Amyotrophic lateral sclerosis (ALS)

(part 1)

Epidemiology

Amyotrophic lateral sclerosis (ALS) is the **most common motor neuron disease in adults.**

Relatively rare disease

Incidence: ↑ with age
average age of onset: 58–60 years
highest incidence: 60-79 years
stable/increase
approximately 1.68 (range 1–2.6) cases per 100 000 persons annually
average survival from onset to death: 2–4 years (respiratory failure)

Prevalence: expected to increase due to aging in population and increased life expectancy
approximately 6 cases per 100 000.

Definition

Amyotrophy = muscle loss
Lateral sclerosis = axonal loss in the lateral spinal cord columns

First description: French neurologist Jean-Martin **Charcot in 1869** (Charcot's disease in France).

ALS, aka "Lou Gehrig's disease," is a progressive and fatal neurodegenerative disorder affecting **motor neurons in the brain and spinal cord.**

The clinical features reflect the presence and location of **upper or lower motor neuron degeneration** at a given time.

With **voluntary muscle** action progressively affected, patients in the later stages of the disease may become totally paralyzed.

Lou Gehrig: baseball player died of ALS in 1941

ALS ASSOCIATION

Clinical presentation

About one-third of patients have bulbar onset, more common in women.

Bulbar functions involve activities of the oropharyngeal muscles.
Symptoms include dysarthria, dysphagia (usually for liquids more than solids), difficulty chewing, and hypersalivation.
There is usually difficulty holding the mouth closed or pursing the lips.

The oculomotor nuclei are spared until "end-stage" and brainstem sensory pathways are not affected.

Lower motor neurons (LMN)

- Brainstem cranial motor nerve nuclei or anterior horn cells
- LMN dysfunction is characterised by muscle weakness, atrophy, and fasciculations

Upper motor neurons (UMN)

- Betz cells in layer V of the primary motor cortex
- UMN dysfunction is characterised by increased and pathological reflexes (including Hoffmann's sign, Babinski, and snout), pathological spread of reflexes, preserved reflexes in a weak limb, and spasticity

Bulbar amyotrophic lateral sclerosis

- Phenotype presents with weakness starting in the muscles controlling speaking and swallowing
- Both LMN and UMN signs are present

Classical amyotrophic lateral sclerosis

- Phenotype presents with muscle weakness starting in the limbs; both LMN and UMN signs are present

Diagnostic criteria

Considerable phenotypic heterogeneity in ALS presentation

Cognitive and behavioural changes in >60% of pts

Frontotemporal dementia in about 15% of pts (ALS and FTD continuum)

Revised El Escorial criteria for diagnosis of amyotrophic lateral sclerosis (ALS)

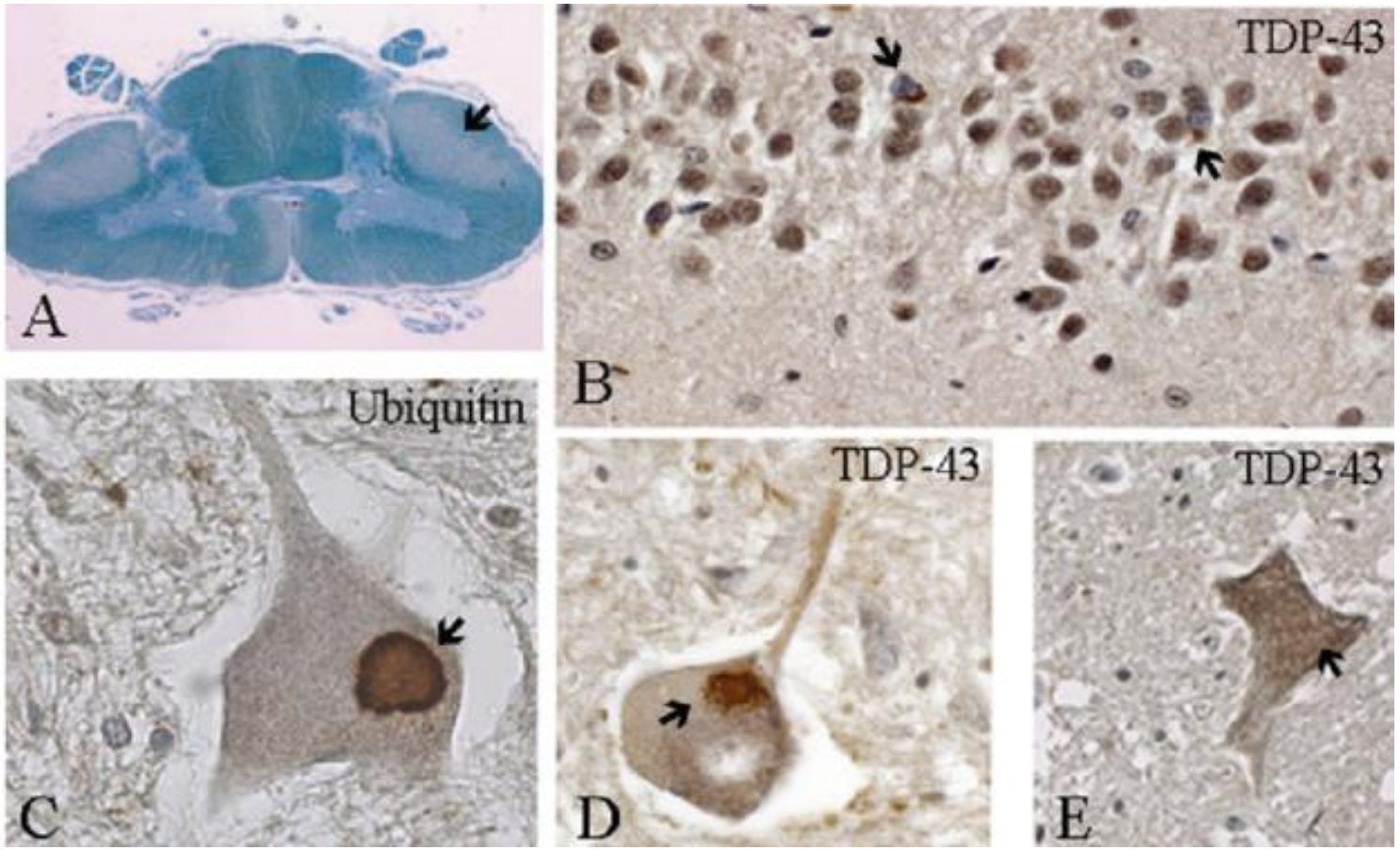
Diagnostic category	Features
Clinically definite ALS	Upper and lower motor neuron signs in bulbar and at least two spinal (lumbosacral, thoracic, or cervical) regions or Upper and lower motor neuron signs in three spinal regions
Clinically probable ALS	Upper and lower motor neuron signs in at least two regions (bulbar or spinal) with some upper motor neuron signs rostral to the lower motor neuron signs
Clinically probable ALS – laboratory-supported*	Clinical evidence of upper and lower motor neuron signs in one body region or of upper motor neuron signs in one region and EMG findings of lower motor neuron involvement in at least two body regions
Clinically possible ALS*	Upper and lower motor neuron signs in only the bulbar or only one spinal region or Upper motor neuron signs in two or more regions or Lower motor neuron signs rostral to upper motor neuron signs

*Other diagnoses are excluded by appropriate neuroimaging and laboratory studies.
EMG, electromyogram.

Neuropathology of ALS

A=atrophic anterior horns and demyelinated corticospinal tracts

B=TDP-43 cytoplasmic inclusions in dentate granules of hippocampus



C-D=ubiquitin- and TDP-43-positive inclusions in spinal cord MNs

E=diffuse cytoplasmic TDP-43 deposition in spinal cord MNs

Genetics of ALS

Mendelian familial ALS = 10-15% (incomplete penetrance in some kindreds)
Substantial genetic componenent in (apparently) sporadic ALS

Year	Locus	Gene	Inheritance	Familial (%)[a]	Sporadic (%)[a]	Disease-associated mechanism	Other associated phenotypes[b]	Refs.
1993	21q22.11	*SOD1*	Autosomal dominant, autosomal recessive, de novo	12	1–2	Oxidative stress, excitotoxicity, mitochondrial dysfunction, axonal transport disruption	Frontotemporal dementia, spastic tetraplegia and axial hypotonia	19
1994	22q12.2	*NEFH*	Autosomal dominant	Unknown	Unknown	Axonal transport disruption	Axonal Charcot–Marie–Tooth disease type 2CC	212
2001	2q33.1	*ALS2*	Autosomal recessive	Unknown	Unknown	Vesicular trafficking defects	Juvenile primary lateral sclerosis, infantile hereditary spastic paraplegia	213
2003	2p13.1	*DCTN1*	Autosomal dominant	Unknown	Unknown	Axonal transport disruption	Distal hereditary motor neuropathy type VIIB, Perry syndrome	214
2004	20q13.32	*VAPB*	Autosomal dominant	Unknown	Unknown	Proteostasis defects	Finkel-type spinal muscular atrophy	215
2004	9q34.13	*SETX*	Autosomal dominant	Unknown	Unknown	Altered ribostasis	Autosomal recessive spinocerebellar ataxia type 1	216
2006	3p11.2	*CHMP2B*	Autosomal dominant	Unknown	Unknown	Proteostasis defects, vesicular trafficking defects	Frontotemporal dementia	217,218
2008	1p36.22	*TARDBP*	Autosomal dominant, autosomal recessive, de novo	4	1	Altered ribostasis, nucleocytoplasmic transport defects	Frontotemporal dementia	38,39
2009	16p11.2	*FUS*	Autosomal dominant, autosomal recessive, de novo	4	1	Altered ribostasis, nucleocytoplasmic transport defects	Frontotemporal dementia, essential tremor	46,47
2010	9p13.3	*VCP*	Autosomal dominant, de novo	1	1	Proteostasis defects	Frontotemporal dementia, Charcot–Marie–Tooth disease type 2Y, inclusion body myopathy with early-onset Paget disease	144
2010	15q21.1	*SPG11*	Autosomal recessive	Unknown	Unknown	DNA damage	Hereditary spastic paraplegia, Charcot–Marie–Tooth disease type 2X	219
2010	10p13	*OPTN*	Autosomal dominant, autosomal recessive	<1	<1	Autophagy, inflammation	Adult-onset primary open-angle glaucoma	220
2011	Xp11.21	*UBQLN2*	X-linked dominant	<1	<1	Proteostasis defects	None	221
2011	5q35.3	*SQSTM1*	Autosomal dominant	1	<1	Autophagy, inflammation	Frontotemporal dementia, distal myopathy, childhood-onset neurodegeneration with ataxia, dystonia and gaze palsy, Paget disease of bone-3	222
2011	9p21.2	*C9orf72*	Autosomal dominant	40	7	Autophagy, global RNA alterations, intracellular trafficking defects, nucleocytoplasmic transport defects, proteostasis defects	Frontotemporal dementia	55,56

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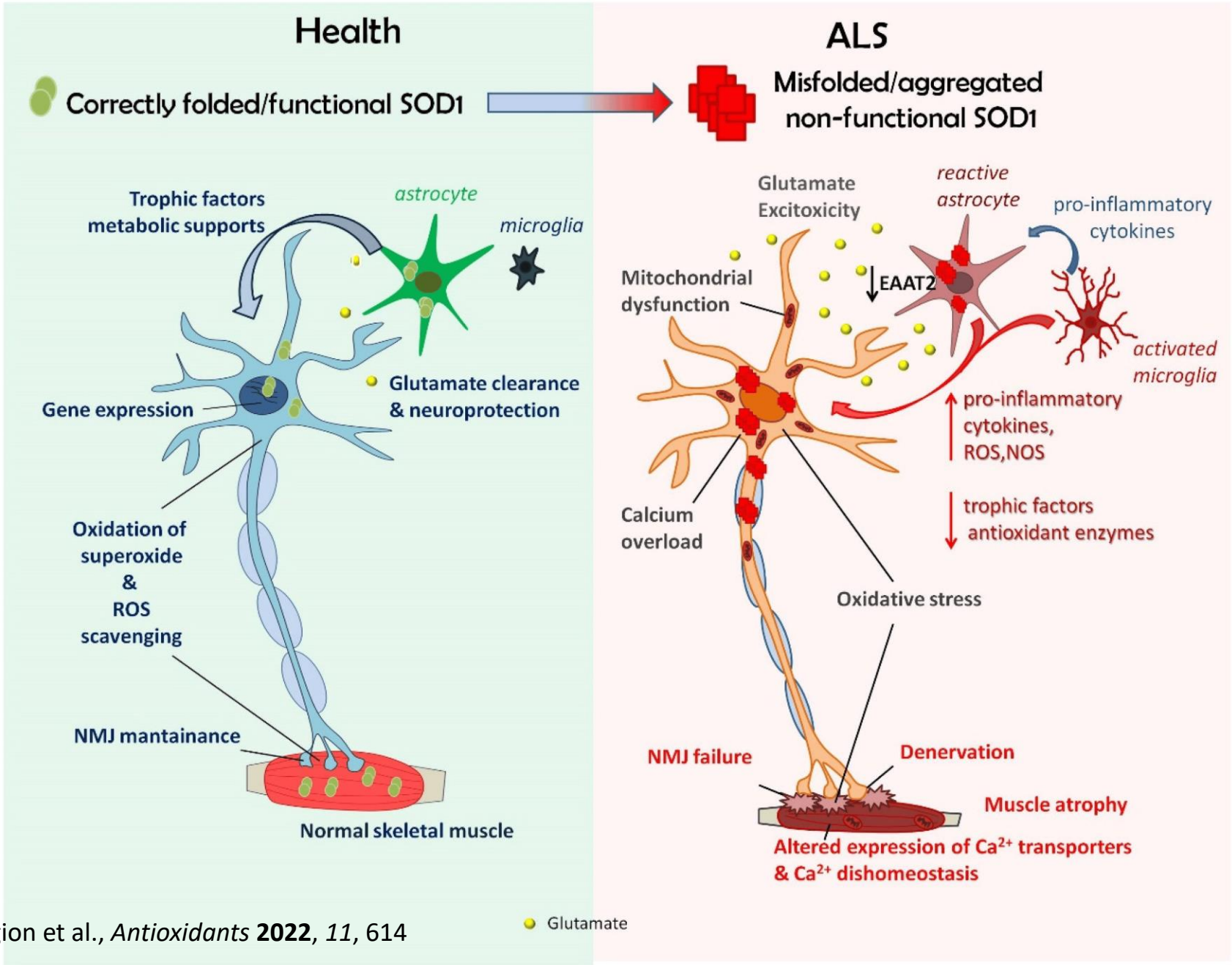
Year	Locus	Gene	Inheritance	Familial (%)[a]	Sporadic (%)[a]	Disease-associated mechanism	Other associated phenotypes[b]	Refs.
2012	17p13.2	*PFN1*	Autosomal dominant	<1	<1	Impaired axonal growth and cytoskeletal organization	None	223
2013	7p15.2	*HNRNPA2B1*	Autosomal dominant	Unknown	Unknown	Altered ribostasis	Inclusion body myositis with early-onset Paget disease with or without frontotemporal dementia 2, multisystem proteinopathy	224
2013	12q13.13	*HNRNPA1*	Autosomal dominant, de novo	Unknown	Unknown	Altered ribostasis	Inclusion body myositis with early-onset Paget disease with or without frontotemporal dementia 3, multisystem proteinopathy	224
2014	2q35	*TUBA4A*	Autosomal dominant	<1	<1	Impaired axonal growth and cytoskeletal organization	Frontotemporal dementia	225
2014	5q31.2	*MATR3*	Autosomal dominant	<1	<1	Altered ribostasis	Distal myopathy with vocal cord and pharyngeal weakness	226
2014	22q11.23	*CHCHD10*	Autosomal dominant	<1	<1	Mitochondrial dysfunction	Frontotemporal dementia, spinal muscular atrophy (Jokela type), isolated mitochondrial myopathy	227
2015	12q14.2	*TBK1*	Autosomal dominant	<1	<1	Autophagy, inflammation	Frontotemporal dementia	112
2016	4q33	*NEK1*	Not established	2	2	DNA damage, impaired cytoskeletal organization and cell cycle	Short-rib thoracic dysplasia 6 with or without polydactylism	112,114
2016	16p13.3	*CCNF*	Autosomal dominant	4	2	Proteostasis defects	Frontotemporal dementia	228
2016	21q22.3	*CFAP410*	Not established	Unknown	Unknown	Impaired cytoskeletal organization	Axial spondylometaphyseal dysplasia, retinal dystrophy with macular staphyloma	107
2017	10q22.3	*ANXA11*	Autosomal dominant	Unknown	Unknown	Dysregulation of calcium homeostasis and stress granule dynamics	Inclusion body myopathy and brain white matter abnormalities	229
2018	12q13.3	*KIF5A*	Autosomal dominant	<1	<1	Impaired cytoskeletal organization and axonal transport	Charcot–Marie–Tooth type 2, hereditary spastic paraplegia	72,73
2018	10q24.31	*ERLIN1*	Autosomal recessive	Unknown	Unknown	Dysregulation of inositol 1,4,5-trisphosphate intracellular ion channels	Hereditary spastic paraplegia	78
2019	3p21.1	*GLT8D1*	Autosomal dominant	Unknown	Unknown	Impaired ganglioside synthesis	None	230
2019	17q21.2	*DNAJC7*	Not established	Unknown	Unknown	Not established	None	84
2021	4p16.3	*HTT*	Autosomal dominant	Unknown	Unknown	Not established/ nucleocytoplasmic transport defects	Huntington disease, Lopes–Maciel–Rodan syndrome	91
2022	9q22.31	*SPTLC1*	De novo	Unknown	Unknown	Disruption of sphingolipid metabolism	Hereditary sensory and autonomic neuropathy type 1A	97,98

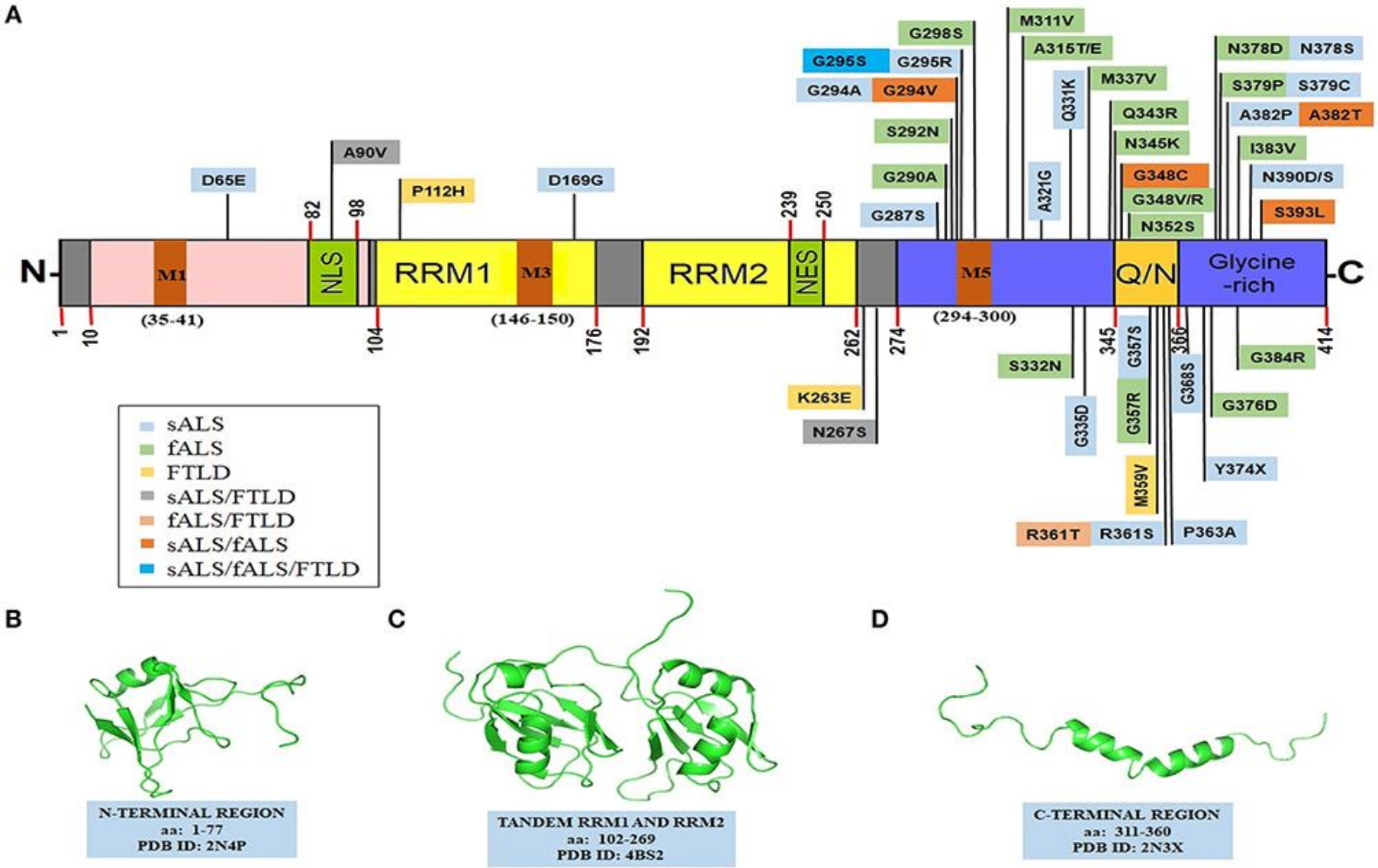
Genes are listed chronologically based on their year of discovery. [a]Percentage of amyotrophic lateral sclerosis (ALS) cases explained by mutations in the corresponding disease-causing genes. [b]Phenotypes associated with the genes extracted from the Online Mendelian Inheritance in Man database.

> 200 SOD1 mutations in ALS



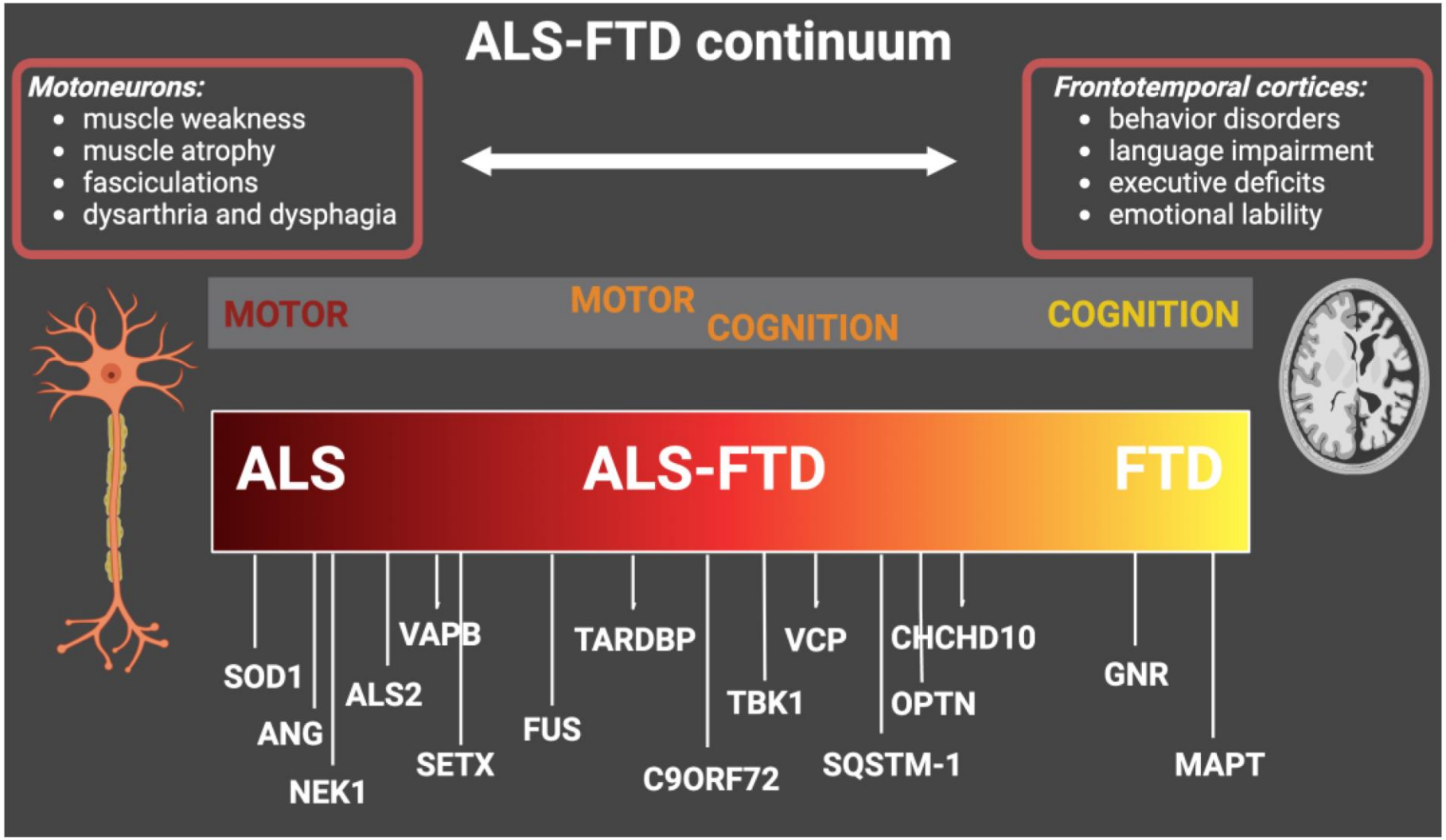
Peggion et al., *Antioxidants* **2022**, *11*, 614

TARDBP mutations



Prasad et al, Front. Mol. Neurosci., vol 12, 14 Feb 2019

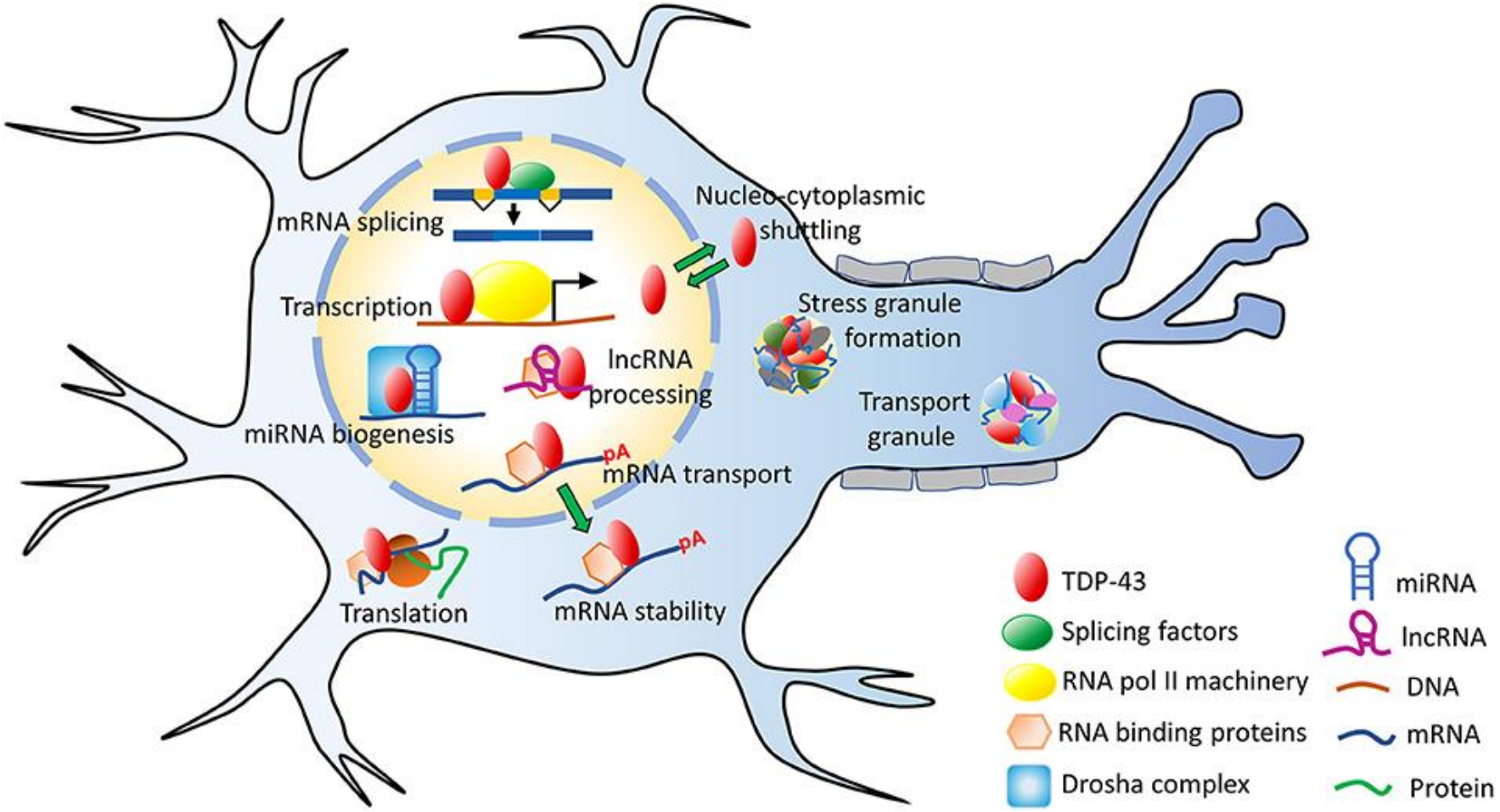
ALS-FTD continuum: a focus on genetic variants



FTD=frontotemporal dementia

De Marchi et al., *Genes* **2023**, *14*(8), 1658

TDP-43 functions

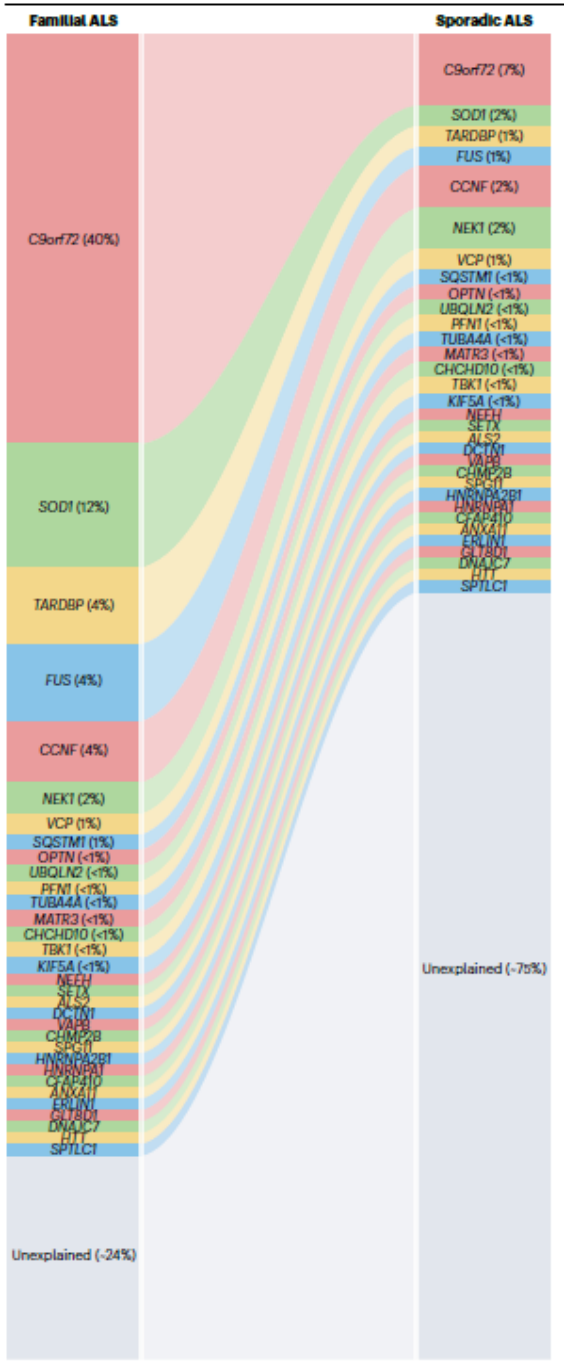


Prasad et al, Front. Mol. Neurosci., vol 12, 14 Feb 2019

Mutations in the known ALS genes explain:

76% fALS

25% sALS



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Gene-environment interactions

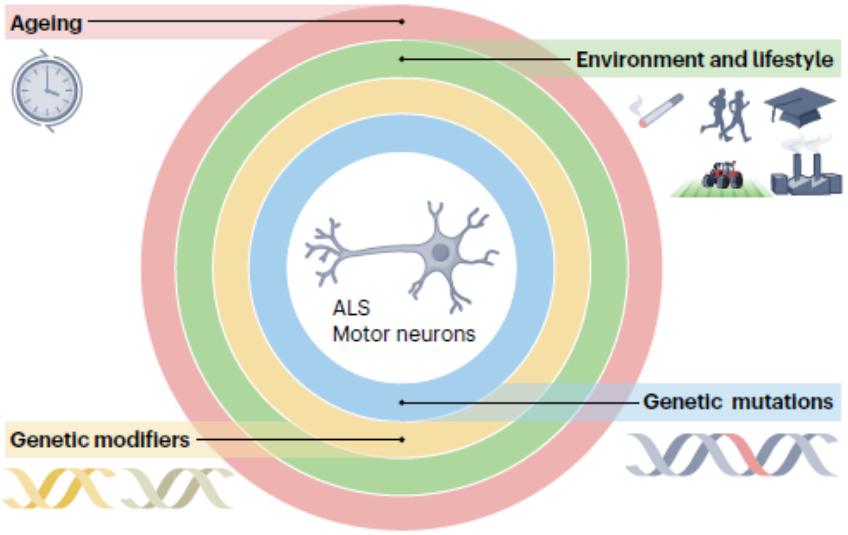
Environmental and lifestyle risk factors:

agricultural and industrial chemicals
occupations
cigarette smoking
heavy exercise
More recently: alcohol consumption
educational attainment
physical exercise
dyslipidemia
smoking

Epigenetic mechanisms:

DNA methylation
miRNA dysregulation
chromatin remodelling
histone modifications

mediate the effect of environmental factors on ALS pathogenesis



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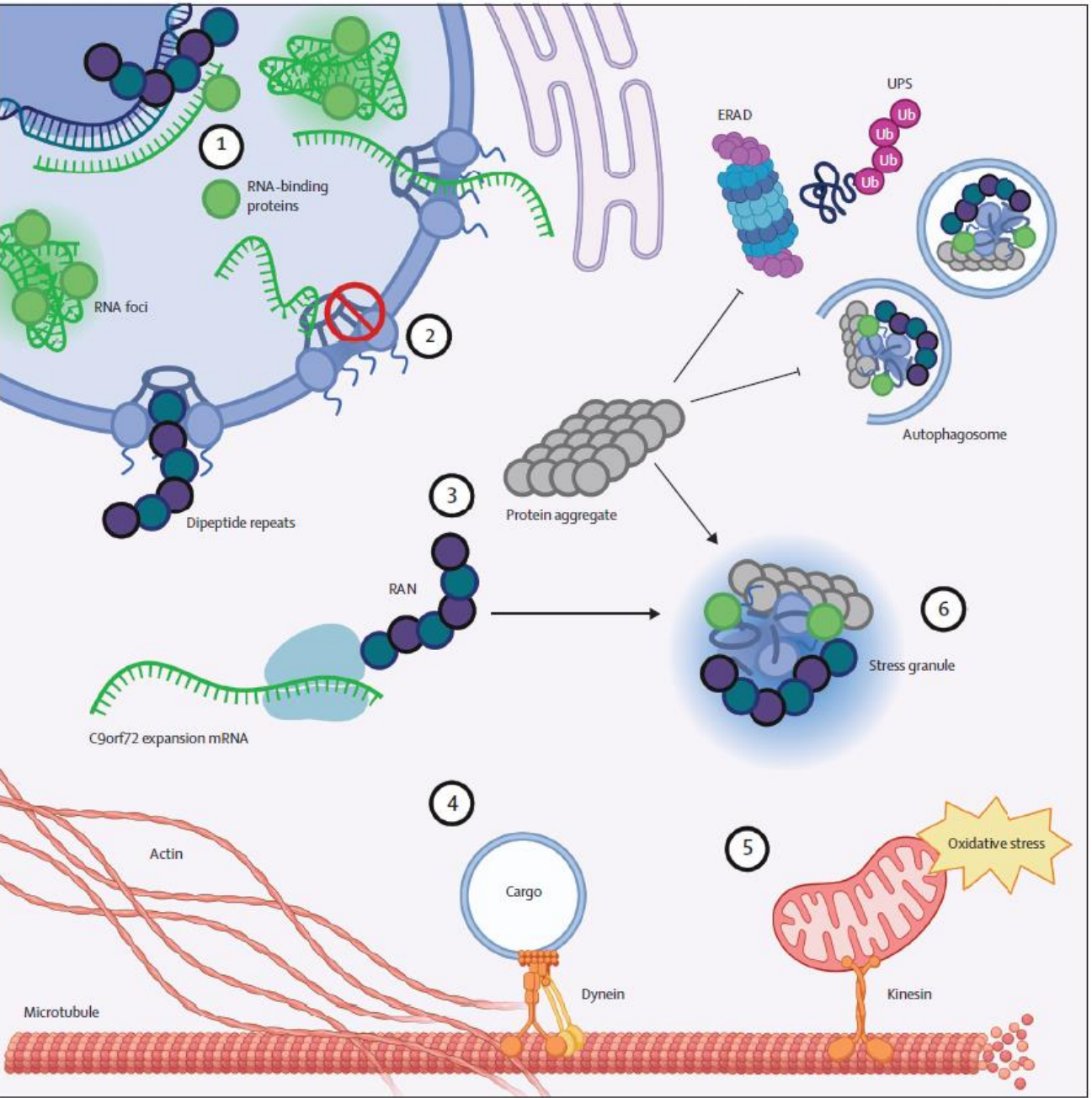
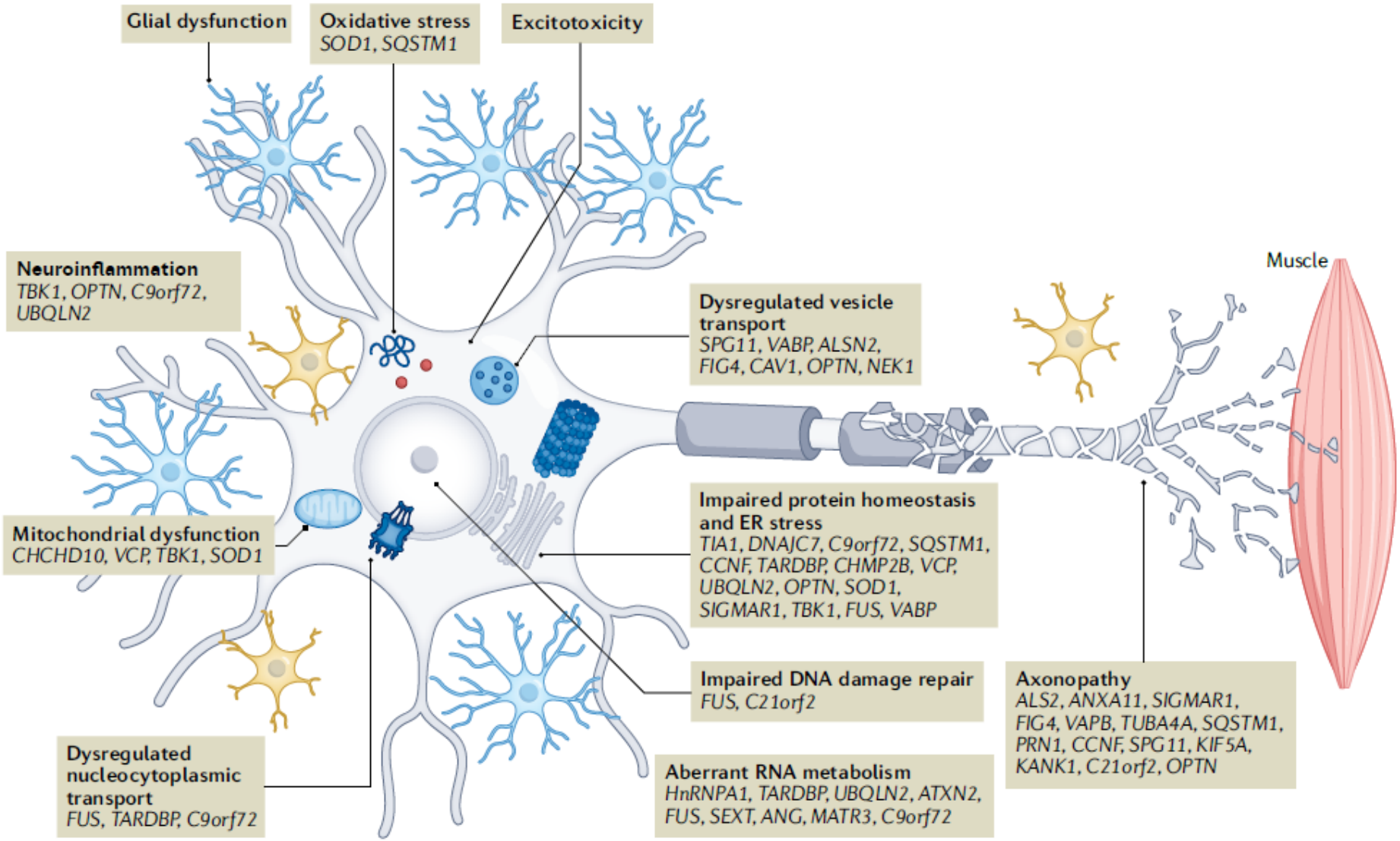
Pathophysiology



- impaired RNA metabolism
- altered proteostasis or autophagy
- cytoskeletal or trafficking defects
- mitochondrial dysfunction
- compromised DNA repair

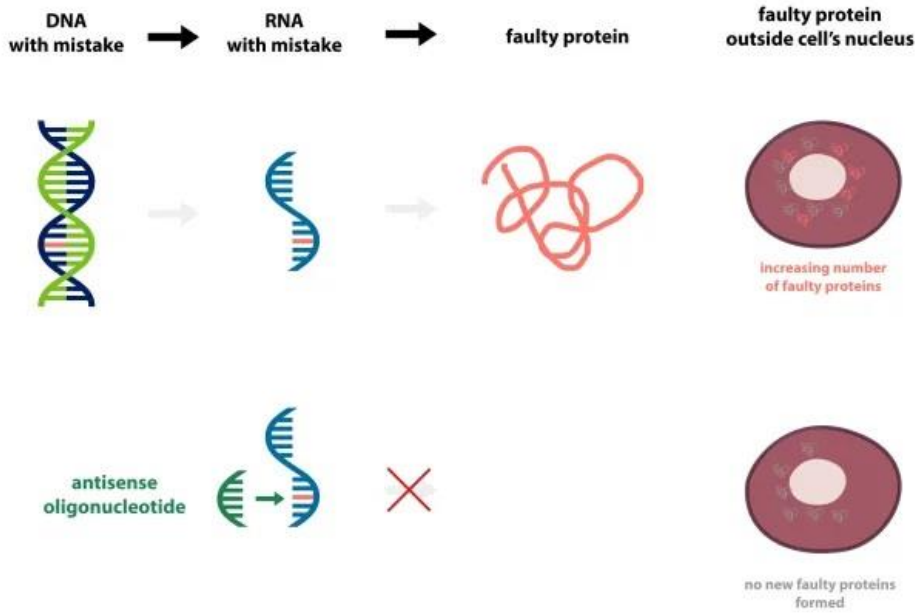
Pathophysiology, genetic causes and risk factors



Nature Reviews Drug Discovery | Volume 22 | March 2023 | 185–212

ALS drugs (I)

1. Tofersen (BIIB067, Qalsody)
Delivery Method: Intrathecal injection (lumbar puncture)
-genetically targeted therapy approved by the FDA in 2023 to treat mutant SOD1-fALS.
-targets RNA produced from mutated *SOD1* genes to block toxic SOD1 proteins from being made, helping improve ALS symptoms and slow down progression of the disease.



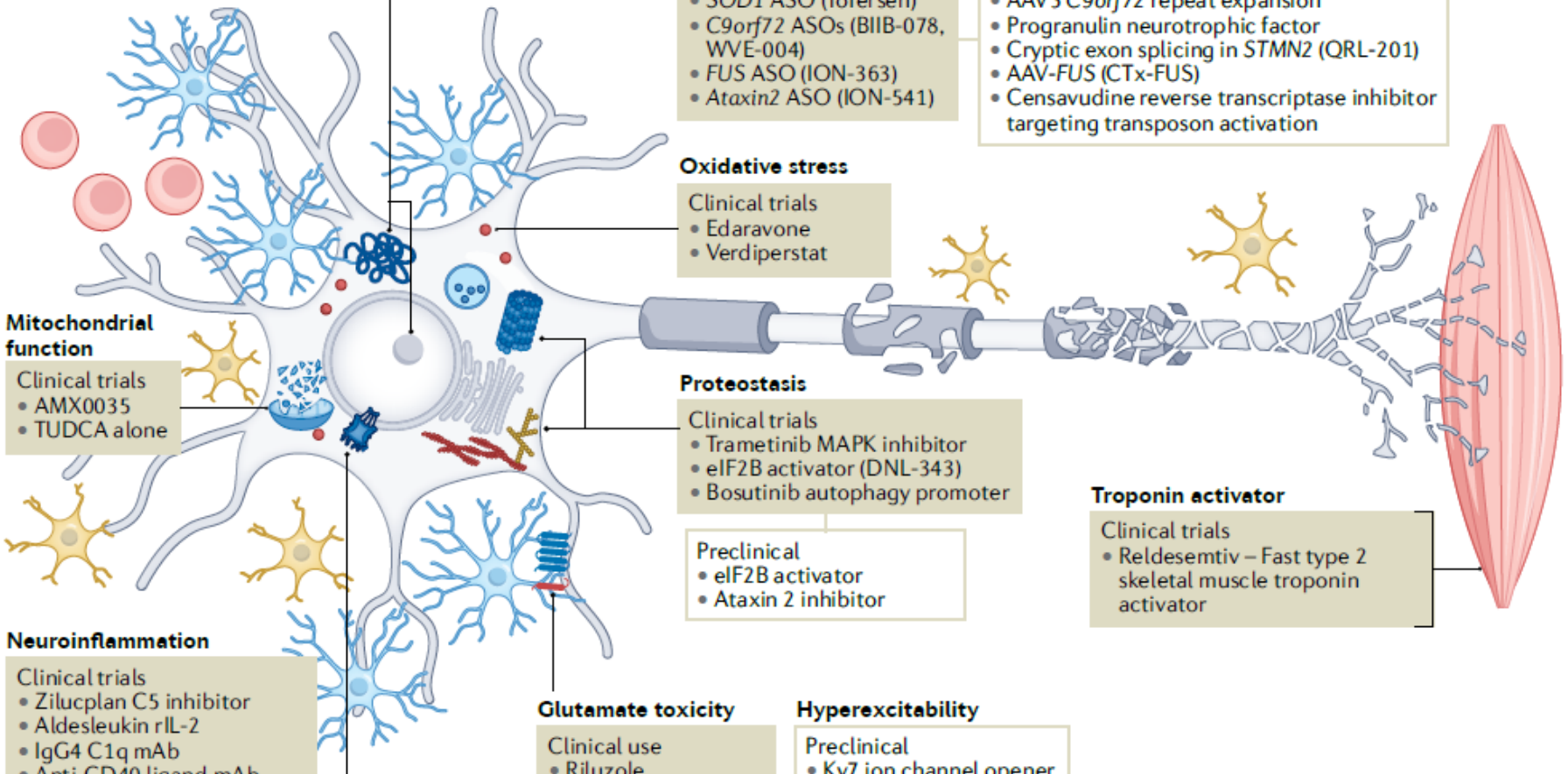
2. Edaravone
Delivery Method: IV or oral suspension (can be administered by mouth or via feeding tube)
The FDA approved Edaravone as an IV treatment for ALS in 2017 followed by an oral suspension in 2022. Edaravone is an antioxidant molecule, intended to slow the loss of physical function and the progression of ALS by preventing nerve damage.

ALS drugs (II)

3. Riluzole
Delivery Method: Tablet, thickened liquid (Tiglutik), or oral film (Exservan)
Rilutek (now generic) was the first FDA-approved drug to treat ALS (1995). It is taken as a tablet. A thickened liquid form of riluzole called Tiglutik was approved by the FDA in September 2018, followed a year later by an oral film formulation called Exservan. Riluzole is intended to slow the progression of ALS by blocking the release of glutamate.

4. Dextromethorphan HBr and Quinidine Sulfate (Nuedexta)
Delivery Method: Capsule
-approved in 2010 in US and prescribed to help treat pseudobulbar affect (PBA), which can cause frequent, involuntary, and unpredictable episodes of crying or laughing that are exaggerated or don't match how the person truly feels
-may also help improve bulbar function in people living with ALS whether they experience PBA or not.

ALS terapeutic targets



Cell therapies

Clinical trials
- Neuronata-R MSCs
- NurOwn MSC-astrocyte like cells
- AstroRx
- RAPA-501 T cell therapy

Multiple targets

Clinical trial
- AMX0035

Preclinical
- M102-S[+]-apomorphine

Genetic therapies

Clinical trials
- *SOD1* ASO (Tofersen)
- *C9orf72* ASOs (BIIB-078, WVE-004)
- *FUS* ASO (ION-363)
- *Ataxin2* ASO (ION-541)

Preclinical
- AAV5 *C9orf72* repeat expansion
- Progranulin neurotrophic factor
- Cryptic exon splicing in *STMN2* (QRL-201)
- AAV-*FUS* (CTx-FUS)
- Censavudine reverse transcriptase inhibitor targeting transposon activation

Oxidative stress

Clinical trials
- Edaravone
- Verdiperstat

Mitochondrial function

Clinical trials
- AMX0035
- TUDCA alone

Proteostasis

Clinical trials
- Trametinib MAPK inhibitor
- eIF2B activator (DNL-343)
- Bosutinib autophagy promoter

Preclinical
- eIF2B activator
- Ataxin 2 inhibitor

Troponin activator

Clinical trials
- Reldesemtiv – Fast type 2 skeletal muscle troponin activator

Neuroinflammation

Clinical trials
- Zilucplan C5 inhibitor
- Aldesleukin rIL-2
- IgG4 C1q mAb
- Anti-CD40 ligand mAb
- CSF1R blocker (BLZ-945)
- Pegcetacoplan C3 regulator
- RIPK1 inhibitor (DNL-788)
- Masitinib
- Ibudilast

Glutamate toxicity

Clinical use
- Riluzole

Hyperexcitability

Preclinical
- Kv7 ion channel opener (QRA-244)

Nucleocytoplasmic transport defects

Clinical trial
- Exportin-1 inhibitor (BIIB-100)

Nature Reviews Drug Discovery | Volume 22 | March 2023 | 185–212

Autophagy - ALS

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2020; 21: 51–62

RESEARCH ARTICLE

HSC70 expression is reduced in lymphomonocytes of sporadic ALS patients and contributes to TDP-43 accumulation

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Rationale and Aim

TDP-43 is degraded not only by UPS and macroautophagy but **also by CMA** through interaction between Hsc70 and ubiquitinated TDP-43
(Huang et al., J Cell Sci. 2014)

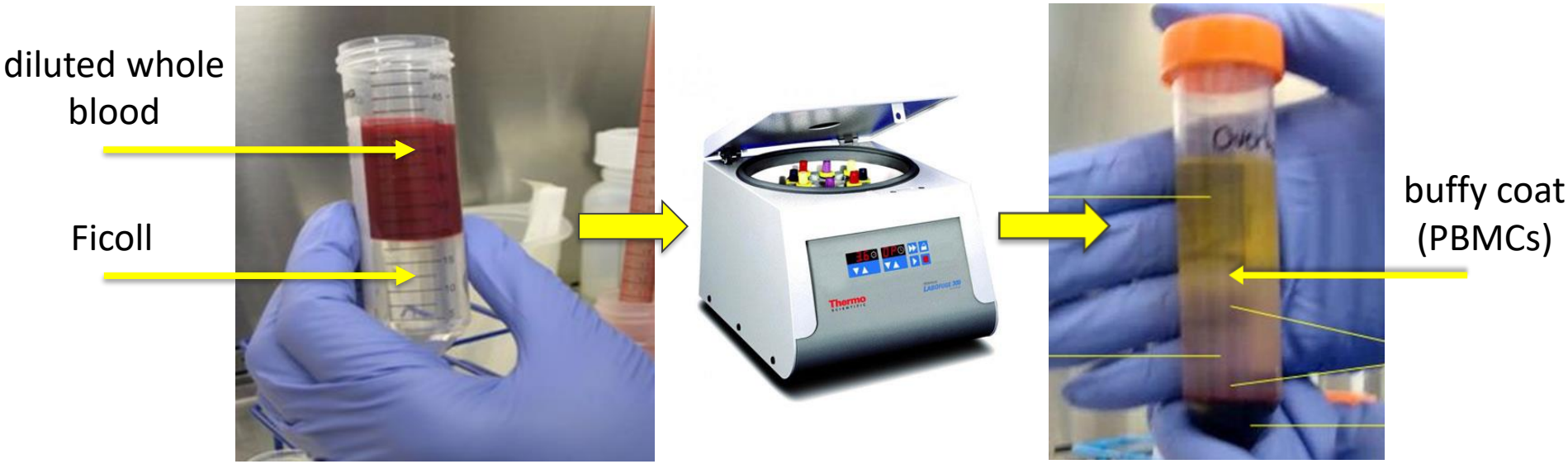
To investigate the existence of systemic alterations of CMA in ALS patients and their role in TDP-43 accumulation

Subjects

	Ctrl n = 30	sALS n = 30
Gender, M/F	16/14	16/14
Age, yr	61.6 ± 10.6 (37-77)	62.6 ± 9.9 (41-78)
Onset, B/S	N/A	9/21
Duration, mo	N/A	32.9 ± 24.5 (3-82)
ALSFRS-R	N/A	24.1 ± 10.2 (6-44)
DPI	N/A	0.92 ± 0.51 (0.45-2.33)
PEG, yes/no	N/A	8/22
NIV, yes/no	N/A	11/19
Riluzole, yes/no	N/A	26/4

Methods

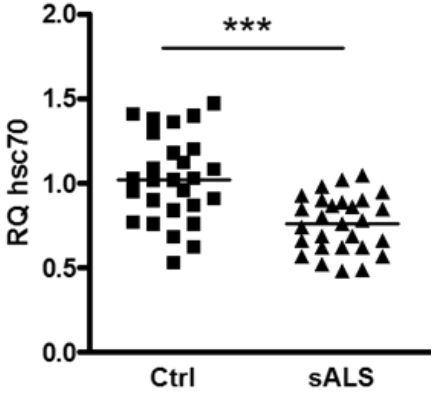
PBMCs isolation through density gradient centrifugation

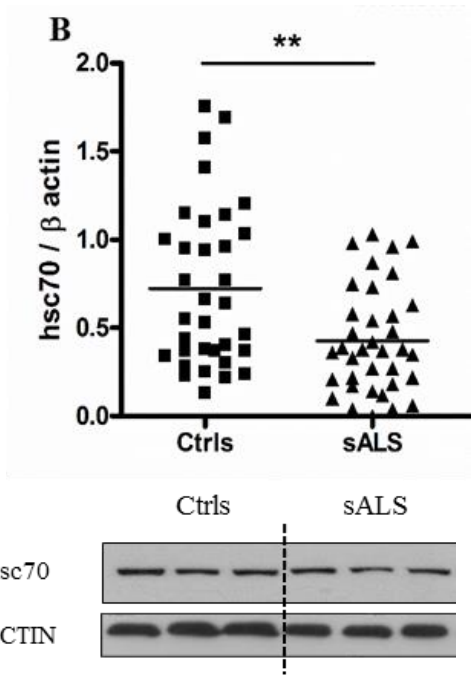


Protein expression → WB
IF
FRA (insoluble proteins)
Dot blot (soluble proteins)

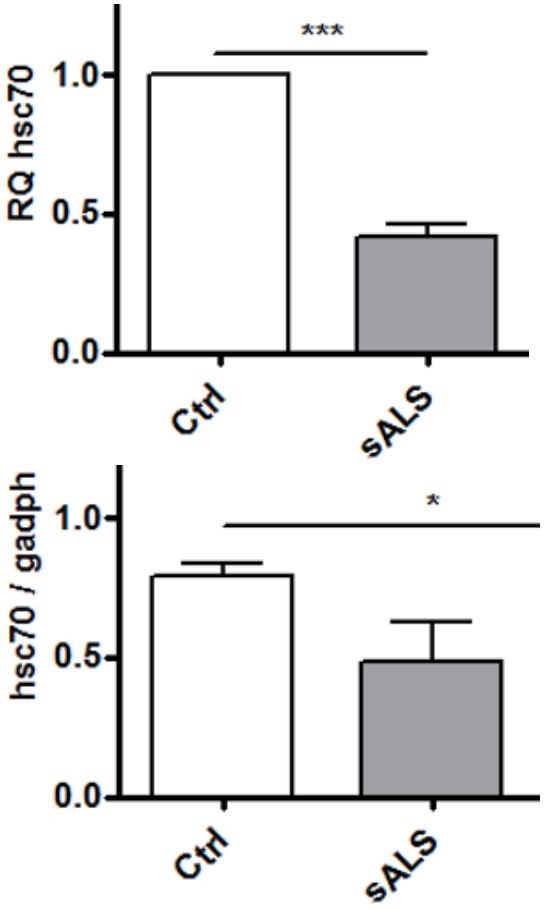
Gene expression → real time PCR

↓ hsc70 in PBMCs





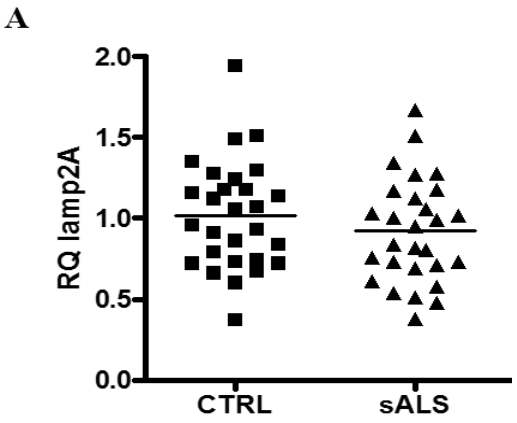
Confirmation of hsc70 reduction in lymphoblastoid cell lines (LCLs)

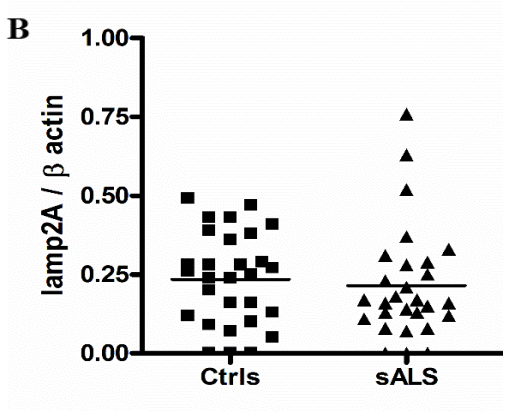


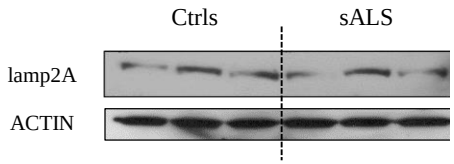
LCLs: Ctrl N = 4
sALS N = 4

Arosio et al., Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2019

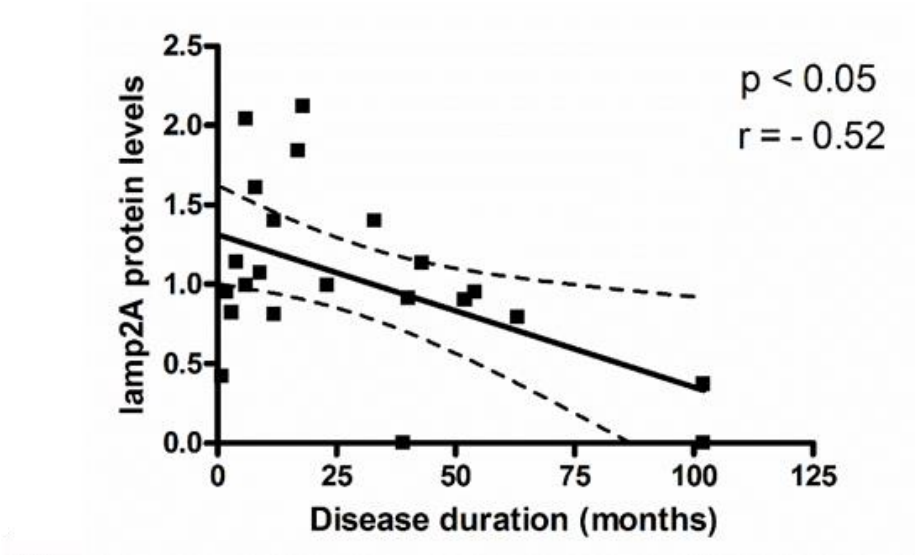
= lamp2A in PBMCs







Negative correlation between lamp2A protein levels and disease duration



Arosio et al., Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2019

Conclusions (I)

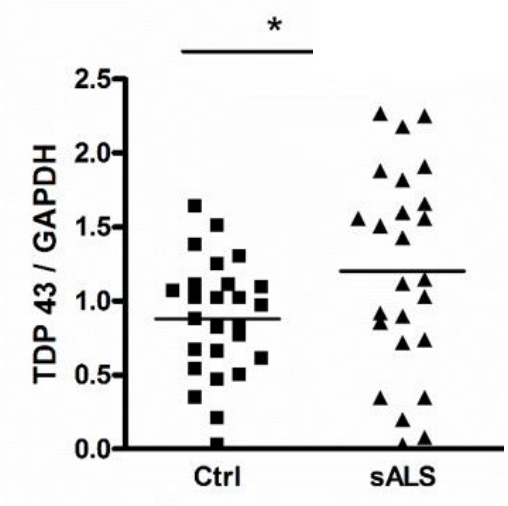
- Hsc70 expression is reduced in sALS PBMCs
- Lamp2A is unchanged, but negatively correlated with disease duration

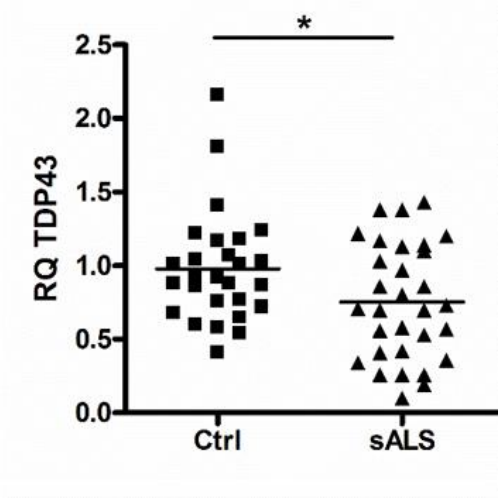
No marked CMA alterations in ALS PBMCs

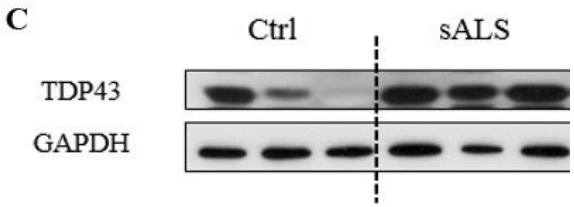
Possible role for CMA dysfunction in patients with longer disease duration

↑ TDP-43 protein

↓ TDP-43 mRNA

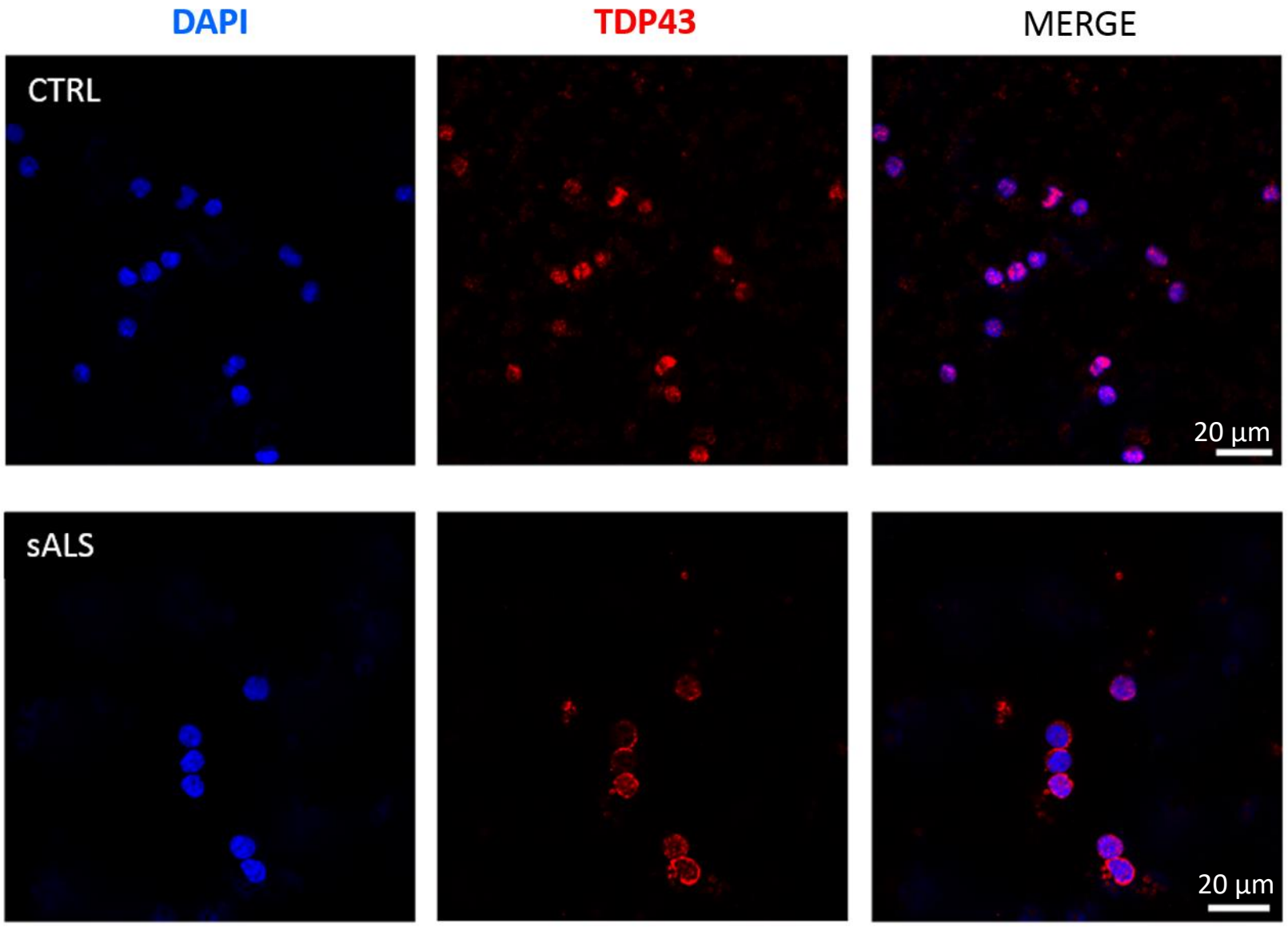






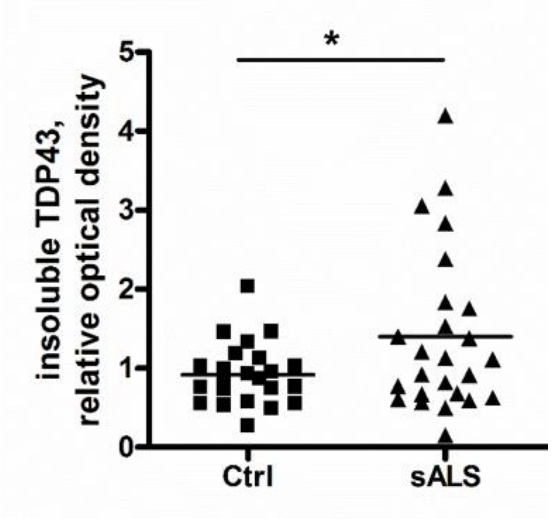
Arosio et al., Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2019

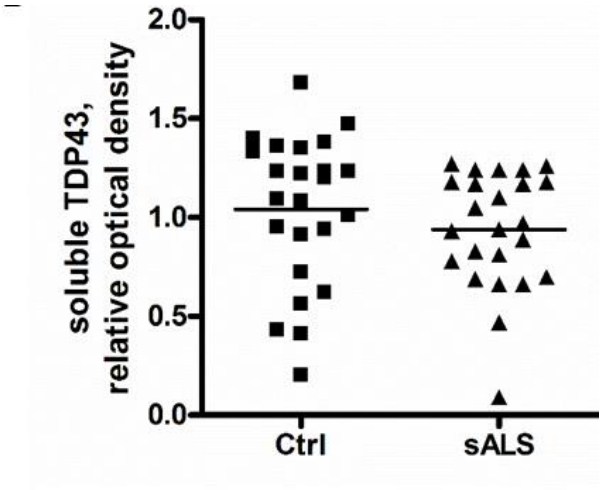
Perinuclear TDP-43 distribution in sALS



Arosio et al., Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2019

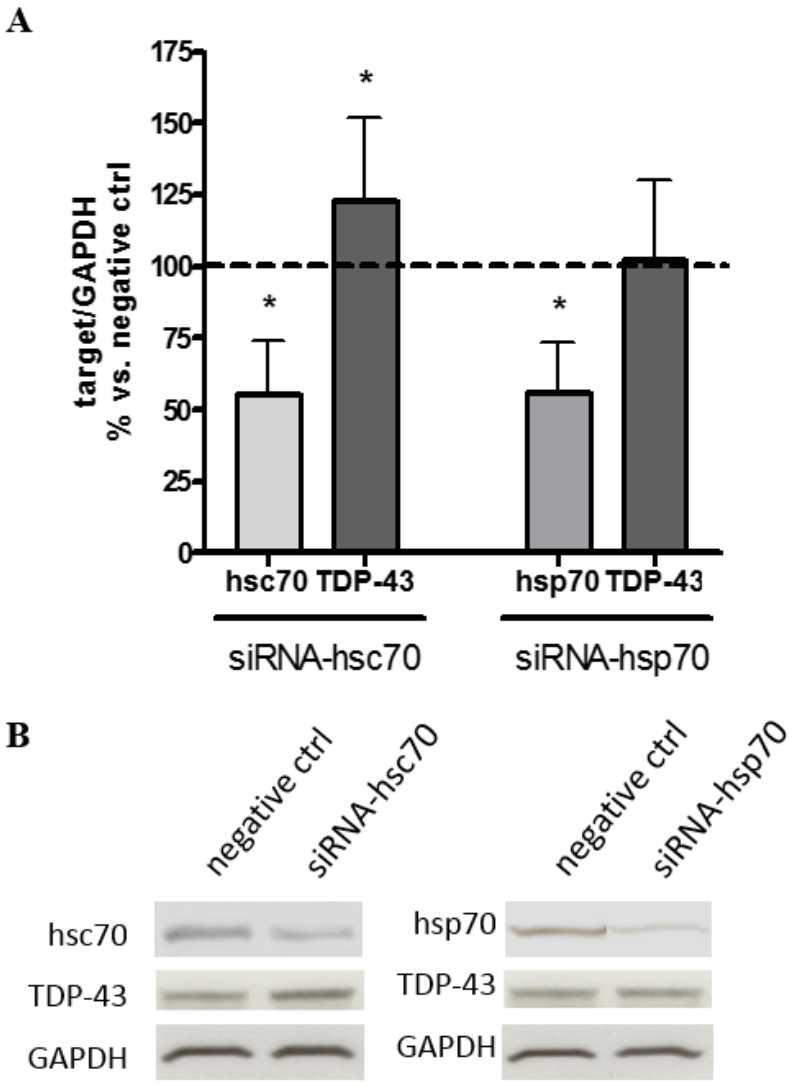
↑ insoluble TDP-43 = soluble TDP-43





Arosio et al., Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2019

Hsc70 knock-down ↑ TDP-43 protein levels in human SH-SY5Y cells



Hsc70 siRNA does not affect TDP-43 mRNA levels

↑ TDP-43 protein levels is ascribable to a reduced clearance

Arosio et al., Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2019

Conclusions (II)

- TDP-43 insoluble protein levels are increased and TDP-43 is mislocalized in sALS PBMCs

PBMCs recapitulate a pathological phenotype typical of motor neurons

- Hsc70 reduction induces TDP-43 protein increase

Hsc70 reduction is a pathogenic mechanism contributing to protein accumulation → hsc70 as possible therapeutic target

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Amyotrophic lateral sclerosis (ALS)

(part 2)

Genetics of ALS

Mendelian familial ALS = 10-15% (incomplete penetrance in some kindreds)
Substantial genetic componenent in (apparently) sporadic ALS

Year	Locus	Gene	Inheritance	Familial (%)[a]	Sporadic (%)[a]	Disease-associated mechanism	Other associated phenotypes[b]	Refs.
1993	21q22.11	*SOD1*	Autosomal dominant, autosomal recessive, de novo	12	1–2	Oxidative stress, excitotoxicity, mitochondrial dysfunction, axonal transport disruption	Frontotemporal dementia, spastic tetraplegia and axial hypotonia	19
1994	22q12.2	*NEFH*	Autosomal dominant	Unknown	Unknown	Axonal transport disruption	Axonal Charcot–Marie–Tooth disease type 2CC	212
2001	2q33.1	*ALS2*	Autosomal recessive	Unknown	Unknown	Vesicular trafficking defects	Juvenile primary lateral sclerosis, infantile hereditary spastic paraplegia	213
2003	2p13.1	*DCTN1*	Autosomal dominant	Unknown	Unknown	Axonal transport disruption	Distal hereditary motor neuropathy type VIIB, Perry syndrome	214
2004	20q13.32	*VAPB*	Autosomal dominant	Unknown	Unknown	Proteostasis defects	Finkel-type spinal muscular atrophy	215
2004	9q34.13	*SETX*	Autosomal dominant	Unknown	Unknown	Altered ribostasis	Autosomal recessive spinocerebellar ataxia type 1	216
2006	3p11.2	*CHMP2B*	Autosomal dominant	Unknown	Unknown	Proteostasis defects, vesicular trafficking defects	Frontotemporal dementia	217,218
2008	1p36.22	*TARDBP*	Autosomal dominant, autosomal recessive, de novo	4	1	Altered ribostasis, nucleocytoplasmic transport defects	Frontotemporal dementia	38,39
2009	16p11.2	*FUS*	Autosomal dominant, autosomal recessive, de novo	4	1	Altered ribostasis, nucleocytoplasmic transport defects	Frontotemporal dementia, essential tremor	46,47
2010	9p13.3	*VCP*	Autosomal dominant, de novo	1	1	Proteostasis defects	Frontotemporal dementia, Charcot–Marie–Tooth disease type 2Y, inclusion body myopathy with early-onset Paget disease	144
2010	15q21.1	*SPG11*	Autosomal recessive	Unknown	Unknown	DNA damage	Hereditary spastic paraplegia, Charcot–Marie–Tooth disease type 2X	219
2010	10p13	*OPTN*	Autosomal dominant, autosomal recessive	<1	<1	Autophagy, inflammation	Adult-onset primary open-angle glaucoma	220
2011	Xp11.21	*UBQLN2*	X-linked dominant	<1	<1	Proteostasis defects	None	221
2011	5q35.3	*SQSTM1*	Autosomal dominant	1	<1	Autophagy, inflammation	Frontotemporal dementia, distal myopathy, childhood-onset neurodegeneration with ataxia, dystonia and gaze palsy, Paget disease of bone-3	222
2011	9p21.2	*C9orf72*	Autosomal dominant	40	7	Autophagy, global RNA alterations, intracellular trafficking defects, nucleocytoplasmic transport defects, proteostasis defects	Frontotemporal dementia	55,56

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FUS (fused in sarcoma)

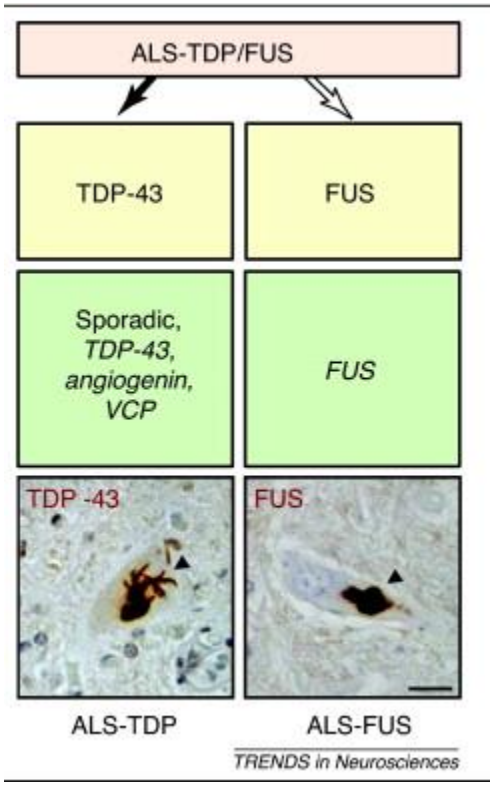
Encoded protein:

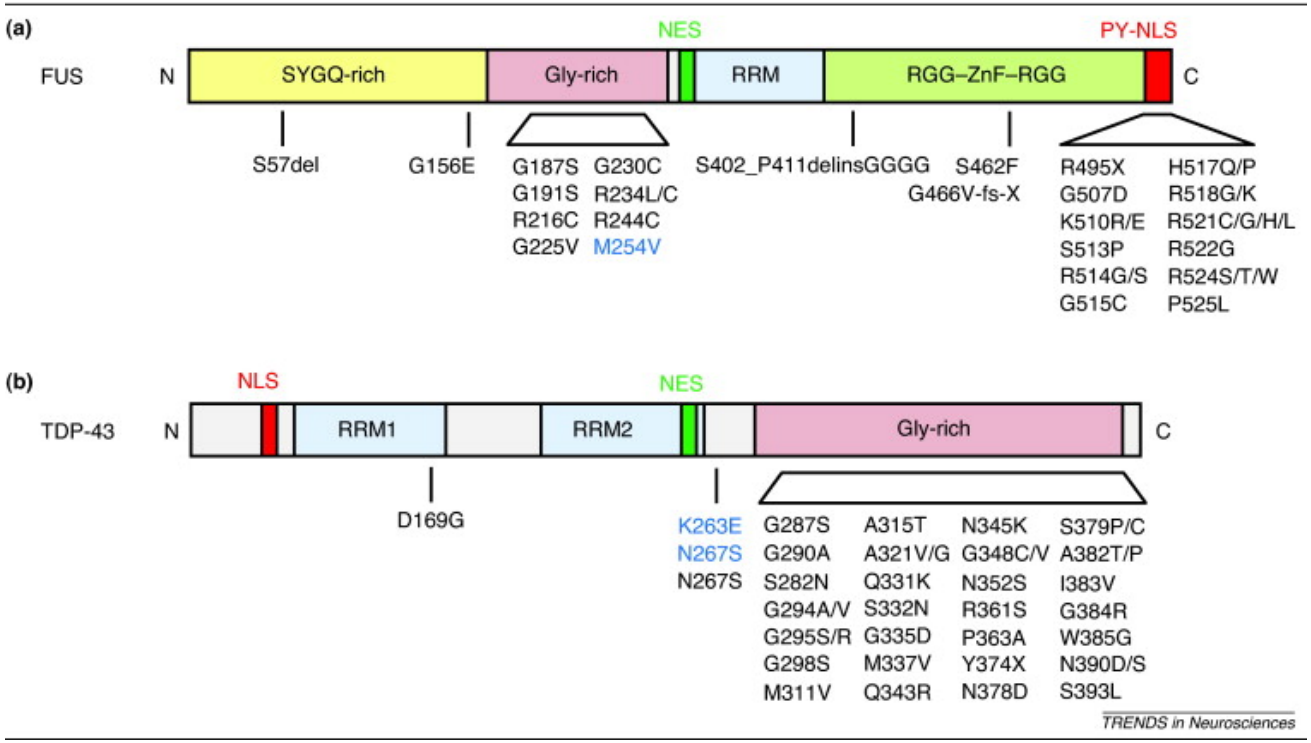
-**RNA binding protein** involved in transcription, alternative splicing, mRNA transport, mRNA stability, mRNA biogenesis

-**also located at the neuromuscular junction** and associated with the transcriptional regulation of acetylcholine receptors in the neuromuscolar junction

RNA metabolism disruption as pathogenic mechanism in ALS

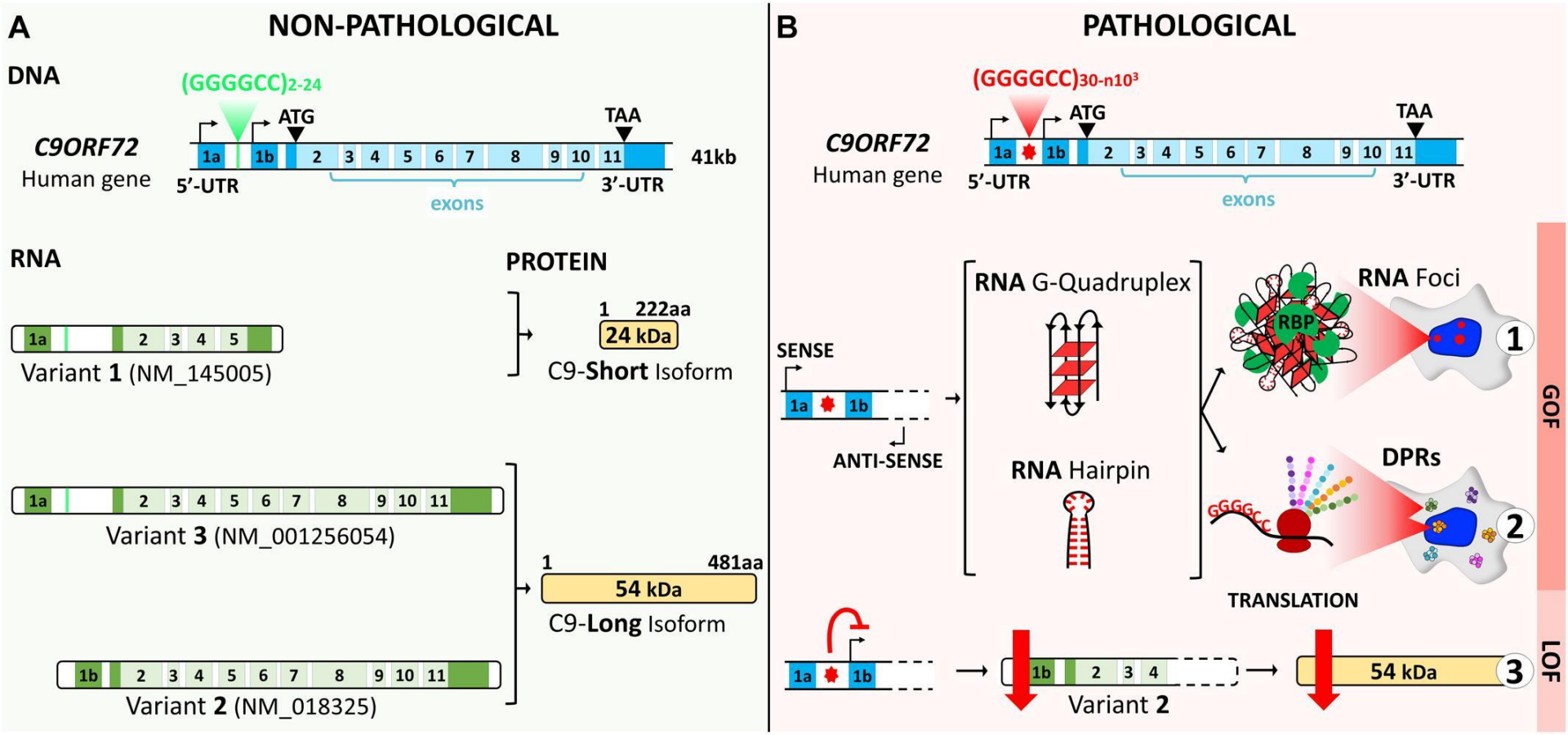
FUS mutations are associated with **nuclear to cytoplasmic mislocalization** and formation of **cytoplasmic inclusions of the mutated protein (similar to TDP-43)**





Dormann et al, Trends in Neurosciences, Volume 34, Issue 7, 2011

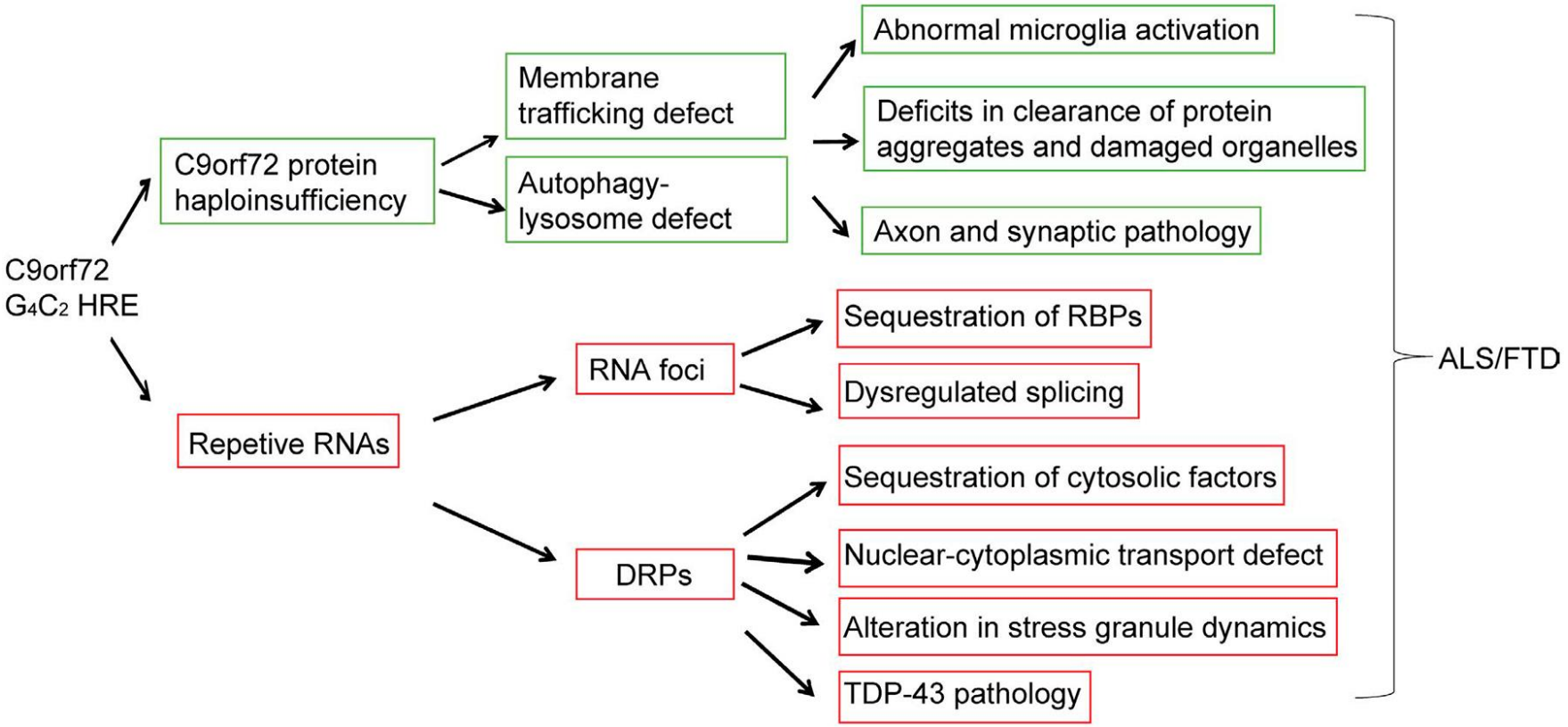
C9ORF72 (chromosome 9 open reading frame 72) expansion



Smeyers et al., Front. Cell. Neurosci., vol 15, 05 May 2021

Pathways affected by *C9ORF72* HRE in ALS/FTD

Both loss of function of C9ORF72 and gain of toxicity from RNA foci and dipeptide repeat proteins (DRPs) contribute to the disease progression.



Pang W et al., J Neurochem. 2021 May;157(3):334-350

FUS and C9ORF72 as therapeutic targets

- to target post-translational FUS acetylation using HDAC inhibitors

- Jacifusen, an ASO targeting FUS mutations, was designed in 2019 to target FUS mRNA and prevent FUS protein production

- In 2022, ASO targetig C9ORF72 mutation (results in cellular and animal models, and in 1 pt with mutation. Need for additional clinical trials.