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GRIN2D-Related Developmental and Epileptic Encephalopathy

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Summary

Clinical characteristics

GRIN2D-related developmental and epileptic encephalopathy (*GRIN2D*-related DEE) is characterized by mild-to-profound developmental delay or intellectual disability, epilepsy, abnormal muscle tone (hypotonia and spasticity), movement disorders (dystonia, dyskinesia, chorea), autism spectrum disorder, and cortical visual impairment. Additional findings can include sleep disorders and feeding difficulties. To date 22 individuals with *GRIN2D*-related DEE have been reported.

Diagnosis/testing

The diagnosis of *GRIN2D*-related DEE is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) missense variant in *GRIN2D* identified by molecular genetic testing

Management

Treatment of manifestations: There is no cure for *GRIN2D*-related DEE. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in pediatric neurology, pediatric ophthalmology, developmental pediatrics, feeding, orthopedics, physical medicine and rehabilitation, physical therapy, occupational therapy, and ethics.

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

GRIN2D-related DEE is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. If the proband represents a simplex case (i.e., the only affected family member) and the *GRIN2D* pathogenic variant

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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 theoretic possibility of parental mosaicism. Once the *GRIN2D* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *GRIN2D*-related developmental and epileptic encephalopathy (*GRIN2D*-related DEE) have been published.

Suggestive Findings

GRIN2D-related DEE **should be considered** in individuals with the following clinical and/or brain MRI findings.

Clinical findings

- Mild-to-profound developmental delay (DD) or intellectual disability (ID); 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
  - Cortical visual impairment

Imaging findings. Brain MRI can show generalized volume loss as a sign of cerebral atrophy.

Establishing the Diagnosis

The diagnosis of *GRIN2D*-related DEE **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) missense variant in *GRIN2D* identified by molecular genetic testing (see Table 1).

Note: (1) 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. (2) Identification of a heterozygous *GRIN2D* variant of uncertain significance does not establish or rule out the diagnosis of this disorder. (3) To date, a null variant in *GRIN2D* has not been reported in any individual with *GRIN2D*-related DEE.

Because the phenotype of *GRIN2D*-related DEE is indistinguishable from many other inherited disorders with developmental delay, intellectual disability, and epilepsy, recommended molecular genetic testing approaches include use of **comprehensive genomic testing** or a **multigene panel**.

Note: Single-gene testing (sequence analysis of *GRIN2D*, followed by gene-targeted deletion/duplication analysis) is not useful and NOT recommended.

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved and is therefore preferred by the authors over use of a multigene panel. **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.

- **An intellectual disability or epilepsy multigene panel** that includes *GRIN2D* 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.

Table 1. Molecular Genetic Testing Used in *GRIN2D*-Related DEE

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
GRIN2D	Sequence analysis [3]	22/22 [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

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. 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. To date, all reported *GRIND2D*-related DEE pathogenic variants have been missense variants [Li et al 2016, Tsuchida et al 2018, Xiang-Wei et al 2019, Stenson et al 2020, Bertoli-Avella et al 2021, Jiao et al 2021, GRIN Portal/Registry].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. To date, *GRIN2D* null variants (including large deletions/duplications) have not been identified as a cause of *GRIN2D*-related DEE.

Clinical Characteristics

Clinical Description

GRIN2D-related developmental and epileptic encephalopathy (*GRIN2D*-related DEE) is characterized by mild-to-profound developmental delay or intellectual disability, epilepsy, abnormal muscle tone (hypotonia and spasticity), movement disorders (dystonia, dyskinesia, chorea), autism spectrum disorder, and cortical visual impairment. Additional findings can include sleep disorders and feeding difficulties.

To date, a pathogenic missense variant in *GRIN2D* has been identified in 22 individuals [Li et al 2016, Tsuchida et al 2018, Xiang-Wei et al 2019, Stenson et al 2020, Bertoli-Avella et al 2021, Jiao et al 2021] and an additional four unpublished individuals enrolled in the GRIN Portal/Registry. The following description of the phenotypic features associated with this condition is based on these reports.

Developmental delay / intellectual disability. All individuals have a variable degree of DD or ID, with 59% (13/22) showing severe/profound ID, 1/22 showing moderate ID, and 1/22 described with mild ID. In 31% (7/22), the level of ID was not specified.

In 36% (8/22), no speech was noted, while 2/22 were able to speak single words.

Of the 22 individuals reported, five (all of whom also had epilepsy) were noted to regress, consistent with an encephalopathic course. In 10% (2/22), the regression was further specified to primarily affect motor skills.

Epilepsy. Eighty-six per cent (19/22) of individuals had seizures. Average age at seizure onset was 11 months (range: 1 day – 41 months, median: 4 months).

When known, seizure type differed at onset and included the following:

- Febrile seizures (1/18)
- Focal seizures (4/18)
- Absence seizures (3/18)
- Generalized seizures (5/18)
- Epileptic spasms (5/18)

Eleven of the 19 individuals with seizures had multiple seizure types after the initial onset of seizures.

Use of anti-seizure medication varied considerably, with differing levels of success. No particularly successful treatment regimen was evident.

EEG findings include hypsarrhythmia, focal and multifocal as well as generalized epileptic discharges; different EEG patterns varied over time.

Other neurologic findings

- Muscular hypotonia: 54% (in 12/22)
- Movement disorder with athetoid movements, jerky movements, ballism, mild dyskinesia, and choreiform movements: 36% (8/22)
- Cortical visual impairment: 32% (7/22)
- Spasticity (primarily of the lower limbs): 18% (4/22)
- Ataxic gait: 3% (3/22)

Behavioral problems

- Autism spectrum disorder: 18% (4/22)
- Recurrent sleeping disorder 27% (6/22)

Feeding difficulties / gastrointestinal abnormalities

- Feeding difficulties in 27% (6/22), including one individual who required tube feeding [Li et al 2016]
- Recurrent vomiting and constipation

Growth. One individual had microcephaly. No other growth abnormalities were observed.

Neuroimaging. MRI, performed in 17 of 22 individuals, was normal in nine individuals and showed signs of brain atrophy in seven individuals, including two with a thin corpus callosum.

Prognosis. As no older individuals with a *GRIN2D*-related DEE have been described to date, reliable prognostic statements are currently not possible.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

Penetrance of *GRIN2D*-related DEE is thought to be 100%.

Prevalence

The prevalence of *GRIN2D*-related DEE in the general population is unknown. To date, reports on fewer than 30 individuals have been published.

Use of an empiric incidence estimation algorithm [Lemke 2020, López-Rivera et al 2022] predicted the number of newborns with a *de novo GRIN2D* variant in the US in 2018 to be 175.

A genetic contribution to neurodevelopmental disorders can be estimated at 0.006% based on the presence of two *de novo GRIN2D* variants in the largest study on *de novo* variants to date [Kaplanis et al 2020].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GRIN2D*.

Differential Diagnosis

Because the phenotypic features associated with *GRIN2D*-related developmental and epileptic encephalopathy (*GRIN2D*-related DEE) 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.
- Developmental and epileptic encephalopathy: see OMIM Developmental and Epileptic Encephalopathy Phenotypic Series.

Of note, malformation of cortical development – described in some individuals with *GRIN1*- or *GRIN2B*-related neurodevelopmental disorder – has not been observed in *GRIN2D*-related DEE.

Management

No clinical practice guidelines for *GRIN2D*-related DEE have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GRIN2D*-related DEE, the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with *GRIN2D*-Related DEE

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	Incl: clinical eval for mvmt disorders, seizures; EEG, brain MRI
Vision	Ophthalmologic eval	To assess for ↓ vision, abnormal ocular mvmt, best corrected visual acuity, refractive errors, strabismus
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status, weight gain, constipation & GERD • Consider eval for gastric tube placement in those w/dysphagia &/or aspiration risk.

Table 2. continued from previous page.

System/Concern	Evaluation	Comment
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)
Development	Developmental assessment	• To incl motor, adaptive, cognitive & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	In persons age >12 mos: screen for presence of behavioral problems incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Ethics consultation	Clinical ethics services	Assess healthcare decisions in context of best interest of child & family's values & preferences.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *GRIN2D*-DEE in order to facilitate medical & personal decision making
Family support & resources		Assess 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; GERD = gastroesophageal reflux disease; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *GRIN2D*-related DEE.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in pediatric neurology, pediatric ophthalmology, developmental pediatrics, feeding, orthopedics, physical medicine and rehabilitation, physical therapy, occupational therapy, and ethics.

Table 3. Treatment of Manifestations in Individuals with *GRIN2D*-Related DEE

Manifestation/Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Educational Issues.	
Central visual impairment	No specific treatment; early intervention w/ vision therapy may help to stimulate visual development.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; no ASM has been demonstrated effective specifically for this disorder. • Education of parents / care givers [1]
Poor weight gain	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs of dysphagia

Table 3. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Muscular hypotonia, spasticity, & movement disorder	Orthopedics / physical medicine & rehab / PT/OT incl stretching to help avoid 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 Educational 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:

- Individualized education plan (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 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.

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-language pathologist) 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 Difficulties

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavioral 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 *GRIN2D*-Related DEE

System/Concern	Evaluation	Frequency
Central visual impairment	Ophthalmologic eval	As clinically indicated
Gastrointestinal	Feeding, nutrition status, weight gain	As clinically indicated; for severely impaired patients: at every visit.
Musculoskeletal	Exam for spasticity & scoliosis by treating orthopedics / physical medicine & rehab / PT/OT	Per treating clinicians
Neurologic	• Monitor those w/seizures. • Assess for new manifestations incl seizures, changes in tone, mvmt disorders.	Per treating neurologist
Psychiatric	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	As clinically indicated
Development	Monitor developmental progress & educational needs.	At each visit
Miscellaneous/ Other		As clinically indicated
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).	At each visit

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

Given the understanding of the drug memantine on *GRIN2D* function [Kotermanski & Johnson 2009], anti-convulsant effects in animal models [Ghasemi & Schachter 2011], and safety profile in children [Chez et al 2007, Erickson et al 2007], memantine was tried in three affected individuals. While one showed a beneficial response, two did not [Li et al 2016, Xiang-Wei et al 2019]. Due to the varying success of treatment with memantine, a targeted treatment recommendation cannot be given at this point.

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

GRIN2D-related developmental and epileptic encephalopathy (*GRIN2D*-related DEE) is an autosomal dominant disorder typically caused by a *de novo* pathogenic missense variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with *GRIN2D*-related DEE whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo GRIN2D* pathogenic missense variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable 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 cells only.

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

- If the proband represents a simplex case (i.e., the only affected family member) and the *GRIN2D* 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 theoretic possibility of parental mosaicism [Rahbari et al 2016].
- 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 found to be 10% [Myers et al 2018].

Offspring of a proband. Individuals with a *GRIN2D*-related DEE are not known to reproduce; however, many are not yet of reproductive age.

Other family members. Given that all probands with *GRIN2D*-related DEE reported to date have the disorder as the result of a confirmed or apparent *de novo GRIN2D* 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 GRIN2D* pathogenic variant. However, based on the theoretic possibility of parental mosaicism (reported to be 10% in one study on apparently asymptomatic parents of children with developmental and epileptic encephalopathy [Myers et al 2018]), the recurrence risk to sibs is estimated to be 1% [Rahbari et al 2016]. Given this risk, prenatal testing 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
- **MedlinePlus**
  Intellectual Disability
- **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
- **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. GRIN2D-Related Developmental and Epileptic Encephalopathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GRIN2D	19q13.33	Glutamate receptor ionotropic, NMDA 2D	GRIN Portal - GRIN2D	GRIN2D	GRIN2D

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 GRIN2D-Related Developmental and Epileptic Encephalopathy (View All in OMIM)

602717	GLUTAMATE RECEPTOR, IONOTROPIC, N-METHYL-D-ASPARTATE, SUBUNIT 2D; GRIN2D
617162	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 46; DEE46

Molecular Pathogenesis

N-methyl D-aspartate receptors (NMDARs) are ligand-gated subunit receptors that mediate excitatory synaptic transmission in the central nervous system. NMDARs, tetrameric assemblies of two GluN1 and two GluN2 subunits, play important roles in brain development, synaptic plasticity, learning, and memory.

The NMDARs encoded by the GRIN gene family include *GRIN1*, *GRIN2A*, *GRIN2B*, *GRIN2C*, *GRIN2D*, *GRIN3A*, and *GRIN3B*.

All GluN subunits have a similar structure: an amino terminal domain (ATD), an agonist-binding domain (ABD; S1 and S2), a transmembrane domain (M1, M2, M3, and M4), and a C-terminal domain (CTD) [Traynelis et al 2010]. Previous studies suggested that three control elements – the pre-M1 helix, the M3 transmembrane helix (especially the SYTANLAAF motif), and the M4 transmembrane helix/pre-M4 region – play important roles in NMDAR channel gating. Moreover, pathogenic missense variants specifically affecting these regions in other NMDAR subunits such as *GRIN1*, *GRIN2A*, and *GRIN2B* have been shown to cause neurodevelopmental disorders with epilepsy.

Mechanism of disease causation. *De novo* missense variants in *GRIN2D* disrupt the GluN-2D-subunit of the NMDAR and result in either loss- or gain-of-function effects on the receptor.

***GRIN2D*-specific laboratory technical considerations.** To date, all reported *GRIND2D*-related DEE-causing pathogenic variants have been missense variants.

Chapter Notes

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The authors (Konrad Platzer, Ilona Krey, and Johannes Lemke) are available to help clinicians evaluate variants of uncertain significance in *GRIN2D* (and all other NMDAR subunit genes) and, if appropriate, can initiate functional testing in the Center for Functional Evaluation of Rare Variants at Emory University, Atlanta, Georgia, USA.

The authors are actively involved in clinical research regarding individuals with GRIN disorders (*GRIN1*, *GRIN2A*, *GRIN2B*, and *GRIN2D*). They would be happy to communicate with persons who have any questions regarding diagnosis of GRIN disorders or other considerations (e.g., variants in GRIN genes not yet associated with a mendelian disorder: *GRIN2C*, *GRIN3A*, and *GRIN3B*).

The authors are also interested in hearing from clinicians treating families affected by developmental and epileptic encephalopathy in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

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