The Peripheral Nervous System in Amyotrophic Lateral Sclerosis: Opportunities for Translational Research

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Although amyotrophic lateral sclerosis (ALS) has been considered as a disorder of the motor neuron (MN) cell body, recent evidences show the non-cell-autonomous pathogenic nature of the disease. Axonal degeneration, loss of peripheral axons and destruction of nerve terminals are early events in the disease pathogenic cascade, anticipating MN degeneration, and the onset of clinical symptoms. Therefore, although ALS and peripheral axonal neuropathies should be differentiated in clinical practice, they also share damage to common molecular pathways, including axonal transport, RNA metabolism and proteostasis. Thus, an extensive evaluation of the molecular events occurring in the peripheral nervous system (PNS) could be fundamental to understand the pathogenic mechanisms of ALS, favoring the discovery of potential disease biomarkers, and new therapeutic targets.

Keywords: motor neuron disease, lower motor neuron syndrome, nerve, neuropathy, CMT, distal SMA, hereditary neuropathy, genetics

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is the most common and severe form of motor neuron disease (MND), an heterogeneous group of disorders defined by prominent motor neuron (MN) degeneration (Saberi et al., 2015; Riva et al., 2016). Recent evidence has challenged such traditional view of selective neuronal loss demonstrating widespread extra-motor involvement in ALS and implying that neuronal populations other than MNs may also be affected (Geser et al., 2008; Brettschneider et al., 2013; McCluskey et al., 2014). Furthermore, an expanded clinical spectrum has now been recognized, as overlapping phenotypes with other neuromuscular disorders (Sabatelli et al., 2016), including peripheral neuropathies, have been described (Rajabally and Jacob, 2008; Bhatt et al., 2009; Sawa et al., 2012). Although in clinical practice MNDs should be differentiated from other peripheral nervous system (PNS) disorders, sensory and autonomic neurons in the dorsal root ganglia (DRG) and lower MNs in the ventral horns share important challenges, as proper stability and functioning of their long projections throughout the body requires a protective environment and efficient communication between the central nervous system (CNS) and the outermost areas of these cells. Nonetheless, differences in
morphology and function may confer different patterns of resistance or vulnerability to specific stressors.

The aim of this review is to dissect PNS involvement in ALS, analyzing the evidence from clinical and pathological data to genetics in order to provide novel pathophysiological insights and potential implication for therapeutic strategies.

**DIAGNOSTIC CHALLENGES IN ALS AND ALS-MIMICS**

In the absence of pathognomonic diagnostic biomarkers, ALS diagnosis relies on clinical findings suggestive of selective upper, and lower MN (LMN) lesion and the exclusion of alternative causes (Ludolph et al., 2015). The wide clinical heterogeneity of the disease led to the development of several phenotypic classifications, mainly dependent on the distribution of UMN and LMN lesions. In patients presenting with isolated signs of LMN involvement (LMN Syndrome – LMNS), the differential diagnosis may be more challenging since the primary disease target may be the cell soma, the axon and its myelin, the neuromuscular junction (NMJ) or the muscle (Riva et al., 2011b; Garg et al., 2017; Muller et al., 2018). Such disorders not only share the motor unit as a common target of damage, but may be potentially underpinned by common pathogenic mechanisms. Within this context, ALS, with special reference to its restricted LMN phenotypes, such as flair legs and flail arm syndromes, shows high overlap in terms of clinical presentation, targets and mechanisms of damage with hereditary axonal neuropathies, such as axonal Charcot-Marie-Tooth neuropathy (CMT2) and distal hereditary motor neuropathy (dHMN) (Fischer and Glass, 2007). Besides the different rate of progression and spreading, distinction between these disorders could be difficult especially in the early phase, as clinical and neurophysiologic studies may be strikingly similar and may not able to discern the primary lesion site. Nonetheless, a recent study supported the value of the electroneurographic split hand index has recently been suggested for distinguishing ALS from mimic disorders (Menon et al., 2014). Moreover, pes cavus, traditionally considered a distinguishing clinical sign of CMT, has also been anecdotally reported in ALS patients (Ceroni et al., 2001), and is estimated to be as high as 2% our case series (data not published).

Notably, the percentage of misdiagnosis in degenerative LMNS has been reported to be as high as 19%; moreover, up to 10% of patients initially diagnosed as ALS are ultimately re-diagnosed as having another disease, including peripheral neuropathy (Davenport et al., 1996; Traynor et al., 2000; Visser et al., 2002). Therefore, in some cases, MND diagnosis remains uncertain, and only follow up can lead to a satisfying level of diagnostic confidence. Of note, we previously showed that biopsy of obturator nerve may be useful in the distinction between these disorders could be difficult especially in the early phase, as clinical and neurophysiologic studies may be strikingly similar and may not able to discern the primary lesion site. Nonetheless, a recent study supported the value of the electroneurographic split hand index has recently been suggested for distinguishing ALS from mimic disorders (Menon et al., 2014). Moreover, pes cavus, traditionally considered a distinguishing clinical sign of CMT, has also been anecdotally reported in ALS patients (Ceroni et al., 2001), and is estimated to be as high as 2% our case series (data not published).

**THE PNS AS A CONVERGING POINT IN ALS**

**Evidence of Peripheral Nervous System Involvement in Human ALS**

Although the circumstances leading to MN damage in ALS are still unknown, different mechanisms have been proposed to explain disease onset and spread. The dying-forward hypothesis states that the primary site of damage resides in the cell soma and subsequently spreads to the peripheral compartments. In the recent years, the dying-back pattern of degeneration has obtained a large attention in the context of ALS pathophysiology (Fischer et al., 2004), suggesting that ALS is a distal axonopathy, a pattern typically seen in peripheral neuropathies with a distal to proximal gradient of damage (England and Asbury, 2004). Therefore, considering that both motor and sensory nerves share mechanisms of axonal degeneration, it may be plausible that in ALS signs of PNS dysfunction may also extend to the sensory system. Notably, other neurodegenerative diseases such as Parkinson’s disease and Alzheimer’s disease show evidence of distal axonopathy (Arendt, 2009; Chung et al., 2009).

While diagnostic assessment in ALS relays on the assumption that non-motor components of the PNS are usually spared, increasing amount of evidence suggests the presence of sensory and autonomic dysfunction in ALS. Sensory symptoms are reported in about 2–30% of cases (Gubbay et al., 1985; Hammad et al., 2007). Numbness, tingling and pain are the most common symptoms reported. Decreased vibration sense and abnormal pain and temperature thresholds are rarely observed during standard examination, however quantitative sensory testing shows abnormal findings in about 10% of patients, rising to almost half of the cases in advanced stages of the disease (Truini et al., 2015; Isak et al., 2017).
Autonomic dysfunction has been reported in 5–30% of cases, while quantitative autonomic testing detected abnormal sudomotor and cardiovagal response in up to 50% of patients (McCluskey et al., 2014; Piccione et al., 2015). Abnormalities in either sensory nerve amplitudes or nerve conduction velocity may be apparent in about 20% of cases (Mondelli et al., 1993; Pugdahl et al., 2008), with higher frequencies reported in patients with longer disease duration (Pugdahl et al., 2007; Isak et al., 2016).

Pathologic studies of the sural nerve in ALS have demonstrated a mild reduction of the number of large nerve fibers (Figure 1B) in most of the examined cases (Bradley et al., 1983; Hammad et al., 2007; Devigili et al., 2011; Luigetti et al., 2012). Clustering of mitochondria, dilation of small vesicles and accumulation of neurofilaments (NF) have also been reported (Dyck et al., 1975; Di Trapani et al., 1987; Heads et al., 1991). Skin biopsy shows in about 80% of ALS patients a reduction of intraepidermal nerve fiber density (Weis et al., 2011; Truini et al., 2015; Dalla Bella et al., 2016; Nolano et al., 2017) and focal axonal swellings, suggesting axonal degeneration (Isak et al., 2017). Interestingly, small nerve fibers in the cornea are also reduced in ALS patients, correlating with bulbar disability scores (Ferrari et al., 2014). Finally, a significant neuronal loss has been observed in DRG of ALS patients, with preferential involvement of large-sized cells (Kawamura et al., 1981). Notably, evidence of pTDP-43 pathology has been shown in Clarke’s column, intermediolateral nucleus and dorsal root ganglia in a subset of cases, proving that these structures are also affected (Nishihira et al., 2008; Brettschneider et al., 2014).

The Role of Genetics in ALS: At the Borders of the Disease Spectrum

The knowledge about ALS genetics has had a relevant acceleration in the last decade, with more than 30 genes identified as pathogenic and more than 100 as ALS-related (Riva et al., 2016). The first gene identified as a cause of ALS was SOD1 in 1993 (Rosen et al., 1993) and together with TARDBP (Sreedharan et al., 2008), FUS (Kwiatkowski et al., 2009), and chromosome 9 open reading frame 72 (C9orf72) (DeJesus-Hernandez et al., 2011; Renton et al., 2011), represent the most common ALS-related genes, covering up to 70% of familial and 10% of sporadic cases (Riva et al., 2016; Chia et al., 2018). ALS-key genes have been associated with almost all clinical ALS phenotypes, although patients with SOD1, and FUS mutations may show preferential LMN involvement (Waibel et al., 2013; Picher-Martel et al., 2016).

The frequency of gene variants in cases with extra-motor involvement is significantly higher compared to the pure ALS phenotype, and has been associated with poorer survival (McCluskey et al., 2014). Prominent sensory involvement had been described in rare mutated cases, with SOD1 and TARDBP genes being reported most frequently (Camdessanche et al., 2011).

Many of the genes involved in ALS are associated also with other neurological disorders sharing common targets of neurodegeneration, such as hereditary spastic paraplegia (HSP), axonal CMT neuropathy and dHMN. Among the genes involved in dHMN and axonal CMT there are Berardinelli-Seip Congenital Lipodystrophy 2 (BSCL2), neurofilament light (NEFL), transient receptor potential cation channel subfamily V member 4 (TRPV4), heat shock protein family B1, B3, and B8 (HSPB1, HSPB3, and HSPB8) (Martini et al., 2000; Rossor et al., 2012). Despite the discrepancy between the major genes mutated in hereditary neuropathies and ALS, each of them exerts pleiotropic functions in neuronal homeostasis, including RNA metabolism, protein quality control, axonal transport, stress response. Therefore, generation of a spectrum of clinical phenotypes from alteration in master genes, broadly involved in key neuronal metabolic pathways, could be expected (Table 1).

Neurofilaments (NF) are composed of three subunits defined by their molecular weight and encoded by the NF light (NEFL), medium (NEFM), and heavy (NEFH) genes (Lieberburg et al., 1989). NFs are specifically expressed in neurons and are the most abundant cytoskeletal components of myelinated axons, regulating their caliber, growth, and conduction rate (Hoffman et al., 1987). Mutations in NEFL are known to cause both axonal and demyelinating forms of CMT with different phenotypes, including pyramidal signs (Mersiyanova et al., 2000; Jordanova et al., 2003; Rebelo et al., 2016; Jacquier et al., 2017). Mutations in NEFH gene are involved in the pathogenesis of sporadic ALS (Figlewicz et al., 1994; Al-Chalabi et al., 1999) but also in CMT (Jacquier et al., 2017; Nam et al., 2017).

The cellular abundance of Pi(3,5)P2, a phosphoinositide involved in the control of vesicles trafficking, is regulated by a phosphoinositide 5-phosphatase encoded by the FIG4 gene. CMT4J cases, clinically characterized by early onset and aggressive disease progression, have been associated with an autosomal dominant pattern of transmission and by biallelic FIG4 mutations (Nicholson et al., 2011). Notably, heterozygous autosomal dominant FIG4 variants have been more recently associated with ALS and identified as ALS11 (Osmanovic et al., 2017).

The valosin containing protein (VCP) is member of the AAA ATPase family of proteins. This protein is ubiquitously expressed, and it is implicated in multiple cellular processes, such as cell survival (Vandermoere et al., 2006; Braun and Zischka, 2008), stress response and DNA and protein quality control (DeLaBarre et al., 2006; Ju et al., 2009; Weihl et al., 2009). Mutations in VCP have been described in patients with autosomal dominant inclusion body myopathy (IBM) associated with Paget disease and fronto-temporal dementia (FTD) (IBMPFD) (Watts et al., 2004), pure ALS patients (Johnson et al., 2010; Miller et al., 2012), and recently also CMT (Gonzalez et al., 2014; Jerath et al., 2015).

The exact function of senataxin (SETX) is unknown but it may be involved in RNA metabolism. Studies have shown a role in DNA transcription and repair (Suraweera et al., 2009; Skourtis-Stathaki et al., 2011). Mutations in STX have been described in ataxia-ocular apraxia 2 (AOA2) (Moreira et al., 2004; Duquette et al., 2005; Fogel and Perlman, 2006; Arning et al., 2008; Airoldi et al., 2010; Fogel et al., 2014), autosomal dominant juvenile ALS (Chen et al., 2004; Zhao et al., 2009; Avermai et al., 2011; Arning et al., 2013; Tripolszki et al., 2017), and in dHMN with pyramidal features (De Jonghe et al., 2002).
# TABLE 1 | Key genes associated with ALS, hereditary neuropathy, and overlapping phenotypes.

| Gene    | Gene name                           | Chromosome | Disease*                  | Inheritance | References                                                                 |
|---------|-------------------------------------|------------|---------------------------|-------------|-----------------------------------------------------------------------------|
| **ALS genes** |                                     |            |                           |             |                                                                             |
| C9orf72 | Chromosome 9 open reading frame 72  | 9p21       | FTD and/or ALS 1          | AD          | DeJesus-Hernandez et al., 2011; Renton et al., 2011                        |
| FUS     | FUS RNA Binding Protein             | 16p11      | ALS6 with or without FTD  | AD/AR       | Vance et al., 2009                                                          |
| OPTN    | Optineurin                          | 10p13      | Open angle glaucoma – ALS12 | AD/AR       | Rezaie et al., 2002 (Glaucoma); Maruyama et al., 2010 (ALS)                |
| PFN1    | Profilin 1                          | 17p13      | ALS18                     | AD          | Wu et al., 2012                                                            |
| SOD1    | Superoxide dismutase 1             | 21q22      | ALS1                      | AD          | Rosen et al., 1993                                                         |
| SQSTM1  | Sequestosome 1                      | 5q35       | Paget disease of bone 3 – FTD and/or ALS3 | AD          | Laurin et al., 2002 (Paget Disease); Fecto et al., 2011 (ALS)               |
| TARDBP  | TAR DNA binding protein            | 1p36       | ALS 10 with or without FTD | AD          | Gitch et al., 2008; Kabashi et al., 2008                                    |
| UBQLN2  | Ubiquilin 2                         | Xp11.21    | ALS15 with or without FTD | X-linked; AD | Deng et al., 2011                                                          |
| **Overlap genes** |                                     |            |                           |             |                                                                             |
| DCTN1   | Dynactin subunit 1                  | 2p13       | dHMNVIIB – Perry syndrome – ALS | AD/AR Risk factor (ALS) | Puls et al., 2003 (dHMN); Munch et al., 2005 (ALS); Farrer et al., 2009 (Perry syndrome) |
| DYNC1H1 | Dynein cytoplasmic 1 heavy chain 1  | 14q32      | CMT2O – dSMA1 – ALS       | AD          | Munch et al., 2004 (ALS); Weedon et al., 2011 (CMT); Harms et al., 2012 (dSMA) |
| FIG4    | FIG4 phosphoinositide 5-phosphatase  | 6q21       | CMT4J – ALS11 – Yunis-Varon syndrome | AR – AD     | Chow et al., 2007, 2009 (CMT, ALS); Campeau et al., 2013 (Yunis-Varon)   |
| GARS    | Glycyl-tRNA synthetase              | 7p15       | CMT2D – dHMNVA – ALS      | AD          | Antonelli et al., 2003 (CMT – dSMA); Kruger et al., 2016 (ALS)             |
| KIF5A   | Kinesin family member 5A            | 12q13      | CMT2 – SPG10 – ALS25      | AD          | Reid et al., 2002; Crimella et al., 2012 (HSP – CMT2); Nicolas et al., 2018 (ALS) |
| MFN2    | Mitofusin 2                         | 1p36       | CMT2A2A – CMT2A2B – dHMNVIA – ALS like | AD/AR       | Zuchner et al., 2004a (CMT2A2A); MiMarchesi et al., 2011 (ALS); Polke et al., 2011 (CMT2A2B) |
| NEFH    | Neurofilament heavy                 | 22q12      | ALS – CMT2CC              | AD – AR     | Figlewicz et al., 1994 (ALS); Rebei et al., 2016 (CMT); Maystadt et al., 2007 (SMA); Azeddine et al., 2013; Kim et al., 2013 (CMT); Ozoguz et al., 2015 (ALS) |
| PLEKHG5 | Pleckstrin homology and RhoGEF domain containing G5 | 1p36 | CMTC; SMA – SMA distal4 – ALS | AR          |                                                                            |
| SETX    | Senataxin                           | 9q34       | dHMN with pyramidal signs – ALS4 juvenile – spinocerebellar ataxia 1 | AD – AR     | De Jonghe et al., 2002 (dHMN); Chen et al., 2004 (ALS); Moreira et al., 2004 (spinocerebellar ataxia) |
| SIGMAR1 | Sigma non-opiod intracellular receptor 1 | 9p13  | ALS16 juvenile – SMA distal 2 | AR          | Al-Saif et al., 2011 (ALS); Li X. et al., 2015 (dSMA2)                        |
| SPAST   | Spastin                             | 2p22       | SPG3 – ALS juvenile       | AD          | Fonknechten et al., 2000 (hHSP); Meyer et al., 2005 (ALS)                  |
| SPG11   | Spatacsin vesicle trafficking related | 15q21     | SPG11 – ALS5 juvenile – CMT2X | AR          | Stevanin et al., 2007 (SPG); Orlicchio et al., 2010 (ALS); Montecchiani et al., 2016 (CMT) |
| VCP     | Valosin containing protein          | 9p13       | IBMPFD- ALS14 with or without FTD – CMT2Y | AD          | Watts et al., 2004 (IBMPFD); Johnson et al., 2010 (ALS); Gonzalez et al., 2014 (CMT) |

(Continued)
The Spastic Paraplegia 11 gene (SPG11) encodes the spatacsin protein, selectively expressed in neuron with a role in axonal growth, transport, and cytoskeletal stability (Perez-Branguli et al., 2014). SPG11 variants were first described in patients with autosomal recessive spastic paraplegia 11 with thin corpus callosum (Hehr et al., 2007). Then, descriptions in juvenile ALS (ALS5) and in CMT2X were also reported (Orlacchio et al., 2010; Daoud et al., 2012; Iskender et al., 2015; Montecchiani et al., 2016).

The dynactin subunit 1 (DCTN1) and kinesin family member 5A (KIF5A) genes encode for dynactin and kinesin subunits, involved in retrograde and anterograde axonal transport, respectively (Hirikawa et al., 2009; Kwinter et al., 2009). DCTN1 and KIF5A variants have been variably described in ALS (Munch et al., 2004, 2005; Liu et al., 2014, 2017; Brenner et al., 2018; Nicolas et al., 2018), CMT, and dHMN (Crimella et al., 2012; Montecchiani et al., 2016).

Finally, pleckstrin homology and RhoGEF domain containing G5 (PLEKHG5) and mitofusin 2 (MFN2) genes, whose mutations are known to cause CMT (Muglia et al., 2001; Zuchner et al., 2004a, 2006; Engelfried et al., 2006; Del Bo et al., 2008; Nicholson et al., 2008; Azzedine et al., 2013; Kim et al., 2013; Lapadre et al., 2018), have been also reported in patients with ALS or an "ALS-like" phenotype (Marchesi et al., 2011; Ozoguz et al., 2015).

**PATHOGENIC MECHANISMS OF PNS DAMAGE IN ALS**

**Peripheral Motor and Sensory Dysfunction in ALS Models**

The strongest evidence supporting the dying-back pattern of degeneration comes from transgenic mice overexpressing the mutated form of human SOD1 G93A (hSOD-1G93A), the most studied ALS model. Axonal pathology precedes spinal MN death and symptom onset, with the NMJ being the first site of morphological alteration (Fischer et al., 2004). Along with disease progression, the burden of axonal pathology overcomes the moderate MN loss in spinal cord, and suggesting that the motor phenotype in these mice models is mainly driven by the PNS damage (Gould et al., 2006; Hagedus et al., 2007). Indeed, interventions leading to complete rescue of MNs in the spinal cord of mutant SOD1 (mSOD1) ALS mice were not sufficient to halt axonal loss and motor phenotype, suggesting that mechanisms of central, and peripheral degeneration may be at least partially independent (Gould et al., 2006; Rouaux et al., 2007; Suzuki et al., 2007).

Despite the wealth amount of data generated from this model about MN degeneration, important concerns remain about the reproducibility of these findings in human ALS. The preferential involvement of spinal compared to cortical MNs, the anatomical differences in CNS organization between mice and humans and the confounding effects of artificial manipulation, such as transgenic overexpression, limit the translation of ALS preclinical research on patients (Kato, 2008; Philips and Rothstein, 2015). Nonetheless, some studies reported evidence of early NMJ alterations and axonal injury preceding MN loss also in ALS patients (Bradley et al., 1983; Dengler et al., 1990; Fischer et al., 2004; Bruneteau et al., 2015). Moreover, progressive NMJ and motor axon loss is a consistent finding also in other transgenic ALS mice with mutations in TARDBP, FUS, and C9orf72 repeat expansion (Picher-Martel et al., 2016). Overexpression of hTDP-43A315T and hTDP-43WT leads to NMJ denervation and loss of corticospinal axons, which in some cases predominate over MN al loss (Wegorzewska et al., 2009; Arnold et al., 2013; Heredewyn et al., 2014). In the hFUSP525L mouse lines, where the mutation is

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**TABLE 1 | Continued**

| Gene    | Gene name                           | Chromosome | Disease*                                                                 | Inheritance | References                                      |
|---------|-------------------------------------|------------|--------------------------------------------------------------------------|-------------|------------------------------------------------|
| CMT/dHMN genes |                                    |           |                                                                          |             |                                                |
| BSCL2   | BSCL2, seipin lipid droplet biogenesis associated | 11q13      | Lipodystrophy, congenital generalized, type 2 – dHMNA – silver spastic paraplegia syndrome | AR – AD     | Magré et al., 2001 (Lypodystrophy); Windpassinger et al., 2004 (dHMNA, Silver syndrome) |
| HSPB1   | Heat shock protein family B (small) member 1 | 7q11       | CMT2F – dHMNIIB                                                          | AD          | Evgrafov et al., 2004 (CMT dHMN)               |
| HSPB3   | Heat shock protein family B (small) member 3 | 5q11       | dHMNIIC                                                                 | AD          | Kolb et al., 2010                              |
| HSPB8   | Heat shock protein family B (small) member 8 | 12q24      | dHMNIIA – CMT2L                                                           | AD          | Irobi et al., 2004 (dHMN); Tang et al., 2005 (CMT) |
| NEFL    | Neurofilament light                 | 8q21       | CMT2E – CMT1F – CMTG                                                      | AD AR       | Mersiyanova et al., 2000 (CMT2E); Jordanova et al., 2003 (CMT1F); Zuchner et al., 2004b (CMT2G) |
| TRPV4   | Transient receptor potential cation channel subfamily V member 4 | 2q24       | HMSN IIC – SMA – scapuloperoneal SMA                                     | AD          | Auer-Grumbach et al., 2010                     |

*OMIM and report from literature. ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; CMT, charcot marie tooth; SMA, spinal muscular atrophy; SPG, spastic paraplegia; HMSN, hereditary motor and sensory neuropathy; Dhrmn, distal hereditary motor neuropathy; UPS, ubiquitin proteasome system; ERAD, endoplasmic reticulum-associated protein degradation; IBMPFD, inclusion body myopathy paget disease frontotemporal dementia.*
conditionally expressed in MNs, the progressive degeneration is preceded by early pre-symptomatic retraction of motor axons (Sharma et al., 2016).

Reflecting evidence of sensory dysfunction in human ALS, transgenic hSOD-1G93A mice also display neurodegeneration in sensory axon, DRG and proprioceptive sensory fibers of muscle spindles. Signs of axonal damage are detected since the pre-symptomatic stage, progressing with a distal-to-proximal gradient (Guo et al., 2009; Vaughan et al., 2015). Furthermore, loss of dorsal root axons has been detected in rodent models overexpressing mutant TDP-43 and FUS (Huang et al., 2011; Arnold et al., 2013), suggesting that ALS-specific proteins may also affect sensory neurons. However, it is still unclear whether the damage comes from nearby disease spreading or arise independently from MNs. Interestingly, transfection of mutant TDP-43 and SOD1 in cultured sensory neurons exert a negative impact on neurites length and arborization after prolonged culture, suggesting a direct effect (Vaughan et al., 2018).

Therefore, the reported evidence demonstrates that all components of the PNS are affected in ALS, although the differing kinetics of damage and progression still point to differences in vulnerability between the sensory and motor axons and neurons.

Unraveling Mechanisms of Vulnerability and Resistance of Peripheral Motor and Sensory Neurons in ALS

Studies addressing the mechanisms of PNS involvement in ALS may provide a unique opportunity for unraveling the determinants of the different patterns of vulnerability of motor and sensory neurons. This would allow the identification of specific protective or deleterious factors amenable of therapeutic intervention. Hereafter, we discuss key factors at the PNS level potentially implied in such differences.

Intrinsic Axonal Vulnerability

Hyperexcitability of the axolemma, due to altered Na+ and K+ conductance properties, has been demonstrated in motor but not sensory axons of ALS patients (Shibuya et al., 2011; Park et al., 2017; Matamala et al., 2018). The consequent increase in Ca2+ influx may be selectively harmful in the motor compartment, since motor axons show a low Ca2+-buffering capacity (Jaiswal, 2013; Leal and Gomes, 2015). In turn, Ca2+ overload leads to the activation of effector proteins such as calpain, a calcium-dependent protease, involved in TDP-43 fragmentation, which predisposes to aggregation, Wallerian degeneration and NMJ disassembly (Yamashita et al., 2012; Conforti et al., 2014; Campanari et al., 2016). Specific demise of MNs may also be driven by the involvement of ALS-key proteins, such as TDP-43 and FUS. They are mRNA-binding proteins, mainly localized in the nucleus, which participate in the metabolism of broad pools of mRNAs, by affecting splicing, stability, transport. Mutations in these proteins affect neurons by both loss and gain of function, leading to altered RNA processing, increasing cytoplasmic translocation and propensity to aggregation (Ratti and Buratti, 2016). They are essential during embryonic development, but only MNs in the cortex and anterior horns display sustained expression of both proteins during lifetime (Huang et al., 2010). Although most of the transcriptome is shared between motor and DRG axons, more than one third is unique (Rotem et al., 2017). It has been estimated that TDP43 binds roughly 30% of the whole transcriptome (Ling et al., 2013), including coding and non-coding RNAs, such as miRNA (Kawahara and Mieda-Sato, 2012). TDP-43 is actively recruited in RNA granules along motor axons for active transport (Fallini et al., 2012). Examples of TDP43-bound mRNAs include human neurofilaments, components of the endosomal trafficking and mitochondrial proteins (Stalekar et al., 2015; Schwenk et al., 2016; Wang et al., 2016). Over-expression of wild type and mutant TDP-43 alters the dynamics of its axonal transport (Alami et al., 2014), leading to mitochondrial toxicity and NMJ loss (Lin et al., 2011; Tripathi et al., 2014; Wang et al., 2016). Furthermore, a transient increase in TDP-43 localization along axonal routes is observed following axotomy, suggesting a role in peripheral nerve regeneration (Moffa et al., 2009). However, TDP-43G344C mice show abnormal persistence of cytoplasmic levels after peripheral injury, impairing axonal regeneration (Swarup et al., 2012). Such finding may provide a potential additional explanation to the paucity of regenerative clusters observed in ventral roots and motor nerves of human and animal ALS (Riva et al., 2011b, 2014; Luigetti et al., 2012). In contrast, sensory nerves still show some level of regeneration capacity in ALS patients, suggesting that efficient repair mechanisms may dampen progressive neurodegeneration (Hammad et al., 2007; Isaacs et al., 2007).

Neuromuscular Junction

The early susceptibility of the NMJ in ALS relies on peculiar features that distinguish it from other peripheral ending structures, including the sensory receptors. It has high energy demands and requires efficient mechanisms of plasticity and repair to cope with the challenges faced by muscle contraction. Oxidative stress, which contributes to ALS pathogenesis (D’Amico et al., 2013), has a great influence on NMJ function, as the early production of reactive oxygen species (ROS) in distal muscles inhibits transmitter release (Kraft et al., 2007; Naumenko et al., 2011) and leads to synaptic loss (Fischer et al., 2011, Fischer et al., 2012). High levels of oxidative stress have also been observed in muscles and spinal cord of ALS patients (D’Amico et al., 2013; Lanfranconi et al., 2017). Mitochondrial dysfunction further participates to NMJ dismantling, as its role in energy production and Ca2+ buffering is essential for proper function and maintenance of the synapse (Fischer-Hayes et al., 2013). Non-neuronal factors are also involved, as terminal schwann cells (TSCs) exert important functions in NMJ stability and repair, adapting their state according to local synaptic environment. Such decoding ability depends on the muscarinic acetylcholine receptor (mAChR), a G-protein-coupled receptor (GPCR) present on the membrane of TSCs, which detects the level of Ach released in the synaptic cleft. SOD1 mutants have been shown to alter the mAChR sensitivity of these cells to local damage, leading to deficient repair of denervated NMJ in ALS mice models (Arbour et al., 2015). Still, such findings need confirmation in humans and other models of ALS, although a
relationship between TDP-43 function and TSC-related receptors has been suggested (Arbour et al., 2017).

**PNS-Related Non-cell Autonomous Toxicity**

Besides TSCs, other non-cell autonomous mechanisms in the PNS may further influence MNs vulnerability. The role of Schwann cells in the peripheral nerve has also been recently re-evaluated in ALS. Early deficits in axonal transport may be initially compensated by the transfer of polyribosomes from Schwann cells to the axonal compartment, boosting local protein synthesis as an adaptive response to mSOD1-induced injury (Verheijen et al., 2014). Moreover, Schwann cells may exert partial protection against the increased production of ROS related to axonal degeneration, as the loss of dismutase activity in these cells accelerated disease progression (Lobsiger et al., 2009). However, pathogenic gain-of-functions SOD1 mutants may affect Schwann cells functioning and protective effects as well (Wang et al., 2012). Neuroinflammatory response within the PNS and alterations of the blood-nerve barrier might offer additional insights in the pathogenesis of ALS (Kang and Rivest, 2007; Beers et al., 2008), as suggested by observations raised in mice models (Pupillo et al., 2014; Nardo et al., 2016, 2018) and in human ALS (Deviğili et al., 2011; Riva et al., 2011a; Gerevini et al., 2016). Pathological studies of sural nerve biopsies of ALS patients have demonstrated, in a subset of cases, the presence of vasculitic-like inflammatory infiltrates associated with normal nerve morphology, suggesting a potential neuroprotective effect of neuroinflammation within the PNS (Deviğili et al., 2011). Indeed, the recruitment of macrophages and stimulation of their phagocytic function in peripheral nerves is important to create a favorable milieu for axonal regeneration, as shown in mSOD1 ALS mice (Nardo et al., 2016).

**Common Grounds for ALS and Hereditary Neuropathies**

Despite the distinctive prognosis and disease course, ALS, related MNDs and hereditary neuropathies show a non-negligible degree of overlap in terms of both clinical presentations and genetics. Therefore, a better understanding of the key cellular pathways involved in both diseases may allow a broader comprehension of the molecular events leading to axonal and MN degeneration in ALS.

**Neuronal Cytoskeleton**

Microtubules, NFs and actin are the main components of axonal cytoskeleton, and impairment in either structure or functioning of any of these components may lead to axonal atrophy, retraction and degeneration or transport defects (Gentil et al., 2015; Kevenaar and Hoogenraad, 2015). Elevated levels of light NFs (NFL) and phosphorylated heavy NFs have been observed in the cerebrospinal fluid and serum of ALS, together with lower mRNA NFL levels in MNs (Volkening et al., 2009; Gaiani et al., 2017; Feneberg et al., 2018). Accumulation of NF components in axons is a prominent feature of both human and animal ALS (Leigh and Swash, 1991; Rouleau et al., 1996; Morrison et al., 2000), and has been observed along both motor and sensory axons in the hSOD-1G93A ALS mouse model (King et al., 2012; Gentil et al., 2015; Sassone et al., 2016). Alterations of ALS-key genes, such as SOD1 and TARDBP, have been shown to affect the stability of NFL mRNA, suggesting that altered stoichiometry between the different NF components may contribute to the disease (Volkening et al., 2009). Mutations in NEFL and NEFH, leading to axonal CMT, promote protein aggregation, aberrant mitochondrial morphology and shortening of axonal length (Yoshihara et al., 2002; Rebelo et al., 2016; Nam et al., 2017). Tubulin Alpha 4a (TUBA4A), encoding for α-tubulin, has been recently identified as a novel ALS gene (Smith et al., 2014). It has been shown that TUBA4A mutations are able to alter microtubule dynamics, with depolymerization and degradation of α-tubulin (Helferich et al., 2018). Although this gene has been described only in cohorts of ALS and FTD patients, a sensory and motor neuronopathy is observed in progressive motor neuronopathy mice mutated in tubulin binding cofactor E (TBCE), a known interactor of α-tubulin (Schafer et al., 2017). Profilin 1 (PFN1) has been found as a rare cause of familial ALS (Wu et al., 2012). It is a crucial protein for the conversion of monomeric (G)-actin to filamentous (F)-actin. Interestingly, although pathogenic variants do not disrupt actin dynamics (Freischmidt et al., 2015), alterations in microtubule growth and increased propensity to cytoplasmic TDP43 aggregation have been described (Matsukawa et al., 2016; Tanaka et al., 2016; Henty-Ridilla et al., 2017), revealing potential cell-type specific mechanisms of neurodegeneration.

**Axonal Transport**

Defects in axonal transport have been clearly observed both in ALS and dHMN. SOD1 and TDP43 mutants impair anterograde and retrograde axonal transport, leading to loss of essential synaptic components, mitochondrial abnormalities, and neurite shortening (Williamson and Cleveland, 1999; Perlson et al., 2009; Alami et al., 2014). Similarly abnormal transport of organelles, such as mitochondria and the endoplasmic reticulum (ER), is found in CMT models due to NEFL mutations (Tradewell et al., 2009). The failure of axon-cell body communication may dampen the activation of repair mechanisms, thus conferring an increase vulnerability of the peripheral compartment, more pronounced for the distal segments (Fischer et al., 2004; Dadon-Nachum et al., 2011). Strategies aiming at reinforcing axonal transport may thus confer protection to a broad range of pathogenic alterations, preserving the axonal routes and its endings.

**Protein Folding**

The highly differentiated and post-mitotic state of MNs exerts a relevant pressure over the protein quality control system of the cell, which is devoted to the correct folding, function and turnover of the whole proteome. HSPB1/27, HSPB8/22, and sigma non-opioid intracellular receptor 1 (SIGMAR1) are three chaperones with a significant expression levels in MNs (Mavlyutov et al., 2010). Mutations of the small heat shock proteins have been mostly associated with a dHMN or axonal CMT2 phenotype, while SIGMAR1 gene variants have been reported also in rare ALS patients (Al-Saif et al., 2011; Rossor et al., 2012). HSPB1 mutants alter both its chaperone activity in NF organization and preservation of axonal stability.
HSPB8 mutant mice develop a progressive motor neuropathy through specific neurite degeneration (Irobi et al., 2010; Bouhy et al., 2018). In addition, alterations in TDP-43 expression, and associated splicing is observed in the muscles of these mice (Cortese et al., 2018). Conversely, there is a significantly higher HSPB8 expression in surviving neurons in the hSOD-1G93A mouse model of ALS (Crippa et al., 2010). Finally, SIGMAR1, together with MFN2 and vesicle-associated membrane protein-associated protein B/C (VAPB), are able to modulate unfolded protein response (UPR) sensors, including protein kinase RNA-like endoplasmic reticulum kinase (PERK) (Nguyen et al., 2015).

**Mitochondrial/Associated Membranes (MAMs)**

The ER and mitochondria have evolved complex sites of interactions, defined as mitochondrial/associated membranes (MAMs), which are important for essential cellular functions, such as calcium homeostasis, autophagy, regulation of mitochondrial dynamics, and axon survival (Giorgi et al., 2015). Both ALS and hereditary neuropathies display dysfunction in one or more of MAM components. A huge number of cellular proteins participate in MAMs, including MFN2 and VAPB, which act as tethering sites between the two organelles (Bernard-Marissal et al., 2015). VAPB mutants affect the interaction with the mitochondrial protein tyrosine phosphatase-interacting protein 51 (PTPIP5) (de Brito and Scorrano, 2008; De Vos et al., 2012). Interestingly, TDP43 and FUS mutants have been shown to decrease ER-mitochondria contacts by disrupting VAPB-PTPIP5 binding (Stoica et al., 2014). MFN2 mutants alter other MAM functions, such as mitochondrial transport, fusion, and autophagosome assembly (Kim et al., 2015). Loss-of-function mutations in SIGMAR1 display decreased ER-mitochondria association, resulting in MN death, and axonal degeneration due to impaired retrograde transport (Bernard-Marissal et al., 2015; Watanabe et al., 2016). 

**THERAPEUTIC PERSPECTIVES**

Due to the high similarity between these neuromuscular disorders and the intimate relationship observed in the molecular pathways involved, it may not be surprising if functional proteins involved in either of the two diseases may provide benefits on their respective counterpart.

Preservation of NMJ is an attractive target to delay muscle denervation and disability in ALS. A drug-screening platform in C. elegans and zebrafish models of ALS identified pimozide, an already approved neuroleptic, as a NMJ stabilizer by blocking T-type Ca2+ channels (Patten et al., 2017). Despite some benefits in neuropathologic measures were reported in hSOD-1G93A mice and human patients in the first report, one study assessing long-term effects showed warned caution, as worsening of survival and muscle function were observed in mutant SOD1, and TDP-43 mice models (Pozzi et al., 2018). Notably, an agonist antibody directed toward muscle-specific kinase (MuSK), a post-synaptic tyrosine kinase receptor essential for NMJ maintenance, preserved motor synapses, delayed muscle denervation and extended lifespan in hSOD-1G93A ALS mice (Cantor et al., 2018). The promising findings of this study still awaits confirmation and replication in other disease models.

Reinforcing the action of factors involved in axonal stability and transport may restore soma-axon communication, delaying NMJ loss and axonal degeneration. Pharmacological inhibition of histone deacetylase 6 (HDAC6), a known client protein of HSPB1, was able to increase the stability of microtubules, rescuing axonal loss, and improving outcome in a CMT2F mouse model with mutant HSPB1 (d’Ydewalle et al., 2011). Interestingly, HDAC6 inhibition was also able to restore axonal transport defects in patient-derived MNs mutated in FUS (Guo et al., 2017). Pharmacologic agents targeting microtubule dynamics, such as noscapine and vinblastine, delayed disease onset and prolonged survival in hSOD-1G93A mice, by reducing microtubule turnover (Fanara et al., 2007).

Inhibition of p38/mitogen-associated protein kinase (MAPK) signaling in MNs was able to restore retrograde axonal transport defects in vivo (Gibbs et al., 2018), together with reduced microglia-induced neuroinflammation in the spinal cord (Kim and Choi, 2010; Zhan et al., 2015; Leal-Lasarte et al., 2017). However, it is remarkable that no significant improvement was observed on the clinical phenotype (Gibbs et al., 2018), suggesting that inhibition of this pathway alone is not sufficient to fully rescue MN function.

Reducing ER stress through either a potentiation of the chaperone system or inhibition of stress-related factors may limit the production rate of misfolded proteins. Enhancing HSPB8 activity has been shown to be protective against accumulation of TDP43 aggregates in MNs (Crippa et al., 2016; Rusmini et al., 2017), and to extend survival of hSOD-1G93A mice (Aurelian et al., 2012). Trehalose, a chemical chaperone known to induce HSPB8, reduces ER stress levels and improve autophagy, delaying disease, and prolonging MN survival in a mouse model (Zhang et al., 2014; Li Y. et al., 2015). Upon UPR activation, cells switch to a state of translational repression and stimulation of chaperones’ synthesis, processes regulated by phosphorylation of the eukaryotic translation initiation factor 2A (eIF2α). Salubrinial and guanabenz, two eIF2α phosphatase inhibitors, protected against MN degeneration in ALS mice (Saxena et al., 2009; Wang et al., 2014), although one study reported that guanabenz accelerated disease progression in an ALS model (Vieira et al., 2015).

Considering their importance in cell physiology, MAMs could represent an important target for therapy in ALS and may prove beneficial for a wide array of downstream signaling cascades relying upon these structures. An agonist of SIGMAR1 was shown to improve muscle activity and motor performance in pre-symptomatic hSOD-1G93A ALS mice (Mancuso et al., 2012). Notably, overexpression of MFN2 prevented NMJ loss and delayed onset and progression in a murine model by raising calpastatin levels, a calpain inhibitor, essential for survival, and function of the NMJ (Wang et al., 2018).

Boosting axonal regeneration through either neuron- or Schwann-targeting factors may also be a valuable alternative strategy in order to preserve motor function (Gilley et al., 2017).
Studies modulating Neuregulin 1 activity, a neurotrophic factor involved in peripheral nerve development and regeneration, in murine hSOD-1G93A ALS lead to increased re-innervation and MN survival (Mancuso et al., 2016; Modol-Caballero et al., 2017). However, other approaches aimed at slowing Wallerian degeneration, such as the mutations in the Slowed Wallerian degeneration (WldS) and Sterile Alpha and TIR Motif Containing 1 (Sarm1) proteins, gave only modest or no results in terms of progression and survival (Fischer et al., 2005; Peters et al., 2018), suggesting that alternative mechanisms may underlie the axonal loss observed in ALS.

**CONCLUSION**

Clinical and pathological studies in both human patients and rodent models suggest that the PNS is involved in ALS pathogenetic cascade. A better comprehension of the molecular events occurring into the PNS may prove essential for a better understanding of MND pathomechanisms and may pave the way to the discovery of novel therapeutic targets. Considering that in ALS neurodegeneration derives from the combination of several dysfunctional pathways, it might be possible that the development of combination therapies acting on multiple cascades located in both the central and the peripheral compartments may show synergistic neuroprotective effect in order to prevent axonal degeneration, MN cell death, and ultimately in prolonging patients' survival.

**AUTHOR CONTRIBUTIONS**

FG and SS contributed to the collection of available evidence and writing. YF, AQ, NR, CL, and LT contributed to the manuscript writing and review of intellectual content of the manuscript, and approved the final version of the manuscript. AQ and NR contributed to the manuscript design.

**REFERENCES**

Ackerley, S., James, P. A., Kalli, A., French, S., Davies, K. E., and Talbot, K. (2006). Characterization of two novel SETX mutations in AOA2 patients reveals aspects of the pathophysiological role of senataxin. *Neurogenetics* 7, 1293–1299. doi: 10.1007/s10048-008-0034-x

Auer-Grumbach, M., Olschewski, A., Papic, L., Kremer, H., Mcentagart, M. E., Uhrg, S., et al. (2010). Alterations in the ankyrin domain of TRPV4 cause congenital distal SMA, scapuloperoneal SMA and HMSN2C. *Nat. Genet.* 42, 160–164. doi: 10.1038/ng.308

Aurelian, L., Laing, J. M., and Lee, K. S. (2012). H11/HspB8 and its herpes simplex virus type 2 homologue ICP10PK share functions that regulate cell life/death decisions and human disease. *Autoimmune Dis.* 2012:395329. doi: 10.1155/2012/395329

Averamia, F., Lunetta, C., Tarlarini, C., Mosca, L., Maestri, E., Marocchi, A., et al. (2011). Mutation in the senataxin gene found in a patient affected by familial ALS with juvenile onset and slow progression. *Amyotroph. Lateral Scler.* 12, 228–230. doi: 10.3109/17482968.2011.566930

Azeddine, H., Zavadakova, P., Plante-Bordeneuve, V., Vaz Pato, M., Pinto, N., Bartaghi, L., et al. (2013). PLEKHG3 deficiency leads to an intermediate form of autosomal-recessive Charcot-Marie-Tooth disease. *Hum. Mol. Genet.* 22, 4224–4232. doi: 10.1093/hmg/ddt274

Beers, D. R., Henkel, J. S., Zhao, W., Wang, J., and Appel, S. H. (2008). CD4+ T cells support glial neuroprotection, slow disease progression, and modify glial morphology in an animal model of inherited ALS. *Proc. Natl Acad. Sci. U.S.A.* 105, 15558–15563. doi: 10.1073/pnas.0807419105

Benedetti, S., Previtali, S. C., Coviello, S., Scarlato, F., Cerri, F., Di Pierri, E., et al. (2010). Analyzing histopathological features of rare charcot-marie-tooth neuropathies to unravel their pathogenesis. *Arch. Neurol.* 67, 1498–1505. doi: 10.1001/archneurol.2010.303

Bernard-Marisal, N., Medard, J. J., Azzedine, H., and Chrast, R. (2015). Dysfunction in endoplasmic reticulum–mitochondria crosstalk underlies SIGMAR1 loss of function mediated motor neuron degeneration. *Brain* 138, 875–890. doi: 10.1093/brain/awv008

Bhatt, A., Farooq, M. U., Aburashed, R., Kassab, M. Y., Majid, A., Bhatt, S., et al. (2009). Hereditary neuropathy with liability to pressure palsies and amyotrophic lateral sclerosis. *Neural. Sci.* 30, 241–245. doi: 10.1007/s10048-009-0034-x

Bouhy, D., Juneca, M., Katona, L., Holmgren, A., Asselbergh, B., De Winter, V., et al. (2018). A knock-in/Knock-out mouse model of HSPB8-associated distal hereditary motor neuropathy and myopathy reveals toxic gain-of-function of mutant HspB8. *Acta Neuropathol.* 135, 131–148. doi: 10.1007/s00401-017-1756-0
Bradley, W. G., Good, P., Rasool, C. G., and Adelman, I. S. (1983). Morphometric and biochemical studies of peripheral nerves in amyotrophic lateral sclerosis. *Ann. Neurol.* 14, 267–277. doi: 10.1002/ana.410140304

Braun, R. J., and Zischka, H. (2008). Mechanisms of Cdc48/VCP-mediated cell death: from yeast apoptosis to human disease. *Biochim. Biophys. Acta* 1783, 1418–1435. doi: 10.1016/j.bbamcr.2008.01.015

Brenner, D., Yilmaz, R., Muller, K., Grehl, T., Petri, S., Meyer, T., et al. (2018). Hot-spot KIF5A mutations cause familial ALS. *Brain* 141, 688–697. doi: 10.1093/brain/awx370

Brett Schneider, J., Arai, K., Del Tredici, K., Toledo, J. B., Robinson, J. L., Lee, E. B., et al. (2014). TDP-43 pathology and neuronal loss in amyotrophic lateral sclerosis spinal cord. *Acta Neuropathol.* 128, 423–437. doi: 10.1007/s00401-014-1299-6

Brett Schneider, J., Del Tredici, K., Toledo, J. B., Robinson, J. L., Irwin, D. I., Grossman, M., et al. (2013). Stages of TDP-43 pathology in amyotrophic lateral sclerosis. *Ann. Neurol.* 74, 20–38. doi: 10.1002/ana.23937

Bruneteau, G., Bauche, S., Gonzalez De Aguilar, J. L., Brochier, G., Mandjee, N., Tanguy, M. L., et al. (2015). Endplate denervation correlates with Nogo-A muscle expression in amyotrophic lateral sclerosis patients. *Ann. Clin. Transl. Neurol.* 2, 362–372. doi: 10.1002/acn3.179

Campanari, M. L., Garcia-Ayllon, M. S., Ciura, S., Saez-Valero, J., and Kabashi, E. (2013). Neuromuscular junction impairment in amyotrophic lateral sclerosis: reassessing the role of acetylcholinesterase. *Front. Mol. Neurosci.* 9:160. doi: 10.3389/fnmol.2016.00160

Campeau, P. M., Lenk, G. M., Lu, J. T., Bae, Y., Burrage, L., Turnpenny, P., et al. (2013). Yunis-Varon syndrome is caused by mutations in FIG4, encoding a phosphoinositide phosphatase. *Am. J. Hum. Genet.* 92, 781–791. doi: 10.1016/j.ajhg.2013.03.020

Cantor, S., Zhang, W., Delestree, N., Remedio, L., Mentis, G. Z., and Burden, S. J. (2018). Preserving neuromuscular synapses in ALS by stimulating MuSK with a therapeutic agonist antibody. *eLife* 7:e34375

Ceroni, M., Curti, D., and Alimonti, D. (2001). Amyotrophic lateral sclerosis and SOD1 gene: an overview. *Func. Neurol.* 16, 171–180.

Chen, Y. Z., Bennett, C. L., Huynh, H. M., Blair, I. P., Puls, I., Irobi, J., et al. (2004). Crimella, C., Baschirotto, C., Arnoldi, A., Porretta-Serapiglia, C., Ciano, C., Gellera, C., Pensato, V., et al. (2016). Amyotrophic lateral sclerosis causes small fiber pathology. *Eur. J. Neurol.* 23, 418–420. doi: 10.1111/ene.12936

D’Amico, E., Factor-Litvak, P., Santella, R. M., and Mitsumoto, H. (2013). Clinical perspective on oxidative stress in sporadic amyotrophic lateral sclerosis. *Free Radic. Biol. Med.* 65, 509–527. doi: 10.1016/j.freeradbiomed.2013.06.029

Dadou, H., Zhou, S., Noreau, A., Sabbagh, M., Belzil, V., Dionne-Laporte, A., et al. (2012). Exome sequencing reveals SPG11 mutations causing juvenile ALS. *Neurobiol. Aging* 33, 839.e5–9. doi: 10.1016/j.neurobiolaging.2011.11.012

Davenport, R. J., Swingler, R. J., Chancellor, A. M., and Warlow, C. P. (1996). Avoiding false positive diagnoses of motor neuron disease: lessons from the Scottish motor neuron disease register. *J. Neurol. Neurosurg. Psychiatry* 60, 147–151. doi: 10.1136/jnnp.60.2.147

De Jonghe, P., Auer-Grumbach, M., Irobi, J., Wagner, K., Plecko, B., Kennerson, M., et al. (2002). Autosomal dominant juvenile amyotrophic lateral sclerosis and distal hereditary motor neuronopathy with pyramidal tract signs: synonyms for the same disorder? *Brain* 125, 1320–1325. doi: 10.1093/brain/awf127

De Vos, K. J., Morotz, G. M., Stoica, R., Tudor, E. L., Lau, K. F., Ackerley, S., et al. (2012). VAPB interacts with the mitochondrial protein PTPIP51 to regulate calcium homeostasis. *Hum. Mol. Genet.* 21, 1299–1311. doi: 10.1093/hmg/ddr559

DeJesus-Hernandez, M., Mackenzie, I. R., Boeve, B. F., Boxer, A. L., Baker, M., Rutherford, N. J., et al. (2011). Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron* 72, 245–256. doi: 10.1016/j.neuron.2011.09.011

Del Bo, R., Moggio, M., Rango, M., Bonato, S., D’angelo, M. G., Ghezzi, S., et al. (2008). Mutated mitofusin 2 presents with intrafamilial variability and brain mitochondrial dysfunction. *Neurology* 71, 1959–1966. doi: 10.1212/01.wnl.0000329035.23005.ac

De La Barre, B., Christianson, J. C., Kopito, R. R., and Brunger, A. T. (2006). Central pore residues mediate the p97/VCP activity required for ERAD. *Mol. Cell* 22, 451–462. doi: 10.1016/j.molcel.2006.03.036

Deng, H. X., Chen, W., Hong, S. T., Boycott, K. M., Gorrie, G. H., Siddique, N., et al. (2011). Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and DLS/dementia. *Nature* 477, 211–215. doi: 10.1038/nature10535

Dengler, R., Konstanzer, A., Kuther, G., Hesse, S., Wolf, W., and Struppler, A. (1990). Amyotrophic lateral sclerosis: macro-EMG and twitch forces of single motor units. *Muscle Nerve* 13, 545–550. doi: 10.1002/mus.880130612

Devigili, G., Uceyler, N., Beck, M., Reiners, K., Stoll, G., Toyka, K. V., et al. (2011). Vasculitis-like neuropathy in amyotrophic lateral sclerosis unresponsive to treatment. *Acta Neuropathol.* 122, 343–352. doi: 10.1007/s00401-011-0837-8

Di Trapani, G., David, P., La Cara, A., Tonali, P., and Laiuromio, P. (1987). Light and ultrastructural studies in sural biopsies of the pseudopolynuropathic form of ALS. *Adv. Exp. Med. Biol.* 209, 111–119. doi: 10.1007/978-1-4684-5302-7_18

Duquette, A., Roddier, K., McNabb-Baltar, J., Gosselin, L., St-Denis, A., Dicaire, M. J., et al. (2005). Mutations in senataxin responsible for Quebec cluster of ataxia with neuropathy. *Ann. Neurol.* 57, 408–414. doi: 10.1002/ana.20408

Dyck, P. J., Stevens, J. C., Mulder, D. W., and Espinosa, R. E. (1977). Frequency of nerve fiber degeneration of peripheral motor and sensory nerves in amyotrophic lateral sclerosis. *Morphometry of deep and superficial peroneal nerves.* Neurology, 25, 781–785.
lateral sclerosis. *Neurobiol. Dis.* 28, 154–164. doi: 10.1016/j.nbd.2007.07.003

Hehr, U., Bauer, P., Winner, B., Schule, R., Olmez, A., Koehler, W., et al. (2007). Long-term course and mutational spectrum of spastic-onset spastic paraplegia. *Ann. Neurol.* 62, 656–665. doi: 10.1002/ana.21310

Helferich, A. M., Brockmann, S. J., Reinders, J., Deshpande, D., Holzmann, K., Brenner, D., et al. (2018). Dysregulation of a novel miR-1825/TRCB/TU14A pathway in sporadic and familial ALS. *Cell Mol. Life Sci.* 75, 4301–4319. doi: 10.1007/s00018-018-2873-1

Henty-Ridilla, J. L., Janues, M. A., and Goode, B. L. (2017). Profilin directly promotes microtubule growth through residues mutated in amyotrophic lateral sclerosis. *Curr. Biol.* 27, 3533.e4–3543.e4. doi: 10.1016/j.cub.2017.10.002

Herdevyn, S., Cirillo, C., Van Den Bosch, L., Robberecht, W., Vanden Berghe, B., De Winter, V., Goethals, S., et al. (2015). Mutations in the PLEKHG5 gene is relevant with autosomal recessive intermediate Charcot-Marie-Tooth disease. *Orphanet J. Rare Dis.* 10, 682–696. doi: 10.1136/jnnp.2006.098798

Hoffman, P. N., Cleveland, D. W., Griffin, J. W., Landes, P. W., Cowan, N. I., and Price, D. L. (1987). Neurofilament gene expression: a major determinant of axonal caliber. *Proc. Natl. Acad. Sci. U.S.A.* 84, 3472–3476. doi: 10.1073/pnas.84.10.3472

Huang, C., Xia, P. Y., and Zhou, H. (2010). Sustained expression of TDP-43 and NEFL cause early onset severe Charcot-Marie-Tooth disease. *Neurosci. Res.* 71, 502–506. doi: 10.1101/sf.2009.05.038

Huang, C., Zhou, H., Tong, J., Chen, H., Liu, Y. J., Wang, D., et al. (2011). FUS transgenic rats develop the phenotypes of amyotrophic lateral sclerosis and frontotemporal lobar degeneration. *PLoS Genet.* 7:e1002011. doi: 10.1371/journal.pgen.1002011

Iapadre, G., Morana, G., Vari, M. S., Pinto, F., Lanteri, P., Tessa, A., et al. (2018). A novel homozygous MFN2 mutation associated with severe and atypical CMT2 phenotype. *Eur. J. Paediatr. Neurol.* 19, 325–330. doi: 10.1016/j.ejpn.2017.12.020

Irobi, J., Bobi, J., Dyck, P. J., Shimono, M., Okazaki, H., Tateishi, J., and Doi, H. (1981). Morphometric comparison of the vulnerability of peripheral motor and sensory neurons in amyotrophic lateral sclerosis. *J. Neuropathol. Exp. Neurol.* 40, 667–675. doi: 10.1097/00005072-198111000-00008

Kevenaar, J. T., and Hoogenraad, C. C. (2015). The axonal cytoskeleton: from organization to function. *Front. Mol. Neurosci.* 8:44. doi: 10.3389/fnmol.2015.00044

Kim, E. K., and Choi, E. J. (2010). Pathological roles of MAPK signaling pathways in human diseases. *Biochim. Biophys. Acta* 1802, 396–405. doi: 10.1016/j.bbadis.2009.12.009

Kim, H. J., Hong, Y. B., Park, J. M., Choi, Y. R., Kim, Y. J., Yoon, B. R., et al. (2010). Mutations in the PLEKHG5 gene is relevant with autosomal recessive intermediate Charcot-Marie-Tooth disease. *Orphanet J. Rare Dis.* 8:104. doi: 10.1186/1750-1172-8-104

Kim, H. J., Nagano, Y., Choi, S. J., Park, S. Y., Kim, H., Yao, T. P., et al. (2015). HDAC6 maintains mitochondrial connectivity under hypoxic stress by suppressing MARCH5/MITOL dependent MFN2 degradation. *Biochem. Biophys. Res. Commun.* 464, 1235–1240. doi: 10.1016/j.bbrc.2015.07.011

King, A. E., Blizzard, C. A., Southam, K. A., Vickers, J. C., and Dickson, T. C. (2009). Inefficient skeletal muscle oxidative function flanks impaired motor neuron phenotype. *J. Neurol. Sci.* 274, 50–56. doi: 10.1016/j.jns.2009.05.038

Kolb, S. J., Snyder, P. J., Poo, E. J., Renard, E. A., Bartlett, A., Gu, S., et al. (2010). Mutant small heat shock protein B3 causes motor neuronopathy: utility of a candidate gene approach. *Neurology* 74, 502–506. doi: 10.1212/WNL.0b013e181ce8f84a

Kraft, A. D., Resch, J. M., Johnson, D. A., and Johnson, J. A. (2007). Activation of the Nrf2–ARE pathway in muscle and spinal cord during ALS-like pathology in mice expressing mutant SOD1. *Exp. Neurol.* 207, 107–117. doi: 10.1016/j.expneurol.2007.05.026

Kriger, S., Battke, F., Sprecher, A., Munz, M., Synofzik, M., Schols, L., et al. (2016). Rare variants in neurodegeneration associated genes revealed by targeted panel sequencing in a German ALS cohort. *Front. Mol. Neurosci.* 9:92. doi: 10.3389/fnmol.2016.00992

Kwiatkowski, T. J. Jr., Bosco, D. A., Leclerc, A. L., Tamrazian, E., Vanderburg, C. R., Russ, C., et al. (2009). Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. *Science* 323, 1205–1208. doi: 10.1126/science.1166066

Kwiterovski, T. J., Dito, N., Sigler, B. P., and Silverman, M. A. (2009). Dynactin regulates bidirectional transport of dense-core vesicles in the axon and dendrites of cultured hippocampal neurons. *Science* 323, 1205–1208. doi: 10.1126/science.1166066

Lanfranconi, F., Ferri, A., Corina, G., Bonazzi, R., Lunetta, C., Slani, V., et al. (2017). Inefficient skeletal muscle oxidative function flanks impaired motor neuron recruitment in amyotrophic lateral sclerosis during exercise. *Sci. Rep.* 7:2951. doi: 10.1038/s41598-017-02811-z
Laurin, N., Brown, J. P., Morissette, J., and Raymond, V. (2002). Recurrent mutation of the gene encoding sequestosome 1 (SQSTM1/p62) in Paget disease of bone. Am. J. Hum. Genet. 70, 1582–1588. doi: 10.1086/340731

Leal, S. S., and Gomes, C. M. (2015). Calcium dysregulation links ALS defective proteins and motor neuron selective vulnerability. Front. Cell. Neurosci. 9:225. doi: 10.3389/fnsc.2015.00225

Leal-Lasarte, M. M., Franco, J. M., Labrador-Garrido, A., Pozo, D., and Roodveldt, C. (2017). Extracellular TDP-43 aggregates target MAPK/MAK/MRK overlapping kinase (MOK) and trigger caspase-3/IL-18 signaling in microglia. FASEB J. 31, 2797–2816. doi: 10.1096/2016f1163R

Leigh, P. N., and Swash, M. (1991). Cytoskeletal pathology in motor neuron disease. Adv. Neurol. 56, 115–124.

Li, X., Hu, Z., Liu, L., Xie, Y., Zhan, Y., Zl, X., et al. (2015). A SIGMAR1 splice-site mutation causes distal hereditary motor neuropathy. Neurology 84, 2430–2437. doi: 10.1212/WNL.000000000001680

Li, Y., Guo, Y., Wang, X., Yu, X., Duan, W., Hong, K., et al. (2015). Trehalose decreases mutant SOD1 expression and alleviates motor dysfunction in early but not end-stage amyotrophic lateral sclerosis in a SOD1-G93A mouse model. Neuroscience 298, 12–25. doi: 10.1016/j.neuroscience.2015.03.061

Lieberburg, I., Spinner, N., Snyder, S., Anderson, J., Goldergab, D., Smulowitz, M., et al. (1989). Cloning of a cDNA encoding the rat high molecular weight neurofilament peptide (NF-H): developmental and tissue expression in the rat, and mapping of its human homologue to chromosomes 1 and 22. Proc. Natl. Acad. Sci. U.S.A. 86, 2463–2467. doi: 10.1073/pnas.86.6.2463

Lin, M. J., Cheng, C. W., and Chen, C. K. (2011). Neuronal function and dysfunction of Drosophila TDP. PLoS One 6:e20371. doi: 10.1371/journal.pone.0020371

Ling, S. C., Polimenidou, M., and Cleveland, D. W. (2013). Converging mechanisms in ALS and FTU: disrupted RNA and protein homeostasis. Neuron 79, 416–438. doi: 10.1016/j.neuron.2013.07.033

Liu, X., Yang, L., Tang, L., Chen, L., and Fan, D. (2017). DCTN1 gene analysis in Chinese patients with sporadic amyotrophic lateral sclerosis. PLoS One 12:e0182572. doi: 10.1371/journal.pone.0182572

Liu, Z. J., Li, H. F., Tan, G. H., Tao, Q. Q., Ni, W., Cheng, X. W., et al. (2014). Identify mutation in amyotrophic lateral sclerosis cases using HaloPlex target enrichment system. Neurobiol Aging 35, 2881.e1-2881.e15. doi: 10.1016/j.neurobiolaging.2014.07.003

Lobsiger, C. S., Boillee, S., Micalonius-Downes, M., Khan, A. M., Feltri, M. L., et al. (2014). ALS-Plus syndrome: non- pyramidal features in a large ALS cohort. J. Neurology 351, 118–124. doi: 10.1007/s00412-014-7022-0

Lonen, P., Kirman, M. C., and Vucic, S. (2014). Cortical dysfunction underlies the development of the split-hand in amyotrophic lateral sclerosis. PLoS One 9:e87124. doi: 10.1371/journal.pone.0087124

Mesiroyanova, I. V., Repepolve, A. V., Polyakov, A. V., Sitnikov, V. F., Dadali, E. L., Oparin, R. B., et al. (2000). A new variant of Charcot-Marie-Tooth disease type 2 is probably the result of a mutation in the neurofilament-light gene. Am. J. Hum. Genet. 67, 37–46. doi: 10.1086/302962

Meyer, T., Schwand, A., Dullinger, J. S., Brocke, J., Hoffmann, K. T., Nolte, C. H., et al. (2005). Early-onset ALS with long-term survival associated with spastin gene mutation. Neurology 65, 141–143. doi: 10.1212/01.wnl.0000167310.32188.0a

Miller, J. W., Smith, B. N., Topp, S. D., Al-Chalabi, A., Shaw, C. E., and Vance, C. (2012). Mutation analysis of VCP in British familial and sporadic amyotrophic lateral sclerosis patients. Neurobiol. Aging 33:2721.e1-2. doi: 10.1016/j.neurobiolaging.2012.06.003

Modol-Caballero, G., Santos, D., Navarro, X., and Herrando-Grabolosa, M. (2017). Neuregulin 1 reduces motorneuron cell death and promotes neurite growth in an in vitro model of motorneuron degeneration. Front. Cell. Neurosci. 11:431. doi: 10.3389/fncel.2017.00431

Moisse, K., Volkering, K., Leystra-Lantz, C., Welch, I., Hill, T., and Strong, M. J. (2009). Divergent patterns of cytosolic TDP-43 and neuronal progranulin expression following axotomy: implications for TDP-43 in the physiological response to neuronal injury. Brain Res. 1249, 202–211. doi: 10.1016/j.brainsci.2008.10.021

Mondelli, M., Rossi, A., Passero, S., and Guazzi, G. C. (1993). Involvement of peripheral sensory fibers in amyotrophic lateral sclerosis: electrophysiological study of 64 cases. Muscle Nerve 16, 166–172. doi: 10.1002/mus.880160208

Mottecchiania, C., Pedace, L., Lo Giudice, T., Casella, A., Mearini, M., Gaudio, F., et al. (2016). ALS5/SPG11/KIAA1840 mutations cause autosomal recessive childhood-onset Charcot-Marie-Tooth disease. Brain 139, 73–85. doi: 10.1093/brain/awv132

Moreira, M. C., Klur, S., Watanabe, M., Nemeth, A. H., Le Ber, I., Moniz, J. C., et al. (2004). Senatorix, the ortholog of a yeast RNA helicase, is mutant in ataxia-oculaurapraxia 2. Nat. Genet. 36, 225–227. doi: 10.1038/ng1303

Morisson, B. M., Shu, I. W., Wilcox, A. L., Gordon, J. W., and Morrison, J. H. (2000). Early and selective pathology of light chain neurofilament in the spinal cord and sciatic nerve of G86R mutant superoxide dismutase transgenic mice. Exp. Neurology 165, 207–220. doi: 10.1006/exnr.2000.7457

Muglia, M., Zappia, M., Timmerman, V., Valentino, P., Gabriele, A. L., Conforti, F. L., et al. (2001). Clinical and genetic study of a large Charcot-Marie-Tooth type 2A family from southern Italy. Neurology 56, 100–103. doi: 10.1212/wnl.56.1.100
Rotem, N., Magen, I., Ionescu, A., Gershoni-Emek, N., Altman, T., Costa, C. J., Riva, N., Gallia, F., Iannaccone, S., Corbo, M., Terenghi, F., Lazzerini, A., et al. (2017). The Peripheral Nervous System in ALS. Front. Neurol. 8:1165. doi: 10.3389/fneur.2017.01165

Rossor, A. M., Kalmar, B., Greensmith, L., and Reilly, M. M. (2012). The distal degeneration of proprioceptive sensory nerve endings in mice harboring a null mutation of spatacsin, defective in ataxia oculomotor apraxia type 2, in transcriptional regulation. Hum. Mol. Genet. 21, 3384–3396. doi: 10.1093/hmg/ddr287

Swarup, V., Aued, J. N., Phaneuf, D., Kizir, A., and Julien, J. P. (2012). Abnormal degenerative responses and impaired axonal outgrowth after nerve crush in TDP-43 transgenic mouse models of amyotrophic lateral sclerosis. J. Neurosci. 32, 1816–1819. doi: 10.1523/JNEUROSCI.2267-12.2012

Sakurai, Y., Nonaka, T., Suzuki, G., Kametani, F., and Hasegawa, M. (2016). Gain-of-function profilin 1 mutations linked to familial amyotrophic lateral sclerosis cause seed-dependent intracellular TDP-43 aggregation. Hum. Mol. Genet. 25, 1420–1433. doi: 10.1093/hmg/ddw024

Tang, B. S., Zhao, G. H., Luo, W., Xia, K., Cai, F., Pan, Q., et al. (2005). Small heat-shock protein 22 mutated in autosomal dominant Charcot-Marie-Tooth disease type 2L. Hum. Genet. 116, 222–224. doi: 10.1007/s00439-004-0118-3

Tradewell, M. L., Durham, H. D., Mushynski, W. E., and Gentil, B. J. (2009). Mitochondrial and axonal abnormalities precede disruption of the neurofilament network in a model of charcot-marie-tooth disease type 2E and are prevented by heat shock proteins in a mutant-specific fashion. J. Neuropathol. Exp. Neurol. 68, 642–652. doi: 10.1097/NEN.0b013e3181a5ddd

Tayor, B. J., Codd, M. B., Corr, B., Forde, C., Frost, E., and Hardiman, O. M. (2000). Clinical features of amyotrophic lateral sclerosis according to the El Escorial and Airlie House diagnostic criteria: a population-based study. Arch. Neurol. 57, 1171–1176.

Tripathi, V. B., Baskaran, P., Shaw, C. E., and Guthrie, S. (2014). Tar DNA-binding protein-43 (TDP-43) regulates axon growth in vitro and in vivo. Neurobiol. Dis. 65, 25–34. doi: 10.1016/j.nbd.2014.01.004

Tropulos, K., Tokor, D., Goudenege, D., Farkas, K., Sulak, A., Tokor, N., et al. (2017). High-throughput sequencing revealed a novel SETX mutation in a Hungarian patient with amyotrophic lateral sclerosis. Brain Behav. 7:00669. doi: 10.1002/brb3.669

Truini, A., Biasiotta, A., Onesti, E., Di Stefano, G., Ceccanti, M., La Cesia, S., et al. (2015). Small-fibre neuropathy related to bulbar and spinal-onset in patients with ALS. J. Neurol. 262, 1014–1018. doi: 10.1007/s00415-015-7672-0

Vance, C., Rogelj, B., Hortobagyi, T., De Vos, K. J., Nishimura, A. L., Sreedharan, J., et al. (2009). Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. Science 323, 1208–1211. doi: 10.1126/science.1165942

Vandermeere, F., El Yazidi-Belkoura, L., Slomianny, C., Demont, Y., Bidaux, G., Adriaensens, E., et al. (2006). The valosin-containing protein (VCP) is a target of Akt signaling required for cell survival. J. Biol. Chem. 281, 14307–14313. doi: 10.1074/jbc.M510003200

Vogel, S. K., Kemp, Z., Hatzipetros, T., Vieira, F., and Valdez, G. (2015). Degeneration of proprioceptive sensory nerve endings in mice harboring amyotrophic lateral sclerosis-causing mutations. J. Comp. Neurol. 523, 2477–2494. doi: 10.1002/cne.23848

Vogel, S. K., Sutherland, N. M., Zhang, S., Hatzipetros, T., Vieira, F., and Valdez, G. (2018). The ALS-inducing factors, TDP43(A315T) and SOD1(G93A),...
directly affect and sensitize sensory neurons to stress. Sci. Rep. 8:16582. doi: 10.1038/s41598-018-34510-8

Verheijen, M. H., Peviani, M., Hendrichsdottir, R., Bell, E. M., Lammens, M., Smit, A. B., et al. (2014). Increased axonal ribosome numbers is an early event in the pathogenesis of amyotrophic lateral sclerosis. PLoS One 9:e87255. doi: 10.1371/journal.pone.0087255

Vieira, F. G., Ping, Q., Moreno, A. J., Kidd, J. D., Thompson, K., Jiang, B., et al. (2015). Guanabenz treatment accelerates disease in a mutant SOD1 mouse model of ALS. PLoS One 10:e0135570. doi: 10.1371/journal.pone.0135570

Visser, J., Van Den Berg-Vos, R. M., Franssen, H., Van Den Berg, L. H., Vogels, O. J., Wokke, J. H., et al. (2002). Mimic syndromes in sporadic cases of progressive spinal muscular atrophy. Neurology 58, 1593–1596. doi: 10.1212/wnl.58.11.1593

Volkering, K., Leystra-Lantz, C., Yang, W., Jaffee, H., and Strong, M. J. (2009). Tar DNA binding protein of 43 kDa (TDP-43), 14-3-3 proteins and copper/zinc superoxide dismutase (SOD1) interact to modulate NFL mRNA stability. Implications for altered RNA processing in amyotrophic lateral sclerosis (ALS). Brain Res. 1305, 168–182. doi: 10.1016/j.brainsci.2009.09.105

Wabel, S., Neumann, M., Rosenbohm, A., Birve, A., Volk, A. E., Weishaupt, J. H., et al. (2013). Truncating mutations in FUS/TLS give rise to a more aggressive ALS-phenotype than missense mutations: a clinico-genetic study in Germany. Eur. J. Neurol. 20, 540–546. doi: 10.1111/ene.12031

Wang, L., Gao, J., Liu, J., Siedlak, S. L., Torres, S., Fujikawa, H., et al. (2018). Mitofusin 2 regulates axonal transport of calpastatin to prevent neuromuscular synaptic elimination in muscle cells. Cell Metab. 28, 400.e8–414.e8. doi: 10.1016/j.cmet.2018.06.011

Wang, L., Popko, B., Tixier, E., and Roos, R. P. (2014). Guanabenz, which enhances the unfolded protein response, ameliorates mutant SOD1-induced amyotrophic lateral sclerosis. Neurobiol. Dis. 71, 317–324. doi: 10.1016/j.nbd.2014.08.010

Wang, L., Pytel, P., Feltri, M. L., Wrabetz, L., and Roos, R. P. (2012). Selective knockdown of mutant SOD1 in Schwann cells ameliorates disease in G85R mutant SOD1 transgenic mice. Neurobiol. Dis. 48, 52–57. doi: 10.1016/j.nbd.2012.05.014

Wang, W., Wang, L., Lu, J., Siedlak, S. L., Fujikawa, H., Liang, J., et al. (2016). The inhibition of TDP-43 mitochonrdial localization blocks its neuronal toxicity. Nat. Med. 22, 869–878. doi: 10.1038/nm.4130

Watanabe, S., Ileva, H., Tamada, H., Nomura, H., Komine, O., Endo, F., et al. (2016). Mitochondria-associated membrane collapse is a common pathomechanism in SIGMAR1- and SOD1-linked ALS. EMBO Mol. Med. 8, 1421–1437. doi: 10.15252/emmm.201606403

Watts, G. D., Wymer, J., Kovach, M. J., Mehta, S. G., Mumm, S., Darwish, D., et al. (2004). Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. Nat. Genet. 36, 377–381. doi: 10.1038/ng1332

Weedon, M. N., Hastings, R., Caswell, R., Xie, W., Paszkiewicz, K., Antoniadi, T., et al. (2011). Small-fiber neuropathy in patients with ALS. Neurology 76, 2024–2029. doi: 10.1212/wnl.0b013e31821e553a

Weilh, C. C., Pestrkon, A., and Kimonis, V. E. (2009). Valosin-containing protein disease: inclusion body myopathy with Paget’s disease of the bone and frontotemporal dementia. Neuromuscul. Disord. 19, 308–315. doi: 10.1016/j.nmd.2009.01.009

Weijs, J., Katona, I., Muller-Newen, G., Sommer, C., Necula, G., Hendrich, C., et al. (2017). Inhibition of TDP-43 mitochondrial localization blocks its neuronal toxicity. Autophagy 10, 588–602. doi: 10.1016/j.autophag.2017.05.004

Williams, C., and Heaton, A. V. (1999). Slowing of axonal transport is a very early event in the toxicity of ALS-linked SOD1 mutants to motor neurons. Neurobiol. Dis. 2, 50–56. doi: 10.1016/S0929-4933(99)00018-4

Windpassinger, C., Auer-Grumbach, M., Irobi, J., Petek, H., Horl, G., et al. (2004). Heterozygous missense mutations in BSCL2 are associated with distal hereditary motor neuropathy and Silver syndrome. Nat. Genet. 36, 271–276. doi: 10.1038/ng1313

Wu, C. H., Fallini, C., Ticozzi, N., Keagle, P. J., Sapp, P. C., Piotrowska, K., et al. (2012). Mutations in the profilin 1 gene cause familial amyotrophic lateral sclerosis. Nature 488, 499–503. doi: 10.1038/nature11280

Yamashita, T., Hideyama, T., Chigusa, K., Teramoto, S., Takano, J., Iwata, N., et al. (2012). A role for calpain-dependent cleavage of TDP-43 in amyotrophic lateral sclerosis pathology. Nat. Commun. 3:1307. doi: 10.1038/ncomms1307

Yoshihara, T., Yamamoto, M., Hattori, N., Misu, K., Mori, K., Koike, H., et al. (2002). Identification of novel sequence variants in the neurofilament-light gene in a Japanese population: analysis of Charcot-Marie-Tooth disease patients and normal individuals. J. Peripher. Nerv. Syst. 7, 221–224. doi: 10.1046/j.1529-8027.2002.02028.x

Zhan, L., Xie, Q., and Tibbetts, R. S. (2015). Opposing roles of p38 and JNK in a Drosophila model of TDP-43 proteinopathy reveal oxidative stress and innate immunity as pathogenic components of neurodegeneration. Hum. Mol. Genet. 24, 757–772. doi: 10.1093/hmg/ddu493

Zhang, X., Chen, S., Song, L., Tang, Y., Shen, Y., Jia, L., et al. (2014). MTOR-independent, autophagic enhancer trehalose prolongs motor neuron survival and ameliorates the autophagic flux defect in a mouse model of amyotrophic lateral sclerosis. Autophagy 10, 588–602. doi: 10.4161/auto.27710

Zhao, Z. H., Chen, W. Z., Wu, Z. Y., Wang, N., Zhao, G. X., Chen, W. J., et al. (2009). A novel mutation in the senataxin gene identified in a Chinese patient with sporadic amyotrophic lateral sclerosis. Amyotroph. Lateral Scler. 10, 118–122. doi: 10.1080/17482960802572673

Zuchner, S., De Jonghe, P., Jordanova, A., Claesys, K. G., Guergueltcheva, V., Cherninkova, S., et al. (2006). Axonal neuropathy with optic atrophy is caused by mutations in mutifusin 2. Ann. Neurol. 59, 276–281. doi: 10.1002/ana.20797

Zuchner, S., Mersinyanov, I. V., Muglia, M., Bissar-Tadmouri, N., Rochelle, J., Dadali, E. L., et al. (2004a). Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. Nat. Genet. 36, 449–451. doi: 10.1038/ng1341

Zuchner, S., Vorgler, M., Sinder, E., and Schroder, J. M. (2004b). The novel neuropathil light (NEFL) mutation Glu397Lys is associated with a clinically and morphologically heterogeneous type of Charcot-Marie-Tooth neuropathy. Neuromuscul. Disord. 14, 147–157. doi: 10.1016/j.nmd.2003.10.003

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