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Charcot-Marie-Tooth disease and hereditary motor neuropathies – Update 2020

Abstract: Inherited peripheral neuropathy is the most common hereditary neuromuscular disease with a prevalence of about 1:2,500. The most frequent form is Charcot-Marie-Tooth disease (CMT, or hereditary motor and sensory neuropathy [HMSN]). Other clinical entities are hereditary neuropathy with liability to pressure palsies (HNPP), distal hereditary motor neuropathies (dHMN), and hereditary sensory and autonomic neuropathies (HSAN). With the exception of HNPP, which is almost always caused by defects of the *PMP22* gene, all other forms show genetic heterogeneity with altogether more than 100 genes involved. Mutation detection rates vary considerably, reaching up to 80 % in demyelinating CMT (CMT1) but are still as low as 10–30 % in axonal CMT (CMT2), dHMN, and HSAN. Based on current information, analysis of only four genes (*PMP22*, *GJB1*, *MPZ*, *MFN2*) identifies 80–90 % of CMT-causing mutations that can be detected in all known disease genes. For the remaining patients, parallel analysis of multiple neuropathy genes using next-generation sequencing is now replacing phenotype-oriented multistep gene-by-gene sequencing. Such approaches tend to generate a wealth of genetic information that requires comprehensive evaluation of the pathogenic relevance of identified variants. In this review, we present current classification systems, specific phenotypic clues, and diagnostic yields in the different subgroups of hereditary CMT and motor neuropathies.

Keywords: Charcot-Marie-Tooth disease, CMT, hereditary motor and sensory neuropathy, HMSN, hereditary neuropathy with liability to pressure palsies, HNPP, distal hereditary motor neuropathy, dHMN, distal spinal muscular atrophy, DSMA, genetic testing algorithms, genotype-phenotype correlation

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Introduction

Charcot-Marie-Tooth (CMT) disease, also denoted as hereditary motor and sensory neuropathy (HMSN), is clinically and genetically closely related to hereditary neuropathy with liability to pressure palsies (HNPP) and distal hereditary motor neuropathies (dHMN), also known as distal spinal muscular atrophy (DSMA). Epidemiological studies reveal highly variable prevalence rates in different countries [1] but as a rough estimate, CMT occurs with a prevalence of 1 in 2,500 and is the most common hereditary neuromuscular disease. CMT, dHMN, and HSAN are genetically highly heterogeneous with close to 100 different genes involved while there is one single major gene for HNPP. By definition, CMT, HNPP, and dHMN are nonsyndromic disorders primarily or predominantly affecting the peripheral nervous system. However, many subtypes can show other neurological and non-neurological features, most frequently in combination with upper and lower motor neuron disease and spinocerebellar ataxia. In this review, we will summarise important and new developments in our understanding of CMT neuropathy and related neuropathies. We propose rational diagnostic algorithms based on genotype-phenotype correlations, mutation detection rates (adapted to [2]), and results of massive parallel sequencing technologies.

Charcot-Marie-Tooth disease (CMT)

CMT results from dysfunction of lower motor neurons and sensory neurons in dorsal root ganglia or their ensheathing glial cells (Schwann cells). The onset of CMT is typically in the first or second decade of life, although it may also start in infancy or at an advanced age. Most patients have slowly progressive distal muscle weakness and atrophy, usually starting in the feet and legs. Deep tendon reflexes are typically hypoactive or absent already at the beginning of the disease course. Foot deformities (most often pes cavus) can be an early sign and may be the only manifestation in mildly affected patients but can also be absent in some cases. With progression of peroneal atrophy patients frequently stumble while walking and develop foot drop and steppage gait. In early-onset cases,

motor milestones can be delayed along with muscular hypotonia. Weakness in the intrinsic hand muscles and hand extensors normally occurs later than lower limb affection. Variation in clinical presentation is generally wide, even within a single family, ranging from patients with severe muscle atrophy and marked hand and foot deformity to individuals whose only finding is pes cavus or minimal distal muscle weakness. Some mutation carriers can even remain without clinical symptoms throughout life. In patients with progressive disease courses proximal muscles can be involved as well. Walking ability is preserved in most cases. Sensory nerve dysfunction is of minor clinical relevance but can generally be detected by neurological examination, nerve conduction studies, and nerve biopsies. While the clinical picture in classical CMT normally gives no clue as regards the underlying genetic cause, there may be specific features pointing towards a distinct genetic subtype (Table 1).

Clinical investigations

Neurophysiologic and nerve biopsy studies are used to distinguish two main types, i. e. the demyelinating form CMT1 (primarily affecting Schwann cells, the myelin-forming glia cells in the peripheral nerves) and the axonal type CMT2 (affecting the axons of peripheral neurons directly). According to a widely accepted classification, patients are classified as demyelinating CMT1 if the motor nerve conduction velocity (mCV) of the median or ulnar nerve is below 38 m/s, while axonal CMT patients have a median mCV of at least 38 m/s [3]. Axonal degeneration is indicated by reduced or absent compound motor or sensory nerve action potentials.

There are several entities designated as dominant or recessive intermediate CMT (DI-CMT, RI-CMT) [4]. The notion of intermediate CMT emerged as a particular pattern of median mCV slowing, different from that of CMT1 (usually <25 m/s) and CMT2 (usually >45 m/s). The mCV limits for intermediate CMT vary in the literature between 25–45 m/s and 30–40 m/s. Moreover, there is considerable overlap of axonal and demyelinating features in many genetic subtypes which complicates classification attempts (Fig. 1). Since sural nerve biopsy is invasive, bears a considerable burden to the patient, and is only rarely indicative of a specific gene defect [5], it is generally considered obsolete when a hereditary neuropathy is suspected. However, nerve biopsies are still useful to rule out or confirm non-genetic causes of peripheral neuropathy. This is relevant for treatable inflammatory neuropathies, particularly to demonstrate non-systemic vasculitic neuropathy.

Laboratory investigations are generally normal apart from mildly or moderately increased creatine kinase (CK) activity in a small fraction (3 %) of demyelinating CMT and 11 % of axonal CMT patients [2]. In particular, patients with *NEFL* and *MME* mutations can show markedly increased CK levels.

Differential diagnosis

Generally, the proportion of genetically determined neuropathies is higher in childhood or youth than in adulthood. Most of the non-genetic causes can be attributed to para- or postinfectious and autoimmune neuritis, toxins, and nutritional deficiencies [6].

An important differential diagnosis is chronic inflammatory demyelinating polyneuropathy (CIDP). Although clinical features can overlap, CIDP is regularly associated with a subacute or fluctuating course, multifocal demyelinating features on electrophysiology, high protein levels in cerebrospinal fluid, and a negative family history. Since immunosuppressive treatment is effective in CIDP and not indicated in CMT, establishing the diagnosis is important. Moreover, neuropathies can also develop as a part of systemic inflammatory diseases such as vasculitis.

Axonal neuropathies can be caused or triggered by a broad variety of neurotoxic drugs (e. g. antiretroviral treatment and cytostatic agents) or substances. Taking a careful clinical history is important to document potential acquired causes of neuropathy.

Demyelinating polyneuropathy can also occur in different rare metabolic and neurodegenerative diseases, such as autosomal recessive metachromatic leukodystrophy, Refsum's disease, Krabbe's disease, X-linked adrenomyeloneuropathy, Pelizaeus–Merzbacher syndrome, the neurologic variant of Waardenburg–Shah syndrome and congenital cataracts with facial dysmorphism and neuropathy syndrome. Peripheral neuropathy may even be the most obvious clinical presentation of some of these conditions making distinction from non-syndromic hereditary neuropathies difficult.

X-linked Fabry disease often presents in childhood with neuropathic pain due to small fibre neuropathy, and early diagnosis is critical for enzyme replacement therapy to prevent renal, cardiac, and cerebrovascular complications. Another group of hereditary disorders sometimes confused with distal motor neuropathies are distal myopathies. The distinction can usually be made by sensory examination and electrophysiological studies.

Table 1: Charcot-Marie-Tooth disease and distal hereditary motor neuropathy forms with particular features.

Gene	OMIM	Type of neuropathy	Particular findings
MPZ	159440	AD CMT1, AD CMT2	Severe: congenital hypomyelination (CHN); Moderate: CMT1; Mild: late-onset CMT2; sometimes hearing loss and impaired pupillary reactions
FBLN5	604580	AD CMT1	Some patients may have age-related macular degeneration
GDAP1	606598	AR CMT1, AD or AR CMT2	AD: variable-onset CMT2; AR: severe early-onset neuropathy (demyelinating or axonal)
SH3TC2	608206	AR CMT1	Variable-onset demyelinating neuropathy; often early-onset scoliosis; nerve biopsy: basal lamina onion bulb formations
MTMR2	603557	AR CMT1	Nerve biopsy: focally folded myelin sheaths
FGD4	611104	AR CMT1	Nerve biopsy: focally folded myelin sheaths
SBF2	607697	AR CMT1	Sometimes early-onset glaucoma; nerve biopsy: focally folded myelin sheaths
NDRG1	605262	AR CMT1	Largely restricted to Gypsy populations
HK1	142600	AR CMT1	Restricted to Gypsy populations
INF2	610982	AD intermediate CMT	Concomitant kidney disease (focal segmental glomerulosclerosis)
MFN2	608507	AD or AR CMT2	Variable-onset axonal neuropathy; sometimes optic atrophy or vocal cord paralysis
RAB7A	602298	AD CMT2 or HSAN	Axonal neuropathy with severe sensory loss or acromutilating sensory neuropathy without weakness
TRPV4	605427	AD CMT2, dHMN, or SMA with contractures	Severe: congenital SMA with arthrogryposis multiplex and respiratory failure; Mild: scapuloperoneal SMA, motor or axonal sensorimotor neuropathy with vocal cord palsy
GARS	600287	AD CMT2 or dHMN	Upper limb predominance; severe phenotypes in children usually due to de novo mutations
BSCL2	606158	AD CMT2 or dHMN	Upper limb predominance, spasticity in lower limbs; allelic with Silver syndrome (SPG17)
TFG	602498	AD CMT2	Proximal muscles predominantly involved
MME	120520	AD or AR CMT2	Late-onset axonal neuropathy; AR disease more severe and earlier onset
HINT1	601314	AR CMT2	Axonal neuropathy, 70–80 % hand and grip myotonia (neuromyotonia)
SLC25A46	610826	AR CMT2 or PCH1	Severe: congenital, lethal pontocerebellar hypoplasia with motor neuron disease (PCH1); Moderate: axonal neuropathy with optic atrophy
DCTN1	601143	AD dHMN	Adult-onset neuropathy, predominant upper extremity involvement, vocal cord palsy, facial weakness
SLC5A7	608761	AD dHMN	Juvenile-onset neuropathy with vocal cord palsy
PLEKHG5	611101	AR dHMN or intermediate CMT	Severe: early-onset motor neuropathy with proximal and distal weakness, respiratory compromise and contractures; Moderate: adult-onset sensorimotor neuropathy
IGHMBP2	600502	AR dHMN or CMT2	Severe: infantile SMA with respiratory distress (diaphragmatic palsy); Moderate: childhood-onset axonal neuropathy
TUBB3	602661	AD CMT2	Congenital fibrosis of the extraocular muscles with concomitant neuropathy (CFEOM) or isolated axonal neuropathy
SACS	604490	AR CMT1 or AR CMT2	Full phenotype: spastic ataxia Charlevoix–Saguenay; Limited disease: axonal-demyelinating neuropathy
MPV17	137960	AR CMT2	Full phenotype: mitochondrial DNA depletion syndrome, a severe disorder with brain and liver involvement that usually leads to early death; Limited disease: non-syndromic axonal neuropathy
CMTX3	302802	X-linked recessive CMT	Early infantile hand muscle weakness; unique 78 kb insertion into chromosome Xq27.1

AD = autosomal dominant, AR = autosomal recessive, CMT1 = demyelinating Charcot-Marie-Tooth disease, CMT2 = axonal Charcot-Marie-Tooth disease, dHMN = distal hereditary motor neuropathy.
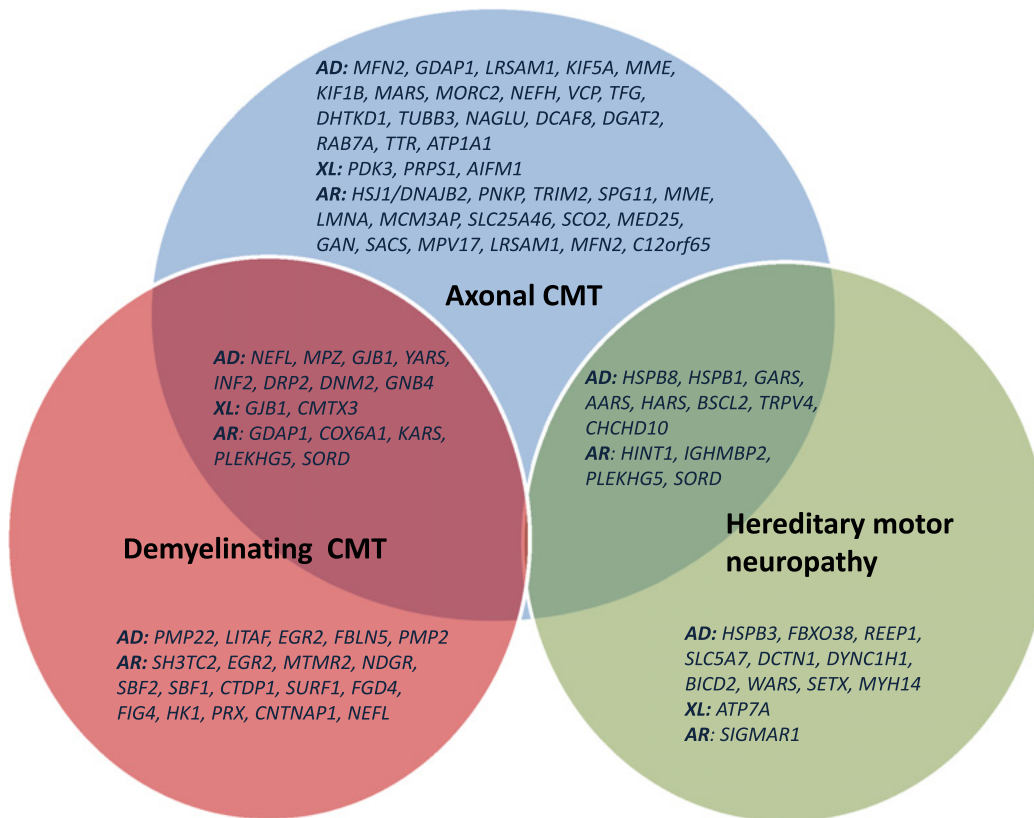
Axonal CMT

AD: MFN2, GDAP1, LRSAM1, KIF5A, MME, KIF1B, MARS, MORC2, NEFH, VCP, TFG, DHTKD1, TUBB3, NAGLU, DCAF8, DGAT2, RAB7A, TTR, ATP1A1
XL: PDK3, PRPS1, AIFM1
AR: HSJ1/DNAJB2, PNKP, TRIM2, SPG11, MME, LMNA, MCM3AP, SLC25A46, SCO2, MED25, GAN, SACS, MPV17, LRSAM1, MFN2, C12orf65

Demyelinating CMT

AD: NEFL, MPZ, GJB1, YARS, INF2, DRP2, DNM2, GNB4
XL: GJB1, CMTX3
AR: GDAP1, COX6A1, KARS, PLEKHG5, SORD

AD: PMP22, LITAF, EGR2, FBLN5, PMP2
AR: SH3TC2, EGR2, MTMR2, NDGR, SBF2, SBF1, CTDP1, SURF1, FGD4, FIG4, HK1, PRX, CNTNAP1, NEFL

Hereditary motor neuropathy

AD: HSPB8, HSPB1, GARS, AARS, HARS, BSCL2, TRPV4, CHCHD10
AR: HINT1, IGHMBP2, PLEKHG5, SORD

AD: HSPB3, FBXO38, REEP1, SLC5A7, DCTN1, DYNC1H1, BICD2, WARS, SETX, MYH14
XL: ATP7A
AR: SIGMAR1

Figure 1: Venn diagram of disease genes for Charcot-Marie-Tooth disease (subdivided into demyelinating and axonal CMT) and distal hereditary motor neuropathy (May 2020). Shaded areas represent overlap phenotypes between subtypes. AD = autosomal dominant, AR = autosomal recessive, XL = X linked.

Genetic diagnosis

Autosomal dominant CMT (AD-CMT) is the most common genetic subtype, followed by X-linked CMT, while autosomal recessive (AR) forms are rare in Middle European populations but are increasingly identified in populations with high consanguinity rates. Mutations in more than 90 genes related to CMT have been reported (Fig. 1), and many of these genes were identified in the past 10 years. Some neuropathy genes are directly linked to development, function, or maintenance of Schwann cells, myelin sheaths, neurons, and their axons while others are involved in more general biological processes (Fig. 2, modified from Weis and Senderek [7]). Molecular genetic diagnosis has become available for the majority (50–80 %) of CMT1 patients, especially for those with AD disease, as seen in larger studies based on conventional genetic analysis, i. e. MLPA and Sanger sequencing [2, 8–12]. This high detection rate is still maintained by three of the 'The Big Four' genes (Fig. 3), while the majority of mutations in rare genes affect only few families. CMT2 has no ma-

jor gene accounting for a considerable proportion of cases and, thus, molecular genetic diagnosis is available only for about 20–30 % patients [2, 8–12]. One obvious limitation of previous studies based on step-wise diagnostic algorithms is the lack of systematic screening of less frequent CMT genes (see below). In an international cross-sectional study summarising data from 13 centres (Inherited Neuropathies Consortium, 10 sites in the USA and one each in the UK, Italy, and Australia), 997 of 1652 patients (60.4 %) received a genetic diagnosis, 91.2 % of demyelinating CMT and 43 % of axonal CMT [13], confirming that the diagnostic yield is higher in demyelinating CMT than in axonal CMT.

Three genetic defects (*PMP22* duplication, *GJB1* or *MPZ* point mutations) are responsible for about 90 % of detectable mutations in patients with demyelinating CMT1. Similarly, the contribution of the three main genetic defects in axonal CMT2 (*GJB1*, *MFN2*, and *MPZ* mutations) to all CMT2 cases with a genetic diagnosis is about 80–85 %.
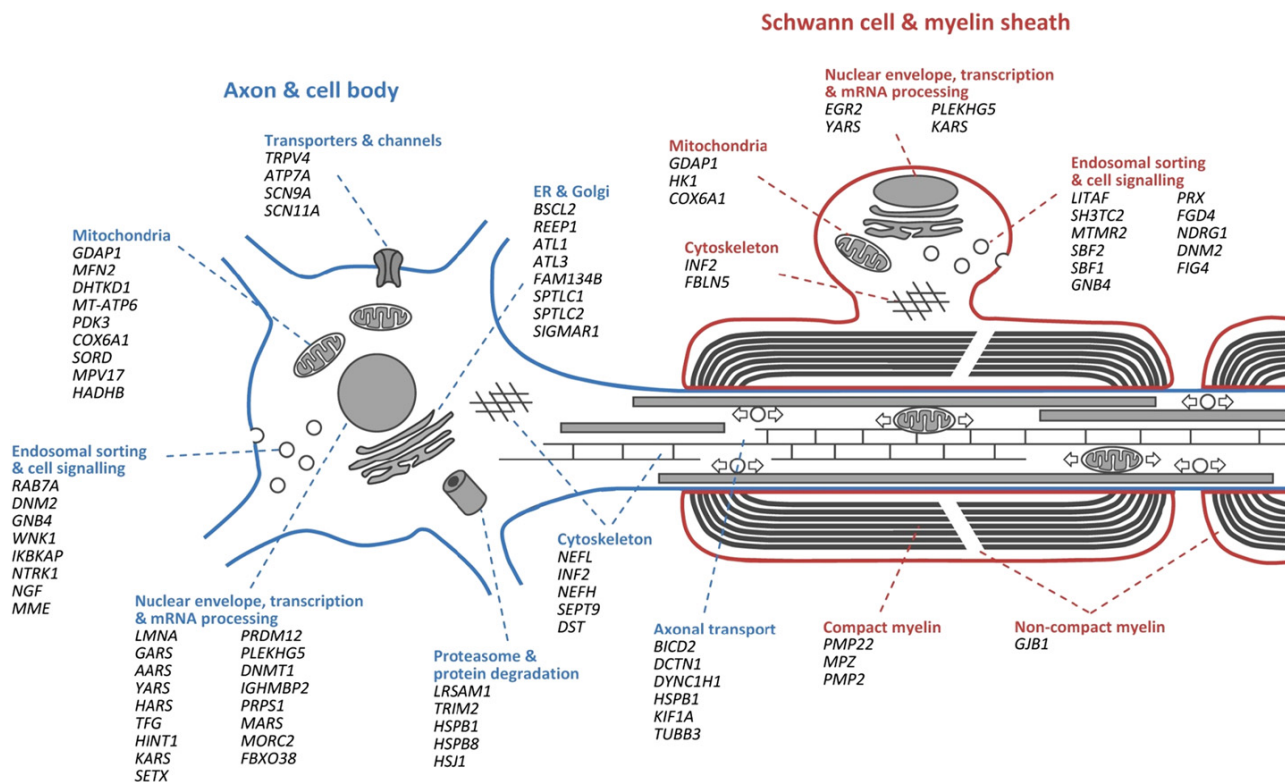
Schwann cell & myelin sheath

Axon & cell body

Transporters & channels
TRPV4
ATP7A
SCN9A
SCN11A

ER & Golgi
BSCL2
REEP1
ATL1
ATL3
FAM134B
SPTLC1
SPTLC2
SIGMAR1

Nuclear envelope, transcription & mRNA processing
EGR2   PLEKHG5
YARS   KARS

Mitochondria
GDAP1
HK1
COX6A1

Mitochondria
GDAP1
MFN2
DHTKD1
MT-ATP6
PDK3
COX6A1
SORD
MPV17
HADHB

Cytoskeleton
INF2
FBLN5

Endosomal sorting & cell signalling
LITAF   PRX
SH3TC2   FGD4
MTMR2   NDRG1
SBF2   DNM2
SBF1   FIG4
GNB4

Endosomal sorting & cell signalling
RAB7A
DNM2
GNB4
WNK1
IKBKAP
NTRK1
NGF
MME

Nuclear envelope, transcription & mRNA processing
LMNA   PRDM12
GARS   PLEKHG5
AARS   DNMT1
YARS   IGHMBP2
HARS   PRPS1
TFG   MARS
HINT1   MORC2
KARS   FBXO38
SETX

Proteasome & protein degradation
LRSAM1
TRIM2
HSPB1
HSPB8
HSJ1

Cytoskeleton
NEFL
INF2
NEFH
SEPT9
DST

Axonal transport
BICD2
DCTN1
DYNC1H1
HSPB1
KIF1A
TUBB3

Compact myelin
PMP22
MPZ
PMP2

Non-compact myelin
GJB1

Figure 2: Proposed pathomechanisms of gene products in hereditary neuropathies. Genes causing axonal CMT or dHMN are marked in blue, genes causing demyelinating CMT are marked in red.

Autosomal recessive CMT and dHMN

In patients with autosomal recessive inheritance, the clinical picture is often more severe and starts in early childhood or even infancy. Autosomal recessive inheritance can be assumed if there are at least two affected offspring of healthy parents or in isolated patients with parental consanguinity. Linkage analysis and homozygosity mapping were in the past used to reduce the number of potential disease genes for subsequent mutation analysis. Demyelinating autosomal recessive CMT is classified in OMIM as CMT4 and axonal autosomal recessive CMT as axonal AR-CMT. In an average Caucasian population autosomal recessive CMT is rare, as reflected by the small proportion of mutation-positive cases (0.9 % *GDAP1* and 0.2 % *SH3TC2*) among 17,000 CMT patients [14].

In a systematic study of 174 families with autosomal recessive CMT, Zimón et al. [15] obtained a mutation detection rate of 41.3 % with mutations identified in 10 different genes. The contribution to the overall diagnostic yield was 10.9 % for *GDAP1* and *HINT1*, 7.5 % for *SH3TC2*, and only 1.1 % for other genes. *HINT1* neuropathy was discov-

ered in 2012 and is among the most frequent causes in the Czech population. It is autosomal recessively inherited and caused by a single mutation in 90 % of Czech patients [16]. The clinical features are axonal neuropathy starting in the first two or three decades, often combined with action neuromyotonia or myokymic discharges.

Recently, biallelic *SORD* mutations were discovered in 38 unrelated families as the most frequent autosomal recessive form of axonal or intermediate CMT or dHMN [17]. All patients shared the mutation p.Ala253GlnfsTer27 in homozygous or compound heterozygous state. Since SORD is an enzyme that converts sorbitol into fructose and the absence of SORD protein results in high intracellular sorbitol accumulation, this might be a target for medical intervention, e. g. with aldose reductase inhibitors.

Whole exome sequencing (WES) applied to 15 autosomal recessive CMT2/dHMN families negative for 94 known neuropathy genes showed novel or very rare variants in genes not previously associated with peripheral neuropathy (*ARHGEF28*, *KBTBD13*, *AGRN*, *GNE*) or associated with other phenotypes (*VRK1*, *PNKP*), underlining the complexity of variant interpretation in WES analysis [18].
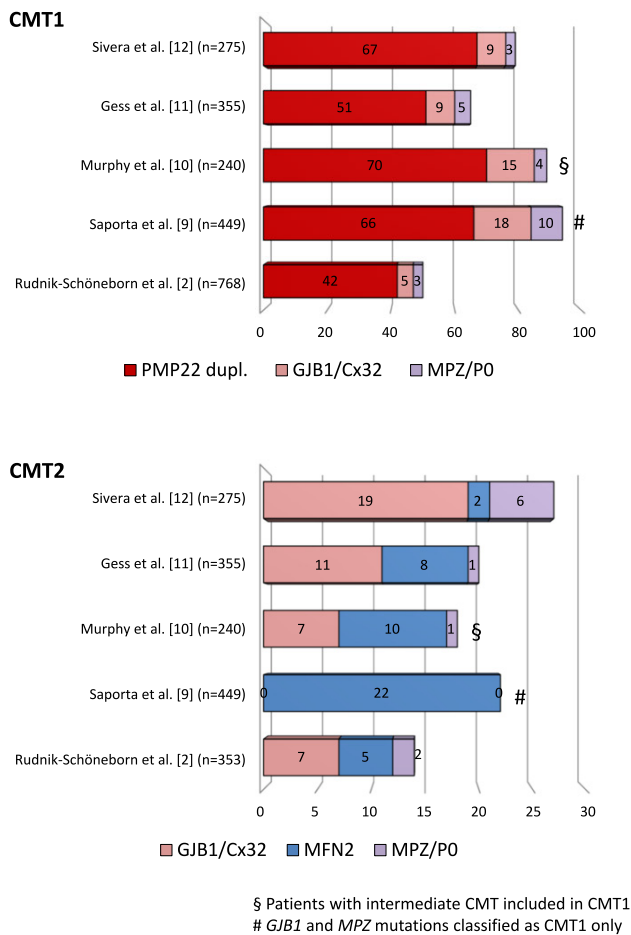
CMT1

CMT2

§ Patients with intermediate CMT included in CMT1
# *GJB1* and *MPZ* mutations classified as CMT1 only

Figure 3: Mutation detection rates of the 'Big Four' genes (%) in demyelinating CMT1 and axonal CMT2 in various studies based on similar diagnostic algorithms (all patients included, not restricted to index patients).

The 'Big Four' – *PMP22*, *GJB1*, *MPZ*, and *MFN2*

PMP22

CMT1A due to a 1.5 Mb genomic duplication on chromosome 17p11 encompassing the *PMP22* gene is by far the most frequent hereditary neuropathy. Duplications, deletions, and rare point mutations of *PMP22* lead to various types of neuropathy with predominant Schwann cell pathology (CMT1A, HNPP [see below], and very rare recessive CMT). The *PMP22* gene encodes the membrane glycoprotein peripheral myelin protein 22 (PMP22); proposed functions include Schwann cell maturation, myelination, myelin maintenance, and adhesion of myelin lamellae. In nerve biopsies of CMT1A patients, de- and remyelinated ax-

ons and classical Schwann cell onion bulb formations are frequent.

In CMT1A, prolonged distal motor latencies may already be present in the first months of life, and slow mCV can be found by age two years in most patients. However, clinical features may not occur until the second decade or even later in life. At the severe end of the phenotypic spectrum, patients can present with delayed motor development along with muscular hypotonia, marked proximal and distal weakness, and loss of ambulation. Age at onset and severity do not correlate with mCV slowing, while muscle weakness correlates with progressive decrease of the amplitudes of compound muscle action potentials. This suggests that secondary axonal pathology is ultimately responsible for the neurological deficits (for review see Bird [19]). Despite the rather uniform genetic cause in most CMT1A patients – *PMP22* gene duplication – there is a wide range of still unexplained clinical severity. In keeping with this, intrafamilial clinical variability can be remarkable in CMT1A pedigrees.

Patients with *PMP22* single nucleotide substitutions and indel variants can have a highly variable clinical and electroneurographic picture depending on the type and localisation of the mutation. Specific amino acid substitutions that are expected to result in a toxic gain of function [20] correlate with severe demyelinating peripheral neuropathy, while heterozygous null alleles (truncating or splicing mutations) mostly result in an HNPP phenotype [21].

GJB1

The *GJB1* gene on chromosome Xq13 encodes the gap junction protein beta 1, also known as connexin 32 (Cx32). Hemizygous or heterozygous *GJB1* mutations are the second most common genetic cause of CMT disease, comprising about 3–4 % of patients in Northern Europe and up to 10–15 % of patients in other countries worldwide [22]. Cx32 is a gap junction protein expressed by Schwann cells and many other cell populations. Cx32 appears to be involved in the trafficking of small molecules through the layers of the Schwann cell plasma membranes at sites of non-compacted myelin, that is, at Schmidt–Lanterman incisures and at nodes of Ranvier. Most *GJB1* mutations are thought to lead to loss of Cx32 functions. However, it was shown that mutations in the untranslated regions of *GJB1* can cause CMTX1 and may be responsible for about 10 % of cases [23]. Morphologically, *GJB1* mutations are associated with reduced myelin thickness, loss of predominantly

large myelinated nerve fibres, and clusters of small, regenerated myelinated nerve fibres.

The disease is X-linked dominantly inherited, i. e. most female mutation carriers develop variable symptoms and signs of a neuropathy. Males with *GJB1* mutations mostly have a demyelinating neuropathy and tend to be more severely affected than seen in CMT1A. Females often have mixed electroneurographic features and have mild to moderate symptoms of a peripheral neuropathy. Clinical manifestations can vary considerably, even within families. Symptoms typically develop in the first three decades, with onset commonly within the first decade in males [24]. Age at onset and severity might be correlated with specific mutations, and hearing loss, central nervous system abnormalities, and central visual, acoustic, and motor pathway involvement have been reported (for review see Bird [19]). In a large Japanese cohort comprising 112 patients, early-onset episodic stroke like episodes were observed in six patients [24].

MPZ

The *MPZ* gene on chromosome 1q22 encodes myelin protein zero, a major transmembrane glycoprotein of peripheral nerve myelin. Myelin protein zero acts as a homophilic adhesion protein that is thought to serve important functions in myelin development and compaction as well as myelin maintenance. Accordingly, initial studies reported demyelinating disease in patients with *MPZ*-related autosomal dominant CMT (CMT1B). Nerve biopsies may show uncompacted myelin lamellae, especially inner and outer lamellae [5]. As in CMT1A signs of repeated de- and remyelination including Schwann cell and basal lamina onion bulb formations as well as axonal loss and endoneurial fibrosis can be observed. *MPZ* mutations can also cause a mixed axonal and demyelinating (intermediate) or a predominantly axonal, often late-onset autosomal dominant neuropathy. In nerve biopsies of late-onset cases, there is a reduction predominantly of large myelinated nerve fibres, and clusters of regenerating nerve fibres are frequent. Some of these clusters are surrounded by concentrically arranged Schwann cell processes, forming so-called 'pseudo-onion bulbs'. It is unclear so far why certain *MPZ* point mutations cause a primary axonal phenotype. One possibility is the interference of these mutations with Schwann cell–axon interactions [25].

The largest study on *MPZ* mutations summarised clinical and molecular data of 103 patients from 71 different families [26]. The cohort was subdivided into infantile, childhood, and adult-onset groups. In the infantile-onset group (40 % of patients), there was delayed motor development and onset of symptoms before 5 years of age, about 30 % of patients required walking aids, and 20 % were wheelchair-bound. Electroneurographically, very slow mCV were obtained (80 % < 15 m/s). In the childhood-onset group (7 % of patients), age at onset was between 6 and 20 years and the clinical and electrophysiological picture was that of classical CMT1. In the adult-onset group (53 % of patients), mean age at onset was 40 years, progression was variable, and electrophysiological findings were mostly classified as CMT2. The authors observed enrichment of different *MPZ* mutations in each group, suggesting that specific *MPZ* mutations can determine clinical severity and the impact on peripheral nerve function.

MFN2

Autosomal dominant *MFN2* mutations on chromosome 1p36 are considered to be one of the most frequent causes of axonal CMT (CMT2A). The encoded mitofusin 2 protein is located in the outer mitochondrial membrane. Mutations alter the equilibrium between fusion and fission of the mitochondrial net and are thought to affect intra-axonal mitochondrial transport and bioenergetics including the OXPHOS system. Histopathologically, the number of myelinated fibres is reduced depending on the onset and duration of the disease and larger myelinated fibres may be preferentially affected. Regenerating axons may tend to form large clusters.

Mutation detection rates vary considerably in different populations, ranging from 2.4 % in a Spanish study [12] up to 21.9 % in a study from the US [9], but mostly accounting for 3–8 % of patients [22]. Age at onset and clinical severity of patients with *MFN2* mutations (CMT2A) can be highly variable and are not related to specific mutations [2]. Early studies implied that CMT2A is characterised by an early childhood onset and severe impairment, while more recent studies found a bimodal distribution of severity [27] with early-onset CMT and severe functional disability on one hand and a milder, slowly progressive late-onset phenotype on the other hand. Optic atrophy and vocal cord palsy were described in about 10 % of 43 French patients [28]. None of these features has been recorded in a series of 20 patients from Germany [2], suggesting that population-specific mutations or the ethnic and genetic background may affect the prevalence of additional clinical features in *MFN2* mutation carriers.

Hereditary neuropathy with liability to pressure palsies (HNPP)

HNPP is typically characterised by recurrent and focal episodes of peripheral nerve dysfunction along with specific electroneurographic features (increase in distal motor latencies, mCV slowing at entrapment sites). Prevalence has been estimated to be 7–16 per 100,000 individuals. Age at onset is usually between 20 and 30 years. The most frequent manifestations are repeated episodes of carpal tunnel syndrome and peroneal palsy with foot drop. The first episode usually occurs in the second or third decade. Recovery from acute focal paresis is often complete and there is usually no significant residual disability. However, irreversible axonal damage may occur at entrapment sites in motor nerves and progress with age [29]. The most characteristic histological features are so-called tomacula, which are concentric myelin thickenings, but they are not pathognomonic. Nerve biopsies also show segmental de- and remyelination and varying large-fibre loss.

Most HNPP cases result from a 1.5 Mb genomic deletion encompassing the *PMP22* gene – the reciprocal event of the *PMP22* duplication observed in CMT1A. Much more rarely, *PMP22* point mutations (usually loss-of-function) and single or multiple exon deletions are found. The diagnostic yield of *PMP22* deletions among patients with suspected HNPP is usually high, reaching over 90 % in some case series, but is much lower in clinical practice. Due to the recurrent/relapsing course of HNPP, differential diagnosis includes carpal tunnel syndrome, CIDP, vasculitic neuropathy, multifocal motor neuropathy, and another relapsing autosomal dominant neuropathy, hereditary neuralgic amyotrophy (HNA). HNA is caused by *SEPT9* mutations, shows predilection for the brachial plexus, and is characterised by episodes of intense pain.

About 10 % of patients with *PMP22* deletions show electrophysiological features similar to CMT1 or CMT2 [2], and several patients were reported with generalised neuropathy [29, 30]. This observation is of practical relevance for molecular genetic diagnostics as it suggests that patients with hereditary neuropathies (except for the clinically distinct HSAN, see paper by Cox et al. [31] in this issue) should generally be screened for *PMP22* copy number variations.

Distal hereditary motor neuropathy (dHMN)

Distal HMN is a pure motor neuropathy characterised by progressive distal muscle weakness and muscular atrophy without sensory impairment. It is also referred to as distal spinal muscular atrophy (DSMA). Indeed, the OMIM classification refers to autosomal dominant forms as HMN and to the autosomal recessive forms and the only known X-linked form as DSMA. HMN has obvious phenotypic overlaps with CMT2 (Fig. 1), which is a motor-predominant neuropathy, but also with proximal spinal muscular atrophy, motor neuron diseases, and hereditary spastic paraplegias.

Current classifications of HMN still partially follow subtypes defined by Harding et al. [32] based on inheritance pattern, age at onset, and the presence of additional features. Most patients have adult-onset autosomal dominant disease (HMN II), some with pronounced upper limb involvement or signs of upper motor neuron involvement (HMN V), and vocal cord paralysis (HMN VII).

Autosomal recessive forms are rare and often clinically more severe. Patients with one particular subtype with infantile onset and diaphragm weakness (HMN VI) usually die within the first three months of life due to respiratory failure. Notably, mutations in the *IGHMBP2* gene have also been found in autosomal recessive CMT2 with a much more benign course and no clinically relevant respiratory impairment even in adults.

Thanks to advances in the identification of novel disease genes, the diagnostic yield in dHMN has increased from 10–20 % by conventional Sanger sequencing attempts [33] to 30–40 % in cohorts who underwent multigene panel testing and WES [34, 35]. The most important dHMN genes in a British study [34] were *IGHMPB2*, *BICD2*, *GARS*, *SYT2*, *TRPV4*, *DHTKD1*, and *MFN2*, while mutations in *HSPB1*, *IGHMBP2*, *GARS*, and *BSCL2* were most frequent in Chinese patients with pure HMN [35]. In keeping with phenotypic similarities, many of the genes are shared between CMT2 and dHMN, indicating overlapping disease mechanisms. Variable phenotypic expressions are seen in many CMT and dHMN subtypes (Table 1).

Major genetic causes of motor neuropathies

In the past years our understanding of pathogenic pathways in motor neuropathies has improved substantially. Autosomal dominant mutations in five genes (*GARS*, *YARS*, *AARS*, *HARS*, *WARS*) encoding aminoacyl-tRNA synthetases (ARSs) cause rare axonal CMT or dHMN [36]. ARSs are responsible for charging amino acids to cognate tRNA molecules. Autosomal recessive mutations in these genes severely reduce the amount of charged tRNA for protein translation and cause severe, early-onset multisystem disease (*GARS*: mitochondriopathy and cardiomyopathy; *YARS*: multisystem disease with developmental delay; *AARS*: infantile epileptic encephalopathy; *HARS*: Usher syndrome). Mutations in autosomal dominant ARS-related neuropathy most likely act as a dominant negative mechanism or a toxic gain-of-function effect [36].

Mutations in chaperone proteins (most commonly *HSPB1*/*HSPB27* and *HSPB8*/*HSPB22*) are reported in 5–8 % of dHMN patients [37]. Chaperones are activated during stress and protect cells against damaged and unstable proteins. The phenotype of HSPB-related neuropathy is characterised by distal lower limb weakness with a wide range of age at onset, mildly elevated CK activity, sometimes along with mild sensory involvement or pyramidal signs. As such there is a considerable overlap between CMT2, dHMN, and motor neuron disease. In a large study in France and Belgium including 510 unrelated patients, the diagnostic yield of *HSPB1* was 5.5 % and 0.8 % in *HSPB8*, while no mutation was found in *HSPB3*, G*ARS*, *BSCL2*, *TRPV4*, or *MFN2* [37].

One striking example of clinical heterogeneity are heterozygous *BSCL2* mutations, which can lead to a broad spectrum of phenotypes ranging from CMT2 over dHMN V with uni-or bilateral wasting of the thenar or dorsalis interosseus muscles to pure spastic paraplegia. The combination of spasticity of the lower limbs accompanied by amyotrophy of the hands has historically also been referred to as Silver syndrome (SPG17). *BSCL2* encodes seipin, an integral endoplasmic reticulum membrane protein, which is highly expressed in nervous tissues, including the brain and spinal cord [38]. Two hot spot mutations in *BSCL2* (p.N88S and p.S90L) have been repeatedly reported.

Late-onset CMT2

The prevalence of hereditary neuropathies starting beyond the fourth decade of life might have been under-estimated. Variants in known CMT2 disease genes (*MPZ*, *MFN2*, *LRSAM1*, and *HSPB1*, amongst others) can lead to late-onset axonal neuropathies. More recently, recessive mutations in the *MME* gene (encoding the metalloprotease neprilysin) have been identified in patients with late-onset CMT2 in several studies [39, 40]. However, it has also been demonstrated that heterozygous loss of function and most likely also missense variants in *MME* are associated with a distinct, incompletely penetrant CMT phenotype consisting of a severe and unusually progressive late-onset axonal neuropathy that manifests predominantly in the lower limbs. Due to usually advanced age at onset (on average around 55 years), this type of CMT poses differential diagnostic challenges with regard to CIDP, paraneoplastic neuropathies, and motor neuron diseases.

Rare genes coming into focus: results of larger NGS studies

At the time of this writing, multigene panel or WES studies in CMT are still disappointing as regards the contribution of additional genes to the overall diagnostic yield. At present, it is difficult to compare the published NGS studies as the inclusion criteria of patients and methods varied or were ill-defined regarding previous genetic tests.

In 2014, a large US study of over 17,000 individuals with neuropathy covering 14 CMT genes was published [14]. No further phenotypic classification was provided, but of all patients who received a genetic diagnosis (18.5 %), *PMP22* duplications and mutations in the Big Four genes accounted for the majority (73.0 %) of positive findings. All other genes tested remained below 1 % of overall mutation frequencies.

In a British NGS panel assay including 56 genes [41], 448 patients were studied after being tested 'negative for the common causes of inherited polyneuropathy'. The diagnostic yield was 31 % (137 patients) in 31 genes. In CMT1, 41 % of patients received a diagnosis with *SH3TC2* mutations being most frequent (10 %). The detection rate was 35.5 % in CMT2 and 26.4 % in dHMN with single contributions of genes not exceeding 5 %.

In the Czech Republic, Lassuthova et al. [42] investigated 198 unrelated patients negative for *PMP22* dup/del and for other frequent CMT genes. The authors used different panels of 59–93 genes. They found causative mutations in 51 (26 %) of patients and concluded that gene panel testing added only 3 % to the conservative methods of MLPA and Sanger sequencing.

In a German study comprising 612 index patients [43], a gene panel analysis of 54–84 genes including deletion/duplication testing of *PMP22*, the genetic diagnosis was established in 121 cases (19.8 %). Pathogenic variants were most frequent in the Big Four genes (43.6 %), followed by *SH3TC2* (9.9 %) and *HINT1* (4.1 %), while other genes accounted for less than 4 % of the whole diagnostic yield.

In Denmark, a targeted gene panel of 63 CMT genes was used to study 195 patients who had not reached a molecular diagnosis by Sanger sequencing and quantitative analysis [44]. The authors found not more than a 5.6 % increase in the diagnostic yield with the introduction of a targeted NGS approach. In Japan, Yoshimura et al. [22] studied 1005 *PMP22* dup/del negative patients using targeted gene panels and found mutations in 40 genes in 301 (30.0 %) patients. Mutations were most commonly seen in the Big Four genes (18.3 %), while the remaining genes contributed less than 2 % each. Interestingly, the prevalence of *PMP22* dup/del was stated to be as low as 23.3 % among Japanese demyelinating CMT patients [22].

Bacquet et al. [45] analysed 123 French *PMP22* dup/del negative patients (23 % CMT1, 52 % CMT2, 9 % dHMN, 7 % HSAN, 6.5 % intermediate CMT) by means of a targeted panel including 81 neuropathy genes. The total detection rate was 40 % and potentially pathogenic variants were found in 9 % of patients. Major contributing genes (more than 5 %) were *MFN2* (7.7 %), *SH3TC2* (6.4 %), *NEFL* (5.1 %), *GDAP1* (5.1 %), and *GAN* (5.1 %).

Cortese et al. [46] enrolled 220 patients from London (UK) and Iowa (USA) after *PMP22* dup/del had been excluded. NGS panel analysis included about 50 genes and resulted in a genetic diagnosis in 67 (30 %) patients. Most frequent mutations were seen in the Big Four genes (11.8 %) followed by *SH3TC2* (3.6 %), while other genes did not reach a proportion of at least 2 %.

Lee et al. [47] used a targeted gene panel (72 genes) to analyse 175 US patients with axonal neuropathy. A genetic cause was only revealed in 4.6 % of patients: in 7 % of patients with a family history, and in 2 % of sporadic patients.

There are only few data from WES studies up to now as summarised in the study by Hartley et al. [48]. The authors performed exome analysis in 50 families in Canada who were screened negative for mutations in common genes according to their clinical presentation. Disease-causing mutations were found in 12 (24 %) families, ranging from 0 % in HSN/HSAN, 24 % in CMT, and 36 % in HMN. Most mutations were detected in well-known genes, but the authors claimed to have identified two novel disease-causing genes.

Suggested diagnostic algorithms

Providing an accurate diagnosis in hereditary neuropathies is important for patients and families although no causal therapy is currently available for any subtype. It allows prediction of the future disease course, prevention of known complications, and appropriate socio-medical counselling. It will also prevent unnecessary and strenuous treatment and eliminate the need for invasive diagnostic steps. Moreover, specific genetic counselling of family members at risk often depends on the precise molecular diagnosis. Genetic counselling has to take into account that there may be subjectively asymptomatic individuals who are identified as mutation carriers by family investigation following the genetic diagnosis in the index patient.

Quantitative analysis of *PMP22* copies is the obvious first-tier analysis in patients with a diagnosis of CMT1 and HNPP (Fig. 4). Moreover, since *PMP22* deletions may occasionally lead to an axonal neuropathy and screening for *PMP22* copy number variations is a rapid and inexpensive test, patients with suspected CMT2 and dHMN should also undergo quantitative assessment of *PMP22* copy numbers. If negative, patients with suspected HNPP should be tested for *PMP22* point mutations and single and multiple exon deletions. In CMT families compatible with X-linked inheritance, *GJB1* analysis may be the next step and should include the analysis of the UTRs and promotor regions.

Gene sequencing has moved in the past 5 years from phenotype-oriented single gene sequencing to multigene panels or exome-wide sequencing. There are various approaches for the design of multigene panels and filtering of exome-wide sequencing data (e. g. CMT-subtype specific panels or broader selection of all known CMT and dHMN genes). Pragmatically, due to the considerable clinical, electrophysiological, and genetic overlap between CMT and dHMN, it seems reasonable to analyse the complete collection of CMT and HMN genes for all cases. The HSAN are usually clearly distinguishable clinically from CMT or dHMN and are caused by mutations in a distinct set of genes that show no overlap with CMT and dHMN apart from *RAB7A* [49]. One challenge arising from the use of next-generation sequencing technologies in a diagnostic setting is that analysis of multiple genes often yields variants in more than one gene and diagnostic laboratories and clinicians then face the difficulty to decide which – if any – of these variants constitutes the relevant disease-causing mutation. In addition to bioinformatic predictions, allele frequencies in control populations, and segregation studies, algorithms previously established for prioritisation of genes in the era of single gene sequencing can be used for assessment of the pathogenic relevance of variants found by high-throughput sequencing.
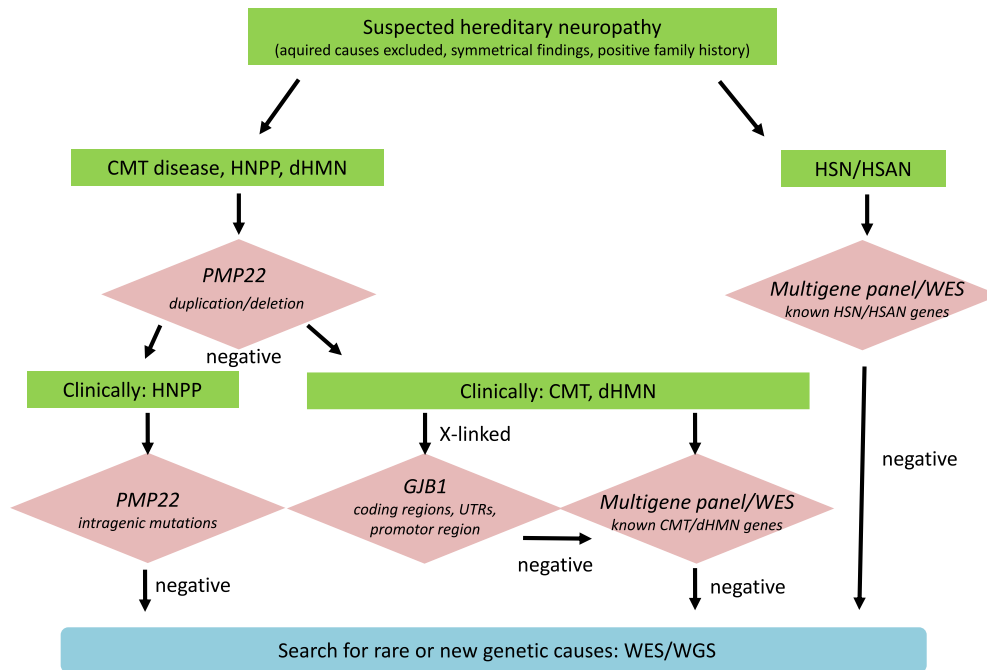
Figure 4: Proposed algorithm for molecular genetic diagnosis of hereditary neuropathies. A clinical subdivision of patients with motor or pure sensory neuropathy is helpful to subdivide patients for *PMP22* copy number analysis or for direct multigene testing. If *PMP22* copy number analysis is not diagnostic (negative), clinical distinction of HNPP and CMT/dHMN will sort out patients for *PMP22* mutation analysis only and those for broader multigene testing. If a pedigree is compatible with X-linked inheritance, it is recommended to analyse coding and non-coding regions of *GBJ1*. Patients who are tested negative for known neuropathy genes may be included in further whole exome or genome sequencing (WES/WGS) to detect mutations in rare and new genes.

Management

Management of most hereditary neuropathies is presently aimed at supportive treatment modalities, addressing leading symptoms. It includes physical treatment, occupational therapy, orthotics, and assistive devices for musculoskeletal dysfunctions [50]. A physical therapy programme for patients with CMT should involve muscle stretching to prevent muscle tightening and loss of strength. Rehabilitation may play an important role in preventing complications and improving the quality of life of patients with CMT. However, the efficacy of rehabilitation, the most appropriate physiotherapy protocol, and the optimal frequency of treatment are still unclear.

Corrective surgery of joint contractures and scoliosis should be undertaken in experienced centres and taking the progressive nature of the disease into account. Since there are different iatrogenic complications associated with therapeutic interventions, it is important to assess risk–benefit ratios and provide appropriate counselling. Respiratory dysfunction should be monitored if present and treated accordingly. Pain control is a difficult issue and includes topical medications (e. g. lidocaine patch), antidepressants (e. g. tricyclics), and anticonvulsants (e. g. gabapentin, pregabalin). In addition, patients have to be informed to avoid possible neurotoxic drugs.

There have been significant advances in potential therapeutic interventions for some forms of hereditary neuropathies related to metabolic disorders [51], Fabry disease [52], and familial amyloid polyneuropathy [53]. However, at the time of writing no causal treatment is available for hereditary neuropathies with selective peripheral nerve involvement. Basic research into therapeutic strategies is being done using transgenic animal models to develop new human applications. Larger clinical trials with different drugs as yet failed to show a therapeutic effect (for review see Rossor et al. [54]). With the foundation of the German CMT Network, several projects were initiated to further understand the natural history of CMT1A and to determine outcome measures and surrogate biomarkers in animal models and patients. One important finding was that phospholipid supplementation in a mouse model of CMT1A showed a dramatic response [55]. A clinical study with lecithine in Germany is planned to start in late 2020 (www.cmt-register.de).

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