



# Amyotrophic Lateral Sclerosis

ORPHA: 803

OMIM: 105400

 EXPORT REPORT BIOLOGY OVERVIEW CLINICAL TRIALS LATEST RESEARCH HYPOTHESIS LAB PREVALENCE**9.68 - 11.7 per 100,000 (2024 estimated)** INHERITANCE**Multifactorial (90% Sporadic), Autosomal dominant (most Familial cases), Autosomal recessive (rare, e.g., ALS2), X-linked (rare)** TAXONOMY & CLINICAL CLASSIFICATION

*"ALS is primarily classified into sporadic (90-95%) and familial (5-10%) forms, further distinguished by site of onset (limb vs. bulbar). Familial cases are linked to genes such as C9orf72, SOD1, TARDBP, and FUS. Recent 2024 projections estimate a prevalence rise to ~11 per 100,000 due to aging populations."*

## 1 CLINICAL ONSET FORMS

- Limb-onset ALS
- Bulbar-onset ALS
- Respiratory-onset ALS

## 2 ETIOLOGICAL CLASSIFICATION

- Sporadic ALS (90-95%)
- Familial ALS (5-10%)
- Juvenile ALS

## 3 GENETIC PHENOTYPES (OMIM)

- ALS1 (SOD1)
- ALS2 (Alsin)
- ALS4 (Senataxin)
- ALS-FTD (C9orf72)
- ALS28
- SPAX11

## PATHOGENESIS & MECHANISM

**"Amyotrophic Lateral Sclerosis (ALS) is a complex neurodegenerative disorder characterized by the progressive loss of upper and lower motor neurons. The pathophysiology is multifaceted, converging on:**

- 1) \*\*Proteinopathy\*\*: Cytoplasmic aggregation of ubiquitinated proteins, primarily TDP-43 (97% of cases), FUS, and SOD1, leading to sequestration of essential cellular factors and toxic gain-of-function.**
- 2) \*\*RNA Dysmetabolism\*\*: Defects in RNA processing, splicing (e.g., STMN2 cryptic splicing), and transport, exacerbated by mutations in RBPs like TDP-43, FUS, and MATR3.**
- 3) \*\*Nucleocytoplasmic Transport Defects\*\*: Disruption of the nuclear pore complex and importins/exportins (e.g., sequestered by C9orf72 dipeptide repeats).**
- 4) \*\*Impaired Proteostasis & Autophagy\*\*: Failure of the ubiquitin-proteasome system and autophagy (TBK1, OPTN, C9orf72, SQSTM1) to clear aggregates.**
- 5) \*\*Mitochondrial Dysfunction & Energy Deficiency\*\*: Impaired mitochondrial function and oxidative stress.**

**Oxidative Stress\*\*: SOD1 mutations cause accumulation of superoxide radicals; general mitochondrial failure leads to energy deficits in metabolically demanding motor neurons.** 6) **\*\*Glutamate Excitotoxicity\*\*:** Reduced uptake by astrocytic EAAT2 leads to calcium overload and neuronal death."



## CELLULAR VULNERABILITY

### PRIMARY CELL TYPES

Upper Motor Neurons (Betz cells in Motor Cortex)

Lower Motor Neurons (Spinal cord anterior horn, Brainstem nuclei)

Astrocytes (loss of glutamate support)

Microglia (neuroinflammation)

Oligodendrocytes (metabolic support failure)

### VULNERABILITY FACTORS

**High Metabolic Demand:** Motor neurons have massive cell bodies and extremely long axons requiring efficient mitochondrial transport and ATP production.

**Low Calcium Buffering Capacity:** Motor neurons lack calcium-binding proteins (e.g., parvalbumin/calbindin), making them susceptible to glutamate excitotoxicity.

**Axonal Transport Reliance:** Dependence on long-range retrograde/anterograde transport for trophic factors and waste clearance.

**Prion-like Propagation:** Anatomical connectivity allows spreading of misfolded proteins (TDP-43, SOD1) across synaptic networks.

**Golgi Fragmentation:** Driven by USP11-ITCH axis defects, leading to autolysosomal failure in neurons.

### THERAPEUTIC IMPLICATIONS

**Gene Therapies:** ASOs (Tofersen, Jacifusen) to degrade toxic RNA (SOD1, FUS, C9orf72).

**Small Molecules:** Edaravone (free radical scavenger), Riluzole (glutamate modulator).

**Autophagy Activators:** Compounds enhancing clearance of aggregates (e.g., Rapamycin analogs, colchicine for TFEB).

**Anti-inflammatory agents:** Targeting microglial activation (e.g., Masitinib).

**Nuclear Transport Restoration:** CRM1 inhibitors or stabilizers of the nuclear pore.

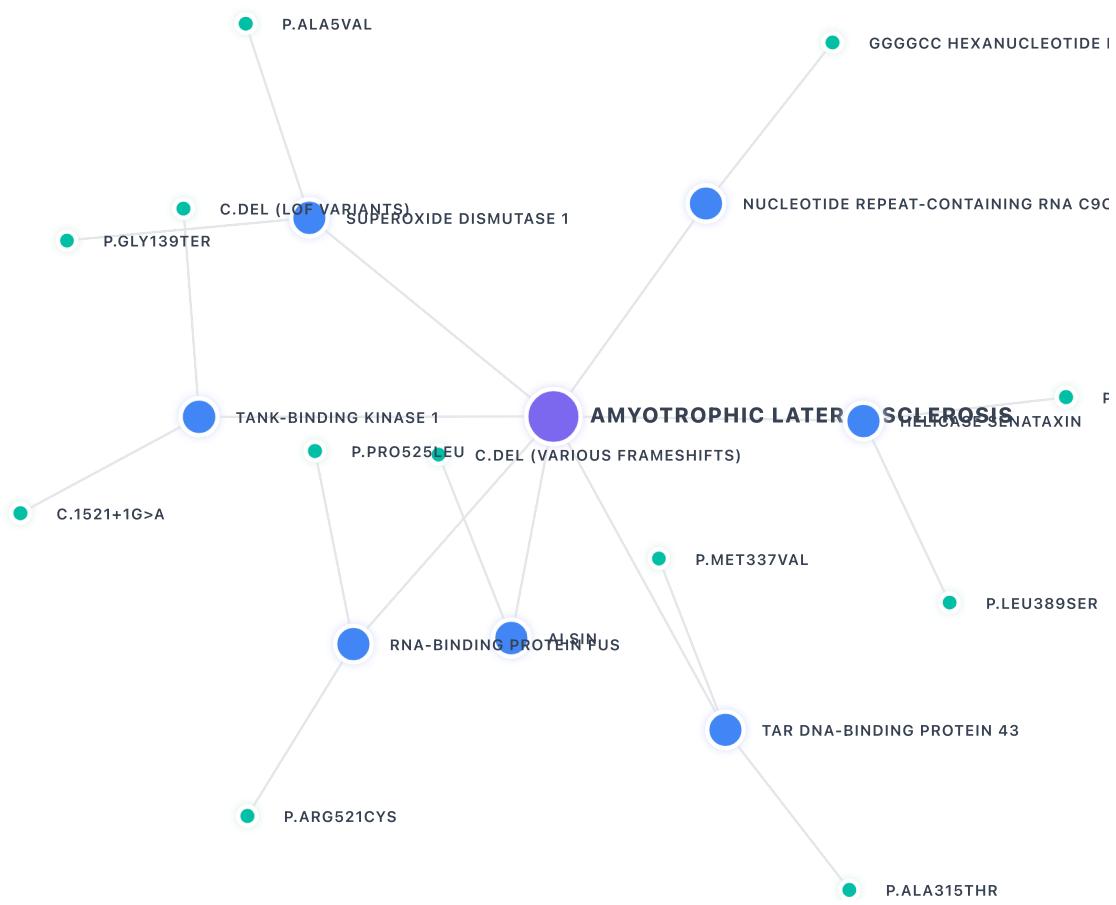


## BIO-RELATIONSHIP GRAPH

DISEASE

PROTEIN

VARIANT



## STRUCTURAL PROTEOMICS LAB

### Alsin

ALPHAFOLD

UNIPROT: Q96Q42

#### MOLECULAR FUNCTION

PLDDT: MEDIUM (70-90 FOR DOMAINS, &lt;50 FOR LOOPS)

*"Guanine nucleotide exchange factor (GEF) for Rab5, Rab21, and Rac1. Regulates early endosome fusion, trafficking, and neurite outgrowth. Acts as a neuroprotective factor against SOD1 toxicity."*

#### FUNCTIONAL DOMAINS

RLD (RCC1-like)

DH/PH (RhoGEF)

VPS9 (RabGEF)

#### THERAPEUTIC POTENTIAL

Challenging (Large scaffold); Gene Therapy candidate

#### INTERACTORS

Rab5, Rac1, SOD1 (mutant)

 SIGNALING PATHWAYS

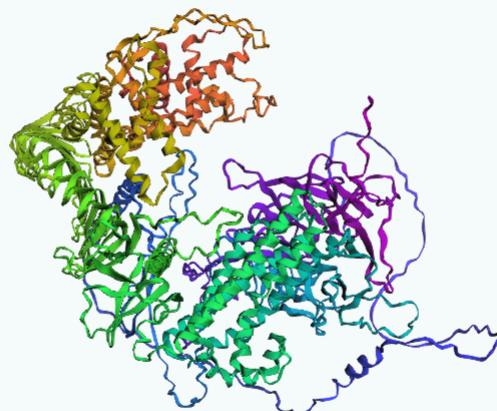
Endosomal Trafficking   Neurite Outgrowth

## PATHOGENIC VARIANTS MAPPED

c.del (various frameshifts)



PATHOGENIC (RECESSIVE)

 ALPHAFOLD 3D STRUCTURE PRIMARY TISSUE: UBIQUITOUS (HIGH IN BRAIN/SPINAL CORD)

## Helicase senataxin

ALPHAFOLD

UNIPROT: Q7Z333

 MOLECULAR FUNCTION

PLDDT: HIGH &gt; 90 (HELICASE CORE)

"RNA/DNA helicase that resolves R-loops (RNA:DNA hybrids) formed during transcription. Promotes transcription termination and prevents genome instability. regulates autophagy via modulation of autophagy gene transcription."

 FUNCTIONAL DOMAINS

N-terminal interaction domain

 THERAPEUTIC POTENTIAL

Targetable (Helicase activity modulation)

Superfamily 1 Helicase domain

Nuclear Localization Signal

## INTERACTORS

RNA Polymerase II

XRN2

ZPR1

 SIGNALING PATHWAYS

DNA Damage Response   RNA Processing   Autophagy

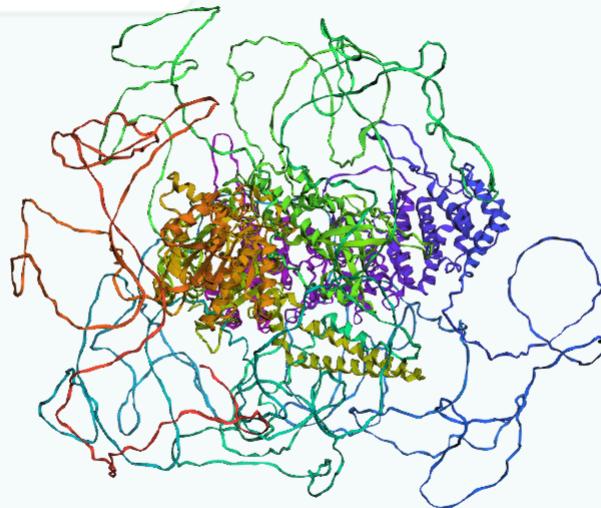
## PATHOGENIC VARIANTS MAPPED

p.Leu389Ser

PATHOGENIC (DOMINANT ALS4)

p.Thr13Pro

PATHOGENIC

 ALPHAFOOLD 3D STRUCTURE PRIMARY TISSUE: UBIQUITOUS

## TAR DNA-binding protein 43

ALPHAFOLD

UNIPROT: Q13148

 MOLECULAR FUNCTION

PLDDT: LOW &lt; 50 (C-TERMINAL DOMAIN)

"RNA-binding protein regulating splicing (e.g., CFTR, STMN2), mRNA stability, and transport. Forms toxic cytoplasmic aggregates in 97% of ALS cases (TDP-43 proteinopathy)."

**FUNCTIONAL DOMAINS**

RRM1 RRM2

C-terminal Glycine-rich (Prion-like domain)

**THERAPEUTIC POTENTIAL**Difficult (Disordered C-term); Strategies:  
ASOs, degradation (PROTACs), aggregation  
inhibitors**INTERACTORS**

HNRNPA1 HNRNPA2B1 UBQLN2

**SIGNALING PATHWAYS**

RNA Splicing Stress Granule Dynamics

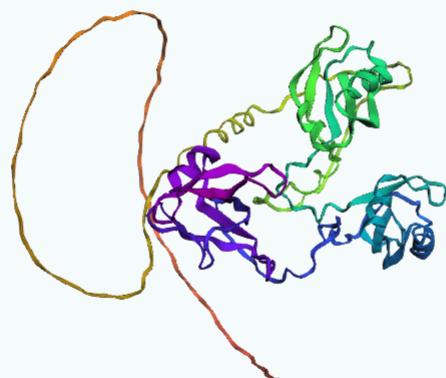
**PATHOGENIC VARIANTS MAPPED**

p.Met337Val

PATHOGENIC

p.Ala315Thr

PATHOGENIC

**ALPHAFOLD 3D STRUCTURE****PRIMARY TISSUE: UBIQUITOUS (NUCLEAR)****RNA-binding protein FUS**

ALPHAFOLD

UNIPROT: P35637

**⚡ MOLECULAR FUNCTION**

PLDDT: LOW &lt; 50 (N-TERMINAL LC DOMAIN)

"Binds DNA/RNA to regulate transcription, splicing, and transport. Mutations in the NLS lead to cytoplasmic mislocalization and liquid-liquid phase separation (LLPS) hardening into aggregates."

**🌐 FUNCTIONAL DOMAINS**

Low Complexity (LC/Prion-like) domain      RRM  
Zinc Finger      RGG repeats      PY-NLS

**🎯 THERAPEUTIC POTENTIAL**

Biologic (ASOs e.g., Jacifusen targeting FUS expression)

**INTERACTORS**

EWS      TAF15      SMN1

**📈 SIGNALING PATHWAYS**

RNA Transport      DNA Damage Response

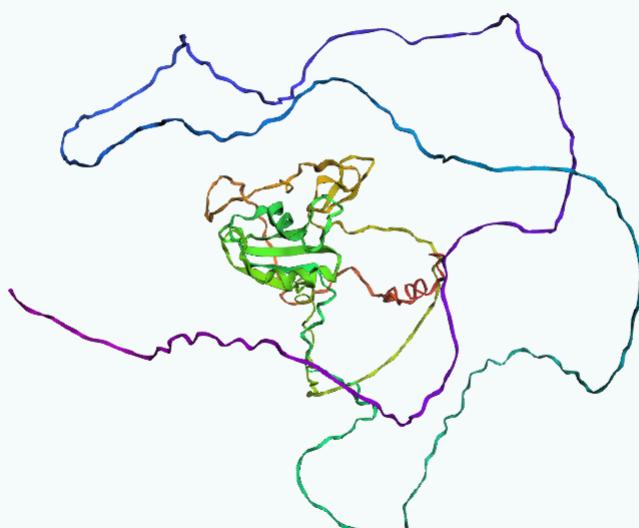
**PATHOGENIC VARIANTS MAPPED**

p.Pro525Leu

PATHOGENIC (JUVENILE ALS)

p.Arg521Cys

PATHOGENIC

**📦 ALPHAFOOLD 3D STRUCTURE****📦 PRIMARY TISSUE: UBIQUITOUS**

# Superoxide dismutase 1

ALPHAFOLD

UNIPROT: P00441

## ⚡ MOLECULAR FUNCTION

PLDDT: HIGH &gt; 90

"Antioxidant enzyme converting superoxide to oxygen and hydrogen peroxide. ALS mutations cause structural instability and toxic gain of function (aggregation) rather than loss of enzymatic activity."

## ⌚ FUNCTIONAL DOMAINS

Copper/Zinc binding domain

Beta-barrel core

## 🎯 THERAPEUTIC POTENTIAL

Good (ASOs approved: Tofersen; Small molecule stabilizers)

## INTERACTORS

CCS (Copper Chaperone)

BCL2

Derlin-1

## ⚡ SIGNALING PATHWAYS

Oxidative Stress Response   Apoptosis

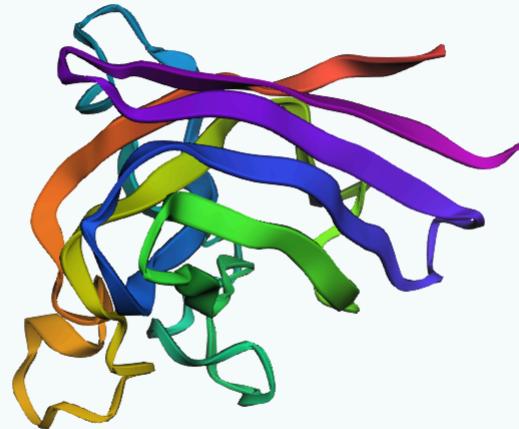
## PATHOGENIC VARIANTS MAPPED

p.Ala5Val

PATHOGENIC (AGGRESSIVE)

p.Gly139Ter

PATHOGENIC

**ALPHAFOLD 3D STRUCTURE****PRIMARY TISSUE: UBIQUITOUS****Nucleotide repeat-containing RNA C9orf72**

ALPHAFOLD

UNIPROT: Q96LT7

**MOLECULAR FUNCTION**

PLDDT: HIGH &gt; 85

"Acts as a Guanine Nucleotide Exchange Factor (GEF) for Rab8/Rab39b, regulating autophagy and vesicular trafficking. Expansion leads to RNA foci and toxic Dipeptide Repeat (DPR) proteins (poly-GA, poly-GR)."

**FUNCTIONAL DOMAINS**

DENN domain (uDENN, cDENN, dDENN)

**THERAPEUTIC POTENTIAL**

Biologic (ASOs targeting repeat RNA)

## INTERACTORS

SMCR8 WDR41 ULK1

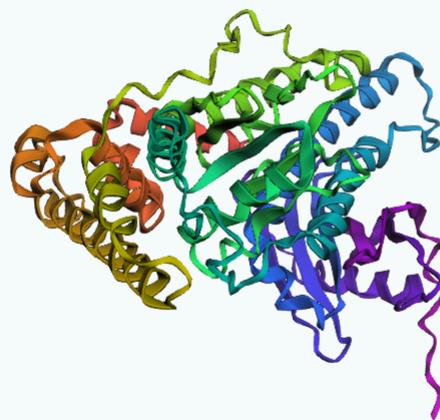
**SIGNALING PATHWAYS**

Autophagy Vesicular Trafficking

**PATHOGENIC VARIANTS MAPPED**

GGGGCC hexanucleotide expansion  
PATHOGENIC (MOST COMMON ALS/FTD CAUSE)

ALPHAFOLD 3D STRUCTURE



PRIMARY TISSUE: BRAIN (NEURONS), IMMUNE CELLS

## TANK-binding kinase 1

ALPHAFOLD

UNIPROT: Q9UHD2

MOLECULAR FUNCTION

PLDDT: HIGH > 90 (KINASE DOMAIN)

"Serine/threonine kinase that plays a central role in innate immunity (IFN induction) and selective autophagy (mitophagy) by phosphorylating receptors like Optineurin (OPTN) and p62."

FUNCTIONAL DOMAINS

Serine/Threonine Kinase domain

Ubiquitin-like domain (ULD)

Scaffold/Dimerization domain (SDD)

THERAPEUTIC POTENTIAL

Small Molecule (Kinase modulators)

INTERACTORS

OPTN SQSTM1/p62 IRF3

SIGNALING PATHWAYS

## PATHOGENIC VARIANTS MAPPED

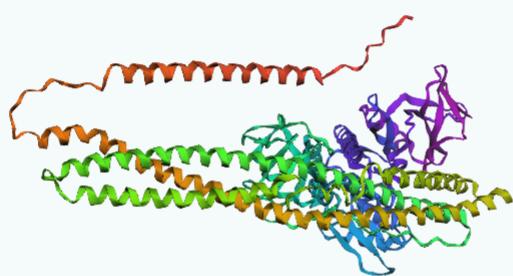
c.del (LOF variants)

PATHOGENIC

c.1521+1G&gt;A

PATHOGENIC

## ALPHAFOLD 3D STRUCTURE



## PRIMARY TISSUE: UBIQUITOUS

## ACTIVE RECRUITMENT PIPELINE

ID	TITLE	PHASE	STATUS
NCT04856982	<b>ATLAS Study: Tofersen for Presymptomatic SOD1-ALS</b> Tofersen (Antisense Oligonucleotide)	3	ACTIVE, ENROLLING
NCT05822945	<b>Phase 2 Study of COYA 302 in Amyotrophic Lateral Sclerosis</b> COYA 302 (Low-Dose IL-2 + Abatacept)	2	ACTIVE, ENROLLING

ID	TITLE	PHASE	STATUS
NCT03127267	<b>Masitinib Confirmatory Phase 3 Trial in ALS</b> Masitinib (Tyrosine Kinase Inhibitor)	PHASE 3	ACTIVE, ENROLLING
NCT05357950	<b>PrimeC Phase 3 Trial for ALS (PARADIGM)</b> PrimeC (Ciprofloxacin/Celecoxib)	PHASE 3	RECRUITING
NCT04220190	<b>RAPA-501 Autologous Hybrid TREG/Th2 Cell Therapy</b> RAPA-501	PHASE 2/3	ACTIVE

### 🕒 CLINICAL PIPELINE ANALYSIS

*"The 2025-2026 clinical pipeline for ALS is robust, with pivotal Phase 3 trials recruiting for both sporadic and familial forms. Key studies include the ATLAS trial for presymptomatic SOD1 mutation carriers, testing the concept of early intervention with Tofersen. Immunomodulation remains a strong theme, with COYA 302 (T-reg enhancement) and Masitinib (mast cell inhibition) advancing in late-stage trials. Novel modalities such as autologous cell therapy (RAPA-501) and synergistic combination drugs (PrimeC) indicate a diversification of therapeutic approaches beyond traditional small molecules."*

#### ATLAS Study: Tofersen for Presymptomatic SOD1-ALS

PHASE 3

ACTIVE, ENROLLING NCT04856982 ↗

Tofersen (Antisense Oligonucleotide)

#### Phase 2 Study of COYA 302 in Amyotrophic Lateral Sclerosis

PHASE 2

ACTIVE, ENROLLING NCT05822945 ↗

COYA 302 (Low-Dose IL-2 + Abatacept)

#### Masitinib Confirmatory Phase 3 Trial in ALS

PHASE 3

ACTIVE, ENROLLING NCT03127267

Masitinib (Tyrosine Kinase Inhibitor)

**PrimeC Phase 3 Trial for ALS (PARADIGM)****PHASE 3**

RECRUITING NCT05357958

PrimeC (Ciprofloxacin/Celecoxib)

**RAPA-501 Autologous Hybrid TREG/Th2 Cell Therapy****PHASE 2/3**

ACTIVE NCT04228198

RAPA-501

 SCIENTIFIC BIBLIOGRAPHY EXPORT TO ZOTERO (RIS)**AI RESEARCH SYNTHESIS**

"The current ALS research landscape in 2026 is characterized by a strategic bifurcation between broad-spectrum neuroprotective agents and precision gene therapies. Recent data highlights the efficacy of Edaravone in real-world settings, alongside emerging Phase 3 contenders like Masitinib and PrimeC which target neuroinflammation and proteostasis respectively. A major breakthrough involves the structural elucidation of cross-seeding mechanisms, particularly between Amyloid- $\beta$  and TDP-43, suggesting a molecular bridge between ALS and Alzheimer's pathology. Furthermore, the USP11-ITCH axis has been identified as a critical regulator of autolysosomal failure, offering a novel druggable target to address the Golgi fragmentation characteristic of motor neuron degeneration."

 KEY RESEARCH PAPERS

***"The selected 2026 bibliography emphasizes three key domains: clinical validation of existing therapies (Edaravone efficacy and safety), exploration of novel molecular mechanisms (USP11-ITCH axis, Golgi fragmentation), and comparative analysis of therapeutic strategies (gene-targeted vs. broad-spectrum). Notable publications include large-scale post-marketing studies in 'Muscle & Nerve' and mechanistic***

***breakthroughs in 'Autophagy' and 'Journal of Genetics and Genomics', reflecting a shift towards integrating clinical outcomes with deep molecular phenotyping."***

### Safety of Intravenous Edaravone in Clinical Practice.

Genge A, Apple S

MUSCLE & NERVE • 2026

### Generalizability of Edaravone Efficacy.

Brooks BR, Ennist DL, Beaulieu D, Apple S

MUSCLE & NERVE • 2026

### Gene-targeted versus broad-spectrum therapies in ALS: comparative lessons and strategic outlook.

Shen Y, Shen S, Luo ZG

JOURNAL OF GENETICS AND GENOMICS • 2026

### Golgi fragmentation driven by the USP11-ITCH axis triggers autolysosomal failure in neurodegeneration.

Xiang Q, Liu Y, Wang J

AUTOPHAGY • 2026

### Trajectory of Mobility Function Decline for People with Motor Neuron Disease.

Sia T, Sheehy TP, Morgan P, Wools CA, Zhao Y, Gibbs R, Mathieson S, Smith AA

ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION • 2026



### VALIDATED DATA SOURCES

ORPHANET

OMIM

UNIPROT

NCBI GENE

CLINVAR

PUBMED

ALPHAFOLD DB

**WEB SEARCH GROUNDING LINKS**

↪ nih.gov  
↪ preprints.org  
↪ orpha.net  
↪ targetals.org  
↪ nih.gov  
↪ pharmacytimes.com  
↪ neurologylive.com  
↪ droracle.ai  
↪ researchgate.net  
↪ prnewswire.com  
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↪ mdpi.com  
↪ researchgate.net  
↪ aginganddisease.org  
↪ als.net  
↪ hopkinsmedicine.org  
↪ frontiersin.org  
↪ cdc.gov  
↪ frontiersin.org  
↪ neupsykey.com  
↪ researchgate.net  
↪ nih.gov  
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↪ vib.be  
↪ nih.gov  
↪ nih.gov  
↪ nih.gov  
↪ drugtargetreview.com  
↪ nih.gov  
↪ biorxiv.org  
↪ nih.gov

## 💡 COMPARATIVE DISCOVERY LAB

**"Cross-disease analysis reveals profound mechanistic overlaps between ALS and Frontotemporal Dementia (FTD), driven by shared genetic drivers (C9orf72, TARDBP) and TDP-43 proteinopathy. Structural homology studies extend this continuum to Alzheimer's Disease, where Amyloid- $\beta$  fibrils have been shown to catalyze TDP-43 aggregation via direct cross-seeding. Additionally, shared deficits in oxytocin signaling and mitochondrial function suggest potential repurposing opportunities for therapies originally developed for Huntington's or Parkinson's disease, targeting common neurodegenerative pathways rather than disease-specific symptoms."**

### COMPARATIVE TARGET

## Frontotemporal Dementia (FTD)

### SHARED GENETIC LOCI

C9orf72   TARDBP   FUS   TBK1   VCP   SQSTM1

### �� SHARED MECHANISM

TDP-43/FUS Proteinopathy & RNA Dysregulation

### ಠ PATHWAY INTERSECTION

RNA transport (KEGG)  
Autophagy (Reactome)  
Protein processing in endoplasmic reticulum

### STRUCTURAL HOMOLOGY INSIGHT

TDP-43 and FUS contain intrinsically disordered regions (prion-like domains) that drive liquid-liquid phase separation (LLPS) and subsequent pathological fibrillization in both diseases.

### 💡 RESEARCH OPPORTUNITY

Targeting shared RNA metabolism defects and autophagy pathways (C9orf72, TBK1).

**COMPARATIVE TARGET**

## Alzheimer's Disease

**SHARED GENETIC LOCI**

APOE (Risk modifier)

TARDBP (Co-pathology)

**🔗 SHARED MECHANISM**

### Cross-seeding of Amyloidogenic Proteins

**↗ PATHWAY INTERSECTION**

Protein folding/misfolding

Oxidative stress response

Mitochondrial dysfunction

**STRUCTURAL HOMOLOGY INSIGHT**

Amyloid- $\beta$  fibrils can bind the amyloidogenic core region of TDP-43, inducing a transition from helical to  $\beta$ -sheet rich structures, accelerating aggregation.

**💡 RESEARCH OPPORTUNITY**

Investigating the catalytic role of Amyloid- $\beta$  (A $\beta$ 42) in promoting TDP-43

aggregation via structural transformation.

**COMPARATIVE TARGET**

## Huntington's Disease

**SHARED GENETIC LOCI**

C9orf72 (Repeat expansion mechanism similarity)

HTT (PolyQ aggregation parallels)

**🔗 SHARED MECHANISM**

### Protein Aggregation & Oxytocin Signaling Impairment

**↗ PATHWAY INTERSECTION**

Oxytocin signaling pathway

**Neurotrophin signaling pathway****STRUCTURAL HOMOLOGY INSIGHT**

Both involve misfolded protein aggregates (SOD1/TDP-43 vs Huntingtin) leading to selective neuronal vulnerability and transcriptional dysregulation.



**RESEARCH OPPORTUNITY** Therapeutic potential of Oxytocin to address early social cognition deficits and psychiatric symptoms common to both.

## Hypothesis Lab

Use our AI-driven engine to generate drug repurposing candidates for **Amyotrophic Lateral Sclerosis** based on the identified molecular mechanisms and cellular vulnerabilities.

### Generate Repurposing Hypotheses

#### **Sirolimus (Rapamycin)**

**SCORE: 75****MTOR INHIBITOR**

ALS pathology involves impaired autophagy and protein aggregation (TDP-43, SOD1). mTOR inhibition by Sirolimus induces autophagy, potentially compensating for defects in TBK1/OPTN/SQSTM1 pathways and enhancing the clearance of cytotoxic aggregates.

#### **Deferiprone**

**SCORE: 85****IRON CHELATOR**

ALS motor neurons exhibit iron accumulation, driving oxidative stress and ferroptosis (linked to Mitochondrial Dysfunction). Deferiprone can cross the blood-brain barrier to chelate

excess iron, reducing reactive oxygen species generation and preserving mitochondrial function.

## Guanabenz

SCORE: 70

### ALPHA-2 ADRENERGIC AGONIST; INHIBITOR OF REGULATORY SUBUNIT OF PROTEIN PHOSPHATASE 1 (PPP1R15A)

Guanabenz inhibits the dephosphorylation of eIF2alpha, prolonging the Integrated Stress Response (ISR). This helps cells manage ER stress caused by the accumulation of misfolded proteins (Proteinopathy) like TDP-43 and FUS, preventing proteotoxicity-induced apoptosis.

## Retigabine (Ezogabine)

SCORE: 80

### KV7 (KCNQ) POTASSIUM CHANNEL OPENER

Motor neuron hyperexcitability and glutamate excitotoxicity are early features of ALS. Retigabine activates Kv7 channels, hyperpolarizing the resting membrane potential and reducing neuronal excitability, thereby protecting against calcium overload and excitotoxic death.

POWERED BY GOOGLE GEMINI, MADE FOR GOOGLE DEEPMIND 2026 GEMINI HACKATHON