

# Farmers market's genetics

By Angela Spivey

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In 2002, N.C. State genetics professor Trudy Mackay was thinking about how to fill in questions left unanswered by studies of the human genome.

So she asked Richard Lyman to go to the State Farmers Market in Raleigh.

It was June, when most people flock to the market for the peaches. Lyman, a research scientist in Mackay's lab, went to the market every morning and afternoon, but he was there for the fruit flies. Using a simple mesh net, he collected more than 1,000 tiny flies that summer, just to end up with 192 pregnant females of the species Mackay wanted.

Those pregnant Raleigh flies are the ancestors of the *Drosophila* Genetic Reference Panel, which Mackay and colleagues describe in the Feb. 9 issue of the prestigious journal *Nature*.

The panel consists of 192 fly lines, or families. Each family's genes have been sequenced, in collaboration with labs at Baylor College of Medicine and the Universitat Autònoma de Barcelona in Spain.

"No one lab could possibly have afforded to create these fly lines," Mackay said.

"The panel is a resource that the *drosophila* community (geneticists who study fruit flies) can focus on that saves a lot of time and energy," said Charles Langley, a professor of genetics at the University of California, Davis, who isn't affiliated with the panel.

Geneticists can study the flies to track complex traits, such as longevity or disease susceptibility, then look for small genetic variants that appear in the flies with those

- **Name:** Trudy Mackay, 59.

**Occupation:** William Neal Reynolds and Distinguished University Professor of Genetics at N.C. State University's College of Agriculture and Life Sciences. She is an internationally recognized expert in the theory and application of quantitative genetics.

## Why did you choose this field of science?

Quantitative genetics (the study of complex genetic traits) seemed to be of great importance in understanding the genetic basis for human health. I chose fly genetics because tests need to be done on a model system that is amenable to breeding and experiment. Flies have always been ideal models for that.

## What is the scientific question that most intrigues you?

How do all of these millions of genetic variants somehow combine to give us both variation and stability? That is, what are the rules that govern how humans are all very different and yet very much the same?

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traits. Unlike a trait that can be traced to one gene - such as blue eyes - complex traits are caused by many different genes that each have a small effect; they also are sensitive to the environment, Mackay said.

The flies themselves as well as their genetic data are freely available to scientists, through the Fly Stock Center in Bloomington, Ind. Flies are free, except for a shipping charge. Each line is named for the starting place of its ancestors: RAL (for Raleigh) and a number (like RAL85 or RAL57).

Many human genes involved in disease have a mirror gene in flies, so findings in flies can be remarkably translatable, to a point, Mackay said.

From studies of twins, scientists expect many differences between people, such as susceptibility to diabetes or to alcohol, to be caused by genetics. Studying the human genome - the whole set of genes in an entire organism - has revealed many small genetic variants that are linked to disease, but those account for only a small fraction of the heritability that is expected.

"Human genome wide association studies have been entirely valuable in providing hints about biology, new pathways, and new drug targets. But it's become apparent that there's a lot more missing than has been found," Mackay said.

Compared to looking for genetic variants in humans, studying the genes of flies requires more up-front sequencing work. But once that's done, it can be easier to pinpoint the exact genetic variant that is causing the differences you can see, such as disease, Mackay said.

## Detailed sequencing

Here's why. In humans, DNA sequences often occur in predictable patterns. So scientists use computer chips to quickly find patterns of genetic variation without pinpointing all the exact tiny variants, Mackay said. But the fly genome is older, and flies have inbred more, so flies have more possible combinations. That means, to find genetic variations in a fly, scientists must sequence its whole genome in detail, as has been done with the 192 families in the reference panel.

"In the flies you've got the problem that you need to know everything, but once you do, it's easier to implicate the



exact causal variant," Mackay said.

A lot of unglamorous work went into creating the fly lines.

After the collection of the pregnant females, the scientists created each family. First, they let each pregnant female have her offspring. Then, the scientists bred a resulting brother and sister. Then they bred the next generation of offspring. They did that 20 times. The result is that within each fly family, all the members are genetically identical, almost like clones. But each line is genetically distinct from the next.

Mackay envisions expanding the resource.

"Sequencing 192 lines is very expensive. But it's not really enough for doing all these fancy causal association studies. It's the first step. But because they're flies, we can breed them easily. Let's say that RAL859 was really passive and RAL57 was really aggressive. We can cross them and make tens of thousands of flies, as many as we want. And now that we know their genotypes, we don't have to do the sequencing again."

In addition, Mackay wants to start tracking differences between the species that she used in the reference panel (*Drosophila melanogaster*) and a different species, *Drosophila simulans*. So Lyman and a student helper returned to the farmer's market this past summer.

Lyman became the lab's field expert years ago, when he began collecting flies for his own experiments to understand fly DNA repair.

"I can't think of a better way to get samples than to go out and collect them yourself," he said.

When Lyman is in collecting mode, he arrives each morning at the market between 6 and 7, when the vendors are just uncovering their boxes and carts. The best days are when it's around 60 degrees outside; any hotter or colder than that and the flies aren't active.

Lyman said that colleagues often tease him about his email address, which because of his middle initial, "F," turns out to be: [rflyman@ncsu.edu](mailto:rflyman@ncsu.edu).



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