MedicalXpress

Gene discovery set to help with mysterious paralysis of childhood

July 29 2012

Alternating hemiplegia of childhood (AHC) is a very rare disorder that causes paralysis that freezes one side of the body and then the other in devastating bouts that arise at unpredictable intervals. Seizures, learning disabilities and difficulty walking are common among patients with this diagnosis.

Researchers at Duke University Medical Center have now discovered that mutations in one gene cause the disease in the majority of patients with a diagnosis of AHC, and because of the root problem they discovered, a treatment may become possible.

The study was published online on July 29 in Nature Genetics.

AHC is almost always a sporadic disease, which means that typically no one else in the family has the disease, said Erin Heinzen, Ph.D., co-author of the study and Assistant Professor of Medicine in the Section of Medical Genetics. "Knowing that we were looking for genetic mutations in children with this disease that were absent in the healthy parents, we carefully compared the genomes of seven AHC patients and their unaffected parents. When we found new mutations in all seven children in the same gene we knew we had found the cause of this disease."

All of the mutations were found in a gene that encodes ATP1A3, one piece of a key transporter molecule that normally would move sodium and potassium ions across a channel between neurons (nerve cells) to regulate brain activity.

In a remarkably broad international collaborative effort, the authors partnered with three family foundations (USA, Italy and France), including scientists from 13 different countries, to study an additional 95 patients and showed over 75 percent had disease-causing mutations in the gene for ATP1A3.

"This study is an excellent example of how genetic research conducted on a world-wide scale really can make a difference for such a rare disorder as AHC," said Arn van den Maagdenberg, Ph.D., and co-author on the study and geneticist from Leiden University Medical Centre in the Netherlands. "It truly was an effort from many research groups that led to this remarkable discovery."

"This kind of discovery really brings home just what the human genome project and next-generation sequencing have made possible," said David Goldstein, Ph.D., Director of the Duke Center for Human Genome Variation and co-senior author on the study. "For a disease like this one with virtually no large families to study, it would have been very difficult to find the gene before next-generation sequencing."

"Ideally what you want from a study like this is a clear indication of how the mutations change protein function so you know how to screen for drugs that will restore normal function or compensate for the dysfunction," said Goldstein, who is also a Professor in Duke Molecular Genetics and Microbiology. "While there is considerably more work to do, our initial evaluation of the mutations suggests that they may alter the behavior of the transporter pump as opposed to reducing its activity, as do other mutations in the gene that cause a less severe neurological disease."

Co-senior author Mohamad Mikati, M.D., Professor of Pediatrics and of Neurobiology, and Chief of Pediatric Neurology at Duke, said, "Many years ago my work with other collaborators on a family with this disease

proved that AHC can be caused by genetic factors, but until now we did not know the underlying gene abnormality.

"The finding that ATP1A3 mutations cause AHC will increase awareness of the disease and the ability to accurately diagnose patients," Mikati said. "While it may take a while for novel drugs to be developed to better treat this disease, we will see an immediate impact through specific testing for mutations in this gene when we suspect a case of AHC. This direct testing will prevent misdiagnoses that too often have caused patients to be treated with inappropriate medications."

Provided by Duke University Medical Center