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Glycogen Storage Disease Type I

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Summary

Clinical characteristics

Glycogen storage disease type I (GSD I) is characterized by accumulation of glycogen and fat in the liver and kidneys resulting in hepatomegaly and nephromegaly. Severely affected infants present in the neonatal period with severe hypoglycemia due to fasting intolerance. More commonly, untreated infants present at age three to four months with hepatomegaly, severe hypoglycemia with or without seizures, lactic acidosis, hyperuricemia, and hypertriglyceridemia. Affected children typically have doll-like faces with full cheeks, relatively thin extremities, short stature, and a protuberant abdomen. Xanthoma and diarrhea may be present. Impaired platelet function and development of reduced or dysfunctional von Willebrand factor can lead to a bleeding tendency with frequent epistaxis and menorrhagia in females. Individuals with untreated GSD Ib are more likely to develop impaired neutrophil and monocyte function as well as chronic neutropenia resulting in recurrent bacterial infections, gingivitis, periodontitis, and genital and intestinal ulcers. Long-term complications of untreated GSD I include short stature, osteoporosis, delayed puberty, renal disease (including proximal and distal renal tubular acidosis, renal stones, and kidney failure), gout, systemic hypertension, pulmonary hypertension, hepatic adenomas with potential for malignancy, pancreatitis, and polycystic ovaries. Seizures and cognitive impairment may occur in individuals with prolonged periods of hypoglycemia. Normal growth and puberty are expected in treated children. Most affected individuals live into adulthood.

Diagnosis/testing

The diagnosis of GSD I is established in a proband by identification of biallelic pathogenic variants in either *G6PC1* (GSD Ia) or *SLC37A4* (GSD Ib). If molecular genetic testing is inconclusive, hepatic enzyme activity analysis is only available for glucose-6-phosphatase catalytic activity (GSD Ia).

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Management

Treatment of manifestations: Uncooked cornstarch alternating with frequent meals and snacks high in complex carbohydrates as directed by a metabolic specialist and metabolic dietitian to maintain normal blood glucose levels, prevent hypoglycemia, and provide optimal nutrition for growth and development. Nutritional supplements to avoid deficiencies. Surgery or other interventions such as percutaneous ethanol injections and radiofrequency ablation for hepatic adenomas; liver transplantation for individuals refractory to medical treatment. Other treatments include lipid-lowering medications for hyperlipidemia, angiotensin-converting enzyme inhibitors to treat microalbuminuria, allopurinol to prevent and/or treat gout, citrate supplementation to prevent urinary calculi or ameliorate nephrocalcinosis, kidney transplantation for end-stage kidney disease, and combined kidney and liver transplant when needed. Management of hypertension with avoidance of beta-blockers; standard treatment of pancreatitis; developmental support and treatment of seizures as needed, antifibrinolytics and deamino-8-d-arginine vasopressin as needed for bleeding diathesis. Human granulocyte colony-stimulating factor (G-CSF) for neutropenia, recurrent infections, enterocolitis and bowel ulcers. Management of polycystic ovaries and/or irregular menstrual cycles per gynecologist. Thyroid supplementation for hypothyroidism. Social worker or counselor for discussion and coping with chronic disease and possible body image considerations.

Surveillance: Home blood glucose monitoring using a glucometer or continuous glucose monitoring; liver ultrasound every 12 to 24 months until age 16 years; liver CT, ultrasound, or MRI with contrast every six to 12 months in individuals beginning at age 16 years or earlier in individuals with hepatic adenomas; growth and nutritional assessment at each visit; surveillance labs to assess liver function, nutrition, and renal function including blood glucose, lactate, lipid panel, serum uric acid, comprehensive metabolic panel (including BUN, creatinine, AST, ALT, bilirubin, albumin, and electrolytes) every six to 12 months; PT/INR and aPTT every six months. Assess for anemia including CBC, iron, TIBC, and ferritin every six to 12 months; CBC with differential count (including WBC with ANC) every three months for those on G-CSF; serum CRP, ESR, TSH, and free T4 levels annually. Bone density every one to two years and serum 25-hydroxyvitamin D annually; renal ultrasound annually beginning at age ten years; blood pressure at each visit; developmental assessment as indicated; evaluation by a gastroenterologist when indicated; colonoscopy when indicated.

Agents/circumstances to avoid: Avoid sucrose, galactose, fructose, high fructose corn syrup, honey, maple syrup, molasses, agave nectar, and sorbitol. Combined oral contraception (including high-dose estrogen) should be avoided in women, particularly those with adenomas. Metformin, amoxicillin/clavulanic acid, and lactate-containing infusions such as Ringer's lactate should be avoided. Glucagon should not be used to treat hypoglycemia.

Evaluation of relatives at risk: Molecular genetic testing (if the family-specific pathogenic variants are known) and/or evaluation by a metabolic physician soon after birth (if the family-specific pathogenic variants are not known) allows for early diagnosis and treatment of sibs at risk for GSD I.

Genetic counseling

GSD I is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a GSD I-causing pathogenic variant, each sib of an affected individual has at conception 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. Carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible if both pathogenic variants have been identified in an affected family member.

Diagnosis

The two major subtypes of glycogen storage disease type I (GSD I) are:

- **GSD type Ia,** caused by the deficiency of glucose-6-phosphatase (G6Pase) catalytic activity; and
- **GSD type Ib,** caused by a defect in glucose-6-phosphate exchanger SLC37A4 (transporter).

The lack of either G6Pase catalytic activity or glucose-6-phosphate exchanger SLC37A4 (transporter) activity in the liver leads to inadequate conversion of glucose-6-phosphate into glucose through normal glycogenolysis and gluconeogenesis pathways, resulting in severe hypoglycemia and many other signs and symptoms typical of the GSD I disorders.

Guidelines for diagnosis and management have been published by the American College of Medical Genetics and Genomics [Kishnani et al 2014] (full text).

Suggestive Findings

GSD I **should be suspected** in individuals with the following clinical, laboratory, and histopathologic findings.

Clinical findings. Signs of hypoglycemia, hepatomegaly, and growth failure

Laboratory findings

- **Hypoglycemia.** Fasting blood glucose concentration <60 mg/dL (reference range: 70-120 mg/dL)
- **Aspartate aminotransferase (AST) and alanine aminotransferase (ALT).** May be mildly elevated, especially at the time of diagnosis or in individuals with hepatic steatosis
- **Lactic acidosis.** Blood lactate >2.5 mmol/L (reference range: 0.5-2.2 mmol/L)
- **Hyperuricemia.** Blood uric acid >5.0 mg/dL (reference range: 2.0-5.0 mg/dL)
- **Hyperlipidemia**
  - Triglycerides >250 mg/dL (reference range: 150-200 mg/dL); hypertriglyceridemia causes the plasma to appear "milky."
  - Cholesterol >200 mg/dL (reference range: 100-200 mg/dL)
- **Glucagon or epinephrine challenge test.** Administration of glucagon or epinephrine causes little or no increase in blood glucose concentration, but both increase serum lactate concentrations significantly. Given other ways to make a diagnosis, challenge testing is no longer recommended.

Histopathologic liver findings. Distention of the liver cells by glycogen and fat; PAS-positive and diastase-sensitive glycogen that is uniformly distributed within the cytoplasm; normal or only modestly increased glycogen as compared with that seen in other liver GSDs (especially GSD III and GSD IX); and large and numerous lipid vacuoles. Fibrosis and cirrhosis do not usually occur in GSD I.

Note: As liver biopsy is invasive, it should only be done when a diagnosis cannot be made using molecular genetic testing. Liver tissue may be obtained at the same time as another surgery (e.g., G-tube placement) as a fresh snap-frozen liver sample and diagnosis can be established using enzyme testing in those with *G6PC1*-related GSD I (see Establishing the Diagnosis).

Establishing the Diagnosis

The diagnosis of GSD I **is established** in a proband by identification of EITHER of the following:

- Biallelic pathogenic (or likely pathogenic) variants in *G6PC1* (GSD Ia) or *SLC37A4* (GSD Ib) on molecular genetic testing
- Deficient hepatic enzyme activity (glucose-6-phosphatase catalytic activity [GSD Ia]) from a liver biopsy specimen. Note: Glucose-6-phosphate exchanger activity (GSD Ib) is no longer clinically available.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *G6PC1* or *SLC37A4* variants of uncertain significance (or of one known pathogenic variant and one variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular Diagnosis

Molecular genetic testing approaches include **gene-targeted testing** (serial single-gene testing, multigene panel) or **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 with a phenotype indistinguishable from many other inherited disorders with hepatomegaly and hypoglycemia are more likely to be diagnosed using genomic testing (see **Option 2**).

Option 1

- **Concurrent gene testing.** Perform sequence analysis and gene-targeted deletion/duplication analysis of *G6PC1* and *SLC37A4* (see Table 1).

  Note: Targeted analysis for pathogenic variants can be performed first in individuals of Ashkenazi Jewish or Amish ancestry; see Table 5.

- **A multigene panel** that includes *G6PC1*, *SLC37A4*, and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel 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. (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(s) are 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.

Enzyme Activity Assay

A sample of 15-20 mg of snap-frozen liver obtained by percutaneous needle biopsy or open biopsy should be shipped on dry ice via overnight delivery to the clinical diagnostic laboratory.

- **Glucose-6-phosphatase (G6Pase) catalytic activity.** The normal G6Pase enzyme activity level in liver is 3.50±0.8 µmol/min/g tissue:
  - In most individuals with GSD Ia, the G6Pase enzyme activity is <10% of normal.

- In rare individuals with milder clinical manifestations, the G6Pase enzyme activity can be higher (between 1.0 and 2.0 µmol/min/g tissue).

- **Glucose-6-phosphate exchanger SLC37A4 (transporter) activity.** G6P exchanger SLC37A4 activity using an in vitro assay is difficult to measure in frozen liver; therefore, fresh (unfrozen) liver is often needed to assay enzyme activity accurately. As a result, most clinical diagnostic laboratories refrain from offering this enzyme activity assay.

Note: Because of its relatively high sensitivity, molecular genetic testing is increasingly the preferred confirmatory test when weighed against the need for liver biopsy to determine the level of enzyme activity. However, liver biopsy can additionally be used to obtain histology and electronic micrographic information, which along with enzyme analysis can be used to further investigate pathology associated with variants of uncertain significance found on genetic testing.

Table 1. Molecular Genetic Testing Used in Glycogen Storage Disease Type I

Gene [1]	Proportion of GSD I Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detected by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
G6PC1	80%	~95% [5]	2 reported [5]
SLC37A4	20%	~95% [5]	3 reported [5]

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. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. 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.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

Clinical Characteristics

Clinical Description

The clinical manifestations of glycogen storage disease type I (GSD I) are poor growth (leading to short stature) and accumulation of glycogen and fat in liver and kidneys (resulting in hepatomegaly and nephromegaly, respectively) [Kishnani et al 2014].

Although some neonates present with severe hypoglycemia, untreated infants more commonly present at age three to four months or a little later (when the feeding interval is typically increased or when infants start sleeping through the night) with additional symptoms of hepatomegaly, lactic acidosis, hyperuricemia, hyperlipidemia, hypertriglyceridemia, and/or hypoglycemic seizures. Hypoglycemia and lactic acidosis can develop after a short fast (2-4 hours).

Untreated children typically have doll-like faces with full cheeks, relatively thin extremities, short stature, and a protuberant abdomen caused by massive hepatomegaly. The spleen may be enlarged in individuals with GSD Ib during infection, or while on treatment with G-CSF. Eruptive xanthoma may be present due to untreated hyperlipidemia and diarrhea may be present secondary to intolerance to uncooked cornstarch in some individuals, or due to inflammatory bowel-like disease. Impaired platelet function and acquired von Willebrand disease can lead to a bleeding tendency, making epistaxis and easy bruising a frequent problem in individuals with poor metabolic control.

Long-term complications of untreated GSD I include the following.

Short stature. Children with GSD I have poor growth and short stature in adulthood; however, with strict compliance with cornstarch and dietary regimens, growth and final adult stature have improved [Weinstein & Wolfsdorf 2002, Mundy et al 2003, Kishnani et al 2014].

Osteoporosis. Frequent fractures and radiographic evidence of osteopenia are common. Bone mineral content can be significantly reduced even in prepubertal children. Individuals with GSD I have low vitamin D levels and poor calcium intake [Banugaria et al 2010]. Poor metabolic control was associated with decreased bone mineral density (BMD), while increased and near-normal BMD was achieved in individuals with GSD Ia, with optimization of metabolic control, compliance with the diet regimen, and vitamin D supplementation. In individuals with GSD Ib, improvement of the BMD was limited by effects of long-standing treatment with G-CSF [Minarich et al 2013, Melis et al 2014].

Delayed puberty. Untreated affected individuals historically showed delayed puberty; however, with adherence to a strict dietary regimen, and optimization of metabolic control, the onset of puberty can be normal [Sechi et al 2013].

Renal disease. Proteinuria, hypertension, renal tubular acidosis (proximal and distal renal acidification defects), renal stones, nephrocalcinosis, and altered creatinine clearance may occur in younger affected individuals and adults with poor metabolic control [Kishnani et al 2014]. With disease progression, interstitial fibrosis becomes evident. Some individuals progress to end-stage kidney disease (ESKD) and may require a kidney transplant. Renal cysts have also been described in individuals with GSD I [Gjorgjieva et al 2018]. Early optimized metabolic control and treatment with an angiotensin-converting enzyme inhibitor when microalbuminuria develops may prevent and/or delay the progression of nephropathy in individuals with GSD I [Martens et al 2009, Okechuku et al 2017, Aoun et al 2020].

Gout. Although hyperuricemia is present in young affected children, gout rarely develops in untreated children before puberty. It also may occur as a feature of GSD I in poorly controlled premenopausal women [Zhang & Zeng 2016].

Systemic hypertension has been reported in infants and younger children [Jonas et al 1988, Bhowmik et al 2015] but is more often detected in the second decade of life, or later in adulthood in association with kidney disease progression [Rake et al 2002].

Pulmonary hypertension. Overt pulmonary hypertension as a long-term complication of GSD I has been reported [Humbert et al 2002]. Those at highest risk typically have a coexisting condition that also predisposes them to developing pulmonary hypertension (e.g., portal hypertension, portocaval shunts, collagen vascular diseases, atrial septal defect) [Kishnani et al 2014, Torok et al 2017].

There is clinical controversy regarding the risk for cardiovascular disease in individuals with GSD I. Despite the development of hyperlipidemia in those with poor control, there is insufficient evidence indicating an increased risk of early atherosclerosis in these individuals [Ubels et al 2002], while some suggest otherwise [Bernier et al 2009]. Metabolic control obviates the risk for hyperlipidemia, kidney disease, and hypertension that may occur in GSD I – and are considered predisposing factors for premature atherosclerosis, cardiovascular strokes, and coronary heart disease [Kishnani et al 2014].

Hepatic adenomas with potential for malignant transformation. GSD I is associated with the development of hepatic adenomas, which can be associated with intrahepatic hemorrhage and acute anemia. Adenomas develop by the second or third decade of life; the risk increases with age [Kishnani et al 2014, Ling et al 2019]. The male:female ratio was 1:2 in 50 published cases of GSD Ia-related adenomas in contrast to other causes of hepatic adenoma showing a female predilection. In 10% of individuals, adenomas undergo malignant transformation into hepatocellular carcinoma (HCC) [Chou et al 2010, Okata et al 2020]. A relationship between poor metabolic control, particularly the degree of hypertriglyceridemia and the development of hepatic

adenomas, has been reported [Wang et al 2011]. However, some individuals develop adenomas despite adequate metabolic control, suggesting that the pathogenesis of adenoma formation and transformation to HCC is more complex and multifactorial [Ling et al 2019, Cho et al 2020].

Pancreatitis may occur as a complication secondary to severe hypertriglyceridemia, particularly in the presence of poor metabolic control and dietary noncompliance. It may occur in adults and/or children [Ai et al 2020]. A child with markedly elevated triglycerides developed life-threatening pancreatitis refractory to supportive therapy (e.g., plasmapheresis) [Rivers et al 2018].

Neurologic and cognitive effects. In one study, brain MRI findings were abnormal in 4/6 individuals with GSD Ia. MRI showed variable degrees of severity involving areas of gliosis and encephalomalacia in the cortical and subcortical areas of the occipital and parietal lobes and frontoparietal transition. There was evidence of subcortical white matter hyperintensities in the occipital lobes, T_2-weighted hyperintense foci in the central white matter that extended toward the peritrigonal regions. White matter cortical and subcortical retracted lesions were reported in one individual. MRI findings were observed in individuals with more severe disease characterized by early onset of symptoms, longer hospital admissions, and elevated levels of uric acid, lactate, and hypertriglyceridemia [Muzetti et al 2021]. In another study, MRI findings showed dilatation of the occipital horns with or without hyperintensity of the occipital lobe subcortical white matter. In addition, EEG findings correlated with the frequency and severity of hypoglycemic episodes, particularly in those with poor metabolic control and lack of dietary compliance [Melis et al 2004]. In one center steno-occlusive cerebral arteriopathy was identified in 6/175 individuals with GSD I; incidence was higher in individuals with GSD Ib than in those with GSD Ia [Hong et al 2020].

Anemia is common in individuals with GSD I, although the pathophysiology appears to differ in individuals with GSD Ia and those with GSD Ib [Wang et al 2012]. Those with GSD Ia and severe anemia are likely to have hepatic adenomas, while GSD Ib-related severe anemia is often associated with enterocolitis and inflammatory bowel disease [Wang et al 2012]. Overall, the cause for anemia is multifactorial, including the restrictive nature of the diet, excessive intake of cornstarch, chronic illness, and kidney disease.

Bleeding diathesis. In one study, 6/10 individuals with GSD Ia developed reduced and/or dysfunctional von Willebrand factor [Mühlhausen et al 2005]. This defect is in addition to a platelet aggregation defect; both bleeding disorders manifest in individuals with poor metabolic control [Rake et al 2002]. Manifestations include epistaxis, easy bruising, menorrhagia which can be life threatening, intrahepatic adenoma hemorrhage, and increased bleeding during surgical procedures.

Neutropenia and impaired neutrophil function. Untreated GSD Ib is associated with chronic neutropenia and impaired neutrophil and monocyte function. Neutropenia has been reported in a small number of individuals with GSD Ia [Weston et al 2000]. Neutropenia is noted typically after the first few years of life, resulting in recurrent bacterial infections including gingivitis, periodontal disease, dental caries, and brain abscess. Individuals also develop oral and genital ulcerations, as well as intestinal mucosal ulcers [Visser et al 1998, Visser et al 2002]. Oral manifestations such as aphthous ulcers and delayed dental maturation and eruption have been reported in a few affected individuals [Mortellaro et al 2005, Dababneh et al 2020]. GSD Ib-related neutropenia may be caused by increased apoptosis attributed to an increase in reactive oxygen species and impaired cell adhesion and migration of neutrophils to inflamed tissues rather than impairment in maturation [Visser et al 2012, Kishnani et al 2014, Kim et al 2017]. Vitamin E as an antioxidant was beneficial in improving neutrophil count as an adjunct therapy to G-CSF [Melis et al 2009]. Veiga-da-Cunha et al [2019] showed that failure to eliminate a phosphorylated toxic analog (1,5-anhydroglucitol-6-phosphate; 1,5AG6P) contributed to neutropenia and neutrophil dysfunction in individuals with GSD Ib. This work led to clinical repurposing of empagliflozin, an inhibitor of the kidney sodium glucose cotransporter 2 (SGLT2) that was able to lower serum 1,5 AG6P and improve neutrophil count and functions [Wortmann et al 2020].

Enterocolitis due to an inflammatory bowel disease-like disorder occurs in some individuals with GSD Ib [Wicker et al 2020] and has been reported in a small number of individuals with GSD Ia [Lawrence et al 2017]. Severe neutropenia in individuals with GSD Ib is associated with more severe inflammatory bowel disease.

Polycystic ovaries. Some females have ultrasound findings consistent with polycystic ovaries. While this may affect ovulation and fertility in some females, in general fertility does not appear to be reduced [Sechi et al 2013].

Irregular menstrual cycles. About half of women with GSD I were found to have irregular menstrual cycles, in some instances women can have a life-threatening menorrhagia [Sechi et al 2013].

Thyroid autoimmunity. The prevalence of thyroid autoimmunity and hypothyroidism has been found to be increased in individuals with GSD Ib. The increased risk of autoimmunity was associated with abnormal T-cell function [Melis et al 2007, Melis et al 2017].

Prognosis

Historically, prognosis was poor for untreated individuals with GSD I and many died at a young age. Early diagnosis and treatment have improved prognosis [Dambska et al 2017]. Normal growth and puberty is expected in children treated early with good metabolic control. Most affected individuals live into adulthood. Despite good metabolic control and early treatment, some individuals still develop hepatic adenoma and proteinuria in adulthood.

Phenotype Correlations by Gene

G6PC1 **(GSD Ia)**

- Better improvement of bone mineral density (BMD) is seen with optimized dietary treatment and vitamin D supplementation.
- Severe anemia is often associated with hepatic adenomas, with kidney failure, persistent menorrhagia, poor nutrition, and is often multifactorial.

SLC37A4 **(GSD Ib)**

- BMD was not associated with metabolic control or granulocyte colony-stimulating factor (G-CSF) treatment in individuals with GSD Ib, suggesting a multifactorial etiology [Minarich et al 2013].
- Severe neutropenia and related enterocolitis and intestinal mucosal inflammation may occur in GSD Ib, leading to severe anemia. Note: Enterocolitis has been noted only in a small subset of individuals with GSD Ia.
- Risk for thyroid autoimmunity and hypothyroidism is increased.

Genotype-Phenotype Correlations

No strong genotype-phenotype correlations that can explain the clinical and biochemical features or the response to treatment have been identified for GSD I [Eminoglu et al 2013, Kishnani et al 2014].

G6PC1. Two case reports suggested that individuals with GSD Ia who are homozygous for the c.648G>T pathogenic splicing variant may be at increased risk of developing hepatocellular carcinoma (HCC) [Nakamura et al 1999, Matern et al 2002]. However, it should be noted that this pathogenic variant is the most common cause of GSD Ia in individuals of Japanese descent. Of 19 Japanese adults who were homozygous for c.648G>T, three had HCC, one had cholangiocellular carcinoma, and seven had hepatic adenoma [Nakamura et al 2001]. A study of 40 individuals who were homozygous for this pathogenic variant found that c.648G>T is associated with a milder phenotype with respect to hypoglycemia [Akanuma et al 2000, Chou & Mansfield 2008].

Individuals with GSD Ia who are homozygous for the pathogenic variant c.562G>C were reported to have a GSD Ib-like phenotype with mild neutropenia [Weston et al 2000, Chou & Mansfield 2008]. This phenotype was not observed in an individual who was compound heterozygous for this pathogenic variant [Eminoglu et al 2013].

SLC37A4. No clear phenotype-genotype correlations have been found in GSD Ib [Melis et al 2005].

Nomenclature

G6Pase is a multicomponent enzyme complex often referred to as the G6Pase system. The classification of GSD I into four subtypes no longer exists. The current classification of GSD I subtypes is GSD Ia and GSD Ib.

Historically, GSD I is also referred to as von Gierke disease after Dr Edgar von Gierke, who first described the disease in 1929.

Prevalence

The overall incidence of GSD I is one in 100,000.

GSD Ia is the most common GSD subtype in individuals of European descent.

In Ashkenazi Jews the estimated carrier frequency of the most common pathogenic variant (p.Arg83Cys) is 1.4% and disease prevalence is one in 20,000.

The increased frequency of some pathogenic variants in different ethnic groups (e.g., c.648G>T in 88% of affected individuals of Japanese ancestry, c.379_380dupTA in 50% of affected Hispanic Americans) may reflect population-specific differences in disease prevalence [Janecke et al 2001, Chou et al 2002, Ekstein et al 2004].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *G6PC1* or *SLC37A4*.

Differential Diagnosis

Disorders that can present clinically like glycogen storage disease type I (GSD I) include those summarized in Table 2.

Table 2. Disorders in the Differential Diagnosis of Glycogen Storage Disease Type I

Gene	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/GSD I	Distinguishing from GSD I
AGL	Debranching enzyme deficiency (GSD III)	AR	• Hepatomegaly • Fasting hypoglycemia • ↑ AST/ALT • Hyperlipidemia	• AST & ALT usually markedly ↑ • Muscle involvement w/↑ CK • Normal uric acid, lactate
FBP1	Fructose-1,6-bisphosphatase deficiency [1]	AR	• Hepatomegaly • Fasting hypoglycemia • ↑ AST/ALT	Fasting hyperlactatemia

Table 2. continued from previous page.

Gene	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/GSD I	Distinguishing from GSD I
GBA1 (*GBA*)	Gaucher disease [2]	AR	• Hepatomegaly • Growth failure • Hyperlipidemia • Pulmonary hypertension (rare) • Bone disease / osteoporosis	• No fasting hypoglycemia • Significant splenomegaly • Bone infarcts, AVN of femoral head & pulmonary involvement in the form of pulmonary infiltrates
GBE1	Branching enzyme deficiency (See GSD IV.)	AR	• Hepatomegaly • ↑ AST/ALT	• Lack of hypoglycemia until end-stage liver disease • Liver cirrhosis
GK	Glycerol kinase deficiency (OMIM 307030)	XL	Hypoglycemia	Ketoacidosis & extremely ↑ glycerol
GYS2	Hepatic glycogen synthase deficiency (GSD 0) (OMIM 240600)	AR	• Fasting hypoglycemia • Ketosis	• Absence of hepatomegaly • Postprandial hyperglycemia & hyperlactatemia
PHKA2 *PHKB* *PHKG2*	Liver phosphorylase kinase deficiency (GSD IX)	XL AR	• Hepatomegaly • Fasting ketosis • Hypoglycemia • ↑ AST/ALT • ↑ lipids	• Male predominance • AST & ALT commonly more severely ↑ • Liver fibrosis
SLC2A2	GLUT2 deficiency (Fanconi-Bickel syndrome; GSD XI) (OMIM 227810)	AR	• Hepatomegaly • Fasting hypoglycemia • Fasting ketosis • ↑ AST/ALT	• Postprandial hyperglycemia • Chronic diarrhea • Hypophosphatemic rickets • Fanconi nephropathy • Significant short stature
SMPD1	Chronic visceral ASMD (Niemann-Pick disease type B) [2] (See ASM Deficiency.)	AR	• Hepatomegaly • Growth failure • Hyperlipidemia • Bone & pulmonary involvement	• No fasting hypoglycemia • Significant splenomegaly

Adapted from Kishnani et al [2019]
AD = autosomal dominant; ALT = alanine aminotransferase; AR = autosomal recessive; ASMD = acid sphingomyelinase deficiency; AST = aspartate aminotransferase; AVN = avascular necrosis; CK = creatine kinase; GSD = glycogen storage disease; MOI = mode of inheritance; XL = X-linked
1. Fructose-1,6-bisphosphatase deficiency is one example of a disorder of gluconeogenesis; others should also be considered.
2. Niemann-Pick disease type B and Gaucher disease are examples of metabolic storage disorders; other metabolic storage disorders should also be considered.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with glycogen storage disease type I (GSD I), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations at Initial Diagnosis in Individuals with Glycogen Storage Disease Type I

System/Concern	Evaluation	Comment
Hepatic	• Serum/plasma concentration of glucose, lactic acid, uric acid, & lipids incl cholesterol & triglycerides, AST, ALT, bilirubin, albumin, PT/INR • Consultation w/metabolic specialist • Liver imaging to evaluate for hepatomegaly • Liver function tests	At diagnosis
Nutrition/Growth	• Measurement of length/height, weight; calculation of BMI • Eval of nutritional status	
Skeletal	Measurement of bone density	Beginning at age 10 yrs or as clinically indicated
	Serum 25-hydroxyvitamin D	At diagnosis
Cardiovascular	Blood pressure	At diagnosis
	• Echocardiogram to detect pulmonary hypertension when indicated • Lipid panel incl triglycerides	Beginning at age 10 yrs or earlier if symptomatic
Renal	Kidney function tests incl BUN, creatinine, urine microalbumin/creatinine ratio, urinary citrate excretion	At diagnosis
	Kidney imaging to evaluate for nephromegaly & kidney stones	Beginning at age 10 yrs
Neurodevelopment	• Developmental assessment • Assess for evidence of seizures.	At diagnosis
Hematologic	• Eval for anemia • Platelet aggregation studies & functional assay to evaluate platelet function • Von Willebrand factor antigen & activity	At diagnosis in those w/bleeding tendency, poor metabolic control &/or undergoing surgical procedures
Immunologic	Complete blood count w/manual differential to evaluate for neutropenia in persons w/: • GSD Ib • GSD Ia due to homozygosity for *G6PC1* pathogenic variant p.Gly188Arg	At diagnosis
Gastrointestinal	• Assess for signs/symptoms of diarrhea, enterocolitis, &/or bowel ulcers. • Serum iron & ferritin	At diagnosis
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of GSD I 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; • Home nursing referral.	At diagnosis

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Guidelines for management have been published by the American College of Medical Genetics [Kishnani et al 2014] (full text).

Treatment includes care by a **metabolic team** (metabolic specialist, metabolic dietician, hepatologist, GI specialist, social worker, genetic counselor, and psychologist).

Medical nutrition therapy to maintain normal blood glucose levels, prevent secondary metabolic derangements, and prevent long-term complications:

- **Uncooked cornstarch.** There is no consensus on the age at which cornstarch therapy should be initiated but a trial is often introduced between ages six months and one year. The severity and recurrence of hypoglycemic episodes determine the timing of cornstarch therapy initiation. Amylase is required to digest cornstarch and may not be produced adequately until age two years. If used earlier, supplementation with pancrelipase (a combination of lipase, protease, and amylase), may help in alleviating the symptoms of intolerance to uncooked cornstarch.

  Historical cornstarch dose recommendations based on body weight resulted in overtreatment and in poor metabolic control. Cornstarch therapy doses are now calculated based on glucose needs determined by hepatic glucose production rate [Ross et al 2020]. Doses are measured by weight and given between meals, spaced apart from meals to maintain normoglycemia. Cornstarch is also recommended at bedtime and overnight in most individuals with GSD I to maintain normoglycemia. Argo® is the preferred brand in the United States in terms of both taste and sustainability. Other brands should be used with caution and switching between brands is not recommended. Glycosade®, a modified, waxy maize extended-release cornstarch, is available in Europe and the United States as a single-dose overnight treatment [Ross et al 2016]. Cornstarch should be uncooked as heat makes it less effective to maintain blood glucose levels. It should be mixed with cold water or sugar-free, lactose-free beverages.

- **Frequent daytime feedings.** Meals and snacks every three to four hours that are rich in complex carbohydrates without (or negligible amount of) simple carbohydrates. A snack before bedtime may be needed. The meal schedule and composition are individualized and based on blood glucose levels, activity schedule, and timing of uncooked cornstarch intake.

- **Overnight continuous feeding via nasogastric tube or a gastrostomy tube** is required in infants and young children to allow them to sleep through the night. Some adults may need overnight tube feeding if they are unable to take cornstarch and/or prefer this to waking up every four to five hours to take cornstarch. The recommended continuous overnight feeding is a glucose infusion or a high-carbohydrate, lactose- and sucrose-free enteral formula. An optimal infusion provides 8-10 mg/kg/min glucose in infants, 6-8 mg/kg/min glucose in older children, and 3-7 mg/kg/min glucose in adults. Continuous overnight tube feedings raise safety concerns of tube dislodgement, leakage, and pump failures that can cause serious hypoglycemia, leading to seizures, brain damage, and/or death [Steunenberg et al 2018]. Safety precautions, such as bed-wetting devices (to detect formula leakage) and feeding pump alarms are strongly recommended to avoid tragic outcomes.

- **Carbohydrates.** The diet should contain ~60% calories from complex carbohydrates (e.g., whole-grain breads, pastas, legumes, rice) including calories from cornstarch. The following should be avoided: sucrose, galactose, fructose, high-fructose corn syrup, honey, maple syrup, molasses, agave nectar, and sorbitol. Reading nutrition labels is important to restrict the intake of simple sugars (naturally present or added) to <5 g/meal and <2 g/snack. This approach allows the intake of certain cheeses, yogurt, and dairy milk with lactose content within these limits. The intake of carbohydrates should be divided between all

meals and snacks with timing based on exercise and activity levels. Excessive carbohydrate intake should be avoided to prevent obesity and to maintain optimal metabolic control.

- **Protein** should be lean, of high biological value, and provide 10%-15% of the recommended total calories. Soy formula (Prosobee®) and unsweetened soy milk can be used in infancy and childhood for meeting carbohydrate and protein needs.
- **Fat** should provide 25%-30% of the total calories. The diet should include heart-healthy fats such as canola oil and olive oil and be limited in trans fats and saturated fats.
- **Nutritional supplements** are essential due to the poor nutritional quality of cornstarch and dietary restrictions (e.g., some major food groups such as fruits are restricted).
    - **Calcium and vitamin D.** To support bone growth and mineralization, calcium citrate or calcium carbonate with vitamin D is recommended to meet the RDA for age.
    - **Complete multivitamin with minerals including iron and zinc.** Supplementation to meet 100% of the RDA for these nutrients is recommended. Sugar-free supplements are recommended.

Hepatic adenomas can be treated with surgery or other interventions including percutaneous ethanol injections and radiofrequency ablation. Liver transplantation should be considered when other interventions fail, or if the adenoma size and or recurrence rate is suspicious of malignant transformation.

Indications for liver transplant include large adenomas with a risk of malignant transformation, rapid increase in size and or number of adenomas, poor metabolic control, and lack of compliance leading to kidney failure (liver-kidney transplant is more beneficial in this case than kidney-only transplant). Liver-only transplant leads to normalization of the blood sugars, lactic acid, and triglycerides. This may delay the onset of kidney disease if clinically unaffected. However, it does not prevent kidney damage once renal disease has set in, warranting modification of the immunosuppressive medications and close monitoring of the kidney to prevent further progression of renal disease due to nephrotoxic effects of the medications.

Hyperlipidemia. Lipid-lowering medications, such as HMG-CoA reductase inhibitors and fibrate (e.g., Lipitor®, gemfibrozil), are used when lipid levels remain elevated despite good metabolic control, especially after puberty to prevent atherosclerosis and pancreatitis.

Renal disease. Low-dose angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril), or angiotensin receptor blockers (e.g., losartan) are used to treat microalbuminuria, an early indicator of renal dysfunction.

Gout. Allopurinol, a xanthine oxidase inhibitor, is used to prevent gout when dietary therapy fails to completely normalize blood uric acid concentration, especially after puberty. It should be discontinued when a woman is planning a pregnancy.

Nephrocalcinosis. Citrate supplementation may help prevent or ameliorate nephrocalcinosis and the development of urinary calculi. In young children, an initial dose of 1 mEq/kg/day in liquid form divided into three doses should be instituted. The dose should be increased based on urinary citrate excretion. In older children and adults, potassium citrate tablets can be started at a dose of 10 mEq/3x/day. Citrate use can cause hypertension and life-threatening hyperkalemia in affected individuals with renal impairment. Potassium and sodium levels should also be monitored. Citric acid containing products should not be taken at the same time as cornstarch.

Kidney transplantation can be performed for end-stage kidney disease (ESKD). Individuals who had kidney-only transplant must be monitored due to continued risk of liver metabolic disease and adenomas.

Combined liver and kidney transplantation is indicated as needed for restoration of metabolic control and treatment of kidney disease.

Hypertension. Treatment of pulmonary hypertension is as in the general population. For systemic hypertension, which may mask hypoglycemia, beta-blockers should be avoided.

Pancreatitis is treated in a standard manner.

Developmental delay and/or neurocognitive issues. Provide therapies, developmental support, and educational support services as needed for those with developmental delay and/or neurocognitive issues. Seizures (if persistent outside of hypoglycemic events) should be managed under supervision of a neurologist.

Bleeding diathesis. Standard management of individuals with platelet dysfunction and reduced or dysfunctional von Willebrand factor includes **antifibrinolytics** and **deamino-8-d-arginine vasopressin (DDAVP)**. DDAVP should be used with caution with monitoring of electrolytes, particularly if the individual is on large volumes of intravenous fluid due to the risk of hyponatremia associated with the antidiuretic effect of DDAVP.

Perioperative care of individuals with GSD I is necessary particularly when undergoing partial hepatectomy for HCA with a risk of hemorrhage [Mollet-Boudjemline et al 2011].

Recurrent infections. Human granulocyte colony-stimulating factor (G-CSF) may increase the number and improve the function of circulating neutrophils and may improve the symptoms of enterocolitis and bowel ulcers in individuals with GSD Ib.

G-CSF should be administered subcutaneously starting at 1.0 µg/kg daily or every other day. The dose should be increased stepwise at approximately two-week intervals until the target absolute neutrophil count (ANC) of 500 to 1.0 x 10^9/L is reached. Avoidance of higher doses of G-CSF is recommended given the side effects.

Individuals on G-CSF should be monitored closely for changes in spleen size (particularly in the absence of infection) and signs of myelodysplasia [Dale et al 2019]. A blood count should be done every three months to assess response to treatment and, although the risk of acute myeloid leukemia is low, to evaluate for the presence of myeloblasts. Imaging performed for liver surveillance (e.g., ultrasound, CT, MRI) should include spleen measurements to identify and monitor splenomegaly. G-CSF has been reportedly associated with giant cell lesions of the maxillofacial complex in individuals with GSD Ib.

Inflammatory bowel disease related enterocolitis. Bowel manifestations and complications improved in individuals with GSD Ib following treatment of neutropenia using G-CSF, as well as anti-inflammatory medications (e.g., salicylates, mesalamine sulfasalazine, and prednisone) [Dale et al 2019, Wicker et al 2020]. Treatment with empagliflozin has reduced the frequency and severity of bowel disease while decreasing the required G-CSF dose [Grünert et al 2020, Wortmann et al 2020].

Other

- **Polycystic ovaries and/or irregular menstrual cycles.** Referral to a gynecologist for management when needed
- **Hypothyroidism.** Thyroid hormone supplementation
- **Social worker or counselor** for discussion and coping with chronic disease and possible body image considerations

Surveillance

Follow GSD I guidelines published by a group of experts in the field [Kishnani et al 2014].

Perform home **blood glucose monitoring** using a glucometer or continuous glucose monitoring (CGM) when available. CGM is a reliable noninvasive tool that assesses glucose trends in real time with good concordance with finger-stick glucose values. The benefits of CGM include improved self-monitoring and management of blood sugars while assessing the effect of treatment regimens on glucose levels in the outpatient setting rather

than the hospital, which does not reflect or capture situations that the individual is likely to encounter. Under supervision of a metabolic dietitian, individuals are able to adjust dietary and cornstarch regimens, empowering them to take control of their own management. CGM allows 24-hour glucose monitoring for hypoglycemia and hyperglycemia (due to overtreatment) in those who may be asymptomatic – information that may be missed if monitoring is done by glucose finger stick. The data generated by CGM are useful for comparing trends and adjusting cornstarch doses and dietary plans as indicated without need for hospitalization [Herbert et al 2018, Peeks et al 2021].

Table 4. Recommended Surveillance for Individuals with Glycogen Storage Disease Type I

System/Concern	Evaluation	Frequency
Liver disease	Serum AST, ALT, albumin, bilirubin, PT/INR, & aPTT to monitor for liver damage	Every 6-12 mos
	Liver ultrasound to assess for adenomas	Every 12-24 mos until age 16 yrs
	Liver CT, ultrasound, or MRI w/IV contrast to assess liver size; eval for adenomas, evidence of portal hypertension, or features of liver carcinoma (nodules, heterogeneous echogenic shadows) [1, 2]	• Every 6-12 mos beginning at age 16 yrs; earlier in those w/hepatic adenomas • Precautions against contrast-assoc kidney injury in those w/signs of kidney involvement
Nutrition/Growth	• Measurement of length/height, weight; calculation of BMI • Eval of bone age if clinically indicated • Eval of nutritional status	At each visit
	Glucose, lactate	Every 6-12 mos
Osteoporosis	Measurement of bone density	Every 1-2 yrs & as clinically indicated beginning at age 10 yrs
	Serum 25-hydroxyvitamin D	Every 12 mos or more frequently as needed
Hyperlipidemia	Lipid panel	Every 6-12 mos
Renal disease / Nephrocalcinosis / Gout	Kidney radiograph; renal ultrasound; CT scan of the abdomen/ stone protocol for nephrocalcinosis	Annually after age 10 yrs
	• Serum creatinine, uric acid • Urine microalbumin/creatinine in random (spot) urine sample • Citrate in urine for risk of stone formation	Every 6-12 mos
Hypertension	Systemic blood pressure measurement	At every visit beginning in infancy
	Echocardiography to assess for pulmonary hypertension	If cardiopulmonary symptoms/signs or evidence of portal hypertension
Neurodevelopment	Developmental assessment	As indicated in those w/DD or cognitive delay
	Assess for seizure activity.	As indicated
Hematology	Assess for anemia w/CBC, iron, TIBC, ferritin.	Every 6-12 mos
	Platelet function (aggregation tests & von Willebrand factor studies) for bleeding tendency	When indicated
Immune dysfunction	CBC w/manual differential (incl WBC & ANC)	Every 3 mos for those on G-CSF

Table 4. continued from previous page.

System/Concern	Evaluation	Frequency
Inflammatory bowel disease / Enterocolitis	Serum CRP, ESR, WBC count w/ANC	Annually
	• Eval by gastroenterologist • Assess w/Pediatric Crohn's Disease Activity Index.	As indicated if signs/symptoms of bowel disease
	Colonoscopy to evaluate extent & severity of bowel disease	When indicated
Thyroid disease	TSH & free T4 levels	Annually

DD = developmental delay; TIBC = total iron binding capacity
1. Franco et al [2005], Chen et al [2018]
2. Serum AFP and CEA levels are not reliable markers of hepatocellular carcinoma [Shieh et al 2012].

Agents/Circumstances to Avoid

Avoid sucrose, galactose, fructose, high-fructose corn syrup, honey, maple syrup, molasses, agave nectar, and sorbitol.

Due to potential negative effects of sex hormones (containing estrogen) on hepatic adenomas, combined oral contraception (including high-dose estrogen) should be avoided in women with GSD I, especially those with adenomas [Sechi et al 2013, Austin et al 2013]. Progestin-only contraceptives may be considered; however, given the potential risk to develop low BMD and osteoporosis, follow-up assessment for bone disease is recommended.

Metformin and lactate-containing infusions such as Ringer's lactate should be avoided.

Amoxicillin/clavulanic acid has been associated with an increased risk of diarrhea in individuals with GSD I (common); there is also a risk for idiopathic liver failure due to clavulanic acid (rare).

Glucagon should not be used to treat hypoglycemia because it is ineffective and may increase the risk of lactic acidosis.

Evaluation of Relatives at Risk

Evaluation of sibs of a proband as early as possible allows for prompt diagnosis and treatment with much-improved outcome. Evaluations include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Evaluation by a metabolic physician soon after birth for symptoms pertaining to GSD I if the family-specific pathogenic variants are not known or if molecular genetic testing is not available.

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 GSD I, certain precautions should be taken:

- Pre-pregnancy counseling regarding diet to avoid low blood glucose and to stress the importance of blood glucose monitoring prior to and during pregnancy
- Baseline ultrasound of liver and kidneys prior to pregnancy
- Consideration of referral to high-risk obstetrician
- Review of medications prior to conception to weigh risks and benefits:
  - Exposure to ACE inhibitors in the second and third trimesters of pregnancy can cause fetal damage and death.
  - No data on the use of allopurinol during pregnancy in humans exist; however, high doses have been shown to interfere with embryo development in animal models.

- Lipid-lowering drugs may also lead to adverse fetal effects and should be avoided during pregnancy.

Metabolic control should be followed closely throughout the pregnancy. Because carbohydrate requirements may increase with pregnancy, glucose levels should be monitored closely and treated accordingly [Ferrecchia et al 2014].

Abdominal ultrasound should be performed every six to 12 weeks. Sechi et al [2013] reported an increase in the size of preexistent adenomas and the development of new adenomas during pregnancy and recommended monitoring by imaging before, during, and after pregnancy. Resection of large (≥5 cm) or growing adenomas before pregnancy has been recommended [Terkivatan et al 2000].

Renal function should be followed closely, as this may worsen during pregnancy [Dagli et al 2010, Yamamoto et al 2010]. Development of renal calculi has been reported in pregnant women with GSD Ib [Dagli et al 2010].

Glucose infusion during labor has been used [Ferrecchia et al 2014].

Platelet count, hemoglobin, and clotting studies should be performed because of the potential for increased bleeding at delivery [Lewis et al 2005].

Therapies Under Investigation

Current dietary treatment prevents hypoglycemia and greatly improves the life expectancy of individuals with GSD I. However, long-term complications – including progressive kidney failure and development of hepatic adenomas that progress to hepatocellular carcinoma – still occur. The development of new therapies for GSD I has recently evolved into new concepts involving the following:

- **Repurposing medical therapeutics to target defective mechanisms involved in GSD I,** for example: empagliflozin, a sodium co-transporter-2 (SGLT2) inhibitor, is FDA approved to treat type 2 diabetes and has been used to treat neutropenia and neutrophil dysfunction in individuals with GSD Ib [Veiga-da Cunha et al 2019]. Based on the concept that the structural analog of glucose 6 phosphate (G-6-P) is 1,5-anhydroglucitol-6-phosphate (1,5-AG6P), nontoxic 1,5-anhydroglucitol (1,5-AG) is phosphorylated to 1,5-AG6P by hexokinases and ADP-dependent glucokinase present in neutrophils. The G-6-P transporter (G6PT) transports both G-6-P and 1,5-AG6P into the endoplasmic reticulum; where it is dephosphorylated, preventing the accumulation of toxic 1,5-AG6P in neutrophils. In individuals with GSD Ib, G6PT activity is defective; toxic levels of 1,5-AG6P accumulate in neutrophils causing inhibition of hexokinases and depletion of intracellular G-6-P leading to impaired function and decreased survival of neutrophils. Empagliflozin inhibits renal SGLT2 leading to urinary excretion of 1,5-AG and reduction of 1,5-AG6P in neutrophils. Reduction of the toxic accumulation of 1,5-AG6P in individuals with GSD Ib improves neutrophil number and function, reducing the frequency of bowel flares, reducing infections, and leading to a reduction or cessation of G-CSF therapy in some individuals [Veiga-da-Cunha et al 2019, Grünert et al 2020, Wortmann et al 2020] (see Safety and Efficacy of Empagliflozin in GSD Ib Patients with Neutropenia).
- **Correcting the primary cause of these disorders using DNA and messenger RNA therapies.** Gene therapy strategies for GSD Ia and GSD Ib have focused on recombinant adeno-associated virus (rAAV) vectors. These studies have shown promising results in animal models [Chou & Mansfield 2011, Chou et al 2015, Kwon et al 2017, Chou et al 2018]. Increased hepatic G6Pase and G6PT activity and improvement of metabolic parameters has been observed in animal models. Strategies to integrate the G6Pase transgene into the genome are being investigated, with promising results [Landau et al 2016, Lee et al 2018, Zhang et al 2020]. Of note, a relatively low level (3% of normal) of hepatic G6Pase activity is needed for survival and to prevent formation of hepatocellular adenomas [Lee at al 2015, Cho et al 2019]. Correction of renal G6Pase deficiency by gene therapy has been less well studied, and the most efficient methods for

transducing kidney cells continue to be investigated [Chou et al 2015]. Identification of AAV serotypes that effectively transduce all affected tissue types (including liver, kidney, and hematopoietic stem cells) would be beneficial [Chou et al 2015].

A Phase I/II clinical trial, Open-Label Safety and Dose-Finding Study of Adeno-Associated Virus Serotype 8-Mediated Gene Transfer of Glucose-6- Phosphatase in Adults With Glycogen Storage Disease Type Ia, has shown promising preliminary results in an ongoing study.

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.

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

Glycogen storage disease type I (GSD I) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *G6PC1* [formerly *G6PC*] or *SLC37A4* pathogenic variant based on family history).
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a GSD I-causing pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [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 asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a GSD I-causing pathogenic variant, each sib of an affected individual has at conception 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. The offspring of an individual with GSD I are obligate heterozygotes (carriers) for a GSD I-causing pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a GSD I-causing pathogenic variant.

Carrier Detection

Molecular genetic testing. Carrier testing for at-risk relatives requires prior identification of the GSD I-causing pathogenic variants in the family.

Biochemical genetic testing. Enzymatic testing is unreliable and not available for use in carrier detection.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on testing at-risk relatives 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

Molecular genetic testing. Once the GSD I-causing pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Biochemical testing. Prenatal testing based on assay of glucose-6-phosphatase catalytic activity [GSD Ia] or glucose-6-phosphate exchanger SLC37A4 (transporter) activity [GSD Ib] is not available because of the low accuracy rate and the risk associated with fetal liver biopsy. The glucose-6-phosphatase catalytic activity in vitro may not differentiate a carrier from either a normal or an affected pregnancy [Chen et al 2002] and thus is not recommended.

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.

- **Association for Glycogen Storage Disease**
  www.agsdus.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  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. Glycogen Storage Disease Type I: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
G6PC1	17q21.31	Glucose-6-phosphatase catalytic subunit 1	G6PC database	G6PC1	G6PC1
SLC37A4	11q23.3	Glucose-6-phosphate exchanger SLC37A4	SLC37A4 database	SLC37A4	SLC37A4

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 Glycogen Storage Disease Type I (View All in OMIM)

232200	GLYCOGEN STORAGE DISEASE Ia; GSD1A
232220	GLYCOGEN STORAGE DISEASE Ib; GSD1B
602671	SOLUTE CARRIER FAMILY 37 (GLUCOSE-6-PHOSPHATE TRANSPORTER), MEMBER 4; SLC37A4
613742	GLUCOSE-6-PHOSPHATASE, CATALYTIC; G6PC

Molecular Pathogenesis

G6PC1 encodes G6Pase (glucose-6-phosphatase catalytic subunit 1), a multicomponent enzyme system localized in the endoplasmic reticulum membrane. It helps catalyze the terminal reaction of both glucogenolysis and gluconeogenesis, hydrolyzing G6P to glucose and inorganic phosphate in hepatocytes and renal cells.

SLC37A4 encodes glucose-6-phosphate exchanger SLC37A4 (transporter), a transport protein that helps transport G6P into the lumen of the endoplasmic reticulum from the cytoplasm and endoplasmic reticulum membrane compartment. G6P transporter is expressed ubiquitously in tissues such as liver, kidney, large intestine, small intestine, skeletal muscle, and (to a lesser extent) the brain and heart, unlike G6Pase.

Mechanism of disease causation. Loss of function

Table 5. Glycogen Storage Disease Type I: Notable Pathogenic Variants by Gene

Gene	Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
G6PC1	NM_000151.3 NP_000142.1	c.79delC (158delC)	p.Gln27ArgfsTer9	1 of 3 variants that account for 21% of pathogenic variants in European population [Seydewitz & Matern 2000, Chou et al 2002]
		c.247C>T	p.Arg83Cys	Accounts for 32% of pathogenic variants in European population & 93%-100% in Jewish population [Stroppiano et al 1999, Janecke et al 2001, Ekstein et al 2004]
		c.248G>A	p.Arg83His	Accounts for 38% of pathogenic variants in Chinese population
		c.562G>C (641G>C)	p.Gly188Arg	1 of 3 variants that account for 21% of pathogenic variants in European population [Seydewitz & Matern 2000, Chou et al 2002]

Table 5. continued from previous page.

Gene	Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
		c.648G>T (G727T)	p.Tyr202Ter [2]	Accounts for 88% of pathogenic variants in Japanese population & 36% of pathogenic variants in Chinese population [Kajihara et al 1995, Lam et al 1998]
		c.1039C>T (1118C>T)	p.Gln347Ter	1 of 3 variants that account for 21% of pathogenic variants in European population; founder variant in Amish population [Seydewitz & Matern 2000, Chou et al 2002]
		c.379_380dupTA (459insTA)	p.Tyr128ThrfsTer3	Accounts for 50% of pathogenic variants in Hispanic population [Rake et al 1999, Matern et al 2002]
SLC37A4	NM_001467.5 NP_001458.1	c.352T>C (521T>C)	p.Trp118Arg	Accounts for 50% of variants in Japanese population [Kure et al 1998, Nakamura et al 1999, Matern et al 2002, Kojima et al 2004].
		c.1015G>T (1184G>T)	p.Gly339Cys	Accounts for 15% of pathogenic variants in European population & for 29% of pathogenic variants in German population [Veiga-da-Cunha et al 1999, Santer et al 2000, Chou et al 2002]
		c.1042_1043delCT (1211delCT)	p.Leu348ValfsTer53	Accounts for 31% of pathogenic variants in European population & for 32% of pathogenic variants in German population [Veiga-da-Cunha et al 1999, Santer et al 2000, Chou et al 2002]

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). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

2. Silent amino acid change (Leu216Leu) that creates a new splice site resulting in premature termination at p.Tyr202Ter [Lam et al 1998]

Chapter Notes

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