

REVIEW ARTICLE

Therapeutic Approaches to Amyotrophic Lateral Sclerosis from the Lab to the Clinic

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Abstract: Amyotrophic Lateral Sclerosis (ALS) is a terminal neuro-degenerative disorder that is clinically recognized as a gradual degeneration of the upper and lower motor neurons, with an average duration of 3 to 5 years from initial of symptoms to death. The mechanisms underlying the pathogenesis and progression of the disease are multifactorial. Therefore, to find effective treatments, it is necessary to understand the heterogeneity underlying the progression of ALS. Recent developments in gene therapy have opened a new avenue to treat this condition, especially for the characterized genetic types. Gene therapy methods have been studied in various pre-clinical settings and clinical trials, and they may be a promising path for developing an effective and safe ALS cure. A growing body of evidence demonstrates abnormalities in metabolic energy at the cellular and whole-body level in animal models and people living with ALS. Using and incorporating high-throughput "omics" methods have radically transformed our thoughts about ALS, strengthened our understanding of the disease's dynamic molecular architecture, differentiated distinct patient subtypes, and created a reasonable basis for identifying biomarkers and novel individualised treatments. Future clinical and laboratory trials would also focus on the diverse relationships between metabolism and ALS to address the issue of whether targeting poor metabolism in ALS is an effective way to change disease progression. In this review, we focus on the detailed pathogenesis of ALS and highlight principal genes, *i.e.*, SOD1, TDP-43, C9orf72, and FUS, as well as targeted ALS therapies. An attempt is made to provide up-to-date clinical outcomes, including various biomarkers that are thought to be important players in early ALS detection.

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1. INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease that affects adults and causes loss of motor neurons in the cortex, brain stem, and spinal cord. The estimated time of the symptoms to develop and cause death in ALS patients is about 3-5 years, yet there have been certain observations that some people live longer and have a slower disease development [1]. ALS was formerly known solely as a neuromuscular disorder, but new imaging techniques and neuropathological data have shown that disease pathology involves non-motor neuraxis [2]. In most cases, the disorder begins in late middle age and manifests as a steady progression of muscle atrophy and fatigue affecting respiratory muscles and reducing the survival rate [3]. The breakdown of upper and lower motor nerves, mostly in the motor cortex, brain stem nuclei, and the anterior horn of a spinal cord, usually causes muscular exhaustion and weakness [4]. The vast majority of ALS cases (90 percent or more) are thought to be intermittent (Sporadic/Standard ALS). Intermittent cases suggest that the illness seems to strike at random, with

no apparent risk factors and no family history of the disease. ALS shows an average annual occurrence of 1.75-3 per 100,000 people and a prevalence of 10-12 per 100,000 in Europe [5, 6]. In the age with a higher risk of developing ALS (45-75 years), the prevalence is considered to be 4-8 per 100,000 people per year [4]. According to the estimations, the chance of developing ALS is 1:350 in men and 1:400 in women [7]. UNC13A is an at-risk genotype, and ATXN2 intermediate repeat expansions increase ALS risk. Age and male sex, in addition to genetic factors, raise the likelihood of ALS [8]. Environmental risk factors for ALS have been identified in many studies, including smoking, BMI, physical activity, occupational and environmental exposures to metals, toxins, methylamino alanine, head injury, and viral infections [9, 10]. However, the causal relationship between these factors and ALS, has yet to be identified. The discovery of a hexanucleotide repeat expansion in C9orf72 (encoding guanine nucleotide exchange C9orf72) was considered a major cause of ALS and Frontotemporal Degeneration (FTD), and one of the major causes of a high prevalence of cognitive and/or behavioural effects in patients who have ALS. Such deductions have characterized ALS as a neurodegenerative disorder rather than naming it a neuromuscular condition [11]. The ALS cases have been observed worldwide; the prevalence of the Western Pacific variant of the disease is 50-100 times higher than everywhere else. There are various ways to classify ALS according to the different criteria that have been used over the years. The sub-group categories of Standard ALS are dependent on the degree of upper

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and lower motor neuron activity, while other classification schemes have various criteria, such as the onset location (bulbar-onset or spinal-onset disease), and the certainty level of diagnosis according to the updated El Escorial classification scheme [12]. There is also a significant disease variation at the genetic level, with more than 20 genes linked with ALS. The four most common genetic triggers for ALS have been identified as hexanucleotide expansions in chromosome 9 open reading frame 72 (C9orf72) and defects in superoxide dismutase 1 (SOD1), TAR DNA binding protein 43 (TARDBP), and fused in sarcoma (FUS) [8]. Molecular genetic methods have been more widely used in ALS science as technology has progressed. Genome-wide correlation experiments and “next-generation” sequencing approaches have aided the hunt for ALS-linked genes in massive sample collections and supplemented “first-generation” tools such as genetic linkage analysis [13]. With downstream consequences and possible triggers fed back into each other, unravelling the temporal aetiology of ALS remains complex. In the vast majority of instances, TDP-43 is involved in the pathogenesis of ALS [8, 14]. It is still unclear when it gets active in disease development, and the function of various TDP-related post-translational modifications. The central part of ALS care is symp-

tom control and respiratory support, with only two FDA-approved medications, riluzole, and edaravone, that tend to mildly delay the progression of the disease and only in some patients [15, 16].

2. PATHOGENESIS OF AMYOTROPHIC LATERAL SCLEROSIS

Recently, there has been a surge in genetic and animal research linking ALS to more than a dozen genetic mutations identified in genes (Table 1) that code for different proteins [11, 17]. Despite these advances, the etiology of ALS remains a mystery [18, 19]. ALS has been linked to various possible pathogenic mechanisms, including impaired proteostasis, RNA dysregulation, altered nucleo-cytoplasmic, endosomal and axonal transport, neuronal inflammation, mitochondrial dysfunction, excitotoxicity, and oligodendrocyte degeneration [20].

2.1. Impaired Proteostasis

Proteome homeostasis, also known as proteostasis, is regulated by factors that influence protein synthesis, aggregation, degradation, and trafficking. According to genetic and experimental data, impaired proteostasis appears to be an important mechanism under-

Table 1. Genes and the proteins that code in the pathogenesis of Amyotrophic lateral sclerosis.

Disease Type	Gene	Locus	Protein	Inheritance	References
ALS1	SOD1	21q22	SOD1	AD, AR	[21]
ALS2	ALS2	2q33.1	Alsin Rho Guanine Nucleotide Exchange Factor	AR	[22]
ALS3	Chromosome 18	18q21	Disulfide redox protein	AR	[23]
ALS4	SETX	9q34.13	Senataxin	AD	[24]
ALS5	SPG11	15q21.1	Spatascin	AR	[25, 26]
ALS6	FUS	16p11.2	FUS (or TLS)	AD	[27, 28]
ALS8	VAPB	20q13	VAPB	AD	[29]
ALS9	ANG	14q11.2	Angiogenin	AD	[30]
ALS10	TARDBP/TDP-43	1p36.2	TDP-43	AD	[31]
ALS11	FIG4	6q21	PI3, 5P2	AD	[32]
ALS12	OPTN	10p13	Optineurin	AD, AR	[33]
ALS13	ATXN2	12q24	Ataxin 2	AD	[34]
ALS14	VCP	9p13	VCP or p97	AD	[35]
ALS15	UBQLN2	Xp11	Ubiquilin 2	XD	[36]
ALS16	SIGMAR1	9p13.3	SIGMAR1	AR	[37]
ALS17	CHMP2B	3p11	CHMP2B	AD	[38]
ALS18	PFN1	17p13	Profilin 1	AD	[39]
ALS19	ERBB4	2q34	Receptor tyrosine protein kinase ErbB-4	AD	[40]
ALS20	HNRNPA1	12q13	hnRNP A1	AD	[41]
ALS21	MATR3	5q31.2	Matrin 3	AD	[42]
ALS22	TUBA4A	2q35	Tubulin α 4A	AD	[43]
ALS23	ANXA11	10q22.3	Annexin A11	AD	[44]
ALS24	NEK1	4q32	NIMA-RELATED KINASE 1	----	[45]
FTDALS1	C9orf72	9p21.3	C9ORF72	AD	[46]
FTDALS2	CHCHD10	22q11	Mitochondrial protein	AD	[47]
FTDALS3	SQSTM1	5q35	p62 or SQSTM1	AD	[48]

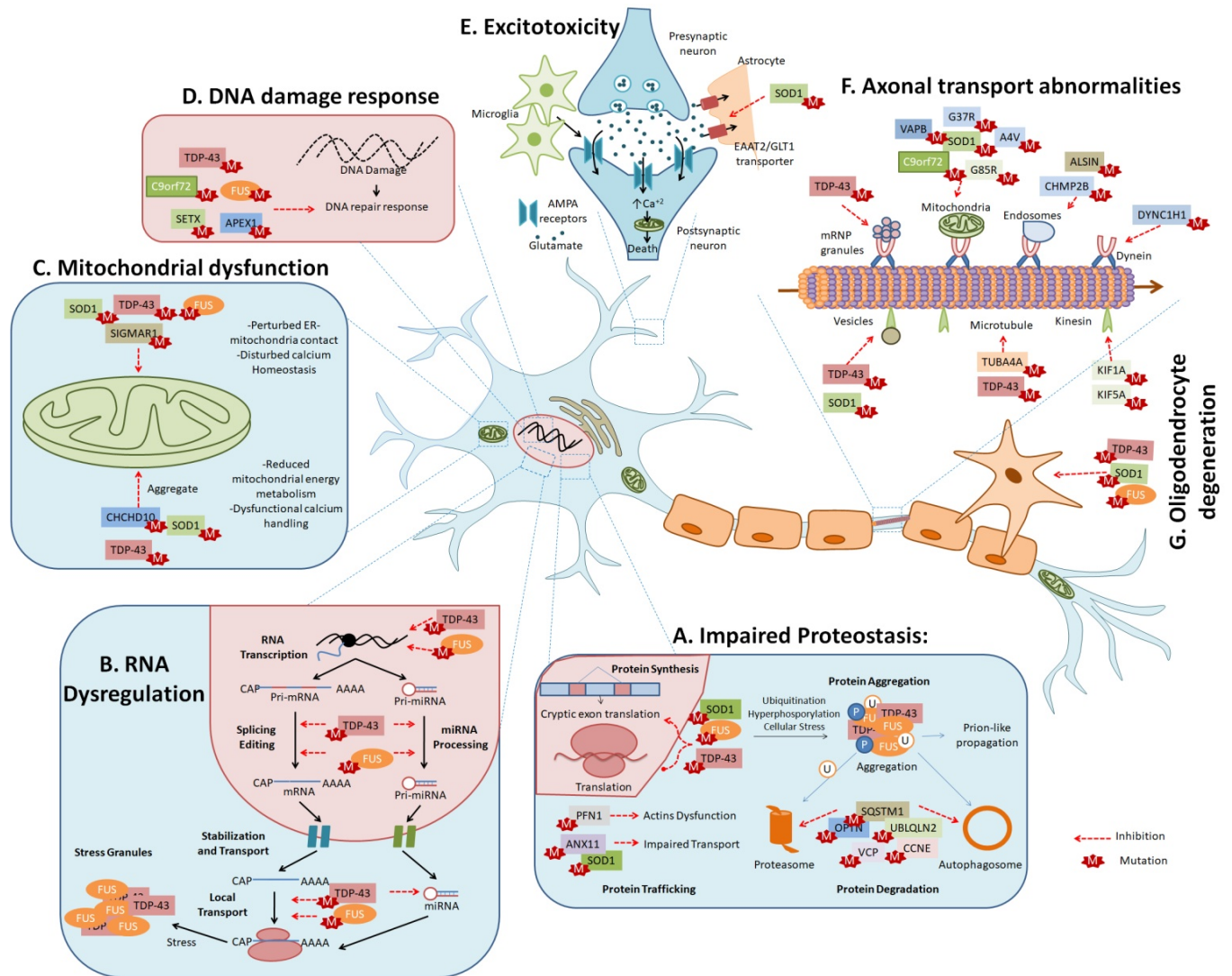


Fig. (1). Pathogenesis of amyotrophic lateral sclerosis. **A.** Impaired protein homeostasis: The genetic mutations that cause ALS are found in protein-encoding genes that participate in protein production (alternative splicing and cryptic exon repression), pathological aggregation (prion-like protein), deficient protein degradation (ubiquitin-proteasome system, and autophagy) and/or trafficking pathways and have a significant impact on the motor proteome homeostasis. Prolonged impaired proteostasis leads to neuronal dysfunction. **B.** RNA dysregulation: Major ALS mutations (TDP-43 and FUS) may alter pr-mRNA splicing, promote mi-RNA biogenesis, influence mRNA transport, impair local translation protein degradation, and increase stress granule (a transient, dynamic, membrane-less cytoplasmic structure that forms in response to cellular stress and results in translation inhibition of most mRNAs except for those involved in cellular recovery) size leading to cellular dysfunction and death. **C.** Mitochondrial dysfunction: The activity of the electron transport chain is required for the generation of cellular ATP. The activity of the complexes involved in the electron transport chain have been shown to be decreased in SOD1, TDP-43 and CHCHD10-related ALS. This results in decreased MMP and ATP generation, and increased generation of ROS. Mitochondrial stress is increased due to dysfunctional cellular pathways resulting in increased ROS generation, and mitochondrial damage. Mutant SOD1 contributes to apoptotic signalling in ALS by binding the anti-apoptotic factor Bcl-2 and promoting a pro-apoptotic conformation of the protein. The Bcl2-SOD1 complex inhibits VDAC ADP permeability and induces mitochondrial hyperpolarisation. **D.** DNA damage response: TDP-43, FUS, C9orf72, SETX, and APEX1 genetic mutations are linked to DNA maintenance and repair biology, as well as impaired DNA damage response. **E.** Excitotoxicity: The presence of mutant SOD1 can damage the glutamate transporter and decrease glutamate uptake ability which increases glutamate concentration in the synapse. **F.** Axonal transport abnormalities: Mutation in the axonal transport mediated by dynein/dynactin and kinesin machinery genes alter the axonal transport of protein, vesicle, and organelle transport between the cell body and nerve terminal. **G.** Oligodendrocyte degeneration: ALS-causing mutant gene expression in oligodendrocytes causes protein aggregates, and endoplasmic reticulum stress leads to neuronal apoptosis. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

lying neuronal dysfunction and neuronal loss in ALS [49-52]. The genetic mutations that cause ALS are found in genes that encode proteins which are participating in protein production (mTARDBP, mTDP-43, mFUS, mTAF15), degradation (mSQSTM1, mUBLQLN2, mOPTN, mVCP, mDNAJC7, and mCCNF), and/or trafficking (mKIF5A, mANXA11, mATXN2, mDCTN1, mALSIN, mC9ORF72, mVAPB, and mOPTN) pathways. As shown in Fig. (1), the involvement of one or more of these defective pathways may significantly impact the motor proteome homeostasis. Prolonged proteostasis leads to neuronal dysfunction, including mitochondrial dys-

function, endoplasmic reticulum stress, excitotoxicity, and synaptic dysfunction [49].

2.2. RNA Dysregulation

RNA metabolism includes complex and regulated processes such as RNA transcription, splicing, intracellular transportation, translation, and degradation [53]. Although a protein network ensures proper RNA processing in normal circumstances, ALS and other neurodegenerative diseases may cause RNA processing and metabolism disturbances [53, 54]. ALS mutations (mSOD1, mTDP-

43, mFUS and mC9orf72) can interfere in processing RNA through multiple pathways (Fig. 1) [54, 55]. MTDP-43, mFUS, and dipeptide repeat proteins from the mC9orf72 intronic expansion can alter pr-mRNA splicing, promote mi-RNA biogenesis, influence mRNA transport, and impair local translation and protein degradation [54-56]. RNA dysregulation is one of the key features in ALS pathogenesis, and defects in RNA processing can lead to cellular dysfunction and death [57].

2.3. DNA Damage Response

Aging is a potential cause for ALS, and it has been linked to increased oxidative damage to DNA in the human brain [58]. Following DNA damage, many DNA repair enzymes are triggered to restore genome integrity, and deficiencies in DNA repair capabilities can lead to motor neuron degeneration [58]. Some genetic mutations associated with DNA maintenance and repair biology (mTDP-43, mFUS, mC9orf72, mSETX, and mAPEX1) have been proposed as potential causes of both sporadic and familial ALS [24, 59, 60].

2.4. Nucleo-cytoplasmic Transport

There is bidirectional communication between the nucleus and the cytoplasm through highly regulated nucleocytoplasmic transport. This process allows the transport of proteins, RNAs, and ribonucleoproteins across the nuclear envelope *via* the nuclear pore complexes [61]. Dysfunction in nucleocytoplasmic transport is increasingly recognized as a major disease mechanism in amyotrophic lateral sclerosis. While a group of proteins ensures proper nucleocytoplasmic transport under normal circumstances, various mutations in ALS result in impaired nucleocytoplasmic transport [61]. These mutations can impair nuclear import by affecting NLS sequences; affect nuclear pore function by toxic dipeptides, producing a downstream of C9orf72 hexanucleotide repeat expansions, or interfere with nucleocytoplasmic transport by increasing the production of cytoplasmic TDP-43 aggregates [62-69].

2.5. Endosomal and Vesicle Transport

ALS development often occurs by changing intercellular communication between neurons and glial cells in the spinal cord. Proteins are secreted by either a classical or an unconventional modality (through the endoplasmic reticulum, the endosomes, the Golgi and then the plasma membrane). In addition to these pathways, one of the potential ways to transport proteins or RNAs is extracellular vehicles (EVs) [70, 71]. These include exosomes, microvesicles, and apoptotic bodies. ALS-causing mutant proteins, such as mC9orf72 hexanucleotide repeat expansions, mTDP-43, and mSOD1, have been retrieved in EVs and transferred across the brain cell as a way of spreading toxicity and disease [72-75]. These findings highlight the importance of EVs disseminating toxic proteins in the cellular CNS environment and the spread of ALS.

2.6. Axonal Transport Abnormalities

Protein, vesicle, and organelle transport between the cell body and nerve terminal is critical in neuronal growth and physiology. One of the main causes of ALS disease is a mutation in axonal transport machinery genes (SOD1, DCTN1, TUBA4A, KIF1A, KIF5A, DYNC1H1, CHMP2B, ALSIN, G85R *etc.*) [76]. Superoxide dismutase-1 (SOD1) gene mutations inhibit quick and slow axonal transport [77]. Evidence shows that axonal transport mediated by dynein/dynactin dysfunction is sufficient to induce motor neuron death [78]. Studies have shown that a functional mutation in DCTN1, which encodes the p150 glued subunit of the dynactin complex, induces a slowly progressive ALS [79]. A mutation of the α -tubulin gene, TUBA4A, has also been reported as a potential cause of ALS. These variants destabilize the microtubule network and reduce its ability to re-polymerize [80]. Other possible ALS pathology mechanisms underlying axonal transport defects include microtubule instability, mitochondria dysfunction, autonomous

toxicity of non-neuron cells in the central nervous system, abnormal aggregation of neuro-filaments, and abnormal calcium handling [76].

2.7. Mitochondrial Dysfunction

In many neurodegenerative conditions, including ALS, mitochondrial dysfunction is a common feature [76, 81]. The disruption of the mitochondrial structure, disturbed calcium homeostasis, perturbed ER-mitochondria contact, and reduced mitochondrial metabolic energy has been broadly documented in ALS patients and linked to pathogenic diseases [76]. The expression of mTDP-43 and mSOD1-G93A resulted in aggregated, shattered, and distended mitochondria [82-84]. In cultured motor neurons, the over expression of mFUS R521G or mR521H resulted in mitochondrial shortening [85]. Mutations in CHCHD10 cause ALS to disrupt mitochondrial cristae [86]. ALS-related mitochondrial dysfunction appears to be directly or indirectly linked to all of the proposed “non-mitochondrial” toxicity pathogenesis related to ALS [86].

2.8. Excitotoxicity

Under normal conditions, *N*-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors are activated by glutamate released from presynaptic neurons, which causes an influx of Na^+ and Ca^{2+} ions into postsynaptic neurons, leading to an action potential. An increase in extracellular glutamate concentration causes classic excitotoxicity [87]. Reduced glutamate reuptake into astrocytes *via* an impaired glutamate transporter (EAAT2/GLT1 transporter) and increased glutamate concentration in the synapse results in longer stimulation of AMPA receptors [87]. Furthermore, activated microglia can also increase glutamatergic stimulation of postsynaptic neurons [87, 88]. This increases Ca^{2+} influx in the motor neurons, and mitochondria begin to buffer Ca^{2+} . When the mitochondria's buffering ability is surpassed, nucleoplasm Ca^{2+} over-activates various Ca^{2+} dependent enzymes, disrupting neuronal physiology and eventually leading to neurodegeneration. The nucleoplasm glutamate content of these damaged neurons is released, resulting in a significant increase in extracellular glutamate concentration and the spread of neurodegeneration [87]. The presence of mutant SOD1 may cause damage to the glutamate transporter and a decrease in glutamate uptake ability [88]. Riluzole, neuroprotective drug that blocks glutamatergic neurotransmission in the CNS and inhibits the release of glutamic acid from neurons, leads to ALS patients' excitotoxicity [89].

2.9. Oligodendrocyte Degeneration

Oligodendrocytes are a specialized glial cell type, where they interact with neuron axons, produce a myelin sheath around them, and provide metabolic support to neurons [90]. Abnormalities in these functions and oligodendrocytes can cause various neurodegenerative disorders and are highly vulnerable to the negative effects of neurodegenerative disease-related gene expression. ALS-causing mutant gene expression (mSOD1, mFUS, and mTDP-43) in oligodendrocytes cause protein aggregates and endoplasmic reticulum stress, leading to neuronal apoptosis [91-93]. Furthermore, the presence of ALS-causing mutant genes most likely makes oligodendrocytes more susceptible to other stressors.

2.10. Neuroinflammation

Neuroinflammation appears to play a significant role in ALS pathogenesis characterized by lymphocyte and macrophage invasion, activation of microglia, reactive astrocytes, and complement involvement [55]. O'Rourke *et al.* [94] recently demonstrated that C9orf72 mutation genes resulted in defects in lysosomal transport, decreased capacity of microglia to clear aggregated protein, and neuroinflammation. Microglia facilitates tissue repair and regeneration during the early, slow-progressing stages of ALS. As the ALS progresses, damaged motor neurons release “danger signals” (mSOD1) that activate microglia and increase the secretion of reac-

tive oxygen species and proinflammatory cytokines [95, 96]. Astrocytes expressing mutant SOD1 are toxic to motor neurons *in vitro* and *in vivo* [97-99]. Recently, astrocytes have been shown to cause motor neuron death by triggering necroptosis [100, 101].

In response to axonal demyelination, oligodendrocyte precursor cells increase their proliferation rate and undergo differentiation to replace dying cells with new mature oligodendrocytes. Though, these newly formed oligodendrocytes show abnormal upregulation of the GPR17 receptor, preventing them from maturing fully, and downregulation of the monocarboxylate transporter MCT1 is supplying lactate and other nutrients to motor neurons. Impaired remyelination has also been linked to poor processing and trafficking of myelin-related mRNAs. As a result of these changes, dysmorphic and immature oligodendrocytes are produced, unable to remyelinate axons and restore trophic support to motor neurons, and the reserve pool of oligodendrocyte precursor cells is depleted due to an elevated turnover rate [102].

3. THERAPEUTIC APPROACHES TO AMYOTROPHIC LATERAL SCLEROSIS

3.1. SOD1 Targeted Approach

The human SOD1 structure contains 153 amino acids with two subunits non-covalently bound with a molecular size of 32 kDa [103, 104]. SOD1 is mainly present in the cytoplasm, nucleus, mitochondria, and lysosomes. Clinical and experimental evidence suggests that mutant SOD1 leads to a marked degree of transcriptional repression, the prevailing mechanism in mutant SOD1-associated ALS, making it an appealing target for genetic therapy. To date, there have been more than 200 SOD1 gene mutations reported, most of which have an autosomal dominant inheritance and missing variants [105, 106].

The disparate effects of mutant SOD1 on various essential cellular processes argue for silencing the SOD1 gene instead of repairing each of these operations individually. Three broad types of gene therapy have shown promise in animal models and are designed to specifically target SOD1; RNA interference, antisense oligonucleotides, and CRISPR [107]. Furthermore, over-expression of macrophage migration inhibitory factor (MIF), a gene therapy technique, has shown promising results in preclinical studies, potentially alleviating SOD1 misfolding [108].

Endogenous RNAi is used to suppress the gene translation process in eukaryotic cells [109, 110]. In sporadic and familial ALS patients' muscles, endogenous microRNA, miR-206, down-regulates and suppresses the SOD1 expression confirmed in mice and dogs [111, 112]. In the preclinical models of mutant SOD1-associated fALS, RNAi-based management therapy can be considered a better option. Lentivirus was the first treatment drug tested on SOD1 transgenic mice in 2005 [113, 114]. In 2013, AAV9 in lentivirus had gained 39 % survival and was used to administer shRNA targeting SOD1. AAV10rh RNAi therapy for SOD1 associated ALS is currently under preliminary phase study [115]. The genetic-based treatment strategy on animal models requires proper study regarding the dose and design of vectors for successful clinical trials.

It was discovered that short synthetic DNA or RNA-based oligonucleotides (ASOs) would decrease the gene expression by binding to mRNA *via* base-pairing and block-translation *via* binding to the 5' UTR region of mRNA and preventing capping, promoting RNase H mediated degradation and obstructing translation before the RNAi pathway discovery (Fig. 2). ASO targeting SOD1 delivery in the CNS of SOD1G93A rats had a dose-dependent effect in SOD1 protein in neuronal and non-neuronal cells [108, 116-118]. Phase III of the clinical trial is the recent 2021 marketing of formalized paraphrase Tofersen (ASO, administered intravenously *via* lumbar puncture). Tofersen, an antisense oligonucleotide, is being investigated in patients with ALS caused by mutations in the SOD1

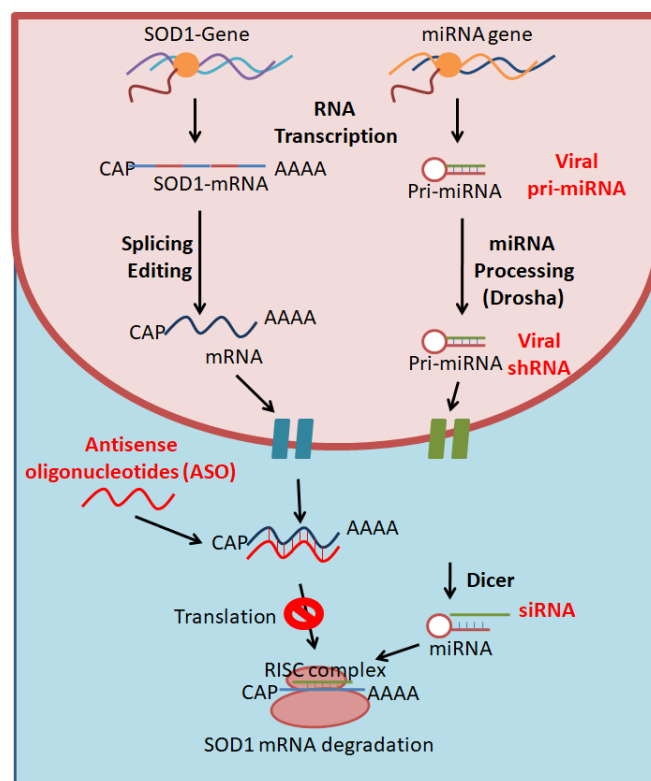


Fig. (2). Schematic of SOD1 targeted approach. Use of artificial RNA interference approaches to silence SOD1 (Right side). Antisense oligonucleotides are easily absorbed by cells, attach to mRNA strands and disrupt the cell's natural production of a SOD1 protein (Left side). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

gene. The necessity of continuous lumbar punctures at different intervals for dosing has a lack of disadvantage for CNS-related disorders [101].

AAV9-delivered, CRISPR/Cas9 system targeting SOD1 gene led to a substantial decrease in SOD1 by 2.5-fold in the brain of SOD1G93A mice [119]. Modern pharmaceutical technology increases the accuracy and eradicates the DNA breaks with the help of novel CRISPR editing methods, including base editing and PRIME editing, leading to secure clinical potential in the future [120].

3.2. TDP43 Targeted Approach

TDP-43 is a transactive response (TAR) DNA binding protein-43 consisting of 414 amino acids and is generally located in the nucleus and cytoplasm. It comprises RNA recognition motifs RRM1 and RRM2, the N-terminal region that is nuclear-localized, a C-terminal region, glycine-rich region, and a nuclear export region [45]. TDP-43 deletion/overexpression induces embryonic lethality in mice and causes toxicity or cell death *in vitro* and animal models [121, 122]. The detection of TDP-43 identified the co-relation between TDP-43 and neurodegenerative disorders as a vital role in the pathophysiology of ALS and FTL [123, 124]. In ALS, a shortened form of TDP-43 is found as ALS aggregates in the cortex and the spinal cord [125, 126] and localizes with stress granules markers [127]. TDP-43 plays an important role in controlling stress granules' formation and disassembly, where TDP-43 deficiency decreases stress granules formation [31, 128]. Thus, TDP-43 has emerged as a promising therapeutic goal for developing successful ALS therapies (Fig. 3), and modulating its post-translational modifications through small molecules presenting a significant opportunity for the discovery of effective drug candidates for the future treatment of ALS, especially those aimed at restoring homeostasis.

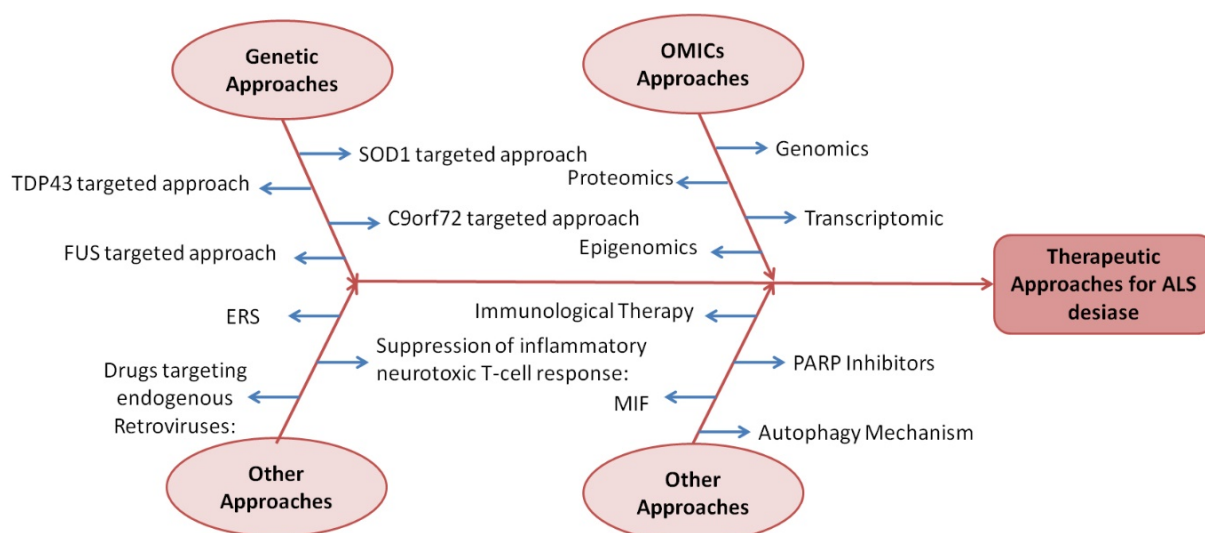


Fig. (3). Therapeutic approaches of ALS. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Methylene Blue (MB) and Dimebon are reported compounds that decreased overexpression of TDP-43 [129]. The administration of rapamycin in mice reduced the presence of cytoplasm TDP-43 positive aggregations and improved motor function. Triptolide is also used to reduce TDP-43 and plays a crucial role in protein aggregation [130]. Curcumin from *Curcuma longa* down-regulates TDP-43 levels in MCF-7 cells and reduces protein aggregation from TDP-43 with improved neuroprotective activity [131]. Anacardic acid modestly improves cell survival in neuronal ALS models by decreasing TDP-43 mRNA expression in ALS motor neurons and reducing the TDP-43 protein [132]. Berberine, a potent autophagy activator, decreases the formation of the aggregates of truncated TDP-43 fragments and targets AMPK/mTOR/ULK1 signaling. It has marked neuroprotective activity in neurodegenerative disorders [133]. Ibudilast is an anti-inflammatory PDE4 inhibitor that modestly cleared TDP-43 aggregates in an *in-vitro* model and protected them from TDP-43 formed aggregates [134]. L-serine diminishes the motor neurons' TDP-43 levels, thereby improving the motor function [135]. Auranofin showed a dose-dependent activity by reducing TDP-43 without producing any side effects [136]. On the other side, paraquat reduced oxidative stress and decreased TDP-43 accumulation in the motor neurons of the ALS-induced mouse model [137]. It is indeed a question to understand these nuclear export signals (NES) experimentally in detail for their export role in ALS as some of the recent studies demonstrated some of the nuclear export signals (FUS NES) are false [138, 139].

3.3. C9orf72 Targeted Approach

Hexanucleotide (HREs) GGGGCC repeat expansions in the first intron of *C9orf72* are regarded as genetic causes for amyotrophic lateral sclerosis. This expansion causes DPR (di-peptide-repeat proteins). The accumulation of RNA foci in neurons causes many downstream pathways and neuronal loss of the hippocampal region, increasing fear and impaired cognitive function. The exact pathogenesis by which abnormal GGGGCC expansion mediates ALS disease remains unknown [46, 65]. Recent studies suggested that GGGGCC expansions result in the RNA binding proteins' sequestration which disrupts the nucleocytoplasmic transport, promotes cell toxicity, and leads to ALS [69, 140]. Hence, *C9orf72* can be used as a targeted approach for ALS. RNA G-quadruplex, a small binding molecule that specifically targets *C9orf72* GGGGCC in drosophila, has been found to improve survival, which can be a promising therapeutic option for ALS [141, 142]. ASO interventions are effective in the prevention of ALS. ASOs bind within the

repeat GGGGCC expansion or the surrounding N-terminal regions of the *C9orf72* mRNA transcript, effectively reduce toxic RNA foci, restore normal gene expression markers, and protect against glutamate toxicity [101, 143]. The AAV-delivered miRNA-based approach can also be used as target *C9orf72* transcripts, with a potentially long-lived therapeutic effect following a single administration where there was a reduction in the level of GGGGCC repeat expansions in the first intron of *C9orf72* in the cortex and cerebellum [46, 144-147]. By inhibiting the transcription products CRISPR is a technology that mediates genome editing and deletes GGGGCC repeat expansions in the first intron of *C9orf72*, leading to decreased RNA foci formation [148]. A clinical trial of metformin is currently underway in C9ALS/FTD patients (NCT04220021). TDP-43 prevents R-loop accumulation and R loop-mediated DNA breaks in neuronal and non-neuronal cells, suggesting that R-loop modulation in TDP-43-deficient cells could aid in developing ALS therapeutics [149, 150].

3.4. FUS targeted Approach

Fused-in-Sarcoma (*FUS*) possesses 526 amino acids, a DNA/RNA binding protein. In the *FUS* gene, mutations at the 16 chromosome site lead to the formation of conditions of ALS cases. *FUS* has been involved in various cellular processes such as translation, transcription, shearing, and DNA repair. These can be used as a targeted approach as it accounts for 1 of 4 cases of ALS [151, 152]. The targeted gene *FUS* can be corrected by using the CRISPR/Cas9 system [153]. CRISPR/Cas9 is a gene-editing technology adapted from the natural genome editing system in bacteria. These technologies cut and replace the desired DNA fragments, with the most simple and expensive tool [154-157]. Antisense oligonucleotide is used to therapeutically target *FUS*-mediated ALS [158].

3.5. Defects in CNS Glucose Metabolism in ALS

Several studies have shown multiple metabolic defects at different steps in the glucose metabolism pathway in the brain and spinal cords of ALS patients and in animal models [159]. Reduced glucose transporter expression, impaired glycolysis, and the pentose phosphate pathway increased glycogen accumulation, decreased pyruvate entry into the TCA cycle, mitochondrial dysfunction, reduced mitochondrial ATP output, increased reactive oxygen species (ROS) production, and glutamate excitotoxicity are among the metabolic defects that lead to ALS [160]. The ability to target CNS glucose metabolism can delay the initiation and progression of

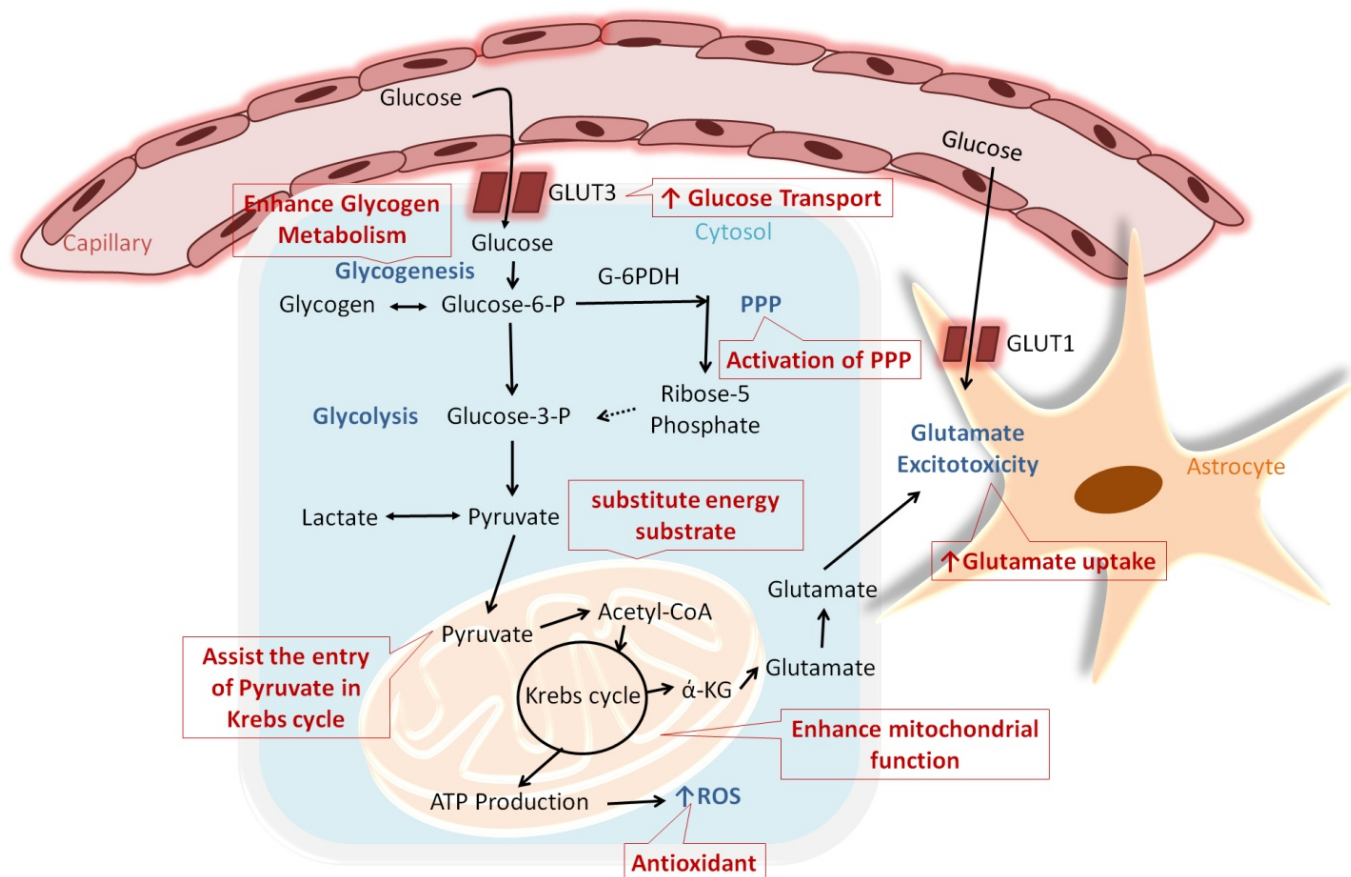


Fig. (4). Targeting CNS glucose metabolism in ALS. Possible approaches or targets in the glucose metabolism pathway include the activation of glucose transport, improved glucose metabolism, the activation of the pentose phosphate pathway (PPP), pyruvate inclusion into the Krebs cycle, the facilitation of glycogenolysis, availability of alternative energy substrates, improved ATP generation, the use of antioxidants targeting reactive oxygen species (ROS), overall mitochondrial improvement and reduced glutamate excitotoxicity. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

ALS. Fig. (4) depicts possible therapeutic approaches or targets in the glucose metabolism pathway in ALS.

3.6. OMIC Approach

3.6.1. Genomics

ALS is developed by the deterioration of upper and lower motor neurons which can be treated by more than one therapeutic approach. One of the advanced approaches known as “OMIC” encompasses genome, transcriptome, proteome, epigenome, and metabolome like different technologies associated with individual patients' phenotype and finally on the base of “one-size-fits-all” elucidated into personalized medicine [161]. “OMIC” plays a significant role in detecting a biological system, including genomics, proteomics, mRNA, metabolites, and epigenomic factors. Numerous omic studies have proposed multiple pathologic mechanisms related to ALS [162].

The genomics application of ALS has been correlated with its biological and clinical complexity [163]. In 1993, the first gene mutation, “SOD1”, was reported, which was later followed by more than 30 responsible genes for ALS (C9orf72, FUS, and TARDBP, etc.). In the advanced development of massive parallel sequencing approaches, whole-exome sequencing (WES) and whole-genome sequencing (WGS) have been explored to solve ALS genomics [164-166]. It was reported that disease modification, clinical diagnosis, and identification of risk variation help to explain the different profiles of ALS patients, and they are more informative in outlining new therapeutic strategies [167]. A strong genome and DNA investigation is now feasible and can be

used to comprehend sporadic ALS (SALS) science, which may provide insights into SALS sensitivity, RNA investigation, SALS gene expression and molecular pathogenesis [168]. It is possible to investigate both genic regions, such as introns and exons and their splicing, and non-genic regions, such as structural, regulatory, and other elements [168, 169]. Micro and nanotechnologies, informatics, and computational biology have the potential to deepen our understanding of molecular pathogenesis and identify therapeutic targets [168, 170-173].

3.6.2. Transcriptomic

ALS pathology depends on gene expression proliferation of mRNA from peripheral cells and nervous tissue [174]. The high-density microarray approach and RNA sequencing are used to identify ALS along with biomarkers and specific patient treatment, in the advancement of high-throughput screening [175, 176]. Maniatis *et al.* reported RNA-seq based approach, also known as “spatial transcriptomics,” which is used to map gene expression changes in different mutated ALS patients [177]. The advancement of microarray technology, which allows for the combined estimation of various genes' transcriptional expressions, has opened up new avenues for a better grasp of ALS pathogenic mechanisms and, more importantly, possible new candidate targets for new therapeutics [178]. The modification of RNA metabolic activities has been recognised as a main dysregulated pathway in ALS. This research has provided new light on the role of modified transcriptional features of microRNAs and ALS-associated ribosomal protein in the disease's pathophysiological pathway in an attempt to comprehend the functional impact of

pervasive RNA dysregulation in the disease's pathological mechanism [178, 179].

3.6.3. Proteomics

Analysing particular protein changes in affected cell culture, CSF body fluid, and brain tissue is an important part of ALS [52]. The investigative efficacy of CSF pNFH levels in *C9ORF72*-ALS patients was studied, and it was found that higher levels of pNFH were observed in ALS or ALS/FTD patients carrying *C9ORF72* expansion [180]. A recent study investigated modules of co-expressed genes or proteins altered in post-mortem cortex samples from patients affected with ALS, FTD, and ALS/FTD, and healthy disease controls. This work acknowledged co-expressed elements (*i.e.*, inflammation, synaptic transmission, and RNA binding proteins) across all the ALS-FTD disease range, which might be beneficial for identifying genes connected with different patient phenotypes [181]. Recent work indicates a genetic link between ALS and proteins involved in cytoskeletal complexities [182]. Mutations in *DCTN1* (dynein-associated polypeptide), *PFN1* (profilin, an actin cytoskeleton regulator), *TUBA4A* (tubulin 4A), and the annexin family member *ANXA11* have all been connected to ALS. Furthermore, kinesins are encoded by the ALS-linked gene *KIF5A20* and the related gene *KIF5C*, which are restricted in sporadic ALS peripheral blood mononuclear cells. This study found that *DCTN1*, *ANXA5* (related to *ANXA11*), and *KIF5* protein levels were changed in *FUS* mutant motoneurons [183]. Eventually, using these proteomic methods to more carefully probe biochemical reactions linearly in disease, especially in research findings of experimental models where the brain and spinal cord specimens can be accumulated at pre-defined time frames, will be insightful [184]. Apart from that, upstream techniques for protein enrichment emphasize new techniques for isolating disease-relevant protein inclusions, such as flow cytometric analysis of inclusions and trafficking (FloIT) [181].

3.6.4. Metabolomics

Metabolomics provide an exceptional way to consider spatio-temporal metabolic turners by analysing body fluids and tissue [185]. So far, one of the most difficult challenges in ALS research has been determining how metabolites in body fluids and the CNS change as the disease progresses [186]. High-throughput approaches have increasingly been used to test a combination of markers in patients with neurological disorders using various analytical methods such as high-performance liquid chromatography accompanied by electrochemical detection [187, 188]. Metabolomics as a guide to pathway knowledge in genome-wide interaction studies may be useful for mapping and understanding the results of various mutations, and even combinations of mutations, in the ALS subtype [189]. Metabolomics data will help in understanding the pathophysiology and drug response. In practice, pharmacometabolomics results can enhance a drug administration strategy as a complementary tool of pharmacokinetics, and shed new light on the drug-response impact and downstream signalling pathways [190]. Cieslarova *et al.* used capillary electrophoresis tandem MS to quantify plasma levels of homocysteine, cysteine, methionine, and glutamic acid in ALS patients and discovered that glutamic acid and homocysteine could be prospective biomarkers for ALS [191, 192]. Lawton *et al.* found that the plasma levels of 23 metabolites were dramatically modified in ALS patients, as were the affiliated pathways such as neural, hypermetabolism, oxidative damage, and mitochondrial dysfunction [192, 193].

3.6.5. Epigenomics

In the advancement of genomics, chromatographic and spectrometric techniques including GC, HPLC, NMR, and MS helped recognise specific metabolite markers and identify separate subgroups of SALS patients, which helped to develop novel targeted personalized treatments [194, 195]. Besides, modifications in ener-

gy metabolism and metabolome, including growth in resting energy spending, are rare before the development of motor symptoms in ALS and associated with disease development. A lipid-specific metabolic abnormality also plays an important part in ALS animal models where augmented triglycerides and total cholesterol (LDL, VLDL, HDL ratio) are involved with slower disease development in ALS patients [196]. A study demonstrated that the negative-regulation of miR-206 is responsible for the specific modulator of skeletal muscle growth [197]. It is also responsible for regeneration after the damage that fastens disease development in mice with ALS. Besides, positive regulation of miR-208B and miR-499 is manifested in the skeletal muscles of patients with slower disease development [198].

3.7. Other Approaches

ALS pathology involves protein aggregation as a main feature which includes deposition of amyloids from different proteins such as TDP-43, SOD1, *C9ORF72*, *FUS*, *OMIC*, *etc.* [199]. These are a few of the widely used approaches for ALS treatment. Despite these, other therapeutic approaches can be considered for the targeted therapy and possibly be useful for ALS treatment.

3.7.1. ERS (Endoplasmic Reticulum Stress)

The ALS pathology involves protein aggregation, which causes the accumulation of unfolded proteins leading to intracellular stress reactions and endoplasmic reticulum stress (ERS) and unfolded protein response, causing the restoration of protein homeostasis so that they can survive under stress conditions for a moderate amount of time [200]. One of the mechanisms for sensitivity regulation of the motor neurons is through ERS which leads to pathological changes that are eventually associated with ALS [201]. The ERS unfolded responses can be considered a promising target that can be used as a novel approach for ALS treatment [202].

3.7.2. Suppression of Inflammatory Neurotoxic T-cell Response

A typical characteristic feature of neurodegenerative diseases includes neuroinflammation; hence, anti-inflammatory therapy can be considered an important approach. Patients with ALS usually show diminished number and function of T-lymphocytes which may suppress microglia activation [203]. Rapamycin was used previously for such conditions that are benefited from immunosuppression [204]. Rapamycin also showed stimulation of autophagy that is well known for ALS treatment, and works through the accumulation of pathological inclusions and reducing the progression. The study was carried out in a rapamycin-treated model of animals with ALS pathology [202, 205].

3.7.3. Drugs targeting endogenous Retroviruses

One of the endogenous retrovirus family, Human Endogenous Retrovirus-K (HERV-K) and its subgroup HML-2, is the active group for transcription [206]. Its reactivation and irregular expression in the tissues of adults may lead to neurodegenerative diseases like ALS. Thus, anti-retroviral therapy with available drugs can be used for ALS treatment [202].

3.7.4. Immunological Therapy

ALS pathology shows different immunological responses and demonstrated similarity with other diseases where it is also observed that fluoride-induced brain cell mitochondria damage plays a critical role in disease pathogenesis [207]. Some models showed promising results while others seem to show no improvement in ALS treatment. Currently, one of the therapies that showed promising outputs is where NogoA was used as a therapy target when it appeared to be overexpressed in the skeletal muscle of the patient suffering from ALS. Therefore, anti-NogoA antibody (ozanezumab) that inhibited NogoA overexpression was tested for ALS-related progression [208].

3.7.5. PARP Inhibitors

PARP, also known as Poly (ADP-ribose) polymerases, is a group of enzymes that help form ADP ribose polymers. These enzymes work by attacking proteins covalently, and this process is known as PARylation. Previously, they have been used for cancer treatment. McGurk *et al.* demonstrated that patients suffering from ALS have elevated levels of PAR in their spinal cord motor neurons, which were found to be non-mutated, while the genes ATXN2 and C9ORF72 showed mutations linked to ALS [209]. The PAR inhibitors showed efficacy in TDP43 protein accumulation models through inducing cell death in rat spinal cord cultures. The XAV939 20 is a well-known potent tankyrase-2 inhibitor that shows a weaker inhibition of tankyrase-1, PARP1/2, and simultaneously reduces TDP-43 accumulation in cytoplasmic foci. These studies confirmed the use of PARP1/2 and tankyrase as important targets for the studies associated with TDP-43 ALS pathology [210].

3.7.6. Autophagy Mechanism

Autophagy is a process in which the body consumes its tissue as a metabolic process under starvation or diseases. Rapamycin, a drug that is a well-established activator of autophagy, acts by inhibiting the mammalian target of rapamycin (mTOR). The *in vitro* and *in vivo* studies revealed that TDP43 mislocalization is rescued; it also reduced neuronal loss, impairment of cognitive function, and certain motor phenotypes. But, mTOR showed a poor response in autophagy stimulation in neurons and thus limited the efficacy of these agents in neurodegenerative disorders [210].

3.7.7. MIF (Macrophage Migration Inhibitory Factor)

The macrophage migration factor, also known as glycosylation factor (GIF), is a protein encoded by the MIF gene. The MIF is one of the important factors in regulating immunity [211]. In one of the stud-

ies, NSC-34 culture showed that macrophage migration inhibitory factor reduced misfolded SOD1 protein accumulation and increased the survival rate of the cell. It also showed chaperone-like activity that changed SOD1 amyloid aggregation pathways through the formation of disordered aggregates that seems to be less toxic for the cell.

These were a few of the additionally listed targeted studies that also work best for ALS treatment. A few of these studies worked hand in hand with the other targeted approaches, while others showed individual mechanisms and novel approaches for the treatment of ALS. The drugs that were previously used to treat other neurodegenerative disorders and cancer treatments also showed potential in ALS treatment. Further, findings and studies will reveal the importance of these targeted studies [212]. The nano-based drug delivery also has an attractive niche for therapeutic delivery [170, 213-220].

4. CLINICAL OUTCOME MEASURES IN AMYOTROPHIC LATERAL SCLEROSIS

Signs of ALS include progressive muscle weakness, loss of function, spasticity, muscle cramps, and often sluggishness of motion with achy muscles. Muscle fatigue in ALS is normally focal at first and then extends to other body parts. This pattern is consistent with the disease's progression, spreading across the motor system and neuroanatomically spreading across the spinal cord [2, 221]. In long-suffering patients, weight loss, the cycle of fasciculation, and muscle cramps occur due to muscle weakness. Patients with classic ALS include a mixture of upper motor neuron (UMN) and lower motor neuron (LMN) activity symptoms on neurological examination. Muscle fasciculation reduced muscle tone and stiffness, and atrophy are also signs of LMN participation. Hyperreflexia is shown as preserved responses in atrophic muscles, augmented mus-

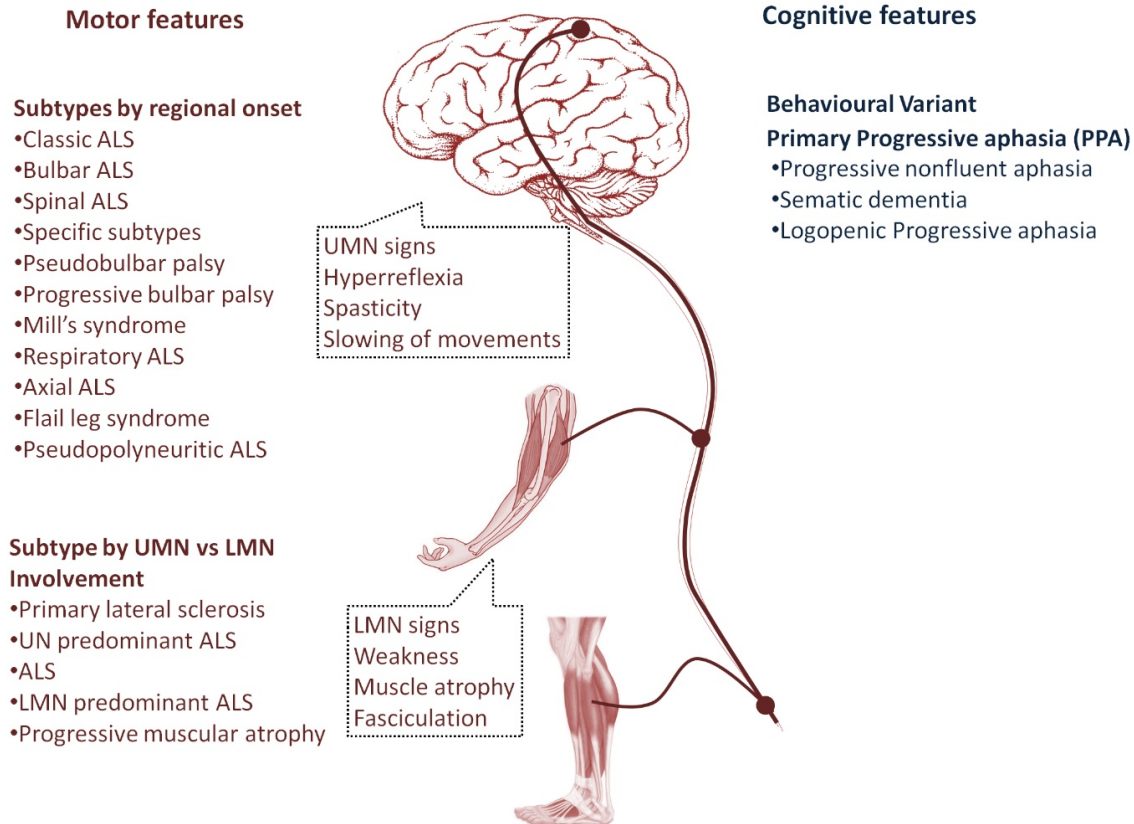


Fig. (5). Individual's observable traits of ALS. The motor characteristics of ALS differ depending on the area and the relative presence of the UMN versus the LMN. Not more than 50% of patients have mental and behavioural characteristics that can be detected [2]. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

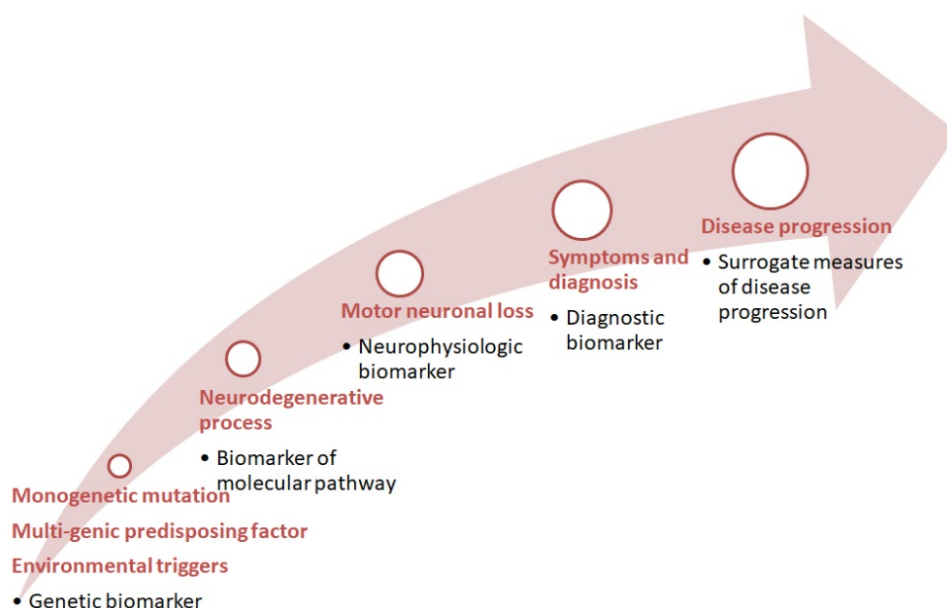


Fig. (6). Framework for biomarker development in ALS. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

cle tone is shown as upper limb flexors, and lower limb extensors are signs of UMN involvement [222]. ALS is increasingly recognized as a scientifically heterogeneous condition with distinct motor and extra motor symptoms, even though most patients have a typical ALS phenotype with spinal or bulbar onset (Fig. 5).

4.1. Neurophysiological Index (NI)

It is a multimetric index extracted by the ulnar nerve-innervated abductor digiti minimi muscle's CMAP amplitude, distal motor latency, and F-wave frequency. Importantly, NI is a responsive parameter for assessing ALS development, making it a promising candidate outcome predictor [223]. The main benefit of NI is that it can be assessed using normal neurophysiological measures, and no special equipment is needed. More research is needed to see whether NI can be used as a consequence factor in ALS clinical trials.

4.2. Biomarkers for ALS

The NIH defines a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention” [224, 225]. Early diagnosis indicators could speed up registration. Early trials could benefit from more enrollment or for comparing actual and expected development rates, eliminating the need for placebos. Biomarkers that indicate disease development can be explored to monitor drug effectiveness. Pharmacodynamic biomarkers may be explored to assess drug efficacy in initial studies (Fig. 6).

4.2.1. Diagnostic Biomarkers

In a broad survey of 638 ALS patients, the value of serum albumin at diagnosis as a biomarker of existence was confirmed, with stages deteriorating in ALS. Augmented existence demonstrated with increasing levels, and albumin levels were associated with markers of inflammatory disease [226]. Prospective treatments may be able to postpone or halt ALS progression. Earlier patients are detected on this irreversible pathological pathway undergoing severe exhaustion and motor neuron attrition, which was intended to happen through speeding up evaluation. When symptoms are localized and subtle, a reliable diagnostic biomarker will aid in the clinical diagnosis phase.

4.2.2. Imaging Biomarkers

Because it is non-aggressive, comparatively cheap, and does not use ionizing radiation, magnetic resonance imaging (MRI) is an

appealing applicant as a biomarker instrument. The multi-modal aspect of MRI makes it ideal for studying anatomical and pathological modifications and processes in real-time. In the sense of ALS, there is a wide body of published work, mostly focusing on the brain and fewer findings have been found on the spinal cord, muscles, and peripheral nerves [227].

4.2.3. Pathophysiology Biomarkers

These types of biomarkers generally help in understanding the cellular pathology or dysfunctional biochemical processes, allowing pathophysiologically related subgroups of people with ALS to be identified (Table 2) [228-243]. Patients belonging to a specific pathophysiologic subgroup will get a positive outcome from a particular treatment (cohort enrichment) based on their particular disease pathways. Only patients with unique patterns of inflammatory cell activation might be included in immunomodulatory therapy trials [244].

4.2.4. Prognostic and Predictive Biomarkers

ALS is a complex disease with a wide range of symptoms, extra-motor activity along development rates. Although the average lifespan is two to five years, it can extend from a few months to over a decade. Patient variability is often visible as they are investigated genetically and by autopsy. It makes more sense to plan clinical studies bearing in mind that population differences are not skewed by predictive testing, as only a subset of patients will benefit from such a new treatment [245]. Furthermore, as uncertainty is minimized, the sample size will be compact, reducing the length along with the clinical trial expenses. A strong predictive biomarker would help stratify patients for improved trial strategy by narrowly discriminating between disease subgroups [246]. One-time measurements are analogous to predictive biomarkers, although, they reflect the likelihood of forecasting a reaction to a specific medication rather than the prognostic natural path of the disease. A 5% weight loss or greater at the time of diagnosis has shown to be an independent poor prognosis biomarker for life. As a result, at any point in the disease's progression, patient stratification for trial entry should take the weight loss percentage at the threshold into account [229]. Routine screening for respiratory complications is a susceptible tool with benefits and drawbacks. SNIP remains a biomarker that might help define prognosis and the prospects for sensitivity to alter from treatment regimens as stability in terms of ease of methodology, serial parameters, time and expertise required, and

Table 2. Summary of potential biomarkers for ALS.

Class of Biomarker	Biomarker Name	Inference	References
Anthropometric markers	Body mass index (BMI)	The graph generally observed as bell shape curve. With lower side BMI Suggest faster disease progression	[228]
	Body weight	Weight loss is the marker for ALS progression in the detected individual	[229]
	Fat mass	There is inverse relationship between gain of fat mass and ALS	[229]
	Fat free mass	There is direct relationship between loss of fat free mass and ALS	[228, 229]
Imaging markers	Brain glucose use	Hypometabolism is observed which is generally detected by PET	[230]
	Spinal cord glucose use	Hypermetabolism is observed which is generally detected by CT/PET	[231]
	Transcranial Magnetic Stimulation (TMS)	Non-invasive neurophysiological technique that assesses UMN functional integrity	[232]
	Electrical Impedance Myography (EIM)	Non-invasive, painless and quantitative method for proximal and distal muscles	[233]
	Motor Unit Number Estimation (MUNE)	It provides a reproducible, quantitative measure of the number of functional motor units	[234]
Muscle markers	Creatine kinase	Increase in the level in ALS	[235]
	Mitochondrial function	There is decrease in the functional activity of the same	[236]
	Pyruvate dehydrogenase kinase 4 (PDK4) levels	Increase in the level in ALS	[237]
	Sphingolipids	Increase in the level in ALS	[238]
Cerebrospinal fluid (CSF) markers	Pyruvate	Increase in the level in ALS	[239]
	Insulin	Decrease in the level in ALS	[240]
	Growth hormone	Decrease in the level in ALS	[240]
Blood related markers	Glucose	Increase in the level in ALS	[241]
	Cholesterol	Variation observed	[241]
Saliva markers	Cortisol	The level of it increases during night time while stress decreases its level	[242]
Neuro Inflammation Markers	bFGF	It is indirect markers helps in understanding interleukin level in ALS	[243]
	VEGF	It is indirect markers helps in understanding interleukin level in ALS	[243]
	MIP-1	Increase in the level in ALS	[243]
Urine Markers	p75 neurotrophin receptor	In ALS generally its level increases	[227]

predictive ability. Patients with severe bulbar or cognitive dysfunction are the exception, and an electrophysiological method may be beneficial in these cases [247, 248]. Despite substantial efforts in each sector, single meaningful biomarkers of ALS remain elusive. Incorporating biomarkers inside a methodology is a useful option to boost their utility, but it raises the risk of false positives, and the more biomarkers used, the larger the sample size required to ensure relevance [248, 249].

4.2.5. Biomarkers of Disease Progression

Extremely responsive markers of disease development, including more detailed measurements of severity, are actually developed and may be applied as surrogate consequence measures. The validation of additional responsive and accurate disease development biomarkers would result in smaller sample sizes and shorter Phase II trials, speeding up the road to effective trials [250]. As long as the change in motor control and longevity in a progressive condi-

tion are the ultimate results desired, clinical trial endpoints usually include factors like existence along with the updated ALS functional rating scale (ALSFRS-R). Such results may require several years of monitoring before a decision can be reached, which is a costly process. These biomarkers adjust consistently in an outburst to therapy, confirming that such an experimental treatment has the desired effect on a pre-clinically identified clinical cascade [248, 251, 252]. ALS pathology shows different immunological responses and demonstrated similarity with other diseases where it is observed that fluorosis plays a critical role in disease pathogenesis.

4.2.6. Pharmacodynamic Biomarkers

The finding of biomarkers in the initial ALS trial would accelerate the production of ALS drugs and increase the odds of a successful Phase III Clinical trial. Candidate therapy is intended to alter identified mechanisms manifested in ALS pathogenesis in a subsection of patients at a specific disease level in the optimal

Phase II study [253] where pharmacokinetic and pharmacodynamic biomarkers and robust disease development effects will be used. Recent advances in preclinical model biomarker development and genetics mean that these objectives are within reach, yet additional exploration is desired to bring these perfect situations to fruition [121]. As one of the most effective biomarkers, the discovery of molecular, imaging, and CSF biomarkers needs special consideration. The quest for ALS-specific biochemical markers in the blood and CSF is ongoing. The discovery of a successful diagnostic ALS test in a biofluid could change how ALS is diagnosed and clinical trials are conducted. ALS trials and therapy discovery may also benefit from a biofluid marker that varies with disease progression or advancement in forecasts [254]. A multicenter prospective study is now underway to see which biomarker would be converted into clinical practice [255]. These findings are important due to the possible extreme effects of biomarkers in the initial stages of ALS trials.

4.2.7. Oxidative Stress Biomarkers

According to recent FDA approvals of the free radical scavenger edaravone in Japan and the United States, the pathology of ALS is due to oxidative damage, which may lead to new therapies. The antioxidant enzyme superoxide dismutase 1 transforms superoxide reactive oxygen species to superoxide and hydrogen peroxide throughout the body [256]. According to one study, ALS patients had poorer antioxidant ability and progressive oxidation protein yields than controls, whereas hemiplegia patients had a protein structure parallel to control mechanisms [257].

4.2.8. Biomarkers of Neuroinflammation

Multiplex analysis and immunoassays have also been suggested for predicting disease length. A part from that, in the context of ALS, IL-9, IL-5, and IL-12 proved to be undesirable analytes, and MIP-1 and G-CSF proved to be desirable analytes [258]. IFN- γ has been linked to disease development, and bFGF, VEGF, and MIP-1 have been linked to a lengthier disease span, indicating that the immune system attempts to maintain homeostasis. This immune profiling technique has the potential to subtype ALS patients and integrate immunological factor recognition with the detection of potential therapeutic targets [259].

CONCLUDING REMARKS AND FUTURE PERSPECTIVE

Lou Gehrig's disease is a progressive disease of the motor neuron community which is synonymously being used for ALS. It is characterized by the gradual degeneration and death of nerve cells in the brain and spinal cord, which ultimately contact the nervous system and the body's voluntary muscles. ALS is a terminal illness that normally kills within a few years of diagnosis, though the disease has slower-progressing variants. It could be caused by genetic and/or environmental factors. Biomarkers are now required to better predict and reliably assess disease development, and improve clinical trials aimed at finding more successful therapies. There is no medicine or treatment available that completely cures the disease, but there are therapeutic agents available which provide symptomatic relief and prevent further complications. Although the biological mechanisms underlying the disease's pathogenesis and development are complex, there is growing evidence that ALS is characterized by early cortical hyperexcitability with altered synaptic integrity, likely induced by the deposition of TAR DNA-binding protein 43 (TDP-43), accompanied by more extensive destruction of neuronal networks [260]. Impeded autophagy is a crucial pathomechanism in ALS, so autophagic control is a treatment modality for the disease [261]. Numerous barriers have been identified as contributing to the failure of translation from bench to bedside in the field of ALS treatment. More than 160 drug candidates or therapeutics for ALS are under different stages of development, with more than 100 global players working around the same. The insufficiency of ALS models is regarded as a major cause of clinical trial

failure. The absence of presymptomatic biological markers, as well as the lag in medical assessment, have seriously restricted the medical applications of potential disease-modifying drugs. It is now widely acknowledged that when patients meet the diagnostic criteria for ALS, a significant disease burden has already occurred during the lengthy presymptomatic phase. To date, preclinical and clinical trials for ALS have used a variety of stem cell types with tailored properties and pharmacological efficacy. The most common are neural stem/progenitor cells (NSCs/NPCs), mesenchymal stem cells (MSCs), and hematopoietic stem cells (HSCs) [262, 263]. BrainStorm Cell Therapeutics Inc. has developed mesenchymal stem cell-based (MSC) therapy for ALS under the phase III clinical trials in the USA [264]. The neurotrophic growth factors (NTFs) improve motor neuron viability in ALS patients, and the developed culture of MSCs can induce the secretion of neurotrophic growth factors. Apellis Pharmaceuticals Inc. has developed pegcetacoplan, a selective C3 therapy intended to control unnecessary complement cascade activation. As per the early results of the Phase I study, pegcetacoplan targets the complementary pathways, especially C3, and can delay ALS development by reducing the inflammation that induces motor neuron death [265]. Its phase II study is ongoing. In clinical development and early clinical ALS trials, various agents that address a wide range of functions of neuronal protein aggregation pathways have shown early promising findings. Among these findings, the functions include targeting mRNA, to start degrading and to stop translating, clearing protein aggregates with antibodies, disrupting protein-protein associations that contribute to aggregation, preventing aggregate formation with vaccines, and sustaining proteostasis by stimulating protein clearance mechanisms [212]. Biogene Inc. has developed mRNA-based drug products that encode for the BIIB078 modified from the C9orf72 gene to prevent abnormal protein production [266]. Appreciatively, the advancement of nanotechnology-based strategies allows for the advancement of treatments, such as the efficient delivery of drugs, genes, and ASOs to the CNS and the promotion of the efficacy of stem cell therapies [267]. The researchers are hopeful that these and other fundamental, translational, and clinical research trials will lead to innovative and more successful ALS therapies in the future.

LIST OF ABBREVIATIONS

AAV	=	Adeno-Associated Viruses
ALS	=	Amyotrophic Lateral Sclerosis
AMPA	=	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid
ANG	=	Angiogenin Gene
ANXA11	=	Annexin A11 Gene
ASOs	=	Antisense Oligonucleotides
ATXN2	=	ataxin-2 gene
C9ORF72	=	Chromosome 9 Open Reading Frame 72
CHCHD10	=	Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 10
CHGB	=	Chromogranin B (Secretogranin 1)
CHMP2B	=	Charged Multivesicular Body Protein 2B
CRISPR	=	Clustered Regularly Interspaced Short Palindromic Repeats
CSF	=	Cerebrospinal Fluid
CT	=	Computed Tomography
DAO	=	D-amino Acid Oxidase
DPR	=	Dipeptide-Repeat
EAAT2/GLT1	=	Excitatory Amino Acid Transporter 2/Glutamate Transporter 1
EGF	=	Epidermal Growth Factor

EIM	=	Electrical Impedance Myography
ELP3	=	Elongator Acetyltransferase Complex Subunit 3
ER	=	Endoplasmic Reticulum
ERBB4	=	Erb-B2 Receptor Tyrosine Kinase 4
ERS	=	Endoplasmic Reticulum Stress
EVs	=	Extracellular Vehicles
fALS	=	Familial ALS
FDA	=	Food and Drug Administration
FTLD	=	Frontotemporal Lobe Dementia
FUS	=	Fused In Sarcoma
G-CSF	=	Granulocyte Colony-Stimulating Factor
HDL	=	High-Density Lipoprotein
HERV-K	=	Human Endogenous Retrovirus-K
HML-2	=	Human Endogenous Retrovirus-K
HNRNPA1	=	Heterogeneous Nuclear Ribonucleoprotein A1
LDL	=	Low-Density Lipoprotein
LMN	=	Lower Motor Neuron
MATR3	=	Matrin-3 Gene
MIF	=	Migration Inhibitory Factor
MIP-1	=	Macrophage Inflammatory Proteins
miRNA	=	micro RNA
mRNA	=	messenger RNA
MSCs	=	Mesenchymal Stem Cells
mSOD1	=	Mutant Superoxide Dismutase 1
MUNE	=	Motor Unit Number Estimation
MVBs	=	Multivesicular Bodies
NEK1	=	NIMA Related Kinase 1
NI	=	Neurophysiological Index
NLS	=	Nuclear Localization Sequence
NMDA	=	N-methyl-D-aspartate
NTFs	=	Neurotrophic Growth Factors
OPTN	=	Optineurin gene
PARP	=	Poly (ADP-ribose) Polymerases
PDK4	=	Pyruvate Dehydrogenase Kinase 4
PET	=	Positron Emission Tomography
PFN1	=	Profilin 1 Gene
RNAi	=	RNA Interference
sALS	=	Sporadic/Standard ALS
SETX	=	Senataxin Gene
SIGMAR1	=	Sigma Non-Opioid Intracellular Receptor 1 gene
SPG11	=	Spastic Paraplegia 11 Gene
SQSTM1	=	Sequestosome 1 Gene
TDP-43	=	TAR DNA-binding Protein
TLS	=	Translocated in Liposarcoma Sarcoma
TMS	=	Transcranial Magnetic Stimulation
TUBA4A	=	Tubulin Alpha 4a Gene
UBQLN2	=	Ubiquilin-2 Gene
UMN	=	Upper Motor Neuron
UPS	=	Ubiquitin-Proteasome System
VAPB	=	Vesicle-Associated Membrane Protein
VEGF	=	Vascular Endothelial Growth Factor
VLDL	=	Very Low Density Lipoprotein

AUTHORS' CONTRIBUTIONS

Vivek P. Chavda conceived the plot. Vivek P. Chavda and Dr. Chirag Patel researched the literature and wrote the manuscript and other co-authors. In addition, Dr. Chirag Patel and Vivek P. Chavda made the figures and revised the manuscript with the help of Dr. Krishna Anand and Dr. Yavuz Nuri Ertas.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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