Case Report

A case report: Alport syndrome and growth hormone deficiency associated with a new *COL4A4* mutation

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Background: Alport syndrome (AS) is a rare progressive hereditary kidney disease that is clinically principally associated with hematuria, proteinuria, and progressive renal dysfunction. This condition not only impairs renal function but also potentially affects auditory and ocular health, significantly impacting the patient's quality of life.

Case Description: This article reports a young girl with AS, combined with dwarfism attributable to growth hormone (GH) deficiency, diagnosed at Wenzhou People's Hospital in 2019. The clinical data and diagnostic steps were retrospectively analyzed. Genetic testing showed that she carried a new mutation in the *COL4A4* gene, c.2317_2318delAG (p.R773Gfs*14), classified as "pathogenic" under the criteria of the American College of Medical Genetics and Genomics (ACMG), confirming her AS diagnosis. Significantly, the patient's height was more than two standard deviations (SDs) below the average for children of her race, sex, and age. The peak GH level post-stimulation was below 5 ng/mL, coupled with a growth rate of less than 5 cm/year, leading to the diagnosis of GH deficiency. Consequently, recombinant human GH (rhGH) therapy was initiated.

Conclusions: After a year of rhGH treatment, we observed a notable increase in her height, without any adverse effects like elevated intracranial pressure, hypothyroidism, or worsening kidney function.

Keywords: Alport syndrome (AS); growth hormone deficiency (GH deficiency); recombinant human growth hormone (rhGH); short stature; case report

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Introduction

Alport syndrome (AS) is clinically characterized by hematuria, proteinuria, and progressive renal dysfunction. Some patients exhibit extrarenal manifestations including sensorineural hearing loss (SNHL) and eye lesions (1). The renal dysfunction progresses to chronic kidney disease and end-stage kidney disease (ESKD) (2). AS is the second-most common genetic kidney disease after autosomal-dominant polycystic kidney disease (3). Growth hormone (GH) deficiency is common in children, manifesting as short stature and developmental delay. Although AS and GH deficiency have been studied independently, no report has yet used recombinant human GH (rhGH) to treat GH deficiency in a patient with AS. We report the clinical manifestations, renal pathology, gene mutations, and treatment of a child with autosomal dominant AS (ADAS) caused by a novel mutation in the *COL4A4* gene, with a literature review. ADAS is uncommon; our report extends the ADAS mutational spectrum. Although there has been no report on AS combined with GH deficiency, clinicians should comprehensively assess and appropriately treat all suspected AS patients. We present this case in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-569/rc).

Highlight box

Key findings

- A young girl with Alport syndrome (AS) was diagnosed with a novel mutation in the *COL4A4* gene and a concurrent growth hormone (GH) deficiency. After treatment with recombinant human growth hormone, she experienced significant height increase without any adverse effects.

What is known and what is new?

- AS exerts pathological effects on the renal, auditory, and ocular systems.
- This report highlights the co-occurrence of AS and GH deficiency and introduces successful treatment insights, offering new therapeutic perspectives.

What is the implication, and what should change now?

- The study indicates that patients with AS who also suffer from GH deficiency can benefit from recombinant human growth hormone, improving their height without adversely affecting kidney function.

Case presentation

General information

The proband (III-2) girl was admitted to the Pediatrics Department of Wenzhou People's Hospital at the age of 4 years and 10 months because of 3-year growth retardation. The results of a urine test were abnormal. The patient was G2P2 (gravida 2, para 2) and had been delivered via cesarean section at term with a birth weight of 2,800 g and a length of 50 cm. There was no history of resuscitation because of asphyxia. The mother stated that all tests performed during pregnancy had been normal and denied any exposure to drugs or radioactive substances during pregnancy. The child had typical development, being able to lift her head at 3 months, roll over at 4 months, sit up at 6 months and walk independently at 1 year. The proband's sister (III-1) exhibited normal intellectual development. The parents of the affected child are not closely related. The first affected individual (II-2) and paternal grandmother (I-2) had a history of hematuria, under microscopy. The affected individual's sister (III-1), mother (II-3), and other family members showed no abnormal manifestations. Apart from the affected individual, all other members of the family had normal growth and development. The family pedigree is shown in *Figure 1*.

All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of Wenzhou People's Hospital (IRB No. KY-2023-236) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Physical examination revealed normal vital signs

At 5 years of age, the proband's height was 97.6 cm [–2.98 standard deviation (SD) from the mean], weight was 12.5 kg (–2.78 SD), body mass index was 13.12 kg/m^2, and growth rate was 4.8 cm/year. Examinations revealed microscopic hematuria without edema, oliguria, and high blood pressure. Kidney function was normal. On further enquiry regarding her medical history, the patient reported a history of tea-colored urine, for which she was not given any specific

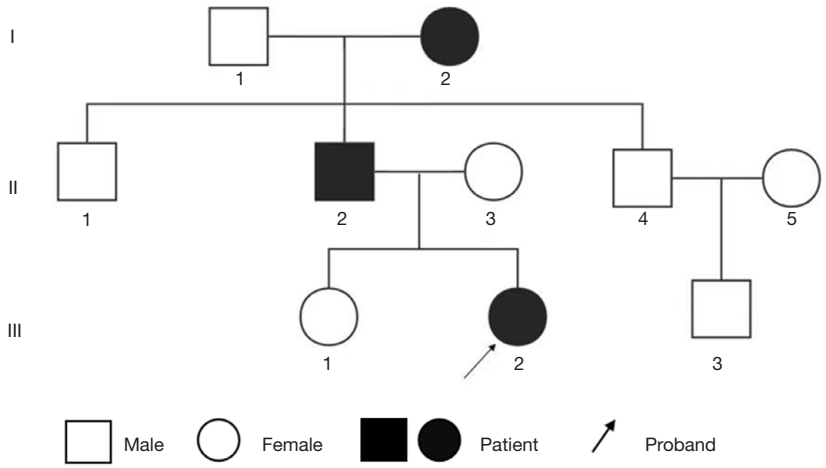

Figure 1 Family pedigree chart of the patient.

treatment. Her skin was normal; jaw arch was high; hairline was not low; both pupils were of equal size, rounded, and sensitive to light; there was no ptosis or epicanthus; vision was normal; the thyroid is not enlarged, and there is no pectus excavatum, pectus carinatum, or scaphoid chest; the chest was shield-shaped. Both breasts were at Tanner stage 1. Examination of the heart, lungs, and abdomen revealed no abnormalities. Muscle strength was normal, but with increased muscle tone. There was hyperreflexia in both knee reflexes, and bilateral Babinski sign. Pubic hair was at PH1 stage (Tanner stage 1, indicating no pubic hair development).

Laboratory tests

Routine urine-test results after admission were: urine protein (–), occult blood 4+, red blood cells 257.2/μL (reference 0–25.0/μL), 24-h urine protein 50 mg (reference 0–150 mg), and serum level of creatinine 24 μmol/L (reference 27–66 μmol/L); Antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-double-stranded DNA antibodies, erythrocyte sedimentation rate, and complement C3 and C4 levels were all within the normal range. Ophthalmological examination revealed no changes in the anterior cone lenses, no perimacular punctation, and no macular retinopathy. Hearing tests revealed no bilateral high-frequency SNHL. Ultrasound examination revealed no abnormalities of the kidneys, ureters, or bladder. Immunofluorescent staining of seven kidney glomeruli yielded: IgM (–), IgA (–), IgG (–), C3 (–), C1q (–), F (–), HBcAg (–), HBsAg (–), Kappa (–), and Lambda (–); the a3 glomerular and renal tubular basement membrane expression levels were normal; and the a5 glomerular basement membrane (GBM), Bowman capsule, and renal tubular basement membranes exhibited segmental weakening. In electron microscopy (EM), the basement membrane was thinned diffusely to <180 nm, the foot processes were segmentally fused, but no electron-dense deposits were noted. Hematoxylin and eosin (HE) staining, periodic acid-Schiff (PAS) staining, phosphotungstic acid-hematoxylin-Azan staining method (PASM), and Masson staining of 42 glomeruli revealed granular and vacuolar degeneration of the renal tubular epithelial cells, atrophy of individual renal tubules, mild renal interstitial edema, scattered inflammatory cell infiltration, and no obvious lesions on the arteriolar walls. There was no obvious proliferation of glomerular mesangial cells or the matrix. For pathological diagnosis, we considered thin basement membrane nephropathy but early AS was not excluded (*Figure 2*). The arginine/clonidine GH stimulation test yielded a peak GH value of 3.52 ng/mL. The insulin-like growth factor-1 (IGF-1) level was 54 ng/mL. Bone age was 3.5 years.

Gene tests

For mutational analysis, samples (2 mL) of peripheral blood were collected from the proband, her parents, sister, grandparents and uncles, and sent to Beijing Jinzhun Medical Laboratory for next-generation sequencing (NGS). The causative gene was identified and verified via Sanger sequencing. The proband exhibited a heterozygous frameshift mutation in *COL4A4*; the coding bases 2317–

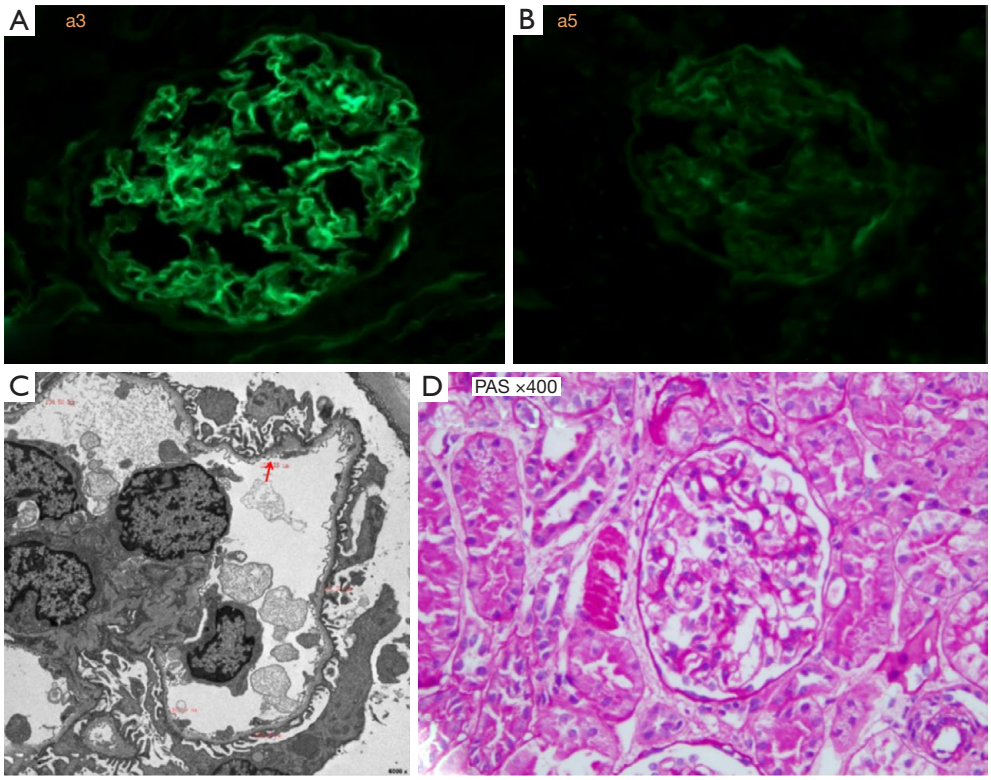

Figure 2 Renal pathology of the proband. (A) Immunofluorescence a3: ×400. Glomerular and renal tubular basement membrane expression levels were normal. (B) Immunofluorescence a5: ×400. Glomerular basement membrane, Bowman capsule, and renal tubular basement membranes exhibited segmental weakening. (C) EM: ×6,000. The red arrow indicates diffuse thinning of the basement membrane to <180 nm and segmental fusion of podocyte foot processes. (D) PAS staining: ×400. Shows mild glomerular lesions. EM, electron microscopy; PAS, periodic acid-Schiff.

2318 were deleted, resulting in a change of arginine 773 to glycine, followed by termination at 786 (*Figure 3*). The structures of the wild-type and mutant proteins differed [please see the UniProt database (4)]. The three-dimensional structure of the protein is shown in *Figure 4*. Compared to normal populations (dbSNP, 1,000 Genomes, ESP6500, EXAC), the mutation frequency at this site was low. A search of the Human Gene Mutation Database (HGMD) did not reveal anything of interest; the ClinVar database lacked any results of pathogenicity analysis. According to the guidelines of the American College of Medical Genetics and Genomics (ACMG) (5), the variant was "likely pathogenic (suspected pathogenic)". Further Sanger sequencing confirmed that the proband's father and grandmother had heterozygous mutations of c.2317_2318delAG in ch2:227924186, but no mutation was found in the other family members. The pedigree showed that the mutation came from the proband's grandmother.

Diagnosis

The proband met the diagnostic criteria for AS (6); the inheritance pattern was autosomal dominant and the genetic diagnosis was *COL4A4* heterozygous, consistent with ADAS. The final diagnosis was indeed ADAS. The patient's height was two SDs lower than that of children of the same race, sex, and age; the peak GH level after stimulation was <5 ng/mL, and the growth rate was <5 cm/year. According to the 2016 Diagnosis and Treatment Guidelines for Children with Short Stature (7), a GH deficiency was diagnosed.

Treatment and follow-up

The proband with AS (III-2) was initially scheduled for outpatient follow-up and did not receive any treatment. To treat the GH deficiency, polyethylene glycol-rhGH (PEG-rhGH) (Jintrolong, GeneScience Pharmaceuticals,

A

Gene	NM No.	Nucleotide alteration	Amino acid change	Variant type	Homozygous/ heterozygous	Source of variation	Genetic pattern	Clinical significance
COL4A4	NM 000092.4exon28	c.2317-2318delAG	p.R773Gfs*14	Deletion	Het	Father	AD	LP

B

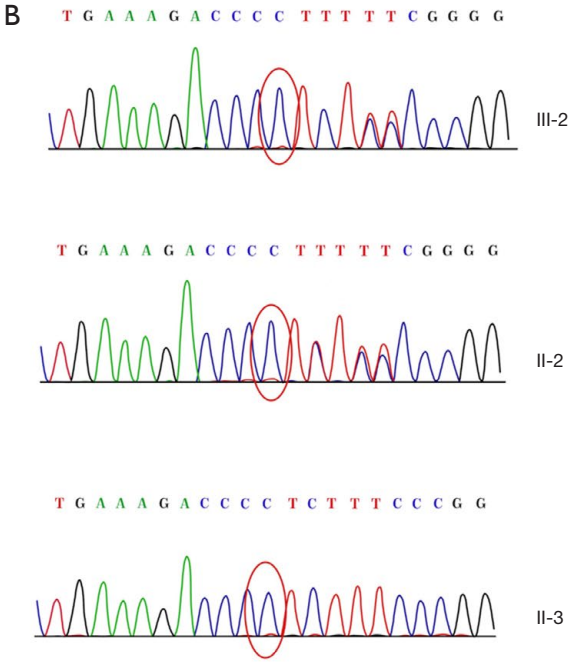

Figure 3 The heterozygous frameshift mutation in the *COL4A4* gene of the proband, leading to a change from arginine to glycine and a premature stop at position 786. (A) Mutational information. (B) *COL4A4* sequencing of the proband and the parents. NM, nuclear mRNA; Het, heterozygous; AD, autosomal dominant; LP, likely pathogenic.

Changchun, China) was commenced on July 29, 2022, after the parents had provided informed consent. However, in March 2023, her urinary protein status became weakly positive, with a total protein level of 250 mg/L, a urinary albumin level of 34.6 mg/L, and a urinary albumin/creatinine ratio (ACR) of 43.8 mg/g. In terms of renal function, the serum level of creatinine was 27 μmol/L. Thus, we commenced fosinopril sodium at 7.5 mg/day. In a re-examination on August 22, 2023, urine protein status was negative, the occult blood status was 3+, the red blood cell count was 281/μL, and the 24-h urine ACR was 30 mg/g. In terms of renal function, the serum level of creatinine was 32 μmol/L. Thus, fosinopril sodium was discontinued.

PEG-rhGH is a 40-kDa hydrophilic polyethylene glycol (PEG) residue coupled with rhGH; this extends the serum half-life of GH and reduces GH immunogenicity (8). We prescribed 0.2 mg/kg subcutaneously each week at bedtime. Initially, the patient's height was 112.1 cm and her weight was 15.3 kg [height standard deviation score (HtSDS) –2.91 SD]. The GH dose was adjusted as her weight changed and GH was continued for 1 year, with a review every 3 months. Fasting blood levels of insulin as well as her thyroid, liver, and kidney function became abnormal. At 1 year, her height was 120 cm, weight was 18.2 kg, and HtSDS was –2.4 SD. Her growth rate was 7.9 cm per year. The parents were satisfied and agreed to continue with PEG-rhGH.

The father (II-2) and grandmother (I-2) of the proband currently exhibit only microscopic hematuria, with no other abnormalities; they remain under follow-up.

Discussion

AS is a hereditary, phenotypically heterogeneous disease that principally affects the glomeruli, the inner ear (the

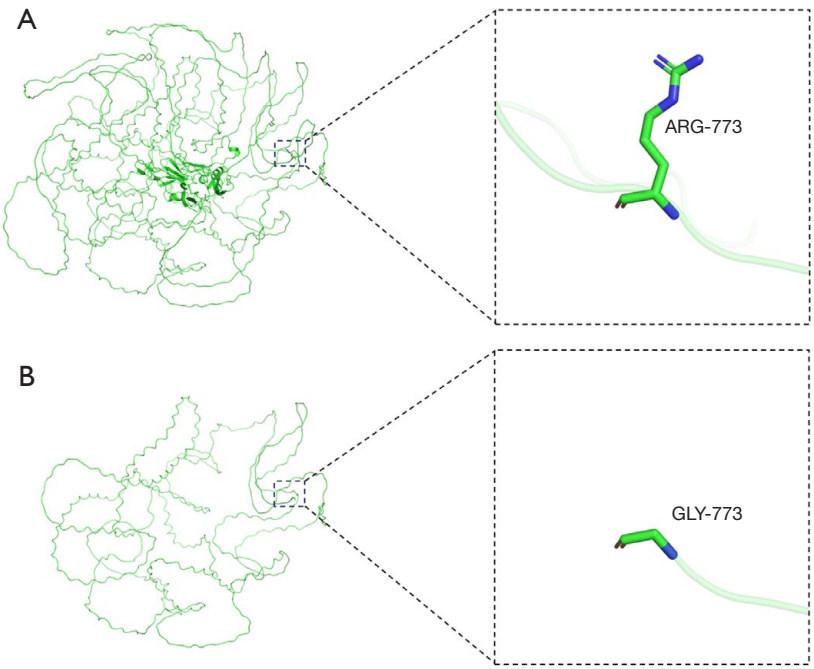

Figure 4 Three-dimensional structures of COL4A4 proteins. (A) Wild-type; (B) the mutant. As mutations that change amino acids 773 to 786 are not known. Only amino acid 773 is shown.

cochlea), and the basilar membrane of the eye; the incidence is approximately 1/10,000 to 1/5,000. The disease was first described by Arthur C. Alport in 1927. Also known as eye-ear-renal syndrome, AS is an inherited progressive nephritis caused by mutations in the *COL4A3*, *COL4A4*, or *COL4A5* genes that encode type IV collagen (7). There are primarily three genetic types: X-linked-dominant inheritance (XL), autosomal-recessive inheritance (AR), and autosomal-dominant inheritance (AD), as well as the recently proposed digenic AS (9-11). Variation in *COL4A5* (XL) due to deletions, duplications, substitutions, or splicing mutations are found in about 80% of AS patients. AR and AD *COL4A3* or *COL4A4* mutations (in chromosome 2) are less common. AS, with its various genetic modes of inheritance, exhibits heterogeneity in both genotype and phenotype (12). However, the vast majority of AS patients will progress to ESKD, making it one of the major genetic kidney diseases that lead to renal failure (9).

We report the clinical manifestations and mutation of a patient with ADAS caused by a *COL4A4* mutation, and an analysis of three family members. All exhibited microscopic hematuria. The father is currently 40 years of age and the grandmother is 70. However, they do not exhibit ESKD, eye damage, and any hearing abnormalities. The literature indicates that hematuria is the most common clinical manifestation of ADAS; all other manifestations are very variable. Proteinuria is the second-most common manifestation. The incidences of eye and hearing problems are low (12,13).

ADAS pathogenesis is attributable to mutation of *COL4A4* (NM_000092) on chromosome 2. The 48 exons encode the type IV collagen α4 chain (1,690 amino acids) (14). Type IV collagen is the principal structural component of the GBM and consists of six different α chains (α1 to α6), three of which combine to form a triple helix. The complete α chain includes a 7S amino-terminal region, an NC1 carboxy-terminal region, and a long collagen domain composed of approximately 1,400 Gly XY (X and Y are other amino acids) repeat units (15,16). The various α chains are expressed differently in various tissues; the glomerular basement, cochlear basement, and lens basement membranes principally feature the α3-α4-α5 triplet where the Bowman α5-α5-α6 triplet is mainly expressed in the basement membranes of cysts and skin (17,18). We found a *COL4A4* mutation that deletes bases 2317–2318, changing arginine 773 to glycine (thus p.R773Gfs*14), and triggering termination at position 786. This mutation changes the protein structure, compromising

formation of the α3-α4-α5 triple helices of the glomerulus, cochlea, and lens basement membranes. The mutation has not been reported previously; we thus expand the ADAS mutational spectrum. This will aid future clinical research.

The impact of heterozygous *COL4A4* mutations on renal function varies among individuals. Carriers may demonstrate compensatory mechanisms that partially alleviate the impact on renal function, particularly in the early stages of the disease, where a normal allele can produce sufficient functional collagen to temporarily maintain the integrity of the GBM. The progression to renal impairment in individuals carrying a heterozygous mutation may be slower or less severe; however, as time progresses and the cumulative damage surpasses the kidney's capacity for compensation, deterioration can occur, a process influenced by the patient's age (12).

The absence of AS symptoms in this child may be partly attributed to the patient's younger age. The severity and onset of AS symptoms exhibit considerable variability among individuals. In the early stages, younger patients may not display typical AS symptoms, attributable to slow disease progression, robust renal compensatory abilities, and individual variability in symptom presentation. This observation underscores the importance of early diagnosis and monitoring in younger patients to promptly identify and manage disease progression (19).

ADAS diagnosis is principally based on clinical manifestations, family history, EM of renal biopsy tissue, immunofluorescent staining of the basement membrane type IV collagen α chain, and genetic analysis. The criteria of the 2023 Expert Recommendations for the Diagnosis and Treatment of AS (6) are: (I) renal tissue EM reveals changes including splitting, layering, uneven thickness, or a lattice-like pattern in the GBM; (II) immunofluorescence staining of renal tissue shows abnormal expression of type IV collagen α3, α4, α5 chains in the GBM or abnormal expression of the type IV collagen α5 chain in the extraglomerular basement membrane (EBM); (III) genetic testing indicates pathogenic variants in the *COL4A3*, *COL4A4*, or *COL4A5* genes, including variants classified as possibly pathogenic according to ACMG criteria. Clinical presentation primarily includes persistent hematuria of glomerular origin or hematuria accompanied by proteinuria. A diagnosis of AS can be established if any of these criteria are met. In a pedigree with three affected individuals, all presenting with hematuria and meeting the diagnostic criteria for AS, genetic testing revealed a heterozygous mutation in *COL4A4*. Pedigree analysis is consistent with autosomal recessive inheritance, confirming the diagnosis of ADAS.

There is no cure or useful treatment for AS. The aim is to slow down disease progression via early drug treatment (20), thereby delaying ESKD development; when ESKD happens, renal replacement therapy is required (21). The current treatment methods include early renin-angiotensin-aldosterone system (RAAS) blockers to delay kidney disease progression followed by second-line angiotensin receptor blockers (ARBs) and aldosterone inhibitors (22,23). AS patients with only hematuria should not then be commenced on acetylcholine esterase inhibitor (ACEI) treatment, but the status of hematuria with microalbuminuria or proteinuria should be closely monitored. If repeated infections develop, RAAS blockers should commence when microalbuminuria recurs (urinary ACR >30 mg/g). Other AS/anti-inflammatory/anti-fibrosis drugs remain under development; some, such as bardoxolone methyl, are in phase III clinical trials (24). However, medical evidence of efficacy is lacking; there are no current recommendations. Our proband presented with hematuria and proteinuria once during follow-up. She received an ACEI for more than 5 months. She currently does not exhibit proteinuria, but long-term follow-up is still needed. The father and grandmother are scheduled for close follow-up in terms of the urinary ACR, the urinary protein level, and renal function. If albuminuria develops, RAAS blockers will be considered.

Our NGS analysis found no significant variants in GH1, GHRHR, or BTK related to the observed phenotype. Although we couldn't directly link the *COL4A4* mutation to GH deficiency, GH and IGF-1's impact on renal function highlights a promising area for further research in AS, potentially key to deciphering its disease mechanisms and formulating treatments.

The kidney is a target organ of both GH and IGF-1. Both materials regulate glomerular hemodynamics and the tubular processing of water, sodium, calcium, and phosphorus. GH increases the levels of mRNA encoding IGF-1 in the kidneys of hypophysectomized rats, and the IGF-1 levels in renal venous blood are higher than those in renal arterial blood (25), indicating that GH stimulates kidney IGF-1 expression. Long-term administration of recombinant human IGF-1 (rh-IGF-1) increases kidney size and improves the glomerular filtration rate (GFR) in hypophysectomized rats, implying that IGF-1 acts directly on the kidney to support glomerular function (26). However, some studies have found that excessive GH levels

trigger kidney hypertrophy. In mice overexpressing GH, the IGF-1 level increases, triggering kidney hypertrophy and (sometimes) glomerulosclerosis and renal failure (27,28). Mice overexpressing IGF-1 exhibit kidney enlargement but not glomerulosclerosis, implying that excessive GH and IGF-1 levels have different effects on the kidneys (26). In summary, appropriate GH prescription may enhance kidney function and delay ESKD progression. However, excess GH may accelerate kidney deterioration. Several long-term studies have found that the GH doses for children with GH deficiency recommended by the current guidelines are safe; kidney function is not affected (29,30).

Conclusions

In summary, this article reports a case of a child diagnosed with autosomal recessive AS with concomitant GH deficiency. Genetic testing revealed a novel heterozygous frameshift mutation, c.2317_2318delAG (p.R773Gfs*14). After receiving PEG-rhGH treatment for 1 year, the child's height increased from 112.1 to 120 cm, with a ΔHtSDS value of 0.51 SD. These observations demonstrate that PEG-rhGH can quickly improve the height of ADAS patients without causing kidney damage, increased intracranial pressure, or thyroid dysfunction. Further follow-up until adulthood will be required to establish the long-term impact on the final height in adulthood.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-569/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-569/coif). F.Z. reports that this work was supported by a grant from the Wenzhou Municipal Science and Technology Bureau project (No. Y2023002) and by a project from Wenzhou People's Hospital (No. 2021YB14). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of Wenzhou People's Hospital (IRB No. KY-2023-236) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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