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Mouse maps, models and mutants

With knowledge and technology, markers and strains in plentiful abundance, it is not unreasonable that the director of the Jackson Laboratory, Kenneth Paigen, should anoint mice as the 'experimental surrogate of ourselves'. If the 1980s were the decade of the transgenic mouse, the 1990s are certain to bring comparable successes in gene replacement, positional cloning and complex trait analysis. So much was evident at the 2nd *Nature Genetics* conference last month*.

Not so long ago, the genetic map of the mouse was kept on a set of 3 × 5 inch index cards at Bar Harbor, and at one conference the gene map was represented by huge chromosome figures with cages of the actual mutant mice suspended at the positions of the mapped loci. How times change. The current genetic map available over the Internet from E. Lander (Whitehead Institute) consists of more than 3,750 microsatellite markers and is being integrated with the positions of more than 1,600 genes (N. Copeland, NCI Frederick Cancer Center). Within a few years, a complete physical map is likely to be a reality. In the meantime, several groups have assembled large backcrosses of selected mouse strains to facilitate high-resolution gene mapping, including a cross involving 188 meioses with data on 666 loci (K. Paigen), and the European Backcross Consortium mapping panel of 1,000 mice typed for 78 anchor loci, which provides an informative panel of recombinants (S. Brown, St Mary's Hospital, London).

A. Ivinson.

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Kenneth Paigen.

Such maps should prove valuable for adding to the collection of loci controlling complex traits (see *News & Views*, page 3). For example, J. Todd (University of Oxford) has identified at least ten type-I diabetes susceptibility loci in mice including the MHC region. Studies using congenic mice suggest that these loci act in concert to exceed a threshold of disease pathology. One of these loci, *Idd-5*, may have only a minor role, but interestingly could turn out to be the bacterial disease resistance gene, *Nramp*, cloned last year by P. Gros (McGill University). Tuberculosis is once again emerging as a threat to public health, with newly resistant strains contributing to more than three million deaths in 1990. The mouse strains susceptible to mycobacterial infection harbour a Gly105Asp substitution in the Nramp transporter that alters the polarity of one of the membrane-spanning regions. Studies of human families susceptible to infectious disease are under way, although no firm linkage to the *Nramp* homologue on human chromosome 2 has been found.

Another important complex trait, hypertension, is best studied in the rat, where different combinations of at least five susceptibility loci conspire to elevate blood pressure in different strains (M. Lathrop, INSERM, Paris). Unfortunately, candidate loci implicated in animal models do not necessarily have the same effects in humans. Such may be the case for the angiotensin-

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converting enzyme and S_A, a good candidate gene because of its high expression in the kidney.

Positional cloning in mice has tended to be overshadowed by more traditional cloning methods, as the density of the classical mouse genetic map has facilitated candidate gene approaches. But several exciting loci should be identified before long. For example, an important model for non-syndromic deafness is *shaker-1*, a locus first mapped in the 1930s. Now it emerges that within a minimum critical region of 500 kilobases sits a newly identified type-I myosin-like gene, which fits well with the notion of a defect in the stereocilia of the ear (S. Brown). Exon trapping has also produced a good candidate for the obesity gene, *ob*, which is expressed primarily in the brain (J. Friedman, Rockefeller University). In 1992, P. Overbeek (Baylor College of Medicine) made the serendipitous discovery of a dominantly acting gene, *inv*, whose disruption by a transgenic inserition scrambles the polarity of embryonic development. Efforts to clone *inv* have been hampered as the transgene appears to have produced a large DNA inversion in the host chromosome, but the flanking deletions are now being examined in detail.

Eric Lander.

Target practice: The technical problems that once hampered the creation of targeted mouse mutants now appear to be over, and the application of this technique not just to single loci but to multiple members of gene families, such as the *hox* (M. Capecchi, University of Utah) and *engrailed* genes (A. Joyner, University of Toronto), are increasingly common. The severe cranial and cerebellar phenotypes of double mutants of *hoxA3* and *hoxD3*, or *En1* and *En2*, provide solid evidence for the interaction of these genes. Insights into the pathways of erythroid differentiation and muscle development are also forthcoming. Disruption of the *Gata-2* transcription factor gene reveals a vital role in the expansion of erythroid stem cells, placing it upstream of its partner, Gata-1, in the erythropoietic pathway (S. Orkin, Children's Hospital, Boston). The transcription factor, myogenin, turns out to be vital for the expression of several key genes in myogenesis (E. Olson, M.D. Anderson Cancer Center, Houston). Myogenin, in turn, is activated by members of the Mef2 family of transactivators, and an ancestral *Mef* gene has been identified in *Drosophila*.

Denise Barlow.

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A. Ivinson

Although mice have yet to offer new insights into the mechanism of triplet repeat expansion associated with hereditary neurodegenerative diseases, the 'knock-out' of the myotonic dystrophy (DM) gene by D. Housman (MIT) should prove enlightening. It is unclear whether expression of the DM gene is elevated or diminished in DM patients harbouring the repeat expansion. However, mice born with a targeted mutation of the DM gene appear perfectly viable, suggesting that more than simply loss of the gene is required for the disease.

Despite welcome progress of late in identifying human genes that are subject to imprinting, mouse genetics continues to provide the best means of analysing imprinting at the molecular level, Xist being one prominent example (A. Ashworth, Chester Beatty Laboratories, London). S. Tilghman (Princeton University) provided convincing evidence in support of an enhancer competition model to explain the reciprocal patterns of expression of the closely-linked genes, *Igf2* and *H19*. The unlinked Igf2 receptor gene appears not to have an imprinted partner, but D. Barlow (Institute of Molecular Pathology, Vienna) has elegantly demonstrated a methylated 'box' that seems to mark the expressed *Igf2r* allele, scotching the notion that imprinting is necessarily synonymous with silencing. As to the function of imprinting, E. Robertson (Harvard) again proved the worth of targeted mouse mutations, suggesting for instance that the primary function of the Igf2 receptor is to control circulating Igf2 levels and thereby restrain embryonic growth.

And finally, a topic that was not discussed, but perhaps should have been, was the marked progress in creating transgenic mice for the production of human monoclonal antibodies, which at least two groups, from the companies of Cell Genesys (page 13 of this issue) and GenPharm (*Nature*, April 28 1994), now describe. It would appear that mice are poised to become 'experimental surrogates' in the literal sense, too. □