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A Case of X-Linked Dominant Inherited Alport Syndrome Resulting from a Novel Mutation in *COL4A5*

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Abstract

Alport Syndrome (AS) is a hereditary disease caused by mutations in type IV collagen genes, especially *COL4A3*, *COL4A4*, and *COL4A5* that affect the renal glomerular basement membrane. This causes nephritis with hematuria, proteinuria, and progressive renal damage, as well as high-frequency deafness and visual impairment. The prevalence of AS is approximately 1 in 5000, and it leads to End-Stage Renal Disease (ESRD) in about 0.5% of adults and 12.9% of children. Despite the identification of associated receptors and pathways, the pathophysiology of AS is poorly understood. There is no specific treatment, although inhibitors of the renin-angiotensin-aldosterone system are often used. Recent progress in molecular biological techniques including next-generation sequencing have facilitated the diagnosis of AS and can assist in the elucidation of the underlying pathophysiological mechanisms. Early diagnosis and therapy of AS is important, especially in children.

Here, we report an AS case resulting from a mutation in *COL4A5*. The patient was a two-year-old Chinese boy. Clinical examination showed occult blood and protein in the urine, the red blood cell count was 573/μl, and there was impaired urinary function while hearing appeared normal. Imaging examinations showed no obvious abnormalities. A renal biopsy was performed and AS was strongly suspected. Genetic testing showed a hemizygous mutation in *COL4A5*, c.4003-2 a>T, chromosome location: chrX: 107924113 and the patient were diagnosed with X-linked AS. He was prescribed a low-sodium diet with oral chlorine sand treatment, and after three months, the urine red blood cell count showed a clear improvement.

This study reports a case of X-linked AS caused a mutation in the *COL4A5* gene. The findings demonstrate the pathogenic role of this mutation in AS and provide insight into the pathological mechanism of this disease.

Keywords: Alport syndrome; Hereditary kidney disease; Collagen; *COL4A5* gene; Mutation; X-linked (XLAS) inheritance

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Background

Alport Syndrome (AS) is a hereditary progressive kidney disease, typified by the presence of blood in the urine, to get with sensorineural deafness and visual impairment, as well as other more rare renal manifestations [1]. It is typified by pathological changes in the glomerular basement membrane [2]. AS is a rare single-gene genetic disease, involving mutations in collagen IV genes, specifically, *COL4A4*, *COL4A4* (2q36.3), and *COL4A5* (Xq22.3) that encode the collagen IV alpha 3, 4, and 5 chains, respectively. AS can thus be divided into three genetic models, differing in terms of the responsible gene and the mode of inheritance, namely, X-Linked AS (XLAS), Autosomal Recessive AS (ARAS), and Autosomal Dominant AS (ADAS). XLAS is caused by mutation in the *COL4A5* gene on the X-chromosome 21-22, and accounts for 85% of AS cases, followed by ARAS and the rare ADAS caused by mutations in *COL4A3* and *COL4A4* variation on chromosome 2.q35 to q37 [3]. AS is second only to Polycystic Kidney Disease (CKD) as an inherited kidney disease, and represents a major cause of end-stage renal disease in children [4]. AS is often misdiagnosed in children, and there is limited therapy for children with end-stage renal disease.

In this study, we discuss a two-year-old Chinese boy with X-linked AS resulting from a *COL4A5* mutation. The patient was brought to the hospital with hematuria after finding blood in the urine. No abnormalities in immune function, renal function, urinary ions, and hearing and sight were observed. Routine urine examination showed urinary occult blood 3+, urinary protein ±, and red

blood cell 573/μl. Genetic analysis found that the proband had a potentially pathogenic mutation in the *COL4A5* gene; as this gene is known to be responsible for XLAS, the patient was diagnosed with XLAS.

Case Presentation

A two-year-old boy was hospitalized after an abnormal urine test; there was no gross hematuria, increased frequency, urgency, or pain associated with urination, nor any cough, rash, and other symptoms present for more than 15 days. The child was a G2P2, and had been born full-term by normal vaginal delivery with no prenatal issues. The child was breastfed with supplementary feeds, was fully vaccinated, and had achieved all normal growth milestones. His parents were not consanguineous and there was no maternal history of stillbirth or abortion. Both the patient's mother and sister, however, had a history of hematuria.

On admission, the blood pressure was 71/50 mmHg, the respiratory rate was 20/min, heart rate was 115/min, and the body temperature was 36.8°C. The child weighed 12 kg and was 90 cm tall, with both measures falling within normal ranges for his age (P25-P50 and P50-P75, respectively). His heart, lungs, and reflexes all appeared normal.

Laboratory examinations showed normal parameters, including immunoglobulin +C3 +C4 +k +λ, erythrocyte sedimentation rate, urine ion content, anti-spectrum and ANCA, *Streptococcus*, urine ion detection, renal function, ANA spectrum and ANCA, bone metabolism three 25-VD iPT (CT), 25-hydroxy determination of vitamin D VIT D23.11 ng/ml. The urine was positive for occult blood (Table 1).

Accessory examination showed normal sonography of the heart, liver, gallbladder, pancreas, spleen, and kidneys. Abdominal probe: the nutcracker (negative). No obvious abnormality was found in the abdominal cavity nor on urinary nuclear MRI. Hearing and visual acuity were normal. A renal biopsy strongly indicated suspected Alport syndrome (Figure 1). On the basis of this and the family history, we conducted genetic testing.

The clinical, laboratory, and imaging results strongly suggested AS. Exome sequencing of the patient, his parents, and sibling was performed, and verified by Sanger sequencing. It was found that the patient had a hemizygous mutation in *COL4A5*, c.4003-2 a>T, chromosome location: chrX: 107924113. The chromosomal position of this variant is chrX: 107924113 (genomic version: hg19), with the transcript NM_033380, located in exon 44, which came from the patient's mother.

Both mother and sister showed heterozygous mutations. This hemizygous mutation is consistent with a pattern of X-linked dominant genetic disease. The mother and sister of the proband carried this mutation, but X chromosome inactivation may have reduced the severity of the disease (Figure 2). These findings, together with the clinical findings, resulted in a diagnosis of X-lined AS caused by *COL4A5* mutation.

Treatment

The patient was treated with oral chlorine sand potassium tablets (10 mg, qd). The urine, renal function, and serum electrolytes were evaluated monthly at first and were then followed up regularly at later stages.

Discussion

AS is a progressive hereditary kidney disease. It is a rare single-gene genetic disease, caused by, the most common form is x-chain Alport syndrome (*COL4A5*) and autosomal AS (*COL4A3* and *COL4A4*), accounting for a small number of cases. Clinical with hematuria, proteinuria, progressive renal injury with or without high frequency sensorineural deaf and visual abnormalities for the clinical features of hereditary nephritis [4,5]. Alport syndrome has various clinical phenotypes and can be divided into three categories according to the genetic mode. Among them, X-Linked Inheritance (XLAS) is the main form of as (mim#301050), accounting for about 80% of cases. Such mutations have a serious impact on male patients. There are mutations in genes encoding the collagen IV alpha chains, specifically, the α3, α4, and α5 chains encoded by *COL4A3*, *COL4A4*, and *COL4A5*, respectively. X-linked AS is the most frequent, representing over 80% of cases. The X-linkage may seriously affect male patients and hemizygous mutations in *COL4A5* have been reported in men. Approximately 60% of these patients develop ESRD before the age of 30, with the incidence rising to 90% by the age of 40 [6,7]. Approximately 90% of men with XLAS develop hearing loss before the age of 40 [8], while about 30% of XLAS men have impaired vision [9]. Females heterozygous for the *COL4A5* mutation may experience mild hematuria or hematuria as severe as men due to random inactivation of the X chromosome in females. About 12% of women with XLAS are estimated to develop renal failure by the age of 40 and 15% to 30% by the age of 60 [10]. The α3, α4, and α5 collagen chains are all expressed in the basement membranes of the glomerulus, Bowman's capsule, cochlea, and retina, amongst others; thus, a deficiency in one or more of the chains will affect the kidney, ear, eye, skin, and muscle function [11,12]. Bilateral Sensorineural Hearing Loss (BSHL) is commonly seen in AS and is usually seen in conjunction with renal symptoms. BSHL reduces hearing in the high- and medium-frequency ranges and develops gradually, with approximately 18% of children below the age of 18 showing hearing loss, rising to 70% of adults. BSHL can thus be used for assessing the prognosis of nephropathy, as earlier onset is associated with higher ESRD risk [13]. In the eye, macular retinopathy and pyramidal lesion are often seen, frequently in combination with hearing impairment. The presence of central and peripheral macular retinopathy is linked to early-onset renal failure. Thinning of the temporal lobe retinal membrane also frequently occurs in AS although this is not associated with vision impairment and may improve. Other more rare ocular manifestations may also occur [14,15].

Although overall AS is classified as rare with a prevalence of about 1:5000-10000 [16], recent population-based genetic investigations have found that this may be an underestimation, with ADAS being between 5 and 16 times more prevalent than other forms of the disorder [17]. In the past, mild hematuria was usually diagnosed as Benign Familial Hematuria (BFH) or Thin Basement Membrane Nephropathy (TBMN), both of which resulted from autosomal COLA4 gene mutations and were usually heterozygous. More recent genetic studies have grouped these two diagnoses together as a single entity (collagen nephropathy), and the prevalence is tough to be considerably higher as it is likely that many cases are either undiagnosed or misdiagnosed [18]. It is second to the polycystic kidney disease is the most common hereditary kidney disease, mainly involving the kidneys, may also show renal symptoms, such as eye problems, such as hearing loss or the severity of the disease according to its genetic and other affected by known or unknown factors and

Table 1: Laboratory tests before and after treatment.

Laboratory examinations	Before treatment	After 3 months treatment	Reference range
Occult blood	3+	3+	negative
Urine protein	±	negative	negative
Red blood cell/ul	455	121	0-7
Microscopic examination of red blood cells/HP	25~30	5~10	<3/HP
The urine trace albumin mg/L	65	30.7	0.0-30.0
24 h urinary protein quantitative g/24 h	0.29	0.09	0.00-0.15

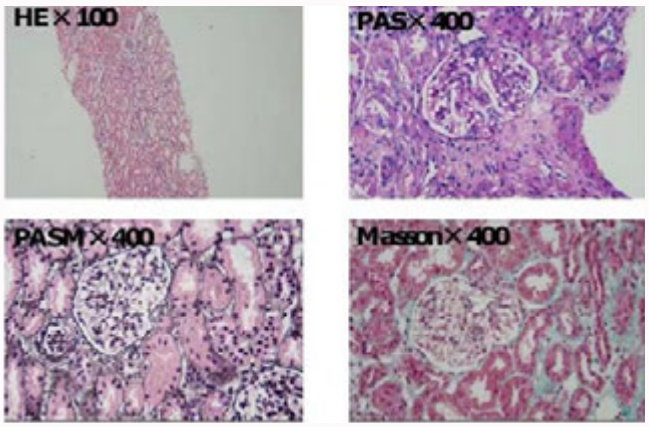

Figure 1: Kidney biopsy pathology.

change [19].

The Glomerular Basement Membrane (GBM) contributes to the filtration function of the kidney. It is formed by an interlocking network of proteins and proteoglycans, including type IV collagen, laminin, and perlecan, amongst others [20]. Structural alterations in these components can disrupt the network and its interactions, altering the function of the GBM and potentially leading to progressive CKD. However, mutations in type IV collagen may cause a wide variety of phenotypes, resulting from the complex interactions between genotype, sex, and X-chromosome inactivation. Furthermore, the type of mutation may also be a factor. Over 1,500 variants have been documented in *COL4A5*, with more than 500 in *COL4A3* and *COL4A4* [21,22]. The most common polymorphism in *COL4A5* is a missense mutation, accounting for approximately 43% of the observed polymorphisms, followed by 34% nonsense mutations, 23% splice variants, 14% small deletions, 7% rearrangements or copy number variations, together with smaller numbers of repetitions and indels [22]. Male patients with XLAS tend to develop renal failure. A European cohort study showed that a large deletion and nonsense mutation resulted in the likelihood of renal failure before the age of 30, while the risk of renal failure from a splice site mutation was 70% and that of the missense mutation was 50% [23]. A cohort study of women with XLAS found a 12% risk of renal failure by the age of 45, rising to 30% by age 60, and 40% by age 80. The reason for this wide prognostic variation is unknown but X-inactivation is a probable cause [24]. ARAS results from homozygous or compound heterozygous mutations in *COL4A3* and *COL4A4* and accounts for approximately 5% of AS cases [25]. These patients, as well as those with ADAS, show a wide variety of symptoms ranging from mild hematuria to renal failure [26].

Clinical manifestations and disease progression differs among AS patients. The current treatment is aimed essentially at slowing the progression of the renal disease to delay renal failure. Nevertheless, most patients require renal replacement therapy [27]. It is thus important to investigate new ways of treating the disease, and investigations into the cellular and molecular functions of the GBM have suggested various possibilities, these include genomic strategies such as gene editing and therapy, RNA therapy, and partner therapy. Current treatment mostly involves the use of Angiotensin-Converting Enzyme (ACE) inhibitors in the Angiotensin Aldosterone System (RAAS) and Angiotensin Receptor Blockade (ARB), which have been found to protect against hypertension, proteinuria, and renal deterioration [28,29]. While ACE inhibitors are the first-line treatment, AT1 receptor antagonists may be used if side effects are experienced. Increased RAAS axis activity has been linked to CKD progression mediated by both hemodynamic (increased pressure in efferent arterioles) and non-hemodynamic processes (increased cytokine production). Targeting RAAS can mitigate these effects and improve renal function [3]. RAAS inhibitors may also be combined with other therapies that have been found to improve the efficiency of treatment efficacy, although there is an increased risk of side effects [30].

Ramipril is an ACE inhibitor. It has been shown in the EARLY PROTECT ALPORT clinical trial (NCT01485978) to be safe and efficacious for treating children with AS, as have animal studies [31,32]. In 2020, an updated guide was issued emphasizing the benefits of early initiation of treatment with RAAS inhibitors and the importance of early diagnosis [33]. Renal function is stable in early childhood (normal GFR, no proteinuria). The only signs of disease in young children are that the GBM is thinner and there may be slight hematuria. In older children, the GBM thickens, leading to the development of proteinuria and fibrosis during adolescence [34]. It is thus recommended that men with XLAS and ARAS should receive RAAS inhibitor therapy when diagnosed. However, female patients with XLAS and ADAS should be treated at the sign of the first symptoms (microalbuminuria) [33].

Recommendations for the use of ACE inhibitors are based on the ESCAPE trial in children with CKD and the EARLY PROTECT trial in children with AS [33]. In men with XLAS (hemizygous *COL4A5* variant), we recommend starting ramipril therapy at diagnosis using an initial dose of 1 mg/m^2/day for three to four months increasing to 6 mg/m^2/day, or maximum tolerated dose. Taking lisinopril as an example, it is recommended that the initial dose be 0.2 mg/kg/day (maximum dose 10 mg/day), titrating upward to 0.6 mg/kg/day (maximum dose 40 mg/day), or maximum tolerated dose. For both drugs, the dose should be adjusted according to the needs of children's growth to maintain a constant mg/m^2 or mg/kg dose and reach the maximum recommended or tolerated dose. For female patients with XLAS (heterozygous *COL4A5* variants), we suggest that when microalbuminuria occurs repeatedly detected without in the absence of infection, defined as the proportion where urinary

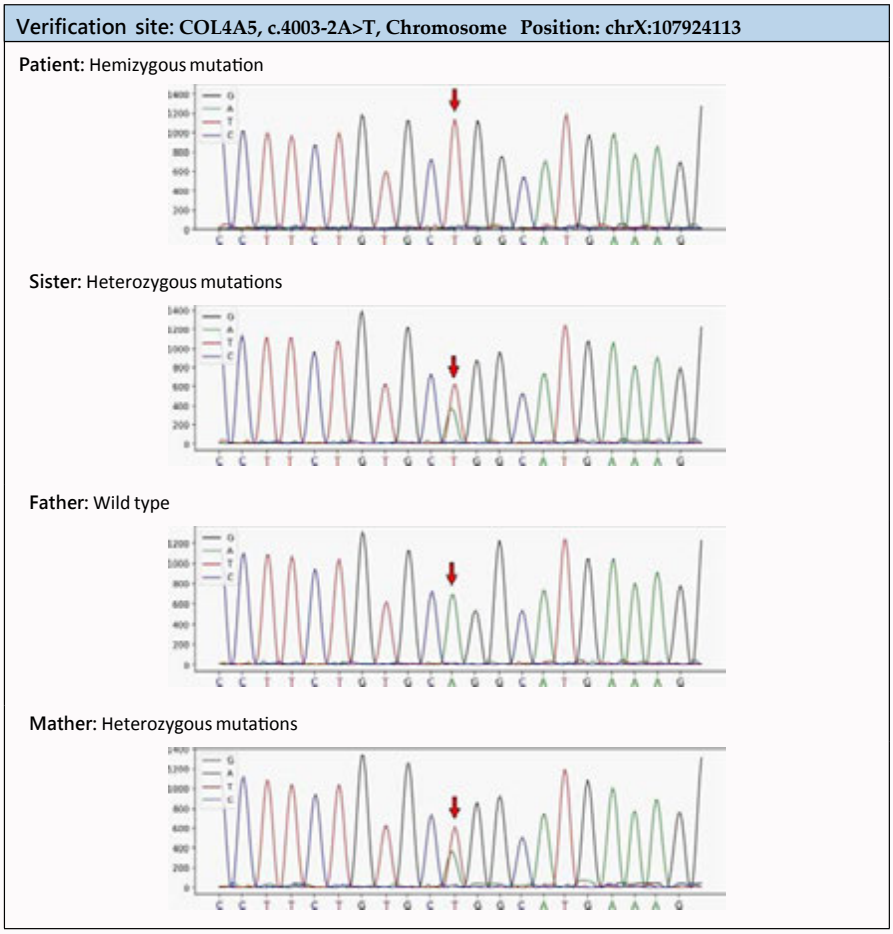

Figure 2: Sequencing analysis shows a hemizygous mutation in *COL4A5*, c.4003-2a>T, chromosome location: chrX: 107924113 in the Alport syndrome patient (Arrow). The chromosomal position of this variant is chrX: 107924113 (genomic version: hg19), with the transcript NM_033380, located in exon 44, which came from the patient's mother (Arrow).

microalbuminuria and creatinine is greater than 30 mg/mg, treatment should be initiated. We hypothesize that the onset of microalbuminuria identifies those heterozygous women at significant risk of developing CKD and renal failure. At present, there is no reliable method for measuring the balance of X-inactivation balance in the kidney. We recommend that the dose of ramipril and lisinopril be the same as for male XLAS patients. Adult female patients should use contraception to prevent the formation of fetal lesions resulting from angiotensin blockade. For both male and female patients with ARAS, we recommend initiating treatment at diagnosis. Both male and female patients with ADAS that have no infection but show symptoms of microalbuminuria (urinary microalbumin creatinine ratio is greater than 30 mg/Mg) should receive treatment. We hypothesize that the presence of microalbuminuria identifies heterozygous individuals at risk of progression to CKD and renal failure [33-37].

There are several drugs currently in clinical trials for AS. These include bardoxolone, an anti-inflammatory factor that activates transcription factor Nrf2 and prevents the activation of the NF-κB pathway [38]. In the *COL4A3* Alport mouse model (129Sv/J), artemisinin (paricalcitol) protected against renal disease and fibrosis. Artemisinin was evaluated in combination with ACE inhibitors and was found to delay ESRD onset [39]. The endothelin A receptor agonist Atrasentan has been found to reduce proteinuria without causing fluid retention [6] and the aldosterone antagonist spironolactone is a useful replacement for ACE inhibitors. In the *COL4A3* Alport animal model (129Sv/J), combined therapy using ACE inhibitors and spironolactone reduced both proteinuria and fibrosis [3] although some mice died prematurely, possibly as a result of side effects [29]. HMG-C enzyme A reductase inhibitors (HMG CoA reductase inhibitors) or statins, commonly used to regulate cholesterol, also show anti-inflammatory and anti-fibrotic effects. For instance, cerivastatin was found to reduce both reduce proteinuria and fibrosis and to prolong the lives of AS mouse models (129Sv/J) [24]. Sparsentan functions as a dual inhibitor of the Angiotensin II Type 1 (AT1) receptor and endothelin A receptors and has shown good efficacy in clinical trials [3]. Metformin has also been shown to be effective in the *COL4A5* mutant AS model (B6) [35] while Olmesartan was shown to downregulate TGF in *COL4A3* Alport mice (129X1/SVJ) β thus preventing tubulointerstitial fibrosis [36]. Olmesartan can also be attached to Hydrophobically modified Glycol Chitosan (HGC) nanoparticles to specifically target the kidney and avoid side effects such as hypotension [37]. These drugs are currently in clinical trials and are expected to be used in clinical treatment in the future to benefit patients. In addition, gene therapy has become a research hotspot, striving to cure the disease at a fundamental level. Gene editing may permanently correct, delete, or replace a gene. Despite significant progress in this field, it has only been tested in a few clinical trials.

AS is a chronic disease that seriously affects the quality of life of patients. XLAS and ARAS usually lead to early renal failure, resulting in patients having to receive renal replacement therapy. This emphasizes the important of early genetic diagnosis and early treatment to prolong the health of patients for as long as possible. At present, there is no specific treatment for patients with AS and the most frequently used treatment is by inhibition of the renin-angiotensin-aldosterone system. Recently this year, with the continuous progress of second-generation sequencing technology, great progress has been made in diagnosis and this technology offers prospects for fully understanding the pathophysiology of the disease and developing new treatments. The identification of prognostic biomarkers is also important, ideally, a urine marker that does not require invasive investigations. A possible biomarker for progression in children may be uEGF/Cr (urinary epidermal growth factor normalized by urinary creatinine) which is lower in AS patients [21]. Currently, the only way to predict the progression of disease to ESRD is the assessment of risk factors (increased proteinuria or hearing loss) or renal damage (nephrotoxic drugs, renal donors [3]. The more progress we make in disease research and the more we know about this disease, the more innovative it will be, and the closer we will be to a cure.

In the present study, we report a case of X-linked AS caused by a *COL4A5* mutation. A hemizygous mutation was found in *COL4A5*, c.4003-2a>t, chromosome location: ChrX: 107924113. This is a novel mutation. This study expands the human gene database, which is conducive to studying the individualized treatment scheme according to genotyping, and providing personalized treatment for patients with AS caused by different genetic mutations. Therefore, the early diagnosis and treatment of AS are very important. Early diagnosis and early intervention can delay complications such as renal failure and help children live a healthier life.

In conclusion, gene therapy has become a research hotspot and may be a potential treatment for the complete cure of Alport syndrome.

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