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GRIN2A-Related Disorders

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Summary

Clinical characteristics

GRIN2A-related disorders encompass a broad phenotypic spectrum that includes developmental delay evolving to intellectual disability (DD/ID), epilepsy, speech and language disorders, movement disorders, and neuropsychiatric disorders. Intellect ranges from normal to profoundly impaired. Observed speech disorders include dysarthria and speech dyspraxia, and both receptive and expressive language delays; more mildly affected individuals may display subtly impaired intelligibility of conversational speech. Epilepsy features include seizure onset usually between ages three and six years, focal epilepsy with language and/or global developmental regression, and electroencephalogram (EEG) abnormalities, including continuous spike-and-wave discharges in sleep or very active centrotemporal discharges. Epilepsy is typically focal and ranges from self-limited epilepsy with centrotemporal spikes to developmental and/or epileptic encephalopathies (DEE/EE), including the syndromes of DEE/EE with spike-wave activation in sleep (DEE/EE-SWAS), which include Landau-Kleffner syndrome. Movement disorders occur less frequently and include ataxia, dystonia, and chorea.

Diagnosis/testing

The diagnosis of a *GRIN2A*-related disorder is established in a proband by the identification of a *GRIN2A* heterozygous pathogenic variant on molecular genetic testing.

Management

Targeted therapy: In some individuals with pathogenic loss-of-function and null *GRIN2A* variants, treatment with the N-methyl-D-aspartate receptor (NMDAR) coagonist L-serine was associated with improvements in behavior, development, EEG features, and/or seizure frequency.

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Supportive care: Significant speech and language deficits require therapy from a speech-language pathologist. Seizures should be treated with anti-seizure medication (ASM). Multidisciplinary care is recommended by pediatric specialists in the fields of including pediatric epilepsy, movement disorders, speech-language disorders, physical therapy, occupational therapy, feeding and nutrition, behavioral disorders, and genetic counseling.

Surveillance: Developmental surveillance in all affected children; routine monitoring of speech and language by a speech-language pathologist should be considered for all children, particularly those diagnosed before reaching school age.

Agents/circumstances to avoid: In individuals with *GRIN2A*-related disorders due to pathogenic missense variants activating the NMDAR (i.e., gain-of-function variants), receptor-specific agonists and other activators (e.g., L-serine) should be avoided as this could result in worsening of symptoms. In individuals with pathogenic missense variants inhibiting the NMDAR as well as null variants, NMDA receptor blockers should be used with caution (e.g., memantine, dextromethorphan, ketamine).

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives in order to identify as early as possible those who would benefit from evaluation for speech disorders and/or seizures and institution of treatment.

Genetic counseling

GRIN2A-related disorders are inherited in an autosomal dominant manner. Some individuals diagnosed with a *GRIN2A*-related disorder have the disorder as the result of a pathogenic variant inherited from an affected parent. Approximately 50% of individuals diagnosed with a *GRIN2A*-related disorder have the disorder as the result of a *GRIN2A* pathogenic variant that occurred as a *de novo* event in the affected individual or, rarely, as a postzygotic *de novo* event in a mosaic, apparently unaffected parent. Each child of an individual with a *GRIN2A*-related disorder has a 50% chance of inheriting the *GRIN2A* pathogenic variant. Once the *GRIN2A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

A *GRIN2A*-related disorder **should be considered** in a proband with the following suggestive clinical findings and family history.

Clinical findings

- Mild-to-profound developmental delay / intellectual disability; some affected individuals may be of normal intellect.
- Focal epilepsy
  - Self-limited epilepsy with centrotemporal spikes
  - Developmental and/or epileptic encephalopathy (DEE/EE) with spike-wave activation in sleep (DEE/EE-SWAS)
  - Infantile-onset DEE, sometimes with epileptic spasms
- Speech and language disorders including dysarthria, speech dyspraxia, aphasia, and nonverbal phenotypes
- Movement disorders including ataxia, dystonia, or choreiform movements
- Hypotonia
- Neuropsychiatric features including behavioral issues, attention-deficit/hyperactivity disorder, autism spectrum disorder, schizophrenia, anxiety disorders, and mood disorders

Family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations) or the proband may have a *de novo* pathogenic variant and therefore be sporadic, with no other family members affected.

Establishing the Diagnosis

The diagnosis of a *GRIN2A*-related disorder **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *GRIN2A* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *GRIN2A* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches should include **comprehensive genomic testing** (exome sequencing, genome sequencing).

Note: Single-gene testing (sequence analysis of *GRIN2A*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Comprehensive genomic testing does not require the clinician to identify which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, all reported *GRIN2A* pathogenic variants are within the coding region or canonical splice sites and are likely to be identified on exome sequencing.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *GRIN2A*-Related Disorders

Gene [1, 2]	Method	Proportion of Pathogenic Variants [2] Identified by Method
GRIN2A	Sequence analysis [3]	85% (206/243) [4]
	Gene-targeted deletion/duplication analysis [5]	15% (37/243) [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene. Several additional individuals with complex chromosomal rearrangements disrupting *GRIN2A* (not included in these calculations) have been reported [Endele et al 2010].
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Strehlow et al [2019]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and gene-targeted microarray designed to detect single-exon deletions or duplications. These methods will detect from single-exon to whole-gene deletions; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected by these methods. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

The clinical spectrum of *GRIN2A*-related disorders is broad and includes developmental delay / intellectual disability (DD/ID), epilepsy, speech and language disorders, movement disorders, and neuropsychiatric disorders. Cognitive function can be normal or show mild-to-profound impairment. The spectrum of epilepsy phenotypes ranges from self-limited epilepsy with centrotemporal spikes (SeLECTS) to developmental and/or epileptic encephalopathies (DEE/EE) with spike-wave activation in sleep (DEE/EE-SWAS) – including Landau-Kleffner syndrome (LKS) – to infantile-onset DEE. Speech and language disorders range from mild speech impairment to aphasia to nonverbal phenotypes. Movement disorders occur less frequently and include ataxia, dystonia, and chorea. *GRIN2A*-related disorders also carry an increased risk for early-onset neuropsychiatric disorders such as anxiety disorders, mood disorders, and schizophrenia as well as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD).

To date, about 400 individuals have been identified with a pathogenic variant in *GRIN2A* [Lemke et al 2013, Lesca et al 2013, Carvill et al 2013, Strehlow et al 2019] (see also grin-portal.broadinstitute.org). The following description of the phenotypic features associated with this condition is based on reports of these individuals.

Table 2. Select Features of *GRIN2A*-Related Disorders

Feature		% of Persons w/Feature [1]
Developmental delay / intellectual disability	Any severity	63% (111/177)
	Mild	45% (33/74)
	Moderate	23% (17/74)
	Severe	11% (8/74)
	Profound	22% (16/74)
Epilepsy	Any type	88% (192/219)
	Focal	83% (121/146)
	Generalized	14% (21/146)
	Epileptic spasms	3% (4/146)
Speech & language disorders	Any type/severity	92% (129/140)
	Moderate [2]	48% (55/115)
	Nonverbal	16% (18/115)
	Speech delays	23% (26/115)
	Temporary speech regression / acquired aphasia	14% (16/115)
Movement disorders [3]		26% (19/72)
Neurobehavioral/psychiatric manifestations		24% (17/70)
Muscular hypotonia		29% (40/139)

Table 2. continued from previous page.

Feature	% of Persons w/Feature [1]
Brain MRI abnormalities [4]	14% (12/85)

1. Strehlow et al [2019]
2. Moderate speech and language impairment includes dysarthria, speech dyspraxia, dysphasia, speech regression with residual impairments, sometimes with additional impairments such as impaired pitch, hypernasality, or imprecise articulation [Turner et al 2015].
3. Movement disorders include ataxia, dystonia, chorea, and complex movement disorders.
4. Several brain abnormalities have been reported including focal cortical dysplasia, dysplastic corpus callosum, hypoplasia of corpus callosum with midline lipoma, hippocampal hyperintensity, hippocampal sclerosis, heterotopia, subcortical lesion, hypoplastic olfactory bulb, cerebellar glioma, enlarged Virchow-Robin spaces, and delayed myelination; 11% of individuals (9/85) also had generalized cortical atrophy.

Developmental delay (DD) and intellectual disability (ID) is observed in 63% (111/177) of affected individuals and ranges from mild to profound. Intellect of the 37% (66/177) of individuals without ID ranges from normal to learning disabled [Strehlow et al 2019].

Epilepsy occurs in approximately 90% of individuals [Strehlow et al 2019].

Seizure onset depends on the type of underlying *GRIN2A* variant [Camp et al 2023] (see Genotype-Phenotype Correlation). The most common seizure type is focal seizures (121/146, 83%), which frequently evolve to bilateral tonic-clonic seizures.

The predominant seizure type(s) in a given individual depends on the epilepsy syndrome. Broadly, *GRIN2A*-related disorders fall into the epilepsy-aphasia syndromes group, which includes DEE/EE-SWAS, of which Landau-Kleffner syndrome (LKS) is a subtype [Carvill et al 2013, Lesca et al 2013]. Related self-limited focal epilepsies such as SeLECTS and related disorders are also included, as well as unclassified phenotypes [Carvill et al 2013, Lemke et al 2013, Lesca et al 2013].

Specific epilepsy syndromes associated with *GRIN2A* pathogenic variants include:

- DEE/EE-SWAS with focal seizures, which may be drug-resistant. The electroencephalogram (EEG) shows marked activation in non-REM sleep of bilateral slow spike-and-wave discharges [Specchio et al 2022].
- In LKS, a subtype of DEE/EE-SWAS, 30% of individuals do not have seizures.
- Self-limited epilepsy with centrotemporal spikes (SeLECTS) with onset in childhood (usually age 3-6 years) with EEG showing centrotemporal discharges [Specchio et al 2022].
- Infantile-onset DEE, with severe-to-profound impairment and sometimes epileptic spasms

EEG most commonly shows focal discharges (86/152; 57%), with centrotemporal spikes (34/152; 22%) or multifocal discharges (28/152; 18%). One third of individuals had SWAS (51/152; 34%). SWAS is defined as marked activation of bilateral slow spike-and-wave discharges in non-REM sleep (previously known as continuous spike-wave in slow-wave sleep [CSWS] or electrical status epilepticus in sleep [ESES]). Generalized discharges (6/152; 4%) or individuals with normal EEG (9/152; 6%) are rare [Strehlow et al 2019].

Speech and language disorders are among the most common features of *GRIN2A*-related disorders [Turner et al 2015, Strehlow et al 2019]. Abnormalities include dysarthria, speech dyspraxia, dysphasia (55/115; 48%), and speech regression with acquired aphasia (16/115; 14%), which is typically seen in LKS.

Mildly affected individuals may display subtly impaired intelligibility of conversational speech, most characterized by dysarthric and dyspraxic features of hypernasality, imprecise consonant production, and impaired pitch and prosody [Turner et al 2015].

Neuroimaging. Brain MRI is normal in the majority of affected individuals (64/85; 75%). Severely affected individuals may show nonspecific abnormalities, such as cerebral atrophy (9/85; 11%) and a thin corpus callosum. A variety of other abnormalities have rarely been reported, including focal cortical dysplasia, dysplastic corpus callosum with delayed myelination, hypoplasia of corpus callosum with midline lipoma, hippocampal sclerosis, heterotopia, hypoplastic olfactory bulb, cerebellar glioma, enlarged Virchow-Robin spaces, and delayed myelination [Reutlinger et al 2010, Pierson et al 2014, Venkateswaran et al 2014, Yuan et al 2014, Strehlow et al 2019].

Other neurodevelopmental features

- Hypotonia (40/139; 29%)
- Movement disorders, including dystonia, chorea, and ataxia (19/72; 26%)

Neurobehavioral/psychiatric manifestations. Seventeen of 70 individuals (24%) had behavioral or psychiatric disorders, such as ADHD (n=6), ASD (n=6), schizophrenia, or anxiety disorders [Strehlow et al 2019, Shepard et al 2024].

Mental health disorders are relatively frequent in individuals with pathogenic null variants in *GRIN2A*. At least 27% of individuals develop early-onset mental health disorders including mood disorders (16%), anxiety disorders (14%), and psychotic disorders including schizophrenia (10%) and, rarely, personality disorders (4%) and eating disorders (1%) [J Lemke et al, unpublished data].

Facial features. No obvious dysmorphic features; some individuals may have nonspecific features.

Interfamilial and intrafamilial variability. Individuals who have the same pathogenic *GRIN2A* variant show similar severity of DD/ID, both within and across families [Strehlow et al 2019].

Prognosis. It is unknown whether life span in *GRIN2A*-related disorders is abnormal. The oldest known individual is 80 years old [J Lemke et al, unpublished data]. Since many adults with mild *GRIN2A* phenotypes have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

Several genotype-phenotype correlations have been observed.

Pathogenic *GRIN2A* missense variants in transmembrane domains (TMD) and linker regions (linker) are associated with severe infantile-onset DEE, whereas missense variants in the amino terminal domain (ATD) and ligand-binding domains (LBD) are associated with speech abnormalities and/or seizures with mild to no ID. Strikingly, both phenotypic groups are significantly correlated with opposing electrophysiologic consequences of the N-methyl-D-aspartate receptor (NMDAR), even though the complex functional alterations caused by a *GRIN2A* variant cannot always easily be reduced to a binary description such as loss or gain of function. Pathogenic missense variants in the LBD may impede agonist binding and thus reduce channel activity, whereas a TMD or linker missense variant may affect formation of the ion channel pore, mediating a gain-of-function effect by, for example, disrupted channel inhibition [Strehlow et al 2019].

Individuals with pathogenic null variants have later mean seizure onset (age 4.5 ± 0.2 years) compared to those with pathogenic missense variants (age 3.1 ± 0.4 years), and individuals with pathogenic missense variants usually have drug-resistant seizures persisting throughout childhood and adolescence [Camp et al 2023].

Mental health disorders are relatively frequent in individuals with pathogenic null variants in *GRIN2A*, including mood disorders, anxiety disorders, and psychotic disorders such as schizophrenia and, rarely, personality disorders [J Lemke et al, unpublished data].

Penetrance

GRIN2A-related disorders show high penetrance and variable expressivity.

In families of mildly affected individuals, carriers of the familial pathogenic *GRIN2A* variant have been observed who were less severely or very rarely not known to be affected [Strehlow et al 2019].

Nomenclature

Table 3. Epilepsy Syndrome Terminology Used in *GRIN2A*-Related Disorders

2022 ILAE Classification [1]	Other Terms
Developmental and/or epileptic encephalopathy with spike-wave activation in sleep (DEE/EE-SWAS) (Note: Landau-Kleffner syndrome [LKS] is a subtype of DEE-SWAS.)	• Epileptic acquired aphasia • Continuous spike-wave during slow-wave sleep (CSWS) • Electrical status epilepticus in sleep (ESES) • Epilepsy aphasia spectrum disorders • Atypical childhood epilepsy with centrotemporal spikes (ACECTS)
Self-limited epilepsy with centrotemporal spikes (SeLECTS)	• Childhood epilepsy with centrotemporal spikes (CECTS) • Benign epilepsy with centrotemporal spikes (BECTS) • Benign rolandic epilepsy of childhood (BREC) • Benign focal epilepsy of childhood (BFEC)

ILAE = International League Against Epilepsy
1. See ILAE Classification and Definition of Epilepsy Syndromes.

Prevalence

The prevalence of *GRIN2A*-related disorders in the general population is unknown. Among 3,038 individuals with neurodevelopmental disorders with epilepsy screened by epilepsy multigene panel sequencing (including *GRIN2A*), seven had (likely) pathogenic variants, suggesting *GRIN2A* accounts for 0.23% of neurodevelopmental disorders [Lemke 2020].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GRIN2A*.

Contiguous gene deletions. Reutlinger et al [2010] described three individuals with 16p13 deletions involving multiple genes and complete or partial heterozygous deletion of *GRIN2A*. All had mild dysmorphic features, intellectual disability, and epilepsy involving the rolandic region.

Differential Diagnosis

Genetic epilepsy syndromes. *GRIN2A*-related epilepsy phenotypes cannot be distinguished from other epilepsy-aphasia syndromes (EAS), apart from the ongoing subtle speech abnormalities that persist into adult life in those with *GRIN2A* pathogenic variants. *GRIN2A*-related infantile-onset developmental and epileptic encephalopathy (DEE) has no distinguishing features from other genetic causes.

Note: While *GRIN2A* pathogenic variants can be associated with EAS, the majority of individuals with EAS do not have an identified genetic cause. A number of copy number variants (CNVs) have been associated with EAS in individual cases.

While no other monogenic causes are known for self-limited epilepsy with centrotemporal spikes (SeLECTS) and Landau-Kleffner syndrome (LKS), pathogenic variants in the genes *SCN2A*, *NHE6/SLC9A6*, *DRPLA/ATN1*, *Neuroserpin/SRPX2*, *OPA3*, *KCNQ2*, *KCNA2*, *CNKSR2*, *SLC6A1*, and *KCNB1* have been found in individuals

with spike-wave activation in sleep (SWAS) [Kessi et al 2018]. Many genetic causes have been found for DEEs [Heyne et al 2018].

Genetic language impairment. A severe speech and language disorder that primarily involves childhood apraxia of speech (CAS) is caused by pathogenic variants in *FOXP2* (see *FOXP2*-Related Speech and Language Disorder). CAS is a disorder of speech motor programming or planning that affects the production, sequencing, timing, and stress of sounds, and the accurate sequencing of speech sounds into syllables and syllables into words. CAS also interferes nonselectively with multiple other aspects of language, including phonology, grammar, and literacy. For other chromosomal and single-gene disorders associated with CAS, see *FOXP2*-Related Speech and Language Disorder, Differential Diagnosis [Morgan et al 2024].

Management

No clinical practice guidelines for *GRIN2A*-related disorders have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GRIN2A*-related disorders, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. *GRIN2A*-Related Disorders: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Assessment of overall growth incl weight, height, & head circumference	
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Evaluate for early intervention & need for special education. • Assess for developmental regression across all areas.
Epilepsy	Neurologic eval	• EEG • Careful clinical history to identify seizures • In infancy & childhood, sleep-deprived or sleep EEG w/ monitoring to capture sleep, as this is essential to identify DEE-SWAS
Speech & language disorders	Consultation w/speech-language pathologist	Assessment for dyspraxia, dysarthria, & language impairment
Movement disorders / Musculoskeletal / Activities of daily living	Orthopedics / physical medicine & rehab / PT & OT eval	In severe DEE cases, consider eval for: • Gross motor & fine motor skills; • Mobility, ADL, & need for adaptive devices; • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills).
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	• Screening for behavior concerns incl sleep disturbances, ADHD, &/or ASD • In persons w/null variants, consider eval for psychiatric disorders (e.g., anxiety, mood, psychotic disorders).
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• Eval of aspiration risk & nutritional status • Consider need for gastrostomy tube in persons w/ dysphagia &/or aspiration risk.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *GRIN2A*-related disorders to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; DEE-SWAS = developmental and epileptic encephalopathy with spike-wave activation in sleep; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *GRIN2A*-related disorders.

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Table 5. *GRIN2A*-Related Disorders: Targeted Therapy

Treatment Class	Mechanism of Action	Specific Drug	Comments
NMDAR coagonists	• Mediates coagonistic effects on NMDAR in neurons via its enantiomer, D-serine • NMDAR coagonists are specifically effective in persons w/*GRIN2A* pathogenic loss-of-function & null variants. [1]	L-serine	Orally available non-essential amino acid Has been demonstrated to cause improvements in behavior, development, EEG pattern, & sometimes also seizure frequency. After description of 1st treated case in 2019, [2] findings were confirmed in a case series in 2022. [3] The results of the 1st Phase IIa clinical trial have been published. [4]

NMDAR = N-methyl-D-aspartate receptor
1. In individuals with *GRIN2A*-related disorders due to pathogenic missense variants activating the NMDAR, receptor-specific agonists and other activators (e.g., L-serine) should be avoided, as this could result in worsening of symptoms [Krey et al 2022].
2. Soto et al [2019]
3. Krey et al [2022]
4. Juliá-Palacios et al [2024]

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 6. *GRIN2A*-Related Disorders: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
	L-serine treatment (*GRIN2A* pathogenic loss-of-function & null variants)	See Targeted Therapy.
Speech & language deficits	Therapy by speech-language pathologist	Therapies, which are individualized to the specific speech disorder, incl linguistic approaches & AAC [Morgan et al 2018].
Neuromuscular / Activities of daily living	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	In persons w/severe DEE, consider need for positioning & mobility devices & disability parking certificate.
Neurobehavioral/ Psychiatric	Standardized treatment by experienced psychiatrist	Many medications may be effective; none has been demonstrated effective specifically for this disorder.
	L-serine treatment (*GRIN2A* pathogenic loss-of-function & null variants)	See Targeted Therapy.
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for severe, persistent feeding issues.	In persons w/DEE, low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment of need for palliative care &/or home nursing

AAC = augmentative and alternative communication; ASM = anti-seizure medication; DEE = developmental and/or epileptic encephalopathy; OT = occupational therapy; PT = physical therapy

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Communication issues. In individuals with DEEs, consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Consultation with a pediatric psychiatrist may be helpful in evaluation and treatment of psychiatric disorders.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. *GRIN2A*-Related Disorders: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Neurologic	• Assess for new manifestations such as seizures, changes in tone, movement disorders, & regression • Assess for more subtle seizure types that many not have been recognized.	
Speech & language disorders	Routine monitoring of speech & language by speech-language pathologist should be considered, particularly in childhood. Parents should be asked by all clinicians about loss of understanding or regression in spoken language skills.	
Neurobehavioral/ Psychiatric	Assess for behavioral disorders (particularly ADHD & ASD) & mental health issues (particularly anxiety, mood, & psychotic disorders).	
Musculoskeletal / Activities of daily living	Physical medicine (particularly in childhood), OT/PT assessment of mobility, & self-help skills depending on child's phenotype	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

In individuals with *GRIN2A*-related disorders due to pathogenic missense variants activating the N-methyl-D-aspartate receptor (NMDAR), receptor-specific agonists and other activators (e.g., L-serine) should be avoided, as this could result in worsening of symptoms [Krey et al 2022].

In individuals with *GRIN2A*-related disorders due to pathogenic missense variants inhibiting the NMDAR as well as null variants, receptor-specific blockers should be used with caution (e.g., memantine, dextromethorphan, ketamine).

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic relatives of an affected individual by molecular genetic testing for the *GRIN2A* pathogenic variant in the family to identify as early as possible those who would benefit from monitoring for developmental disorders, epilepsy, speech-language disorders, behavioral and psychiatric disorders, and EEG abnormalities.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Several treatments are now under investigation in individuals with *GRIN2A* pathogenic gain-of-function (GOF) variants:

- **NMDAR blocker (memantine).** In one individual with a GOF missense variant in *GRIN2A*, seizure burden was reduced with the NMDAR blocker memantine. However, cognitive function did not improve [Pierson et al 2014]. Thereafter, multiple studies reporting the use of memantine have been published. However, these studies are inconclusive due to either lack of confirmation of the pathogenicity of the reported variants (including lack of confirmation that the variant causes GOF), or the observed treatment outcomes were subjective and poorly quantified. Of note, one study reported benefit with memantine in individuals with pathogenic *GRIN1* variants [Xu et al 2021].

- **GluN2B negative allosteric modulator (radiprodil).** Three individuals with infantile epileptic spasms syndrome were treated with the GluN2B negative allosteric modulator radiprodil. One infant became spasm-free and two showed clinical improvement without being spasm-free. After radiprodil withdrawal, one infant continued to be spasm-free, while the two others experienced seizure worsening requiring the use of the ketogenic diet and other anti-seizure medications [Auvin et al 2020].

  A clinical trial on the evaluation of radiprodil in children with *GRIN*-related disorders is currently being performed with a focus on children with pathogenic gain-of-function missense variants (NCT05818943).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

GRIN2A-related disorders are inherited in an autosomal dominant manner.

Note: Compound heterozygous *GRIN2A* pathogenic null variants were reported in a child with a severe developmental and epileptic encephalopathy [Strehlow et al 2022]. Her heterozygous parents had milder manifestations largely consistent with a *GRIN2A*-related disorder.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with a *GRIN2A*-related disorder have the disorder as the result of a pathogenic variant inherited from an affected parent. Because considerable clinical variability can be observed among heterozygous family members, an affected parent may have different manifestations of a *GRIN2A*-related disorder than the proband.
- Approximately 50% of individuals diagnosed with a *GRIN2A*-related disorder have the disorder as the result of a *GRIN2A* pathogenic variant that occurred as a *de novo* event in the affected individual [Strehlow et al 2019] or, rarely, as a postzygotic *de novo* event in a mosaic, apparently unaffected parent [Fernández-Marmiesse et al 2018].
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism [Fernández-Marmiesse et al 2018]. Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- The family history of some individuals diagnosed with a *GRIN2A*-related disorder may appear to be negative because of failure to recognize the disorder in family members, or variable clinical expressivity

(e.g., subtle speech abnormality or learning difficulties). Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *GRIN2A* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. The specific *GRIN2A*-related phenotype may vary considerably among heterozygous family members, ranging from isolated speech dysfunction to epileptic encephalopathy with spike-wave activation in sleep (EE-SWAS) [Carvill et al 2013, Lemke et al 2013, Lesca et al 2013, Turner et al 2015].
- If the *GRIN2A* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental gonadal mosaicism [Fernández-Marmiesse et al 2018].
- If the parents have not been tested for the *GRIN2A* pathogenic variant but are clinically unaffected, sibs of a proband are still presumed to be at increased risk for a *GRIN2A*-related disorder because of the possibility of variable clinical expressivity / mild or subclinical phenotype in a heterozygous parent and the possibility of parental gonadal mosaicism.

Offspring of a proband. Each child of an individual with a *GRIN2A*-related disorder has a 50% chance of inheriting the *GRIN2A* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *GRIN2A* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *GRIN2A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for *GRIN2A*-related disorders is possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most centers would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Asociación Española De Grinpatías**

Spain
Phone: +34 660 339 770
Email: info@grinpatias.org
grinpatias.org

- **Associazione MGrin2a Italia**
  Italy
  assmgrin2aitalia.it
- **CureGRIN Foundation**
  Phone: 303-881-3425
  curegrin.org
- **Simons Searchlight**
  GRIN2A
- **American Epilepsy Society**
  aesnet.org
- **Dyspraxia Foundation**
  United Kingdom
  Phone: 01462 454986; 01462 454986
  dyspraxiafoundation.org.uk
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Epilepsy and Seizures
- **GRIN Registry**
  grin-portal.broadinstitute.org
- **GRIN Variant Patient Registry**
  grin2b.com/grin-registry/

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. GRIN2A-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GRIN2A	16p13.2	Glutamate receptor ionotropic, NMDA 2A	GRIN Portal - GRIN2A	GRIN2A	GRIN2A

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for GRIN2A-Related Disorders (View All in OMIM)

138253	GLUTAMATE RECEPTOR, IONOTROPIC, N-METHYL-D-ASPARTATE, SUBUNIT 2A; GRIN2A
245570	EPILEPSY, FOCAL, WITH SPEECH DISORDER AND WITH OR WITHOUT IMPAIRED INTELLECTUAL DEVELOPMENT; FESD

Molecular Pathogenesis

The N-methyl-D-aspartate receptor (NMDAR) is a glutamate-activated ion channel permeable to sodium, calcium, and potassium ions that is highly expressed throughout the brain and plays important roles in mediating excitatory neurotransmission critical for development, learning, memory, and other higher cognitive functions. The NMDAR is a heterotetrametric molecule composed of two NMDA receptor 1 subunits (GluN1) and two different NMDA receptor 2 subunits (GluN2A and GluN2B). The GluN2A subunit is encoded by *GRIN2A* [Matta et al 2011].

In vitro tests on *Xenopus laevis* oocytes and transfected mammalian fibroblasts show that pathogenic variants in *GRIN2A* can lead to a gain or loss of function of the NMDAR [Myers et al 2023].

Mechanism of disease causation. *GRIN2A*-related disorders can be caused by two functional mechanisms:

- Loss of function (usually associated with milder phenotypes, such as speech abnormalities and/or seizures with mild intellectual disability or normal intellect)
- Gain of function (usually associated with more severe phenotypes, such as severe developmental and epileptic encephalopathies)

Chapter Notes

Author Notes

Dr Vincent Strehlow (vincent.strehlow@medizin.uni-leipzig.de) and Dr Johannes R Lemke (johannes.lemke@medizin.uni-leipzig.de) are actively involved in clinical research regarding individuals with *GRIN2A*-related disorders. They would be happy to communicate with persons who have any questions regarding diagnosis of *GRIN2A*-related disorders or other considerations. They further encourage families and caregivers to enroll affected individuals in the global GRIN registry (grin-portal.broadinstitute.org).

Professor Ingrid Scheffer and Dr Ken Myers are happy to assist with enquiries related to patient management. Professor Angela Morgan is happy to assist with enquiries related to speech and language management.

Contact Dr Vincent Strehlow and Dr Johannes R Lemke to inquire about review of *GRIN2A* variants of uncertain significance.

Acknowledgments

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