*Nature Reviews Drug Discovery* | AOP, published online 22 June 2012; doi:10.1038/nrd3780

NEURODEVELOPMENTAL DISORDERS

# Exploring the links between SHANK2 and autism

Previous studies have identified a *de novo* microdeletion in *SHANK2* (which encodes a molecular scaffolding protein enriched in neuronal synapses) in autism spectrum disorder (ASD), but the role of this mutation in ASD pathogenesis is unclear. Now, a recent paper in *Nature* shows that *Shank2*-mutant mice recapitulate many of the behavioural phenotypes that are characteristic of ASD. Moreover, the study suggests that hypofunction of NMDA receptors (NMDARs) is the underlying molecular cause of impaired social interaction and shows that this impairment could be pharmacologically reversed.

To elucidate the link between the *de novo SHANK2* microdeletion and ASD, the authors generated transgenic mice that carried the same mutation as the human microdeletion. These mutant mice (*Shank2*$^{-/-}$ mice) showed autistic-like impairments in social interaction and in learning and memory. They also exhibited higher levels of anxiety, repetitive behaviours and hyperactivity compared to wild-type mice.

At the cellular level, *Shank2*$^{-/-}$ mice had normal basal synaptic transmission at hippocampal Schaffer collateral–CA1 pyramidal (SC–CA1) synapses, and the postsynaptic morphology and numbers of excitatory synapses were unchanged. However, synaptic plasticity, as assessed by long-term potentiation (LTP) and long-term depression (LTD), was severely impaired. Further experiments showed that this impairment was due to NMDAR hypofunction and associated impairment of NMDAR signalling.

To examine whether NMDAR hypofunction directly contributes to ASD-like behaviours in *Shank2*$^{-/-}$ mice, the authors tested the effect of NMDAR modulators in these mice. Intraperitoneal injection of D-cycloserine (a partial NMDAR agonist) improved social interaction of *Shank2*$^{-/-}$ mice. Furthermore, intraperitoneal injection of CDPPB — a positive allosteric modulator of metabotropic glutamate receptor 5 (mGluR5) that ultimately enhances NMDAR function — restored the impaired LTP and LTD at SC–CA1 synapses without affecting basal synaptic transmission, and fully normalized NMDAR signalling. These CDPPB-treated *Shank2*$^{-/-}$ mice also had enhanced improvement in social interaction compared with mice treated with D-cycloserine. However, other behaviours (for example, anxiety-like behaviours) were not improved.

Together, these results suggest a causal link between mutations in *SHANK2*, reduced NMDAR function and impaired social behaviour.


The authors also suggest that targeting mGluR5 could be a novel strategy for treating ASD associated with impaired NMDAR function.

*Man Tsuey Tse*

**ORIGINAL RESEARCH PAPER** Won, H. *et al.* Autistic-like social behaviour in *Shank2*-mutant mice improved by restoring NMDA receptor function. *Nature* **486**, 261–265 (2012)