nature genetics

Old mice, new tricks

A look back at 'This Week's Citation Classic' in the 29 July 1985 edition of *Current Contents* finds a paper by Donald W. Bailey titled "Recombinant-inbred strains. An aid to finding identity, linkage, and function of histocompatibility and other genes." (*Transplantation* **11**, 325–327; 1971). Given the length of time it takes to generate even a few strains of recombinant inbred lines (RILs), the resource that Bailey described was no small achievement. The original eight CXB strains, which crossed the continent twice with Bailey before being permanently housed at the Jackson Lab, were at the leading edge of an effort to speed the mapping of both mendelian and complex traits. This line of work has reached a new milestone with the three reports (pages 225, 233, 243) in this issue on the integration of transcriptional profiling with mouse and rat RILs to map quantitative trait loci (QTLs) that contribute to heritable variation in gene expression. These studies illustrate how different lines of research can intersect in unexpected ways.

As Karl Broman describes in his News and Views article (page 209), the construction of RILs is relatively straightforward. Two distinct inbred lines with phenotypic variation are crossed and then sibling-mated for at least 20 generations to produce a new inbred line in which the recombination events that occur in the initial cross are frozen in an essentially inexhaustible resource. Each strain can be genotyped with a panel of markers, and phenotypic data can be accumulated over time to build a rich and permanent database. Standard QTL mapping strategies can then be applied to identify loci that influence complex traits, even if they are not highly heritable. QTL mapping in RILs has perhaps been most successfully carried out in plants. Organisms such as *Arabidopsis thaliana* or *Zea mays* can be inbred by self-mating, thus generating hundreds of strains—and a corresponding degree of statistical power—in relatively short periods of time. Producing sufficient numbers of rodent RILs, however, has remained costly and laborious, limiting its application.

If increasing the number of strains is an obstacle, why not compensate by increasing the number of phenotypic data points? Enter the microarray. In 2001, Ritsert Jansen and Jan-Peter Nap (*Trends Genet.* **17**, 388–391; 2001) proposed a merger of genetics (genetic variation in a segregating population) and genomics (transcriptional profiling), which they called 'genetical genomics'. The central idea is that the mRNA expression level of a gene could serve as a phenotype. With the array providing a high-throughput source of data and the segregating RIL population providing a controlled genetic background, the approach promised to increase statistical power and identify 'expression QTLs' (eQTLs), which might map to *cis*-regulatory regions or to unlinked *trans*-acting factors. Such eQTLs would be good candidates for QTLs that influence the actual cellular or organismal phenotype. As Jansen and Nap noted, however, "…the whole-genome data necessary to validate the concept outlined here are not yet available in the public domain".

Needless to say, the availability of such data is no longer an issue. In the interim, we have also seen the publication of the sequences of the mouse and rat genomes, as well as the generation of a large number of polymorphic markers for genotyping. Several laboratories have also shown that a substantial amount of the variation in gene expression is heritable—a prerequisite for the 'transcriptotype' to serve as a genetically accessible phenotype.

Would it work? Emphatically, yes, although the first applications of genetical genomics, or 'expression genetics' in Broman's apt words, were not to RILs but to yeast, an F_2 cross of inbred mouse strains, maize and human families in the CEPH database (*Science* **296**, 752–755, 2002; *Nature* **422**, 297–302, 2003; *Nat. Genet.* **35**, 57–64, 2003; *Nature* **430**, 743–747, 2004; and *Proc. Natl. Acad. Sci. USA* **102**, 1572–1577, 2005). Each cited example showed that mRNA levels could be treated as a quantitative trait, with *cis*- and *trans*-regulatory QTL mapped and, at least in yeast, identified at the nucleotide level.

The three papers in this issue complete the vision of Jansen and Nap in extending the method to extensively phenotyped strains of rodent RILs. Bystrykh *et al.* and Chesler *et al.* analyzed the BXD mouse RILs, which have been well studied since they were first generated by Benjamin Taylor, a colleague of Don Bailey's at the Jackson Lab. As each group focused on a specific cell or tissue type, a comparison of the identified QTLs allows the first glimpse of the tissue-specificity of transcriptional networks governing distinct cellular phenotypes. A considerable number of eQTLs were common to both brain and hematopoietic stem cells, and Chesler *et al.* suggest that expression profiling of easily accessible lymphocytes may therefore be a useful way to identify genetic variation that contributes to a broad spectrum of phenotypes.

The companion paper by Hübner *et al.* uses the BXH/HXB panel of rat RILs, first developed by Vladimir Kren and Michal Pravenec in the Czech Republic. This panel is derived from a cross of the Brown-Norway strain and the spontaneously hypertensive rat (SHR) strain, which serves as a model for hypertension and the metabolic syndrome. Hübner and colleagues go further in potentially tying rat eQTLs to human disease. They select those rat eQTLs that map to previously detected QTLs for hypertension in the SHR strain and show that 73 of the human orthologs lie in QTLs for human hypertension.

The expression genetics approach is likely to expand greatly in the near future, with additional tissues being analyzed and a proposal to generate 1,000 strains of RILs (*Nat. Genet.* **36**, 1133–1137; 2004). Although the computational challenge is obvious, the WebQTL online tool developed by Chesler *et al.* (http://www.webqtl.org/) shows how decades of phenotypic data can be seamlessly integrated with expression data to allow *in silico* mapping of QTLs. In combination with efforts to elucidate transcriptional networks through biochemical methods, expression genetics in RILs ensures that genetics itself will contribute to the assembly of the wiring diagram of the genome. ■