

Glycogen Storage Disorders Panel, Sequencing

Glycogen storage diseases (GSDs) are a group of inborn errors of metabolism, typically caused by enzyme defects, resulting in a buildup of glycogen in the liver, muscles, and other organs. Specific clinical presentation and age of onset depends on the particular type of GSD; there are many types and subtypes, and other disorders may have overlapping phenotypes.

Disease Overview

Common clinical features of these disorders include:

- Hepatomegaly
- Poor growth or short stature
- Hypoglycemia (marked by fatigue, irritability, headaches, pallor)
- Muscle weakness and/or pain
- Cardiomyopathy
- Exercise intolerance
- Liver disease (cirrhosis)

Testing Strategy

Depending on the type of GSD suspected, consideration may be given to laboratory workup that may include the following tests:

- Serum creatine kinase
- Blood glucose (fasting/nonfasting)
- Cholesterol
- Liver enzymes (eg, alanine transaminase [ALT] and aspartate transaminase [AST])
- Triglycerides
- Uric acid
- Urine organic acids
- Plasma acylcarnitines
- Blood lactate
- Imaging studies (magnetic resonance imaging [MRI] or ultrasound)
- Tissue biopsy

Genetics

Etiology

Pathogenic germline variants in genes associated with GSDs or related disorders (see [Genes Tested](#) table)

Inheritance

Primarily autosomal recessive (AR); rarely autosomal dominant (AD) or X-linked (XL)

Penetrance

Variable, depending on the specific type of GSD

Tests to Consider

[Glycogen Storage Disorders Panel, Sequencing 3001627](#)

Method: Massively Parallel Sequencing

Preferred molecular test to confirm or rule out a diagnosis of a GSD or related disorder following clinical and/or biochemical presentation

See [Related Tests](#).

Test Interpretation

Clinical Sensitivity

Variable, depending on the specific type of GSD

Analytical Sensitivity:

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate ^a (%)	Analytical Sensitivity (PPA) 95% Credibility Region ^a (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

^aGenes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result	Variant(s) Detected	Clinical Significance
Positive	One or more pathogenic or likely pathogenic variants detected	Confirms a diagnosis of heritable GSD or related disorder Specific diagnosis depends on the variant(s) detected
See note	One or more variants of uncertain significance detected	Unknown if variant(s) are disease-causing or benign
Negative	No pathogenic variants detected	Diagnosis of GSD or related disorder is less likely, though not excluded

Limitations

- A negative result does not exclude a diagnosis of a GSD.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
 - Variants outside the coding regions and intron-exon boundaries of targeted gene(s)
 - Regulatory region and deep intronic variants, including GBE1 (NM_000158.4) intron 15
 - Includes an Ashkenazi Jewish founder mutation in GBE1 (HGMD ID: CX153579)
 - Noncoding transcripts
 - The following exons are not sequenced due to technical limitations of the assay:
 - ENO3 (NM_001374524) exon(s) 1
 - OXCT1 (NM_001364299) exon(s) 5
 - OXCT1 (NM_001364300) exon(s) 1
 - OXCT1 (NM_001364303) exon(s) 1
 - PFKM (NM_001354735) exon(s) 4
 - PFKM (NM_001354736) exon(s) 4

- PFKM (NM_001354740) exon(s) 1
- PFKM (NM_001354741) exon(s) 2
- Large deletions/duplications in any of the tested genes
- The following may not be detected:
 - Deletions/duplications/insertions of any size by massively parallel sequencing
 - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
 - Low-level somatic variants

Genes Tested

Gene	MIM #	Disorder	Inheritance
<i>ACAT1</i>	607809	Alpha-methylacetoacetic aciduria	AR
<i>AGL</i>	610860	GSD IIIa	AR
		GSD IIIb	AR
<i>ALDOA</i>	103850	GSD XII	AR
<i>ALDOB</i>	612724	Hereditary fructose intolerance	AR
<i>CPT2</i>	600650	Carnitine palmitoyltransferase II deficiency	AD, AR
<i>ENO3</i>	131370	GSD XIII	AR
<i>FBP1</i>	611570	Fructose-1, 6-bisphosphatase deficiency	AR
<i>G6PC</i>	613742	GSD Ia	AR
<i>GAA</i>	606800	GSD II (Pompe disease)	AR
<i>GBE1</i>	607839	GSD IV	AR
<i>GYG1</i>	603942	GSD XV	AR
<i>GYS1</i>	138570	GSD 0, muscle	AR
<i>GYS2</i>	138571	GSD 0, liver	AR
<i>LAMP2</i>	309060	Danon disease	XL
<i>LDHA</i>	150000	GSD XI	AR
<i>NHLRC1</i>	608072	Myoclonic epilepsy of Lafora	AR
<i>OXCT1</i>	601424	Succinyl-CoA:3-oxoacid CoA transferase deficiency	AR
<i>PFKM</i>	610681	GSD VII	AR
<i>PGAM2</i>	612931	GSD X	AR
<i>PGK1</i>	311800	Phosphoglycerate kinase 1 deficiency	XL
<i>PGM1</i>	171900	Congenital disorder of glycosylation type It	AR

Gene	MIM #	Disorder	Inheritance
<i>PHKA1</i>	311870	GSD IXd	XL
<i>PHKA2</i>	300798	GSD IXa1	XL
		GSD IXa2	XL
<i>PHKB</i>	172490	GSD IXb	AR
<i>PHKG2</i>	172471	GSD IXc	AR
<i>PRKAG2</i>	602743	Hypertrophic cardiomyopathy 6	AD
		GSD of heart	AD
		Wolff-Parkinson-White syndrome	AD
<i>PYGL</i>	613741	GSD VI	AR
<i>PYGM</i>	608455	GSD V (McArdle disease)	AR
<i>RBCK1</i>	610924	Polyglucosan body myopathy 1	AR
<i>SLC16A1</i>	600682	Erythrocyte lactate transporter defect;	AD
		Familial hyperinsulinemic hypoglycemia 7	AD
		Monocarboxylate transporter 1 deficiency	AD, AR
<i>SLC2A2</i>	138160	Fanconi Bickel syndrome	AR
<i>SLC37A4</i>	602671	GSD Ib	AR
		GSD Ic	AR

Additional Resources

Chen MA, Weinstein, DA. [Glycogen storage diseases: diagnosis, treatment and outcome](#). IOS Press. 2016;1:45-72.

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Martiniuk F, Chen A, Mack A, et al. [Carrier frequency for glycogen storage disease type II in New York and estimates of affected individuals born with the disease](#). *Am J Med Genet.* 1998;79(1):69-72.

Santalla A, Nogales-Gadea G, Encinar AB, et al. [Genotypic and phenotypic features of all Spanish patients with McArdle disease: a 2016 update](#). *BMC Genomics.* 2017;18(Suppl 8):819.

Scriver CR, Beaudet AS, Sly WS, et al, eds. *The Metabolic and Molecular Basis of Inherited Disease*. 8th ed. McGraw-Hill; 2001.

Stone WL, Basit H, Adil A. [Glycogen storage disease](#). In: *StatPearls*. StatPearls Publishing; 2021. [Updated: Jun 2021; Accessed: Aug 2021]

Related Information

[Ashkenazi Jewish Genetic Diseases](#)
[Ashkenazi Jewish Genetic Diseases Panel](#)

Related Tests

[Glycogen Storage Disease, Type 1A \(G6PC\), 9 Variants 2013740](#)

Method: Polymerase Chain Reaction/Fluorescence Monitoring

[Pompe Disease \(GAA\), Enzyme Activity in Leukocytes 2014463](#)

Method: Quantitative Fluorometry

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