Integrating the genotype and phenotype in hominid paleontology

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Competing interpretations of human origins and evolution have recently proliferated despite the accelerated pace of fossil discovery. These controversies parallel those involving other vertebrate families and result from the difficulty of studying evolution among closely related species. Recent advances in developmental and quantitative genetics show that some conventions routinely used by hominid and other mammalian paleontologists are unwarranted. These same advances provide ways to integrate knowledge of the genotype into the study of the phenotype. The result is an approach that promises to yield a fuller understanding of evolution below the family level.

Paleontology relies on the fossil record to identify past organisms and understand many of their biological dimensions. As contemporary genetics illuminates the relationship between genotype and phenotype, the ability of fossilized anatomies to inform us about past organisms changes and expands. This is most evident in studies of large-scale organismal evolution, such as the origins of animal body plans during the Cambrian period (1–3), the evolution of limbs (4–6), and the appearance of teeth in early fishes (7). Even within more restricted groups, such as mammals, new knowledge of dental developmental genetics has elucidated evolutionary phenomenon (8–10).

However, the significant impact that modern genetics can make on paleontological investigations at lower taxonomic levels has yet to be felt. Here, I will use human evolutionary studies to illustrate how the integration of genetics and paleontology can advance understanding. Although my examples are primate-specific, the problems within the field of human paleontology are not unique, and the methods I advocate to advance hominid studies are widely applicable across other taxa.

Practical problems such as the phylogenetic proximity of taxonomic units and small and fragmentary fossil samples seriously complicate paleontological research at the subfamily level. Within hominid paleontology, these difficulties and limitations have generated three widespread, often tacit, questionable presumptions: (*i*) most anatomical traits are independent, (*ii*) most anatomical traits are adaptively informative, and (*iii*) small-scale morphological change is almost always parsimonious. Because some of the most contentious debates within hominid paleontology stem from these conventions, this discipline provides an appropriate example with which to illustrate how an integrated phenotypic–genotypic research approach promises to move us toward a better understanding of evolution below the family level.

Presumption 1: Anatomical Traits Are Independent

Virtually every anatomical feature on every primate bone and tooth has been named, often many times (Fig. 1; ref. 11, p. 76). Although atomization of anatomy and nomenclature has facilitated communication for centuries, many of these "traits" are currently used uncritically, despite the fact that this highly refined nomenclature does not necessarily translate into functionally, developmentally, or evolutionarily relevant anatomical units.

Cladistics (12) is a powerful tool for reconstructing phylogenetic relationships, but it is a tool whose power is proportional to the number of independent characters available for analysis. Cladistic analyses rely on the fundamental principle that the traits analyzed are independent (12–16). In human paleontology, this principle is routinely violated as functionally and developmentally linked traits are subdivided for analytical purposes. Sometimes this is because analysts are eager to squeeze the most out of the small available fragments of anatomy. Sometimes it is because the nomenclatural history of the traits themselves obfuscates the underlying biology. The continuing controversies involving hominid phylogenetics (e.g., ref. 16 vs. 17), with no clear pattern emerging from the repeated and varying analyses already undertaken, represent strong signals that a powerful method is being compromised by the input of data that do not meet the method's requirements. (For more specific critiques see refs. 18–20; for counter arguments, see refs. 21 and 22. Ref. 23 highlights other problems with cladistic analyses within paleoanthropology.)

There are direct but complex relationships between organismal anatomy and its genetic underpinnings. For example, >250 genes are known to be involved in the development of the dentition (http://bite-it.helsinki.fi). This is only a subset of all genes expressed in tooth development. Exactly what genes constitute the necessary or sufficient sets for generating various aspects of dental patterns remains unknown (24). As there may be only 30,000–40,000 genes in humans (25), how should we view the 468 craniodental characters used in a recent cladistic analysis of hominids (26), or the 25 dental traits used in another (27)? Are the characters developmentally and evolutionarily independent? Based on developmental genetic studies of mice, McCollum (19) and McCollum and Sharpe (28) warn that such presumptions are questionable. Quantitative genetic and correlation studies of population variation in mice (29, 30) and primates (31) demonstrate empirically that such assumptions of independence are unfounded.

Morphological integration (32), or modularity (33), 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. These sets need to be identified before their development, function, and/or evolution can be studied.

Olson and Miller (32), founders of this approach, studied morphological integration in the postcanine dentition of the South American monkey *Aotus trivirgatus*. They 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

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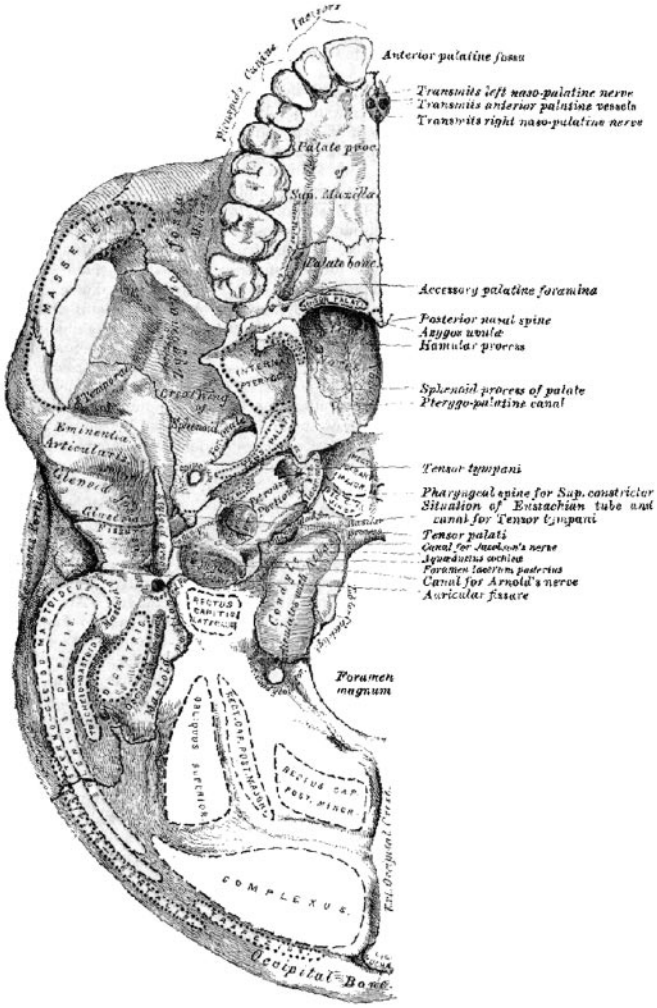

Fig. 1. Drawing of the inferior view of the human skull from a well known anatomy textbook (11) showing the nature of anatomical nomenclature.

compared with mandibular molars. Their results suggest the presence of pleiotropic effects and a complex relationship between the upper and lower jaws. More importantly, they demonstrate that evolutionary analyses of isolated tooth size measurements significantly oversimplify the evolution of the dentition.

The concept of morphological integration was revived by Cheverud (31) and has been further refined (33–35). Building from this idea, complex analyses of shape (morphometrics) are starting to be successfully incorporated into quantitative genetic analyses (36). For example, Leamy *et al.* (30) tested for the presence of morphological integration in the mouse skull and demonstrated the existence of at least two integrated sets within the cranium: the face and the neurocranium. These sets are not limited to mice but also appear to exist in New and Old World monkeys and humans (31, 37). Genetic evidence in the form of associated quantitative trait loci (QTLs) also supports this pattern of cranial morphological integration (30). Similarly, morphological integration is seen in the mandible, including a pattern of associated QTLs that correlate with phenotypic sets (38–42).

Similar effects have been identified in baboon dental variation (43–46). Quantitative genetic analyses demonstrate the presence of shared genetic effects among teeth in the same tooth row and between the maxilla and mandible. More critically, researchers have found that genetic variation in traits that appear unrelated to the dentition and craniofacial area, such as body size, contribute significantly to dental variation in baboons (43, 44). These results from baboon studies confirm and extend genetic correlations identified previously by human odontologists (47), as well as those of Olson and Miller (32).

One method exists for predicting this interdependence (developmental genetics) and another for assessing and characterizing it (quantitative genetics). A phylogenetic analysis using morphological sets instead of anatomical trait lists for characters may prove to be more conclusive (as some recent analyses are showing; refs. 48–54) than parsimony analyses of atomized characters.

Presumption 2: Most Anatomical Traits Are Adaptively Informative

This presumption is, in many ways, an extension of the first, but in the functional, rather than phylogenetic, realm. If all anatomical features were evolutionarily independent, then selection could operate on each one individually. Therefore, each trait on a fossil might be easily and individually evaluated in terms of its potential adaptive significance, and scenarios about adaptation might be developed.

An organism is an amalgamation of developmentally and functionally integrated and interrelated sets of correlated traits. Because of pleiotropy, selective pressure applied to one trait can result in phenotypic change in other traits, even when the traits are functionally independent, so long as there is not strong selection to keep the dependent trait stable.

Pleiotropic effects may figure in one of the most heated debates in hominid paleontology, which concerns the locomotor repertoire of *Australopithecus afarensis*. Virtually all paleoanthropologists agree that there was a fundamental shift toward bipedality in this taxon (55–61). However, numerous skeletal features of *A. afarensis* have been interpreted as intermediate in morphology between modern humans and modern chimpanzees (debate reviewed by Latimer, ref. 62). Were these intermediate features functionally significant, indicating that this species practiced an adaptively significant amount of arboreality (55–57)? Or did these features disadvantage climbing and indicate a lack of selection for arboreality (58–62)?

One of the pivotal traits in this argument is the length of the *A. afarensis* phalanges. As evidenced by modern arboreal hominoids, long digits can be advantageous for climbing (62), and *A. afarensis* phalanges are intermediate in length between long modern ape phalanges and derived, abbreviated modern human phalanges. Does this observation indicate that this extinct hominid climbed in the trees more than humans but less than chimpanzees (63)? Or could the shortened fingers of *A. afarensis* be a pleiotropic effect of selection for shorter toes (64)? How might we decide?

Developmental genetics shows that the fore- and hindlimbs of quadrupeds share the same basic patterning mechanism (4–6) and suggests that evolution in one set of limbs, or even digits, can result in concomitant evolution in the other. The classic example of this is the panda's "thumb," a highly derived radial sesamoid (65, 66). Here, the hindlimb anatomical homologue, the tibial sesamoid, is also elongated and enlarged, with no apparent adaptive significance. There are, of course, cases of fore- and hindlimb evolutionary independence, e.g., *Tyrannosaurus rex*, moles, tarsiers, and thumbless colobines.

The mechanisms underlying population-level variation have been shown to be directly relevant to diversity at higher taxonomic levels and are therefore useful for addressing evolutionary questions (5, 8, 67–69). If hand phalangeal length is strongly and genetically correlated with pedal phalangeal length among early hominids, then strong selection for shorter toes could have reduced the mean hand phalangeal length.

Genetic covariance between traits is critical for understanding many other aspects of human evolution. For example, ever since Darwin (70), sexual dimorphism has been looked at adaptively, but new empirical data show that it is not so simple (71–75). The mosaic pattern of sexual dimorphism makes these analyses even more complex, because canine dimorphism and body size dimorphism are clearly dissociated in primate evolution. Analyses of genetic covariance and QTL effects may represent a way to clarify these complex relationships (e.g., ref. 76).

Paleontological research that includes genetics in the neontological component will be able to extract more information from fossilized skeletal morphology than classical approaches alone (e.g., refs. 77–81). Until we answer the question of how morphological variation arises, specific evolutionary scenarios of adaptation will be stimulating, but most will remain premature.

Presumption 3: Small-Scale Morphological Change Is Almost Always Parsimonious

This presumption is related to the idea that traits are difficult to change or evolve. The evolvability of a character has been defined as "the ability or potential to respond to selective challenges" (ref. 82, p. 23; also, see refs. 80 and 81). Although this definition is fairly straightforward, the quantification of it is not (82). The evolvability of a trait is determined by its level of additive genetic variation and pleiotropic affects. One of the goals of paleontology is to understand the factors that contribute to morphological trends, identifying selective pressures and/or developmental constraints (83). Determining a trait's evolvability is consequently important. Mathur and Polly (84) compared amelogenin protein sequence variation and enamel complexity across a diverse group of vertebrates. They found a negative correlation, suggesting that selective constraints on enamel proteins increase as enamel structural complexity increases. However, are similar trends seen across lower-level taxonomic groupings? A recent study by Macho *et al.* (85) that models three-dimensional microstructure of enamel across hominoid taxa suggests not.

Enamel has played a critical role in interpretations of hominid evolution, although the majority of studies have focused on enamel thickness rather than structure. Some hominid taxa have absolutely and relatively thicker molar enamel than others (86, 87). Over the last 20 years, especially with the advent of cladistics, this continuously varying trait has often been categorized discretely (16, 88). Early hominids with "thick" enamel are often identified as direct human ancestors, whereas early hominids with "thin" enamel are interpreted as more closely related to the thin-enameled extant African apes (89). For some paleoanthropologists, enamel thickness has almost become as critical a character as bipedalism (89, 90). Functionally, enamel thickness does appear to correlate with diet across primate taxa (91), but does it have the phylogenetic valence at the subfamily level often attributed to it?

To investigate this question and others related to primate dental evolution, my collaborators and I have undertaken a quantitative genetic analysis of dental variation in a colony of captive, pedigreed baboons housed at the Southwest Foundation for Biomedical Research (SFBR) (43–46). We have found the coefficient of variation for enamel thickness to be equal to or larger than that of most other metric traits in this baboon population, as well as in other primate species. A significant proportion of this phenotypic variance in molar enamel thickness results from the additive effects of genes, with h^2 estimated as 0.32–0.44 (46). Understanding additive genetic effects on phenotypes is critical to evolutionary studies, as well as to animal and plant breeders, because these effects reflect how strongly the trait will respond to both natural and artificial selection (92–94). Additionally, we found that neither tooth size nor sex were significant covariates of enamel thickness, indicating that the genetic influences on enamel thickness variation are independent of those that determine tooth size and/or sex of the individual. This apparent genetic independence reduces the concern that pleiotropic effects are confounding the development of enamel thickness, and the trait should be readily responsive to selection.

For hominid paleontologists studying recently recovered Mio-Pliocene dental remains (89, 95, 96, 98), an important consideration involves the rate at which enamel thickness could respond to selection. Using a basic model (99), we estimated that the population mean for baboon molar enamel thickness could double in ≈250,000 years, or 50,000 generations, with a culling of fewer than 4 in 10,000 individuals per generation. Although this model is overly simplistic, it does demonstrate that enamel thickness could rapidly track dietary shifts through evolutionary time and that the potential for parallel evolution in this trait is high (i.e., enamel thickness is prone to homoplasy). Our quantitative genetic study of enamel thickness shows that this character is probably inappropriately weighted in many early hominid phylogenetic reconstructions. A developmental study of fossilized enamel growth suggests the same (100, 101).

Enamel thickness is not the only trait for which analytical caution is needed. Most phenotypes that have been studied are responsive to selection (102), and selection pressures lower than those estimated from the fossil record can move phenotypic means significantly in the laboratory (102–105). Although heritability estimates may not be the best way to measure evolvability (82), evidence of high evolvability at the species level can be found in other types of genetic analyses. For example, species comparisons of butterflies have shown that eyespot patterns on wings can rapidly evolve, needing only a small number of changes in regulatory genes (106). All of this clearly makes the paleontologist's task of identifying the most phylogenetically informative traits difficult and complex. Genetic analyses provide the tools with which the most informative traits can be revealed and pleiotropic affects can be identified.

An Integrative Approach

The ultimate goal of the integrative approach advocated here for subfamily-level paleontology is the understanding of anatomical and behavioral evolution from a combined genotypic and phenotypic perspective. To illustrate how this integration might proceed for one character, I will elaborate on our study of baboon enamel thickness. As described above, the first steps have been taken

toward a synthesis of quantitative and developmental genetic analyses. More steps remain. We hope to identify specific genes and gene products involved in determining enamel thickness and to then integrate this genetic and developmental information with the pattern of enamel thickness seen among extant and fossil primates.

A genetic linkage map based on highly polymorphic human microsatellite loci has been constructed for the SFBR baboon population (107), so it will be possible to search for marker loci that cosegregate through the pedigree with particular phenotypic variants (QTL analyses; see reviews in refs. 108 and 109). The genetic mechanisms controlling enamel thickness are unknown, and data from the medical literature is inconclusive. Proteins from at least six different genes are involved in enamel formation, including amelogenin, enamelin, and ameloblastin, which are found on both autosomal and sex chromosomes (110). Disruptions in these genes result in enamel mineralization pathologies such as *amelogenesis imperfecta* (AI) (110). Abnormalities in actual enamel thickness are associated with variations in the number of sex chromosomes (111–115). However, many versions of AI show inheritance patterns consistent with the localization of major loci on autosomes (116–120) and nonpathological primate enamel thickness variation is not sexually dimorphic (44, 115, 121). A developmental gene expression study reported by Lezot *et al.* (122) found that *Dlx2* (a member of the *distalless* homeobox gene family) expression in the later stages of incisor development in mice is inversely related to enamel thickness. Therefore, enamel thickness may be determined in part by homeobox genes that control earlier morphogenesis. Through our genetic linkage analysis, we can test the hypothesis that microsatellites close to one or more of these candidate genes (amelogenin, *Dlx2*, etc.) will cosegregate through the baboon pedigrees with particular enamel thickness variants.

When using this type of hypothesis testing, quantitative genetic approaches and gene expression studies can be highly complementary. Other examples of population-based approaches and comparative cross-taxon gene expression studies are proving to be successful in the search for the genetic mechanisms underlying other types of phenotypic evolution (5, 8, 9, 123, 124). For example, when Jernvall and colleagues (9, 124) studied gene expression patterns in mouse and vole molar development, they found four genes that have spatial expression patterns that correlate with the morphological differences between these two rodents. Through a different approach, Line (123) was able to estimate the relative influence of PAX9 and MSX1 on the development of dental fields through a study of a human genetic dental pathology.

The next step in this approach is the confrontation of the fossil data with these new genetic insights. There is a rich fossil record of baboon evolution over the last several million years in Africa that enables us to track the evolution of myriads of dental characters, including enamel thickness, through time. Using the fossil record, we can determine whether morphologically integrated sets evolved in concert and when and in what order these sets of traits evolved. Once the genotypic and phenotypic dimensions of these traits have become clear, larger-scale evolutionary questions can be addressed, including possible changes in selective pressures, such as ecological or dietary shifts.

The study of baboon enamel thickness has broad application across mammals. Many developmental processes of bone and enamel development are highly conserved (48, 125–127). It has also been shown that genes underlying intraspecific variation can determine interspecific variation (68). Therefore, the genetic mechanisms underlying enamel thickness in baboons are likely to be homologous with the mechanisms underlying variation in enamel thickness in humans and other mammals.

The Future

The standard response to controversy in paleontology is that more fossils will resolve the issue. Indeed, the paleontological record below the family level is too often inadequate, and more fossils are clearly needed. However, it is already evident that, even for species with adequate fossil records, new and different approaches like those suggested here will be necessary.

Developmental genetics offers insights into the manner in which DNA segments interact among themselves and with the environment to create organisms that vary along and between species lineages. Quantitative genetics enable us to decipher genetic mechanisms from the minor phenotypic variation seen in living populations. These two approaches are proving productively complementary to each other (128, 129) and can be integrated with the expanding fossil record. Fossils provide the necessary temporal dimension to the study of evolutionary developmental biology (4, 8, 48, 97). The integration of fossils and genetics has already successfully yielded broad insights at higher taxonomic levels. Applying such integration at and below the family level promises to accelerate and extend our understanding of evolution.

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1. Raff, R. A. (1996) *Shape of Life* (Univ. of Chicago Press, Chicago).
2. Knoll, A. H. & Carroll, S. B. (1999) *Science* **284,** 2129–2137.
3. Carroll, S. B. (2001) *Nature* **409,** 1102–1109.
4. Shubin, N., Tabin, C. & Carroll, S. (1997) *Nature* **388,** 639–648.
5. Shubin, N. (2002) *J. Morphol.* **252,** 15–28.
6. Tickle, C. (2002) *J. Morphol.* **252,** 29–37.
7. Smith, M. M. (2003) *Evol. Dev.* **5,** 394–413.
8. Jernvall, J. (2000) *Proc. Natl. Acad. Sci. USA* **97,** 2641–2645.
9. Jernvall, J., Keränen, S. V. E. & Thesleff, I. (2000) *Proc. Natl. Acad. Sci. USA* **97,** 14444–14448.
10. Salazar-Ciudad, I. & Jernvall, J. (2002) *Proc. Natl. Acad. Sci. USA* **99,** 8116–8120.
11. Gray, H. (1901) *Gray's Anatomy* (reprinted 1995) (Barnes & Noble Books, New York), 15th Ed.
12. Hennig, W. (1996) *Phylogenetic Systematics*, trans. by Davis, D. D. & Zangerl, R. (Univ. of Illinois Press, Urbana).
13. Mishler, B. D. (1994) *Am. J. Phys. Anthropol.* **94,** 143–156.
14. Skelton, R. R. & McHenry, H. M. (1992) *J. Hum. Evol.* **23,** 309–349.
15. Skelton, R. R. & McHenry, H. M. (1998) *J. Hum. Evol.* **34,** 109–113.
16. Strait, D. S., Grine, F. E. & Moniz, M. A. (1997) *J. Hum. Evol.* **32,** 17–82.
17. Leiberman, D. E., Pilbeam, D. R. & Wood, B. A. (1996) *J. Hum. Evol.* **30,** 97–120.
18. Asfaw, B., White, T., Lovejoy, O., Latimer, B., Simpson, S. & Suwa, G. (1999) *Science* **284,** 629–635.
19. McCollum, M. A. (1999) *Science* **284,** 30–35.
20. Asfaw, B., Gilbert, W. H., Beyene, Y., Hart, W. K., Renne, P. R., WoldeGabriel, G., Vrba, E. S. & White, T. D. (2002) *Nature* **416,** 317–320.
21. Strait, D. S. & Grine, F. E. (1999) *Science* **285,** 1209 (lett).
22. Manzi, G., Bruner, E. & Passarello, P. (2003) *J. Hum. Evol.* **44,** 731–736.
23. Curnoe, D. (2003) *Homo.* **53,** 225–234.
24. Peters, H. & Balling, R. (1999) *Trends Genet.* **15,** 59–65.
25. Venter, J. C., Adams, M. D., Myers, E. W., Li, P. W., Mural, R. J., Sutton, G. G., Smith, H. O., Yandell, M., Evans, C. A., Holt, R. A., *et al.* (2001) *Science* **291,** 1304–1351.
26. Zeitoun, V. (2000) *Bull. Mem. Soc. Anthropol., Paris Nouvelle Ser.* **12,** 1–200.
27. Stringer, C. B., Humphrey, L. T. & Compton, T. (1997) *J. Hum. Evol.* **32,** 389–402.
28. McCollum, M. A. & Sharpe, P. T. (2001) *BioEssays* **23,** 481–493.
29. Atchley, W. R., Rutledge, J. J. & Cowley, D. E. (1981) *Evolution (Lawrence, Kans.)* **35,** 1037–1055.

30. Leamy, L. J., Routman, E. J. & Cheverud, J. M. (1999) *Am. Nat.* **153,** 202–214.
31. Cheverud, J. M. (1982) *Evolution (Lawrence, Kans.)* **36,** 499–516.
32. Olson, E. & Miller, R. (1958) *Morphological Integration* (Univ. of Chicago Press, Chicago).
33. VonDassow, G. & Munro, E. (1999) *J. Exp. Zool.* **285,** 307–325.
34. Magwene, P. M. (2001) *Evolution (Lawrence, Kans.)* **55,** 1734–1745.
35. Stock, D. W. (2001) *Philos. Trans. R. Soc. London B* **356,** 1633–1653.
36. Klingenberg, C. P. (2002) *Gene* **287,** 3–10.
37. Cheverud, J. M. (1996) *Am. Zool.* **36,** 44–50.
38. Cheverud, J. M., Routman, E. J. & Irschick, D. J. (1997) *Evolution (Lawrence, Kans.)* **51,** 2006–2016.
39. Cheverud, J. M. (2001) in *The Character Concept in Evolutionary Biology*, ed. Wagner, G. P. (Academic, San Diego), pp. 411–433.
40. Klingenberg, C. P. & Leamy, L. J. (2001) *Evolution (Lawrence, Kans.)* **55,** 2342–2353.
41. Klingenberg, C. P., Leamy, L. J., Routman, E. J. & Cheverud, J. M. (2001) *Genetics* **157,** 785–802.
42. Workman, M. S., Leamy, L. J., Routman, E. J. & Cheverud, J. M. (2002) *Genetics* **160,** 1573–1586.
43. Hlusko, L. J. (2000) Ph.D. thesis (Pennsylvania State University, University Park).
44. Hlusko, L. J., Weiss, K. M. & Mahaney, M. C. (2002) *Am. J. Phys. Anthropol.* **117,** 182–189.
45. Hlusko, L. J. & Mahaney, M. C. (2003) *Arch. Oral Biol.* **48,** 663–672.
46. Hlusko, L. J., Suwa, G., Kono, R. & Mahaney, M. C. (2003) *Am. J. Phys. Anthropol.*, in press.
47. Scott, G. R. & Turner, C. G., II (1997) *The Anthropology of Modern Human Teeth* (Cambridge Univ. Press, New York).
48. Lovejoy, C. O., Cohn, M. J. & White, T. D. (1999) *Proc. Natl. Acad. Sci. USA* **96,** 13247–13252.
49. Ackermann, R. R. & Cheverud, J. M. (2000) *Am. J. Phys. Anthropol.* **111,** 489–501.
50. Marroig, G. & Cheverud, J. M. (2001) *Int. J. Org. Evol.* **55,** 2576–2600.
51. Strait, D. S. (2001) *Am. J. Phys. Anthropol.* **114,** 273–297.
52. Ackermann, R. R. (2002) *J. Hum. Evol.* **42,** 167–187.
53. Lieberman, D. E., McBratney, B. M. & Krovitz, G. (2002) *Proc. Natl. Acad. Sci. USA* **99,** 1134–1139.
54. Athreya, S. & Glantz, M. M. (2003) *Am. J. Phys. Anthropol.* **122,** 134–146.
55. Jungers, W. L. & Stern, J. T. (1983) *J. Hum. Evol.* **12,** 673–684.
56. Stern, J. T. & Susman, R. L. (1983) *Am. J. Phys. Anthropol.* **60,** 279–317.
57. Susman, R. L., Stern, J. T. & Jungers, W. L. (1984) *Folia Primatol.* **43,** 113–156.
58. Latimer, B., Ohman, J. C. & Lovejoy, C. O. (1987) *Am. J. Phys. Anthropol.* **74,** 155–175.
59. Latimer, B. & Lovejoy, C. O. (1989) *Am. J. Phys. Anthropol.* **78,** 369–386.
60. Latimer, B. & Lovejoy, C. O. (1990) *Am. J. Phys. Anthropol.* **83,** 13–23.
61. Lovejoy, C. O., Meindl, R. S., Ohman, J. C., Heiple, K. G. & White, T. D. (2002) *Am. J. Phys. Anthropol.* **119,** 97–133.
62. Latimer, B. (1991) in *Origine(s) de la Bipédie Chez Les Hominidés*, Editions du CNRS, eds. Senut, B. & Coppens, Y. (Cahiers de Paléoanthropologie, Paris), pp. 169–176.
63. Pilbeam, D. (1986) *Am. Anthropol.* **88,** 295–312.
64. White, T. D. & Suwa, G. (1987) *Am. J. Phys. Anthropol.* **72,** 485–514.
65. Davis, D. D. (1966) *Folia Biotheoretica* **6,** 5–8.
66. Gould, S. J. (1980) *The Panda's Thumb* (Norton, New York).
67. Stern, D. L. (2000) *Evolution (Lawrence, Kans.)* **54,** 1079–1091.
68. Gompel, N. & Carroll, S. B. (2003) *Nature* **424,** 931–935.
69. Kopp, A., Graze, R. M., Shizhong, X., Carroll, S. B. & Nuzhdin, S. V. (2003) *Genetics* **163,** 771–787.
70. Darwin, C. (1871) *The Descent of Man, and Selection in Relation to Sex* (D. Appleton & Co., New York).
71. Reno, P. L., Meindl, R. S., McCollum, M. A. & Lovejoy, C. O. (2003) *Proc. Natl. Acad. Sci. USA* **100,** 9404–9409.
72. Cheverud, J. M. & Dow, M. M. (1985) *Evolution (Lawrence, Kans.)* **39,** 1335–1351.
73. Leigh, S. R. & Shea, B. T. (1995) *Am. J. Primatol.* **36,** 37–60.
74. Moore, S. L. & Wilson, K. (2002) *Science* **297,** 2015–2018.
75. Lande, R. (1980) *Evolution (Lawrence, Kans.)* **34,** 292–305.
76. Vaughn, T. T., Pletscher, L. S., Peripato, L. S., King-Ellison, K., Adams, E., Erikso, C. & Cheverud, J. M. (1999) *Genet. Res.* **74,** 313–322.
77. Tague, R. G. (1995) *Am. J. Phys. Anthropol.* **97,** 213–233.
78. Reno, P. L., McCollum, M. A., Lovejoy, C. O. & Meindl, R. S. (2000) *J. Morphol.* **246,** 59–67.
79. Leigh, S. R. (2003) in *Homoplasy in Human and Primate Evolution*, eds. Lockwood, C. & Fleagle, J. (in press).
80. Collard, M. & O'Higgins, P. (2001) *Evol. Dev.* **3,** 322–331.
81. Hamrick, M. W. (2001) *J. Hum. Evol.* **40,** 339–351.
82. Hansen, T. F., Armbruster, W. S., Carlson, M. L. & Pélabon, C. (2003) *J. Exp. Zool. B Mol. Dev. Evol.* **296B,** 23–39.
83. Maynard Smith, J., Burian, R., Kauffman, S., Alberch, P., Campbell, J., Goodwin, B., Lande, R., Raup, D. & Wolpert, L. (1985) *Q. Rev. Biol.* **60,** 265–287.
84. Mathur, A. K. & Polly, P. D. (2000) *J. Mamm. Evol.* **7,** 23–42.
85. Macho, G. A., Jiang, Y. & Spears, I. R. (2003) *J. Hum. Evol.* **45,** 81–90.
86. Martin, L. (1985) *Nature* **314,** 260–263.
87. Shellis, R. P., Beynon, A. D., Reid, D. J. & Hiiemae, K. M. (1998) *J. Hum. Evol.* **35,** 507–522.
88. Andrews, P. (1995) *Nature* **376,** 555–556.
89. Senut, B., Pickford, M., Gommery, D., Mein, P., Cheboi, K. & Coppens, Y. (2001) *C. R. Acad. Sci. Ser. IIa* **332,** 137–144.
90. Aiello, L. C. & Collar, M. (2001) *Nature* **410,** 526–527.
91. Dumont, E. R. (1995) *J. Mammal.* **76,** 1127–1136.
92. Falconer, D. S. (1989) *Introduction to Quantitative Genetics* (Longman, Harlow, U.K.), 3rd Ed.
93. Lynch, M. & Walsh, B. (1998) *Genetics and Analysis of Quantitative Traits* (Sinauer, Sunderland, MA).
94. Hartl, D. L. & Jones, E. W. (2001) *Genetics* (Jones & Bartlett, Boston), 5th Ed.
95. Brunet, M., Guy, F., Pilbeam, D., Mackaye, H. T., Likius, A., Ahounta, D., Beauvilain, A., Blondel, C., Bocherens, H., Boisserie, J. R., *et al.* (2002) *Nature* **418,** 145–151.
96. Haile-Selassie, Y. (2001) *Nature* **412,** 178–181.
97. Cohn, M. J. (2001) *Novartis Found. Symp.* **232,** 47–57.
98. White, T. D., Suwa, G. & Asfaw, B. (1994) *Nature* **371,** 306–312.
99. Lande, R. (1976) *Evolution (Lawrence, Kans.)* **30,** 314–334.
100. Dean, M. C., Leakey, M. G., Reid, D., Schrenk, F., Schwartz, G. T., Stringer, C. & Walker, A. (2001) *Nature* **414,** 628–631.
101. Moggi-Cecchi, J. (2001) *Nature* **414,** 595–597.
102. Barton, N. J. & Turelli, M. (1989) *Annu. Rev. Genet.* **23,** 337–370.
103. Haldane, J. B. S. (1949) *Evolution (Lawrence, Kans.)* **3,** 51–56.
104. Kurtén, B. (1959) *Cold Spring Harbor Symp. Quant. Biol.* **24**, 205–215.
105. Gingerich, P. D. (1983) *Science* **222,** 159–161.
106. Brakefield, P. M., Gates, J., Keys, D., Kesbeke, F., Wijngaarden, P. J., Monteiro, A., French, V. & Carroll, S. B. (1996) *Nature* **384,** 236–242.
107. Rogers, J., Mahaney, M. C., Witte, S. M., Nair, S., Newman, D., Wedel, S., Rodriguez, L. A., Rice, K. S., Slifer, S. H., Perelygin, A., *et al.* (2000) *Genomics* **67,** 237–247.
108. Rogers, J., Mahaney, M. C., Almasy, L., Comuzzie, A. G. & Blangero, J. (1999) *Yearbook Phys. Anthropol.* **42,** 127–151.
109. Mackay, T. F. C. (2001) *Annu. Rev. Genet.* **35,** 303–339.
110. Robinson, C., Brookes, S. J., Shore, R. C. & Kirkham, J. (1998) *Eur. J. Oral Sci.* **106,** Suppl. 1, 282–291.
111. Alvesalo, L., Tammisalo, E. & Hakola, P. (1985) *Ann. Hum. Biol.* **12,** 421–427.
112. Alvesalo, L., Tammisalo, E. & Therman, E. (1987) *Hum. Genet.* **77,** 345–348.
113. Alvesalo, L., Tammisalo, E. & Townsend, G. (1991) *J. Dent. Res.* **70,** 1057–1060.
114. Townsend, G., Jensen, B. L. & Alvesalo, L. (1984) *Am. J. Phys. Anthropol.* **65,** 367–371.
115. Alvesalo, L. & Tammisalo, E. (1981) *Am. J. Hum. Genet.* **33,** 464–469.
116. Bell, E., Townsend, G., Wilson, D., Kieser, J. & Hughes, T. (2001) *Am. J. Hum. Biol.* **13,** 690–698.
117. Wright, J. T., Johnson, L. B. & Fine, J.-D. (1993) *Arch. Oral Biol.* **38,** 945–955.
118. Wright, J. T., Kiefer, C. L., Hall, K. I. & Grubb, B. R. (1996) *J. Dent. Res.* **75,** 966–973.
119. Hart, T. C., Bowden, D. W., Bolyard, J., Kula, K., Hall, K. & Wright, J. T. (1997) *Hum. Mol. Genet.* **6,** 2279–2284.
120. Clark, F. H. & Clark, C. S. (1933) *J. Heredity* **24,** 425–429.
121. Harris, E. F., Hicks, J. D. & Barcroft, B. D. (2001) *Am. J. Phys. Anthropol.* **115,** 223–237.
122. Lezot, F., Thomas, B., Hotton, D., Forest, N., Orestes-Cardoso, S., Robert, B., Sharpe, P. & Berdal, A. (2000) *J. Bone Miner. Res.* **15,** 430–441.
123. Line, S. R. (2001) *J. Theor. Biol.* **211,** 67–75.
124. Keränen, S. V. E., Åberg, T., Kettunen, P., Thesleff, I. & Jernvall, J. (1998) *Dev. Genes Evol.* **208,** 477–486.
125. Geddes, A. D. (1996) in *Principles of Bone Biology*, eds. Bilezikian, J. P., Raisz, L. G. & Rodan, G. A. (Academic, San Diego), pp. 1343–1354.
126. Zhao, Z., Weiss, K. M. & Stock, D. W. (2000) in *Development, Function and Evolution of Teeth*, eds. Teaford, M. F., Smith, M. M. & Ferguson, M. W. J. (Cambridge Univ. Press, New York), pp. 152–172.
127. Teaford, M. F., Smith, M. M. & Ferguson, M. W. J., eds. (2000) in *Development, Function and Evolution of Teeth* (Cambridge Univ. Press, New York).
128. Palsson, A. & Gibson, G. (2000) *Dev. Genes Evol.* **210,** 617–622.
129. Zimmerman, E., Palsson, A. & Gibson, G. (2000) *Genetics* **155,** 671–683.