

Alport Syndrome With Kidney Cysts Is Still Alport Syndrome



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INTRODUCTION

Alport syndrome is characterized by hematuria, progressive kidney failure, hearing loss, and ocular abnormalities.¹ X-linked inheritance caused by pathogenic *COL4A5* variants is much more common than recessive disease with 2 pathogenic variants in *COL4A3* or *COL4A4*. Individuals with a heterozygous pathogenic *COL4A3* or *COL4A4* variant (sometimes called “autosomal dominant Alport syndrome” or “thin basement membrane nephropathy”) have hematuria but rarely develop kidney failure, hearing loss, or the ocular features.² The *COL4A3-COL4A5* genes correspond to the collagen IV $\alpha 3$ to $\alpha 5$ chains that form the major structural network within the basement membranes of the kidney, cochlea, and eye, which explains the typical clinical manifestations.

Overall, X-linked Alport syndrome affects about 1 in 2000 of the population and heterozygous *COL4A3* or *COL4A4* variants occur in 1 in 100.³ However, even X-linked Alport syndrome is often unrecognized because affected individuals have milder disease or an atypical phenotype. Milder disease occurs in women, and in men with pathogenic variants located in certain regions of the collagen IV $\alpha 5$ chain, or involving substitutions with certain amino acids.³

Atypical phenotypes with Alport syndrome are recognized increasingly. Thus, many affected individuals present with proteinuria rather than hematuria and are often initially diagnosed with steroid-resistant nephrotic syndrome or focal segmental glomerular sclerosis (FSGS).⁴ Focal segmental glomerular sclerosis probably occurs with pathogenic *COL4A3-COL4A5* variants because the abnormal glomerular basement membrane results in loss of the overlying podocytes⁵ and the development of

secondary glomerular hyperfiltration. Similar changes also occur in the cornea⁶ and presumably in the retina where the temporal retina is thinned overlying Bruch’s membrane.⁷ Pathogenic changes in the genes affected in Alport syndrome are the most common variants found in cohorts with focal segmental glomerular sclerosis.⁴ In addition, pathogenic *COL4A3* to *COL4A5* variants are common in familial IgA glomerulonephritis where the thinned glomerular basement membrane may enable IgA to pass from the glomerular capillaries into the mesangium.

Kidney cysts have also been reported more often in individuals with pathogenic *COL4A3-COL4A5* variants and the diagnosis of Alport syndrome.^{8,9} We describe here a man with renal impairment and multiple bilateral kidney cysts in whom genetic testing identified a pathogenic *COL4A5* variant consistent with the diagnosis of X-linked Alport syndrome.

CASE PRESENTATION

A 49-year-old man was referred for management of kidney failure by his family doctor. He had hypertension and gout but no other significant medical history. He had not been aware of his kidney function until this time, but his current serum creatinine level was 297 $\mu\text{mol/l}$ (normal 60–110) corresponding to an estimated glomerular filtration rate of 20 ml/min per 1.73 m^2 (normal >90), with a urinary red blood cell count of 109 red blood cells $\times 10^6/\text{l}$ (normal <10) and urinary albumin:creatinine of 128.6 (normal <2.5). The patient had a family history of kidney disease, with a maternal grandfather who developed kidney failure and a 69-year-old mother, a brother, and a sister all with mildly impaired kidney function. None of the affected family members knew the cause of their

kidney impairment, and in particular, none was known to have kidney cysts.

The patient was evaluated for Alport syndrome and stated that his hearing was normal, and he did not undergo formal audiometry. He had no central fleck retinopathy on retinal imaging or temporal retinal thinning on optical coherence tomography (Heidelberg instruments) (Figure 1a). There was a subtle nasal fleck retinopathy but its significance was not clear (Figure 1b).

An abdominal magnetic resonance imaging scan revealed multiple bilateral kidney cysts (Figure 1c). The kidney volume as evaluated by the ellipsoid calculation method (volume = length \times width \times depth \times Pi / 6) was 188 ml and 190 ml for the right and left kidneys, where the normal values were 219 ml and 213 ml, respectively. There were no cysts in the liver, pancreas, or spleen.

The patient then underwent whole genomic screening using a “Cystic and ciliopathy” and a “Glomerulopathy” gene panel that included *COL4A3-COL4A5*. A *COL4A5* variant was identified (c.358G>A, p.Gly120Ser) that was considered Likely Pathogenic based on the criteria of the American College of Medical Genetics and Genomics (PM1, PM2, PP2, PP3), consistent with the diagnosis of X-linked Alport syndrome. No pathogenic variant was found in the *PKD1* or *PKD2* genes that are affected in autosomal dominant polycystic kidney disease (ADPKD), nor in *HNF1b*, *GANAB*, or *DNAJB11*, nor in any of the other genes in the cyst and ciliopathy panel.

The patient had a fistula constructed and hemodialysis was commenced, as well as a workup for kidney

transplantation. His 2 children and other family members were referred for counseling and genetic testing.

DISCUSSION

The management of this individual demonstrates the advantages of genetic testing to identify the cause of inherited kidney disease. The presence of multiple kidney cysts and late-onset kidney failure, with inheritance consistent with AD disease, together with apparently normal hearing, suggested a cystic kidney disease, most likely ADPKD. The cysts were probably too numerous for age-related cystic change.

The patient also had hematuria and a family history of kidney impairment that was consistent with X-linked Alport syndrome. He did not have the typical hearing loss or central fleck retinopathy, but the subtle peripheral flecks were a possible clue to the diagnosis.

Kidney cysts, however, have been reported previously in Alport syndrome. They occur in males and females with a pathogenic *COL4A5* variant and X-linked disease, and those with a heterozygous *COL4A3* or *COL4A4* variant and thin basement membrane nephropathy or AD Alport syndrome.^{8,9} Cysts in *COL4A3-COL4A5*-associated disease are distinguished from those in ADPKD by being fewer, smaller, and not substantially distorting the kidney outline or increasing the kidney volume. They affect both the cortex and medulla. They are associated with any pathogenic *COL4A3* to *COL4A5* variants, first occur before the age of 50 years, and may be associated with normal kidney function but are more common when

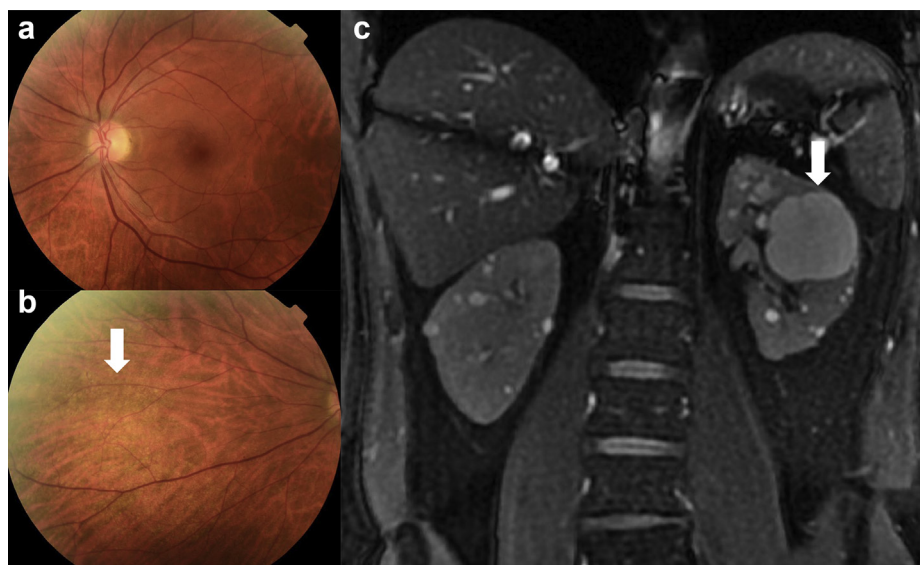


Figure 1. (a) Central view of the patient’s left retina that demonstrates no central or peripheral fleck retinopathy. (b) Nasal view revealing a subtle peripheral fleck retinopathy (arrow) that suggests Alport syndrome. (c) Coronal T2 MR image revealing multiple bilateral cortical and medullary cysts of varying sizes, with the largest on the left measuring 40 mm across (arrow). There were no solid renal lesions found and no cysts in the liver, pancreas, or spleen. MR, magnetic resonance.

proteinuria is also present. These features imply that cysts occur with more severe disease, but too few pathogenic variants have been reported for genotype-phenotype correlations. The cysts are not large enough to worsen kidney function themselves, and, at present, no specific treatment is required. Cysts have not been described in the liver or other abdominal organs with *COL4A3*- to *COL4A5*-associated disease.

The explanation for the cysts in Alport syndrome is unclear, but the collagen IV $\alpha 3$ to $\alpha 5$ chains are found in the basement membranes in the glomerulus, Bowman's capsule, and distal tubule. Kidney cysts occur too in a canine model of AD Alport syndrome.¹⁰ Pathogenic variants in *COL4A1* affecting the collagen IV $\alpha 1$ chain also result in kidney cysts in hereditary angiopathy, with nephropathy, aneurysms and muscle cramps syndrome ("HANAC").¹¹ This rare condition is more typically associated with cerebral small vessel disease and porencephaly, than kidney cysts. *COL4A1* is expressed in the vascular basement membranes in the brain and elsewhere, including membranes in the glomerulus and proximal and distal kidney tubules. Increased fluid pressure or hypertension in addition to thinned and weakened membranes¹² may result in cyst formation.

The cysts in Alport syndrome can be distinguished from those in ADPKD which are typically more numerous, larger, and associated with cysts in the liver, and sometimes spleen and pancreas. Inheritance in ADPKD is clearly AD with affected individuals in each generation having multiple cysts. Conversely, in Alport syndrome, there is dysmorphic hematuria, and proteinuria, and, in the case of X-linked or recessive disease, hearing loss, and ocular abnormalities.

The importance of describing this patient is that hematuria and a family history of renal impairment suggest Alport syndrome (Table 1). The demonstration of a hearing loss or ocular abnormalities makes the diagnosis of Alport syndrome even more likely. Finding kidney cysts should not discourage the clinician or the laboratory from considering the diagnosis of Alport syndrome and that the cysts are caused by pathogenic *COL4A3-COL4A5* variants (Table 1). This means that cystic and ciliopathy gene panels should also include the *COL4A3*, *COL4A4* and *COL4A5* genes. Genetic testing (often whole-genome sequencing) for ADPKD detects *COL4A3-COL4A5* pathogenic variants, but whole-exome sequencing performed for a glomerulonephritis or Alport gene panel may not detect a variant in *PKD1* or *PKD2* when the diagnosis is actually ADPKD.

It is still unclear how often cysts occur with pathogenic *COL4A3-COL4A5* variants and the age when cysts can first be found. Making the distinction

Table 1. Teaching points

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| 1. Alport syndrome should be suspected when there is persistent glomerular hematuria, especially when there is a family history of hematuria or renal impairment. |
| 2. Alport syndrome should also be suspected when there is proteinuria or kidney failure or familial IgA glomerulonephritis and no other obvious cause. |
| 3. The finding of a hearing loss or fleck retinopathy increases the likelihood of Alport syndrome with pathogenic variants in <i>COL4A3-COL4A5</i> . |
| 4. Kidney cysts are under-recognized with pathogenic <i>COL4A3-COL4A5</i> variants and Alport syndrome. |
| 5. Finding kidney cysts should not discourage genetic testing of the <i>COL4A3-COL4A5</i> genes when there are grounds for suspecting Alport syndrome. |

between Alport syndrome and ADPKD or age-related kidney cysts is important because their management is different. All males with X-linked Alport syndrome should be treated with renin-angiotensin-aldosterone blockade from the time of diagnosis, and all women from the onset of proteinuria. Those with ADPKD may require specific treatment to slow down cyst expansion. In addition, the prognosis is different. Individuals with ADPKD develop kidney failure by their late 50s, and 90% of men with X-linked Alport syndrome reach kidney failure by 40 years and 30% of women by 70 years. The prognosis for family members is also different. On average, half of the sons and half of the daughters of an individual with ADPKD inherit the mutation and develop kidney failure. In contrast, a man with X-linked Alport syndrome has none of his sons affected but all his daughters inherit the mutation. Although the risk of kidney failure for these women is small, they pass on the pathogenic variant to half their own sons who will themselves develop kidney failure.

This patient illustrates the extended clinical phenotype associated with pathogenic *COL4A3-COL4A5* variants and indicates that the finding of kidney cysts where Alport syndrome is suspected should not discourage genetic testing for variants in the *COL4A3*, *COL4A4* and *COL4A5* genes (Table 1). Indeed, the presence of cysts in a young person with a family history of hematuria may suggest a pathogenic *COL4A3-COL4A5* variant. These cysts are not currently considered to contribute significantly to kidney impairment, and no cyst-specific treatment is required.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The patient provided written permission for this manuscript, and its submission was approved by the Northern Health Low Risk Ethics Committee.

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