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Alone in a crowd

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Mice with a mutation associated with autism show deficits in social behaviors and increased inhibitory neurotransmission, consistent with the suggestion that autism can result from excessive inhibition.

Out of hundreds of possibilities, just one can occasionally get the job done. Gene-association studies have identified many candidate genes associated with autism. Now Tabuchi *et al*. report that mice with one disease-associated mutation show behavior consistent with autism in a recent article in *Science*.

Researchers previously identified mutations in the cell-adhesion molecules neuroligin-3 and 4 in familial forms of autism. Neuroligins are synaptic proteins that bind to neurexins, which have also been associated with autism. Mice express a homolog to neuroligin-3.

The authors generated mice with an autism-associated arginine-to-cysteine mutation in the extracellular domain of neuroligin-3 (R451C). R451C mutant mice showed normal locomotor, motor and anxiety behaviors. However, these mice showed abnormal social behaviors. Although R451C mutant and wild-type mice explored unfamiliar objects for similar lengths of time, relative to wild-type mice, R451C mutant mice spent less time interacting with unfamiliar mice that were enclosed in transparent cages. However, R451C mutant and wild-type mice interacted similarly with freely moving mice, suggesting that R451C mutant mice show deficits in the initiation of social interactions, like people with autism.

Some people with autism show enhanced cognitive skills. In the Morris water maze, R451C mutant mice learned the location of a submerged platform faster than did wild-type mice. When the platform was removed, R451C mutant mice swam past its former location more than did wild-type mice, suggesting enhanced spatial memory in the mutant mice.

What is the mechanism of autism-related behavior in R451C mutant mice? R451C mutant mice showed a 90% reduction in neuroligin-3 protein in the forebrain relative to wild-type mice. However, neuroligin-3 mRNA levels were similar in R451C mutant and wild-type mice, suggesting that the R451C mutation destabilizes neuroligin-3. R451C mutant mice showed increased expression of vesicular GABA transporter (VGAT) and gephyrin, which is involved in the scaffolding of inhibitory synapses. Although in the somatosensory cortex, R451C mutant mice had more VGAT-positive puncta relative to wild-type mice, R451C mutant and wild-type mice had similar numbers of inhibitory synapses, suggesting that the R451C mutation affects the strength, but not the number of inhibitory synapses.

Whole-cell recordings in the somatosensory cortex showed an

increase in the frequency of spontaneous inhibitory but not excitatory events (miniature postsynaptic currents) in R451C mutant relative to wild-type mice, suggesting enhanced inhibitory neurotransmission in R451C mutant mice. Consistent with this suggestion, exogenous GABA elicited a bigger response in neurons from R451C mutant relative to wild-type mice. In contrast, neuroligin-3 knockout mice showed normal neurotransmission, suggesting that R451C is a gain-of-function mutation.

Although the R451C mutation is rare among people with autism, these data are consistent with previous suggestions that autism and autism spectrum disorders may be caused by an imbalance between excitatory and inhibitory neurotransmission. According to the authors, regulation of inhibitory neurotransmission may benefit people with autism.

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1. Tabuchi, K. *et al.* A neuroligin-3 mutation implicated in autism increases inhibitory synaptic transmission in mice. *Science* 06 Sep 2007 (doi: 10.1126/science.1146221). | Article |