CMT Type 2: Causes and Symptoms

[The following information about the various forms of type 2 CMT was compiled by CMTA Scientific Advisory Board Member Steven Scherer, MD, PhD, from the University of Pennsylvania. You can read the brief comments about the gene flaw which causes each type and the medical problems associated uniquely with that type. At the end, there is a comprehensive list of references from which the materials have been drawn.]

CMT2

CMT2 patients show little if any slowing in their nerve conductions, and biopsies show the loss of myelinated axons but little segmental demyelination/remyelination. Whereas the original descriptions of CMT2 identified patients affected at an older than typical CMT1 patients, the mutations that cause these late onset cases have proven difficult to identify. Rather, *MFN2* mutations, the commonest cause of CMT2 identified to date, cause an axonal neuropathy that mainly has an onset in childhood. All other types of CMT2 are rare; many more genetic causes remain to be discovered.

CMT2A1 (OMIM 118210)

A dominant mutation in *KIF1B*, the gene encoding kinesin1B a and b isoforms, has been identified in one (CMT2A1) kindred (Zhao et al., 2001). Kinesin1B is a molecular motor for orthograde axonal transport. Because mice that are heterozygous for a loss-of-function mutation develop neuropathy, and the mutation identified in this family causes loss-of-function, haplotype insufficiency is the likely basis of neuropathy.

The age of clinical onset ranged from 3 to 15 years. Weakness was confined to the lower legs, affecting the anterior/peroneal and posterior/tibial groups. The clinical electrophysiology on one 11-year-old boy showed an absent sural response, and length-dependent, chronic denervation. A sural nerve biopsy showed decreased numbers of myelinated axons.

CMT2A2 (OMIM 609260)

Dominant mutations in *Mitofusin 2* (*MFN2*) cause CMT2A2. Mitofusin 2 is localized in the outer membrane of mitochondria and is required for their normal fusion (Chen et al., 2003). This affects their function, as mitochondria isolated from cultured fibroblasts of CMT2A2 patients generate ATP less efficiently than those from normals.

Most *MFN2* mutations have been identified in individuals with a severe axonal neuropathy, with an onset in childhood (Verhoeven et al., 2006). These patients have more proximal weakness and atrophy than patients with CMT1, suggesting the term Severe Early Onset Axonal Neuropathy (Nicholson et al., 2008). Many patients with early onset become wheelchair-dependent. *MFN2* mutations have also been found in CMT2 patients with an onset in young adults, and penetrance may be variable even within a family. A few patients have optic neuropathies, myelopathy, and even cerebral dysfunction. Sensory and motor amplitudes are reduced or absent, and motor conduction velocities are normal or slowed to 37 m/s. Biopsies show loss of large myelinated axons and clusters of regenerated axons.

CMT2B (OMIM 600882)

Dominant mutations in *RAB7* cause CMT2B. *RAB7* is associated with late endosomes, including those that mediate retrograde axonal transport of growth factors. The mutations that cause CMT2

alter structure of the binding pocket for GDP and GTP binding, thereby increasing their on and off rates of binding; this could affect retrograde axonal transport (McCray et al., 2010).

Affected patients have length-dependent weakness and severe sensory loss, distal ulcerations in the feet are common, often leading to toe amputations. Electrophysiological studies and nerve biopsies provide evidence of axonal loss that is length- and time-dependent. Thus, CMT2B shares a similar clinical picture with HSAN1, although spontaneous pain is not a feature of CMT2B (Auer-Grumbach, 2008).

CMT2C (OMIM 606071)

Some dominant mutations in *TRPV4* cause CMT2C; these are distinct from other dominant mutations that cause developmental abnormalities in bone (OMIM 113500, 184252, 156530). TRPV4 is a cation channel that is found in many cell types, including axons. The dominant TRPV4 mutants may generate an abnormal channel that injures axons, thereby causing an axonal neuropathy (Landoure´ et al., 2010).

Patients are variably affected (Zimon et al., 2010). The most severely affected patients have severe proximal and distal weakness, including involvement of the vocal cords, even arthrogryposis and scoliosis. Sensory abnormalities are mild by comparison.

CMT2D (OMIM 601472)

Dominant mutations in *Glycyl-tRNA Synthase* (*GARS*) cause CMT2D. GARS encodes the enzyme that couples glycine to its tRNA. There is only one *GARS* gene, and it is expressed in every cell type and is presumed to be required for cellular function. How *GARS* mutations cause an axonal neuropathy is unknown.
Patients with CMT2D have a motor greater than sensory neuropathy, to the point that some cases (even belonging to the same family) have been considered have HMN V (Sivakumar et al., 2005). In the few reported cases, the onset varies from childhood to adolescence. The distinguishing feature of CMT2D is that the weakness of the intrinsic hand muscles is out of proportion to that in the distal legs, but this does not hold in cases with onset in childhood (James et al., 2006).

CMT2E (OMIM 162280)

Dominant mutations in *NEFL* cause CMT2E. *NEFL* encodes the smallest of the three subunits that comprise neurofilaments, which are the predominant cytoskeletal element in axons.

The age of onset and clinic phenotype vary considerably (Jordanova et al., 2003). In a large Russian kindred, clinical manifestations become apparent in the 2nd or 3rd decades, followed by slow progression, with mildly reduced or normal median motor conduction velocities (38-52 m/s). Other mutations cause an early onset (even a Déjérine-Sottas-like phenotype), and motor conductions can be slowed well into the demyelinating range; these patients have been referred to as CMT1F, but this is not a classic demyelinating neuropathy as nerve biopsies do not show abundant remyelinated axons. Rather, biopsies show loss of large myelinated axons, and the biopsies from the patients who have "demyelinating" mutations show abnormally enlarged axons containing disorganized groups of neurofilaments.

CMT2F (OMIM 606595)

Dominant mutations in *HSPB1* have been reported to cause CMT2F; other mutations produce a more purely motor phenotype, HMN IIb (see below). *HSPB1* encodes heat shock protein 27 kDa (HSP27), which is one of several small chaparone proteins with diverse cellular functions. HSP27 directly interacts with HSP22, which is affected in CMT2L (and HMN IIa).

The clinical onset of weakness ranges from the second to the fourth decade, followed by the development of prominent weakness in the distal muscles of the legs then arms.

CMT2G (OMIM 608591)
The gene for CMT2G is localized to 12q12-q13.3, based on the analysis of a single, large family with CMT2 (Nelis et al., 2004).

CMT2H (OMIM 607731)
CMT2H is based on a single, consanginous family in which affected members have a severe axonal neuropathy and myelopathy. It maps to the region of the *GDAP1* gene.

CMT2I (OMIM 606677) and CMT2J (607736)
Many different dominant mutations in *MPZ* cause a dominantly inherited axonal neuropathy that is sometimes referred to as CMT2-I, CMTJ, or CMT2-P0; the most common and well described of these is Thr124Met (De Jonghe et al., 1999). Individuals are clinically normal until at least young adulthood, then develop what has been often termed an "axonal neuropathy" at age 30-50. The neuropathy is often painful, and the weakness that can progress to the point that a wheelchair is needed; poorly reactive pupils and hearing loss complete the clinical pictures. Median/ulnar motor nerve conductions are typically show mild slowing (25-40 m/s) after the onset of disease, but this may be more related to axonal loss than de/remyelination. Biopsies show decreased numbers of myelinated axons and clusters of regenerated axons. CMT2I denotes families in which the pupillary findings and hearing loss are absent; these are present in families with CMT2J.

CMT2K (OMIM 607831)
Dominant mutations in *GDAP1* cause CMT2K. GDAP1 is a component of the outer mitochondrial membrane, and is required for normal fission (see section on CMT4A).

The clinical onset ranges from infancy to childhood, and weakness and sensory loss worsen with time. Motor conductions are not slowed.

CMT2L (OMIM 608673)
Dominant mutations in *HSPB8* cause CMT2L (Tang et al., 2005); other *HSPB8* mutations cause HMN IIa (see below). *HSPB8* encodes heat shock protein 22 kDa, which is one of several small chaparone proteins with diverse cellular functions. HSP22 directly interacts with HSP27, which is affected in CMT2F (and HMN IIb).

In the single kindred reported to date, the clinical onset of weakness ranged from 15 to 33 years. Weakness developed first in the muscles of the distal legs then in the distal arms.

CMT2M
This is an alternative name for DI-CMTB**.**

CMT2N (OMIM 613287)
Dominant mutations in *Alanyl TRNA Synthase* (*AARS*) cause CMT2N (Latour et al., 2010). *AARS* encodes the enzyme that couples alanine to its tRNA. *AARS* gene is expressed in every cell type and is presumed to be required for cellular function. How *AARS* mutations cause an axonal neuropathy is unknown.

AARS mutations have been described in two families. The neuropathy is quite variable – the age of clinical onset ranges from 10-54 years, and 3 individuals (ages 9, 30, and 50) are asymptomatic; even the clinical neurophysiology was normal for the two oldest. Other family members, in contrast, have weakness and sensory loss in their distal arms and legs; their median motor velocities range from 32 m/s to normal.

Hereditary Neuralgic Amyotrophy (OMIM 162100)
Hereditary Neuralgic Amyotrophy (HNA) is considered here because it is a non-syndromic axonal neuropathy, albeit with several unique features that set it apart from CMT2.

Dominant mutations in *SEPT9* cause HNA. SEPT9 is a member of a large family of filament-forming GTPases, members of which have diverse cellular functions (Hall and Russell, 2004). Point mutations have been found in some families, but owing to a founder effect, the most common mutation in North America is a 38 kB duplication, which includes the exon in which the point mutations are found (Landsverk et al., 2009). Transcripts from patients with the duplication contain two repeats of this exon.

Except for the younger age of onset and more frequent attacks, the clinical characteristics of patients with HNA is similar to patients with idiopathic neuralgic amyotrophy (van Alfen and van Engelen, 2006), which is a more common disease (and not caused by *SEPT9* mutations). Both groups of patients have attacks of severe pain in the neck, arm(s), and/or shoulder(s), followed by weakness and sensory loss in the distribution of the affected part of the brachial plexus. Any part of the brachial plexus and its related nerves can be affected, but there is a predilection for the upper part, and especially the long thoracic nerve. The clinical electrophysiology is consistent with an acute focal neuropathy, and biopsies suggest an inflammatory process that causes a vascular infarction of the affected nerve(s). Thus, *SEPT9* mutations likely cause neuropathy in a non-cell autonomous manner.

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