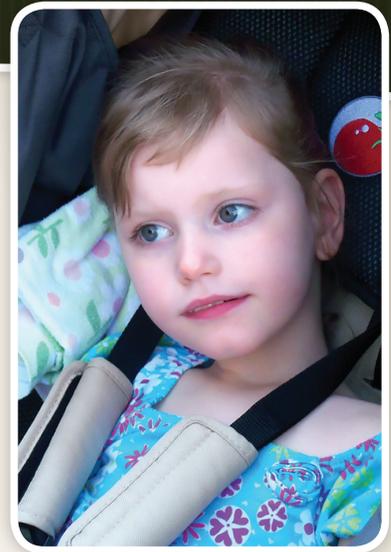


CDKL5

DISORDER



An Introductory Guide

History
Diagnosis
Symptoms
Treatments and Therapies
Resources
...and more

Foreword

In the decade since gene changes in CDKL5 were first linked to Rett syndrome, much has been learnt about the CDKL5 disorder. Whilst individuals with CDKL5 mutations share some clinical features with those with MECP2 mutations causing Rett syndrome, we now know that they should be considered to be distinct disorders. In addition to careful clinical delineation of the disorder, laboratory-based research studies and the development of a mouse model for CDKL5 deficiency will enhance our understanding of the biological processes contributing to the CDKL5 disorder, which will hopefully ultimately lead to targeted therapies.

It is therefore very timely that the key clinical and genetic features of the CDKL5 disorder should be brought together into this information booklet, along with the current approaches to the management of the complications of the disorder, and details of local specialist services and CDKL5 support organizations. We hope you will find this resource of value.



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Director, Western Sydney Genetics Program
Head, Discipline of Genetic Medicine,
Sydney Medical School, University of Sydney, Australia

Introduction

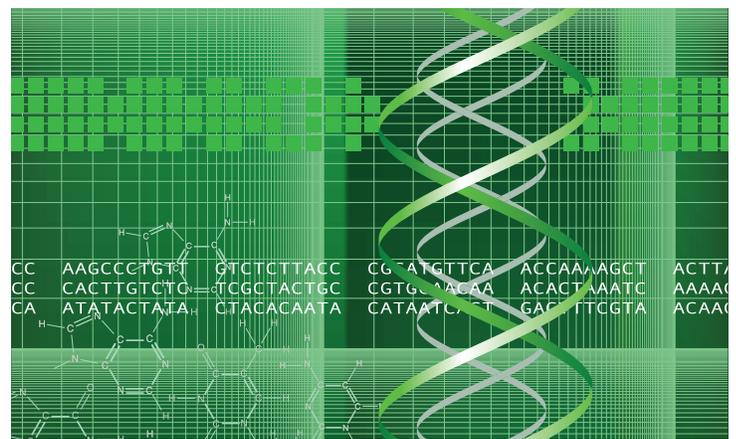
This information leaflet is aimed at providing information to professionals who may be involved in the assessment, diagnosis and treatment of children with CDKL5 disorder, along with diagnosed patients and their families. This is not intended to be a comprehensive guide, but rather an introduction to the complex clinical features that children with CDKL5 disorder may exhibit. This disorder has only been recently recognized and there is still much to learn about the clinical spectrum of CDKL5. Not all features described must be present in an affected individual. There also may be other clinical manifestations that will become apparent as we learn more.

What is CDKL5?

CDKL5 (Cyclin-Dependent Kinase-Like 5) disorder is a rare genetic condition that was first identified in 2004. It is caused by mutations in the CDKL5 gene, which is found on the X-chromosome. Although many cases have been identified in boys, because of the location of the gene, this disorder mainly affects girls. The cause of a CDKL5 mutation and the incidence of CDKL5 disorder are not known at this time.

The CDKL5 gene provides instructions for making a protein that is essential for normal brain and neuron development. Although relatively little is known about this protein's function, it may play a role in regulating the activity of other genes, including the MECP2 gene of Rett Syndrome.

CDKL5 disorder typically presents itself with seizures in the first few weeks or months of life, followed by severe neuro-developmental delay. Many children now known to have CDKL5 disorder were previously thought to have a variation of Rett Syndrome known as atypical Rett because of similar characteristics. However, in 2012, the "CDKL5 disorder," became recognized as a distinct condition.

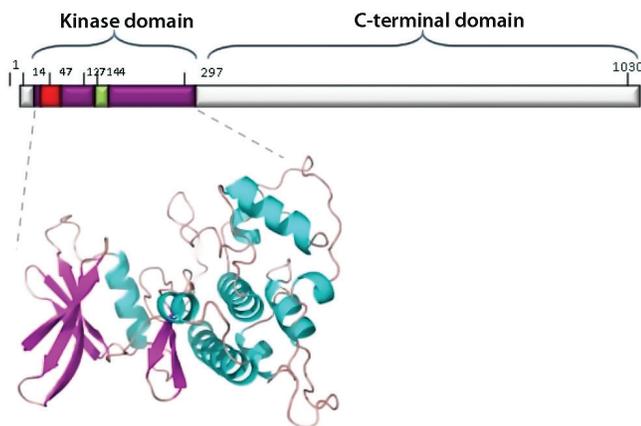


How can CDKL5 disorder be recognized?

The most prominent feature of CDKL5 disorder is the early onset of seizures. The onset of seizures can happen within the first hours, days, weeks, or months of life. Children who have been diagnosed with CDKL5 disorder may have seizures starting within hours of birth, or as late as 8 months to 2 years of age. Some mothers have described feeling seizures even in the pre-natal period. Seizures manifest as tonic seizures with myoclonic clusters and tonic/clonic seizures. They generally happen in or around sleep at the original onset of seizures, but as time passes, they may appear during waking hours as well.

It is common for these first seizures not to be detected on an EEG, and some children may be misdiagnosed with Benign Sleep Myoclonus, or Sandifer Syndrome. It is important to note that the absence of seizure activity on EEG (or a “normal” EEG) does not necessarily exclude the diagnosis of CDKL5-related seizure activity.

While CDKL5 disorder mainly affects girls, it should not be excluded as a diagnosis for boys. There are many boys who have been diagnosed worldwide. For additional symptoms, please see the Clinical Symptoms A-Z section further in this booklet.



CDKL5 gene
Photo credit: Biocomputing UP

Some of the symptoms of CDKL5 disorder

- Seizures
- Developmental delays
- Autism
- Low muscle tone
- Apraxia
- Cortical blindness
- Scoliosis
- Small, cold feet
- Absent or limited speech
- Limited hand skills
- Feeding difficulties
- Gastrointestinal problems



Diagnosis

How do you diagnose CDKL5 Disorder?

With the introduction of more sophisticated genetic testing, CDKL5 disorder is now being diagnosed in children at a relatively early age. Genetic testing prior to 2009, which sequenced the gene, would not necessarily have picked up deletions. A number of individuals subsequently diagnosed with CDKL5 disorder previously were given a negative result. Therefore, a child with the phenotype who has previously tested negative, yet does not have a genetic diagnosis, should be re-tested to include deletion and duplication testing of the CDKL5 gene.

The diagnosis is based off of a simple blood test. More recently, some labs use a buccal swab of the cheek. The blood or saliva swab is then sent to a special laboratory that performs the genetic test. Please see the end of this booklet for a list of some of the more common labs that perform this test. It is recommended to contact one of the labs and get the necessary information on how to send the sample. They can also advise you on when the results will be available. This time frame is typically four to six weeks. It is advisable to work directly with your physician and insurance company to determine the cost and coverage of such genetic testing. Recently, CDKL5 testing has become widely available in epilepsy and developmental delay genetic panels, thereby allowing testing of multiple potential disease causing genes all at the same time at a cost similar to just testing the CDKL5 gene alone.

Multidisciplinary Approach to Care

A diagnosis of CDKL5 is a complex medical situation. In general, most patients would benefit greatly from a multidisciplinary approach to care. The goal is to enrich patients' and their families' lives by helping them lead a life as normal as possible. Providing patients and families with timely and accurate information and support in the decision making process is the top priority.

It is important to find a Primary Care Physician and/or a Specialty Clinic (like a CDKL5 Center of Excellence or a Rett Syndrome Clinic) that can maintain a family-centered approach and foster a trusting relationship. Successful care starts with a healthy respect for the family, health care team and other service providers.

The following is a list of specialists that should be considered in each child's multidisciplinary team:

- **Neurology/Epileptology**
- **Gastroenterology**
- **Pulmonary**
- **Cardiology**
- **Orthopedics**
- **Ophthalmology**
- **Rehab Medicine**
- **Developmental Pediatrics**
- **Behavioral Psychology**
- **Nursing**
- **Nutrition**
- **Physical Therapy**
- **Speech Therapy**
- **Assisted Augmentative Communication (AAC) Therapy**
- **Occupational Therapy**
- **Social work**



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Clinical Symptoms: A to Z

Abdominal Distension

Abdominal distension can be due to gastroparesis, obstruction, constipation or aerophagia, which commonly accompanies the abnormal breathing some children with CDKL5 experience. Very severe cases may be helped by percutaneous gastrostomy (PEG or G-tube), while other cases may also be helped by medication. A full gastrointestinal workup is indicated to determine the likely etiology of the abdominal distention, including abdominal X-rays, upper GI, gastric emptying studies, endoscopy, and food allergy testing.

Aerophagia

Air swallowing can be significant and may interfere with eating and full respiratory effort. The reason for air swallowing is not fully understood but may be behavioral, or due to pain, discomfort or anxiety.

Apraxia

Apraxia results from dysfunction of the cerebral hemispheres, especially the parietal lobe, and is often present in people with CDKL5. Apraxia includes limb-kinetic apraxia (the inability to make fine, precise movements with an arm or leg), ideomotor apraxia (the inability to make the proper movement in response to a verbal command), ideational apraxia (the inability to coordinate activities with multiple, sequential movements, such as dressing, eating, and bathing), verbal apraxia (difficulty coordinating mouth and speech movements), constructional apraxia (the inability to copy, draw, or construct simple figures) and oculomotor apraxia (difficulty moving the eyes on command). Apraxia may be accompanied by aphasia. Generally, treatment for individuals with apraxia includes physical, speech, or occupational therapy.

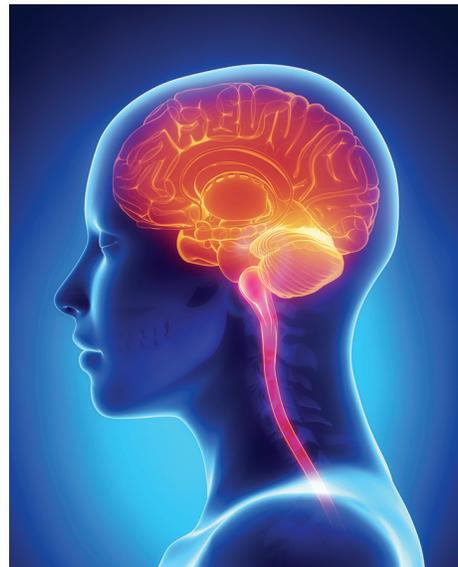
Aspiration Pneumonia

This symptom may be due to poor coordination and low tone of the muscles involved in swallowing. The epiglottis should fold over the trachea to prevent the food or fluid from being inhaled, but fails

to do so. Careful assessment of swallowing by an experienced speech therapist, as well as a swallowing study is essential. Positioning is key to enhance proper swallowing, as is the texture of the food and consistency of fluid.

Autism

Individuals with CDKL5 may exhibit varying degrees of impaired social interaction, such as avoidance of eye contact or perseveration on people or objects. Repetitive behaviors may occur such as stimming, manic walking and manipulating objects. Other features include difficulty in motor coordination and attention, behavioral outbursts and lack of safety awareness.



Bone Density

It is not yet known how commonly osteoporosis occurs in CDKL5. However, there are many anecdotal reports of affected individuals with low bone density and bone fractures. Bone density should be monitored over time by an endocrinologist, especially if there is a suggestion of precocious puberty. Osteoporosis should be considered particularly in those who have never walked or who have sustained fractures. Bone density is also affected by anti-convulsants. A DEXA bone density scan should be undertaken in the event of a fracture or simply to provide a baseline.

Bruxism

Teeth grinding can be severe and can occur while awake or sleeping. Involving a dentist is important to prevent tooth decay and enamel problems.

Cardiac problems

Some people have experienced Long QT Syndrome, which is more commonly associated with Rett Syndrome. Other cardiac concerns are abnormalities in heart rate such as tachycardia and bradycardia, and non-specific changes relating to T waves. It is best practice to ensure that individuals with a CDKL5 disorder have annual ECGs and a cardiac event monitor if arrhythmias are a concern. Structural heart defects do not appear to be a common problem in CDKL5, but a few cases have been reported. Because of these known cases, a baseline echocardiogram may be warranted.

Constipation

Constipation is a common problem in affected individuals. It is important to treat vigorously and actively with an emphasis on prevention. Bowel habits can change over time and can be a source of pain and discomfort. Even if dietary fiber is adequate, check the daily free water intake, which may be low.

Cortical Visual Impairment (CVI)

CVI is a form of visual impairment that is related to the brain rather than the eyes. For some diagnosed with CDKL5 disorder, this can be severe but may improve over time. It is important to seek an appropriate vision speciality evaluation, care, and therapeutic options. Children with CDKL5 disorder tend to have a distinctive sideways glance.

Epilepsy/Seizures

Seizures are almost always seen in CDKL5 disorder. Studies have suggested that children with CDKL5 disorder exhibit 3 stages of epilepsy. Stage I is early epilepsy

("Clinical Symptoms" continued on next page)

(onset 1–10 weeks) with a normal EEG, despite frequent seizures. Stage II involves the development of epileptic encephalopathy with infantile spasms and hypsarrhythmia, in about 50% of cases. Stage III appears as late, multifocal and myoclonic epilepsy, although this may not always be the case. Seizures are often difficult to control despite the use of antiepileptic medications, vagal nerve stimulators, the ketogenic diet and surgery. Puberty may bring about changes in seizure pattern and activity.

Feeding Difficulties

Dysphagia is common in CDKLS. Affected individuals may have difficulty with chewing, tongue movement, and swallowing, due in part to low muscle tone and apraxia. This may impair adequate nutrition or contribute to respiratory symptoms (aspiration, coughing, or choking during feeding). Poor weight gain and episodes of aspiration require swallowing studies under fluoroscopic examination and pH studies to evaluate for GERD. In severe cases, percutaneous gastrostomy (PEG) might be recommended by the gastroenterologist and surgeons. Persistent reflux may need medication or surgical correction.

Gastrointestinal problems

Constipation, diarrhea, intestinal gas, and gastric reflux are all common problems. Constipation may not always be palpable and should not be excluded until a bowel x-ray or ultrasound has been performed. Low gut motility, as well as slow gastric emptying, can also be evident in children with CDKLS. There is anecdotal evidence that these individuals may be more susceptible to volvulus and intussusception, which are medical emergencies. Therefore, when presented with a rapid clinical deterioration with no apparent cause, there should be a high index of suspicion for a life-threatening gastrointestinal complication.

Hand Stereotypies

Hand stereotypies are involuntary. This manifests as finger tapping, hand mouthing, hand wringing and hand/arm flap-

ping. Many people with the disorder have non-functional hand use. However, therapy should be encouraged to increase independence and decrease maladaptive behavior.

Hypotonia

Hypotonia is seen almost universally across the CDKLS spectrum. It is important for the child to be seen regularly by orthopedic specialists in order to assess the level of scoliosis, hip alignment, and joint laxity.

Impaired Sleep

This includes difficulty going to sleep, waking up in the middle of the night, night terrors, and inappropriate laughing and jerking. Once awake, children with CDKLS can take a long time to fall asleep again due to irregular breathing patterns, seizure activity and general restlessness. Many of those with CDKLS disorder will have significant impairment of sleep. They can have consecutive days and nights without sleep, but they can also have periods of sleep lasting days on end. Many families use medications to aid sleep in consultation with the child's neurologist or primary physician.

Involuntary Behaviors

Many families report crying, laughing and erratic behavior for no apparent reason. As the child gets older, the families are able to interpret these behaviors to be related to pain, gelastic seizures, or other seizure activity. A person with CDKLS disorder who is experiencing severe crying should be taken for an urgent medical evaluation and receive a full work-up to exclude illness or possible gastrointestinal obstruction.

Mobility

There is a wide range of abilities across the CDKLS spectrum. Some affected patients will never walk, while others walk independently or with assistance. Some have almost no hand skills while others perform skilled purposeful actions. Mobility can improve with intensive physical and occupational therapies.

Range of Motion

Contractures may develop over time in individuals who are not freely mobile. This can be assessed by checking for full passive range of motion. In order to maintain good range of motion, physical and occupational therapy should be a consistent intervention throughout a person's life.

The Spine: Scoliosis/Kyphosis/Lordosis

The chance of developing scoliosis increases with age, although statistics are not yet available as to this risk. There should be close monitoring of the spine for the development of a deformity. If detected, referral to a spinal surgeon is recommended.

Stimming

Stimming is a term often used in autism. A challenge for many children with CDKLS is repetitive and restricted behaviors (RRB). Some examples are also common in autism and Rett Syndrome: continuously mouthing objects and hands, head swaying, hand flapping and clapping. Similar to obsessive compulsive disorder (OCD), repetitive behavior appears like a need for sameness and a resistance to novelty in which some children with CDKLS may resist obstruction or interruption of their rituals. It is not yet understood why this happens and there is little consensus about treatment. However, most professionals label RRBs as purposeless and maladaptive. Alternative theories suggest that the person may be seeking sensory (self-)integration, pleasurable sensations, creating distraction from stress, or that the repetitive behavior is being triggered by a possible underlying biomedical cause such as neurological dysfunction.

Vasomotor (autonomic) disturbances

Sympathetic tone is often high due to poor autonomic regulation. Symptoms often include cardiac arrhythmias and cold hands and feet. Treat the skin gently, encourage activities using the whole body, and monitor hands and feet for appropriate circulation and temperature.

Treatment Options



The CDKL5 gene is located on the short [p] arm of the X chromosome at position 22 indicated by a red line.

Antiepileptic Drugs/Medications (AEDs)

Seizures with CDKL5 disorder are difficult to treat. It is important to note that some families are very successful on low dose mono-therapy; however, some have adjunctive therapy. It is common for a child to go through several AED's or combination of medications. Physicians should work closely with families to ensure that appropriate dosing is maintained to ensure quality of life.

Ketogenic Diet

The ketogenic diet has been particularly successful for some children. Many families report increase in awareness and alertness and a decrease in seizure frequency. The ketogenic diet is a viable option for oral feeding, as well as naso-gastric tube, or G Tube feeding. Some families have tried a modified Atkins diet or a medium chain triglyceride (MCT) diet in lieu of the standard ketogenic diet. Regardless of diet choice, it is imperative for a neurologist and certified nutritionist be involved and close medical follow-up maintained.

Vagal Nerve Stimulator (VNS)

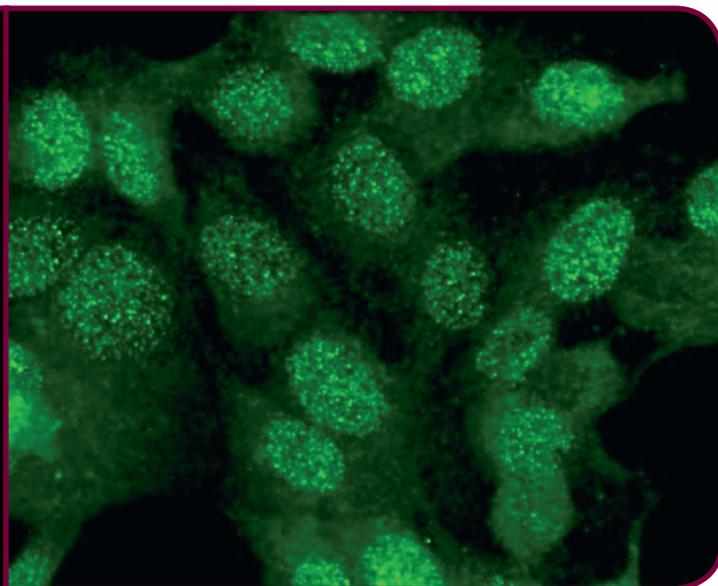
VNS is an implantable device which produces an electrical current that is carried to the brain by the vagal nerve. This device allows for the customization of the duration and frequency of stimulation. The optimal setting for these may vary between cases, with some seeing success on a lower setting and others with a more rapid setting. The VNS has been particularly effective in treating seizures and may be used in conjunction with additional anti-epileptic medications.

Neurosurgery

Neurosurgery can occasionally offer seizure control when other treatments have failed. There are multiple options that can be discussed with a neurosurgeon.

Steroid Treatment

Steroid treatments under the direct supervision of a neurologist/epileptologist have shown some efficacy for those that have Infantile Spasms as part of their seizure disorder. There is evidence that some patients with a modified hypsarrhythmia or non-convulsive status epilepticus may respond to steroid treatment.



Therapeutic Interventions

Hippotherapy/Equine Therapy

The term “Hippotherapy,” means “treatment with the help of the horse.” Hippotherapy is a form of physical, occupational, and speech and language therapy that utilizes equine movement as a tool to achieve functional outcomes. The movement provided by the horse is a multidimensional movement, which is variable, rhythmic and repetitive. Hippotherapy is an excellent tool for increasing trunk strength and control, improving balance, improving motor planning, and building overall postural strength and endurance. Equine movement offers well-modulated sensory input to vestibular, proprioceptive, tactile and visual channels. This type of therapy may also include the use of a mechanical horse.

Hydrotherapy (Aquatic Therapy)

Hydrotherapy is a therapeutic procedure which attempts to improve function through the application of aquatic therapeutic exercises. Aquatic therapy differs from land therapy due to the specific properties of water. These unique properties decrease joint compression forces, may reduce inflammation, and provide feedback for improving posture. The resistance of the water during exercise provides a safe environment for addressing balance, strength, and postural deficits. For patients who may have difficulty exercising on land, aquatic therapy provides a comfortable and therapeutic medium through which they may gain strength and endurance.

Music Therapy

Music therapists assess emotional wellbeing, physical health, social functioning, communication abilities, and cognitive skills through musical responses. Music therapy has enormous value in aiding communication skills, improving gross and fine motor skills, attention in children, and general motivation and emotional wellbeing. It can also reduce stereotypies and increase functional hand use. Music can also be used to help relax and calm the patient.

Occupational Therapy

Occupational therapy is the use of individualized treatments to develop, recover, or maintain the skills used in daily activities.

Many times, therapy goals are set for the patients to become self-sufficient for feeding, dressing, writing, holding crayons, zipping up a jacket, putting on shoes, opening a door, or buckling a seat belt. The therapist can give ideas for ways to modify tasks to meet the children's needs. Some examples of these types of helpful modifications are modified drinking cups, utensils, toys, puzzles, and crayons for writing. This therapy can increase fine motor skills as well as allow the patient to participate in more activities from day to day. Another crucial side to Occupational Therapy is sensory integration. Many patients are tactile defensive or sensory seeking. In either case, a skilled therapist can aid in developing a sensory program that fits the patient.

Physical Therapy

Physical therapy helps maintain, restore, and improve the movement, activity, and health of patients. This enables individuals of all ages to have optimal functionality and an enhanced quality of life. This is important in ensuring good postural management to prevent scoliosis and joint deformities, develop or maintain transitional skills, increase motor ability, stimulate hand use, improve body awareness, reduce muscle pain, and increase protective responses. Intensive physical therapy programs have also been successful in many cases. This particular type of intensive therapy can include, but is not limited to, the “Universal Exercise Unit,” and “Therasuit.”

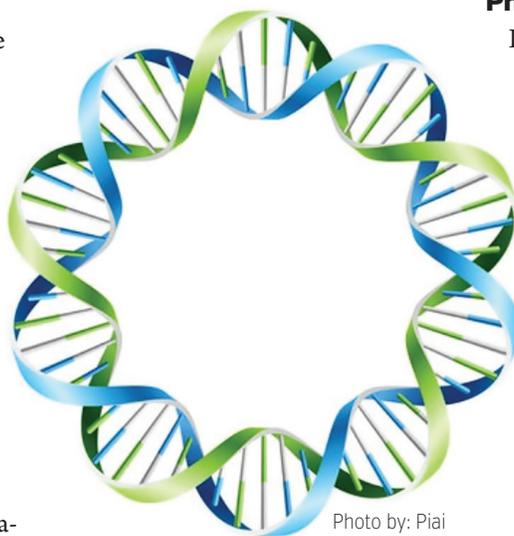


Photo by: Piai

Speech & Language

Supporting communication skills for those diagnosed with CDKLS is vital to improve concentration and develop effective communication methods. Augmentative communication should be used; many modalities of communication may prove successful. Interactive eye gaze technology used to facilitate communication for those diagnosed with CDKLS is emerging and looks promising for some affected individuals. Augmentative communication may also prove useful in the assessment of cognitive function. Speech and language therapists also have a responsibility to identify eating difficulties and provide advice about the textures of food and drink, adapted utensils, and

["Therapeutic Interventions" continued on next page]

("Therapeutic Interventions" continued from previous page)

altering the pace of eating as dysphagia and aspiration pneumonia are common problems.

Vision Services

The goal of visual rehabilitation is to maximize the use of functional vision. Vision Therapy is an individualized program designed to correct visual motor and perceptual cognitive deficiencies. Children affected by CDKL5 disorder show a range of functional vision due to varying degrees of CVI (Cortical Visual Impairment).

Taking this into consideration, vision teaching strategies need to be individualized and tailored to the abilities of each child. Vision Therapy offers comprehensive procedures designed to enhance the brain's ability to properly interpret visual information. This can aid in improving abilities such as:

- **eye alignment**
- **eye tracking and eye teaming**
- **eye focusing abilities**
- **eye movements**
- **visual processing**
- **hand-eye coordination**

Individuals affected by CVI may also benefit from sessions with an Orientation and Mobility Specialist, as well as a vision teacher (not to be confused with a vision therapist). These services are offered through most school districts for children who receive a legally blind status. The Orientation and Mobility Specialist is trained to help children who cannot see to gain confidence and be safe while learning to navigate their environment. The vision teacher is an educator that is certified to teach children with visual challenges.



Behavior & Learning

There are several types of behavior and learning therapies to consider for achieving positive and meaningful outcomes that improve quality of life. These therapies, which were developed for autism but are very successful across other developmental disorders, can be individual programs or conducted in a group setting. Some of the more popular therapies are mentioned below. This is not intended to be a comprehensive list and we encourage you to explore all programs that might be beneficial to your child.

Applied Behavior Analysis (ABA) focuses on positive reinforcement strategies that support useful behavior while decreasing undesirable behaviors. It is not a "one size fits all" approach; your child's skills, needs, preferences, interests and family should all be considered in planning treatment goals that foster a positive intervention. There are a number of ABA techniques recognized as successful, including Pivotal Response Treatment (PRT), Verbal Behavior Therapy, Relationship Development Intervention (RDI), and Social Communication/Emotional Regulation/Transactional Support (SCERTS). Always check credentials of those who claim to be qualified in behavior analysis.

Early Start Denver Model (ESDM) is a comprehensive behavioral early intervention approach for children ages 12-48 months. The program integrates a relationship-focused developmental model of ABA.

Floortime therapy is based on the premise that adults can help children expand their circles of communication by meeting them at their developmental level and building on their strengths. It encourages you to literally engage your child on the floor, working towards six specific developmental milestones that are crucial for emotional and intellectual growth. Many psychologists, educational specialists, and speech and occupational therapists have formal training in Floortime techniques.

Sensory Integration Therapy is useful with challenges in processing sensory information such as movement, touch, smell, sight, and sound. It identifies disruptions and suggests a variety of techniques that improve how the brain interprets and integrates this information.

Professionals

CDKL5 Centers of Excellence

Children's Hospital Colorado

Anschutz Medical Campus
13123 East 16th Ave.
Aurora, CO 80045

Lead Physician: **Dr. Tim Benke**

To schedule an appointment, please contact

Tristen Dinkel at: rettclinic@childrenscolorado.org

Boston Children's Hospital

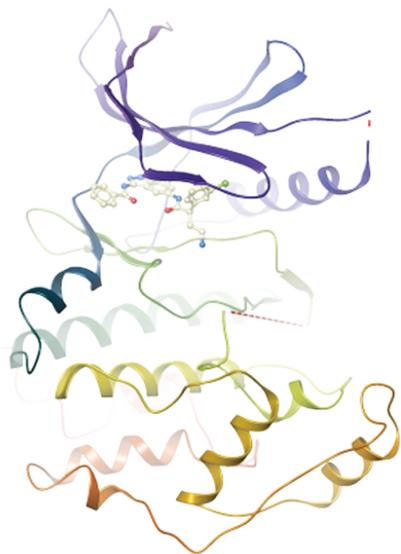
300 Longwood Avenue
Boston, MA 02115

Lead Physicians: **Dr. Walter Kaufmann and
Dr. Heather Olson**

The Cleveland Clinic

Main Campus
Mail Code S60
9500 Euclid Avenue
Cleveland, OH 44195
[216] 444-5559

Lead Physician: **Dr. Sumit Parikh**



Human CDKL5 kinase domain photo credit: SGC

CDKL5 Testing Laboratories

With the help of your child's doctor's office, you can send blood samples to a special laboratory that performs the genetic test for CDKL5. The list below contains some of the more common labs that perform this test.

Medical Genetics Laboratories

Baylor College of Medicine

Houston, TX 77030

[713]798-6555 or [800]411-4363 Fax: [713]798-2787

University of Chicago

Genetic Services Laboratories

Chicago, IL

[888]824-3637 or [773]834-0555 Fax: [312]729-2808

Greenwood Genetic Center

Diagnostic Laboratories

106 Gregor Mendel Circle
Greenwood, SC 29646

[864]941-8100 or [888]442-4363 Fax: [864]941-8141

Claritas Genomics (formerly Children's Hospital Boston)

Cambridge, MA

clientservices@claritasgenomics.com

[617]553-5880 or [855]373-9003 Fax: [617]553-5842

Center for Human Genetics, Inc

Boston University School of Medicine

Cambridge, MA

617-492-7083

Emory Genetics Laboratory

2165 N. Decatur Rd.

Decatur, GA 30033

Email: domglab@emory.edu

[404]778-8500 or [855]831-7447 Fax: [404]778-8559

GeneDX

207 Perry Parkway

Gaithersburg, MD 20877

www.genedx.com

[301]519-2100 Fax: [301]519-2892

CDKL5 Resources and Foundations

International Foundation for CDKL5 Research
www.cdkl5.com

CDKL5 Canada
www.cdkl5canada.ca

CDKL5 Association in Italy
www.cdkl5.org

CDKL5 UK
www.cdkl5uk.org

CDKL5 Japan
27801323403000020013.vpweb.jp/default.html

CDKL5 Netherlands
www.cdki-5.nl

L'Albero di Greta – Onlus – Associazione Italiana CDKL5
www.lalberodigreta.org

CDKL5 International Database
<http://www.cdkl5.com/Research/database.aspx>

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The CDKL5 International Database

The CDKL5 International Database is a vitally important research tool in which all families (world-wide) affected by CDKL5 are encouraged to participate. IFCR has partnered with researchers Helen Leonard and Jenny Downs at the Telethon Kid's Institute [Australia] in the development of the database as we recognize its importance in research, treatments, interventions and clinical trials. The database has been active since 2012 and is in collaboration with the CDKL5 Centers of Excellence to create a comprehensive database that includes clinical information. As the number of patients being reported continues to grow, a better understanding of the clinical picture of CDKL5 is starting to emerge.

Why is this database and patient participation so important? CDKL5 is still so new and rare that the only way to truly understand this disorder and all the complications, treatments, interventions and natural progression of this disorder is to compile the data from as many patients as possible so it can be thoroughly evaluated. Research can then be directed in a more targeted approach, and the information contained in the database is critical for any clinical trials in the future. Once we understand the spectrum of CDKL5 and have a good picture of what is happening in the lives of those affected, we are then able to begin to make widespread and meaningful changes that can improve the quality of lives for those affected. We highly encourage all families to take part in this project so that all children and adults living with CDKL5 have the best chance for treatments and a cure.

Emerging results regarding the following topics is available at www.cdkl5.com

Description and Treatment of Epilepsy in CDKL5

Epilepsy is the most common symptom of CDKL5 disorder and early onset refractory epilepsy continues to be one of the identifying characteristics of this disorder.

Motor Development in CDKL5

There is variability within the CDKL5 disorder in regard to gross motor abilities.

Gastrointestinal Problems identified in CDKL5 Disorder

Consistent with the picture in other neurological disorders, gastrointestinal symptoms occur frequently in the CDKL5 disorder, affecting both males and females.

Please visit CDKL5 International Research Database at:

<http://www.cdkl5.com/Research/Database.aspx>

to learn more about participating in this important research!

