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Critical review

Human *GRIN2B* variants in neurodevelopmental disorders

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ABSTRACT

The development of whole exome/genome sequencing technologies has given rise to an unprecedented volume of data linking patient genomic variability to brain disorder phenotypes. A surprising number of variants have been found in the *N*-methyl-D-aspartate receptor (NMDAR) gene family, with the *GRIN2B* gene encoding the GluN2B subunit being implicated in many cases of neurodevelopmental disorders, which are psychiatric conditions originating in childhood and include language, motor, and learning disorders, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), developmental delay, epilepsy, and schizophrenia. The *GRIN2B* gene plays a crucial role in normal neuronal development and is important for learning and memory. Mutations in human *GRIN2B* were distributed throughout the entire gene in a number of patients with various neuropsychiatric and developmental disorders. Studies that provide functional analysis of variants are still lacking, however current analysis of *de novo* variants that segregate with disease cases such as intellectual disability, developmental delay, ASD or epileptic encephalopathies reveal altered NMDAR function. Here, we summarize the current reports of disease-associated variants in *GRIN2B* from patients with multiple neurodevelopmental disorders, and discuss implications, highlighting the importance of functional analysis and precision medicine therapies.

1. Introduction

N-methyl-D-aspartate receptors (NMDARs) are a family of ionotropic glutamate receptors that mediate a slow, Ca^{2+} permeable component of excitatory synaptic transmission in the central nervous system (CNS). NMDARs are a tetrameric assembly of two glycine-binding GluN1 subunits and two glutamate-binding GluN2 subunits. The GluN1 subunit is expressed throughout the CNS, whereas the four subtypes of GluN2 (A–D) subunits have differential temporal and spatial expression patterns (1,2). The GluN2B subunit encoded by *GRIN2B* is highly expressed prenatally, and its expression level starts to decline after birth in most brain regions (1). The early expression of this NMDAR subunit suggests it may play an important role in brain development, circuit formation, and perhaps cellular migration and differentiation, as well as synaptic plasticity (3). GluN2B expression dominates during rapid cortical synaptogenesis in late embryogenesis and early postnatal development (4). Neonate lethality of *GRIN2B* knock-out mice was observed (5), while overexpression of *GRIN2B* in the forebrain of mice enhanced hippocampal long-term potentiation and spatial memory performance (6).

In light of the important role of *GRIN2B* in controlling NMDAR function, the time course of synaptic currents and plasticity, mutation-related disruption in the GluN2B subunit expression or function might give rise to a number of neurodevelopmental phenotypes that reflect alterations in circuit formation, neuronal connectivity, synaptic plasticity, and excitatory transmission. Since the identification of the first disease-causing mutations in NMDARs (7,8) over 60 variants in the *GRIN2B* have been reported in the literature identified in individuals from patient cohorts with a number of neurodevelopmental disorders, including intellectual disability (ID), developmental delay (DD), autism spectrum

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disorder (ASD), epileptic encephalopathy (EE), schizophrenia (SCZ), and to a lesser extent attention deficit hyperactivity disorder (ADHD), cerebral visual impairment (CVI), and Alzheimer's disease (AD) (Fig. 1 and Table 1). We expect the discovery of additional rare *GRIN2B* genetic variants and *de novo* mutations to grow as more clinics utilize exome sequencing as a tool in diagnostic programs to better understand the molecular basis for neurodevelopmental disorder(s) in pediatric patient populations. *GRIN2B* variants and *de novo* nonsynonymous mutations with neurological disease has recently been reviewed (55,56). Here we review all missense, nonsense, frameshift, or splice site *GRIN2B* mutations identified in individuals from patient cohorts with defined neurodevelopmental and psychiatric disorders such as ID and DD (7,9–15,17,18,21,29,54), EE (7,13,15,16,53,54), ASD (18–20,22–26,54), SCZ (19,20,26,27), AD (28), and CVI (11). The *GRIN2B* variants identified thus far occurred throughout the entire NMDAR subunit protein. That is, variants were found in the amino-terminal domain (ATD), agonist-binding domain (ABD), transmembrane domain (TM), and carboxyl-terminal domain (CTD) (Fig. 1). In spite of the increasing number of reports of new *GRIN2B* variants due to the recent advances of next-generation sequencing technologies, studies that provide thorough functional analyses of the effects of disease-causing mutations on NMDARs are still lacking. Such functional information is central to understanding the pathogenicity of these *de novo* mutations and rare variants, and thus is an important priority in future genetic studies. Here, we provide a domain-specific review of *GRIN2B* variants revealing that rare *de novo* mutations in the ABD and TM domains, but not the ATD and CTD domains, are absent in the exomes of a large control population sample (Table 1; 35). Furthermore, many of these ABD and TM rare variants result in significant alteration of NMDA receptor channel properties (7,13,16,24,34,54).

2. *GRIN2B* mutations with chromosome translocation

Chromosome translocation involves rearrangement of parts between non-homologous chromosomes. To date, two male subjects with *de novo* chromosome translocations in the *GRIN2B* gene have been reported: t(9;12)(p23;p13.1) and t(10;12)(q21;p13.1) (7). Fluorescence *in situ* hybridization (FISH) studies also found breakpoints in 12p13.1 in both translocations, disrupting the *GRIN2B* gene. Both subjects demonstrated moderate to severe mental disability, behavioral anomalies, and abnormal electroencephalogram (EEG). The 12-year-old subject also had other manifestations such as microcephaly and eye anomalies. Further, a *de novo* chromosome inversion (inv(12)(p13.1q21.31)) and three microdeletions with breakpoints in exon 1 or exon 2 of *GRIN2B* were identified in four patients with similar ID and DD symptoms (7,18,29,30). Thus, the *GRIN2B* gene seems to be critical for neuronal development, and translocation disruption in *GRIN2B* could lead to pronounced cognitive phenotypes. More importantly, functional studies on *GRIN2B* translocations are needed, since disruption in the *GRIN2B* gene might lead to receptor trafficking defects, NMDAR hypofunction, and alteration of endogenous modulator affinities. Interestingly, a translocation disrupting the *GRIN2A* gene (t(16;17)(p13.2;q11.2)), which encodes the GluN2A subunit, was also associated with severe mental disability and seizures in a 26-year-old male subject. This same translocation was identified in 3 similarly affected relatives (7). Further, a microdeletion encompassing the *GRIN2A* gene (16p13.2p13.13) was identified in three patients with variable mild to severe intellectual disability and seizures (8) and overlapping duplications of chromosome 12p points towards *GRIN2B* in a series of patients with a variable DD and ID phenotype (31). Thus, a comparative analysis of *GRIN* translocations and microdeletions could be informative.

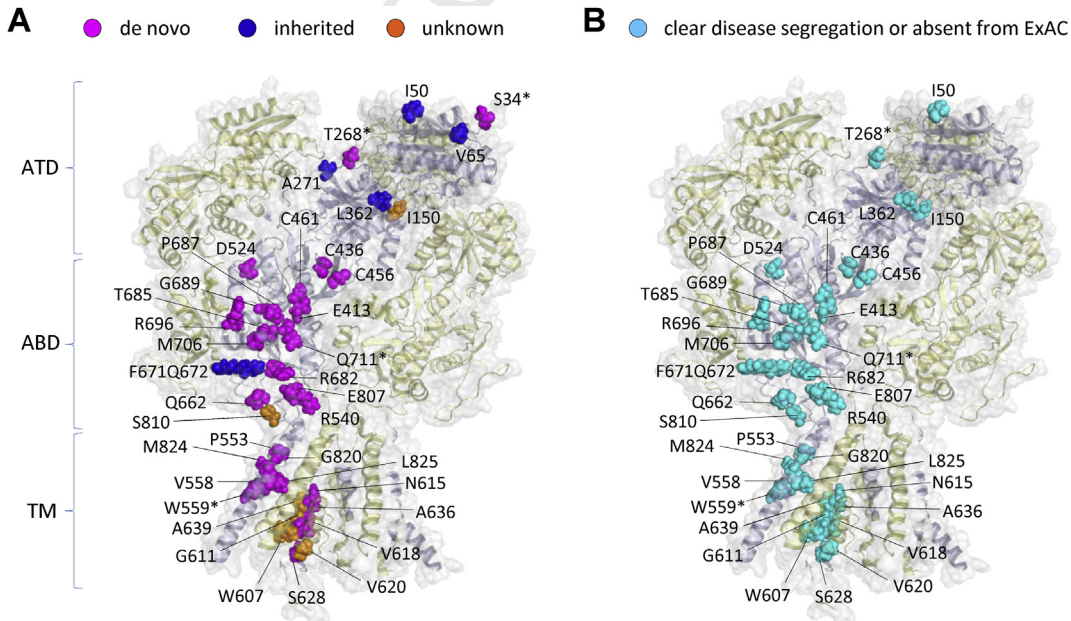

Fig. 1. Locations of GluN2B mutations. Ribbon structures of a tetramer GluN1/GluN2B receptor (37,38) illustrates receptor architecture (light yellow: GluN1; light blue: GluN2B). The amino terminal domain (ATD) is shown, the S1 and S2 regions describe two portions of the polypeptide chain that comprise the agonist binding domain (ABD), and three transmembrane helices (M1, M3, M4) and the M2 re-entrant pore loop comprise the transmembrane domain (TM). **A**, Residues harboring *de novo* mutations are highlighted in MAGENTA, transmitted mutations in BLUE, and variants of unknown origin in ORANGE. **B**, Residues harboring mutations in human patients with a clear disease segregation or absent from ExAC are highlighted in CYAN. In both panels an (*) indicates that the variant results in a truncated protein. The residue alanine at position 590 is not shown due to poor resolution of crystal structure in this region. The variants V18 in the signal peptide, and Q1014, G1026, R1099, T1228, A1267, T1273, K1293, M1331, M1339, N1352, S1415, L1424, S1452 in the carboxyl terminal domain (CTD) are not present in the crystal structure and therefore not shown.

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