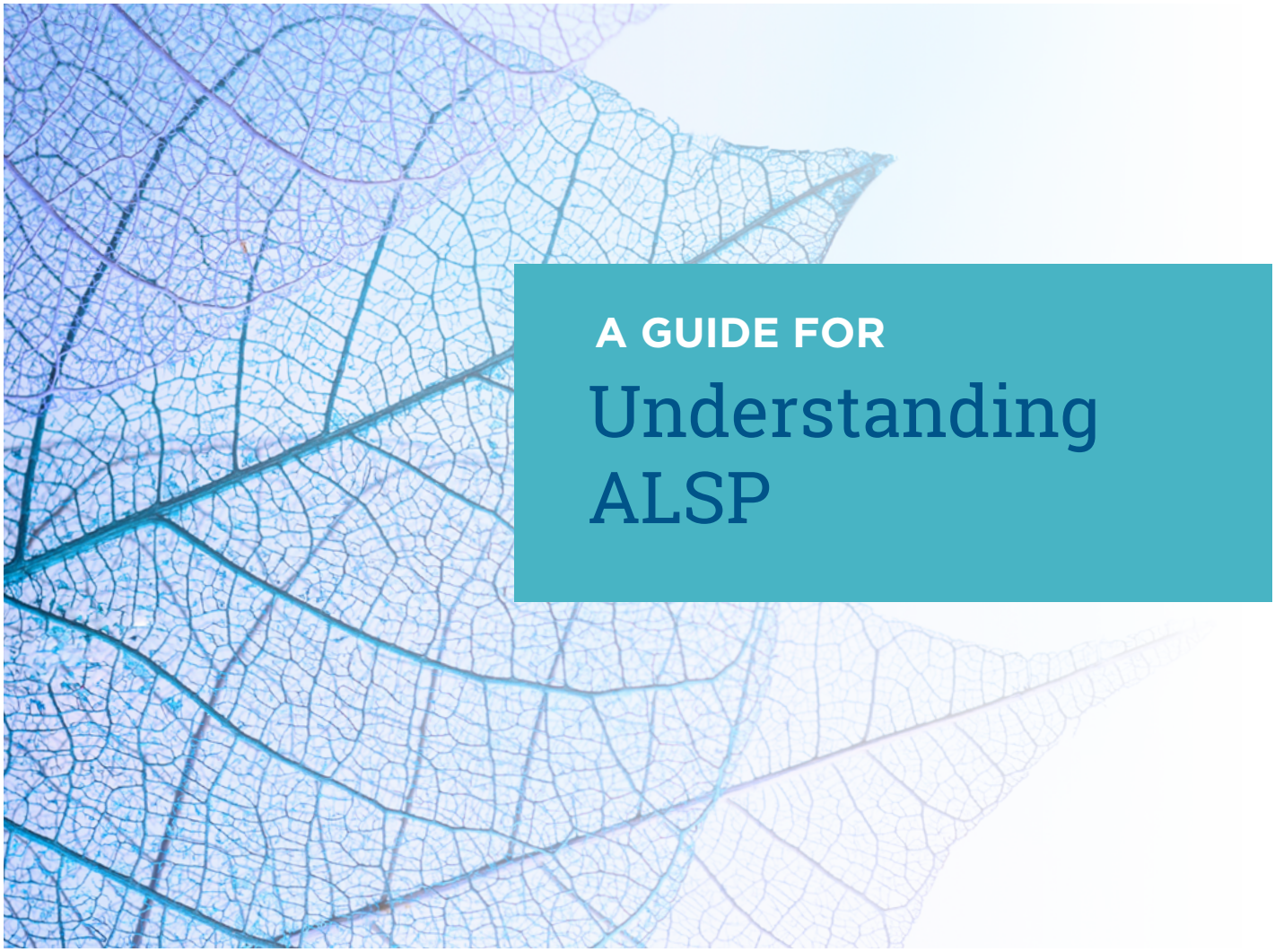

A GUIDE FOR

Understanding ALSP

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About ALSP

A diagnosis of ALSP can be challenging and overwhelming, and it can also raise many questions. Learning about the disease and what to expect can help individuals and families understand the diagnosis and prepare for the future. Researchers, care providers, and those who have been affected by ALSP have contributed collective knowledge and important medical information about the disease, and research is growing.

What is ALSP?

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare genetic disease caused by a defect in the DNA (mutation) of the *CSF1R* gene. When there is a mutation in this gene, certain brain cells called microglia malfunction and lose their ability to protect the brain and fight disease, leading to ALSP symptoms. ALSP is a progressive disease (meaning it gets worse over time) and those living with the disease will eventually require full-time support for personal care and medical management. There is no cure for ALSP yet, but research is ongoing.

You may find that ALSP may be referred to as hereditary diffuse leukoencephalopathy with spheroids (HDLS), pigmentary orthochromatic leukodystrophy (POLD), or *CSF1R*-related leukoencephalopathy.

> It's so helpful to see that there is more information about ALSP for patients and caregivers. Until recently, it was so difficult to find any information about ALSP. You had to really dig and read through the research and academic publications. It was overwhelming for patients and families, but today that is changing.
>
> **-Serena, *CSF1R* carrier**

1. ALSP is an adult-onset leukodystrophy.

ALSP is a type of leukodystrophy (a disease that affects the white matter of the brain). ALSP is an adult-onset leukodystrophy, meaning that symptoms appear in adulthood. On average, symptoms first appear around age 43, but can begin in the 30s and in some cases as late as the 70s. **ALSP makes up 10 to 25 percent of adult-onset leukodystrophies.**

2. ALSP is rare.

This progressive disease is estimated to affect **approximately 10,000 people in the United States, 15,000 in Europe and 4,000 in Japan.** However, since the disease is rare, it is difficult to predict exactly how many people live with ALSP.

3. ALSP is genetic.

A person who has the *CSF1R* gene mutation has a 50 percent chance of passing the gene on to each child. Individuals who carry the mutation are highly likely to develop ALSP. Some ALSP patients may not have a clear family history of transmission from generation to generation.

> The ALSP community has become more connected in the last couple of years. On social media, you can join groups where you can connect with others with ALSP, ask questions, and hear what others are saying about their experience.
>
> **-Heidi, ALSP Caregiver**
> **Founder, Sisters' Hope Foundation**

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Clinical Course and Symptoms

ALSP affects every person differently. The symptoms and progression of ALSP can vary even among family members. ALSP is also a progressive disease, meaning that a diverse range of symptoms will develop at different times and become more severe as time passes. Symptoms often begin with mild memory, thinking, and behavioral changes and progress to loss of movement and declined mental abilities.

Typically, symptoms first appear when individuals are in their 30s or 40s, but can occur as late as their 70s. On average, disease progression (from first symptoms to death) occurs over six to eight years. There are few reports of individuals who carry the mutation and live past their 70s without exhibiting symptoms. Researchers continue to work to better understand ALSP.

> Out of the five people in my family who lived with ALSP, they had similarities in symptoms, but they all presented a little differently. It is always good to remember that no one is going to look exactly the same.
>
> **-Heidi, ALSP Caregiver**
> **Founder, Sisters' Hope Foundation**

Pre-Symptomatic

With genetic testing, individuals can find out whether they have the *CSF1R* mutation before developing symptoms or before there is evidence of disease through brain imaging and other tests.

People who have a confirmed genetic mutation but have no evidence of ALSP may be referred to as "carriers" or "pre-symptomatic." Individuals who carry the mutation will most likely develop ALSP.

Pre-symptomatic testing can help individuals and families prepare for the future. Deciding to undergo genetic testing is a personal decision. Talk to your loved ones, health care team, and genetic counselors to help determine what is right for you.

No two cases of ALSP are the same. Individuals will be impacted in distinct ways, and some may experience more symptoms than others.

Initial Symptoms

The onset of ALSP can be gradual, making signs and symptoms difficult to identify early on. Many patients present with only one or two symptoms, which most commonly include cognitive impairment. Possible early symptoms include:

Memory & Thinking

- Difficulty with problem solving, learning, and concentration
- Difficulty with speech

Personality & Behavioral

- Anxiety and depression
- Lack of interest and indifference to previously enjoyed activities
- Personality changes, such as irritability, lack of self-control, poor judgment, and distraction

Physical

- Tremor (involuntary shaking or movement) and muscle stiffness (rigidity, spasticity)
- Gait disturbances and slow movement (bradykinesia)

Other possible symptoms include stroke-like episodes, sensory dysfunction, dizziness, fatigue, and seizures.

> “Personality changes are extremely difficult. Individuals with ALSP feel guilty for how the disease is making them behave. Family and friends also have a difficult time coping with this symptom when they don’t understand why their loved one is acting out. It’s important to remember it’s the disease that is causing these personality changes.
>
> **- Tanya, MS, Licensed Certified Genetic Counselor (LCGC)**

Disease Progression

Every individual presents differently, and disease progression can be rapid or slow, taking anywhere from two years to three decades. However, the average time span is between six and eight years. Over this period of time, signs of ALSP in all three areas become apparent and individuals will most likely need daily care. Initial symptoms will worsen and may include:

Memory & Thinking

- Forgetfulness and worsening issues with memory and thinking
- Worsening difficulty with speech

Personality & Behavioral

- Severe anxiety and depression
- Severe lack of interest and irritability
- Seizures
- Inability to feel pain, touch, or vibrations

Physical

- Worsening tremor, muscle stiffness, and weakness (hypertonia)
- Issues with muscle control (ataxia), fine movements, balance, overactive reflexes (hyperreflexia), and slow movement
- Difficulty making purposeful movements (apraxia) and judging distance (dysmetria)
- Difficulty sensing vibration, body position, touch, and pain (hypoesthesia)
- Muscle weakness that results in slurred speech (dysarthria) and difficulty swallowing (dysphagia)

Other possible symptoms include stroke-like episodes, bone cysts, and optic and peripheral nerve dysfunction.

Disease Advancement

As ALSP advances, symptoms progress and individuals eventually decline into a vegetative state where they will require full-time care. As brain cells break down, the immune system becomes severely weakened leaving individuals susceptible to infections and pneumonia, which can result in further decline in overall health.

While it can be difficult, knowing what may occur throughout the disease can help individuals and families approach care decisions and plan for the future.

Genetics and Diagnosis

What Causes ALSP?

ALSP is caused by a mutation to the *CSF1R* gene. The mutation causes a type of protein receptor, called the colony stimulating factor 1 receptor (CSF-1 receptor), to not work as intended. The CSF-1 receptor protein is important to cells that impact brain function; these cells are called microglia.

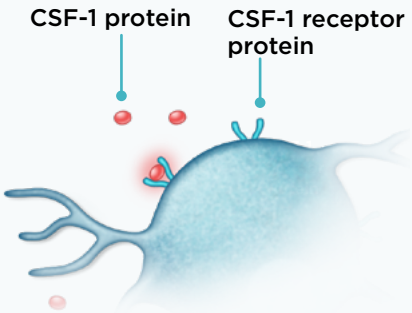
Non-functioning microglia are recognized as a primary underlying cause of ALSP.

Individual without ALSP

Working *CSF1R* gene

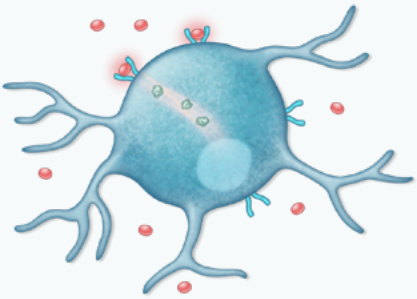
When CSF-1 protein attaches (binds) to these receptors, the receptors turn on (activate) a series of proteins inside the cell that keep the microglia healthy and functioning.

Functioning CSF-1 receptor protein



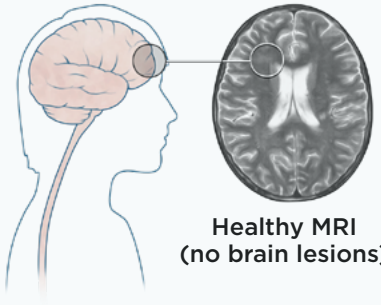
The *CSF1R* gene is responsible for producing the CSF-1 receptor protein, which is found on the outer membrane of microglia. These receptors are activated by CSF-1 protein.

Healthy microglia function



Functioning microglia monitor and maintain the central nervous system

Microglia respond to various types of cellular and metabolic distress signals to help regulate responses for repair, maintenance, and protection of various parts of the central nervous system (brain and spinal cord).



Healthy MRI (no brain lesions)

Protect
Repair
Maintain

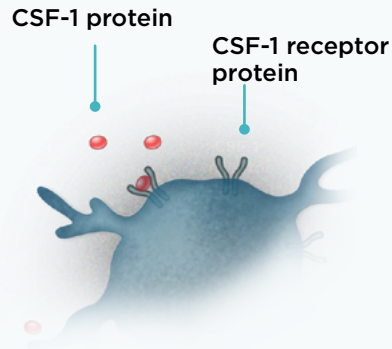
Genetics and Diagnosis

Individual with ALSP

Mutated *CSF1R* gene

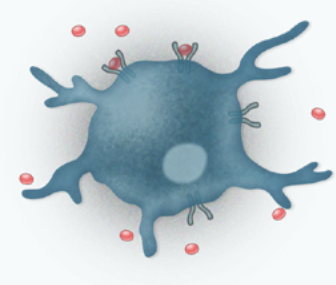
A mutated *CSF1R* gene causes the CSF-1 receptor protein to not be able to work as intended. CSF-1 protein is likely not able to activate the CSF-1 receptor protein.

Non-functioning CSF-1 receptor protein



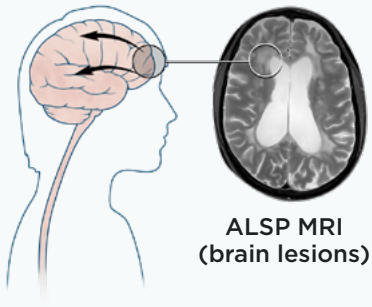
When CSF-1 receptor protein isn't working, it can cause microglia to become dysfunctional (meaning the cells don't work as intended), leading to cell death and abnormal distribution throughout the brain.

Microglia dysfunction and death



Non-functional microglia cannot protect the central nervous system against disease

Magnetic resonance imaging (MRI) show white matter lesions in people with ALSP. Lesions typically develop in the frontal region before moving to other parts of the brain.



Protect
Repair
Maintain

How is ALSP inherited?

The *CSF1R* gene is autosomal dominant, which means that just one copy of the mutated gene from either parent is enough to cause the disease.

Since the onset of ALSP symptoms occurs later in life, the disease is often diagnosed after the childbearing years, when many individuals have already had children.

> **A person who has the *CSF1R* gene mutation has a 50 percent chance of passing the gene on to each child, regardless of their gender. The *CSF1R* gene mutation does not skip generations. ALSP can also occur spontaneously; these individuals still have a 50 percent chance of passing the gene mutation on to their children.**

How is ALSP diagnosed?

Diagnosis is mainly clinical and is confirmed through magnetic resonance imaging (MRI) and genetic testing for the *CSF1R* mutation. MRIs may reveal the impact of ALSP in the form of lesions in the brain's white matter, often first appearing in the frontal region.

Since ALSP symptoms are similar to other diseases, especially other leukodystrophies, it can often be misdiagnosed. Genetic testing to identify a *CSF1R* mutation can be an important step in confirming an ALSP diagnosis. To receive genetic testing for ALSP, an individual must be over the age of 18.

Learn more about genetic testing at ALSPinfo.com

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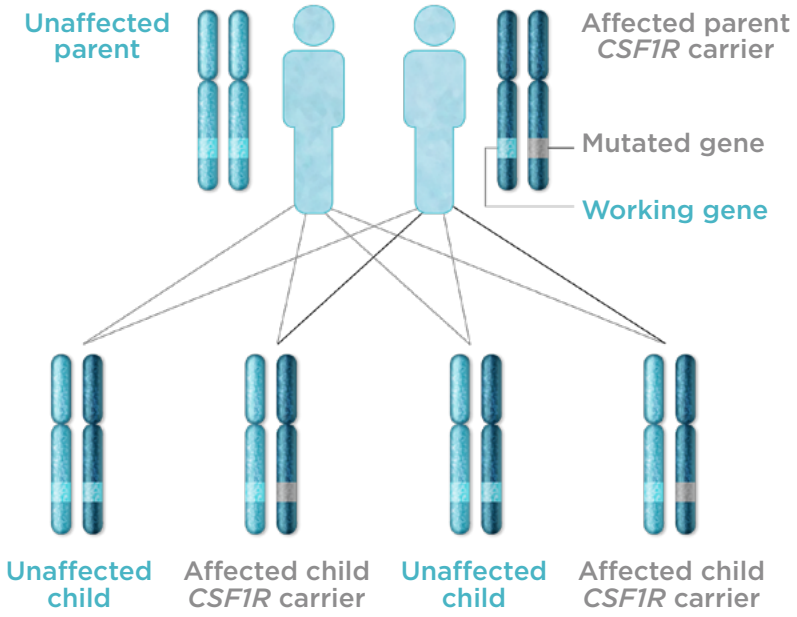
Autosomal dominant inheritance



Unaffected children	Have two working copies of the *CSF1R* gene	Cannot develop ALSP	Cannot pass on a mutated *CSF1R* gene to future children
Affected children (*CSF1R* carriers)	Have one mutated copy of the *CSF1R* gene and one working copy	Likely to develop ALSP	Have a 50% chance of passing on mutated *CSF1R* gene to future children

Management and Ongoing Research

How is ALSP treated?

There are no FDA-approved therapies for ALSP. Existing care and management practices focus on symptom relief and maintaining quality of life. Commonly prescribed treatments do not target the cause or slow the progression of ALSP. A care plan for ALSP may include:

- Medications that temporarily alleviate motor, mood, and behavior symptoms like antidepressants, muscle relaxants, and antiseizure medications
- Supportive therapies including physical, occupational, and speech therapies, which may help individuals maintain abilities and quality of life

What research is being done?

Researchers are currently looking to better understand the symptoms and impact of ALSP through a natural history study. This type of study collects information about the natural history of a disease in the absence of a disease-specific intervention. Knowledge of a disease's natural history can benefit drug development for rare diseases like ALSP. Researchers are also working to develop investigational treatments and clinical studies to evaluate potential treatments for ALSP.

How can I be involved in research?

Participating in research may help advance understanding of the disease and lead to new treatments for current and future generations.

To learn about ALSP natural history studies & clinical studies visit ClinicalTrials.gov and search for "ALSP."

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What can I do now?

- **Confirm diagnosis** through MRIs and genetic testing.
- **Do research** and find resources, such as **ALSPinfo.com** and **SistersHopeFoundation.org**.
- **Get involved** with the ALSP community for support and to stay on top of information—follow Sisters' Hope Foundation on social media for the latest updates.
- **Build your care team**—talk to your neurologist about what physicians and therapists should be part of your team.
- **Identify a support network** of family and friends. Consider a health care proxy.
- **Learn about ongoing research** and clinical trials you may be eligible for through **ClinicalTrials.gov**.

> "I got involved in the research for the future generations—for my children and my grandchildren.
>
> **- Serena, *CSF1R* carrier**

Vigil Neuroscience, Inc. has developed the resource, "A Guide for Understanding ALSP," for informational and educational purposes only. The information presented should not replace medical assessment and care. Always consult with your health care team before making any medical decisions.

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