A VISUAL GUIDE TO CLN3 A FORM OF BATTEN DISEASE

INFORMATION FOR FAMILIES LIVING WITH CLN3 DISEASE

Amicus Therapeutics has developed this educational resource in collaboration with the rare disease community and thought leaders.

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What are the signs and symptoms of CLN3 disease?

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

The signs and symptoms of CLN3 disease usually begin in early childhood and tend to progress in a predictable way for many years.[5] Children who have CLN3 disease usually seem healthy and develop normally for the first few years of their lives. Vision problems are the first symptoms to appear in 4 out of 5 people with CLN3 disease.[3]

Next, behavior problems and a decline in cognitive (thinking) abilities develop, which are often followed by seizures and problems with motor skills, such as speaking and walking. All of the signs and symptoms of CLN3 disease are progressive, meaning they get gradually worse over time.[12]

AGE 5-6 YEARS[3,10,13]

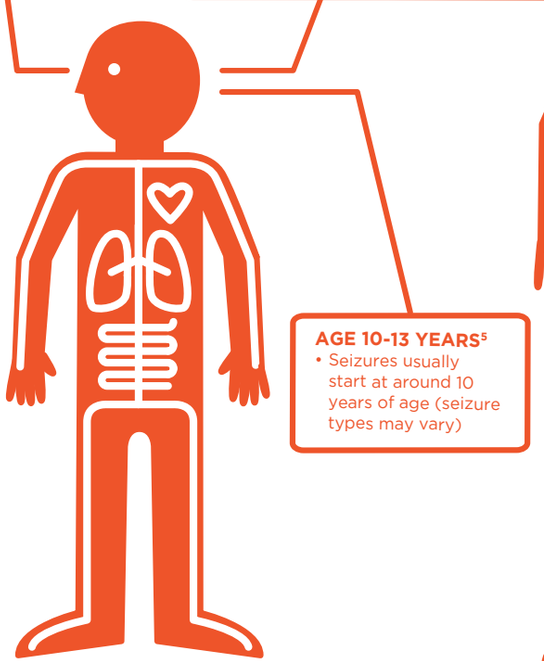
- Rapidly progressing vision problems, including night blindness, sensitivity to light, loss of peripheral vision (ability to see things to the side when the eye is looking forward) and loss of visual acuity (sharpness of vision)

AGE 7-9 YEARS[3,12]

- Gradually worsening cognitive problems, such as difficulties with attention, memory and understanding language
- Anxiety, depression and other mood problems
- Behavioral problems (angry outbursts, uncooperative or aggressive behavior)
- Hallucinations (seeing things that aren't there) and psychotic symptoms
- Problems with sleep, such as difficulty falling asleep, awakening frequently during the night and nightmares

AGE 10-13 YEARS[5]

- Seizures usually start at around 10 years of age (seizure types may vary)



MIDDLE SCHOOL AGED[3]

- Speech problems such as echolalia (repetitive speech patterns) and dysarthria (muscle weakness that makes it difficult to pronounce words clearly)
- Difficulties in controlling body movements
- Problems with walking

LATER TEENS & EARLY ADULTHOOD[3]

- Loss of memory and general reasoning abilities
- Loss of the ability to speak
- Difficulties with swallowing (also called dysphagia) and/or chewing that may require the eventual use of a feeding tube

- Heart problems, including enlargement of the heart and abnormal heartbeat rhythm[14]
- Severe movement problems (including limb rigidity and involuntary movements)[3]
- Shuffling and/or abnormally slow gait that progresses to a complete inability to walk[3]
- Death usually occurs in the third decade of life (CLN3 disease may progress at different rates in different people; however, the average lifespan from when symptoms first appear to death is about 15 years)[3,10]

What do these words mean?

A glossary of words that are important to understand when discussing CLN3 disease:

- ***Cell:*** basic building block of all living things
- ***Deoxyribonucleic acid (DNA):*** substance within genes that contains instructions, or code, for making proteins, including enzymes
- ***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
- ***Lipopigments:*** cellular substances containing fats that have a greenish-yellow color when viewed under certain types of microscopes
- ***Lysosomal disorders:*** (*also known as lysosomal storage disorders*) a group of more than 70 diseases that result from accumulation of waste products in lysosomes
- ***Lysosome:*** a sac found in cells that contains enzymes that digest cell waste
- ***Neurodegenerative:*** resulting in or characterized by damage to neurons/the nervous system, especially the neurons in the brain
- ***Neuron:*** a specialized cell that transmits nerve impulses
- ***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

What is CLN3 disease?

CLN3 disease is one of a small group of closely related, rare, genetic **neurodegenerative** disorders called neuronal ceroid lipofuscinoses (NCLs). All of the NCLs are part of a larger group of diseases called **lysosomal disorders**.[1]

CLN3 disease is the most common of the NCLs. It has been estimated to occur in 0.09 to 7.0 of every 100,000 live births worldwide.[2]

CLN3 disease is caused by certain **gene variants** (also known as mutations) in a gene called ceroid lipofuscinosis neuronal 3, or *CLN3.* Variants in this gene are passed down from parent to child in an autosomal recessive pattern (see ***How does CLN3 disease run in families?***).[1] Scientists have identified more than 60 different variants of the *CLN3* gene that cause CLN3 disease.[3,4]

Names used for CLN3 disease (as well as the other NCLs) have changed over time[3,5,6]

Before the gene variants that cause the different NCLs were discovered, these diseases were classified mostly by the age when **signs** and **symptoms** began: congenital (present at birth), infantile, late infantile, juvenile and adult.

Additionally, CLN3 disease was originally called Batten disease after Frederick Batten, one of the doctors who first described the condition.

All of these older names are sometimes still used today, but now the NCLs are also named after the specific **genes** associated with them. Also, "Batten disease" is now sometimes used as an umbrella term to refer to all of the NCLs collectively.

How does CLN3 disease affect the body?

Scientists know that CLN3 disease is caused by certain variants in the *CLN3* gene. The job of this gene is to provide instructions to the body on how to make a specific protein, the CLN3 protein, which is needed for **cells** to function properly.[3]

CLN3 disease is also known to have 2 central features: progressive damage to **neurons** (specialized cells that transmit nerve impulses), especially in the brain, and the buildup of fatty materials called **lipopigments** in parts of the cells called **lysosomes**.[7]

However, there are still many things about CLN3 disease that scientists do not yet understand.[4]

For example, the exact role that the CLN3 protein plays in the body is not known.[4] How variants of the *CLN3* gene lead to neuronal damage and the buildup of lipopigments in cells is also not yet fully understood.[7]

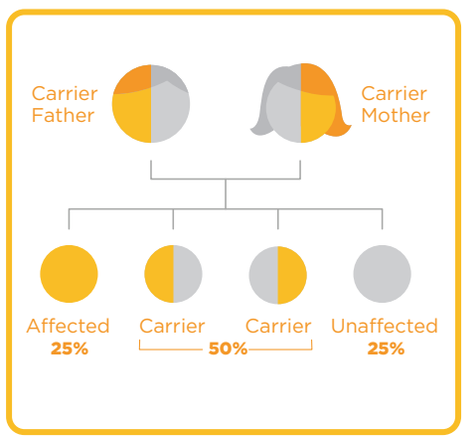
And although neuronal damage is known to be the cause of many of the symptoms of CLN3 disease, it is not yet known what causes the damage itself. The buildup of lipopigments in the cells may play a role, but other mechanisms may be involved.[7]

How does CLN3 disease run in families?[1,8]

People have 2 copies of most of the genes in their cells—1 inherited from their father and 1 from their mother.

In people with CLN3 disease, both of their copies of the *CLN3* gene have a variant that causes CLN3 disease.

People who have 1 normal *CLN3* gene and 1 *CLN3* gene with a variant do not develop the disease, but they can still pass the variant down to their children. These people are called carriers of CLN3 disease. Many carriers of CLN3 disease are not aware that they have the disease-causing variant.



Whether or not a person gets CLN3 disease depends on their parents' genes and how they are passed down. For example (see graphic at left):

If *both parents are carriers*, each of their children will have a 25% chance of inheriting 2 *CLN3* genes with a disease-causing variant (1 from each parent) and, therefore, developing the condition.

If *1 parent is a carrier and the other parent is not* (ie, does not have a disease-causing variant), none of their children will develop CLN3 disease, but each of their children will have a 50% chance of being a carrier.

This is called an autosomal recessive inheritance pattern.

How do gene variants cause CLN3 disease?[9]

ALL PEOPLE HAVE INFORMATION INHERITED FROM THEIR PARENTS THAT IS CODED INTO THEIR CELLS. THIS INFORMATION IS STORED IN A MATERIAL CALLED **DEOXYRIBONUCLEIC ACID**, OR **DNA**. DNA IS PASSED DOWN FROM PARENTS TO CHILDREN THROUGH GENES.

SOMETIMES CHANGES OR ERRORS EXIST IN THE DNA CODE THAT MAKES UP A PARTICULAR GENE. THESE CHANGES ARE WHAT PRODUCE VARIANTS OF A GENE. SOME GENETIC VARIANTS CAN CAUSE DISEASES OR HAVE OTHER SIGNIFICANT EFFECTS ON HOW THE GENE FUNCTIONS.

IN PEOPLE WITH CLN3 DISEASE, VARIANTS IN THE *CLN3* GENE INTERFERE WITH THE BODY'S ABILITY TO PRODUCE A PROTEIN BELIEVED TO BE NEEDED FOR CELLS TO FUNCTION PROPERLY. THIS CAUSES A CASCADE OF PROBLEMS THAT LEAD TO THE SIGNS AND SYMPTOMS OF CLN3 DISEASE.[3]

What happens when a doctor suspects CLN3 disease?[10,11]

A doctor may suspect CLN3 disease in children who develop worsening vision, experience a decline in cognitive abilities, and/or have seizures.

Because problems with vision are frequently the first indication of CLN3 disease, ophthalmologists (doctors who specialize in vision and the eye) often play an important role in recognizing and diagnosing CLN3 disease.

A variety of different tests may be used to help determine whether a person has CLN3 disease.

Specialized *studies of the eyes* can identify problems typically seen in CLN3 disease.

Blood tests can detect abnormalities in the lymphocytes (types of white blood cells) that are characteristic of CLN3 disease.

Examination of *tissue biopsies* (samples) can reveal distinctive shapes formed by lipopigment buildup in the cells.

Genetic testing (analysis of DNA obtained from blood or another body fluid or tissue) can confirm the presence of disease-causing variants of the *CLN3* gene.

Today, most diagnoses of CLN3 disease are confirmed by genetic testing.[11] Genetic testing can also be used to diagnose CLN3 disease prenatally (before birth).[10,11]

Because of the age when signs and symptoms start to appear, most people who have CLN3 disease are diagnosed when they are about 7 to 9 years old.[3]

Other resources that may be helpful are listed below. (Also, be sure to speak with a health-care professional about any questions or concerns.)

- **Batten Disease Family Association (BDFA)**
- **Batten Disease Support and Research Association (BDSRA)**
- **Beyond Batten Disease Foundation (BBDF)**
- **Brain Foundation**
- **National Organization for Rare Disorders (NORD)**
- **European Organisation for Rare Diseases (EURORDIS)**

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How is CLN3 disease treated?

Many medications are available that can help reduce the severity of the signs and symptoms of CLN3 disease. For example, psychiatric medications (such as antidepressants and antipsychotics) may be prescribed to help manage mood and behavioral symptoms, and muscle relaxants may be used to help manage movement problems.[3,6] Because CLN3 disease typically affects multiple organ systems, a team of specialized health-care professionals may work together to help manage the signs and symptoms of the disease.[6,11]

There are currently no approved treatments that can reverse, slow down or cure CLN3 disease. However, possible new approaches to the treatment of CLN3 disease have been identified and are being explored in preclinical and clinical research. For example, gene therapy—an experimental technique that uses genes to treat disease[9]—is being researched to see if doctors can treat CLN3 disease by inactivating mutated genes or inserting healthy genes into a patient's cells.[1,11]

To learn more about research and clinical trials for CLN3 disease, please visit **clinicaltrials.gov** or **clinicaltrialsregister.eu**, or talk to a health-care professional.

CLN3 disease may be slightly different in girls than in boys.

SIGNS AND SYMPTOMS MAY BE MORE SEVERE AND MAY BECOME WORSE MORE RAPIDLY. VISION LOSS MAY BEGIN AT AN OLDER AGE[3,5]

BEHAVIOR PROBLEMS MAY START EARLIER[3]

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