Myofibrillar Myopathy, DES-related: DES Gene Sequencing

Test Code: SDESX
Turnaround time: 6 weeks
CPT Codes: 81479 x1

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%. A restrictive ventilatory defect can result from respiratory muscle weakness. 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 filament 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.

Click here for the GeneTests summary on this condition.

Genes

DES

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of myofibrillar myopathy

Methodology

PCR amplification of 9 exons contained in the DES 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: In one study of 80 unrelated individuals with myofibrillar myopathy, mutations in the DES gene were identified in 8% of affected individuals. 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

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* 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\textsuperscript{TM} 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.

**Related Tests**

- 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.