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. DNMT2-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 DNMT2 mutations can be associated with dominant intermediate CMT [OMIM#606482] or CMT2 (1, 2). Some individuals with DNMT2-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 DNMT2 are a rare cause of CMT. Thus far, only a few families with DNMT2-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 DNMT2. The DNMT2 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 DNMT2 gene, all in the PH domain. Mutations identified thus far have been missense mutations or small deletions (2, 4). Mutations in DNMT2 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 DNMT2 by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the DNMT2 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 DNMT2- Clinical Checklist and patient consent form with each sample.
**DNM2 sequencing analysis**

- **Sample specifications:** 3 to 10 cc of blood in a purple top (EDTA) tube
- **Cost:** $1560
- **CPT codes:** 81406
- **Turn-around time:** 4-6 weeks

**DNM2 deletion/duplication analysis**

- **Sample specifications:** 3 to 10 cc of blood in a purple top (EDTA) tube
- **Cost:** $1000
- **CPT codes:** 81405
- **Turn-around time:** 4 weeks

**Testing for a known mutation in additional family members by sequence analysis**

- **Sample specifications:** 3 to 10 cc of blood in a purple top (EDTA) tube
- **Cost:** $390
- **CPT codes:** 81403
- **Turn-around time:** 3-4 weeks

**Prenatal testing for a known mutation by sequence analysis**

- **Sample specifications:** 2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
- **Cost:** $540
- **CPT codes:** 81403
- **Turn-around time:** 1-2 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:**


Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS’ NEEDS