Classification of the hereditary motor and sensory neuropathies

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Abbreviations

AD	autosomal dominant
AR	autosomal recessive
CCFND	congenital cataracts facial dysmorphism neuropathy
CHN	congenital hypomyelinating neuropathy
CMT	Charcot-Marie-Tooth
Cx 32	connexin 32
DSD	Dejerine-Sottas disease
EGR	early growth response
HMSN	hereditary motor and sensory neuropathy
HMSNL	hereditary motor and sensory neuropathy Lom
HNPP	hereditary neuropathy with liability to pressure palsies
MTMR2	myotubularin-related protein 2
NDRG1	N-myc downstream-regulated gene
NF-L	neurofilament-light gene
PMP-22	peripheral myelin protein 22
Po	myelin protein zero

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The classification of the hereditary motor and sensory neuropathies is currently in a state of constant change. Like many other hereditary diseases, the original clinical classification is being supplemented and partially replaced by a genetic classification. One of the limiting factors at present is that all the causative genes for the hereditary motor and sensory neuropathies have not been described. This means that a combination of a clinical classification and an incomplete genetic classification is in use which inevitably leads to confusion for the practising clinician not least because the clinical literature tends to refer to these diseases as the hereditary motor and sensory neuropathies (HMSN) and the genetic literature uses the term Charcot-Marie-Tooth disease (CMT). In terms of nomenclature these terms are only interchangeable to a limited extent (HMSN I/CMT1 and HMSN II/CMT2).

Charcot-Marie-Tooth syndrome (also known as peroneal muscular atrophy) was originally described as a single disease [1] but earlier in this century was recognized to be heterogeneous [2,3]. The classification system that has been most widely used to date, the hereditary motor and sensory neuropathy classification (HMSN), is based on clinical and electrophysiological criteria. HMSN is divided into seven forms (HMSN I to VII) but only the terms HMSN I, II and III were ever in common usage as the other forms are rare (HMSN IV (Refsum's syndrome), HMSN V (+ spastic paraplegia), HMSN VI (+ optic atrophy), HMSN VII (+ retinitis pigmentosa)) [1]. HMSN I refers to a demyelinating neuropathy with reduced nerve conduction velocities (typically median nerve motor conduction velocity less than 38 m/s); HMSN II is an axonal neuropathy with normal or near normal motor nerve conduction velocities; HMSN III is a severe demyelinating neuropathy starting in infancy with typical median nerve motor conduction velocities below 10 m/s. Following the description of some of the underlying genes for these disorders the term CMT became favoured in the genetic literature such that CMT1 refers to HMSN I and CMT2 donates HMSN II (Table 1). The difficulties have arisen as more genes or loci were described with some authors using the CMT system and others the HMSN system. Two examples of this confusion are HMSN III and the demyelinating autosomal recessive hereditary motor and sensory neuropathies. There is no CMT equivalent of HMSN III as the most common underlying genetic defects causing HMSN III were found to be *de novo* point mutations of the two genes that usually cause CMT1 (HMSN I), PMP-22 and Po [4,5] (Table 1). Therefore

Table 1. Classification of Charcot-Marie-Tooth disease

Clinical type	Inheritance	Locus/Gene
1. Demyelinating		
Charcot-Marie-Tooth type 1 autosomal dominant (CMT 1/HMSN I)		
CMT 1A	AD	Duplication 17p11.2/PMP-22
		Point mutation PMP-22
CMT 1B	AD	Point mutation Po
CMT 1C	AD	Unknown
CMT 1D	AD	Point mutation EGR2
Charcot-Marie-Tooth type 1 x-linked (CMT 1X)		
CMT 1X	X-linked	Point mutation Cx32
Dejerine-Sottas disease (HMSN III)		
DSD A	AD (AR)	Point mutation PMP-22
DSD B	AD (AR)	Point mutation Po
DSD C	AD	Point mutation EGR 2
DSD D	AD	8q23–q24
Congenital hypomyelinating neuropathy (CHN)		
CHN A	AD	Point mutation PMP-22
CHN B	AD	Point mutation Po
CHN C	AD (AR)	Point mutation EGR2
Hereditary neuropathy with liability to pressure palsies (HNPP)		
HNPPA	AD	Deletion 17p11.2/PMP-22
		Point mutation PMP-22
HNPP B	AD	Unknown
Charcot-Marie-Tooth type 1 autosomal recessive (CMT1 AR)		
CMT1 AR A (CMT4A)	AR	8q13–21.1
CMT1 AR B1 (CMT4B1)	AR	11q22/MTMR2
CMT1 AR B2 (CMT4B2)	AR	11p15
CMT1 AR C	AR	5q23-q33
CMT1 AR D (HMSNL)	AR	8q24/NDRG1
CMT1 AR E (CCFDN)	AR	18q
CMT1 AR F (CMT4F)	AR	19q13.1-13.3
2. Axonal		
Charcot-Marie-Tooth type 2 autosomal dominant (CMT 2/HMSN II)		
CMT 2A	AD	1p35–p36
CMT 2B	AD	3q13–q22
CMT 2C	AD	Unknown
CMT 2D	AD	7p14
CMT 2E	AD	8p21/NF-L
CMT 2F	AD	Point mutation Po
CMT 2G (HMSNP)	AD	3q13.1
Charcot-Marie-Tooth type 2 x-linked (CMT 2X)		
CMT 2X	X-linked	Xq24–q26
Charcot-Marie-Tooth type 2 autosomal recessive (CMT2 AR)		
CMT2 AR A	AR	1q21.2–21.3
CMT2 AR B (CMT4C)	AR	Unknown

AD, Autosomal dominant; AR, Autosomal recessive; PMP-22, Peripheral myelin protein 22; Po, Myelin protein zero; EGR2, Early growth response 2; Cx32, Connexin 32, MTMR2, Myotubularin-related protein 2; NDRG1, N-myc downstream-regulated gene 1; NF-L, Neurofilament-light gene.

HMSN III is now considered to be a more severe form of CMT1 (HMSN I) rather than a separate condition. The confusion is further compounded because the genetic literature uses the term Dejerine Sottas disease (DSD) for HMSN III (DSD A = PMP-*22* point mutations, DSD B = Po point mutations). The other very confusing area is the autosomal recessive hereditary motor and sensory neuropathies. One genetic classification refers to these as CMT4 [6] but more recent descriptions of new loci that don't fit into the CMT4 classification (CMT 4A, CMT 4B and CMT 4C) use other terms including HMSNL [7] and CCFND [8] (Table 1). Currently, for the reasons outlined above, a combination of the old clinical classification based on the basic division into HMSN I(CMT1) and HMSN II(CMT2) and a more detailed genetic classification is in use. A recent up to date and clearly presented classification using this principle is that of Schenone *et al.* [9].

The question that needs to be addressed now is how the HMSNs should be classified in the future when all the causative genes have been described. There are advantages and disadvantages to almost every classification system that could be devised. The original clinical/electrophysiological/pathological classification alone would not be sufficient as some diseases have already been described that are very similar from a clinical/electrophysiological/pathological point of view but have many different underlying genetic causes. Examples of this are HMSN IA (CMT 1A), HNPP and CMT 4B. HMSN IA (CMT 1A) describes an autosomal dominant demyelinating neuropathy but can be caused by a duplication of PMP-*22* or point mutations in PMP-*22* [9]. HNPP (hereditary neuropathy with liability to pressure palsies) can be caused by a deletion of PMP-*22* or point mutations in PMP-*22* [9]. CMT 4B refers to an autosomal recessive demyelinating neuropathy with focally folded myelin but can be caused by at least two different genes, myotubularin-related protein *2* [10] and an as yet unidentified gene on chromosome 11p15 [11]. Another way to classify the HMSNs would be to maintain the basic classification into demyelinating and axonal types which is already in common use, i.e. HMSN I(CMT1) and HMSN II (CMT2). This seems sensible but there are some difficulties as some genes (e.g. Po) can cause both a demyelinating and an axonal neuropathy. Po usually causes demyelinating neuropathies, i.e. HMSN IB (CMT 1B), DSD and congenital hypomyelinating neuropathy (CHN) [12], but it has recently been shown to occasionally cause HMSN II (CMT2), an autosomal dominant axonal neuropathy [13]. A classification based on the division into demyelinating and axonal forms would have to take this into account. A third possibility is to use a genetic classification alone. It has been anticipated that when all the underlying genetic defects in HMSN are known that perhaps a genetic classification dividing the HMSNs into PMP-*22* related disorders, Po-related disorders, Connexin 32-related disorders, etc. could be used. From a practising clinicians point of view this would not be a good idea as the clinician will always want to determine if the neuropathy is demyelinating or

axonal before deciding which genetic tests to do rather than order a battery of time consuming and expensive genetic tests first.

The first question when deciding what classification system to use is to decide whether to use the CMT or HMSN nomenclature as the continuing use of both terms will only cause confusion in the future. As CMT has been employed in the genetic literature and more often than not new genes are described in CMT terms, I think CMT rather than HMSN should be used but I think it is reasonable to retain the terms DSD and CHN as they imply increasing levels of severity. In Table 1, the CMT nomenclature has been retained as the primary nomenclature but the appropriate HMSN terms are shown where relevant. When dealing with a patient that one suspects has an inherited neuropathy, the most important questions in the clinical setting are whether the neuropathy is axonal or demyelinating and whether the inheritance pattern can be ascertained from the family history. I would therefore suggest that the best classification would be one which takes this into account and maintains the basic distinction of CMT into demyelinating and axonal forms and then further divides them by inheritance pattern into dominant, x-linked and recessive forms as suggested in Table 1. This is not always as straightforward as it sounds as in certain conditions such as DSD A, DSD B and CHN C, point mutations in the relevant genes, PMP-*22*, Po and EGR*2* can exist in the heterozygous or the homozygous state [4,5,12,14,15]. Therefore DSD A, DSD B and CHN C can be autosomal dominant or recessive depending on the point mutation.

One of the most important principles of any classification system is to keep it as simple as possible which is increasingly difficult with the CMTs for the reasons outlined above. The practice of subdividing groups into A, B C, etc. works well and should be maintained as it is easy to apply. This system is already well established for CMT1 (CMT 1 A, B, C, and D) and CMT*2* (CMT *2* A, B, C and D) [9]. Recently a new form of autosomal dominant CMT2 has been described in a Russian family secondary to a point mutation in the neurofilament-light gene on chromosome 8p21 [16]. The authors have termed this CMT 2E. Although some authors have used the term CMT 2E to described CMT *2* secondary to Po point mutations [9], it is probably more appropriate to keep this term for the new neurofilament-light gene associated CMT2. Po point mutation associated CMT2 could then be called CMT 2F. CMT *2* could be also further extended to include the proximal form of CMT *2*, i.e. HMSNP [17], which would be termed CMT *2*G (Table 1).

This system could also be used for DSD and CHN. DSD is already subdivided into DSD A and DSD B where DSD A refers to PMP-*22* point mutations and DSD B to Po point mutations. This could then be expanded by adding DSD C for DSD associated with point mutations in EGR *2* [18] and DSD D for autosomal dominant DSD linked to chromosome 8q23–q24 [19]. CHN could similarly be divided into CHN A, B and C, where CHN A refers to CHN with point mutations in PMP-*22* [20], CHN B point mutations in Po [12] and CHN C point mutations in EGR*2* [15].

The most difficult area in classification presently is the autosomal recessive hereditary motor and sensory neuropathies. It would be useful to stick to the basic system where demyelinating forms are referred to as CMT1 and axonal forms as CMT2 with the addition of a descriptive system based on the inheritance pattern. The demyelinating autosomal recessive CMTs would then be termed CMT1 AR and the axonal autosomal recessive CMTs termed CMT2 AR (Table 1). These could then be further subdivided using the A, B, C system such that CMT1 AR would be divided into CMT1 AR A, B1, B*2*, C, D, E and F. This differs from the current system of CMT 4 A/CMT 4B/HMSNL/CCFND and the current terms used for these conditions are given in parentheses in Table 1. CMT1 AR A is CMT 4 A [6]; CMT1 AR B1 is CMT 4B1, caused by mutations in myotubularin-related protein *2* [10]; CMT1 AR B*2* is CMT 4B*2*, linked to chromosome 11p15 [11]; CMT1 AR C is linked to chromosome 5q23-q33 [21]; CMT1 AR D is HMSNL, which has recently been shown to be due to mutations in a new gene, N-myc downstream-regulated gene 1 [*22*,*23*]; CMT1 AR E is CCFND linked to chromosome 18q [24] and finally CMT1 AR F also called CMT 4F refers to the newest form of AR CMT linked to chromosome 19q13.1–13.3 [25]. In Table 1, CMT*2* AR has been similarly divided into A and B such that CMT2 AR A refers to the recessive axonal form of CMT linked to chromosome 1q21.1–21.3 [26] and CMT2 AR B refers to the old CMT4C which has yet to be linked [6].

There is no perfect classification system for Charcot-Marie-Tooth disease but when all the causative genes are known it must be remembered that whatever classification system is adopted, it must be easily applicable by the practising clinician to direct appropriate genetic testing.

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