GENE MAPPING

Just what geneticists have been waiting for…

Although geneticists would not survive without mutations, they could easily live without the tedious hassle of finding them. And, generally speaking, the bigger the model organism, the harder the slog. But things might be set to change, as Benjamin Kile and colleagues now report the result of a systematic and relatively straightforward way of identifying mutations in mouse genes. By borrowing a technique used in fruitflies, they have identified 88 new point mutations on a portion of chromosome 11 — and all by simply crossing mice and scoring the colour of their coat.

Among model systems, mice are arguably the most promising organisms in which to study the function of human genes, particularly those that are involved in disease. However, traditional methods of identifying loci by screening for a mutant phenotype often involve large pedigrees, low efficiency, laborious mapping tools and difficulty in maintaining the mutant strains. The new approach, published in *Nature*, seems to have solved these problems. At the heart of it is the use of a so-called 'balancer' chromosome, which, owing to engineered inversions, allows mutations on its homologue to be inherited without recombining.

The authors created a mouse chromosome 11 containing a 24 cM inversion that included ~700 genes and could be detected phenotypically by the presence of a dominant mutation (*Agouti*) that gives mice yellow fur. The crossing scheme — which is used routinely in flies — goes as follows: a wild-type male that has been mutagenized using the chemical mutagen N-ethyl-N-nitrosourea (ENU) is crossed to a balancer-carrying (yellow) female. Yellow-furred F1 mice, some of which contain a balanced mutation on chromosome 11, are then crossed to a mouse with a balancer plus a chromosome that confers a dominant curly-coat phenotype. The only offspring in the F2 generation to have a yellow non-curly coat are those with a balanced ENU-mutagenized chromosome 11; these can now be mated to each other to characterize the phenotype of the homozygous mutation and to maintain the mutant line.

Of the 88 new mutations that were found in this way, 55 were lethal, whereas the remainder had phenotypes that affected various organs, including the skin, nervous system and blood cells. Balancer chromosomes are now being generated for other regions of the mouse genome, making phenotype-driven screens as easy as they are in flies: mutations are identified in only three generations, are mapped without further crosses and stocks are maintained without the fuss of molecular genotyping. As Janet Rossant points out in a related News and Views piece, such screens will contribute enormously to annotating the mammalian genome — but only if they are accompanied by much needed improvements in phenotyping tools.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPER Kile, B. T. *et al.* Functional genetic analysis of mouse chromosome 11. *Nature* **425**, 81–86 (2003)

FURTHER READING Rossant, J. A balancing act. *Nature* **425**, 29–32 (2003) | Justice, M. J. Capitalizing on large-scale mouse mutagenesis screens. *Nature Rev. Genet.* **1**, 109–115 (2000)

WEB SITE

Monica Justice's laboratory: http://www.mouse-genome.bcm.tmc.edu/labs/justice_index.asp

IN BRIEF

RNA INTERFERENCE

MicroRNAs and small interfering RNAs can inhibit mRNA expression by similar mechanisms.

Zeng, Y. *et al. Proc. Natl Acad. Sci. USA* **100**, 9779–9784 (2003)

Evidence from plants indicates that small interfering RNAs (siRNAs) and microRNAs (miRNAs) are functionally interchangeable, although this is not the case in worms. The authors show that in human cultured cells, as in plants, endogenous miRNAs can inhibit the expression of fully complementary RNAs, and that siRNAs can do the same to RNAs with some mismatch. They propose that the siRNA and miRNA mechanisms of action might be interchangeable, depending on the level of target complementarity.

DEVELOPMENTAL GENETICS

The gene *csd* is the primary signal for sexual development in the honeybee and encodes an SR-type protein.

Beye, M. *et al. Cell* **114**, 419–429 (2003)

Twenty percent of animal species are haplodiploid, but the genes that are involved in this sex-determination system largely remain a mystery. Now, the honeybee sex-determining gene *csd* has been identified, positionally cloned and characterized. *csd* encodes a short (385 amino acid) protein with highly divergent alleles, as predicted for a sex-determining gene. RNAi-mediated knockdown of *csd* caused females to develop as male larvae, which confirmed the key role of *csd*.

EPIGENETICS

Transposable elements: targets for early nutritional effects on epigenetic gene regulation.

Waterland, M. & Jirtle, R. J. *Mol. Cell. Biol.* **23**, 5293–5300 (2003)

Our early diet could affect our susceptibility to chronic adult diseases by influencing DNA methylation. By supplementing the diet of mice with a phenotype that depends on the methylation status of a specific transposable element, Waterland and Jirtle were able to increase CpG methylation of the element and change the phenotype of the offspring. So, nutrition can affect epigenetic gene regulation through metastable alleles that are associated with transposable elements.

HUMAN GENETICS

Human handedness and scalp hair-whorl direction develop from a common genetic mechanism.

Klar, A. J. S. *Genetics* **165**, 269–276 (2003)

The genetic basis of human handedness remains elusive despite extensive studies and continues to be one of the last clear-cut battlegrounds between the polarized advocates of 'nature' and 'nurture'. Amar Klar attacked the problem obliquely by showing that there is an association between handedness and an asymmetric trait that is unaffected by cultural influences: scalp hair-whorl direction. His data clearly support a simple Mendelian genetic explanation for handedness.