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DNM2 analysis for Charcot Marie Tooth Disease

Clinical Features:

Charcot Marie Tooth Disease is a group of inherited neuropathies characterized by chronic motor and sensory neuropathy resulting in progressive distal muscle weakness and sensory loss. Development of high-arched feet and loss of deep tendon reflexes is common. *DNM2*-associated CMT is characterized by evidence of axonopathy or combined evidence of myelinopathy and axonopathy with nerve conduction velocities that overlap CMT Types 1 and 2, suggesting that *DNM2* mutations can be associated with dominant intermediate CMT [OMIM#606482] or CMT2 (1, 2). Some individuals with *DNM2*-associated CMT caused by mutation of a specific amino acid also have subclinical neutropenia (3).

Inheritance:

CMT has a prevalence of 1 in 3,300, but mutations in *DNM2* are a rare cause of CMT. Thus far, only a few families with *DNM2*-associated CMT have been described, all with an autosomal dominant pattern of inheritance (2, 3). Recurrence risk is 50%.

Molecular Genetics:

CMT can be caused by mutations in a large number of genes, including *DNM2*. The *DNM2* gene [OMIM#602378], located at 19p13.2, encodes the dynamin 2 protein, a ubiquitously expressed GTPase primarily involved in endocytosis and membrane trafficking (4). The protein is composed of 5 different domains, including a pleckstrin homology (PH) domain. To date, fewer than ten CMT-associated mutations have been identified in the *DNM2* gene, all in the PH domain. Mutations identified thus far have been missense mutations or small deletions (2, 4). Mutations in *DNM2* have also been associated with dominant centronuclear myopathy [OMIM#606482].

Additional Resources:

Charcot Marie Tooth Association
700 Chestnut Street
Chester PA 19013-4867
Phone: 800-606-2682; 610-499-9264
Email: info@charcot-marie-tooth.org
http://www.charcot-marie-tooth.org/

European Charcot-Marie-Tooth Consortium
Department of Molecular Genetics
University of Antwerp
Belgium
Fax: 03 2651002
Email: gisele.smeyers@ua.ac.be

The Muscular Dystrophy Association
3300 E. Sunrise Drive
Tucson, AZ 85718
800-572-1717
http://www.mda.org/

The Hereditary Neuropathy Foundation
1751 2nd Ave Suite 103
New York NY 10128
Phone: 877-463-1287; 212-722-8396
Email: info@hnf-cure.org
www.hnf-cure.org

Test methods:

We offer mutation analysis of all 22 coding exons and intron/exon boundaries of *DNM2* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *DNM2* gene by oligonucleotide array-CGH to identify copy number changes involving one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Array-CGH will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Please send a completed DNM2- Clinical Checklist and patient consent form with each sample.

DNM2 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1560
CPT codes:	81406
Turn-around time:	4 weeks

DNM2 deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References:

1. Bird T. Charcot-Marie-Tooth Hereditary Neuropathy. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 1998.
2. Fabrizi GM, Ferrarini M, Cavallaro T et al. Two novel mutations in dynamin-2 cause axonal Charcot-Marie-Tooth disease. Neurology 2007: 69: 291-295.
3. Züchner S, Noureddine M, Kennerson M et al. Mutations in the pleckstrin homology domain of dynamin 2 cause dominant intermediate Charcot-Marie-Tooth disease. Nat Genet 2005: 37: 289-294.
4. Bitoun M, Maugenre S, Jeannet PY et al. Mutations in dynamin 2 cause dominant centronuclear myopathy. Nat Genet 2005: 37: 1207-1209.

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