DLG4
ICD-10-CM Code Request Coordination and Maintenance Committee Meeting

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SHINE Syndrome Foundation

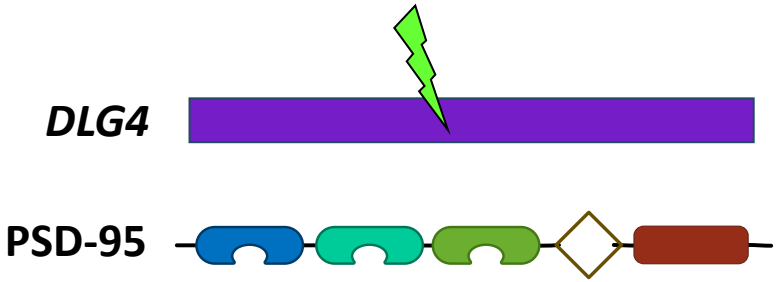
Love Fearlessly! SHINE Fearlessly!

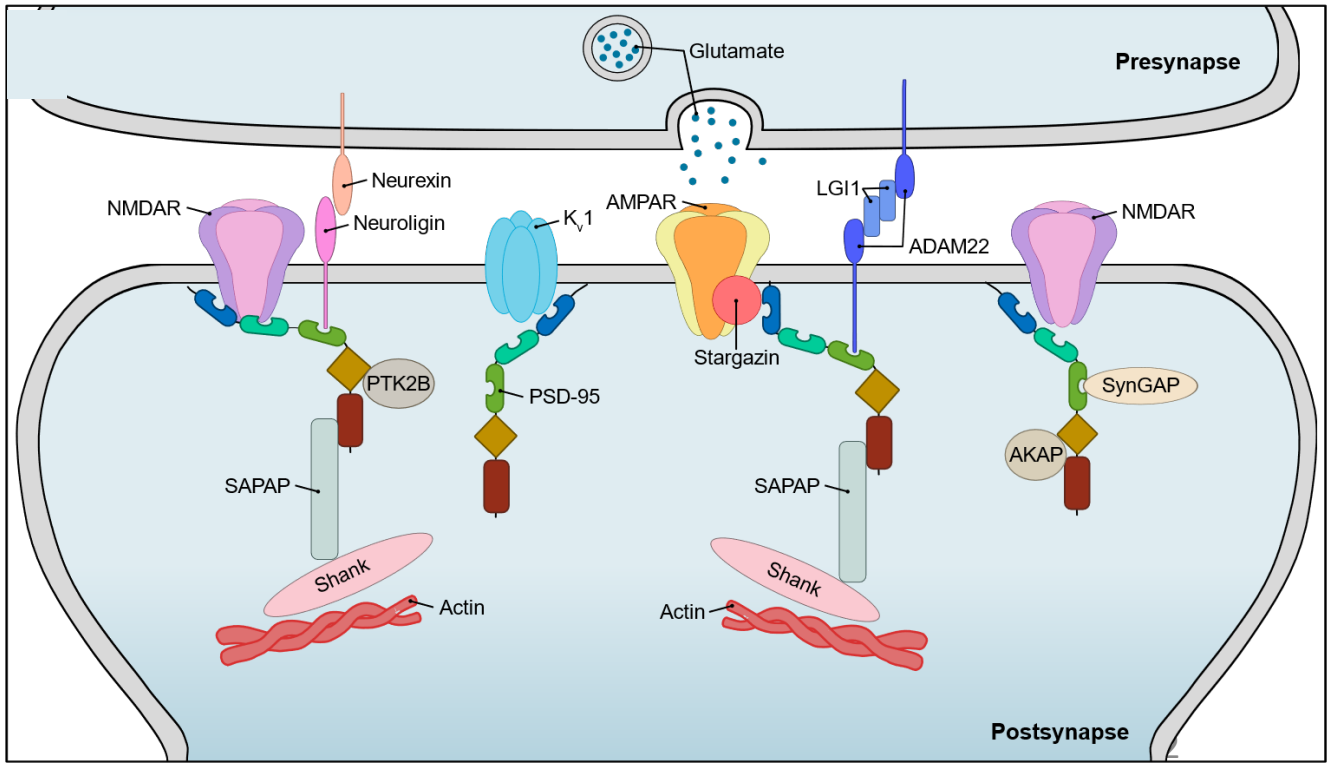
Our mission is to improve the quality of life for children and families impacted by SHINE Syndrome through supporting collaborative research among international medical professionals, nurturing a family community, and raising worldwide awareness.

DLG4-Related Synaptopathy

Newly defined neurodevelopmental disorder

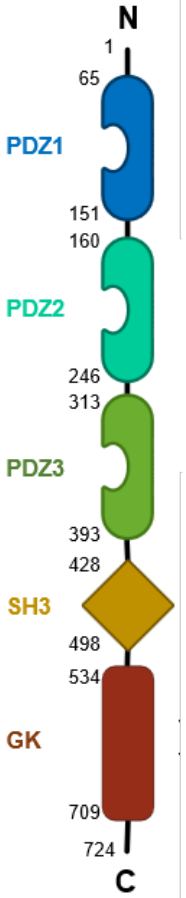
Heterozygous pathogenic variants in *DLG4*, encoding a protein (PSD-95) expressed in the postsynapses of excitatory neurons.





DLG4-Related Synaptopathy timeline

PSD-95



ARTICLE

DLG4-related synaptopathy: a new rare brain disorder

Agustí Rodríguez-Palmero et al.[#]

Genetics in Medicine (2021) 23:888–899; https://doi.org/10.1038/s41436-020-01075-9

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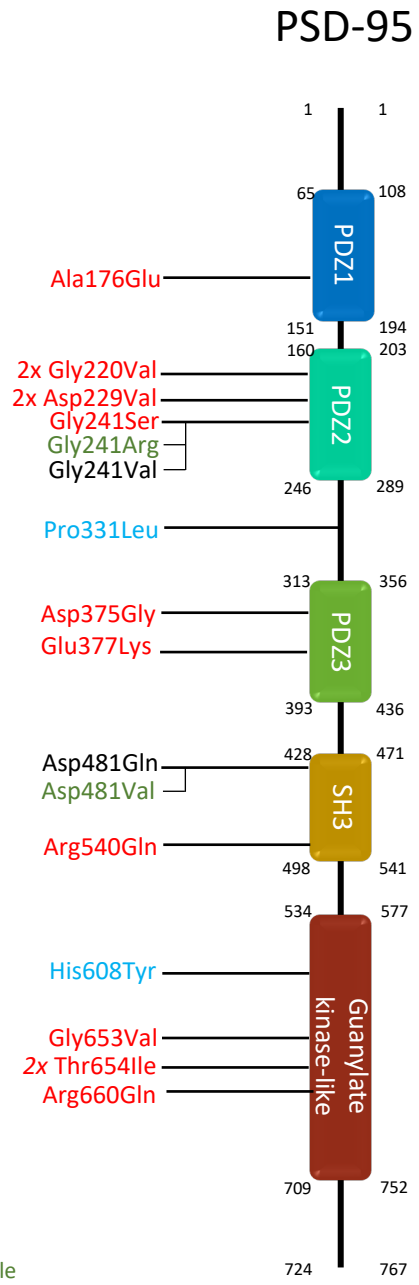
	individuals
2017	N=9
↓	
021	N=53
↓	
2023	N > 130

90 different variants
75 protein truncating
15 missense

DLG4 variant distribution

DLG4 missense variants

Approx. 15 different variants
Mainly in the functional domains



DLG4 truncating variants

Approx. 75 different variants
Distributed through out the gene

Red: Likely pathogenic/pathogenic
Blue: Clinical symptoms fit, but low in silico prediction
Black: clinical information not available
Green: also found in GnomAD, but clinical information not available

Disease name

618793

INTELLECTUAL DEVELOPMENTAL DISORDER, AUTOSOMAL DOMINANT 62; MRD62

Alternative titles; symbols

MENTAL RETARDATION, AUTOSOMAL DOMINANT 62

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Sleeping disturbances
Hypotonia
Intellectual disability
Neurological
Epilepsy

Clinical phenotype – data of 53 individuals

Feature	% of Persons	Comment
Intellectual disability	100 % (45/45)	Most commonly in the mild to moderate range
Developmental delay in more than one developmental domain	84% (38/45)	Developmental regression is observed in 40% (17/43), more common in those with ESES (22% versus 9%)
Autism spectrum disorder	56% (24/43)	More commonly found in individuals who have moderate to severe ID
Attention deficit/hyperactivity disorder	57% (20/35)	Observed more frequently in individuals with ASD
Anxiety	53% (20/38)	Not applicable
Epilepsy	53% (25/47)	Generalized or focal; electrical status epilepticus in sleep (ESES) may also occur
Hypotonia	53% (23/43)	Not applicable
Ophthalmologic findings	50% (23/46)	Including nystagmus and/or strabismus
Abnormal movements	46% (19/41)	Most commonly stereotypies and ataxia
Sleep problems	44% (17/38)	Including issues with sleep onset and/or sleep maintenance
Joint laxity	36% (16/44)	Not applicable
Vomiting	28% (10/35)	Vomiting can be episodic or occur in association with seizures, fatigue, and/or motion sickness
Marfanoid habitus	23% (9/38)	Including a long face, slender body habitus, pectus excavatum, and/or long and thin fingers

From Tümer et al. 2023, GeneReviews

Epilepsy phenotype – *data of 35 individuals*

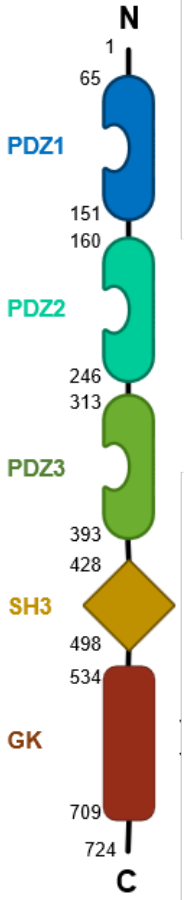
Category	Electroclinical feature	# of individuals (%)
Seizure type (*n=33*)	Focal	18 (54.5)
Seizure type (*n=33*)	Focal to bilateral	3 (9.1)
Seizure type (*n=33*)	Tonic-clonic	12 (36.4)
Seizure type (*n=33*)	Absences	4 (12.1)
Seizure type (*n=33*)	Myoclonic	3 (9.1)
Seizure type (*n=33*)	Tonic	2 (6.1)
Seizure type (*n=33*)	Spasms	2 (6.1)
Seizure type (*n=33*)	Atonic	1 (3.0)
Seizure type (*n=33*)	Unknown onset	1 (3.0)
Seizure type (*n=33*)	Status epilepticus	1 (3.0)
Seizure frequency at last follow up (*n=32*)	Seizure free	19 (59.4)
Seizure frequency at last follow up (*n=32*)	Rare	5 (15.6)
Seizure frequency at last follow up (*n=32*)	Daily	3 (9.4)
Seizure frequency at last follow up (*n=32*)	Monthly	3 (9.4)
Seizure frequency at last follow up (*n=32*)	Weekly	2 (6.3)
Interictal EEG (*n=30*)	Multifocal	17 (56.7)
Interictal EEG (*n=30*)	Focal	5 (16.7)
Interictal EEG (*n=30*)	Generalized	2 (6.7)
Interictal EEG (*n=30*)	Encephalopatic	2 (6.7)
Interictal EEG (*n=30*)	Hypsarrythmia	1 (3.3)
Ictal EEG (*n=6*)	Electrodecremental	3 (50.0)
Ictal EEG (*n=6*)	Multifocal	3 (50.0)
Ictal EEG (*n=6*)	Generalized	2 (33.3)
Ictal EEG (*n=6*)	Focal	2 (33.3)

Electroclinical features	Mean
Mean SWI in ESES/DEE-SWAS individuals (% of NREM sleep) (*n=6*)	70; range 40-100
Mean age of ESES/DEE-SWAS onset (years)	6.1; range 3-8

From Kassabian and Levy et al. To be submitted to Epilepsia

Phenotype Genotype correlation – *No clear correlation*

***DLG4* missense variants**



***DLG4* truncating variants**

There is a need for identifying new individuals

Current treatment – *symptomatic, no cure yet available*

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	General management	Not applicable
Epilepsy	Standardized treatment w/ASM by experienced neurologist or epileptologist	• Many ASMs may be effective; none have demonstrated efficacy specifically for this disorder. • Education of parents/caregivers
Migraine	Standard treatment per Neurology	Consider migraine mimics such as sinus disease in children with 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 Neurology	Not applicable
Eye issues	Standard treatment per Ophthalmologist	For refractive errors, strabismus
Eye issues	Low vision services	• Children: Through early intervention programs and/or school • Adults: Low vision clinic and/or community vision services/occupational therapy/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.

From Tümer et al. 2023, GeneReviews

Need for an ICD-10-CM code for *DLG4*-related synaptopathy (SHINE syndrome)

- **To define the disease in an individual**

  Currently, physicians have to use other codes that may describe the symptoms and associated conditions, but not the underlying disease. Other healthcare professionals will not necessarily know the underlying problem, but only the symptoms indicated in the electronic medical record.
- **Epidemiologic studies**
  - Prevalence estimation: *DLG4 is rare but the prevalence is unknown*
  - Defining all the characteristics of the disease including morbidity and mortality: *not available*
- **Understanding disease progression**

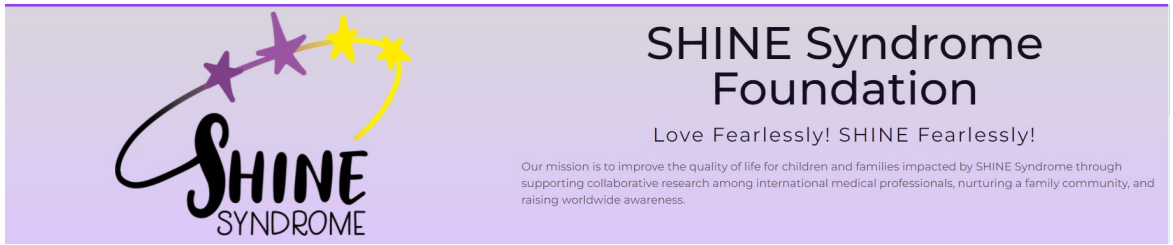
  No information yet available
- **Help with access to benefits and services**
- **Access to newly-approved medicine (e.g. for epilepsy)**

  A diagnosis code will make the approval process of a given medicine for SHINE syndrome easier
- **Genotype phenotype correlations**

  This information is crucial to design pharmacological and non-pharmacological treatments and track outcomes of clinical interventions. No phenotype-genotype correlations have yet been identified.

and the current ICD-10-CM codes do not cover these needs

Thank you for your consideration

Zeynep Tümer, MD, PhD, DMSc

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