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# Amyotrophic Lateral Sclerosis

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## 1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative motor neuron disease for which no successful treatment presently exists. ALS is also termed Charcot's disease (maladie de Charcot), after the French clinician Jean Martin Charcot who first described its features in 1869 (Charcot 1869) or Lou Gehrig's disease in the United States, after the New York Yankees baseball player afflicted with the condition. Within Europe ALS is often referred to as Motor Neuron Disease, describing the cells chiefly affected, although this term may also more generally refer to a wider group of motor neuron diseases.

ALS is characterized by the degeneration of motor cortex, brainstem and/or motor neurons associated with the spinal cord, resulting in muscle weakness and loss of voluntary muscle control. Progressive paralysis ensues, and respiratory failure is the usual cause of death. *Amyotrophic* refers to the lack (*a-*) of muscle (*-myo-*) nourishment (*-trophic*), resulting in wasting of the fibers; *Lateral* refers to the lateral corticospinal tract of affected neurons between the brain and spinal cord; *Sclerosis* is the resultant hardening of the tissue. The incidence of ALS globally ranges from 0.3 to 2.4 cases per 100,000 (Sathasivam 2010). Approximately 95% of ALS cases are random or sporadic (SALS), whereas 5 or more percent are inherited (familial ALS, FALS), with a subset of these arising from known genetic determinants.

Despite the initial description of the disorder about 150 years ago, and significant progress in the understanding of its pathology, ALS remains an ill-defined terminal disease with few medicinal options and an average duration of only a few years. Nonetheless, new developments in ALS research are slowly emerging in diagnostics, in elucidating molecular mechanisms behind the disease, and in generating treatments. Improved technologies and recent research insights, when coupled with meaningful collaborations between scientists and clinicians hold promise for exciting progress. Thus, we discuss here the current understanding of ALS in terms of its clinical presentation, and its molecular and cellular basis. In particular, we highlight new insights into the genetics of the inherited disease, with a focus on the mutant gene products Cu,Zn-superoxide dismutase (Cu,ZnSOD), Fused in Sarcoma/Translated in Lipsarcoma (FUS/TLS) and the Tar-DNA binding protein 43 (TDP-43). The standard care regimen will also be described, along with a focus on novel

therapeutic strategies and developments for improving the outlook for patients with this terminal disease.

## 2. Clinical phenotype

The initial onset of ALS (both FALS and SALS) typically begins with one of several patterns. Seventy five percent of patients have “spinal onset,” affecting the limbs (Kiernan et al. 2011). Within this group a “cervical” subset will have muscle weakness in the upper limbs, while symptoms of the “lumbar” subset will arise in the lower limbs. In ALS, affected cells include the upper motor neurons (UMN) in the motor cortex and/or lower motor neurons (LMN) in the brainstem and spinal cord. Presentation of pure UMN symptoms, sometimes referred to as primary lateral sclerosis (PLS), includes decelerated speech, weakness and spasticity, hyperreflexia, pseudobulbar affect (inappropriate emotionality including bursts of crying or laughing). Presentation of pure LMN symptoms, known as progressive muscular atrophy (PMA), includes severe weakness and hyperreflexia, in addition to loss of muscle tone, muscle atrophy, cramps and twitching (termed fasciculations) (Sathasivam 2010; Lomen-Hoerth 2008). A combination of UMN and LMN symptoms may also occur. Onset is usually asymmetrical, although progressive wasting and spreading will most likely ensue (Swash 1998).

Fewer patients have “bulbar onset” ALS, which targets muscles of the face and neck; this form is more common in women and the elderly (Forbes, Colville, and Swingler 2004; McCombe and Henderson 2010) and has a worse prognosis. Symptoms of the UMN-based bulbar variant (pseudobulbar palsy) include emotional responses (as mentioned above), slurred speech (dysarthria), excessive yawning and jerking of the jaw (Wicks 2007; Kuhnlein et al. 2008). The LMN-based affliction (bulbar palsy) manifests as tongue fasciculation resulting in dysarthria, drooling, difficulties in swallowing (dysphagia) and wasting of the tongue (Kuhnlein et al. 2008). Several rare, additional phenotypes exist, including a respiratory onset form, which shares the poorest prognosis with the bulbar onset form (Chio et al. 2011).

The characteristic clinical course of ALS is a progressive loss of voluntary movement, with symptoms spreading to more distant locations (Haverkamp, Appel, and Appel 1995), and the end result being paralysis and death from respiratory failure. Treatment with a ventilator may assist breathing and improve the quality of life (Radunovic et al. 2009). However, eventually the patient may enter a “locked-in” state, where communication is only possibly with the help of an electronic device, and ultimately, even oculomotor function may be impaired (Sharma et al. 2011). In addition to facial, limb and behavioral impairments, frontotemporal dementia (FTD) occurs in a subset of ALS patients (Murphy, Henry, and Lomen-Hoerth 2007), with negative implications for treatment and survival (Olney et al. 2005). Frontotemporal dementia (FTD) patients can also display ALS-like symptoms, suggesting that some aspects of these two diseases may overlap (Ferrari et al. 2011). Unfortunately, treatment of ALS is mostly palliative; the sole approved drug, riluzole (as discussed in section 4), extends life for only a few months (Miller et al. 2007). Typically, half of diagnosed ALS patients will succumb to the disease within about 3 years, 20-25% within 5 years and a small minority can survive 10 years and beyond (Talbot 2009; Testa et al. 2004; Forsgren et al. 1983). Post-mortem staining of the degenerating tissues in motor neurons of the motor cortex, brainstem and spinal cord with eosin and hematoxylin may reveal Bunina bodies and/or ubiquitin-positive-inclusions of the skein-like or hyaline form (most commonly the Lewy body-like variety), among others (Leigh et al. 1991). Thus, the underlying multi-pathway cellular dyshomeostasis leading to the complicated, heterogeneous

clinical phenotypes associated with ALS and its variants so far remains mysterious and is under intense investigation.

The distinction between familial and sporadic cases of ALS is not always clear-cut, due to incomplete genetic penetrance, complicating environmental factors and diagnostic difficulties. FALS has been attributed to approximately 5% of ALS cases (Byrne and Hardiman 2010; Talbot 2010), although higher levels in certain geographical regions have been reported (Haberlandt 1959; Murros and Fogelholm 1983). It has been suggested that even rates for the familial disease as high as 13.5% might be underestimates (Andersen 2006), due to the complicating variable of reduced penetrance in some families, causing miscategorization of some FALS cases as SALS (Williams, Floate, and Leicester 1988). FALS is usually inherited in a Mendelian, autosomal dominant manner (Veltema, Roos, and Bruyn 1990), with autosomal recessive and X-linked modes of inheritance occurring rarely (Donkervoort and Siddique 1993; Andersen et al. 1996). The clinical symptoms of FALS and SALS are generally similar, but may be more homogeneous within individual FALS-afflicted families than between them (Horton, Eldridge, and Brody 1976). The mean age of onset at about 48-52 years for FALS (Mulder et al. 1986; Li, Alberman, and Swash 1988) is earlier than the mean at approximately 56 years for SALS (Li, Alberman, and Swash 1988; Haverkamp, Appel, and Appel 1995) and the survival period is also shorter for FALS than for SALS (Mulder et al. 1986). A small minority of ALS patients exhibit juvenile onset (usually before age 25), which is generally characterized by longer survival (Aggarwal and Shashiraj 2006; Ben Hamida, Hentati, and Ben Hamida 1990). Juvenile-onset ALS can occur in an autosomal dominant form, linked to several known genes (Blair et al. 2000) or in a form that may be recessive or sporadic (Hadano et al. 2001).

The lifetime risk of ALS is about 1 in 400, [in the United Kingdom (Alonso et al. 2009)], yet due to the very short survival rate of about 3 years (Donkervoort and Siddique 1993), the disease prevalence is low, ranging from only 0.8 per 100,000 people (in Mexico) to 8.4 per 100,000 (in Sweden) (Olivares, Esteban, and Alter 1972; Gunnarsson and Palm 1984). The yearly incidence of ALS globally varies only slightly worldwide, from as few as 0.3 diagnoses per 100,000 persons in Hong Kong-China (Fong et al. 1996) to 2.4 cases per 100,000 in Finland (Fong et al. 1996), excepting a few, documented, high-occurrence clusters [e.g. an ALS-Parkinsonism-like disease frequency in Guam of up to 100 times greater than average in the middle of the 20<sup>th</sup> century (Steele and McGeer 2008)]. More studies of non-Caucasian populations are needed to evaluate ALS rates across all ethnic groups (Cronin, Hardiman, and Traynor 2007). The gender ratio for ALS varies somewhat between studies, and with factors such as age and ethnicity (McCombe and Henderson 2010; Abhinav et al. 2007) but consistently shows an increased risk for males. This variability may be due to regional, environmental or genetic differences among patients or, to a decrease in the skewing of ALS cases toward men over time (Worms 2001). Interestingly, the ratio also tends more toward gender equality in FALS than in SALS (Mulder et al. 1986; Li, Alberman, and Swash 1988).

No diagnostic test for ALS is currently available. The Revised El Escorial criteria (Brooks et al. 2000), developed by the World Federation of Neurology, are a set of findings used in the diagnosis of ALS. They categorize the case as “definite,” “probable” or “possible,” based on clinical UMN and LMN observations and electrophysiological data. These criteria are commonly used for participation in clinical trials, although they have been suggested to be inappropriate for general clinical practice (Andersen et al. 2005) and not sensitive enough as an early diagnostic tool (Kiernan et al. 2011). Earlier diagnosis is in fact highly associated

with a longer survival (Testa et al. 2004; Haverkamp, Appel, and Appel 1995), although the median duration between first symptoms and diagnosis was found to be about a year for many cases (Chio 1999; Spuler et al. 2011). Another measure sometimes used in research or private practice is the revised ALS Functional Rating Scale (ALSFRS-R), a scoring tool to monitor the disease progression of patients (Cedarbaum et al. 1999). These measures and others [e.g. the Awaji criteria, (de Carvalho et al. 2008)] are undoubtedly useful. However, objective laboratory tests (e.g. for ALS-specific blood or cerebrospinal fluid biomarkers) would represent a major stride in diagnosis, and some progress is underway in this area (Turner et al. 2009), though validation is still needed.

Current diagnosis of ALS is typically by process of elimination. The trained clinician will assess the presence of UMN and/or LMN symptoms and any evidence of disease progression, then test to eliminate potentially overlapping syndromes. For FALS, the presence of an affected family member can aid diagnosis, and trigger genetic testing, if appropriate (Andersen 2000). Due to the heterogeneity of presentation (Chio et al. 2011), the exclusion of ALS mimics is a very important part of diagnosis. Conditions with overlapping symptoms may include spinal disease or injury (e.g. compression), enzyme or vitamin deficiency (B-12 etc.), cancers, myopathy, neuropathy, infections such as Lyme or HIV, thyroid problems, myasthenia gravis, Kennedy's disease, Tay-Sachs diseases, lead poisoning and multiple sclerosis, among others (Sathasivam 2010; Lomen-Hoerth 2008; Traynor et al. 2000; Silani et al. 2011). Elimination of these ALS mimics is non-trivial, especially since misdiagnosis is very common (Chio 1999; Traynor et al. 2000). Conversely, false positive diagnosis of ALS (estimated at around 10%) can also have marked impacts on patient prognosis and treatment (Davenport et al. 1996; Ludolph and Knirsch 1999). Magnetic resonance imaging (MRI) is one of the most commonly performed diagnostic tests to image the condition of the brain and neck, to eliminate injury as a cause of symptoms. Electromyography (EMG) and nerve conduction studies are useful for evaluating muscle and nerve status. Blood tests (to determine blood count, erythrocyte sedimentation, specific enzyme abnormalities such as creatine kinase) are also useful (Talbot 2009). Less commonly, CSF tests, psychological tests and muscle biopsies are performed to rule out other conditions. Therefore, diagnosis is made by careful examination of the clinical presentation coupled to evaluation by laboratory tests.

### 3. Pathophysiology

Despite a multitude of genetic, biochemical, cellular and clinical investigations, current ALS research suggests that there is no definitive single cause for the disease and/or that the cellular pathways involved employ much complexity. Thus, further research is required on all fronts to elucidate the underlying pathophysiological mechanisms. We focus on several key disease-implicated proteins, and discuss advances and controversies in our understanding of how mutations may give rise to the disease. We include our own studies on ALS-linked mutations in Cu,Zn superoxide dismutase (SOD), which account for a very significant proportion of genetically defined FALS cases. We also address other genetic factors and environmental influences that have been implicated in ALS.

#### 3.1 Genetic factors

Many recent significant advances in ALS research result from investigations of genetic lesions and their consequent biological defects leading to the disease. Most of these genetic

abnormalities in ALS alter expressed proteins through missense and nonsense mutations, but some genetic linkages are presently not yet connected to a specific underlying protein defect. ALS cases arising from genetic defects have been further divided into subtypes dependent on gene mapping, linkage analysis and phenotype (Table 1). The more characterized subtypes are referred to as ALS1 through ALS14. We have also included in Table 1 several other genes implicated in ALS susceptibility (Al-Chalabi et al. 1999; He and Hays 2004; Munch et al. 2005; Munch et al. 2004). Below, we describe the distribution of >130 distinct mutations in ALS1 (Cu,ZnSOD) within the protein structure, and provide current hypotheses for how this multitude of distinct substitutions affect Cu,ZnSOD structure and function, leading to an ALS phenotype. We also focus on proteins involved in predominately sporadic ALS cases. In particular, we highlight recent results that point to mutation-induced dysfunctions of ALS6 (FUS/TLS) and ALS10 TDP-43 (also involved in certain familial ALS cases), two proteins that are involved in DNA/RNA synthesis and gene regulation, implicating a role for RNA metabolic defects in the disease.

ALS Sub-type	Gene	MIM Gene Number	Locus	Protein	MIM Phenotype	Age of Onset	Notes
ALS1	<i>SOD1</i>	147450	21q22.1   21q22.11	Cu,Zn superoxide dismutase	105400	Adult	AD, AR, Sp
ALS2	<i>ALS2</i>	606352	2q33.1	Alsin	205100	Juvenile	AR
ALS3	-	-	18q21	-	606640	Adult	AD
ALS4	<i>SETX</i>	608465	9q34.13	Senataxin	602433	Juvenile	AD
ALS5	<i>SPG11</i>	-	15q15-q21.1	Spatacsin	602099	Any age	AR
ALS6	<i>FUS</i>	137070	16p11.2	Fused in sarcoma	608030	Adult	AD, AR, Sp
ALS7	-	-	20p13	-	608031	Adult	AD
ALS8	<i>VAPB</i>	605704	20q13.33	VAMP-associated protein B	608627	Adult	AD
ALS9	<i>ANG</i>	105850	14q11.1-q11.2	Angiogenin	611895	Adult	AD, Sp
ALS10	<i>TARDBP</i>	605078	1p36.22	TDP-43	612069	Adult	AD, Sp
ALS11	<i>FIG4</i>	609390	6q21	Phosphoinositide 5-phosphatase	612577	Adult	AD
ALS12	<i>OPTN</i>	602432	10p13	Optineurin	613435	Adult	AD, AR, Sp
ALS13	<i>ATXN2</i>	601517	12q24.1	Ataxin-2	183090	-	Suscept
ALS14	<i>VCP</i>	601023	9p13.3	Valosin-containing protein	613954	Adult	AD
-	<i>DCTN</i>	601143	2p13	Dynactin	105400	-	Suscept
-	<i>NEFH</i>	162230	22q12.2	Heavy neurofilament subunit	105400	-	Suscept
-	<i>PRPH</i>	105400	12q12-q13	Peripherin	105400	-	Suscept
-	<i>UBQLN2</i>	-	Xp11.2	Ubiquilin	-	Any age	X-linked

Table 1. ALS subtypes. ALS phenotypes map to many chromosomal loci, and often to specific proteins implicated in the disease. Data for this table were compiled from the Online Mendelian Inheritance in Man® (MIM) website (<http://omim.org>) and other sources (Pasinelli and Brown 2006; Ticozzi et al. 2011; Boillee, Vande Velde, and Cleveland 2006; Deng et al. 2011) MIM gene and phenotype numbers are included for reference. Abbreviations in Notes column: AD, autosomal dominant; AR, autosomal recessive; Sp, sporadic; Suscept, aids susceptibility to ALS; X-linked, Chromosome X linkage

### 3.1.1 Cu,Zn superoxide dismutase

Cu,ZnSOD was first isolated from bovine erythrocytes in the late 1930s (Mann and Keilin 1938). The protein was then termed hemocuprein for its copper content, apparent from the blue color of the crystalline protein. In the 1950s, Cu,ZnSOD was purified from brain (Porter and Folch 1957), where it accounts for approximately 1% of neuronal cytosolic protein (Siddique and Deng 1996). McCord and Fridovich biochemically characterized the protein in 1969, and discovered that it catalyzed the dismutation of superoxide radicals to hydrogen peroxide and oxygen (McCord and Fridovich 1969). Reactive oxygen species, such as

superoxide, were subsequently linked to aging and to many diseases. This cytosolic protein was discovered to be unusually stable, surviving organic extraction in the original purifications (McCord and Fridovich 1969) and maintaining enzymatic activity under harsh conditions, such as denaturants and heat (Forman and Fridovich 1973; Malinowski and Fridovich 1979; Hallewell et al. 1991). Our labs routinely use heat denaturation of host proteins when purifying Cu,ZnSOD from heterologous expression systems (Shin et al. 2009). This unusual enzymatic stability could be involved ALS etiology.

Members of our groups have analyzed the biochemical, biophysical and structural properties of wild-type and ALS-linked mutant Cu,ZnSOD proteins. The first Cu,ZnSOD X-ray crystal structure (Tainer et al. 1982; Tainer et al. 1983), revealing the fold and structure-based mechanism of catalysis, was from the bovine enzyme and was later followed by our crystal structure of human Cu,ZnSOD (Figure 1) (Parge, Hallewell, and Tainer 1992).

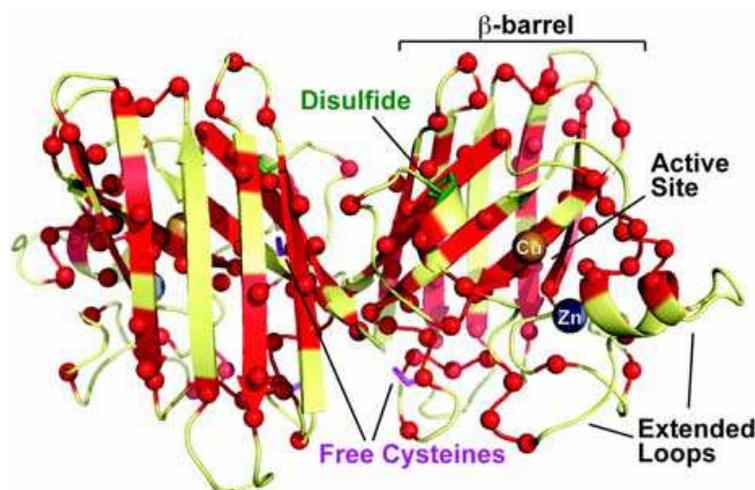


Fig. 1. Human Cu,ZnSOD crystal structure (PDB ID 1PU0) and known ALS mutation sites. Cu,ZnSOD exists as a homodimer and each subunit consists of a single Greek-key motif barrel-like domain, flanked by extended loops that form the active site cleft and house catalytic Cu and Zn ions (large labeled spheres). The smaller red spheres denote C $\alpha$  ALS mutation site positions mapped onto this cartoon representation of the protein. The conserved disulfide bond (green) in each subunit conveys stability, while free cysteine residues (magenta) are implicated in irreversible unfolding

Our latest published structures of Cu,ZnSOD (Shin et al. 2009) were derived from the eukaryotic thermophile *Alvinella pompejana*, a deep-sea thermal vent worm that we and others discovered contains particularly stable proteins (Burjanadze 2000; Henscheid et al. 2005; Kashiwagi et al. 2010; Piccino et al. 2004). *Alvinella pompejana* Cu,ZnSOD allowed us to obtain both the first sub-angstrom resolution crystal structure of Cu,ZnSOD, and a co-crystal structure with the H<sub>2</sub>O<sub>2</sub> product. These structures revealed that the copper ion likely moves within the active site during catalysis (Shin et al. 2009). Structural and computational analyses showed that electrostatic guidance (Getzoff et al. 1992; Getzoff et al. 1983; Perry et al. 2010) aids catalysis, allowing Cu,ZnSOD to be one of the fastest enzymes known.

Our initial structural studies on human Cu,ZnSOD were conducted prior to the discovery that ALS was correlated with mutations in Cu,ZnSOD (Deng et al. 1993; Rosen 1993). Greater than 130 Cu,ZnSOD mutations, occurring at ~70 of the 153 amino acids that comprise a single subunit of human Cu,ZnSOD (Figure 1), are now implicated in causing ALS; the

vast majority of these are autosomal dominant in inheritance. These Cu,ZnSOD associated ALS mutations also constitute the majority of ALS cases that have been genetically defined, approximately 20% of FALS cases and ~1-3% of SALS cases. Mapping of the ALS mutations onto the human Cu,ZnSOD structure prompted our suggestion of a 'framework destabilization' hypothesis (Deng et al. 1993). This destabilization hypothesis suggests that ALS SOD mutations promote local unfolding events in Cu,ZnSOD that can drive self-aggregation and potentially aberrant interactions with other proteins, dysregulating the normal cellular functions of this highly abundant protein in neuronal cells.

Alternative hypotheses include a gain of function mechanism, for example a change of SOD chemistry so that the enzyme performs other reactions (such as peroxidation and increased tyrosine nitration), or exhibits an increase or decrease in catalytic activity (Beckman et al. 1993; Brown 1995; Crow et al. 1997; Rosen 1993; Wiedau-Pazos et al. 1996; Wong and Borchelt 1995; Zhang et al. 2002). However, support for these other hypotheses is unclear. Certain mutations are known to make a more active enzyme, while others produce a less active protein, and some have with relatively unchanged chemistry. Some mutations (such as H46R and H48Q) remove copper binding, rendering the protein non-catalytic, thus suggesting that gain of enzymatic function or increased activity is unlikely. Transgenic mice harboring SOD1 mutations present ALS-like symptoms (Gurney et al. 1994), but transgenic SOD1 knockout mice do not (Reaume et al. 1996). This indicates that a loss of normal catalytic activity or a gain of abnormal activity may not be important in propagating ALS. Also, activity-altering mutations would be expected to be focused in and around the active site, rather than occurring across the entire Cu,ZnSOD fold.

Protein aggregates are observed within neural cells from Alzheimer's, Huntington's and Parkinson's individuals (Dobson 2001; Soto 2001; Wanker 2000). Likewise, proteinaceous aggregates were discovered in neurons of ALS patients (Leigh et al. 1991). We observed *in vitro* that purified FALS A4V and H43R mutants form fibrous aggregates, and that two free cysteines within the protein are not required for this aggregation. These two ALS mutants bound Congo Red and Thioflavin T dyes that typically bind amyloid-like  $\beta$ -sheet structures (Figure 2) (DiDonato et al. 2003). Notably, the kinetics of forming aggregates and the binding affinity for dyes were more enhanced for the more clinically aggressive mutant A4V mutant. In cellular inclusions, aggregates were found to be immunoreactive for Cu,ZnSOD, and did not dissociate readily in the presence of detergents or reductants (Bruijn et al. 1998; Durham et al. 1997). Also, the detection of Cu,ZnSOD-containing inclusions often precedes ALS-like symptoms, and the aggregates are similar to Lewy bodies found in Parkinson's disease (Johnston et al. 2000; Kato et al. 2001).

ALS mutant SODs interact and/or co-precipitate with additional proteins to form the inclusions observed in cells from ALS patients; these inclusions resemble those characteristic of other neurodegenerative disease. These associated proteins include 1) proteins involved in stress response pathways, namely Derlin-1 (Nishitoh et al. 2008) and Rac1 (Harras et al. 2008), 2) chromogranin proteins associated with neurosecretory vesicles (Urushitani et al. 2006), 3) the cytosolic chaperone Hsc70 (Wang et al. 2009), 4) the SOD copper chaperone (Kato et al. 2001), and 5) the dynein complex heavy chain, which is used in neural retrograde transport (Kieran et al. 2005; Zhang et al. 2007). Thus, local destabilizing SOD1 mutations, leading to interactions and/or co-precipitation of these proteins within aggregates, may impact normal cellular functions. It was also recently discovered that neural membrane fluidity was altered in transgenic ALS mice that harbor a FALS SOD mutation (Miana-Mena et al. 2011). The authors hypothesize that membranes may be altered through lipid

peroxidation, yet misfolded SODs may also play a role by interacting with membranes. Other hypotheses for the involvement of mutant SOD in ALS include disruption of the ubiquitin and proteasome system, altering mitochondrial function, playing a role in glutamatergic neurotransmission leading to excitotoxicity, and interference with axonal transport systems (Bastos et al. 2011; Kiernan et al. 2011; Ticozzi et al. 2011). Thus, we suggest that the framework destabilization hypothesis, unlike other suggested hypotheses, provides a unified mechanism for ALS mutant phenotype: This hypothesis encompasses the widespread distribution of ALS mutation sites within the protein, and is further supported by the observed *in vitro* aggregation results and the cellular analyses that are also in keeping with other aggregation-prone neurodegenerative diseases.

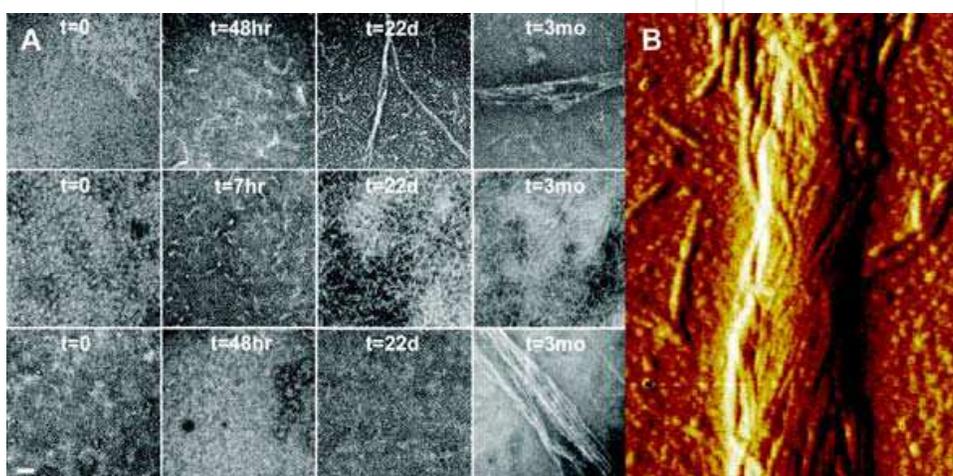


Fig. 2. FALS SOD mutants promote the formation of filamentous aggregates. (A) Electron micrographs of H43R and A4V fibers reveals diameters of 2-15 nm implying a loss of dimer assembly specificity. Samples of H43R (top row), A4V (middle row) and wild-type (bottom row), all in the C6A, C111S SOD background lacking free Cys, were subjected to conditions designed to perturb the SOD fold. The scale bar = 40 nm. (B) Atomic force micrograph (phase mode) of large H43R bundles. Adapted from (DiDonato et al. 2003)

### 3.1.2 FUS/TLS

The *FUS* gene, representing the ALS6 subtype of amyotrophic lateral sclerosis, encodes the “fused in sarcoma” protein, initially characterized as one of the fusion proteins generated by carcinogenic oncogenes (Crozat et al. 1993; Rabbitts et al. 1993). The alternative name TLS stands for “translocation in liposarcoma”, and the gene product is often referred to as FUS/TLS, as we will do for the remainder of this chapter. FUS/TLS is a 526 amino acid protein of the TET family (which stands for Translocated in liposarcoma/Ewing's sarcoma/TATA-binding protein-associated factor 15). FUS/TLS binds both DNA and RNA, and like Cu,ZnSOD, is ubiquitously expressed. The protein is divided into distinct motifs and regions, which are responsible for different functions [see Figure 3 and the following reviews (Dormann and Haass 2011; Lagier-Tourenne and Cleveland 2009; Perry, Shin, and Tainer 2010)]. FUS/TLS plays a role in transcription activities within the cell via interactions with a variety of proteins, including transcription factors and hormone receptors (Cassiday and Maher 2002; Lagier-Tourenne and Cleveland 2009) (Cassiday and Maher 2002; Lagier-Tourenne and Cleveland 2009; Law, Cann, and Hicks 2006). FUS/TLS may also function in DNA damage responses by binding to non-coding RNA elements transcribed by the 5'

regulatory region of the cell-cycle kinase cyclin D1 gene. This binding event recruits FUS/TLS to interact with and inhibit CREB-binding protein and p300 histone acetyltransferase, further repressing cyclin D1-mediated transcription (Perry, Shin, and Tainer 2010). FUS/TLS has also been implicated in RNA processing, such as splicing, transport and maturation (Lagier-Tourenne and Cleveland 2009). In neurons, FUS/TLS is transported to dendritic spines upon activation of glutamate receptor mGluR5 (Fujii et al. 2005).

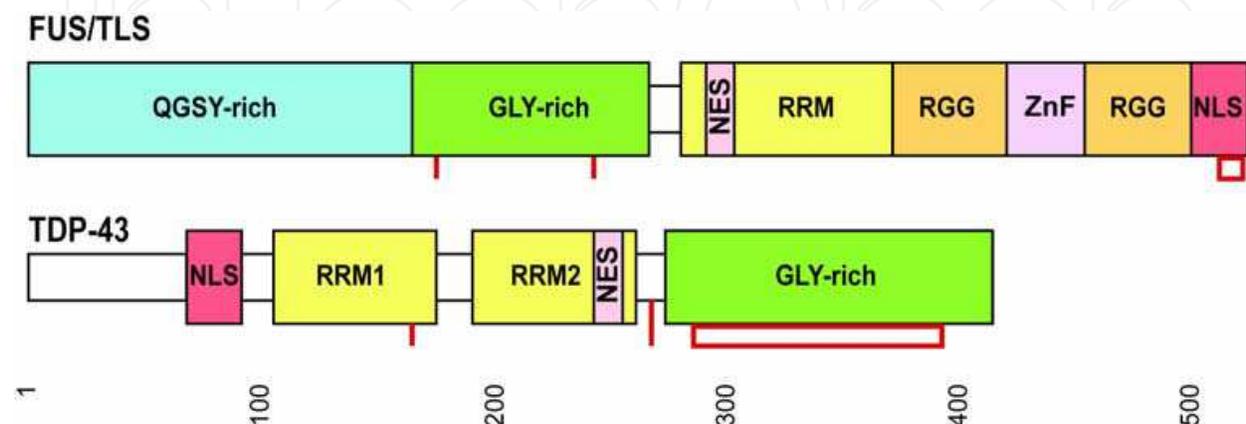


Fig. 3. Schematic diagrams of the FUS/TLS and TDP-43 proteins. Both proteins contain similar motifs, bind DNA and RNA, and are involved in both ALS and FTD. (Top) FUS/TLS contains QGSY- and Gly-rich regions, an RNA recognition motif (RRM) with a nuclear export signal (NES), a pair of RGG-motifs flanking a Zinc-finger (ZnF), and a nuclear localization signal (NLS). (Bottom) The TDP-43 protein has its NLS at the N-terminus, two RRM motifs with the latter containing an NES, and a C-terminal Gly-rich region. Red bars indicate ALS mutation sites, and red boxes indicate ALS hotspots that contain multiple ALS mutation sites. Numbers below indicate amino acid positions

The *FUS* gene was implicated in ALS after the discovery that a locus within chromosome 16 was linked to both autosomal dominant (Ticozzi et al. 2011; Vance et al. 2009) and recessive manifestations of the disease (Kwiatkowski et al. 2009). *FUS* mutations have since been identified in patients with sporadic ALS, and according to recent reviews [see (Kiernan et al. 2011; Ticozzi et al. 2011)], *FUS* mutants are estimated to account for approximately 4-5% of FALS and 1% of SALS cases. Interestingly, mutations in FUS/TLS are also involved in FTD [see (Mackenzie, Rademakers, and Neumann 2010)]. The disease-promoting mechanisms in mutant *FUS*-mediated ALS are not understood, but aggregate formation has been observed (Deng et al. 2010; Vance et al. 2009; Dormann and Haass 2011). The FUS/TLS mutations tend to cluster mainly at the C-terminal glycine-rich region and NLS (Dormann and Haass 2011; Lagier-Tourenne and Cleveland 2009; Perry, Shin, and Tainer 2010), instead of throughout the entire structure as observed in Cu,ZnSOD. Similar to Cu,ZnSOD mutant pathology is the observation that inclusions containing FUS/TLS are found within the cytosol within diseased neural cells (Dormann et al. 2010). Interestingly, NLS mutations that yield a greater concentration of FUS/TLS within the cytosol correlate with a more rapid onset and aggressiveness of the disease. Also, some of the most severe NLS mutations cause substitutions in amino acids required for an interaction with transportin, a nuclear import receptor (Dormann et al. 2010). Mutant cytosolic FUS/TLS may also be incorporated into stress granules that may serve as an inclusion precursor (Dormann and Haass 2011).

Additionally, FUS/TLS has been predicted to contain prion-like regions within its amino-acid sequence, which may also contribute to the formation of aggregates (Udan and Baloh 2011).

### 3.1.3 TDP-43

TDP-43, named for binding to TAR DNA of the human immunodeficiency type 1 virus, is also a DNA and RNA binding protein like FUS/TLS. TDP-43 is encoded by the *TARDBP* gene, and is classified as the ALS10 subtype. TDP-43 is composed of 414 residues, and includes functional motifs shared with FUS/TLS (Figure 3). Functions for TDP-43 include transcriptional regulator (Abhyankar, Urekar, and Reddi 2007; Ayala, Misteli, and Baralle 2008), and TDP-43 was also implicated in binding UG-repeat sequences, resulting in pathogenic consequences that include cystic fibrosis (Mantovani et al. 2007). Like FUS/TLS, TDP-43 has been implicated in both ALS and FTD pathology (Arai et al. 2006; Mackenzie, Rademakers, and Neumann 2010; Dormann and Haass 2011; Perry, Shin, and Tainer 2010). Presently, over 35 mutations in TDP-43 have been implicated in these two diseases, including ~0.5-2% of sporadic ALS cases (Arai et al. 2006) and ~3-5% of autosomal dominant FALS cases (Lagier-Tourenne and Cleveland 2009; Ticozzi et al. 2011). TDP-43 aggregates are also found within diseased neural cells, where the protein is found to be highly ubiquitinated and phosphorylated, as well as being truncated (Arai et al. 2006; Neumann et al. 2006). These aggregates are generally localized to the cytoplasm, while nuclear levels of TDP-43 are significantly diminished. Interestingly, analysis of the aggregates suggests that these deposits are not composed of amyloid-like structures (Kwong et al. 2008). Cu,ZnSOD is not found within the TDP-43 or the FUS/TLS aggregates; however, a recent report states that mutant Cu,ZnSOD interacts with TDP-43 (Higashi et al. 2010), and was shown to co-immunoprecipitate with FUS/TLS for a function in stabilizing histone deacetylase 6 (HDAC6) mRNA (Kim et al. 2010). ALS mutations in TDP-43 appear to enhance this interaction with FUS/TLS (Ling et al. 2010). Therefore, additional research is required to clearly define these provisional links between TDP-43, FUS/TLS and/or Cu,ZnSOD in ALS pathology.

The majority of mutations found within TDP-43 ALS patients are missense mutations toward the C-terminal end of the protein, beginning at the glycine-rich segment. Recent research has identified the possibility that like FUS/TLS, TDP-43 also contains a prion-like element at its C-terminus. This region contains Gln and Asn residues similar to yeast Q/N prion domains. This represents yet another structural element that may initiate the formation of aggregates within ALS10 type cells. Currently, research on the function of TDP-43 and its roles in various pathologies including ALS and FTD is on the rise. Changes in TDP-43 structure and stability behind its ALS pathology may also influence the expression and activities of various cellular machinery within neural cells [see detailed reviews: (Dormann and Haass 2011; Lagier-Tourenne and Cleveland 2009; Lagier-Tourenne, Polymenidou, and Cleveland 2010; Perry, Shin, and Tainer 2010; Swarup et al. 2011)].

### 3.1.4 Other ALS subtypes

Research is being initiated on the defective genes for the other, more rare, ALS subtypes [see more detailed reviews (Boillee, Vande Velde, and Cleveland 2006; Kiernan et al. 2011; Pasinelli and Brown 2006; Strong et al. 2007; Ticozzi et al. 2011) for further information on these lesser-characterized ALS subtypes]. Many proteins encoded by these ALS subtype genes share the ability to modulate gene expression and/or RNA metabolism; this includes

the *ANG* (ALS9) and *SETX* (ALS4) gene products, along with those of *FUS/TLS*, *TDP-43* and *SOD1* (Strong 2010). Also, the *VAPB* (ALS8) mutant shares the ability to form aggregates (Suzuki et al. 2009). Notably, the native alsin protein encoded by the *ALS2* gene has been observed to offer protection against Cu,ZnSOD mutational effects in certain cells (Hadano et al. 2007). Many mutations in *ALS2* are nonsense mutations that lead to truncations in the gene product, which can destabilize the protein, resulting in proteasomal degradation (Yamanaka et al. 2003). Another study suggests that alsin loss may cause neurons to be more vulnerable to excitotoxicity, via glutamate receptors (Lai et al. 2006). Co-localization has not yet been observed between Cu,ZnSOD and *FUS/TLS* or *TDP-43*. However, optineurin, which is encoded by *OPTN* and represents ALS12, does appear to colocalize with Cu,ZnSOD, *FUS/TLS* and *TDP-43* [see (Ito et al. 2011)], and the interaction of optineurin with at least with the former two, appears to be mutually exclusive. A comprehensive study of a five generation family with ALS lead to the discovery that mutations in *UBQLN2*, which encodes the ubiquitin-like protein ubiquilin 2, cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia (Deng et al. 2011). Also, excitingly, two very recent research findings have identified the largely uncharacterized locus 9p21 *C9ORF72* gene product to be linked to a significant proportion of dominant cases of ALS/FTD (Renton et al, 2011; DeJesus-Hernandez et al. 2011) Thus, it currently appears that genetic lesions may lead to ALS by different pathways, and continued research will be needed to establish whether there are one, several or many more general mechanistic themes that lead to the ALS phenotypes.

### 3.2 Other factors

Non-genetic risk factors for ALS, including environmental factors and physical injury, are being actively pursued. Although the effects of these risks of ALS are difficult to deconvolute (e.g. the prevalence of ALS in athletes), the involvement of these factors may enhance underlying, genetic predispositions to the disease, or may indeed have a direct link to ALS.

#### 3.2.1 Diet/Lifestyle

The role of diet in ALS was assessed when considerably higher prevalence levels of ALS were noted in certain Western Pacific populations (50-100-fold). Non-genetic causes for these ALS cases have been suggested to be due to high levels of  $\beta$ -methyl-amino-L-alanine. This non-standard amino acid is highly concentrated in a certain seed that is consumed by animals that provide food for the inhabitants of Guam (Bastos et al. 2011; Ince and Codd 2005). A recent study has highlighted adverse effects from high levels of branched-chain amino acids (BCAAs) on the ion channels of mice. The researchers discovered an increased sodium current within motor neurons, resembling that observed in the transgenic Cu,ZnSOD G93A mouse model for ALS. The increased sodium current promotes hyperexcitability of the cells, which may lead to excitotoxicity, subsequent calcium influx and apoptosis (Carunchio et al. 2010; Manuel and Heckman 2011). BCAAs are commonly used as a supplement by athletes, and therefore might account for the increased incidence of ALS seen in Italian soccer (Chio et al. 2005) and American football (Abel 2007) players.

Smoking was proposed as another potential risk factor for ALS (Kamel et al. 1999), and continues to provoke interest (Armon 2009). Several studies reported no ill effects of smoking on ALS (Schmidt et al. 2010) (Okamoto et al. 2009), others implicated a gender-specific effect (Alonso et al. 2010), and a recent study of 832 ALS patients suggested smoking increased ALS incidence by  $\sim 1.4$  fold (Wang et al. 2011).

### 3.2.2 Injury and trauma

Neuronal injury may result in excessive stimulation by  $\alpha$ -amino-hydroxy-5-methylisoxasole-4 propionic acid (AMPA), glutamate or kainite, leading to excitotoxicity and downstream apoptosis (Perry, Shin, and Tainer 2010; Beal 1992). Thus, head trauma may be linked to the increased incidence of ALS observed in Italian soccer players, American football players, and military personnel, all of whom more commonly have head injuries (Horner et al. 2008; Miranda et al. 2008). Other forms of trauma, such as electrical shock, have also been correlated to ALS [for a broader list and additional details, see the review by (Bastos et al. 2011)].

### 3.2.3 Environmental toxins

Exposure to environmental toxins is actively investigated as a potential contributing factor to ALS. Several metals have been implicated in increased risk for ALS after occupational exposure to lead, residency in areas with high levels of selenium, and accidental contact with mercury (Bastos et al. 2011). Inhabitants of Guam who exhibit ALS-like symptoms have been exposed to potentially high levels of aluminum (Wicklund 2005). More complex molecules implicated in increased risk of ALS include formaldehyde, pesticides that are suspected to cause ALS in Italian soccer players, and chemical agents to which military personnel have been subjected. Yet, a causative effect between ALS and such factors is difficult to establish. One reason for this is the relatively small sample size in some of these studies. A second reason is the difficulty in deconvoluting which specific factor or combination of factors contributed to the disease, as in the case for the soccer players. Third, some of the ALS patients within the studies may have had an undetected genetic defect, and the additional environmental factor accelerated the course of the disease.

## 4. Therapeutic progress

The only approved treatment for ALS is riluzole, which functions to reduce glutamate-induced excitotoxicity in ALS individuals, and is licensed by Sanofi-Aventis with the brand name Rilutek. Riluzole only modestly slows the progression of ALS, with a 9% gain in the probability of surviving one year, and a small beneficial effect for limb function, but not muscle strength (Miller et al. 2007). Several other drugs that gave positive results in animal models failed in human trials. However, additional clinical trials now underway are aimed at producing new ALS therapies by using varied strategic approaches that go beyond the modulation of glutamate levels [reviewed in (Zoccolella, Santamato, and Lamberti 2009)(see <http://clinicaltrials.gov>)]. Exciting progress in this regard includes the commencement of a phase I clinical trial by Neuralstem that aims to establish the safety and feasibility of using stem cells to treat ALS, by injecting these cells directly into the spinal cord (see <http://neurology.emory.edu/ALS/Stem%20Cell.html>). This development is based on initial studies showing that human fetal neuronal stem cells could delay the onset and progression in a rat model of ALS (Xu et al. 2006).

The Northeast ALS consortium (NEALS), a non-profit consortium bringing together scientific and clinical investigators from now 97 institutions across in the United States, Puerto Rico, Canada and Ireland, forms a central component of many of the clinical trials (<http://www.alsconsortium.org>). For example, as part of NEALS, a stage III trial of ceftriaxone, which has been recently observed to modulate glutamate uptake, is being conducted by Massachusetts General Hospital with the National Institute of Neurological

Disorders and Stroke. Ceftriaxone is a semi-synthetic cephalosporin antibiotic, originally approved by the FDA for treating bacterial infections. Combination therapies are also being analyzed, including a phase II a trial by Phoenix Neurological Associates LTD of riluzole in conjunction with tretinoin and pioglitazone. Tretinoin, used to treat acute promyelocytic leukemia (Sanz 2006), is a retinoic acid derivative, and as such may have neuroprotective properties (Choi et al. 2009; Lee et al. 2009). The oral anti-diabetic pioglitazone has anti-inflammatory properties that showed positive responses in an ALS mouse model (Schutz et al. 2005). Tamoxifen is currently in stage II clinical trials for treating ALS, based on an observation by clinicians that an ALS patient also receiving tamoxifen for breast cancer had an unusually mild form of the disease (see <http://www.alsa.org/research/clinical-trials/trial-tamoxifen.html>). Tamoxifen may also help protect cells from glutamate toxicity (Maenpaa et al. 2002) in addition to inhibiting protein kinase C mediated spinal inflammation and prolonging life expectancy in a mouse model of ALS (Traynor et al. 2006; Zoccolella, Santamato, and Lamberti 2009).

Several other compounds with neuroprotective activities are undergoing clinical trials. These include rasagiline, which was reported to have neuroprotective properties in an ALS mouse model (Waibel et al. 2004). Rasagiline is currently used as a therapy for Parkinson's disease, functioning as a selective inhibitor of monoamine oxidase B, and is now under phase II clinical trials for ALS treatment by the University of Kansas. Neuraltus Pharmaceuticals is targeting an anti-inflammatory response through transforming macrophage cells from a neurotoxic to a protective state, with the compound 'NP001' that is now in phase II clinical trials (see <http://www.neuraltus.com>). Biogen Idec and Knopp Biosciences have an interesting small molecule therapeutic, dextramipexole, which also has a neuroprotective function, through increasing the efficiency of mitochondria in neurons (Gribkoff and Bozik 2008). Dextramipexole is the R(+) enantiomer of an already licensed compound, pramipexole, which is used for the treatment of both Parkinson's disease and restless legs syndrome. Pramipexole functions as a non-ergot dopaminergic autoreceptor antagonist, but has dose-limiting side effects that include orthostatic hypotension and hallucination, due its dopaminergic receptor activity. Dempramipexole, on the other hand, has a much lower affinity for dopaminergic receptors, and in phase II trials was well tolerated at levels considerably higher than the maximum daily dose of pramipexole (Bozik et al. 2011). Dextramipexole also showed positive trends in slowing functional decline and improving survivability in phase II, and is now undergoing a multi-national phase III study.

Approaches specifically targeting Cu,ZnSOD include arimoclomol, a compound developed by CytRx corporation, that activates chaperones to perturb protein aggregation. Arimoclomol was observed to extend life in an ALS mutant Cu,ZnSOD mouse model (indirectly supporting the framework destabilization model for Cu,ZnSOD mutations), and is currently at the Phase II/III stage (Kalmar et al. 2008). Cornell University and the Muscular Dystrophy Association are studying pyrimethamine, an anti-malarial drug shown in one study to substantially reduce Cu,ZnSOD levels in mice (Lange 2008), although a separate study at the University of Massachusetts Medical School did not observe this pyrimethamine effect in either cells or animal models of disease (Wright et al. 2010). Moving away from small molecule based therapies, Isis Pharmaceuticals is taking an siRNA approach to combat FALS mutant Cu,ZnSOD, with Isis-SOD1RX entering into phase I clinical trials. Isis-SOD1RX is antisense oligonucleotide to SOD1 that is infused directly into the cerebral spinal fluid, due to an inability to pass the blood brain barrier. This siRNA was shown to reduce both Cu,ZnSOD protein and mRNA levels throughout the brain and spinal cord in animal models (Smith et al. 2006).

Other recent therapeutic approaches target muscle deficiencies in ALS. Cytokinetics developed 'CK-2107357', an activator of the fast skeletal muscle troponin complex, increasing cellular sensitivity to calcium, which results in an increase in skeletal muscle force and a decrease in the time to muscle fatigue. In phase IIa trials, CK-2107357 showed evidence of clinical effect, as well as being suitably safe and tolerated. Acceleron Pharma is developing ACE-031, a protein therapeutic that builds muscle and increases strength by inhibiting signaling through the activin type IIb cell surface receptor (Cadena et al. 2010). ACE-031 increased skeletal muscle mass and strength in disease models of amyotrophic lateral sclerosis (ALS), muscular dystrophy, glucocorticoid-induced muscle loss and age-related muscle loss (sarcopenia). An extended phase II clinical trial in Canada for Duchenne Muscular Dystrophy was recently terminated, and is pending further analysis of safety data.

## 5. Future research

Evidently, much work remains on all fronts from uncovering disease mechanisms to developing new therapies for ALS. The very recent publication determining that mutations in ubiquilin 2 are a cause of dominantly inherited X-linked ALS and ALS/dementia has opened up a new area of ALS research (Deng et al. 2011). Ubiquilin 2 functions as part of the protein degradation pathway, revealing pathological roles for this pathway in ALS and suggesting new therapeutic opportunities for treating ALS, since ubiquilin 2 was found in skein-like inclusions of a wide variety of ALS cases (Deng et al. 2011). Another area of important focus is improvement of animal models for ALS, as the utility of these has come into question (Benatar 2007; Bedlack, Traynor, and Cudkowicz 2007). One problem is that treatment in these animal models typical begins before the onset of disease symptoms, whereas this is not possible for ALS individuals, due to a lack of understanding of causative factors and potential differences in pathogenic mechanisms between SALS and FALS. Notably, when guidelines on improving animal study criteria were implemented, therapeutic benefits from a host of compounds that included ceftioxone and even riluzole were no longer observed (Scott et al. 2008), further highlighting issues with the use and understanding of current models. Improved experimental ALS models will also be of use to further our understanding of the causative factors of SALS, such as potentially toxic effects of smoking on motor neurons. Future therapeutic studies also need to take into consideration overcoming problems within clinical trials, such as the small sample sizes and short durations of study, making assessment of milder effects that are expected with many of the therapeutics more challenging.

Once key advance that is likely to influence the future direction of research is the generation of ALS stem cells from adult skin cells from an individual with ALS (Dimos et al. 2008). Now, stem cells from different patients can be isolated and used to grow different motor neuron cell lines for more detailed analyses, or potentially for high-throughput screening.

## 6. Conclusions

There has been some exciting progress in our understanding of ALS, including recent developments in the genetics and molecular mechanisms behind this most common form of motor neuron disease. New discoveries include the identification of two ALS-linked proteins, FUS/TLS and TDP-43, which are involved in DNA/RNA metabolism. However, we still have to clearly establish whether aggregation or loss of the wild-type functions of either of these two proteins is the underlying cause of the disease phenotype. Studies behind

the pathogenicity of Cu,ZnSOD mutations in ALS are also continuing, with the recent data supporting an initial concept that mutation-induced structural instability of the protein drives aggregation events, which ultimately prove toxic to the neuronal cell. Encouragingly, several distinct therapeutic strategies are in play aiming to at least delay the progression of the disease. These strategies range from small molecule inhibitors, some of which are in later stages of clinical trials, to siRNA and stem cell based approaches. We hope that the rapid pace of research findings and the ongoing clinical trials will shortly produce novel therapies that can help fight against this terrible disease.

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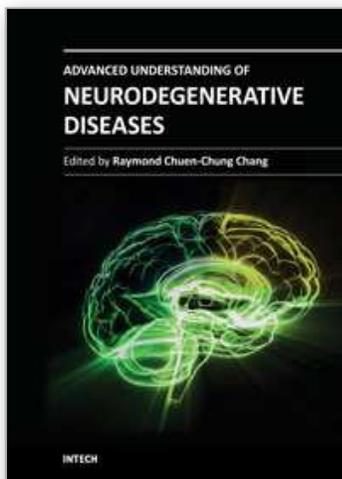
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## **Advanced Understanding of Neurodegenerative Diseases**

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Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis and spinal muscular atrophy. This book provides a clear explanation of different neurodegenerative diseases with new concepts of understand the etiology, pathological mechanisms, drug screening methodology and new therapeutic interventions. Other chapters discuss how hormones and health food supplements affect disease progression of neurodegenerative diseases. From a more technical point of view, some chapters deal with the aggregation of prion proteins in prion diseases. An additional chapter to discuss application of stem cells. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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