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Hereditary Fructose Intolerance

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Summary

Clinical characteristics

Following dietary exposure to fructose, sucrose, or sorbitol, untreated hereditary fructose intolerance (HFI) is characterized by metabolic disturbances (hypoglycemia, lactic acidemia, hypophosphatemia, hyperuricemia, hypermagnesemia, hyperalaninemia) and clinical findings (nausea, vomiting, and abdominal distress; chronic growth restriction / failure to thrive). While untreated HFI typically first manifested when fructose- and sucrose-containing foods were introduced in the course of weaning young infants from breast milk, it is now presenting earlier, due to the addition of fructose-containing nutrients in infant formulas. If the infant ingests large quantities of fructose, the infant may acutely develop lethargy, seizures, and/or progressive coma. Untreated HFI may result in renal and hepatic failure. If identified and treated before permanent organ injury occurs, individuals with HFI can experience a normal quality of life and life expectancy.

Diagnosis/testing

The diagnosis of HFI is established in a proband with suggestive metabolic disturbances and clinical findings following dietary exposure to fructose, sucrose, or sorbitol and either biallelic pathogenic variants in *ALDOB* identified on molecular genetic testing or – now rarely – deficient hepatic fructose 1-phosphate aldolase (aldolase B) activity on liver biopsy. Note: Fructose tolerance testing ("fructose challenge") in the diagnosis of HFI should be avoided because it is dangerous and, when used in the past, could result in death.

Potential sources of fructose should be removed immediately if HFI is suspected.

Management

Treatment of manifestations: Acute manifestations (e.g., lethargy, seizures, or progressive coma and/or renal and hepatic failure) should be managed symptomatically in a hospital setting, including administration of intravenous glucose (dextrose), supportive treatment of hepatic and/or renal insufficiency, and treatment of metabolic acidosis, if present.

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Prevention of primary manifestations: Dietary restriction of fructose, sucrose, sucralose, and sorbitol is the cornerstone of HFI treatment. During hospitalizations, special caution is advised to avoid use of fructose-containing intravenous fluids, as well as fructose-containing infant formulas and pharmaceuticals. Given that reduced fruit and vegetable intake is a dietary requirement, daily supplementation with a "sugar-free" multivitamin is recommended to prevent micronutrient deficiencies, specifically water-soluble vitamins.

Surveillance: No formal guidelines for surveillance exist. Once the diagnosis of HFI has been made, periodic evaluation of liver function, renal function, and growth is reasonable, particularly if compliance with the fructose/sucrose/sorbitol/sucralose-restricted diet is not absolute.

Agents/circumstances to avoid: Enteral or parenteral exposure to fructose, sorbitol, sucrose, sucralose, and polysorbate, including fructose, fructose-containing oligosaccharides, high-fructose corn syrup, honey, agave syrup, inverted sugar, maple-flavored syrup, molasses, palm or coconut sugar, and sorghum. In addition, medicines and formulas in which fructose/sucrose may not be listed as a primary component need to be avoided; examples include syrups, enema solutions, some immunoglobulin solutions, and many infant and pediatric nutritional drinks.

Although vaccinations are generally safe in children with HFI, the two potentially harmful vaccines are the sucrose-containing rotavirus vaccines, Rotarix® pre-established oral suspension and RotaTeq®, the only rotavirus vaccines approved for use in the US. Any individual with a severe adverse reaction immediately following administration of either vaccine should be thoroughly investigated for the possibility of HFI.

Evaluation of relatives at risk: Presymptomatic diagnosis of HFI is warranted for sibs of a proband in order to avoid life-threatening complications by restricting fructose intake as soon as possible.

Genetic counseling

HFI is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ALDOB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither pathogenic variant. Once the *ALDOB* 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

No consensus clinical diagnostic criteria for hereditary fructose intolerance (HFI) have been published.

Suggestive Findings

HFI **should be suspected** in individuals with the following characteristic clinical findings (following dietary exposure to fructose, sucrose, sorbitol, and/or sucralose), metabolic disturbances, and family history.

Note that the clinical presentation of HFI can be multifaceted and nonspecific, making it difficult to suspect based on clinical findings alone. If HFI is suspected, potential sources of fructose need to be removed immediately (see Table 10).

Clinical findings

- Nausea, vomiting, and abdominal distress (including pain, distention, ascites, and hepatomegaly)
- Chronic growth restriction / failure to thrive
- Any individual with a severe adverse reaction (e.g., vomiting, hypoglycemia, lethargy, liver or renal insufficiency) immediately following administration of either of the two sucrose-containing vaccines,

Rotarix® pre-established oral suspension and RotaTeq®, should be thoroughly investigated for the possibility of hereditary fructose intolerance.

Metabolic disturbances. See Table 1 for characteristic metabolic disturbances.

Table 1. Characteristic Metabolic Disturbances in Hereditary Fructose Intolerance

Metabolic Disturbance	Metabolite Concentration in Plasma	Reference Range
Hypoglycemia	Glucose <60 mg/dL	70-120 mg/dL
Lactic acidemia	Lactate >2.5 mmol/L	0.5-2.2 mmol/L
Hypophosphatemia	Phosphate <5 mg/dL	5.0-8.8 mg/dL
Hyperuricemia	Uric acid >5.0 mg/dL	2.0-5.0 mg/dL
Hypermagnesemia	Magnesium >2.6 mg/dL	1.6-2.6 mg/dL
Hyperalaninemia	Alanine >439 nmol/mL	143-439 nmol/mL

Other supportive laboratory findings include changes in urine electrolytes and/or amino acids consistent with a proximal renal tubule defect, increased abnormal transferrin isoelectric focusing [Pronicka et al 2007, Quintana et al 2009, Di Dato et al 2019, Magalhães et al 2020], and/or elevations of multiple plasma lysosomal enzymes [Ferreira et al 2017], particularly aspartylglucosaminidase [Michelakakis et al 2009].

Note: The fructose tolerance testing ("fructose challenge") to diagnose HFI can result in death and should not be used.

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of HFI **is established** in a proband with suggestive metabolic disturbances and clinical findings following dietary exposure to fructose, sucrose, sorbitol, and/or sucralose and EITHER of the following:

- Biallelic pathogenic (or likely pathogenic) variants in *ALDOB* on molecular genetic testing (Table 2)

  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 *ALDOB* variants of uncertain significance (or identification of one known *ALDOB* pathogenic variant and one *ALDOB* variant of uncertain significance) does not establish or rule out a diagnosis of this disorder.

- Deficient hepatic fructose 1-phosphate aldolase (aldolase B) activity on liver biopsy

Note: Because of the relatively high sensitivity of *ALDOB* molecular genetic testing, it is increasingly the preferred confirmatory test for HFI and can obviate the need for liver biopsy.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of HFI has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *ALDOB* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Most multigene panels dealing with carbohydrate metabolism and/or liver dysfunction are likely to include *ALDOB* and other genes of interest (see Differential Diagnosis), and thus, are 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*. (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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in Hereditary Fructose Intolerance

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method [3]
ALDOB	Sequence analysis [4]	75%-100%
	Gene-targeted deletion/duplication analysis [5]	0%-25% [6, 7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Cross & Cox [1990], Dursun et al [2001], Sánchez-Gutiérrez et al [2002], Santer et al [2005], Gruchota et al [2006], Davit-Spraul et al [2008], Coffee et al [2010], Esposito et al [2010], Ferri et al [2012], Bijarnia-Mahay et al [2015].
4. 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.
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. No large deletions were identified by Southern blotting in 56 individuals from Spain [Sánchez-Gutiérrez et al 2002].
7. A large (6.5-kb) intragenic deletion with an allele frequency of 11% was identified in a small Italian cohort [Ferri et al 2012].

Deficient hepatic fructose 1-phosphate aldolase (aldolase B) activity on liver biopsy. Specific fructose-1-phosphate aldolase B enzyme assays and fructose assay enzyme panels on frozen liver tissue may be important options to establish the diagnosis in individuals with clinical and biochemical features of HFI in whom molecular genetic testing has failed to identify biallelic *ALDOB* pathogenic variants.

Note: While molecular genetic testing is the first-line diagnostic test for HFI, assay of aldolase B activity on liver biopsy, which is more invasive but more sensitive than molecular genetic testing, can be used if necessary.

Clinical Characteristics

Clinical Description

Hereditary fructose intolerance (HFI) typically manifests when fructose- and sucrose-containing foods are introduced in the course of weaning young infants from breast milk [Ali et al 1998]. Manifestations include nausea, bloating/ascites, vomiting, sweating, abdominal pain, enlarged liver, and growth retardation [Odièvre et al 1978].

Impaired gluconeogenesis following fructose ingestion results in acute hypoglycemia that is refractory to glucagon [Van Den Berghe et al 1973]. Infants who ingest large quantities of fructose may develop lethargy, seizures, and/or progressive coma, or neonates given a 24% sucrose solution for analgesia during minor procedures may develop hypoglycemia leading to death.

Presently, the clinical presentation of HFI can be multifaceted and nonspecific. The classic presentation of the infant transitioning to solids and developing hypoglycemia is still true; however, with fructose-containing components added to infant formulas, clinical presentation can be earlier than five to six months of age [Li et al 2018]. A high index of suspicion for HFI must exist in any instance of an infant with recurrent or profound hypoglycemia, metabolic acidosis, recurrent emesis, liver dysfunction, and/or renal insufficiency, to name just a few sentinel signs and symptoms. Key biochemical features of HFI include hypermagnesemia, hyperuricemia, hypophosphatemia, and metabolic acidosis (see Table 1) [Bouteldja & Timson 2010]. HFI is one of the few inborn errors of metabolism in which hypoglycemia occurs in the immediate postprandial state.

Other variable common findings in HFI include the following.

Liver involvement

- Hepatomegaly with steatosis and lipid vacuolization may remain a persistent complication despite fructose restriction and resolution of initial fibrosis, including in individuals ascertained by family history and treated from birth [Odièvre et al 1978].
- A potential long-term risk of developing hepatic adenoma and fibrosis [Ghannem et al 2020] exists.
- There have been multiple examples of persistent hepatomegaly, non-alcoholic fatty liver disease, and abnormal carbohydrate-deficient transferrin testing [Aldámiz-Echevarría et al 2020, Di Dato et al 2019, Buziau et al 2020]. The pathophysiology underlying these phenomena is unknown.
- Lenticular cataracts with hepatic fibrosis in untreated adolescents and adults [Ananth et al 2003] may occur.

Kidney involvement

- Chronic renal insufficiency, specifically proximal tubular dysfunction, may also persist despite fructose restriction. Typically, resolution of renal disease occurs shortly after starting fructose restriction [Odièvre et al 1978]. In rare historical instances, dietary modification did not affect renal dysfunction [Mass et al 1966, Morris 1968].
- More recently longitudinal study of adults with HFI revealed higher glomerular filtration and higher systolic blood pressure versus controls, potentially predisposing individuals with HFI to greater cardiovascular risk [Simons et al 2020]. Anecdotally, the authors have seen persistent renal tubular dysfunction that progressed to Stage IV chronic kidney disease in an individual in whom HFI was untreated until age five years, and then treated aggressively until the present age of 19 years.

- Chronic renal disease may be a result of early, chronic exposure, as some reported individuals tended to manage themselves with inadequate self-restriction of fructose- and sucrose-containing foods. It may also be in part due to ongoing primary defects in aldolase function and ATPase interaction within the proximal tubule, leading to dysfunctional acid-base regulation, renal tubular insufficiency (manifesting as glucosuria, aminoaciduria, and phosphaturia), and nephrocalcinosis despite strict dietary restrictions [Mass et al 1966, Morris 1968, Lu et al 2001, Steinmann & Santer 2011].

Other

- Coagulopathy [Hosková & Mrskos 1977]
- Isolated poor growth (i.e., in the absence of other symptoms or affected organ systems) [Mock et al 1983]
- Intermittent vomiting in the setting of fructose aversion and pristine dentition [Newbrun et al 1980]

Prognosis. Typically, when complete dietary fructose, sucrose, sorbitol, and/or sucralose restriction is implemented early in life and adherence is maintained (see Management, Prevention of Primary Manifestations), the prognosis for individuals with HFI is excellent (i.e., normal neurocognitive development, health, and life expectancy).

Conversely, when individuals with HFI do not adhere to recommended dietary restrictions, chronic liver and/or renal disease are expected (as detailed above).

Heterozygotes (carriers) are not at increased risk of developing HFI. While carriers are generally asymptomatic, in older publications hyperuricemia was observed in some presumed or obligate carriers, suggesting that heterozygotes may be predisposed to gout/crystal arthropathy [Oberhaensli et al 1987, Seegmiller et al 1990]. This observation was substantiated more recently, when *ALDOB* heterozygotes showed a postprandial increase in plasma uric acid concentration in response to fructose ingestion compared to controls [Debray et al 2018].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified for HFI; clinical severity and extent of organ damage appear to depend on an individual's nutritional environment.

Nomenclature

"Fructosaemia," a term originally proposed by Levin et al [1963] to describe the presence of abnormal quantities of fructose in plasma, is now considered obsolete. This finding, which is not specific to HFI, is also observed in fructokinase deficiency and other disorders [Hommes 1993].

Prevalence

HFI is rare, making precise prevalence estimates challenging.

Population-based estimates for the prevalence (based on results of carrier testing for common *ALDOB* pathogenic variants and use of the Hardy-Weinberg principle after correction for the estimated detection rate) are between 1:18,000 and 1:31,000 (Table 3).

It is important to note that the US study that targeted five specific *ALDOB* variants may have underestimated the prevalence in persons of non-European ancestry [Lazarin et al 2013]. Applying a Bayesian framework to population-based genomic data, Schrodi et al [2015] devised posterior probability density prevalence estimates for HFI; based on available data, prevalence of HFI was estimated as 1:34,461 (95% credible interval 1:16,800 to 1:94,500).

Table 3. HFI Prevalence by Population Based on Carrier Testing for Specific *ALDOB* Pathogenic Variants

		UK [2]	Germany [3]	Poland [4]	United States		
					All [5]	ME [5]	AA [5]
Extrapolated HFI prevalence [1]		1:18,000	1:26,000	1:31,000	1:60,000	1:38,000	1:205,000
Variants tested	p.Ala150Pro	●	●	●	●		
	p.Ala175Asp		●		●		
	p.Asn335Lys		●		●		
	Other				p.Tyr204Ter, p.Asn120LysfsTer32		

AA = African American; ME = Middle Eastern

1. Extrapolated prevalence based on detection rate of variants tested

2. Based on the UK population prevalence of the p.Ala150Pro variant, the final estimate for the incidence of HFI was 1:18,000 live births [James et al 1996].

3. Santer et al [2005]

4. Gruchota et al [2006]

5. In a large carrier screening study of multiple disorders in an ethnically diverse population in the United States, overall carrier frequency for an *ALDOB* pathogenic variant was 1:122 (~0.8%). Carrier frequencies in persons self-identifying as Middle Eastern (n=388) and African American (n=678) were 1:97 (~1.0%) and 1:226 (~0.4%), respectively. Using the Hardy-Weinberg principle, these data yield disease frequency estimates of 1:60,000 for all the US population, 1:38,000 for the US population identified as Middle Eastern, and 1:205,000 for the US population identified as African American [Lazarin et al 2013].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

In addition to hereditary fructose intolerance (HFI), the following acquired and hereditary disorders should be considered in the evaluation of hepatic insufficiency, unexplained jaundice, and hypoglycemia, or in the setting of Reye-like illness in infancy or early childhood [Saudubray et al 2016].

Acquired disorders to consider in the evaluation of hepatic insufficiency, unexplained jaundice, and hypoglycemia, or in the setting of Reye-like illness in infancy or early childhood

- Infectious hepatitis, sepsis, or disseminated intravascular coagulation
- Autoimmune liver disease
- Neonatal hemochromatosis, which is considered a congenital alloimmune hepatitis
- Toxic ingestion
- Hemophagocytic lymphohistiocytosis (See Familial Hemophagocytic Lymphohistiocytosis.)

Table 4. Hereditary Disorders to Consider in the Evaluation of Hepatic Insufficiency, Unexplained Jaundice, and Hypoglycemia, or in the Setting of Reye-Like Illness in Infancy or Early Childhood

Gene	Disorder	MOI
ACADM *ACADVL* *HADHA*	Fatty acid oxidation disorders (e.g., MCAD deficiency, LCHAD deficiency, VLCAD deficiency)	AR

Table 4. continued from previous page.

Gene	Disorder		MOI
AGL *G6PC1* *GBE1* *PHKA1* *PHKA2* *PHKB* *PHKG2* *PYGL* *SLC37A4*	Hepatic glycogenosis: GSD Ia & Ib, GSD III, GSD IV, GSD VI, GSD IX (See Phosphorylase Kinase Deficiency.)		AR XL
ALG6 *MPI* *PMM2* (42 genes) [1]	Congenital disorders of glycosylation (See Congenital Disorders of N-Linked Glycosylation & Multiple Pathway Overview & footnote 1.)		AR
ARG1 *ASL* *ASS1* *CPS1* *NAGS* *OTC* *SLC25A13* *SLC25A15*	Urea cycle disorders		XL AR
ATP7B	Wilson disease		AR
BCKDHA *BCKDHB* *DBT*	Maple syrup urine disease		AR
DGUOK *MPV17* *POLG* *TWNK*	Hepatocerebral mtDNA depletion syndromes (e.g., *DGUOK*-, *MPV17*-, *POLG*-, & *TWNK*-related disorders)		AR
FAH	Tyrosinemia type 1		AR
PCCA *PCCB*	Organic acidemias, e.g.,	Propionic acidemia	AR
MCEE *MMAA* *MMAB* *MMADHC* *MMUT*		Isolated methylmalonic acidemia	
FBP1		Fructose-1,6-bisphosphatase deficiency	
GALT	Galactosemia (See Classic Galactosemia & Clinical Variant Galactosemia.)		AR
SERPINA1	Alpha-1 antitrypsin deficiency		AR
TALDO1	Transaldolase deficiency (OMIM 606003)		AR

AR = autosomal recessive; GSD = glycogen storage disease; LCHAD = long-chain 3-hydroxyacyl-coa dehydrogenase; MCAD = medium-chain acyl-coenzyme A dehydrogenase; MOI = mode of inheritance; mtDNA = mitochondrial DNA; VLCAD = very long-chain acyl-CoA dehydrogenase; XL = X-linked

1. Forty-two different enzymes in the N-linked oligosaccharide synthetic pathway or interactive pathways are currently recognized to be deficient in each of the types of CDG-N-linked or among the multiple-pathway disorders.

In addition to HFI, severe infection/sepsis and hereditary disorders including mitochondrial disorders and the disorders summarized in Table 5 should be considered in the evaluation of infants with hyperlacticemia in combination with hypoglycemia.

Table 5. Hereditary Disorders to Consider in the Evaluation of Infants with Hyperlacticemia in Combination with Hypoglycemia

Gene	Disorder		MOI
ACADM *ACADVL* *HADHA*	Fatty acid oxidation disorders (e.g., MCAD deficiency, LCHAD deficiency, VLCAD deficiency)		AR
FBP1	Disorders of gluconeogenesis, e.g.,	Fructose-1,6-bisphosphatase deficiency	AR
DLAT *DLD* *PDHB* *PDHX* *PDP1*		Primary pyruvate dehydrogenase complex deficiency	AR
PDHA1 *PDK3*			XL
PCCA *PCCB*	Organic acidemias, e.g.,	Propionic acidemia	AR
MCEE *MMAA* *MMAB* *MMADHC* *MMUT*		Isolated methylmalonic acidemia	
FBP1		Fructose-1,6-bisphosphatase deficiency	
GYS2	Glycogenosis (e.g., hepatic glycogen synthase deficiency [GSD 0; OMIM 240600])		AR
HMGCL	Disorders of ketone metabolism (e.g., HMG-CoA-lyase deficiency [OMIM 246450])		AR

AR = autosomal recessive; LCHAD = long-chain 3-hydroxyacyl-coa dehydrogenase; MCAD = medium-chain acyl-coenzyme A dehydrogenase; MOI = mode of inheritance; VLCAD = very long-chain acyl-CoA dehydrogenase; XL = X-linked

In addition to HFI, renal tubular acidosis and hereditary disorders including mitochondrial disorders and the autosomal recessive hereditary disorders summarized in Table 6 should be considered in the evaluation of infants with renal Fanconi / aminoaciduria and failure to thrive:

Table 6. Hereditary Disorders to Consider in the Evaluation of Infants with Renal Fanconi/Aminoaciduria and Failure to Thrive

Gene	Disorder
ALG6 *MPI* *PMM2* (42 genes) [1]	Congenital disorders of glycosylation (See Congenital Disorders of N-Linked Glycosylation & Multiple Pathway Overview & footnote 1.)
CFTR	Cystic fibrosis
CTNS	Cystinosis
SLC2A2	Fanconi-Bickel syndrome (OMIM 227810)

AR = autosomal recessive; MOI = mode of inheritance

1. Forty-two different enzymes in the N-linked oligosaccharide synthetic pathway or interactive pathways are currently recognized to be deficient in each of the types of CDG-N-linked or among the multiple-pathway disorders.

Note: **Type I congenital disorders of glycosylation** should be considered in the differential diagnosis of HFI [Adamowicz et al 2007, Pronicka et al 2007] due in part to the overlap in manifestations (including potential for hepatic insufficiency, failure to thrive, and aminoaciduria / renal Fanconi syndrome), and, more importantly, because HFI causes a secondary disorder of glycosylation [Quintana et al 2009] reflecting inhibitory effects of fructose-1-phosphate on phosphomannose isomerase [Jaeken et al 1996].

In HFI, clinical analysis of transferrin glycosylation may be positive, and should correct once fructose is adequately restricted and liver disease subsides. The pattern of abnormal glycosylation is not characteristic of a particular glycosylation defect; thus, when there is clinical suspicion for HFI, *ALDOB* molecular genetic testing or aldolase B activity in liver should be considered. It should also be noted that in individuals who self-restrict fructose, quantifiable glycosylation abnormalities may resolve spontaneously, and thus transferrin glycosylation should be used with caution – and not in isolation – in the diagnosis of HFI.

Fructose malabsorption (or "dietary fructose intolerance"), in which fructose transporters in the small intestine are dysfunctional, is distinct from HFI. Symptoms that overlap with those observed in HFI include diarrhea, bloating, and increased flatulence with ingestion of fructose-containing substances. In severe cases, vomiting and abdominal pain may exist, leading to potential confusion with symptoms of HFI. The two disorders can be distinguished clinically by the presence of fructose in the urine in HFI and the presence of fructose in the stool in fructose malabsorption. Hydrogen breath test may be positive in fructose malabsorption; however, this requires oral fructose loading, which is potentially hazardous in the setting of true HFI [Müller et al 2003]. (See Agents/Circumstances to Avoid.)

Sucrase-isomaltase deficiency (OMIM 222900). Manifestations similar to those of HFI can also be seen in sucrase-isomaltase deficiency, but simple fructose is well tolerated in that disorder.

Autoimmune sensitivity to fructose in food protein-induced enterocolitis syndrome (FPIES) has also been reported [Fiocchi et al 2014].

Other

- In addition to HFI, infection, toxic ingestion, and neoplasm should be considered in the evaluation of adult- or childhood-onset of chronic liver disease.
- In addition to HFI, gastroesophageal reflux, pyloric stenosis, urea cycle disorders, or galactose epimerase deficiency should be considered in the evaluation of infantile or childhood-onset unexplained vomiting.
- In children or adults with early-onset and unexplained cataracts, cerebrotendinous xanthomatosis or galactokinase deficiency (OMIM 230200) should be considered.
- The co-occurrence of HFI and other conditions (e.g., phenylketonuria, celiac disease, and Duchenne muscular dystrophy) has delayed diagnosis and/or initiation of treatment of HFI in some instances [Celiker et al 1993, Ciacci et al 2006, Paolella et al 2012].

Management

No clinical practice guidelines for hereditary fructose intolerance have been published.

Note: If HFI is suspected, potential sources of fructose need to be removed immediately (see Table 9).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hereditary fructose intolerance (HFI), the evaluations summarized in Table 7 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 7. Recommended Evaluations Following Initial Diagnosis in Individuals with Hereditary Fructose Intolerance

System/Concern	Evaluation	Comment
Baseline status	By biochemical geneticist or pediatrician w/ interest in metabolic disorders	Identify any metabolic disturbances (e.g., hypoglycemia, metabolic acidosis).
Dietary management	By dietician w/experience in managing inherited metabolic diseases	• Remove potential sources of fructose immediately. • Assess current diet & nutritional status. • Advise affected person, family members, & caregivers about dietary guidelines.
Ophthalmologic involvement	By ophthalmologist	To incl best corrected visual acuity, slit lamp exam for lenticular opacities
Hepatic involvement	Assess liver enzymes, coagulation factors, albumin, & bilirubin to characterize extent of acute liver disease.	Referral to hepatologist as needed
Renal involvement	Assess renal function (BUN, creatinine, cystatin C) & electrolytes (particularly potassium, phosphorous, calcium, & magnesium).	Referral to nephrologist as needed
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of HFI to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.

BUN = blood urea nitrogen; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Management by multidisciplinary specialists, including gastroenterology, nephrology, ophthalmology, and clinical/metabolic nutrition, is recommended.

Table 8. Treatment of Manifestations in Individuals with Hereditary Fructose Intolerance

Manifestation/ Concern	Treatment	Considerations/Other
Acute presentation	Symptomatic in hospital setting	Incl: • Intravenous glucose (dextrose) • Supportive treatment of hepatic insufficiency (incl fresh frozen plasma or exchange transfusion) • Treatment of metabolic acidosis, if present
Acute episodes of intoxication	In hospital setting	Immediate & complete elimination of fructose (by substitution of fructose w/other carbohydrate sources incl glucose, maltose, & cornstarch) to rapidly reverse symptoms & normalize related metabolic disturbances
Dietary restriction of fructose, sucrose, & sorbitol	By nutritionist w/specific experience in treating HFI & other inherited metabolic diseases	• See Prevention of Primary Manifestations. • Dietary assessment should be ongoing as the child grows, develops different tastes, & tries different foods.
	Incl ongoing education of children & adults re need for dietary restriction	

Table 8. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Other	Medically approved alert bracelet/necklace worn at all times	
Hepatomegaly	• Remove sources of fructose. • Treat manifestations of hepatic insufficiency (e.g., hypoalbuminemia, coagulopathy).	Abdominal ultrasound & assessment of liver enzymes
Renal involvement	Remove sources of fructose.	• Monitor renal function until normalized. • If necessary, implement renal replacement therapy.

Prevention of Primary Manifestations

Dietary restriction of fructose, sucrose, and sorbitol is necessary for the treatment/management of HFI (Table 9). Specific ingredients to avoid include fructose, high-fructose corn syrup, honey, agave syrup, inverted sugar, maple-flavored syrup, molasses, palm or coconut sugar, and sorghum.

Also to avoid are medicines and formulas in which fructose/sucrose may not be listed as a primary component, examples of which include syrups, enema solutions, some immunoglobulin solutions, and many infant and pediatric nutritional drinks. When ingredients are listed, the terms "sugar," "table sugar," "natural flavorings," and even in some cases "sugar-free" or "no added sugar" (with no further clarification on the type of carbohydrate used) should raise suspicion for the presence of fructose, sucrose, or sorbitol.

An extensive list of tolerated and non-tolerated sugars in HFI can be found online at a site curated by the Boston University HFI laboratory. Alternatively, for those who have access, a "green, yellow, red" food list is available through Genetic Metabolic Dietitians International (www.gmdi.org). The authors caution against following diets for fructose intolerance (or "fructose malabsorption"), as these are treating a different disease and are not as restrictive as the diets for HFI, and thus could result in exacerbation of HFI.

Dietary restriction should be strictly followed and maintained, especially in infancy. Currently, there are no specific guidelines regarding dietary fructose limits in any age group.

Ensuring adequate vitamin supplementation in the setting of reduced fruit and vegetable intake is imperative. Daily supplementation with a "sugar-free" multivitamin is recommended to prevent micronutrient deficiencies, specifically the water-soluble vitamins.

Tolerance of dietary fructose probably depends on an individual's residual enzyme activity. Furthermore, because actual fructose content in foods may be unreliably reported or difficult to ascertain, adherence to complete dietary restriction of fructose, sucrose, sorbitol, and sucralose may be difficult to attain and unrealistic for some individuals with HFI.

Table 9. Dietary Guidelines for Hereditary Fructose Intolerance (HFI)

Food Category	Foods Permitted	Foods Prohibited
Dairy	Any milk, cheese, eggs	Milk products w/added sugar (sweetened yogurt, fruit yogurt, milkshake, chocolate milk)
Meat	Beef, veal, lamb, pork	Ham, bacon, hot dogs, processed meats; any other meat where sugar is used in processing
Fish	All fish	None
Poultry	Chicken, turkey	None

Table 9. continued from previous page.

Food Category	Foods Permitted	Foods Prohibited
Cereal	Cooked or ready-to-eat cereals (except sweetened & sugar-coated cereals)	Sweetened/sugar-coated cereals
Fruit	None	All fruits, fruit juices, incl squashes & cordials, & fruit extracts
Vegetables	Asparagus, cabbage, cauliflower, celery, green beans, green peppers, lettuce, nuts, onions, potatoes, spinach, wax beans	All other vegetables, incl sweet potatoes
Bread	Breads prepared w/o fructose, sucrose, sugar, or sorbitol; soda crackers & saltines	Any breads or crackers prepared w/fructose/sucrose/sugar/sorbitol
Fat sources	Butter, margarine, oil, mayonnaise/mustard prepared w/o sugar	Mayonnaises, mustards, & salad dressings made w/ sugar
Desserts & sweeteners	Dietetic jello, dietetic ice cream, dietetic puddings; natural yogurt; glucose, dextrose, dextrin, maltose & zero-calorie sweeteners	All desserts containing sugar (cake, pie, cookies, candy, jello, ice cream, sherbet, honey, fruit juice); sugar, sucrose, sorbitol, fructose
Miscellaneous	Vegetable juices, coffee, tea, salt, pepper, broths/soups from permitted vegetables; some sugar substitutes; some dietetic beverages; pasta; rice; cinnamon, garlic, poppy seeds; peanut butter (when pure & w/o added sugars)	Ketchup & any other sauces/condiments containing sugar, jam, jelly, preserves, carbonated beverages/soda; peanut butter if prepared w/added sugars; chewing gum w/sorbitol

Adapted from www.bu.edu/aldolase/HFI/treatment

During hospitalizations, special caution should be taken to avoid use of fructose-containing intravenous fluids. Although reported accidental and iatrogenic fructose infusion-related deaths prompted greater awareness of HFI in hospital settings [Locher 1987, Sachs et al 1993, Curran & Havill 2002, Müller et al 2003], danger remains in hospital settings when specific dietary (and infusion) restrictions may not be adequately disclosed [Cox 1993].

The following are recommendations:

- During any hospitalization, all members of the care team should be aware of the diagnosis of HFI, and the patient is advised to always wear a medically approved alert bracelet/necklace that provides information about the diagnosis of HFI.
- "Red flags" should be placed in the patient's chart or medical record to alert practitioners to the HFI diagnosis and to the medical risks associated with exposures to foods and/or medications (oral or parenteral) containing fructose, sucrose, sorbitol, or sucralose.
- For parenteral medications, hospital pharmacists should clear use of medications on a case-by-case basis.
- The 24% sucrose solution (routinely administered to hospitalized neonates for minor procedures) **should not be given** to neonates known to have HFI.
- Oral fructose challenge is no longer considered a favorable approach to diagnosis of HFI.

Note: Although there is no single list of medications for these or related sugars, an advanced search on www.medicines.org.uk using the search term "fructose OR sorbitol OR sucrose OR sucralose" yielded 1,574 results (accessed 11-18-20). Many such medications are oral suspensions or chewable flavored tabs designed for pediatric use. Also listed were injectable medications including immunoglobulin solutions (e.g., trastuzumab, filgrastim, some intravenous immunoglobulin solutions), vaccines (see Agents/Circumstances to Avoid), and iron supplements, as well as enema solutions and rinsing aids. For many preparations, it may not be apparent that fructose or similar compounds are present.

Surveillance

There are no formal guidelines for surveillance for individuals with HFI (e.g., frequency of subspecialty visits with physicians and/or dieticians with expertise in management of inherited metabolic diseases).

Once the diagnosis of HFI has been made, periodic evaluation of liver function, renal function, and growth is reasonable, particularly if there are concerns regarding compliance with the fructose/sucrose/sorbitol/sucralose-restricted diet.

Note: Isoelectric focusing of transferrin (or N-glycan evaluation by MS/MS) and/or monitoring of plasma lysosomal enzymes (aspartylglucosaminidase aspartylglucosaminidase and alpha-manosidase) may be elevated in untreated HFI, and thus, have been suggested as markers of disease control in HFI. None of these clinically available tests have definitively proven utility in diagnosis or surveillance [Pronicka et al 2007, Michelakakis et al 2009, Quintana et al 2009, Ferreira et al 2017, Di Dato et al 2019, Magalhães et al 2020].

Table 10. Recommended Surveillance for Individuals with Hereditary Fructose Intolerance

System/Concern	Evaluation	Frequency
Diet/Nutrition	• Dietary assessment by nutritionist as child grows, develops different tastes, & tries different foods • Monitor for vitamin & mineral deficiencies.	Every 3-4 mos in 1st yr of life; every 6-12 mos thereafter
Liver dysfunction/ NAFLD	Abdominal ultrasound, liver function tests to assess progression of NAFLD	Every 6-12 mos
Renal dysfunction	BUN, creatinine, cystatin C, urine amino acids, plasma electrolytes to assess renal function (in setting of unintentional, ongoing ingestion of fructose)	Every 6-12 mos
Hypoglycemia	Plasma glucose	As needed for findings such as lethargy, seizures, jitteriness, diaphoresis
Chronic excess fructose ingestion	• N-glycan eval • Plasma lysosomal enzyme analysis • Dietary intake assessment	Every 6-12 mos

BUN = blood urea nitrogen; NAFLD = non-alcoholic fatty liver disease

Agents/Circumstances to Avoid

Great care should be taken to avoid enteral or parenteral exposure to fructose, sorbitol, sucrose, sucralose, and polysorbate, as administration of these substances to individuals with HFI can be fatal.

The following resources can be valuable in determining medical and dietary safety:

- Dietary guidance (including prohibited foods) outlined in Table 9
- An extensive list of tolerated and non-tolerated sugars in HFI, and HFI dietary tips, which can be found online at a site curated by the Boston University HFI Laboratory

Note: Fructose tolerance testing ("fructose challenge") to diagnose HFI can be hazardous and should not be used.

Vaccinations are generally safe in children with HFI. An oral or parenteral (intramuscular or subcutaneous) vaccine can be safely given with fructose content up to 2.4 mg/kg per dose [Maiorana et al 2020]. This includes most standardized vaccines in the US and Europe. However, the following are exceptions, based on fructose content relative to the weight of the child:

- The vaccines M-M-RVAXPRO and Proquad® should ONLY be administered to children with HFI who weigh more than 6.5 kg (as the vaccines contain ~16.5 mg sucrose) [Maiorana et al 2020].

- Rotarix® white powder and solvent for oral suspension (available in Europe only) contains 22.5 mg sucrose/sorbitol and should ONLY be administered to children with HFI who weigh more than 9.3 kg [Maiorana et al 2020].

Vaccines **to be avoided in any child** with HFI (regardless of weight) are Rotarix® pre-established oral suspension and RotaTeq®, both of which contain >1000 mg sucrose per dose [Maiorana et al 2020]. Note that these are the only licensed formulations of rotavirus vaccine in the US (www.cdc.gov/vaccines/vpd/rotavirus/public) and are routinely administered at ages two months, four months, and six months, typically prior to the discovery that an infant has HFI. Therefore, any child with unexplained vomiting, hypoglycemia, lethargy, or liver or renal insufficiency following rotavirus vaccination should be investigated thoroughly for the possibility of HFI.

Evaluation of Relatives at Risk

Once the *ALDOB* pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of apparently asymptomatic older and younger sibs in order to identify individuals who would benefit from fructose restriction (see Prevention of Primary Manifestations) and avoidance of rotavirus vaccinations containing high concentrations of sucrose (see Agents/Circumstances to Avoid).

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

Pregnancy Management

There are few reports of management of pregnant women with HFI or pregnancy-related complications in HFI. In general, in familial reports in which pregnancies are not expressly discussed, it appears that HFI in a pregnant mother does not cause harm to the mother or the child provided that strict fructose avoidance is followed during the pregnancy.

In one family a woman with enzymatically documented HFI had three children (presumably from the same father), all of whom also had HFI [Marks et al 1989]. Most complications observed in these children seem to have resulted from their own poorly controlled HFI or comorbidities in early childhood, rather than maternal effects of HFI per se. The first child developed failure to thrive and cirrhosis and died at age six months of *E coli* sepsis and pulmonary edema. The second child, who had HFI complicated by transfusion-acquired HIV infection, died at age five years from complications of acquired immunodeficiency syndrome. In her third pregnancy, which proceeded normally, the mother was maintained on a strict fructose-restricted diet. The child also had HFI but thrived on a fructose-restricted diet.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register 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

Hereditary fructose intolerance (HFI) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *ALDOB* 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 *ALDOB* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are generally asymptomatic and are not at risk of developing HFI (see Clinical Description, **Heterozygotes**).

Sibs of a proband

- If both parents are known to be heterozygous for an *ALDOB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither pathogenic variant.
- Intrafamilial clinical variability has been observed in sibs who inherited biallelic *ALDOB* pathogenic variants [Caciotti et al 2008].
- Heterozygotes (carriers) are generally asymptomatic and are not at risk of developing HFI (see Clinical Description, **Heterozygotes**).

Offspring of a proband. Unless an affected individual's reproductive partner also has HFI or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ALDOB*.

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

Carrier Detection

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

Related Genetic Counseling Issues

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

Family planning

- The optimal time for determination of genetic risk 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

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

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.

- **National Library of Medicine Genetics Home Reference**
  Hereditary fructose intolerance
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.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. Hereditary Fructose Intolerance: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ALDOB	9q31.1	Fructose-bisphosphate aldolase B	Hereditary Fructose Intolerance Mutational Database ALDOB database	ALDOB	ALDOB

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 Hereditary Fructose Intolerance (View All in OMIM)

229600	FRUCTOSE INTOLERANCE, HEREDITARY; HFI
612724	ALDOLASE B, FRUCTOSE-BISPHOSPHATE; ALDOB

Molecular Pathogenesis

Together with fructokinase and triokinase, the enzyme aldolase B participates in fructose metabolism, mostly in the liver, renal cortex, and intestinal mucosa. Aldolase B splits fructose-1-phosphate into dihydroxyacetone phosphate and glyceraldehyde. Hepatic formation of glycogen from fructose is principally catalyzed by aldolase B.

HFI results from loss of aldolase B function. Normally aldolase B rapidly converts intravenous fructose to glucose, resulting in hyperglycemia; fructose may also be converted to lactate, provoking metabolic acidosis. Accumulation of fructose-1-phosphate in the setting of diminished aldolase B function inhibits gluconeogenesis and glycogenolysis, causes overutilization and diminished regeneration of ATP, and impairs protein glycosylation.

Mechanism of disease causation. HFI is caused by loss of function of the enzyme aldolase B.

Table 11. Notable *ALDOB* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_000035.4 NP_000026.2	c.178C>T	p.Arg60Ter (Arg59Ter)	Six most common HFI variants in US & European populations incl Turkey [Dursun et al 2001], Spain [Sánchez-Gutiérrez et al 2002], Central Europe [Santer et al 2005], France [Davit-Spraul et al 2008], US [Coffee et al 2010], & Italy [Ferri et al 2012]
	c.360_363delCAAA	p.Asn120LysfsTer32 (delta E4E)	
	c.448G>C	p.Ala150Pro (Ala149Pro) [2]	
	c.524C>A	p.Ala175Asp (Ala174Asp)	
	c.1005C>G	p.Asn335Lys (Asn334Lys)	
	c.1013C>T	p.Ala338Val (Ala337Val)	
	c.612T>G	p.Tyr204Ter (Tyr203Ter)	Santer et al [2005]
NM_000035.4	c.324+1G>A (IVS3+1G>A)	--	Common in northern India [Bijarnia-Mahay et al 2015]

1. Variant designation that does not conform to current naming conventions
2. Most common in all studies

Chapter Notes

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