Danon Disease: **LAMP2** Gene Sequencing

**Condition Description**

Danon Disease is an X-linked disorder that can affect cardiac muscle, skeletal muscle, and mental retardation. Affected individuals have also been described with hypertrophic cardiomyopathy, proximal muscle weakness, hepatomegaly, peripheral pigmentary retinopathy, and elevated creatine kinase. Presentation can be variable even within a family. Affected individuals usually die in their teens or twenties due to heart failure; heart transplantation has been shown to be an effective treatment. Females have been reported to display symptoms of Danon disease, as well. Symptoms reported in affected females include skeletal myopathy, atrial fibrillation, mild left ventricular enlargement with systolic dysfunction on echocardiogram, pigmentary retinopathy, mild intellectual impairment, mental retardation, and death from cardiac disease. While cardiomyopathy in affected males occurs before the age of 20, most affected females develop cardiomyopathy in adulthood.

Mutations in the **LAMP2** gene (Xq24) have been associated with Danon disease. One study reported that the prevalence of Danon disease was 1% of patients with hypertrophic cardiomyopathy (2 of 197 patients). In this study, Danon disease was responsible for 50% of the cases of hypertrophic cardiomyopathy (CMH) with clinical skeletal myopathy (2 of 4 patients); none of the 41 patients with isolated CMH had Danon disease. In another study, genetic analyses of 24 subjects with increased left ventricular wall thickness and electrocardiogram suggesting ventricular preexcitation found 4 **LAMP2** mutations. Clinical features associated with defects in **LAMP2** included male sex, severe hypertrophy, early onset (at 8 to 17 years of age), ventricular preexcitation, and asymptomatic elevations of two serum proteins. Mutations in heterozygous state appeared to be responsible for unusual heart disease in some females.

Although this disorder was originally described as a variant of glycogen storage disease II due to accumulation of glycogen in muscle and lysosomes seen in some patients, acid alpha-glucosidase and other enzymes of glycogen metabolism are normal. Glycogen, however, is not always increased in affected individuals. The subsequent identification of the structural lysosome-associated membrane protein-2 gene as responsible for the disorder enabled the proper identification of Danon disease as resulting from a defect of the lysosomal membrane.

For patients with suspected Danon disease, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

**Genes**

**LAMP2**

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of Danon disease
- Carrier testing in adult females with a family history of Danon disease

**Methodology**

PCR amplification of 9 exons contained in the **LAMP2** gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

**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: ~99%

### Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

#### Type: Whole Blood

Specimen Requirements:

In EDTA (purple 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 EGL Genetics, please submit a copy of the sequencing report with the test requisition.

### Related Tests

- Deletion/duplication analysis of the **LAMP2** gene by CGH array is available for those individuals in whom sequence analysis is negative (YE).
- X-Linked Intellectual Disability panels are available for 30, 60, and 90+ genes.
- 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 adult females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.