



## Fructose-1,6-Bisphosphatase Deficiency

Synonyms: FBP1 Deficiency; FBPase Deficiency; Fructose 1,6 Diphosphatase Deficiency

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### Summary

#### Clinical characteristics

Fructose-1,6-bisphosphatase (FBP1) deficiency is characterized by episodic acute crises of lactic acidosis and ketotic hypoglycemia, manifesting as hyperventilation, apneic spells, seizures, and/or coma. Acute crises are most common in early childhood; nearly half of affected children have hypoglycemia in the neonatal period (especially the first 4 days) resulting from deficient glycogen stores. Factors known to trigger episodes include fever, fasting, decreased oral intake, vomiting, infections, and ingestion of large amounts of fructose.

In untreated individuals, symptoms worsen progressively as continued catabolism leads to multiorgan failure (especially liver, brain, and later heart). Morbidity and mortality are high. Sepsis, blindness, and Reye syndrome-like presentation have been reported.

In between acute episodes, children are asymptomatic. While the majority of affected children have normal growth and psychomotor development, a few have intellectual disability, presumably due to early and prolonged hypoglycemia.

#### Diagnosis/testing

The diagnosis of FBP1 deficiency is established in a proband with suggestive clinical and metabolic findings by identification of EITHER biallelic *FBP1* pathogenic variants on molecular genetic testing OR deficient fructose-1,6-bisphosphatase 1 (FBP1) activity in liver or mononuclear white blood cells. Molecular genetic testing is generally preferred because of its widespread availability and accuracy.

#### Management

*Treatment of manifestations:* Intervention (oral or IV glucose) should take place early in an acute crisis while the blood glucose is normal due to the possibility of delayed hypoglycemia, which only occurs relatively late in the course of acute metabolic decompensation.

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The mainstay of routine daily management is prevention of hypoglycemia by avoiding fasting (including use of uncooked cornstarch overnight), consuming frequent meals, and appropriate management of acute intercurrent illnesses.

*Prevention of primary manifestations:* Routine daily management to prevent hypoglycemia, attention to agents/circumstances to avoid, and routine immunizations, including annual influenza vaccine to reduce the risk of infection, which can precipitate hypoglycemia.

*Surveillance:* Long-term monitoring of developmental milestones in affected children and quality of life issues for affected individuals and their parents/caregivers; monitoring for excessive weight gain at each visit.

*Agents/circumstances to avoid:* Food items or medicines that contain fructose, sucrose, glycerol, and/or sorbitol, especially during acute crisis in infancy or early childhood. Although small amounts of fructose ( $\leq 2$  g/kg/day) are generally well tolerated, single ingestion of high dose of fructose ( $> 1$ g/kg) is harmful, especially in younger children. Fructose tolerance testing ("fructose challenge") to diagnose FBP1 deficiency can be hazardous and should not be performed.

*Evaluation of relatives at risk:* When the familial *FBP1* variants are known, it is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of preventive measures.

*Pregnancy management:* For a pregnant woman with FBP1 deficiency, consider referral to a high-risk obstetric center and consultation with a metabolic physician. Home glucose monitoring and consumption of uncooked cornstarch at night as needed as carbohydrate requirements increase during pregnancy. During labor, continuous glucose infusion is recommended to maintain euglycemia.

## Genetic counseling

FBP1 deficiency is inherited in an autosomal recessive manner. When both parents are known to be heterozygous for an *FBP1* pathogenic variant, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *FBP1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

## Diagnosis

Formal diagnostic criteria for fructose-1,6-bisphosphatase (FBP1) deficiency have not been established.

## Suggestive Findings

FBP1 deficiency **should be suspected** in individuals with the following characteristic clinical features and metabolic findings.

### Clinical features

- Episodes of acute crisis may manifest as hyperventilation, apneic spells, seizures, and/or coma, most commonly in neonates and infants. The course of illness is precipitous and may be lethal, especially in neonates and infants.
- Other features can include episodic irritability, tachycardia, hypotonia, and hyperhidrosis.
- Hepatomegaly is common.
- Inter-crisis periods are uneventful with normal development and growth.

**Metabolic findings.** A strong clinical suspicion should arise in individuals with recurrent episodes of ketotic hypoglycemia with lactic acidosis and urinary organic acid analysis showing a glycerol and glycerol-3-phosphate

peak. Although this combination is fairly specific for FBPI deficiency, establishing the diagnosis requires enzyme assay and/or molecular genetic testing (see Establishing the Diagnosis).

- Hypoglycemia (plasma glucose <40mg/dL in neonates; <60 mg/dL in older infants, children, and adults; reference range 70-120 mg/dL)
- High anion-gap metabolic acidosis
  - Lactic acidemia (plasma lactate >2.5 mmol/L; reference range: 0.5-2.2 mmol/L) with possible elevated lactate:pyruvate ratio and hyperalaninemia.
  - Ketosis (individuals with low ketones have been reported)
- Elevated glycerol 3-phosphate is an important biomarker for this disorder on urine organic acid analysis. Glycerol 3-phosphate is more specific as glycerol is also elevated in glycerol kinase deficiency (see [NROBI-Related Adrenal Hypoplasia Congenita](#)) [Nakai et al 1993]. It is important to collect the urine sample in the period of crisis, as the glycerol 3-phosphate level returns to normal once the individual is in the well state [Moey et al 2018].
- Pseudo-hypertriglyceridemia. Although plasma triglycerides are commonly increased, it is not the triglycerides but the glycerol levels that are high (often referred to as "pseudo-hypertriglyceridemia"). The commonly available biochemical assays for plasma triglycerides cannot differentiate glycerol from triglycerides, and hence overestimate the triglyceride levels due to the high concentration of glycerol in plasma [Afroze et al 2013]. Glycerol blanking methods can be used to measure the true levels of triglycerides [Cole 1990].
- Hyperuricemia (plasma uric acid >5.0 mg/dL; reference range 2.0-5.0 mmol/L)
- Increased free fatty acids (in some cases)

## Establishing the Diagnosis

The diagnosis of fructose-1,6-bisphosphatase 1 deficiency **is established** in a proband with suggestive clinical and metabolic findings by identification of EITHER biallelic *FBPI* pathogenic (or likely pathogenic) variants on molecular genetic testing (Table 1) OR deficient fructose-1,6-bisphosphatase 1 (FBPI) activity in liver or mononuclear white blood cells. Molecular genetic testing is generally preferred because of its widespread availability and accuracy.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *FBPI* variants of uncertain significance (or of one known *FBPI* pathogenic variant and one *FBPI* variant of uncertain significance) does not establish or rule out the diagnosis.

## Molecular Genetic Testing

When the clinical and metabolic findings suggest the diagnosis of fructose-1,6-bisphosphatase deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *FBPI* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

Note: Pathogenic variants reported frequently in individuals of certain ancestries are noted in Table 7. Given the rarity of fructose-1-6-bisphosphatase deficiency, the efficacy of targeted testing for specific pathogenic variants in individuals of these ancestries is not known.

- **A multigene panel** (such as one for hypoglycemia or lactic acidosis) that includes *FBP1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of fructose-1,6-bisphosphatase deficiency, some panels may not include *FBP1*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

**Table 1.** Molecular Genetic Testing Used in Fructose-1,6-Bisphosphatase Deficiency

Gene <sup>1</sup>	Method	Proportion of Pathogenic Variants <sup>2</sup> Detectable by Method
<i>FBP1</i>	Sequence analysis <sup>3</sup>	~90% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	~10% <sup>6</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Kikawa et al [1997], Prahl et al [2006], Afroze et al [2013], Takagi et al [2013], Lebigot et al [2015], Santer et al [2016], Ijaz et al [2017], Bhai et al [2018], Moey et al [2018], Pinheiro et al [2019]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. Herzog et al [2001], Åsberg et al [2010], Lebigot et al [2015], Santer et al [2016], Bhai et al [2018]

## Analysis of Fructose-1,6-Bisphosphatase (FBP1 or FBPase) Activity

While enzymatic activity in leukocytes and liver is very specific, testing is not widely available [Besley et al 1994, Lebigot et al 2015]: spectrophotometric analysis to estimate enzyme activity in leukocytes is performed in a few laboratories worldwide. The usual assay tests FBP1 activity by measuring the amount of NADPH formed – a nonspecific assay as NADPH may be formed from other reactions within the cells. Specificity can be achieved by testing for FBP1 activity in the presence and absence of AMP, a specific inhibitor for the enzyme [Lebigot et al 2015]. FBP1 stability in untreated blood samples at +4 °C lasts 24 hours, and therefore samples can be transported long distances to a reference laboratory.

## Clinical Characteristics

### Clinical Description

The manifestations of fructose-1,6-bisphosphatase (FBP1) deficiency are generally episodic due to lactic acidosis and ketotic hypoglycemia, which are often triggered by fasting or febrile infections. The episodes of acute crisis

are most frequent in early life – neonatal period, infancy, and early childhood – and subsequently decrease in frequency. In FBP1 deficiency, several metabolic derangements can occur with or without hypoglycemia.

Classically, FBP1 deficiency manifests in the first year of life. Nearly half of affected infants present within the first four days of life with an acute crisis. Neonatal presentation results from hypoglycemia due to deficient glycogen stores [Steinmann & Santer 2016].

Acute crises are characterized by episodes of hyperventilation, apneic spells, seizures, and/or coma, often with hepatomegaly. Muscular hypotonia may also be present. This may be associated with transient liver dysfunction (transaminitis), which does not require specific treatment [Bhai et al 2018]. With age, the frequency of attacks decreases and episodes are characterized by irritability, somnolence, hypotonia, and dyspnea.

Factors known to trigger episodes include fever, fasting, decreased oral intake, vomiting, infections, and ingestion of large amounts of fructose. Episodes tend to be recurrent. Often four to five episodes occur before the correct diagnosis is established [Lebigot et al 2015].

In between crises, children are asymptomatic and the majority experience normal growth and psychomotor development [Steinmann & Santer 2016]. A few children with brain injury and/or intellectual disability have been reported, probably related to early and prolonged hypoglycemia [Li et al 2017, Moey et al 2018].

In untreated individuals, symptoms worsen progressively as continued catabolism leads to multiorgan failure (especially liver, brain, and later heart). Morbidity and mortality are high. Sepsis, blindness, and Reye syndrome-like presentation have been reported [Lebigot et al 2015, Bhai et al 2018].

## Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

## Nomenclature

Baker & Winegrad [1970] first described deficiency of hepatic fructose-1,6-bisphosphatase 1 (hence the eponymous Baker-Winegrad disease) in a child with hypoglycemia and metabolic acidosis on fasting.

## Prevalence

Fructose-1,6-bisphosphatase deficiency is rare. Approximately 150 affected individuals have been reported to date.

An estimated prevalence of fructose-1,6-bisphosphatase deficiency is 1:350,000 in the Dutch population [Visser et al 2004] and <1:900,000 in the French population [Lebigot et al 2015]. The disorder may be more frequent in populations with higher rates of consanguinity [Santer et al 2016].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *FBP1*.

## Differential Diagnosis

Table 2a provides a comparative analysis of disorders with clinical similarities to fructose-1,6-bisphosphatase (FBP1) deficiency. Table 2b compares the biochemical parameters of these disorders.

Information on mitochondrial respiratory chain and Krebs cycle disorders and fatty acid oxidation defects follows Table 2b.

**Table 2a.** Disorders (and Associated Genes) of Interest in the Differential Diagnosis of Fructose-1,6-Bisphosphatase Deficiency

Gene(s)	Disorder <sup>1</sup>	Differential Diagnosis Disorder: Features Overlapping w/FBP1 Deficiency	Distinguishing Between FBP1 Deficiency & Differential Diagnosis Disorder
<i>ACAT1</i>	Beta-ketothiolase deficiency (OMIM 203750)	Ketolytic defect characterized by ketotic hypoglycemia or hyperglycemia & metabolic acidosis	In BKD: ↑ of specific metabolites on urine organic acids by GCMS can include 2-methylacetacetate, 2-methyl-3-hydroxybutyryl CoA, & tiglylglycine.
<i>ALDOB</i>	Hereditary fructose intolerance <sup>2</sup>	<ul style="list-style-type: none"> <li>When weaned onto sucrose- or fructose-containing foods, infants can manifest nausea, bloating, vomiting, sweating, abdominal pain, &amp; growth restriction.</li> <li>Chronic liver &amp; renal disease occur in untreated children.</li> </ul>	<ul style="list-style-type: none"> <li>Overall, HFI has a more chronic course than FBP1D.</li> <li>Children w/HFI have strong aversion to sweets &amp; often have renal tubular dysfunction, (not seen in FBP1D).</li> <li>Children w/FBP1D do not have GI symptoms or FTT w/chronic fructose ingestion.</li> </ul>
<i>G6PC1</i> <i>SLC37A4</i>	Glycogen storage disease type I <sup>3</sup>	<ul style="list-style-type: none"> <li>Accumulation of glycogen &amp; fat in liver &amp; kidneys, resulting in hepatomegaly &amp; renomegaly</li> <li>Untreated infants present at age 3-4 mos w/hepatomegaly, lactic acidosis, hyperuricemia, hyperlipidemia, hypertriglyceridemia, &amp;/or hypoglycemic seizures.</li> </ul>	Detection of glycerol in FBP1D (on urine organic acid analysis) is useful in differentiating the disorders.
<i>PC</i>	Pyruvate carboxylase deficiency <sup>4</sup>	Episodes of acute vomiting, tachypnea, & acidosis are usually precipitated by metabolic stress or infection; episodes may be very similar to FBP1D (w/↑ lactate-to-pyruvate ratio, hyperalaninemia, hypoglycemia, & metabolic acidosis).	The neurologic involvement, severe ID, & recurrent seizures characteristic of PCD types A & B are not observed in FBP1D.
<i>PGM1</i>	PGM1-CDG (See <a href="#">Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview</a> .)	Presents more commonly w/rhabdomyolysis; however, episodic hypoglycemia & metabolic acidosis may also occur.	<ul style="list-style-type: none"> <li>Short stature, birth defects (incl cleft palate, bifid uvula), &amp; dilated cardiomyopathy may be present in PGM1-CDG.</li> <li>Transferrin isoforms are abnormal &amp; aid in diagnosis of PGM1-CDG.</li> </ul>
Multiple	Fatty acid oxidation defects (FAODs)	FAODs can present in neonates w/hypoglycemia, hyperammonemia, & ↓/absent ketones.	<ul style="list-style-type: none"> <li>Typically hypoketotic hypoglycemia</li> <li>↑ acylcarnitine in MS/MS</li> </ul>
Multiple	Mitochondrial respiratory chain disorders & Krebs cycle disorders	Multisystem involvement in which the most metabolically active organs are most affected (e.g., brain, liver, kidney, heart)	Mitochondrial disorders have a more chronic course than FBP1D.

BKD = beta-ketothiolase deficiency; CDG = congenital disorder of glycosylation; FBP1D = FBP1 deficiency; FTT = failure to thrive; HFI = hereditary fructose intolerance; ID = intellectual disability; MS/MS = tandem mass spectrometry; PCD = pyruvate carboxylase deficiency

1. Disorders included in this table are inherited in an autosomal recessive manner with the exception of mitochondrial respiratory chain and Krebs cycle disorders, which may be inherited in an autosomal recessive manner, an autosomal dominant manner, or by maternal inheritance.

2. Hereditary fructose intolerance is due to deficiency of enzyme aldolase B, which facilitates the breakdown of fructose-1-phosphate into dihydroxyacetone phosphate and glyceraldehyde.

3. GSDI is due to the deficiency of enzyme glucose-6-phosphatase.

4. Pyruvate carboxylase enzyme aids in the irreversible carboxylation of pyruvate to oxaloacetate.

**Table 2b.** Biochemical Parameters of Disorders in the Differential Diagnosis of Fructose-1,6-Bisphosphatase Deficiency

Biochemical Parameter	FBP1	BKT	HFI	GSDI	PCD	FAOD	Respiratory Chain Defects
↑ lactate	Fasting	During crisis	Fasting	Permanent, also increased w/fasting	Permanent	Fasting	Permanent
Lactate/pyruvate ratio	20-40	–	–	–	>30	–	>20
Ketosis	↑↑/–	↑↑	↑	↑↑/–	↑↑↑	–	↑↑
Triglycerides	Pseudo-hyper	↑	N	↑	N	N	N
Glucose	L	L	L	N/L	L/N/H	N/L	L
Ammonia	N	↑	N	N	↑↑	↑	N/↑↑
Alanine	↑↑	N	↑↑	N	↑↑	N	↑↑
Citrulline	N	N	N	N	H	N	N
Liver dysfunction (transaminitis)	↑/–	↑	↑	↑	↑	N	↑/–
Uric acid	↑	N	N	↑	N	N	N
Organic acids in urine	Ketonuria, glycerol, glycerol-3-phosphate	2-methylacetacetate, 2-methyl-3-hydroxybutyryl CoA, tiglylglycine	Ketonuria	Ketonuria	Lactate/ketonuria	↑ C16-C22	Lactate

↑ = increased; ↑↑ = moderately increased; ↑↑↑ = severely increased; BKT = beta-ketothiolase deficiency; FAOD = fatty acid oxidation defect; GSDI = glycogen storage disease type 1; H = high; HFI = hereditary fructose intolerance; L = low; N = normal; PCD = pyruvate carboxylase deficiency

**Fatty acid oxidation defects (FAODs)** are mitochondrial disorders caused by defective beta-oxidation of fatty acids. FAODs can present in neonates with hypoglycemia, hyperammonemia, and reduced/absent ketones. As ketones could be normal in FBP1 deficiency, diagnosis of FAOD is based on elevated acylcarnitine profiles on MS/MS.

**Mitochondrial respiratory chain and Krebs cycle disorders.** Mitochondrial respiratory chain disorders are a heterogeneous group of disorders that share involvement of the cellular bioenergetic machinery due to molecular defects affecting the mitochondrial oxidative phosphorylation system. The variable presentation can include neonatal metabolic acidosis with increased lactate. The usual disease course is a gradually progressive loss of developmental milestones; however, more rapid decline occurs with episodic crises. Urine organic acid profile may reveal distinctive elevation of fumaric acid or other Krebs cycle intermediates, reflecting the site of the enzyme deficiency. See [Mitochondrial Disorders Overview](#).

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in a child diagnosed with fructose-1,6-bisphosphatase (FBP1) deficiency who is not in acute crisis, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended [Wang et al 2017, Bhai et al 2018].

Note that the management of possible multisystem complications resulting from early and prolonged hypoglycemia are not discussed in this *GeneReview*.

**Table 3.** Recommended Evaluations Following Initial Diagnosis of Fructose-1,6-Bisphosphatase Deficiency for a Child Not in Acute Crisis

Evaluation/Concern	Comment
Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietician	<ul style="list-style-type: none"> <li>Consider obtaining baseline blood gas, lactate, ketones, CK. <sup>1</sup></li> <li>Assess growth parameters (height, weight, head circumference).</li> <li>Assess diet &amp; nutritional status.</li> </ul>
Hepatomegaly	<ul style="list-style-type: none"> <li>Abdominal ultrasound to assess for hepatomegaly</li> <li>Baseline liver function tests</li> <li>Baseline serum lipid panel <sup>2</sup></li> <li>Baseline serum uric acid</li> </ul>
Developmental assessment	Referral to developmental pediatrician to assess motor, adaptive, cognitive, & speech/language skills; need for early intervention / special education
Consultation w/clinical geneticist &/or genetic counselor	Incl genetic counseling
Family support/resources	Assess: <ul style="list-style-type: none"> <li>Use of community or online resources such as Parent to Parent;</li> <li>Need for social work involvement for parental support.</li> </ul>

1. Elevation of CK has been noted in at least one individual in acute crisis [Bhai et al 2018]. This may indicate rhabdomyolysis secondary to energy deficiency.

2. See pseudo-hypertriglyceridemia in Suggestive Findings.

## Treatment of Manifestations

An international survey of 126 patients from 36 centers revealed widely varying practices of fructose/sucrose restriction; the authors concluded that internationally accepted guidelines for management and surveillance were needed [Pinto et al 2018].

**Management of acute crises.** Acute crises are more frequent in early life – neonatal period, infancy, and early childhood – with gradual decrease afterwards.

Intervention (oral glucose or IV dextrose) should take place early in an acute crisis while the blood glucose is normal due to the possibility of delayed hypoglycemia, which only occurs relatively late in the course of acute metabolic decompensation.

The family must be given the contact information for an expert metabolic center and a clear emergency outpatient treatment plan during illness (Table 4) and emergency letters/cards with information on principles of acute in-patient treatment (Table 5).

**Emergency outpatient treatment.** The threshold for emergency outpatient evaluation and treatment should be low. Acute management guidelines are available from the [British Inherited Metabolic Disease Group](#). See [protocol](#) (pdf).

Laboratory evaluations during acute illnesses should include pH and blood gases, glucose (laboratory and bedside strip test), urea and electrolytes, complete blood count, lactate, blood culture, and urine ketones.

The child should receive emergency treatment if the child is vomiting, complaining of stomach pain, or not wanting to eat or drink, irrespective of associated symptoms (e.g., fever, cough, cold).



**Table 4.** Emergency Outpatient Treatment in Individuals with Fructose-1,6-Bisphosphatase Deficiency

Manifestation/Concern	Treatment	Considerations
<b>Mildly ↑ catabolism (fever, cough, or cold; loose stools; continues to eat; not assoc w/lethargy)</b>	<ol style="list-style-type: none"> <li>1. Restriction of fructose, sucrose, glycerol, &amp; sorbitol</li> <li>2. ↑ frequency of carbohydrate feedings</li> <li>3. Intake of glucose polymers</li> </ol>	<ul style="list-style-type: none"> <li>• Trial of outpatient treatment at home requires good communication between family &amp; providers.</li> <li>• Frequent reassessment of patient</li> </ul>
<b>Ketonuria</b>		An early indicator of impending crisis

**Acute in-patient treatment.** Acute manifestations of hypoglycemia (lethargy, encephalopathy, seizures, hyperhidrosis), often occurring in the setting of intercurrent illness and/or inadequate caloric intake, should be managed symptomatically and with generous caloric support in a hospital setting, with aggressive treatment and supportive care of any identified or clinically suspected acute conditions.

**Table 5.** Acute In-Patient Treatment in Individuals with Fructose-1,6-Bisphosphatase Deficiency

Manifestation/Concern	Treatment	Considerations
<b>Hypoglycemia</b>	<ol style="list-style-type: none"> <li>1. IV glucose bolus (2 mL/kg of 10% dextrose) followed by continuous infusion of glucose at high rates (10% dextrose infusion)</li> <li>2. Transition to oral/enteral feeds as clinically tolerated</li> </ol>	The symptoms of acute illness typically subside soon after administration of IV dextrose & child should recover quickly (w/in hrs), usually w/no residual damage.
<b>Metabolic acidosis</b>	<ol style="list-style-type: none"> <li>1. IV glucose bolus as above</li> <li>2. If pH remains &lt;7.1 or worsens, administer NaHCO<sub>3</sub> as 1/2 the calculated dose over a 30-min period.</li> <li>3. Restrict fructose, glycerol, sucrose, &amp; sorbitol.</li> </ol>	<ul style="list-style-type: none"> <li>• Acidosis usually corrects quickly w/out NaHCO<sub>3</sub> infusion.</li> <li>• No consensus exists re restriction of dietary fructose &amp; sucrose.</li> </ul>
<b>Hepatomegaly &amp; ↑ transaminases</b>	None	Transient findings that resolve spontaneously

IV = intravenous; NaHCO<sub>3</sub> = sodium bicarbonate

## Prevention of Primary Manifestations

The main principles of routine daily management are the following:

- Prevention of hypoglycemia (by avoiding fasting and consuming frequent meals). Slowly absorbed carbohydrates such as uncooked cornstarch (1-2 g/kg) mixed in milk or water at bedtime may be introduced to children after age six to 12 months who have nocturnal hypoglycemia [Pinto et al 2018].
- Appropriate management of acute intercurrent illnesses, which can exacerbate the need for glucose
- Restriction of food items or medicines that contain fructose, sucrose, glycerol, and/or sorbitol

Also advised are routine immunizations, including annual influenza vaccine, to reduce the risk of infections that can precipitate hypoglycemia.

## Surveillance

No formal guidelines for long-term surveillance for individuals with FBPI deficiency exist. Table 6 summarizes long-term surveillance based on the natural history of the disorder.

**Table 6.** Recommended Long-Term Surveillance for Individuals with Fructose-1,6-Bisphosphatase Deficiency

Manifestation/ Concern	Evaluation	Frequency/Comment
<b>Delayed acquisition of developmental milestones</b>	Monitor developmental milestones.	At each visit
	Neuropsychological testing using age-appropriate standardized assessment batteries	As needed
	Standardized quality-of-life assessment tools for affected individuals & parents/caregivers	As needed
<b>Excessive weight gain</b>	Measurement of growth, weight, & head circumference	At each visit

## Agents/Circumstances to Avoid

Avoid ingestion of food items or medicines that contain fructose, sucrose, glycerol, and/or sorbitol, especially during acute crises in infancy or early childhood.

Although small amounts of fructose ( $\leq 2$  g/kg/day) are well tolerated by individuals with FBP1 deficiency, single ingestion of high doses of fructose ( $>1$ g/kg) is harmful, especially in younger children.

The fructose tolerance testing ("fructose challenge") to diagnose FBP1 deficiency can be hazardous and should not be performed.

## Evaluation of Relatives at Risk

It is appropriate to clarify the status of apparently asymptomatic older and younger at-risk sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of measures to prevent acute crises (frequent feedings and avoidance of fasting) and prompt treatment of infections / febrile illnesses. Evaluations should include targeted molecular genetic testing if the *FBP1* pathogenic variants in the family are known.

For newborns who may be at risk for FBP1 deficiency, it is important to avoid fasting, to feed regularly, and to monitor for hypoglycemia and acidosis while awaiting results of biochemical and/or molecular genetic testing. Monitoring for hypoglycemia can include use of bedside glucometers and clinical monitoring for lethargy, poor intake, vomiting, hypothermia, and/or tachypnea. A low threshold for starting an intravenous infusion of 5%-10% dextrose may help prevent triggering of an acute crisis, especially in newborns who have low birth weight, are preterm, or have a diabetic mother.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

Although successful pregnancies have been reported in women with FBP1 deficiency [Åsberg et al 2010], certain precautions should be taken:

- **Pre-pregnancy**
  - Counseling that emphasizes the importance of frequent eating in preventing hypoglycemia and the use of blood glucose monitoring for early detection of hypoglycemia
  - Consider referral to a high-risk obstetric center and consultation with a metabolic physician.
- **During pregnancy**
  - Close home glucose monitoring for early detection of hypoglycemia
  - Maintenance of glycemic control by taking uncooked cornstarch at night as needed [Krishnamurthy et al 2007, Sugita et al 2014]

- In the third trimester when the physiologic requirements of energy are highest, increase in dietary intake and glucose monitoring as needed
- **During labor.** Continuous glucose infusion to maintain euglycemia

## Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

Fructose-1,6-bisphosphatase (FBP1) deficiency is inherited in an autosomal recessive manner.

### Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *FBP1* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *FBP1* pathogenic variant and to allow reliable recurrence risk assessment. (Although a *de novo* pathogenic variant has not been reported in *FBP1* deficiency to date, *de novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

### Sibs of a proband

- If both parents are known to be heterozygous for an *FBP1* pathogenic variant, each sib at conception has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** Unless an affected individual's reproductive partner also has *FBP1* deficiency or is a carrier, offspring will be obligate heterozygotes (carriers) for one of the *FBP1* pathogenic variants identified in the proband.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of an *FBP1* pathogenic variant.

## Carrier Detection

**Molecular genetic testing.** Carrier testing for at-risk relatives requires prior identification of the *FBP1* pathogenic variants in the family.

Note: Biochemical enzyme-based testing is not reliable for carrier detection.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

### Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

**Molecular genetic testing.** Once the *FBP1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Note: Biochemical testing is not a reliable method for prenatal diagnosis as FBP1 enzyme activity has been reported to be low in human placenta [Papamarcaki & Tsolas 1991].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **Metabolic Support UK**  
United Kingdom  
**Phone:** 0845 241 2173  
[metabolicsupportuk.org](http://metabolicsupportuk.org)

## Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

**Table A.** Fructose-1,6-Bisphosphatase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>FBP1</i>	9q22.32	Fructose-1,6-bisphosphatase 1	<a href="#">FBP1 database</a>	<a href="#">FBP1</a>	<a href="#">FBP1</a>

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for Fructose-1,6-Bisphosphatase Deficiency ([View All in OMIM](#))

229700	FRUCTOSE-1,6-BISPHOSPHATASE DEFICIENCY; FBPD
611570	FRUCTOSE-1,6-BISPHOSPHATASE 1; FBPI

## Molecular Pathogenesis

Fructose-1,6-bisphosphatase 1 (FBPase, or FBPI) is a key enzyme of the gluconeogenic pathway. Its deficiency impairs glucose production from all gluconeogenic precursors, including dietary fructose. As a result, euglycemia in persons with FBPI deficiency depends on glycogen stores in the liver. During glycemic stress (including catabolic states such as infections and fasting), glycogen stores are depleted and the gluconeogenic substrates pyruvate, alanine, and glycerol accumulate (Figure 1). The subsequent conversion of pyruvate into lactate and acetyl CoA results in lactic acidemia and ketosis.

Deficient conversion of glucose-1-phosphate to glucose also activates the pentose phosphate pathway, causing both the production of ribose-5-phosphate and the synthesis of purines and pyrimidines. The subsequent breakdown of purines and pyrimidines results in hyperuricemia.

**Mechanism of disease causation.** Loss of fructose-1,6-bisphosphatase 1 function

**FBPI-specific laboratory technical considerations.** *FBPI* comprises one noncoding exon (exon 1) and seven coding exons; it spans more than 31 kb [el-Maghrabi et al 1995]. Deletions of exons 2, 3, 3-7, and 8 as well as whole-gene deletions have been reported.

(The six *FBPI* introns are in the same positions in the rat gene.)

**Table 7.** Notable *FBPI* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
<a href="#">NM_000507.3</a>	c.-24-26_170+5192 (deletion exon 2)	--	Observed in the homozygous state in affected persons in Armenia & Turkey [Santer et al 2016]
<a href="#">NM_000507.3</a> <a href="#">NP_000498.2</a>	c.472C>T	p.Arg158Trp	Frequently observed in France, India, Pakistan, Saudi Arabia, & Brazil [Lebigot et al 2015, Ijaz et al 2017, Bhai et al 2018, Moey et al 2018, Pinheiro et al 2019]
	c.611_614delAAAA	p.Lys204ArgfsTer72	Observed in India & Pakistan [Ijaz et al 2017, Bhai et al 2018]
	c.685C>T	p.Glu229Ter	Common in Morocco [Prahl et al 2006, Lebigot et al 2015]
	c.841G>A	p.Glu281Lys	Common in India, Pakistan, & Saudi Arabia [Afroze et al 2013, Santer et al 2016, Ijaz et al 2017, Bhai et al 2018]
	c. 959dupG	p.Ser321ValfsTer13	Common in Japan; observed in China, Korea, & in North Americans & Europeans [Kikawa et al 1997, Herzog et al 2001, Takagi et al 2013, Lee et al 2019]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.



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