U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Tümer Z, Dye TJ, Prada C, et al. *DLG4*-Related Synaptopathy. 2023 Jun 22. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

DLG4-Related Synaptopathy

Zeynep Tümer, MD, PhD, DMSc,[1,2] Thomas J Dye, MD,[3] Carlos Prada, MD,[4] Alexandre M White-Brown, MSc,[5] Alex MacKenzie, MD,[5] and Amanda M Levy, MSc[1]

Created: June 22, 2023.

Summary

Clinical characteristics

DLG4-related synaptopathy is characterized by developmental delay, intellectual disability (most commonly in the mild-to-moderate range), and autism spectrum disorder. About half of affected individuals have epilepsy. Regression in motor development and/or language has been reported in about 40% of affected individuals. Other neurologic findings can include hypotonia, movement disorder (most commonly stereotypies and ataxia), dystonia, tremor, and migraine headaches. Sleep disturbance is common, with sleep onset and/or sleep maintenance difficulties being frequently reported. Strabismus is the most common ocular finding followed by hyperopia, nystagmus, and cortical blindness. Vomiting is observed in a number of individuals and can be triggered by seizures, motion sickness, or fatigue. Joint laxity is a relatively common finding (36.9%), and scoliosis is noted in 20% of individuals.

Diagnosis/testing

The diagnosis of *DLG4*-related synaptopathy is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in *DLG4* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no cure for *DLG4*-related synaptopathy. Supportive care includes standard treatment for developmental delay / intellectual disability, epilepsy, migraine, ataxia, dystonia, refractive errors,

Author Affiliations: 1 Department of Clinical Genetics, Kennedy Center, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; Email: zeynep.tumer@regionh.dk; Email: marie.amanda.bust.levy@regionh.dk. 2 Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; Email: zeynep.tumer@regionh.dk. 3 Division of Neurology, Division of Pulmonary – Sleep Medicine, Cincinnati Children's Hospital Medical Center; Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio. 4 Division of Genetics, Genomics & Metabolism Ann & Robert H Lurie Children's Hospital of Chicago;, Department of Pediatrics, Feinberg School of Medicine of Northwestern University, Chicago, Illinois; Email: cprada@luriechildrens.org. 5 Department of Medical Genetics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada; Email: awhitebrown@cheo.on.ca; Email: mackenzie@cheo.on.ca.

strabismus, and cerebral visual impairment. Behavioral therapy may aid those who have insomnia, while pharmacotherapy may be considered in those who have refractory sleep disturbance.

Surveillance: At each visit, monitor those with seizures; assess for new manifestations such as seizures, changes in tone, movement disorders, and migraine headaches; monitor developmental progress and educational needs; assess mobility and self-help skills; and assess for signs/symptoms of sleep disturbance. At each visit after infancy, assess for behavioral issues such as anxiety, autism spectrum disorder, attention-deficit/hyperactivity disorder, aggression, or self-injury. Annually or as clinically indicated, ophthalmology evaluation; and 24-hour EEG in those with significant cognitive/behavioral delay, developmental regression, or abnormal routine EEG.

Genetic counseling

DLG4-related synaptopathy is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Rarely, individuals diagnosed with *DLG4*-related synaptopathy inherited a *DLG4* pathogenic variant from a heterozygous or mosaic parent. In general, the risk to other family members is presumed to be low. However, once a *DLG4* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *DLG4*-related synaptopathy have been published.

Suggestive Findings

DLG4-related synaptopathy **should be considered** in individuals with the following clinical brain MRI findings and family history.

Clinical findings

- Mild-to-severe developmental delay (DD) or intellectual disability (ID)

AND

- Any of the following features presenting in infancy or childhood:
  - Generalized hypotonia
  - Developmental regression
  - Movement disorder, including stereotypies, ataxia, dystonia, and tremor
  - Generalized or focal epilepsy, with or without epileptic encephalopathy
  - Sleep problems, including issues with sleep onset and/or sleep maintenance
  - Neuropsychiatric/behavioral issues, such as autism spectrum disorder, attention-deficit/hyperactivity disorder, and/or anxiety
  - Ophthalmologic involvement, including strabismus, nystagmus, hyperopia, and cortical blindness
  - Skeletal manifestations, such as joint laxity and scoliosis
  - Gastroenteric disturbances, such as feeding difficulties at birth or in early infancy, gastroesophageal reflux disease, and/or vomiting
  - Nonspecific dysmorphic features (See Clinical Description.)

Brain MRI findings

- Brain or cerebellar atrophy
- Abnormalities of the corpus callosum
- Abnormalities of the hippocampus, including a dysmorphic appearance

Family history. Because *DLG4*-related synaptopathy is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of *DLG4*-related synaptopathy **is established** in a proband with suggestive clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *DLG4* identified by molecular genetic testing (see Table 1).

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) Identification of a heterozygous *DLG4* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability (ID) may begin with a large **multigene panel** (including all the known ID-related genes at the time of genetic testing) or **exome/genome sequencing**. Note: Single-gene testing (sequence analysis of *DLG4*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An ID or epilepsy multigene panel** that includes *DLG4* 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 *DLG4*-related synaptopathy and how recently it has been described, some panels for ID or epilepsy may not yet include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome or genome 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.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved prior to testing. **Exome sequencing** is most commonly used and yields results similar to an ID/epilepsy multigene panel, with the additional advantage that exome sequencing includes genes recently identified as causing ID, whereas some multigene panels may not.

  Genome sequencing is also possible and has the additional advantage of detecting single or multiexon deletions/duplications and deep intronic variants.

  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 *DLG4*-Related Synaptopathy

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
DLG4	Sequence analysis [3]	100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported [7]

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, unless the testing is on a whole genome sequencing platform. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020] and from Rodríguez-Palmero et al [2021]
5. For synonymous or deep intronic variants that are predicted to affect splicing by in silico tools, RNA testing (RT-PCR or RNA sequencing) on blood can be considered to establish the pathogenicity of the variant [Z Tümer, personal observation] (see Molecular Genetics).
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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Zeesman et al [2012]) may not be detected by these methods. For review of individuals with a larger 17p13.1 deletion that include *DLG4* and adjacent genes, see Genetically Related Disorders.
7. Gene-targeted deletion/duplication analysis has not identified any deletions/duplications to date [Rodríguez-Palmero et al 2021].

Clinical Characteristics

Clinical Description

To date, about 100 individuals have been identified with a pathogenic variant in *DLG4* [Rodríguez-Palmero et al 2021; Authors, personal observation]. Information about individuals with larger deletions of 17p13.1 that include *DLG4* and adjacent genes is not included in this chapter. The following description of the phenotypic features associated with *DLG4*-related synaptopathy is based on 53 reported individuals.

Table 2. Select Features of *DLG4*-Related Synaptopathy

Feature	% of Persons w/Feature [1]	Comment
Intellectual disability	100% (45/45)	Most commonly in mild-to-moderate rage
Developmental delay in >1 developmental domain	84% (38/45)	Developmental regression is observed in 40% (17/43).
Autism spectrum disorder	56% (24/43)	More commonly found in persons who have moderate-to-severe ID
Attention-deficit/hyperactivity disorder	57% (20/35)	Observed more frequently in persons w/ASD
Anxiety	53% (20/38)	
Epilepsy	53% (25/47)	Generalized or focal; ESES may also occur.
Hypotonia	53% (23/43)	
Ophthalmologic findings	50% (23/46)	Incl nystagmus &/or strabismus
Abnormal movements	46% (19/41)	Most commonly stereotypies & ataxia
Sleep issues	45% (17/38)	Incl issues w/sleep onset &/or sleep maintenance
Joint laxity	36% (16/44)	

Table 2. continued from previous page.

Feature	% of Persons w/Feature [1]	Comment
Vomiting	29% (10/35)	Vomiting can be episodic or occur in assoc w/seizures, fatigue, &/or motion sickness.
Marfanoid habitus	24% (9/38)	Incl long face, slender body habitus, pectus excavatum, &/or long & thin fingers

ASD = autism spectrum disorder; ESES = electrical status epilepticus in sleep; ID = intellectual disability
1. The numerator is the number of known individuals with this feature and the denominator is the number of individuals evaluated for the specific feature.

Developmental delay (DD) and intellectual disability (ID). DD before age two years is one of the first signs of *DLG4*-related synaptopathy, although DD may not be appreciated until later in childhood. DD in more than one developmental domain is seen in most individuals. Others may have isolated motor or language delay, with a subset (approximately 20%) being nonverbal. ID is ubiquitous in individuals reported in the literature, with a relatively equal frequency of affected individuals falling into the mild, moderate, and severe ranges. The average age of walking is 20.7 months, and the average age of first words is 32.2 months.

Regression in motor development and/or language has been reported in about 40% of affected individuals. Most of the individuals with language regression (with or without motor regression) had autism spectrum disorder (ASD), but not all the individuals with ASD had language regression.

- Epilepsy can be associated with developmental regression, as about 50% of individuals with epilepsy were reported to have regression, compared to 22% of those without epilepsy.
- Infection may also be another triggering factor for developmental regression.

Other neurologic features

- Hypotonia is observed in about half of affected individuals, while spasticity has only been observed in a few individuals.
- Movement disorders, most commonly stereotypies and ataxia, develop in about half of affected individuals, often becoming apparent in childhood. Dystonia and tremor are also observed in some affected individuals.
- Migraine headache is reported by several parents and may be an underdiagnosed feature.

Epilepsy. About 50% of affected individuals have epilepsy.

- Both generalized and focal seizures have been described, although focal seizures are more common.
- Febrile seizures, infantile spasms, and electrical status epilepticus in sleep (ESES) have also been observed [Tassinari & Rubboli 2019].
- The mean age of onset of the first seizure is six years (range: 6 months to 15 years).
- EEG may show focal abnormalities (which may be multifocal), an abnormal background, or, less frequently, generalized abnormalities.

Neuropsychiatric/behavioral issues

- ASD is reported in 56% of affected individuals and is more often diagnosed in those with moderate-to-severe ID than in those with mild ID. ASD is also common in individuals with language regression, but not all those with ASD have language regression.
- Attention-deficit/hyperactivity disorder (ADHD) is reported in 57% of affected individuals and tends to occur more frequently in those with a co-occurring ASD diagnosis.
- Anxiety, which can be triggered by different factors such as sound or separation, is reported in about 50% of affected individuals and may be present starting in childhood.

Sleep disturbances are common, with sleep onset and/or sleep maintenance difficulties being frequently reported.

- Circadian rhythm abnormalities, including advanced sleep-wake phase, have also been seen.
- The sleep disturbances may overlap with nocturnal epilepsy.

Growth. Prenatal and postnatal growth is typically in the normal range for weight, length/height, and head circumference.

Ophthalmologic. Strabismus is the most common ocular finding, followed by hyperopia, nystagmus, and cortical blindness. Myopia, amblyopia, and slow upgaze are also seen but less frequently.

Neuroimaging. Thirty percent of individuals who have undergone neuroimaging have abnormalities, including atrophy of the cerebrum/cerebellum, thinning of the corpus callosum, and a dysmorphic appearance (abnormal morphology) of the hippocampus. Abnormal imaging is more common in individuals with moderate or severe ID.

Other associated features

- **Gastrointestinal issues.** Vomiting is observed in a number of individuals and can be triggered by seizures, motion sickness, or fatigue.
- **Musculoskeletal features.** Joint laxity is a relatively common finding (36%), and scoliosis is noted in 20% of individuals. Marfanoid habitus (long face, slender body habitus, pectus excavatum, and/or long and thin fingers) has been noted in some individuals.
- **Facial features.** No specific dysmorphic features have been observed. If present, dysmorphic features are nonspecific.

Prognosis. Life expectancy in *DLG4*-related synaptopathy is unknown. One reported individual is alive at age 47 years [Rodríguez-Palmero et al 2021], demonstrating that survival into adulthood occurs. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that this condition is often unrecognized, and thus underreported, in adults.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

This condition is sometimes referred to by the acronym SHINE (*s*leep disturbances, *h*ypotonia, *i*ntellectual disability, *n*eurologic disorder, and *e*pilepsy).

Prevalence

DLG4-related synaptopathy is rare, but its exact prevalence is unknown. Only 53 individuals with pathogenic *DLG4* variants have been published [Rodríguez-Palmero et al 2021]. However, through collaborations with the SHINE Syndrome Foundation (see Resources), approximately 100 individuals diagnosed with a pathogenic *DLG4* variant have been identified.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *DLG4*.

Contiguous gene deletions in the 17p13.1 region encompassing *DLG4* and adjacent genes have been reported [Zeesman et al 2012]. These individuals have distinctive facial features, microcephaly, mild developmental delay, joint laxity, and intellectual disability. Thus, there is a partial overlap with features of *DLG4*-related synaptopathy.

Sporadic tumors (including digestive system neoplasms like esophageal and gastric cancer) can contain a somatic *DLG4* variant occurring in a single tumor that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable, and individuals do not have features of *DLG4*-related synaptopathy [Zhang et al 2022].

Differential Diagnosis

The phenotypic features associated with *DLG4*-related synaptopathy are not sufficiently characteristic to diagnose this condition without molecular genetic testing. Clinical features of *DLG4*-related synaptopathy overlap with several nonspecific syndromic intellectual disabilities, especially those observed in other synaptopathies such as *SYNGAP1*-related intellectual disability.

All disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Phenotypic Series:

- Autosomal dominant intellectual developmental disorder
- Autosomal recessive intellectual developmental disorder
- Nonsyndromic X-linked intellectual developmental disorder
- Syndromic X-linked intellectual developmental disorder

Management

No clinical practice guidelines for *DLG4*-related synaptopathy have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *DLG4*-related synaptopathy, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. *DLG4*-Related Synaptopathy: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• If not already performed, brain MRI can be considered in those w/abnormal neurologic exam &/or seizures. • Baseline routine EEG • Consider 24-hour EEG to evaluate for ESES or subclinical seizure activity, particularly in persons w/developmental regression or abnormal routine EEG. • Assess older children, adolescents, & adults for signs/symptoms of migraine headaches.
Ataxia / Movement disorders	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Neuropsychiatric	Neuropsychiatric eval	• Formal autism eval in those w/findings suggestive of ASD • For persons age >12 months: screening for ADHD, anxiety, &/or depression
Behavioral	Behavioral/clinical psychology eval	For persons aged >12 months: screening for behavioral concerns such as aggression, impulsivity, & self-injury
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Scoliosis & joint laxity • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Eyes	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, & strabismus that may require referral for subspecialty care &/or low vision services
Respiratory	Assessment for signs/symptoms of sleep disturbances	• Sleep diary for eval of circadian disruption • Consider polysomnogram & referral to sleep specialist. • Assess for concurrent medications that could be contributing to sleep disruption.
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of *DLG4*-related synaptopathy to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community and 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; ESES = electrical status epilepticus in sleep; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Such evaluations may include measurement of vitamin D and vitamin B_2 levels. In children with sleep disruption, iron, ferritin, and total iron-binding capacitiy can be measured.

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *DLG4*-related synaptopathy.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. *DLG4*-Related Synaptopathy: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by experienced neurologist or epileptologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Migraine	Standard treatment per neurologist	Consider migraine mimics, such as sinus disease, in children w/speech-language delay
Ataxia	Physical medicine & rehab / PT & OT / movement disorder specialist	• Adjustments to classroom or therapy setting to allow for better truncal support • Mobility, ADL, & need for adaptive devices for home/school
Dystonia	Standard treatment per neurologist	
Eye issues	Standard treatment per ophthalmologist	For refractive errors, strabismus
	Low vision services	• Children: through early intervention programs &/or school • Adults: low vision clinic &/or community vision services / OT / mobility services
Cerebral visual impairment	No specific treatment	Early intervention program to stimulate visual development
Sleep disturbances	• Behavioral therapy for insomnia • Consider pharmacotherapy for refractory cases	Assess for concurrent medications that could be contributing to sleep disruption.
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. 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 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, privatesupportive 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).
- 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 during infancy or early childhood 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 and adolescents 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 5 are recommended.

Table 5. *DLG4*-Related Synaptopathy: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	Monitor those w/seizures as clinically indicated.	At each visit
	Assess for new manifestations such as seizures, changes in tone, movement disorders, & migraine headaches.	
	Consider 24-hour EEG in those w/significant cognitive/behavioral delay, developmental regression, or abnormal routine EEG.	As clinically indicated
Development	Monitor developmental progress & educational needs.	At each visit
Neuropsychiatric/ Behavioral	Behavioral assessment for anxiety, ADHD, ASD, aggression, or self-injury	At each visit after infancy
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	At each visit
Ophthalmologic involvement	Ophthalmology eval	Annually, or as clinically indicated
Respiratory	Clinical assessment for signs/symptoms of sleep disturbance	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; 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.

Pregnancy Management

Although there has not as yet been documentation of a pregnancy in a person with *DLG4*-related synaptopathy, it is possible for those who are mildly affected.

In general, women with *DLG4*-related synaptopathy who have epilepsy or seizures are at greater risk for mortality during pregnancy than pregnant women without seizures; use of anti-seizure medication (ASM) during pregnancy reduces this risk. However, exposure to ASM may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which the medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from ASM exposure is often less than that associated with exposure to untreated maternal seizures. Therefore, ASM to treat maternal seizures during pregnancy is typically recommended. Discussion of the risks and benefits of using a given ASM during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

See MotherToBaby for further information on medication use during pregnancy.

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

DLG4-related synaptopathy is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most probands reported to date with *DLG4*-related synaptopathy whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo DLG4* pathogenic variant.
- Rarely, individuals diagnosed with *DLG4*-related synaptopathy inherited a *DLG4* pathogenic variant from a parent with somatic mosaicism or parents with suspected germline mosaicism [Rodríguez-Palmero et al 2021].
- 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 [Rodríguez-Palmero et al 2021]. 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 a parent of the proband is known to have the *DLG4* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *DLG4* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is only slightly greater than that of the general population because of the possibility of parental germline mosaicism [Rodríguez-Palmero et al 2021].

Offspring of a proband. Each child of an individual with *DLG4*-related synaptopathy has a 50% chance of inheriting the *DLG4* pathogenic variant.

Other family members. Given that most probands with *DLG4*-related synaptopathy reported to date have the disorder as the result of a *de novo DLG4* 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

Once the *DLG4* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **SHINE Syndrome Foundation**

  Email: contact@shinesyndrome.org

  https://shinesyndrome.org/wp/

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**

  Phone: 202-387-1968

  Fax: 202-387-2193

  www.aaidd.org

- **MedlinePlus**

Intellectual Disability

- **CoRDS Registry for SHINE Syndrome**
  A patient-centered exploration of DLG4-related synaptopathy.
  www.shinesyndrome.org/wp/cords
- **Simons Searchlight Research Registry for DLG4 Synaptopathy/SHINE Syndrome**
  https://shinesyndrome.org/wp/simons/

Molecular Genetics

Note on Table A, **Locus-Specific Databases**: see also the DECIPHER database.

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. DLG4-Related Synaptopathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DLG4	17p13.1	Disks large homolog 4	DLG4 @ LOVD DLG4 - DECIPHER	DLG4	DLG4

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 DLG4-Related Synaptopathy (View All in OMIM)

602887	DISCS LARGE MAGUK SCAFFOLD PROTEIN 4; DLG4
618793	INTELLECTUAL DEVELOPMENTAL DISORDER, AUTOSOMAL DOMINANT 62; MRD62

Molecular Pathogenesis

DLG4 encodes disks large homolog 4 (DLG4), also called postsynaptic density protein 95 (PSD-95), which plays a crucial role in the postsynaptic region of excitatory (glutamatergic) neurons, as it organizes the key components of the postsynaptic density essential for synaptic signaling, development, and survival. DLG4 contains three PDZ domains, a SH3 domain, and a GK domain. DLG4 interacts directly or indirectly with several proteins, including glutamate receptors (such as NMDA and AMPA receptors), ion channels (such as Shaker type K^+ channels), cell adhesion molecules (such as neuroligin), transmembrane proteins (such as ADAM22), and SYNGAP1, which are also involved in neurodevelopmental disorders with or without epilepsy. The overlapping symptoms observed in *DLG4*-related synaptopathy and other neurodevelopmental disorders suggest that pathogenic variants in *DLG4* likely disrupt the normal function of glutamatergic synapses during development and later in life, either directly or indirectly by affecting the normal function of DLG4 interaction partners [Levy et al 2022].

Mechanism of disease causation. Most reported disease-causing *DLG4* variants are protein truncating and predicted to be loss of function (LoF) variants.

There are also a few heterozygous likely pathogenic *DLG4* missense variants that may also be LoF variants, but this hypothesis has yet to be proven [Levy et al 2022]. Furthermore, a silent variant was shown to affect RNA splicing and predicted to be a LoF variant [Rodríguez-Palmero et al 2021]. Further, for variants where RNA escapes nonsense-mediated decay, a dominant-negative effect cannot be excluded.

***DLG4*-specific laboratory technical considerations: gene annotation.** *DLG4* variants are in general annotated using one of the following transcripts:

- NM_001321075.3 consists of 20 exons and encodes the alpha isoform of 724 amino acids (NP_001308004.1). This isoform is the major isoform expressed in the brain.
- NM_001365.4 consists of 22 exons and encodes the beta isoform of 767 amino acids (NP_001356.1).

The main difference between these two transcripts is the presence of two extra exons at the 5' end of the gene in the longer transcript (NM_001365.4).

In case of synonymous or deep intronic variants that are predicted to affect splicing by in silico tools, RNA testing (RT-PCR or RNA sequencing) could be considered to establish the pathogenicity of the variant. This can be successfully performed using peripheral blood, as the gene is expressed in low levels in this tissue [Z Tümer, personal communication].

Chapter Notes

Author Notes

Zeynep Tümer, zeynep.tumer@regionh.dk

- Clinical work: genetic diagnosis of neurodevelopmental disorders and congenital imprinting disorders
- Research interests: understanding the underlying molecular mechanisms involved in monogenic and complex neurodevelopmental disorders
- Web page: www.rigshospitalet.dk

Thomas J Dye, thomas.dye@cchmc.org

- Clinical work: pediatric sleep medicine, neurodevelopmental disorders, sleep-related movement disorders and epilepsy
- Research interests: understanding sleep and circadian disruption of neurodevelopmental disorders
- Web page: www.cincinnatichildrens.org

Carlos Prada, cprada@luriechildrens.org

- Clinical work: neurofibromatosis, RASopathies, lysosomal storage disorders, metabolic disorders, and implementation of genomics in clinical care
- Research interests: development of biomarkers for rare diseases, clinical trials, and gene discovery
- Web page: www.luriechildrens.org

Alexandre White-Brown, awhitebrown@cheo.on.ca

- Research interests: development of strategies to improve the diagnostic care of individuals with rare genetic disease; exploring the use of artificial intelligence to identify patients with undiagnosed rare genetic diseases

Alex MacKenzie, MacKenzie@cheo.on.co

- Clinical work: general pediatrician
- Research interests: therapies for rare neurogenetic disorders
- Web page: www.cheoresearch.ca

Amanda Levy, marie.amanda.bust.levy@regionh.dk

- Research interests: understanding the genetic and functional mechanisms of rare neurodevelopmental disorders

Acknowledgments

The patient support group SHINE Syndrome Foundation is acknowledged for collaboration and their contribution to understanding the phenotype and genotype of the condition. The board members of the foundation have also made invaluable suggestions to the chapter.

Revision History

- 22 June 2023 (ma) Review posted live
- 5 December 2022 (zt) Original submission

References

Literature Cited

Levy AM, Gomez-Puertas P, Tümer Z. Neurodevelopmental disorders associated with PSD-95 and its interaction partners. Int J Mol Sci. 2022;23:4390. PubMed PMID: 35457207.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Rodríguez-Palmero A, Boerrigter MM, Gómez-Andrés D, Aldinger KA, Marcos-Alcalde Í, Popp B, Everman DB, Lovgren AK, Arpin S, Bahrambeigi V, Beunders G, Bisgaard AM, Bjerregaard VA, Bruel AL, Challman TD, Cogné B, Coubes C, de Man SA, Denommé-Pichon AS, Dye TJ, Elmslie F, Feuk L, García-Miñaúr S, Gertler T, Giorgio E, Gruchy N, Haack TB, Haldeman-Englert CR, Haukanes BI, Hoyer J, Hurst ACE, Isidor B, Soller MJ, Kushary S, Kvarnung M, Landau YE, Leppig KA, Lindstrand A, Kleinendorst L, MacKenzie A, Mandrile G, Mendelsohn BA, Moghadasi S, Morton JE, Moutton S, Müller AJ, O'Leary M, Pacio-Míguez M, Palomares-Bralo M, Parikh S, Pfundt R, Pode-Shakked B, Rauch A, Repnikova E, Revah-Politi A, Ross MJ, Ruivenkamp CAL, Sarrazin E, Savatt JM, Schlüter A, Schönewolf-Greulich B, Shad Z, Shaw-Smith C, Shieh JT, Shohat M, Spranger S, Thiese H, Mau-Them FT, van Bon B, van de Burgt I, van de Laar IMBH, van Drie E, van Haelst MM, van Ravenswaaij-Arts CM, Verdura E, Vitobello A, Waldmüller S, Whiting S, Zweier C, Prada CE, de Vries BBA, Dobyns WB, Reiter SF, Gómez-Puertas P, Pujol A, Tümer Z. DLG4-related synaptopathy: a new rare brain disorder. Genet Med. 2021;23:888-99. PubMed PMID: 33597769.

Sarma AK, Khandker N, Durczewski L, Brophy GM. Medical management of epileptic seizures: challenges and solutions. Neuropsychiatric Dis Treat. 2016;24:467-85.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Tassinari CA, Rubboli G. Encephalopathy related to status epilepticus during slow sleep: current concepts and future directions. Epileptic Disord. 2019;21:82-7. PubMed PMID: 31180330.

Zeesman S, Kjaergaard S, Hove HD, Kirchhoff M, Stevens JM, Nowaczyk MJM. Microdeletion in distal 17p13.1: A recognizable phenotype with microcephaly, distinctive facial features, and intellectual disability. Am J Med Genet Part A. 2012;158A:1832-6. PubMed PMID: 22753084.

Zhang Y, Li J, Feng D, Peng X, Wang B, Han T, Zhang Y. Systematic analysis of molecular characterization and clinical relevance of liquid-liquid phase separation regulators in digestive system neoplasms. Front Cell Dev Biol. 2022;9:820174. PubMed PMID: 35252219.

License