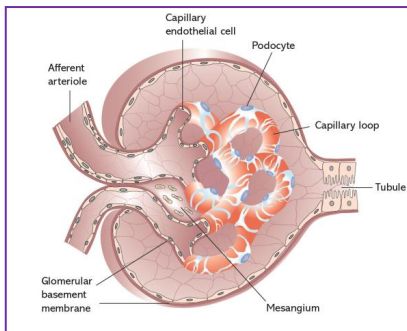


Alport's syndrome



Alport's syndrome (AS) is a disorder of the Glomerular Basement Membrane, part of the Glomerular filtration unit, and is the second highest cause of inherited chronic kidney disease (CKD) after polycystic kidney disease. Alport's syndrome can also cause hearing loss. About 1 in 5000 individuals are affected. This number accounts for 2-3% of all cases of CKD. In 2008, there were 448 patients with alport's syndrome on renal replacement therapy (either one of the forms of dialysis or a transplant).

- Those affected will have visited their GP with haematuria (blood in the urine) during childhood, or early adult life. These problems will often have coincided with a minor infection, such as a cough or a cold
- They may be no awareness of a family history of renal problems, or any connection between pink urine in a child and a relative with CKD, so the diagnosis is often not made for several years
- Once a diagnosis of alport's syndrome has been made, it is important to offer screening to other relatives who may be affected
- Sometimes further cases are diagnosed within a family following a diagnosis of a relative
- Males and females are often not equally affected – males tend to be more badly affected, while females may only ever have blood and protein in urine, and possibly high blood pressure. A few females, however, will develop CKD, usually in later life
- Counselling and screening are available for all family members who may be at risk of having the gene

Who was Alport?

Professor Arthur Cecil Alport was a South African physician who came to London to work at St Mary's Hospital. While there, he met a family in which several individuals, across three generations, had haematuria and deafness. Some of the men went on to develop renal failure.

Alport recognised that the haematuria and deafness did not occur in the same individuals by chance – and he suggested that this combination represented a specific clinical syndrome. He also commented on the striking difference in the severity of the condition between males and females. He reported his findings in the British Medical Journal in 1927, but it was not until 1961 that the syndrome was named after him.

What is Alport's Syndrome?

After Alport's 1927 report, many other families with inherited renal problems were reported as being similar to Alport's original family and frequently, these families were labelled as having 'alport's syndrome'. In fact, a number of clinically distinct families were collected together and, when doctors tried to work out the pattern of inheritance in this group of families, it proved extremely difficult.

It became necessary to establish a set of strict criteria that would enable the identification of families with the same condition as Alport's original family. Patients in whom a diagnosis of AS is being considered, and sometimes their relatives, are now screened specifically for evidence of:

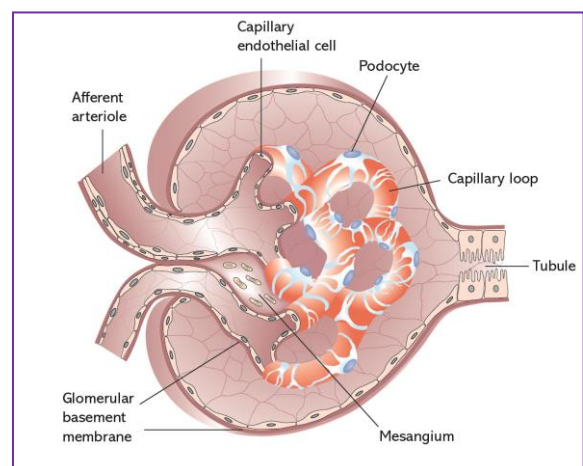
- A family history of chronic renal failure or haematuria
- High-tone deafness – not everyone will be affected
- Specific signs in the eye – *Anterior Lenticonus* and *Macular Flecks*
- Specific changes seen on the renal biopsy when viewed under the electron microscope

Chronic kidney disease

Initially, there will be blood in urine (haematuria) only, although proteinuria (protein in the urine) may also develop. Occasionally, the proteinuria is so marked that nephrotic syndrome is diagnosed. Later, the blood pressure starts to rise and, in men, renal function declines slowly. Once the blood creatinine has reached $*200 \mu\text{mol/l}$ patients can be advised that a form of dialysis or a transplant will be required, on average, 16 months later.

*This is very roughly 50% of kidney function, which would be classed as Stage three of Kidney Disease.

Transplanted patients usually do very well, and AS does not recur in the transplanted kidney. However, apart from the usual risks of rejection, there is a small risk of rejection due to *Antiglomerular Basement Membrane Glomerulonephritis* (also known as Alport anti GBM Disease.). This is because the body recognises the 'normal' gene instead of the Alport's gene and tries to reject the kidney.



The Glomerulus
Fast Facts – Renal Disorders (www.fastfacts.com)

Only about 2% of kidney transplants are lost because of this, and genetic testing makes it possible to predict which patients are at an increased risk. Anti GBM disease causes a rapid rejection despite intervention, and the problem may recur in subsequent transplants.

Loss of hearing

People with AS have normal hearing at birth and during early childhood, so their speech develops normally. Mothers of affected boys often notice that their son's hearing is not quite as good as it used to be at around ten years of age; an audiogram performed then is likely to reveal mild to moderate high-tone deafness. During the next ten years, the hearing loss slowly increases until, eventually, hearing aids may be prescribed.

In adult life, hearing loss tends to plateau at around -80 to -90 dB and some useful hearing nearly always remains. After receiving a transplant, there is often a mild improvement in hearing.

Signs in the eye

Two characteristic changes are often found in the eyes of adults with AS, which are probably specific to AS (during childhood, AS does not usually affect eyesight).

- **Anterior lenticonus** The lens may slowly become cone-shaped, causing myopia (short-sightedness). Very rarely, problems arise that require lens extraction, but usually the problems caused by lenticonus are minor
- **Macular flecks** White flecks scattered around the retina become visible, both around the macula (central part of the retina), and also peripherally (towards the edge). They have no effect on vision and their only significance is their use in diagnosis

How does 'classic' Alport's Syndrome affect males? (Classic AS is usually X-linked)

While men with AS can have very varied forms of the condition, the pattern is often quite consistent within families. For the majority of families who have 'classic' AS, the outline below may give people some idea of what to expect:

- Haematuria by five years (often only visible to the naked eye during infections such as coughs and colds)
- Hearing beginning to deteriorate by ten years
- Blood pressure beginning to rise by 15 years
- Renal function beginning to decline by 20 years
- Chronic renal failure by 25 years

This is only a guide, and some men may have a much milder form of AS. By contrast, a few may need dialysis or transplant whilst still in their teens.

How does 'classic' Alport's Syndrome affect females? (Classic AS is usually X-linked)

The majority of females with classic Alport's Syndrome are only mildly affected and are often called 'carriers', as they may only discover their status after they have had an affected son. The only universal finding is microscopic haematuria, which is usually detectable by 20 years of age.

During childhood the haematuria may be intermittent. About one third of female carriers develop renal issues eventually, and about half develop high tone deafness, but usually with less hearing loss than their affected male relatives. The eye signs are found in one third of gene carriers, and the lifetime risk of renal impairment is up to 15%.

How is Alport's Syndrome inherited?

The majority of cases of Alport's syndrome are inherited in an X-linked pattern, like haemophilia and Duchenne muscular dystrophy. Other patterns of inheritance (*autosomal dominant* and *autosomal recessive*) are rare in AS.

- Everyone has 46 chromosomes in each cell in their bodies
- In males these include one X and one Y chromosome
- Females carry two XX chromosomes
- If a man has a mutation in the AS gene on his X chromosome, he will develop the condition - there is no comparable gene on the Y chromosome to compensate
- As females have two X chromosomes (and therefore 2 copies of the XL Alport's gene), the presence of the altered AS gene on one X does not necessarily mean that symptoms/signs of Alport's Syndrome will develop as the normal AS gene on the other X chromosome often compensates to a considerable degree

Children of females with X-linked Alport's syndrome

A woman whose mother is known to carry X-linked Alport's syndrome starts off with a 50:50 chance of being a carrier herself. She should be tested clinically for the characteristic signs and if all of these are negative, her carrier risk can be reduced from 50% to 2%. If the specific mutation within the gene is known in her family then she can have a definitive blood test instead in order to determine her carrier status.

For a female carrier there is a 50:50 risk in each pregnancy that the child will inherit the mutation in the Alport's syndrome gene, regardless of that child's sex. A son who inherits that gene will develop Alport's, but a daughter who inherits the same gene will be a carrier like her mother, but is most likely to be only mildly clinically affected.

Children of males with X-linked alport's syndrome

The sons of men with X-linked alport's syndrome will always be unaffected, because a man never passes his X chromosome down to his son – boys always get their Y chromosome from their fathers and their X chromosome from their mothers.

All the daughters of affected males are 'obligate' carriers, however, because they will inherit a mutated copy of the gene for X-linked alport's syndrome from their father, together with a second, normal copy from their mother.

Rare forms of alport's syndrome

Autosomal recessive alport's syndrome shows many similarities clinically to X-linked alport's syndrome, but males and females are affected with equal severity, and both may develop renal failure by their mid-teens. Hearing problems are commonly found too and the characteristic changes may also be found in their eyes. Autosomal recessive alport's syndrome is caused by mutations in other collagen genes that are on chromosome 2.

For a child to be affected, he or she must inherit two mutations in the same gene, one from each parent (i.e. they are both carriers). Carriers are asymptomatic but often have microscopic haematuria. Their renal function is normal. Each time they have another child there is a one in four risk that the child will be affected, regardless of the child's sex.

Autosomal dominant alport's syndrome is even rarer, with just a few families affected around the world. Males and females are affected with equal severity, and renal failure often does not occur until middle age. An affected individual has a 50:50 chance of passing the gene on, regardless of the child's sex, and anyone who inherits the gene is affected.

Key Points

- Alport's syndrome is an inherited condition that affects 1 in 5000 people and causes chronic renal failure and hearing loss
- Alport's syndrome affects the Glomerular Basement Membrane in the Glomerulus
- Once a diagnosis of alport's syndrome has been made, it is important to offer screening to other relatives who may be carriers, or affected
- A son who inherits X-linked alport's syndrome will manifest in the usual way, but a daughter who inherits a mutation in the X-linked gene is most likely to be only mildly affected
- DNA linkage studies and mutation testing have shown that the gene for alport's syndrome is on the X chromosome in most families
- Occasionally alport's syndrome is inherited in an autosomal recessive or autosomal dominant way, in which case the severity of the disease will be

the same in affected males and females and the pattern of inheritance will be different

- In 2008, there were 448 patients with Alport's syndrome on renal replacement therapy (one of the forms of dialysis or a transplant).

Genetic research to date

Towards the end of the 1980's, DNA linkage studies proved conclusively that the gene for Alport's Syndrome is on the X chromosome in most families, and in 1990 the actual gene was found. It is called the COL4A5 gene because it codes for the alpha 5 chain of type IV collagen.

The gene product is actually only a fairly minor component of the Glomerular Basement Membrane (GBM), which may be why renal function at birth is normal. As the years go by, however, the GBM becomes leaky and so the kidney becomes less efficient as a filter.

It took some time to determine the complete message of the normal COL4A5 collagen gene and, since then, scientists have concentrated on trying to detect the 'mutations' (i.e. alterations) in the gene in families with AS.

So far, several hundred different mutations have been identified, as nearly every family has its own unique mutation. Once the specific mutation has been found in a particular family it becomes possible to offer accurate carrier tests to relatives and prenatal diagnosis, if this is requested.

The mutation is detectable in up to 90% of families who clinically have Alport's syndrome. We do not know yet if the remaining mutations are in the same genes and just eluding detection, or in an area nearby that is responsible for controlling gene expression, or located elsewhere.

Current research

Now researchers want to see whether there is any link between the actual genetic mutation in a family and the way in which individuals are affected. For example, there is some evidence that families with a big deletion (piece missing) in the gene are more likely to develop anti GBM antibody nephritis.

In future, it is possible that pharmacological treatments will be influenced by knowledge of an individual's unique genetic make-up.

Finally, very early experiments are underway in pigs to look at the feasibility of gene therapy for inherited renal disorders. It will be difficult because the new gene being inserted will have to be targeted directly at the kidneys.

