Adenosine Monophosphate Deaminase 1 (AMPD1) Deficiency: \textit{AMPD1} Gene Sequencing

\textbf{Condition Description}

Adenosine monophosphate deaminase 1 (AMPD1) deficiency, also known as myoadenylate deaminase (MADA) deficiency, is a disorder of purine metabolism that leads to a deficiency in the production of ATP. It is the most common enzyme deficiency identified in muscle, with a prevalence of almost 2\% in the general population. The typical age of presentation is late adolescence to early adulthood. Affected individuals have generalized exertional muscle pain, cramps and fatigue. Other presenting features include post-exertional myoglobinuria and rhabdomyolysis. Completely asymptomatic individuals have also been reported.

Serum creatine kinase (CK) is usually normal or only slightly elevated. Aerobic exercise testing is typically normal. Muscle histology is normal but muscle histochemistry shows reduced AMPD1 enzyme activity. AMPD1 deficiency is caused by mutations in the \textit{AMPD1} gene (1p21). AMPD1 deficiency is an autosomal recessive condition.

Two mutations, c.133C>T (p.Q45X, previously known as p.Q12X) and c.242C>T (p.P81L, previously known as p.P48L), account for the majority of reported mutations in Caucasians and African Americans. Full gene sequence analysis is also available for individuals with documented AMPD1 deficiency when no or one mutation identified by common mutation testing.

\textbf{Genes}

\textit{AMPD1}

\textbf{Indications}

This test is indicated for:

- Confirmation of a biochemical diagnosis of AMPD1 deficiency when common mutation testing identified no or one mutation
- Carrier testing in adults with a family history of AMPD1 deficiency when common mutation testing identified no or one mutation

\textbf{Methodology}

\textbf{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.

\textbf{Detection}

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: \textasciitilde99\%

\textbf{Specimen Requirements}

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

\textbf{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**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Common mutation testing for the two common *AMPD1* mutations is available and is recommended before *AMPD1* full gene sequencing.
- Deletion/duplication analysis of the *AMPD1* gene by CGH array is available for those individuals in whom sequence analysis is negative.
- A two-tiered rhabdomyolysis panel that includes testing for the two common *AMPD1* mutations is also available.
- Sequence and deletion/duplication analysis are available for the *AMPD3* gene.
- Custom diagnostic 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.