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CASE REPORT

Alport syndrome: a genetically confirmed x-linked case with early family screening

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ABSTRACT

Introduction: Alport syndrome (AS) is a hereditary nephropathy caused by pathogenic variants in the type IV collagen genes (*COL4A3*, *COL4A4*, or *COL4A5*), leading to structural defects in the glomerular basement membrane, cochlea, and eye. The disease classically presents with hematuria, proteinuria, progressive renal failure, sensorineural hearing loss, and ocular anomalies. This article aims to emphasize the importance of early genetic diagnosis in pediatric AS, highlight that massive proteinuria may serve as an early marker of disease severity, and illustrate the clinical impact of family screening in resource-limited settings. **Case Presentation:** We report the case of a 10-year-old boy with X-linked Alport syndrome, confirmed by the identification of a pathogenic hemizygous *COL4A5* variant. The patient had a significant family history of renal and auditory involvement among three maternal uncles. Clinical examination revealed bilateral mixed hearing loss and hypertension without edema. Urinalysis demonstrated microscopic hematuria and nephrotic-range proteinuria (5 g/24 h; protein/creatinine ratio > 200 mg/mmol) with preserved renal function. Ophthalmologic evaluation revealed crystalline corneal flecks. Due to the unavailability of ultrastructural and immunohistochemical testing, diagnosis relied on genetic confirmation. Early initiation of ACE inhibitor therapy was followed by family cascade screening, which identified an affected maternal cousin and a 4-month-old infant sibling, enabling early nephroprotective management. **Conclusion:** This case highlights the crucial role of molecular testing for diagnosis and family screening in AS, particularly in resource-limited settings. The presence of massive proteinuria may signal severe glomerular basement membrane involvement and a higher risk of rapid progression to end-stage renal disease. Early identification allows for prompt nephroprotective therapy, which significantly improves the long-term prognosis.

Keywords: Alport syndrome, *COL4A5*, Hematuria, Proteinuria, Pediatric nephrology, Genetic diagnosis, Family screening.

1. INTRODUCTION

Alport syndrome (AS) is an inherited disorder of the glomerular basement membrane (GBM) resulting from pathogenic variants in the *COL4A3*, *COL4A4*, or *COL4A5* genes, which encode the α3, α4, and α5 chains of type IV collagen, the main structural component of the GBM, cochlea, and lens capsule. Defects in this collagen network lead to progressive renal insufficiency, hearing impairment, and characteristic ocular lesions such as anterior lenticonus and retinal flecks. (1). AS affects approximately 1 in 50 000 live births. The disease is classically inherited in an X-linked pattern (85%), followed by autosomal recessive (15%) and autosomal dominant (< 1%) forms. The severity and age at onset vary depending on the mutation type and zygosity, with males with truncating *COL4A5* variants typically progressing faster to end-stage kidney disease (ESKD). (2)

Despite progress, the diagnostic delay remains significant in many regions due to limited access to molecular testing and electron microscopy. Here, we report a pediatric case of genetically confirmed X-linked AS in Algeria, highlighting the diagnostic pathway, therapeutic management, and the importance of early family screening.

2. CASE PRESENTATION

We present the case of a 10-year-old boy who was referred to the Pediatric Nephrology Consultation at CHU Beni Messous for evaluation of persistent microscopic hematuria and proteinuria detected on routine urinalysis. He was the eldest child of healthy non-consanguineous parents. The family history was remarkable for three maternal uncles with chronic kidney disease and hearing loss; the three of them are on hemodialysis, though none had a confirmed genetic diagnosis or a renal biopsy due to lack of electron microscopy. The detailed family pedigree is shown in Figure 1.

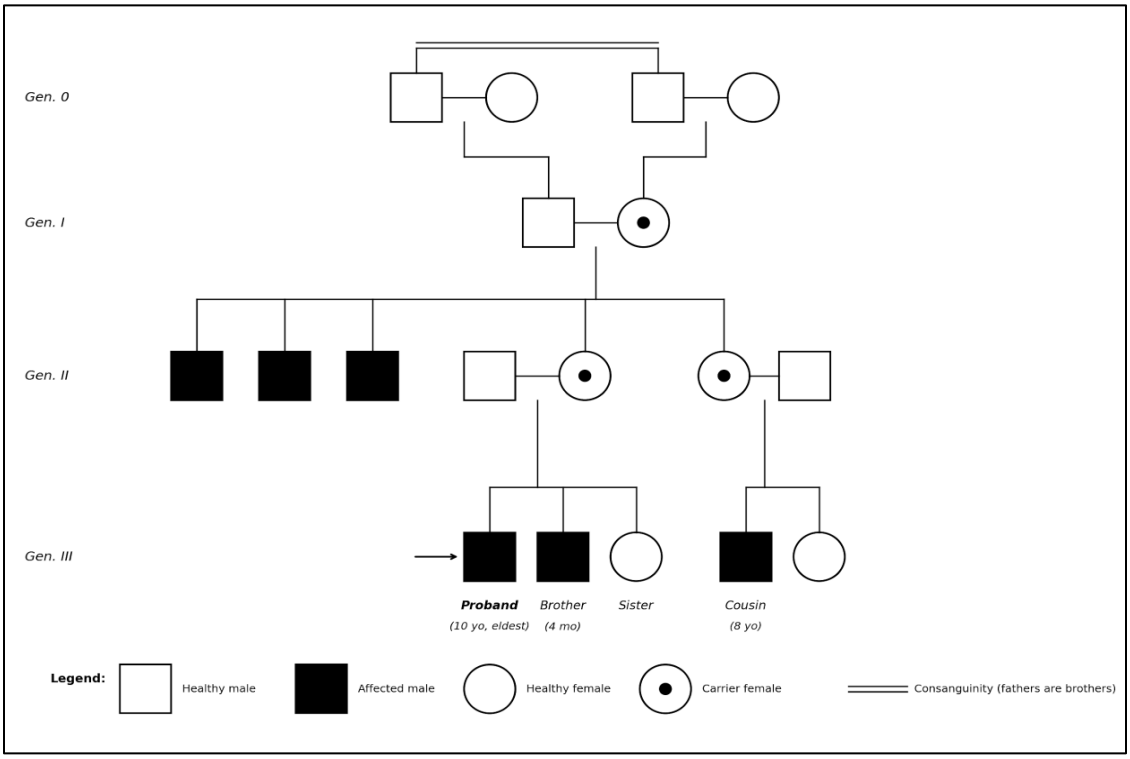

Figure 1. Family pedigree. The proband (10-year-old boy, arrow, eldest of the sibship) harbors a hemizygous COL4A5 duplication variant. Three maternal uncles are affected (filled squares) and currently on hemodialysis. The proband's mother and one maternal aunt are obligate carriers (circle with central dot); the aunt's affected son (8-year-old cousin) and the proband's 4-month-old younger brother were identified through cascade family screening.

Clinical findings: Physical examination revealed a normally nourished boy with high blood pressure 144/77 mm Hg > P99 (AAP 2017) and no edema. Growth parameters were appropriate for age. Cardiopulmonary and abdominal examinations were unremarkable.

Laboratory data: Urinalysis showed persistent microscopic hematuria and proteinuria. Quantitative proteinuria reached a nephrotic-range proteinuria 5 g/24 h (> 1 g/m²/24 h). Serum creatinine was 10 mg/L, with normal urea, electrolytes, and estimated GFR > 90 mL/min/1.73 m².

Audiologic and ophthalmologic evaluation: Pure-tone audiometry revealed bilateral mixed hearing loss. Ophthalmologic examination identified crystalline corneal flecks without lenticonus or retinal changes.

Renal imaging and histology: Renal ultrasound was normal. Renal biopsy was not performed due to the unavailability of ultrastructural and immunohistochemical studies required to confirm GBM abnormalities.

Genetic testing was performed at Laboratoire CERBA (Saint-Ouen-l'Aumône, France), a reference laboratory for rare-disease molecular diagnostics, using the ECCTV3 Alport Syndrome Comprehensive Panel. This targeted next-generation sequencing (NGS) panel analyzes nine genes associated with Alport syndrome and related nephropathies (CD151, COL4A3, COL4A4, COL4A5, COL4A6, FN1, LMX1B, MYH9, PXDN). Sequencing was carried out on Illumina MiSeqDx / NextSeq2000 platforms with a bioinformatics pipeline (SeqOne) covering coding exons and exon-intron junctions at a minimum depth of 30× and > 99% coverage. Variants were interpreted according to the ACMG/AMP classification standard (PMID 25741868).

Molecular analysis identified a hemizygous duplication variant in the *COL4A5* gene (NM_033380.3:c.4668dup), leading to a frameshift and premature stop codon (p.Pro1557ThrfsTer12). According to ACMG criteria, this variant was classified as likely pathogenic (class 4), confirming the diagnosis of X-linked Alport syndrome (OMIM 301050). The full genetic report is summarized in Figure 2.

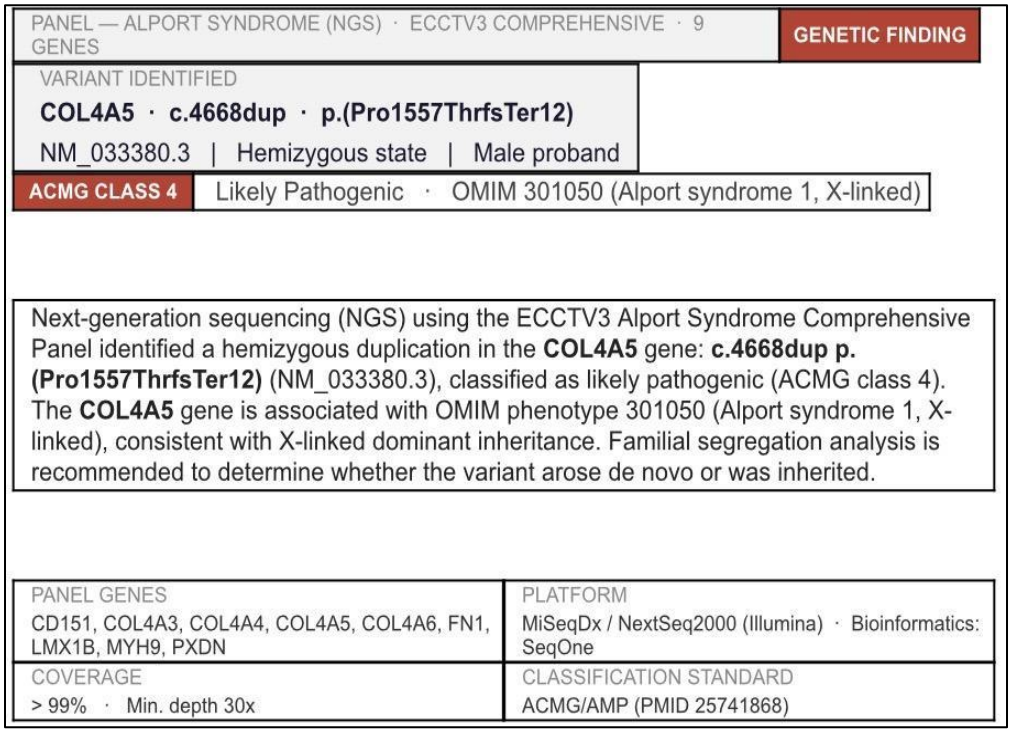

Figure 2. Summary of the NGS genetic report (ECCTV3 Alport Syndrome Comprehensive Panel, 9 genes). A hemizygous duplication c.4668dup, p.(Pro1557ThrfsTer12) in the COL4A5 gene (NM_033380.3) was identified in the male proband and classified as likely pathogenic (ACMG class 4). The COL4A5 gene is associated with OMIM phenotype 301050 (Alport syndrome 1, X-linked). Sequencing was performed on MiSeqDx / NextSeq2000 (Illumina) platforms with > 99% coverage at a minimum depth of 30×, using the ACMG/AMP classification standard (PMID 25741868).

Treatment and outcome: The patient was started on angiotensin-converting enzyme inhibitor (ACEi) therapy (captopril 4 mg/kg/day) with close monitoring. Early family cascade screening identified an affected 8-year-old maternal cousin and a younger brother at 4 months of age, enabling early nephroprotective and audiologic management.

After two years of disease progression, the patient presents with nephrotic-range proteinuria and a decline in renal function (plasma creatinine 18 mg/L, eGFR 36 mL/min). The maximal dose of captopril has been reached, prompting a switch to an angiotensin II receptor blocker. Should there be no adequate response, the use of an SGLT2 inhibitor will be discussed.

3. DISCUSSION

AS results from mutations affecting the α3α4α5(IV) collagen network essential for GBM stability. In the X-linked form, males develop the full triad of renal, auditory, and ocular symptoms, whereas female carriers may show isolated hematuria or mild proteinuria but can also progress to CKD. Mutations in *COL4A5* are heterogeneous (missense, nonsense, and splicing variants). Null mutations (large deletions, nonsense, or frameshift) are associated with early ESKD and more severe extrarenal features, while glycine substitutions in the collagenous domain may cause a milder phenotype. (3). In this case, the genetic diagnosis enabled accurate classification and informed family screening, demonstrating the value of molecular testing even in resource-limited environments.

The clinical spectrum of AS ranges from isolated microscopic hematuria to early-onset ESKD. Proteinuria usually develops in late childhood or adolescence and accelerates progression. Extrarenal manifestations include sensorineural hearing loss, anterior lenticonus, perimacular flecks, and recurrent corneal erosions. Diagnosis relies on combining clinical features, family history, and laboratory data with histologic and genetic findings. In many developing countries, absence of electron microscopy or immunostaining hampers biopsy confirmation, making molecular diagnosis the gold standard.

The 2024 ERA–EDTA and ERKNet consensus recommends genetic testing for all individuals with persistent hematuria or unexplained FSGS, as well as for family members of known cases. (4). The identification of a hemizygous frameshift variant in *COL4A5* resulting in a truncated α5(IV) collagen chain is consistent with a severe molecular defect of the glomerular basement membrane. Truncating variants of *COL4A5* have been associated with earlier onset of proteinuria, faster progression to chronic kidney disease, and more frequent extrarenal manifestations compared with missense variants.

In this context, the early presentation of nephrotic-range proteinuria (5 g/24 h) with initially preserved renal function, although atypical for the classical description of X-linked Alport syndrome, may reflect the severity of the underlying genetic defect. Emerging evidence suggests that massive proteinuria can occur early in patients harboring truncating *COL4A5* variants and may represent a marker of aggressive glomerular involvement and unfavorable renal prognosis. The cornerstone of therapy remains renin–angiotensin system (RAS) blockade (ACE inhibitors or ARBs). Early initiation significantly delays ESKD.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, including dapagliflozin, have emerged as promising nephroprotective agents in proteinuric chronic kidney disease. Their rationale in Alport syndrome is supported by their hemodynamic effects on intraglomerular pressure, reduction of albuminuria, and anti-inflammatory and anti-fibrotic properties. Pivotal adult CKD trials (DAPA-CKD, EMPA-KIDNEY) included only a small number of AS patients and no children, limiting direct extrapolation of their results to the pediatric population. (6)

Nevertheless, early pediatric evidence is emerging. Liu et al. reported the first pediatric experience of dapagliflozin in proteinuric kidney disease, including five children with Alport syndrome (four *COL4A5*, one *COL4A3*); all eight evaluable patients showed a significant reduction in proteinuria at 12 weeks, with good tolerance. (10) An international non-interventional observational study by Gross and Boeckhaus (ASN Kidney Week 2023) enrolled 99 patients with Alport syndrome across 12 countries, including 10 children aged 9–17 years. Among adults, albuminuria decreased by 34% at 1–3 months and remained reduced by 24% at 11.7 months of treatment, supporting a sustained antiproteinuric effect. (11)

The first dedicated pediatric randomized controlled trial, DOUBLE PRO-TECT Alport (NCT05944016), is currently recruiting under the German Society of Pediatric Nephrology. It is a phase 3, multicenter, double-blind, placebo-controlled trial enrolling participants aged 10–39 years with genetically or histologically confirmed AS, stable maximal RAS blockade, and an elevated urinary albumin-to-creatinine ratio. The primary endpoint is the change in UACR from baseline to week 48, with eGFR change at week 52 as a key secondary endpoint. The trial aims to demonstrate the superiority of add-on dapagliflozin over standard of care in delaying the progression of CKD in this young at-risk population; its results are expected to substantially modify pediatric treatment recommendations. (12) A second pediatric trial, EPPIK (sparsentan in selected pediatric proteinuric glomerular diseases, including Alport syndrome), is also under way. (7)

In the meantime, off-label use of SGLT2 inhibitors in pediatric Alport syndrome should be considered on a case-by-case basis in specialized centers, particularly in patients with progressive proteinuria despite optimized ACE inhibitor or ARB therapy, as is being considered for our patient. Other emerging therapies include endothelin receptor antagonists (sparsentan, atrasentan) (7), bardoxolone methyl — an Nrf2 activator (8), and gene and mRNA therapies (pre-clinical phase) (9). Supportive management includes strict blood pressure control, lipid management, nephrotoxin avoidance, and periodic audiologic/ophthalmologic monitoring.

Family screening is essential in AS. Identification of affected relatives allows early therapy and counseling, while preventing unsuitable kidney donation from asymptomatic carriers. Early detection in the infant sibling of this case illustrates the impact of proactive genetic testing. In low- and middle-income countries, limited access to molecular testing and EM often delays diagnosis. Implementing

affordable NGS panels and regional reference laboratories is a priority. Pediatricians should be aware that early hematuria, even isolated, warrants investigation for AS.

Limitations: Segregation analysis within the family has not yet been performed. Genetic testing of the mother and affected maternal relatives would allow confirmation of carrier status and inheritance pattern, refine genetic counseling, and improve risk stratification. Nevertheless, the strong clinical concordance within the family and the identification of a likely pathogenic *COL4A5* variant provide robust support for the diagnosis.

4. CONCLUSION

This case illustrates the expanding genetic and clinical spectrum of Alport syndrome and underscores the importance of early genetic diagnosis and family screening. Even in resource-limited settings, prioritizing molecular confirmation and early initiation of ACE-inhibitor therapy can significantly improve renal outcomes. Integrating genomic medicine into pediatric nephrology enables earlier diagnosis, better risk prediction, and more personalized care.

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REFERENCES

1. Kashtan CE, Ding J, Garosi G, Heidet L, Massella L, Nakanishi K, et al. Alport syndrome: a unified classification of genetic disorders of collagen IV α345: a position paper of the Alport Syndrome Classification Working Group. Kidney Int. 2018;93(5):1045–51. https://doi.org/10.1016/j.kint.2017.12.018
2. Kang E, Park BH, Lee H, Kim YC, Kim DK, Oh KH, et al. A comprehensive review of Alport syndrome: definition, pathophysiology, clinical manifestations, and diagnostic considerations. Kidney Res Clin Pract. 2025;44(4):566–75.
3. Kruegel J, Rubel D, Gross O. Alport syndrome — insights from basic and clinical research. Nat Rev Nephrol. 2013;9(3):170–8. https://doi.org/10.1038/nrneph.2012.259
4. Torra R, Furlano M, Navarro-Muñoz M, Heidet L, Leal Lasarte M, Murer L, et al.; ERKNet, ERA Genes&Kidney and ESPN Inherited Renal Disorders Working Group. Diagnosis, management and treatment of the Alport syndrome — 2024 guideline on behalf of ERKNet, ERA and ESPN. Nephrol Dial Transplant. 2025;40(6):1091–106. https://doi.org/10.1093/ndt/gfae265
5. Pan S, Chen Q, Chen X, Wang J, Li Y, Zhang L, et al. Case report of Alport syndrome caused by a novel de novo COL4A5 mutation. Front Genet. 2023;14:1216809. https://doi.org/10.3389/fgene.2023.1216809
6. Lo Re C, Massella L, Vivarelli M. From RAAS blockade to regenerative medicine: evolving treatment strategies in Alport syndrome. Pediatr Nephrol. 2026;41:607–19.
7. Trachtman H, Rheault MN, Gipson DS, Somers MJG, Fornoni A, Kramer M, et al. Sparsentan for treatment of pediatric patients with selected proteinuric glomerular diseases: design of the phase 2 EPPIK study: PO1980. J Am Soc Nephrol. 2021;32(10S):609. https://doi.org/10.1681/ASN.20213210S1609c
8. Warady BA, Pergola PE, Agarwal R, Andreoli S, Appel GB, Bangalore S, et al. Effects of bardoxolone methyl in Alport syndrome. Clin J Am Soc Nephrol. 2022;17(12):1763–74. https://doi.org/10.2215/CJN.02400222
9. Zhao Y, Zheng Q, Xie J. Exploration of gene therapy for Alport syndrome. Biomedicines. 2024;12(6):1159. https://doi.org/10.3390/biomedicines12061159
10. Hamdani G, Denburg M, Furth S, Goldstein SL, Harshman LA, Kallash M, et al. Sodium-glucose co-transporter 2 inhibitors (SGLT2i) for pediatric kidney disease: the future is near. Front Pediatr. 2025;13:1521425. https://doi.org/10.3389/fped.2025.1521425
11. Gross O, Boeckhaus J. SGLT2 inhibition in Alport syndrome: first large-scale trial to plan a randomized controlled trial in children. Paper presented at: American Society of Nephrology Kidney Week 2023; 2023 Nov 1–5; Philadelphia, PA, USA.
12. Gross O, Boeckhaus J, Weber LT, Heerspink HJL, Simon JF, et al.; study group of the German Society of Pediatric Nephrology. Protocol and rationale for a randomized controlled SGLT2 inhibitor trial in paediatric and young adult populations with chronic kidney disease: DOUBLE PRO-TECT Alport (NCT05944016). Nephrol Dial Transplant. 2025;40(4):679–87. https://doi.org/10.1093/ndt/gfae180