

# Hereditary Neuropathies

The hereditary neuropathies are a heterogeneous group of disorders that can be divided into two major subgroups: neuropathies in which the neuropathy is the sole or primary feature and neuropathies in which the neuropathy is part of a more generalised neurological or multisystem disorder. This review will focus on the common hereditary neuropathies in the first group, Charcot-Marie-Tooth disease (CMT), hereditary neuropathy with liability to pressure palsy (HNPP), hereditary sensory and autonomic neuropathy (HSAN), distal hereditary motor neuropathy (dHMN) and hereditary neuralgic amyotrophy (HNA).

## Charcot-Marie-Tooth disease

CMT is the most common inherited neuromuscular disorder, affecting 1 in 2,500 individuals.<sup>1</sup> Although CMT is both clinically and genetically heterogeneous, the cardinal clinical features are distal muscle wasting and weakness, reduced or absent tendon reflexes, distal sensory loss and a high incidence of foot deformities. Disease onset usually occurs during the first decades of life, the course is slowly progressive, and severity is highly variable even within the same kinship, only rarely leading to severe impairment. Historically CMT has been classified into two main subgroups neurophysiologically: CMT1 (demyelinating) with upper limb motor nerve conduction velocities (MCV) less than 38m/s, and CMT2 (axonal) with upper limb MCV greater than 38m/s.<sup>2</sup> Dominant intermediate CMT, a subgroup of CMT with MCV ranging from 25 to 45m/s, is a recent addition to the classification.<sup>3</sup>

CMT can be inherited as an autosomal dominant (AD), recessive (AR) or X-linked trait. Autosomal dominant and X-linked CMT are the most prevalent forms of CMT in UK/northern European and US populations, whereas autosomal recessive CMT is more common in countries with high rates of consanguinity. Apparent sporadic cases are common and may be due to a number of causes including lack of family history, reduced penetrance, variable disease expression, de novo dominant mutations or autosomal recessive inheritance. Currently greater than 20 causative genes have been identified for CMT (Table 1).

## Autosomal dominant CMT1

This is the most common form of CMT in most populations. Patients usually present with the 'classical CMT' phenotype characterised by difficulty in walking and foot deformity, usually starting in the first two decades of life. Distal wasting and weakness are generally more prominent in the lower limbs and frequently associated with distal sensory loss and reduced or absent tendon reflexes. Nerve conduction velocity is homogeneously slow with MCV in the median nerve below 38m/s. Nerve biopsy shows demyelination with typical onion bulbs reflecting repeated cycles of de- and remyelination.

The most common form is CMT1A secondary to the chromosome 17 duplication containing the peripheral myelin protein 22 gene (PMP22). This accounts for 70% of all CMT1 cases in European populations.<sup>4</sup> Point mutations in the PMP22 gene are rare and affected patients either have CMT1A, HNPP or a more severe form of CMT.<sup>15</sup>

CMT1B is a less common form of CMT1 and it is associated with myelin protein zero (MPZ) gene mutations. Patients usually present with an early onset demyelinating neuropathy (CMT1B). MPZ mutations can also cause a late onset axonal neuropathy (CMT2).<sup>6</sup>

Mutations in the EGR2 and LITAF genes are very rare causes of CMT1 and like PMP22, mutations in EGR2 can also present with a severe CMT1 phenotype. The final gene associated with CMT1 is NEFL,<sup>7</sup> although mutations in this gene more commonly cause CMT2.

## Severe CMT1

A more severe form of CMT1, also called Dejerine Sottas disease (DSD) and congenital hypomyelinating neuropathy (CHN) usually presents in the first decade with very slow MCV. This is usually caused by de novo dominant mutations in the common CMT1 genes, MPZ, PMP22 and EGR2. In rare instances mutations in the same genes can be inherited as an autosomal recessive trait.<sup>1</sup>

## Hereditary neuropathy with liability to pressure palsies

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant inherited disorder characterised by recurrent palsies at points vulnerable to pressure. It is usually due to a deletion of the same portion of chromosome 17 which is duplicated in CMT1A, but rarely it is caused by PMP22 point mutations.

## X-linked CMT1

This is the second most common form of CMT and is caused by mutations in the connexin 32 gene. Clinically males are more severely affected and usually present with a demyelinating neuropathy, whereas females are less affected and often only have a mild neuropathy with nerve conduction velocities in the axonal range. Central nervous system involvement is occasionally seen but is often asymptomatic.<sup>8</sup>

## Autosomal dominant CMT2

It is estimated that about 24% of patients with dominantly inherited CMT have CMT2. Unlike AD CMT1 where more than 95% of the causative genes have been identified, only 25% of the causative genes for AD CMT2 are known.

Mitofusin 2 (MFN2) gene mutations, which cause CMT2A, are the major cause of CMT2, causing approximately 20% of all cases.<sup>9</sup> Patients usually present with the 'classical CMT phenotype', which is indistinguishable



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The hereditary neuropathies are the commonest inherited neurological diseases and are a significant cause of disability in the population

**Table 1: Charcot-Marie-Tooth disease: Classification and clinical features.**

Type	Inheritance	Gene/Locus	Phenotype
CMT 1A	AD	Dup 17p (PMP22) PMP22 (point mutation)	Classic CMT1 Classic CMT1/DSD/CHN
CMT 1B	AD	MPZ	CMT1/ DSD/CHN/ CMT2
CMT 1C	AD	LITAF	Classic CMT1
CMT 1D	AD	EGR2	Classic CMT1/DSD/CHN
CMT 1	AD	NEFL	CMT1/CMT2
HNPP	AD	Del 17p (PMP-22) PMP-22 (point mutation)	Typical HNPP Typical HNPP
HNA	AD	SEPT 9	Recurrent neuralgic amyotrophy
CMT 1X	X-linked	GJB1	Males CMT1/ Females CMT2
CMT4A	AR	GDAP1	CMT1/CMT2
CMT4B1	AR	MTMR2	Severe CMT1/facial/ bulbar/focally folded myelin
CMT4B2	AR	MTMR13	Severe CMT1/glaucoma /focally folded myelin
CMT4C	AR	KIAA1985	Severe CMT1/scoliosis /cytoplasmic expansions
CMT4D (HMSNL)	AR	NDRG1	Severe CMT1/gypsy /deafness/tongue atrophy
CMT4E	AR	EGR2	CMT1/DSD/CHN
CMT4F	AR	PRX	CMT1/sensory/ focally folded myelin
CCFDN	AR	CTDP1	CMT1/gypsy/cataracts dysmorphic features
HMSN Russe	AR	10q22-q23	CMT1
CMT1	AR	PMP22 (point mutation)	CMT1/DSD/CHN
CMT1	AR	MPZ	CMT1/DSD/CHN/CMT2
CMT2A	AD	KIF1B $\beta$	Classic CMT2
CMT2A	AD	MFN2	Classic CMT2 / more progressive / optic atrophy
CMT2B	AD	RAB7	CMT2 with predominant sensory involvement and sensory complications
CMT2C	AD	12q23-q24	CMT2 with vocal cord and respiratory involvement
CMT2D	AD	GARS	CMT2 with predominant hand wasting/weakness or dHMN-V
CMT2E	AD	NEFL	CMT2 but can have slow MCVs in CMT1 range +/- early onset severe disease
CMT2F	AD	HSP27	Classic CMT2 or dHMN-II
CMT2G	AD	12q12-q13.3	Classic CMT2
CMT2L	AD	HSP22	Classic CMT2 or dHMN-II
CMT2	AD	MPZ	CMT1 or CMT2
CMT2 (HMSNP)	AD	3q13.1	CMT2 with proximal involvement
ARCMT2A	AR	LMNA	CMT2 proximal involvement and rapid progression described/ also causes muscular dystrophy/ cardiomyopathy/lipodystrophy
ARCMT2B	AR	19q13.3	Typical CMT2
ARCMT2	AR	GDAP1	CMT1 or CMT2 usually early onset and severe/vocal cord and diaphragm paralysis described/rare AD CMT2 families described
CMT2X	X-linked	Xq24-q26	CMT2 with deafness /mental retardation
DI-CMTA	AD	10q24.1-25.1	Typical CMT
DI-CMTB	AD	DNM2	Typical CMT
DICMTC	AD	YARS	Typical CMT

AD = autosomal dominant; AR = autosomal recessive; Dup = duplication; Del = deletion; PMP-22= peripheral myelin protein 22; MPZ = myelin protein zero; LITAF = Lipopolysaccharide-induced tumor necrosis factor; EGR2 = early growth response 2; GJB1 = gap junction protein, beta 1; GDAP1 = ganglioside-induced differentiation-associated protein 1; MTMR2 = myotubularin-related protein 2; MTMR13 = myotubularin-related protein 13; KIAA1985 = KIAA1985 protein; NDRG1 = N-myc downstream-regulated gene 1; PRX = periaxin; CTDP1 = CTD phosphatase, subunit 1; KIF1 $\beta$  = Kinesin family member 1B- $\beta$ ; MFN2 = Mitofusin 2; RAB7 = RAS-associated protein RAB7; GARS = glycyl-tRNA synthetase; NEFL = neurofilament, light polypeptide 68kDa ; HSP 27 = heat shock 27kDa protein 1; HSP 22 = heat shock 22kDa protein 8; LMNA = Lamin A/C; DN2 = dynamin 2; YARS = tyrosyl-tRNA synthetase; SEPT9 = septin 9.

from autosomal dominant CMT1. Neurophysiology shows MCV above 38m/s with reduced motor action potentials (MAPS) and reduced or absent sensory action potentials (SAPS). Nerve biopsy is consistent with an axonal neuropathy. Patients may have a more progressive, early onset severe phenotype. Approximately 20% of MFN2 mutations are de novo dominant, accounting for many of the

'sporadic' CMT2 cases. Extensor plantar responses and increased reflexes have been occasionally reported.

Recently, axonal CMT with optic atrophy (previously known as HSMNVI) has been shown to be caused by mutations in the MFN2 gene.<sup>10</sup> MFN2 gene is located near the KIF1B $\beta$  gene which has been associated with CMT2A in a single Japanese family. As stated above,

MPZ and NEFL mutations can also cause AD CMT2 and should be screened after MFN2.

Other causes of AD CMT2 are rare. RAB7 mutations cause a neuropathy with prominent sensory involvement, ulcerations, osteomyelitis and amputations whereas GARS mutations are associated with a neuropathy which is predominantly upper limb and motor (Table 1).

**Table 2: Hereditary sensory and autonomic neuropathy: Classification and clinical features.**

Type	Inheritance	Gene/Locus	Phenotype
HSANI	AD	SPTCL1	Mainly sensory with complications and pain, with occasional motor problems early on
CMT2B	AD	RAB7	Sensorimotor but more sensory than normally seen with CMT
HSAN I	AD	3p24-p22	Sensory, cough, gastroesophageal reflux
HSAN II	AR	HSN2	Severe sensory complications with mutilations, onset in the first 2 decades of life
HSAN III	AR	IKBKAP	Familial dysautonomia, Riley-Day syndrome, Prominent autonomic features, absence fungiform papillae of the tongue
HSAN IV	AR	NTRK1	Congenital insensitivity to pain with anhidrosis (CIPA), mental retardation, with the unmyelinated fibers being mainly affected
HSAN V	AR	NTRK1	Congenital insensitivity to pain with mild anhidrosis, no mental retardation, with the small myelinated fibers being mainly affected
HSAN V	AR	NGFβ	Congenital insensitivity to pain, minimal autonomic involvement, no mental retardation, mainly unmyelinated fibers affected
Channelopathy associated insensitivity to pain	AR	SCN9A	Congenital insensitivity to pain

AD = autosomal dominant; AR = autosomal recessive; SPTCL1 = Serine palmitoyltransferase, long chain base subunit-1; RAB 7 = RAS-associated protein RAB7; HSN2 = HSN2 gene; IKBKAP = IκB kinase complex-associated protein; NTRK1 = neurotrophic tyrosine kinase, receptor type 1; NGFβ = nerve growth factor beta polypeptide, SCN9A = sodium channel voltage gated type IX alpha-subunit.

**Table 3: Distal hereditary motor neuropathy: Classification and clinical features.**

Type	Inheritance	Gene/Locus	Specific phenotype
dHMNI	AD	Unknown	Juvenile onset dHMN
dHMNII	AD	HSP27	Adult onset dHMN/CMT2F
dHMNII	AD	HSP22	Adult onset dHMN/CMT2L
dHMNIII	AR	11q13	Early onset, slowly progressive
dHMNIV	AR	11q13	Juvenile onset, diaphragmatic involvement
dHMNV	AD	GARS	Upper limb onset, slowly progressive/CMT2D
dHMNV	AD	BSLC2	Upper limb onset/ sometimes lower limb spasticity (Silver syndrome)
dHMNVI	AR	IGHMBP2	Spinal muscular atrophy with respiratory distress (SMARD1), infantile onset
dHMNVII	AD	2q14	Adult onset, vocal cord paralysis
dHMNVII	AD	DCTN1	Adult onset, vocal cord paralysis, facial weakness
dHMN/ALS4	AD	SETX	Early onset, pyramidal signs
dHMN-J	AR	9p21.1-p12	Juvenile onset, pyramidal features, Jerash

AD = autosomal dominant; AR = autosomal recessive; HSP 27 = heat shock 27kDa protein 1; HSP 22 = heat shock 22kDa protein 8; GARS = glycyl-tRNA synthetase; BSLC2 = Berardinelli-Seip congenital lipodystrophy gene; IGHMBP2 = immunoglobulin mu binding protein 2; DCTN1 = dynactin; SETX = senataxin

**Autosomal Recessive CMT**

AR CMT is less common than AD CMT, accounting for less than 10% of CMT cases in a typical northern European population. In certain ethnic groups, particularly with high rates of consanguinity, the prevalence of AR CMT is 40% of all cases of CMT.<sup>11</sup> Ten causative genes so far have been described for the demyelinating forms of autosomal recessive CMT, AR CMT1 (called CMT4 in many classifications), including mutations in PMP22, MPZ and EGR2 genes (Table 1). These are usually severe, early-onset disorders with moderate to severely slow motor conduction velocities. They usually have a progressive clinical course often with proximal muscle involvement. Particular genes are associated with certain clinical features or specific ethnic groups (Table 1). CMT4A, secondary to GDAP1 mutations, accounts for 25% of cases of AR CMT. GDAP1 mutations can either cause AR CMT1 or AR CMT2 and can be associated with diaphragmatic and vocal cord involvement.

Mutations in the genes encoding MTMR2 and MTMR13 cause CMT4B1 and CMT4B2 respectively, demyelinating neuropathies characterised pathologically by focally folded myelin. Other genes associated with CMT4 are periaxin and KIAA1985 (Table 1), the latter is associated with early onset of scoliosis.

Two forms of CMT4 have been reported only in gypsy communities in Europe: CMT4D due to mutations in the NDRG1 gene and a demyelinating neuropathy with cataracts and facial dysmorphism (CCFDN) due to CTDP1 mutations.

AR CMT2 is rare and only two causative genes have been identified, GDAP1 and Lamin A/C (LMNA). LMNA mutations cause a severe axonal neuropathy with proximal muscle involvement.

**Dominant intermediate CMT**

A 'classical CMT phenotype' characterised by intermediate nerve conduction velocities and histological evidence of both axonal and demyelinating features<sup>12</sup> has been described

for which two causative genes have been identified to date, DNM2 and YARS (Table 1).

**Hereditary sensory and autonomic neuropathies (HSAN)**

HSAN is less common than CMT, comprising a group of five heterogeneous disorders characterised by variable sensory and autonomic dysfunction. Many of the causative genes have now been identified.<sup>13,14</sup> They can be inherited as an autosomal dominant or recessive trait. Clinical features are detailed in Table 2.

**Distal hereditary motor neuropathies (dHMN)**

Patients with distal HMN present with a classical 'CMT phenotype' without sensory involvement. Clinically it is difficult to distinguish distal HMN from CMT, but neurophysiology is crucial, confirming the normal sensory function. Distal HMNs were previously subdivided into seven types based on clinical features, age of onset and inheritance, but the identification of causative genes has revealed

greater heterogeneity within these groups. Genotype / phenotype details are given in Table 3 and it can be seen that three of the causative genes also cause AD CMT2 (GARS, HSP 22 and HSP 27).

### Hereditary Neuralgic Amyotrophy (HNA)

HNA is an autosomal dominant disorder causing recurrent episodes of painful brachial plexopathy due to mutations in Septin 9 gene.<sup>15</sup> Each individual episode is clinically indistinguishable from sporadic neuralgic amyotrophy.

### Conclusions

The hereditary neuropathies are the commonest inherited neurological diseases and are a significant cause of disability in the population. In the last 15 years there have been major

advances in the understanding of the genetic causes of this heterogeneous group of conditions. Many of the genes are now known and the commoner genes are widely available as diagnostic tests (chromosome 17 duplication, PMP-22, CX32, MPZ, Mitofusin 2 and GDAP1 mutations). Genetic testing can be used for diagnostic, predictive or ante-natal screening. Although currently knowledge of the genetic cause of a hereditary neuropathy does not lead to a specific treatment, it can help give the patient an accurate prognosis. Many patients find it very useful to have a genetic diagnosis despite the lack of treatment options. A genetic diagnosis can prevent unnecessary tests such as nerve biopsies, especially in children, and can also prevent trials of potentially dangerous immunosuppressive treatments when a diag-

nosis of an inflammatory neuropathy is being considered (e.g. patients with connexin 32 mutations have occasionally being diagnosed as having chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)).

The era of potential therapies for CMT has arrived with the first large scale trials now happening for the commonest subtype, CMT1A secondary to the chromosome 17 duplication (trials of high dose ascorbic acid, which has been shown to be useful in an animal model). However, genetic counselling, appropriate physiotherapy, expert orthotic advice, orthopaedic intervention when necessary and other symptomatic interventions including pain relief still remain the cornerstones of current management. Many patients benefit from being under the care of a dedicated multidisciplinary team.

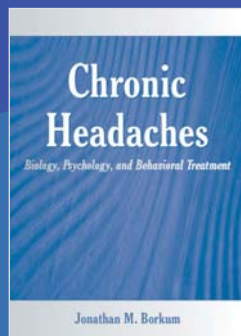
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# Chronic Headaches

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