



Leukodystrophy

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
National Institutes of Health

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What are the leukodystrophies?

Leukodystrophy refers to genetic diseases that predominantly affect the white matter of the central nervous system (CNS). White matter is tissue made up of bundles of nerve fibers (axons) that connect nerve cells. The fibers are covered and protected by an insulating layer of proteins and fatty materials (lipids) called myelin. Myelin provides nutritional support to nerve cells and helps speed up signals between them, allowing them to send and receive messages quickly. It is also commonly referred to as the myelin sheath.

Leukodystrophy is not a single disorder. It is a group of rare, primarily inherited neurological disorders known as the leukodystrophies that result from the abnormal production, processing, or development of myelin and other components of CNS white matter, such as the cells called oligodendrocytes and astrocytes. Oligodendrocytes and astrocytes belong to a group of cells called glial cells which surround, support, and insulate nerve cells.

Leukodystrophies are usually progressive, meaning they get worse as time goes on. Some forms are present at birth, while others may not produce symptoms until a child becomes a toddler. A few leukodystrophies mostly affects adults.

What causes these disorders?

All leukodystrophies are the result of genetic defects (mutations).

Myelin, which is whitish in color and makes up much of the white matter in the brain, is a complex substance made up of many different proteins and lipids (fatty substances). Production, degradation, and maintenance of each protein and lipid are controlled by a specific group of genes. Each type of leukodystrophy is caused by a defect in one of the genes that control the structure or amount of one of the proteins or lipids in myelin. Mutations in any of these genes can affect how the lipid or protein works and can interrupt the normal formation, processing, and development of myelin and the function of white matter. Damage to or destruction of myelin can slow or delay the speed of brain signals or keep them from reaching their destination.

What are the symptoms?

Symptoms of leukodystrophy vary according to the specific type and may be difficult to recognize in the early stages of the disorder. Each type of leukodystrophy affects myelin differently and in different parts of the CNS, leading to a range of symptoms.

The most common symptom is a gradual functional decline in an infant or child who previously appeared well. Progressive loss may appear in

- muscle tone
- balance and mobility
- walking (gait)

- speech
- ability to eat
- vision
- hearing
- behavior

Other symptoms may include:

- learning disabilities
- bladder issues
- breathing problems
- developmental delay
- muscle control disorders
- seizures

How many different leukodystrophies are there?

Scientists have identified more than 50 different leukodystrophies. Specific types include:

- **Alexander disease**—a disorder characterized by the destruction of white matter and the formation of abnormal clumps of protein called Rosenthal fibers that accumulate in astrocytes in the brain. Alexander disease is caused by mutations in the *GFAP* gene.
- **Autosomal dominant leukodystrophy with autonomic diseases (ADLD)**—a rare, slowly progressive disorder characterized by the onset of autonomic dysfunction (dysfunction of the nerves that regulate nonvoluntary body functions, such as heart rate, blood pressure, and sweating), difficulty coordinating movements (ataxia), and mild

cognitive impairment. People with ADLD develop symptoms in adulthood, usually in their 40s or 50s. The disorder is caused by mutations in the *LMNB1* gene which is responsible for making lamin B1 protein. Lamin B1 is a structural protein that helps determine the shape of the cell nucleus and plays an important role in cell division and gene expression, including expression of the genes for oligodendrocyte development and production of some myelin proteins.

- **Canavan disease**—a neurological disorder in which the brain degenerates into spongy tissue full of small fluid-filled spaces. It is caused by a mutation in the *ASPA* gene which makes an enzyme called aspartoacylase. Aspartoacylase is primarily present in oligodendrocytes, contributes to the manufacture of myelin, and is responsible for breaking down (metabolizing) the brain chemical N-acetyl-L-aspartate or N-acetyl-L-aspartic acid.
- **Cerebrotendinous xanthomatosis (CTX)**—a rare, genetic disorder characterized by abnormal storage of fats (lipids) in many areas of the body. It affects the body's ability to metabolize fats, causing them to form fatty yellow nodules called xanthomas which accumulate in the body—especially in the brain, where abnormal giant cells filled with the fatty substance can be seen in the white matter, and the tendons that attach muscle to bone. CTX is caused by mutations in the sterol 27-hydroxylase (*CYP27A1*) gene. If diagnosed early, CTX can be effectively treated.

- **Childhood ataxia with central nervous system hypomyelination** or CACH (also called vanishing white matter disease or VWMD)—a disorder characterized by ataxia, muscle stiffness (spasticity), and damage to the optic nerve (optic atrophy). It is caused by mutations in any of the 5 genes that make the protein eukaryotic initiation factor 2B (eIF2B), which helps regulate protein synthesis, a process that governs the production of protein, including that which contributes to myelin, in cells. Mutations in any of these 5 genes results in partial loss of eIF2B function, making it difficult for cells to regulate protein synthesis.
- **Krabbe disease**, also called globoid cell leukodystrophy—a rare, inherited metabolic disorder characterized by globoid cells (abnormal cells that have more than one nucleus) in the white matter. Krabbe disease is caused by a defect in the *GALC* gene, leading to malfunction of galactocerebrosidase, an essential enzyme for myelin metabolism, and consequent accumulation of a toxic myelin breakdown product.
- **Metachromatic leukodystrophy (MLD)**—a disorder characterized by the toxic buildup of lipids and other storage materials in cells in CNS white matter and the peripheral nerves. Individuals with MLD have mutations in the *ARSA* or *PSAP* genes, which cause a deficiency of the enzyme arylsulfatase A and a decreased ability to break down sulfatides. Sulfatides are essential components of the myelin sheath. However, an excess of sulfatides can be toxic to the nervous system, gradually destroying myelin-producing cells and leading to nervous system impairment.

- **Pelizaeus-Merzbacher disease**—a rare, progressive, degenerative disorder in which coordination, motor abilities, and intellectual function deteriorate. It is caused by a mutation in the gene that controls the production of a myelin protein called proteolipid protein-1 (PLP1).
- **Refsum disease:**
 - *Adult Refsum disease (ARD)*—a rare disease that causes weakness or numbness of the hands and feet (peripheral neuropathy). People with ARD lack the enzyme in peroxisomes that breaks down phytanic acid, a type of fat found in certain foods. Peroxisomes are cell structures required for the normal function of the brain, eyes, liver, kidneys, and bone. In ARD, phytanic acid accumulates and is toxic to myelin.
 - *Infantile Refsum disease (IRD)*—an inherited disorder that damages the white matter of the brain and affects motor movements.

Although ARD and IRD have similar names, they are separate disorders caused by different defects in the *PHYH* or *PEX7* genes which result in disruption of the breakdown of phytanic acid.

There are many other leukodystrophies, and some are still unidentified.

How are these disorders diagnosed?

Generally, a diagnosis of leukodystrophy is made based on medical and family health history, physical and neurological examinations, imaging scans such as magnetic resonance imaging (MRI) or computed tomography (CT), and other laboratory tests.

However, even with the help of imaging, lab tests, and clinical observations, leukodystrophy can be difficult to diagnose. A physician will use other specialized tests such as DNA sequencing to check for genetic disorders. Whole-exome and whole-genome sequencing—tests that map out and analyze the genetic information contained in all of a person's genes—often are used to identify and pinpoint specific genetic defects.

Doctors still are finding new types of leukodystrophy and discovering forms that are difficult to precisely diagnose.

What treatments are available?

Treatment for most types of leukodystrophy is symptomatic and supportive, and may include:

- medications
- physical, occupational, and speech therapies
- nutritional, educational, and recreational programs

Medications can be used to manage muscle tone, seizures, and spasticity. Physical, occupational, and speech therapies may improve mobility, function, and cognitive problems. Nutritional, educational, and recreational programs also may be helpful, depending on the needs of the individual.

Stem cell or bone marrow transplantation is showing promise for a few types of leukodystrophy.

One of the leukodystrophies is now a treatable disease. With an early accurate diagnosis, CTX can be effectively treated with chenodeoxycholic acid (CDCA) replacement therapy. CDCA helps the body metabolize or break down fats such as cholesterol and can slow or stop progression of the disease.

What research is being done?

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge of the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. NINDS, a component of the National Institutes of Health (NIH), is the primary NIH organization for research on leukodystrophies.

NINDS, in collaboration with the NIH Office of Rare Diseases Research at the National Center for Advancing Translational Sciences and the National Institute of Diabetes and Digestive and Kidney Diseases, supports the Lysosomal Disease Network (LDN). LDN uses limited resources to create centers with expertise in lysosomal diseases to help solve major challenges in diagnosis, disease management, and therapy. Goals of LDN include clinical trial readiness, newborn screening, long-term outcomes, and global reach.

NINDS also supports researchers who are working with the Global Leukodystrophy Initiative Clinical Trials Network (GLIA-CTN)—a consortium of scientists, industry stakeholders, and patient advocacy leaders that promotes advances in the diagnosis and treatment of leukodystrophies. GLIA-CTN supports the collection, analysis, and sharing of clinical data and biological specimens; educating clinicians; and training new researchers to pave the way for transformative therapeutic trials across the leukodystrophies.

NINDS-supported scientists are creating various animal models to gain a better understanding of the leukodystrophies and using the models to develop better, more effective therapies for these disorders.

Other investigators funded by NINDS are studying specific types of leukodystrophy. In one study, researchers are looking at the role of inflammation in Alexander disease to determine if it plays a role in causing disease progression and whether it could be a therapeutic target for treating the disease.

Another research project is studying the therapeutic impact of newly combined treatments using gene therapy, stem cell transplantation, and small molecule neuroprotection in people with Krabbe disease to reduce neuroinflammation, cell death, and neurodegeneration. The goal of this study is to develop safer and more effective treatments for the disorder.

Scientists supported by NINDS also are looking for ways to reduce the overproduction of the structural protein lamin B1 which is seen in ADLD in an effort to correct myelin abnormalities or halt disease progression.

In another NINDS-funded project, researchers are working to identify mutations in myelin protein that cause either Pelizaeus-Merzbacher disease or spastic paraplegia type 2—two x-linked leukodystrophies.

More information about leukodystrophy research supported by NINDS and other NIH Institutes and Centers may be found using NIH RePORTER (projectreporter.nih.gov), a searchable database of current and past research projects supported by NIH and other Federal agencies. RePORTER also includes links to publications and resources from these projects.

How can you help research?

Join a clinical trial.

Many neurological disorders do not have effective treatment options. Clinical trials offer hope for many people and an opportunity to help researchers find better ways to safely detect, treat, or prevent disease. For information about finding and participating in a clinical trial, contact the NIH's Patient Recruitment and Public Liaison office at 800-411-1222. You can find information about clinical trials for leukodystrophies, as well as those for other neurological and other disorders, at ClinicalTrials.gov.

Where can I get more information?

For more information on neurological disorders or research programs funded by NINDS, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN

P.O. Box 5801
Bethesda, MD 20824
Tel: 800-352-9424
www.ninds.nih.gov

Information also is available from the following organizations:

Canavan Disease Research

Tel: 800-83-2194
<http://www.canavanresearch.org>

Canavan Foundation, Inc.

Tel: 877-422-6282
<http://www.canavanfoundation.org>

Canavan Research Foundation

Tel: 203-240-2326
<http://www.canavan.org>

Genetic Alliance

Tel: 202-966-5557; 800-336-4363
<http://www.geneticalliance.org>

Global Dare Foundation

(Adult Refsum Disease)
<https://www.defeatadultrefsumeverywhere.org>

Hunter's Hope Foundation

[A Leukodystrophy Resource]
Tel: 716-667-1200; 877-984-4673
www.huntershope.org

MLD Foundation

(Metachromatic Leukodystrophy)
Tel: 800-617-8387; 503-656-4808
www.mldfoundation.org

Myelin Project

Tel: 800-869-3546; 310-459-1071
www.myelin.org

National Organization for Rare Disorders (NORD)

Tel: 203-744-0100; Voice Mail: 800-999-6673
<https://rarediseases.org>

National Tay-Sachs and Allied Diseases Association

Tel: 617-227-4463
www.ntsad.org

Pelizaeus-Merzbacher Disease Foundation

Tel: 254-313-9107
<https://www.pmdfoundation.org>

United Leukodystrophy Foundation

Tel: 815-748-3211; 800-728-5483
<https://ulf.org>

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National Center for Advancing Translational Sciences

Rare Diseases Clinical Research
Network (RDCRN)
<https://ncats.nih.gov/rdcrn>



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