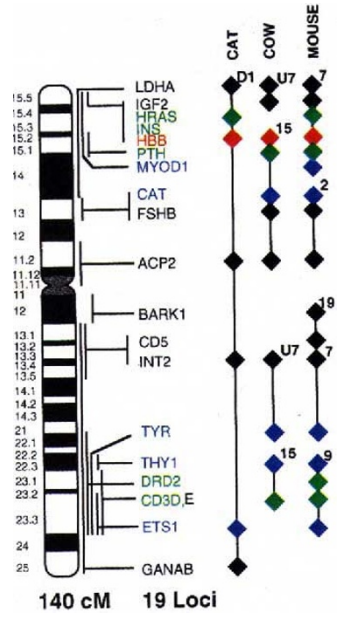
nature genetics February

Of mice and men (and cows and cats)

A compendium of the chromosomal locations of more than 300 human genes and their homologues in three mammalian species will be a boon in comparative mapping studies.

LAST year was the year of the microsatellite, most notably manifested in the mapping of the human[1,2] and mouse[3] genomes using an abundant supply of these highly polymorphic markers. Microsatellites represent alterations in the length of short nucleotide repeats throughout the genome, and have many advantages over the more conventional but relatively uninformative restriction fragment length polymorphisms (RFLPs). They are amenable to a simple and easily automated analysis, and seem to be evenly spread throughout the genome, which gives them a distinct edge over other classes of repetitive sequence markers. The rapidly expanding supply of these 'second generation' markers has already led to a stunning increase in the density of landmarks strung throughout the human and mouse genomes — for instance, more than 1,000 mapped microsatellites were reported in the human genome[1,2] towards the end of 1992. Before too long, investigators will probably have at their disposal maps with evenly spaced landmarks whose average spacing is 1 centimorgan (about 1 megabase) or less[4].

But these new markers have one big drawback: in general they are anonymous stretches of DNA and do not represent coding sequences of genes, which limits their usefulness in drawing comparisons between the genomic organization of different organisms. Coding sequences usually exhibit less sequence divergence and are therefore not as likely to manifest polymorphisms as non-coding stretches. Ideally, in the next few years the dense microsatellite maps will be integrated with more established compilations of known genes that have been mapped with precision not only in humans, but increasingly in other species as well.



Representative gene map of the human chromosome 11 showing the syntenic relationships of these loci in mice, cats and cattle. Colours show reference loci[5].

Writing in this month's *Nature Genetics*, Stephen O'Brien and his colleagues announce a major step in this direction[5]. They have compiled a total of 321 cloned and mapped human genes that will be a valuable series of anchor loci for comparative mapping purposes. O'Brien *et al.* have chosen three other species — mouse, cow and cat — to illustrate the utility of these genes. Inclusion of the first animal was mandatory, while the other two are becoming increasingly popular in genetic mapping studies (although to date the number of loci mapped in them is less than a tenth that in humans or mice). Together, these four species represent four different mammalian orders, primates, rodents, artiodactyls and carnivores.

There are essentially two reasons for producing such comparative maps. First, the defined locations of these genes of known function are crucial not only for human geneticists (for elucidating the potential connection with hereditary disease loci, for example) but also for such people as veterinarians and breeders, in that the identification of mapped genes and traits may have important economic or agricultural ends. That point has been underscored lately with the elucidation of the molecular basis of severe genetic disorders in horses, cattle and pigs[6].

The second reason for comparing different mammalian gene maps is to shed light on the genomic organization and evolution of related species with a resolution that cannot be achieved by karyotype analysis. Clusters of gene loci that are physically linked (or syntenic) on a chromosome are often, but not always, conserved through evolution. Identification of such exceptions to the rule plays a large part in determining the patterns of evolutionary divergence. For example, although genes mapped to human chromosome 12 are conserved on single chromosomes in cats and cattle, they are dispersed on at least four different chromosomes in mice[7]. Nonetheless, the mapping of murine genes usually allows accurate predictions of where their human homologues might be, with important consequences for the identification of animal models of human diseases.

To complement the new maps using microsatellites (also termed type II markers[5,7]), O'Brien *et al.* have selected 321 known genes (type I markers) which will facilitate comparisons between species and provide a framework to monitor the progress of mapping projects in various organisms relying on the more informative microsatellite markers. In time, the two will converge to form the ultimate genetic map. The 321 genes chosen to compile the map have all been cloned and, where possible, are evenly distributed along the chromosomes, giving an average spacing of 5 and 10 centimorgans in the mouse and human genomes, respectively. After choosing as many established human and mouse 'reference loci' (as suggested by gene mapping committees), the authors selected genes in areas subject to recombination between species as well as other loci of particular medical significance. Although the final compilation suffers from some deficiencies (such as uneven spacing) and does not place a premium on practical considerations (including sequence availability and amplification criteria), it is a suitable starting point to accelerate the pace of gene mapping in some mammals, and perhaps to launch projects in others that have been neglected so far.

Kevin Davies

Kevin Davies is Editor of Nature Genetics.

Also in this month's *Nature Genetics*: disruption of the *PAX-3* paired box gene by a chromosomal translocation in the solid tumour, alveolar rhabdomyosarcoma; defects in the neurofibromin gene associated with melanoma and neurofibrosarcoma; and a surprising variety of phenotypes resulting from flaws in the retinal protein, peripherin.

1. NIH/CEPH Collaborative Mapping Group *Science* **258**, 67–86 (1992).
2. Weissenbach, J. *et al. Nature* **359**, 794–801 (1992).
3. Dietrich, W. *et al. Genetics* **131**, 423–447 (1992).
4. Goodfellow, P. N. *Nature* **359**, 777–778 (1992).
5. O'Brien, S. *et al. Nature Genet.* **3**, 103–112 (1993).
6. Womack, J. *Nature* **360**, 108–109 (1992).
7. O'Brien, S. J. *Curr. Op. Genet. Devl.* **1**, 105–111 (1992).