Molecular Drive: How Real, How Important?

A British geneticist has proposed a process by which a population might undergo cohesive genetic change not predicted by classical theory

For more than a year now Gabriel Dover of the University of Cambridge, England, has been enthusiastically promoting a concept he terms molecular drive. Dover argues that the phenomenon explains certain unusual characteristics of multigene families. And, if his speculations prove to be correct, molecular drive might be the basis of an unpredicted mode of speciation.

With the flirtation between molecular biology and evolutionary biology now well advanced, Dover's exposition of molecular drive and its consequences appears to offer grounds for finally consummating the relationship. This, at least, is the inference that is certain to be drawn by many from Dover's latest disquisition of his controversial thesis.*

Some commentators argue, however, that consummation is premature, that molecular drive, although a new and interesting concept in some respects, does not provide evolutionary biologists, dazzled by the wizardry of molecular biology, with the link they imagine it does. Part of the seductiveness of molecular drive and all that Dover claims for it undoubtedly derives from its combination of much that is new and impressive in molecular biology with much that is controversial and current in evolutionary biology, such as punctuated equilibrium and speciation.

Molecular drive, says Dover, is "a possible genetic mechanism for the origin of evolutionary novelty that is operationally different from those of natural selection and genetic drift." There are two key features to molecular drive that differentiate it from selection and drift. First, fixation of new genetic variants is under the influence of internal forces, the underlying mechanisms of molecular drive itself. And second, contrary to conventional models of genetic changes in populations in which the progeny of one genotype thrives at the expense of another, the outcome of molecular drive is that a population changes in unison, not through the differential survival of a subsection of it.

All eukaryotic genomes contain what appears to be an excessive amount of DNA; that is, they are composed of more sequences than are required for encoding proteins. Some of the excess sequences undoubtedly have a role in regulating gene expression, some make up the intervening sequences that split the coding sequences of genes, but most appear to be composed of multiple families of repeated sequences. So far no function has been firmly attributed to any of these families, although various hypotheses implicate them in regulation of gene expression and in chromosome architecture.

In addition to these enigmatic nongenic repeated sequences, the genome contains families of repeated genes, such as those for ribosomal RNA, transfer RNA, globins, histones, immunoglobulins, proteins of the major histocompatibility complex, actins, and, no doubt, many more. It is to both genic and nongenic families of repeat sequences that molecular drive applies.

One curious feature of repeated sequences requires explanation. Generally speaking, individual members of a family of repeated sequences show a greater similarity within a species than between related species. Variation accumulates between species, yet individual members within a species are not evolving independently, a pattern that has come to be known as concerted evolution.

Homogenization occurs, apparently, through a constant turnover of repeated sequences produced by one or more of three mechanisms—unequal crossing over, transposition, and gene conversion. "These mechanisms, which can be either random or biased in activity, provide the driving force of a cohesive genetic change in a population." says Dover. This is molecular drive.

Unequal crossing over affects tandem arrays of repeats and occurs principally when homologous chromosomes pair during meiosis. Nonreciprocal crossing over, through slippage in the pairing, results in expansion and contraction in copy number in the repeat family. With sequence variants arising from time to time, "the process may lead to stochastic fixation of one or another variant member throughout the array and throughout the population."

The most striking example of transposition is of course the transposable element, a sequence usually several thousand base pairs in length and comprising shorter stretches of base pairs that facilitate its insertion and excision from the genome. While unequal crossing over affects arrays principally on homologous chromosomes, transposition clearly results in the transfer of sequences between nonhomologous chromosomes. And those sequences which can combine sequence duplication with transposition can effect interchromosomal infection more readily. Duplicative transposition is very likely to be important in the explosive increase in copy number that is frequently observed between species.

Gene conversion is the most contentious of the three mechanisms, and, when it includes a bias in the direction of change, the most powerful. Similar sequences on homologous or nonhomologous chromosomes may occasionally pair up, and any mismatch in sequences between them is eliminated. With alleles A and a, random repairing will generally lead to parity in the frequencies of A + A and a + a. "Nevertheless," says Dover, "random fluctuations in the frequencies of the direction of conversion (Aa → aa versus Aa → AA) may lead to the accidental fixation of one variant or another throughout a family and eventually throughout a population."

Dictated by the chemical and physical characteristics of the sequences involved, gene conversion can apparently be biased favoring one variant over another. Although biased conversion has so far been experimentally demonstrated only in certain fungi, its operation in higher organisms is clearly possible.

In his *Nature* paper Dover describes variations in genes for ribosomal RNA, histones, and two nongenic repeat families between seven sibling species of *Drosophila*. The comparison apparently reveals the operation of unequal exchange and gene conversion, with different rates of fixation of variants between different types of sequences. A second comparison involves the fixation of species-diagnostic variants in a family of 40,000 repeated sequences distributed, among 40 chromosomes, the MIF-1 fam-

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ily, in several mouse species. Assuming one conversion per generation and no bias in conversion, the time needed for fixation of the variants in the species would be 10^8 years, which is about two orders of magnitude longer than the species diverged, according to the fossil record. A bias of 1.2 in conversion would reduce fixation time to 10^6 years, the same as indicated by the fossil record.

Acceleration of fixation of a variant is an important aspect of molecular drive, but more profound is its effect on the pattern of inheritance of variants. With traditional Mendelian segregation, an allele possessed by only one parent will be passed on to just half of the progeny. The variant will increase in frequency in the population only if those progeny carrying the variant are reproductively more successful than those without it. Because molecular drive may carry a variant from its chromosome of origin to chromosomes derived from the other parent, Mendelian inheritance no longer applies. Molecular drive will propel a new variant through a population in a cohesive manner, even if it confers no reproductive or other advantage.

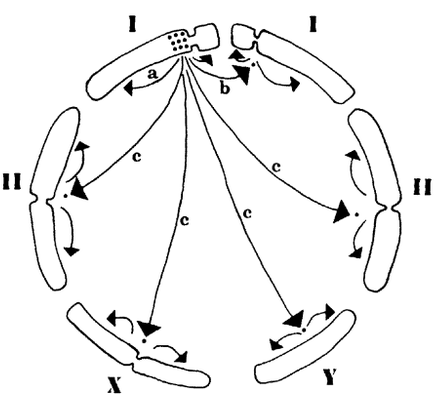
The process of cohesive spread is mediated by the fact that in a sexually reproducing population there is, over a very long period of time, a mixing of chromosomes effectively as a single gene pool due to random meiotic assortment and genetic fusion. The combination of chromosome turnover in a population and a relatively slow fixation of a new variant through the chromosomes means that at any moment during the fixation process "there is in each individual the same average ratio of new and old variants for a particular family," explains Dover. This is a crucial genetic aspect of the consequence of molecular drive because it means that, if the new variant has a phenotypic effect, selection will not favor or discriminate between individuals because they are all more or less equivalent; the genetic variance in a population is kept low. The population evolves as a unit and it begins to become genetically distinct from other populations of the same species with which it does not have reproductive contact.

Having navigated the idea of drive from nonconventional fixation of variants, to an unexpected pattern of genetic change, Dover takes the final and most speculative leap, to a new mode of speciation, accidental speciation. He suggests that speciation might result from the above described cohesive population change, if, for instance, the repeat family involved in some way affects development, or if it affects the chromosomes so that viable hybrids with members of other populations cannot form.

"Molecular drive is not an alternative to the evolutionary processes of natural selection and genetic drift," asserts Dover. "It constitutes a third mode of evolution that would be subject to selection and genetic drift in an interesting variety of real biological situations."

The concept of molecular drive has caught the imagination of many people. "It might explain the sequence data that are not explained in other ways," suggests Thomas Petes of the University of Chicago. "It's good and new," comments Robert Selander of the University of Rochester. "It was unanticipated."

There are voices of caution too. For instance, Ford Doolittle of Dalhousie University, Halifax, Nova Scotia, considers it unwise to lump unequal crossing over, transposition, and gene conversion under a single umbrella term. "They are different processes with different consequences," he notes. And Alec Jeffreys of the University of Leicester, England, is uneasy with the way the term molecular drive has become a "catch-all for anything that changes in the genome."



Molecular drive

A sequence variant might move (a) intrachromosomally, (b) to homologous chromosomes, and (c) to nonhomologous chromosomes. The variant is driven through the array and consequently through the population.

There's no doubt that concerted evolution is real and that, in general, families of repeated sequences are to some degree homogenized. But there is also no doubt that it is not a universal phenomenon. Jeffreys notes that the globin clusters should be candidates for homogenization but that they appear to be relatively immune to it. He also says that the Alu family of repeats in humans has more variation between sequences than one might expect, even though there are distinct family differences when compared with other species. Jeffreys is not saying that such problems discredit the idea of drive, but he does suggest that it might be more complex than has so far been appreciated. "The idea is worth kicking about, but it is far from proven."

The question of speciation through molecular drive is even more speculative than the process itself, a point Dover accepts. Evidence in favor of speciation through alteration of chromosome structure, for instance, is at best equivocal. Richard Flavell of the Plant Breeding Institute, Cambridge, England, has shown the apparent association of changes in repeat families with speciation in certain cereal plants. "But," he comments, "we cannot say whether the change is the cause or the consequence of speciation." Moreover, there is a good deal of evidence indicating that extensive changes in repeat families can be tolerated in viable hybrids.

It is perfectly possible, even likely, that shifts in certain families of repeated sequences might influence embryological development. But, again, the link cited by Dover has yet to be established experimentally.

Dover does not claim that molecular drive accounts for all or even most speciation events, but some people feel that in his enthusiastic promulgation of the idea he might be overstating its importance. "Gabriel knows that there are cases in which species are separated by their behavior or geography rather than their ability to form viable hybrids," says John Maynard Smith, a population geneticist at the University of Sussex, England. "There will probably be cases of what he describes, but he pays insufficient attention to known mechanisms." Dover counters by saying that, by its nature, all discussion of mechanisms of speciation are speculative to a degree.

There are those who consider the issue of speciation to be so important, and the potential contribution of molecular biology so great, that ideas should be advanced here only with the greatest of caution. Doolittle, for instance, judges the connection between the molecular changes associated with drive and speciation to be so uncertain, and so in need of experimental tests, that to promote the suggestion so vigorously now might be counterproductive. Selander agrees. "The idea of drive, he's nailed right. But the claims for speciation are unnecessary and unhelpful."

Contrariwise, Flavell and Walter Fitch of the University of Wisconsin argue that without speculation scientific ideas never get anywhere. The consensus is perhaps expressed best by Arnheim who says: "This is the germ of an interesting idea. Now let's see it documented with great vigor."—ROGER LEWIN