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FAMILIAL GATM-ASSOCIATED FANCONI SYNDROME WITH PROGRESSIVE CKD

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ABSTRACT
Fanconi syndrome is a generalized proximal tubular disorder characterized by urinary wasting of bicarbonate, phosphate, glucose, amino acids, and other solutes. Hereditary forms are uncommon and are increasingly recognized with advances in molecular diagnostics. We report familial Fanconi syndrome associated with a heterozygous glycine amidinotransferase (GATM) variant, demonstrating a phenotypic spectrum from infancy to adulthood. A female infant presented with failure to thrive, hypophosphataemic rickets, glycosuria without hyperglycaemia, and normal anion gap metabolic acidosis consistent with proximal tubular dysfunction. Her father had childhood-onset renal rickets with progressive skeletal deformities requiring multiple orthopaedic procedures and subsequently developed chronic kidney disease (CKD). Whole-exome sequencing in the child identified a heterozygous GATM variant, c.1084G>C (p.Val362Leu), which was confirmed in the father by Sanger sequencing. Co-segregation of the variant with the phenotype across two generations supports possible pathogenic relevance. This report highlights the importance of considering hereditary proximal tubulopathies in children with rickets and normal vitamin D levels and illustrates the possible progression from isolated tubular dysfunction to chronic structural kidney disease in GATM-associated disease.

KEYWORDS: Fanconi syndrome, GATM, hypophosphataemic rickets, chronic kidney disease

1. INTRODUCTION
Fanconi syndrome results from generalized dysfunction of the proximal renal tubule, leading to urinary wasting of bicarbonate, phosphate, glucose, amino acids, uric acid, and other low-molecular-weight solutes [1,4,9,10]. The clinical expression depends on age, severity, and duration of these losses. Children commonly present with growth failure and hypophosphataemic rickets, while older patients may develop muscle weakness, osteomalacia, electrolyte abnormalities, nephrocalcinosis, and chronic kidney disease (CKD) [1,4]. Recognition of the combined biochemical pattern is important because glycosuria without hyperglycaemia, renal phosphate wasting, and normal anion gap metabolic acidosis indicate generalized proximal tubular dysfunction rather than an isolated disorder of phosphate metabolism [1,9,10].
Fanconi syndrome may be acquired or inherited. Important inherited causes include cystinosis, Dent disease, Lowe syndrome, Fanconi–Bickel syndrome, mitochondrial disorders, and recently characterized monogenic defects affecting proximal tubular function [4,11–19]. These conditions can overlap clinically with fibroblast growth factor 23-mediated hypophosphataemic disorders; assessment of acid–base status, urine glucose and protein, and tubular phosphate handling, including the tubular maximum phosphate reabsorption corrected for glomerular filtration rate (TmP/GFR), helps distinguish generalized tubular dysfunction from isolated phosphate wasting [20–23].
GATM-associated Fanconi renotubular syndrome is an uncommon autosomal dominant mitochondrial tubulopathy that may progress from isolated tubular dysfunction to CKD [2,3,8]. GATM encodes mitochondrial L-arginine:glycine amidinotransferase (AGAT), which catalyses the first and rate-limiting step of creatine biosynthesis [2,24,25]. Disease-associated GATM variants can promote abnormal intramitochondrial protein aggregation, oxidative stress, tubular injury, and progressive interstitial fibrosis [2,3]. Because few affected families have been described, the age-related clinical spectrum and long-term renal course remain incompletely defined [2,8].
We describe a familial case of Fanconi syndrome associated with a heterozygous GATM variant, demonstrating the clinical spectrum from infancy to adulthood across two generations. The contrasting phenotypes of the child and her father illustrate the potential evolution from early biochemical and skeletal manifestations to chronic tubulointerstitial disease and CKD.

2. CASE REPORT

2.1 Index child

A one-year-old female child born to non-consanguineous parents presented with poor weight gain, reduced oral intake, and failure to thrive following an initial period of normal growth during early infancy. There was no history of recurrent infections, gastrointestinal losses, polyuria, fractures, seizures, or significant intercurrent illness. Developmental assessment demonstrated mild delay predominantly affecting gross motor milestones.

She was born at term by lower-segment caesarean section with a birth weight of 2.8 kg. Meconium-stained liquor was noted; however, she cried immediately after birth and did not require neonatal intensive care admission.

Clinical examination demonstrated growth failure, with weight and height below the expected centiles for age. Wrist widening suggestive of rickets was present. Mid-upper arm circumference was reduced, consistent with undernutrition. Cardiovascular, respiratory, abdominal, neurological, and ophthalmological examinations were otherwise unremarkable.

2.2 Family history

The father had childhood-onset renal rickets associated with progressive skeletal deformities requiring multiple corrective orthopaedic procedures. He subsequently developed CKD in adulthood. A paternal female relative reportedly had severe hypophosphataemic rickets resulting in wheelchair dependence, suggesting a hereditary disorder with probable autosomal dominant transmission (Figure 1).

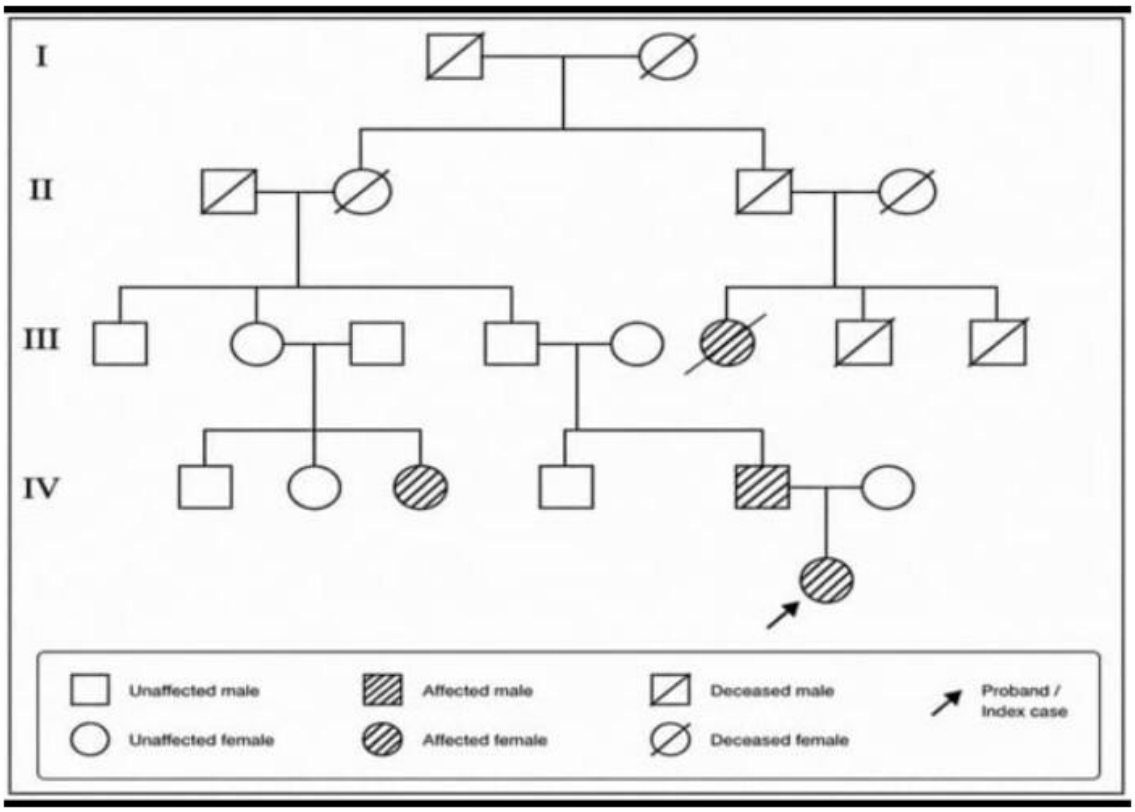

Fig. 1. Pedigree of the family showing affected individuals across successive generations. The arrow identifies the index case.

2.3 Investigations and diagnostic assessment

Initial biochemical investigations (Table 1) demonstrated preserved renal function, hypophosphataemia, elevated alkaline phosphatase, and normal serum calcium. Normal anion gap metabolic acidosis with reduced serum bicarbonate was present. Urinalysis showed glycosuria in the absence of hyperglycaemia and mild proteinuria, suggesting proximal tubular dysfunction. Further urinary studies demonstrated inappropriate phosphate wasting and proximal renal tubular acidosis. Tubular maximum phosphate reabsorption corrected for glomerular filtration rate (TmP/GFR) was reduced, confirming renal phosphate wasting.

Table 1. Comparative investigations of the index child and father across different stages of disease

Parameter	Index child	Father – childhood	Father – adulthood	Normal range
Serum creatinine (mg/dL)	0.3	0.8	1.4–1.9	Child: 0.2–0.5; adult: 0.6–1.2
Serum bicarbonate (mEq/L)	12	17	15	22–28

Parameter	Index child	Father – childhood	Father – adulthood	Normal range
Serum phosphorus (mg/dL)	2.6	2.0	3.1	Child: 4.5–6.5; adult: 2.5–4.5
Serum potassium (mEq/L)	4.1	3.7	3.0	3.5–5.0
Alkaline phosphatase (U/L)	1164	460	560	Child: <400; adult: 40–130
Urine glucose	1+	Positive	4+	Negative
TmP/GFR (mg/dL)	2.3	Not available	0.73	2.8–4.4
Kidney ultrasonography	No nephrocalcinosis	Not available	Increased cortical echogenicity with poor corticomedullary differentiation	Normal renal echotexture and corticomedullary differentiation
Genetic testing	Heterozygous GATM variant c.1084G>C (p.Val362Leu)	Not performed	Same variant confirmed by Sanger sequencing	—
Clinical renal status	Preserved renal function	Fanconi syndrome	CKD stage 2	Normal renal function

The combination of hypophosphataemic rickets, glycosuria without hyperglycaemia, metabolic acidosis, and a strong family history supported the diagnosis of hereditary Fanconi syndrome. Differential diagnoses included cystinosis, Dent disease, Lowe syndrome, mitochondrial cytopathies, and FGF23-mediated hypophosphataemic rickets. However, the absence of corneal crystals, ocular manifestations, nephrocalcinosis, neurodevelopmental abnormalities, and significant low-molecular-weight proteinuria, together with generalized proximal tubular dysfunction and vertical familial transmission, favoured hereditary Fanconi syndrome [4].

Whole-exome sequencing identified a heterozygous missense variant in exon 8 of GATM, c.1084G>C (p.Val362Leu), initially classified as a variant of uncertain significance. Targeted Sanger sequencing confirmed the same heterozygous variant in the father, supporting segregation with the disease phenotype (Figure 2) [5].

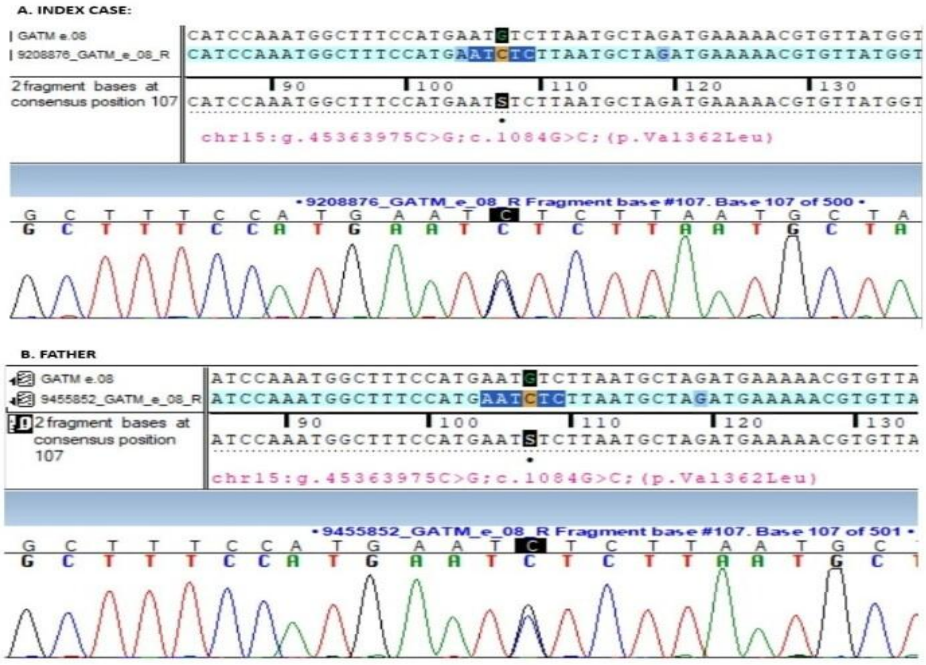

Fig. 2. **Sanger sequencing chromatograms demonstrating the heterozygous GATM c.1084G>C (p.Val362Leu) variant in (A) the index child and (B) her father.**

2.4 Treatment and follow-up

The child was initiated on alkali therapy with bicarbonate and citrate supplementation, oral phosphate replacement, vitamin D therapy, and nutritional rehabilitation. A thiazide trial intended to reduce urinary bicarbonate losses

was discontinued because of allergic intolerance. Follow-up demonstrated modest improvement in weight gain and developmental progression. Serum bicarbonate improved, although ongoing high-dose alkali supplementation remained necessary. Renal function remained preserved during follow-up.

2.5 Father's phenotype

The father had a longstanding history suggestive of hereditary proximal tubular dysfunction beginning in childhood. Early clinical features included leg pain, difficulty ambulating, rachitic rosary, Harrison sulcus, and progressive lower-limb deformities. During adolescence and early adulthood, he underwent multiple orthopaedic interventions, including osteotomies and intramedullary fixation for severe genu valgum and progressive skeletal deformities.

In adulthood, he continued to demonstrate persistent metabolic acidosis, hypokalaemia, glycosuria, and phosphate wasting, with gradual progression to CKD stage 2. Ultrasonography showed increased cortical echogenicity and poor corticomedullary differentiation, suggesting chronic tubulointerstitial disease. He remained on long-term alkali therapy, phosphate supplementation, calcitriol, and regular nephrology follow-up.

3. DISCUSSION

This familial report illustrates the phenotypic continuum of hereditary Fanconi syndrome from early biochemical disease in infancy to chronic structural kidney disease in adulthood. The child presented with classical paediatric manifestations of generalized proximal tubular dysfunction, whereas the father represented a later phenotype characterized by longstanding skeletal morbidity and CKD [2,4,8]. Their presentation across two successive generations is consistent with the autosomal dominant pattern described in GATM-associated disease [2,8].

The proximal tubule normally reabsorbs most filtered bicarbonate, phosphate, glucose, amino acids, uric acid, and low-molecular-weight proteins [1,9]. Generalized impairment therefore produces a recognizable constellation of normal anion gap metabolic acidosis, hypophosphataemia, glycosuria despite normoglycaemia, aminoaciduria, and variable tubular proteinuria [1,4,9,10]. Chronic phosphate depletion and acidosis impair skeletal mineralization, explaining the child's wrist widening and growth failure and the father's severe deformities requiring repeated orthopaedic procedures [1,4,20].

In the index child, the combination of normal vitamin D levels, metabolic acidosis, glycosuria, and inappropriate renal phosphate loss shifted the diagnostic focus away from nutritional rickets and isolated FGF23-mediated hypophosphataemia toward a hereditary proximal tubulopathy [20–23]. Cystinosis, Dent disease, Lowe syndrome, and Fanconi–Bickel syndrome were considered, but their characteristic ocular, neurological, nephrocalcific, proteinuric, or metabolic features were not evident [13–19]. The vertical family history further supported an autosomal dominant disorder.

GATM encodes mitochondrial L-arginine:glycine amidinotransferase (AGAT), an enzyme that catalyses transfer of an amidino group from arginine to glycine to generate guanidinoacetate, the first committed step in creatine synthesis [2,24,25]. In GATM-associated Fanconi syndrome, the proposed mechanism is a toxic gain of function rather than simple enzyme deficiency: mutant AGAT forms abnormal fibrillary aggregates within proximal tubular mitochondria, causing mitochondrial damage, oxidative stress, cellular injury, and progressive interstitial fibrosis [2,3]. This mechanism provides a biological explanation for progression from tubular solute wasting to structural kidney damage and declining glomerular filtration in some affected individuals [2,6,8].

The different ages and disease stages represented in this family offer a longitudinal perspective. The child currently has prominent biochemical and skeletal manifestations with preserved renal function, whereas the father has persistent tubular abnormalities, chronic ultrasonographic changes, and CKD. Published GATM-associated cases likewise indicate that proximal tubular dysfunction may precede loss of kidney function by years [2,8]. Early recognition may therefore create an opportunity to correct acidosis and phosphate depletion, reduce skeletal complications, and establish renal surveillance before irreversible damage becomes apparent [7].

The c.1084G>C (p.Val362Leu) GATM variant remains formally classified as a variant of uncertain significance under current ACMG/AMP criteria [5]. Its presence in both affected individuals and the compatible multigenerational phenotype provide segregation evidence, but segregation in a small family is not independently sufficient to establish pathogenicity [26,27]. Robust reclassification would require integration of population frequency, computational and functional evidence, additional unrelated cases, and well-validated experimental data [5,28,29,35]. Accordingly, the findings support possible pathogenic relevance but should not be presented as definitive proof of causality.

Management remains supportive and should be individualized according to biochemical losses and skeletal status. Alkali therapy is used to correct chronic metabolic acidosis, phosphate supplementation addresses renal phosphate wasting, vitamin D or active vitamin D therapy supports mineralization when indicated, and nutritional rehabilitation is particularly important for children with growth failure [1,4,20,32]. Treatment requires biochemical monitoring to avoid complications of over-replacement and should be accompanied by assessment of growth, bone deformity, mobility, serum electrolytes, bicarbonate, phosphate, urinary abnormalities, blood pressure, and kidney function. Persistent metabolic acidosis is also clinically relevant in CKD because it contributes to bone and muscle complications and may accompany disease progression [30,31].

This report emphasizes the value of careful family history and appropriately selected genetic testing in unexplained childhood rickets with evidence of generalized proximal tubular dysfunction. Exome sequencing can be useful when phenotypically overlapping inherited disorders remain plausible, although all detected variants

require interpretation in the clinical and familial context [33,34]. Once a candidate variant is identified, targeted testing of relatives, genetic counselling, and long-term follow-up may clarify segregation and the evolving phenotype. Limitations of this report include the small number of genetically tested affected individuals, the absence of functional studies for p.Val362Leu, and limited longitudinal observation of the child.

4. CONCLUSION

This familial case demonstrates the spectrum of GATM-associated Fanconi syndrome from childhood proximal tubular dysfunction to adult CKD across two generations. The coexistence of hypophosphataemic rickets, glycosuria without hyperglycaemia, and normal anion gap metabolic acidosis should prompt evaluation for generalized proximal tubular dysfunction, particularly when there is a suggestive family history. Early recognition may facilitate correction of chronic solute losses, prevention or reduction of skeletal complications, genetic counselling, family screening, and long-term renal surveillance. Although segregation of the GATM c.1084G>C (p.Val362Leu) variant with the phenotype supports possible pathogenic relevance, additional affected families and functional evidence are required to establish causality.

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AUTHOR CONTRIBUTIONS (CREDIT)

Shreyas Venkata Sai Malepati: Conceptualization, data curation, investigation, methodology, manuscript drafting, writing – review and editing. **Sandhya Suresh:** Supervision, methodology, validation, manuscript review and editing. **Umamaheswari B:** Clinical evaluation, investigation, resources, manuscript review. **Manikantan S:** Supervision, validation, critical revision of the manuscript. **Anitha Ramavajula:** Data interpretation, formal analysis, manuscript review.

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No funding or financial support was received for this study.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this report are available from the corresponding author upon reasonable request, with appropriate protection of patient confidentiality.

ETHICS DECLARATION

Institutional Review Board approval was not required for this case report according to institutional policy.

PATIENT CONSENT STATEMENT

Written informed consent for publication was obtained from the patient's guardians and the affected family member.

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