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Pursuing Fast, Affordable Hearing Loss Screening

Eliot Shearer at the University of Iowa Carver College of Medicine is developing a method to simultaneously screen all 66 known deafness genes using the MiSeq® system.

Eliot Shearer is a National Institute on Deafness and Communication Disorders (NIDCD) predoctoral research fellow in the M.D./Ph.D. program at the University of Iowa Carver College of Medicine. He is a member of the Molecular Otolaryngology and Renal Research Labs (MORL) directed by Richard Smith, M.D., a prominent researcher in the field of hearing loss genetics. The MORL is widely recognized for discovering nearly 25% of all known deafness genes and offering genetic testing for deafness for more than a decade. The overall goal of the lab is to uncover genetic causes of deafness and make screening for genetic hearing loss comprehensive, fast, and affordable to everyone.

Q: How is deafness caused and determined?

Eliot Shearer (ES): Nonsyndromic hearing loss is the most common sensory deficit, affecting up to 1 in 500 newborns. Most hearing loss in the United States develops as a result of genetic factors that damage the inner ear. There are more than 60 known genes that can cause deafness and typical screening methods are performed on a gene-by-gene basis. At the MORL, we have used Sanger sequencing for more than 10 years for genetic testing. Sanger sequencing, which was invented in 1977, is the gold standard for genetic testing, but due to the low efficiency of this method, we can only offer tests for 12 of the known deafness genes. We receive DNA samples from people all over the world who have deafness. Unfortunately, using currently available methods, we can't actually provide a genetic diagnosis for many of these families.

Q: How will the MiSeq system help you study deafness?

ES: The ultimate goal is to change the way health care is provided to those who are affected by hearing loss. Our objective is to make genetic testing the first test that's ordered after it is determined that a patient has hearing loss. Using the Illumina MiSeq system paired with our targeted capture OtoSCOPE platform, we will be able to screen all known 66 genes for deafness at the same time, making testing faster, less expensive, and more accessible.

> "Our goal is to run all 66 genes on the MiSeq system with an overall turnaround time of two to three months, compared to running one gene in the same amount of time with Sanger sequencing."

As a predoctoral research fellow in the M.D./Ph.D. program at the University of Iowa Carver College of Medicine, Eliot Shearer performs both clinical testing and research in the Molecular Otolaryngology and Renal Research Labs.

Q: How do you design a test to detect all 66 genes?

ES: OtoSCOPE uses a method called targeted sequence capture to isolate only the exons of the genes that are known to cause hearing loss. We take a patient's DNA sample, pull out just the DNA that is responsible for deafness, and sequence it. During bioinformatics analysis, we clean up the sequencing reads, align them to the human genome, and look at the 66 genes we're interested in. From there we compare test results to our database of known hearing loss variants to identify any known deafness mutations within the test genes.

Q: What do you like about the MiSeq workflow?

ES: There are two primary reasons that we like the MiSeq system. The first is that we can run the same libraries we've run on the HiSeq system on the MiSeq. We don't have to do any extra work and we don't have to change our workflow. Because we have been using Illumina sequencing for more than two years now, we are used to the sequencing workflow and the mechanics of the sequencing technology used in the MiSeq system. Secondly, the Illumina MiSeq is accessible to a lab of our size, thereby allowing us to offer OtoSCOPE, which is the vital link between the patient and their genetic diagnosis.

Q: How does the quality of the data from the MiSeq system compare to what you are used to?

ES: Overall the quality looks very good. We are used to looking at Illumina data, so it's easy for us to run the MiSeq data in our established bioinformatics workflows. We are happy with the output. So far it looks great. It's on a smaller scale than the HiSeq system, but the quality is as good or better.

Q: How will using the MiSeq system affect the cost of genetic testing?

ES: It's huge. We calculated that if we were to sequence all 66 deafness genes with Sanger sequencing it would take a year of lab work and cost about $75,000 per sample. Next-generation sequencing has brought that cost down significantly, but the output of the HiSeq system meant that we would have to wait to have many samples to run to keep the cost economical. With the MiSeq system, we don't have to wait. Our goal is to get it to less than $500 per sample. We believe we will reach that goal in the near future.

Q: How much time will you save using the MiSeq system?

ES: We can run 12 samples in a single run in one day on the MiSeq system. Our goal is to run all 66 genes on the MiSeq system with an overall turnaround time of two to three months, compared to sequencing one gene in the same amount of time with Sanger sequencing. We are also doing a lot of deafness gene discovery and we're really excited to have the MiSeq system. When we send our research samples to a sequencing center, it can take two months or more to get data back. Now we can get our data within a day.

Q: What influenced your decision to use the MiSeq system?

ES: We like the Illumina sequencing technology and were already familiar with the output. It's imperative that we are comfortable with the data that we are getting off the sequencer. It was also important for us to see published data for whatever sequencing system we were going to invest in. There are more than 1,500 published articles using Illumina sequencing technology, which made us very comfortable with our investment.

> "It [the MiSeq system] will allow us to be more flexible in how we design our experiments."

Q: How will using the MiSeq system impact your laboratory?

ES: The MiSeq system will dramatically drop the turnaround time of the lab workflow from two months to one week. We can run a small number of samples on the MiSeq system, get data back, figure out whether we are doing things right, and then run some more samples. We can quickly change and adapt our experiments. We don't need to wait until we have a large number of samples to sequence. What's really exciting is that if a few samples look good on the MiSeq system, we can accumulate more samples and run the same exact libraries on the HiSeq system for higher throughput at a sequencing center with no change in our preparation techniques at all. It will allow us to be more flexible in how we design our experiments.

Q: How do you see the MiSeq system impacting health care?

ES: It's going to be huge for individuals with hearing loss. Currently, a patient with hearing loss, often a child, that comes to see us in the clinic receives a history, physical exam, and a hearing test. We administer a CT or MRI of the inner ear to check for any abnormalities along with blood and urine tests to decide if any other system is affected. Then we screen for each possible deafness gene individually. All this adds up to a lot of health care dollars.

We want to provide people with a single genetic test for hearing loss. In January 2012, we'll start offering the first comprehensive genetic test for deafness. By obtaining a pinpointed genetic diagnosis, we are bringing personal genomics directly into the clinic to help those with hearing loss.

Learn more about the MiSeq system at www.illumina.com/miseq

Learn more about OtoSCOPE at www.morl-otoscope.org

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Pub. No. 770-2011-036 Current as of 19 January 2012

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