Archives of Oral Biology (2003) **48**, 663–672

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Archives of Oral Biology

www.elsevier.com/locate/archoralbio

Genetic contributions to expression of the baboon cingular remnant

Leslea J. Hlusko[a,*], Michael C. Mahaney[b]

[a]*Department of Anthropology, University of Illinois at Urbana-Champaign, 109 Davenport Hall, MC-148, Urbana, IL 61801, USA*
[b]*Department of Genetics, Southwest Foundation for Biomedical Research, P.O. Box 760549, San Antonio, TX 78245, USA*

Accepted 23 April 2003

KEYWORDS
Quantitative genetics;
Heritability;
Interconulus;
Papio hamadryas;
Dental variation;
Cingulum

Summary Primitive mammalian molar morphology is characterised in part by a ridge of enamel that encircles the entire base of the molar crown, the cingulum. Many higher primates have reduced the cingulum, but often retain remnant features on the lingual surface of maxillary molars and the labial surface of mandibular molars. Two of these remnants in cercopithecoid primates, the interconulus and interconulid, are morphologically similar though the interconulus is found on maxillary molars and the interconulid is located on mandibular molars.

Here we present results from a quantitative genetic analysis of expression of these two traits in a sample of 479 modern savannah baboons from the Southwest Foundation for Biomedical Research (SFBR). We found that both traits are significantly heritable with little variance attributable to other factors, such as sex, age, and molar crown size. Bivariate analyses yielded point estimates for genetic correlations between left and right side expression that are either equal to or not significantly different from 1.0; meaning that 100% of their additive genetic variance is due to the effects of the same gene or suite of genes. By contrast, our estimates of the genetic correlations between maxillary and mandibular expression of this trait range from 0.52 to 0.72, suggesting that 28–52% of the additive genetic variance in the interconulus and interconulid is due to the effects of shared genes. These results demonstrate that intra-arch expression is characterised by complete pleiotropy whereas inter-arch expression is caused by incomplete pleiotropy. These results are relevant to dental developmental studies as well as paleontological analyses of the evolution of the primate dentition.

Introduction

The tribosphenic, primitive mammalian molar is characterised by a cingulum, a ridge of enamel encircling the entire base of the crown. Early primates retained a full cingulum on the maxillary molars, such as in *Pelycodus* and *Tetonius homunculus* from the early Eocene. The mandibular molar cingulum in these primates is less complete and often appears as a ridge of enamel only on the labial surface (e.g. *Pelycodus*, and *Northarctus*). In other early primates, the cingulum is reduced to a remnant feature on the lingual side of maxillary molars, especially on the mesiolingual aspect (e.g. *Leptadapis* and *Absarokius*). Lingual cingula on the maxillary molars of the Oligocene *Aegyptopithecus* and other primates are shown in Fig. 1. In general, the fossil evidence shows that the cingulum reduced

*Corresponding author. Tel.: +1-217-244-4914; fax: +1-217-244-3490.
E-mail address: hlusko@uiuc.edu (L.J. Hlusko).

0003-9969/$ – see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0003-9969(03)00132-8

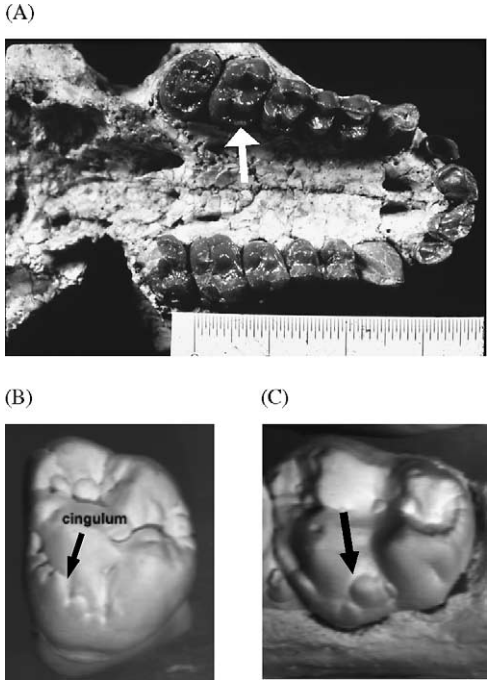

Figure 1 This shows maxillary cingular remnants (marked by arrows) in several primates. (A) Maxillary dentition of *Aegyptopithecus zeuxis* (photo courtesy of Elwyn L. Simons); (B) upper left third molar of a 2.5 million years old hominid from the Omo, Ethiopia (specimen number L 50-2); (C) upper left third molar of a baboon in the SFBR colony with the highest degree of interconulus expression.

over time, resulting in differentially expressed remnants on the labial surface of mandibular molars and lingual surface of maxillary molars.[1]

In extant primates, the most complete cingular remnants are found in the prosimians, such as the labial remnants on maxillary and mandibular molars of *Ptilocercus* (a tree shrew), *Galago* and *Arctocebus*, and the lingual cingulum on maxillary molars of *Lemur catta* and *Hapalemur griseus*.[2] Compared to the prosimians, the cingulum is all but lost in many modern anthropoids. However the ancillary features that sometimes flank the outer edges of anthropoid molar crowns are considered to be remnants of the primitive cingulum.[3–5] These remnant features include the parastyle, protostyle, Carabelli's cusp in humans, mesostyle, and interconulus of maxillary molars, and protostylid and interconulid of the mandibular molars.[3,4,6–9] Similar to what is seen for the cingulum in the fossil record and in the prosimians, the cingular remnants in anthropoids are typically found most strongly expressed on the lingual side of maxillary molars and on the labial surface of mandibular molars.

The cingulum and its remnants may be a functional adaptation. James[2] suggested that its role is to protect the gums during mastication. Others proposed that the cingulum adds strength to the molar crown when crushing hard food objects.[10,11] Delson[12] argued that the cingulum was incorporated into the wall of some primate molars, creating the marked molar basal flare in some taxa, strengthening the crown during chewing. Similarly, Mizoguchi[13] proposed that Carabelli's cusp, a human cingular remnant, acts to resist excessive biomechanical stresses in labiolingually narrow molars. Carabelli's cusp has also been suggested to increase molar surface area thereby counteracting heavy attrition in microdontic populations.[14] Clearly, a wide range of adaptive explanations have been offered for the presence of a cingulum and cingular remnants. Unfortunately though, these explanations remain speculative until we understand more about the genetic and developmental processes that result in the presence or absence of a complete cingulum, its remnants, and the genetic and developmental relationship between maxillary and mandibular expression.

Much research has recently been undertaken to investigate the genetic mechanisms underlying patterning across the dental arcade (e.g.[15–17]) and of cusps on the same crown.[18–20] See Zhao et al.[21] and Peters and Balling[22] for more complete reviews of our current understanding of tooth development. These developmental studies suggest that cingula and cingular remnants may result from the patterning mechanism that establishes the overall cusp arrangement. However, despite the vast amount of work done to better understand cusp patterning, virtually no research has yet focused on the development of the cingulum or its supposed derivatives. Questions concerning the genetic and developmental processes underlying cingular remnants need to be addressed before confidence can be placed in any adaptive or phylogenetic inference from their variation. Additionally, we need to understand the genetic relationship between maxillary and mandibular traits that are morphologically similar—are they also developmentally homologous?

This paper presents the results of quantitative genetic analyses to estimate the genetic contributions to variation in expression of two cingular remnants (the interconulus and interconulid) in modern baboons. Given the serial, repetitive nature of the dentition, we expect that teeth along the tooth row will share most, if not all genetic contributions to their variation. The relationship between the maxillary and mandibular genetic patterning mechanisms is virtually unknown, and therefore the first empirical evidence will be presented here.

Materials

Data for this study were obtained from 479 pedigreed baboons (*Papio hamadryas*) who are part of a much larger breeding colony at the Southwest Foundation for Biomedical Research (SFBR) in San Antonio, Texas. The pedigree sample studied consisted mainly of olive baboons (*P. hamadryas anubis*), yellow baboons (*P. hamadryas cynocephalus*), and their hybrids,[23] with a female to male sex ratio approximating 2:1, and ranging in age from 4.6 to 30 years. While strict genetic management has been employed to prevent unwanted inbreeding in the pedigrees to which the animals in this study belong, all non-founder animals in these pedigrees were the results of matings that were random with respect to dental, skeletal, or auxological phenotypes. Since birth or, in the case of some of the oldest of the founders, arrival at the SFBR colony, all animals have been housed out of doors in social group cages and maintained on monkey chow diets to which they have ad libitum access. Animal care personnel and staff veterinarians provide daily maintenance as well as health care to all animals in accordance with the Guide for the Care and Use of Laboratory Animals.[24] All procedures related to their treatment during the conduct of this study were approved by the Institutional Animal Care and Use Committee in accordance with the established guidelines.

Data collection methods

Dental data were collected from casts of 479 individuals comprising five subsets of the pedigreed breeding colony. These subsets contain large sibships and at least three generations.

Impressions of the animals' dentitions were made while they were anaesthetised intramuscularly with ketamine followed by intravenous ''RAAK'' (Rompun, Atropine, Acepromazine, and Ketamine) to affect relaxation. Both the maxillary and mandibular postcanine dentition were moulded using a rapidly setting impression material commonly used by dentists (Coltene President© gel). This procedure is approved by the Institutional Animal Care and Use Committee, in accordance with the established guidelines. Positive casts were poured with high resolution dental plaster within 1 week of moulding. Casts were used for the assessment of variation.

The interconulus and interconulid were scored using a protocol similar to that developed by Turner et al.,[25] familiarly known as the Arizona State University human dental plaque system. In this method direct comparisons are made between the tooth in question and a tooth with a previously established standard expression of the trait being investigated. This system of established expression types has contributed greatly to the unification of the field of human odontology since it facilitates cross-study comparisons. A similar system was developed using the SFBR baboon colony as the standards (or types) for these two traits.[26] A score of zero was given when the feature was obscured, too worn, or otherwise not ascertainable. One is the lowest expression and five is the strongest expression (Fig. 2). All data were collected by one researcher (LJH) to reduce interobserver error.

All metric data were collected from digital images of each molar. Digital images were made of the molar casts using a digital camera (Pixera© Professional, Pixera Corporation, Los Gatos, CA) and a 18—108 mm F2.5 zoom lens (D.O. Industries©, Navitar Inc., Rochester, NY). This protocol is described in detail elsewhere.[27]

Mesiodistal length was measured as the maximal length of the molar. Interproximal wear was not accounted for because of the large amount of variation in the mesial and distal marginal ridges. Buccolingual distance was measured in two positions, first as the maximal width of the tooth oriented through the mesial loph and second as the maximal width of the tooth oriented through the distal loph. Note that the orientation of these latter measurements is not always directly perpendicular to the mesiodistal axis

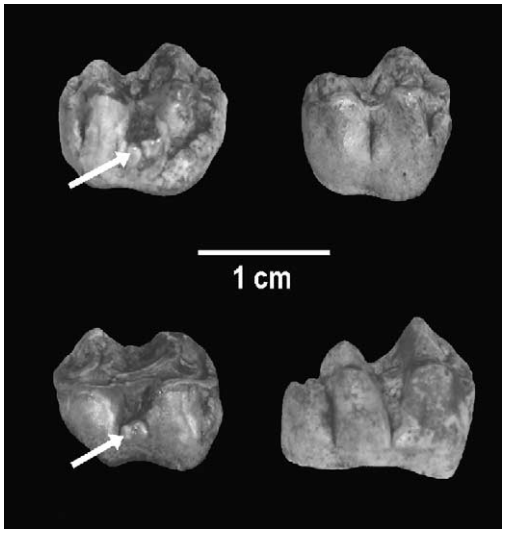

Figure 2 Variation in SFBR baboon molar cingular remnant expression. Top row: lingual view of maxillary right third molars; right is no expression of interconulus and left is highest degree of expression. Bottom row: labial/buccal view of mandibular right molars; right is a third molar with no expression and left is a first molar with highest degree of expression. White arrows highlight the specific interconulus and interconulid features.

of the tooth. Intraobserver error was between 0.8 and 2.6%.

Analytical methods

All pedigree data management and preparation were accomplished using the routines implemented in the computer package PEDSYS.[28] For the purposes of the analyses presented in this paper, the animals were organised into 11 extended pedigrees. An additional 787 baboons for whom dental data were not collected were used to facilitate reconstruction of these pedigrees, which ranged in size from 67 to 171 members, with a mean size of 118 animals. The largest of the pedigrees is three generations deep and the smallest is two generations deep. Each of the 11 pedigrees contained between 10 and 59 animals with data for all 12 traits assessed.

Statistical genetic analyses were conducted by means of a maximum-likelihood based variance decomposition approach implemented in the computer package SOLAR.[29] This approach, that was developed following methodology originally proposed by Hopper and Mathews[30] and Boehnke et al.,[31] has been described in detail elsewhere.[32] In short, we use this approach to partition the phenotypic variance (σ^2_P) into components corresponding to the additive genetic (σ^2_G) and non-genetic—i.e. environmental—(σ^2_E) effects. Because these components are additive, such that $\sigma^2_P = \sigma^2_G + \sigma^2_E$, we estimated the heritability, or proportion of the phenotypic variance attributable to additive genetic effects, as $h^2 = \sigma^2_G/\sigma^2_P$. We estimated the proportion of the phenotypic variance attributable to non-genetic factors as $e^2 = 1 - h^2$. In addition to these terms, we simultaneously estimated the mean effects of sex, age, and three measures of molar crown size (mesiodistal length, mesial and distal buccolingual width) on interconulus expression score for each molar studied.

Bivariate analyses were accomplished using multivariate extensions to the methods described above. These analyses were employed to determine the extent to which normal variation in the degree of expression of the interconulus and interconulid were attributable to the additive effects of shared genes and shared non-genetic factors. This is determined by estimating the additive genetic and environmental (non-additive-genetic) correlations, ρ_G and ρ_E, between trait pairs. Respectively, these two correlations estimate the effects of shared genes (i.e. pleiotropy) and shared, unmeasured, non-additive-genetic factors on the phenotypic variance in a trait. We used maximum-likelihood estimates of the two correlations to obtain estimates of total phenotypic correlation, ρ_P, between trait pairs as described elsewhere.[33]

Significance of the maximum-likelihood estimates for heritability and other parameters was assessed by means of likelihood ratio tests.[34] The maximum-likelihood for the general model in which all parameters were estimated was compared to that for restricted models in which the value of the parameter to be tested was held constant at some value (usually zero or one). Twice the difference in the log likelihoods of the two models compared is distributed asymptotically approximately as either a 1/2:1/2 mixture of χ^2 with a point mass at zero for tests of parameters like h^2 (for which a fixed value of zero in a restricted model is at a boundary of the parameter space) or a χ^2 variate for tests of covariates (for which zero is not a boundary value).[30] In both cases degrees of freedom are obtained as the difference in the number of estimated parameters in the two models.[30] 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.[31]

Results

Means and standard deviations for the two non-metric traits for all 12 molars are presented in Table 1. The interconulus is present in approximately 44% of the baboon sample. The interconulid is present in approximately 75% of the population, depending largely on the position of the molar along the tooth row. Frequency distributions are presented in Table 2. While the data in these tables are from related individuals, making tests of significance not accounting for this fact inappropriate, these

Table 1 Descriptive statistics for the interconulus and interconulid.[a]

	LM^1	RM^1	LM_1	RM_1	LM^2	RM^2	LM_2	RM_2	LM^3	RM^3	LM_3	RM_3
Mean	1.6	1.5	2.8	2.6	1.6	1.6	2.3	2.1	2.1	2.0	2.1	1.9
S.D.	0.71	0.61	0.78	0.82	0.90	0.82	0.90	0.91	1.24	1.18	1.18	1.15
N	318	304	292	299	320	310	306	303	305	293	255	264

[a] Note that these are based on ordinal scale data.

Table 2 Frequency distributions of interconulus and interconulid.

Trait	XRM1I	XRM2I	XRM3I	XLM1I	XLM2I	XLM3I	DRM1I	DRM2I	DRM3I	DLM1I	DLM2I	DLM3I
0	49	33	65	46	28	52	62	48	122	70	44	142
1	251	277	212	235	273	205	23	125	184	20	84	135
2	153	117	90	164	118	87	162	211	89	129	212	95
3	23	37	56	30	35	72	177	59	42	182	98	55
4	3	15	34	4	24	37	46	29	28	68	32	35
5	0	0	22	0	1	26	9	7	14	10	9	17
Total	479	479	479	479	479	479	479	479	479	479	479	479

summaries are presented to provide a general appreciation of the population of animals from which we obtained the data for the subsequent statistical genetic analyses.

Total heritability is estimated as the proportion of the total phenotypic variance due to the additive effects of genes, whereas the residual heritability describes these effects after the covariate variance has been accounted for. All of the heritability estimates for the interconulus were significant at $P \leq 0.001$ and range between 0.33 and 0.73 (Table 3). All but one of the interconulid heritability estimates were significant at $P \leq 0.001$ except for the mandibular left third molar trait, where $P = 0.018$. The interconulid heritability estimates ranged between 0.41 and 0.64. Because ordinal scale data on interconulus and interconulid expression were analysed as if they varied on a continuous scale, it is likely that our maximum-likelihood estimates are somewhat less precise than they would be if modelled more exactly. Improving the fit of the maximisation routines to better accommodate ordinal scale variables such as these would increase both the precision of our estimates and the statistical power of the analyses. Therefore, the heritability estimates presented here and their statistical significance are probably conservative.

As expected with dental traits, age played a minor and inconsistent role in the variance of degree of expression for the interconulus or interconulid (Table 3), though it did play a minor role in some teeth due to the effect of wear on assessing trait expression. Additionally, sex was not a consistently significant covariate and when included in the model did not account for a large amount of the total variance, indicating that the interconulus and interconulid are not sexually dimorphic. Molar width had a minor and inconsistent effect. Molar length had a significant positive effect on cingular remnant expression for second molars.

In total, covariates accounted for 0—10% of the phenotypic variance in cingular remnant expression in these baboons. For the maxillary interconulus, the combined effects of the covariates was negligible, accounting for 0—4% of the overall phenotypic variance. The contribution of covariates to the variance in expression of the mandibular trait was also low, ranging from 0 to 10%.

The results of bivariate quantitative genetic analyses, including genetic correlations between antimeric pairs, molars in the same dental arch series, and occluding maxillary and mandibular pairs, are presented in Table 4.

The estimated genetic correlation for the degree of expression between right and left molars of the same arch (for both maxillary and mandibular arches) was 1 for three of the pairs and not significantly different from 1 for the other three (see Table 4).

The estimated genetic correlations between first, second, and third molars along the tooth row ranged from 0.72 to 1.00. All of these serial genetic correlations were significantly different from zero and half were found to be significantly different from one.

The estimated genetic correlation for the degree of expression on the maxillary and mandibular molars ranged between 0.53 and 0.73. All six of these estimates were significantly different from zero ($P < 0.01$) and five were significantly different from one ($P < 0.01$).

Discussion

Our results are consistent with three conclusions concerning the genetic contributions to variance in expression of these two cingular remnants in this pedigreed population of baboons. (1) There is a significant heritable component to variation in expression of both traits; (2) intra-arch expression is characterised by complete pleiotropy; and (3) inter-arch expression is characterised by incomplete pleiotropy. Each of these results is discussed below.

First, our results demonstrate that these two cingular remnants, the interconulus and interconulid, are heritable and therefore a significant proportion of the variance in each trait in this population is

Table 3 Quantitative genetic analytical results for baboon cingular remnants.[a]

	RM^1	RM^2	RM^3	LM^1	LM^2	LM^3	RM_1	RM_2	RM_3	LM_1	LM_2	LM_3
Total h^2	0.393	0.499	0.725	0.333	0.442	0.541	0.408	0.528	0.511	0.635	0.523	0.378
Total c^2	None	0.031	0.013	0.032	0.040	None	0.003	0.095	None	None	0.105	0.102
Total e^2	0.607	0.470	0.263	0.635	0.518	0.459	0.59	0.377	0.489	0.365	0.372	0.52
Residual h^2	0.393 ± 0.146	0.515 ± 0.153	0.734 ± 0.144	0.344 ± 0.153	0.46 ± 0.139	0.541 ± 0.11	0.409 ± 0.126	0.583 ± 0.155	0.511 ± 0.135	0.635 ± 0.119	0.584 ± 0.166	0.421 ± 0.202
β length		↑↑		↑	↑↑			↑↑↑			↑↑↑	↑
β width				↓							↓	↑
β age		↑			↑		↑	↑↑↑				
β sex												↓
β age^2		↑										
β age × sex		↓	↓		↓		↓	↓				

[a] Direction of arrow indicates direction of covariate effect; ↑: significant $P < 0.10$; ↑↑: significant $P < 0.01$; ↑↑↑: significant $P < 0.001$; total h^2: proportion of total phenotypic variance due to additive effects of genes; total c^2: proportion of total phenotypic variance due to effects of significant covariates; total e^2: proportion of total phenotypic variance due to random, unmeasured effects; residual h^2: proportion of residual phenotypic variance (i.e. remaining after accounting for proportion due to significant covariate effects) due to additive genetic effects ± the standard error.

Table 4 Bivariate genetic correlations for baboon cingular remnants.

	ρ_G	P ($\rho_G = 0$)	P ($\rho_G = 1$)	ρ_G^2
Antimeric pairs				
RM^1—LM^1	0.986 ± 0.054	0.00002	0.8	0.97
RM^2—LM^2	1	<0.000001	—	1.00
RM^3—LM^3	1	<0.000001	—	1.00
RM_1—LM_1	0.982 ± 0.029	<0.000001	0.5	0.96
RM_2—LM_2	1	<0.000001	—	1.00
RM_3—LM_3	0.972 ± 0.031	<0.000001	0.3	0.95
Serial pairs				
RM^1—RM^2	0.878 ± 0.179	0.002	0.5	0.77
RM^2—RM^3	0.981 ± 0.024	<0.000001	0.4	0.96
LM^1—LM^2	1	<0.000001	—	1.00
LM^2—LM^3	0.886 ± 0.057	<0.000001	0.002	0.79
RM_1—RM_2	0.825 ± 0.082	0.00005	0.003	0.68
RM_2—RM_3	0.932 ± 0.050	<0.000001	0.05	0.87
LM_1—LM_2	0.899 ± 0.054	<0.000001	0.009	0.81
LM_2—LM_3	0.927 ± 0.057	<0.000001	0.13	0.86
Occluding pairs				
RM^1—RM_1	0.710 ± 0.207	0.009	0.08	0.50
RM^2—RM_2	0.526 ± 0.142	0.005	<0.000001	0.28
RM^3—RM_3	0.647 ± 0.117	0.0001	<0.000001	0.42
LM^1—LM_1	0.605 ± 0.162	0.003	0.005	0.37
LM^2—LM_2	0.733 ± 0.104	0.00001	0.00004	0.54
LM^3—LM_3	0.716 ± 0.102	0.000002	0.00002	0.51

attributable to the additive effects of genes. We found that the total heritability estimates for both traits ranged from 0.33 to 0.73. From quantitative genetic theory and animal breeding practice, a trait's likely response to selection is largely a function of the heritability and the selection differential.[35] All other things being equal, the greater the proportion of the variance in a trait that is due to the additive effects of genes, the more susceptible that trait is to the effects of selection. Non-heritable variation is unlikely to be evolutionarily important. Therefore, the results reported here demonstrate that these two cingular remnants are genetically determined to some degree and consequently able to respond to selective pressure. However, at this time we do not know what these pressures may have been or how strongly they may have affected the evolution of the cingulum, if at all.

A drawback to applying modern quantitative genetics to evolutionary questions is that we cannot be certain that past genetic mechanisms were the same as what we see today, a problem with all historical sciences. However, research in developmental genetics shows a close relationship in gene function between distantly related taxa. For example, the patterning of the vertebral column is coded for by the same *Hox* gene family in both mice and humans,[36,37] and functions remarkably similar to its fly homologue, HOM-C, that is responsible for axial formation.[38] Given that the earliest true primates lived only ~55 million years ago, it is reasonable to assume that many, if not all, the genes which influence morphological variation in the dentition of extant primate species are the same as those that did so in extinct members of the order. Additional support for this assumption stems from dental developmental genetics research showing that genes involved in mouse early dental patterning are the same as those seen in human early dental patterning.[39] Genetic sequencing and hybridisation studies also argue for strong genetic similarities between extant primates, and therefore their common ancestors. For example, baboons and humans are estimated to be ~92—95% genetically similar,[40] with an evolutionary divergence approximately ~23.5 million years ago.[41,42] Rogers et al.[43] report substantial conservation of the order of human microsatellite loci throughout the baboon genome: i.e. linkage maps for seven baboon autosomes are identical to their human counterparts, with the remainder reflecting a few rearrangements of large syntenic regions in humans.

The application of our knowledge of extant primate genetic mechanisms to fossil data is appropriate because of these close genetic relationships and the apparent conservation of developmental mechanisms. However, because heritability estimates from

modern populations are not necessarily informative of past selective pressures, as these estimates are highly sensitive to the sample population structure and non-genetic covariates that contribute to variation (such as household effects, environment, measurement error, etc.), it is the revelation of shared genetic effects that are of particular interest to evolutionary questions, for example, the results determined from the intra- and inter-arch genetic correlations.

We interpret genetic correlations at or near unity for expression of the cingular remnant in antimeres to indicate that most, if not all, the additive genetic variance in the expression of the trait within a dental arch is shared. This is evidence for complete pleiotropy. That is to say that the activity of the same gene or suite of genes influences variation in expression of this trait on both the right and left sides of each dental arch. This is consistent with a long-standing assumption, hitherto untested for a complex dental trait in primates, that the development of dental morphological and metric variation on either side of the dental arcade is controlled or influenced by the same genes.[3]

By contrast, our bivariate analyses of inter-arch variation in expression of the cingular remnants suggest incomplete pleiotropy. Although a significant proportion of the additive genetic variance in expression of the interconulus, for example, on a maxillary molar is attributable to the additive effects of genes that also influence variation in the expression of the interconulid of the corresponding mandibular tooth, a substantial proportion of the genetic variance in the expression of these traits remains unique to each arch. That is, variation in the degree of expression of the interconulus and interconulid appears to be coded for by overlapping but non-identical sets of genes.

The genetics underlying the patterning of the dentition has been the focus of a large amount of research (e.g.[2,6,15,17,44–47]). Tooth form in the maxillary and mandibular arches is strikingly similar, suggesting that they result from the same patterning process. However, these teeth are not identical morphologically, and may result from a ''mirror-image'' process.[17] There are numerous animals that have an obvious disjunction in the maxillary and mandibular genetic mechanisms resulting in different maxillary and mandibular tooth morphologies, such as toothcombs in lemurs and the loss of only the upper incisors in some ungulates.

Though our knowledge of the early development of the dentition is continually increasing,[17,21,22,48,49] 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

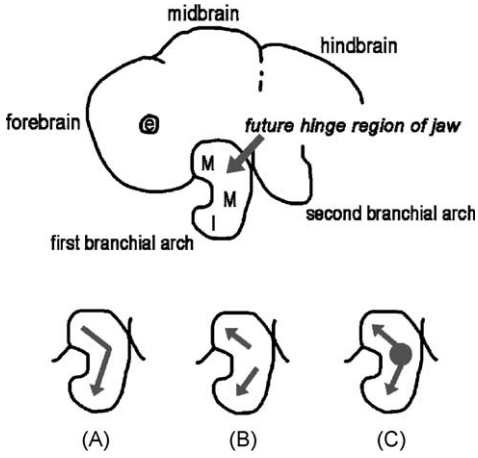

Figure 3 Sketch of an E10.5 day mouse embryo showing the pre-patterning of the dentition as two parallel axes. Top drawing shows the first branchial arch in perspective to the second branchial arch and fore-, mid-, and hindbrains. Three hypotheses of pattern signaling are shown as follows: (A) a unidirectional axis, analogous to the way *Hox* genes program the body axis; (B) two parallel unidirectional axes, analogous to the axes of the fore- and hindlimbs; (C) a mirror-image axis programmed by an organising center represented by the black dot. Rostral is to the left and caudal to the right. e: eye; M: presumptive molar region; I: presumptive incisor region (adapted from Weiss et al.[17], Fig. 5).

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 (see Fig. 3 adapted from[17]). Gene expression studies to date have been unable to provide clear evidence as to which, if any, of these models is potentially correct. Therefore, other methods of investigation are merited in order to maximise our knowledge of these genetic mechanisms. Our results in baboons provide the first statistical genetic evidence that some aspects of differential dental development in the maxilla and mandibular are attributable to the activities of different genes.

Ultimately these findings are important to paleontological research because they provide evidence of genetic correlations between dental traits. Dental traits have long been found to be correlated (e.g.[50–66]), but it was unclear how much of this correlation was due to shared genetic effects and how much to shared non-genetic effects. Here

we present for the first time estimates of the genetic correlations between two dental traits.

Quantitative genetic analyses are useful for paleontological studies since they can identify and quantify traits that are genetically correlated. This type of approach also has the potential to help us understand current dental development and the evolution of those developmental mechanisms through application to the fossil record.

Conclusion

We have performed quantitative genetic analyses on expression variation of the interconulus and interconulid in a population of modern savannah baboons from the Southwest Foundation for Biomedical Research ($n = 479$). We found that both of these cingular remnants were significantly heritable and not consistently or largely affected by age, sex, or tooth size.

Bivariate analyses estimated that 100% of the additive genetic effects contributing to variance in these traits are shared between antimeres, i.e. expression on opposite molars of the same dental arch. This means that the same gene or set of genes codes for degree of expression on the right and left sides of the dentition.

Further bivariate analyses estimated that maxillary and mandibular expression of these traits is neither completely independent not completely dependent in terms of the additive effects of genes. Rather, interconulus and interconulid expression is coded for by overlapping but non-identical sets of genes.

These results demonstrate that quantitative genetic analyses offer insight to the genetic correlations between traits, providing data for weighting traits in phylogenetic analyses. Additionally, these analyses are informative to our understanding of modern dental patterning and development, ultimately applicable to the evolution of these genetic mechanisms through the fossil record.

Acknowledgements

Many thanks to A. Walker, K. Weiss, and J. Rogers for project support and development. Thanks also to E.L. Simons for use of his photograph in Fig. 1. We also express our appreciation to D. Carey and the veterinarian staff at the Southwest Foundation for Biomedical Research and the Southwest National Primate Research Center, San Antonio, Texas, and D. Pillie for assistance with the dental casting. Pilot research was funded by National Science Foundation Grant SBR 9804907 (to K. Weiss) and a National Science Foundation Dissertation Improvement Grant (LJH). Continued funding was provided by the National Science Foundation Grant BCS-0130277. NIH/NCRR P51 RR013986 supports the Southwest National Primate Research Center.

References

1. Hartwig WC, editor. The primate fossil record. New York: Cambridge University Press; 2002.
2. James WW. The jaws and teeth of primates. London: Pitman; 1960.
3. Scott GR, Turner CG II. The anthropology of modern human teeth. New York: Cambridge University Press; 1997.
4. Swindler DR. Primate dentition. New York: Cambridge University Press; 2002.
5. Hillson S. Teeth. New York: Cambridge University Press; 1986.
6. Dahlberg AA. The evolutionary significance of the protostylid. *Am J Phys Anthropol* 1950;**8**:15—25.
7. Aiello L, Dean C. An introduction to human evolutionary anatomy. New York: Academic Press; 1990.
8. Hillson S. Dental anthropology. New York: Cambridge University Press; 1996.
9. Butler PM. The evolution of tooth shape and tooth function in primates. In: Teaford MF, Smith MM, Ferguson MWJ, editors. Development, function and evolution of teeth. New York: Cambridge University Press; 2000. p. 201—11.
10. Macho GA, Spears IR. Effects of leading on the biomechanical behavior of molars of *Homo*, *Pan*, and *Pongo*. *Am J Phys Anthropol* 1999;**109**:211—27.
11. Spears IR, Macho GA. Biomechanical behaviour of modern human molars: implications for interpreting the fossil record. *Am J Phys Anthropol* 1998;**106**:467—82.
12. Delson E. Evolutionary history of the Cercopithecidae. In: Szalay F, editor. Approaches to primate paleobiology. Contributions to primatology, vol. 5. New York: S. Kargel; 1975. p. 167—217.
13. Mizoguchi Y. Adaptive significance of the Carabelli trait. *Bull Natl Sci Museum, Ser D (Anthropol)* 1993;**19**:21—58.
14. Haeussler AM, Irish JD, Morris DH, Turner CG III. Morphological and metrical comparisons of San and central Sotho dentitions from southern Africa. *Am J Phys Anthropol* 1989;**78**:115—122.
15. Thomas BL, Sharpe PT. Patterning of the murine dentition by homeobox genes. *Eur J Oral Sci* 1998;**106**:48—54.
16. Thomas BL, Tucker AS, Ferguson C, Qiu M, Rubenstein JLR, Sharpe PT. Molecular control of odontogenic patterning: positional dependent initiation and morphogenesis. *Eur J Oral Sci* 1998;**106**:44—7.
17. Weiss KM, Stock DW, Zhao Z. Dynamic interactions and the evolutionary genetics of dental patterning. *Crit Rev Oral Biol Med* 1998;**9**:369—98.
18. Jernvall J, Kettunen P, Karavanova I, Martin LB, Thesleff I. Evidence for the role of the enamel knot as a control center in mammalian tooth cusp formation: non-dividing cells express growth stimulating *Fgf-4* gene. *Int J Dev Biol* 1994;**38**:463—9.
19. Vaahtokari A, Aberg T, Thesleff I. Apoptosis in the developing tooth: association with an embryonic signaling center and suppression by EGF and FGF-4. *Development* 1996;**122**:121—9.
20. Kettunen P, Thesleff I. Expression and function of FGFs-4, -8, and -9 suggest functional redundancy and repetitive use as epithelial signals during tooth morphogenesis. *Dev Dyn* 1998;**211**:256—68.

21. Zhao Z, Weiss KM, Stock DW. Development and evolution of dentition patterns and their genetic basis. In: Teaford MF, Smith MM, Ferguson MWJ, editors. Development, function and evolution of teeth. New York: Cambridge University Press; 2000. p. 152–72.
22. Peters H, Balling R. Teeth: where and how to make them. *Trends Genet* 1999;**15**:59–65.
23. Williams-Blangero S, Vandeberg JL, Blangero J, Konigsberg LW, Dyke B. Genetic differentiation between baboon supspecies: relevance for biomedical research. *Am J Primatol* 1990;**20**:67–81.
24. National Research Council. Guide for the care and use of laboratory animals. Washington (DC): National Academy Press; 1996.
25. Turner CG II, Nichols CR, Scott GR. Scoring procedures for key morphological traits of the permanent dentition: the Arizona State University Dental Anthropology system. In: Kelley MA, Larsen CS, editors. Advances in dental anthropology. New York: Wiley; 1991. p. 13–31.
26. Hlusko LJ. Expression types for two cercopithecoid dental traits: the interconulus and interconulid. *Int J Primatol* 2002;**23**:1309–18.
27. Hlusko LJ, Weiss KM, Mahaney MC. Statistical genetic comparison of two techniques for assessing molar crown size in pedigreed baboon. *Am J Phys Anthropol* 2002;**117**:182–9.
28. Dyke B. PEDSYS: a pedigree data management software. San Antonio (TX): Southwest Foundation for Biomedical Research; 1996.
29. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet* 1998;**62**: 1198–211.
30. Hopper JL, Mathews JD. Extensions to multivariate normal models for pedigree analysis. *Ann Hum Genet* 1982;**46**: 373–83.
31. Boehnke M, Moll PP, Kottke BA, Weidman WH. Partitioning the variability of fasting plasma glucose levels in pedigrees. Genetic and environmental factors. *Am J Epidemiol* 1987; **125**:679–89.
32. Wang XL, Mahaney MC, Sim AS, Wang J, Blangero J, Almasy L, et al. Genetic contribution of the endothelial constitutive nitric oxide synthase gene to plasma nitric oxide levels. *Arterioscler Throm Vasc Biol* 1997;**17**:2147–3153.
33. Mahaney MC, Blangero J, Comuzzie AG, VandeBerg JL, Stern MP, MacCluer JW. Plasma HDL cholesterol, triglycerides, and adiposity. A quantitative genetic test of the conjoint trait hypothesis in the San Antonio Family Heart Study. *Circulation* 1995;**92**:3240–8.
34. Edwards AWF. Likelihood. Baltimore (MD): Johns Hopkins University Press; 1992.
35. Falconer D. Introduction to quantitative genetics. New York: Longman; 1989.
36. Kessel M, Gruss P. Homeotic transformations of murine vertebrae and concomitant alteration of *Hox* codes induced by retinoic acid. *Cell* 1991;**67**:89–104.
37. Condie B, Capecchi M. Mice homozygous for a targeted disruption of *Hoxd-3* (*Hox-4.1*) exhibit anterior transformations of the first and second cervical vertebrae. *Development* 1993;**119**:579–95.
38. Gilbert SF. Developmental biology. 5th ed. Sunderland (MA): Sinauer Associates; 1997.
39. Davideau J-L, Demri P, Hotton D, Gu T-T, MacDougall M, Sharpe PT, et al. Comparative study of MSX-2, DLX-5, and DLX-7 gene expression during early human tooth development. *Pediatr Res* 1999;**46**:650–6.
40. VandeBerg JL, Williams-Blangero S. Advantage and limitations of nonhuman primates as animal models in genetic research on complex diseases. *J Med Primatol* 1997;**26**:113–9.
41. Goodman M, Porter CA, Czelusniak J, Page SL, Schneider H, Shoshani J, et al. Toward a phylogenetic classification of primates based on DNA evidence complemented by fossil evidence. *Mol Phylog Evol* 1998;**9**:585–98.
42. Kumar S, Hedges SB. A molecular timescale for vertebrate evolution. *Nature* 1998;**392**:917–20.
43. Rogers J, Mahaney MC, Witte SM, Nair S, Newman D, Wedel S, et al. A genetic linkage map of the baboon (*Papio hamadryas*) genome based on human microsatellite polymorphisms. *Genomics* 2000;**67(3)**:237–47.
44. Osborn HF. Trituberculy: a review dedicated to the late Professor Cope. *Am Nat* 1897;**XXXI**:993–1016.
45. Butler PM. The ontogeny of molar pattern. *Biol Rev* 1956;**31**:30–70.
46. Osborn JW. A model simulating tooth morphogenesis without morphogens. *J Theor Biol* 1993;**164**:409–19.
47. Osborn JW. Morphogenetic gradients: fields vs. clones. In: Butler PM, Joysey KA, editors. Development, function and evolution of teeth. New York: Academic Press; 1978. p. 171–201.
48. Thesleff I, Sharpe PT. Signalling networks regulating dental development. *Mech Dev* 1995;**67**:111–23.
49. Stock DW, Weiss KM, Zhao Z. Patterning of the mammalian dentition in development and evolution. *BioEssays* 1997;**19**:481–90.
50. Bolk L. Das Carabellische Höckerchen. *Schweizerische Vierteljahrsschrift für Zahnheilkunde* 1915;**25**:81–104.
51. Garn SM, Lewis AB, Vicinus JH. Third molar polymorphism and its significance to dental genetics. *Yrbk Phys Anthropol* 1963;**11**:257–76.
52. Garn SM, Lewis AB, Kerewsky RS. Sex interrelationships of the mesial and distal teeth. *J Dent Res* 1965;**44**:350–3.
53. Garn SM, Lewis AB, Kerewsky RS. Shape similarities throughout the dentition. *J Dent Res* 1967;**46**:1481.
54. Garn SM, Lewis AB, Kerewsky RS. Relationship between buccolingual and mesiodistal tooth diameters. *J Dent Res* 1968;**47**:495.
55. Keene HJ. The relationship between third molar agenesis and the morphologic variability of the molar teeth. *Angle Orthodontist* 1965;**35**:289–98.
56. Keene HJ. The relationship between Carabelli's trait and the size, number and morphology of the maxillary molars. *Arch Oral Biol* 1968;**13**:1023–5.
57. Davies PL. Relationship of cusp reduction in the permanent mandibular first molar to agenesis of teeth. *J Dent Res* 1968;**47**:499.
58. Potter RH, Yu P-L, Dahlberg AA, Merritt AC, Conneally PM. Genetic studies of tooth size factors in Pima Indian families. *Am J Hum Genet* 1968;**20**:89–100.
59. Scott GR. Classification, sex dimorphism, association, and population variation of the canine distal accessory ridge. *Hum Biol* 1977;**49**:453–69.
60. Scott GR. Interaction between shoveling of the maxilllary and mandibular incisors. *J Dent Res* 1977;**56**:1423.
61. Scott GR. Lingual tubercles and the maxillary incisor-canine field. *J Dent Res* 1977;**56**:1192.
62. Scott GR. The relationship between Carabelli's trait and the protostylid. *J Dent Res* 1978;**57**:570.
63. Scott GR. Association between the hypocone and Carabelli's trait of the maxillary molars. *J Dent Res* 1979;**58**:1403–4.
64. Brook AH. A unifying aetiological explanation for anomalies of human tooth number and size. *Arch Oral Biol* 1984;**29**:373–8.
65. Fleagle J, Kitahara-Frisch J. Correlation and adaptation in the dentition of Lar Gibbons. In: Preuschoft H, Chivers DJ, Brockelman WY, Creel N, editors. The lesser apes. Edinburgh: Edinburgh University Press; 1984. p. 192.
66. Harris EF, Bailit HL. A principal components analysis of human odontometrics. *Am J Phys Anthropol* 1988;**75**:87–99.