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Intrafamilial phenotypic variability due to a missense pathogenic variant in FBP1 gene

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ABSTRACT

Background: FBPase deficiency as an autosomal recessive disorder is due pathogenic variants in the FBP1 gene. It usually presents with hyperlactic acidemia and hypoglycaemia starting from early childhood. Here, genotypes and phenotypes of all reported patients and their distributions are presented. In addition, we present an Iranian family with two affected children presenting with unusual symptoms due to pathogenic variants in the *FBP1* gene.

Clinical evaluations and laboratory assessments were performed for the affected members. Whole exome sequencing (WES) was applied in order to find the causal variant. In addition to segregation analysis within the family, variant pathogenicity analyses and predictions were done via bioinformatics tools and according to ACMG guidelines. The genotypes and detailed clinical features were documented for all patients.

Results: The study included a population of 104 patients with different variants of the *FBP1* gene; 75 were homozygotes. The average age of onset was 14.97 months. The most frequent clinical features were metabolic acidosis (71 cases), hypoglycemia (70 cases), vomiting (46 cases), hyperuricemia (37 cases), and respiratory distress (25 cases). 74 families were from Asia. The most common genotypes were c.841G > A/c.841G > A and c.472C > T/c.472C > T. WES test showed a pathogenic homozygous variant, c.472C > T in two cases of a family: a six-and-a-half-year-old girl with an older brother with different symptoms. All laboratory evaluations in the patient were normal except for the blood sugar. The patient experienced her first hypoglycemic episode at age 3.

Conclusions: This is an unusual presentation of FBPase deficiency with intrafamilial phenotypic variability.

1. Introduction

Fructose-1,6-bisphosphatase (FBPase) deficiency as an autosomal recessive metabolic disease was described by Baker and Winegrad (1970). It affects the liver and involves the gluconeogenesis pathway. This disorder is defined by episodic acute crises of lactic acidosis and ketotic hypoglycemia. FBPase deficiency is caused by pathogenic variants in the *FBP1* gene. FBPase acts as an essential enzyme in the metabolic pathway of gluconeogenesis [1–3]. As it is known, gluconeogenesis leads to the production of glucose from non-glucose substances such as lactate, pyruvate, glycerol, and alanine. Gluconeogenesis mainly occurs after a limited period of fasting in adults, although it happens more quickly in younger individuals because of insufficient storages of glycogen to supply their need for glucose [4,5]; thus, gluconeogenic substrates including lactate, alanine, and glycerol increase in the human body. In addition, it can lead to a fatal condition in neonates and infants via lacking glycogen storage [6–8].

The early presentations of FBPase deficiency are fasting hypoglycemia and hyperlactic acidaemia Followed by hyperventilation, tachycardia, dyspnoea, muscular hypotonia, hepatomegaly, irritability, seizure, and lethargy that may lead to coma [2,9]. In most patients, similar episodes are triggered by catabolic factors such as infections, fever, diarrhea, massive fructose intake, and prolonged fasting before two years of age. It is highlighted that the affected children don't present any symptoms between episodes of crisis, and will have a normal psychomotor development [7,10].

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It is known that biallelic *FBP1* pathogenic variants lead to enzyme deficiency; approximately 97 variants including small intragenic deletions/insertions, missense, nonsense, and splice variants have been reported in this gene. About 31 of these variants are missense. A missense variant, c.472C > T (p.Arg158Trp), has been reported in 8 patients yet [7,11,12]. Here, we present genotypes and phenotypes of all reported patients and their distributions. In addition, we describe an Iranian family with two affected children presenting with unusual symptoms due to a homozygous variant in the *FBP1* gene.

2. Materials and methods

2.1. Review Literature

The study focused on patients who had pathogenic or likely pathogenic variants in the *FBP1* gene. Individual data was collected based on clinical characteristics and genetic analyses for the disease. A comprehensive search was conducted on PubMed, ScienceDirect, and John Wiley and Springer databases to find published reports on the genetics of Fructose-1, 6-Bisphosphatase Deficiency across the globe. In our study, we used the following keywords to search and collect data from relevant studies: "likely pathogenic/pathogenic variant" " *FBP1* genetic analysis", " *FBP1* molecular findings", "*FBP1*", and "FBPase Deficiency" along with the search terms "phenotypic variability." The information collected included the number of patients, age of onset, gender, clinical symptoms, variant type, zygosity, geographic location, and ethnicity. Using the criteria extracted from relevant studies, we selected the most frequent variants for further analysis and calculated the mutation frequencies in patients and different countries.

2.2. Molecular Analyses

DNA extraction was performed from peripheral blood. WES was applied using an Illumina Novaseq6000 platform with a mean read depth of 150×. The alignment and variant calling were done using the reference genome GRCh38 version. To filter the variants with a minimal allele frequency (MAF) of more than 0.01, the following databases were used: Exome Sequencing Project 6500 (http://evs.gs.washington.edu/EVS/), the Exome Aggregation Database (http://exomad.broadinstitute.org/) and the Exome Aggregation Consortium database (http://exac.broadinstitute.org). The pathogenicity of variants was predicted according to MutationTaster (http://www.mutationtaster.org/), SIFT (https://sift.bii.a-star.edu.sg/), PROVEAN (http://provean.jcvi.org/index.php), CADD (https://cadd.gs.washington.edu/home). The ACMG was used for the classification of variants [13–15]. Segregation analysis and variant confirmation were done using Sanger sequence.

3. Results

3.1. Clinical Presentations

A six-and-a-half-year-old girl with normal development and growth presented with recurrent hypoglycaemic episodes at the ages of 3, 4, and 6.5 years. During these episodes, she experienced weakness, malaise, abdominal pain, vomiting, and loss of consciousness after a viral or bacterial infection. Her 11-year-old brother has also been experiencing similar hypoglycaemic attacks for three years of age; his first episode with a presentation of tonic convulsions, but other episodes presented with weakness, malaise, and disorientation. The parents of these children were consanguineous.

The initial laboratory evaluations during the onset of hypoglycemic episodes revealed the following serum markers: insulin = 3.1 μIU/mL, GH = 0.36 ng/mL, ACTH = 15.8 pg/mL, lactate = 27 mg/dL, ammonia = 26 μg/dL, IGF-1 = 192.3 ng/mL, AST = 26 IU/L, ALT = 20 IU/L, ALK. p = 557 U/L, LDH = 310 IU/L, CPK = 84 IU/L, amylase = 61 U/L, lipase = 23 IU/L, and BUN = 9.7 mg/dL. All these values were within normal ranges, except for blood sugar, which was noted as abnormal during episodes of hypoglycemia.

3.2. Variant analyses

Considering the patient's presentation, a whole exome sequencing (WES) test followed by variant confirmation by direct Sanger sequencing. The results showed Chr9–97,372,298 G A: c.472C > T (p.Arg158Trp) in exon 4 (Fig. 1). The patient's parents were heterozygotes while her sibling was homozygote for this variant. Forty-nine variants were found in the patients.

Among the 102 patients identified from the literature, the data encompassed a wide range of clinical features and genotypic variants. The two patients from our own study were part of a specific family with unique clinical presentations.

The study included a population of 104 patients from 99 families, all of whom possessed different variants of the *FBP1* gene; 73 of them were homozygotes. Three families reported having multiple sick children; for instance, family 66 had two sick children and one ailing daughter. Additionally, 72 families had one sick daughter and one suffering son, while 87 families had two sick sons and one daughter's patient. There were 48 male cases and 38 female cases, and 14 cases had not noted their sexes. Detailed information on parental consanguineous marriages is not reported in the literature. We included one patient in our study, along with 21 articles that had patients with abnormal expression of Fructose 1,6-bisphosphatase. The articles were used to collect data for analysis, and these patients were added to the study. In our study, we found that infection and starvation were the most common triggers for the onset of illness in our studied patients.

The most frequent clinical features were metabolic acidosis (71 cases), hypoglycemia (70 cases), vomiting (46 cases), hyperuricemia (37 cases), and respiratory distress (25 cases). Other common symptoms included hepatomegaly, loose motion, fever, and lethargy, all of which, along with the five most frequent symptoms, are depicted in Fig. 2A and Table 1.

The age of onset was noted in 79 cases; the average age of onset was determined to be 14.97 months ranging from birth to 6.5 years old. From a molecular analysis, we found that 73 different variants of the *FBP1* gene were present as homozygotes, while 29 were present as compound heterozygotes.

In this study, 17 missense variants, 17 indel variants, 5 splice site variants, 5 large deletion/duplication variants, and 4 nonsense variants

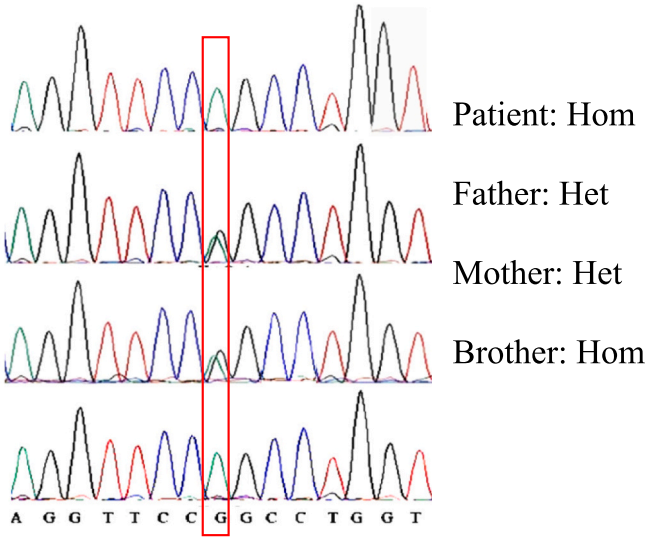

Fig. 1. Electropherograms of the c.472C > T (p.Arg158Trp) in reverse strand in family members.

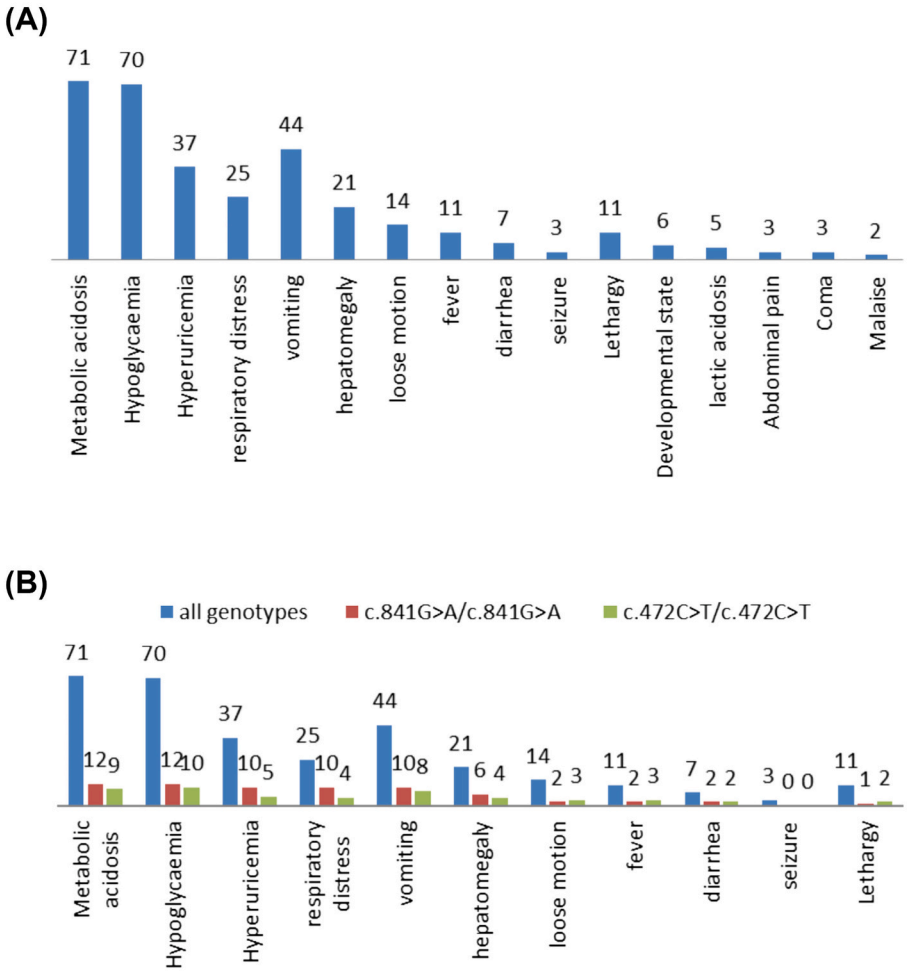

Fig. 2. A) Clinical symptoms and their frequencies. B) Frequencies of phenotypes of the most common genotypes (c.841G > A/c.841G > A, c.472C > T/c.472C > T), with red and green color, respectively.

were identified. The most common variants were c.841G > A (missense), c.960-961insG (indel), and c.472C > T (missense) accounting for 37, 25, and 24 alleles, respectively (Table 2).

3.3. Geographical distribution of the genotypes

In 99 families, ethnicity was known; 76 families were from Asia, 17 had European descendants, 2 were from Brazil, 1 was from Africa and one had a mixed ethnicity (European-American) (Fig. 3A).

3.4. Genotype-Phenotype Structure

Seventy-five percent of the genotypes were homozygotes (Fig. 3B). Five common homozygous genotypes in our study were as follows: c.841G > A/c.841G > A, c.472C > T/c.472C > T, c.960-961insG/c.960-961insG, c.117_118insACCTGC/ c.117_118insACCTGC, and c.778G > A/ c.778G > A responsible for 18, 11, 6, 5 and 2, respectively. There are some phenotypes related to specific genotypes.

The mean age of onset in patients with c.841G > A/c.841G > A genotype was 7.38 months.

The most clinical symptoms in homozygous patients were metabolic acidosis (12 cases), hypoglycemia (12 cases), hyperuricemia (10 cases), respiratory distress (10 cases) and vomiting (10 cases) (Fig. 2B). A low level of blood ammonia was noted in 5 cases with this genotype.

The mean age of onset in patients with c.472C > T/c.472C > T was 17.37 months. The most clinical symptoms in homozygous patients were hypoglycemia (10 cases), metabolic acidosis (9 cases), vomiting (10 cases), hyperuricemia (5 cases), respiratory distress (4 cases), and diarrhea (2 cases). A low level of blood ammonia was noted in 3 cases with this genotype. Lactic acidosis and keto acidosis have appeared in genotype c.960-961insG/c.960-961insG. In homozygous patients with c.778G > A variant showed hypoglycemia lactic acidosis, and vomiting.

4. Discussion

FBPase deficiency as an autosomal recessive disorder involves the gluconeogenesis pathway leading to a variety of symptoms in different patients. Our study shows that metabolic acidosis, hypoglycemia, vomiting, hyperuricemia, and respiratory distress are the most common clinical features. The homozygous c.841G > A/c.841G > A, c.472C > T/c.472C > T, c.960-961insG/c.960-961insG are the most common genotypes. Here, we present the first family having two siblings with different phenotypes indicating intrafamilial phenotypic variability. To our knowledge, this is the first reported case of Fructose-1,6-bisphosphatase deficiency where the homozygous c.472C > T variant (p.Arg158Trp) is associated with significant intrafamilial phenotypic variability.

In general, the largest number of reported cases comes from Asia. This disease may be widespread in this continent. In Europe, 24 % of families have been reported, but in other continents, limited families have been reported. Regarding the mutation types in this disease, the following are common: c.841G > A/c.841G > A, c.472C > T/c.472C > T, c.960-961insG/c.960-961insG, and c.117_118insACCTGC/ c.117_118insACCTGC. Most of these mutation types are prevalent in the

Table 1
A literature review of reported cases with FBP1 gene mutations as well as the patient was reported in the study.

No.	ethnicity	sex	Age of onset	Triggers	Metabolic acidosis	Hypoglycemia	Hyperuricemia	Signs and Symptoms	Developmental state	Blood ammonia	Genotype	ref
1	France	M	25mo	Infection	+	+	NR	Malaise, vomiting	NR	NR	c.48_48delC/c.472C > T	[2]
2	Greece	M	2y	Infection	NR	+	NR	Loss of consciousness	NR	NR	c.865dupA/c.865dupA	[2]
3	NR	M	12 h	Birth	+	+	NR	NR	NR	NR	c.825 + 1G > A/c.960_961insG	[2]
4	France, Colombia	M	48 h	Food refusal	+	–	NR	NR	NR	NR	c.427-1del/E1del	[2]
5	Turkey	F	14mo	Infection	+	+	NR	NR	NR	NR	c.731–738delins20/ c.731–738delins20	[2]
6	NR	M	10mo	Hyperprotidic diet	NR	NR	NR	Reye syndrome, Glycerol Uria	NR	NR	g.97,364,754-97,382.011del/ g.97,364,754-97,382.011del	[2]
7	Pakistan	F	17mo	NR	+	NR	+	diarrhea, vomiting, fits, and coma	–	NR	c.472C > T/c.472C > T	
8	Pakistan	M	12 m	NR	+	+	NR	vomiting and diarrhea	–	NR	c.472C > T/c.472C > T	
9	Indian	M	12 mo	NR	+	NR	+	respiratory distress, vomiting, hepatomegaly	NR	Low	c.841G > A/c.841G > A	[8]
10	Indian	M	2d	NR	+	+	+	respiratory distress, vomiting, hepatomegaly, fever	NR	High	c.841G > A/c.841G > A	[8]
11	Indian	M	1d	NR	+	+	+	respiratory distress, vomiting, hepatomegaly, fever	NR	Low	c.472C > T/c.472C > T	[8]
12	Indian	M	6mo	NR	+	+	+	respiratory distress, vomiting, hepatomegaly, fever	NR	Low	c.841G > A/c.841G > A	[8]
13	Indian	M	12 mo	NR	+	+	+	respiratory distress, vomiting, hepatomegaly,	NR	NK	c.841G > A/c.841G > A	[8]
14	Indian	M	7d	NR	NR	+	NR	respiratory distress, vomiting,	NR	NK	c.841G > A/c.841G > A	[8]
15	Indian	M	7mo	NR	NR	+	NR	respiratory distress, hepatomegaly, diarrhea	NR	NK	c.472C > T/c.472C > T	[8]
16	Nepal	F	12 mo	NR	+	+	+	respiratory distress, vomiting, hepatomegaly, diarrhea	NR	NK	c.778G > A/c.778G > A	[8]
17	Indian	M	4mo	NR	+	+	+	respiratory distress, hepatomegaly, seizure	NR	NK	c.349 T > C/c.349 T > C	[8]
18	Indian	M	1d	NR	+	+	+	respiratory distress, hepatomegaly, diarrhea	NR	NK	c.841G > A/c.841G > A	[8]
19	Indian	F	4mo	NR	+	+	+	respiratory distress,	NR	Low	c.841G > A/c.841G > A	[8]
20	Nepal	M	1d	NR	NR	NR	NR	respiratory distress, diarrhea	NR	NK	c.841G > A/c.841G > A	[8]
21	Bangladesh	M	18mo	NR	+	+	+	respiratory distress, vomiting, hepatomegaly, lethargy	NR	Low	c.841G > A/c.841G > A	[8]
22	Indian	F	1d	NR	+	+	+	respiratory distress, vomiting, hepatomegaly, lethargy, diarrhea	NR	Low	c.841G > A/c.841G > A	[8]
23	Indian	M	12 m	NR	+	+	+	respiratory distress, vomiting, hepatomegaly, lethargy	NR	Low	c.472C > T/c.472C > T	[8]
24	Indian	F	7mo	NR	+	+	+	Fever, mild Hepatomegaly	NR	Low	c.426 + 1G > T/c.609-612delAAAA	[8]
25	Indian	F	NR	NR	+	+	NR	Fever, mild Hepatomegaly	NR	Low	c.472C > T/c.472C > T	[8]
26	Indian	M	Neo	NR	+	NR	NR	Respiratory Distress, Vomiting, Diarrhea	NR	NR	DelofE3/DelofE3	[8]
27	Pakistani	M	1y	NR	+	+	NR	Vomiting, Diarrhea	NR	NR	c.609-612delAAAA/c.609-612delAAAA	[21]
28	Pakistani	M	2y	NR	+	+	NR	vomiting	NR	NR	c.841G > A/c.841G > A	[21]
29	Pakistani	F	1.5y	NR	+	+	NR	Vomiting and loose motion	NR	NR	c.472C > T/c.472C > T	[21]
30	Pakistani	M	9mo	NR	+	+	+	vomiting	NR	NR	c.841G > A/c.841G > A	[21]
31	Pakistani	M	2.5y	NR	+	+	NR	Vomiting and loose motion	NR	NR	c.472C > T/c.472C > T	[21]
32	Pakistani	M	2d	NR	–	NR	NR	Vomiting, Diarrhea, Fever	NR	NR	c.472C > T/c.472C > T	[21]
33	Pakistani	F	1y	NR	+	+	NR	Vomiting and loose motion	NR	NR	c.841G > A/c.841G > A	[21]
34	Pakistani	F	6mo	NR	+	+	+	Vomiting and loose motion	NR	NR	c.841G > A/c.841G > A	[21]
35	Pakistani	M	2y	NR	+	+	+	vomiting	NR	NR	c.472C > T/c.472C > T	[21]

(*continued on next page*)

Table 1 (*continued*)

No.	ethnicity	sex	Age of onset	Triggers	Metabolic acidosis	Hypoglycemia	Hyperuricemia	Signs and Symptoms	Developmental state	Blood ammonia	Genotype	ref
36	London	M	30mo	starving	+	+	NR	Fatigue, Unconscious, Dysuria, Hyperventilation	NL	High	c.490G > A/c.923C > G	[22]
37	London	M	1d	Infection	+	−	NR	Noisy breathing, Tachypnoea, Wet cough, Vomiting	Del	NR	c.472C > T/c.472C > T	[23]
38	Korea	F	4y	starving	+	+	+	Complex febrile convulsions, Loss of consciousness, Abdominal pain, Fever, Lethargy	NR	NR	c.490G > A/c.960_961insG	[24]
39	Saudi Arabia	F	1d	NR	+	+	+	Respiratory distress	NL	NL	c.114-115insCTGCAC/c.114-115insCTGCAC	[25]
40	Saudi Arabia	F	1d	NR	+	+	−	Hepatomegaly	NL	NL	c.114-115insCTGCAC/c.114-115insCTGCAC	[25]
41	Saudi Arabia	F	1y	NR	+	+	+	Hepatomegaly	NL	NR	c.841G > T/c.841G > T	[25]
42	Saudi Arabia	M	1y	NR	+	+	−	NR	NL	NR	c.114-115insCTGCAC/c.114-115insCTGCAC	[25]
43	Saudi Arabia	M	5mo	NR	−	+	NR	Hepatomegaly	Del	NR	c.334-2A > T/c.334-2A > T	[25]
44	Saudi Arabia	M	2y	NR	+	+	NR	NR	NR	NL	c.959dupG/c.959dupG	[25]
45	China	M	4y	Starving Infection	+	+	NR	Convulsion, Loss of consciousness, Coma, Fever	Del	NR	c.333 + 1_333 + 2delinsTC/c.490G > A	[26]
46	Japan	F	1d	NR	+	+	NR	Respiratory distress	NR	NR	c.841G > A/c.960_961insG	[27]
47	Japan	M	18mo	NR	+	+	+	Pallor, Hepatomegaly, Kussmaul respiration	NR	High	c.530C > A/c.268 T > G	[28]
48	Chaina	F	3d	NR	+	+	+	Fever, Vomiting, Convulsions, Coma	NL	NR	c.704delC/c.960_961insG	[29]
49	Chaina	F	4y	NR	+	+	+	Convulsion, Vomiting	NL	NR	c.825 + 1G > A/c.960_961insG	[29]
50	Chaina	F	8mo	NR	+	+	+	Vomiting, Convulsions, Fainting	NR	NR	c.355G > A/c.355G > A	[29]
51	Chaina	M	1d	Starving	+	+	+	Vomiting, Convulsions, Coma, hepatomegaly	Del	NR	c.490G > A/c.720_729del	[29]
52	India	F	3y	Starving	+	+	+	Abdominal pain, Vomiting, Loose stools, Lethargy, Seizure, Hepatomegaly, Altered sensorium	NR	NR	Insertiona331-bpAlu/Insertiona331-bpAlu	[30]
53	Sweden	M	1d	Infection	+	+	+	Vomiting, Somnolence, Generalized seizure	NL	NR	c.778G > A/c.881G > A	[31]
54	Sweden	M	1d	Infection	+	+	NR	Fever, Vomiting	NR	NR	c.648C > G/c.648C > G	[31]
55	German-Turkish	F	36 h	NR	+			lactic acidosis, pronounced ketonuria and glyceroluria	NL	NR	c.35delA/c.35delA	[32]
56	Pakistani	F	13mo	NR	+	+		hypoglycaemia and lactic acidosis, vomiting	NL	NR	c.778G > A/c.778G > A	[32]
57	German	M	5y	NR	+	+		lactic acidosis and keto acidosis	NL	NR	c.960-961insG/c.960-961insG	[32]
58	Iranian	F	3mo	NR	+	+		drowsiness, hypoglycaemia and severelactic acidosis, otitis media	NL	NR	c.966delC/c.966delC	[32]
59	Morocco	NR	NR	NR	NR	NR	NR	NR	NL	NR	c.685C > T/c.685C > T	[33]
60	Japan	F	1d		+	+		Tachypnoea	NL	NR	c.960-961insG/c.960-961insG	[34]
61	Japan	F	11mo		+	+		Vomiting	NL	NR	c.960-961insG/c.960-961insG	[34]
62	Japan	F	12 mo		+	+		Lethargy	NL	NR	c.960-961insG/c.960-961insG	[34]
63	Japan	F	16mo		+	+		Vomiting	NL	NR	c.490G > A/c.960-961insG	[34]
64	Japan	M	48mo		+	+		Vomiting	NL	NR	c.490G > A/c.960-961insG	[34]
65	Japan	M	8mo		+	+		Vomiting	NL	NR	c.490G > A/c.960-961insG	[34]
66	Japan	F	1mo		+	+		Drowsiness	NL	NR	c.530C > A/c.960-961insG	[34]
67	Japan	F	12 mo		+	+		Vomiting	NL	NR	c.88G > T/c.88G > T	[34]
	Saudi Arbia	F	NR	NR	NR	NR	NR	NR	NR	NR	c.117_118insACCTGC/c.117_118insACCTGC	[35]
		M	NR	NR	NR	NR	NR	NR	NR	NR	c.117_118insACCTGC/c.117_118insACCTGC	[35]
68		M	NR	NR	NR	NR	NR	NR	NR	NR	c.117_118insACCTGC/c.117_118insACCTGC	[35]

(*continued on next page*)

Table 1 (*continued*)

No.	ethnicity	sex	Age of onset	Triggers	Metabolic acidosis	Hypoglycemia	Hyperuricemia	Signs and Symptoms	Developmental state	Blood ammonia	Genotype	ref
69	Saudi Arbia	M	NR	NR	NR	NR	NR	NR	NR	NR	c.117_118insACCTGC/ c.117_118insACCTGC	[35]
70	Saudi Arbia	F	NR	NR	NR	NR	NR	NR	NR	NR	c.841G > T/c.841G > T	[35]
71	Saudi Arbia	F	NR	NR	NR	NR	NR	NR	NR	NR	c.841G > T/c.841G > T	[35]
72	Saudi Arbia	M	NR	NR	NR	NR	NR	NR	NR	NR	c.117_118insACCTGC/ c.117_118insACCTGC	[35]
73	Japan	F	14mo	NR	+	+	+	Febrile infectious disease and manifested hyperventilation	NR	NR	c.581 T > C/c.851C > G	[36]
	Japan	F	22y	NR	+	+	+	Hypoglycaemic lactic, acidosis	NR	NR	c.491G > A/c.581 T > C	[37]
74		M	18mo	NR	+	+	+	Pale face, hepatomegaly, and kussmaul respiration	NR	NR	c.530C > A/c.268 T > G	[38]
75	Armenia	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.-24–26_170 + 5192del/c.-24–26_170 + 5192del	[39]
76	Turkey	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.-24–26_170 + 5192del/c.-24–26_170 + 5192del	[39]
77	Turkey	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.-24–26_170 + 5192del/c.-24–26_170 + 5192del	[39]
78	Pakistan	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.841G > A/ c.841G > A	[39]
79	Pakistan	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.841G > A/ c.841G > A	[39]
80	Pakistan	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.881G > A/ c.881G > A	[39]
81	Germany	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.841G > A/ c.841G > A	[39]
82	Germany	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.490G > A/ c.490G > A	[39]
83	Germany	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.490G > A/ c.490G > A	[39]
84	Turkey	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.704dupC/ c.704dupC	[39]
85	Turkey	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.359C > T/ c.881G > A	[39]
86	Germany	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.841G > A/ c.841G > A	[39]
87	Germany	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.619G > C/ delexon8	[39]
88	Germany	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.959dupG/ delexons1–8	[39]
	Swedish	M	6mo	NR	+	+	+	Vomiting and developed lactic acidosis, and gastrointestinal bleeding	NR	NR	c.778G > A/c.881G > A	[40]
		M	neo	NR	+	+	+	Vomiting	NR	NR	c.778G > A/c.881G > A	[40]
89		F	7mo	NR	+	+	NR	Vomiting, and acidosis	NR	NR	c.778G > A/c.881G > A	[40]
90	Swedish	M	NEO	NR	+	+	+	High fever and vomiting	NR	NR	c.648C > G/ c.648C > G	[40]
91	Japan	F	10y	NR	+	+	+	Vomiting	NR	NR	c.960insG/c.960insG	[41]
92	India	F	16mo	NR	+	+	+	Vomiting and fast breathing	NL	NR	c.426 + 1G > A/ c.611_614delAAAA	[42]
93	UAE	NR	NR	NR	NR	NR	NR	NR	NR	NR	c.616_619delAAAG/ c.616_619delAAAG	[43]
94	Turkey	F	2y	NR	+	+	+	Vomiting	NR	NR	c.960-961insG/c.960-961insG	[44]
95	Turkey	M	5.5y	NR	+	NR	NR	Respiratory distress	+	NR	c.960-961insG/c.960-961insG	[44]
96	Korea	M	1 mo	NR	+	+	NR	Vomiting	NL	NR	c.490G > A/c.838delT	[45]
97	Brazil	M	4y	NR	+	+	+	Hepatosplenomegaly	NL	NR	c. 472C > T/c.986 T > C	[46]
98	Brazil	F	30y	NR	+	+	+	Seizure	NL	NR	c. 472C > T/c.472C > T	[46]
99	Iranian	F	6.5y	Infection	−	+	−	Weakness, malaise, abdominal pain, vomiting, loss of consciousness	NL	NL	c.472C > T/c.472C > T	This study

M: Male/ F: Female/ H: Hour/ M: Month/ D: Day/ Y: Year/ NR: Not Reported/ NL: Normal/ Del: Delayed/ +: Present/ -: Absent/ E: Exon/ In: Intron/Hom: Homozygote/ CH: Compound Heterozygote.

Table 2
All variants of the FBP1 gene and their frequencies.

Variant		ACMG classification	No.
Missense			
c.841G > A	p.Glu281Lys	P	37
c.472C > T	p.Arg158Trp	P	24
c.490G > A	p.Gly164Ser	P	11
c.778G > A	p.Gly260Arg	P	8
c.530C > A	p.Ala177Asp	VUS	3
c.268 T > G	p.Phe90Val	VUS	2
c.349 T > C	p.Cys117Arg	LP	2
c.355G > A	p.Asp119Asn	LP	2
c.581 T > C	p.Phe194Ser	LP	2
c.491G > A	p.Gly164Asp	LP	1
c.851C > G	p.Pro284Arg	LP	1
c.881G > A	p.Gly294Glu	LP	7
c.923C > G	p.Pro308Arg	LP	1
c.359C > T	p.Pro120Leu	VUS	1
c.619G > C	p.Gly207Arg	VUS	1
c.490G > A	p.Gly164Ser	P	1
c.986 T > C	p.Leu329Pro	LP	1
Nonsense			
c.841G > T	p.Glu281Ter	LP	6
c.648C > G	p.Tyr216Ter	LP	4
c.685C > T	p.Gln229Ter	LP	2
c.88G > T	p.Glu30Ter	P	2
Splice			
c.334-2A > T	p.?	LP	2
c.825 + 1G > A	p.?	LP	2
c.333 + 1_333 + 2delinsTC	p.?	LP	1
c.426 + 1G > T	p.?	LP	1
c.426 + 1G > A	p.?	LP	1
Indels			
c.960-961insG	p.Ser321ValfsTer13	LP	25
c.114-115insCTGCAC	p.Leu38_Cys39insLeuHis	LP	6
c.117_118insACCTGC	p.Cys39_Thr40dup	LP	6
c.609-612delAAAA	p.Lys204Argfs*72	P	3
c.35delA	p.Asn12ThrfsTer3	LP	2
c.731–738delins20	p.Arg244_Tyr245delinsGlnThrAlaTrpSerSer	LP	2
c.865dupA	p.Met289Asnfs*45	LP	2
c.966delC	p.Asp323ThrfsTer7	LP	2
c.427-1del	p.Lys143_Pro189del	P	1
c.48_48delC	p.Phe17Serfs*15	P	1
c.704delC	p.Pro235GlnfsTer42	P	1
c.704dupC	p.Asp236Rfs*2	LP	1
c.720_729del	p.Tyr241GlyfsTer33	P	1
c.611_614delAAAA		P	1
c.616_619delAAAG		LP	2
c.959dupG	p.Ser321Ifs*13	LP	1
c.838delT	p.Tyr280ThrfsTer25	LP	1
Large Indels			
Del of Exon 3	Large deletion	P	2
g.97,364,754-97,382.011del	Large deletion	LP	2
c.-24–26_170 + 5192del	Large deletion	P	6
Del of Exon 1	Large deletion	P	1
Insertiona331-bpAlu	Large insertion	P	2

Asian population. Certain types of mutations might cause specific symptoms with a higher frequency. Genetic variations in many disorders may have different distributions among various populations [16,17]. The most frequent variant is c.841G > A, c.472C > T (missense), and c.960-961insG (indel). Some variants may have ethnic-specific frequency and may be due to a founder effect [18,19].

In most cases, FBPase deficiency presents during the first 4 days of the patient's life [9], and according to research done on patients in Malaysia and France, all the known cases until 2015 had their first decompensation by the age of 2 years [2,7], while the patient in this study did not present any symptoms before 3 years of age. While the age of onset for the two cases presented in our study aligns with the reported range of 3 years (within the average onset age of 14.97 months to 6.5 years), these cases are noteworthy for several reasons that highlight their uniqueness: 1) Phenotypic Variability and intrafamilial Differences: The two siblings from our study exhibited significant phenotypic variability despite having the same genetic mutation. 2) Unusual Symptoms: The clinical presentations of the two siblings included symptoms not commonly highlighted in the literature for FBPase deficiency. Specifically, the presence of abdominal pain and severe hypoglycemia leading to loss of consciousness was more pronounced in these patients compared to the broader cohort of 102 literature-based cases. 3) Delayed Onset: Although the age of onset for the two siblings falls within the reported range, the fact that their symptoms became apparent at 3

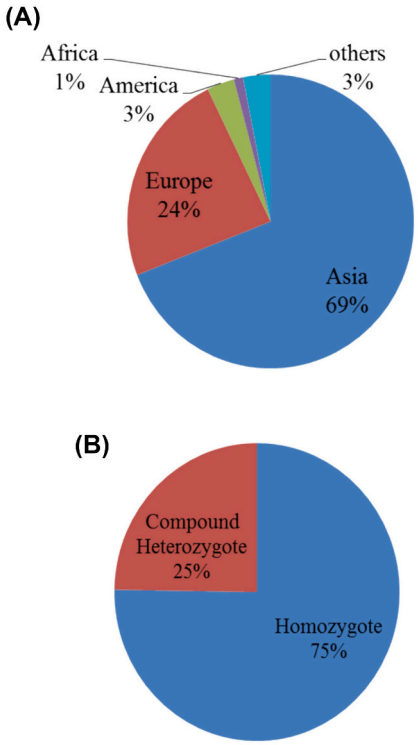

Fig. 3. A) Frequencies of 97 families for FBPase all over the world. The most frequent was in Asia (69 %, 77 cases). B) The percentage of cases with homozygous or compound heterozygous genotypes.

years of age, rather than earlier, is noteworthy.

It's worth noting that said disease normally presents as an autosomal recessive disorder [2], and therefore commonly the patient's family doesn't show symptoms of the disease, except for rare cases where siblings both present symptoms of FBPase deficiency [20]. The patient in this report has a brother with the same variant, who experienced his first hypoglycemic attack at the age of 3 and was presented with tonic convulsions during the first attack. After the first attack, the symptoms of both siblings were the same. As stated, both patients share similar gene mutations, yet the symptoms aren't identical. In a typical case of FBPase deficiency, the patient experiences frequent attacks of irritability, dyspnea and tachycardia, and muscular hypotonia, along with the typical symptoms of hyperuricemia, acidosis, and hypoglycaemia [2]; but gastrointestinal symptoms like abdominal pain and nausea aren't part of the symptoms of this disease [11]. The patient in this study presented with occasional attacks of abdominal pain, nausea and vomiting, and severe hypoglycemia that resulted in loss of consciousness. It is worth noting that during the attacks, patients show signs of low blood sugar, metabolic acidosis, hyperlacticaemia, increase in levels of uric acid, as well as hyperammonemia [20], while the patient in question did not show any changes in her lab work during the attacks. The patient's brother who has the same symptoms also experiences tonic convulsions during the attacks of hypoglycemia. FBPase deficiency is in most cases a life-threatening disorder with frequent metabolic attacks, due to severe hypoglycaemia, hyperlactatemia, metabolic acidosis, and liver dysfunction resulting in multi-organ failure during the metabolic attacks [8]. The attacks in this patient happened less frequently and approximately yearly and were less severe and not life-threatening, as the patient just showed symptoms of lethargy and abdominal pain, ending with confusion and loss of consciousness before the patient regained consciousness. The finding that 75 % of the genotypes in our study were homozygous for pathogenic variants in the FBP1 gene is noteworthy and can be attributed to several factors; the high frequency of homozygous genotypes can often be linked to consanguinity. Specific mutations in the FBP1 gene might occur more frequently due to the presence of mutation hotspots. Furthermore, In regions with high consanguinity or isolated communities, certain pathogenic variants may become more prevalent due to the limited genetic diversity of the founders [18,19].

The observation of intrafamilial phenotypic variability in our study, particularly among siblings with the same pathogenic variant in the FBP1 gene, raises important questions about the factors contributing to this variability. Despite having identical genetic mutations, the affected siblings in our study presented with differing clinical symptoms and disease severities. Several factors could explain these discrepancies; 1) while the primary mutation in the FBP1 gene is the same, other genetic variants, known as genetic modifiers, can influence disease expression. 2) Differences in epigenetic regulation could lead to variations in the expression levels of the FBP1 gene or other related genes, influencing the clinical manifestations of FBPase deficiency. 3) Environmental factors such as diet, exposure to infections, and overall health can play a significant role in the clinical presentation of metabolic disorders.

As mentioned above, FBPase deficiency is a metabolic autosomal recessive disorder with attacks of hypoglycaemia and metabolic acidosis starting at a very early age, but the patient in this report did not show the typical severity and symptoms normally associated with this disease, starting with a later onset and novel symptoms like abdominal pain that aren't present in a classic case of FBPase deficiency, and a new mutation of the gene associated with this disease. The literature data offer a comprehensive view of the disease across different populations, while our cases highlight specific aspects of phenotypic variability and unique clinical presentations.

Ethics approval and consent to participate

This research was conducted due to the Declaration of Helsinki and was approved by the ethics committee of Guilan University of Medical Sciences (ID = IR.GUMS.REC.1402.143), and all ethical guidelines were adhered to throughout the study. The participants were fully informed about the research's objectives and procedures and were guaranteed the confidentiality of their personal information. They had the freedom to withdraw from the study at any time, and if they wished, access to the research findings was available to them.

Consent for publication

Informed consent for publication was obtained from all the study participants.

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CRediT authorship contribution statement

Setila Dalili: Validation, Formal analysis. **Nasrin Sedighi Pirsaraei:** Validation, Formal analysis. **Ameneh Sharifi:** Writing – original draft, Validation, Resources, Formal analysis, Data curation. **Alireza Pouryousef:** Formal analysis, Data curation. **Fatemeh Aghaee:** Formal analysis. **Reza Bayat:** Formal analysis, Data curation. **Babak Ghavami:** Formal analysis, Data curation. **Bahareh Rabbani:** Validation, Formal analysis, Data curation. **Nejat Mahdieh:** Writing – original draft, Validation, Resources, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

All data generated or analyzed during this study are included in this

published article.

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