can be overcome by tinkering with the procedure. "There is no question that it should work in human DNA," says Nelson.

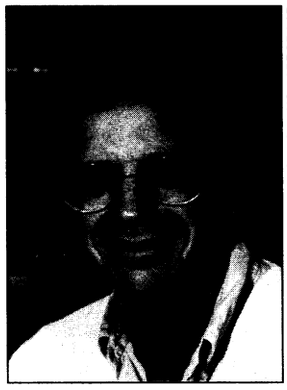
If so, GMS should lend itself to a powerful mapping method called linkage disequilibrium analysis, which compares the genomes of individuals from different families which nonetheless share a particular genetically determined trait. This method assumes that two apparently unrelated people sharing a trait will both have inherited the gene for it from a distant common ancestor. Over the intervening generations, their genomes will have become so thoroughly shuffled up that only those sequences very closely linked to the gene in question will be common between them. Linkage disequilibrium offers the possibility of ultrafine resolution mapping, and whereas many of the markers used in standard linkage analysis are too widely spaced to exploit this potential, says Brown, "the theoretical resolution of GMS is much higher."

For now, however, gene mappers are waiting for GMS's bugs to be ironed out. And while RDA has been shown to work with mammalian DNA, there is a similar reluctance to take up the technique, as some researchers have found it difficult to master. "You just have to fool around with it in the lab and not get discouraged," says Lorraine Flaherty, a mouse geneticist at the State University of New York in Albany, who is using RDA to map genes for a mouse model of polycystic kidney disease. The huge promise of GMS and RDA, however, says Stanford's Myers, makes it important to persevere with both. "You always have a signal-to-noise problem with new techniques," he says.

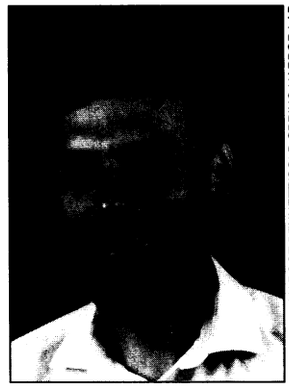
In the short term, say most gene mappers, the best hope of identifying genes underlying complex genetic disorders lies in developing high-throughput, automated versions of existing marker-by-marker genotyping methods. "I think we are going to see a flood of results with this [existing] technology," says John Todd of the Wellcome Trust Center for Human Genetics in Oxford, whose group published a paper in *Nature* earlier this month describing the use of automated genotyping to conduct a genomewide screen for genes underlying insulin-dependent diabetes.

Maybe so, but Millennium's Duyk, for one, believes that for some particularly intractable diseases, this technology probably won't be efficient enough, no matter how automated. And even if the next generation of gene-mapping technology is not based directly on GMS or RDA, argues Duyk, the obvious way forward is to look for methods that—like these techniques—can scan the entire genome in one pass. "The standard way we've survived for 10 years," he concludes, "just ain't going to cut it."

–Peter Aldhous



MARLENA EMMONS/COLD SPRING HARBOR LAB



MARGOT BENNETT/COLD SPRING HARBOR LAB

Mouse mappers. Michael Wigler *(left)* and Nikolai Lisitsyn have used representational difference analysis to map genes in mice.

Additional Reading

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MICROSCOPY

A Sideways Look at Chemical Activity

Microscopists, who generally look down on the objects they're trying to image, are beginning to peer sideways to get a better view. In recent years, scientists have been using the up and down movements of force microscopes to scan the atomic-scale features of material landscapes. The instrument has a tiny tip sensitive to attractive or repelling atomic forces. As it skims the contours of molecules or atoms the tip moves vertically, and the plot of those movements forms a topographical map. But the atomic force microscope (AFM) can also yield another important piece of information—the frictional, or lateral, force on the tip.

On page 2071 of this issue, C. Daniel Frisbie and his colleagues in the lab of Charles Lieber at Harvard University, and others at the Massachusetts Institute of Technology, show how these sideways forces can reveal clues about a surface's chemistry—something topographic maps can't do. Such chemical information "together with the [spatial] image could be very important," notes Richard Colton, an AFM researcher at the Naval Research Lab in Washington, D.C. It could, for example, allow researchers prospecting for new drug compounds to quickly search for reactive molecules by swiping an AFM tip across a sample containing many such compounds.

The key to this work was to chemically modify the AFM tip and surface in a controlled way. The group used self-assembled monolayers to attach two kinds of hydrocarbon molecules to the tip. One is capped with a carboxylic acid that's hydrophilic, or attracted by water; the other ends with a methyl group, which is hydrophobic, or repelled by water. Using a lithographic technique, they also applied these hydrophilic and hydrophobic molecules to a gold surface in a pattern resembling concentric boxes.

When the scientists measured the topography of the surface, it appeared to be smooth. But when they plotted frictional forces, their map matched the box pattern. Friction was highest when hydrophilic molecules (which form hydrogen bonds) on the tip touched hydrophilic molecules on the surface. It was lower when hydrophobic areas on the tip encountered their counterparts on the surface or where the hydrophobic and hydrophilic molecules came in contact. Furthermore, the force that was required to pull the tip from the surface, measured for each combination, correlated quite nicely with the friction measurements.

Lieber has no trouble pointing to examples of how "chemical force microscopy," as he dubs this AFM application, could be useful. One is to study the principles of adhesion and lubrication, which are still rather elusive on the molecular level. But it's biological applications that really fire the imagination of AFM researchers. In medical diagnostics, for example, Lieber suggests that an array of potential drug molecules could be put on a surface, then scanned using a tip coated with a receptor molecule; the scanning could quickly reveal the strongest interaction, and thus the molecule best suited to bind to that receptor. AFM researchers have already begun to explore these uses, showing that sometimes a sideways move can be a real step forward.

–Jocelyn Kaiser