

# CLN8 Disease

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Contributor: Catherine Yang

CLN8 disease is an inherited disorder that varies in severity and primarily affects the nervous system. The condition is generally separated into less-severe and more-severe forms, based on the types of signs and symptoms that develop and life expectancy.

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## 1. Introduction

The less-severe form of CLN8 disease, sometimes referred to as Northern epilepsy, is characterized by recurrent seizures (epilepsy) and a decline in intellectual function that begins between ages 5 and 10. The seizures in this form may be resistant to treatment and are often the generalized tonic-clonic type, which involve muscle rigidity, convulsions, and loss of consciousness. Some people with this form of CLN8 disease also experience partial seizures, which do not cause a loss of consciousness. The seizures occur approximately one to two times per month until adolescence; by early adulthood the frequency decreases to about four to six times per year. By middle age, seizures become even less frequent. In addition to seizures, affected individuals experience a gradual decline in intellectual function and develop problems with coordination and balance. Vision problems may occur in early to mid-adulthood. Individuals with the less-severe form of CLN8 disease often live into late adulthood.

The more-severe form of CLN8 disease typically begins between ages 2 and 7. The seizures in this form involve uncontrollable muscle jerks (myoclonic epilepsy). Individuals with the more-severe form have a more pronounced decline in intellectual function and usually lose the ability to speak. Vision loss is also common. People with this form of CLN8 disease have increasing difficulty walking and coordinating movements (ataxia), eventually becoming immobile. Individuals with the more-severe form of CLN8 disease usually survive only into late childhood or adolescence.

CLN8 disease is one of a group of disorders known as neuronal ceroid lipofuscinoses (NCLs), which may also be collectively referred to as Batten disease. All these disorders affect the nervous system and typically cause worsening problems with vision, movement, and thinking ability. The different NCLs are distinguished by their genetic cause. Each disease type is given the designation "CLN," meaning ceroid lipofuscinosis, neuronal, and then a number to indicate its subtype.

## 2. Frequency

The less-severe form of CLN8 disease appears to affect only individuals of Finnish ancestry, particularly those from the Kainuu region of northern Finland, which is why it is sometimes called Northern epilepsy. Approximately 1 in 10,000 individuals in this region have the condition. The prevalence of the more-severe form of CLN8 disease is unknown. Collectively, all forms of NCL affect an estimated 1 in 100,000 individuals worldwide.

## 3. Causes

Mutations in the *CLN8* gene cause CLN8 disease. The *CLN8* gene provides instructions for making a protein whose function is not well understood. The CLN8 protein is thought to play a role in moving materials in and out of a cell structure called the endoplasmic reticulum. The endoplasmic reticulum is involved in protein production, processing, and transport to different parts of the cell. The CLN8 protein may also play a role in helping the endoplasmic reticulum regulate levels of fats (lipids) in cells. In certain cells, including nerve cells, the CLN8 protein is thought to be active outside of the endoplasmic reticulum, but its function is unknown.

A specific mutation in the *CLN8* gene is found in all individuals in northern Finland with the less-severe form of CLN8 disease. This mutation probably leads to production of a protein with reduced function. Because there is likely still some normal function of the CLN8 protein, features of this form are less severe compared to other cases of CLN8 disease. Affected individuals have a reduction in the levels of certain lipids in the brain, likely due to a decrease in CLN8 protein activity, but the effect of this reduction is unclear. Individuals with this form of CLN8 disease have mild brain abnormalities resulting from nerve cell death in the brain, but the cause of the cell death is unknown. Unlike other forms of NCL that result in the accumulation of proteins and other substances in cells, contributing to cell death, the less-severe form of CLN8 disease is associated with very little buildup in cells.

Some *CLN8* gene mutations are thought to drastically reduce the function of the CLN8 protein. Other mutations likely impair transport of the protein to the endoplasmic reticulum, so that it cannot perform its function. It is unclear how a loss or reduction of CLN8 protein leads to the signs and symptoms of CLN8 disease. Unlike the less-severe form, in the more-severe form of CLN8 disease, proteins and other substances accumulate in cell structures called lysosomes. While accumulations of these substances occur in cells throughout the body, nerve cells appear to be particularly vulnerable to damage caused by the abnormal cell materials; however, it is unclear how mutations in the *CLN8* gene are involved in this buildup. Widespread loss of nerve cells in CLN8 disease leads to the neurological signs and symptoms and, in the case of the more-severe form, early death.

### 3.1. The Gene Associated with CLN8 Disease

- CLN8

## 4. Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

## 5. Other Names for This Condition

- neuronal ceroid lipofuscinosis 8

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