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Review

# The molecular genetics of non-ALS motor neuron diseases

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**Abstract**

Hereditary disorders of voluntary motor neurons are individually relatively uncommon, but have the potential to provide significant insights into motor neuron function in general and into the mechanisms underlying the more common form of sporadic Amyotrophic Lateral Sclerosis. Recently, mutations in a number of novel genes have been associated with Lower Motor Neuron (*HSPB1*, *HSPB8*, *GARS*, Dynactin), Upper Motor Neuron (Spastin, Atlastin, Paraplegin, *HSP60*, *KIF5A*, *NIPA1*) or mixed ALS-like phenotypes (Alsin, Senataxin, *VAPB*, *BSCL2*). In comparison to sporadic ALS these conditions are usually associated with slow progression, but as experience increases, a wide variation in clinical phenotype has become apparent. At the molecular level common themes are emerging that point to areas of specific vulnerability for motor neurons such as axonal transport, endosomal trafficking and RNA processing. We review the clinical and molecular features of this diverse group of genetically determined conditions and consider the implications for the broad group of motor neuron diseases in general.


*Keywords:* Motor Neuron; Axonal transport; Hereditary motor neuropathy; Neurodegeneration; Soinal muscular atrophy

## 1. Introduction

The selective death of motor neurons is the cardinal feature of a number of disorders that are individually uncommon but together result in significant morbidity in the population. The term Motor Neuron Disease is often used interchangeably with Amyotrophic Lateral Sclerosis (ALS) to describe the best characterised and most common of these diseases. Although the pattern of weakness, the balance of upper and lower motor neuron features and the degree of extra-motor involvement may vary, the hallmark of this clinical entity is the combination of relentlessly progressive neurological disability and typical autopsy findings of ubiquinated intracellular inclusions in the surviving anterior horn motor neurons of the spinal cord. The term 'motor neuron disease' could equally be used to encompass a group of inherited disorders with their own recognisable clinical features but in which motor neurons are affected in relative isolation. The essential feature, the relatively selective loss of specialised neurons in the motor output pathway, links all these disorders but this can be obscured by a confusing array of diagnostic nomenclatures and classifications that emphasise the differences in clinical presentation. As a result disorders described as forms of "ALS" show considerable overlap with others classified as forms of Spinal Muscular Atrophy (SMA), Hereditary Motor Neuropathy (HMN), Hereditary Spastic Paraplegia or Charcot–Marie–Tooth Type 2 (CMT2) (Fig. 1).

Research into the molecular genetics of motor neuron disorders has progressed rapidly in the decade since the first description of mutations in the Superoxide Dismutase (*SOD1*) gene in familial forms of ALS. As well as offering benefits to families in the form of diagnosis, genetic counselling and more recently reproductive options such as Pre-implantation Genetic Diagnosis (PGD), genetic research offers the hope of providing valuable clues into the nature of the selective vulnerability of motor neurons that underlies both familial and sporadic forms of these conditions. The highly specialised nature of motor neurons has prompted researchers to suggest critical functions that could be disrupted in MND [1]. These include the demands on intracellular processes and axonal transport created by the uniquely long axonal processes, the susceptibility to oxidative,

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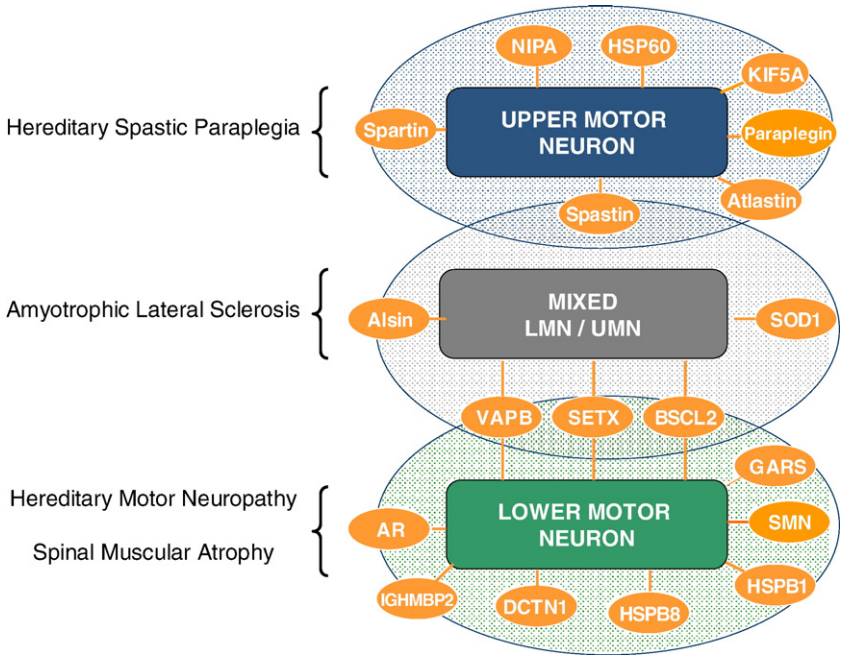


Fig. 1. Schematic of the relationship between the organisation of the motor output pathway, the diagnostic groups and individual genes associated with motor neuron disorders. MND—motor neuron disease, UMN—upper motor neuron, LMN—lower motor neuron.

thermal and other cellular stresses found in large, metabolically active but non-dividing cells, and the stringent developmental process that requires molecularly identified neurons to associate with specific predetermined muscle fibres before the system is refined by a process of Programmed Cell Death. Mutations in the *SOD1* gene, which account for around 20% of the familial cases of ALS, were discovered in 1993 and it was hoped that this would be an opening for vital insights into the molecular processes that underlie selective vulnerability. Almost a decade later research on *SOD1* has resulted in a large amount of new information in this area but many of the central questions regarding the nature of this vulnerability remain unanswered.

As the revolution in molecular genetics has advanced, positional cloning studies involving small numbers of families with a similar phenotype, or even individual families, have identified an increasing number of loci associated with motor neuron degeneration. Mutations in the genes underlying many of these loci have been demonstrated and with each new gene discovery the cellular processes vital to motor neuron survival are more clearly defined. This review focuses on the clinical and molecular features of disorders in which recently described genetic mutations have been associated with a relatively pure motor neuron specific phenotype.

Sporadic Amyotrophic Lateral Sclerosis has an incidence of approximately 2/100,000 per year and a prevalence of approximately 6–7/100,000. Familial ALS, accounting for approximately 10% of cases therefore can be estimated to have an incidence of 2 per million per year and is therefore self-evidently a rare disorder. The exact incidence of most of the specific genetic disorders discussed below is unknown at present. However, even though they are individually rare, compared with typical ALS lifespan may be prolonged. It seems likely that pure inherited non-ALS motor neuron disorders are much commoner than previously recognised and collectively may even approach the prevalence of more typical mixed motor and sensory forms of Charcot–Marie–Tooth disease.

## 2. Lower motor neuron disorders

### *2.1. Small Heat Shock Proteins HSPB1 and HSPB8*

The Heat Shock Proteins are a phylogenetically ancient and diverse group of proteins that contribute to cellular protection in response to various stress stimuli. This occurs at least in part through protection against the abnormal unfolding of proteins [2]. The small Heat Shock Proteins (sHSPs) are a sub-group that consists of 10 different proteins of around 27 kDa in humans that all share a highly conserved motif named the α-crystallin domain after the first member of the family to be characterised [3]. In 2004, mutations in two members of this family were found to cause an autosomal dominant progressive motor neuropathy [4,5]. A missense mutation in *HSPB1* (formerly known as *HSP27*), the most widely studied of the small sHSPs, was found in a Russian family previously linked to a locus at 7q11–q21 as well as in 5 other previously unlinked families. While in the initial family both motor and sensory symptoms were present, and the condition was classified as CMT2F, in all but one of the additional families the symptoms were limited to the motor system and the term HMN-II was used [4]. Since the initial report an additional mutation (P182S) has also been found in a Japanese family [6] and another (R127W) has been found in four Chinese families who share an ancestral haplotype [7]. Information on the clinical phenotype associated with *HSPB1* mutations is limited [7,8]. Onset of symptoms from 15 to 60 years of age has been described, typically with slowly progressive symmetrical weakness and wasting of the distal

limbs, most notable in the peroneal muscles, that first manifests as difficulty with running or walking. Lower limb symptoms typically precede upper limb symptoms by several years. In individuals heterozygous for the R127W mutation the average time for progression to requiring a stick for mobility was over a decade (range 8–20 years) and to requiring a wheelchair was around 20 years (16–20 years) [7]. Deep tendon reflexes are reduced or lost and no other parts of the CNS are clinically involved. Motor symptoms predominate in all families and sensory involvement where it occurs consists of mild loss of pin prick and vibration sense in a stocking distribution. No clear correlation between specific features of the phenotype and the genotype has been found and one particular mutation (S135F) has been found both in a family where sensory involvement is common and another where no sensory abnormalities have been found [4]. Electrophysiology, as well as sural nerve biopsy findings in a single case, has been consistent with an axonal neuronopathy [7,8] (Table 1).

*HSPB8* (also known as *HSP22*) was identified in 2001 through its binding of *HSPB1* [9]. A missense mutation in *HSPB8* was found to be responsible for the motor neuropathy observed in a large Belgian family with HMN II in which the locus had previously been mapped to 12q24 [5,10]. Mutations were also found in a further 3 families with a similar phenotype and independently in a Chinese family with a motor sensory neuropathy previously mapped to the same region as CMT2L [11,12]. All 5 instances involve the same amino acid residue (lysine 141). In the originally described Belgian family the disorder is relatively aggressive with onset of symptoms in the distal lower limbs usually in the teens or early 1920s and progression to complete paralysis of distal muscle groups in less than 5 years [13]. We have observed a more benign rate of progression in an English family with the K141E mutation. Sensory involvement has been observed in one of the five families, deep tendon reflexes are reduced or lost and motor conduction velocities are maintained on electrophysiological testing.

A large number of studies into the cytoprotective and oncogenic functions of the sHSPs, particularly *HSPB1*, have been published (reviewed in [14]). A function shared by most of the sHSPs is the ability to act as a molecular chaperone [15–17]. Under normal conditions, the sHSPs are found in vivo as oligomers that can contain > 30 sub-units [18]. In the presence of cellular stressors where conditions favour proteins adopting non-native states and the risk of undesirable interactions such as non-specific aggregation, the sHSPs are up-regulated and activated through phosphorylation by specific protein kinases [9,19–21]. In response, the oligomers dissociate allowing the dimeric proteins to interact with a large number of potential substrates which are maintained in a folding-competent state until conditions allow them to undergo re-folding [22]. In addition a number of functions have been described specifically for *HSPB1* including a direct anti-apoptotic effect [23–26], transcriptional regulation [27,28], resistance to oxidative stress [29–31], and a role in development, cell differentiation [23,32] and axonal outgrowth in the CNS [33].

A directly neuroprotective role has also been attributed to sHSPs particularly in relation to diseases where abnormal protein accumulation is a central feature such as Alzheimer's, Parkinson's or Huntington's Diseases (reviewed [34–36]). Significantly for the present discussion upregulation of *HSPB1* is found in motor neurons in a mouse model of familial ALS [37]. Transfection and over-expression of *HSPB1*, alone and in association with *HSP70*, has also been shown to protect neurons in culture from apoptosis associated with mutant forms of *SOD1* [38].

The reported mutations in *HSPB1* are found within conserved functional domains, all but 1 within the α-crystallin domain. The S135F mutation, but not wild type *HSPB1*, has been shown to disrupt the self assembly of neurofilament light chains when both proteins are transiently expressed and reduce cell survival when transfected into mouse neuroblastoma (N2a) cells [4]. The P182L mutation is situated in the C-terminal, outside the α-crystallin domain, in a highly conserved I–P–I

Table 1
Genes associated with pure motor neuron phenotypes

| Gene | Locus | | | Mutations (Families) | Onset[a] | UMN | LMN | Sensory | Limbs | Other |
|---|---|---|---|---|---|---|---|---|---|---|
| *SOD1* | ALS1 | 21q22 | AD | >100 | Adult | +++ | +++ | | U=L | FTD |
| *HSPB1* | HMN | 7q11 | AD | 5 (11) | Adult | | +++ | ++ | U<L | |
| *HSPB8* | dHMN-II | 12q24 | AD | 2 (5) | Adult | | +++ | | U<L | |
| *GARS* | dSMA-V | 7q15 | AD | 5 (5) | Adult | | +++ | ++ | U>L | |
| *DCTN1* | | 2q13 | AD | 5 (5) | Adult | + | +++ | | U>L | Bulbar/Facial FTD |
| *ALSIN* | ALS2 | 2q33 | AR | 9 (9) | Infancy | +++ | ++ | | U≤L | Bulbar |
| *SETX* | ALS4 | 9q34 | AD | 3 (3) | Juvenile | +++ | +++ | + | U=L | |
| *VAPB* | ALS8 | 20q13 | AD | 1 (7) | Adult | ++ | +++ | | U>L | Bulbar Tremor |
| *BSCL2* | dSMA-V | 11q13 | AD | 2 (17) | Juvenile | ++ | ++ | + | U>L | |
| *SPG4* | SPG4 | 2p22 | AD | >150 | Juvenile | +++ | + | + | U<L | Cognitive Impairment |
| *PGN* | SPG3A | 14q11 | AR | 7 (7) | Juvenile | +++ | + | | U<L | Ataxia |
| *ATL1* | SPG7 | 16q24 | AD | 19 (32) | Infancy | +++ | | | U<L | |
| *HSP60* | SPG13 | 2q33 | AD | 1 (1) | Adult | +++ | | ++ | U=L | |
| *KIF5A* | SPG10 | 12q13 | AD | 4 (4) | Juvenile | +++ | | | U<L | |
| *NIPA1* | SPG6 | 15q11 | AD | 2 (6) | Juvenile | +++ | | | U<L | |

UMN—upper motor neuron features, LMN—lower motor neuron features, AD—autosomal dominant, AR—autosomal recessive, FTD—frontotemporal dementia, +++—typical feature, ++—occasional feature, +—infrequent feature, U—upper limb, L—lower limb.

[a] Wide variation in age of onset and clinical features is seen (see text), details are for the most typical presentation associated with each gene.

motif that has previously been shown to participate in the amino terminal interactions that underlies the formation of dimers—the minimal functional unit of sHSPs [39]. The mutation apparently has the effect of stabilising *HSPB1* binding resulting in prominent insoluble cytoplasmic aggregates when expressed in mouse cortical neurons (Fig. 3). Mutant protein sequestrates specific proteins within the cytoplasm preventing their normal distribution down the axons. These include wildtype *HSPB1* and specific components of the axonal cytoskeleton including the neurofilament medium chain and p150-Dynactin (*DCTN1*—see below) suggesting that mutant HSPB1 might impair axonal transport [40].

The mutations at lysine 141 in *HSPB8* also increase its binding to *HSPB1* and causes cytoplasmic aggregate formation in cell culture [5]. The residue at the equivalent position in the α-crystallin domain has also been found to be mutated in both αA-crystallin, and αB-crystallin in autosomal dominant cataracts and desmin related myopathy, respectively [41,42]. A residue with positive charge (lysine, arginine or histidine) at this site in the domain is highly conserved across both the sHSP family and between species [2] and is known to be essential for normal oligomer formation and chaperone function [43]. Loss of chaperone function has been demonstrated directly for both the K141N and K141E mutations. In cell culture wild-type *HSPB8* but not the mutant protein was able to reduce the accumulation of insoluble protein aggregates when co-transfected with a fragment of either huntingtin or the androgen receptor containing expanded polyglutamine tracts [17]. Together, these results suggest that abnormal protein aggregation, either directly or through loss of normal chaperone function may be central to the neuropathic effect of *HSPB1* and *HSPB8* mutations. Aggregates may be directly toxic or have an effect by disrupting essential neuronal functions such as axonal transport, as was seen for the P182L mutation in *HSPB1*.

### 2.2. Glycyl-tRNA Synthetase (GARS)

On first consideration a ubiquitously expressed housekeeping gene such as the *GARS* gene that encodes the enzyme Glycyl-tRNA Synthetase would seem an unlikely candidate for a disorder specific to neurons. The enzyme catalyses the joining, through esterification, of the amino acid glycine to the specific subset of tRNA species that carry the corresponding cognate anti-codon sequence prior to translation [44]. Linkage to a locus on the short arm of chromosome 7 was identified initially in a family with a late onset form of distal motor neuropathy, termed distal SMA type V (dSMA-V) [45]. Later, linkage to the same locus was also demonstrated in a family in which both motor and sensory symptoms were present resulting in the classification CMT2D [46]. In 2003, it was shown that in both families, along with 3 others with similar phenotypes the condition was due to mutations in the *GARS* gene [47]. Unique mutations were found in families from North America, Bulgaria, Mongolia, France and more recently a family from England/Australia [47,48]. We are also aware of others from the British population. Mutations are spread throughout the gene including a number lying outside any known functional domain with no obvious hot-spots [48].

The phenotypic spectrum and pathological findings associated with *GARS* mutations were recently well reviewed by Sivakumar et al. [48]. A distinctive recognisable feature is the early prominent involvement of the hands, with wasting particularly of the thenar eminence and first dorsal interossei muscles found at presentation in all the cases examined (Fig. 2). The phenotypes have been classified as dSMA-V or CMT2D based on the presence or absence of sensory symptoms however this appears to be simply a distinction of severity as almost half the patients without sensory symptoms had not developed lower limb involvement after an average of almost 20 years from the onset of hand symptoms while all the patients with loss of sensation had developed weakness and atrophy of peroneal and foot muscles at an average of just over 3 years from the onset of

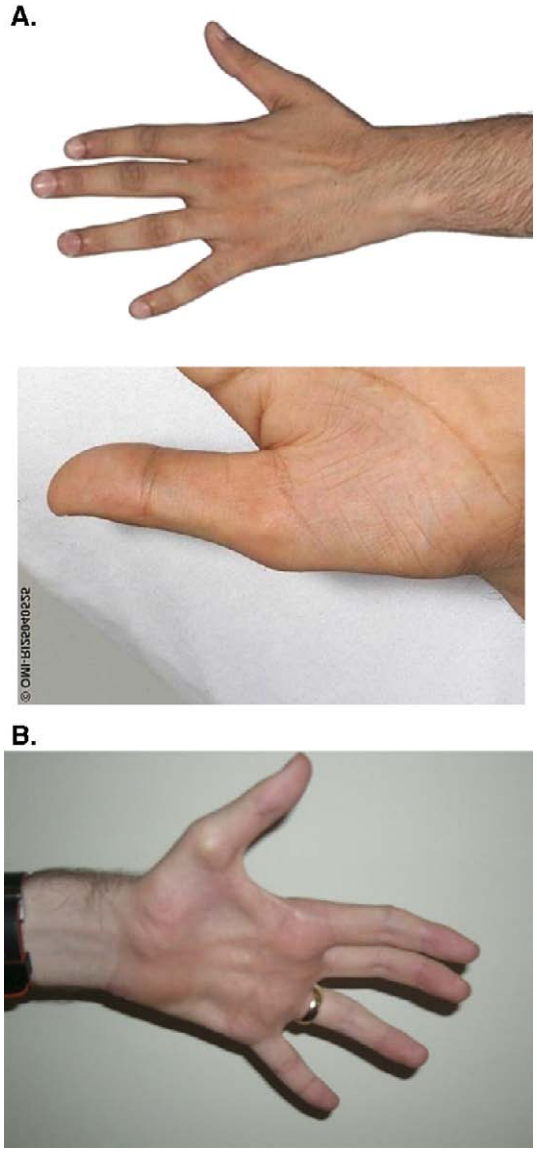


Fig. 2. Wasting of the 1st interosseus and thenar muscles is a prominent early feature in Silver Syndrome, associated with *BSCL2* mutations; (B) dSMA-V associated with *GARS* mutations.

hand symptoms. The severity and consequently the classification as either dSMA or CMT2 is related to the specific mutation found in a family. The mutations L129P, H418R and G526R consistently result in the milder motor-limited condition, G240R consistently gives rise to the severer form with sensory involvement and the E71G mutation found in a large family form Mongolia is intermediate with different individuals having phenotypes that would be classified under both terms. Non-penetrance may be relatively common especially in the families where the dSMA phenotype is found [48]. Progression is slow with loss of mobility being unusual even after several decades. Overall, motor symptoms predominate in all cases and weakness and wasting is limited to the distal muscles with no other systems involved. Available electrophysiology and sural nerve biopsy data are consistent with an axonal neuronopathy [48].

Currently, little is known about the mechanism by which *GARS* mutations affect neuronal survival. Transient expression of tagged forms of mutant *GARS* protein in neuronal-like cells in culture has not resulted in an obvious cellular phenotype in our hands (unpublished data). It is possible that a critical loss of function results in inadequate amounts of glycine–tRNA conjugates resulting in an effect on the translation of other proteins essential to motor neuron maintenance. Candidates include the proteins containing the glycine rich CAP-gly domain, usually found in Cytoskeletal-associated proteins (CAPs) which provide a link between vesicles and microtubules and have a role in axonal transport [48], or the arg-gly rich carboxy terminal repeats that are recognised by the SMN protein and are involved in the biogenesis of small nuclear Ribonuclear proteins (snRNPs) [49]. Other possibilities are suggested by the recent finding of mutations in the Tyrosyl-tRNA Synthetase (*YARS*) in three families affected by a motor-sensory neuropathy classified as Dominant Intermediate CMT1C [50]. Unlike the GARS protein, expression of YARS in neuronal-like cells in culture demonstrates concentration of the protein distally in extending processes. A specific failure of protein translation at critical sites such as synapses or the growth cones of developing neurons could be a unifying mechanism underlying the disorders associated with these two amino acid–tRNA synthetases (Fig. 3).

### 2.3. Dynactin (DCTN1)

The dynactin complex acts as a link between dynein, the major retrograde transport motor in axons, the microtubule network and transported cargo vesicles in neurons (reviewed in [51]). Disruption of this system through mutations in dynein or components of the dynactin complex in mice results in a motor neuron degeneration phenotype [52,53]. In 2003 a mutation in the p150 subunit of dynactin (*DCTN1*) was found in a family in which a highly unusual motor neuron disorder had been linked to 2p13 [54]. The most common presenting symptom was stridor due to vocal cord weakness at ages ranging from 23 to 44. Bulbar involvement, along with facial weakness was eventually seen in all cases. Progressive weakness of distal muscle groups was typically first apparent in the upper limbs accompanied by muscle atrophy and reduced tendon reflexes. There was no sensory involvement. Postmortem in 1 case confirmed the loss of motor neurons from the anterior horn and cranial nerve nuclei but did not show the accumulation of neurofilament associated with anterograde transport defects in other forms of motor neuron disease. Instead, inclusions of accumulated dynein and dynactin were found in the cell bodies of surviving neurons [55]. A further 4 mutations have now been reported in families with ALS, in some cases in association with fronto-temporal dementia, and in a small number of sporadic ALS cases [56,57]. In these families, a greater clinical

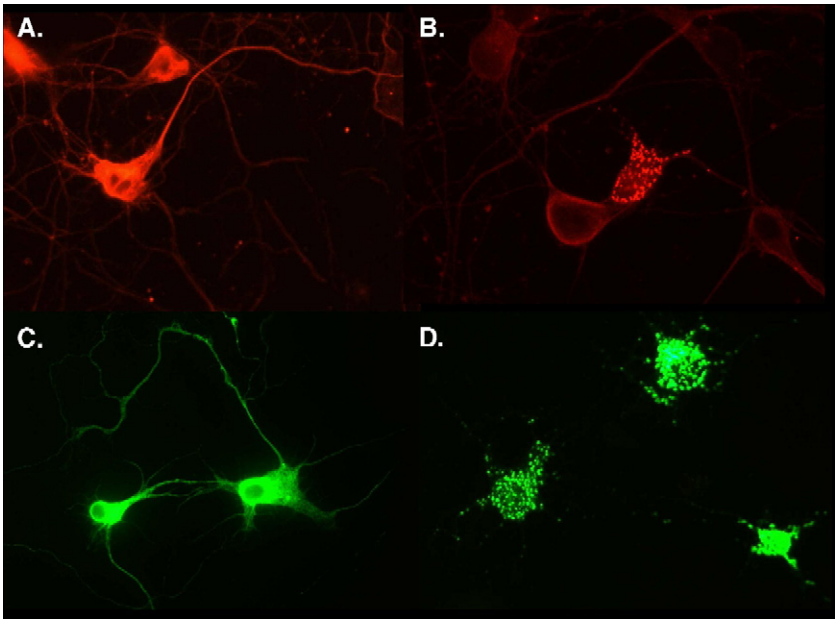


Fig. 3. Abnormal accumulation of mutant protein is a feature of a number of inherited motor neuron disorders. Mouse cortical neurons expressing: (A) wildtype *HSPB1*, (B) mutant P182L *HSPB1*, (C) wildtype *VAPB*, (D) mutant P56S *VAPB*.

variability was seen including non-penetrance in some cases. In the initially reported family the mutation G59S was found to lie in the highly conserved CAP-gly motif (see discussion of *GARS* above) and resulted in decreased binding of *DCTN1* to microtubules, while the reported M571T and R785W mutations lie in the predicted dynein binding domain. Although screening for variants in dynein itself has found no association [57,58] the p150-dynactin mutations confirm the central position of retrograde as well as anterograde transport in motor neuron function.

## 3. Mixed upper and lower motor neuron disorders

### 3.1. Alsin—ALS2

A distinct form of recessive juvenile ALS (designated ALS3) with prominent facial and bulbar involvement was linked to 2q33 in 1994 in a large inbred Tunisian family [59]. Two groups independently demonstrated that mutations in the gene Alsin (*ALS2*) were responsible for this phenotype [60,61]. A total of 9 mutations, all involving frame shift or truncating mutations, have been described, frequently in consanguineous families [62–65]. The clinical phenotype has been divided into 3 overlapping groups. The term Infantile Ascending Hereditary Spastic Paraplegia (IAHSP) has been applied to 6 families in which affected individuals develop symptoms of spastic paraplegia in the lower limbs at 1–2 years of age. Upper limb involvement follows by the end of the first decade with bulbar involvement becoming apparent at around the same time or soon afterwards and leading eventually to anarthria [62,64,65]. Involvement of the extra-ocular muscles resulting in gaze paralysis is a variable feature. The condition is severe and progressive with loss of independent mobility by around 4–5 years, loss of the ability to sit by the mid-teens and a reduced life expectancy. Intellectual function is thought to be preserved however abnormalities on MRI, including cerebral atrophy and hyperintense signal in the internal capsule and parieto-occipital periventricular white matter, may indicate more diffuse CNS involvement [65]. A further 2 families in which the term Juvenile Primary Lateral Sclerosis has been applied have essentially the same phenotype [60,66]. Members of the large Tunisian family in which the ALS2 locus was first mapped have a later onset form of the disorder with initial symptoms of either gait abnormality or pseudobulbar palsy first appearing at 3–10 years. The range of symptoms in this family is similar to the infantile form although the presence of amyotrophy of the lower limbs and hands in some cases justify the classification as a form of ALS [67].

The Alsin protein is distributed widely in the CNS and other tissues as a highly expressed long form (6.5 kb) and a less common short form (2.6 kb) [60]. All but one of the described mutations affects the long form only. As predicted based on homology Alsin has been shown to function as a guanine-exchange factor (GEF) and is required for the activation of at least 2 proteins with GTPase activity [68–70]. The first of these, *RAB5A*, is associated with the regulation of the fusion, internalization and trafficking of endosomal vesicles [71]. Ectopically and endogenously expressed Alsin has been found to localise to the cytoplasmic surface of endosomes and results in the enlargement of early endosomes in vitro [68,72]. This function is mediated by the carboxyl terminal VPS9 domain, one of 3 GEF domains found in Alsin, and requires homo-oligomerisation of the protein [73]. The second protein known to be activated through the action of Alsin is Rac1 (ras-related C3 botulinum toxin substrate 1) [69], a GTPase associated with regulation of axonal development through signaling cues that influence actin dynamics at the growth cone [74,75]. Alsin has been demonstrated co-localising with Rac1 in the growth cone and transient expression in cortical neurons stimulates neurite outgrowth [69]. This function is mediated by the Db1 Homology and Pleckstrin Homology (DH/PH) domain—the 2nd of the 3 GEF domains. Transient expression of Alsin protects NSC34 (motor neuron-like) cells from the toxic effect of the mutant forms of *SOD1*. The use of deletion constructs showed that this neuroprotective function is also mediated by the DH/PH domain and does not require either the amino terminal RCC1, or carboxy-terminal VPS9 GEF domains [76]. The null mutations responsible for ALS2 result in unstable products that are rapidly cleared by the proteasome [72] suggesting that complete loss of the activating function of Alsin on either intracellular trafficking or growth cone dynamics (or both) could be responsible for the motor neuron degeneration seen in this disorder. A recently described knock-out mouse model that lacks any working copy of the Alsin gene was found to have subtle abnormalities of the endosomal pathway as well as reduced numbers of Purkinje cells and spinal motor neurons, although clinically, no motor system abnormalities could be detected at up to 21 months of age [77].

### 3.2. Senataxin—ALS4

A very large 8 generational pedigree from Maryland, originally described in 1964 as an unusual form of CMT, and subsequently designated ALS4, has been linked to a locus at 9q34, [78]. In 2004 heterozygous missense mutations in the gene Senataxin were found in this family as well as 2 additional families that had shown linkage to the region [79]. Although a number of terms have been used to describe this condition, ‘Juvenile ALS’ is probably the most accurate. The condition is characterised by early onset of a slowly progressive muscle weakness associated with both UMN signs (hyperreflexia and extensor planter responses) and LMN signs (distal muscle wasting that usually affects lower limbs initially and occasionally decreased tendon reflexes). In contrast to sporadic ALS, and despite the long duration of the condition, respiratory and bulbar involvement does not seem to occur. Decreased vibration sense and facial weakness have been reported in a minority of cases. The age of onset has varied between families. In the Maryland kindred, the average age was 17 years (range 1–63), while in the European families onset in infancy or early childhood was typical [78,80,81]. Electrophysiology is consistent with an axonal disease process affecting predominantly the motor nerves and post-mortem findings from 2 cases confirmed loss of motor neurons from the anterior horns and detected

ubiquitin staining axonal spheroids in both the spinal cord and brainstem [78].

Senataxin was initially identified and named when mutations in the gene were found to cause Ataxia-Ocular Apraxia 2 (AOA2) [82]. This is an autosomal recessive form of spinocerebellar ataxia with onset of ataxia in adolescence accompanied in some cases by apraxia of eye movements, elevated serum AFP, and impaired proprioception and vibration sense. Interestingly slowly progressive distal amyotrophy beginning in the late 1920s is a consistent feature and is a prominent part of the phenotype leading to early loss of mobility in some families [83,84]. A total of 17 senataxin mutations have been found in AOA2 families, 12 of which are nonsense or frameshift mutations [82,83]. Currently, little is known about the function of senataxin. Expression is widespread in human tissues and within the CNS. Senataxin was originally named because of homology to a yeast protein *Sen1p*. Much of the large protein product (2,677 amino acids) appears to be novel; however sequence at the carboxy-terminal includes a helicase domain that shows homology to those found in proteins involved in RNA processing. One protein that shares this domain is encoded by the gene *IGHMBP2* (Immunoglobulin Mu Binding Protein 2), mutations in which have previously been found to cause autosomal recessive Spinal Muscular Atrophy with Respiratory Distress (SMARD) [85]. The presence of this domain suggests that senataxin could belong to the group of genes associated with motor neuron disorders with possible roles in mRNA biogenesis or regulation that includes both *IGHMBP2* and *SMN1* itself.

### 3.3. Vamp Associated Protein B—ALS8

A novel linkage to 20q13 was described in 2004 in a large Brazilian family of Portuguese extraction with a predominantly lower motor neuron disorder with some unusual additional features [86]. Patients developed symptoms in the second to fourth decade; typically either of a postural tremor, fasciculations or painful muscle cramps, before going on to develop slowly progressive lower motor neuron signs and symptoms in all limbs. A minority of affected individuals also had upper motor neuron signs and 7 out of 12 originally reported individuals eventually developed bulbar involvement prompting the authors to classify the condition as an atypical form of ALS. Muscle biopsy showed neurogenic changes and NCVs were preserved on electrophysiology. The following year a mutation (P56S) in the gene for VAMP-associated Protein B, *VAPB*, was found to be responsible for the disorder in this family and a further 6 Brazilian families with motor neuron disorders [87]. A surprising clinical diversity was seen for this single mutation. While some of the additional patients had a similar slowly progressing atypical ALS phenotype, in 5 patients from one family, the condition behaved like typical ALS with malignant progression of both upper and lower motor neuron symptoms resulting in death in less than 5 years from first onset of symptoms. In another family the clinical picture was much milder with onset of lower motor neuron symptoms in the 4th–6th decade, affecting mainly proximal muscle groups. Pyramidal signs and bulbar involvement were not present and the postural tremor was uncommon in this group leading the authors to describe them as a form of adult onset SMA. All 7 families shared a common haplotype and further analysis suggests a founding event in the Brazilian population around the mid-15th century. This event may have been the occurrence of the mutation itself or the point where a mutation, previously existing in the Portuguese population, was introduced into the Brazilian population [88]. Although the timing of this event would fit with first contact between Europeans and Brazil, so far the mutation has not been reported in the European population.

*VAPB* is named for its association with the Vesicle Associated Membrane Proteins (*VAMP*) that forms part of the SNARE complex – the protein machinery involved in vesicle membrane binding and exocytosis – and is expressed widely in the CNS and other human tissues [89]. Three human *VAMP*-associated proteins are known, all of which share a carboxy terminal MSP (major sperm protein) domain, a central coiled-coiled domain, and an amino terminal putative transmembrane domain that is required for its binding to both *VAMP1* and the homologous *VAPA*. However, while the orthologues of *VAPA* localise to the neuromuscular junction [90] and are involved in control of neurotransmitter release [91] evidence suggests *VAPB* associates with intracellular membranes and microtubules [92] and may be involved with vesicle tracking in the endoplasmic reticulum and Golgi apparatus. Introduction of the P56S mutation in cell culture causes *VAPB* to lose its normal association with the ER and form dense cytoplasmic aggregates [87]. As with other aggregate forming mutations in proteins associated with motor neuron degeneration it is not yet clear whether these aggregates are directly neurotoxic, disrupt fundamental neuronal functions, or act through sequestering and reducing the function of binding partners. In the case of *VAPB*, the binding partners include proteins known to be essential for neurotransmission.

### 3.4. Seipin (BSCL2)

The eponym Silver Syndrome has been given to a distinctive autosomal dominant disorder in which early weakness and wasting of the intrinsic muscles of the hands is associated with evidence of upper motor neuron involvement in the form of increased tone and reflexes in the lower limbs. This constellation of signs and symptoms was first described by J.R. Silver in 1966 in 2 large families [93] one of which was later involved in establishing linkage to a locus at 11q12–q14, designated SPG17 [94]. This locus was also identified in a family that had been classified as having distal HMN-type V [95] and in 2004 mutations in the Berardinelli–Seip Congenital Lipodystrophy gene (*BSCL2*) were found in both families along with 14 others from throughout Europe and 1 from Brazil. Two mutations, N88S and S90L, accounted for all 17 families although haplotype analysis suggested that the mutations had occurred independently several times. The Austrian families have now been shown to share a common ancestor in the 17th century [96,97]. We have also observed the N88S change as a de novo

mutation in a sporadic case. Mutations were not found on testing a further group of 25 individuals with a Silver Syndrome phenotype of upper limb amyotrophy and lower limb spasticity confirming previous observations that this phenotype is clinically heterogeneous [94,96].

Clinical information from these and a further 4 families that have been reported has shown considerable variation in the phenotype [97,98]. The average age of onset of symptoms is around 20 years but has varied from infancy to the sixth decade with thenar wasting or gait abnormalities being the most common initial presentations. Auer-Grumbach et al. [97] reviewed 90 patients with the N88S mutation and noted a number of different clinical sub-groups, several of which were found within the same family in most cases. A number of mutation positive individuals (average age 43 years, range 13–84) were either unaffected or had sub-clinical abnormalities on testing only. The most common grouping of symptoms involved prominent weakness and wasting of the intrinsic muscles of the hands either alone or in association with a variable degree of pyramidal tract symptoms in the lower limbs. In some individuals, this pattern was reversed with muscle wasting and weakness more pronounced in the lower limbs. In these cases spasticity and other UMN signs were less prominent and the condition has the appearance of a form of HMN or SMA. Finally, in some patients, the clinical picture is dominated by spasticity of the lower limbs with minimal or absent amyotrophy of the upper limbs and can appear as a form of Hereditary Spastic Paraplegia. In all groups, spasticity was associated with foot deformity that was rated as either severe or very severe in almost a third of patients. Some exceptional features included decreased or absent reflexes in the lower limbs in 3 patients and mild sensory deficits in 7 patients in association with severe motor involvement. Electrophysiological studies were consistent with an axonal neuronopathy and reflected the upper limb predominance.

As its name suggests, *BSCL2* was first described in association with distinct autosomal recessive congenital lipodystrophy, however, there is no clinical overlap between this and the neurological disorder and the recessive mutations, with a single exception, have all been nonsense, frame-shift insertion/deletion or splice-site mutations [99]. The protein Seipin is expressed in several tissues but a smaller brain specific transcript is found in throughout the CNS [96]. The function of the protein is essentially unknown; analysis of the sequence suggests an integral transmembrane domain and some homology to an AAA ATPase domain found in the much larger gene Midasin (*MDN1*), itself a distant evolutionary cousin of Dynein [100]. The 2 dominant mutations associated with motor neuron degeneration both disrupt the same N-glycosylation consensus sequence (N–X–S/T) which is likely to prevent the protein from adopting its normal tertiary structure. The wild-type protein shows localisation to the ER, but like a number of the proteins already discussed, the non-glycosylated mutants have been found to form dense cytoplasmic aggregates [96]. The mechanism by which this leads to decreased motor neuron survival is yet to be determined.

### 3.5. Neurofilament subunit genes (NF-H and NF-L)

Neurofilaments are neuronal specific intermediate filaments made up light (NF-L), medium (NF-M), and heavy (NF-H) subunits. The accumulation of neurofilaments, particularly NF-H, in the cytoplasm and proximal axons of motor neurons is an early pathological hallmark of sporadic ALS [101]. Mutations in the light subunit, or overexpression of either the light or heavy subunits in transgenic mice models result in similar pathological changes in the motor neurons [102,103]. As a result there has been investigation into a possible role for the human neurofilament genes in ALS but the results remain uncertain. Studies have focused on the tail domain of NF-H which contains a repeated amino acid sequence (X–K–S–P–Y–K), abbreviated as the KSP repeat. Two common alleles containing 44 (short, S) or 45 (long, L) repeats are found in the population. Two separate studies have found deletions in the NF-H tail removing up to 5 KSP repeats in a small percentage of patients with either sporadic or familial ALS [104,105], however the same variants were also found in unaffected family members or unrelated controls. Two smaller studies, one including familial ALS cases only, have failed to find NF-H deletions [106,107]. It is possible that deletions in this domain act as low penetrance predisposing alleles, however Al-Chalabi et al. noted that in the ALS cases the NF-H allele that did not contain the deletion was invariably the L allele, while the unaffected individuals almost always had the S allele [104] raising the possibility that a length discrepancy between the 2 alleles in complex may be the critical element. This idea is not supported however by an association study that examined the distribution of the L and S alleles in a cohort of sporadic ALS patients in Russia and observed an increase in the SS genotype in cases versus controls [108]. The role of variants of the NF-H gene in ALS remains a question requiring investigation. The neurofilament light subunit has also been implicated in an inherited dominant disorder characterised by early onset motor neuron degeneration classified as a form of CMT (CMT2E/CMT1F) due to the usual co-existence of sensory symptoms, although these are occasionally absent or limited to reduced vibratory sense [109–112].

## 4. Upper motor neuron disorders

### 4.1. Spastin—SPG4

As the commonest form of dominant pure Hereditary Spastic Paraplegia (pHSP) a considerable literature exists on the Spastin gene and its mutations (reviewed [113]). Since it was shown in 1999 that mutations in Spastin were responsible for the linkage of pHSP to 2p22–p21 [114] more than 150 mutations have been demonstrated accounting for an estimated 30–40% of dominant pure spastic paraplegia [115,116]. More recently, 2 studies have found 12–15.5% of sporadic cases, with a compatible phenotype of pHSP affecting the lower limbs, had mutations in the spastin gene [117,118]. In some cases, the apparent sporadic nature is due to a parent being an asymptomatic carrier and no truly de novo cases were

demonstrated. Overall, 6% of carriers are thought to be asymptomatic and a further 20% are unaware of symptoms prior to gene testing [119]. This reflects the broad range of age of onset that has been reported, from infancy to the 9th decade. Overall more than half mutation carriers will not develop symptoms until after the age of 30 years although this is not a function of the type of mutation found in the family [120]. In the majority of cases the phenotype is of slowly progressive spasticity in the lower limbs with loss of mobility around 2 decades after the onset of symptoms, although there is good evidence that the rate of progression is more rapid in patients with later onset of symptoms [119]. Symptoms found consistently in a minority of patients include urinary urgency, upper limb hyper-reflexia or weakness, and decreased vibration sense or muscle wasting in the lower limbs. Complex phenotypes have been described in a number of families segregating with a spastin mutation, including cerebellar ataxia, epilepsy [121], thinning of the corpus callosum [122,123], and mental retardation [123]. More significantly, there is growing evidence that progressive cognitive decline is a common feature [124–127] first becoming evident by examination from 40 years of age and progressing to clinically evident dementia in the 7th–8th decades. This is consistent with the available post-mortem information that has found that neuropathological changes extend to many parts of the CNS [128,129].

The spectrum of mutations found in SPG4 families is skewed towards truncating and splice site mutations, with missense amino acid changes accounting for only around 25% of mutations and clustering strongly in the conserved AAA cassette ATPase domain [115,119]. Neurons appear to be unusually sensitive to haploinsufficiency of spastin as splice site mutations that result in both normal and aberrant splice-forms of the protein are sufficient to produce the full clinical picture [130,131]. Investigation of spastin in cell culture systems has led to varying conclusions about the subcellular localisation of the wild-type protein depending on the different methodologies employed (summarised in [113,132]). Staining for endogenously expressed spastin indicates either a nuclear localisation [133] or both nuclear and perinuclear cytoplasmic distribution [134]. In motor neurons, spastin is enriched in cellular regions where dynamic microtubules are found including the distal axon [135]. This last finding is consistent with the growing evidence that spastin has a role in microtubule turnover.

The AAA ATPase domain of spastin shows homology the protein katanin that is involved in microtubule disassembly [136] and evidence suggests there may be a similar relationship between spastin and microtubules. Transient expression of wild-type spastin reduces microtubule staining [137] while mutations that disrupt the ATPase activity of the protein result in spastin co-localising with the microtubules in a filamentous pattern [138]. Evans et al. [139] found that the binding of ATP to spastin promoted this interaction while the ability of the enzyme to hydrolyse ATP to ADP is required for microtubule severing, which they were able to directly visualise. This model of activity is supported by the *Drosophila* model where the orthologue of spastin is enriched at the synaptic boutons. Selective RNAi knockdown of the *Drosophila* protein resulted in an underdevelopment of the synapses that was reversible through the action of nocodazole—a microtubule destabilising agent [140]. A second possible role for spastin is suggested by the recent finding that spastin interacts with *CHMP1B* (Chromatin Modifying Protein 1B), a component of an *e*ndosomal *s*orting *c*omplex *r*equired for *t*ransport (ESCRT-III) [132]. This interaction occurs through an amino terminal MIT domain which shares homology with the MIT domain found in spartin, the protein mutated in Troyer syndrome (SPG20); a complicated form of recessive spastic paraplegia in association with dysarthria, distal muscle wasting, short stature and developmental delay. Reid et al. note that roles for spastin in both membrane trafficking and microtubule regulation is not inconceivable as a single protein may well need to interact with both transport vesicles and the cytoskeletal structures that mediate such transport [132].

### 4.2. Atlastin 1—SPG3A

Mutations in the gene Atlastin were described in 2001 as a cause of an early onset form of dominant pure spastic paraplegia, previously linked to chromosome 14q11–q21 [141]. A total of 19 mutations in 32 families have been described, accounting for an estimated 10% of this phenotype [141–151]. Onset of symptoms is most commonly in infancy or early childhood and can impair the development of walking, however there is wide variation within families and 1 family has been described in which only adult onset spasticity was found. Spasticity and increased reflexes are mostly restricted to the lower limbs but are frequently severe enough to eventually require walking aids or a wheelchair. Sensory involvement is limited to decreased vibration but is rare in comparison to families with spastin mutations. Other CNS involvement has not been described.

Atlastin is highly expressed in the CNS compared to other tissues and consistent with the clinical phenotype particularly high expression is seen in the pyramidal cells of the cerebral cortex [152]. The protein contains a large GTPase domain that shares greatest homology with *GBP1* (Guanylate Binding Protein 1)—a member of the dynamin family of GTPases known to be essential at several stages of vesicle trafficking. Mutations in another member of this family, dynamin-2, results in motor neuron degeneration as part of a dominant intermediate form of CMT [153]. Two genes closely homologous to atlastin are present in the human genome leading to the renaming of the original protein atlastin1 [152]. Unlike other members of the dynamin family atlastin1 also contains a transmembrane domain and is found as a homo-oligomer localised in the Golgi apparatus. The reported mutations tend to cluster in the GTPase domain, including the recurrent R239C mutation that disrupts an essential RD motif, however their effect on the localisation and function of atlastin is yet to be examined. Currently the evidence suggests that atlastin mutations are likely to affect vesicle trafficking and processing at the Golgi apparatus.

### 4.3. Paraplegin—SPG7

Both pure and complicated spastic paraplegia has been reported in association with recessive mutations in the paraplegin gene at chromosome 16q24. The condition was mapped in a large consanguineous family with an adult onset pure spastic paraplegia, occasionally associated with dysarthria and optic disk pallor [154]. Mutations in paraplegin have been demonstrated in a further 6 families, 2 of which have a complex phenotype with ataxia and cerebellar atrophy on MRI [155–157]. Onset occurs in the 2nd to 3rd decade and there is slow progression affecting independent mobility after 20–30 years. Spasticity and weakness is greatest in the lower limbs and distal muscle wasting in both hands and feet has been reported. Paraplegin is a mitochondrial protein and is homologous to yeast mitochondrial ATPases that are known to form a complex at the inner mitochondrial membrane with functions including ATP mediated protein degradation, regulation of splicing and chaperoning the assembly of respiratory chain proteins [158]. A knockout mouse missing both copies of the murine homologue develops a motor phenotype with retrograde degeneration of axons in the long tracts of the spine and the optic nerve. Prior to the degeneration of axons hypertrophic and morphologically abnormal mitochondria are apparent by electron microscopy. Deficiency of respiratory chain proteins and ATP synthesis is only seen late in the disease course but accumulation of neurofilaments, axonal swellings and impairment of retrograde transport are found at an earlier stage [159]. These observations point to aberrant intracellular trafficking rather than a deficiency in oxidative phosphorylation as the critical abnormality despite the mitochondrial localisation of paraplegin.

### 4.4. Others (HSP60, KIF5A, NIPA1)

A mutation in *HSP60*, a mitochondrial chaperone with a central role in normal protein folding in the mitochondria, is responsible for a pure dominant spastic paraplegia in a single large French family (SPG13). The functionally null V72I mutation was described in 2002 and is associated with a relatively severe phenotype with frequent involvement of upper as well as lower limbs [160,161]. Kinesin Heavy Chain (*KIF5A*) is a component of the major anterograde motor complex for axonal transport in neurons [162]. Mutations in *KIF5A* have been found in 4 families with a pure lower limb spastic paraplegia (SPG10) with age of onset varying between late childhood and adulthood [163–166]. Modeling of the N256S mutation in *Drosophila* and yeast orthologues confirms the expected disruption of anterograde transport resulting in abnormal cytoplasmic accumulations of organelles and membrane vesicles. Interestingly a mutation in a second kinesin subunit *KIF1Bβ* has been associated with the degeneration of LMNs, along with sensory neurons, in a 3 generational Japanese family affected by CMT2 [167]. The phenotype associated with *KIF1Bβ* has been designated CMT2A1 after mutations in the gene Mitofusion-2 (*MFN2*) were found to be a more frequent cause of CMT2 linking to this region of 1p36 (designated CMT2A2) [168]. Again mouse models have confirmed the expected deficits in axonal transport associated with *KIF1Bβ* mutations [167]. Also emerging as a cause of dominant pure spastic paraplegia in multiple families are mutations in the gene *NIPA1* (Non Imprinted in Prader-Willi/Angelman syndrome 1, SPG6). Six families with juvenile onset have been reported, with a recurrent mutation at glycine106 found in 4 cases. The function of the protein product remains unknown but the presence of 9 transmembrane domains suggests that *NIPA1* is either a receptor or involved in transmembrane transport or signaling [169–172].

## 5. Conclusions

### 5.1. Physical disruption of normal axonal function is a common theme

As the genes responsible for increasing numbers of familial forms of motor neuron disorders are identified, analysis of their function appears to provide continuing confirmation of the areas of motor neuron vulnerability first suggested by the nature of the neurons and overlapping aspects of the pathology of ALS [1]. Principal amongst the recurring themes is that of physical disruption to intracellular trafficking in the axon. In many instances the nature of this disruption is obvious and direct, as with *DCTN1* or *KIF5A* mutations, however evidence is accumulating that even with proteins not directly involved in axonal transport secondary effects on axoplasmal flow are common, as with the sequestration of p150 dynactin in *HSPB1* aggregates or the unexpected evidence of early disruption of retrograde and anterograde transport despite the mitochondrial localisation of paraplegin. The discovery of connections to vesicle trafficking and the endosomal transport pathway have been a feature of recent publications. Direct associations with this system have been suggested for Alsin, *VAPB*, Spastin and Atlastin. In addition mutations in an ESCRT-III component *CHMP2B* have recently been described in a family with frontotemporal dementia (late onset spasticity was also found in most cases) [173] and mutations in *VPS54*, a component of the Golgi-associated Retrograde Protein (GARP) complex, cause a motor neuron syndrome in mice [174]. The idea that the failure to transfer essential structural components, trophic factors or even RNAs up or down the uniquely long axons of motor neurons could result in dysfunction that demonstrates both cell type specificity and length-dependent selectivity is an appealing framework for understanding inherited disorders of the motor neuron.

### 5.2. Motor neuron specificity is relative

As well as steadily increasing the number of ‘motor neuron’ associated genes continuing research provides accumulating experience of the phenotypic variation associated with mutations in each gene. This variation has proved to be extensive, illustrating in some cases the arbitrary nature of our diagnostic classifications (Fig. 1). Experience has also shown that rarely, if ever, is a motor neuron disorder truly restricted to just this population of neurons. As in sporadic ALS, sub-clinical sensory

involvement is frequently evident electrophysiologically or on examination. The example of *GARS* shows that the difference between presentation as a pure motor neuropathy or as a motor–sensory neuropathy can be merely a matter of severity and this may be true for other causes of HMN or CMT2. Involvement of other parts of the CNS may also be more common than previously appreciated as illustrated by the examples of cognitive decline with spastin mutations and the early cranial nerve involvement seen with mutations in p150 dynactin. These associations, along with the finding of upper limb predominance seen with genes such as *GARS* and *BSCL2* suggest that at least some mechanisms of motor neuron death are more complicated than can be explained by simple length dependent models.

### *5.3. Genetic heterogeneity suggests motor neuron degeneration is a final common pathway*

Despite the growing list of genes associated with motor neuron disorders many families with clear dominant inheritance of an appropriate phenotype are not found to have mutations in any of the relevant genes or linkage to known loci. Even for pure spastic paraplegia families, where spastin and atlastin gene testing is now widely available around half the families will not presently acquire a genetic diagnosis. As research continues it becomes less likely that a gene yet to be found will account for a very large proportion of any particular phenotype. Instead the number and variety of genes already discovered is likely to be at least matched by those yet to be identified. This heterogeneity leads to the conclusion that at a genetic level motor neuron degeneration could be a common final expression of disruptions in a number of cellular systems. The genetic diversity that has been found to underlie these Mendelian forms of motor neuron disorders sheds light not only on the nature of the possible genetic factors that may predispose to the more common sporadic form of ALS but also on the high degree of genetic complexity that is likely to be involved.

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