REGIONAL CENTRE FOR BIOTECHNOLOGY
Seminar series

Pathogenic *SYNGAP1* haploinsufficiency impairs cognitive development by disrupting the maturation of dendritic spine synapses.

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Abstract

Mutations that cause Intellectual Disability (ID) are increasingly found in genes that encode for synaptic proteins. However, it remains unclear how genetic mutations that disrupt synapse function impact intellectual ability. In the *SynGAP1* haploinsufficiency mouse model of ID, we found that dendritic spine synapses (DSS) develop prematurely during early postnatal development. Premature DSS maturation severely disrupted the balance of excitation and inhibition in the developing hippocampus, which corresponded with the first evidence of behavioral abnormalities. Inducing *SYNGAP1* haploinsufficiency in mature animals had minimal impact on hippocampal DSS function, while repairing pathogenic *SYNGAP1* mutations in adults did not improve basic behavioral and cognitive abnormalities. These data demonstrate that developing excitatory synapses *in vivo* are exquisitely sensitive to SynGAP protein levels and *SYNGAP1* mutations present during development lead to enduring intellectual disability. Thus, we concluded that *SYNGAP1* haploinsufficiency syndrome is characterised by a fundamental disruption to the pace of neural development, and this leads to the failure of cognitive and social maturation during childhood.