

## **Delineating the *GRIN1* spectrum – a distinct genetic NMDA receptor encephalopathy**

Johannes R. Lemke, Kirsten Geider, Katherine L. Helbig, Henrike O. Heyne, Ingo Helbig, Jacques Michaud, Bodo Laube, Steffen Syrbe with the help of the *GRIN1* study group\*

\*Georgianne L. Arnold, Deborah Bartholdi, Vikas Bhambhani, Emilia Bijlsma, Saskia Biskup, Carolina Courage, Carolien G. de Kovel, Christel Depienne, Dennis J. Dlugos, Emily S. Doherty, Thomas Dorn, Eirik Frengen, Amy Goldstein, Julia Hentschel, Delphine Heron, Helle Hjalgrim, Bobby Koeleman, Gerhard Kurlemann, Dennis Lal, Caroline Nava, Vinodh Narayanan, Bernd A. Neubauer, Doriana Misceo, Rikke Møller, Christeen R. Pedurupillay, Amélie Piton, Deepa S. Rajan, Keri Ramsey, Erik Riesch, Joaquim Sa, Petter Strømme, Heinrich Vogt, Sarah Weckhuysen

We aimed to determine the phenotypic spectrum of disorders caused by mutations in *GRIN1* encoding the NMDA receptor subunit GluN1 and to investigate the functional consequences of the underlying mutations. For this, we evaluated gene panel and exome sequencing data of 1443 individuals with neurodevelopmental disorders for mutations in *GRIN1*. Identified and previously described *de novo* mutations were investigated for functional consequences in *Xenopus laevis* oocytes. We identified *GRIN1 de novo* mutations in 13 individuals with intellectual disability. An additional heterozygous *GRIN1* variant was associated with idiopathic focal (rolandic) epilepsy and another homozygous variant segregated with severe intellectual disability within a family. Furthermore, we reviewed and analyzed the phenotypes of eight previously reported *GRIN1* cases. All 21 *GRIN1 de novo* mutations resulted in a distinct phenotype of severe intellectual disability with absent speech, profound developmental delay, muscular hypotonia, hyperkinetic movement disorder, oculogyric crises, cortical blindness, and epilepsy. Mutations cluster within transmembrane segments and resulted in loss of channel function of varying severity with a dominant-negative effect. *De novo GRIN1* mutations account for approximately 1% of cases with severe intellectual disability. The presence of cortical visual impairment and movement disorders discriminates *GRIN1*-associated disorders from other genetic NMDA receptor encephalopathies such as *GRIN2A*- and *GRIN2B*-associated disorders. Despite variability of functional consequences of the identified *GRIN1* mutations, the resulting clinical phenotype appears to be relatively homogeneous and recognizable.