Glycogen Storage Disease V (McArdle Disease): **PYGM** Gene Sequencing

**Condition Description**

Myophosphorylase deficiency (or McArdle disease) is an autosomal recessive disorder caused by mutations in the myophosphorylase gene (**PYGM**) located on chromosome 11 (11q13). Patients experience exercise intolerance with premature fatigue, myalgias, and cramps that are exacerbated by exercise. A second wind phenomena is described in many patients and is characterized by an improved exercise tolerance after a brief reduction in the intensity of exercise or a brief rest. This response is mediated by an adaption to the substrate-limited oxidative phosphorylation by increased mobilization and delivery of free fatty acids to muscle as an energy source, increased blood flow, and increased glucose oxidation. About half of patients experience acute muscle necrosis and myoglobinuria after exercise. This rhabdomyolysis can produce acute renal failure.

Muscle weakness is present in approximately 33% of patients. The onset of exercise intolerance is often observed in childhood, but clinical ascertainment is usually in the second or third decade. Atypical variants of the disease may occur and be confined to complaints of easy fatigability without cramps or myoglobinuria. In some individuals, weakness may not be apparent until the seventh or eighth decade of life.

Serum creatine kinase is elevated in over 90% of patients with myophosphorylase deficiency. Forearm ischemic exercise testing produces essentially no increase in venous lactate. Muscle pathology often shows subsarcolemmal and intermyofibrillar vacuoles filled with glycogen. Histochemical staining for myophosphorylase activity is absent.

Three point mutations (**R49X**, **G204S**, and **K542T**) account for 71% of the McArdle disease alleles. For patients in whom only one or no mutations are identified through target testing, full sequence analysis can be used to detect the other mutation(s).

Please [click here](#) for the GeneReviews summary on this condition.

**Genes**

**PYGM**

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of myophosphorylase deficiency.
- Carrier testing in adults with a family history of myophosphorylase deficiency.

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient’s genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient’s gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Detection**

Clinical Sensitivity:

112 out of 112 mutations were found in 56 patients with McArdle disease through sequencing of the **PYGM** gene. In a second study, 68 out of 68 mutations were found in 34 patients with McArdle disease through sequencing of **PYGM**.

Analytical sensitivity: ~99%.

Mutations in the promoter region, some mutations in the introns and other regulatory element mutations, and large deletions cannot be detected by this analysis.

Results of molecular analysis should be interpreted in the context of the patient’s biochemical phenotype.

**References:**


**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood
Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

Special Instructions

Please submit copies of diagnostic biochemical test results along with the sample. Contact the laboratory if further information is needed.

Related Tests

- Myophosphorylase Deficiency (McArdle Disease): Targeted Mutation Testing (MA)
- Known Mutation Analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.