Detecting, testing, treating rare diseases: Technology delivers new era of personalization

March 11 2014

A team of researchers from the National Institutes of Health, Emory University and Cedars-Sinai – specialists in identifying and treating very rare diseases – used three innovative tools to detect a previously unknown gene mutation, test potential therapies in the lab, and initiate personalized drug treatment for a boy with a lifelong history of uncontrollable seizures that caused significant impact on his cognitive and social development.

"This personalized medical approach exemplifies the power of current research tools and shows the immense potential of applying these technologies for future patients," said Tyler Mark Pierson, MD, PhD, a pediatric neurologist and member of the Department of Pediatrics and the Department of Neurology at Cedars-Sinai. Pierson, a member of the research faculty at the Cedars-Sinai Regenerative Medicine Institute, is first author of an article in *Annals of Clinical and Translational Neurology* that published online March 3 ahead of print.

Pierson was a member of the National Institutes of Health's Undiagnosed Diseases Program when he was introduced to the patient and his family. The child was first seen at the NIH-UDP when he was 6; he was diagnosed with early-onset epileptic encephalopathy of unknown etiology. The patient had experienced treatment-resistant seizures since 3 months of age, which caused significant issues with brain development resulting in global developmental delay. The NIH-UDP is a program of

NIH's National Human Genome Research Institute (NHGRI), Office of Rare Diseases Research, and Clinical Center.

The researchers identified a "de novo" gene mutation – one that occurs for the first time in a member of a family – in a gene called GRIN2A. The discovery required an analysis of the patient's genetic makeup in search of the one gene that changed, setting this detrimental series of events in motion. Pierson and his colleagues at the NIH-UDP and Emory University used a recently developed technique called exome sequencing, which focuses on this "functional" part of the genome. They further employed a unique set of data bases and "filters" to streamline their search and screen out false positive results, which are fairly common with new-generation technology that rapidly analyzes thousands of genetic sequences.

"Genome-scale sequencing is a powerful new tool in medical diagnostics. The data it returns, however, can be challenging to interpret, especially for ultra-rare disorders. The rapid bench-to-bedside story of the GRIN2A variation in this family is an example of the coalescence of expertise in medicine, medical genomics and basic science around a single child. This is the type of collaboration that will be needed in an age where we will struggle to connect vast data-collecting capability with the health of individual people," said David Adams, MD, PhD, pediatrician and biochemical geneticist at NHGRI.

Pierson added that many other genes have been associated with several forms of epilepsy in infancy, but only few other instances of early-onset epileptic encephalopathy involved the GRIN2A gene. The GRIN2A gene influences electrochemical events that affect the flow and strength of electrical impulses in the brain.

Having identified the de novo gene defect, the researchers conducted laboratory experiments to confirm the resulting protein dysfunction and

its effects on electrical-regulating mechanisms.

"We then performed lab studies with several drugs that were already approved by the Food and Drug Administration and which we thought might block the seizure activity. Memantine, a drug developed to treat Alzheimer's disease, was shown to have some effect. This medication was previously found to have anticonvulsant effects in animal models of epilepsy and has been safely used in children with autism," said Hongjie Yuan, MD, PhD, scientist in the Department of Pharmacology at the Emory University School of Medicine.

Based on the lab studies, memantine gradually was added to the patient's regimen, which included three anti-seizure drugs that had provided little or no control. With memantine, the number of seizures dropped dramatically, and two of the drugs were discontinued.

"We believe this GRIN2A mutation initiated changes in the child's brain that led to intractable seizures, which contributed to his poor development and cognitive deficits," Pierson said. "It is conceivable that earlier intervention of this personalized medicine approach could have altered the course of the disorder and possibly the child's neurological development. Our results suggest that children with early-onset epileptic encephalopathy should undergo evaluation for similar gene variants, with the possibility of using memantine or other anti-seizure medications to reduce long-term effects."

Pierson has continued his work with rare undiagnosed neurogenetic diseases at Cedars-Sinai with the Pediatric Neurogenetics and Neuromuscular Clinic and his laboratory in the Regenerative Medicine Institute. Pierson was also a co-author on a recent article published in Nature Communications by his Emory University and NIH colleagues that provides a more thorough description of how the GRIN2A mutation results in epilepsy.

More information: *Annals of Clinical and Translational Neurology*. "GRIN2A mutation and epileptic encephalopathy: personalized therapy with memantine." Published online March 3. onlinelibrary.wiley.com/doi/10 … 002/acn3.39/abstract

Provided by Cedars-Sinai Medical Center