

Reply to “Humans as second orangutans: sense or nonsense?”

DOI 10.1002/bies.200900012

We reply to Stoneking's⁽¹⁾ criticisms of our article⁽²⁾ *via* science.

1. “The authors...carried out phylogenetic analyses of selected morphological and fossil characters.”

This is a common misunderstanding. For our analyses of extant taxa we reviewed all features in any publication proposing a human-ape relationship (finding that studies supporting a human-chimp relationship repeated the same features) and also included features we uncovered in the literature and through our own investigations. We sought to verify each feature and its presence in stated taxa, contacting (extant) authors for explication. We truncated published lists significantly when features were not verifiable and out-group comparison slim. For systematic rigor, we included only verified features in taxonomically broad outgroups. Following cladistic procedure, through broad outgroup comparison, we distinguished primitive from derived states; the latter informed hypotheses of hierarchically nested clades. Stoneking misrepresents this as “selecting” features. Widely used phylogenetic software repeatedly generated highly correlated relationships of and between human-orangutan and chimpanzee-gorilla sister groups. Although fossils limited comparison to preserved morphology, computer-generated cladistic analyses demonstrated significant correlation of a hominid (= humans + fossil relatives)-orangutan-clade sister group.

2. “I...note that previous analyses of fossil characters have followed the genetic evidence in grouping humans with chimpanzees.”

This neither validates “genetic evidence” or any claim of phylogenetic relatedness, nor tests any molecularly or morphologically based hypothesis. Morphology is interpreted in the context of a presumed human-chimpanzee relationship, thereby undermining any claim of phylogenetic reliability. Yet theories of relationship between fossil taxa, which also inform “molecular clocks,” are only possible through morphological comparison.

3. “How do the authors reconcile this...with molecular genetic evidence, going back 40 years...that unequivocally indicate that African apes (specifically, chimpanzees) are our nearest living relatives?”

Although often conflated, “evidence/data” and “interpretation” are different. Thus, while Zuckerkandl and Pauling⁽³⁾ demonstrated decreasing similarity in hemoglobin between human, gorilla, horse, chicken, and fish, they acknowledged inference of phylogenetic propinquity upon *assuming* that if lineages continually change, more recently divergent taxa should be more similar molecularly than distantly divergent taxa as a function of the amount of change accumulated since

time of divergence. They then sought corroboration of their “molecular assumption” (MA)⁽⁴⁾ from the accepted, morphologically based theory of decreasing relatedness among these taxa. Thereafter, the MA (also⁽⁵⁾) morphed into fact. Yet, if the assumption is incorrect, 40 years of embracing it is irrelevant.

We do not deny demonstration of molecular similarity, but question its phylogenetic significance, since comparison of overall similarity is phenetic, not cladistic (*e.g.*^(6,7)). Systematists know well that shared similarity often reflects primitive retention, not phylogenetic propinquity (*e.g.*^(8,9–11)). Ironically, vis-à-vis the philosophy of science, since Zuckerkandl and Pauling sought support of their MA in a morphologically based theory of relatedness, morphology should falsify a molecular alternative. If the validity of scientific theories derives from potential falsification (*e.g.*^(12,13–16)), the application of the MA to different molecules or protein or DNA sequences cannot validate it because internal consistency resists falsification.

The elevation of a hypothetical human-chimpanzee relationship to fact led to data interpreted in its context being taken as evidence of corroboration. For instance, while Yunis and Prakash⁽¹⁷⁾ stated clearly that their interpretation of chromosome banding patterns was based on first accepting an assumed (((human-chimpanzee)-gorilla)-orangutan))-Old World monkey))) relationship, they are cited as demonstrating this relationship (*e.g.*⁽¹⁸⁾). The Chimpanzee Consortium's⁽¹⁹⁾ human-chimpanzee genome comparison and Patterson et al.'s⁽²⁰⁾ speculation on human-chimpanzee hybridization continue the practice of interpreting data both in the context of a relationship and as verification of it. This is not hypothesis testing.

Not widely appreciated is the confinement of DNA sequence analyses primarily to the region coding for metabolically active proteins, enzymes, etc (reflecting adaptation, not organismal change),⁽⁴⁾ which constitutes only c. 2–3% of the metazoan genome;⁽²¹⁾ since mtDNA is metabolically functional it can be treated similarly.⁽⁴⁾ Thus, while assertions such as demonstrating c. 99% similarity between humans and chimpanzees in a ~90 kb stretch of coding DNA⁽²²⁾ are generalized to “humans and chimpanzees are c. 99% similar in their DNA”,⁽²²⁾ this extrapolation derives from a minimal fraction of the genome.⁽⁴⁾ Similarly, although The Chimpanzee Consortium⁽¹⁹⁾ claimed c. 98% identity between human and chimpanzee genomes, they were less focused on “gene expression patterns and promoter regions,” than “on protein-coding sequences” (p. 83). Nevertheless, studies of gene expression in organs (*e.g.*⁽²³⁾) only characterize activity in the adult – the typical focus of molecular “systematists” – not pathways underlying organ development.

It is therefore crucially significant that ca. 97–98% of the metazoan genome is noncoding, largely comprising promoter/control regions and developmentally regulated genes as well as introns (which may have regulatory function at least early in development). Although one can identify start-stop

sequences, linearity of DNA bases does not, as in the coding region, constitute a gene. Rather, since in a noncoding region “gene” introns separate exons, it is only through RNA-mediated intron splicing and transcription (sense, antisense, or some combination thereof) that a “gene” and its “product” are specified.⁽²⁴⁾ Furthermore, local three-dimensional DNA topographies determine functional noncoding elements.⁽²⁵⁾ Thus, even if noncoding region DNA sequences were verifiable as in coding regions (a difficulty because of lack of colinearity with specific proteins), noncoding DNA sequence alone without consideration of three-dimensional topography and alternative splicing is meaningless.

What cannot be ignored is the role of the metazoan noncoding region in development of structure, which is highly constrained (*e.g.*^(26,27–31)), especially with regard to homeobox genes and meristic structures. If molecular change was real and random, it should mostly impact the vast non-coding region, causing failure of developmental processes, organismal death, and/or wanton emergence of novel features.⁽⁴⁾ Yet, as Darwin recognized,⁽³²⁾ like tends to beget like.

Underlying this consistency are classes of “housekeeping” molecules, particularly heat shock proteins, which function to prevent molecular change (review⁽³³⁾). The non-coding region, regulation of development, and the interrelation of DNA, RNA, and transcription factors, can thus be appreciated as a hierarchy of instructional information from gene regulatory networks (GRNs) underlying basic body plans to differentiation gene batteries (DGBs) involved in the terminal differentiation of tissues and structures.⁽³⁴⁾ Thus, instead of a fictional chasm between the “molecular” and “morphological” (begging the question, “If true, from whence does structure arise?”), there is a continuum from molecular interaction to the emergence of structure. Consequently, comparative study of such continua (including signaling pathways and the recruitment of regulatory molecules), not sequence similarity, should inform the reconstruction of phylogenetic relationships.^(35,36)

The existence of a molecular-development-structure continuum underscores the relevance of morphology in phylogenetic analysis especially because, until GRNs and DGBs are understood in detail, morphology is their proximate realization. Witness experiments on bird beaks. Altered expression of regulatory molecules led to change in not only beak size, but also in all attendant structures (soft and hard tissue, including vascularization and innervation) simultaneously.^(37–40) Hence, we consider features, largely associated with knuckle walking, that, for most of the 20th century, were embraced as synapomorphic of chimpanzees and gorillas (*e.g.*^(41,42,43)) as compelling evidence of their relatedness, as we also do derived features shared uniquely by humans and orangutans.^(2,44–46)

4. “The authors...claim that homoplasy...and alignment problems...render phylogenetic analyses of DNA sequence data inaccurate. But no specific examples are given...”

Homoplasy cannot be demonstrated; it is hypothesized when one of two or more competing theories of relatedness becomes preferred, which by default “makes” the shared features supporting alternatives “non-phylogenetic”, *e.g.* homoplastic (*e.g.*⁽⁴⁷⁾). Accepting chimpanzee-gorilla and human-orangutan theories of relatedness renders molecular similarities, if not primitive retentions, homoplastic. But since the MA presumes that change is cumulative, homoplasy is conveniently ruled out. As for alignment, see Marks⁽⁴⁸⁾ and The Chimpanzee Consortium⁽¹⁹⁾ regarding assumptions of deletion, addition, or both, and sequence-length difference.

5. “The authors criticize molecular genetic analyses of human-chimpanzee relationships for having “extremely limited” outgroup sampling...[but] the studies cited...would be regarded by most as...more than adequate.”

Perhaps by molecular anthropologists, but not most systematists (*e.g.*^(9,16)).

6. “The authors cannot point to any molecular genetic study which has suggested anything other than a human-African ape relationship, regardless of which species were included as outgroups.”

Molecular analyses assume that the taxon in which they are rooted is entirely primitive, so using orangutan, gibbon, or monkey is irrelevant. And it is in the context of this assumption that humans, chimpanzees, and gorillas are sorted on the basis of overall similarity. Nevertheless, interpretation of retroviral sequences yielded various relationships.⁽⁴⁹⁾ In a few instances,^(18,50,51) when the “correct” phylogeny of primates was not achieved, the molecules/genes concerned were discarded as unreliable. How many “incorrect” phylogenies have not been published?

7. “One can frame [the] question as a four-taxon problem, without any outgroup.”

This is phenetic distance analysis, not phylogenetic reconstruction, and not informative.

8. “The failure of most recent molecular genetic studies to address a human-orangutan alternative to the accepted human-chimpanzee relationship indicates that this question is considered fully answered and hence not worthy of further attention.”

Certitude in evolutionary science is unsustainable.^(14,52)

9. “Even more egregious...is the...failure of the authors to realize...short interspersed elements (SINEs)...which are expected to behave as perfect phylogenetic characters.”

Nikaido et al.⁽⁵³⁾ first used SINEs (and LINEs) in phylogenetic reconstruction. From (using) a small sample of (cet)artiodactyls they focused on hippopotami, which they united with cetaceans on assumptions that Stoneking reiterates: “independent insertion events would occur between exactly the same two base pairs”; “parallel changes involving SINEs should be extremely rare”; “deletions of inserted elements hardly ever occur”; and “reversals involving SINEs should also be extremely rare.” Yet, since retroviruses

mirror the “stochastic” insertion behavior of SINEs and are subject to deletion and homoplasy⁽⁴⁹⁾ one wonders why SINEs are exempt from these common phenomena.

Driving Nikaido *et al.*'s analysis was phenetic similarity only between camel, pig, peccary, chevrotain, deer, giraffe, sheep, cow, hippo, humpback, and beaked, with no outgroup comparison. The inferred relationship was (((((camel)-(pig-peccary))-(chevrotain-pecoran)))-(hippo-whale))). But analysis of morphology (*e.g.*, number of stomach chambers and a multitude of dental, cranial, and postcranial features) strongly corroborates the hypothesis that hippopotami (whale-related or not) constitute the sister of a (((((suid-camelid)-((chevrotain)))-((pecoran)))))) clade (*e.g.*, Refs^(54,55–57)). In terms of the molecular development of structure continuum, this hypothesis is difficult to ignore.

Hillis⁽⁵⁸⁾ commentary on Nikaido *et al.*'s article is significant: “almost every new molecular approach to phylogenetic inference has been ballyhooed as capable of “revolutionizing” the field. . .[but] no one technique is a perfect solution for all phylogenetic problems” (p. 9979); “even if convergence and reversal are extremely rare for SINE/LINE insertion events, the characters are not immune from problems of lineage sorting of ancestral polymorphisms” (p. 9980); “examples of. . .convergence have been demonstrated in experimental. . . studies” (p. 9980); “although SINE/LINE insertion studies provide a welcome. . .source of phylogenetic data, they are not magic bullets” (p. 9981).

We agree. There is no phylogenetic magic bullet, molecular or morphological, but the desire to find one persists. Although rejecting much of her data as unreliable Ruvolo⁽¹⁸⁾ proclaimed demonstration of a human-chimpanzee relationship. Yet Salem *et al.*⁽⁵¹⁾ claimed a human-chimpanzee-gorilla trichotomy remained unresolved until their SINE (Alu repeat) analysis. Since, as with the MA, the internal consistency of SINE assumptions resists testing with other molecular data, the undeniable molecular-structural continuum makes morphologically and developmentally based phylogenies not only powerful alternative hypotheses, but sources for testing these assumptions.

10a. “What is classified as the same morphological character in two different species may easily reflect different genetic changes. . .Enamel thickness is cited as a trait linking orangutans with humans (both having thick enamel) and chimpanzees with gorillas (both having thin enamel).”

The latter, as with other claims about our article, is false. Thin enamel, being common amongst mammals, is the primitive condition.

10b. “More detailed 3-dimensional studies of molar enamel. . .[demonstrates] that. . .not. . .all [is] captured in a simple thin versus thick enamel classification.”

Stoneking again reveals systematic misunderstanding. “Thick molar enamel” is derived relative to “thin molar enamel”. Amongst taxa with thick enamel, some have thicker

enamel overall or in certain areas, while others have differing degrees of dentine horn extension, etc.

11. “In sum, there is no reason to expect that morphological characters are necessarily good phylogenetic characters.”

Only if one ignores the regulation of development.

12. “Sometimes the conventional wisdom is overturned, and alternative views do deserve to be heard – but if publication in a peer-reviewed journal is to have any meaning at all, editors and reviewers have a responsibility to ensure that well-established contributory evidence is not dismissed in a superficial way.”

Science may benefit. Thanks to Stoneking, molecular assumptions and overgeneralizations are bared, as is the lack of understanding of coding *versus* non-coding regions, constraints on molecular change, the developmental continuum from the molecular through the morphological, systematics, and hypothesis testing.

In most sciences, one would never state that one “knows” anything for certain – that only one source of information trumps all others. Hopefully, some scientifically committed will rise to the challenge of treating evolutionary science as a science.

References

1. Stoneking M. 2009. Humans as second orangutans: sense or nonsense? *BioEssays* **31**: 1010–2.
2. Grehan J, Schwartz JH. 2009. Evolution of the second orangutan: phylogeny and biogeography of hominid origins. *J Biogeogr* DOI: 10.1111/j.1365-2699.2009.02141.x.
3. Zuckerkandl E, Pauling L. 1962. Molecular disease, evolution, and genic heterogeneity. In: Kasha M, Pullman B, ed; *Horizons in Biochemistry*. New York: Academic Press. p 189–225.
4. Schwartz JH, Maresca B. 2006. Do molecular clocks run at all? a critique of molecular systematics. *Biol Theory* **1**: 1–15.
5. Caccone A, Powell JR. 1989. DNA divergence among hominoids. *Evolution* **43**: 925–42.
6. Nelson G, Ladiges PY. 2009. Biogeography and the molecular dating game: a futile revival of phenetics? *Bull Soc Géol France* **180**: 39–43.
7. Schwartz JH. 2005. Molecular systematics and evolution. In: Meyer RA, editor. *Encyclopedia of Molecular Cell Biology and Molecular Medicine (EMCBMM)*. Weinheim: Wiley-VCH Verlag. p 515–540.
8. Clark WELG. 1949. *History of the Primates: an Introduction to the Study of Fossil Man*. London: British Museum. (Natural History).
9. Eldredge N, Cracraft J. 1980. *Phylogenetic Patterns and the Evolutionary Process: method and Theory in Comparative Biology*. New York: Columbia University Press.
10. Hennig W. 1950. *Grundzüge einer Theorie der Phylogenetischen Systematik*. Berlin: Deutscher Zentralverlag.
11. Simpson GG. 1961. *Principles of Animal Taxonomy*. New York: Columbia University Press.
12. Kitts DB. 1977. Karl Popper, verifiability, and systematic zoology. *Syst Zool* **26**: 185–94.
13. Patterson C. 1978. Verifiability in systematics. *Syst Zool* **27**: 218–22.
14. Popper KR. 1968. *The Logic of Scientific Discovery*. New York: Harper Torchbooks.
15. Wiley EO. 1975. Karl R. Popper, systematics, and classification: a reply to Walter Bock and other evolutionary taxonomists. *Syst Zool* **24**: 233–43.
16. Wiley EO. 1981. *Phylogenetics: the theory and practice of phylogenetic systematics*. New York: Wiley.

17. **Yunis JJ, Prakash O.** 1982. The origin of man: a chromosomal pictorial legacy. *Science* **215**: 1525–30.
18. **Ruvolo M.** 1997. Molecular phylogeny of the hominoids: inferences from multiple independent DNA sequence data sets. *Mol Biol Evol* **14**: 248–65.
19. **Consortium CSaA.** 2005. Initial sequence of the chimpanzee genome and comparison with the human genome. *Nature* **437**: 69–87.
20. **Patterson N, Richter DJ, Gnerre S., et al.** 2006. Genetic evidence for complex speciation of humans and chimpanzees. *Nature* **441**: 1103–8.
21. **Eisen JA.** 2000. Assessing evolutionary relationships among microbes from whole-genome analysis. *Curr Opin Microbiol* **3**: 475–80.
22. **Wildman DE, Uddin M, Liu G., et al.** 2003. Implications of natural selection shaping 99.4% nonsynonymous DNA identity between humans and chimpanzees: enlarging genus. *Homo. Proc Natl Acad Sci (USA)* **100**: 7181–8.
23. **Khaitovich P, Hellmann I, Enard W., et al.** 2005. Parallel patterns of evolution in the genomes and transcriptomes of humans and chimpanzees. *Science* **309**: 1850–4.
24. **Ast G.** 2005. The alternative genome. *Sci Am* **292**: 59–65.
25. **Parker SCJ, Hansen L, Abaan HO., et al.** 2009. Local DNA topography correlates with functional noncoding regions of the human genome. *Science* **324**: 389–92.
26. **Duboule D.** 1994. How to make a limb? *Science* **266**: 575–6.
27. **Duboule D.** 2007. The rise and fall of Hox gene clusters. *Development* **134**: 2549–60.
28. **García-Fernández J.** 2005. The genesis and evolution of the Homeobox gene cluster. *Nat Rev Gen* **6**: 881–92.
29. **Gerhart J, Kirschner M.** 1997. Cells, Embryos, and Evolution: toward a Cellular and Developmental Understanding of Phenotypic Variation and Evolutionary Adaptability. Malden, MA: Blackwell.
30. **Gilbert S.** 2006. Developmental Biology. Sunderland, MA: Sinauer.
31. **Tarchini B, Duboule D, Kmita M.** 2006. Regulatory constraints in the evolution of the tetrapod limb anterior—posterior polarity. *Nature* **443**: 985–8.
32. **Schwartz JH.** 2005. Darwinism versus Evo-Devo: a late 19th c. debate. In: Mueller-Wille S, Reinberger H-J, eds; A Cultural History of Heredity III: 19th and early 20th Centuries. Berlin: Max Planck Institute for the History of Science. p 67–84.
33. **Maresca B, Schwartz JH.** 2006. Sudden origins: a general mechanism of evolution based on stress protein concentration and rapid environmental change. *Anat Rec (Part B: New Anat)* **289**: 38–46.
34. **Davidson EH, Erwin DH.** 2006. Gene regulatory networks and the evolution of animal body plans. *Science* **311**: 796–800.
35. **Schwartz JH.** in press: Organismal biology, molecular systematics, and phylogenetic reconstruction In: Masters J, Gamba M, Génin F, eds; Leaping Ahead: Advances in Prosimian Biology. New York: Springer Science.
36. **Schwartz JH.** in press: Organismal innovation. In O'Brien MJ, Shennan SJ, ed; In Innovations in Cultural Systems: Contributions from Evolutionary Anthropology. Cambridge, MA: MIT Press.
37. **Abzhanov A, Protas M, Grant BR., et al.** 2004. Bmp4 and morphological variation in beaks in Darwin's finches. *Science* **305**: 1462–5.
38. **Ferrara N, Gerber HP, LeCouter J.** 2003. The biology of VEGF and its receptors. *Nat Med* **9**: 669–76.
39. **Kirschner MW, Gerhart JC.** 2005. The Plausibility of Life: Resolving Darwin's Dilemma. New Haven: Yale University Press.
40. **Wu P, Jiang T-X, Suksaweang S., et al.** 2004. Molecular shaping of the beak. *Science* **305**: 1465–6.
41. **Delson E, Andrews PJ.** 1975. Evolution and interrelationships of the catarrhine primates. In Luckett P, Szalay F, ed; Phylogeny of the Primates. New York: Plenum. p 405–446.
42. **Schultz AH.** 1936. Characters common to higher primates and characters specific for man. *Q Rev Biol* **11**: 259–83, 425–55.
43. **Schultz AH.** 1968. The recent hominoid primates. In Washburn SL, Jay PC, ed; Perspectives on Human Evolution. New York: Holt, Rinehart and Winston. p 122–195.
44. **Schwartz JH.** 1988. History, morphology, paleontology, and evolution. In Schwartz JH, ed; Orang-Utan Biology. London: Oxford University Press. p 68–85.
45. **Schwartz JH.** 2004. Barking up the wrong ape – australopiths and the quest for chimpanzee characters in hominid fossils. *Colleg Anthropol* **28**: 87–101.
46. **Schwartz JH.** 2005. The Red Ape: Orangutans and Human Origins. Boulder, CO: Westview Press.
47. **Schwartz JH.** 2008. Cladistics. In Regal B, ed; Icons of evolution. Westport CT: Greenwood Press. p 517–544.
48. **Marks J.** 2003. what it means to be 98% chimpanzee. Berkeley: University of California Press.
49. **Johnson WE, Coffin JM.** 1999. Constructing primate phylogenies from ancient retrovirus sequences. *Proc Natl Acad Sci (USA)* **96**: 10254–60.
50. **Romero-Herrera AE, Lehmann H, Castillo O., et al.** 1976. Myoglobin of the orangutan as a phylogenetic enigma. *Nature* **261**: 162–4.
51. **Salem A-H, Ray DA, Jinchuan X., et al.** 2003. Alu elements and hominid phylogenetics. *Proc Natl Acad Sci (USA)* **100**: 12787–91.
52. **Popper KR.** 1962. Conjectures and Refutations: the Growth of Scientific knowledge. London: Routledge and Kegan Paul.
53. **Nikaido M, Rooney AP, Okada N.** 1999. Phylogenetic relationships among cetartiodactyls based on insertions of short and long interspersed elements: Hippopotamuses are the closest extant relatives of whales. *Proc Natl Acad Sci (USA)* **96**: 10261–6.
54. **Boisserie J-R.** 2005. The phylogeny and taxonomy of Hippopotamidae (Mammalia, Artiodactyla): a review based on morphology and cladistic analysis. *Zool J Linn Soc* **143**: 1–26.
55. **Carroll RL.** 1988. Vertebrate Paleontology and Evolution. New York: Freeman.
56. **Romer AL.** 1964. The Vertebrate Body. Philadelphia: W.B. Saunders.
57. **Simpson GG.** 1945. The principles of classification and a classification of the mammals. *Bull Amer Mus Nat Hist* **85**: 1–350.
58. **Hillis DM.** 1999. SINES of the perfect character. *Proc Natl Acad Sci (USA)* **96**: 9979–81.



Jeffrey H. Schwartz¹ and John Grehan²

¹Jeffrey H. Schwartz is Professor of Physical Anthropology and History and Philosophy of Science, University of Pittsburgh and on the editorial boards of the Open Journals of Paleontology and Philosophy. His focus in over 200 publications (including 12 books) has been development and evolution, systematics, phylogenetic reconstruction, and hypothesis testing.

²John Grehan is a Director of Science and Research at the Buffalo Museum of Science and a research associate of the Invertebrate Section at the Carnegie Museum of Natural History. He is interested in the spatial geometry of animal and plant distribution as a methodological foundation of evolutionary theory.

Correspondence: Jeffrey H. Schwartz, Department of Anthropology, University of Pittsburgh, Pennsylvania, United States 15260
E-mail: jhs@pitt.edu

DOI 10.1002/bies.200900137
Published online in Wiley InterScience
(www.interscience.wiley.com)