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Researchers ferret out function of autism gene

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The structure of the protein NHE9 is one piece of the puzzle of what causes autism. Credit: Kalyan Kondapalli and Rajini Rao

Researchers say it's clear that some cases of autism are hereditary, but

have struggled to draw direct links between the condition and particular genes. Now a team at the Johns Hopkins University School of Medicine, Tel Aviv University and Technion-Israel Institute of Technology has devised a process for connecting a suspect gene to its function in autism.

In a report in the Sept. 25 issue of *Nature Communications*, the scientists say mutations in one such autism-linked gene, dubbed NHE9, which is involved in transporting substances in and out of structures within the cell, causes communication problems among brain cells that likely contribute to autism.

"Autism is considered one of the most inheritable neurological disorders, but it is also the most complex," says Rajini Rao, Ph.D., a professor of physiology in the Institute for Basic Biomedical Sciences at the Johns Hopkins University School of Medicine. "There are hundreds of candidate genes to sort through, and a single genetic variant may have different effects even within the same family. This makes it difficult to separate the chaff from the grain, to distinguish harmless variations from disease-causing mutations. We were able to use a new process to screen variants in one candidate gene that has been linked to autism, and figure out how they might contribute to the disorder."

An estimated one in 88 children in the United States is affected by autism spectrum disorders, a group of neurological development conditions marked by varying degrees of social, communication and behavioral problems. Scientists for years have looked for the biological roots of the problem using tools such as genome-wide association studies and gene-linkage analysis, which crunch genetic and health data from thousands of people in an effort to pinpoint disease-causing genetic variants. But while such techniques have turned up a number of gene mutations that may be linked to autism, none of them appear in more than 1 percent of people with the condition. With numbers that low, researchers need a way to screen variants in order to make a definitive

link, Rao says.

For the new study, Rao and her collaborators focused on NHE9, which other researchers had flagged as a suspect in attention-deficit hyperactivity disorder, addiction and epilepsy as well as autism spectrum disorders. The gene was already known to be involved in transporting hydrogen, sodium and potassium ions in and out of cellular compartments called endosomes, and the team wondered how this function might be related to neurological conditions.

Rao's collaborators at Tel Aviv University and Technion-Israel Institute of Technology constructed a computer model of the NHE9 protein based on previous research on a distant relative in bacteria. They then used the model to predict how autism-linked variants in the NHE9 gene would affect the protein's shape and function. Some of them were predicted to cause dramatic changes, while other changes appeared to be more subtle.

Rao's team next tested how these variant forms of NHE9 would affect a relatively simple organism often used in genetic studies: yeast. "Using yeast to screen the function of variants was a quick, easy and inexpensive way of figuring out which were worth further study, and which we could ignore because they didn't have any effect," Rao says. To do that, the team engineered the yeast form of NHE9 to have the variants seen in autistic people.

For those mutations that did have a detectable effect on the yeast, the team moved on to a third and more challenging step, in mouse brains. They homed in on astrocytes, a type of brain cell that clears the signaling molecule glutamate out of the way after it has performed its job of delivering a message across a synapse between two nerve cells. Using lab-grown mouse astrocytes with variant forms of NHE9, the researchers found a change in the pH (acidity) inside cellular compartments called endosomes, which in turn altered the ability of cells to take up glutamate.

Because endosomes are the vehicles that deliver cargo essential for communication between brain cells, changing their pH alters traffic to and from the cell surface, which could affect learning and memory, Rao says. "Elevated glutamate levels are known to trigger seizures, perhaps explaining why autistic patients with mutations in NHE9 and related genes also have seizures," she notes.

Rao and her team hope that pinpointing the importance of this trafficking mechanism in autism spectrum disorders may lead to the development of new drugs for autism that alter endosomal pH. As the use of genomic data becomes increasingly commonplace in the future, the step-wise strategy devised by her team can be used to screen gene variants and identify at-risk patients, she says.

More information: www.nature.com/ncomms/2013/130 … full/ncomms3510.html

Provided by Johns Hopkins University School of Medicine

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