

Motor neuron disease

Amyotrophic lateral sclerosis (ALS)

Today

Westcamp-Barmada 2020 (Groups G and H)

Coming up-

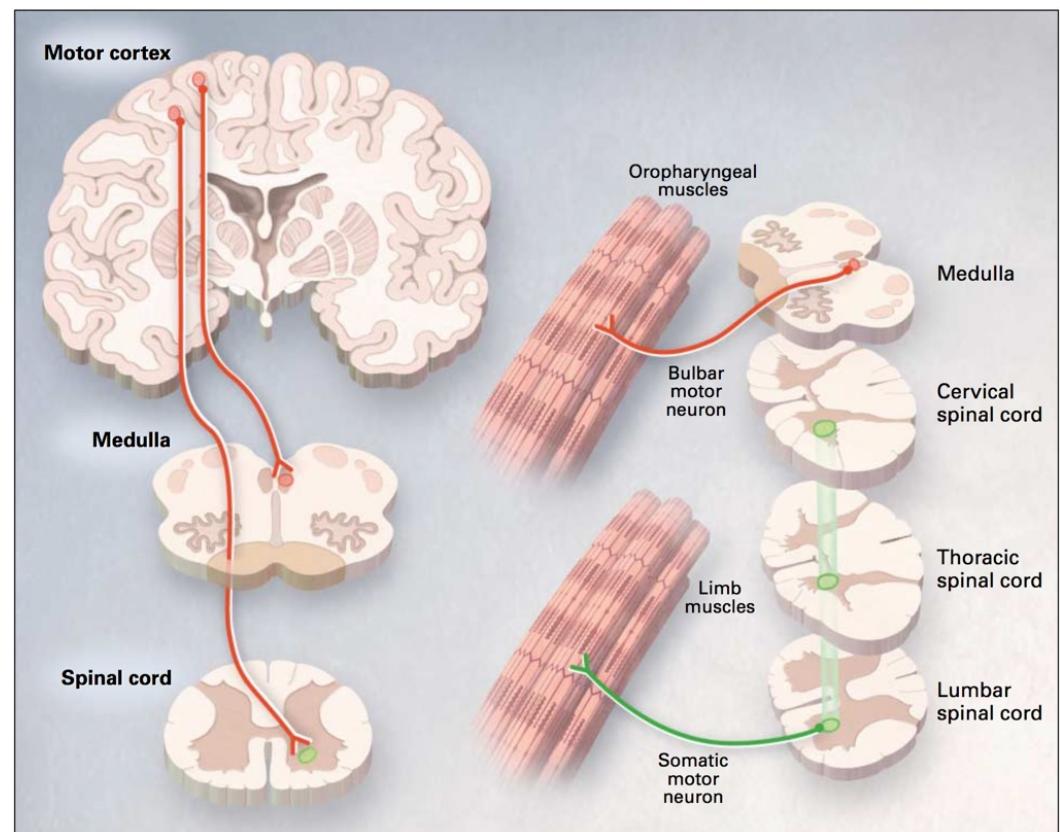
FEBRUARY BREAK

Mon, Feb 24- Spinal Motor Atrophy- Arbab-Liu-2023 (Groups I and J)

Motor neuron diseases

Neurological disorders that destroy motor neurons, the cells that control skeletal muscle activity required for walking, breathing, speaking, and swallowing.

- Amyotrophic lateral sclerosis
- Progressive bulbar palsy
- Primary lateral sclerosis
- Progressive muscular atrophy
- Spinal muscular atrophy
- Kennedy's disease
- Post-polio syndrome



ALS- Lou Gehrig's Disease



Lou Gehring (1903-1941)

2 years

First described in 1869 by Jean-Martin Charcot

“Amyotrophy”—atrophy of muscle fibers

“Lateral sclerosis”—spinal cord gliosis

~5% familial, >90% sporadic

Twin studies show heritability of ~61%

Life expectancy following diagnosis 2-5 years

Half of patients live less than 3 years

10% live more than 10 years



Stephen Hawking (1942-2018)

55 years



Incidence of ALS

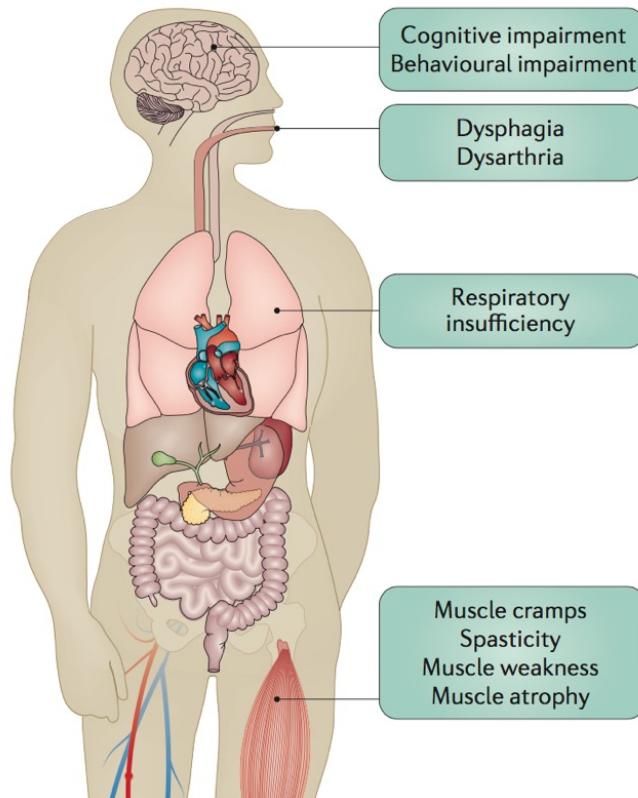
White: 1.80 per 100,000

African-American: 0.80

Hispanic: 0.58 per 100,000

<http://www.alsa.org>, Cruz, P&T, 2018

Clinical manifestation of ALS



Early symptoms

- Fasciculations (muscle twitches) in the arm, leg, shoulder, or tongue
- Muscle cramps
- Tight and stiff muscles (spasticity)
- Muscle weakness affecting an arm, a leg, neck or diaphragm.
- Slurred and nasal speech
- Difficulty chewing or swallowing

ALS disease progression

Later symptoms

Loss of ability to swallow (dysphagia), speak or form words (dysarthria), and breath (dyspnea)

Loss of movement- standing or walking, use of hands and arms

Difficulty swallowing and chewing food

Increased metabolism-burn calories at a fast rate

Weight loss and malnutrition ↗

Anxiety and depression

Some will develop dementia over time

Loss of ability to breathe → ventilator

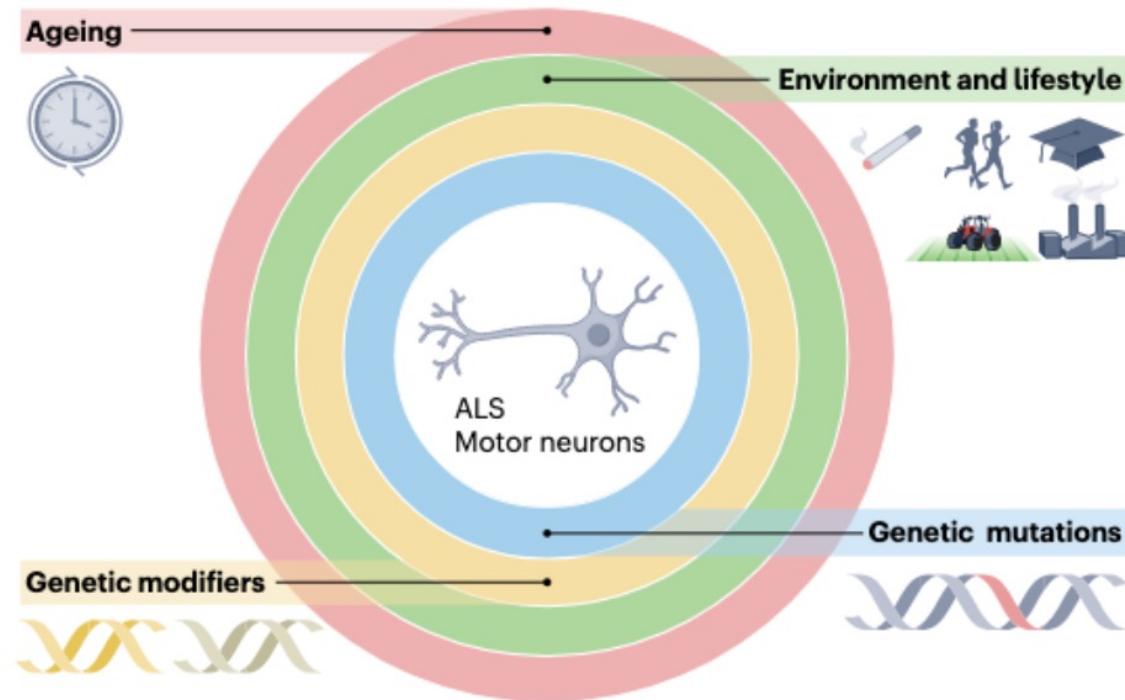
Increased risk of pneumonia

King's clinical staging	Staging	MITOS functional staging
Presymptomatic	0	Functional involvement (disease onset)
Involvement of one clinical region (disease onset)	1	Loss of independence in one functional domain
Involvement of two clinical regions	2	Loss of independence in two functional domains
Involvement of three clinical regions	3	Loss of independence in three functional domains
Substantial respiratory or nutritional failure	4	Loss of independence in four functional domains
Death	5	Death

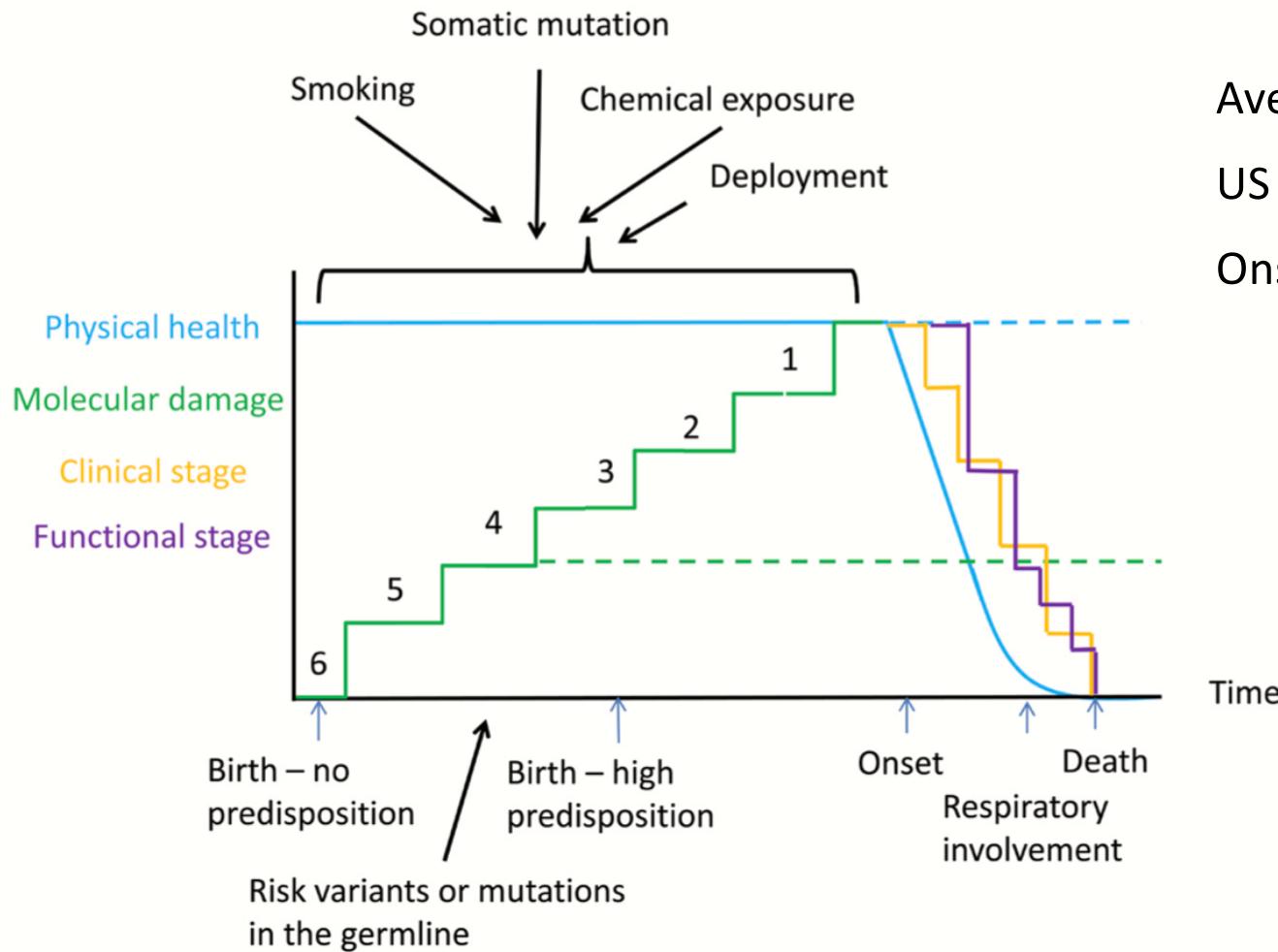
Number of body regions affected and the presence of respiratory or nutritional failure

Domains: bulbar, gross motor, fine motor and respiratory

Genes and environment in ALS



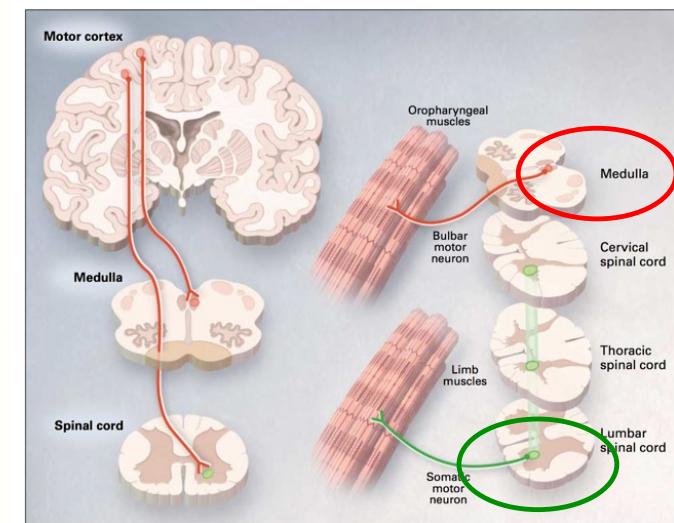
A model for time-course of ALS



Average age of onset: 55 years

US cases: 300,000

Onset: Spinal or Bulbar



Martin et al, F1000 Res, 2017

Environmental onset of ALS



1904

An ALS-like disorder described in the Chamorro people of Guam

An epidemic occurred in the 1940s.

At the epidemic's peak in the 1950s, the prevalence, incidence, and death rate of ALS among the Chamorro on Guam were 50-100 times that of the worldwide average

~12 cases per year between 1940 and 1960

Four villages- over 175 cases per 100,000 people

1955

Rates have greatly declined



Environmental onset of ALS

Cycad plants produce the neurotoxin BMAA (β -methylamino-L-alanine)

BMAA is made by symbiotic cyanobacteria

BMAA becomes concentrated in the cycad seed

But- concentrations are extremely low

Fruit bats eat cycad seeds and concentrate BMAA

People eat fruit bats

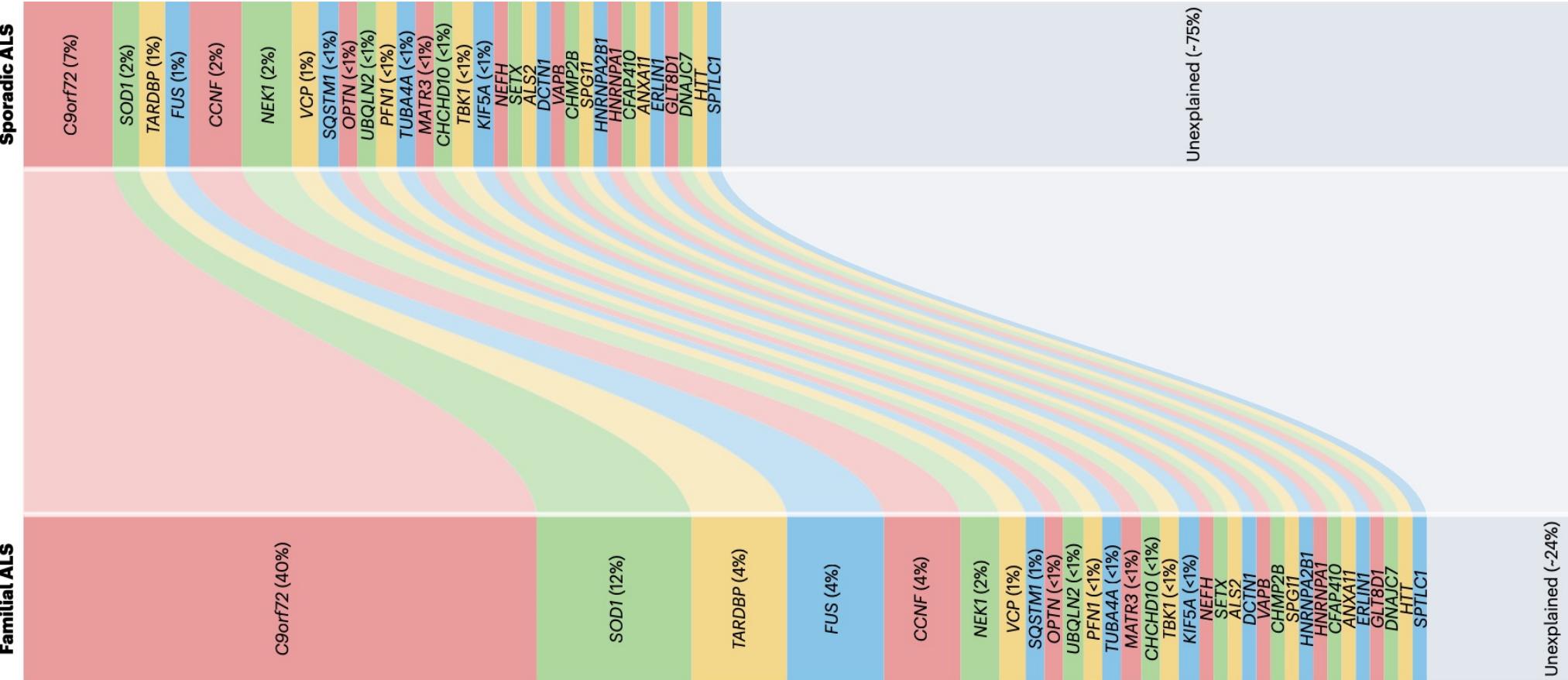


Cycas circinalis

<https://www.mda.org/alsn/article/bats-and-nuts-yield-environmental-clue-to-als-on-guam>

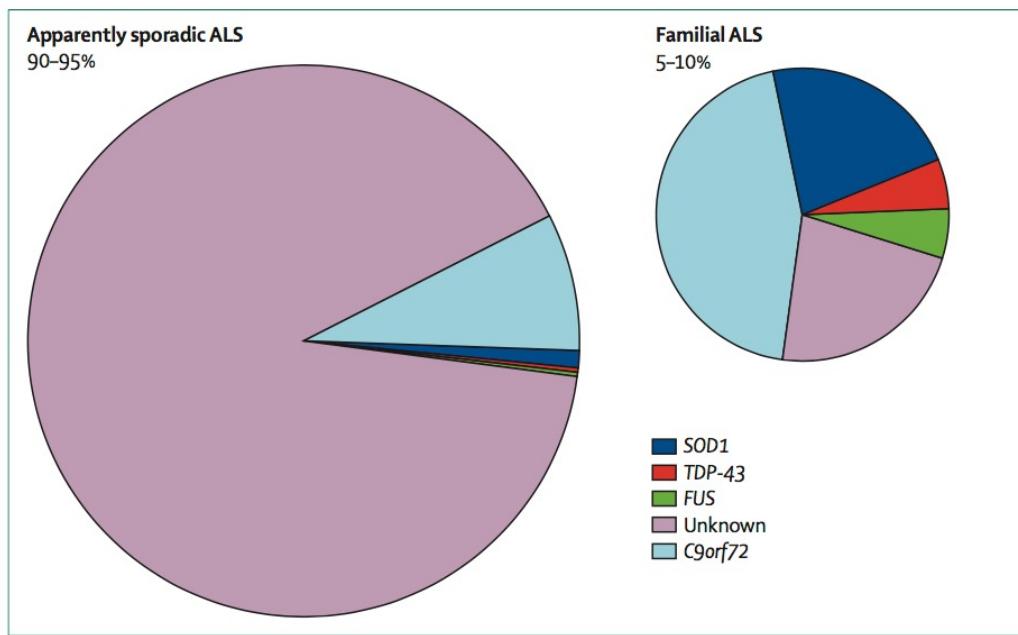
Fruit bat (Flying fox)

Genetics of ALS



Akcimen-Traynor-Nat Rev Genetics

Genetics of ALS



Super Oxide Dismutase (**SOD1**)

TAR DNA-binding protein 43 (**TDP-43**, transactive response DNA binding protein)

C9orf72 (RNA regulation, autophagy)

FUS RNA binding protein (transcription, alternative splicing)

Turner et al, Lancet, 2013

Identified genes contributing to ALS

Table 1 | Main genes implicated in amyotrophic lateral sclerosis

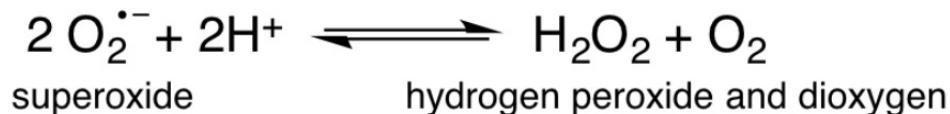
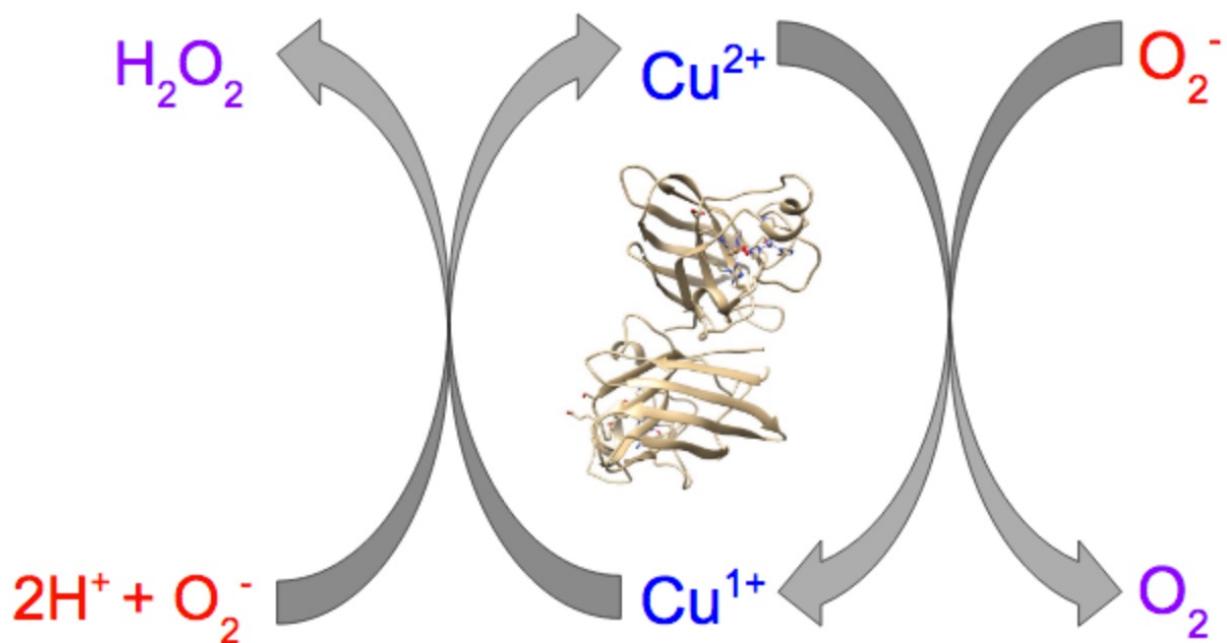
Locus	Gene (protein)	Inheritance	Implicated disease mechanisms	Refs
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ALS10	TARDBP (TAR DNA-binding protein 43)	AD	RNA metabolism	27,245
ALS11	FIG4 (polyphosphoinositide phosphatase)	AD	Endosomal trafficking	246
ALS12	OPTN (optineurin)	AD or AR	Autophagy	247
ALS13	ATXN2 (ataxin 2)	AD	RNA metabolism	248

Hardiman et al, Nat Rev, 2017

TDP43



SOD1- Super oxide dismutase



https://chem.libretexts.org/Courses/Saint_Marys_College_Notre_Dame_IN/CHEM_342%3A_Bio-inorganic_Chemistry/Readings/Metals_in_Biological_Systems_%28Saint_Mary%27s_College%29/Antioxidant%3A_Cu_Zn_Superoxide_dismutase_%28SOD1%29

SOD1- Super oxide dismutase

SOD1 knockout mice do not develop ALS

SOD1 mutations result in a gain of toxic properties

SOD1 transgenic mice have an aggressive disease

Mice have dysfunction in many cellular pathways

Protein misfolding

Proteasome impairment

Excitotoxicity

Oxidative stress

Endoplasmic reticulum stress

Impaired axonal transport

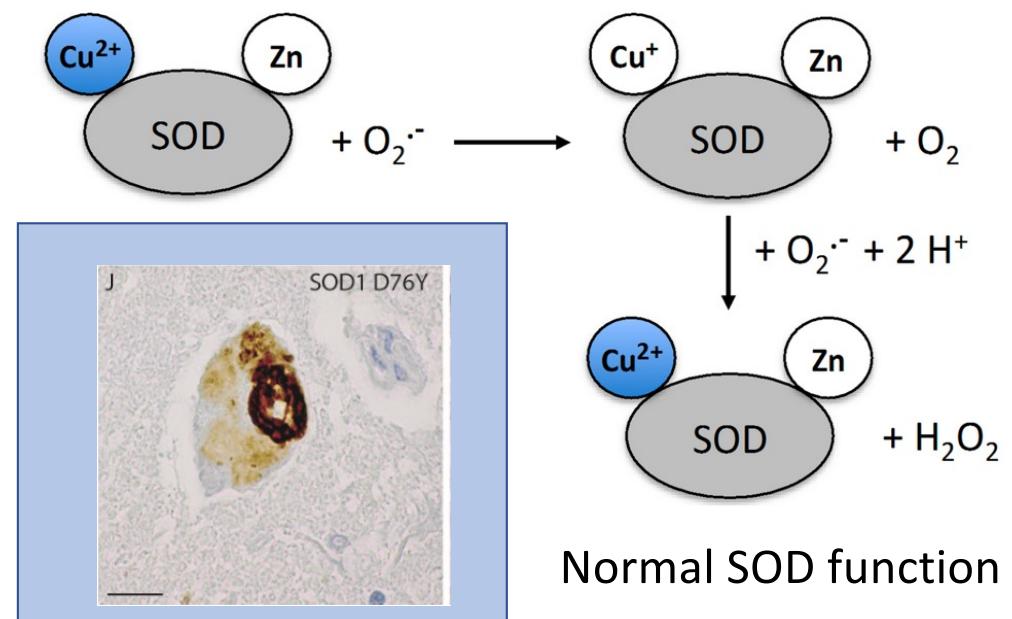
Inflammation

RNA processing

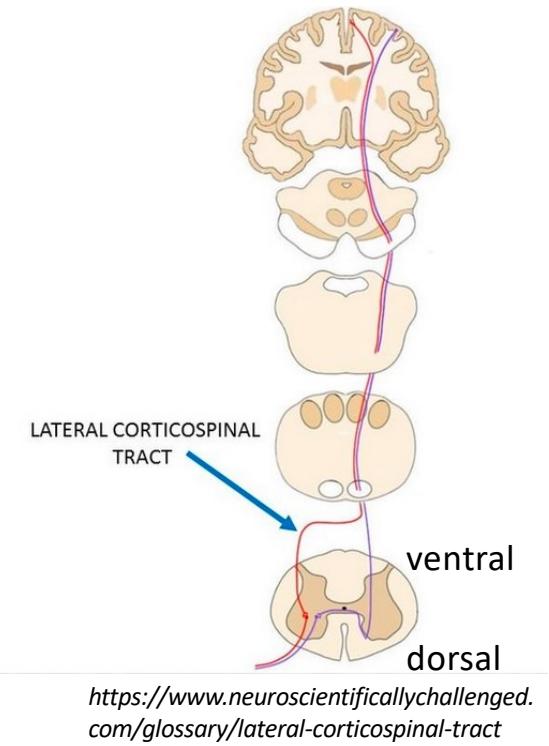
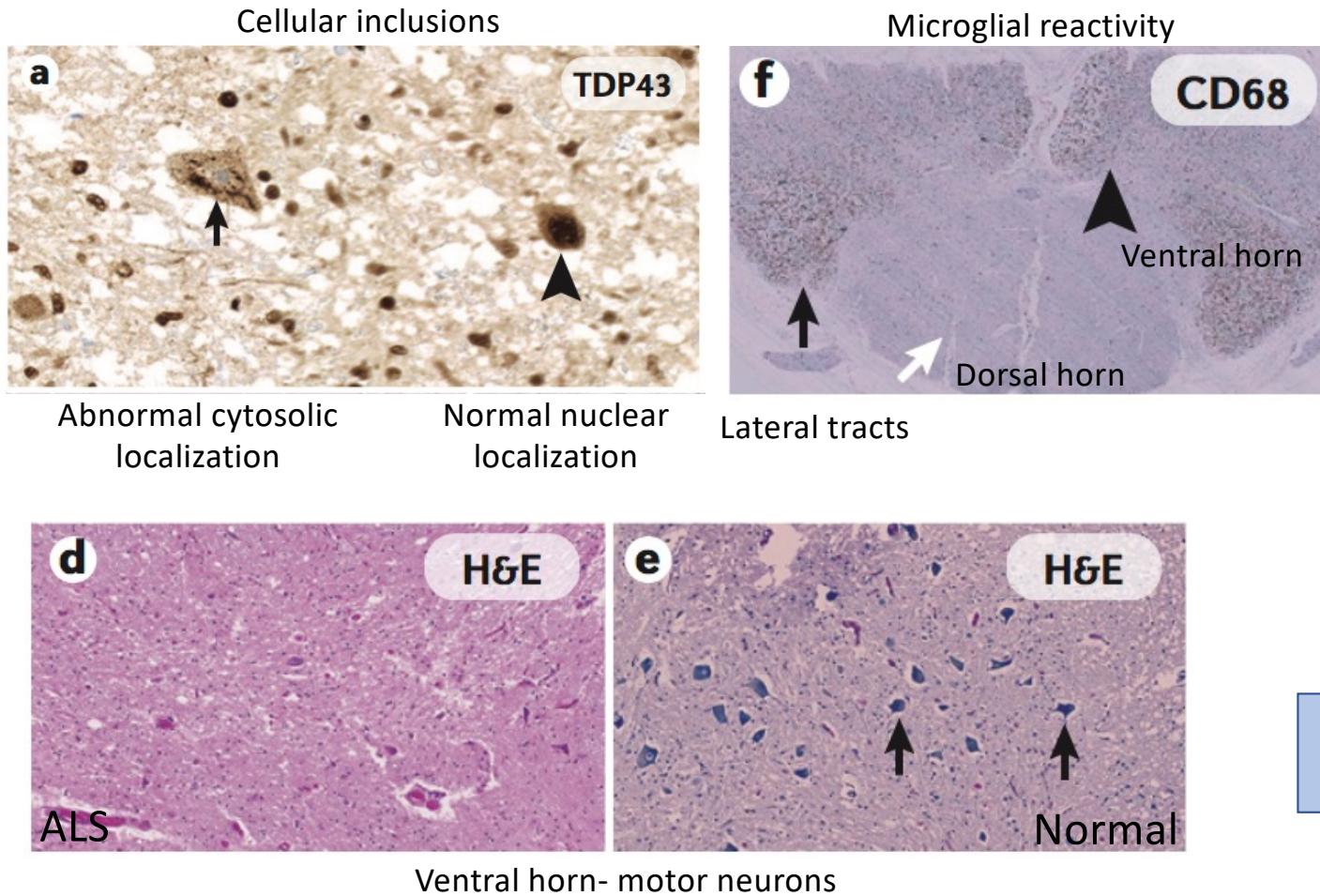
Mitochondrial function

Oxidative stress

Hardiman et al, Nat Rev, 2017;
<https://www.intechopen.com/books/current-advances-in-amyotrophic-lateral-sclerosis/superoxide-dismutase-and-oxidative-stress-in-amyotrophic-lateral-sclerosis>



Cellular pathology in ALS



Dorsal horn- sensory
Ventral horn- motor

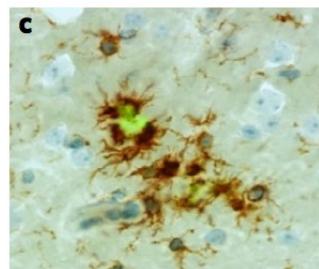
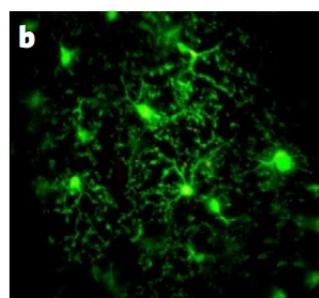
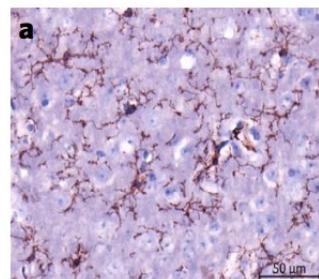
Hardiman et al, Nat Rev, 2017

Microglia- Immune cells of the brain

Three states of microglia

Housekeeping

- Synaptic remodeling
- Migration, phagocytosis
- Myelin homeostasis

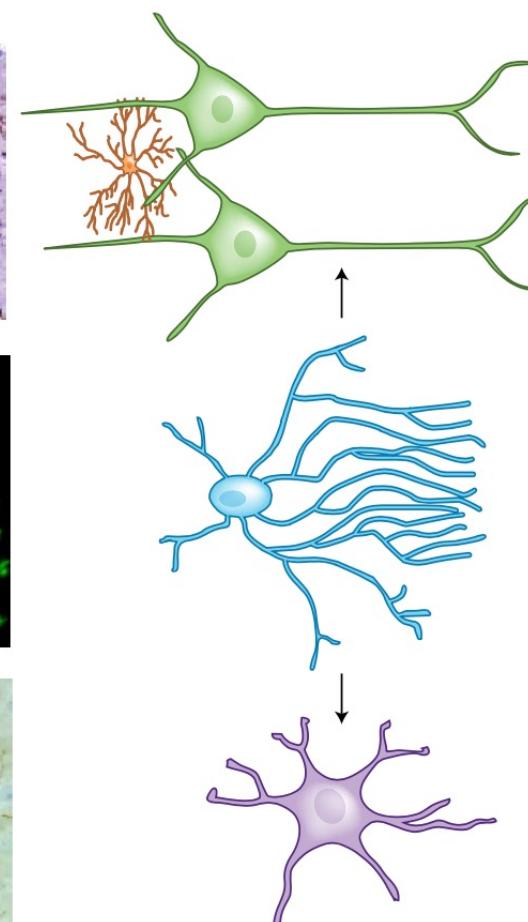


Sensor

- Extensive process network
- Dynamic movement
- Sense damage and pathogens

Responsive

- Neuroinflammatory response
- Phagocytic response
- Cytokine production



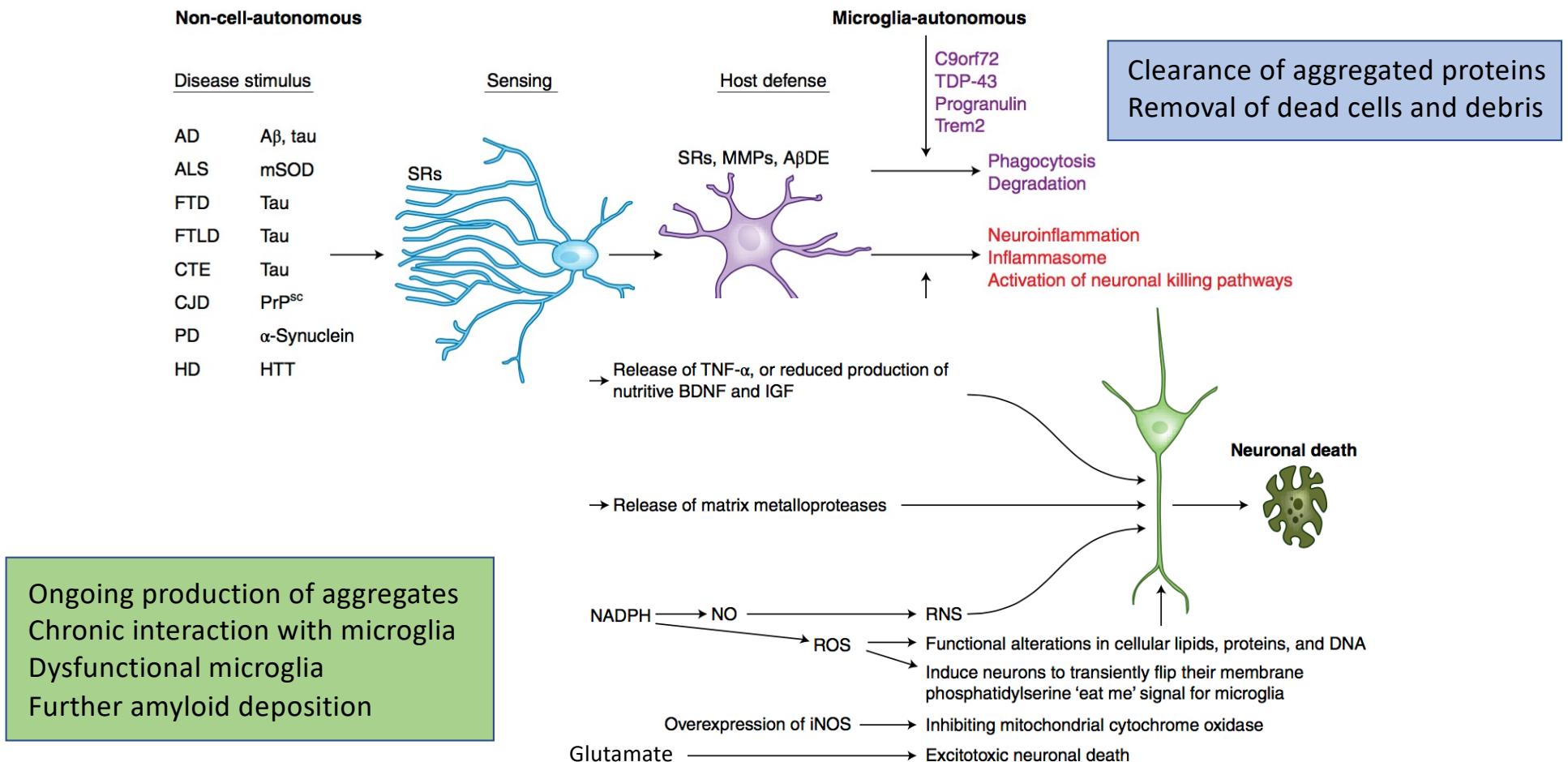
Nurturer:
TGF β r (homeostasis)
Chemokine receptors (migration)
C1q (synaptic remodeling)
Trem2 (apoptotic neuron removal)

Sentinel:
Sensome

Warrior:
Phagocytic receptors
Antimicrobial peptides
Pattern-recognition receptors
RNS, ROS production

Hickman, *Nat Neuro*, 2018

Activated microglia- the good and the bad



Identified genes contributing to ALS

ALS14	VCP (valosin-containing protein)	AD	Autophagy	36
ALS15	UBQLN2 (ubiquilin-2)	XD	UPS and autophagy	34
ALS16	SIGMAR1 (sigma non-opioid intracellular receptor 1)	AD	UPS and autophagy	249,250
ALS17	CHMP2B (charged multivesicular body protein 2B)	AD	Endosomal trafficking	251
ALS18	PFN1 (profilin 1)	AD	Cytoskeleton	97
ALS19	ERBB4 (receptor tyrosine-protein kinase erbB 4)	AD	Neuronal development	252
ALS20	HNRNPA1 (heterogeneous nuclear ribonucleoprotein A1)	AD	RNA metabolism	82
ALS21	MATR3 (matrin 3)	AD	RNA metabolism	83
ALS22	TUBA4A (tubulin α 4A)	AD	Cytoskeleton	102
ALS-FTD1	C9orf72 (guanine nucleotide exchange C9orf72)	AD	RNA metabolism and autophagy	5,6
ALS-FTD2	CHCHD10 (coiled-coil-helix-coiled-coil-helix domain-containing 10)	AD	Mitochondrial maintenance	253
ALS-FTD3	SQSTM1 (sequestosome 1)	AD	Autophagy	254
ALS-FTD4	TBK1 (serine/threonine-protein kinase TBK1)	Unknown	Autophagy	53,54

AD, autosomal dominant; AR, autosomal recessive; UPS, ubiquitin–proteasome system; XD, X-linked dominant

Hardiman et al, Nat Rev, 2017

Pathogenic hexanucleotide repeats in *C9orf72*

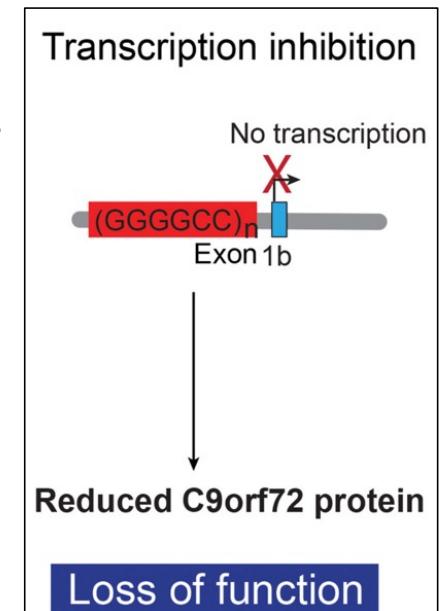
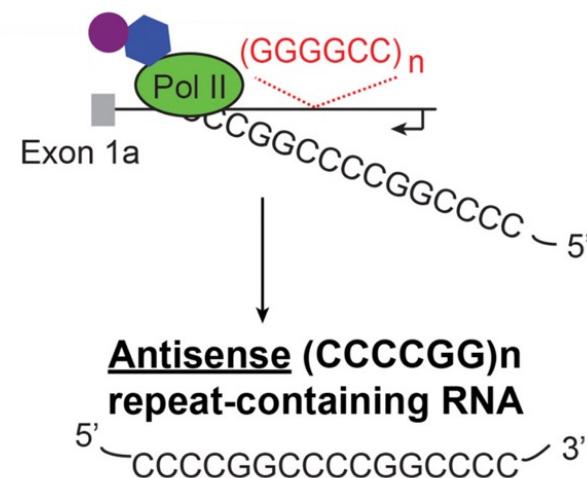
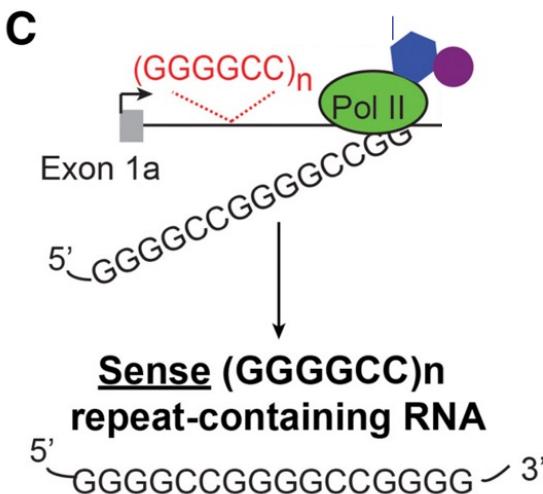
C9orf72 is the most frequent genetic cause of ALS (and FTD)

Genetic alteration is intronic hexanucleotide (G4C2) repeat expansions

Intron 1 contains a GGGGCC hexanucleotide

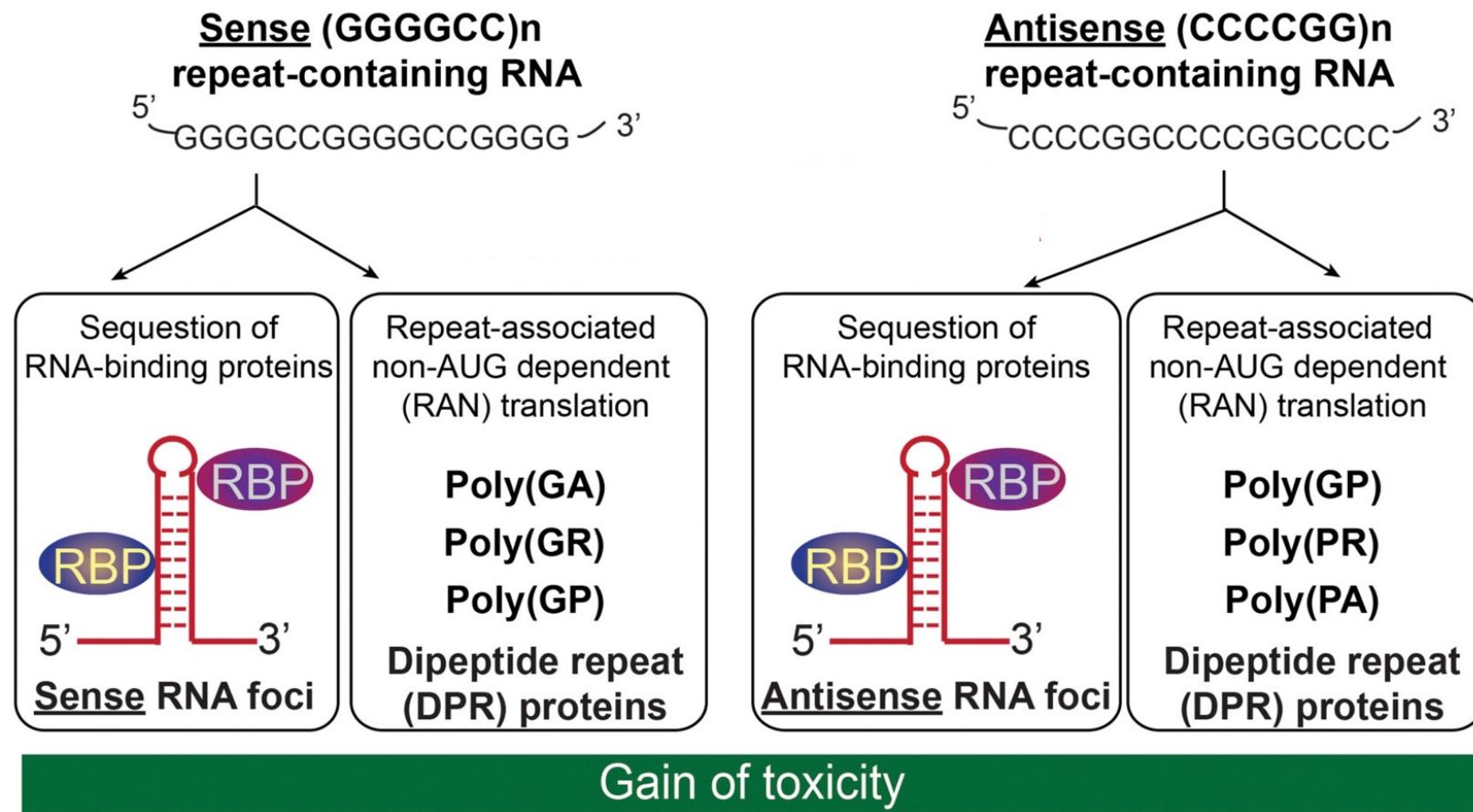
Normally repeated between 2 and 30 times

Inherited mutations – 100s → 1000s in nervous system

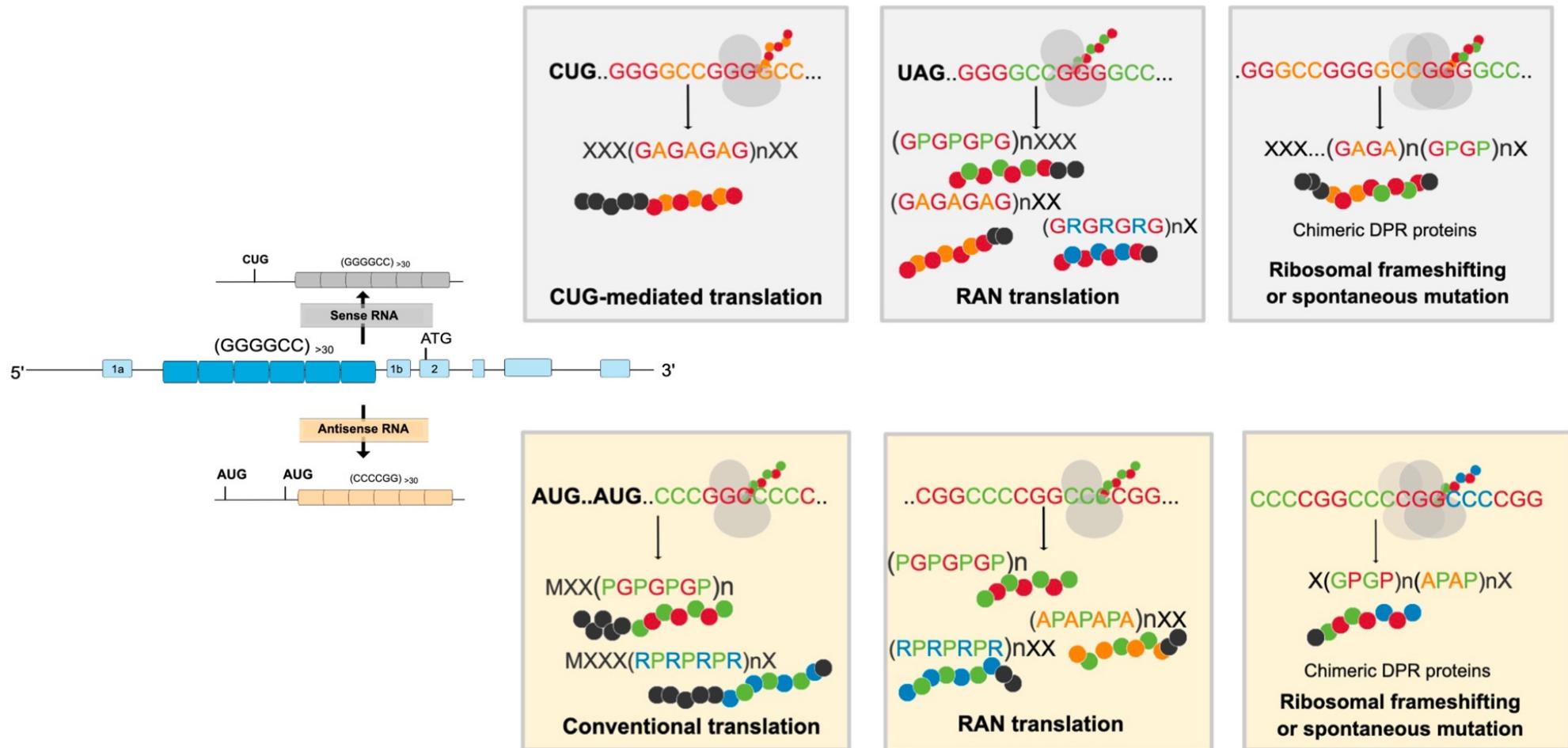


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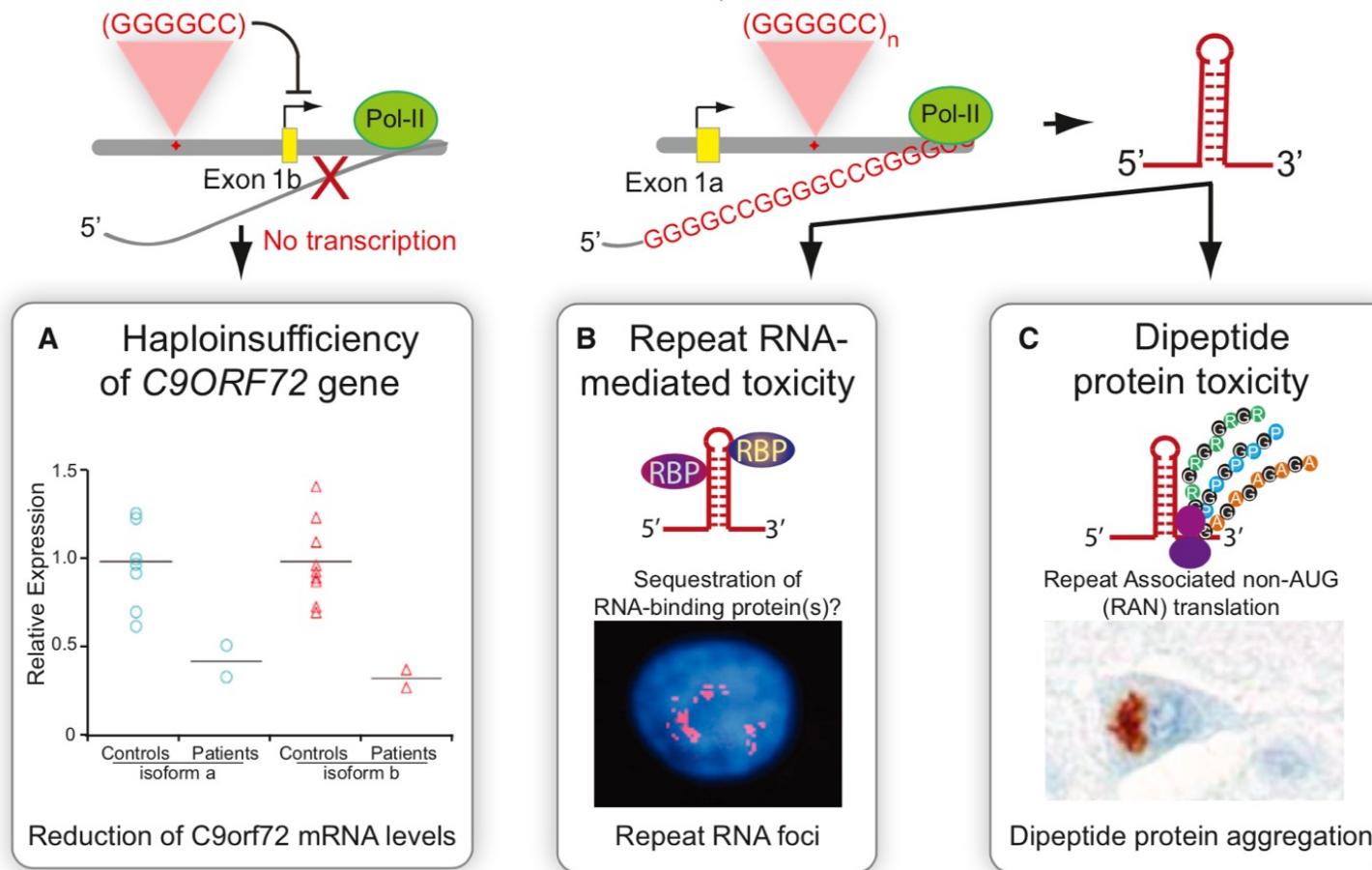
Multiple pathogenic mechanisms



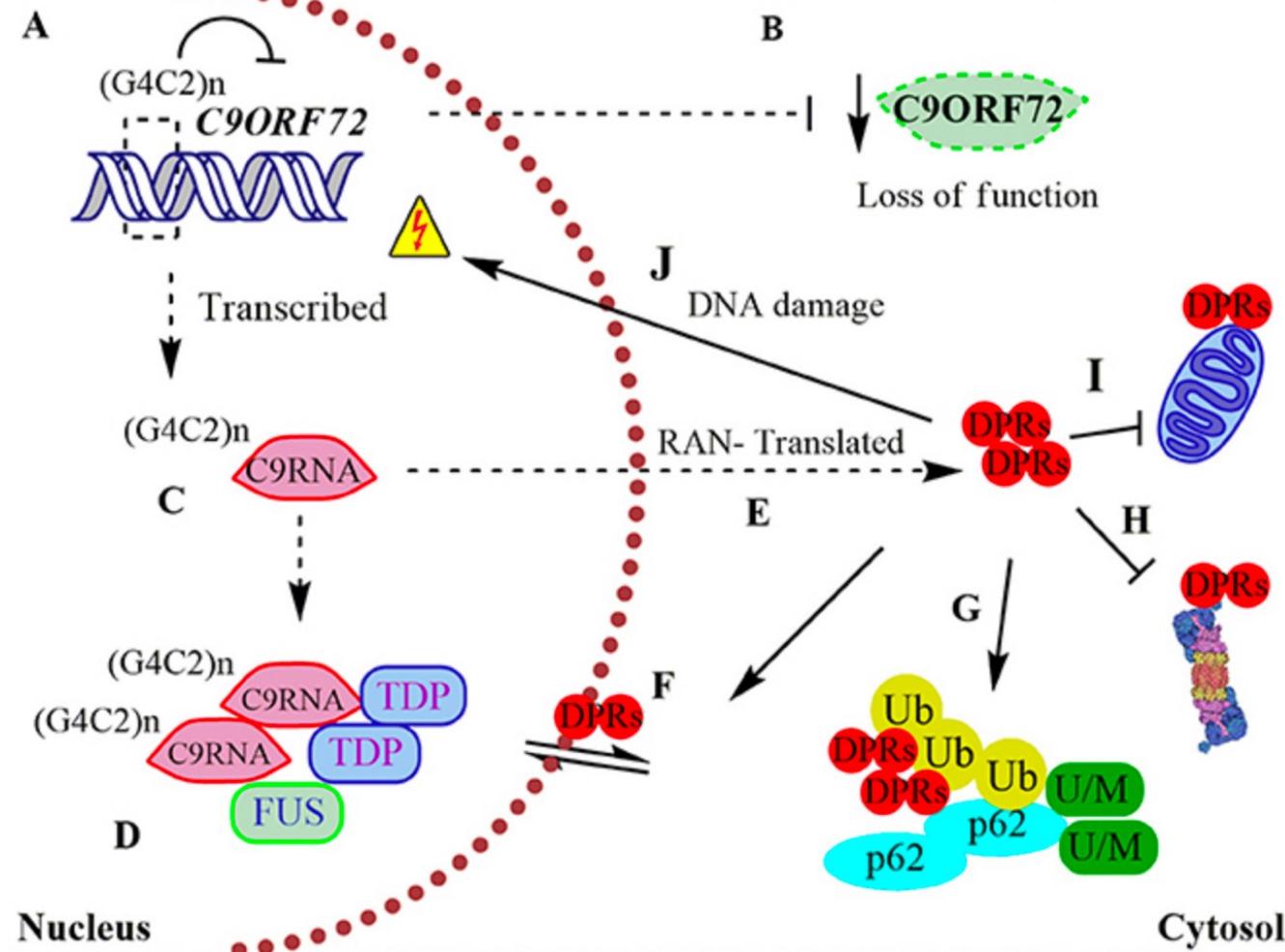
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Disruptions in:
Mitophagy
Autophagy
Proteasomes

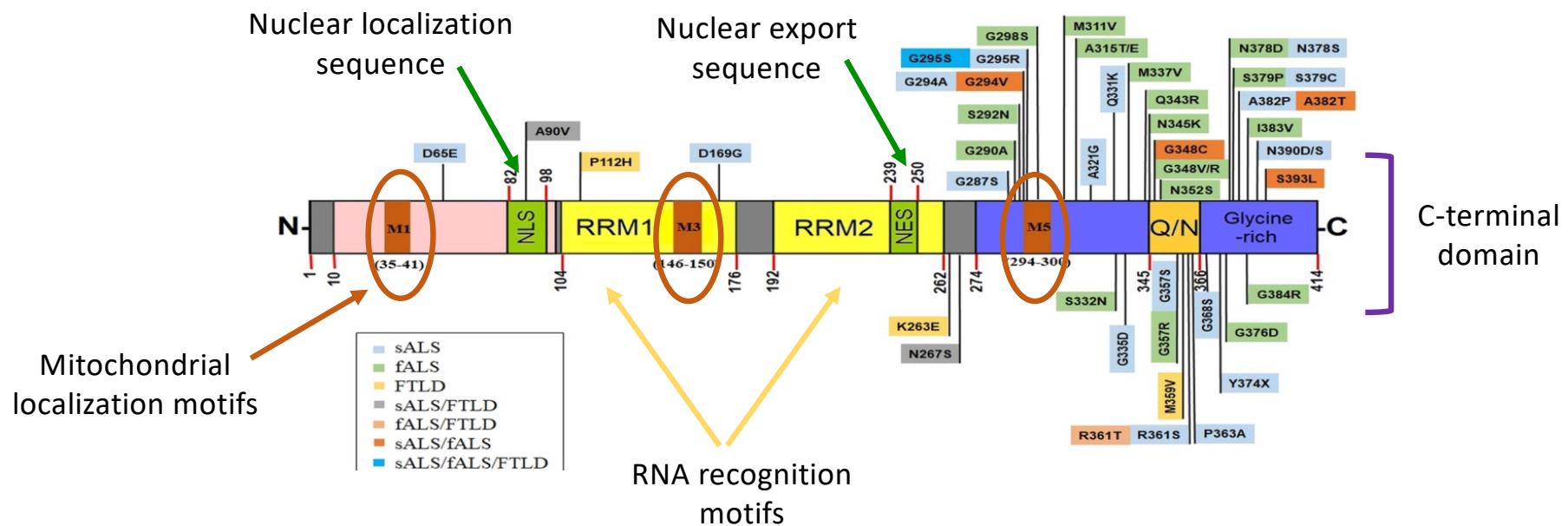
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Hardiman et al, Nat Rev, 2017

TDP43 in ALS

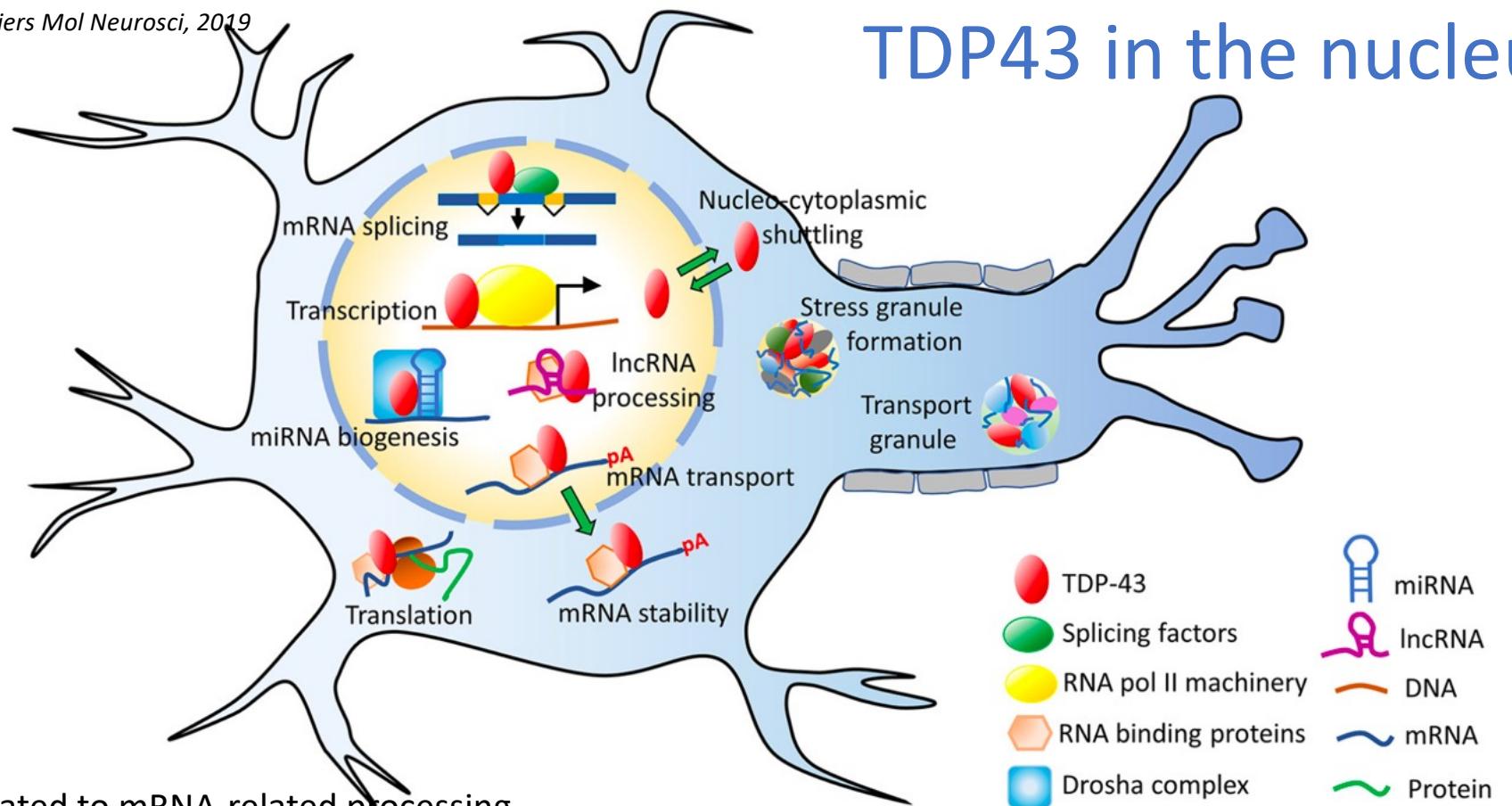


Hyper-phosphorylated and ubiquitinated TDP-43 in brain and spinal cord

TDP43 Mutations in 5-10% familial ALS cases

Up to 97% of sporadic ALS have TDP-43 inclusions

TDP43 in the nucleus



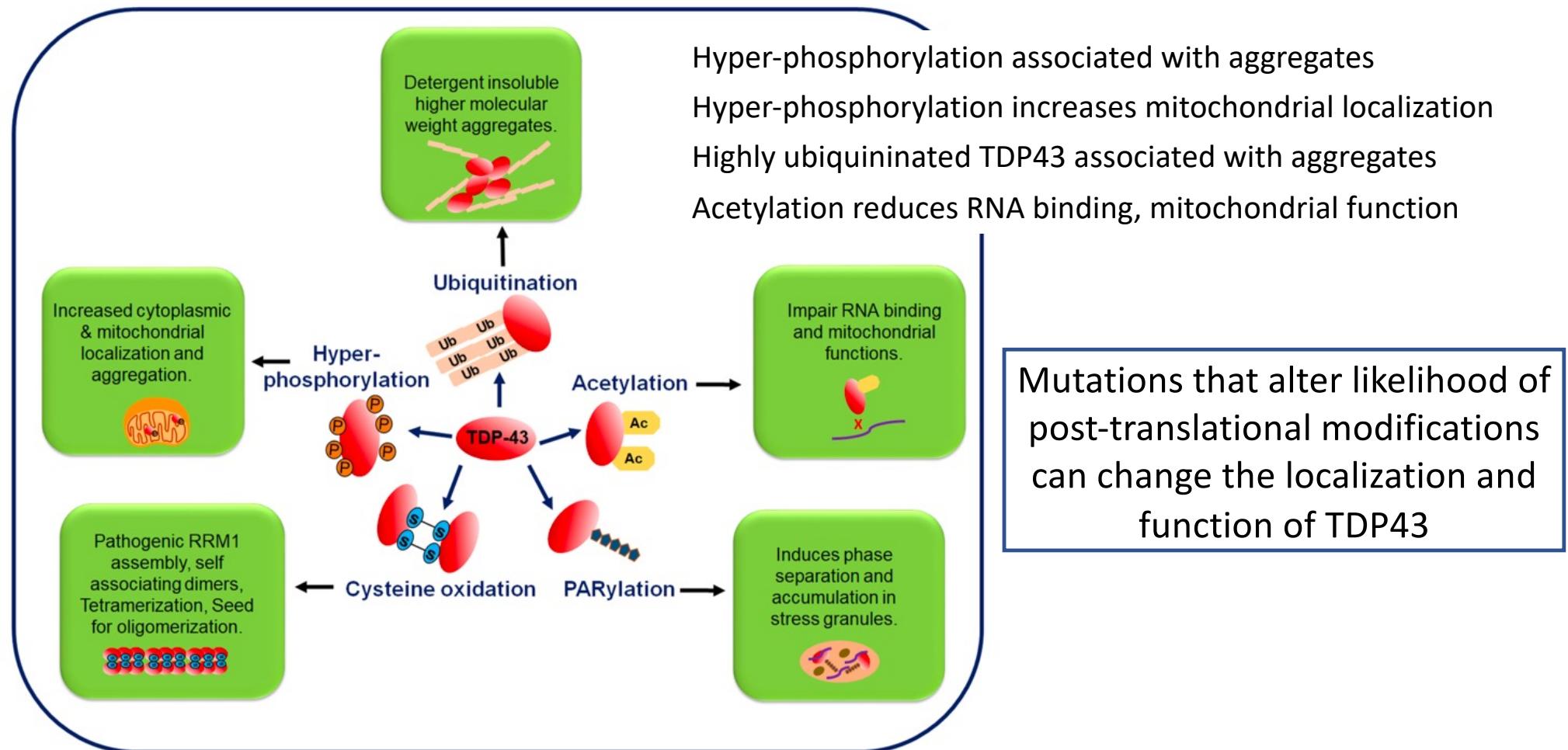
Functions related to mRNA-related processing

Regulates transcription, splicing, maintaining RNA stability

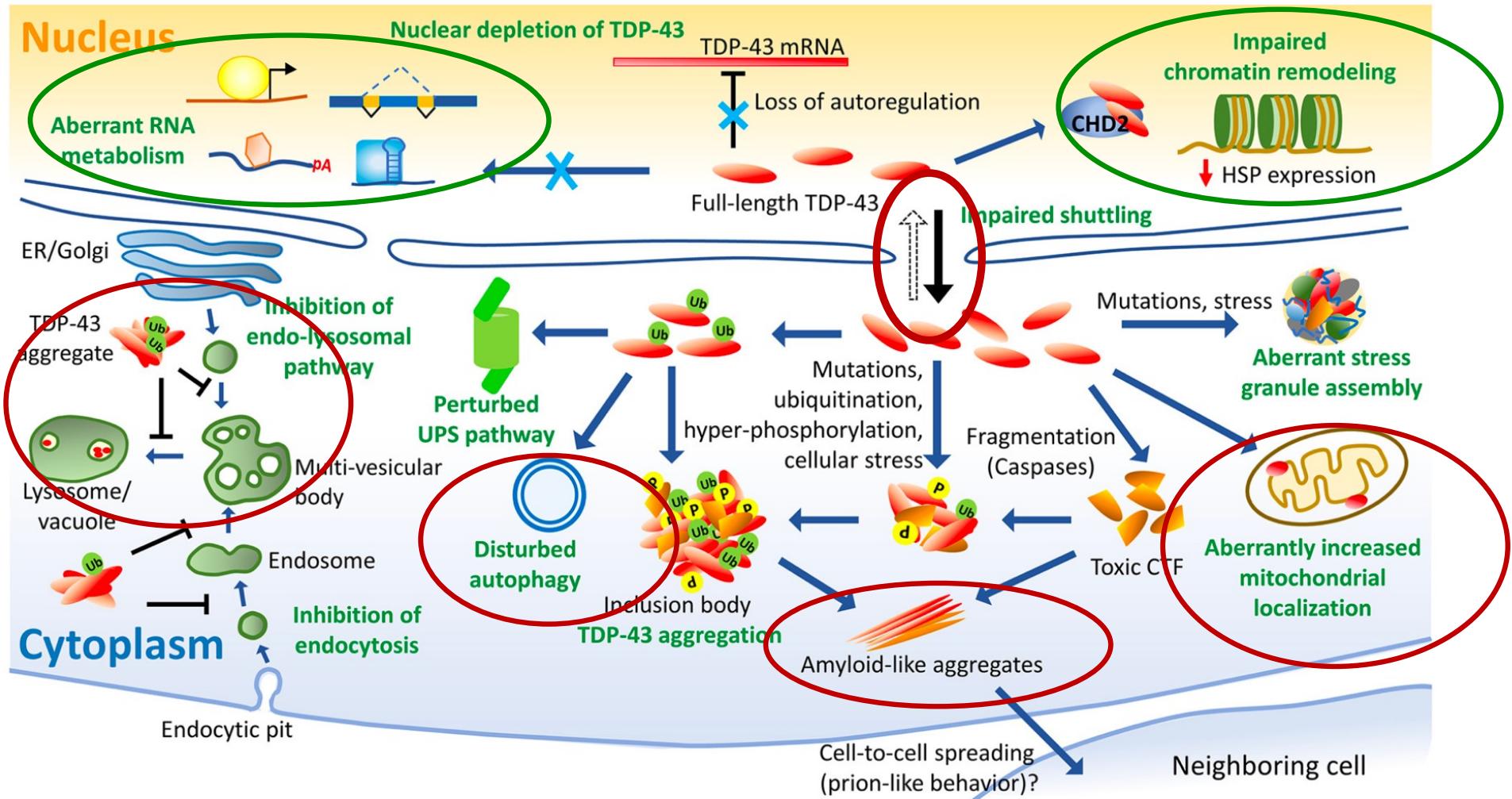
Able to shuttle between nucleus cytoplasm

Cytoplasmic TDP-43 involved in the stress granule formation, ribonucleoprotein (RNP) transport

Post-translation modifications of TDP43

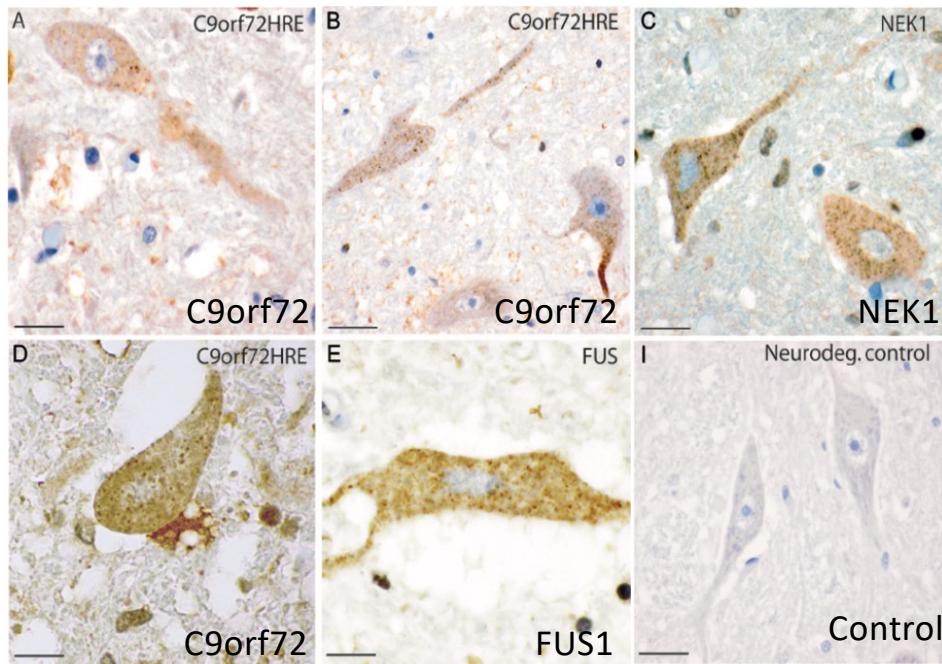


Altered TDP43 function disrupts cellular processes



Prasad et al, *Frontiers Mol Neurosci*, 2019

SOD1 inclusions in patients with ALS caused by other genes

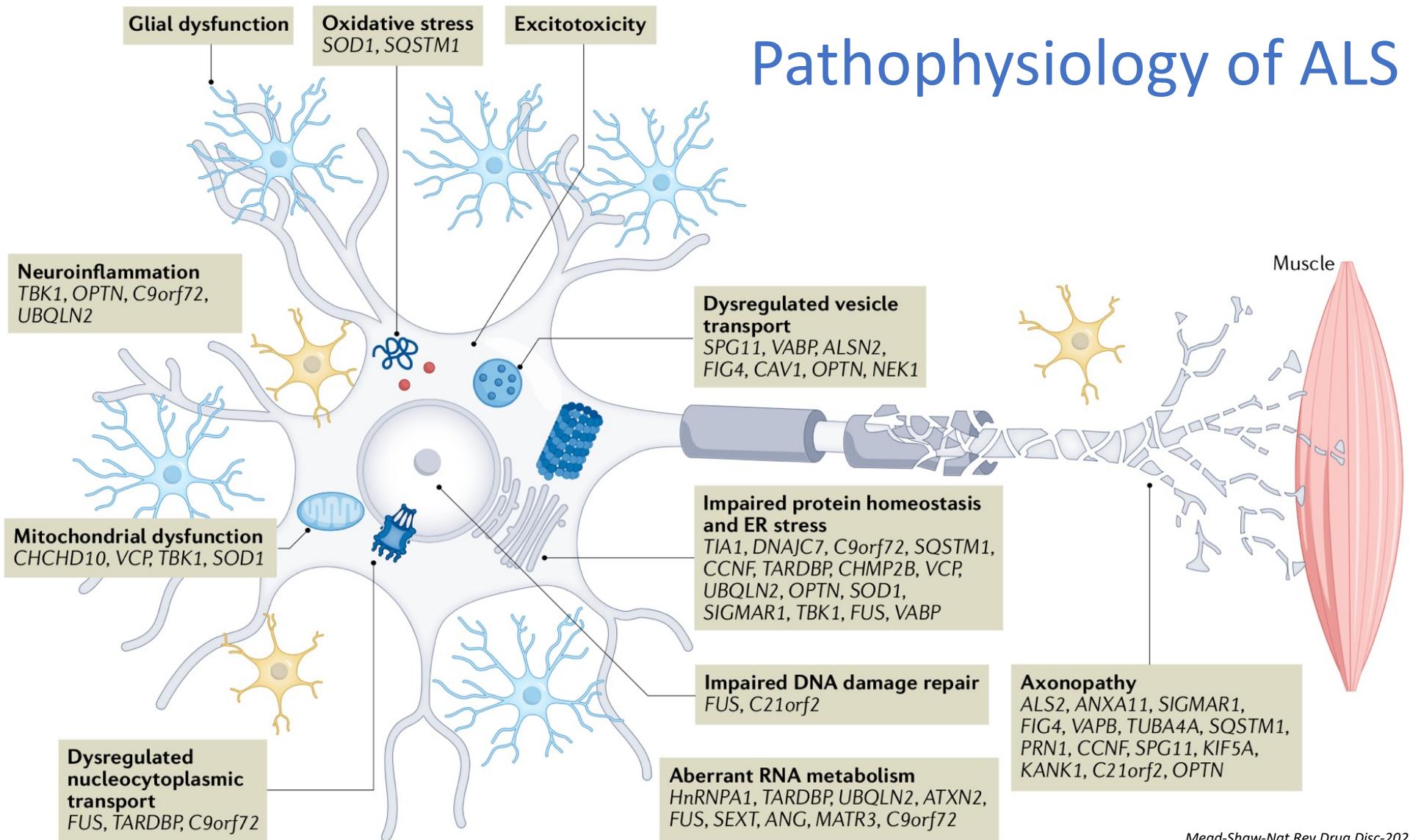


SOD1 inclusions in patients carrying other mutations

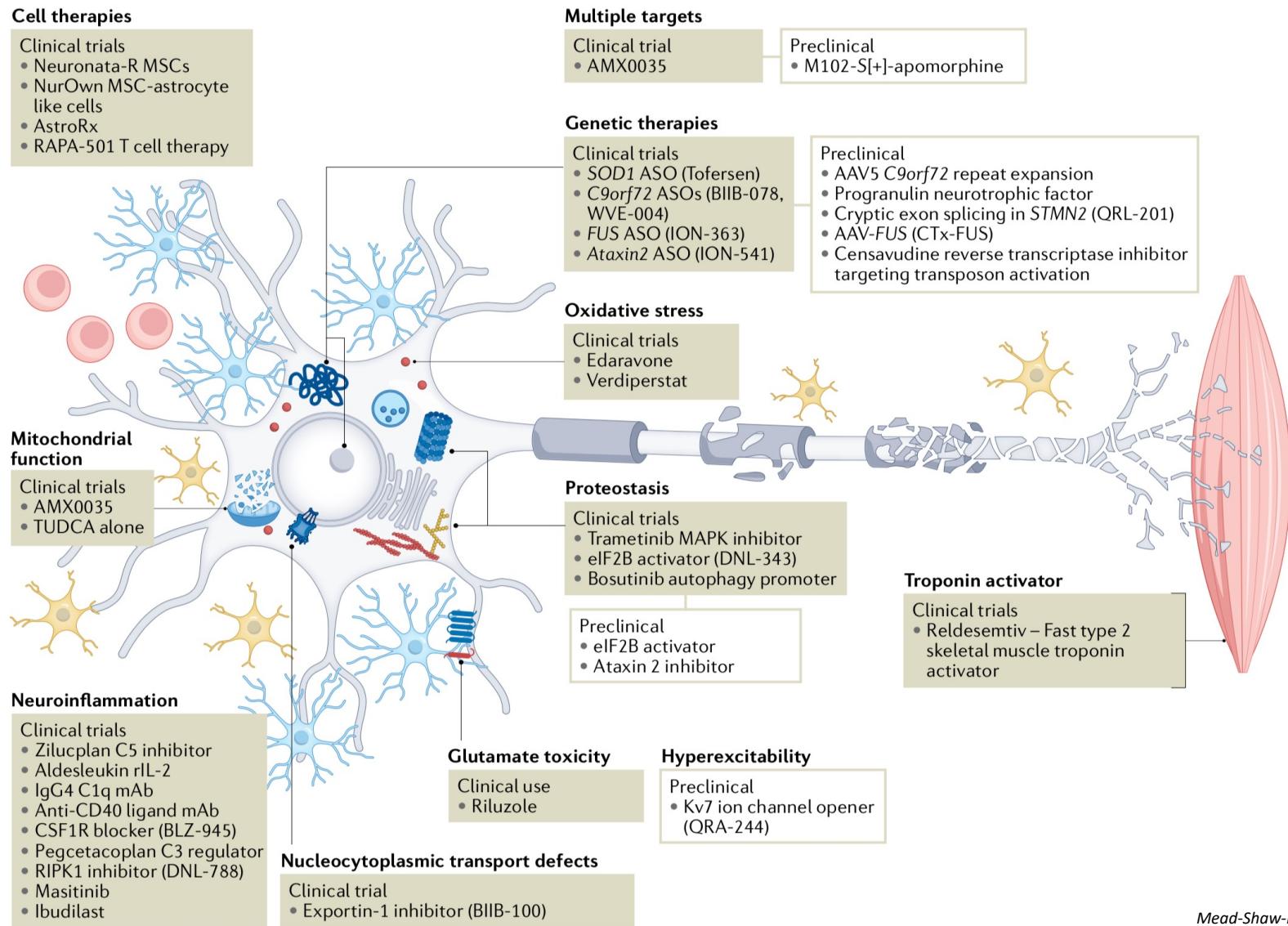
Misfolding of SOD1- a common downstream event

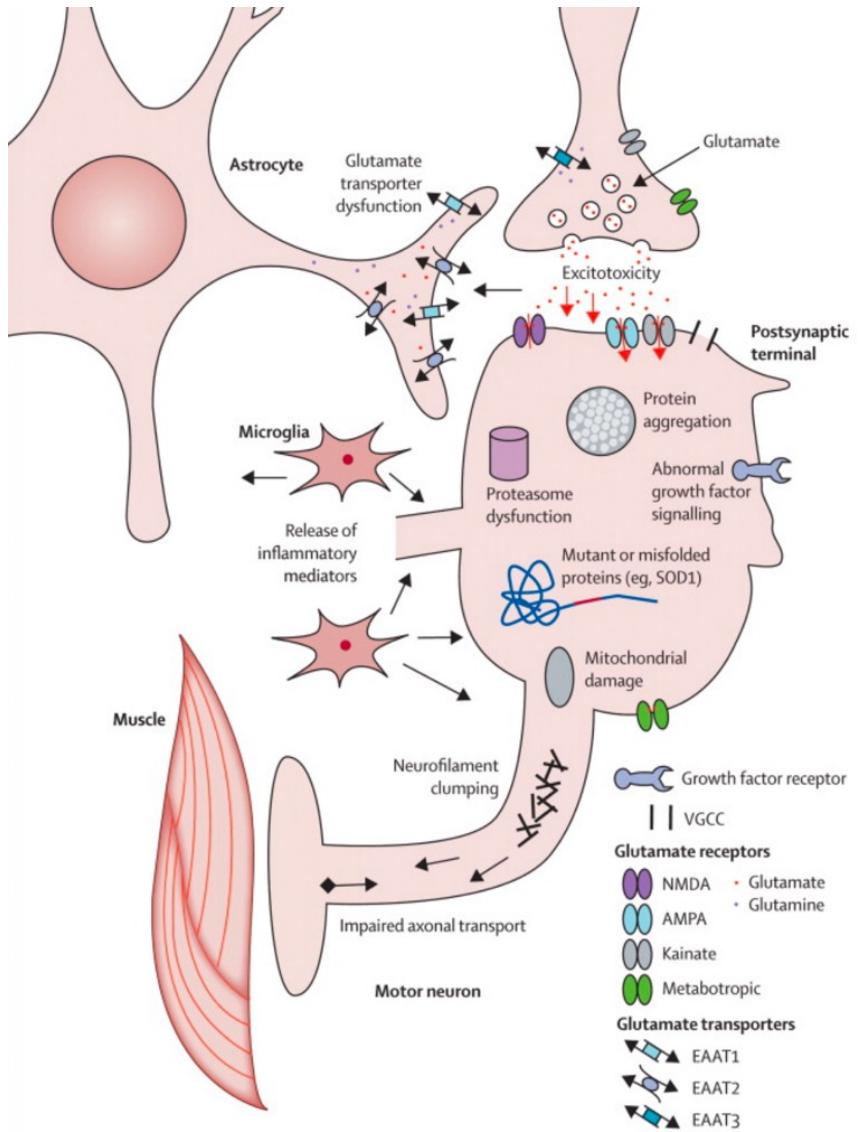
Anti-SOD therapeutic could be more broadly useful

Pathophysiology of ALS



Mead-Shaw-Nat Rev Drug Disc-2022





Excitotoxicity

Disrupted in axon transport

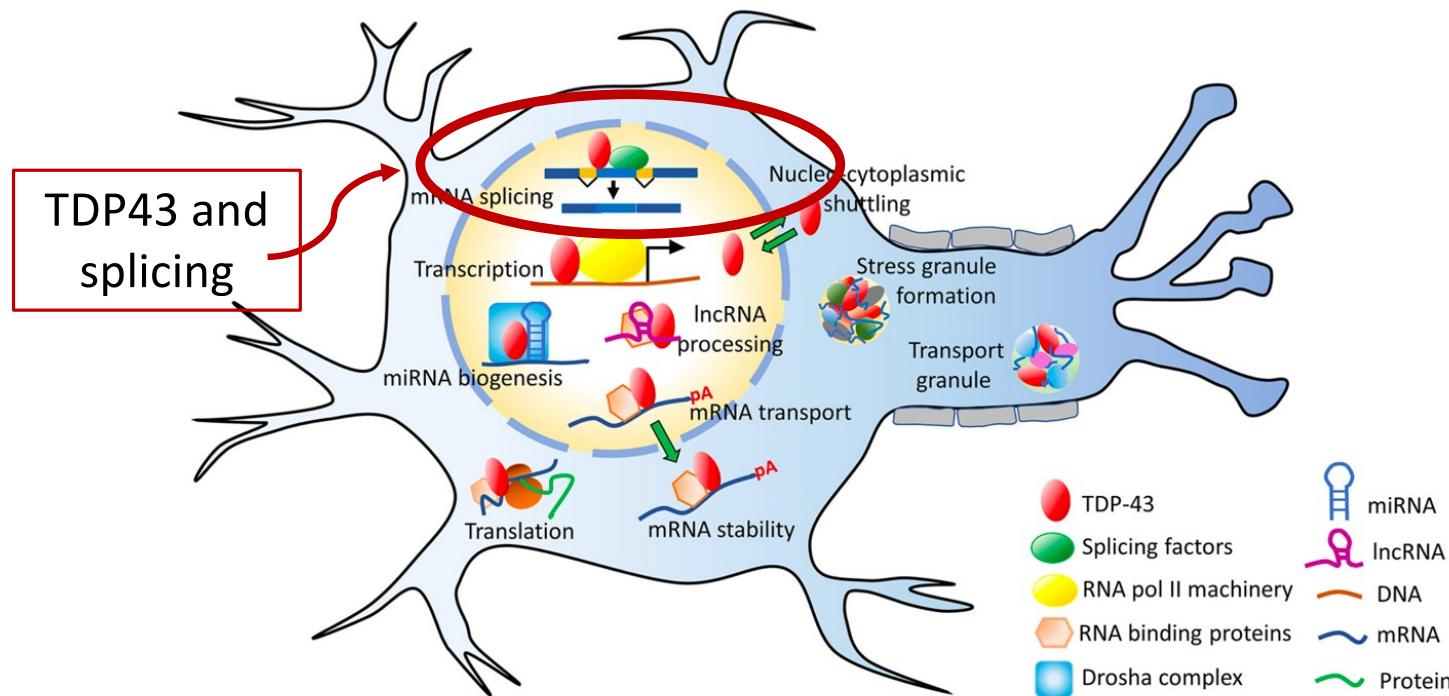
Disrupted in synaptic mechanism

Altered reuptake mechanisms

Enhanced glutamate release

Increased glutamate in synaptic cleft

TDP43 in the nucleus



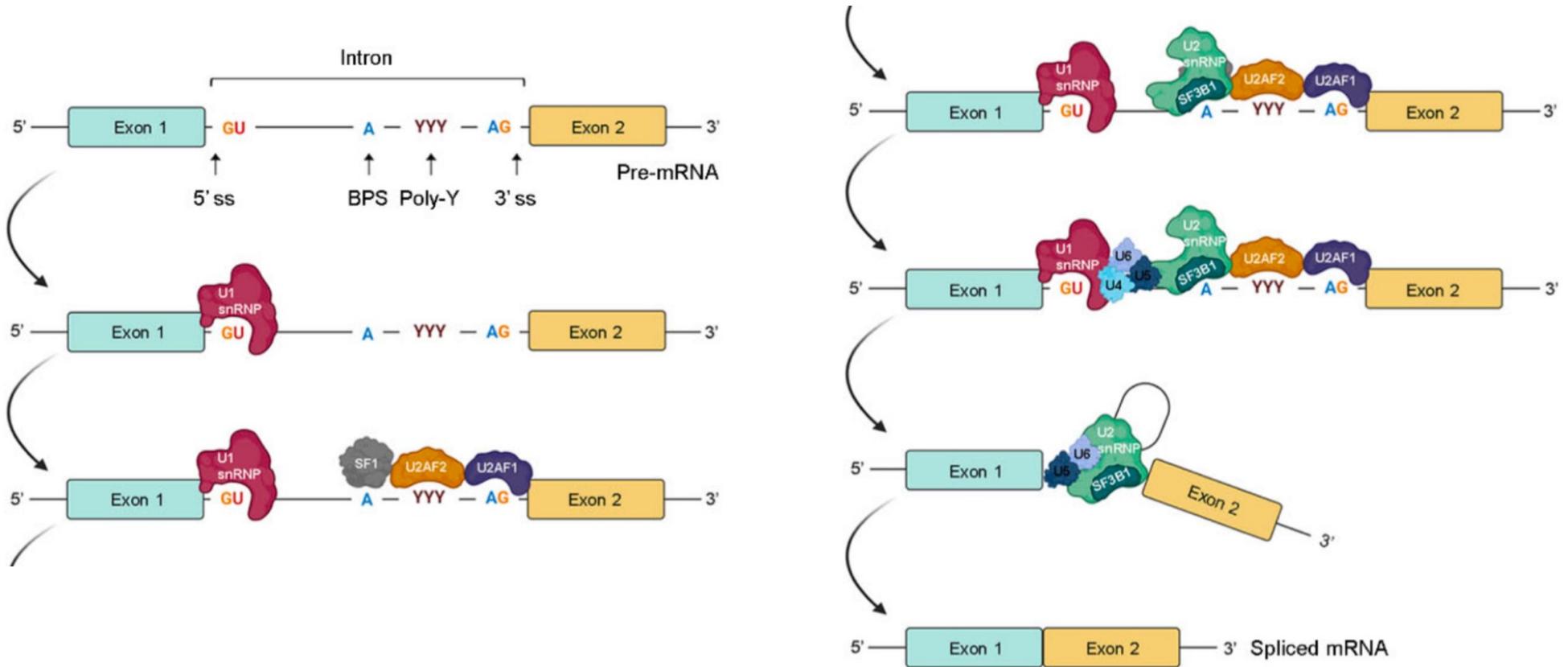
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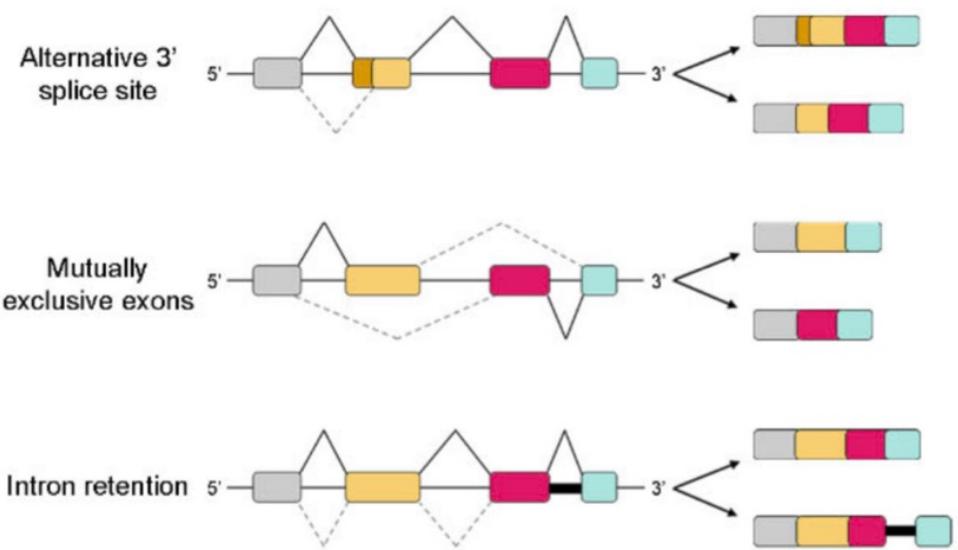
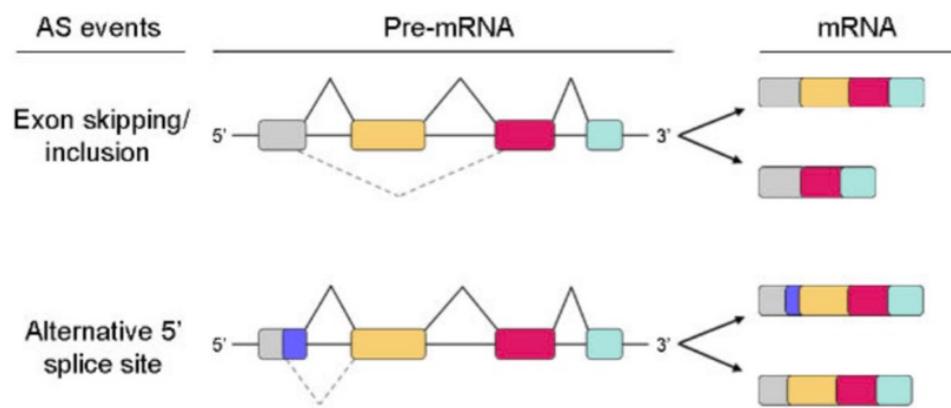
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RNA splicing



Alternative splicing



Current ALS therapies

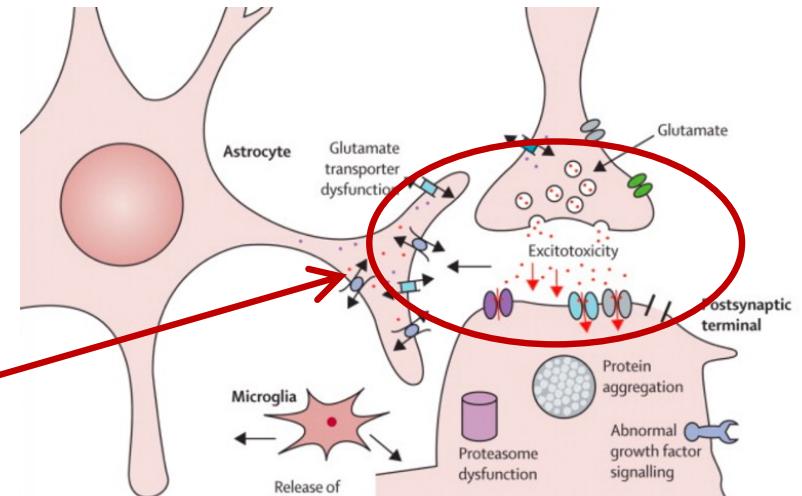
Riluzole (Rilutek)

First ALS treatment approved by FDA (1995)

Mechanism:

Blocks glutamate release from presynaptic terminals

Can extend life 2-3 months



Edaravone (Radicava)

FDA approval 2017

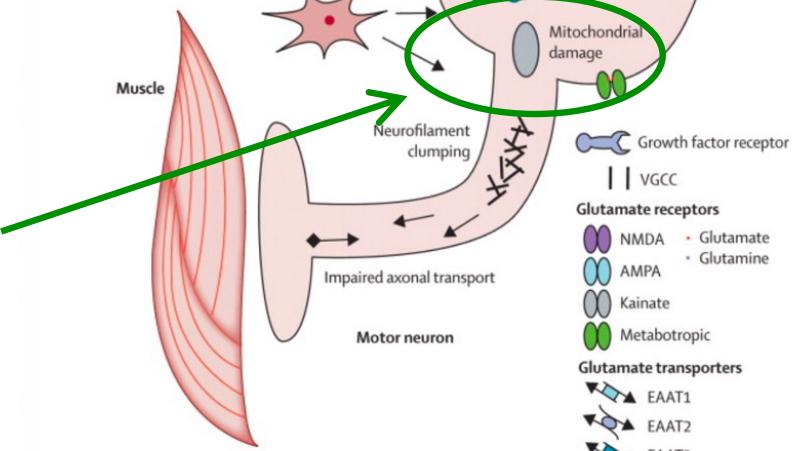
Mechanism:

Antioxidant, reduction in reactive oxygen species (ROS)

Slowed disease progression in 24 month trial by 33%

Delays onset of ventilator dependence or tracheostomy

May not work in all patients?



Current ALS therapies

Relyvrio (sodium phenylbutyrate/taurursodiol)

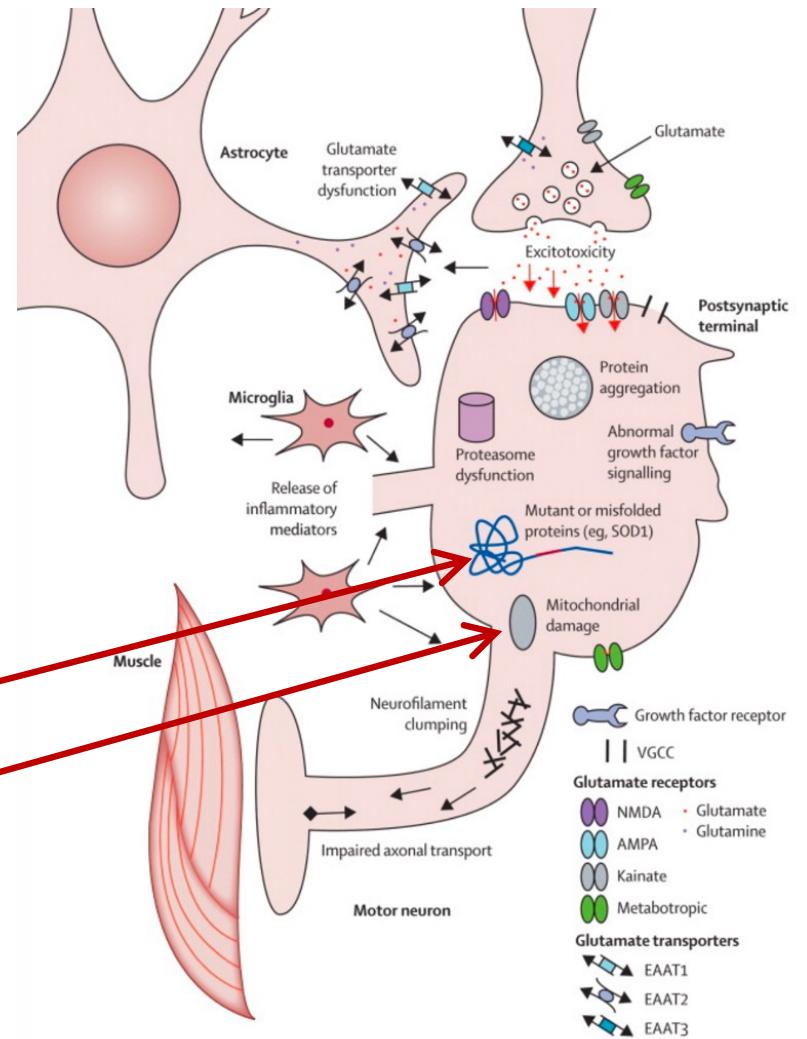
FDA approval 2022

Mechanism:

Pan-histone deacetylase (HDAC) inhibitor/bile acid

Phenylbutyrate- upregulation of chaperone proteins,
reduction of ER stress

Taurursodiol effect on mitochondria



Cruz, P&T, 2018; <https://www.alzforum.org/therapeutics/relyvrio>