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Dear Gabby:

First of all, let me say that I thought Lewin, who tends to be contentious, did a reasonably fair job on molecular drive. He did, as you said, get the definition more or less straight and he summarized some of the data in support. Second, from your point of view, widespread discussion of your proposals should be seen as very constructive. When one proposes a "big" idea, one should expect a "big" response. But the discussion inherent in the response is a critical and desirable testing ground. So far I think molecular drive is standing up well. For my own part, I am unable to add to the discussion of speciation since I am simply too ignorant on the whole subject.

Now, with regard to the "universal phenomenon" problem. The quote is somewhat ambiguous. Molecular drive may be universal in the sense that it goes on in all species and in many genes. On the other hand, there may be some genes that are "protected" from drive either by molecular mechanisms or by selective pressure.... could that be what was meant by not being universal? I don't think it helps you at all to insist on absolute universality. Everything we know about biology tells us that rules are there to be broken. Look at the genetic code in mitochondria.

Regarding your specific questions to me, the following. We have published the sequences of two monkey Alus (see attached). They differ as much from one another as they do from the known human Alus and the various human Alus differ from one another to the same extent. Therefore, while the massive differences between the rodent and primate Alus are clear, there is no information regarding interspecies differences for Alu within old world primates. Schmid has done some work on comparative structure of primate Alus which suggests that the sort of interspecies differences you are looking for might indeed exist (reference: Houck and Schmid, J. Mol. Evol. 17, 148-155, 1981) Regarding the old world primates however, the relevant data are simply not available. Because of the nature of the Alu sequences, it is impossible to look at the class as a whole.....neat restriction cuts do not exist. And as you have pointed out in your letter, whole family analysis is what is needed. Regarding Alu I add one more point. Recent information shows clearly that there are subclasses of Alu sequences within each species. First, there are the genes for 7S RNA (Nelli and coworkers).

These are Alu "monomer" units broken by an insertion of about 150 base pairs of sequence unrelated to Alu. The segment is highly conserved since the rodent and human 7S RNAs (the gene products) are essentially identical. Thus, while some Alus are homogenized within a species, the 7S genes appear immune. The conservation fits with the recently reported critical function of 7S RNA (paper by Blobel in recent Nature). Second, Jeff Saffer in my lab recently sequenced an odd-ball monkey Alu (actually, it is the sequence I referred to as LS-2 in my talk in July). It hybridizes only very weakly with a cloned Alu probe and in the regions of homology diverges more than 20 percent from human Alu consensus. In two regions it is not at all homologous to typical Alus. The poly A stretch at the end of the first monomer is replaced by alternating ACs and the end of the second monomer, just before the poly A stretch, is completely different. Jeff also recognized that the AC alternating stretch just described by Hamada et al. (PNAS 79, 6455), in human DNA is flanked on one side by what are clearly Alu sequences. Therefore, this type of Alu may well represent a new class.

Finally to get to the most important point. The Kpn family in primates is emerging as quite comparable to MIF. Enclosed is a paper by Giovanna Grimaldi and myself which includes the critical information. The paper is submitted to Nucleic Acids Research but we have not yet heard if it is accepted. So that you don't have to wade through what is less interesting to you, I have marked the relevant discussions and data. In short, the restriction analysis clearly says that different subfamilies have different frequencies in monkeys compared to humans. The abundant 1.9 kbp HindIII fragment of humans is the one Laura Manuelidis sequenced; in monkeys it is minor, the major band being the homologous 2.5 kbp HindIII segment. So while the question of rate remains unanswerable regarding Alu, there is already a partial answer for the Kpn. You will also find relevant information in Joe Maio's work, Nucleic Acids Res. 10, 3175, 1982.

One more point, Giovanna and I point out in the paper that our data includes a very tentative hint that the rates of homogenization may differ at different points within the typical Kpn family member segments. Do you have anything comparable for MIF?

Very best regards,

Sincerely,

Maxine Singer

Encl.