CUL3 deficiency causes social deficits and anxiety-like behaviors by impairing excitation-inhibition balance via promoting Cap-dependent translation

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Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders with symptoms including social deficits, anxiety, and communication difficulties. However, ASD pathogenic mechanisms are poorly understood. Mutations of CUL3, which encodes Cullin 3 (CUL3), a component of an E3 ligase complex, are thought of as risk factors for ASD and schizophrenia (SCZ). CUL3 is abundant in the brain, yet little is known of its function. Here we showed that CUL3 is critical for neurodevelopment. CUL3 deficient mice exhibited social deficits and anxiety-like behaviors with enhanced glutamatergic transmission and neuronal excitability. Proteomic analysis revealed eIF4G1, a protein for Cap-dependent translation, as a potential target of CUL3. ASD-associated cellular and behavioral deficits could be rescued by pharmacological inhibition of the eIF4G1 function and chemogenetic inhibition of neuronal activity. Thus, CUL3 is critical to neural development, neurotransmission, and excitation-inhibition (E-I) balance. Our study reveals novel insight into pathophysiological mechanisms of ASD and SCZ.