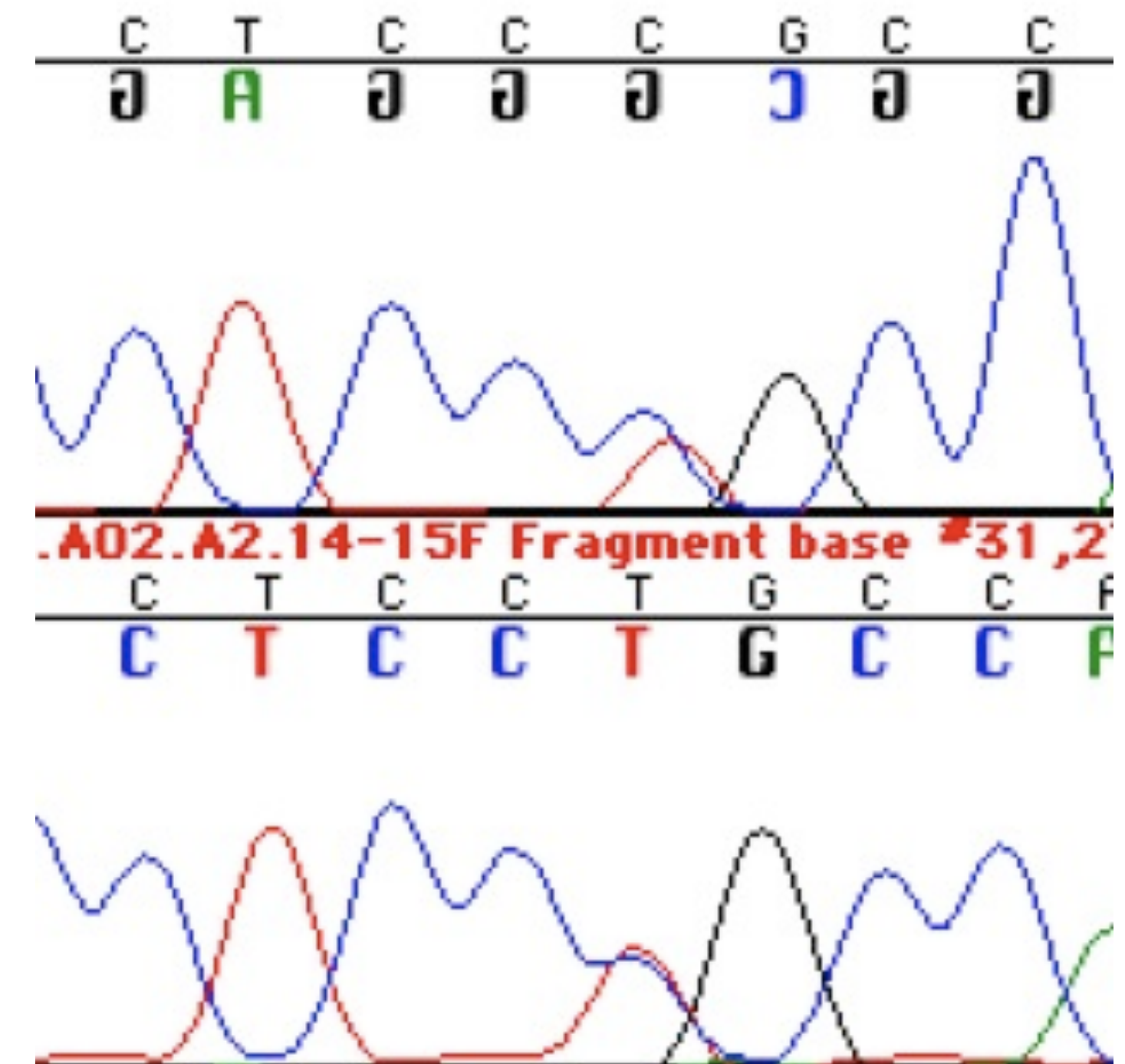
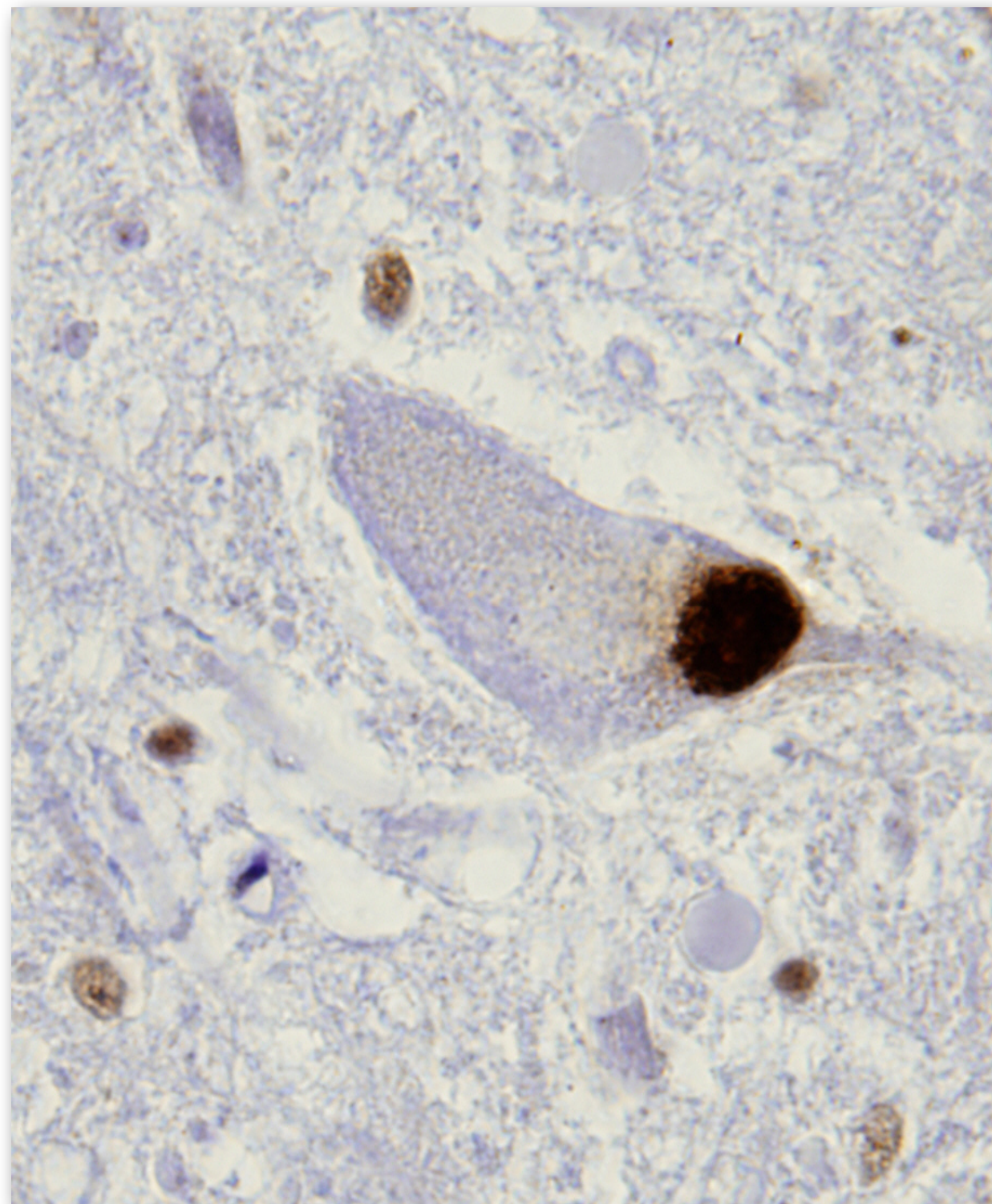


Genetics of human neurodegenerative disease

Aaron D. Gitler, Ph.D.

Rosalind Chuang, M.D.



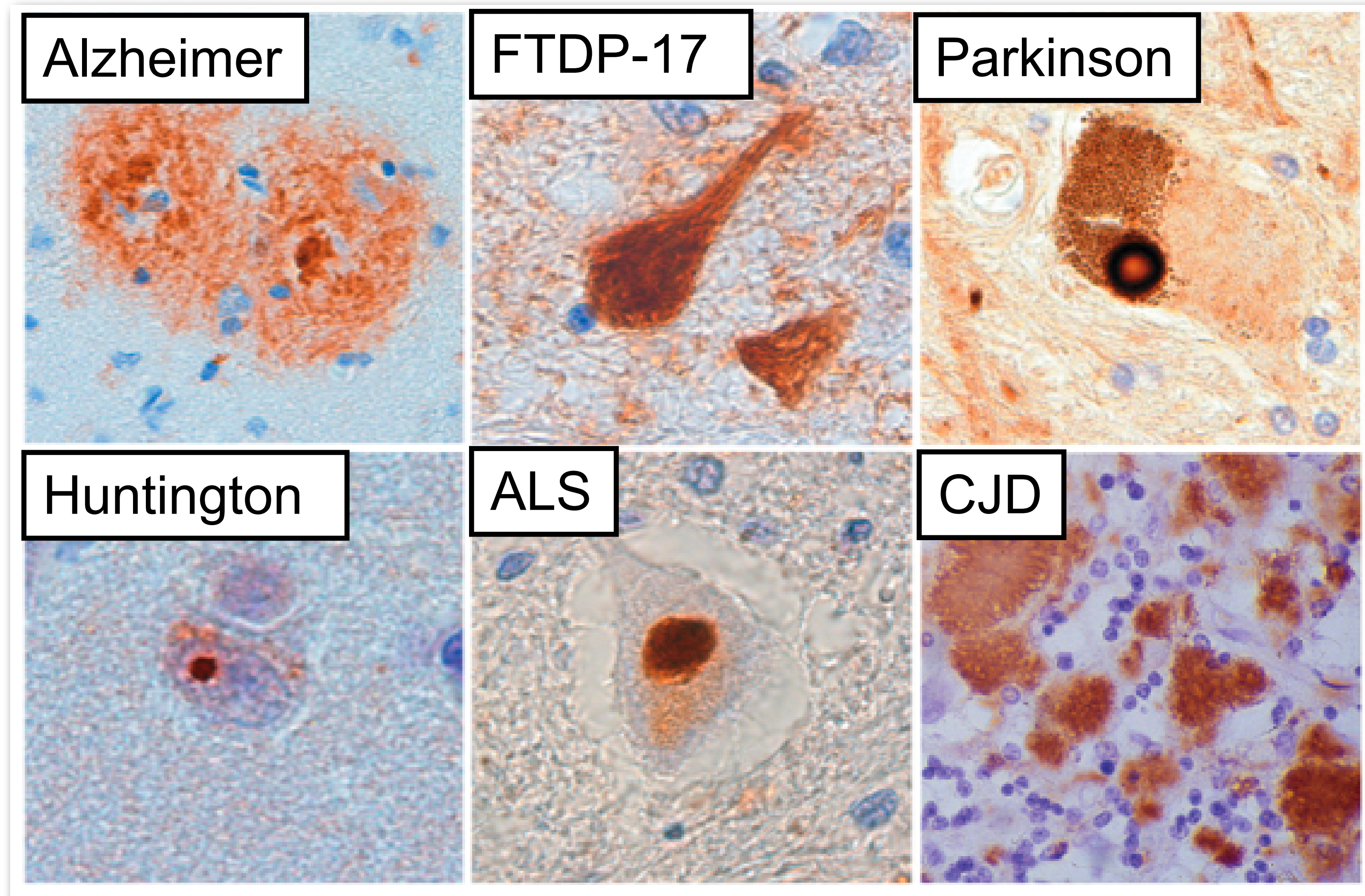
Neurodegenerative Diseases



Alzheimer Disease
Parkinson Disease
Huntington Disease
Frontotemporal Dementia
Lou Gehrig's Disease (ALS)



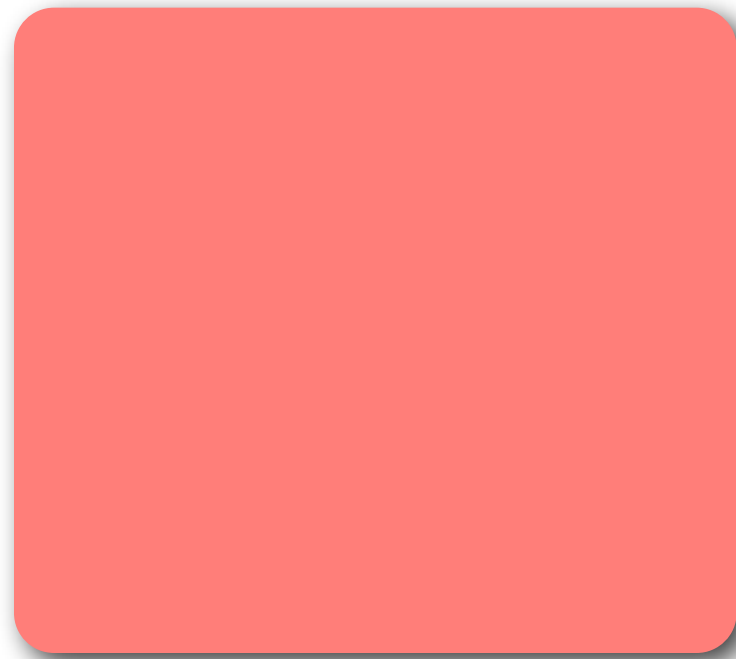
Protein Aggregates in Neurodegenerative Diseases



Protein Aggregates in Neurodegenerative Diseases

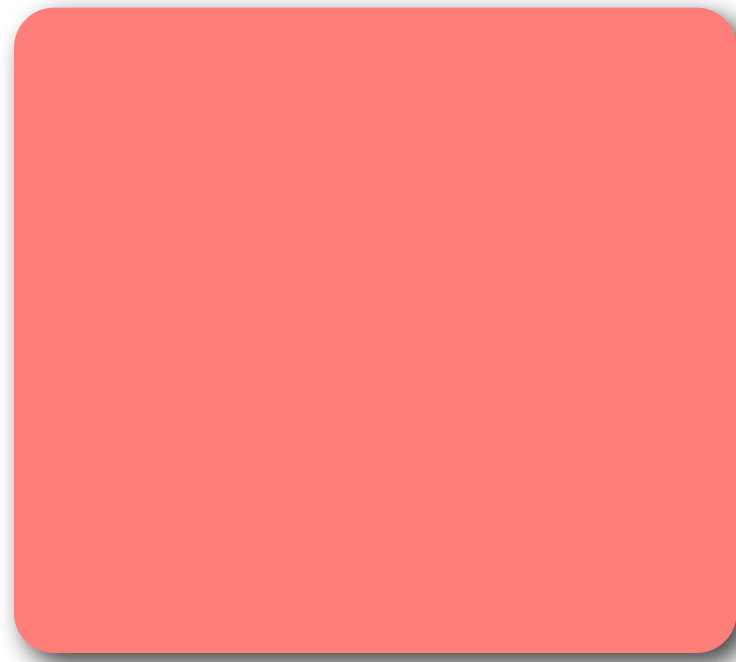
Protein Aggregates in Neurodegenerative Diseases

Normal Protein

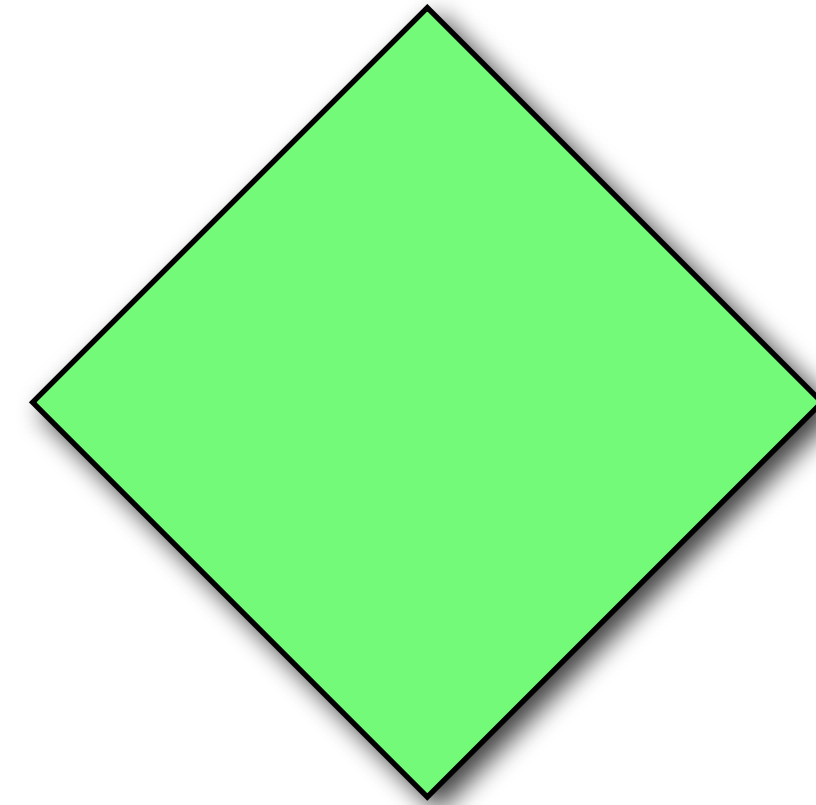


Protein Aggregates in Neurodegenerative Diseases

Normal Protein

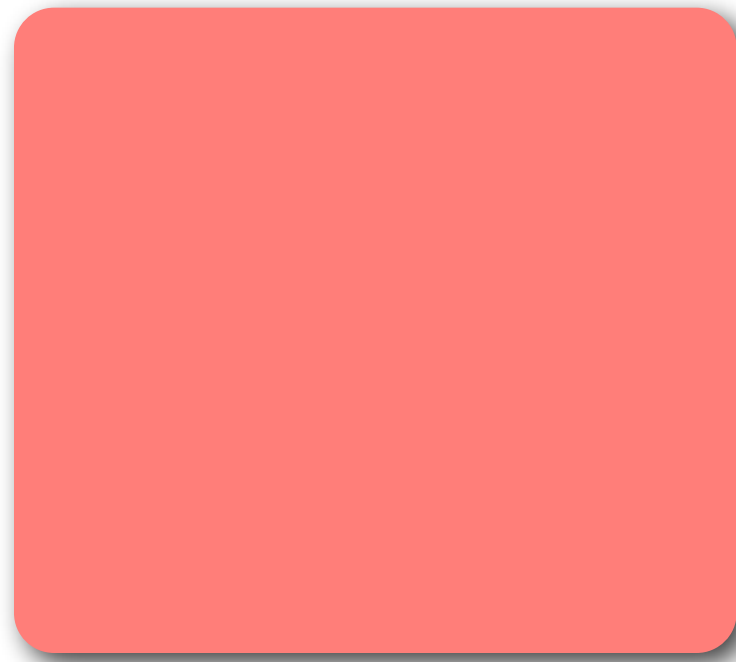


Misfolded Protein

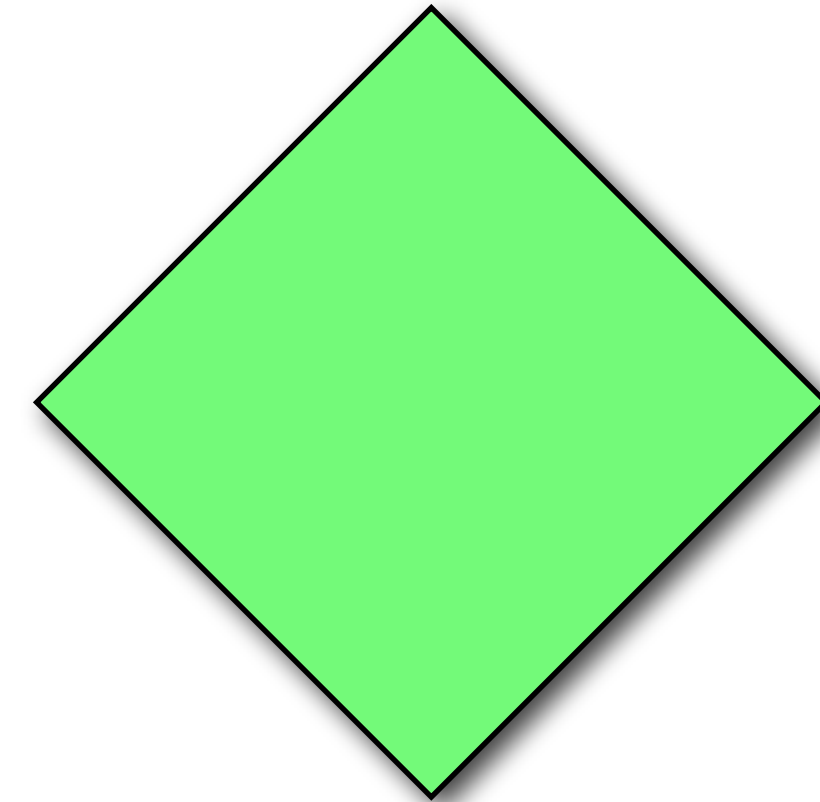


Protein Aggregates in Neurodegenerative Diseases

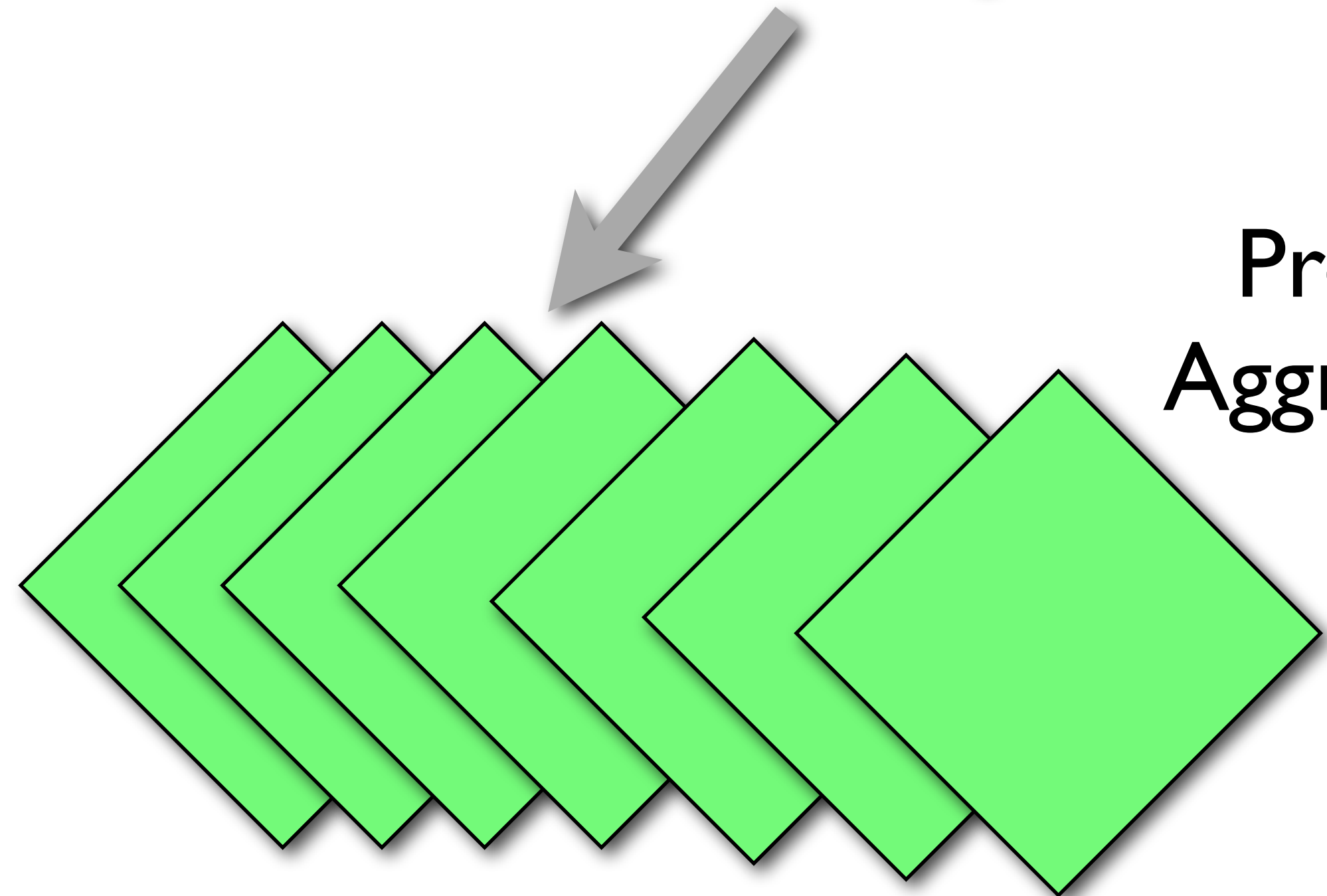
Normal Protein



Misfolded Protein



Protein
Aggregates

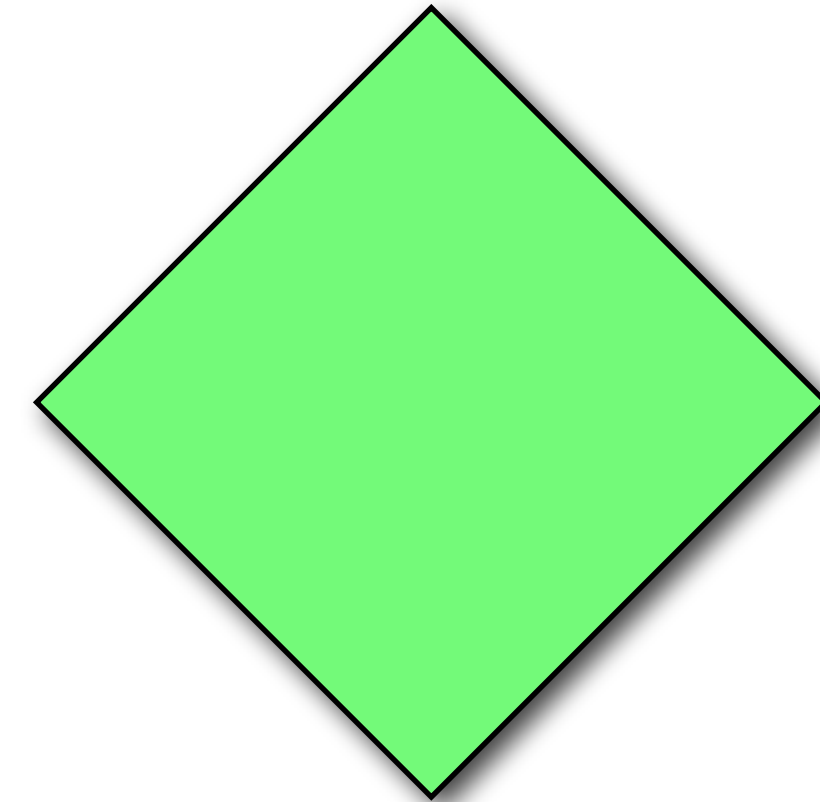


Protein Aggregates in Neurodegenerative Diseases

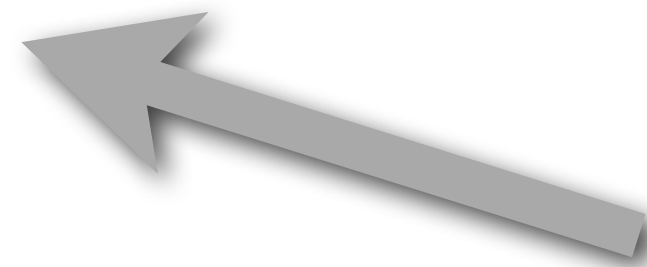
Normal Protein



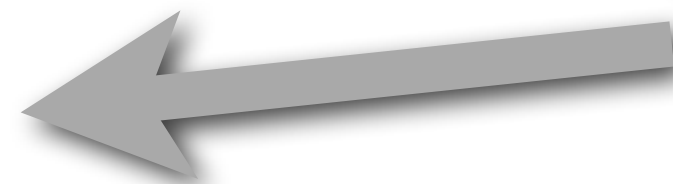
Misfolded Protein



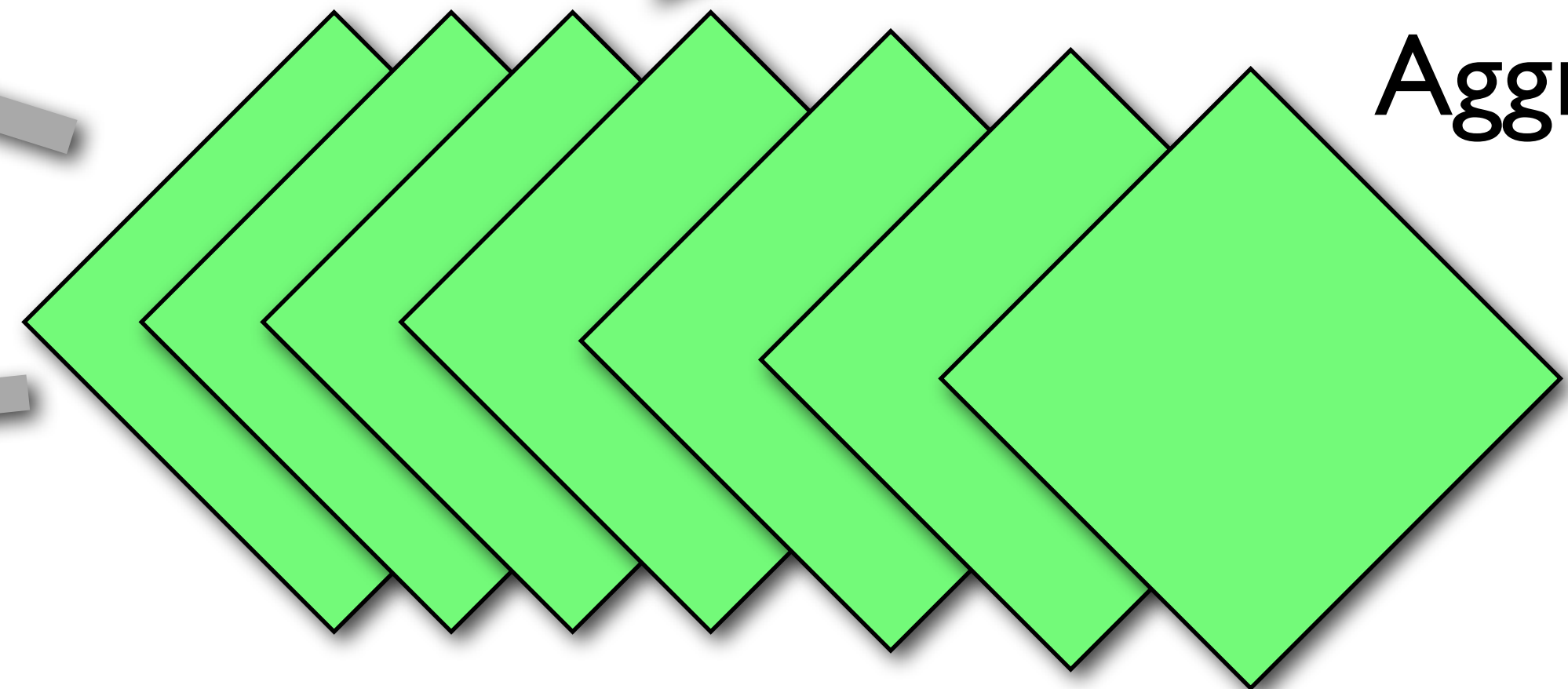
Loss of Protein's
Normal Function



Toxic Gain of
Function



Protein
Aggregates



Today's Plan

1. Huntington's Disease
2. Alzheimer's Disease
3. Frontotemporal Dementia
4. Amyotrophic lateral sclerosis (ALS)
5. Parkinson's Disease

Today's Plan

1. Huntington's Disease

2. Alzheimer's Disease

3. Frontotemporal Dementia

4. Amyotrophic lateral sclerosis (ALS)

5. Parkinson's Disease

Huntington's Disease

- Early stages:
 - Psychiatric changes: depression, impulsivity, irritability, personality changes, executive dysfunction
 - Interpersonal conflicts at work and home may lead to loss of employment or relationships
 - Motor: Subtle changes in eye movements or coordination, subtle involuntary movements (chorea)
- Middle Stages
 - Psychiatric: Prominent symptoms of depression and personality changes with outbursts of aggressive behaviors and social disinhibition. Mild dementia.
 - Motor: more prominent chorea, gait abnormalities, swallowing difficulties
 - Mostly independent in activities of daily living but increasingly depend on others for help.
 - Usually unemployed.
- Late stage:
 - Psychiatric : dementia, mute. Unable to communicate.
 - Motor: severe chorea or gait disturbance. Incontinence.
 - Total dependence for care. Feeding through PEG tube.
- Median survival after onset of motor symptoms is 15-18 years.

The Huntington's Gene



The Huntington's Gene



CAG CAG CAG CAG CAG CAG CAG CAG

The Huntington's Gene



CAG CAG CAG CAG CAG CAG CAG CAG



QQQQQQQQQQ polyQ (Normally ~5-20)

The Huntington's Gene



The Huntington's Gene



CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG

CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG

CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG

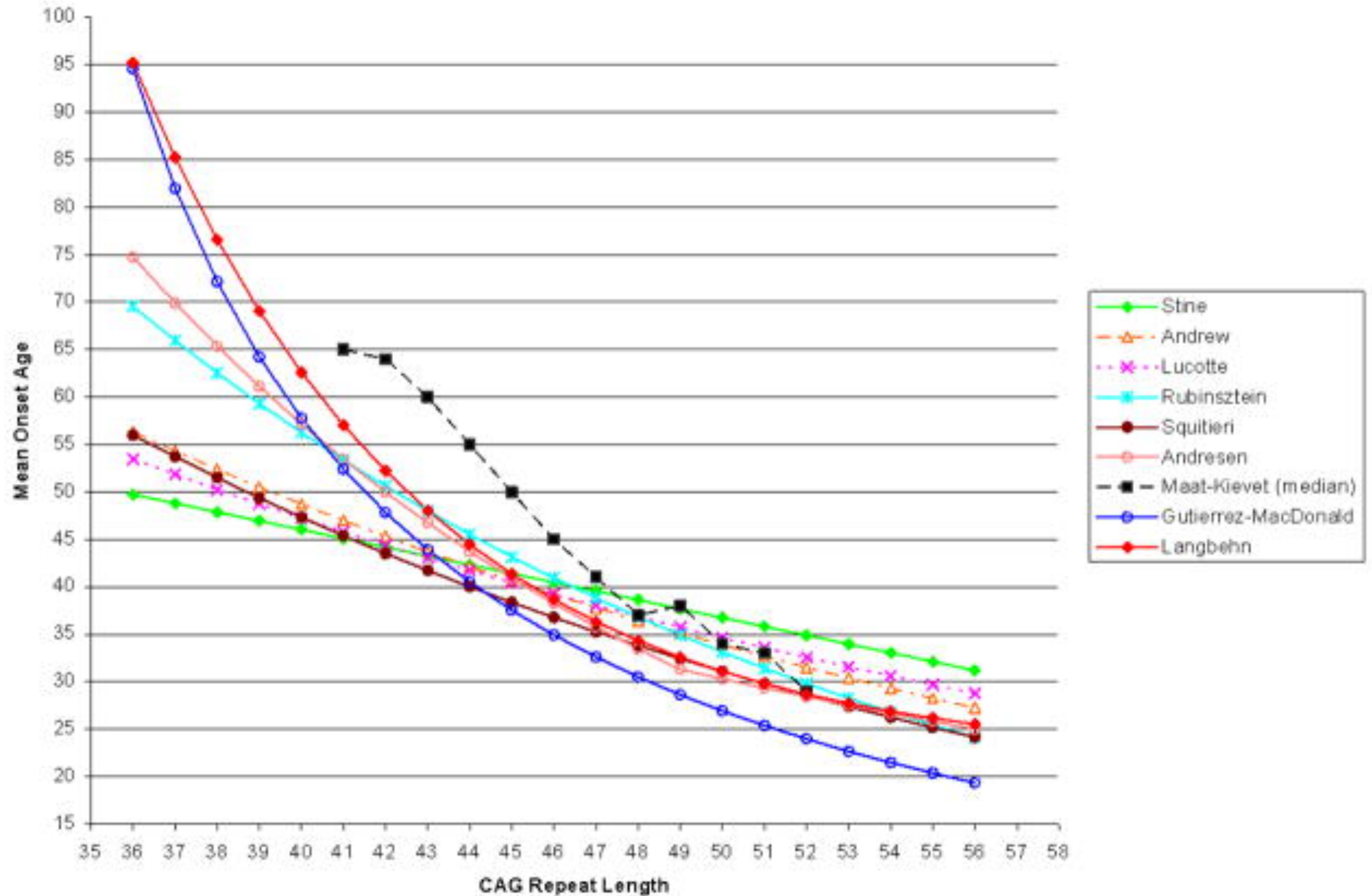
CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG



Expanded polyQ causes Huntington's Disease (>40 Q's)

A diagram showing a 2x20 grid of 'Q' characters. A blue arrow points to the 9th character in the top row.

HD age of onset correlates to CAG repeat length



Discussion on genetic testing for HD

- Guidelines for testing established by International Huntington's Disease Society and World Federation of Neurology for Huntington's Disease
- Current process for asymptomatic (*predictive*) testing
 - Process of 3 separate visits
 - Meet with genetic counselor at each visit
 - Disclosure of test results in person
- What are the ethical dilemmas?
 - Predictive testing in children (<18 yo)
 - Direct to consumer testing
 - Would *you* want to know?

Polyglutamine Disease Genes

Disease	Mutation/ repeat unit	Gene name (protein product)	Putative function	Normal repeat length	Pathogenic repeat length
SCA1	(CAG) _n	<i>SCA1</i> (ataxin 1)	Transcription	6–39	40–82
SCA2	(CAG) _n	<i>SCA2</i> (ataxin 2)	RNA metabolism	15–24	32–200
SCA3 (MJD)	(CAG) _n	<i>SCA3</i> (ataxin 3)	De-ubiquitylating activity	13–36	61–84
SCA6	(CAG) _n	<i>CACNA1A</i> (<i>CACNA1_A</i>)	P/Q-type α 1A calcium channel subunit	4–20	20–29
SCA7	(CAG) _n	<i>SCA7</i> (ataxin 7)	Transcription	4–35	37–306
SCA17	(CAG) _n	<i>SCA17</i> (TBP)	Transcription	25–42	47–63
DRPLA	(CAG) _n	<i>DRPLA</i> (atrophin 1)	Transcription	7–34	49–88
SBMA	(CAG) _n	<i>AR</i> (androgen receptor)	Steroid-hormone receptor	9–36	38–62
HD	(CAG) _n	<i>HD</i> (huntingtin)	Signalling, transport, transcription	11–34	40–121

Today's Plan

1. Huntington's Disease

2. Alzheimer's Disease

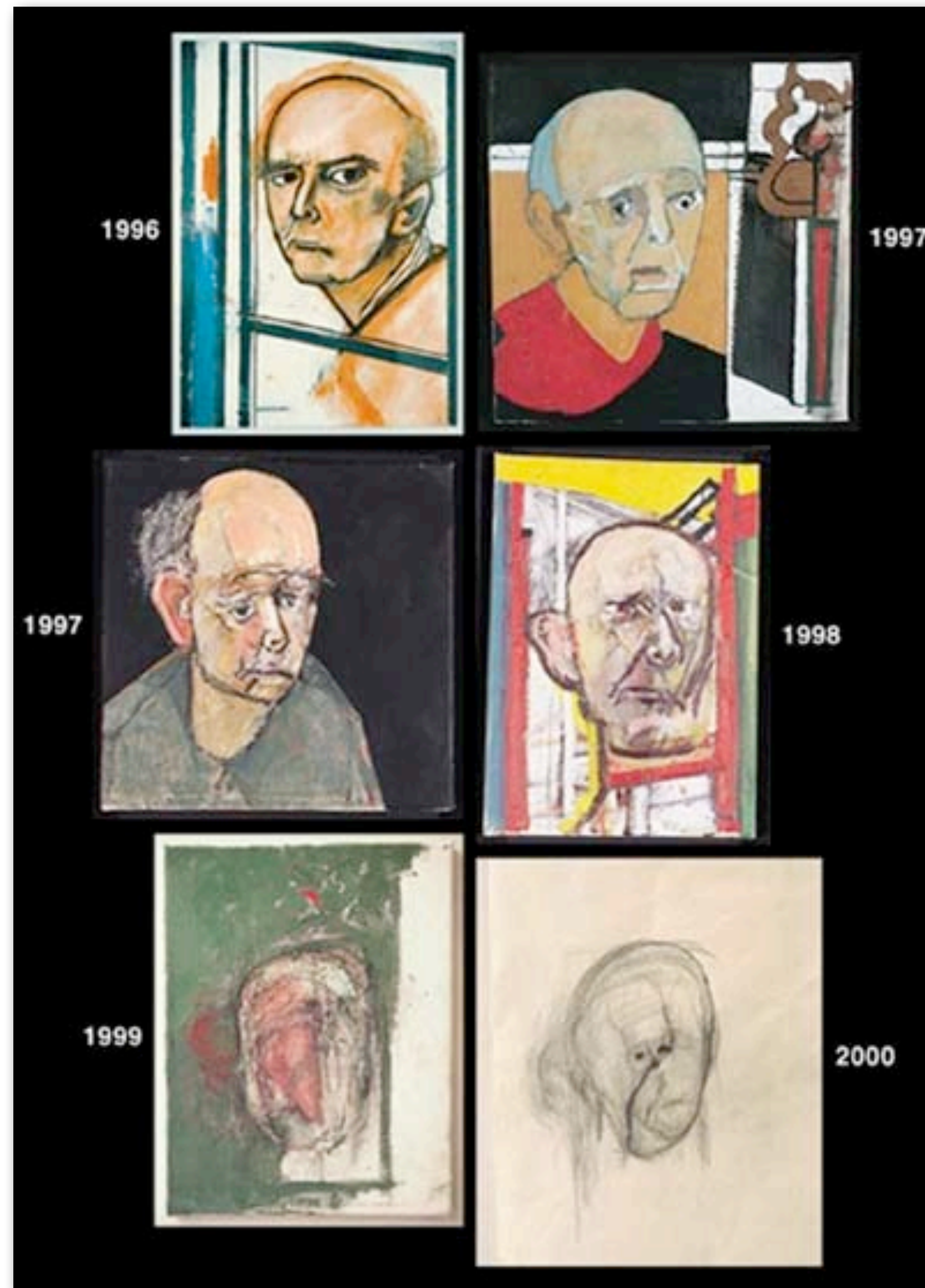
3. Frontotemporal Dementia

4. Amyotrophic lateral sclerosis (ALS)

5. Parkinson's Disease

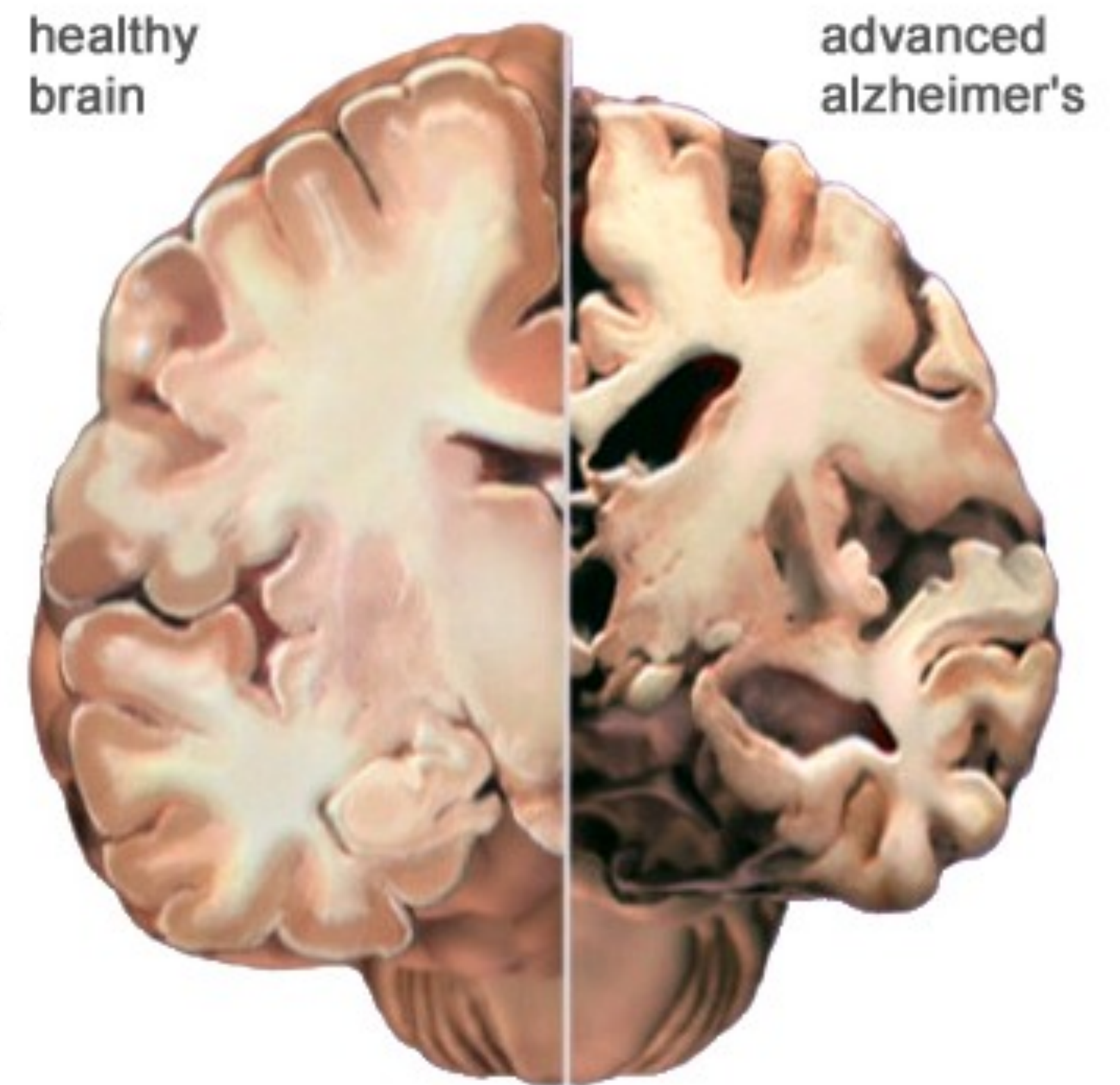
Alzheimer's Disease

**Artist charts his slide
into dementia
Six self-portraits by
artist William
Utermohlen chronicle
his experience with
Alzheimer's disease.**

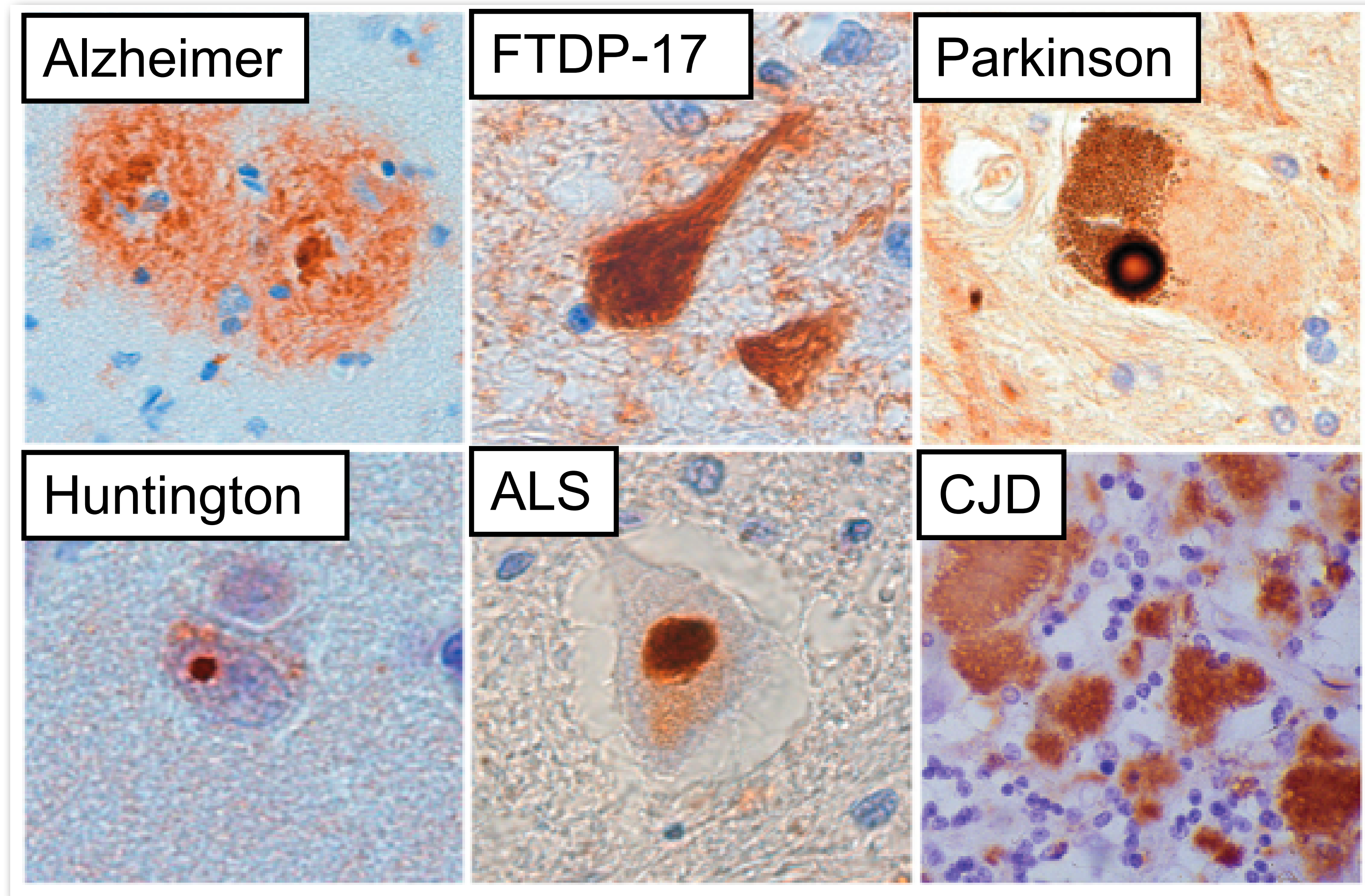


Alzheimer's Disease

- Most common form of age-related dementia
- Most common neurodegenerative disease
- Sixth-leading cause of death in U.S
- By 2050, 1 out of 85 people worldwide will have AD
- Mostly sporadic disease
- Mendelian forms of AD account for ~5% of cases
- Can these rare genetic forms provide insight to sporadic cases?

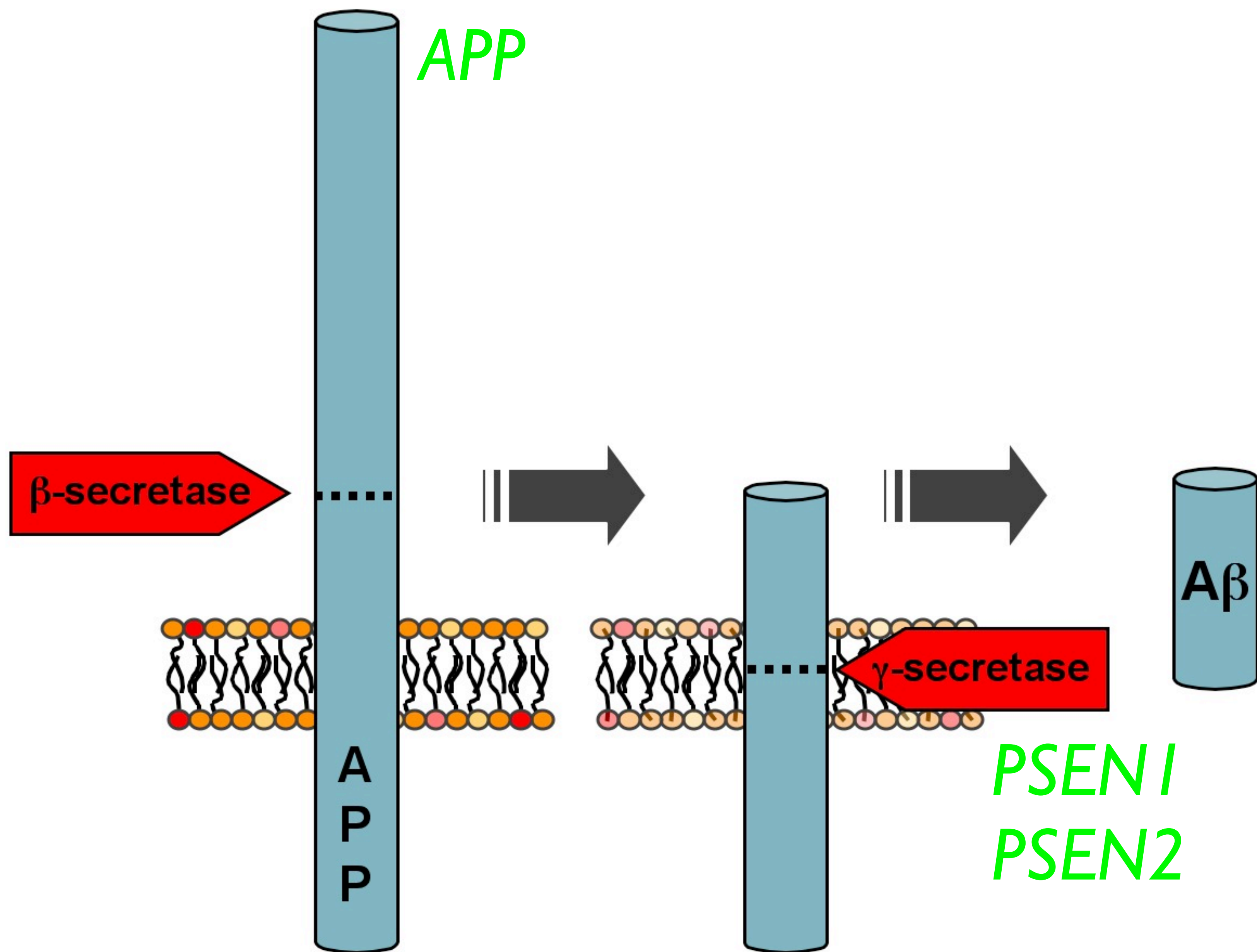


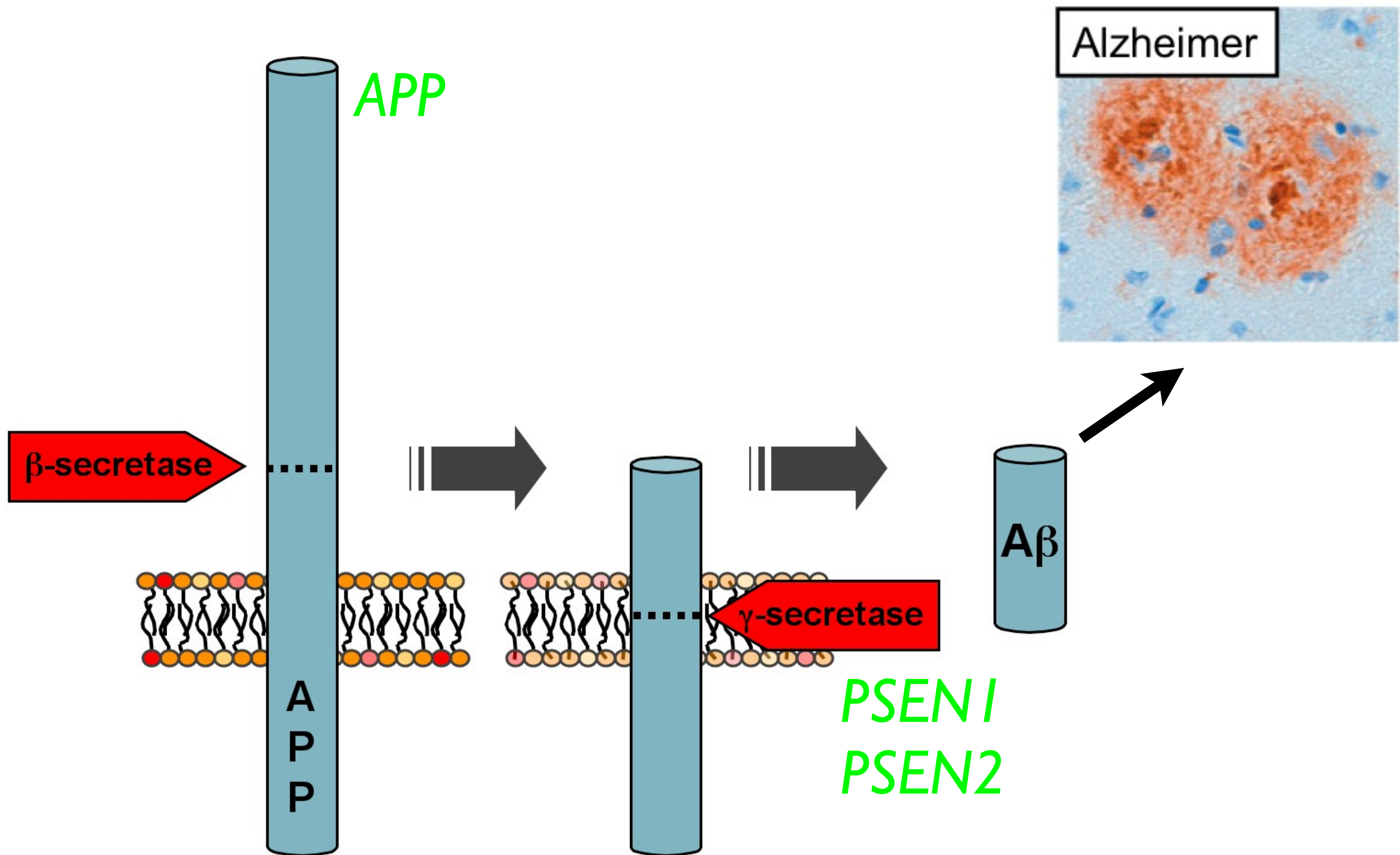
Protein Aggregates in Neurodegenerative Diseases



Mendelian Genes for Alzheimer's Disease

Gene	Protein	Location	Inheritance
<i>APP</i>	Beta-amyloid precursor protein	21q21.3	dominant
<i>PSEN1</i>	presenilin 1	14q24.2	dominant
<i>PSEN2</i>	presenilin 2	1q42.13	dominant

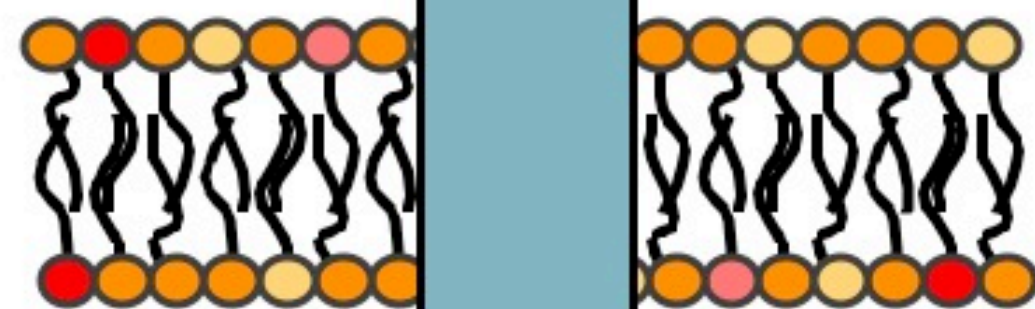




What is another potential genetic cause of AD?

β -secretase

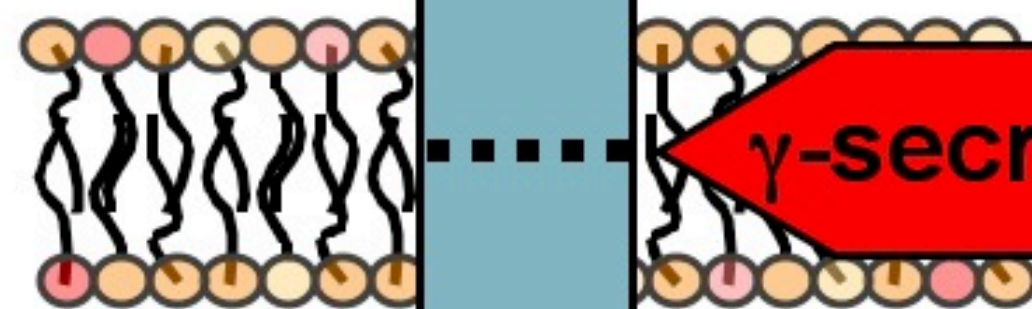
APP



A
P
P



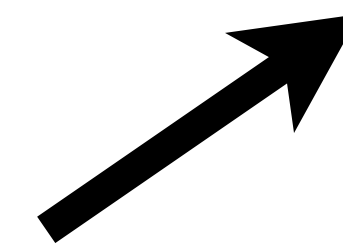
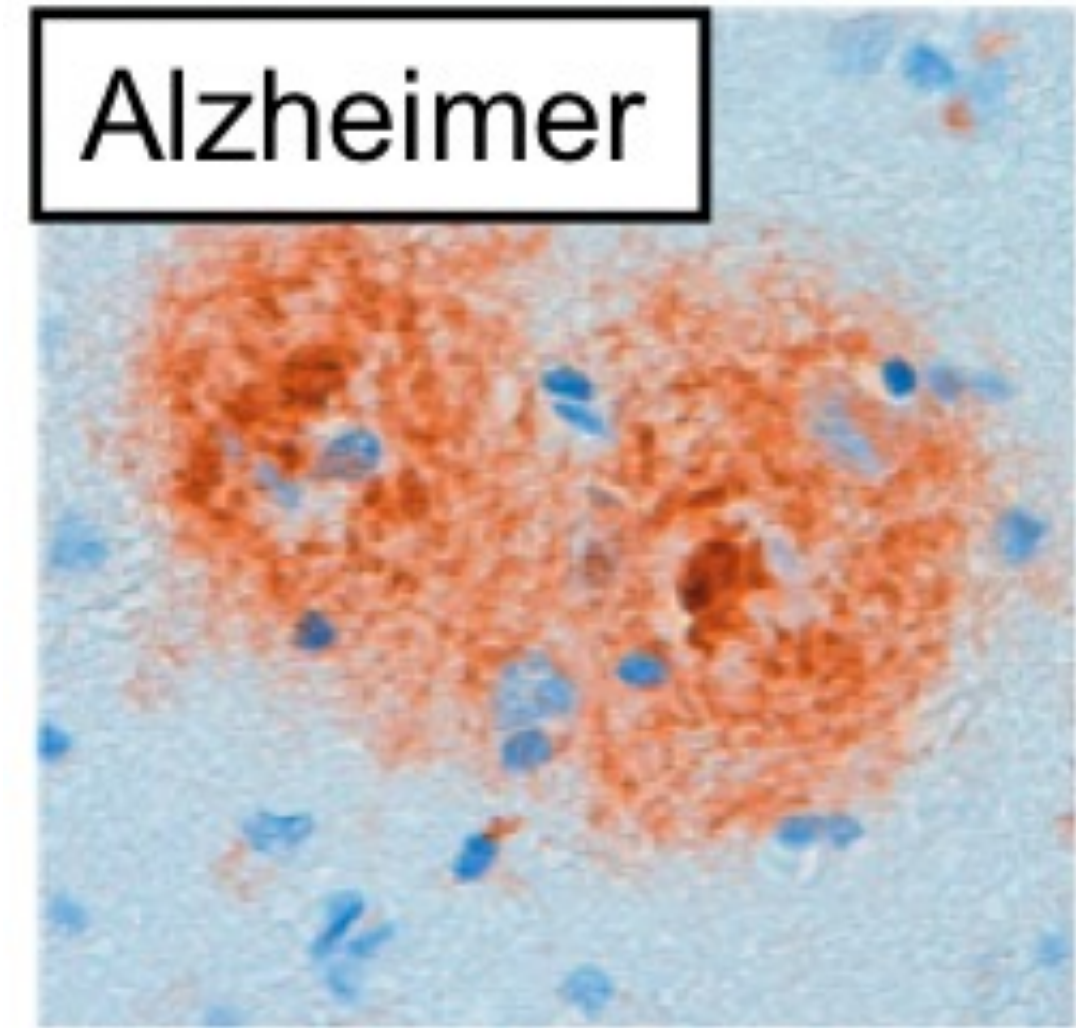
γ -secretase



PSEN1
PSEN2

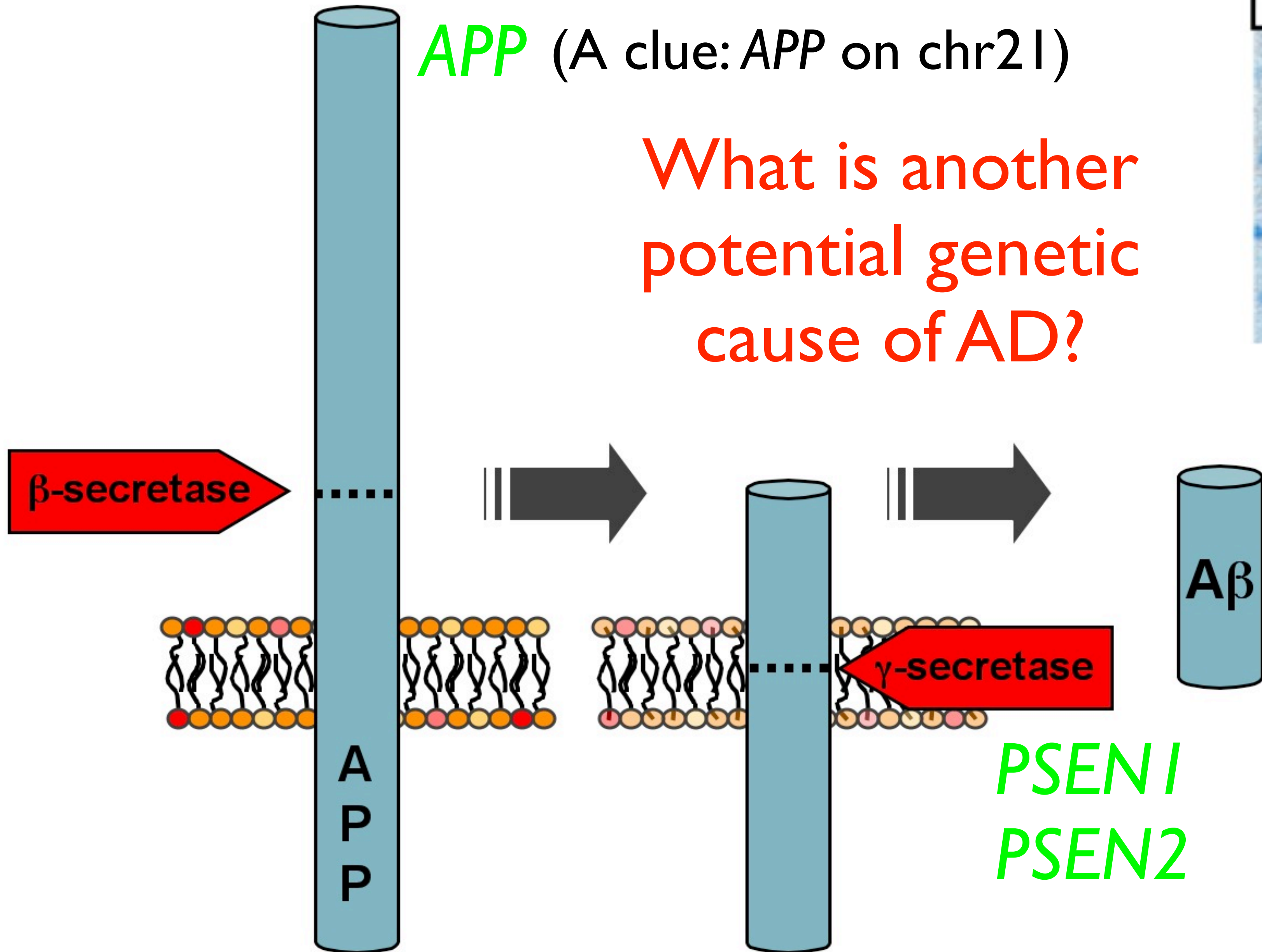
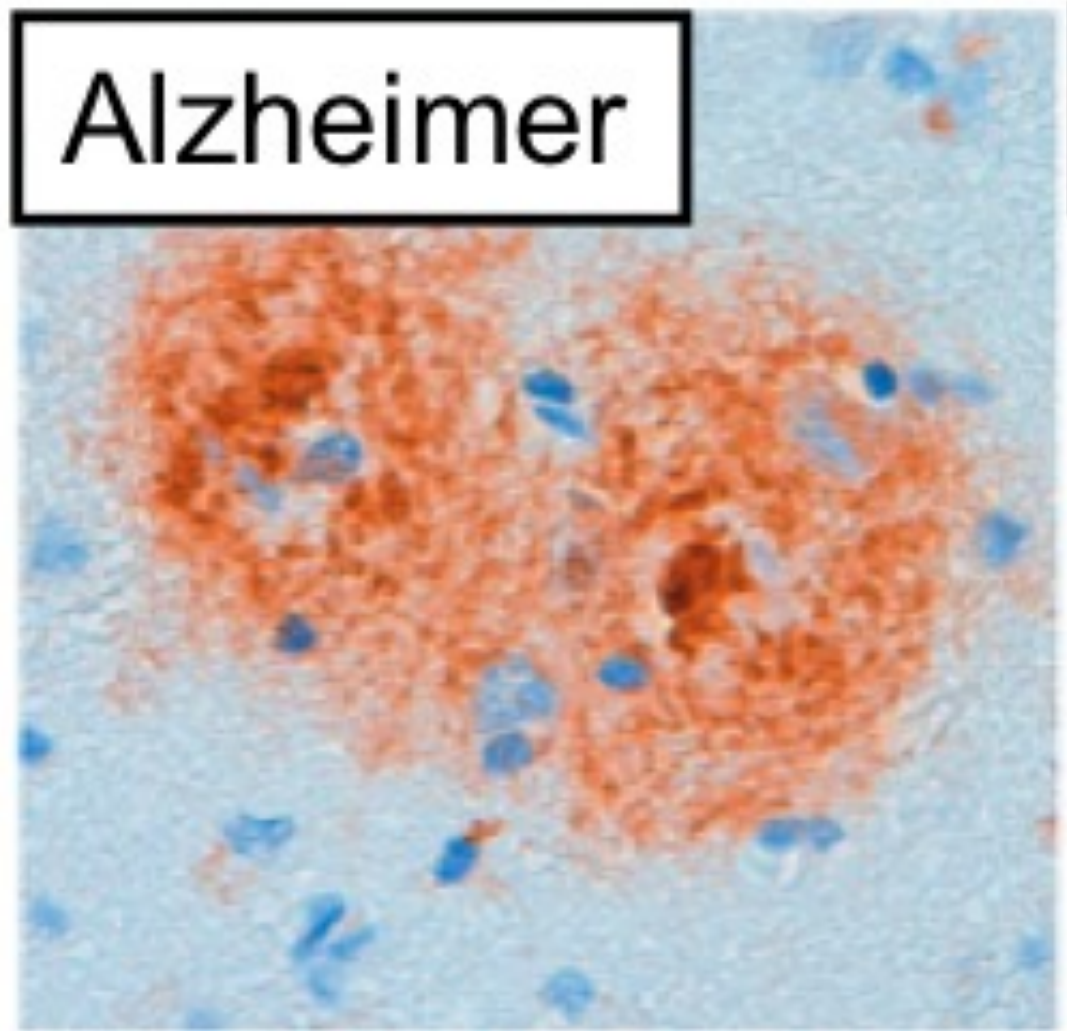


Alzheimer



APP (A clue: *APP* on chr21)

What is another
potential genetic
cause of AD?



Susceptibility Loci for Alzheimer's Disease

Gene	Protein	Polymorphism	OR (95% CI)
<i>ABCA7</i>	ATP-binding cassette, A7	rs3764650	1.23 (1.18-1.28)
<i>APOE</i>	Apolipoprotein E	rs429358 (E4)	3.81 (3.37-4.30)
<i>BIN1</i>	Bridging integrator 1	rs744373	1.17 (1.13-1.2)
<i>CD2AP</i>	CD2-associated protein	rs9349407	1.12 (1.08-1.16
<i>CD33</i>	CD33 molecule (siglec 3)	rs3865444	1.12 (1.08-1.16
<i>CLU</i>	Clusterin	rs11136000	1.14 (1.11-1.17)
<i>CR1</i>	Complement component receptor	rs3818361	1.17 (1.14-1.21)
<i>MS4A4E</i>	Membrane-spanning 4-domain A4E	rs670139	1.08 (1.05-1.11)
<i>MS4A6A</i>	Membrane-spanning 4-domain A6A	rs610932	1.11 (1.07-1.14)
<i>PICALM</i>	Phosphatidylinositol binding clathrin assembly protein	rs3851179	1.14 (1.11-1.17)

Two SNPs determine APOE variants

Variant	rs429358	rs7412
$\epsilon 2$	T	T
$\epsilon 3$	T	C
$\epsilon 4$	C	C

1 copy of $\epsilon 4$ allele = ~2 times increased risk for AD
2 copies of $\epsilon 4$ allele = ~11 times increased risk for AD

Today's Plan

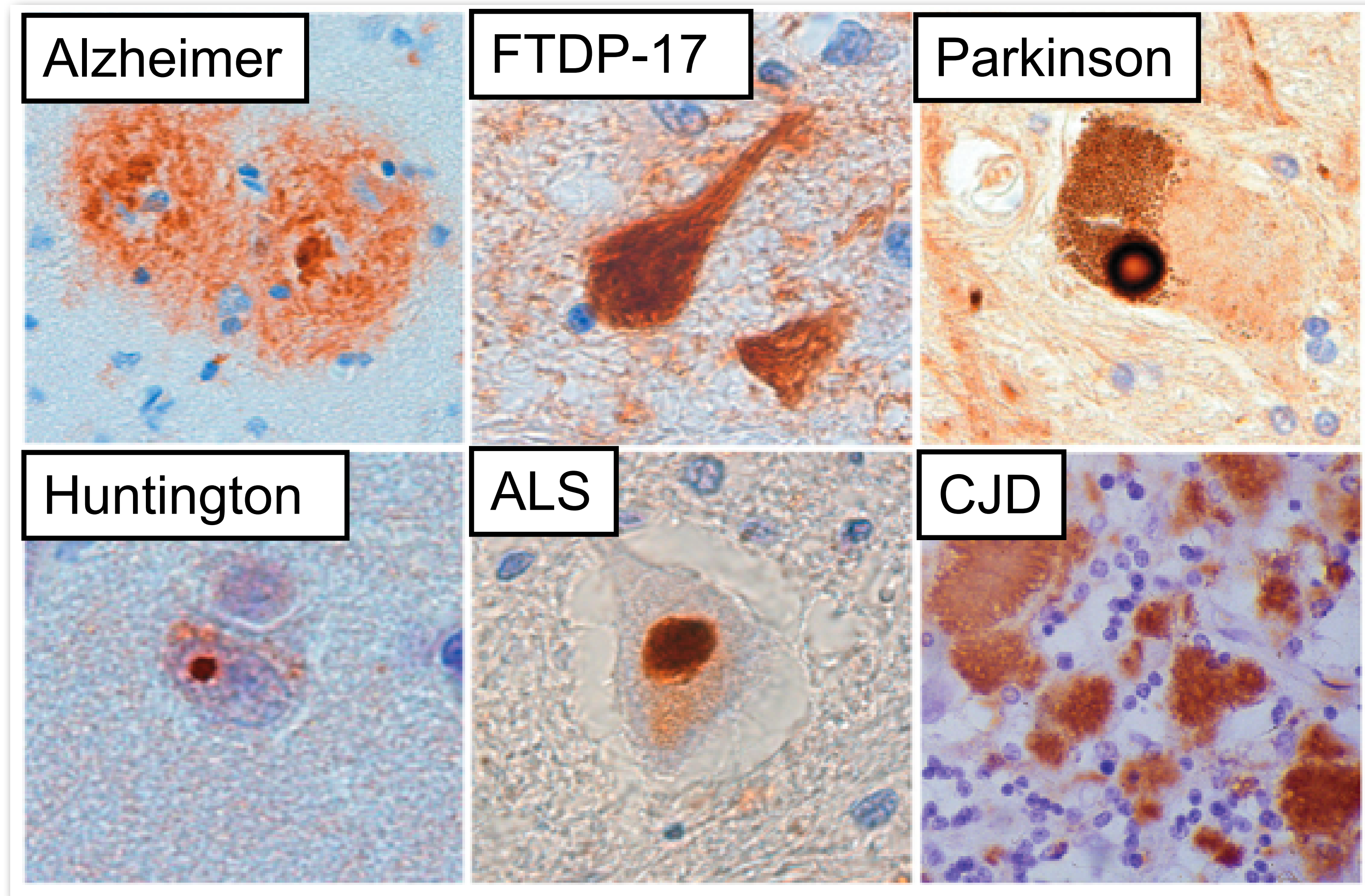
1. Huntington's Disease
2. Alzheimer's Disease
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4. Amyotrophic lateral sclerosis (ALS)
5. Parkinson's Disease

Frontotemporal lobar dementias (FTLDs)



- Degeneration in frontal and temporal lobes of the brain
- >12% of people treated at dementia clinics
- Onset in 50's and 60's
- Language difficulties and inappropriate behavior
- Shoplift, overeat, excessive interest in sex

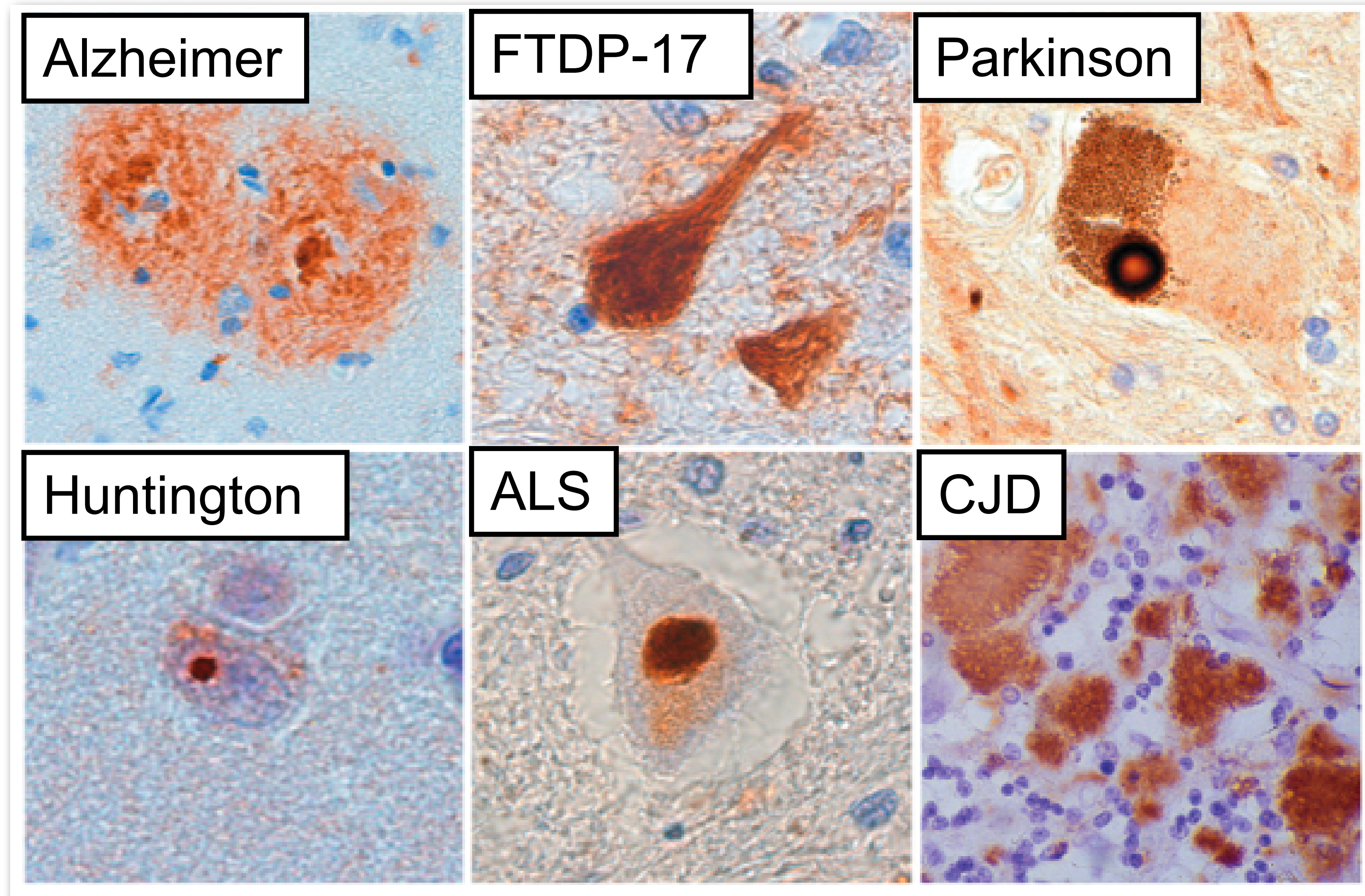
Protein Aggregates in Neurodegenerative Diseases



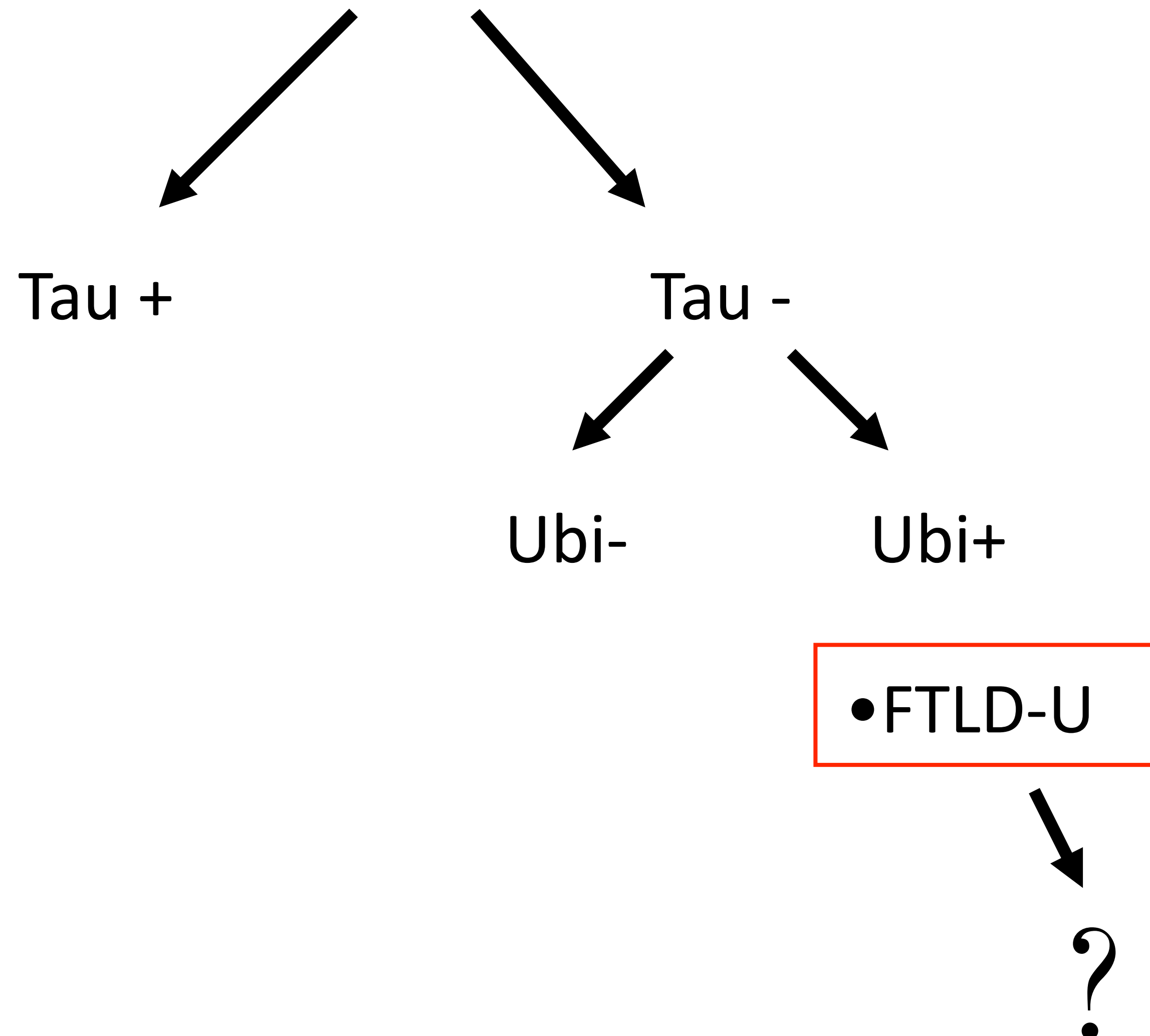
Mendelian Genes for FTD

Gene	Protein	Location	Inheritance
<i>CHMP2B</i>	Chromatin modifying protein 2B	3p11.2	dominant
<i>GRN</i>	Granulin	17q21.31	dominant
<i>MAPT</i>	Microtubule-associated protein tau	17q21.31	dominant
<i>VCP</i>	Valosin-containing protein	9p13.3	dominant

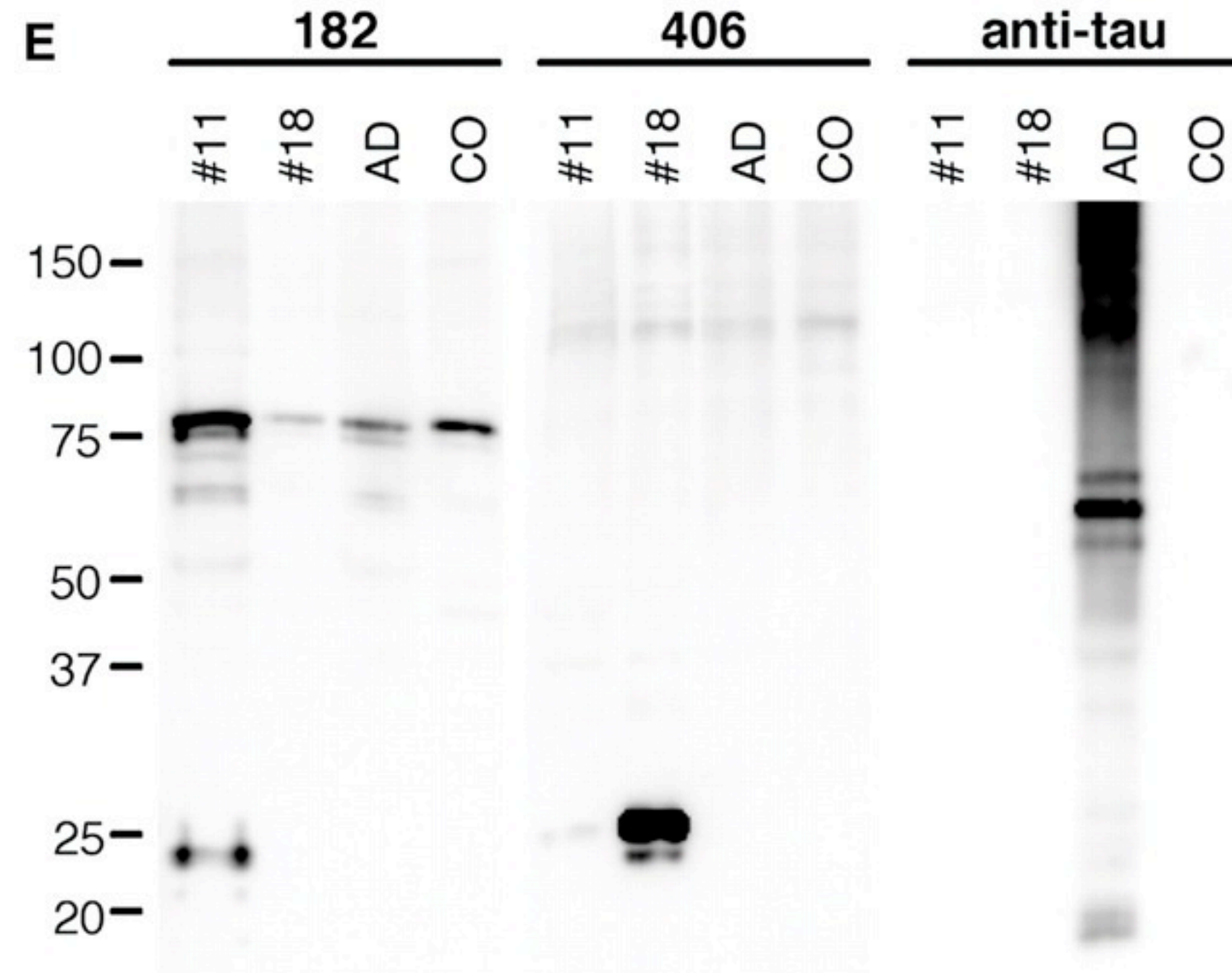
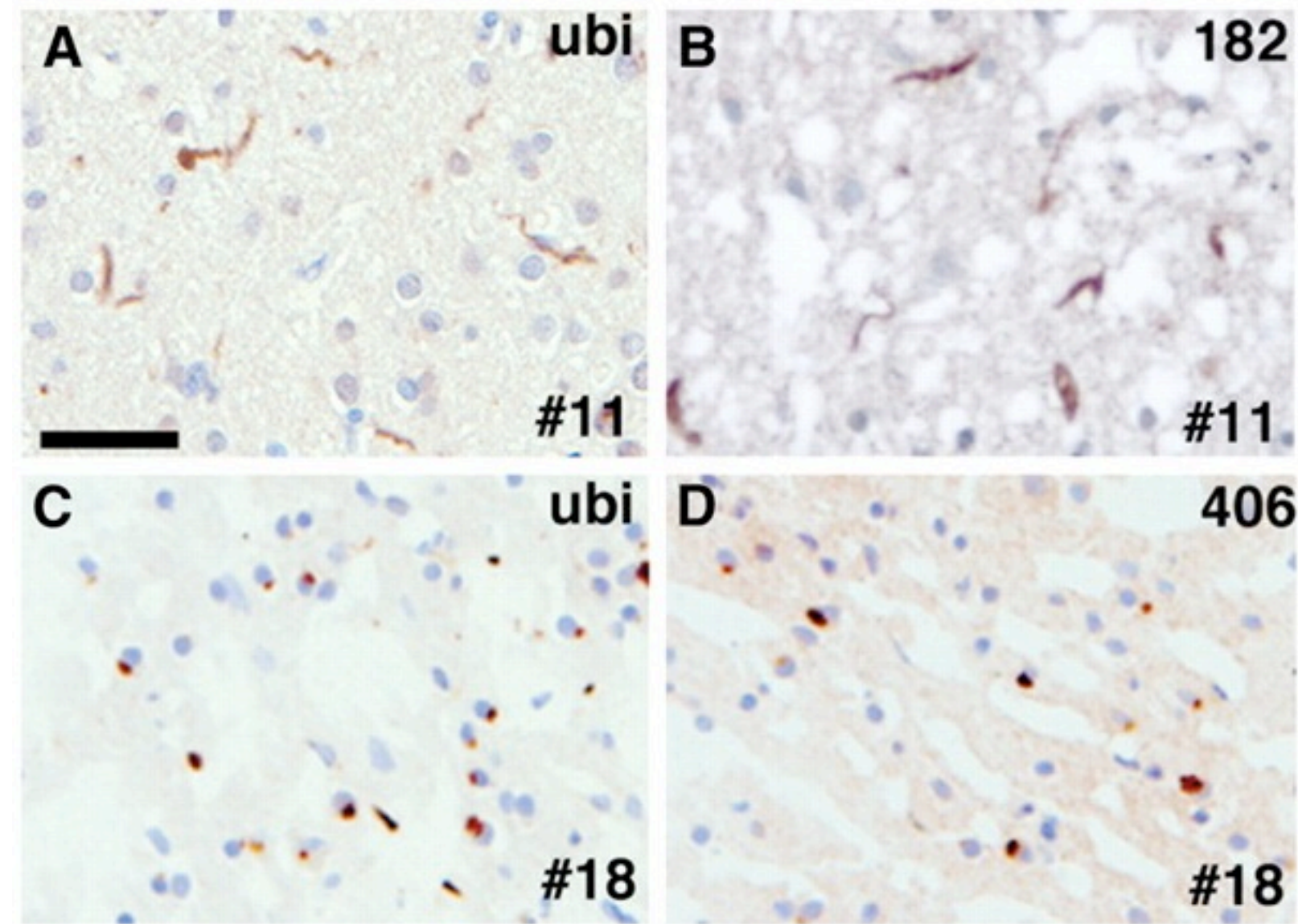
Protein Aggregates in Neurodegenerative Diseases



Frontotemporal lobar dementias (FTLDs)



TDP-43



F

1 MSEYIRVTEDENDIEPIEIPSEDDGTVLLSTVTAQFPGACGLRYRNPVSQCMRGVRLVEGILHAPDAGWGN

71 LVYVVNYPKDNKRKMDDETDAASSAVKVKRAVQKTSDLIVLGLPWKTTEODLKEYFSTFGEVLMVOVKKDLK

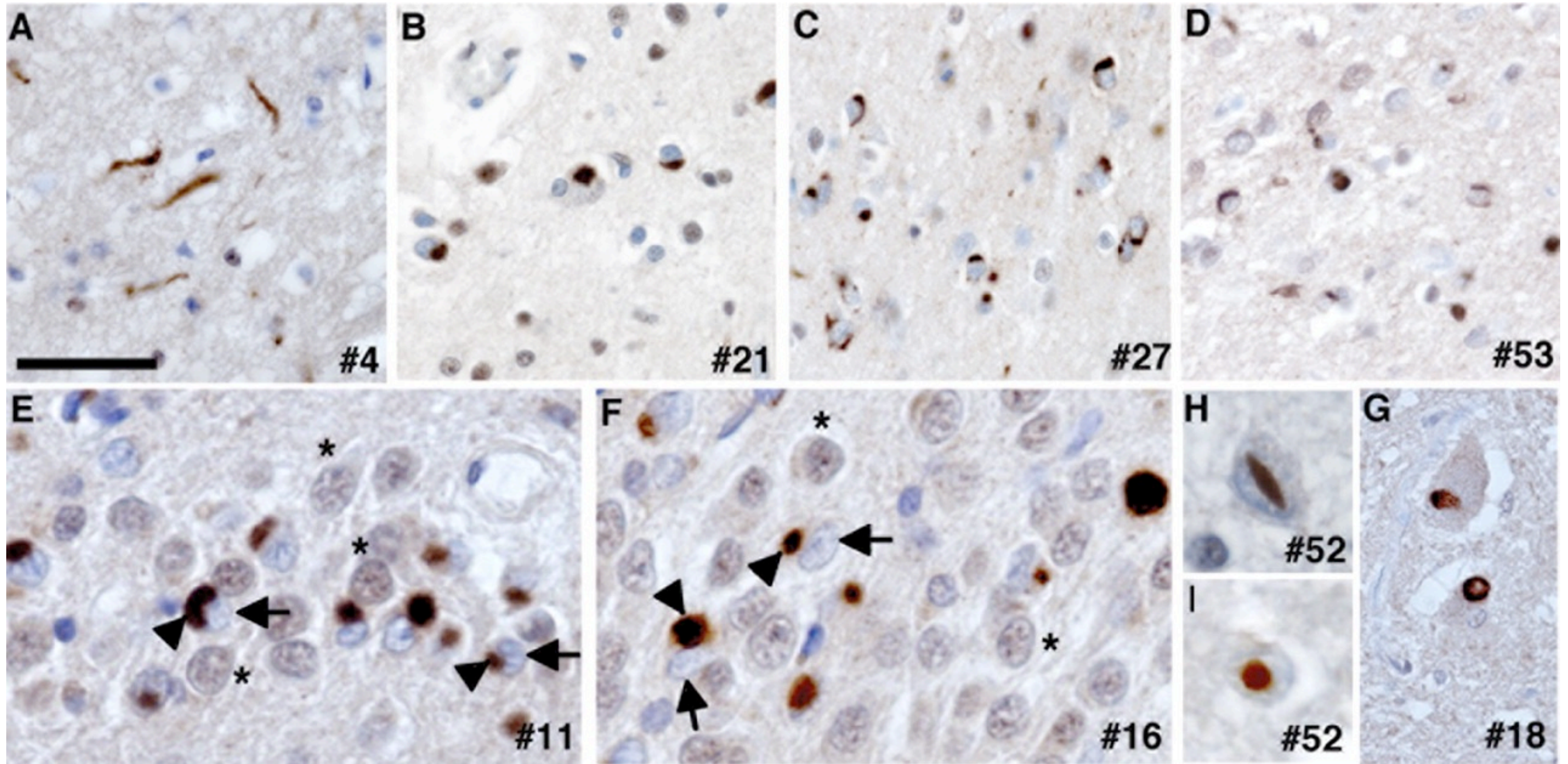
141 TGHSKGFGFVRFTTEYETOVKVMSORHMIDGRWCDCKLPNSKQSQDEPLRSRKVFVGRCTEDMTEDELREF

211 FSOYGDVMDVFIKPFRAFAFVTFADDOIAOSLCGEDLIKGISVHISNAEPKHNSNRQLERSGRFGGNP

281 GGFGNQGGFGNSRGGGAGLGNNQGSNMGGGMNFGAFSINPAMMAAAQAALQSSWGMMGLASQQNQSGPS

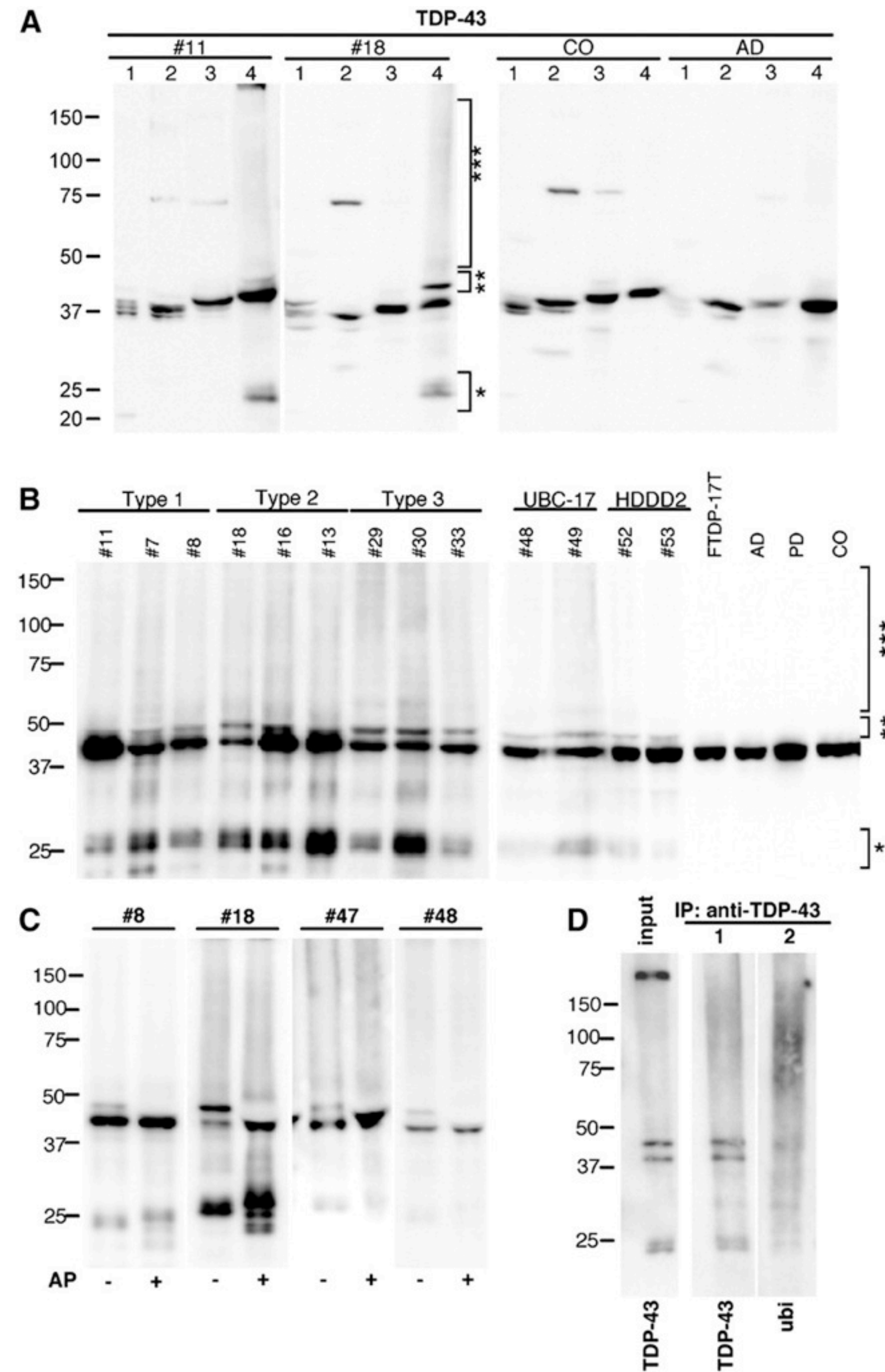
351 GNNQNQGNMQREPNQAFGSGNNSYSGSNSGAAIGWGSASNAGSGSGFNNGGFGSSMDSKSSGWGM

TDP-43 pathology in FTLD-U



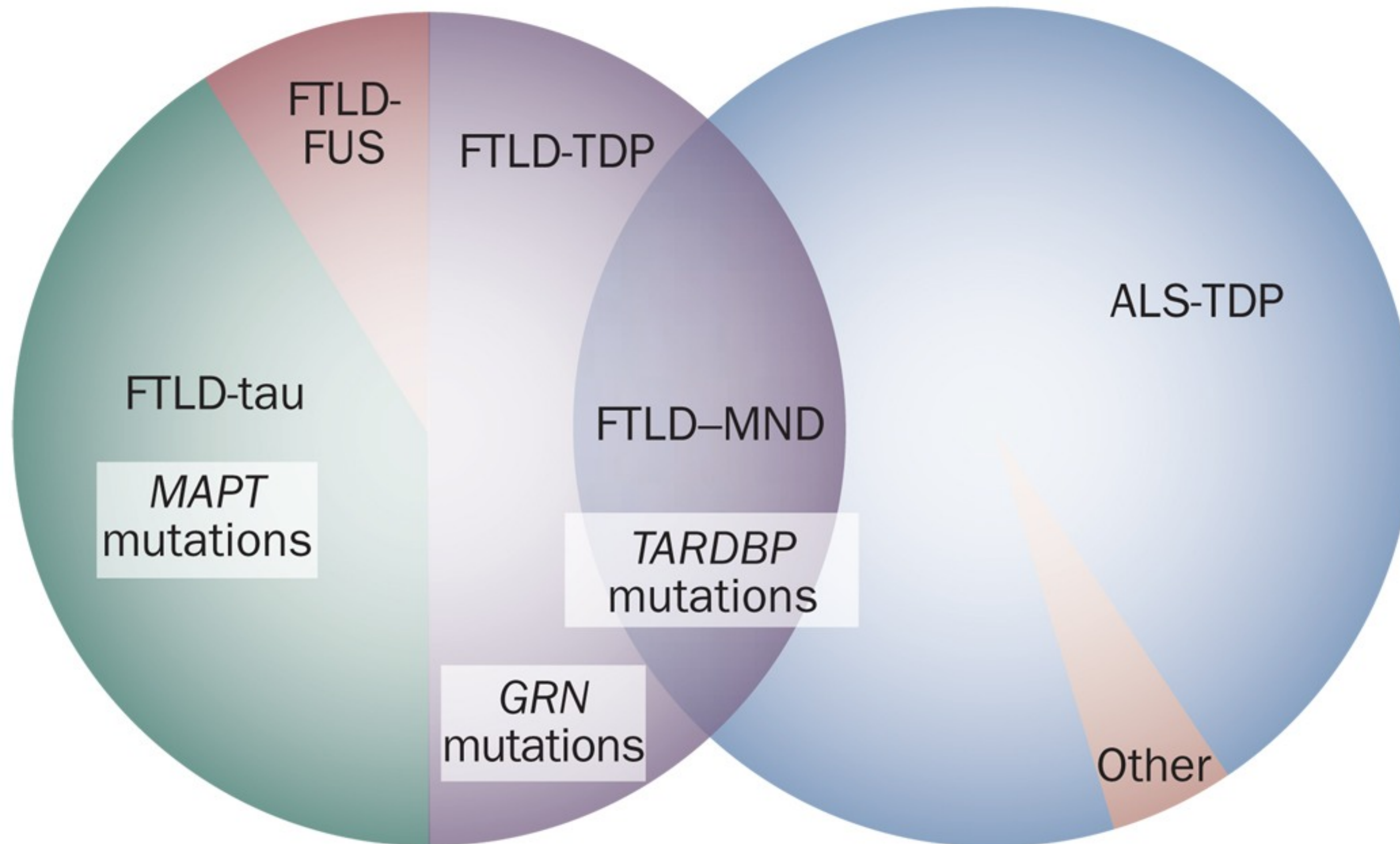
TDP-43

“biochemical signature”

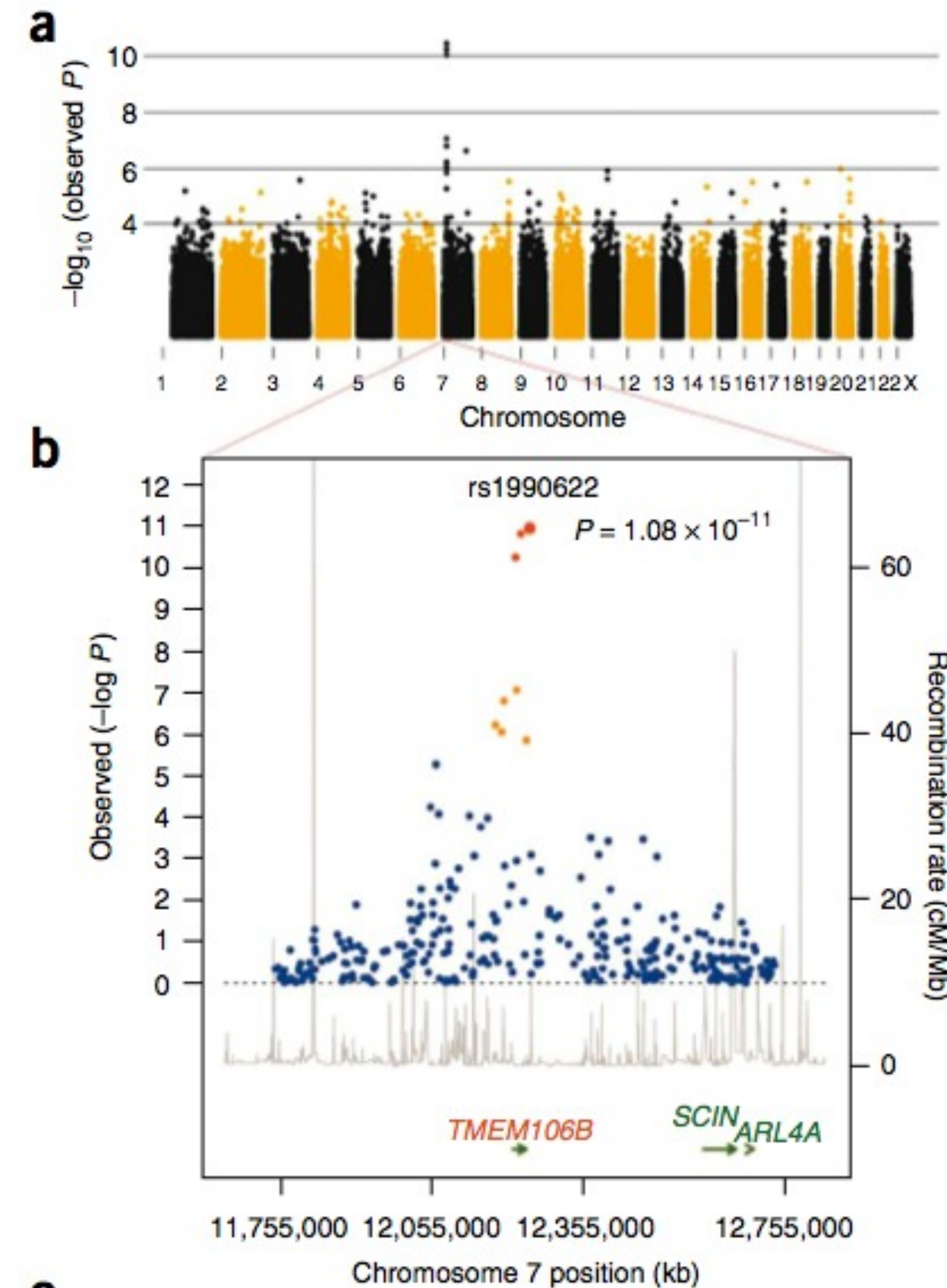


Neumann et al.,
Science 2006

Pathological subtypes of FTLD and ALS



GWAS for frontotemporal dementia susceptibility loci



rs1990622
TMEM106B
OR 1.64 (1.41-1.89)

REPORTS

Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

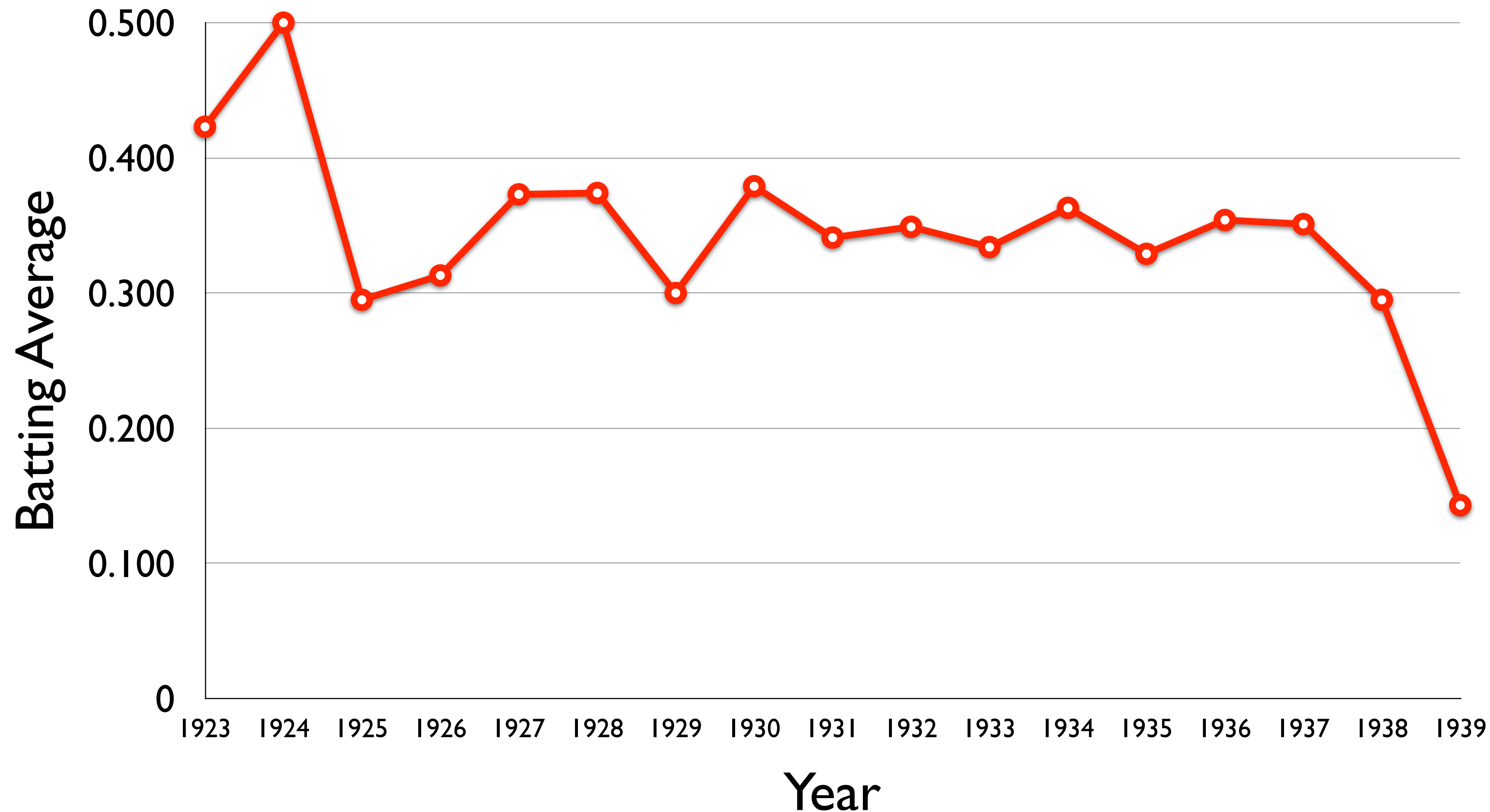
Manuela Neumann,^{1,11*} Deepak M. Sampathu,^{1*} Linda K. Kwong,^{1*} Adam C. Truax,¹
Matthew C. Micsenyi,¹ Thomas T. Chou,² Jennifer Bruce,¹ Theresa Schuck,¹ Murray Grossman,^{3,4}
Christopher M. Clark,^{3,4} Leo F. McCluskey,³ Bruce L. Miller,⁶ Eliezer Masliah,⁷
Ian R. Mackenzie,⁸ Howard Feldman,⁹ Wolfgang Feiden,¹⁰ Hans A. Kretzschmar,¹¹
John Q. Trojanowski,^{1,4,5} Virginia M.-Y. Lee^{1,4,5†}

***Science*, October 6, 2006**

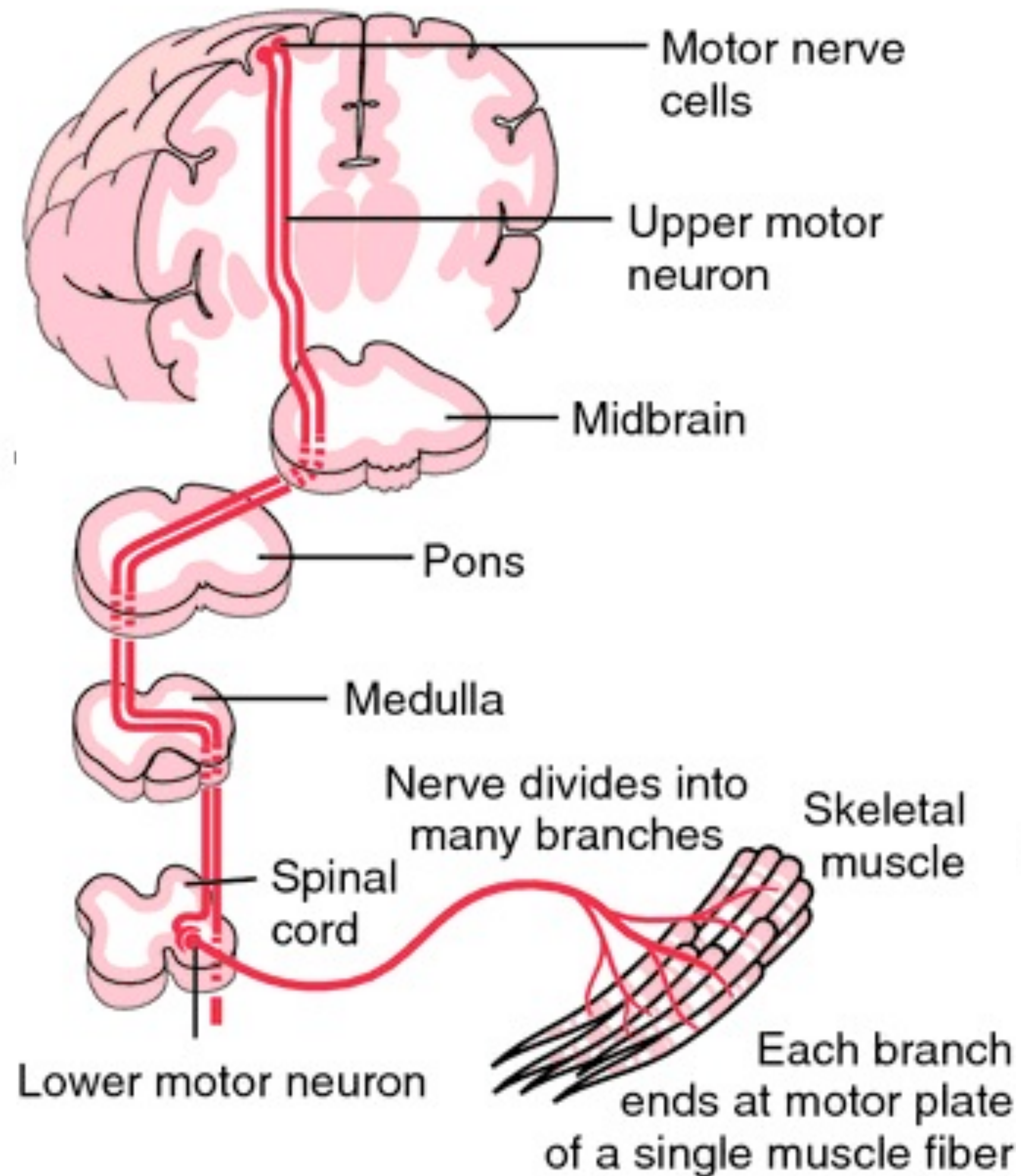
Today's Plan

1. Huntington's Disease
2. Alzheimer's Disease
3. Frontotemporal Dementia
4. Amyotrophic lateral sclerosis (ALS)
5. Parkinson's Disease

Lou Gehrig's career batting average

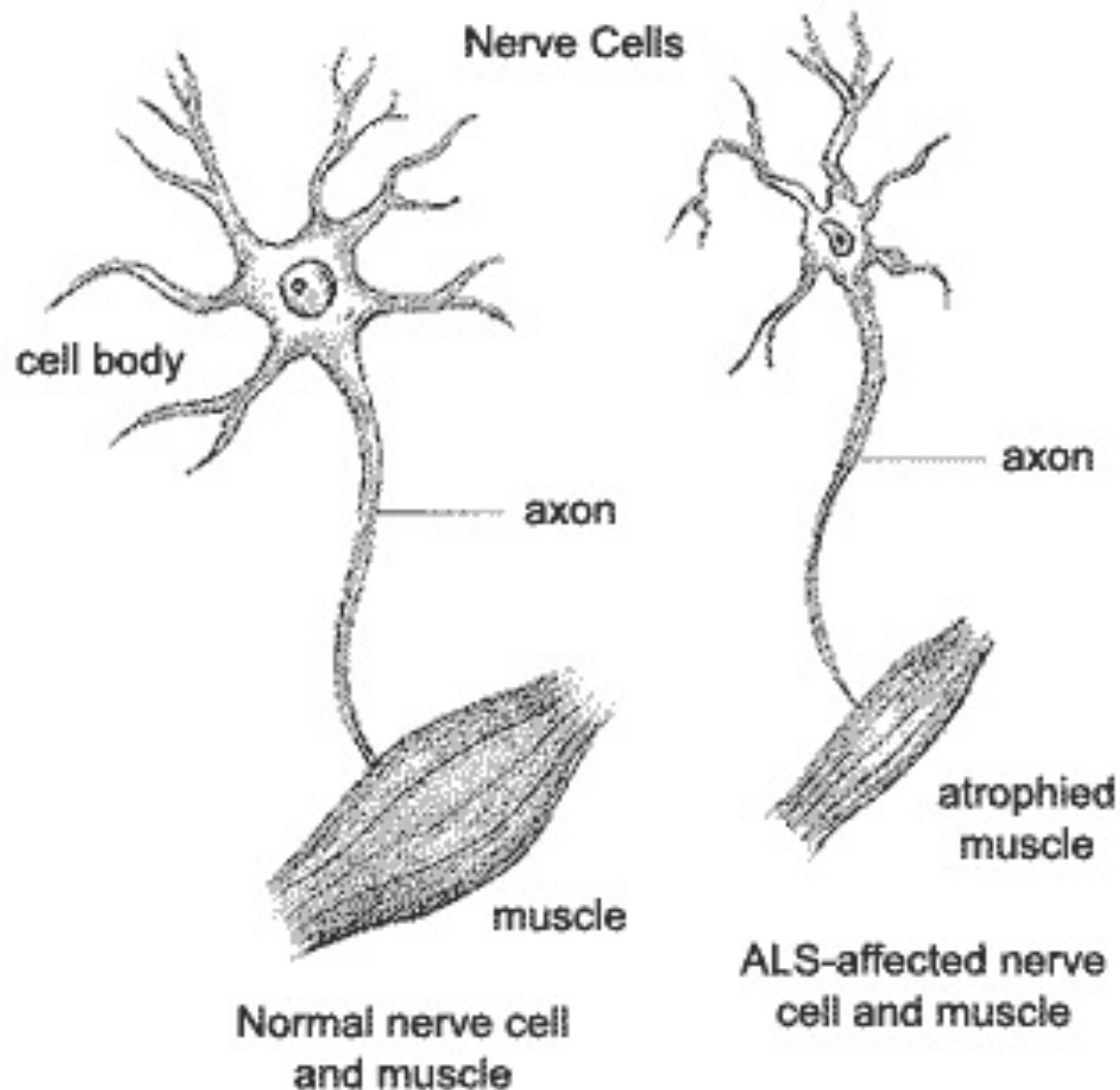


Amyotrophic Lateral Sclerosis (ALS)



- Affects adults in mid-to-late life
- progressive muscle weakness
- muscle atrophy
- Selective degeneration of motor neurons in brain-stem and spinal cord
- Sporadic and Familial Forms
- *SOD1* mutations linked to FALS
- *SOD1* mutations only account for ~2% of ALS. What are other causes?

Amyotrophic Lateral Sclerosis (ALS)

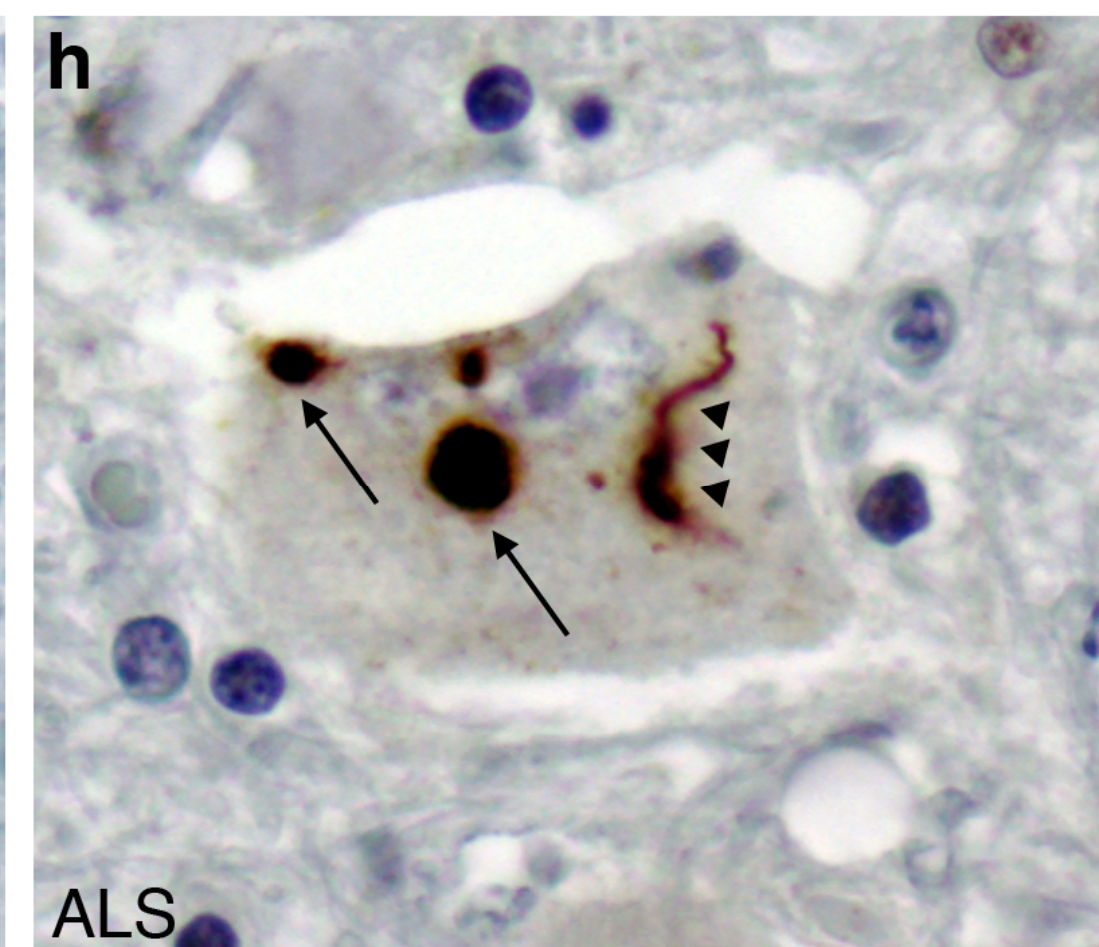
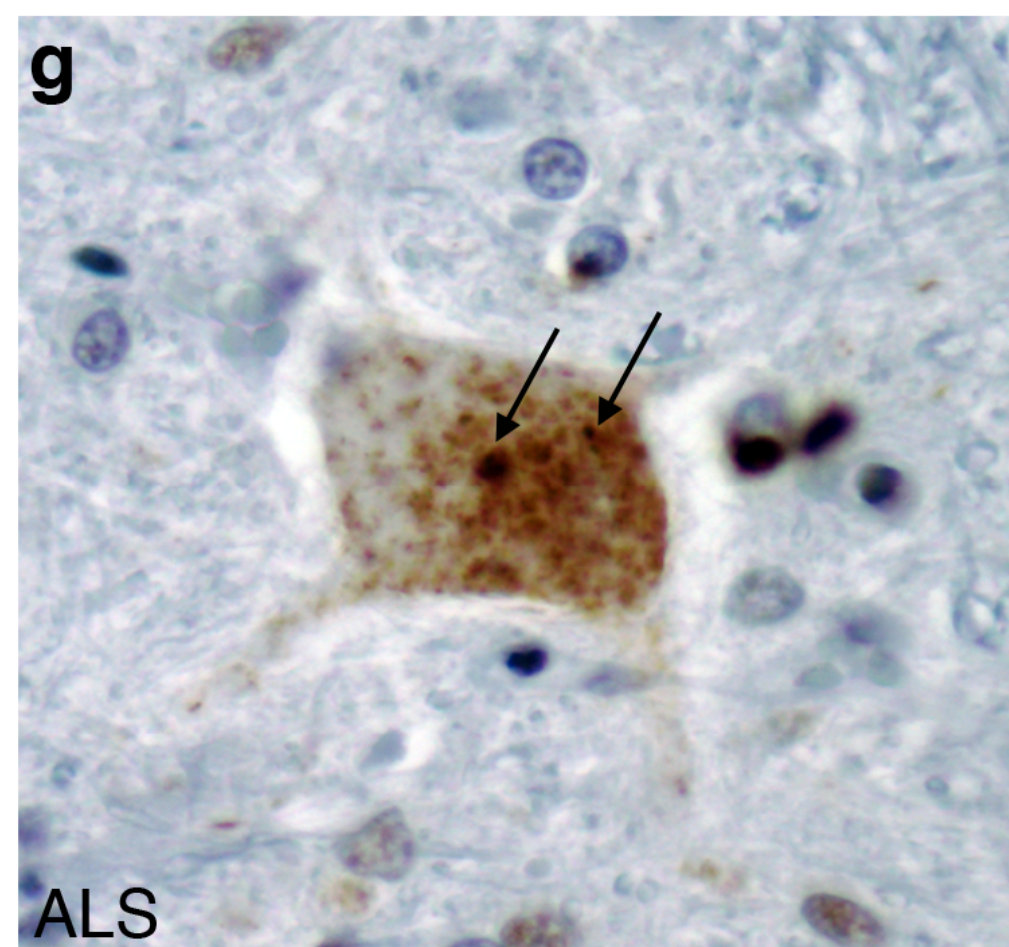
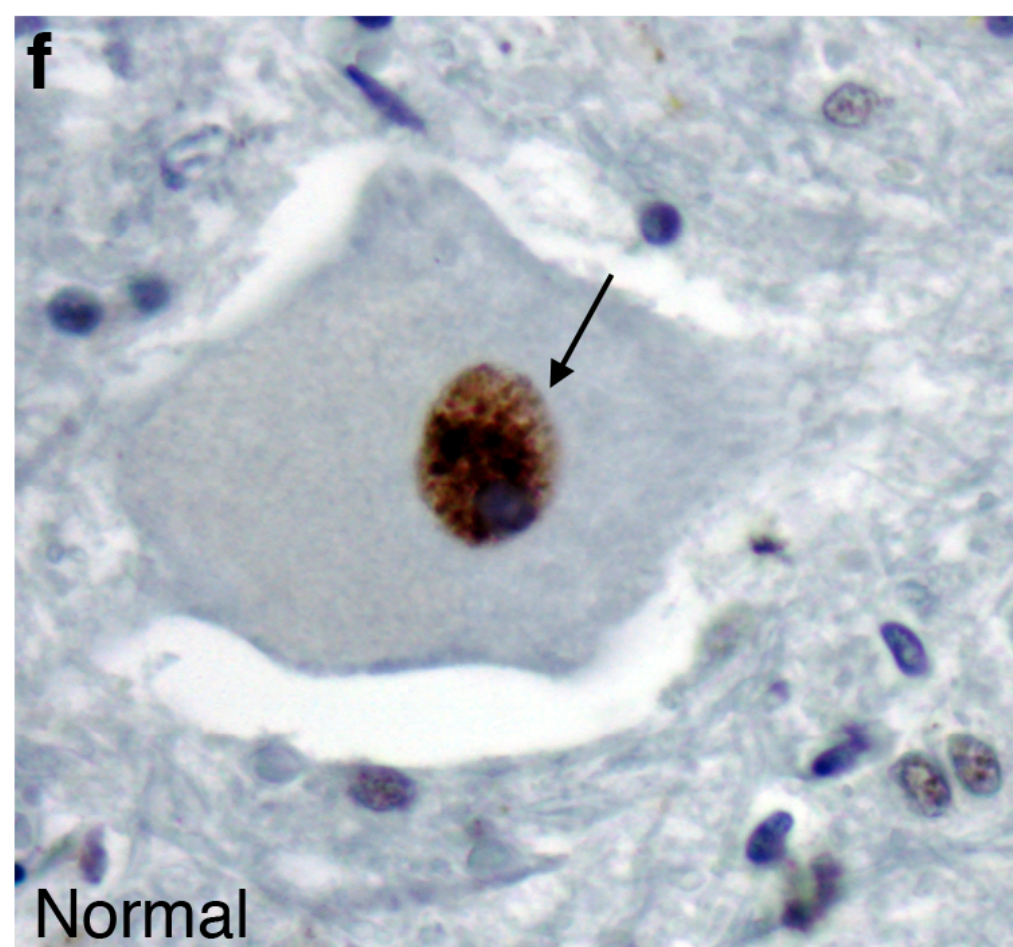
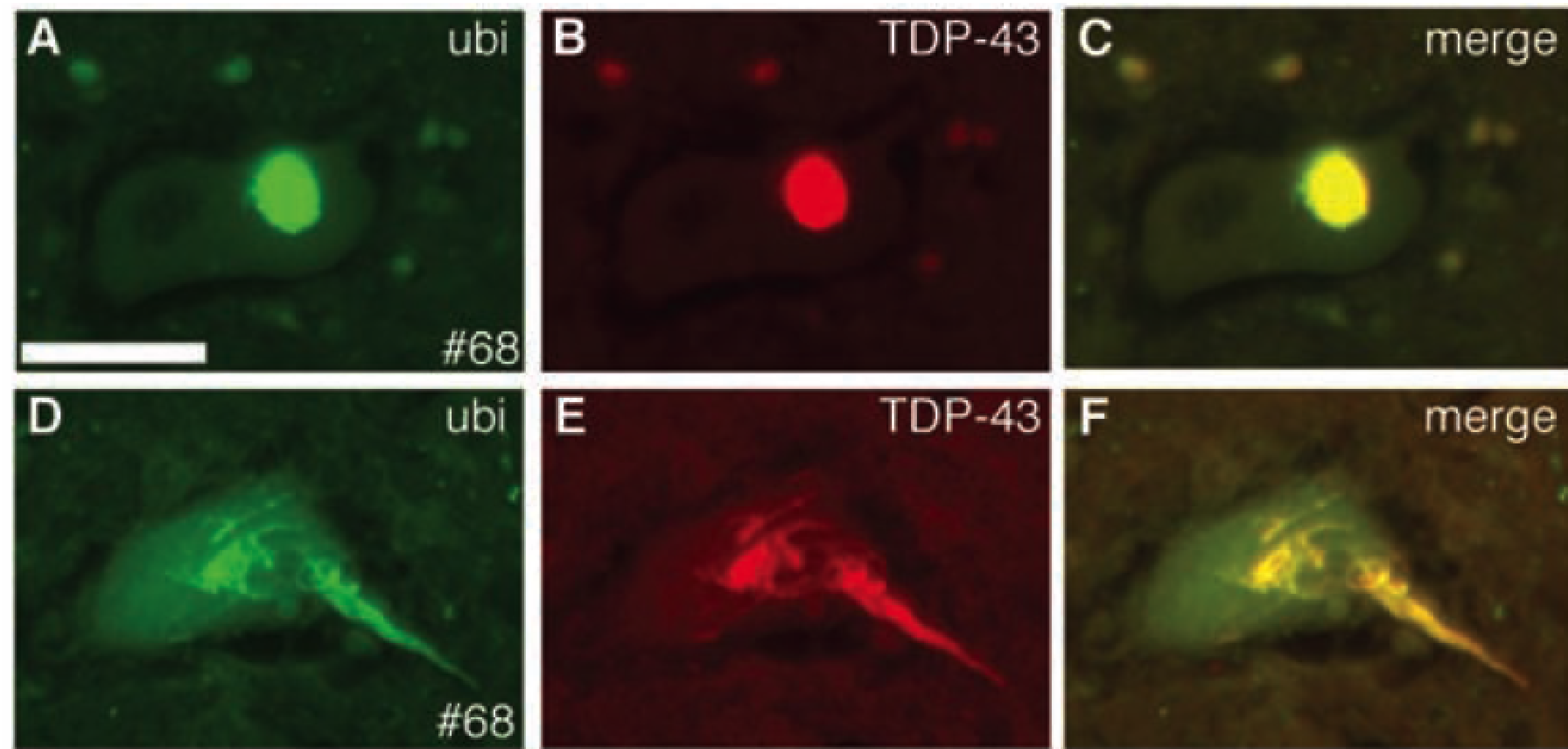


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Stephen Hawking



TDP-43 pathology in sporadic ALS

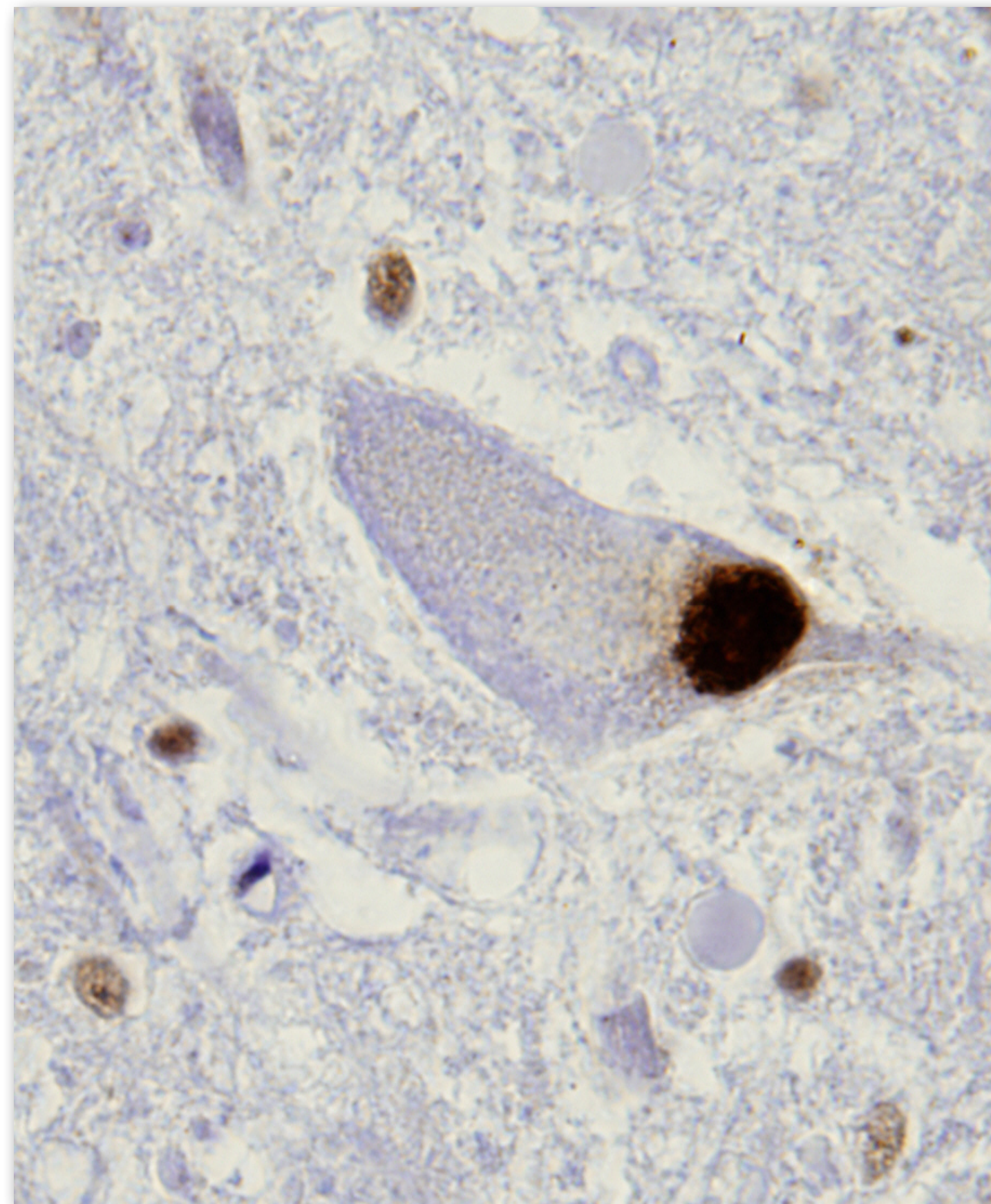


Editorial

TDP-43 in amyotrophic lateral sclerosis: Pathophysiology or patho-babel?

Jeffrey D. Rothstein, MD, PhD

Department of Neurology, Johns Hopkins University, Baltimore, MD



TDP-43 Mutations Linked to ALS

TDP-43 A315T Mutation in Familial Motor Neuron Disease

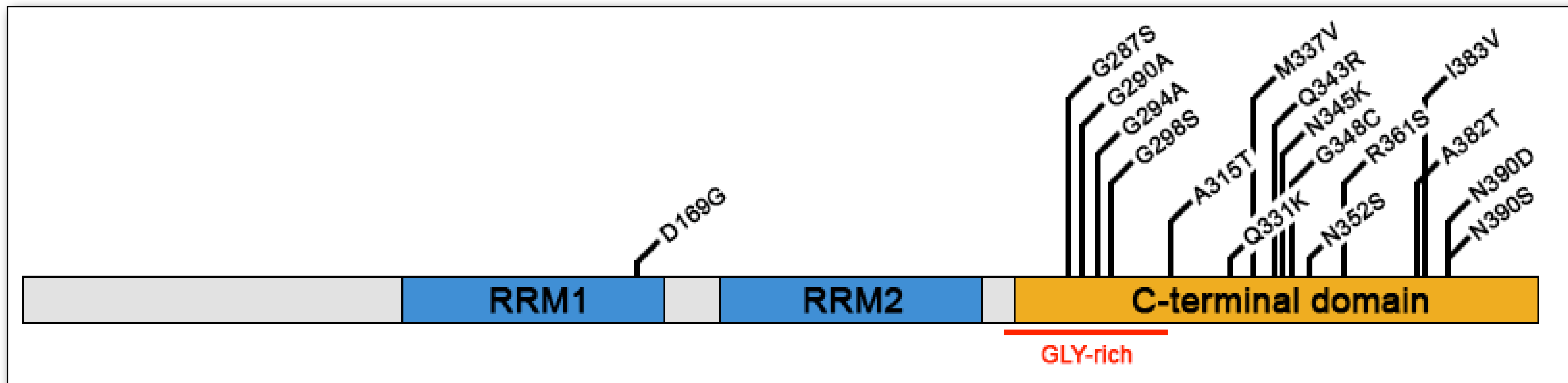
Michael A. Gitcho, PhD,^{1,2} Robert H. Baloh, MD, PhD,² Sumi Chakraverty, MS,^{1,3} Kevin Mayo, BS,³ Joanne B. Norton, RN,^{1,3} Denise Levitch, RN,^{1,3} Kimmo J. Hatanpaa, MD, PhD,⁴ Charles L. White III, MD,⁴ Eileen H. Bigio, MD,^{5,6} Richard Caselli, MD,⁷ Matt Baker, BSc,⁸ Muhammad T. Al-Lozi, MBBS,² John C. Morris, MD,^{1,2,9} Alan Pestronk, MD,² Rosa Rademakers, PhD,⁸ Alison M. Goate, DPhil,^{1-3,10} and Nigel J. Cairns, PhD, FRCPATH^{1,2,9}

TDP-43 Mutation in Familial Amyotrophic Lateral Sclerosis

Akio Yokoseki, MD,¹ Atsushi Shiga, Mmed,^{1,2} Chun-Feng Tan, MD, PhD,³ Asako Tagawa, MD,¹ Hiroyuki Kaneko, Mmed,^{1,2} Akihito Koyama, Mmed,^{1,2} Hiroto Eguchi, MD,⁴ Akira Tsujino, MD,⁴ Takeshi Ikeuchi, MD, PhD,² Akiyoshi Kakita, MD, PhD,³ Koichi Okamoto, MD, PhD,⁵ Masatoyo Nishizawa, MD, PhD,¹ Hitoshi Takahashi, MD, PhD,³ and Osamu Onodera, MD, PhD²

TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis

Edor Kabashi^{1,6}, Paul N Valdmanis^{1,6}, Patrick Dion¹, Dan Spiegelman¹, Brendan J McConkey², Christine Vande Velde¹, Jean-Pierre Bouchard³, Lucette Lacomblez⁴, Ksenia Pochigaeva⁴, Francois Salachas⁴, Pierre-Francois Pradat⁴, William Camu⁵, Vincent Meininger⁴, Nicolas Dupre^{1,3} & Guy A Rouleau¹



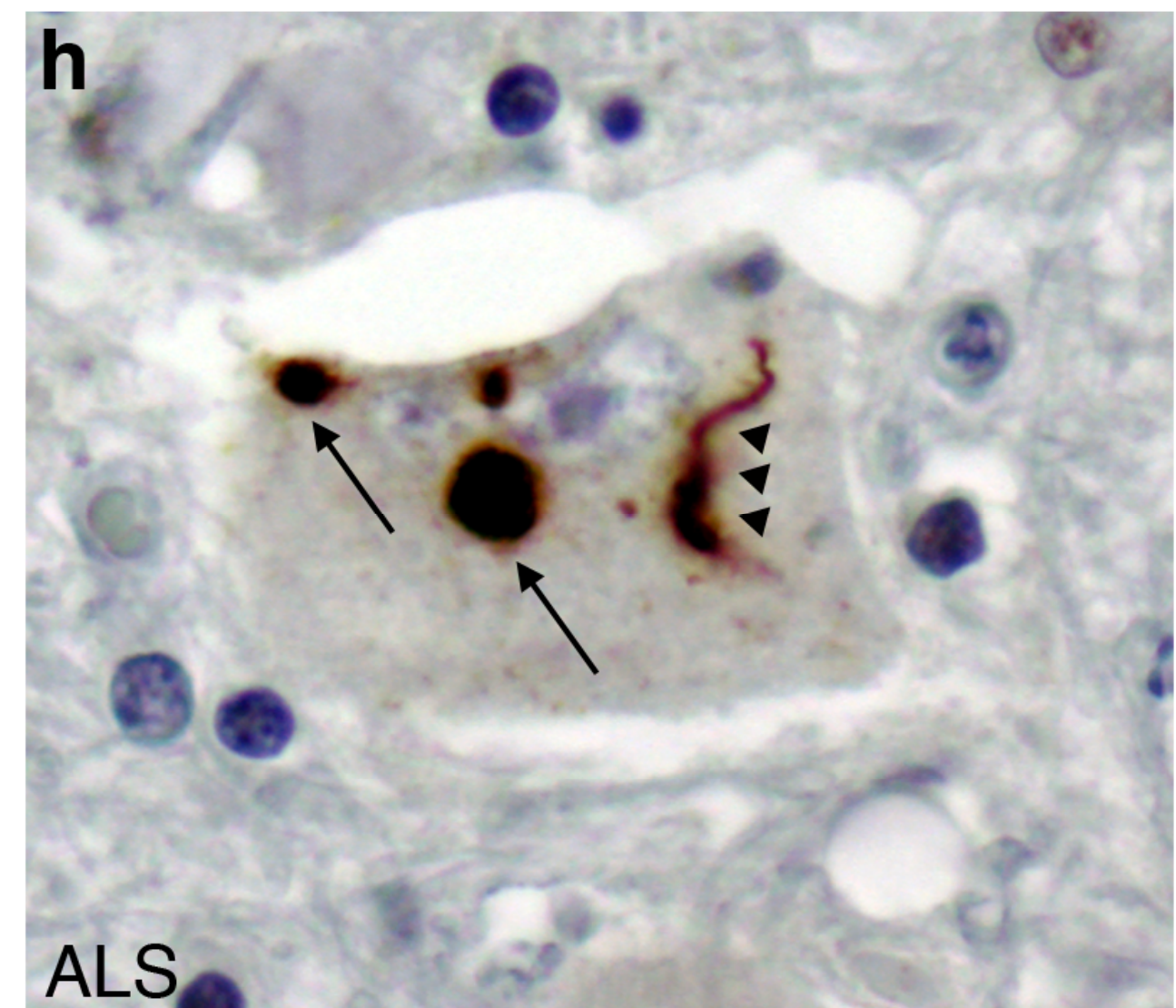
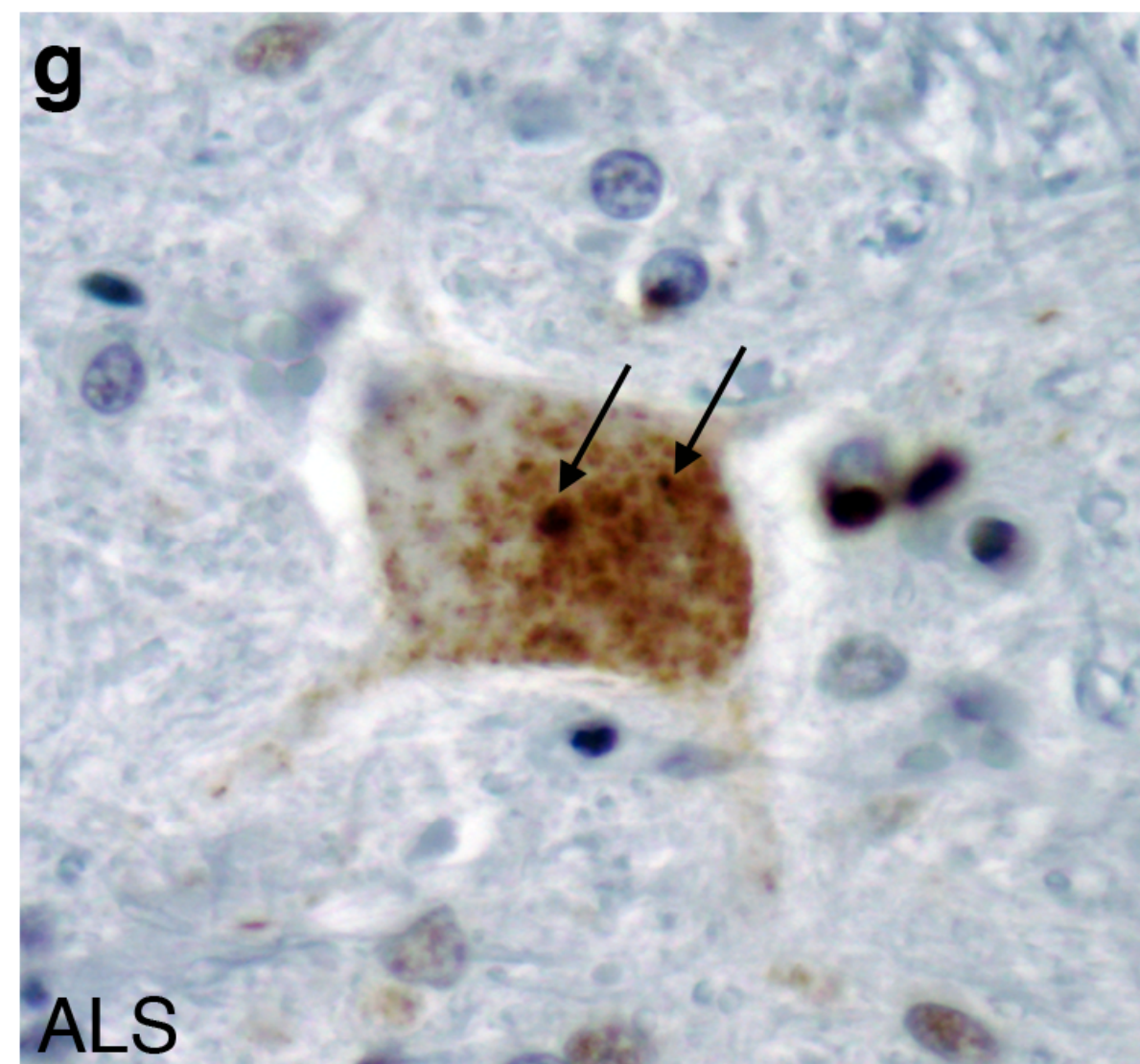
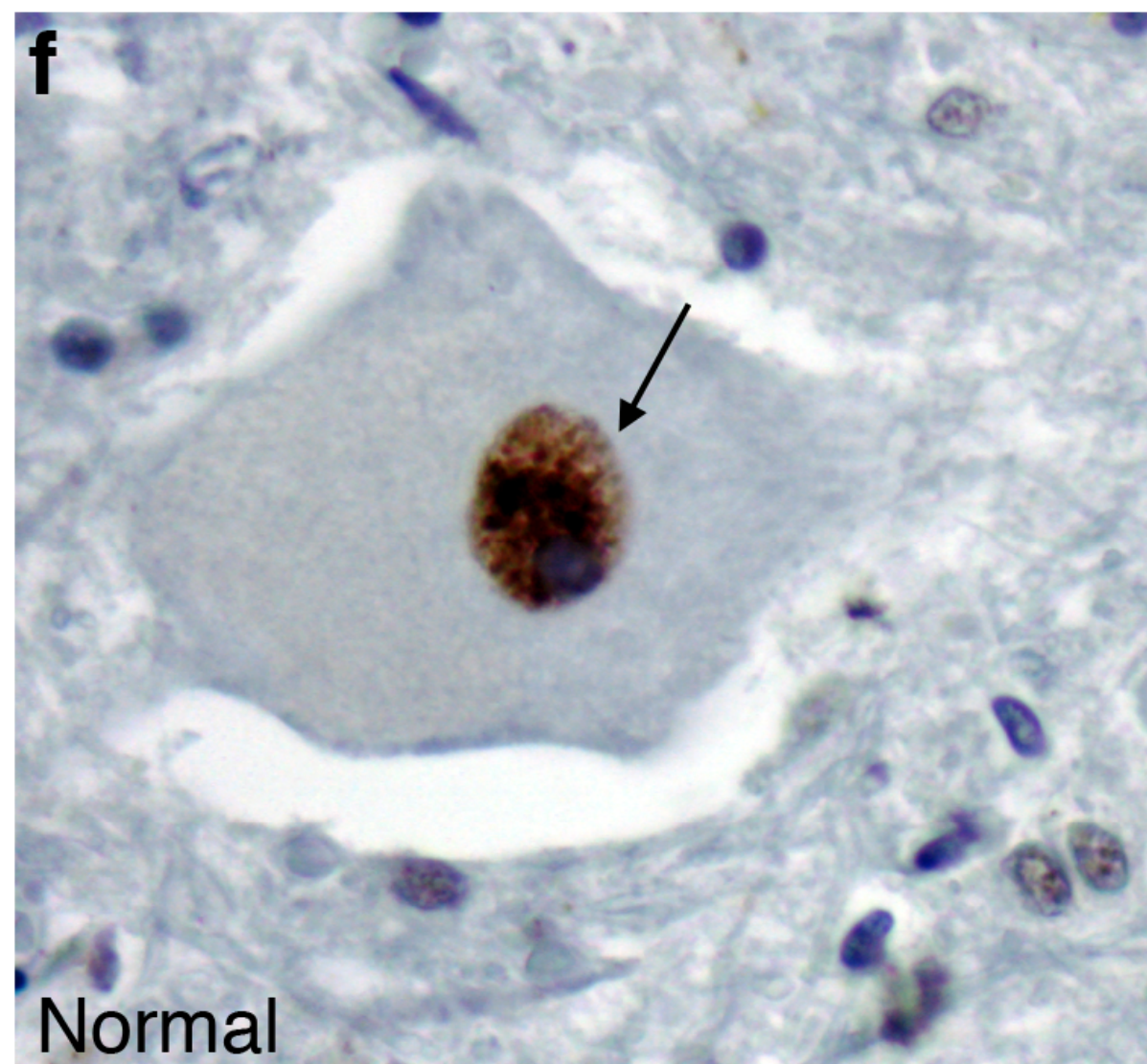
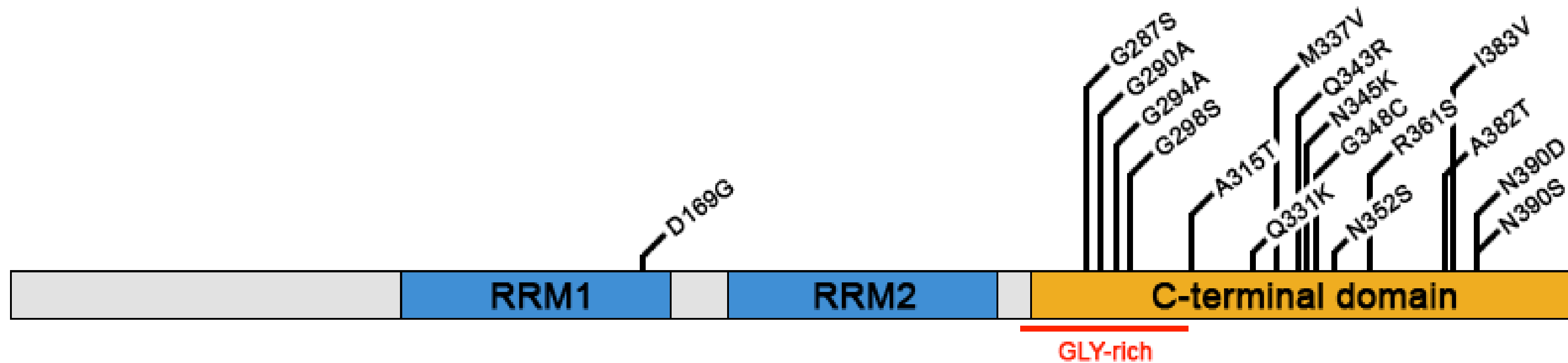
TDP-43 Mutations in Familial and Sporadic Amyotrophic Lateral Sclerosis

Jemeen Sreedharan,^{1*} Ian P. Blair,^{3,4*} Vineeta B. Tripathi,^{1*} Xun Hu,¹ Caroline Vance,¹ Boris Rogelj,¹ Steven Ackerley,^{1,2} Jennifer C. Durnall,³ Kelly L. Williams,³ Emanuele Buratti,⁵ Francisco Baralle,⁵ Jacqueline de Belleruche,⁶ J. Douglas Mitchell,⁷ P. Nigel Leigh,¹ Ammar Al-Chalabi,¹ Christopher C. Miller,^{1,2} Garth Nicholson,^{3,4,8*} Christopher E. Shaw^{1*†}

TARDBP mutations in amyotrophic lateral sclerosis with TDP-43 neuropathology: a genetic and histopathological analysis

Vivianna M Van Deerlin, James B Leverenz, Lynn M Bekris, Thomas D Bird, Wuxing Yuan, Lauren B Elman, Dana Clay, Elisabeth McCarty Wood, Alice S Chen-Plotkin, Maria Martinez-Lage, Ellen Steinbart, Leo McCluskey, Murray Grossman, Manuela Neumann, I-Lin Wu, Wei-Shiung Yang, Robert Kalb, Douglas R Galasko, Thomas J Montine, John Q Trojanowski, Virginia M-Y Lee, Gerard D Schellenberg, Chang-En Yu

How do TDP-43 mutations cause disease?



Another RNA binding protein linked to ALS

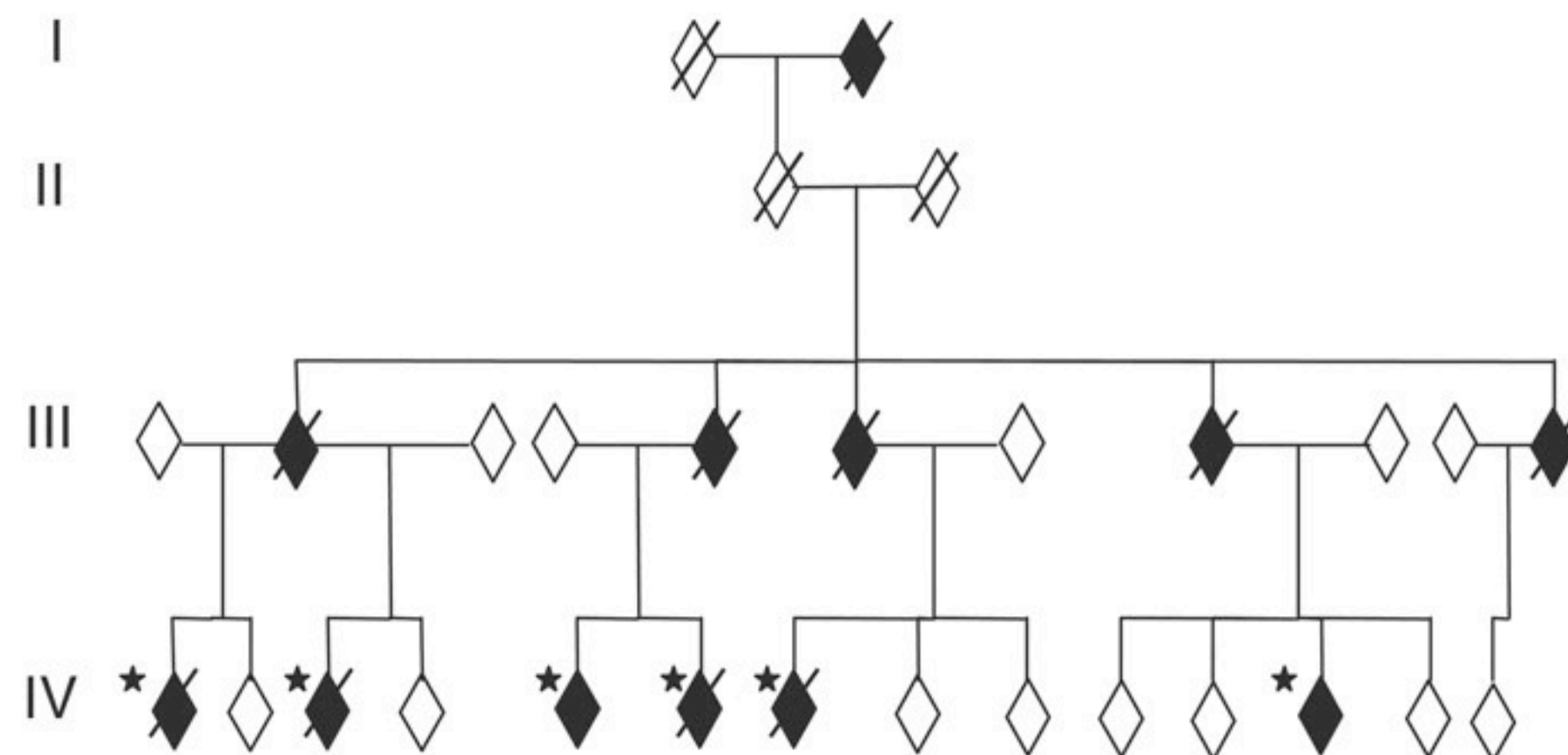
Mutations in FUS, an RNA Processing Protein, Cause Familial Amyotrophic Lateral Sclerosis Type 6

Caroline Vance,^{1*} Boris Rogelj,^{1*} Tibor Hortobágyi,^{1*} Kurt J. De Vos,^{2*}
Agnes Lumi Nishimura,¹ Jemeen Sreedharan,¹ Xun Hu,¹ Bradley Smith,¹
Deborah Ruddy,¹ Paul Wright,¹ Jeban Ganesalingam,¹ Kelly L. Williams,³ Vineeta Tripathi,¹
Safa Al-Saraj,¹ Ammar Al-Chalabi,¹ P. Nigel Leigh,¹ Ian P. Blair,^{3,5} Garth Nicholson,^{3,4,5}
Jackie de Belleruche,⁶ Jean-Marc Gallo,¹ Christopher C. Miller,^{1,2} Christopher E. Shaw^{1†}

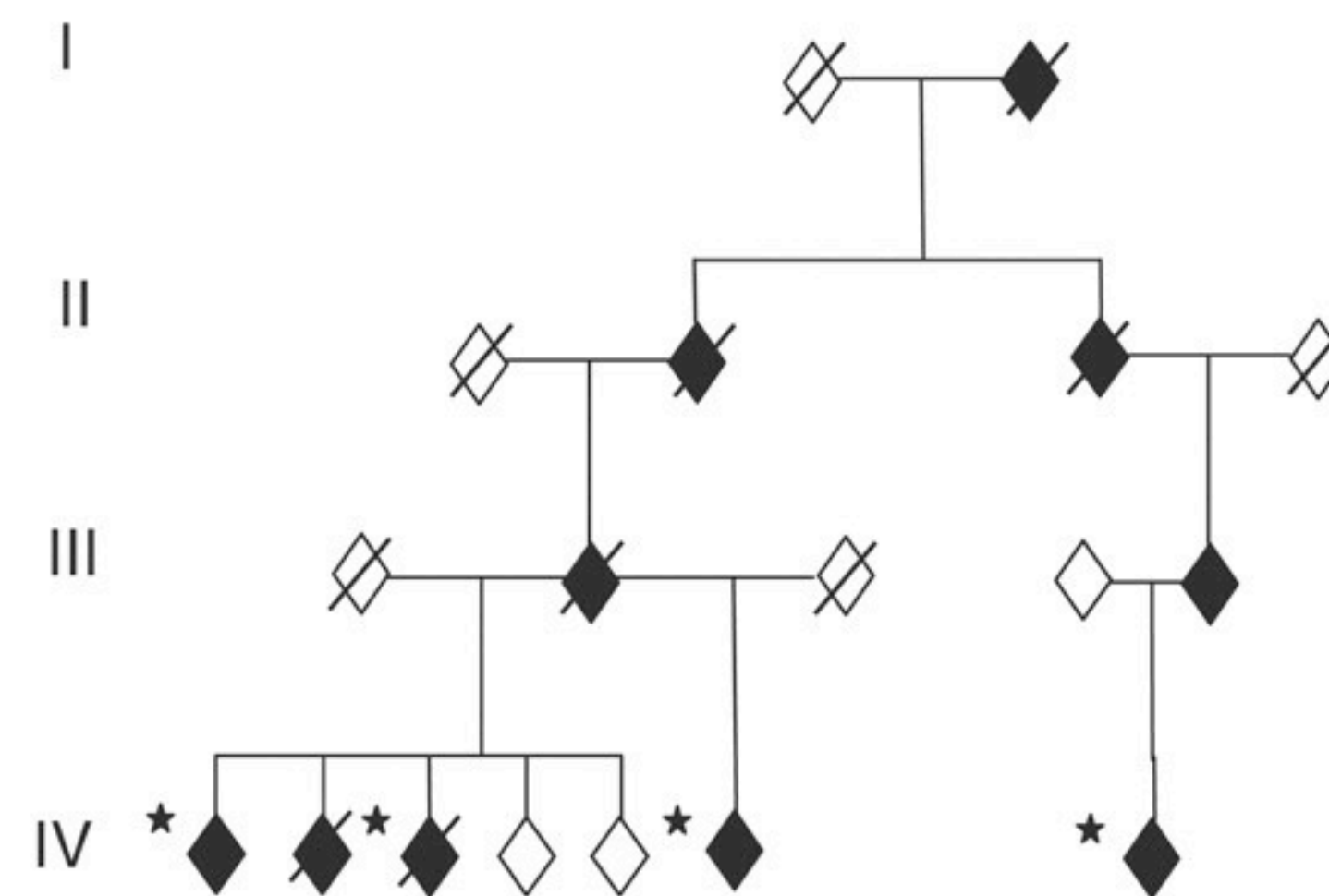
Mutations in the *FUS/TLS* Gene on Chromosome 16 Cause Familial Amyotrophic Lateral Sclerosis

T. J. Kwiatkowski Jr.,^{1*} D. A. Bosco,^{1,2} A. L. LeClerc,^{1,2} E. Tamrazian,¹ C. R. Vanderburg,³
C. Russ,^{1,4} A. Davis,¹ J. Gilchrist,⁵ E. J. Kasarskis,⁶ T. Munsat,^{7†} P. Valdmanis,⁸ G. A. Rouleau,⁸
B. A. Hosler,¹ P. Cortelli,⁹ P. J. de Jong,¹⁰ Y. Yoshinaga,¹⁰ J. L. Haines,¹¹ M. A. Pericak-Vance,¹²
J. Yan,¹³ N. Ticozzi,^{1,2,14} T. Siddique,¹³ D. McKenna-Yasek,¹ P. C. Sapp,^{1,15} H. R. Horvitz,¹⁵
J. E. Landers,^{1,2} R. H. Brown Jr.^{1,2*}

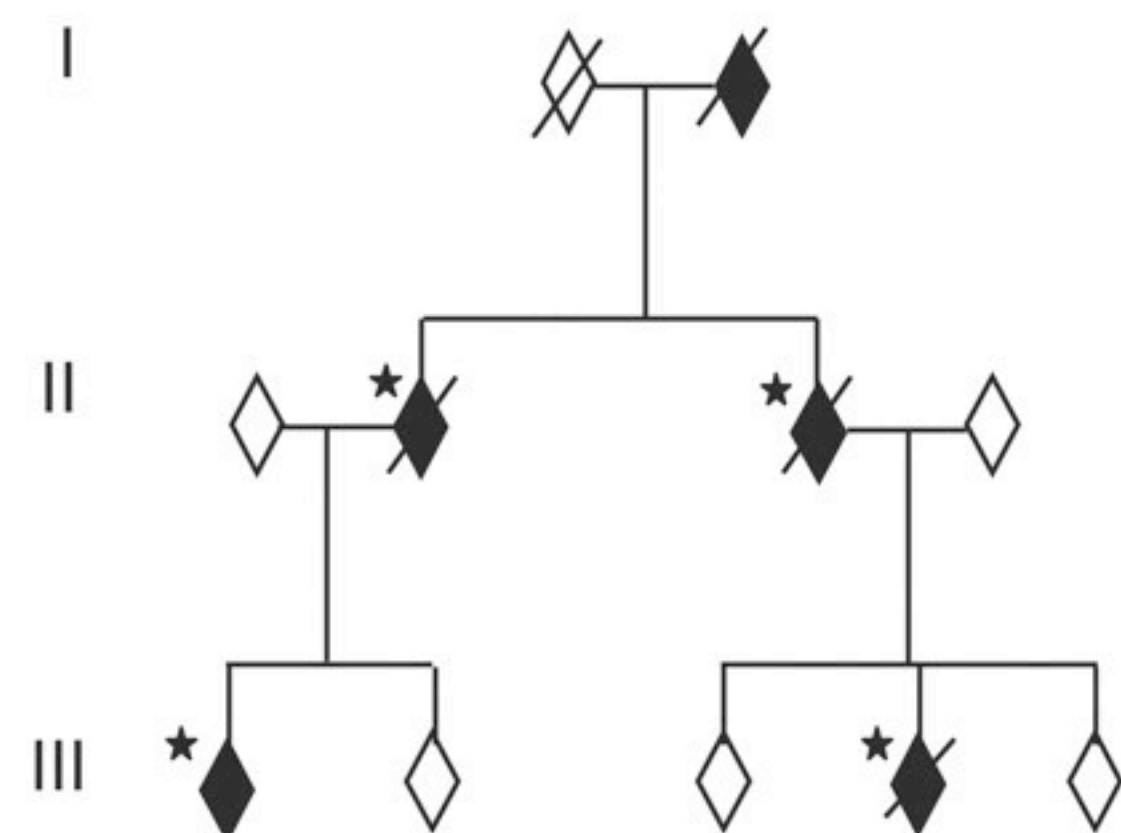
A- F1



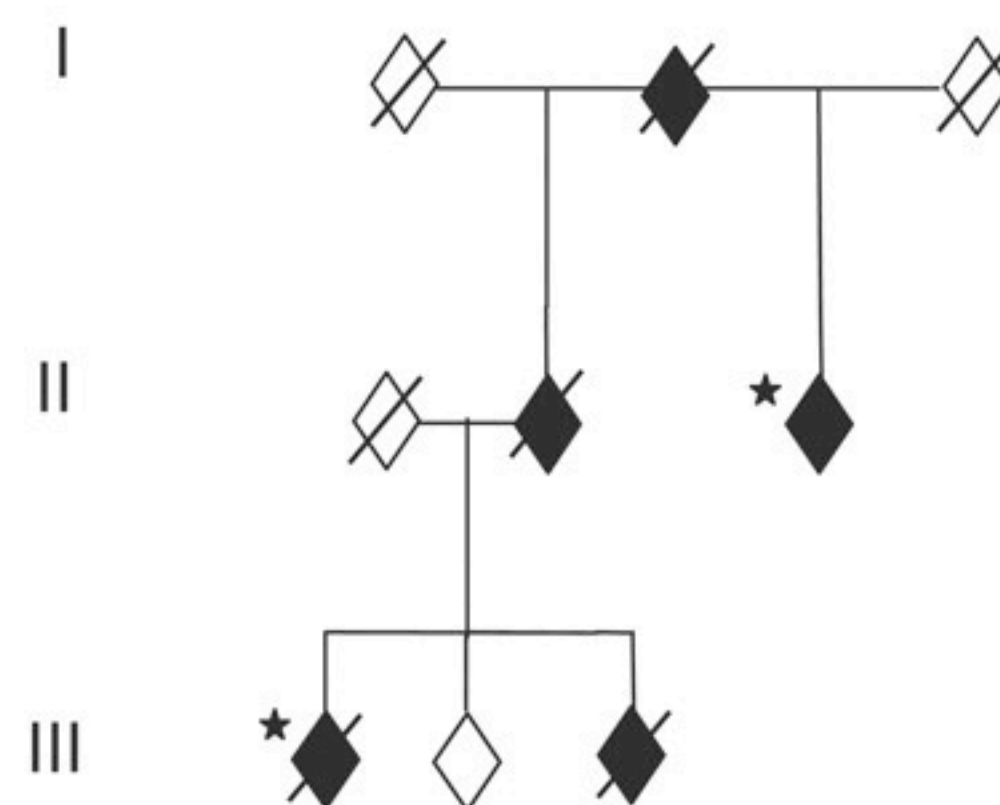
B- ALS53



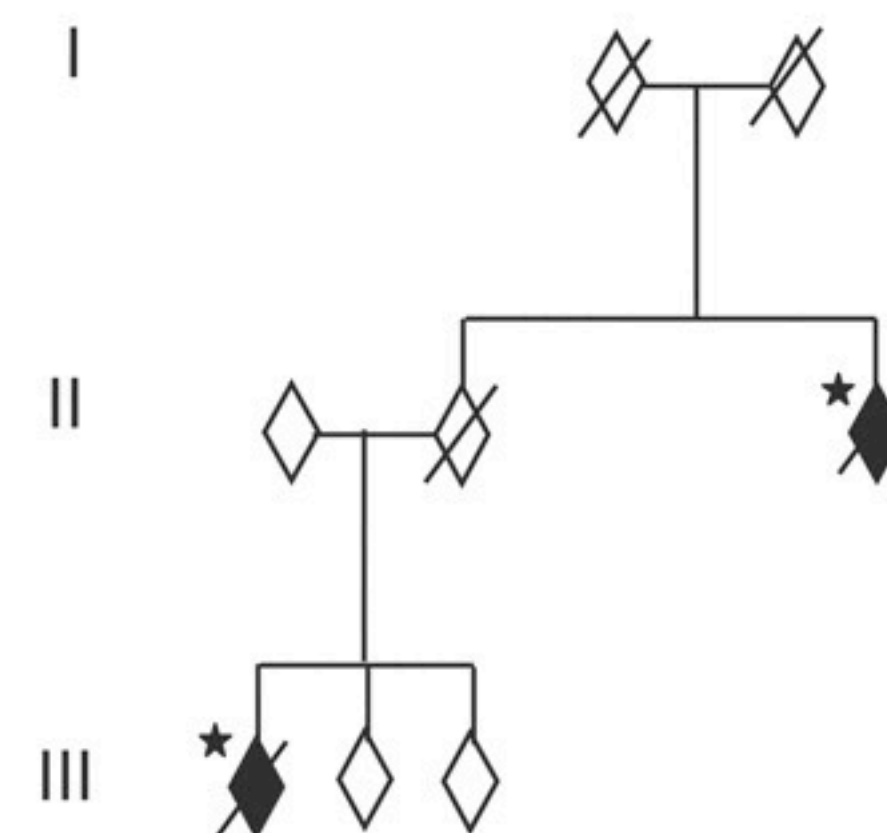
C- F1015



D- ALS156



E- F1083

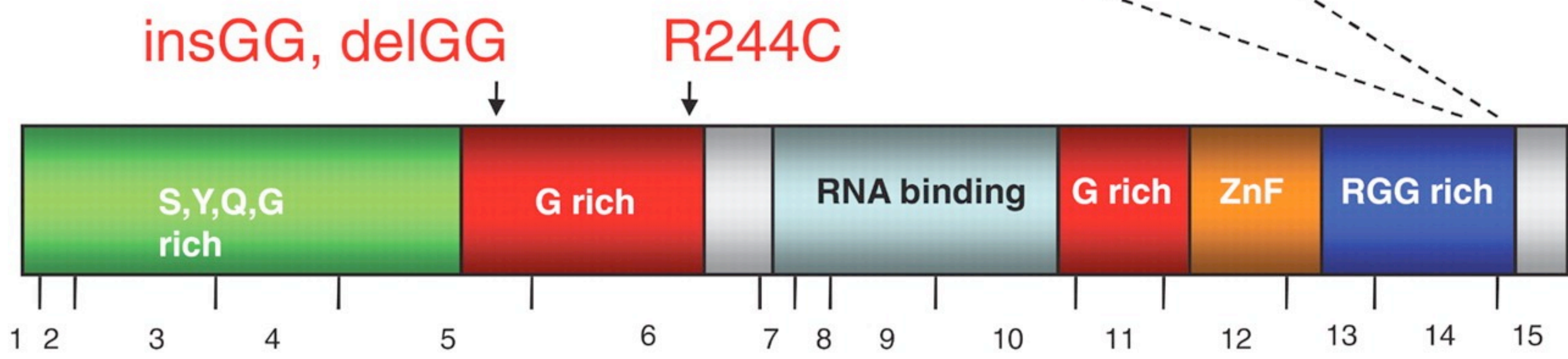


514 RGEHRQDRRERPY 526

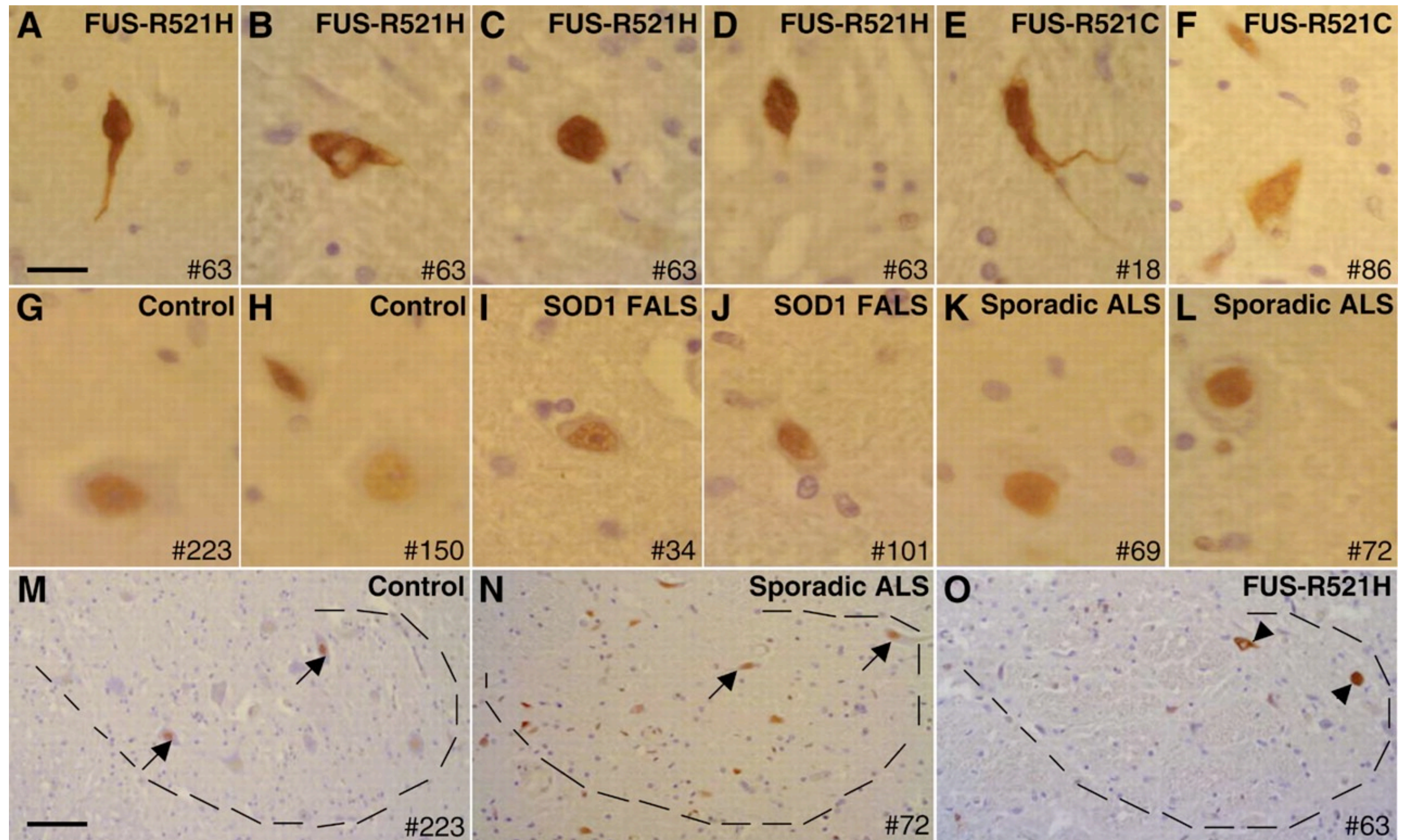
SC QK HG SL

C
G T

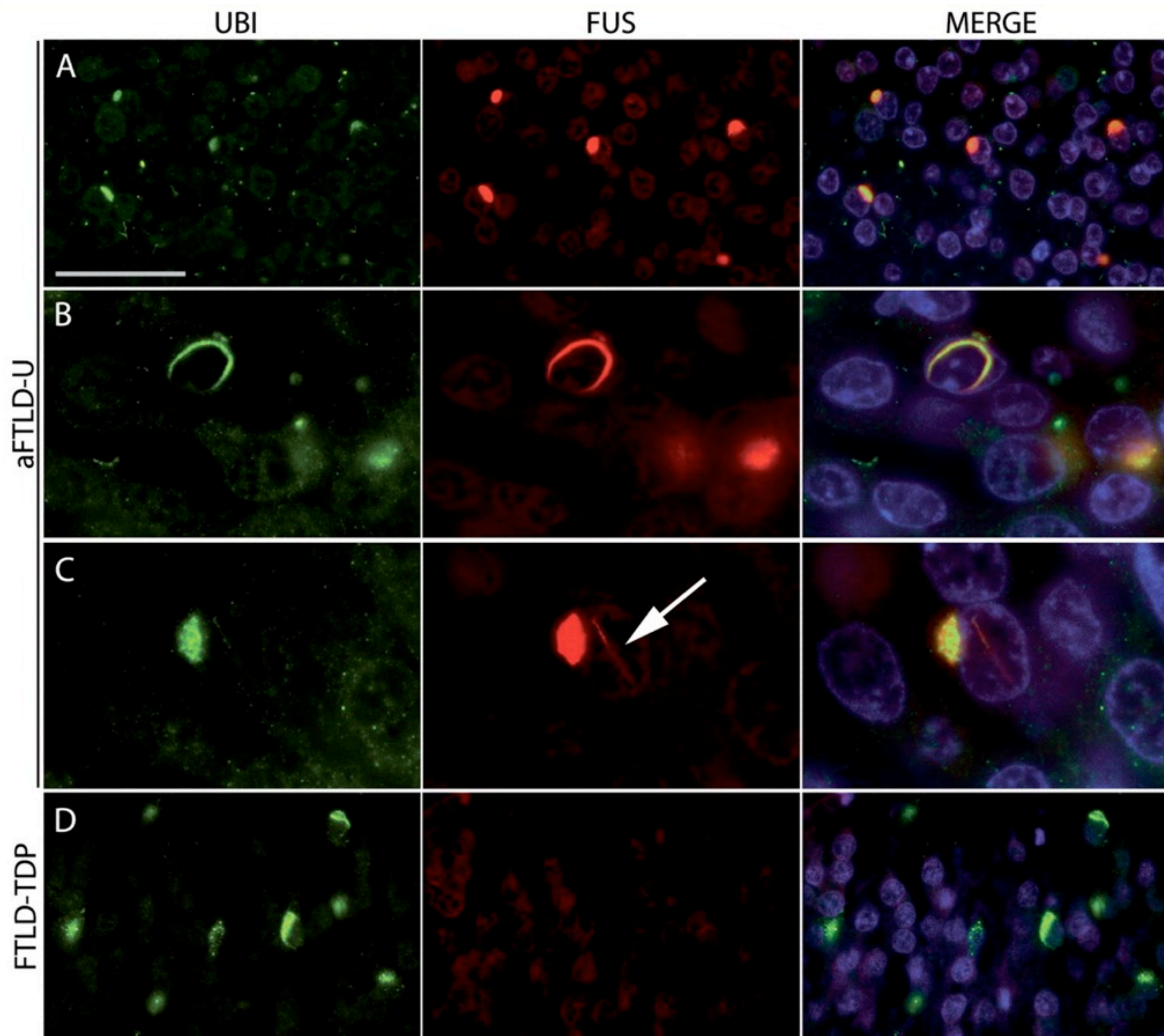
FUS/TLS



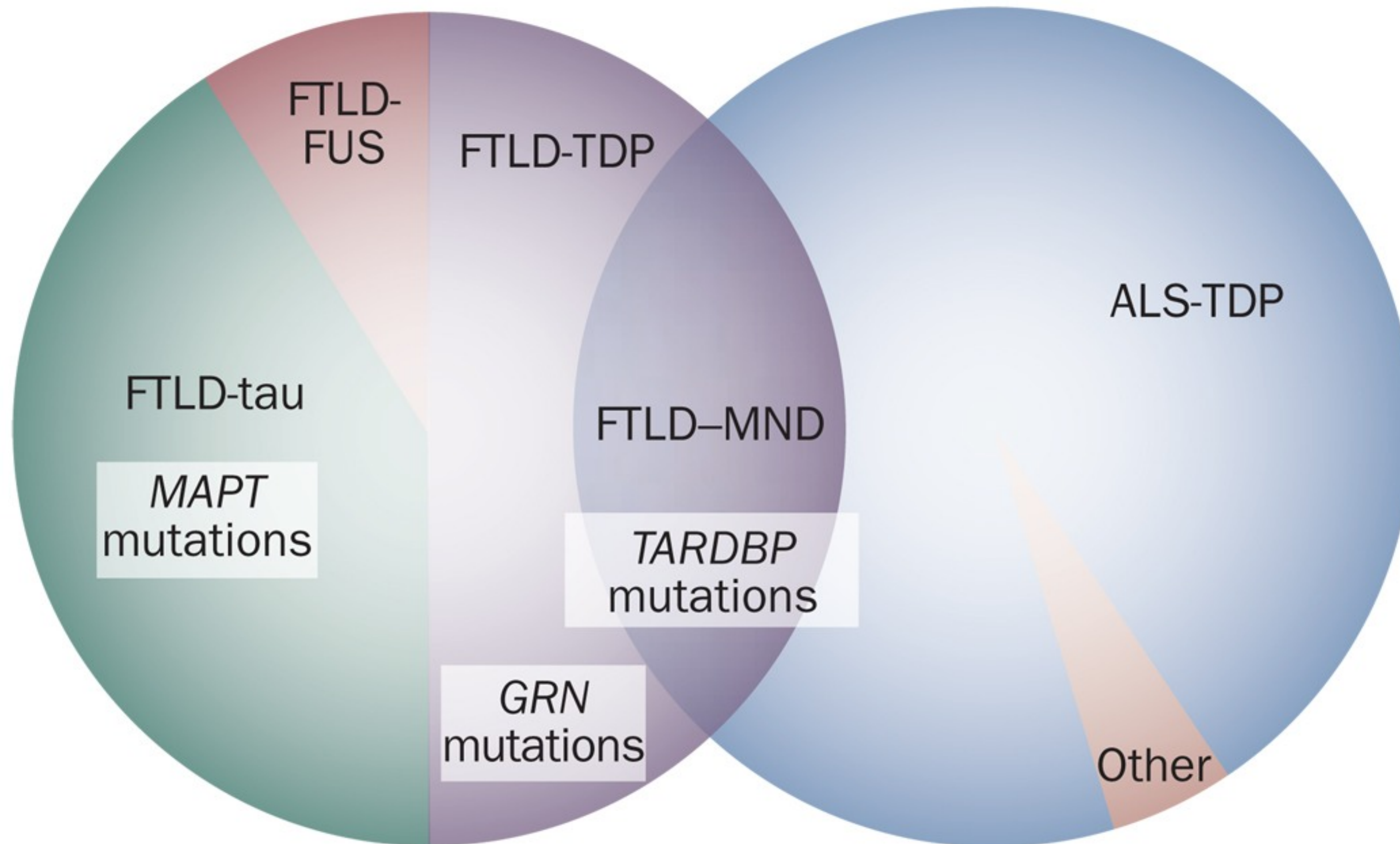
FUS pathology in ALS cases with FUS mutations



FUS pathology in aFTLD-U



Pathological subtypes of FTLD and ALS



Mendelian Genes for ALS

Gene	Protein	Location	Inheritance
<i>ANG</i>	Angiogenin	14q11.2	dominant
<i>ALS2</i>	alsin	2q33.1	recessive
<i>FIG4</i>	SAC1 lipid phosphatase domain containing	6q21	recessive
<i>FUS</i>	Fused in sarcoma	16p11.2	both
<i>OPTN</i>	Optineurin	10p13	both
<i>SETX</i>	Senataxin	9q34.13	dominant
<i>SOD1</i>	Superoxide dismutase 1	21q22.11	both
<i>SPG11</i>	Spastic paraplegia 11	15q21.1	recessive
<i>TARDBP</i>	TDP-43	1p36.22	dominant
<i>UBQLN2</i>	Ubiquilin 2	Xp11.21	x-linked dominant
<i>VAPB</i>	VAMP	20q13.32	dominant
<i>VCP</i>	Valosin-containing protein	9p13.3	dominant

Some different ways to identify
new ALS disease genes

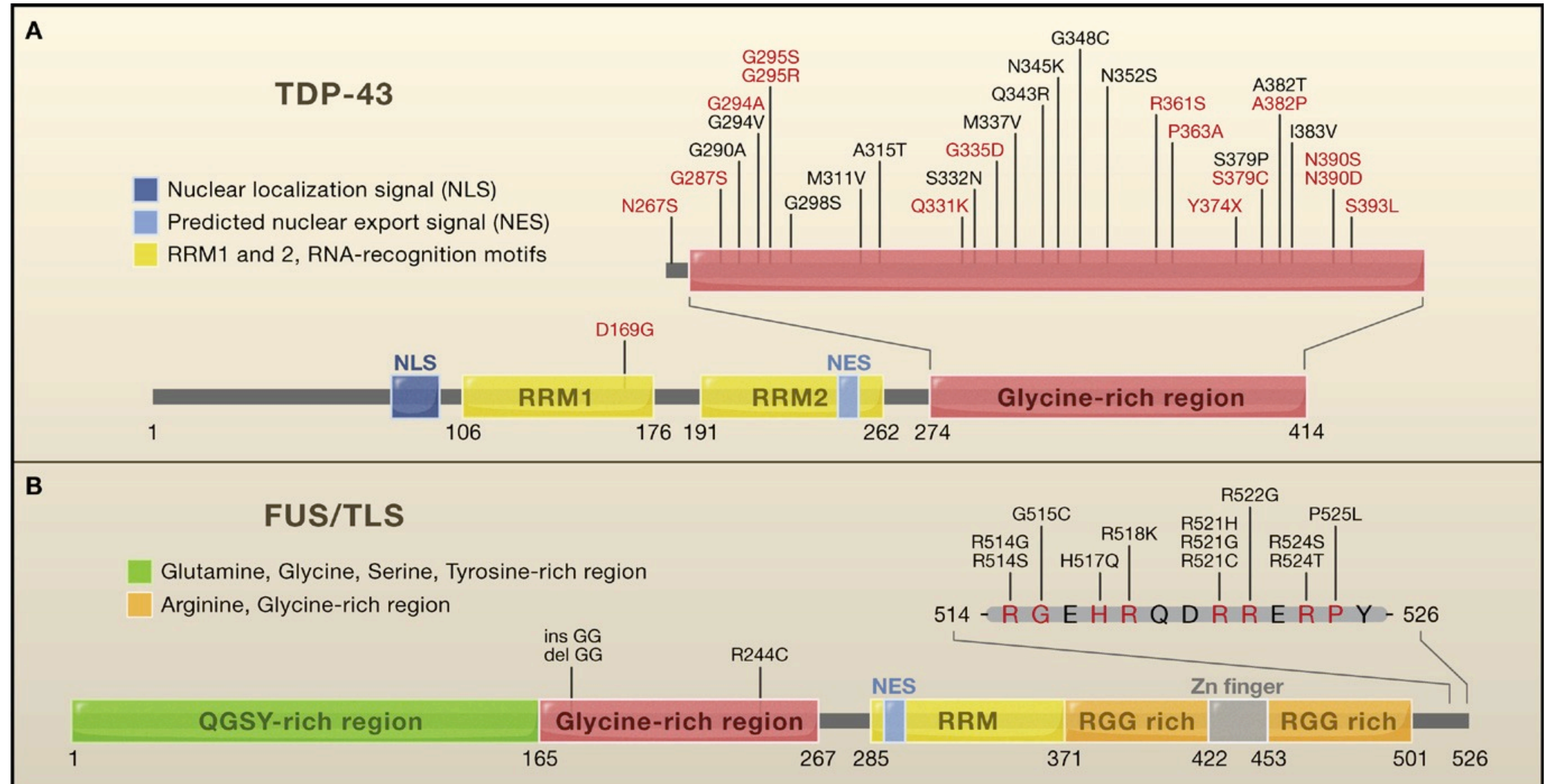
Rethinking ALS: The FUS about TDP-43

Clotilde Lagier-Tourenne¹ and Don W. Cleveland^{1,*}

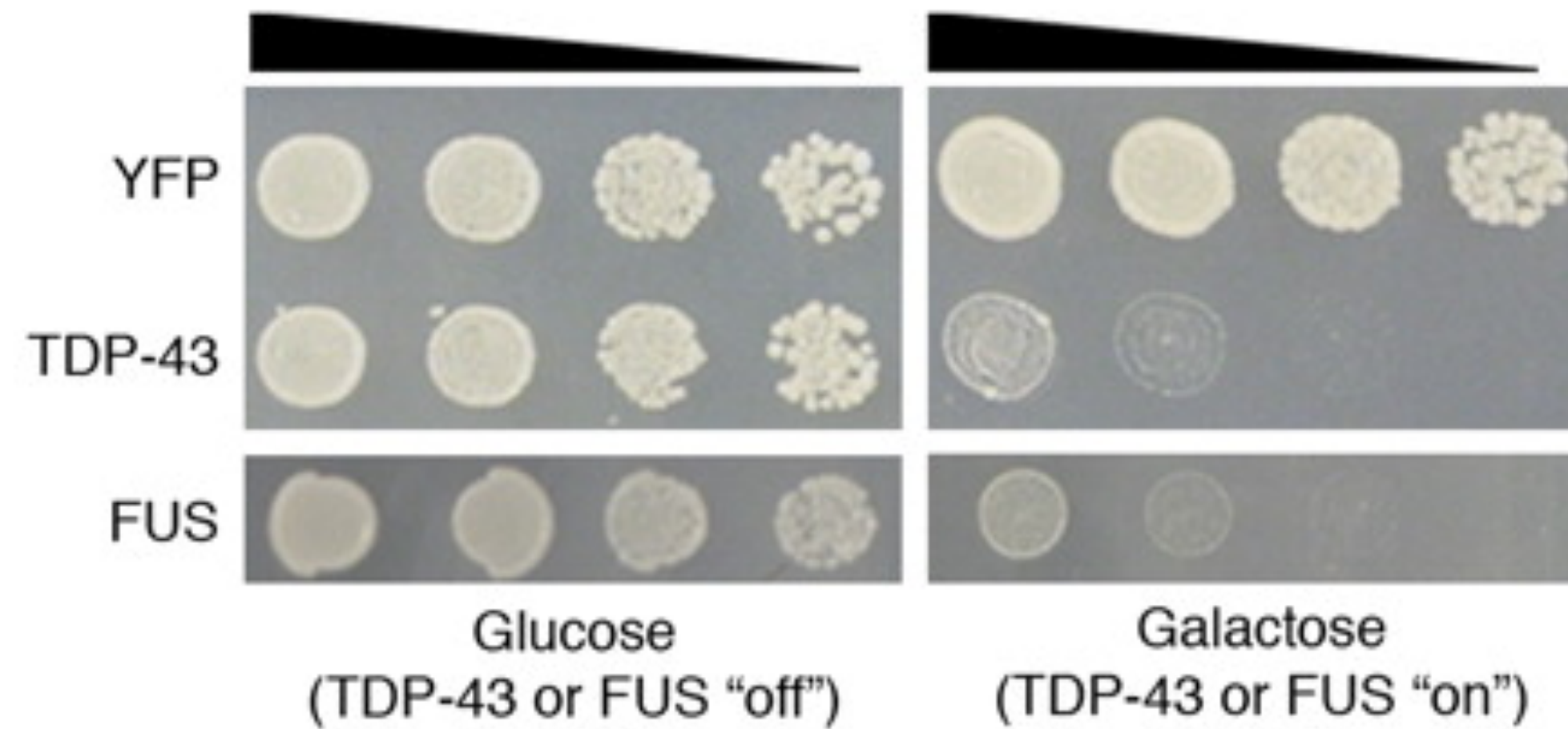
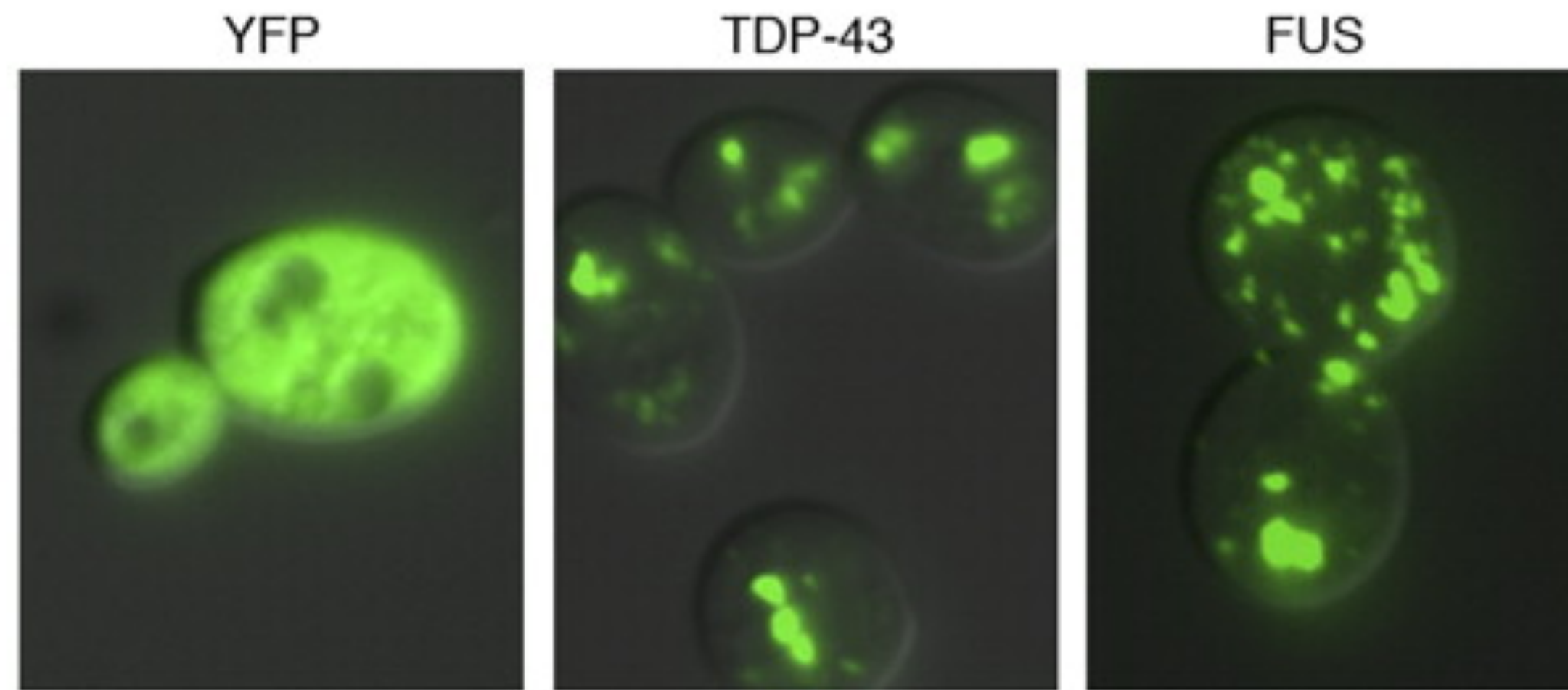
¹Ludwig Institute for Cancer Research and Department of Cellular and Molecular Medicine, University of California San Diego, La Jolla, CA 92093-0670, USA

*Correspondence: dcleveland@ucsd.edu

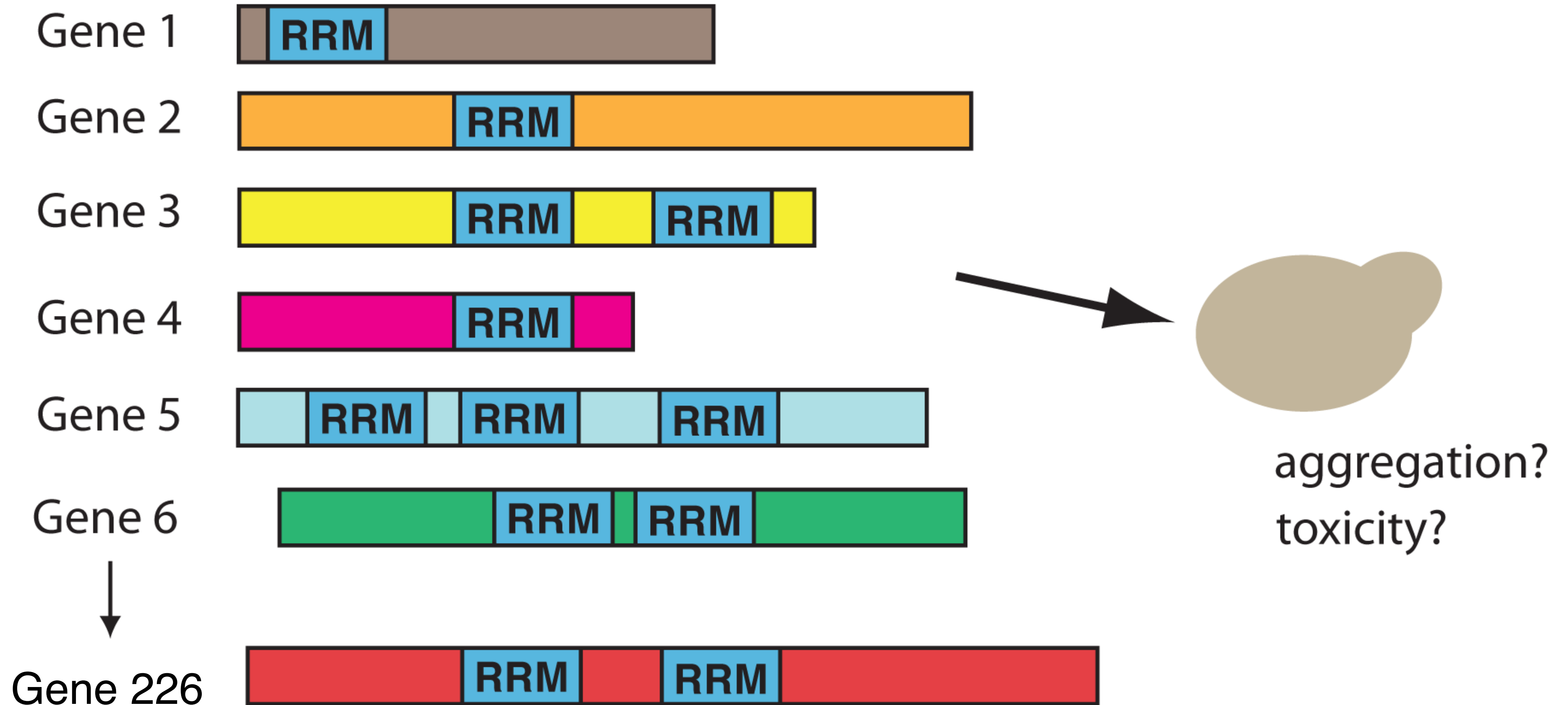
DOI 10.1016/j.cell.2009.03.006

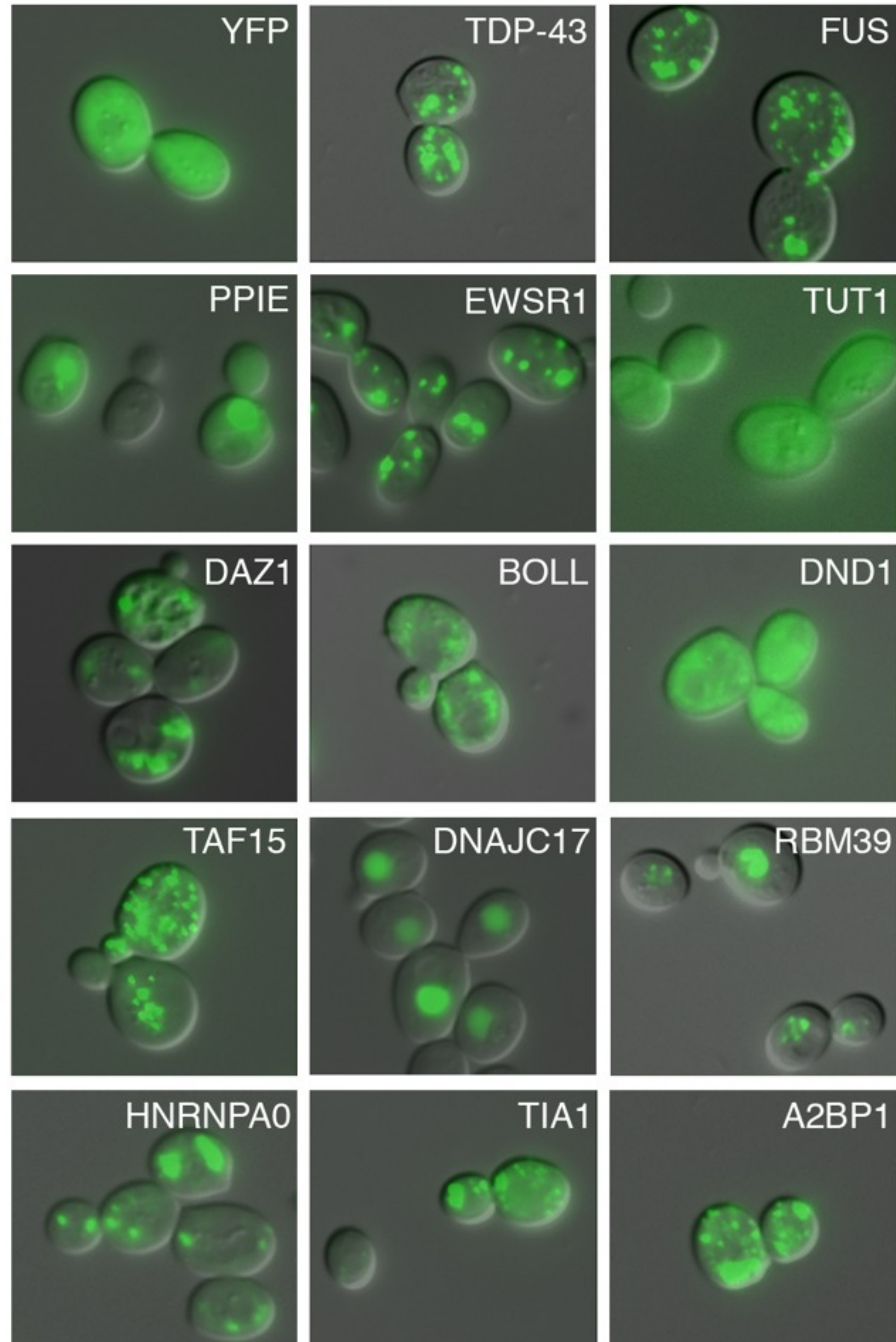


TDP-43 and FUS in yeast cells



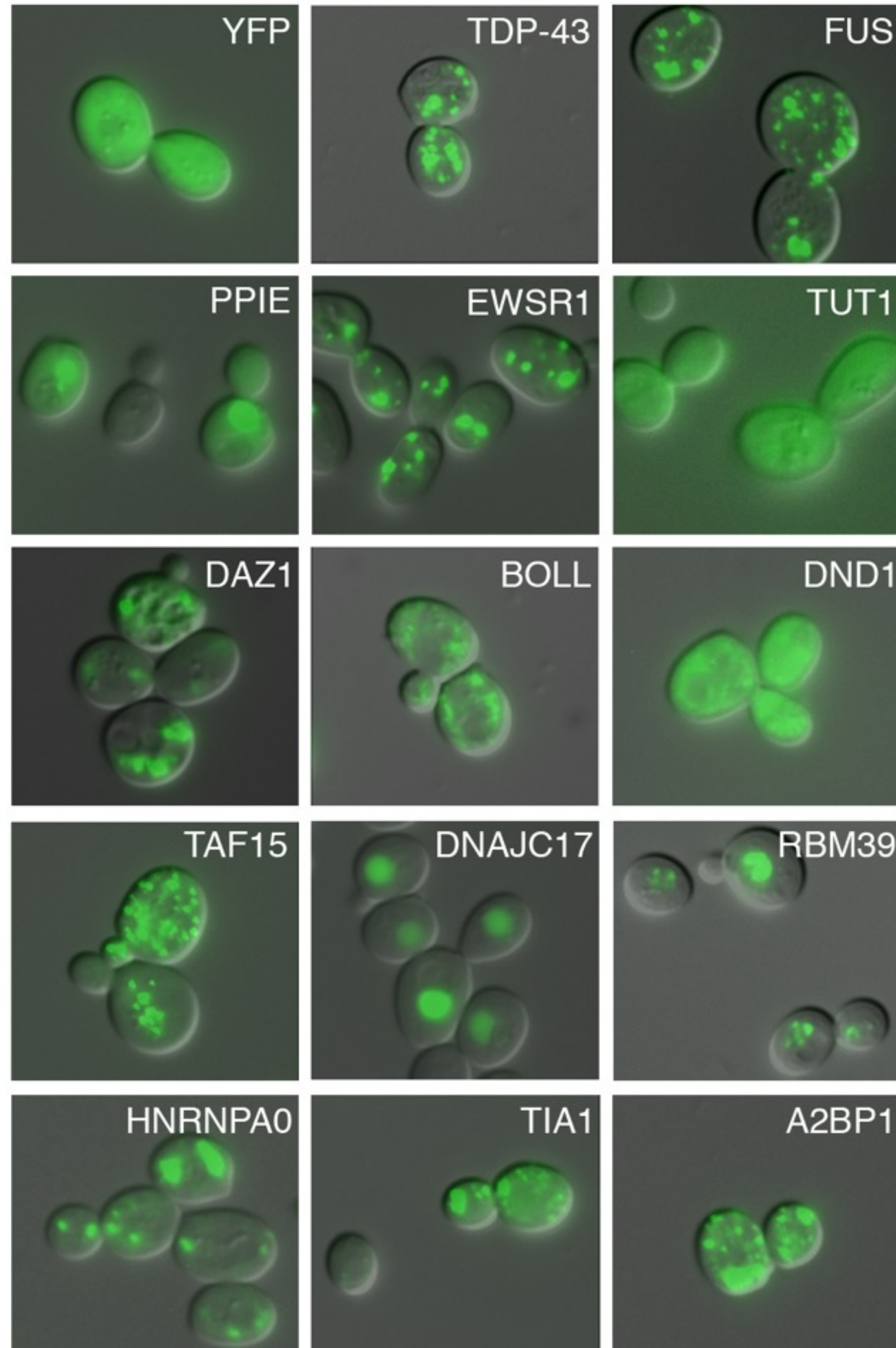
A simple yeast functional screen to find more TDP-43- and FUS-like genes





Screened all human RNA
binding proteins in yeast

35 aggregate and are toxic



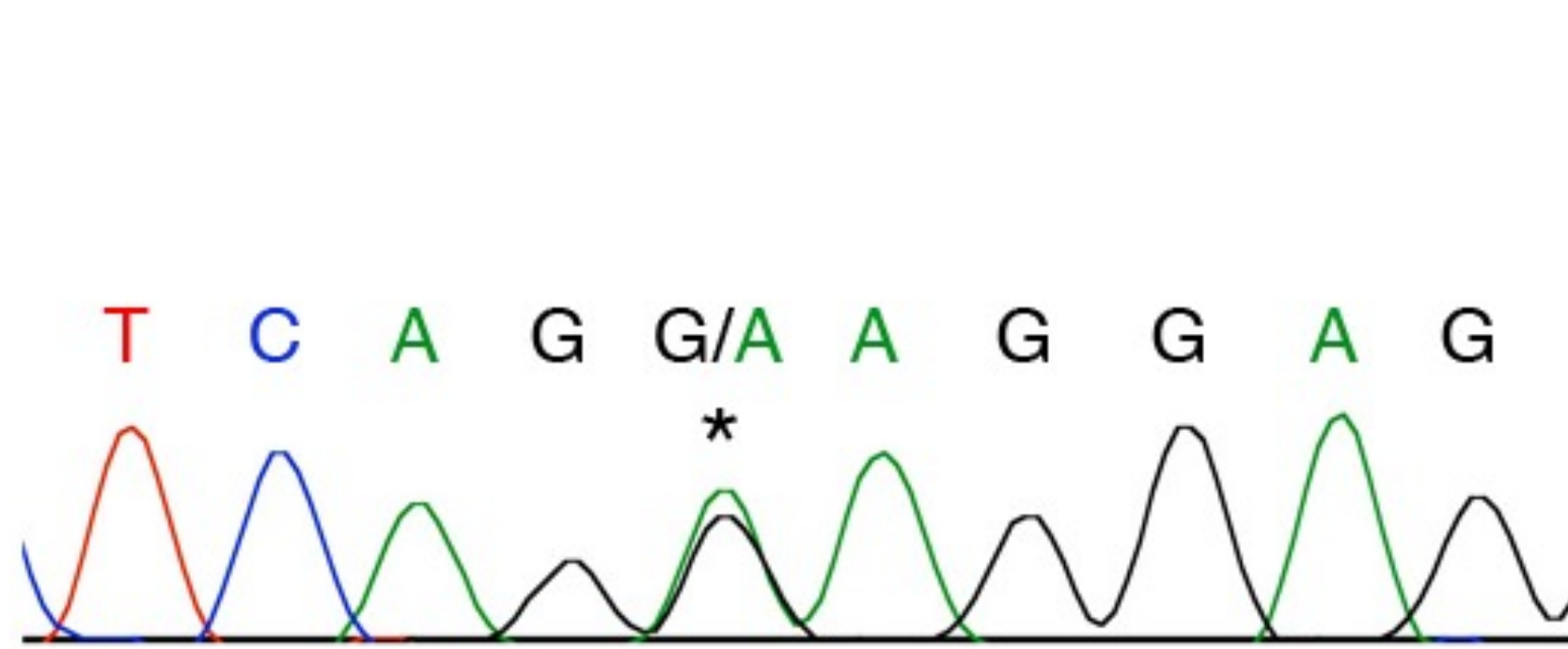
Screened all human RNA
binding proteins in yeast

35 aggregate and are toxic

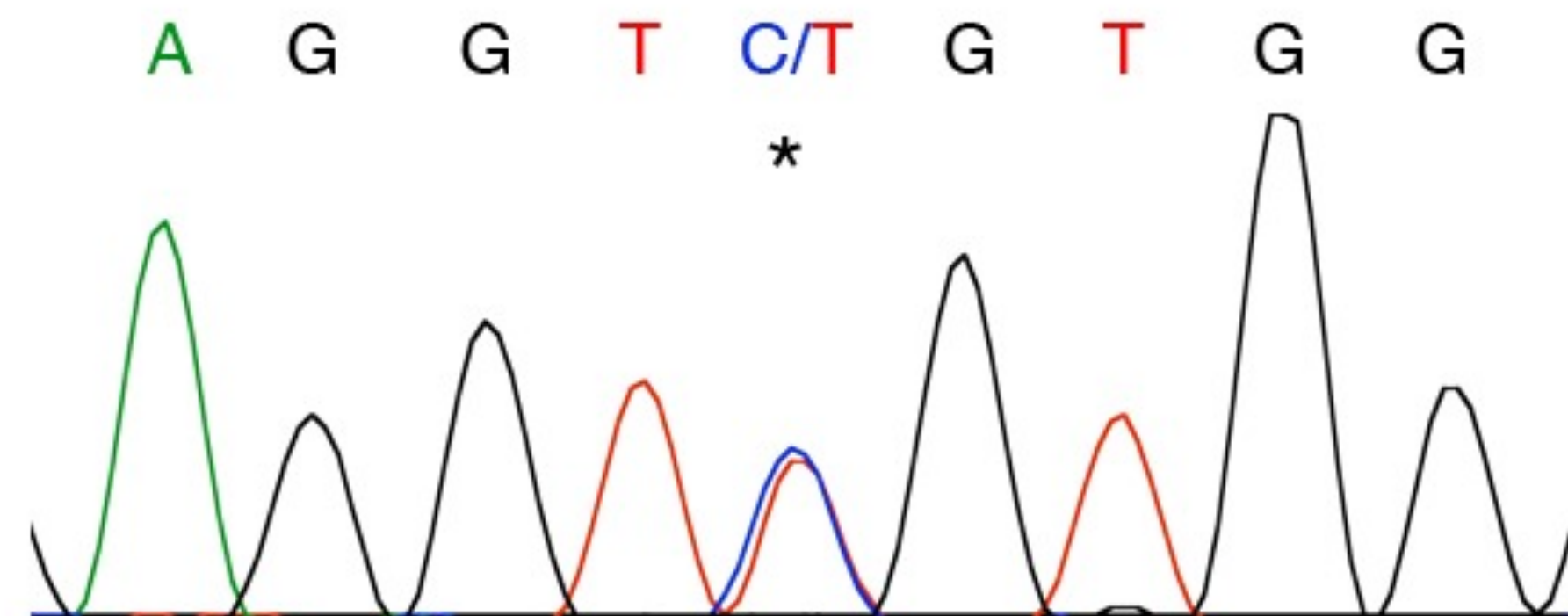
Used bioinformatics to identify
a **prion-like domain** in
TDP-43, FUS, and 8 other genes
from yeast screen

Identified variants in TAF15 in ALS patients

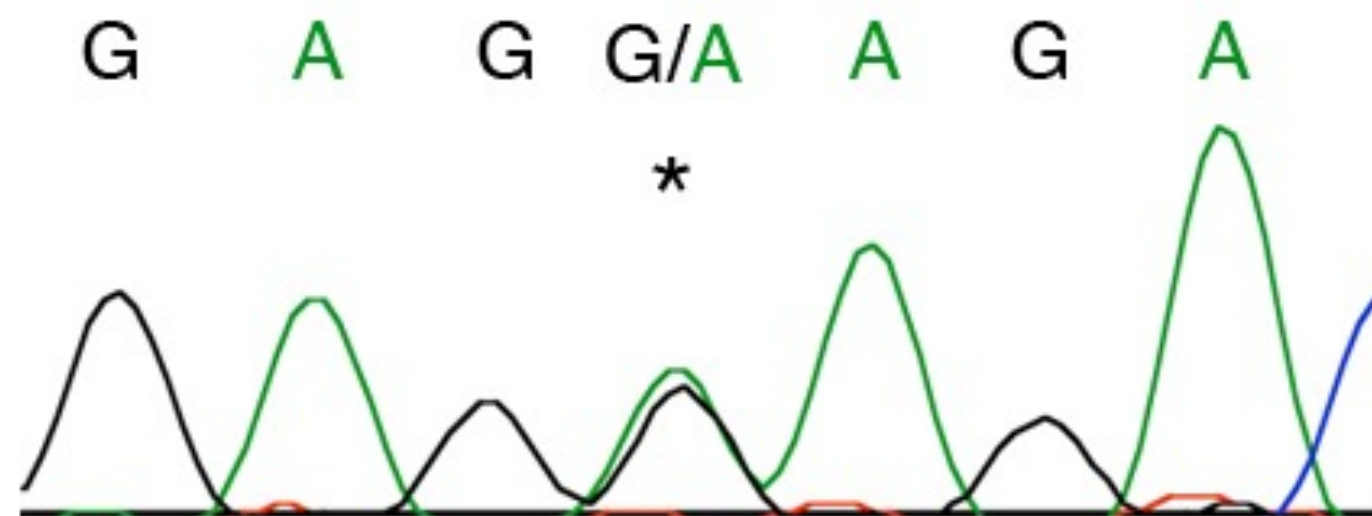
Sequenced 735 sporadic ALS cases and 1,328 healthy controls



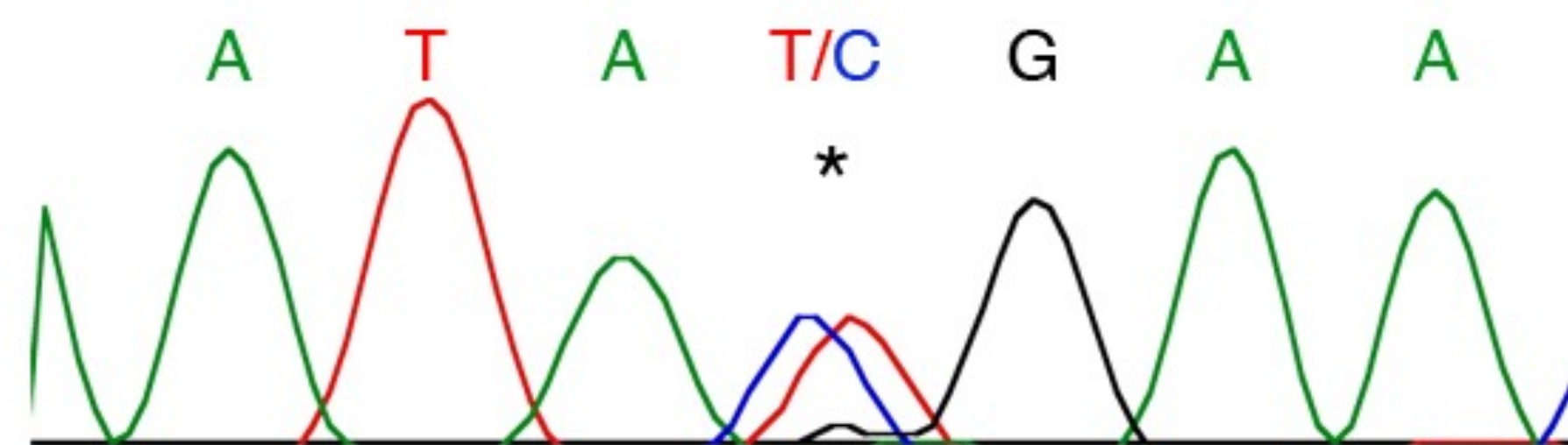
1258 G>A
G391E



1308 C>T
R408C



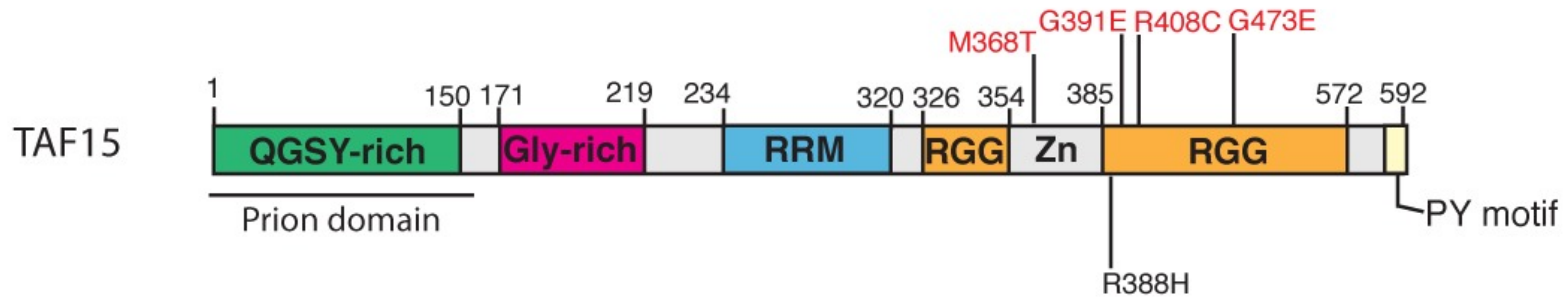
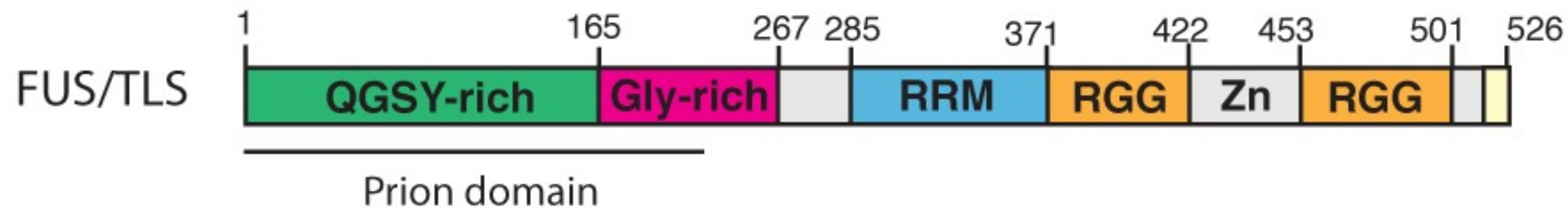
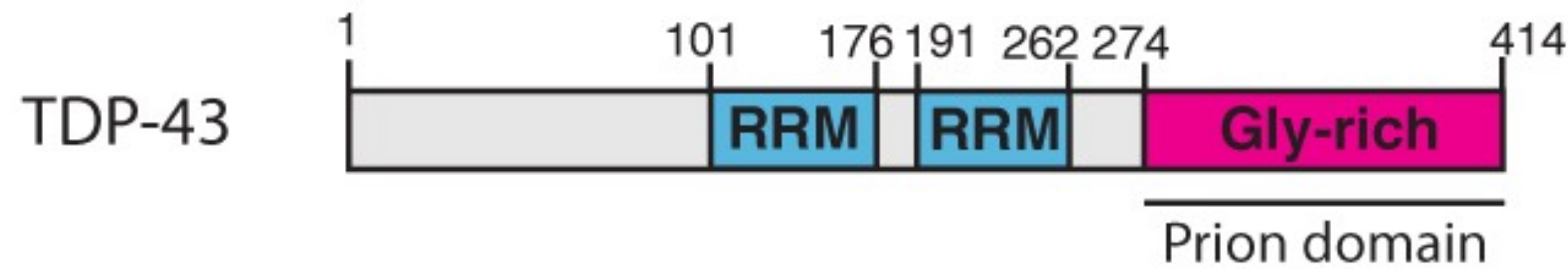
1418 G>A
G473E



1103 T>C
M368T

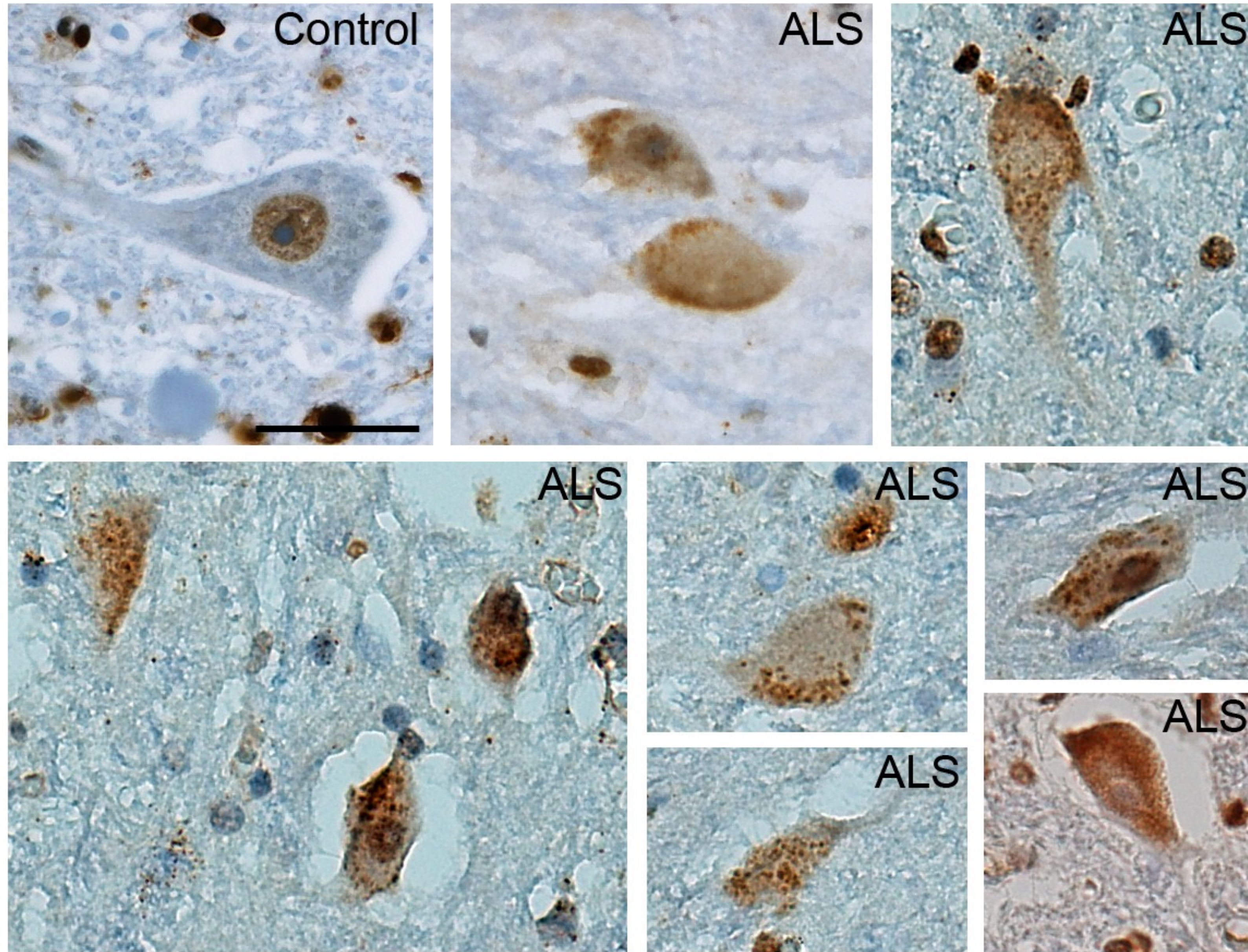
Also SNP genotyped ~4,608 healthy controls and these variants were absent

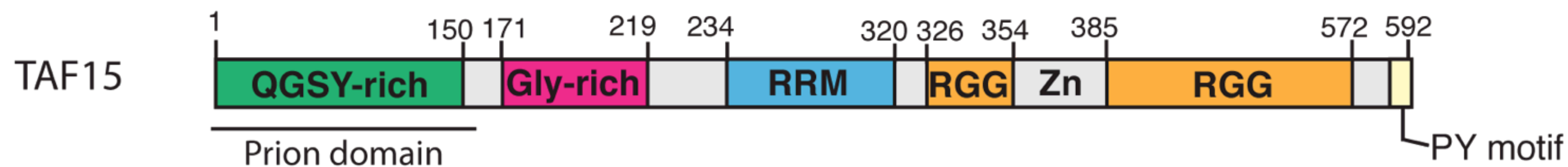
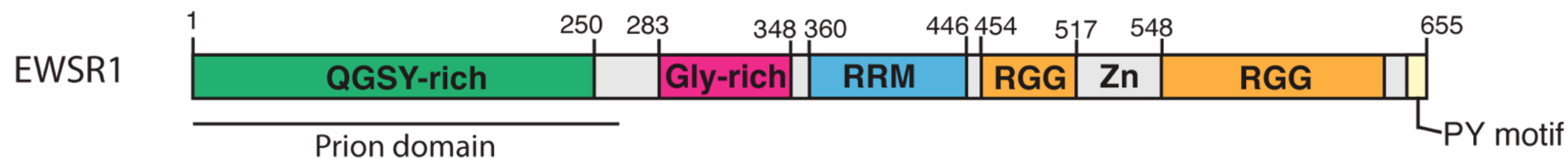
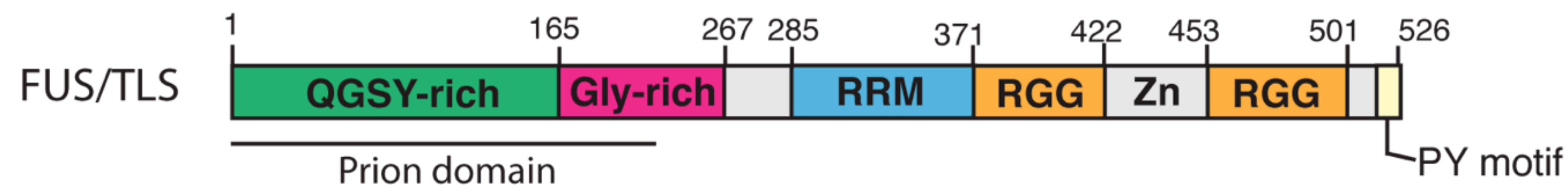
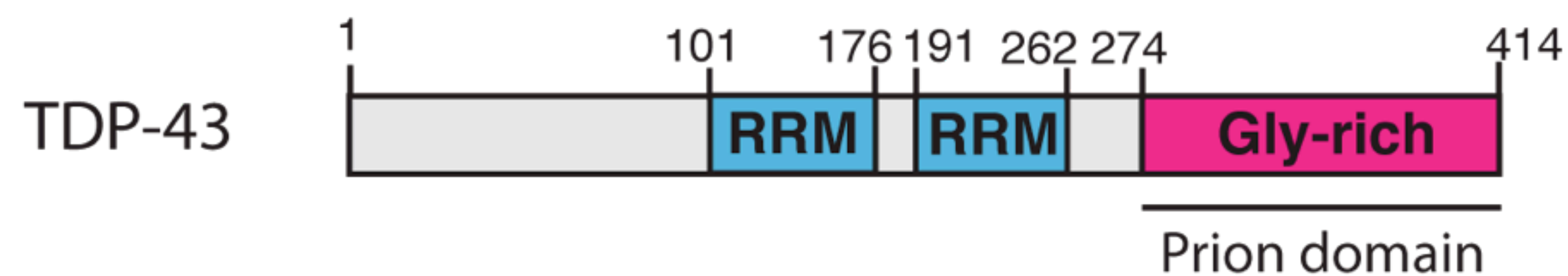
TAF15 mutations in ALS

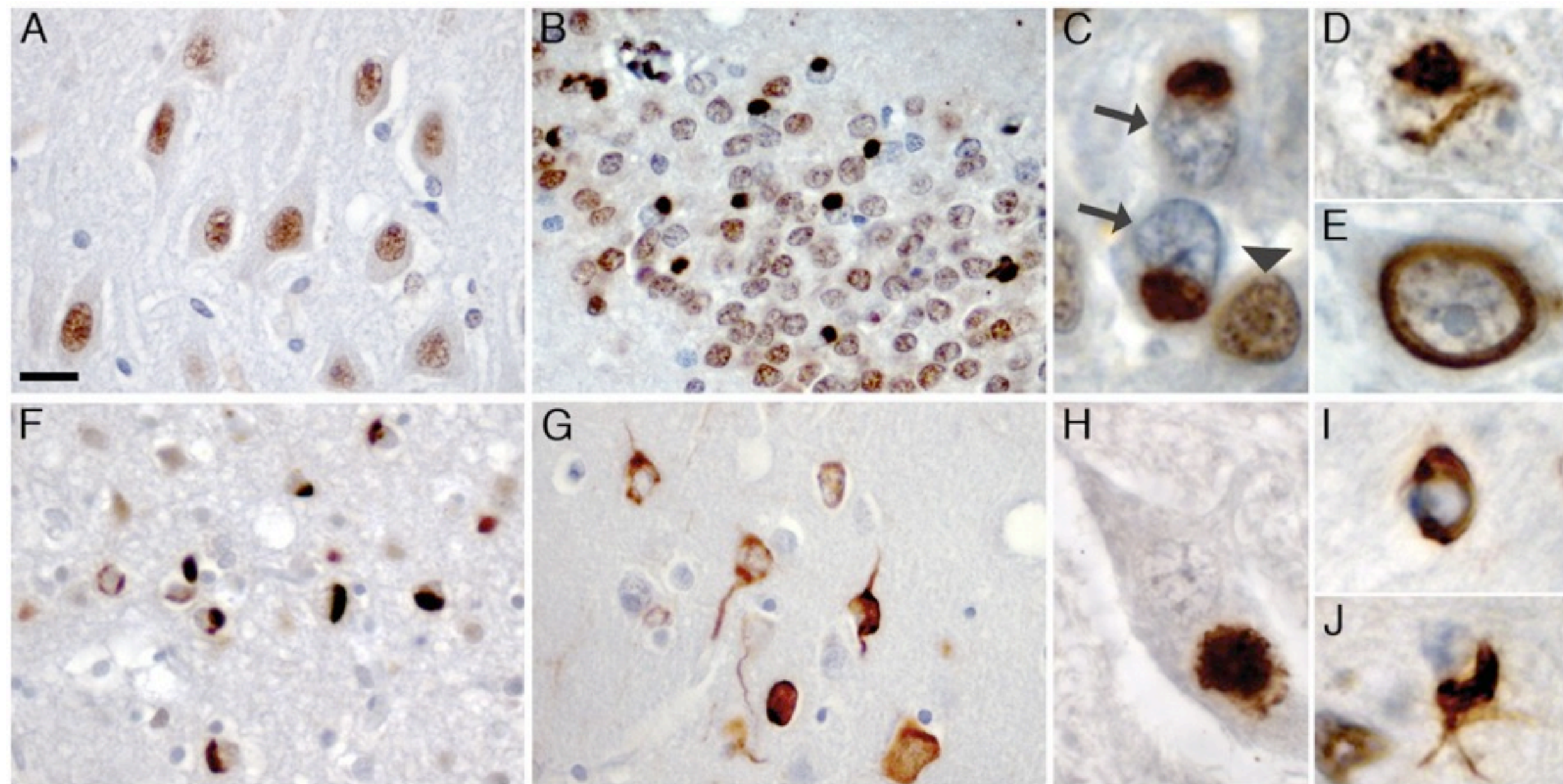


	358						416	463		483
Human	WVCPNPSCGNMNFARRNSCNQCNEPRPEDSRPS	T	GGDFRGRG	YGGERGYRGR	GGGRGGDRG			YGGDRGGGYG	GGDRGGGYGGDR	
Mouse	WVCPNPSCGNMNFARRNSCNQCNEPRPEDSRPS	E	GGDFRGRG	YGGERGYRGR	GGGRGGDRG			YGGDRGG	YGGDRGG	YGGDR
Dog	WVCPNPSCGNMNFARRNSCNQCNEPRPEDSRPS		GGDFRGRG	YGGERGYRGR	GGGRGGDRG			YGGDRGGGYG	GGDRGGGYGGDR	
Chicken	WVCPNPSCGNMNFARRNSCNQC		GGDFRGRG	GGYGGERGYRGR	GGGRGGDRG			YGGDRGGGYG	GGDRGGGYGGDR	

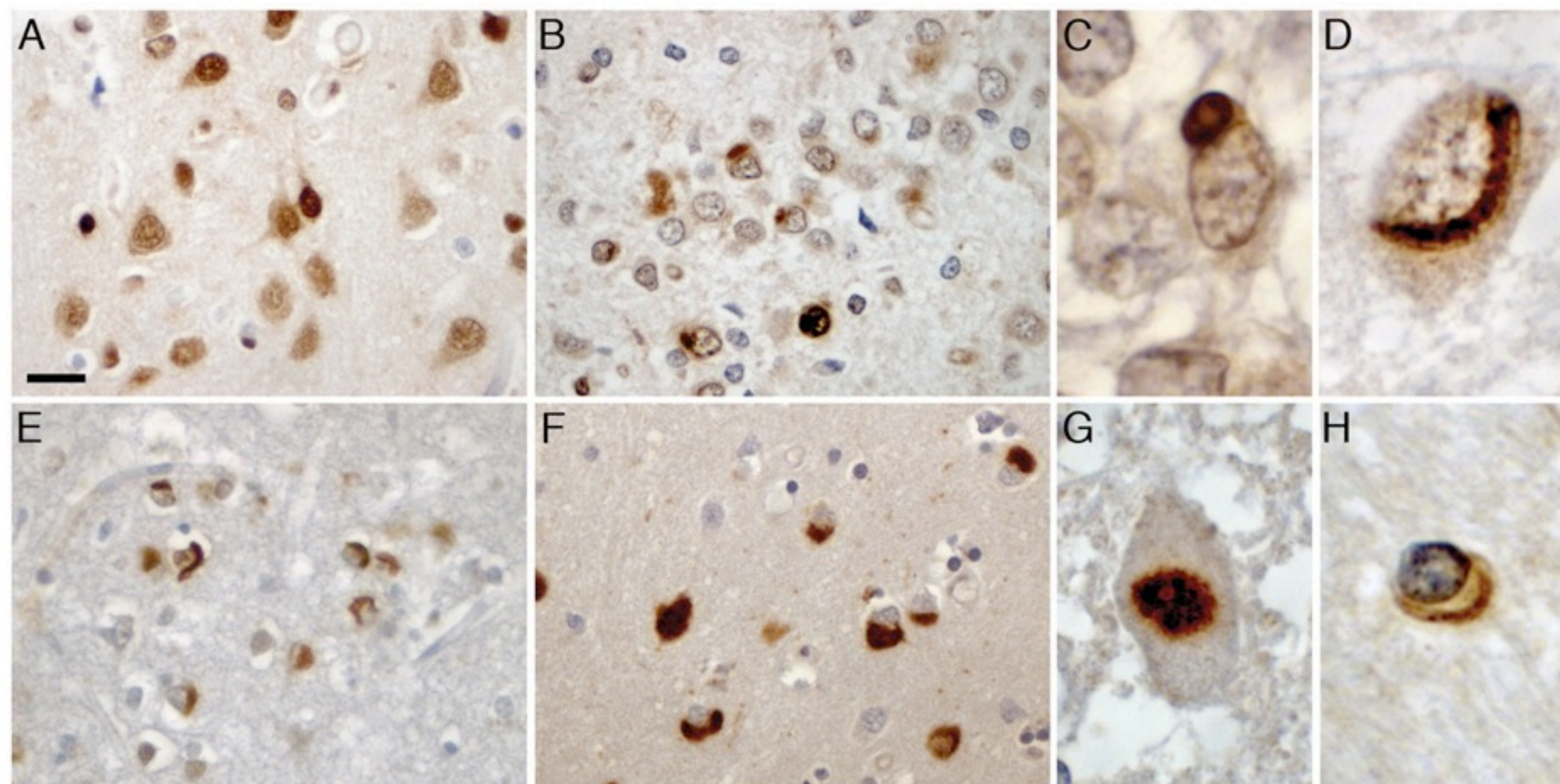
TAFI5 mislocalization in ALS spinal cord neurons





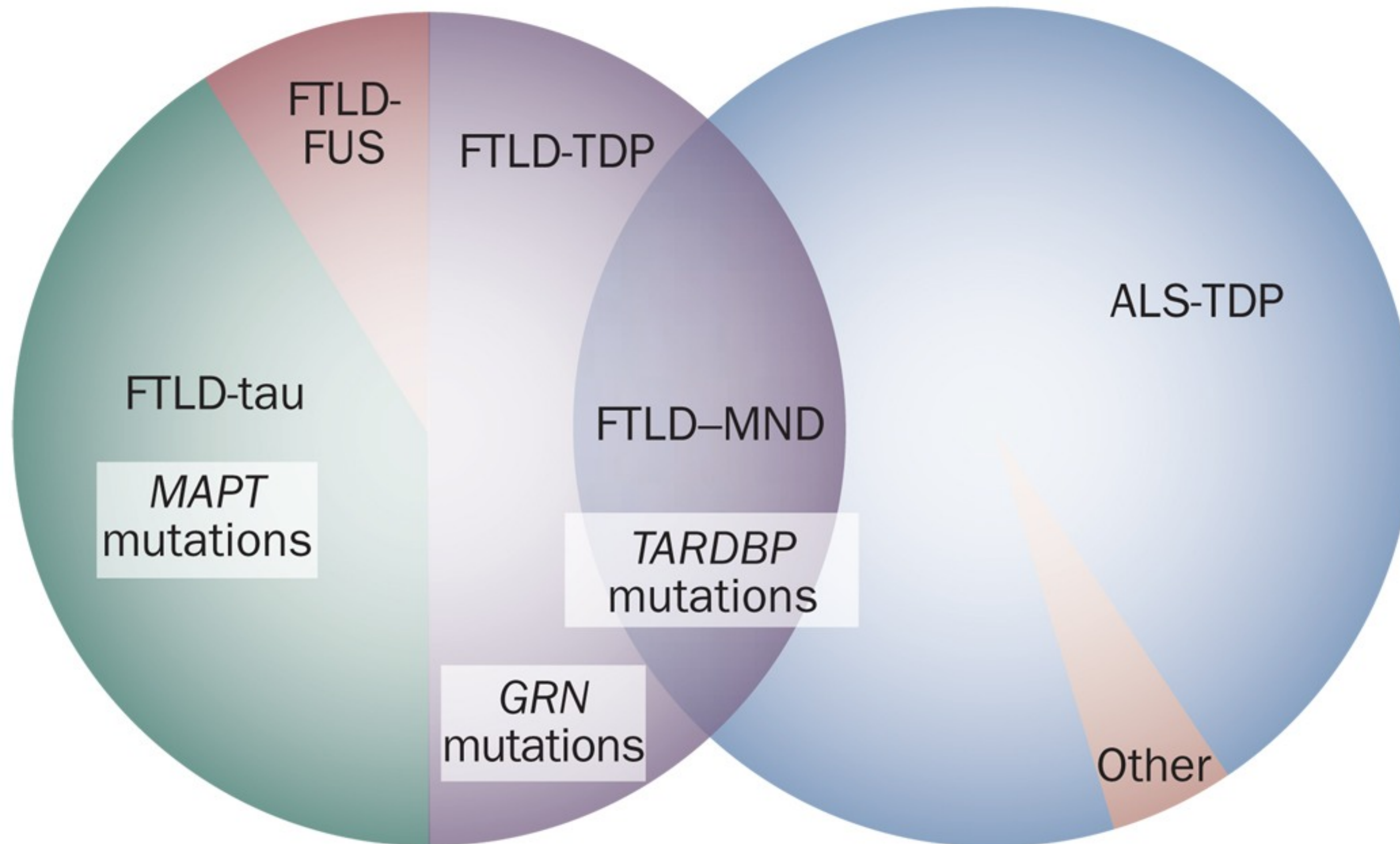


TAFI5 pathology
in FTLD-FUS

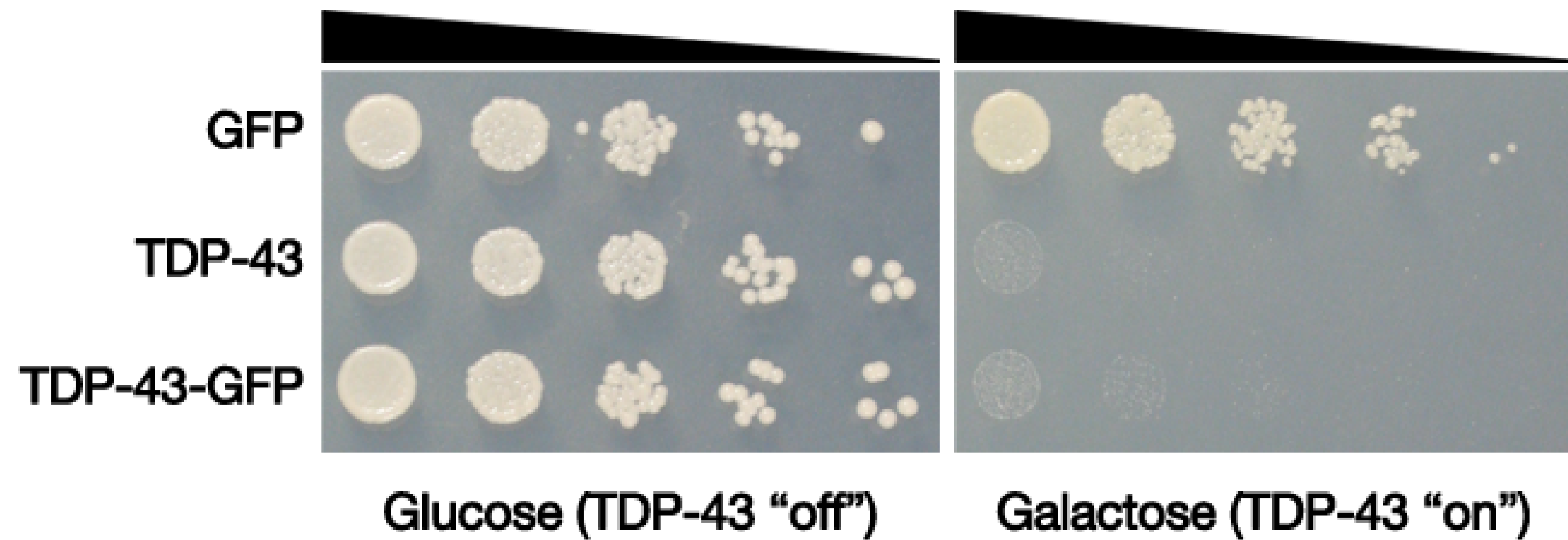
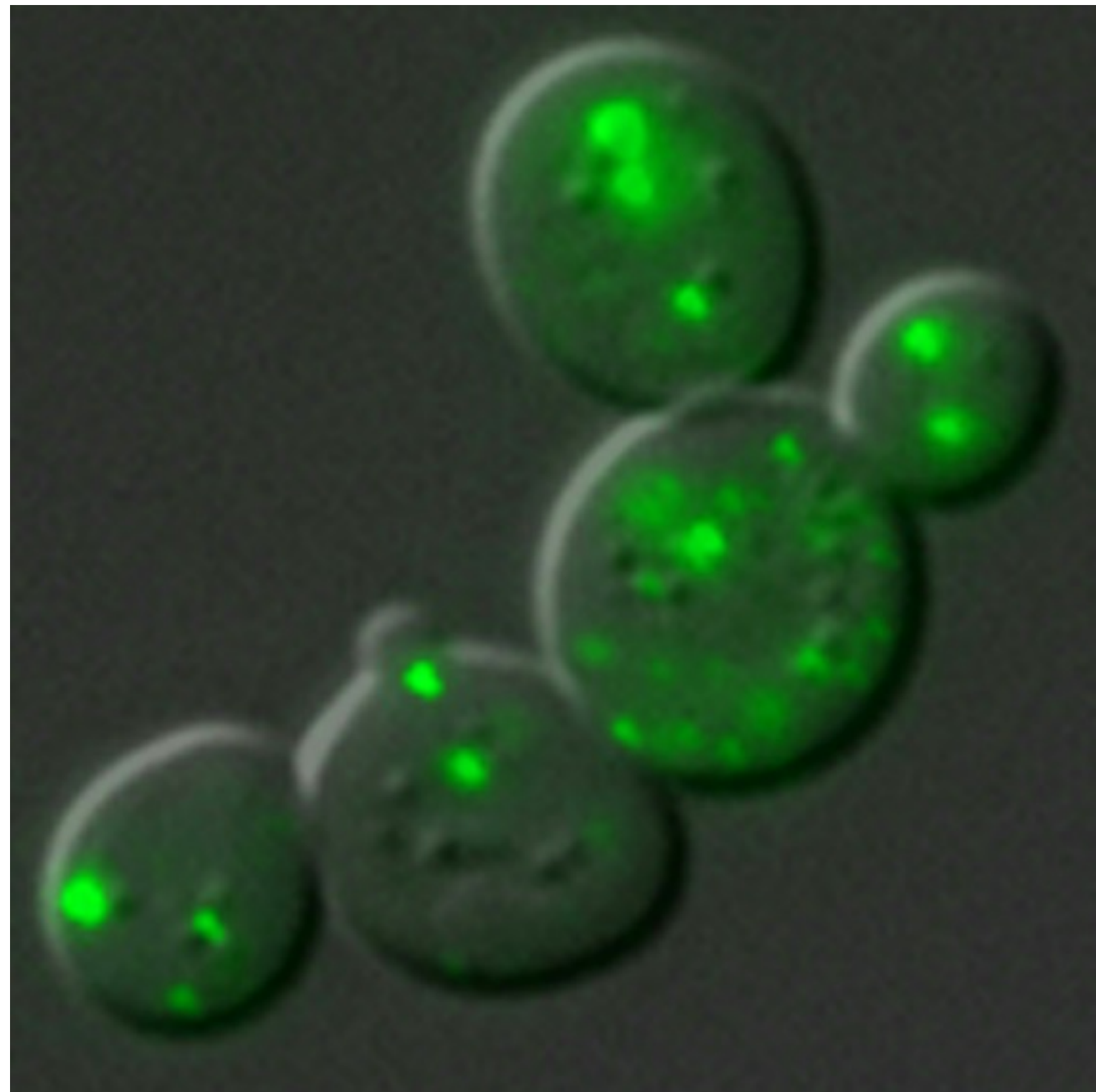


EWSR1 pathology
in FTLD-FUS

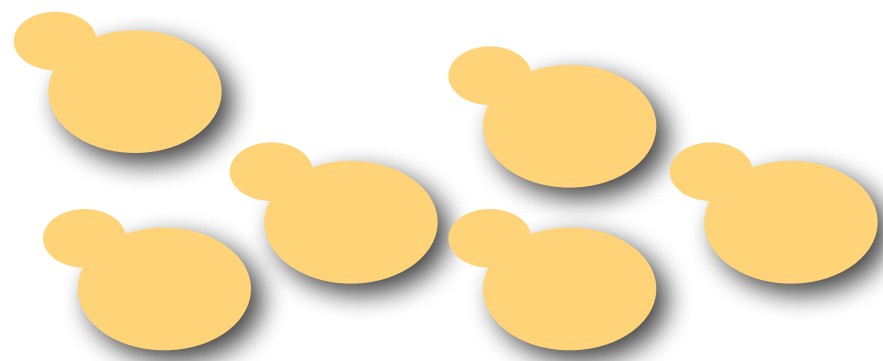
Pathological subtypes of FTLD and ALS



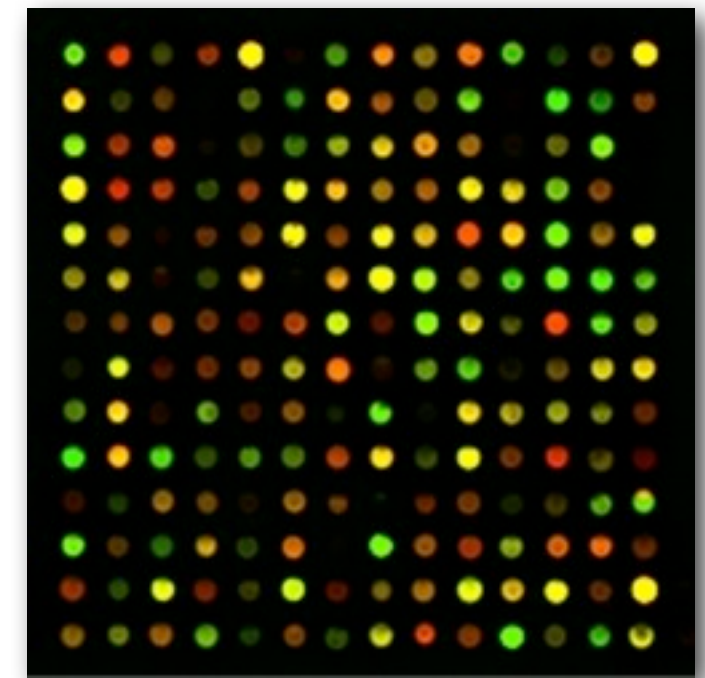
TDP-43 aggregation and toxicity in yeast cells



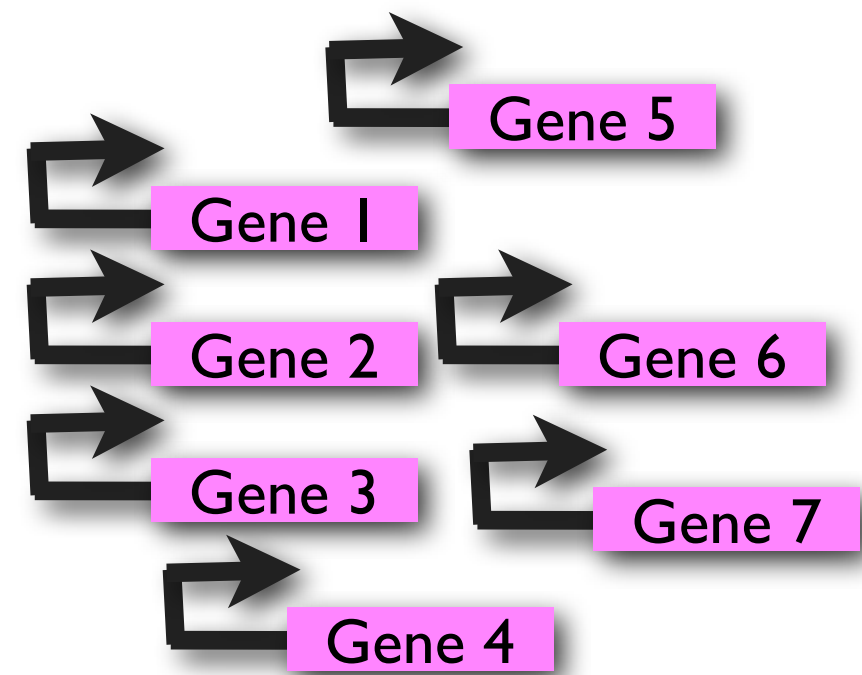
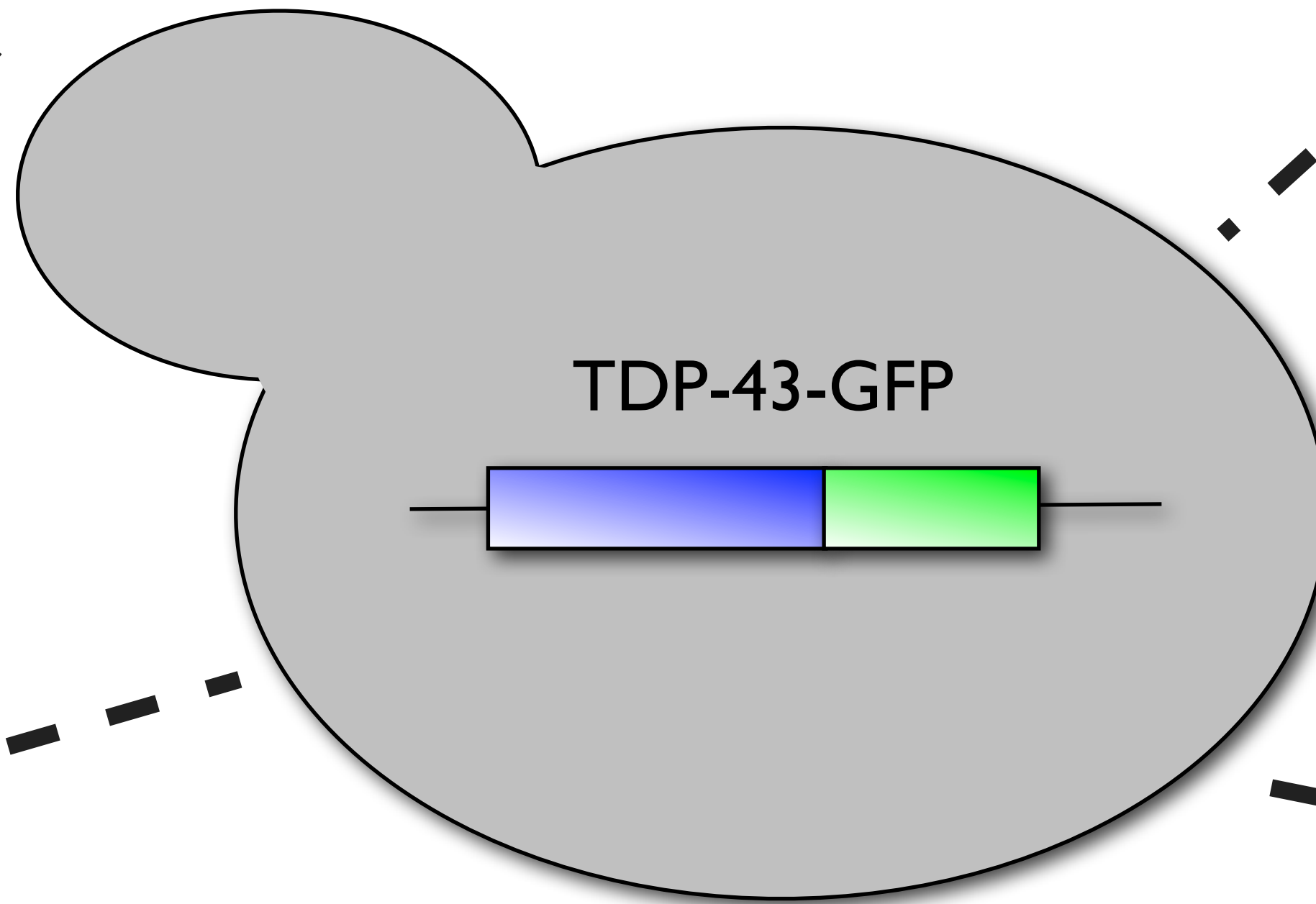
Synthetic lethal screen



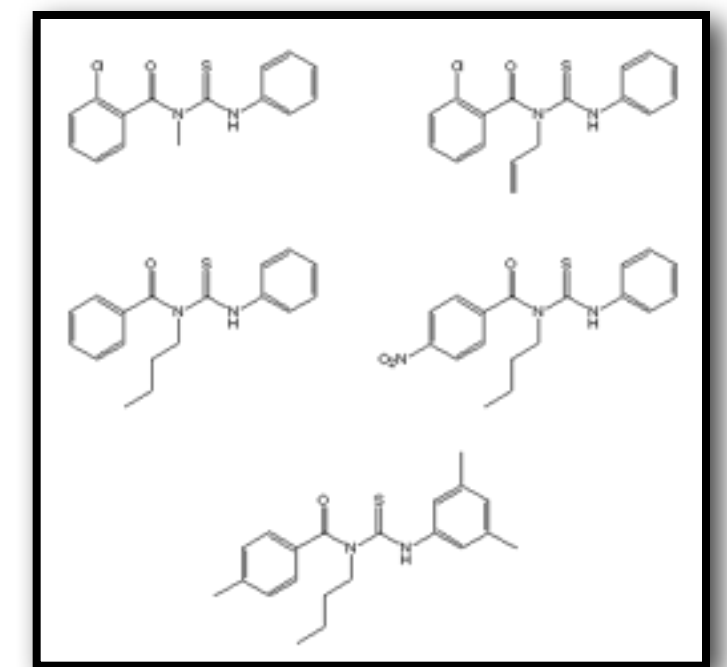
Yeast Screens to Define Mechanisms of TDP-43 Toxicity in ALS



Transcriptional
profiling

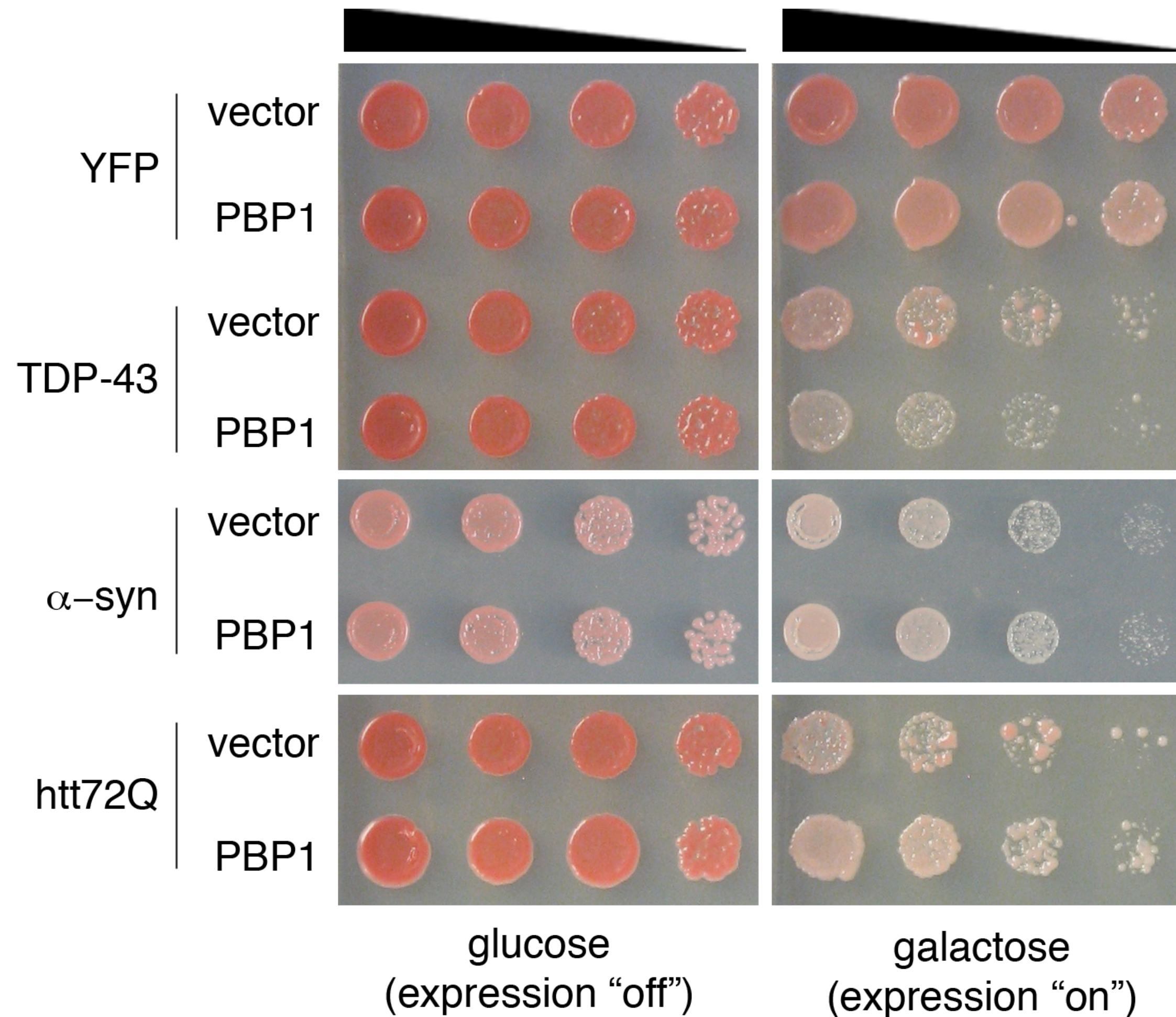


Overexpression screen

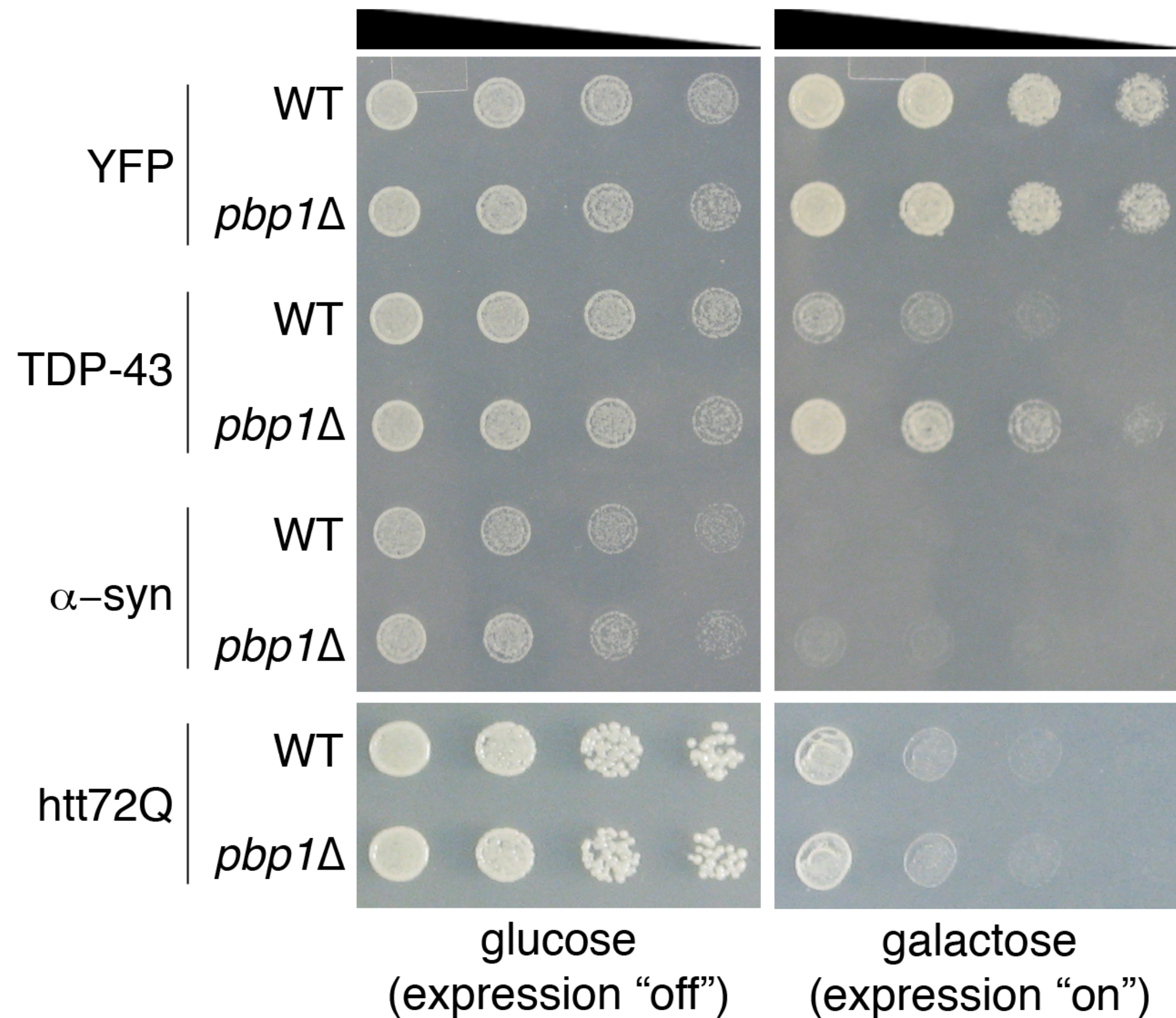


Small molecule
screen

PBP1 overexpression enhances TDP-43 toxicity



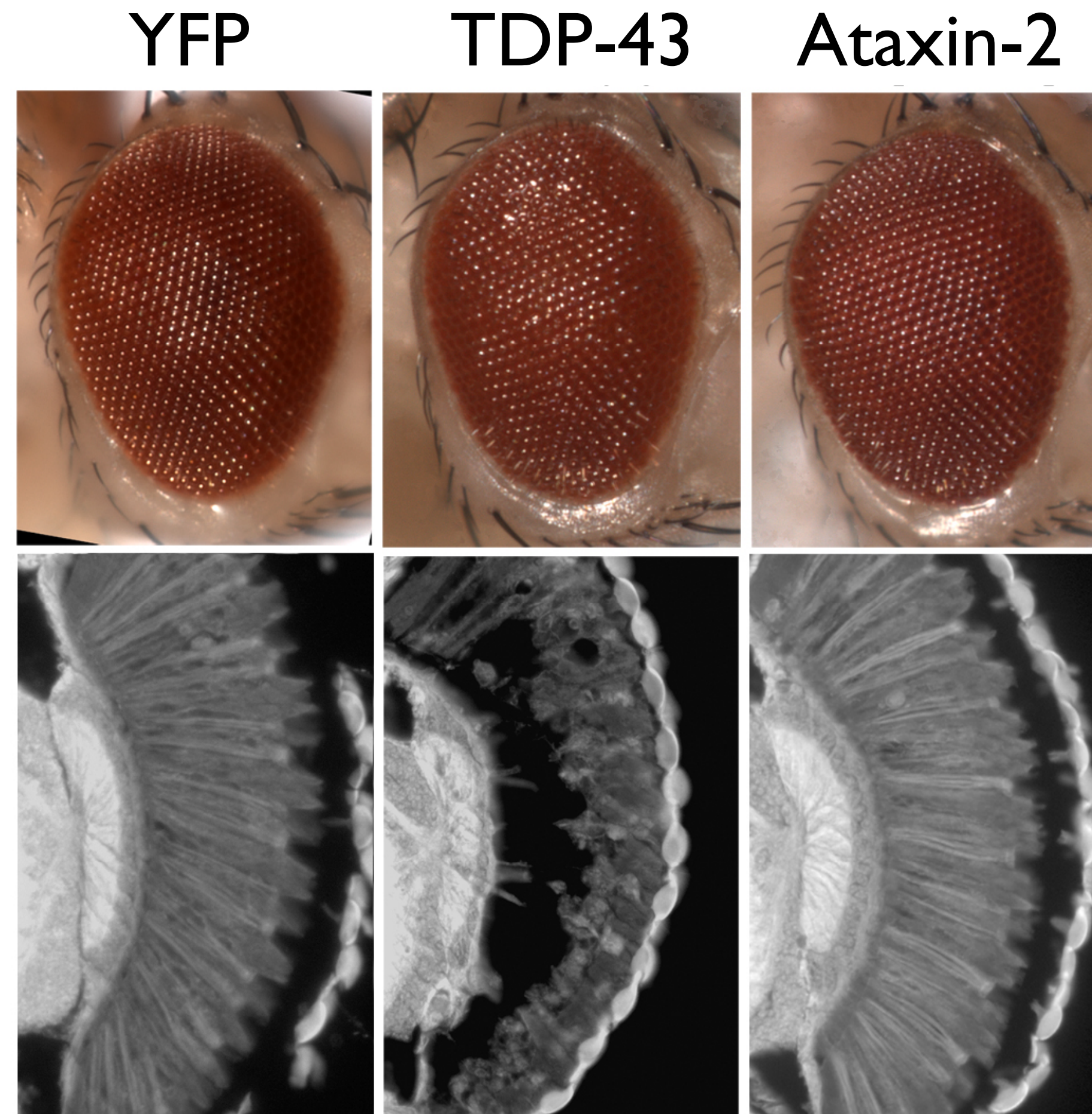
PBP1 deletion suppresses TDP-43 toxicity



Ataxin-2 is a Polyglutamine Disease Gene

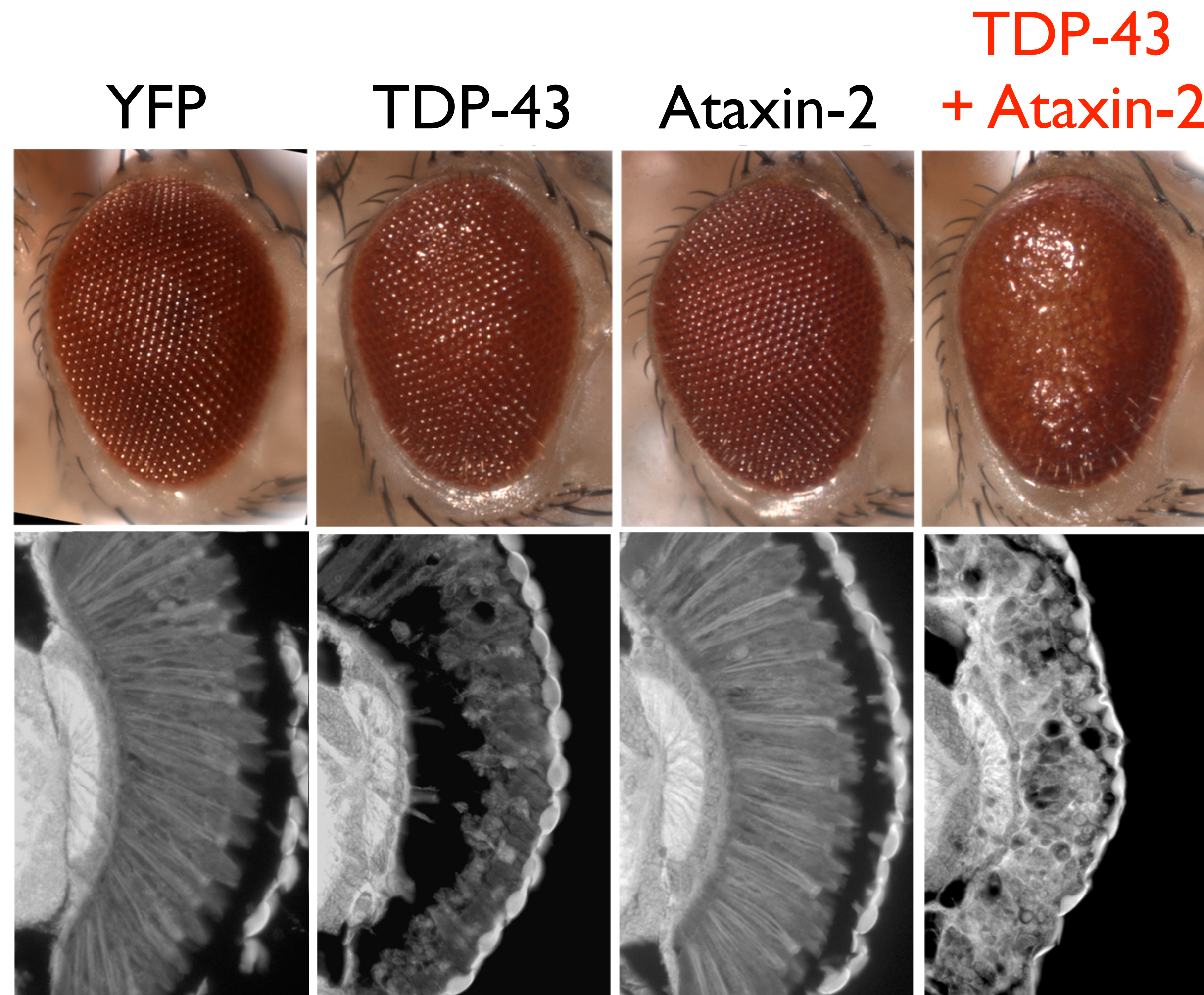
Disease	Mutation/ repeat unit	Gene name (protein product)	Putative function	Normal repeat length	Pathogenic repeat length
SCA1	(CAG) _n	<i>SCA1</i> (ataxin 1)	Transcription	6–39	40–82
SCA2	(CAG) _n	<i>SCA2</i> (ataxin 2)	RNA metabolism	15–24	32–200
SCA3 (MJD)	(CAG) _n	<i>SCA3</i> (ataxin 3)	De-ubiquitylating activity	13–36	61–84
SCA6	(CAG) _n	<i>CACNA1A</i> (<i>CACNA1_A</i>)	P/Q-type α 1A calcium channel subunit	4–20	20–29
SCA7	(CAG) _n	<i>SCA7</i> (ataxin 7)	Transcription	4–35	37–306
SCA17	(CAG) _n	<i>SCA17</i> (TBP)	Transcription	25–42	47–63
DRPLA	(CAG) _n	<i>DRPLA</i> (atrophin 1)	Transcription	7–34	49–88
SBMA	(CAG) _n	<i>AR</i> (androgen receptor)	Steroid-hormone receptor	9–36	38–62
HD	(CAG) _n	<i>HD</i> (huntingtin)	Signalling, transport, transcription	11–34	40–121

Ataxin-2 dramatically modulates TDP-43 toxicity in *Drosophila*



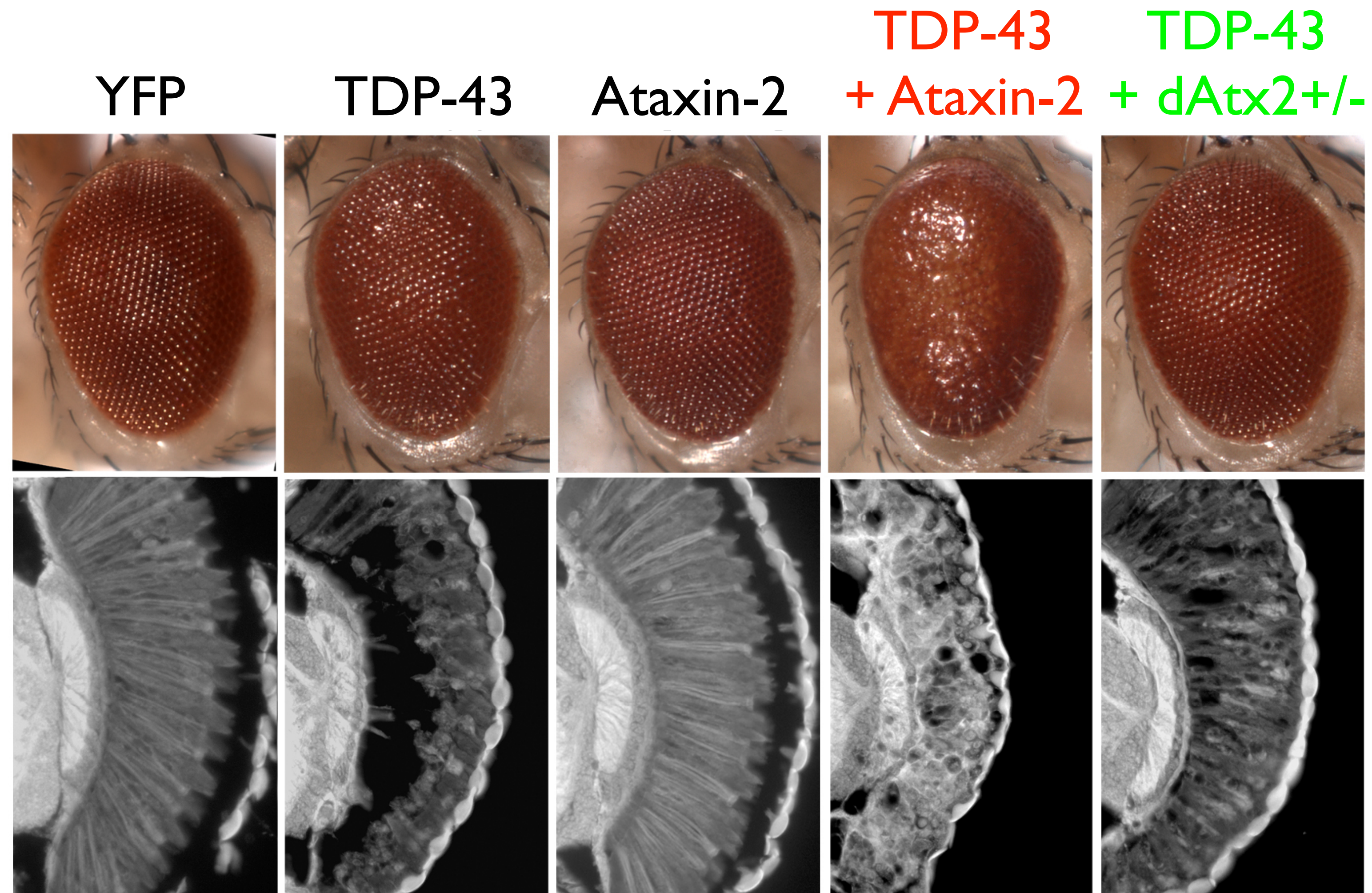
Nancy Bonini and Hyung-Jun Kim

Ataxin-2 dramatically modulates TDP-43 toxicity in *Drosophila*



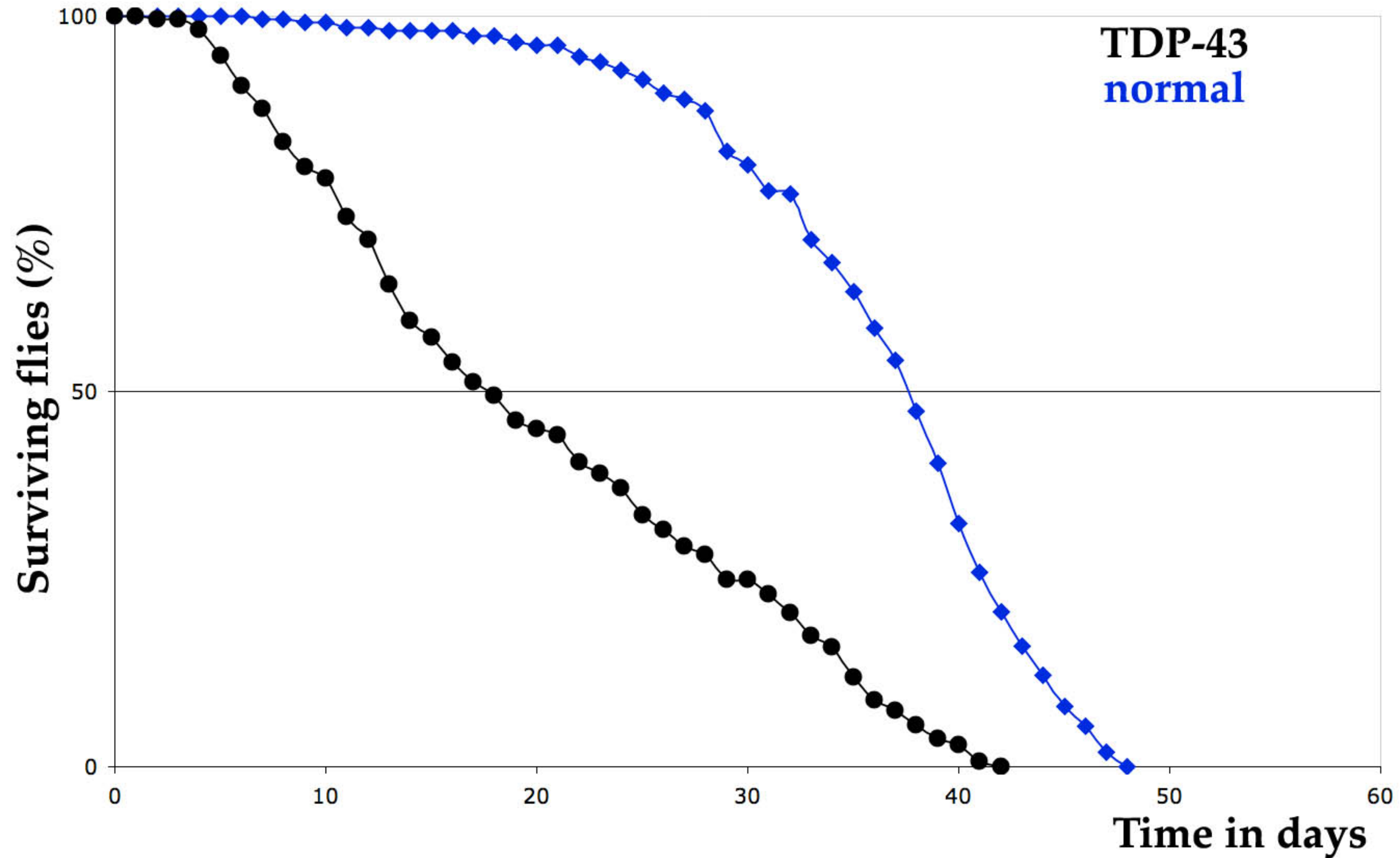
Nancy Bonini and Hyung-Jun Kim

Ataxin-2 dramatically modulates TDP-43 toxicity in *Drosophila*



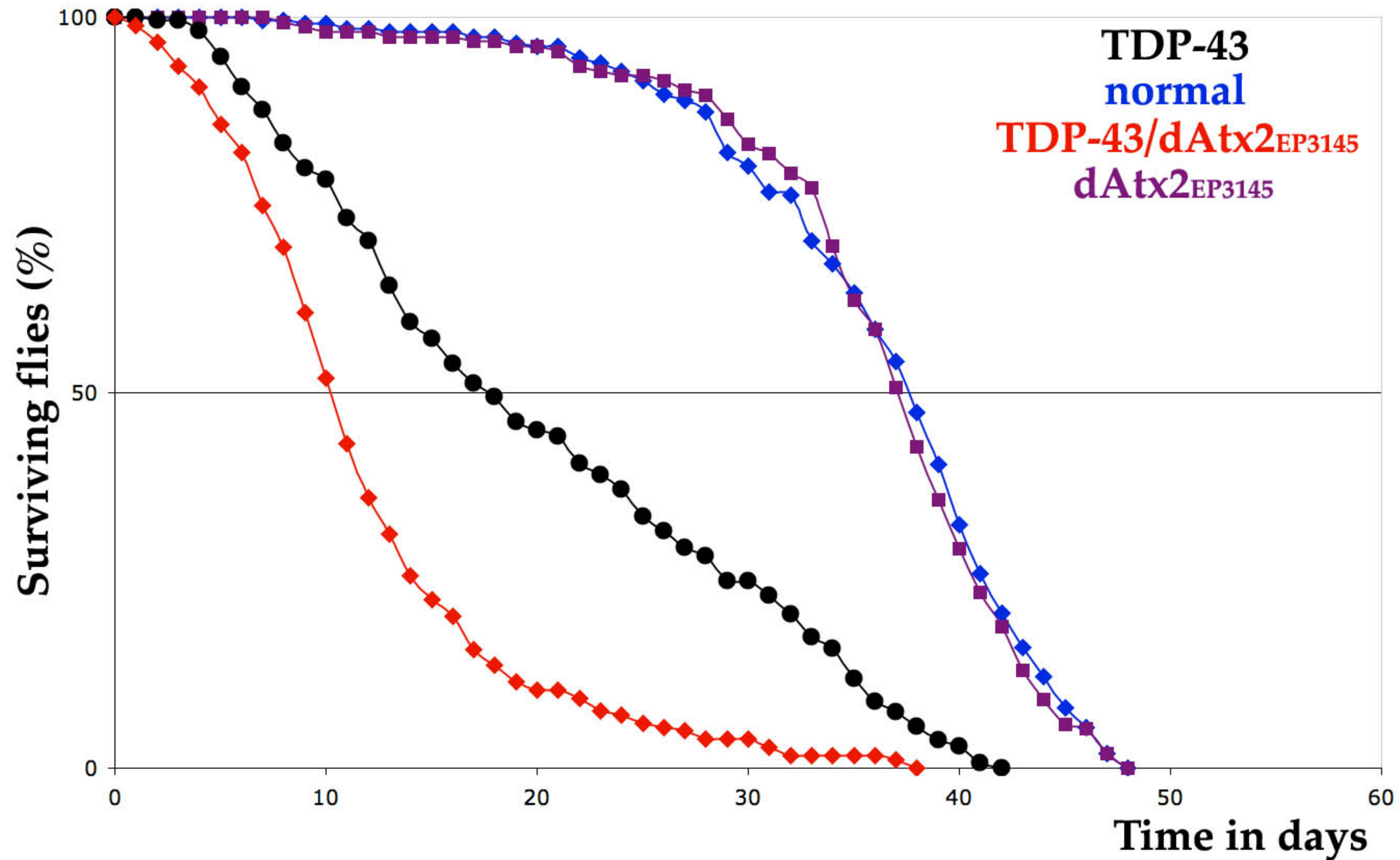
Nancy Bonini and Hyung-Jun Kim

Ataxin-2 dramatically modulates TDP-43 toxicity in *Drosophila*

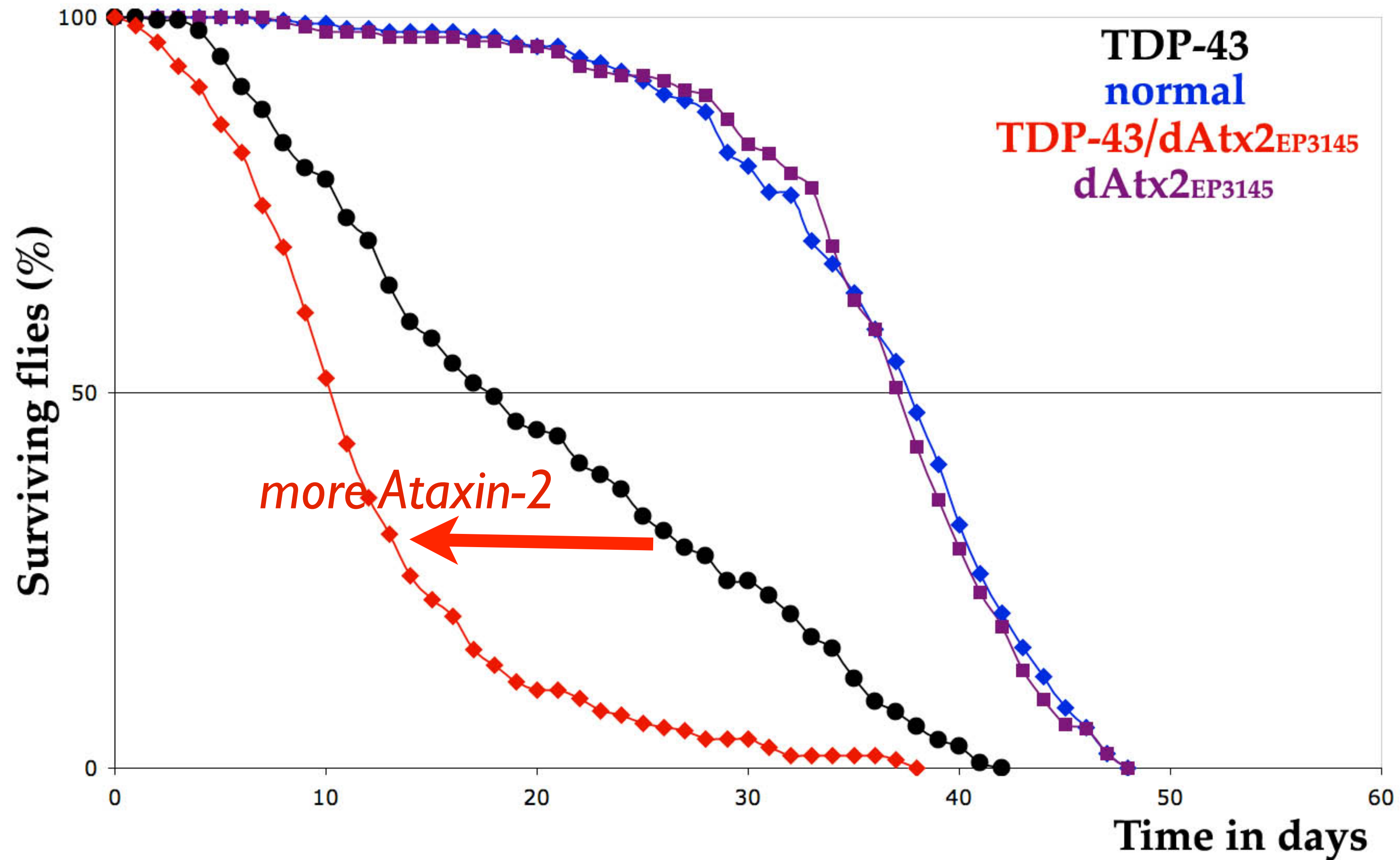


Nancy Bonini and Hyung-Jun Kim

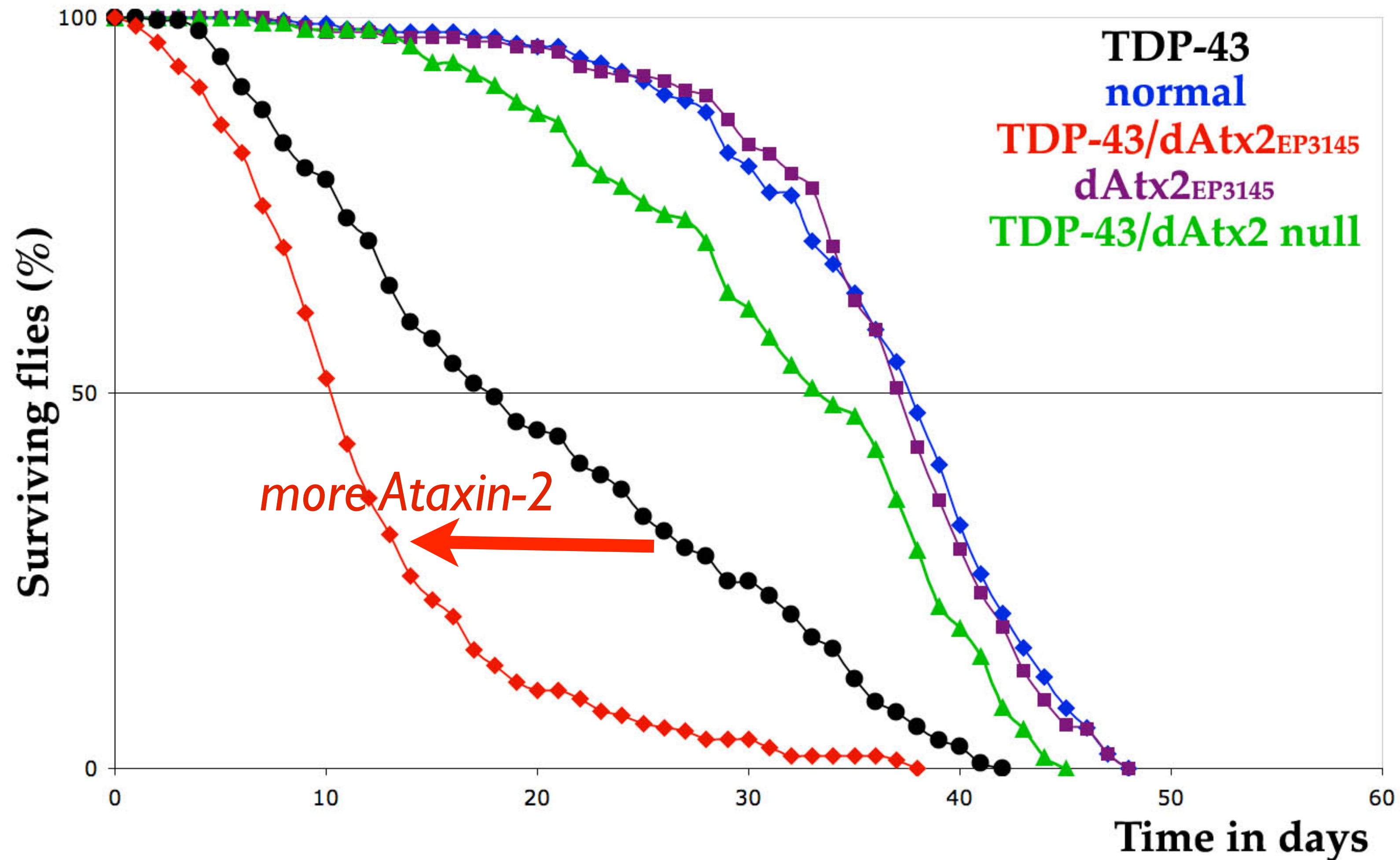
Ataxin-2 dramatically modulates TDP-43 toxicity in *Drosophila*



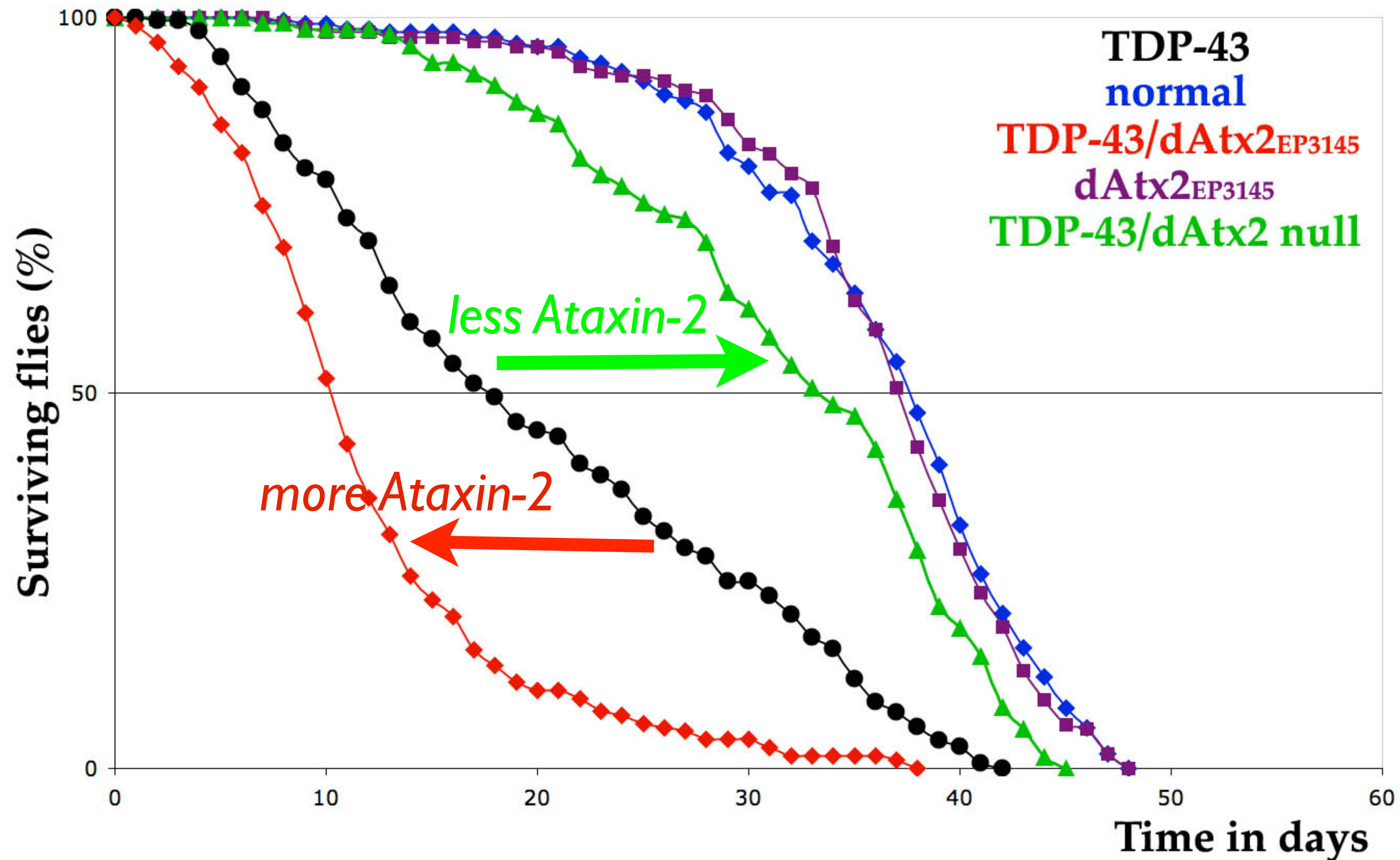
Ataxin-2 dramatically modulates TDP-43 toxicity in *Drosophila*



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Ataxin-2 dramatically modulates TDP-43 toxicity in *Drosophila*



Ataxin-2 is a Polyglutamine Disease Gene

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SCA3 (MJD)	(CAG) _n	<i>SCA3</i> (ataxin 3)	De-ubiquitylating activity	13–36	61–84
SCA6	(CAG) _n	<i>CACNA1A</i> (<i>CACNA1_A</i>)	P/Q-type α 1A calcium channel subunit	4–20	20–29
SCA7	(CAG) _n	<i>SCA7</i> (ataxin 7)	Transcription	4–35	37–306
SCA17	(CAG) _n	<i>SCA17</i> (TBP)	Transcription	25–42	47–63
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SBMA	(CAG) _n	<i>AR</i> (androgen receptor)	Steroid-hormone receptor	9–36	38–62
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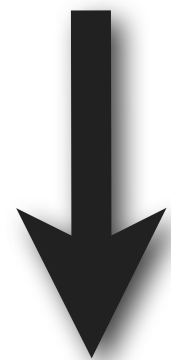
The Ataxin-2 Gene



The Ataxin-2 Gene



CAG CAG CAG CAG CAG CAG CAG CAG



QQQQQQQQQQ

polyQ (Normally 22)

The Ataxin-2 Gene



The Ataxin-2 Gene



CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG

CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG

CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG

CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG

Expanded polyQ causes Spinocerebellar Ataxia-2 (SCA2) (35 Qs or more)

Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q

Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q Q

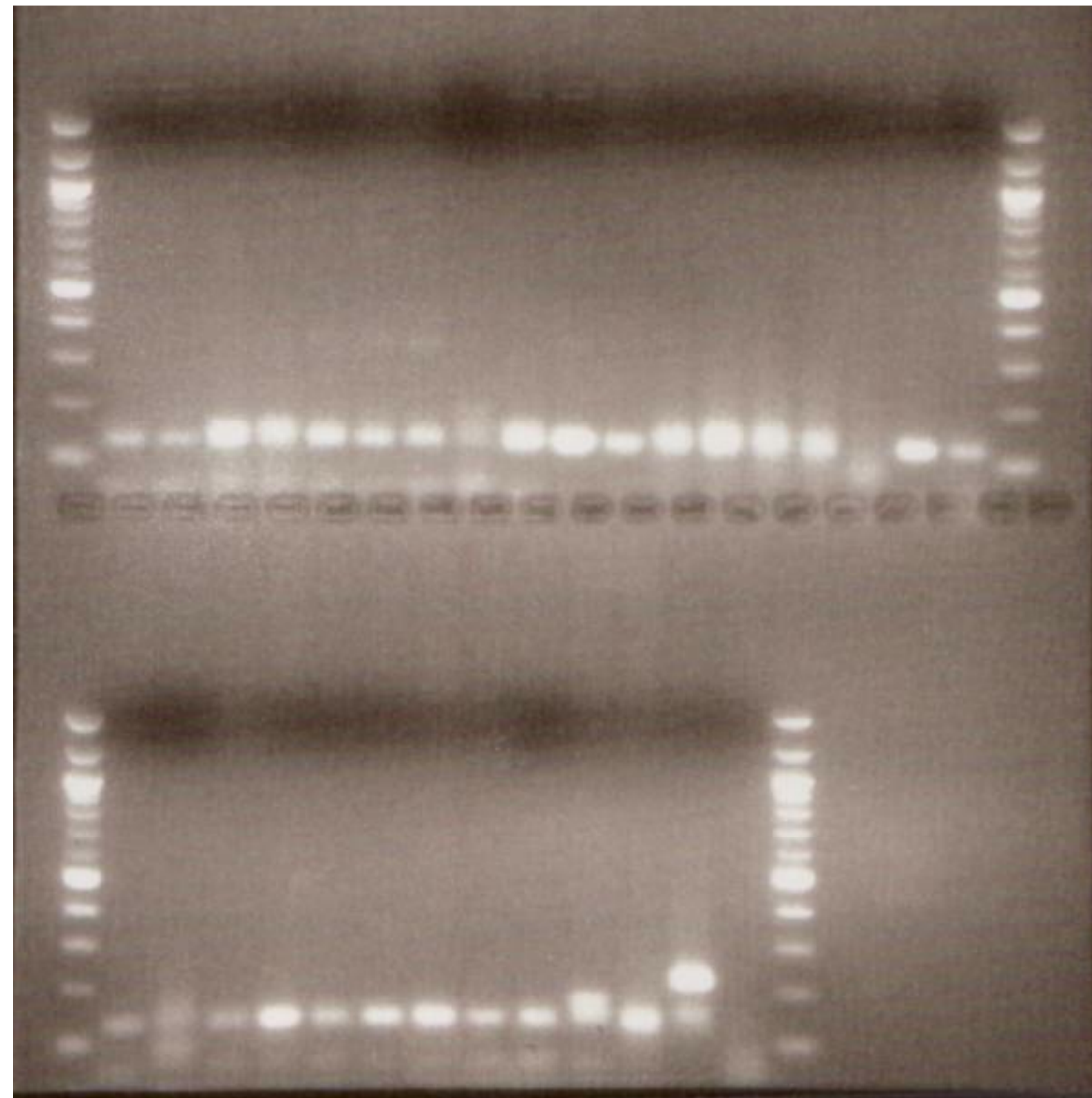
Ataxin-2 and ALS?



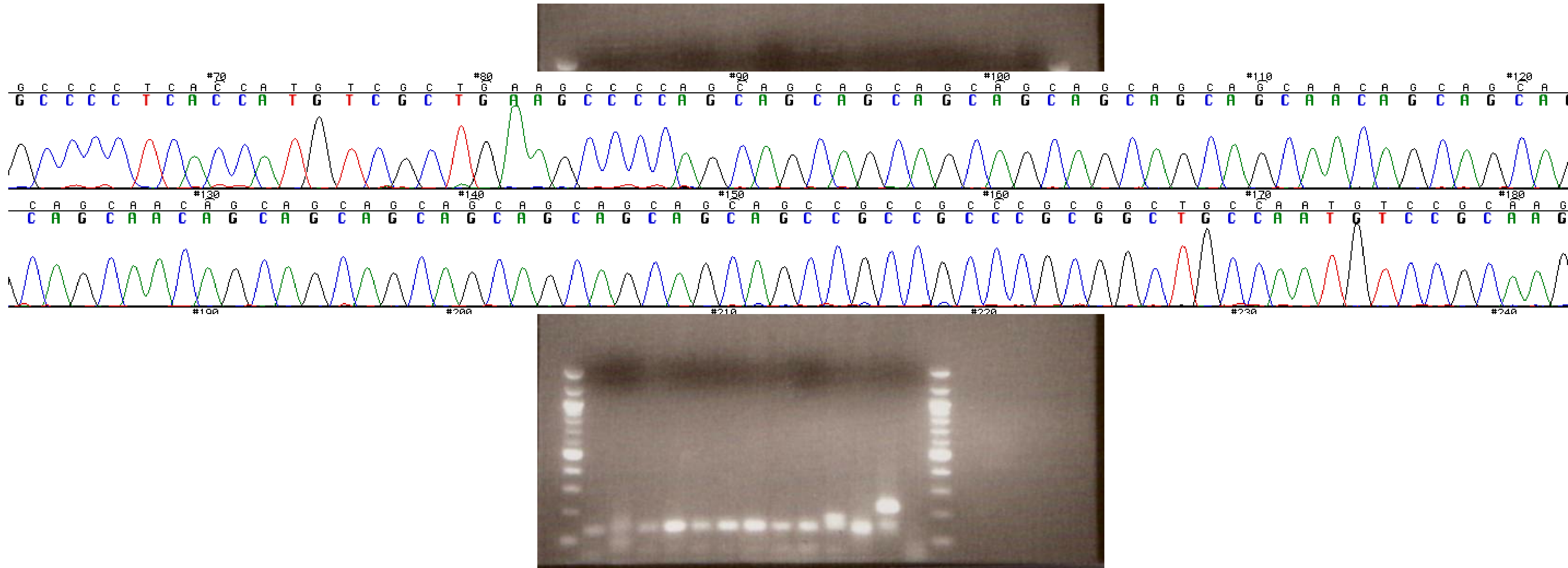
Ataxin-2 and ALS?



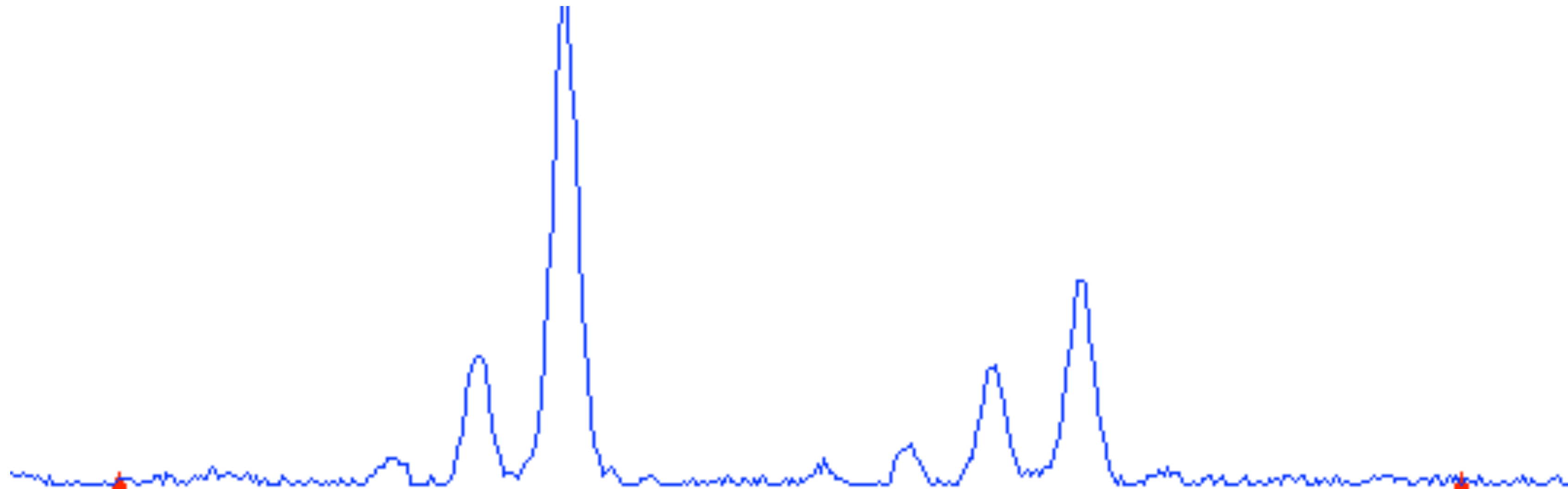
Are intermediate-length polyQ repeats in Ataxin-2 linked to ALS?



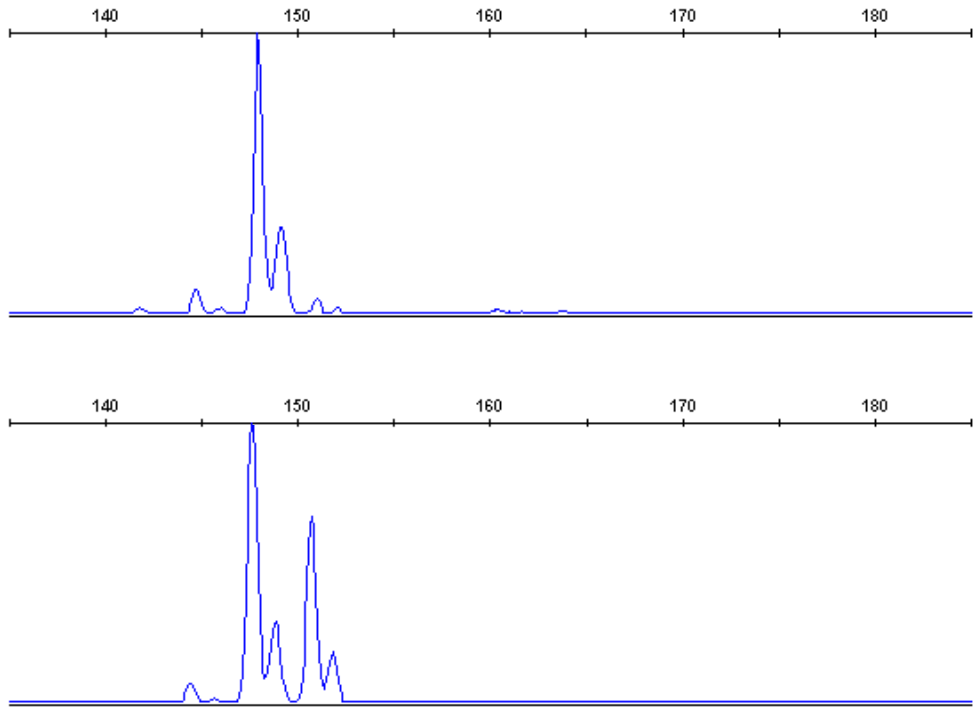
Are intermediate-length polyQ repeats in Ataxin-2 linked to ALS?



Are intermediate-length polyQ repeats in Ataxin-2 linked to ALS?



Ataxin-2 polyQ length
(allele 1/allele2)

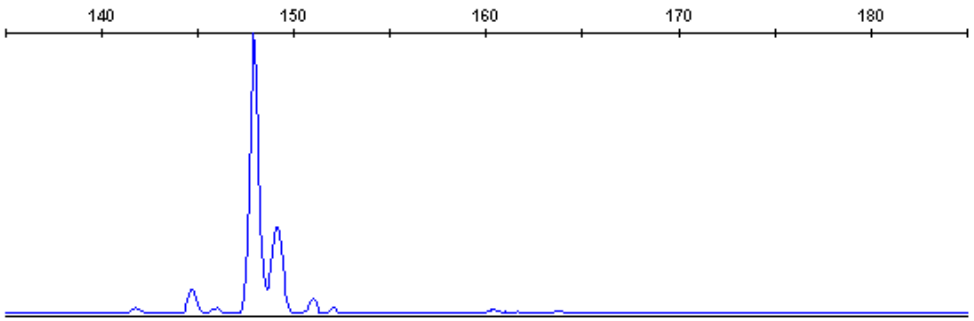


22/22

Normal

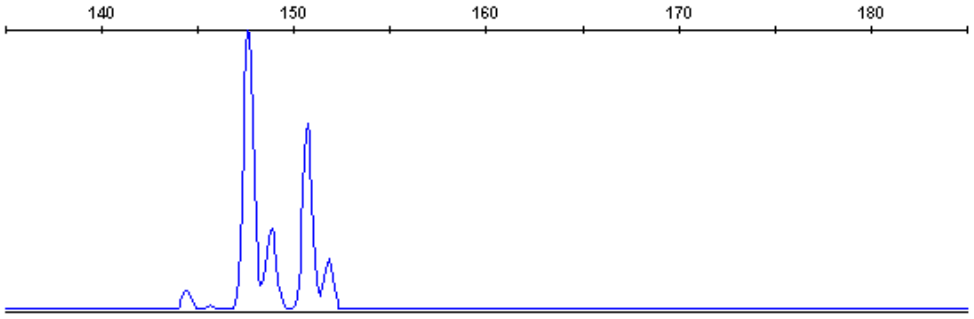
22/23

Ataxin-2 polyQ length
(allele 1/allele2)

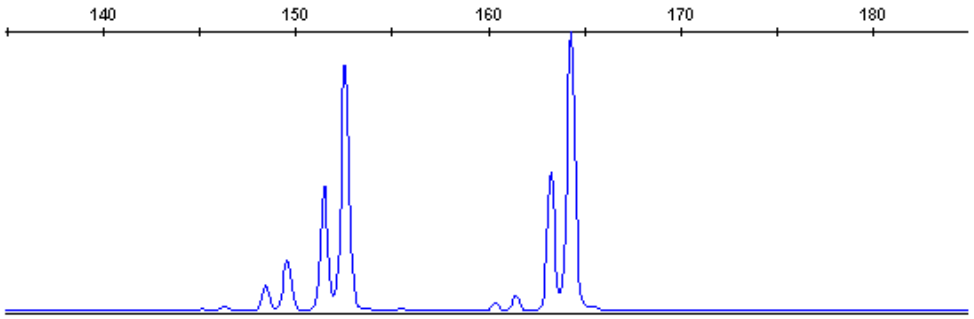


22/22

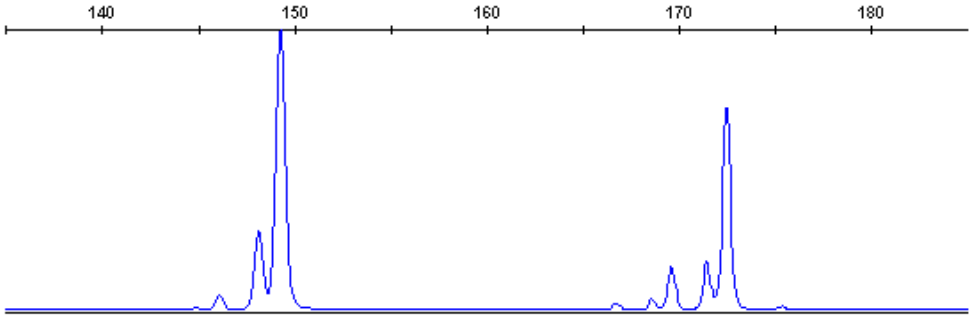
Normal



22/23

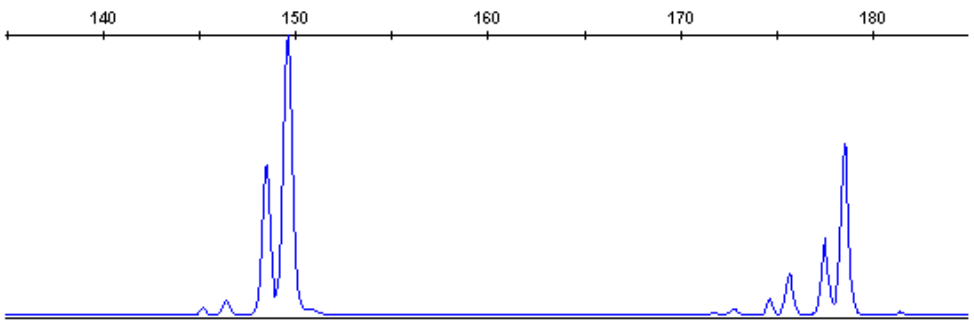


22/27

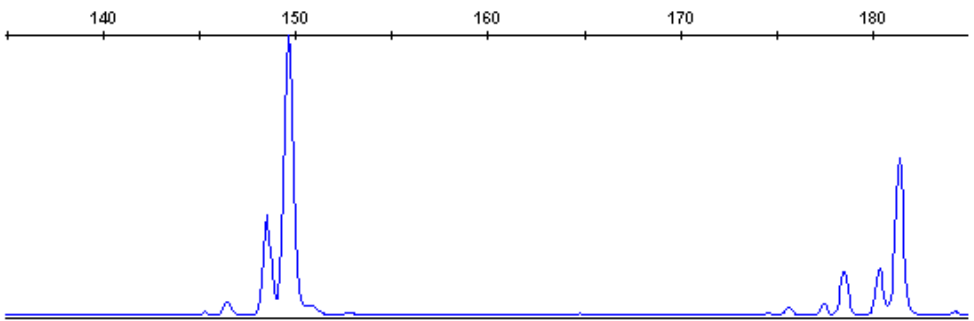


22/30

ALS



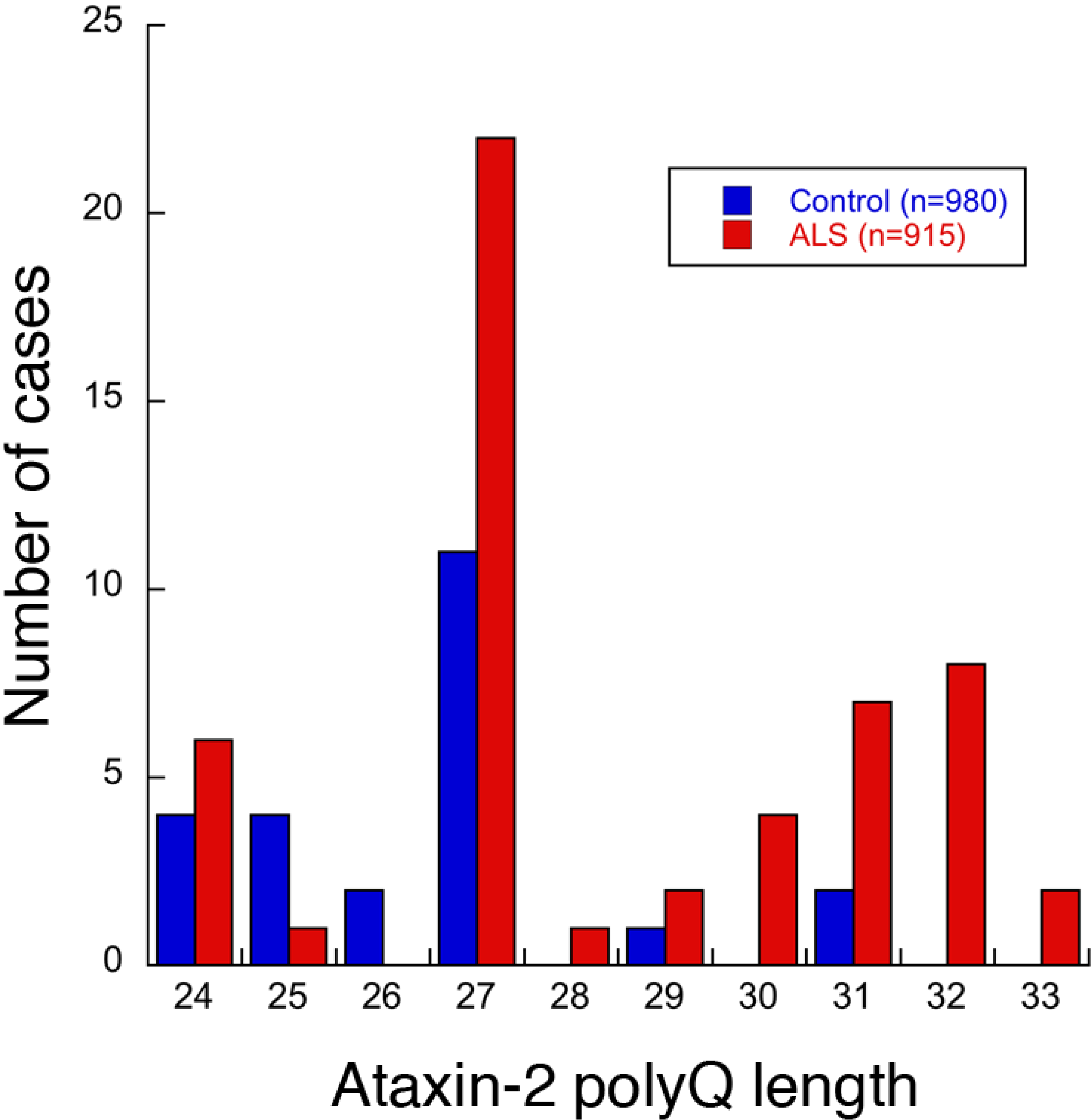
22/32



22/33

Intermediate-length Ataxin-2 polyQ expansions
are associated with increased risk for ALS

Control	n	# with repeats ≥ 27	%	P-value (Fisher's)
Control	980	14	1.4%	
ALS	915	43	4.7%	3.6×10^{-5}



Ataxin-2 polyQ expansions in ALS

Elden et al., *Nature* 2010

North America, 915 ALS patients and 980 healthy controls

PolyQ 27-33 ($P=3.6 \times 10^{-5}$)

Li et al., *Human Molecular Genetics* 2011

Europe, 1294 ALS patients and 679 healthy controls

PolyQ >30 ($P=6.2 \times 10^{-3}$)

Corrado et al., *Human Genetics* 2011

Italy, 232 ALS patients and 395 healthy controls

PolyQ >30 ($P=8.9 \times 10^{-4}$)

Van Damme et al., *Neurology* 2011

Belgium and the Netherlands, 1,948 ALS patients and 2,002 healthy controls

PolyQ >28 ($P=0.036$)

Ross et al., *Human Molecular Genetics* 2011

Mayo Clinic Jacksonville 532 ALS patients and 4,877 healthy controls

PolyQ >30 ($P=0.001$)

* Also identified association with PSP (progressive supranuclear palsy)

Daoud et al., *Archives of Neurology* 2011

French and French Canadian, 556 ALS cases and 471 controls

PolyQ >29 ($P=2.4 \times 10^{-4}$)

Chen et al., *Neurobiology of Aging* 2011

Chinese, 345 ALS patients and 350 healthy controls

PolyQ >27 ($P=0.040$)

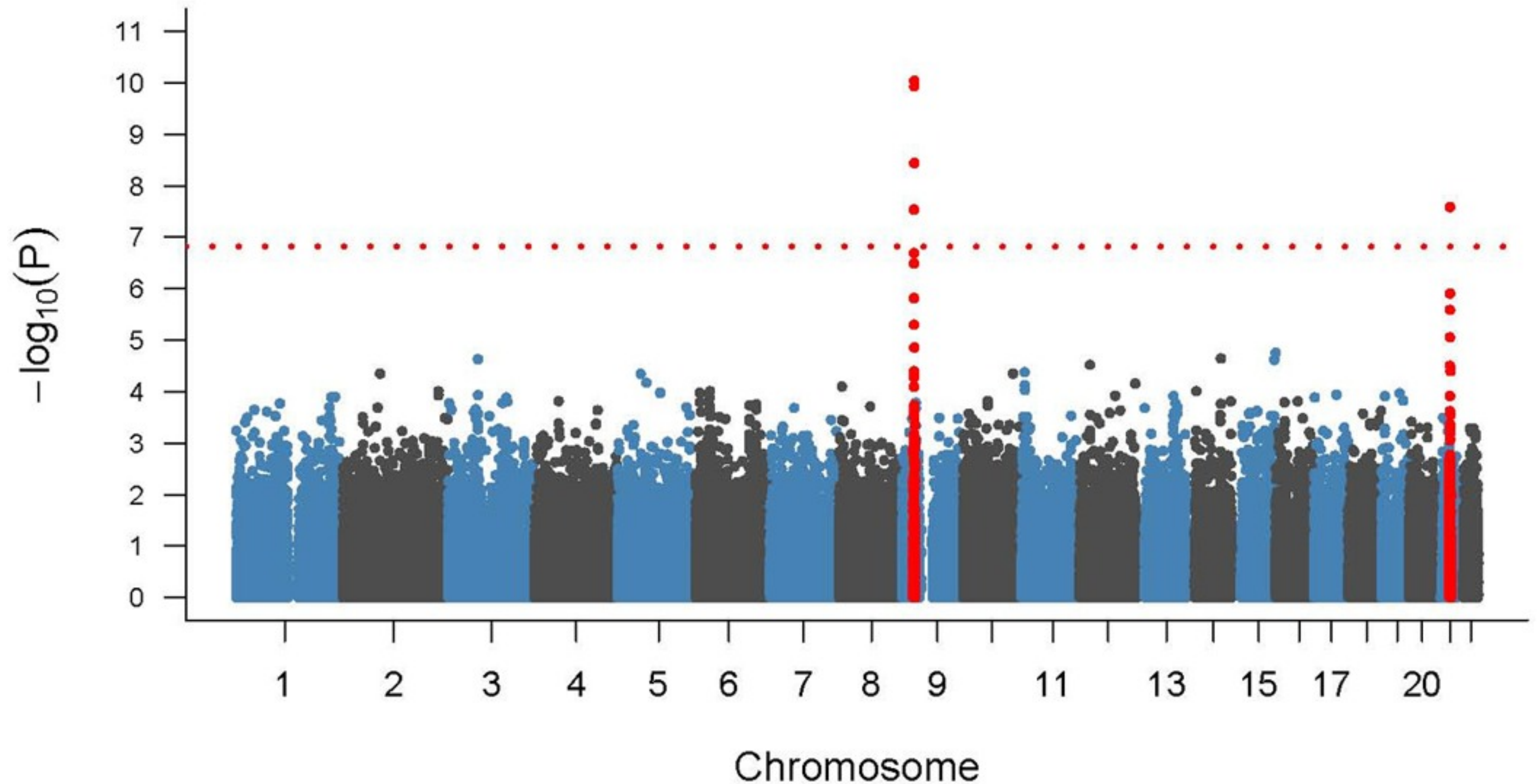
Editorial

Fischbeck KH and Pulst SM,
“Amyotrophic lateral sclerosis
and spinocerebellar ataxia 2”,
Neurology 2011

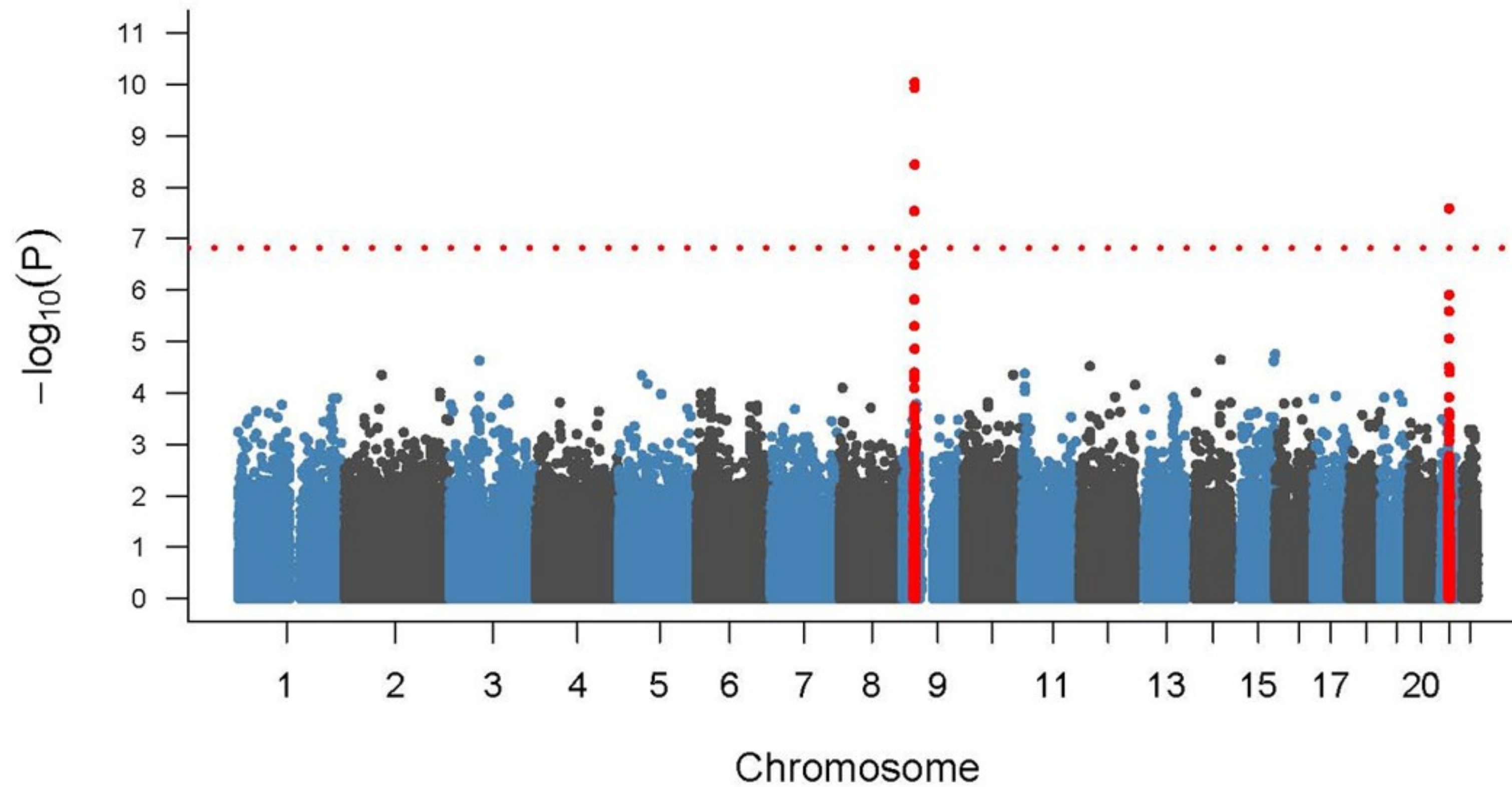
Susceptibility Loci for ALS

Gene	Protein	Location	Polymorphism	OR (95% CI)
<i>UNC13A</i>	unc-13 homolog A	19p13.11	rs12608932	1.18 (1.13-1.24)
<i>GWA_9p21.2</i>	Unknown	9p21.2	rs2814707	1.25 (1.19-1.32)
<i>ATXN2</i>	ataxin 2	12q24.12	PolyQ	n.a.

Genome Wide Association Studies (GWAS) links 9p21 to ALS



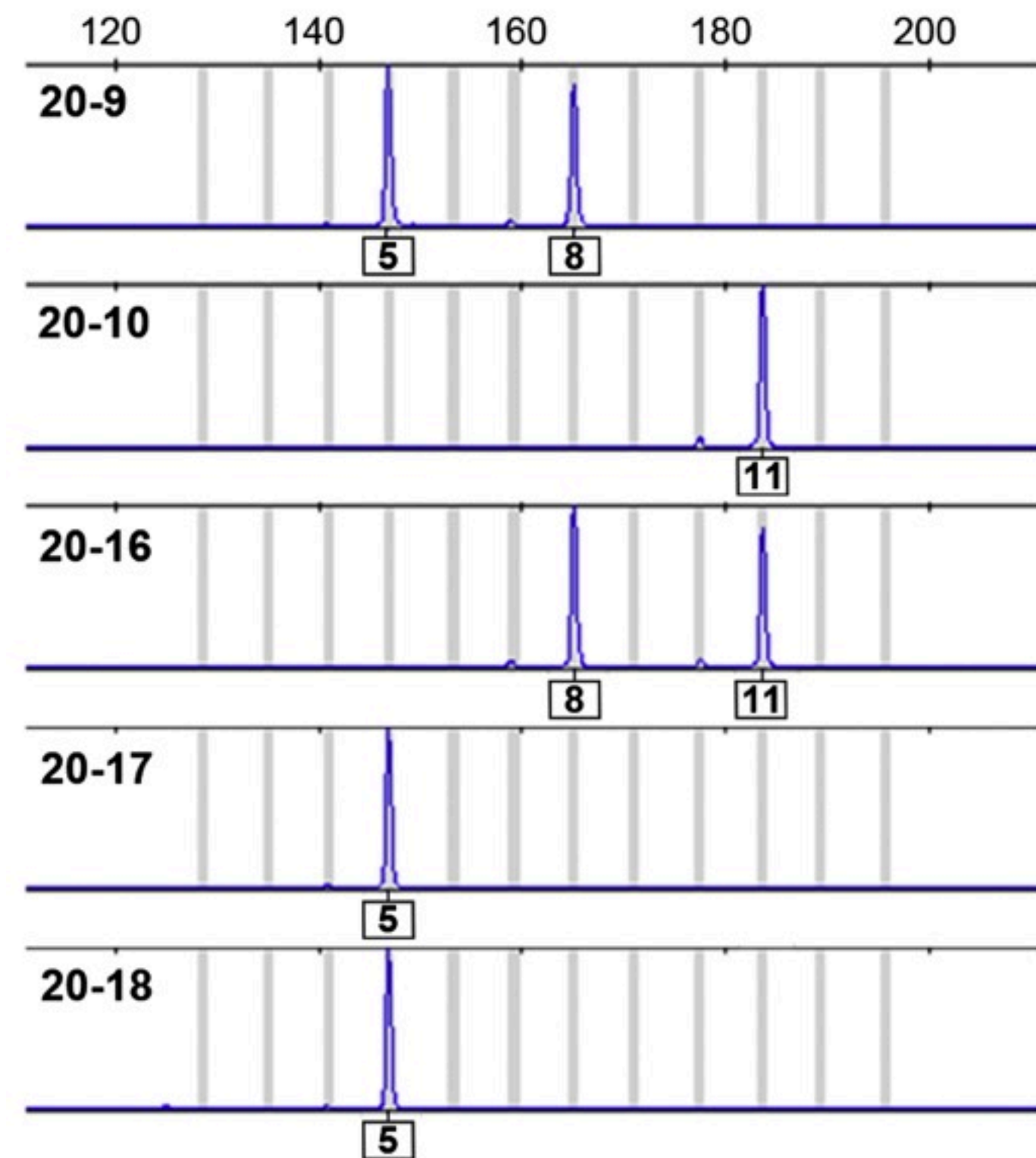
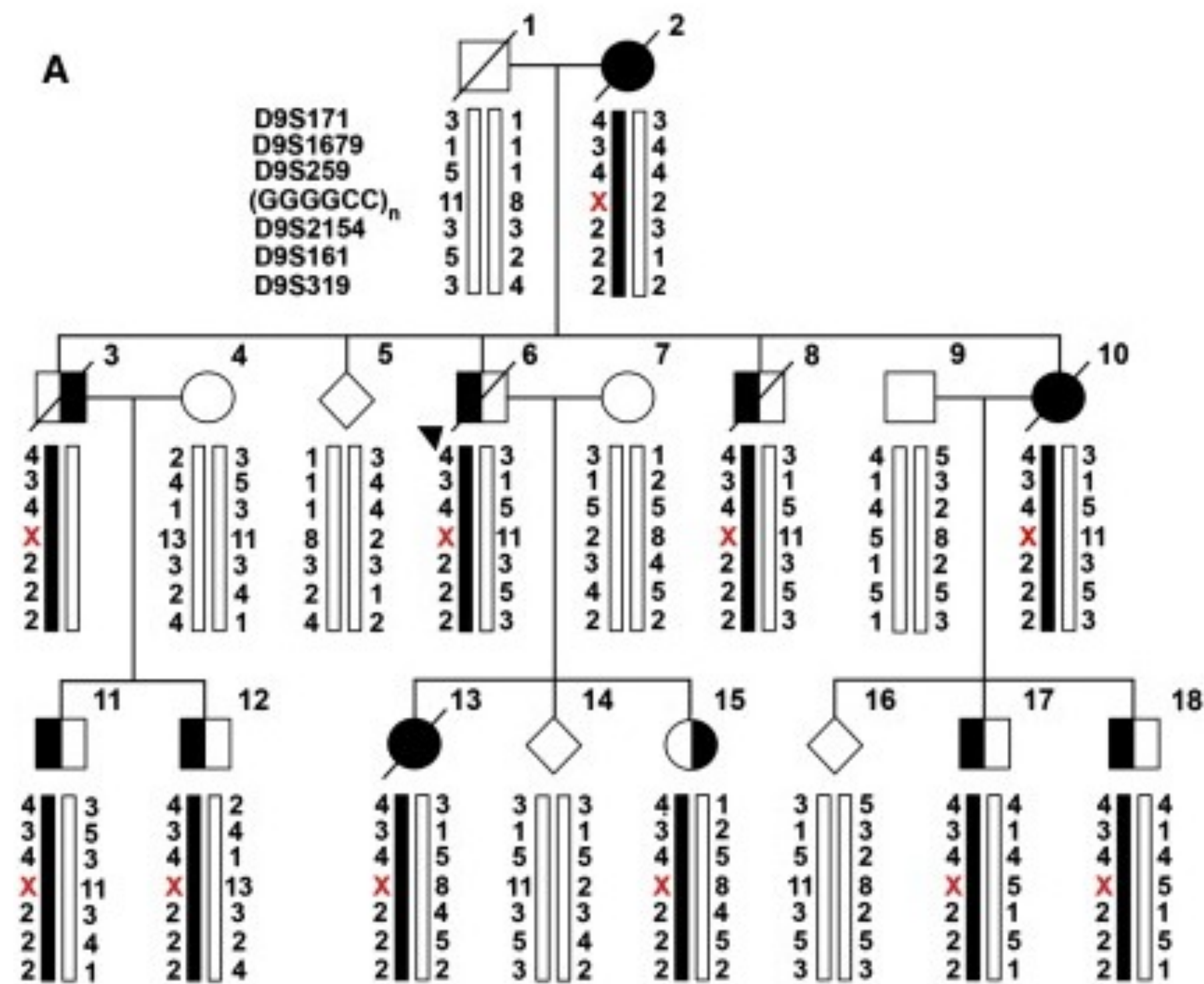
How would you identify the mutated gene(s) on 9p21?

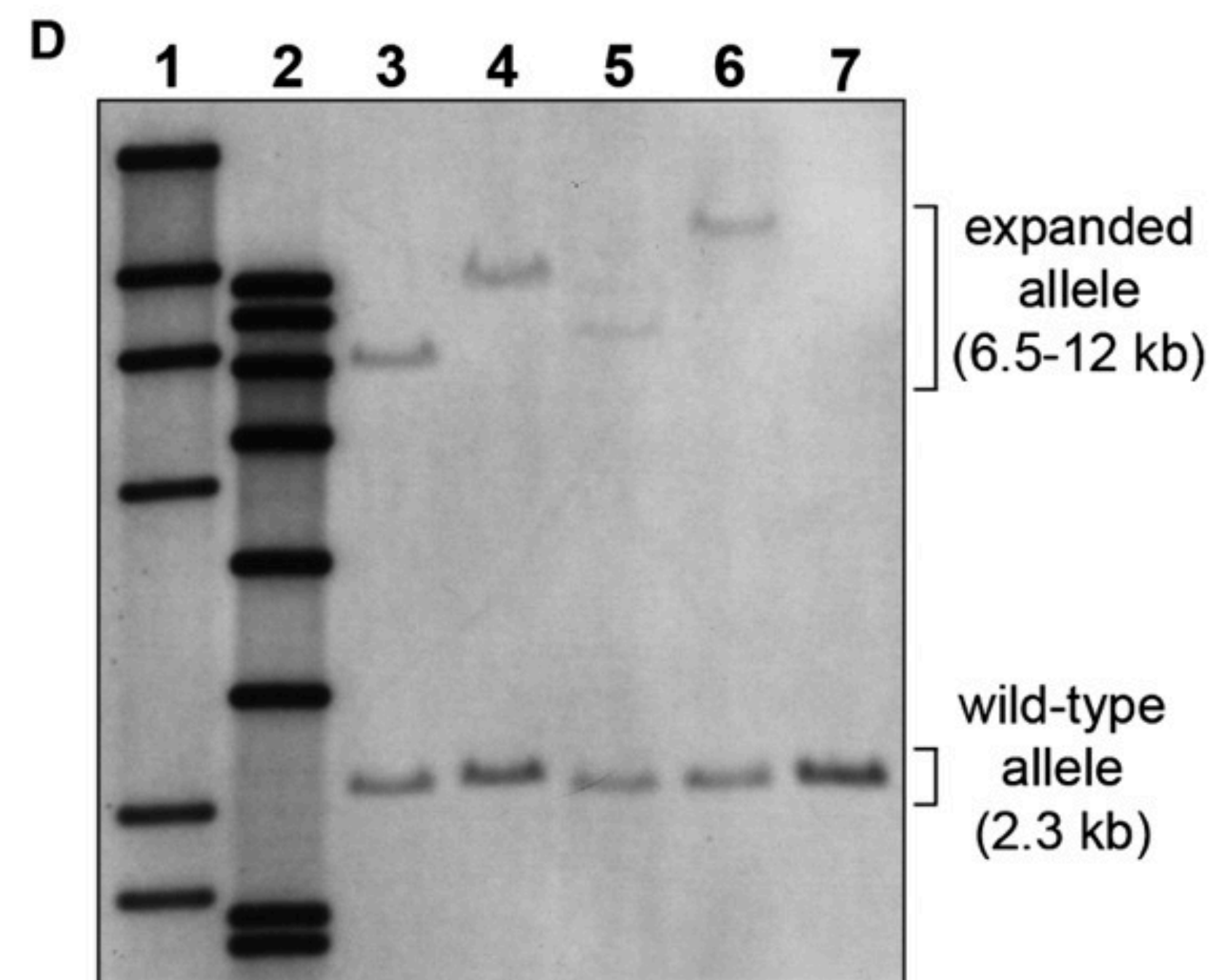
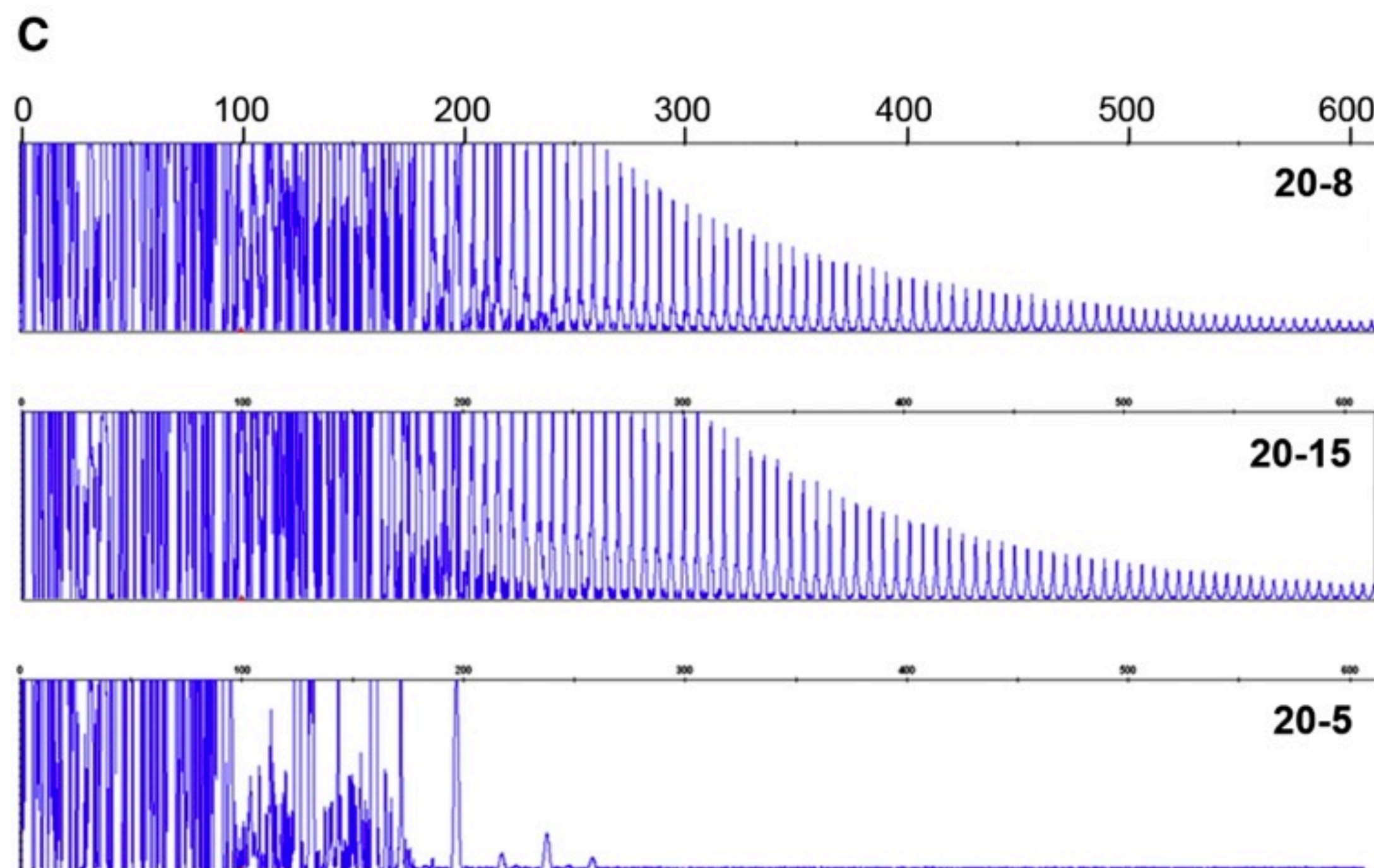
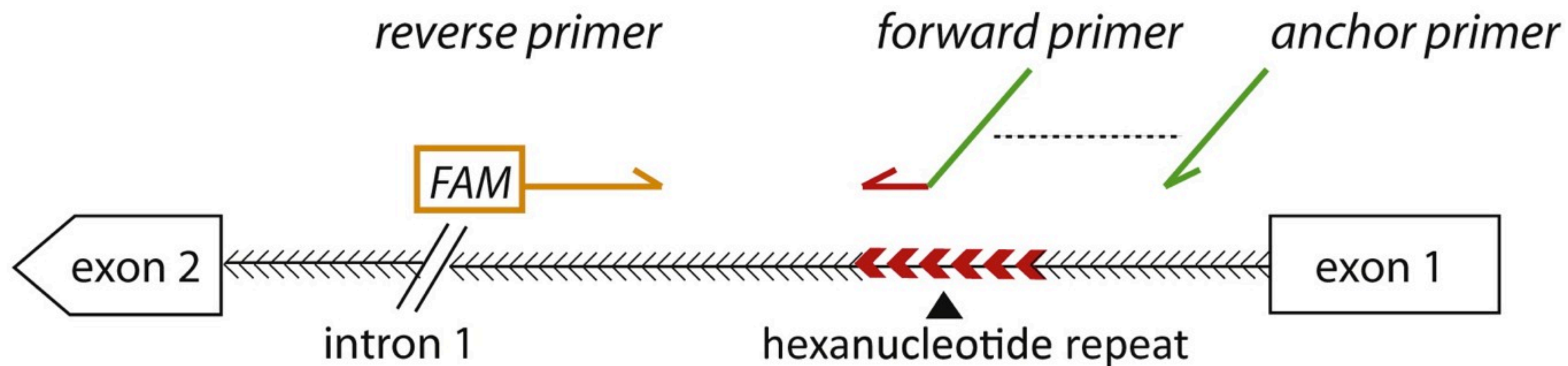


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GACCTGATAAAGATTAACCAAGAAGAAAACAAGGAGGGAAAC
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GGAAGTCTCAGGAGTCGCGCGCTA**GGGGCCGGGGCCGGGGCC**GGGGCGTGGTCGGGGCGGG
CCCGGGGGCGGGCCCGGGGCGGGGCTGCGGTTGCGGTGCCTGCGCCCGCGGGCGGGCGGA





Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of *C9ORF72* Causes Chromosome 9p-Linked FTD and ALS

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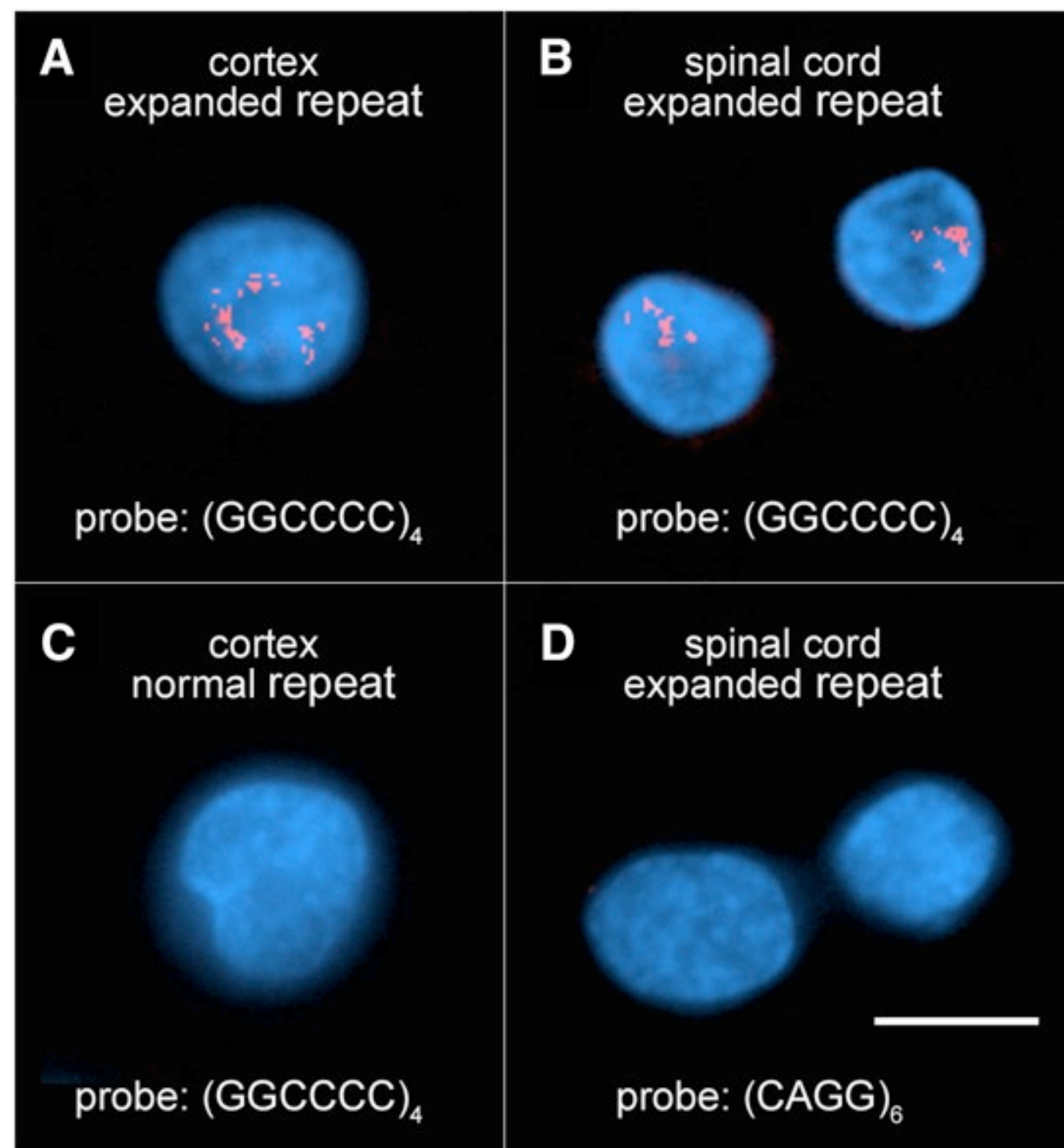
DOI 10.1016/j.neuron.2011.09.011

A Hexanucleotide Repeat Expansion in *C9ORF72* Is the Cause of Chromosome 9p21-Linked ALS-FTD

Alan E. Renton,^{1,38} Elisa Majounie,^{2,38} Adrian Waite,^{3,38} Javier Simón-Sánchez,^{4,5,38} Sara Rollinson,^{6,38} J. Raphael Gibbs,^{7,8,38} Jennifer C. Schymick,^{1,38} Hannu Laaksovirta,^{9,38} John C. van Swieten,^{4,5,38} Liisa Myllykangas,¹⁰ Hannu Kalimo,¹⁰ Anders Paetau,¹⁰ Yevgeniya Abramzon,¹ Anne M. Remes,¹¹ Alice Kaganovich,¹² Sonja W. Scholz,^{2,13,14} Jamie Duckworth,⁷ Jinhui Ding,⁷ Daniel W. Harmer,¹⁵ Dena G. Hernandez,^{2,8} Janel O. Johnson,^{1,8} Kin Mok,⁸ Mina Ryten,⁸ Danyah Trabzuni,⁸ Rita J. Guerreiro,⁸ Richard W. Orrell,¹⁶ James Neal,¹⁷ Alex Murray,¹⁸ Justin Pearson,³ Iris E. Jansen,⁴ David Sondervan,⁴ Harro Seelaar,⁵ Derek Blake,³ Kate Young,⁶ Nicola Halliwell,⁶ Janis Bennion Callister,⁶ Greg Toulson,⁶ Anna Richardson,¹⁹ Alex Gerhard,¹⁹ Julie Snowden,¹⁹ David Mann,¹⁹ David Neary,¹⁹ Michael A. Nalls,² Terhi Peuralinna,⁹ Lilja Jansson,⁹ Veli-Matti Isoviita,⁹ Anna-Lotta Kaivorinne,¹¹ Maarit Hölttä-Vuori,²⁰ Elina Ikonen,²⁰ Raimo Sulkava,²¹ Michael Benatar,²² Joanne Wu,²³ Adriano Chiò,²⁴ Gabriella Restagno,²⁵ Giuseppe Borghero,²⁶ Mario Sabatelli,²⁷ The ITALSGEN Consortium,²⁸ David Heckerman,²⁹ Ekaterina Rogaeva,³⁰ Lorne Zinman,³¹ Jeffrey D. Rothstein,¹⁴ Michael Sendtner,³² Carsten Drepper,³² Evan E. Eichler,³³ Can Alkan,³³ Ziedulla Abdullaev,³⁴ Svetlana D. Pack,³⁴ Amalia Dutra,³⁵ Evgenia Pak,³⁵ John Hardy,⁸ Andrew Singleton,² Nigel M. Williams,^{3,38} Peter Heutink,^{4,38} Stuart Pickering-Brown,^{6,38} Huw R. Morris,^{3,36,37,38} Pentti J. Tienari,^{9,38} and Bryan J. Traynor^{1,14,38,*}

How do GGGGGCC expansions in *C9ORF72* cause FTLD/ALS?

Clues



Today's Plan

1. Huntington's Disease
2. Alzheimer's Disease
3. Frontotemporal Dementia
4. Amyotrophic lateral sclerosis (ALS)
5. Parkinson's Disease

Parkinson's Disease

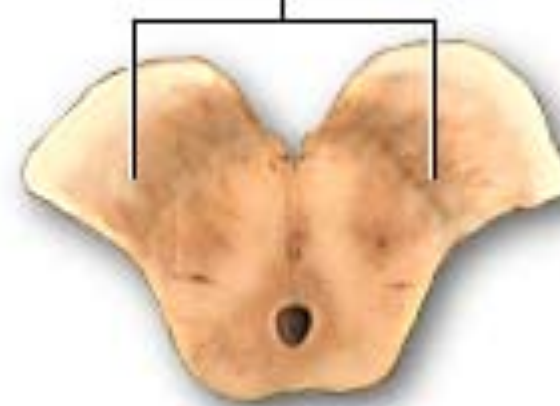


Cut section
of the midbrain
where a portion
of the substantia
nigra is visible

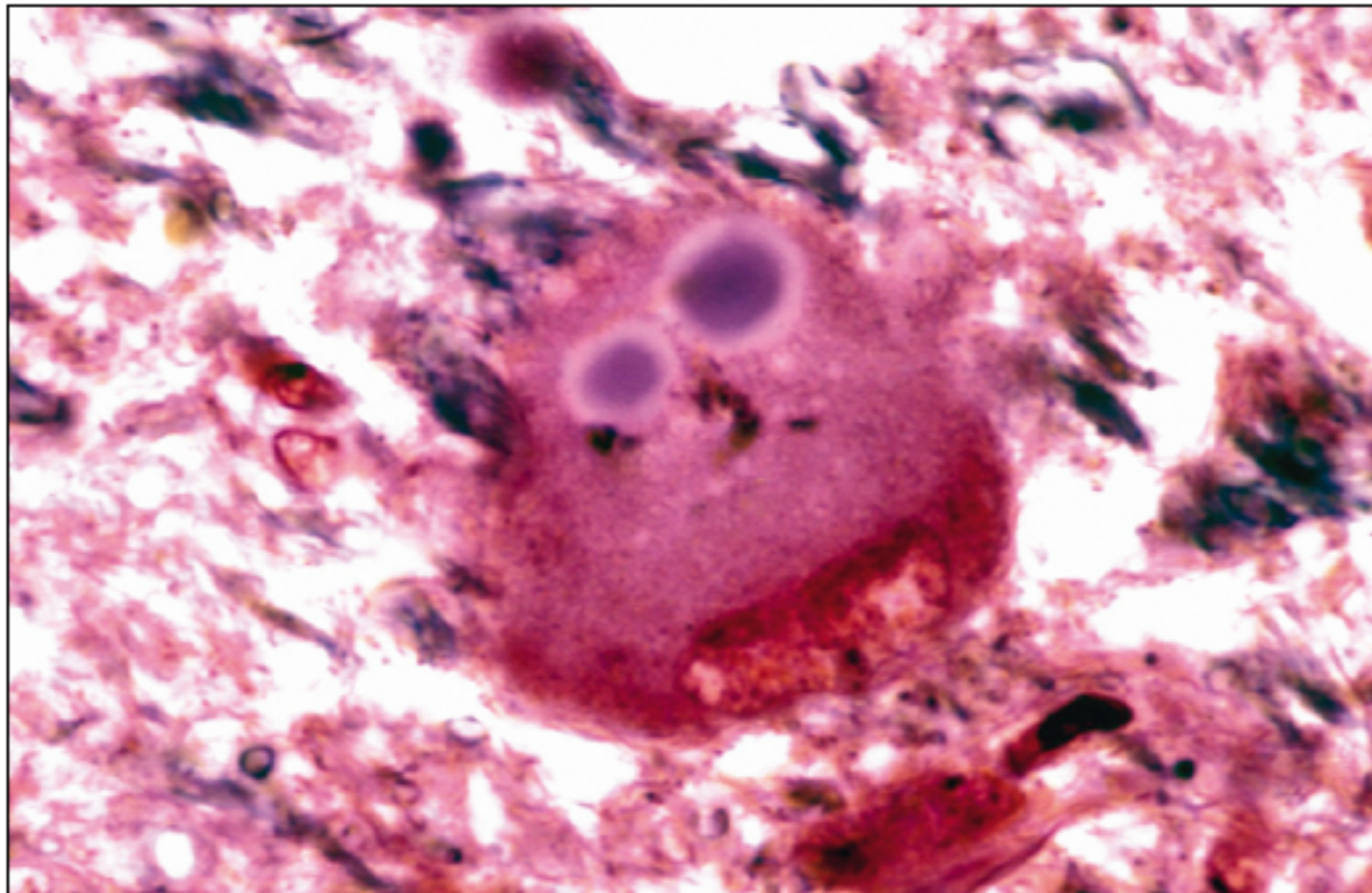
Substantia nigra



Diminished substantia
nigra as seen in
Parkinson's disease



ADAM.

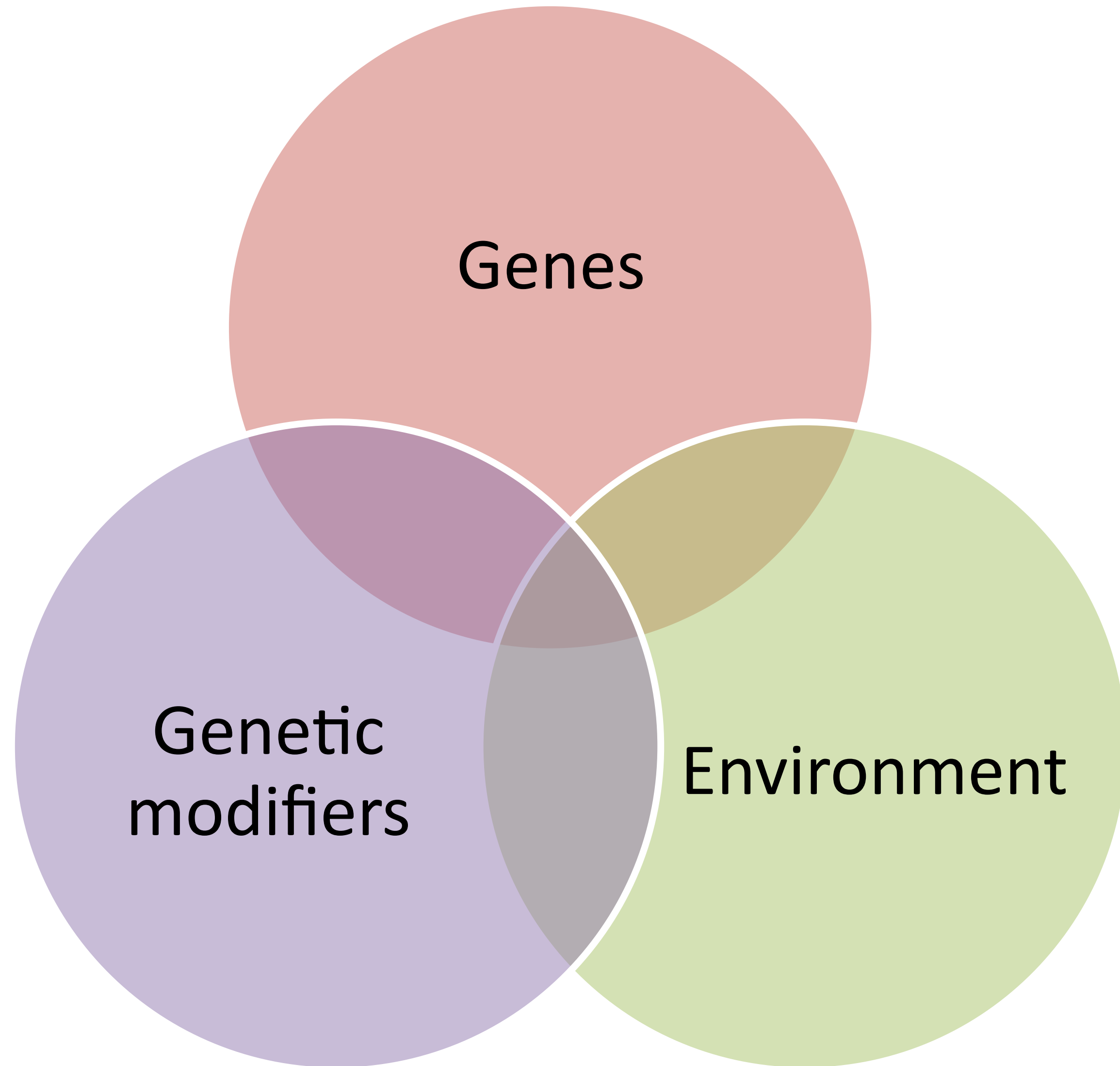


Science Photo Library

Parkinson's disease: light micrograph of section through neuron containing two Lewy bodies



What causes Parkinson's Disease?



Parkinson's Disease

- 5-10% of PD patients have a family history
- 3%* of all PD cases have mutations in known PD genes

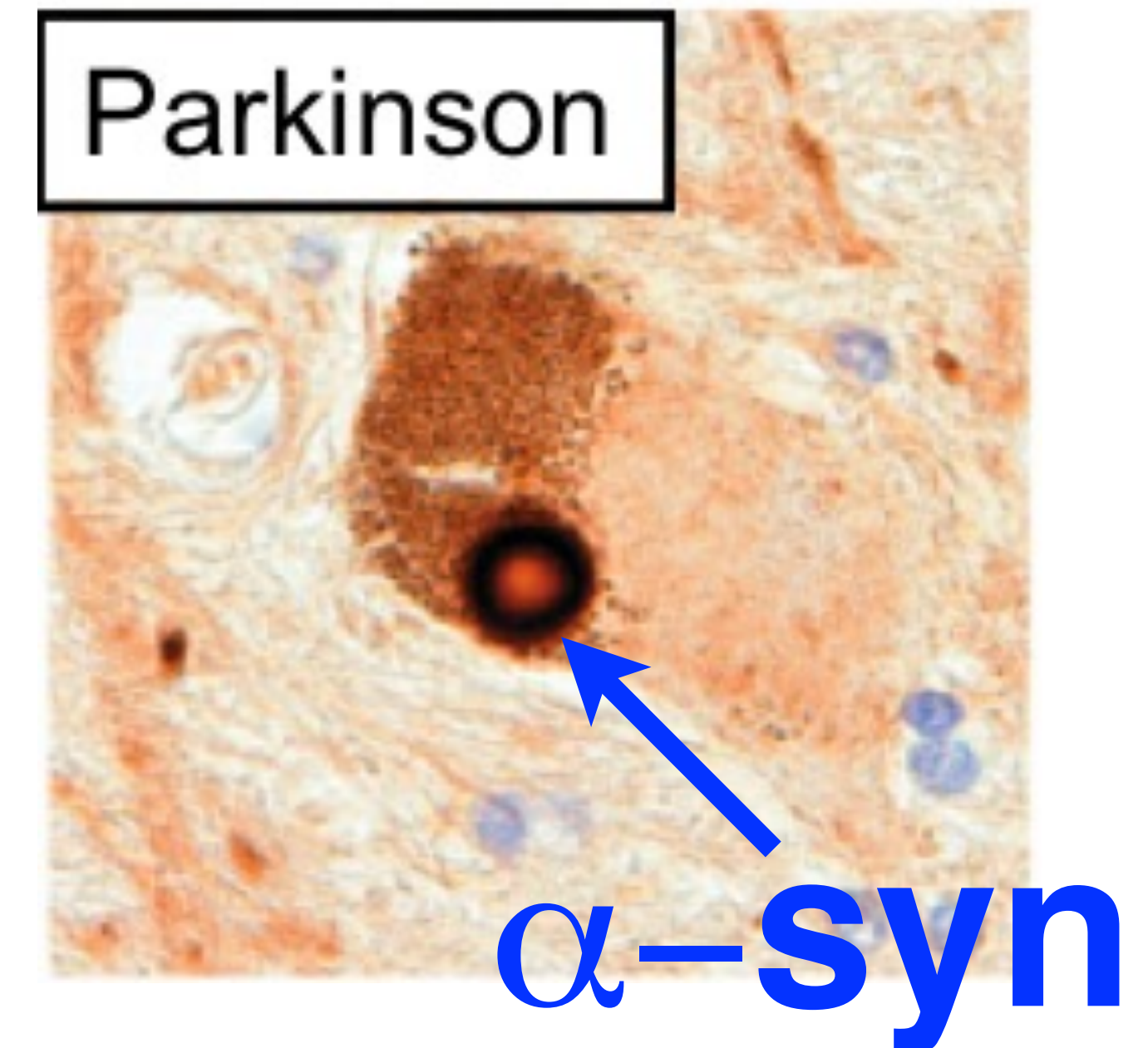
*Some papers suggest 5-10% of PD patients have a gene mutation

Monogenic parkinsonism

Locus	Chromosomal Location	Protein	Function	Inheritance
<i>PARK1</i>	4q21	α -Synuclein	Unknown	dominant
<i>PARK2</i>	6q25.2-q27	Parkin	E3 Ubiquitin Ligase	recessive
<i>PARK3</i>	2p13	Unknown		dominant
<i>PARK4</i>	4p15*			
<i>PARK5</i>	4p14	UCH-L1	Ubiquitin C-terminal hydrolase	dominant
<i>PARK6</i>	1p36	PINK1	Contains serine/threonine kinase domain (localized to mitochondria)	recessive
<i>PARK7</i>	1p36	DJ-1	Similar to Hsp31; oxidative stress sensor or antioxidant	recessive
<i>PARK8</i>	12p11.2-q13.1	LRRK2	Contains kinase (plus other domains)	dominant
<i>PARK9</i>	1p36	ATP13A2	Transmembrane Cationic ATPase	recessive

α -synuclein (α -syn)

- First gene associated with familial parkinsonism (Polymeropoulos 1997)
 - Autosomal dominant
 - Rare cause of familial parkinsonism: only ~15 families identified
 - Not found in sporadic PD
 - Component of Lewy bodies and Lewy neurites
- 3 point mutations: A53T, A30P, E46K
 - Increases aggregation [Conway & Lansbury 1998]
- Duplications
 - Resembles idiopathic PD
 - Penetrance only 33% in one family
- Triplications (Singleton 2003)
 - Early onset, rapidly progressive parkinsonism with dementia, autonomic dysfunction (Fuchs 2007)



Monogenic parkinsonism

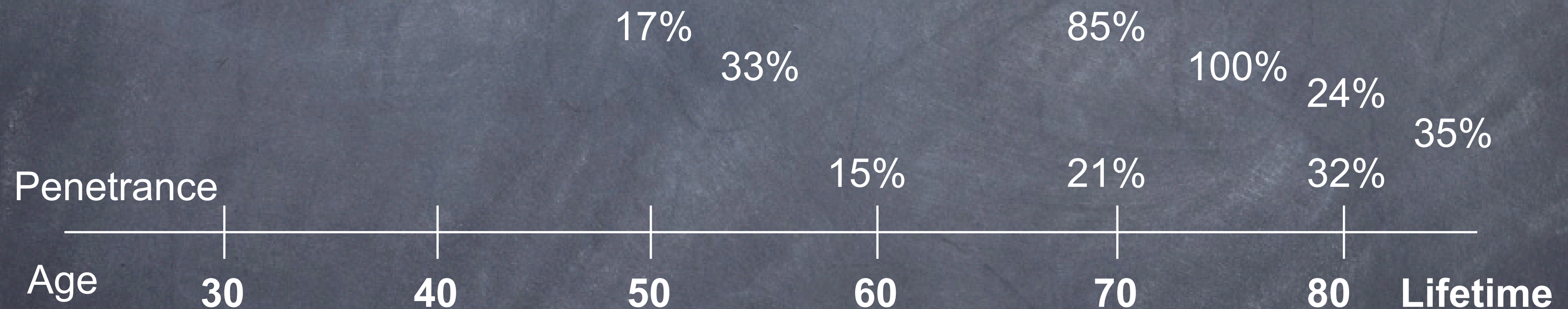
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LRRK2 (PARK8)

- Loci first mapped in a large Japanese family to Chr 12
- Most common cause of genetic parkinsonism
 - Zimprich 2004, Paisan-Ruiz 2004
 - 5-15% of families with AD inheritance carry LRRK2 mutations
- 6 recurrent pathogenic mutations
 - R1441G, R1141C, N1437H, Y1699C, G2019S, I2020T
 - G2019S most prevalent
 - Accounts for ~7% of familial PD and 1-2% of sporadic pts of European ancestry
- Function:
 - Protein kinase
 - Associated with mitochondria membrane
 - Mutations alter phosphorylation activity
- Phenotype: “classic PD”

Penetrance of LRRK2 G2019S mutation

Incomplete and age dependent:



Kachergus Am J Hum Gen 2005

Lesage Ann Neurol 2005

Clark Neurology 2006

Ozelius NEJM 2006

Goldwurm Neurology 2007

Monogenic parkinsonism

Locus	Chromosomal Location	Protein	Function	Inheritance
<i>PARK1</i>	4q21	α -Synuclein	Unknown	dominant
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<i>PARK9</i>	1p36	ATP13A2	Transmembrane Cationic ATPase	recessive

Exome sequencing identified two new PD genes

- VPS35
 - Austrian kindred with 16 affected individuals
 - 7 affected members still alive had missense mutation c.1858G>A (Zimprich et al. 2011)
 - Seven additional families with autosomal dominant mode also had same mutation.
 - Incomplete penetrance
 - Late onset L-dopa responsive “classic” PD
 - May be as common as SNCA
- EIF4G1
 - First identified in French kindred (Chartier-Harlin 2011)
 - Identified later in other families in U.S., Canada, and Ireland, but may have founder effect

Genetics of sporadic PD

Web-Based Genome-Wide Association Study Identifies Two Novel Loci and a Substantial Genetic Component for Parkinson's Disease

Chuong B. Do^{1*}, Joyce Y. Tung¹, Elizabeth Dorfman¹, Amy K. Kiefer¹, Emily M. Drabant¹, Uta Francke¹, Joanna L. Mountain¹, Samuel M. Goldman², Caroline M. Tanner², J. William Langston², Anne Wojcicki¹, Nicholas Eriksson^{1*}

¹ 23andMe, Mountain View, California, United States of America, ² Parkinson's Institute, Sunnyvale, California, United States of America

OPEN ACCESS Freely available online

PLOS GENETICS

Comprehensive Research Synopsis and Systematic Meta-Analyses in Parkinson's Disease Genetics: The PDGene Database

Christina M. Lill^{1,2,3,4}, Johannes T. Roehr^{1,5}, Matthew B. McQueen⁶, Fotini K. Kavvoura^{7,8,9}, Sachin Bagade², Brit-Maren M. Schjeide¹, Leif M. Schjeide¹, Esther Meissner¹, Ute Zauft¹, Nicole C. Allen², Tian Liu^{1,10}, Marcel Schilling^{1,5}, Kari J. Anderson¹¹, Gary Beecham¹², Daniela Berg^{13,14}, Joanna M. Biernacka¹¹, Alexis Brice^{15,16,17,18}, Anita L. DeStefano^{19,20}, Chuong B. Do²¹, Nicholas Eriksson²¹, Stewart A. Factor²², Matthew J. Farrer²³, Tatiana Foroud²⁴, Thomas Gasser^{13,14}, Taye Hamza²⁵, John A. Hardy²⁶, Peter Heutink²⁷, Erin M. Hill-Burns²⁵, Christine Klein²⁸, Jeanne C. Latourelle¹⁹, Demetrius M. Maraganore²⁹, Eden R. Martin¹², Maria Martinez^{30,31}, Richard H. Myers¹⁹, Michael A. Nalls³², Nathan Pankratz²⁴, Haydeh Payami²⁵, Wataru Satake³³, William K. Scott¹², Manu Sharma^{13,14}, Andrew B. Singleton³², Kari Stefansson³⁴, Tatsushi Toda³³, Joyce Y. Tung²¹, Jeffery Vance¹², Nick W. Wood^{35,36}

Cyrus P. Zabetian³⁷, The International Parkinson's Disease Genetics Consortium¹, Tanzi², Muir

Abstract

Although the causes of Parkinson's disease (PD) are thought to be primarily environmental, recent studies suggest that a number of genes influence susceptibility. Using targeted case recruitment and online survey instruments, we conducted the largest case-control genome-wide association study (GWAS) of PD based on a single collection of individuals to date (3,426 cases and 29,624 controls). We discovered two novel, genome-wide significant associations with PD—rs6812193 near *SCARB2* ($p = 7.6 \times 10^{-10}$, OR = 0.84) and rs11868035 near *SREBF1/RAI1* ($p = 5.6 \times 10^{-8}$, OR = 0.85)—both replicated in an independent cohort. We also replicated 20 previously discovered genetic associations (including *LRRK2*, *GBA*, *SNCA*, *MAPT*, *GAK*, and the *HLA* region), providing support for our novel study design. Relying on a recently proposed method based on genome-wide sharing estimates between distantly related individuals, we estimated the heritability of PD to be at least 0.27. Finally, using sparse regression techniques, we constructed predictive models that account for 6%–7% of the total variance in liability and that suggest the presence of true associations just beyond genome-wide significance, as confirmed through both internal and external cross-validation. These results indicate a substantial, but by no means total, contribution of genetics underlying susceptibility to both early-onset and late-onset PD, suggesting that, despite the novel associations discovered here and elsewhere, the majority of the genetic component for Parkinson's disease remains to be discovered.

Abstract

More than 800 published genetic association studies have implicated dozens of potential risk loci in Parkinson's disease (PD). To facilitate the interpretation of these findings, we have created a dedicated online resource, PDGene, that comprehensively collects and meta-analyzes all published studies in the field. A systematic literature screen of ~27,000 articles yielded 828 eligible articles from which relevant data were extracted. In addition, individual-level data from three publicly available genome-wide association studies (GWAS) were obtained and subjected to genotype imputation and analysis. Overall, we performed meta-analyses on more than seven million polymorphisms originating either from GWAS datasets and/or from smaller scale PD association studies. Meta-analyses on 147 SNPs were supplemented by unpublished GWAS data from up to 16,452 PD cases and 48,810 controls. Eleven loci showed genome-wide significant ($P < 5 \times 10^{-8}$) association with disease risk: *BST1*, *CCDC62/HIP1R*, *DGKQ/GAK*, *GBA*, *LRRK2*, *MAPT*, *MCCC1/LAMP3*, *PARK16*, *SNCA*, *STK39*, and *SYT11/RAB25*. In addition, we identified novel evidence for genome-wide significant association with a polymorphism in *ITGA8* (rs7077361, OR 0.88, $P = 1.3 \times 10^{-8}$). All meta-analysis results are freely available on a dedicated online database (www.pdgene.org), which is cross-linked with a customized track on the UCSC Genome Browser. Our study provides an exhaustive and up-to-date summary of the status of PD genetics research that can be readily scaled to include the results of future large-scale genetics projects, including next-generation sequencing studies.

Susceptibility Loci for Parkinson's Disease

Gene	Protein	Polymorphism	OR (95% CI)
<i>ACMSD</i>	Unknown	rs6710823	1.40 (1.20-1.63)
<i>BST1</i>	Bone marrow stromal cell antigen 1	rs11724635	1.16(1.10-1.22)
<i>CCDC62</i>	Unknown	rs12817488	1.17 (1.09-1.25)
<i>FAM475</i>	Unknown	rs6812193	1.12 (1.08-1.17)
<i>GAK/DGKQ</i>	Unknown	rs1564282	1.29 (1.20-1.38)
<i>GBA</i>	Glucocerebrosidase	N370S	3.51 (2.55-4.83)
<i>GPNMB</i>	Glycoprotein NMB	rs156429	1.12 (1.08-1.16)
<i>GWA_8p22</i>	Unknown	rs591323	1.12 (1.08-1.17)
<i>LRRK2</i>	Leucine-rich repeat kinase 2	rs34637584	9.62 (6.43-14.37)
<i>MAPT</i>	Microtubule-associated protein tau	H1/H2	1.29 (1.25-1.33)
<i>MCCC1</i>	Unknown	rs11711441	1.18 (1.13-1.24)
<i>PARK16</i>	Unknown	rs11012	1.26 (1.18-1.34)
<i>SETD1A</i>	Unknown	rs4889603	1.14 (1.09-1.19)
<i>SNCA</i>	alpha-synuclein	rs356220	1.30 (1.26-1.35)
<i>SREBF1</i>	Unknown	rs11868035	1.18 (1.19-1.38)
<i>STK39</i>	Serine threonine kinase 39	rs2102808	1.28 (1.19-1.38)

GBA locus

- Mutations cause Gaucher's disease
 - Lysosomal storage disease
 - Glucocerebrosidase gene
 - Common disease in Ashkenazi Jews
 - Many phenotypes:
 - Early or juvenile onset: clinical heterogeneity from hepatosplenomegaly to neurological dysfunction

GBA and PD

- First noticed that relatives of Gaucher patients had PD more frequently than expected than chance
- GBA mutations occur more frequently in Jewish PD population compared to controls
 - 18% of PD patients carried GBA mutations vs 4% in age matched controls (Gan-Or 2008)
 - Another Israeli study: 33%
- GBA mutations can occur in non-Jewish PD populations
 - PD patients are 3.4 times more likely to carry the four screened GBA mutations (Clark et al 2007)
 - Toronto Western: 5.6% (Sato et al.)
 - Venezuela: 12% of EOPD (Eblan et al.)

GBA increases risk for PD

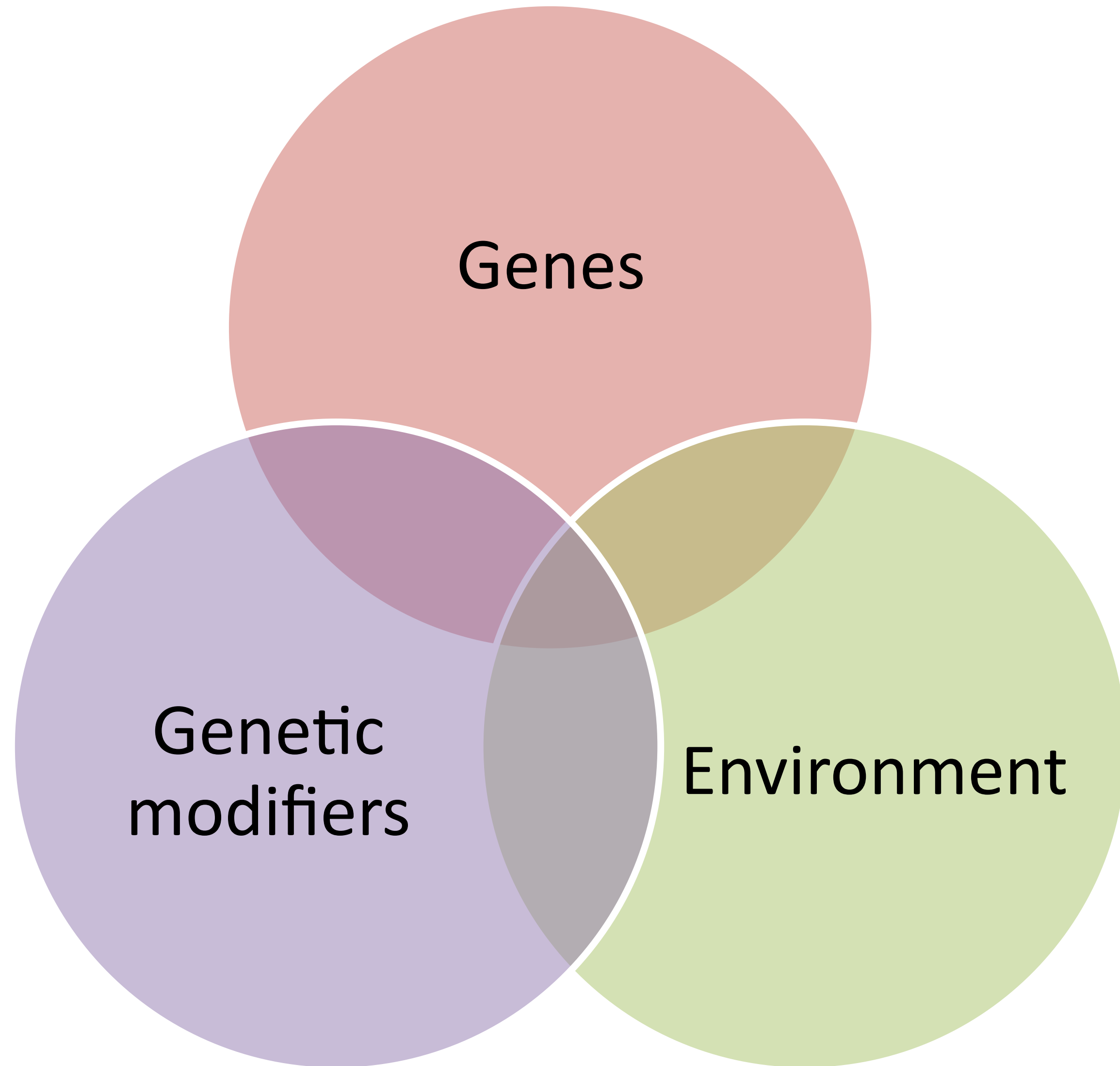
- Severe GBA mutations increased risk of PD by 13-fold compared to 2-fold risk from mild mutations
- 14% of LRRK2 G2019S mutation carriers had concurrent GBA mutations.

GBA story is incomplete

Jewish population has higher mutation frequency in LRRK2 G2019S *and* GBA

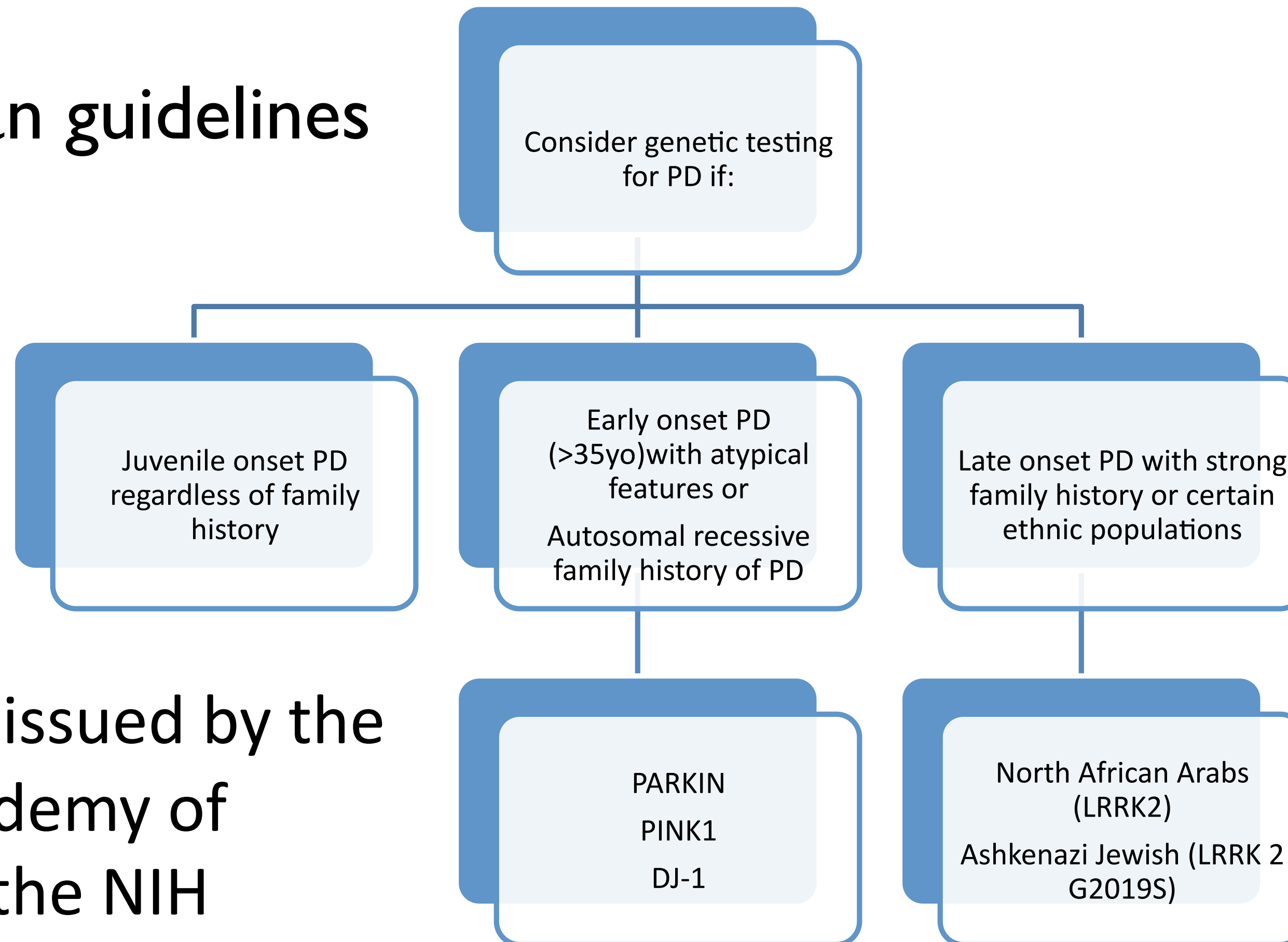
But, the frequency of PD in Ashkenazi Jewish population is *not* increased
Prevalence of PD comparable to worldwide
17% of parkinsonian patients in GBA families did NOT carry the GBA mutation (Lesage 2011)

What causes Parkinson's Disease?



When to perform genetic testing in *sporadic* PD

European guidelines



No guidelines issued by the American Academy of Neurology or the NIH

Insights into clinical utility of genetic testing in neurodegenerative disease

Insights into clinical utility of genetic testing in neurodegenerative disease

- Symptomatic versus Asymptomatic testing

Insights into clinical utility of genetic testing in neurodegenerative disease

- Symptomatic versus Asymptomatic testing
- How does this affect the person?

Insights into clinical utility of genetic testing in neurodegenerative disease

- Symptomatic versus Asymptomatic testing
- How does this affect the person?
- How does the person place himself in the context of disease?

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- How much sense would I have in my life if I were to develop the disease?

Insights into clinical utility of genetic testing in neurodegenerative disease

- Symptomatic versus Asymptomatic testing
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- How does the prospect of developing a disease affect a person's life?

Insights into clinical utility of genetic testing in neurodegenerative disease

- Symptomatic versus Asymptomatic testing
- How does this affect the person?
- How does the person place himself in the context of disease?
- How much sense would I have in my life if I were to develop the disease?
- How does the prospect of developing a disease affect a person's life?
 - Hobbies? Education? Profession? Relationships?

Insights into clinical utility of genetic testing in neurodegenerative disease

Paternalism versus Autonomy

My clinical experience with genetic testing in patients with PD

“*I will* have PD”

- Case 1: 57 year old woman with a family history of Parkinson's disease who is asymptomatic
 - She has a SNP associated with mildly increased risk for developing PD
 - She travels from Las Vegas every year for neurological examination by a movement disorders specialist to evaluate for signs of PD
- She has planned her life to account for developing PD:
 - Early retirement
 - Bought long term care insurance
 - Moved into a single story home

“But I can’t have PD because I don’t have the gene”

- Case 2: 69 year old retired lawyer with a 8 year history of parkinsonism on exam
 - He does not carry any SNPs associated with PD
 - Sequencing for LRRK2 mutation is negative
 - He refutes the diagnosis of PD because he does not have the gene and refuses to take medications to treat the symptoms
 - He is now in a wheelchair
 - Moved into a nursing home

Benefits of knowing genetic status

The New York Times

Google Co-Founder Has Genetic Code Linked to Parkinson's

By Miguel Heft

Published: September 18, 2008

MOUNTAIN VIEW, Calif. — [Sergey Brin](#), a Google co-founder, said Thursday that he has a gene mutation that increases his likelihood of contracting Parkinson's disease, a degenerative disorder of the central nervous system that can impair speech, movement and other functions.

Mr. Brin, who made the announcement on a blog, says he does not have the disease and that the exact implications of the discovery are not clear. Studies show that his likelihood of contracting Parkinson's disease in his lifetime may be 20 percent to 80 percent, Mr. Brin said.

LRRK2 G2019S



Benefits of knowing genetic status

“...I carry the G2019S mutation and when my mother checked her account, she saw she carries it too.

*The exact implications of this are not entirely clear. ...
Nonetheless it is clear that I have a markedly higher chance of developing Parkinson's in my lifetime than the average person. In fact, it is somewhere between 20% to 80% depending on the study and how you measure....*

This leaves me in a rather unique position. **I know early in my life something I am substantially predisposed to. I now have the opportunity to adjust my life to reduce those odds ...**

I feel fortunate to be in this position. Until the fountain of youth is discovered, all of us will have some conditions in our old age only we don't know what they will be. **I have a better guess than almost anyone else for what ills may be mine -- and I have decades to prepare for it.”** Sergey Brin

LRRK2 G2019S

The Google logo, featuring the word "Google" in its characteristic multi-colored font.

Arguments in favor of genetic testing

- Making informed life decisions
- Improved prognostication
- Assistance with family planning

Implications for physicians

- Are physicians prepared to address issues arising from genetic testing?
- Should genetic counseling be required for everyone prior to genetic testing or result disclosure?

Take Home Messages

1. Connection between **genetics** and **pathology**
2. Rare **mendelian** forms of disease may inform mechanisms of **sporadic** disease
3. Clinical utility of genetic testing for neurodegenerative disease risk alleles?
4. Implications for knowing genetic status