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Glycogen Storage Disease Type IV

Synonyms: Andersen Disease, Glycogen Branching Enzyme Deficiency, Glycogen Storage Disease IV, GSD IV

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Summary

Clinical characteristics

The clinical manifestations of glycogen storage disease type IV (GSD IV) discussed in this entry span a continuum of different subtypes with variable ages of onset, severity, and clinical features. Clinical findings vary extensively both within and between families.

- The *fatal perinatal neuromuscular subtype* presents in utero with fetal akinesia deformation sequence, including decreased fetal movements, polyhydramnios, and fetal hydrops. Death usually occurs in the neonatal period.
- The *congenital neuromuscular subtype* presents in the newborn period with profound hypotonia, respiratory distress, and dilated cardiomyopathy. Death usually occurs in early infancy.
- Infants with the *classic (progressive) hepatic subtype* may appear normal at birth, but rapidly develop failure to thrive; hepatomegaly, liver dysfunction, and progressive liver cirrhosis; hypotonia; and cardiomyopathy. Without liver transplantation, death from liver failure usually occurs by age five years.
- Children with the *non-progressive hepatic subtype* tend to present with hepatomegaly, liver dysfunction, myopathy, and hypotonia; however, they are likely to survive without progression of the liver disease and may not show cardiac, skeletal muscle, or neurologic involvement.
- The *childhood neuromuscular subtype* is rare and the course is variable, ranging from onset in the second decade with a mild disease course to a more severe, progressive course resulting in death in the third decade.

Diagnosis/testing

The diagnosis is established in a proband by the demonstration of glycogen branching enzyme (GBE) deficiency in liver, muscle, or skin fibroblasts or the identification of biallelic pathogenic variants in *GBE1* on molecular genetic testing.

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Management

Treatment of manifestations: Management should involve a multidisciplinary team including specialists in hepatology, neurology, nutrition, medical or biochemical genetics, and child development. Liver transplantation is the only treatment option for individuals with the progressive hepatic subtype of GSD IV who develop liver failure; however, the risk for morbidity and mortality is high, in part because of the extrahepatic manifestations of GSD type IV, especially cardiomyopathy. Children with skeletal myopathy and/or hypotonia warrant developmental evaluation and physical therapy as needed. Those with cardiomyopathy warrant care by a cardiologist. Heart transplant may be an option in individuals with severe cardiac involvement.

Prevention of secondary complications: Prevent nutritional deficiencies (e.g., of fat-soluble vitamins) by ensuring adequate dietary intake; prevent perioperative bleeding by assessment of a coagulation profile and use of fresh frozen plasma as needed.

Surveillance: No clinical guidelines for surveillance are available. The following evaluations are suggested (with frequency varying according to disease severity): liver function tests including liver transaminases, albumin, and coagulation profile (PT and PTT); abdominal ultrasound examination; echocardiogram; neurologic assessment; nutritional assessment. If cardiomyopathy was not observed on baseline screening echocardiogram at the time of initial diagnosis, repeat echocardiograms every three months during infancy, every six months during early childhood, and annually thereafter.

Evaluation of relatives at risk: If the *GBE1* pathogenic variants have been identified in an affected family member, test at-risk relatives to allow for early diagnosis and management of disease manifestations.

Genetic counseling

GSD IV is inherited in an autosomal recessive manner. Each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Although affected sibs are expected to manifest the same subtype of GSD IV, the age of onset and presentation may differ. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible based on molecular testing if the pathogenic variants in the family have been identified. If the pathogenic variants have not been identified, GBE testing on cultured amniocytes can be performed for prenatal diagnosis.

Diagnosis

The diagnosis of glycogen storage disease type IV (GSD IV) is suspected based on the clinical presentation and the finding of abnormally branched glycogen accumulation in muscle or liver tissue. The diagnosis is confirmed by the demonstration of glycogen branching enzyme (GBE) deficiency in liver, muscle, or skin fibroblasts [Brown & Brown 1983], and/or the identification of biallelic pathogenic variants in *GBE1*.

Suggestive Findings

Glycogen storage disease type IV (GSD IV) **should be suspected** in individuals with the features below. While subtypes with variable ages of onset, severity, and clinical features have been recognized, the GSD IV phenotype represents a continuum that ranges from mild to severe [Burrow et al 2006].

Clinical features by subtype:

- **Fatal perinatal neuromuscular subtype.** Decreased fetal movements, polyhydramnios, and fetal hydrops that may be detected prenatally; arthrogryposis, severe hypotonia, muscle atrophy at birth, early neonatal death

- **Congenital neuromuscular subtype.** Profound neonatal hypotonia at birth, respiratory failure, dilated cardiomyopathy, early infantile death
- **Classic (progressive) hepatic subtype.** Failure to thrive, hepatomegaly, liver dysfunction, progressive liver cirrhosis with portal hypertension, ascites, and esophageal varices, hypotonia, and cardiomyopathy; death typically by age five years from liver failure
- **Non-progressive hepatic subtype.** Liver dysfunction, myopathy, and hypotonia in childhood
- **Childhood neuromuscular subtype.** Chronic, progressive myopathy; dilated cardiomyopathy in some individuals

Laboratory features

- **Liver enzymes** typically elevated in the hepatic subtypes
- **Hypoalbuminemia**
- Prolonged **partial thromboplastin time** (PTT) and **prothrombin time** (PT) with progressive deterioration of liver function

Imaging features. Abdominal ultrasound examination typically reveals enlarged liver with signs of fibrosis or cirrhosis.

Histopathology of affected tissues (e.g., liver, heart, muscle) reveals:

- Markedly enlarged hepatocytes that contain periodic acid-Schiff (PAS)-positive and diastase-resistant inclusions, features characteristic of the abnormally branched glycogen found in GSD IV. Widespread infiltrates of foamy histiocytes with intra-cytoplasmic deposits within the reticuloendothelial system (RES) have been reported [Magoulas et al 2012]. Interstitial fibrosis with wide fibrous septa and distorted hepatic architecture are observed [Moses & Parvari 2002].
- On electron microscopy, fine fibrillary aggregates of electron-dense amylopectin-like material within the cytoplasm of hepatocytes in some individuals.

Establishing the Diagnosis

The diagnosis of glycogen storage disease type IV (GSD IV) **is established** in a proband by the presence of the above suggestive findings AND identification of:

- Reduced glycogen branching enzyme (GBE) activity (most commonly assayed in cultured skin fibroblasts but may also be assayed in muscle or liver tissue); OR
- Biallelic pathogenic variants in *GBE1* on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, 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. Because the phenotype of GSD IV is broad, 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 liver dysfunction and/or cardiomyopathy are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of GSD IV, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *GBE1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *GBE1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by liver dysfunction, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. In addition, many laboratories now offer rapid or critical exome sequencing, which can provide results within a shorter time frame, and thus potentially provide an earlier diagnosis and guide management or treatment decisions.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 IV

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
GBE1	Sequence analysis [3]	62/84 (74%) [4, 5]
	Gene-targeted deletion/duplication analysis [6]	8/84 (10%) [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Magoulas et al [2012]
5. Of 42 affected individuals, 37 had at least one identifiable variant detected by sequencing analysis; 28 individuals had biallelic pathogenic variants, and six had one identifiable pathogenic variant, implying that the second causative variant was not identified.
6. 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.
7. Of the 42 affected individuals, three were homozygous for exon or multiexon deletions and two were compound heterozygous for one exon or multiexon deletion and one sequence variant detectable by sequence analysis [Li et al 2012, Magoulas et al 2012].

Clinical Characteristics

Clinical Description

The clinical manifestations of glycogen storage disease type IV (GSD IV) span a continuum from mild to severe [Burrow et al 2006]. Within this continuum several different subtypes with variable age of onset, severity, and clinical features have been recognized. While prognosis tends to depend on the subtype of GSD IV, clinical findings vary extensively both within and between families.

The **fatal perinatal neuromuscular subtype**, the most severe subtype, presents in utero with fetal akinesia deformation sequence, including decreased fetal movements, polyhydramnios, and fetal hydrops. Newborns may have arthrogryposis, severe hypotonia, and muscular atrophy, often resembling infants with the severe forms of spinal muscular atrophy [Tay et al 2004]. Death usually occurs in the neonatal period, frequently as a result of cardiopulmonary compromise.

The **congenital neuromuscular subtype** presents in the newborn period with profound hypotonia, respiratory distress, dilated cardiomyopathy, and death in early infancy typically from cardiopulmonary compromise [Moses & Parvari 2002]. Li et al [2012] recently reported two unrelated infants with this subtype of GSD IV who were also small for gestational age. Both died between ages two and three months.

The **hepatic subtype**, the most common presentation of GSD IV, can be classified as either progressive (classic) or non-progressive.

- In the **progressive** hepatic subtype, children may appear normal at birth, but then rapidly deteriorate in the first few months of life with failure to thrive, hepatomegaly, and elevated liver enzymes. This stage is typically followed by progressive liver dysfunction and cirrhosis with hypoalbuminemia, prolonged partial thromboplastin time (PTT) and prothrombin time (PT), portal hypertension, ascites, and esophageal varices. Muscle tone, often normal at the time of diagnosis, progresses to generalized hypotonia within the first one to two years of life [Magoulas et al 2012]. Without liver transplantation, death from liver failure usually occurs by age five years [Chen 2001, Moses & Parvari 2002]. Dilated cardiomyopathy and progressive cardiac failure, reported to occur following orthotopic liver transplantation, have resulted in death [Sokal et al 1992, Rosenthal et al 1995].
- In the less common **non-progressive** hepatic subtype, presentation can be in childhood with hepatomegaly, liver dysfunction, myopathy, and hypotonia. These individuals tend to survive without evidence of progression of the liver disease [Moses & Parvari 2002]. They also may not show cardiac, skeletal muscle, or neurologic involvement. Liver enzymes are usually abnormal in childhood at the time of presentation, but subsequently may return to (and remain) normal [McConkie-Rosell et al 1996].

The **childhood neuromuscular subtype** of GSD IV is rare [Reusche et al 1992, Schröder et al 1993]. Individuals typically present in the second decade and may have mild-to-severe myopathy and dilated cardiomyopathy. The natural history is variable: some individuals have a mild disease course throughout life while others have a more severe, progressive course resulting in death in the third decade.

Genotype-Phenotype Correlations

Genotype-phenotype correlations remain unclear, but are emerging [Ziemssen et al 2000, Magoulas et al 2012].

- Individuals with the perinatal and congenital subtypes tend to have two null variants, including nonsense, frameshift, and splice site variants leading to premature truncation of the protein likely resulting in complete absence of glycogen branching enzyme (GBE) activity;
- Individuals with the classic hepatic subtype tend to be compound heterozygotes for a null and a missense variant.

These generalizations notwithstanding, considerable overlap exists both between and within the subtypes of GSD IV [Li et al 2010].

Nomenclature

Glycogen storage disease type IV was referred to as glycogenosis IV in early publications.

Prevalence

Glycogen storage disease type IV is rare, accounting for approximately 3% of the glycogen storage diseases [Chen 2001] for an overall incidence of approximately 1:600,000-1:800,000.

To date, more than 50 individuals with molecularly confirmed GSD IV have been reported [Fernandez et al 2010, Li et al 2010, Li et al 2012, Magoulas et al 2012, Mochel et al 2012, Ravenscroft et al 2013, Paradas at al 2014, Akman et al 2015, Sampaolo et al 2015, Bendroth-Asmussen et al 2016, Dainese et al 2016, Franco-Palacios et al 2016, Said et al 2016, Iijima et al 2018].

Genetically Related (Allelic) Disorders

Adult-onset polyglucosan body disease (APBD) is the only other phenotype known to be associated with mutation of *GBE1* (see Adult Polyglucosan Body Disease). APBD is characterized by adult-onset progressive neurogenic bladder, gait difficulties (i.e., spasticity and weakness) resulting from mixed upper- and lower-motor neuron involvement, sensory loss predominantly in the distal lower extremities, and mild cognitive difficulties (often executive dysfunction). In APBD, GBE activity is reduced or normal. Affected individuals are either homozygous or compound heterozygous for a pathogenic missense variant in *GBE1* including p.Tyr329Ser, p.Arg515His, and p.Arg524Gln [Lossos et al 1998, Ziemssen et al 2000, Klein et al 2004]. Inheritance is autosomal recessive.

Differential Diagnosis

Perinatal and Congenital Neuromuscular Subtypes of GSD IV

The differential diagnosis of the perinatal and congenital neuromuscular subtypes of GSD IV includes the disorders summarized in Table 2a.

Table 2a. Other Genes of Interest in the Differential Diagnosis of Perinatal and Congenital Neuromuscular Subtypes of GSD IV

Gene(s)	Differential Diagnosis Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/perinatal & congenital neuromuscular subtypes of GSD IV	Distinguishing from perinatal & congenital neuromuscular subtypes of GSD IV
SMN1	Spinal muscular atrophy	AR	• ↓ fetal movement • Arthrogryposis • Severe congenital hypotonia • Cardiopulmonary compromise	• Tongue fasciculations • ↓ or absent deep tendon reflexes
GAA	Pompe disease	AR	• Profound hypotonia • Respiratory distress	Hypertrophic cardiomyopathy rather than dilated cardiomyopathy
>10 genes [1]	Zellweger spectrum disorder	AR	• Profound hypotonia • Respiratory distress	Rhizomelic chondrodysplasia punctata & biochemical peroxisomal abnormalities

Table 2a. continued from previous page.

Gene(s)	Differential Diagnosis Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/perinatal & congenital neuromuscular subtypes of GSD IV	Distinguishing from perinatal & congenital neuromuscular subtypes of GSD IV
>40 genes [2]	Congenital disorders of glycosylation	AR (XL)	• Hypotonia • Liver disease • Cardiomyopathy	• Seizures • Stroke-like episodes

AR = autosomal recessive; GSD = glycogen storage disease; MOI = mode of inheritance; XL = X-linked
1. See Zellweger spectrum disorder.
2. See OMIM Phenotypic Series: Congenital disorders of glycosylation, type I and Congenital disorders of glycosylation, type II.

Classic Hepatic Subtype of GSD IV

The differential diagnosis of the classic hepatic subtype of GSD IV includes other glycogen storage disorders and mitochondrial DNA depletion syndromes. Examples of these categories of disorders are described in Table 2b.

Table 2b. Other Genes of Interest in the Differential Diagnosis of the Classic Hepatic Subtype of GSD IV

Gene	Differential Diagnosis Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/classic hepatic subtype of GSD IV	Distinguishing from classic hepatic subtype of GSD IV
AGL	GSD III	AR	• Hepatomegaly • Liver disease • Myopathy	• Hypoglycemia • Hyperlipidemia
DGUOK	Deoxyguanosine kinase deficiency	AR	• Severe hypotonia • Liver disease	• Nystagmus • Lactic acidosis • Developmental regression
MPV17	*MPV17*-related mtDNA maintenance defect	AR	• Liver disease • Hepatomegaly • Hypotonia	• Vomiting • Diarrhea • Failure to thrive

AR = autosomal recessive; GSD = glycogen storage disease; MOI = mode of inheritance; mtDNA = mitochondrial DNA

Childhood Neuromuscular Subtype of GSD IV

The differential diagnosis of the childhood neuromuscular subtype of GSD IV includes mitochondrial myopathies and the disorders summarized in Table 2c.

Table 2c. Other Genes of Interest in the Differential Diagnosis of the Childhood Neuromuscular Subtype of GSD IV

Gene(s)	Differential Diagnosis Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/childhood neuromuscular subtype of GSD IV	Distinguishing from childhood neuromuscular subtype of GSD IV
DMD	Duchenne muscular dystrophy	XL	• Dilated cardiomyopathy • Myopathy	• Calf pseudohypertrophy • Abnormal dystrophin staining on muscle biopsy
>30 genes [1]	Limb-girdle muscular dystrophy	AR AD	• Myopathy • Cardiomyopathy (in some)	Winged scapula

Table 2c. continued from previous page.

Gene(s)	Differential Diagnosis Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/childhood neuromuscular subtype of GSD IV	Distinguishing from childhood neuromuscular subtype of GSD IV
Mitochondrial DNA	Mitochondrial myopathies (Kearns-Sayre, MERRF)	Mat	• Muscle weakness or exercise intolerance • Heart failure	• Dementia • Movement disorders • Stroke-like episodes • Deafness • Blindness • Vomiting • Seizures

AD = autosomal dominant; AR = autosomal recessive; GSD = glycogen storage disease; Mat = maternal; MOI = mode of inheritance; XL = X-linked

1. See Chu & Moran [2018] and OMIM Phenotypic Series: Muscular dystrophy, limb-girdle, autosomal recessive and Muscular dystrophy, limb-girdle, autosomal dominant.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with glycogen storage disease type IV (GSD IV), 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 Following Initial Diagnosis in Individuals with Glycogen Storage Disease Type IV

System/Concern	Evaluation	Comment
Hepatic	Liver function studies incl albumin, transaminases, & coagulation profile	
Cardiac	Referral to cardiologist for baseline echocardiogram & electrocardiogram	To assess for cardiomyopathy
Development	Neurodevelopmental evaluation	
Neurologic	Referral to neurologist for comprehensive examination & baseline assessment of skeletal muscle involvement	To monitor disease progression
Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Management should involve a multidisciplinary team including specialists in hepatology, neurology, nutrition, medical or biochemical genetics, and child development.

Hepatic Manifestations

Liver transplantation is the only treatment option for individuals with the progressive hepatic subtype of GSD IV who develop liver failure. Of the 20 individuals with GSD IV who have received a liver transplant to date, two required a second liver transplant and six died: four from sepsis, one from hepatic artery thrombosis, and one from cardiomyopathy. The prognosis in persons with GSD IV who undergo liver transplantation is poor because of the significant risk for morbidity and mortality, which is in part attributed to the extrahepatic manifestations of GSD type IV, especially cardiomyopathy [Davis & Weinstein 2008, Magoulas et al 2012, Troisi et al 2014, Choi et al 2018].

Selecting appropriate candidates for liver transplantation can be complex. Histologic, molecular, or clinical predictors of disease progression are likely to be useful in stratifying patients prior to liver transplantation [Davis

& Weinstein 2008]. Factors such as glycogen branching enzyme (GBE) activity may not be the best predictor of outcome since the level of GBE activity in different tissues can vary by disease subtype and severity.

Neurologic Manifestations

Children with skeletal myopathy and/or hypotonia who experience motor developmental delay warrant developmental evaluation and physical therapy as needed.

Cardiac Manifestations

For those with cardiomyopathy, care by a cardiologist is warranted. Individuals with severe cardiomyopathy secondary to glycogenosis may be candidates for cardiac transplantation [Ewert et al 1999]; however, consideration of potential contraindications to cardiac transplantation, including myopathy, liver failure, and cachexia, is essential before pursuing this treatment option.

Prevention of Secondary Complications

Nutritional deficiencies (e.g., of fat-soluble vitamins) can be prevented by ensuring adequate dietary intake based on frequent assessments by and recommendations of a dietitian experienced in managing children with liver disease.

Bleeding due to coagulopathy can occur especially with surgical procedures; therefore, it is recommended that a coagulation profile be assessed before surgical procedures and fresh frozen plasma be given preoperatively as needed.

Surveillance

No clinical guidelines for surveillance are available.

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

System/Concern	Evaluation	Frequency
Hepatic	• Liver function tests incl liver transaminases, albumin, & coagulation profile (PT & PTT) • Abdominal ultrasound examination	Frequency according to severity
Cardiac	Echocardiogram	If cardiomyopathy was not seen on echocardiogram at diagnosis, repeat echocardiogram every 3 mos in infancy, every 6 mos in early childhood, & annually thereafter.
Neurologic	Neurologic assessment	Frequency according to severity
Gastrointestinal	Nutritional assessment	

Evaluation of Relatives at Risk

If the *GBE1* pathogenic variants have been identified in an affected family member, at-risk relatives can be tested so that those with the pathogenic variants can be evaluated for involvement of the liver, skeletal muscle, and heart to allow for early diagnosis and management of disease manifestations.

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

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 IV (GSD IV) 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., carriers of one *GBE1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Affected sibs are expected to manifest the same subtype of GSD IV; however, age of onset and presentation may differ.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with GSD IV are obligate heterozygotes (carriers) for a pathogenic variant in *GBE1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *GBE1* pathogenic variant.

Carrier Detection

Molecular genetic testing. Molecular genetic testing is the preferred method for determining an individual's carrier status. Carrier testing for at-risk family members requires prior identification of the *GBE1* pathogenic variants in the family.

Biochemical genetic testing. Analysis of glycogen branching enzyme (GBE) activity alone is not sufficient to determine carrier status since enzyme activity in carriers may be within the normal range.

Related Genetic Counseling Issues

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

Family planning

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

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. 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 of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *GBE1* pathogenic variants have been identified in an affected family member, molecular genetic prenatal testing for the familial *GBE1* pathogenic variants and preimplantation genetic testing are possible.

Biochemical genetic testing. Prenatal testing is possible by analysis of glycogen branching enzyme (GBE) activity in amniocytes or cultured chorionic villi obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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
- **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
- **National Library of Medicine Genetics Home Reference**
  Glycogen storage disease type IV
- **European Reference Network for Hereditary Metabolic Disorders (MetabERN)**
  MetabERN
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **EUROMAC**
  Spain
  www.euromacregistry.eu

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 IV: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GBE1	3p12.2	1,4-alpha-glucan-branching enzyme	GBE1 database	GBE1	GBE1

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 IV (View All in OMIM)

232500	GLYCOGEN STORAGE DISEASE IV; GSD4
607839	GLYCOGEN BRANCHING ENZYME; GBE1

Molecular Pathogenesis

Glycogen branching enzyme (GBE), a 702-amino acid protein, catalyzes the transfer of alpha-1,4-linked glucosyl units from the outer end of a glycogen chain to an alpha-1,6 position on the same or a neighboring glycogen chain. Branching of the chains is essential to increase the solubility of the glycogen molecule and, consequently, reduce the osmotic pressure within cells [Thon et al 1993]. The GBE protein contains two highly conserved domains at the N- and C-terminals with sequences similar to isoamylase (glycoside hydrolase) and alpha-amylase, respectively. These two domains flank the alpha-amylase catalytic domain that encompasses the central portion of the enzyme [Moses & Parvari 2002].

The underlying molecular defects in *GBE1* lead to the production of little or no functional GBE, resulting in abnormally formed glycogen (with fewer branch points and longer unbranched outer chains) with an amylopectin-like structure that accumulates in various tissues, most commonly the liver, heart, muscle, brain, spinal cord, peripheral nerve, and skin [Thon et al 1993, Chen 2001, Moses & Parvari 2002]. It has been postulated that alteration in the glycogen branching structure that makes it less soluble may result in a foreign body reaction that leads to the tissue injury and dysfunction observed in GSD IV [Howell 1991]; however, the specific pathogenic mechanisms remain unknown.

Mechanism of disease causation. Loss of function.

Table 5. Notable *GBE1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Genotype-Phenotype Correlation [1]
NM_000158.3 NP_000149.3	c.986A>C	p.Tyr329Ser	Non-progressive hepatic, APBD
	c.1544G>A	p.Arg515His	APBD
	c.1571G>A	p.Arg524Gln	Classic hepatic, non-progressive hepatic, APBD

APBD = adult-onset polyglucosan body disease

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. Li et al [2012]

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Chapter Notes

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