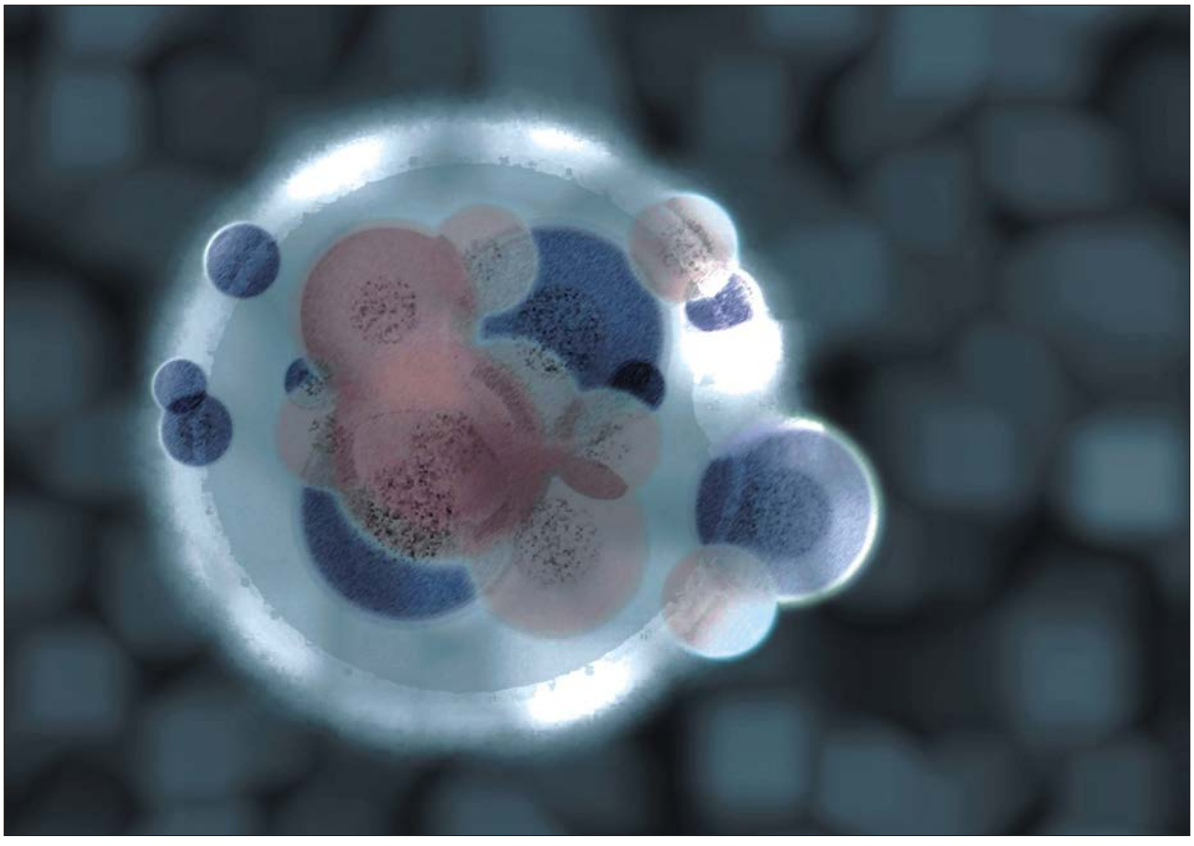

Journal of Biological Sciences

ISSN 1727-3048

science alert

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Gene Linked to Severity of Autism's Social Dysfunction Identified

With the help of two sets of brothers with autism, Johns Hopkins scientists have identified a gene associated with autism that appears to be linked very specifically to the severity of social interaction deficits.

The gene, GRIP1 (glutamate receptor interacting protein 1), is a blueprint for a traffic-directing protein at synapses -- those specialized contact points between brain cells across which chemical signals flow.

Identified more than a decade ago by Richard L. Huganir, Ph.D., Professor and Director of the Solomon H. Snyder Department of Neuroscience at the Johns Hopkins University School of Medicine, and a Howard Hughes Medical Institute investigator, GRIP1 regulates how fast receptors travel to a cell's surface, where they are activated by a brain-signaling chemical called glutamate, allowing neurons to communicate with one another.

The new study, which tracked two versions of GRIP1 in the genomes of 480 people with autism, was published March 22 in the Proceedings of the National Academy of Sciences, and lends support to a prevailing theory that autism spectrum disorders (ASD), molecularly speaking, reflect an imbalance between inhibitory and excitatory signaling at synapses.

"The GRIP1 variants we studied are not sufficient to cause autism by themselves, but appear to be contributing factors that can modify the severity of the disease," says Tao Wang, M.D., Ph.D., Assistant Professor, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine. "GRIP1 mutations seem to contribute to social interaction deficits in the patients we studied."

The Johns Hopkins researchers examined a part of the genomes of 480 patients with autism and compared these with 480 people of similar ethnicity without the disorder. They analyzed about 50 genes known to make proteins involved in a brain-signaling pathway, ultimately focusing their investigation on GRIP1, a protein found at both inhibitory and excitatory synapses, according to Wang.

Initially, looking under a microscope at normal mouse neurons and neurons with a mutant version of GRIP1, the investigators marked the receptor proteins with green fluorescence, added a chemical that promotes their "disappearance" deep inside a cell and timed the rates at which they disappeared -- leaving a cell unable to respond to signals from other cells. They also timed the reemergence of the protein back to the cell surface. With the GRIP1 mutant neurons, the receptors recycled to the surface twice as fast as in the normal neurons.

"If the receptors are recycling faster, the number of receptors on the surface is greater, so the cells are more sensitive to glutamate," Huganir explains. "The quicker the recycling, the more receptors on the surface and the stronger the excitatory transmission."

Even if just the excitatory synapses are affected, and the inhibitory ones don't change, that alone affects the relative balance of signaling, Huganir says.

Next, using 10 mice genetically engineered to lack both normal and mutant GRIP proteins, researchers watched what happened when each animal was put into a box where it could choose between spending time with a mouse it hadn't encountered before, or an inanimate object. They compared the behaviors of these mice with 10 normal mice put into the same social situation. Mice lacking both GRIP1 and GRIP2 spent twice as much time as wild-type (normal) mice interacting with other mice as they did with inanimate objects.

"These results support a role for GRIP1 in social behavior and implicate its variants in modulating autistic behavior," Wang says.

Finally, the team looked at the behavioral analyses of individuals in two families, each with two autistic brothers,

and correlated their scores on standard diagnostic tests that assessed social interaction with their genotypes for GRIP1 variants.

In one family, the brother with two copies of the GRIP1 mutant variety scored lower on social interaction tests than his brother who had only one copy of the GRIP1 variant. The boys' mother, although not diagnosed as autistic, had a history of restricted interests, poor eye contact and repetitive behavior. Tests showed she also carried one copy of the variant.

In a second family, the autistic brother with one copy of the GRIP1 variant had lower social interaction scores than his autistic sibling without a GRIP1 variant.

Because the GRIP1 gene resides in synapses where other genes also implicated in autism have been found, this location is potentially important in terms of clinical relevance, says Huganir. The team plans to sequence hundreds more synaptic proteins in autistic patients to look for mutations and then follow up with functional analyses.

This study was supported in part by research grants from Autism Speaks Foundation and the National Institute of Child Health and Human Development. Authors on the paper from Johns Hopkins, in addition to Huganir and Wang, are Rebeca Mejias, Abby Adamczyk, Victor Anggono, Tejasvi Niranjan, Gareth M. Thomas, Kamal Sharma, M. Daniele Fallin, Walter E. Kaufmann, Mikhail Pletnikov and David Valle.

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