**Myofibrillar Myopathy, DES-related: DES Gene Deletion/Duplication**

**Condition Description**

The term myofibrillar myopathy refers to a group of genetically distinct disorders linked by common morphologic features observed on muscle histology. The predominant presenting symptom is slowly progressive weakness; a minority of individuals experience sensory symptoms, muscle stiffness, aching, or cramps. The weakness can involve both proximal and distal muscles; however, distal muscle weakness is 25% more common than proximal weakness. Peripheral neuropathy is present in about 20% of affected individuals. Overt cardiomyopathy is present in 15%-30%. Age of onset can vary from early childhood to the late seventies.

The diagnosis of myofibrillar myopathy is based on clinical findings, electromyography (EMG), nerve conduction studies, and, most importantly, muscle histology. Objective clinical signs or EMG findings of peripheral neuropathy are present in about 20% of affected individuals, but muscle biopsy studies suggest an even higher frequency of peripheral nerve involvement. Muscle histology reveals: (1) characteristic alterations in trichromatically stained frozen sections consisting of amorphous, hyaline, or granular material in a variable proportion of the muscle fibers; (2) sharply circumscribed decreases of oxidative enzyme activity in many abnormal fiber regions; (3) intense congophilia of many hyaline structures, best observed under rhodamine fluorescence optics; and (4) small vacuoles in a variable number of fibers. The combination of these findings points to the diagnosis of myofibrillar myopathy. Serum creatine kinase concentration can be normal or elevated to no greater than seven times the upper limit of normal.

To date, the genetic basis of myofibrillar myopathy has been elucidated in only a minority of cases. In one study of 80 unrelated individuals with myofibrillar myopathy, the genetic basis was established in 46% of affected individuals. Mutations have been identified in DES, the gene encoding desmin (8%); CRYAB, encoding alpha crystallin B chain (3%); TTID/MYOT, encoding myotilin (13%); LDB3 (ZASP), encoding LIM domain-binding protein 3 (14%); FLNC, encoding filamin C (4%); and BAG3, encoding Bag3 (4%). Myofibrillar myopathy may be inherited in an autosomal dominant manner. The inheritance pattern in some families cannot be determined because of the late onset of the disease in many affected individuals and because parents who are mildly affected heterozygotes may have deceased before becoming symptomatic for MFM.

This test is specific for the DES gene (2q35), also called desminopathy.

Desminopathies may present in the first decade of life, usually with cardiomyopathy. Variable expressivity has been observed in kinships with mutations in DES, with some family members showing signs of cardiomyopathy only, some showing signs of both myopathy and cardiomyopathy, and some with reduced penetrance who have signs of neither myopathy nor cardiomyopathy.

For patients with suspected desminopathy, 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**

**DES**

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of myofibrillar myopathy in individuals who have tested negative for sequence analysis

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region. Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**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**

- Sequence analysis of the *DES* gene is available and is required before deletion/duplication analysis.
- Analysis of the *TTID/MYOT* gene is also available.
- 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 individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.