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## **The Phylogenetic Position of Genus *Tarsius*: Whose Side are You On?**

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## INTRODUCTION

The accurate placement of the genus Tarsius (commonly known as the tarsier) is the fundamental key to deriving a phylogenetic classification for the order Primates. Depending on where the tarsier is placed with respect to the tooth-combed primates (lemurs and lorises) and the anthropoid primates (monkeys and apes), there are three alternative classificatory schemes whereby the primates are divided into two named subclades (Figure 1). If tarsiers are grouped with the lemurs and lorises, then the division is between Prosimii and Anthropoidea (Fig. 1a); if they are grouped with monkeys and apes, then the division is between Strepsirrhini and Haplorhini (Fig. 1b). Alternatively, if tarsiers are considered sister to all other living primates, then the division is between Tarsiiformes and Simiolemuriformes (Fig. 1c). Each of these classificatory schemes has proponents in the literature and is upheld by varying degrees of morphological character support, as will be reviewed below. The primary purpose of this chapter, however, is to consider the genetic data as they are currently known and to determine if these data show convincing support for any one of these three phylogenetic hypotheses.

The systematics of tarsiers relative to other primates has been controversial from the time that biologists first began to attempt systematic arrangements of life on earth. Indeed, early systematists did not even recognize genus Tarsius as a primate, instead classifying it as either a jerboa or an opossum (Buffon, 1765; Linnaeus, 1767-1770). Much later, in 1916, a ferment of controversy was aroused when F. Wood Jones published his surprising "tarsioid theory of human origins. This theory was sufficiently unconventional and disturbing to prompt a symposium of the Zoological Society of London in 1919 in which the sole purpose was to discuss the relationship of Tarsius to other primates. The findings of this symposium were inconclusive. In the ensuing years, hypotheses of the relationship of tarsiers to other living primates can be distilled into three major schemes, as shown in Figure 1. It was Gregory (Gregory, 1915) who first placed tarsiers with lemurs and lorises into the suborder Prosimii. This classification has received support from a number of more recent authorities on

primate evolution (e.g., Le Gros Clark, 1971; Simons, 1972; Simpson, 1945) and has been widely accepted by the larger scientific community as the assumed primate classification (e.g., Kim and Takenaka, 2000; Wu et al., 2000). In temporal parallel, the classification proposed by Pocock (Pocock, 1918), in which Tarsius is grouped with monkeys and apes in the order Haplorhini, has also received support from a number of prominent primatologists (e.g., Aiello, 1986; Hill, 1953; Ross, 1994; Szalay and Delson, 1979) though it has received far less recognition from the general scientific community. The latter classificatory scheme is distinguished from the previous by its explicitly character-based perspective. Finally, the third scheme has been proposed more recently than either the prosimian or the haplorhine classifications of Tarsius (Gingerich, 1978; Schwartz, 1978a; Schwartz, 1978b), but has been largely ignored by most primate systematists.

Many of the controversies related to these opposing classifications derive from arguments founded on fossil data and the hypothesized relationships of tarsiers to extinct Paleocene and Eocene fossil lineages. It is my goal to avoid these arguments as much as possible, leaving the arduous task of interpreting the fossil record to the paleontologists, as it should be. For further discussion of these issues and the fossil data supporting the various viewpoints, there are a number of excellent primary and secondary reviews (e.g., Beard, 1998; Beard et al., 1988; Beard et al., 1991; Ross et al., 1998). It is the task of this chapter to review the neontological data as they pertain to the phylogenetic affinities of the genus Tarsius, both morphological (although this is not a novel endeavor; see especially Aiello, 1986; Cartmill, 1982; Cartmill, 1994; Ross, 1994) and genetic.

#### SOMATIC CHARACTER EVIDENCE FOR TARSIER AFFINITIES

As mentioned above, Gregory (1915) was one of the first to classify tarsiers with lemurs and lorises into a single suborder Lemuroidea, within which three "series" were identified to individually recognize the distinctions among lemurs, lorises and tarsiers. Simpson (1945) followed suit with his definitive classification of the mammals, explicitly following Gregory's arrangement

though renaming the suborder Prosimii and identifying the three series as the infraorders Lemuriformes, Lorisiformes, and Tarsiiformes. In reviewing these two works, however, it is clear that the rationale for the unified grouping of the three infraorders related more to the perceived "primitiveness" of the "lower primates", and to perceptions of relatedness to Eocene fossil lineages, than to any fixed idea of character support for their historical unity. Indeed, both men remarked on the large morphological gaps between tarsiers and the other prosimians, with Gregory even noting that the similarities of the tarsier and anthropoid cranial arterial "condition has been derived from" (p. 429) the lemuriform pattern. He goes on to say that the contrast between lemuriforms and tarsiiforms, and their presumed fossil antecedents, is so great as to "warrant us in looking for the common stem form of the Lemuroidea in the Paleocene or even earlier".

Although Simpson (1945) formalized the prosimian-anthropoid classification, Le Gros Clark (1971) is largely responsible for its information content. Le Gros Clark established the perception of the primate order as a taxon that showed progressive evolutionary trends rather than unique defining characteristics. In this view, the order began with tree shrews and culminated with humans, showing trends for increasingly enlarged brains, perfected vision, reduced olfaction, and grasping extremities. Accordingly, the discrimination of two major subdivisions within the order was somewhat arbitrary and based primarily on the distinction of two evolutionary grades: lower primates and higher primates. Le Gros Clark further concluded that the fossil record showed that early tarsiods had developed their peculiar specializations to an advanced degree in the early Eocene and thus they could not have "provided a basis for the subsequent evolution of the Anthroidea in which such specializations are absent" (p. 332).

The plesiotarsiiform-simiolemuriform classification was originally conceived by Gingerich (1974) and was based on the stratophenetic linkage of tarsiers to Eocene omomyines and microchoerines, and these taxa to Paleocene plesiodapiforms. The temporal connection of these primate groups was further

strengthened by stratigraphic proximity, dental similarities, and certain aspects of middle ear morphology. The plesiotarsiiform half of the order was later revised to exclude plesiadapiforms with the name changed to Tarsiiformes to reflect the new taxon composition of the suborder (Gingerich, 1981). By and large, however, either arrangement is more a reflection of Gingerich's vehement belief that the "linking between primitive anthropoids and Eocene adapoids is one of the strongest in all of primate phylogeny" (1978; p. 253) more than it is a reflection of tarsier's separateness. The fact that Schwartz's work on dental homologies (Schwartz, 1978a; Schwartz, 1978b) supported Gingerich's initial views has done little to buffer them from the disregard of other systematists. The most serious problem with Gingerich's hypothesis in its original formulation is that it requires independent evolution of the lemur- and tarsier-like euprimate lineages from a pre-plesiadapiform. Given that it is now well-accepted that plesiadapiforms were not stem primates (Beard, 1990; Beard and Wang, 1991; Kay et al., 1992), Gingerich's evolutionary scenario requires convergent evolution of three of the most significant defining features of euprimates: replacement of claws by nails on at least some digits, enlargement and forward rotation of the orbits, and a postorbital bar.

Clearly, the previous two classificatory schemes both recognize and depend on the fossil record for their foundation. The strepsirrhine-haplorhine classification, on the other hand, relies almost entirely on neontological data. Pocock (1918) was the first to assert that the dissimilarity of the structure of the nose and upper lip of Tarsius compared to lemuriforms "severs" their potential phylogenetic connection, bringing tarsiers closer in line with anthropoids instead. Indeed, the word strepsirrhine is derived from the primitive retention in lemurs and lorises of a naked, moist rhinarium that exhibits a lateral cleft between the medial and lateral nasal processes. In tarsiers and anthropoids, on the other hand, the rhinarium is covered with dry, hairy skin and the lateral cleft is completely fused (Hill, 1953).

Although proposed by Pocock (1918) and adopted by Hill (1953), the strepsirrhine-haplorhine classification has gained most of its authority since the

introduction of cladistic methods. Cladistically-inclined primatologists have spent much of their time seeking to discover synapomorphies that ally tarsiers either with lemuriforms or with anthropoids. Cartmill (1982) described the pursuit as complicated, at best, due to the difficulty of the problem:

- "[T]he phylogenetic histories of some organisms have been so muddled by convergence, parallelism, and evolutionary reversal that many false phylogenies can be supported ... Unfortunately for primate biologists, Tarsius may well be such an organism." (p. 281)

Despite the difficulty of the problem, an impressive list of putative haplorhine synapomorphies have been presented in the literature (Table 1). Even so, doubt persists, particularly as the distribution of these characters among Oligocene anthropoids implies that many of them must be convergently derived in living tarsiers and anthropoids (Simons and Rasmussen, 1989). Continued application of phylogenetic methods to the analysis of morphological character data has unfortunately been unable to resolve the question. Although Kay et al. (1997), employing the most extensive morphological data set to date, found support for the strepsirrhine/haplorhine dichotomy, subsequent analysis by the same authors identified some uncertainty in their previous conclusions (Ross et al., 1998). This latter study found that when the data were analyzed as individual cranial and postcranial data partitions, the former supported a monophyletic Haplorhini, whereas the latter supported a monophyletic Prosimii.

## GENETIC DATA

In cases of phylogenetic uncertainty relating to extensive morphological homoplasy, it is often the case that genetic data can resolve the problem. Unlike morphological data, molecular characters (i.e., DNA sequence data) and character states are obvious and not prone to subjective interpretation. Given that the alignment is accurate (which, in certain cases, can be quite problematic -- though that issue will not be addressed here), molecular characters are usually defined as the individual sites along the DNA strand, with the states defined as the individual nucleotides, A, C, G, and T. Thus, except in cases of alignment

uncertainty, subjectivity and potential investigator bias are completely removed from the process of defining characters and their states. This should therefore alleviate much of the controversy that has surrounded morphological analysis of tarsier affinities. The earliest attempts to apply genetic data to phylogenetic questions are best described as genetic distance data, such as immunodiffusion (Goodman and Moore, 1971) and DNA hybridization measures (Sibley and Ahlquist, 1984). Both of these methods are "indirect", however, in that they summarize the differences and similarities among taxa into a single pairwise measure. Thus, they cannot distinguish homology from similarity, nor provide information about direction of character change. The small number of shared derived characters between two closely related taxa can easily be swamped by the much larger number of shared primitive characters. Clearly then, neither of these methods can be considered very sensitive, though their utility for providing a rapid assessment of genomic-level similarities holds some appeal.

Genetic distance methods have been essentially replaced by character-based methods derived from DNA sequence data. These data permit the investigator to employ traditional cladistic methods (such as parsimony) to genetic data, much as they have been applied to morphological data. One of the greatest advantages of DNA sequence data, however, has been the development of likelihood methods for phylogenetic analysis. Likelihood methods have been developed for incorporating knowledge of molecular evolutionary properties, such as transition/transversion rate ratio bias, codon bias, and site-specific rate variation, directly into the model and thus the analysis, giving them far more power than traditional parsimony analysis (Felsenstein, 1973; Yang et al., 1995). Such models are currently not employed for the analysis of morphological data, though ongoing work promises breakthroughs for this application (Lewis, 2001). Lastly, due to the enormity of the potential data set (i.e., the millions of individual base pairs contained in the combined mitochondrial and nuclear genomes) there are virtually limitless characters from which to choose. Potentially then, systematists interested in resolving the placement of genus Tarsius could objectively employ multiple molecular data sets, using a variety of optimality criteria (i.e., maximum parsimony, maximum likelihood, and

minimum evolution) (Swofford et al., 1996) and thus discover the hypothesis that is maximally supported by the data and the methods. Indeed, molecular phylogeneticists and other geneticists have gathered and analyzed an enormous amount of DNA sequence data, but most unfortunately for those interested in resolving the tarsier enigma, these data and analyses leave us as uncertain as have the morphological studies.

Another form of genetic data have recently emerged as potentially useful for such difficult phylogenetic questions. These genetic characters, usually referred to as SINEs (short interspersed nuclear elements), are non-autonomous transposable elements that are "interspersed" throughout the nuclear genome. These elements vary in length from about 150-500 base pairs, and according to some authorities, can be considered as ideal phylogenetic characters. The main portion of a SINE is presumably non-functional, and thus hypothetically, is a neutral phylogenetic marker. Also, there is a strong assumption that these characters integrate irreversibly into the nuclear genome. Although it is conceivable that a specific SINE could be deleted from a genome subsequent to integration, it is hard to imagine a mechanism whereby this could happen invisibly. Because a signature repeat is formed that flanks both ends of a SINE sequence upon integration, subsequent deletion would likely leave some portion of the signature flanking sequence, or, if the deletion was larger, would also remove a portion of the surrounding ancestral sequence. In either case, the deletion would be detectable in a comparison of related sequences. Thus, polarity can also be determined in that the shared absence of a SINE is virtually certain to be the ancestral state. Finally, due to the enormous size of the typical mammalian genome, SINE integrations observed at homologous positions are regarded as characters with infinitesimal probabilities of convergence or parallelism. For all of these reasons, some workers are convinced that SINEs are the ideal phylogenetic characters. Unfortunately, however, SINEs appear to have accumulated in the genome through multiple waves of fixation. Thus, the nonlinear accumulation and relatively small number of integration events limit their use for *de novo* phylogenetic reconstruction. It has been alternatively argued therefore that they are ideal for testing the veracity of competing

hypotheses, such as might be the case for the limited number of phylogenetic hypotheses that have been proposed for tarsier affinities (Schmitz et al., 2001).

### Genetic Studies Supporting Haplorhini

At first glance, the genetic evidence for tarsier's placement with the anthropoid primates appears to be overwhelming. Over the past 20 or so years, there have been many, many publications of genetic data that support a monophyletic Haplorhini (Baba et al., 1982; Bailey et al., 1991; de Jong and Goodman, 1988; Koop et al., 1989a; Koop et al., 1989b; Porter et al., 1995; Stanhope et al., 1993). These accumulating studies, along with the extensive list of putative morphological synapomorphies (Table 1), have served to solidify support for the strepsirrhine/haplorhine division among primate systematists. A close inspection of these studies, however, shows that they are all taken from the nuclear genome, and that over 50% of them are from the globin family of genes. Although the first observation is not of particular concern --- the nuclear genome is by far the most extensive set of potential genetic data sets --- the second observation is of some consequence. Because a substantial number of these studies derive from the globin family, they can not be said to be independent samples of phylogenetic history. To draw a morphological analogy, this is equivalent to basing a primate phylogeny strictly on dental characters, without attention to other aspects of the overall anatomy of the organisms under investigation.

Even so, advocates of the strepsirrhine/haplorhine division can take heart in at least two new studies that have sampled nuclear genetic characters outside of the globin family. Both studies found support for tarsier's placement with the Anthropoidea in Alu repeat data (Schmitz et al., 2001; Zietkiewicz et al., 1999). Alu repeats are the largest family of SINEs in the primate genome, with more than half a million copies dispersed throughout the genome. The Zietkiewicz et al. (1999) study employed a maximum likelihood approach to examine the phylogenetic relationships among Alu sequences taken from tarsier, human, lemur, sifaka, and galago. In all analyses, tarsier and human sequences form a

clade that excludes the strepsirrhines sampled by the study. This phylogenetic result was also substantiated by similarities in Alu RNA secondary structure in humans and tarsiers. The Schmitz et al. (2001) study reached a similar conclusion, though these authors were careful to point out that only three of the 118 Alu markers examined supported this relationship. This latter observation emphasizes the point that even if there is a unique evolutionary branch that unites tarsiers and anthropoids, it is short indeed.

### Genetic Studies Supporting Prosimii

Genetic support for one of the alternative arrangements, the prosimian/anthropoid division, has received much less impressive support from genetic data. Although there are two mtDNA studies that appear to provide robust support for tarsier's placement with lemurs and lorises (Hasegawa et al., 1990; Hayasaka et al., 1988), these two studies are based on a single data set, one that spans the ND3&4 region of the mitochondrial genome. Moreover, a subsequent investigation found that there was a taxon sampling bias in the Hasegawa et al. (1990) study that had a strong effect on the estimation of molecular evolutionary parameters (Yang and Yoder, 1999), raising the possibility that the phylogenetic results could be similarly biased. Thus, until very recently, proponents of a monophyletic Prosimii could find very little support in molecular phylogenetic studies.

This appeared to change rather dramatically with the publication of one of the most comprehensive molecular data sets to have ever been generated for the investigation of mammalian relationships (Murphy et al., 2001). This study of nearly 10,000 base pairs of nuclear and mitochondrial DNA, drawn from 15 independent genetic regions, for 64 placental mammals, reached the conclusion that "lemur (Strepsirhini) and tarsier (Tarsiiformes) were found to be sister taxa (bootstrap  $\geq$  80%) that were separated from anthropoids by a deep divergence." (p. 615). Given that this is one of the most extensive data sets ever to have been applied to the problem of tarsier affinities (albeit indirectly applied, in that this was not an original concern of the study), it momentarily appeared that the

problem had been solved. Subsequent analysis of this data set, however, has shown that there are a number of flaws in the study (Yoder and Huelsenbeck, 2001). Firstly, nearly 40% of the complete data set is missing for genus Tarsius, and secondly, there is an extreme taxon sampling bias in that only one strepsirrhine (genus Lemur) is represented. The authors of the subsequent study have thus re-examined the original data set in an effort to control for missing data, test for the effects of taxon sampling bias, and finally, to investigate the influence of various character partitions on the phylogenetic results. With regard to missing data effects, a combined data set for which all missing data were excluded was found to be supportive of the results of the original study. As before, a monophyletic Prosimii was recovered with strong statistical support. Alterations in the taxon sample were also found not to effect the original conclusions. When the data were analyzed by partition (coding nuclear versus non-coding nuclear versus mitochondrial), however, it was discovered that all three potential resolutions (Fig. 1) of tarsier affinities could be recovered, and each with strong statistical support. Clearly, this latter result casts doubt on the confidence that we might place in the conclusion of a monophyletic Prosimii. And, as a final blow to the perceived power of the original study, its authors have found by using likelihood ratio tests that the tarsier plus strepsirrhine topology can not be shown to be significantly preferred to alternative topologies (Murphy & Eizirik, pers. com.).

### **WHY CAN'T WE DECIDE?**

Situations of extreme phylogenetic uncertainty, such as seems to be the case with tarsier affinities, often relate to problems of short internal branches confounded by long external branches. In other words, it can happen that speciation and cladogenesis occur very rapidly and are then followed by a long period of independent evolution for the resulting lineages. To reconstruct these internal events is quite problematic for any data set, but most especially for molecular data due to the effects of saturation along internal branches and convergent evolution among terminal branches (Felsenstein, 1978; Huelsenbeck, 1997). This is almost certainly the situation faced at the deepest region of primate

phylogeny wherein the initial divergences among strepsirrhines, tarsiers, and anthropoids occurred (Figure 2). There are numerous genetic data sets that support the contention that the strepsirrhine-tarsier-anthropoid is a virtual trichotomy, with tarsiers being so derived as to be almost unresolvable as primates (Andrews et al., 1998; Dutrillaux and Rumpler, 1988; Hayasaka et al., 1993; Inoue-Murayama et al., 1998; Jaworski, 1995; Mai, 1985; Sarich and Cronin, 1976). It is possible that these events occurred in such a short geological period that the amount of data required to solve the problem may not be worth the effort and expense involved in generating the data. Given the debate in the systematics community over the relative advantages of large character samples versus large taxon samples (Graybeal, 1998; Hillis, 1996; Kim, 1996; Kim, 1998; Purvis and Quicke, 1997; Rannala et al., 1998; Yang and Goldman, 1997), it seems that the only way that the problem can ever be "resolved" will be to generate a character set on the order of the Murphy et al. (2001) study for a taxon sample that can be considered comprehensive for primates. Given the effort involved with such a study, many might ask if it is worth our while.

In examining Figure 2, many might ask "who cares what happened in such a short interval of primate evolutionary history?" I would argue that the issue is far from trivial. It is important not only for determining a phylogenetically-consistent classification for primates, but also for investigating the relationship between morphological evolution and temporal constraint. If we determine that tarsiers *do* share a unique evolutionary history with monkeys and apes, then we also know that many of the presumed haplorhine synapomorphies evolved within a remarkably short geological interval. If, on the other hand, an alternative topology is found to be more accurate, then the presumed synapomorphies instead become sympleisiomorphies or parallelisms, thereby altering our perception of the ancestral primate condition and/or the evolutionary pressures applied to the primate condition. Thus, as we continue to investigate tarsier's placement among the primates, we are actually holding a magnifying glass to that essential period of evolutionary history wherein the defining characteristics of the primate clade were being established.



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**Table 1 - Putative Haplorhine Synapomorphies**

| CHARACTERS  | PRIMARY REFERENCE(S)   |
|---|--|
| Dry, hairy rhinarium and fused lateral cleft fo nasal processes | Pocock (1918)  |
| Characteristics of intracranial blood supply                    | Szalay (1975); Rosenberger and Szalay (1980); Cartmill et al. (1981); MacPhee and Cartmil (1987) |
| Bony contributions to postorbital spetum                        | Pocock (1918); Hershkovitz (1974); Cartmill (1980)   |
| Patterns of craniogenesis                                       | Starck (1975)  |
| Mode of placentation  | Hubrecht (1897); Pocock (1918); Luckett (1974; 1975)   |
| Absence of tapetum lucidum                                      | Martin (1973)  |
| Presence of fovea centralis                                     | Wolin and Massoupust (1970)  |
| Reduced olfactory bulbs   | Rosenberger and Szalay (1980)  |
| Loss of subtympanic recess beneath the ectoympanic              | Cartmill et al. (1981)   |
| Anterior accessory chamber of auditory bulla                    | Cartmill and Kay (1978)  |
| Annular bridge of auditory bulla absent                         | MacPhee and Cartmill (1986)  |
| Apical interorbital septum                                      | Cave (1973)  |
| Loss of olfacotry recess  | Cave (1973)  |
| Delayed puberty   | Groves (1986); Shoshani et al. (1996)  |
| Separation of foramen rotundum and orbital fissure              | Shoshani et al. (1996)   |
| Sperm morphology  | Robson et al. (1997)   |
| Relative size of brain components                               | Joffe and Dunbar (1998)  |
| Retinal photoreceptor types                                     | Hendrickson et al. (2000)  |
|   |  |

## FIGURE LEGENDS

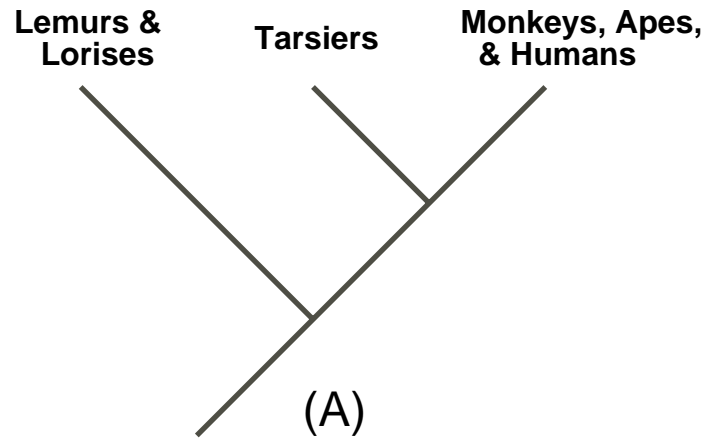
### Figure 1

Three alternative hypotheses of higher-level primate interrelationships.

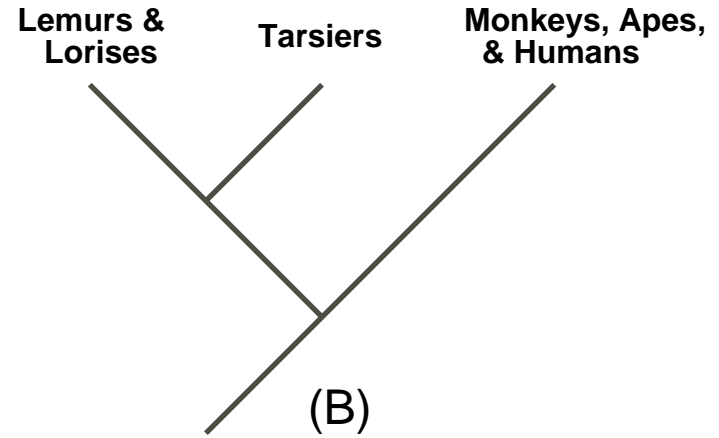
### Figure 2

Schematic diagram illustrating problem of short internal branches within deepest region of primate phylogeny.

## Strepsirrhini and Haplorhini



## Prosimii and Anthropoidea



## Tarsiiformes and Simiolemuriformes

