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A Rare Genetic Variant in SLC2A2 c.682 C > T (p.Arg228Ter) Underlying Complex Tubular Dysfunction and Progressive Bone Disease in Fanconi–Bickel Syndrome: A Novel Mutation with Systemic Implications

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ABSTRACT

Background: Fanconi–Bickel Syndrome (FBS) is a rare metabolic disorder caused by pathogenic variants in the SLC2A2 gene, leading to defective glucose transport and characteristic hepatorenal glycogen storage. We report a 3-year-old male presenting with failure to thrive, progressive abdominal distension, rickets, and biochemical evidence of proximal renal tubular dysfunction, including hypophosphatemia, metabolic acidosis, glucosuria, and hypouricemia.

Results: Exome sequencing revealed a homozygous nonsense variant, NM_000340.2 (SLC2A2):c.682C>T (p.Arg228Ter), classified as pathogenic and consistent with Fanconi–Bickel Syndrome. The patient was managed with oral phosphate and bicarbonate supplementation, along with nutritional rehabilitation. Despite good adherence, serum phosphate levels remained low, and there was limited improvement in growth velocity and skeletal deformities, highlighting the chronic and refractory nature of the disease.

Conclusions: Early genetic diagnosis is essential in children presenting with refractory rickets and renal tubular dysfunction. Identification of the novel p.Arg228Ter variant expands the known mutation spectrum of SLC2A2 and supports genotype–phenotype correlations. Timely molecular confirmation facilitates prognosis assessment, genetic counseling, and multidisciplinary care planning in affected families..

KEYWORDS: SLC2A2, Fanconi–Bickel Syndrome, p.Arg228Ter, hypophosphatemia, renal tubular dysfunction, exome sequencing

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INTRODUCTION

Background

Fanconi–Bickel syndrome (OMIM #227810), a rare autosomal recessive disorder classified under glycogen storage disease type XI, is caused by pathogenic variants in the SLC2A2 gene located on chromosome 3q26.1–q26.3. The SLC2A2 gene (OMIM 138160) contains 11 exons and encodes the glucose transporter protein GLUT2, which consists of 524 amino acids and is situated in the cell membrane. GLUT2 is expressed in hepatocytes, renal proximal tubular cells, pancreatic beta cells, enterocytes, neurons, and astrocytes. Loss of GLUT2 function disrupts glucose and galactose transport, leading to intracellular glycogen accumulation and widespread metabolic dysregulation affecting both hepatic and renal systems.

The clinical phenotype commonly presents in infancy or early childhood with hepatomegaly, growth retardation, abdominal distension, polyuria, polydipsia, hypophosphatemic rickets, and developmental delay. Biochemical findings include fasting hypoglycemia, postprandial hyperglycemia, glucosuria, phosphaturia, aminoaciduria, metabolic acidosis, hypophosphatemia, and elevated alkaline phosphatase levels. To date, fewer than 200 cases have been reported in the literature, with over 80 SLC2A2 pathogenic variants identified, including missense, nonsense, frameshift, and splice-site mutations.

In our patient, exome sequencing revealed a homozygous nonsense variant c.682C>T (p.Arg228Ter) in the SLC2A2 gene. This variant is listed as pathogenic in ClinVar; however, no peer-reviewed clinical case reports have documented this mutation to date, making this potentially the first indexed case of Fanconi–Bickel syndrome associated with this specific variant.

Management involves the prevention of hypoglycemia and supplementation of electrolytes. While classical nutritional strategies such as frequent feeding and overnight feeding may provide partial benefit, comprehensive nutritional support throughout the day and night has been proposed to improve growth and metabolic stability.

METHODS

Clinical data were obtained and evaluated at KLE Dr. Prabhakar Kore Hospital, Belagavi, Karnataka, India. Genomic DNA was

isolated from peripheral blood using standard protocols, and exome sequencing was performed on the Ion GeneStudio S5 platform (Thermo Fisher Scientific) using the Ion AmpliSeq™ Exome RDY Kit for enrichment and the Ion 540™ Kit for templating and chip loading.

Reads were aligned to the GRCh38/hg38 reference genome, and variant calling and annotation were performed using the Varstation® platform. This identified a homozygous nonsense variant in SLC2A2 (c.682C>T; p.Arg228Ter), classified as pathogenic according to ACMG/AMP guidelines.

Written informed consent was obtained from the patient's legal guardian, and the study was approved by the Institutional Ethics Committee of KLE Dr. Prabhakar Kore Hospital, Belagavi, Karnataka, India.

RESULTS

We report a 3-year-old male child, the first-born of a second-degree consanguineous marriage, born at term via spontaneous vaginal delivery with a birth weight of 2.34 kg. The child required oxygen support for two days due to delayed cry at birth and received phototherapy for 48 hours for neonatal hyperbilirubinemia.

Developmental delay was noted from six months of age, accompanied by progressive abdominal distension. The child achieved head control at 9–10 months, sitting with support at 18 months, independent sitting by 2 years, standing with support at 2.5 years, and independent walking by 3 years. At present, child's developmental age corresponds to approximately 1.5 years, yielding a developmental quotient of 40%. Notably, the child's dentition was age-appropriate.

Between 7 months and 3 years of age, he was evaluated by an orthopedic surgeon for progressive bone deformities and was empirically treated with calcium and vitamin D without significant improvement. At 16 months, the child was referred to a pediatric neurologist for evaluation of delayed motor milestones; however, no neurological etiology was identified. Due to persistent rickets, abdominal distension, and polyuria, he was referred to a pediatric nephrologist for further assessment.

On admission, the child appeared chronically ill and malnourished. Physical examination revealed a disproportionately large head, sparse scalp hair, frontal bossing, rachitic rosary, widened wrists, bowing of the legs, a protuberant abdomen, and a waddling gait. The mother also reported nocturnal polydipsia with the child consuming approximately 500 mL of water overnight along with significant polyuria. Anthropometric assessment revealed a weight of 9.4 kg and height of 72 cm (both below the 3rd percentile, approximately −3 SD), with an abdominal girth of 48 cm.

Laboratory evaluation showed hypophosphatemia, with a serum phosphorus level of 1.2 mg/dL (normal: 3.1–6.0 mg/dL), while serum calcium was 8.7 mg/dL (normal: 8.5–10.5 mg/dL) and free calcium was 1.16 mmol/L (normal: 1.12–1.32 mmol/L). Serum bicarbonate was reduced at 14.5 mmol/L (normal: 22–28 mmol/L), and arterial blood gas analysis showed a pH of 7.3 (normal: 7.35–7.45) with bicarbonate at 17 mmol/L (normal: 22–26 mmol/L), consistent with metabolic acidosis.

Urinalysis showed glucosuria (4+), with a spot urinary glucose of 3256 mg/dL, and spot urinary phosphorus was 28 mg/dL (normal: <20 mg/dL). Additional findings included hypouricemia (uric acid 0.9 mg/dL, normal: 3.4–7.0 mg/dL), vitamin D deficiency (19.2 ng/mL, sufficient: >30 ng/mL), and elevated parathyroid hormone (PTH) at 83.5 pg/mL (normal: 15–65 pg/mL). Fasting blood glucose was low at 65 mg/dL (normal: 70–100 mg/dL) while postprandial blood glucose was elevated at 156 mg/dL (normal: <140 mg/dL).

Thyroid function tests were within normal limits: free T4 at 0.95 ng/dL (normal: 0.8–2.0 ng/dL) and TSH at 2.80 µIU/mL (normal: 0.5–5.0 µIU/mL). Renal function tests showed serum urea of 32.5 mg/dL (normal: 10–40 mg/dL) and creatinine of 0.17 mg/dL (normal: 0.2–0.8 mg/dL), while serum potassium was 3.52 mmol/L (normal: 3.5–5.5 mmol/L).

Liver function tests showed mildly elevated transaminases: SGOT (AST) at 47 U/L (normal: 1–40 U/L), SGPT (ALT) at 39 U/L (normal: 1–41 U/L), and ALP at 1444 U/L (normal: 0–281 U/L). Serum albumin was 4.5 g/dL (normal: 3.5–5.0 g/dL), and total/direct bilirubin levels were 0.12/0.10 mg/dL (normal: total <1.2 mg/dL, direct <0.3 mg/dL).

Abdominal ultrasonography showed mild hepatomegaly, with a liver span of 10.6 cm, while Doppler studies of the portal vein and superior mesenteric artery were normal. A wrist X-ray showed classical signs of active rickets, including metaphyseal fraying and cupping.

To confirm the diagnosis, next-generation sequencing (NGS) was performed, which revealed a homozygous nonsense mutation c.682C>T (p.Arg228Ter) in exon 6 of the SLC2A2 gene (NM_000340.2) located on chromosome 3:171006036. This mutation, which is known to be pathogenic, confirmed the diagnosis of Fanconi–Bickel Syndrome (FBS) with an autosomal recessive inheritance. Liver biopsy was not performed, as the legal guardians declined the procedure. Therefore, histopathological confirmation could not be obtained. However, based on the clinical presentation and laboratory findings, a diagnosis of Fanconi Syndrome was suspected.

Figure 1: Photograph showing frontal bossing, increased abdominal volume, and wrist widening, consistent with clinical features of Fanconi–Bickel Syndrome.

According to the American College of Medical Genetics and Genomics (ACMG) guidelines, the variant is classified as pathogenic. This is a nonsense alteration that introduces a premature stop codon at amino acid position 228, and is predicted to undergo nonsense-mediated decay. Loss of function in SLC2A2 is a known and well-established mechanism for disease, fulfilling PVS1 criterion. The variant is located in exon 6, which is part of biologically relevant transcripts, further validating its functional significance.

Currently, the child receives maintenance therapy consisting of oral bicarbonate at a dose of 6.3 mEq/kg/day to correct persistent metabolic acidosis and oral phosphate supplementation at 2.5 mEq/kg/day to address hypophosphatemic rickets. Despite adherence to this regimen, serum phosphate levels remain persistently low (1.4 mg/dL), indicating refractory phosphate wasting. In addition to pharmacological therapy, comprehensive nutritional rehabilitation and supportive dietary measures are being provided, aimed at optimizing growth and metabolic balance.

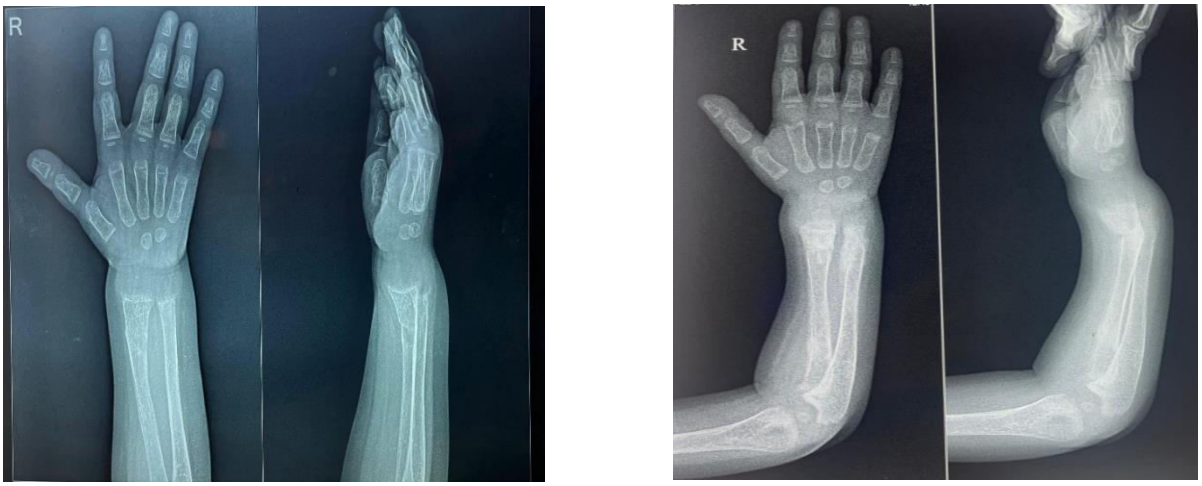

Figure 2a, 2b: Radiograph of upper limb X-rays before and after treatment, showing metaphyseal cupping and fraying consistent with rickets.

The child has been under regular follow-up and is now 45 months old. Despite ongoing supportive care, there has been no improvement in growth parameters, with both height and weight remaining unchanged compared to baseline. Abdominal girth at the last follow-up also remained the same, with no reduction noted, indicating persistent abdominal distension and ongoing clinical and biochemical features consistent with Fanconi Syndrome.

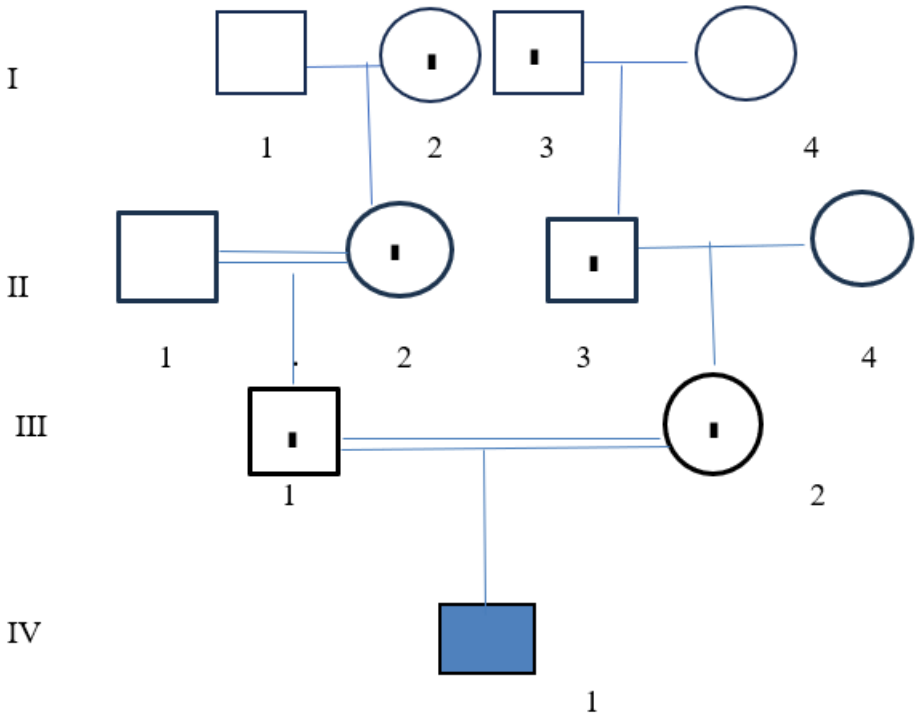

Figure 3: Family pedigree showing the proband (IV-1, 4 years old) with a homozygous SLC2A2 variant. Both parents (III-1, 28 years old; III-2, 24 years old) are obligate heterozygous carriers.

DISCUSSION

The diagnostic odyssey in rare genetic disorders such as Fanconi–Bickel Syndrome (FBS) is often prolonged. In this case, exome sequencing identified a homozygous nonsense variant in the SLC2A2 gene (c.682C>T; p.Arg228Ter), predicted to produce a truncated, nonfunctional GLUT2 protein. To the best of our knowledge, this exact variant has not been previously reported in the literature and is therefore considered novel. Its pathogenicity is supported by its predicted effect on protein function, absence in population databases, and in silico analysis consistent with ACMG/AMP criteria for pathogenic variants.

Due to the autosomal recessive inheritance pattern and second-degree parental consanguinity, a homozygous mutation was expected. Nevertheless, a search for compound heterozygous variants was also undertaken during the genetic evaluation.

The clinical diagnosis in our patient was based on hallmark features of the syndrome: hepatomegaly, fasting hypoglycemia, glucosuria, hypophosphatemia, hypouricemia, rickets, and renal tubular acidosis.

Whole exome sequencing enabled the identification of a homozygous nonsense variant in the SLC2A2 gene (c.682C>T; p.Arg228Ter), confirming the clinical diagnosis. This highlights the growing diagnostic capacity in India, where integration of genomic testing with clinical evaluation is improving recognition and management of rare metabolic disorders.

The patient's developmental delay appears to be multifactorial in origin, related to chronic malnutrition, persistent acidosis, electrolyte imbalances, and skeletal deformities. Interestingly, his dentition was within normal limits, underscoring the variability in phenotypic expression even among patients with confirmed SLC2A2 mutations.

Management of Fanconi–Bickel Syndrome remains largely supportive and focuses on phosphate and bicarbonate supplementation, along with nutritional rehabilitation. Despite good adherence to treatment and escalation of phosphate doses beyond physiological requirements, serum phosphate levels in our patient remained low (1.4 mg/dL), and growth velocity as well as developmental progress continued to be suboptimal. This highlights the chronic and refractory nature of the disease and the importance of early recognition and long-term multidisciplinary care.

While serum lactate and ketone profiling was not performed, intermittent urine ketone positivity (trace to +2) suggested episodes of ketosis, likely during metabolic stress. This highlights the need for comprehensive longitudinal metabolic monitoring in Fanconi–Bickel syndrome.

Although parental carrier testing could not be performed due to financial constraints, the presence of consanguinity supports autosomal recessive inheritance. Genetic counseling remains crucial to address recurrence risk and consider carrier testing and prenatal options.

This case adds to the limited pool of well-documented FBS cases with defined genetic mutations and supports the importance of integrating clinical, biochemical, and molecular findings for early diagnosis and optimal care.

CONCLUSION

This case highlights the critical importance of early genetic evaluation in children presenting with refractory rickets and renal tubular dysfunction. Detection of a novel homozygous nonsense SLC2A2 variant (c.682C>T; p.Arg228Ter) expands the known mutation spectrum of Fanconi–Bickel Syndrome and provides valuable insights for prognosis and genetic counseling. Despite adherence to supportive therapy, including nutritional rehabilitation and phosphate supplementation, our patient exhibited persistent growth failure and abdominal distension, underscoring the chronic and progressive nature of this rare disorder. The increasing availability of genomic technologies in India has the potential to shorten the diagnostic odyssey for similar patients, enabling timely diagnosis, individualized management, and improved quality of life, while supporting informed family counseling and future reproductive planning.

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