A VISUAL

GUIDE

TO UNDERSTANDING

CDKL5
DISORDER

INFORMATION FOR FAMILIES LIVING WITH CDKL5 DISORDER

What is CDKL5 disorder?

(Note: some words that may be unfamiliar are **highlighted** and are defined in the glossary at the end of this brochure)

CDKL5 disorder (also called CDKL5 deficiency disorder, or just CDKL5) is a rare, **neurological**, genetic disease caused by certain variants in a **gene** called *CDKL5* (cyclin-dependent kinase-like 5). These variants prevent the *CDKL5* gene from functioning correctly.[1]

Scientists do not yet fully understand the full spectrum of disorders related to the *CDKL5* gene. Only certain variants of the *CDKL5* gene lead to CDKL5 disorder.[1]

The *CDKL5* gene is located on the X **chromosome**. More than 85% of people who have CDKL5 disorder are female. Males who have CDKL5 disorder tend to be more severely affected.[2-4]

Exactly how many people have CDKL5 disorder is not currently known. But as awareness of CDKL5 disorder grows, more and more diagnoses are being made.[1]

What is the function of the *CDKL5* gene?

The *CDKL5* gene provides instructions to the body for making a protein (called the CDKL5 protein) that's needed for the brain and **nervous system** to develop and work normally.[4]

The CDKL5 protein acts as a kinase, which is a type of **enzyme** that changes the way other proteins function in the body. Researchers have not yet identified all of the other proteins that CDKL5 controls.[4]

Is CDKL5 disorder related to any other disorders?

The **signs** and **symptoms** of CDKL5 disorder can be very similar to those seen in other neurological disorders, such as infantile spasms, West syndrome, Lennox-Gastaut, early onset epilepsy of infancy, autism, FOXG1 and Rett syndrome. Genetic testing is required for a definite diagnosis of CDKL5 disorder.[3,5,6]

CDKL5 disorder was once considered an atypical form of Rett syndrome. Although many of the features and symptoms of the two disorders can be very similar, there are also differences between them. One important example is that people who have Rett syndrome often regress (meaning that they lose skills or abilities, such as walking or talking, that they had previously mastered), and this does not happen in patients who have CDKL5 disorder. Scientists now believe that CDKL5 disorder is a distinct condition that is closely related to Rett syndrome. However, a lot of research still remains to be done to clarify the relationship between CDKL5 disorder and Rett syndrome.[4]

EVERY PATIENT IS **UNIQUE**

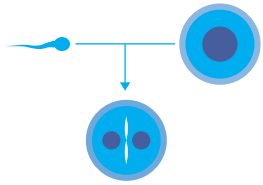
How do variants of the *CDKL5* gene happen?

Everyone has information called **deoxyribonucleic acid**, or **DNA**, coded into his or her **cells**.

DNA is inherited through genes that are passed down from the person's mother and father.

Sometimes, **gene variants** (also called mutations) occur in the DNA code that makes up a particular gene that can change the way the gene functions.

Most gene variants are passed down from parents to their children. But in some cases, new changes in the DNA code of a gene can happen spontaneously around the time of conception.



These new DNA changes happen in either the sperm cell, the egg cell, or the fertilized egg. They produce a type of gene variant called a ***de novo*** variant (or *de novo* mutation). *De novo* variants are not part of either parent's DNA (*"de novo"* means new).

Research suggests that most gene variants associated with CDKL5 disorder are *de novo*. This means that CDKL5 disorder may not run in families in the same way many genetic diseases do. Exactly why *de novo* variants of the *CDKL5* gene happen is not known.[1]

How is CDKL5 disorder treated?[4]

No specific treatment currently exists for CDKL5 disorder. However, therapies are available that can help manage its symptoms, such as:

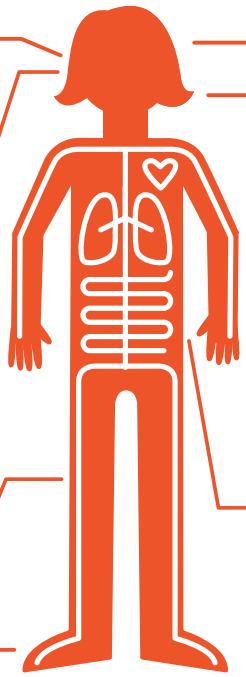
- Anti-epileptic drugs (AEDs)
- Vagal nerve stimulators
- Dietary changes/modifications
- Physical, occupational and speech therapies

Although no specific treatment for CDKL5 disorder has yet been approved, new research is taking place.
To learn more about research and clinical trials for CDKL5 disorder, visit clinicaltrials.gov or clinicaltrialsregister.eu, or talk to a health-care provider.

What are the signs and symptoms of CDKL5 disorder?

Although the signs and symptoms of CDKL5 disorder affect many different parts of the body, almost all of them are related in some way to problems with the brain and nervous system.

Signs and symptoms of CDKL5 disorder tend to follow certain characteristic patterns, but they can vary significantly among different people who have the disorder. Some people who have CDKL5 disorder have only mild signs and symptoms, while others may be much more severely affected. Not everyone with CDKL5 disorder will have all of the signs and symptoms listed below.



BEHAVIORAL SYMPTOMS[2,5]
- Episodes of laughing or crying that happen for what appears to be no reason
- Hypersensitivity to touch (eg, dislike of hair brushing)
- Disrupted sleep

EYES/EYESIGHT[4,5,7]
- Lack of eye contact or poor eye contact
- Frequent sideways glances
- Cortical visual impairment, or cortical blindness (a form of blindness caused by problems in the brain)

FACIAL APPEARANCE[2,5]
- Microcephaly (unusually small head)
- High, broad forehead
- Large, deep-set eyes
- Smaller-than-normal space between nose and upper lip
- Upturned nose
- Full lips
- Widely-spaced teeth

MOUTH/SPEECH/FEEDING[5]
- Grinding of the teeth (bruxism)
- Limited or absent speech
- Difficulties with eating

HANDS[5]
- Repetitive hand movements such as clapping, tapping or mouthing (stereotypies)
- Limited ability to make small, focused hand movements (eg, picking up small objects)

DIGESTIVE SYSTEM[5]
- Backflow of acidic stomach contents into the esophagus (gastroesophageal reflux)
- Constipation

LEGS[5]
- Difficulties in standing and walking

FEET[5]
- Small, cold feet

SYSTEMIC (FULL-BODY) SYMPTOMS[5-7]

Seizures
- Start within the first 3 months of life (as early as the first week after birth)
- Are resistant to treatment
- Change with age, usually following a predictable pattern
- Occur daily in most people

Other
- Low muscle tone
- Diminished motor (movement) skills

What happens when a doctor suspects CDKL5 disorder?[1]

CDKL5 disorder may be suspected in a person who is experiencing a characteristic pattern of symptoms (usually including seizures and developmental delays).

Genetic testing is done to check for variants of the *CDKL5* gene that are known to cause CDKL5 disorder. Various tests may be conducted, such as those that evaluate genes associated with epilepsy or intellectual disability.

Results of the genetic testing are reviewed with an expert in neurogenetics or another related discipline.

If test results show a variant of the *CDKL5* gene that is known to be associated with CDKL5 disorder:

The person is diagnosed with CDKL5 disorder.

If test results show a variant of the *CDKL5* gene that is NOT already known to be associated with CDKL5 disorder:

More testing is done to determine the likelihood that the variant is responsible for the person's symptoms.

If test results show a normal *CDKL5* gene:

More testing is done to identify the cause of the person's symptoms.

What do these words mean?

Cell: the basic building block of all living things

Chromosome: structure that contain genes

De novo *variant or mutation:* an alteration in a gene that is present for the first time in one family member and can be passed to future generations

Deoxyribonucleic acid (DNA): substance within genes that contains instructions, or code, for making proteins, including enzymes

Enzyme: a special type of protein that speeds up chemical reactions that take place within a cell

Gene: the basic unit of heredity contained within each cell, made up of DNA, that is passed from parent to child

Gene variant: (also known as mutation) a change to the structure of a gene that can alter the gene's function, sometimes resulting in diseases or conditions

Nervous system: the network of nerve cells in the body

Neurological: related to the anatomy and functions of the nervous system and brain

Sign: objective evidence of a disease or condition that can be recognized by the patient, as well as others

Symptom: subjective evidence of a disease or condition that can be recognized only by the patient

Other resources that may be helpful are listed below.*

- **CDKL5 UK**
  curecdkl5.org
- **Epilepsy Foundation**
  epilepsy.com
- **EURORDIS**
  eurordis.org
- **International Foundation for CDKL5**
  cdkl5.com
- **National Organization for Rare Disorders**
  rarediseases.org

*These links will take you to sites that are not owned or maintained by Amicus Therapeutics. Amicus Therapeutics is not responsible for the information contained on third-party sites.

References: **1.** Hector RD, Kalscheuer VM, Hennig F, et al. CDKL-5 variants: improving our understanding of a rare neurologic disorder. *Neurol Genet.* 2017;3(6):e200. doi: 10.1212/NXG.0000000000000200. **2.** Archer HL, Evans J, Edwards S, et al. CDKL5 mutations cause infantile spasms, early onset seizures, and severe mental retardation in female patients. *J Med Genet.* 2006;43(9):729-734. **3.** Mangatt M, Wong K, Anderson B, et al. Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome. *Orphanet J Rare Dis.* 2016;11:39. doi: 10.1186/s13023-016-0418-y. **4.** Bahi-Buisson N, Bienvenu T. CDKL5-related disorders: from clinical description to molecular genetics. *Mol Syndromol.* 2012;2(3-5):137-152. **5.** Fehr S, Wilson M, Downs J, et al. The CDKL5 disorder is an independent clinical entity associated with early-onset encephalopathy. *Eur J Hum Genet.* 2013;21(3)266-273, doi: 10.1038/e-jhg.2012.156. **6.** Zhao Y, Zhang X, Bao X, et al. Clinical features and gene mutational spectrum of CDKL5-related diseases in a cohort of Chinese patients. *BMC Med Genet.* 2014;15:24. doi: 10.1186/1471-2350-15-24. **7.** Kilstrup-Nielsen C, Rusconi L, La Montanara P, et al. What we know and would like to know about CDKL5 and its involvement in epileptic encephalopathy. *Neural Plast.* 2012;2012:728267. doi: 10.1155/2012/728267.

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Amicus Therapeutics, Inc.
1 Cedar Brook Drive
Cranbury, NJ 08512
USA

Amicus Therapeutics UK LTD
One Globeside
Fieldhouse Lane
Marlow SL7 1HZ
United Kingdom

Amicus Therapeutics®