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NEWS AND COMMENTARY

Chromosomal evolution

Inversions: the chicken or the egg?

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Over the last century, we have learned much about the mechanisms underlying mutation by studying changes that accumulate in DNA sequences. But, what about changes that occur to the chromosomes in which DNA is packed? Since the 1930s, it has been well known that chromosomes undergo enormous structural changes with consequences more dramatic than those of simple point-mutations or small insertions and deletions. Paradoxically, the molecular mechanisms underlying chromosome evolution are still largely unknown.

A recent paper by Ranz *et al*. (2007) sheds new light on this issue by using *Drosophila* data to challenge the current consensus. The most widely accepted ideas on the mechanism that generates chromosomal rearrangements arise from the fact that duplicated and/or repetitive DNA fragments are often associated with their breakpoints. This is the case in many *Drosophila* lineages, where transposable elements (TEs) have been found in inversion breakpoints. In humans and mice too, segmental duplications and rearrangements co-occur more frequently than would be expected under a random breakage model. These facts immediately suggest a mechanism for the origin of rearrangements. It is called ectopic recombination, also known as illegitimate recombination or non-allelic homologous recombination. This type of recombination uses the same cellular machinery as meiotic recombination, but takes place among non-homologous sites at different loci. If these sequences are located on the same chromosome and in inverted orientation, the consequence of recombination is a chromosomal inversion (Figure 1) (Finnegan, 1989).

These ideas have led to many studies, most of which use *Drosophila* as a model organism, not only because of the usual historical reasons—easy management, well-known phylogenies and so on—but also because a large number of species-specific and polymorphic inversions have been catalogued. Cloning and sequencing of the breakpoint regions of different rearrangements from *Drosophila* and other diptera has been revealing. To date, in four of ten analyses, strong evidence implicating TEs was found. In two other analyses, the presence of TEs was also described at the breakpoints, whereas the other four studies showed no trace of TEs. Besides TEs, other repetitive sequences have also been described at the breakpoints of chromosomal rearrangements.

Just as the original evidence favouring ectopic recombination came from *Drosophila*, Ranz *et al*. (2007) combine experimental data and computational studies based on that genus to propose an alternative mechanism. They analyse the sequence at the breakpoints of 29 fixed inversions in different species in the *melanogaster* group. The main results of their detailed analyses are: firstly, in 18 out of 29 cases, duplications of non-repetitive elements are present in opposite orientations at the inversion breakpoints. Crucially, the duplications appear only in one species, the one carrying the rearrangement; secondly, for the remaining inversions, only sequences from one of the breakpoints appear to be duplicated, which is incompatible with the ectopic recombination model.

The most parsimonious, although not the only, explanation to these observations is that inversions have arisen by a mechanism other than ectopic recombination. In this new model, the duplications at the breakpoints are not the cause, but rather the consequence of some of the inversion events. Following the production of two staggered breaks at different locations of the same

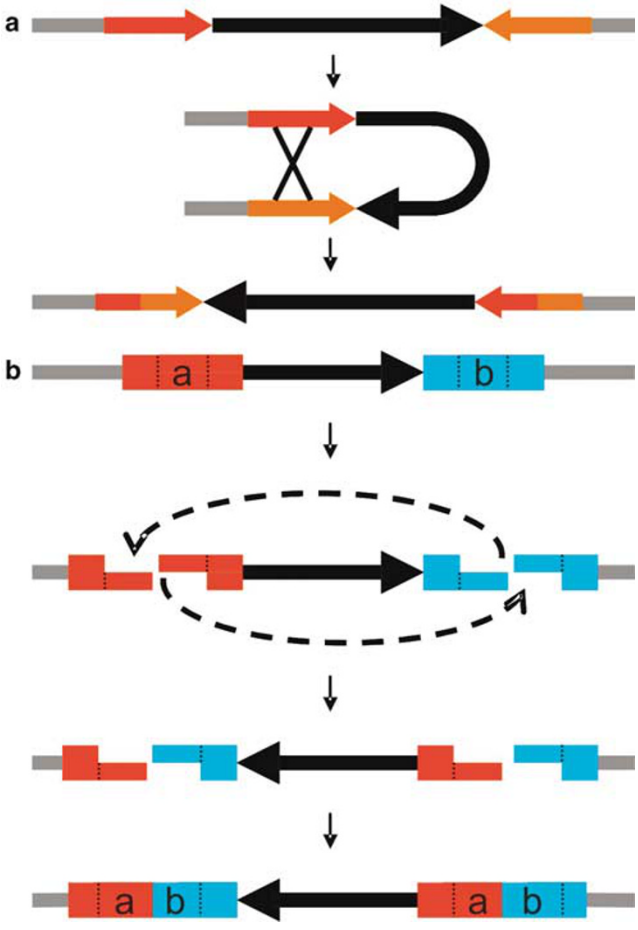

Figure 1 Alternative models to explain the origin of chromosomal inversions. (**a**) Ectopic recombination model. (**b**) Staggered breaks model. The inverted segment is represented by a black arrow. Red and orange arrows in panel a represent repetitive sequences (for example, a transposable element) and their orientation. Red and blue rectangles in panel b represent two non-homologous regions at the same chromosome.

chromosome, the repair mechanism does not rejoin 5′ ends to their own 3′, but to the 3′ end of the other breakpoint. Afterwards, the remaining gaps are filled up, and inverted duplications originate from both ends of the inversion (Figure 1). Depending on the length of the staggered regions, duplicated sequences from one or both of the breakpoints would be detected.

These results challenge the idea of ectopic recombination as the only major cause of chromosomal rearrangements. However, unequivocal evidence favouring the ectopic recombination model in Diptera has been described for four inversions which are polymorphic, and therefore presumably younger, particularly in cases where two complementary fragments of a TE are found at the two breakpoints of an inversion (Caceres *et al*., 1999; Casals *et al*., 2003; Richards *et al*., 2005; Sharakhov *et al*., 2006). It seems clear that different rearrangements have originated in different ways. Indeed, different major mechanisms might act in different lineages, even within the *Drosophila* genus. For example, although several examples have been reported supporting the ectopic recombination model in fungi, invertebrates and, to a lesser extent, in plants, its role remains unclear in vertebrates (Coghlan *et al*., 2005).

The mere presence of a TE at a breakpoint should not be taken as evidence of its role in the generation of the rearrangement, since they are abundant and may act as secondary invaders. In fact, the expected decrease of recombination at the breakpoints of inversion heterokaryotypes (Navarro *et al*., 1997) would favour the accumulation of TEs due to reduced excision rates (Charlesworth and Langley, 1989; Charlesworth *et al*., 1994) only while inversions are segregating. Once inversions reach fixation, recombination is no longer reduced, thus increasing the possibility of excision for any given TE.

A final remarkable feature of the new model is that the breakpoints would accumulate in genomic regions that are more prone to chromosomal breakages. The fact that the same breakpoints seem to occur over and over again in different rearrangements, which is usually presented as evidence for the ectopic recombination model (Armengol *et al*., 2003), would also make sense under the new model. This interpretation is in agreement with the new evidence from humans suggesting that the association of segmental duplications and rearrangements may be due to the two phenomena having higher frequencies in the same unstable regions (Bailey *et al*., 2004). As Sherlock Holmes said while solving the Boscombe Valley Mistery, 'Evidence is a very sticky thing…it may seem to point very straight to one thing, but if you shift your own point a little, you may find it pointing in an equally uncompromising manner to something entirely different'.

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