TOOLBOX

Autism mutations lead to scores of symptoms in rodents

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14 MARCH 2012

Mutations in more than 100 autism-associated genes lead to shared neurobiological deficits in mice, including alterations in the shape of their brains and changes to the electrical properties of neurons, according to a study published 20 February in *Molecular Autism*[1].

The researchers use the analysis to argue against relying solely on assessments of social behavior to validate mouse models for autism.

Mouse models allow researchers to investigate the neurobiology of autism-linked genes in ways that wouldn't be possible in humans. For example, they permit researchers to **look directly at brain tissue** and to test the effects of experimental drugs. Mice can also be engineered to carry gene variants implicated in human diseases, then used to validate autism candidate genes by identifying autism-related symptoms in these animals.

In mouse models of autism, researchers typically look for behaviors that **recapitulate the core deficits of autism**: social impairment, language deficits, and **repetitive and restricted behaviors**. But this hinges on identifying very human behaviors in non-human animals.

Instead, in the new study, researchers assessed all the biological changes in mice with mutations in genes that are already associated with autism.

They used the **ToppGene** online resource, which uses the Mammalian Phenotype Ontology database[2], a catalog of the brain and behavioral changes in mutant mice and rats, to examine the effects of mutations in 112 autism-associated genes. These include **FOXP1**, **MeCP2** and 31 genes that function at the **synapse**, the junction between neurons, such as **SHANK3** and **NRXN1**.

The researchers identified 60 symptoms that were the most common in the autism model mice and found that they clustered into four main categories. The first, alterations in the shape of brains and neurons, includes abnormal development in specific brain regions, abnormal migration of neurons and abnormal development of **dendritic spines**, the signal-receiving branches of neurons.

The second category includes neurobiological abnormalities, such as sensory sensitivity, an overactive startle response and a high susceptibility to seizures. The third, higher-order behaviors, includes anxiety, motor impairments, and deficits in learning and memory and social behavior.

The final category, the electrical properties of neurons, includes alterations to the electrical potential that allows neurons to transmit signals, and to the ion channels that maintain this potential.

There were no consistent changes to the electrical properties of neurons in the mouse models: Signaling was elevated in some models and impaired in others. This calls into question a theory of autism that is based on an **imbalance between excitatory and inhibitory** neuronal signal inputs, the researchers say.

The fact that the mouse models of autism share a variety of neurological deficits that are not direct measures of social behavior supports using alternative methods to validate them, the researchers say.

They also suggest that using mouse strains that have social deficits reminiscent of autism to identify new candidate genes may not be the most effective approach to studying the disorder.

The data can help direct researchers to appropriate assays with which to study mouse models of autism, and help them hone in on the neurological characteristics of the disorder, the researchers say.

References:

1: Buxbaum J.D. *et al. Mol. Autism* **3**, 1 (2012) **PubMed**

2: Smith C.L. *et al. Genome Biol.* **6**, R7 (2005) **PubMed**