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Scientists find autism-associated synapse alterations

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A Stanford University School of Medicine researcher has pinpointed the mechanism by which a gene associated with both autism and schizophrenia influences behavior in mice.

In a study to be published online on Oct. 12 in the Proceedings of the National Academy of Sciences, a team led by Thomas Sudhof, MD, the Avram Goldstein Professor in the School of Medicine and professor of molecular and cellular physiology, characterized key neurophysiological changes wrought by the deletion of a particular gene in bioengineered mice. The team further identified behavioral changes in the mice that are similar to some symptoms of autism and schizophrenia.

The boundaries separating cognitive disorders including autism, schizophrenia, depression and obsessive-compulsive disorder are not sharply drawn. In all of these overlapping disorders, mutations in not one but hundreds of genes appear to be able to cause the symptoms, suggesting an unprecedented heterogeneity that has baffled scientists in the field.

For example, autism — a term often used to cover a group of related disorders — is highly heritable, and researchers have identified a large number of gene mutations associated with the disorders on this spectrum. However, no single gene mutation has been found to account for more than a small fraction of patients, though each mutation appears to be able to cause the disorder.

"One of the most perplexing things about autism is the heterogeneity of the disease," said Sudhof, who is also a Howard Hughes Medical Institute investigator. "Autism might be one disease, or it might be thousands of diseases."

There is much confusion about what constitutes autism. While clinicians have defined it by a variety of behavioral symptoms, other researchers have tried to define it genetically. Sudhof is taking a different route in which he hopes to puzzle out, at the physiological level, what all of these genes are doing.

Sudhof suspects that, while the number of different genes involved is large, the protein products of these genes participate in a much smaller number of common pathways. Thus, two genes may encode two proteins that seem totally unrelated but, in fact, interact closely. A deficiency in either's function could result in the same outward defect.

Several large, independent genetic studies have shown that one gene whose deletion occurs in about 0.5 percent of autism cases, but not at all in healthy people, encodes a protein called neurexin-1alpha — one of a family of molecules, collectively known as neurexins, that Sudhof discovered about 20 years ago.

One-half of a percent might not sound like much, but that's more than most other genes contributing to autism, Sudhof said. Given current estimates that upwards of 673,000 American children have autism, several thousand of them carry the deletion.

"Because of our longstanding interest in neurexin-1alpha, we already had mice that were bioengineered to be lacking in neurexin-1alpha," said Sudhof. "So we decided to look closely at those mice to see whether this genetic deficiency led to any changes in communication between neurons and, if so, whether the disrupted or altered communication was

correlated with any observable behavioral abnormalities reminiscent of those associated with human cognitive disorders such as autism or schizophrenia."

The investigators compared a particular area in mutant mice's brains with their counterparts in a control group of normal mice and made several observations. In this brain region (and presumably others as well, Sudhof noted) the mutant mice had alterations in their synapses — the gaps between nerve cells where signals are transmitted from one cell to another, in the aggregate determining the complex circuitry that underpins how we think, feel and move.

The defect, moreover, was confined to one of the two broad classes of synapses: excitatory, as opposed to inhibitory. "This selective change in the strength of one type of synapse, but not the other type, alters the balance between the two," said Sudhof.

Just as autistic or schizophrenic patients are in many respects normal, mice lacking the neurexin-1alpha gene were not grossly dysfunctional or survival-challenged. "The deletion didn't leave the mice unable to eat or to learn or to mate and procreate. If anything, they were actually better than the control mice at executing tasks requiring motor coordination," such as balancing atop a rotating rod without falling off, Sudhof said.

Importantly, though, the mutant mice exhibited discrete behavioral differences — repeated stereotypical behaviors such as self-grooming, impaired nest-building activity and so forth — suggestive of those associated with autism or schizophrenia, according to Sudhof.

Having demonstrated that the neurophysiological effects of neurexin-1alpha — a gene strongly implicated in autism and schizophrenia — correspond to behavioral abnormalities reminiscent of these cognitive disorders, Sudhof plans to use a new grant awarded by

the National Institutes for Health to expand his search.

The NIH had put aside $60 million of its allocation as part of the economic stimulus package specifically for research on autism, and Sudhof's proposal was chosen amid heavy competition.

He and his colleagues in the Stanford Institute for Neuro-Innovation and Translational Neurosciences intend to use the grant to find out if other genes (such as those just identified in a study published in Nature on Oct. 7) affect the nervous system. The investigators will use established techniques to inactivate or increase the activity of 81 autism-associated genes in cultured mouse neurons, and then assess whether these changes affect neural development, synapse density and synapse function. If any of these effects are found, the gene modifications will be tested in whole mice.

Recently, Sudhof received a $1.65 million government grant to expand his efforts to include many more such genes.

Source: Stanford University Medical Center (news : web)