Help solve the puzzle

Meet Mike Ronemus, a research professor at CSHL. Mike is also a father—to a young boy with autism. “For me,” he says, “this is not just a job; it’s personal.”

Cold Spring Harbor Laboratory has one of the world’s largest and most successful research programs in autism genetics. Ronemus and his colleagues, led by Professor Michael Wigler, are using Next-Gen sequencing to comprehensively search for DNA mutations in autistic children. The team has discovered that autistic children have a higher rate of spontaneous DNA mutations—“new” mutations that don’t occur in either parent. This information is already changing how we think about autism spectrum disorders.

Ronemus filmed a Public Service Announcement with Cablevision to raise awareness and support for autism research at CSHL. “All this is possible because of contributions from private foundations and individuals—including my own,” he says. Check out the PSA online at cshl.edu/mike/

Jaclyn Jansen

$2.7 billion/10 years

to sequence the first human genome

$3000/2 weeks

to sequence six human genomes today

neurons in the mouse cortex and about 1000 synapses, or communications bridges, between each neuron. This means that scientists must map 10 billion connections to get a good idea of how the mouse brain is wired. “The conventional approach relies on microscopy to create this map,” says Zador. But these projects are highly labor intensive and come at the tremendous cost of more than $10 million per year.

Zador has devised a method to genetically tag individual neurons with short sequences of DNA. This is akin to stamping a barcode on each one. In a trick of genetic engineering, Zador’s team has found a way to drag the barcodes to the synapses where neighboring cells exchange messages. There, the barcodes are glued together. The fused DNA barcodes then can be isolated and sequenced with Next-Gen sequencing technology, just like any other DNA sample. Mathematical programs called algorithms enable Zador’s team to make sense of the sequences in order to map connections not just between two cells but throughout the brain. If successful—it remains in the proof-of-concept stage—barcoding and Next-Gen sequencing may enable the team to generate a full-brain map for as little as $10,000 per brain, rather than tens or hundreds of millions.

The CSHL sequencing facility is what turned this project into a reality. “I absolutely would not have thought of this project or been able to pursue it anywhere else,” says Zador. “With all of the open discussion here at the Lab between people in different fields, I was able to see the power of sequencing and all it can do.”

Sequencing single cells to diagnose cancer

CSHL scientists are also using Next-Gen sequencing to revolutionize cancer research. “Our goal has been to develop new kinds of diagnostics—to inform clinicians about the type of cancer cells they are treating so they can choose the best therapeutics,” says Research Professor Jim Hicks, one of the lead scientists on the project.

A single tumor is made up of many different types of cells. Some may be susceptible to specific cancer treatments while others may be resistant to these same drugs. Doctors currently must biopsy a tumor in order to identify the aberrant cell types it harbors. Even then, pathology reports only provide a limited overview of the cancer.

Hicks and other members of Professor Mike Wigler’s lab made a breakthrough when they developed methods to sequence cells one at a time. “We can extract DNA from blood samples or urine, so a minimally invasive blood test can replace a biopsy.”

The next challenge has been to distinguish one type of cancer cell from another. Hicks and colleagues found that, in individual cancer cells, regions of the genome are duplicated or deleted. “These changes, called copy number variations, can be used to identify different types of cancer cells.” This discovery means that it is no longer necessary to sequence the entire genome. Rather, Next-Gen sequencing is employed as a simple counting tool. “You can think of it as a small survey of the genome that lets us see where regions are deleted or duplicated,” says Hicks. The advantage is that you can identify populations of cancer cells with a fraction of the sequencing data.

“The cheapest full genome sequence is at least a few thousand dollars, but we have devised a way to determine the origins of a cell for just $10,” says Hicks, who hopes the work will lead to a marketable tumor diagnostic in the near future.

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Autism is a genetic disease
1 out of 68 children is affected
I’m Mike, a Researcher at CSHL
This is my fight

Jaclyn Jansen