ALS: the fall to the frozen

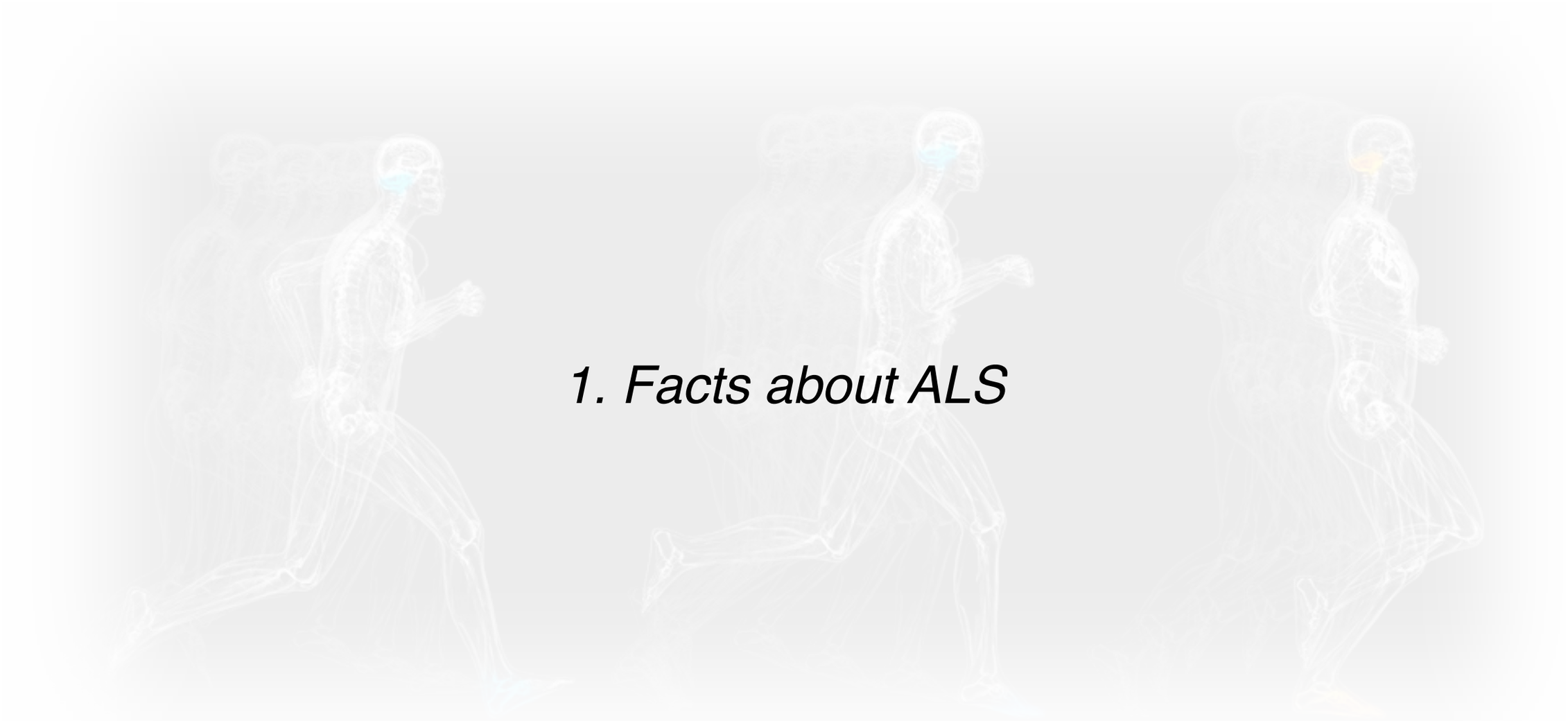
Roderick (Chenmengxiao) Pan
MacMillan Group
Princeton University
Nov. 14th, 2023

1. Facts about ALS

2. Symptoms and phenotypes

3. What do we know about the cause?

4. Clinical practices and social impacts



1. Facts about ALS

Facts about ALS

Name

“No” “muscle” “nourishment”

From the spinal cord to the side

An abnormal hardening…

A progressive neurodegenerative disease that causes loss of muscle control

Facts about ALS

Current knowledge

5,000+
People are diagnosed per year

2-5 years
Is the average life expectancy

Every **90 mins**
someone is diagnosed and someone passes away from ALS

90 percent
of cases occur without family history

10 percent
of cases are linked with family history

$250,000
is the estimated out-of-pocket cost for caring an ALS patient

$2 billion
is the estimated cost to develop a drug to slow or stop the progression of ALS

There is NO CURE for ALS

https://www.als.org/understanding-als/what-is-als

Facts about ALS

History

French neurologist Jean-Martin Charcot identified and named the disease as ALS

1874

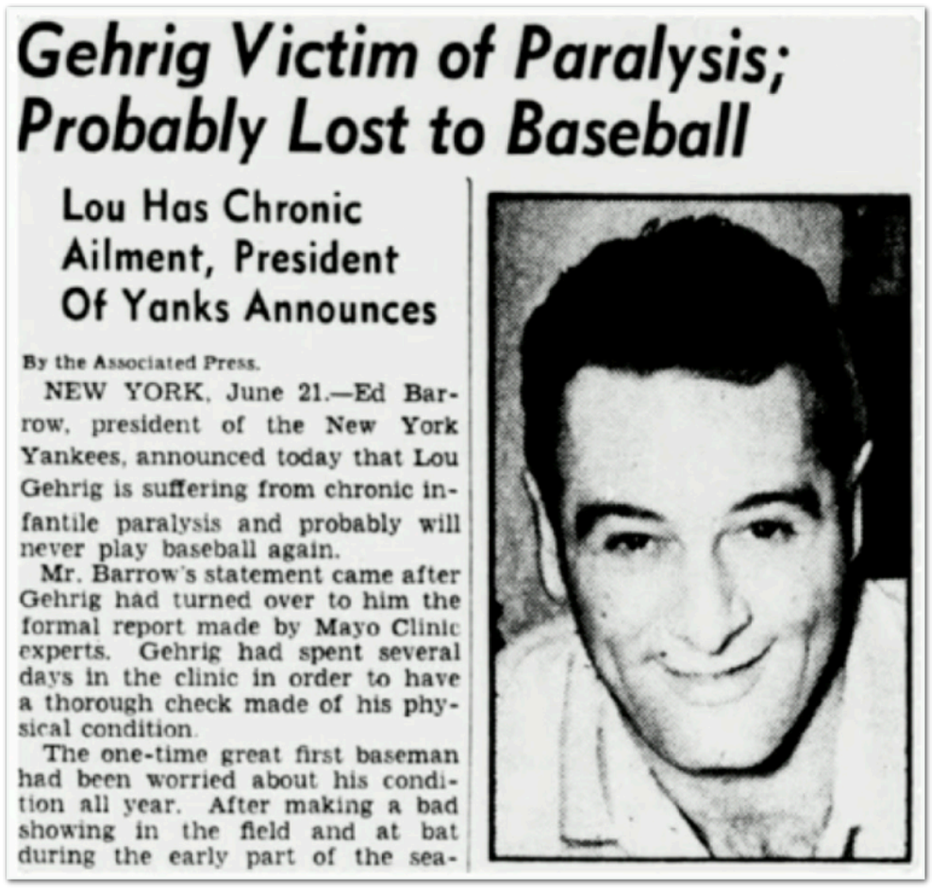
1939

ALS gains mainstream attention

https://www.pharmaceutical-technology.com/features/history-of-als

Facts about ALS

Lou Gehrig drew public attention



Gehrig Victim of Paralysis; Probably Lost to Baseball

Lou Has Chronic Ailment, President Of Yanks Announces

By the Associated Press.

NEW YORK, June 21.—Ed Barrow, president of the New York Yankees, announced today that Lou Gehrig is suffering from chronic infantile paralysis and probably will never play baseball again.

Mr. Barrow's statement came after Gehrig had turned over to him the formal report made by Mayo Clinic experts. Gehrig had spent several days in the clinic in order to have a thorough check made of his physical condition.

The one-time great first baseman had been worried about his condition all year. After making a bad showing in the field and at bat during the early part of the sea-

- *Gehrig was diagnosed with ALS on his 36th birthday during a visit to the Mayo Clinic on June 19, 1939.*

- *Prior to his diagnosis, Gehrig noticed a loss of strength, slipping, and loss of coordination while playing on the field.*

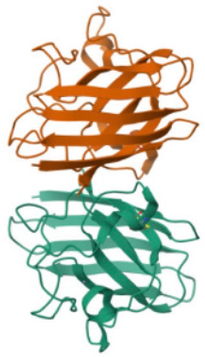
> *“ I might have been given a bad break, but I’ve got an awful lot to live for. ”*
>
> *Iconic 1939 "Luckiest Man on the Face of the Earth" speech at Yankee Stadium*

Facts about ALS

History

French neurologist Jean-Martin Charcot identified and named the disease as ALS

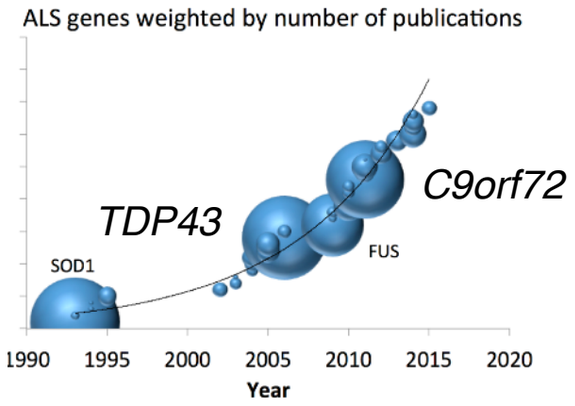
1874



SOD1

First ALS gene identified

1993



2006

2011

1939

ALS gains mainstream attention

Lou Gehrig's disease

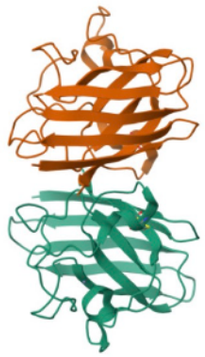
https://www.pharmaceutical-technology.com/features/history-of-als

Facts about ALS

History

French neurologist Jean-Martin Charcot identified and named the disease as ALS

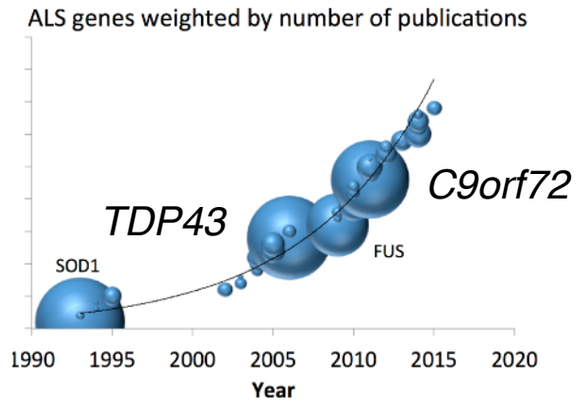
1874



SOD1

First ALS gene identified

1993



Research into environmental factors became another core focus for ALS cause

1995

2006

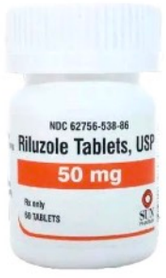
2011

2017

2021

ALS gains mainstream attention

Lou Gehrig's disease



Riluzole

First ALS drug FDA approved

Second ALS drug FDA approved

and alternative dosages

……

Biogen offers compassionate-use access

https://www.pharmaceutical-technology.com/features/history-of-als

Facts about ALS

Risk factors

Male
gender is consistently detected as a factor associated with a 1.5 times increased risk of developing ALS compared with female gender.

Smoking
increases ALS risk, possibly caused by nicotine, oxidative stress, or one of the many other known toxic substances.

Military
veterans are more likely to be diagnosed with the disease than the general public.

Occupation

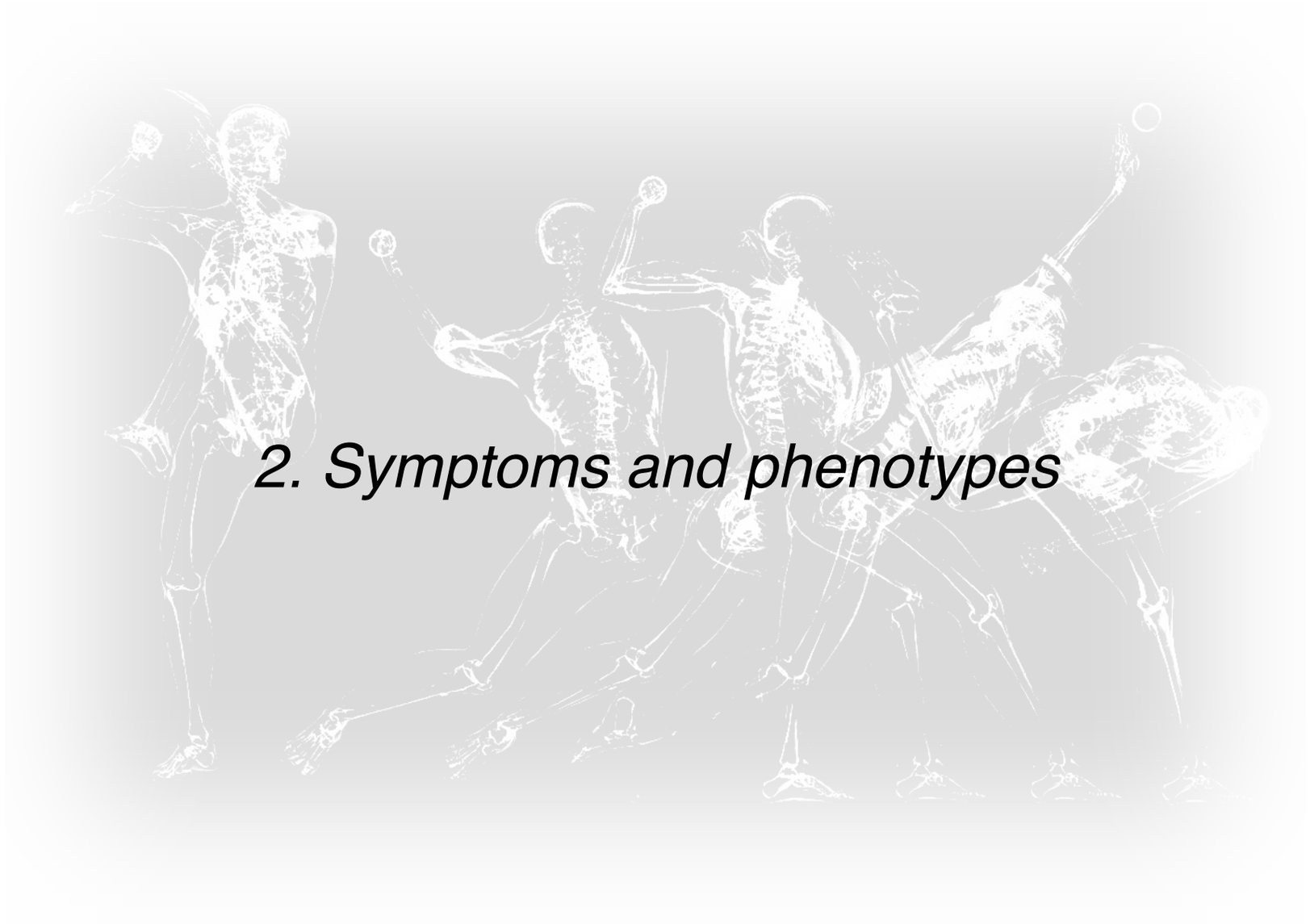
Toxin

Trauma

Athletics

Cognitive performance

Oskarsson B., Horton D.K., Mitsumoto H., Neurol Clin. **2015**, 33(4)



2. Symptoms and phenotypes

ALS symptoms and phenotypes

Symptoms along disease progression

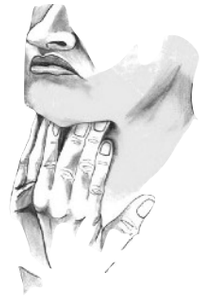
Functionality and independence

2/3 of the patients
disease onset in the **limbs**

- Difficulty in gripping objects
- Balance issues…

1/3 of the patients
disease onset in the **bulbar muscle**

- Poor articulation and slurring speech
- An unusually hoarse or quiet voice…



https://alsnewstoday.com/stages-of-als/
https://www.mda.org/disease/amyotrophic-lateral-sclerosis/signs-and-symptoms/stages-of-als

ALS symptoms and phenotypes

Symptoms along disease progression

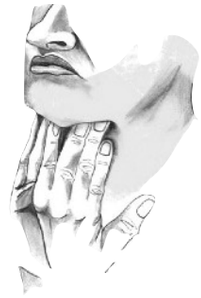
Functionality and independence

2/3 of the patients
disease onset in the **limbs**

- Difficulty in gripping objects
- Balance issues…

1/3 of the patients
disease onset in the **bulbar muscle**

- Poor articulation and slurring speech
- An unusually hoarse or quiet voice…



- Muscles become completely paralyzed and others are weakened
- Rely on aids like walkers or wheelchairs
- Speaking and breathing problem

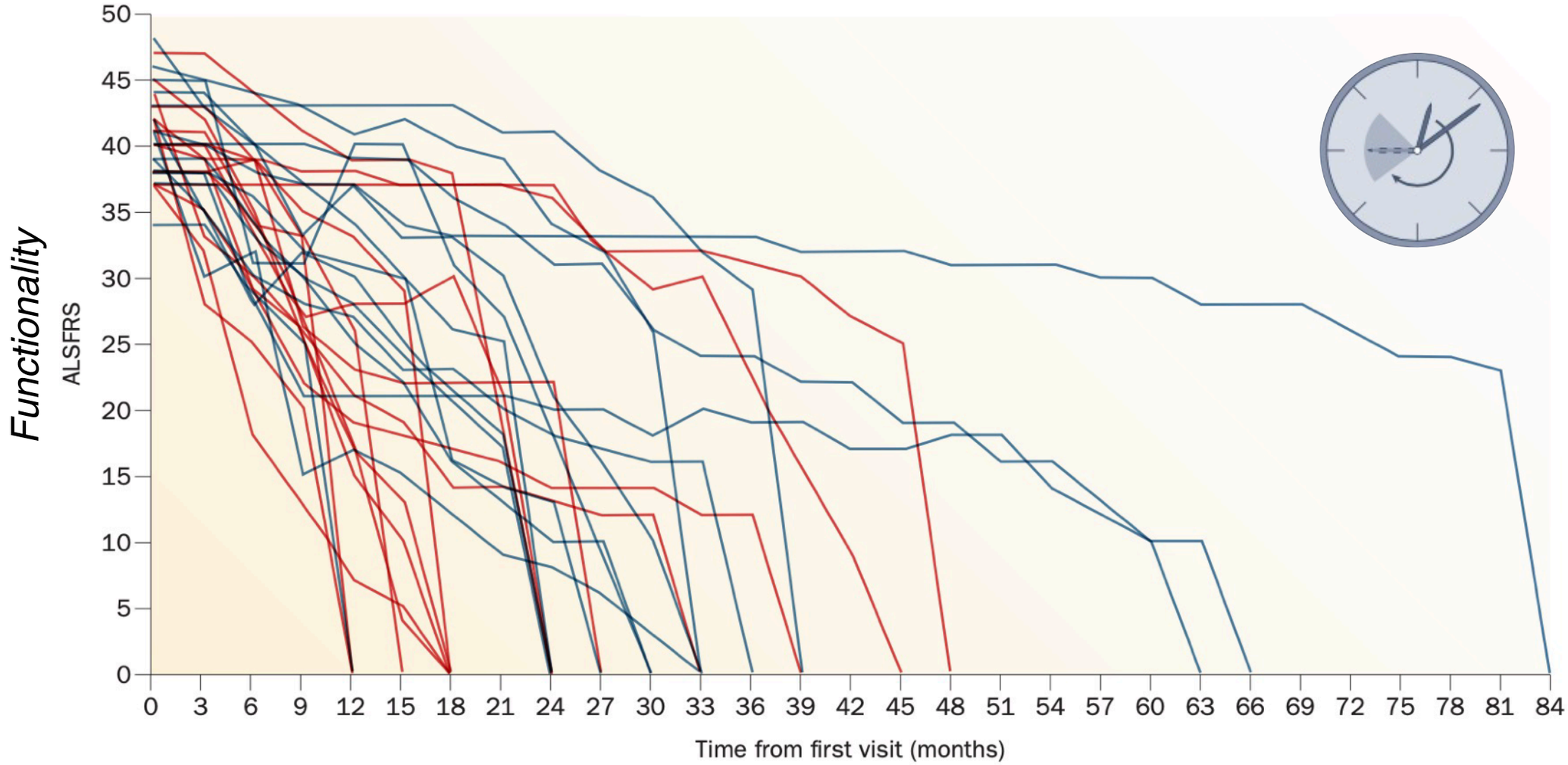
- Mobility is extremely limited
- Inability to communicate without assistance
- Aids in feeding and breathing are required

Respiratory failure
is the most common cause of death in ALS.
Others including malnutrition, pulmonary embolism…

https://alsnewstoday.com/stages-of-als/
https://www.mda.org/disease/amyotrophic-lateral-sclerosis/signs-and-symptoms/stages-of-als

ALS symptoms and phenotypes

Varied timelines of disease progression



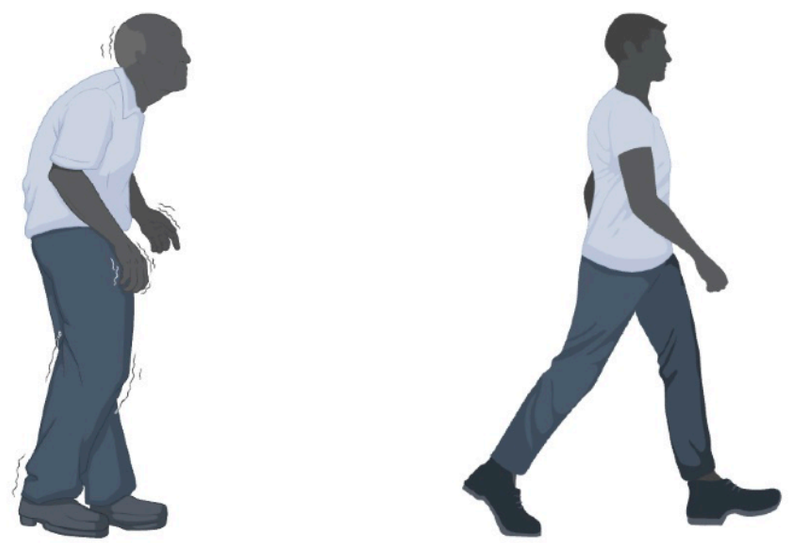
The average survival time is three years, about 20% of people with ALS live five years, 10% survive 10 years and 5% live 20 years or longer.

Patients with bulbar-onset suffers worse prognosis, respiratory-onset worst

Swinnen, B., & Robberecht, W., Nature Reviews Neurology, 2014, 10(11), 661–670.

ALS symptoms and phenotypes

Aging-related disease and juvenile onset



The majority of ALS starts in fifth or sixth decade of life

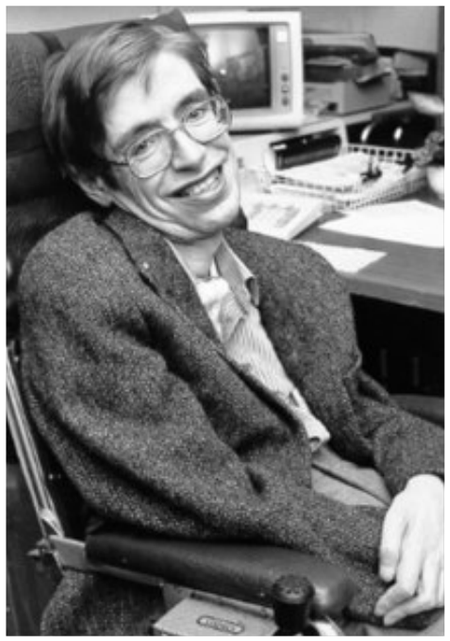
The older the onset, the more impacted bulbar system and poorer prognosis

Juvenile onset (<25ys) usually show slower progression

https://www.scientificamerican.com/article/stephen-hawking-als/
Swinnen, B., & Robberecht, W., Nature Reviews Neurology, 2014, 10(11), 661–670.

ALS symptoms and phenotypes

Juvenile onset and Stephen Hawking's case



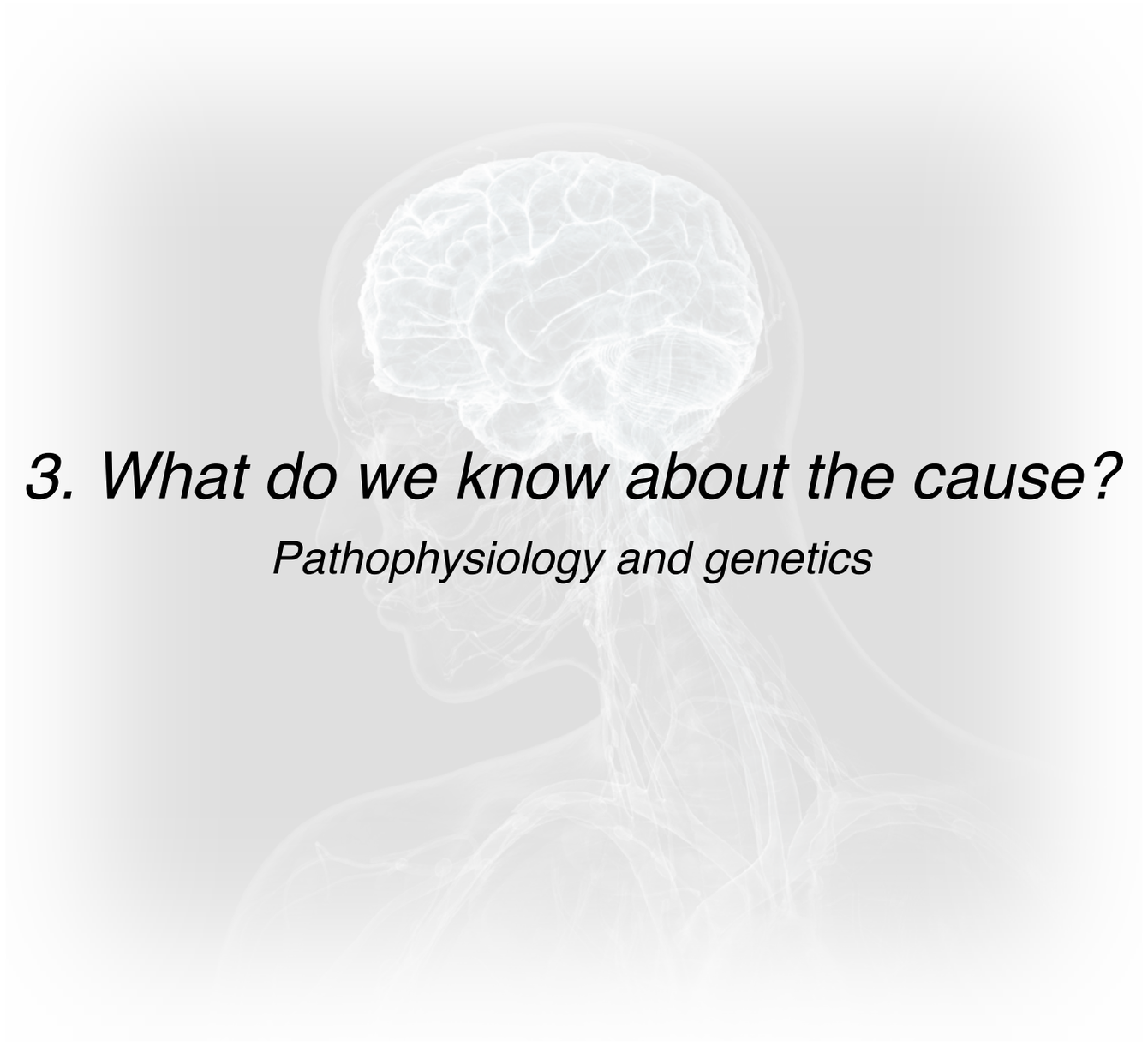
Stephen Hawking 1942-2018
Theoretical physicist, cosmologist and author

- ***Disease onset at the age of 21, 1962***
- ***Starting speaking through computer in 1985***

Active mind, psychological well-being, excellent care…

An extreme outlier

https://www.scientificamerican.com/article/stephen-hawking-als/
https://en.wikipedia.org/wiki/Stephen_Hawking

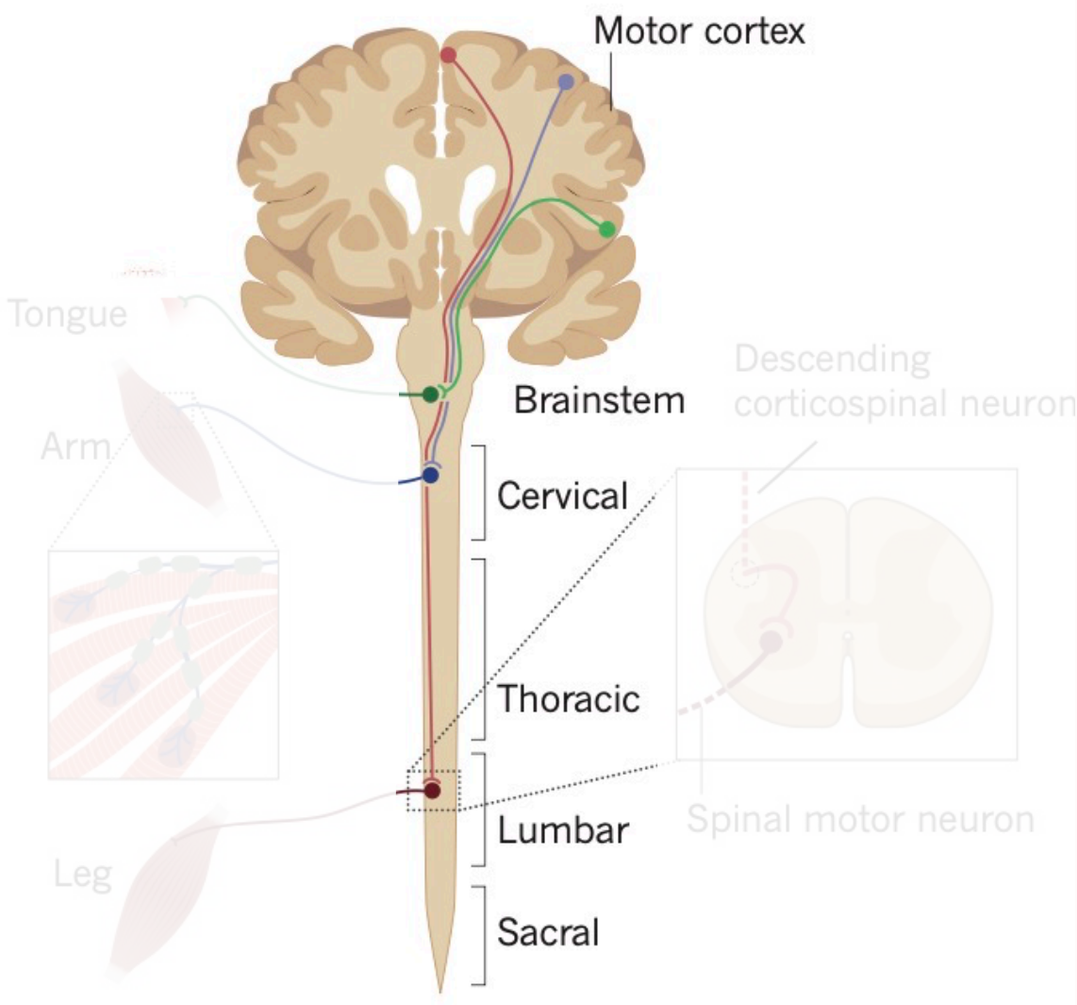


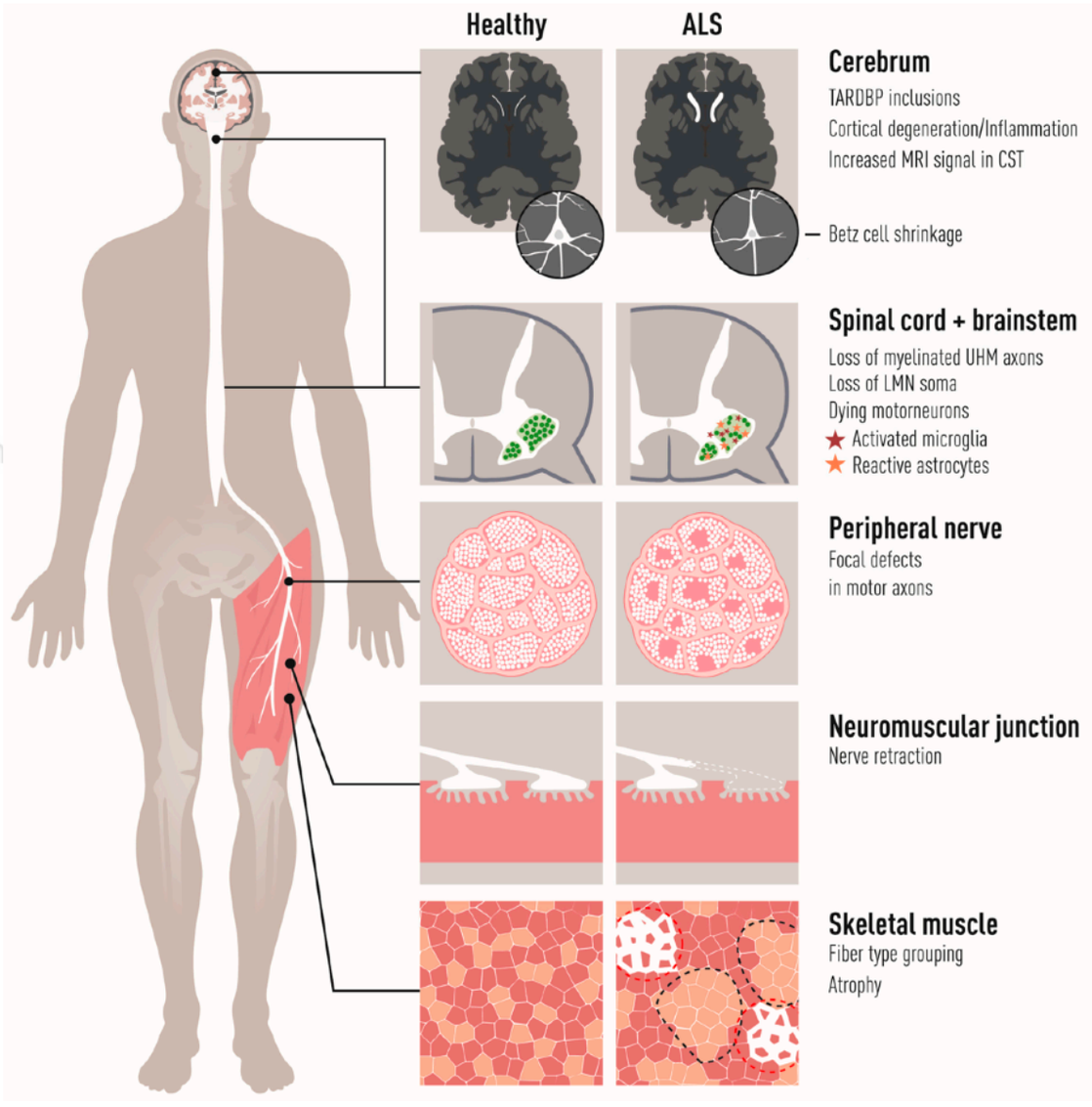
3. What do we know about the cause?

Pathophysiology and genetics

ALS pathophysiology and genetics

Motor neurons' disease





Degeneration of motor neurons

Schweingruber, C., & Hedlund, E. Biology, **2021**, 11(8)

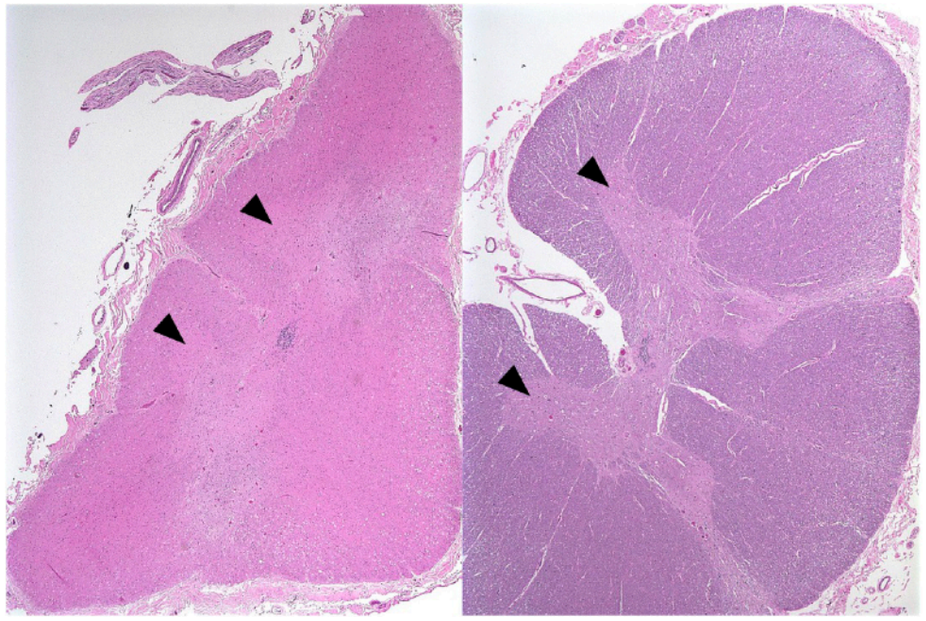
Taylor, J. P., Brown, R. H., Jr, & Cleveland, D. W., Nature, **2016**, 539(7628)

ALS pathophysiology and genetics

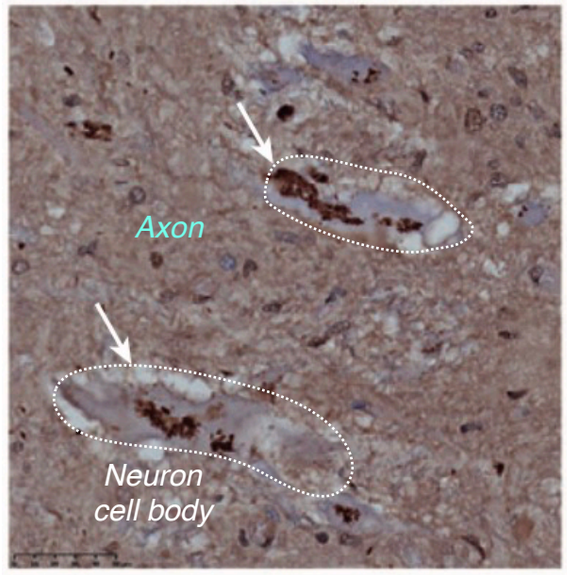
Motor neurons' disease

Degeneration of motor neurons

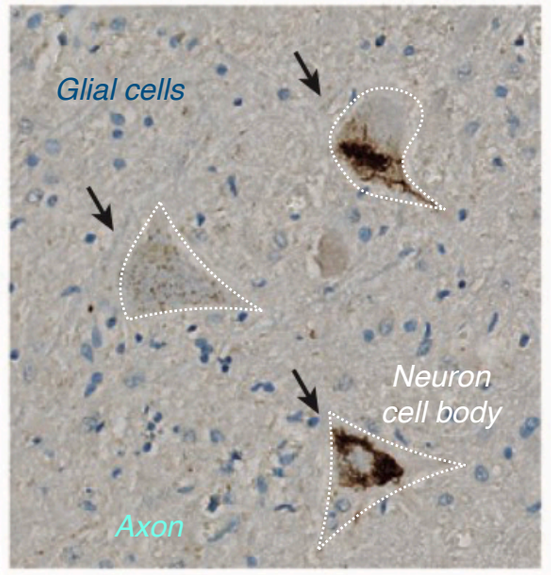
Neurons shrink and accumulate inclusions



Thoracic spinal cord of ALS patient (left) compared with age matched control (right).



SOD1 aggregates in SOD1-related familial ALS



TDP-43 cytoplasmic inclusions in sporadic ALS

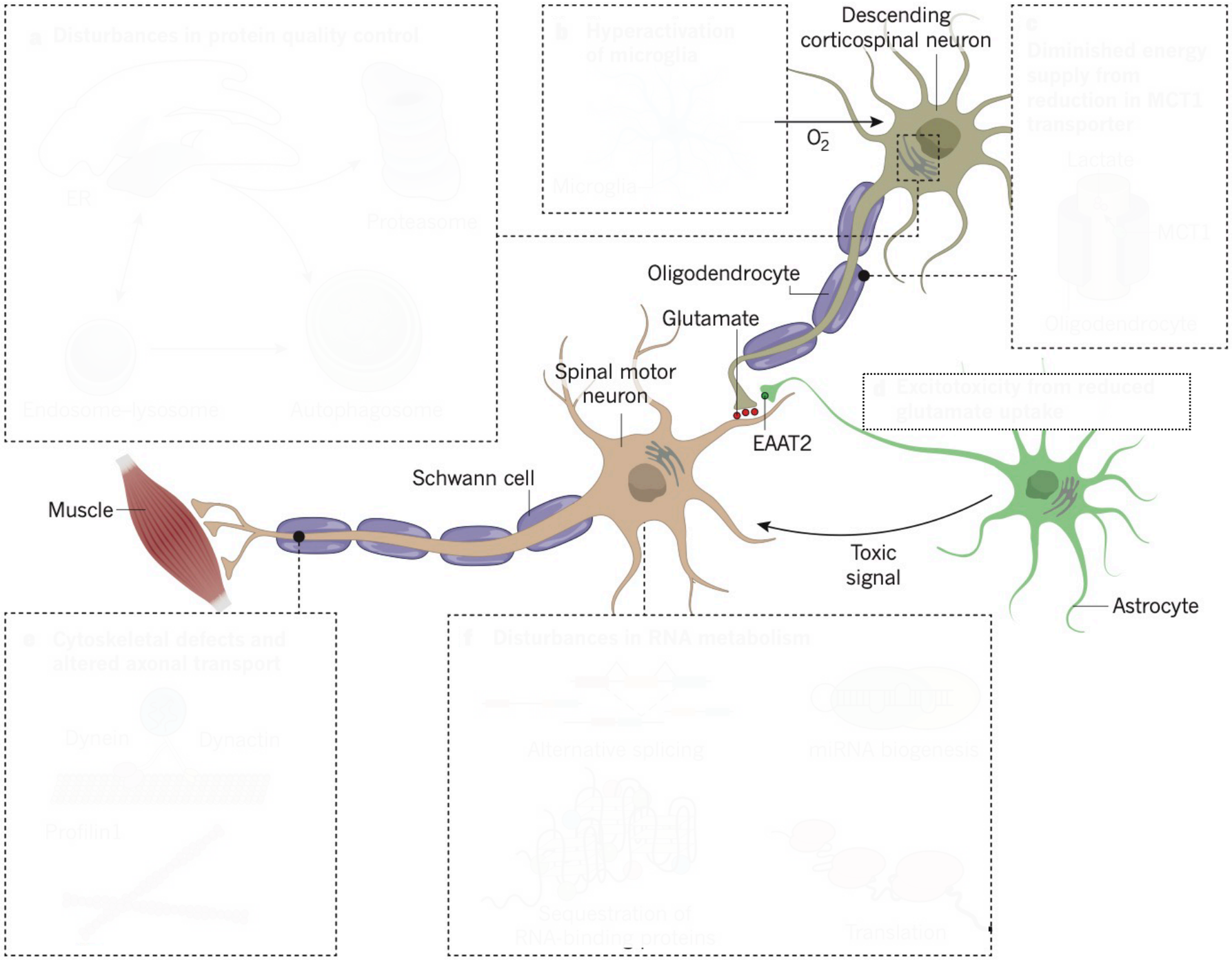
How does this happen?

https://www.pathologyoutlines.com/topic/cnsals.html

Taylor, J. P., Brown, R. H., Jr, & Cleveland, D. W., Nature, **2016**, 539(7628)

ALS pathophysiology and genetics

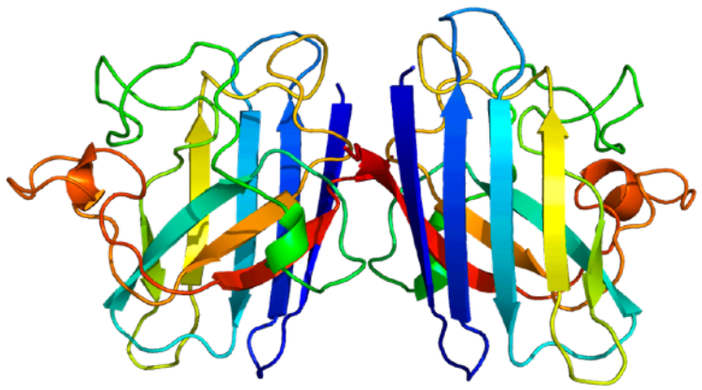
Main theories



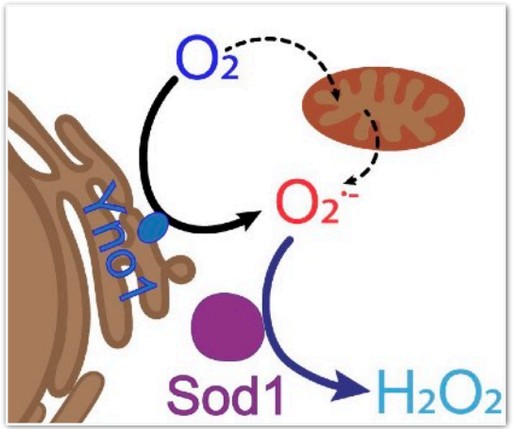
Taylor, J. P., Brown, R. H., Jr, & Cleveland, D. W., Nature, **2016**, 539(7628)

ALS pathophysiology and genetics

Mystery of SOD1



SOD1 dimer
First ALS gene discovered in 1993



Cu–Zn superoxide dismutase

Is it due to the reduced activity and subsequent ROS damage?

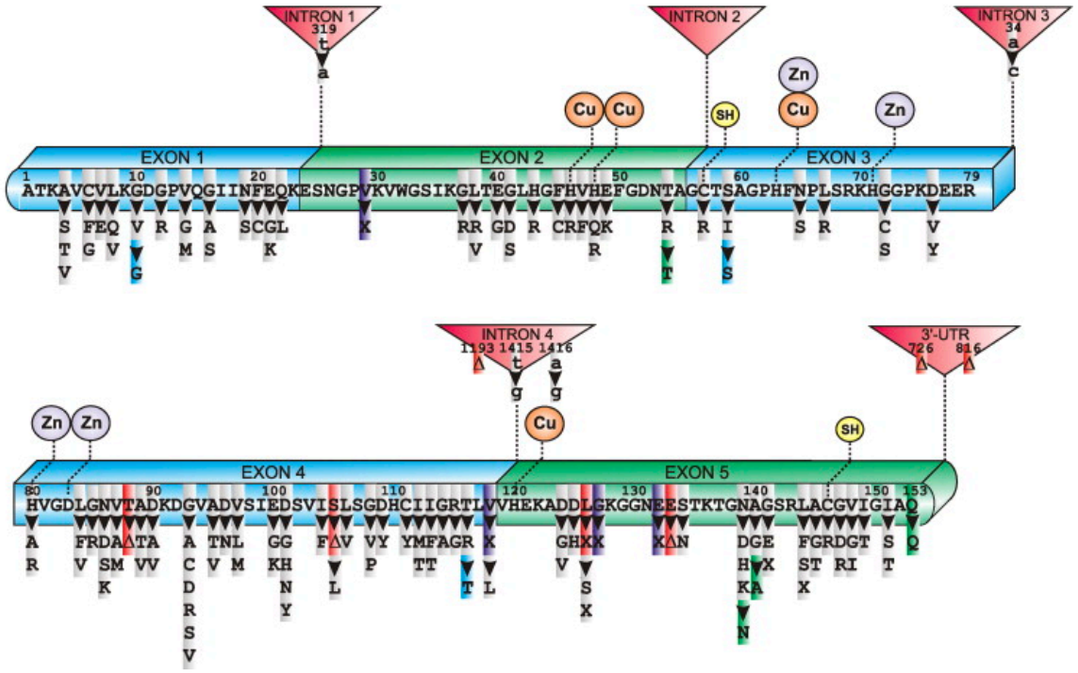
Rosen, D. R., Siddique, T., et al. Nature, **1993**, 362(6415)

ALS pathophysiology and genetics

Mystery of SOD1

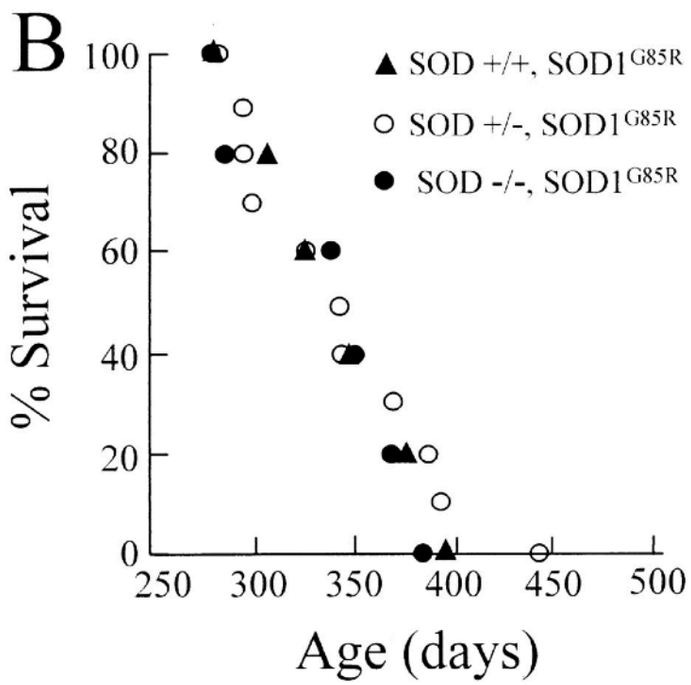
Counterargument 1

170 ALS-causing SOD1 mutations in its 153 aa peptide



Counterargument 2

Native dismutase activity has no effect on SOD1-ALS disease progression



In many years since the discovery of mutations in SOD1, no consensus on the main toxicity of mutant SOD1 has emerged

Turner, B. J., & Talbot, K. Progress in neurobiology, **2008**, 85(1)

Bruijn, L. I., Houseweart, M. K., et al. Science, **2018**, 281(5384)

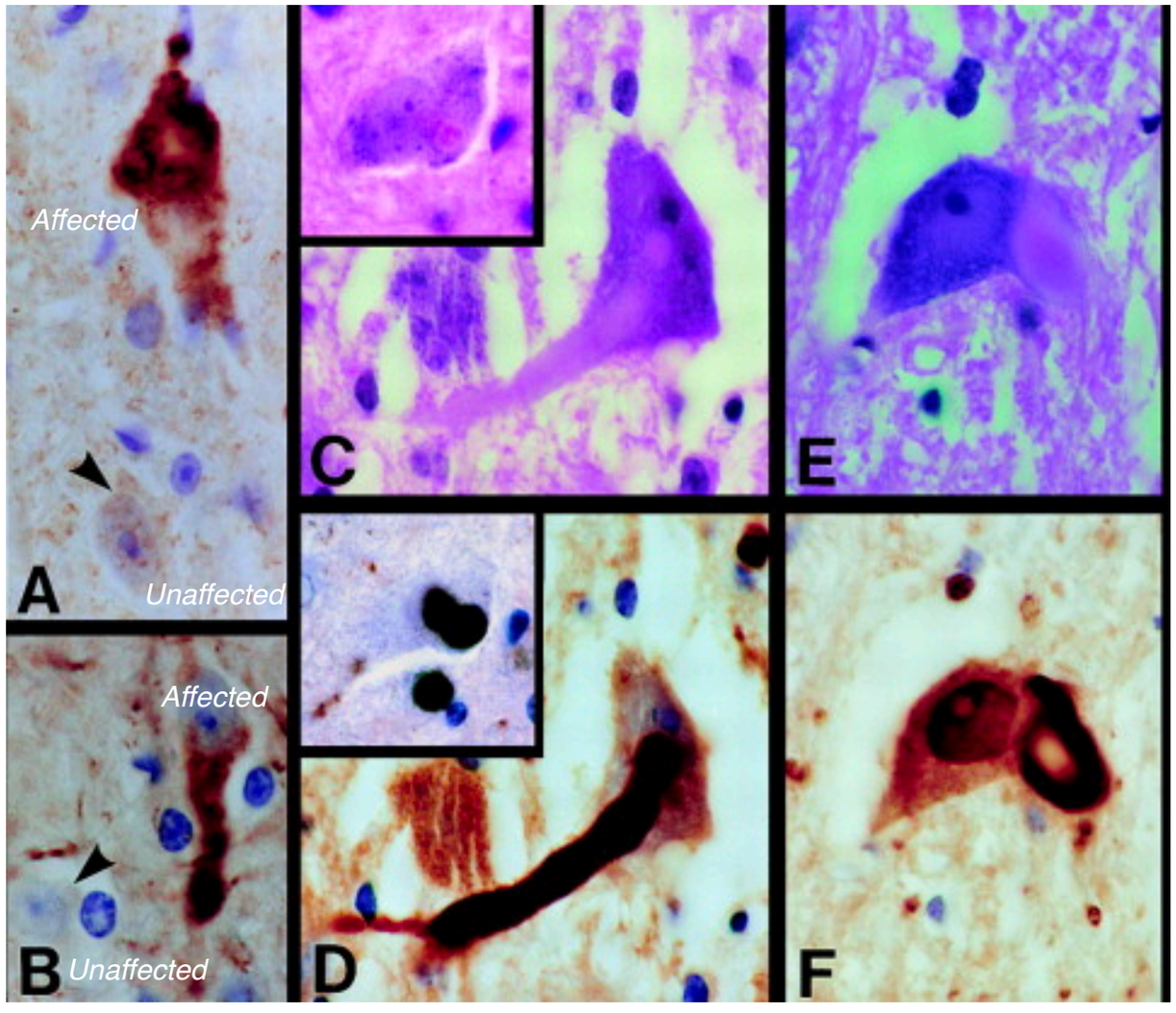
ALS pathophysiology and genetics

A prominent finding: SOD1 aggregates

SOD1 aggregates
Ubiquitinated

SOD1 stain

Ub stain

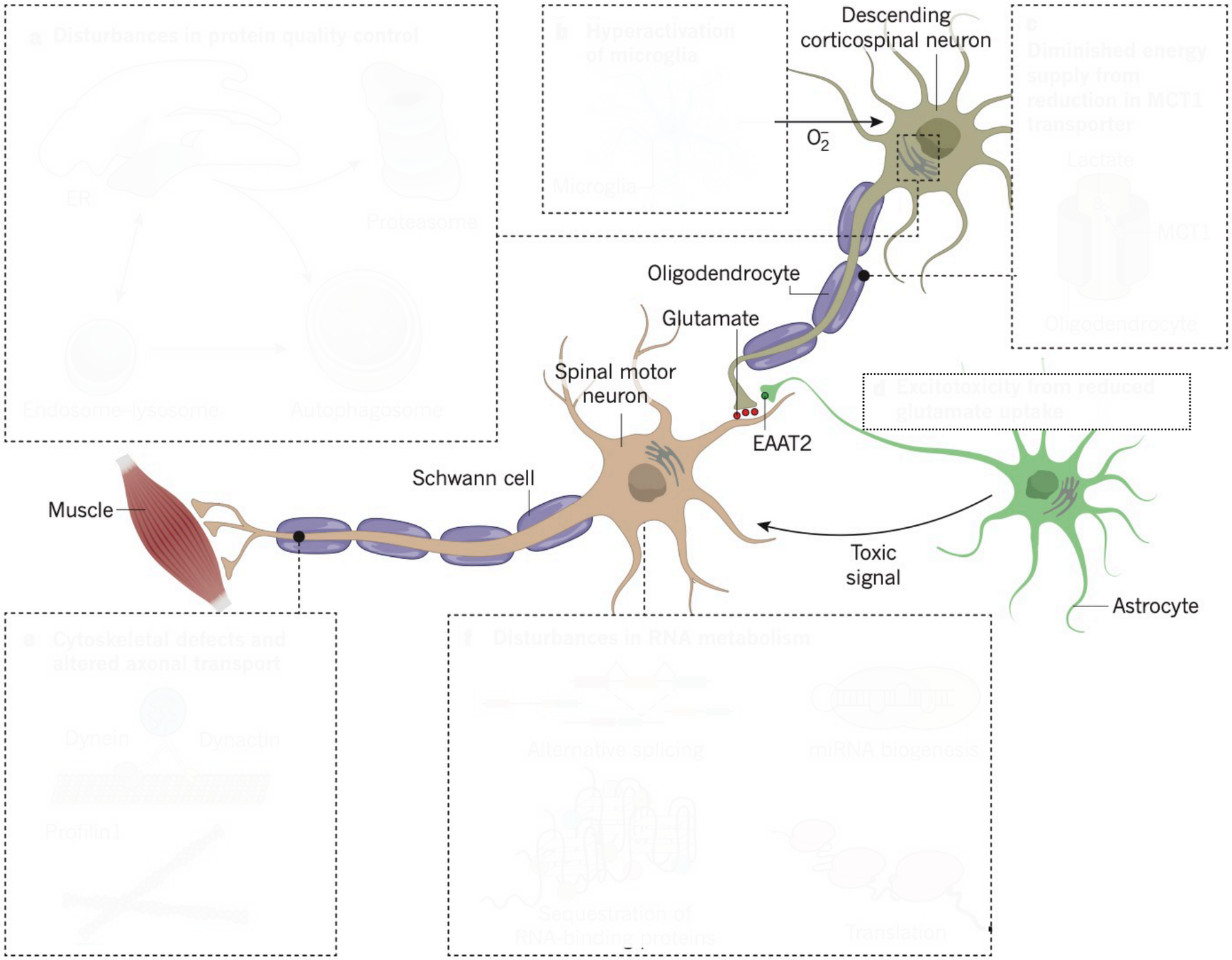


Misfolded SOD1 forms ubiquitinated cytoplasmic inclusions that can occur early in ALS and that escalate as the disease progresses

Bruijn, L. I., Becher, M. W., et al. Neuron, **1997**, 18(2)

ALS pathophysiology and genetics

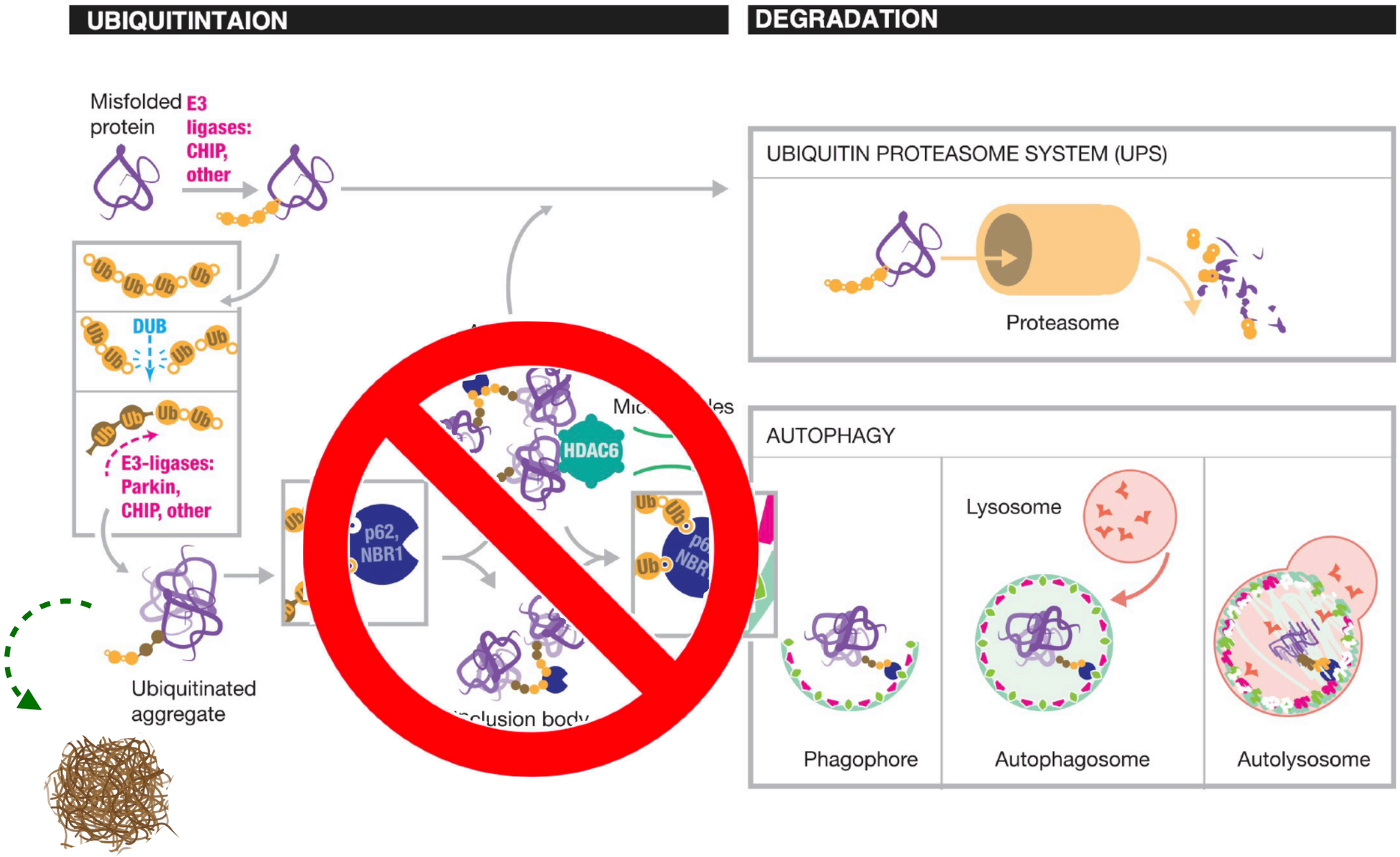
Main theories



Taylor, J. P., Brown, R. H., Jr, & Cleveland, D. W., Nature, **2016**, 539(7628)

ALS pathophysiology and genetics

Disturbance of PQC



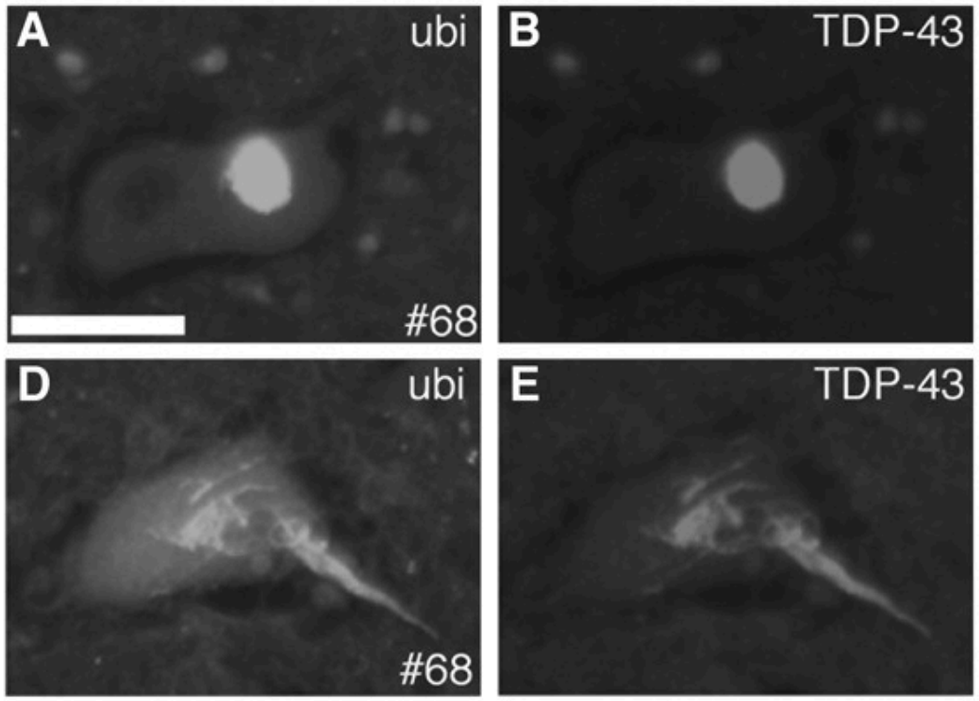
Insoluble inclusions

Mutation of autophagy adaptors found to cause ALS
VCP, SQSTM1, UBQLN2, OPTN, TBK1……

Shaid, S., Brandts, C. H., Serve, H., & Dikic, I. Cell death and differentiation, **2013**, 20(1)

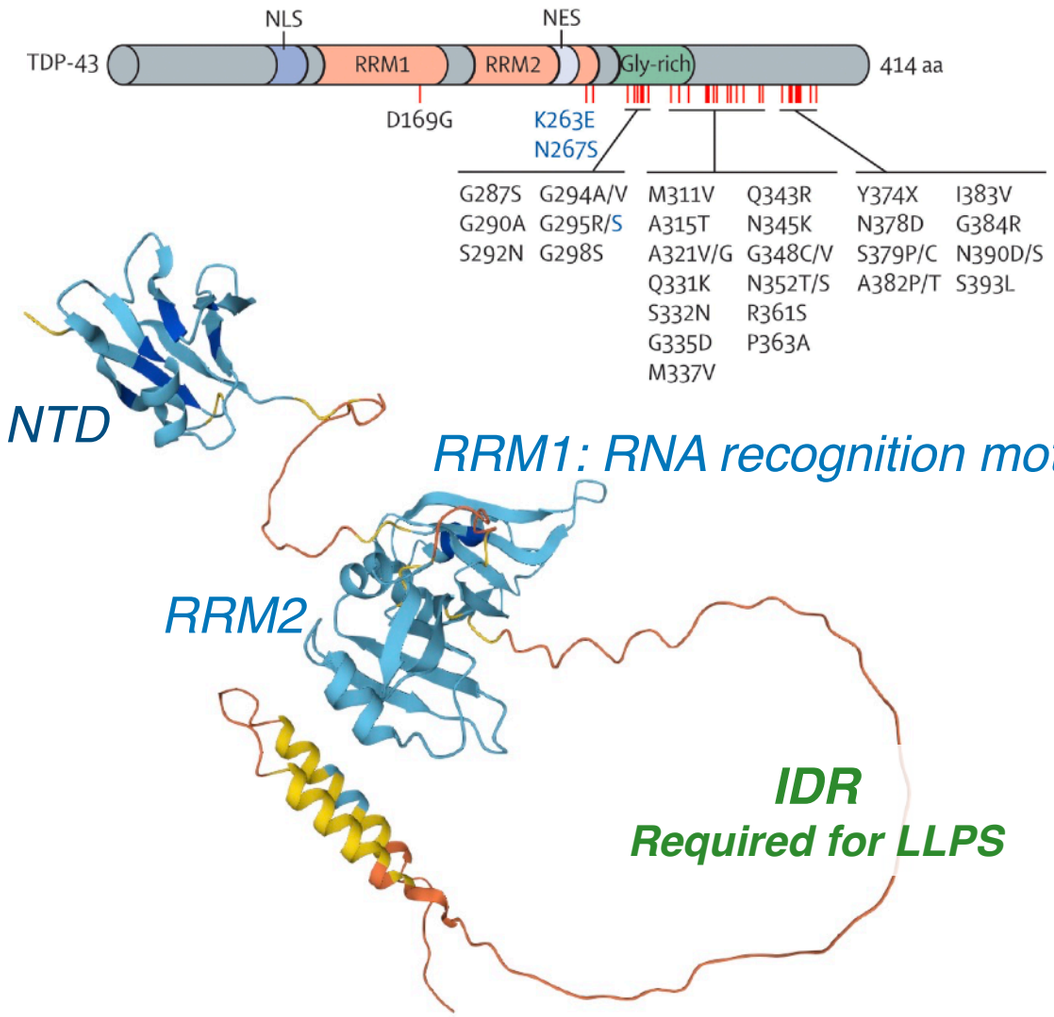
ALS pathophysiology and genetics

TDP43 condensations



Ubiquitinated TDP-43 aggregates in >90% ALS patients' motor neurons and glial cells

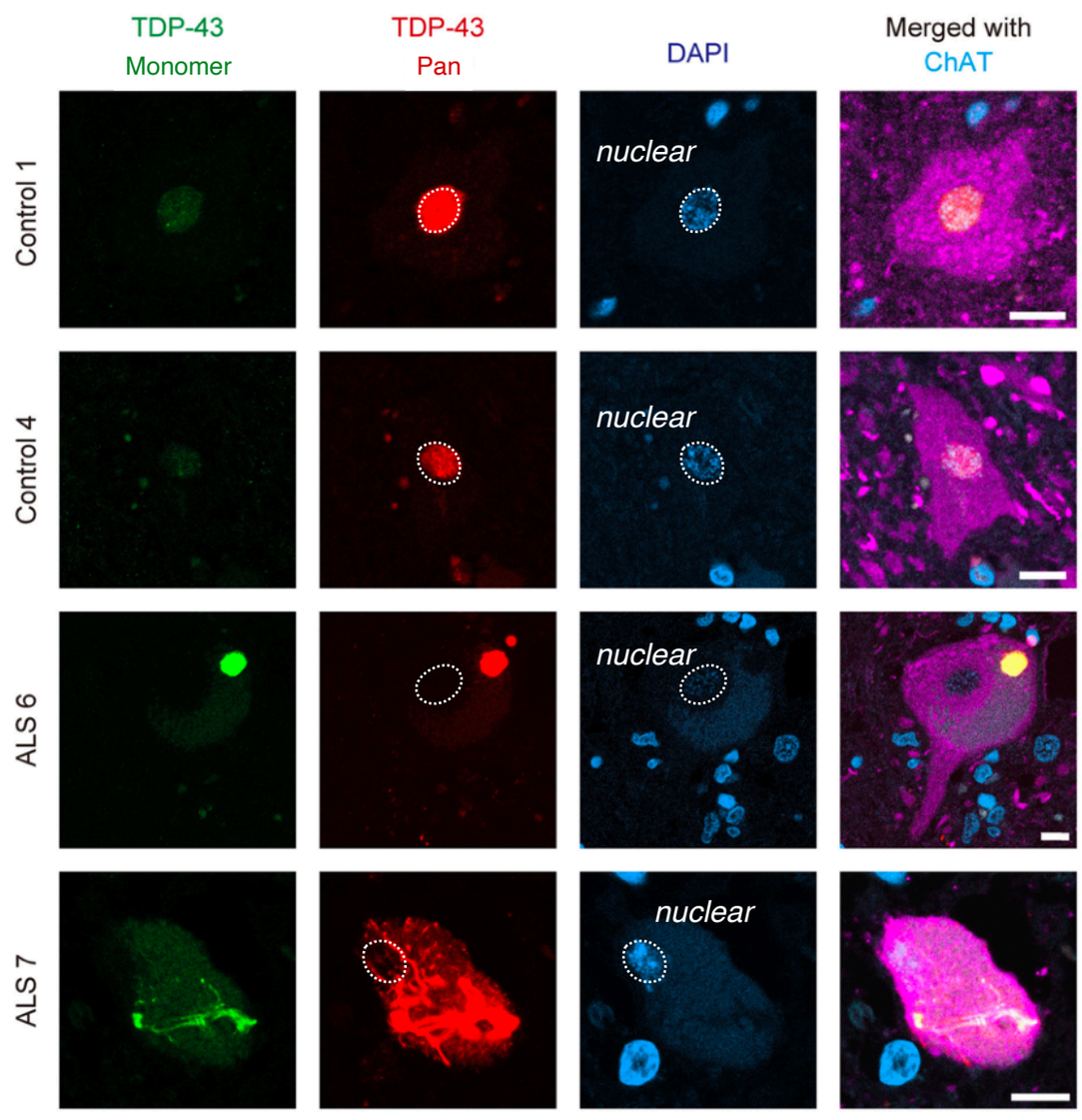
ALS-causing mutations mostly in C-term…



Neumann, M., Sampathu, D. M., et al. Science, **2006**, 314(5796)

ALS pathophysiology and genetics

TDP43 condensations

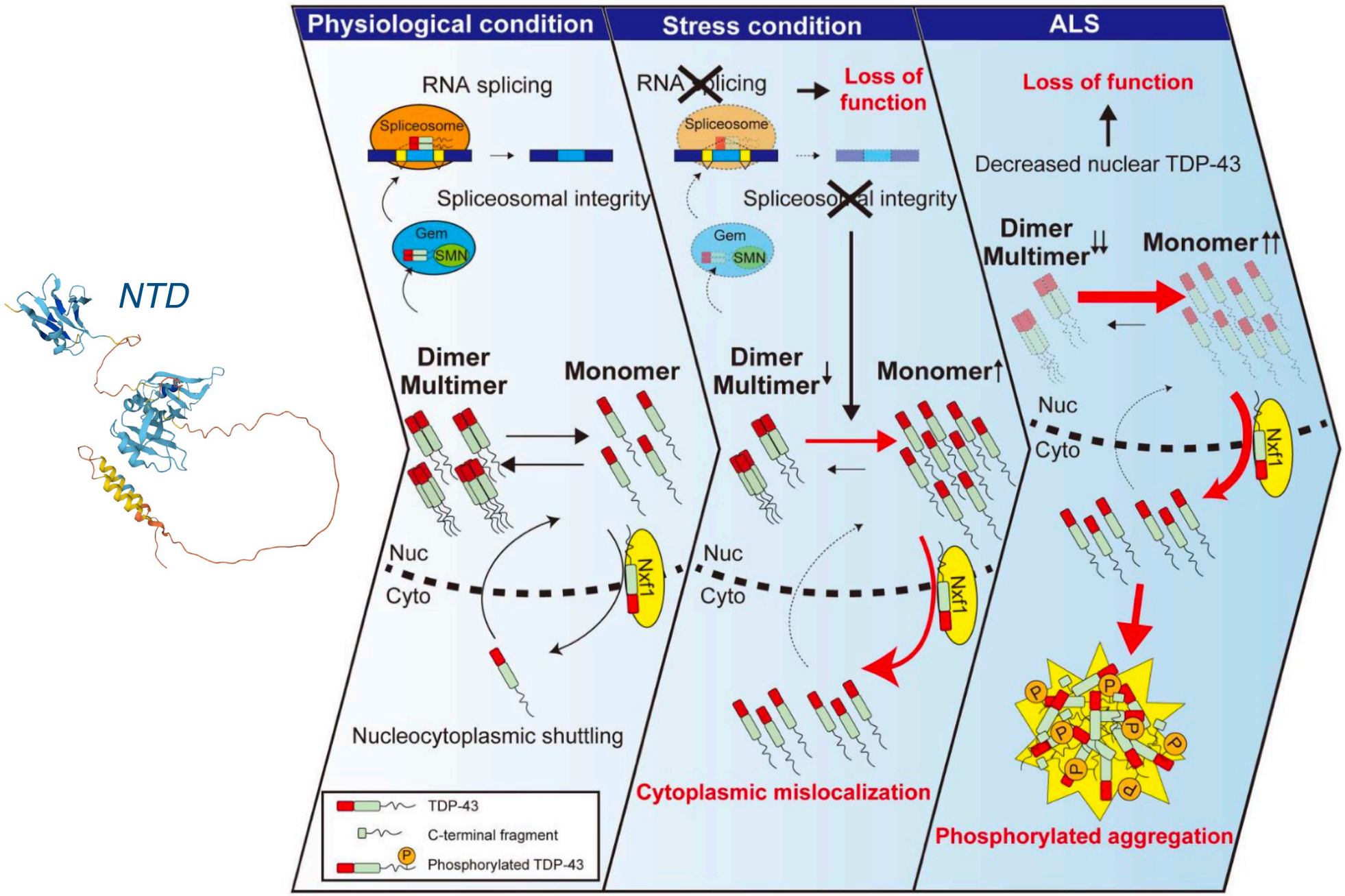


TDP-43 mislocalization and aggregation is now recognized widely as the hallmark of all forms of ALS

Oiwa, K., Watanabe, S., Science advances, **2023**, 9(31)

ALS pathophysiology and genetics

TDP43 condensations

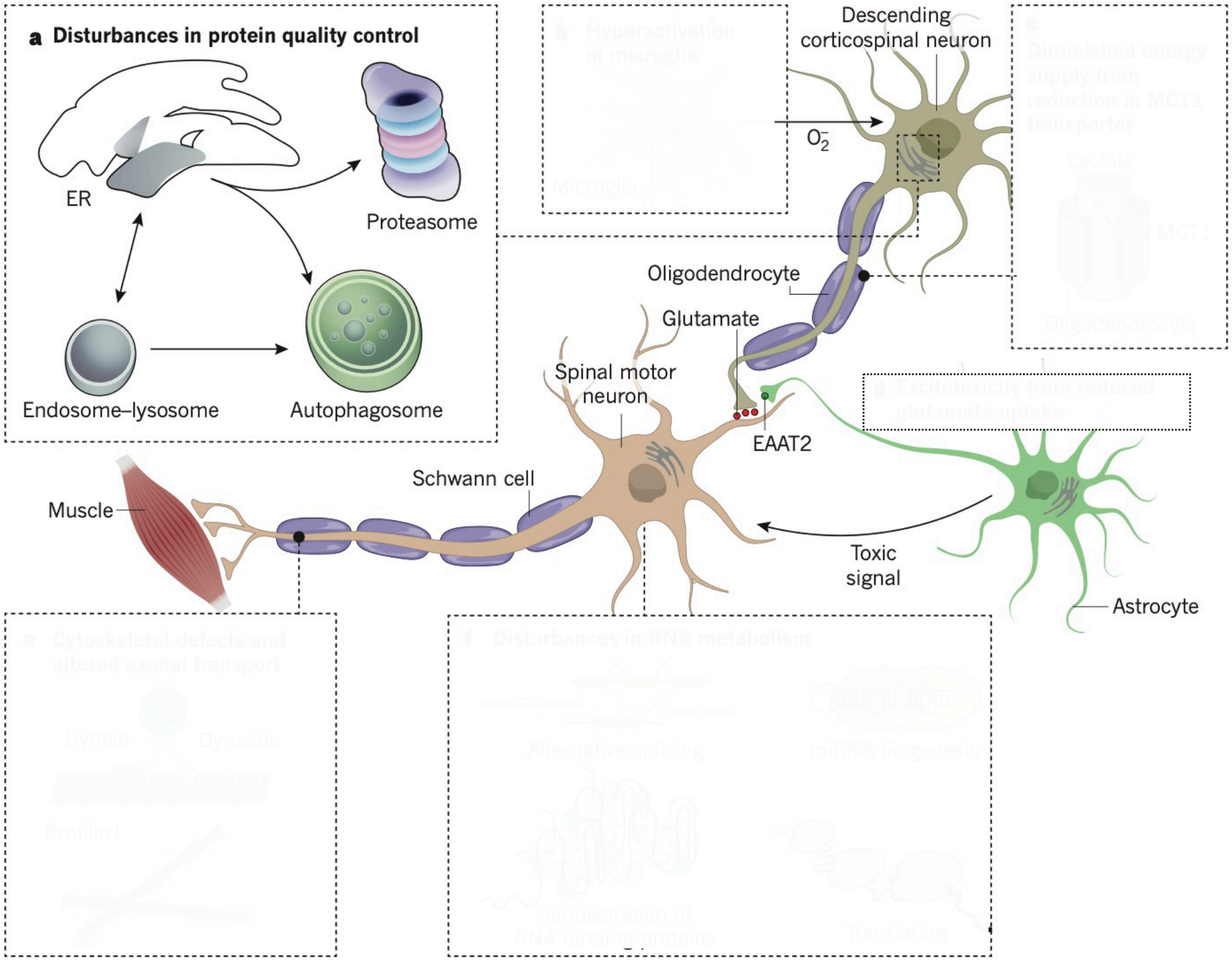


A recent model accounting for TDP43 mislocation

Oiwa, K., Watanabe, S., Science advances, **2023**, 9(31)

ALS pathophysiology and genetics

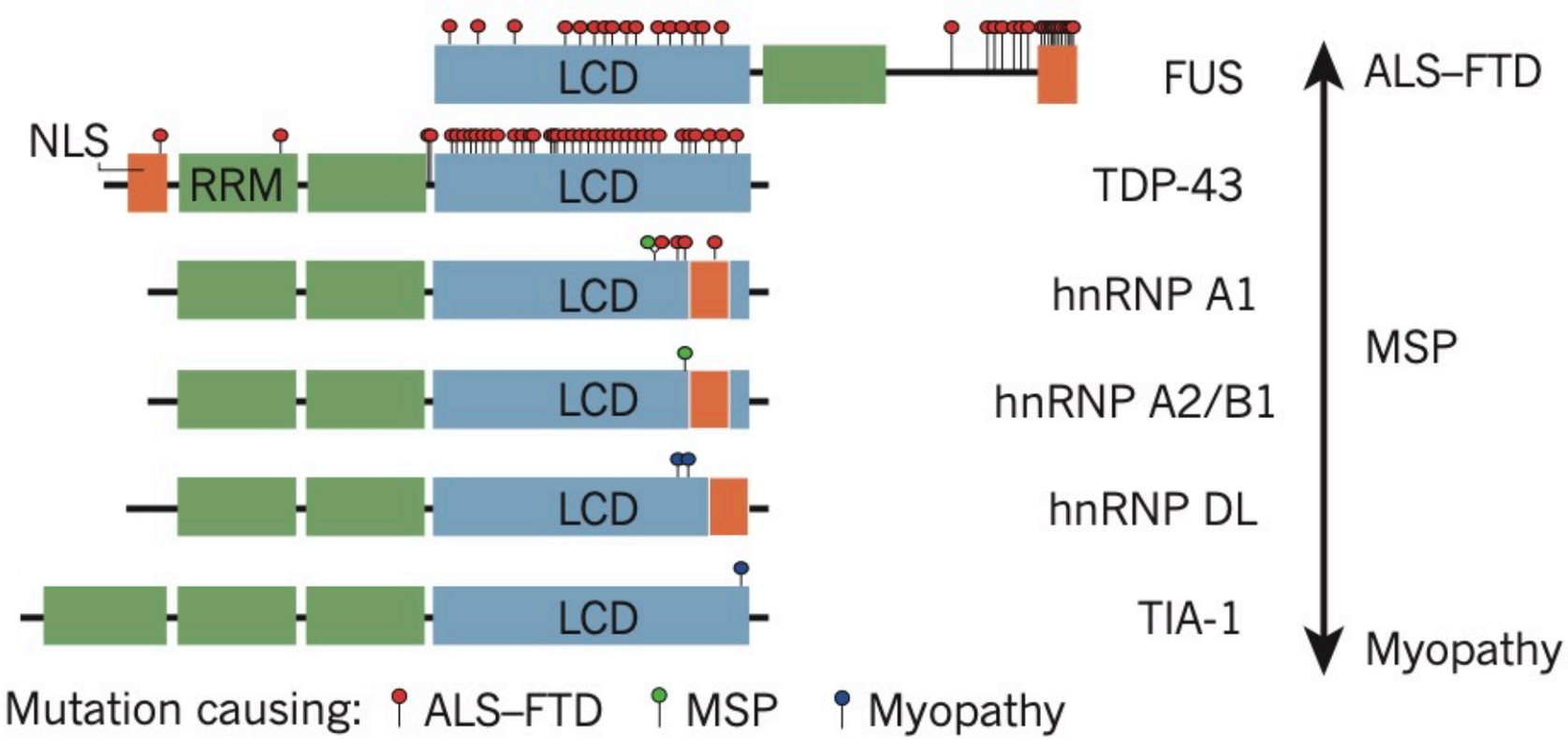
Main theories



Taylor, J. P., Brown, R. H., Jr, & Cleveland, D. W., Nature, **2016**, 539(7628)

ALS pathophysiology and genetics

ALS-causing RBP disturbances



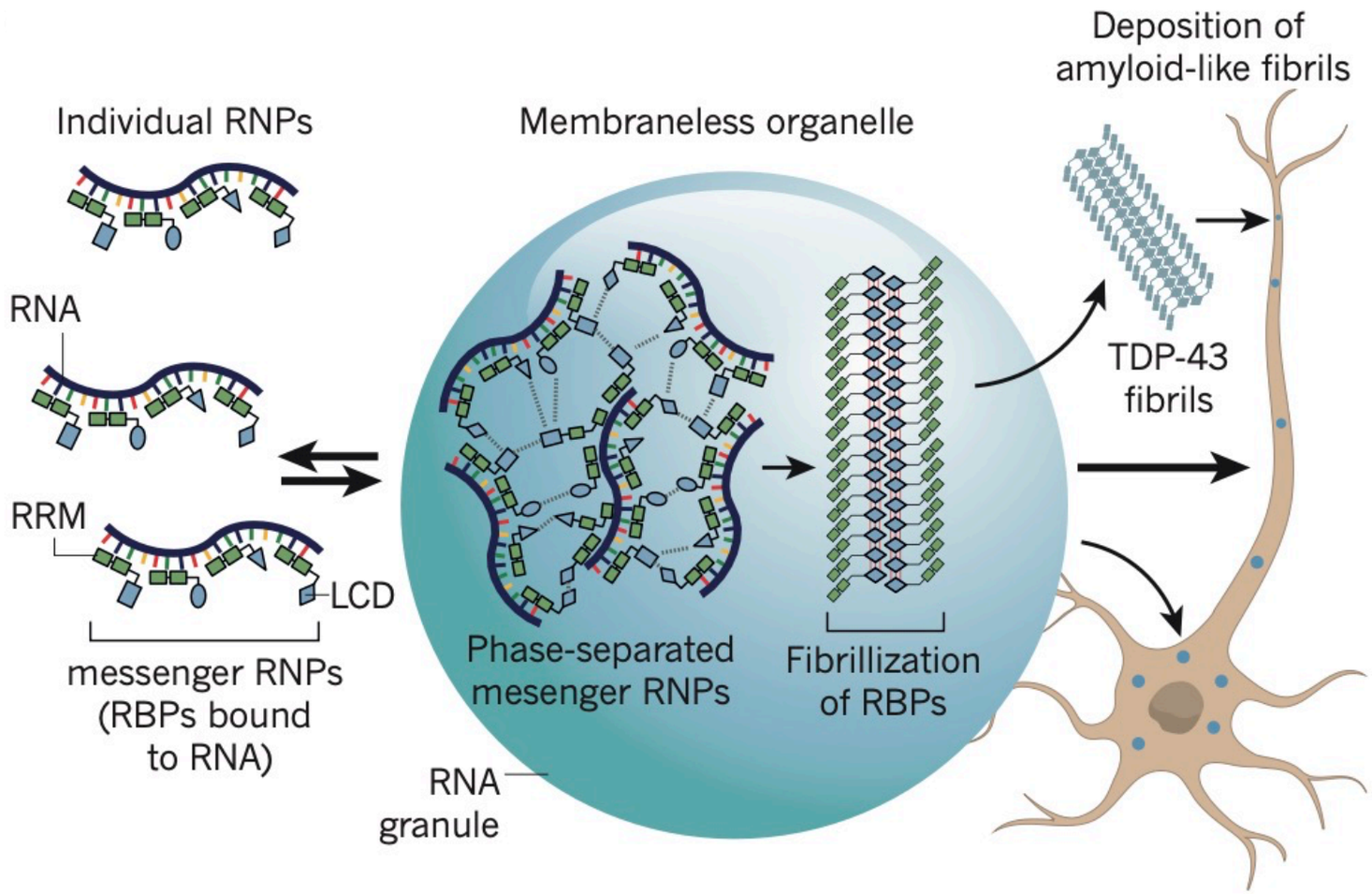
ALS mutations are found in members of the hnRNP family of proteins that regulates RNA metabolism at every stage of the RNA life cycle

They bind to thousands of RNA targets

Taylor, J. P., Brown, R. H., Jr, & Cleveland, D. W., Nature, **2016**, 539(7628)

ALS pathophysiology and genetics

RBP-RNA pathogenic phase separation



Accumulation of RBPs	+	***mRNAs influx***	=	***LLPS persistent condensates***

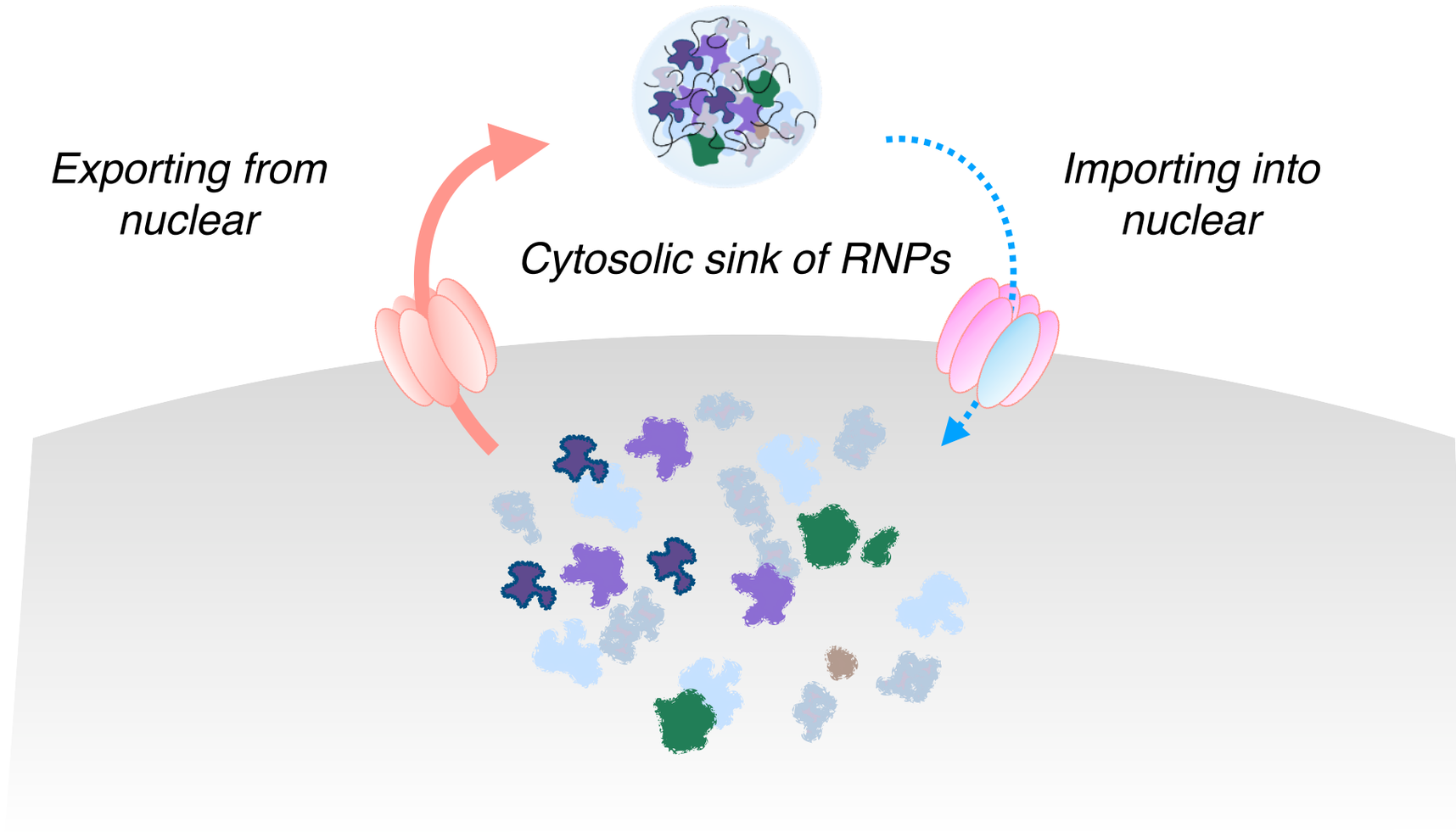
Mutations, misregulations, impared transportation

Hyperassembly of stress granules

Taylor, J. P., Brown, R. H., Jr, & Cleveland, D. W., Nature, **2016**, 539(7628)

ALS pathophysiology and genetics

RBP-RNA pathogenic phase separation



Accumulation of RBPs + ***mRNAs influx*** = ***LLPS persistent condensates***

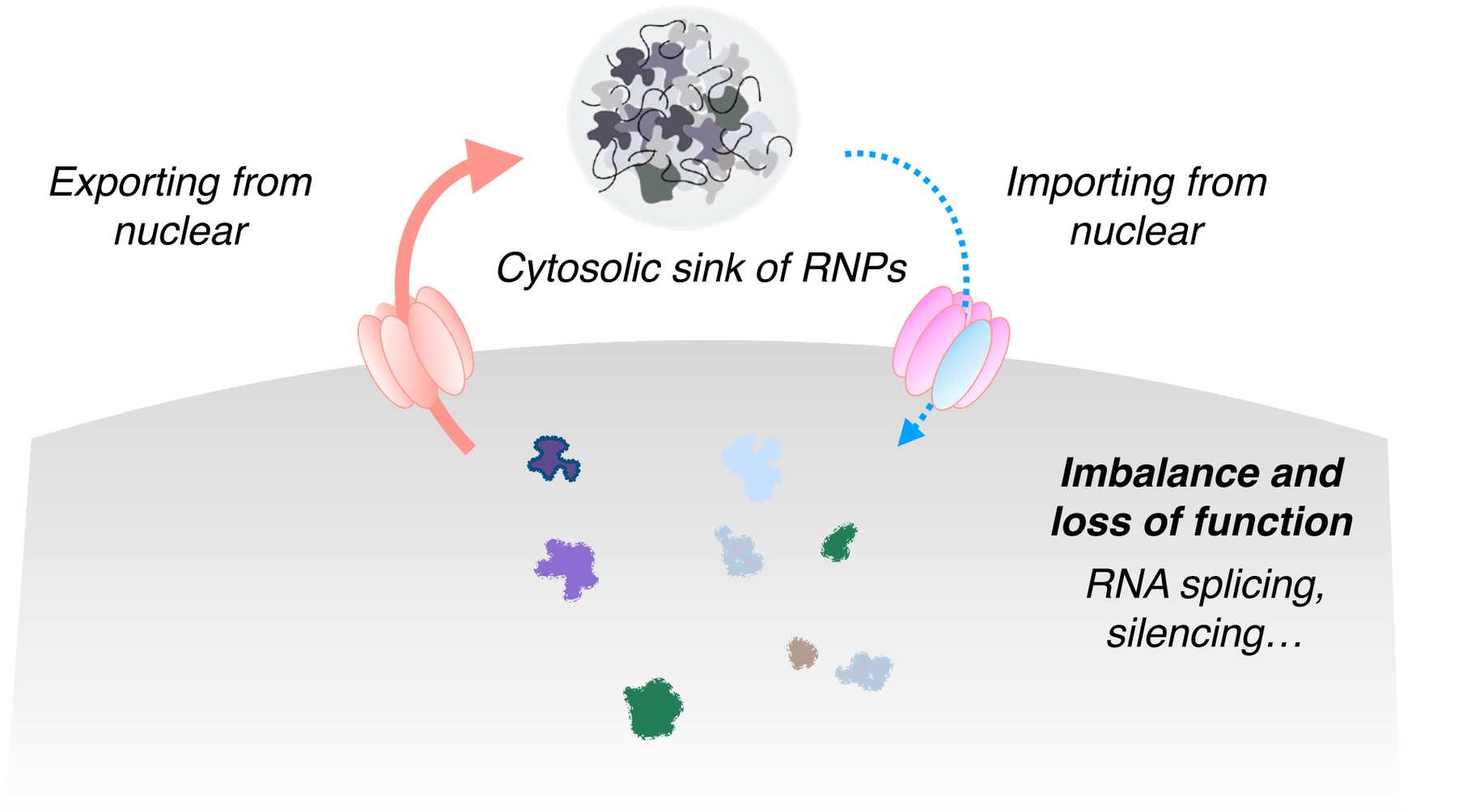
Mutations, misregulations, impared transportation

Hyperassembly of stress granules

Taylor, J. P., Brown, R. H., Jr, & Cleveland, D. W., Nature, **2016**, 539(7628)

ALS pathophysiology and genetics

RBP-RNA pathogenic phase separation



Accumulation of RBPs + ***mRNAs influx*** = ***LLPS persistent condensates***

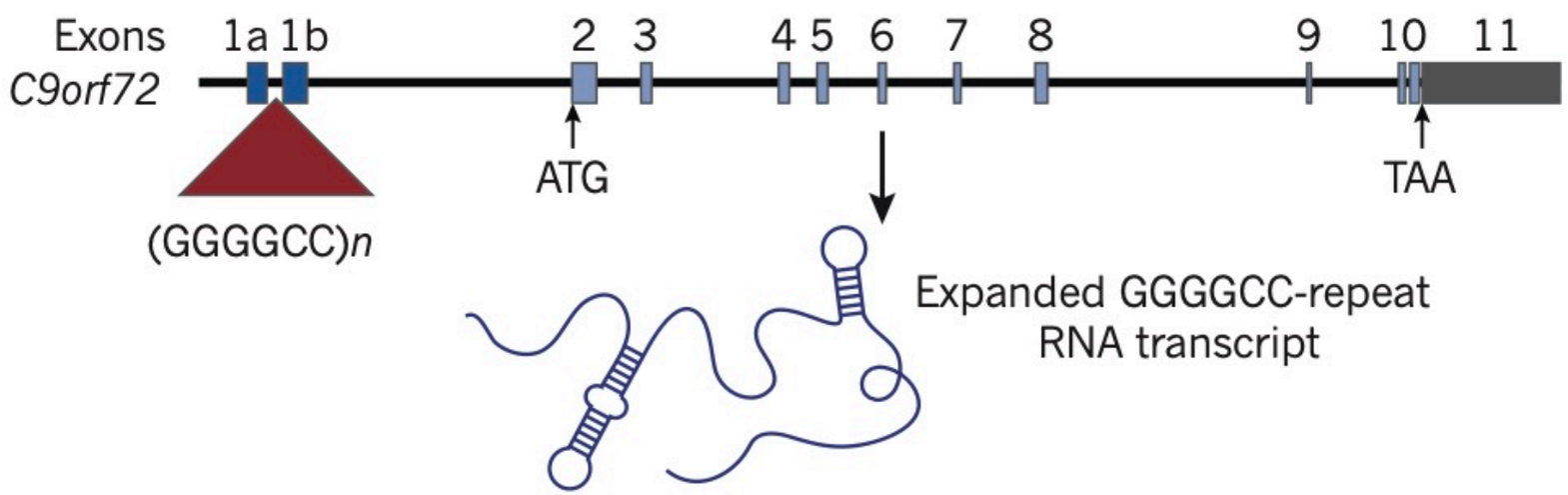
Mutations, misregulations, impared transportation

Hyperassembly of stress granules

Taylor, J. P., Brown, R. H., Jr, & Cleveland, D. W., Nature, **2016**, 539(7628)

ALS pathophysiology and genetics

C9orf72



First discovered through sequencing of non-coding region of chromosome 9p21

n = 2 - 23 in healthy individuals

n > 60 in affected individuals

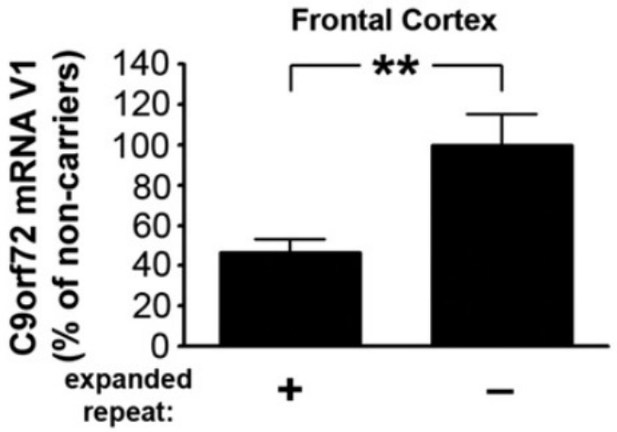
Renton, A. E., Majounie, E., Waite, A., et al. Neuron, **2011**, 72(2)

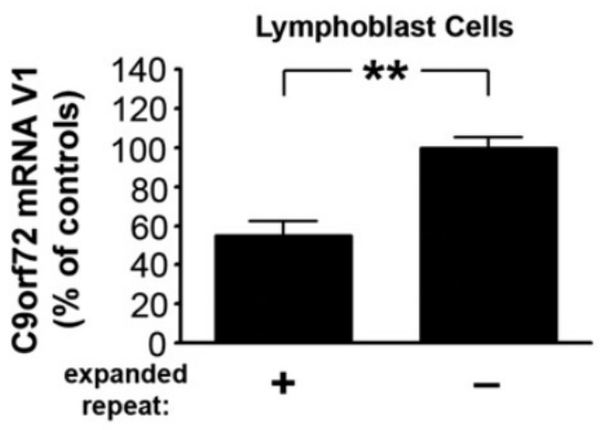
DeJesus-Hernandez, M., Mackenzie, I. R., Boeve, B. F., et al., Neuron, **2011**, 72(2)

ALS pathophysiology and genetics

C9orf72 loss of function

Decreasing of transcripts level





C9orf72 KO mice

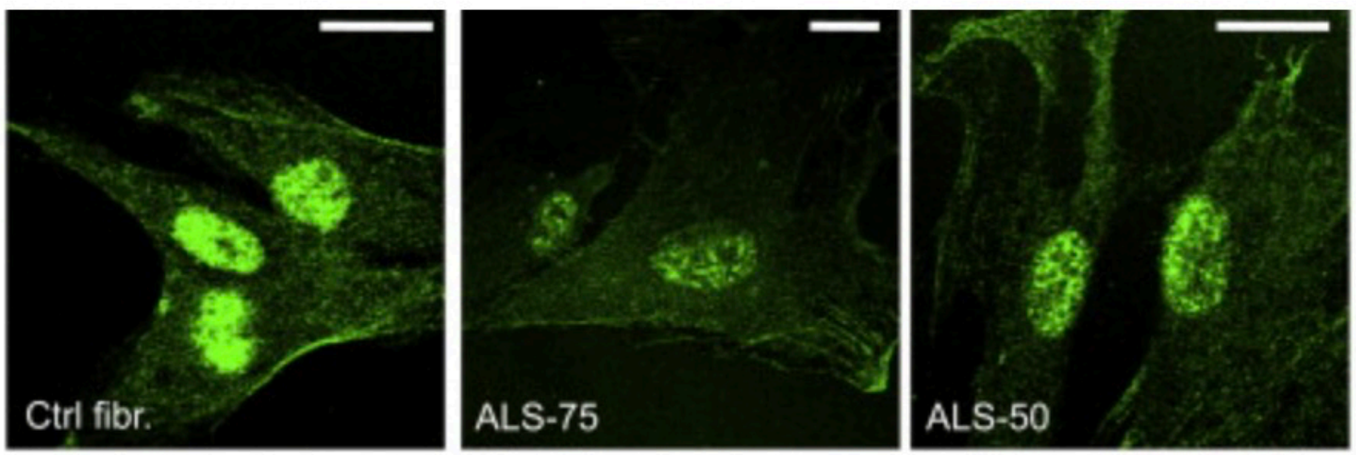
No ALS /FTD features

Aged normally

Non-cell-autonomous inflammatory

Loss of function not considered as the essential cause

Loss of protein level



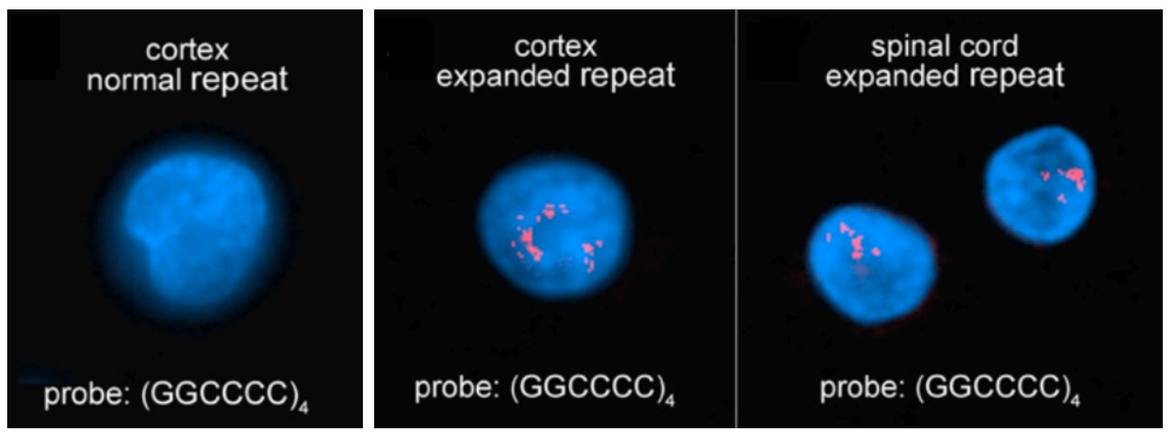
Renton, A. E., Majounie, E., Waite, A., et al. Neuron, **2011**, 72(2)

DeJesus-Hernandez, M., Mackenzie, I. R., Boeve, B. F., et al., Neuron, **2011**, 72(2)

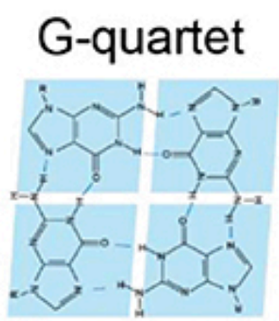
ALS pathophysiology and genetics

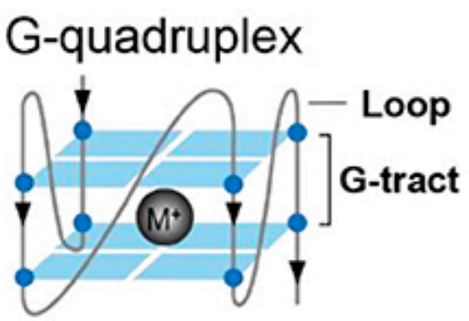
C9orf72 gain of function

Abnormal RNA foci

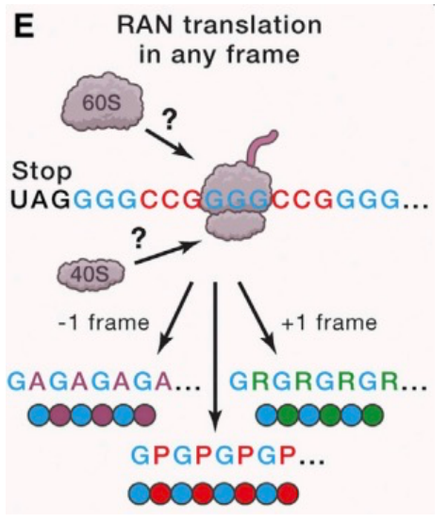


Ctrl *C9 ALS patient*

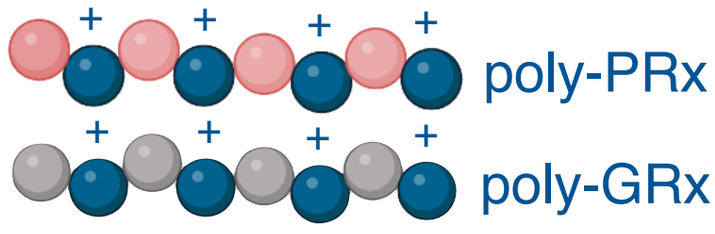




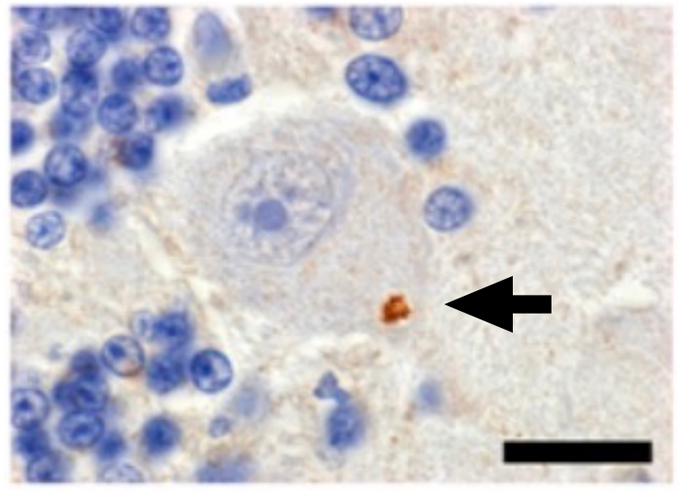
Dipeptide repeat DPR cytosolic inclusions



Repeat Associated Non-AUG (RAN)



Toxic peptides

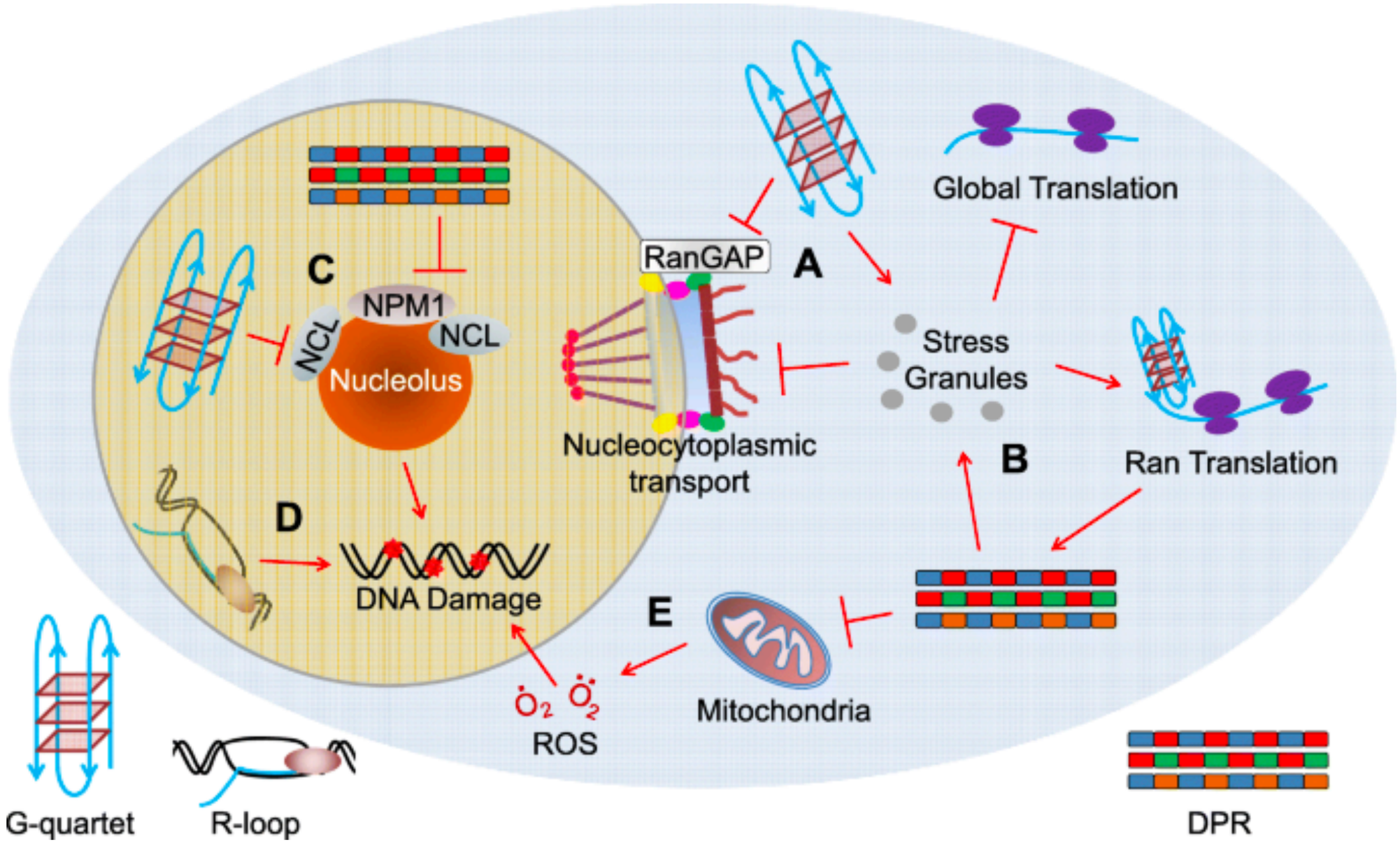


Ash, P. E., Bieniek, K. F., T. F., Caulfield, et al. Neuron, **2013**, 77(4)

DeJesus-Hernandez, M., Mackenzie, I. R., Boeve, B. F., et al., Neuron, **2011**, 72(2)

ALS pathophysiology and genetics

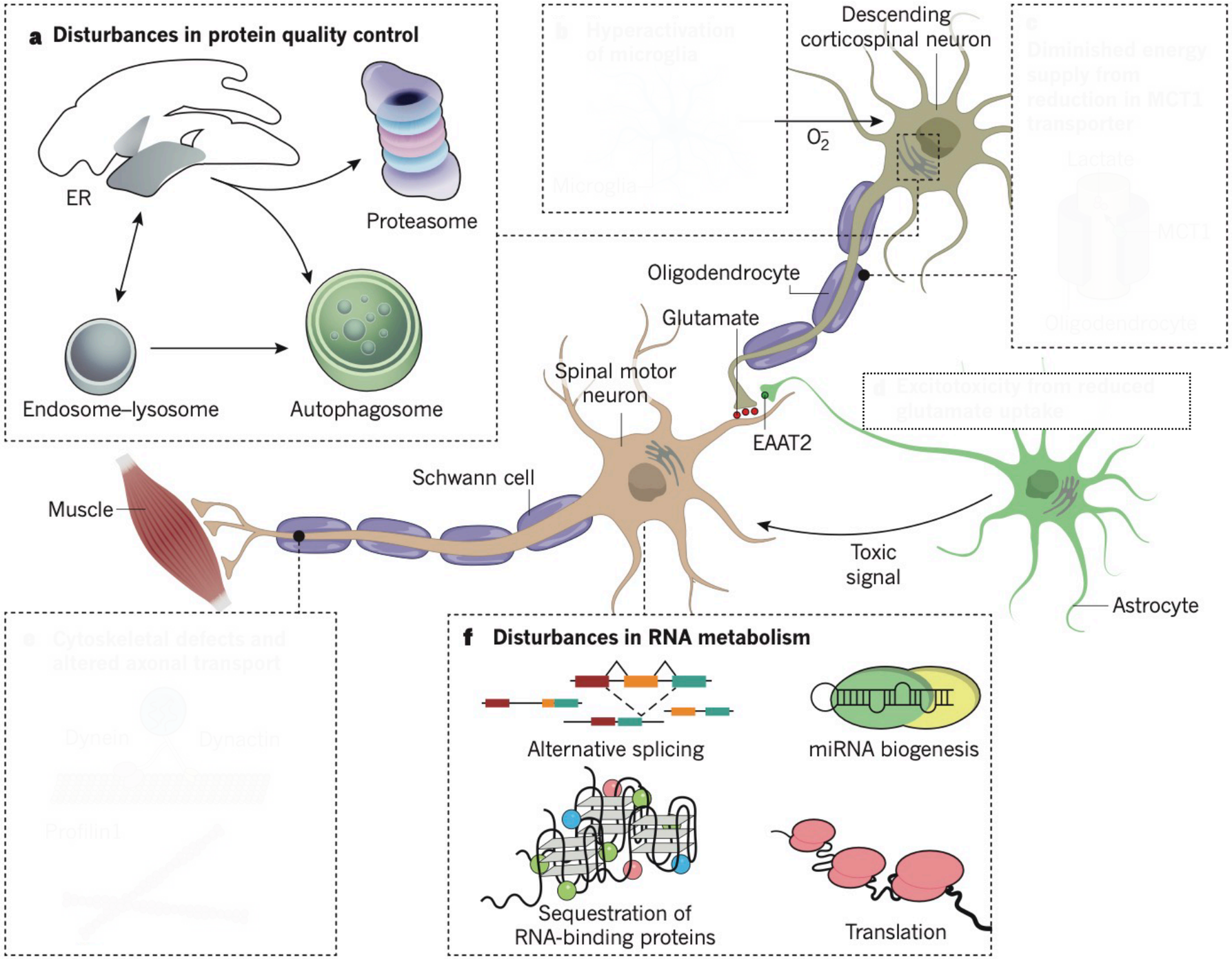
C9orf72 gain of function



Tang, X., Toro, A., T G, S., Gao, J., Chalk, J., Oskarsson, B., & Zhang, K., Molecular neurodegeneration, **2020**, 15(1)

ALS pathophysiology and genetics

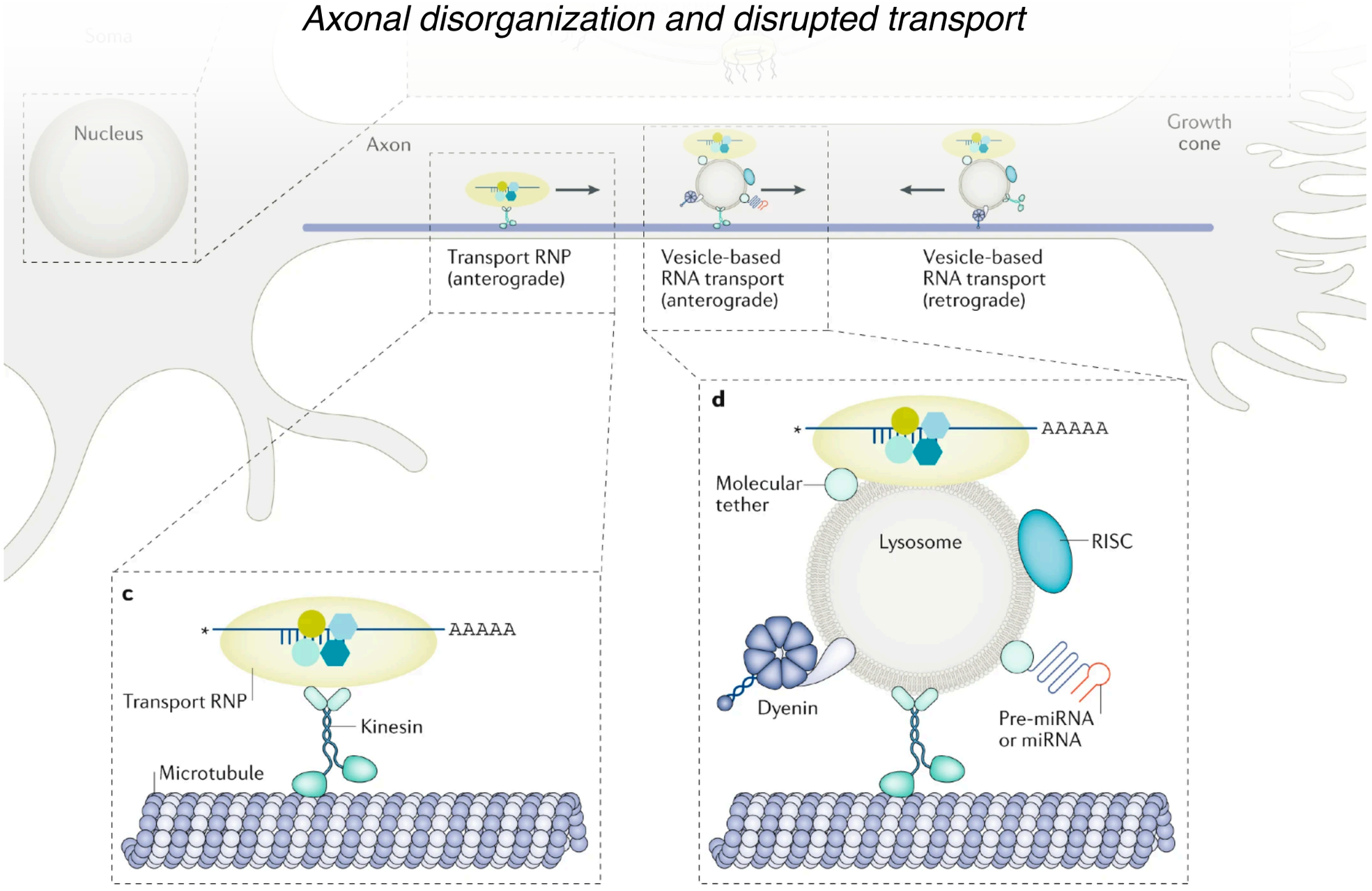
Main theories



Taylor, J. P., Brown, R. H., Jr, & Cleveland, D. W., Nature, **2016**, 539(7628)

ALS pathophysiology and genetics

Axonal disorganization and disrupted transport

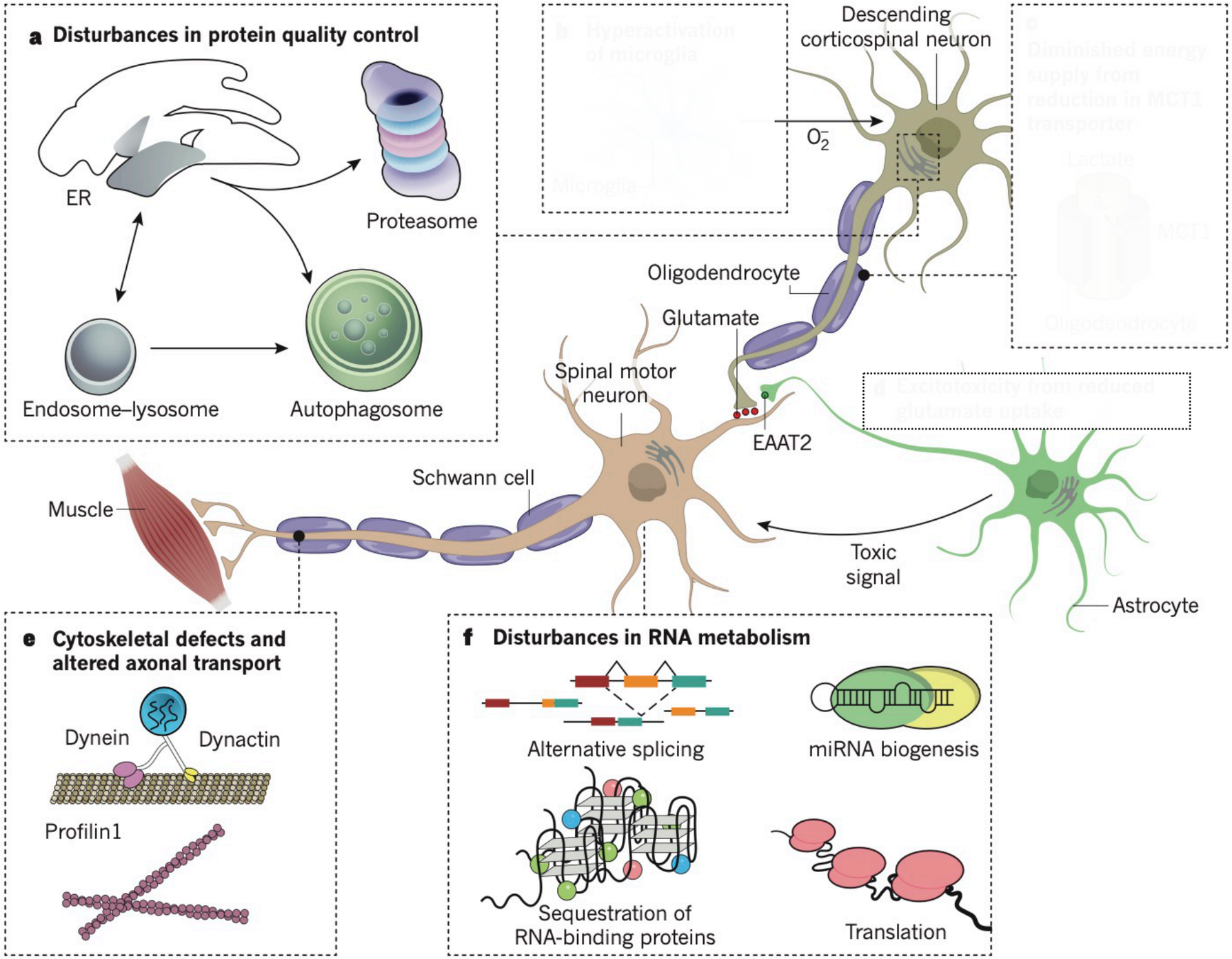


To quickly respond to synaptic signals, neurons must transport all necessary components for translation (mRNA, ribosomes and translation factors) to distal sites for ***local protein synthesis***

ALS-causing mutation: KIF5A, DCTN1, NEFH, TUBA4A……

ALS pathophysiology and genetics

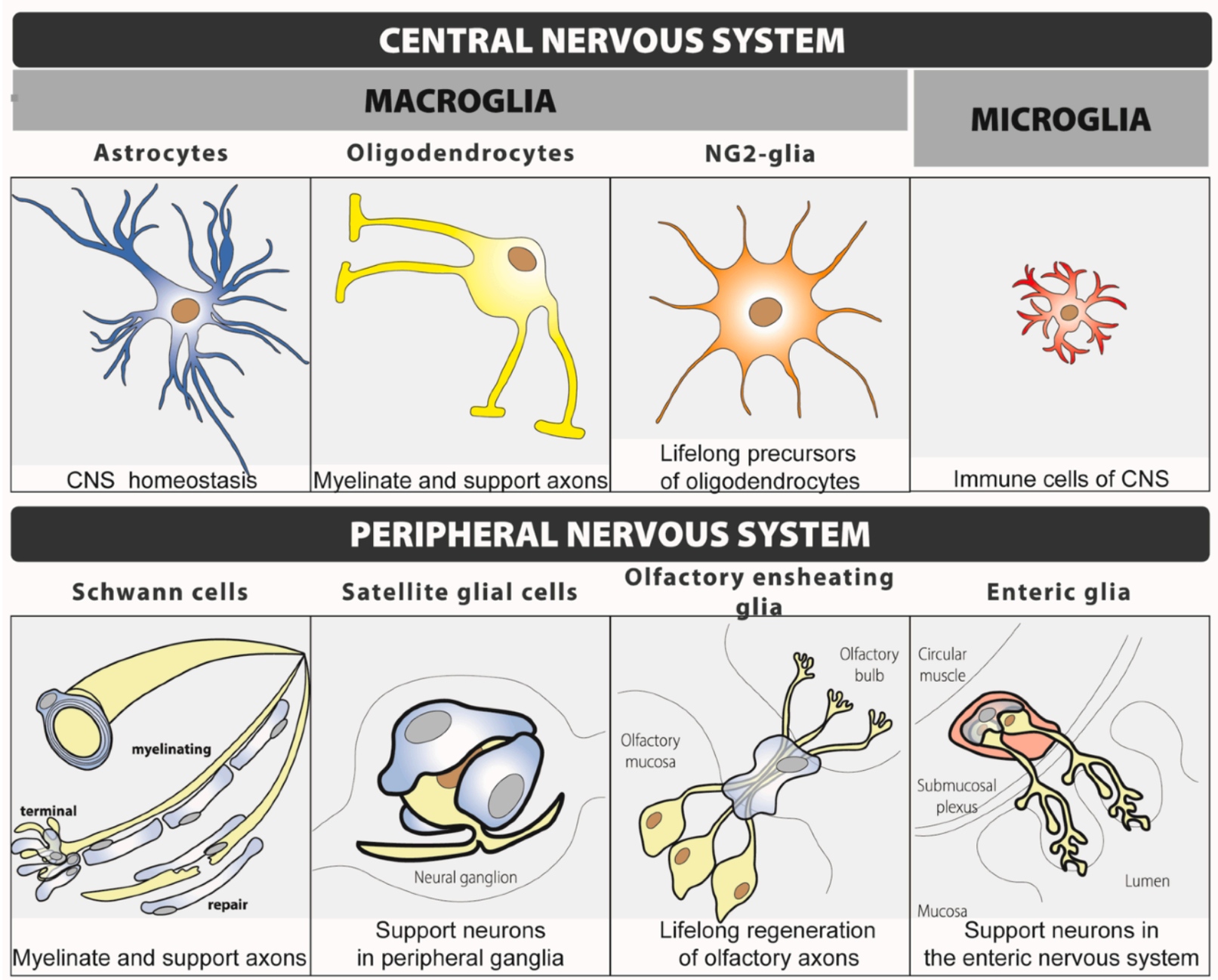
Main theories



Taylor, J. P., Brown, R. H., Jr, & Cleveland, D. W., Nature, **2016**, 539(7628)

ALS pathophysiology and genetics

The crucial role of glia cells

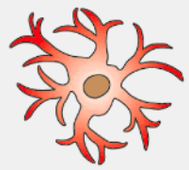


Vila-Pueyo, M., Gliga, O., Gallardo, V. J., & Pozo-Rosich, P. International journal of molecular sciences, **2023**, 24(16)

ALS pathophysiology and genetics

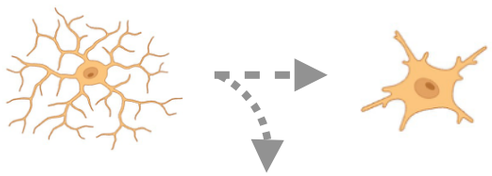
Neuroinflammation in ALS

MICROGLIA



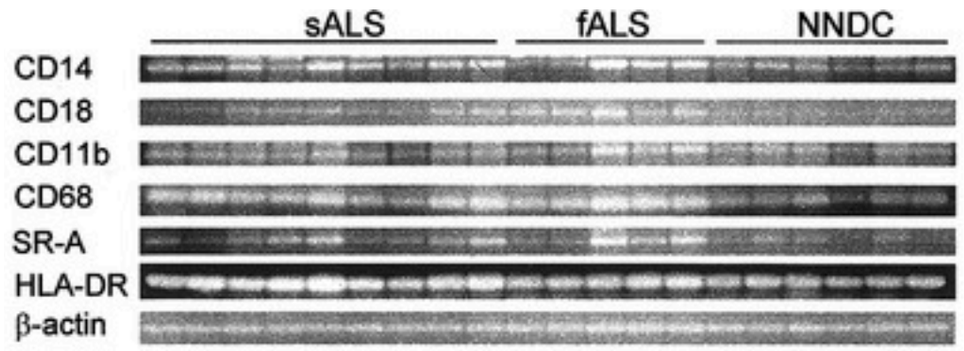
Immune cells of CNS

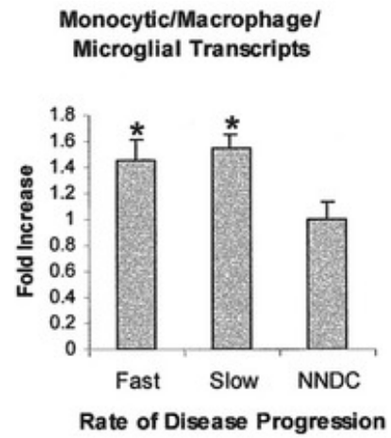
hyperactivated
in all types of ALS



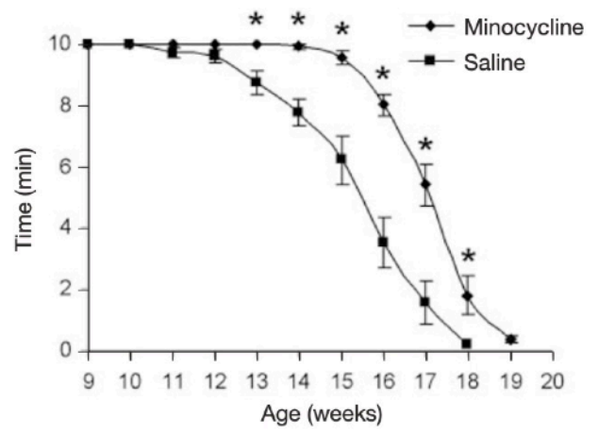
Oxygen radicals, nitric oxide, and cytokines…

Release of cytotoxic
and inflammatory mediators





Activation of microglias — faster rate of disease progression



	Saline (n=10)	Minocycline (n=10)	P value
Onset	90.3±2.2	109±1.5	<0.001
Mortality	125.6±3.4	136.8±1.2	<0.01

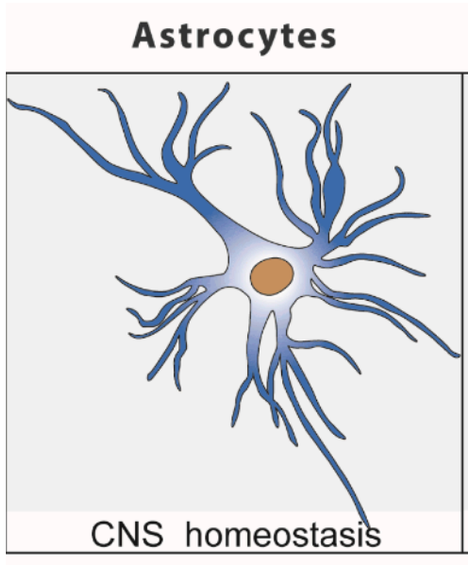
Inhibited activation — delayed onset and prolonged survival

Kawamata, T., Akiyama, H., Yamada, T., & McGeer, P. L., The American journal of pathology, **1992**, 140(3)

Zhu, S., Stavrovskaya, I. G., Drozda, M., et al. Nature, **2002**, 417(6884)

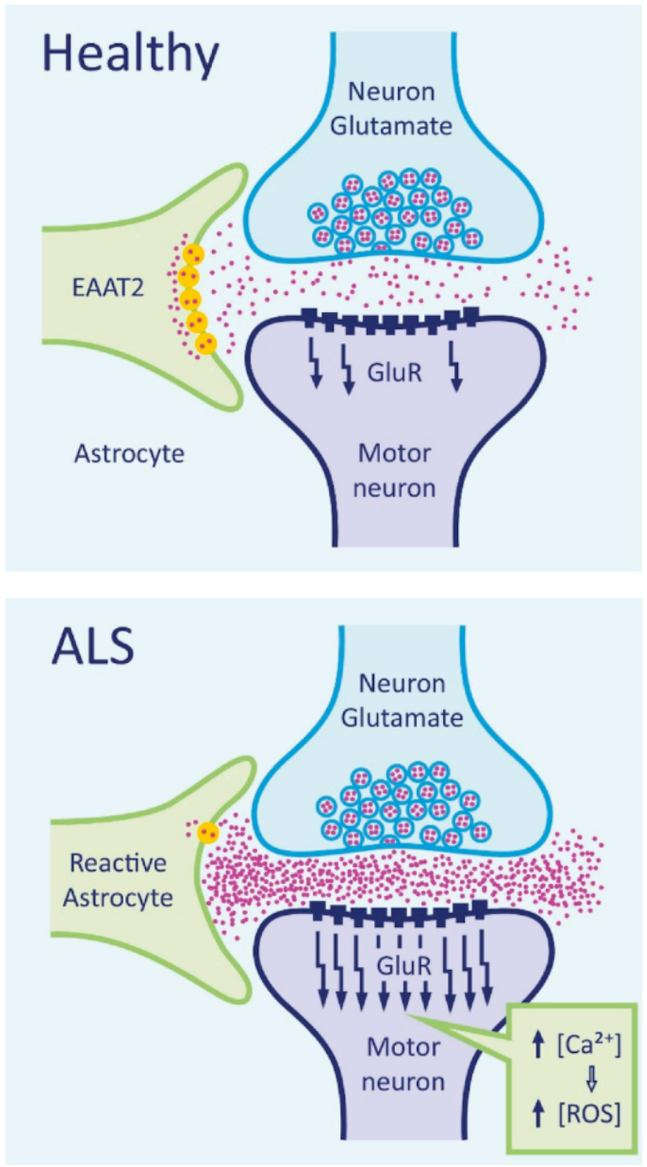
ALS pathophysiology and genetics

Glutamate excitotoxicity



Provides motor neurons with nutrients, ion buffering, and ***recycling of the neurotransmitter glutamate***

One of the earliest proposed mechanisms



Wang, G Y et al. 2020

Glutamate recycled through EAAT2 transporter into astrocyte to ***prevent excessive firing*** *of lower moter neurons*

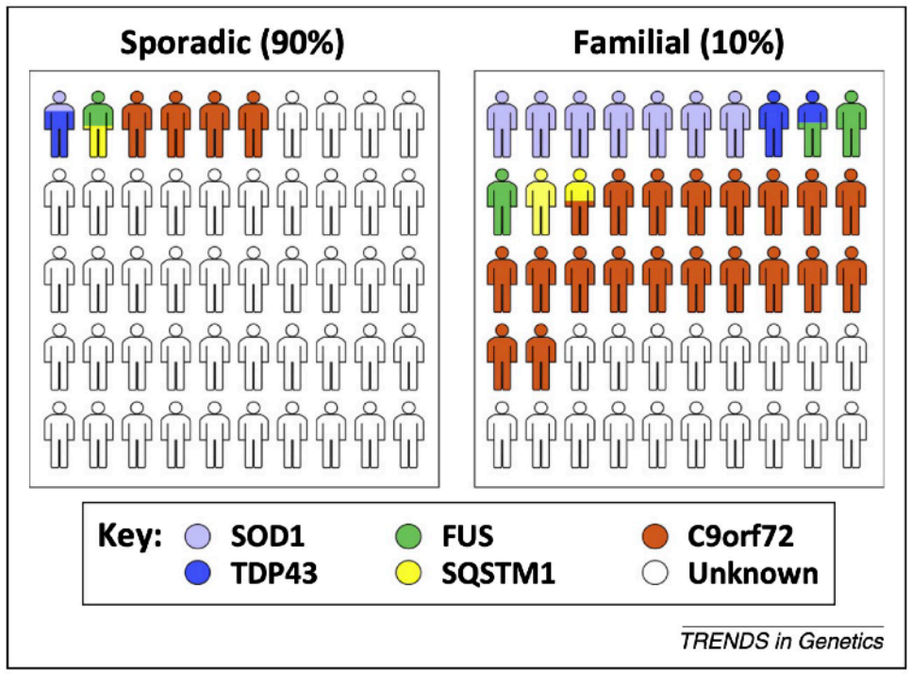
Repetitive firing *caused by accumulated synaptic glutamate*

Calcium influx, endoplasmic reticulum (ER) and mitochondrial stress

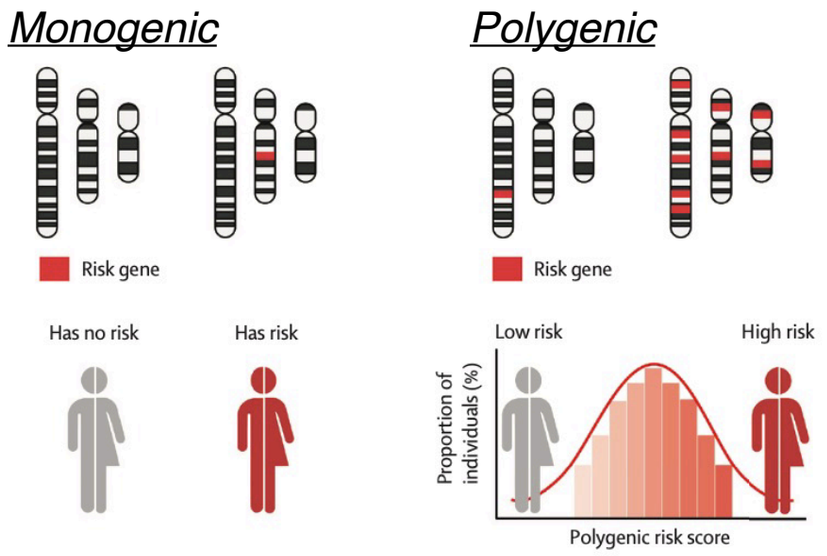
Taylor, J. P., Brown, R. H., Jr, & Cleveland, D. W., Nature, **2016**, 539(7628)

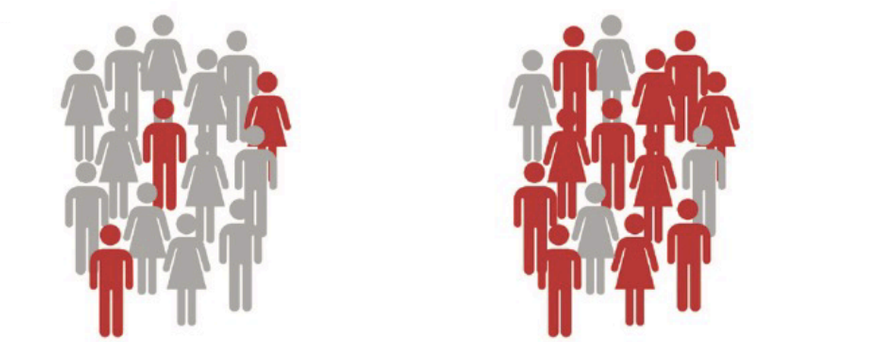
ALS pathophysiology and genetics

"Familiar and sporadic"



*Although **sporadic ALS** should refer strictly to disease that presents without a family history of ALS, this term is sometimes mistakenly used to refer to ALS that occurs without a genetic basis*



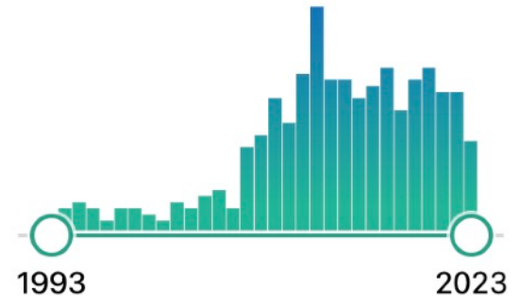


Lattante, S., Ciura, S., Rouleau, G.A., Kabashi E., Trends Genet. **2015**, 31(5)
Goutman, S. A., Hardiman, O., Al-Chalabi, A., Chió, A., Savelieff, M. G., Kiernan, M. C., & Feldman, E. L. The Lancet. Neurology, **2022**, 21(5)

ALS pathophysiology and genetics

Treasure hunting in ALS genetics

RESULTS BY YEAR



"Genome Analysis Sporadic ALS"
> 300 results

Great demand of whole-genome sequencing in ALS research

to identify known pathogenic mutations in up to 70% of familial and 15% of sporadic cases

Sequencing technology development to enable easier whole genome sequencing

4. Clinical practices and social impacts

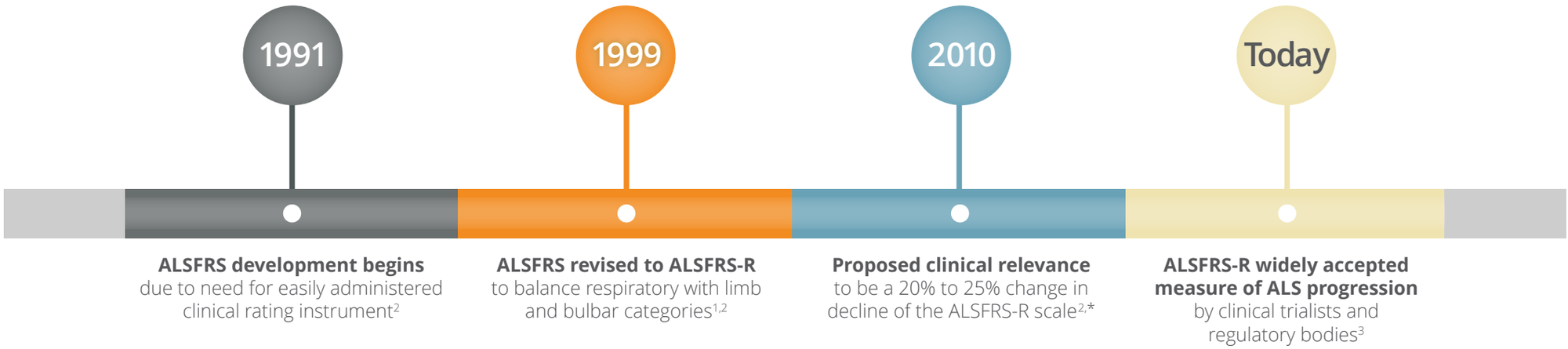
There is no cure, but there is hope

Clinical practices against ALS

Diagnosis

Revised ALS Functional Rating Scale (ALSFRS-R)

A questionnaire-based scale as the gold standard measure of disability progression



Administered by a healthcare provider

Speech, salivation, swallowing

Handwriting, cutting food, dressing and hygiene

Turing in bed, walking, climbing stairs

Dyspnea, otthopnea, respiratory insuffiency

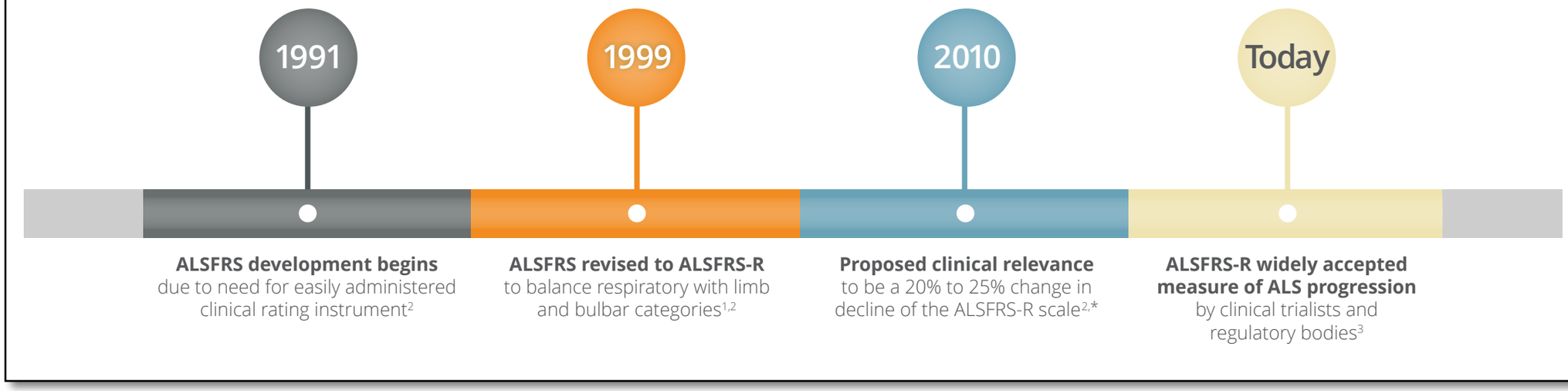
https://www.alspathways.com/assessing-function/

Clinical practices against ALS

Diagnosis

Revised ALS Functional Rating Scale (ALSFRS-R)

A questionnaire-based scale as the gold standard measure of disability progression



Speech

- **4** Normal
- **3** Detectable speech disturbance
- **2** Intelligible with repeating
- **1** Speech combined with nonvocal communication
- **0** Loss of useful speech

Speech, salivation, swallowing

Handwriting, cutting food, dressing and hygiene

Turing in bed, walking, climbing stairs

Dyspnea, otthopnea, respiratory insuffiency

https://www.alspathways.com/assessing-function/

Clinical practices against ALS

Gene testing

High penetrance

- *C9orf72*
- *SOD1*
- *FUS*
- *TARDBP*

High risk, strongly associated

- *ALS2, CHMP2B, KIF5A, NEK1, UBQLN2 …*

Gene targeted by FDA-approved therapy

Whole-genome sequencing

---

*Free Genetic Testing with **ALS Identified***

sponsored by Biogen

ALSIdentified™

1) A diagnosis of ALS

or

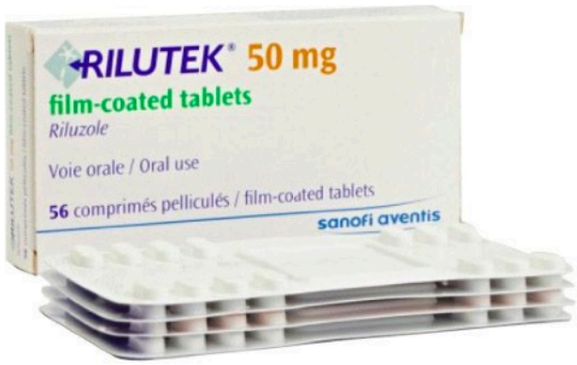
2) A family history of ALS. This includes patients both familial ALS as well as patients with seemingly sporadic ALS

https://www.als.org/understanding-als/symptoms-diagnosis

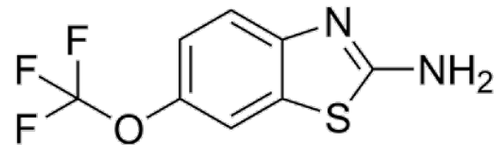
Clinical practices against ALS

FDA-approved therapies

1995 Riluzole (oral pill fomulation)



Inhibits glutamate release
by bloking voltage-sensitive Ca^{2+} channel



2018 Tiglutik (thickened liquid formulation)

2019 Exservan (oral film formulation)

for patients with severe swallowing difficulties

2-3 months expansion of lifespan

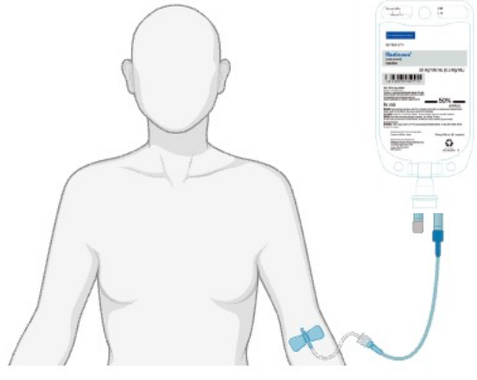
https://www.als.org/navigating-als/living-with-als/fda-approved-drugs

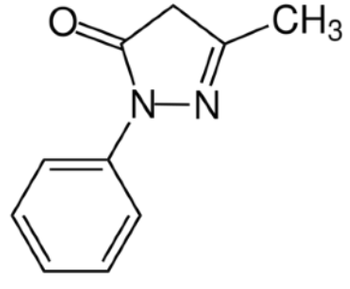
Clinical practices against ALS

FDA-approved therapies

2017 Radicava (IV infusion)

Radicava®
(edaravone) IV infusion 30mg/100mL





Radical scavenger, protects neurons from oxidative damage

2022 Radicava (oral suspension)

Radicava ORS®
(edaravone) Oral Suspension 105mg/5mL

6 months expansion of lifespan

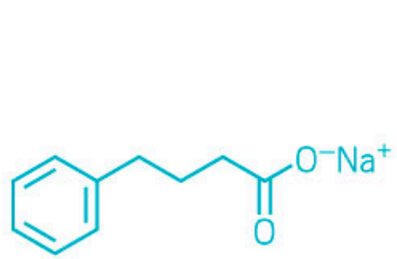
https://www.als.org/navigating-als/living-with-als/fda-approved-drugs

Clinical practices against ALS

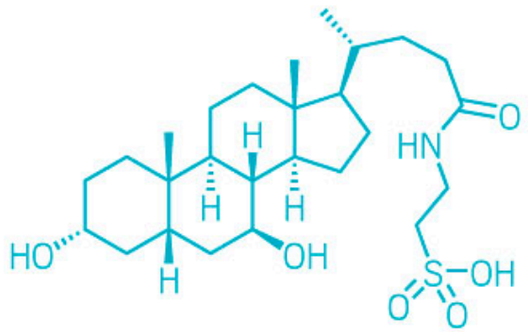
FDA-approved therapies

2022 RELYVRIO (AMX0035)

relyvrio™ (sodium phenylbutyrate and taurursodiol) for oral suspension 3 g/1 g



Sodium phenylbutyrate



Taurursodiol

Act to prevent nerve cell death by blocking stress signals in cells

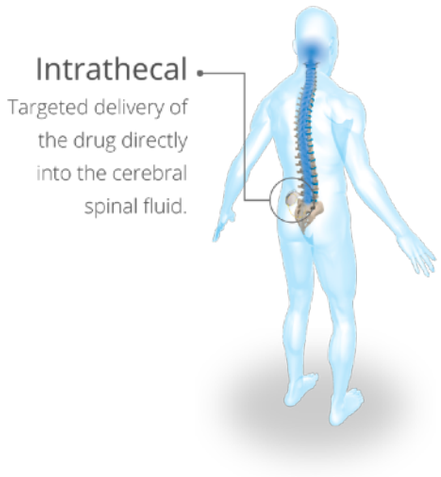
6-10 months expansion of lifespan

https://www.als.org/navigating-als/living-with-als/fda-approved-drugs

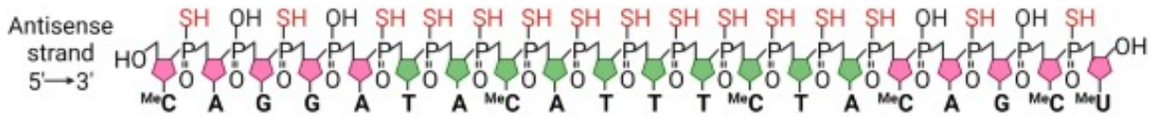
Clinical practices against ALS

FDA-approved therapies

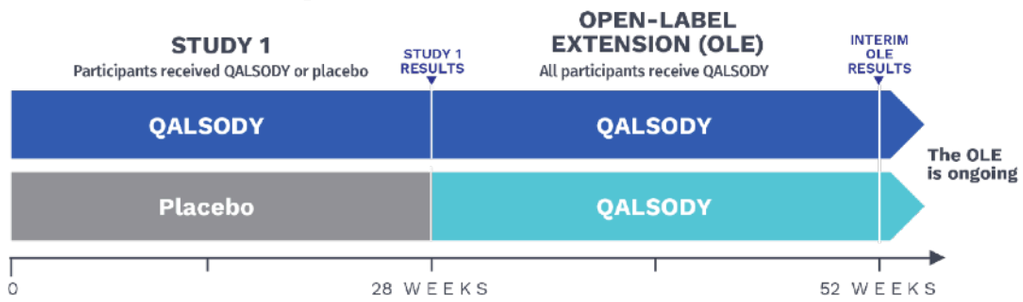
2023 Accelerated Approval
QALSODY (monthly injection)



Antisense therapy *against SOD1*



Open-label extention



Compassionate use access

Enable patients access to investigational medical products for treatment outside of a traditional clinical trial

Pre-symptomatic prevention (till 2027)

To determine whether tofersen can delay the onset of signs or slow declines in function once signs or symptoms appear

Delayed disease progression

https://www.qalsody.com/

https://www.als.org/navigating-als/living-with-als/fda-approved-drugs

Clinical practices against ALS

Ongoing clinical trials

Drug Name	Therapy Type	Target	Phase
ION-363 (jacifusen)	ASO	*FUS* mRNA	Phase 3
AP-101	*Monoclonal antibody*	*Misfolded and aggregated SOD1*	Phase 2*
BIIB105 / ION-541	ASO	*ATXN2* mRNA	Phase 1/2*
WVE-004	ASO	*C9orf72* mRNA	Phase 1/2**
APB-102 / AMT-162	miRNA	*SOD1* mRNA	Phase 1/2

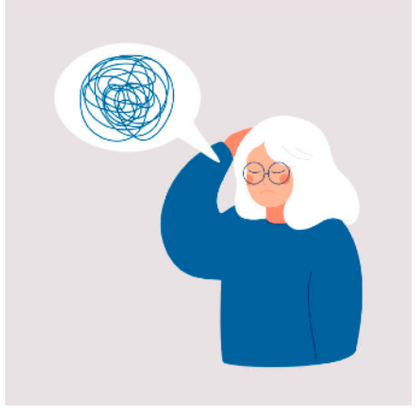
74 clinical trials ongoing

https://iamals.clicdata.com/v/eKU04ajTv7TA

Clinical practices against ALS

Supportive care

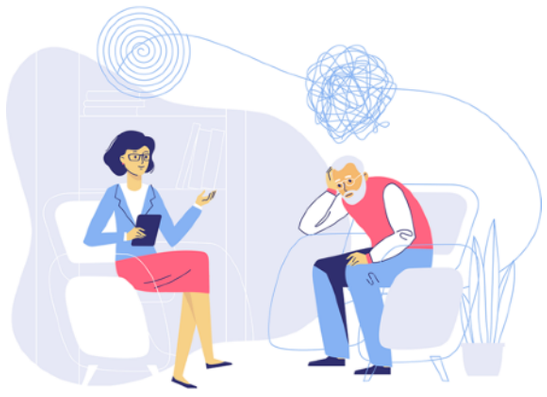
Speech Therapy



Respiratory Therapy

Physical therapy

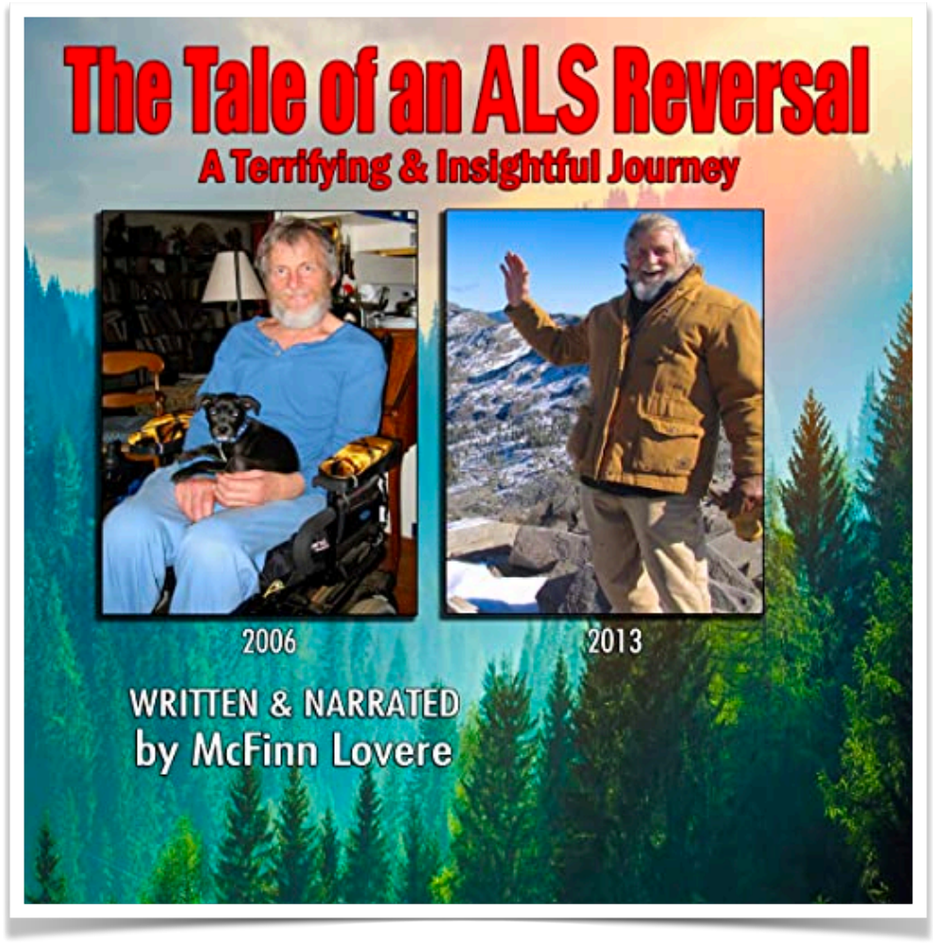
Psychotherapy



Clinical practices against ALS

ALS reversal

“To gather and study rare reversal cases and replicate them in other patients”



https://alsreversals.com/

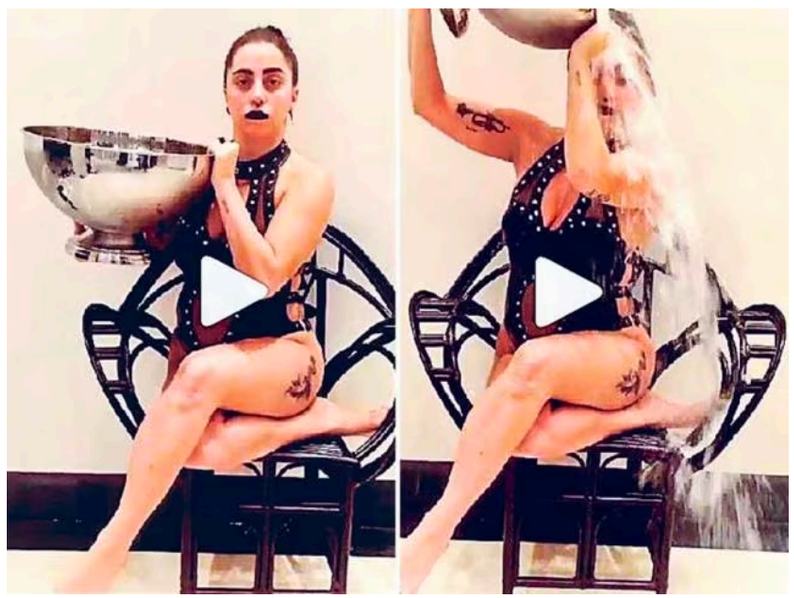
https://www.als.org/blog/als-reversals-what-are-they-and-how-can-we-make-them-happen-more-often

Bringing attention to ALS

ice-bucket challenge

Bringing attention to ALS

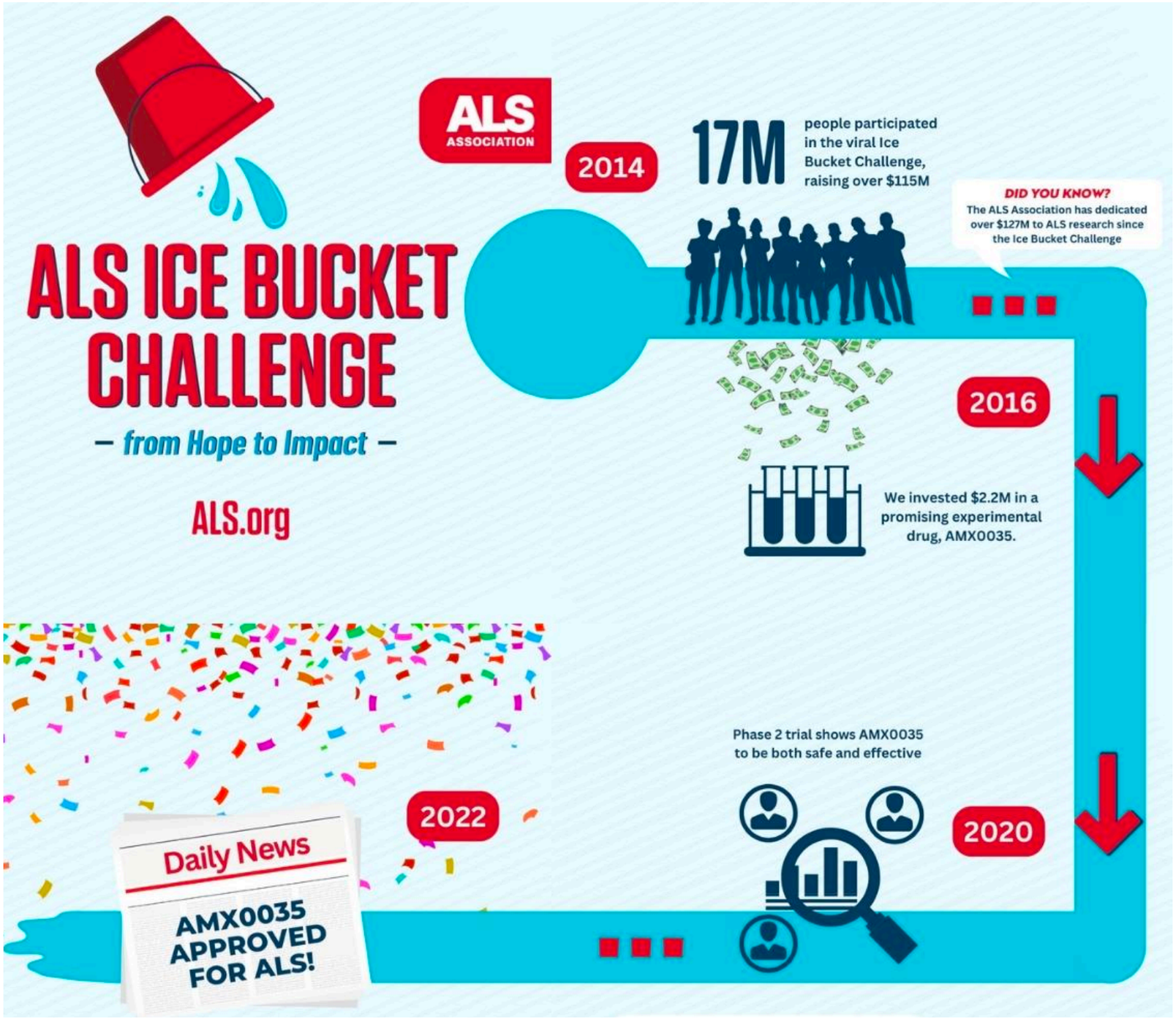
ice-bucket challenge



Dave MacMillan did ice-bucket challenge another kind…

Bringing attention to ALS

ice-bucket challenge



5,000+
People are diagnosed per year

2-5 years
Is the average life expectancy

Every **90 mins**
someone is diagnosed and someone passes away from ALS

90 percent
of cases occur without family history

10 percent
of cases are linked to gene mutation

$250,000
is the estimated out-of-pocket cost for caring an ALS patient

$2 billion
is the estimated cost to develop a drug to slow or stop the progression of ALS

There is NO CURE for ALS

5,000+
People are diagnosed per year

2-5 years
Is the average life expectancy

Every **90 mins**
someone is diagnosed and someone passes away from ALS

90 percent
of cases occur without family history

Thank you!

10 percent
of cases are linked to gene mutation

$250,000
is the estimated out-of-pocket cost for caring an ALS patient

$2 billion
is the estimated cost to develop a drug to slow or stop the progression of ALS

There is no cure but there is
HOPE