

What is Alport Syndrome (AS)?

AS is an inherited condition that causes kidney failure and hearing loss. The common form of AS (called classic Alport syndrome) is caused by an alteration in a particular gene that lies on the X chromosome.

What are genes and chromosomes?

Our genes are the unique set of instructions inside our bodies that make each of us individual. There are many thousands of genes, each carrying a different instruction. As well as determining how we look, our genes control the way each cell, or building block, of the body works. Genes lie on tiny structures called chromosomes. Each chromosome contains thousands of genes.

Most of our body cells have 46 chromosomes, arranged in 23 pairs. We inherit one of each pair from our mother and the other from our father. Chromosomes are numbered 1-22 according to their size. The final pair are the sex chromosomes, and they are given the letters X and Y rather than numbers.

- Females have two X chromosomes, one inherited from their mother and the other from their father.
- Males have one X chromosome (inherited from their mother) and a Y chromosome (inherited from their father).

The gene that is altered in classic AS is called the **COL4A5** gene. This gene can be altered in many different ways.

Why is the COL4A5 gene important?

The instruction that this particular gene gives is important in the formation of proteins in the glomerular basement membrane (GBM). The GBM acts like a filter in our kidneys and allows fluid containing waste products from the body to move from our blood vessels to the urine. At the same time, it has to stop blood cells and protein from leaking out.

If there is an alteration (mistake) in the COL4A5 gene the GBM becomes leaky and fails to do its job properly as a filter.

In the eye and ear, similar proteins made by the same gene are important for the shape of the lens in the eye, the retina at the back of the eye, and the structure of the inside of the inner ear.

Can both men and women have classic AS?

As women have two X chromosomes, they get two copies of the COL4A5 gene, so even if one of those genes contains an alteration, they have a normal second copy of the gene on their other X chromosome. This normal copy usually seems to protect a woman who carries an altered gene from most of its effects. Some carrier women do develop kidney problems, but this tends to be in later life.

Men only have one X chromosome and therefore only have one copy of the COL4A5 gene. If that gene is altered then a man will develop full-blown classic AS, as there is no normal copy of the gene to act as a back-up.

What happens to a man who has classic AS?

The first signs of the condition are very mild. Nearly all boys with classic AS have small amounts of blood in their urine by the age of 5 years. The blood may not be visible, and may only be detectable on a urine test. Later protein leaks out, the blood pressure rises and the kidneys fail, but the speed with which this happens varies. Many affected men need to have kidney dialysis in their teens or early twenties, but a few do not need this until they are 30 to 40 years old. Kidney transplantation is usually successful.

About 85% of boys have some degree of hearing loss by 15 years and many boys will need hearing aids by the time they are 25 years. About one-third of all boys develop a change in their eye lenses, which causes short sightedness.

What about women who have the COL4A5 gene alteration?

Many women who carry the gene alteration are mildly affected and often do not know about it until they have a son who is diagnosed with classic AS. By the age of 20 years, all carrier women have a small amount of blood in their urine, but this is often only picked up on a urine test as it is usually not visible. About a third of all carrier women develop high blood pressure and about half have some hearing loss, although usually not as severe as in affected men. About 15% of carrier women do eventually develop kidney problems, and this may progress to kidney failure, so long term follow-up is recommended for all carriers of X-linked AS.

How is classic AS inherited?

It is inherited when someone who has an alteration in the COL4A5 gene passes it to his or her child.

Most families with AS have the classic X-linked type of AS described above. However, a few families show a different pattern of genetic inheritance when there are mutations in genes other than COL4A5.

MEN Men only have one X chromosome, which is passed to each of their daughters. Their sons inherit their Y chromosome. In other words:

- All the daughters of men with classic AS will inherit the altered gene and be carriers.
- None of their sons will be affected.

WOMEN Women have two X-chromosomes, and they only pass one of these to any child, be it a boy or a girl. There are four possible outcomes to each pregnancy that a carrier woman may have:

- A boy without the gene alteration.
- A boy with the gene alteration.
- A girl without the gene alteration.
- A girl with the gene alteration.

NEW MUTATIONS In about 15% of people with AS the gene alteration has just arisen in them rather than being inherited from a parent. This is called a new mutation. People with a new mutation have the same chance of passing the gene on to their children as individuals who inherited the gene alteration.

DNA tests

We can screen patients DNA for alterations in the COL4A5 gene. Once we know the specific alteration in a patient we can test other family members to see if they have inherited it too.

Rarer (“non-classic”) forms of AS

Most families with AS have the classic X-linked type of AS described above. However, a few families show a different pattern of genetic inheritance when there are mutations in genes other than COL4A5.

An autosomal recessive pattern

In this type, an affected person inherits two copies of a mutation in either the COL4A3 or COL4A4 gene, one from each parent. Males and females with 2 mutations are affected equally severely, and their parents will all be carriers of a single mutation, which usually causes a mild condition called benign familial haematuria; however long term follow-up is recommended.

An autosomal dominant pattern

This type is extremely rare. Men and women can be affected. Anyone inheriting just one copy of an altered gene in COL4A3 or COL4A4 will have Alport’s syndrome.

For more information

If you need more information please contact your local Genetics Department. If in the South East Thames region please contact:

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Websites:

<http://www.kidneyresearchuk.org/campaigns/action-for-alports/action-for-alports.php>

<http://www.guysandstthomas.nhs.uk/services/managednetworks/genetics>

Factual information presented in this communication is based on accurate contemporaneous peer reviewed literature. Evidence of sources can be provided on request.

Seen in clinic by.....

Draft August 2012