Why Do Inbred Mice Evolve So Quickly?

There is enormous interest these days in testing the efficacy of putative molecular clocks, part of which exercise includes determining which is the most appropriate and reliable method for analyzing the raw data. It was this latter aspect of the controversy that Walter M. Fitch and William R. Atchley of the University of Wisconsin recently embarked upon. And what better database to use than a selection of inbred mice strains, whose genetic profiles and evolutionary history are known in a degree of detail unparalleled in the rest of the animal world.

In applying five different methods of estimating phylogeny to ten different inbred mice strains Fitch and Atchley found themselves faced with two surprises. First, all five methods produced virtually the same trees with very similar weightings, a rare occurrence in the business of molecular phylogeny. This meant that although the mouse genetic data were clearly robust in reflecting the history of these strains, they were of no use in discriminating between the senstivity of the different analytical methods. The second surprise was the very large degree of genetic divergence revealed between the different, though very closely related, strains. The disparity is so large, say Fitch and Atchley, that it cannot be explained by conventional ideas of population genetics. So far they have been unable to come up with a convincing alternative explanation, and they set out their data and questions about them on page 1169 of this issue in the hope that others might have better luck. Although some observers express skepticism that the data might be illusory, because of potential problems with historical records of some of the inbred lines, this challenge is certain to stir some strong reactions.

The Wisconsin researchers are not the first to notice a high rate of divergence among inbred mice. For instance, rapid change of jaw shape and other morphological characters have been documented over very short periods of time in some strains. There has remained the possibility in these cases that the large morphological shift is the consequence of the sum of very small changes in many different genes. What Fitch and Atchley's data appear to show, by contrast, is a rapid and substantial change at single gene loci.

Typical genetic diversity among mammalian populations is 9 percent, which means that nine out of every 100 gene loci are occupied by different variants or alleles. Data from 97 loci in the ten strains studied by Fitch and Atchley indicate that heterozygosity in the strains' ancestral population from which they derived some 150 years ago was close to this level. The process of producing an inbred strain involves mating from a sibling pair through 20 or more generations, which effectively removes any heterozygosity within the descendants: any individual from such a homozygous population in effect represents a random gamete from the ancestral population. If no genetic change had occurred between the ancestral stock and the ultimate inbred strains, heterozygosity across the strains would be very similar to the original figure, 9 percent. In fact, an artificial population derived from the ten strains Fitch and Atchley examined would have a heterozygosity of 33 percent, a figure that would be considerably boosted if a couple of pairwise comparisons between very closely related strains were not included in the calculation.

Four possible explanations of a high heterozygosity across modern populations immediately suggest themselves: a simple, random segregation of alleles present in the original population; a degree of residual heterozygosity in the inbred lines; unrecorded contamination of the lines from other strains; the fixation of new mutants. Fitch and Atchley dismiss the first, because of the relatively low initial heterozygosity. Residual heterozygosity is demonstrably low in these strains (less than 2 percent), and so the second explanation falls.

The third possibility, that of outside contamination, is an oft-cited anodyne, and with good reason: there are several well-documented cases of the unplanned intrusion of outsider's genes into otherwise pure inbred lines. A long list of reasons argues against contamination as the source of heterozygosity among the ten strains examined here, however, not least of which is the very robust phylogenetic pattern revealed by the group of analytical techniques applied to them at the inception of this study. Contamination is simply too facile and weak an explanation to retreat to.

All of which leaves the rapid fixation of new mutations. Certainly, the degree of genetic divergence between the strains implies a fixation rate of variants per locus per year of 1.4×10^{-3}, which is several orders of magnitude higher than in natural populations. The problem with this attractive idea is that there is simply no direct evidence for an elevated mutation rate in inbred strains as Franklin M. Johnson of the National Institute of Environmental Health Science, North Carolina, has demonstrated. Also, commercial breeders only rarely see mutants. Coupled with this is the observation that the great majority of loci have only two variants, which might be interpreted as the retention of the ancestral heterogeneity. However, the very high heterogeneity across modern populations argues against this. What appears to have happened is that, although the selection of alleles present in the modern populations is very similar to, if not identical with, that of the ancestral stock, the distribution of alleles among the inbred strains appears to be nonsimple and nonrandom. The question is, how did this occur?

One possibility is that in developing the original strains breeders unconsciously selected highly heterozygous pairs for the beginning of mating. For such artificial selection to apply so consistently among the different lines tests credulity, and in any case it cannot explain the differences between some of the very closely related lines that were derived from an established inbred group, such as DBA/1 and DBA/2. Another idea adduces genetic mechanisms that can select between two possibilities, such as gene conversion and gene switching. This would reconcile apparently high mutation rates with the existence of pairs of alleles for most loci. Alas, this is not supported by evidence either.

Whatever the mechanism, it will be of interest in the context of origin of species, specifically the rate at which such events might occur. Few would wish to extrapolate without restraint between the highly artificial breeding of an inbred strain and conditions that apply in nature, but the greatly accelerated rate of the fixation of variants in what is effectively a small, isolated population bears taking note, especially as it is in the apparent absence of selection.

—ROGER LEWIN