# Batten disease

**What is Batten disease?**

Batten disease is the common name for a broad class of rare, fatal, inherited disorders of the nervous system also known as neuronal ceroid lipofuscinoses, or NCLs. In these diseases, a defect in a specific gene triggers a cascade of problems that interferes with a cell's ability to recycle certain molecules. The disease has several forms that share some of the same features and symptoms but vary in severity and age when symptoms first begin to appear. Each form is caused by a mutation in a different gene. Although "Batten disease" originally referred specifically to the juvenile-onset form of NCL, the term Batten disease is increasingly used to describe all forms of NCL.

Most forms of Batten disease/NCLs usually begin during childhood. Children with the disease often appear healthy and develop normally before they begin to show symptoms. Children with the infantile or late-infantile forms usually show symptoms earlier than age 1 year. Common symptoms for most of the forms include vision loss, seizures, delay and eventual loss of skills previously acquired, dementia, and abnormal movements. As the disease progresses, children may develop one or more symptoms including personality and behavior changes, clumsiness, learning difficulties, poor concentration, confusion, anxiety, difficulty sleeping, involuntary movements, and slow movement. Over time, affected children may suffer from worsening seizures and progressive loss of language, speech, intellectual abilities (dementia), and motor skills. Eventually, children with Batten disease become blind, wheelchair bound, bedridden, unable to communicate, and lose all cognitive functions. There is no cure for these disorders but a treatment for one of the forms (CLN2 disease) has been approved by the U.S. Food and Drug Administration (see Treatment section).

Children with all forms of Batten disease have a greatly shortened life expectancy. Generally, the increased risk for early death depends on the form of the disease and age of the child at disease onset. Children with infantile Batten disease die prematurely, often in early childhood, while those with later-onset forms may live into their teens to their thirties. If the disease develops in adulthood, the symptoms tend to be milder and may not affect life expectancy.

**What causes Batten disease?**

Batten disease is an inherited genetic disorder that appears to affect the function of tiny bodies within cells called lysosomes. Lysosomes are the "recycle bin" of the cell and regularly break down waste, proteins, and naturally occurring fatty compounds called lipids into smaller components that can be discarded out of the cell or recycled. Lipids include fatty acids, oils, waxes, and sterols. In Batten disease/NCLs, the mutated genes do not produce the proper amounts of proteins important for lysosomal function. Each gene (representing a form of the disease) provides information for a specific protein that is in turn, defective and not produced. These proteins are needed for brain cells (neurons) and other cells to work efficiently. The lack of a functional protein causes the abnormal buildup of "junk" material in the lysosomes—as well as the abnormal buildup of the residue called lipofuscin that occurs naturally as part of the lysosomal breakdown of lipids. It is not known whether the lipofuscin itself is toxic or if the buildup is a marker of impaired lysosomal function.

**How are the forms of Batten disease and the NCLs classified?**

The NCL disorders are classified by the gene that causes the disorder, although they are sometimes described by the child's age at the time symptoms begin to appear. Each gene is called CLN (ceroid lipofuscinosis, neuronal) and given a different number designation as its subtype. Because of the different gene mutations, signs and symptoms range in severity and progress at different rates. The disorders generally include a combination of vision loss, epilepsy, and dementia. Some forms of the NCLs are:

- **CLN1 disease, infantile onset.** The CLN1 gene, found on chromosome 1, directs the production of an enzyme called palmitoyl-protein thioesterase 1 (PPT1). (A chromosome is a threadlike structure that contains all the genetic information needed and resides inside the nucleus of most cells). A deficiency in the PPT1 protein or its

poor operation allows the abnormal buildup of lipids and proteins. In the classic infantile form, symptoms are seen before age 1 and progress rapidly. Developmental skills such as standing, walking, and talking are not achieved or are gradually lost. Children often develop seizures by age 2 and eventually become blind. By age 3 children may become completely dependent on their caregivers, and some may need a feeding tube. Most affected children die in early to mid-childhood.

- **CLN1 disease, juvenile onset.** Some children with CLN1 abnormalities develop the disease after infancy—around age 5 or 6—and have slower disease progression. Affected children may live into their teenage years. Others may not develop symptoms until adolescence and may live into adulthood.
- **CLN2 disease, late-infantile onset.** The CLN2 gene, found on chromosome 11, produces an enzyme called tripeptidyl peptidase 1 that breaks down proteins. The enzyme is insufficiently active in CLN2 disease. Developmental delay begins around the end of age 2. Children develop seizures and begin to gradually lose the ability to walk and speak. Brief, involuntary jerks in a muscle or muscle group (called myoclonic jerks) typically begin around age 4-5. By age 6 most children are completely dependent on their caregivers, and many will require a feeding tube. Most children with CLN2 disease die between the ages of 6–12 years.
- **CLN2 disease, later-onset.** Some children with CLN2 abnormalities develop the disease later in childhood —around age 6 or 7—and have slower disease progression. In later-onset CLN2 disease, loss of coordination (ataxia) may be the initial symptom. Affected children may live into their teenage years.
- **CLN3 disease, juvenile onset (ages 4-7).** The disease is caused by a mutation in the CLN3 gene, found on chromosome 16. The gene directs the production of a protein called battenin, which is found in the membranes of the cell. Most children suffering from CLN3 disease have a missing part in the gene which in turn results in inability for the protein to be produced. Rapidly progressive vision loss begins between ages 4 and 7. Children develop learning and behavior problems, and slow cognitive decline (dementia) and then start having seizures around age 10. In the teenage years, children affected by CLN3 disease develop slow movement, stiffness, and loss of balance (also referred as parkinsonism). They also develop difficulty with speech and language. As they age, children and teenagers become increasingly dependent on their caregivers. Most children with the disease die between the ages of 15 and 30.
- **CLN4 disease, adult onset.** Also known as Kufs disease type B, this very rare form typically begins in early adulthood (normally around age 30) and causes problems with movement and early dementia. The symptoms progress slowly, and CLN4 disease does not cause blindness. It is related to mutations in the DNAJC5 gene on chromosome 20. The age of death varies among affected individuals.
- **CLN5 disease, variant late-infantile onset.** This disease is caused by problems with a lysosomal protein called CLN5, whose function is unknown. The CLN5 gene is located on chromosome 13. Children progress normally for the first few years of life before they start losing skills and develop behavior problems. Seizures and myoclonic jerks begin usually between ages 6 and 13. Vision deteriorates and is eventually lost. Children have learning disabilities and problems with concentration and memory. Some may need a feeding tube. Most children with CLN5 live into their late childhood or teenage years.
- **CLN6, variant late-infantile onset.** The gene CLN6, located on chromosome 15, directs the production of the protein CLN6, also called linclin. The protein is found in the membranes of the cell (most predominantly in a structure called the endoplasmic reticulum). Its function has not been identified. Symptoms vary among children, but typically start after the first few years of life and include developmental delay, changes in behavior, and seizures. Children eventually lose skills for walking, playing, and speech. They also develop myoclonic jerks, problems sleeping, and vision loss. Most children with CNL6 die during late childhood or in their early teenage years.
- **CLN6, adult onset.** Also known as Kufs disease Type A, this form of CLN6 disease shows signs in early adulthood that include epilepsy, inability to control muscles in the arms and legs (resulting in a lack of balance or coordination, or problems with walking), and slow but progressive cognitive decline.
- **CLN7, variant late-infantile onset.** This disease is caused by mutations in the CLN7 gene located on chromosome 4, which produces the protein MFSD8—a member of a protein family called the major facilitator superfamily. This superfamily is involved with transporting substances across the cell membranes. As with all the other forms of Batten disease, the defect in the gene results in lack of production of the protein. Developmental delays begin after a few years of what seems to be a normally-developing child. Children usually develop epilepsy between the ages of 3 and 7, along with problems sleeping and myoclonic jerks. Children begin to lose the ability to walk, play, and speak as the disease progresses, with a rapid advancement of symptoms seen between the ages of 9 and 11. Most children with the disorder live until their late childhood or teenage years.
- **CLN8 disease with Epilepsy with Progressive Mental Retardation (EPMR).** Abnormalities in the CLN8 gene cause epilepsy with progressive decline in mental function. The gene, located on chromosome 8, encodes a protein also called CLN8, which is found in the membranes of the cell—most predominantly in the endoplasmic reticulum (part of the recycling-bin machinery of the cell). The protein's function has not been identified. Onset of symptoms begins between ages 5 and 10 and include seizures, cognitive decline, and behavioral changes. Seizures typically become very intermittent after adolescence. Loss of speech occurs in some individuals. Affected individuals can live into adulthood. A very rare form of the disorder is sometimes called Northern Epilepsy syndrome, because it occurs in certain families in an area of Finland.

- **CLN8 disease, late-variant onset.** Affected children begin showing symptoms between ages 2 and 7, which include loss of vision, cognitive problems, unsteadiness, myoclonic jerks, and behavioral changes. Children develop treatment-resistant epilepsy and a marked loss of cognitive skills by age 10. Many children lose the ability to walk or stand unassisted. Life expectancy is uncertain; some children have lived into their second decade of life.
- **CLN10 disease.** This very rare disease is caused by a mutation in the CTSD gene, located on chromosome 11, which produces a protein known as cathepsin D. Cathepsin D is an enzyme that breaks apart other proteins in the lysosome. The disease typically is seen soon after birth, although it can occur later in childhood or adulthood. Some children have microcephaly—an abnormally small head size with reduced brain size.
  - In the congenital form, seizures may occur before birth but are hard to differentiate from normal baby movements.Following birth, babies may have seizures that do not respond to treatment, problems with breathing that can progress to respiratory failure, and obstructive sleep apnea.Babies may die shortly after birth or within the first weeks of life.
  - A late-infantile form of the disease features a later onset of symptoms and slower disease progression.As children age, they develop seizures and progressive problems with vision, balance, and intellectual skills.Affected individuals also may have problems coordinating muscle movement and trouble with walking (called ataxia) as well as very stiff muscles (spasticity).Children with the disease often die in early childhood.

**How many people have these disorders?**

It is not known how many people have Batten disease, but by some estimates it can be as frequent as in 1 in 12,500 people in some populations. It affects an estimated 2 to 4 out of every 100,000 children in the United States. Many more individuals may be carriers (see below) of a defective gene that can cause any of the NCL diseases. Although NCL diseases are rare, the childhood onset variants are the most common neurodegenerative disorders of childhood. Occasionally an NCL disease occurs in more than one person in families that carry the defective genes.

**How are NCLs inherited?**

People normally have two copies of the same gene in their cells, one comes from the father and one from the mother. This means that, in some cases, the cells have a “back up” system if only one copy is needed for the cell to function properly. Batten disease is caused when both copies (one from each parent) of the specific gene causing the disease are defective. This is known as autosomal recessive disease. People who only have one defective copy (carriers) will not develop symptoms and are usually unaware of their carrier condition. The rare exception may be for Adult NCL (see below).

If both parents carry one defective gene that causes NCL, there is a 1 in 4 chance during each pregnancy of having a child with the disease. At the same time, during each pregnancy there is 50 percent chance for the baby to inherit only one copy of the defective gene, which would make the child a “carrier” like the parent, as a normal copy will be inherited from the other parent. Carriers most often are not affected by the disease but can pass the abnormal gene to their children in a similar fashion to which they inherited it from their own parents. Finally, there is a 1 in 4 chance for the baby to inherit two completely normal genes.

At risk for any form of Batten disease are children whose parents have Batten disease, and children whose parents are carriers of an NCL gene that causes the disorder but aren’t severely affected by the disorder, if at all.

Adult NCL/Kufs disease B may be inherited as an autosomal recessive or, less often, as an autosomal dominant disorder. In autosomal dominant inheritance, everyone who inherits a defective of the disease gene develops the disease, even when they may have inherited a normal copy.

**How are these disorders diagnosed?**

Following a review of the person’s individual and family medical history and a neurological exam, several tests can be used to diagnose Batten disease and other neuronal ceroid lipofuscinoses. Currently, most diagnoses of Batten disease are made by genetic testing. Possible diagnostic tests include:

- DNA analysis/genetic testing can confirm the presence of a mutated gene that causes an NCL disease, as well as be used in prenatal (before birth) diagnosis of the disease. Increasingly, the NCL genes are being included on commercially available epilepsy genetic panels that test several genes at the same time.
- measurement of enzyme activity can be used to confirm or rule out CLN1 and CLN2 disease.
- blood or urine tests can detect abnormalities that may indicate Batten disease. For example, elevated levels of a chemical called dolichol are found in the urine of many individuals with NCL and the presence of abnormal white

blood cells that contain holes or cavities—called vacuolated lymphocytes—is common to certain disease mutations.
- skin or tissue sampling can show distinctive shapes formed by lipofuscin accumulation—some look like half-moons while others look like fingerprints—when viewed under a special microscope. The lipofuscins also take on a greenish-yellow color when viewed under an ultraviolet light microscope.
- electroencephalograms (EEG) monitor brain activity through the skull, using electrodes that are placed on the scalp. Telltale patterns in the brain's electrical activity suggest an individual has seizures and some patterns along with findings on the exam and clinical history may be strongly suggestive of a specific type of NCL disease.
- electrical studies of the eyes, which include visual-evoked responses (which measure electrical activity in the brain generated by sight) and electroretinograms (used to detect abnormalities with the retina), can identify various eye problems common in several NCLs. The greenish-yellow color of lipofuscins can sometimes be detected by examining the back of the eye. These are less frequently performed now, as most diagnosis can be made with DNA testing.
- diagnostic imaging using computed tomography (CT) and magnetic resonance imaging (MRI) scans can help doctors look for changes in the brain's appearance.

**Is there any treatment?**

No specific treatment is known that can reverse the symptoms of any form of Batten disease. In 2017 the Food and Drug Administration approved an enzyme replacement therapy for CLN2 disease (TTP1 deficiency) called cerliponase alfa (Brineura®) that has been shown to slow or halt the progression of symptoms. There are no treatments that can slow or stop disease progression for other NCL disorders.

Seizures can sometimes be reduced or controlled with antiseizure drugs. Other medicines are available to treat anxiety, depression, parkinsonism (stiffness and difficulty with walking/doing tasks), and spasticity (muscle stiffness). Additional medical problems can be treated appropriately as they arise. Physical and occupational therapy may help those with the disease retain function as long as possible. Support groups can help affected children, adults, and families to share common concerns and experiences, and to cope with the severe symptoms of the disease.

**What research is being done?**

The National Institute of Neurological Disorders and Stroke (NINDS), a part of the National Institutes of Health (NIH), conducts research and supports studies of the brain and central nervous system through grants to major medical institutions across the country. NIH is the leading supporter of biomedical research in the world.

Much of NINDS' research on Batten disease and the neuronal ceroid lipofuscinoses focuses on gaining a better understanding of the disease, gene therapy, and developing novel drugs to treat the disorders.

**CLN1 Disease.** Scientists are using a modified safe virus to deliver a replacement, functioning gene to the brain (gene therapy). In gene therapy, the correct gene code is attached to an adeno-associated virus—a small virus that causes a very slight immune reaction that doesn't seem to be harmful to humans—and the virus allows for the gene to be delivered to cells at specific sites. Scientists hope the replacement gene will take over for or restore the production of the protein in the cell. Other researchers are using a novel adeno-associated virus to understand the gene mutation in juvenile-onset NCL disease and how it contributes to nerve cell loss. Researchers hope the results will determine if the virus will be effective in treating the disease in humans.

Scientists are combining gene therapy with bone marrow transplantation to treat infantile Batten disease. Using a mouse model of the disease, they found some effectiveness in using stand-alone gene therapy but no detectable increase in palmitoyl-protein thioesterate-1 (PPT1) activity in the brain using bone marrow transplants alone. The combined therapy was shown to extend life span with improved motor function. Researchers now hope to determine the effectiveness of novel combinations of small molecule drugs, gene therapy, and bone marrow transplantation in this model of the disease. None of these studies have been done in children suffering from CLN1 disease.

NIH researchers have identified a potential new drug—the NtBuHA molecule—to treat CLN1 disease. The scientists tested the NtBuHA molecule in a mouse model of disease and found that the compound greatly reduced the waxy buildup, protected neurons in the brain, slowed the deterioration in motor coordination, and extended the animals' lifespans. Another molecular project is studying lanthionine ketamine, a natural compound found in the brain that activates a cell's ability to recycle its contents (a process called autophagy). The compound and its derivative, lanthionine ketamine ethyl ester, have been shown to have neuroprotective properties and may lead to research into the development of new molecules capable of treating a variety of neurological disorders in which the cellular

recycling process has been disrupted.

**CLN2 Disease.** Several studies seek to assess the natural history of Batten disease and find ways to treat it. One NINDS-funded project is studying the genetic and observable characteristics of how the disease progresses in children of all ages who have been diagnosed with late-infantile Batten disease. The study is running parallel with an NIH-supported study that is evaluating the effectiveness of a new drug for the disorder that will be delivered by gene therapy. Another study will refine and validate the Unified Batten Disease Rating Scale as a clinical rating instrument for Batten disease. Currently there have been no systematic clinical studies of Batten disease using a standardized rating instrument.

**CLN3 Disease.** The amino acid glutamate—a chemical involved in the way cells speak with each other—is constantly recycled by neurons and supportive cells. Excessive glutamate can damage or kill nerve cells, and elevated glutamate levels have been found in the brains of children with the CLN3 gene mutation. NINDS-funded researchers are using a mouse model to investigate the metabolic recycling pathways responsible for the regulation of glutamate levels in the brain. By studying a compound that might improve the ability of support cells to recycle glutamate and prevent glutamate toxicity within neurons, researchers hope to develop a potential therapy for children with juvenile Batten disease.

It is likely that multiple medications/approaches or a combination of multiple drugs with activity against ceroid along with gene therapy may be required as treatment against the different NCLs.

NINDS helps fund the Lysosomal Diseases Network, a combined network of research centers, clinical investigators, patient advocacy groups, and other interested parties that advocate for research on diagnosing, managing, and treating lysosomal and related diseases, including Batten disease. Research emphasis includes quantitative analysis of the central nervous system structure and function, the development of biomarkers (biological measures that may indicate the presence or accurately predict the rate of disease progression in a person, or the effectiveness of a therapy), and longitudinal studies of the natural history and treatment of the disease.

For additional information about clinical research on Batten disease and NCL disorders, visit ClinicalTrials.gov, a registry and results database of clinical studies of human participants conducted around the world. More information about research on NCL disorders supported by NINDS and other NIH Institutes and Centers can be found using NIH RePORTER, a searchable database of current and past research projects.

**How can I help research?**

NINDS supports the NIH NeuroBioBank, a collaborative effort involving several brain banks across the United States that supply investigators with tissue from people with neurological and other disorders. Tissue from individuals with Batten disease is needed to allow scientists to study this disorder more intensely. The goal is to increase the availability of, and access to, high quality specimens for research to understand the neurological basis of the disease. Prospective donors can begin the enrollment process by visiting https://neurobiobank.nih.gov/donors-why/.

**Where can I find more information?**

**BRAIN**
P.O. Box 5801
Bethesda, MD 20824
800-352-9424

Information also is available from the following organizations:

**Batten Disease Support and Research Association**
1175 Dublin Road
Columbus, OH 43215
info@bdsra.org
Tel: 800-448-4570
Fax: 866-648-8718

**Children's Brain Disease Foundation [A Batten Disease Resource]**

Parnassus Heights Medical Building, Suite 900
Suite 900
San Francisco, CA 94117
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**Nathan's Battle Foundation [For Batten Disease Research]**
459 State Road 135 South
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**Hide and Seek Foundation for Lysosomal Storage Disease Research**
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