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CASE REPORT

Gastroenterology

Johanson–Blizzard syndrome caused by novel UBR1 mutation in four Saudi patients

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Abstract

Johanson–Blizzard syndrome (JBS) is a rare genetic disorder caused by Ubiquitin Protein Ligase E3 Component N-Recognin1 (UBR1) gene mutations. It is characterized by exocrine pancreatic insufficiency, craniofacial deformities, sensorineural hearing loss, and a broad variety of intellectual disabilities. The aim of our study is to report four pediatric cases (three of which are siblings, and the fourth patient is unrelated) that presented some features of JBS. The cases have been confirmed by genetic testing to have mutations in the UBR1 gene. This case series study was conducted retrospectively, giving a detailed description of the demographic and clinical information of these four cases, and reflecting our experience with this subset of patients. All these cases have been treated at the King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia, and were identified by their clinical and laboratory markers that favor JBS. A novel homozygous missense mutation c.2075 T > C (p. Ile692Thr) in exon 18 (UBR1: NM_174916.3) was identified and confirmed by Sanger sequencing in all our cases outlined in this paper. These presented cases illustrate the phenotypic variability and complexity of JBS and the importance of physical examination to reach a diagnosis. The identified novel mutation in this study broadens the spectrum of UBR1 mutations that contribute to JBS.

KEYWORDS

alae nasi aplasia, exocrine pancreatic insufficiency, JBS, UBR1 gene mutation

1 | INTRODUCTION

Johanson–Blizzard syndrome (JBS) (OMIM:243800) is an exceedingly uncommon genetic disorder that is caused by Ubiquitin Protein Ligase E3 Component N-Recognin1 (UBR1) gene mutations.[1] This malformation syndrome is characterized by severe congenital exocrine pancreatic insufficiency (EPI), craniofacial deformities, sensorineural hearing loss (SNHL), and a broad variety of intellectual deficiencies.[2,3] Several studies have described other organ abnormalities, including urogenital, anorectal, and cardiac anomalies.[4]

JBS has been recorded globally in less than 100 cases.[5] Consanguineous paternity is prevalent, and JBS incidence is gender-neutral.[6] JBS is inherited in an autosomal recessive pattern. Homozygous or compound-heterozygous mutations of the UBR1 gene (chr15q15.2) constitute the majority of the cases. This gene encodes a 1749-amino-acid enzyme called E3 ubiquitin-protein ligase component N-recognin 1, which is part of the N-end rule pathway. This ligase enzyme recognizes and binds proteins with unstable N-terminal residues, ubiquitinating and degrading them.[7] Most UBR1 mutations that are associated with JBS prevent E3 ubiquitin-protein ligase

synthesis. UBR1 is widely expressed in pancreatic acinar cells, and UBR1 protein deficiency results in a progressive inflammatory process that fails to induce apoptotic cell death in the pancreas, craniofacial tissues, and nervous system.

Patients with JBS have several symptoms and indicators. Based on a cohort of 61 patients, crucial clinical features for JBS include EPI, nasal wing aplasia or hypoplasia, and oligodontia of permanent teeth.[5] EPI usually presents at birth or in infancy. Infants with malabsorption and pancreatic insufficiency may fail to thrive and develop short stature. Small infants with JBS may have small "beak-shaped" noses due to nasal alae aplasia or hypoplasia.[8] Cleft lip and palate, microcephaly, thin upper lip, and nasolacrimal anomalies are additional craniofacial features that may be seen in JBS. Aplasia cutis in the skull and dental anomalies, causing cone-shaped primary teeth and scant permanent teeth, are often seen.[8] There were also reports of cardiomyopathy and congenital heart defects like atrial septal defect (ASD) and ventricular septal defect (VSD). Several endocrine disorders, including hypothyroidism, hypopituitarism, and type 2 diabetes mellitus, have been documented. It has come to our attention that only three cases of JBS have been reported in Saudi Arabia.[9,10] Sequencing of UBR1 for one of those cases revealed a novel homozygous missense variant in the UBR1 gene.[9]

The aim of this study is to report four pediatric cases who presented with some features of JBS and were confirmed by genetic testing to have previously unreported mutations in the UBR1 gene.

2 | METHODOLOGY

This case series study which is registered with institution review board number 2022-CR-08, describes four new JBS pediatric cases from two unrelated Saudi families. This descriptive study was conducted in a retrospective fashion, giving a detailed description of the demographic and clinical information of these four cases and reflecting our experience with this subset of patients. Our reported cases were treated in the order in which they were discovered. They have been addressed and treated by the pediatric gastroenterology service at King Faisal Specialist Hospital and Research Center (KFSH & RC)-Jeddah branch, Saudi Arabia and were identified by their clinical and laboratory markers that favor a JBS and were eventually confirmed to have a genetic mutation of the UBR1 gene. Parents of our reported cases have not been tested genetically. This paper documented the data in accordance with the CARE checklist of items to cover when writing a case report.[11]

3 | MOLECULAR ANALYSIS

After obtaining informed written consent from parents/patients, a venous blood sample was withdrawn from each index patient and then sent to the Baylor Genetics Laboratory at KFSH and RC-Riyadh. High-throughput next-generation sequencing (NGS) was implemented to detect variants in the UBR1 gene and other related genes. Genomic deoxyribonucleic acid (DNA) was extracted according to standard procedures and fragmented by sonicating genomic DNA and ligating it to the Illumina multiplexing adapters. The adapter-ligated DNA is then amplified by polymerase chain reaction (PCR) using primers with sequencing barcodes (indexes). For the target enrichment procedure, the precapture library is enriched by hybridizing to biotin-labeled in solution probes. The DNA sequence was mapped to and analyzed in comparison with the published human genome build (UCSC hg19 reference sequence). The variants were interpreted according to American College for Medical Genetics (ACMG) guidelines and patient phenotypes.[12] Variants are confirmed by Sanger sequencing if NGS data quality is insufficient for that locus.

4 | CLINICAL DESCRIPTION OF OUR FOUR CASES

4.1 | Case 1

A 17-year-old Saudi boy presented to the pediatric gastroenterology clinic at the age of 12 year with a history of chronic cough, diarrhea, and poor weight gain. He was born full-term to a first-degree cousin's parents and had an unremarkable prenatal and postnatal history. At the age of 7 years, he was evaluated in the pediatric pulmonology clinic for his chronic cough and diarrhea. He also reported intermittent soft bowel movements with greasy stools. Laboratory work-up, at that time, showed normal white blood cell count (WBC), hemoglobin (Hb), platelet count, kidney function, serum electrolytes, liver enzymes, and pancreatic enzymes. Blood film morphology showed a normocytic normochromic picture. Chest X-ray showed central bilateral peribronchial cuffing with left retrocardiac atelectasis. He was suspected of having cystic fibrosis (CF). However, the genetic testing for cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations was negative. He was managed with albuterol and steroid inhalations, omeprazole, fat-soluble multivitamins supplementation, and oral pancrelipase enzyme at a dose of five to six capsules (Creon 10; each capsule contains: lipase 10,000 units, amylase 8000 units, and protease 600 units) per day with meals. At the age of 12 years, he was referred to the pediatric gastroenterology clinic for additional workup due to his nonconclusive genetic study for CFTR and pancreatic insufficiency without a history of significant respiratory illnesses. An

in-depth physical examination revealed dysmorphic features including hypoplastic alae nasi, scalp aplasia cutis, and small and malformed teeth. His other systemic exams were unremarkable. He had normal academic achievement with no intellectual disability. Table 1 shows the main presentation features of the four cases. As shown in Table 2, his repeated workup showed mild leukopenia, moderate to severe neutropenia, normal Hb, normal platelets count, normal thyroid function test, low serum vitamin A level (238 µg/L), and low fecal elastase level. An Abdominal CT scan showed an excess of fat within the retroperitoneum, while the pancreatic tissue could not be identified. Pure tone audiometry revealed normal hearing. JBS was suspected based on his symptoms and physical features. Whole-exome sequencing (WES) testing revealed the presence of a novel homozygous missense mutation (c.2075 T > C; p. Ile692Thr) in the UBR1 gene (UBR: NM_174916.3). Patient continued on oral pancrelipase (Creon 10; each capsule contains: lipase 10,000 units, amylase 8000 units, and protease 600 units) as 4 capsules with the main meal, omeprazole 20 mg daily., and multivitamins one tablet daily (the tablet contains 751 IU of vitamin A, 45 mg of vitamin C, 400 IU of vitamin D3, 50 IU of vitamin E, 0.6 mg of vitamin B1, 0.6 mg of vitamin B2, 6 mg of niacin, 0.6 mg of vitamin B6,15 mcg of biotin, acid 3 mg of pantothenic, 5 mg of zinc, 0 mcg of selenium, and 400 mcg of vitamin K1). During the last 5 years, his weight has maintained between the fifth and 10th percentile, (–0.89 z-score), and his height was near the 25th percentile (equivalent to –1.2 z-score). His diarrhea improved significantly afterward and his ADEK vitamin levels were normalized Figure 1.

4.2 | Case 2

This patient is a 16-year-old boy who is the younger brother of case 1. He was born full-term with an uneventful prenatal and perinatal history. Similar to his brother, he initially presented at the age of 6 years with chronic diarrhea that affected his growth. He also had recurrent ear infections with perforation of the tympanic membrane bilaterally. He was referred to the pediatric gastroenterology service at the age of 9 years for further evaluation of his chronic diarrhea and dysmorphic features. His physical examination showed dysmorphic features in the form of triangular face, small ala nasi and small and deformed teeth. His weight was 19.5 kg (fifth percentile, –1.27 z-score), and his height was 110 cm (1.5th percentile, –1.84 z-score). Systemic examinations were unremarkable. The main presentation features are shown in Table 1. His complete blood count and differential (CBCD) parameters were normal until the age of 10 years when he started to have leukopenia (WBC: 2.1×10^9–3.40×10^9/L) and mild microcytosis that persisted over the last few years. Other hematological and biochemical investigations were unremarkable as shown in Table 2. His serum lipase level was low at 4 U/L (reference range: 13–16 U/L), fecal elastase level was also low at 6.6 µg/mL stool (normal value > 200 µg/mL), and fecal fat was 1.5/100 g stool (normal value < 2.8 g/100 g). Otoscopic examination confirmed perforation of the left tympanic membrane and ear discharge. Suspected cystic fibrosis was not investigated by sweat chloride measurement but investigated with genetic test for CFTR gene mutations which revealed a homozygous sequence variation of a missense mutation (c.443 T > C; p.I148T) and three allele polymorphism IVS9(TG)10/10-(T)7/7 of CFTR gene comprising c. 1408 G > A (p.V470M), c.2562 T > G (p.T854T), and c.4389 G > A (p.Q1463Q). All of these variations were nondeleterious CFTR gene mutations.[13–15] He was managed with pancrelipase (Creon 10; for constitution see above) 2–4 capsules with each meal, ADEK supplement one tablet daily, and omeprazole 20 mg daily. JBS was suspected based on his family history and clinical and laboratory findings. WES testing confirmed the same homozygous missense mutation in the UBR1 gene as his brother. During his follow-up treatment in the pediatric gastroenterology service, he continued his management of pancreatic insufficiency in the presence of occasional, moderate diarrhea. His ADEK vitamins levels stabilized. Both his height and weight remained in the fifth percentile.

4.3 | Case 3

The patient is a 13-year-old girl who was the sister of cases 1 and 2 in this series. She was born full-term with an unremarkable prenatal and perinatal history. She was referred to the pediatric gastroenterology clinic at the age of 7 years with a history of chronic dry cough and persistent diarrhea as four to five watery stools per day in moderate amounts. Her physical examination showed low weight (below 3rd centile, –0.84 z-score) and some dysmorphic features such as a triangular face, hypoplastic nasal alae, microdontia (persistent primary dentition), and hypoplastic upper jaw. Her other systemic examinations were unremarkable with normal female genitalia (Table 1). Her baseline investigations, as shown in Table 2, including normal CBCD, urea and electrolytes, hepatic enzymes, thyroid hormones, and serum amylase level. Her serum lipase level was low (4 U/L). Serum vitamin D and vitamin K level were normal while the serum vitamin A level was low (174 µg/L). Fecal elastase level was low (≤20 µg/mL stool). Pure tone audiometry revealed normal hearing. She was suspected of having CF but her genetic testing of CFTR was unremarkable. Her WES genetic test revealed that she inherited the same mutation in the UBR1 gene as her older brothers, and found to be a carrier (heterozygous) for a CGM-confirmed variant in

TABLE 1 shows the main presentation features of the four cases.

Feature	Patient # 1	Patient # 2	Patient# 3	Patient # 4
Current age (years)	17	16	13	7
Age at diagnosis (years)	12	9	7	5
Gender	Male	Male	Female	Female
Exocrine pancreatic insufficiency	Yes	Yes	Yes	Yes
Craniofacial deformities	Hypoplastic alae nasi, aplasia cutis, and a forehead hairline extension	Triangular face, hypoplastic alae nasi, small chin	Triangular face, hypoplastic nasal alae, and hypoplasticupper jaw.	Upsweeping of the frontal hairline, hypoplasticala nasi.
Intellectual disability	No	No	No	No
Growth failure	No	Yes	No	Yes, on GH
Hearing assessment	Normal	Moderate to moderately severe CHL on the left ear and mild CHL on the right ear	Normal	Moderate SNHL with hearing aids
Teeth anomalies	Microdontia	Microdontia	Microdontia	No
Urogenital anomalies	No	No	No	No
Echocardiogram	Normal heart structure and function	Normal heart structure and function	Hemodynamically stable, 2 millimeters ASD	Normal heart structure and function
Hypothyroidism	No	No	No	Yes
Nutrition	Pediasure + high calorie/high protein diet	Pediasure + high calorie/high protein diet	Pediasure + high calorie/high protein diet	Pediasure + high calorie/high protein diet
Failure to thrive	Weight and height on 25% percentile	Weight and height on < 5% percentile	Weight on 3% and height on the 10% percentile	Weight and height on < 3% percentile

Abbreviations: ASD, atrial septal defect; CHL, conductive hearing loss; GH, growth hormone.

TABLE 2 initial laboratory investigation for the four cases.

Test/Units	Patient # 1	Patient # 2	Patient # 3	Patient # 4	Reference range
White blood cell count (10^9/L)	6.6	4.9	4.7	7.7	3.9–11
Hemoglobin (g/L)	115	118	108	103	135–180
Platelets count (10^9/L)	386	371	353	312	155–435
Absolute neutrophil count (10^9/L	2.7	3.91	1.5	2.6	1.35–7.50
Total protein (g/L)	77	75	76	70	66–87
Serum albumin (g/L)	48	42	43	40	39–49
ALT (U/L)	9	14	44	59	0–41
AST (U/L)	21	27	21	93	0–40
GGT U/L	14	14	11	53	May–49
Lipase (U/L)	4	4	4	5	13–60
Amylase (U/L)	45	41	42	137	28–100
Urea (mmol/L)	6.8	3.7	5.5	2.3	2–6.2
Serum creatinine (umol/L)	41	51	47	33	62–106
Hba1c (%)	0.056	0.053	5.4	Not done	4.8–5.9
FT4 (pmol/L)	19	17	21	18	12–22
TSH (mU/L)	1.7	3	4.5	8.3	0.36–4.7
Vitamin E (mg/L)	6.1	7.5	7.3	Not done	5.5–15.5
Vitamin A (ug/L) (Retinol)	238	285	174	Not done	343–838
25-hydroxyvitamine-D (nmol/L)	49	37	52	Not done	60–200: Optimum level, 25 60: moderate deficiency, <25: severe deficiency.
Vitamin K1 (ng/mL)	0.12	1.7	2.2	Not done	0.2–3.2 ng/mL
Fecal fat (g/100 g stool)	Not done	1.5 on therapy	Not done	>60	<60/100 g stool
Fecal elastase (μg/mL)	≤27	<6.6	≤20	<15	>200
UBR1 gene test	All four cases were homozygous for the missense variant of UBR1 exon 18: c.2075 T > C. (p.Ile692Thr), references rs1235759223				

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin.

the C2 gene (c.841_849 + 19del) that may cause C2 deficiency when inherited as homozygous. Based on her clinical presentation, positive family history of JBS, laboratory findings, and WES test results, she was diagnosed as JBS, and she was started on creon and nutritional support management and was noted to have weight gain afterward.

4.4 | Case 4

A 7-year-old girl was presented to our clinic with a history of short stature and hypothyroidism. She had been on growth hormone therapy for 1 year and was taking thyroxine 25 μg (mcg) daily for hypothyroidism. The patient's mother reported that she had been noticing fatty stool in her daughter for the past 3 years. The stool was often loose and floated in the toilet. The patient had no other symptoms such as abdominal pain, nausea, vomiting, or diarrhea. She had been growing at a slower rate than her peers and was below the third percentile for weight and height (−5 z-score). The patient was born at term, and she was small for gestational age (birth weight 2 kg). Her parents were not related and had no significant medical history. The patient lived with her parents and two healthy siblings. She was in first grade at school with no academic impairment. Physical examination revealed a body weight of 11 kg and a height of 85 cm (both below

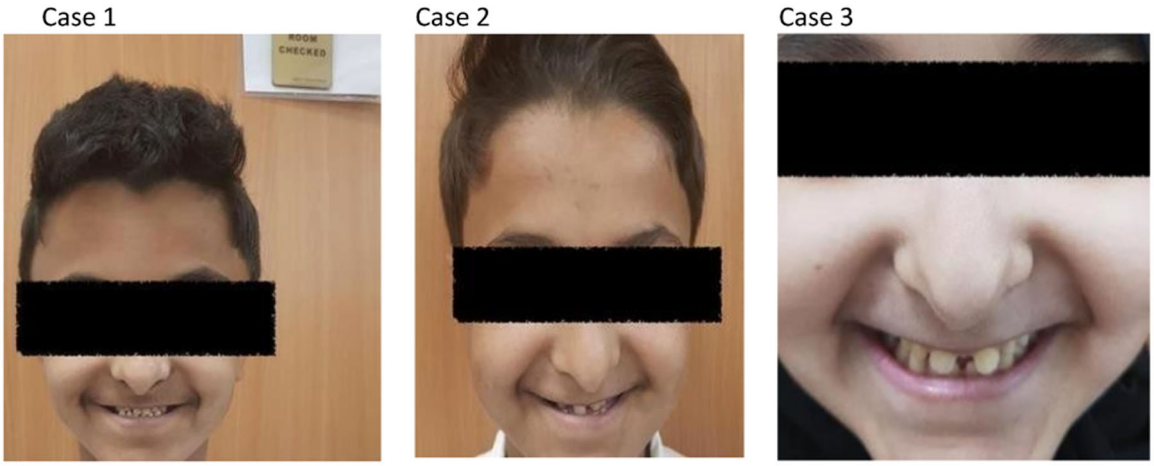

FIGURE 1 The main presentation features for three of the four cases.

the third percentile; –5 z-score). Other findings included an upswept frontal hairline, hypoplastic alae nasi, microdontia, and a capillary hemangioma on the inner part of the left leg (Table 1). There were no other abnormalities in the systemic examination. Laboratory workup is shown in Table 2. Initial CBCD showed normal Hb level, however, during her follow-up she developed mild anemia (Hb: 96 g/L) with microcytosis. She had normal bone and renal profiles with mild elevation of alanine aminotransferase (59 U/L) and aspartate aminotransferase (93 U/L). Amylase was high (137 U/L) while lipase was low (5 U/L). She found to have mild hypothyroidism with high thyroid-stimulating hormone (8.3 mU/L) level and normal free thyroxine (FT4: 18 pmol/L). TSH normalized to 4.5 mU/L after 8 weeks of levothyroxine supplementation at a daily dosage of 25 µg. Fecal elastase level was also low ≤15 µg/mL stool. Pure tone audiometry revealed bilateral mild to moderately severe SNHL necessitating hearing aids.

Echocardiography was normal. Ultrasound examination of the abdomen revealed increased liver echogenicity, a dilated gallbladder, and a 0.9 cm splenule. WES test revealed identical homozygous mutations in the UBR1 gene (C2075T > C; p. Ile692Thr), consistent with JBS. The diagnosis of JBS for the patient was established by her clinical symptoms, lab tests, and WES analysis. She is currently being treated with growth hormone (0.33 mg SC injection daily), pancreatic enzyme replacement (Creon 10,) as one capsule four times daily with meals, and hearing aids.

5 | DISCUSSION

EPI is a condition resulting from lack of production of pancreatic enzymes that usually presents with steatorrhea, failure to thrive, and symptoms of several fat-soluble vitamins deficiency. EPI could be diagnosed by direct endoscopic assessment of pancreatic enzymes, and indirect by presence of steatorrhea (more than 60 fat globules/100 g of stool), and pancreatic elastase level less than 200 µg/mL. These case series used the pancreatic fecal elastase level as a criterion to define and classify EPI into mild (100–200), moderate (50–100), and severe (<50 µg/mL) categories. Pediatric EPI could result from congenital anomalies (such as pancreatic agenesis or inherited isolated enzyme deficiency), congenital/inherited conditions resulting in recurrent acute pancreatitis with subsequent EPI (such as pancreatic divisum, cationic trypsinogen gene mutation), or several inherited syndromes that have different genetic background with variable systems involvement but commonly have EPI. Table 3 show the clinical characteristics of four condition that have EPI.

In this paper, we present four children with JBS (three of them are siblings, and the fourth patient is unrelated) who presented with a typical dysmorphic facial appearance, of JBS, EPI, and some additional features of JBS. All four cases had a novel missense mutation c.2075 T > C (p. Ile692Thr) in the UBR1 gene. This mutation affects a highly conserved amino acid residue in the UBR1 protein and is likely to impair its function. The molecular characteristics of this detected mutation are shown in Table 2. However, further functional studies are needed to confirm its pathogenicity and to elucidate its role in the development of JBS. This mutation has not been reported before in JBS patients and adds to the genetic diversity of this disorder.

The exact incidence and prevalence of JBS worldwide are unknown. JBS has been recorded globally in less than 100 cases.[5] According to Orphanet,[16] the prevalence of JBS in Europe has been estimated to be around 1/250,000 live births. There are only a few case reports of JBS from different regions, including Saudi Arabia,[9,10] however, no systematic data on the regional

TABLE 3 comparing Johanson–Blizzard syndrome (JBS) to other inherited syndromes with pancreatic insufficiency.

Condition	Cystic fibrosis	Schwachman-diamond syndrome	JBS	Pearson marrow-pancreas syndrome
Gene name (location)	CFTR (chr7q31.2)	SBSD (chr7q11)	UBR1 (chr15q15.2)	mtDNA deletion
Disease pattern	Ductular	Acinar	Acinar	Acinar
Pancreatic pathology	Lipomatosis	Lipomatosis	Lipomatosis	Fibrosis
Associated features	FTT, DM, and pulmonary manifestations	FTT, DM, short stature, neutropenia, and skeletal abnormalities	FTT, DM, facial dysmorphism, and SNHL	FTT, DM, sideroblastic anemia, and neuromuscular impairment
Exocrine PI complications	Persistent respiratory failure	Intermittent leukemia	Persistent EPI	Persistent EPI, early death
Treatment	PERT, and respiratory Support	PERT, G-CSF, and BMT	PERT, hormone, and hearing aid	PERT

Abbreviations: BMT, bone marrow transplantation; DM, diabetes mellitus; FTT, failure to thrive; G-CSF, granulocyte-colony stimulating factor; mtDNA, mitochondrial DNA, PERT, pancreatic enzyme replacement therapy; SBSD, Schwachman–Bodian–diamond syndrome gene.

distribution of JBS patients are available. The clinical manifestations of JBS are highly variable. The most common features are EPI (>90%), microdontia, and craniofacial deformities (>90%).[5,17] Additional symptoms occur with different frequencies such as SNHL (~75%), scalp defects (~65%), developmental and intellectual delays (~60%), short stature (~60%), hypothyroidism (~40%), microcephaly (~35%), genitourinary malformations (~30%), and congenital heart defects (25%).[18–21] In our case series, we observed a similar spectrum of clinical features as reported in the literature. All these four patients had EPI with craniofacial deformities, three patients with hypodontia, two of them with hearing loss, one with scalp aplasia cutis, one with recurrent ear infections, one with hypothyroidism that necessitate treatment with levothyroxine, and with growth retardation requiring growth hormone supplementation. Additionally, one of our cases has small ASD, one has a splenule and another one has a capillary hemangioma on her leg. Splenule and capillary hemangioma have never been linked to JBS before. These findings suggest that JBS may have variable expressivity and is influenced by other genetic or environmental factors.

CF and JBS are rare genetic causes of EPI with overlapping symptoms such as pancreatic insufficiency, malabsorption, and failure to thrive, making their differentiation challenging.[22,23] However, JBS can be distinguished from CF by its distinct craniofacial dysmorphism. Three of our cases were first suspected to have CF by genetic testing and no sweat chloride test has been done on any of them, but the implementation of a thorough physical examination has led to a more accurate diagnosis. Therefore, a high index of suspicion is required for including the JBS in the workup of children with EPI. All the cases we have shown here have had stable clinical courses over the length of 2–7 years of follow-up.

The strengths of our study include the identification of a novel UBR1 mutation causing JBS, the comprehensive description of the clinical features and laboratory findings of four patients from two families, and the long-term follow-up of the patients. The limitations of our study include the retrospective design, the small sample size, and the lack of functional studies to confirm the pathogenicity of the mutation. Our study contributes to the existing literature on JBS and highlights the importance of early diagnosis and multidisciplinary management of this rare disorder. To our knowledge, those cases of patients have not been published in any other study.

In conclusion, we report a novel homozygous missense mutation in the UBR1 gene causing JBS in four Saudi patients (three of which are siblings, and the fourth patient is unrelated). Our report may help healthcare providers who treat similar patients and eventually add to the current scarce literature on the subject. The unique discovery of this UBR1 gene variant may extend the database of this syndrome. This expands the spectrum of UBR1 mutations and

phenotypic variability associated with JBS. JBS is a rare disorder that requires early diagnosis and multidisciplinary management to improve the quality of life and prognosis of patients. Genetic testing for UBR1 mutations is crucial for confirming the diagnosis and providing genetic counseling.

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The parents of each patient in our study were informed how these conditions would be addressed and treated including genetic testing. They had given their permission to present their children (including showing genetic test result and photography pictures) in this publication by signing a consent form. The IRB board at our institution has approved the proposal. The authors have no funding to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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