NEWS

Defects in autism risk genes may lead to slower signals

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Molecular mode: In worms, neuroligin is expressed in the tips of cells that send chemical messages (top), and neurexin is found in the muscle cells that receive those messages (above).

> Mutations in two genes **linked to autism** — neurexin and neuroligin — slow down neuronal signaling, according to research published 2 August in *Science*[1].

Analyzing the mutations in the nematode *Caenorhabditis elegans*, the study found that mutations in these genes affect signaling at **synapses**, the connections between neurons, in the opposite direction than is typical.

The mammalian forms of these genes, **NRXN1** and **NLGN1,** are among the strongest candidates for autism risk. Both genes code for proteins found at synapses, and mutations in both have been found in people with the disorder.

“For the most part, these genes have been thought about in a developmental context, conferring risk through changes in how synapses form and mature,” says lead investigator **Joshua Kaplan**, professor of genetics at Harvard University. “Our study suggests that in addition to those effects in development, there could be an effect on how synapses function.”

In mice and people, NRXN1 resides mostly at the tip of the neuron sending the signal, also called

the **presynaptic terminal**. On the other, or postsynaptic, end, where the signal is received, is NLGN1. This distribution pattern is reversed in worms.

The new study suggests that neurexin and neuroligin are part of a system that can send signals in reverse — from postsynaptic to presynaptic cells.

“We have to think more broadly,” says **Nils Brose**, director of the Max Planck Institute for Experimental Medicine in Germany, who was not involved in the research. “I think it’s fascinating that loss of genes [on one side of the synapse] affects the other side of the synapse indirectly and that this is equally likely to contribute to [the disorder].”

Sluggish synapse:

In a 2008 study, Kaplan and his collaborators found evidence of reverse signaling in worm neuromuscular junctions, which link motor neurons and muscle cells[2]. They discovered that blocking a molecule found only in muscle disrupts signals from the neurons to the muscle.

The new study suggests that neurexin and neuroligin provide the basis for this retrograde signaling system.

The researchers found that removing neuroligin, which is at the signal-transmitting end in worms, slows the release of the message from the presynaptic end. Increasing neurexin at the postsynaptic end has the opposite effect, triggering a briefer, faster release of message.

The researchers speculate that the neurexin-neuroligin complex mediates signaling by recruiting a presynaptic protein called tomosyn, which inhibits release of the chemical message.

“This is the first study to look in careful cell-biological detail at the function of these proteins in *C. elegans*,” says **Peter Scheiffele**, professor of cell biology and biological development at the University of Basel in Switzerland, who was not involved in the study. “The hope is that by putting together information from different organisms, we will get a better understanding of the key function of these proteins and their dysfunction in autism.”

To determine whether this system also works in mammals, the researchers reanalyzed experiments in mice by another group, in which all three forms of neuroligins had been knocked out.

As in worms, signaling between neurons in the brainstem of these mice is slower than in that of controls, says Kaplan. The fact that mice and worms host these proteins on opposite ends of a synapse suggests that the proteins’ precise location doesn’t matter, he says.

Still, understanding what happens in mammals will take some work.

“I think this will motivate researchers to look at whether there are scenarios in mammalian systems like this as well,” says Scheiffele. “There is a good possibility that there are circuits in the mammalian system set up like in *C. elegans* and we just don’t know yet that they exist.”

Kaplan’s team is investigating whether mutations inother candidate genes for autism also influence signaling speed.

It’s not yet clear how a slower synapse might influence cognition.

It’s possible that losing the precise timing of signals alters how the brain processes sensory information as it relates to time and space.

“The individual would not know when things happened in the environment and might confuse things over a long range of time,” says Kaplan.

Brain imaging research suggests that children with autism have a **delayed response to sound**, for example[3]. And sensory tests show that they struggle to **parse the order of different events**[4].

References:

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