one another in the sequence of calcification have a higher degree of genetic correlation than cusps that are not. Alternatively, a higher degree of genetic correlation could be anticipated between cusps within a lophid, following the pattern of coalescence.

The baboons yielded genetic correlations between molar cusps that follow neither expectation. Rather, all cusps on the M_1 have a genetic correlation that is not statistically distinguishable from one, save for the metaconid–hypoconid ($\rho_G = 0$) and the entoconid–hypoconid. For the M_2 and M_3, all cusps have overlapping but non-identical genetic effects (partial genetic correlations) except for the metaconid–hypoconid that are genetically independent ($\rho_G = 0$) and the protoconid–entoconid that have $\rho_G = 1$. Therefore, the most evident intercuspal relationships are diagonal across the crown: 1) the complete genetic correlation between the protoconid and entoconid ($\rho_G = 1$), and 2) the lack of a genetic correlation between the metaconid and hypoconid ($\rho_G = 0$) (see Fig. 1B).

Additionally, this pattern of genetic correlations estimated for the baboons does not follow expectations from gene expression and knock-out studies of mouse molars. Tooth crowns consist of enamel produced by inner enamel epithelium overlying dentin that is produced by dental mesenchyme [see Zhao et al. (2000), Jernvall and Thesleff (2000), and Tucker and Sharpe (2004) for reviews]. Non-proliferative, epithelial signaling centers known as enamel knots (EKs) mediate the formation of cusps in mouse molars (Jernvall et al., 1994). The primary EK complex is followed by secondary EKs that are located at the tip of each putative cusp, and it is known that in mice these secondary EKs are not directly induced by cell migration from the primary EK (Matalova et al., 2005). However, these secondary EKs are responsible for regulating the formation of their respective cusps (Butler, 1956; Keränen et al., 1998; Jernvall et al., 2000).

Gene expression studies of mouse tooth development have not yet identified any genes that are specific to a cusp to the exclusion of other cusps (Keränen et al., 1998; Jernvall and Jung, 2000; Jernvall et al., 2000). Based on a comparison of gene expression patterns in mouse and vole molars, Jernvall et al. (2000) proposed that rodent molars consist of a repeated pre-pattern, such that each lophid is a repetition of the mesial most cusp pair. Two contrasting predictions follow from this observation. First, we may expect the buccolingual cusp pairs to show the highest genetic correlations. Alternatively, the two lingual and two buccal cusps may be more closely genetically correlated as the distal cusp is a repeat of the mechanism determining the mesial cusp. Neither is the case in this baboon population, as the most consistent pattern was diagonal protoconid–entoconid ($\rho_G = 1$) and metaconid–hypoconid ($\rho_G = 0$).

Although secondary EKs express the same suite of gene products as the primary EK and the primary EK is critical to proper tooth formation, it is widely recognized that the genetic mechanisms required to make an organ are not necessarily the same mechanisms that result in minor phenotypic variation. Gene expression studies of secondary EK placement indicate that an upstream regulator, as yet unidentified, underlies the spatial differences of mouse versus vole secondary EK location (Keränen et al., 1998; Jernvall et al., 2000). The quantitative genetic analyses reported here may be indicative of similarly unknown genetic factors.

The discordance between our genetic analyses and previous gene expression studies may also result from the differential development of mouse and primate secondary EKs. Mouse secondary EKs appear simultaneously after the disappearance of the primary EK, whereas primates and many other multicusped organisms such as viverravids, bats, and *Monodelphis* have a sequential cascade (Butler, 1956; Marshall and Butler, 1966; Jernvall, 1995; Polly, 1998). Further developmental and embryological research is needed to address the disjunction between these quantitative genetic analyses and what is known of tooth development.

Although considerably more research is needed to empirically investigate the mechanisms that underlie the pattern of genetic correlations seen in the baboons, we propose two hypotheses to test. First, it is possible that the genetic "pre-pattern" proposed for rodents by Jernvall et al. (2000) does not accurately reflect the mechanisms that determine primate molar patterns. The protoconid has repeatedly been described as the primary cusp (Butler, 1956). However, the protoconid and entoconid may represent the primary pre-pattern in these baboons, rather than the protoconid and metaconid as would be expected if the mesial-most cercopithecoid cusps form the initial pattern. As Butler notes (1956:52), "Ridges are less stable than cusps, and they must be used with caution as guides to cusp homology."

A second hypothesis derives from our understanding of molar functional morphology. The protocone of the maxillary molar occludes into the central basin of the mandibular molar. If the protocone and protoconid are the primary cusps around which the patterning of the other cusps accord, selection may results for the protoconid and entoconid to be highly genetically correlated so as to provide a crown length and width that occludes properly with the protocone. Diagonally positioned cusps, if genetically correlated, would provide a certain amount of regulation over the overall length and width of the crown. The opposite diagonal set of cusps, by lacking a certain degree of genetic correlation would provide variance that could be a more ready source of morphological variation without compromising the general occlusal relationship with the maxillary crown.

Our main goal for the next stage of this project is to collect and analyze data for the maxillary molars, and to expand the sample to include both sides of the dental arcade. Although the pattern of genetic correlations was consistent across all three molars, more confidence can be placed in these unusual results if the antimeres yield the same results.

In the meantime, our second speculative hypothesis could also be tested by exploring phenotypic correlations between cusps on the same molar crown. For example, Suwa et al. (1994) noted that the *A. boisei* talonid expansion has a relatively large entoconid, and that the *A. robustus* talonid expansion consists of a larger hypoconulid (see their Table 6). Do these contrasting expansions statistically correlate with variance in the trigonid cusps?

As with all quantitative genetic analyses, the primary caveat is that the genetic architecture for one population may not necessary represent that of other populations. There may be different genetic correlations between the trigonid and talonid cusps across primate taxa. For example, Erdbrink (1965, 1967) noted different phenotypic correlations between cusp areas depending on the occlusal fissure pattern of human molars.

Although phenotypic correlations do not necessarily reflect an underlying genetic correlation, phenotypic variances and covariances do often result from underlying genetic variances and covariances (Lande, 1979; Cheverud, 1988). As an example of this, Marroig and Cheverud (2005) found that genetic lines of least evolutionary resistance for size allometry can explain the vast array of cranial variance present in most New World Monkeys, despite the 30 million years of divergent evolution. And the modularity found in these New World Monkeys also appears to describe Old World Monkey cranial variation (Cheverud, 1989; Hallgrímsson et al., 2004). Such studies demonstrate that a cautious application of quantitative genetic results across primate taxa may yield significant new insights to morphological evolution.

Given the highly conserved nature of developmental pathways (Carroll et al., 2001) and the similarities between human and mouse tooth development (Davideau et al., 1999), the population-level genetic architecture seen in the baboons may well be representative of

other primate species. We plan to carry out studies of phenotypic correlations specifically designed to test this hypothesis.

Returning to our second specific aim, analyses of morphologically homologous cusps along the tooth row indicate that variation in basal cusp area is determined by the same genetic effects on each crown. This result is intriguing when contrasted to the overall pattern of intercusp correlations. The M_1 cusps have high genetic correlations that are not statistically different from one, save for the lack of a correlation between the metaconid and hypoconid, and between the entoconid and hypoconid ($\rho_G = 0$). The M_2 and M_3 have much lower genetic correlation estimates, although they also demonstrate the complete lack of a genetic correlation between the metaconid and hypoconid. Both of these more distal crowns also yielded a genetic correlation of one between the protoconid and entoconid, as was seen for the M_1. Therefore, a pattern of diagonal cusp area interrelationships is maintained along the tooth row, but the level of the genetic correlation among the other cusp pairs is significantly higher in the M_1 compared to the M_2 and M_3.

Previous work on mammalian dental variation demonstrates the M_1 to be the least variable of all teeth along the molar row (e.g., Gingerich, 1974; Gingerich and Schoeninger, 1979; Gingerich and Winkler, 1979; Harris and Dinh, in press). Basal cusp area studies show the same pattern (Macho, 1994; Uchida, 1998a). Previous heritability studies found that the least variable tooth returned the highest heritability estimate (Alvesalo and Tiggerstedt, 1974). Here we find that the M_1 does not return higher heritability estimates, but that the cusps on this crown do have much higher genetic correlations than those estimated on the M_2 and M_3. If the genetic architecture seen in the baboons is also found in other taxa, these high genetic correlations within the M_1 may underlie the reduced phenotypic variability observed in other species.

Numerous studies demonstrate that patterns of phenotypic variability appear to reflect developmental cascades (Polly, 1998; Kondo and Yamada, 2003; Kondo and Townsend, 2006). It is difficult to compare variance in this population to variance in other studies because individuals in this baboon colony are related (violating the assumption of independence in most statistical analyses). Therefore, the distributions for many of the dental phenotypes are significantly leptokurtic and familial relationships must be accounted for in the analysis of variance. However, we have provided the coefficient of variation (CV) for each of the cuspal phenotypes (Table 2). These data show that there is no clear difference in the CVs for these cusps, although the metaconid CV is the highest on the M_1 and M_2.

Our data reveal tentative evidence for what may be an expected trend, that is for cusp areas on adjacent crowns to have higher genetic correlations than do those on spatially and temporally more distant crowns. This decrease in pleiotropy may result from changing patterns of epistasis (or gene–gene interactions) as molar crowns are in developmentally different environments given the differences in ontogenetic timing. Alternatively, the decrease in pleiotropy may result from different selective pressures acting on the various molar crowns over evolutionary time.

The results of our bivariate analyses of cusp areas and crown widths suggest that the gene or genes that influence buccolingual width also exert more of an influence on the areas of buccal cusps than those of lingual cusps. In both cases, the pleiotropic effect is incomplete (i.e., the genetic correlation is significantly less than one), which we interpret to mean that a portion of the variation in cusp area and crown width is due to the effects of genes not shared with the other trait.

Interestingly though, the buccal cusps have a significantly higher genetic correlation with width than do the lingual cusps. The functional cusps on the mandibular molars—those that occlude with the maxillary molars—are those on the buccal side. The buccal cusps are also larger than are those on the lingual side. Therefore, the higher genetic correlation between total buccolingual width and the buccal cusps may have resulted from functional selective pressures to withstand the greater forces imposed on the buccal half of the crown during mastication.

The quantitative genetic analysis of mandibular molar cusp area reveals a pattern of genetic correlations that do not conform to our expectations from what is known about tooth development. Rather, we find a pattern that can be explained, perhaps, by a response to functional pressures exerted on the genetic architecture over evolutionary time. Further research is needed to test this hypothesis.

CONCLUSIONS

We performed a quantitative genetic analysis of variation in mandibular molar cusp size in a captive pedigreed breeding population of baboons housed at the Southwest National Primate Research Center. Results from these analyses indicate that this phenotype is heritable and sexually dimorphic. Approximately 15–42% of the total phenotypic variance is due to the additive effects of genes.

We found a pattern of genetic correlation and lack of correlation that is repeated on the first, second, and third molars. The entoconid and protoconid have a high genetic correlation that is not significantly different from one. In contrast, the metaconid and hypoconid do not have a genetic correlation.

The first molar genetic correlations are typically higher than those found for the more distal molars, but the pattern of $\rho_G \approx 1$ between entoconid and protoconid, and $\rho_G \approx 0$ between metaconid and hypoconid is found on all three crowns. These genetic correlations do not accord with expectations from developmental genetics or embryological studies. Further analyses are needed to explore this disjunction. In the meantime, we tentatively suggest a functional hypothesis that may have shaped the genetic architecture of cusp area interrelatedness over evolutionary time.

Variation along the tooth row appears to be influenced by the same genetic effects, as morphological homologues have genetic correlations that are high or not significantly different from one. This is similar to results from the serial analyses of other phenotypes (Hlusko and Mahaney, 2003; Hlusko et al., 2004).

As would be expected, there is a genetic correlation between cusp size and buccolingual width, although this correlation is higher in the buccal cusps compared to the lingual cusps. The buccal cusps are the functional cusps for the mandibular molars, and also the larger of the cusps. This result might be explained by a genetic architecture that has evolved in response to functional pressures moreso than the result of developmental cascades,

similar to our possible explanation for the cusp area interrelationships mentioned above. Clearly, further research is needed to determine whether or not functional versus developmental explanations best accord with the genetic architecture of minor population-level dental variation.

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