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GRIN1-Related Neurodevelopmental Disorder

Synonym: *GRIN1*-Related Developmental and Epileptic Encephalopathy

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Summary

Clinical characteristics

GRIN1-related neurodevelopmental disorder (*GRIN1*-NDD) is characterized by mild-to-profound developmental delay / intellectual disability (DD/ID) in all affected individuals. Other common manifestations are epilepsy, muscular hypotonia, movement disorders, spasticity, feeding difficulties, and behavior issues. A subset of individuals show a malformation of cortical development consisting of extensive and diffuse bilateral polymicrogyria. To date, 72 individuals with *GRIN1*-NDD have been reported.

Diagnosis/testing

The diagnosis of *GRIN1*-NDD is established in a proband who has either a heterozygous *de novo GRIN1* pathogenic missense variant (64 individuals reported) or biallelic *GRIN1* pathogenic missense or truncating variants (8 individuals from 4 families reported).

Management

Treatment of manifestations: Standard treatment of DD/ID, seizures, feeding problems, and behavioral issues.

Surveillance: In infancy: regular assessment of swallowing, feeding, and nutritional status to determine safety of oral vs gastrostomy feeding. For all age groups: routine monitoring of developmental progress, educational needs, and behavioral issues.

Genetic counseling

GRIN1-NDD is inherited in either an autosomal dominant or autosomal recessive manner:

- *Autosomal dominant inheritance:* All probands with a heterozygous *GRIN1* pathogenic variant reported to date whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo GRIN1* pathogenic missense variant. If the *GRIN1* pathogenic variant found in the proband cannot be

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detected in the leukocyte DNA of either parent, the recurrence risk to sibs is presumed to be greater than that of the general population because of the theoretic possibility of parental mosaicism.
- *Autosomal recessive inheritance:* At conception, each sib of an individual with biallelic *GRIN1* pathogenic variants has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

Once the *GRIN1*-NDD pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for *GRIN1*-related neurodevelopmental disorder have not been established.

Suggestive Findings

GRIN1-neurodevelopmental disorder (*GRIN1*-NDD) **should be considered** in individuals with the following clinical and/or brain MRI findings.

Clinical findings

- Mild-to-profound developmental delay or intellectual disability
  AND
- Any of the following presenting in infancy or childhood:
  - Epilepsy
  - Muscular tone abnormalities such as hypotonia and spasticity
  - Dystonic, dyskinetic, or choreiform movement disorder
  - Autism spectrum disorder
  - Microcephaly
  - Cortical visual impairment

Brain MRI findings. A subset of individuals show a malformation of cortical development consisting of extensive and diffuse bilateral polymicrogyria. See Figure 1.

Establishing the Diagnosis

The diagnosis of *GRIN1*-related neurodevelopmental disorder **is established** in a proband who has **one of the following** on molecular genetic testing (see Table 1):

- A heterozygous *de novo* pathogenic (or likely pathogenic) missense variant in *GRIN1* (64 individuals have been reported)
- Biallelic pathogenic (or likely pathogenic) missense or truncating variants in *GRIN1* (8 individuals from 4 families have been reported)

Note: (1) Per ACMG/AMP 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 [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Because the phenotype of *GRIN1*-related neurodevelopmental disorder is often nonspecific and indistinguishable from many other inherited disorders, it is most likely to be diagnosed by either gene-targeted testing (i.e., a multigene panel) (see Option 1) or genomic testing (which does not require the clinician to determine which gene is likely involved) (see Option 2).

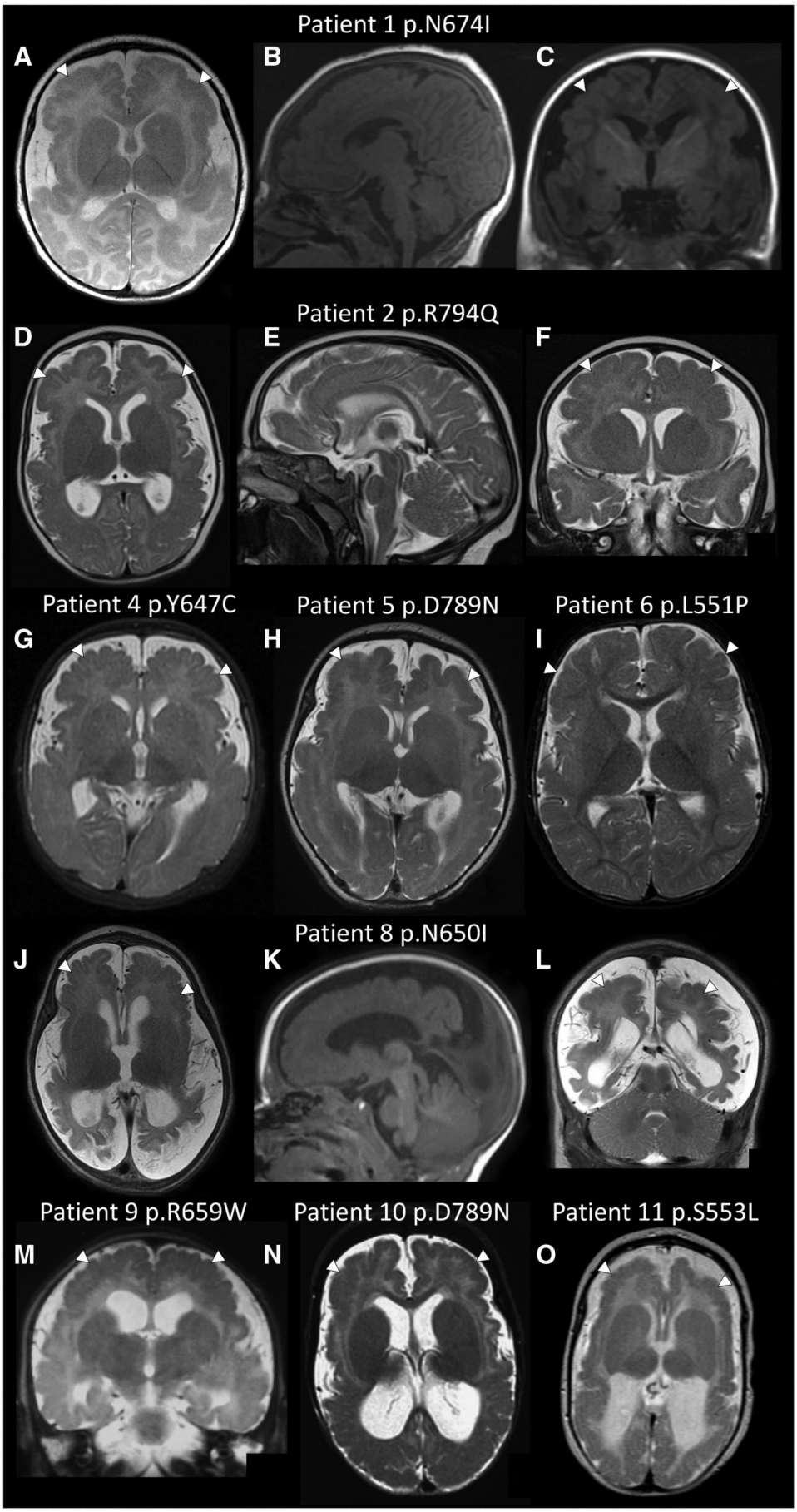

Figure 1. Brain MRI findings of polymicrogyria in children with *GRIN1* neurodevelopmental disorder demonstrating bilateral

extensive polymicrogyria (white arrowheads) that is more severe anteriorly

Note in most images (except I): Increased extra-axial spaces and enlarged lateral ventricles suggesting cerebral volume loss. Images B, C, and K are T_1-weighted; all others are T_2-weighted. Patient 1 at age two months (A-C) and Patient 2 at age five months (D-F): axial, midline sagittal, and coronal images. Patient 4 at age three months (G), Patient 5 at age six weeks (H), and Patient 6 at age eight months (I): axial images. Patient 8 at age three months (J-L): axial, sagittal, and coronal images. Patient 9 at age four months (M): coronal image. Patient 10 at age eight months (N) and Patient 11 at age two months (O): axial images.

Reproduced from Fry et al [2018]

Option 1

A multigene panel that includes *GRIN1* and other genes of interest (see Differential Diagnosis) 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. 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*. Of note, given the rarity of *GRIN1*-related neurodevelopmental disorder, some panels for intellectual disability may not include this gene. (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.

Option 2

Comprehensive genomic testing, which does not require the clinician to determine which gene is likely involved, yields results similar to a multigene panel but has two advantages:

- A multigene panel may not include all rare genes recently identified as causing intellectual disability; and
- Comprehensive genomic testing may be able to detect pathogenic variants in genes that – for technical reasons – do not sequence well.

Exome sequencing is most commonly used; genome sequencing is also possible.

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 *GRIN1*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
GRIN1	Sequence analysis [3]	100%
	Gene-targeted deletion/duplication analysis [4]	Unknown [5]

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. 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.
4. 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 a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

GRIN1-related neurodevelopmental disorder (*GRIN1*-NDD) is characterized by mild-to-profound developmental delay / intellectual disability in all affected individuals. Epilepsy (seen in 65%), muscular hypotonia (66%), and movement disorders (48%) are common manifestations.

To date, 72 individuals with *GRIN1*-NDD have been reported, including 64 individuals with *de novo* heterozygous pathogenic missense variants and eight individuals from four families with biallelic pathogenic missense or truncating variants [Firth et al 2009, Hamdan et al 2011, Allen et al 2013, Redin et al 2014, Farwell et al 2015, Ohba et al 2015, Zhu et al 2015, Bosch et al 2016, Halvardson et al 2016, Helbig et al 2016, Kobayashi et al 2016, Lemke et al 2016, Retterer et al 2016, Vanderver et al 2016, Chen et al 2017, Ortega-Moreno et al 2017, Rossi et al 2017, Tan et al 2017, Zehavi et al 2017, Dillon et al 2018, Fry et al 2018, Paderova et al 2018, Papa et al 2018, Pironti et al 2018, Staněk et al 2018]. The following description of the phenotypic spectrum associated with *GRIN1*-NDD is based on these reports. In 62 of the 72 reported individuals, clinical information was sufficient to draw conclusions on the overall phenotype (54 individuals heterozygous for a *de novo* missense variant and 8 individuals with homozygous variants). Of note, phenotypic data on 11 individuals with a heterozygous *de novo* variant comes from the DECIPHER database.

Developmental delay (DD) and intellectual disability (ID). All affected individuals have a variable degree of DD or ID (profound in 17%, severe in 71%, moderate in 7%, mild in 5%). No active speech has been noted in 48% of individuals.

Epilepsy. Seizures occurred in 65% of individuals. Some affected individuals presented with different seizure types over time. Where specified, seizures have been classified as epileptic spasms (13%), generalized seizures (68%), and focal seizures (20%). Seizure types reported among generalized and focal seizures comprise tonic, tonic-clonic, atonic, and/or myoclonic seizures, bilateral eyelid myoclonus, focal dyscognitive seizures, absence seizures, focal motor seizures, gelastic seizures, and status epilepticus.

Onset of seizures ranged from birth to 11 years with a median onset of 22.5 months. In 27 individuals on whom follow up or outcome on treatment with anti-seizure medication was available, 17 had refractory seizures and ten were well controlled with standard anti-seizure medication.

Other neurologic findings

- Muscular hypotonia (in 66%)
- Spasticity (40%)
- Movement disorders (48%); where specified, affected individuals showed signs of dystonic (13%), dyskinetic (11%), and/or choreiform movements (15%).
- Cortical visual impairment (34%)
- Oculogyric crisis (11%)

Behavioral findings. Signs of autism spectrum disorder were observed in 22%. Other behavior issues included stereotypic movements (32%), self-injurious behavior (7%), and sleep disorder (15%).

Feeding difficulties / gastrointestinal abnormalities. Feeding difficulties were reported in 31% of individuals. Severe muscular hypotonia, gastroesophageal reflux, or oral-pharyngeal dysphagia with chewing and swallowing difficulty caused persistent feeding problems, requiring G-tube insertion in a subset of individuals.

Growth. Growth restriction or short stature was seen in 11% while microcephaly was documented in 27%.

Neuroimaging. A malformation of cortical development (MCD) consisting of extensive diffuse bilateral polymicrogyria has been seen in 11 individuals [Fry et al 2018]. Polymicrogyria-affected brain regions comprised frontal, perisylvian, parietal, and temporal areas with some occipital sparing. Additional variable findings included increased extra-axial spaces, enlarged lateral ventricles, reduced white matter volume, thinning of the corpus callosum, and abnormal hippocampi. The MCD was similar in appearance to tubulinopathy-related or *GRIN2B*-related dysgyria [Platzer et al 2017]. See *GRIN2B*-Related Neurodevelopmental Disorder.

Other signs repeatedly noted in individuals without an MCD were generalized volume loss or cerebral atrophy (23%).

Signs of a leukoencephalopathy have been noted in two individuals with nonspecific hyperintensities of the white matter [Vanderver et al 2016, Pironti et al 2018].

Other

- Scoliosis has been seen in 11% of affected individuals.
- No specific dysmorphic facial features have been observed. If present, dysmorphic features are nonspecific.

Prognosis. Psychomotor regression or loss of acquired skills has specifically been noted in one individual starting at age 3.5 years with loss of speech, impaired social interaction, drooling, and loss of sphincter control [Papa et al 2018].

It is unknown if life span in *GRIN1*-NDD is abnormal. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

De novo heterozygous pathogenic variants in individuals with a malformation of cortical development (MCD) are located in the domains S2 and M3 [Fry et al 2018]. As there are only a few individuals with causative *GRIN1* variants in these regions who do not have an MCD, a genotype-phenotype correlation is possible.

All three children from a family with a homozygous nonsense *GRIN1* variant displayed a fatal developmental epileptic encephalopathy leading to death between ages five days and five months [Lemke et al 2016]. A comparable clinical course has not been reported in the five individuals with homozygous *GRIN1* missense variants located in the amino-terminal domain [Bosch et al 2016, Lemke et al 2016, Rossi et al 2017] or in any

individual with a *de novo* variant. The heterozygous parents of children homozygous for *GRIN1* variants did not show any manifestations of *GRIN1*-NDD.

Penetrance

Penetrance of *GRIN1*-related neurodevelopmental disorder is thought to be 100%.

Prevalence

The prevalence of *GRIN1*-NDD in the general population is unknown. To date, reports on fewer than 100 individuals have been published.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GRIN1*.

Differential Diagnosis

Because the phenotypic features associated with *GRIN1*-related neurodevelopmental disorder are not sufficient to diagnose this condition, all disorders with the following features should be considered in the differential diagnosis:

- Intellectual disability without other distinctive findings (See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.)
- Early-onset epileptic encephalopathy (See OMIM Phenotypic Series.)
- Polymicrogyria (See Polymicrogyria Overview.)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GRIN1*-NDD, the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with *GRIN1*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval	Assessment for cortical visual impairment & oculogyric crisis
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	Assessment for feeding difficulties, nutrition, weight gain, constipation, & gastroesophageal reflux disease
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	Exam for muscular hypotonia, spasticity, & scoliosis To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Mobility & ADL & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Neurologic	Neurologic eval	To incl clinical eval for movement disorders, seizures; EEG, brain MRI

Table 2. continued from previous page.

System/Concern	Evaluation	Comment
Development	Developmental assessment	To incl: • Eval of motor, speech/language, general cognitive, & vocational skills • Motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screen for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD.
Miscellaneous/ Other	Family supports & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.
	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Table 3. Treatment of Manifestations in Individuals with *GRIN1*-Related Neurodevelopmental Disorder

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Educational Issues.	
Central visual impairment	No specific treatment; early intervention w/ vision therapy may help to stimulate visual development.	
Seizures	Standardized treatment w/ASMs by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Muscular hypotonia, spasticity, & movement disorder	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help prevent contractures & falls	Consider need for positioning & mobility devices, disability parking placard.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy

1. Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of 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 and 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; however, 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 if 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.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - 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 into 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.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth,

feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. 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 AAC expertise. 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.

Social/Behavioral 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 is 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.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 4. Recommended Surveillance for Individuals with *GRIN1*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Frequency
Eyes	Ophthalmologic eval	At time of diagnosis & then as clinically indicated
Gastrointestinal	Feeding, nutrition status, weight gain	As clinically indicated
Musculoskeletal	Exam for muscular hypotonia, spasticity, & scoliosis	
Neurologic	Monitor those w/seizures.	
Psychiatric	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Miscellaneous/ Other	Monitor developmental progress & educational needs.	

Evaluation of Relatives at Risk

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

GRIN1-related neurodevelopmental disorder (*GRIN1*-NDD) is inherited in one of two ways:

- In an autosomal dominant manner, typically caused by a *de novo* pathogenic missense variant
- In an autosomal recessive manner

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- All probands reported to date with autosomal dominant *GRIN1*-NDD whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo GRIN1* pathogenic missense variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *GRIN1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism. Although theoretically possible, no instances of germline mosaicism have been reported to date.
- Theoretically, if the parent is the individual in whom the *GRIN1* pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents: if the *GRIN1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is presumed to be greater than that of the general population because of the theoretic possibility of parental mosaicism.
- In a study assessing mosaicism in the apparently asymptomatic parents of children with developmental and epileptic encephalopathy, the frequency of parental somatic and (inferred) germline mosaicism was 10% [Myers et al 2018]. This frequency results in an increased recurrence risk to sibs, which is estimated to be 1% [Rahbari et al 2016].

Offspring of a proband

- Each child of an individual with a *GRIN1*-NDD has a 50% chance of inheriting the *GRIN1* pathogenic variant.
- Individuals with *GRIN1*-NDD are not known to have reproduced; however, many are not yet of reproductive age.

Other family members. Given that all probands with autosomal dominant *GRIN1*-NDD reported to date have the disorder as a result of a *de novo GRIN1* pathogenic variant, the risk to other family members is presumed to be low.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with autosomal recessive *GRIN1*-NDD are obligate heterozygotes (i.e., carriers of one *GRIN1* pathogenic variant).
- To date, heterozygous (carrier) parents have been asymptomatic and, thus, are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygous (carrier) sibs are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with *GRIN1*-NDD are not known to have reproduced.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *GRIN1* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *GRIN1* pathogenic variants in the family.

Related Genetic Counseling Issues

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Autosomal dominant inheritance. Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo GRIN1* pathogenic variant. However, there is a frequency of (inferred) germline mosaicism of 10% and a consecutive recurrence risk to sibs of 1% based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016, Myers et al 2018]. Given this risk, prenatal and preimplantation genetic testing may be considered.

Autosomal recessive inheritance. Once the *GRIN1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Autosomal dominant and autosomal recessive inheritance. 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.

- **CureGRIN Foundation**

Phone: 303-881-3425
www.curegrin.org

- **American Epilepsy Society**
  www.aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  www.canadianepilepsyalliance.org
- **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

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. GRIN1-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GRIN1	9q34.3	Glutamate receptor ionotropic, NMDA 1	GRIN1 database	GRIN1	GRIN1

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 GRIN1-Related Neurodevelopmental Disorder (View All in OMIM)

138249	GLUTAMATE RECEPTOR, IONOTROPIC, N-METHYL-D-ASPARTATE, SUBUNIT 1; GRIN1
614254	NEURODEVELOPMENTAL DISORDER WITH OR WITHOUT HYPERKINETIC MOVEMENTS AND SEIZURES, AUTOSOMAL DOMINANT; NDHMSD
617820	NEURODEVELOPMENTAL DISORDER WITH OR WITHOUT HYPERKINETIC MOVEMENTS AND SEIZURES, AUTOSOMAL RECESSIVE; NDHMSR

Molecular Pathogenesis

N-methyl-D-aspartate receptors (NMDARs) are ligand-gated ion channels expressed throughout the brain mediating excitatory neurotransmission. Signaling via NMDAR plays an important role in brain development, learning, memory, and other higher cognitive functions. NMDARs are diheterotetramers or triheterotetramers composed of two glycine-binding GluN1subunits (encoded by *GRIN1*) and two glutamate-binding GluN2 subunits (encoded by *GRIN2A* through *GRIN2D*) [Traynelis et al 2010]. Simultaneous binding of both agonists

activates the NMDAR, which opens a cation-selective pore leading to an influx of Ca^{2+} and depolarization. The GluN1 subunit is ubiquitously expressed from embryonic stage to adulthood [Paoletti et al 2013]. Although the GluN1 subunit is encoded by a single gene (*GRIN1*), alternative splicing results in eight isoforms. There are differences in GluN1 isoform expression, but its functional significance is unclear.

Gene structure. The *GRIN1* transcript deemed clinically most relevant (NM_007327.3) comprises 20 exons. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. In autosomal dominant *GRIN1*-NDD, only *de novo* missense variants have been reported to date. *De novo* missense variants cluster within or in close proximity to the ligand-binding domain S2 as well as the transmembrane domains M1-M4 [Lemke et al 2016]. No *de novo* truncating variants deemed to be causative have been reported to date.

In autosomal recessive *GRIN1*-NDD, three families with a homozygous missense variant located in the amino-terminal domain and one family with three affected individuals with a homozygous nonsense variant have been reported [Bosch et al 2016, Lemke et al 2016, Rossi et al 2017].

Normal gene product. The isoform deemed clinically most relevant (NP_015566.1) consists of 938 amino acids and contains an amino-terminal domain, two ligand-binding domains (S1 and S2), four transmembrane domains (M1-M4), a calmodulin domain, and a C-terminal domain.

Abnormal gene product. Functional evaluation of missense variants has determined that some cause loss of function and some cause gain of function of the NMDA receptor [Lemke et al 2016, Fry et al 2018, Xiangwei et al 2018].

Chapter Notes

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Revision History

- 1 April 2021 (aa) Revision: incorporated parental mosaicism data from Myers et al [2018]

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