

**Heat Shock 27 kDa Protein-Related Disorders
 via *HSPB1* Gene Sequencing (Test #387)
 Charcot-Marie-Tooth Disease, Axonal, Type F
 Distal Hereditary Motor Neuropathy, Type IIB**

Brief Description of Clinical Features: Charcot-Marie-Tooth disease type 2F (CMT2F; OMIM #606595) and distal hereditary motor neuropathy type IIB (HMN2B; OMIM #608634) represent a phenotypic continuum of distal neuropathy with weakness and wasting starting in the distal limbs. In CMT2F distal sensory loss is evident while in HMN2B it is not, thus differentiating the two disorders (Houlden et al. *Neurology* 71:1660-1668, 2008). Among affected members of the first reported CMT2F family clinical signs first appeared between 15 and 25 years of age (Ismailov et al. *Eur J Hum Genet* 9:646-650, 2001). Depressed or absent deep tendon reflexes were present early. Muscle weakness and atrophy of the lower leg resulted in foot drop and steppage gait. Later, atrophy of the upper limb muscles causing claw-hand deformity was evident, and mild to moderate sensory impairments occurred in the feet and hands in all the patients.

Genetics: A family demonstrating autosomal dominant inheritance of axonal type Charcot-Marie-Tooth disease (Ismailov et al. 2001), was later found to have a missense mutation in the gene that encodes the heat shock 27 kDa protein (*HSPB1*, OMIM #602195; Evgrafov et al *Nat Genet* 36:602-606, 2004). Subsequently, patients with distal hereditary motor neuropathy were found to have *HSPB1* mutations (Evgrafov et al. 2004). *HSPB1*-related CMT and distal HMN are inherited as autosomal dominant disorders although reports of recessive inheritance and *de novo* dominant mutations are known (Houlden et al. 2008).

Description of This Particular Test: The small 27 kDa heat shock protein is encoded by exons 1 – 3 of the *HSPB1* gene located on chr 7q11. 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_000007.13 mRNA: NM_001540.3
 Protein: NP_001531.1 mRNA and Protein: CCDS 5583.1

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

Sensitivity of Test: Among a cohort of 301 individuals with CMT and 115 with dHMN, Evgrafov et al (2004) found *HSPB1* mutations in 4 families with dHMN and one with CMT. Tang et al. (*Arch Neurol* 62:1201-1207, 2005) identified an *HSPB1* founder mutation (p.Cys379Thr) among a cohort of 114 unrelated Chinese CMT patients.

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 <i>HSPB1</i>, Exons 1-3:	\$ 390
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x3	83898 \$ 85	Sequencing x3 83904 \$125
Separation x1	83894 \$ 40	Interpretation/Report x1 83912 \$ 70

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

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