

Dynactin-Related Disorders via *DCTN1* Gene Sequencing (Test #382) Distal Hereditary Motor Neuronopathy, Type VIIB Perry Syndrome

Brief Description of Clinical Features: Distal hereditary motor neuronopathy type VIIB (HMNVIIB; OMIM #607641) is one of several disorders with hallmark features of slowly progressive distal motor neuronopathy without sensory loss. Onset is in childhood or young adulthood and initial signs often include weakness and wasting of extensor muscles of the lower extremities, followed by involvement of the upper limbs. Distal hereditary motor neuronopathy type VIIB is differentiated from other forms by findings of breathing difficulty due to vocal fold paralysis and progressive facial weakness. Use of sensory signs on physical examination to differentiate distal hereditary motor neuronopathy from Charcot-Marie-Tooth disease can be problematic because of variability in presentation of sensory loss. Therefore, electrophysiological studies are recommended (Irobi et al *Hum Mol Genet* 13:195-202, 2004). Perry syndrome (OMIM #168605) is a neuropsychiatric disorder with onset in the 5th decade of life. The earliest sign is depression not responsive to antidepressant drugs or electroconvulsive therapy (Perry et al. *Arch Neurol* 32:108-113, 1975). Other clinical presentations include sleep disturbances, exhaustion, and weight loss. Later in the course of disease parkinsonism and respiratory failure occur. Postmortem examination in a series of cases was remarkable for reduced taurine content and other neurochemical imbalances, and severe neuronal loss (Perry et al. *Neurology* 40:1882-1887, 1990). In other cases, however, normal brain taurine content has been reported (Purdy et al. *Ann Neurol* 6:523-531, 1979; Roy et al. *Neurology* 38:637-639, 1988).

Genetics: Distal hereditary motor neuronopathy, type VIIB and Perry syndrome are inherited as autosomal dominant disorders. Mutations in the gene encoding dynactin 1 (*DCTN1*; OMIM 601143) are the cause of both disorders. In the cases thus far reported, all mutations have resulted in amino acid substitutions.

Description of This Particular Test: Dynactin 1 is encoded by the *DCTN1* gene located on chr 2p13. Testing is accomplished by amplifying the 32 coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences: **Genomic:** NC_000002.10 **mRNA and Protein:** CCDS 1939.1

Indication for Testing: Individuals with clinical symptoms consistent with a distal neuropathy with unilateral or bilateral vocal cord paralysis; or individuals with parkinsonism, depression, weight loss, and central hypoventilation. Family history consistent with autosomal dominant inheritance.

Sensitivity of Test: *DCTN1* mutations have been found in fewer than ten families with either HMNVIIB or Perry syndrome, therefore clinical sensitivity cannot be estimated. Analytical sensitivity should be high because all *DCTN1* mutations reported to date or of the type expected to be detected by DNA sequencing of genomic DNA.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of *DCTN1*** **\$ 1690**

CPT Codes:

Sample Ascertainment x1	183890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x31	83898 \$ 560	Sequencing x31	83904 \$ 850
Separation x1	83894 \$ 110	Interpretation/Report x1	83912 \$ 100

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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