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Structural Insights into Protein Mutations Related to Autism Spectrum Disorders: A Systematic Review

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Autism Spectrum Disorder (ASD) is a multifaceted neurodevelopmental condition characterized by difficulties in social interactions and communication, alongside repetitive behaviors and restricted interests. Its etiology is complex, involving genetic, environmental, and epigenetic factors, with significant contributions from mutations in synaptic proteins, including neuroligins (NLGNs), neurexins (NRXNs), neuronal calcium sensor- 1 (NCS-1), and SHANK family proteins. Structural changes caused by mutations in these proteins can lead to synaptic dysfunction, disrupt scaffolding, and impact neuronal circuitry, which reflects the symptoms of ASD. The purpose of this study is to compile the most recent findings regarding protein structure and how specific mutations in these proteins contribute to ASD. This systematic review conducted a comprehensive analysis of research published from 2014 to 2024, collected from databases such as Web of Science, Scopus, and the Protein Data Bank (PDB). Research that employed X-ray crystallography, cryo-EM, NMR spectroscopy, and other advanced structural biology methods for molecular modeling was prioritized. After evaluating the findings of the final 40 studies, mutations in the synaptic proteins SHANK3 (R12C, L68P, S557N), NLGN3 (R451C), NLGN4 (R101Q), and NRXN1 destabilize protein structure, reduce synaptic adhesion, and disrupt neurotransmitter clustering, which influences ASD symptoms. An R102Q mutation in the NCS-1 protein decreases the flexibility of loops L2 and L3 and alters the salt bridge network, contributing to ASD pathology. Additionally, mutations in CNTN4 affect GABA receptor distributions that impact synaptic signaling, and structural defects in CTTNBP2 and ASH1L mutations disrupt dendritic spine development, leading to synaptic abnormalities related to ASD behaviors. Advanced techniques reveal the molecular structure underlying ASD in animal models, which provide interventions like gene transplantation that can mitigate the effects of these mutations. However, challenges persist in finding treatments for the numerous molecular mechanisms contributing to ASD, emphasizing the need for further research into the structure of all ASD-related proteins.

Biography

Mitu Rani Das is a PhD student in Structural Biology at the Institute of Science Tokyo University. She is particularly passionate about researching the genetic causes of Autism and exploring potential prevention and treatment strategies through the lens of molecular and structural biology. Mitu completed her Master's in Structural Biology at Tokyo Medical and Dental University (TMDU), Japan, and a master's in public health at North South University, Bangladesh. She holds a B.Sc. in Speech and Language Therapy from Dhaka University and completed her internship at CRP Hospital, Bangladesh. She worked extensively with children with Neuro-developmental conditions, addressing communication challenges and difficulties related to feeding and swallowing caused by neurological or psychological factors.

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