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Study finds likely genetic source of muscle weakness in six previously undiagnosed children

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Scientists at the Translational Genomics Research Institute (TGen), using state-of-the-art genetic technology, have discovered the likely cause of a child's rare type of severe muscle weakness.

The child was one of six cases in which TGen sequenced—or decoded—the genes of patients with Neuromuscular Disease (NMD) and was then able to identify the genetic source, or likely genetic source, of each child's symptoms, according to a study published April 8 in the journal *Molecular Genetics & Genomic Medicine*.

"In all six cases of myopathy, or muscle weakness, these children had undergone extensive, expensive and invasive testing—often over many years—without a successful diagnosis, until they enrolled in our study," said Dr. Lisa Baumbach-Reardon, an Associate Professor of TGen's Integrated Cancer Genomics Division and the study's senior author.

This is a prime example of the type of "personalized medicine" TGen uses to zero in on diagnoses for patients, and to help their physicians find the best possible treatments.

"Our results demonstrate the diagnostic value of a comprehensive approach to genetic sequencing," said Dr. Baumbach-Reardon. "This type of next-generation sequencing can greatly improve the ability to identify pathogenic, or disease-causing, genetic variants with a single,

timely, affordable test."

In one of the six cases, TGen researchers found a unique disease-causing variant, or mutation, in the CACNA1S gene for a child with severe muscle weakness in addition to ophthalmoplegia, or the inability to move his eyes. Properly functioning CACNA1S is essential for muscle movement. More specifically, CACNA1S senses electrical signals from the brain and enables muscles to contract.

"To our knowledge, this is the first reported case of severe congenital myopathy with ophthalmoplegia resulting from pathogenic variants in CACNA1S," said Dr. Jesse Hunter, a TGen Senior Post-Doctoral Fellow, and the study's lead author.

Learning the specific genetic cause of symptoms is a key step in finding new therapeutic drugs that could treat the patient's disease.

In another closely related case, TGen's genetic testing found a pathogenic variant in the RYR1 gene in a case of calcium channel myopathy. When the brain sends an electrical signal, CACNA1S opens the RYR1 calcium channel flooding muscles with calcium and causing them to contract. When either partner of this duo doesn't function correctly, devastating muscle weakness results.

Five of the six cases involved patients under the care of Dr. Saunder Bernes, a neurologist at Barrow Neurological Institute at Phoenix Children's Hospital. Dr. Bernes referred all five cases to TGen for genetic sequencing in an effort to find the causes of the children's muscle weakness.

A sixth patient, under the care of Dr. Judith Hall at the University of British Columbia, also underwent genetic sequencing at TGen.

"Without this type of deep genetic analysis, we might never have discovered the source of each of these children's disease," said Dr. Bernes, whose young patients' previous tests included muscle biopsies, EMG, MRI, EKG and limited gene sequencing. "Now we are in a much better position to find new treatments for these and other children with similar symptoms."

In three of the six cases, the children had Collagen 6 myopathies, or weaknesses. Collagen is essential to holding together muscles, tendons, skin, cartilage and the disks between vertebras. In all three cases, TGen researchers identified a pathogenic variant, or disease-causing mutation, in the COL6A3 gene, or likely pathogenic variants in the COL6A6 gene.

In still another case, TGen testing identified the genetic culprit of the child's muscle weakness as a pathogenic EMD variant associated with Emery-Dreifuss muscular dystrophy. EDMD usually results in slowly progressive weakness and muscle wasting in the arms and legs, and causes contractures of the elbow, neck muscles, and the Achilles tendon.

"Reporting these cases raises awareness about how often each child with muscle disease is unique, requiring personalized medical treatment beginning with genetic diagnosis through sequencing like we perform at TGen." Dr. Hunter said. "This study provided answers to families with these difficult-to-treat and rare illnesses."

More information: Novel pathogenic variants and genes for myopathies identified by whole exome sequencing, *Molecular Genetics & Genomic Medicine*, 2015.

Provided by The Translational Genomics Research Institute