Letter to the Editor

The Rates of Nucleotide Substitution in the Human and Rodent Lineages: A Reply to Li and Wu¹

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Li and Wu (1986), in responding to my discussion (Easteal 1985) of their earlier paper (Wu and Li 1985), make some points that require further comment.

First, I suggested that the phylogenetic scheme assumed by Wu and Li in their relative-rate test was not firmly supported by the fossil record. Li and Wu argue that an alternative scheme, which I suggested, is at variance with the generally accepted view of eutherian evolution. They fail to point out, however, that there is great diversity of opinion about the branching order of the major eutherian lineages. Many of the schemes that have been proposed are reviewed by Szalay (1977), whose own analysis of the morphology of extant taxa suggests that the species are related in the order that I suggested (with the exception that he considers rabbits to be close relatives of rodents). It is worth noting that this scheme is in broad agreement with the pattern of conservation of linkage groups (Womack and Moll 1986) and with the comparison of the nucleotide sequences of mitochondrial genomes (Hasegawa et al. 1985).

Li and Wu contend that even if their assumed branching order is not correct, the potential errors in divergence times are too small to account for the differences in substitution rate. Divergence times, however, are no less subject to varied interpretation than are branching orders. Views have changed, theories are disputed, discussions are tempered by cautionary comments, and the data are few (Clemens et al. 1979; Kielan-Jaworowska et al. 1979; Szalay and Delson, 1979; Novacek, 1982).

Furthermore, the fossil record provides evidence only of morphological divergence, but phylogenetic divergence does not necessarily occur at the same time as morphological divergence (Wake et al. 1983). Even if the potential for error in estimates of the morphological divergence times were as small as Li and Wu suggest, this would not mean that the potential for error in phylogenetic divergence time estimates is also small. It is possible that the taxa being compared diverged from each other either more recently or at a much earlier time than has been supposed.

Second, Wu and Li's (1985) original analysis of paralogous genes is broadly consistent with a substitution-rate difference between human and mouse lineages. There are, however, some anomalies (Easteal 1985, table 2). I proposed a scheme, involving gene conversion, to explain these. The scheme requires the existence of a mouse globin gene more distantly related to the mouse E and F genes than are the mouse and human A genes. Li and Wu suggest that no such gene exists. They are correct that there is no known gene with a greater degree of nucleotide sequence difference but not that there is no more distantly related gene. There is evidence for such a gene—the Bh3 pseudogene.

Hutchison et al. (1984) have shown that the Bh3 gene is probably homologous to primate δ-globin genes and that it has been converted by mouse β-globin genes since the primate-rodent split. The δ-globin gene appears to have experienced similar exchanges with the adult β-globin gene in man and with an ε- or γ-globin gene in lemurs (Jeffreys et al. 1982). The ancestral δ-globin gene also appears to have diverged

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from the β-, ε-, and γ-globin genes well before the primate-rodent divergence (Martin et al. 1983; Hutchison et al. 1984). The mouse Bh3 globin pseudogene could therefore have converted the mouse E and F genes to be less like the human and mouse A genes before it was itself converted by the mouse A gene. It is not possible to know whether it did this since its original sequence no longer exists, but it is quite conceivable.

There appear to be three other ways of explaining the anomalies, none of which is entirely satisfactory. First, it is possible that only the mouse E and F genes are evolving faster than the human genes and that the mouse A gene is evolving at the same rate as the human genes. For this explanation to be valid it must be assumed that whatever is causing the difference between the two lineages can affect some genes but not others. It is unlikely that generation time or the efficiency of DNA repair systems, the possible causes suggested by Wu and Li (1985), could do this.

The second explanation is that gene conversion has occurred between human A and E and between human A and F genes. However, this provides an explanation of only some of the anomalous data. It does not explain how the difference between the mouse A and mouse E and F genes is the same as the difference between the human A and mouse E and F genes. The former difference is expected to be greater than the latter if no gene conversion is occurring in the mouse genes and if there is a rate difference between the lineages.

The third explanation is that the anomaly is due to stochastic error. Stochastic error might explain the difference between the human A–mouse E, F comparison and the mouse A–human E, F comparison; these are expected to be the same but are observed to be different. However it seems to be an unlikely explanation for the similarity among the (1) human A, mouse A–human E, F or (2) human A, mouse A–mouse E, F comparisons. Under the hypothesis of rate variation between the lineages, differences are expected within both of these sets of comparisons; but none is observed. It seems unlikely that in both sets of comparisons stochastic error has occurred to the degree and in the direction necessary to exactly cancel out the expected differences. Stochastic error tends to produce heterogeneity and not homogeneity among estimates; if the estimates were inaccurate because of stochastic error, we would expect them also to be different from each other.

Thus, of the four possible explanations for the heterogeneity of nucleotide differences between genes, one, stochastic error, is unconvincing and the remaining three require that at least the A gene has evolved at a constant rate in the two lineages. Under the scheme that I put forward, which is as plausible as the other three, all the genes could have evolved at a constant rate.

LITERATURE CITED


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