New autism-causing genetic variant identified

25 March 2015

Quinn, an autistic boy, and the line of toys he made before falling asleep. Repeatedly stacking or lining up objects is a behavior commonly associated with autism. Credit: Wikipedia.

Using a novel approach that homes in on rare families severely affected by autism, a Johns Hopkins-led team of researchers has identified a new genetic cause of the disease. The rare genetic variant offers important insights into the root causes of autism, the researchers say. And, they suggest, their unconventional method can be used to identify other genetic causes of autism and other complex genetic conditions.

A report on the study appears in the April 2 issue of the journal *Nature*.

In recent years, falling costs for genetic testing, together with powerful new means of storing and analyzing massive amounts of data, have ushered in the era of the genomewide association and sequencing studies. These studies typically compare genetic sequencing data from thousands of people with and without a given disease to map the locations of genetic variants that contribute to the disease. While genomewide association studies have linked many genes to particular diseases, their results have so far failed to lead to predictive genetic tests for common conditions, such as Alzheimer's, autism or schizophrenia.

"In genetics, we all believe that you have to sequence endlessly before you can find anything," says Aravinda Chakravarti, Ph.D. , a professor in the Johns Hopkins University School of Medicine's McKusick-Nathans Institute of Genetic Medicine. "I think whom you sequence is as important—if not more so—than how many people are sequenced."

With that idea, Chakravarti and his collaborators identified families in which more than one female has autism spectrum disorder, a condition first described at Johns Hopkins in 1943. For reasons that are not understood, girls are far less likely than boys to have autism, but when girls do have the condition, their symptoms tend to be severe. Chakravarti reasoned that females with autism, particularly those with a close female relative who is also affected, must carry very potent genetic variants for the disease, and he wanted to find out what those were.

The research team compared the gene sequences of autistic members of 13 such families to the gene sequences of people from a public database. They found four potential culprit genes and focused on one, CTNND2, because it fell in a region of the genome known to be associated with another intellectual disability. When they studied the gene's effects in zebrafish, mice and cadaveric human brains, the research group found that the protein it makes affects how many other genes are regulated. The CTNND2 protein was found at far higher levels in fetal brains than in adult brains or other tissues, Chakravarti says, so it likely plays a key role in brain development.

Specifically, mutations in CNNTD2 disrupted the

connections called synapses that form among brain cells. "This is consistent with recent findings that many gene mutations associated with autism are involved in synapse development," says Richard Huganir, Ph.D. , director of the Solomon H. Snyder Department of Neuroscience, who participated in the research. "The results of this study add to the evidence that abnormal synaptic function may underlie the cognitive defects in autism."

While autism-causing variants in CTNND2 are very rare, Chakravarti says, the finding provides a window into the general biology of autism. "To devise new therapies, we need to have a good understanding of how the disease comes about in the first place," he says. "Genetics is a crucial way of doing that."

Chakravarti's research group is now working to find the functions of the other three genes identified as possibly associated with autism. They plan to use the same principle to look for disease genes in future studies of 100 similar autism-affected families, as well as other illnesses. "We've shown that even for genetically complicated diseases, families that have an extreme presentation are very informative in identifying culprit genes and their functions—or, as geneticists are taught, 'treasure your exceptions.'" Chakravarti says.

More information: *Nature*, DOI: 10.1038/nature14186

Provided by Johns Hopkins University School of Medicine