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Primate Evolution at the DNA Level and a Classification of Hominoids

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Summary. The genetic distances among primate lineages estimated from orthologous noncoding nucleotide sequences of β-type globin loci and their flanking and intergenic DNA agree closely with the distances (delta $T_{50}H$ values) estimated by cross hybridization of total genomic single-copy DNAs. These DNA distances and the maximum parsimony tree constructed for the nucleotide sequence orthologues depict a branching pattern of primate lineages that is essentially congruent with the picture from phylogenetic analyses of morphological characters. The molecular evidence, however, resolves ambiguities in the morphological picture and provides an objective view of the cladistic position of humans among the primates. The molecular data group humans with chimpanzees in subtribe Hominina, with gorillas in tribe Hominini, orangutans in subfamily Homininae, gibbons in family Hominidae, Old World monkeys in infraorder Catarrhini, New World monkeys in semisuborder Anthropoidea, tarsiers in suborder Haplorhini, and strepsirhines (lemuriforms and lorisiforms) in order Primates. A seeming incongruency between organismal and molecular levels of evolution, namely that morphological evolution appears to have speeded up in higher primates, especially in the lineage to humans, while molecular evolution has slowed down, may have the trivial explanation that relatively small genetic changes may sometimes result in marked phenotypic changes.

Key words: Noncoding nucleotide sequences — DNA hybridization — Primate phylogeny — Maximum parsimony — Cladistic classification

Introduction

The Linnaean system of taxonomic classification, by virtue of its hierarchical ranks for nested taxa, provides a formal nomenclature or vocabulary that is well suited for describing the cladistic relationships that exist among species. Ever since Darwin (1859) proposed that taxonomic classifications should group species according to their recency of common ancestry, research in systematics has become increasingly concerned with identifying monophyletic groups or clades and with revising traditional taxonomic classifications so that they reflect the cladistic hypotheses best supported by the data. When revisions are now proposed they are usually in the direction of having taxa represent clades instead of grades, the latter being rather arbitrary groupings for species with primitive features of morphology or for species with advanced features of morphology (Simpson 1961). Progress toward a consistently cladistic classification for the primates has been impeded by ambiguities in the morphological picture of primate phylogeny and by an anthropocentric view of nature that persists. As expressed in extreme form in pre-Darwinian taxonomy, this anthropocentric view placed humans on a pedestal between the animals and the angels in a kingdom all to ourselves. In modern taxonomy the anthropocentric view is expressed by the gradistic division of the order Primates into suborder Pro-

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simii for the small-brained primates (grouping infraorders Lemuriformes, Lorisiformes, and Tarsiiformes) and suborder Anthropoidea for the large-brained primates (grouping superfamilies Ceboidea, Cercopithecoidea, and Hominoidea) and further by the gradistic division of Hominoidea into an ape family Pongidae for the nonhuman hominoids (the fossil apes and the living gibbons, orangutans, gorillas, and chimpanzees) and a human family Hominidae for humans alone.

Phylogenetic analyses of morphological features indicate that Lemuriformes and Lorisiformes are sister groups (closest living relatives) but disagree on whether the dwarf and mouse lemurs (Cheirogaleidae) belong with other Malagasy lemurs in Lemuriformes or in Lorisiformes with the African galagos and pottos and Asian lorises (see Fleagle 1988 for review). Moreover, these morphological studies do not unambiguously establish the cladistic position of the Tarsiiformes, which includes the Philippine and Indonesian tarsiers in the genus *Tarsius* as the only living representatives of this ancient primate clade. A widely held view is that Primates divides cladistically into Strepsirhini (Lemuriformes and Lorisiformes) and Haplorhini (Tarsiiformes and Anthropoidea) (Aiello 1986; Fleagle 1988), but Simons and Rasmussen (1989) challenge this view. The morphological evidence divides Anthropoidea into infraorders Platyrrhini for ceboids (the New World monkeys) and Catarrhini for cercopithecoids (the Old World monkeys) and hominoids. The morphological evidence also indicates that Hominoidea divides into a gibbon or lesser ape clade and a great ape–human clade containing orangutans, gorillas, chimpanzees, and humans, but has not unambiguously resolved the branching pattern of the great ape–human clade.

In recent papers (Goodman et al. 1989; Koop et al. 1989) we have shown that the genetic record of evolution in DNA provides a view of primate phylogeny that is essentially congruent with the morphological evidence. The molecular data, however, resolve ambiguities in the morphological picture and provide an objective view of the cladistic position of humans among the apes. Using available sequence data on the β-type globin loci (ϵ, γ, $\psi\eta$, δ, β) and their flanking and intergenic DNA from primates and other mammals, we aligned orthologous nucleotide sequences and constructed most parsimonious trees from the aligned orthologues. The sequence data for the Cheirogaleidae consisted of a 2000-base sequence spanning the dwarf lemur's γ-globin locus, and the maximum parsimony tree constructed for γ-globin orthologues strongly grouped dwarf lemur with brown lemur (a lemurid) rather than with galago, indicating that Cheirogaleidae belongs in Lemuriformes and not in Lorisiformes (Tagle et al. 1988; Koop et al. 1989). The sequence data for *Tarsius* were more than five times greater, consisting of nucleotide sequences spanning each of the five β-type loci, and the ϵ, γ, $\psi\eta$, δ, and β maximum parsimony trees all congruently placed Tarsiiformes in suborder Haplorhini as the sister group of Anthropoidea (now treated taxonomically as a semisuborder); in turn, Lemuriformes (represented by all five loci in the case of brown lemur) and Lorisiformes (represented by galago ϵ and γ loci) were sister groups that joined together to form suborder Strepsirhini (Koop et al. 1989).

To resolve the branching pattern of the great ape–human clade, we (Goodman et al. 1989; Koop et al. 1989) combined nucleotide sequencing results from several studies (Koop et al. 1986; Miyamoto et al. 1987, 1988; Fitch et al. 1988; Maeda et al. 1988). These combined results gave us a data set of aligned human, chimpanzee, gorilla, orangutan, rhesus monkey, and spider monkey orthologues. Each orthologue represented 10.8 kb of continuous noncoding sequence starting upstream of the $\psi\eta$-globin locus and ending downstream of it before reaching the δ locus. The maximum parsimony and maximum likelihood trees constructed using these aligned orthologues provided overwhelming evidence for the separation of orangutan from a monophyletic human–chimpanzee–gorilla branch and, together with other DNA studies (Sibley and Ahlquist 1984, 1987; Holmquist et al. 1988; Caccone and Powell 1989; Ueda et al. 1989; Williams and Goodman 1989), significant evidence that human and chimpanzee lineages shared the most recent common ancestor.

Sarich et al. (1989), in criticizing the DNA hybridization data of Sibley and Ahlquist (1984, 1987) and Bonner et al. (1980), claimed that these hybridization data did not accurately measure the distances among orthologous primate DNAs. Yet the DNA hybridization distances reported by Sibley and Ahlquist (1987) for catarrhines and by Bonner et al. (1980) for more anciently separated primate lineages agree closely with the distances that we found on comparing orthologous noncoding sequences from intron, flanking, and intergenic regions of the β-type globin loci of different primates (Koop et al. 1989). In this paper, we increase these comparisons mainly with (1) orthologous gibbon sequences (Fitch et al. 1989; Fitch, Bailey, Slightom, and Goodman, unpublished data), thereby having all five major hominoid lineages represented, and (2) additional orthologous galago sequences, more distal 5′ flanking γ sequence and the noncoding sequence from a galago β-globin locus (Tagle, Benson, and Goodman, unpublished data) being added to that previously published for galago ϵ and γ loci (Tagle et al. 1988). Further, we match the distal 5′ γ galago se-

	HUM	CHI	GOR	ORA	HLA	MAC	ATE	TAR	GAL	LEM	RAB	GOA
HUMAN		1.7	1.8	3.3	4.3	7.0	10.8	24.6	28.9	22.6	31.7	31.1
		1.7	1.8	3.4	4.5	7.4	11.6	29.8	36.5	26.9	41.2	40.2
CHIMP	15801		1.7	3.5	4.7	7.0	10.8	25.8	31.6	23.4	32.4	31.6
			1.8	3.6	4.8	7.4	11.7	31.7	41.1	28.0	42.4	41.1
GORILLA	12543	11683		3.5	4.7	7.2	10.9	26.0	30.0	23.8	33.8	32.3
				3.6	4.8	7.5	11.8	32.0	38.3	28.6	44.8	42.2
ORANG	16752	10591	10779		4.7	7.3	10.8	24.8	28.0	23.1	30.2	31.5
					4.8	7.7	11.7	30.2	35.0	27.6	38.6	40.8
GIBBON	7523	7119	7513	7212		7.5	9.8	26.3	29.3	23.2	33.1	31.8
						8.0	10.5	32.4	37.2	27.7	43.7	41.4
MACACA	16453	15639	11769	11160	7182		11.9	26.0	31.4	24.3	32.4	33.3
							13.0	32.0	40.8	29.3	42.4	43.9
ATELES	11896	9784	10418	11236	6789	10660		27.1	29.7	25.3	33.7	32.6
								33.6	37.8	30.8	44.7	42.7
TARSIER	8010	4577	3913	5118	2352	5537	4197		30.6	25.4	34.3	34.2
									39.3	31.0	45.8	45.6
GALAGO	6197	3753	3558	3387	2103	3892	2221	5341		21.9	36.2	36.4
										25.9	49.5	49.7
LEMUR	5033	2351	2217	3466	1229	2534	2196	4657	3933		30.1	29.4
											38.4	37.4
RABBIT	6084	2467	2163	3179	979	3052	2194	5224	4605	3701		35.7
												48.5
GOAT	3747	2419	2266	3143	1650	2421	1866	3444	3065	2568	1837	

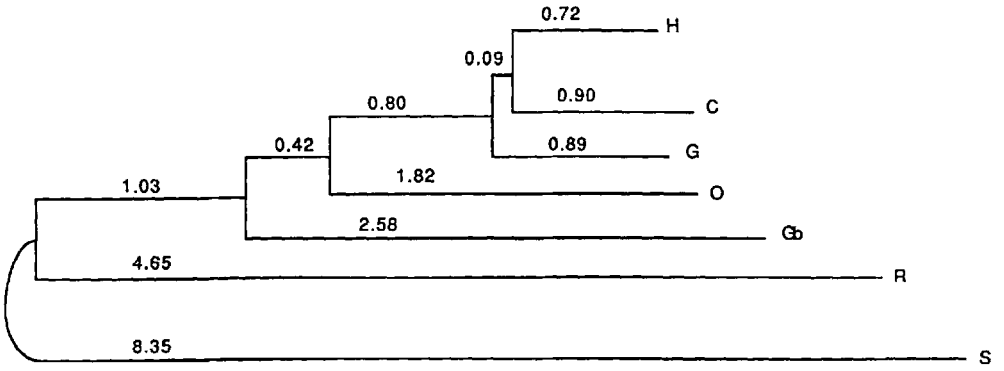
Fig. 1. Interspecies distances as estimated from pairwise comparisons of orthologous noncoding sequences from β-type globin loci and their flanking and intergenic DNA. The numbers above the diagonal are percent sequence difference values (calculated as the number of substitutions plus the number of gaps divided by the total number of shared nucleotide positions plus the total number of gaps, with the product of the division multiplied by 100) uncorrected for superimposed substitutions (top numbers in the slots) and corrected for superimposed substitutions (bottom numbers in the slots) by the method of Jukes and Cantor (1969). For each slot the numbers below the diagonal are the number of aligned nucleotide sequence positions in the pairwise comparison. Because the duplicated γ-globin genes of catarrhine primates show patchy conversions in intron 2 regions (Slightom et al. 1988), we did not include γ intron 2 sequences on compiling the orthologous noncoding sequences for the present study.

quence with the orthologous rabbit sequence (Margot et al. 1989). We also add more 5′ flanking γ sequence from gorilla and, in all new regions of the expanded alignment, the matching human orthologue.

Interspecies DNA Distances and Branching Pattern in Primate Evolution

Figure 1 presents a matrix of percent sequence difference values found in pairwise comparisons of human, chimpanzee, gorilla, orangutan, gibbon, macaque, spider monkey, tarsier, galago, lemur, rabbit, and goat orthologues. Each orthologue consists of noncoding nucleotide sequences from the genomic region containing the β-type genes of that species. As pointed out in Goodman et al. (1989), the coding sequences of the five types of loci (ϵ, γ, $\psi\eta$, δ, β) in this genomic region of a primate account for less than 5% of the region and the noncoding nonregulatory sequences account for at least 95% of the region. The most extensive stretch of continuous noncoding nonregulatory DNA from this genomic region, that we have sequenced in each of the five hominoids and in rhesus and spider monkeys, is the 10.8-kb long stretch that crosses the η-globin pseudogene or $\psi\eta$ locus. In the case of the gibbon $\psi\eta$ region, it is still being sequenced (Fitch et al., unpublished) but consists presently of about 6.5 kb of confirmed sequence. The bottom of Fig. 2 presents the matrix of percent sequence differences for these extensive $\psi\eta$ orthologues from the seven primates. Figure 3 compares the percent sequence difference values from these orthologous comparisons of sequenced noncoding DNAs to the interspecies DNA distances reported from DNA hybridization data by Sibley and Ahlquist (1987) for catarrhines and by Bonner et al. (1980) for more anciently separated primate lineages.

In Fig. 3, the global measures of genomic sequence divergence provided by the delta $T_{50}H$ values of the DNA hybridization data correlate closely with the percent sequence difference values from pairwise comparisons of the known orthologous noncoding nucleotide sequences. The correlation for



H	-----						
C	1.62	-----					
G	1.72	1.85	----				
O	3.44	3.55	3.55	-----			
Gb	4.46	4.92	4.65	4.90	-----		
R	7.74	7.89	7.74	7.79	8.39	-----	
S	11.48	11.69	11.47	11.60	11.83	13.00	-----
	H	C	G	O	Gb	R	S

Fig. 2. Neighbor-joining tree for the data set of orthologous noncoding sequences spanning the $\psi\eta$-globin locus and extending toward the δ locus. This data set consisted of human (H), chimpanzee (C), gorilla (G), orangutan (O), gibbon (Gb), rhesus monkey (R), and spider monkey (S) orthologues. Below the tree is the distance matrix used to calculate the neighbor-joining tree by the algorithm of Saitou and Nei (1987). The distance matrix is shown as percent sequence difference values corrected for superimposed mutations by the method of Jukes and Cantor (1969). Branch lengths represent the number of changes per 100 base positions incorporated along each lineage.

the anciently separated primate lineages is perhaps even more amazing than for the catarrhines, in that one would expect the delta $T_{50}H$ values to become less accurate at these larger phylogenetic distances. Indeed on this basis, Sarich et al. (1989) discounted the finding of Bonner et al. (1980) that the lemuriform branch of primates evolves at the DNA level at a much slower rate than either the lorisiform or tarsier branches. Yet, we see the same pattern for the orthologous noncoding sequences from β-type globin loci and their flanking and intergenic regions (Koop et al. 1989). In fact in the tree that summarized the combined results from all orthologous noncoding nucleotide sequence positions and calculated branch lengths by the procedure of Fitch and Margoliash (1967), we found the length of the lemur branch to be only one-half the length of the galago branch (Fig. 4 in Koop et al. 1989).

Our strongest evidence for the branching pattern of major primate clades comes from the maximum parsimony trees constructed for the separate sets of aligned nucleotide sequence orthologues, these sets representing the ϵ, γ, η, δ, and β loci proper and the extended 10.8-kb $\psi\eta$ region (Koop et al. 1989). As reviewed in the introduction to this paper, these trees support the division of Primates into Strepsirhini (the lemuriform–lorisiform clade) and Haplorhini (the tarsier–Anthropoidea clade), and Anthropoidea into Platyrrhini (the New World monkey clade) and Catarrhini (the Old World monkey–hominoid clade).

The extended $\psi\eta$ region orthologues provide the largest portion of the parsimony evidence on the cladistic relationships of hominoid lineages. Figure 4 shows the most parsimonious tree found for this data set of spider monkey, rhesus monkey, gibbon, orangutan, gorilla, chimpanzee, and human orthologues. The number on the stem to each node is the difference in tree lengths between the most parsimonious tree and the nonparsimonious tree that adds the least length in breaking up the clade represented by that stem. Thus the human–chimpanzee clade is supported by a difference value of 8, the human–chimpanzee–gorilla clade by 54, the human–chimpanzee–gorilla–orangutan clade by 20, and the human–chimpanzee–gorilla–orangutan–gibbon clade by 40. The support for a human–chimpanzee clade comes from the full 10.8-kb $\psi\eta$ region; this follows from the fact that the nonparsimonious trees that added the least length above the maximum parsimony length either joined human and gorilla orthologues first or joined chimpanzee and gorilla orthologues first (each orthologue being about 10.8 kb long). However, the support for the other clades depicted by the stems of the maximum parsimony tree comes from only that portion of the extended $\psi\eta$ region (about three-fifths of it) that has so far been sequenced in gibbon; in each case in the nonparsimonious tree that added the least length to the maximum parsimony length, the gibbon branch either broke up the clade in question or was the branch that left the clade to join an outside branch.

	β GLOBIN CLUSTER NONCODING SEQUENCE % DIVERGENCE	10.8KB ψη SEQUENCE % DIVERGENCE	GENOMIC DNA-DNA HYB. $\Delta T_{50}H$	
HUMAN-CHIMP	1.7	1.6	1.6[1]	
HUMAN GORILLA	1.8	1.7	2.3	
HUMAN-ORANG	3.3	3.4	3.6	
HUMAN-GIBBON	4.3	4.3	4.8	
HUMAN-RHESUS	7.0	7.4	7.3	6.9[2]
HUMAN-ATELES	10.8	10.6	-	11.2
CHIMP-GORILLA	1.7	1.8	2.2	
CHIMP-ORANG	3.5	3.5	3.6	
CHIMP-GIBBON	4.7	4.8	5.1	
CHIMP-RHESUS	7.0	7.5	7.3	
GORILLA-ORANG	3.5	3.5	3.6	
GORILLA-GIBBON	4.7	4.5	4.5	
GORILLA-RHESUS	7.2	7.4	7.2	
ORANG-GIBBON	4.7	4.8	4.9	
ORANG-RHESUS	7.3	7.4	7.4	
GIBBON-RHESUS	7.5	7.9	7.1	
HUMAN-TARSIER	24.6	-	-	25.4
HUMAN-GALAGO	28.9	-	-	28.0
HUMAN-LEMUR	22.6	-	-	22.3
ATELES-TARSIER	27.1	-	-	26.4
ATELES-GALAGO	29.7	-	-	30.7
ATELES-LEMUR	25.3	-	-	24.5
TARSIER-GALAGO	30.6	-	-	30.2
TARSIER-LEMUR	25.4	-	-	25.8
GALAGO-LEMUR	21.9	-	-	22.1

[1]From Sibley and Ahlquist (1987) *J. Mol. Evol.*26:99-121.
[2]From Bonner *et al* (1980) *Nature* 286:420-423.

Fig. 3. Comparison of interspecies distances as estimated from orthologous noncoding sequences and as estimated from cross hybridization of total single-copy genomic DNAs. The distance values are not corrected for superimposed substitutions. The percent divergence values for β-globin cluster noncoding sequences are taken from Fig. 1. In the column labeled 10.8-kb $\psi\eta$ sequence, the gibbon is not represented by the full 10.8 kb of this noncoding region but is represented by about 6.5 kb of it (see text).

Taxonomic Conclusions

As noted in the introduction, traditional taxonomic classifications are mixtures of grades and clades with modern revisions usually favoring the substitution of clades for grades. The classification of hominoid genera used by Simpson (1945), and later revised by him (Simpson 1963), serves as a starting point for the further revisions that we propose to achieve a strictly cladistic classification. We shall ignore the fossil hominoids as outside our data and field of expertise but do not see any insurmountable difficulties in eventually including them in a classification that reflects the cladistic hypotheses best supported by the combined evidence from living and fossil forms. Simpson (1945) divided superfamily Hominoidea into the Pongidae for all apes and the Hominidae for humans; he subdivided Pongidae into two subfamilies: Hylobatinae containing *Hylobates* (common gibbons) and *Symphalangus* (siamang gibbons) and Ponginae containing *Pongo* (orangutans), *Pan* (chimpanzees), and *Gorilla* (gorillas). He followed this same scheme in his 1963 work, except that he placed all extant gibbons in *Hylobates* and, similarly, he placed the living African apes (common chimpanzees, pygmy chimpanzees, and gorillas) in *Pan*. This showed that the living African apes are more closely related to one another than to orangutans and that the great apes (orangutans, chimpanzees, and gorillas) are more closely related to one another than to the gibbons or lesser apes. If only humans could be ignored,

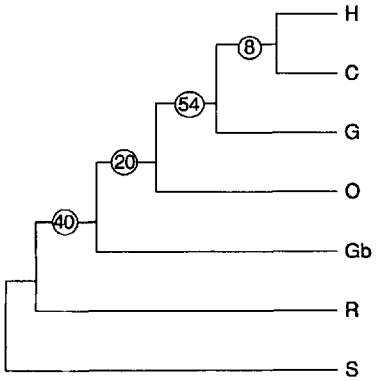


Fig. 4. The maximum parsimony tree found for the seven extended $\psi\eta$ region nucleotide sequence orthologues after examining all 945 of the possible unrooted trees that seven sequences can form. The circled number on each stem to a branching node is the difference in tree lengths between the maximum parsimony tree and the nonparsimonious tree that adds the least length in breaking up the clade represented by that stem. For example, the maximum parsimony tree requires 2036 sequence changes (number of nucleotide substitutions plus number of insertions and deletions), and each nonparsimonious tree that adds the least length (gorilla grouping with either human first or chimpanzee first) requires 2044 sequence changes; thus the circled number on the stem to the human–chimpanzee clade is 8.

Simpson's 1963 classification was strictly cladistic. Because humans could not be ignored, Simpson placed us in the family Hominidae; only this time accepting the evidence that the extinct ape genus *Australopithecus* was the direct ancestor of *Homo*, he removed *Australopithecus* from Pongidae and placed it in Hominidae. Despite these cladistic re-

finements of his 1945 classification, his widely accepted 1963 classification of hominoid genera still has Pongidae as a grade taxon in that not only are the great apes of his Pongidae more closely related to humans than to gibbons, but also the African great apes are much more closely related to humans than to orangutans and gibbons. Simpson had accepted the protein evidence (Goodman 1962, 1963; Zuckerkandl 1963) that the African apes share a more recent common ancestry with humans than with orangutans but rejected the proposal that the African apes belong with humans in Hominidae rather than with orangutans in Pongidae (Goodman 1962, 1963). He reasoned that each of the lineages to the living apes have been conservative lineages but that the lineage to humans has diverged markedly in morphology and behavior from these ape lineages and has entered a new adaptive zone, thus on a grade basis deserving a new family.

At the genetic level of sequenced proteins and sequenced DNA, we find the human lineage to be just as conservative or even more conservative than each of the other hominoid lineages. Moreover, we know that a single mutational event, even as small as a point mutation if it happens to occur at a functionally important site in the DNA sequence, can sometimes have a very large phenotypic effect on its bearer. Thus it seems to us that to use grade concepts in taxonomy is unreliable. These concepts reflect a lingering anthropocentric view of nature and convey subjective judgments as to which features of morphology and behavior are important. The use of cladistic concepts provides a more objective basis for classification.

We propose the following cladistic classification of extant hominoid genera.

Superfamily Hominoidea
  Family Hominidae
    Subfamily Hylobatinae
      Hylobates
    Subfamily Homininae
      Tribe Pongini
        Pongo
      Tribe Hominini
        Subtribe Gorillina
          Gorilla
        Subtribe Hominina
          Pan
          Homo

We are agreeing here with Simpson (1945, 1963) that the different ape genera within Hominoidea when viewed in the light of all mammalian systematics should be grouped together in the same family, but because we want a strictly cladistic classification the rules of taxonomic nomenclature require that all these ape genera be placed in the family Hominidae. By using the categories of subfamily, tribe, and subtribe we can group the genera according to their cladistic relationships as inferred from the branching pattern shown in Figs. 2 and 4. The least strongly supported grouping is that which places *Pan* and *Homo* together to the exclusion of *Gorilla.* Clearly, the divergence evidence for this is weak. However, the parsimony evidence, in which orthologous noncoding sequences specifically group *Pan* and *Homo,* appears to be statistically significant (Williams and Goodman 1989). We have chosen to group chimpanzees with humans in subtribe Hominina rather than in genus *Homo* for two reasons. Firstly, the divergence between the two chimpanzee species, *P. troglodytes* (common chimpanzees) and *P. paniscus* (pygmy chimpanzees), is less than the divergence between chimpanzees (*Pan*) and humans (*Homo*). Secondly, our scheme still allows paleoanthropologists to group australopithecine species closer to *Homo sapiens* than to any living apes. This can be done within the genus *Homo* by using the categories of subgenus and species.

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