Geneticists find causes for severe childhood epilepsies

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Krishna Veeramah, the study's first author, and his colleagues took advantage of the high-throughput DNA sequencing capabilities offered by the UA Genetics Core, housed at the UA BIO5 Institute. Credit: Patrick McArdle/UANews

(Medical Xpress)—Using a state-of-the-art DNA sequencing technique, UA researchers have discovered genetic mutations underlying seizure disorders in previously undiagnosed children.

Researchers at the University of Arizona have successfully determined

the genetic mutations causing severe epilepsies in seven out of 10 children for whom the cause of the disorder could not be determined clinically or by conventional genetic testing.

Instead of sequencing each gene one at a time, the team used a technique called whole-exome sequencing that deciphers nearly all human genes simultaneously.

"My initial hope was that we would find something in one out of the 10 children in our study. But a 70 percent success rate is beyond anyone's imagination," said study leader Michael Hammer, who is a research scientist in the UA's Arizona Research Labs Division of Biotechnology and a member of the UA BIO5 Institute.

For Hammer, the research hit very close to home. Just last year, his lab tracked down the mutation that had caused the severe – and ultimately fatal – epilepsy in his teenage daughter.

"I figured, if we could do this for one child, we could do it for others." Hammer explained. "These are children who have had every test imaginable and tried every possible drug combination, and nobody has figured out where their seizures come from and how to stop them."

The children who participated in the study, published online in the journal *Epilepsia*, all suffered from severe seizure disorders, and most of them started having seizures within the first year or two after birth.

Unlike individuals afflicted with epilepsy later in life, many of whom can live normal lives with the right medical oversight and medications, early-onset epilepsy can be devastating. Children often develop other severe complications such as intellectual disability, autism and loss of muscle tone or coordination. Early death is not uncommon.

"Because their seizures are not well controlled, and that firestorm of electrical activity in the brain is bad for brain development, the damage can be extensive," added Linda Restifo, a professor in the UA department of neurology and a BIO5 member who co-authored the study. "The earlier the seizures start and the more severe and frequent they are, the more likely they are to leave the child with permanent developmental disability."

"The sooner we can catch problems in children and understand what is causing them, the better the chance we have to try and correct them," Hammer added.

To identify changes in the DNA that are the most likely cause of the disorders, the team focused on a class of mutations called de novo mutations: "typos" in the DNA sequence that are present only in the child. In order to find such mutations, the study included both parents and their child.

Overall, the team found 15 mutations in nine children, seven of which are known or likely to cause epilepsy. No mutations could be found in one of the children.

"In four of the patients. we found mutations that were already known to be associated with epilepsy," said Krishna Veeramah, a postdoctoral fellow in Hammer's group and the study's first author. "However, three patients had mutations in genes that were not previously associated with epilepsy in humans but presented plausible explanations for the disorder."

"The fact that we found three genes – in a study involving only 10 subjects – that had never been implicated in epilepsy before suggests that many more genetic defects related to developmental brain disorders remain to be discovered," Veeramah said.

One of the participants in the study was Ashley Wilhelm, a 14-year-old girl from Phoenix, Ariz., whose seizures started when she was only 5 months old. Her first seizures appeared to be triggered by fever, leading doctors to believe they were just that – a side effect of the fever.

"But she soon began to have more and more seizures, and they would last half an hour or longer," said her mother, Ann. "We had all sorts of tests done, but the doctors kept saying her brain was normal, and that they didn't see any reason she'd have those seizures."

Ashley, whose development has severely suffered as a consequence of the repeated seizures, was enrolled in the study through her neurologist, Dinesh Talwar, who co-authored the paper.

Even though her treatment is unlikely to change with the new information, the family said the results brought "more relief than we can explain."

"Since insurance wouldn't pay for the testing, and we couldn't afford it on our own, we were very grateful we were able to participate in the study," said Jeff Wilhelm, Ashley's father. "If such a test could be done much earlier, it would ease the pain for everyone involved. What if our son had decided not to consider having children of his own out of concern they might have the disorder?"

"The results from this study have at last given us a breakthrough," said the mother of another participating teenager. "We had pursued every possible avenue to understand what might be responsible for his epilepsy – magnetic resonance imaging, CT scans, searches for gross chromosome abnormalities or markers associated with epilepsy – with no success."

"Although the discovery doesn't yet give us a treatment, it gives us hope

for finding one," she said. "As more research is done on this mutation, drugs to control our son's seizures will be identified. If more children with epilepsy can be studied and families with children with similar mutations can organize and share resources, there will be more progress."

Hammer said the approach is applicable to other conditions in which conventional genetic testing has failed to reveal the cause.

"Our work bridges research and clinical practice," he added. "We can sequence all the genes in your genome in a matter of days and report it to the patient's family and the physician. That may make a difference in the treatment and management of the disorder in question."

Centers with the capabilities to do this kind of analysis are few and far between.

"Other centers that do this kind of work will sequence your genome and tell you where and what the mutation is in the DNA sequence, but it's not that simple," Hammer said. "In most cases, we find a mutation in a gene not previously known to cause disease, so we need to perform a follow-up study to find out what that mutation actually does."

To perform these follow-up studies, the UA team has established collaborations with leading scientists at the UA and at other institutions.

"Right now, the benefit to families is primarily to get answers," said Restifo. "The long-term goal is to collect this kind of information from more children, which will hopefully lead to new research into medications that improve brain development and function."

Hammer added: "In the meantime, a molecular diagnosis provides immediate relief to the unnecessary guilt parents might feel for their role

in causing their child's suffering. They want answers, not endless doctors visits and tests with negative results, or to have their hopes raised and dashed over and over."

Encouraged by the success of their approach so far, Hammer and his colleagues already have bigger plans.

"We hope to involve other clinical areas such as cardiology, immunology, gastroenterology – anything that we can apply molecular diagnostics or clinical genomics to at the UA, we want to explore. We want to make the University the core for clinical diagnostics using new sequencing technologies for at least the entire Southwest."

UA pediatric geneticist Robert Erickson, another co-author and member of the UA Steele Children's Research Center added, "these efforts will be very important in the diagnosis of newborns with unusual birth defects."

More information: onlinelibrary.wiley.com/doi/10 … 1/epi.12201/abstract

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