

BEHAVIORAL GENETICS

Abuzz About Behavior

Researchers are tracking down the genes underlying variations in alcohol dependence, sleepiness, and other behaviors by studying specially bred fruit flies

RALEIGH, NORTH CAROLINA—Humans can be short-tempered or mild mannered, shy or boisterous, neat or slovenly—and every combination in between. Understanding the complex genetic networks that underlie behavior—and, ultimately, what makes each of us unique—is a mind-boggling task. Now, Robert Anholt, Trudy Mackay, and their colleagues have developed a resource that may help researchers begin to figure out how genes make us who we are.

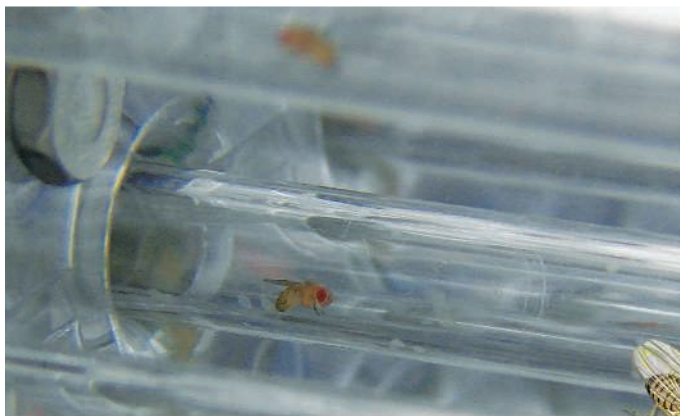
Together with a dozen colleagues at North Carolina State University (NCSU) in Raleigh, as well as collaborators in Europe and Canada, this husband-and-wife team has established a collection of inbred fruit flies (*Drosophila melanogaster*) from a wild population in North Carolina and are correlating patterns of gene expression with specific behaviors in the insects. The work could steer biomedical researchers to genes that influence aspects of human behavior, says Anholt. “What Trudy and Robert are doing will be very important for the discovery of genetic changes that contribute to behavior,” says Catherine “Katie” Peichel, an evolutionary geneticist at the Fred Hutchinson Cancer Research Center in Seattle, Washington.

The project began a decade ago. Twice, in 1999 and 2002, Mackay’s NCSU collaborator Richard Lyman showed up at Raleigh’s farmers’ market and picked off the fruit flies that emerged as crates of freshly harvested peaches were opened. Individual females were placed in vials, and each fly that reproduced became the progenitor of a single line of flies. Their offspring were allowed to mate only with each other, resulting, after several generations, in a line of genetically identical individuals that display consistent behavior. Each line is genetically—and behaviorally—different from all the others. The overall goal is to capture the genetic variation in the North Carolina wild fruit fly population in these wild-derived inbred lines.

To date, the NCSU group has established 345 lines, and the researchers have used microarrays to determine the level

of activity of 18,000 genes in 40 of them. Surprisingly, the expression of about 10,000 genes varies from one line to the next, Mackay and Anholt reported at the annual meeting here earlier this month of the American Genetic Association.

The team has also tracked variation in behavior from line to line under different conditions. Then, by looking for differences in gene expression in lines that differ most in a particular behavior, they can zoom in on



Genes in a bottle. In fruit flies, variation in sleep correlates with gene activity, helping to pinpoint relevant genes.

genes likely to underlie that particular behavior. And, drilling down further, the researchers use existing lines of *D. melanogaster* with mutations in every gene, as well as techniques for manipulating genes in this species, to pin down what each gene does and how it might influence a particular behavior.

The analyses reveal not just individual genes but sets of genes that act in concert. Taken together, “these are the genes that are contributing to the variation in the trait you are looking at,” says William Etges, an evolutionary biologist at the University of Arkansas, Fayetteville. Synchronized genes are likely to be part of a common biochemical pathway; thus known genes in a set provide clues about the function of uncharacterized genes in that cluster.

To get at the genetic underpinnings of sleep, for example, NCSU’s Susan Harbison has compared gene-expression patterns of flies that keep quite different schedules, some spending 20 hours a day resting, others barely pausing for four. She reported that different sets of genes were turned up for nappers and

for nighttime snoozers—out of the hundreds correlated with sleep, only 78 were common to night and day resting, she reported.

Another project, spearheaded by NCSU postdoc Tatiana Morozova, is probing the genetic underpinnings of the fruit flies’ responses to alcohol. Morozova monitors which lines are sensitive to ethanol vapor—measured by how long it takes individuals to lose their ability to cling to a tilted screen—and which ones become more tolerant when the exposure is repeated. In people, tolerance is a risk factor for alcoholism. She found a wide range in both sensitivity and tolerance, but the two traits were not linked. “You can’t tell who will develop tolerance” based on who is sensitive, Morozova reported.

The gene-expression analysis revealed 195 genes that appear to play a role in sensitivity to alcohol and about 600 linked to tolerance. Many of the genes that underlie sensitivity and tolerance play a role in metabolism, but few were common to both responses. And many have human counterparts. Anholt, Mackay, and Morozova are now investigating whether some of these genes correlate with alcohol tolerance in humans.

NCSU postdoctoral fellow Katherine Jordan is using the inbred lines to look for genes that regulate the insects’ responses to a variety of psychoactive drugs. “There’s no uniform pattern,” she reported. “It’s very similar to how humans react to these drugs.” She has identified several dozen genes whose variations in activity correlated with differences in the flies’ responses, and she is now focusing on a handful that might influence the efficacy of these medications.

These early results are fueling widespread interest in the inbred lines. Soon, anyone will be able to order the lines from a stock center, and microarray data will be available on a public database. And the U.S. National Human Genome Research Institute in Bethesda, Maryland, has just awarded Baylor College of Medicine \$5.75 million to sequence the genomes of individuals from 192 of the lines; the sequences will be publicly available once they are completed, Mackay notes. “It’s the next generation [of genetic studies],” predicts Michael Ritchie, an evolutionary biologist at the University of St. Andrews in Fife, U.K. “You can see people asking not just about two or three genes but about [whole] networks.”

—ELIZABETH PENNISI

