

## **GRIN2B**

### **Patient Description: (Pending)**

#### **Disease/Syndrome Features:**

*GRIN2B* mutations have been identified in individuals with mild to severe intellectual disability with behavioral anomalies. Several of these patients also had abnormal EEG findings such as irregular slow dysrhythmia. *GRIN2B* was disturbed either by *de novo* chromosomal translocation or by *de novo* frameshift, missense, or splice-site mutations [Endele 2010].

Inquiry into the genetic etiology of seizure disorders has repeatedly considered *GRIN2B* as a candidate gene. In epileptic encephalopathies, seizure activity itself is thought to contribute to the cognitive impairments observed in patients. *GRIN2B* mutations have been found in individuals with West syndrome, an epileptic encephalopathy characterized by infantile spasms and an EEG pattern called hypsarrhythmia, as well as in an individual with focal epilepsy and global developmental delay [Lemke 2014]. Furthermore, whole exome sequencing by the Epi4K Consortium identified a patient with developmental delay, intellectual disability, and epilepsy along with a *de novo GRIN2B* mutation [Consortium 2013].

Additionally, a multiplex targeted sequencing approach developed to detect rare causes of complex phenotypes identified recurrent mutations in *GRIN2B* in a cohort of probands with autism spectrum disorders (ASD) [O’Roak 2012]. Finally, a systematic meta-analysis of genome wide association studies has identified a link between *GRIN2B* variants and risk for schizophrenia [Allen 2008, Tamminga 2015].

#### **Protein/Pathway:**

*GRIN2B*, glutamate ionotropic receptor NMDA type subunit 2B, encodes the glutamate-binding NR2B subunit of the NMDA receptor. NMDA receptors are neurotransmitter-gated cation channels located at excitatory synapses in the mammalian brain and are critical in the regulation of synaptic function. For example, the mouse ortholog, *Grin2b*, appears to have a role in forming dendritic spines in hippocampal pyramidal cells, and mice deficient in *Grin2b* die perinatally [Endele 2010].

NMDA receptors are heterotetramers of two glycine-binding NR1 subunits and two NR2 subunits of types A, B, C, or D. The NR2 subunit type underlies physiological properties of the receptor as a whole, and NR2B is the principal subunit type in early stages of development. NR2 subunits consists of an N-terminal domain, a ligand binding domain, three transmembrane segments, a pore loop, and an intracellular carboxy-terminal domain. One pathogenic missense mutation observed in patients is predicted to substitute a cysteine for a highly conserved arginine at position 682 within the ligand binding domain. This substitution results in the loss of three hydrogen bonds and may destabilize the tertiary structure of the domain [Endele 2010].

Several disease causing mutations in *GRIN2B* have been characterized by electrophysiology in *Xenopus laevis* oocytes. p.Val618Gly and p.Asn615Ile mutations are within the channel pore domain and are found in patients with West syndrome. A patient with focal epilepsy and intellectual disability was found to have a p.Arg540His mutation in the glutamate-binding domain. Each of these mutations resulted in a channel with decreased Mg<sup>2+</sup> block and increased Ca<sup>2+</sup> permeability which could explain the hyperexcitability that underlies epilepsy [Lemke 2014].

### **Publications:**

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- Endele, S., Rosenberger, G., Geider, K., Popp, B., Tamer, C., Stefanova, I., ... Kutsche, K. (2010). Mutations in GRIN2A and GRIN2B encoding regulatory subunits of NMDA receptors cause variable neurodevelopmental phenotypes. *Nature Genetics*, 42(11), 1021–1026. <https://doi.org/10.1038/ng.677>
- Consortium, E., Allen, A. S., Berkovic, S. F., Cossette, P., Delanty, N., Dlugos, D., ... Winawer, M. R. (2013). De novo mutations in epileptic encephalopathies. *Nature*, 501(7466), 217–221. <https://doi.org/10.1038/nature12439>
- Lemke, J. R., Hendrickx, R., Geider, K., Laube, B., Schwake, M., Harvey, R. J., ... Weckhuysen, S. (2014). *GRIN2B* mutations in west syndrome and intellectual disability with focal epilepsy. *Annals of Neurology*, 75(1), 147–154. <https://doi.org/10.1002/ana.24073>
- O’Roak, B. J., Vives, L., Fu, W., Egerton, J. D., Stanaway, I. B., Phelps, I. G., ... Shendure, J. (2012). Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders. *Science (New York, N.Y.)*, 338(6114), 1619–1622. <https://doi.org/10.1126/science.1227764>
- Tamminga C.A., Zukin R.S. (2015). Schizophrenia: Evidence implicating hippocampal GluN2B protein and REST epigenetics in psychosis pathophysiology. *Neuroscience*. Nov 19;309:233-42. <https://doi.org/10.1016/j.neuroscience.2015.07.038>

### **Support Groups and Information:**

[GRIN2B Foundation](#)

Facebook community: GRIN2B Parent Support group (private group, >500 members)

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