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Case Report

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Phenotypic-Genotypic Discordance in Renal Tubular Acidosis with Hypokalemic Rhabdomyolysis and a TRAPPC2 Variant: A Case Report

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Abstract

Background

Renal tubular acidosis (RTA) encompasses disorders of renal acid–base regulation that may cause hypokalemia, metabolic bone disease, and growth retardation. Distal RTA (dRTA) is characterized by hyperchloremic, normal-anion-gap metabolic acidosis with urine pH >5.5. Distinguishing proximal from distal RTA is challenging when clinical, biochemical, and genetic findings are discordant. Hypokalemia-induced rhabdomyolysis is uncommon, and the coexistence of RTA with spondyloepiphyseal dysplasia tarda (SEDT) remains poorly characterized.

Case presentation

A normotensive man in his early twenties presented with an eight-year history of recurrent hypokalemic flaccid quadriparesis, myalgia, polyuria, short stature, severe back pain, and impaired mobility. During an acute episode, serum potassium was 1.7 mmol/L and creatine phosphokinase (CPK) was 17,384 U/L, suggesting hypokalemia-induced rhabdomyolysis. Subsequent investigations demonstrated hyperchloremic normal-anion-gap metabolic acidosis, urine pH >5.5, a positive urinary anion gap, hypercalciuria, hypophosphatemia, hypouricemia, and bilateral medullary nephrocalcinosis, supporting a distal RTA phenotype. Imaging revealed osteomalacia, pseudofractures, kyphosis, and bilateral sacroiliitis; dual-energy X-ray absorptiometry (DEXA) scan showed severe osteoporosis. Back pain and sacroiliitis initially suggested seronegative spondyloarthropathy (SSpA), but normal inflammatory markers, negative HLA-B27, and lack of response to immunomodulatory therapy prompted diagnostic reconsideration. Whole-exome sequencing identified heterozygous GATM c.181C>G (p.Pro61Ala) and hemizygous TRAPPC2 c.176T>C (p.Met59Thr) variants of uncertain significance. The GATM variant is associated with Fanconi renotubular syndrome type 1, despite the predominantly distal RTA phenotype. Maternal Sanger sequencing confirmed heterozygosity for the TRAPPC2 variant. Disproportionate short

stature and skeletal abnormalities raised suspicion of coexisting X-linked SEDT. Treatment with potassium citrate, sodium bicarbonate, calcium, cholecalciferol, and teriparatide improved symptoms and bone mineral density at one year, although mild metabolic acidosis persisted.

Conclusions

This case highlights the diagnostic complexity of discordant renal tubular phenotypes and genetic findings. Hypokalemic rhabdomyolysis and metabolic bone disease may provide important diagnostic clues. Sacroiliitis may mimic inflammatory spondyloarthritis, emphasizing the need to consider metabolic and skeletal disorders. Further segregation and functional studies are needed to clarify the identified variants and investigate a possible association between RTA and SEDT.

Key words

Renal tubular acidosis ·hypokalemia ·rhabdomyolysis ·metabolic bone disease ·Fanconi syndrome ·GATM gene ·spondyloepiphyseal dysplasia tarda ·TRAPPC2 gene ·case report.

Introduction

Renal tubular acidosis (RTA) encompasses a group of disorders characterized by impaired renal net acid excretion, resulting in persistent hyperchloremic metabolic acidosis despite preserved glomerular filtration (1). Based on their underlying pathophysiological mechanisms, RTA is classified into four distinct types (2). Distal RTA (type 1) is a rare genetic disorder characterized by impaired distal nephron proton (H^+) secretion during metabolic acidosis. Proximal RTA (type 2) results from defective proximal tubular bicarbonate reabsorption, type 3 represents a mixed defect, and type 4 arises from aldosterone deficiency or resistance (2). RTA is further classified etiologically as primary (genetic or idiopathic) or secondary (acquired) (3). A targeted evaluation can establish the genetic or acquired etiology in most patients (1). dRTA can be transmitted as an autosomal recessive (AR) or autosomal dominant (AD) trait (2). Primary dRTA typically presents in childhood and is associated with mutations in ATP6V1B1, ATP6V0A4, SLC4A1, and CA2, encoding B1 and A4 subunits of H^+-ATPase pump, the chloride bicarbonate or anion exchanger 1 (AE1), and carbonic anhydrase II (CA II), respectively. More recently, FOXI1, WDR72, and ATP6V1C2 variants have also been implicated in primary dRTA (4). Patients with dRTA typically manifest hypokalemia, with or without paralysis, nephrolithiasis, nephrocalcinosis, and nonspecific musculoskeletal symptoms. Chronic disease may lead to osteomalacia, rickets in children, and osteoporosis (4).

Proximal RTA (pRTA) may occur as an isolated defect or as part of generalized proximal tubular dysfunction, as seen in Fanconi syndrome (5). The cardinal features of Fanconi syndrome are generalized aminoaciduria and low-molecular-weight proteinuria, with additional findings including glucosuria, phosphaturia, bicarbonaturia, natriuresis, kaliuresis, and polyuria (1). Familial or hereditary pRTA has been rarely reported. Autosomal dominant (AD) pRTA has been documented in only a few families (3). Reichold et al. (2018) demonstrated that heterozygous

missense variants in glycine amidinotransferase (GATM) cause familial Fanconi syndrome, with early-onset manifestations and progression to glomerular failure in middle adulthood (6). Conversely, acquired dRTA may result from systemic disorders, including autoimmune diseases (Sjögren syndrome, systemic lupus erythematosus, chronic active hepatitis, and primary biliary cirrhosis), medications (amphotericin B, foscarnet, and lithium), and environmental toxins (4).

Hypokalemia-induced rhabdomyolysis is rarely reported in RTA, as most patients are diagnosed earlier through other clinical manifestations. Its pathogenesis is attributed to impaired muscle perfusion and metabolism secondary to hypokalemia, resulting in muscle injury (7).

X-linked spondyloepiphyseal dysplasia tarda (SEDT) is a rare hereditary cause of short stature in childhood, associated with mutations in the trafficking protein particle complex subunit 2 (TRAPPC2) gene located on chromosome Xp22 (8).

Here, we report a diagnostically challenging case presenting with biochemical and phenotypic features of dRTA, despite the identification of a GATM missense variant associated with Fanconi renotubular syndrome type 1 (FRTS1). The patient also had hypokalaemia-induced rhabdomyolysis, which was recognized retrospectively. The initial suspicion of spondyloarthropathy was reconsidered in light of the metabolic bone disease, characteristic skeletal abnormalities, and genetic findings suggestive of X-linked SEDT. This case highlights the complexity of genotype–phenotype correlations in renal tubular disorders and raises the possibility of an association between RTA and SEDT.

Case presentation

Patient information

A normotensive man in his early 20s presented with an 8-year history of recurrent hypokalemic flaccid quadriparesis. His first episode occurred at age 14, characterized by quadriparesis, myalgia, polyuria. There was no preceding history of carbohydrate-rich meal, strenuous exercise, gastrointestinal loss, laxative or diuretic use, heat intolerance, tremor, or hearing impairment. Three subsequent episodes were associated with hypokalemia and treated with intravenous and oral potassium for presumed hypokalemic periodic paralysis. Persistent back pain developed at age 16, without features of uveitis, enthesitis, aortic involvement, or apical pulmonary fibrosis. At age 19, nerve conduction studies (NCS) and electromyography (EMG) suggested non-inflammatory myopathy. Serum thyroid-stimulating hormone (TSH) was 40.70 μIU/mL, prompting a diagnosis of hypothyroid myopathy and initiation of levothyroxine. Pelvic MRI subsequently revealed active bilateral sacroiliitis despite normal C-reactive protein (CRP) and negative HLA-B27 status. He was diagnosed with HLA-B27-negative ankylosing spondylitis and prescribed sulfasalazine (2000 mg/day) and tofacitinib (10 mg/day), alongside treatment for hypokalemia, hypothyroidism, iron, and vitamin D deficiency. Both immunomodulatory agents were discontinued after 2 months due to lack of improvement, while levothyroxine was continued.

Two years later, he presented with progressive, atraumatic height loss (141 to 139 cm), severe back pain, myalgia, restricted spinal movement, and inability to walk unaided. For the preceding year, he had experienced difficulty rising from a seated position and combing his hair. Proximal and distal muscle weakness frequently rendered him bedridden. There was no significant drug or toxin exposure, ocular or oral dryness, or skin rash. His mother had chronic low back pain but had not been evaluated.

Clinical Findings on admission

Examination revealed spinal tenderness, height 139 cm (previously 141 cm), weight 39 kg, BMI 20 kg/m², and arm span 154 cm, indicating disproportionate short stature. Mid-parental and target heights were 156 cm and 156 ± 8.5 cm, respectively. Musculoskeletal examination showed loss of thoracic kyphosis, barrel-shaped chest, restricted spinal flexion and lateral bending, and a positive Schober's test. Straight-leg raising (SLR) was limited by pain. Proximal myopathy, bilateral knee tenderness with restricted movement, and an antalgic gait were noted. Neurological examination was otherwise unremarkable, with upper-limb power of 4/5; lower-limb power could not be assessed due to severe pain.

Diagnostic assessment

Complete blood count, erythrocyte sedimentation rate (ESR; 8 mm/h), and high-sensitivity C-reactive protein (CRP) were normal. Arterial blood gas analysis (ABG) revealed normal-anion-gap metabolic acidosis (pH 7.30, PCO_2 23 mmHg, bicarbonate 12.5 mmol/L; anion gap 15 mmol/L). Investigations **(Table 1)** demonstrated hypokalemia, hyperchloremia, hypophosphatemia, hypouricemia, hypercalciuria, a positive urinary anion gap, urine pH >5.5, and vitamin D deficiency.

Table 1

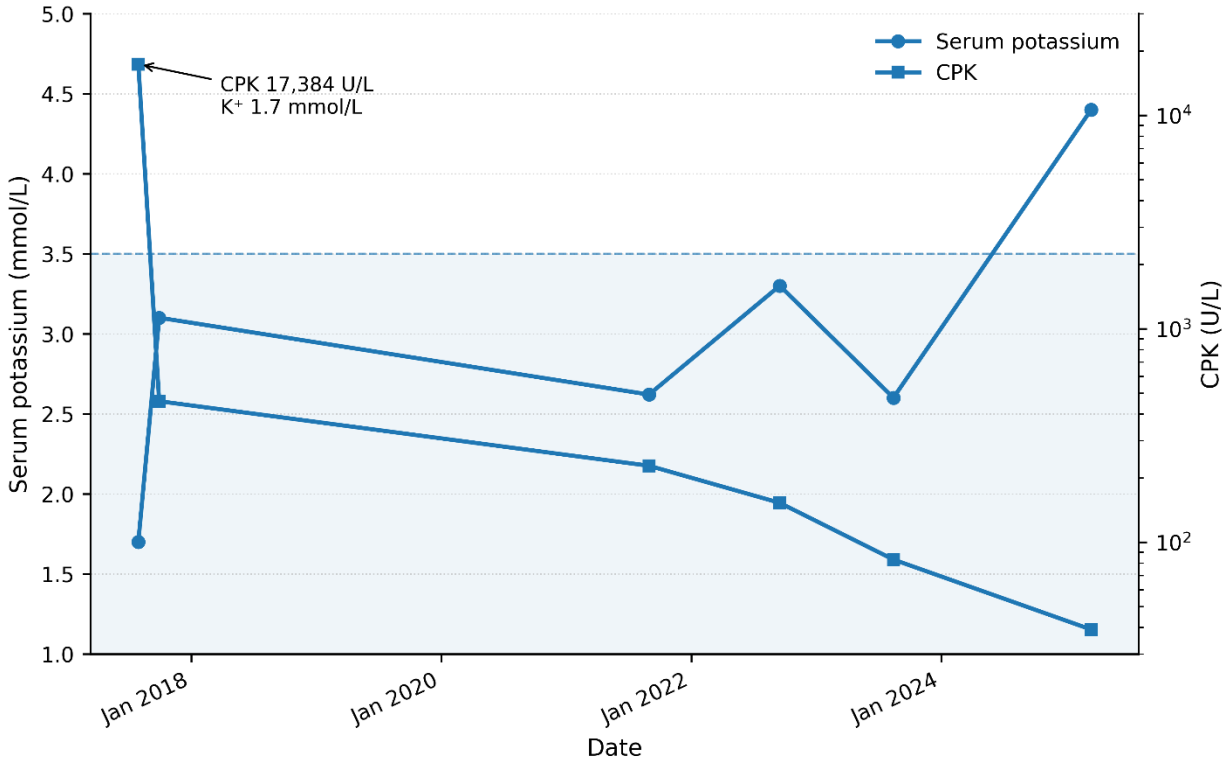
Summary of investigations of the patient at initial presentation to our center

Test	Result	Reference range
Blood parameters		
Fasting plasma glucose	4.1 mmol/L	3.5–6.0 mmol/L
2hrs after 75 gm glucose	4.9 mmol/L	<7.8 mmol/L
Serum sodium	136 mmol/L	135-145 mmol/L
Serum potassium	2.8 mmol/L	3.5–5.1 mmol/L
Serum chloride	110 mmol/L	98–106 mmol/L
Serum bicarbonate	11 mmol/L	21–31 mmol/L
Serum albumin-corrected calcium	6.5 mg/dL	8.3–10.6 mg/dL
Serum phosphate	2.5 mg/dL	Adult: 2.5–4.5 mg/dL; Child: 4.0–7.0 mg/dL
Serum uric acid	2.6 mg/dl	3.5-7.2 mg/dl
Serum creatinine	0.56 mg/dL	0.70–1.20 mg/dL
Serum vitamin D 25(OH)	19.7 ng/mL	>20 ng/mL
iPTH	23.4 pg/mL	18.5–88 pg/mL
Serum alkaline phosphatase	228 U/L	55-149 U/L
Serum TSH	1.96 µIU/mL	0.35–5.50 µIU/mL
FT4	1.45 ng/dL	0.89–1.76 ng/dL
CPK	83 U/L	30-200 U/L
Urine parameters		
Urine RME	Proteinuria + (UTI excluded)	Nil

24 hrs Urine sodium	133.2 mmol/24 hrs	40.0 – 220.0 mmol/24 hrs
24 hrs Urine potassium	118.2 mmol/24 hrs	25.0 – 125.0 mmol/24 hrs
24 hrs Urine chloride	216.0 mmol/24 hrs	110 – 250 mmol/24 hrs
24 hrs Urine calcium	349 mg/day	100 – 300 mg/day
Urine pH during arterial pH of 7.3	7	<5.5
Urine anion gap (Na+ + K+ - Cl-)	35.4 mmol/L (Positive)	Negative
Bicarbonate load test (urine pH)	Before-8	Impaired urinary acidification
	After-7.5	
24 hrs Urine volume	3600 ml/24 hrs	>3000 ml/24 hrs (polyuria)

Abbreviations: iPTH =intact parathyroid hormone (iPTH); FT4= free thyroxin; TSH= thyroid-stimulating hormone; CPK= creatinine phosphokinase; RME= routine microscopic examination

Initial serum potassium and creatine phosphokinase (CPK) levels were 1.7 mmol/L and 17,384 U/L, respectively. During follow-up from 2017 to 2023, CPK progressively normalized (458, 228.3, 153, and 83 U/L) with intermittent potassium supplementation, coconut water intake, and potassium correction, consistent with hypokalemic rhabdomyolysis **(Fig. 1).**



153

154 **Figure 1. Temporal relationship between serum potassium and CPK levels during follow-**
155 **up.** The highest CPK level (17,384 U/L) occurred during severe hypokalemia (serum potassium
156 1.7 mmol/L). CPK levels subsequently declined with improvement in serum potassium. The
157 shaded area represents serum potassium below 3.5 mmol/L. CPK is displayed on a logarithmic
158 scale to accommodate the wide range of observed values.

159 USG raveled bilateral medullary nephrocalcinosis. Imaging revealed osteomalacic changes,
160 bilateral medullary nephrocalcinosis, and pseudofractures (Fig. 2), along with kyphosis, pelvic
161 narrowing, pubic symphysis diastasis, partial collapse of the third sacral vertebral body, and
162 sacroiliitis (Fig. 3). Bone mineral density (BMD) revealed severe osteoporosis (Table 2)**.**
163 Evaluation for secondary causes of dRTA was undertaken; autoimmune markers for connective
164 tissue diseases and the extractable nuclear antigen (ENA) profile were negative.

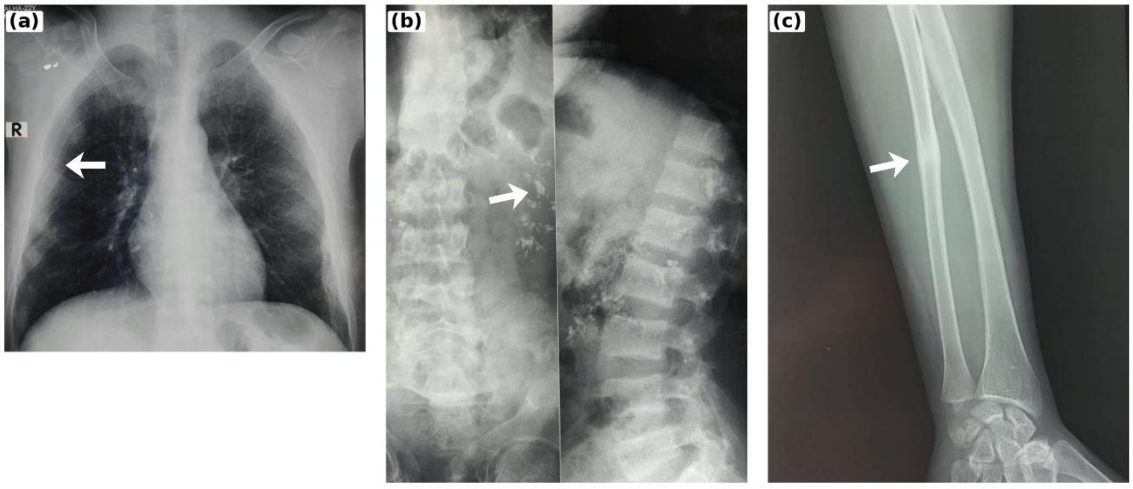
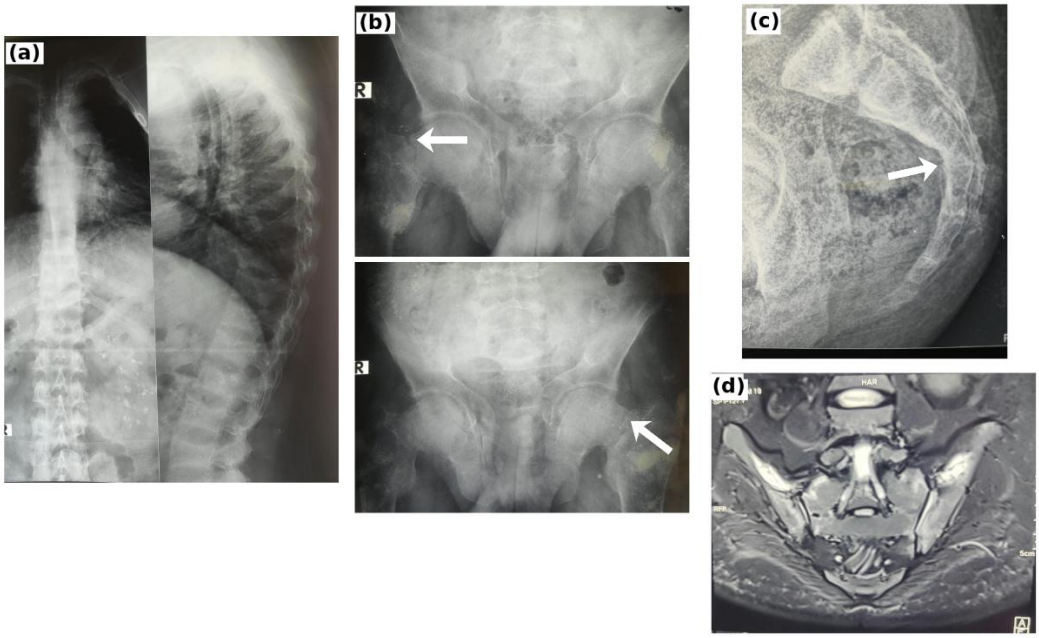


Figure 2. Radiographic findings in a patient with distal renal tubular acidosis. (a) Chest X-ray (posteroanterior view) showing radiolucent lines consistent with osteomalacia involving the right 4th–7th ribs laterally and 2nd–9th ribs posterolaterally. (b) Lumbar spine radiographs (AP and lateral views) showing bilateral medullary nephrocalcinosis, generalized reduction in bone density, flattening of vertebral bodies. (c) X-ray of the left forearm showing a pseudofracture of the radius.



173

174 **Figure 3. Radiographic and MRI findings.** (a) Thoracic spine radiographs (AP and lateral
175 views) showing kyphosis. (b) Pelvic radiographs (AP views) showing pseudofractures involving
176 both femoral neck, pubic symphysis diastasis, and narrowing of the pelvic outlet. (c) Partial
177 collapse of sacral 3rd vertebra (d) MRI of the sacroiliac joints showing bilateral moderate-to-
178 marked active sacroiliitis.

179 **Table 2**

180 Initial and One-Year Follow-up DEXA scans showing marked BMD improvement

Scan Site/ Region	**Z-Score (Initial)**	**Z-Score (Follow up)**
AP Spine/ L1-L4	-5.5	-2.8
Left Femur/ Neck	-3.2	-0.9
Left Femur/total	-4.3	Not mentioned
Right Femur/Neck	-3.3	-1.2

Right Femur/ Total	-4.2	Not mentioned
Right Forearm	-7.0	Not mentioned

Abbreviations: DEXA = Dual energy x-ray absorptiometry; BMD= Bone mineral density

Genetic testing

Based on biochemical and imaging findings, a provisional diagnosis of dRTA with nephrocalcinosis, osteomalacia, severe osteoporosis, hypothyroidism was made. For back pain our differential diagnosis was SSpA. Discordant biochemical and radiological findings raised diagnostic uncertainty, prompting genetic analysis to investigate an inherited renal tubular disorder and associated skeletal dysplasia.

A peripheral blood sample was collected from our patient for next-generation whole exome sequencing (WES). Genomic DNA extracted from the patient's blood sample was enriched for targeted regions using a hybridization-based protocol and subsequently used for exome library preparation. Targeted gene capture was performed based on the GRCh38 genome assembly to sequence protein-coding regions. Sequencing libraries achieved a mean coverage depth of >90× on the Illumina sequencing platform. According to the American College of Medical Genetics and Genomics (ACMG) classification, the variant was categorized as variant of uncertain significance (VUS). In silico prediction parameters the identified variant to be damaging by Mutation Taster, GenoCanyon, fitCons and DANN. The variant is rare in the Genome Aggregation Database (gnomAD) and reported in ClinVar database(RCV001115229). Genetic analysis identified a heterozygous/AD GATM (NM_001482.3) gene c.181C>G/p. Pro61 Ala variant Fanconi Renotubular syndrome 1 (OMIM#134600) VUS missense mutation in exon 2. XLR/ Hemizygous

TRAPPC2(NM_001011658.4) gene c.176T.C/p. Met 59Thr variant Spondyloepiphyseal dysplasia tarda (OMIM#313400) VUS missense mutation in exon 4.

Given the X-linked inheritance pattern of SEDT, Sanger sequencing was performed in the patient's mother, revealing a heterozygous TRAPPC2 (NM_001011658.4) c.176T>C (p.Met59Thr) variant (rs2046291142) in exon 4 (**Fig. 4).**

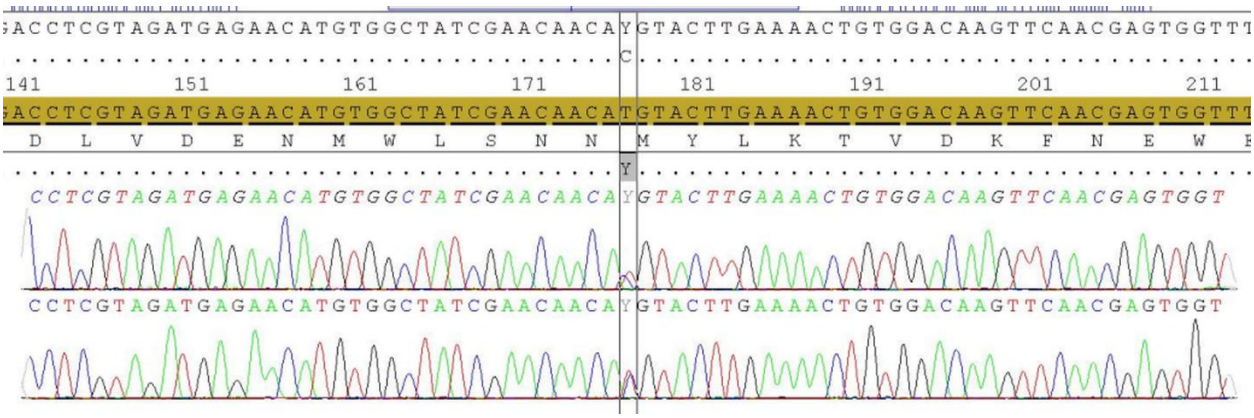


Figure 4. Sanger sequencing chromatogram confirming the heterozygous TRAPPC2 variant c.176T>C (p.Met59Thr) in the patient's mother. The variant was identified in the proband by whole-exome sequencing.

Therapeutic intervention

At presentation, the patient was initiated on alkali replacement therapy with potassium citrate syrup (20 mL daily in two divided doses) and sodium bicarbonate tablets (600 mg, two tablets three times daily), providing a calculated total alkali supply of approximately 1–2 mEq/kg/day.

Treatment for the associated severe osteoporosis included teriparatide 20 µg subcutaneously once daily, calcium carbonate 500 mg three times daily, and cholecalciferol 1000 IU once daily. Levothyroxine 75 µg once daily was prescribed for concomitant hypothyroidism. Sulfasalazine (1 g twice daily) was also initiated because spondyloarthropathy was initially considered in the differential diagnosis in view of the patient's back pain and sacroiliitis.

Follow-up and outcomes

At the first follow-up, approximately seven months after treatment initiation, the maternal Sanger sequencing results became available, prompting reconsideration of the initial diagnosis of spondyloarthropathy. Sulfasalazine was subsequently discontinued, while all other medications were continued at their previous doses. At one year follow-up, the patient demonstrated marked clinical improvement, with resolution of pain and substantial improvement in bone mineral density (BMD) parameters following teriparatide therapy. His anorexia subsided, and his body weight increased from 39 kg to 49 kg, returning to his pre-illness weight. However, he reported posterior protrusion of the buttocks, a skeletal feature consistent with spondyloepiphyseal dysplasia tarda (SEDT). Follow-up biochemical investigations continued to reveal mild metabolic acidosis, possibly reflecting inadequate alkali replacement relative to the patient's increased body weight. Accordingly, the potassium citrate dose was increased to optimize alkali replacement. Calcium, cholecalciferol, teriparatide, and levothyroxine were continued as indicated for the associated skeletal disease and hypothyroidism.

Discussion

RTA refers to a group of disorders characterized by defective renal hydrogen ion secretion or impaired reabsorption of filtered bicarbonate (HCO_3^-), resulting in persistent normal anion gap metabolic acidosis (2). Distal renal tubular acidosis (dRTA) results from impaired proton secretion by collecting duct α-intercalated cells (9). Inherited dRTA typically presents in infancy, childhood, or young adulthood, whereas acquired dRTA, secondary to disorders or medications, occurs at any age, predominantly in adults (2). The biochemical hallmark of dRTA is hyperchloremic normal anion gap metabolic acidosis with urine pH >5.5, often accompanied by hypokalemia, muscle weakness, nephrolithiasis/nephrocalcinosis, and metabolic bone disease (4). Patients with dRTA show reduced NH4 + secretion and low titratable acidity in urine (1). In children, dRTA is usually primary, presenting with growth failure, polyuria, and polydipsia. Severe hypokalemia may cause muscle weakness, neck flop, or transient paralysis, particularly during diarrheal dehydration. Rickets/osteomalacia and ultrasonographic or radiological evidence of nephrocalcinosis/nephrolithiasis may occur (1). Our patient presented with a similar clinical and biochemical presentation.

Children with proximal renal tubular acidosis (pRTA) typically develop growth retardation, anorexia, and polyuria. Associated Fanconi syndrome causes urinary loss of phosphate, glucose, uric acid, low-molecular-weight proteins, and amino acids. Rickets/osteomalacia and hypokalemic weakness or paralysis also suggest Fanconi syndrome, whereas nephrocalcinosis and urolithiasis are uncommon here (1). With rare exceptions nephrolithiasis/nephrocalcinosis typically distinguishes dRTA from pRTA (4). Besouw et al emphasized that, clinically dRTA should not be prematurely excluded in patients with proximal tubulopathy, particularly young children with

nephrocalcinosis (9). The mechanism of proximal tubular damage in dRTA remains unclear but may involve pathways shared with Dent disease and Lowe syndrome (9). Although our patient presented with growth retardation, polyuria, anorexia, hypophosphatemia, hypouricemia, proteinuria, and osteomalacia; the presence of nephrocalcinosis strongly favored dRTA as a diagnosis; however, whole-exome sequencing showed Fanconi Renotubular syndrome 1 (FRS1), classified as variant of uncertain significance (VUS).

Metabolic bone disease in dRTA primarily results from chronic systemic acidosis (4). Acidemia promotes bone calcium-phosphate release, reduces tubular calcium-phosphate reabsorption, and increases citrate reabsorption, causing hypercalciuria, hyperphospaturia, and hypocitraturia that favour calcium stone formation and oxalate/phosphate deposition, leading to tubular and interstitial (3). Acidemia reduces IGF-1 levels, hepatic IGF-1 expression, and growth hormone receptor mRNA, contributing to growth retardation (3).

Fanconi syndrome can be hereditary or acquired (3). Primary inherited Fanconi syndrome is caused by a mutation in the sodium-phosphate cotransporter (NaPi-II) (5). Recent genetic studies have linked mutations in SLC34A1, EHHADH, HNF4A, and NDUFAF6 to familial Fanconi syndrome (10). Only five GATM variants causing Fanconi syndrome have been reported in 6 families, and its epidemiology, clinical phenotype and genotype remains unclear (10). GATM-related Fanconi syndrome manifests in childhood, with renal function progressively deteriorating toward ESRD in the third to sixth decades (10). Our patient was found to have an autosomal dominant GATM variant associated with FRS1.

Hereditary dRTA accompanied by proximal tubular dysfunction including low-molecular-weight proteinuria, generalized hyperaminoaciduria, hypophosphatemia with hyperphosphaturia, and

hypouricemia with hyperuricosuria has been reported in two siblings carrying an ATP6V1B1 mutation by Kashoor et al (5). Here we can see that, previous reports have described complex cases with discordance between genotypic and phenotypic findings. However, whereas previously reported cases showed a genetic diagnosis of dRTA with phenotypic features of pRTA, our patient demonstrated a genetic diagnosis of pRTA with phenotypic features of dRTA. The molecular mechanisms that render a mutated protein dysfunctional are complex and may involve an array of defects spanning from internal sequestration of a given transporter to its mistargeting to the plasma membrane (11). Such complex molecular mechanisms might underlie the novel genetic variant identified in our patient, potentially contributing to the unusual phenotypic presentation.

Severe hypokalemia may induce rhabdomyolysis (RM) by impairing skeletal muscle perfusion (12). RM involves skeletal muscle necrosis with the release of intracellular contents into the bloodstream, typically causing a CK elevation exceeding 10 times the upper limit of normal (13). Overt rhabdomyolysis typically develops when serum potassium falls below 2.0 mmol/L (14). Untreated hypokalemia may progress from mild myalgia to tetraplegia or severe acute kidney injury due to the release of intracellular muscle components, including CPK and myoglobin, into the circulation (15). A retrospective review of the patient's clinical records and investigation reports, from his first presentation eight years ago until his first presentation at our center, revealed that when his serum potassium level was below 2 mmol/L, he presented with quadriparesis and markedly raised CPK levels. Following improvement in hypokalemia, the CPK levels gradually decreased, suggesting the presence of hypokalemia-induced rhabdomyolysis during his initial episodes. RM is a rare manifestation of dRTA.

Agrawal et al. reported that, to their knowledge, secondary dRTA had not previously been documented in seronegative spondyloarthropathy (SSpA) (4). Therefore, diagnosing our patient with SSpA solely on the basis of back pain and bilateral sacroiliitis may had been inappropriate. The lack of clinical improvement with immunomodulatory therapy further supports the possibility of an alternative diagnosis. Hypophosphatemia itself may cause enthesitis and sacroiliitis, mimicking SSpA (4). Therefore, hypophosphatemia or RTA itself may have contributed to the development of sacroiliitis in our patient.

X-linked spondyloepiphyseal dysplasia tarda (X-linked SEDT) is a rare X-linked skeletal dysplasia that predominantly affects males and is an uncommon cause of childhood-onset short stature. It is characterized by abnormalities of the vertebral bodies and epiphyses of long bones, resulting in a short trunk and premature osteoarthritis. Affected individuals typically exhibit disproportionate short stature, a relatively short trunk, a barrel-shaped chest, and an arm span exceeding their height (8). Lou et al. described SEDT as a rare, late-onset X-linked recessive osteochondrodysplasia, with an estimated prevalence of 1.7 cases per million individuals (16). The principal diagnostic approaches include obtaining a detailed three-generation family history, which may indicate an X-linked inheritance pattern, and conducting a comprehensive radiographic skeletal survey. The characteristic radiological features are best visualized on lateral thoracolumbar spine radiographs and include generalized flattening of vertebral bodies (platyspondyly), reduced intervertebral disc spaces, and distinctive superior and inferior vertebral endplate humps involving the posterior two-thirds of the flattened vertebral bodies. These characteristic changes are most evident during late childhood and adolescence, although progressive secondary arthritic changes may obscure them in later adulthood. Premature-onset osteoarthritis represents the major long-term complication,

predominantly involving the spine and hip joints. Hip involvement can be particularly severe, occasionally requiring joint replacement during early adulthood (17).

Several pathogenic variants in TRAPPC2 have been identified, although missense variants are uncommon (8). Of the 58 reported pathogenic variants, 32 are insertions or deletions, 10 are splice-site variants, and 9 are nonsense variants. Reported missense variants include c.139G>T (p.Asp47Tyr), c.218C>T (p.Ser73Leu), c.239A>G (p.His80Arg), c.248T>C (p.Phe83Ser), and c.389T>A (p.Val130Asp) (8). Zhang et al. identified a novel hemizygous missense variant in exon 5 of TRAPPC2 (c.260A>C, p.His87Pro). The patient's mother was a heterozygous carrier, whereas the father had no detected variant (8). In our patient, disproportionate short stature, kyphosis, broad chest, knee pain suggestive of premature osteoarthritis and some suggestive radiological findings raised suspicion of X-linked SEDT. Furthermore, genetic analysis, supported by Sanger sequencing results from the patient and his mother, suggests a potentially novel missense variant in the TRAPPC2 gene. To our knowledge, the coexistence of dRTA and SEDT has not been previously reported.

Taken together, the biochemical and radiological findings support a dRTA phenotype, despite the identification of a GATM variant associated with Fanconi renotubular syndrome type 1. Severe hypokalemia plausibly explains the rhabdomyolysis, while the skeletal abnormalities and TRAPPC2 variant raise suspicion of coexisting SEDT; however, further functional and genetic studies are required to establish causality and clarify these potential associations. The strength of this case lies in comprehensive clinical, biochemical, radiological, and genetic evaluation, while its limitation is the lack of functional validation and further genetic segregation studies.

Conclusion

This case highlights a rare phenotypic–genotypic discrepancy, with clinical and biochemical features of distal renal tubular acidosis (dRTA) despite the identification of a GATM missense variant associated with Fanconi renotubular syndrome type 1, suggesting a possible proximal tubular component. Hypokalaemia-associated rhabdomyolysis represented an additional uncommon manifestation of the underlying renal tubular disorder. The coexistence of disproportionate short stature, skeletal deformities, characteristic radiological abnormalities, a family history of chronic low back pain, and a TRAPPC2 missense variant raised the possibility of spondyloepiphyseal dysplasia tarda (SEDT). Although bilateral sacroiliitis on magnetic resonance imaging initially raised suspicion of spondyloarthropathy (SpA), normal inflammatory markers, negative HLA-B27, and the presence of hypophosphatemia and metabolic bone disease provided alternative explanations for the sacroiliac and skeletal abnormalities. This case underscores the importance of integrating biochemical, radiological, and genetic findings when evaluating complex renal tubular and skeletal disorders. Further genetic segregation and functional studies are required to clarify the significance of the identified variants and investigate a possible association between SEDT and dRTA.

Abbreviations

RTA	Renal tubular acidosis
dRTA	Distal renal tubular acidosis
pRTA	Proximal renal tubular acidosis

FRTS1	Fanconi renotubular syndrome type 1
GATM	Glycine amidinotransferase
SEDT	Spondyloepiphyseal dysplasia tarda
AD	Autosomal dominant
AR	Autosomal recessive
RM	Rhabdomyolysis
SSpA	Seronegative spondyloarthropathy
DEXA	Dual-energy X-ray absorptiometry
TRAPPC2	Trafficking protein particle complex subunit 2
ENA	Extractable nuclear antigen
WES	Whole exome sequencing
VUS	Variant of uncertain significance

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365 **Supplementary Information**

366 Additional File 1: Clinical Timeline (Word document) has been attatched.

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Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from the patient for genetic testing and participation.

Consent for publication

Written informed consent for publication of the clinical details, laboratory results, and accompanying images (including Sanger sequencing chromatograms) was obtained from the patient. A copy of the consent form is available for review by the Editor.

Availability of data and materials

No datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no conflict of interest.

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Author contributions

TN: Conceptualization, data collection, literature review, manuscript drafting, MLB: manuscript revision, SS: Final approval of manuscript, TH: Supervision, critical review.

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