GENOME EVOLUTION

Making sense of antisense transcription

The biological relevance of naturally occurring antisense transcription (NAT) has long been debated. Is this transcriptional plasticity really intentional or is it simply a manifestation of leaky RNA transcription machinery? By comparing the genomic organization of genes with or without antisense transcripts between humans and the pufferfish *Fugu rubripes* (or *Takifugu rubripes*), Dahary *et al.* now show that antisense overlap seen in the human genome is real and remarkably conserved throughout vertebrate evolution.

They reason that separation between two neighbouring overlapping genes with a sense–antisense relationship would be negatively selected through evolution. Database searches and Antisensor algorithms allowed the authors to identify 236 sense–antisense gene pairs in human with orthologues in pufferfish. Of these, 23.3% remained consecutive and preserved their orientation in pufferfish. Sense–antisense pairs tend to maintain their gene order significantly more often than

genes that originate from the same strand, which implies that NAT constrains gene-order rearrangements.

Intriguingly, the authors found that the average distance between ‘same-strand’ gene pairs is 11-fold larger in humans than in pufferfish, in contrast to a 2.5-fold difference for antisense gene pairs. Could antisense transcription affect genome expansion? Further comparisons between mammalian genomes support the view that NAT sets a rigorous control on genome expansion and affects mammalian evolution in a manner similar to that observed for humans and fish.

As it has been estimated that antisense gene pairs might comprise ~10% of all human genes, the authors point out that antisense transcription might impose a significant restriction on the gene order and genome expansion throughout vertebrate evolution. With its involvement in gene-expression mechanisms and various human diseases, who can now say that antisense transcription doesn’t make any sense?

Ekat Kritikou

References and links

ORIGINAL RESEARCH PAPER Dahary, D. *et al.* Naturally occurring antisense: transcriptional leakage or real overlap? *Genome Res.* March 2005 (doi:10.1011/gr3308405)

WEB SITES

LEADS-Antisensor: <http://www.laborweb.com/antisense>
Compugen Research and Development: <http://www.cgen.com/research>

GENE NETWORKS

The flexible network

The increasing trend towards a systems approach to biology has fuelled great interest in how genes interact with each other in networks. Although networks show robustness, in that they can often compensate for the loss of one or more component, the set of interactions that can occur between components is generally thought to be fairly rigid. Now, using *Drosophila* genetics to probe interactions between genes in different genetic contexts, Ralph Greenspan

and Bruno van Swinderen show that genetic networks can, in fact, be remarkably flexible.

The approaches that are generally used to reconstruct biological networks rely on information about specific types of readily definable interactions, such as protein–protein interactions or co-expression. But this doesn’t capture information about interactions in a broader sense, in terms of how they contribute to a particular phenotype. As an alternative approach, the authors defined a network of genes involved in a simple behaviour in *Drosophila melanogaster*. They first took flies that were heterozygous for a mutation in the *Syntaxin 1A* (*Syx1A*) gene, which show a behavioural phenotype at increased temperatures, and carried out a screen for alleles of other genes that suppress the phenotype.

The genes identified were then tested for epistatic interactions as a measure of their participation in a common network. This was done by quantifying the behavioural phenotypes in flies that carried overexpression alleles of each possible pair of genes, and was carried

out both in the presence and absence of the *Syx1A* mutant allele. In both cases, several strong epistatic relationships were seen, indicating functional interactions between genes. Strikingly, however, the set of epistatic interactions within the network was changed markedly between the two genetic backgrounds: some interactions that were seen in one background disappeared completely in the other, and in other cases a positive interaction in one context became negative in the other.

So, instead of a strictly defined set of interactions within a network, the functional relationships among genes can undergo significant changes in different contexts. This has important implications for future studies of gene networks, suggesting that models of gene interactions that are built up from data on molecular interactions or expression data might not be providing us with the whole picture.

Louisa Flintoft

References and links

ORIGINAL RESEARCH PAPER van Swinderen, B. & Greenspan, R. J. Flexibility in a gene network affecting a simple behaviour in *Drosophila melanogaster*. *Genetics* 31 January 2005 (doi:10.1534/genetics.104.032631)

FURTHER READING Greenspan, R. J. The flexible genome. *Nature Rev. Genet.* 2, 383–387 (2001) | Kitano, H. Biological robustness. *Nature Rev. Genet.* 5, 826–837 (2004)

WEB SITE

The Neurosciences Institute web site: www.nsi.edu