

Clinical phenotype, family segregation, and follow-up of pediatric distal renal tubular acidosis associated with a homozygous SLC4A1 p.G701D variant

Qinying Feng

57105762@qq.com

Beijing Jishuitan Hospital Guizhou Hospital

Juan Lu

Beijing Jishuitan Hospital Guizhou Hospital

Wangming Zhang

Beijing Jishuitan Hospital Guizhou Hospital

Xinzhong Zhou

Beijing Jishuitan Hospital Guizhou Hospital

Xiaoyu Song

Beijing Jishuitan Hospital Guizhou Hospital

Anhua Mo

Beijing Jishuitan Hospital Guizhou Hospital

Xiaoying Li

Beijing Jishuitan Hospital Guizhou Hospital

Lianyang Lin

Beijing Jishuitan Hospital Guizhou Hospital

Li Liu

Nanming District Maternal and Child Health Care Hospital

Wanqing Xie

Beijing Jishuitan Hospital Guizhou Hospital

Yuxi Yang

Beijing Jishuitan Hospital Guizhou Hospital

Case Report

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Abstract

Background

We report a case of SLC4A1-related distal renal tubular acidosis (dRTA) in a child with marked skeletal deformities, confirmed by family segregation analysis, and describe the clinical features, genetic findings, and follow-up changes.

Methods

We retrospectively reviewed the clinical history, laboratory findings, imaging results, genetic testing data, family segregation results, treatment course, and follow-up findings of a child with recurrent hypokalemia, growth retardation, and bilateral lower-limb deformities. Relevant studies were also reviewed for comparison.

Results

The patient was a 5-year-old boy with recurrent hypokalemia and progressive bilateral lower-limb deformities. Laboratory tests showed persistent hypokalemia, hyperchloremic normal-anion-gap metabolic acidosis, impaired urinary acidification, and abnormalities of bone metabolism. Imaging demonstrated rickets-like changes in both lower limbs and renal medullary abnormalities. Trio whole-exome sequencing identified a homozygous SLC4A1 c.2102G > A (p.G701D) variant, which was classified as likely pathogenic according to ACMG criteria. Sanger sequencing showed that both parents were heterozygous carriers of the same variant, consistent with autosomal recessive inheritance. Based on the clinical and genetic findings, the patient was diagnosed with hereditary SLC4A1-related dRTA. Potassium supplementation and alkali therapy corrected the severe hypokalemia present at admission, and subsequent follow-up showed near-normal serum potassium levels. However, TCO₂ remained below the normal range and hyperchloremia persisted, whereas vitamin D and inorganic phosphate levels improved during follow-up.

Conclusions

This case supports the SLC4A1 p.G701D variant as the main pathogenic finding underlying dRTA in this child. In children presenting with orthopedic manifestations associated with hypokalemia, growth delay, and deformities, an underlying renal tubular disorder should be considered. Early evaluation of electrolytes, acid-base status, and genetic findings, together with family segregation analysis and longitudinal follow-up, may improve diagnostic accuracy and clinical management in hereditary dRTA.

Key learning points

What was known

SLC4A1 is a disease-causing gene for hereditary distal renal tubular acidosis.

Autosomal recessive SLC4A1-related dRTA is generally more severe than autosomal dominant disease.

Skeletal manifestations may obscure the underlying renal tubular disorder in affected children.

This study adds

This report identifies a homozygous SLC4A1 p.G701D variant in a Chinese child with dRTA.

Family segregation analysis confirmed heterozygous parental carriage, supporting autosomal recessive inheritance.

Longitudinal follow-up documented partial biochemical correction and improvement in growth parameters.

Potential impact

Children presenting initially to orthopedics with deformity and growth retardation should be screened for renal tubular disorders.

Early electrolyte, acid-base, and genetic evaluation may shorten diagnostic delay in hereditary dRTA.

Family validation and follow-up strengthen interpretation of rare pediatric dRTA-associated variants.

Introduction

Distal renal tubular acidosis (dRTA) is a group of metabolic disorders caused by impaired acid excretion in the distal nephron.^[1] Its general features include hyperchloremic normal anion-gap metabolic acidosis, as well as hypokalemia, nephrocalcinosis, kidney stones, growth retardation and bone metabolism disorders. Long-term undiagnosed dRTA in childhood often leads to rickets-like changes, bone pain, gait abnormalities and lower limb deformities due to chronic acidosis and disorders of bone mineralization, severely affecting growth and development and quality of life.^[1, 2]

The major disease-causing genes of hereditary dRTA include ATP6V1B1, ATP6V0A4 and SLC4A1. Among them, SLC4A1 encodes anion exchanger 1 (AE1/band 3), which is located on the basolateral membrane of type A intercalated cells in the collecting duct and mediates Cl⁻/HCO₃⁻ exchange to maintain distal urinary acidification.^[1, 3]

Pathogenic mutations in SLC4A1 can cause autosomal dominant or recessive dRTA, and certain red blood cell-related abnormalities may also occur. SLC4A1-related dRTA shows considerable phenotypic heterogeneity, and some children may present with bone system disorders first, which can be mistaken for nutritional rickets or other primary bone diseases.^[4, 5]

We present a child with recurrent hypokalemia, growth retardation and bilateral lower-limb deformities who was ultimately diagnosed with hereditary distal renal tubular acidosis caused by a homozygous SLC4A1 variant. In this report, we describe the clinical phenotype, genetic features and follow-up changes of this case in the context of the relevant literature, with the aim of improving early recognition and genetic diagnosis of pediatric dRTA.^[4, 5]

1. Case Information

1.1 General Information

The patient was a 5-year-old boy who was admitted because of recurrent hypokalemia and growth retardation for approximately 4 years, together with bilateral lower-limb deformities for more than 3 years. He had visited multiple hospitals because of hypokalemia, but the reason has not been found. He had previously received oral potassium supplementation, but treatment was not continued regularly, and no systematic blood gas monitoring or genetic evaluation had been performed. In the past three years, the deformities of both lower limbs have gradually worsened, and he walks abnormally. At admission, the main clinical considerations were renal hypokalemia and complex bilateral lower-limb deformities.

There was no known family history of a similar disorder. Subsequent genetic testing showed that both parents were heterozygous carriers of the SLC4A1 c.2102G > A locus, and the patient was homozygous for the variant; thus, it was determined to be an autosomal recessive inheritance.

1.2 Physical Examination

The patient had growth retardation, bilateral lower-limb deformities, abnormal gait, and rickets-like signs. At admission, his height was 89 cm and weight was 12.7 kg. Imaging and medical records indicated abnormal lower limb alignment, significant knee deformities, and abnormal thoracic appearance. The main course of the patient's illness is shown in Fig. 1.

2. Ancillary Tests

2.1 Electrolytes and Acid-Base Balance

During the hospitalization, the child had multiple re-examinations indicating persistent hypokalemia, with the lowest blood potassium level being approximately 2.2 mmol/L; TC02 was repeatedly below the normal range; and hyperchloremia was also present. Blood gas analysis showed a decreased pH, a significant reduction in HCO₃⁻, an increased negative BE, and a basically normal anion gap, consistent with hyperchloremic normal anion gap metabolic acidosis. Overall, these findings support metabolic acidosis caused by impaired distal urinary acidification.^[1]

2.2 Urine and Renal Tubule-Related Tests

Urinalysis showed abnormalities, including an elevated urine pH. Decreased urine osmolality suggested impaired concentrating function. Twenty-four-hour urine testing showed abnormalities in renal tubular-related parameters, which, together with chronic hypokalemia and acidosis, supported renal tubular dysfunction and renal electrolyte/acid-base imbalance.

2.3 Bone Metabolism-Related Tests

The child had insufficient vitamin D, and bone turnover markers such as β -CTX and P1NP were significantly elevated, indicating a high bone turnover state. In the context of chronic acidosis, these findings suggested increased skeletal buffering and impaired bone mineralization.^[2, 6]

2.4 Imaging Tests

X-rays of both lower extremities showed decreased bone density, sparse trabeculae, and abnormal metaphyses, consistent with rickets-like changes; there were obvious deformities in both lower extremities, consistent with the serial clinical photographs, suggesting persistence of the skeletal phenotype. Renal ultrasonography showed abnormal echoes in the medullary regions of both kidneys, suggesting medullary abnormality or sponge kidney-like changes and supporting chronic renal tubular disease.^[1] The imaging results are shown in Fig. 6, and the summary of main clinical and laboratory data is presented in Table 1.

Table 1
Summary of Major Clinical Findings and Laboratory Data

I.Basic Information and Major Clinical Manifestations					
Category	Item		Result		
Demographics	Proband		Male, 5 years old (at initial presentation)		
Chief complaints/ Clinical manifestations	Skeletal abnormalities		Bilateral knee valgus deformity,bilateralpes planus,changes in gait		
Clinical considerations	Renal involvement		Distal renal tubular acidosis(dRTA)with companion nephrocalcinosis		
II.Imaging Examinations					
Category	Item		Result		
Bilateral kneeX-ray	Radiographic findings		Bilaterallhipdysplasia;proximal tibial metaphyseal irregularity;lowbone density; suggests changes in rickets		
Urinary system ultrasound	Ultrasound findings		Bilateral renal parenchymal abnormalities, considering nephrocalcinosis;nonevident abnormalities of ureters,bladder,and anterior prostate		
III.Key Laboratory Results at Initial Presentation(2025-08)					
Category	Item		Result		
Blood gas analysis	pH		7.24↓		
Blood gas analysis	HCO3-(C)		12.0 mmol/L↓		
Blood gas analysis	K+		2.20 mmol/L↓		
Blood gas analysis	Cl-		113.0 mmol/L↑		
Blood gas analysis	Ionized calcium (Ca ⁺⁺)		1.01 mmol/L ↓		
Blood gas analysis	Lactic acid		1.50mmol/L↑		
IV.Follow-up Biochemical Results					
Parameter	2025/9/3	2025/10/13	2025/11/14	2025/12/15	Reference Range
K+(mmol/L)	3.36	3.32	3.71	2.98	3.7–5.2
Cl-(mmol/L)	116.3	116.2	114.1	115.3	98–110
Ca (mmol/L)	2.14	2.12	2.13	2.03	2.1–2.8
Inorganic phosphate (mmol/L)	1.2	1.75	1.78	1.48	1.25–1.93
TCO2(mmol/L)*	15.2	14.8	19.9	14.2	20.0–31.0
25(OH)D (ng/mL)	18.71	—	—	—	30–100
V.Genetic Study Results					
Category	Item		Result		
Whole-exome sequencing (WES)	Pathogenic variant		SLC4A1 gene:c.2102G > A (p.Gly701Asp,p.G701D)		
Sanger validation	Parental testingresults		Probandis a compound heterozygote;bothparents are heterozygous carriers		
Geneticinterpretation	Inheritancepattern		Consistentwithautosomalrecessiveinheritance		
Notes:1)The key laboratory results at initial presentation are based on the blood gas analysis performed on 2025-08-08.					
2)Follow-up results are summarized from subsequent outpatient visits.					
3)TCO2 reflects acid-base status during the follow-up period.					

3. Genetic Testing Results

3.1 Whole Exome Sequencing Results

The patient underwent trio whole exome sequencing. The results showed a homozygous SLC4A1 c.2102G > A (p.G701D) variant, which was classified as likely pathogenic in the report. This variant has been associated with distal renal tubular acidosis, with or without hematologic manifestations, in previous reports.^[1, 3, 4, 7, 8] The report also clearly stated that the clinical phenotype was consistent with the patient's "renal calcification, renal tubular acidosis, rickets, and abnormal lower limb bone development".

The report also indicated that family analysis showed that both parents had a heterozygous variant c.2102G > A in the SLC4A1 gene. Family data are shown in Fig. 2.

3.2 Sanger Sequencing Verification

Sanger sequencing further confirmed that the proband was homozygous for the variant and that both parents were heterozygous carriers (Fig. 3). Proband: SLC4A1 c.2102G > A homozygous; Mother: SLC4A1 c.2102G > A heterozygous; Father: SLC4A1 c.2102G > A heterozygous. These findings supported autosomal recessive segregation of the variant in this family and provided strong evidence for the molecular diagnosis of this case.

3.3 Genetic Interpretation

SLC4A1 encodes the AE1 protein, which is located on the basolateral membrane of type A intercalated cells in the collecting duct and mediates Cl⁻/HCO₃⁻ exchange. [1, 3] Impaired AE1 function can reduce distal urinary acidification and lead to chronic metabolic acidosis and hypokalemia. [1, 3] The p.G701D variant identified in this patient has been reported previously and is one of the significant hotspot mutations associated with SLC4A1-related dRTA. Based on the combination of phenotypic, biochemical and family-verification results for this case, it is believed that this site is the main pathogenic variant in this case.

4. Diagnosis and Treatment

4.1 Hospitalization Treatment Process

Based on recurrent hypokalemia, hyperchloremic normal-anion-gap metabolic acidosis, impaired urinary acidification, renal medullary abnormalities, bone metabolism disorder, rickets-like skeletal changes, and a homozygous SLC4A1 variant, the final diagnosis was as follows:

4.1.1 Hereditary distal renal tubular acidosis associated with SLC4A1

4.1.2 Hypokalemia

4.1.3 Rickets-like bone changes/metabolic bone disease

4.1.4 Bilateral lower-limb deformities

4.1.5 Growth delay

During hospitalization, the child received potassium supplementation, alkali therapy, and supportive treatment. After discharge, he continued oral potassium citrate and alkali therapy, with regular follow-up of electrolytes, acid-base status, bone metabolism indices, and imaging findings. Laboratory indicators at the end of hospitalization improved compared to those at admission, suggesting effective treatment.

4.2 Outpatient Follow-up Results

After discharge, the child was followed up at the outpatient clinic from September 2025 to April 2026. The results showed that serum potassium improved overall but fluctuated, chloride remained persistently elevated, TCO₂ remained below the normal range but improved, inorganic phosphate and vitamin D recovered, and renal function remained stable. During the same period, growth indicators showed that the child's height increased from 89 cm in August 2025 to 101 cm in April 2026, and weight increased from 12.7 kg to 19.0 kg, suggesting that the overall growth status improved during the treatment and follow-up process. The main biochemical follow-up results are shown in Table 2, growth and development indicators are shown in Table 3, dynamic changes of key biochemical indicators are shown in Fig. 4, and the follow-up results of the child's appearance are shown in Fig. 5.^[9]

Table 2
Biochemical parameters during hospitalization and follow-up

Time	Age	K (mmol/L)	Cl (mmol/L)	TCO2 (mmol/L)	AG (mmol/L)	Ca (mmol/L)	IP (mmol/L)	Mg (mmol/L)	Cr (μmol/L)	Vitamin D (ng/mL)	PTH (pg/mL)	Cir
Hospitalization period (multiple test ranges)	5y	2.20–3.39	113.0–117.9	12.9–16.8	6.7–13.0	2.10–2.12	0.83–0.93	0.91–1.04	27–61	19.84	17.1	Sch a a w h n g a a b p a vi
2025/9/3	5y	3.36↓	116.3↑	15.2↓	8.5	2.14	1.20↓	1.09↑	—	18.71↓	—	A d t l c h a a vi d
2025/10/13	6y	3.32↓	116.2↑	14.8↓	9.1	2.12	1.75	0.98	38	—	—	L a p ir p re n
2025/11/14	6y	3.71	114.1↑	19.9↓	6.8↓	2.13	1.78	0.92	—	—	—	T p le ir th o re h a s
2025/12/15	6y	2.98↓↓	115.3↑	14.2↓	8.3	2.03↓	1.48	1.05↑	61	—	—	A fl e a b ir th re d p
2026/1/26	6y4mo	3.58↓	111.1↑	18.5↓	11.38	2.25	1.87	0.97	—	—	—	It ir c b n re n
2026/3/9	6y5mo	3.58↓	110.4↑	18.9↓	13.88	2.33	2.03↑	0.96	27	56.66	8.00↓	V re n ir p s ir b p h

Abbreviations: K, serum potassium; Cl, serum chloride; TCO2, total carbon dioxide; AG, anion gap; Ca, serum calcium; IP, inorganic phosphate; Mg, serum magnesium; Cr, serum creatinine; Vitamin D, 25-hydroxyvitamin D; PTH, parathyroid hormone. Values during hospitalization are shown as ranges derived from multiple measurements. Arrows indicate values outside the reference range. Early follow-up in September 2025 still showed hypokalemia, hyperchloremia, low TCO2, and vitamin D deficiency. Follow-up from October 2025 to April 2026 demonstrated partial improvement of hypokalemia and hyperchloremic metabolic acidosis, with gradual recovery of inorganic phosphate and vitamin D levels.

Time	Age	K (mmol/L)	Cl (mmol/L)	TCO2 (mmol/L)	AG (mmol/L)	Ca (mmol/L)	IP (mmol/L)	Mg (mmol/L)	Cr (μmol/L)	Vitamin D (ng/mL)	PTH (pg/mL)	C ir
2026/4/13	6y7mo	3.52↓	112.4↑	19.9↓	11.42	2.31	1.73	0.91	32	—	—	O tr ir th b c r e c a d c p

Abbreviations: K, serum potassium; Cl, serum chloride; TCO2, total carbon dioxide; AG, anion gap; Ca, serum calcium; IP, inorganic phosphate; Mg, serum magnesium; Cr, serum creatinine; Vitamin D, 25-hydroxyvitamin D; PTH, parathyroid hormone. Values during hospitalization are shown as ranges derived from multiple measurements. Arrows indicate values outside the reference range. Early follow-up in September 2025 still showed hypokalemia, hyperchloremia, low TCO2, and vitamin D deficiency. Follow-up from October 2025 to April 2026 demonstrated partial improvement of hypokalemia and hyperchloremic metabolic acidosis, with gradual recovery of phosphate and vitamin D levels.

Table 3

Growth parameters during follow-up

Time	Height(cm)	Weight(kg)
2025/8/7	89	12.7
2025/9/7	91	14
2025/10/11	92	14.6
2025/11/11	93	15.8
2025/12/14	95	16.5
2026/3/5	100	18.8
2026/4/21	101	19.0
Height and weight measurements were recorded longitudinally during follow-up to assess growth recovery after treatment.		

5. Discussion

5.1 This case is consistent with the diagnostic features of hereditary dRTA

The key pathophysiological abnormality in dRTA is impaired acid excretion in the distal nephron, resulting in reduced urinary acidification. The typical biochemical features include hyperchloremic normal anion gap metabolic acidosis, often accompanied by hypokalemia. In this case, the child experienced recurrent hypokalemia, hyperchloremia, blood gas analysis indicating decreased HCO3⁻ and decreased pH, and no significant increase in anion gap, which are consistent with the classic biochemical manifestations of dRTA. Combined with elevated urine pH, decreased urine concentrating function, and abnormal renal imaging, it supports the dysfunction of the distal renal tubules.^[1, 10]

5.2 Chronic acidosis is an important pathological basis for skeletal manifestations

A notable feature of this case was the prominent orthopedic presentation at onset. The child visited due to bilateral lower limb deformities, abnormal gait, growth retardation, and rickets, and the bone damage was actually secondary to long-term chronic acidosis. During chronic acidosis, bone tissue, as an important buffering system, releases calcium salts and phosphates to participate in acid-base balance, and over time can lead to bone mineralization disorders, abnormal bone turnover, and rickets-like manifestations. The abnormal elevation of bone metabolism indicators, imaging showing decreased bone density and abnormal metaphyseal regions, all support the diagnosis of metabolic bone disease secondary to chronic acidosis.^[6]

Therefore, for children with main manifestations such as lower limb deformities, rickets-like changes, or growth retardation, clinical practice should not merely stop at the diagnosis of "nutritional rickets" or "orthopedic deformities", but should further assess electrolytes, blood gases, urine acidification function, and renal conditions to avoid missing potential renal tubular diseases.^[2]

5.3 SLC4A1-related dRTA has a clear molecular basis

SLC4A1 is one of the important pathogenic genes for hereditary dRTA.^[1, 4] The encoded AE1 protein is expressed on the erythrocyte membrane and in the type A intercalated cells of the renal collecting ducts. When the function of AE1 in the kidneys is impaired, it can affect the basal lateral Cl⁻/HCO3⁻ exchange, leading to distal acid secretion disorder, and subsequently causing chronic metabolic acidosis and hypokalemia. Different SLC4A1 variants may lead to autosomal dominant or autosomal recessive inheritance patterns and may be accompanied by varying degrees of renal and hematologic manifestations.^[1, 3]

The p.G701D variant identified in this case has been reported previously, and the proband in the family is homozygous, while the parents are heterozygous, with a clear segregation pattern;the Sanger sequencing results further strengthen the genetic evidence. Compared with some literature reports of SLC4A1-related cases, this case does not show obvious hemolytic anemia manifestations, suggesting that even in the same gene or even similar variant background, the clinical phenotype still has certain heterogeneity. The possible mechanism diagram is shown in Fig. 7.^[4, 5]

5.4 The clinical value of this case lies in "orthopedic onset + genetic confirmation"

The clinical value of this case lies not simply in identifying a rare variant, but in establishing a relatively complete chain of evidence from orthopedic presentation to biochemical abnormalities, genetic confirmation, and follow-up verification. Therefore, this case has strong clinical implications for pediatrics, orthopedics, nephrology and genetic counseling. In addition, compared with previous reports, this case further supplements the family segregation evidence and longitudinal follow-up data of the SLC4A1 p.G701D homozygous variant-related dRTA in the Chinese pediatric background, and again suggests that AR-type cases usually have earlier onset and more obvious bone phenotypes. The comparison of reported SLC4A1-related pediatric dRTA cases with this case is shown in Table 4.^[4, 5, 11, 12]

Table 4
Comparison of previously reported pediatric SLC4A1-related dRTA cases and the present case

Literature	Region / study type	Case details	SLC4A1 variant / inheritance	Main clinical manifestations	Skeletal manifestations	Renal / hematologic manifestations	Similarities and differences compared with the present case
Khositseth et al., 2007	Thailand; pediatric case series	17 pediatric dRTA cases, including 12 with AE1/SLC4A1 variants	Included G701D and related AE1 variants; mainly autosomal recessive	Growth retardation, muscle weakness, hypokalemic hyperchloremic metabolic acidosis	Some patients had rickets-like changes	Nephrocalcinosis was reported; some patients had compensatory hemolysis, and a few had severe hemolysis	Similar to the present case in childhood onset, acidosis, and hypokalemia; different in that skeletal deformity was more prominent in the present case, and no clear severe hematologic abnormality has been observed so far
Anacleto et al., 2010	Philippines; pediatric family study	Seven families with pediatric dRTA	Autosomal recessive dRTA in Filipino children was frequently caused by SLC4A1 variants, and G701D was common	Childhood onset with typical dRTA manifestations	Often accompanied by growth retardation and abnormal bone metabolism	Homozygous G701D may be associated with abnormal red blood cell morphology	Highly similar to the present case, particularly in the childhood, autosomal recessive, G701D-related molecular background; the present case further adds complete family segregation and follow-up data
Park et al., 2018	Laos; case report	Two families with three patients with autosomal recessive dRTA	SLC4A1-related autosomal recessive dRTA	Failure to thrive, metabolic acidosis, hypokalemia	Marked rickets-like manifestations	Renal involvement was reported	Similar in childhood onset and prominent skeletal disease; the present case adds more complete family segregation analysis and more continuous follow-up data
Guerra Hernández et al., 2023	Mexico; two pediatric cases	Two pediatric patients	Heterozygous SLC4A1 variants; autosomal dominant	Relatively mild manifestations and later diagnosis	Skeletal involvement was relatively mild	Main presentation was dRTA, and maximal urine pCO ₂ testing could be normal	In contrast to the present case, this patient had a homozygous/autosomal recessive pattern with a more severe phenotype and more prominent skeletal manifestations, suggesting that autosomal recessive SLC4A1-dRTA is often more severe than autosomal dominant disease
Yang et al., 2023	Literature review / systematic analysis	Published SLC4A1-dRTA patients	Summarized autosomal dominant and autosomal recessive patterns	Autosomal recessive cases usually had earlier onset and more severe manifestations	Autosomal recessive cases were more likely to have growth retardation and bone disease	Overall phenotype was more severe in autosomal recessive than in autosomal dominant cases	The present case is consistent with the typical features summarized in that review, namely autosomal recessive inheritance, early onset, and obvious skeletal disease, and also includes complete family segregation and follow-up data
Present case	China; single-family case	5-year-old boy	SLC4A1 c.2102G > A (p.G701D) homozygous variant; both parents heterozygous carriers	Hyperchloremic metabolic acidosis, hypokalemia, clinically diagnosed dRTA	Marked bilateral lower-limb deformities and obvious rickets-like skeletal changes	Abnormal renal ultrasonography; family Sanger sequencing completed; no evidence of severe hematologic	Represents a typical pediatric autosomal recessive SLC4A1-related dRTA case and adds evidence for the p.G701D variant in a Chinese patient, together with

AR, autosomal recessive; AD, autosomal dominant; dRTA, distal renal tubular acidosis. The present case is compared with representative previously reported pediatric SLC4A1-related dRTA cases in terms of genotype, inheritance pattern, clinical manifestations, skeletal phenotype, and follow-up characteristics.

Major clinical events from initial presentation to diagnosis, treatment, and follow-up are summarized chronologically.

The proband carried a homozygous SLC4A1 c.2102G > A (p.G701D) variant, whereas both parents were heterozygous carriers, consistent with autosomal recessive inheritance.

Sanger sequencing confirmed the homozygous SLC4A1 c.2102G > A (p.G701D) variant in the proband and heterozygous carriage in both parents.

(A) Serum potassium (K⁺); (B) serum chloride (Cl⁻); and (C) total carbon dioxide (TCO₂). At the early stage of hospitalization, the patient showed marked hypokalemia, hyperchloremia, and low TCO₂, consistent with hyperchloremic metabolic acidosis. After potassium supplementation, citrate-based alkali therapy, and supportive treatment, serum potassium and TCO₂ generally increased, whereas chloride gradually decreased, indicating partial correction of hypokalemia and hyperchloremic metabolic acidosis, although mild residual abnormalities persisted during follow-up.

(A) Radiographs of the lower limbs showed decreased bone density, sparse trabeculae, and metaphyseal abnormalities consistent with rickets-like changes.

Literature	Region / study type	Case details	SLC4A1 variant / inheritance	Main clinical manifestations	Skeletal manifestations	Renal / hematologic manifestations	Similarities and differences compared with the present case
						abnormality at present	relatively complete family and follow-up data
AR, autosomal recessive; AD, autosomal dominant; dRTA, distal renal tubular acidosis. The present case is compared with representative previously reported pediatric SLC4A1-related dRTA cases in terms of genotype, inheritance pattern, clinical manifestations, skeletal phenotype, and follow-up characteristics.							
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(A) Radiographs of the lower limbs showed decreased bone density, sparse trabeculae, and metaphyseal abnormalities consistent with rickets-like changes.							

5.5 Relationship with other candidate variants

In the supplementary testing of other extended families, a heterozygous NHERF1 variant of uncertain significance of the NHERF1 gene was found, but the segregation pattern of this variation in the corresponding family was not clear, and currently there is a lack of sufficient literature and functional evidence to support it as a clear pathogenic variant; at the same time, the extended family and the main child of this case in SLC4A1 did not have the same pathogenic main line. Therefore, currently it is not sufficient to consider that this NHERF1 variation is the core explanatory factor for the main disease phenotype of this case. This article does not discuss it as the main pathogenic clue.

5.6 Limitations

This study is a single case report and still has certain limitations:

- (1) The current follow-up period is still limited, and there is a lack of long-term observation of skeletal deformities and growth outcomes;
- (2) No functional experiments at the cellular or protein level were conducted, and it is still impossible to directly verify the impact of the p.G701D site on the localization or function of the AE1 protein;
- (3) Although no obvious hematological abnormalities were observed in this case, the SLC4A1-related red blood cell phenotype still deserves long-term attention.

6. Conclusion

In this case, the child presented with recurrent hypokalemia, growth retardation, and bilateral lower limb deformities. Through comprehensive analysis of biochemistry, imaging, and genetics, it was ultimately diagnosed as hereditary distal renal tubular acidosis caused by a homozygous mutation in the SLC4A1 gene. This case suggests that rickets-like manifestations and lower-limb deformities in children may mask underlying metabolic disorders such as renal tubular acidification defects. For children with clinical manifestations of unexplained hypokalemia, growth retardation, bone deformities, or refractory rickets, early assessment of acid-base balance, urine acidification function, and genetics should be conducted to improve the early diagnosis rate and prognosis.

Abbreviations

dRTA, distal renal tubular acidosis; WES, whole-exome sequencing; AE1, anion exchanger 1; TCO₂, total carbon dioxide; AG, anion gap; PTH, parathyroid hormone.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Beijing Jishuitan Hospital Guizhou Branch (approval number: KT2025051610) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent to participate in this study was obtained from the patient's legal guardian.

Consent for publication

Written informed consent for publication of the patient's clinical data and images was obtained from the patient's legal guardian.

Availability of data and materials

The whole-exome sequencing data generated in this study are publicly available in the NCBI Sequence Read Archive (SRA) under accession number SRR38892179, within BioProject PRJNA1472244 and BioSample SAMN60483649. The public dataset can be accessed through the NCBI SRA database. Other clinical data supporting this case are included in this published article and its supplementary information files or are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FQY conceived and designed the study, interpreted the data, and drafted the manuscript. LJ, ZWM, and MAH collected the clinical and follow-up data. LXY, ZXZ, and SXY contributed to clinical evaluation, laboratory interpretation, and literature review. LLY, XWQ, LL, and YYX assisted with data organization, figure and table preparation, and manuscript revision. All authors read and approved the final manuscript.

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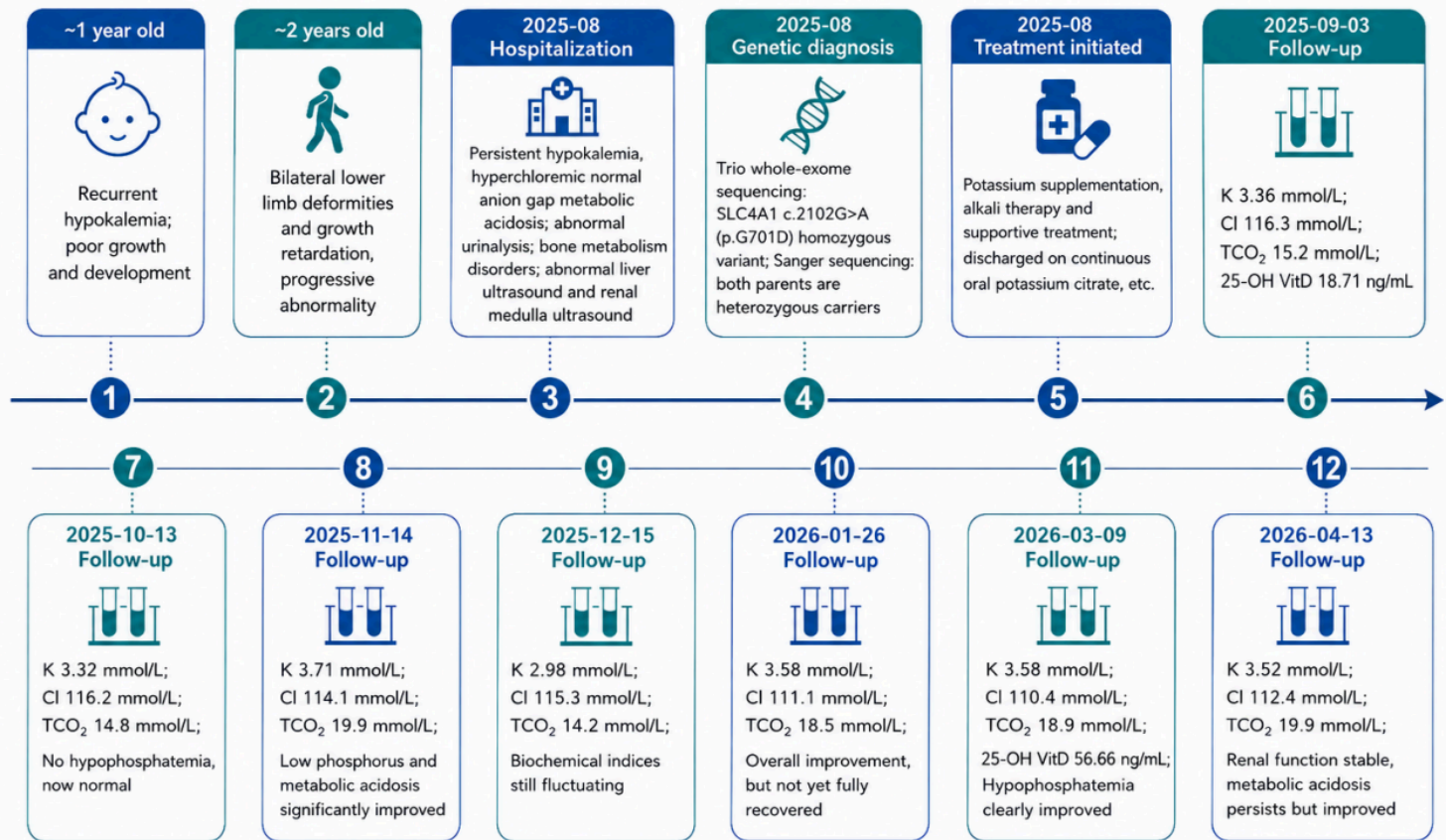
Not applicable.

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Figures

A case of distal renal tubular acidosis associated with a homozygous *SLC4A1* p.G701D variant in a child



Note: K, potassium; Cl, chloride; TCO₂, total carbon dioxide; 25-OH VitD, 25-hydroxyvitamin D.

Figure 1

Clinical timeline of the patient.

Major clinical events from initial presentation to diagnosis, treatment, and follow-up are summarized chronologically.

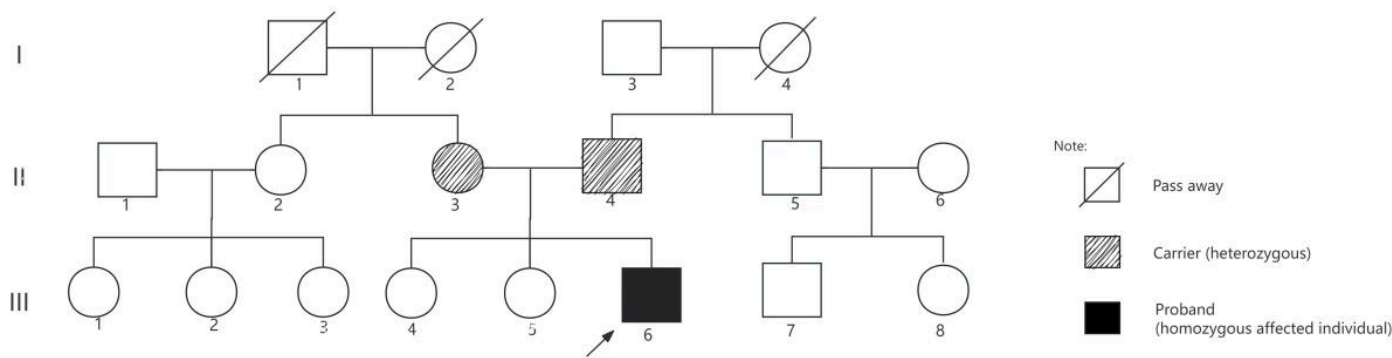


Figure 2

Pedigree of the family.

The proband carried a homozygous *SLC4A1* c.2102G>A (p.G701D) variant, whereas both parents were heterozygous carriers, consistent with autosomal recessive inheritance.

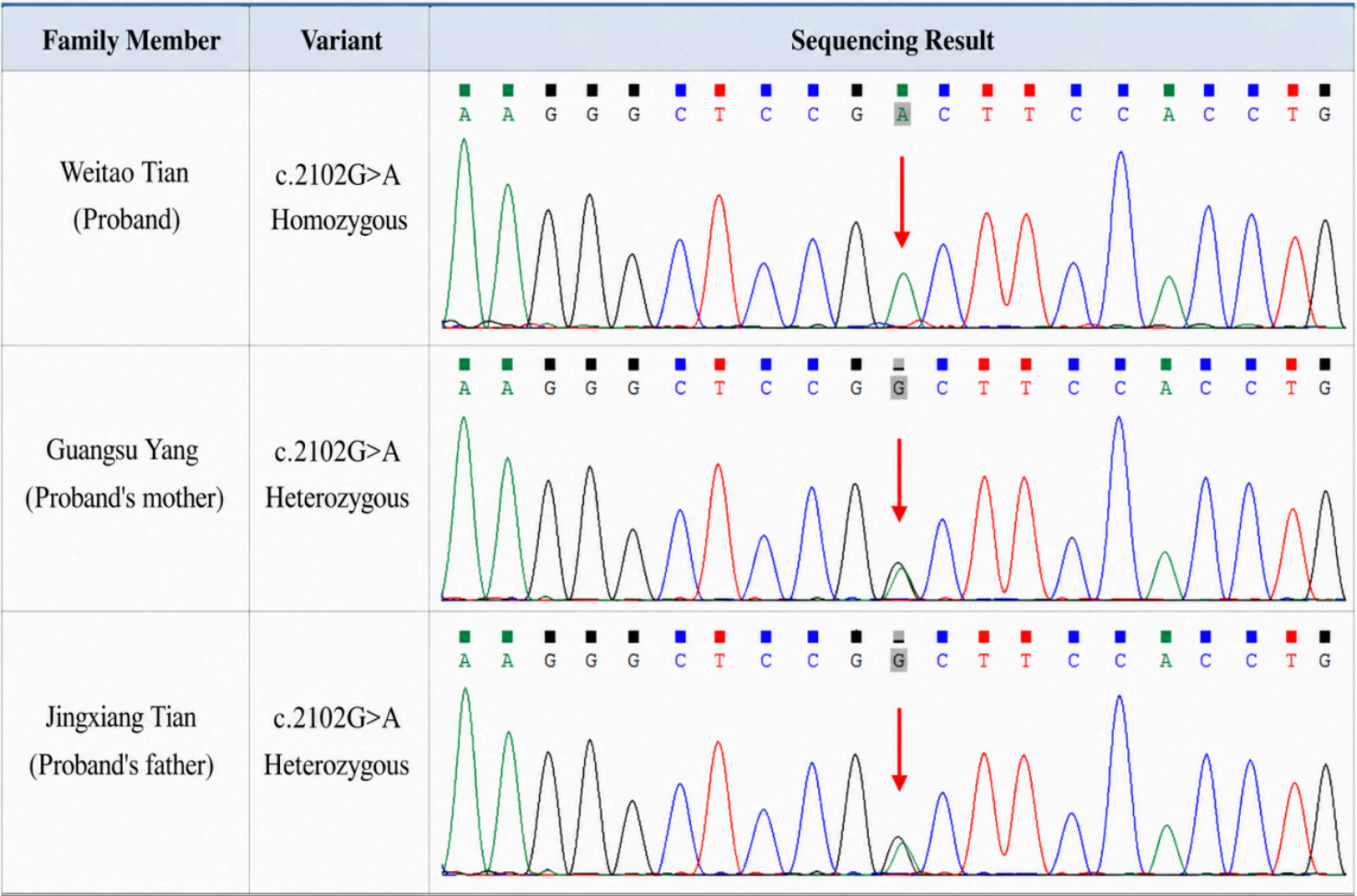


Figure 3

Sanger sequencing chromatograms.

Sanger sequencing confirmed the homozygous SLC4A1 c.2102G>A (p.G701D) variant in the proband and heterozygous carriage in both parents.

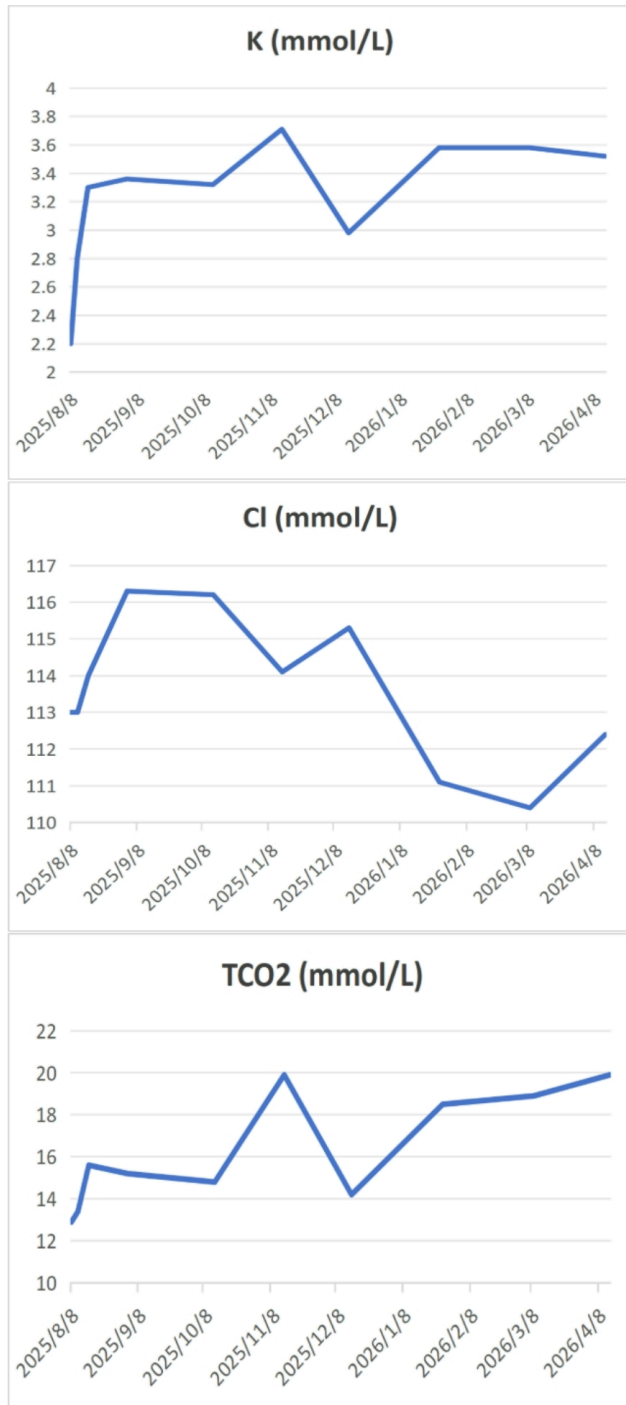


Figure 4

Dynamic changes in serum potassium, chloride, and total carbon dioxide during treatment and follow-up.

(A) Serum potassium (K⁺); (B) serum chloride (Cl⁻); and (C) total carbon dioxide (TCO₂). At the early stage of hospitalization, the patient showed marked hypokalemia, hyperchloremia, and low TCO₂, consistent with hyperchloremic metabolic acidosis. After potassium supplementation, citrate-based alkali therapy, and supportive treatment, serum potassium and TCO₂ generally increased, whereas chloride gradually decreased, indicating partial correction of hypokalemia and hyperchloremic metabolic acidosis, although mild residual abnormalities persisted during follow-up.



Serial clinical photographs demonstrate the evolution of bilateral lower-limb deformity during treatment and follow-up.

(A) 2025/8/6; (B) 2025/10/12; (C) 2025/11/12; (D) 2026/3/5; (E) 2026/4/21.

Figure 5

Serial photographs of lower-limb deformity during follow-up.

Serial clinical photographs demonstrate the evolution of bilateral lower-limb deformity during treatment and follow-up.

(A) 2025/8/6; (B) 2025/10/12; (C) 2025/11/12; (D) 2026/3/5; (E) 2026/4/21.

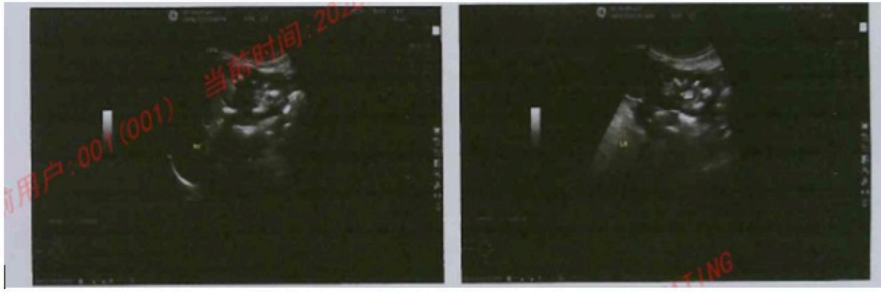


Figure 6

Radiographic and renal ultrasound findings.

(A) Radiographs of the lower limbs showed decreased bone density, sparse trabeculae, and metaphyseal abnormalities consistent with rickets-like changes.

(B) Renal ultrasonography showed abnormal echoes in the medullary regions of both kidneys, suggesting medullary abnormality or sponge kidney-like changes.

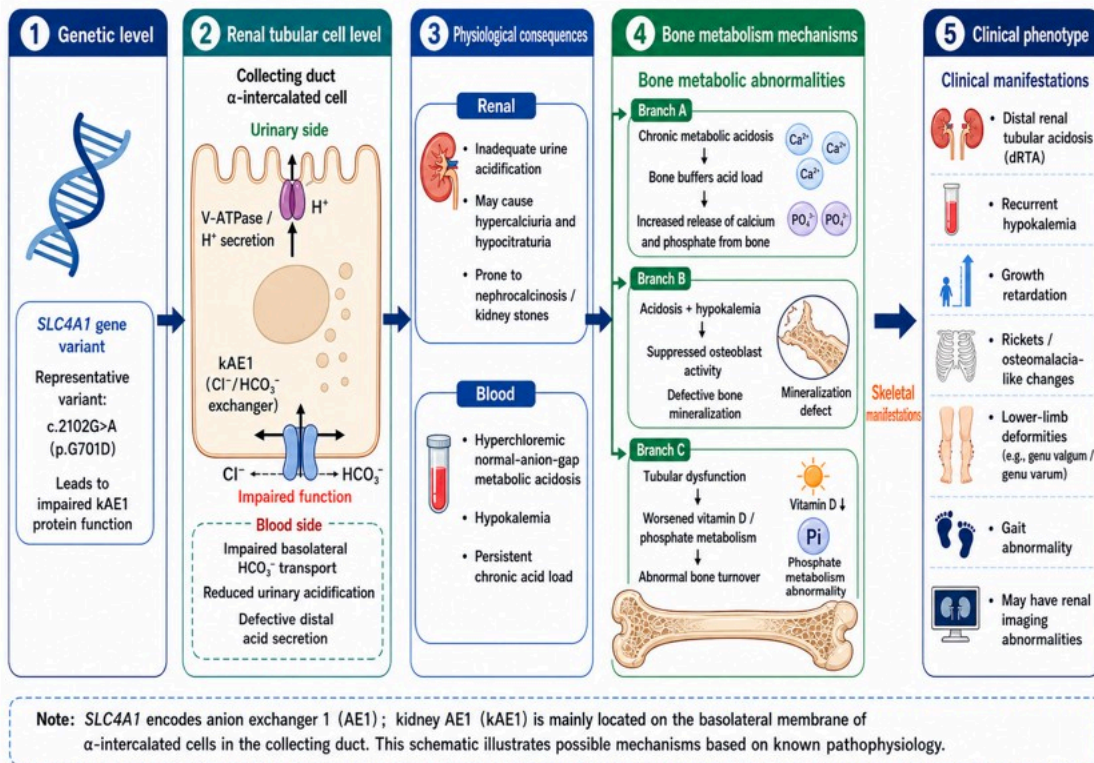


Figure 7

Proposed mechanism by which the SLC4A1 variant leads to dRTA and skeletal manifestations.

The SLC4A1 p.G701D variant may impair AE1-mediated basolateral Cl⁻/HCO₃⁻ exchange in type A intercalated cells, resulting in defective distal urinary acidification, chronic metabolic acidosis, hypokalemia, and secondary skeletal abnormalities, including impaired mineralization and rickets-like deformities.