Rare gene variants linked to high risk of broad range of seizure disorders

April 15 2010

Scientists at Duke University Medical Center have uncovered evidence suggesting that people missing large chunks of DNA on chromosome 16 are much more likely than others to develop a chronic seizure disorder during their lifetime.

"We found that the presence of this genetic variant is one of the strongest risk factors for all forms of epilepsy, possibly accounting for as many as 300,000 cases of epilepsy world-wide," said Erin Heinzen, an assistant professor in the Center for Human Genome Variation at Duke University Medical Center and the lead author of the study appearing online in the American Journal of Human Genetics. Heinzen says the variants are quite rare, but when they do appear they are likely to produce an effect.

Previous studies at Duke and elsewhere found that genetic alterations at this particular stretch of DNA (located at chromosome 16p13.11) are linked to higher risk of schizophrenia, mental retardation, and very specific forms of epilepsy, but this is the first study to show that the deletion is related to a much broader spectrum of seizure disorders as well.

Scientists took DNA from 3,800 patients diagnosed with a wide range of epilepsy and seizure disorders and compared it to DNA from 1,300 healthy volunteers. The research team used genome-wide screening to identify the presence of deletions or duplications of especially long stretches of DNA, known as copy number variants.

They found that 23 of the patients with epilepsy had deletions on chromosome 16 at 16p13.11, but no such deletions appeared in the DNA of the healthy volunteers. They also discovered that the deletion included seven genes and that at least one of the two copies of each of these genes had been shut down in the affected patients. "That means that the amount of protein normally produced by these genes is likely reduced in these patients," says Heinzen.

"Interestingly, we found that patients who had similar-sized deletions sometimes had very different-looking neurologic disorders," said Rodney Radtke, MD, a neurologist and professor of medicine at Duke and a co-author of the study. "It's puzzling to us that deletions at this site can cause such widely differing disorders - schizophrenia and a wide range of seizure disorders. It suggests that there may be additional molecular and biological networks in play that we know nothing about. This offers us an opportunity to figure out how genetic factors are contributing to the development of epilepsy."

"While the proportion of epilepsy explained by this deletion is small, at about half a percent, that still amounts to a huge number of patients globally," Radtke said. "The eventual impact on our understanding of what predisposes an individual to developing epilepsy could be much greater."

Researchers performed additional studies on the DNA of 10 of the 23 epilepsy patients with the deletion to try to tease out which biological pathways were activated by the loss of normal gene expression - which might lead to susceptibility to one disorder over another - but the tests were inconclusive.

The chromosome 16 deletions may provide a new window into the underlying causes of epilepsy, and may help establish mechanistic connections between different forms of epilepsy and schizophrenia. But

more important, says senior author and Duke geneticist David Goldstein, PhD, is the possibility that deletions and other rare mutations underlie a variety of relatively common disorders.

"We feel that the real significance of this work is the example it provides," Goldstein said. "We were fortunate that this deletion was identified using technologies that would not have detected the vast majority of rare and harmful mutations. This has convinced us to rely more heavily on sequencing technologies that will detect most of the mutations in patient genomes."

Goldstein, director of the Center for Human Genome Variation, hopes that the Duke team's genetic findings may lead to new therapeutic directions and new targeted prevention regimens in at-risk patients. "Although it is still early, we feel these results provide pretty strong encouragement that genetics could play a key role in helping to understand and mitigate the effects of a sometimes devastating disease that has been with us for thousands of years."

Provided by Duke University Medical Center