Cincinnati Children's
Heart Institute

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LAMP2 Sequencing

Mutations in *LAMP2* cause Danon disease, a lysosomal glycogen storage disease with intracytoplasmic vacuoles containing autophagic material and glycogen in skeletal and cardiac muscle. Danon disease is clinically characterized by the triad of cardiomyopathy, myopathy, and variable degrees of mental retardation (1). The cardiomyopathy in Danon disease resembles hypertrophic cardiomyopathy, but is further characterized by progressive clinical deterioration with LV systolic dysfunction and enlarging cavity size leading rapidly to cardiac death in males (2). Patients also may have ECGs with increased voltages and Wolff-Parkinson-White pattern (2). Although skeletal myopathy and intellectual disability are key features, cases have been reported with cardiomyopathy as an isolated finding (2, 3, 4).

Danon disease is inherited in an X-linked manner. Nonsense, frameshift, and exon skipping mutations have been reported. *LAMP2* is located at Xq24 and contains 9 exons. Females may also develop cardiomyopathy, and less frequently have skeletal myopathy or mental retardation (3, 5). However, affected males typically develop cardiomyopathy which resembles HCM before age 20, while affected females may be more likely to develop DCM in adulthood (3).

Indication

Danon disease should be considered in individuals with a clinical presentation of cardiomyopathy, skeletal myopathy, and mental retardation with apparently X-linked inheritance. Cardiomyopathy has been shown to be the isolated finding in some patients with *LAMP2* mutations and sequencing may be indicated for patients with isolated cardiomyopathy, particularly those with a rapidly progressing clinical course. Males are expected to present with cardiomyopathy prior to age 20, while female carriers may present in adulthood.

Shipping Instructions

Please enclose a test requisition form with sample. All information must be complete before sample can be processed. Samples may be shipped at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship To:

Cincinnati Children's
Hospital Medical Center
Attn: Heart Institute Diagnostic Lab
240 Albert Sabin Way,
Room S4.381
Cincinnati, OH 45229-3039

Methodology:

All coding exons as well as the exon/intron boundaries and a portion of untranslated regions of the gene(s) are amplified by PCR. Genomic DNA sequences from both forward and reverse directions are obtained by automatic fluorescent detection using an *ABI PRISM® 3730 DNA Analyzer*. Sequence variants different from National Center for Biotechnology Information GenBank references are further evaluated for genetic significance. If a mutation is identified, a known familial mutation analysis will be available for additional family members.

Sensitivity & Accuracy:

Greater than 98.5% of the mutations in exons 1-9 of *LAMP2* are detectable by sequence based methods. Sequencing does not detect deletions or duplications in carrier females but may detect these changes in affected males.

References:

1. Nishino, I., Fu, J., Tanji, K., et al. (2000). Primary *LAMP-2* deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). *Nature*. 406: 906-910.

2. Maron, B.J., Roberths, W.C., Arad, M., et al. (2009). Clinical Outcome and Phenotypic Expression in *LAMP2* Cardiomyopathy. *JAMA*. 301(12): 1253-1259.

3. Sugie, K., Yamamoto, A., Murayama, K., et al. (2002). Clinicopathological features of genetically confirmed Danon disease. *Neurology*. 58: 1773-1778.

4. Arad, M., Maron, B.J., Gorham. J.M., et al. (2005) Glycogen Storage Diseases Presenting as Hypertrophic Cardiomyopathy. *The New England Journal of Medicine*. 352(4): 362-372.

5. Yang, Z., McMahon, C.J., Smith, L.R., et al. (2005). Danon Disease as an Underrecognized Cause of Hypertrophic Cardiomyopathy in Children. *Circulation*. 112: 1612-1617.

Specimen:

Peripheral blood in EDTA tube
Adult: 5-10mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact Amy Shikany at 513-803-3317

Turnaround Time:

Full Mutation Analysis 2-4 weeks
Known Mutation Analysis 1-2 weeks

CPT Codes:

Full Genome Sequencing	81405
Additional Family Members	81403