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Alport Syndrome

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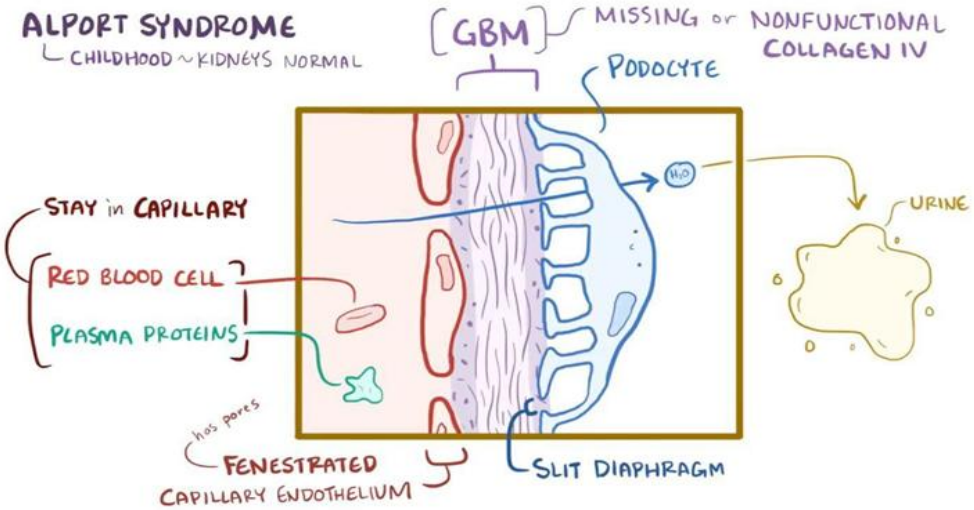
Abstract: ***Alport syndrome is a genetically and phenotypically heterogeneous disorder of glomerular, cochlear, and ocular basement membranes resulting from mutations in the collagen IV genes COL4A3, COL4A4, and COL4A5. Alport syndrome can be transmitted as an X-linked, autosomal recessive, or autosomal dominant disorder. Individuals with Alport syndrome have a significant lifetime risk for kidney failure, as well as sensorineural deafness and ocular abnormalities. The availability of effective intervention for Alport syndrome–related kidney disease makes early diagnosis crucial, but this can be impeded by the genotypic and phenotypic complexity of the disorder. This review presents an approach to enhancing early diagnosis and achieving optimal outcomes. Diagnosis is conventionally made pathologically, but recent advances in comprehensive genetic analysis have enabled genetic testing to be performed for the diagnosis of AS as first-line diagnosis. Because of these advances, substantial information about the genetics of AS has been obtained and the genetic background of this disease has been revealed, including genotype–phenotype correlations and mechanisms of onset in some male XLAS cases that lead to milder phenotypes of late-onset end-stage renal disease (ESRD). There is currently no radical therapy for AS and treatment is only performed to delay progression to ESRD using nephron-protective drugs. Angiotensin-converting enzyme inhibitors can remarkably delay the development of ESRD.***

Keywords: XLAS, ARAS, ADAS, ACE, ARB, ESRD, GBM, TBM,COL4A5, COL4A4, COL4A3, end-stage renal disease

1. Introduction



The modern era of Alport syndrome can be said to have begun in the 1970s with reports of unique ultrastructural abnormalities in glomerular basement membranes of patients with the disease. Alport syndrome, also known as hereditary nephritis is a genetic disorder arising from the mutations in the genes encoding alpha-3, alpha-4, and alpha-5 of type 4 collagen (COL4A3, COL4A4, COL4A5) or collagen 4 α345 network. These type IV collagens constitute the glomerular basement membrane (GBM). AS has been reported to develop in approximately one in 5000 people; it comprises 0.5% of newly developed end-stage renal disease (ESRD) cases in adults and 12.9% in children. Type IV collagen has six different α chains, α1 to α6, which construct triple helix structures in which the three chains are combined. The combination of three α-chains is organ-specific: in the GBM, cochlea basement membrane, and base of the ocular lens, the triplet α3–α4–α5 is present, while in Bowman's capsule and skin basement membrane, it is α5–α5–α6. When an abnormality occurs in the α-chain, these triple helix structures are broken, causing nephropathy, sensorineural hearing loss, and eye lesions. AS is divided into X-linked Alport syndrome (XLAS), autosomal recessive Alport syndrome (ARAS), and autosomal dominant Alport syndrome (ADAS), according to its mode of inheritance. The distribution of these cases is reported to be as follows: 80% XLAS, 15% ARAS, and 5% ADAS. XLAS is caused by abnormality of COL4A5, while ADAS and ARAS are caused by abnormality in COL4A3 or COL4A4.It is characterized by renal failure, bilateral sensorineural hearing loss, and eye abnormalities. Eventually, the patients present with proteinuria, hypertension, progressive loss of kidney function (gradual decline in GFR), and end-stage renal disease (ESRD).

Table 1: Alport Syndrome Classification

Inheritance	*Affected Gene(s)*	*Genetic State*
X-Linked	*COL4A5*	Hemizygous (males)
		Heterozygous (females)
Autosomal	*COL4A3* or *COL4A4*	Recessive (homozygous or compound heterozygous)
		Dominant (heterozygous)
Digenic	*COL4A3*, *COL4A4*, and *COL4A5*	*COL4A3* & *COL4A4* variants in *trans* (recessive)
		COL4A3 & *COL4A4* variants in *cis* (dominant)
		Variants in *COL4A5* and in *COL4A3* or *COL4A4* (non-Mendelian)
Suspected	—	Clinical, pedigree, tissue data are highly suggestive of Alport syndrome, but genetic data are not confirmatory

What causes Alport syndrome

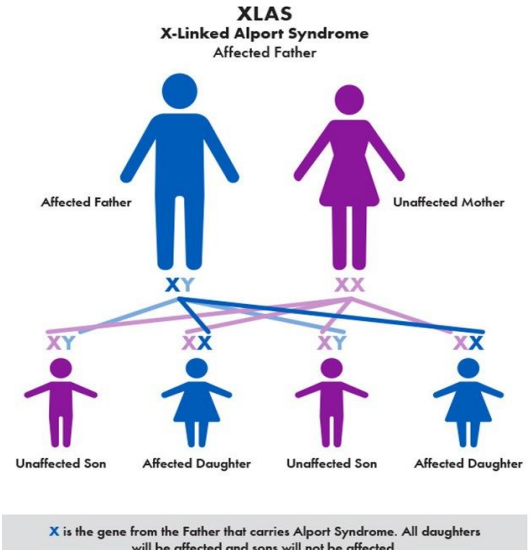
Alport syndrome is an inherited disease, which means it is passed down through families. It is caused by changes in your genes (mutations) to a protein called collagen. Collagen is important to the normal structure and function of the kidneys. Changes to collagen can also cause problems with the eyes and ears. That's because collagen helps maintain healthy tissue in the eyes and ears.

Clinical characteristics and diagnostic features

Table 1 shows the diagnostic features established by the members of the Working Group for Alport Syndrome in the Japanese Society of Pediatric Nephrology (JSPN) in 2015. The main criterion is persistent haematuria. When patients fulfil one or more secondary features, or two or more accessory features, in addition to the primary feature, they can be diagnosed with AS. Symptoms differ depending on the mode of inheritance, with their features described below.

1) XLAS

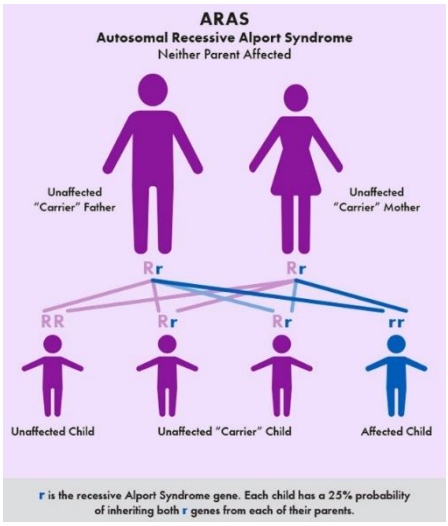
In XLAS, there is often a family history of haematuria (with or without proteinuria) or renal failure. However, in approximately 15% of cases, there are de novo variants without a family history. Microscopic haematuria is observed in all male cases. In female patients, it is observed in approximately 98% with haematuria and Table 1 Diagnostic features of Alport syndrome (revised in February 2015) prepared by the Working Group on Alport Syndrome of the Japanese Society of Pediatric Nephrology In addition to the primary feature, patients satisfy one or more secondary features If there is no corresponding item in secondary features, patients should satisfy two or more of the accessory features If patients have only the primary feature and have a family member diagnosed with Alport syndrome, the case is set as a "suspected case" Asymptomatic carriers can be diagnosed with any one feature of type IV collagen (II-1 or II-2) among the secondary features For all features, those caused by other diseases should be excluded, for example, a family history of kidney failure due to diabetes or senile deafness *1 Persisted for more than 3 months, which was confirmed by urinalysis on at least two occasions. As a rare situation, there is a possibility that haematuria may disappear at the time when renal failure progresses to the end stage, in which case appropriate examination such as of kidney dysfunction should be performed *2 This refers to a homozygous or heterozygous mutation of COL4A3 or COL4A4, or a hemizygous (male) or heterozygous (female) mutation of the COL4A5 gene *3 Type IV collagen α5 chain exists not only in the glomerular basement membrane and Bowman's capsule, but also in the skin basement membrane. Upon immunostaining using anti-α5-chain antibody, normal glomeruli and skin basement membrane are stained linearly and continuously. However, glomeruli, Bowman's capsule, and the skin basement membrane of male patients with X-linked Alport syndrome are completely negative. In glomeruli, Bowman's capsule and skin basement membrane of female patients are partially stained. In autosomal recessive Alport syndrome, the α3-, α4-, and α5 chains are not stained in glomerular basement membranes, whereas in Bowman's capsule and skin, normal α5-chain staining is shown. Note that the above is a typical pattern, but an atypical pattern also exists. Moreover, Alport syndrome cannot be ruled out even if α5 chain expression shows completely normal pattern *4 Glomerular basement membrane-specific abnormalities include broad irregular thickening of the glomerular basement membrane and reticulation of the lamina densa. Extensive thinning of the glomerular basement membrane frequently seen in benign familial haematuria is also seen in Alport syndrome, which can be the only finding of the glomerular basement membrane. In these cases, there is a high possibility of Alport syndrome if the cases show hearing loss, ocular abnormalities, or a family history of renal failure *5 Specific ocular abnormalities include anterior lenticonus, posterior subcapsular cataract, posterior polymorphous dystrophy, and retinal flecks.



2) ARAS

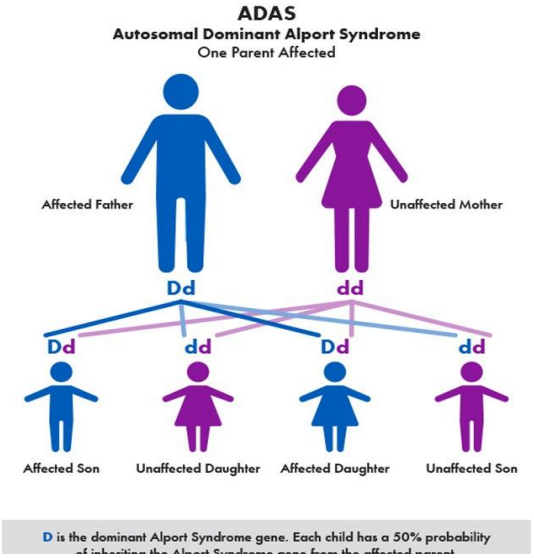
Clinically, ARAS shows symptoms similar to those in male XLAS patients. There are no gender differences in clinical symptoms and incidence, and this condition sporadically occurs in one generation. Families with monoallelic variant carriers are often asymptomatic or show only microscopic haematuria (and mild proteinuria). For the genetic diagnosis

of ARAS, analysis of at least one familial member (ideally, both parents) is necessary to prove that two heterozygous variants are located in trans positions on two different alleles (either COL4A3 or COL4A4). In terms of the clinical findings that we previously reported, the median age of ESRD development is 21 years. Sensorineural deafness was observed at a median age of onset of 20 years.



3) ADAS

Recently, we published an article regarding the clinical picture, pathology, and genetic background of ADAS. The median age for detecting proteinuria was 17.0 years, and that for developing renal insufficiency was 70 years. In addition, both hearing loss and eye lesion were reported to occur quite rarely. Moreover, three of 16 patients with pathological findings showed focal segmental glomerular sclerosis (FSGS), as revealed by light microscopy. It has also been reported that, in approximately 10% of patients with familial focal segmental glomerulosclerosis, COL4A3 or COL4A4 mutations are identified, suggesting that there are many undiagnosed ADAS patients.



Etiology

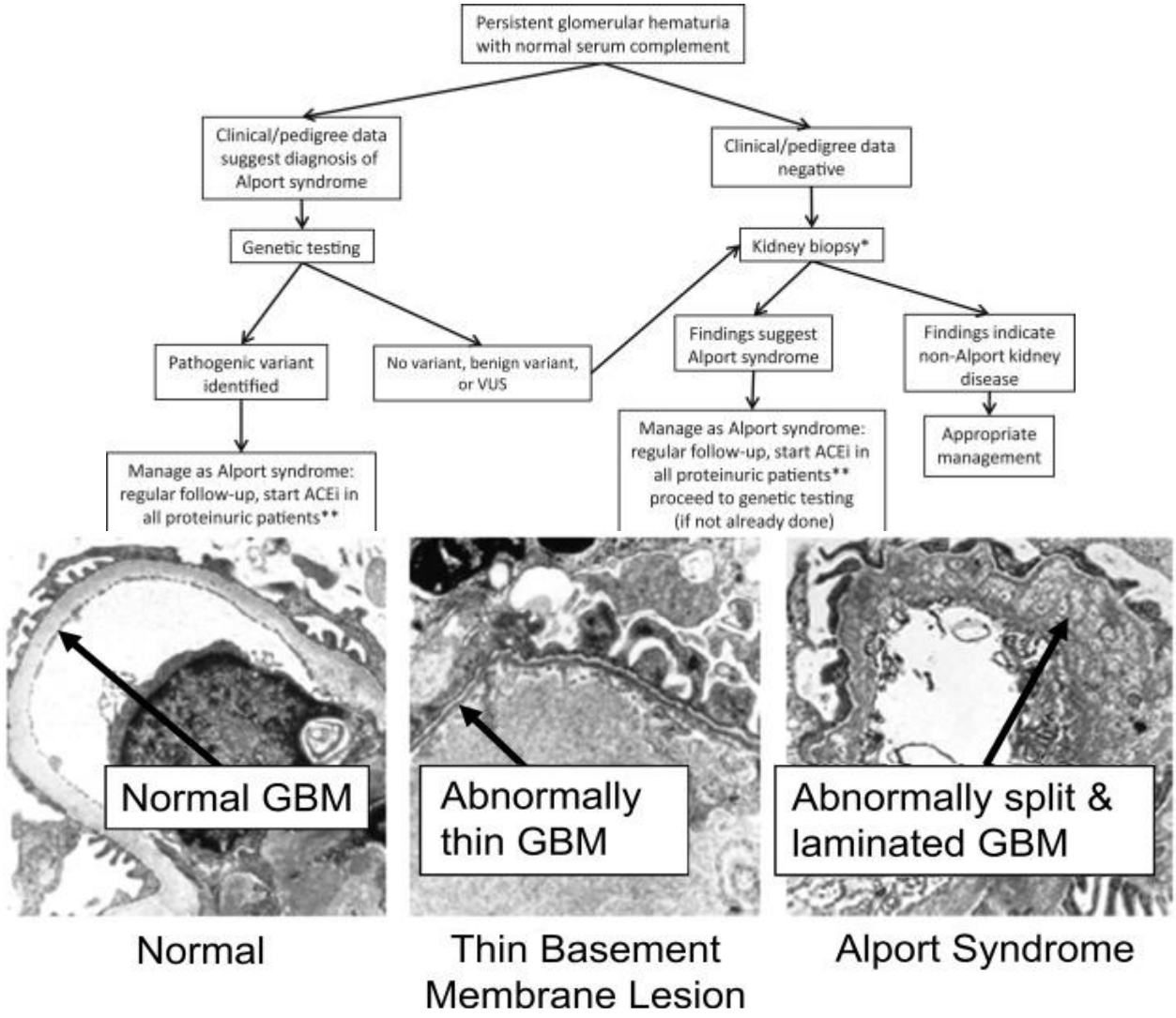
In 80% of cases, Alport syndrome is inherited in an X-linked pattern and caused by *COL4A5* gene mutations, although other inheritance patterns do exist. It can be inherited as an autosomal recessive or dominant pattern by mutations in *COL4A3* or *COL4A4* gene. Approximately 80% of men with the XLAS develop some degree of hearing loss till they reach teenage.

Epidemiology

Alport syndrome affects about 1 in 50,000 new-borns and males are more likely to be symptomatic than females. It is estimated that approximately 30,000 to 60,000 people in the United States (US) have this disorder. In the US, the overall incidence of end-stage renal disease (ESRD) in children is about 3% and 0.2% in the adult population.

Pathophysiology

The pathophysiology of Alport syndrome is impaired production and deposition of collagen 4 α345 network in the basement membranes of the glomerulus, cochlea (inner ear), and eye. ARAS transmission is due to mutations in both the alleles of COL4A3 and COL4A4, whereas ADAS is caused by heterozygous mutations. With the use of next-generation sequencing (NGS), it has shown that ADAS accounts for a greater number of cases. Compared to XLAS, patients with ADAS have a slower rate of progression to ESRD and less likely to have extra-renal manifestations. The glomerular basement membrane (GBM) in Alport syndrome is more prone to proteolytic injury leading to activation of adhesion kinase in podocytes, endothelin receptors, glomerular inflammation, and tubulointerstitial fibrosis and ESRD.



Diagnostic Test

- **Urine test:** A urine test will help find protein and blood in your urine.
- **Blood test:** A blood test will help find levels of protein, and wastes in your blood.
- **Glomerular filtration rate (GFR**): A blood test will be done to know how well your kidneys are filtering the wastes from your body.
- **Kidney biopsy:** In this test, a tiny piece of your kidney is removed with a special needle, and looked at under a microscope.
- **Hearing test:** A hearing test will be done to see if your hearing has been affected.
- **Vision test:** A vision test will be done to see if you vision has been affected.
- **Genetic test:**This can help confirm the diagnosis and determine the genetic type of Alport syndrome you may have.

Differential Diagnosis

The differential diagnosis includes:

- Immunoglobulin A nephropathy
- Thin GBM disease
- Acute post-streptococcal glomerulonephritis
- Medullary cystic disease
- Multicystic renal dysplasia
- Polycystic kidney disease

The most important diagnostic consideration in patients with Alport syndrome is thin basement membrane (TBM) disease, which is a collagen 4 related nephropathy closely related to Alport syndrome. In many individuals with the disorder, the same genes appear to be involved. Unlike those with Alport syndrome, few extra-renal findings are present, and symptoms are less severe, with progression to renal impairment rarely found. Differentiating these disease processes is a challenge, particularly in younger or female patients who are less likely to have other associated symptoms.

2. Signs and Symptoms

With all types of Alport syndrome the kidneys are affected. The tiny blood vessels in the glomeruli of the kidneys are damaged and cannot filter the wastes and extra fluid in your body. Many people with Alport syndrome also have hearing problems and abnormalities with their eyes.

Other signs and symptoms may include:

- Blood in the urine (haematuria), the most common and earliest sign of Alport syndrome
- Protein in the urine (proteinuria)
- High blood pressure (hypertension)

- Swelling in the legs, ankle, feet and around the eyes (called edema)

These signs and symptoms may differ, based on age, gender and inherited type of Alport syndrome.

3. Complications

Alport syndrome affects multiple organ systems. It can lead to the following complications:

- End-stage renal disease (ESRD)
- Hearing loss
- Visual defects
- Leiomyomatosis (smooth muscle overgrowth in the respiratory and gastrointestinal tract)
- Aneurysms of the thoracic and abdominal aorta
- Mental Retardation

4. Treatment

No definite treatment exists for Alport syndrome. Research indicates that angiotensin-converting enzyme (ACE) inhibitors can reduce proteinuria and the progression of kidney disease. Thus, the use of ACE inhibitors is reasonable in patients with Alport syndrome who have proteinuria with or without hypertension; the same is true for angiotensin-receptor blockers (ARBs). Both classes of drugs apparently help to reduce proteinuria by decreasing intraglomerular pressure. Moreover, by inhibiting angiotensin II, a growth factor that is implicated in glomerular sclerosis, these drugs have a potential role in slowing sclerotic progression.

Proteinuria, hearing loss, lenticonus, retinopathy, and reduced levels of GBM collagen IV a5 chain all correlate with an increased likelihood of early-onset renal failure in males,18,30,31 but the risks have not been studied prospectively. Hearing continues to deteriorate in adulthood and is helped with hearing aids, but affected individuals should protect their hearing from additional insults throughout life. The lenticonus also worsens but can be corrected with lens replacement.32 The retinopathy progresses but does not affect vision or require treatment.

Some individuals do not respond to or cannot tolerate ACE inhibitors. These individuals may be treated with drugs known as angiotensin receptor blockers (ARBs). ARBs prevent angiotensin II from binding to the corresponding receptors on blood vessels.

Combination therapy with an ACE inhibitor, an ARB, a non-dihydropyridine calcium channel blocker, and a statin (benazepril, 10-20 mg/day; valsartan, 80-160 mg/day; diltiazem, 60-120 mg/day; and Fluvastatin, 40-80 mg/day), safely ameliorated albuminuria, hypertension, lipid abnormalities, and glomerular selectivity in Alport syndrome patients and halted long-term progression in those without kidney insufficiency. The 4-month study included nine albuminuric adults with Alport syndrome whose creatinine clearance was > 20 ml/min/1

Although treatment may slow the progression of kidney disease in Alport syndrome, there is no cure for the disorder and no treatment has thus far been shown to completely stop kidney decline. The rate of progression of kidney decline in individuals with Alport syndrome is highly variable. In many affected individual's kidneys function eventually deteriorates to the point where dialysis or a kidney transplant is required.

Dialysis is a procedure in which a machine is used to perform some of the functions of the kidney — filtering waste products from the bloodstream, helping to control blood pressure, and helping to maintain proper levels of essential chemicals such as potassium. End-stage renal disease is not reversible so individuals will require lifelong dialysis treatment or a kidney transplant.

A kidney transplant is preferred for individuals with Alport syndrome over dialysis and has generally been associated with excellent outcomes in treating affected individuals. Some individuals with Alport syndrome will require a kidney transplant in adolescence or the teen-age years, while others may not require a transplant until they are in their 40s or 50s. Most females with XLAS and some individuals will ADAS syndrome never require a transplant. If a kidney transplant is indicated, great care must be taken in selecting living related kidney donors to ensure that affected individuals are not chosen. Alport syndrome does not recur in kidney transplants. However about 3% or less of transplanted Alport patients make antibodies to the normal collagen IV proteins in the transplanted kidney, causing severe inflammation of the transplant (anti-GBM nephritis).

5. Goals

- The goals of treatment include monitoring and controlling the disease and treating the symptoms**.**
- Improve patient's quality of life.
- Prevent or reduce complications.

6. Conclusion

It is now clear that a variant in *COL4A3*, *COL4A4*, and *COL4A5* is a risk factor for CKD. Whether one thinks of people with these variants as having a single disease with a spectrum of phenotypes (Alport syndrome) or as having distinct disorders (Alport syndrome or thin basement membrane nephropathy), it is crucial that they have regular follow-up by a primary provider or nephrologist and initiation of ACE-inhibitor therapy when appropriate. It is likewise crucial that clinicians attempt to establish a definitive diagnosis in people with persistent glomerular hematuria. Individuals diagnosed with Alport syndrome or found to have *COL4A* variants should be informed by clinicians about Alport syndrome registries to help further our understanding of the disease and responses to intervention.

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