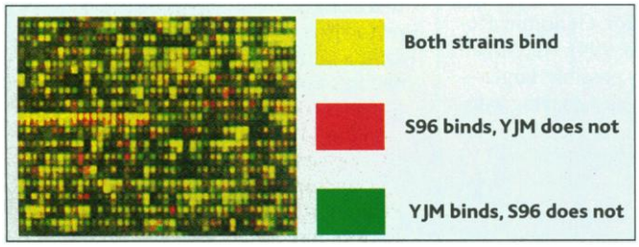
GENOMICS

DNA Chips Survey an Entire Genome

Rack up another jackpot for DNA chips. Already these postage stamp–sized arrays of DNA snippets have proven themselves adept at providing snapshots of all the genes expressed in particular tissues. Now they appear poised to reshape the future of gene mapping, the effort of tracking down which genes contribute to different traits. Earlier this year, one U.S. team used DNA chips to map thousands of commonly varying sites in DNA fragments sampled throughout the human genome (*Science*, 15 May, p. 1077). And now, in work described on page 1194, researchers report for the first time that they have used chips to map an entire genome—that of yeast—in one fell swoop.



On display. Composite computer image of two DNA chips reveals binding patterns of DNA fragments from yeast strains S96 and YJM.

The success, say genetics researchers, could pave the way to a better understanding of conditions, such as virulence in pathogenic microorganisms and susceptibility to heart disease in humans, thought to be caused by the contributions of several genes. "This is a brand-new age. It's really exciting," says Jasper Rine, a geneticist at the University of California, Berkeley. Still, because current chips offer complete surveys only of relatively small genomes, or samples of larger ones, advances in identifying the microbial genes are expected to come much faster.

Pinpointing the location of the genes for traits controlled by single genes is relatively straightforward. Researchers simply compare the DNA of families that share the trait in question to see how often it's inherited together with "markers" at known locations along the chromosomes. But conventional gene-mapping techniques can look only at how a relatively small number of genetic markers differ between individuals, and it becomes unwieldy when tracking so-called quantitative traits that may be caused by the combined workings of several genes scattered throughout the genome.

To circumvent that problem, geneticists Elizabeth Winzeler, Dan Richards, and Ronald Davis, along with their colleagues at Stanford and Duke universities, turned to the DNA chip technology currently under development at the biotech firm Affymetrix, in Santa Clara, California. Affymetrix researchers had previously designed chips composed of over 150,000 snippets of yeast DNA dotted across a 2-centimeter-square silicon wafer. These snippets correspond to overlapping DNA fragments from a complete yeast genome sequenced in 1996. Researchers at Affymetrix and elsewhere have shown that they can create an instant snapshot of all the proteins being made in given cells by exposing such chips to the cell's RNA molecules—each of which corresponds to an active gene—and seeing where the RNAs bind to the known sequences on the chip (*Science*, 3 June 1994, p. 1400).

To map yeast genes, the Stanford, Duke, and Affymetrix researchers took advantage of the same basic chip technology. Their strategy consisted of two parts. First, they created a map of the yeast genome with known genetic landmarks along the way. Next, they showed they could use this map to track the inheritance patterns of markers—and thus of genes—through generations of yeast.

For the mapping phase, the researchers obtained DNA from two different yeast strains, called S96 and YJM789, and used enzymes to break them into small pieces. After tagging the pieces with a fluorescent compound that allows them to be detected, the team applied the fragments to the chips, one yeast strain at a time. If the two sequences matched exactly, the pieces would bind to those in the array. The result was two chips, each displaying different patterns of bright spots showing where the DNA fragments being tested correspond to those on the chip.

Because the S96 genome is virtually identical to that of the strain used to prepare the chip, almost all of the S96 fragments matched those on the chip. But tests on the second strain—YJM789—revealed over 3000 spots on the array with little fluorescence, denoting mismatches, or differences, with the reference strain. The researchers have not yet determined what most of those differences are. But even without that information, Winzeler says, the spots can still serve as genetic markers.

To make a map, the researchers had to figure out where each marker belonged on the yeast genome. That was straightforward, because the full sequence of the yeast genome is known along with the sequence of each of the snippets on the chip. By comparing the sequences of the snippets that didn't bind to any of the test yeast fragments with the genome sequence, the researchers could determine where each of their genetic landmarks fell on the genome.

In the next step in their study, the researchers used this map to locate—simultaneously—four control genes whose positions in the yeast genome were already known, plus a previously unidentified gene involved in yeast's resistance to an antifungal compound known as cycloheximide. Strain YJM789 is susceptible to the drug, while S96 is not. So the researchers mated the organisms and tested their progeny. By looking for genetic markers shared by all the drug-resistant progeny, the researchers were able to pinpoint the location of the drug resistance gene to a 57,000–base pair region on chromosome 15. The researchers also found that the control genes mapped to their expected locations. The team hopes to extend this demonstration to track down the multiple genes that contribute to virulence, says Duke team member John McCusker.

FROM WINZELER *ET AL.*

Rine says the work is "a terrific demonstration" of how researchers can now analyze entire genomes in a single step—an achievement that should aid efforts to map multigene traits. But Kenneth Weiss, a geneticist at Pennsylvania State University in University Park, cautions that identifying the genes responsible for complex human traits may still be difficult. He notes, for example, that some 50 genes may influence susceptibility to heart disease and that many different combinations of mutations in those genes may all lead to the same outward manifestation: heart trouble. That's likely to frustrate efforts to link the condition to just a few key genes. But at least the chips will allow researchers to try something that was previously impossible.

–ROBERT F. SERVICE

IMMUNOLOGY

How Embryos May Avoid Immune Attack

The portrait of an infatuated mother coddling her newborn baby is a fixture in most family photo albums. But before such a touching picture could be taken, the baby had to survive a potentially fatal conflict with its mother: developing as an essentially foreign tissue within the womb without triggering a hostile immune attack. How the fetus does that has long been a mystery, but new results in this issue may provide an answer.

Previous explanations have included the possibility that the mother somehow suppresses her immune responses to the baby, or that the placenta acts as an anatomical barrier to her immune cells. But on page 1191, Andrew Mellor, David Munn, and their colleagues at the Medical College of Georgia in Augusta report evidence indicating instead that the embryo actively shuts down the mother's natural defenses. In their scenario, embryonic cells in the placenta manufacture