

The Case | Familial occurrence of retinitis pigmentosa, deafness, and nephropathy

Claudia Izzi¹, Pietro Maffei², Gabriella Milan², Regina Tardanico³, Paolo Foini⁴, Jan Marshall⁵, Alessandra Marega⁶ and Francesco Scolari^{1,4}

¹Second Division of Nephrology, Spedali Civili di Brescia, Montichiari Hospital, Montichiari, Italy; ²Department of Medical and Surgical Sciences, University of Padua, Padua, Italy; ³Department of Pathology, Spedali Civili di Brescia, Brescia, Italy; ⁴Department of Nephrology, University of Brescia, Brescia, Italy; ⁵The Jackson Laboratory, Bar Harbor, Maine, USA and ⁶Division of Nephrology, Dialysis and Transplantation, Azienda Ospedaliero-Universitaria di Udine, Udine, Italy

Correspondence: Francesco Scolari, Second Division of Nephrology, Spedali Civili di Brescia, Montichiari Hospital, 25018 Montichiari, Italy. E-mail: fscolari@tin.it

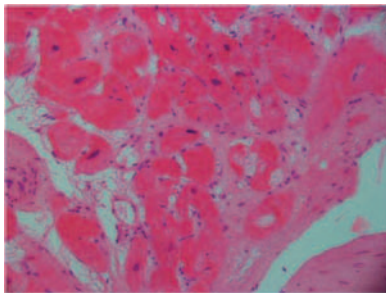


Figure 1 | Endomyocardial biopsy showing severe interstitial fibrosis and moderate myocellular hypertrophy (hematoxylin and eosin; original magnification × 20).

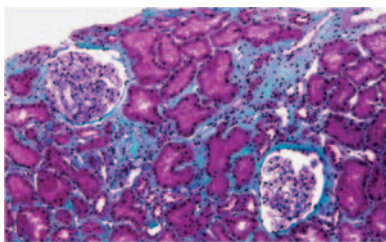


Figure 2 | Renal biopsy showing focal areas of interstitial fibrosis and tubular atrophy and normal glomeruli (hematoxylin and eosin; original magnification × 100).

A 49-year-old woman was admitted with chronic renal failure. Her previous history included poor vision, with photophobia at 3 years; retinitis pigmentosa resulting in legal blindness by age 40; sensorineural hearing loss by age 20 progressing to deafness. By the age of 27, she developed congestive heart failure; echocardiography showed dilated cardiomyopathy. Myocardial biopsy showed interstitial fibrosis and myocellular hypertrophy (Figure 1). Chronic renal failure (serum creatinine 1.5 mg/dl) was found with negative urinalysis. At the age of 42, insulin resistance was first documented.

At admission, her weight was 63 kg, height 145 cm, body mass index 30 kg/m². She had normal intelligence. Serum creatinine was 1.6 mg/dl; creatinine clearance 38 ml/min; urinalysis negative;

urinary osmolality 360 mosmol/kg. Ultrasonography revealed small kidneys with a few bilateral cysts. Renal biopsy showed interstitial fibrosis, tubular atrophy (Figure 2).

Family characterization (Figure 3) revealed unaffected parents, a phenotypically normal sister, and a brother who died at 1 year from congenital heart disease. A 43-year-old brother had retinitis pigmentosa, sensorineural deafness, hepatic fibrosis, adult-onset dilated cardiomyopathy, chronic renal failure (serum creatinine 1.4 mg/dl; creatinine clearance 55 ml/min) with negative urinalysis, small kidneys and hepato-splenic enlargement by ultrasound. Liver rigidity, measured by transient elastography (Fibroscan, Echosens, Paris, France), was significantly increased.

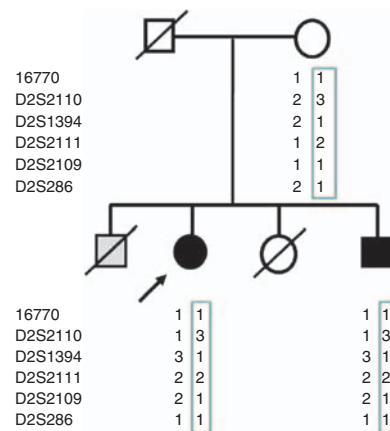


Figure 3 | Haplotype of kindred surrounding the ALMS1 region. Arrow indicates the index case. Males and females are indicated by squares and circles, respectively; blackened circles and squares represent affected individuals; gray shading indicates a possible case of Alström syndrome with infantile congestive heart failure, but no other genetic or clinical information is available. Slash indicates deceased individuals from whom DNA was not available. Both affected individuals share a common haplotype defined by markers 16770, D2S210, D2S1394, D2S2111, D2S2109, and D2S286.

What is your diagnosis?

SEE NEXT PAGE FOR ANSWERS

The Diagnosis | Alström syndrome, a rare ciliopathy with tubulointerstitial renal involvement

The complex spectrum of phenotypes of our patients is consistent with those described for ciliopathies, which are genetic disorders resulting from dysfunction of cilia usually involving the kidneys.¹ The combination of tubulointerstitial nephritis, retinitis pigmentosa, and liver fibrosis can be observed in nephronophthisis, a ciliopathy causing the most frequent hereditary tubulointerstitial nephritis.² However, metabolic abnormalities are not typical features of nephronophthisis, whereas they are part of the clinical spectrum of two pleiotropic ciliopathies, Bardet-Biedl (BBS) and Alström syndrome (ALMS).¹ Mutational analysis of the known variants in *BBS 1-12* genes (microarray analysis; Asper Biotech, Tartu, Estonia) did not reveal mutations. Sequencing analysis of all exons of the *ALMS1* gene revealed, in both affected individuals, a heterozygous frameshift mutation (S524fsX535) inherited from the mother. Haplotype analysis found identical haplotypes in the 2p13 *ALMS1* region in the two sibs (Figure 3).

ALMS is a rare recessive ciliopathy caused by mutations in *ALMS1*, a novel gene of unknown function. The major phenotypes are observed in young children; other phenotypes emerge as the child develops. The diagnosis of ALMS relies primarily on clinical findings and can be proven by molecular testing when two mutations are identified. However, two disease-causing mutations are not easily identified, suggesting that some patients can harbor mutations in the promoter/intronic regions.³⁻⁵ To help clinicians in making the diagnosis, a set of age-related diagnostic criteria have been proposed.⁵

Our patients fulfilled the diagnostic criteria for adult ALMS, showing a combination of two major criteria (retinitis pigmentosa and *ALMS1* mutation in a single allele) and at

least four minor criteria (sensorineural hearing loss, hepatic fibrosis, dilated cardiomyopathy, and renal disease).

Renal disease develops with age in all individuals with ALMS. Onset occurs in early adolescence/adulthood, with polyuria and polydipsia. Renal insufficiency leading to end-stage renal disease occurs in 50% of patients. Histopathological changes include interstitial fibrosis and tubular atrophy. Similar fibrotic infiltrations underlie many of the other clinical phenotypes, particularly cardiac, pulmonary, and hepatic disease, suggesting common pathogenic mechanisms.³⁻⁵ The mechanisms of the induction of fibrosis are unknown. Further insights into the function of the *ALMS1* protein will contribute to elucidate this process, increasing the knowledge of molecular mechanisms involved in fibrogenesis.

Tubulointerstitial nephritis due to ALMS is a challenging diagnosis. A high index of suspicion should be maintained in patients presenting with familial recessive tubulointerstitial renal disease, retinal degeneration, and sensorineural hearing loss. The presence of hepatic, cardiac involvement, and metabolic abnormalities should raise the level of suspicion.

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