DLG4-Related Synaptopathy (SHINE Syndrome): A Comprehensive Disease Characterization

Summary

DLG4-related synaptopathy (also called **SHINE syndrome**) is a rare, autosomal-dominant neurodevelopmental disorder caused by heterozygous, almost always *de novo*, predominantly loss-of-function variants in **DLG4**, the gene encoding the excitatory postsynaptic scaffold protein **PSD-95** (postsynaptic density protein 95). The disorder was formally defined and named in a landmark 2021 cohort of 53 patients (42 previously unpublished) carrying 45 different DLG4 variants, of which 39 were predicted to lead to loss of protein function [PMID: 33597769]. Its key identifiers are OMIM 618793 (Intellectual developmental disorder, autosomal dominant 62 / IDD62), MONDO:0032919, MedGen/UMLS C5394083, DOID:0061035, and GARD 0025775. The acronym SHINE captures its cardinal features: **S**leep disturbances, **H**ypotonia, **I**ntellectual disability/impairment, **N**eurological disorders, and **E**pilepsy.

Mechanistically, PSD-95 is a membrane-associated guanylate kinase (MAGUK) scaffold that stabilizes and traffics NMDA- and AMPA-type glutamate receptors at the postsynaptic density of excitatory synapses, governing synaptic maturation and plasticity. Loss of one functional DLG4 allele produces PSD-95 haploinsufficiency, disorganizing the glutamatergic postsynaptic density and impairing synaptic maturation and plasticity. The gene is among the most loss-of-function-intolerant genes in the human genome (gnomAD pLI = 1.0; LOEUF = 0.14), providing strong population-genetic support for a haploinsufficiency mechanism. The resulting clinical picture is dominated by early-onset global developmental delay, intellectual disability, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD), accompanied by hypotonia, sleep disturbance, movement disorders, and epilepsy (present in ~50%, with a distinctive regression-associated ESES/DEE-SWAS subtype in >25% of those with epilepsy).

Diagnosis is molecular, established by clinical whole-exome or whole-genome sequencing; splice-site and deep-intronic variants may require RNA/functional confirmation. There is currently **no disease-modifying therapy**; management is entirely supportive and symptom-directed, including antiseizure medications for epilepsy, developmental and rehabilitative

therapies, sleep and behavioral management, and — in at least one reported adolescent case — clozapine for treatment-resistant psychosis. This report integrates 10 confirmed findings and 19 reviewed papers to provide a full disease-knowledge-base characterization across all 15 requested sections.

Key Findings

Finding 1 — Definition and core identity of the disorder

DLG4-related synaptopathy is a rare autosomal-dominant neurodevelopmental disorder caused by *de novo* variants in DLG4/PSD-95. It was defined by the landmark cohort of Rodríguez-Palmero and colleagues, who reported *"the clinical and genetic features of 53 patients (42 previously unpublished) with DLG4 variants"* and proposed *"we designate this group of disorders as DLG4-related synaptopathy"* [PMID: 33597769]. Of the 45 different DLG4 variants they identified, *"39 were predicted to lead to loss of protein function and the majority occurred de novo"* [PMID: 33597769].

The disorder maps to the following identifiers: **OMIM 618793** (Intellectual developmental disorder, autosomal dominant 62 / IDD62), **MONDO:0032919**, **MedGen/UMLS C5394083**, **DOID:0061035**, and **GARD 0025775**. The causal gene **DLG4** is HGNC:2903, NCBI Gene 1742, UniProt **P78352**, located at chromosome **17p13.1**, and encodes PSD-95.

Finding 2 — Core clinical phenotype

The predominant clinical features are early-onset global developmental delay, intellectual disability, ASD, and ADHD. The original cohort found that *"the clinical picture was predominated by early onset global developmental delay, intellectual disability, autism spectrum disorder, and attention deficit-hyperactivity disorder, all of which point to a brain disorder"* [PMID: 33597769]. Additional features include hypotonia, sleep disturbance, movement disorders, strabismus, scoliosis, and joint hypermobility. Notably, the study refined an earlier claim: *"Marfanoid habitus, which was previously suggested to be a characteristic feature of DLG4-related phenotypes, was found in only nine individuals"* (9/53), and there was no distinct facial dysmorphism.

Epilepsy is a major feature. A dedicated epilepsy study noted that *"even though epilepsy is present in 50% of the individuals, it has not been investigated in detail"* and reported that *"encephalopathy related to status epilepticus during slow-wave sleep (ESES)/developmental epileptic encephalopathy with spike-wave activation during sleep (DEE-SWAS) was diagnosed in >25% of the individuals"* [PMID: 38135915]. Focal seizures were the most common type.

Suggested HPO terms: Intellectual disability (HP:0001249), Seizure (HP:0001250), Autistic behavior (HP:0000729), Attention deficit hyperactivity disorder (HP:0007018), Muscular hypotonia (HP:0001252), Sleep disturbance (HP:0002360), Strabismus (HP:0000486), Scoliosis (HP:0002650), Joint hypermobility (HP:0001382), Global developmental delay (HP:0001263), Cerebellar vermis atrophy (HP:0006855).

Finding 3 — Molecular mechanism (PSD-95 scaffolding of glutamate receptors)

PSD-95 scaffolds NMDA and AMPA receptors at the excitatory postsynaptic density; its loss impairs synaptic maturation and plasticity. As summarized in a review, *"postsynaptic density protein-95 (PSD-95) is a major regulator of synaptic maturation by interacting, stabilizing and trafficking N-methyl-d-aspartic acid receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid receptors (AMPARs) to the postsynaptic membrane"* [PMID: 29169997]. The original disease paper states that *"postsynaptic density protein-95 (PSD-95), encoded by DLG4, regulates excitatory synaptic function in the brain"* [PMID: 33597769].

At the molecular level, protein-truncating variants and at least one deep-intronic variant act by reducing functional protein. A patient-derived DLG4 V692Wfs*12 transcript illustrates the mechanism:* "the mutant transcript escapes nonsense-mediated decay but results in reduced PSD-95 protein expression"* [PMID: 42565830], demonstrating that even a transcript that evades NMD ultimately yields reduced PSD-95 protein — consistent with haploinsufficiency.

Suggested GO/CL terms: postsynaptic density (GO:0014069), dendritic spine (GO:0043197), glutamatergic synapse (GO:0098978), regulation of synaptic plasticity (GO:0048167); glutamatergic neuron (CL:0000679).

Finding 4 — Extreme loss-of-function intolerance supports haploinsufficiency

DLG4 is among the most constrained genes in the human genome. gnomAD constraint metrics for DLG4 (ENSG00000132535, chr17:7,187,187–7,219,841, GRCh38) show **pLI** = **1.0**; observed LoF variants = 7 versus expected 93.8 (**oe_lof** = **0.075**, 90% CI 0.042–0.140, i.e. **LOEUF** = **0.14**); LoF Z

= 7.60; missense Z = 6.06 (oe_mis = 0.55). This extreme depletion of loss-of-function variation in the general population is exactly the population-genetic signature expected for a haploinsufficient, dominant neurodevelopmental gene, and it strongly corroborates the mechanistic model that a single loss-of-function allele is sufficient to cause disease.

Finding 5 — Model organisms recapitulate cognitive, behavioral, and synaptic-plasticity deficits

Multiple mouse models and patient-derived cellular models support the disease mechanism:

- **PSD-95-null mice** show paradoxically enhanced hippocampal LTP with severely impaired learning: *"in mutant mice lacking PSD-95, the frequency function of NMDA-dependent LTP and LTD is shifted to produce strikingly enhanced LTP at different frequencies of synaptic stimulation"* and *"this frequency shift is accompanied by severely impaired spatial learning"* [PMID: 9853749].
- **PDZ1/2 ligand-binding-deficient PSD-95 knock-in mice** show reduced PSD accumulation of PSD-95/PSD-93/AMPARs, abnormal anxiety, and impaired spatial, working, and remote memory [PMID: 23268962].
- **Dlg4−/− mice** model ASD-relevant behavior: they *"showed increased repetitive behaviors, abnormal communication and social behaviors, impaired motor coordination, and increased stress reactivity and anxiety-related responses"* [PMID: 20952458].
- A **patient-derived Dlg4 V692Wfs*12/+ knock-in mouse** faithfully models the human disorder: *"Dlg4V692Wfs*12/+ mice recapitulate several hallmark features of SHINE syndrome, often in a sex-specific manner"* — including reduced PSD-95, learning/cognitive-flexibility deficits (male-biased), and sleep abnormalities [PMID: 42565830].
- A **patient iPSC line** (AOUMEYi004-A) carrying c.2155A>T p.(Arg719*) was established for in vitro disease modeling [PMID: 42462545].

Finding 6 — Management is supportive; no disease-modifying therapy

There is no targeted or curative therapy. Care is symptom-directed: antiseizure medications for epilepsy, developmental/rehabilitative therapies, and management of sleep and behavior. Antiseizure medication response was assessed retrospectively across 35 patients with epilepsy, with variable response and frequent refractoriness in the ESES/DEE-SWAS forms [PMID: 38135915]. For treatment-resistant psychosis, an adolescent with SHINE syndrome and early-onset schizophrenia/catatonia improved markedly on clozapine: *"after failing three antipsychotic drug treatments, the patient was started on clozapine, which resulted in significant*

improvements in positive and negative symptoms" [PMID: 37386468]. Experimental PSD-95-directed agents (e.g., nerinetide/Tat-NR2B9c, which disrupt the PSD-95/nNOS interaction) exist but are being developed for stroke and pain, **not** for this disorder [PMID: 40712457].

Finding 7 — Protein architecture and variant spectrum

PSD-95 (UniProt P78352, 724 aa) is a MAGUK with a characteristic modular architecture: three PDZ domains (PDZ1 aa 65–151, PDZ2 aa 160–246, PDZ3 aa 313–393), an SH3 domain (aa 428–498), and a guanylate kinase-like (GK) domain (aa 534–709), plus an N-terminal disordered region (aa 15–35). Twenty-two experimental PDB structures have been deposited. Pathogenic variants span the entire gene and include nonsense/frameshift (e.g., c.2155A>T p.Arg719*; c.2074_2075 frameshift p.Val692Trpfs*12 in the GK domain), splice-site, a deep-intronic pseudoexon variant (c.2105+235C>T), and six missense variants. *"The six missense variants identified were suggested to lead to structural or functional changes by protein modeling studies"* [PMID: 33597769], and across cohorts *"the majority [are] predicted to be protein-truncating"* [PMID: 37525972].

Finding 8 — Diagnosis, inheritance, and epidemiology

Diagnosis is molecular, established by clinical whole-exome or whole-genome sequencing identifying a heterozygous DLG4 variant; RNA/functional studies resolve splice and deep-intronic variants. In the landmark cohort, most cases were simplex/*de novo*: *"the majority occurred de novo (four with unknown origin)"* [PMID: 33597769]. A deep-intronic variant was *"identified using whole genome sequencing"* [PMID: 37525972], underscoring the value of WGS plus RNA studies when exome sequencing is unrevealing. Brain MRI and EEG (including sleep EEG/video-polygraphy for ESES/DEE-SWAS) are used for phenotyping: *"data on awake and sleep electroencephalography (EEG) and/or video-polygraphy and brain magnetic resonance imaging were collected"* [PMID: 38135915]. The disorder is ultra-rare (~53 patients in the defining 2021 series, with additional case reports since); no population prevalence or incidence has been established, and it is under-ascertained, including late/adolescent diagnoses [PMID: 40444229].

Finding 9 — Anatomy and temporal course

This is a brain-centered disorder affecting glutamatergic excitatory synapses. PSD-95 is *"an essential scaffolding protein during synaptogenesis and neurodevelopment"* [PMID: 29169997], localizing to the postsynaptic density of excitatory synapses. Primary organ: brain/nervous system; cell type: glutamatergic neurons (CL:0000679); subcellular compartment: postsynaptic density/dendritic spine (GO:0014069, GO:0043197). Some patients show cerebellar vermis

atrophy on MRI (HP:0006855, ~33% in the original small series). Onset is early (infancy/early childhood) with global developmental delay; the course is chronic and lifelong and generally non-degenerative, but developmental/verbal-motor regression can occur in those who develop status epilepticus in sleep: *"regression in verbal and/or motor domains was observed in all individuals who su[ffered status epilepticus]"* [PMID: 38135915].

Finding 10 — Purely genetic etiology; high evolutionary conservation

DLG4-related synaptopathy is monogenic with no established environmental, infectious, lifestyle, or gene-environment contribution; *de novo* germline DLG4 variants arise sporadically, consistent with *"the majority occurred de novo"* [PMID: 33597769]. No protective alleles or modifier genes have been identified. ClinVar (accessed 2026) lists ~445 DLG4 variant records: ~207 pathogenic, ~60 likely pathogenic, and ~316 of uncertain significance. DLG4/PSD-95 is deeply conserved: orthologs include mouse Dlg4 (NCBI Gene 13385, MGI:1277959), rat Dlg4 (NCBI Gene 29495), zebrafish dlg4a/dlg4b, Drosophila dlg1 (discs large), and C. elegans dlg-1; the MAGUK/PDZ–SH3–GK architecture is conserved from invertebrates to humans.

Comprehensive Section-by-Section Report

1. Disease Information

Overview. DLG4-related synaptopathy (SHINE syndrome) is a rare autosomal-dominant neurodevelopmental "synaptopathy" — a disorder of synaptic structure and function — caused by heterozygous, predominantly *de novo* loss-of-function variants in DLG4 (PSD-95). It presents in infancy/early childhood with global developmental delay and evolves into a lifelong picture of intellectual disability, autism, ADHD, hypotonia, sleep disturbance, movement disorders, and (in ~50%) epilepsy [PMID: 33597769, 38135915].

Key identifiers. OMIM **618793** (IDD62); MONDO:**0032919**; MedGen/UMLS **C5394083**; DOID:**0061035**; GARD **0025775**. Gene: DLG4 (HGNC:2903, NCBI Gene 1742, UniProt P78352, 17p13.1). A specific ICD-10/ICD-11 code is not assigned to this ultra-rare entity; it is captured under intellectual disability / developmental disorder categories. MeSH indexing is via DLG4/PSD-95 and intellectual disability terms.

Synonyms. SHINE syndrome (Sleep disturbances, Hypotonia, Intellectual disability, Neurological disorders, Epilepsy); Intellectual developmental disorder, autosomal dominant 62 (IDD62); DLG4-related synaptopathy; PSD-95-related neurodevelopmental disorder.

Information source. The knowledge base derives from aggregated disease-level resources (OMIM, ClinVar, gnomAD) plus published patient cohorts and case reports — i.e., published individual-patient data aggregated into cohorts, not routine EHR mining.

2. Etiology

Causal factors. Purely genetic: heterozygous DLG4 variants, most arising *de novo* [PMID: 33597769]. No environmental, infectious, or lifestyle cause is established (Finding 10).

Genetic risk factors. The causal variant itself is the sole established risk factor. DLG4 is extremely LoF-intolerant (pLI = 1.0; LOEUF = 0.14), meaning even a single loss-of-function allele confers disease (Finding 4). No susceptibility loci or modifier genes have been established.

Environmental risk factors / protective factors / gene-environment interactions. None identified. No protective alleles are known. Because most cases are *de novo*, advanced parental age (a general contributor to *de novo* mutation rates) is a plausible but unproven population-level consideration; this is not disease-specific evidence.

3. Phenotypes

Phenotype	Type	HPO term	Onset	Frequency/Notes
Global developmental delay	Clinical sign	HP:0001263	Infancy/early childhood	Predominant feature [PMID: 33597769]
Intellectual disability	Clinical sign	HP:0001249	Childhood	Core, variable severity [PMID: 33597769]
Autism spectrum disorder	Behavioral	HP:0000729	Childhood	Predominant [PMID: 33597769]
ADHD	Behavioral	HP:0007018	Childhood	Predominant [PMID: 33597769]
Hypotonia	Clinical sign	HP:0001252	Neonatal/ infancy	Common ("H" in SHINE)
Sleep disturbance	Symptom	HP:0002360	Childhood	Common ("S" in SHINE); modeled in mouse [PMID: 42565830]
Epilepsy/seizures	Clinical sign	HP:0001250	Childhood	~50%; focal most common [PMID: 38135915]
ESES/DEE-SWAS	Clinical sign	HP:0002133	Childhood	>25% of epilepsy patients; regression-associated [PMID: 38135915]
Movement disorder	Clinical sign	HP:0100022	Variable	Reported [PMID: 33597769]
Strabismus	Physical	HP:0000486	Childhood	Reported
Scoliosis	Physical	HP:0002650	Childhood	Reported
Joint hypermobility	Physical	HP:0001382	Childhood	Reported
Marfanoid habitus	Physical	HP:0001519	—	Only 9/53 — NOT characteristic [PMID: 33597769]
Cerebellar vermis atrophy	Imaging	HP:0006855	—	~33% in small series

Severity/progression. Severity is variable; the disorder is chronic and lifelong and generally non-degenerative. However, verbal/motor **regression** occurs in individuals who develop status epilepticus in sleep (ESES/DEE-SWAS) [PMID: 38135915].

Quality-of-life impact. Substantial: intellectual disability, autism, epilepsy, and sleep disturbance collectively impair communication, learning, independence, and family functioning. No disease-specific EQ-5D/SF-36/PROMIS data are available.

4. Genetic/Molecular Information

Causal gene. DLG4 (HGNC:2903; NCBI Gene 1742; OMIM gene 602887; UniProt P78352; 17p13.1) encoding PSD-95.

Pathogenic variants. Variants span the gene and are predominantly protein-truncating (nonsense, frameshift, splice-site), with a minority of missense and at least one deep-intronic pseudoexon variant. Examples: c.2155A>T p.(Arg719*) [PMID: 42462545]; c.2074_2075 frameshift p.(Val692Trpfs*12) in the GK domain [PMID: 42565830]; c.2105+235C>T deep-intronic [PMID: 37525972]. Of 45 variants in the defining cohort, 39 were predicted loss-of-function, and the six missense variants were modeled to disrupt structure/function [PMID: 33597769].

Variant classification (ClinVar, 2026). ~445 DLG4 records: ~207 pathogenic, ~60 likely pathogenic, ~316 uncertain significance (Finding 10). Per ACMG/AMP, truncating variants in this LoF-intolerant gene generally meet PVS1.

Allele frequency. Pathogenic variants are absent/vanishingly rare in gnomAD, consistent with *de novo* origin and extreme constraint (pLI = 1.0, LOEUF = 0.14).

Origin. Germline, predominantly *de novo* [PMID: 33597769]. No somatic disease association.

Functional consequence. Loss of function / haploinsufficiency (reduced PSD-95 protein) [PMID: 42565830]; some missense variants may act via structural disruption.

Modifier genes / epigenetics / chromosomal abnormalities. None established. DLG4 sits at 17p13.1; larger 17p deletions encompassing DLG4 could plausibly contribute but are not a defined mechanism for this entity.

5. Environmental Information

Not applicable. This is a monogenic disorder with no established environmental factors, lifestyle factors, or infectious agents (Finding 10) [PMID: 33597769].

6. Mechanism / Pathophysiology

Molecular pathway. Glutamatergic synaptic signaling. PSD-95 is the central organizer of the excitatory postsynaptic density (PSD), where it clusters and traffics NMDARs and AMPARs and couples them to downstream signaling (e.g., nNOS, SynGAP, CaMKII) [PMID: 29169997, 20554866].

Causal chain.

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DLG4 LoF variant (de novo, heterozygous)
        │
        ▼
Reduced functional PSD-95 protein (haploinsufficiency)
        │  (transcript may escape NMD but yields less protein — <a href="https://pubmed.ncbi.nlm
        ▼
Disorganized excitatory postsynaptic density:
  ↓ clustering/trafficking of NMDARs & AMPARs (<a href="https://pubmed.ncbi.nlm.nih.gov/23268962
        │
        ▼
Impaired synaptic maturation & aberrant plasticity
  (altered LTP/LTD; <a href="https://pubmed.ncbi.nlm.nih.gov/9853749/" rel="noopener noreferrer"
        │
        ▼
Disrupted neural circuit development (glutamatergic neurons)
        │
        ▼
Clinical manifestations: developmental delay, ID, ASD/ADHD,
hypotonia, sleep disturbance, epilepsy
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Upstream vs downstream. Upstream: the DLG4 variant and reduced PSD-95. Downstream: receptor mis-clustering, altered synaptic plasticity, circuit dysfunction, and behavior.

Cellular process. Synaptogenesis, synaptic maturation, and plasticity in glutamatergic neurons. **Protein dysfunction:** loss of function of a scaffold (not aggregation). **Immune/metabolic involvement:** none established. **Biochemical:** receptor scaffolding defect at the PSD.

Molecular profiling. No disease-specific human transcriptomic/proteomic/metabolomic signatures are published; mechanistic evidence derives from mouse models and in vitro biochemistry [PMID: 9853749, 23268962, 20952458, 20554866]. Patient iPSC lines now enable such profiling [PMID: 42462545].

Suggested GO terms: GO:0014069 (postsynaptic density), GO:0098978 (glutamatergic synapse), GO:0048167 (regulation of synaptic plasticity), GO:0007416 (synapse assembly), GO:0035249 (synaptic transmission, glutamatergic). **CL:** CL:0000679 (glutamatergic neuron).

7. Anatomical Structures Affected

- **Organ level:** Brain / central nervous system (primary). Body system: nervous system. **UBERON:** brain (UBERON:0000955), cerebral cortex (UBERON:0000956), hippocampus (UBERON:0002421), cerebellar vermis (UBERON:0004720; atrophy in a subset, HP:0006855).
- **Tissue/cell level:** Nervous tissue; glutamatergic excitatory neurons (CL:0000679).
- **Subcellular level:** Postsynaptic density (GO:0014069), dendritic spine (GO:0043197), postsynaptic membrane (GO:0045211).
- **Lateralization:** Bilateral (diffuse CNS involvement).

8. Temporal Development

- **Onset:** Early — infancy/early childhood, with global developmental delay as the presenting feature; insidious/chronic onset.
- **Progression:** Chronic, lifelong, generally non-degenerative. Epilepsy (including ESES/DEE-SWAS) typically emerges in childhood. **Regression** in verbal/motor domains occurs specifically in those developing status epilepticus in sleep [PMID: 38135915].
- **Critical period:** The ESES/DEE-SWAS window in childhood represents a period of vulnerability (regression) and a potential opportunity for intervention (seizure control). Diagnosis may be delayed to adolescence/adulthood [PMID: 40444229, 42462545].

9. Inheritance and Population

- **Inheritance:** Autosomal dominant (OMIM 618793), predominantly *de novo*; *"the majority occurred de novo (four with unknown origin)"* [PMID: 33597769].
- **Penetrance/expressivity:** Presumed high penetrance for LoF variants; expressivity is variable (severity ranges; epilepsy in ~50%).
- **Anticipation/mosaicism/founder effects/consanguinity:** Not applicable/not reported (dominant, *de novo*, sporadic). Consanguinity is not relevant. Germline mosaicism is theoretically possible (as for any *de novo* disorder) but not specifically documented.
- **Carrier frequency:** Not applicable (dominant, *de novo*).
- **Epidemiology:** Ultra-rare; ~53 patients in the defining series with subsequent case reports. **No reliable prevalence/incidence estimate exists**; the disorder is under-ascertained.

- **Demographics:** No ethnic predilection established. Mouse models suggest possible sex-biased severity (male-biased cognitive deficits in the knock-in model [PMID: 42565830]), but human sex-ratio data are not established.

10. Diagnostics

- **Genetic testing (definitive):** Clinical whole-exome sequencing (WES) or whole-genome sequencing (WGS) identifying a heterozygous DLG4 variant; multi-gene neurodevelopmental/epilepsy/ID panels including DLG4; chromosomal microarray for larger 17p13.1 deletions. RNA/functional studies are required to interpret splice-site and deep-intronic variants (e.g., c.2105+235C>T identified by WGS) [PMID: 37525972, 42462545].
- **Phenotyping studies:** Brain MRI (may show cerebellar vermis atrophy); EEG including **sleep EEG/video-polygraphy** to detect ESES/DEE-SWAS [PMID: 38135915].
- **Biomarkers/laboratory tests:** No specific biochemical biomarker; diagnosis is molecular. No metabolic, proteomic, or metabolomic diagnostic markers.
- **Clinical criteria:** No formal consensus criteria; diagnosis rests on compatible neurodevelopmental phenotype plus a pathogenic DLG4 variant.
- **Differential diagnosis:** Other monogenic synaptopathies and neurodevelopmental disorders (e.g., SHANK-, SYNGAP1-, GRIN-, and other MAGUK/PSD-related disorders); Marfanoid habitus previously led to confusion but is not characteristic [PMID: 33597769].
- **Screening:** No population/newborn screening. Cascade testing is generally unnecessary given the *de novo* nature; parental testing informs recurrence-risk counseling.

11. Outcome/Prognosis

- **Survival/mortality:** No evidence of markedly reduced life expectancy; the disorder is non-degenerative. Mortality data are not established (ultra-rare).
- **Morbidity/function:** Substantial lifelong disability from intellectual disability, autism, epilepsy, and behavioral/sleep problems. Many individuals require lifelong support.
- **Disease course/complications:** Epilepsy (including refractory ESES/DEE-SWAS with associated regression), psychiatric complications (including treatment-resistant psychosis/catatonia in at least one adolescent [PMID: 37386468]), and orthopedic issues (scoliosis).
- **Prognostic factors:** Development of status epilepticus in sleep predicts regression [PMID: 38135915]; severity appears to correlate broadly with the degree of PSD-95 loss. No validated prognostic biomarkers.

12. Treatment

No disease-modifying therapy exists. Management is supportive and multidisciplinary.

Modality	Details	NCIT suggestion
Antiseizure medications	Mainstay for epilepsy; ESES/DEE-SWAS forms often refractory; response variable across 35 patients [PMID: 38135915]	NCIT:C264 (Anticonvulsant Agent)
Antipsychotic (clozapine)	Effective for treatment-resistant psychosis/ catatonia after failing 3 antipsychotics [PMID: 37386468]	NCIT:C371 (Clozapine)
Developmental/ rehabilitative therapy	Physical, occupational, speech therapy; special education	NCIT:C15351 (Rehabilitation Therapy)
Sleep/behavioral management	For sleep disturbance and ASD/ADHD behaviors	—
Experimental PSD-95-directed agents	Nerinetide/Tat-NR2B9c, small molecules — developed for stroke/pain, NOT this disorder [PMID: 40712457]	—

Pharmacogenomics/gene/cell/RNA/targeted/immuno-therapies: None established for this indication. Patient iPSC lines [PMID: 42462545] and patient-derived knock-in mice [PMID: 42565830] provide platforms for future therapeutic development.

13. Prevention

- **Primary prevention:** Not possible (*de novo* genetic origin).
- **Secondary/tertiary prevention:** Early developmental intervention; sleep-EEG surveillance to detect and treat ESES/DEE-SWAS early (to mitigate regression); management of complications (scoliosis, psychiatric symptoms).
- **Genetic counseling:** Recurrence risk is low for parents of a child with a confirmed *de novo* variant (bounded by the small possibility of parental germline mosaicism); affected individuals who reproduce carry a 50% transmission risk. Prenatal/preimplantation testing is technically possible for a known familial variant.

14. Other Species / Natural Disease

- **Taxonomy/orthologs:** DLG4/PSD-95 is deeply conserved. Mouse *Dlg4* (NCBI Gene 13385, MGI:1277959); rat *Dlg4* (NCBI Gene 29495); zebrafish *dlg4a/dlg4b*; Drosophila *dlg1* (discs large); C. elegans *dlg-1*. The MAGUK PDZ–SH3–GK architecture is conserved from invertebrates to humans (Finding 10).
- **Natural disease in other species:** No naturally occurring DLG4 disorder is documented in companion animals or wildlife (OMIA); disease knowledge derives from engineered models.
- **Comparative/evolutionary:** High conservation of the scaffold and its receptor-clustering function underlies the strong translational validity of rodent models.

15. Model Organisms

Model	Type	Key phenotype recapitulation	PMID
PSD-95-null mouse	Mammalian knockout	Enhanced hippocampal LTP; severely impaired spatial learning	[9853749]
PDZ1/2 ligand-binding-deficient PSD-95 knock-in	Mammalian knock-in	↓ PSD accumulation of PSD-95/PSD-93/AMPARs; abnormal anxiety; impaired spatial/working/remote memory	[23268962]
Dlg4−/− mouse	Mammalian knockout	Increased repetitive behavior; abnormal social/communication behavior; impaired motor coordination; anxiety	[20952458]
Dlg4 V692Wfs*12/+ patient-derived knock-in	Mammalian knock-in	Reduced PSD-95; learning/cognitive-flexibility deficits (male-biased); sleep abnormalities — "recapitulate several hallmark features of SHINE syndrome"	[42565830]
AOUMEYi004-A iPSC line (c.2155A>T p.Arg719*)	Human iPSC	Pluripotent; three-germ-layer differentiation; platform for neuronal modeling	[42462545]

Model strengths: Rodent models robustly reproduce cognitive, behavioral, synaptic-plasticity, and (in the newest knock-in) sleep phenotypes, with a patient-specific variant. **Limitations:** Species differences in cognition/epilepsy; sex-specific effects require careful design; iPSC models capture cellular but not circuit-level phenotypes. **Resources:** MGI (Dlg4, MGI:1277959), IMPC, Cellosaurus (iPSC line).

Mechanistic Model / Interpretation

DLG4-related synaptopathy is a textbook **haploinsufficiency synaptopathy**. The convergent evidence — extreme population-genetic constraint (pLI = 1.0, LOEUF = 0.14), a predominance of *de novo* protein-truncating variants, direct demonstration of reduced PSD-95 protein from a patient variant, and faithful recapitulation of cognitive/behavioral/sleep phenotypes in a patient-derived knock-in mouse — locks together into a single coherent causal chain: **one lost DLG4 allele → less PSD-95 → a disorganized glutamatergic postsynaptic density → impaired synaptic maturation and aberrant plasticity → abnormal circuit development → the SHINE clinical phenotype.**

Two clinically important nuances emerge. First, the relationship between synaptic plasticity and cognition is not simply "less plasticity = worse learning": PSD-95-null mice show *enhanced* LTP yet *impaired* learning [PMID: 9853749], indicating that PSD-95 sets the correct dynamic range and metaplasticity of synapses, not merely their strength. Second, epilepsy — specifically the ESES/DEE-SWAS subtype — is a modifiable driver of the worst outcomes (regression), making its early detection via sleep EEG a high-yield clinical priority [PMID: 38135915].

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Population genetics          Molecular biology            Model systems              Clinic
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pLI=1.0, LOEUF=0.14   →      ↓PSD-95 protein       →      KO/KI mice: learning,  →   GDD, ID, ASD/AD
(LoF not tolerated)          disorganized PSD             sleep, behavior deficits    epilepsy, slee
                             (↓NMDAR/AMPAR clustering)    iPSC platform               (regression i
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Evidence Base

PMID	Title (abbreviated)	Role in this report
33597769	*DLG4-related synaptopathy: a new rare brain disorder*	Landmark cohort (n=53); defines disorder, name, core phenotype, *de novo* LoF mechanism, variant spectrum
38135915	*Developmental epileptic encephalopathy in DLG4-related synaptopathy*	Epilepsy in ~50%; ESES/DEE-SWAS >25%; regression; EEG/MRI diagnostics; ASM response
42565830	*Patient-derived mouse model reproduces SHINE syndrome*	Reduced PSD-95 protein; knock-in recapitulates hallmark features (sex-specific)
9853749	*Enhanced LTP and impaired learning in PSD-95 mutant mice*	Synaptic-plasticity/learning link
23268962	*PDZ1/2 ligand-binding-deficient PSD-95 knockin mice*	Receptor clustering, memory, anxiety deficits
20952458	*Dlg4 deletion and ASD/Williams-relevant phenotypes*	ASD-relevant behavior in knockout
29169997	*PSD95: schizophrenia or autism?*	PSD-95 scaffolding function; synaptogenesis role
37386468	*Clozapine in adolescent with SHINE syndrome*	Treatment of treatment-resistant psychosis
37525972	*Deep intronic DLG4 variant*	WGS diagnosis; protein-truncating predominance
42462545	*hiPSC line from DLG4 patient (c.2155A>T p.Arg719)**	WES diagnosis; iPSC modeling platform
40444229	*Late-onset diagnosis of SHINE syndrome*	Under-ascertainment; SHINE acronym; AD inheritance
40712457	*PSD-95/nNOS PPI disruption*	Experimental PSD-95-directed agents (stroke/pain, not this disorder)
20554866	*NMDAR signaling complexes / lipid rafts*	PSD-95 organizes NMDAR complexes in vivo

Additional supporting/context papers on PSD-95-interacting partners and MAGUK biology: [PMID: 18248606], [21878521], [37928066], [19467332], [29798891], [26609151].

Limitations and Knowledge Gaps

- **Epidemiology:** No reliable prevalence or incidence; the entity is ultra-rare and under-ascertained. Sex ratio and age distribution in humans are undefined.
- **Human molecular profiling:** No published patient transcriptomic/proteomic/metabolomic datasets; mechanistic inference relies on rodent and in vitro models.
- **Genotype–phenotype correlation:** Not yet quantified — whether missense/hypomorphic vs truncating variants, or variant location within domains, predicts severity or epilepsy risk remains open.
- **Penetrance/expressivity:** Assumed high penetrance but not formally quantified; drivers of variable expressivity (including the ~50% epilepsy split) are unknown.
- **Therapeutics:** No disease-modifying therapy; supportive-care evidence is limited to retrospective series and single case reports.
- **Missense mechanism:** Whether some missense variants act by dominant-negative rather than simple loss-of-function is not fully resolved.

Proposed Follow-up Experiments / Actions

1. **Establish an international patient registry** to derive prevalence, natural-history, sex-ratio, and genotype–phenotype data.
2. **Systematic sleep-EEG surveillance study** to define the incidence, timing, and treatment responsiveness of ESES/DEE-SWAS and its link to regression — a directly actionable clinical priority.
3. **Patient-iPSC-derived neuron/organoid profiling** (transcriptomics, proteomics, electrophysiology) to define human cell-autonomous consequences of PSD-95 loss and to build a drug-screening platform [building on

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4. **Genotype–phenotype analysis** across the expanding ClinVar/cohort variant set, stratified by variant type and PSD-95 domain, to test whether GK-domain or PDZ-domain variants confer distinct risks.

5. **Preclinical therapeutic testing** in the patient-derived knock-in mouse [PMID: 42565830] — e.g., ASO-mediated upregulation of the wild-type allele, or agents that stabilize the residual PSD, and rigorous evaluation of sex-specific responses.
6. **Prospective ASM comparative-effectiveness study** for the ESES/DEE-SWAS subtype, given its refractoriness and outsized impact on outcomes.

Evidence types: human clinical [33597769, 38135915, 37386468, 40444229, 42462545, 37525972]; model organism [9853749, 23268962, 20952458, 42565830, 20554866]; in vitro / review [29169997, 40712457]; computational/population-genetic [gnomAD constraint, ClinVar].
