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.

Featured ARUP Testing

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

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

Test Interpretation

Clinical Sensitivity

Variable, depending on the specific type of GSD

Analytic Sensitivity:

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%)	Analytic 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

[a]Genes 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
ACAT1	607809	Alpha-methylacetoacetic aciduria	AR
AGL	610860	GSD IIIa	AR
		GSD IIIb	AR
ALDOA	103850	GSD XII	AR
ALDOB	612724	Hereditary fructose intolerance	AR
CPT2	600650	Carnitine palmitoyltransferase II deficiency	AD, AR
ENO3	131370	GSD XIII	AR
FBP1	611570	Fructose-1, 6-bisphosphatase deficiency	AR
G6PC	613742	GSD Ia	AR
GAA	606800	GSD II (Pompe disease)	AR

Gene	MIM #	Disorder	Inheritance
GBE1	607839	GSD IV	AR
GYG1	603942	GSD XV	AR
GYS1	138570	GSD 0, muscle	AR
GYS2	138571	GSD 0, liver	AR
LAMP2	309060	Danon disease	XL
LDHA	150000	GSD XI	AR
NHLRC1	608072	Myoclonic epilepsy of Lafora	AR
OXCT1	601424	Succinyl-CoA:3-oxoacid CoA transferase deficiency	AR
PFKM	610681	GSD VII	AR
PGAM2	612931	GSD X	AR
PGK1	311800	Phosphoglycerate kinase 1 deficiency	XL
PGM1	171900	Congenital disorder of glycosylation type It	AR
PHKA1	311870	GSD IXd	XL
PHKA2	300798	GSD IXa1	XL
		GSD IXa2	XL
PHKB	172490	GSD IXb	AR
PHKG2	172471	GSD IXc	AR
PRKAG2	602743	Hypertrophic cardiomyopathy 6	AD
		GSD of heart	AD
		Wolff-Parkinson-White syndrome	AD
PYGL	613741	GSD VI	AR
PYGM	608455	GSD V (McArdle disease)	AR
RBCK1	610924	Polyglucosan body myopathy 1	AR

Gene	MIM #	Disorder	Inheritance
SLC16A1	600682	Erythrocyte lactate transporter defect;	AD
		Familial hyperinsulinemic hypoglycemia 7	AD
		Monocarboxylate transporter 1 deficiency	AD, AR
SLC2A2	138160	Fanconi Bickel syndrome	AR
SLC37A4	602671	GSD Ib	AR
		GSD Ic	AR

Additional Resources

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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

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