ALPORT SYNDROME FOUNDATION®

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Patient Guide

By Patients for Patients

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Developed by the Emerging Leadership Council and
Medical Advisory Committee of Alport Syndrome Foundation

This document is intended to help answer some initial questions you may have after receiving a diagnosis of Alport syndrome and/or to help loved ones understand this disease. For a glossary of common terms you will see throughout this guide, please refer to our Alport Vocabulary Terms page. Please note that in this document, “males” refers to birth sex males (XY chromosomes) and “females” refers to birth sex females (XX chromosomes).

What is Alport syndrome?

Alport syndrome is a rare, genetic condition that is passed from parent to child. It can also occur spontaneously, meaning that no one else in the family has been affected before.

Regardless of sex assigned at birth, Alport syndrome affects the kidneys and may progress to kidney failure. It also may cause hearing loss and/or changes to the eyes.

Alport syndrome uniquely impacts individuals based on a number of factors, such as genetics. The signs, symptoms, and rates of disease progression can vary greatly from person to person, even within families. Alport syndrome is considered a type of chronic kidney disease.

What causes Alport syndrome?

Alport syndrome is caused by genetic mutations in a person’s DNA. Individuals with Alport syndrome typically have defects in their COL4A3, COL4A4, or COL4A5 genes (or a combination of these).

The mutation causes a protein called type IV collagen to form incorrectly. Type IV collagen is a building block of the basement membranes found in the kidneys, inner ears, and eyes, as well as the aorta, lungs, uterus, and other tissues. Because these tissues don’t have the type IV collagen they need, the affected organs may begin to lose function over time. For example, in the kidneys, this defect in the collagen within the glomerular basement membrane leads the glomerular filtration barrier to fail which in turn causes kidney damage. This can show up as blood or protein in the urine. Collagen changes in the inner ear can cause unilateral (one ear) or bilateral sensorineural hearing loss (both ears and commonly associated with Alport syndrome), although the exact mechanisms behind this process are still being studied.

Who does Alport syndrome affect?

Alport syndrome can occur in people of all ages, sexes, and ethnicities. Recent research suggests it’s likely that more people have Alport syndrome than previously thought, thanks to increased awareness and genetic testing. However, it is still considered a rare disease, meaning it affects less than 200,000 people in the United States.

The main symptoms of Alport syndrome and their similarity to other more common kidney diseases can make it difficult to diagnose. For example, blood (hematuria) and protein (proteinuria) in the urine are classic symptoms of several chronic kidney diseases besides Alport

syndrome. Females who experience hematuria are often incorrectly labeled as “carriers.” This is a misnomer and Alport females with symptoms should be routinely monitored and treated.

Because Alport syndrome is rare, patients often report receiving an incorrect initial diagnosis. Alport syndrome can sometimes present similarly to other kidney diseases such as steroid-resistant focal segmental glomerulosclerosis (FSGS), IgA nephropathy, minimal change disease, or thin basement membrane nephropathy (benign familial hematuria). Collecting a full patient history — including all of the patient’s symptoms and family history — can help health care providers make an accurate diagnosis.

How is Alport syndrome diagnosed?

For individuals with a "suspected diagnosis," there are many important reasons to gain a confirmed diagnosis: earlier access to treatment, ability to identify other family members who may be at risk, clinical trial participation, and more. Currently, non-invasive and affordable diagnostic options are available for patients and families.

No-charge/minimum-charge genetic testing (based on insurance coverage) is becoming more readily available to suspected patients and can be performed with a simple blood test, cheek swab, or saliva sample. Patients who undergo genetic testing are encouraged to connect with a certified genetic counselor to best interpret their results. Information on how to obtain genetic testing can be found on ASF's website.

For many years, the most common way of diagnosing Alport syndrome was through a kidney biopsy. In a kidney biopsy, a small sample of tissue is taken using a needle that is placed through the skin and into the kidney. The sample is then examined under a microscope by a pathologist. This is typically an outpatient procedure. Your nephrologist may wish to perform a biopsy even after a positive genetic test result in instances where the genetic test result is inconclusive, to assess the current level of damage to structures within the kidney, or to rule out any additional problems affecting the kidney.

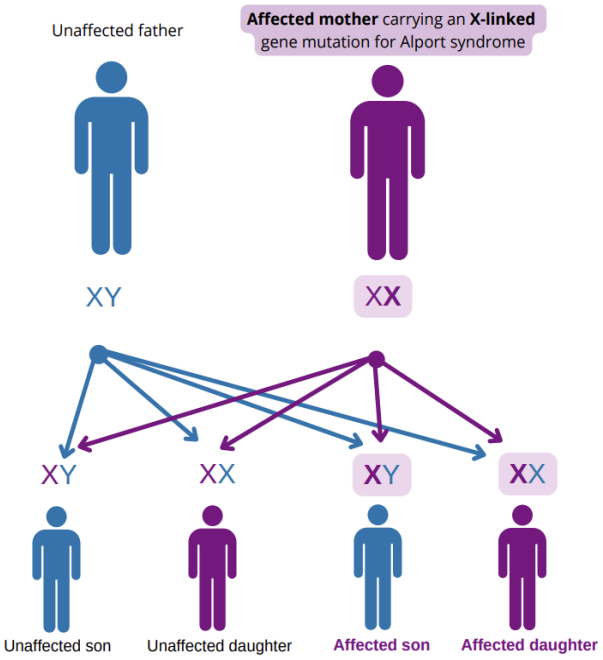
What are the genetic types of Alport syndrome?

The four genetic types of Alport syndrome include: X-linked (affecting COL4A5 gene), autosomal recessive (affecting COL4A3 or COL4A4 genes), autosomal dominant (also affecting COL4A3 or COL4A4 genes), or digenic (affects multiple genes such as COL4A3, COL4A4, COL4A5, and/or COL4A6). For a more detailed explanation of each genetic type, please see our Genetics Overview web page.

Please see the following two pages for inheritance pattern infographics.

X-linked Alport Syndrome

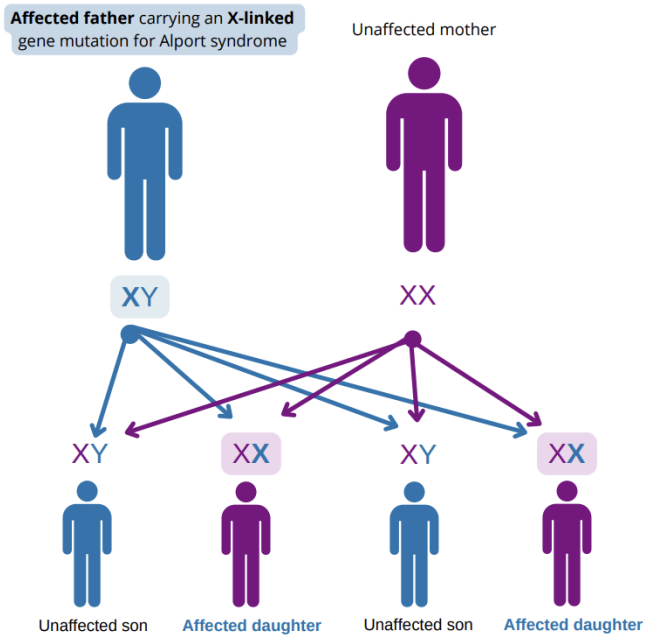
Inheritance Through Mother



X is the mutated gene from the Mother that is inherited by the child/children. In this case, there is a 50% chance with each birth (son or daughter) that the child will inherit the genetic mutation for Alport syndrome and be affected.

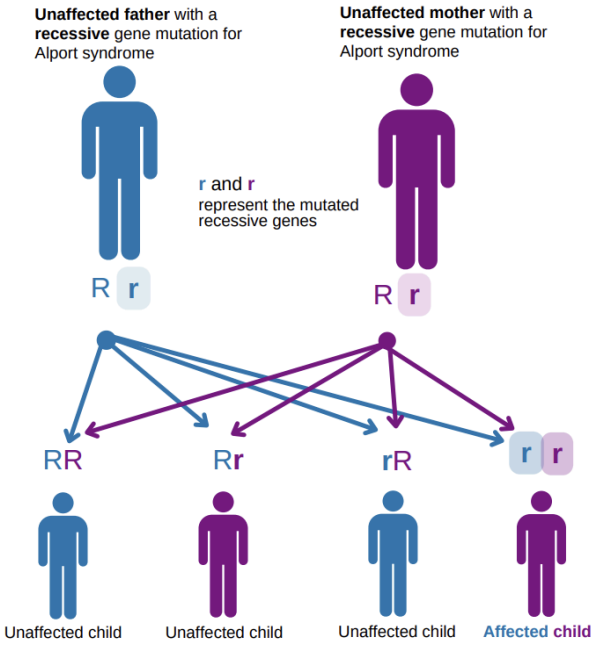
X-linked Alport Syndrome

Inheritance Through Father



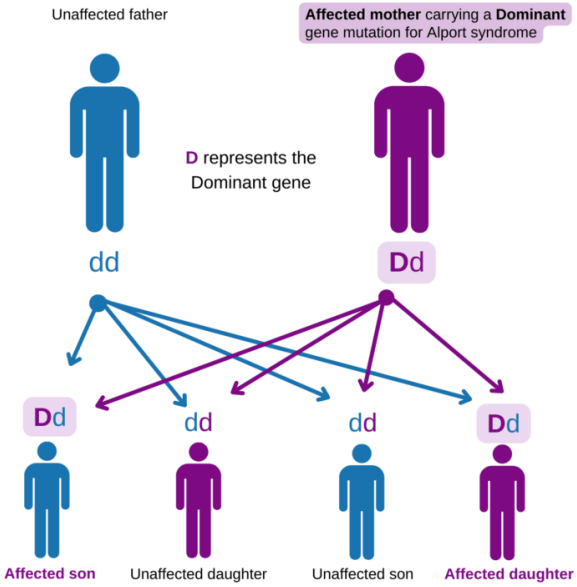
X is the mutated gene from the father that is inherited by the child/children. In this case, all the daughters will inherit the genetic mutation for Alport syndrome and be affected, and the sons will not inherit the gene nor be affected.

Autosomal Recessive Inheritance Pattern



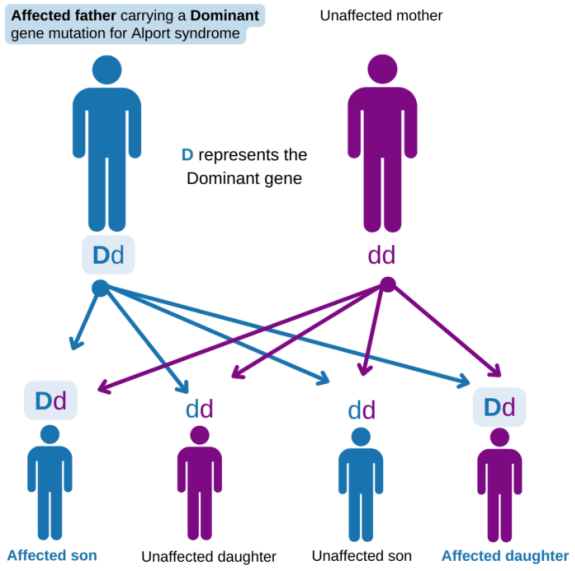
r and **r** represent the mutated recessive genes inherited by the child/children from the parents. In this case, each child, regardless of sex assigned at birth, has a 25% chance of inheriting both recessive genes from each of their parents.

Autosomal Dominant Alport Syndrome Inheritance Through Mother



D represents the mutated Dominant gene inherited by the child/children from the affected mother. In this case, each child, regardless of sex assigned at birth, has a 50% chance of inheriting the Dominant mutated gene for Alport syndrome from the affected parent.

Autosomal Dominant Alport Syndrome Inheritance Through Father



D represents the mutated Dominant gene inherited by the child/children from the affected father. In this case, each child, regardless of sex assigned at birth, has a 50% chance of inheriting the Dominant mutated gene for Alport syndrome from the affected parent.

What are the most common symptoms of Alport syndrome?

The primary symptoms for many patients with Alport syndrome are blood in the urine (hematuria), protein in the urine (proteinuria), and high blood pressure (hypertension).

Hematuria is typically the first Alport symptom, regardless of age, birth sex, or genetic type. As hematuria can be overlooked or attributed to other conditions, sometimes the presence of hearing loss in young patients can be the first noticeable indication of Alport syndrome, if they experience it. As a reminder, Alport females with hematuria are not “carriers” and should be regularly monitored and treated.

Most of the time, blood in the urine is microscopic and invisible to the naked eye. However, blood in the urine can occasionally become visible, and urine looks reddish brown or tea-colored. This often happens with a cold/flu/virus/infection and goes away when the individual recovers.

If there is protein in the urine, it is also usually microscopic. One visible sign you may notice is that urine is very foamy when freshly passed.

As Alport syndrome progresses, high blood pressure can become worse. Also with worsening kidney function and proteinuria, you can retain fluid, causing swelling that’s often seen in the ankles or calves. Other kidney-related symptoms that occur as the disease progresses to stage 5 kidney disease include a metallic taste in the mouth, loss of appetite, increased fatigue, and limited urine output.

Many patients also experience hearing loss and eye abnormalities due to the collagen defect. These symptoms can appear before or after the kidney symptoms are detected. No studies have yet been conducted to truly understand the prevalence of hearing loss and/or eye conditions. However, data on the prevalence of these disease aspects are currently being collected in the ASF Alport Patient Registry.

There are also well-documented reports of worsening protein in the urine and preeclampsia during pregnancy, and thus women with Alport syndrome should be closely monitored as “high risk.”

What are the less common effects of Alport syndrome?

There are less common, but documented ways Alport syndrome can affect individuals. While type IV collagen is mainly found in the kidneys, eyes, and ears, it is also found in lesser amounts in other parts of the body, such as the heart, lungs, and esophagus.

A small group of individuals experience noncancerous tumors of the smooth muscle (leiomyomas) found in the throat, windpipes, and genital tract. This condition is called diffuse leiomyomatosis. Diffuse leiomyomatosis can cause breathing, swallowing, or reproductive difficulties. Some patients with X-linked Alport syndrome may be at risk to develop leiomyomas, although this is rare.

There are both self-reported and documented cases of aortic aneurysm experienced by Alport syndrome patients of both sexes. The aorta is a large blood vessel that carries blood from the heart to the rest of the body. An aortic aneurysm is a bulge in the aorta that can lead to life-threatening consequences if not detected and properly treated. You can be screened by a cardiac specialist for aortic aneurysm through noninvasive imaging tests.

How is Alport syndrome treated?

There is currently no cure for Alport Syndrome and no FDA-approved therapies to treat this specific condition. However, there are medications that can help reduce some of the renal symptoms and prolong kidney function.

Medications that are used to treat high blood pressure are often prescribed, even if patients don't have high blood pressure. These drugs are known as ACE inhibitors (such as lisinopril or ramipril) and ARB medications (such as losartan). These drugs have been shown to slow the leak of protein into the urine and slow the decline of kidney function. Other medications, such as diuretics, may be used later in the course of the disease to help manage retention of fluids that cause swelling.

An additional type of medication, SGLT2 inhibitors, have been shown to decrease the risk of kidney failure, heart attacks, and death in patients with diabetes, and was approved by the FDA in 2021 to treat non-diabetic patients with chronic kidney disease. While they have not been studied specifically in patients with Alport syndrome, they are increasingly being used in addition to ACEs/ARBs in adult Alport patients to help reduce the risk of kidney failure. Research is ongoing to see if this drug class is safe and effective in pediatric patients with kidney disease.

Current research, including active patient clinical trials, seeks to better understand the disease and find additional treatment options. If patients reach end-stage renal disease, when their kidneys can no longer meet the demands of the body, dialysis can help do the work of the kidneys until a transplant can be performed. ASF's website includes information about dialysis options and preparing for transplant.

At this time, there are no treatments available to repair or prevent Alport-related hearing loss. However, many Alport patients note that daily use of hearing aids can be very helpful in social, educational, and work environments. Ocular (eye) changes cannot be prevented. Some eye abnormalities do not require treatment and most others are readily treatable. Regular exams with an audiologist and ophthalmologist are strongly encouraged to monitor for hearing and eye changes.

What are the common side effects of treatment?

Chronic kidney disease itself, as well as some of the medications prescribed for Alport syndrome (ACE inhibitors), can cause high potassium (hyperkalemia). It is usually treated with a low potassium diet (cutting out potatoes, tomatoes, avocados, etc.) and/or potassium-binding medications to help rid the body of excess potassium.

Keeping potassium under control is critical. High potassium levels can go undetected and cause serious consequences, such as arrhythmia (irregular heart beat).

Another common side effect of treatment is low blood pressure (hypotension), which can cause fatigue, drowsiness, dizziness, and fainting. ACE inhibitors can also cause a dry cough after you take the medication. If this is experienced due to the ACE inhibitor, you can talk with your nephrologist about switching to an ARB.

Can individuals delay the effects of Alport syndrome?

The best ways to delay the effects of Alport syndrome are to be informed about the disease, find a nephrologist who is familiar with Alport syndrome (if possible), and develop an open line of communication with health care providers.

Additionally, it is important to maintain healthy lifestyle habits, take medications as prescribed, follow dietary recommendations as set by a nephrologist or renal dietitian, recognize emotional and mental health effects, and seek support when needed. Alport patients, and all those with chronic kidney disease, should always consult with their nephrologist regarding the use of over-the-counter (OTC) drugs, as some widely used medications (such as NSAIDs) can adversely affect the kidneys or ears.

Because Alport syndrome is rare, many providers do not have a great deal of experience in treating this condition and its complex set of symptoms. If new symptoms or challenges arise, it's important that patients share them with their medical provider(s).

Often, informed patients are one of the most helpful resources in educating providers about their experiences, symptoms, and even about new research or clinical trial opportunities. Asking questions and motivating providers to do their own research can help ensure the needs of patients are met. Self-advocacy is key in ensuring the best possible outcomes. Alport Syndrome Foundation is dedicated to providing peer support and engagement for all individuals with Alport syndrome and their families. For connection opportunities and/or general inquiries, email ASF: info@alportsyndrome.org.

Can living with Alport syndrome affect emotional and mental health?

Living with a rare, genetic condition, such as Alport syndrome, can affect one's emotional well-being. Many individuals with Alport syndrome have reported experiencing emotions, such as:

- guilt in having passed a genetic disease down to a child
- anxiety about an unknown future of disease progression
- frustration over the fatigue that can come with kidney disease and/or hearing loss
- coping with a rare disease that is unseen by others
- frustration with health care providers who are not familiar with Alport syndrome

It is important for patients and their families to know they are not alone in these feelings, experiences, and concerns. Open communication with a healthcare team is essential in finding a treatment plan that optimizes the health of the patient as defined by the patient.

We also encourage patients to connect with others living with Alport syndrome via our Facebook Support Group, virtual Direct Connect meetings, at our Alport Connect meetings, and through webinars or other meetings organized by ASF. These resources offer encouragement, education, and support. Engaging with the larger patient community can serve as an important reminder that Alport patients live productive and fulfilling lives despite their diagnosis. ASF staff members can also connect individuals or families to one another any time by request.

What kinds of health care providers are most helpful in treating Alport syndrome?

It is very important for all individuals with Alport syndrome to have regular visits with certain medical specialists, such as:

- **Nephrologists**: Meeting regularly with a nephrologist allows for early treatment with the goal of prolonging kidney function. They can also help guide decisions around dialysis and transplant if that should become necessary.
- **Renal dietitians**: Renal dieticians work with patients in all stages of chronic kidney disease. They provide nutritional education and monitoring, and help create healthy meal plans based on an individual's lab values, needs, and preferences.
- **Audiologists and ophthalmologists**: Hearing specialists (audiologists) and eye specialists (ophthalmologists) can provide early assessment and intervention for hearing loss and eye conditions. Getting a baseline of hearing and eye health is helpful to detect any changes early.

Additionally, heart specialists (cardiologists), lung specialists (pulmonologists), digestive specialists (gastroenterologists), and female reproductive specialists (OB/GYNs) may also be needed to evaluate and/or treat some of the less common symptoms associated with Alport syndrome. Typically, patients will serve as a centralized contact point when simultaneously seeing multiple specialists.

What other types of support may be helpful?

Geneticists and genetic counselors: These health care providers specialize in interpreting genetic test results and can explain how Alport genetic mutations affect individual patients. They can also answer questions about who else in a family may be at risk of having Alport syndrome and how the genetic variant is inherited or passed down in families for the purpose of family

planning.

Mental health professionals: Clinical psychologists, clinical psychiatrists, mental health counselors, licensed clinical social workers, and faith-based counselors are all types of mental health professionals that can help individuals cope with the emotional toll of having a life-long condition.

Educational specialists: Families with children who have Alport-related hearing loss are advised to work with their school system (K–12). An Individualized Education Plan (IEP) can be created that specifically includes evaluations over time and individualized accommodations to support successful learning. Often, these accommodations change as the student's hearing loss progresses. Hearing loss is covered by the Americans with Disabilities Act and ensures that students have access to often simple, but critical, modifications at school that make their learning environment suitable.

How Can I Participate in Ongoing Alport Syndrome Research?

People living with Alport syndrome can advance critical research that will help everyone with our rare disease. By capturing your symptoms and health outcomes, researchers can learn more about disease progression across all genetic types. Here are a few ways patients can get actively involved in ongoing research projects:

ASF Alport Patient Registry: Perhaps the most important thing patients and caregivers can do to advance research that may lead to potential treatments and/or a cure is to participate in a patient registry. The ASF Alport Patient Registry is funded and administered by Alport Syndrome Foundation and collects information through brief surveys in a secure online platform. This information will be used by researchers who wish to study our rare disease. All information shared in the platform is completely de-identified so that no names or identifying information is accessible to any researcher accessing the data.

NEPTUNE Natural History Study: The NEPTUNE natural history study aims to recruit Alport patients with diverse genetic mutations. The study will include collection of biosamples (blood and urine), as well as clinical data such as blood pressure readings, hearing measurements, and family history. Study site locations are open across the United States.

Active Clinical Trials: Another option to help advance Alport research directly is to consider participating in a clinical trial. ASF lists up-to-date information about active trials enrolling adult and pediatric Alport patients around the world. ASF has also put together some considerations and questions to ask when deciding whether a clinical trial is right for you or a family member.

Scientific Advisory Research Network (SARN) Projects: Members of our SARN are invited to present opportunities to our community to help with their research. Some of the projects we've been able to help with include ophthalmology research with Dr. Al-Rabadi, pregnancy and genetic research with Dr. Perin, renal cyst research with Dr. Korstanje, and more. To learn about current volunteer research opportunities, sign up for free membership with ASF or email ASF Staff at info@alportsyndrome.org.

About Alport Syndrome Foundation

Alport Syndrome Foundation is a non-profit organization led by and dedicated to the Alport community of patients and families. Our mission is to improve the lives of people living with Alport syndrome through education, advocacy, awareness, and investment in research. ASF staff and leadership are composed of patients and families who are personally affected by Alport syndrome.

Resources for Patients & Families:	**Resources for Medical Professionals:**	**Resources for Researchers & Pharma Industry:**
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