



# Brain Biorepositories

**South Florida Neuroscience Symposium 2023  
June 10th**

Björn Oskarsson, MD, FAAN  
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

# Overview



History of our current  
understanding



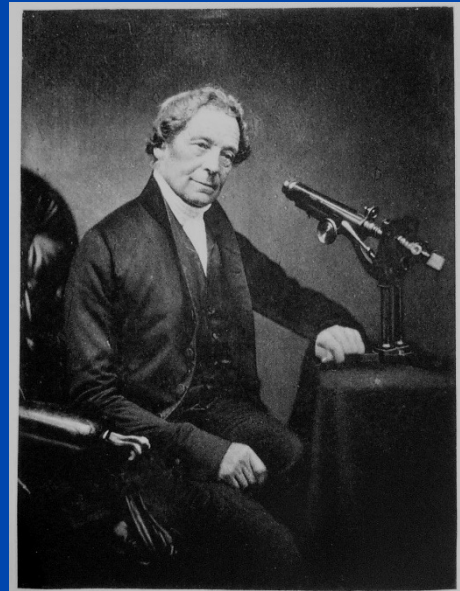
Current  
understanding



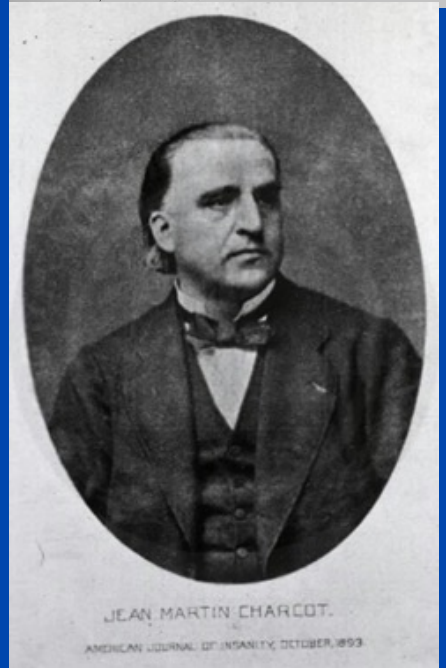
Resource for  
exploration and  
discovery

# 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**



*Joseph Jackson Lister*  
*from a photograph by. Maull & Co. London*

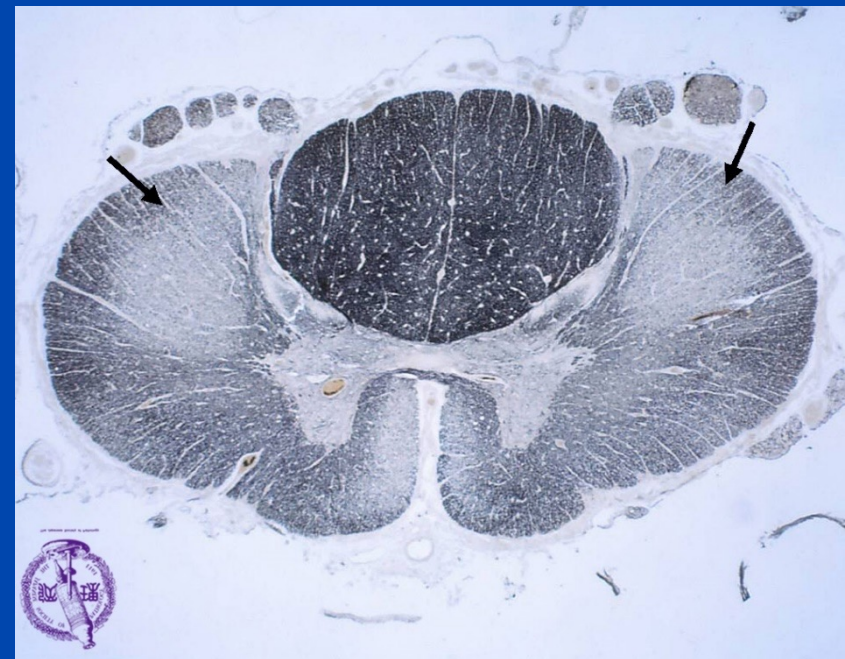
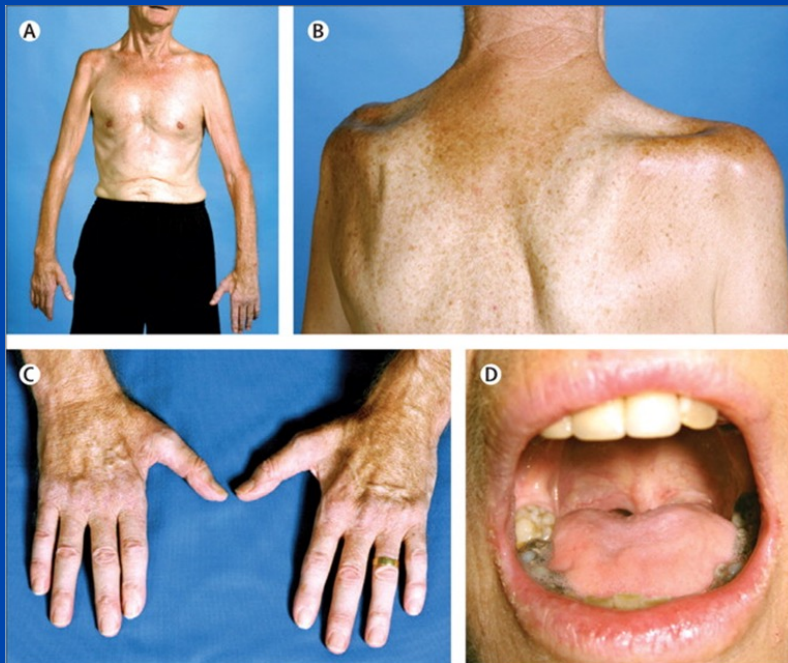


JEAN MARTIN CHARCOT.  
AMERICAN JOURNAL OF INSANITY, OCTOBER, 1893

# Amyotrophy and Lateral Sclerosis

Amyotrophy - wasting of muscle tissue

Lateral – to the side  
Sclerosis - hardening



# History of ALS

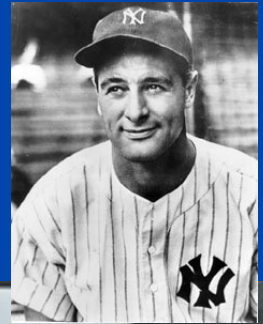
- **1869 - ALS - Charcot**
- 1880 - Familial ALS (PMA) - Osler
- 1887 - Neuron - Ramon y Cajal
- 1904 - Primary Lateral Sclerosis - Spiller
- 1993 - SOD1- first cause - Brown and Siddique
- 2008 - TDP43 - Trojanowski and Lee
- 2011 - C9orf72 - most common known cause  
Rademakers / Traynor et al



Ramon y Cajal

# ALS

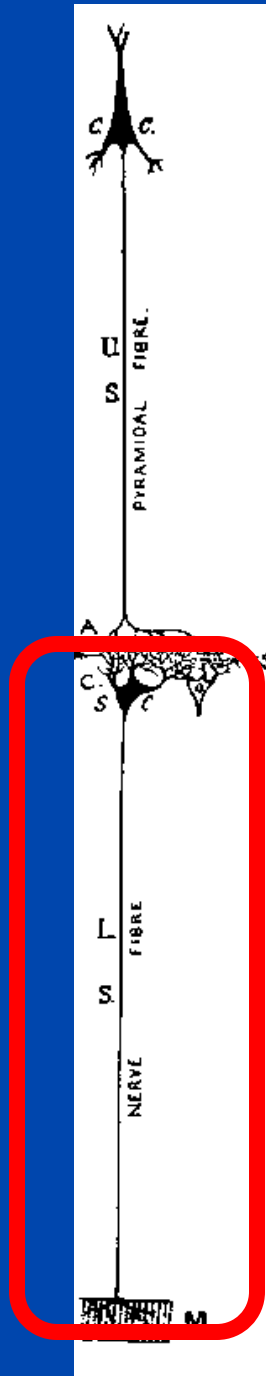
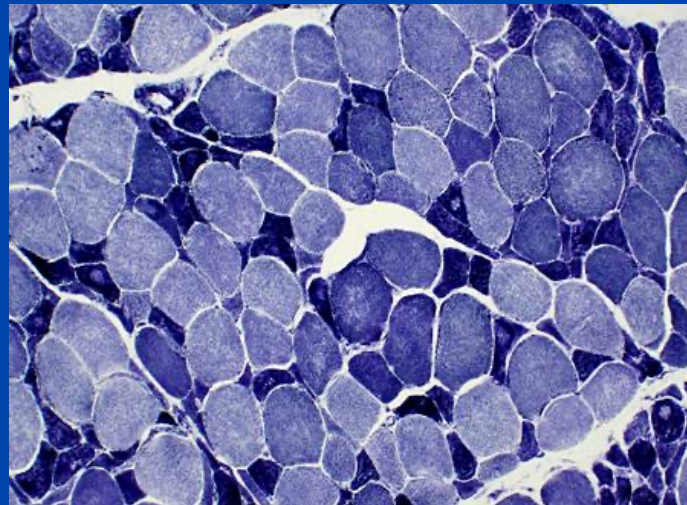
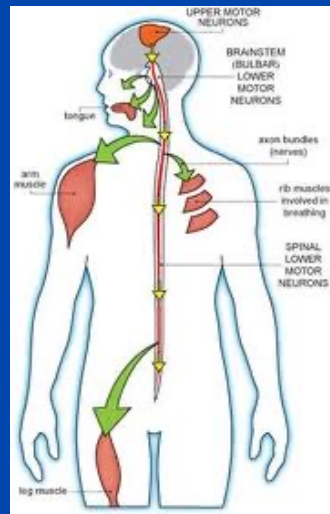
- Amyotrophic Lateral Sclerosis
  - Motor Neuron disease
  - Lou Gehrig's disease
  - Charcot's disease
- Progressive
- Upper and lower motor neuron disease
- Face/Bulbar or limb onset
- Breathing muscle weakness leading to death



Lou Gehrig at Mayo Clinic

# Lower Motor Neuron

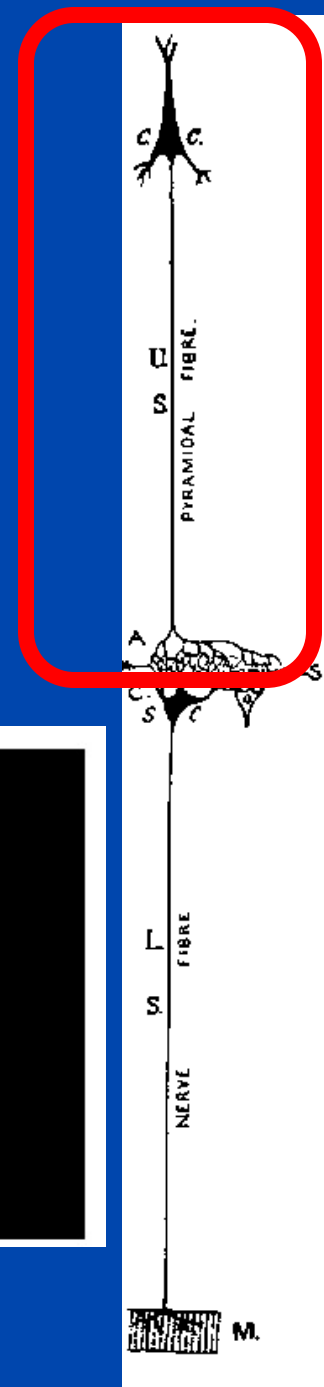
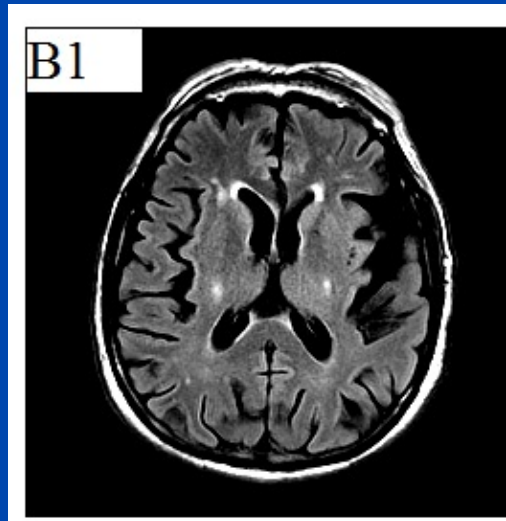
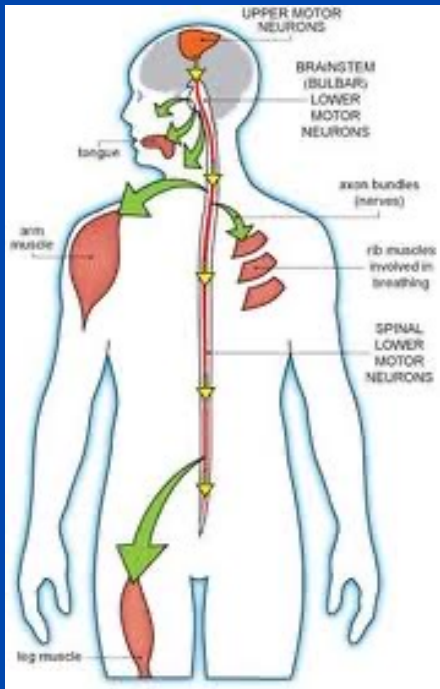
- Weakness
- Atrophy
- Fasciculations
- Cramps





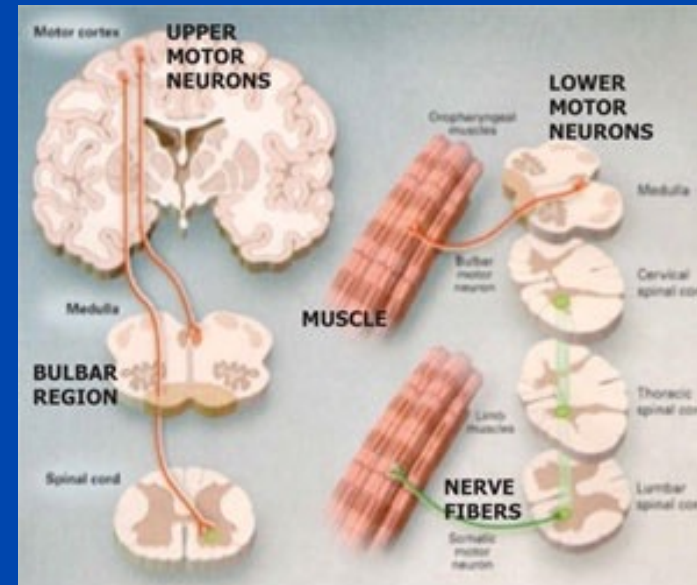
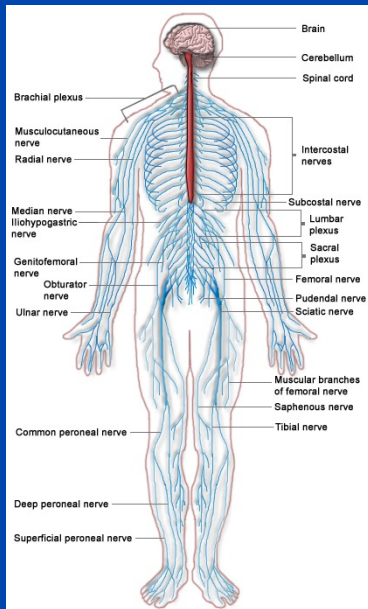
# Upper Motor Neuron

- Weakness
- Spasticity
- Clumsiness



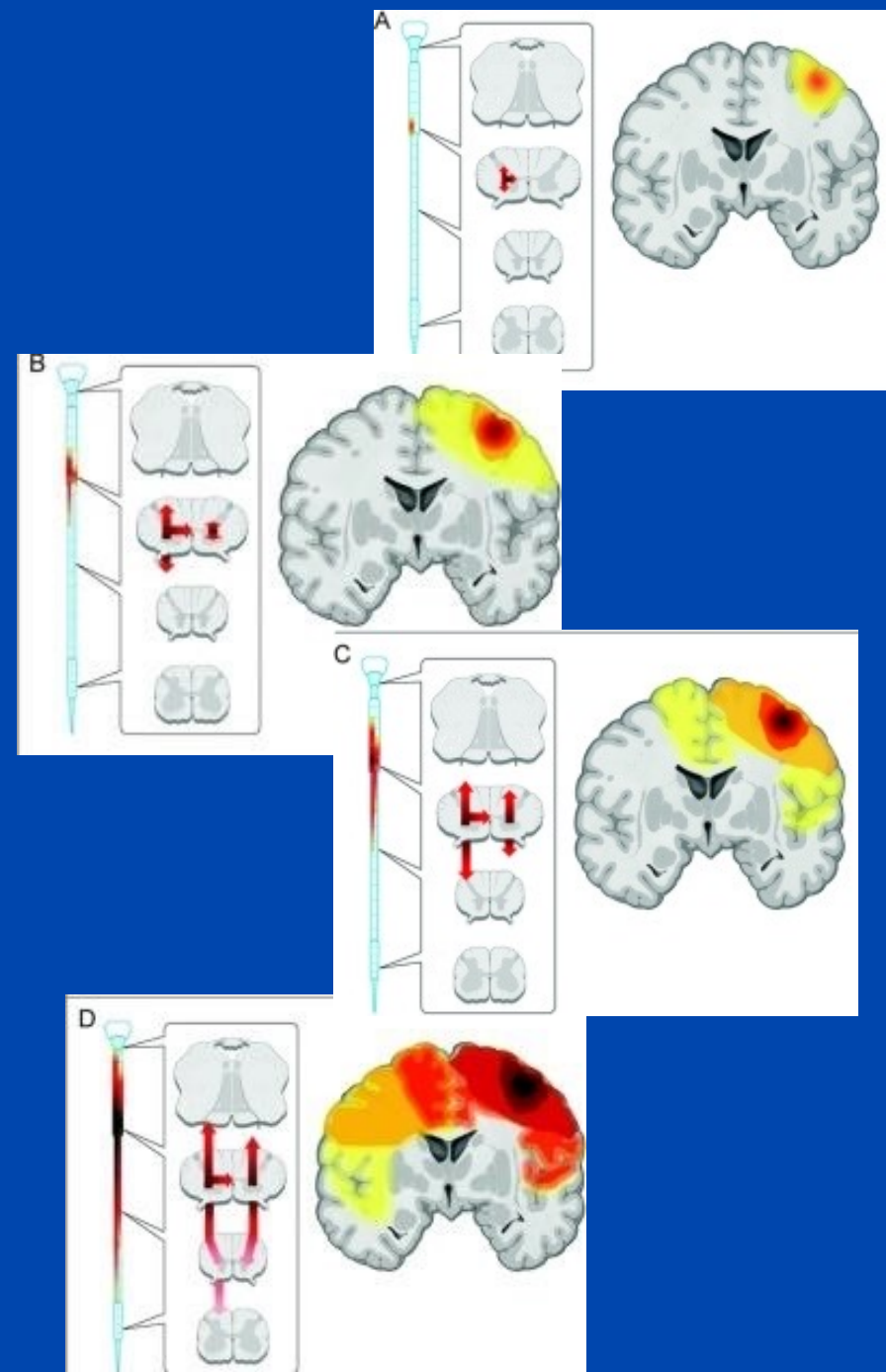
# Clinical

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



# Spread of disease

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



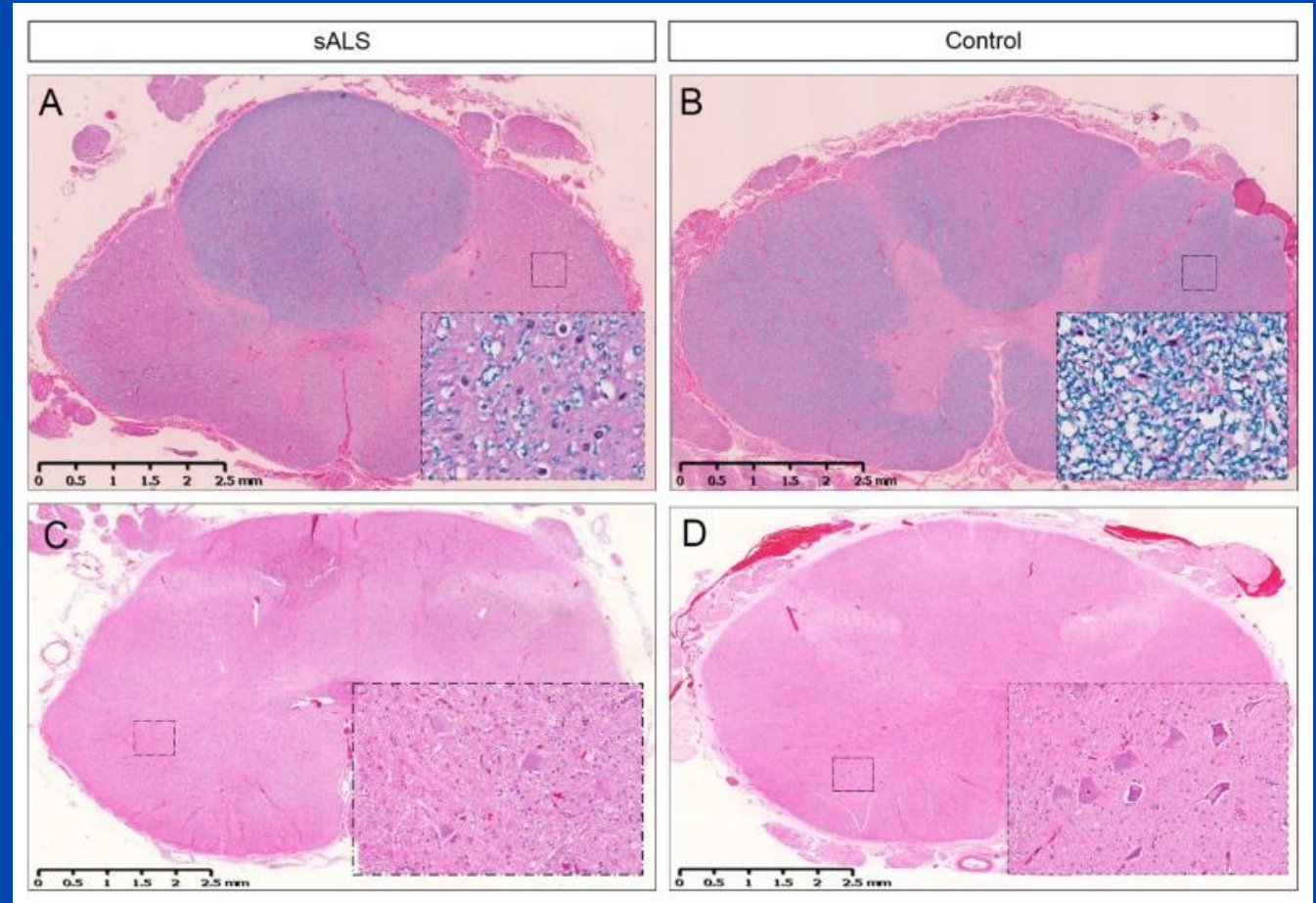
Pictures from Ravits et al 2009

# Look and learn



# Neuropathology

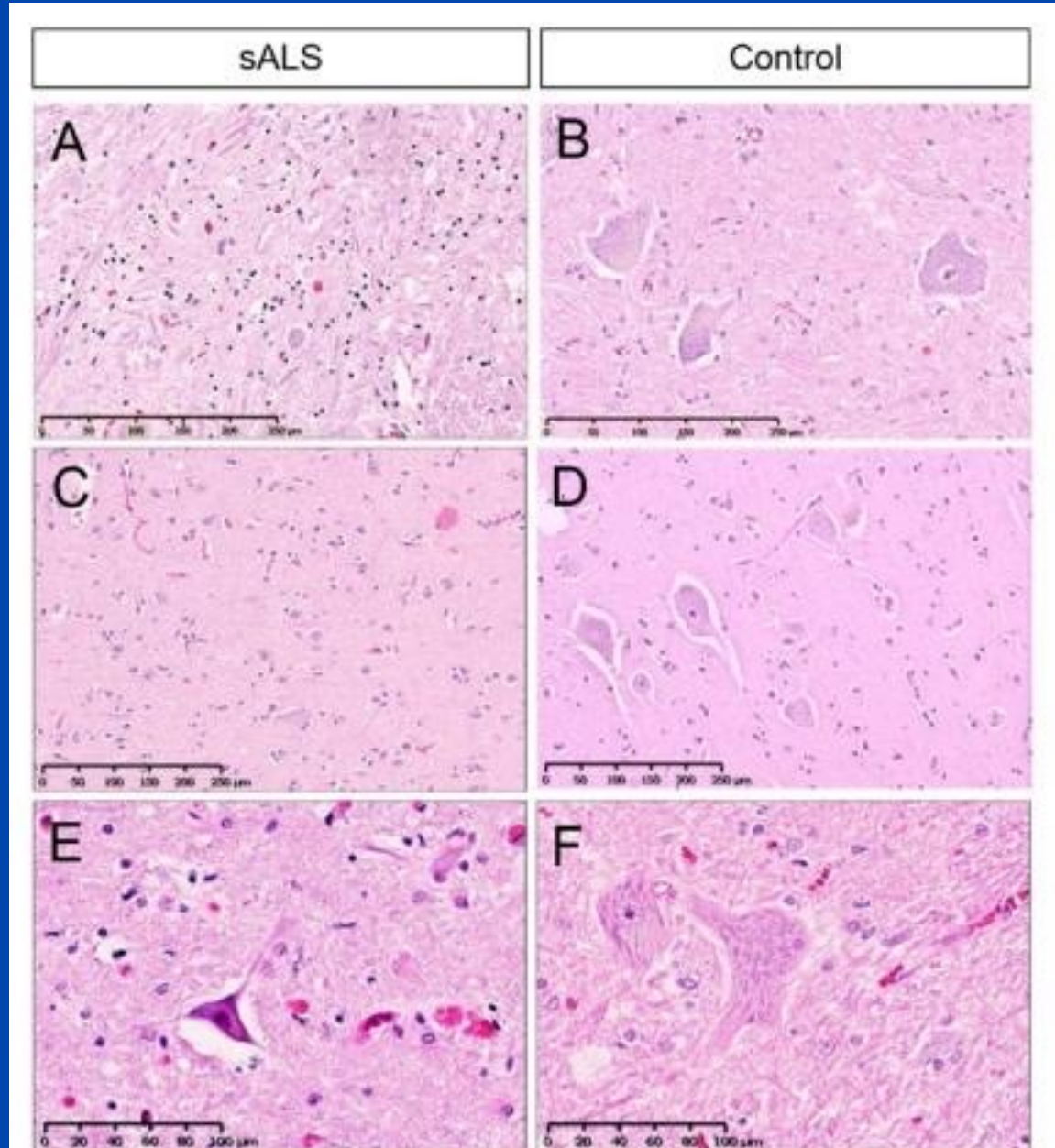
- Lateral sclerosis
- Anterior horn disease



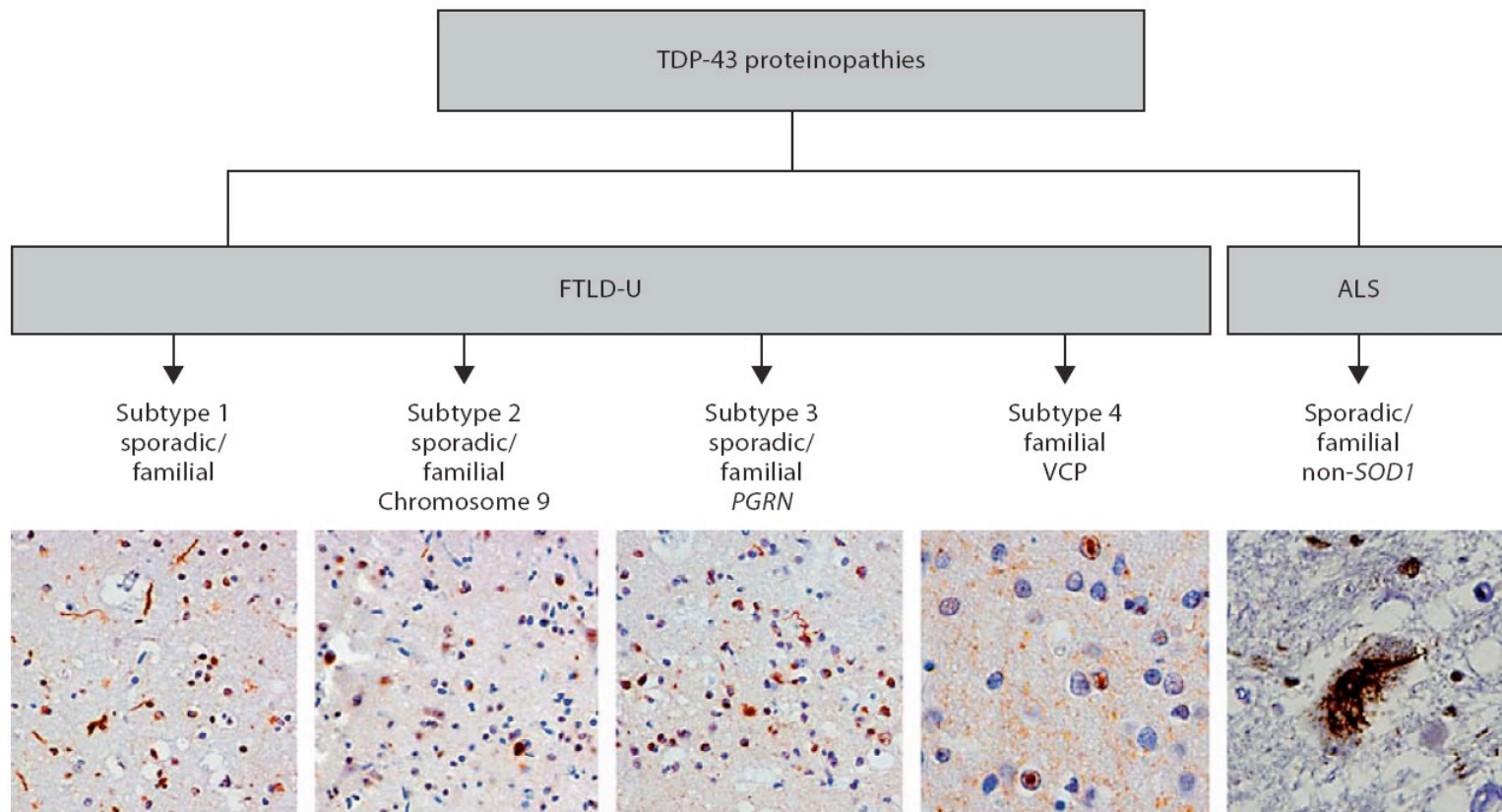
Saberi 2015

# Neuropathology

- Loss of cortical neurons
- Contracted



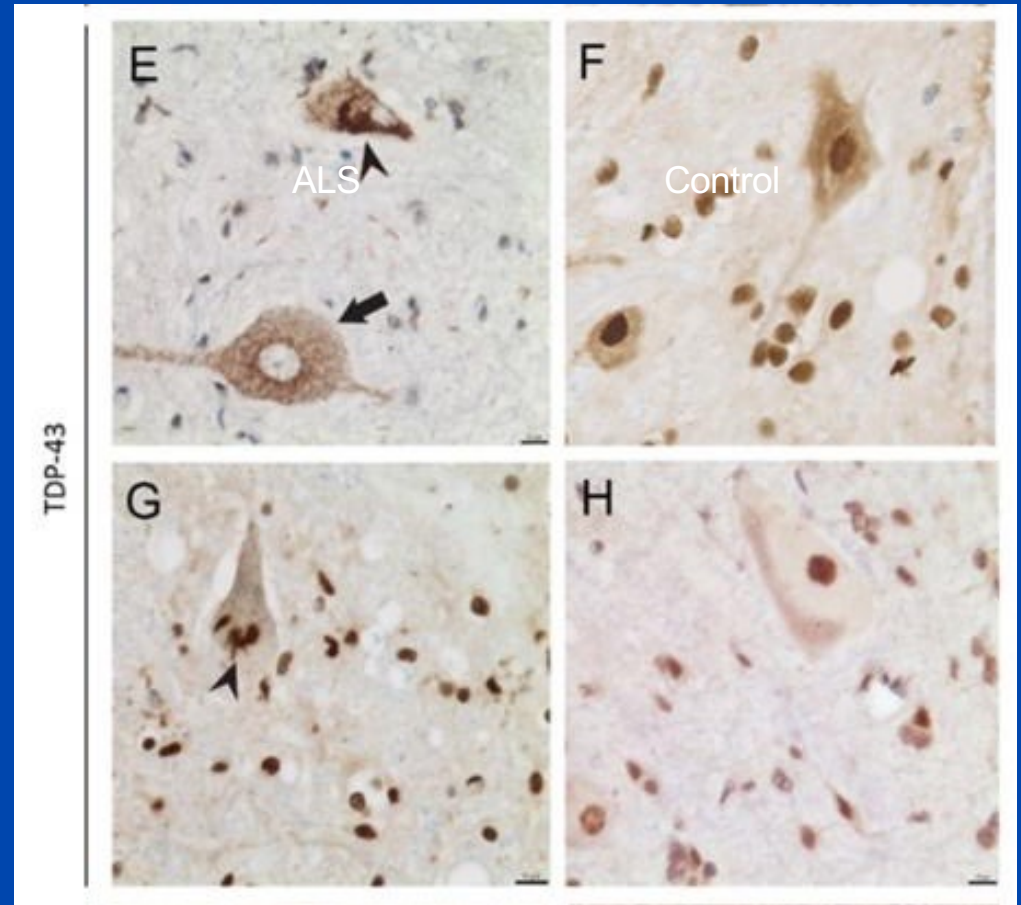
# TDP-43 Proteinopathies



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

# Neuropathology TDP-43

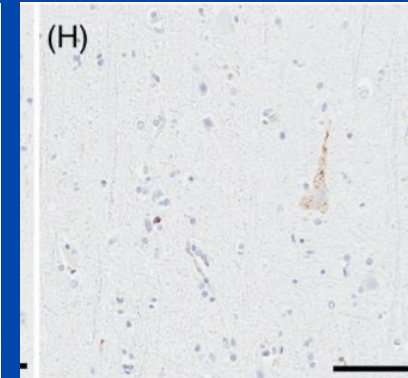
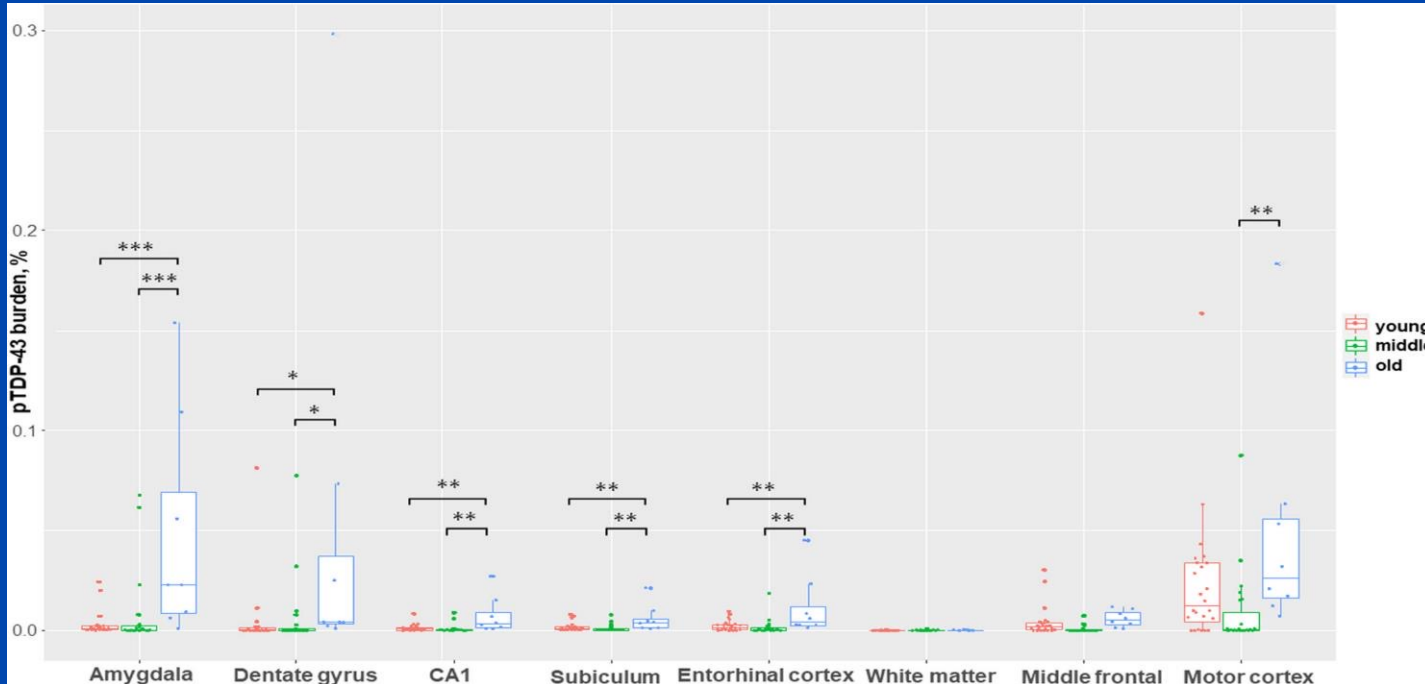
- Ubiquitin-positive inclusions
- Made up largely by TDP-43
- **Nuclear clearing**



Saberi 2015

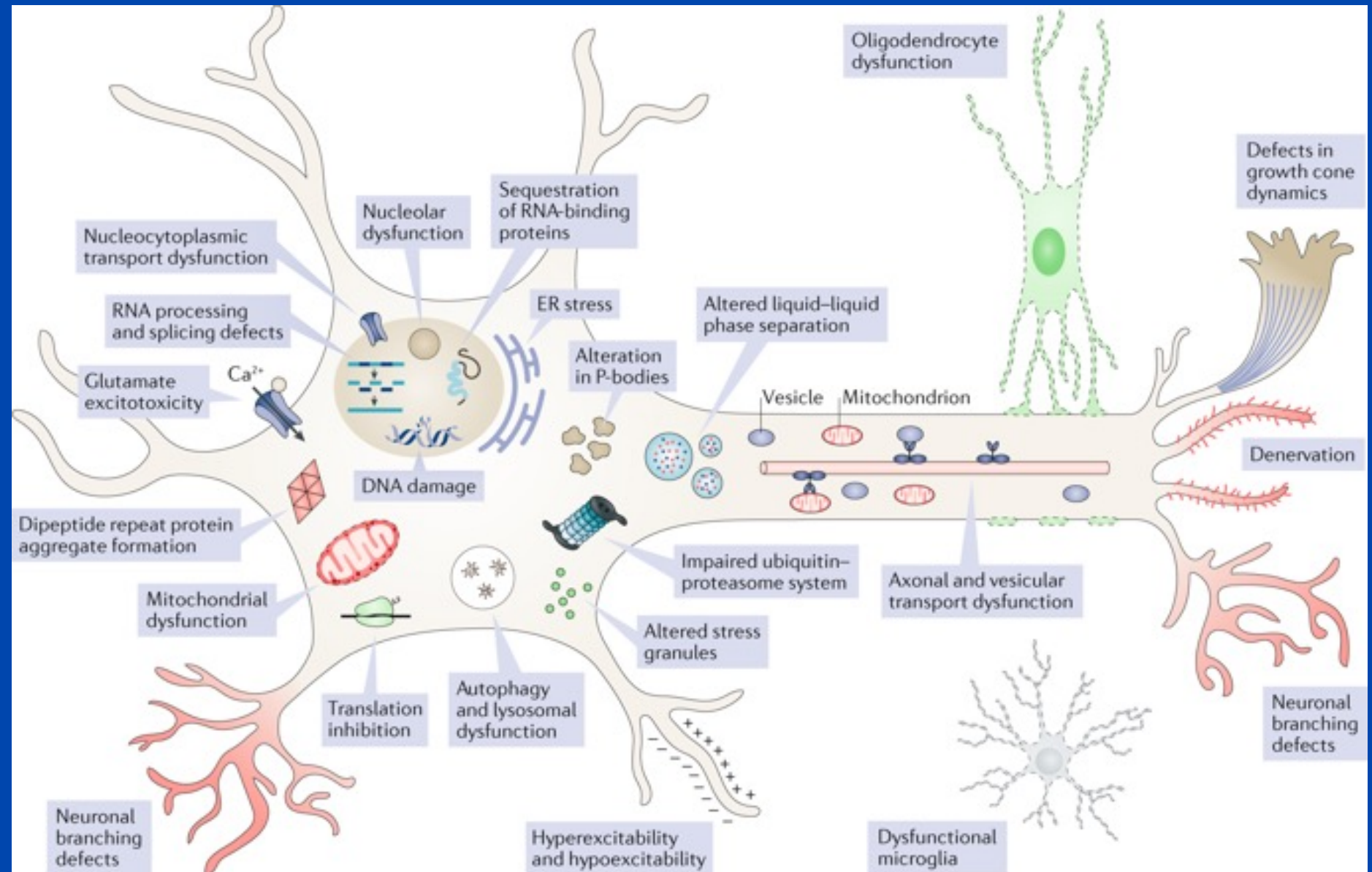


# TDP pathology is sparse in ALS

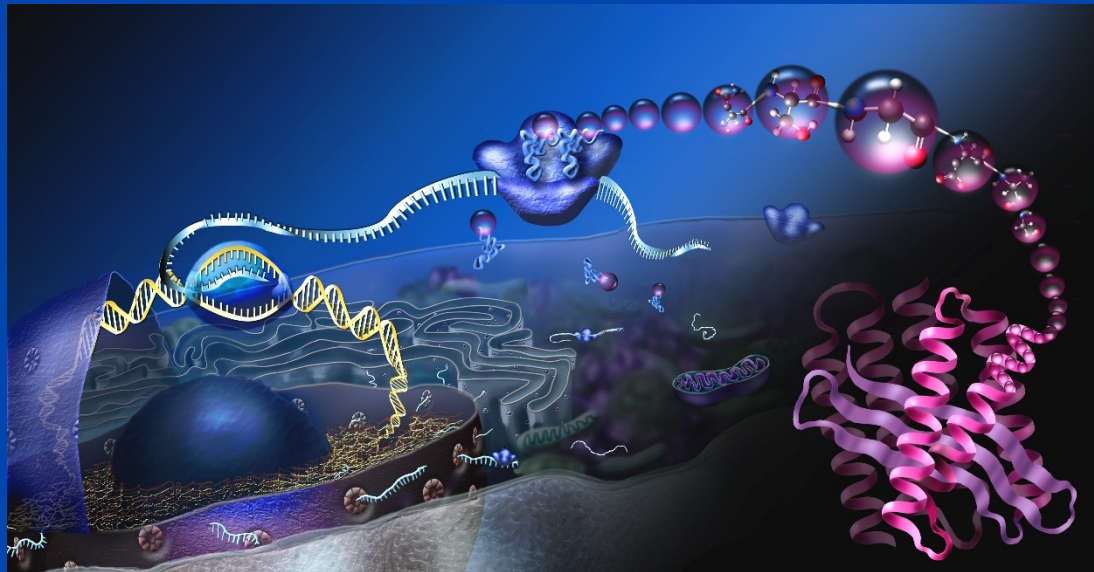
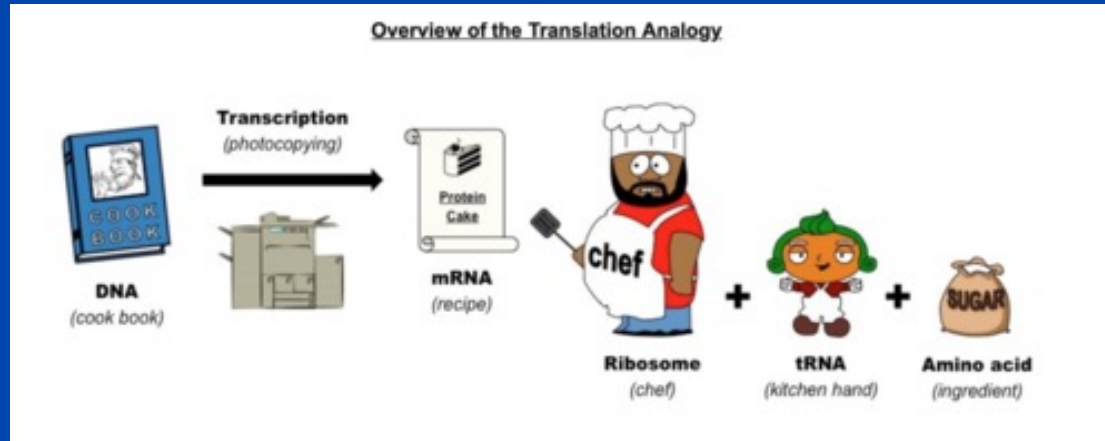


Old age amyotrophic lateral sclerosis and limbic TDP-43 pathology  
Murakami et al Brain Pathology: 17 June 2022, DOI: (10.1111/bpa.13100,

# ALS (C9orf72)



# Central Dogma of Biology

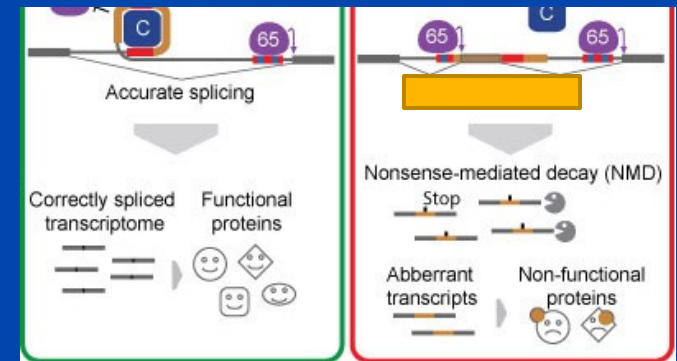


CK-12 Foundation

# The Guardians of the Transcriptome

## TAR DNA binding protein (TDP 43)

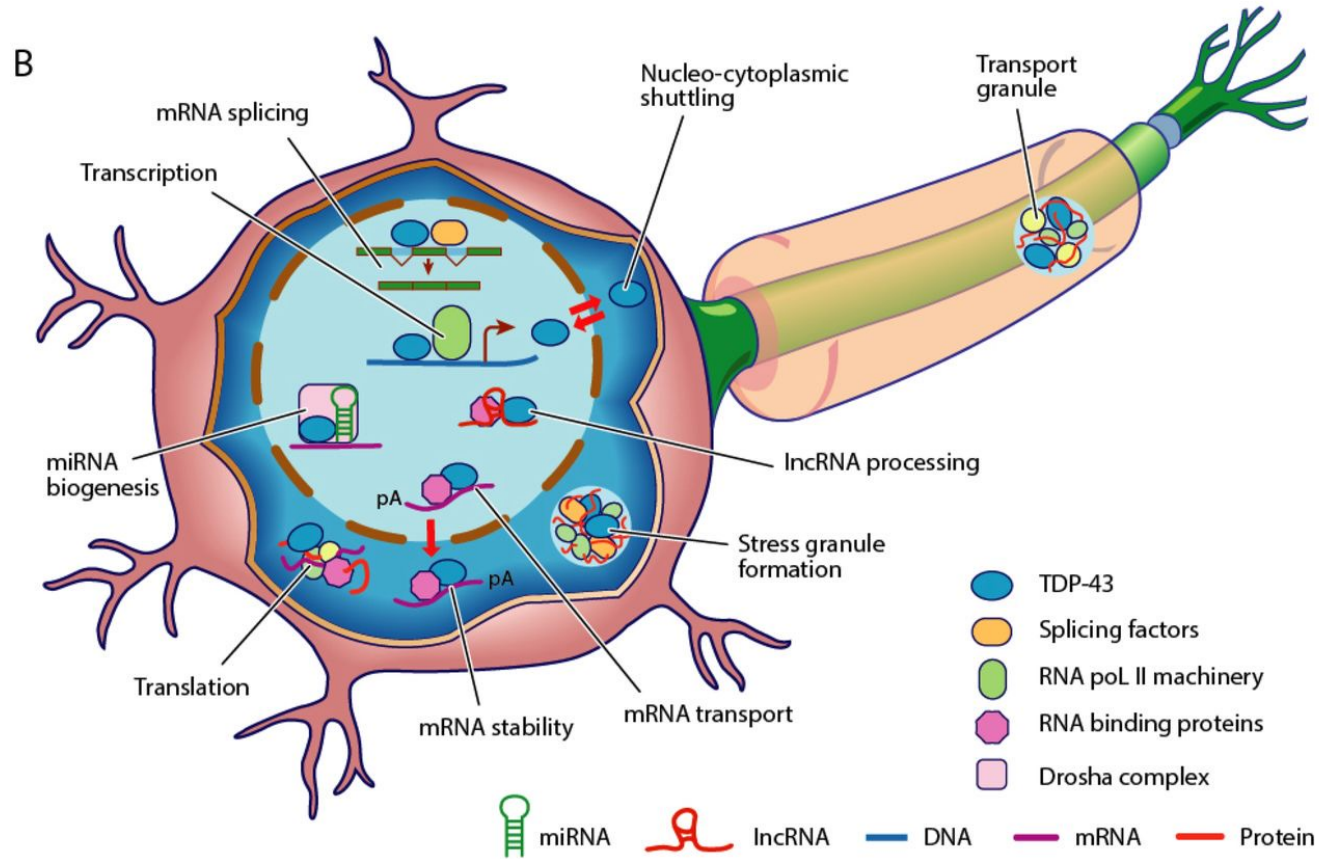
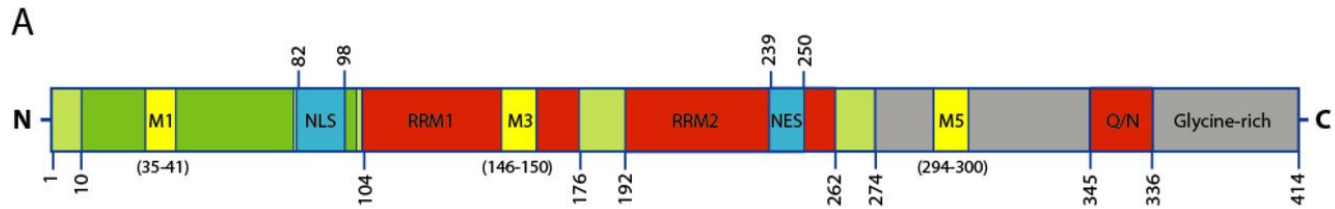
- Major component of ubiquitinated inclusions
- 414-amino-acid nuclear protein
- *TARDBP* gene on chromosome 1
- Highly conserved widely expressed protein



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

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



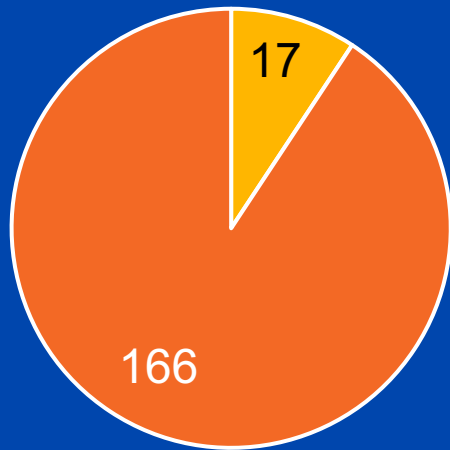
Eva Maria Johanna de Boer et al. *J Neurol Neurosurg Psychiatry* 2021;92:86-95

# Mayo ALS brain bank

- The ALS autopsy program is in its 22<sup>nd</sup> 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.

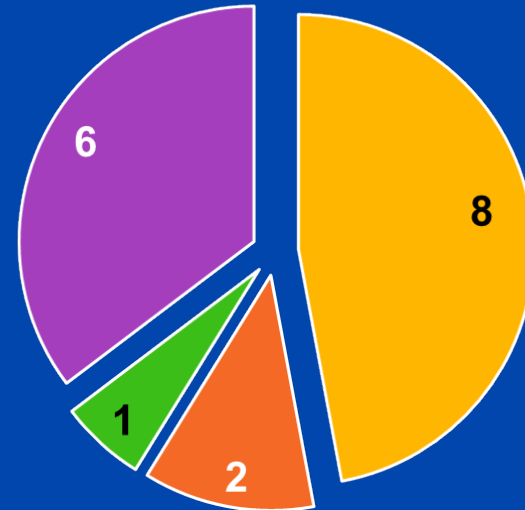
# Genotypes

## Sporadic



■ C9orf72 ■ Not Identified

## Genotypes in Familial ALS



■ SOD1 ■ C9 ■ TARDBP ■ Not Identified

# 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***

Yuka Koike<sup>1,2</sup>, Sarah Pickles<sup>1,2</sup>, Virginia Estades Ayuso<sup>1</sup>, Karen Jansen-West<sup>1</sup>, Yun A. Qi<sup>2</sup>, Ziyi Li<sup>1</sup>, Lillian M. Daugherty<sup>1</sup>, Mei Yue<sup>1</sup>, Yong-ju Zhang<sup>1,2</sup>, Casey N. Cook<sup>1,2</sup>, Dennis W. Dickson<sup>1,2</sup>, Michael Ward<sup>1</sup>, Leonard Petrucelli<sup>1,2,3,4</sup>, Mercedes Prudencio<sup>1,2,4</sup>

<sup>1</sup> Department of Neurosciences, Mayo Clinic, Jacksonville, Florida, United States of America, <sup>2</sup> Mayo Clinic, Oklahoma School of Biomedical Sciences, Jacksonville, Florida, United States of America, <sup>3</sup> Center for Alzheimer's and Related Disorders, National Institute of Aging, NIH, Bethesda, Maryland, United States of America, <sup>4</sup> National Institute of Neurological Disorders and Stroke, NIH, Bethesda, Maryland, United States of America

\* [pickles@mayo.edu](mailto:pickles@mayo.edu) (S.P.); [prudencio@mayo.edu](mailto:prudencio@mayo.edu) (M.P.)

**nature**

Article

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

<https://doi.org/10.1038/s41586-022-04424-7>

Received: 2 April 2021

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Open access

X. Rosa Ma<sup>1,2</sup>, Mercedes Prudencio<sup>3,4</sup>, Yuka Koike<sup>3,5</sup>, Sarat C. Vatsavaya<sup>1,4</sup>, Garam Kim<sup>1,4</sup>, Fred Harbinski<sup>1</sup>, Adam Briner<sup>1,4</sup>, Caitlin M. Rodriguez<sup>1</sup>, Caiwei Guo<sup>1</sup>, Tetsuya Akiyama<sup>1</sup>, H. Broder Schmidt<sup>1</sup>, Beryl B. Cummings<sup>1</sup>, David W. Wyatt<sup>1</sup>, Katherine Kurlyo<sup>1</sup>, Georgiana Miller<sup>1</sup>, Shila Mekhoubad<sup>1</sup>, Nathan Sallee<sup>1</sup>, Gemechu Mekonnen<sup>1,6,7</sup>, Laura Ganser<sup>1</sup>, Jack D. Rubien<sup>1</sup>, Karen Jansen-West<sup>1</sup>, Casey N. Cook<sup>2,3</sup>, Sarah Pickles<sup>2,3</sup>, Björn Oskarsson<sup>1</sup>, Neill R. Graff-Radford<sup>1</sup>, Bradley F. Boeve<sup>1</sup>, David S. Knopman<sup>1</sup>, Ronald C. Petersen<sup>1</sup>, Dennis W. Dickson<sup>1,2</sup>, James Shorter<sup>1,2</sup>, Sui Myong<sup>10,11</sup>, Eric M. Green<sup>1</sup>, William W. Seeley<sup>1,4</sup>, Leonard Petrucelli<sup>1,2,3,4</sup> & Aaron D. Gitler<sup>1,2</sup>

**frontiers**  
in Cell and Developmental Biology

ORIGINAL RESEARCH  
published: 13 January 2022  
doi: 10.3389/fncel.2021.830642

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

Giulia del Rosso<sup>1,2†</sup>, Yari Carlomagno<sup>1,2†</sup>, Tiffany W. Todd<sup>1</sup>, Caroline V. Jones<sup>1</sup>, Mercedes Prudencio<sup>1,2</sup>, Lillian M. Daugherty<sup>1</sup>, Mei Yue<sup>1</sup>, Karen Jansen-West<sup>1</sup>, Jimei Tong<sup>1</sup>, Wei Shao<sup>1</sup>, Yanwei Wu<sup>1</sup>, Morica Castaneda-Casey<sup>1</sup>, Lilla Tabassian<sup>1</sup>, Björn Oskarsson<sup>1</sup>, Karen Ling<sup>1</sup>, Frank Rigo<sup>1</sup>, Dennis W. Dickson<sup>1,2</sup>, Tso-Pang Yao<sup>1</sup>, Leonard Petrucelli<sup>1,2</sup>, Casey N. Cook<sup>1,2</sup> and Yong-ju Zhang<sup>1,2</sup>

OPEN ACCESS

RESEARCH ARTICLE

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

Axel D. Meneses, BS,<sup>1,2</sup> Shunsuke Koga, MD, PhD,<sup>1</sup> Zonghua Li, PhD,<sup>1</sup> Justin O'Leary, BS,<sup>1</sup> Fuyao Li, BS,<sup>1</sup> Kai Chen, MS,<sup>1</sup> Aya Murakami, MD, PhD,<sup>1</sup> Wenhui Qiao, PhD,<sup>1</sup> Ashu Kuri, BS,<sup>1</sup> Michael G. Heckman, MS,<sup>1</sup> Lounia White, BS,<sup>1</sup> Marling Xie, PhD,<sup>1</sup> Yixing Chen, BS,<sup>1</sup> Nicole A. Finch, MS,<sup>1</sup> Melina J. Lim, BS,<sup>1</sup> Marion Delenclos, PhD,<sup>1</sup> Michael A. DeTure, PhD,<sup>1</sup> Cynthia Linares, BS,<sup>1</sup> Nicholas B. Martin, BS,<sup>1</sup> Tadafumi C. Ikezu, MS,<sup>1</sup> Marka M. van Blitterswijk, MD, PhD,<sup>1</sup> Long Jun Wu, PhD,<sup>1,4</sup> Pamela J. McLean, PhD,<sup>1,3</sup> Rosa Rademakers, PhD,<sup>1,4</sup> Owen A. Ross, PhD,<sup>1,3</sup> Dennis W. Dickson, MD,<sup>1,3</sup> Guojun Bu, PhD,<sup>1,3</sup> and Na Zhang, MD, PhD,<sup>1,3</sup>

Pickles et al.  
*Acta Neuropathologica Communications* (2022) 10:107  
<https://doi.org/10.1186/s40478-022-01408-6>

Acta Neuropathologica Communications

RESEARCH Open Access

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

Sarah Pickles<sup>1,2†</sup>, Tania F. Gendron<sup>1,2†</sup>, Yuka Koike<sup>1,2</sup>, Mei Yue<sup>1</sup>, Yuping Song<sup>1</sup>, Jennifer M. Kachergus<sup>3</sup>, J. Shi<sup>3</sup>, Michael DeTure<sup>1,2</sup>, E. Aubrey Thompson<sup>3</sup>, Björn Oskarsson<sup>1</sup>, Neill R. Graff-Radford<sup>1</sup>, Bradley F. Boeve<sup>5</sup>, Ronald C. Petersen<sup>5</sup>, Zbigniew K. Wszolek<sup>4</sup>, Keith A. Josephs<sup>5</sup>, Dennis W. Dickson<sup>1,2</sup>, Leonard Petrucelli<sup>1,2</sup>, Casey N. Cook<sup>1,2†</sup> and Mercedes Prudencio<sup>1,2</sup>

ARTICLES  
<https://doi.org/10.3389/fncel.2021.80975-6>

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

Manling Xie<sup>1,2,3</sup>, Yong U. Liu<sup>4,5,6,7,8</sup>, Shunyi Zhao<sup>1</sup>, Lingxin Zhang<sup>1</sup>, Dale B. Bosco<sup>1</sup>, Yuan-Ping Wang<sup>9</sup>, Jun Zhong<sup>10</sup>, Udit Sheth<sup>11</sup>, Yuka A. Martens<sup>12</sup>, Na Zhao<sup>13</sup>, Chia-Chen Liu<sup>14</sup>, Yongxian Zhuang<sup>1</sup>, Liewei Wang<sup>15</sup>, Dennis W. Dickson<sup>16</sup>, Mark P. Mattson<sup>17</sup>, Guojun Bu<sup>18</sup> and Long-Jun Wu<sup>19,20</sup>

*Acta Neuropathologica* (2023) 145:159–173  
<https://doi.org/10.1007/s00401-022-02324-2>

ORIGINAL PAPER

**LATE-NC staging in routine neuropathologic diagnosis: an update**

Peter T. Nelson<sup>1</sup>, Edward B. Lee<sup>2</sup>, Matthew D. Cykowski<sup>3</sup>, Irina Alafuzoff<sup>4</sup>, Konstantinos Arfanakis<sup>5,6</sup>, Johannes Attems<sup>7</sup>, Carol Brayne<sup>8</sup>, María M. Corrada<sup>9</sup>, Brittany N. Dugger<sup>10</sup>, Margaret E. Flanagan<sup>11</sup>, Bernardino Ghetti<sup>12</sup>, Lea T. Grinberg<sup>13</sup>, Murray Grossman<sup>14</sup>, Michel J. Groth<sup>15</sup>, Glenda M. Halliday<sup>16</sup>, Masato Hasegawa<sup>17</sup>, Suvi R. K. Hoque<sup>18</sup>, Sally Hunter<sup>19</sup>, Kurt Jellinger<sup>20</sup>, Claudia H. Kawas<sup>21</sup>, C. Dirk Keene<sup>22</sup>, Naomi Kouri<sup>23</sup>, Galor G. Kovacs<sup>24,25,26</sup>, James B. Leverenz<sup>27</sup>, Caitlin S. Latimer<sup>28</sup>, Jan B. Mackenzie<sup>29</sup>, Qinwen Mao<sup>30</sup>, Kirsty E. McAleese<sup>31</sup>, Richard Merrick<sup>32</sup>, Thomas J. Montine<sup>33</sup>, Melissa E. Murray<sup>34</sup>, Liisa Myllykangas<sup>35</sup>, Sukruti Nag<sup>36</sup>, Jaana H. Nelmer<sup>37</sup>, Kathy L. Newell<sup>38</sup>, Robert A. Risman<sup>39</sup>, Yuko Saito<sup>40</sup>, S. Ahmad Sajjadi<sup>41</sup>, Katharine E. Schwetty<sup>42</sup>, Andrew F. Tack<sup>43</sup>, Dietmar B. Thal<sup>44,45</sup>, Sandra O. Tomiyama<sup>46</sup>, Juan C. Troncoso<sup>47</sup>, Shih-Hsiu J. Wang<sup>48</sup>, Charles L. White III<sup>49</sup>, Thomas Wisniewski<sup>50</sup>, Hyun-Sik Yang<sup>51</sup>, Julie A. Schneider<sup>52</sup>, Dennis W. Dickson<sup>53</sup>, and Manuela Neumann<sup>54</sup>

Received: 27 March 2022 | Accepted: 1 June 2022  
DOI: 10.1111/apa.13100

RESEARCH ARTICLE

**Old age amyotrophic lateral sclerosis and limbic TDP-43 pathology**

Aya Murakami<sup>1</sup> | Shunsuke Koga<sup>1</sup> | Hiroaki Sekiya<sup>1</sup> | Björn Oskarsson<sup>2</sup> | Kevin Boylan<sup>2</sup> | Leonard Petrucelli<sup>1</sup> | Keith A. Josephs<sup>3</sup> | Dennis W. Dickson<sup>1</sup>

Khalil et al. *Molecular Neurodegeneration* (2022) 17:80  
<https://doi.org/10.1186/s13024-022-00585-1>

Molecular Neurodegeneration

RESEARCH ARTICLE Open Access

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

Bilal Khalil<sup>1</sup>, Deepak Chhangani<sup>2†</sup>, Melissa C. Wren<sup>1</sup>, Courtney L. Smith<sup>1,3</sup>, Jennifer H. Lee<sup>1,3</sup>, Xingli Li<sup>4</sup>, Christian Putinger<sup>1</sup>, Chh-Wei Tsai<sup>1</sup>, Gael Fortin<sup>1</sup>, Dmytro Mordere<sup>1</sup>, Junli Gao<sup>1</sup>, Felix Liu<sup>1</sup>, Chun Kim Lim<sup>5</sup>, Jingliao Chen<sup>6</sup>, Ching-Chieh Chou<sup>7</sup>, Cara L. Craft<sup>8,9</sup>, Amanda M. Gleeson<sup>10,11</sup>, Christopher J. Donnelly<sup>11</sup>, Todd E. Golde<sup>12</sup>, Leonard Petrucelli<sup>13</sup>, Björn Oskarsson<sup>14</sup>, Dennis W. Dickson<sup>15</sup>, Ke Zhang<sup>16</sup>, James Shorter<sup>17</sup>, Shige H. Yoshimura<sup>18</sup>, Sami J. Barmada<sup>19</sup>, Diego E. Rincon-Limas<sup>20,21</sup> and Wilfried Rossoll<sup>11</sup>



# 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

# Acknowledgements

- Our patients
- Our families
- Brain bank
  - Dennis Dickson, MD
  - Luc Pregent
- Clinic Team
  - Jamie Zernicke, RN
  - Jennifer Reidell, RSW
  - Angelica Gicalone, OT
  - Gleydiane De Oliveira, PT
  - Sara Reising, ST
  - Melissa Stewart, RD
  - Molly Kilpatrick, MD
  - Beth Rush, PhD
- Neuromuscular group
  - Jaimin Shah, MD
  - Devon Rubin, MD
  - Elliot Dimberg, MD
  - Elizabeth Mauricio, MD
  - Chris Lamb, MD
- Clinical Research team
  - Megan Donahue, PM, CCRC
  - Lisa Thuro, CCRC
  - Jany Paulet, MD, CCRC
  - Alex Burch, CCRC
  - Colette McHugh-Strong, JD, CCRC
  - Brittney Mullins, MS, ACRC
  - Huy Tran, ACRC
- Basic research
  - Len Petrucelli, PhD
  - Rosa Rademakers, PhD
  - Tania Gendron, PhD
  - Marka van Blitterswijk, MD, PhD
  - Veronique Belzil, PhD
  - Wilfried Rossoll, PhD
  - John Fryer, PhD
  - Yong-Jie Zhang, PhD
- Funding
  - ALSA
  - State of Florida
  - MDA



Still point in blue Sandra Murphy Pak 2018