

**Glycyl tRNA Synthetase-Related Disorders
 via GARS Gene Sequencing (Test #383)
 Charcot-Marie-Tooth Disease, Type 2D
 Distal Hereditary Motor Neuronopathy, Type V**

Brief Description of Clinical Features: Charcot-Marie-Tooth disease type 2D (CMT2D; OMIM #601472) and distal hereditary motor neuronopathy type V (HMNV; OMIM #600794) represent a phenotypic continuum of distal neuropathy with weakness and wasting starting in the distal limbs, predominately the hands. In CMT2D distal sensory loss is evident while in HMNV it is not, thus differentiating the two disorders (Irobi et al. *Hum Mol Genet* 13:195-202, 2004; Sivakumar et al. *Brain* 128:2304-2314, 2005). Onset is usually between childhood and young adulthood and progression is slow. Early signs in many patients are transient cramping and pain in the hands after exposure to cold, and cramping in calf muscles following exertion (Goldfarb and Sivakumar GeneReviews, 2007). Denervation is evident by electromyography, although sensory motor nerve conduction potentials are normal (Ionasescu et al. *Hum Mol Genet* 5:1373-1375, 1996; Sivakumar et al. 2005).

Genetics: Charcot-Marie-Tooth disease, type 2D and distal hereditary motor neuronopathy, type V are inherited as autosomal dominant disorders. Mutations in the gene encoding glycyl tRNA synthetase (*GARS*; OMIM 600287) are the cause of both neuropathies (Antonellis et al. *Am J Hum Genet* 72:1293-1299, 2003). Variation in phenotypic expression exists between and within families. Most patients have an affected parent and the incidence of *de novo* mutations is not known. In the cases thus far reported, all mutations have resulted in amino acid substitutions.

Description of This Particular Test: Glycyl tRNA synthetase is encoded by the *GARS* gene located on chr 7p15. Testing is accomplished by amplifying the 17 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_000007.12 **mRNA and Protein:** CCDS 43564.1

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

Sensitivity of Test: *GARS* mutations have been found in less than ten families with either CMT2D or HMNV, therefore clinical sensitivity cannot be estimated. Analytical sensitivity should be high because all *GARS* 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 GARS** **\$ 940**

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x17	83898	\$290	Sequencing x17	83904	\$440
Separation x1	83894	\$ 60	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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