Regulation of a synaptic pathway in Autism spectrum disorders

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Neurexin-LRRTM is a key synapse organizing complex, which controls the molecular composition and functional properties of excitatory synapses. Both neurexins and LRRTMs are implicated in cognitive disorders such as autism spectrum disorders (ASD) and schizophrenia. Lack of LRRTM4 in mice reduces excitatory synapse number and function by up to 35% across brain regions and compromises several forms of synaptic plasticity. Here, we investigated the functional significance of neurexin interaction with LRRTMs. We found that LRRTMs have a differential requirement for protein domains of neurexin but require the heparan sulfate (HS) modification to induce presynaptic differentiation. Also, we generated a series of mutations in LRRTM4 substituting closely spaced stretches of positively charged residues with alanine. We found that the modified HS chains of neurexin binds to positive residues within the LRR 5-8 domains of LRRTM4. Our study reveals a novel mode of interaction between neurexins and LRRTMs which is essential for the development of excitatory synapses.