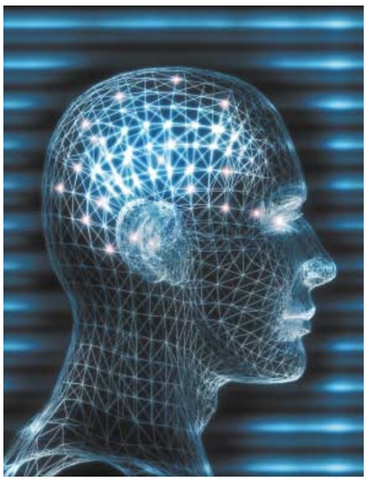
NEUROGENETICS

It's all in the mind



Many have sought to determine the relative effects of nature versus nurture on human behaviour and personality, but as behavioural responses are difficult to measure and assess reliably, genotype–behaviour correlations have remained inconclusive. By correlating genotype with an easy-to-measure aspect of brain physiology, Hariri *et al.* now show that a polymorphism in the promoter region of a serotonin transporter (5HTT) is associated with differences in anxiety-related behaviour that might result from increased neuronal activity in the amygdala.

Two common alleles of *5HTT* exist in human populations — one with a short and the other with a long variable repeat sequence in the promoter — that have been differentially associated with anxiety in healthy individuals. The polymorphism affects serotonin transporter function, probably leading to increased synaptic levels of serotonin, which is known to modulate emotional behaviour. Previous studies have hinted at a weak link between this polymorphism and differences in human personality and behaviour, which is supported by the behavioural phenotype of *5HTT* knockout mice.

A separate report linked physiological responses of brain regions, such as the amygdala, to individual differences in emotion and temperament. So Hariri and colleagues decided to test whether the *5HTT* promoter polymorphism correlated with physiological responses in the amygdala because physiology might be a more reliable manifestation of genetic variation than is behaviour. Using non-invasive neuroimaging, the authors tested a cohort of healthy individuals divided into two subgroups according to their *HTT* allele and subjected them to fearful visual stimuli. The results were quite clear-cut — the response of the right amygdala, which processes such stimuli, was greater in the carriers of the short allele (both homozygotes and heterozygotes). Additional tests showed that other brain physiological responses of the two groups were the same, indicating the specific involvement of the amygdala in this response.

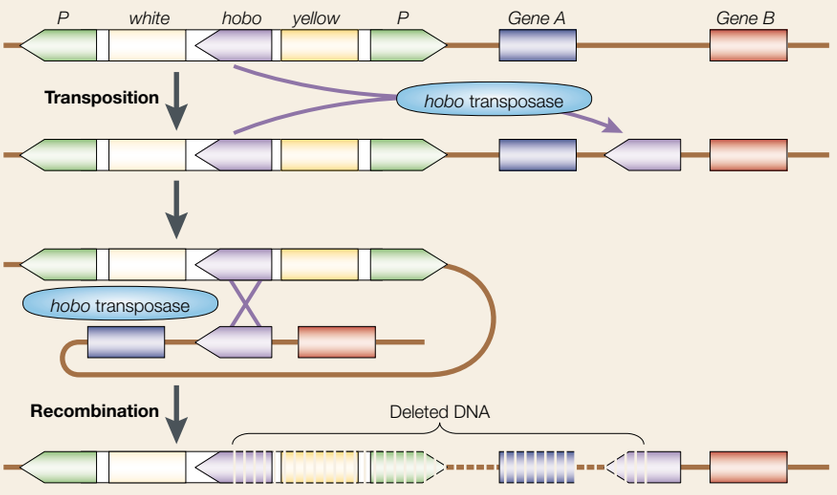
The authors propose that this increased activity of the amygdala in

TECHNOLOGY

Hopping all over

The *P* transposable element holds a venerable position in *Drosophila* genetics. Ever since the discovery of its mutagenic properties about 30 years ago, it has been been a component of countless fly genetic techniques, from ectopic expression to mutagenesis. The completion of the *Drosophila melanogaster* genome sequence brings a new urgency to the fly field — that of understanding the biological role of every transcription unit. A group of fly geneticists, headed by Bill Gelbart, has now risen to this challenge: by combining the intrinsic properties of the *P* element and that of another transposon, *hobo*, they have produced a hybrid construct that can generate molecularly defined deletions *in vivo*, in an unbiased and systematic way. Given the high density and efficiency at which deletions are generated — based on two successful cases — this method could become the most user-friendly way to annotate the fly genome.

The construct developed by Huet *et al.* — called *P*(*wHy*) — consists of a single *hobo* element contained between two *P* element ends (see figure). In the presence of *P* transposase, the *P*(*wHy*) jumps around, and so stable strains of flies can be generated in which *P*(*wHy*) elements are inserted in single copies anywhere in the genome. If the *P* element is in charge of 'carrying' the *P*(*wHy*), then the *hobo* element is in charge of deleting the surrounding sequence. Unlike the *P* transposase, the *hobo* transposase has two functions: first, it causes *hobo* to hop, by conservative transposition, to a nearby location. Then, it catalyses homologous recombination between the old and the new *hobo* copies. This last step leads to the deletion of the genomic sequence between the newly transposed *hobo* element and its parent sequence within the *P*(*wHy*), with the length of the sequence depending on how far out the new *hobo* element has hopped. The direction and the occurrence of the deletion event is reliably monitored by the



Modified from figure 1 of Kornberg, T. Another arrow in the *Drosophila* quiver. *Proc Natl Acad. Sci USA* **99**, 9607–9608 (2002).

the short-allele carriers is probably due to increased neuronal activity that, in turn, might be caused by increased synaptic levels of serotonin. These results imply that there is a direct genetic link between serotonin receptor function and the response of a particular part of the brain to emotional information. Serotonin has been previously linked to depressive and suicidal behaviour, and the authors suggest that the amygdala might also mediate these behaviours. Such an approach could prove to be powerful in future investigations of the potential links between behavioural differences and genetic polymorphisms.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPER Hariri, A. R. *et al.* Serotonin transporter genetic variation and the response of the human amydgala. *Science* **297**, 400–403 (2002)

loss of one of the two visible markers in *P*(*wHy*) that are on either side of *hobo*. A broad set of genomic deletions — which can be up to 400 kb but with the highest density ~60 kb — can be generated in this way, all of which, importantly, start at one end of the hybrid element.

This deletion technique is not the first gene disruption method known in flies: RNA interference and targeted gene knockouts have been used by many labs over the past few years. What makes the *P*(*wHy*) deletion system so appealing, however, is that it can be applied globally to the genome. Moreover, as the components of *P*(*wHy*) have their equivalents outside *Drosophila*, it might not be long before this phenotypic analysis tool takes a leap into other eukaryotes.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPER Huet, F. *et al.* A deletion-generator compound element allows deletion saturation analysis for genomewide phenotypic annotation. *Proc. Natl Acad. Sci. USA* **99**, 9948–9953 (2002)

FURTHER READING Kornberg, T. Another arrow in the *Drosophila* quiver. *Proc. Natl Acad. Sci. USA* **99**, 9607–9608 (2002)

IMMUNOGENETICS

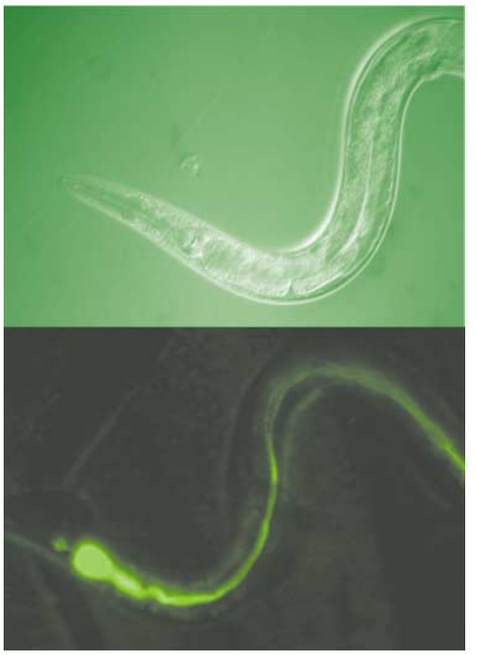
C. elegans — an innate choice?

Much of what we know about innate immunity — an organism's immediate response to pathogen infection — comes from studies in *Drosophila*, which have shown that the components of innate immunity are highly conserved. Two papers now illustrate how *Caenorhabditis elegans*, another genetically tractable organism, might also be a useful model for studying innate immunity. Their results show that *C. elegans* has an inducible response to pathogen infection and that this response shares many features with innate immunity in other organisms.

Kim *et al.* assayed the progeny of mutagenized worms, which had been exposed to the bacterium *Pseudomonas aeruginosa* for enhanced susceptibility to pathogen (esp) infection. From a screen of 14,000 haploid genomes, they isolated two mutants, *esp2* and *esp8*, that die much faster on exposure to *P. aeruginosa* than wild-type worms do. High-resolution SNP mapping revealed the chromosomal locations of the mutant genes, which were identified by phenotypic rescue — the *esp2* mutant was rescued by the gene *sek-1*, and *esp8* by *nsy-1*.

sek-1 encodes a MAP kinase kinase (MAPKK) homologue of mammalian MKK3/MKK6 and MKK4, and *nsy-1* encodes an orthologue of the mammalian MAPKKK ASK1. Because these kinases activate the p38 kinase family and the JNK MAP kinases in mammals, the authors tested the role of p38 and JNK in the *C. elegans* defence response. The *esp2* and *esp8* mutants had markedly reduced levels of p38 MAPK activity. Moreover, the knockdown of *pmk-1*, one of two *C. elegans* p38 orthologues, by RNA interference produced a strong esp phenotype. Knockdown of *pmk-2* and a *jnk* mutation, however, produced no enhanced susceptiblity to *P. aeruginosa* infection. Together these results show that the p38 MAPK pathway is required for innate responses to pathogen infection, which is an important discovery as this signalling pathway is also crucially required in mammals for inflammatory and innate-immune response signalling pathways.

Mallo *et al.* used an expression screen to look for *C. elegans* genes upregulated in response to infection by the bacterium *Serratia marcescens*. Of 7,500 cDNAs surveyed, several were induced



An *esp2* mutant worm, after exposure to GFP-labelled *P. aeruginosa*. Nomarski (top) and fluorescence (bottom) images, courtesy of Dennis Hyong-Kun Kim, Frederick Ausubel and Rhonda Feinbaum.

over twofold, most of which encoded lectins, which function in innate immunity in other organisms. Also upregulated was lysozyme 1. As lysozymes have been implicated in innate-immune responses, Mallo *et al.* overexpressed *lys-1* in worms to see if this would enhance their resistance to *S. marcescens*. It did, although only against a less pathogenic strain of the bacterium, possibly because this strain does not produce proteases that degrade the enzyme, whereas the more pathogenic strain does. The authors also assayed *Dbl-1* mutants for their susceptibility to *S. marcescens* infection, because *Dbl-1* — a TGF-β-related gene — regulates some of the genes induced in the screen. *Dbl-1* mutants were extremely susceptible to *S. marcescens* infection and, surprisingly, also to infection by the *E. coli* strain OP50, which *C. elegans* is often cultured on.

So, 30 years after its discovery in *Drosophila*, these studies show that *C. elegans* also has an innate-immune response — the components of which are conserved in other organisms — and the ease with which this response can be investigated genetically in worms.

Jane Alfred

References and links

ORIGINAL RESEARCH PAPER Kim, D. H. *et al.* A conserved p38 MAP kinase pathway in *Caenorhabditis elegans* innate immunity. *Science* **297**, 623–626 (2002) | Mallo, G. V. *et al.* Inducible antibacterial defense system in *C. elegans*. *Curr. Biol.* **12**, 1209–1214 (2002)

FURTHER READING Kimbrell, D. & Beutler, B. The evolution and genetics of innate immunity. *Nature Rev. Genet.* **2**, 256–267 (2001)