IN BRIEF

EVOLUTION

Chemical etiology of nucleic acid structure: The α-threofuranosyl-(3′->2′) oligonucleotide system.

Schöning, K. -U. *et al. Science* **290**, 1347–1351 (2000)

Schöning *et al.* have synthesized and studied a chemical analogue of RNA, which is derived from a sugar ring that contains four carbons (tetrose) instead of the more usual five found in ribose. This simple RNA, called L-α-threofuranosyl or TNA, can form stable double helices with itself and also with complementary RNAs and DNAs. The cross-pairing properties and the simplicity of its self-assembly make TNA a good candidate for a natural nucleic acid and a possible precursor of RNA.

DEVELOPMENTAL BIOLOGY

Genetic control and evolution of sexually dimorphic characters in *Drosophila*.

Kopp, A. *et al. Nature* **408**, 553–559 (2000)

Abdominal pigmentation and morphology in *Drosophila melanogaster* are sexually dimorphic features that require the homeotic and the sex-determination pathways. This paper reveals the genetic circuitry that integrates the two signalling inputs and that culminates in the differential expression of *bric-a-brac* (*bab*) in the two sexes. Expression studies in monomorphic species indicate that changes in the way that sex- and homeotic-specific pathways control *bab* expression might have been responsible for the evolution of some sexually dimorphic characters.

HUMAN GENETICS

Dominant modifier *DFNM1* suppresses recessive deafness *DFNB26*.

Riazuddin, S. *et al. Nature Genet.* **26**, 431–434 (2000)

While mapping a new, recessive deafness locus (*DFNB26*) in a large consanguineous family, these authors discovered a dominant, deafness-suppressing modifier locus. When family members were typed for the *DFNB26*-linked haplotype on chromosome 4q31, homozygotes were found among both deaf and hearing family members. A second genome scan to test for modifier loci revealed a dominant modifier, *DFNM1*, on chromosome 1. Candidate genes at both loci are being investigated.

RNA EDITING

Requirement of the RNA editing deaminase ADAR1 gene for embryonic erythropoiesis.

Wang, Q. *et al. Science* **290**, 1765–1768 (2000)

Just how important is RNA editing? Wang *et al.* answered this question by making a knockout of *Adar1*, which encodes a member of the Adar family of RNA editors. When the authors created mouse chimeras derived from *Adar*$^{-/+}$ ES cells, they found high levels of embryonic lethality. Embryos died at a critical stage in erythropoiesis. The results suggest that some processes in embryogenesis are very sensitive to levels of RNA editing.

MULTIFACTORIAL GENETICS

A map of fear

Many medically important diseases are caused by multiple genetic factors, the effects of which are influenced by the environment. Because of these multiple influences, mapping the genetic basis (quantitative trait loci or QTL) for the variation in continuous traits is seldom easy. The use of animals as models for human diseases has definite advantages; however, work in mice exemplifies several problems common to QTL mapping studies. For instance, current methods do not distinguish between a single, large-effect QTL and one QTL that contains multiple loci of small effect. Another limitation is that the inbred strains of mice that are used in the lab for mapping experiments are genetically homogenous and therefore may not be representative of genetic variation in the wild.

Mott *et al.* report a solution to the twofold problem of stock homogeneity and the need for a finer QTL mapping resolution. Their improved technique is illustrated by mapping five QTL for emotionality in mice.

The classical way of mapping QTL involves crossing two inbred lines that differ in the mean phenotype of a given trait. Repeated intercrosses or backcrosses onto one parental strain are then conducted to single out the regions with the QTL from the rest of the genome. To increase the resolution in QTL mapping, Mott *et al.* abandoned simple crosses between inbred lines in their mapping studies in favour of a genetically heterogeneous stock, which was established 30 years ago from eight inbred founder strains. The highly recombinant nature of the heterogeneous stock genome (which is a fine genetic mosaic of its founders) gives a 30-fold increase in the resolution for QTL mapping, allowing mapping of QTL to under 0.5 cM with fewer than 2,000 animals. Because the heterogeneous stock was derived from eight different lines, it is also genetically diverse.

Heterogeneous stock mapping can only be successful if it is accompanied by a robust statistical method for analysing the mapping data. Conventional experimental designs rely on the co-segregation of a single parental marker with the genomic region that is associated with the QTL effect. However, the QTL region can be resolved only if the parental strains differ at the markers in the first place. If two parental lines carry QTL that have opposite effects, but are flanked by the same markers in both strains, then single-marker analysis would not be able to tell the two QTL apart in the mapping population. The alternative approach used by the authors involves using multiple — not single — markers to find QTL in heterogeneous stock animals.

The test bed for this method was the mapping of five small-effect QTL that were previously found to be associated with fearfulness in mice. Single-marker analysis only detected two QTL, but multipoint dynamic programming (DP) analysis mapped the remaining three loci.

This method for detection and fine mapping of QTL is fast, robust and cost-effective — and promises to go far beyond an anxious mouse. Multipoint DP analysis can be extended to map many traits in parallel on the same set of mice. As any type of marker is suitable, single nucleotide polymorphisms or microsatellites can also be used for high-resolution, genome-wide scans.

Tanita Casci

⊛ References and links
ORIGINAL RESEARCH PAPER Mott, R. *et al.* A method for fine mapping quantitative trait loci in outbred animal stocks. *Proc. Natl Acad. Sci. USA* **97**, 12649–12654 (2000)
WEB SITES Jonathan Flint's lab | Software analysis