

# Niemann-Pick Disease

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Niemann-Pick disease is a condition that affects many body systems. It has a wide range of symptoms that vary in severity. Niemann-Pick disease is divided into four main types: type A, type B, type C1, and type C2. These types are classified on the basis of genetic cause and the signs and symptoms of the condition.

genetic conditions

## 1. Introduction

Infants with Niemann-Pick disease type A usually develop an enlarged liver and spleen (hepatosplenomegaly) by age 3 months and fail to gain weight and grow at the expected rate (failure to thrive). The affected children develop normally until around age 1 year when they experience a progressive loss of mental abilities and movement (psychomotor regression). Children with Niemann-Pick disease type A also develop widespread lung damage (interstitial lung disease) that can cause recurrent lung infections and eventually lead to respiratory failure. All affected children have an eye abnormality called a cherry-red spot, which can be identified with an eye examination. Children with Niemann-Pick disease type A generally do not survive past early childhood.

Niemann-Pick disease type B usually presents in mid-childhood. The signs and symptoms of this type are similar to type A, but not as severe. People with Niemann-Pick disease type B often have hepatosplenomegaly, recurrent lung infections, and a low number of platelets in the blood (thrombocytopenia). They also have short stature and slowed mineralization of bone (delayed bone age). About one-third of affected individuals have the cherry-red spot eye abnormality or neurological impairment. People with Niemann-Pick disease type B usually survive into adulthood.

The signs and symptoms of Niemann-Pick disease types C1 and C2 are very similar; these types differ only in their genetic cause. Niemann-Pick disease types C1 and C2 usually become apparent in childhood, although signs and symptoms can develop at any time. People with these types usually develop difficulty coordinating movements (ataxia), an inability to move the eyes vertically (vertical supranuclear gaze palsy), poor muscle tone (dystonia), severe liver disease, and interstitial lung disease. Individuals with Niemann-Pick disease types C1 and C2 have problems with speech and swallowing that worsen over time, eventually interfering with feeding. Affected individuals often experience progressive decline in intellectual function and about one-third have seizures. People with these types may survive into adulthood.

## 2. Frequency

Niemann-Pick disease types A and B is estimated to affect 1 in 250,000 individuals. Niemann-Pick disease type A occurs more frequently among individuals of Ashkenazi (eastern and central European) Jewish descent than in the general population. The incidence within the Ashkenazi population is approximately 1 in 40,000 individuals.

Combined, Niemann-Pick disease types C1 and C2 are estimated to affect 1 in 150,000 individuals; however, type C1 is by far the more common type, accounting for 95 percent of cases. The disease occurs more frequently in people of French-Acadian descent in Nova Scotia. In Nova Scotia, a population of affected French-Acadians were previously designated as having Niemann-Pick disease type D, however, it was shown that these individuals have mutations in the gene associated with Niemann-Pick disease type C1.

## 3. Causes

Niemann-Pick disease types A and B is caused by mutations in the *SMPD1* gene. This gene provides instructions for producing an enzyme called acid sphingomyelinase. This enzyme is found in lysosomes, which are compartments within cells that break down and recycle different types of molecules. Acid sphingomyelinase is responsible for the conversion of a fat (lipid) called sphingomyelin into another type of lipid called ceramide. Mutations in *SMPD1* lead to a shortage of acid sphingomyelinase, which results in reduced break down of sphingomyelin, causing this fat to accumulate in cells. This fat buildup causes cells to malfunction and eventually die. Over time, cell loss impairs function of tissues and organs including the brain, lungs, spleen, and liver in people with Niemann-Pick disease types A and B.

Mutations in either the *NPC1* or *NPC2* gene cause Niemann-Pick disease type C. The proteins produced from these genes are involved in the movement of lipids within cells. Mutations in these genes lead to a shortage of functional protein, which prevents movement of cholesterol and other lipids, leading to their accumulation in cells. Because these lipids are not in their proper location in cells, many normal cell functions that require lipids (such as cell membrane formation) are impaired. The accumulation of lipids as well as the cell dysfunction eventually leads to cell death, causing the tissue and organ damage seen in Niemann-Pick disease types C1 and C2.

### 3.1. The Genes Associated with Niemann-Pick Disease

- *NPC1*
- *NPC2*
- *SMPD1*

## 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

- lipid histiocytosis
- neuronal cholesterol lipidosis
- neuronal lipidosis
- NPD
- sphingomyelin lipidosis
- sphingomyelin/cholesterol lipidosis
- sphingomyelinase deficiency

## References

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