CONDITION

Isoleucine 33 amyloidosis

Isoleucine 33 amyloidosis is an inherited condition in which abnormal transthyretin protein builds up in nerves, the heart, and other tissues.

WHAT IT IS
Inherited transthyretin amyloidosis caused by the Phe33Ile variant

BODY SYSTEM
Nerves, heart and circulation, and digestive system

MAIN SYMPTOMS
Numbness, weakness, dizziness, shortness of breath

WHAT CAUSES IT
Inherited TTR gene change causing unstable transthyretin

HOW IT IS DIAGNOSED
TTR genetic testing with amyloid confirmation or heart imaging

MAIN TREATMENT
TTR-targeting medicines, symptom care, and sometimes transplantation

CAN IT BE CURED?
No - current treatments can slow progression

IS IT AN EMERGENCY?
Sometimes - fainting, chest pain, or severe breathlessness

LONG-TERM OUTLOOK
Progressive, but treatment can preserve function longer

Overview

Isoleucine 33 amyloidosis is a rare inherited form of transthyretin amyloidosis. It is usually grouped with hereditary transthyretin amyloidosis, also called variant transthyretin amyloidosis or ATTRv amyloidosis.

Transthyretin, shortened to TTR, is a protein made mainly by the liver. It normally carries thyroid hormone and vitamin A-related proteins through the blood. In this condition, a change in the TTR gene makes the protein less stable. The protein can break apart, fold incorrectly, and collect as amyloid deposits in body tissues.

The name "isoleucine 33" describes the protein change. Isoleucine replaces another amino acid, phenylalanine, at position 33 of the mature TTR protein. Because laboratory reports may count the protein's signal sequence, the same change may be written as Phe33Ile , Phe53Ile ,

or p.Phe53Ile .

Amyloid deposits can interfere with peripheral nerves, which carry messages between the brain, spinal cord, and body. They may also affect the nerves that control automatic functions such as blood pressure and digestion. Some people develop amyloid deposits in the heart.

This condition matters because damage can gradually increase and may not fully reverse. However, treatments that reduce or stabilize TTR can slow progression. An accurate diagnosis is important because treatment differs from that used for other forms of amyloidosis.

Symptoms

Symptoms are not identical in everyone. Published information about this particular TTR variant comes from relatively small numbers of people, so its full range is not known.

Peripheral neuropathy is common in hereditary TTR amyloidosis. This means damage to nerves outside the brain and spinal cord. Symptoms often begin in the feet and legs and may later affect the hands.

Possible nerve-related symptoms include:

Autonomic neuropathy affects nerves that control functions you do not consciously manage. It can cause dizziness or faintness when standing because blood pressure falls. Other possible effects include diarrhoea, constipation, alternating bowel habits, feeling full quickly, nausea, sexual difficulties, or problems emptying the bladder.

If amyloid affects the heart, its walls may become thick and stiff. This is called amyloid cardiomyopathy. It can cause shortness of breath, reduced stamina, ankle swelling, a racing or irregular heartbeat, dizziness, or fainting.

Unexplained weight loss can occur, particularly when digestive symptoms or swallowing problems make eating difficult. Kidney or eye involvement is possible in hereditary TTR amyloidosis, but nerve and heart problems are usually the main concerns.

- Tingling, burning, numbness, or pain in the feet
- Reduced ability to feel heat, cold, or injury
- Leg or hand weakness
- Poor balance or difficulty walking
- Carpal tunnel symptoms, such as hand tingling or weakness

Causes and risk factors

Isoleucine 33 amyloidosis is caused by a pathogenic change in one copy of the TTR gene. It follows an autosomal dominant inheritance pattern. This means a person with the variant has a 1 in 2 chance of passing it on in each pregnancy.

Inheriting the variant does not always predict whether symptoms will develop, when they will begin, or how severe they will become. This is called reduced or age-related penetrance. Two relatives with the same variant may have different symptoms.

A family history can raise suspicion, but its absence does not rule out the condition. Relatives may have been misdiagnosed, developed symptoms late in life, or carried the variant without recognised symptoms. A variant can also occasionally be found in someone whose family history is unknown.

Age is relevant because amyloid deposits usually build up over time. The specific gene variant, family background, and other factors that are not fully understood may influence whether the nerves, heart, or both are affected.

This condition is not caused by diet, alcohol use, infection, or anything a person did.

Diagnosis

Diagnosis usually combines your symptoms and examination findings with genetic testing and evidence that amyloid is present. Because several conditions can cause neuropathy, thickened heart walls, or autonomic symptoms, careful testing is needed.

Blood or saliva testing can identify the TTR variant. A positive genetic result shows that the variant is present, but it does not by itself prove that current symptoms are caused by amyloid.

Tests may include:

In the right circumstances, a characteristic bone-tracer scan combined with tests showing no abnormal monoclonal protein can establish ATTR cardiomyopathy without a heart biopsy. This approach does not replace genetic testing, which distinguishes inherited ATTR from wild-type ATTR.

A biopsy may be needed if results are uncertain or another form of amyloidosis is possible. A small tissue sample may be taken from abdominal fat, a salivary gland, an affected organ, or another site. If amyloid is found, the protein should be accurately typed. Mass spectrometry is a laboratory method that can identify the amyloid protein.

- Nerve conduction studies to assess how well peripheral nerves work

- An electrocardiogram and heart ultrasound to examine heart rhythm and structure
- Cardiac MRI to look for patterns of heart muscle damage
- Blood tests for heart strain, kidney function, and other causes of neuropathy
- Blood and urine tests for abnormal antibody proteins linked to AL amyloidosis
- A nuclear medicine bone-tracer scan when ATTR heart amyloidosis is suspected

Treatment and management

Treatment aims to slow further amyloid formation, protect organ function, and manage symptoms that are already present. The best approach is based on whether the nerves, heart, or both are involved, as well as local medicine approvals and access.

TTR gene-silencing medicines reduce the liver's production of transthyretin. Some use small interfering RNA, while others use antisense technology. Different medicines are approved for different forms or stages of hereditary ATTR amyloidosis. They require ongoing monitoring and do not usually repair established nerve or heart damage.

TTR stabilizers bind to the transthyretin protein and make it less likely to break apart. Some are used for ATTR cardiomyopathy. The available choices and eligibility rules differ between countries.

Treatment may also address the condition's effects:

Heart medicines commonly used for other conditions are not always tolerated in cardiac amyloidosis, especially when blood pressure is low. Medication changes should therefore be supervised by a team familiar with amyloidosis.

Liver transplantation was historically used because the liver produces most circulating TTR. It may still be considered in selected circumstances, but it is major surgery and does not always stop progression. Normal, or wild-type, TTR can continue collecting on existing deposits. Heart transplantation or combined organ transplantation may be considered for carefully selected people with advanced organ damage.

Regular follow-up commonly includes checks of strength, sensation, walking, blood pressure, weight, heart rhythm, heart function, and kidney health.

- Neuropathic pain may be managed with medicines aimed at nerve pain
- Physiotherapy, mobility aids, and occupational therapy can support safety and independence
- Blood-pressure measures may reduce dizziness caused by autonomic neuropathy

- Nutrition support can help with weight loss or digestive symptoms
- Heart treatment may address fluid retention, rhythm problems, or conduction problems
- A pacemaker may be needed if the heart's electrical system becomes unreliable

Complications

Progressive peripheral neuropathy can lead to weakness, falls, loss of hand function, or reduced mobility. Loss of sensation can allow foot injuries or burns to go unnoticed, so routine foot care is important.

Autonomic nerve damage may cause repeated faintness, falls, dehydration, poor nutrition, bladder problems, or severe bowel disruption. Persistent vomiting, diarrhoea, or difficulty eating can contribute to weight and muscle loss.

Heart involvement can lead to heart failure, in which the heart cannot fill or pump effectively enough for the body's needs. Amyloid may also disturb the heart's electrical system, causing slow, fast, or irregular rhythms. Blood clots and stroke can occur in association with some abnormal rhythms.

Complications are not inevitable. Their likelihood is influenced by which organs are involved, how advanced the condition is at diagnosis, and how it responds to treatment.

Prevention

The inherited TTR variant cannot be prevented through lifestyle changes. Food choices, exercise, and supplements cannot remove the gene change.

If the variant has been identified in a family, adult relatives can consider genetic counselling and predictive testing. Counselling can explain what a positive, negative, or uncertain result may mean before testing takes place.

People planning a family may wish to discuss reproductive options with a genetics service. These choices are personal and may include natural conception, prenatal testing, donor eggs or sperm, adoption, or in vitro fertilisation with testing of embryos.

For someone who carries the variant but has no symptoms, planned monitoring may detect early changes. This does not prevent inheritance or guarantee that complications will be avoided, but it may allow treatment to be considered sooner if the condition becomes active.

Living with it and what to expect

Isoleucine 33 amyloidosis is generally a progressive condition, meaning that amyloid-related problems can increase over months and years. The pace cannot be predicted from the gene result alone. Some people mainly develop neuropathy, while others have significant heart involvement or a mixture of both.

Current treatments can slow the production or misfolding of TTR. They are less likely to restore nerves or heart tissue that have already been seriously damaged. Starting effective treatment before advanced organ damage may help preserve function, but no treatment can promise a particular result.

Follow-up remains important even when symptoms seem stable. Nerve function, mobility, blood pressure, nutrition, heart rhythm, and heart pumping or filling can change at different rates. New symptoms should be discussed rather than automatically attributed to amyloidosis, because common and treatable conditions can occur as well.

Daily life may involve pacing activities, planning around fatigue or bowel symptoms, using mobility support, and allowing more time when standing up. Regular movement within your abilities can help maintain strength and balance. Checking feet for injuries is useful when sensation is reduced.

Genetic results can affect relatives as well as the person tested. Genetic counselling, amyloidosis support organisations, and psychological support may help with decisions about testing, family planning, work, and adapting to changing abilities.

When to get medical help

Arrange routine medical review if you develop new or increasing numbness, weakness, balance problems, bowel changes, dizziness on standing, ankle swelling, breathlessness during usual activities, or unexplained weight loss. These symptoms do not prove that amyloidosis is worsening, but they deserve assessment.

Contact your amyloidosis or cardiology team promptly if you have repeated fainting, rapidly increasing swelling, a new irregular heartbeat, or a clear decline in walking or hand function.

Seek emergency care for:

These symptoms can have several causes and require urgent assessment rather than waiting for a routine appointment.

- Chest pain or pressure

- Severe or sudden shortness of breath
- Fainting with slow recovery, injury, or palpitations
- New facial drooping, arm weakness, or difficulty speaking
- Inability to keep fluids down with signs of dehydration

Common questions

What does "isoleucine 33" mean?

It describes the amino acid found at position 33 of the mature transthyretin protein. Isoleucine has replaced phenylalanine, so the variant is also called Phe33Ile. Some genetic reports count an additional 20-amino-acid signal sequence and call it Phe53Ile.

Is this the same as AL amyloidosis?

No. Isoleucine 33 amyloidosis involves inherited, abnormal transthyretin. AL amyloidosis is caused by abnormal antibody light-chain proteins made by plasma cells in the bone marrow. The treatments are very different, which is why accurate amyloid typing matters.

Will my children inherit it?

If you carry the variant, each child has a 1 in 2 chance of inheriting it. Inheriting the variant does not reveal exactly when symptoms will begin or whether they will occur. A genetics service can explain testing and family-planning options.

Can a genetic test tell me how severe it will be?

No. It can confirm whether the TTR variant is present, but it cannot reliably predict the age of onset, affected organs, or rate of progression. Your family history may provide some clues, but relatives can still have different experiences.

Do I need a biopsy?

Not always. ATTR heart amyloidosis can sometimes be diagnosed using characteristic heart imaging, a bone-tracer scan, and blood and urine tests that exclude AL amyloidosis. A biopsy may be necessary when findings are unclear or when the amyloid type must be confirmed.

Can it be cured?

There is currently no treatment that reliably removes the inherited variant and reverses all existing organ damage. TTR-targeting medicines can slow progression, while supportive treatment can reduce symptoms and protect daily function.

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