

# A Rare Case of Autosomal Recessive Alport Syndrome Due to Mutation in COL 4A4 Gene with 1 Base Pair Duplication of Cytosine Nucleotide

## —A Rare Mutation in Alport Syndrome

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## Abstract

**Background:** Alport syndrome (AS) is a rare genetic disorder due to mutations in type IV collagen genes. **The case:** A 16-year-old boy was referred for management of moderate renal disease and hypertension that was disclosed after routine testing for sensorineural deafness. Laboratory tests showed serum creatinine at 200  $\mu\text{mol/L}$ , microscopic hematuria and proteinuria at 2.6 g/day. Diagnosis of Alport syndrome (AS) was established by kidney biopsy and genetic testing that disclosed a rare AS-mutation. The biopsy showed focal and segmental glomerulosclerosis, without deposits on immunofluorescent stains, and abnormal glomerular basement membrane with a basket-weave appearance on electron microscopy. Genetic testing showed homozygous frameshift insertion in COL4A4 gene that consisted of 1 base pair duplication of cytosine nucleotide resulting in splice-site changes. Genetic testing of both parents did not show abnormality, indicating a new mutation in this patient. He was treated with Ramipril 5 mg daily and diet low in salt and protein. By 1 year later; he remained stable with serum creatinine at 219  $\mu\text{mol/L}$ , albumin at 39 g/L and protein excretion at 450 mg/day. **Conclusion:** AS can evolve due to new cytosine mutations in aggressive renal disease that can be ameliorated with angiotensin-converting enzyme inhibitors.

## Keywords

Alport Syndrome, Angiotensin Converting Enzyme Inhibitors, Genetic Testing, Microscopic Hematuria

## 1. Introduction

Alport syndrome (AS) is an inherited disease characterized by early-onset progressive renal failure that is associated with persistent hematuria, high tone sensorineural hearing loss, and lenticonus with macular flecks on ophthalmoscopy [1]. It results from mutations in the type IV collagen genes (*COL4A3*, *COL4A4* and *COL4A5*) that constitutes major skeleton of the affected sites [2]. AS was first reported, by Cecil A Alport in 1927, as an X-linked disease in males [3]. Subsequently, the disease was well defined by its lamellated glomerular basement membrane (on electron microscopy scan) and genetic testing. With such diagnostic measures; its prevalence has been estimated at 1:5000 live births [4]. Furthermore; its mode of inheritance was disclosed as; X-linked disease with pathogenic mutation in the *COL4A5* gene (80%). On the other hand; pathogenic mutations in *COL4A3* or *COL4A4* genes phenotypically present as; 1) autosomal recessive inheritance with paired pathogenic mutations (15%), or 2) autosomal dominant inheritance with one mutant copy (5%) [5]. The disease was described as more aggressive with glycine substitutions with (Arginine, Glutamine, Asparagine, Valine, and Tryptophan) as compared to the rare (Alanine, Serine, and Cytosine) residue [6]. In this case report, we describe our encounter with a patient with autosomal recessive AS due to a rare and isolated case of cytosine mutation that resulted in early-onset and moderate renal disease.

## 2. The Case

A 16-year-old boy was referred for management of moderate renal disease. The latter was diagnosed after routine testing for sensorineural deafness. The patient had uncomplicated normal vaginal delivery to consanguineous parents. She was the 3<sup>rd</sup> child with no significant disease in the previous or subsequent 2 children. He denied fever, shortness of breath, oedema, abdominal pain, skin rash and joint pains. The patient did not have past history of significant medical illness, surgery, allergy or chronic intake of medications. On his initial physical examination, the patient was conscious, oriented X3 and without distress of shortness of breath or pain. Blood pressure was 160/100 mm Hg. He was afebrile with a body weight of 55 kg. He did not have lymphadenopathy, goiter, jugular venous distension or oedema. Systemic examination did not show abnormality. Laboratory investigations showed normal peripheral leucocytic and platelets counts. Hemoglobin was normal with normal MCV. Serum urea and creatinine were elevated at 12 mmol/L and 200  $\mu$ mol/L, respectively. Serum glucose, electrolytes and liver functions were normal except for albumin at 34 g/L. Serum cholesterol and TSH were normal. Urine routine and microscopy showed 3(+) protein with 25 RBCs/HPF yet no pyuria. Serum complements (C3 & C4), IgA and protein electrophoresis were normal. ANA, anti-ds DNA, ANCA, anti-GBM antibodies, RA, hepatitis B surface antigen and anti-HCV antibodies were negative. Twenty-four-hour urine showed creatinine clearance at 0.6 ml/second and protein excretion at 2.6 g/day. Chest x-ray and ECG were normal. Abdominal and pelvic ultrasound was normal except

for mild increase in kidney cortical echogenicity. Ophthalmological assessment revealed anterior lenticonus. Kidney biopsy showed a total of 18 glomeruli; of which 4 were globally sclerosed and 2 with segmental sclerosis. Immunohistochemical stains were negative for IgG, IgA, IgM, C3c and C4d. Electron microscopy showed irregular thinning and thickening of glomerular basement membranes with lamellated and basket-weave appearance and without Immune deposits (**Figure 1**). Genetic testing, by next-generation sequencing (NAG) bioinformatic analysis revealed a homozygous frameshift insertion in COL4A4 gene. It consisted of 1 base pair duplication of C nucleotide resulting in splice site changes. This variant was predicted to be disease-causing by bioinformatics prediction tool (SIFT, Polyphen2, and Mutation Taster) [7]. Genetic testing of both parents did not show abnormality. He was treated with Ramipril 5 mg daily and diet low in salt and protein. Six months later; the patient remained stable with serum creatinine at 219  $\mu\text{mol/L}$ , albumin at 39 g/L and protein excretion at 450 mg/day.



**Figure 1.** Photomicrograph of an electron microscopy of a kidney biopsy, of the patient, showing irregular thinning and thickening of glomerular basement membrane with basket-weave appearance.

### 3. Discussion

AS is a genetic disease with variable phenotypic presentations. However, rapidly progressive kidney disease is inevitable in patients with hypertension, proteinuria and low glomerular filtration rate as in our patient [8]. Moreover, he presented himself as unique in many aspects. Firstly, he lacked family history of AS and parental genetic disease indicating a new pathogenic mutation in the patient (index case). Hence and unfortunately; parenteral genetic counseling of would have been limited in his case. Secondly; his mutation was in COL 4A4 gene with 1 base pair duplication of cytosine base, which is extremely rare. This frameshift insertion has not been in the Genome Aggregation Database (gnomAD) population database and Clin Var [9]. Thirdly; he presented with an early onset and rapidly progressive

course contrary to previous reports [6]. Finally, and fortunately; and his disease was ameliorated by angiotensin receptor antagonist (Ramipril). At present, there are no specific curative treatments for Alport syndrome however there is a strong international effort in pursuit of future therapies. Currently, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers slow down the progression of kidney disease and can delay the onset of kidney failure by years [10]. Transplantation can rarely be associated with the formation of antibodies to type IV collagen in the donor kidney resulting in progressive graft failure as a result of Goodpasture syndrome (Alport post-transplant anti-GBM disease) [11]. Gene therapy has been frequently discussed, but delivering it to the podocytes in the glomerulus that normally produce the type IV collagen in the glomerular basement membrane is challenging [12].

#### 4. Conclusion

AS can evolve due to new cytosine mutations in aggressive renal disease and can be ameliorated with angiotensin-converting enzyme inhibitors.

#### Author's Contributions

Prof/Kamel El-Reshaïd conceived the study, participated in its design, and drafted the manuscript. Dr. Shaikha Al-Bader participated in the study design, follow-up of patients, data collection and tabulation of data.

#### Data Availability Statement

The data provided in the current review are available from the references.

#### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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