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Jian Lu, *et al.*
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Comment on “Chromosomal Speciation and Molecular Divergence—Accelerated Evolution in Rearranged Chromosomes”

Navarro and Barton (1, 2) proposed a very interesting model of speciation—based on the parapatric model (3)—that postulates a period of continuous gene flow between nascent species. During this period, adaptive mutations linked with chromosomal inversions may not be able to spread through the whole species’ range as readily as those in the colinear regions. The authors invoked a special kind of Hill-Robertson effect (4), which reduces the efficacy of positive selection when linkage is strong. Chromosomal inversion or rearrangement suppresses recombination and hence compromises the fitness advantage of adaptive mutations within the chromosome. The retardation permits different populations to evolve different adaptive systems that may be reproductively incompatible with each other.

A prediction of the model in (1) is that both neutral and adaptive divergence between closely related species should be higher on rearranged than on colinear chromosomes. By analyzing 115 genes from human and chimpanzee, Navarro and Barton reported

that the level of neutral divergence on rearranged chromosomes was slightly higher than that on colinear chromosomes. The most striking observation however, was that the extent of adaptive evolution on rearranged chromosomes, as measured by K_A/K_S ratio (5), was more than twice that on colinear chromosomes.

This conclusion is highly significant on several fronts. First, it suggests that continuous gene flow is not an impediment to speciation. This issue touches on the concept that reproductive isolation is required for speciation, which has been vigorously debated recently (6–16). Second, it postulates that many of the amino acid changes in the apes may be adaptive. While this postulate has been suggested (17), the analysis of Navarro and Barton takes the suggestion a step further by implying that the changes may in fact be differentially adapted between the incipient humans and chimpanzees. Differential adaptation is probably where the Darwinian view of speciation and the neo-Darwinian interpretation diverge the most (6).

To address this fundamental issue, it is imperative to have a negative control. As noted above, the key observation in (1) was that the K_A/K_S ratio for human-chimpanzee genes was twice as high in the rearranged regions than in the colinear regions. Before attributing the higher ratio to parapatric speciation however, it is necessary to rule out the possibility that the rearranged regions studied happened to contain a larger number of rapidly evolving genes than the colinear regions. For this purpose, we compared the human genes studied in (1) with genes from Old World monkeys, which diverged from human-chimpanzee about 35 million years ago, or with genes from gibbon or orangutan, which diverged from human-chimpanzee more than 12 million years ago. Between these more distantly related species, changes that accrued to the K_A/K_S value during the human-chimpanzee parapatric speciation should be diminished in proportion to the total divergence. The average K_A/K_S values for the two sets of genes studied in (1) are shown. The value (1.61) is indeed higher for genes on the rearranged chromosomes, but is lower than the reported 2.2 (1) because some genes were excluded in our comparison and because of a minor difference in how average K_A/K_S was calculated. The important point is that the average ratio for rearranged versus colinear chromosomes (R/C) is greater than 1, and thus confirms the results in (1). However, when the comparison is made between human and an outgroup species, the R/C ratio is still as high as that between human and chimpanzee. Therefore, the observation of $R/C > 1$ reported in (1) may be largely explained by a bias in the distribution of rapidly evolving genes among chromosomes. Genes on some chromosomal regions may happen to be more rapidly evolving than on others. Indeed, some of the genes on the rearranged chromosomes—such as those encoding glycoporphins (18, 19) and protamines (20)—are known for their rapid evolution among higher primates, not just African apes. This uneven distribution is not associated with chromosome rearrangements that occurred in the last 6 million years. In addition, the R/C ratio for K_S is not greater than 1 between human and chimpanzee when all genes are combined.

We wish to emphasize that this comment does not contradict the elegant model of parapatric speciation driven by differential adaptation (2). Our main point is that the evidence reported in (1) has a simpler explanation not connected to speciation. Finding evidence for or against the model in (2), or parapatric models of speciation in general (21), remains a fascinating but elusive goal.

Table 1. Comparison of K_S and K_A values between human, chimpanzee, and outgroup species. Gene numbers are given in parentheses. The K_S and K_A values were computed by the method in (5), as implemented in the GCG software package (version 10.3). Sequences of 109 nonredundant coding genes used in (1) for human and chimpanzee were downloaded from NCBI. Genes for glycoporphin A and protamine 1 were excluded because they are known to be rapidly evolving in all higher primates (see text). Eighty-five outgroup sequences were found, 64 from an Old World monkey, and 21 from either orangutan or gibbon. In computing average K_A/K_S , comparisons in which $K_S = 0$ were computed using the smallest nonzero value (0.002 for human-chimpanzee and for human-outgroup) in place of K_S .

Divergence measures	Chromosomes		R/C
	Rearranged (R)	Colinear (C)	
<i>Full data set (109 genes)</i>			
Human-Chimpanzee			
K_A/K_S	0.780 (54)	0.483 (55)	1.61
K_A	0.007 (54)	0.005 (55)	1.40
K_S	0.016 (54)	0.017 (55)	0.94
<i>Overlapping data set (85 genes)</i>			
Human-Chimpanzee			
K_A/K_S	0.820 (42)	0.581 (43)	1.41
K_A	0.007 (42)	0.006 (43)	1.16
K_S	0.016 (42)	0.014 (43)	1.14
Human-Outgroup (mean)			
K_A/K_S	0.623 (42)	0.443 (43)	1.41
K_A	0.031 (42)	0.024 (43)	1.30
K_S	0.061 (42)	0.059 (43)	1.03

TECHNICAL COMMENT

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