Duplicitous duplications: Is *Sd* selfish DNA or a treacherous neomorph?

D. P. Kasbekar

One way genes evolve is by duplication; while one copy of the duplicated genomic segment can retain its function the other may accumulate mutations to assume novel roles. Tandem duplications are produced at surprisingly high frequencies by unequal crossing-over between small stretches of homologous DNA sequences—such sequences may arise from insertion of transposable elements—located at distinct sites within the same region of parental chromosomes[1]. Conversely, even after each member of a duplicated element has functionally diverged and become a distinct gene, the two may retain enough sequence similarity to engage in unequal crossing-over, in which one or the other gene may be lost. This is thought to be responsible for certain human thalassaemias[2] and red-green colour blindness[3]. But tandem duplications would appear to have few phenotypic consequences immediately upon their generation other than the relatively minor effects of gene dosage alteration because very few genes are known to be dosage-sensitive. Recent reports suggest otherwise. Occasionally tandem duplications can yield novel phenotypes that are unrelated to dose alteration. That is, they behave as *neomorphs* (mutant alleles producing an effect qualitatively different from that of the wild-type allele) rather than as *hypermorphs* (mutant alleles whose effects are similar to, but greater than those of the wild-type allele). This is because the duplication breakpoint juxtaposes sequences, either producing novel fusion proteins or imposing novel expression patterns upon existing genes.

Perhaps the most dramatic case is that of the *Sd* locus, situated on chromosome 2 of the much-studied fruit fly *Drosophila melanogaster*. *Sd* is a genetic element that is responsible for the phenomenon of segregation distortion in males. Chromosomes that carry the *Sd* genetic element are designated SD and those lacking it SD^+. Distorting males are heterozygous, with SD and an SD^+ homologue, and induce dysfunction of spermatids that receive SD^+. Consequently, they transmit a vast excess of SD chromosomes to their progeny. The sensitivity of the SD^+ chromosome to *Sd*-induced spermatid dysfunction has been traced to a satellite DNA sequence, called Responder (Rsp^s), in the centromeric heterochromatin of chromosome 2. In fly populations free of SD chromosomes, Rsp^s confers a fitness advantage relative to flies lacking it (Rsp^i, Responder-insensitive), but introduction of SD reverses their relative fitness values[4]. It is not surprising that all SD chromosomes isolated from natural populations bear Rsp^i, because the *Sd* Rsp^s combination is suicidal.

Given the insidious manner of *Sd*'s action it was tacitly assumed that it represented some foreign DNA sequence that behaved selfishly. This assumption was consistent with results showing that deletions of *Sd* from SD chromosomes restored normal segregation and addition of extra doses of the homologous region from SD^+ chromosomes to SD/SD^+ males did not alleviate distortion. *Sd* has now been cloned[5], and instead of foreign DNA a 5-kilobase (kb) tandem duplication was found. This tandem duplication is uniquely associated with all SD chromosomes, absent from all SD^+ chromosomes, and detectably altered in some revertants. However, the duplication alone is not sufficient for *Sd* activity; flanking nonduplicated regions are also required. This is consistent with the finding that some of the cDNAs specific to SD are coded for by elements within the duplication as well as by flanking regions that extend to 40-50 kb beyond the duplication. It may not be a mere coincidence that some of these cDNAs span a topoisomerase II gene located just proximal to the tandem duplication. Since topoisomerase II is required for chromosome condensation, the possibility that *Sd* acts by a subtle alteration of the expression of this gene cannot be ruled out. It would be interesting to determine whether mutations in topoisomerase II affect the Sd phenotype.

The *Bar* (*B*) mutation in *Drosophila*[6] and the *Knotted Kn1-0* mutation of

maize[7] offer additional examples of neomorphic tandem duplications. *B* flies have narrow eyes because of a ten-fold reduction in facet number, and the *Knotted* mutation interferes with development of vascular tissues in the leaf blade. These phenotypes are not a consequence of a simple increase in gene copy number but are specific to their associated duplication breakpoints. In both cases loss of a repeat unit reverts the phenotype, and gain, by unequal crossing-over, of an additional repeat (triplication) exacerbates it. Thus the duplication breakpoint itself responds to dose changes, thereby demonstrating that neomorphic mutations can, in turn, display dosage effects.

A more subtle 'neomorphic' interaction between the elements of a tandem duplication is revealed by the *zeste*[1] mutation in *Drosophila*, which suppresses expression in the eye of *white* (w^+) genes that are paired. Pairing refers to the close location of the w^+ genes in the genome, either in *trans*, as on homologous chromosomes, or in *cis*, as in tandem duplications. The giant transposing element TE146(Z) carries two copies of w^+ in tandem and a derivative, TE146(Z:SR100)SZ, carries the two copies in inverted order. *zeste*[1] suppresses *white* in both TE146(Z) and TE146 (Z:SR100)SZ. However, the tandem, but not the inverted pair, was found to be very sensitive to rearrangement breakpoints on the homologous chromosome 'opposite' the TE insertion site[8]. This shows that the interaction between the w^+ genes in tandem and that in inverted orientation are different. In other words, a tandem duplication could give rise to novel interactions among genes because of novel juxtapositions of regulatory elements.

Recently a human peripheral neuropathy, Charcot-Marie Tooth disease type IA (CMTIA), which is inherited as an autosomal dominant, was localized to a duplication on the short arm of chromosome 17 (ref. 9). Might CMTIA also be a neomorph that bites the hand that bears it?

1. Goldberg M. L., Sheen J. Y., Gehring, W. and Green, M. M., *Proc. Natl. Acad. Sci. USA*, 1983, **80**, 5017.
2. Collins, F. S. and Weissman, S. M., *Prog. Nucl. Acid Res. Mol. Biol.*, 1984, **31**, 315.
3. Nathans, J., Piantanida, T. P., Eddy, R. L., Shows, T. B. and Hogness, D. S., *Science*, 1986, **232**, 203.
4. Wu, C. J., True, J. R. and Johnson, N., *Nature*, 1989, **341**, 248.
5. Powers, P. A. and Ganetzky, B., *Genetics*, 1991, **129**, 133.
6. Tsubota, S., Rosenberg, D., Szostak, H., Rubin, D. and Schedl, P., *Genetics*, 1989, **122**, 881.
7. Veit B., Vollbrecht, E., Mathern, J. and Hake, S., *Genetics*, 1990, **125**, 623.
8. Gubb, D., Ashburner, M., Roote, J. and Davis, T., *Genetics*, 1990, **126**, 167.
9. Lupski, J. R. *et al.*, *Cell*, 1991, **66**, 219.

D. P. Kasbekar is in the Centre for Cellular and Molecular Biology, Hyderabad 500 007, India.