HIGHLIGHTS

GENE MAPPING

Mapping with a mouse-click

Identifying the genetic basis for human complex traits is no easy task (see accompanying highlight on Crohn disease) but it can be made simpler by using mouse genetics to deliver candidate genes. These genes can be uncovered by studying natural phenotypic variation in inbred strains of mice. But going from phenotype to gene can take years of experimental crosses, phenotypic characterization and genotypic analysis. It would therefore be a quantitative geneticist's dream to be able to feed phenotypic and genotypic data into a computer and get it to deliver the location of a candidate quantitative trait locus (QTL) in milliseconds. Grupe *et al.* might have done just that by developing a computational method that can identify genomic regions likely to contain QTL.

The authors built an online genotypic repository consisting of 700 newly identified single nucleotide polymorphisms (SNPs) from 15 inbred strains of mouse, to which they added over 2,800 published SNPs with extended strain allelic information. Using this SNP database, their program builds a SNP map of an inbred strain, which is compared to that of another strain. It then identifies the haplotypes that associate most strongly with the phenotypic differences between the strains. This process is repeated in a pairwise manner for all mouse strains for which phenotypic information is available to yield the chromosomal intervals most likely to be correlated with a particular phenotype. The location of experimentally determined QTL intervals was correctly predicted by this method, and its performance was shown, statistically, to be robust.

This new method removes the strain from QTL mapping and also samples more genetic variation because it carries out multiple comparisons across many different inbred strains. However, the pain hasn't been removed completely from complex trait mapping, as the ultimate goal is to identify a specific genetic variant, not just an interval. But a pain-free solution to QTL mapping could be around the corner, as the authors' next project is to link the existing database with genome-wide information on tissue-specific gene expression.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPER Grupe, A. *et al.* *In silico* mapping of complex disease-related traits in mice. *Science* **292**, 1915–1918 (2001)

TELOMERES

Fanning the flames

Telomerase — the riboprotein enzyme responsible for maintaining chromosome ends — has a complex function in the genesis and progression of cancer: although it is reactivated in many human cancers, its loss in mice sends the incidence of epithelial tumours soaring. In the June issue of *Nature Genetics*, Ron DePinho and colleagues explain these apparently contradictory observations by dissecting the function of

telomerase in tumour initiation from its role in progression.

The authors crossed *Terc*^{-/-} mice, which lack the RNA component of telomerase, with *Apc*^{Min} mice, which have an inactivating mutation in one copy of the *Apc* tumour suppressor gene, and develop multiple intestinal neoplasia as a consequence of losing their second *Apc* allele. Tumour initiation and progression were assessed by counting intestinal polyps (microadenomas) and frank tumours (macroadenomas), respectively. *Terc*^{-/-} mice develop chromosomal instabilities as their telomeres gradually shorten, and chromosome instability becomes manifest in the second generation, increasing further in generations 3 and 4. Surprisingly, although third- and fourth-generation *Terc*^{-/-} *Apc*^{Min} mice had more microadenomas than did *Terc*^{+/+} *Apc*^{Min} mice, the number and size of their macroadenomas decreased significantly. This corresponded with a striking increase in survival compared with mice that had longer telomeres. What seems to be happening is that loss of telomerase allows more neoplasias to initiate, but these rarely progress to frank malignancy, even though they clearly have chromosomal instabilities as judged by increased numbers of anaphase bridges.

Why, despite this chromosomal instability, do *Terc*^{-/-} *Apc*^{Min} mice develop fewer

macroadenomas than their *Terc*^{+/+} counterparts? The answer seems to lie in their intact checkpoint mechanisms: all the macroadenomas from *Terc*^{-/-} *Apc*^{Min} mice tested positive for *Trp53*, and p53 levels were upregulated. Likewise, compared with *Terc*^{-/-} *Apc*^{Min} tumours, rates of apoptosis were increased and rates of cell division were decreased: proliferation was almost completely suppressed in fourth-generation *Terc*^{-/-} *Apc*^{Min} mice. The authors speculate that the DNA damage signals generated by chromosomal end fusions and subsequent breakage at anaphase in these tumours switch on the p53 checkpoint and halt tumour progression.

So does telomerase status affect the progression of human colorectal cancer? The authors looked at sporadic colorectal tumours of different grades, and found that anaphase bridge formation rose sharply in high-grade premalignant tumours and carcinoma *in situ*, whereas metastatic tumours had fewer anaphase bridges. This is consistent with the finding that telomerase is activated relatively late in tumour progression. Our lack of telomerase lights the match, but ultimately it is telomerase reactivation, augmented by the loss of checkpoints such as those controlled by p53, that fans the flames leading to malignancy.

Cath Brooksbank, Editor,
Nature Reviews Cancer

References and Links

ORIGINAL RESEARCH PAPER Rudolph, K. L. *et al.* Telomere dysfunction and evolution of intestinal carcinoma in mice and humans. *Nature Genet.* **28**, 155–159 (2001)
LINKS The DePinho homepage | Telomeres & telomerase-related sites