GRIN2B-related neurodevelopmental disorder

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The GRIN2B

-related neurodevelopmental disorder is a rare disease caused by mutations in the

GRIN2B

gene, which encodes the GluN2B subunit of NMDA receptors. Most individuals with

GRIN2B

-related neurodevelopmental disorder present with intellectual disability and developmental delay. Motor impairments, autism spectrum disorder, and epilepsy are also common. A large number of pathogenic

de novo

mutations have been identified in

GRIN2B

. However, it is not yet known how these variants lead to the clinical symptoms of the disease. Recent research has begun to address this issue. Here, we describe key experimental approaches that have been used to better understand the pathophysiology of this disease. We discuss the impact of several distinct pathogenic

GRIN2B

variants on NMDA receptor properties. We then critically review pivotal studies examining the synaptic and neurodevelopmental phenotypes observed when disease-associated GluN2B variants are expressed in neurons. These data provide compelling evidence that various GluN2B mutants interfere with neuronal differentiation, dendrite morphogenesis, synaptogenesis, and synaptic plasticity. Finally, we identify important open questions and considerations for future studies aimed at understanding this complex disease. Together, the existing data provide insight into the pathophysiological mechanisms that underlie

GRIN2B

-related neurodevelopmental disorder and emphasize the importance of comparing the effects of individual, disease-associated variants. Understanding the molecular, cellular and circuit phenotypes produced by a wide range of

GRIN2B

variants should lead to the identification of core neurodevelopmental phenotypes that characterize the disease and lead to its symptoms. This information could help guide the development and application of effective therapeutic strategies for treating individuals with

GRIN2B

-related neurodevelopmental disorder.