MDA® ENGAGE

2023 Care and Research Symposium

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Dept. of Neurology Columbia University

Columbia University College of Physicians and Surgeons | IGM Institute for Genomic Medicine | Gertrude H. Sergievsky Center at CUMC | Motor Neuron Center

Introductions

Medical school mistake

Neuromuscular Fellowship Redemption

Faculty Good Fortune

Columbia ALS Center

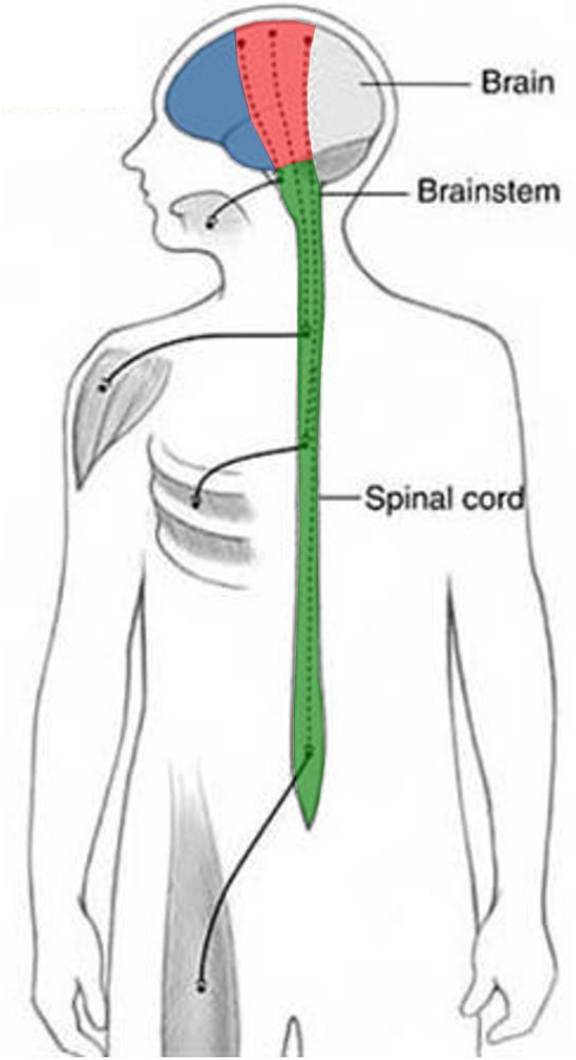
Spinal Muscular Atrophy Clinic

Peds and Adult MDA Care Center

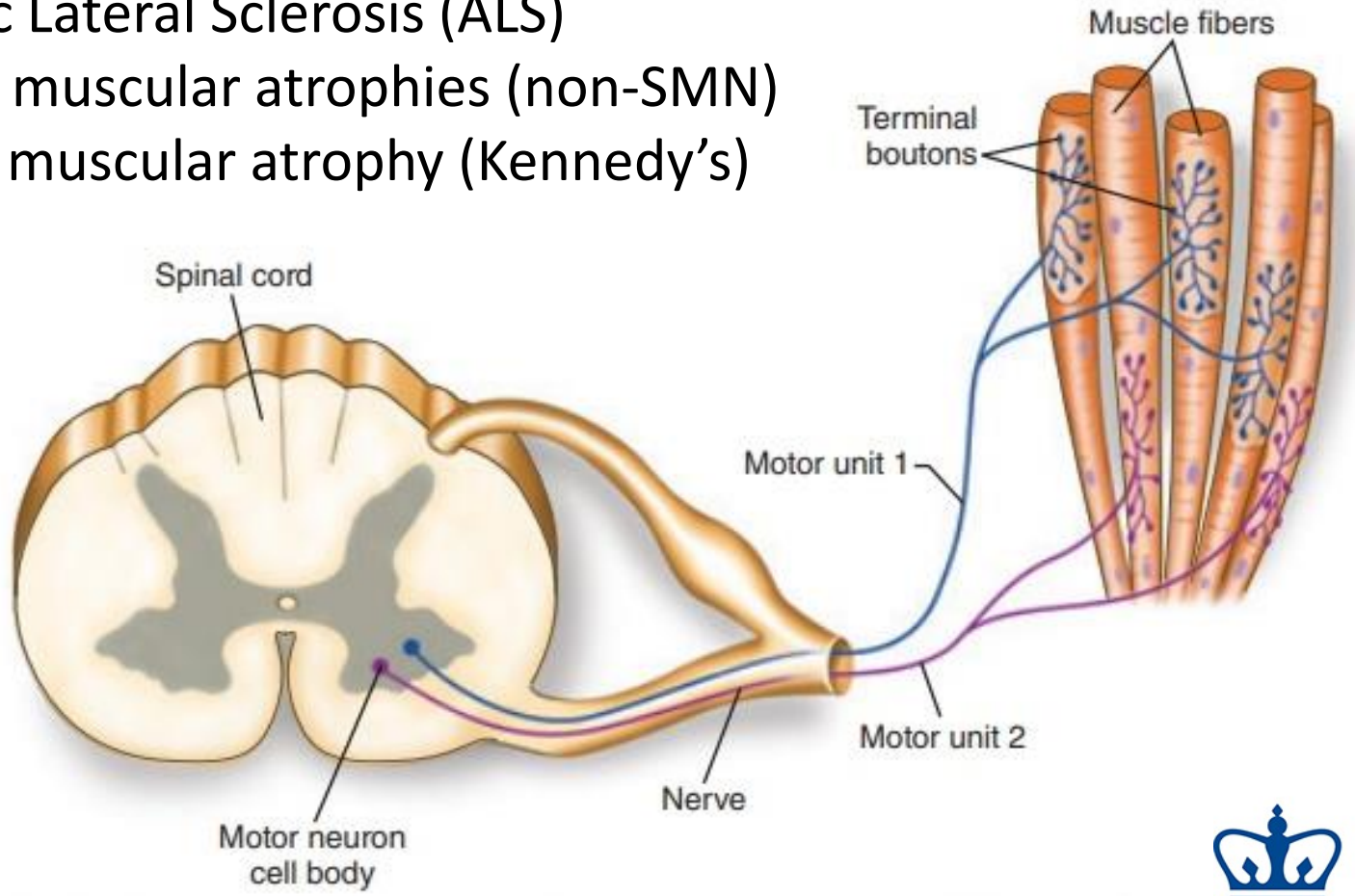
Introductions

- MDA
  - Strategic medical advisory team
- Big Tent Advantages
  - Common voice for advocacy
  - Overlapping clinical needs and clinical expertise
  - Shared disease mechanisms
  - Research in one benefits many
    - Learn more by breaking down silos
    - Therapy developments especially

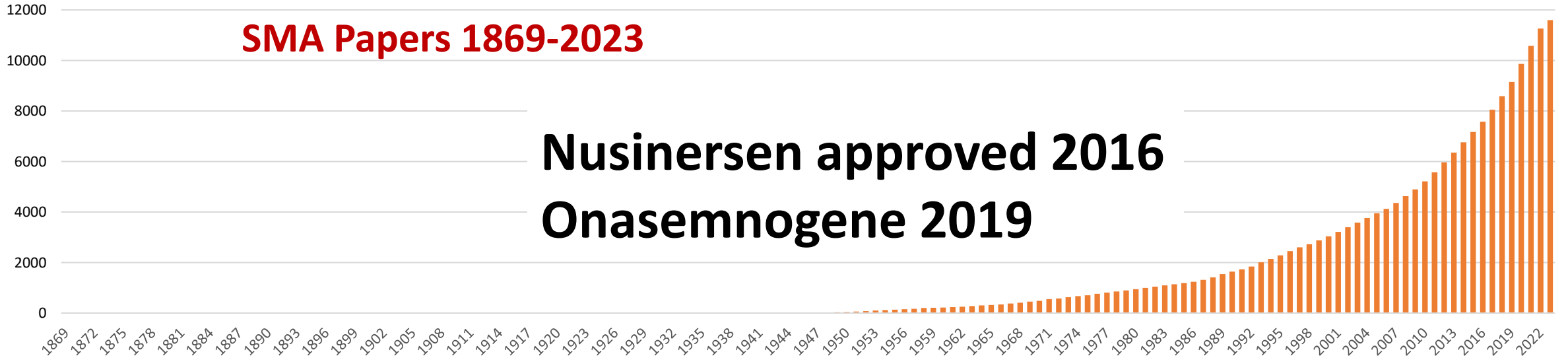
Motor Neurons



- Spinal muscular atrophy (SMN)
- Amyotrophic Lateral Sclerosis (ALS)
- Other spinal muscular atrophies (non-SMN)
- Spinobulbar muscular atrophy (Kennedy's)

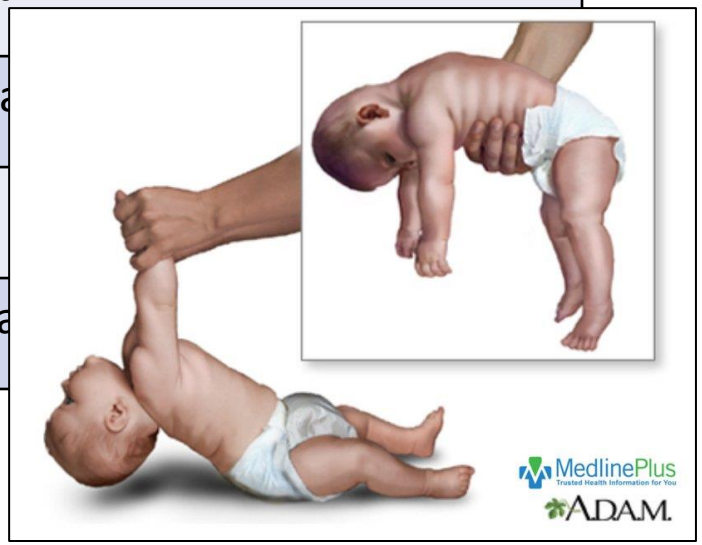


Research Progress for ALS and SMA



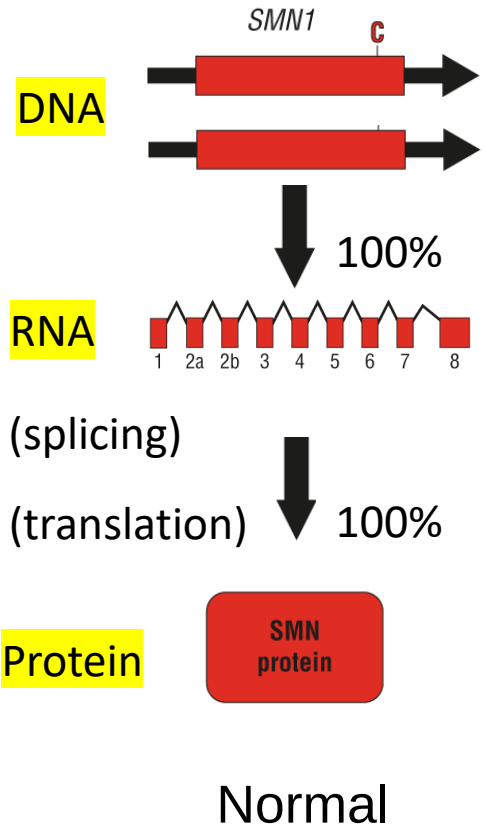
Spinal Muscular Atrophy

Type	Historical Name	Age of Onset	Maximal Function
0	Fetal	In utero	No movement
I	Werdnig-Hoffman	0-6 mo	Never sit
II	Intermediate	7-18 mo	Never sta
III	Kugelberg-Welander	>18 mo	Walk
IV	Adult	Teens + above	Walk una



Shared genetic cause: Missing or defective SMN1 gene

Spinal Muscular Atrophy

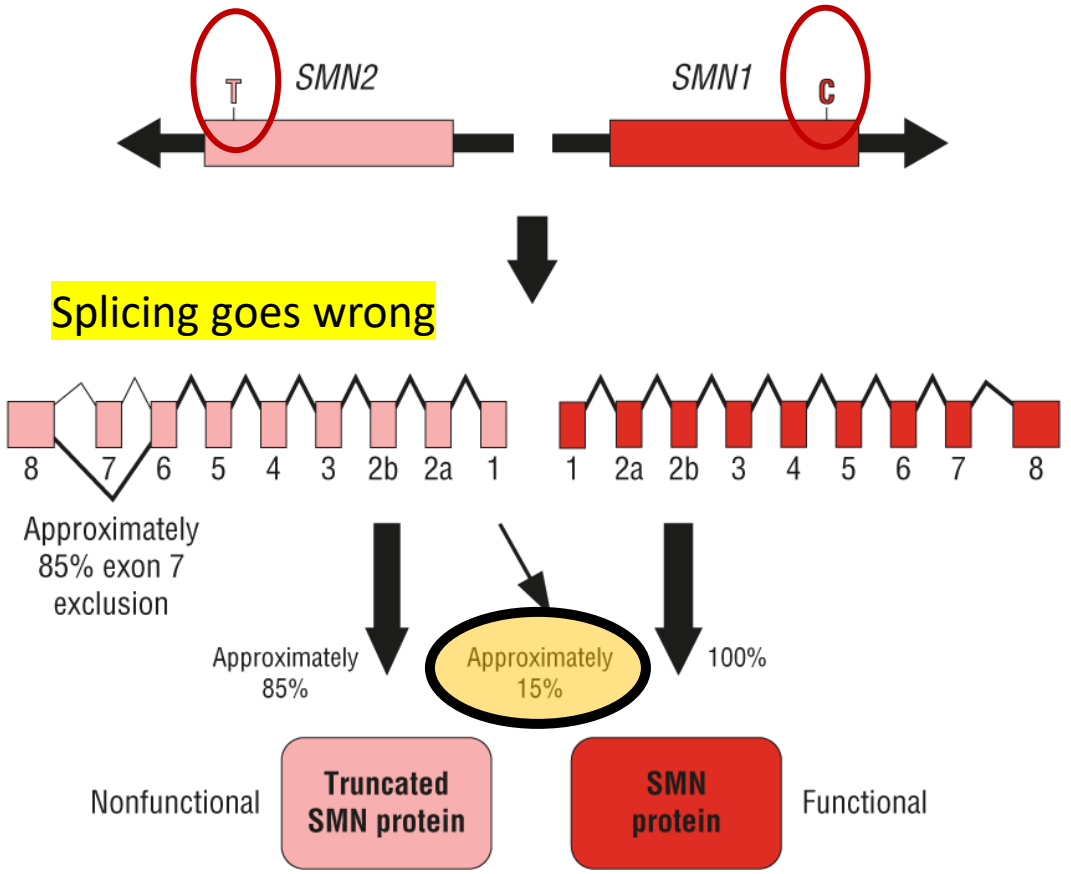


Normal

Arch Neurol. 2011;68(8):979-984. doi:10.1001/archneurol.2011.74

Spinal Muscular Atrophy

Type	Copies of SMN2
0	1
I	2
II	>2
III	≥3
IV	≥3



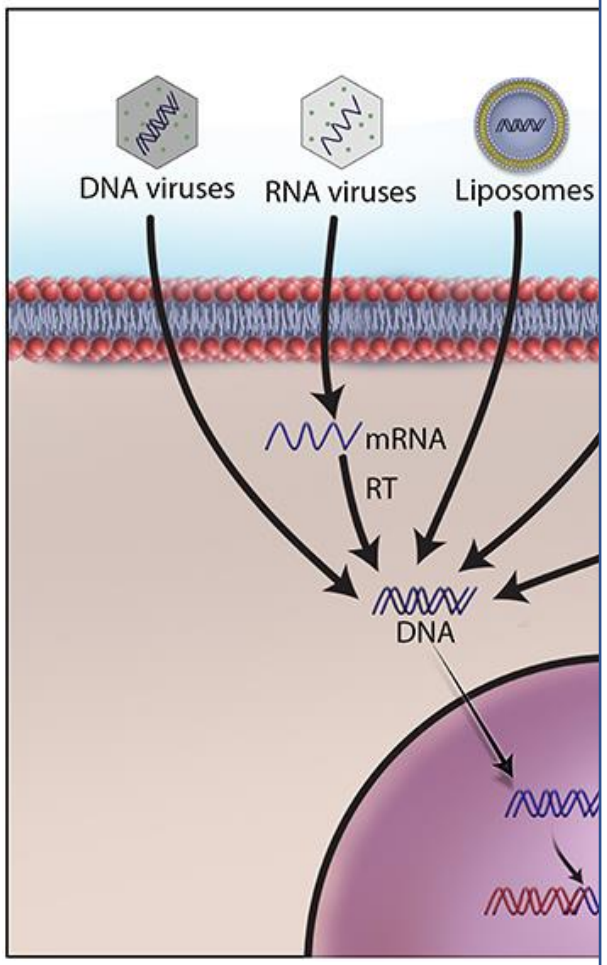
Onasemnogene/Zolgensma

Drive *SMN2* expression

Nusinersen/Spinraza
Risdiplam/Evrysdi

Arch Neurol. 2011;68(8):979-984. doi:10.1001/archneurol.2011.74

Gene Therapy



Goswami et al., Frontiers in On[illegible]

Gene Therapy 101

MDA®
COMMUNITY EDUCATION

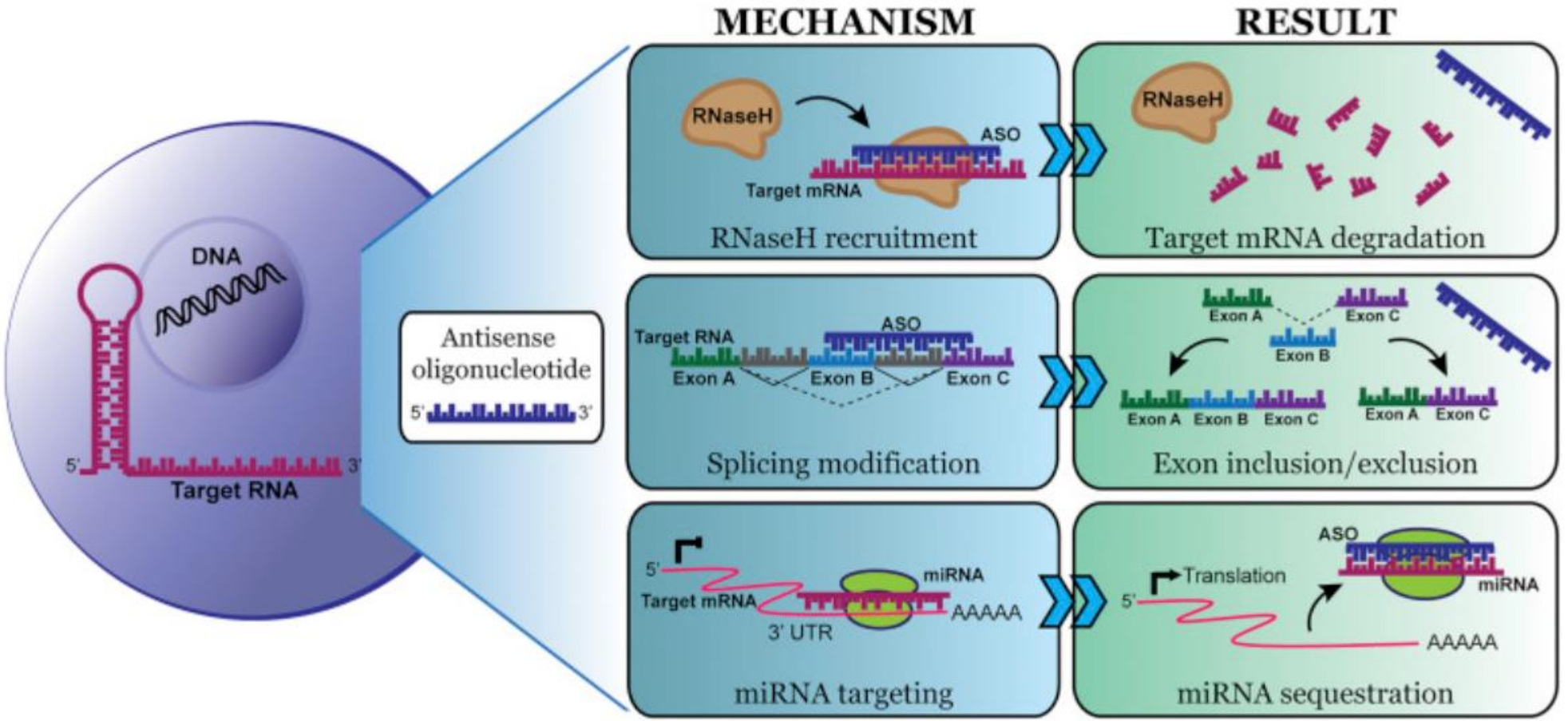
Presenters:
Natalie Goedeker, CPNP
Craig Zaidman, MD
Washington University in St. Louis

Thursday, June 15, 2023
4:00-5:30pm EST
Also available in Spanish

against virus
e given once generally
nune responses when given
anufacture large quantities
some cell types
old deliver small genes
gulate the amount made

ses:
muscular dystrophy
yotubular myopathy
e muscular dystrophy

Anti-sense Oligonucleotides (ASO's)



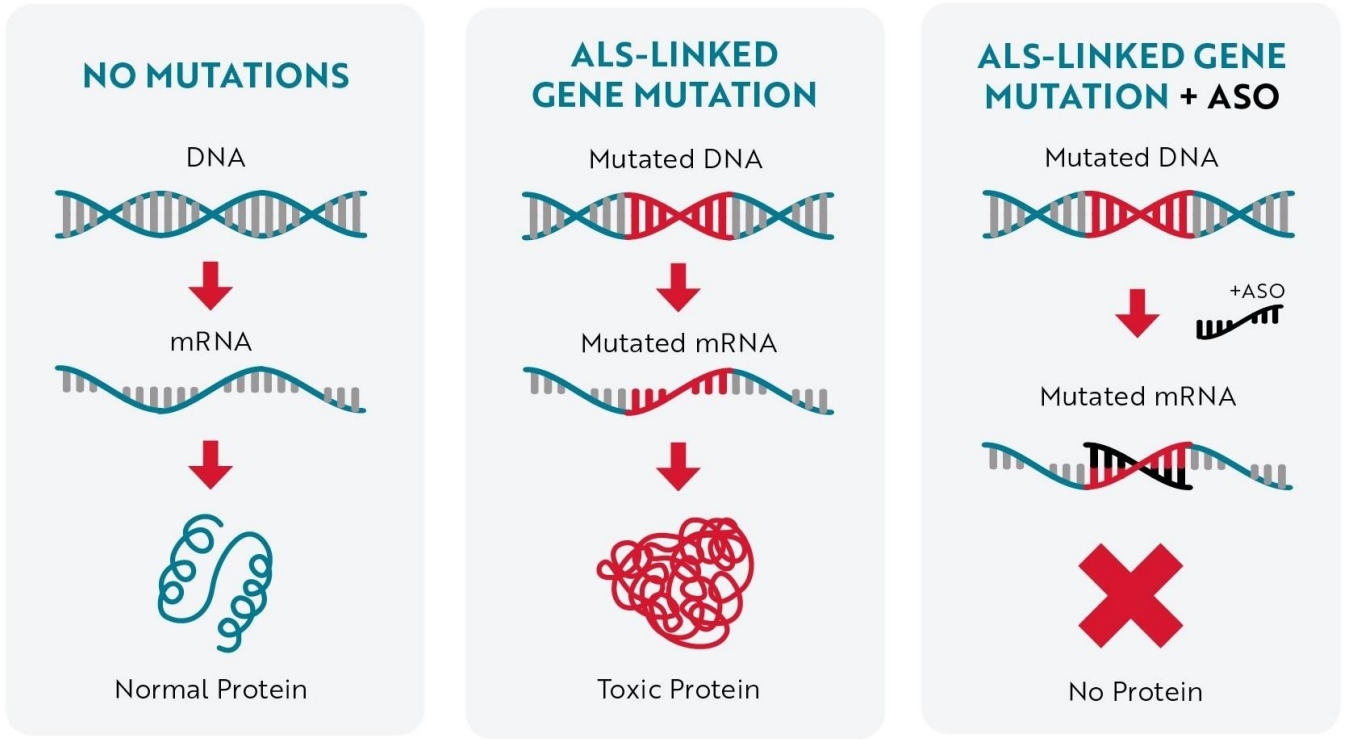
ALS

SMA

Duchenne

ALS Treatment in 2023

- Accelerated approval for ALS due to *SOD1* mutations
  - Tofersen (Qalsody): intrathecal injection



Lessons from Nusinersen

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

Amyotrophic Lateral Sclerosis

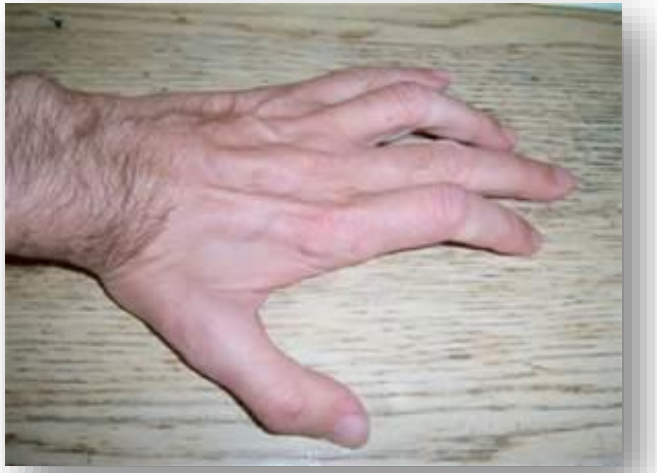
LOU GEHRIG DAY

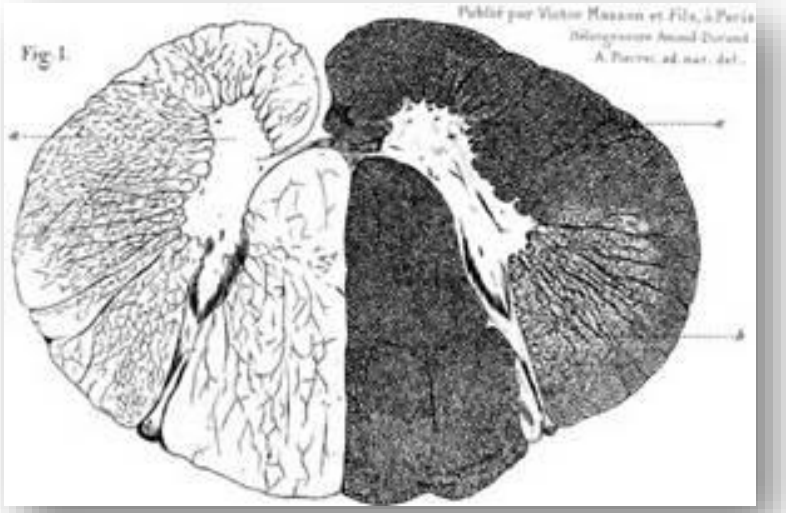
JUNE 2, 2021

4·ALS

Amyotrophic Lateral Sclerosis

- Late 19th Century
  - Description based on clinical features and pathological findings
- Amyotrophy:
  - The visible wasting of muscles
- Lateral Sclerosis:
  - Seen on pathology





Constellation of ALS Symptoms

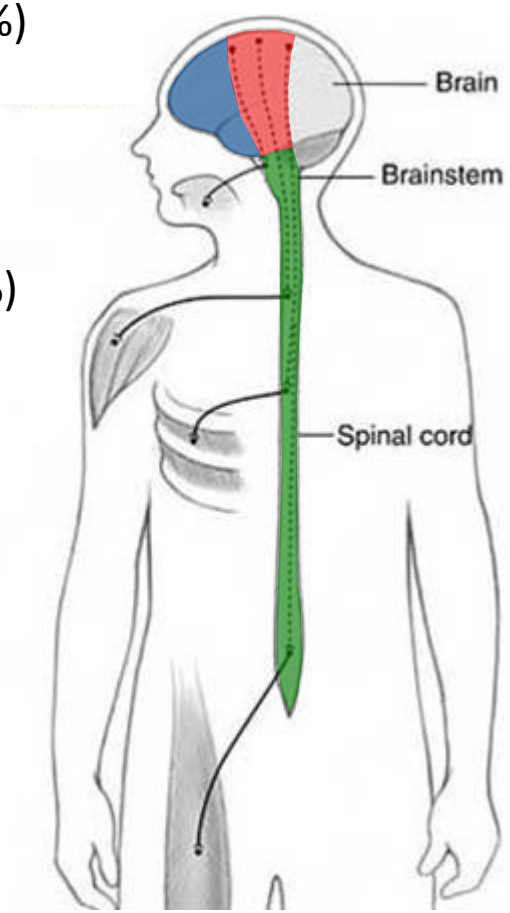
Generalized (5%)

Bulbar (25%)

Respiratory (4%)

Arms (33%)

Legs (33%)



- Progressive neuronal degeneration
  - Upper motor neurons (UMN)
    - Pseudobulbar affect
    - Spasticity
    - Hyper-reflexia
  - Lower motor neurons (LMN)
    - Fasciculations
    - Weakness
    - Atrophy
  - Non-motor neurons
    - Cortical: Executive dysfunction
    - Dorsal root ganglia: numbness
    - Basal ganglia: movement disorders

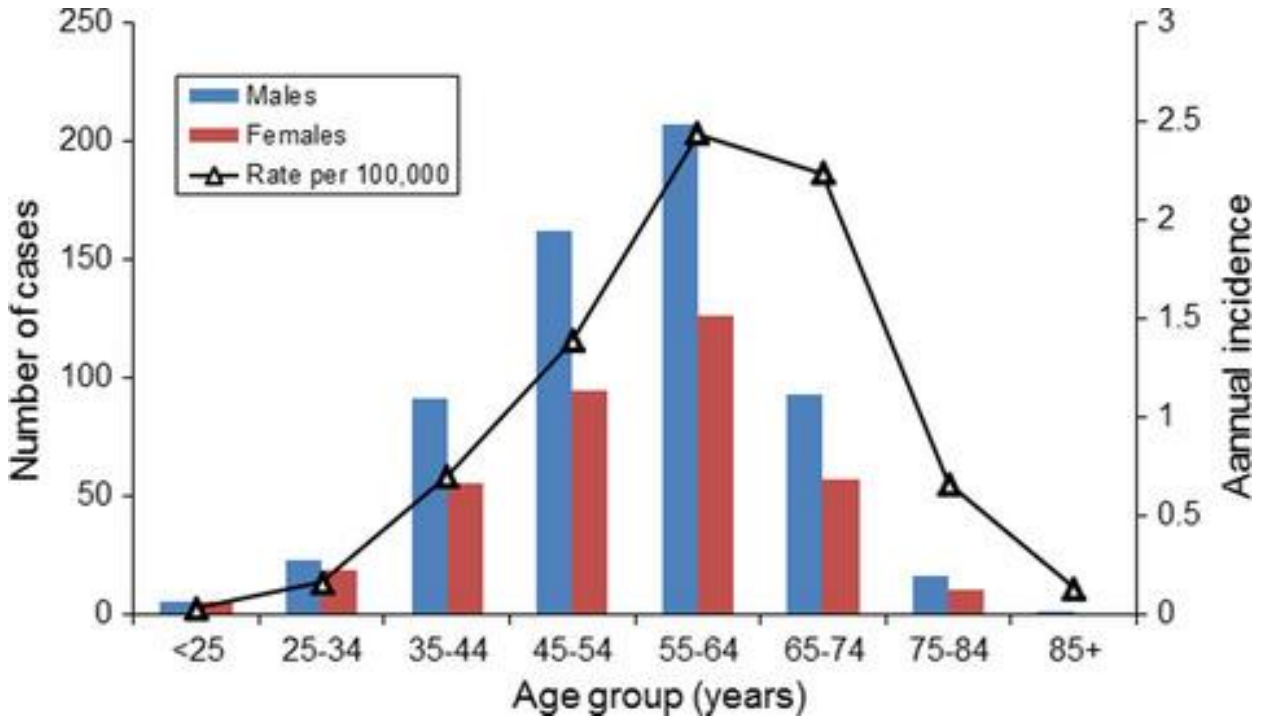
PLS (5%)

PMA (10%)

FTD (7%)

ALS

- A common rare disease:
  - White males: 1 in 372
  - NY Metro: 1,000
  - World: 300,000



Zhou et al Brain Behav 2018 8(11)

- 10% have family history
- 90% do not
- 15% have identifiable gene mutations

ALS Gene Discovery

Definitive Gene Contribution in 5,600 PALS (European)

Gene	Proportion
All Genes	11.4%
C9ORF72	8%
Non-C9	3.4%
SOD1	1.3%
TARDBP	0.5%
TBK1	0.4%
NEK1	0.3%
FUS	0.3%
ATXN2	0.3%

WVE-004

Tofersen approved

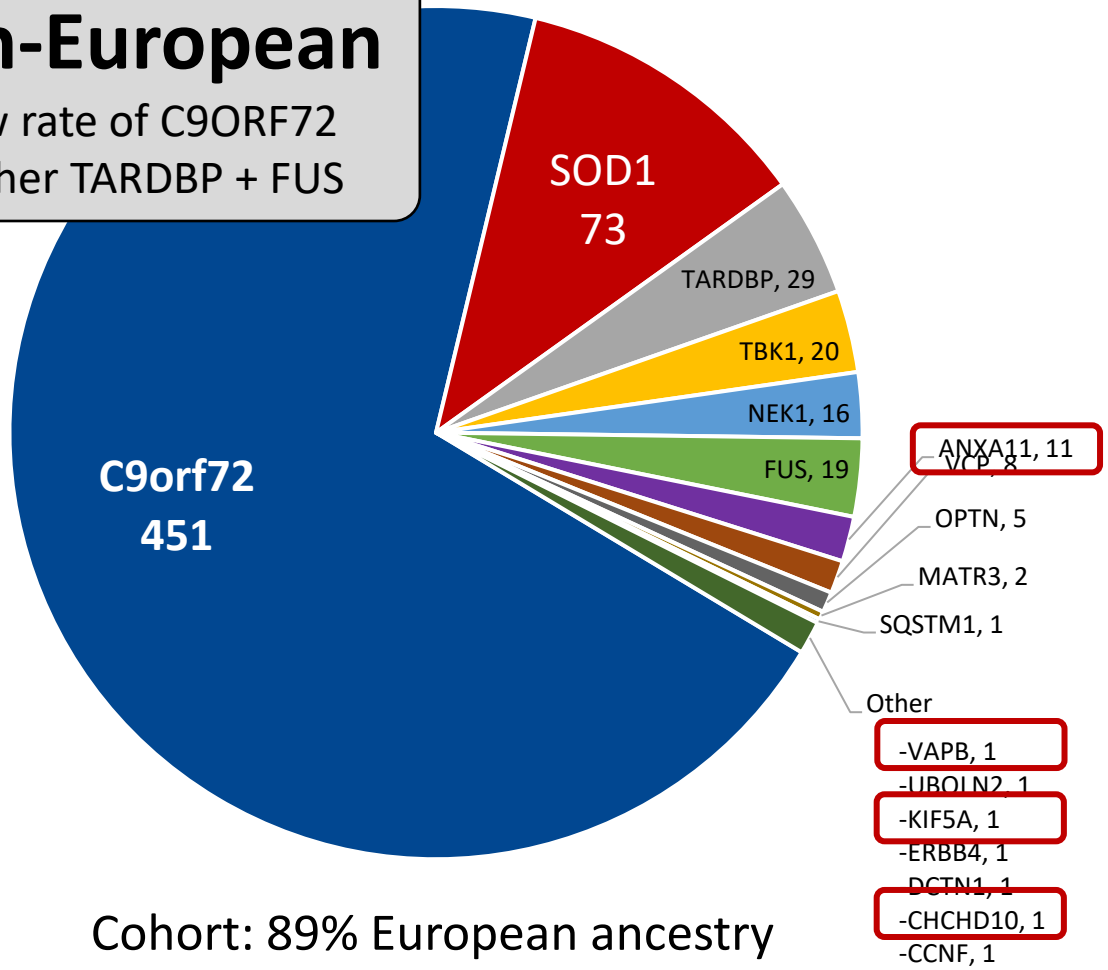
SilenceALS

ION363 (FUSion)

BIIB105 (ALSpire)

Non-European

- Low rate of C9ORF72
- Higher TARDBP + FUS



Cohort: 89% European ancestry

ALS Genetic Testing Guidelines

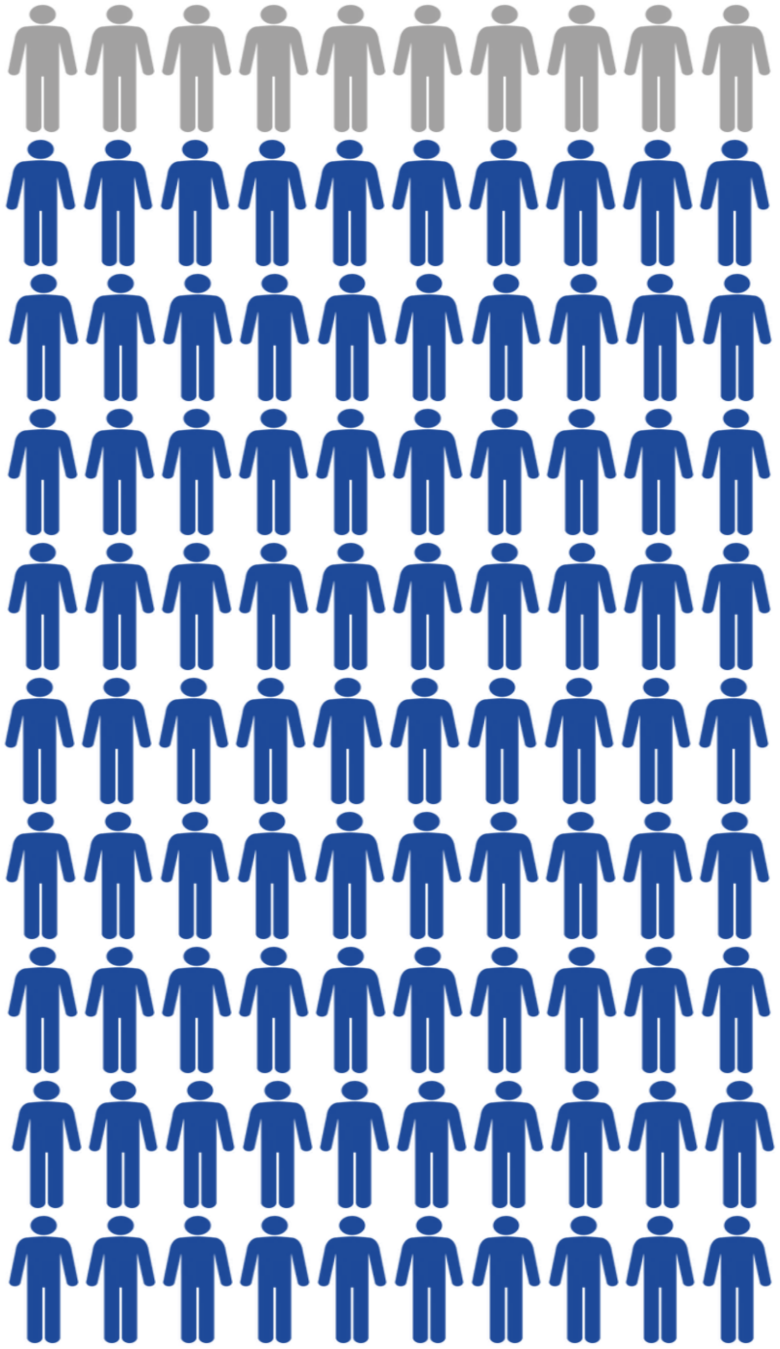
- "Everything, everyone, all at once"
  - 15% have an identifiable cause
    - 60% of those WITH family history
    - 10% of those WITHOUT a family history
  - Genotype-phenotype correlations are poor
    - Hard to predict which gene
  - Dual mutation carriers do happen (2%)
  - Shortens time to treatment or clinical trial

Genetic Testing Information:

Currently free at:
- Invitae Genetics
- Prevention Genetics

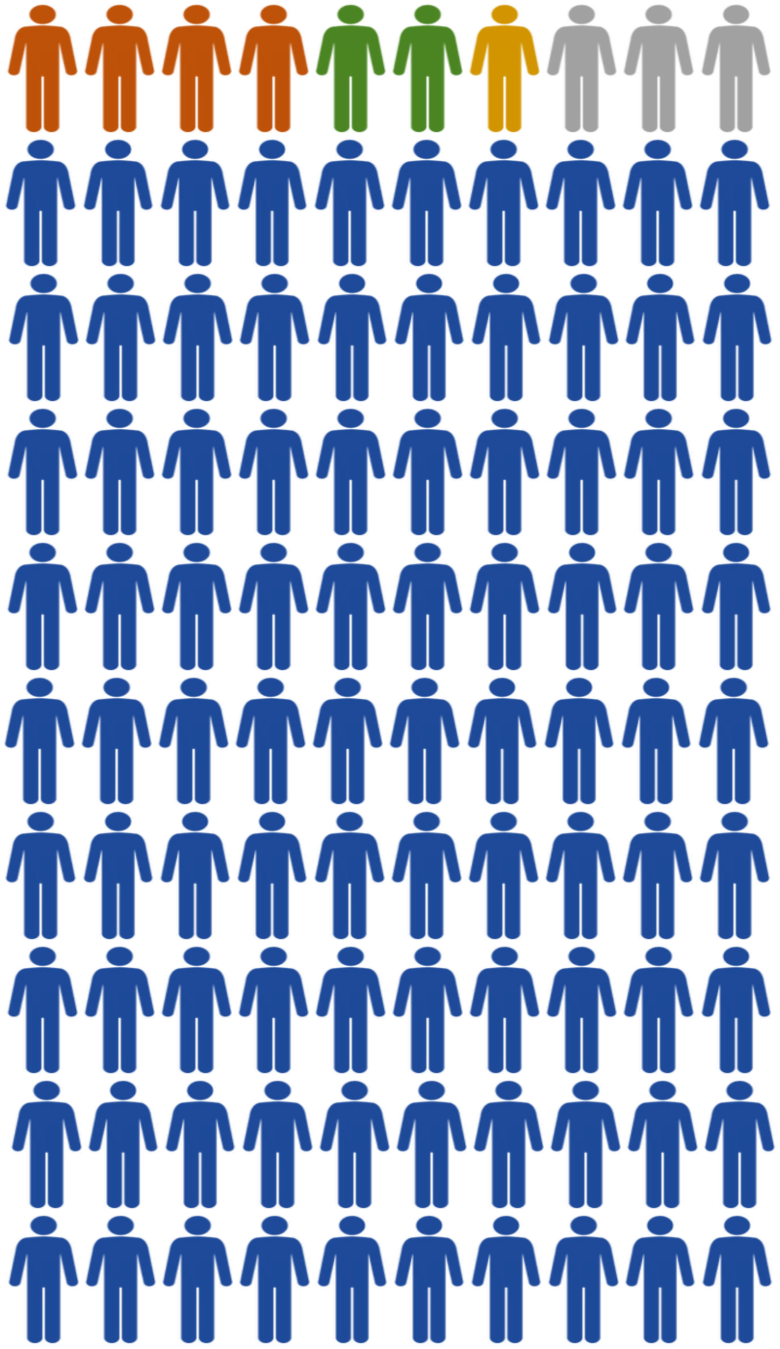
Almost always covered by:
- Medicaid
- Medicare
- Commercial Insurers

Patient pay is "inexpensive"



Family History of ALS/FTD: 10%

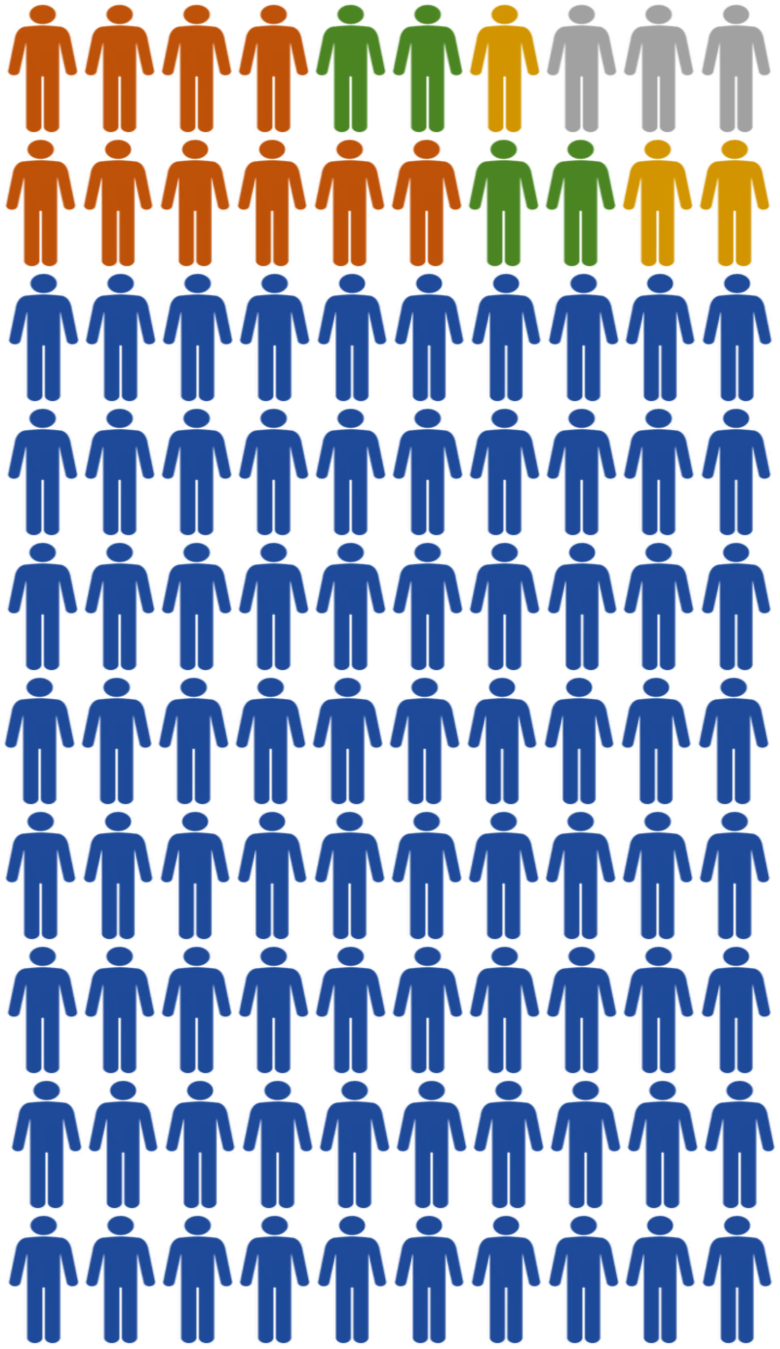
Singleton/Sporadic ALS: 90%



Family History of ALS/FTD: 10%

- C9ORF72
- SOD1
- Other (TARDBP/FUS)

Singleton/Sporadic ALS: 90%



Family History of ALS/FTD: 10%

C9ORF72

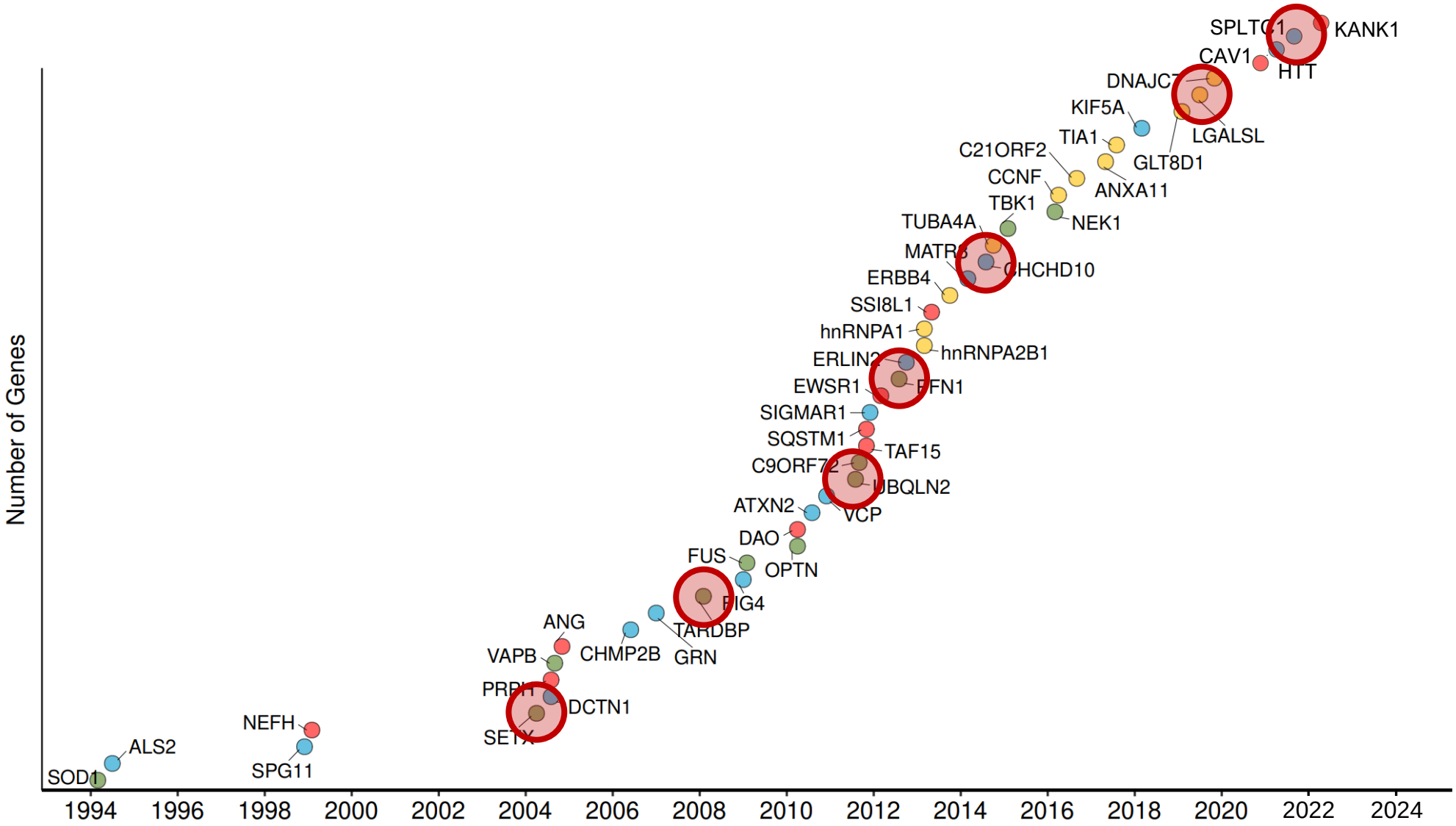
SOD1

Other (TARDBP/FUS)

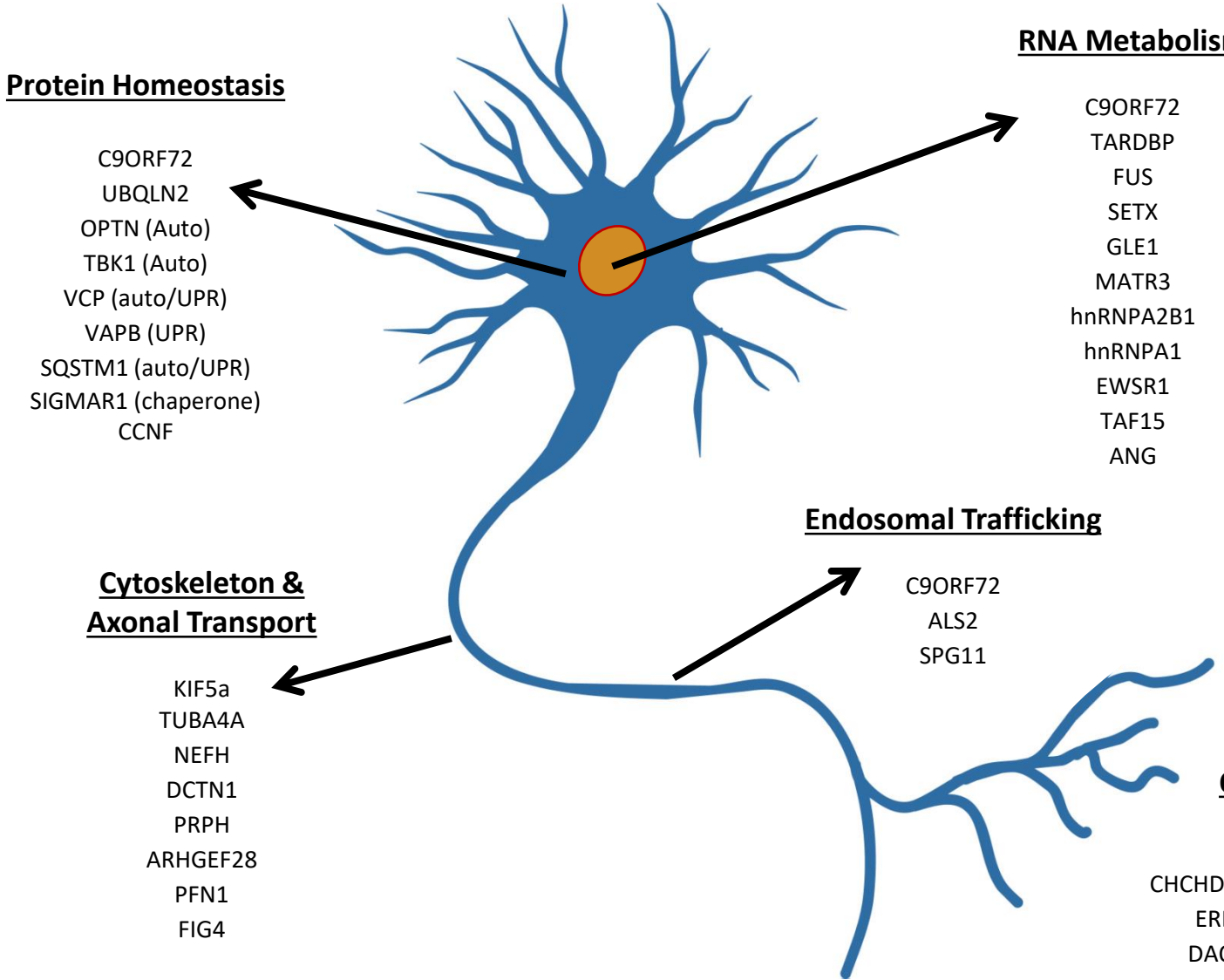
Singleton/Sporadic ALS: 90%

MORE genes remain to be discovered

ALS Gene Discovery



ALS Genes Implicate Driver Mechanisms



Protein Homeostasis

C9ORF72
UBQLN2
OPTN (Auto)
TBK1 (Auto)
VCP (auto/UPR)
VAPB (UPR)
SQSTM1 (auto/UPR)
SIGMAR1 (chaperone)
CCNF

RNA Metabolism

C9ORF72
TARDBP
FUS
SETX
GLE1
MATR3
hnRNPA2B1
hnRNPA1
EWSR1
TAF15
ANG

Endosomal Trafficking

C9ORF72
ALS2
SPG11

Cytoskeleton & Axonal Transport

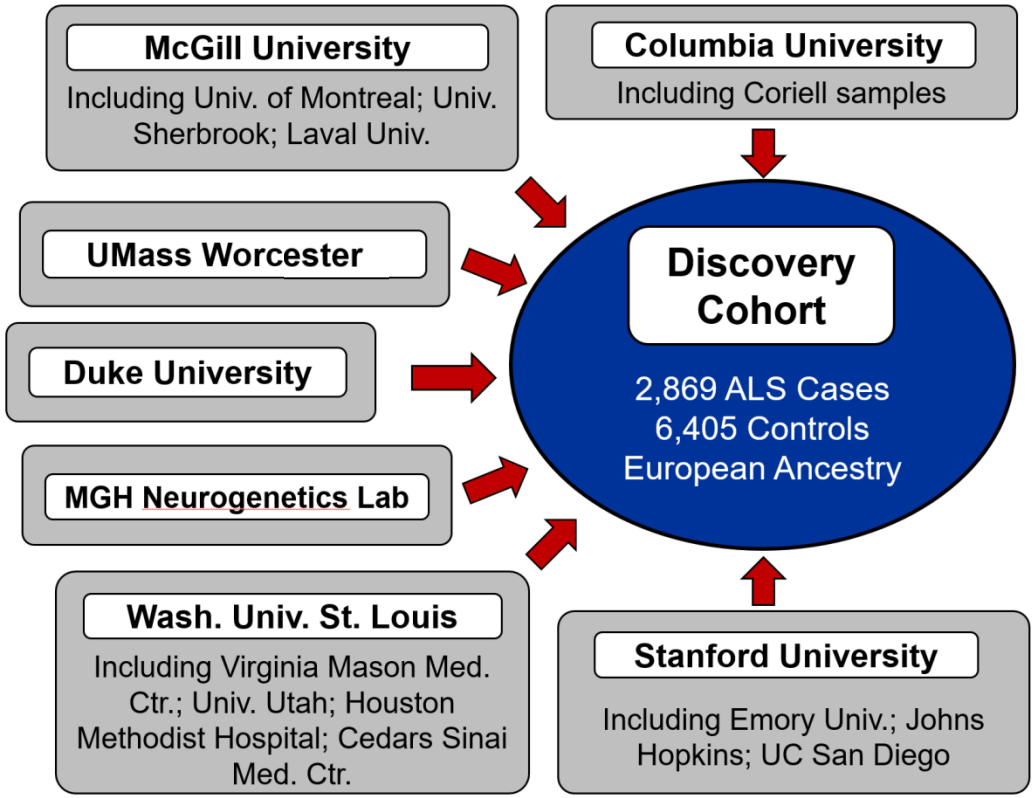
KIF5a
TUBA4A
NEFH
DCTN1
PRPH
ARHGEF28
PFN1
FIG4

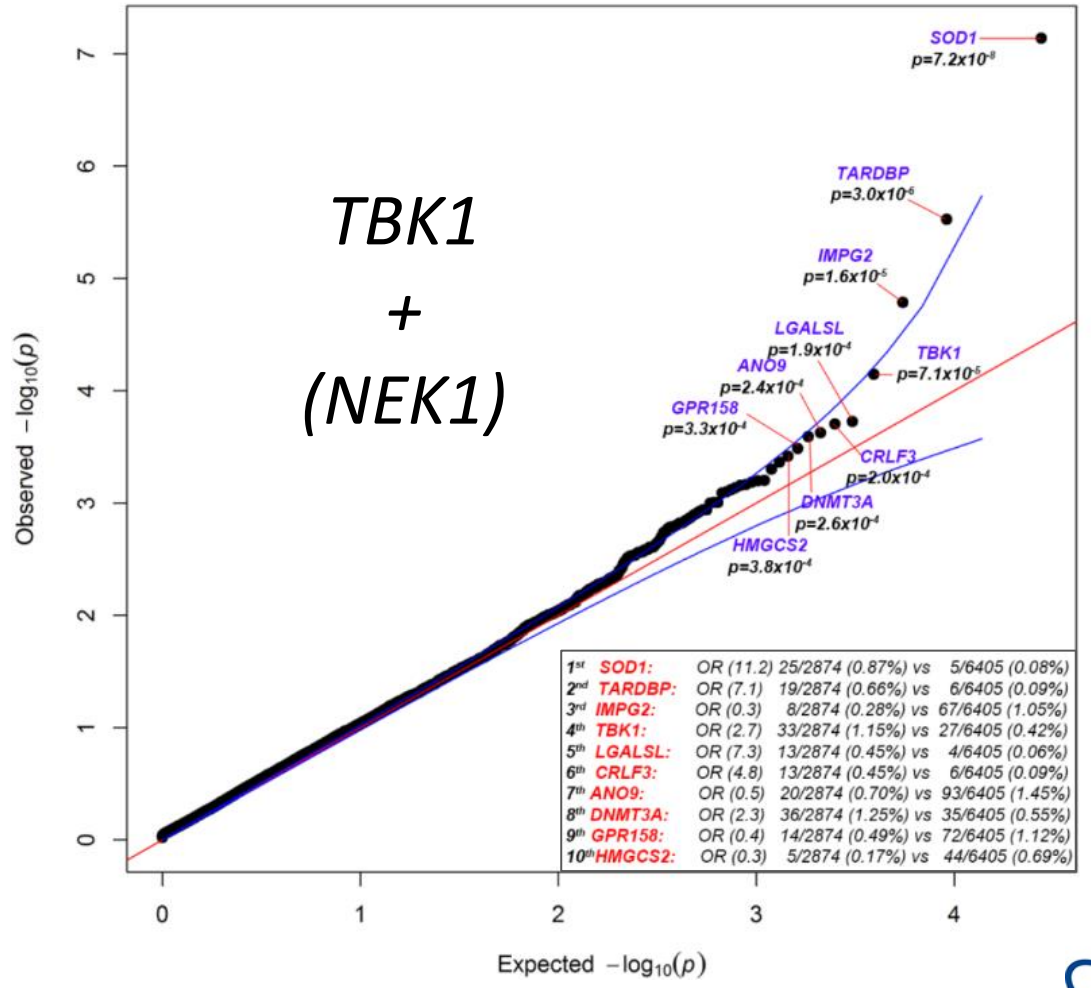
Other Pathways

SOD1- antioxidant
CHCHD10- mitochondrial integrity
ERBB4- synaptic signaling
DAO- amino acid oxidation

MORE pathways remain to be discovered

ALS Exome Consortium: 9000 participants



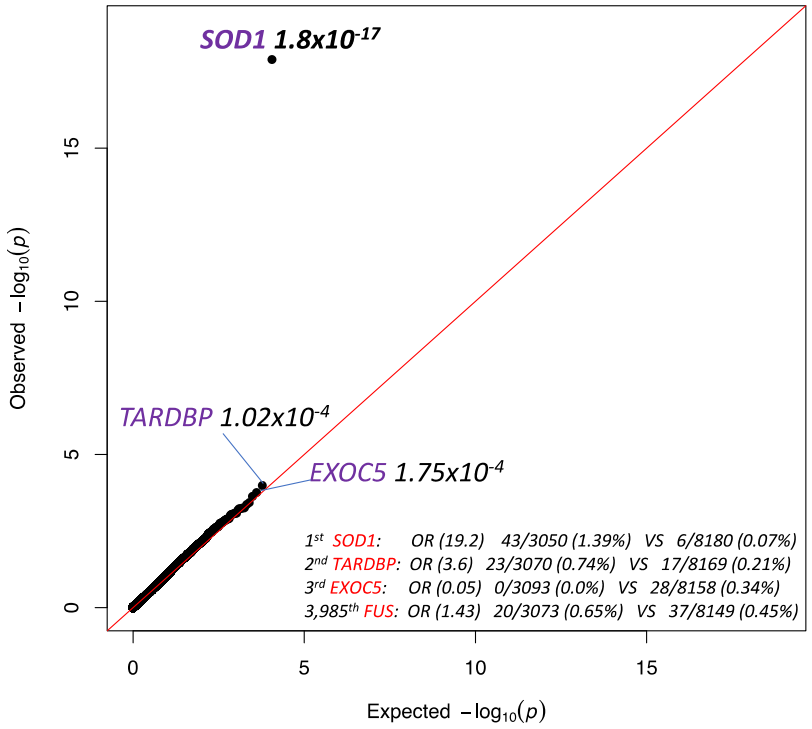


Cirulli et al. *Science* 2015

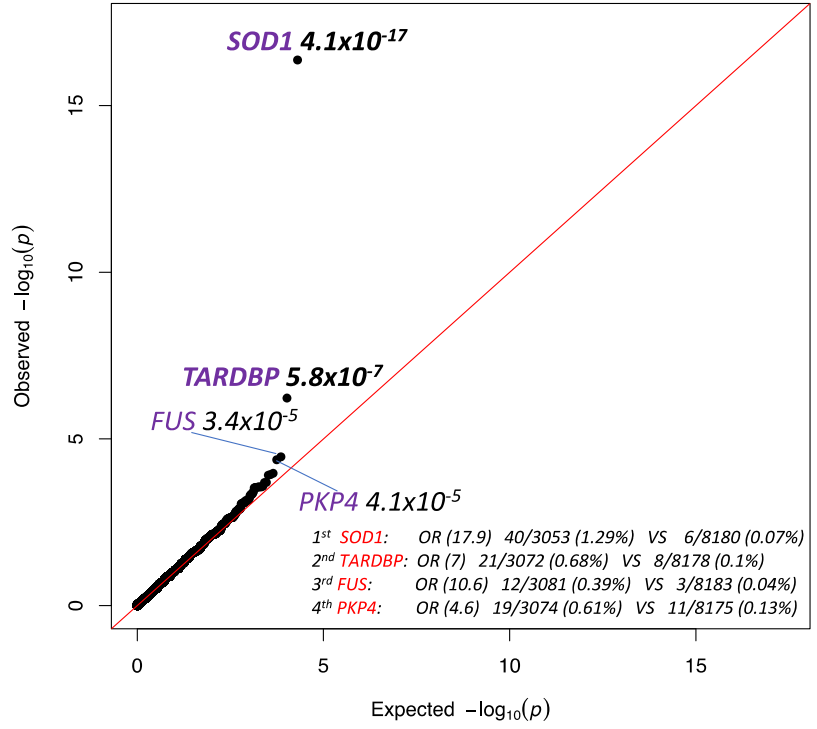
Next Iteration: 11,000 participants

LOF + coding | no Polyphen filter | ExAC MAF 0.1% | LOO-MAF 0.1%

Standard gene collapsing



Domain unit collapsing



Current Iteration: 27,000 participants

CUMC Precision Medicine ALS

Biogen

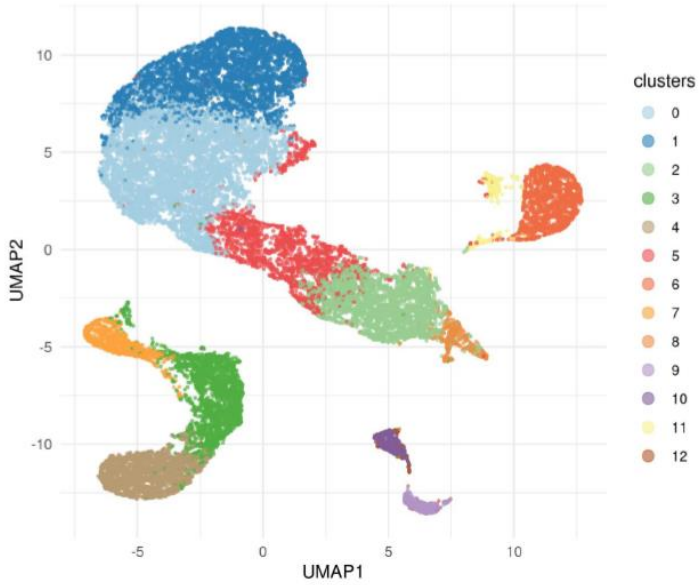
ALS Seq Consortium

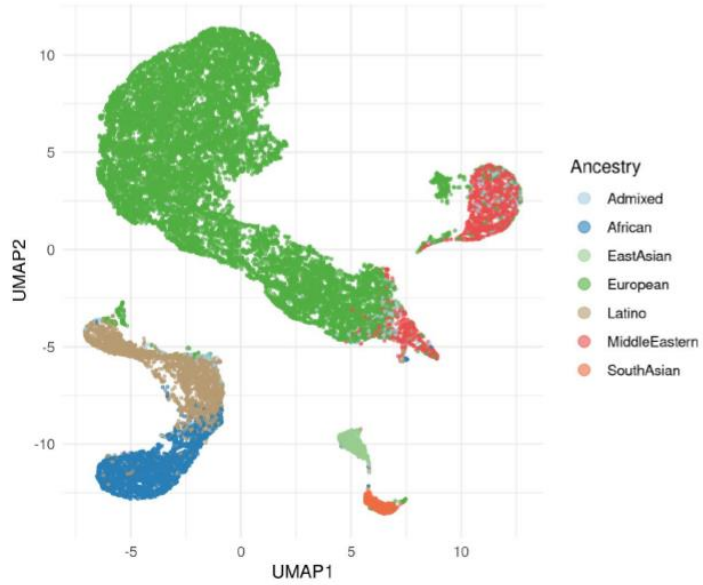
GTAC

NEW YORK GENOME CENTER®

ALS Consortium

Method	Cases	Controls
Initial Cohort	6,295	24,274
Kinship, FlashPCA+PLINK-NN	5,887	21,309





Future Iteration: 100,000 participants

CUIMC Precision Medicine ALS

Biogen

ALS Seq Consortium

NEW YORK GENOME CENTER® ALS Consortium

GTAC

NIH

UMASS LOWELL

ALS Compute AnVIL

+

project MinE Make it yours

ASO Summary for Gene Positive ALS

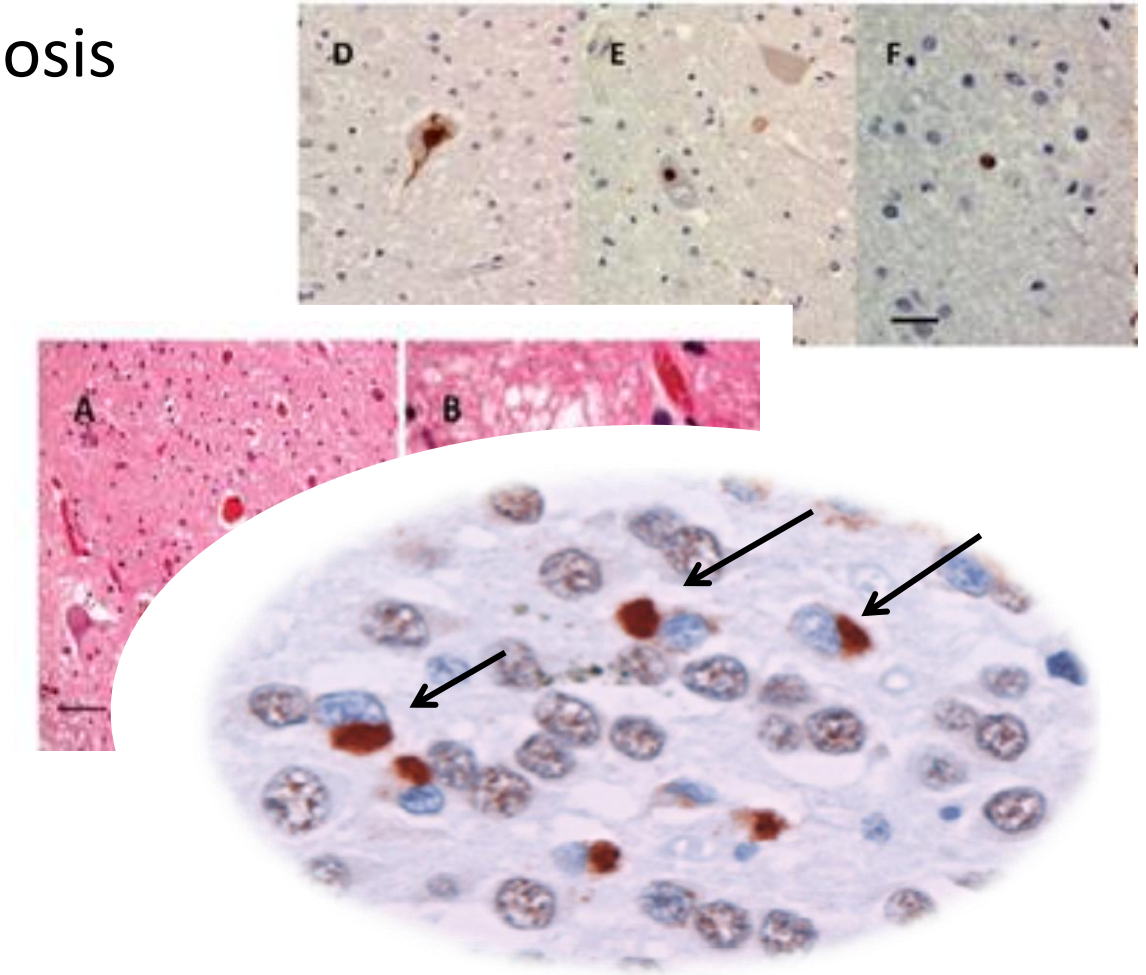
- Currently approved:
  - SOD1: tofersen
- In Clinical Trials:
  - ATXN2: BIIB105 (ALSpire)
  - FUS: jacifusen (FUSion)
- N-of-1 (SilenceALS)
  - TARDBP
  - Other rare genes
- Negative or Halted:
  - C9ORF72: BIIB078
  - C9ORF72: WVE-004
- Wrong kind of mutation:
  - OPTN
  - TBK1
  - Other “loss of function”

What about Gene Negative ALS?

Shared ALS Neuropathology

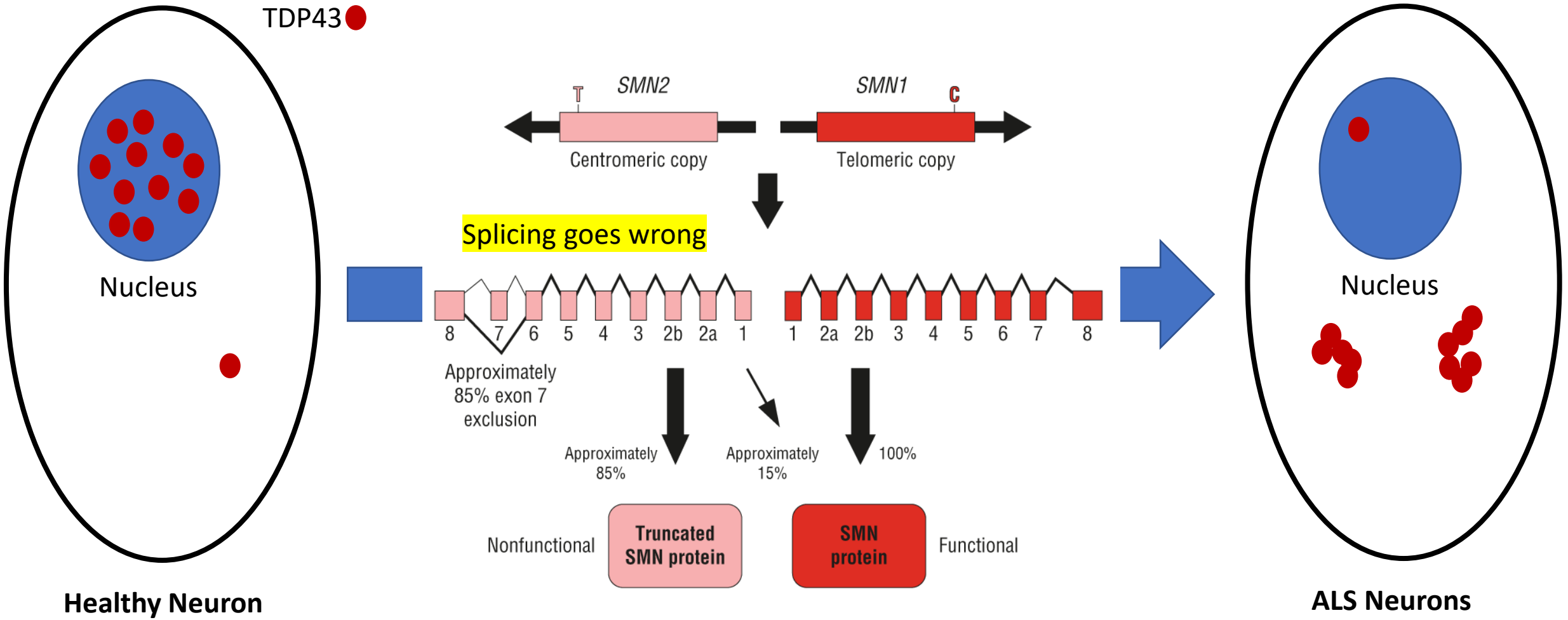
- Loss of neurons and reactive gliosis

- Commonly
  - Lewy-body or skein inclusions
    - Neurons and reactive astrocytes
    - SOD1, peripherin, ubiquitin
  - Bunina bodies
    - Neurons
    - Cystatin C +
  - TDP43 mislocalization
    - Depleted from nuclei
    - Aggregated in cytoplasm

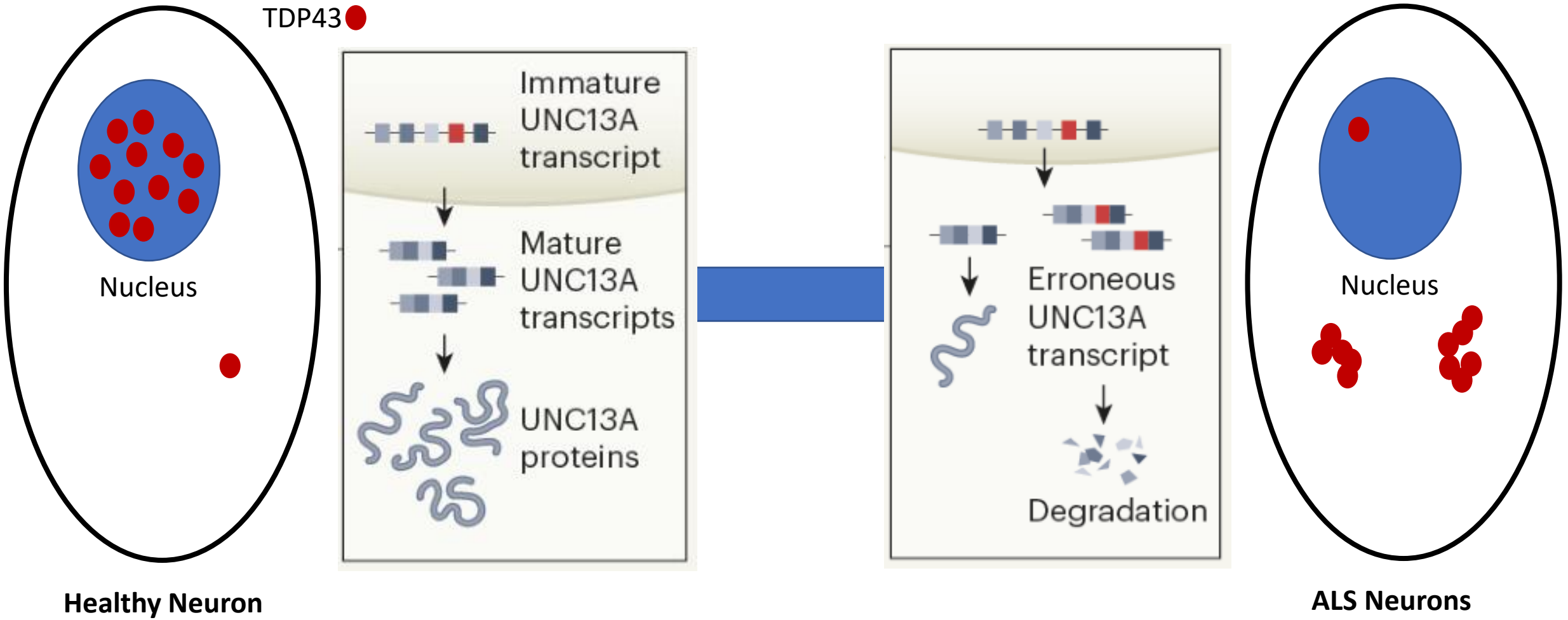


Pics: Cooper-Knock et al. *Brain* 2012; Yuna Ayala

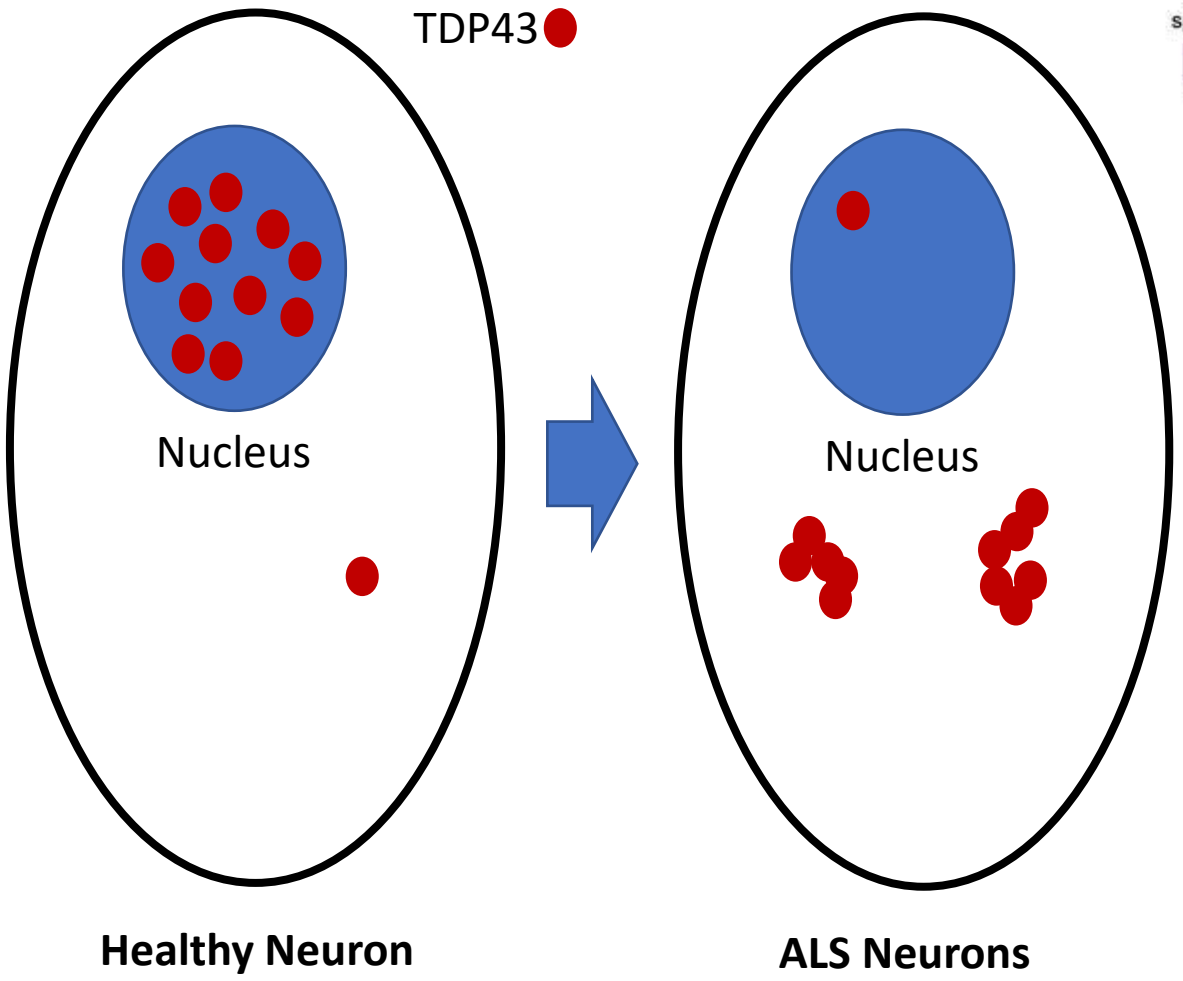
Gene Therapy for Gene Negative ALS

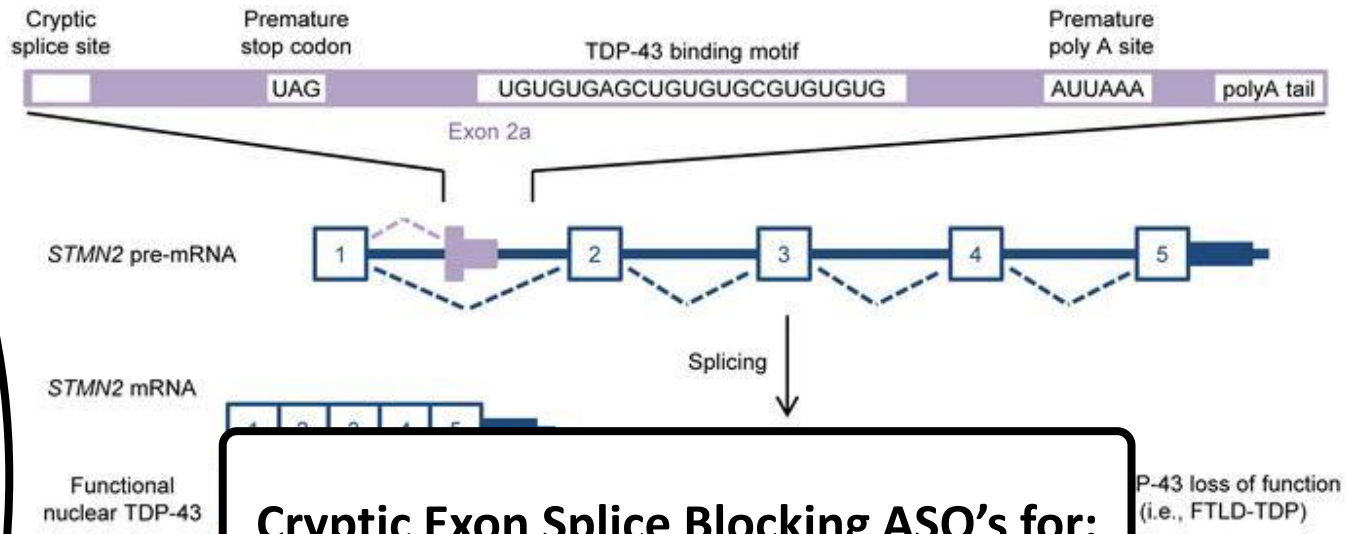


Gene Therapy for Gene Negative ALS



Gene Therapy for Gene Negative ALS





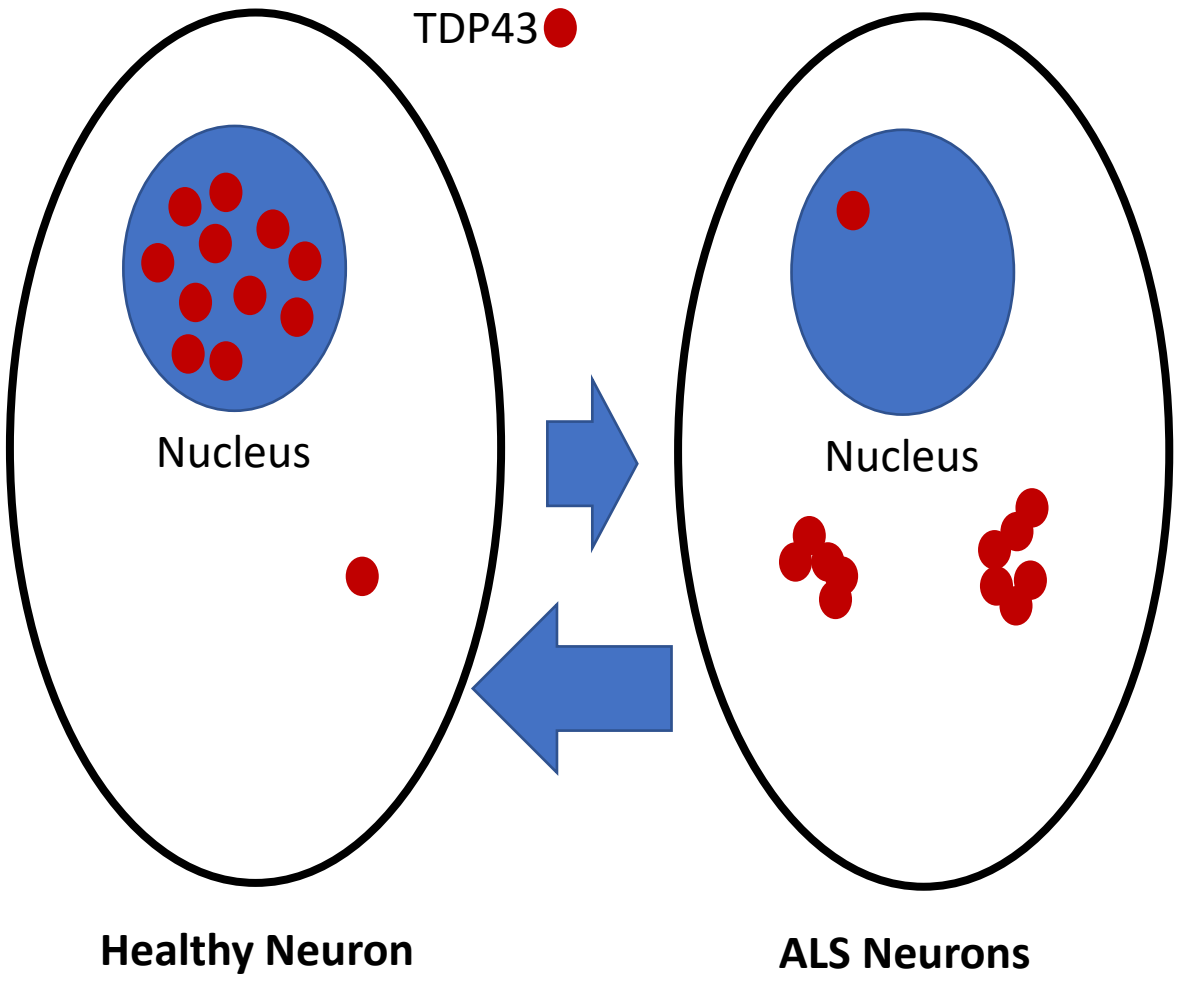
Cryptic Exon Splice Blocking ASO's for:
Stathmin 2
UNC13A
Several others

Reduce
- see
- caus
- causes neuronal dysfunction cell models

Increased stathmin protein
- rescues neurodegeneration in models

Pudencio et al. JCI 2020

Gene Therapy for Gene Negative ALS



ATXN2

Increased ATXN2 worsens toxicity

Variants in ATXN2 increase risk of ALS

Risk variants in ATXN2 increase ATXN2

Anti-ATXN2 ASO to decrease ATXN2

Take away points

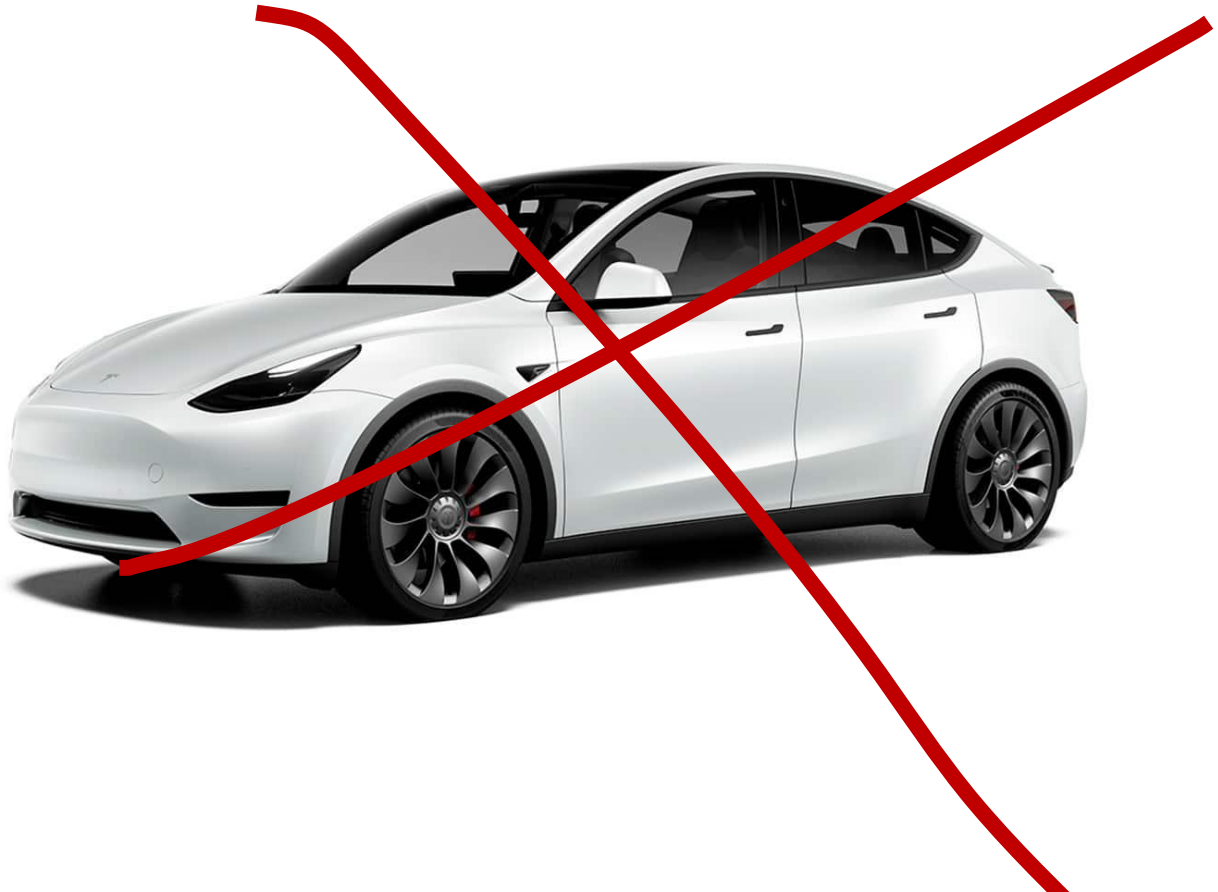
- Rapid advances in genetic therapies have revolutionized the care of patients with SMA
- Genetic therapy is just beginning for Gene Positive ALS
- Lessons gleaned from SMA and genetic ALS are poised to impact gene negative cases too
- Diverse neuromuscular diseases benefit from cross-pollenization and collaboration

Electric self-driving vehicle

Car Body
Tires
Seats
Radio

- Engine
- Batteries
- Charging Stations
- GREAT GPS
- High rez cameras
- Fast processors
- Artificial Intelligence
- Data, data, data

Effective Motor Neuron disease therapy



- Disease understanding
- Medicinal chemistry
- Biomarkers
- Sensitive outcomes
- Skilled Trial Centers
- Artificial Intelligence
- Data, data, data