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REVIEW

Distinct roles of *GRIN2A* and *GRIN2B* variants in neurological conditions [version 1; peer review: 2 approved]

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Abstract
Rapid advances in sequencing technology have led to an explosive increase in the number of genetic variants identified in patients with neurological disease and have also enabled the assembly of a robust database of variants in healthy individuals. A surprising number of variants in the *GRIN* genes that encode *N*-methyl-D-aspartate (NMDA) glutamatergic receptor subunits have been found in patients with various neuropsychiatric disorders, including autism spectrum disorders, epilepsy, intellectual disability, attention-deficit/hyperactivity disorder, and schizophrenia. This review compares and contrasts the available information describing the clinical and functional consequences of genetic variations in *GRIN2A* and *GRIN2B.* Comparison of clinical phenotypes shows that *GRIN2A* variants are commonly associated with an epileptic phenotype but that *GRIN2B* variants are commonly found in patients with neurodevelopmental disorders. These observations emphasize the distinct roles that the gene products serve in circuit function and suggest that functional analysis of *GRIN2A* and *GRIN2B* variation may provide insight into the molecular mechanisms, which will allow more accurate subclassification of clinical phenotypes. Furthermore, characterization of the pharmacological properties of variant receptors could provide the first opportunity for translational therapeutic strategies for these *GRIN*-related neurological and psychiatric disorders.

Keywords
NMDA receptors, GRIN2A, GRIN2B, GluN2A, GluN2B, mutations, neurological disorder , psychiatric disorders, autism, epilepsy, intellectual disability, ADHD, schizophrenia, precision medicine

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 1 published 20 Nov 2019	✓	✓

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Introduction

Ionotropic glutamate receptors are ligand-gated ion channels that mediate excitatory synaptic transmission throughout the central nervous system. These receptors can be classified into at least three distinct families, and nomenclature is based on the initial discovery of selective activating agonists AMPA, kainate, and *N*-methyl-D-aspartate (NMDA) for their corresponding receptors, which arise from *GRIA*, *GRIK*, and *GRIN* genes, respectively. The *GRIN* gene family encodes three classes of NMDA receptor (NMDAR) subunits: the glycine-binding GluN1 (product of *GRIN1*), glutamate-binding GluN2 (*GRIN2A*, *GRIN2B*, *GRIN2C*, and *GRIN2D*), and the enigmatic glycine-binding GluN3 (*GRIN3A* and *GRIN3B*), the role of which remains poorly understood[1,2]. Most NMDARs are tetrameric assemblies of two GluN1 and two GluN2 subunits. In terms of the evolutionary history of the NMDAR, it appears that four GluN2 paralogs (GluN2A–D) were produced by two rounds of gene duplication in a common vertebrate ancestor; the rounds diverged during early vertebrate evolution principally at their carboxyl-terminal domain (CTD)[3]. The first round of duplication gave rise to two GluN2 genes (the ancestors of GluN2A/B and GluN2C/D), and the second round gave rise to the four extant paralogs[4]. Having a common ancestry, GluN2A and GluN2B molecular structure and function should be similar, except for the divergent CTDs. However, there are strong differences between these two subunits on almost every level, including in how clinically relevant missense variants impact the receptor and patient. In this review, we will focus on the molecular and functional basis as to why GluN2A and GluN2B show strikingly different effects when missense mutations arise (for example, *de novo* in key gating motifs and different neurological disorders).

Glutamate receptor structure and function

All NMDAR subunits contain four semi-autonomous domains: an amino-terminal domain (ATD), agonist-binding domain (ABD), transmembrane domain (TMD), and CTD (Figure 1). The bilobed ABD of GluN2 binds L-glutamate within a cleft between two rigid lobes, S1 and S2, which form a clamshell-like structure that undergoes pronounced conformation changes upon ligand binding. The S1 lobe of the ABD, which resides distal to the ion channel, forms an interface between the ABD of adjacent subunits, allowing them to act as dimers[5]. For NMDARs, one GluN1 and one GluN2 ABD form a dimer, two of which exist within each tetrameric receptor[6]. The S2 lobe that is proximal to the channel contains primarily the polypeptide chain that connects the two transmembrane helices (M1 and M3) through flexible linkers and a two-turn helix (the pre-M1 helix) that lies parallel to the plane of the membrane. The S2 lobe undergoes considerable movement as the agonist binds to "close the clamshell" within the ABD of each subunit, which is the initial conformational change of several that ultimately lead to opening of the ion channel pore[7]. This combination of agonist binding and clamshell closure provides the energy to drive channel opening in all ionotropic glutamate receptors[6,8–11].

Most information on NMDAR location and function exists for diheteromeric receptors that are a tetrameric assembly of two GluN1 subunits and two identical GluN2 subunits[1,2]. NMDARs are maximally activated when glycine binds to the ABD of GluN1 and L-glutamate binds to the ABD of GluN2[1]. Three transmembrane helices (M1, M3, and M4) form the pore and are directly coupled to the ABD in all glutamate receptor subunits, and the pore is lined by a re-entrant loop (referred to as M2)[12,13]
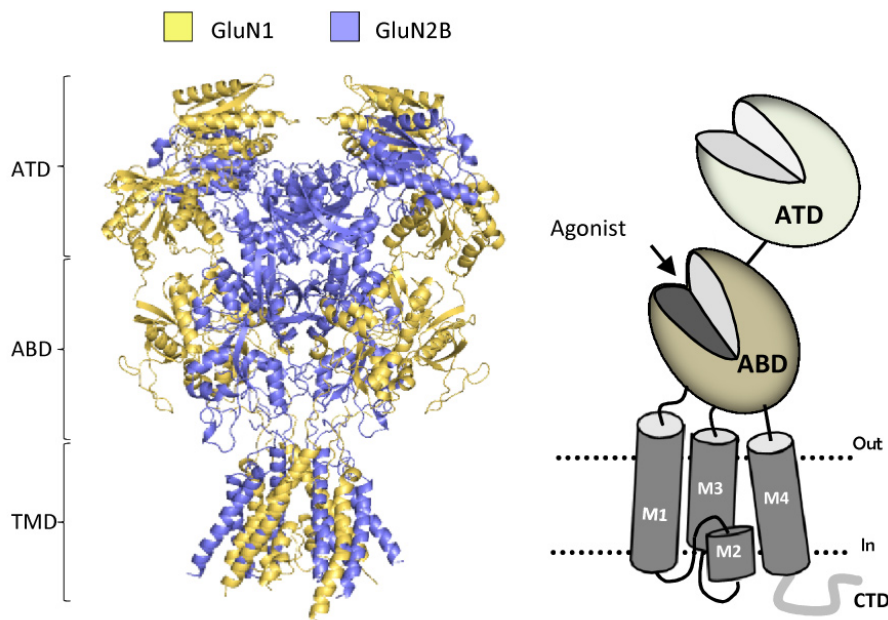
Figure 1. Domains of *N*-methyl-D-aspartate (NMDA) receptors. The crystal structure for GluN1/GluN2B receptors is shown in the left panel[13] depicting the amino-terminal domain (ATD), the agonist-binding domain (ABD), and the transmembrane domain (TMD). Not shown is the intracellular carboxyl-terminal domain (CTD). The right panel displays a schematic of a *GRIN* subunit, and the subdomains and the clamshell features of the ATD and ABD are indicated.

that controls ion permeation and block[14]. Not surprisingly, single amino acid variants in these transmembrane helices, in the linkers that couple transmembrane helices to the ABD, and in the pore-lining re-entrant M2 loop can affect gating, ion permeation, and block[15–21]. Part of the activation gate—the structure that occludes the flux of ions in the closed state—involves the M3 segment, including a highly conserved motif (SYTANLAAF)[10]. The process of opening and closing is highly dependent on these nine residues, residues in the pre-M1 region and a region preceding the fourth TMD[1,6,22–24].

The NMDAR is permeable to Ca^{2+} in addition to Na^+ and K^+[14,22,25–27], and the intraneuronal Ca^{2+} entry subsequent to NMDAR activation can engage intracellular signaling systems that lead to changes in gene expression[28], changes in post-translational modifications[29], and ultimately changes in synaptic strength[30]. Once the pore opens, extracellular Mg^{2+} can join the traffic of ions moving through the channel to reach a deep binding site in the pore, the occupancy of which establishes channel block in a voltage-dependent manner (reviewed in 14). This endows the receptor with the ability to detect neuronal activity (in the form of depolarization) and simultaneous synaptic activity (in the form of release of glutamate). This coincidence detector is a central feature enabling NMDARs to participate in some, but not all, forms of synaptic plasticity[31]. Some NMDARs can undergo desensitization during persistent activation[32], and the time course of desensitization for NMDARs is much slower than that for AMPA receptors[1]. Both speed and extent of desensitization are subunit-dependent[33,34], providing further separation of temporal signaling properties that depend on the frequency of synaptic input[35].

There are profound differences in the properties of NMDARs that contain GluN2A compared with GluN2B. For example, the open probability with GluN2A is higher than with GluN2B[35,36]. In addition, glutamate and glycine are both less potent at GluN2A compared with GluN2B[37] and thus GluN2A-containing NMDARs show a faster deactivation time course following removal of glutamate than GluN2B-containing NMDARs[38]. The deactivation time course following glutamate removal sets the duration of the synaptic current[39] and thus GluN2A NMDARs will produce a faster synaptic current in comparison with GluN2B. GluN2A-containing receptors also desensitize more rapidly than GluN2B-containing receptors, which show a much slower desensitization time course[35]. These two receptors show different sensitivity to extracellular negative allosteric modulators such as Zn^{2+}[40,41], and the Zn^{2+} binding site in the ATD shows much higher potency for GluN2A than GluN2B[42]. These functional properties, as well as the intracellular CTD that controls receptor targeting to different regions of the plasma membrane, will enable a variety of distinct functions for GluN2A- and GluN2B-containing NMDARs in neurons. There is strong evidence for perisynaptic NMDARs which could play a range of different roles[43,44]. Some evidence suggests that GluN2A preferentially distributes to the postsynaptic density, compared with GluN2B, which also distributes throughout the dendrite at extrasynaptic sites[45]. This distinct localization has also been suggested to influence the participation of these two

receptor subunits in different forms of synaptic plasticity[46–48]. Moreover, there are distinct roles of NMDARs of different subunit composition in neuroprotective signaling and cell death signaling that reflect both their localization and ability to pass current and Ca^{2+}[49–52]. However, the subcellular distributions of GluN2A and GluN2B are not absolute, and both subunits can be found both synaptically and extrasynaptically.

Developmental expression profile of GluN2A and GluN2B

The temporal expression profile of different NMDAR subunits is precisely controlled to coincide with critical periods in the development of different brain structures[53–58]. Indeed, *GRIN2* gene expression in the brain changes throughout the postnatal developmental stages[59]. The GluN2B subunit is highly expressed in the prenatal stages and its expression drops at the postnatal stages, becoming focally expressed in the forebrain. However, GluN2A is expressed at apparently low levels in the prenatal stages and increases upon birth[53,60]. In rodents, *GRIN2A* mRNA appears detectable by *in situ* hybridization studies around postnatal day 6. There is a progressive developmental change from predominantly GluN1/GluN2B receptors to GluN1/GluN2A receptors in many brain regions[58,61–63], including thalamic and cortical neurons during the early postnatal development[64]. The decrease in GluN2B-containing NMDARs at synapses is corroborated with the detection of shorter excitatory postsynaptic currents and a decrease in sensitivity to a specific GluN1/GluN2B receptor antagonist, ifenprodil[65,66]. The prenatal expression of *GRIN2B* in NMDAR subunit has been taken as evidence for an important role in brain development, circuit formation, and possibly cell migration and differentiation[67]. In early postnatal development and late embryogenesis, GluN2B expression dominates during rapid cortical synaptogenesis[68]. Kutsuwada *et al.* observed neonate lethality of global *GRIN2B* knockout mice[69], whereas Tang *et al.* reported that overexpression of *GRIN2B* in the forebrain of mice enhanced spatial memory performance and long-term hippocampal potentiation[70].

It is not surprising that the many recent reports on human variants in *GRIN* genes show different clinical phenotypes (discussed below) given that the modular structure of the receptor can compartmentalize the different actions of variants in different domains, thereby impacting different functional modalities. In addition, the distinct roles of GluN2A and GluN2B in synaptic signaling and circuit function enabled by their different developmental expression profile[58,61–63], the compartmentalization[62], and the functional attributes mean that variants in these two genes could have very different effects and different age-dependent phenotypes. For example, more pronounced effects might be observed for *GRIN2B* variants in terms of neurodevelopment, and effects of the mutations might present early in postnatal stages and manifest as neurodevelopmental disorders, developmental delays (DDs), and intellectual disability (ID)[71]. However, the effect of *GRIN2A* will start to show in the later postnatal stage as the expression of *GRIN2A* starts to increase and thus the influence of GluN2A-containing NMDARs becomes important. Most of the GluN2A variants were identified in patients with epileptic seizures and epileptic

encephalopathies[72]. In most cases when variants reduce Mg^{2+} inhibition and otherwise show enhanced NMDAR function, the patients show epileptic encephalopathy (EE), which may reflect not just DD from persistent and intractable seizures but perhaps excitotoxic neuronal cell death[73]. Interestingly, variants in GluN1 will impact all NMDARs and thus would be expected to have even further distinct effects compared with GRIN2A and GRIN2B[74]. However, in this review, we restrict our summary of recent studies to rare de novo variants discovered in the GRIN2A and GRIN2B genes. We highlight an emerging understanding of the functional and clinical consequences of these variants in the context of receptor expression, localization, and the unique roles that GluN2A and GluN2B subunits play. We speculate that viewing the phenotypic differences for patients with GRIN2A and GRIN2B through the lenses of these different properties will provide greater insight into disease mechanism and this information will create the possibility of instituting mechanism-based novel therapeutic treatments.

The increase in genetic information identifies a large number of disease-associated variants

The number of rare variants associated with neurological disease is expanding rapidly. Since the identification of the first disease-causing variants in NMDARs in 2010[75,76], over 500 variants in all GRIN genes coding for NMDARs—found in all four semi-autonomous domains, (the ATD, the ABD, the TMD, and the CTD)—have been reported in ClinVar or from patient cohorts in the literature. These include 249 variants in the GRIN2A and 204 variants in the GRIN2B (ClinVar). The increasing use of next-generation whole exome sequencing in clinical practice promises to identify even more rare de novo variants in GRIN genes linked to neurological disorders as diagnostic whole exome sequencing efforts expand and become common practice outside academic medical centers[71,77,78]. The rapid identification of numerous rare genetic variants should be followed by functional analysis of these variants, which, though more time-intensive, is an essential step in establishing their role in neurological disease. In addition, functional evaluation provides mechanistic insight toward disease etiology and potential treatment options. Fortunately, the NMDARs encoded by these genes can be easily expressed in heterologous systems and their function, though complex, is reasonably well understood[1,2,6]. Multiple groups are expanding efforts to fill the gap between genetic identification of rare variants and elucidation of their functional consequences[6,23,73,74,79–98]. With continued effort, all disease-associated variants eventually should be identified and functional characterization of these variants will inform the subdivision of variants into a limited set of groups with more homogenous clinical and functional phenotypes. This will allow direct comparison of variants with similar effects between different subunits and help elucidate the roles that these subunits play during development. It will also transform diagnoses and treatment options since variant function eventually will be readily available for clinicians in real time. However, at the moment, there remains a significant lag in efforts to obtain this functional information compared with the amount of new sequencing being performed.

Comparison of patient phenotype for GRIN2A and GRIN2B missense and nonsense variants

Among the variants identified in the GRIN gene family, those in GRIN2A (46%) and GRIN2B (38%) account for the vast majority, followed by GRIN1 variants (14%; ClinVar)[72]. It is important to note that all of these genes can co-assemble to form functional receptors, meaning that the GRIN variants should be thought of as a larger set of variants since variants in all three genes can produce similar gain-of-function (GoF) or loss-of-function (LoF) effects on NMDARs. Moreover, every NMDAR contains GluN1 and thus these variants in particular will impact both GluN2B- and GluN2A-containing NMDARs. However, there will be differences in the overall effects for GRIN2A versus GRIN2B genes depending on their regional and developmental expression profile, in addition to the different roles that they can play in circuit function. Thus, it will be useful to stratify variants by gene and by GoF and LoF even though they impact an overlapping set of NMDAR complexes expressed in the brain. Given that the most common GRIN variants are in GRIN2A and GRIN2B, a comprehensive evaluation of these two subunits provides an opportunity to understand the structural, functional, and genetic bases for disorders that these patients have. Functional consequences of many GRIN2A and GRIN2B variants have been assessed in heterologous expression systems and so we will focus on the effects of rare variants in these two genes.

An assessment of the genetic variation in the healthy population together with an evaluation of GRIN2A and GRIN2B variants in patients with neurological disease provides information about the regional tolerance of different domains of the GluN2 subunit. This approach reveals insight into protein function and information about the regions of the receptor that cannot tolerate even modest changes in amino acid side chain properties[81]. Such regions appear to have undergone purifying selection and this determination can aid in future in silico predictions of the impact of missense variants. Evaluation of GRIN2A and GRIN2B revealed that the ABD, TMDs, and the linker regions between these domains were particularly intolerant to genetic variation and suggests that these domains are under greater selection pressure[82,83]. These two regions appear to harbor the most disease-associated variants within the GRIN2A and GRIN2B genes[72,82–84]. Evaluation of phenotypic severity for a cohort of patients harboring GRIN2A variants showed stratification in severity across variants with different functional effects and localizations[85]. There are some subtle differences in regions that are insensitive to variation that reflects different functions of GluN2A and GluN2B subunits. There are examples where different patients (that is, different genetic backgrounds) harbor the same de novo GRIN missense variant in their genome; in these cases, the patients display similar but non-identical clinical phenotypes[21,23,84–88]. As the databases of genetic variation within the standing population expand, there will be an ever-increasing precision with which we can define intolerant regions, and we expect that more specific examples of intolerant regions that differ between the two subunits will emerge. In this review, we also compiled a list of GRIN2A and GRIN2B variants with phenotypes

published in the literature and not found in the gnomAD database (http://gnomad.broadinstitute.org; Table 1).

GRIN2A predominantly is associated with epilepsy and intellectual disability

More than 240 missense and nonsense variants have been reported for *GRIN2A*. *De novo* variants in *GRIN2A* can be found in phenotypically normal neonates with a structurally normal brain at birth[85,89]. Multiple patients appear to have had uncomplicated pregnancies and normal deliveries with excellent appearance, pulse, grimace, activity, respiration (APGAR) scores and no immediate complications. However, patients can begin to show neurological abnormalities at a young age (during the first year of life)[89], presumably as a result of increasing expression of *GRIN2A* with development[60]. This most often manifests as abnormal electroencephalography (EEG) and myoclonic jerks progressing to a seizure disorder. Several studies

have suggested that benign focal epilepsy with centrotemporal spikes (BECTS) seems to be caused by both missense and nonsense *de novo* mutations within the *GRIN2A* gene: Three reports from 2013 showed that *GRIN2A* gene variants are more likely to occur in epilepsy subtypes that are believed to be a more severe variant of BECTS such as atypical benign partial epilepsy of childhood, Landau–Kleffner syndrome, and continuous spike waves during slow wave sleep[99–101]. An intriguing aspect of these epilepsy patients who harbor *GRIN2A* variants is that the variants can produce both GoF and LoF, as inferred by nonsense variants that produce protein truncation. Patients with a deletion that removes the *GRIN2A* gene also show hyperexcitability[76]. The mechanisms that ultimately promote hyperexcitability in patients lacking *GRIN2A* are not yet known, by likely due to haploinsufficiency although it appears that they in some way enhance circuit excitability[102]. Interestingly, there is no firm evidence to suggest that *GRIN2A* variants

Table 1. Phenotypes reported across *GRIN2A* and *GRIN2B* subdomains.

| Phenotypes (top) or Variant Type (bottom) | # reported in *GRIN2A* / # reported in *GRIN2B* | | | | | |
	ATD	ABD	ABD-TMD Linkers	TMD	CTD	Other
Epi	25 / 3	41 / 13	5 / 4	19 / 12	9 / 0	26 / 1
ID	28 / 13	32 / 35	4 / 9	19 / 23	8 / 9	22 / 15
ASD	4 / 6	5 / 13		4 / 3	2 / 6	1 / 5
Language delay/Verbal dyspraxia/Aphasia syndrome	14 / 0	22 / 0	5 / 1	10 / 0	1 / 1	7 / 0
LKS	1 / 0	3 / 0	1 / 0		1 / 0	1 / 0
ADHD/Rett-like syndrome/Behaviorial anomalies	2 / 1	3 / 0	1 / 1	1 / 1		1 / 2
IS	1 / 0	1 / 0		0 / 2		
CVI				1 / 3		
Hypotonia/Dystonia	3 / 0	0 / 1	0 / 1	9 / 1		2 / 1
LGS		0 / 1				
MD		3 / 1	3 / 1	4 / 2		1 / 0
West syndrome		0 / 1		0 / 2		
Dysmorphic features	1 / 0	1 / 0	0 / 1	2 / 1		3 / 0
SCZ/Bipolar disorder	1 / 2				1 / 2	2 / 0
Macrocephaly or Abnormality of nervous system					1 / 1	3 / 1
Missense variant	12 / 7	31 / 29	4 / 8	20 / 23	7 / 8	
Nonsense variant	8 / 4	3 / 2	0 / 1	0 / 2	3 / 2	
Splice junction variant	9 / 0	7 / 3	1 / 0	0 / 1		
Frame-shift variant	5 / 4	9 / 1		4 / 0	2 / 3	
Indel variant			1 / 0		1 / 1	
Other						31 / 17

The table compares genetic variants in *GRIN2A* and *GRIN2B* genes with phenotypes as reported in the literature and absent in the gnomAD database (http://gnomad.broadinstitute.org). ABD, agonist-binding domain; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; ATD, amino-terminal domain; CTD, carboxyl-terminal domain; CVI, cerebral visual impairment; Epi, epilepsy/seizures; ID, intellectual disability (including developmental delay); IS, infantile spasms; LGS, Lennox–Gastaut syndrome; LKS, Landau–Kleffner syndrome; MD, movement disorder; SCZ, schizophrenia; and TMD, transmembrane domains (M1-M4). Other, refers to chromosome deletions, insertions, duplications that affect *GRIN2A* or *GRIN2B* genes. References 21, 73, 75, 76, 80, 82–86, 89–92, 94, 96, 98–101, 103–153.

contribute to the two most common epilepsy syndromes: idiopathic generalized epilepsy and temporal lobe epilepsy[154]. *GRIN2A* variants are linked to autism spectrum disorder (ASD) but to a lesser degree than seen with *GRIN2B* variants (Table 1).

GRIN variants have been identified both by screening of a select set of genes assembled as a panel or by whole exome sequencing, which provides good coverage over much of the exome, although certain GC-rich regions of DNA (for example, the 5' region of *GRIN2D*) are often under-represented. Nevertheless, these approaches have discovered a large number of *de novo* variants in neurological patients. A functional analysis has been published in the peer-reviewed literature for a number of *GRIN2A* variants[73,75,79,83,86,90–93]. In addition, there is a comprehensive functional summary on the websites as a resource (http://functionalvariants.emory.edu). Below, a subset of these published variants is discussed to illustrate some important commonalities and distinctions.

The functional consequences of several variants reported in the gnomAD database, some of which showed functional changes, were evaluated. One clinical case report is for a missense variant (GluN2A-V452M) from a patient with early infantile EE/Ohtahara syndrome[155]. Another example of a variant proposed to cause a disease phenotype is a heterozygous *GRIN2A* variant that produces GluN2A-N447K in a male with Rolandic epilepsy. EEG monitoring showed remarkable interictal high voltage spikes and spike-and-slow waves in the bilateral central-temporal regions, predominantly on the right hemisphere. The GluN2A-N447K variant is located in the S1 segment of the extracellular ABD of GluN2A. Residue N447 is highly conserved across higher vertebrates yet the Asn447Lys variant is present multiple times in gnomAD. Whole cell patch clamp recording of GluN2A-N447K reveals a GoF effect and an increase in NMDAR current density by about 1.2-fold, an enhancement of glutamate potency by two fold, and reduced sensitivity to Mg^{2+} inhibition[93]. Experimental substitution of Asn447 to alanine (uncharged) or glutamic acid (negatively charged) did not change NMDAR function, suggesting that the positive charge associated with lysine may have altered NMDAR function. The patient became seizure-free when treated with a combination of valproate and lamotrigine[93].

A child with epileptic encephalopathy (EE) and severe cognitive impairment possessed a GoF missense *GRIN2A* variant that produced GluN2A-L812M. This position in the linker between the ABD and TMD regions is intolerant to change, as all amino acid substitutions (seven to date) at this position produced a GoF variant that showed increased agonist potency, increased open probability, and reduced sensitivity to endogenous negative modulators such as extracellular Mg^{2+} and protons[73]. The variant NMDARs' activities were enhanced by virtually every measure and would be expected to lead to profound overactivation, which could drive excitotoxic mechanisms. Memantine is able to inhibit the GluN2A-L812M-containing NMDARs, and treatment with memantine led to a persistent reduction of the child's seizure burden[89].

A heterologous *de novo* variant was found in a 3-year-old female with early-onset EE, abnormal EEG, and severe DD[75]. The variant substituted an evolutionarily conserved asparagine for a lysine (GluN2A-N615K) in the membrane re-entrant loop, which lines the channel pore and creates a constriction that controls ion selectivity of the channel[6,156,157]. This variant alters the voltage-dependent channel block by Mg^{2+} and decreases in Ca^{2+} permeability. Co-expression of GluN2-N615K with GluN1 and wild-type GluN2A in the same receptor complex, called triheteromeric receptors (comprised of GluN1:GluN2A:GluN1: GluN2A-N615K subunits), produces an intermediate effect, indicating that the negative impact caused by the variant on channel properties cannot be fully negated by the presence of one normal subunit copy of GluN2A in the receptor complex[21,92].

GRIN2B is predominantly associated with developmental delay, intellectual disability, and autism spectrum disorder

Over 200 variants in *GRIN2B* are found in patients from cohorts with any one of several neurodevelopmental disorders[71] such as ID (including DD)[14,75,80,82–84,91,94–96,98,103–108,111,112,114,120,122,123,128,130,135,139–147,149–153], ASD[75,80,82,84,91,98,104,105,108,111,135,140,144,148,151–153], EE and seizure disorders[21,80,82,84,98,103,120,130,135,138,139,141,145], schizophrenia[71,111,114,137,148], and, to a lesser extent, attention-deficit/hyperactivity disorder[80,84,106], cerebral visual impairment[146,158], and Alzheimer's disease[159] have been reported in the literature. For these various phenotypes, virtually all of the patients display mild to profound DD or ID or both. In addition to exhibiting these neurological phenotypes, some patients exhibit abnormalities in muscle tone that includes spasticity or hypotonia[151,158]. *GRIN2B* has been linked as a potential gene in which variations could increase the risk of autism[104,105,160]. A number of other characteristics, including microcephaly, movement disorders, Rett-like syndrome, language disorders have been observed in some patients[75,96,115,142,158].

The *GRIN2B* variants identified thus far occur throughout the entire NMDAR subunit protein. That is, missense and nonsense variants have been identified in the ATD, ABD, TMD, and CTD domains. Homozygous *Grin2b*-deletion mice die at early postnatal stages because of impaired suckling response and show impaired hippocampal long-term depression, whereas heterozygous mice show reduced expression of GluN2B but survive[69]. Thus, *GRIN2B* is an essential gene for normal development. *GRIN2B de novo* variants with neurological diseases have been reviewed[71,77,161], and functional data exist for many *GRIN2B* variants in published scientific journals (see below) or online databases (http://functionalvariants.emory.edu).

Large cohort studies for ID or ASD have identified that LoF variants in *GRIN2B* segregate with a broad spectrum of these neurological phenotypes[75,105]. One such LoF variant is the missense variant GluN2B-E413G[106], which produces DD and ID. Studies conducted on neural progenitor cells (NPCs) generated from induced pluripotent stem cells found that neurons with heterozygous GluN2B-E413G, which is in the glutamate-binding pocket, caused a 50-fold decrease in glutamate signaling and reduced the maturation states of the

neurons. Verification of failure to phosphorylate serine 133 in cAMP response element-binding protein (CREB) by NMDAR stimulation further confirms that the E413G variant in GluN2B impaired NMDAR signaling in the NPCs[94]. This study shows that *GluN2B*-containing NMDARs are critical for signal transduction in neural stem cells and deficits in this process impair cellular differentiation. The E413G variant is in close proximity to the glutamate-binding site but is not in physical contact with the agonist glutamate. Modelling of the protein structure suggests that GluN2B-E413 can alter agonist dissociation by increasing the ability of water to compete with agonist binding, thereby accelerating glutamate unbinding and likely rendering the synaptic NMDAR response time course briefer than that for wild-type NMDARs[82,95].

The *GRIN2B* variant encoding GluN2B-C461F, which was identified in a patient with Lennox–Gastaut syndrome and autistic features, is a LoF NMDAR variant. Cys461 is located in S1 of the ABD, close to the orthosteric glutamate-binding site. When co-transfected with GluN1-4b, an early developmental isoform of *GRIN1*, GluN1:GluN2B-C461F receptors reduced glutamate potency by 71-fold compared with wild-type controls[80]. This is in keeping with decreased glutamatergic neurotransmission in animal models of ASD (for example, BTBR mice), in which the phenotype can be improved by a selective AMPAKINE (AMPA receptor–positive allosteric modulator). Lennox–Gastaut syndrome is a severe type of childhood epilepsy. Also, during early development, high expression of variant GluN2B subunits could compromise neurotransmitter-based signaling (for example, GABA release via presynaptic NMDARs), circuit operation between distinct cell types (interneurons/principal neurons), and the balance of excitation and inhibition[80]. This is in line with the association of mutations in *GABRB3* with Lennox–Gastaut syndrome and autism[162–164]. In addition, synaptic pruning and synapse refinement are GluN2-dependent events that occur generally at a time of a switch in subunit expression from GluN2B to GluN2A[64] and thus could be influenced by altered GluN2B function. This could be one contributing factor that is an underlying substrate for developmental effects of *GRIN2B* variants[165].

The GluN2B-P553L variant was identified in a patient with severe ID[107]. This variant was found to minimally affect glutamate potency, but the rate of desensitization of GluN1–GluN2B-P553L was markedly increased and currents were small in HEK cells[80,83]. Pro553 is located at the proximal end of the first TMD, within the pre-M1 linker that connects S1 to M1. Spatially, P553 is adjacent to the highly conserved nine-residue signal-transduction element (SYTANLAAF) in M3 of the same subunit, which is involved in coupling ligand binding to channel opening, and controls channel open probability[6]. Thus, the variant Pro553Leu may form different interactions with Asn649 or Leu650 (or both) in the SYTANLAAF motif, which could interfere with gating.

GluN2B-N615I and GluN2B-V618G variants are both associated with West syndrome, which is a triad of infantile spasms,

hypsarrhythmia, and ID[103]. GluN2B-N615 and -V618 are located in the M2 re-entrant loop, which forms part of the ion channel. N615 is located just above the narrowest constriction in the pore, which is also influenced by analogous residues in the GluN1 subunit (for example, GluN1-N616). Val618 in GluN2B is located deep in the channel pore, within the M2-M3 linker and with the CH_3 side chain that has been suggested to be rotated away from the channel pore. This side-chain will interact with residues in M2 and M3 membrane helices of GluN1[80,98]. For GluN2B-N615I and GluN2B-V618G, voltage-dependent Mg^{2+} inhibition was lost, resulting in a GoF phenotype that will allow increased NMDAR current under normal resting conditions, which may underlie increased neuronal excitability in West syndrome. The onset of symptoms in the patient coincided with the high expression profile of GluN2B in late infancy (<1 year old)[62,103].

Variants at the same residue position in GluN2A and GluN2B resulted in different disease phenotypes

A variant in both *GRIN2A* and *GRIN2B* that occurs at the same homologous position of these GluN2 subunits in NMDAR has been identified. Functionally, both GluN2A-N615K and GluN2B-N615I and GluN2B-N615K variants that substitute an evolutionarily conserved asparagine in the membrane re-entrant loop resulted in a loss of Mg^{2+} block[21,75,80,84]. However, the resulting neurological phenotypes were found to be different. A 3-year-old female with a GluN2A-N615K variant exhibits early-onset EE, an abnormal EEG, and a severe DD[75], whereas for a GluN2B-N615I variant, the patient had West syndrome, hypsarrhythmia, and ID due to neurodevelopment disorders[80,84] and GluN2B-N615K patient had ID and DD[84]. This further validates our hypothesis that rare variants in intolerant domains in *GRIN2A* are more likely to cause an epileptic phenotype but that variants in *GRIN2B* are more aligned with abnormal developmental phenotypes.

Other cases for which the genetic variants were found on different GluN2 subunits at a homologous amino acid are GluN2A-P552R and GluN2B-P553L. GluN2A-P552R was identified in a patient with delayed psycho-motor development, ID, inability to speak, and epilepsy since 9 months of age[83,107]. The GluN2A-P552R variant shows increased sensitivity to glutamate and glycine but with a slower activation and deactivation time course. The GluN2B-P553L variant presents in a patient with severe ID and DD[80,83,98,107]. This variant was found to reduce glutamate potency by 1.7-fold but increase the rate of glutamate current desensitization[80,83]. Thus, whereas one variant should increase charge transfer for each synaptic current, the other should diminish it.

In most situations, the GluN2A or GluN2B variants exist as a single allele (that is, are heterozygous) in the patients and therefore patients also have one copy of the wild-type allele. Therefore, it would be important to understand the effects of rare variants in both diheteromeric and triheteromeric NMDARs. As the NMDARs exist as a heterotetramer with two obligatory GluN1 subunits, the possibility exists that a diheteromer (for example, GluN1/GluN2A/GluN1/GluN2A) or

triheteromer (for example, GluN1/GluN2A/GluN1/GluN2B) harbors a single disease variant GluN2 subunit.

To understand the *GRIN2* variant effects in the presence of wild-type allele, NMDAR subunits were engineered to co-express as GluN1/GluN2A/GluN1/GluN2A-P552R and GluN1/GluN2A-P552R/GluN1/GluN2A-P552R, analyzed for response time course to glutamate and glycine, and compared with wild-type control GluN1/GluN2A. Single channel recording from single copy variant–containing receptors did not alter mean channel open time or chord conductance as compared with the wild-type channel. For the NMDARs with two copies of GluN2A-P552R, there is a significant increase in mean open time and reduced channel conductance when compared with the wild-type or single copy mutant. These data suggest that the GluN2A-P552R variants can alter stability and conformation of the open pore or its access portals only when both GluN2A subunits contain the P552R variant[83].

Precision medicine

As more precise diagnoses for individuals are achieved, the basis of disease etiology will be better defined. We anticipate that novel drug development and a more mechanism-based use of currently approved drugs can improve clinical outcomes. For pharmacological treatment, the knowledge of risk factors, disease subtype, or underlying genetic variation should allow a choice of therapies proven effective in individuals with similar characteristics. For rare variants that are thought to contribute to or cause a disease, unique treatments that alter the function of the target or its downstream effects could provide novel therapies. This collection of ideas together can be described as precision medicine, an idea that is enabled by recent advances in technology on multiple fronts. There are several opportunities for potential precision medicine among the *GRIN* variants. For example, it seems reasonable that therapies already approved by the US Food and Drug Administration that inhibit NMDAR receptors might have utility against symptoms produced by GoF *GRIN* variants provided that some of the ongoing neurological symptoms reflect expression of aberrant protein rather than errant processes during development or cell loss driven by excitotoxicity. Likewise, although there are no currently available NMDAR potentiators approved for clinical use, supplementation with the co-agonists glycine, D-serine, or perhaps D-cycloserine might provide a way to augment NMDAR function, although

there remains no systematic evaluation of this possibility in animal models or patients[96].

Personalized medicine through pharmacological intervention on patients harboring *de novo GRIN2A* and *GRIN2B* variants has been attempted. However, caution must be exercised as the potential drugs available (for example, memantine) are non-selective blockers of NMDARs, meaning that one may induce a block at some sites that are not contributing to the pathology. Memantine binding was also affected by the presence of bound Mg^{2+} in the channel, which reduced memantine potency more for GluN2A and GluN2B than GluN2C or GluN2D[166]. Kinetic and molecular docking results indicated overlapping sites for Mg^{2+} and memantine, with Mg^{2+} binding at the level of the asparagine residues, whereas memantine binds just above the channel pore[167]. Among the NMDAR subtypes, memantine has been suggested to be more potent at GluN2C- and GluN2D-containing NMDARs, the latter of which are expressed in GABAergic interneurons[53,168]. Nevertheless, over-active receptors may be attenuated, and some degree of voltage-dependent block potentially restored, to compensate for a reduced Mg^{2+} block by a rare variant. However, again caution is emphasized as several distinct disease variants in the channel pore can also alter the effect of candidate therapies, and already there are examples among the *GRIN* genes in which the variant renders a potential drug candidate less effective. For example, memantine was more potent at GluN1/GluN2B-N615I and less potent at GluN1/GluN2B-V618G, compared with wild-type receptors, which holds important implications for therapeutics. Interestingly, dextromethorphan showed increased potency for some variant receptors compared with wild-type receptors[90].

Of the various mutations studied in detail, two result in LoF (C461F and P553L) and two in GoF (N615I and V618G). On this basis, memantine cannot be considered an all-encompassing treatment for NMDAR mutations and will be therapeutically beneficial for only selected GoF channel variants unless compensatory NMDAR is large. Still, there are some examples in which NMDAR block by memantine showed some utility[86,89,97]. The inhibition of NMDAR-mediated currents by memantine at negative membrane potentials was comparable between wild-type and N615I- or V618G-expressing neurons. This supports a role for this medication as a potential therapy to mimic a loss Mg^{2+} block at the potentials in neurons.

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Competing Interests: No competing interests were disclosed.

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Competing Interests: No competing interests were disclosed.