Hereditary ATTR amyloidosis
A closer look at an inherited condition
What is hereditary ATTR (hATTR) amyloidosis?

hATTR amyloidosis is caused by a gene change (mutation) that affects the function of a protein in the blood called transthyretin (TTR). This protein is made primarily in the liver. hATTR amyloidosis is a rare condition that affects an estimated 50,000 patients worldwide.

Individuals with hereditary ATTR amyloidosis may have a range of symptoms that may seem unrelated. Symptoms can affect several parts of the body, including the nervous (nerve), cardiac (heart), and gastrointestinal (digestive) systems.

How hATTR amyloidosis develops

TTR, a naturally occurring protein made primarily in the liver, helps carry substances such as vitamin A.

Gene mutations can lead to changes in the TTR protein that cause it to misfold (take on an abnormal shape).

The change in shape causes the protein to gather and build up in the nervous (nerve), cardiac (heart), and gastrointestinal (digestive) systems. These gathered proteins are called amyloid fibrils. These amyloid fibrils build up and form deposits, which is what causes symptoms.
hATTR amyloidosis—an inherited condition

hATTR amyloidosis is passed down through family members, and is inherited in an autosomal dominant fashion, meaning a person only needs to inherit one copy of the affected gene from one parent in order to develop the condition.

Genes are located on structures known as chromosomes. Every individual has two copies of the TTR gene, one inherited from each parent. When one parent carries an autosomal dominant mutation, any child will have a 50% chance of inheriting that mutation.

A family member may inherit the TTR gene with a mutation, but having the mutation does not mean he or she will develop hATTR amyloidosis.

hATTR amyloidosis can be passed down to children, an important consideration for people who may be thinking about starting a family.
hATTR amyloidosis can cause a range of symptoms

The symptoms of hATTR amyloidosis can vary widely among people with the same mutation and even within families, though some do see a pattern of symptoms develop. Different symptoms may appear at different times for each individual. The age that initial symptoms appear may vary, ranging from the mid-20s to the mid-60s.

hATTR amyloidosis affects several parts of the body, including:

- The peripheral nervous system, which is made up of nerves that branch out from the brain and spinal cord and communicate with the rest of the body including your arms and legs
  - Polyneuropathy is caused by damage to the nerves of the peripheral nervous system, resulting in improper function

- The cardiac system, which includes the heart and blood vessels, transports blood through veins and delivers oxygen to cells in the body
  - Cardiomyopathy is a disease of the heart muscle that leads to heart failure

- The autonomic nervous system, which is made up of nerves that connect the brain and spinal cord to organs such as the heart, stomach, and intestines, and helps to control bodily functions such as breathing, digestion, and heart rate
  - Autonomic dysfunction occurs when the autonomic nervous system is not working correctly and may affect involuntary bodily functions
The varying symptoms of hATTR amyloidosis

Autonomic Dysfunction
Symptoms of autonomic dysfunction include:
- Urinary tract infections
- Excessive sweating
- Dizziness upon standing
- Sexual dysfunction
- Nausea and vomiting
- Diarrhea
- Severe constipation
- Unintentional weight loss

Cardiomyopathy
Symptoms of cardiomyopathy include:
- Increasing fatigue
- Dizziness
- Shortness of breath
- Leg swelling (edema)
- Palpitations and abnormal heart rhythms (atrial fibrillation)
- Chest pain

Peripheral Neuropathy
Peripheral neuropathy includes symptoms such as:
- Tingling
- Numbness
- Carpal tunnel syndrome
- Burning pain
- Loss of sensitivity to temperature
- Weakness
- Kidney dysfunction

Other Symptoms
- Glaucoma
- Blurred or spotty vision
- Abnormalities of the pupil or blood vessels on the white of the eye
- Detached retina
- Progressive dementia
- Headache
- Loss of movement control
- Seizures
- Weakness
- Stroke-like episodes
Getting the right diagnosis is key

Misdiagnosis is common with hATTR amyloidosis because the symptoms can resemble those of other conditions. Learning about the symptoms of hATTR amyloidosis can help you identify them if they occur.

Take the next step

If you experience symptoms or become aware of a family history, speak to your healthcare professional to determine the right plan of action. Because the condition is rare and affects different parts of the body, it may be necessary for your healthcare professional to refer you to a specialist who is more familiar with hATTR amyloidosis. Even if you haven’t experienced any symptoms but are aware of a family history, your doctor can refer you to a genetic counselor.

Getting started with genetic counseling

Genetic counseling can help you understand your chances of inheriting the condition as well as make you familiar with the testing process and implications of a diagnosis. Genetic counselors are available to help you understand the issues related to genetic testing—from personal risk to possible insurance impact, and can help you determine if a genetic test may be right for you.
**Treatment**

Due to the progressive nature of hATTR amyloidosis, managing the symptoms of the condition is an ongoing process. Physicians may prescribe medications to treat these symptoms and reduce the daily impact they may have.

Currently, there are no approved treatments for hATTR amyloidosis in the US, though some patients may benefit from a liver transplant, which could substantially reduce the amount of TTR protein made in the body.

It’s important to talk to your doctor if you begin to experience symptoms or learn about a family history of hATTR amyloidosis.

Research is underway to evaluate potential treatment options for patients with hATTR amyloidosis.
Get the facts about hereditary ATTR amyloidosis

Learn more about hATTR amyloidosis at www.hATTRbridge.com

Sources for additional information and assistance

Amyloidosis Foundation: visit www.amyloidosis.org
Amyloidosis Support Groups: visit www.amyloidosisisupport.org
Amyloidosis Research Consortium: visit www.arci.org
National Organization for Rare Disorders: visit www.raredisease.org
Global Genes: visit www.globalgenes.org
Clinical Trial Information: visit www.clinicaltrials.gov

Alnylam Act™

www.alnylam.com/patients/alnylam-act

Alnylam Pharmaceuticals is sponsoring third-party genetic testing and counseling programs for individuals who may carry a gene mutation known to be associated with hereditary ATTR amyloidosis at no charge. The Alnylam Act™ (formerly known as Alnylam Assist™) program was created to potentially enable diagnosis through genetic screening and to provide genetic counseling to help people make more informed decisions about their health. These services are available only in the United States. At no time does Alnylam receive patient-identifiable information.

Your doctor will need to sign you up for the Alnylam Act™ program in order for you to receive genetic screening and counseling at no charge.
Right away, I wanted to know if I can do something about this.

— Sandie, living with hATTR amyloidosis
References:
Ruberg DL. *Circulation.* 2012;126(10):1286-1300.

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