# Metabolic Myopathy Panel

**Panel Gene List:** *ACAD9, ACADM, ACADVL, AGL, ALDOA, CPT2, ETFA, ETFB, ETFDH, FKRP, GAA, GYG1, GYS1, HADHA, HADHB, ISCU, LDHA, LPIN1, PFKM, PGAM2, PGK1, PGM1, PHKA1, PYGM, RYR1, SLC22A5, SLC25A20, SUCLA2, TANGO2, TK2*

**Clinical Features:**
Metabolic myopathies are a clinically and genetically heterogeneous group of disorders caused by defects in cellular muscle metabolism resulting in muscle weakness, recurrent myoglobinuria, and exercise intolerance. Symptoms typically include exertional fatigue, cramping, myalgia and myoglobinuria which usually occur during periods of high energy demand such as exercise, illness or fasting. The age-of-onset of clinical symptoms depends on the specific diagnosis and can range from the neonatal period to adulthood. Metabolic myopathies may be distinguished from other neuromuscular disorders as they tend to have acute onset, episodic, or recurrent symptoms.[1] The biochemical features may include abnormal acylcarnitine profile, elevated creatine kinase (may only be present episodically), and exercise-induced myogloginuria.[1,2]

The GeneDx Metabolic Myopathy panel includes genes causing glycogen storage disorders, fatty acid oxidation disorders and other well-established metabolic myopathies. Confirmation of a clinical diagnosis can help direct treatment and medical management.

***Classes of Metabolic Myopathies:***
Metabolic myopathies are classified into distinct categories based on the cellular mechanism of disease and include abnormalities in lipid metabolism including disorders related to fatty acid oxidation and carnitine deficiencies, glycogen storage disorders of muscle and mitochondrial disorders. Mitochondrial disorders are a broad class of disorders that can cause metabolic myopathy but in many cases these disorders are associated with additional characteristic findings, including lactic acidosis, ophthalmologic, neurologic and/or gastrointestinal findings. Evaluation for metabolic myopathies caused by mitochondrial disorders is available as a separate test at GeneDx using the Combined Mitochondrial Genome Panel (test #615).

**Glycogen storage diseases (GSDs)** are caused by defects in the production of or degradation of glycogen. The clinical features of GSDs vary depending on the specific diagnosis but can include abnormal liver enzymes, premature fatigue during endurance exercise, and the “second wind” phenomenon. Examples of GSD-related metabolic myopathies include McArdle disease and Pompe disease. **Fatty acid Oxidation (FAO) disorders** are caused by defects in the cellular processing of medium and long-chain fatty acids for energy production during times of increased energy demand. The clinical features of

FAO disorders include muscle pain and weakness precipitated by illness, fasting, or exercise, and abnormal acylcarnitine profile that can normalize outside of metabolic crises. Examples of FAO disorders include carnitine palmitoyl transferase II (CPT2) deficiency and very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency.

**Genetics:**
All of the disorders tested for in this panel are inherited in an autosomal recessive manner with the exception of glycogen storage disease type IX (*PHKA1* gene) and phosphoglycerate kinase deficiency (*PGK1* gene) which are X-linked and *RYR1*-related disorders, which can be inherited in an autosomal dominant or recessive manner.

**Test Methods:**
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV).
The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. For the *FKRP* gene sequencing but not deletion/duplication analysis, is performed. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

**References:**
1. Berardo et al. (2010) Curr Neurol Neurosci Rep 10 (2):118-26 (PMID: 20425236)
2. Wanders et al. (2010) Journal Of Inherited Metabolic Disease 33 (5):479-94 (PMID: 20490924

| Class of Disorders | Gene Name | Associated Disorder(s) | OMIM# |
|---|---|---|---|
| Glycogen storage diseases | *AGL* | Glycogen storage disease III (GSDIII) | #232400 |
| | *ALDOA* | Glycogen storage disease XII (GSDXII) | #611881 |
| | *GAA* | Glycogen storage disease II (GSDII) / Pompe disease | #232300 |
| | *GYG1* | Glycogen storage disease XV (GSDXV) / Polyglucosan body myopathy type 2 (PGBM2) | #613507, #616199 |
| | *GYS1* | Muscle glycogen storage disease 0 (GSD0B) | #611556 |
| | *LDHA* | Glycogen storage disease XI (GSDXI) | #612933 |
| | *PFKM* | Glycogen storage disease VII (GSDVII) / Tarui disease | #232800 |
| | *PGAM2* | Glycogen storage disease X (GSDX) | #261670 |
| | *PGM1* | Glycogen storage disease XIV (GSDXIV) / Congenital disorder of glycosylation type 1t (CDG1T) | #614921 |
| | *PHKA1* | Glycogen storage disease IX (GSDIX) | #300559 |
| | *PYGM* | Glycogen storage disease V (GSDV) / McArdle disease | #232600 |
| Disorders of fatty acid, carnitine, and lipid metabolism | *ACAD9* | ACAD9 deficiency | #611126 |
| | *ACADM* | Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency | #201450 |
| | *ACADVL* | Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency | #201475 |
| | *CPT2* | Carnitine palmitoyltransferase II (CPT2) deficiency | #255110, #600649, #608836 |
| | *ETFA* | Glutaric aciduria II (GAII) | #231680 |
| | *ETFB* | Glutaric aciduria II (GAII) | #231680 |
| | *ETFDH* | Glutaric aciduria II (GAII) | #231680 |
| | *HADHA* | Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) / Mitochondrial trifunctional protein (MTP) deficiency | #609016, #609015 |
| | *HADHB* | Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) / Mitochondrial trifunctional protein (MTP) deficiency | #609015 |
| | *LPIN1* | Autosomal recessive acute recurrent myoglobinuria (ARARM) | #268200 |
| | *SLC22A5* | Primary/systemic carnitine deficiency (PCD) | #212140 |
| | *SLC25A20* | Carnitine-acylcarnitine translocase deficiency (CACTD) | #212138 |

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| Other metabolic myopathies | *FKRP* | Muscular dystrophy-dystroglycanopathy types 5A, 5B, and 5C | #613153, #606612, #607155 |
| | *ISCU* | Hereditary myopathy with lactic acidosis | # 255125 |
| | *PGK1* | Phosphoglycerate kinase deficiency | # 300653 |
| | *RYR1* | Central core disease / Minicore myopathy | #117000, #255320 |
| | *SUCLA2* | Mitochondrial DNA depletion syndrome-5 (MTDPS5) | #612073 |
| | *TANGO2* | Metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration | # 616878 |
| | *TK2* | Mitochondrial DNA depletion syndrome-2 (MTDPS2) | #609560 |