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Whole exome sequencing closer to becoming 'new family history'

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Approximately one-fourth of the 3,386 patients whose DNA was submitted for clinical whole exome testing received a diagnosis related to a known genetic disease, often ending a long search for answers for them and their parents, said researchers from the Baylor College of Medicine departments of molecular and human genetics and pediatrics and the Baylor Human Genome Sequencing Center and the University of Texas Health Science Center at Houston.

In an online report in the *Journal of the American Medical Association*, the scientists led by Drs. Yaping Yang, laboratory director of the Whole Genome Laboratory at Baylor, and Christine Eng, professor of molecular and human genetics at Baylor and senior director of Baylor's Medical Genetics Laboratories, found a molecular diagnosis (meaning a genetic mutation or variation linked to a disease) in 25 percent of the large group of cases – confirming in this much larger group of patients the diagnostic yield from their initial report on the first 250 cases that appeared in the *New England Journal of Medicine* a little more than a year ago.

"The findings in this report, I believe, will forever change the future practice of pediatrics and medicine as a whole," said Dr. James R. Lupski, professor of molecular and human genetics and pediatrics at Baylor and a coauthor of the report. "It is just a matter of time before genomics moves up on the physician's list of things to do and is ordered before formulating a differential diagnosis. It will be the new 'family history' that, better yet, gets you both the important variants inherited

from each parent and the new mutations that contribute to disease susceptibility."

In fact, a large percentage of the diagnoses made were patients who inherited a new mutation (in the egg or sperm) that was not previously seen in their parents.

"The routine application of new genome methods in the clinic is not only benefitting patients but changing the way we think about research," said Dr. Richard Gibbs, director of the Baylor College of Medicine Human Genome Sequencing Center and an author of the report.

"It has been wonderful to watch this very large team of colleagues bridging from the patient in clinic to the very most cutting edge genomic technology to give families answers where previously there were none," said Dr. Arthur Beaudet, professor of molecular and human genetics who was chair of the department when the Whole Gene Laboratory was begun and who began the Baylor College of Medicine Medical Genetics Laboratories.

"The diagnostic rate holds for the entire set of undiagnosed 3,386 patients who underwent whole exome sequencing between June 2012 and August 2014," said Eng, who reported on a detailed analysis of 2,000 consecutive patients.

The procedure involved sequencing the DNA of the patients using new sequencing technologies referred to as next generation sequencing and comparing those results to the normal reference. Any disease associated mutations were then also compared with the parent's DNA to determine if the child inherited it from one or both parents to better understand the cause of the disease. In this study, the whole exome sequencing also identified ways in which physicians could intervene clinically to ameliorate or eliminate negative symptoms and to give families more

information about the possible disease course.

In addition to confirming the 25 percent diagnostic rate in a much larger group of patients, the newest study shows that rare genetic events contribute in a very big way to disease susceptibility, said Yang, first author of the *JAMA* study.

Among the major contributors to disease are de novo events in which a single change occurs for the first time in the make-up of a gene (known as a Mendelian mutation) in a patient, uniparental disomy (in which a person inherits two copies of a mutation from the same parent), mosaicism and copy number, she said.

"Clinical exome sequencing can assist diagnosis in a wide range of disorders that are diagnostic dilemmas," said Lupski, a clinical pediatric geneticist at Texas Children's Hospital. Many of the patients in the study were referred from Texas Children's or other medical centers across the United States.

"Rare variants and Mendelian disease are important contributors to disease populations. This is in sharp contrast to the thinking of population geneticists who investigate (by genome wide association studies) how common variants contribute to disease susceptibility. We find 'rare variants' in aggregate actually contribute to disease susceptibility in a big way. The individual diseases may be rare, but there are thousands of such diseases and many more being defined through genomics," said Lupski.

"I expect that in a few years, we will learn of the importance of whole exome sequencing in adult medicine and in fields of pediatrics outside of development," said Dr. Sharon Plon, professor of pediatrics and molecular and human genetics at Baylor, as well as director of the Baylor Cancer Genetics Clinic and a member of the Texas Children's Cancer

Center. "We are currently performing an NIH-supported clinical trial of whole exome sequencing in childhood cancer patients to learn of its potential utility for these patients."

In the detailed study of 2,000 patients, 504 patients received a molecular diagnosis of which 280 patients had a single gene mutation that caused disease (autosomal dominant), 181 were autosomal recessive (two mutated genes), 65 were X-linked (mutation on the X chromosome) and one was presumed inherited through the mitochondria. In five cases, the patient inherited two copies of the mutated gene from the same parent (uniparental disomy). Of the dominant mutations, 208 were de novo mutations not inherited from either parent, 32 were inherited and 40 not determined because parental samples were not available for laboratory analysis.

Among the de novo mutations, five demonstrated mosaicism, which suggested that the mutation occurred after fertilization. Mosaicism means that the patient has a small population of cells with a different genetic pattern than most of the cells in the body.

The researchers found 708 presumptive causative variant alleles in the 504 cases, with most of the variants being novel and not previously reported. Of note, almost 30 percent of the diagnoses occurred in disease genes only identified by researchers in the last three years. In 65 cases, there was no available genetic test other than exome sequencing to find the mutated gene at the time the test was ordered.

Twenty-three patients (about 5 percent) had mutations in two different genes, which could account for various aspects of the patient's medical condition.

"Doctors generally try to find one diagnosis that explains all the issues a patient may have. We have found that in some cases, a patient may have

a blended phenotype of two different conditions," said Eng. "That patients may have two different rare genetic diseases to explain their condition was an unexpected finding prior to the use of whole exome sequencing."

In the 2,000 cases, incidental findings of medically actionable results that could result in early diagnosis, screening or treatment were found in 92 patients. Three patients had more than one finding.

"For the 25 percent of cases that received a molecular diagnosis, this information ended the diagnostic odyssey, provided more informed medical management and allowed for precise determination of reproductive risks, but in relatively few cases, resulted in specific treatment to reverse the condition," the authors wrote.

Provided by Baylor College of Medicine