Successful treatment of rare neurodegenerative disease exemplifies potential of precision medicine

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A 20-month-old girl suffering from a rare neurodegenerative disease was diagnosed by exome sequencing and successfully treated. The case, which exemplifies the potential of precision medicine, involved scientists at Columbia University Medical Center (CUMC) and Duke University, and is described in two papers that were published in the online journal Cold Spring Harbor Molecular Case Studies.

Without advanced genetic testing, the child would most likely have been misdiagnosed and would have succumbed to the illness, called Brown-Vialetto-Van Laere Syndrome 2 (BVVLS2), a progressive and usually fatal neurodegenerative disease. This is the earliest that a patient with this disease was effectively treated, made possible only through whole exome sequencing.

"Being able to diagnose a genetic disease doesn’t always mean we’re able to use what we know to treat or cure the patient, so this case was unusual," said study leader David B. Goldstein, PhD, professor of genetics and development and director of the Institute for Genomic Medicine at CUMC. "Nonetheless, it demonstrates how exome or whole genome sequencing can benefit patients. As we learn more about the genetics of disease and discover new treatments, cases like this will become increasingly common."

The girl was first seen at age 15 months at Duke University Hospital. Doctors suspected that her symptoms, which included gait abnormalities, arm weakness, vision problems, and excessive drooling, were due to an autoimmune disorder. After four months of steroid treatment failed to improve her condition, she was referred to Dr. Goldstein, then director of Duke's Center for Human Genome Variation. Sequencing of her exome (the protein-coding portion of the DNA) and other genetic testing conducted at Duke and at CUMC, revealed that she had mutations in both copies of the SLC52A2 gene. Such mutations cause severe riboflavin (vitamin B2) deficiency, leading to BVVLS2. The CUMC researchers, including Slavé Petrovski, PhD, an associate research scientist and co-author of the two papers, showed that the mutations in SLC52A2 disrupted the typical expression of the protein, and confirmed the diagnosis.

BVVLS2 is difficult to diagnose, according to Dr. Goldstein, who is now also professor of genetics and development at CUMC. The signs and symptoms are similar to those of other conditions, and blood tests for riboflavin appear normal because the vitamin deficiency occurs inside red blood cells rather than in the general circulation.

Just a month after the patient was referred for genetic testing, the diagnosis was confirmed and the child was treated with oral riboflavin supplements. Within weeks, her symptoms began to improve. Clinical follow-up over eight months suggests that the improvement will be long-lasting.

"There’s no question that every child with a presumed genetic disease should have their exome sequenced," said Dr. Goldstein. "Sequencing only tells us exactly what a patient has, and what to do therapeutically, a fraction of the time. But it happens often enough that it’s worth doing on a routine basis. Our intention at Columbia is to ensure that any such patients have their genomes carefully interpreted.

Cold Spring Harbor Molecular Case Studies is a new publication from Cold Spring Harbor Laboratory presenting genomic and molecular analyses of individuals or groups of patients, alongside clinical findings, to provide insights into disease development and treatment.

The first paper is titled, "Exome sequencing results in successful riboflavin treatment of a rapidly progressive neurological condition." In addition to Dr. Goldstein, contributors are: Slavé Petrovski (CUMC, University of Melbourne, Austin Health and Royal Melbourne Hospital, Melbourne, Victoria, Australia), Vandana Shashi (Duke University School of Medicine, Durham, NC), Steven Petrou (Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia), Kelly Schoch (Duke), Keisha Melodi McSweeney (CUMC), Ryan S. Dhindsa (CUMC), Brian Krueger (CUMC), Rebecca Crimian (Duke), Laura E. Case (Duke), Roha Khalid (Duke), Maysantoine A. El-Dairi (Duke), Yong-Hui Jiang (Duke), and Mohamad A. Mikati (Duke).

The second paper is titled, "Sustained therapeutic response to riboflavin in a child with a progressive neurological condition, diagnosed by whole-exome sequencing." The other contributors are Vandana Shashi (Duke), Slavé

Petrovski (CUMC and University of Melbourne), Kelly Schoch (Duke), Rebecca Crimian (Duke), Laura E. Case (Duke), Roja Khalid (Duke), Maysantine A. El-Dairi (Duke), Yong-Hui Jiang (Duke), and Mohamad A. Mikati (Duke).

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Columbia University Medical Center