

REVIEW ARTICLE

Unraveling the Genetics of Distal Hereditary Motor Neuronopathies

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Abstract

The hereditary motor neuronopathies (HMN [MIM 158590]) are a heterogeneous group of disorders characterized by an exclusive involvement of the motor part of the peripheral nervous system. They are usually subdivided in proximal HMN, i.e., the classical spinal muscular atrophy syndromes and distal hereditary motor neuronopathies (distal HMN) that clinically resemble Charcot-Marie-Tooth syndromes. In this review, we concentrate on distal HMN. The distal HMN are clinically and genetically heterogeneous and were initially subdivided in seven subtypes according to mode of inheritance, age at onset, and clinical evolution. Recent studies have shown that these subtypes are still heterogeneous at the molecular genetic level and novel clinical and genetic entities have been delineated. Since the introduction of positional cloning, 13 chromosomal loci and seven disease-associated genes have been identified for autosomal-dominant, autosomal-recessive, and X-linked recessive distal HMN. Most of the genes involved encode protein with housekeeping functions, such as RNA processing, translation synthesis, stress response, apoptosis, and others code for proteins involved in retrograde survival. Motor neurons of the anterior horn of the spinal cord seems to be vulnerable to defects in these housekeeping proteins, likely because their large axons have higher metabolic requirements for maintenance, transport over long distances and precise connectivity. Understanding the molecular pathomechanisms for mutations in these genes that are ubiquitous expressed will help unravel the neuronal mechanisms that underlie motor neuropathies leading to denervation of distal limb muscles, and might generate new insights for future therapeutic strategies.

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Introduction

In 1886, Charcot, Marie, and Tooth published what is considered to be the first clear description of hereditary motor and sensory neuropathy (HMSN or CMT) (Charcot and Marie, 1886; Tooth 1886). Subsequent clinical, morphological, and electrophysiological studies demonstrated that this syndrome is heterogeneous leading to the delineation of three distinct groups of peroneal muscular atrophy syndromes (Dyck et al., 1993):

1. hereditary motor and sensory neuropathy (HMSN including CMT type 1 and 2);
2. distal hereditary motor neuro(no)pathy (HMN, also known as distal spinal muscular atrophy [SMA], or spinal CMT); and
3. a predominantly sensory form, hereditary sensory and autonomic neuropathy (HSN or HSAN).

The distal HMN were considered to be a separate entity because they presented as a clinically, electrophysiologically, and morphologically exclusive motor neuropathy. They are often referred to as neuronopathies instead of neuropathies based on the hypothesis that the primary pathological process resides in the cell body of the anterior horn cell and not in the axons. To what extent the involvement is always exclusively motor is still a matter of debate because minor sensory abnormalities have been described. This controversy is not only limited to distal HMN, because mild neurophysiological and neuropathological abnormalities in sensory nerves have also been described in other motor neuronopathies such as familial amyotrophic lateral sclerosis (ALS) (Ben Hamida et al., 1987), and Werdnig-Hoffmann disease or SMA type 1 (Carpenter et al., 1978). This indicates that although the brunt of the injury in motor neuronopathies falls on the motor neurons there might also be minor sensory involvement (Christodoulou et al., 2000).

In one of the earliest reports on distal HMN, Nelson and Amick described a family with an autosomal-dominant mode of inheritance and onset in early adult life (Nelson and Amick, 1966). Subsequently, kinships with an autosomal-recessive inheritance and isolated patients were described (Emery, 1971). Patients were described with variable onset ages, ranging from infancy to adult life. Recently, a Brazilian family with recessive X-linked distal muscular

atrophy affecting upper and lower limbs was reported (Takata et al., 2004). To our knowledge, this is the first distal HMN family with a clear X-linked transmission pattern. In a population study in north-east England, distal HMN represented approx 10% of the peroneal muscular atrophies (Pearn and Hudgson, 1979).

Concentric needle electromyography examinations of distal HMN patients show chronic denervation of wasted muscle, with motor units of increased amplitude and duration. Motor nerve conduction velocities (NCV) remain normal unless compound muscle action potentials are measured in severely wasted muscles. Sensory nerve action potentials are usually normal but there have been reports of minor sensory involvement (Carpenter et al., 1978; Ben Hamida et al., 1987; Frequin et al., 1991).

Sural nerve biopsy examination has rarely been performed in distal HMN patients and usually showed normal findings supporting the electrophysiological diagnosis of exclusive chronic anterior horn cell degeneration. McLeod and Prineas studied sural nerves and found a normal density of myelinated fibers with normal fiber diameter distribution, and no evidence of degeneration of single fibers (McLeod and Prineas, 1971). Occasionally, minor abnormalities have been described in sensory nerves but it was often difficult to differentiate these from age-related alterations. Muscle biopsy in a distal HMN-II patient showed nonspecific neurogenic atrophy (Timmerman et al., 1992). An autopsy study of spinal cord ventral horn and hypoglossal nucleus of the medulla in a distal HMN-VII patient with bulbar weakness, showed abnormal inclusions of dynactin and dynein, which are proteins essential for retrograde axonal transport, in motor neurons (Puls et al., 2005).

Often, unusual or additional features are present in "complicated" distal HMN, including congenital onset without subsequent progression (van der Vleuten et al., 1998); onset and predominance in the hands (Christodoulou et al., 1995; Gross et al., 1998); associated vocal cord paralysis (McEntagart et al., 2001); early bilateral vocal fold paralysis, bulbar and facial weakness (Puls et al., 2005); diaphragm paralysis (Grohmann et al., 1999); and pyramidal tract signs (De Jonghe et al., 2002). In some kinships several of these additional signs occur simultaneously such as predominant hand involvement and pyramidal tract signs (van Gent et al., 1985).

Based on the age at onset, the mode of inheritance and the presence of additional features, a classification in seven subtypes has been proposed (Harding, 1993). The descriptions of these subtypes were often based on a limited number of patients belonging to small families. However, with the advent of molecular genetic studies, the clinical phenotype in several new distal HMN kinships have been studied in great detail. In general, these studies nicely confirmed the previously delineated phenotypes but they also showed considerable intra- and interfamilial phenotypic heterogeneity in several subtypes. Also some clinical phenotypes did not fit into the existing classification and therefore represent novel clinical entities (van der Vleuten et al., 1998; Christodoulou et al., 2000; De Jonghe et al., 2002). The identification of several distal HMN loci and genes has shown that the clinical heterogeneity is indeed based on genetic heterogeneity. Even clinically homogeneous distal HMN subtypes turn out to be genetically heterogeneous. Here we describe the distal HMN entities and concentrate on the forms for which molecular genetic studies have provided convincing evidence that they represent separate genetic entities.

Autosomal-Dominant Distal HMN

Autosomal-dominant inheritance is the most common mode of inheritance in distal HMN. Of the seven subtypes described in the classification of Harding (Emery, 1971), four forms had an autosomal-dominant inheritance pattern; i.e., distal HMN types I, II, V, and VII. For all of these forms, except distal HMN-I, genetic loci have been mapped. Two novel distal HMN entities with clear autosomal-dominant inheritance and not included in the distal HMN classification have emerged; i.e., congenital non-progressive distal HMN (van der Vleuten et al., 1998) and early-onset distal HMN with pyramidal tract signs (De Jonghe et al., 2002). So far, six genes (*HSPB1*, *HSPB8*, *GARS*, *BSCL2*, *DCTN1*, and *SETX*) were shown to be involved in the autosomal-dominant forms of distal HMN (Irobi et al., 2004b).

Distal HMN Type I

The description of distal HMN type I [MIM 182960] is based on a small series of patients and no large pedigrees have been reported. Patients present between 2 and 20 yr with a classical peroneal

muscular atrophy syndrome and a normal life expectancy (Harding, 1993). We studied a small distal HMN-I family in which all patients developed clear weakness in the feet before the age of 5 yr. Patients had a "pure" distal HMN phenotype and showed severe distal wasting and weakness in adult life. The grandmother in this family became wheelchair-dependent. We excluded linkage to all known autosomal-dominant distal HMN loci showing that distal HMN-I is probably a distinct genetic entity (data unpublished). Whether HMN-I is a clinically and genetically homogeneous entity, is however doubtful. For example, we have identified a young (4-yr-old) patient from an Austrian family with distal HMN-II caused by a dominant *HSP27* mutation, indicating that there might be an overlap between distal HMN types I and II.

Distal HMN Type II

Distal HMN type II [MIM 158590] has an onset between 20 and 40 yr. We reported a Belgian distal HMN-II family in which the disease started between the age of 15 and 20 yr (Timmerman et al., 1992). This family could have been diagnosed as distal HMN-I, but the age of onset is later than in our small distal HMN-I family described earlier. Also, older patients in the distal HMN-II family sometimes mentioned a later onset age without a clear pattern of anticipation. The presenting symptoms are paresis of the extensor muscles of the big toe and later of the extensor muscles of the feet. The disease initially progressed rapidly and within 5 yr a complete paralysis of all distal muscles of the lower extremities occurred. Later on, weakness and atrophy was also present in the hands and the proximal muscles of the legs. Some older patients became wheelchair-dependent. Pyramidal tract signs were absent at the initial and follow-up examination. Sensory abnormalities were usually absent, but some older patients had reduced vibration sense in the legs. The patients usually did not have pes cavus. Normal motor and sensory NCVs were found in 10 clinically affected individuals, and a biopsy of the superficial peroneal nerve in an older patient showed some nonspecific alterations, which were considered to be age-related. Distal HMN closely resembles Charcot-Marie-Tooth (CMT)2 apart from the absence of sensory abnormalities in distal HMN (Harding and Thomas, 1980a,b). In 1996, we reported linkage to chromosome

12q24 in the large distal HMN-II family (Timmerman et al., 1996), and this locus was later confirmed in an extended unrelated Czech pedigree with the same phenotype.

Recently, a large six-generation family with a typical CMT2 phenotype was reported from the Hunan and Hubei provinces of China. Interestingly, molecular genetic analysis revealed linkage of this family to the same chromosomal region as defined for distal HMN-II and this novel CMT2 locus was designated as CMT2L (Tang et al., 2004). The disease onset in the Chinese family was between 15 and 33 yr of age with symmetrical muscle wasting and a predominating weakness of the distal parts of the lower limbs, decreased or absent deep tendon reflexes, and mild-to-moderate sensory impairment including pain weakness of the lower limbs. Two patients had weakness and atrophy in both distal and proximal muscles of the lower limbs (Tang et al., 2004). The CMT2L locus overlaps with the distal HMN-II interval indicating that both disorders might be allelic; a hypothesis that was later confirmed by the identification of mutations in the same gene (Tang et al., 2005b). In the Belgian, the unrelated Czech distal HMN-II and CMT2L families, we and others identified a missense mutation (K141N) in the α -crystallin domain of the small heat shock 22KDa protein 8 gene (*HSPB8/HSP22*) on chromosome 12q24.3 (Irobi et al., 2004c; Tang et al., 2005b). In two other distal HMN families (Bulgarian and English), a heterozygous transition involving the same lysine residue was found (K141E). Interestingly, missense mutations in the molecular partner of HSP22, the small heat shock 27KDa protein 1 gene (*HSPB1/HSP27*) were also found to be associated with distal HMN and CMT2 (CMT2F) (Evgrafov et al., 2004; Tang et al., 2005a). The distal HMN phenotype associated with HSP27 mutations showed a variable age of onset from juvenile to adulthood suggesting that these patients could also be classified as either distal HMN-I or distal HMN-II (Table 1). Missense mutations in the HSP22 and HSP27 stress proteins are associated with dysfunction of the axon cytoskeleton, formation of aggregates and oxidative stress-mediated cell death (Mehlen et al., 1995), relevant for the pathological mechanism in distal HMN (Fig. 1). Now that the genetic basis of distal HMN-II has been unravelled, it is currently unknown how these stress proteins exert their function in the peripheral nervous

system. Deciphering the molecular pathway of HSP22/HSP27 function in relation to distal HMN is currently ongoing and may provide novel insights for future therapeutic strategies.

Distal HMN Type V

Distal HMN type V (MIM 600794) is characterized by its peculiar distribution of muscle weakness and wasting, which starts and predominates in the upper limbs (Harding 1993). The disease is characterized by adolescent onset, selective weakness and atrophy of thenar and first dorsal interosseus muscles progressing to involve foot and peroneal muscles in most but not all patients. Subsequently, 50% of the patients develop weakness in the lower limbs. In a branch of a large Bulgarian family mild pyramidal tract signs and rarely Babinski signs were present. No sensory symptoms, except for slightly reduced vibration sense in the feet, were observed in 30% of the patients. Neurophysiological studies confirmed chronic denervation in distal muscles with reduced compound muscle action potentials, features consistent with both motor neuronal and axonal pathology. Sural nerve biopsy showed mild-to-moderate selective loss of small- and medium-sized myelinated and small unmyelinated axons, although sensory nerve action potentials were not significantly decreased (Sivakumar et al., 2005). Distal HMN-V was mapped to chromosome 7p. Interestingly, a locus overlapping this distal HMN-V region was mapped in a CMT family from Iowa in which hand muscle involvement was also a prominent feature. The disease, however, was designated as CMT2D as it affected individuals who also had sensory abnormalities (Ionasescu et al., 1996). The coincidence of distal HMN type V and CMT2D mapping to the same locus, and the similarity of clinical phenotypes with predominant hand involvement, had raised the question whether both neuropathies could be allelic and thus caused by different mutations within the same gene (Christodoulou et al., 1995; Sambuughin et al., 1998). This hypothesis was further supported by the observation that both distal HMN-V and CMT2D segregated in a single large Mongolian family linked to chromosome 7p (Sambuughin et al., 1998). Final proof that distal HMN-V and CMT2D are indeed allelic, came from the observation that missense mutations in the glycyl tRNA-synthetase gene

Table 1
Loci and Genes for Distal Hereditary Motor Neuropathies

Gene	Locus	Disease	Inheritance/phenotype	References	OMIM no.
<i>Distal HMN subtypes after A.E. Harding</i>					
Unknown	Unknown	Distal HMN type I	AD juvenile onset with distal wasting and weakness	Harding (1993)	606595
<i>HSP22</i>	12q24.3	Distal HMN type II	AD adult onset with distal muscle wasting and weakness	Irobi et al. (2004c); Evgrafov et al. (2004); Tang et al. (2004)	158590, 608673
<i>HSP27</i>	7q11-q21	CMT 2F, CMT2L			
Unknown	11q13	Distal HMN type III	AR early adult onset, slow progressive muscle wasting and weakness and no diaphragmatic paralysis	Viollet et al. (2002)	607088
Unknown	11q13	Distal HMN type IV	AR juvenile onset, severe muscle wasting and weakness and diaphragmatic paralysis	Viollet et al. (2002, 2004)	607088
<i>GARS</i>	7p15	Distal HMN type V CMT2D	AD upper limb predominance; occasionally pyramidal features	Christodoulou et al. (1995); Antonellis et al. (2003)	600794, 601472
<i>BSCL2</i>	11q12-q14	Distal HMN type V Silver Syndrome	AD prominent hand muscle weakness and wasting, and mild to severe spasticity of the lower limbs	Windpassinger et al. (2004)	600794, 270685
<i>IGHMBP2</i>	11q13.2-13.4	Distal HMN type VI SMARD1	AR severe infantile form with respiratory distress	Grohmann et al. (1999, 2001)	604320
Unknown	2q14	Distal HMN type VII	AD adult onset with vocal cord paralysis	McEntagart et al. (2001)	158580
<i>DCTN1</i>	2p13	Distal HMN type VII	AD adult onset with vocal fold paralysis and facial weakness	Puls et al. (2003)	607641
Unknown	Xq13-q21	X-linked distal HMN	X-linked recessive, juvenile onset with distal wasting and weakness	Takata et al. (2004)	300489
<i>Additional forms:</i>					
<i>SETX</i>	9q34	Distal HMN / ALS4	AD early onset with pyramidal tract signs	Chance et al. (1998); De Jonghe et al. (2002); Chen et al. (2004)	602433
Unknown	9p21.1-p12	Distal HMN-J	AR juvenile onset with pyramidal features	Middleton et al. (1999); Christodoulou et al. (2000)	605726
Unknown	12q23-q24	Congenital distal SMA	AD congenital nonprogressive distal HMN with contractures	van der Vleuten et al. (1998)	600175

The table is based on the classification of distal HMN by Harding (1993), including four autosomal-dominant (I, II, V, and VII) and three recessive (III, IV, and VI) subtypes. We added two dominant, one recessive, and one X-linked recessive distal HMN entities: i.e., congenital nonprogressive distal HMN (van der Vleuten et al., 1998), ALS4 or distal HMN with pyramidal tract signs (De Jonghe et al., 2002), distal HMN-Jerash (Middleton et al., 1999), and X-linked recessive distal HMN (Takata et al., 2004). Disease-causing mutations in the respective genes can be retrieved from the Inherited Peripheral Neuropathy Mutation Database at <http://www.molgen.ua.ac.be/CMTMutations/>. OMIM numbers can be obtained from the database of Online Mendelian Inheritance in Man at <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive and X-linked recessive.

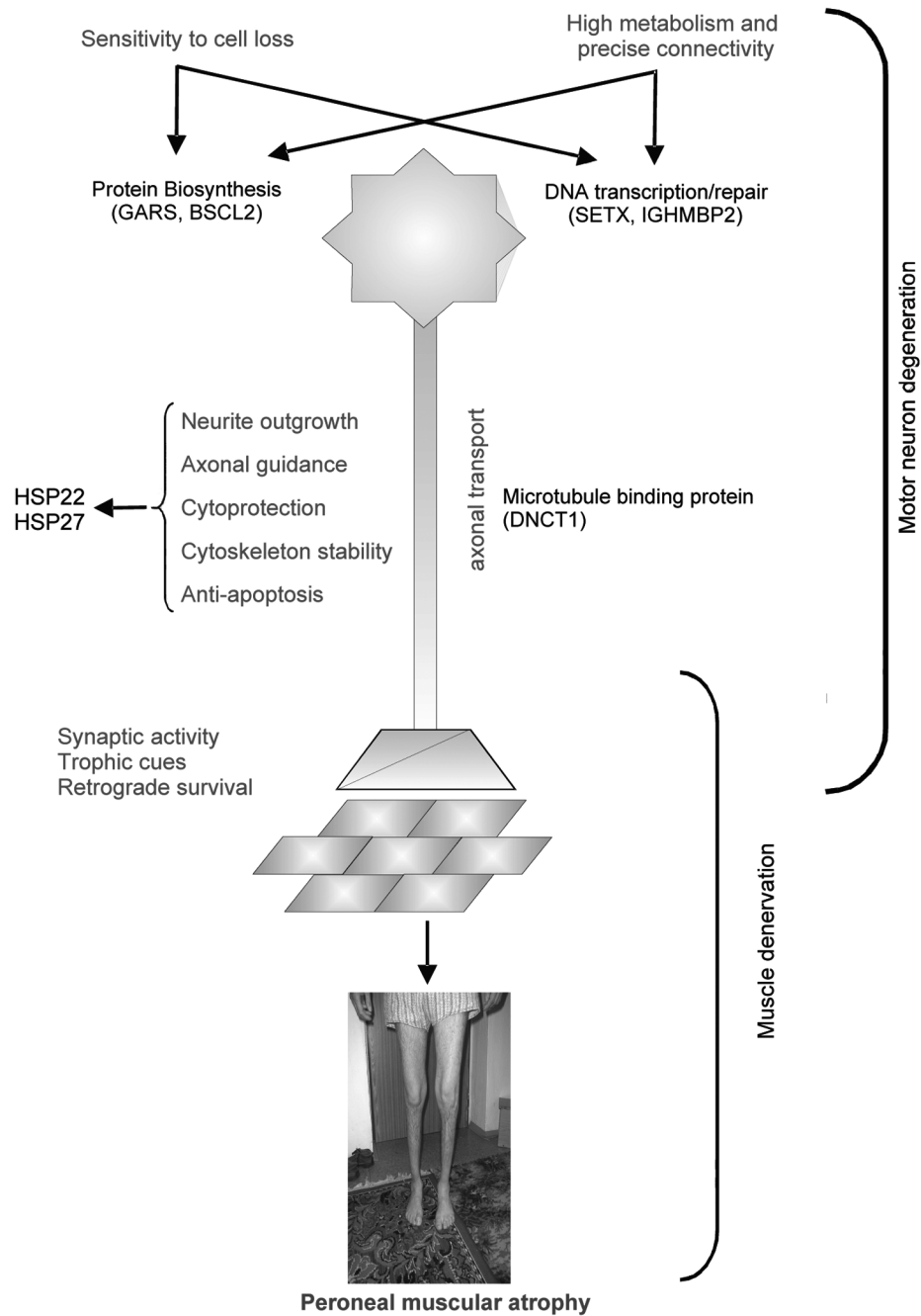


Fig. 1. Schematic representation of the molecular pathways involved in distal HMN. Most of the implicated gene products have a loss or gain of toxic function related to DNA/RNA processing (IGHMBP2, SETX), protein synthesis (GARS, BSCL2), stress response (HSP22, HSP27), apoptosis (HSP27), axonal trafficking, and editing (HSP27, DCTN1). Recent studies suggest that ubiquitously expressed genes may exert their function in neurite outgrowth and axonal guidance. Therefore defects in those genes may induce motor neuron degeneration. Understanding the molecular pathomechanisms in these neuronal processes is pivotal for rescuing motor neuron loss in distal HMN, resulting in a peroneal muscular atrophy.

(GARS) are present in families with distal HMN-V and CMT2D (Antonellis et al., 2003).

The aminoacyl-tRNA synthetases are major protein components in the translation machinery, and are responsible for charging their associated tRNAs with the correct amino acid. Why mutations in a housekeeping gene such as GARS result in neuropathy remains an enigma. It is conceivable that neurons are more prone to a loss or decrease in tRNA-synthetase, resulting in a reduction of protein products reaching synaptic termini (Fig. 1). However, GARS could also have an alternative function or interact with an unknown molecular partner in the peripheral nerve. Interestingly, we have very recently identified novel mutations in tyrosyl-tRNA synthetase (YARS) in three unrelated dominant intermediate CMT families (Jordanova et al., 2006). YARS is thus the second aminoacyl-tRNA synthetase found to be involved in peripheral neuropathies. Interestingly, YARS localizes in axonal termini of differentiating primary motor neurons and neuroblastoma cultures, and this specific distribution was significantly reduced in cells expressing mutant YARS proteins. This could have an effect on synaptic plasticity, resulting in axonal degeneration leading to axonal loss, and ultimately to a motor and sensory peripheral neuropathy (Jordanova et al., 2006).

Distal HMN Type V and Silver Syndrome Are Phenotypic Variants

A large Austrian distal HMN family with a phenotype similar to distal HMN-V was excluded from the disease locus on chromosome 7p, demonstrating genetic heterogeneity in distal HMN-V (Auer-Grumbach et al., 2000). A genome-wide search in this family demonstrated linkage to chromosome 11q12-q14. Interestingly, the linkage region overlaps with the locus for Silver syndrome, a complicated form of hereditary spastic paraplegia (SPG17) (Patel et al., 2001). Individuals with Silver syndrome have spasticity of the legs accompanied by amyotrophy of the hands and occasionally also of the lower limbs (Silver, 1966). Other families with Silver syndrome were reported in the literature (Lander et al., 1976; van Gent et al., 1985; de Visser et al., 1988), but it is unknown if these families link to 11q12-q14. Recently, two missense mutations (N88S and S90L) were found in the Berardinelli-Seip congenital lipodystrophy (BSCL2) gene in the Austrian

distal HMN family and in 16 additional families diagnosed as distal HMN-V or Silver syndrome (Windpassinger et al., 2004). Mutations in BSCL2 seem to be associated with a variety of motor neuropathies (Irobi et al., 2004a; Windpassinger et al., 2004). The phenotypes include classical Silver syndrome, distal HMN-V, severe spastic paraplegia with amyotrophy predominantly affecting the lower limbs and distal HMN types I and II with a pure distal motor neuropathy starting and predominating in the lower limbs. A careful clinical study of the large Austrian distal HMN-V family with a BSCL2 mutation showed considerable intrafamilial variability (Auer-Grumbach et al., 2005).

The observation that the same mutation can be associated with different phenotypes raises the interesting possibility of a modifier effect (Auer-Grumbach et al., 2005; Irobi et al., 2004a). These observations also broaden the clinical phenotype of disorders associated with BSCL2 mutations, with consequences for molecular genetic testing. Furthermore, null mutations in BSCL2, which encodes the protein seipin, have been identified in autosomal-recessive Berardinelli-Seip congenital lipodystrophy (Magre et al., 2001). Little is known on the normal function of seipin, but it is a transmembrane protein of the endoplasmic reticulum and shows homology to midasin, an AAA (ATPases associated with various cellular activities) domain-containing nuclear protein that is involved in RNA transport (Agarwal and Garg, 2004). Similar to the mutant small HSPs in distal HMN-II, mutant seipin results in aggregate formation, which is a hallmark of neurodegeneration (Agarwal and Garg, 2004; Windpassinger et al., 2004). Future functional studies will decipher the specific neuronal activities of BSCL2 in both upper and lower motor neuron degeneration.

Distal HMN Type VII

The hallmark feature of distal HMN-VII is vocal cord paralysis although the distribution of weakness is also unusual and initially affects the upper limbs. The clinical phenotype was delineated mainly based on the study of two large pedigrees; a large Welsh kindred and a smaller family from England (Young and Harper, 1980; Pridmore et al., 1992). A molecular genetic linkage study mapped the locus in both families to chromosome 2q14 (McEntagart et al., 2001). This study also confirmed the hypothesis that

both families may have a common founder because both families share a common disease haplotype. Further genealogical studies subsequently identified the common ancestor. The gene involved in distal HMN-VII linked to 2q14 remains unknown. A recent re-examination of the clinical phenotype confirmed the earlier descriptions (McEntagart et al., 2002). The disease typically presents in the second decade but an earlier onset age before the age of 10 is occasionally observed. Weakness and wasting is initially confined to the small muscles of the hand and thenar eminence. Subsequently, weakness and wasting of the distal muscles of the lower limbs occurs. In one person of the extended Welsh family, lower limb involvement preceded that in the upper limbs by 10 yr. All but a few patients developed a hoarse voice, which resulted from unilateral or bilateral vocal cord paralysis. In the English branch, some older patients at the age of 60 yr have only wasted hands. Patients develop vocal paralysis at variable ages and vocal cord paralysis preceded upper limb weakness and wasting in some individuals. Otherwise cranial nerves were entirely normal. Deep tendon reflexes were lost and sensation remained intact. Progression is slow and compatible with a normal life span. Recently, another distal HMN-VII family was found to be linked to 2p13 (Puls et al., 2003). In this 2p13-linked family a missense mutation (G59S) was found in the gene encoding dynactin (*DCTN1*), a microtubule motor protein essential for retrograde axonal transport. The mutation affects the p150^{Glued} subunit of dynactin; this mutation is predicted to distort the folding of the dynactin microtubule-binding domain (Puls et al., 2003). Impaired axonal transport has been postulated to play a role in the pathophysiology of multiple neurodegenerative disorders (Fig. 1). The genetic defect in the Welsh family is currently unknown (Young and Harper, 1980; McEntagart et al., 2001) and allelic variants of *DCTN1* may be a genomic risk factor for other motor neuron diseases (Munch et al., 2004).

Puls and colleagues (2005) have recently reported the clinical and neuropathological findings of the distal HMN-VII family with the *DCTN1* mutation. Affected family members had a distinct clinical phenotype characterized by early bilateral vocal fold paralysis affecting the adductor and abductor laryngeal muscles, causing difficulty breathing. These findings were more pronounced on the left side, presumably because the left recurrent laryngeal

nerve is longer than the right. They later experienced weakness and atrophy in the face, hands, and distal legs. The extremity involvement was greater in the hands than in the legs, and it had a particular predilection for the thenar muscles. Skin biopsy data showed morphological abnormalities of epidermal nerve fibers, and autopsy in one patient revealed motor neuron degeneration and axonal loss in the ventral horn of the spinal cord. The *DCTN1* mutation caused a unique pattern of motor neuron degeneration associated with the accumulation of dynein and dynactin in neuronal inclusions (Puls et al., 2005).

Early Onset Distal HMN With Pyramidal Tract Signs

In 1964, an American family was reported as a variant of CMT neuropathy (Myriantopoulos et al., 1964). Re-evaluation of the clinical and electrophysiological data showed that it was in fact a pure motor neuropathy. The disorder is characterized by juvenile onset and slowly progressive distal limb amyotrophy and weakness starting in the lower limbs. Many patients had pyramidal tract signs including brisk reflexes and Babinski signs. Postmortem examination showed severe loss of motor neurons in the brain stem and spinal cord (Rabin et al., 1999). Because of the combination of lower and upper motor neuron degeneration the diagnosis was changed to autosomal dominant juvenile amyotrophic lateral sclerosis (ALS). However, several characteristics are unusual for ALS; the stereotyped course of weakness and weakness first affecting the lower limbs and only later on spreading to the hands, the absence of cranial nerve involvement, and the normal life expectancy. A molecular genetic linkage analysis mapped the locus (ALS4; OMIM 602433) for this disorder on chromosome 9q34 (Chance et al., 1998). Subsequently, distal HMN families were also reported to be linked to the ALS4 locus on 9q34 (De Jonghe et al., 2002). The disease onset was usually in the first decade, reflexes were often brisk, and Babinski signs were sometimes present. Some patients had pes cavus. However, patients occasionally had normal or reduced reflexes and no Babinski signs. The phenotype in these patients can be diagnosed as distal HMN-I. Since the clinical phenotype in these families is strikingly similar to the original ALS4 family (Rabin et al., 1999), it was suggested that ALS4 and

distal HMN with pyramidal tract signs might be one and the same disorder (De Jonghe et al., 2002).

This was confirmed by the identification of missense mutations in the senataxin gene (*SETX*) in the American ALS4 family and in two distal HMN families from Austria and Belgium (Chen et al., 2004) (Table 1). Although its function remains unknown, the senataxin protein contains a DNA/RNA helicase domain with strong homology to the immunoglobulin μ -binding protein 2 protein (*IGHMBP2*), which is affected in distal HMN-VI (Grohmann et al., 2001; Chen et al., 2004). Interestingly, nonsense mutations in the *SETX* gene lead to the autosomal-recessive ataxia-oculomotor apraxia type 2 (AOA2) (Moreira et al., 2004; Duquette et al., 2005). These observations suggest that mutations in *SETX* may cause neuronal degeneration through dysfunction of the helicase activity or other steps in RNA processing and DNA repair (Chen et al., 2004).

Congenital Nonprogressive Distal SMA

Congenital nonprogressive distal SMA was not present in the original classification of distal HMN (Harding, 1993). This clinical entity was described in two families (Fleury et al., 1985; Frijns et al., 1994). In the Dutch family described by Fleury, patients have a clinically nonprogressive syndrome with antenatal onset in more than half of the patients associated with arthrogryposis. Weakness, atrophy, and congenital contractures are restricted to the lower part of the body. The severity is variable within this family. The least affected individuals have slight paresis of the foot extensors, slight deformity of the feet, and absence of ankle reflexes. Severely affected patients have paralysis of the distal parts of the legs with serious paresis of the muscles of the trunk, pelvic girdle, and proximal muscle groups of the legs. Serious deformities of the legs and trunk, including scoliosis, develop. A molecular genetic linkage study mapped the gene defect in this family to chromosome 12q23-24 (van der Vleuten et al., 1998). The linkage region does not overlap with the distal HMN type II locus at 12q24.3 (Irobi et al., 2000), but overlaps with the candidate interval for dominant scapulo-shoulder SMA (SPSMA) (Isozumi et al., 1996). The family described by Frijns has a similar phenotype but there are some slight differences. Patients also have hyperlaxity of elbows, wrist, and finger joints, jaw muscles and neck flexors are slightly weak and

a mild degree of scapular winging might be present. A linkage study in this family excluded linkage to the chromosome 12q23-24 locus indicating genetic heterogeneity in this syndrome.

Autosomal-Recessive Distal HMN

The original classification of distal HMN includes three autosomal-recessive forms and encompasses both pure and complicated phenotypes (Emery, 1971). Even though autosomal-recessive subtypes are less common than the dominant forms, two loci and one gene have been identified. As is often the case in autosomal-recessive disorders, the study of consanguineous families from inbred populations was instrumental in this success. So far three autosomal-recessive distal HMN types have been mapped, the distal HMN-Jerash type on chromosome 9p21-p12 (Middleton et al., 1999), the distal HMN-VI or SMA with respiratory distress 1 (*SMARD1*) on 11q13 (Grohmann et al., 1999), and distal HMN types III-IV with juvenile and early adult-onset on chromosome 11q13.3 (Viollet et al., 2002, 2003).

Distal HMN Type III

The only large family reported with this phenotype is an extended inbred Libanese family (Viollet et al., 2002). One of the patients was previously reported by Pearn (Pearn and Hudgson, 1979). The most severely affected patient developed weakness in the distal legs at the age of 9 mo. At the age of 6 yr, she was still able to stand up alone but could not walk without aid. She had a slight kyphoscoliosis and marked lumbar hyperlordosis. Interestingly, a chest X-ray showed hypomobility of the right hemidiaphragm but respiratory function was normal. All tendon reflexes were absent and there were no pyramidal tract signs. The disease gene was mapped to chromosome 11q13, in a genetic interval encompassing the *IGHMBP2* gene, which cause *SMARD1* (see Distal HMN-VI). In this family, the *IGHMBP2* gene was excluded as the causative gene by sequence analysis (Viollet et al., 2002), but genomic rearrangements of *IGHMBP2* were not investigated (Guenther et al., 2004). Recently, the distal HMN-III locus was refined in a series of 12 European families and a founder effect was present in 8 of 12 families. The candidate interval corresponds to a region of 1Mb and is located telomeric to the *IGHMBP2* gene. Ten genes have been reported

in this interval, but the causative gene has not yet been identified (Viollet et al., 2004).

Distal HMN Type IV

Distal HMN-IV is defined as an autosomal-recessive distal HMN with late onset and a mild course. In one branch of the Libanese distal HMN-III family linked to chromosome 11q13, two individuals had a later onset and a much milder course (Viollet et al., 2002). The patients developed the first symptoms around the age of 20 yr. The oldest patient, at the age of 43 yr developed a limping gait after walking for a long distance or climbing stairs. The other patient, at the age of 26 yr was not limited in her ability to walk or climb stairs. No abnormalities were noted on chest X-rays.

Distal HMN Type VI

Distal HMN-VI with respiratory distress, also known as SMARD1, is a severe, autosomal-recessive infantile neuropathy. The most prominent symptoms are diaphragmatic paralysis and predominant involvement of the upper limbs and distal muscles. Patients develop severe respiratory distress necessitating artificial ventilation (Bertini et al., 1989). Distal HMN-VI is clinically and genetically distinct from proximal (SMA). It results from mutations in the *IGHMBP2* gene on chromosome 11q13 (Grohmann et al., 1999; Grohmann et al., 2001) (Table 1). Like the survival motor neuron (SMN1) protein, the protein affected in proximal SMA (Lefebvre et al., 1995), the *IGHMBP2* protein colocalizes with the RNA-processing machinery in both the cytoplasm and the nucleus (Miao et al., 2000). Diers and coworkers recently investigated the peripheral nerves, skeletal muscle, and neuromuscular junctions of five unrelated patients and three siblings with genetically confirmed SMARD1 (Diers et al., 2005). In addition to the motor neuropathy, sensory nerve biopsies show Wallerian degeneration and axonal atrophy similar to the ultrastructural findings described in SMA. Neuromuscular junctions may be dysmorphic and even lack a terminal axon. These findings indicate that the loss of *IGHMBP2* leads to length-dependent axonal degeneration, affecting motor more than sensory axons.

Distal HMN–Jerash Type

Autosomal-recessive distal HMN was reported in consanguineous families living in the Jerash

region of Jordan (Middleton et al., 1999). The onset was between 6 and 10 yr. The disease started with distal atrophy and weakness of the lower limbs. Upper limb involvement followed within 2 yr. In the initial stage knee jerks were brisk and a Babinski sign was sometimes present. Later on tendon reflexes became reduced and Babinski signs disappeared. Interestingly, the analysis of three sural nerve biopsy specimens showed mild loss of axons involving large and small myelinated fibers with regenerative clusters. There were no myelin abnormalities. Electrophysiological studies showed normal or moderately reduced NCV when recorded from wasted muscles. Sensory nerve conduction amplitudes were normal. Homozygosity mapping was used to assign the distal HMN–Jerash (distal HMN–J) locus to chromosome 9p21.1–p12 (Christodoulou et al., 2000), but the gene involved is currently unknown (Table 1).

Recessive X-Linked Distal HMN

Takata and colleagues recently mapped the first locus for an X-linked recessive distal HMN in a Brazilian family (Takata et al., 2004). The disease starts in the first decade with weakness and atrophy initially affecting the lower limbs. The hands become affected later. Foot deformities like pes cavus and pes varus were often present. The disease progression was very slow and independent gait was preserved even late in life. There were no pyramidal tract signs. Electrophysiological studies revealed a distal neurogenic electromyography pattern in seven of nine affected individuals; sensory responses were normal in all patients. Muscle biopsy revealed both neurogenic and myogenic findings, whereas sural nerve biopsy appeared normal. Molecular genetic analysis with microsatellite markers along the X-chromosome mapped to Xq13.1–q21 (Takata et al., 2004), similar to a region in which an X-linked form of spastic paraplegia has been mapped (Claes et al., 2000).

Discussion

Distinguishing Motor Neuronopathies From Axonal Neuropathies

The peripheral nerve pathology affecting the distal portion of axons with preservation of parent cell

bodies, is called axonal neuropathy (axonopathy) whereas disorders affecting cell bodies and their axons are neuronopathies (McLeod, 1995). The CMT2 variants are usually described as axonal neuropathies, whereas distal HMNs are often referred to as neuronopathies. This distinction however, seems arbitrary because the clinical symptoms and signs in distal HMN have a, by definition, distal distribution that is indistinguishable from CMT2. This distribution suggests that the main pathology resides in the axons probably owing to a common length-dependent mechanism. In fact, families with HMSN, in particular the axonal CMT neuropathy (CMT2), have been linked to some of the loci identified for distal HMN and the genes involved sometimes lead to distal HMN or CMT2 (Table 1). Also, owing to lack of autopsy studies, little is known about the status of the anterior horn motor neuron bodies in distal HMN.

Why Are Motor Neurons Selectively Vulnerable?

A characteristic that separates motor neurons from other cells is their peculiar morphology (Bruijn et al., 2004). The axons of lower motor neurons (up to 1-m long) run in peripheral nerves and terminate at neuromuscular junctions of innervated muscles. This size demands a high metabolic load and precise connectivity on the normal sized cell body (Bruijn et al., 2004). The crucial question is: What defines the neuronal cell death specificity and selectivity in neurodegeneration? There are several susceptibility factors that might be implicated including differences in subtype transmitter metabolism, variations in subtype connectivity, the size of the neuron, differences in regulatory circuits firing patterns, variations in glial environment homeostasis, availability of blood supply in specific regions, and differences in gene expression. These susceptibility factors may increase the vulnerability of motor neuron cell death during disease.

The seven disease-causing genes identified so far for autosomal-dominant and -recessive distal HMN have diverse functions, and their expression is not restricted to motor neurons. However, it is not clear how defects in these ubiquitously expressed genes result in motor neuron degeneration leaving other tissues unaffected. Nevertheless, recent studies suggest that ubiquitous processes might have specific functions in neurites and growth cones, defects that

may induce motor neuron cell death (LaMonte et al., 2002; Holzbaur 2004; Jablonka et al., 2004b; Jordanova et al., 2006). In proximal SMA, it has been hypothesized that SMN functions in neuronal development by associating with distinct molecular factors in the cytoplasm and in neurites (Jablonka et al., 2001). Thus, by forming different macromolecular protein complexes in particular subcellular regions, the range of functions of culprit proteins may be broadened (Briese et al., 2005). Specific protein interactions or changes in these interaction mechanisms may be important to explain the neuron-specificity of distal HMN and proximal SMA. We showed that the missense mutations in the HSP22 protein do not disrupt interaction with HSP27 but instead strengthen the interaction, and lead to the formation of aggregates (Irobi et al., 2004c). The sequestration of HSP27 into these aggregates might inhibit or reduce the anti-apoptotic effects of HSP27 and ultimately lead to motor neuron dysfunction. Furthermore, the mutations are associated with a reduced ability to promote neuronal survival compared to the wild-type protein and thus appear to be a potent protective factor for neuronal cells (Evgrafov et al., 2004; Irobi et al., 2004c). Recent evidence from animal and cell culture models of proximal SMA points to roles for the *SMN1* gene in neurite outgrowth and axonal transport (Briese et al., 2005). Disruption of these functions might be particularly detrimental to motor neurons given their high metabolic demands and precise connectivity requirements, thus providing a possible explanation for the specificity of motor neuron susceptibility in SMA (Briese et al., 2005). Mouse models that recapitulate the known distal HMN mutations are essential for understanding the causes and mechanisms of motor neuron pathology.

The Significance of Upper Motor Neuron, Pyramidal Tract, and Sensory Neuron Involvement in Distal HMN

Upper motor neuron (corticospinal motor neurons; CSMN) involvement was observed in some forms of distal HMN, including early-onset distal HMN with pyramidal features, distal HMN-V/Silver syndrome and distal HMN Jerash type. Why the upper motor neurons and their pyramidal tracts are thus involved in some distal HMN forms and spared in others is still unknown. However, the degree of involvement seems to be variable between families

and even within families. Also other neuronal cell types such as sensory neurons may be affected to a certain degree, again showing a broad inter- and intrafamilial variability. In the absence of sensory symptoms and signs, individuals are diagnosed as distal HMN and when sensory signs are overt they are designated CMT2.

The anatomical and morphological development of CSMN has been extensively characterized (Jones et al., 1982; Terashima 1995), but strategies to repair, maintain, and modify CSMN and lower motor neurons are limited by a lack of understanding of the molecular controls governing their development, including neuron type-specific differentiation, survival, and connectivity (Arlotta et al., 2005). Arlotta and colleagues, recently identified genes specifically expressed in CSMN, that exhibit increasing levels of expression as CSMN develop. These genes might control intermediate and later aspects of CSMN differentiation, such as process outgrowth and synapse formation (Arlotta et al., 2005). Genetics and functional studies with these proteins may enable the identification of modifying factors and define molecular pathways, which will help to unravel why ubiquitously expressed proteins result in a specific phenotype.

Lessons From Genes Associated With Distal HMN

An increasing number of ubiquitously expressed genes are now identified as the genetic culprit of distal HMN. The first gene identified for a recessive form of distal HMN was *IGHMBP2* (Grohmann et al., 2001). Interestingly, *IGHMBP2* and the *SMN1* genes are involved in the pre-mRNA splicing machinery, a house keeping function in various cellular processes (Campbell et al., 2000; Meister et al., 2000; Jablonka et al., 2001; Pellizzoni et al., 2001; Ogino et al., 2004). The *SETX* gene, mutated in autosomal-dominant distal HMN/ALS4, has a helicase activity and is important for RNA processing and perhaps DNA single strand break (Chen et al., 2004) (Fig. 1). Mutations in *GARS* could affect protein synthesis that is also relevant for motor neuron maintenance and integrity (Antonellis et al., 2003). Axonal transport of mRNAs for some of these genes may play an essential role in axonal growth, synaptic function, and cell viability of motor neurons (Jablonka et al., 2004a). Indeed tyrosyl-tRNA synthetase (*YARS*), the second aminoacyl-tRNA synthetase found to be involved in

CMT, localizes in axonal termini of differentiating primary motoneurons and neuroblastoma cultures (Jordanova et al., 2006). Of interest to axonal transport is the function of the *DCTN1* gene, which encodes for a subunit of the dynactin complex required for dynein-mediated retrograde transport of vesicles and organelles along microtubules (Puls et al., 2003). The recent identification of mutations in *HSP22* and *HSP27* in distal HMN provided the first evidence that mutations in small heat shock proteins play an important role in motor neuron disorders (Evgrafov et al., 2004; Irobi et al., 2004c). *HSP27* is involved in the organization of the neurofilament network, which is important for the maintenance of the axonal cytoskeleton and transport (Perng et al., 1999) and mutant *HSP27* affects the neurofilament assembly (Evgrafov et al., 2004). *HSP27* was also shown to colocalize with actin and tubulin in lamellopodia, filopodia, focal contacts and mature neurites, and growth cones. Disruption of the actin cytoskeleton with cytochalasin D results in aberrant neurite initiation and extension, effects which may be attributable to alterations in actin polymerization (Williams et al., 2005). The mutant small HSP proteins may thus lead to dysfunction of the axonal transport and dysregulate the cytoskeleton causing motor neuron death (Fig. 1). Mutations in the small *HSP* genes, as well as in the *BSCL2* gene, result in aggregates formation suggesting a role for inefficient protein folding and reduced maintenance activities (Fig. 1) (Irobi et al., 2004c; Windpassinger et al., 2004). The recent findings on axon-specific functions of *SMN* and *YARS* are important from a neuropathological perspective for future investigations into the causes of neuronal cell loss observed in peripheral neuropathy.

In summary, there is a need to understand the function and dysfunction of ubiquitous processes in the neurites, synapse, motor end plate, and the neuromuscular junction innervating the distal limb muscles. It is of vital importance to decipher the maintenance activities in the motor neuron and also to identify possible axonal modifiers that might indicate the existence of a distinct functional complex in neuronal processes.

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