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SHORT REPORT

Genetic, Clinical, and Biochemical Characterization of a Large Cohort of Palestinian Patients With Fanconi-Bickel Syndrome

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ABSTRACT

This study aims to investigate the clinical, biochemical, and genetic characteristics of Fanconi-Bickel syndrome (FBS) in a cohort of 20 individuals from Palestine and to identify novel pathogenic variants. A retrospective analysis was conducted on medical records from Al-Makassed Hospital's pediatric department spanning 2015 to 2023. Individuals diagnosed with FBS via molecular genetic testing were included in the study. Among the 20 genetically confirmed FBS patients, hepatomegaly was prevalent in 95%, whereas 70% exhibited both developmental delay and hypophosphatemic rickets, and 68.4% experienced growth retardation. Hypertriglyceridemia (HTG) was universal. Elevated liver enzymes and alkaline phosphatase were common, along with hypophosphatemia (95%) and urinary abnormalities. Genetic analysis revealed five distinct SLC2A2 pathogenic variants, including three previously unreported variants: p.Gln23Arg (c.68A > G), p.Thr353Arg (c.1058_1059delinsGG), and an exon 7 deletion. This study presents the largest single-center cohort of FBS patients, expanding our understanding of the disorder's phenotypic and genotypic spectrum. Despite FBS generally carrying a favorable prognosis, timely diagnosis remains crucial to prevent severe complications.

1 | Introduction

Fanconi-Bickel syndrome was first identified in 1949 by Guido Fanconi and Horst Bickel [1], describing a patient with hepatorenal glycogenosis and renal tubulopathy. In 1976, Hug associated the condition with liver phosphorylase kinase deficiency, calling it Glycogen Storage Disease XI (GSD XI) [2]. However, a 1999 study disproved this, finding normal phosphorylase kinase levels in similar cases [3]. In 1997, Santer et al. identified a defect in the SLC2A2 gene, which encodes the GLUT2 transporter, as the cause of the syndrome [4]. Consequently, the term GSD XI is no longer used [5].

GLUT2 is a low-affinity transporter that facilitates the movement of monosaccharides such as glucose, galactose, mannose, and fructose [6]. It is mainly found in hepatocytes, kidney proximal tubules, pancreatic β-cells, enterocytes, and certain neuronal cells [7]. In the liver, GLUT2 regulates glucose homeostasis [8], whereas in β-cells, it helps trigger insulin release by sensing extracellular glucose levels [4].

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FBS is inherited in an autosomal recessive pattern. It is caused by biallelic variants in the SLC2A2 gene, leading to GLUT2 deficiency, which affects carbohydrate metabolism [6]. It presents with postnatal growth retardation, hepatomegaly, fasting hypoglycemia, postprandial hyperglycemia, hypophosphatemic rickets, and severe renal tubulopathy [6], primarily affecting the proximal tubules. Biochemical tests reveal polyuria, glucosuria, amino-aciduria, phosphaturia, and renal tubular acidosis [9]. FBS is rare, with only 144 cases reported between 1987 and 2020 [7].

FBS should be suspected in infants presenting with hepatomegaly, hypophosphatemic rickets, and signs of proximal tubular acidosis based on biochemical tests [10]. Diagnosis is confirmed by molecular testing of the SLC2A2 gene, with around 70 pathogenic variants identified [7]. Currently, there is no cure for FBS, and management remains symptomatic, highlighting the importance of early diagnosis to prevent complications. This includes fluid and electrolyte replacement, bicarbonate for acidosis, and vitamin D and phosphate for rickets. Slowly absorbed carbohydrates, like undercooked corn starch (UCCS), are used to control hypoglycemia and hyperglycemia while ensuring adequate calorie intake [6]. Galactose intolerance is common in FBS, and dietary restriction is recommended to prevent complications like lactic acidosis [11].

The prognosis is generally favorable; however, the attained height is expected to fall below the median for age and gender. Even though renal and hepatic glycogenosis develop, hepatomegaly usually regresses after puberty with appropriate treatment, and renal glomerular filtration rate remains normal or slightly decreased in most individuals [12].

This cohort presents clinical, biochemical, and genetic data from 20 FBS individuals in Palestine, identifying five pathogenic variants, including three novel mutations not previously reported in literature.

2 | Methods

This study was approved by the Research Ethics committee at Al-Makassed charitable Hospital. This is a retrospective analysis of the medical records of all individuals diagnosed with FBS in the pediatric department at Al-Makassed Islamic charitable Hospital, Jerusalem in the period between 2015 and 2023, which included 20 individuals. All individuals with a confirmed diagnosis of FBS by molecular genetic testing were included in the study.

3 | Results

A total of 20 genetically confirmed Fanconi-Bickel syndrome (FBS) individuals were studied at our hospital, with 19 from the Gaza Strip and one from the West Bank. The median age at presentation was 18 months, with 70% (14/20) presenting before age 2, and one presentation was relatively delayed at 10 years of age as he presented to the orthopedic department with severe skeletal deformities; see Figure 1. Hepatomegaly was the most common clinical feature, seen in 95% (19/20) of patients. Other common findings included polyuria, rickets, failure to thrive, and developmental delay. Among the 20 individuals, 14 had developmental delays, 10 exhibited global delays in motor, language, and fine motor skills, whereas 3 had isolated motor delay, and one had delays in both motor and language skills. Some children did not achieve independent walking until the age of 4–4.5 years. Speech delays were generally mild, except for two patients who began speaking in two-word sentences at the ages of 3 and 4 years, respectively. For those seen in follow-up, marked improvement in development was observed. Cognitive impairment was not documented in older children, with only one individual showing mild learning difficulties. Sociodemographic and clinical characteristics are shown in Table 1.

A detailed biochemical profile of 20 individuals is summarized in Table 2. Laboratory results were plotted to age-specific

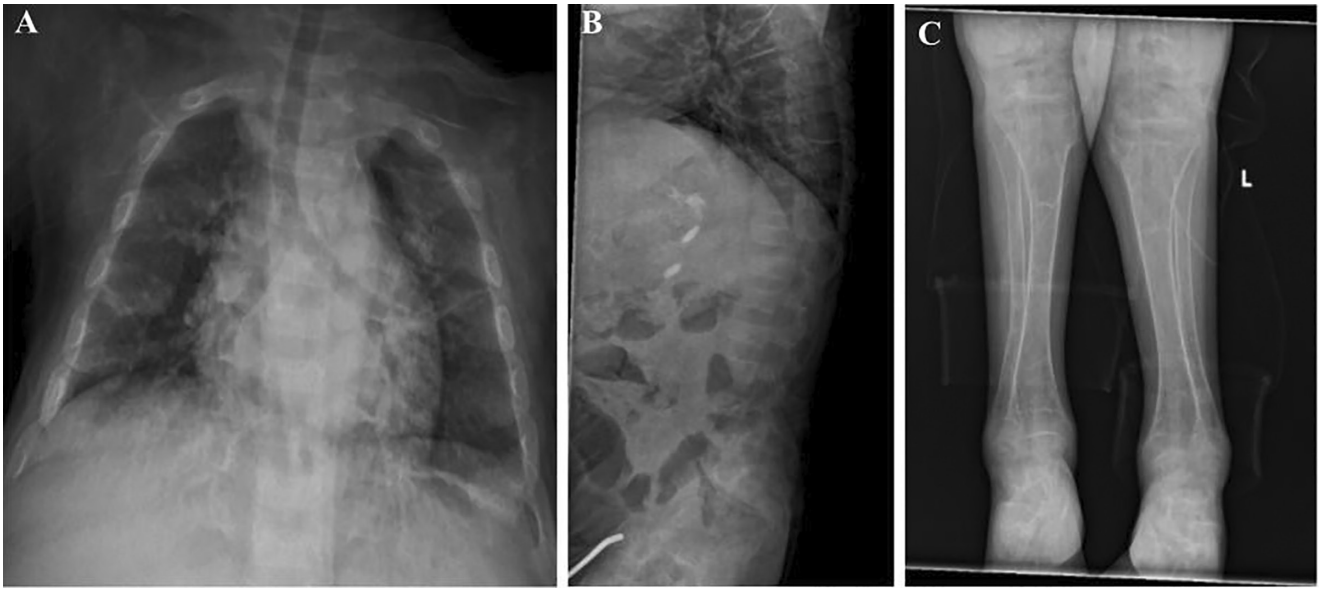

FIGURE 1 | (A–C) shows the skeletal survey of the patient with latest presentation (10 years old). (A) Rachitic rosary, osteopenia and broad ribs. (B) Bowing of the tibia, irregular wide metaphysis, genu valgum and severe osteopenia. (C) Shows platyspondyly and osteopenia.

TABLE 1 | Descriptive analysis of sociodemographic characteristics, initial clinical presentation, and identified variants in SLC2A2 gene of FBS individuals.

FBS sociodemographic characteristics		
Parameters		**Values**
Gender		
Male, *n* (%)		11 (55%)
Female, *n* (%)		9 (45%)
Age (mean ± SD) months		27.15 ± 28.08
Birth Weight (mean ± SD) grams		2965 ± 485.87
Consanguinity, *n* (%)		17 (85%)
Family History of FBS, *n* (%)		10 (50%)
Clinical presentation of FBS individuals		
	Frequency	**Percentage**
Developmental delay	14/20	70%
Hepatomegaly	19/20	95%
Splenomegaly	2/20	10%
Features of rickets	14/20	70%
Hyperglycemia	3/20	15%
Hypoglycemia	4/20	20%
Diarrhea	4/20	20%
Polyuria	14/20	70%
Failure to thrive[a]	13/19	68.4%
The identified variants in SLC2A2 gene		
		Number of individuals
R301X (c.901 C > T)	Exon 7	9
Q23R (c.68A < G)	Exon 2	4
Exon 7 Deletion	Exon 7	5
P417L (c.1250C > T)	Exon 10	1
T353R (c.1058_1059delinsGG)	Exon 8	1

Abbreviations: FBS, Fanconi Bickel Syndrome; N, number; SD, Standard deviation.
[a]Growth parameters were evaluated using the standard deviation (*Z*-score) as defined by the guidelines of the Center for Disease Control and Prevention (CDC) [13].

normal values [14] and revealed patterns indicative of proximal tubular dysfunction. Glucosuria, proteinuria, and generalized aminoaciduria were present in 100% of cases, whereas calciuria was seen in 94.7%. Despite these abnormalities, kidney function was generally preserved; only 3 individuals (15%) had mildly elevated creatinine levels. Plasma tests revealed abnormal lipid and bone profiles in most individuals, along with frequent liver enzyme abnormalities. Abdominal ultrasounds confirmed hepatomegaly in 94.7% (18/19), with increased liver echogenicity in 15.8%. Bilateral nephrocalcinosis was found in one case, which resolved on follow-up, and no splenomegaly was reported.

Genetic testing identified five types of variants in the *SLC2A2* gene (NM_000340.2): a nonsense variant, c.901C > T (p.Arg301*), in 45%; missense variants, c.68A > G (p.Gln23Arg), c.1250C > T (p.Pro417Leu), and c.1058_1059delinsGG (p.Thr353Arg), in 30%; and an exon 7 deletion, c.26508-20_c.26695 + 1497del (p.Ser259Asnfs*71), in 25%. Notably, the exon 7 deletion, c.68A > G (p.Gln23Arg), and c.1058_1059delinsGG (p.Thr353Arg) variants have not been previously reported. Both c.68A > G (p.Gln23Arg) and c.1058_1059delinsGG (p.Thr353Arg) were absent from population databases and predicted to be damaging by in silico tools. These variants were found in multiple affected individuals from different Palestinian families and were classified as likely pathogenic according to ACMG guidelines.

Management involves a galactose-free, low-fat diet for all individuals, with soya-based milk for those younger than 2 years.

TABLE 2 | Descriptive analysis of the FBS diagnosed patients presenting serum and urine laboratory results.

Serum laboratory results			
	Mean ± SD[a]	**Frequency**	**Percentage**
Liver function test			
High AST level	82.28 ± 83.67 U/L	12/20	60%
High ALT level	48.37 ± 50.13 U/L	12/20	60%
High INR	1.04 ± 0.18	4/19	21%
Bone profile			
Low serum calcium level	9.85 ± 0.63 mg/dL	2/20	10%
Low serum phosphate level	2.13 ± 0.82 mg/dL	19/20	95%
High ALP level	881.39 ± 673.73 U/L	15/20	75%
Kidney function test			
High Serum Creatinine Level	0.33 ± 0.26 mg/dL	3/20	15%
Lipid profile			
Hypertriglyceridemia	360.2 ± 181.25 mg/dL	20/20	100%
Urine laboratory results			
		Frequency	**Percentage**
Generalized aminoaciduria		15/15	100%
Low tubular reabsorption of phosphate		13/19	68.4%
Glucosuria		20/20	100%
Calciuria		18/19	94.7%

Abbreviation: SD, standard deviation.
[a]Mean was calculated for all tested individuals.

Cornstarch was prescribed to 17 of 20 patients. Additionally, 19 individuals received phosphate supplements (52.6–367 mg/kg/day), and 19 were treated with vitamin D (400–4000 IU/day) or vitamin D3 (0.25–2 μg/day).

4 | Discussion

FBS is a rare autosomal recessive disorder caused by dysfunctional GLUT2 [6]. Diagnosis should be suspected based on clinical features, biochemical tests, and imaging studies and confirmed by molecular testing [6, 9].

Herein we present the largest retrospective cohort of 20 FBS individuals diagnosed and treated at a single tertiary center, all homozygous for their respective pathogenic variants. Of the five variants identified, two (c.901C > T (p.Arg301*) in exon 7 and c.1250C > T (p.Pro417Leu) in exon 10) were previously reported in the Middle East [15], whereas three (exon 7 deletion, p.Gln23Arg (c.68A > G) in exon 2, and p.Thr353Arg (c.1058_1059delinsGG) in exon 8) are novel. Our analysis revealed no clear genotype–phenotype correlation.

FBS presents with hepatomegaly and proximal tubular dysfunction, leading to glucose, protein, calcium, amino acid, and phosphate loss, which results in hypophosphatemic rickets and polyuria [6]. Individuals often experience failure to thrive and developmental delay. Although postprandial hyperglycemia and fasting hypoglycemia are common [6], they were underreported in our cohort, likely due to insufficient awareness about the disease's nature amongst families and physicians.

Multiple inborn errors of metabolism can manifest with hepatomegaly and renal tubular dysfunction; however, a thorough clinical and biochemical assessment enables differentiation from FBS. Key differential diagnoses include cystinosis, characterized by corneal deposits and dibasic aminoaciduria (cystine, ornithine, lysine, and arginine); glycogen storage disease type I, which typically presents with severe hypoglycemia, hyperuricemia, lactic acidosis, hepatomegaly, and hyperlipidemia; tyrosinemia type I, marked by hepatic dysfunction and elevated levels of tyrosine and succinylacetone; and galactosemia, which leads to hepatic dysfunction and cataract due to galactose accumulation following milk ingestion. Importantly, all patients with FBS demonstrate glucosuria, as noted in our cohort. Although this feature is nonspecific, its absence in cases of renal tubular dysfunction makes a diagnosis of FBS unlikely [16].

GLUT2, located on the basolateral membrane of hepatocytes, is essential for regulating glucose uptake and release during feeding and fasting states [8]. In FBS, the loss of GLUT2 function leads to increased intracellular glucose, reducing glycogenolysis and promoting glycogen storage, resulting in hepatomegaly [7]. Although hepatomegaly is common in FBS,

its presence is not mandatory for diagnosis [17]. In our study, almost all individuals exhibited hepatomegaly, with only one exception. Splenomegaly, previously reported in FBS, was observed in only two patients.

The latest presentation in our cohort was an individual who presented at 10 years of age. He had a long history of severe failure to thrive and chronic metabolic acidosis. He was referred to the orthopedic department at our hospital for correction of severe skeletal deformities that made him confined to a wheelchair. Subsequent assessment revealed hypophosphatemic rickets, hepatosplenomegaly, glucosuria, and aminoaciduria. Genetic testing confirmed FBS (homozygous exon 7 deletion in SLC2A2). His severe symptoms highlight the importance of early diagnosis and intervention for better prognosis.

Transient or permanent neonatal diabetes is an atypical presentation of FBS, documented in 15 individuals [18]. A 2020 study indicated that the incidence of transient neonatal diabetes in FBS might be underestimated, as dysglycemia might have resolved by the time of diagnosis [19]. Among our cohort, only one individual developed infantile diabetes at 9 months, with elevated HbA1c between 7% and 8%. Managing his hyperglycemia posed challenges due to unclear evidence on insulin use, because of the risk of hypoglycemia. Consequently, endocrinology prescribed a small dose of short-acting insulin: 0.5 IU for pre-prandial readings over 100 mg/dL and 1 IU for readings over 200 mg/dL. Over 3 months, he experienced a few episodes of hyperglycemia and no instances of hypoglycemia. His HbA1c improved to 6.8, demonstrating that the use of insulin for treating dysglycemia in FBS necessitates a case-specific approach, and should be decided based on follow-up and monitoring of the affected individuals.

Other complications previously reported in the literature, such as liver failure and renal failure, were not observed in our cohort.

Socioeconomic factors, such as limited access to healthcare and insufficient medication supply, play a crucial role in treatment adherence and outcomes for patients with Fanconi-Bickel syndrome, particularly in Gaza. Challenges like poverty and restricted border access can hinder consistent care, impacting overall prognosis. Although this study did not collect specific socioeconomic data, future research should explore these aspects to fully understand their influence on the management and progression of FBS.

5 | Conclusion

This study represents the largest cohort of FBS from a single tertiary center and expands the known phenotypic and genotypic spectrum of the disease. FBS has an overall favorable prognosis. However, delayed recognition can result in severe deformities, underscoring the critical need for heightened clinical awareness and early intervention.

Author Contributions

The conception and design of the study (N.D., T.H., A.A., I.I.), acquisition of data (T.H., A.A., I.I.), analysis and interpretation of data (N.D., T.H., A.A., I.I.), drafting the article and revising it critically for important intellectual content: all authors.

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Ethics Statement

Informed written consent for the publication of clinical data and photos was obtained from the legal guardians, and the study was approved by the Research Ethics Committee at Al-Makassed Charitable Hospital.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.14648.

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