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Transposon-Induced Hotspots for Genomic Instability

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Although the potential of transposable elements (TEs) to produce genomic rearrangements, such as inversions and translocations, has been appreciated for some time from the results of laboratory experiments, estimates of the frequency and evolutionary importance of such events in natural populations have been difficult to come by. Now, with the ability to obtain nucleotide sequence data on a large scale, we are starting to learn about the nature and frequency of TE-induced changes in the structure of their host genomes. Not only is direct evidence being provided to support predictions that TEs can initiate chromosomal rearrangements by ectopic recombination and other mechanisms, but surprising examples of massive local genomic instability are being reported that were not predicted by earlier models of TE behavior. In this issue, a remarkable example of an unprecedented degree of genome restructuring is reported in a study of the breakpoints of a TE-induced inversion in *Drosophila buzzatii* (Caceres et al. 2001).

Genomic Rearrangements are Abundant in *Drosophila*

The unusually rich inversion polymorphism seen in many species of the *Drosophila* genus provides fertile ground for study of the mechanisms involved in generating genomic rearrangements. The rate of chromosomal reshuffling in *Drosophila* appears to be higher than that of any other animal or plant taxon that has been studied similarly (Ranz et al. 2001). *D. buzzatii* is a cactophylic species associated with host plants of the *Opuntia* genus. The species originated in Argentina and is distributed widely in South America. Recently this species colonized the Mediterranean region of the Old World and Australia. Chromosome 2 of *D. buzzatii* is polymorphic for two major structural configurations that are found throughout the species range. The standard ancestral configuration, *2st*, has a gene order consistent with that of other closely related species. The second form, *2j*, was derived from the standard form and contains an inversion of a centrally located segment that represents approximately one-third of the euchromatic fraction of that chromosome. In earlier work with the *D. buzzatii* system, Caceres et al. (1999) elegantly implicated ectopic recombination between two members of a foldback (FB) transposable element family, named *Galileo*, as the mechanism of induction of the *2j* inversion. They not only showed the presence of the two *Galileo* elements at the inversion breakpoints (BPs), but also identified small direct duplications of host DNA (the signatures left by a TE insertion) which provided direct proof of inversion induction by the *Galileo* elements. Now, in a followup study, they report a detailed molecular analysis of a 7.1-kb stretch of DNA surrounding the inversion BPs in multiple lines of flies sampled from natural populations throughout the species range. Such a detailed analysis allowed a reconstruction of the evolutionary sequence of events that occurred in these regions.

Massive Reshuffling in a Short Period of Evolutionary Time

The results of this study are remarkable in two ways. They demonstrate, first, the unprecedented frequency and complexity of molecular rearrangements in the relatively short chromosomal regions surrounding the inversion breakpoints and, second, the remarkable rapidity of these changes on an evolutionary timescale. The rearrangements identified in 30 *2j* chromosomes included 22 insertions of 10 TEs, 13 deletions, one duplication, and an internal inversion. The frequency of insertions (per kb per chromosome) was at least two orders of magnitude higher than those observed in earlier studies of euchromatic regions of *D. melanogaster* and other *Drosophila* species. Furthermore, the use of multiple lines of flies from natural populations by Caceres et al. (2001) allowed detailed characterization of the complex molecular events that occurred in the hotspot regions.

The average rate of nucleotide substitution of unique DNA sequences immediately adjacent to the inversion BPs was found to be significantly lower in the inverted *2j* chromosomes compared with that for the *2st* chromosomes. On this basis, the observed changes in the *2j* chromosome were estimated to have taken place in <84,000 years. This contrasts with 485,000 years that was estimated as the age of the *2st* chromosomes. The rapidity of reshuffling in the *2j* breakpoint regions is even faster than that reported for the *adh1* region of maize, in which an intergenic region more than doubled in size, mainly during the last three million years, due to the activity of retrotransposons (SanMiguel et al. 1998).

What is the Mechanism of Hotspot Induction?

The absence of insertions and structural rearrangements in the homologous regions of the uninverted (*2st*) chromosome, in the *D. buzzatii* study, possibly implicates the inversion as the most likely explanation for the rearrangement hotspots. Although it is expected that TEs will accumulate around inversion BPs because of the protection afforded by the reduction of recombination in these regions (Montgomery et al. 1987), a number of observations suggest that other factors are also involved. These include: (1) the restriction of rearrangements to a very short region around the BPs, (2) the absence of retrotransposons, the most common type of *Drosophila* TE, in the hotspot regions, (3) the absence of insertions in homologous regions of uninverted chromosomes, and (4) the presence of deletions and other rearrangements in the hotspot regions, in addition to the insertions. The authors favor an alternative hypothesis for hot spot induction, namely the presence of the initial insertions of *Galileo*. Members of the FB TE family are known to be associated with unstable mutations and chromosomal rearrangements, as well as insertions nested within one another (SanMiguel et al. 1996).

A predominant feature of the region under discussion is the frequent nesting of new TE insertions within earlier insertions. This is reminiscent of the behavior of LTR retrotransposons that are found most frequently in methylated, presumably locally heterochromatic regions of the *adh* region of the maize genome, often in nested clusters (SanMiguel et al. 1996). Accumulation in nested clusters is also observed in the telomeric regions of some species, for example, the silkworm *Bombyx mori* (Takahashi et al. 1997)

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and the green alga *Chlorella vulgaris* (Higashiyama et al. 1997), and in nested regions elsewhere in the genome, sometimes referred to as TE "landing pads" in yeast (Kim et al. 1998).

Hotspot Insertion Profiles do Not Represent *Drosophila* TE Diversity

Of particular interest is the observation that the TEs identified in the hotspot regions adjacent to the inversion BPs are far from being representative of the diversity of *Drosophila* elements. Class II elements that transpose using a DNA intermediate are overwhelmingly represented in the identified insertions. These include the newly discovered families of *FB* elements (*Galileo*, *Kepler* and *Newton*) and representatives of the *hAT* (*hobo*, *Activator*, *Tam*) superfamily of elements. The abundance of *FB* elements provides some explanation for the present observations because of the known high level of instability and recombinogenic properties of these elements (Hoffman-Liebermann et al. 1985).

Interestingly, no representatives of the Class I retroelements were identified clearly in the sampled region. This is surprising given the abundance of these elements in *Drosophila* genomes. However, *ISBu-1*, one of the elements newly discovered in this study, has subsequently been identified as a member of a novel class of abundant Dipteran mobile elements named *mini-me* (Wilder and Hollocher 2001). These elements appear to represent a new subclass of retroposons that have the potential to provide a prolific source of microsatellite variation in many *Drosophila* species. In fact, the presence of the *ISBu-1* insertion in the *D. buzzatii 2j* chromosome was cited as a prime example of the recent mobility of some members of this new subclass of TEs (Wilder and Hollocher 2001).

Remaining Questions

How are we to assess the overall evolutionary significance of these results in *D. buzzatii*? Are the *D. buzzatii* results an interesting, but rare, anomaly? This species belongs to the *D. repleta* group of the *Drosophila* subgenus. The second chromosome of *repleta* group species is homologous to the *3R* chromosome of *D. melanogaster*. The latter species is a member of the subgenus *Sophophora* which diverged from the *Drosophila* subgenus 40–62 million years ago. So far, no reports of any genomic regions exhibiting rapid evolution comparable to those now reported in *D. buzzatii* have been made following the sequencing of the genome of *D. melanogaster* (Adams et al. 2000) With the rapid appearance of new sequence data predicted in the near future, intra- and inter-specific genomic comparisons combined with enhanced tools for finding novel repetitive DNA, we should soon start to have some of the answers to these and related questions.

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