Metabolic Storage Disorders Panel, 51 Genes

Indications for Ordering

Confirm diagnosis of metabolic storage disorder for individuals with suggestive clinical findings

Test Description

- Targeted capture of all coding exons and exon/intron junctions followed by massively parallel sequencing
- Sanger sequencing to confirm all significant variants

Tests to Consider

Primary test

Metabolic Storage Disorders Panel Sequencing, 51 genes 2008831

- May be used to confirm a diagnosis of metabolic storage disorder in individuals with suggestive clinical and biochemical findings
- Not a first-line test for Pompe disease

Related tests

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Mucopolysaccharides Screen - Electrophoresis and Quantitation, Urine 0081352

- Use to evaluate symptomatic individuals with suspected mucopolysaccharidoses

Disease Overview

Symptoms

- Genes tested are involved in lysosomal and glycogen metabolism and implicated in
  - Mucopolysaccharidoses
  - Lipidoses
  - Oligosaccharidoses
  - Lysosomal transport disorders
  - Glycogenoses
- Affects multiple tissues and organs due to abnormal substance accumulation
- Clinical phenotype of particular disorder type may be heterogenous and vary in onset and severity
- Clinical phenotypes may overlap among disorders

Genetics

Genes – See table for genetic information

Test Interpretation

Clinical sensitivity – disease dependent

Results

- One copy of a pathogenic variant detected in the *DNAJC5* gene
  - Confirms the diagnosis and etiology of a metabolic storage disorder
- One copy of a pathogenic variant in the *IDS* or *GLA* gene
  - Confirms the diagnosis and etiology of a metabolic storage disorder in males
  - Confirms carrier status in females
- No pathogenic variant detected in the *DNAJC5* gene in males or females, or in the *IDS* or *GLA* gene in males, in clinically affected individuals
  - Diagnosis of a metabolic storage disorder is reduced, but not excluded
- Two pathogenic variants on opposite chromosomes in one of the 48 tested genes with autosomal recessive inheritance listed in the table below
  - Diagnosis and etiology of a metabolic storage disorder is confirmed
- One pathogenic variant detected in any of the 48 tested genes with autosomal recessive inheritance listed in table below
  - Individual is a carrier
- No pathogenic variants detected in any of the 48 tested genes with autosomal recessive inheritance listed in table below
  - Diagnosis of a metabolic storage disorder is reduced, but not excluded
- Inconclusive – variants of unknown clinical significance may be identified in any of the 51 genes analyzed

Limitations

- Not determined or evaluated
  - Deep intronic or regulatory region mutations
  - Large deletions and duplications
  - Variants in genes not listed
- Diagnostic errors can occur due to rare sequence variations

Gene Symbol	Gene Name	NM #	OMIM #	Condition	Inh.	Prevalence/Incidence	Mutations Detected by Sequencing
AGA	aspartylglucosaminidase	000027	613228	aspartylglucosaminuria	AR	unknown; predominantly identified in Finnish population but may include any ethnicity	Cys163Ser mutation identified in majority of Finnish individuals
AGL	amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase	000642	610860	glycogen storage disease IIIa/b/c/d	AR	1/100,000; North African Jews ~1/5,400; Faroese ~1/3,600 (incidence)	95%
ARSA	arylsulphatase A	000487	607574	metachromatic leukodystrophy	AR	1/40,000-60,000; Habbanite Jews 1/75; Israeli Arabs 1/8,000; Western Navajo 1/2,555 (prevalence)	90-95%
ARSB	arylsulphatase B	000046	611542	mucopolysaccharidosis type VI (Maroteaux-Lamy)	AR	Turkish population in Germany 1/43,261; Swedish population 1/1,505,160 (birth prevalence)	unknown
CLN3	ceroid lipofuscinosis, neuronal 3	001042432	607042	ceroid lipofuscinosis, neuronal, 3	AR	1/300,000-7/100,000 (birth prevalence)	>98%
CLN5	ceroid lipofuscinosis, neuronal 5	006493	608102	ceroid lipofuscinosis, neuronal, 5	AR	1/300,000-7/100,000 live births (birth prevalence)	90-95%
CLN6	ceroid lipofuscinosis, neuronal 6, late infantile, variant	017882	606725	ceroid lipofuscinosis, neuronal, 6; ceroid lipofuscinosis, neuronal, 4A	AR	1/300,000-7/100,000 live births (birth prevalence)	92%
CLN8	ceroid lipofuscinosis, neuronal 8 (epilepsy, progressive with mental retardation)	018941	607837	ceroid lipofuscinosis, neuronal, 8; ceroid lipofuscinosis, neuronal, 8, Northern epilepsy variant	AR	1/300,000-7/100,000 live births (birth prevalence)	~ 90-95%
CTNS	cystinosis, nephropathic (cystinosin)	004937	606272	cystinosis; nephropathic/ atypical; nephropathic/late-onset juvenile or adolescent; nephropathic/ocular; non-nephropathic	AR	1/100,000-200,000; 1/26,000 in Brittany (prevalence)	unknown
CTSA	cathepsin A (PPGB)	000308	613111	galactosialidosis	AR	unknown; estimated prevalence <1/1,000,000	unknown
DNAJC5	DnaJ (Hsp40) homolog, subfamily C, member 5	025219	611203	ceroid lipofuscinosis, neuronal, 4B, autosomal dominant	AD	1.3-7/100,000 (birth prevalence)	unknown
ENO3	enolase 3 (beta, muscle)	053013	131370	glycogen storage disease XIII	AR	unknown	unknown
G6PC	glucose-6-phosphatase, catalytic (glycogen storage disease type 1, von Gierke disease)	000151	613742	glycogen storage disease Ia	AR	1/20,000 in Ashkenazi Jews (prevalence)	94%
GAA	glucosidase, alpha acid	000152	606800	glycogen storage disease II (Pompe disease)	AR	African Americans 1/14,000; Portuguese 1/600,000 (incidence)	83-93%
GALC	galactosylceramidase	000153	606890	Krabbe disease	AR	1/100,000 (prevalence); higher in Druze and Muslim Arabs in Israel	~55-65%
GALNS	galactosamine (N-acetyl)-6-sulphate sulphatase	000512	612222	mucopolysaccharidosis IVA (Morquio syndrome A)	AR	1/200,000 (incidence); 1/76,000 in Northern Ireland	~86-99%
GBA	glucosidase, beta acid	001005741	606463	Gaucher disease, perinatal lethal, types I/II/III/IIIC	AR	1/57,000-1.16/100,000 (prevalence); type 1 1/855 in Ashkenazi Jewish population	~99%
GBE1	glucan (1,4-alpha-) branching enzyme (glycogen branching enzyme)	000158	607839	glycogen storage disease IV, polyglucosan body disease, adult form	AR	1/600,000-800,000 (incidence)	91%
GLA	galactosidase alpha	000169	300644	Fabry disease/Fabry disease, cardiac variant	XL	1/80,000-117,000 (incidence)	~99%
GLB1	galactosidase beta	000404	611458	GM1-gangliosidosis, types I/II/III; mucopolysaccharidosis, type IVB (Morquio)	AR	1/100,000-200,000 (prevalence)	~99%

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GM2A	GM2 ganglioside activator protein	000405	613109	GM2-gangliosidosis, AB variant	AR	extremely rare	~99%
GNPTAB	N-acetylglucosamine-1-phosphate transferase, alpha and beta subunits	024312	607840	mucolipidosis II alpha/beta (I-cell disease), mucolipidosis III alpha/beta	AR	1/100,000-400,000 (prevalence); 114/100, 000 in the Irish Travellers community in Republic of Ireland	>95%
GNS	glucosamine (n-acetyl)-6-sulphatase (Sanfilippo disease IIID)	002076	607664	mucopolysaccharidosis type IIID (Sanfilippo disease type D)	AR	rare	~87%
GUSB	glucuronidase beta	000181	611499	mucopolysaccharidosis VII (Sly syndrome)	AR	rare	~99%
GYS1	glycogen synthase 1 (muscle)	002103	138570	glycogen storage disease type 0, muscle	AR	extremely rare	unknown
GYS2	glycogen synthase 2 (liver)	021957	138571	glycogen storage disease, type 0	AR	rare	unknown
HGSNAT	heparan-alpha-glucosaminide N-acetyltransferase	152419	610453	mucopolysaccharidosis type IIIC (Sanfilippo C)	AR	0.03-0.21/100,000 (birth prevalence)	unknown
HYAL1	hyaluronoglucosaminidase 1	007312	607071	mucopolysaccharidosis type IX (hyaluronidase deficiency)	AR	rare	unknown
IDS	Iduronate 2-sulphatase	000202	300823	mucopolysaccharidosis II (Hunter syndrome)	XL	1/100,000-170,000 (incidence of male births)	82-91%
IDUA	iduronidase, alpha-L	000203	252800	mucopolysaccharidosis I (Hurler/Hurler-Scheie/Scheie syndrome)	AR	1/100,000 (prevalence severe form); 1/500,000 (prevalence attenuated form)	~ 99%
LDHA	lactate dehydrogenase A	005566	150000	glycogen storage disease XI	AR	rare	unknown
LIPA	lysosomal acid lipase A, cholesterol esterase	000235	613497	cholesteryl ester storage disease, lysosomal acid lipase deficiency, Wolman disease	AR	~1/130,000-170,000 (prevalence in Caucasian and Hispanic populations)	unknown
MAN2B1	mannosidase, alpha, class 2B, member 1	000528	609458	mannosidosis, alpha, types I/II	AR	rare	~98%
MANBA	mannosidase, beta A, lysosomal	005908	609489	mannosidosis, beta	AR	rare	unknown
MCOLN1	mucolipin 1	020533	605248	mucolipidosis IV	AR	1/40,000 (incidence); 70-80% of individuals have Ashkenazi Jewish ancestry	~77% for individuals of Ashkenazi Jewish ancestry
MFSD8	major facilitator superfamily domain containing 8	152778	611124	ceroid lipofuscinosis, neuronal, 7	AR	1.3-7/100,000 live births (birth prevalence)	unknown, estimate >95%
NAGA	N-acetylgalactosaminidase alpha	000262	104170	Schindler disease, types I/II; Kanzaki disease	AR	very rare	unknown
NAGLU	alpha-N-acetylglucosaminidase (mucopolysaccharidosis IIIb)	000263	609701	mucopolysaccharidosis type IIIB (Sanfilippo B)	AR	0.28/100,000 (birth prevalence in Taiwan)	unknown
NEU1	sialidase 1 (lysosomal sialidase)	000434	608272	sialidosis, types I/II	AR	rare	unknown
NPC1	Niemann-Pick disease, type C1	000271	607623	Niemann-Pick disease, types C1/D	AR	1/150,000 (prevalence in Western Europe)	90%
NPC2	Niemann-Pick disease, type C2	006432	601015	Niemann-Pick disease, type C2	AR	1/150,000 (prevalence in Western Europe)	4%
PFKM	phosphofructokinase, muscle	000289	610681	glycogen storage disease VII	AR	rare	unknown
PPT1	palmitoyl-protein thioesterase 1 (ceroid lipofuscinosis, neuronal 1, infantile, CLN1)	000310	600722	ceroid lipofuscinosis, neuronal, 1	AR	1.3-7/100,000 live births (birth prevalence)	>98%
PYGL	phosphorylase, glycogen (liver)	002863	613741	glycogen storage disease VI	AR	1/1,000 in Mennonite population	unknown
PYGM	phosphorylase, glycogen (muscle)	005609	608455	glycogen storage disease V (McArdle disease)	AR	1/100,000–200,000 (prevalence)	~99%
SGSH	sulphamidase, heparan sulphate sulphatase (mucopolysaccharidosis IIIa)	000199	605270	mucopolysaccharidosis type IIIA (Sanfilippo A)	AR	0.28-4.1/100,000 (birth prevalence)	>95%

Gene Symbol	Gene Name	NM #	OMIM #	Condition	Inh.	Prevalence/Incidence	Mutations Detected by Sequencing
SLC17A5	solute carrier family 17 (anion/sugar transporter), member 5	012434	604322	sialic acid storage disorder, infantile Salla disease	AR	rare, reported mainly in individuals from Finland and Sweden	p.Arg39Cys identified in up to 95% of individuals with Salla disease of Finish heritage
SLC37A4	solute carrier family 37 (glycerol-6-phosphate transporter), member 4 (G6PT1)	001164277	602671	glycogen storage disease IB/IC	AR	1/100,000 (incidence)	95%
SMPD1	sphingomyelin phosphodiesterase 1	000543	607608	Niemann-Pick disease, types A/B	AR	1/40,000 in Ashkenazi Jewish population (type A incidence), 1/250,000 (prevalence type A and B)	>95%
SUMF1	sulphatase modifying factor 1	182760	607939	multiple sulfatase deficiency	AR	1/1,400,000 (birth prevalence)	unknown
TPP1	tripeptidyl peptidase I (CLN2)	000391	607998	ceroid lipofuscinosis, neuronal, 2	AR	1.3-7/100,000 live births (birth prevalence)	97%
Inh. = inheritance; AD = autosomal dominant; AR = autosomal recessive; XL = X-linked							