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GRIA2-Related Neurodevelopmental Disorder

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Summary

Clinical characteristics

The clinical phenotype of *GRIA2*-related neurodevelopmental disorder (*GRIA2*-NDD) comprises global developmental delay, cognitive and language impairment with poor or absent speech in almost all individuals, and varying combinations of tone abnormalities at birth, early-onset developmental and epileptic encephalopathy, complex movement disorders with or without epilepsy, and neurobehavioral and/or psychiatric disorders. Some affected individuals have normal early development followed by variable regression with impaired social and/or language skills. About half of individuals are nonverbal. Several individuals are unable to walk, and several have gait abnormalities, including gait dyspraxia and ataxia. Nearly half of affected children develop seizures including early-onset tonic-clonic, focal, and focal to bilateral tonic-clonic seizures, most of which are refractory to treatment. Some children present with movement disorders, including chorea, dystonia, and dyskinesia.

Diagnosis/testing

The diagnosis of *GRIA2*-NDD is established in a proband with suggestive findings and a heterozygous pathogenic variant in *GRIA2* identified by molecular genetic testing.

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Management

Treatment of manifestations: There is no cure for *GRIA2*-NDD. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in neurology, developmental pediatrics, speech-language therapy, otorhinolaryngology, sleep disorders, orthopedics / physical medicine and rehabilitation, physical therapy and occupational therapy, feeding therapy, gastroenterology, ophthalmology, hearing impairment, and medical genetics and genetic counseling.

Genetic counseling

GRIA2-NDD is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo GRIA2* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the possibility of parental germline mosaicism. Given this risk, prenatal and preimplantation genetic testing may be considered.

GeneReview Scope

The scope table outlines the current understanding of the clustering of distinctive features in the four broad phenotypic spectra (abnormal body tone, epilepsy, movement disorder, and neurobehavioral and/or psychiatric disorders) of *GRIA2*-related neurodevelopmental disorder (*GRIA2*-NDD). Of note, the spectrum within and between these four major phenotypic features remains to be determined pending reporting of more individuals with *GRIA2*-NDD.

GRIA2-Related Neurodevelopmental Disorder: Phenotypic Spectrum

Major Phenotypic Feature (in Addition to Developmental Delay / Intellectual Disability)	Typical Age of Onset
Abnormal body tone (hypo- or hypertonia)	Birth
Epilepsy (focal &/or generalized-onset seizures). Known electroclinical syndromes include epileptic spasms syndrome and developmental & epileptic encephalopathy.	<12 months
Movement disorder (dyspraxia; ataxia; choreoathetoid movements; dystonia)	
Neurobehavioral and/or psychiatric disorders (ASD; ADHD; repetitive behaviors; aggressive, self-harming behaviors; stereotypies)	Early childhood

ADHD = attention-deficit/hyperactivity disorder; ASD = autistic spectrum disorder

Diagnosis

Formal diagnostic criteria for *GRIA2*-related neurodevelopmental disorder (NDD) have not been established.

Suggestive Findings

GRIA2-NDD **should be considered** in a proband with the following clinical and brain MRI findings and family history.

Clinical findings

- **Developmental delay (DD) and/or intellectual disability (ID)** (present in all individuals)

AND any of the following features presenting in infancy or childhood:

- **Body tone abnormalities**
  - Congenital-onset abnormal muscle tone (generalized hypotonia or hypertonia)
  - Feeding difficulties during infancy associated with abnormal muscle tone
- **Epilepsy.** Early-onset and typically treatment-resistant focal and/or generalized seizures

- **Movement disorders.** Several types of movement disorders may occur including gait dyspraxia, ataxia, choreoathetoid movements, and dystonia.
- **Neurobehavioral and/or psychiatric disorders**
  - Autism spectrum disorder, attention-deficit/hyperactivity disorder, repetitive behaviors, obsessive-compulsive findings, inappropriate laughing/screaming spells, aggressive or self-injurious behavior
  - Stereotypies (including hand wringing, hand clapping, mouthing, and rubbing automatisms)
- **Other features**
  - Microcephaly (or deceleration of head growth)
  - Cerebral visual impairment, broadly defined here as bilateral visual impairment due to non-ocular causes (i.e., based in the brain) in the presence of normal pupil reactivity
  - Skeletal abnormalities (scoliosis, spinal fusion, femoral anteversion)
  - Hypothyroidism
  - Sleep apnea

Note: The constellation of findings may occasionally resemble *MECP2* disorders with findings of stereotypic hand movements (including hand wringing, hand clapping, mouthing, and rubbing automatisms), gait abnormalities (including gait dyspraxia and inability to walk), microcephaly (or deceleration of head growth), and motor/sensory abnormalities (including abnormal muscle tone and hypersensitivity).

Brain MRI findings. Brain MRI is usually normal; however, two out of 33 affected individuals are reported to have delayed myelination and nonspecific white matter changes and/or cerebellar atrophy characterized by prominent vermian involvement (see Salpietro et al [2019], Figure 2).

Family history. Because *GRIA2*-NDD is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family).

Establishing the Diagnosis

The diagnosis of *GRIA2*-NDD **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *GRIA2* 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 both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variant" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *GRIA2* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Note: Single-gene testing (sequence analysis of *GRIA2*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

An intellectual disability multigene panel that includes *GRIA2* 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.* (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 does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, all pathogenic *GRIA2* variants reported (e.g., missense, nonsense) are within the coding region that can 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 *GRIA2*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2, 3] Detectable by Method
GRIA2	Sequence analysis [4]	30/33 [5]
	Gene-targeted deletion/duplication analysis [6]	3/33 [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Three individuals with contiguous gene deletions (not included in this table) have also been reported [Salpietro et al 2019] (see Genetically Related Disorders).
4. 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.
5. Salpietro et al [2019], Alkelai et al [2021], Zhou et al [2021], Cai et al [2022], Coombs et al [2022], Latsko et al [2022], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than that of gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

The clinical phenotype of *GRIA2*-related neurodevelopmental disorder (*GRIA2*-NDD) comprises global developmental delay, cognitive and language impairment with poor or absent speech in almost all individuals, and varying combinations of tone abnormalities at birth, early-onset developmental and epileptic encephalopathy, complex movement disorders with or without epilepsy, and neurobehavioral and/or psychiatric disorders.

Some affected individuals have normal early development, followed by variable regression with impaired social and/or language skills. About half of individuals are nonverbal. Several individuals are unable to walk, and several have gait abnormalities, including gait dyspraxia and ataxia.

Nearly half of affected children develop seizures including early-onset tonic-clonic, focal, and focal to bilateral tonic-clonic seizures, most of which are refractory to treatment. Some children present with movement disorders, including chorea, dystonia, and dyskinesia.

Neurobehavioral and/or psychiatric disorders can include autism spectrum disorder, obsessive-compulsive findings, hyperactivity, inappropriate laughing/screaming spells, repetitive behaviors, and stereotypic movements.

Several individuals have either microcephaly or head growth deceleration during infancy.

To date, 33 individuals, ranging in age from three months to 31 years, have been reported with a pathogenic variant in *GRIA2* [Salpietro et al 2019, Zhou et al 2021, Cai et al 2022, Coombs et al 2022, Huang et al 2022, Ji et al 2022, Latsko et al 2022]. The information in Table 2 and the description that follows are based on these reports.

Table 2. *GRIA2*-Related Neurodevelopmental Disorder: Select Features

Feature		# of Persons w/Feature (n=33)
Motor delays		33
Speech & language delays / absent speech		25
Intellectual disability &/or developmental delay	**Moderate**	24
	Severe	9
Neurobehavioral &/or psychiatric disorders		21
Findings resembling *MECP2* disorders		16
Epilepsy		15
Movement disorders		6

Tone abnormalities at birth. Muscular hypotonia was present in three individuals. Spasticity, including muscular hypertonia, that was non-progressive was present in some individuals.

Developmental delay (DD) and intellectual disability (ID) ranging from moderate to severe were present in all reported individuals. Most individuals had delays in gross motor milestones, and several individuals never acquired the ability to walk independently.

All affected individuals had delays (or regression) of speech and language development, and in most cases they could only speak a few intelligible words.

Neurobehavioral and/or psychiatric disorders. Several individuals had autism spectrum disorder and attention-deficit/hyperactivity disorder. Some had repetitive behavior patterns, impaired social interaction, inappropriate laughing/screaming spells, aggressive or self-injurious behavior, and stereotypies (including hand wringing, hand clapping, mouthing, and rubbing automatisms).

Findings resembling *MECP2* disorders. Between ages two and six years, 16 children (both male and female, in equal numbers) developed several features that resembled Rett syndrome (i.e., low muscle tone, stereotypic hand movements, gait abnormalities) as well as developmental stagnation in which development slows down or stops altogether; abnormal sleep rhythm; and irregular breathing pattern with frequent episodes of hyperventilation.

Epilepsy. Fifteen of 33 individuals had seizures with median age of onset around age three months (range: 1-15 months). Common seizure types included tonic-clonic seizures, myoclonic seizures, and infantile spasms. Fever was a common trigger. Twelve individuals displayed multiple seizure types over time.

Among the 15 individuals with seizures, epilepsy could be classified as generalized onset in three, focal onset in five, and of unknown onset in seven. Known electroclinical epilepsy syndromes included epileptic spasms syndrome and developmental and epileptic encephalopathy.

Seizures were controlled with standard anti-seizure medications in only two of 12 individuals.

EEG features included polyspikes, slow spike-and-wave, and bilateral temporal non-synchronized epileptic activity.

Movement disorders were observed in two individuals who presented with dyskinesia, dystonia, and choreiform movements.

Other findings

- **Feeding difficulties.** During early infancy, two children had swallowing difficulties leading to impaired feeding, choking, and regurgitation, requiring gastrostomy tube placement.
- **Growth.** Progressive microcephaly was observed in four out of 29 individuals, where occipitofrontal circumference (OFC) was more than two standard deviations below the mean, with deceleration of head growth usually during early infancy.
- **Ophthalmologic findings.** Impaired visual interaction due to abnormal communication during the first few months of life has been noted in several affected individuals. Two individuals had cerebral vision impairment with abnormal ocular motility and (usually intermittent) strabismus.
- **Prognosis.** It is unknown whether life span in *GRIA2*-NDD is abnormal.

  Two infants died before age six months with sudden unexplained death in epilepsy (patients 17 and 20 in Salpietro et al [2019]). Within the first two months of life, these infants had tonic or clonic seizures associated with breathing difficulties and no response to several anti-seizure medications.

  One reported female with tonic seizures beginning at age eight years, moderate ID/DD, no Rett-like features, and normal brain imaging is alive at age 31 years (patient 23 in Salpietro et al 2019]), demonstrating that survival into adulthood is possible when the phenotype is milder. 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

No clear genotype-phenotype correlations have been identified to date in *GRIA2*-NDD. However, strong correlations have been observed between two specific recurrent pathogenic variants and the phenotypes of the affected individuals (see Table 7).

- The pathogenic variant p.Ala639Ser, which affects a conserved alanine residue proximal to the SYTANLAAF domain essential for channel gating, was present in two infants who died before age six months with sudden unexplained death in epilepsy (patients 17 and 20 in Salpietro et al [2019]). Within the first two months of life, these infants had tonic or clonic seizures associated with breathing difficulties and no response to several anti-seizure medications. EEGs showed a multifocal spike and/or burst suppression-like pattern. Brain MRI showed cortical and/or cerebellar atrophy.
- The pathogenic variant p.Val647Leu was present in three children with developmental and epileptic encephalopathy and overlapping electroclinical features (polyspikes, slow spike-and-wave, and bilateral temporal non-synchronized epileptic activity) (patients 16, 18, and 21 in Salpietro et al [2019]).

Of note, the pathogenic variant p.Ala643Val, reported to date in one individual, is the only *GRIA2* pathogenic variant observed to cause gain of function (rather than loss of function) of the ligand-gated AMPAR receptor

(which is encoded by *GRIA2*) [Coombs et al 2022] (see Table 7). In addition, the anti-seizure medication perampanel (the only approved anti-seizure medication that blocks the AMPAR receptor) improved behavior, mood, alertness, and fine motor control in this individual [Coombs et al 2022]. Of note, the individual was also treated using a modified Atkin diet with medium chain triglyceride oil supplementation, which might have contributed to the reduction in the disease manifestations [Neal et al 2009, Chang et al 2013].

Prevalence

The prevalence of *GRIA2*-NDD in the general population is 0.0000084 for *de novo* variants [Gillentine et al 2022].

To date, 33 individuals with *GRIA2*-NDD from Europe, North America, and Asia have been reported.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GRIA2*.

Contiguous gene deletions. Deletions in the 4q32.1 region encompassing *GRIA2* and adjacent genes have been identified in individuals with intellectual disability, speech delay, and (in some) autistic features. Additional findings include developmental delay and joint hypermobility [Salpietro et al 2019]. Note that to date epilepsy, movement disorders, features resembling *MECP2* disorders, and brain imagining abnormalities have not been described in individuals with 4q32.1 contiguous gene deletions.

Differential Diagnosis

Because *GRIA2*-related neurodevelopmental disorder is associated with a broad phenotypic spectrum, all disorders with intellectual disability without other distinctive clinical features or findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

In persons with abnormal developmental milestones, epilepsy, and features resembling *MECP2* disorders, the genes listed in Table 3 may be of specific interest.

Table 3. Selected Genes of Interest in the Differential Diagnosis of *GRIA2*-Related Neurodevelopmental Disorder

Gene	Disorder	MOI
FOXG1	Rett syndrome, congenital variant (OMIM 613454)	AD
GRIA1	*GRIA1*-NDD (OMIM 619931, 619927)	AD AR
GRIA3	*GRIA3*-NDD (OMIM 300699)	XL
GRIA4	*GRIA4*-NDD (OMIM 617864)	AD
GRIN1	*GRIN1*-NDD	AD AR
GRIN2A	*GRIN2A*-NDD (See *GRIN2A*-Related Speech Disorders and Epilepsy.)	AD
MECP2	*MECP2* disorders	XL

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; NDD = neurodevelopmental disorder; XL = X-linked

Management

No clinical practice guidelines for *GRIA2*-related neurodevelopmental disorder (*GRIA2*-NDD) have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with *GRIA2*-NDD and similar disorders.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GRIA2*-NDD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. *GRIA2*-Related Neurodevelopmental Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measure length/height, weight, & OFC	
Neurologic	Neurologic eval	To include: • Brain MRI • EEG if history of seizures • Eval for movement disorders • Eval for sleep apnea
Development	Developmental assessment / physical medicine & rehab / PT & OT eval	To include assessment of: • Motor, adaptive, cognitive, & speech-language ability • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills • Early intervention / special education • Speech therapy
Speech & language	Eval by speech-language therapist	Consider need for augmentative & alternative communication (AAC)
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns including ADHD, ASD
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To include assessment of: • Contractures, clubfoot, & kyphoscoliosis • Mobility, ADL, & need for adaptive devices
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk, nutritional status, & growth • Consider eval for gastrostomy tube placement in persons w/ dysphagia &/or aspiration risk. • Eval for gastroesophageal reflux disease & constipation.
Eyes	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, strabismus, & best corrected visual acuity
Hearing	Audiologic eval	To assess for hearing loss
Endocrine	Endocrinologic eval	Consider testing for hypothyroidism.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *GRIA2*-NDD to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
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; MOI = mode of inheritance; OFC = occipitofrontal circumference; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *GRIA2*-NDD.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists (see Table 5).

Table 5. *GRIA2*-Related Neurodevelopmental Disorder: 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. • Consider perampanel for treatment of seizures, behavior, alertness, mood, & fine motor control affected by gain-of-function variants. [1] • Education of parents/caregivers [2]
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Sleep apnea	Otorhinolaryngologist / sleep specialist	Seizures should be considered in the differential diagnosis for sleep apnea.
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Bowel dysfunction	Monitor for constipation.	Stool softeners, prokinetics, osmotic agents, or laxatives as needed
Eyes	Ophthalmologist	Refractive errors, strabismus
	Ophthalmic subspecialist	More complex findings (e.g., cataract, retinal dystrophy)
	Low vision services	• Children: through early intervention programs &/or school district • Adults: low vision clinic &/or community vision service / OT / mobility services
Cerebral visual impairment	No specific treatment	Early intervention program to stimulate visual development

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Hearing	Hearing aids may be helpful per otolaryngologist.	Community hearing services through early intervention or school district
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 involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. A published case study details success in perampanel treatment an individual with a *GRIA2* gain-of-function variant in the AMPAR negative allosteric modulator [Coombs et al 2022]. Use of perampanel was associated with marked reduction in seizure burden and developmental improvements (see Genotype-Phenotype Correlations).
2. 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.
  - Vision and hearing 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 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.

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).

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 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.

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 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

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *GRIA2*-Related Neurodevelopmental Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters (incl OFC) • Eval of nutritional status & safety of oral intake	At each visit
Gastrointestinal	• Monitor for constipation & gastroesophageal reflux disease. • Monitor feeding needs, esp in early infancy.	
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency, or abnormal respiratory pattern (episodes of hyperventilation).	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, or movement disorders.	
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Behavioral assessment for anxiety, ADHD, ASD, aggression, & self-injury	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Ophthalmologic involvement	Monitor those w/abnormal ocular motility or strabismus.	Per treating ophthalmologist(s)
Respiratory	Monitor abnormal breathing patterns (irregular breathing & hyperventilation episodes).	At each visit
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; OFC = occipitofrontal circumference; OT = occupational therapy; PT = physical therapy

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

GRIA2-related neurodevelopmental disorder (*GRIA2*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with *GRIA2*-NDD whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo GRIA2* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk counseling.
- 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 germline (or somatic and germline) mosaicism.* Note: 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.

    * A parent with somatic and germline mosaicism for a *GRIA2* pathogenic variant 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 a parent of the proband is known to have the *GRIA2* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *GRIA2* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Individuals with *GRIA2*-NDD are not known to reproduce; however, many are not yet of reproductive age.

Other family members. Given that all probands with *GRIA2*-NDD reported to date have the disorder as a result of a *de novo GRIA2* pathogenic variant, the risk to other family members is presumed to be low.

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

Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo GRIA2* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal and preimplantation genetic testing may be considered.

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 Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **American Epilepsy Society**
  www.aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  www.canadianepilepsyalliance.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com
- **MedlinePlus**
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net

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. GRIA2-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GRIA2	4q32.1	Glutamate receptor 2	GRIA2 database	GRIA2	GRIA2

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 GRIA2-Related Neurodevelopmental Disorder (View All in OMIM)

138247	GLUTAMATE RECEPTOR, IONOTROPIC, AMPA 2; GRIA2
618917	NEURODEVELOPMENTAL DISORDER WITH LANGUAGE IMPAIRMENT AND BEHAVIORAL ABNORMALITIES; NEDLIB

Molecular Pathogenesis

The AMPA-type glutamate receptors (AMPARs) are ligand-gated cation channels, expressed in both neurons and glia, that mediate most of the fast excitatory transmission in the central nervous system [Hansen et al 2021]. AMPARs have also been implicated in the development and maintenance of synaptic plasticity (including both long-term potentiation and depression; reviewed in Isaac et al [2007] and Cull-Candy & Farrant [2021]) and synaptogenesis [Ashby & Isaac 2011, Kwon & Sabatini 2011]. As such, genetic alterations in the genes that encode AMPAR subunits such as *GRIA2* likely cause neurodevelopmental disorders via a disruption of more than just excitatory transmission.

Mechanism of disease causation. A range of disease-associated variants have been identified across *GRIA2* that can produce either loss or gain of receptor function.

GRIA2 variants such as nonsense, frameshift, or truncating variants may lead to a loss of function via haploinsufficiency.

- Missense *GRIA2* variants may cause disease through several mechanisms. In vitro patch clamp studies have shown that missense variants can lead to changes in a range of receptor properties such as kinetics (i.e., deactivation and desensitization) and pharmacology (i.e., glutamate potency), among others [Salpietro et al 2019, Coombs et al 2022]. It is currently unknown how these changes might affect broader synaptic function and circuit/network functions and development.
- The specific *GRIA2* missense variant p.Ala643Val exhibits gain of function, with greatly slowed deactivation, markedly reduced desensitization, and increased glutamate sensitivity [Coombs et al 2022].

Table 7. *GRIA2* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001083619.3 NP_001077088.2	c.1915G>T	p.Ala639Ser	Variant reported in 2 infants w/SUDEP (See Genotype-Phenotype Correlations.)
	c.1928C>T	p.Ala643Val	Variant likely causes gain of function of the ligand-gated AMPAR receptor [Coombs et al 2022] (See Genotype-Phenotype Correlations.)
	c.1939G>C	p.Val647Leu	Variant reported in 3 children w/DEE & overlapping electroclinical features [Salpietro et al 2019] (See Genotype-Phenotype Correlations.)

DEE = developmental and epileptic encephalopathy; SUDEP = sudden unexplained death in epilepsy
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.

Chapter Notes

Author Notes

Allan Bayat and Henry Houlden are shared last authors.

Dr Stephanie Efthymiou, Dr Vincenzo Salpietro, and **Ms Elisa Rumbos Siurana** are actively involved in clinical research regarding individuals with *GRIA2*-related neurodevelopmental disorder (*GRIA2*-NDD) and are working on characterizing the functional effects of *GRIA2* variants using in vitro electrophysiology methods. They would also be happy to communicate with persons who have any questions regarding diagnosis of *GRIA2*-NDD or other considerations.

Contact information: s.efthymiou@ucl.ac.uk (Stephanie Efthymiou), v.salpietro@ucl.ac.uk (Vincenzo Salpietro), elisa.siurana.17@ucl.ac.uk (Elisa Rumbos Siurana)

Web page: www.neurogenetics.co.uk/meet-the-team

The team led by **Dr Allan Bayat** is also actively involved in research regarding all *GRIA* genes: *GRIA1*, *GRIA2*, *GRIA3*, and *GRIA4*. They are also using in vitro electrophysiology methods to functionally evaluate the effects of all *GRIA* missense variants.

Their aims are to deep-phenotype *GRIA*-related disorders, to find new genotype-phenotype correlations, to identify clinical biomarkers suggestive of loss- or gain-of-function variants, and to explore the role of perampenal as precision therapy for individuals with gain-of-function variants.

Dr Bayat would be happy to communicate with persons who have any questions regarding diagnosis of *GRIA*-NDD or other considerations. Contact him to inquire about potential functional evaluation of all *GRIA* variants of uncertain significance. No tissue samples are needed for functional testing.

Contact information: abaya@filadelfia.dk or bayabayabayat@hotmail.com

Web page: epi-care.eu/collaborative-genetic-research

Dr Vincenzo Salpietro is also interested in hearing from clinicians treating families affected by *GRIA2*-NDD in whom causative variant has been identified through molecular genetic testing.

Contact **Dr Stephanie Efthymiou** and **Ms Elisa Rumbos Siurana** to inquire about review of *GRIA2* variants of uncertain significance.

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