# CHARCOT MARIE TOOTH DISEASE AND RELATED DISORDERS – AN EVOLVING LANDSCAPE

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## Abstract

### Purpose of review

Charcot-Marie-Tooth disease (CMT) and related disorders are the commonest group of inherited neuromuscular diseases and represent a heterogeneous group of disorders. This review will cover recent advances in genetic diagnosis and the evolving genetic and phenotype landscape of this disease group. We will review recent evidence of the increasingly recognised phenotypic overlap with other neurodegenerative conditions including hereditary spastic paraplegia (HSP), hereditary ataxias and mitochondrial diseases and highlight the importance of deep phenotyping to inform genetic diagnosis and prognosis.

### Recent findings

Through whole exome sequencing and multicentre collaboration new genes are being identified as causal for CMT expanding the genetic heterogeneity of this condition. In

addition an increasing number of variants have been identified in genes known to cause complex inherited diseases in which the peripheral neuropathy is part of the disorder and may be the presenting feature. The recent discovery of a repeat expansion in the *RFC1* gene in cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) highlights the prevalence of late-onset recessive conditions which have historically been considered to cause early onset disease.

**Summary:** CMT is an evolving field with considerable phenotypic and genetic heterogeneity and deep phenotyping remains a cornerstone in contemporary CMT diagnostics.

**Key words:** Charcot Marie Tooth Disease, Inherited Neuropathies, Next generation sequencing.

## INTRODUCTION

Charcot Marie Tooth (CMT) disease and related disorders (Hereditary Sensory Neuropathy (HSN) and Hereditary Motor neuropathy (HMN)) are a clinically and genetically heterogeneous group of disorders. Historically the prevalence of this group of disorders had been estimated at 1:2,500 (1) but more recent epidemiological studies report a varied prevalence rate amongst different populations ranging from 11.8/100 000 in North of England to 82.3/100 000 in Norway (2,3). Over 100 genes have been identified as causal for CMT and related disorders, resulting mainly from the increasing use of next generation sequencing (NGS) technologies which have revolutionised the diagnostic approach in patients.

CMT is classically a length dependent neuropathy characterised by distal weakness, sensory loss, reduced or absent deep tendon reflexes and foot deformities. Onset often occurs in the first two decades of life and whilst the disease is slowly progresses over decades it generally does not affect life expectancy.

Historically the classification of CMT has been based on neurophysiological findings (4) with an upper limb motor nerve conduction velocity (MNCV) of 38 m/s distinguishing between demyelinating CMT (CMT1) (MNCV <38 m/s) and axonal CMT (CMT2) (MNCV >38 m/s). The latter group can be further divided into motor and sensory (CMT2), motor predominant (HMN) and sensory predominant (HSN) neuropathies. An additional group includes intermediate CMT with MNCV between 25-45 m/s.

CMT and related disorders encompass inherited neuropathies where the neuropathy is the primary feature of the disease whereas neuropathy can also be part of a more complex neurological or multisystem disorder (5). There is increasing overlap between these two

groups with patients presenting with an isolated neuropathy but evolving to have a more complex condition with time.

We will discuss the evolving landscape of CMT in clinical practice including the increasingly recognised prevalence of complex neuropathy syndromes, the resulting diagnostic challenges and prognostic implications and highlight the continuing importance of deep phenotyping.

## GENETIC DIAGNOSIS OF CMT AND RELATED DISORDERS

In recent years NGS targeted CMT gene panels have become the most common tool used in CMT diagnostics. Targeted gene panels use specific capture kits which ensure that only the genomic regions of known CMT genes are targeted and sequenced.

A commonly used diagnostic approach is to first screen chromosome 17p duplication with conventional methods such as multiplex ligation probe amplification (MLPA) in CMT1 patients. After exclusion of this or if the neuropathy is axonal, customised targeted NGS panels are used which either cover specific genes groups (eg. CMT1 and intermediate CMT1, CMT2 and intermediate CMT, HSN or HMN) or all CMT and related disorder genes depending on the patient's phenotype (6).

In our clinical practice, after confirmation or exclusion of the 17p rearrangement, gene panels achieve a genetic diagnosis in about 30% of the remaining CMT patients (7), which is in keeping with other practices (8–12). Although 'phenotype-specific' panels as described above are helpful in reducing the need to interpret variants which are not relevant to the phenotype, there is an increasing move towards using a unified neuropathy panel to not only include genes causing CMT and related disorders but also genes that cause disorders where neuropathy is part of a more complex neurological syndrome. This is to account for both the

genetic heterogeneity of CMT and the increasing overlap between CMT and other neurodegenerative disorders such as hereditary spastic paraplegia (HSP), hereditary ataxias and mitochondrial diseases.

Whole exome sequencing (WES) and whole genome sequencing (WGS) are predominantly used as research tools and frequently employed in patients where targeted NGS panels have not identified any pathogenic variants in known CMT genes. Apart from improving the diagnostic yield in patients with CMT (13–16), WES and WGS enable the identification of novel causes and also aid the phenotypic expansion of known CMT genes. From our own practice an example of the former is the recent identification of a recessive pentanucleotide repeat expansion in *RFC1* gene as a cause of cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) highlighting the prevalence of late-onset recessive conditions which have historically been considered to cause early onset disease (17). An example of the latter is a case of Silver-like syndrome with preferential involvement of the extensor muscles in the upper limbs caused by recessive variants in *SIGMAR1* (18)

## OVERLAPPING PHENOTYPES AND MULTISYSTEM DISEASES

There is considerable overlap between CMT and other neurodegenerative disorders such as HSP, hereditary ataxias and mitochondrial disease (5). For some of these disorders, neuropathy can be the initial clinical manifestation and therefore a broader diagnostic approach may be required whereby HSP, Ataxia and mitochondrial targeted panels are requested early in the diagnostic process, and more extended testing with WES and/or WGS, may be warranted.

***Hereditary Spastic Paraplegia (HSP)***

The overlap between CMT and HSP is observed both phenotypically and genetically. Prime examples include the 'Silver' syndrome phenotype and many subtypes of distal HMN (e.g. secondary to *BSCL2, REEP1* mutations) where in addition to the motor neuropathy, patients often display a pyramidal syndrome (which may be subtle) (5,18,19). The kinesin group of genes involved in anterograde axonal transport including *KIF1A* and *KIF5A* are often associated with a more complex phenotype which as well as a neuropathy may include autism spectrum disorder in patients with *KIF1A* mutations (20,21), or varying degrees of neuropathy and upper motor neurones signs in patients with mutations in *KIF5A* (22–24). Mutations in the *SPG11* gene causing autosomal recessive HSP and frequently associated with thin corpus callosum and axonal peripheral neuropathy have been found as a significant cause of autosomal recessive CMT2 (25). In this series, patients had typical signs of slowly progressive axonal neuropathy and only a few patients had pyramidal signs and thin corpus callosum on MRI suggesting the importance of screening this gene in CMT2 patients.

***Ataxia***

*Friedreich's Ataxia (FRDA)*

FRDA is the most common autosomal recessive (AR) hereditary ataxia caused by biallelic GAA-trinucleotide-repeat expansions in the *FXN* gene. Clinically it is characterised by early onset progressive cerebellar gait and limb ataxia, dysarthria, areflexia, loss of position sense and progressive motor weakness due to an axonal neuropathy. Other frequent features include scoliosis, pes cavus, cardiomyopathy and diabetes mellitus. Late-onset Friedreich's Ataxia (LOFA) is defined when disease onset occurs after the age of 25 and is usually characterised by a milder phenotype, with lower limb spasticity and retained reflexes (26). Rarely, cases of LOFA have been reported to mimic CMT2 (26). Furthermore atypical cases of FRDA with

later age of onset and slower disease progression have been described with compound heterozygosity for the GAA trinucleotide-repeat expansion and a single nucleotide variant (SNV) in the *FXN* gene (27,28). In our CMT cohort, an 80-year old patient with late onset, slowly progressive sensory-predominant axonal neuropathy and mild lower limb spasticity who carried an initial clinical diagnosis of CMT2, has recently been confirmed to have FRDA due to a G130V missense mutation in heterozygosity with a trinucleotide repeat expansion (unpublished data).

Testing for FRDA should be considered in late onset neuropathy cases with a complex phenotype (severe proprioceptive loss, pyramidal signs or square wave jerks on eye movement testing) and is important since targeted NGS gene panels will not detect trinucleotide repeat expansions. Therefore, testing for these will be guided by phenotyping and clinical suspicion.

*Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)*

ARSACS is an early onset autosomal recessive spinocerebellar ataxia associated with spasticity and peripheral neuropathy with slow conduction velocities (CVs) due to biallelic mutations in the *SACS* gene. Following the identification of the *SACS* gene, several case series have broadened the clinical and genetic spectrum of the disease, and patients with isolated sensorimotor neuropathy have been described (29,30). A peripheral neuropathy with slow CVs in the context of a complex neurological syndrome is rare (5) and on this premise Vill and colleagues described nine patients with ARSACS from six unrelated families originally diagnosed with hereditary motor and sensory neuropathy (31). All but one of the patients had early disease onset with delayed motor milestones, toe walking or gait instability. Independent ambulation was preserved in all patients and none had upper motor

neuron signs. Mild cerebellar signs were observed in some of the patients. Nerve conduction studies showed mixed demyelinating and axonal findings in seven patients, three of which had upper vermis atrophy on MRI. Aside from careful clinical phenotyping which may reveal subtle cerebellar and/or pyramidal signs in atypical cases, deep phenotyping with ancillary tests such as MRI brain and optical coherence tomography (OCT) will help identify features such as the characteristic MRI appearance of the pons (32) and the retinal nerve fibre changes associated with ARSACS (33).

***Mitochondrial diseases***

Similar to the identification of *SACS* variants in genetically undiagnosed CMT cases, variants in nuclear-encoded mitochondrial genes such as *MPV17* (34,35) and *POLG* (36) and in the mitochondrial encoded *MT-ATP6* have been described.

Recessive mutations in *MPV17* cause mitochondrial DNA depletion syndrome 6 (MTDPS6), also known as Navajo neurohepatopathy, a multisystem disorder presenting in the first year of life with liver failure, metabolic acidosis, cerebral leukoencephaolopathy and peripheral neuropathy(37,38). Affected siblings from three unrelated kindreds with juvenile onset sensorimotor neuropathy without hepatocerebral involvement have been described with homozygous variants in *MPV17* (34,35). Three families carried the recurring mutation c.122G>A (p.R41Q) homozygously and one family carried a novel homozygous c.376-9T>G near-splice variant which was confirmed to cause skipping of exon 6 (p.Asp126_Tyr136 del). All patients presented with a slowly progressive, length-dependent axonal peripheral sensorimotor neuropathy with variable age of onset between 8 and 23 years. None of the patients had central nervous system involvement and only two patients had elevated serum lactate levels.

Recessive variants in *POLG* are classically associated with mitochondrial depletion syndromes or progressive external ophthalmoplegia. Phillips and colleagues recently identified recessive *POLG* variants in two patients with axonal sensorimotor neuropathy by WES. One patient had late onset predominant sensory axonal neuropathy which later in life was complicated by the presence of subtle eye movement abnormalities and carried a previously reported homozygous *POLG* mutation (p.Trp748Ser) (39) which resulted from uniparental disomy of the long arm of chromosome 15(36). The second patient had a more complex phenotype characterised by sensorimotor neuropathy associated with psychomotor development and achalasia with vomiting.

We have previously reported mutations in *MT-ATP6* gene as a cause of CMT2 in 1.1% of our CMT2 patients (40). Patients typically present with motor predominant axonal neuropathy and in some patients additional features such as learning difficulties, pyramidal signs and early proximal lower limb weakness are observed. Furthermore in few patients a rapid decompensation following a febrile illness is described.

The increasing identification of mutations in both mitochondrial and nuclear encoded mitochondrial genes associated with CMT like presentations highlights the importance of both mitochondrial and nuclear genome sequencing in the molecular diagnostic evaluation of patients with CMT2 which have important clinical implications for genetic counselling and prognosis.

## Novel CMT genes

The list of causative genes for CMT and the related disorders continues to rapidly expand as NGS technique are increasingly used in diagnostic and research practice. Table 1 summarises the current causative genes and a few recent examples are describe below.

A result of a large collaborative study with data sharing from more than 20 CMT research groups (41) is the identification of mutations in the *ATP1A1* gene, encoding the alpha-1 subunit of the $NA^+/K^+$-ATPase, as a cause of autosomal dominant CMT2 (2 families from Europe, 2 families from USA, 2 families from Australia and 1 from South Korea) (42). The phenotype was consistent with a length-dependent axonal sensorimotor neuropathy with variable age of onset and disease severity. Mutations in *ATP1A1* gene are likely to act through haploinsuffiency, similarly to *ATP1A2* and *ATP1A3* gene mutations which are responsible for distinct neurological disorders of the central nervous system.

Aminoacyl-tRNA synthetases (ARSs) are enzymes ubiquitously expressed in cells and variants in at least five genes (*GARS*, *AARS*, *HARS*, *WARS* and *YARS*) belonging to this superfamily have been associated with CMT and related disorders. Through multicentre collaboration using WES, a recurring variant in the *WARS* gene (p.His257Arg) has been described as a novel cause of autosomal dominant distal HMN in three unrelated families from Taiwan and Belgium (43).

Mutations in contactin-associated protein 1 (*CNTNAP1*) have been reported in multiple unrelated kindreds with severe congenital hypomyelinating neuropathy. The phenotype is often complicated by leukodystrophy, respiratory distress, inconsistent presence of arthrogryposis and variable survival rate (44–47).

The recent report of mutations in the mitochondrial copper-binding cytochrome c oxidase (COX) assembly protein (SCO2) in two families with autosomal recessive CMT2 (48) expands the phenotypic spectrum of this mitochondrial disease usually associated with fatal infantile cardioencephalomyopathy with severe COX deficiency (49). The two unrelated patients had a distinct phenotype with predominant length dependent motor axonal neuropathy. Apart from phenotypic variability between affected individuals, additional

clinical features included ptosis, facial weakness, facial fasciculations and dysarthria. Serum lactate was only slightly elevated in one patient although lactate to pyruvate ratio was normal.

## Late onset recessive conditions

Late onset genetic neuropathies represent a diagnostic challenge to clinicians and in most cases a genetic diagnosis is not reached. Late onset disorders are usually sporadic and rarely occur in siblings and were historically considered most likely autosomal dominant perhaps with reduced penetrance. Autosomal recessive inherited neuropathies are usually characterised by early disease onset but more recently late onset recessive conditions have been described. One of the most recent discoveries is the identification of a bi-allelic intronic pentanucleotide repeat expansion in the replication factor C subunit (*RFC1*) causing CANVAS. The recessive repeat expansion was also found in 62% of patients with sensory neuronopathy and cerebellar involvement (17). More importantly the study highlighted the high diagnostic rate in sporadic patients with well-defined clinical features of CANVAS (92%) and 100% of cases with familial CANVAS. Although CANVAS syndrome is a complex syndrome with multisystem involvement, patients are often referred and managed in specialist peripheral neuropathy clinics since a major and often the first feature is the sensory neuronopathy. Interestingly *RFC1* is involved in DNA repair and similarly mutations in many DNA repair genes such as senataxin (*STX*), aprataxin *(APTX), ATM* (Ataxia Telangiectasia) have been associated with degenerative neurological disorders in which ataxia and neuropathy are common clinical features, suggesting a specific susceptibility of the peripheral nerves and cerebellum to DNA damage.

Among the late onset AR-CMT2 cases, the metalloendopeptidase (MME) gene appears to be the most common cause in the Spanish (50) and Japanese populations (11). The phenotype

described in the Spanish population is homogeneous and characterised by late onset motor predominant neuropathy with frequent cramps and sensory involvement in later stages of the disease. Although nerve conduction studies usually demonstrate an axonal neuropathy, slowing of motor conduction velocities in the intermediate and even in the demyelinating range has initially led to a diagnosis of chronic inflammatory demyelinating neuropathy in two patients (50). In both Spanish and Japanese cohorts heterozygous carriers did not have any symptoms of neuropathy and clinical and neurophysiological assessments were normal (11,50) suggesting that mutations in MME do not cause AD CMT2 as has been suggested in one paper (51).

## CONCLUSION

CMT clinical practice is a rapidly evolving landscape with a growing number of causative genes identified by NGS based molecular genetic techniques. An increasing number of variants have been identified in genes known to cause complex inherited diseases in which the peripheral neuropathy is part of the disorder and may be the presenting feature. Such cases present a diagnostic challenge for clinicians who need to consider additional phenotyping (including MRI of the central nervous system) and genetic testing outside the current diagnostic pathway for CMT and related disorders. The emerging evidence for inherited peripheral neuropathies to be occasionally caused by mutations in mitochondrial genes suggest monitoring for involvement of other organs, particularly the heart, may be warranted in these cases, and the prognosis more guarded than for typical CMT. Deep phenotyping of patients, however, remains central to the interpretation of genetic data.

**Key points**

- Next generation sequencing techniques continue to uncover novel genetic causes in CMT.
- Recently novel genes including recessive genes have been identified in late onset inherited motor and sensory neuropathies
- Increasing evidence has emerged showing that genes known to cause complex inherited disorders may present with an isolated neuropathy.

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**Conflict of interests**

There are no conflict of interests.

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