

**Heat Shock 22 kDa Protein-Related Disorders
 via *HSPB8* Gene Sequencing (Test #389)
 Charcot-Marie-Tooth Disease, Axonal, Type L
 Distal Hereditary Motor Neuronopathy, Type IIA**

Brief Description of Clinical Features: Charcot-Marie-Tooth disease type 2L (CMT2L; OMIM #608673) and distal hereditary motor neuronopathy type IIA (HMN2A; OMIM #158590) represent a phenotypic continuum of distal neuropathy with weakness and wasting starting in the distal limbs. In CMT2L distal sensory loss is evident while in HMN2A it is not, thus differentiating the two disorders (Irobi et al. *Nat Genet* 36:597-601, 2004). Among eighteen affected members of the first reported CMT2L family, clinical signs of lower limb weakness first appeared between 15 and 33 years of age (Tang et al. *Hum Genet* 114:527-533, 2004). Most affected individuals had symmetric muscle wasting and weakness of the distal lower limbs, absent or decreased deep tendon reflexes, and mild to moderate sensory loss. Upper limb weakness and wasting developed subsequent to lower limb involvement in one third of the patients. Most affected family members had high-arched feet. All affected elderly family members were severely affected, but none were wheelchair bound. Four families with exclusively lower motor neuron disease with *HSPB8* mutations have also been described (Timmerman et al. *J Neurol Sci* 109:41-48, 1992; Timmerman et al. *Hum Mol Genet* 5:1065-1069, 1996; Irobi et al. 2004). Disease onset is between 15 and 25 years of age and paresis of the great toe extensor muscles was found to be the presenting sign (Irobi et al. 2004). Foot extensor muscles are eventually affected and disease progression is rapid, culminating in paralysis of the distal muscles of the lower legs.

Genetics: A family demonstrating autosomal dominant inheritance of axonal type Charcot-Marie-Tooth disease (Tang et al. *Hum Genet* 114:527-533, 2004) was later found to have a missense mutation in the gene that encodes the heat shock 22 kDa protein (*HSPB8*, OMIM #608014; Tang et al. *Hum Genet* 116:222-224, 2005). Similarly, a small number of families with distal hereditary motor neuronopathy were also found to have *HSPB8* mutations (Timmerman et al. 1996; Irobi et al. 2004). *HSPB8*-related CMT and distal HMN are inherited as autosomal dominant disorders, and two missense mutations affecting the same amino acid residue (p.Lys141Asn and p.Lys141Glu) have thus far been identified.

Description of This Particular Test: The small 22 kDa heat shock protein is encoded by exons 1 – 3 of the *HSPB8* gene located on chr 12q24. Testing is accomplished by amplifying the 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_000012.11 mRNA: NM_014365.2
 Protein: NP_055180.1 mRNA and Protein: CCDS 9189.1

Indication for Testing: Individuals with clinical symptoms consistent with a distal neuropathy with or without distal sensory loss.

Sensitivity of Test: *HSPB8* is probably a rare cause of the axonal form of CMT and distal HMN.

Turn Around Time: Maximum of 40 days although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *HSPB8*, Exons 1-3: \$ 440

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x4	83898	\$100	Sequencing x4	83904	\$140
Separation x1	83894	\$ 50	Interpretation/Report x1	83912	\$ 80

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

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