Teaching Genomics, Plainly

Day one of neurochemistry class left junior Nathan Achilly dumbfounded. He had sauntered in, confident that this course would follow the same path as his previous lab experiences at Franklin & Marshall College (F&M), in Lancaster, Pennsylvania: a predetermined project, a known outcome, a 100-point lab report.

But on that first day in 2010, professor Rob Jinks stood waving a list of seven mysterious genes. Researchers at the nearby Clinic for Special Children had recently linked mutations in those genes with diseases in Amish and Mennonite patients. The students’ assignment was to find out if the genes were the culprits.

The clinic team, two physicians and a molecular geneticist, did not have the resources to determine whether the mutations actually caused the slew of neurological and other symptoms. That required “functional data,” observations in cells and animals confirming that the mutations incited problems that could explain the diseases.

Jinks sent his class after that functional data. “It was like, OK, here are some genes and a list of symptoms. Pick one and go,” says Achilly.

Aided by an HHMI grant and Jinks’ steady encouragement, the students boldly advanced. Through a semester—followed by a year of independent study for some—pairs of students searched databases of gene sequences, engineered bacteria to shuttle mutated genes into cells, and captured images of how those cells reacted to the alterations. In December 2010, over shared pizza, the students handed their evidence to the clinicians.

“We just sat there with our mouths open,” recalls clinic physician Kevin Strauss. Jinks, his 13 undergraduate students, and the clinic group published their results on January 17, 2012, in *PLoS ONE*, revealing the mechanisms behind seven perplexing genetic conditions plaguing the local community.

The audacious and controversial experiment was a far cry from the typical college “canned lab,” in which students might count wrinkled peas or extract caffeine from coffee. With real-life gene sleuthing as the focus, students would need to find time to learn the neuroscience content necessary to pass a standardized exam. And their teacher would have to manage seven diverging projects.

Jinks wasn’t worried. The students taking this upper-level course had already taken a prerequisite neurobiology course; they would simply be learning content to solve problems rather than to pass a
test. And he had experience managing several students doing independent study projects at once.

Jinks knew he could do it—with HHMI support. Awarded in 2008, the $1.3 million HHMI grant was structured broadly to bolster genetic analysis and bioinformatics at F&M, allowing for the recruitment of instructors, the career development of current faculty, and outreach to high school teachers to help boost their understanding of bioinformatics. Jinks, who had long studied vision in horseshoe crabs, first tapped those HHMI funds in 2009, to embark on a sabbatical at the University of Pennsylvania. There he performed protein experiments, learned DNA sequencing, and analyzed genetics to better understand vision-related diseases in children.

When he returned to F&M, he approached the Lancaster clinic’s research team to collaborate. Physicians Strauss and Holmes Morton, alongside molecular geneticist Erik Puffenberger, had already been teaching an F&M course, describing in colorful case studies their work with patients from the Amish and Mennonite communities.

These so-called Plain People are named for their eschewing of cars, televisions, and other modern conveniences. Because the 50,000 Amish in Lancaster County descended from only 50 to 200 original settlers, and because they tended to intermarry, they—along with the Mennonites—have a high rate of certain genetic disorders. The smaller gene pools and clear family histories make it easier for researchers to trace possible genetic causes. Since 2009, the clinic team has been discovering new genetic illnesses at a rate of 5 to 10 each year.

Their success fueled Jinks’ bold and risky idea: to restructure his neurochemistry course to support the clinic team’s genetic discoveries. “It was probably ambition coming off a really exciting sabbatical,” he says. “But it is a very unique population of patients and a great group of students.”

Mutations and Behavior Changes

Jinks went forward with the restructured course, teaching undergraduates how to make strong connections between the bedside and bench. Some students did so literally, by going to the clinic to meet patients and taking that experience back to the lab. Independent study student Rebecca Willert, for example, studied a Mennonite family in which five members displayed a form of intellectual disability characterized by learning delays. Through gene mapping and sequencing of family members’ genomes, the clinic team had come up with a single gene as the possible culprit. Puffenberger handed over that information to Willert, in addition to—with the patients’ consent—medical records data detailing symptoms and onset.

By searching bioinformatic databases, Willert hypothesized that the normal gene, called CRADD, regulates how brain cells sprout and maintain proper connections. Her cellular studies showed that the mutated version of CRADD found in the Mennonite family alters the ability of the CRADD protein to interact with other proteins necessary to initiate programmed cell death. Thus, her findings offered a potential reason for the patients’ cognitive and learning deficits.

With Strauss and team, Willert shared her scientific sleuthing story with the family and at the annual meeting of the Society for Neuroscience in Washington, D.C., in November 2011.

“We were looking for answers to whatever would cause this,” says family member Geneva Martin, whose three sons, brother-in-law, and sister-in-law are affected. “It helps just to know.”

Willert says that meeting the family helped her gain a better focus in the lab. “I could put a name and face on what I had been studying for so long,” she says, “and actually see the kids and how they interacted.”

Now she can imagine how a mutation in a nerve cell might translate into the behavioral changes that she saw. It also helped her better design the experiments that she conducted this past summer when she was hired by the clinic team to continue her work.

Shaking off those first-day jitters, Achilly took to the project as well. After two years uncovering how a mutation in an enzyme involved in protein synthesis might cause Usher syndrome type IIIb, characterized by hearing loss and progressive vision loss, Achilly, who graduated in May, has expanded his sights beyond a medical degree. He now plans to pursue an M.D., Ph.D. in translational neuroscience.

“The two years of experience that I gained from Rob’s lab have changed my life in many ways,” he says. “The critical thinking involved, thinking of these things as puzzles, has been captivating.”

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For more information: Among other colleges and universities, Franklin & Marshall College recently won another HHMI grant to advance its work with the Clinic for Special Children (see Institute News).