Medical Xpress

New test scans all genes to ID single mutation causing rare disorders

October 19 2014

Audrey Lapidus adored her baby's sunny smile and irresistible dimples, but grew worried when Calvin did not roll over or crawl by 10 months and suffered chronic digestive problems. Four neurologists dismissed his symptoms and a battery of tests proved inconclusive. Desperate for answers, Audrey and her husband agreed to have their son become UCLA's first patient to undergo a powerful new test called exome sequencing.

Using DNA collected from Calvin's and his parents' blood, a sophisticated sequencing machine rapidly scanned the boy's genome, compared it to his parents' and flagged a variant on his 18th chromosome. Calvin was diagnosed with Pitt-Hopkins Syndrome, a rare genetic disorder affecting only 250 children worldwide. At last Audrey and her husband had a concrete diagnosis and clear direction for seeking the best treatment for their son.

Now a landmark UCLA study makes a persuasive argument for the routine clinical use of exome sequencing as a valuable tool for diagnosing children like Calvin with rare genetic disorders. Published Oct. 18 online by the *Journal of the American Medical Association*, the findings show that exome sequencing produced a definitive diagnosis in 40 percent of UCLA's most complex cases – a quantum leap from the field's 5-percent success rate two decades ago.

"Our study is the first to show that sequencing a child's genome together with his or her parents' dramatically improves geneticists' ability to reach

a firm diagnosis in rare disorders," said corresponding author Dr. Stan Nelson, vice chair of human genetics and a professor of pathology and laboratory medicine at David Geffen School of Medicine at UCLA. "We discovered a genetic cause for the conditions affecting 40 percent of the hundreds of young children who come to UCLA for exome sequencing due to developmental delays or intellectual disabilities."

The UCLA Clinical Genomics Center was established in 2011 as one of three facilities in the world (including Baylor and Harvard) to put DNA sequencing to clinical use.

Unlike earlier diagnostics that study one gene at a time, this test rapidly sifts through all of the 37-million base pairs in a person's 20,000 genes to tease out the single DNA change causing a rare genetic disorder. It focuses on the exome, the protein-coding portions of genes that account for only 1 percent of DNA but nearly 85 percent of the glitches known to cause human diseases.

In this two-year study, Nelson worked with first author Hane Lee, an assistant adjunct professor of pathology, to sequence and analyze the exomes of 814 children whose symptoms had baffled previous clinicians despite exhaustive genetic, biochemical and imaging tests.

Here's how it worked. The UCLA center funneled the raw data from sequencing the genomes of each child and their parents through its informatics pipeline to identify variants from the standard human genome. The average person's exome contains more than 20,000 variants, nearly all benign.

Next the team applied a series of filters to the data based on the patient's family history and other relevant aspects of his or her condition. The researchers hunted for all genes and mutations linked by medical literature to the patient's symptoms. Finally UCLA's Genomics Data

Board, a multidisciplinary team of experts, reviewed the findings to reach a diagnosis.

The typical turnaround time is under eight weeks, though test results have been returned to physicians within 10 days in medically urgent situations. With preauthorization, many insurance providers cover the cost to sequence a child and both parents. If not, the out-of-pocket fee runs $6,650.

Audrey Lapidus says that having a diagnosis for Calvin "meant the world." A former journalist, she investigated the disorder extensively, launched the Pitt-Hopkins Research Foundation and helped raise $1 million to fund studies at six universities. She is passionate about advocating exome sequencing to parents and physicians, who often don't inform families that the test is available.

Understanding the origin of Calvin's disease also carried an emotional price. Pitt-Hopkins Syndrome can cause delayed intellectual development, motor delays, breathing problems and seizures. Now an adorable 3-year-old, Calvin still cannot walk and may never speak. Still, Lapidus and her husband would rather know what to expect for their son and plan ahead than continue living in diagnostic limbo.

"All families deserve a clear diagnosis of their child's condition," said Dr. Wayne Grody, director of the UCLA Clinical Genomics Center and a professor of pathology, human genetics and pediatrics at the David Geffen School of Medicine at UCLA and Mattel Children's Hospital UCLA. "Exome sequencing plays an important role in identifying the precise cause of a child's illness. This is immediately useful to families and physicians in understanding how the disease occurred, preventing unnecessary testing, and developing the best strategies to treat it."

The Clinical Genomics Center provides extensive pre- and post-test

genetic counseling to guide families through the tests and prepare them for the results. The team also coordinates multidisciplinary care with UCLA specialists to address the medical complications associated with each child's illness.

"Many parents of a child with a genetic disorder postpone getting pregnant for fear of having a child with the same disease," said Naghmeh Dorrani, genetic counselor. "Exome sequencing can ease this concern by helping us to identify the risk of recurrence and offer parents appropriate prenatal testing options."

"Many parents of a child with a genetic disorder postpone getting pregnant for fear of passing the same disease on to future children," said Naghmeh Dorrani, UCLA genetic counselor. "Exome sequencing can ease this concern by helping us to identify the risk of recurrence and offer parents appropriate prenatal testing options."

Provided by University of California, Los Angeles

Citation: New test scans all genes to ID single mutation causing rare disorders (2014, October 19) retrieved 4 May 2024 from
https://medicalxpress.com/news/2014-10-scans-genes-id-mutation-rare.html