Neurodevelopmental and neuropsychiatric behaviour defects arise from 14-3-3ζ deficiency.

ABSTRACT

Complex neuropsychiatric disorders are believed to arise from multiple synergistic deficiencies within connected biological networks controlling neuronal migration, axonal pathfinding and synapse formation. Here, we show that deletion of 14-3-3ζ causes neurodevelopmental anomalies similar to those seen in neuropsychiatric disorders such as schizophrenia, autism spectrum disorder and bipolar disorder. 14-3-3ζ-deficient mice displayed striking behavioural and cognitive deficiencies including a reduced capacity to learn and remember, hyperactivity and disrupted sensorimotor gating. These deficits are accompanied by subtle developmental abnormalities of the hippocampus that are underpinned by aberrant neuronal migration. Significantly, 14-3-3ζ-deficient mice exhibited abnormal mossy fibre navigation and glutamatergic synapse formation. The molecular basis of these defects involves the schizophrenia risk factor, DISC1, which interacts isoform specifically with 14-3-3ζ. Our data provide the first evidence of a direct role for 14-3-3ζ deficiency in the aetiology of neurodevelopmental disorders and identifies 14-3-3ζ as a central risk factor in the schizophrenia protein interaction network.

Keyword: Neurodevelopment; Neuropsychiatric disorder; Schizophrenia; Synapse; 14-3-3z.