

**VIEWPOINT**

# Multimodal mouse model for autism

BY ALAN PACKER

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Alan Packer

Given the strong statistical support for genes disrupted by spontaneous, or *de novo*, mutations in autism, I'm always on the lookout for papers that tell us something new about the biological roles of these high-confidence risk factors.

A paper published in this month's *Nature Neuroscience* provides a good example of what to look for as scientists try to build an integrated picture of autism at the levels of cells and circuits<sup>1</sup>. The paper accomplishes a rare feat, linking human genetics with physiology, behavior and a therapeutic in a compelling mouse model of autism.

The researchers looked at the **autism candidate** gene **TBR1**, which encodes a transcription factor. TBR1 is expressed in nondividing neurons of the cortex and has a key role in establishing both the overall regional identity of the frontal cortex in mice and, in particular, the differentiation of layer 6 neurons that communicate with the thalamus<sup>2</sup>.

Consistent with these results, mice lacking TBR1 show aberrant projection of axons — neuronal fibers that project to and communicate with other neurons —in the cerebral cortex and thalamus.

A *Cell* paper published late last year included TBR1 in a network analysis of nine high-confidence autism risk genes and established it as **the most highly connected gene** in a network implicating layer 5/6 cortical neurons as a locus of autism pathology<sup>3</sup>.

With all of the attention paid to TBR1's role in the cortex, it comes as a bit of a surprise to read in the new paper that mice lacking only one copy of TBR1 show no obvious alterations in the development of the cortex. Instead, the mice have impaired projections of neurons, but only in the amygdala.

## Single blow:

Often, mouse models of autism completely lack a particular candidate gene. The *de novo* mutations found by sequencing **exomes** — the protein-coding portions of the genome — suggest, however, that in many cases the loss of a single copy should be sufficient to result in a phenotype.

In the case of mice lacking one copy of TBR1, the finding of a defect in the amygdala raises the possibility that this region of the brain is the most sensitive to the lowered dosage of the TBR1 protein. It also suggests that careful assessment of mice lacking a single copy of risk genes should be the norm rather than the exception.

The new paper helps the field in several other ways. Although the statistical support is strongest for *de novo* mutations that dramatically disrupt gene function, by far the most common events are missense mutations, those that change only a single amino acid.

Our only hope for identifying the true risk variants in this class is to show that the changes have some sort of functional effect.

In the case of TBR1, the researchers show that one such missense variant fails to rescue the axonal defects in the mutant mouse, suggesting that this is a bona fide loss-of-function mutation. A systematic assessment of missense variants will add to the body of evidence implicating particular genes in autism and should ultimately have clinical relevance as well.

The paper goes further, implicating genes such as **NTNG1**, **CDH8**, and CNTN2 as key factors in mediating the effect of TBR1 on axonal growth in the amygdala. The evidence implicating these genes in autism ranges from weak to modest, but they should be taken more seriously by virtue of their clear role in TBR1-dependent functions in the mouse.

Finally, the researchers show a range of abnormal behaviors in the TBR1 mutant mice, including impaired social interaction, and they report that D-cycloserine ameliorates these behavioral deficits. Because D-cycloserine promotes excitatory signaling through the NMDA receptor, the experiments provide the first link between TBR1 activity and neuronal signaling. These results collectively establish TBR1 mutants as important mouse models of autism.

I should note that investigators have also observed positive effects of D-cycloserine on five other autism models: mice lacking SHANK2, neuroligin-1 or GLUD1, and the BTBR and BALB/c strains<sup>4-8</sup>.

A small, short-term trial carried out ten years ago reported a significant improvement in social withdrawal symptoms in individuals with autism<sup>9</sup>, but the paper trail ends there. A larger trial of D-cycloserine in people with autism is under way, and principal investigator Christopher McDougle says the data are being analyzed. He says an important next step might be to study D-serine, a stronger activator of the NMDA receptor than D-cycloserine. D-serine is being tested as a treatment for schizophrenia.

*Alan Packer is senior scientist at the Simons Foundation Autism Research Initiative.*

## References:

- 1: **Huang T.N.** *et al. Nat. Neurosci.* Epub ahead of print (2014) [PubMed](#)
- 2: Hevner R.F. *et al. Neuron* **29**, 353-366 (2001) [PubMed](#)
- 3: Willsey A.J. *et al. Cell* **155**, 997-1007 (2013) [PubMed](#)
- 4: Won H. *et al. Nature* **486**, 261-265 (2012) [PubMed](#)
- 5: Blundell J. *et al. J. Neurosci.* **30**, 2115-2129 (2010) [PubMed](#)
- 6: Yadav R. *et al. PLoS One* **7**, e32969 (2012) [PubMed](#)
- 7: Burket J.A. *et al. Brain Res. Bull.* **96**, 62-70 (2013) [PubMed](#)
- 8: Benson A.D. *et al. Brain Res. Bull.* **99**, 95-99 (2013) [PubMed](#)
- 9: Posey D.J. *et al. Am. J. Psychiatry* **161**, 2115-2117 (2004) [PubMed](#)