Sequencing works in clinical setting to help -- finally -- get a diagnosis

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Advanced high-speed gene-sequencing has been used in the clinical setting to find diagnoses for seven children out of a dozen who were experiencing developmental delays and congenital abnormalities for mysterious reasons.

"I thought if we could obtain even a couple of relatively secure diagnoses out of the 12 patients, that would prove the value of deploying sequencing approaches systematically in patients with unknown but apparently genetic conditions," said David Goldstein, Ph.D., director of the Duke Center for Human Genome Variation and professor of molecular genetics and microbiology.

"Few sequencing studies have approached the problem as we did, taking a very heterogeneous group of patients," Goldstein said. "Getting a likely diagnosis about half of the time is quite stunning and strongly motivates next-generation sequencing for all patients that fail to get a genetic diagnosis through traditional testing."

The research team used next-generation sequencing, a new technology that can rapidly read a person's entire genome or just their exome, the sections of DNA that make the proteins, which direct physiological activities. The cost of such sequencing is becoming lower, making it feasible to do the study in a clinical setting.

The work was published online on May 8, in the Journal of Medical Genetics.

"There are up to 50,000 live births in America each year with the children having features of developmental delays, intellectual disabilities or congenital abnormalities similar to those we studied," said Vandana Shashi, M.D., co-author and associate professor of pediatrics in the Duke Center for Human Genetics. "Many of these children remain without diagnoses and we could systematically try to help identify a cause."

Shashi said families involved with the study often expressed relief just to have a diagnosis, even when a condition remained difficult or impossible to treat.

"Just knowing what was causing the problem took away the mystery, which gives families some comfort," Shashi said.

Goldstein said that simply studying more patients with sequencing tools would facilitate discovery by searching for similarities among patients that have mutations in the same or similar genes.

With time, this would also reveal more diagnoses, said lead author Anna Need, Ph.D., who works in the Duke Center for Human Genome Variation.

"Despite the fact that we ended up with a short list of gene variants for each person we studied and ran other tests, we had no real evidence of a related disease because there haven't been other reported conditions or people with mutations in those genes," Need said. "Some of the people we had no results for yet may get answers as their variants become associated with diseases through other sequencing."

The results of this study also are important for genetic counseling, Goldstein said.

For example, some of the likely diagnoses are due to new mutations that happened in the children, known as de novo mutations. In these cases, the parents would be less likely to pass it on through a subsequent pregnancy, for example.

Another lesson of the study was that some of these individuals may have multiple genetic conditions. Shashi noted one child received a diagnosis for only one of several conditions she had.

"We may not find all of the genetic causes, but over time the success of this type of testing and the

information we learn will only grow," Need said. "Out of the genes we found, two have been found to be associated with disease through recent studies by other researchers."

Goldstein said it is imperative to set up large genetic databases in tertiary medical centers, which have the doctors and scientists who can evaluate patients who might benefit from next-generation sequencing. They would also have the team to do the genomic sequencing, and then, to follow up with biological tests that show the function of the gene.

Goldstein said that hospitals with the right systems in place can note a patient's clinical features and then examine a patient's cells or do a relatively general protein localization assay in cells to get an idea about gene function.

"This is a generalized follow-up system for any of the candidate genes, and the work can be done at a tertiary hospital center for virtually any candidate gene, but not by the diagnostic companies, which don't do any functional testing," Goldstein said. "That's why I see a role for this effort being grounded in an academic research environment."

Provided by Duke University Medical Center

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