

MARC program at Arizona State University in Tempe, worries that some underrepresented minority students would be pushed aside if the program were opened up to everybody. "Many minority students aren't as prepared to apply for things like MARC," says Bustos. "Majority students are more likely to say, 'Hey, this is a great opportunity.'"

Still, a few MARC directors say that the program might benefit from broader eligibility standards. "It's important for students to hear a diversity of views," says health psychologist Cathie Atkins, an associate dean at San Diego State University, who notes that the university's MARC program includes workshops that are open to non-MARC students. "I'd like to see NIH go to a three-pronged standard [that includes socioeconomic factors]," she says, "so long as MARC students still demonstrate a desire to look at the racial disparities in our health

care system."

Poodry says that NIH officials have resisted suggestions over the years to modify the MARC criteria to focus on low socioeconomic status rather than race. "The problem was, compared to whom?" he asks. "We could never figure out how to craft a definition of 'disadvantaged' that would work."

NIH has never figured out how to tell if MARC is delivering on its promise, either. Institutions submit reports on how many MARC scholars graduate, but Poodry admits that the material has never been analyzed. The long-term goal of turning MARC students into applicants for NIH's bread-and-butter R01 awards is even more elusive. "We have anecdotes but no hard data," says Poodry. A 1995 study "fell short of our expectations," he says, "and Congress has never asked us for that type of scorecard." Two years ago, NIH gave the National Academy

of Sciences \$1.5 million to review 20 programs aimed at boosting the number of underrepresented minorities, including MARC and two other undergraduate programs. But it will be at least another year before the academy issues its report.

Whatever the academy concludes about the effectiveness of the MARC program, most directors already believe fiercely in the importance of trying to attract more minorities into science. "I don't apologize for running a program that serves minorities," says Robert Koch, a cell biologist at California State University, Fullerton, and longtime MARC director. "I have a personal commitment to this program, and I feel that this is the only way we are going to make progress." Adds Rocha, "Even if NIH backed away [from MARC], we'd still try to attract more minorities into science."

—JEFFREY MERVIS

Genetics

Scientists Dream of 1001 Complex Mice

Geneticists want to create 1000 new lines of inbred mice to help them sort out the genes behind complex diseases such as diabetes and cancer

OXFORD, U.K.—As any lover of fine Scotch will tell you, a little complexity is a good thing. The trick for the distiller is to produce a complex, but consistent, product. Geneticists trying to sort out the genes that trigger some of medicine's most common ailments face a similar challenge. They need to capture the natural variation that exists in human populations but in a way that is reproducible in the lab.

Despite the sequencing of human, mouse, and other genomes, researchers are a long way from understanding how genes contribute to most common ailments, from depression to diabetes to skin cancer. Sorting out the tangle of genetic and environmental factors that lead to such maladies is one of the biggest challenges of the postgenome era.

Already, several multimillion-dollar projects—including the \$110 million human HapMap (*Science*, 24 May 2002, p. 1391)—are under way to help scientists tease apart the intricate connections. Now a group of mouse geneticists is poised to add a new megabiology effort. They are hoping to win support—and at least \$50 million over 10 years—to create as many as 1000 new lines of inbred mice.

The geneticists propose to cross eight

commonly used mouse strains for four generations, producing litters with all 1680 possible permutations of great-grandparents. They will then turn to inbreeding, performing brother-sister matings until the offspring of each strain are essentially clones. Not all strains will survive the inbreeding, but after



Identical quintuplets. Inbred mice such as these from the A/J line can help researchers track down the genes behind complex traits.

20 generations—about 7 years—the scientists hope to end up with a palette of roughly 1000 different strains. Together, these so-called recombinant inbred (RI) lines would reflect much of the genetic variation present in natural populations. Yet each individual line would have the advantage of being easily reproduced, cookie-cutter fashion, in exact

copies. "Mouse genetics has been focused on making things simpler. We want to make things more complicated," says geneticist Robert Williams of the University of Tennessee Health Science Center in Memphis, one of the leaders of the RI proposal.

Supporters of the RI lines say they would significantly speed the path to specific genes as well as uncover new interactions among genes. Skeptics agree that a new approach is needed but caution that the logistics and expense of producing such a resource may outweigh its benefits.

At a meeting here in early July,* several dozen statisticians, geneticists, and other biologists gathered to discuss the RI project and other methods for tracking down quantitative trait loci (QTLs). These are regions of the genome that seem to play a role in complex traits such as weight gain or susceptibility to cancer. Although scientists using a variety of methods have been fingering increasing numbers of QTLs in both mice and humans, getting from general locale to specific gene is much more difficult. The successes—for example, the connection between depression and the serotonin transporter gene (*Science*, 18 July, p. 386)—have been hard won.

One of the factors confounding the search in humans is that people who carry a susceptibility gene may also carry other protective genes, masking the effect of the disease-prone allele in epidemiological studies. "You can't study complex genetics the way you'd like to in humans," says geneticist Gary Churchill of the Jackson Laboratory in

* Complex Trait Consortium 2nd Annual Meeting, 1–3 July 2003. www.complextrait.org

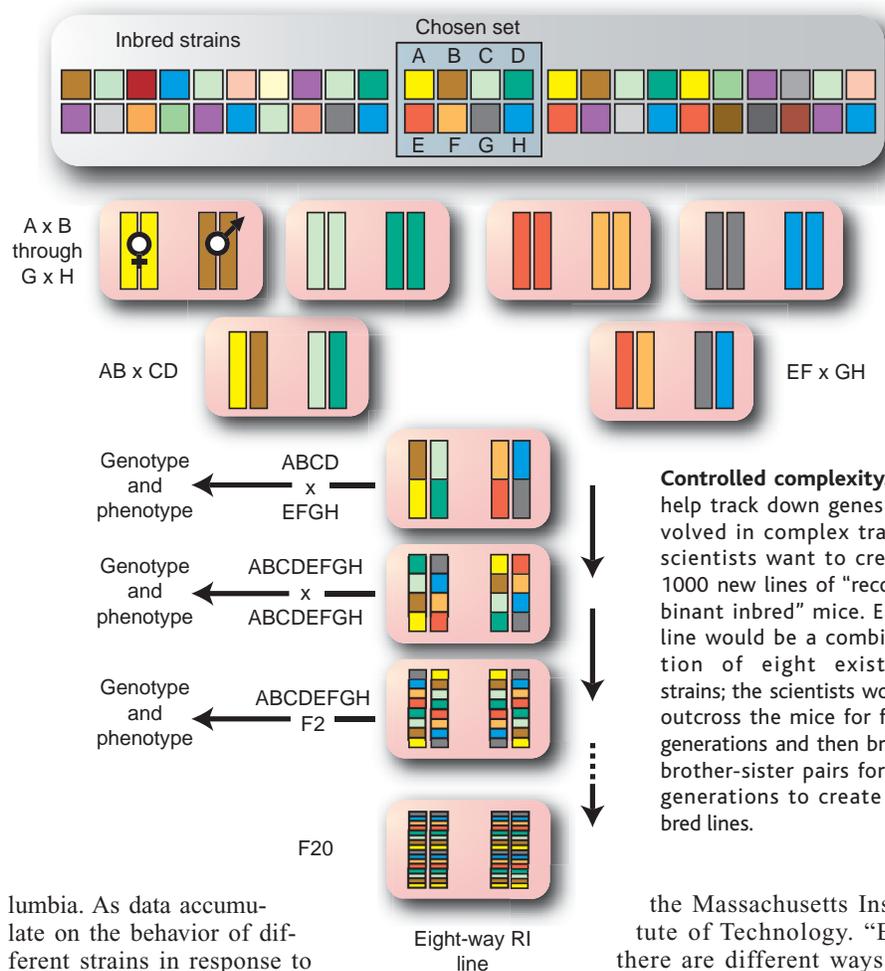
Bar Harbor, Maine. "You can't develop inbred lines, and you can't arrange matings."

To date, most studies that use mice and other animals to discover the role of genes have relied on two standard genetic techniques, mutagenesis and traditional crosses. In mutagenesis, scientists expose mice to chemicals or radiation that disrupt DNA and then look for interesting traits in the offspring. Such studies are very effective for elucidating the role of single genes; indeed, international researchers are working to create a stock of mice with a mutation in every single gene (*Science*, 2 June 2000, p. 1572). But these studies are less useful for understanding how multiple genes work together, Churchill says. "Natural variation is fundamentally different from mutagenesis. Diabetes doesn't arise because of a point mutation. It's a genetic background that interacts with the environment."

To get at more-complex traits, scientists can cross existing strains of mice, screen the offspring for traits of interest, and then look for genetic regions that the affected animals share. For example, a scientist looking for genes related to obesity can cross a mouse from a heavy strain with one from a more svelte line and then, after several generations, search for genes that the heavy cousins have in common. But the problem with such crosses is that they are unique events. Like any wild mating, the assortment of genes in the offspring is random, and once the mice die, their particular genetic mixture can't be recreated. "You measure the mice, and poof, they're gone. If there's an interesting one, you can't go back and put it on a high-fat diet," Churchill says.

RI lines offer a solution. Scientists will be able to quickly trace the origin of any DNA segment in an RI line back to one of the original eight founder strains, speeding the search for genes shared by lines that have a particular trait. And by simply breeding any male-female pair from the desired line, researchers can create more mice with exactly the same mix of genes. Because of the way the RI lines are derived from the original eight-way cross, each line would be at least a second cousin to all the other RI lines. That means that researchers widely separated in space or time could experiment on matching sets of cousins, exposing them to different diets, cancer-causing chemicals, or mental stresses, for example. The results of such screens would be cumulative for each line.

Indeed, the project's proponents want to build a publicly accessible database in which to collect experimental results from around the world so that a neuroscientist in the Netherlands, say, could build on the work of an endocrinologist in British Co-



lumbia. As data accumulate on the behavior of different strains in response to different conditions, scientists will be able to run ever more sophisticated and powerful computer searches for the genes that play a role in disease-related traits. "If there's some connection between bone density and blood pressure, then the evidence will be there," Churchill says.

Williams and Churchill are part of an unofficial group, the Complex Traits Consortium, that is interested in tracking down the variations behind multigenic traits. Along with several colleagues, they hatched the idea of creating hundreds of RI lines at a meeting a year ago; they have since refined it based on input from the consortium's e-mail list server. Early results with more than 100 existing RI lines—developed by Williams and at several other laboratories—are promising. At the Oxford meeting, Leonid Bystrykh and Gerald de Haan of the University of Groningen, Netherlands, described how the strains had enabled them to identify several genes that affect the proliferation of blood stem cells in mice and are apparently linked to several types of leukemia in humans.

But the project's price tag—estimated at \$50 million—gives some people pause. "Everyone would love it if such a resource existed," says Mark Daly, a geneticist at

the Massachusetts Institute of Technology. "But there are different ways of going about [finding QTLs]. ... Any project of this magnitude requires a great deal of justification and careful thought."

Churchill, Williams, and the other proponents agree that the idea needs some fine-tuning. Before they put together a formal proposal for funders, they say, they need to decide which lines to use as parental strains, exactly how many lines they ultimately want to make, and how and where the resulting lines will be stored and distributed. But Churchill is impatient. In the meantime, he says, "we're going to start making some RIs in our lab. Once the population reaches a certain size, people will begin to understand what the technology can do."

At this stage, argues Joseph Nadeau of Case Western Reserve University School of Medicine in Cleveland, mouse geneticists should be exploring several options for finding QTLs. He and his colleagues, for instance, are carefully breeding mice so that a single chromosome from one inbred strain is substituted in the genome of another strain. "The more resources we have, the better," agrees Churchill. The trick, they both concede, will be finding enough money to support such exquisite complexity.

—GRETCHEN VOGEL

SOURCE: COMPLEX TRAIT CONSORTIUM; ILLUSTRATION: C. SLAYDEN