Abstract: 60O

Single point mutation of miRNA-873 and the synaptic protein neurexin induce autism-like behavioural changes and hippocampal dysfunction in a mouse model.

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Autism spectrum disorders (ASD) affects 2% of Australians and accounts for ~30% of NDIS funding. Disordered social interaction, repetitive patterns of behaviour and impaired communication define ASD. The heterogeneity of ASD may be explained by underlying rare and/or de novo single-point mutations, especially involved in synaptic activity. It is most common in males (4:1) and co-morbidities include epilepsy and anxiety. In this study we studied the brains of mice possessing point mutations in microRNA-873 and neurexin found in an Australian individual with ASD and severe cognitive impairment.

In the present study CRISPR was used to induce the appropriate point mutations in miR-873 and neurexin in mice. Male mice were tested for cognitive function and social interaction. In siblings, hippocampal function was tested in terms of long-term potentiation (LTP), input-output curves, and the ability to induce epileptiform activity.

Sociability was impaired in miR-873 mutant but not in neurexin mutant mice. These miR-873 mice were also anxious. When a food reward in response to a nose-poke was tested, control mice learned to change when sweet pellet delivery from the right/left sides was changed, while neither mutant group learned over the 7 days of testing. Hippocampal slice LTP and input/output relationships were markedly impaired in both mutant groups compared with controls. In isolated hippocampal neurons, excitatory synaptic potential frequency was doubled in neurons transfected with mutated miR-873.

miRNAs modulate mRNA transcription. We have previously found that miR-873 impairs transcription of the synaptic proteins SHANK3, neurexin 2, neuroligin and SYNGAP1. Here we demonstrate behavioural deficits that mimic those found in an individual with miR-873 point mutation in a mouse model of this mutation.