

LETTER TO THE EDITOR

Family Genetic Screening to Identify Cases of Alport Syndrome: A Case Study Report



To the Editor:

A proposed reclassification consolidates thin basement membrane nephropathy and Alport syndrome into a broader definition evidenced by chronic kidney disease with COL4A3/4/5 variants. It also recognizes that women with X-linked disease and autosomal heterozygotes with microscopic hematuria may be at risk for progressive kidney disease.¹ Additionally, an expert panel recommends genetic testing for all individuals with hematuria and a lamellated glomerular basement membrane or hearing loss, lenticonus, or a fleck retinopathy, as they may have Alport syndrome.²

We report results for a family in which 8 members in 3 generations had Alport syndrome (Fig 1). The male proband died from kidney failure. The proband's wife was unaffected, and genetic information from his deceased parents was unavailable. The proband had 3 daughters, 2 with variants consistent with Alport syndrome. The oldest daughter had proteinuria (~100 mg/dL) and a serum creatinine of 1.53 mg/dL. Her hearing and vision were normal, and she had a COL4A5 missense variant (c.5030G>A, p.Arg1677Gln) in exon 51 classified as pathogenic. This woman had 2 daughters and 1 son. One

daughter and the son had variants consistent with Alport syndrome. The affected daughter had no proteinuria and a serum creatinine of 0.67 mg/dL; her hearing and vision were not evaluated. She had a missense variant in COL4A5 and a heterozygous missense variant in COL4A3, which was likely pathogenic. The son had trace proteinuria (~20 mg/dL) and a serum creatinine of 0.97 mg/dL. He had hearing loss in his right ear and his vision in both eyes was 20/13. He had the same COL4A5 missense variant as his sister and mother and all had hematuria.

The proband's other affected daughter had no proteinuria, and serum creatinine was 0.80 mg/dL. Her vision and hearing were normal. She had a COL4A5 missense variant (c.5030G>A, p.Arg1677Gln) in exon 51 classified as pathogenic, and 2 of her 3 sons also had COL4A5 missense variants (c.5030G>A, p.Arg1677Gln) consistent with Alport syndrome. The first affected son had COL4A5 and had trace proteinuria, hematuria, and a serum creatinine of 0.95 mg/dL. His vision was normal, but he had right-sided hearing loss. The second affected son also had COL4A5 but had no proteinuria, and had a serum creatinine of 0.61 mg/dL. His hearing and vision were not evaluated.

These results demonstrate the importance of family screening to identify individuals often not diagnosed in routine clinical practice, but who could benefit from closer monitoring and early intervention. While there are no approved therapies for Alport syndrome, both angiotensin-converting enzyme inhibitors and angiotensin receptor

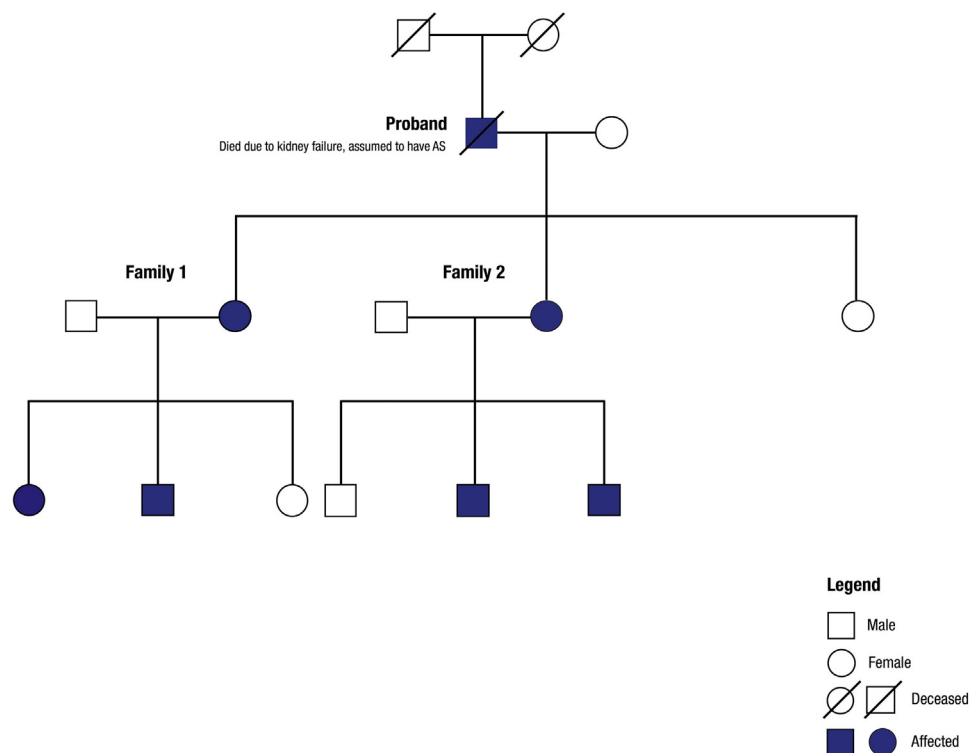


Figure 1. Pedigree of the family in whom variants were found. Family tree showing a single family in which 8 members across 3 generations had Alport syndrome.

blockers may be beneficial.^{3,4} Such individuals might also benefit from future available therapies.

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