



## Family Planning Guide *For Patients by Patients*

Developed by Alport Syndrome Foundation's  
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## Background

Alport Syndrome Foundation (ASF) is often contacted by individuals hoping to understand what their diagnosis means as they consider planning a family. The gene mutations (or pathogenic variants) that are known to cause Alport syndrome are most commonly passed from parent to child, although spontaneous mutations do occur without a genetic link to a previous generation.

Family planning with any genetic disease is a sensitive, personal, and complex matter. There are decisions to make, but there are no right or wrong choices. We are providing this guide in the interest of supporting informed decision-making for patients, whatever their situation or decision may be.

Our [Emerging Leadership Council \(ELC\)](#), a volunteer group of young adults affected by Alport syndrome, felt it was important to develop a guide for patients on this topic. Organized by ASF, the volunteers met with the Renal Special Interest Group within the National Society of Genetic Counselors to help develop guidance for patients. ASF extends gratitude to our corporate partners, Natera and Sanofi, for their generous support of the ELC's efforts.

Thousands of members of ASF have knowingly and/or unknowingly passed on this disease to their children. Each Alport syndrome family has their own story and experience. Individuals that are considering planning a family and would like to connect with other parents that have made these decisions are welcome to contact [info@alportsyndrome.org](mailto:info@alportsyndrome.org). ASF staff can connect patients to others who have chosen a variety of options in their family planning.

Because there are different [genetic types of Alport syndrome](#), it's important to understand how a specific type of genetic mutation might be passed on to an individual's child/children. This can only be conclusively determined through genetic testing. If an individual has a diagnosis of Alport syndrome through biopsy or family history, this information is valuable for a treatment plan and health monitoring. Genetic testing can lead to a definitive diagnosis, earlier treatment, opportunities to participate in research and/or clinical trials, and an understanding of who else in their family may be affected.



## What is genetic testing?

Genetic testing is a method for diagnosing specific conditions passed from parent to child and those that occur spontaneously. It can also be used to rule out these conditions in an at-risk individual. Genetic testing is usually performed using a sample of blood or saliva. DNA sequencing is the most common genetic test used to diagnose Alport syndrome.

DNA is the chemical structure that makes up our genetic code. It is the blueprint that allows our body to develop and function. DNA may be thought of as a string of code that provides information, called genes, for the body to read. The body is able to read these genes and carry out whatever function that message provides. In the case of Alport syndrome, the genes affected are COL4A3, COL4A4, COL4A5, and less frequently, COL4A6.

A process called DNA sequencing allows scientists to read these genes and determine if there are any problems with their messages. If any problems are found, medical professionals may be able to predict some information about how severe Alport syndrome may present and the likelihood of it being passed down from parent to child.

## Genetic testing: who, where, how?

Testing should be completed at a CLIA-certified clinical laboratory, per the recommendation of renal genetic specialists. The Clinical Laboratory Improvement Amendments (CLIA) regulate laboratory testing, and require certification by the the U.S. government before accepting human samples for testing. If additional family members are being tested, it's preferable to have all the testing completed at the same laboratory.

If Alport syndrome is the correct clinical diagnosis, genetic testing of the type IV collagen genes is expected to find a disease-causing mutation (pathogenic variant) in most cases. If the mutation is already known in a family, a negative (normal) test in an at-risk family member is considered trustworthy.

**Alport patients (or those with a suspected diagnosis) that live in the United States and would like assistance identifying a qualified laboratory that can provide a genetic test kit are welcome to contact [info@alportsyndrome.org](mailto:info@alportsyndrome.org) or visit [alportsyndrome.org](http://alportsyndrome.org). [Click here to find a genetic counselor](#) in your area.**

## Questions to consider asking health care providers about genetic testing

- How is the sample collected? (blood, saliva? at home or in an office?)
- How long does it take to receive results?
- What happens to the sample after testing is completed?
- Where are the results stored?
- Who has access to the results?
- Does the doctor have a preferred genetic testing company?
- Who will share the results with the patient?
- Will the testing company or the doctor's office refer the patient to a genetic counselor before the test and/or to review the results? If not, can the doctor help secure an appointment with one?
- Does the genetic testing facility or company offer genetic counseling services as needed after the results are provided to the patient?



## **Why is genetic testing preferred over diagnosis obtained through family health history?**

Not all families have a “classic” Alport syndrome lineage. Family history may be deceiving or incomplete. If specific medical tests have not been ordered, family members may not be aware of early or mild signs of the disease, or may not wish to share this information. Alternatively, a person may not have any suspicious family history because they have a de novo (non-inherited, spontaneous) mutation, have autosomal recessive Alport syndrome, or affected family members have not developed symptoms due to younger age or the variability of symptom severity. In rare cases of hidden parentage or uncertainty about genetic maternity or paternity, an accurate family health history may not be available to the patient. Genetic testing is therefore the preferred method of clarifying a diagnosis.

## **How much does genetic testing cost?**

As testing in the United States has become more widely available, costs have come down significantly in recent years. Generally, a genetic test for Alport syndrome can be obtained for \$300 or less. Genetic counselors are experienced in navigating the details of diagnostic genetic testing, often more so than nephrologists, including the available pricing options. Depending on a patient’s individual policy and deductible, the insurance company may cover testing from 0% to 100%.

## **Can genetic testing results affect insurance and employment?**

Informed consent for genetic testing should include a conversation about the risks as well as the benefits. Risks of a confirmed diagnosis of a chronic health condition by either clinical or genetic testing include difficulty purchasing life, long-term, or disability insurance. A law in the United States called the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies and most employers to take discriminatory action against a person based on knowledge about their personal or family genetic health history. However, there are exceptions to this law. Concerned patients are encouraged to discuss this issue in more detail with a genetic counselor. More information can be found at [www.ginahelp.org](http://www.ginahelp.org). In most cases, genetic test results are treated as protected health information (under HIPAA protections), which cannot be accessed by employers.

## **What is the role of a genetic counselor?**

Genetic counselors have advanced training to guide and support patients seeking more information about how inherited diseases and conditions might affect them or their families. They also can help interpret genetic test results based on your personal and family history. This information can then be used to advise patients on a variety of topics such as treatment, disease progression, and family planning. Genetic counselors can assist patients and families identify the right options for them at that point in time. It is a nonjudgmental process with the goal of facilitating informed health care decisions. A prenatal genetic counselor’s role is similar, but they will also focus on exploring patient goals and options for family planning.



## What are the goals of genetic counseling?

In general, the main goals of genetic counseling are to provide guidance for decision-making around health care, education about genetic conditions and how they are inherited, and short-term counseling and support regarding the psychological impact of having a genetic condition.

The beginning of a session typically includes questions about what the patient hopes to accomplish by attending the appointment. Many people go to a genetic counseling appointment without any specific goals in mind, may not know what to expect, and that is OK. The genetic counselor will guide the visit according to the questions and concerns that arise.

## What should patients expect in an appointment with a genetic counselor?

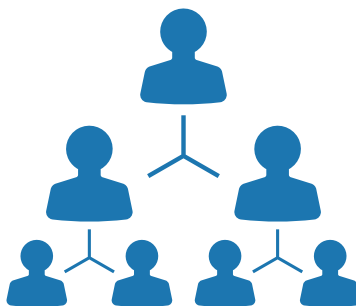
In general, genetic counseling visits are more conversational, but may be tailored depending on the needs of the patient. Genetic concepts may be discussed to varying degrees, however, no prior knowledge of genetics is required. A visit may take place in an office or a clinical exam room, or through a telemedicine appointment. Initial visits may last anywhere between 20 minutes to an hour. If a patient has received results from a genetic test, the results will be discussed, with the opportunity for the patient to ask questions. A genetic counselor may explore different scenarios and ask a patient/couple to think through the pros and cons of each.

## How can patients maximize an appointment with a genetic counselor?

In addition to medical information, genetic counselors will often need to discuss specific family history in order to obtain an accurate picture of the patient's condition and how it will impact their family. The counselor will ask questions about family history such as:

- Does anybody in the family (children, brothers/sisters, parents, aunts/uncles, cousins, grandparents) have a diagnosis of Alport syndrome?
- If so, did they have genetic testing? If yes, what were the results?
- Does anybody in the family have kidney disease?
- Does anyone see a nephrologist?
- Has the patient or anyone in the family been told there is blood in their urine?
- Has the patient or anyone in the family been told there is protein in their urine?
- Has the patient or anyone in the family had a kidney biopsy? What were the results?
- Has the patient or anyone in the family had a kidney transplant?
- Are any of the patient's relatives on dialysis?
- Has anyone in the family been diagnosed with hearing loss?

Not everyone is able to answer these questions about their family history, as they may not be able to get many details due to privacy, adoption, or strained relationships. This does not impact an individual's ability to benefit from genetic counseling.



## Tips for patients needing to gather health information from family members to assess risk

Genetic testing is a personal health decision. Because shared genes are the definition of a biological family, the decision to have a genetic test often has a wider impact than one patient's own health. If possible, being open about the reason for gathering family health information is best. This may lead to difficult family conversations about the right to privacy. It is especially relevant in families with identical twins, where a genetic diagnosis in one individual essentially guarantees the diagnosis in the other.

Another reason to have these discussions before deciding to pursue genetic testing is that if a test is positive, a genetic counselor will help to identify at-risk family members based on the pattern of inheritance and encourage patients to share their test results with at-risk family members. A genetic counselor may offer a sample letter that patients can share with family members to alert them to their risk. A family meeting with the genetic counselor may be appropriate in some cases to process the pros and cons of having a known genetic diagnosis in the family.

## Pregnancy considerations in Alport syndrome

It is important to note that while pregnancy in chronic kidney disease patients has been well-studied, this is not the case in Alport syndrome specifically. However, several case studies in pregnant Alport syndrome patients have been published. In planning pregnancy, members of ASF's Medical Advisory Committee encourage consultation with a nephrologist and an obstetrician experienced in high-risk pregnancies for the following reasons:

- **The protocol for women with Alport syndrome is to stop taking any ACE/ARB medications during pregnancy and to resume these medications after giving birth. Specific instructions on when and how to resume these medications will be given by the nephrologist.**
- Based on patient experiences, women with Alport syndrome are at higher risk for preeclampsia in pregnancy, although this has not been clinically studied. Women that are planning pregnancy are strongly encouraged to discuss this risk with their nephrologist and obstetrician.
- ASF is aware of Alport syndrome patients that have had their babies tested for Alport syndrome while in the womb. This is something to discuss with a patient's health care team, if interested.
- Patients may experience anxiety or fear associated with pregnancy with a genetic disease. Many patients have discussed these concerns at in-person and/or virtual meetings organized by ASF. Speaking about this with a qualified mental health professional can be helpful. ASF can connect patients with others who are currently pregnant or who have been through pregnancy as an Alport patient to a facilitate healthy, non-judgmental conversation for the purpose of sharing concerns.



## Video resources for women living with Alport syndrome

ASF recorded a [video presentation titled “Women and Girls with Alport Syndrome”](#) in August 2020 for its annual Alport Connect patient meeting. The video features a panel of experts moderated by ASF Co-Founder, Sharon Lagas, an X-linked Alport patient. The panel experts are females as well, including nephrologists and researchers Dr. Michelle Rheault of the University of Minnesota and Dr. Leslie Inker of Tufts University Medical Center. The panel also includes obstetrics gynecologist (OBGYN) Dr. Erin McKelvey from Cleveland Clinic, who has expertise with pregnancy in women with chronic kidney disease.

The entire video is valuable for women living with Alport syndrome, and the topic of pregnancy begins at the 12:48 minute mark.

The [2021 video “Alport Syndrome Female Diagnosis Stories”](#) also addresses some of the emotional challenges of pregnancy and raising children with Alport syndrome experienced by female patients.

## What topics should patients consider before pursuing genetic testing for themselves or a child?

- What is thought/hoped to change if genetic testing results are positive? Negative? Uncertain results?
- The patient may learn more specific information about personal risk of progressing to end-stage renal disease, hearing loss, or other symptoms.
- Based on the type of Alport syndrome, a patient may inadvertently diagnose other members of the family (i.e the mother of a male with X-linked Alport syndrome may learn that she also has the condition). A patient may learn that family members who had discussed living kidney donation are no longer eligible.
- If planning a family, identifying a genetic mutation may raise the possibility of prenatal genetic diagnosis for the patient’s child. How might that change family planning, if at all?





## **Family planning options for current pregnancies**

- **CVS/Amnio testing:** After 11 weeks gestation, the fetus can be tested for a genetic condition such as Alport syndrome so that a parent/couple can be informed of the diagnosis during the pregnancy. The choice of test type depends on how far along the patient is in the pregnancy. CVS is done between 11-14 weeks and amniocentesis is done at 15-22 weeks. Only one procedure is typically needed, not both. Both procedures are low risk when performed at an experienced facility.
- **Continuation:** After prenatal diagnosis of a genetic condition, the pregnant person/couple choose to continue the pregnancy with the knowledge that the child will be affected by the disease.
- **Adoption:** Adoption is a legal process where a biological parent/couple signs over rights of a child to another adult who agrees to care for that child. Adoptions can be “open” or “closed,” which indicates whether they may or may not be in contact with the biological parent(s) in the future.
- **Termination:** Termination is the option to stop or end a pregnancy by a medical procedure (abortion) because the pregnant person/couple feels it is not the right time, the pregnancy is high risk, and/or the fetus has a genetic condition or abnormality that the family wishes to avoid. Options to terminate a pregnancy currently vary by state in the United States.

## **Family planning options for future pregnancies**

- **In vitro fertilization (IVF) with preimplantation testing:** In this process, eggs are harvested from an individual after taking medications to stimulate the release of eggs (ovulation). The sperm are combined with the eggs to create an embryo. Typically, a process called intracytoplasmic sperm injection (ICSI) is used to take one sperm and put it into the egg to fertilize it. After fertilization, one cell of the embryo is taken to perform genetic testing. Usually, the cell is tested for sporadic chromosome conditions (e.g. Down syndrome) and for a genetic condition such as Alport syndrome that the couple is concerned about. Only embryos without the condition(s) are implanted into the person who is planning to carry the pregnancy.
- **Surrogacy:** In surrogacy, an individual volunteers to carry a pregnancy for another individual who cannot carry a pregnancy. Typically, a legal contract is signed regarding care during the pregnancy, and the developing baby is legally adopted by the person/couple who initiated the surrogacy. IVF and a donor egg may be used to create the embryo.
- **Donor sperm/egg:** This is a process where a fertility bank is used to identify a person to be a donor of eggs and/or sperm to enable a pregnancy. This method can be used when a couple is trying to reduce the risk of having a child with an inherited disorder or when spontaneous conception is not successful/possible.
- **Spontaneous pregnancy:** This is when conception is achieved by sexual intercourse without the aid of reproductive assistance and without knowing the genetic status of the embryo before the pregnancy begins.

## Other testing options for diagnosing Alport syndrome

### Kidney (renal) biopsy

Kidney biopsy is another tool for diagnosis and may be medically recommended by a nephrologist when it is important to understand the level of disease progression in an Alport syndrome patient. A biopsy is typically an outpatient procedure used to remove small kidney tissue samples that can be examined under a microscope to look for signs of damage. The information gained can be more valuable than laboratory results alone. Increasingly, interventional radiology is being used for biopsy procedures, using ultrasound imaging technology in real-time. This can lead to improvement in the quality of patient safety, specimen quality, and reduce potential complications (<https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-022-02860-1>).

When a biopsy is used to diagnose Alport syndrome, results can present with findings such as focal segmental glomerulosclerosis (FSGS) or thin basement membrane disease. FSGS can have various causes, but if it is caused by a type IV collagen mutation, the recommended treatment is different. If FSGS is noted in the biopsy results, it is important to gain a full and accurate diagnosis of the cause of the thinning or scarring of the kidney. There are multiple causes of FSGS. When the immune system is causing the damage, treatment typically consists of steroids and/or other immunosuppressant medications, which have their own side effects. Genetic mutations, such as those found in Alport syndrome, can cause scarring that looks identical to immune-mediated FSGS on kidney biopsy and cannot be identified without genetic testing. Because Alport syndrome mutations do not involve the immune system, treatments that suppress the immune system are not effective. For this reason, genetic testing for FSGS is recommended in the following situations: 1) if a patient has a family history of microscopic hematuria, kidney failure, or FSGS; 2) if thin basement membranes are seen on the biopsy along with FSGS; or 3) if the initial course of immunosuppressant medications is ineffective. Genetic testing is typically secured through a minimally invasive blood or saliva test.

Kidney biopsy may indicate Alport syndrome but does not necessarily clarify inheritance (<https://www.ncbi.nlm.nih.gov/books/NBK1207/>). A kidney biopsy is not a diagnostic tool that will identify specific genotype-phenotype information (personalized prognosis based on type of genetic mutation of patient).

### Skin biopsy

When kidney biopsy is not recommended and genetic testing is not possible, a skin biopsy could be performed as a potentially helpful diagnostic tool. However, it is important to understand both the percentage of accuracy a skin biopsy can offer and in which genetic types it is applicable:

- Males with X-linked Alport syndrome: Based on scientific studies, approximately 80% of males will show complete absence of epidermal basement membranes, indicating Alport syndrome. However, approximately 20% of males with X-linked Alport syndrome show normal staining on biopsy slides. Those patients will not be accurately diagnosed with Alport syndrome through skin biopsy.
- Females with X-linked Alport syndrome: Approximately 60%-70% of heterozygous females exhibit discontinuous staining of the collagen  $\alpha 5(\text{IV})$  chain [van der Loop et al. 1999]. This is attributed to X-chromosome inactivation. This translates to 30%-40% of X-linked females not being accurately diagnosed through skin biopsy.
- Individuals with autosomal recessive Alport syndrome: These patients will have normal skin reactivity for the collagen  $\alpha 5(\text{IV})$  chain, meaning that skin biopsy will not be an effective diagnostic tool for these Alport syndrome patients.

## Resources for support after diagnosis

A return visit with the genetic counselor and/or geneticist is frequently recommended if the result is positive for Alport syndrome and/or presumed positive based on family history and genetic findings (such as a variant of uncertain significance or "VUS").

When a genetic test result shows a VUS, sometimes genetic counselors recommend and facilitate testing for other family members to try to clarify the result. Other times, based on contributing factors such as family history, the VUS result may be treated as a presumed positive. However, the American College of Medical Genetics and Genomics (ACMG) does not recommend using a VUS for clinical decision-making. It is recommended that patients ask about the next steps after an initial genetic counseling visit and mutually agree on what will take place.

Even if the patient is aware of family members with the same diagnosis, or a medical professional has explained that an Alport diagnosis is likely, nothing can prepare an individual for the moment of understanding a confirmed diagnosis through medical diagnostics. A genetic counselor can offer short-term support and may refer a patient to longer-term mental health counseling if needed.

Mental health providers, religious leaders, family members, and trusted friends can also be sources of support.

Alport Syndrome Foundation (ASF), led by and dedicated to patients, provides many free resources at [www.alportsyndrome.org](http://www.alportsyndrome.org), including tip guides, videos, opportunities to participate in research, and channels to speak directly with other patients and families.

Questions or requests to speak with ASF staff and/or other patients can be directed to [info@alportsyndrome.org](mailto:info@alportsyndrome.org). ASF also moderates a private [Facebook Support Group](#) where patients and caregivers can ask questions and connect with patients around the world who can relate to their experiences and concerns.



## Additional resources for genetic disease education and support

### Alport Syndrome Foundation Resources

[ASF Genetics Guide](#)

[Alport Syndrome Genetics: Understanding Gene Mutations](#)

[Why Diagnose Alport Syndrome Females?](#)

[Promoting Early Diagnosis & Treatment of Alport Syndrome – Dr. Clifford Kashtan \(ASF Medical Advisory Committee member\)](#)

### Other Genetic Disease Resources

[National Human Genome Research Institute](#)

[GINA Help](#)

[Genes in Life](#)

[National Society of Genetic Counselors - Find a Genetic Counselor Tool](#)

[American College of Medical Genetics and Genomics - Find a Genetic Clinic Tool](#)

[US Surgeon General's "My Family Health Portrait Tool"](#)

[GlobalGenes Rare Concierge Program](#)

[Genetic Discrimination - NIH - explanation of federal laws and types of state laws](#)

[CDC resources for family planning](#)

[CDC - What is Genetic Counseling?](#)

[NIH - Broad Topics Related to Genetic Family Planning](#)

[Life Happens - a national non-profit providing education about life insurance](#)

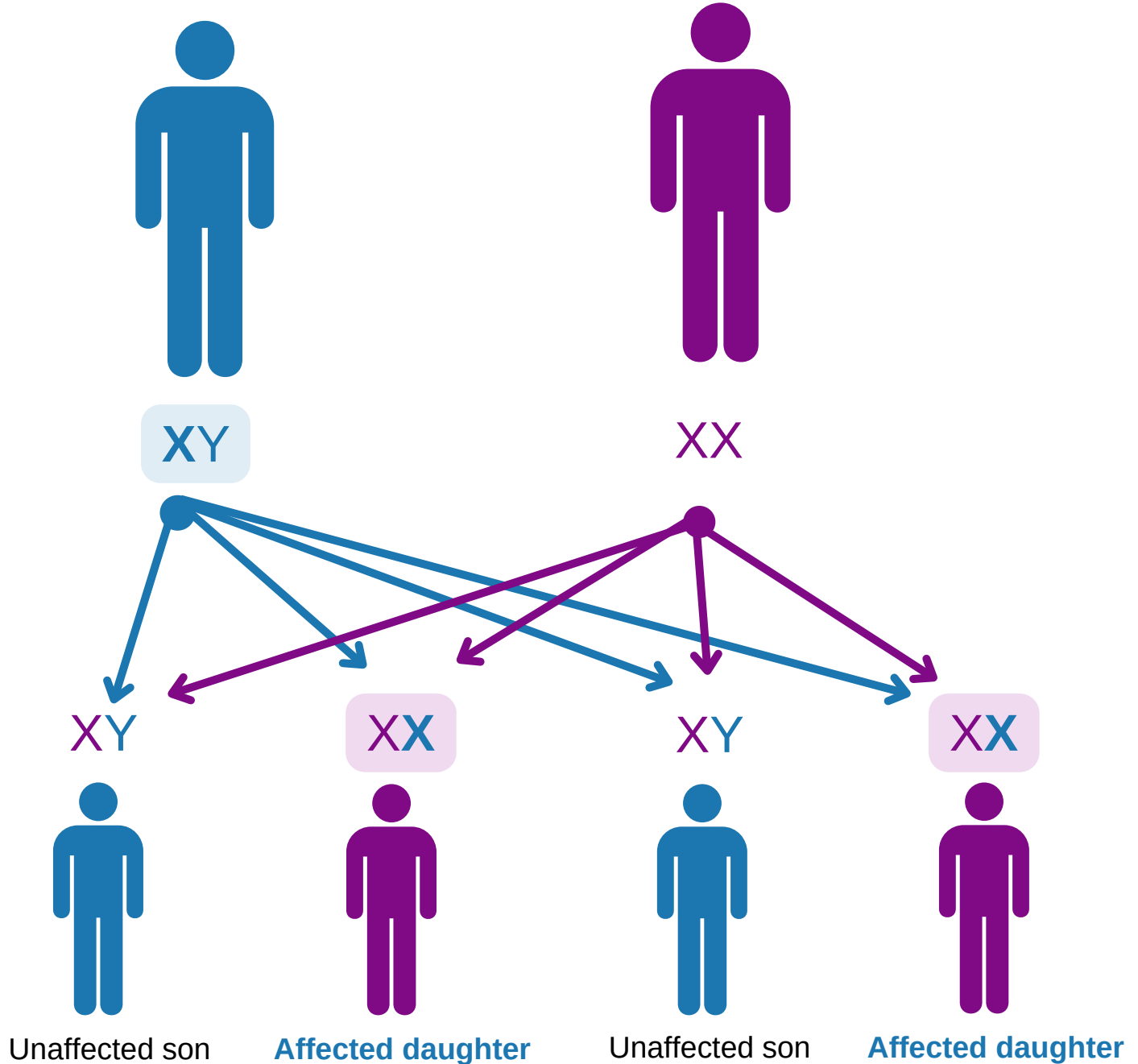


# X-linked Alport Syndrome

## Inheritance Through Father

**Affected father** carrying an **X-linked** gene mutation for Alport syndrome

Unaffected mother



**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.

# X-linked Alport Syndrome

## Inheritance Through Mother

Unaffected father

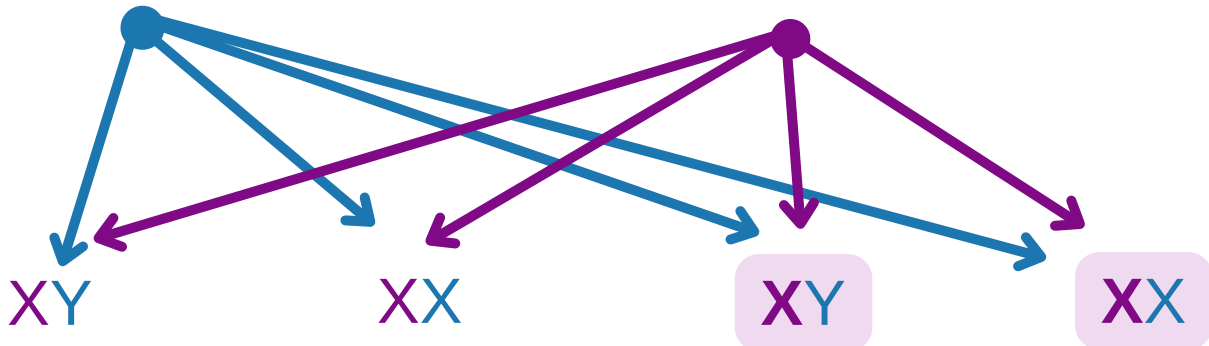
**Affected mother** carrying an **X-linked** gene mutation for Alport syndrome



XY



XX



XY

XX

XY

XX



Unaffected son



Unaffected daughter



Affected son

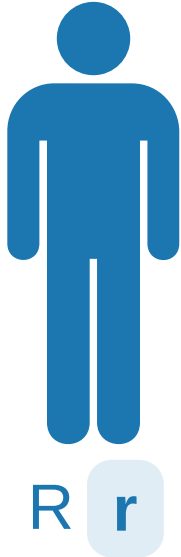


Affected daughter

**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.

# Autosomal Recessive Inheritance Pattern

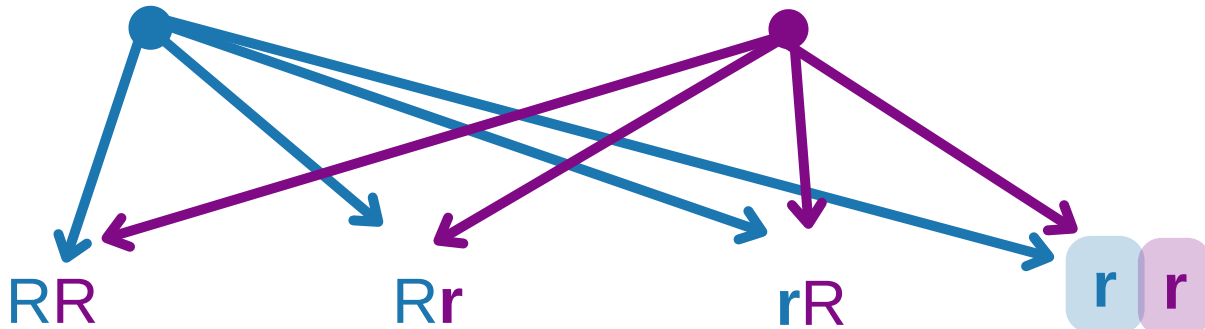
Unaffected father with a **recessive** gene mutation for Alport syndrome



Unaffected mother with a **recessive** gene mutation for Alport syndrome



$r$  and  $r$  represent the mutated recessive genes



Unaffected child



Unaffected child



Unaffected child



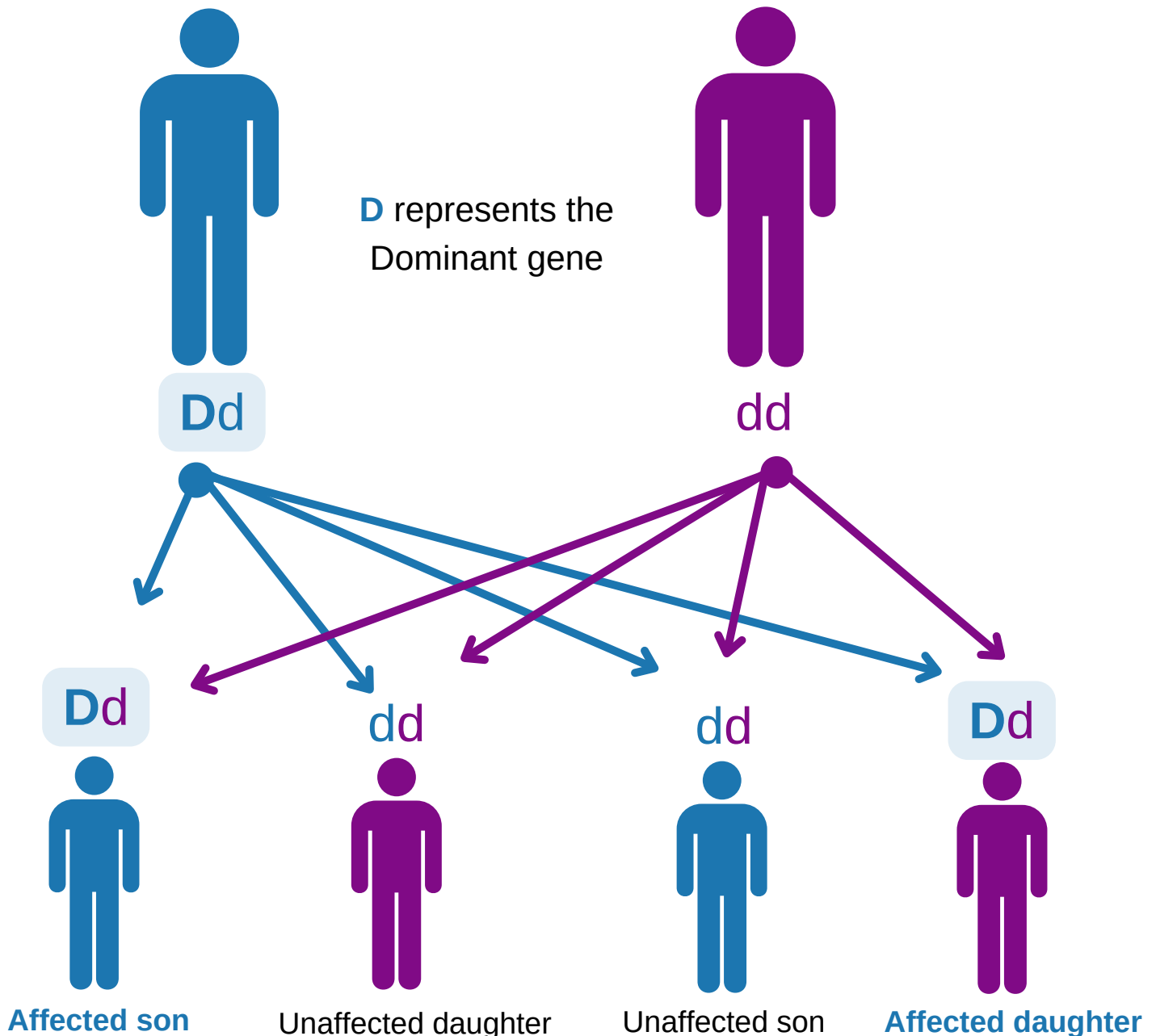
**Affected child**

$r$  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 Father

**Affected father** carrying a **Dominant** gene mutation for Alport syndrome

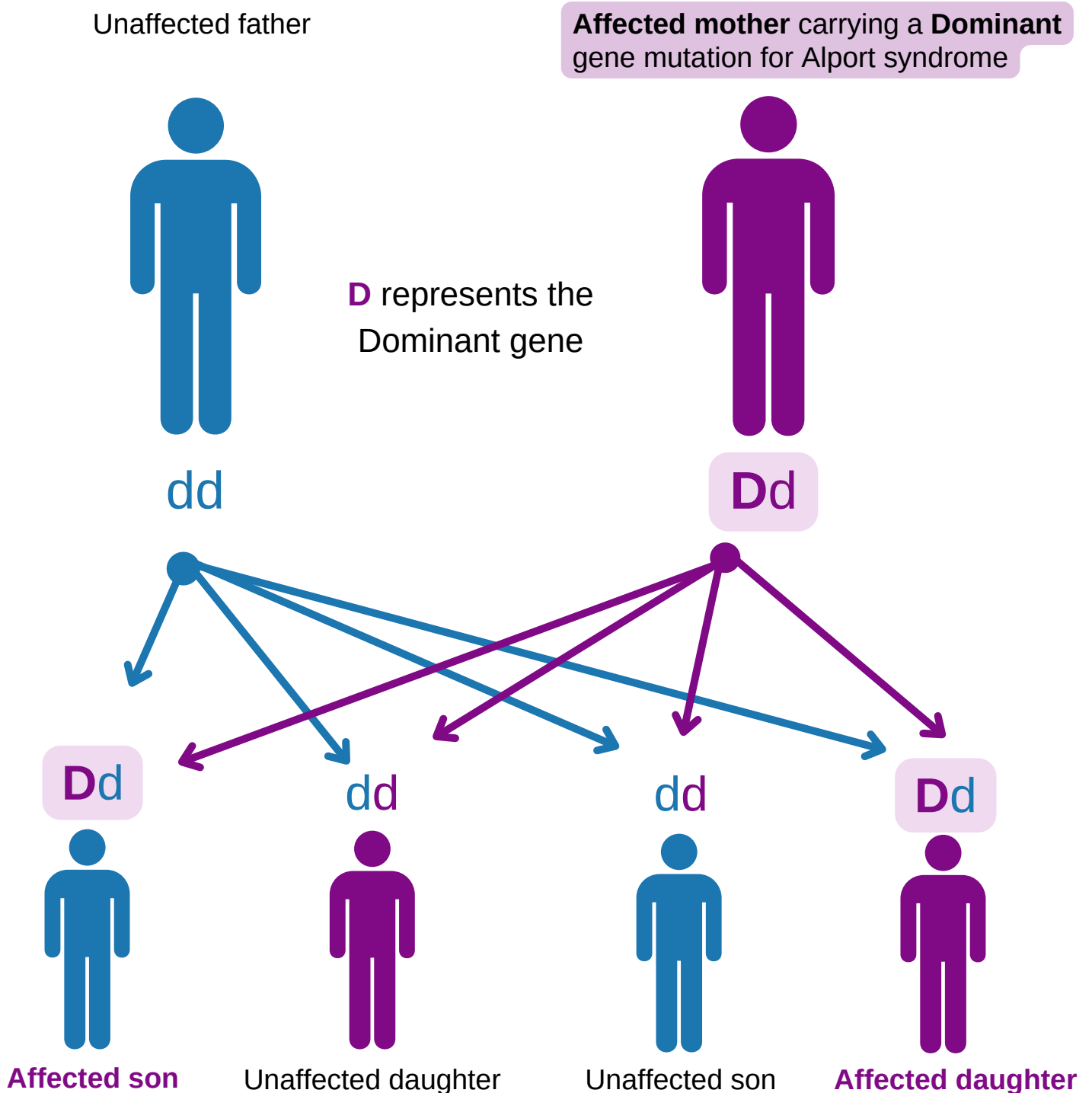
Unaffected mother



**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.



# 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.

# About Alport Syndrome Foundation

Alport syndrome 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.

We are grateful to the following volunteers and partners that made this resource possible for patients and families:

**Mary-Beth Roberts MS, CGC**

**ASF Emerging Leadership Council**



## Resources for patients and families:

- Educational Materials
- Network of Support
- Patient and Family Meetings
- Webinars
- Patient Advocacy
- Legislative Advocacy
- Awareness Efforts
- Research Investment

## Resources for medical professionals:

- CME/CNE Online (free)
- Diagnosis Information
- Recommended Treatment Guidelines
- Current Research
- Clinical Trial Updates
- Genetics Guide