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GRIN2A-Related Speech Disorders and Epilepsy

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Summary

Clinical characteristics

GRIN2A-related speech disorders and epilepsy are characterized by speech disorders in all affected individuals and a range of epilepsy syndromes present in about 90%. Severe speech disorders observed can include dysarthria and speech dyspraxia, and both receptive and expressive language delay/regression; 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) showing continuous spike-and-wave discharges in sleep or very active centrotemporal discharges. Seizure types include seizures associated with aura of perioral paresthesia, focal or focal motor seizures (often evolving to generalized tonic-clonic), and atypical absence seizures. Epilepsy syndromes can include: Landau-Kleffner syndrome (LKS), epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS), childhood epilepsy with centrotemporal spikes (CECTS), atypical childhood epilepsy with centrotemporal spikes (ACECTS), autosomal dominant rolandic epilepsy with speech dyspraxia (ADRESD), and infantile-onset epileptic encephalopathy.

Diagnosis/testing

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

Management

Treatment of manifestations: Significant speech/language deficits require therapy from a speech pathologist. Seizures should be treated with anti-seizure medication (ASM). Many different ASMs may be effective, and no one medication has been demonstrated to be effective specifically for these disorders.

Prevention of secondary complications: Monitoring for possible adverse effects of ASMs.

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

Agents/circumstances to avoid: In individuals with ECSWS, phenytoin, barbiturates and carbamazepine should be avoided as they are rarely effective, may worsen the EEG, and have negative effects on neuropsychological outcomes.

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 prompt evaluation for speech disorders and/or seizures and institution of treatment.

Genetic counseling

GRIN2A-related speech disorders and epilepsy are inherited in an autosomal dominant manner. The proportion of *GRIN2A*-related speech disorders and epilepsy caused by a *de novo* pathogenic variant is unknown. Each child of an individual with a *GRIN2A*-related speech disorder and epilepsy has a 50% chance of inheriting the *GRIN2A* pathogenic variant. Once the *GRIN2A* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

In general, a *GRIN2A* pathogenic variant **should be considered** in an individual presenting with an otherwise unexplained combination of the following speech disorders and/or epilepsy features, seizure types, epilepsy syndromes [Tsai et al 2013].

Speech disorders

- Acquired aphasia
- Auditory agnosia (impaired recognition of sounds)
- Dysarthria
- Speech dyspraxia

Epilepsy features

- Onset in early childhood (usually age 3-6 years)
- Focal epilepsy with language and/or global developmental regression
- Electroencephalogram (EEG) showing continuous spike-and-wave discharges in sleep or very active centrotemporal discharges

Seizure types

- Most commonly, focal seizures
- Sometimes occurring with an aura of perioral paresthesia, and often evolving to generalized tonic-clonic seizures

Epilepsy syndromes

- Landau-Kleffner syndrome (LKS)
- Epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS)
- Childhood epilepsy with centrotemporal spikes (CECTS)
- Atypical childhood epilepsy with centrotemporal spikes (ACECTS)

- Autosomal dominant rolandic epilepsy with speech dyspraxia (ADRESD)
- Infantile-onset epileptic encephalopathy

Note: Detailed descriptions of each epilepsy syndrome can be found in Clinical Description.

Establishing the Diagnosis

The diagnosis of *GRIN2A*-related speech disorder and epilepsy **is established** in a proband by identification of either a heterozygous pathogenic (or likely pathogenic) variant in *GRIN2A* or a heterozygous deletion involving *GRIN2A* using molecular genetic testing (see Table 1). Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel or single-gene testing) or **genomic testing** (chromosomal microarray analysis or comprehensive genomic sequencing).

Gene-targeted testing requires that the clinician develop a hypothesis about which gene(s) are likely involved, whereas genomic testing may not. The phenotypes of many genetic epileptic encephalopathies overlap; thus, most children with a *GRIN2A*-related speech disorder and epilepsy are diagnosed by CMA or multigene panel (see Recommended Testing) or by comprehensive genomic sequencing (see Testing to Consider).

Recommended Testing

Chromosomal microarray analysis (CMA) using oligonucleotide or SNP arrays is recommended first when developmental impairment/intellectual disability and/or dysmorphic features are present. The ability to determine the size of the deletion depends on the type of microarray used and the density of probes in the 16p13.2 region.

A multigene panel that incorporates both sequence analysis and deletion/duplication analysis and includes *GRIN2A* and other genes of interest (see Differential Diagnosis) is recommended when epilepsy associated with speech dyspraxia and dysarthria are the primary findings (see Table 1). Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Testing to Consider

Comprehensive genomic testing (when available) including exome sequencing and genome sequencing may be considered if the phenotype alone is insufficient to support gene-targeted testing). For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Single-gene testing (sequence analysis of *GRIN2A,* followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found may be considered first in individuals with features that are highly suggestive of

GRIN2A-related speech disorder and epilepsy. However, because many of these features overlap with those of other genetic epileptic encephalopathies, multigene panels or comprehensive genomic testing are often performed in lieu of single-gene testing.

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

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method [3]
GRIN2A	Sequence analysis [4]	58/71
	Gene-targeted deletion/duplication analysis [5]	13/71 [6]
	CMA	See footnote 7.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Based on the combined results of published reports of *GRIN2A*-related disorders [Endele et al 2010, Reutlinger et al 2010, Lesca et al 2012, Carvill et al 2013, DeVries & Patel 2013, Lemke et al 2013, Lesca et al 2013, Conroy et al 2014, Dimassi et al 2014, Venkateswaran et al 2014, Yuan et al 2014, Allen et al 2016, Fainberg et al 2016]. In one proband, *GRIN2A* was disrupted by an inherited translocation detectable by karyotype [Endele et al 2010]; this was categorized as "detectable by sequence analysis."
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
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.
6. Of these 13 probands: 9 had small losses of genetic material (<292 kb), resulting in partial deletion of *GRIN2A*; 3 had large deletions (>0.9 Mb) affecting multiple genes (in 2 of the 3 *GRIN2A* was entirely deleted); and 1 had a small intragenic duplication.
7. CMA is appropriate to define breakpoints of large deletions.

Clinical Characteristics

Clinical Description

The clinical spectrum of *GRIN2A*-related speech disorders and epilepsy is broad and may vary within a family (e.g., from mild isolated speech impairment to rolandic epilepsy with speech dyspraxia) [Turner et al 2015b].

Disease progression is variable: some individuals have normal development and spontaneous remission of seizures, while others develop medically refractory epilepsy and severe developmental impairment. Language and/or global developmental regression often occurs in those with the more severe epilepsy-aphasia disorders.

Speech and language were impaired in 100% of individuals in a study of the speech manifestations of *GRIN2A*-related disorders [Turner et al 2015a]. Abnormalities included dysarthria and speech dyspraxia, and both receptive and expressive language delay/regression.

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

Intellectual disability, observed in 38%-67% of affected individuals, ranges from mild to severe [Carvill et al 2013, Lemke et al 2013].

Epilepsy occurs in approximately 90% of individuals [Lemke et al 2013, Lesca et al 2013].

Seizure onset is typically between ages three and six years (mean 4.6 years), although individuals may present from infancy to adolescence [Endele et al 2010, Lesca et al 2012, Carvill et al 2013, Lemke et al 2013, Venkateswaran et al 2014].

The most common seizure type overall is focal seizures. These are often associated with an aura of perioral paresthesia, and frequently evolve to generalized tonic-clonic convulsions. The predominant seizure type(s) in a given individual vary depending on which clinical syndrome is present.

The most common *GRIN2A*-related speech disorder and epilepsy is epilepsy-aphasia syndromes (EAS), a spectrum of disorders that includes: Landau-Kleffner syndrome (LKS); epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS); childhood epilepsy with centrotemporal spikes (CECTS); atypical childhood epilepsy with centrotemporal spikes (ACECTS); and autosomal dominant rolandic epilepsy with speech dyspraxia (ADRESD) [Tsai et al 2013]. Other epilepsy phenotypes can be broadly divided into infantile-onset epileptic encephalopathy and unclassified childhood epilepsy.

Landau-Kleffner syndrome (LKS) [Landau & Kleffner 1957, Wang et al 2006, Hughes 2011]

- Onset in childhood (peak age range 5-8 years)
- Acquired aphasia, with auditory agnosia (impaired recognition of sounds) frequently described as the earliest feature
- Seizures in approximately 70% of cases, most commonly atypical absence, with focal motor, atonic, and focal seizures evolving to bilateral tonic-clonic seizures also described
- Developmental regression limited to language domains
- Normal development prior to onset of aphasia or isolated language impairment
- EEG showing frequent, sleep-activated, bilateral sharp and slow wave discharges (centrotemporal or perisylvian field), eventually evolving to continuous spike-and-wave in sleep (CSWS)

Epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS) [Van Bogaert 2013]

- Onset in childhood (peak age range 4-5 years)
- Seizures in approximately 80% of cases, most commonly hemiclonic or generalized tonic-clonic in sleep and atypical absence while awake
- Global developmental regression (as distinct from the pure language regression of LKS)
- EEG showing near-continuous (>85% of recording), bilateral sharp and slow wave discharges in slow wave sleep (i.e., CSWS)

Childhood epilepsy with centrotemporal spikes (CECTS) [Guerrini & Pellacani 2012]

- Onset is in childhood (peak age range 5-8 years; range 3-13 years).
- Seizures have a characteristic aura of perioral paresthesia which may involve the tongue, cheeks, and mouth. There is often speech arrest and a motor component involving the oropharyngeal muscles, unilateral facial tonic or clonic activity, and (less commonly) an upper limb. The majority of events occur during sleep, and classically involve drooling. Bilateral tonic-clonic seizures are also commonly observed.
- Seizure frequency is low: half of patients have fewer than six seizures in their lifetime.
- Epilepsy follows a self-limited course with duration less than five years in the majority of individuals.
- Development is essentially normal, though mild deficits in language, computation, and motor skills may be apparent when compared to healthy controls [Staden et al 1998, Lillywhite et al 2009, Garcia-Ramos et al 2015].
- EEG background is normal and shows focal epileptiform discharges from the centrotemporal regions, potentiated in sleep. In 40% of affected individuals, the centrotemporal discharges are bilateral and independent.

Atypical childhood epilepsy with centrotemporal spikes (ACECTS) [Aicardi & Chevrie 1982]

- Epilepsy course is similar to CECTS with onset and spontaneous remission occurring in childhood.
- Seizures are different from those seen in CECTS, and include negative myoclonus and atypical absence seizures.
- Developmental regression or slowing is coincident with seizure onset; however, long-term developmental outcome may be normal.
- EEG is similar to CECTS in that focal centrotemporal discharges potentiated in sleep are seen; however, focal or diffuse background slowing is also often present.

Autosomal dominant rolandic epilepsy with speech dyspraxia (ADRESD) [Scheffer 2000, Turner et al 2015b]

- Seizure characteristics and epilepsy course are identical to CECTS in most family members. One individual had an encephalopathic presentation associated with cognitive regression.
- Affected individuals have oral and speech dyspraxia with dysarthria.
- Individuals may have isolated speech dysfunction without seizures.
- Cognitive function is usually within the normal range.

Infantile-onset epileptic encephalopathy [Endele et al 2010, Venkateswaran et al 2014, Yuan et al 2014, Allen et al 2016]

- Multiple different seizure types may be present, including tonic seizures, focal impaired awareness with evolution to bilateral seizures, infantile spasms, and myoclonic seizures.
- Severe intellectual disability was seen in the three individuals reported.
- EEG findings vary in the few reported cases and include background slowing, hypsarrhythmia, and focal spikes.
- Brain MRI may show bilateral parenchymal volume loss and thin corpus callosum.

Unclassified childhood-onset epilepsy [Reutlinger et al 2010, DeVries & Patel 2013]

- Focal seizures are the most commonly seen; myoclonic, eyelid myoclonia, and atypical absence have also been reported.
- Development ranges from normal to severely impaired.
- Mild dysmorphic features may be present in individuals with a contiguous gene deletion.
- EEG usually shows multifocal epileptiform discharges.

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.

EEG most commonly shows bilateral epileptiform discharges (usually spike or spike-wave) in the central-temporal or temporal-parietal regions which may be independent or bilaterally synchronous. These abnormalities become more frequent in sleep, often evolving to continuous spike-and-wave in sleep (CSWS). CSWS is defined as near-continuous (>85% of non-REM sleep recording) bilateral sharp and slow wave discharges in slow wave sleep. CECTS is classically associated with a horizontal dipole; tangential dipole across the Sylvian fissure has been reported in LKS [Morrell et al 1995, Dalla Bernardina et al 2005].

Brain imaging. Brain MRI is normal in the vast majority. Severely affected individuals may have enlargement of extra-axial spaces and a thin corpus callosum [Reutlinger et al 2010, Pierson et al 2014, Venkateswaran et al 2014, Yuan et al 2014]. One individual with focal cortical dysplasia was reported [Lesca et al 2013].

Positron emission tomography (PET) showing diffuse cortical hypometabolism was reported in one individual [DeVries & Patel 2013].

Genotype-Phenotype Correlations

Genotype-phenotype correlation is observed in a number of families in which all individuals heterozygous for the *GRIN2A* pathogenic variant have an epilepsy-aphasia syndrome (EAS) phenotype. However, the specific EAS phenotype may vary considerably within the family, including one individual with isolated speech dysfunction and another with epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS) [Carvill et al 2013, Lemke et al 2013, Lesca et al 2013, Turner et al 2015a].

For single-nucleotide variants (SNVs) and small intragenic copy number variants (CNVs), the genomic region in which the pathogenic variant occurs does not appear to have any relationship to the phenotype. Specifically, the pathogenic variants associated with infantile-onset epileptic encephalopathies do not cluster in a region distinct from the location of pathogenic variants associated with the epilepsy-aphasia syndromes (EAS).

Penetrance

GRIN2A-related speech disorders and epilepsy show incomplete but high penetrance and variable expressivity.

Penetrance is not clearly different for males and females.

Nomenclature

Landau-Kleffner syndrome (LKS) has also been referred to as epileptic acquired aphasia.

Epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS) has also been referred to as continuous spike-and-wave during slow-wave sleep (CSWS) and electrical status epilepticus during sleep (ESES).

Childhood epilepsy with centrotemporal spikes (CECTS) has been commonly referred to as benign epilepsy with centrotemporal spikes (BECTS) and benign rolandic epilepsy of childhood (BREC).

Atypical childhood epilepsy with centrotemporal spikes (ACECTS) has been known as atypical benign partial epilepsy (ABPE), pseudo-Lennox syndrome, and atonic-benign childhood epilepsy with centrotemporal spikes.

Prevalence

The prevalence of *GRIN2A*-related speech disorders and epilepsy in the general population is unknown; however, estimates can be made for some of the classic disorders.

GRIN2A pathogenic variants account for 9%-20% of epilepsy-aphasia syndrome (EAS), with pathogenic variants more likely to be present in persons with more severe phenotypes and a positive family history [Lesca et al 2012, Carvill et al 2013].

GRIN2A pathogenic variants are present in [Lemke et al 2013, Conroy et al 2014, Allen et al 2016]:

- 4.8%-7.7% of Landau-Kleffner syndrome (LKS)
- 17.6% of epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS)
- 0%-4.9% of childhood epilepsy with centrotemporal spikes (CECTS)
- 13.5% of atypical childhood epilepsy with centrotemporal spikes (ACECTS)
- 2% of early-onset epileptic encephalopathy

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Non-*GRIN2*-related genetic epilepsy

- Epilepsy-aphasia syndrome (EAS). While *GRIN2A* is the gene most commonly associated with EAS, the majority of individuals with this group of syndromes do not have an identified genetic cause. A number of CNVs have been associated with EAS in individual cases. Pathogenic variants in *RBFOX1* and *RBFOX3* may play a contributory role in some cases [Lal et al 2013, Turner et al 2015b]. At present, no clinical features differentiate *GRIN2A*-related EAS from EAS of other genetic causes.
- Non-EAS childhood-onset focal epilepsy and infantile-onset epileptic encephalopathy. Each phenotype has only a small number of reported cases associated with a *GRIN2A* pathogenic variant. Clinical data currently available are insufficient to distinguish those with a *GRIN2A* pathogenic variant from those with other genetic causes.

Non-genetic causes of epilepsy. Focal epilepsy and epileptic encephalopathy may have many non-genetic causes, including autoimmune and infectious processes. A non-genetic cause should be more strongly considered when a history of any of the following is present:

- Maternal substance abuse during pregnancy
- Significant complications in the perinatal period
- Significant cerebral insult (e.g., central nervous system infection, hypoxic-ischemic injury, major head trauma, toxic ingestion/exposure)

Non-*GRIN2A*-related genetic language impairment. A severe speech and language disorder that primarily involves developmental verbal dyspraxia is caused by pathogenic variants in *FOXP2* (see *FOXP2*-Related Speech and Language Disorders) [Lai et al 2001]. *FOXP2* regulates *CNTNAP2*, and *CNTNAP2* missense variants and deletions have been associated with childhood apraxia of speech; however, evidence of a causative link is at present limited [Worthey et al 2013, Centanni et al 2015].

Hearing impairment is a common cause of language-specific developmental delay or regression, thus in children with delayed speech development or regression in speech, the auditory system should be assessed (see Hereditary Hearing Loss and Deafness Overview).

Structural brain abnormality. Brain malformations and acquired structural brain anomalies can present with a constellation of symptoms that can mimic the *GRIN2A*-related disorders. Worster-Drought syndrome (OMIM 185480) involves congenital bilateral perisylvian lesions, most commonly polymicrogyria [Christen et al 2000]. Affected children typically have seizures, expressive language delay, dysarthria, and oromotor apraxia.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *GRIN2A*-related speech disorder and epilepsy, the following evaluations are recommended:

- Consultation with a speech and language pathologist
- Epilepsy consultation (if not done at the time of initial assessment)
- Sleep-deprived or sleep EEG with monitoring to capture slow-wave sleep (if not done at the time of initial assessment), as this is essential to diagnosing or excluding continuous spike-and-wave in sleep (CSWS).
- Neuropsychological assessment
- Hearing testing
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Speech/language deficits. Individuals with significant speech/language deficits may benefit from therapy by a speech pathologist. The therapies, which are individualized to the specific speech disorder, often include linguistic approaches and augmentative and alternative communication [Murray et al 2014].

Seizures, if present, should be treated with anti-seizure medication (ASM). Many different ASMs may be effective, and no one medication has been demonstrated to be effective specifically for *GRIN2A*-related disorders.

In one individual a good response to refractory epilepsy was achieved with topiramate [Venkateswaran et al 2014].

In one individual seizure burden was reduced with the addition of memantine; however, cognitive function did not improve [Pierson et al 2014].

Ketogenic diet and vagal nerve stimulator may also be considered in patients with refractory epilepsy.

Treatment for epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS) and Landau-Kleffner syndrome (LKS) includes ASMs such as valproic acid, benzodiazepines, and corticosteroids. Sulthiame, ethosuximide, and levetiracetam may also be effective.

Of note, intravenous immunoglobulin has not been proven to be efficacious [Striano & Capovilla 2013, Van Bogaert 2013].

Caregivers. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Prevention of Secondary Complications

ASMs are associated with possible adverse reactions (e.g., sedation, gastrointestinal symptoms, changes in appetite [increase or decrease], weight gain or loss, and rash) which vary according to the specific medication. Patients on ASM should be monitored closely for adverse reactions and, if they develop, a change to an alternate ASM should be considered.

Corticosteroids are associated with a wide variety of possible adverse reactions, including weight gain with cushingoid appearance, skin thinning and purpura, alopecia, acne, posterior subscapular cataract, glaucoma, exophthalmos, cardiac arrhythmias, hypertension, gastrointestinal upset, pancreatitis, hypokalemia, osteoporosis, avascular necrosis, myopathy, behavioral/psychiatric disturbance, diabetes mellitus, adrenal insufficiency, and increased infection risk. If complications of corticosteroid therapy become of concern, gradual tapering and alternate therapy should be considered.

Surveillance

Routine monitoring of speech and language by a speech pathologist should be considered for all children, particularly those diagnosed before reaching school age.

Developmental surveillance should be conducted in all affected children.

Agents/Circumstances to Avoid

In individuals with epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS), phenytoin, barbiturates and carbamazepine should be avoided as they are rarely effective, may worsen the EEG, and have negative effects on neuropsychological outcomes [Striano & Capovilla 2013, Van Bogaert 2013].

Evaluation of Relatives at Risk

Using molecular genetic testing for the *GRIN2A* pathogenic variant found in an affected family member, it is appropriate to evaluate apparently asymptomatic at-risk relatives in order to identify as early as possible those who would benefit from institution of treatment. Of note, some individuals heterozygous for a *GRIN2A* pathogenic variant who have only relatively mild speech dysfunction may benefit from early evaluation and intervention by a speech and language pathologist.

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

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

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 speech disorders and epilepsy are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with a *GRIN2A*-related speech disorder and epilepsy have an affected parent. There is considerable clinical variability within families.
- A proband with a *GRIN2A*-related speech disorder and epilepsy may have a *de novo GRIN2A* pathogenic variant; however, the proportion of *GRIN2A*-related speech disorders and epilepsy caused by a *de novo* pathogenic variant is unknown because to date an insufficient number of parents of simplex cases (i.e., a single occurrence in a family) have been tested.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. (Although no instances of germline mosaicism have been reported, it remains a possibility.)
- The family history of some individuals diagnosed with a *GRIN2A*-related speech disorder and epilepsy may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, or variable clinical severity. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of 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 the parents have been tested for the *GRIN2A* pathogenic variant identified in the proband and:
  - A parent of the proband has the *GRIN2A* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. Some familial cases have demonstrated reduced penetrance and phenotypic variability.

- The *GRIN2A* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be low but greater than that of the general population because of the theoretic possibility of germline mosaicism.

- If the parents have not been tested for the *GRIN2A* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for a *GRIN2A*-related speech disorder and epilepsy because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with a *GRIN2A*-related speech disorder and epilepsy has a 50% chance of inheriting the *GRIN2A* pathogenic variant. Some familial cases have demonstrated reduced penetrance and phenotypic variability.

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.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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 testing for a pregnancy at increased risk and preimplantation genetic testing for a *GRIN2A*-related speech disorder and epilepsy are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal 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
  www.curegrin.org
- **Simons Searchlight**
  GRIN2A
- **American Epilepsy Society**
  www.aesnet.org
- **Dyspraxia Foundation**
  United Kingdom
  Phone: 01462 454986; 01462 454986
  www.dyspraxiafoundation.org.uk
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Epilepsy Information Page
- **GRIN Registry**
  www.grin-portal.broadinstitute.org
- **GRIN Variant Patient Registry**
  http://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 Speech Disorders and Epilepsy: 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 Speech Disorders and Epilepsy (View All in OMIM)

138253	GLUTAMATE RECEPTOR, IONOTROPIC, N-METHYL-D-ASPARTATE, SUBUNIT 2A; GRIN2A

Table B. continued from previous page.

245570	EPILEPSY, FOCAL, WITH SPEECH DISORDER AND WITH OR WITHOUT IMPAIRED INTELLECTUAL DEVELOPMENT; FESD

Molecular Pathogenesis

N-methyl-D-aspartate (NMDA) receptors are glutamate-activated ion channels permeable to sodium, calcium, and potassium ions, thought to be primarily important in mediation of excitatory processes in the human brain. The NMDA receptor is a heterotetramer composed of two NMDA-receptor 1 subunits (NR1) and two different NMDA-receptor subunits (NR2A and NR2B). The NR2A subunit is encoded by *GRIN2A* [Matta et al 2011].

Gene structure. *GRIN2A* comprises 14 exons [Endele et al 2010]. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Of probands with pathogenic variants, 41/71 (58%) had missense variants, 8/71 (11%) nonsense variants, 8/71 (11%) splice site variants, and 13/71 (18%) copy number variations; the remaining proband had a translocation affecting *GRIN2A* without loss of genetic material.

One recurrent splice site variant (c.1007+1G>A) located in intron 4 has been identified in six apparently unrelated probands [Carvill et al 2013, Lemke et al 2013]. Four missense variants (c.1553G>A, c.1845C>A, c.2146G>A, and c.2927A>G) have been reported in two probands each [Endele et al 2010, Lesca et al 2013, Conroy et al 2014, Allen et al 2016, Fainberg et al 2016].

In two nonfamilial cases, a recurrent pathogenic variant (c.1845C>A) has been associated with severe intellectual disability and refractory early-onset epileptic encephalopathy [Endele et al 2010, Allen et al 2016].

Table 2. *GRIN2A* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1007+1G>A	Splice region	NM_000833.4 NP_000824.1
c.1553G>A	p.Arg518His	
c.1845C>A	p.Asn615Lys	
c.2146G>A	p.Ala716Thr	
c.2927A>G	p.Asn976Ser	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The human *GRIN2A* gene product contains 1464 amino acids.

Abnormal gene product. In in vitro models, NMDA receptors with *GRIN2A* pathogenic variants demonstrate reduced inhibition by both Zn^{2+} and Mg^{2+}, and have shorter closed-state and longer open-state durations, all of which suggests that *GRIN2A* pathogenic variants lead to increased neuronal excitability [Endele et al 2010, Lesca et al 2012, Lemke et al 2013].

Chapter Notes

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