Brain Biorepositories

South Florida Neuroscience Symposium 2023
June 10th

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Director ALS Center of Excellence
Mayo Clinic Florida

What is ALS?

- “When you think that you understand ALS it turns out to be the opposite”
- - J. Ravits

MAYO CLINIC

Overview

History of our current understanding

Current understanding

Resource for exploration and discovery

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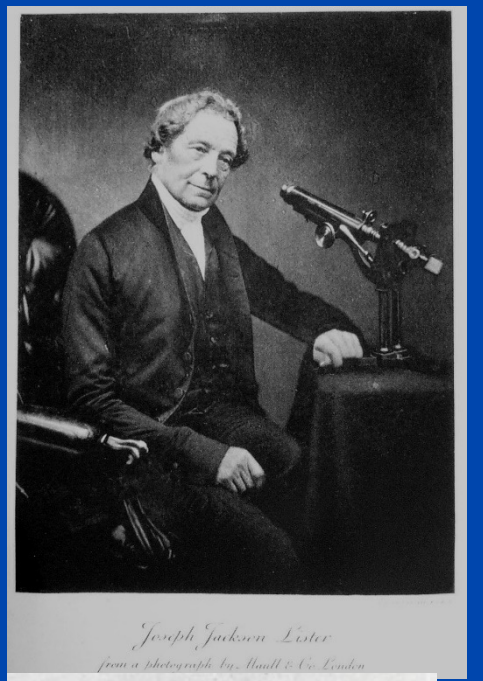
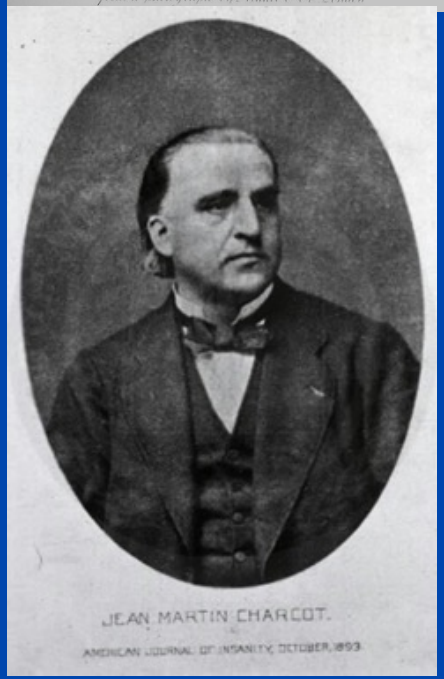
History

- Modern medicine 1800's
- Development of functional microscope 1830's - Lister
- 1838 Cells proposed by Schleiden and Schwann
- 1849 Progressive Muscular Atrophy - Duchenne
- **1869 Amyotrophic Lateral Sclerosis - Charcot**





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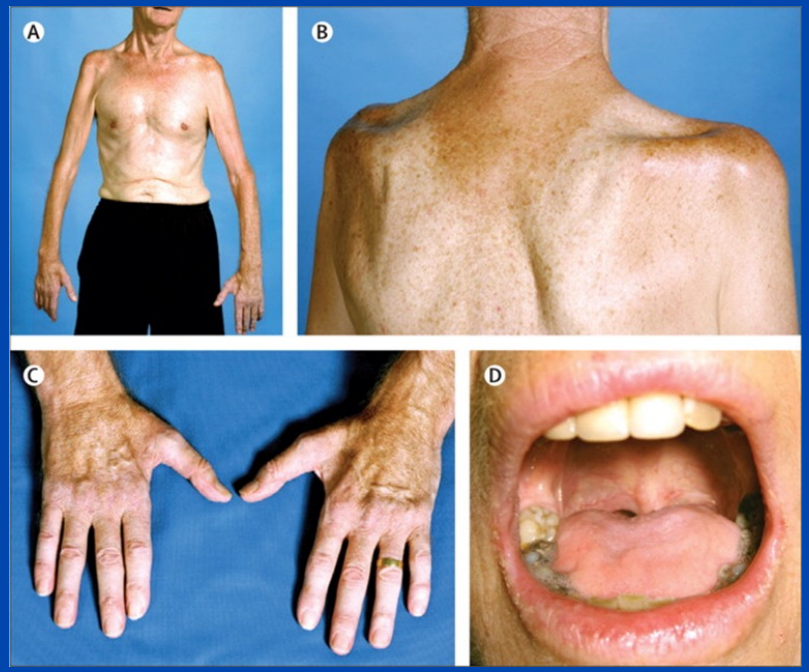
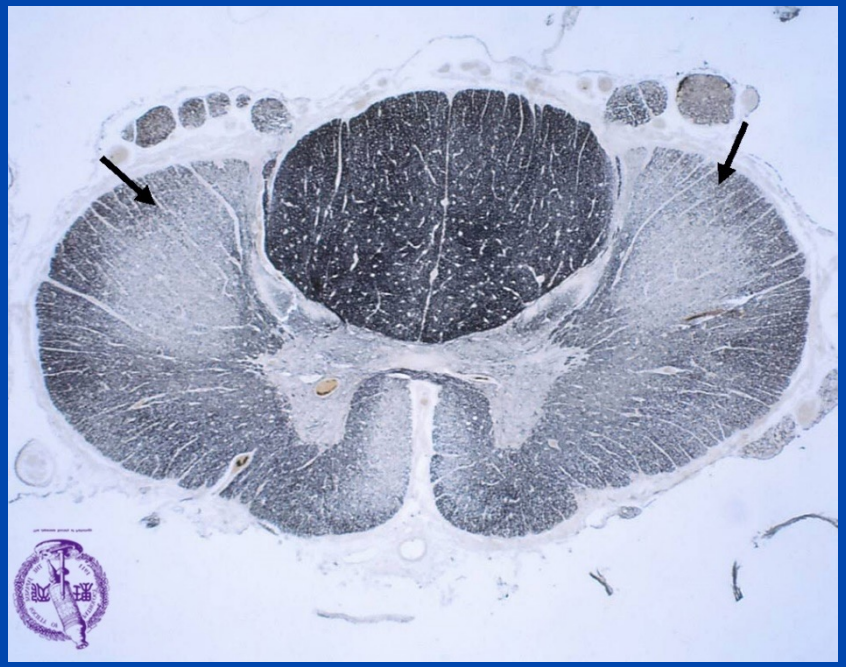
Amyotrophy and Lateral Sclerosis

Amyotrophy - wasting of muscle tissue



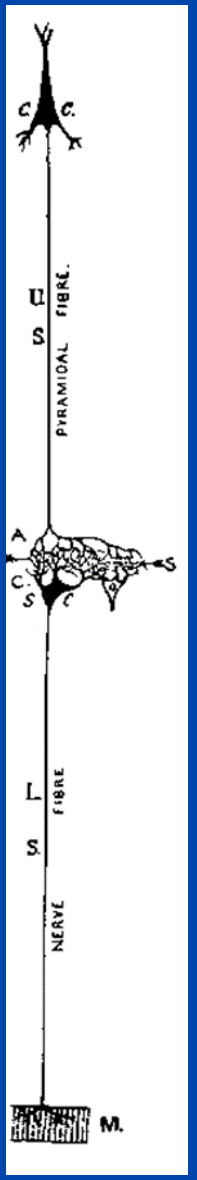
Lateral – to the side

Sclerosis - hardening



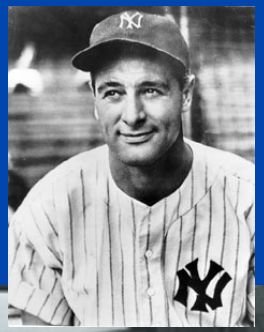
History of ALS

- **1869 - ALS - Charcot**
- 1880 - Familial ALS (PMA) - Osler
- 1887 - Neuron - Ramon y Cajal
- 1904 - Primary Lateral Sclerosis - Spiller
- 1993 - SOD1- first cause - Brown and Siddique
- 2008 - TDP43 - Trojanowski and Lee
- 2011 - C9orf72 - most common known cause
  Rademakers / Traynor et al



Ramon y Cajal

ALS



- Amyotrophic Lateral Sclerosis
  - Motor Neuron disease
  - Lou Gehrig's disease
  - Charcot's disease

Lou Gehrig at Mayo Clinic

- Progressive
- Upper and lower motor neuron disease
- Face/Bulbar or limb onset
- Breathing muscle weakness leading to death

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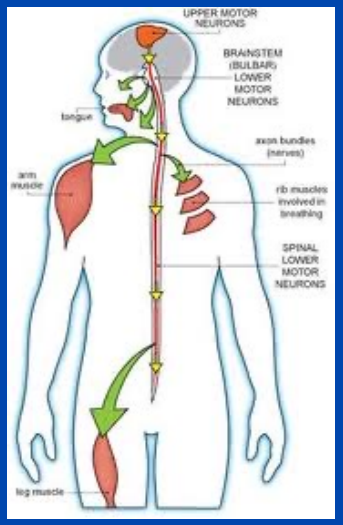
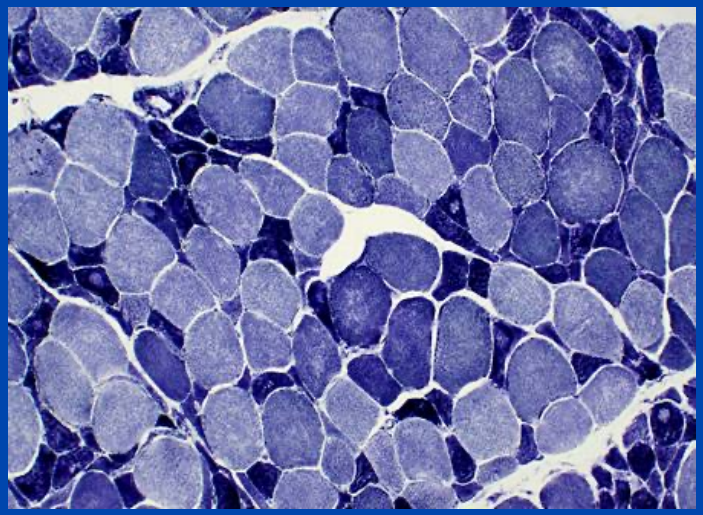
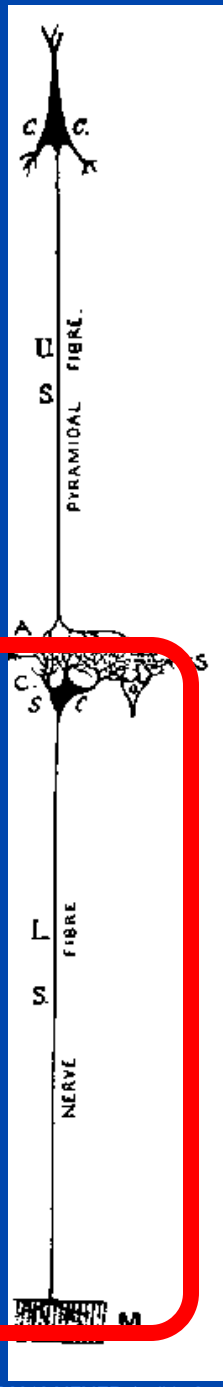
Lower Motor Neuron

- **Weakness**
- **Atrophy**
- **Fasciculations**
- **Cramps**

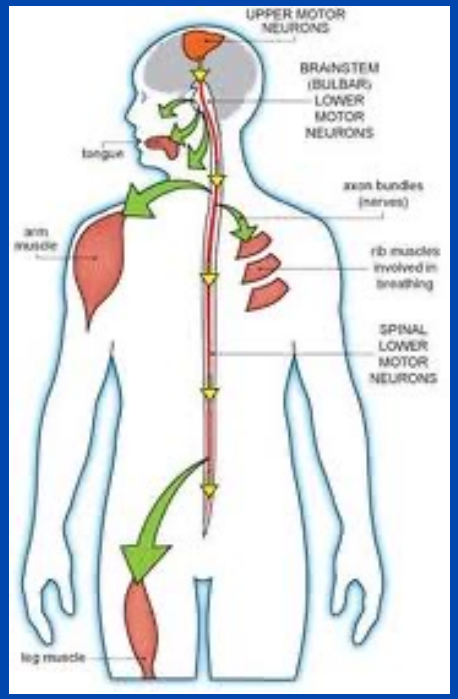


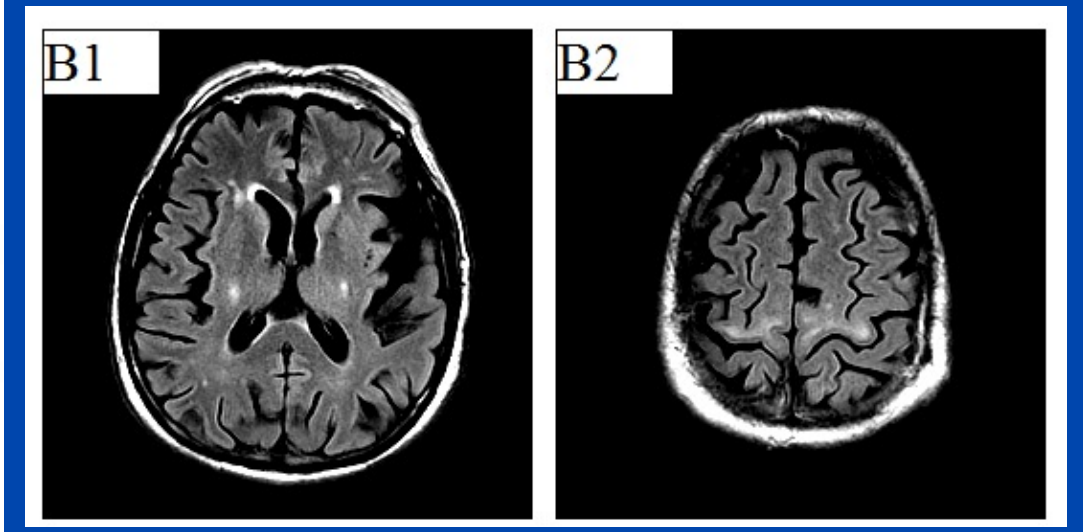


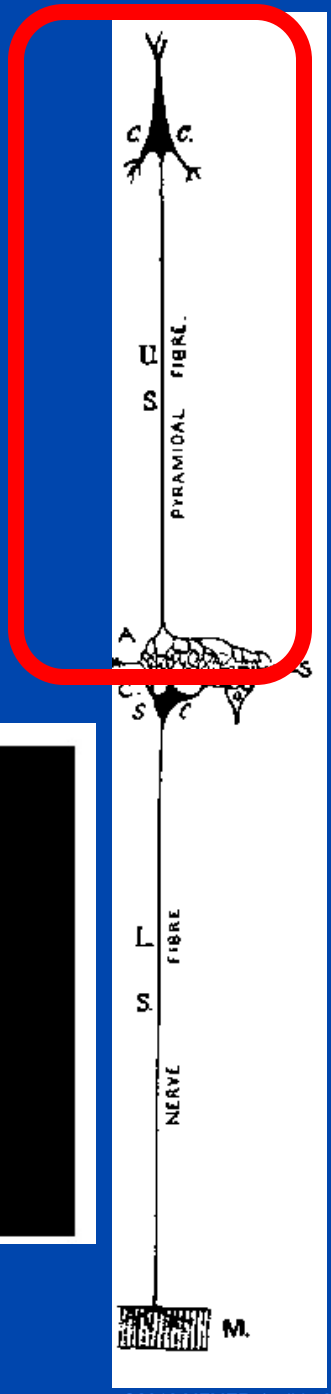


Upper Motor Neuron

- **Weakness**
- **Spasticity**
- **Clumsiness**

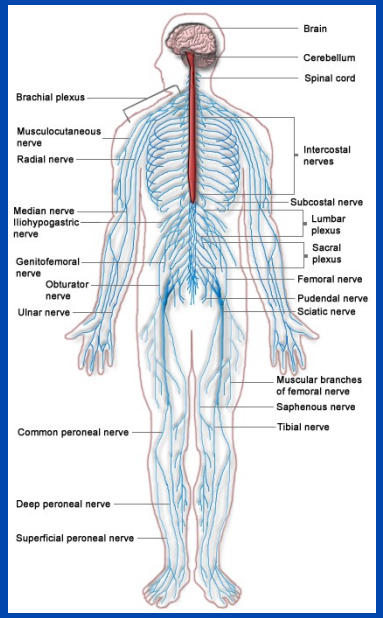


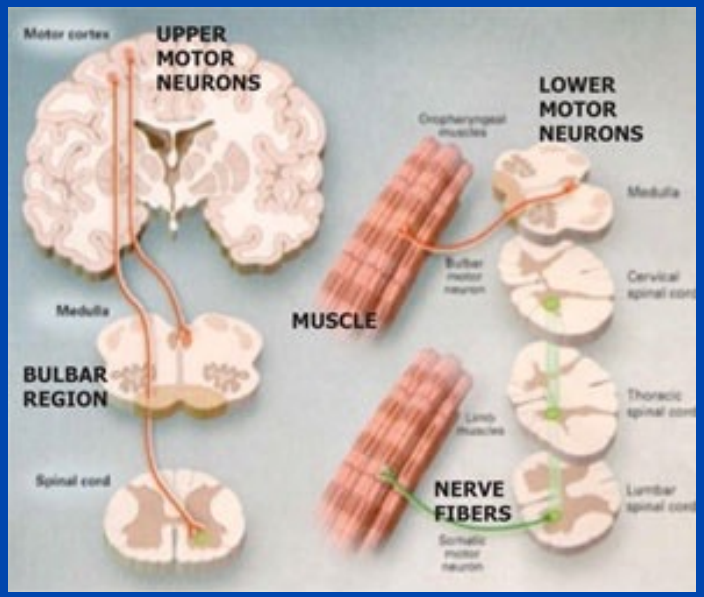




Clinical

- **Weakness**
- Onset is 1/3 bulbar / arm / leg (4% thoracic/global)
- Spreads contiguously through the body
- Painless, progressive, no sensory loss





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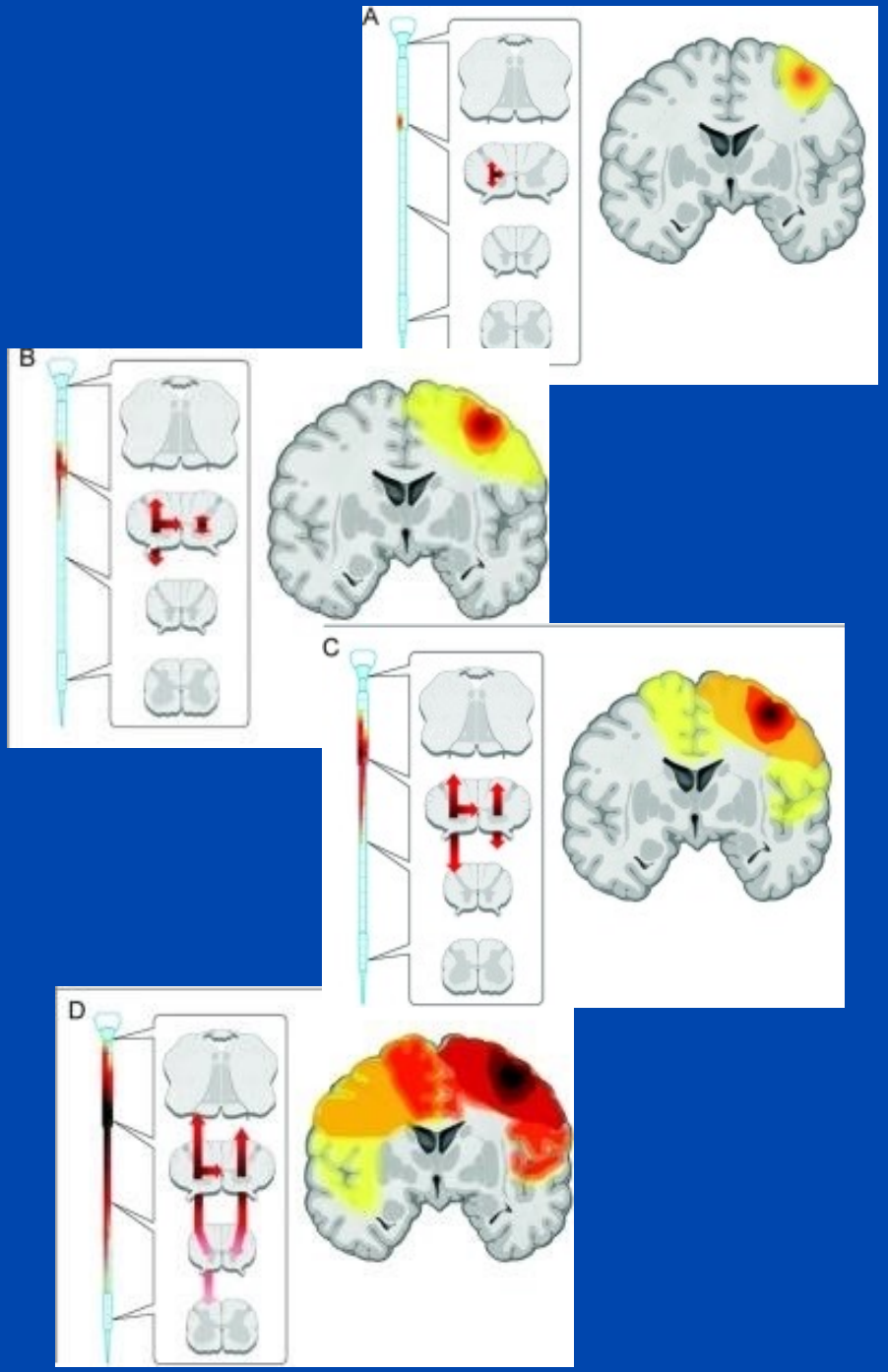
Spread of disease

- Centrifugal
- Affecting “mostly” anterior horn cells and frontal cortical neurons



Pictures from Ravits et al 2009

Look and learn

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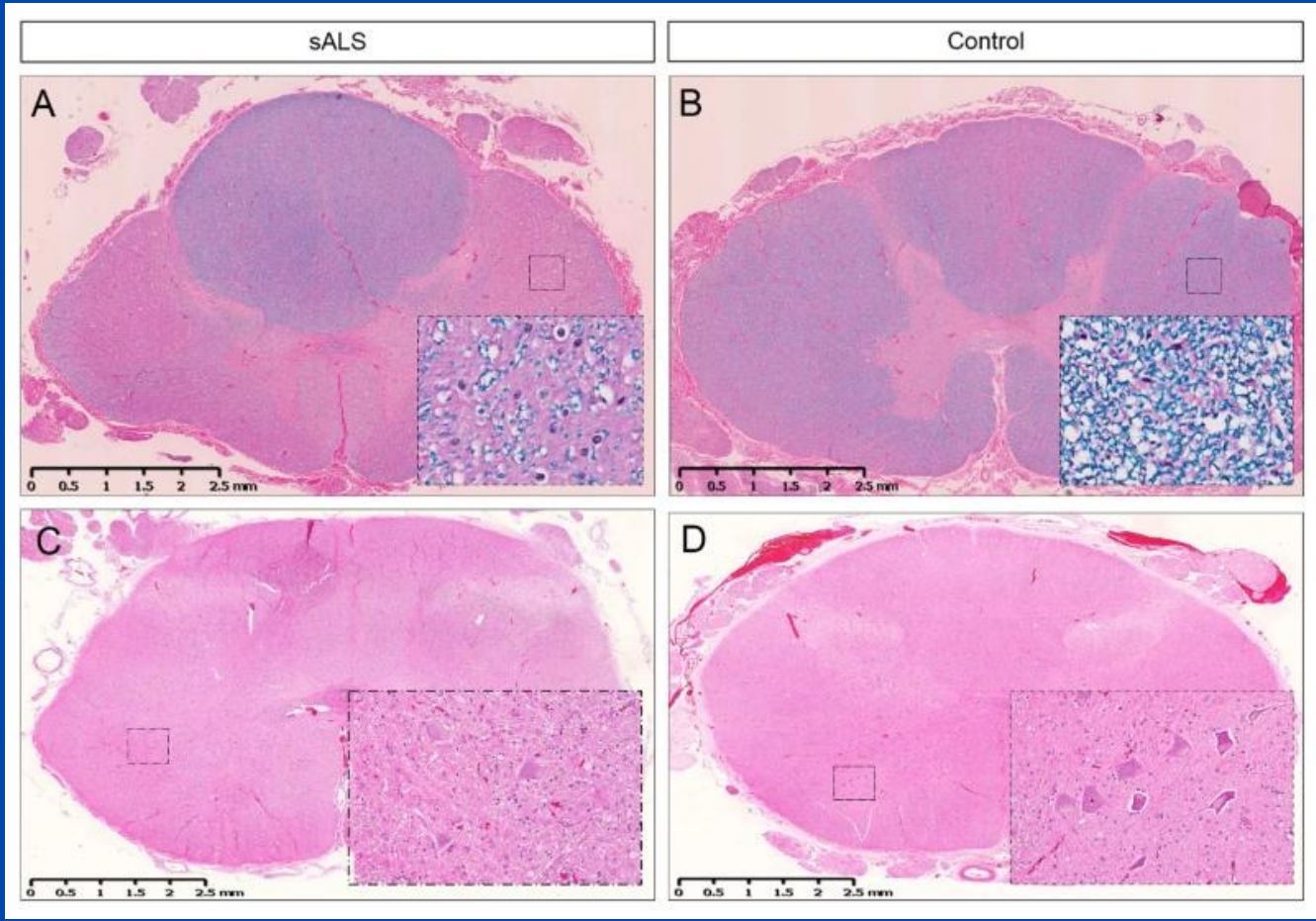
Neuropathology

- Lateral sclerosis
- Anterior horn disease



Saberi 2015

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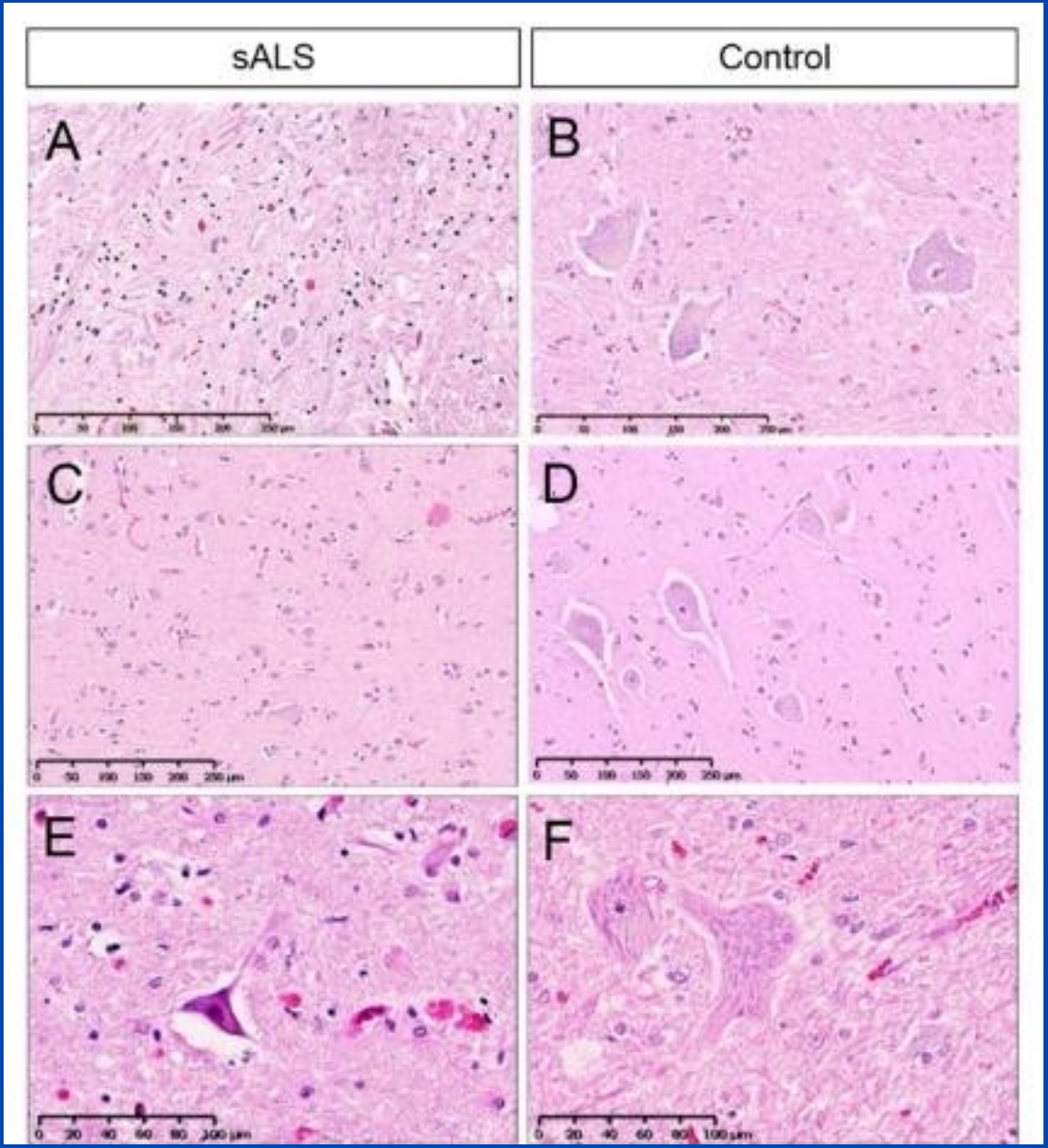
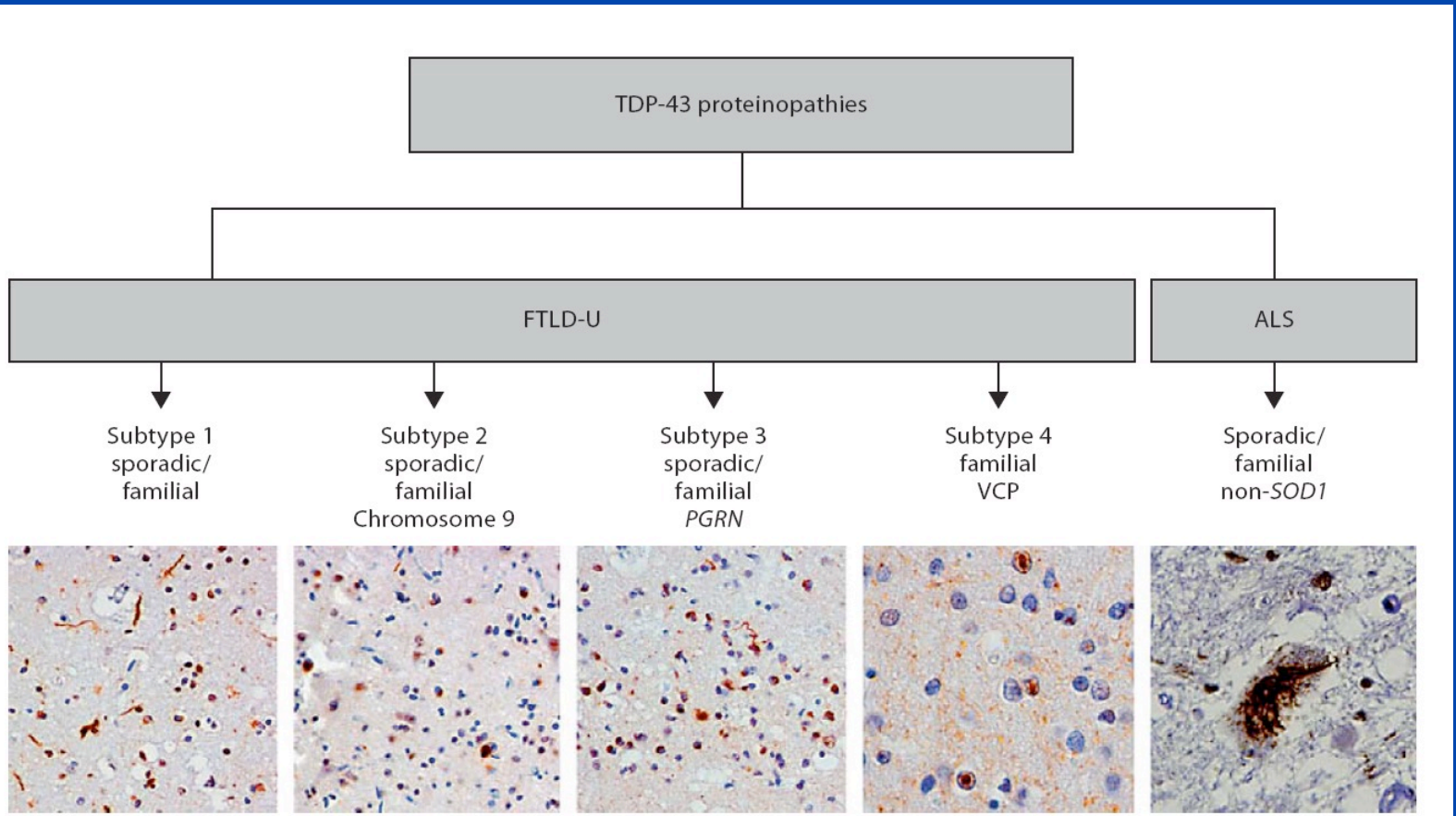
Neuropathology

- Loss of cortical neurons
- Contracted



Saberi 2015

TDP-43 Proteinopathies



LK Kwong, K Uryu, JQ Trojanowski, VMY Lee Neurosignals 2008

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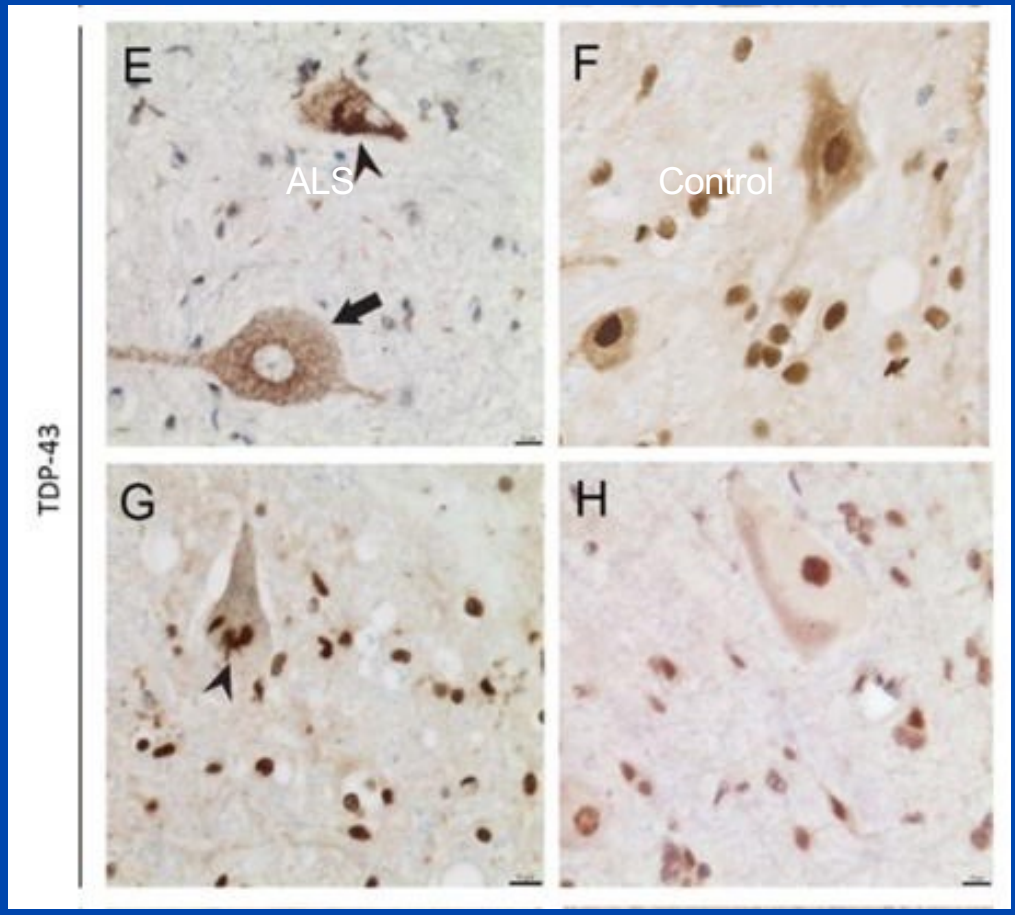
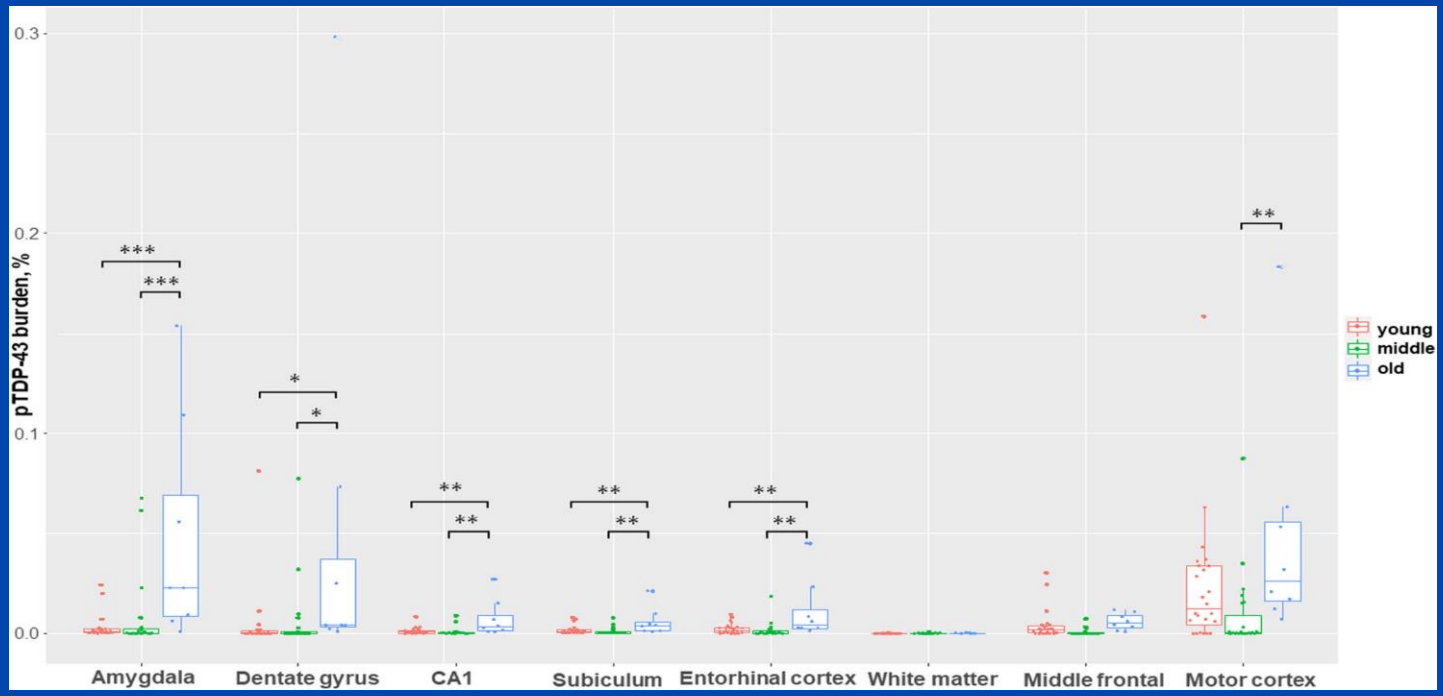
Neuropathology TDP-43

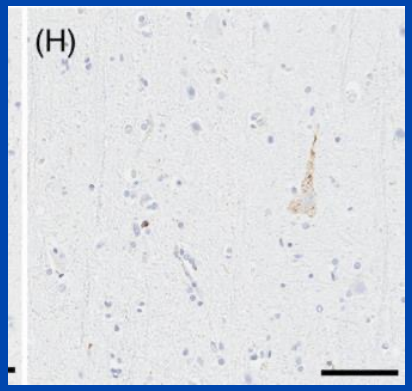
- Ubiquitin-positive inclusions
- Made up largely by TDP-43
- **Nuclear clearing**



Saberi 2015

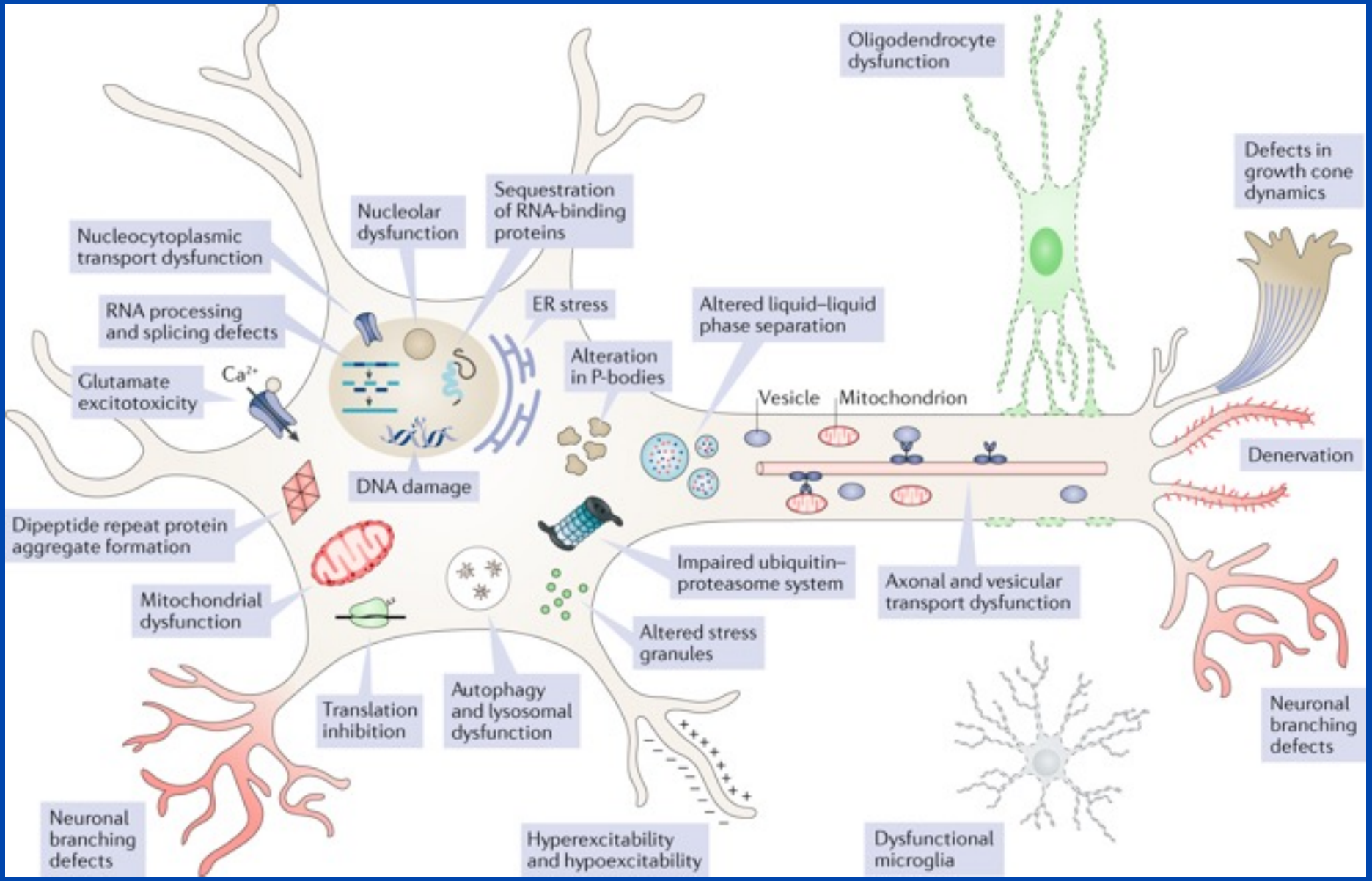
TDP pathology is sparse in ALS





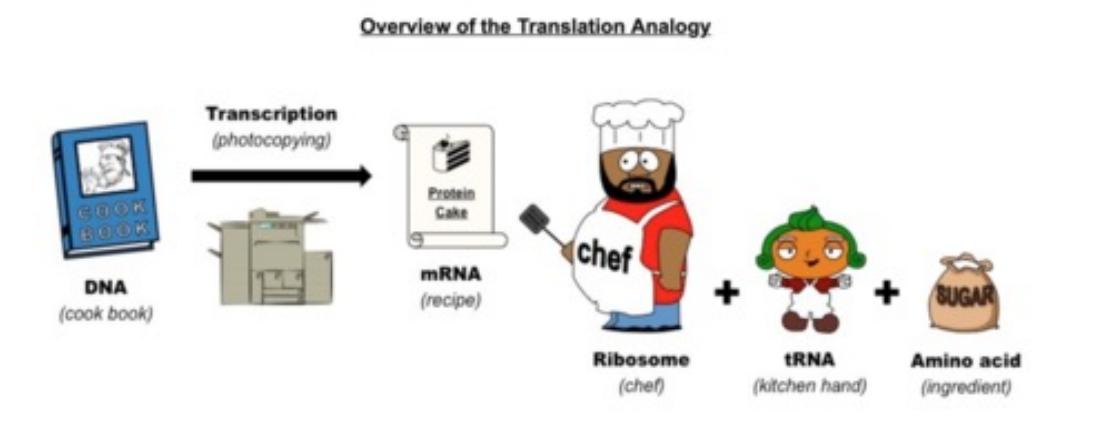
Old age amyotrophic lateral sclerosis and limbic TDP-43 pathology
Murakami et al **Brain Pathology: 17 June 2022, DOI: (10.1111/bpa.13100)**

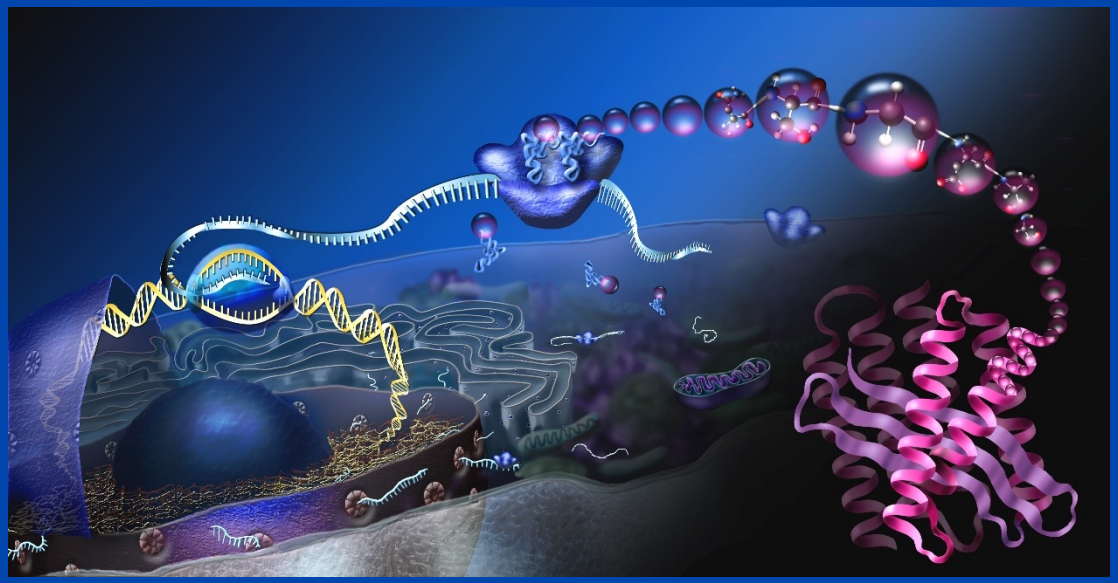
ALS (C9orf72)



Balendra et al 2018

Central Dogma of Biology

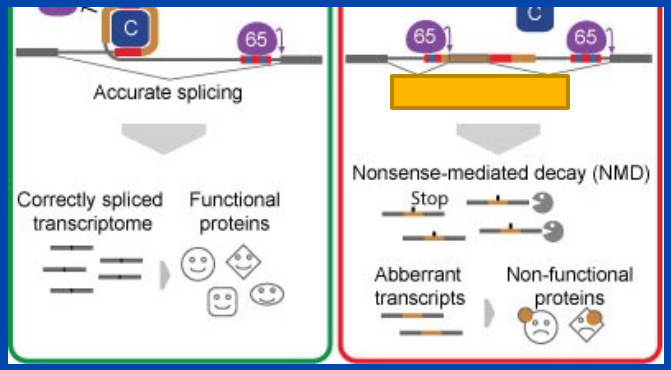




CK-12 Foundation

The Guardians of the Transcriptome
TAR DNA binding protein (TDP 43)

- Major component of ubiquinated inclusions
- 414-amino-acid nuclear protein
- *TARDBP* gene on chromosome 1
- Highly conserved widely expressed protein



Modified from J. Ule

- Physiologic function in CNS
  - Transcription regulation and exon skipping
  - DNA binding
  - mRNA binding with export sequence
- Mislocalization leads to splicing errors in Stathmin2, UNC13A, others
- Cryptic peptides

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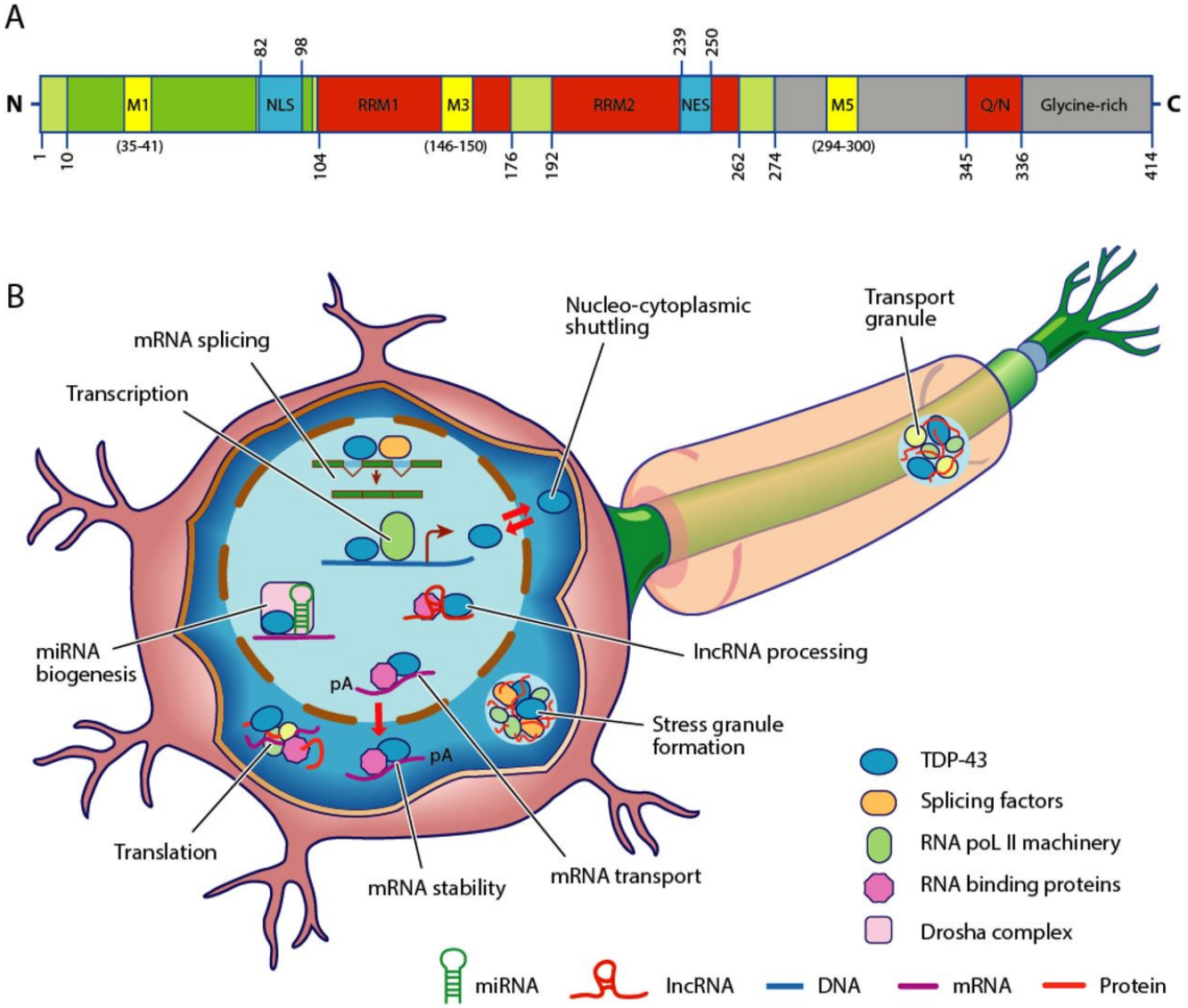
(A) Structure of TAR DNA-binding protein 43 (TDP-43) protein.



Eva Maria Johanna de Boer et al. J Neurol Neurosurg Psychiatry 2021;92:86-95

JNNP

Mayo ALS brain bank

- The ALS autopsy program is in its 22nd year
- The bank contains 200+ ALS and 16 PLS and 9 other motor neuron disease brains and spinal cords.
- Donations are collected from all three Mayo Clinic sites, with a majority from Mayo Clinic Florida
- The tissue samples are used for a wide range of research on the pathology and genetics of motor neuron disorders, including basic studies at the cellular level and biochemical studies examining changes in proteins and other molecules.

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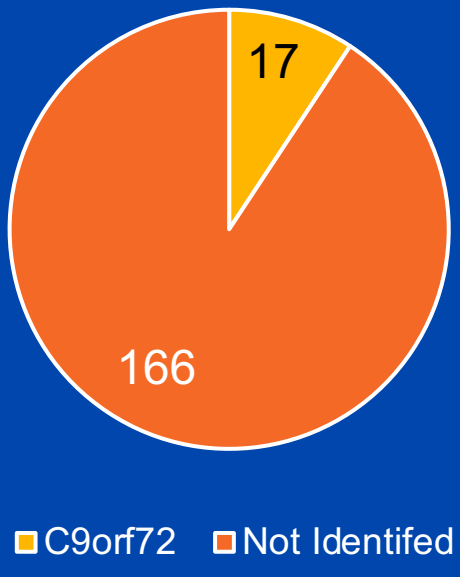
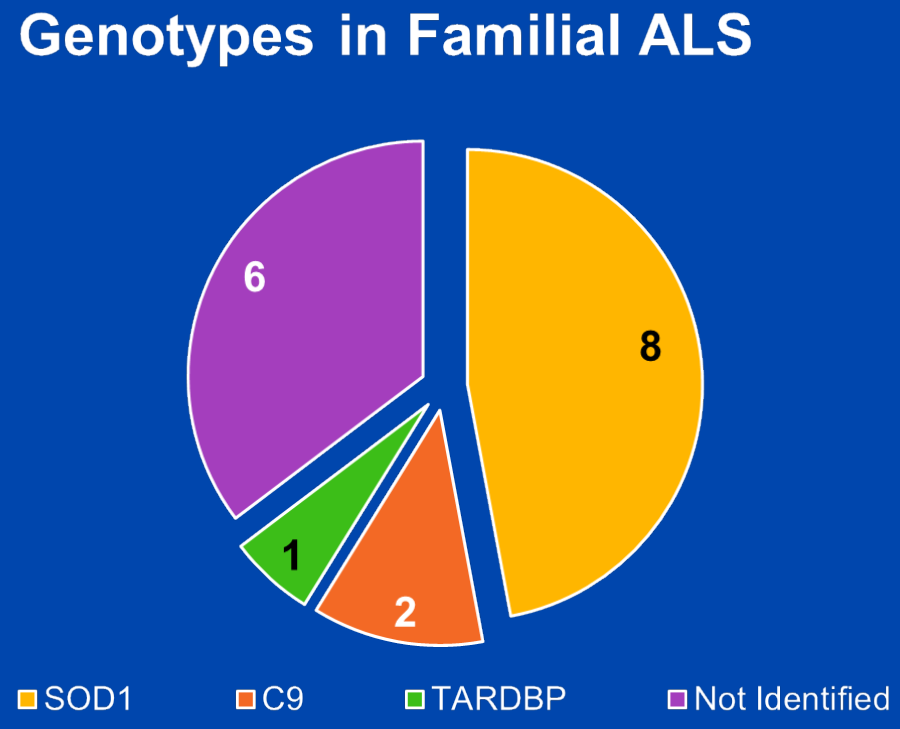
Genotypes





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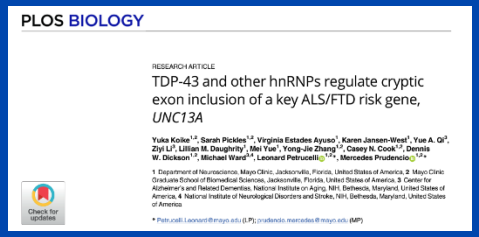
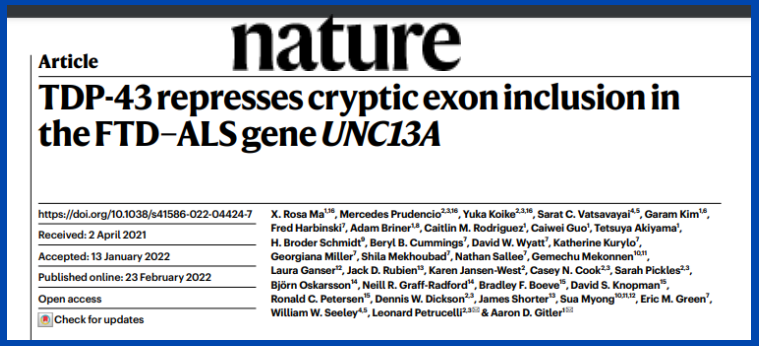
Publications from 2022-23


PLOS BIOLOGY

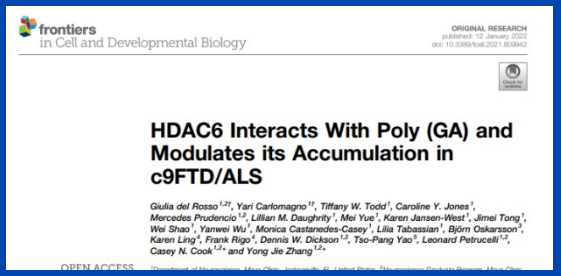
RESEARCH ARTICLE

TDP-43 and other hnRNPs regulate cryptic exon inclusion of a key ALS/FTD risk gene, *UNC13A*


Article

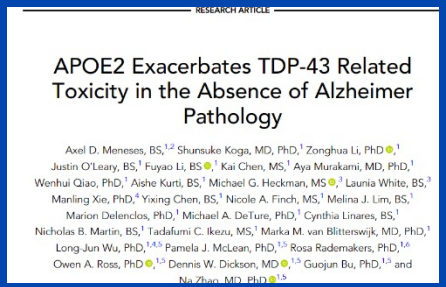
nature

TDP-43 represses cryptic exon inclusion in the FTD–ALS gene *UNC13A*

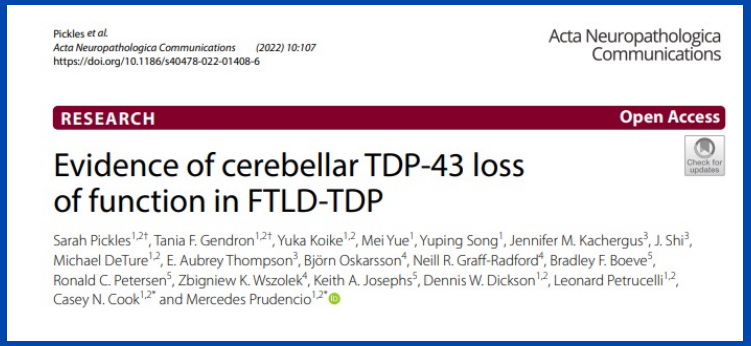

frontiers in Cell and Developmental Biology

ORIGINAL RESEARCH

HDAC6 Interacts With Poly (GA) and Modulates its Accumulation in c9FTD/ALS

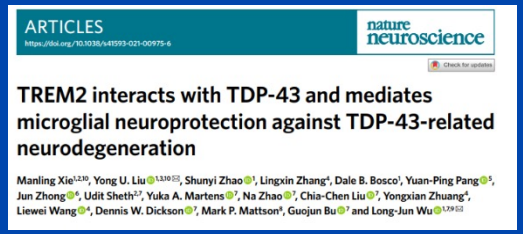

RESEARCH ARTICLE

APOE2 Exacerbates TDP-43 Related Toxicity in the Absence of Alzheimer Pathology


Acta Neuropathologica Communications

RESEARCH Open Access

Evidence of cerebellar TDP-43 loss of function in FTLD-TDP

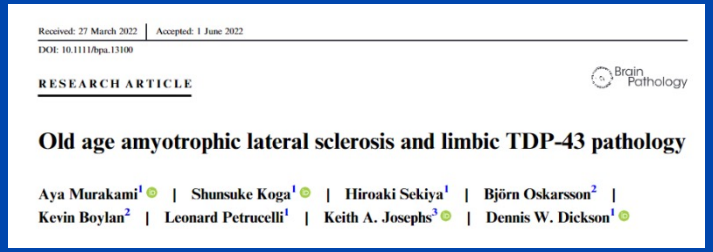

ARTICLES

nature neuroscience

TREM2 interacts with TDP-43 and mediates microglial neuroprotection against TDP-43-related neurodegeneration


ORIGINAL PAPER

LATE-NC staging in routine neuropathologic diagnosis: an update


RESEARCH ARTICLE

Brain Pathology

Old age amyotrophic lateral sclerosis and limbic TDP-43 pathology


RESEARCH ARTICLE Open Access

Molecular Neurodegeneration

Nuclear import receptors are recruited by FG-nucleoporins to rescue hallmarks of TDP-43 proteinopathy

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Mayo Clinic Florida ALS Center

- Tissue bank
- Cross sectional blood biomarker study
- Longitudinal Blood and CSF
- TARGET ALS Longitudinal Blood and CSF
- TAPESTRY Whole genome sequencing
- PLS Natural History (Closed)
- REFINE (Closed)
- ALSpire ATXN2 ASO phase 1
- Calico Phase 1 (Closed)
- COMBAT Ibudilast phase II-III
- HIMALAYA Sanofi phase II
- TJ-68 against muscle cramps
- Healy Platform phase II
- Mayo Stem Cell phase II (Closed)

Mangurian Building

Birdsall Research Building

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Acknowledgements

- Our patients
- Our families
- Brain bank
  - Dennis Dickson, MD
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- Clinic Team
  - Jamie Zernicke, RN
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  - Huy Tran, ACRC
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  - Len Petrucelli, PhD
  - Rosa Rademakers, PhD
  - Tania Gendron, PhD
  - Marka van Blitterswijk, MD, PhD
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  - Wilfried Rossoll, PhD
  - John Fryer, PhD
  - Yong-Jie Zhang, PhD
- Funding
  - ALSA
  - State of Florida
  - MDA

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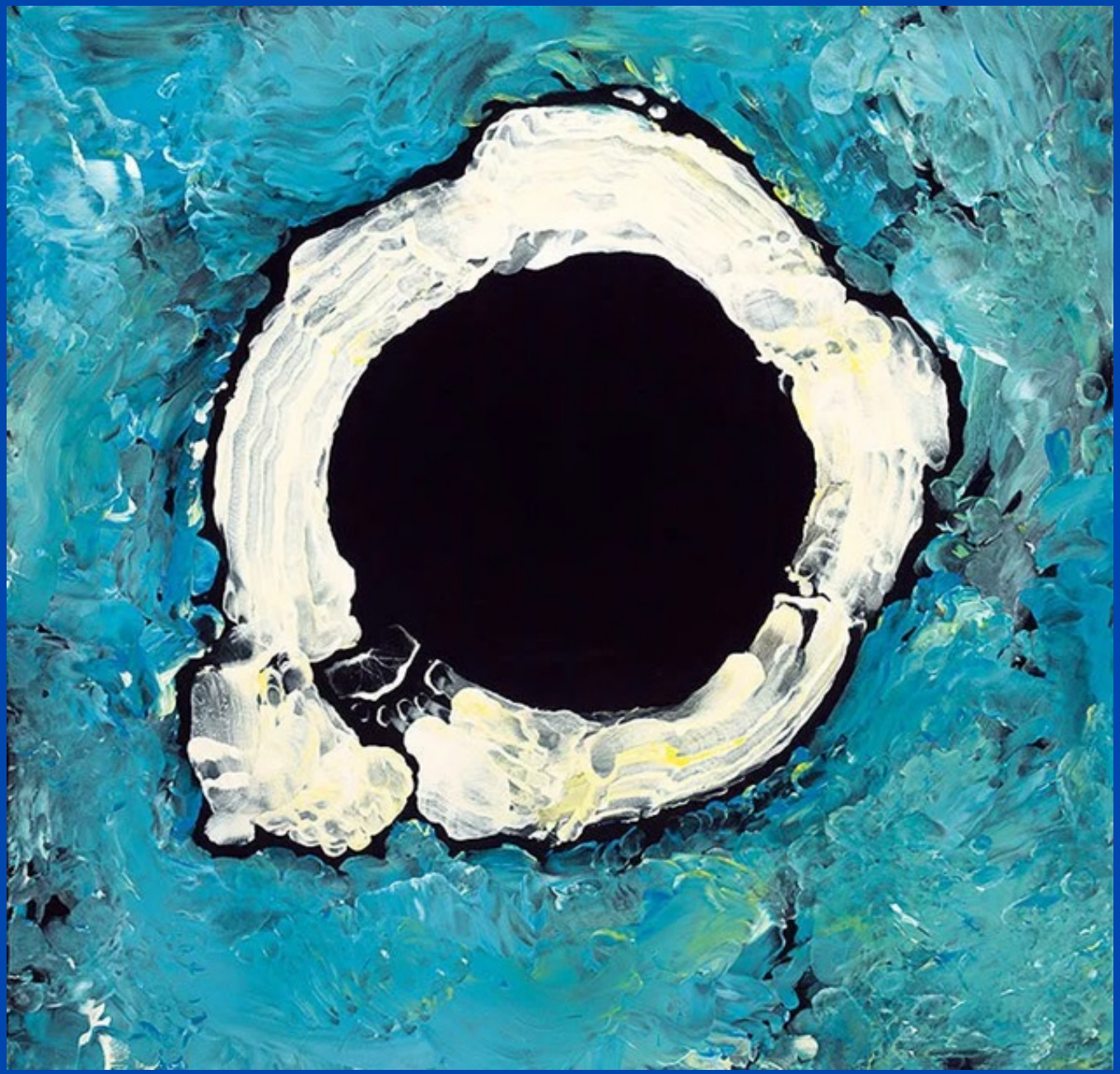

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Still point in blue Sandra Murphy Pak 2018