DISEASE OVERVIEW

HEREDITARY TRANSTHYRETIN AMYLOIDOSIS

David and his daughter Sarah both have hATTR amyloidosis.

Amyloidosis Research Consortium

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KNOWLEDGE IS POWER

ABOUT THE **AMYLOIDOSIS RESEARCH CONSORTIUM**

The Amyloidosis Research Consortium (ARC) is a nonprofit organization dedicated to driving advances in the awareness, science, and treatment of amyloid diseases. ARCs mission is to improve and extend the lives of those with amyloidosis. ARC is committed to collaborative efforts that accelerate the pace of discovery, expand patient access to the most effective care, and improve short- and long-term outcomes. Working with partners in industry, government, and academia, ARC seeks to spark innovation and to bring promising treatments from labs to clinics. Our outreach and educational efforts inform and empower patients, families, caregivers, physicians, and researchers.

To learn more about ARC or speak with a specialist on our team:

- Visit **www.arci.org**
- Call **1.617.467.5170**

Amyloidosis Research Consortium

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INTRODUCTION

Hereditary transthyretin amyloidosis (hATTR) is a rare, systemic disease passed down through families. Caused by genetic mutations in the transthyretin (TTR) gene, it leads to a buildup of abnormal proteins called amyloid in one or more organs and tissues, impairing their function. Left untreated, hATTR can cause life-threatening complications. Early diagnosis and treatment are critical to prevent or delay progression of hATTR.

A diagnosis of hereditary transthyretin amyloidosis (hATTR) can be confusing and emotionally painful, bringing up many feelings and questions. It is important to learn as much as possible about the disease, its cause, its treatment, and how it might affect you and those you love. A well-informed patient is better able to be an active partner with their health care team in making decisions about treatment, managing their care, and advocating for their needs.

This booklet is here to serve as a comprehensive resource and a guide for making informed treatment decisions.

AMYLOIDOSIS

WHAT IS AMYLOIDOSIS?

Amyloidosis is a group of diseases caused when misfolded proteins, called amyloid, build up and form fibrils that deposit in the body's organs and tissues, affecting their ability to function. Amyloid fibrils typically accumulate in the heart, kidney, and nerves; less often in the liver, spleen, gastrointestinal tract, and airway. These can impair multiple organs and nerves or be localized in one area of the body. Symptoms are often mistaken for more common conditions.

Over 30 different proteins can cause amyloidosis. Each protein has different associated symptoms and treatments, and is linked with a unique sub-type of amyloidosis. Each sub-type is referred to by an "A" for amyloid, followed by an abbreviation for the abnormal protein. For example, AL amyloidosis is caused by abnormal immunoglobulin **L**ight chains, and ATTR is caused by abnormal transthyretin (**TTR**) protein. Treatment is determined by the type of amyloid and which organs and tissues are affected.

Amyloid is a starch-like substance caused by the misfolding of proteins. Amyloid binds together into rigid, linear structures (called fibrils) that accumulate in tissues and organs.

WHY ARE PROTEINS SO IMPORTANT?

Many thousands of proteins do essential work inside our cells. Each has a specific job to keep us healthy.

DNA instructions control the shape and structure of proteins. Normal proteins fold into a specific shape, do their tasks, and are then recycled or removed from the body.

In amyloidosis, mutated proteins form incorrectly (misfold), which makes them unable to do their tasks and difficult for the body to remove. These misfolded proteins then accumulate in the body and form fibrils, known as amyloid, in organs and tissues, such as

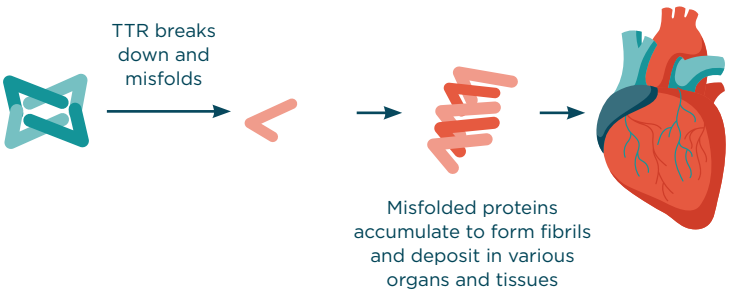
the heart, kidney, or nerves. As they accumulate over time, they impact the function of organs causing symptoms to flare, telling us something is wrong.

Many different proteins can misfold and lead to different types of amyloidosis, but they all share the same abnormal structure. Diagnostic tests can identify specific types of amyloid.

Abnormal transthyretin (TTR) proteins are seen in two types of amyloidosis: hereditary transthyretin amyloidosis (hATTR) and wild-type ATTR (ATTRwt). In hATTR, amyloid deposits are caused by inherited genetic mutations. In ATTRwt, they develop as part of the aging process, typically in men over 60. The natural course of disease for hATTR and ATTRwt differ, making it important to correctly identify the type.

WHAT IS HEREDITARY TRANSTHYRETIN AMYLOIDOSIS (hATTR)?

Hereditary transthyretin amyloidosis (hATTR) is a rare systemic form of amyloidosis. A mutation in the transthyretin (TTR) gene causes the protein to become unstable, then misfold and form amyloid deposits. Strands of amyloid fibrils accumulate in multiple organs and nerves, impairing their function. There are more than 120 mutations that are known to cause hATTR and each is passed down from parents to children. Depending on the specific mutation, symptoms can begin as early as 30 years of age, although most present later in life. Without treatment, the condition worsens over time.



Symptoms vary depending on the affected organs and systems. In hATTR, amyloid fibrils most commonly accumulate in the peripheral nerves (nerves that control sensation and movement in the extremities), autonomic nerves (nerves that control organ function, such as digestion and blood pressure), and the heart. Other organs can be involved including the eyes and gastrointestinal tract.

Untreated, the disease is progressive, and ultimately, fatal. Symptoms mimic more common conditions, making hATTR amyloidosis difficult to recognize and diagnose. Early identification and treatment are essential to improve outcomes.

The TTR gene provides instructions for producing a protein called transthyretin, which is mostly made in the liver. Normally, it transports vitamin A (retinol) and a hormone called thyroxine throughout the body. TTR mutations lead to transthyretin proteins that misfold into amyloid deposits.

HOW COMMON IS hATTR?

The exact incidence of hATTR is unknown, but the disease is endemic in certain parts of Portugal, Brazil, Sweden, and Japan. In the United States, up to 6,400 people have hATTR. For Americans of European decent, it is estimated to be more common, occuring in 1 in 100,000.

The disease is more common in northern Portugal, where it affects one in 538. It's also more prevalent in those of African American and Irish ancestry. However, it's not limited to these groups. It has been found across all ethnicities and occurs equally in men and women.

Annual incidence of hATTR in Europe is estimated at 0.3 new cases per million people, with a prevalence of 5.2 cases per 1 million inhabitants. In Japan, there are some 400 reported cases.

Because amyloidosis is often misdiagnosed, the actual incidences may be much higher than what has been reported.

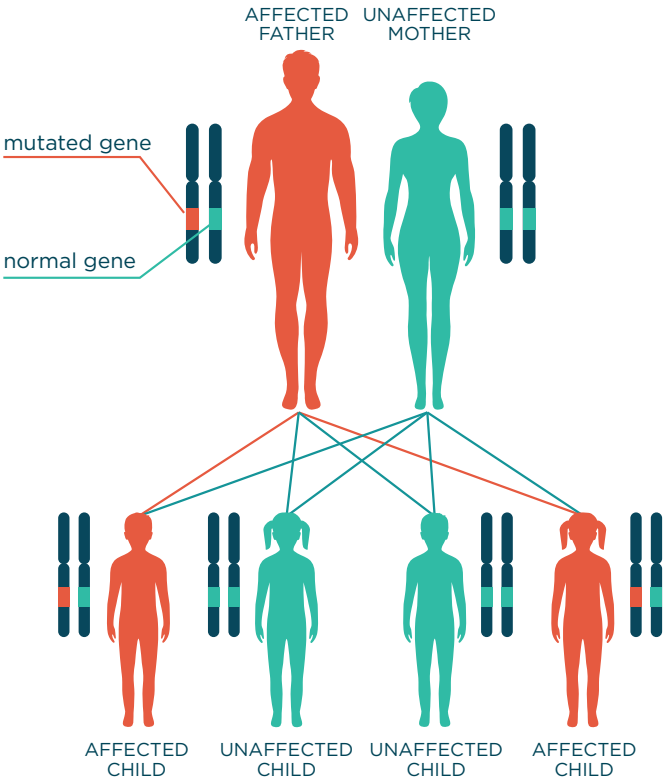
INHERITANCE

HOW IS hATTR INHERITED?

hATTR amyloidosis is caused by changes (mutations) in the TTR gene. These alter the DNA sequence, making it different from that found in most people.

Every child inherits two copies of each gene: one from their mother and one from their father. hATTR is inherited in an autosomal dominant pattern. This means that inheriting only one copy of the mutated gene can cause the condition. A new (de novo) mutation can also happen, but it's rare. Most patients diagnosed with hATTR have inherited the gene from one of their parents.

AUTOSOMAL DOMINANT INHERITANCE PATTERN



WHAT ARE THE DIFFERENT TTR MUTATIONS?

More than 120 TTR mutations have been identified. V122I, T60A, and V30M are the most common variants found in the United States. All alter the structure of transthyretin, making it unable to form correctly and carry out its normal functions.

The V122I mutation is associated with cardiomyopathy and is more likely to be seen in those with West African ancestry. In the U.S., it is estimated that 3.2% of African Americans have this mutation.

While some TTR mutations are associated with primarily either nerve or cardiac manifestations, most patients have a combination of symptoms. Regardless of the specific TTR variant, the symptoms and progression of hATTR are unpredictable, and its effects can vary even among members of the same family.

The V30M variant causes mainly nerve-related symptoms. It's found in families from Portugal, Spain, France, Sweden, Japan and their descendants. The V122I mutation is most often associated with cardiac complications. It's carried by 3-4% in those of West African descent, a common lineage among African Americans. The T60A mutation, found in those of Irish ethnicity, is the most common TTR mutation in the UK. It commonly affects both the peripheral nervous system and the heart.

HOW LIKELY AM I TO DEVELOP SYMPTOMS IF I HAVE THE TTR MUTATION?

Penetrance is a term used to define how likely you are to be affected by a disease if you have the disease-causing gene.

If a certain gene has "complete penetrance", 100% of individuals with the gene will develop the corresponding disease. hATTR has "variable penetrance", which means that some mutations have a higher penetrance than others. Other factors, including family

history, geographic region, ethnic group, and sex, can influence a patient's probability of developing hATTR, as well as the age that symptoms start to appear (age of onset). Not everyone who has a mutation will develop the disease.

In Portugal, 80% of those with the V30M mutation have disease onset by age 50 and 91% by their 70th birthday. In Sweden, the penetrance is much lower, with hATTR onset in only 11% of carriers by age 50 and 52% by 80 years. Among those of West African lineage with the V122I mutation, a majority will not develop symptoms of hATTR amyloidosis by the age of 80.

Each child of a parent with hATTR amyloidosis has a 50% chance of inheriting the TTR mutation. Most who have it will develop the disease, although it may differ in severity from that of their parent. Some people with a TTR mutation never develop hATTR amyloidosis.

SYMPTOMS

HOW DOES hATTR AFFECT THE BODY?

hATTR is a systemic, progressive disease that can affect multiple organs and areas of the body. It can cause many different symptoms. These emerge in adulthood, typically from 30 to 65 years of age.

The peripheral nervous system

Peripheral neuropathy—or damage to nerves in the hands, feet, and lower legs—is common in hATTR amyloidosis. Pain, numbness, tingling, weakness, or burning is typically felt on both sides of the body (polyneuropathy). There may be more sensitivity to pain and reduced sensitivity to heat. As the disease progresses, muscles can become stiff and weak. Coordination can be affected, making it hard to walk or do activities that require fine motor skills. Carpal tunnel syndrome in both wrists may be caused by the deposition of amyloid, and can be one of the first symptoms of hATTR.

The autonomic nervous system

Autonomic nerves control the function of internal organs, such as the gut, bladder, stomach, and glands. hATTR can affect heart rate, blood pressure, digestion, perspiration, and other body processes. Symptoms of autonomic neuropathy can include dizziness when you stand up quickly (orthostatic hypotension); recurring urinary tract infections (due to urinary retention); sexual dysfunction; abnormal sweating; and alternating bouts of diarrhea and constipation.

The heart

Amyloid deposits can cause congestive heart failure (weakness of the heart that leads to a buildup of fluid in the lungs and surrounding body tissues); hypertrophic cardiomyopathy (thickening of the heart muscle); coronary artery disease; an irregular heartbeat (arrhythmia); or syncope (fainting). Symptoms can

include nausea, weight loss, shortness of breath, inability to sleep, fatigue, dizziness, and swelling in the legs (edema).

The kidneys

A buildup of amyloid fibrils can lead to nephrotic syndrome, typically in those with the V30M mutation. Symptoms include excess loss of protein in the urine and swelling in the lower legs. The stomach, arms, and lungs can become swollen. In cases of kidney (renal) failure, dialysis may be needed to filter blood.

The gastrointestinal tract

Amyloid deposits in the digestive system, or gastrointestinal (GI) tract, can cause nausea and vomiting, chronic diarrhea, constipation, a feeling of being full after eating small amounts of food (early satiety), and bouts of severe alternating diarrhea and constipation.

The eyes

About 20% of TTR mutations affect the eyes. Symptoms can include dark floaters (spots or shapes in the field of vision); dry eyes; increased pressure in the eyes (glaucoma); cloudiness in the clear gel that fills the eyeball (vitreous opacity); abnormal blood vessels in the eye; or pupils with an irregular appearance. Vision can be impaired.

Other symptoms

Less common symptoms of hATTR may include skin changes, hearing loss, shortness of breath, anemia, and lumbar spinal stenosis.

WHAT ARE OTHER NONSPECIFIC SYMPTOMS?

Nonspecific symptoms are those that can be caused by a wide range of illnesses. Fatigue is one example. Others may include fever, general malaise, weight loss, difficulty concentrating, or stiffness. The onset of hATTR amyloidosis is typically slow, occurring over many years. Because the disease is rare, physicians

tend to attribute symptoms to other, more common disorders. Misdiagnoses often lead to treatment for unrelated diseases and delayed access to appropriate therapeutic options.

RED FLAG SYMPTOMS OF hATTR
The systemic nature of hATTR can make it difficult to recognize. Red flags include progressive neuropathy on both sides of the body (polyneuropathy) and one or more of the following symptoms:
Signs of early autonomic dysfunction, such as dry mouth or incontinence
Symptoms of heart failure, such as fatigue or edema
Severe chronic diarrhea, constipation, or bouts of constipation and diarrhea
Unexplained weight loss
Carpal tunnel syndrome in both wrists (bilateral carpal tunnel)
Floaters or vitreous opacity

WHAT SHOULD I TELL MY DOCTOR?

It's important to tell your doctor about all of your symptoms and how they have progressed over time. Clusters of red flag symptoms (see table) can raise the suspicion of hATTR amyloidosis. It's also important let your doctor know if any of your relatives have had similar illnesses. A family history can support a diagnosis of hATTR amyloidosis, but not having affected relatives doesn't rule it out, especially if you're older than 50 years of age.

Ask your healthcare provider for a referral to a center that specializes in the diagnosis and management of amyloidosis. To develop the best treatment plan, your primary care doctor and other specialists should coordinate care with experts at these centers.

DIAGNOSIS

WHAT DIAGNOSTIC TEST WILL I NEED?

A correct diagnosis is essential for effective and timely treatment. Biopsy is the gold standard for diagnosing hATTR. Usually, a small sample of fat is taken from the patient's lower abdomen to test, but the biopsy could also be a sample of skin, or tissue from an affected organ. The sample(s) are then stained with Congo red dye and viewed under a microscope with polarized light. Stained amyloid has a characteristic "apple-green birefringence," meaning it will appear green under polarized light. While biopsy is the gold standard, this test is not 100% accurate.

Once the presence of amyloid is confirmed, the type of amyloid protein needs to then be determined through a process known as laser microdissection with mass spectrometry. Genetic testing is then required to differentiate hATTR amyloidosis from nonhereditary, wild-type ATTR (ATTRwt) amyloidosis. Differentiating between them is important for making sound personal and medical decisions.

Although an endomyocardial biopsy (biopsy of the heart tissue) is still the definitive diagnostic tool, nuclear imaging (scintigraphy) is emerging as a highly accurate, noninvasive option. The workup can also include a combination of other tests to determine extent of organ involvement. These can include symptom evaluation, blood work, electrocardiography (ECG), echocardiography, multimodal imaging, other organ biopsies, and genetic testing. Nerve conduction and small fiber studies are used to test nerve damage. Heart function is assessed with ECG and echocardiography as well as cardiac magnetic resonance imaging (CMR).

WHAT DO I NEED TO KNOW ABOUT GENETIC TESTING AND COUNSELING?

Genetic testing identifies changes in chromosomes, genes, or proteins. When DNA chains are examined for genetic markers of TTR variants, the analysis identifies more than 99% of TTR disease-causing mutations. Test results can confirm or rule out hATTR and help you understand the probability of developing or

passing on the disease, but they can't predict its onset, severity, or rate of progression.

Genetic testing has benefits and risks. The decision to have it done is personal and complex. It's a voluntary choice that requires your informed consent. It's important to understand the test, what it can and can't tell you, and the possible consequences of the results.

Most of the risk involves emotional, social, or financial consequences of the test results. Some people may feel angry, depressed, anxious, or guilty. Certain blood relatives may be affected, creating tension in the family. There's also the possibility of genetic discrimination when trying to obtain life insurance.

Benefits can include relief from uncertainty and an opportunity to make informed decisions about your health care. Test results often prompt patients to seek new monitoring and treatment options, or revisit family planning decisions.

A genetic counselor can walk you and your family through the pros and cons of genetic testing, including the social and emotional aspects. You'll also receive information on the nature and implications of genetic disorders. This process can help you turn knowledge into power.

SHOULD I GET A SECOND OPINION?

Because hATTR is a rare condition, it can be hard to find clinicians who have seen many cases. This makes it important to seek a second opinion before starting treatment. Many insurance companies cover the cost if the patient or doctor requests it.

ARC and other advocacy groups can help you find centers that specialize in the diagnosis and treatment of hATTR.

ARC PATIENT SUPPORT AND RESOURCES

The Amyloidosis Research Consortium (ARC) is a nonprofit organization with a mission to advance scientific discovery, improve access to state-of-the-art care, and empower patients with innovative educational tools and support. Please see the companion booklet in the hATTR series, **Treatment Overview for Hereditary Transthyretin Amyloidosis**, for more information on hATTR, or check out our free online tool, My Amyloidosis Pathfinder, to personalize your treatment goals:

MAP | My Amyloidosis Pathfinder

MAP is a free, easy-to-use tool that captures your treatment preferences, goals, and challenges so you can effectively communicate with your amyloidosis care teams.

As part of your MAP experience, you can also find and compare specialty treatment centers and receive personalized matches to clinical trials.

My Amyloidosis Appointment Companion

Treatment Center Selector

Clinical Trial Finder

www.myamyloidosispathfinder.org

GLOSSARY

Amyloid. A starch-like substance caused by the misfolding of proteins. Amyloid binds together into rigid, linear structures (fibrils) that accumulate in tissues and organs.

Autonomic nervous system. Regulates processes in the body's blood vessels, glands, and organs; works automatically, without a person's conscious effort, to control blood pressure, breathing, digestion, and other functions.

Autosomal dominant. One of many ways that a trait or disorder can be passed down through families. With an autosomal dominant disease, you can get the disease with an abnormal gene from only one parent.

Beta pleated sheet. Polypeptide chains that have a wavelike appearance and run alongside each other.

Birefringence. The phenomenon shown by certain materials in which a ray of light is split into two rays (double refraction).

Cardiac magnetic resonance imaging (CMR). A diagnostic technique that uses harmless radio waves rather than x-rays to create images; currently the most accurate and reproducible technique for imaging the heart.

Cardiomyopathy. A type of progressive heart muscle disease in which the heart is abnormally enlarged, thickened, and/or stiffened.

Carpal tunnel syndrome. A common condition that causes pain, numbness, and tingling in the hand and arm; caused when one of the major nerves to the hand, the median nerve, is squeezed or compressed as it travels through the wrist.

Congo red. A histological staining technique that is the gold standard technique for the diagnosis of amyloidosis. When added to a tissue sample, the stain will identify and highlight the presence of amyloid fibrils.

DNA. Deoxyribonucleic acid is the hereditary material in humans and all other organisms. Nearly every cell in a person's body has the same DNA.

Endomyocardial biopsy (EMB). A surgical procedure where a doctor takes a small sample of your heart muscle tissue for testing.

Fibrils. Long strand of normally soluble proteins that clump together to form insoluble fibers resistant to degradation.

Genetic counseling. The process by which the patients or relatives at risk of an inherited disorder are advised of the consequences and nature of the disorder, the probability of developing or transmitting it, and the options open to them in management and family planning.

Genetic discrimination. When people are treated differently by their employer or insurance company because they have a gene mutation that causes or increases the risk of an inherited disorder.

Genetic variant. An alteration in the most common DNA nucleotide sequence.

Gold standard. A diagnostic test or benchmark that is widely considered the best available under reasonable conditions.

Hereditary transthyretin amyloidosis (hATTR). A rare, progressive form of systemic amyloidosis caused by an inherited genetic mutation that causes a buildup of amyloid in multiple organs and tissues.

Informed consent. The process of disclosing appropriate information to patients so they can make an informed and voluntary choice to accept or refuse getting medical care, diagnostic tests, or treatment.

Nerve conduction studies. A diagnostic test used to evaluate the function, especially the ability of electrical conduction, of the motor and sensory nerves of the human body.

Nuclear imaging. A branch of medical imaging that uses small amounts of radioactive material to diagnose, determine the severity of, or treat a variety of diseases.

Peripheral neuropathy. Damage to or disease affecting nerves, which may impair sensation, movement, gland or organ function, or other aspects of health.

Peripheral nervous system. The network of nerves that transmits information from your central nervous system (brain and spinal cord) to the rest of your body.

Polyneuropathy. Damage that affects peripheral nerves (peripheral neuropathy) in roughly the same areas on both sides of the body; symptoms include weakness, numbness, and burning pain.

Proteins. Large, complex molecules coded by our genes that play a central role in biological processes. The work they do in cells is required to maintain the structure, function, and regulation of tissues and organs.

Scintigraphy. A diagnostic technique in which a two-dimensional picture of internal body tissue is produced through the detection of radiation emitted by a radioactive substance administered into the body.

Syncope. A temporary loss of consciousness usually related to insufficient blood flow to the brain; also called fainting or passing out.

Transthyretin amyloidosis. A progressive condition characterized by the buildup of abnormal deposits of a protein called amyloid in the body's organs and tissues.

Transthyretin. A protein mainly produced in the liver that transports vitamin A (retinol) and a hormone called thyroxine throughout the body.

TTR gene. Provides instructions for producing a protein called transthyretin.

Vitreous opacity. Floaters, spots, or shadows caused by opaque cell fragments in the vitreous humor or lens of the eye.

Wild-type transthyretin amyloidosis (ATTRwt). Acquired amyloidosis with a normal (nonmutated) transthyretin protein; typically causes cardiac dysfunction and is seen in men 60 years or older.

NOTES

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