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# Clinical Spectrum of Amyotrophic Lateral Sclerosis (ALS)

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Amyotrophic lateral sclerosis (ALS) is primarily characterized by progressive loss of motor neurons, although there is marked phenotypic heterogeneity between cases. Typical, or "classical," ALS is associated with simultaneous upper motor neuron (UMN) and lower motor neuron (LMN) involvement at disease onset, whereas atypical forms, such as primary lateral sclerosis and progressive muscular atrophy, have early and predominant involvement in the UMN and LMN, respectively. The varying phenotypes can be so distinctive that they would seem to have differing biology. Because the same phenotypes can have multiple causes, including different gene mutations, there may be multiple molecular mechanisms causing ALS, implying that the disease is a syndrome. Conversely, multiple phenotypes can be caused by a single gene mutation; thus, a single molecular mechanism could be compatible with clinical heterogeneity. The pathogenic mechanism(s) in ALS remain unknown, but active propagation of the pathology neuroanatomically is likely a primary component.

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neuromuscular disease characterized by degeneration of the upper and lower motor neurons resulting in dysfunction of the somatic muscles of the body (Cleveland and Rothstein 2001; Bradley 2009). The term "amyotrophic lateral sclerosis" was coined by the French neurologist Jean-Martin Charcot in the 1800s: "amyotrophic" refers to muscular atrophy, and "lateral sclerosis" describes the scarring or hardening of tissues in the lateral spinal cord. The major neuropathological features of ALS are (1) extensive loss of lower motor neurons from the anterior horns of the spinal cord and brainstem (Hughes 1982; Ghatak et al. 1986); (2) degeneration and loss of Betz cells (large pyramidal cell neurons) in the primary motor cortex and degeneration of the lateral corticospinal tracts, which contain the axons projecting from the primary motor cortex to the motor neurons (Hammer et al. 1979; Udaka et al. 1986; Maekawa et al. 2004); and (3) reactive gliosis, which corresponds to hypertrophy of glial cells in the motor cortex and spinal cord in the areas of degeneration (Murayama et al. 1991; Kawamata et al. 1992; Schiffer et al. 1996).

ALS is the most common form of motor neuron disease, with a mean incidence of 2.8/

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100,000 in Europe and 1.8/100,000 in North America, and a mean prevalence of 5.40/100,000 in Europe and 3.40/100,000 in North America (Chio et al. 2013). Men are slightly more frequently affected than women, with a male:female incidence rate ratio of 1.4 (Logroscino et al. 2010). The median survival period following onset is independent of sex and is usually 2–4 yr (Logroscino et al. 2010). In most cases, disease onset occurs during late adulthood, but juvenile (before 25 yr) and "young-onset" ALS cases (before 45 yr), respectively, represent ~1% and ~10% of all cases (Turner et al. 2012). In a recent epidemiological analysis of ALS combining 37 studies, the mean age for typical ALS disease onset (adult onset) was estimated at 61.8 ± 3.8 yr (range 54–67 yr) and the mean age for ALS diagnosis at 64.4 ± 2.9 yr (range 58–68 yr) (Chio et al. 2013).

## ALS CLINICAL PHENOTYPES

In ALS, there is generally a striking dissimilarity in the degree of involvement of the upper motor neurons (UMNs) and the lower motor neurons (LMNs), the body regions affected, the degrees of involvement of other systems, especially cognition and behavior, and the progression rates among clinical phenotypes (Ravits and La Spada 2009). Phenotypes can be so distinctive that they would seem to have differing underlying biology; however, the known neuropathology is more consistent and does not clearly correlate with the different phenotypic subtypes of disease. The question is often posed as to whether ALS is one disease with a common fundamental pathogenic mechanism or multiple diseases with different mechanisms. The answer may lie somewhere in between.

Approximately 10% of ALS cases are genetically transmitted mainly by way of dominant gene mutations, which have now been identified in ~60%–70% of cases of the familial fraction of the disease (Haverkamp et al. 1995). These mutations are predominantly associated with Mendelian-inherited and primarily autosomal dominant mutations in genes encoding Cu/Zn superoxide dismutase (SOD1), TAR-DNA binding protein 43 (TDP-43), fused in sarcoma/translocated in liposarcoma (FUS/TLS), and C9ORF72, but have been associated with mutations in other genes as well (reviewed in the ALS Mutation Database 2007; Deng et al. 2011; Stewart et al. 2012; Wu et al. 2012; Renton et al. 2014). The 10% of cases with known family history of ALS are referred to as familial ALS (fALS), and the remaining 90% of cases with no known familial history are referred to as sporadic ALS (sALS). In the sALS group, about 5% will still harbor gene mutations seen in fALS, indicating that they have been misclassified based on the genetic history, and some will harbor genetic variations that may be predisposing, such as the ataxin-2 intermediate repeat expansions (Elden et al. 2010). Phenotypically, fALS and sALS are indistinguishable. Heterogeneity occurs even in the same gene mutation within a family. The fact that many different gene mutations have identical or at least highly similar clinical phenotypes suggests that there are multiple mechanisms that cause ALS, and that ALS is likely a syndrome. But the fact that one single genotype can cause different phenotypes indicates that single mechanisms can lead to multiple phenotypes. The explanation for this is unknown, but, traditionally, phenotypic variation is thought to result from the complex interplay between multiple genes and gene–environment interactions.

Clinical phenotypes of ALS can be grossly classified based on the level and anatomical area of motor neuron involvement and pattern of onset (Table 1). Typical, or "classical," ALS involves simultaneous UMN and LMN signs and is usually fatal within 4 yr of onset. Muscle weakness begins in a discrete body region and advances steadily over time and space. It usually begins in any of the three main body regions (face, arm, and leg), although it rarely begins in the muscles affecting the trunk and/or respiration. Pathological burden is normally distributed between UMNs and LMNs with a possible slight skew to LMN dominance (Ravits et al. 2007a). Atypical forms of the disease are cases in which there is much longer survival, or pure UMN or LMN involvement. These atypical forms may contain instances of spastic paraplegia, autoimmune diseases, or demyelinating

**Table 1.** ALS phenotypes based on anatomical region of neuropathology

| | Anatomical region of involvement | | | |
|---|---|---|---|---|
| | Neuronal region | | Somatic region | |
| Phenotypic variant | UMN | LMN | Bulbar muscles | Limb muscles |
| Based on neuronal level of involvement | | | | |
| Typical ALS | + | + | + | + |
| PLS | ++ | − | + | + |
| PMA | − | ++ | +/− | ++ |
| Based on somatic region of involvement | | | | |
| Bulbar ALS | − | ++ | ++ | − |
| Pseudobulbar ALS | ++ | − | ++ | − |
| Limb ALS | + | + | − | ++ |
| Limb variants | +/− | ++ | − | ++ |
| Mill's variant | ++ | − | − | ++ |

Adapted from data in Ravits et al. 2013.

ALS, amyotrophic lateral sclerosis; UMN, upper motor neuron; LMN, lower motor neuron; +/−, possible but not typical; +, typical and to variable degree; ++, primary feature.



LMN disease, to name a few of the many possible causes, and are typically referred to by distinct clinical designations, highlighting the distinctiveness of phenotypes but also raising the question of whether or not these are fundamentally different biological conditions or the extremes of one continuum.

Primary lateral sclerosis (PLS) refers to a syndrome predominantly involving UMN degeneration; it remains unclear whether this phenotype is a discrete disorder or a variant of ALS (Rowland 1999; Swash et al. 1999; Le Forestier et al. 2001; Zhai et al. 2003; Singer et al. 2005). In the majority of PLS patients, symptoms begin in the legs and ascend relatively symmetrically to the arms and bulbar muscles. There is contention about the involvement of LMNs in PLS, especially when sensitive tools such as electromyography (EMG) are used (Gordon et al. 2006; Singer et al. 2007). Patients with clinically distinct PLS and no EMG abnormalities 4 yr after symptom onset can often survive for decades (Gordon et al. 2006; Tartaglia et al. 2007), whereas patients with minor EMG changes or some LMN involvement may have lower survival and poorer prognosis, which is consistent with more typical ALS patients presenting with predominant UMN signs (Gordon et al. 2009). Frontotemporal dementia (FTD), cognitive impairment, and altered behavior occur in PLS comparable with ALS (Grace et al. 2011).

Progressive muscular atrophy (PMA) refers to a syndrome with predominant LMN involvement. As opposed to typical ALS, PMA onset can occur in any body region, has a higher occurrence in males, and generally has a later onset. Approximately 30% of PMA patients develop UMN symptoms within 18 mo of disease onset (Visser et al. 2007; Kim et al. 2009). Patients with PMA show the same frontotemporal pattern of cognitive involvement as is seen in typical ALS, suggesting there is no correlation between the degree of UMN involvement and cognitive involvement (Raaphorst et al. 2011). Neurophysiological studies of central motor conduction using transcranial magnetic stimulation show abnormalities in 50%–63% of patients with clinical PMA (Kaufmann et al. 2004; Floyd et al. 2009).

The clinical phenotype designations PLS and PMA are based on the level of the underlying pathology. Other phenotypic designations for ALS are based on the body region first affected at disease onset (Table 1). Bulbar-onset ALS (bulbar palsy) describes patients whose onset is in the muscles of speech, chewing, and swallowing and is traditionally signified with predominant LMN involvement, whereas the pseudobulbar variant is indicative of pre-

dominantly UMN involvement. Both bulbar and pseudobulbar forms of the disease have similar progression. Bulbar onset has a higher predominance in females and is highly associated with cognitive involvement, altered and exaggerated emotional expression (Turner et al. 2010), and often directly correlates with depression. Sequential functional MRI studies during the course of bulbar- and limb-onset ALS provide direct observations of the interrelationship between brainstem and spinal-cord-derived neural networks (Kollewe et al. 2011). The initial onset of ALS in the limbs, which occurs in more than two-thirds of patients, is often referred to as "limb-onset" and is considered the primary typical form of ALS. Limb-onset ALS itself consists of some variants that are predominantly LMN syndromes that tend to be slowly progressive. The upper extremity regional variant consists of weakness exclusively confined initially to the upper extremities and can often be described under different names such as hanging arm syndrome, brachial amyotrophic diplegia, and Vulpian–Bernhart syndrome (Gamez et al. 1999). Patients often have bilateral upper extremity weakness and atrophy that affects the proximal arms and shoulders (Katz et al. 1999; Wijesekera et al. 2009). There is no difference in age of onset between this variant and typical ALS, although the former is more common in males. The lower extremity regional variant is confined to the legs and can be alternatively identified as the pseudopolyneuritic variant of ALS, flail leg syndrome, and leg amyotrophic diplegia (Wijesekera et al. 2009). It is relatively rare, consisting of ~3%–3.5% of all motor neuron disease cases, and occurs predominantly in men and largely in the LMN, with slow progression and a mean survival ranging from 76–96 mo. Finally, Mill's variant (hemiplegic ALS) is a rare ALS variant phenotype characterized by a progressive hemiplegic pattern of motor deficit that ascends from the leg or descends from the arm, resembling a type of PLS (Rajabally et al. 2005; Baumer et al. 2014). Scarce literature on Mill's variant exists, although one positron emission tomography (PET) study on a patient showed a distinct lateralization of microglial activation in the hemisphere contralateral to the hemiplegia (Turner et al. 2005).

Clinical phenotypes of ALS can also involve nonmotor regions. The overlap between frontotemporal dementia (FTD) and ALS is well documented and discussed below (Kiernan and Hudson 1994; Abe et al. 1997; Strong et al. 1999; Lomen-Hoerth et al. 2002, 2003), with up to 15% of FTD patients and 30% of ALS patients experiencing overlapping symptoms. At this time, it is uncertain whether behaviorally or cognitively impaired ALS has distinctly different pathobiological mechanisms from typical ALS, or is simply an extension of a singular disease spectrum (Strong et al. 2009). A survival difference of more than 1 yr exists between comorbid FTD/ALS patients compared with those with ALS alone (Olney et al. 2005). In addition to dementia, other systems can be involved in what otherwise seems to be typical ALS, including extrapyramidal motor systems (Knirsch et al. 2000; Pradat et al. 2002; Gamez et al. 2008; Kovacs et al. 2009), supranuclear gaze systems (Averbuch-Heller et al. 1998; Donaghy et al. 2011), and the autonomic nervous system (Grosskreutz et al. 2006; van der Graaff et al. 2009). Defects in energy metabolism including weight loss, hypermetabolism, and hyperlipidemia have been associated with ALS, suggesting that other regions of the central nervous system (CNS), such as the hypothalamus, may be implicated or that these symptoms are all part of one systemic disease (Dupuis et al. 2011). There is sufficient clinical, neuropathological, and neuroimaging evidence in the literature suggesting that these atypical symptoms should be considered part of the neuropathological spectrum of ALS/motor neuron disease (MND) (McCluskey et al. 2009).

## NEUROPATHOLOGICAL HETEROGENEITY OF ALS

ALS is neuropathologically defined as the loss of UMNs (Betz cells in layer V of area 4 of Brodmann) and LMNs (alpha motor neurons in the motor nuclei of the brainstem and Rexed Lamina IX of the anterior horns in the spinal columns). Wallerian/axonal degeneration in the

projecting pathways from the UMNs is typically observed in the corpus callosum, centrum semiovale, internal capsule, cerebral peduncle, basis pontis, medullary pyramids, and lateral columns in typical ALS. Similar degeneration is seen in the anterior roots and peripheral nerves of LMNs, leading to muscle denervation. In addition, there are astrogliosis, spongiosis, and microglial activation, indications of a more primary role for non-neuronal cells in the disease (Boillee et al. 2006; Haidet-Phillips et al. 2011; Lasiene and Yamanaka 2011). Similar neuropathology is reported for other ALS clinical phenotypes such as PMA and PLS, differing mostly in their anatomical distribution of pathology rather than the nature and composition of the pathology itself (Pringle et al. 1992; Ince et al. 2003). Distinct pathological change is also identified in the motor and extramotor areas of the brain and spinal cord of patients whose disease was clinically limited to the LMNs (Geser et al. 2011). PLS neuropathology also shows changes in the LMNs, which display the same molecular pattern as seen in typical disease (Kobayashi et al. 2010).

Although traditional neuropathology typically features loss of motor neurons in the brainstem and ventral horn of the spinal cord, accompanied with signs of inflammation such as astrocyte activation and proliferation of microglia (Philips and Robberecht 2011), molecular neuropathology is redefining postmortem changes. Often appearing either skein-like or dense and round, ubiquitinated inclusions in the cytoplasm of motor neurons of patients are a classical neuropathological indicator of ALS (Leigh et al. 1988; Lowe et al. 1988). In fALS cases in which a SOD1 mutation is identified, the primary component of these protein inclusions is SOD1 itself (Kato et al. 2000). Normally, SOD1 is a soluble, ubiquitously expressed, free-radical scavenging enzyme that exists as a functional homodimer. There is also increasing evidence supporting the presence of misfolded SOD1 in sporadic cases with no SOD1 mutations (Bosco et al. 2010; Forsberg et al. 2010; Pokrishevsky et al. 2012; Grad et al. 2014), suggesting a more expanded role for SOD1 in ALS pathology. fALS cases in which mutations in the gene encoding FUS, an RNA-binding transcriptional activator, have been identified and also result in pathological inclusions in the cytosol of neural cells (Huang et al. 2010; Sun et al. 2011). The presence of ubiquitinated protein deposits primarily composed of TDP-43, a nuclear protein involved in DNA and RNA processing that has been translocated to the cytoplasm, hyperphosphorylated, and cleaved, have also been identified in ~50% of brains from FTD patients (Arai et al. 2006; Neumann et al. 2006). In addition, essentially all sALS and nearly all fALS cases, except those associated with mutations in the genes encoding SOD1 and FUS regardless of clinical phenotype (including PLS and PMA), seem to have the hallmark neuropathological deposition of ubiquitinated TDP-43 in the cytoplasm of CNS cells, suggesting that ALS may be a TDP-43 proteinopathy. Heat maps of the distribution of TDP-43 pathology show that abnormalities are widely present in the brain, not just in motor regions (Geser et al. 2008). Despite their structural, functional, and pathological similarities, FUS and TDP-43 do not colocalize within pathological inclusions in the cytoplasm (Huang et al. 2010; Sun et al. 2011), suggesting that the two proteins are involved in the pathology via distinct, albeit related, mechanisms. Finally, the discovery of GGGGCC hexanucleotide repeat expansions within the *C9ORF72* gene in ALS patients has now been identified as the most common mutation in families with ALS or FTD (Mackenzie et al. 2013). Hexanucleotide expansion in *C9ORF72* is found in nearly 40% of all fALS cases and up to 7% of sALS (Maniecka and Polymenidou 2015). In normal individuals, the hexanucleotide repeat length is typically no longer than 25–30 units, but in ALS patients possessing a *C9ORF72* mutation, repeat length can exceed 700 (DeJesus-Hernandez et al. 2011; van Blitterswijk et al. 2013). C9ORF72-associated ALS cases typically present with TDP-43 aggregation and p62-positive/TDP-43-negative ubiquitinated inclusions in the cerebellar and hippocampal regions (Al-Sarraj et al. 2011; Troakes et al. 2012). Mutations within *C9ORF72* result in the subsequent production of aggregating dipeptide-re-

peat (DPR) proteins (Ash et al. 2013; Mori et al. 2013), which are generated by an alternative type of translation called repeat-associated non-ATG (RAN) translation (Zu et al. 2013).

In addition to neuroanatomic pathology, there is a growing body of knowledge regarding the systemic changes that occur in ALS. These include ultrastructural abnormalities in hepatic cells, skin cells, muscle mitochondria, systemic glutamate metabolism, inflammatory cytokine production, immunological changes, glucose metabolism, and lipid metabolism. Skeletal muscle is the single largest organ by mass and is the end-organ of the motor neurons. Skeletal muscles generate target-derived neurotrophic factors that can substantially affect motor neuron survival. Part of the hypermetabolism that is becoming defined in ALS patients may be caused by abnormal mitochondrial energy production in skeletal muscle (Desport et al. 2005), generating a large amount of cytotoxic reactive oxygen species (Muller et al. 2007) that could interact with cells from the CNS (Bogdanov et al. 2000). Thus, in addition to the myriad of neuropathological phenotypes associated with the broader ALS syndrome, one may also take into consideration the systemic effects of the disease when formulating potential therapeutic interventions.

## NEUROANATOMIC PROPAGATION IN ALS

The phenotypic heterogeneity within ALS that appears to present as distinct motor neuron phenotypes in reality exists within a continuum. Features that are common to most phenotypes, besides the primary degeneration of motor neurons, are focal initial neuropathology and progressive contiguous spread. Understanding the focality and spread of pathology is important to understanding pathogenesis and may provide new ways to approach therapy. There are a number of clinical observations common to the majority of ALS motor phenotypes. First, initial symptoms appear focally in random regions of the body (Ravits et al. 2007b). They may appear in bulbar muscles such as masticatory, facial, pharyngeal, tongue, or laryngeal muscles; in limb muscles such as shoulder, forearm, hand, thigh, knees, or foot muscles; or in axial or respiratory muscles. When ALS begins in the limbs, where detection may be lateralized, deficits typically are unilateral. These observations suggest that at the onset of disease, the pathological process that underlies clinical symptoms is focal and stochastically (randomly) located in the nervous system (Ravits et al. 2007a). Next, disease progresses by contiguity (Fig. 1). This is shown in two ways: First, the motor dysfunction in a focal body region where symptoms initially appear becomes progressively worse in this same region over time (Fig. 2); second, the motor dysfunction spreads outward to contiguous regions, progressing, for example, from one side of the body to the other or from one region to the next. This suggests that the underlying pathology is propagating neuroanatomically, starting discretely within an area of the neuraxis and then spreading to contiguous regions (Ravits et al. 2007a). Furthermore, whereas initial symptoms appear in focal body regions such as the head, arm, trunk, or leg, both UMN and LMN characteristics of these symptoms are maximal in these same regions. That is, the focal body area where symptoms first appear is the area that has maximal UMN and LMN degeneration, suggesting that at the onset of disease, UMN, LMN, and peripheral muscle degenerations are connected, not independent. After disease is triggered and begins spreading contiguously, degeneration proceeds independently at the UMN and LMN levels. For example, when onset of symptoms begins in the arm, LMN clinical deficits progress from one arm to the other, which is consistent with neuronal anatomy of LMNs in the spinal cord. Conversely, UMN clinical deficits progress from the arm to the ipsilateral leg, which is consistent with the somatotopic anatomy of the cerebral cortex. In light of differences between UMN and LMN somatotopic structures and spread distances, initial signs of degeneration that are seen in one body region progress differently between the UMN and LMN levels to other body regions over time, and motor deficits become increasingly complex, subsequently resulting in increasing complexity of phenotypes. Finally, the

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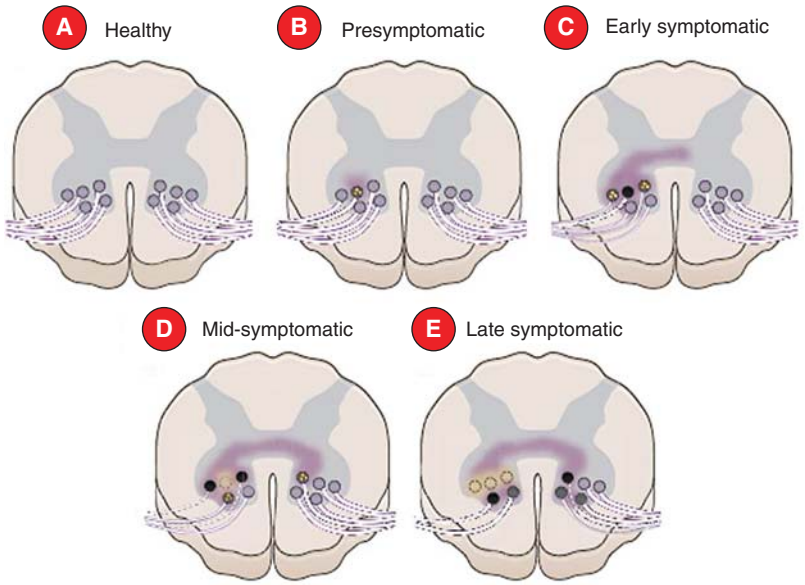


**Figure 1.** Clinical pathology of ALS spreads in a contiguous and temporal fashion. In the healthy spinal cord (*A*), global neuronal integrity is intact. In the presymptomatic stage (*B*), dysfunction within motor neurons begins but remains local and does not yet translate to a clinical presentation. Subsequent neuronal degeneration and sequential spread of cellular dysfunction begin to have an effect on motor neuron function and result in early signs of symptoms (*C*). Neurotoxicity propagates from neuron to neuron and region to region, resulting in a cascade effect that ultimately destroys motor neurons regionally (*D*) and is transmitted to adjacent anatomical regions, ultimately resulting in systemic motor neuron dysfunction that presents as severe disease (*E*).

rates of clinical progression are determined by the kinetics of pathogenic propagation. Whereas the phenotypes are largely determined by the configuration of underlying degeneration, the rates of progression are largely determined by the overall kinetics of intercellular molecular pathology (Fujimura-Kiyono et al. 2011). Most studies of progression rates measure overall functional deficits and do not analyze regional progression or independently measure UMN and LMN progression. Detailed studies show rates of decline in different body regions (Andres et al. 1987; Munsat et al. 1988). It remains unclear as to whether progression is similar at the UMN and LMN levels, and whether overall progression is a summation between them. Interestingly, PLS and PMA, in which the pathological burden is predominantly at one level, generally have better prognoses than ALS, perhaps attributable to the fact that disease is primarily at one motor neuron level rather than two. Why that is remains unresolved and is a clear discerning factor between atypical and typical forms of ALS.

The above clinical observations of ALS phenotypic progression point to a disease paradigm in which focal and random initiation of pathology and subsequent spread contribute significantly to ALS biology (Ravits and La Spada 2009), harkening to the prion-like spread of pathology (Guest et al. 2011; Grad et al. 2015). Notably, the prion paradigm suggests that pathogenesis at the molecular level involves a process of cell-to-cell propagation of pathogenic factor(s) (Fig. 3), which provides an important framework for understanding pathogenesis in which initial molecular changes begin as a point source and induce cellular, neurophysiological, and eventual clinical changes (Polymenidou and Cleveland 2011; Grad et al. 2015). Nonetheless, specific aspects of the neuroanatomic propagation model remain uncertain. For example, one study identified that up to 14% of secondary regions involved in disease progres-

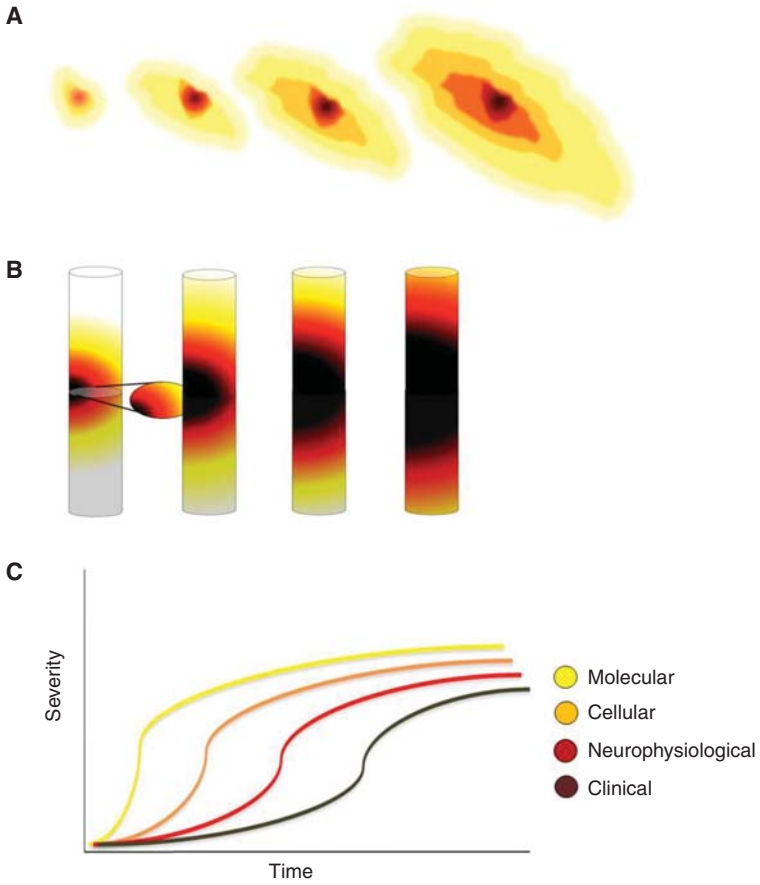


**Figure 2.** Models of temporal-spatial progression in ALS. (*A*) Spatial spread begins at a focal point followed by sequential progression outward in space. (*B*) Summation and saturation occur when the sequential changes progress neuroanatomically in a postmitotic finite compartment such as the motor system. (*C*) The sequential changes progress temporally from molecular to cellular to neurophysiological and ultimately to clinical levels over time. (Figure adapted with permission from Ravits 2014.)

sion were noncontiguous skip lesions to different regions of the neuraxis (Gargiulo-Monachelli et al. 2012); thus, multifocal onset has been proposed for ALS (Kanouchi et al. 2012; Sekiguchi et al. 2014). Other factors besides neuroanatomic propagation may also contribute to disease phenotype (Ganesalingam et al. 2009; Chio et al. 2011). Recently, spread of pathogenic factor(s) through the cerebrospinal fluid pathway has been postulated (Smith et al. 2015).

Clinical observation along with functional imaging has identified two distinct types of pathological propagation in ALS: contiguous spread and network spread. Contiguous spread advances side-to-side independent of synaptic connection (Ravits and La Spada 2009; Kanouchi et al. 2012), whereas network spread advances end-to-end in functionally and anatomically connected networks and thus is dependent on synaptic connectivity (Brooks 1991; Seeley et al. 2009). Both types appear to be involved in ALS. Neuropathological evidence of disease focality and spread is difficult to obtain since neuropathology is performed postmortem, not at disease onset, and thus reflects accumulation of pathological changes throughout the course of the disease. In addition, pathological studies are cross-sectional and often

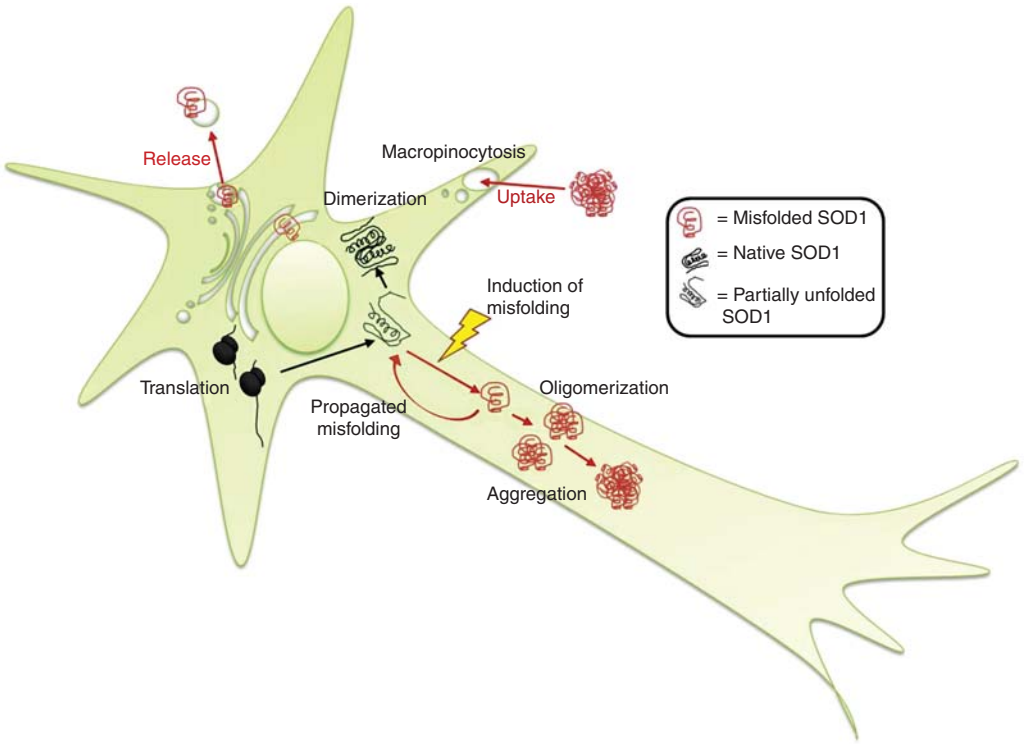


**Figure 3.** Intermolecular and intercellular prion-like propagation of misfolded protein. Specific misfolded proteins have been shown to have prion-like propagated misfolding properties that may contribute to the contiguous spread of ALS pathology. For example, SOD1 misfolding can be induced by a variety of intracellular and extracellular stresses. Once a misfolded template is present, it can induce subsequent cycles of template-directed misfolding, converting neighboring SOD1 molecules into pathological isoforms, which can subsequently form oligomers and aggregates over time. Misfolded SOD1 can also accumulate in the ER–Golgi system, where it can enter the vesicle-mediated secretory pathway and exit the cell via secretion. Alternatively, large proteinaceous aggregates containing misfolded SOD1 are subsequently taken up by neighboring cells via macropinocytosis. (From Grad et al. 2015; adapted, with permission, from the authors.)



difficult to correlate to clinical phenotypes including site of clinical onset, distribution between UMN and LMN changes, and kinetics of spread; however, a gradient of neuronal loss originating from the site of onset in the LMN column has been observed (Ravits et al. 2007a; Brettschneider et al. 2014).

A pathological hallmark in the majority of ALS cases is TDP-43 proteinopathy, defined as the nuclear translocation and aggregation of the protein in the cytoplasm. Recently, gradients of degeneration based on the neuroanatomical spread of TDP-43 pathology have been identified (Brettschneider et al. 2013), and a pathological staging system has been proposed based on what appears to be a systematic neuroanatomical gradation of pathological changes (Braak et al. 2013). However, it remains unclear as to how this pathological staging relates to differences in disease duration between cases of ALS with different etiologies, or even between patients with similar disease origins. Although few detailed studies of PLS and PMA have been performed, they do show that both PLS (Kobayashi et al. 2010; Kosaka et al. 2012) and PMA (Ince et al. 2003; Geser et al. 2011) have concurrent UMN and LMN involvement, although the disease burdens vary significantly, and both carry the TDP-43 proteinopathy signature.

## ALS AND FRONTOTEMPORAL DEMENTIA

Over the last two decades, there has been growing evidence that clinical signs of frontotemporal dementia (FTD) can be seen in patients primarily diagnosed with ALS, implying clinical overlap between these two disorders. This has led to a view that ALS and FTD share a common biology and exist on the same pathological spectrum. Clinically, it is now recognized that up to 50% of ALS patients have some degree of cognitive or behavioral impairment, and up to 33% of FTD patients have evidence of motor neuron involvement (Kiernan and Hudson 1994; Strong et al. 1999; Lomen-Hoerth et al. 2002). In addition to clinical overlap between FTD and ALS, there is evidence of shared neuropathological features at the molecular level: >95% of ALS patient nervous systems and 50% of FTD patient nervous systems share the common molecular signature of TDP-43 proteinopathy (Arai et al. 2006; Neumann et al. 2006). These observations reinforce the notion that ALS together with ALS-FTD could be considered progressive disorders that are part of a connected spectrum of multisystem degeneration. Additionally, the single most common genetic cause of either ALS or FTD is mutation in *C9ORF72*, which can cause either disease or an overlap of the two (DeJesus-Hernandez et al. 2011; Renton et al. 2011).

FTD pathology is associated with neurodegeneration that typically presents as gross atrophy of the frontal and temporal lobes (Cairns et al. 2007). Typically, in FTD patients, frontal and temporal areas show reduction and spongiform morphology because of extensive neuronal loss. Cases of ALS with FTD cognitive impairment characteristically show signs of spongiform degeneration in frontal and precentral gyrus (cortical layers II and III) and diffuse subcortical gliosis (Yoshida 2004; Strong et al. 2009). Neuronal loss is also observed in the anterior cingulate gyrus as well as in the substantia nigra and amygdala (Strong et al. 2009). Generally, neuronal degeneration is progressive and increases during the course of the disease, even though the dynamics of this process may vary among different individuals. Clinically, FTD has three main clinical phenotypes: primary progressive aphasia, semantic dementia, and behavioral variant. Extensive studies over the last several years have sought direct relationships between FTD clinical phenotypes, molecular neuropathological signature, and genetic subtypes, but only broad correlations have been identified (Sieben et al. 2012; Pan and Chen 2013). As with ALS clinical phenotypes, FTD phenotypes are largely determined by the anatomic distribution of pathology in early disease (Chow 2011). Thus, FTD phenotypes can also be viewed as a disease in which onset is initiated from a focal point. Based on elaborate neuroimaging studies, propagation has been shown to be a critically important component of FTD pathobiology, similar to that observed in ALS (Seeley 2008; Seeley et al. 2009; Zhou et al. 2012). However, genetics also indicate that the pathobiology is complex beyond anatomical considerations alone, because, for example, mutations in genes such as *SOD1* and *TARDBP* have a primarily ALS phenotype and mutations in genes such as *PRGN* have a primarily FTD phenotype, underscoring that anatomy is only one of a number of components of disease biology.

## CONCLUDING REMARKS

Classical ALS and its heterogeneous "atypical" phenotypes, including PLS and PMA, provide a unique window into the neuroanatomic onset and progression of pathology. For classical ALS, each patient has a focal and randomly located site of onset, a variable mix of UMN and LMN involvement, and spatiotemporal progression. These aspects of disease point to the importance of cell-to-cell propagation in disease pathogenesis. The mechanisms of pathological progression in "atypical" forms of the disease are less clear and may or may not involve prion-like pathogenic mechanisms, suggesting that in some cases they may result from an entirely different mechanism. Propagation biology is equally applicable to fALS as well as to FTD, underscoring the ubiquitous nature of this mechanism. Increasing knowledge about prion-like propagation of protein misfolding in

this and other neurodegenerative diseases is shedding light on possible underlying cellular and molecular mechanisms, although multiple pathogenic mechanisms may be involved (Sibilla and Bertolotti 2017). The fact that different gene mutations cause identical clinical phenotypes suggests that multiple mechanisms exist for developing disease and that ALS is etiologically a syndrome. However, once ALS is initiated, clinical observations and patterns in neuropathology suggest that there must ultimately be common mechanisms in ALS; prion-like propagation of pathology could be such a principal component of ALS pathogenesis.

Finally, in developing rationally designed therapies for ALS, further refinement of the definition of the disease may be required, which would have important implications for the future development of treatment and clinical trials. For example, a treatment targeting the prion-like spread of ALS via propagating pathology would not necessarily work in some "atypical" ALS patients in which this mechanism may not be occurring, even though it is possible that a more narrow disease definition based solely on evidence of propagating pathology could result in the exclusion of bona fide cases of ALS. Nonetheless, more stringent phenotypic classification could serve to facilitate the identification and evaluation of novel treatments for ALS phenotypes that share a common mechanism of pathology. In the end, the ultimate goal in ALS research is a rationally designed therapy that effectively stops disease progression, and understanding propagation will contribute to this quest.

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# Clinical Spectrum of Amyotrophic Lateral Sclerosis (ALS)

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