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Whole-exome sequencing shows potential as diagnostic tool

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Among a group of 2,000 patients referred for evaluation of suspected genetic conditions, whole-exome sequencing provided a potential molecular diagnosis for 25 percent, including detection of a number of rare genetic events and new mutations contributing to disease, according to a study appearing in *JAMA*. The study is being released to coincide with the American Society of Human Genetics annual meeting.

Whole-exome sequencing analyzes the exons or coding regions of thousands of genes simultaneously using next-generation sequencing techniques. By sequencing the exome of a patient and comparing it with a normal reference sequence, variations in an individual's DNA sequence can be identified and related back to the individual's medical concerns in an effort to discover the genetic cause of the medical disorder, according to background information in the article.

Yaping Yang, Ph.D., and Christine M. Eng, M.D., of the Baylor College of Medicine, Houston, and colleagues, had previously conducted a pilot study of whole-exome sequencing that included 250 patients. This current study included 2,000 patients (primarily pediatric, 88 percent), with clinical whole-exome sequencing analyzed between June 2012 and August 2014. Tests were ordered by the patient's physician for suspected genetic conditions. Peripheral blood, tissue, or extracted DNA samples were collected from patients or their parents. The majority of the patients had neurological disorders or developmental delay (87.8 percent; neurological, neurological plus other organ systems, and specific neurological groups) and 12.2 percent of patients had nonneurological

disorders (nonneurological group).

A molecular diagnosis was reported for 504 patients (25.2 percent) with 58 percent of the diagnostic mutations not previously reported. Molecular diagnosis rates for each phenotypic (physical manifestations) category were 143/526 (27.2 percent) for the neurological group, 282/1,147 (24.6 percent) for the neurological plus other organ systems group, 30/83 (36.1 percent) for the specific neurological group, and 49/244 (20.1 percent) for the nonneurological group.

In the 2,000 cases, 95 medically actionable incidental findings were reported in 92 patients (4.6 percent). Three patients had more than 1 such finding. In 59 patients (3 percent), the incidental findings occurred in genes included in the American College of Medical Genetics and Genomics list of 56 genes recommended to be disclosed. The remaining 33 patients (1.7 percent) had mutations in genes reported based on the researcher's local criteria for reporting of medically actionable results.

"A molecular diagnosis rate of 25 percent was observed in our pilot study of 250 cases and has remained consistent in this larger series of predominantly pediatric patients with diverse clinical presentations most notable for intellectual disability and neurological phenotypes," the authors write.

They add that approximately 30 percent of positive cases reported herein harbored presumptive causative mutations in disease genes discovered since 2011, reflecting the benefits of an accelerating pace of disease gene discovery. "Whole-exome sequencing testing is a platform suitable for timely incorporation of new disease genes because it interrogates entire coding regions, making it possible to automate the updating of disease gene annotation for clinical reporting, even after the initial analysis is completed."

The researchers conclude that the "observed flexibility and yield of whole-exome sequencing may offer advantages over traditional molecular diagnosis approaches in certain patients."

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