Sequencing studies help pinpoint gene in Prader-Willi syndrome

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As so many genome studies do, this study published online in the journal *Nature Genetics* began with a single patient and his parents who were in search of a diagnosis.

The parents of this first patient sought genetic testing for Prader-Willi syndrome when he was only a year old, but the test, which was still in its infancy, came back negative. For the next 12 years, his parents were left in limbo. He had many features of the disease – including lack of muscle tone, feeding difficulties and failure to thrive early on. Autism spectrum disorder and mild intellectual disability became evident as he grew older.

Dr. C. Thomas Caskey, then with UTHealth and now with Baylor College of Medicine, referred the patient to Dr. Christian Schaaf, an assistant professor of molecular and human genetics at Baylor College of Medicine and a faculty member at the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, for an evaluation. Schaaf agreed that the boy had many of the outward signs consistent with Prader-Willi, but others were lacking, such as the morbid obesity, which is typically caused by a very aggressive appetite.

Dr. Manuel L. Gonzalez-Garay (co-first and co-corresponding author), assistant professor and bioinformatics expert at the University of Texas Health Science Center at Houston's Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases, identified a single change (called a point mutation) in the gene MAGEL2 using highly accurate whole genome sequencing information from Complete

Genomics, Inc., of Mountain View California. This gene is located in the area of chromosome 15, which researchers knew was involved in Prader-Willi syndrome. The single base deletion found in this GC-rich and difficult to sequence gene is a frame-shift mutation that disrupts activity of the protein product of MAGEL2.

Prader-Willi syndrome is an imprinted disease, which means only one of the two copies of the gene inherited from your parents is working. The other is "silenced," usually during the formation of eggs or sperm. In this case, neither parent had a mutation, meaning that the mutation occurred first in this child. However, it still mattered whether the mutation came from the mother or the father.

The team from UTHealth and Complete Genomics then performed an involved analysis that determined that the mutated gene was on the paternal chromosome 15.

"Because the mom's copy of the gene is silenced and the dad's copy is deficient, there is no functional copy of the gene in his body," said Schaaf. "It was a nice collaboration among Baylor, UTHealth and Complete Genomics. But it was only one patient. When you identify a new gene and want to prove that it is the real cause of disease, you really need to identify several patients with mutations in the same gene, and show that they also have similar clinical manifestations. You also ought to consider the severity of the mutation and how rare the mutation is."

To start, they began to look for other patients. They asked the Baylor Whole Genome Sequencing Laboratory to find out if there had been similar mutations found in patients who had their exomes or protein-coding portions of the genome sequenced. They searched through the records of 1,200 and found three more patients with mutations in the same gene. One of the three had classic Prader-Willi syndrome, the other two were classified as Prader-Willi like. All three children had the

standard molecular testing for Prader-Willi when they were infants, with negative results.

"This is the first report of point mutations causing Prader-Willi syndrome," said Schaaf. "Always before, researchers had identified deletions in the chromosome or uniparental disomy, which means that both chromosomes 15 were inherited from the mother, and none from the father. We have shown that also a single base pair alteration (of nucleotides in the genetic material) can cause Prader-Willi syndrome."

The Baylor lab began offering the testing on July 15. Not only does it offer testing for the mutation but also to identify whether the mutation occurs on the gene from the mother or the father.

"This study speaks to the value of collaboration and the power of the whole genome testing," said Schaaf. "It showed me again how important it is to these families to find 'an answer'. Many have been through years of uncertainty, with dozens of diagnostic tests coming back with negative results. Finding the cause puts things at rest, and empowers the families, as they can get better anticipatory guidance and better estimate of recurrence risk within their family."

Perhaps some day, he said, it might be possible to "un-silence" the silenced copy of the gene. "It's been done in mice with other diseases involving imprinted genes, and there's some evidence it might work in humans as well."

More information: Truncating mutations of MAGEL2 cause Prader-Willi phenotypes and autism, DOI: 10.1038/ng.2776

Provided by Baylor College of Medicine

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