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Glycogen Storage Disease Type VI

Synonym: GSD VI

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Summary

Clinical characteristics

Glycogen storage disease type VI (GSD VI) is a disorder of glycogenolysis caused by deficiency of hepatic glycogen phosphorylase. This critical enzyme catalyzes the rate-limiting step in glycogen degradation, and deficiency of the enzyme in the untreated child is characterized by hepatomegaly, poor growth, ketotic hypoglycemia, elevated hepatic transaminases, hyperlipidemia, and low prealbumin level. GSD VI is usually a relatively mild disorder that presents in infancy and childhood; rare cases of more severe disease manifesting with recurrent hypoglycemia and marked hepatomegaly have been described. More common complications in the setting of suboptimal metabolic control include short stature, delayed puberty, osteopenia, and osteoporosis. Hepatic fibrosis commonly develops in GSD VI, but cirrhosis and hypertrophic cardiomyopathy are rare. Clinical and biochemical abnormalities may decrease with age, but ketosis and hypoglycemia can continue to occur.

Diagnosis/testing

The diagnosis of GSD VI is established in a proband with typical clinical findings and/or biallelic pathogenic variants in *PYGL* identified by molecular genetic testing.

Management

Treatment of manifestations: Some individuals with GSD VI may not require any treatment, but treatment with cornstarch and protein improves growth, stamina, and ameliorates biochemical abnormalities including hypoglycemia and ketosis. Even in those with no hypoglycemia, a bedtime dose of cornstarch improves energy and prevents ketosis.

Surveillance: Monitoring of blood glucose and blood ketone levels at least several times per month during times of stress including illness, intense activity, periods of rapid growth, or any time at which intake of food is

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reduced. Annual liver ultrasound examinations should start at age five years. Bone density exam is recommended when puberty is complete.

Agents/circumstances to avoid: Excessive amounts of simple sugars; glucagon administration as a rescue therapy for hypoglycemia; growth hormone therapy for short stature; contact sports when hepatomegaly is present.

Evaluation of relatives at risk: If the family-specific pathogenic variants are known, it is appropriate to offer molecular genetic testing to at-risk sibs so that early treatment and avoidance of factors that exacerbate disease can be initiated.

Genetic counseling

GSD VI is inherited in an autosomal recessive manner. 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. Carrier testing for at-risk relatives and prenatal diagnosis for pregnancies at increased risk are possible if the pathogenic variants in the family are known.

Diagnosis

Glycogen storage disease type VI (formerly known as Hers disease) is a disorder affecting hepatic glycogenolysis due to a deficiency of glycogen phosphorylase. This critical enzyme catalyzes the rate-limiting step in glycogen degradation.

Suggestive Findings

Glycogen storage disease type VI (GSD VI) **should be suspected** in individuals with the following:

- Hepatomegaly
- Poor growth
- Ketotic hypoglycemia
- Elevated hepatic transaminases
- Hyperlipidemia
- Low prealbumin level
- Abdominal ultrasound showing hepatomegaly with diffuse echogenicity

Establishing the Diagnosis

The diagnosis of GSD VI **is established** in a proband with typical clinical findings and/or biallelic pathogenic (or likely pathogenic) variants in *PYGL* identified by 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).

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 any likely pathogenic variants. (2) Identification of biallelic *PYGL* variants of uncertain significance (or of one known *PYGL* pathogenic variant and one *PYGL* variant of uncertain significance) does not establish or rule out the diagnosis.

A liver biopsy is reserved for those in whom the diagnosis cannot be confirmed by molecular genetic techniques [Kishnani et al 2019].

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of GSD VI is fairly 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 other inherited disorders with hepatomegaly 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 VI, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**. Single-gene testing is recommended when the affected individual is from a high-risk population (see Prevalence) or has an affected relative.

- **Single-gene testing.** Sequence analysis of *PYGL* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions; 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.

  Targeted analysis for the founder pathogenic variant, c.1620+1G>A (also known as IVS13+1G>A), can be performed first in individuals of Mennonite ancestry.

- A **glycogen storage disease multigene panel** that includes *PYGL* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (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

When the phenotype is indistinguishable from many other inherited disorders characterized by glycogen storage disorder, **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.

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 VI

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
PYGL	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown but rare [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 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. Data derived from personal experience and the subscription-based professional view of the Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Typical presentation. Glycogen storage disease type VI (GSD VI) is usually a relatively mild disorder presenting in infancy and childhood with abdominal distention, hepatomegaly, and growth restriction.

Hypoglycemia. If present, hypoglycemia is mild and may manifest during an illness after prolonged fasting. Ketotic hypoglycemia after an overnight fast is the salient feature of this disorder.

Liver concerns

- **Fibrosis/cirrhosis occurrence.** Fibrosis commonly develops in GSD VI, but cirrhosis is rare [Roscher et al 2014, Wilson et al 2019].
- **Tumor risk.** While rare, hepatic adenomas and hepatocellular carcinoma can develop [Manzia et al 2011, Roscher et al 2014].

Muscle concerns

- **Muscle hypotonia and fatigue with exercise** have been reported [Beauchamp et al 2007]. Delay in motor milestones may occur in untreated children.
- **Muscle cramping** is a common complaint in GSD VI if protein deficiency is present. The cramping is usually in the lower extremities and typically occurs with activity and overnight [DA Weinstein, unpublished data].
- **Hypertrophic cardiomyopathy.** Secondary muscle involvement can occur from overstorage of glycogen. Rare cases of hypertrophic cardiomyopathy have been reported [Roscher et al 2014].

Growth

- **In untreated individuals.** Poor growth and delayed puberty are common findings.
- **With treatment**
  - Growth normalizes;
  - Final height is usually appropriate for genetic potential.

Skeletal concerns

- Osteopenia and osteoporosis are common in untreated individuals.

- Bone mineral density can normalize with treatment [Chen & Weinstein 2016].

Renal concerns

- Due to the overstorage of glycogen and high protein diet, the consensus guidelines recommend screening for kidney disease.
- Renal abnormalities including proteinuria, however, are rarely seen in GSD VI [Okechuku et al 2017].

Intellectual development is normal in most children.

Atypical form. Rare variants with severe and recurrent hypoglycemia, severe hepatomegaly, and postprandial hyperlactatemia have been described [Beauchamp et al 2007].

Adulthood. Clinical and biochemical abnormalities may improve with age and many adults are asymptomatic.

Genotype-Phenotype Correlations

No clear genotype-phenotype correlation exists.

The Mennonite pathogenic variant, c.1620+1G>A generates a transcript lacking all or part of exon 13 while maintaining the reading frame. Either protein isoform is expected to have some residual enzyme activity, which may explain the milder GSD VI phenotype in the Mennonite population [Chang et al 1998].

Nomenclature

GSD VI (Hers disease) was first reported by Hers [1959] and Stetten & Stetten [1960]. GSD VI was referred to as Hers disease based on Hers' prediction that the GSDs were a heterogeneous group that would ultimately be categorized into specific types.

GSD VI now refers to liver glycogen phosphorylase deficiency.

Prevalence

Liver glycogen phosphorylase deficiency affects approximately 1:65,000-85,000 live births; however, many people with this condition are undiagnosed. GSD VI is equally prevalent in males and females. The Mennonite population is at increased risk for GSD VI, with a prevalence of 1:1,000 resulting from the founder variant c.1620+1G>A. It is estimated that 3% of the Mennonite population are heterozygous (i.e., are carriers) for this pathogenic variant [Chang et al 1998]. There also appears to be an increased prevalence of GSD VI in Scotland and Northern Africa, but the frequency is not known [Chen & Weinstein 2016].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of Glycogen Storage Disease Type VI

Disorder	Gene(s)	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/GSD VI	Distinguishing from GSD VI
Phosphorylase kinase deficiency (GSD IX)	*PHKA2* *PHKB* *PHKG2*	XL AR	• Hepatomegaly • Fasting ketosis • Hypoglycemia • ↑ AST/ALT • ↑ lipids	• Male predominance • AST & ALT commonly more severely ↑
Hepatic glycogen synthase deficiency (GSD 0) (OMIM 240600)	*GYS2*	AR	• Fasting hypoglycemia • Ketosis	• Absence of hepatomegaly • Postprandial hyperglycemia & hyperlactatemia
Glucose-6-phosphatase deficiency (GSD Ia)	*G6PC1*	AR	• Hepatomegaly • Fasting hypoglycemia • ↑ AST/ALT • Hyperlipidemia	• Severe fasting lactic acidosis • Hyperuricemia • Marked hyperlipidemia
Glucose-6-phosphate transporter deficiency (GSD Ib)	*SLC37A4*	AR	• Hepatomegaly • Fasting hypoglycemia • ↑ AST/ALT • Hyperlipidemia	• Neutropenia • Crohn disease • Hyperuricemia
Debranching enzyme deficiency (GSD III)	*AGL*	AR	• Hepatomegaly • Fasting hypoglycemia • ↑ AST/ALT • Hyperlipidemia • Low prealbumin	• AST & ALT usually markedly ↑ • Muscle involvement w/↑ CK
Branching enzyme deficiency (GSD IV)	*GBE1*	AR	• Hepatomegaly • ↑ AST/ALT • ↓ prealbumin	Lack of hypoglycemia until end-stage liver disease
GLUT2 deficiency (Fanconi-Bickel syndrome; GSD XI) (OMIM 227810)	*SLC2A2*	AR	• Hepatomegaly • Fasting hypoglycemia • Fasting ketosis • ↑ AST/ALT • Low prealbumin	• Postprandial hyperglycemia • Chronic diarrhea • Hypophosphatemic rickets • Fanconi nephropathy
Fructose-1,6-bisphosphatase deficiency [1]	*FBP1*	AR	• Hepatomegaly • Fasting hypoglycemia • ↑ AST/ALT	Fasting hyperlactatemia
Alpha-1 antitrypsin deficiency-related hepatitis [2]	*SERPINA1*	AR	• Hepatomegaly • ↑ AST/ALT	Lack of fasting hypoglycemia & ketosis
Glycerol kinase deficiency (OMIM 307030)	*GK*	XL	Hypoglycemia	Ketoacidosis & extremely ↑ glycerol
PRKAG2 deficiency (See Hypertrophic Cardiomyopathy Overview.)	*PRKAG2*	AD	• Nonlysosomal glycogen accumulation primarily in skeletal & cardiac muscle	• Ventricular pre-excitation & mild-to-severe cardiac hypertrophy • No hypoglycemia

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/GSD VI	Distinguishing from GSD VI
Niemann-Pick disease type B [3] (See ASM Deficiency.)	*SMPD1*	AR	• Hepatomegaly • Growth failure • Hyperlipidemia	• No fasting hypoglycemia • Significant splenomegaly • Bone & pulmonary involvement
Gaucher disease [3]	*GBA1* (*GBA*)			

Adapted from Kishnani et al [2019]
AD = autosomal dominant; AR = autosomal recessive; ASM = acid sphingomyelinase; 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; other should also be considered.
2. Alpha-1 antitrypsin deficiency-related hepatitis is one example of a primary liver disease; other primary liver diseases should also be considered.
3. Niemann-Pick disease type B and Gaucher disease are examples of metabolic storage disorders; other metabolic storage disorders should also be considered.

Mitochondrial disorders should also be considered in the differential diagnosis of GSD VI (see Mitochondrial Disorders Overview).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with glycogen storage disease type VI (GSD VI), 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 GSD VI

System/Concern	Evaluation	Comment
Gastrointestinal/ Hepatic	• Assessment of liver size • Abdominal ultrasound	Involvement of specialists in GSD VI (gastroenterologist, endocrinologist, metabolic geneticist)
Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling

Treatment of Manifestations

Note: Some individuals with GSD VI may not require any treatment, but most have better growth and stamina with therapy.

Table 4. Treatment of Manifestations in individuals with GSD VI

Manifestations/ Concern	Treatment	Considerations/Other
Hypoglycemia	• Frequent small meals • Uncooked cornstarch (1-1.5 g/kg) 1-4x/day • Protein 2-3 g/kg body weight per day • Glycosade [1] from waxy maize, proven beneficial in children age >5 yrs & adults to extend overnight fast duration	Doses adjusted to keep glucose concentrations at 75-100 mg/dL (4.2-5.6 mmol/L) & beta-OH-butyrate concentrations ≤0.2 mmol/L
Hepatomegaly	• Restricted intake of simple sugars (<5 g) • Restricted intake of total carbohydrates (15-30 g per meal)	To ↓ liver size

Table 4. continued from previous page.

Manifestations/ Concern	Treatment	Considerations/Other
Growth restriction	Cornstarch & protein supplementation	• Growth normalizes w/treatment • Growth hormone contraindicated
Decreased bone density	• Cornstarch & protein supplementation • Calcium & Vitamin D	Primarily due to ketosis
Muscle cramping	Protein 2-3 grams per kg body weight per day	Muscle cramping is usually due to undertreatment & protein deficiency.

1. Extended-release cornstarch

General Nutrition Recommendations

[Kishnani et al 2019]

Protein

- Diet should be high in protein and provide 2-3 g protein/kg body weight or 20%-25% of total calories.
- Protein intake should be distributed throughout the day.
- Protein should be consumed at each meal and snack, before bedtime, and before physical activities.

Carbohydrates

- Carbohydrates should provide 45%-50% of total calories.
- Complex carbohydrates should be consumed with each meal to provide a sustained source.
- Overtreatment with cornstarch can be detrimental.
- Small amounts of dairy and fruits are allowed in the diet.
- Simple sugars should be limited to 5 g.

Fats

- Fats should provide 25%-30%of total calories.
- Diet should include good sources of poly-and mono-unsaturated fatty acids.
- Saturated fats should provide <10% of total calories.
- Cholesterol should be restricted to <300 mg/day.

Surveillance

Table 5. Recommended Surveillance for Individuals with GSDVI

System/Concern	Evaluation	Frequency
Ketosis	Blood ketone level upon wakening using portable blood ketone meter.	At least several times per month [1]; goal is to maintain blood beta-OH-butyrate concentrations <0.3 mmol/L.
Hypoglycemia	Self-glucose monitoring	At least several times per month & as needed [1]
Gastrointestinal	Liver ultrasound	Annually beginning at age 5 yrs
Skeletal	Bone density	When puberty is complete & as clinically indicated
Renal	24-hr urine to screen for microalbuminuria	Annually

1. Glucose and ketone levels should also be measured during times of stress including illness, intense activity, periods of rapid growth, or any time at which intake of food is reduced and before and after changes are made to the amount of cornstarch or protein intake. Monitoring recommendations should be tailored to individual needs.

Agents/Circumstances to Avoid

Avoid the following:

- Excessive amounts of simple sugars to prevent excessive hepatic glycogen deposition
- Glucagon administration as a rescue therapy for hypoglycemia because blood glucose concentrations will not increase
- Growth hormone for short stature because it usually exacerbates ketosis and may increase the risk of complications
- Contact sports when hepatomegaly is present (or use appropriate cautions)

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic at-risk sibs to identify as early as possible those who would benefit from prompt initiation of treatment and avoidance of factors that exacerbate disease.

Molecular genetic testing is indicated if the pathogenic variants in the family are known.

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

Pregnancy Management

A pregnant woman with GSD VI must be vigilant in monitoring for hypoglycemia and ketosis during pregnancy. Cornstarch and protein supplementation (2-4x/day) are needed during pregnancy to prevent ketosis and premature labor. The goal is to maintain euglycemia throughout pregnancy to prevent morbidity and mortality to the fetus due to activation of counterregulatory hormones resulting in lipolysis and ketosis. Increasing protein intake may be necessary to provide an alternate source of glucose via gluconeogenesis.

Therapies Under Investigation

An extended-release cornstarch preparation is presently being tested as part of the Clinical Trials GLYDE study (NCT02318966). This experimental product may improve maintenance of normoglycemia with fasting for a longer duration and may reduce the number of doses of cornstarch required.

There is also an ongoing trial looking for a biomarker for glycogen storage disease (NCT02385162).

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 VI (GSD VI) 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 *PYGL* 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- The offspring of an individual with GSD VI are obligate heterozygotes (carriers) for a pathogenic variant in *PYGL*.
- A higher carrier rate for GSD VI exists in the Mennonite population (see Prevalence), increasing the risk that an affected individual may have a reproductive partner who is heterozygous for a pathogenic variant in *PYGL*. If the reproductive partner of the proband is heterozygous for a *PYGL* pathogenic variant, offspring are at 50% risk of being affected and 50% risk of being carriers.

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

Carrier Detection

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

Biochemical testing is not reliable for carrier testing.

Related Genetic Counseling Issues

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

Family planning

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

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

Prenatal Testing and Preimplantation Genetic Testing

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

Biochemical testing is not reliable for prenatal diagnosis.

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
- **European Reference Network for Hereditary Metabolic Disorders (MetabERN)**
  MetabERN
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **University of Florida GSD International Natural History Registry**
  Phone: 352-273-6655
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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 VI: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PYGL	14q22.1	Glycogen phosphorylase, liver form	PYGL database	PYGL	PYGL

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 VI (View All in OMIM)

232700	GLYCOGEN STORAGE DISEASE VI; GSD6
613741	GLYCOGEN PHOSPHORYLASE, LIVER; PYGL

Molecular Pathogenesis

Glycogen phosphorylase, which requires pyridoxal phosphate as a cofactor, cleaves the α(1→4) glycosidic bonds between the glycosyl residues at the periphery of the glycogen molecule to release glucose-1-phosphate. This enzymatic reaction is the rating-limiting process in glycogenolysis, and it is repeated until the proximal four residues before the branch point of that particular glycogen chain are reached. The three isoforms of glycogen phosphorylase – muscle, liver, and brain – are encoded by different genes.

Liver glycogen phosphorylase, encoded by *PYGL*, forms a homodimer that has a regulatory domain and a catalytic domain:

- **Regulatory domain**
  - Contains the phosphorylation peptide and the AMP binding site;
  - Interacts with the phosphorylase kinase, allosteric effectors, and phosphatase.
- **Catalytic domain** binds to glycogen.

Mechanism of disease causation. GSD VI results from a loss of function of liver glycogen phosphorylase [Burwinkel et al 1998, Beauchamp et al 2007]. Most pathogenic variants are missense variants affecting activation or binding of substrate or pyrophosphate.

Table 6. Notable *PYGL* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_002863.3	c.1620+1G>A (IVS13+1G>A)	--	Mennonite founder variant [Chang et al 1998]

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

Chapter Notes

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