Extreme alternative splicing

The fruit fly demonstrates extreme alternative splicing

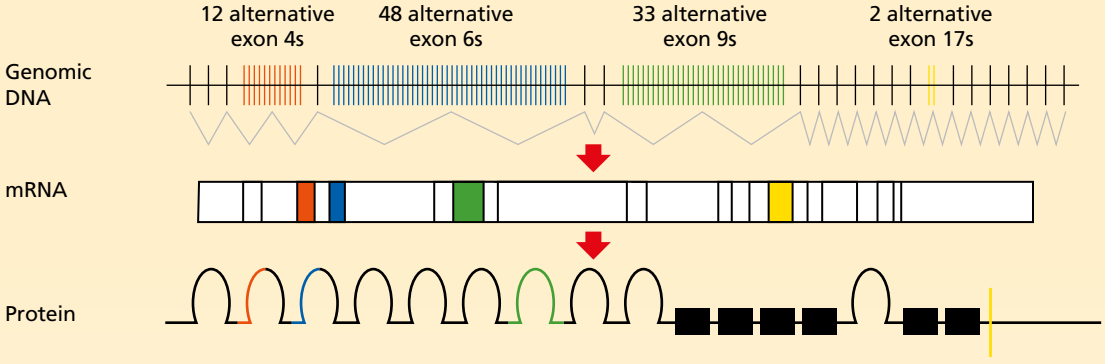

Figure 1 Extreme alternative splicing in the fruit fly *DSCAM* gene

In the mid-1970s, researchers sequencing DNA were surprised to find that coding sequences were not continuous. The terms intron (for *intragenic* regions) and exons (for *expressed* regions) were introduced.

Most introns are removed during mRNA maturation in a process called RNA splicing. Precise removal of introns is critical for the accurate synthesis of proteins during translation. This is not always a simple process. The largest human gene, the X-linked *Duchenne Muscular Dystrophy* (*DMD*) gene, has 96 introns scattered across 2.6Mb of DNA, each of which has to be removed to make a functional molecule of mRNA. In the early 1980s, researchers realised that some genes could make different proteins by using different exons within the same transcript. They called this alternative splicing (see Biological Sciences Review, Vol. 33, No. 3, p. 6). This process reaches extremes in some circumstances.

Down's syndrome happens in individuals with three copies of chromosome 21 rather than two (Biological Sciences Review, Vol. 29, No. 3, pp. 37–40). There are about 250 genes on human chromosome 21, all of which have three copies in someone with Down's syndrome. Not all chromosome 21 genes contribute to the Down's phenotype but one of the key genes is *DSCAM* (*Down's Syndrome Cell Adhesion Molecule*). This gene is highly expressed in the fetal brain and plays a key role in brain development. In humans, *DSCAM* has only a small number of alternative splice variants. But homologues of *DSCAM* are found in other animals, including insects, and the fruit fly *Drosophila melanogaster* has taken alternative splicing to extreme levels. Its *DSCAM* gene can make over 38 000 splice variants and therefore over 38 000 different, but related, cell-adhesion molecules. How?

The *D. melanogaster DSCAM* gene has 12 different versions of exon 4, 48 versions of exon 6, 33 versions of exon 9 and two versions of exon 17 (see Figure 1). Through alternative splicing, every transcript contains one version of exons 4, 6, 9 and 17, and RNA sequencing analyses of fruit fly brains suggest all combinations are possible. This one gene can therefore produce 12 × 48 × 33 × 2 = 38 016 different cell adhesion molecules. As their name suggests, cell adhesion molecules, which sit on the outside of cells, act like a kind of intercellular glue that holds cells together. It may be that in Down's syndrome, too much DSCAM protein is produced and this affects cell–cell interactions during brain development, thus disrupting brain function.

Professor Kevin O'Dell, University of Glasgow