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

NLM Citation: Benke TA, Demarest S, Angione K, et al. CDKL5 Deficiency Disorder. 2024 Apr 11. 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/

CDKL5 Deficiency Disorder

Synonyms: Cyclin-Dependent Kinase-Like 5 (CDKL5) Deficiency Disorder (CDD), *CDKL5*-Related Developmental and Epileptic Encephalopathy

Tim A Benke, MD, PhD,[1] Scott Demarest, MD,[1] Katie Angione, MS,[1] Jenny Downs, BAppSci, GradCertPubHlth, MSc, PhD,[2] Helen Leonard, MBChB, MPH,[2] Jacinta Saldaris, PhD,[2] Eric D Marsh, MD, PhD,[3] Heather Olson, MD, MS,[4] and Isabel Haviland, MD[4]

Created: April 11, 2024.

Summary

Clinical characteristics

CDKL5 deficiency disorder (CDD) is a developmental and epileptic encephalopathy (DEE) characterized by severe early-onset intractable epilepsy and motor, cognitive, visual, and autonomic disturbances. Movement disorders include chorea, dystonia, and stereotypical hand and leg movements.

Although females are more commonly affected than males (female-to-male ratio is approximately 4:1), the severity of manifestations in heterozygous females and hemizygous males can be equivalent. However, the severity of the phenotype can vary depending on the type and position of the *CDKL5* pathogenic variant, pattern of X-chromosome inactivation in females, and presence of postzygotic mosaicism in males or females, who can have mild manifestations.

Diagnosis/testing

The diagnosis of CDD is established in a female proband with suggestive clinical findings and a heterozygous *CDKL5* pathogenic variant identified by molecular genetic testing.

The diagnosis of CDD is established in a male proband with suggestive clinical findings and a hemizygous *CDKL5* pathogenic variant identified by molecular genetic testing.

Author Affiliations: 1 University of Colorado School of Medicine / Children's Hospital Colorado, Aurora, Colorado; Email: tim.benke@cuanschutz.edu; Email: scott.demarest@cuanschutz.edu; Email: kaitlin.angione@childrenscolorado.org. 2 Telethon Kids Institute, Nedlands, Australia; Email: jenny.downs@telethonkids.org.au; Email: helen.leonard@telethonkids.org.au; Email: jacinta.saldaris@telethonkids.org.au. 3 Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Email: marshe@chop.edu. 4 Boston Children's Hospital, Boston, Massachusetts; Email: heather.olson@childrens.harvard.edu; Email: isabel.haviland@childrens.harvard.edu.

Management

Treatment of manifestations: International consensus recommendations for the assessment and management of individuals with CDD have been published. The management of individuals with CDD is complex and requires multiple specialty evaluations; referral to a CDKL5 Center of Excellence may allow families to coordinate care more easily for affected individuals.

Targeted therapy: Ztalmy® (ganaxolone) is a targeted therapy for the treatment of epilepsy associated with CDD in individuals aged two years and older. This is the first approved treatment for seizures associated with CDD and the first treatment specifically for CDD.

Supportive care: Multidisciplinary care by specialists in the fields of pediatric neurology including pediatric epilepsy, feeding and nutrition, sleep disorders, behavioral disorders, orthopedics, physical therapy, occupational therapy, speech-language disorders, and genetic counseling.

Surveillance: Annual assessments by a medical home / primary care physician and specialists.

Genetic counseling

CDD is inherited in an X-linked manner. Approximately 99% of affected individuals represent simplex cases (i.e., a single occurrence in the family). The majority of individuals who represent simplex cases have the disorder as the result of a *de novo* germline or (rarely) postzygotic *CDKL5* pathogenic variant. Rarely, an individual with CDD has the disorder as the result of a *CDKL5* pathogenic variant inherited from a heterozygous or mosaic mother. If the mother of the proband has a *CDKL5* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Females who inherit the pathogenic variant will be heterozygous and are at high risk of being affected, although skewed X-chromosome inactivation and the possibility of other attenuating factors may result in a variable phenotype. Males who inherit the pathogenic variant will be hemizygous and will most likely be severely affected. Once the *CDKL5* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

For the purposes of this *GeneReview*, the terms "male" and "female" are narrowly defined as the individual's biological sex at birth as it determines clinical care [Caughey et al 2021].

Diagnostic criteria for CDKL5 deficiency disorder (CDD) have been proposed [Olson et al 2019, Amin et al 2022, Das 2023].

Suggestive Findings

CDD **should be suspected** in females and males with motor and cognitive developmental delays and epilepsy with onset in the first year of life (developmental delays and early-onset epilepsy constitute the minimal clinical diagnostic criteria proposed by Olson et al [2019]). Note: (1) Although females are more commonly affected than males with this X-linked disorder, the severity of manifestations in affected females and males can be equivalent. (2) The severity of the phenotype can vary depending on the type and position of the *CDKL5* pathogenic variant, pattern of X-chromosome inactivation in females, and presence of postzygotic mosaicism.

Common clinical findings [Olson et al 2019] (full text)

- **Early-onset epilepsy**
  - Typically beginning within the first two months of life (up to age 12 months)
  - Usually severe, with multiple episodes per day

    - Seizure types vary over time. Epileptic spasms (without hypsarrhythmia in 50%) are the initial seizure type in nearly 25% of individuals; other seizure types include tonic, focal, myoclonic, and generalized tonic-clonic; and mixed types that include features of spasms, tonic seizures, and hypermotor seizures. EEG findings may be normal in early infancy.
    - Refractory to anti-seizure medications (ASMs)
- **Severe developmental delays / intellectual disability** involving motor, communication (speech and language), and cognitive development
- Cerebral visual impairment manifesting as:
    - Abnormal eye movements that include esotropia, exotropia, and horizontal and rotatory nystagmus
    - Abnormal fixation and responsiveness to bright lights
- Tone abnormalities, including generalized hypotonia
- Sleep disturbances
    - Inability to maintain nighttime sleep for extended periods
    - Excessive daytime sleepiness
- Movement abnormalities
    - Stereotypies of hands (e.g., putting hands in mouth), arms (e.g., flapping, waving), or legs (e.g., leg crossing)
    - Generalized chorea
    - Dystonia
- Autonomic dysfunction
    - Constipation
    - Gastroesophageal reflux disease
    - Abnormal breathing pattern

Brain MRI findings. Brain MRI findings, if present, are variable and nonspecific and include progressive cortical and cerebellar atrophy with reduction in both gray and white matter [Leonard et al 2022, Specchio et al 2023].

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

Establishing the Diagnosis

Female proband. The diagnosis of CDD **is established** in a female proband with suggestive clinical findings and a heterozygous *CDKL5* pathogenic (or likely pathogenic) variant identified by molecular genetic testing [Olson et al 2019, Amin et al 2022, Das 2023] (see Table 1).

Male proband. The diagnosis of CDD **is established** in a male proband with suggestive clinical findings and a hemizygous *CDKL5* pathogenic (or likely pathogenic) variant identified by molecular genetic testing [Olson et al 2019, Amin et al 2022, Das 2023] (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *CDKL5* variant of uncertain significance does not establish or rule out the diagnosis. (3) While most individuals with CDD have a germline (i.e., constitutional) *CDKL5* pathogenic variant, some individuals have a postzygotic (i.e., mosaic) *CDKL5* pathogenic variant, including single-nucleotide variants, deletions, and inversions (see Molecular Genetics).

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

Note: Single-gene testing (sequence analysis of *CDKL5*, followed by gene-targeted deletion/duplication analysis) is rarely used today and typically NOT recommended.

Option 1

An epilepsy multigene panel that includes *CDKL5* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (5) Mosaic (i.e., postzygotic) pathogenic variants of *CDKL5* have been identified in some individuals. Therefore, the depth of sequencing may determine the yield of molecular diagnostic testing using these panels.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. Note: Unlike exome sequencing, genome sequencing can identify variants outside of the coding region, large deletions, and rearrangements. Although most *CDKL5* coding variants identified by genome sequencing are within exons [Taylor et al 2015], intronic *CDKL5* missense variants associated with abnormal splicing [Olson et al 2019] and rare disease-associated deletions in the 5' untranslated region have been reported [Nemos et al 2009, Bahi-Buisson et al 2010, Liang et al 2011, Mei et al 2014, Schoch et al 2020].

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 CDKL5 Deficiency Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
CDKL5	Sequence analysis [3]	84% [4, 5]
	Deletion/duplication analysis [6]	16% [4, 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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Demarest et al [2019] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Intronic *CDKL5* missense pathogenic variants associated with abnormal splicing [Olson et al 2019] and rare disease-associated deletions in the 5' untranslated region have been reported [Nemos et al 2009, Bahi-Buisson et al 2010, Liang et al 2011, Mei et al 2014]. Further, mosaic missense variants identified in individuals with CDD were detectable by next-generation sequencing [Stosser et al 2018].
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 and array comparative genomic hybridization (CGH). Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
7. Mosaic deletions and inversions disrupting *CDKL5* have been identified by array CGH and optical genome mapping [Bartnik et al 2011, Cope et al 2021].

Clinical Characteristics

Clinical Description

CDKL5 deficiency disorder (CDD) is a developmental and epileptic encephalopathy (DEE) characterized by severe early-onset epilepsy and motor, cognitive, visual, and autonomic disturbances [Bahi-Buisson et al 2008, Nemos et al 2009, Castrén et al 2011, Melani et al 2011, Bahi-Buisson et al 2012, Fehr et al 2015, Fehr et al 2016, Mangatt et al 2016]. Movement disorders include chorea, dystonia, and stereotypical hand and leg movements [Olson et al 2019, Olson et al 2021, Leonard et al 2022]. Cardiac involvement is nonspecific [Stansauk et al 2023].

Because the full spectrum of phenotypic severity is still emerging, especially given the possibility of mosaicism (in males and females) and the potential for skewed X-chromosome inactivation (in females), an individual with a *de novo CDKL5* pathogenic variant may have a mild phenotype (for example, minimal epilepsy and global developmental delays).

To date, approximately 500 individuals have been identified with CDD [Leonard et al 2022]. The following description of the phenotypic features associated with CDD is based on these reports.

Although females are more commonly affected than males (female-to-male ratio is approximately 4:1 [Demarest et al 2019]), the severity of manifestations in heterozygous females and hemizygous males can be equivalent. However, the severity of the phenotype can vary depending on the type and position of the *CDKL5* pathogenic variant, pattern of X-chromosome inactivation in females, and presence of postzygotic mosaicism in males or females, who can have mild manifestations [Demarest et al 2019, MacKay et al 2021, Wong et al 2023].

Table 2. CDKL5 Deficiency Disorder: Frequency of Select Features

Feature [1]	% of Persons w/Feature
Development delay / intellectual disability	100%

Table 2. continued from previous page.

Feature [1]		% of Persons w/Feature
Epilepsy		>99% [2]
Sleep disturbances		90%
Cerebral visual impairment		80%
Gastrointestinal problems		70%
Feeding problems requiring gastrostomy tube placement		30%
Movement disorders		25%
Musculoskeletal abnormalities		20%
Respiratory problems	Apnea/hypoventilation	20%
	Lower respiratory infections	10%
Behavioral problems		Unknown

Based on Leonard et al [2022], the International CDKL5 Disorder Database (ICDD), and International CDKL5 Clinical Research Network (ICCRN)

1. Families who care for children with CDD rank seizures as a top concern, followed closely by communication, sleep disorders, and vision issues [Neul et al 2023].

2. Fewer than 1% of individuals with CDD do not have epilepsy [Fehr et al 2016, MacKay et al 2020, Jakimiec et al 2020, Aznar-Laín et al 2023].

Development. Gross motor, fine motor, and speech-language development are impaired in all affected individuals.

Gross motor abnormalities are accompanied by generalized hypotonia. Approximately 60% of individuals achieve sitting and approximately 20% achieve independent walking.

Approximately 40%-70% of individuals cannot grasp and hold objects.

Approximately 20% of individuals have spoken language. Most children can use some simple nonverbal communication methods.

Cerebral visual impairment, which affects 80% of individuals, may affect development in each of these areas.

Epilepsy. Most individuals have early-onset and severe intractable epilepsy. Seizures are variable in type over time. Epileptic spasms are the initial seizure type in nearly 25% of individuals (and in those individuals, 50% of seizures occur without hypsarrhythmia on EEG). Other seizure types include tonic, focal, myoclonic, and generalized tonic-clonic seizures, and mixed types that include features of spasms, tonic seizures, and hypermotor seizures.

In general, epilepsy is medically refractory throughout life but shows some improvements with age. In up to 40% of individuals there may be a relative temporary improvement in seizures ("honeymoon period") around ages one to two years [Fehr et al 2016, Demarest et al 2019].

EEG features may be normal in early infancy but subsequently evolve to abnormal background activity that can include a Lennox-Gastaut pattern.

Neuroimaging. Nonspecific but abnormal brain imaging may be more evident in males than in females; findings can include progressive cortical and cerebellar atrophy with reduction in white and gray matter thickness [Leonard et al 2022].

In one study, brain MRIs in 64% (n=14/22) of individuals were normal in the first year of life. Follow-up MRIs showed progressive cortical and cerebellar atrophy. These findings, which can be seen in other DEEs, were hypothesized to be due to either CDD pathogenesis or severe intractable epilepsy [Specchio et al 2023].

Sleep disturbances. Abnormal sleep patterns, typically with inability to maintain sleep, are common [Mangatt et al 2016]. Parents report lack of sleep overall for several nights followed by excessive somnolence in more severe cases. This feature is typically lifelong [Hagebeuk et al 2013].

Cerebral visual impairment. Abnormal visual function manifests as abnormal eye movements that include horizontal and rotatory nystagmus and dysconjugate eye movements with reduced tracking and fixation associated with difficulties in visually oriented tasks such as reaching. Response to bright light can be abnormal (e.g., lack of blink). There may be improvement of visual fixation and task performance with age [Demarest et al 2019, Olson et al 2019, Brock et al 2021].

Gastrointestinal problems. Constipation and gastroesophageal reflux disease requiring medical management are typically lifelong.

Feeding problems. While one third of individuals may require gastrostomy tube placement for feeding, the remainder usually have some degree of feeding challenges (likely influenced by hypotonia of the pharyngeal muscles) that may be associated with increased risk of aspiration.

Movement disorders. The incidence of movement disorders may be underappreciated due to variability in ascertainment. Chorea, dystonia, and stereotypical leg crossing are not uncommon. Abnormal movements such as stereotypical hand movements may be present.

Musculoskeletal involvement may include scoliosis and large joint abnormalities associated with severe hypotonia (subluxation/dislocation of hips and knees).

Respiratory problems. Aspiration pneumonia due to impaired ability to clear respiratory secretions may be more prevalent in those with severe hypotonia.

Behavioral problems. Occasionally, autistic behaviors including abnormal socialization and repetitive behaviors have been described.

Genotype-Phenotype Correlations

While genotype-phenotype correlations are emerging [MacKay et al 2021], there are two caveats regarding ascertainment: (1) the frequency of recurrent *CDKL5* pathogenic variants is relatively low; and (2) measurements of severity with sufficient granularity to differentiate clinical severity have only recently become available.

CDKL5 pathogenic variants causing CDD are typically loss-of-function variants [Hector et al 2017b, Olson et al 2019, Leonard et al 2022]; however, duplications [Szafranski et al 2015] and missense gain-of-function variants [Frasca et al 2022] associated with different, and often milder, neurologic manifestations have been reported.

Phenotypes associated with nonsense alterations throughout the protein appear equally severe, suggesting that truncating variants located within the terminal region of the gene may be less severe [Wong et al 2023].

Nomenclature

CDKL5 deficiency disorder (CDD) was previously referred to as an early-onset seizure variant (Hanefeld variant) of Rett syndrome [Leonard et al 2022] and as *CDKL5*-related developmental and epileptic encephalopathy (*CDKL5*-DEE) in the International League Against Epilepsy (ILAE) Classification and Definition of Epilepsy Syndromes [Zuberi et al 2022].

Prevalence

The prevalence of CDD in the general population is unknown. An incidence of 2.36 in 100,000 live births (95% CI: 0.805-5.59) was estimated based on identification of CDD in four of 333 Scottish children with epilepsy tested over three years using an epilepsy multigene panel [Symonds et al 2019]. Note that this may or may not be an underestimate more broadly given the variability of the CDD phenotype and limited molecular investigations of individuals who are mildly affected (i.e., ascertainment bias).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CDKL5*.

Contiguous gene deletions. Larger deletions that include *CDKL5* may involve additional manifestations depending on the gene content of the deleted segment. For example, encephalopathy and features of Nance-Horan syndrome (OMIM 302350) were reported in an individual with a deletion encompassing *CDKL5* and *NHS* [Van Esch et al 2007].

Differential Diagnosis

Table 3. Developmental and Epileptic Encephalopathies in the Differential Diagnosis of CDKL5 Deficiency Disorder

Gene(s)	Disorder	MOI
ARX	*ARX*-related DEE (OMIM 308350)	XL
FOXG1	FOXG1 syndrome	AD
GABRA1	*GABRA1*-related DEE (OMIM 615744)	AD
GABRB3	*GABRB3*-related DEE (OMIM 617113)	AD
GABRG2	*GABRG2*-related DEE (OMIM 618396)	AD
GRIN2A	*GRIN2A*-related speech disorders & epilepsy	AD
KCNQ2	*KCNQ2*-related developmental & epileptic encephalopathy (OMIM 613720)	AD
KCNT1	*KCNT1*-related epilepsy	AD
MECP2	*MECP2* classic Rett syndrome (See *MECP2* Disorders.)	XL
	MECP2 duplication syndrome	XL
PCDH19	*PCDH19*-related DEE (OMIM 300088)	XL
SCN1A	*SCN1A* seizure disorders	AD
SCN2A	*SCN2A*-related DEE (OMIM 613721)	AD
SCN8A	*SCN8A*-related epilepsy w/encephalopathy	AD
SLC2A1	Classic glucose transporter type 1 deficiency syndrome (See Glucose Transporter Type 1 Deficiency Syndrome.)	AD (AR) [1]
STXBP1	*STXBP1* encephalopathy w/epilepsy	AD

Table 3. continued from previous page.

Gene(s)	Disorder	MOI
UBE3A	Angelman syndrome	See footnote 2.

Adapted from Leonard et al [2022], Supplementary Figure 2
AD = autosomal dominant; AR = autosomal recessive; DEE = developmental and epileptic encephalopathy; MOI = mode of inheritance; XL = X-linked
1. Glucose transporter type 1 deficiency syndrome (Glut1 DS) is most commonly inherited in an autosomal dominant manner. Rarely, Glut1 DS is inherited in an autosomal recessive manner.
2. Individuals with Angelman syndrome (AS) typically have the disorder as the result of a *de novo* genetic alteration associated with a very low recurrence risk. Less commonly, an individual with AS has the disorder as the result of a genetic alteration associated with an imprinting pattern of autosomal dominant inheritance or variable recurrence risk.

Classic Rett syndrome (see *MECP2* Disorders). CDKL5 deficiency disorder (CDD) was previously considered an early-onset seizure variant of Rett syndrome prior to the updating of Rett syndrome classification [Neul et al 2010], gene discovery, and wider use of genetic testing. While stereotypical hand movements may be present in CDD, they are rarely similar qualitatively to those seen in individuals with classic Rett syndrome. Though this distinction is subjective, the hand stereotypies common to Rett syndrome (such as wringing, tapping/touching, mouthing with evolution over time) are less distractible compared to those seen in CDD (such as mouthing, flapping). In addition, very early-onset seizures and cerebral visual impairment are not generally seen in classic Rett syndrome.

Management

International consensus recommendations for the assessment and management of individuals with CDKL5 deficiency disorder (CDD) have been published [Amin et al 2022] (full text).

The management of individuals with CDD is complex and requires multiple specialty appointments; referral to a CDKL5 Center of Excellence may allow families to more easily coordinate care for affected individuals (to date, ten CDKL5 Centers of Excellence have been established in the United States).

Evaluations Following Initial Diagnosis

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

Table 4. CDKL5 Deficiency Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of OFC, length, & weight	• Smaller OFC is assoc w/↑ severity of disorder. [1] • Poor weight gain can reflect nutritional status.
Neurologic	Eval of epilepsy by neurologist or epileptologist	• EEG to assess EEG background, epileptiform activity, & seizure type & correlate w/clinical semiology • Prolonged video EEGs may be required to characterize spells of unclear etiology or rule out subclinical status epilepticus.
	Eval of movement disorders	To characterize movement disorder, if present, & ascertain effect on gross & fine motor skills
Ophthalmologic/ Vision	Ophthalmologist	Assess for visual acuity, abnormal ocular movement, refractive errors, & strabismus
	Neurologist	Assess for cerebral visual impairment

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Development	Primary care / developmental assessment	Incl assessments for: • Motor, adaptive, cognitive, & speech-language delays • Early intervention program / IEP or 504 plan
Sleep disorder	By PCP, sleep specialist, or neurologist	Characterize: • Issues assoc w/sleep initiation &/or maintenance; • Presence of snoring, apnea, &/or excessive limb movements. Consider sleep study.
Neurobehavioral/ Psychiatric	By PCP / developmental pediatrician	Persons age >12 mos: screening for concerns incl sleep disturbances
Gastrointestinal/ Feeding/Nutrition	Primary care / gastroenterology / nutrition / feeding team assessments	• Incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in persons w/ dysphagia, poor weight gain, excessive feeding times (greater than 30 minutes per meal), &/or ↑ aspiration risk.
Respiratory	By pulmonologist	Assess for any of the following: • Aspiration pneumonia • Excessive or chronic cough • Need for mgmt of oral secretions
Musculoskeletal	By PCP, orthopedist, neurologist, rehab medicine specialist, &/or PT	• Annual assessments of nutritional status & bone health, incl 25-hydroxyvitamin D intake • Clinical eval of spine; spine radiograph for baseline or to compare w/previous studies for presence of progressive scoliosis; referral to orthopedist if Cobb angle >45 degrees for consideration of surgical correction • Annual assessments of large joint hypo- & hypermobility that may affect function; referral for radiographs & further interventions if indicated
Activities of daily living	Rehab, PT/OT evals	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kypho-scoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Communication	Speech-language therapist	Assessment for augmentative communication devices & strategies
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of CDD to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	By PCP	Assess need for: • Community or online resources such as Parent to Parent • Social work involvement to connect families w/parental support, respite, & assistance w/establishing guardianship (see Transition to Adulthood: Caring for Your Child at Age 18 and Beyond). • Palliative care involvement &/or home nursing referral

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; CDD = CDKL5 deficiency disorder; IEP = individual education plan; MOI = mode of inheritance; OFC = occipital frontal circumference; OT = occupational therapy/therapist; PCP = primary care physician; PT = physical therapy/therapist

1. Cutri-French et al [2020]

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

Treatment of Manifestations

There is no cure for CDD to date [Olson et al 2021, Leonard et al 2022].

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Ztalmy® (ganaxolone) is a targeted therapy for the treatment of epilepsy associated with CDD in individuals ages two years and older (see Table 5). This is the first approved treatment for seizures associated with CDD and the first treatment specifically for CDD [Knight et al 2022].

Table 5. CDKL5 Deficiency Disorder: Targeted Therapy

Treatment Class	Mechanism of Action	Specific Drug	Dose	Comments
Neuroactive $GABA_A$ receptor positive modulator	Allosteric $GABA_A$ positive modulator [1]	Ztalmy® (ganaxolone)	See package insert.	• Overall, treatment is assoc w/ modest reduction in seizure burden. [1] • Primary side effect is somnolence.

1. Knight et al [2022]

Supportive Care

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 6).

Table 6. CDKL5 Deficiency Disorder: Treatment of Manifestations

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

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• An approach to seizure mgmt that balances seizure control w/side effects & attempts to limit number of ASMs to ideally ≤2. [1] • Education of parents/caregivers [2]
	Targeted therapy for treatment of CDD-assoc epilepsy	See Table 5.
Movement disorders	Pharmacologic therapies	May incl therapies such as baclofen, botulinum toxin, or other specific agents to treat movement disorders.
Poor weight gain	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when there are clinical signs of dysphagia (choking, chronic cough, history of aspiration pneumonia) or prolonged feeding times (>30 mins per meal)
Cerebral visual impairment	Address in psychoeducational activities & therapies.	Incl in early intervention programs &/or school district & consistent w/federal law re access to educational services by visually impaired individuals
Sleep disorders	• Interventions (e.g., CPAP or supplemental oxygen) that address central &/or obstructive sleep apnea • Pharmacologic therapy to address disorders of sleep initiation & sleep maintenance [3]	Excessive daytime somnolence, abnormal sleep patterns, & psychiatric behaviors can be influenced by polypharmacy as well as poor nocturnal sleep quality.
Neurobehavioral/ Psychiatric	• Therapies to address features of ASD such as applied behavioral analysis • Pharmacologic therapies for anxiety	Pharmacologic therapies w/sedative side effects to be carefully weighed against overall benefits & effect on abilities to participate in education, therapies, sleep, & general quality of life.
Gastrointestinal	Pharmacologic therapies	Stool softeners, prokinetics, osmotic agents, or laxatives as needed. Continuous use of these agents is safe.
Musculoskeletal	• Vitamin D supplementation if indicated • PT/OT • Referral for orthopedic surveillance & correction	Orthopedic corrections may be indicated for scoliosis &/or large joint displacements.
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. • Referral to community or online family support resources such as Parent to Parent

Based on Olson et al [2021], Amin et al [2022]
ASD = autism spectrum disorder; ASM = anti-seizure medication; CPAP = continuous positive airway pressure; OT = occupational therapy; PT = physical therapy
1. See Therapies Under Investigation for additional proposed therapies for epilepsy that are potentially indicated based on prior use and approvals (such as for infantile spasms or Lennox-Gastaut syndrome).
2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
3. Atkin et al [2018], Bruni et al [2019]

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, including a teacher of the visually impaired (TVI), 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. This includes access to assistive and augmentative communication [Townend et al 2020, Sigafoos et al 2023]. Specific recommendations regarding type of therapy (such as applied behavior analysis [ABA]) can be made by a developmental pediatrician. Overall, the goal of therapy is to maintain skills and meet individual goals; insurance requirements for progress or meeting specific goals on developmental skills to maintain access to therapies are not appropriate.
  - 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.
  - This is in accordance with the Free Appropriate Public Education (FAPE) federal rules. FAPE is an educational right of children with disabilities in the United States that is guaranteed by the Rehabilitation Act of 1973 and the Individuals with Disabilities Education Act (IDEA). The US Supreme Court has determined that services must be provided that will allow children to learn and make progress. Families should work with schools to develop an IEP that recognizes this.
- 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.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended. In general, annual assessments by a medical home/primary care physician and specialists are needed.

Table 7. CDKL5 Deficiency Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Constitutional	Measurement of OFC, length, & weight	Annually, or more frequently as required for mgmt
Neurologic	Monitor those w/seizures as clinically indicated.	At each annual visit
	Assess for new manifestations such as seizures, changes in tone, & movement disorders.	At each visit
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake • Eval of feeding time	
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Assessment for sleep, anxiety, ADHD, ASD, aggression, & self-injury	
Gastrointestinal	Monitor for feeding, nutrition, constipation, & GERD.	
Respiratory	Monitor for evidence of aspiration & respiratory insufficiency.	
Musculoskeletal	• Physical medicine, OT/PT assessment of mobility, self-help skills • Assessment of large joint mobility (e.g., hip surveillance)	
	• Clinical eval of spine • Spine radiograph as needed to identify progressive scoliosis • Referral to orthopedist if Cobb angle >45 degrees for consideration of surgical correction	At each annual visit
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, assistance w/establishing guardianship [see Transition to Adulthood: Caring for Your Child at Age 18 and Beyond], referral to a CDKL5 Center of Excellence, or other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit
Transition to Adult Care	Develop realistic plans for adult life (see Transitions from Pediatric Epilepsy to Adult Epilepsy Care).	Starting by ~age 10 yrs

GERD = gastroesophageal reflux disease; OFC = occipital frontal circumference; OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Several therapies have been investigated or are ongoing for CDD [Leonard et al 2022] including the following:

- Soticlestat/TAK935 (NCT03694275) [Demarest et al 2023]
- Ataluren (NCT02758626) [Devinsky et al 2021a]

- Fenfluramine (NCT03861871, NCT05064878) [Devinsky et al 2021b]
- Canabidiol [Devinsky et al 2018]
- Ketogenic diet [Müller et al 2016, Lim et al 2017, Zhang et al 2022]
- Vagal nerve stimulation [Lim et al 2018]
- Protein and gene replacement therapies have been proposed.

Clinical trials and registries assessing natural history and outcome measures are ongoing (NCT05558371, NCT05373719, NCT04486768).

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.

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

CDKL5 deficiency disorder (CDD) is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- Approximately 99% of affected individuals represent simplex cases (i.e., a single occurrence in the family). The majority of individuals who represent simplex cases have the disorder as the result of a *de novo* germline or (rarely) postzygotic *CDKL5* pathogenic variant.
- Rarely, an individual with CDD has the disorder as the result of a *CDKL5* pathogenic variant inherited from a heterozygous mother [Fraser et al 2019, Siri et al 2021]. A mother who is heterozygous for a *CDKL5* pathogenic variant may have favorably skewed X-chromosome inactivation that results in her being unaffected or mildly affected. Of note, the absence of favorably skewed X-chromosome inactivation in blood does not rule out the possibility of favorably skewed X-chromosome inactivation in the brain.
- *CDKL5* molecular genetic testing is recommended for the mother of the proband to evaluate her genetic status and to inform recurrence risk assessment.
- Evaluation/testing of the father of the proband is not required. If the proband is female, it is presumed that the father is not hemizygous for the *CDKL5* pathogenic variant, as males with CDD are not known to reproduce. If the proband is male, the father will not have CDD and will not be hemizygous for the *CDKL5* pathogenic variant.
- Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in germ (gonadal) cells only.
- If the *CDKL5* pathogenic variant found in the proband cannot be detected in maternal leukocyte DNA, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Presumed maternal germline mosaicism has been reported in families with sib recurrence [Weaving et al 2004, Hagebeuk et al 2015].

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

- If the mother of the proband has a CDKL5 pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Females who inherit the pathogenic variant will be heterozygous and are at high risk of being affected, although skewed X-chromosome inactivation and the possibility of other attenuating factors may result in a variable phenotype.
  - Males who inherit the pathogenic variant will be hemizygous and will most likely be severely affected [Demarest et al 2019, Wong et al 2023]. Note: Although manifestations may be milder in males with mosaic, postzygotic *CDKL5* pathogenic variants, the phenotype in hemizygous males with germline pathogenic variants is typically severe.
- If the proband represents a simplex case and if the *CDKL5* pathogenic variant cannot be detected in maternal leukocyte DNA, the risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism. Presumed maternal germline mosaicism has been reported in families with sib recurrence [Weaving et al 2004, Hagebeuk et al 2015].

Offspring of a proband

- Each child of a female proband with CDD has a 50% chance of inheriting the *CDKL5* pathogenic variant. Females with CDD generally do not reproduce; mildly affected females are not known to have reproduced.
- Males with CDD are not known to reproduce.

Other family members. The risk to other family members depends on the genetic status of the proband's mother: if the mother of the proband has a *CDKL5* pathogenic variant, her family members may be at risk.

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 young adults who are at risk of having a *CDKL5* pathogenic variant.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CDKL5* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Males with a hemizygous *CDKL5* pathogenic variant will most likely have severe intellectual disability. The phenotype in heterozygous females is difficult to predict and can range from mildly (in very rare cases) to severely affected.

Note: Because presumed maternal germline mosaicism for a *CDKL5* pathogenic variant has occasionally been reported, it is appropriate to offer prenatal testing to the parents of a child with CDD whether or not the *CDKL5* pathogenic variant has been identified in maternal leukocyte DNA [Weaving et al 2004, Hagebeuk et al 2015].

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.

- **CDKL5 Alliance**
  www.cdkl5alliance.org
- **CDKL5 Centers of Excellence**
  International Foundation for CDKL5 Research
  www.cdkl5.com/cdkl5-centers-excellence
- **CDKL5 Research Collaborative**
  www.cdkl5research.org
- **International Foundation for CDKL5 Research**
  Phone: 330-294-5005
  Email: info@cdkl5.com
  www.cdkl5.com
- **International CDKL5 Disorder Database Registry (ICDD)**
  This registry allows families to learn about CDD, search the registry, and enter their own data. The registry is partnered with several patient advocacy groups.
  The CDKL5 Disorder

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. CDKL5 Deficiency Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CDKL5	Xp22.13	Cyclin-dependent kinase-like 5	CDKL5 @ LOVD	CDKL5	CDKL5

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 CDKL5 Deficiency Disorder (View All in OMIM)

300203	CYCLIN-DEPENDENT KINASE-LIKE 5; CDKL5
300672	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 2; DEE2

Molecular Pathogenesis

CDKL5, an X-linked gene, encodes cyclin-dependent kinase-like 5 (CDKL5), a 115-kD serine-threonine kinase and member of the CMGC family, which includes cyclin-dependent kinases (CDK), MAP kinases, glycogen synthase kinases (GSK), and cyclin-dependent kinase-like (CDKL) [Manning et al 2002]. CDKL5 is expressed throughout the central nervous system, primarily in neurons, where it localizes to the dendritic spines of excitatory synapses as well as the nucleus [Jaffe et al 1989]. Its expression increases postnatally and is stabilized at peak levels in adult rodents and humans [Chen et al 2010, Hector et al 2016, Baltussen et al 2018].

CDKL5 interacts with PSD-95 [Zhu et al 2013], gephyrin [Uezu et al 2016, De Rosa et al 2022], NGL-1 [Ricciardi et al 2012], Shootin1 [Nawaz et al 2016], actin [Chen et al 2010], the microtubule-binding proteins (MAP1s and

EB2), which are directly phosphorylated by CDKL5 [Baltussen et al 2018], as well as MeCP2, DNMT1, AMPH1, and HDAC4 [Zhu & Xiong 2019].

Loss of CDKL5 leads to a global reduction in excitatory synapse numbers [Ricciardi et al 2012, Della Sala et al 2016], reduced PSD-95 [Lupori et al 2019, Negraes et al 2021] and synapsin [Negraes et al 2021], with loss of AMPA-type glutamate receptors (GluA2 [Yennawar et al 2019]) and increased NMDA-type glutamate receptors (GluN2B [Okuda et al 2017]). Inhibitory synaptic currents are affected in some CDKL5 mouse models [Tang et al 2017].

Analysis of *CDKL5* pathogenic variants has confirmed that CDKL5 kinase function is central to the pathogenesis of CDKL5 deficiency disorder (CDD) [Hector et al 2017b, Demarest et al 2019]. However, the precise role of loss of CDKL5 function in causing CDD-related manifestations could be due to several mechanisms including chronic CDKL5 dysfunction, compensatory effects due to CDKL5 dysfunction during a critical developmental period, or secondary effects due to severe and intractable epilepsy.

Mechanism of disease causation. Loss of function

Note: Duplications [Szafranski et al 2015] and missense gain-of-function variants [Frasca et al 2022] associated with milder neurologic manifestations have been reported. Missense variants (especially novel ones) outside of the kinase domain (where most *CDKL5* pathogenic missense variants cluster) should be interpreted with caution, as the functional significance of these variants may be unknown [Diebold et al 2014].

***CDKL5*-specific laboratory technical considerations**

- ***CDKL5* transcripts.** *CDKL5* has multiple transcripts and alternatively spliced exons [Hector et al 2016, Hector et al 2017a]. Historically, the longest transcripts, NM_003159 and NM_001037343, have been used in clinical diagnostic testing. However, the transcript NM_001323289 is the most highly expressed in the brain and contains 170 nucleotides at the 3' end of its last exon that are noncoding in other transcripts [Keehan et al 2022]. This has led to pathogenic *CDKL5* variants within this region being missed by clinical testing laboratories [Bodian et al 2018, Schoch et al 2020, Keehan et al 2022]. Thus, it is critical that clinical testing laboratories assess for *CDKL5* variants in this transcript.
- **Mosaicism.** Mosaic (or postzygotic) *CDKL5* variants including single-nucleotide variants and deletions have been identified in individuals with CDD [Bartnik et al 2011, Stosser et al 2018, Cope et al 2021]. Therefore, attention to the sensitivity of the diagnostic method used (e.g., next-generation sequencing or array comparative genomic hybridization) is recommended.
- **Noncoding variants.** Deleterious *CDKL5* missense variants and deletions in intronic regions have been reported [Nemos et al 2009, Bahi-Buisson et al 2010, Liang et al 2011, Mei et al 2014, Schoch et al 2020]. Thus, consideration of genome sequencing for individuals with features consistent with CDD who do not have a *CDKL5* variant detected on multigene panel testing or exome sequencing is recommended.
- **Variants of uncertain significance.** Maternal testing is helpful for assessing the pathogenicity of *CDKL5* variants of uncertain significance, especially missense variants (especially novel ones) outside of the kinase domain.

Chapter Notes

Author Notes

Tim Benke, MD, PhD
Ponzio Family Endowed Chair in Neurology Research
Medical Director, Rett Clinic
Research Director, Neuroscience Institute
Children's Hospital Colorado

Professor of Pediatrics, Neurology, Pharmacology & Otolaryngology
University of Colorado School of Medicine
International CDKL5 Clinical Research Network

Tim Benke (tim.benke@cuanschutz.edu) and all authors are actively involved in clinical research regarding individuals with a developmental and epileptic encephalopathy (DEE) including Rett syndrome, *MECP2*-related disorders, CDKL5 deficiency disorder (CDD), and FOXG1 syndrome. They would be happy to communicate with persons who have any questions regarding diagnosis of these and similar disorders or other considerations.

Eric Marsh (marshe@chop.edu) is also interested in hearing from clinicians treating families of individuals with a DEE in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Drs Tim Benke, Scott Demarest, Jenny Downs, Helen Leonard, Heather Olson, and Isa Haviland to inquire about individuals with *CDKL5* variants of uncertain significance or pathogenic variants with a divergent phenotype.

Acknowledgments

The authors recognize the following support: NIH-NINDS: R21 NS112770 (Benke), U01NS114312 (PD/Benke); NIH-NICHD: U54 HD061222 (PD/Percy), Rocky Mountain Rett Association (Benke), International Foundation for CDKL5 Research (all), Children's Hospital Colorado Foundation: Ponzio Family Chair in Neurology Research (Benke), NIH-NINDS: 5K23NS107646 (Olson), Loulou Foundation (Olson, Haviland), NIH-NIMH: 2T32MH112510 (Haviland).

Revision History

- 11 April 2024 (bp) Review posted live
- 22 August 2023 (tb) Original submission

References

Literature Cited

Amin S, Monaghan M, Aledo-Serrano A, Bahi-Buisson N, Chin RF, Clarke AJ, Cross JH, Demarest S, Devinsky O, Downs J, Pestana Knight EM, Olson H, Partridge CA, Stuart G, Trivisano M, Zuberi S, Benke TA. International consensus recommendations for the assessment and management of individuals with CDKL5 deficiency disorder. Front Neurol. 2022;13:874695. PubMed PMID: 35795799.

Atkin T, Comai S, Gobbi G. Drugs for insomnia beyond benzodiazepines: pharmacology, clinical applications, and discovery. Pharmacol Rev. 2018;70:197-245. PubMed PMID: 29487083.

Aznar-Laín G, Fernandez-Mayoralas DM, Caicoya AG, Rocamora R, Perez-Jurado LA. CDKL5 deficiency disorder without epilepsy. Pediatr Neurol. 2023;144:84-9. PubMed PMID: 37201242.

Bahi-Buisson N, Girard B, Gautier A, Nectoux J, Fichou Y, Saillour Y, Poirier K, Chelly J, Bienvenu T. Epileptic encephalopathy in a girl with an interstitial deletion of Xp22 comprising promoter and exon 1 of the CDKL5 gene. Am J Med Genet B Neuropsychiatr Genet. 2010;153B:202-7. PubMed PMID: 19455595.

Bahi-Buisson N, Nectoux J, Rosas-Vargas H, Milh M, Boddaert N, Girard B, Cances C, Ville D, Afenjar A, Rio M, Heron D, N'Guyen Morel MA, Arzimanoglou A, Philippe C, Jonveaux P, Chelly J, Bienvenu T. Key clinical features to identify girls with CDKL5 mutations. Brain. 2008;131:2647-61. PubMed PMID: 18790821.

Bahi-Buisson N, Villeneuve N, Caietta E, Jacquette A, Maurey H, Matthijs G, Van EH, Delahaye A, Moncla A, Milh M, Zufferey F, Diebold B, Bienvenu T. Recurrent mutations in the CDKL5 gene: genotype-phenotype relationships. Am J Med Genet A. 2012;158A:1612-9. PubMed PMID: 22678952.

Baltussen LL, Negraes PD, Silvestre M, Claxton S, Moeskops M, Christodoulou E, Flynn HR, Snijders AP, Muotri AR, Ultanir SK. Chemical genetic identification of CDKL5 substrates reveals its role in neuronal microtubule dynamics. EMBO J. 2018;37:e99763. PubMed PMID: 30266824.

Bartnik M, Derwińska K, Gos M, Obersztyn E, Kołodziejska KE, Erez A, Szpecht-Potocka A, Fang P, Terczyńska I, Mierzewska H, Lohr NJ, Bellus GA, Reimschisel T, Bocian E, Mazurczak T, Cheung SW, Stankiewicz P. Early-onset seizures due to mosaic exonic deletions of CDKL5 in a male and two females. Genet Med. 2011;13:447-52. PubMed PMID: 21293276.

Bodian DL, Schreiber JM, Vilboux T, Khromykh A, Hauser NS. Mutation in an alternative transcript of CDKL5 in a boy with early-onset seizures. Cold Spring Harb Mol Case Stud. 2018;4:a002360. PubMed PMID: 29444904.

Brock D, Fidell A, Thomas J, Juarez-Colunga E, Benke TA, Demarest S. Cerebral visual impairment in CDKL5 deficiency disorder correlates with developmental achievement. J Child Neurol. 2021;36:974-80. PubMed PMID: 34547934.

Bruni O, Angriman M, Melegari MG, Ferri R. Pharmacotherapeutic management of sleep disorders in children with neurodevelopmental disorders. Expert Opin Pharmacother. 2019;20:2257-71. PubMed PMID: 31638842.

Castrén M, Gaily E, Tengstrom C, Lahdetie J, Archer H, Ala-Mello S. Epilepsy caused by CDKL5 mutations. Eur J Paediatr Neurol. 2011;15:65-9. PubMed PMID: 20493745.

Caughey AB, Krist AH, Wolff TA, Barry MJ, Henderson JT, Owens DK, Davidson KW, Simon MA, Mangione CM. USPSTF approach to addressing sex and gender when making recommendations for clinical preventive services. JAMA. 2021;326:1953-61. PubMed PMID: 34694343.

Chen Q, Zhu YC, Yu J, Miao S, Zheng J, Xu L, Zhou Y, Li D, Zhang C, Tao J, Xiong ZQ. CDKL5, a protein associated with Rett syndrome, regulates neuronal morphogenesis via Rac1 signaling. J Neurosci. 2010;30:12777-86. PubMed PMID: 20861382.

Cope H, Barseghyan H, Bhattacharya S, Fu Y, Hoppman N, Marcou C, Walley N, Rehder C, Deak K, Alkelai A, Vilain E, Shashi V, et al. Detection of a mosaic CDKL5 deletion and inversion by optical genome mapping ends an exhaustive diagnostic odyssey. Mol Genet Genomic Med. 2021;9:e1665. PubMed PMID: 33955715.

Cutri-French C, Armstrong D, Saby J, Gorman C, Lane J, Fu C, Peters SU, Percy A, Neul JL, Marsh ED. Comparison of core features in four developmental encephalopathies in the Rett Natural History Study. Ann Neurol. 2020;88:396-406. PubMed PMID: 32472944.

Das SM. ClinGen Rett and Angelman-like Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CDKL5 Version 3.0. 2023.

Della Sala G, Putignano E, Chelini G, Melani R, Calcagno E, Michele Ratto G, Amendola E, Gross CT, Giustetto M, Pizzorusso T. Dendritic spine instability in a mouse model of CDKL5 disorder is rescued by insulin-like growth factor 1. Biol Psychiatry. 2016;80:302-11. PubMed PMID: 26452614.

Demarest S, Jeste S, Agarwal N, Arkilo D, Asgharnejad M, Hsiao S, Thibert R. Efficacy, safety, and tolerability of soticlestat as adjunctive therapy for the treatment of seizures in patients with Dup15q syndrome or CDKL5 deficiency disorder in an open-label signal-finding phase II study (ARCADE). Epilepsy Behav. 2023;142:109173. PubMed PMID: 37011526.

Demarest ST, Olson HE, Moss A, Pestana-Knight E, Zhang X, Parikh S, Swanson LC, Riley KD, Bazin GA, Angione K, Niestroj LM, Lal D, Juarez-Colunga E, Benke TA. CDKL5 deficiency disorder: relationship

between genotype, epilepsy, cortical visual impairment, and development. Epilepsia. 2019;60:1733-42. PubMed PMID: 31313283.

De Rosa R, Valastro S, Cambria C, Barbiero I, Puricelli C, Tramarin M, Randi S, Bianchi M, Antonucci F, Kilstrup-Nielsen C. Loss of CDKL5 causes synaptic GABAergic defects that can be restored with the neuroactive steroid pregnenolone-methyl-ether. Int J Mol Sci. 2022;24:68. PubMed PMID: 36613509.

Devinsky O, King L, Bluvstein J, Friedman D. Ataluren for drug-resistant epilepsy in nonsense variant-mediated Dravet syndrome and CDKL5 deficiency disorder. Ann Clin Transl Neurol. 2021a;8:639-44. PubMed PMID: 33538404.

Devinsky O, King L, Schwartz D, Conway E, Price D. Effect of fenfluramine on convulsive seizures in CDKL5 deficiency disorder. Epilepsia. 2021b;62:e98-e102. PubMed PMID: 33979451.

Devinsky O, Verducci C, Thiele EA, Laux LC, Patel AD, Filloux F, Szaflarski JP, Wilfong A, Clark GD, Park YD, Seltzer LE, Bebin EM, Flamini R, Wechsler RT, Friedman D. Open-label use of highly purified CBD (Epidiolex(R)) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. Epilepsy Behav. 2018;86:131-7. PubMed PMID: 30006259.

Diebold B, Delepine C, Gataullina S, Delahaye A, Nectoux J, Bienvenu T. Mutations in the C-terminus of CDKL5: proceed with caution. Eur J Hum Genet. 2014;22:270-2. PubMed PMID: 23756444.

Fehr S, Leonard H, Ho G, Williams S, de Klerk N, Forbes D, Christodoulou J, Downs J. There is variability in the attainment of developmental milestones in the CDKL5 disorder. J Neurodev Disord. 2015;7:2. PubMed PMID: 25657822.

Fehr S, Wong K, Chin R, Williams S, de Klerk N, Forbes D, Krishnaraj R, Christodoulou J, Downs J, Leonard H. Seizure variables and their relationship to genotype and functional abilities in the CDKL5 disorder. Neurology. 2016;87:2206-13. PubMed PMID: 27770071.

Frasca A, Pavlidou E, Bizzotto M, Gao Y, Balestra D, Pinotti M, Dahl HA, Mazarakis ND, Landsberger N, Kinali M. Not just loss-of-function variations: identification of a hypermorphic variant in a patient with a CDKL5 missense substitution. Neurol Genet. 2022;8:e666. PubMed PMID: 35280940.

Fraser H, Goldman A, Wright R, Deciphering Developmental Disorders S, Banka S. A maternally inherited frameshift CDKL5 variant in a male with global developmental delay and late-onset generalized epilepsy. Am J Med Genet A. 2019;179:507-11. PubMed PMID: 30624022.

Hagebeuk EE, Marcelis CL, Alders M, Kaspers A, de Weerd AW. Two siblings with a CDKL5 mutation: genotype and phenotype evaluation. J Child Neurol. 2015;30:1515-9. PubMed PMID: 25762588.

Hagebeuk EE, van den Bossche RA, de Weerd AW. Respiratory and sleep disorders in female children with atypical Rett syndrome caused by mutations in the CDKL5 gene. Dev Med Child Neurol. 2013;55:480-4. PubMed PMID: 23151060.

Hector RD, Dando O, Landsberger N, Kilstrup-Nielsen C, Kind PC, Bailey ME, Cobb SR. Characterisation of CDKL5 transcript isoforms in human and mouse. PLoS One. 2016;11:e0157758. PubMed PMID: 27315173.

Hector RD, Dando O, Ritakari TE, Kind PC, Bailey ME, Cobb SR. Characterisation of Cdkl5 transcript isoforms in rat. Gene. 2017a;603:21-6. PubMed PMID: 27940108.

Hector RD, Kalscheuer VM, Hennig F, Leonard H, Downs J, Clarke A, Benke TA, Armstrong J, Pineda M, Bailey MES, Cobb SR. CDKL5 variants: Improving our understanding of a rare neurologic disorder. Neurol Genet. 2017b;3:e200. PubMed PMID: 29264392.

Jaffe DB, Marks SS, Greenberg DA. Antagonist drug selectivity for radioligand binding sites on voltage-gated and N -methyl-D-aspartate receptor-gated Ca 2+ channels. Neuroscience Letters. 1989;105:227-32. PubMed PMID: 2562062.

Jakimiec M, Paprocka J, Smigiel R. CDKL5 deficiency disorder-a complex epileptic encephalopathy. Brain Sci. 2020;10:107. PubMed PMID: 32079229.

Keehan L, Haviland I, Gofin Y, Swanson LC, El Achkar CM, Schreiber J, VanNoy GE, O'Heir E, O'Donnell-Luria A, Lewis RA, Magoulas P, Tran A, Azamian MS, Chao HT, Pham L, Samaco RC, Elsea S, Thorpe E, Kesari A, Perry D, Lee B, Lalani SR, Rosenfeld JA, Olson HE, Burrage LC; Undiagnosed Diseases N. Wide range of phenotypic severity in individuals with late truncations unique to the predominant CDKL5 transcript in the brain. Am J Med Genet A. 2022;188:3516-24. PubMed PMID: 35934918.

Knight EMP, Amin S, Bahi-Buisson N, Benke TA, Cross JH, Demarest ST, Olson HE, Specchio N, Fleming TR, Aimetti AA, Gasior M, Devinsky O, Marigold Trial G. Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2022;21:417-27. PubMed PMID: 35429480.

Leonard H, Downs J, Benke TA, Swanson L, Olson H, Demarest S. CDKL5 deficiency disorder: clinical features, diagnosis, and management. Lancet Neurol. 2022;21:563-76. PubMed PMID: 35483386.

Liang JS, Shimojima K, Takayama R, Natsume J, Shichiji M, Hirasawa K, Imai K, Okanishi T, Mizuno S, Okumura A, Sugawara M, Ito T, Ikeda H, Takahashi Y, Oguni H, Imai K, Osawa M, Yamamoto T. CDKL5 alterations lead to early epileptic encephalopathy in both genders. Epilepsia. 2011;52:1835-42. PubMed PMID: 21770923.

Lim Z, Wong K, Downs J, Bebbington K, Demarest S, Leonard H. Vagus nerve stimulation for the treatment of refractory epilepsy in the CDKL5 deficiency disorder. Epilepsy Res. 2018;146:36-40. PubMed PMID: 30071384.

Lim Z, Wong K, Olson HE, Bergin AM, Downs J, Leonard H. Use of the ketogenic diet to manage refractory epilepsy in CDKL5 disorder: experience of >100 patients. Epilepsia. 2017;58:1415-22. PubMed PMID: 28605011.

Lupori L, Sagona G, Fuchs C, Mazziotti R, Stefanov A, Putignano E, Napoli D, Strettoi E, Ciani E, Pizzorusso T. Site-specific abnormalities in the visual system of a mouse model of CDKL5 deficiency disorder. Hum Mol Genet. 2019;28:2851-61. PubMed PMID: 31108505.

MacKay CI, Bick D, Prokop JW, Munoz I, Rouse J, Downs J, Leonard H. Expanding the phenotype of the CDKL5 deficiency disorder: are seizures mandatory? Am J Med Genet A. 2020;182:1217-22. PubMed PMID: 32034940.

MacKay CI, Wong K, Demarest ST, Benke TA, Downs J, Leonard H. Exploring genotype-phenotype relationships in the CDKL5 deficiency disorder using an international dataset. Clin Genet. 2021;99:157-65. PubMed PMID: 33047306.

Mangatt M, Wong K, Anderson B, Epstein A, Hodgetts S, Leonard H, Downs J. Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome. Orphanet J Rare Dis. 2016;11:39. PubMed PMID: 27080038.

Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. Science. 2002;298:1912-34. PubMed PMID: 12471243.

Mei D, Darra F, Barba C, Marini C, Fontana E, Chiti L, Parrini E, Dalla Bernardina B, Guerrini R. Optimizing the molecular diagnosis of CDKL5 gene-related epileptic encephalopathy in boys. Epilepsia. 2014;55:1748-53. PubMed PMID: 25266480.

Melani F, Mei D, Pisano T, Savasta S, Franzoni E, Ferrari AR, Marini C, Guerrini R. CDKL5 gene-related epileptic encephalopathy: electroclinical findings in the first year of life. Dev Med Child Neurol. 2011;53:354-60. PubMed PMID: 21309761.

Müller A, Helbig I, Jansen C, Bast T, Guerrini R, Jahn J, Muhle H, Auvin S, Korenke GC, Philip S, Keimer R, Striano P, Wolf NI, Pust B, Thiels C, Fogarasi A, Waltz S, Kurlemann G, Kovacevic-Preradovic T, Ceulemans B, Schmitt B, Philippi H, Tarquinio D, Buerki S, von Stulpnagel C, Kluger G. Retrospective evaluation of low long-term efficacy of antiepileptic drugs and ketogenic diet in 39 patients with CDKL5-related epilepsy. Eur J Paediatr Neurol. 2016;20:147-51. PubMed PMID: 26387070.

Nawaz MS, Giarda E, Bedogni F, La Montanara P, Ricciardi S, Ciceri D, Alberio T, Landsberger N, Rusconi L, Kilstrup-Nielsen C. CDKL5 and Shootin1 interact and concur in regulating neuronal polarization. PLoS One. 2016;11:e0148634. PubMed PMID: 26849555.

Negraes PD, Trujillo CA, Yu NK, Wu W, Yao H, Liang N, Lautz JD, Kwok E, McClatchy D, Diedrich J, de Bartolome SM, Truong J, Szeto R, Tran T, Herai RH, Smith SEP, Haddad GG, Yates JR, 3rd, Muotri AR. Altered network and rescue of human neurons derived from individuals with early-onset genetic epilepsy. Mol Psychiatry. 2021;26:7047-68. PubMed PMID: 33888873.

Nemos C, Lambert L, Giuliano F, Doray B, Roubertie A, Goldenberg A, Delobel B, Layet V, N'Guyen MA, Saunier A, Verneau F, Jonveaux P, Philippe C. Mutational spectrum of CDKL5 in early-onset encephalopathies: a study of a large collection of French patients and review of the literature. Clin Genet. 2009;76:357-71. PubMed PMID: 19793311.

Neul JL, Benke TA, Marsh ED, Suter B, Silveira L, Fu C, Peters SU, Percy AK; Rett syndrome Natural History Study Group. Top caregiver concerns in Rett syndrome and related disorders: data from the US natural history study. J Neurodev Disord. 2023;15:33. PubMed PMID: 37833681.

Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, Leonard H, Bailey ME, Schanen NC, Zappella M, Renieri A, Huppke P, Percy AK; RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. 2010;68:944-50. PubMed PMID: 21154482.

Okuda K, Kobayashi S, Fukaya M, Watanabe A, Murakami T, Hagiwara M, Sato T, Ueno H, Ogonuki N, Komano-Inoue S, Manabe H, Yamaguchi M, Ogura A, Asahara H, Sakagami H, Mizuguchi M, Manabe T, Tanaka T. CDKL5 controls postsynaptic localization of GluN2B-containing NMDA receptors in the hippocampus and regulates seizure susceptibility. Neurobiol Dis. 2017;106:158-70. PubMed PMID: 28688852.

Olson HE, Daniels CI, Haviland I, Swanson LC, Greene CA, Denny AMM, Demarest ST, Pestana-Knight E, Zhang X, Moosa AN, Fidell A, Weisenberg JL, Suter B, Fu C, Neul JL, Percy AK, Marsh ED, Benke TA, Poduri A. Current neurologic treatment and emerging therapies in CDKL5 deficiency disorder. J Neurodev Disord. 2021;13:40. PubMed PMID: 34530725.

Olson HE, Demarest ST, Pestana-Knight EM, Swanson LC, Iqbal S, Lal D, Leonard H, Cross JH, Devinsky O, Benke TA. Cyclin-dependent kinase-like 5 deficiency disorder: clinical review. Pediatr Neurol. 2019;97:18-25. PubMed PMID: 30928302.

Ricciardi S, Ungaro F, Hambrock M, Rademacher N, Stefanelli G, Brambilla D, Sessa A, Magagnotti C, Bachi A, Giarda E, Verpelli C, Kilstrup-Nielsen C, Sala C, Kalscheuer VM, Broccoli V. CDKL5 ensures excitatory synapse stability by reinforcing NGL-1-PSD95 interaction in the postsynaptic compartment and is impaired in patient iPSC-derived neurons. Nat Cell Biol. 2012;14:911-23. PubMed PMID: 22922712.

Schoch K, Tan QK, Stong N, Deak KL, McConkie-Rosell A, McDonald MT, Undiagnosed Diseases N, Goldstein DB, Jiang YH, Shashi V. Alternative transcripts in variant interpretation: the potential for missed diagnoses and misdiagnoses. Genet Med. 2020;22:1269-75. PubMed PMID: 32366967.

Sigafoos J, Roche L, O'Reilly MF, Lancioni GE, Marschik PB. Updated systematic-narrative review on communication intervention in Rett Syndrome: 2010-2022. Augment Altern Commun. 2023;39:241-55. PubMed PMID: 37526342.

Siri B, Varesio C, Freri E, Darra F, Gana S, Mei D, Porta F, Fontana E, Galati G, Solazzi R, Niceta M, Veggiotti P, Alfei E. CDKL5 deficiency disorder in males: five new variants and review of the literature. Eur J Paediatr Neurol. 2021;33:9-20. PubMed PMID: 33989939.

Specchio N, Trivisano M, Lenge M, Ferretti A, Mei D, Parrini E, Napolitano A, Rossi-Espagnet C, Talenti G, Longo D, Proietti J, Ragona F, Freri E, Solazzi R, Granata T, Darra F, Bernardina BD, Vigevano F, Guerrini R. CDKL5 deficiency disorder: progressive brain atrophy may be part of the syndrome. Cereb Cortex. 2023;33:9709-17. PubMed PMID: 37429835.

Stansauk J, Fidell A, Benke T, Schaffer M, Demarest ST. Analysis of electrocardiograms in individuals with CDKL5 deficiency disorder. Am J Med Genet A. 2023;191:108-11. PubMed PMID: 36372969.

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((R))): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Stosser MB, Lindy AS, Butler E, Retterer K, Piccirillo-Stosser CM, Richard G, McKnight DA. High frequency of mosaic pathogenic variants in genes causing epilepsy-related neurodevelopmental disorders. Genet Med. 2018;20:403-10. PubMed PMID: 28837158.

Symonds JD, Zuberi SM, Stewart K, McLellan A, O'Regan M, MacLeod S, Jollands A, Joss S, Kirkpatrick M, Brunklaus A, Pilz DT, Shetty J, Dorris L, Abu-Arafeh I, Andrew J, Brink P, Callaghan M, Cruden J, Diver LA, Findlay C, Gardiner S, Grattan R, Lang B, MacDonnell J, McKnight J, Morrison CA, Nairn L, Slean MM, Stephen E, Webb A, Vincent A, Wilson M. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain. 2019;142:2303-18. PubMed PMID: 31302675.

Szafranski P, Golla S, Jin W, Fang P, Hixson P, Matalon R, Kinney D, Bock HG, Craigen W, Smith JL, Bi W, Patel A, Wai Cheung S, Bacino CA, Stankiewicz P. Neurodevelopmental and neurobehavioral characteristics in males and females with CDKL5 duplications. Eur J Hum Genet. 2015;23:915-21. PubMed PMID: 25315662.

Tang S, Wang IJ, Yue C, Takano H, Terzic B, Pance K, Lee JY, Cui Y, Coulter DA, Zhou Z. Loss of CDKL5 in glutamatergic neurons disrupts hippocampal microcircuitry and leads to memory impairment in mice. J Neurosci. 2017;37:7420-37. PubMed PMID: 28674172.

Taylor JC, Martin HC, Lise S, Broxholme J, Cazier JB, Rimmer A, Kanapin A, Lunter G, Fiddy S, Allan C, Aricescu AR, Attar M, Babbs C, Becq J, Beeson D, Bento C, Bignell P, Blair E, Buckle VJ, Bull K, Cais O, Cario H, Chapel H, Copley RR, Cornall R, Craft J, Dahan K, Davenport EE, Dendrou C, Devuyst O, Fenwick AL, Flint J, Fugger L, Gilbert RD, Goriely A, Green A, Greger IH, Grocock R, Gruszczyk AV, Hastings R, Hatton E, Higgs D, Hill A, Holmes C, Howard M, Hughes L, Humburg P, Johnson D, Karpe F, Kingsbury Z, Kini U, Knight JC, Krohn J, Lamble S, Langman C, Lonie L, Luck J, McCarthy D, McGowan SJ, McMullin MF, Miller KA, Murray L, Németh AH, Nesbit MA, Nutt D, Ormondroyd E, Oturai AB, Pagnamenta A, Patel SY, Percy M, Petousi N, Piazza P, Piret SE, Polanco-Echeverry G, Popitsch N, Powrie F, Pugh C, Quek L, Robbins PA, Robson K, Russo A, Sahgal N, van Schouwenburg PA, Schuh A, Silverman E, Simmons A, Sørensen PS, Sweeney E, Taylor J, Thakker RV, Tomlinson I, Trebes A, Twigg SR, Uhlig HH, Vyas P, Vyse T, Wall SA, Watkins H, Whyte MP, Witty L, Wright B, Yau C, Buck D, Humphray S, Ratcliffe PJ, Bell JI, Wilkie AO, Bentley D, Donnelly P, McVean G. Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. Nat Genet. 2015;47:717-26. PubMed PMID: 25985138.

Townend GS, Bartolotta TE, Urbanowicz A, Wandin H, Curfs LMG. Development of consensus-based guidelines for managing communication of individuals with Rett syndrome. Augment Altern Commun. 2020;36:71-81. PubMed PMID: 32720526.

Uezu A, Kanak DJ, Bradshaw TW, Soderblom EJ, Catavero CM, Burette AC, Weinberg RJ, Soderling SH. Identification of an elaborate complex mediating postsynaptic inhibition. Science. 2016;353:1123-9. PubMed PMID: 27609886.

Van Esch H, Jansen A, Bauters M, Froyen G, Fryns JP. Encephalopathy and bilateral cataract in a boy with an interstitial deletion of Xp22 comprising the CDKL5 and NHS genes. Am J Med Genet A. 2007;143:364-9. PubMed PMID: 17256798.

Weaving LS, Christodoulou J, Williamson SL, Friend KL, McKenzie OL, Archer H, Evans J, Clarke A, Pelka GJ, Tam PP, Watson C, Lahooti H, Ellaway CJ, Bennetts B, Leonard H, Gécz J. Mutations of CDKL5 cause a severe neurodevelopmental disorder with infantile spasms and mental retardation. Am J Hum Genet. 2004;75:1079-93. PubMed PMID: 15492925.

Wong K, Junaid M, Demarest S, Saldaris J, Benke TA, Marsh ED, Downs J, Leonard H. Factors influencing the attainment of major motor milestones in CDKL5 deficiency disorder. Eur J Hum Genet. 2023;31:169-78. PubMed PMID: 35978140.

Yennawar M, White RS, Jensen FE. AMPA receptor dysregulation and therapeutic interventions in a mouse model of CDKL5 deficiency disorder. J Neurosci. 2019;39:4814-28. PubMed PMID: 30952813.

Zhang J, Ma J, Chang X, Wu P, Li S, Wu Y. Efficacy of ketogenic diet in CDKL5-related epilepsy: a single arm meta-analysis. Orphanet J Rare Dis. 2022;17:385. PubMed PMID: 36274176.

Zhu YC, Li D, Wang L, Lu B, Zheng J, Zhao SL, Zeng R, Xiong ZQ. Palmitoylation-dependent CDKL5-PSD-95 interaction regulates synaptic targeting of CDKL5 and dendritic spine development. Proc Natl Acad Sci U S A. 2013;110:9118-23. PubMed PMID: 23671101.

Zhu YC, Xiong ZQ. Molecular and synaptic bases of CDKL5 disorder. Dev Neurobiol. 2019;79:8-19. PubMed PMID: 30246934.

Zuberi SM, Wirrell E, Yozawitz E, Wilmshurst JM, Specchio N, Riney K, Pressler R, Auvin S, Samia P, Hirsch E, Galicchio S, Triki C, Snead OC, Wiebe S, Cross JH, Tinuper P, Scheffer IE, Perucca E, Moshé SL, Nabbout R. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022;63:1349-97. PubMed PMID: 35503712.

License