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Rare Diseases Clinical Research Network

Inherited Neuropathies Consortium

Information for Professionals
Charcot-Marie-Tooth disease - Advanced Description of Diseases
Charcot-Marie-Tooth disease (CMT) is the eponym for a group of non-syndromic inherited neuropathies that affect motor and sensory axons of the peripheral nervous system. It is also called Hereditary Motor and Sensory Neuropathy (HMSN), and in the older literature, Peroneal Muscular Atrophy. CMT is a common disease, with an estimated prevalence of 1/2500. Depending on which axons are affected (depending on the specific form of CMT), motor, sensory, and/or autonomic functions are progressively impaired. These impairments typically begin in the longest axons and progress over time, so that affected patients have weakness, sensory loss, and/or autonomic dysfunction first in the feet and lower legs, followed by the hands. The clinical onset may be as early as infancy or childhood or as late as middle age.
The genetics of CMT is complicated. Mutations in about 50 genes cause the various forms of CMT and the closely related conditions of Hereditary Motor Neuropathy (HMN) and Hereditary Sensory and Autonomic Neuropathy (HSAN). Two further complications are that different mutations in the same gene can cause different phenotypes, and that the same phenotype can be caused by mutations in different genes. A unifying principle is that both the dominantly (CMT1) and the recessively (CMT4) inherited forms of demyelinating CMT are caused by mutations in genes expressed by myelinating Schwann cells. Thus, a cell autonomous effect of the mutant gene in myelinating Schwann cells caused demyelination. Similarly, with a few potential exceptions, the dominantly (CMT2) and recessively inherited forms of axonal CMT, as well as the related conditions of HMN and HSAN, are caused by mutations in neuronally expressed genes; the mutant gene has cell autonomous effects in neurons.
Classifying Hereditary Neuropathies
Beginning with the pioneering work of Dyck and colleagues, CMT was separated into type 1 and type 2 (Shy et al., 2005). CMT1 is characterized by slowed conduction velocities in motor nerves (typically 10-40 m/s in the arms) and histological evidence of segmental demyelination and remyelination, in addition to axonal loss. These findings were extended by several groups, including Harding and Thomas (Harding and

Thomas, 1980), who proposed that forearm motor conduction velocities of 38 m/s separated CMT1/HMSN I from CMT2/HMSN II. Based on their analysis of patients of known genotypes, Kennerson et al. (Kennerson et al., 2001) suggested raising the cutoff to 45 m/s, and proposed using the term "Dominant-Intermediate CMT (DI-CMT)" for kindred characterized by conduction velocities that overlapped CMT1 and CMT2.

CMT1 is more common than CMT2, and the responsible mutation can be found in a much higher proportion of patients (>95% for CMT1 vs. ~25% for CMT2). Of the 968 CMT1 probands reported by Latour et al. (Latour et al., 2006), CMT1A resulting from *PMP22* duplication is by far the most common (76%), followed by CMT1X (11%) and CMT1B (6%); CMT1C (<1%), CMT1D (<1%), and CMT1A resulting from missense mutations (some forms are called CMT1E; <1%) are all relatively rare. CMT1 with an associated tremor is termed Roussy-Lévy syndrome; the original kindred has CMT1B, but it is more commonly associated with CMT1A (Thomas et al., 1997).

CMT3, Déjérine-Sottas Neuropathy, and Congenital Hypomyelinating Neuropathy are terms used to describe individuals with severe neuropathy with a clinically recognized onset in infancy (Congenital Hypomyelinating Neuropathy; OMIM 605253) or before three years of age (Déjérine-Sottas Neuropathy, also known as CMT3/HMSN III; OMIM 145900). Many patients ultimately require wheelchairs, but some do surprisingly well (Gabreëls-Festen, 2002). Scoliosis and hearing loss are frequent components of the clinical picture. Motor nerve conduction velocities are typically very slow (<10 m/s), with marked temporal dispersion but no conduction block. Nerves are often enlarged, and biopsies often reveal prominent "onion bulbs" (supernumerary Schwann cells that surround axons) and a complete absence of fibers containing normal/thick myelin sheaths; in most cases, axons have inappropriately thin myelin sheaths for the axonal caliber and/or are segmentally demyelinated. Historically, Déjérine-Sottas neuropathy was thought to be recessively inherited, but new, dominant mutations in *MPZ* and *PMP22* are the commonest causes (Tyson et al., 1997; Gabreëls-Festen, 2002); rarer causes include dominant mutations of *EGR2* as well as recessive mutations of *MPZ*, *PMP22*, *PRX*, *EGR2*, and *FIG4*. Because mutations have not been identified in some cases, other genetic causes remain to be discovered.

HSAN includes disorders that predominantly affects sensory and autonomic neurons and/or their axons. HMN includes various disorders that affect motor axons in a length-dependent manner. The apt term, "severe, early-onset axonal neuropathy", has been proposed for the forms of CMT that fit this description (Nicholson et al., 2008), including many cases caused by dominant *MFN2* mutations as well as several autosomal recessive forms of CMT2.

Please use the links in the right side menu: Each genetic disorder is discussed in groups.

Comments are based on the primary literature, as well as the following websites:

- OMIM (www.ncbi.nlm.nih.gov/sites/entrez?db=omim)
- Inherited Peripheral Neuropathies (www.molgen.ua.ac.be/CMTMutations)
- GeneTests (www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=cmt1)

I apologize for any mistakes or unclear statements, and for not referencing more

original papers. Please contact me with your questions, comments, and concerns (sscherer@mail.med.upenn.edu).

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HNPP and CMT1

Prior to the discovery of their common genetic origin, a relationship between Hereditary Neuropathy with Liability to Pressure Palsies (HNPP) and CMT1A had not been suspected because they are so clinically distinct. Deletion and duplication of *PMP22* cause HNPP and CMT1A, respectively (Shy et al., 2005). Two homologous DNA sequences flanking the *PMP22* gene are the molecular basis for its deletion/duplication: their high degree of homology promotes unequal crossing over during meiosis, which simultaneously generates both a deleted and a

duplicated *PMP22* allele. Although *de novo* mutations occur, most patients inherit their deletion or duplication. *PMP22* encodes peripheral myelin protein 22 kDa (PMP22), an intrinsic membrane protein of unknown function, and a component of compact myelin. Decreased and increased levels of PMP22 are thought to cause demyelination in HNPP and CMT1A, respectively.
HNPP (OMIM 162500)
HNPP is a dominantly inherited disease, probably at least as common as CMT1A, but many patients are unaware that they have a neuropathy unless they develop an episodic mononeuropathy, usually at one of the typical sites of nerve compression (Pareyson et al., 1996). In order of frequency, these are the peroneal nerve at the fibular head, the ulnar nerve at the elbow, the brachial plexus, the radial nerve at the spiral groove, and the median nerve at the wrist (Li et al., 2002). Other nerves may be affected, and atypical presentations have been described. Over half of the patients recover completely, usually within days to months, but deficits may persist. During the acute episodes of pressure palsies, electrophysiological studies may show conduction block.
In addition to focal changes at common sites of nerve entrapment, genetically affected individuals develop a mild, chronic, sensory and motor polyneuropathy. Sensory velocities are diffusely slowed, most distinctly in the upper extremities. Motor nerve conduction velocities are minimally slowed, but distal motor latencies are consistently prolonged, especially at sites prone to entrapment. Biopsies of unpalsied nerves show focal thickenings (tomacula) caused by folding of the myelin sheath, as well as segmental demyelination and remyelination.
Although deletion of *PMP22* is by far the commonest cause of HNPP, other *PMP22* mutations that also result in complete loss of function produce the same clinical picture.
CMT1A (OMIM 118220)
CMT1A is a dominantly inherited disease. The clinical onset is often said to occur in the first or second decade (Birouk et al., 1997; Thomas et al., 1997), but neuropathy can be detected clinically by age 5, and nerve conduction velocities are abnormally slowed even earlier. Affected patients have weakness, atrophy, and sensory loss in the distal legs followed by the distal arms; foot deformities and areflexia are variably present. There is considerable variability in the degree of neurological deficits within families, and even between identical twins, indicating that other factors modulate disease severity. Serial examinations of sensory and motor function worsen gradually (Shy et al., 2008). Atypical presentations are reported, including cranial nerve involvement, proximal weakness, diaphragmatic weakness, calf hypertrophy, and cramps.
Sensory responses are typically absent. Forearm motor conduction velocities are abnormally slowed, from 5-35 m/s; most average around 20 m/s. The lack of

conduction block or temporal dispersion, and the high correlation between the conduction velocities in different motor nerves, are hallmarks. Velocities are slow in children, even before the clinical onset of disease. In individual patients, the motor nerve conduction velocities remain constant over many years, whereas the motor amplitudes decrease, albeit slowly. Nerve biopsies evolve during the disease: demyelination is more prevalent in children, and "hypomyelinated" axons (remyelinated axons with myelin sheaths that are inappropriately thin for the axonal caliber) become relatively more numerous with age (Gabreëls-Festen et al., 1992). Biopsies also show age-related loss of myelinated axons; disability correlates with axonal loss (Krajewski et al., 2000).
Although duplication of *PMP22* is by far the commonest cause of CMT1A, a few *PMP22* mutations produce a similar clinical picture (that has been referred to as CMT1E). Most missense *PMP22* mutations, however, produce more severe neuropathy than CMT1A – CMT3/Déjérine-Sottas neuropathy (see below).
CMT1B (OMIM 118200)
Dominant mutations in *MPZ* cause CMT1B (Shy et al., 2004). *MPZ* encodes P0, the major protein of peripheral nerve myelin. P0 is an IgG-like adhesion molecule with a single intramolecular disulfide bond. P0 forms tetramers, which interact to form the molecular glue of compact myelin (Arroyo and Scherer, 2000).
More than 100 different *MPZ* mutations have been identified (Shy et al., 2004). A few mutations likely cause haplotype insufficiency from a simple loss-of-function; these are associated with an exceptionally mild phenotype. For most mutations, the clinical phenotype can be related to the degree of dys/demyelination as judged by conduction slowing and nerve biopsies – ranging from Congenital Hypomyelinating Neuropathy, to typical CMT1, to the exceptionally mild phenotypes noted above. In addition to causing loss of function, these mutations cause an abnormal gain of function; possibilities include a dominant-negative effect on the normal protein and an unfolded protein response (Pennuto et al., 2008). Mutations that result in unpaired cysteines are prone to cause a severe phenotype. About 25 mutations, however, have a peculiar clinical presentation – sometimes termed CMT2I, CMT2J, or CMT2-P0 (see below); the cellular basis of this phenotype remains to be determined. Most *MPZ* mutations causes an early onset, demyelinating neuropathy (that could often be labeled CMT3/Déjérine-Sottas neuropathy, although some patient have a favorable clinical course) or a late-onset phenotype (described below); few patients have a CMT1-like phenotype.
CMT1C (OMIM 601098)
Dominant mutations in *LITAF* cause CMT1C (Street et al., 2003). LITAF has been found to have several functional roles; how dominant *LITAF* mutations cause demyelination is unknown.
The clinical onset varies from 6-30 years. Affected patients have weakness and

sensory loss in a distal distribution. Motor nerve conductions are slowed (16-33 m/s) and nerve biopsies show remyelinated axons.
CMT1D (OMIM 607687)
Dominant mutations in *EGR2* cause CMT1D. *EGR2* encodes a transcription factor, EGR2/Krox20, which, along with Sox10, increases the expression of many myelin-related genes (Svaren and Meijer, 2008). Dominant Krox20 mutants probably cause demyelinating neuropathy because they reduce the activity of wildtype Krox20 on myelin gene expression.
EGR2 mutations are rare, and most cause a severe, demyelinating neuropathy - Déjérine-Sottas Neuropathy or Congenital Hypomyelinating Neuropathy. A few mutations, however, are associated with a milder/CMT1 phenotype. Affected individuals have weakness and sensory loss in their distal extremities; these findings worsen with age.
CMT1E (OMIM 118300)
OMIM considers CMT1E to be CMT1 and deafness, caused by a subset of dominant *PMP22* mutations, to be a distinct entity. Dr. Thomas Bird (see GeneTests website), has offered a more reasonable definition - that CMT1E is caused by a subset of *PMP22* mutations (besides the more common *PMP22* duplication) that result in a similar clinical picture to CMT1A.
CMT1F (OMIM 607734)
OMIM considers CMT1F to be CMT1 caused by autosomal dominant *NEFL* mutations. As discussed below (see CMT2E), this subset of *NEFL* mutations cause a severe, early-onset neuropathy with demyelinating features that are likely the result of a severe axonal pathology.
CMT1X (OMIM 302800)
CMT1X is so-named because it was linked to the X chromosome. Because female carriers are often affected, it is considered to be an X-linked dominant trait (Kleopa and Scherer, 2006). Mutations in *GJB1*, the gene that encodes connexin32 (Cx32), cause CMT1X; hundreds of different mutations have been identified. Cx32 forms gap junctions, which are channels on apposed cell membranes that permit the diffusion of ions and small molecules. Cx32 is localized to incisures and paranodal loops of myelinating Schwann cells, and likely forms gap junctions between adjacent layers of the myelin sheath. The loss of these gap junctions is thought to lead to demyelination and axonal loss - the chief pathological findings in humans and mice with *GJB1/Gjb1* mutations.
For affected males, the clinical onset is between 5 and 20 years of age. The initial symptoms include difficulty running and frequently sprained ankles, progressing to involve the gastrocnemius and soleus muscles to the point where assistive devices are required for ambulation. Weakness, atrophy, and sensory loss also develop in the hands, particularly in thenar muscles. These clinical manifestations are the result

of a chronic, length-dependent axonal loss, and are nearly indistinguishable from those seen in patients with CMT1A or CMT1B. However, muscle atrophy, particularly of intrinsic hand muscles, positive sensory phenomena, and sensory loss may be more prominent in CMT1X patients. Forearm median or ulnar motor velocities are typically in the range of 30-40 m/s (“intermediate”); sensory responses are typically absent except in young children.
Affected women usually have a later onset than men, after the end of second decade, and a milder version of the same phenotype at every age, because only a fraction of their myelinating Schwann cells express the mutant *GJB1* allele owing to the randomness of X-inactivation. Women may even be asymptomatic, and a few kindreds have been reported to have “recessive” CMT1X. Even in this kindred, however, at least some obligate carriers have electrophysiological evidence of peripheral neuropathy.
Many *GJB1* mutations appear to be associated with electrophysiological, clinical, and/or MRI findings of CNS involvement. Subclinical involvement is common: many patients have delayed brainstem auditory evoked responses (BAER), and central visual and motor pathways may also be affected. Because these electrophysiological findings have not been found in patients with a deleted *GJB1* gene, they may represent a gain of function. Clinical manifestations (spasticity, extensor plantar responses, and hyperactive reflexes) have been reported in patients with the some mutations; the degree of these findings may be masked by the peripheral neuropathy. More striking CNS findings have been reported in individual patients with duplication of amino acids 55-61 (cerebellar ataxia and dysarthria) or the Val63Ile mutation (mental retardation), but the relationship of these abnormalities to *GJB1* mutations is unproven. Acute, transient encephalopathy associated with MRI changes suggesting CNS myelin dysfunction have been described; the acute deficits appear to have been triggered by travel to high altitudes, fever, or strenuous physical activity (Taylor et al., 2003).

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CMT2
CMT2 patients show little if any slowing in their nerve conduction, 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. On the contrary, *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 kinesin-1B a and b isoforms, has been identified in one (CMT2A1) kindred (Zhao et al., 2001). Kinesin-1B 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 normal individuals.
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 (Landouré 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 rather than a sensory neuropathy, to the point that some cases (even belonging to the same family) have been considered to 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 the heat shock protein 27 kDa (HSP27), which is one of several small chaperone proteins with diverse cellular functions. HSP27 directly interacts with HSP22, which is involved 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, consanguineous 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 CMT2I, CMT2J, 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, and 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 picture. Median/ulnar motor nerve conductions typically show mild slowing (25-40 m/s) after the onset of disease, but this may be more related to axonal loss rather 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 the heat shock protein 22 kDa, which is one of several small chaperone proteins with diverse cellular functions. HSP22 directly interacts with HSP27, which is involved 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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http://rarediseasesnetwork.epi.usf.edu/INC/professional/disorders/Dominant-IntermediateCMT/

Dominant-Intermediate CMT
Because motor conduction velocities are a traditional mean to classify CMT patients, Davis et al. (Davis et al., 1977) proposed the term “dominant-intermediate” for patients with dominantly inherited CMT and median motor conduction velocities between 25-45 m/s, which likely included some CMT1X kindreds. Kennerson et al. (Kennerson et al., 2001) adopted this term to accommodate families in which there is uncertainty regarding whether the neuropathy is primarily axonal or demyelinating because affected members have “intermediate” conduction velocities (25-54 m/s in their index family). Note that CMT1X (which is clearly a demyelinating neuropathy in animal models) fits this description, is not usually classified as a DI-CMT. Many families with CMT1B could also be classified as DI-CMT, but this is usually not done, as the wide range of phenotypes caused by dominant *MPZ* mutations is well described. Similarly, some families with CMT2E, CMT2N, and likely others, could be classified as DI-CMT.
DI-CMTA (606483)
A single family defines this entity, which has been mapped to 10q24.1-q25.1 (Verhoeven et al., 2001). The clinical onset of weakness is before 10 years, and median nerve motor conduction velocities range from 25-45 m/s.
DI-CMTB (OMIM 696482)
Some dominant mutations in *Dynamin 2* (*DNM2*) cause DI-CMTB; these are distinct from other dominant mutations that cause centronuclear myopathy. Dynamin 2 is a GTPase that is required for endocytosis and other cellular functions; it is an essential enzyme and is expressed in all cells. How dominant mutations cause a neuropathy is unknown.
In six kindreds, the age of onset varied from 2-51 years (Claeys et al., 2009).

Patients showed progressive, distal weakness and sensory loss that is typical of CMT; in some kindred progression was marked and patients became wheelchair-dependent. Median motor conduction velocities range from 25 m/s to normal (>50 m/s); sensory responses were relatively preserved. Sural nerve biopsies show loss of myelinated axons and clusters of regenerated axons. Teased fibers from one kindred showed shortened myelin internodes; this would be expected to decrease conduction velocity. Two families had associated neutropenia and one family had unusual cataracts.
DI-CMTC (OMIM 608323)
Dominant mutations in *Tyrosyl-tRNA Synthase* (*YARS*) cause DI-CMTC. YARS catalyzes the aminoacylation of tyrosine to its tRNA. It is an essential enzyme and is expressed in all cells. How dominant mutations cause a neuropathy is unknown.
Two families have been described (Jordanova et al., 2003). In one, the onset is in the first to second decades, with progressive development of weakness and sensory loss in distal extremities. The median motor response ranged between 30-40 m/s. Sural nerve biopsies showed aged-related loss of myelinated axons and clusters of regenerated axons. In the other, the onset was between 7 and 59 years, with weakness confined to the distal legs; the median motor velocity ranged from 33 m/s to normal.

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CMT4
Recessively inherited, demyelinating neuropathies are called CMT4 (Parman et al., 2004; Vallat et al., 2005). All cause a severe neuropathy; many patients ultimately require wheelchairs. CMT4A/*GDAP1* mutations and CMT4C/*SH3TC2* mutations appear to be the most common. CMT4F has more sensory involvement than the other forms; CMT4B1, CMT4B2, and CMT4C have distinctive pathological findings. Except for periaxin, many other cell types express the genes associated with CMT4; myelinating Schwann cells express all of the genes associated with CMT4, so that demyelination is cell autonomous.
CMT4A (OMIM 214400)
Recessive mutations in *GDAP1* cause CMT4A. GDAP1 is a protein that is localized in the outer membrane of mitochondria, and is required for normal fission (Niemann et al., 2005).
Although some recessive *GDAP1* mutations cause milder phenotypes, individuals with CMT4A have an early onset (typically by age 2), progressive neuropathy that results in severe proximal and distal weakness, and may cause inability to walk and vocal cord paresis (Bouhouche et al., 2007). Sensory nerve responses are absent, and motor nerve responses show variable degrees of slowing. Biopsies show a marked loss of myelinated axons, and occasional rudimentary onion bulbs. Other *GDAP1* mutations cause dominant axonal CMT (CMT2K) or recessive axonal neuropathy (AR-CMT2C/CMT2B3). Because definite evidence that recessive *GDAP1* mutations cause a demyelinating neuropathy is lacking, CMT4A may be a misnomer.
CMT4B-1 (OMIM 601382) and CMT4B-2 (OMIM 604563)
Recessive mutations in *MTMR2* and *MTMR13* cause CMT4B-1 and CMT4B-2, respectively (Previtali et al., 2007). MTMR2 and MTMR13 form a tetramer in which MTMR2 requires the “dead” phosphatase MTMR13 to dephosphorylate the 3’ phosphate of PI(3)P and PI(3,5)P2, which tag vesicles and organelles to coordinate membrane traffic and homeostasis. The MTMR2 and MTMR13 mutants associated with CTM4B do not function, and mice with homozygous targeted genetic alterations of *Mtmr2* or *Mtmr13* confirm that loss of function causes demyelination. The ablation of *Mtmr2* in Schwann cells alone is sufficient to cause demyelination, but it remains to be determined why this occurs.
For CMT4B1, the clinical onset was between 2 and 3 years, with difficulties walking. Distal weakness and sensory loss worsens to the point that patient stop deambulating independently by their 20s. Facial, bulbar, and diaphragmatic involvement often develop. Early in the disease, sensory responses are absent or reduced, and median motor nerve conductions are slowed, 15-20 m/s. Nerve biopsies show a loss of myelinated axons, and an outfolding of the myelin sheaths is a prominent feature in all but one of the reported cases of CMT4B1.
For CMT4B2, the clinical onset occurs by age 10, with difficulties walking. Distal weakness and sensory loss worsens to the point that patients stop ambulating independently between 10-43 years. Early in the disease, sensory responses are absent or reduced, and median motor nerve conductions are slowed, 16-21 m/s. Nerve biopsies show reduced numbers of myelinated axons, and an outfolding of the

myelin sheaths. Early-onset glaucoma and hearing loss are additional features in some families.
CMT4C (OMIM 601596)
Recessive mutations in *SH3TC2* cause CMT4C. SH3TC2 is an effector of Rab11, which regulates recycling endosomes. SH3TC2 mutants do not interact with Rab11, resulting in reduced endosomal recycling, which thus appears to be required for normal myelination (Roberts et al., 2010). Why myelinating Schwann cells are selectively affected, whereas *SH3TC2* is widely expressed, remains unexplained.
The clinical onset is typically in childhood, but onset in the 30s has been reported. The degree of weakness is similarly variable, and slow progression is the usual course. Some patients become wheelchair-dependent. Scoliosis is a frequent feature of CMT4C, and various cranial neuropathies have been noted in some patients. Sensory responses are absent and motor nerve conduction velocities in the arms range from 14-34 m/s with reduced amplitudes. Nerve biopsies show reduced numbers of myelinated axons, onion bulbs (that may mostly be comprised of basal lamina) and a peculiar ensheathment of unmyelinated axons.
CMT4D (OMIM 601455)
Recessive mutations in *NDRG1* cause CMT4D. NDRG1 belongs to the superfamily of a/b hydrolases, but the crucial catalytic residues are not present. Myelinating Schwann cells, but not neurons, express NDRG1 (Berger et al., 2004), but its function in myelinating Schwann cells is unknown.
CMT4D has mainly been found in the Roma population (Kalaydjieva et al., 1998); a founder effect causes a common mutation. It clinical presents as a gait disorder between 2-10 years, followed by difficulty using the hands, with commensurate atrophy. Sensation is reduced in distal extremities. Impaired hearing is common, and scoliosis is often noted. Motor conductions are ~10 m/s, and sensory responses are absent. Biopsies show reduced numbers of myelinated axons and prominent onion bulbs.
CMT4E (OMIM 605253)
Recessive mutations in *EGR2* cause CMT4E. *EGR2* encodes a transcription factor, EGR2/Krox20, which, along with another transcription factor, Sox10, increases the expression of many myelin-related genes. A single kindred has been found to date, in which three siblings have a severe demyelinating neuropathy (diagnosed as Congenital Hypomyelinating Neuropathy) caused by a homozygous Ile268Asn mutation (Warner et al., 1998). The affected children were floppy at birth and had delayed motor milestones. Motor amplitudes were extremely low or absent, and conduction velocity was 3 m/s. A biopsy revealed markedly reduced numbers of myelinated axons. Mice that are homozygous for the Ile268Asn mutation also fail to myelinate, presumably because this EGR2 mutant fails to interact with a Nab2, a transcriptional co-activator (Baloh et al., 2009).
CMT4F (OMIM 145900)
Recessive mutations in *PRX* cause CMT4F. *PRX* encodes periaxin, a cytoplasmic protein that is expressed exclusively in myelinating Schwann cells. Along with DRP2, periaxin appears to be part of a complex that interacts with the dystroglycan complex. *Prx*-null mice have disrupted cytoplasmic channels on the outside of the myelin sheath (called Cajal bands); this may slow intracellular transport and result in

abnormally short myelin internodes (and consequently, slowed conduction; (Court et al., 2004), but how this leads to demyelination remains to be proved.
Most affected individuals have delayed motor development, with distal leg weakness and atrophy developing by age 10 and hand weakness by age 15, followed by continued slow progression. In addition, patients may have a sensory ataxia and distal paresthesias. Sensory and motor responses are often absent; when the motor response is present, conduction velocity is extremely slowed (2-3 m/s). Nerve biopsies show a severe depletion of myelinated axons, as well as onion bulbs. Some milder cases (homozygous for either a Arg715stop or a Arg1070stop mutation) have also been reported: affected patients also have an early onset gait disorder, but slower progression, preserved motor responses in the arms, and faster motor conduction velocities (10-20 m/s). The milder effects of these mutations may owe to the preservation of the short isoform of periaxin; mutations that cause the more severe phenotype affect both the short and the long isoforms.
CMT4G (OMIM 605285)
CMT4G is the name given to CMT-Russe in OMIM. It is an autosomal recessive neuropathy that is mostly found in the Roma. It has been mapped to 10q23.2. Weakness in the distal legs is noted between 8-16 years, progressing with age to nearly complete paralysis of the legs accompanied by foot deformities. Hand weakness begins in the early 20s, and progresses with age. Sensory nerve responses are absent and median motor conduction velocities average 33 m/s, without prolonged distal latencies. Sensory nerve biopsies show loss of large myelinated axons, and remarkable numbers of clusters of regenerated axons (Thomas et al., 2001). CMT4G appears to be misclassified: it has more features of a primary axonal neuropathy than a primary demyelinating neuropathy.
CMT4H (OMIM 609311)
Recessive mutations in *FGD4* cause CMT4H (Delague et al., 2007; Stendel et al., 2007). *FGD4* encodes frabin, a widely expressed guanine nucleotide exchange factor (GEF) for Cdc42, one of the small rhoGTPases (including Rac1 and RhoA) that regulate cellular morphogenesis, including myelination. Because the GTP-bound form of Cdc42 is active, loss of frabin function is predicted to decrease Cdc42 activity. The milder demyelination seen in CMT4H than in Cdc42-null nerves (in mice) suggests Cdc42 has other GEFs. Further support for the role of RhoGTPases in myelination is the identification of a mutation in another GEF, *ARHGEF10*, in an autosomal dominant, asymptomatic syndrome of slowed NCVs and modestly thinner myelin sheaths (Verhoeven et al., 2003).
Patients were clinically affected in the first decade, even as infants, with severe distal weakness and sensory loss. Progression is slow. Severe scoliosis may be present. Sensory responses are absent, and motor responses in the arms show marked slowing (<13 m/s). Biopsies show severe loss of myelinated axons, and myelin outfoldings that are reminescent of those seen in CMT4B1 and CTM4B2.
CMT4J (OMIM 611228)
Recessive mutations in *FIG4* cause CMT4J (Chow et al., 2007). FIG4 encodes a PI(3,5)P2 5' phosphatase. Like MTMR2/13, FIG4 is a phosphatase, but it forms a complex with Vac14 and Fab1 kinase that ultimately activates PI(3,5)P2 production. Thus, loss of FIG4 or Vac14 function produces less, not more, PIP2 in yeast and

vertebrate cells – the opposite of what is expected in CMT4B1 and CMT4B2. In addition to its distinct clinical phenotype, it is suspected that neuronal abnormalities contribute to the clinical phenotype. *Fig4*-deficient and *Vac14*-null mice have a widespread neuronopathy (including sensory and motor neurons) with characteristic intracellular vacuoles. Nevertheless, there is compelling evidence of demyelination in some patients with compound heterozygous *FIG4* mutations that produce partial loss of function in yeast, and in mice with homozygous *Fig4* mutations, but the contribution of the demyelination to the clinical picture is unclear.
At least some cases of CMT4J are clinically distinctive from CMT, with abrupt declines of strength, and an electrophysiological appearance of a motor neuronopathy. Sensory symptoms are absent and signs are minimal (Zhang et al., 2008). In keeping with this motor predominant picture, other *FIG4* mutations cause motor neuron disease (Chow et al., 2009).

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http://rarediseasesnetwork.epi.usf.edu/INC/professional/disorders/AR-CMT2/

AR-CMT2: Autosomal Recessive Axonal Neuropathy (or CMT2B1-5)
These are all rare disorders; most have been found in just a few families. The term, "severe, early-onset axonal neuropathy" (SEOAN), describes well the individuals with AR-CMT2C/CMT2B3, AR-CMT2D/CMT2B4, and AR-CMT2E/CMT2B5.
AR-CMT2A/CMT2B1 (OMIM 605588)
Recessive mutations of *LMNA* cause AR-CMT2A/CMT2B1. LMNA encodes a component of the nuclear envelope, and dominant *LMNA* mutations are associated with a variety of syndromes.
Most affected individuals are from north Africa, where the Arg298Cys mutation is common (Tazir et al., 2004). For this mutation, the clinical age of onset typically ranges from 12 to 24 years. Progression can be strikingly rapid: forearm muscles may be affected within months after onset, and pelvic girdle weakness within 4 years. Some patients, however, do not progress to have proximal limb involvement. Electrophysiological studies are fully consistent with an axonal neuropathy affecting myelinated motor and sensory axons.
AR-CMT2B/CMT2B2 (OMIM 605589)
Recessive mutations in *MED25* cause AR-CMT2B/CMT2B2 (Leal et al., 2009). MED25 is a subunit of the human activator-recruited co-factor, whose role in neuron biology remains to be determined.
Affected individuals had clinical onset between 28 and 42 years, and developed weakness and atrophy in the distal muscles of the arms and legs, as well as distal sensory loss. Sensory nerve responses were typically absent, and motor conductions showed variable degrees of slowing.
AR-CMT2C/CMT2B3 (no OMIM)
Recessive mutations in *GDAP1* cause AR-CMT2C/CMT2B3, although this has yet to be officially recognized in OMIM (and given a number). GDAP1 is a protein that is localized to the outer membrane of mitochondria, and is required for normal fission (Niemann et al., 2005).
Although some recessive *GDAP1* mutations cause milder phenotypes, individuals with AR-CMT2C/CMT2B3 have an early onset (typically by age 2), progressive neuropathy that results in severe proximal and distal weakness, and may cause inability to walk and vocal cord paresis (Bouhouche et al., 2007). Sensory nerve responses are absent, and motor nerve responses show variable degrees of slowing. Other *GDAP1* mutations cause dominant axonal CMT (CMT2K). Whether other recessive *GDAP1* mutations truly cause a primary, demyelinating neuropathy (CMT4A) needs to be clarified.
AR-CMT2D/CMT2B4 (no OMIM)
Recessive mutations in *MFN2* cause AR-CMT2C/CMT2B4 (Nicholson et al., 2008), although this has yet to be officially recognized in OMIM (and given a number). MFN2 is a protein that is localized in the outer membrane of mitochondria, and is required for normal fusion (see section on CMT2A2).
The clinical onset is by age 3, and the neuropathy progresses to cause profound

distal weakness, atrophy, and sensory loss. Sensory responses are absent and motor responses are minimally slowed.
AR-CMT2E/CMT2B5 (no OMIM)
Recessive mutations in *NEFL* cause CMT2B5 (Yum et al., 2009), although this has yet to be officially recognized in OMIM (and given a number). *NEFL* encodes the light subunit, one of three subunits that comprise neurofilaments, which are the predominant cytoskeletal element in axons.
The neuropathy can be clinically detected before age 2, with hypotonia and delayed motor milestones. Weakness and sensory loss progress through childhood, leading to severe distal and even proximal weakness and sensory loss. The sensory nerve responses disappear during childhood, and the motor and sensory responses are slowed well into the demyelinating range (~20 m/s). Nerve biopsies show no large myelinated axons, and axons lack neurofilaments. Based on the analysis of mice and quail that have recessive *Nefl* mutations, the likely basis of slowed conduction is that the myelinated axons fail to enlarge normally during development; it is not a true demyelinating neuropathy.
Giant Axonal Neuropathy (OMIM)
Recessive mutations in *Gigaxonin* (*GAN*) cause giant axonal neuropathy (Bomont et al., 2000). Gigaxonin is required for the ubiquitination and degradation of microtubule-associated protein 1B light chain (Yang et al., 2007).
Originally, patients with Giant Axonal Neuropathy were described as having a childhood onset of an axonal neuropathy, with associated upper motor neuron and cerebellar findings, and kinky hair. Some patients, however, have a much milder disease, with few clinical CNS findings, so this disorder is discussed here. Electrophysiology demonstrates distal axonal loss, and nerve biopsies reveal the characteristic finding of enlarged axons containing large bundles of neurofilaments (Yang et al., 2007).

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http://rarediseasesnetwork.epi.usf.edu/INC/professional/disorders/CMT-X-linked/

X-linked forms of CMT
There are six X-linked hereditary neuropathies. CMT1X is demyelinating neuropathy, and is discussed above. X-linked HMN associated with *ATP7A* mutations (no OMIM) is discussed below.
CMTX1 (OMIM 302800)
This is an alternative name for CMT1X. The name CMT1X indicates that this is a demyelinating, non-syndromic neuropathy.
CMTX2 (OMIM 302801)
CMTX2 maps to Xp22.2 and is associated with mental retardation. Because the neuropathy is overshadowed by other elements of this syndrome, it is incorrect to view this disorder as a form of CMT.
CMTX3 (OMIM 302802)
CMTX3 maps to Xq26-q28. The original kindreds had associated mental retardation and spasticity, but another did not (Huttner et al., 2006). Affected men have length-dependent chronic denervation, beginning in the legs in the first decade; the hands are affected later. Pain and paresthesias often precedes sensory loss and intermediate conduction slowing (25-57 m/s). Sensory responses were typically absent. Women may be mildly affected.
CMTX4 (OMIM 310940)
CMTX4 (or Cowchock syndrome) maps to Xq24-q26 is characterized by neuropathy, hearing loss and mental retardation. Because of the syndromic nature of this disorder, it is incorrect to view this disorder as a form of CMT.
CMTX5 (OMIM 301070)
CMTX5 is one of a number of syndromes associated with mutations in *PRPS1* (de Brouwer et al., 2010), and is associated with deafness and optic neuropathy (Kim et al., 2007). Because of the syndromic nature of this disorder, it is incorrect to view this disorder as a form of CMT.

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http://rarediseasesnetwork.epi.usf.edu/INC/professional/disorders/HSAN/

Hereditary Sensory and Autonomic Neuropathies (HSAN)
In HSAN, sensory (and variably autonomic) neurons and/or axons are affected. Motor neurons/axons are relatively or completely spared, except in HSAN1. With the likely exception of *NGFB*, the mutant genes are expressed by neurons and probably have cell autonomous effects. Diminished sensation of pain is common to all of these diseases, with the horrible consequences of delayed healing, Charcot arthropathies, infections, osteomyelitis, and amputations. Not all causes of altered pain sensation and/or autonomic function, however, are associated with neuropathy. Recessive mutations in *SCN9A*, which encodes the voltage-gated Na^+ channel, Nav1.7, cause the absence of pain but not neuropathy (Congenital Indifference to Pain; OMIM 253000). Primary Erythermalgia (OMIM 133020, caused by dominant mutations in *SCN9A*), Paroxysmal Extreme Pain Disorder (OMIM 167400, caused by dominant mutations in *SCN9A*), Cold-Induced Sweating 1 (OMIM 272430, caused by recessive mutations in *CRLF1*), and Cold-Induced Sweating 2 (OMIM 610313, caused by recessive mutations in *CLCF1*), are not listed because an associated neuropathy is not adequately documented. HSAN associated with spastic paraplegia (OMIM 256840, caused by recessive mutations in *CCT5*), is not listed because it is a syndromic condition. Because mutations in these genes have been found only in ~20% of affected patients, many causes remain to be discovered (Rotthier et al., 2009). Altogether, HSAN is the rarest kind of hereditary neuropathy; HSAN1, 3, and 4 appear to be the most common.
HSAN1 (OMIM 162400)
Dominant mutations in *SPTLC1* cause HSAN1 (Dawkins et al., 2001). *SPTLC1* encodes serine palmitoyltransferase long chain subunit 1, the enzyme that catalyzes the condensation of serine and palmitoyl-CoA, which is the first and rate-limiting step in the *de novo* synthesis of ceramide. Mutants may allow other amino acids to be incorporated in place of serine (Eichler et al., 2009), but how this results in neuropathy remains to be determined.
According to Auer-Grumbach (Auer-Grumbach, 2008), “the main and consistent feature […] is the reduction of sensation sense which is mainly distributed to the distal parts of the upper and lower limbs.” The onset varies between the second and fifth decades, with chronic progression. As the disease progresses, loss of pain sensation gives way to unheeded injuries, which can result in osteomyelitis and even amputation. Spontaneous fractures and Charcot joints further complicate matters. Length-dependent weakness caused by motor axon loss is a later feature. HSAN1 shares a similar clinical picture with CMT2B, except that some HSAN1 patients experience spontaneous pain. Electrophysiological studies document loss of sensory and motor axons in a length- and time-dependent manner; some patients have demyelinating features (Houlden et al., 2006). Nerve biopsies confirm these electrophysiological findings, and autopsies show marked loss of sensory neurons.
HSAN2A (OMIM 201300)
Recessive mutations in *WNK1* cause HSAN2. WNK1 is a member of the family of With No Lysine Kinases, and regulates the function of ion channels and transporters in a

variety of cell types, and presumably in neurons/axons, too. Although a global deletion of *WNK1* may be lethal, a neuronal-only loss of WNK function caused by mutations in one exon that is mainly expressed by PNS neurons causes HSAN2A (Shekarabi et al., 2008).
A progressive loss of sensation, including pain, begins in childhood, and may culminate in ulcers, osteomyelitis, and amputation. Overt autonomic dysfunction is not seen. Sensory responses are absent, whereas motor responses are normal, and sensory nerve biopsies show severe loss of myelinated and unmyelinated axons.
HSAN2B (OMIM 613115)
Recessive mutations in *FAM134B* cause HSAN2. *FAM134B* encodes a protein of the cis-Golgi, and is strongly expressed in sensory, autonomic, and CNS neurons (Kurth et al., 2009).
Impaired sensation, mutilating ulcers, and arthropathy begins in childhood. Nerve conductions and biopsies appear to show a loss of sensory axons in a length-dependent manner.
HSAN3/Familial Dysautonomia/Riley-Day Syndrome (OMIM 223900)
Recessive mutations in *IKBKAP* cause HSAN3. Most patients are homozygous for a mutation in a donor splice site; this causes a cell type specific reduction in the levels of IKBKAP protein. IKBKAP is a component of the Elongator complex, which has diverse cellular functions, including the acetylation of microtubules (which increases their stability) and neuronal maturation (Creppe et al., 2009).
HSAN3 is almost exclusively found in individuals of Eastern European Jewish extraction, 1/30 are heterozygous for the donor splice site mutation (Axelrod and Gold-von Simson, 2007). HSAN3 can be recognized in infants, who have hypothermia, swallowing problems, lack of tearing, postural hypotension, lack of fungiform papilla, absent deep tendon reflexes, and absent flare response to intradermal histamine. Gastrointestinal dysmotility and aspiration are common, and episodes of vomiting or hypertension can be disabling. The loss of pain sensation is not as great as in other forms of HSAN; trophic ulcers, osteomyelitis and amputations appear to be less common, too, but Charcot arthropathies and unrecognized fractures are problems. Serial sensory testing indicates that sensory function of multiple modalities, including those subserved by large myelinated axons, diminishes with age. Scant electrophysiological data indicate that motor responses are normal, whereas sensory responses are diminished and likely disappear with age. Sensory nerve biopsies show a selective loss of unmyelinated axons, and autopsies demonstrate a loss of sensory and some kinds of autonomic neurons.
HSAN4/CIPA syndrome (OMIM 256800)
Recessive mutations in *NTRK1* cause HSAN4. *NTRK1* encodes TrkA, a receptor for nerve growth factor (NGF), but also neurotrophin-3. Based on the neurobiology of *Ntrk1*-null mice, autonomic and small sensory neurons likely die in utero, so that HSAN4 is really a congenital neuronopathy. These neurons, and the cholinergic neurons in the basal forebrain, express TrkA; the NGF is probably provided by other cells in their environment (Bibel and Barde, 1999).
The acronym CIPA stands for Congenital Insensitivity to Pain with Anhydrosis. In addition to these features, patients may develop unexplained high fevers, ulcers, osteomyelitis, and amputations. Patients have diminished intelligence, and often exhibit

self-mutilating behavior. Sensory and nerve conductions are normal because large myelinated axons are not affected; sensory nerve biopsies show an absence of unmyelinated and small myelinated axons – these belong to the neurons that are known to depend on NGF for their survival during development.
HSAN5 (OMIM 162030)
Recessive mutations in *NGFB* cause HSAN5 in a single family. *NGFB* encodes NGF, the principle ligand for the TrkA receptor. Mature NGF is a dimer, produced by the proteolytic cleavage of pro-NGF. Most of the mutant protein remains as pro-NGF (Larsson et al., 2009), which is a ligand for the low-affinity neurotrophin receptor, p75, but not for TrkA. Like *Ntrk1*-null mice, the autonomic and small sensory neurons likely die in utero in *Ngfb*-null mice, so that HSAN5 is likely to be a congenital neuronopathy (Bibel and Barde, 1999).
Our knowledge of this disorder comes from a single family with an Arg211Trp missense mutation (Einarsdottir et al., 2004). Patients who are homozygous for this mutation develop Charcot arthropathy in childhood, but unlike patients who have HSAN4, they have a limited sense of pain, do sweat, and have normal intelligence; these discrepancies may owe to the preserved TrkA signaling mediated by the mutant protein or by an alternative ligand, neurotrophin-3, in nociceptive, sympathetic, and cholinergic neurons in the basal forebrain, respectively. Sensory and motor nerve conductions are normal; biopsies show a loss of unmyelinated and small myelinated axons – the very ones that are known to depend on NGF for their survival during development. Some adult patients who are heterozygous for this *NGFB* mutation develop Charcot arthropathies and variable symptoms of neuropathy, but a surprisingly number of unmyelinated and small myelinated axons are absent in sensory nerve biopsies (Minde et al., 2009). It remains to be determined whether the phenotype of heterozygous patients owes to haplotype insufficiency or a dominant effect of the mutant protein.
HSAN with cough and gastro-esophageal reflux (OMIM 608088)
HSAN with cough and gastro-esophageal reflux is an autosomal dominant disorder that maps to 3p22-p24 (Spring et al., 2005). Affected patients have a cough, likely due to severe reflux and not vocal cord paralysis, and a sensory neuropathy. Electrophysiological testing showed diminished sensory amplitudes, and sensory nerve biopsies showed loss of myelinated axons.

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http://rarediseasesnetwork.epi.usf.edu/INC/professional/disorders/HMN/

Hereditary Motor Neuropathies (HMN)
The current classification is based on the seven types of “distal hereditary motor neuronopathies” proposed by Harding (Harding, 1993), according to their clinical

features and pattern of inheritance. "Distal spinal muscular atrophy" is an alternative name. They can be conceptualized as length-dependent neuropathies of only motor axons, although sensory axons may be minimally involved. If a myelopathy is also present (presumably caused by a length-dependent axonopathy of descending axons to the spinal cord), as occurs in HMN V, HMN Jerash, and ALS4, then this must be distinguished from hereditary amyotrophic lateral sclerosis. A genetic cause could be found in 17/110 probands (15%) of patients with HMN, somewhat higher for those associated with myelopathy (Dierick et al., 2008), so that many causes remain to be discovered. Altogether, HMN may account for ~10% of patients who have been labeled as CMT (Harding and Thomas, 1980). Whereas one can conceptually account for the selective vulnerability of sensory and autonomic neurons in HSAN4 and 5, why they should be spared in the various forms of HMN remains unexplained.

HMN I (OMIM 182960)

HMN I was proposed to be a dominant inherited motor neuropathy with onset between 2-20 years. Although there are scattered clinical reports of individuals with this phenotype, the only genetic cause that has been found is one patient with a Pro182Ser mutation in *HSPB1*, who had foot drop before age 10 (Kijima et al., 2005).

HMN II (OMIM 158590, 608634, 613376)

HMN II was proposed to be a dominant inherited motor neuropathy with adult onset. Dominant mutations in *HSPB8*, *HSPB1*, and *HSPB3* cause this phenotype, and are called HMN IIa, IIb, and IIc, respectively. *HSPB8*, *HSPB1*, and *HSPB3* encode heat shock protein 22 (HSP22), 27 (HSP27), and 27 kDa, respectively, all of which encode a member of the family of 11 small HSPs. These proteins form oligomeric complexes with each other and serve diverse cellular functions, but the common phenotype of these different dominant mutations suggests a final common pathway to an axonal neuropathy.

Two different missense mutations that affect the same amino acid (Lys141Asn and Lys141Glu) in HSPB8 have been identified in four families with HMN IIa (Irobi et al., 2004). The Lys141Asn mutation was found in two large families. In one family, the age of onset ranged from 14-35 years. Clinical neurophysiology demonstrated length-dependent denervation and no sensory nerve involvement, and a sensory nerve biopsy in one patient was normal. (Note that the Lys141Asn mutation was also reported in the only CMT2L family reported to date (Tang et al., 2005); unlike the HMN IIa patients, affected individuals had clinical, electrophysiological, and histological evidence of sensory axonal involvement). The HSP22 mutants show enhanced interaction with HSP27, leading to the formation of aggregates in transfected cells.

Nine different dominant, missense mutations in *HSPB1* cause HMN IIb (Evgrafov et al., 2004; Houlden et al., 2008); one mutation (Ser135Phe) was also reported to cause CMT2F. The clinical onset varies between 20 and 50 years, except for one patient (with a Pro182Ser mutation), who had foot drop before age 10 (Kijima et al., 2005); this could be considered to be the one genetically confirmed example of HMN I. A homozygous recessive mutation (Leu99Met) produced a similar phenotype, which should probably be called HMN III, although the age of onset is older than the 2-20 years used in Harding's (1993) classification. EMG shows severe denervation in distal weak muscles, and sensory findings are minimal to none, although some patients had diminished sural amplitudes (Houlden et al., 2008), again underscoring the difficulty of

separating HMN II from CMT2. HSP27 mutants form abnormal aggregates and may have abnormal interactions with cytoskeletal proteins.
Building on the observation that mutations in two different HSPs caused HMN II, Kolb et al (Kolb et al., 2010) sequenced the genes for 10 different small HSPs in a cohort of 28 patients who had an unexplained axonal neuropathy. They identified a heterozygous mutation in *HSPB3* in two sisters with HMN. The proband developed distal leg weakness in her 20s and had minimal sensory findings at age 51, including a normal sural sensory amplitude. EMG showed acute and chronic denervation in distal muscles.
HMN III (no OMIM) and HMN IV (OMIM 607088)
HMN III and IV were proposed to be recessively inherited forms of HMN that were separated by their age of onset and severity. They are also called Spinal Muscular Atrophy, Distal, Autosomal Recessive, 3 (DSMA3) in OMIM. In addition to the patient with a homozygous (Leu99Met) mutation, a gene causing this phenotype has been mapped to 11q13 in one large family, in which affected members had their clinical onset from infancy to adulthood (Viollet et al., 2002), thus encompassing both HMN III and IV.
HMN V (OMIM 600794)
HMN V was proposed to be dominantly inherited HMN with upper limb predominance. Dominant mutations in *GARS* (Antonellis et al., 2003) or *BSCL2* (Windpassinger et al., 2004) cause this phenotype. GARS catalyzes the aminoacylation of glycine to its tRNA, and is an essential enzyme and is expressed in all cells. How dominant mutations cause a motor neuropathy (or CTM2D) is unknown.
Patients with *GARS* mutations typically present with weakness in the intrinsic hand muscles, followed by the distal legs, with clinical onset from the second to fourth decades, with slow progression. Some patients have reduced sensation, perhaps to different degrees depending on the mutation, adding to the difficulty in discerning HMN V from CMT2D.
BSCL2 encodes seipin. Homozygous, loss of function mutations cause congenital generalized lipodystrophy type 2, whereas two different dominant mutations (Asn88Ser and Ser90Leu), both of which affect glycosylation, cause HMN V. The unglycosylated mutants accumulate in the endoplasmic reticulum and likely induce an unfolded protein response that is presumably detrimental to certain neuronal types (e.g., motor neurons) that have the longest axons (Ito and Suzuki, 2007).
Concurrent myelopathy is often present with *BSCL2* mutations (Auer-Grumbach et al., 2005); this is known as Silver syndrome (OMIM 270685). Even in the same kindred, a dominant *BSCL2* mutation can produce a clinical picture of prominent weakness of intrinsic hand muscles, with or without spastic paraparesis, and others had a spastic paraparesis without hand weakness (SPG17). Taking all of these phenotypes together, the clinical onset is rare before age 10, and some patients did not have clinical manifestations until their 60s. Extremely slow progression is the rule; only one patient lost deambulation.
HMN VI/SMARD1 (OMIM 604320)
Recessive mutations in *IGHMBP2* cause HMN VI/SMARD1 (spinal muscular atrophy with respiratory distress type 1)/Distal Spinal Muscular Atrophy Type 1. IGHMBP2 is a DNA and RNA helicase that is associated with ribosomes in the cytoplasm of neurons

(Guenther et al., 2009). Mutations associated with HMN VI cause the loss of helicase activity.
Affected infants have low birth weights, difficulty breathing, distal weakness, contractures, diaphragmatic eventration. In a hierarchical cluster analysis, “the combination of ‘manifestation of respiratory failure between 6 weeks and 6 months’ AND (‘presence of diaphragmatic eventration’ OR ‘preterm birth’) predicted the presence of *IGHMBP2* mutations with 98% sensitivity and 92% specificity” (Guenther et al., 2007). Sensory responses are absent, and motor responses, if present, show slowed conduction that is probably explained by the underdeveloped axonal diameters seen in nerve biopsies (similar to patients with homozygous, recessive *NEFL* mutations). Biopsies also show axonal loss. In one autopsied case, motor neurons did not appear to be lost. Thus, HMN VI appears to be a lethal, congenital axonal neuropathy, but there may be exceptional patients who survive with a severe neuropathy (Joseph et al., 2009).
HMN VII (OMIM 158580)
Dominant mutations in *DCTN1* cause HMN VIIa, which is characterized by distal weakness and vocal cord paralysis. *DCTN1* encodes the p150Glued subunit of dynactin, which is the motor for retrograde axonal transport. The Gly59Ser mutant protein has reduced binding to microtubules, and likely results in reduced retrograde axonal transport (Puls et al., 2003). Other *DCTN1* mutations have been found in patients with sporadic motor neuron disease; whether these are causal remains to be shown.
Only a single family has been reported (Puls et al., 2005). Dysphagia, stridor, or hand weakness are the initial symptoms, with onset between 23 and 44 years; weakness subsequently develops in the legs but patients do not require wheelchairs. Abduction of the left vocal cord was weaker than the right, likely related to the greater length of the left recurrent laryngeal nerve. The (median-innervated) abductor pollicus brevis is weaker and had a smaller compound muscle action potential than does the (ulnar-innervated) adductor digiti minimi. Sensory exams and sensory responses are normal, but skin biopsies show some mild abnormalities. An autopsy on one affected patient showed “more intense staining and coarser and more irregularly shaped granules” of dynactin and dynein in hypoglossal motor neurons.
A mutation on 2q14 causes HMN VIIb (McEntagart et al., 2001). In the single reported family, weakness and atrophy typically develop in the second decade, followed by weakness in the distal legs. Hoarseness develops before or after the onset of hand weakness.
X-linked HMN associated with *ATP7A* mutations (no OMIM)
Some mutations in *ATP7A* cause X-linked HMN (Kennerson et al., 2010). *ATP7A* encodes a copper transporter. Complete loss of function *ATP7A* mutations cause Menkes disease (OMIM 309400), and partial loss of function mutations cause Occipital Horn Syndrome (OMIM 304150); motor neuropathy has not been reported with either disorder. Further, unlike the latter disorders, serum copper and ceruloplasmin levels are normal in patients the X-linked distal HMN. The ATP7A mutants associated with X-linked distal HMN are missense mutations of amino acides in the transmembrane domain; the mutants had delayed movement from the trans-Golgi to the plasma membrane in response to a copper challenge.

Distal weakness and atrophy and minimal sensory findings are the clinical findings, beginning at age1-10 years for the Thr994Ile mutation and 10-60 years for the Pro1386Ser mutation. The electrophysiology data mirror these clinical findings.
ALS4 (OMIM 602433)
Dominant mutations in *SETX* cause HMN/ALS4 (Chen and el., 2004). These mutations are distinct from the autosomal recessive mutations that cause Ataxia-Oculomotor Apraxia Type 2 (OMIM 208920), a syndrome that includes a prominent axonal neuropathy (Anheim et al., 2009). *SETX* encodes senataxin, a DNA and RNA helicase related to IGHMBP2. Senataxin is localized throughout the cell, but is particularly concentrated in the nucleolus of differentiated, non-dividing cells (Chen et al., 2006).
Patients typically become symptomatic in the second decade, with difficulty walking, followed by weakness and atrophy of distal muscles in the arms and legs. The patients who believed they were asymptomatic had physical findings of upper and lower motor neuron involvement (Rabin et al., 1999). Weakness was progressive in symptomatic patients, and involved proximal muscles. Increased deep tendon reflexes and extensor plantar responses are frequently noted. Sensory exams are minimally altered and sensory nerve responses are normal. Distal motor responses have reduced or absent amplitudes, with length-dependent denervation on needle exam. Autopsies show loss of myelinated axons in motor as well as sensory nerves/roots, and mild involvement of the lateral corticospinal tract.
HMN Jerash type (OMIM 605726)
HMN Jerash type is an autosomal recessive distal HMN that was found in one Jordanian kindred and mapped to 9p21.1-p12 (Christodoulou et al., 2000). Clinical onset is age 6-10 years, with distal atrophy and weakness. Younger patients have a myelopathy, but these findings progressively disappear as the disease progresses. Sensory exams are normal, sensory nerve responses are normal, and sural nerve biopsies showed mild loss of myelinated axons. Motor responses are reduced or absent in distal muscles, with slowing of conduction.

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