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Glycogen Storage Disease Type III

Synonyms: Cori Disease, Debrancher Deficiency, Forbes Disease, Glycogen Debranching Enzyme (GDE) Deficiency

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Summary

Clinical characteristics

Glycogen storage disease type III (GSD III) is characterized by variable liver, cardiac muscle, and skeletal muscle involvement. GSD IIIa is the most common subtype, present in about 85% of affected individuals; it manifests with liver and muscle involvement. GSD IIIb, with liver involvement only, comprises about 15% of all affected individuals. In infancy and early childhood, liver involvement presents as hepatomegaly and failure to thrive, with fasting ketotic hypoglycemia, hyperlipidemia, and elevated hepatic transaminases. In adolescence and adulthood, liver disease becomes less prominent. Most individuals develop cardiac involvement with cardiac hypertrophy and/or cardiomyopathy. Skeletal myopathy manifesting as weakness may be evident in childhood and slowly progresses, typically becoming prominent in the third to fourth decade. The overall prognosis is favorable but cannot be predicted on an individual basis. Long-term complications such as muscular and cardiac symptoms as well as liver fibrosis/cirrhosis and hepatocellular carcinoma may have a severe impact on prognosis and quality of life. To date, it is unknown if long-term complications can be alleviated and/or avoided by dietary interventions.

Diagnosis/testing

The diagnosis of GSD III is established in a proband by identification of biallelic pathogenic variants in *AGL*. If molecular genetic testing is inconclusive, debranching enzyme activity can be measured in either blood cells (leukocytes or erythrocytes), skin fibroblasts, or liver or muscle biopsy.

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Management

Treatment of manifestations: Dietary management tailored to the individual patient remains the primary therapy. Frequent feeds (every 3-4 hours) are needed to maintain euglycemia in infancy. Toward the end of the first year of life, several doses per day (~1 g/kg) of cornstarch may be required to avoid hypoglycemia. Protein intake of 3 g/kg is recommended; extra protein supplementation may be needed. For those with night-time hypoglycemia, Glycosade® extended-release cornstarch or continuous nocturnal drip-feeding can be used. Titration of dietary protein and cornstarch is based on self-monitored capillary blood glucose and ketone concentrations, to maintain euglycemia and to prevent ketosis, hypercholesterolemia, and hypertriglyceridemia. Maltodextrin or rapidly absorbable carbohydrates prior to exercise to prevent hypoglycemia during physical activity; oral fructose and sucrose ingestion to improve exercise tolerance. High-fat diet to reduce cardiomyopathy can be considered. Up-to-date individualized emergency letters; perioperative glucose infusion for surgeries to prevent hypoglycemia. Liver transplantation is reserved for those with severe hepatic cirrhosis, liver dysfunction, and/or hepatocellular carcinoma. Liver transplantation may exacerbate myopathy and cardiomyopathy. Vitamin D and calcium supplementation to prevent osteoporosis.

Surveillance: Aspartate aminotransferase, alanine transaminase, liver function as needed (e.g., albumin, bilirubin, ammonia, and clotting studies), creatine kinase (CK), lipid profile every six to 12 months, liver ultrasound every six to 12 months in children and every 12 to 24 months in adults, liver MRI as needed. To identify periods of suboptimal metabolic control, measured preprandial blood glucose and blood ketones or urine ketones on waking. Neurologic, physical therapy, and musculoskeletal assessments; NT-proBNP, CK-MB, electrocardiogram, and echocardiogram every 12 to 24 months in those with GSD IIIa, and every five years in those with GSD IIIb; measurement of height, weight, body mass index, head circumference, and assessment of diet and exercise as needed based on age; serum calcium and 25(OH)-vitamin D annually; regular bone density measurement is recommended.

Agents/circumstances to avoid: High carbohydrate intake, steroid-based drugs, growth hormone replacement therapy, medications that can cause rhabdomyolysis. Use with caution: hormonal contraceptives, statins for control of hyperlipidemia, and beta blockers.

Evaluation of relatives at risk: Diagnosis of at-risk sibs at birth allows for early dietary intervention to prevent hypoglycemia.

Pregnancy management: Increased monitoring and support during pregnancy of women with GSD III because of increased glucose needs during pregnancy. Although gestational diabetes can occur, oral glucose tests are not indicated. Glucose infusion and regular monitoring of blood glucose, ketones, blood gases, and CK is necessary during labor and perinatally to prevent ketonuria and risk of hyperketosis, metabolic acidosis, and acute rhabdomyolysis. Glucose management requires balancing undertreatment against the risks assocated with overtreatment (e.g., fetal hyperinsulinemic hypoglycemia).

Genetic counseling

GSD III is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *AGL* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected with GSD III, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *AGL* pathogenic variants. Once the *AGL* pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members and prenatal and preimplantation genetic testing for a pregnancy at increased risk are possible.

GeneReview Scope

Glycogen Storage Disease Type III (GSD III): Included Phenotypes
• GSD IIIa (~85% of all GSD III). Liver and muscle involvement, resulting from enzyme deficiency in both liver and muscle • GSD IIIb (~15% of all GSD III). Only liver involvement, resulting from enzyme deficiency in liver only

For synonyms and outdated names see Nomenclature.

Diagnosis

Suggestive Findings

Glycogen storage disease type III (GSD III) **should be suspected** in individuals with any of the following clinical and laboratory findings.

Clinical findings

- Hepatomegaly (presenting feature in ~98%, typically in infancy or early childhood)
- Failure to thrive / short stature (presenting feature in ~49%)
- Hepatic cirrhosis and hepatic adenomas (in adolescence and adulthood)
- Weakness / myopathy
- Exercise intolerance
- Hypertrophic cardiomyopathy

Laboratory findings

- Ketotic hypoglycemia or ketotic normoglycemia with fasting; elevated ketone concentrations after an overnight fast in untreated individuals
- Elevated creatine kinase (once toddlers become active)
- Hyperlipidemia, elevated serum triglycerides, and/or cholesterol postprandially initially increases and subsequently decreases, reaching lowest concentrations preprandially.
- Elevated transaminase levels
- Uric acid and lactate are usually normal [Chen 2001, Wolfsdorf & Weinstein 2003], although lactate can be increased postprandially.

Note: Blood glucose, ketones, lactate, and lipid levels are affected by diet and timing of blood draw and proximity to the last meal and/or duration of fasting.

Establishing the Diagnosis

The diagnosis of GSD III **is established** in a proband by identification of biallelic *AGL* pathogenic variants on molecular genetic testing. If molecular genetic testing cannot establish a diagnosis, analysis for debranching enzyme activity deficiency can be considered in either circulating blood cells (leukocytes or erythrocytes), cultured skin fibroblasts, or liver or muscle tissue after biopsy (see Analysis of Debranching Enzyme Activity).

Molecular Diagnosis

Molecular genetic testing approaches include **gene-targeted testing** (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

- **Single-gene testing.** Sequence analysis of *AGL* 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 (see Table 1).
- **A multigene panel** that includes *AGL* 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. Focused exome analysis can be expanded in some laboratories (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.

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

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
AGL	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	<5% [4]

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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Sentner et al [2016] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Analysis of Debranching Enzyme Activity

The debranching enzyme is a single polypeptide with two catalytic sites, amylo-1,6-glucosidase (EC 3.2.1.33) and 4-alpha-glucanotransferase (EC 2.4.1.25). If molecular genetic testing is inconclusive, debranching enzyme

activity can be measured enzymatically, ideally in tissues that are obtained as noninvasively as possible. Liver or muscle biopsy is rarely required to establish the diagnosis of GSD III.

Note: (1) Analysis of debranching enzyme activity in white blood cells is not available in the United States. (2) To distinguish GSD IIIa (liver and muscle involvement; 85% of affected individuals) from GSD IIIb (liver only; 15% of affected individuals), muscle biopsy may be considered to measure debranching enzyme activity and glycogen content since normal serum CK concentrations do not preclude muscle involvement, and information on genotype-phenotype correlations is insufficient for clinical subtyping.

Clinical Characteristics

Clinical Description

Glycogen storage disease type III (GSD III) is characterized by variable liver, skeletal muscle, and cardiac muscle involvement. GSD IIIa (~85% of all GSD III) is characterized by liver and muscle involvement, and GSD IIIb (~15% of all GSD III) is characterized by liver involvement only, typically present in childhood with hepatomegaly and ketotic hypoglycemia with markedly elevated liver transaminases and hypertriglyceridemia.

Liver disease. The spectrum of presentation may include severe hypoglycemia or asymptomatic hepatomegaly. When euglycemia is maintained and ketosis is avoided, hepatomegaly regresses and other abnormal laboratory values (e.g., elevated aspartate aminotransferase and alanine transaminase, increased serum concentration of triglycerides) normalize or come close to baseline [Bernier et al 2008]. Liver disease can be progressive, resulting in liver fibrosis; in some individuals, cirrhosis and hepatocellular carcinoma occur. It is unknown whether early optimal nutritional management can completely prevent these chronic liver complications.

Liver histology shows prominent distension of hepatocytes by glycogen; fibrous septa and periportal fibrosis are frequently present. Fibrosis increases over time and is typically greater in individuals with GSD III than in the other forms of GSD (Differential Diagnosis). The degree of liver fibrosis may be assessed by a FibroScan® examination.

Elevated prothrombin time and low serum concentration of albumin are noted in those with GSD III who develop cirrhosis [Demo et al 2007].

Hepatic adenomas are reported in 6.9% of individuals [Sentner et al 2016]. It is unknown if optimized dietary treatment reduces the formation of hepatic adenomas.

In GSD III, hepatic cirrhosis (not adenomas) leads to hepatocellular carcinoma [Demo et al 2007]. In contrast, in GSD I hepatocellular carcinoma develops in existing adenomas. Several individuals requiring liver transplantation due to cirrhosis and/or hepatocellular carcinoma have been reported.

Childhood myopathy can occur, and may progress slowly, becoming prominent in the third to fourth decade of life. Proximal muscles are primarily affected but involvement of distal muscles (including the calves, peroneal muscles [Lucchiari et al 2007], and hands) is also seen. Foot deformities, genu valgum, kyphosis, and scoliosis have been reported [Ben Chehida et al 2019].

Altered perfusion [Wary et al 2010] with impaired dynamic muscle glycogenolytic capacity [Preisler et al 2015] and nerve dysfunction may contribute to exercise intolerance and muscle weakness [Hobson-Webb et al 2010], respectively.

Myopathy may be partially avoided, and existing skeletal myopathy can be improved with high-protein diet and avoidance of excessive carbohydrate intake [Valayannopoulos et al 2011, Sentner et al 2012, Derks & Smit 2015, Hoogeveen et al 2021].

Cardiac involvement occurs in most individuals with GSD IIIa (reported in 58% of persons with GSD IIIa included in the International Study on Glycogen Storage Disease [Sentner et al 2016]). Most individuals display electrocardiographic and/or echocardiographic signs of left ventricular hypertrophy.

Cardiomyopathy often appears during childhood; rarely, it has been documented in the first year of life. Its clinical significance is uncertain, as most affected individuals are asymptomatic; however, severe cardiac dysfunction, congestive heart failure, and sudden death have occasionally been reported [Austin et al 2012, Focardi et al 2020].

Cardiac myopathies can be improved with high-protein diet and avoidance of excessive carbohydrate intake [Valayannopoulos et al 2011, Sentner et al 2012, Derks & Smit 2015]. Possible benefit of high-fat diet on cardiomyopathy has been reported [Rossi et al 2020]. It is not known whether cardiac signs and symptoms can be avoided with optimal treatment.

Growth may be compromised by poor metabolic control. Catch-up growth is usually observed with optimized, individualized dietary management. The risk of overtreatment resulting in obesity should be considered.

Osteoporosis and osteopenia are common findings in individuals with GSD III. Mundy et al [2008] suggested that the cause of the osteoporosis is probably multifactorial with muscle weakness, abnormal metabolic environment, and suboptimal nutrition playing roles in pathogenesis. Melis et al [2016] also hypothesized a multifactorial etiology, with metabolic imbalance resulting from chronic hyperlipidemia and reduced serum levels of insulin-like growth factor 1, insulin, and osteocalcin.

Polycystic ovary disease may be seen in women with GSD III; fertility does not appear to be affected [Chen 2001, Sentner et al 2016].

Type 2 diabetes mellitus may occur in individuals with GSD III [Sentner et al 2016]. The optimal treatment for type 2 diabetes in individuals with GSD III is as yet undefined [Oki et al 2000, Ismail 2009, Spengos et al 2009].

Prognosis. Long-term complications such as muscular and cardiac symptoms as well as liver fibrosis/cirrhosis, hepatocellular carcinoma, and type 2 diabetes may have a severe impact on the quality of life. It is unknown to what extent early optimal nutritional management can completely prevent these long-term complications.

Genotype-Phenotype Correlations

There is a clear genotype-phenotype correlation with at least two pathogenic variants in exon 3 (c.18_19delGA and c.16C>T) associated with GSD IIIb; both generate truncated proteins with few amino acids. It is thought that alternative exon or translation initiation in muscle isoforms does not require exon 3, thus leading to normal enzyme activity in the muscles of persons with GSD IIIb who have an exon 3 deletion [Shen et al 1996, Elpeleg 1999]. A possible explanation was proposed by Goldstein et al [2010] in which the exon 3 pathogenic variant is bypassed using a downstream start codon, thus creating a fully functioning isoform without the exon 3 pathogenic variants.

No clear genotype-phenotype correlations between other *AGL* pathogenic variants and disease severity have been reported. An overrepresentation of non-missense *AGL* variants [Sentner et al 2016] but also heterogeneity even within a given family has been noted [Lucchiari et al 2007]. A possible association of frameshift, nonsense, and splice site variants with a severe phenotype has been proposed [Perveen et al 2020]. Some *AGL* variants may be associated with a more severe (e.g., c.3965delT, c.4529dupA) or more attenuated (c.4260-12A>G) phenotype [Shaiu et al 2000, Cheng et al 2009].

Nomenclature

Abnormal glycogen with short outer chains was first reported by Illingworth & Cori [1952] in an affected individual followed by Dr GB Forbes. Hence, GSD III is also known as limit dextrinosis, Cori disease, and Forbes disease.

Other terms used to refer to GSD III include AGL deficiency and amylo-1,6-glucosidase deficiency.

Prevalence

GSD III is rare, with an estimated prevalence of 1:100,000.

Certain populations have an increased prevalence as the result of a founder effect:

- The Inuit population in Nunavik (Canada) (~1:2,500) [Rousseau-Nepton et al 2015]
- The Faroese (~1:3,100) [Santer et al 2001]
- North African Jews from Israel (~1:5,400) [Parvari et al 1997]

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Findings in glycogen storage disease type III (GSD III) that may help distinguish it from other forms of GSD presenting with fasting intolerance-related signs and symptoms include the following:

- A history of hepatomegaly, hypoglycemia, and failure to thrive in childhood
- Elevated serum creatine kinase (CK) in the setting of a hepatic GSD in a young child
- Remarkably elevated serum transaminases (often ~500 U/L) prior to commencement of treatment. No other GSD is associated with such marked elevation of aspartate aminotransferase and alanine transaminase [Chen 2001, Wolfsdorf & Weinstein 2003].
- Elevated excretion of urinary glucose tetrasaccharide [Heiner-Fokkema et al 2020]
- Liver histology. Fibrosis increases over time in GSD III and is typically greater than in the other forms of GSD: fibrosis is not a feature of GSD I, and steatosis is less than that seen in GSD I; fibrosis can also be seen in GSD IV and less prominent fibrosis occurs in GSD IV and GSD IX.

Selected examples of metabolic disorders that present with signs and symptoms related to fasting intolerance are reviewed in Table 2. Note: The disorders reviewed in Table 2 do not represent a comprehensive differential diagnosis of all clinical and biochemical findings in GSD III; such a differential diagnosis is beyond the scope of this *GeneReview*.

Table 2. Selected Metabolic Disorders Presenting with Fasting Intolerance in the Differential Diagnosis of GSD III

Gene(s)	Disorder	MOI	Clinical & Biochemical Findings
ALDOB	Hereditary fructose intolerance	AR	Hypoglycemia on fructose/sucrose/sorbitol ingestion; GI symptoms; liver dysfunction (incl ↑ bilirubin & prolonged clotting time, hypoalbuminemia) & renal tubular dysfunction; absence of hyperlipidemia
FBP1	Fructose-1,6-bisphosphatase deficiency	AR	(Hypo)ketotic hypoglycemia w/↑ lactate usually triggered by fasting ± concurrent infection; biochemical tests normal between attacks; no muscle involvement

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Clinical & Biochemical Findings
G6PC1 *SLC37A4*	GSD Ia & GSD Ib	AR	GSD III & GSD I may be indistinguishable in infancy but some important differences may help distinguish them: GSD III does not usually have ↑ uric acid & lactate seen in GSD I; in contrast to GSD I, ketotic hypoglycemia is seen in GSD III, & ketones are grossly ↑ in morning urine samples of untreated persons; hypoglycemia & hypertriglyceridemia are more severe in GSD I than in GSD III; persons w/GSD I usually lack muscle symptoms & may show nephromegaly; in contrast to GSD III, neutropenia can be seen in GSD Ib.
GALT *GALE* *GALK*	Classic galactosemia, epimerase deficiency galactosemia, & galactokinase deficiency (OMIM 230200)	AR	Liver dysfunction & hypoglycemia on (ga)lactose ingestion; GI symptoms; ↑ bilirubin & prolonged clotting time, hypoalbuminemia, renal tubular dysfunction; absence of hyperlipidemia & muscle involvement
GBE1	GSD IV	AR	Lack of severe hypoglycemia until end-stage liver disease; liver cirrhosis may present early in infancy; clinical presentation is extremely heterogenous.
GYS2	GSD 0a (OMIM 240600)	AR	Absence of hepatomegaly together w/postprandial hyperglycemia & hyperlactatemia in GSD0a
PHKA1 *PHKA2* *PHKB* *PHKG2*	Phosphorylase kinase deficiency causing GSD IX [1]	AR XL [2]	The phenotypes of GSD VI & GSD IX are clinically indistinguishable. Affected persons present w/ketotic hypoglycemia & hepatomegaly & do not have ↑ serum CK, but ↓ stamina, ↓ muscle strength, & muscle pain may occur. Blood lactate is usually normal. AST & ALT are usually not as high as in GSD III.
PYGL	GSD VI	AR	
SLC2A2	GSD XI (OMIM 227810)	AR	Postprandial hyperglycemia & renal tubular disease (Fanconi syndrome) incl glucosuria, w/hypophosphatemic rickets
Various (e.g., *ACADM* *ACADVL* *ETFA* *ETFB* *ETFDH*)	Mitochondrial fatty acid oxidation disorders (e.g., MCAD, VLCAD, MADD [3])	AR	Hypoketotic hypoglycemia after prolonged fasting; absence of hyperlipidemia; specific plasma acylcarnitine & urine organic acid profiles

ALT = alanine transaminase; AR = autosomal recessive; AST = aspartate aminotransferase; CK = creatine kinase; GI = gastrointestinal; GSD = glycogen storage disease; MADD = multiple acyl-CoA dehydrogenase deficiency; MCAD = medium-chain acyl-coenzyme A dehydrogenase; MOI = mode of inheritance; VLCAD = very long-chain acyl-coenzyme a dehydrogenase deficiency; XL = X-linked

1. Phosphorylase kinase (PhK) is responsible for activation of hepatic glycogen phosphorylase that cleaves the terminal glucose moieties from the glycogen chain.

2. PHKA2-related liver PhK deficiency and *PHKA1*-related muscle PhK deficiency are inherited in an X-linked manner. *PHKB*-related liver and muscle PhK deficiency and *PHKG2*-related liver PhK deficiency are inherited in an autosomal recessive manner.

3. MADD is caused by biallelic pathogenic variants in *ETFA*, *ETFB*, or *ETFDH*. MCAD is caused by biallelic pathogenic variants in *ACADM*. VLCAD is caused by biallelic pathogenic variants in *ACADVL*.

Management

Evaluations Following Initial Diagnosis

Based on the 2010 ACMG practice guidelines, the investigations summarized in Table 3 are recommended to characterize the clinical phenotype and to adjust dietary treatment on an individual basis.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Glycogen Storage Disease Type III

System/Concern	Evaluation	Comment
Hepatic	• Glucose, AST, ALT, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, international normalized ratio, albumin, bilirubin, creatinine • Consultation w/biochemical geneticist • Liver ultrasound to assess liver size & structure	
Myopathy	• CK • Developmental assessment (incl gross & fine motor assessment) • Neuromuscular consultation, incl strength, endurance, exercise tolerance, & pain assessment • PT consultation	• Neuromuscular assessment (e.g., muscle ultrasound, dynamometry) should be performed subsequently based on physical status, function, symptoms, or need. • Electromyography/nerve conduction tests in those w/suspected peripheral neuropathy
Cardiovascular	• CK-MB, troponin I/T, NT-proBNP • Electrocardiogram • Echocardiogram	
Nutrition/ Growth	• Measure length/height, weight; BMI. • Eval of nutritional status • Assess & optimize dietary intake for exercise & activity levels.	
Skeletal	• Serum calcium & 25(OH)-vitamin D • Bone mineral density • Orthopedic consultation as needed	
Endocrine	Assess for signs of hirsutism, hyperandrogenism, & insulin-resistance.	• Females w/GSD III may develop polycystic ovaries from a young age. • Avoid estrogen (may contribute to hepatocellular neoplasm).
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of GSD III 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; • Emergency letters to prevent/ manage metabolic decompensation.	

ALT = alanine transaminase; AST = aspartate aminotransferase; BMI = body mass index; BNP = B-type natriuretic peptide; CK = creatine kinase; GSD = glycogen storage disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MOI = mode of inheritance; NT = N-terminal; PT = physical therapist

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Medical nutrition therapy. The mainstay of management of GSD III is a high-protein diet with cornstarch supplementation to maintain euglycemia while balancing macronutrient and total caloric intake.

- **Frequent feedings in infancy** (every 3-4 hours) are recommended. Unlike the diet used to treat infants with GSD I, the diet used to treat infants with GSD III can include fructose and galactose, as individuals with GSD III can utilize these sugars.

- **Cornstarch.** Toward the end of the first year of life, cornstarch is tolerated and can be used to prevent hypoglycemia. Initially several doses per day may be required (typical starting dose ~1 g/kg). The doses can be titrated based on the results of glucose and ketone monitoring.

  As an alternative for uncooked cornstarch, Glycosade® extended-release cornstarch can be used [Ross et al 2015]. One gram of cornstarch per kilogram of body weight may be sufficient to maintain normal blood glucose levels for four hours or longer in individuals with GSD III.

- **High-protein diet.** Protein intake of 3 g/kg or 25% of total energy is recommended in children or adults, respectively. With gluconeogenesis being intact, protein-derived glucogenic amino acids can be used as an alternate source for glucose during times of fasting. A high-protein diet prevents breakdown of endogenous muscle protein in times of glucose need and preserves skeletal and cardiac muscles. High-protein supplements may be needed.

- Skeletal muscle metabolism may be impaired during exercise in GSD III. Consumption of maltodextrin or rapidly absorbable carbohydrates can prevent hypoglycemia during physical activity. Fructose or sucrose prior to exercise may improve exercise tolerance but does not completely prevent exercise-induced damage [Preisler et al 2015].

- Titration of protein and cornstarch in the diet is the primary treatment for elevated cholesterol and triglyceride concentrations, which usually result from suboptimal metabolic control.

- It has been shown that high-fat diet can reduce cardiomyopathy in individuals with GSD III [Rossi et al 2020].

Emergency protocol. A personalized emergency letter based on an emergency protocol to avoid dangerous hypoglycemia should be established. Personalized emergency letters in different languages can be generated via www.emergencyprotocol.net [Rossi et al 2021]. If the enteral intake cannot be guaranteed, an intravenous (IV) infusion of 10% dextrose (with sodium chloride and potassium chloride) should be given as soon as possible. Efforts should be made to correct ketosis, as it can induce vomiting and worsen the catabolic state. Serum concentrations of electrolytes, glucose, ketones, and creatine kinase (CK) should be monitored.

Surgery. Persons with GSD III undergoing surgery should be admitted the night before the procedure and start an IV infusion containing 10% dextrose within two hours of the last cornstarch dose or the last meal. Continue glucose and ketone monitoring overnight and during the procedure. Do not stop IV dextrose infusion abruptly, as dangerous hypoglycemia can occur from an iatrogenic hyperinsulinemic state. Slowly taper IV fluids once optimal oral intake has been established and tolerated.

Liver transplantation. Hepatic complications are not the main cause of morbidity in individuals with GSD III; modern treatment strategies and good metabolic control can prevent major complications. Liver transplantation should therefore be viewed as a treatment of last resort for individuals with GSD III. Liver transplantation will cure the fasting intolerance-associated hypoglycemias in both GSD IIIa and GSD IIIb. However, the (cardio)muscular enzymatic defect persists in individuals with GSD IIIa. The risk of hypoglycemia decreases with age in individuals with GSD III, and because transplantation has been associated with worsening myopathy and cardiomyopathy, liver transplantation is only indicated in affected individuals with severe hepatic cirrhosis, liver dysfunction, and/or hepatocellular carcinoma [Davis & Weinstein 2008].

Osteoporosis may occur in adults with GSD III, as bone mineralization is adversely affected in acidic environments. Good metabolic control leads to decreased ketosis, improved muscle strength, and increased bone mineralization. Supplementation with vitamin D and/or calcium is also recommended to augment bone mineralization. If dietary calcium intake is insufficient, calcium supplementation should be prescribed.

Surveillance

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

System/Concern	Evaluation	Frequency
Hepatic	AST, ALT, liver function as needed (e.g., albumin, bilirubin, ammonia, & clotting studies), CK, lipid profile	Every 6-12 mos
	Liver ultrasound & FibroScan® (if possible) to screen for adenomas & hepatic fibrosis	Every 6-12 mos in children; every 12-24 mos in adults
	Liver MRI in those w/abnormal liver ultrasound	CT/MRI every 6-12 mos in older persons based on lab & clinical findings
Glucose homeostasis	• Measure blood glucose preprandially. [1] • Measure blood ketones on waking using a portable blood ketone meter **OR** measure urine ketones on waking w/urine dipsticks. [2] • Continuous glucose monitoring can be helpful for many.	At least several times per month to identify periods of suboptimal metabolic control; goal is to maintain blood ketone/beta-OH-butyrate concentrations <0.3 mmol/L
Neuromuscular/ Musculoskeletal	• Direct & functional neuromuscular assessment of strength & endurance • Assessment of exercise tolerance & pain • PT assessment in children incl gross & fine motor skills • In adults: musculoskeletal assessment for alterations in alignment (hypermobility, ↑ width of base of support, anterior pelvic tilt, genu valgum & recurvatum, hindfoot valgus, & forefoot varus) & assessment for adaptive equipment	• Annual neuromuscular, PT, & musculoskeletal assessments in adults based on signs/symptoms • Follow-up assessments (e.g., muscle ultrasound, dynamometry) based on physical status, function, & symptoms • Note: Statins can worsen myopathy.
Cardiomyopathy	• NT-proBNP, CK-MB • Electrocardiogram • Echocardiogram • Additional investigations (e.g., heart MRI) may be indicated.	• GSD IIIa: every 12-24 mos • GSD IIIb: every 5 yrs • Note: Exercise restriction is usually not recommended.
Gastrointestinal/ Nutrition/Growth	• Measure height, weight, & head circumference to monitor growth. • Assess & optimize dietary intake for exercise & activity levels.	Frequency based on age of affected person
Skeletal	Serum calcium & 25(OH)-vitamin D	Every 12 mos
	Measure bone mineral density.	On average every 4-5 yrs, starting in childhood
	Orthopedic consultation	As needed
Endocrine	Eval of signs of hirsutism, hyperandrogenism, & insulin resistance	• In females at each visit, as females w/GSD III may develop polycystic ovaries from a young age • Avoid estrogen (may contribute to hepatocellular neoplasm).

ALT = alanine transaminase; AST = aspartate aminotransferase; B-type natriuretic peptide = BNP; CK = creatine kinase; NT = N-terminal; PT = physical therapy

1. Hypoglycemia is uncommon in older children and adults on waking since counterregulation can raise blood glucose concentrations; however, monitoring blood glucose concentrations preprandially can reveal periods of suboptimal control.

2. Elevated ketones reflect poor metabolic control, as ketones are produced when glucose is unavailable and instead fatty acid oxidation is used as a source of energy.

Agents/Circumstances to Avoid

Avoid the following:

- High carbohydrate intake. Excess sugar is stored as glycogen, which cannot be broken down, resulting in hepatomegaly.
- Steroid-based drugs, which interfere with glucose metabolism and utilization. Long-term steroid usage itself can cause failure to thrive and muscle weakness.
- Growth hormone replacement therapy, which interferes with glucose metabolism and worsens ketosis. Growth hormone therapy has been associated with adenoma growth and complications in GSD I; therefore, growth hormone should only be used in individuals with documented growth hormone deficiency.
- Medications that can cause rhabdomyolysis

Use the following with caution:

- Hormonal (estrogen) contraceptives in women. Estrogen is known to contribute to both benign and malignant hepatocellular tumors.
- Statins for control of hyperlipidemia. Use of statins requires CK monitoring because of the potential of exacerbating the muscle disease of GSD IIIa.
- Beta blockers, which can cause hypoglycemia and mask the signs and symptoms associated with the adrenergic response during hypoglycemia

Evaluation of Relatives at Risk

Diagnosis of at-risk sibs at birth allows for early dietary intervention to prevent development of hypoglycemia associated with GSD III.

- If the *AGL* pathogenic variants in the family are known, molecular genetic testing is the best way to determine the genetic status of an at-risk sib.
- If the *AGL* pathogenic variants in the family are not known, diagnosis can be established by presence of fasting ketotic hypoglycemia.

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

Pregnancy Management

Increased monitoring and support are required in pregnancy of women with GSD III. The goal during all trimesters of the pregnancy and peripartum is to maintain normoglycemia and to avoid upregulation of counterregulatory hormones, which result in lipolysis, increased mitochondrial fatty acid oxidation, and hyperketosis [Kishnani et al 2010].

Throughout the entire pregnancy, adequate protein is necessary to provide an alternate source of glucose via gluconeogenesis. Hyperemesis may cause secondary hyperketosis and hypoglycemia. The metabolic requirements will gradually increase throughout the second and third trimesters, necessitating dietary adjustments to meet the glucose demands of the fetus.

Women with GSD III may be at risk of gestational diabetes, but oral glucose tests are contraindicated.

Ketonuria for healthy women in labor is generally accepted as a normal physiologic response [Toohill et al 2008] but should be prevented in women with GSD III due to the risks of hyperketosis, metabolic acidosis, and acute rhabdomyolysis. Administration of a glucose infusion and regular monitoring of blood glucose, ketones, blood gases, and CK is necessary during labor and perinatally. Glucose management requires balancing between the

previously mentioned signs of undertreatment and the risks of overtreatment (e.g., fetal hyperinsulinemic hypoglycemia).

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

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

Risk to Family Members

Parents of a proband

- The parents of an affected child are usually heterozygotes (i.e., carriers of one *AGL* pathogenic variant).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *AGL* 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, it is possible that 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]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include the following:
  - A single- or multiexon deletion in the proband was not detected by sequence analysis and resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband [Ponzi et al 2019, Xiao et al 2019].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *AGL* 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 inheriting neither of the familial *AGL* pathogenic variants.
- Clinical variability may be observed between affected sibs [Lucchiari et al 2007].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- The offspring of an individual with GSD III are obligate heterozygotes (carriers) for a pathogenic variant in *AGL*.

- If the reproductive partner of an affected person is a carrier, the offspring are at a 50% risk of being affected. This is more likely to occur in populations with a higher prevalence of GSD III as the result of a founder effect (see Prevalence).

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

Carrier Detection

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

Related Genetic Counseling Issues

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

Family planning

- The optimal time for determination of genetic risk 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.
- Carrier testing for reproductive partners of known carriers should be considered, particularly if consanguinity is likely.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, 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 genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *AGL* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for GSD III 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.

- **Associac¸ao Brasileira de Glicogenose**

  Brazil

  www.abglico.com.br

- **Association for Glycogen Storage Disease**

  www.agsdus.org

- **MedlinePlus**

  Glycogen storage disease type III

- **National Organization for Rare Disorders (NORD)**
  Glycogen Storage Disease Type III
- **Asociacion Española de Enfermos de Glucogenosis**
  Spain
  www.glucogenosis.org
- **Association Belge BOKS**
  Belgium
  www.boks.be
- **Association for Glycogen Storage Disease UK (AGSD-UK)**
  9 Lindop Road
  Altrincham Cheshire WA15 9DZ
  United Kingdom
  Phone: 0161 980 7303
  www.agsd.org.uk
- **Association Francophone des Glycogénoses**
  France
  www.glycogenoses.org
- **Associazione Italiana Glicogenosi**
  Italy
  www.aig-aig.it
- **Canadian Association for Glycogen Storage Disease**
  Canada
  www.canadianagsd.org
- **European Reference Network for Hereditary Metabolic Disorders (MetabERN)**
  MetabERN
- **Glucolatino (Latin America)**
  glucolatino.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **Rare Diseases South Africa**
  www.rarediseases.co.za
- **Scandinavian Association for Glycogen Storage Disease**
  www.sagsd.org

- **Selbsthilfegruppe Glykogenose Deutchland e.V.**
  Germany
  www.glykogenose.de
- **Volwassenen Kinderen en Stofwisselingsziekten**
  Netherlands
  www.stofwisselingsziekten.nl

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 III: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AGL	1p21.2	Glycogen debranching enzyme	AGL database	AGL	AGL

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 III (View All in OMIM)

232400	GLYCOGEN STORAGE DISEASE III; GSD3
610860	AMYLO-1,6-GLUCOSIDASE, 4-ALPHA-GLUCANOTRANSFERASE; AGL

Molecular Pathogenesis

To make glycogen, glucose molecules forming uridine diphosphate glucose are added via alpha 1,4 linkages to the matrix for glycogen, called glycogenin. This process is catalyzed by glycogen synthase. When the chain reaches a certain length, "branching enzyme" cleaves off the terminal portion of the chain and attaches it via an alpha 1,6 linkage to the parent chain. This process is repeated over and over again on all the different branches of the chain and the complex glycogen molecules are created.

When digestion of a meal is complete, insulin levels decrease and glucagon is secreted. In a process mediated by the enzyme glycogen phosphorylase, these hormones stimulate cleavage of glucose molecules from the terminal strands of glycogen as glucose-1-phosphate. This process continues until four glucose molecules remain before the alpha 1,6 bond. At this point, the human debranching enzyme with its two distinct catalytic activities comes into play. The 1,4-α-D-glucan 4-α-D-glycosyl transferase component transfers the terminal three glucose molecules to the parent chain and the amylo-1,6-glucosidase component cleaves the alpha 1,6 bond to release free glucose.

With debranching enzyme deficiency, glycogen cannot be completely degraded and as a consequence, an abnormal glycogen with branched outer points called "limit dextrin" accumulates.

AGL encodes six different isoforms that differ in the 5' end by using several cryptic splice sites upstream of the translation initiation site. Isoform 1 is present in liver, muscle, kidney, and lymphoblastoid cells. Isoforms 2, 3, and 4 are present in the muscle and heart. Isoform 1 contains exons 1 and 3; isoforms 2, 3, and 4 start with exon 2. Isoforms 1 through 4 all contain exon 3 which includes the normal initiation codon for protein translation. Exons 4-35 are present in all isoforms [Bao et al 1996, Bao et al 1997]. The glycogen binding site is encoded by exons 31 and 32 and the active site is encoded by exons 6, 13, 14, and 15 [Elpeleg 1999].

Mechanism of disease causation. Loss of function

Table 5. Notable *AGL* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000642.3 NP_000633.2	c.16C>T	p.Gln6Ter	Assoc w/GSD IIIb phenotype [Shen et al 1996]
	c.18_19delGA	p.Gln6HisfsTer20	Assoc w/GSD IIIb phenotype [Shen et al 1996]
	c.1222C>T	p.Arg408Ter	Founder variant in Faroe Islanders [Santer et al 2001]
	c.2039G>A	p.Trp680Ter	3 common variants that together account for ~28% of pathogenic variants in persons of European origin [Demo et al 2007]
	c.2590C>T [1]	p.Arg864Ter [1]	
	c.3682C>T	p.Arg1228Ter	
	c.3965delT	p.Val1322AlafsTer27	Assoc w/more severe phenotype [Shaiu et al 2000]
	c.4456delT	p.Ser1486ProfsTer18	Founder variant in North African Jewish persons [Parvari et al 1997] & those of Inuit descent [Rousseau-Nepton et al 2015]
	c.4529dupA	p.Tyr1445dup	Assoc w/more severe phenotype [Cheng et al 2009]
	c.4260-12A>G	--	Assoc w/milder phenotype [Shaiu et al 2000]

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. One of the most common variants in the US (10.3%)

Chapter Notes

Author Notes

Research priorities have been defined for liver glycogen storage disease (GSD) and also for GSD III [Peeks et al 2020].

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Revision History

- 6 January 2022 (sw) Comprehensive update posted live
- 29 December 2016 (bp) Comprehensive update posted live

- 6 September 2012 (me) Comprehensive update posted live
- 15 March 2011 (cd) Revision: targeted mutation analysis no longer listed in the GeneTests Laboratory Directory as clinically available
- 21 October 2010 (cd) Revision: deletion/duplication analysis available for *AGL*
- 3 March 2010 (me) Review posted live
- 5 November 2009 (daw) Original submission

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