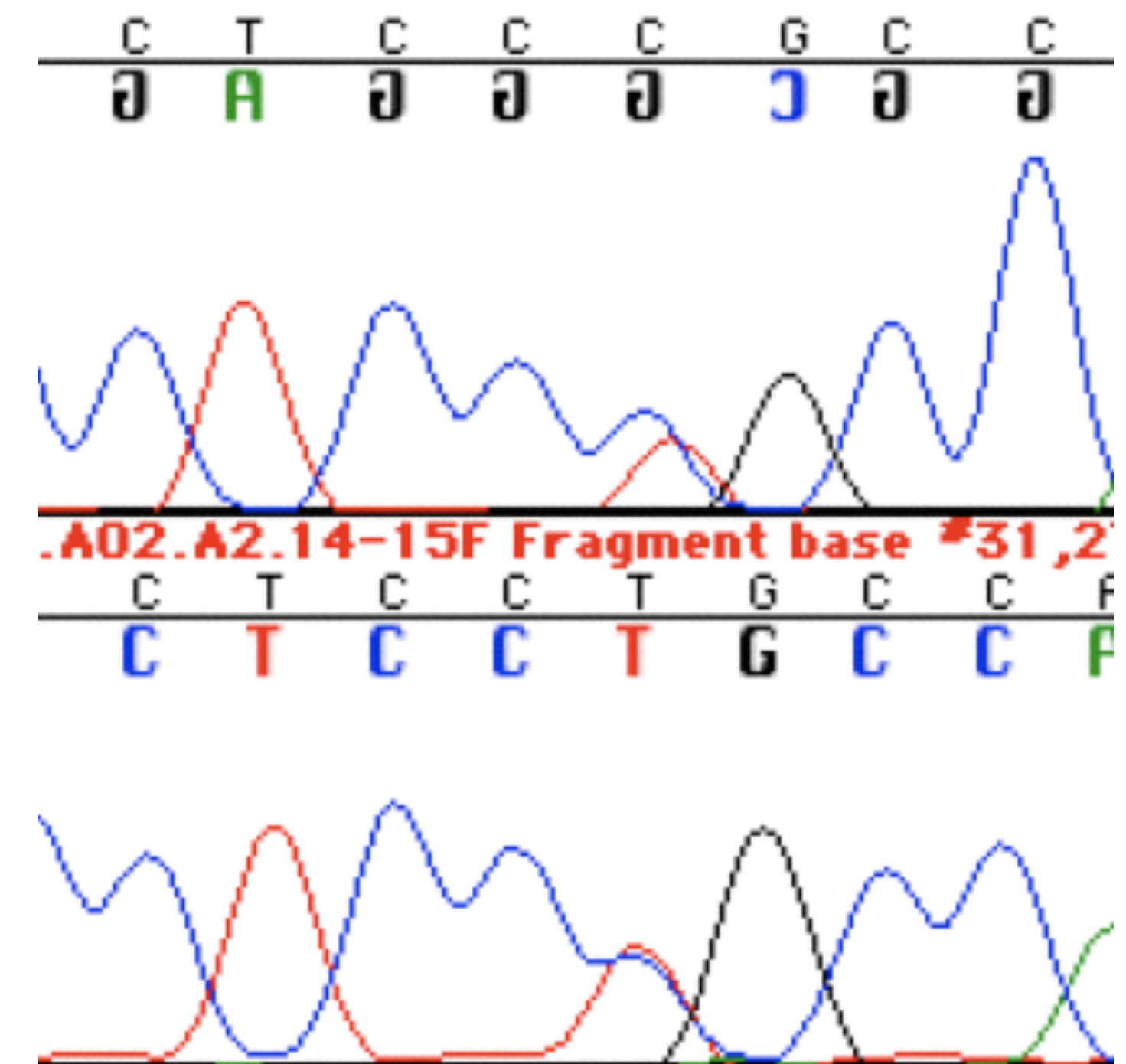
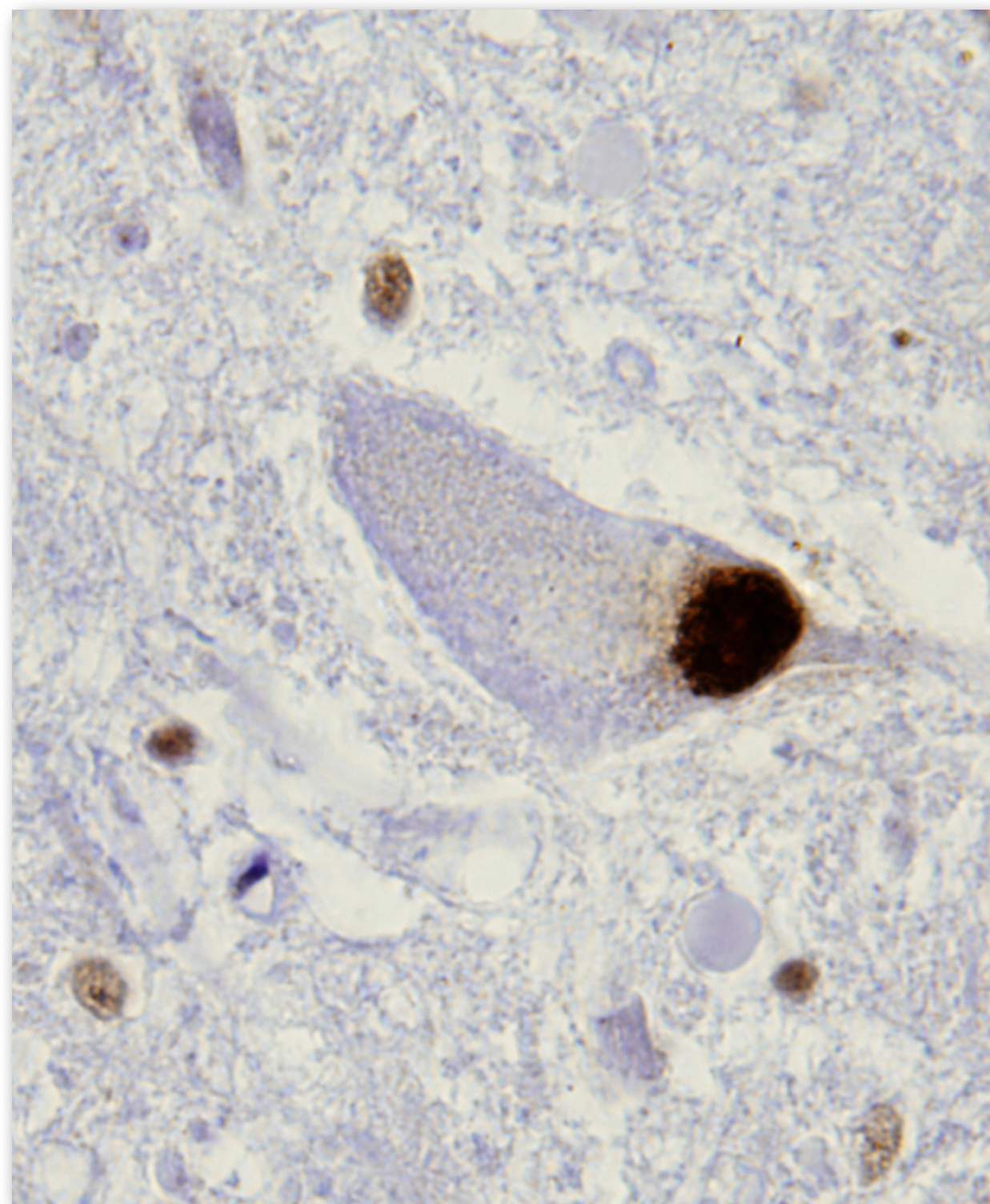


Genetics of human neurodegenerative disease

Aaron D. Gitler, Ph.D.

Rosalind Chuang, M.D.



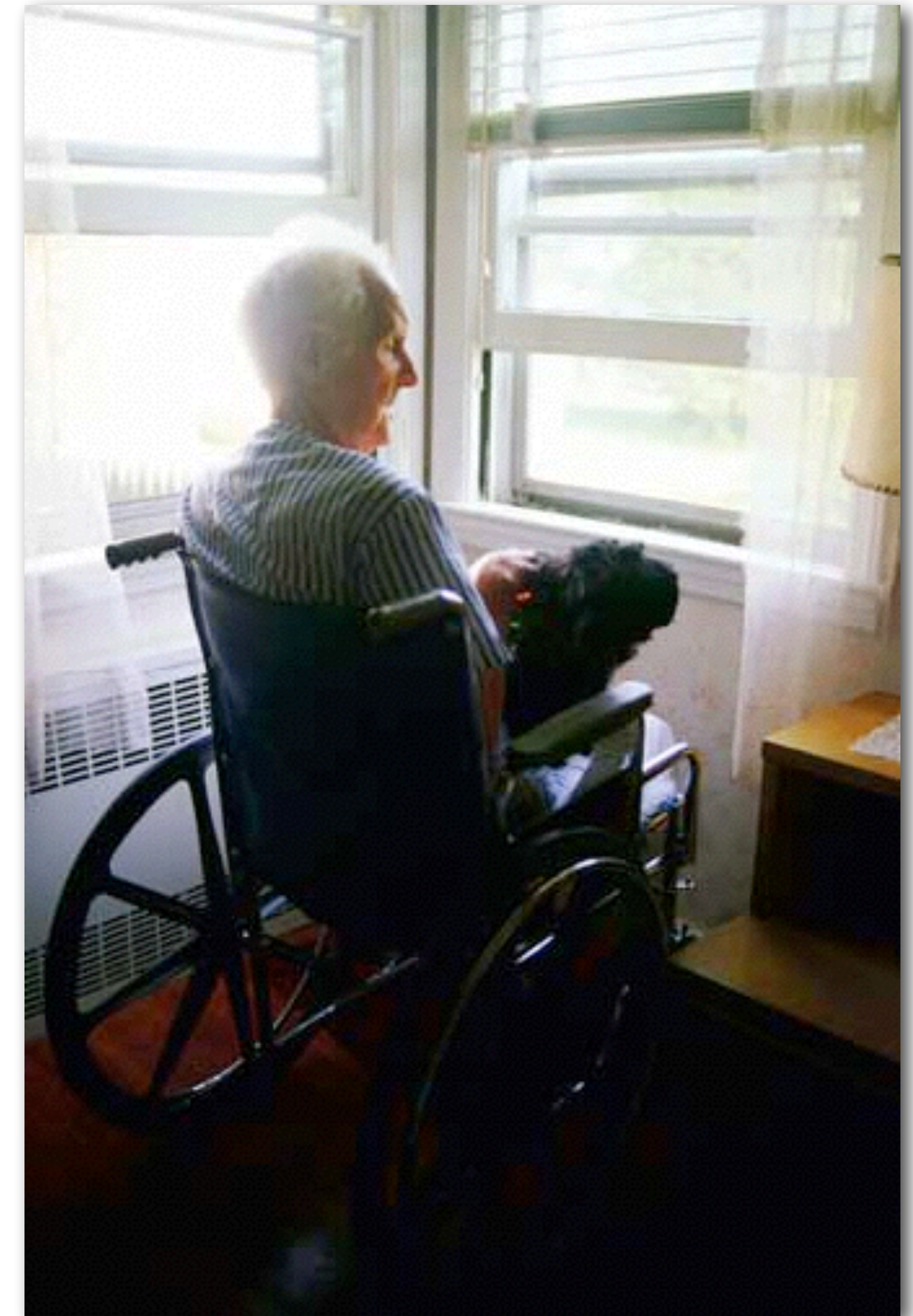
Today's Plan

1. Katherine Moser (Chuang)
2. Alzheimer's Disease (Gitler)
3. Frontotemporal Dementia (Gitler)
4. Amyotrophic lateral sclerosis (ALS)
(Gitler)
5. Parkinson's Disease (Chuang)

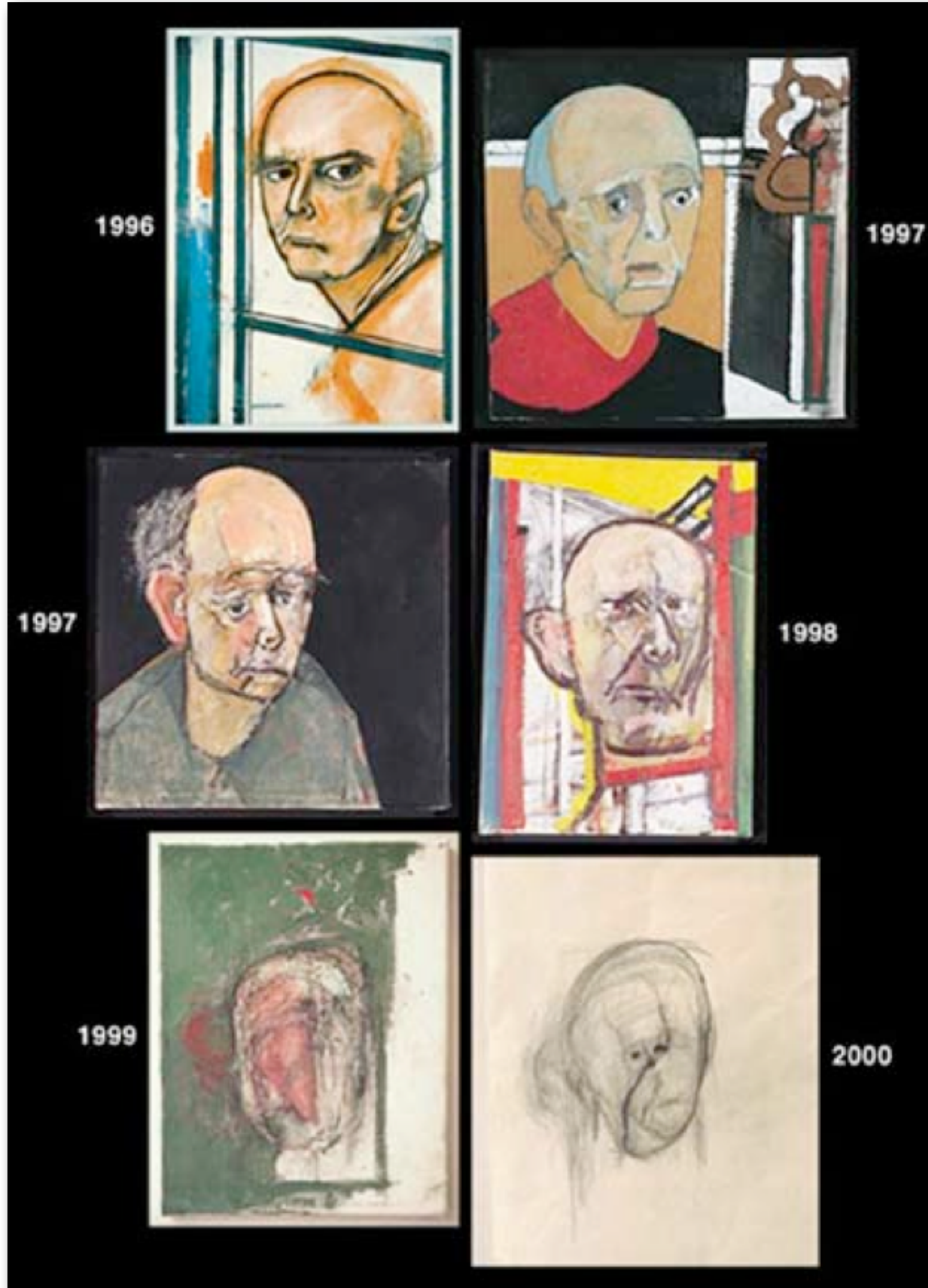
Neurodegenerative Diseases



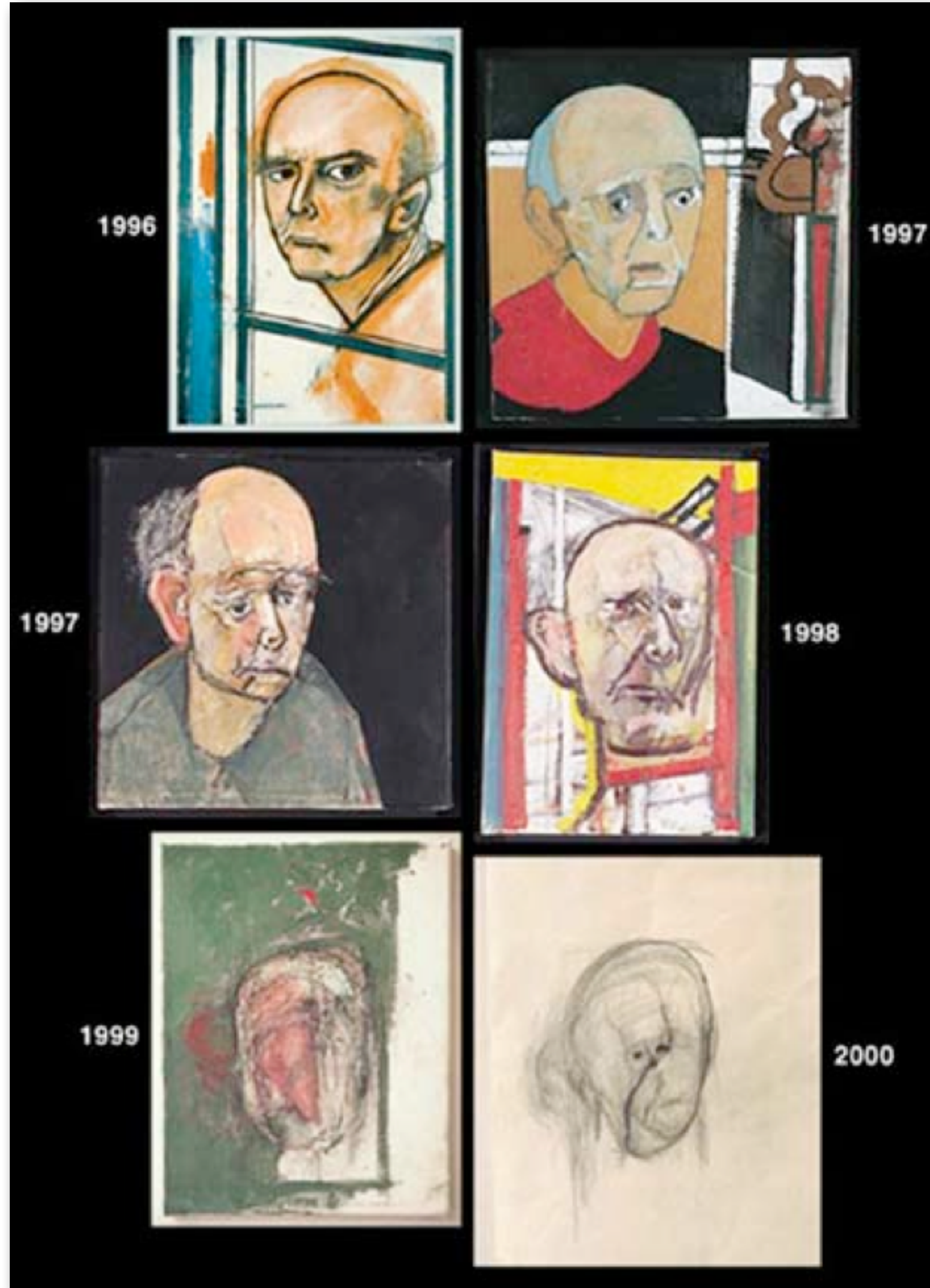
Alzheimer Disease
Parkinson Disease
Huntington Disease
Frontotemporal Dementia
Lou Gehrig's Disease (ALS)



Alzheimer's disease



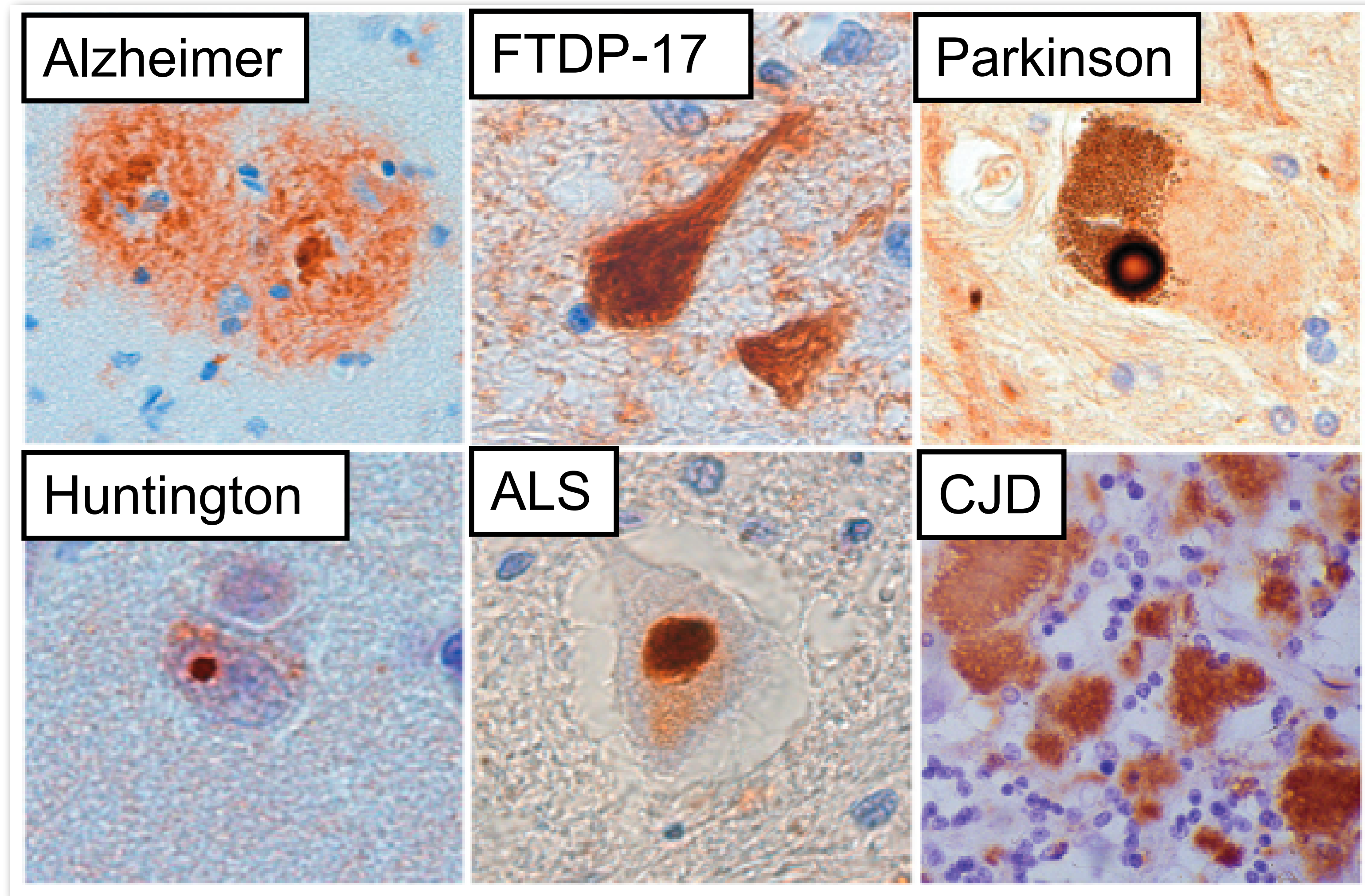
Alzheimer's disease



Parkinson's disease



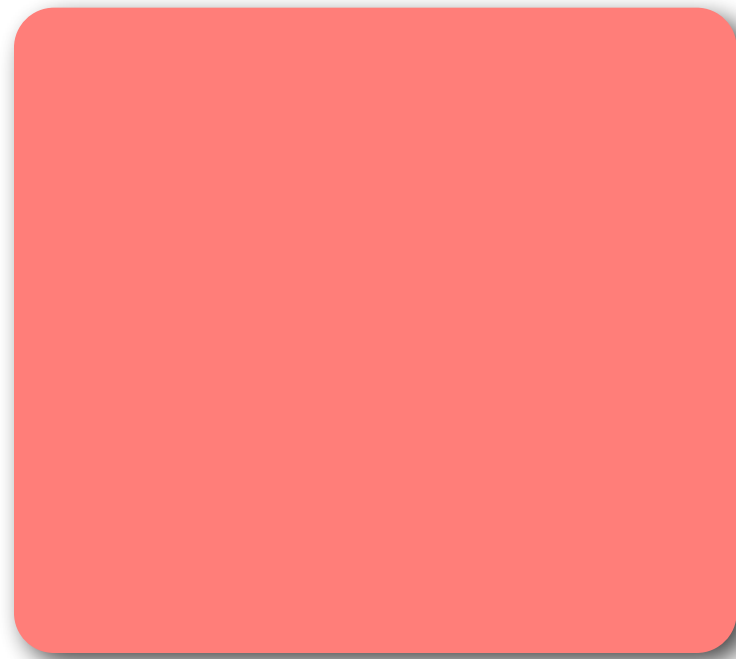
Protein Aggregates in Neurodegenerative Diseases



Protein Aggregates in Neurodegenerative Diseases

Protein Aggregates in Neurodegenerative Diseases

Normal Protein

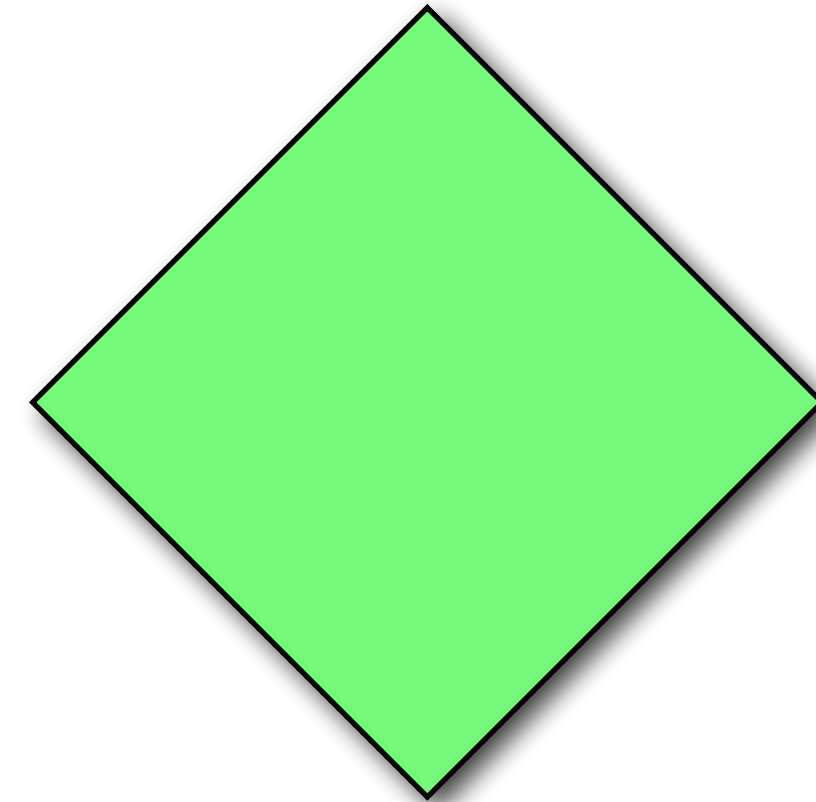


Protein Aggregates in Neurodegenerative Diseases

Normal Protein



Misfolded Protein

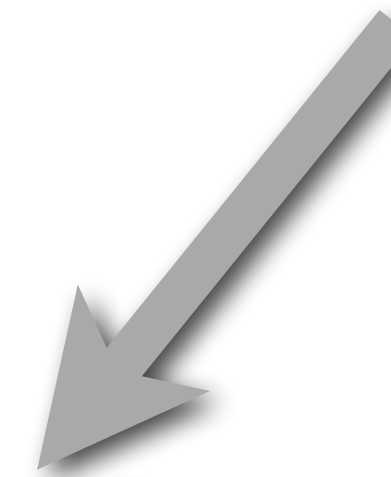
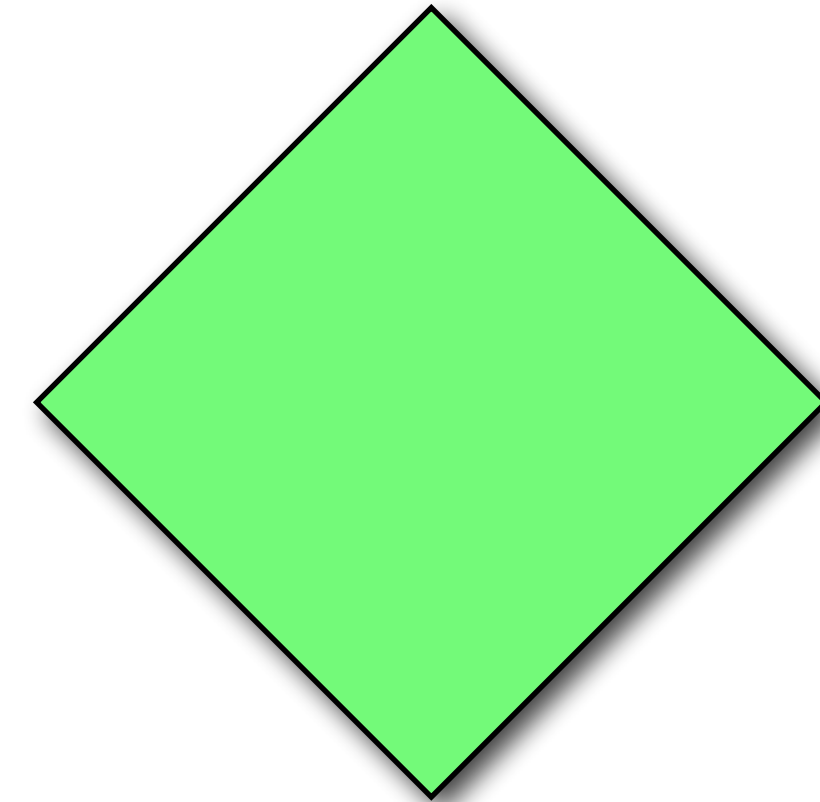


Protein Aggregates in Neurodegenerative Diseases

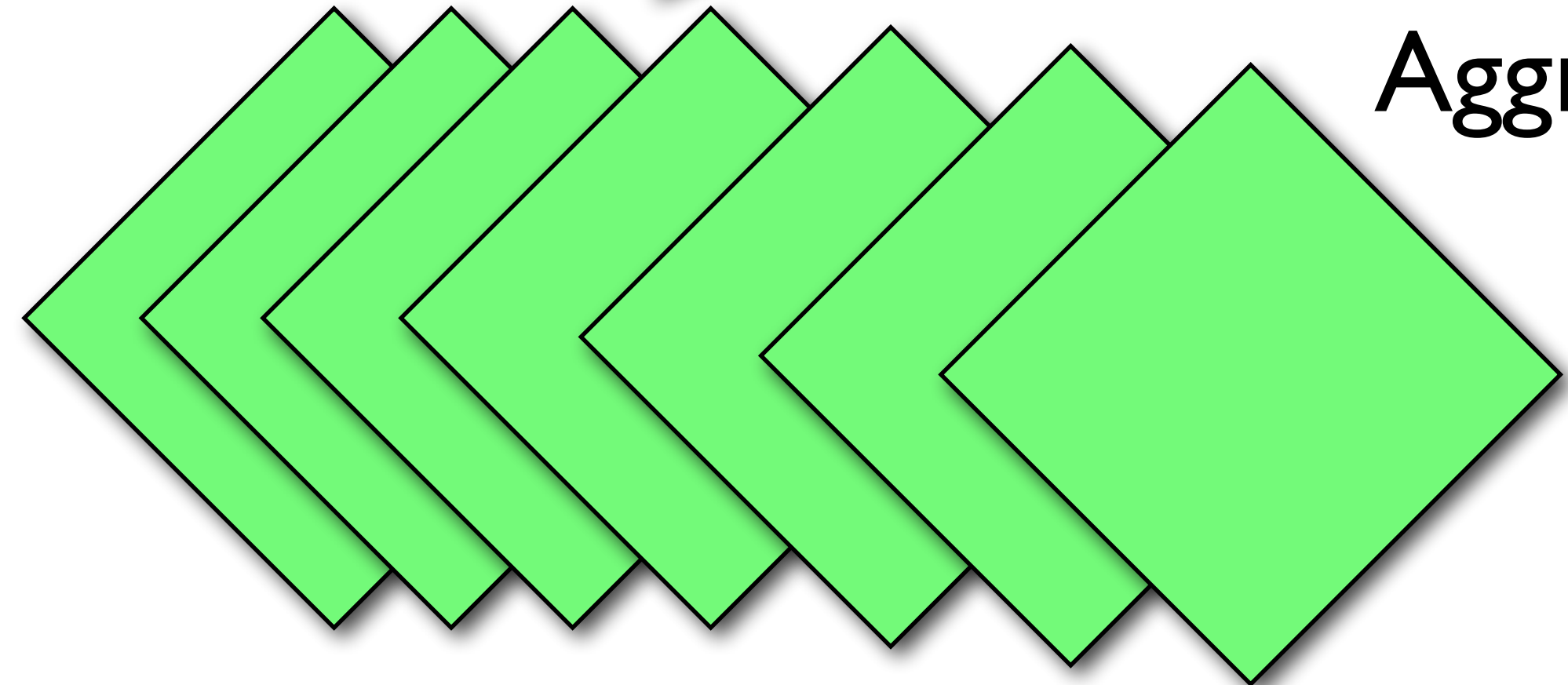
Normal Protein



Misfolded Protein



Protein
Aggregates

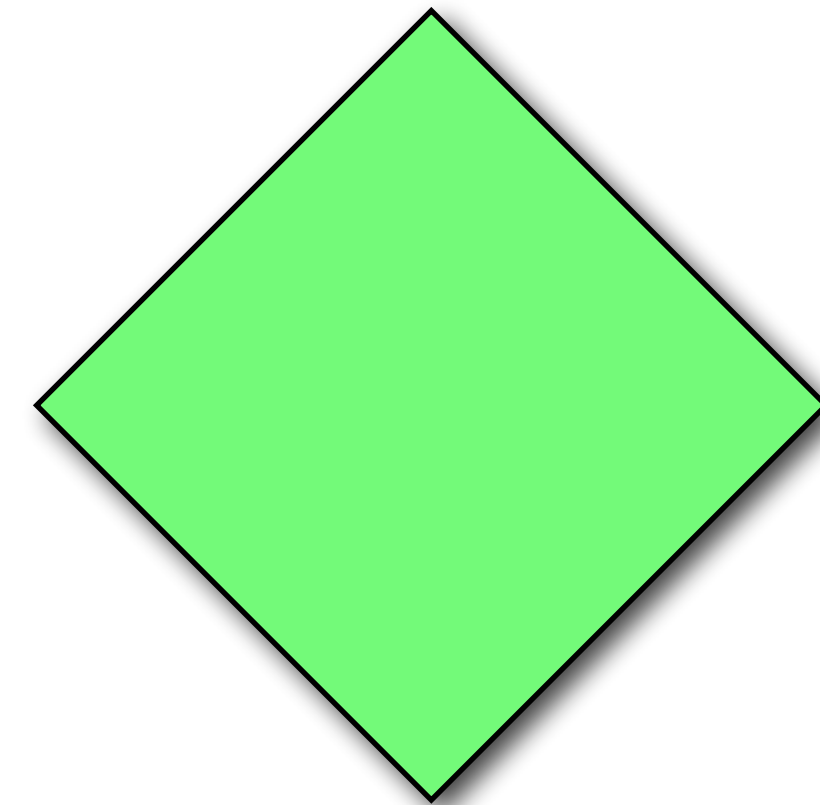


Protein Aggregates in Neurodegenerative Diseases

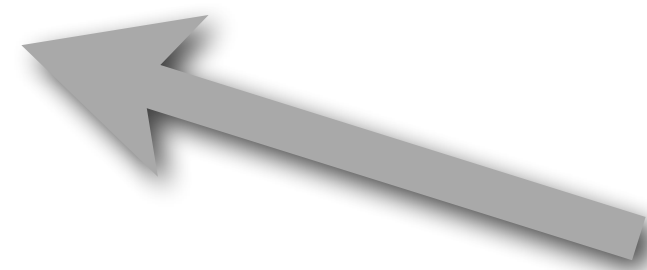
Normal Protein



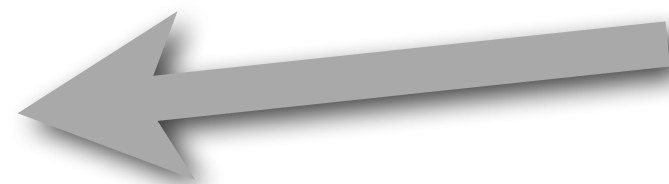
Misfolded Protein



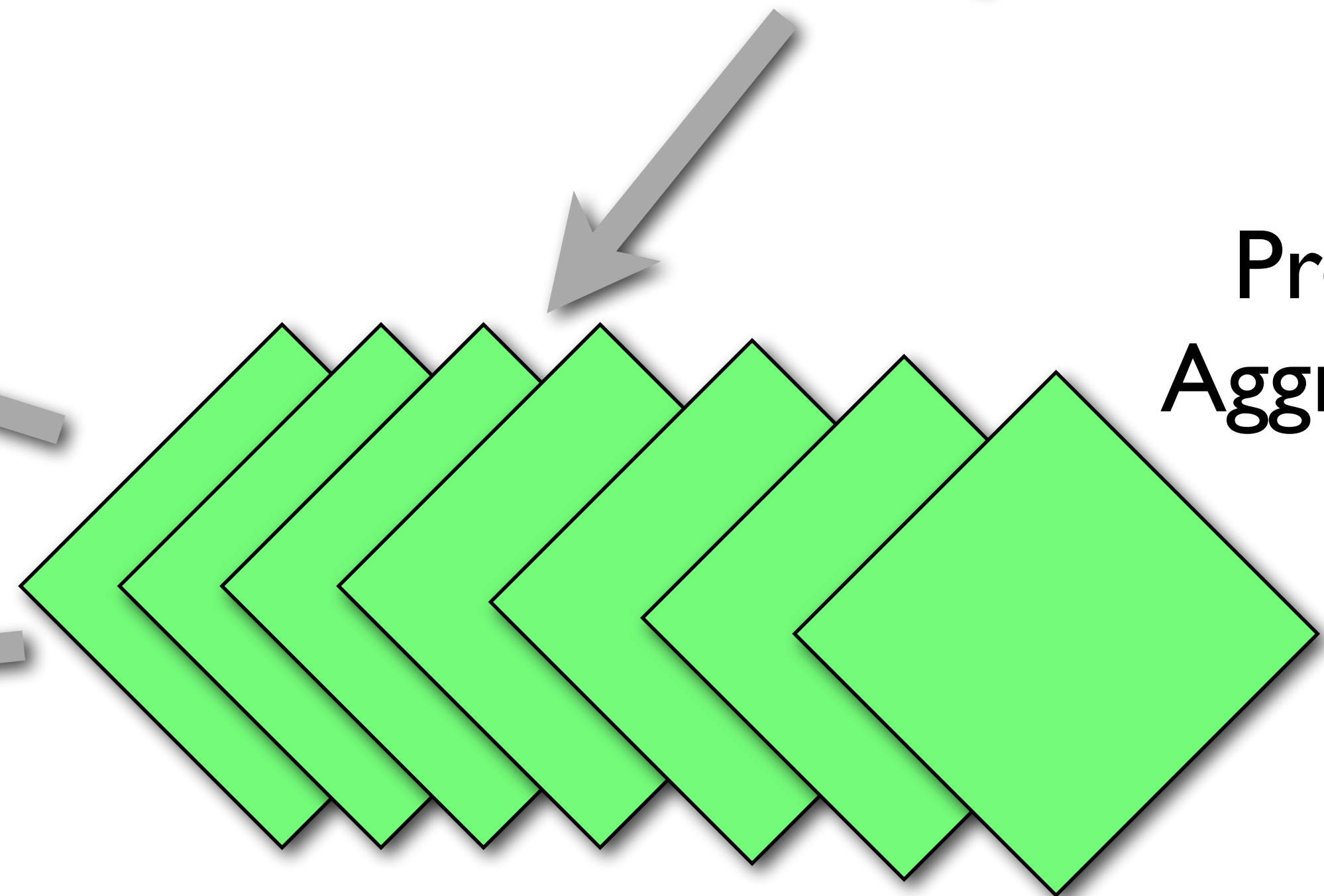
Loss of Protein's
Normal Function



Toxic Gain of
Function



Protein
Aggregates

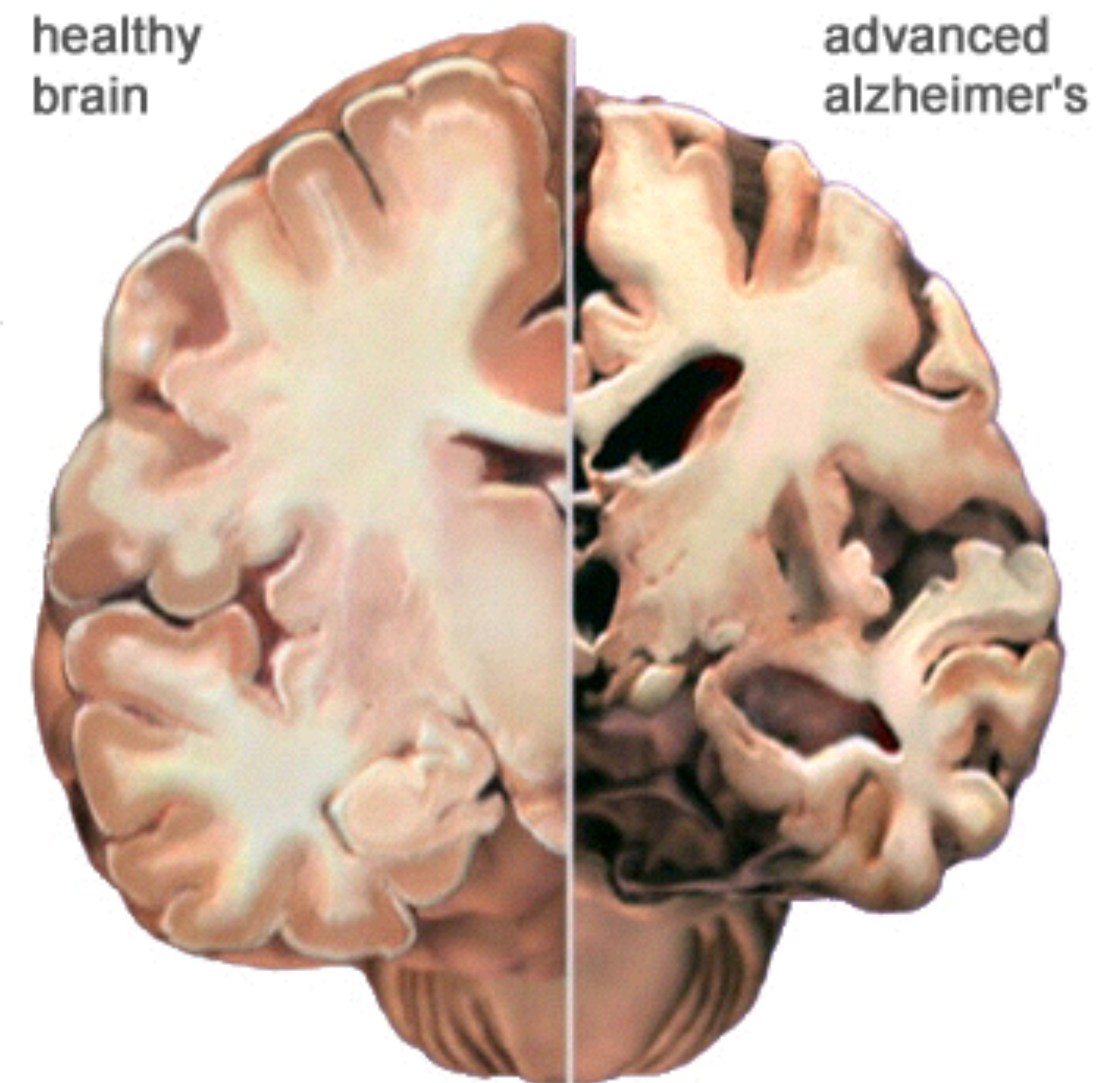


Today's Plan

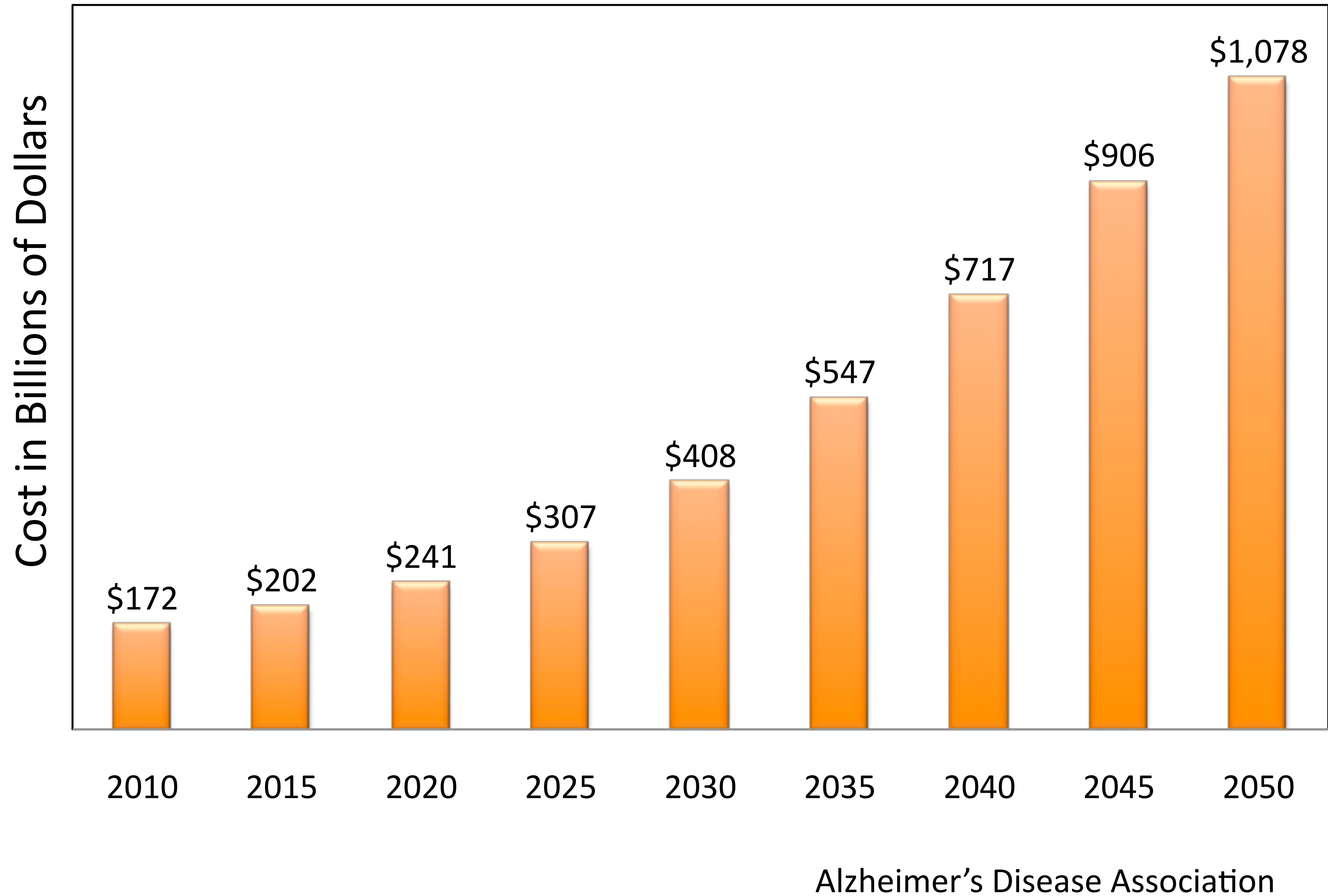
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2. Alzheimer's Disease (Gitler)
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4. Amyotrophic lateral sclerosis (ALS)
(Gitler)
5. Parkinson's Disease (Chuang)

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?

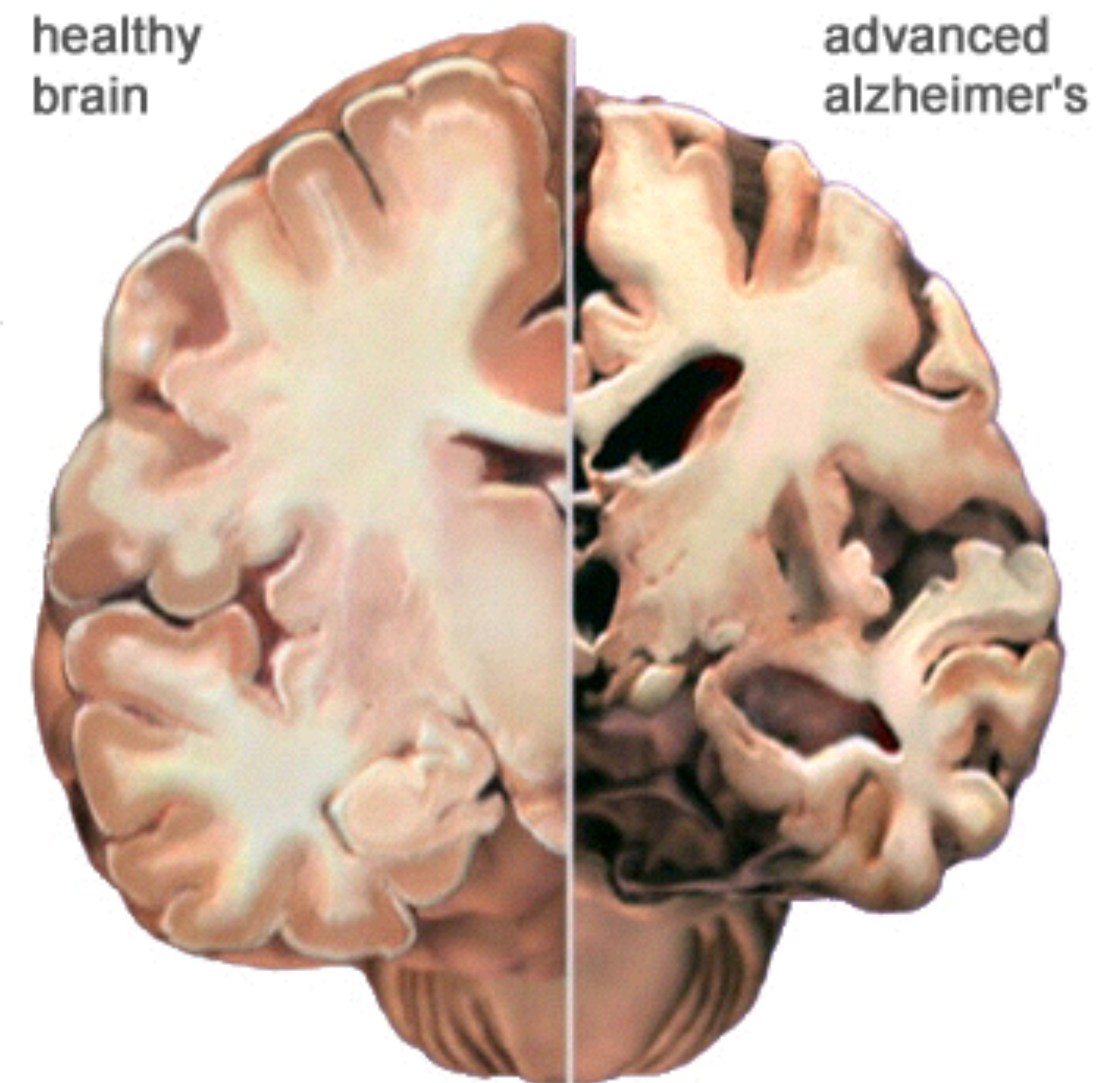


Exploding costs of Alzheimer's disease

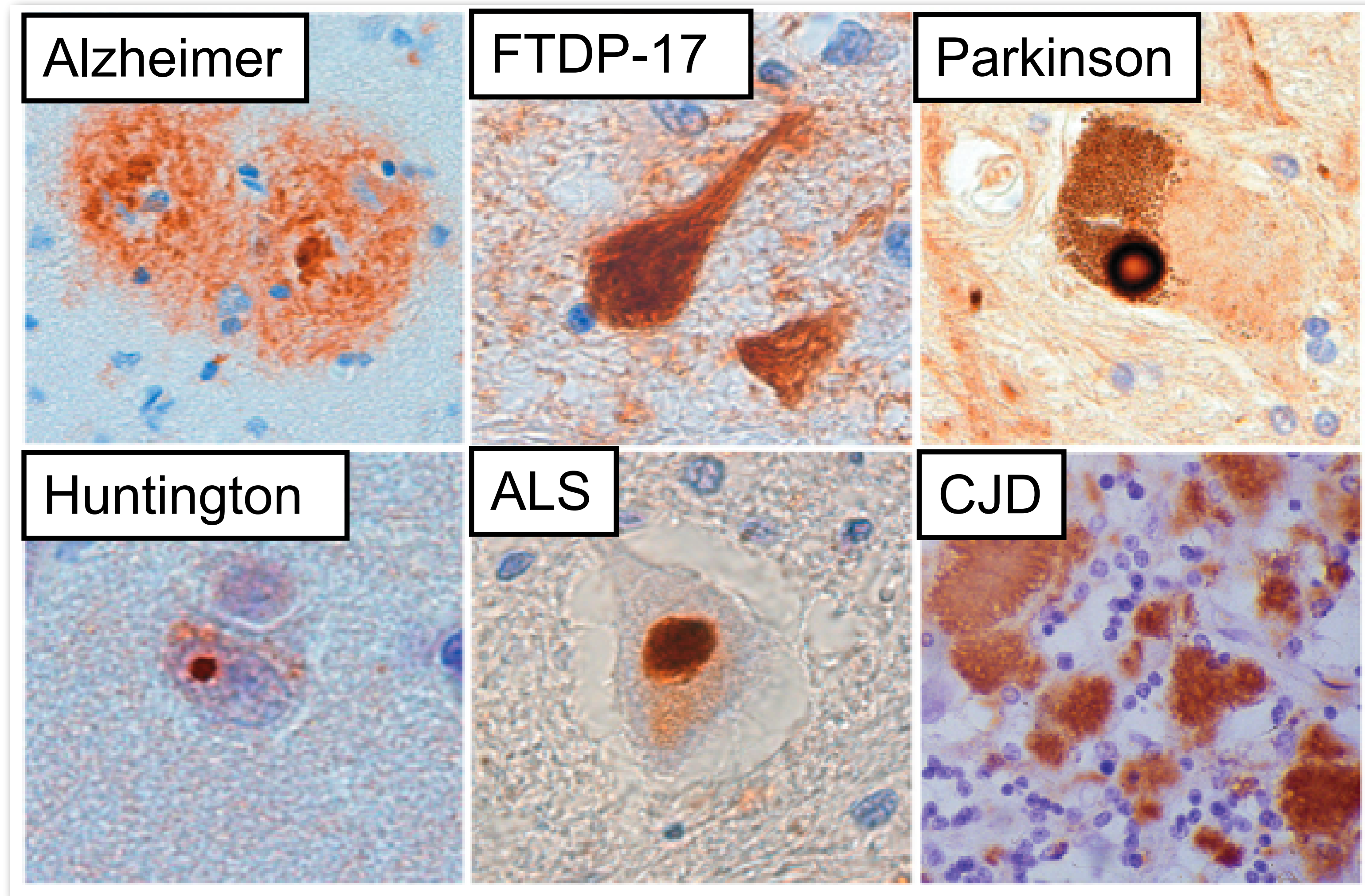


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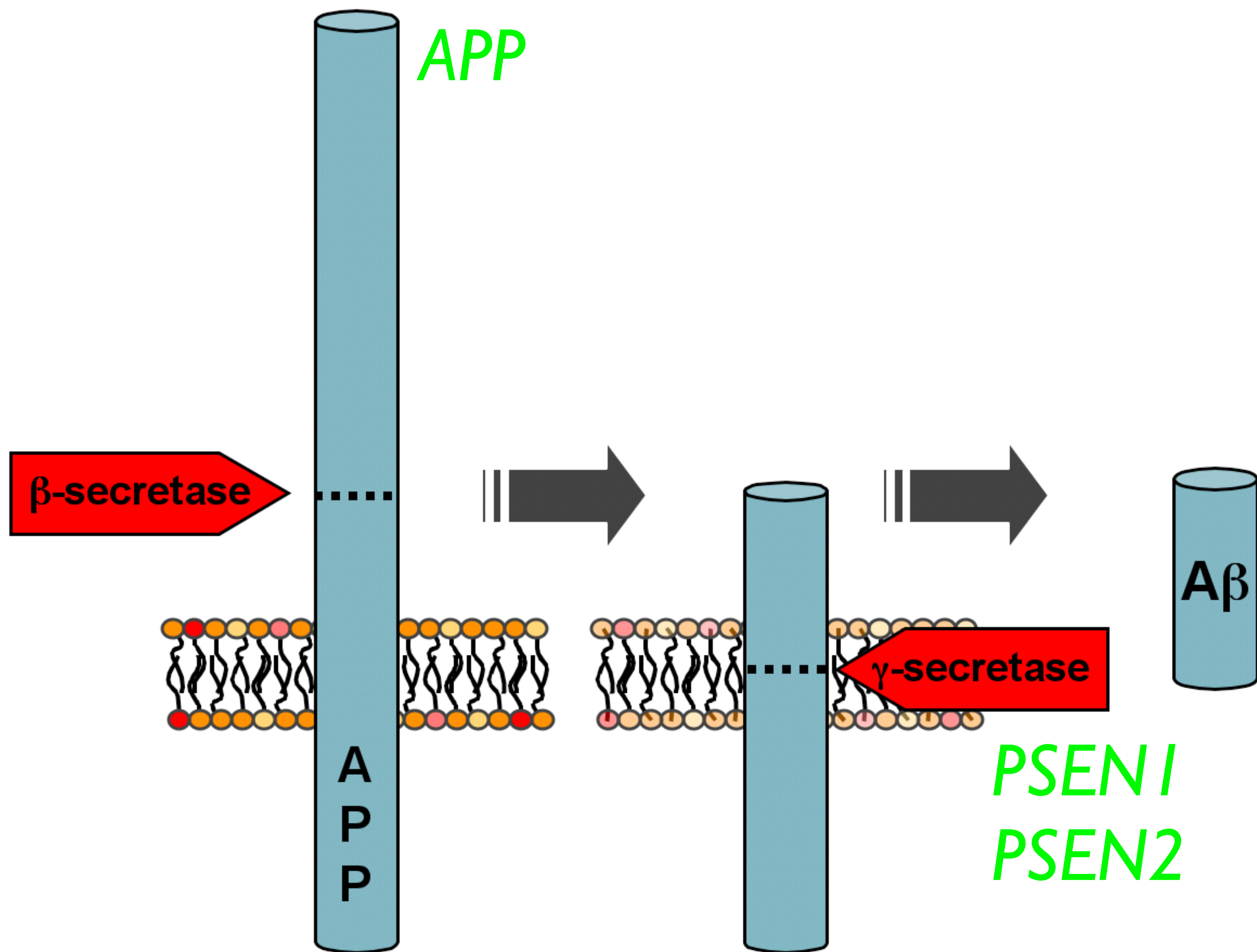


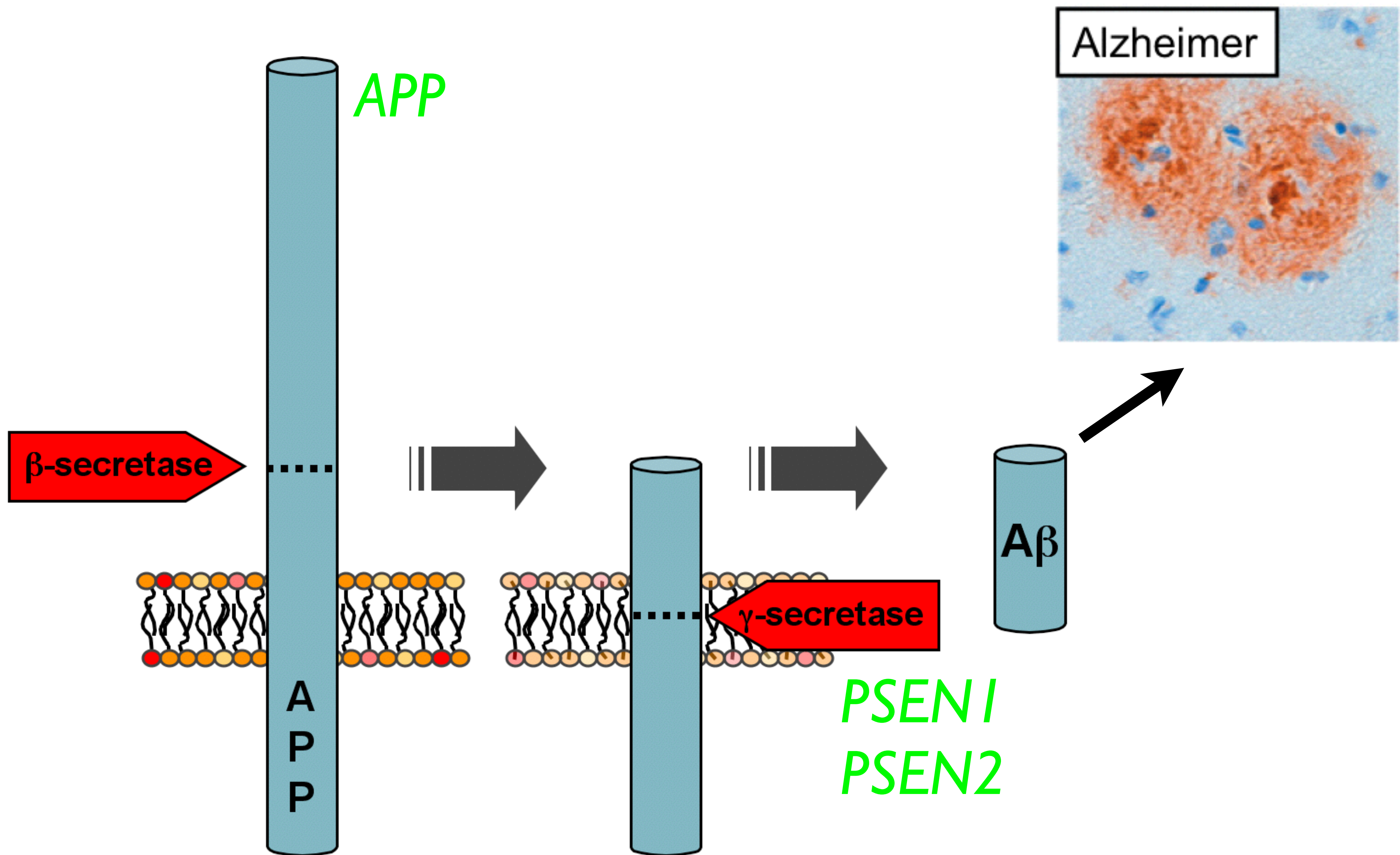
Protein Aggregates in Neurodegenerative Diseases



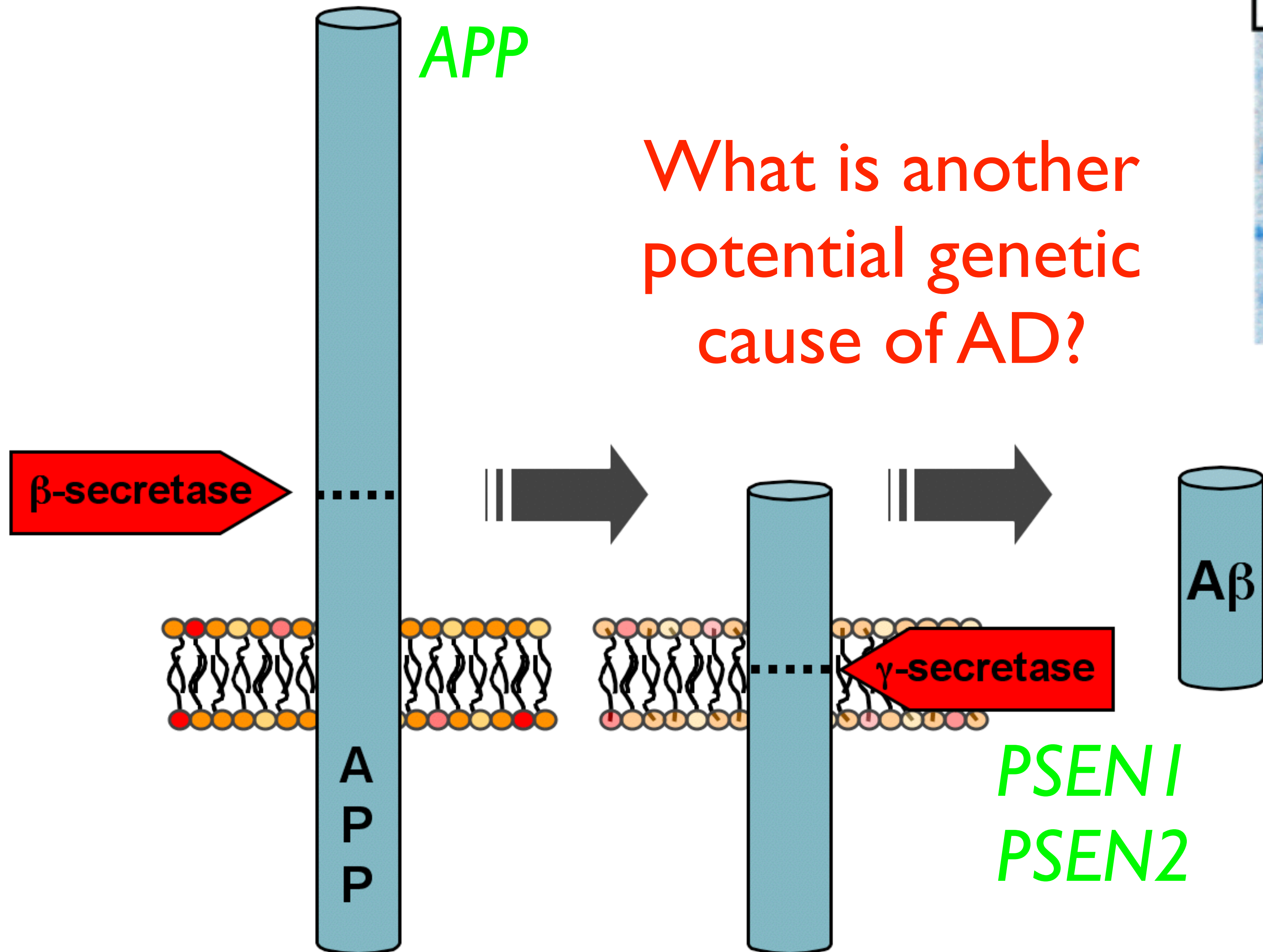
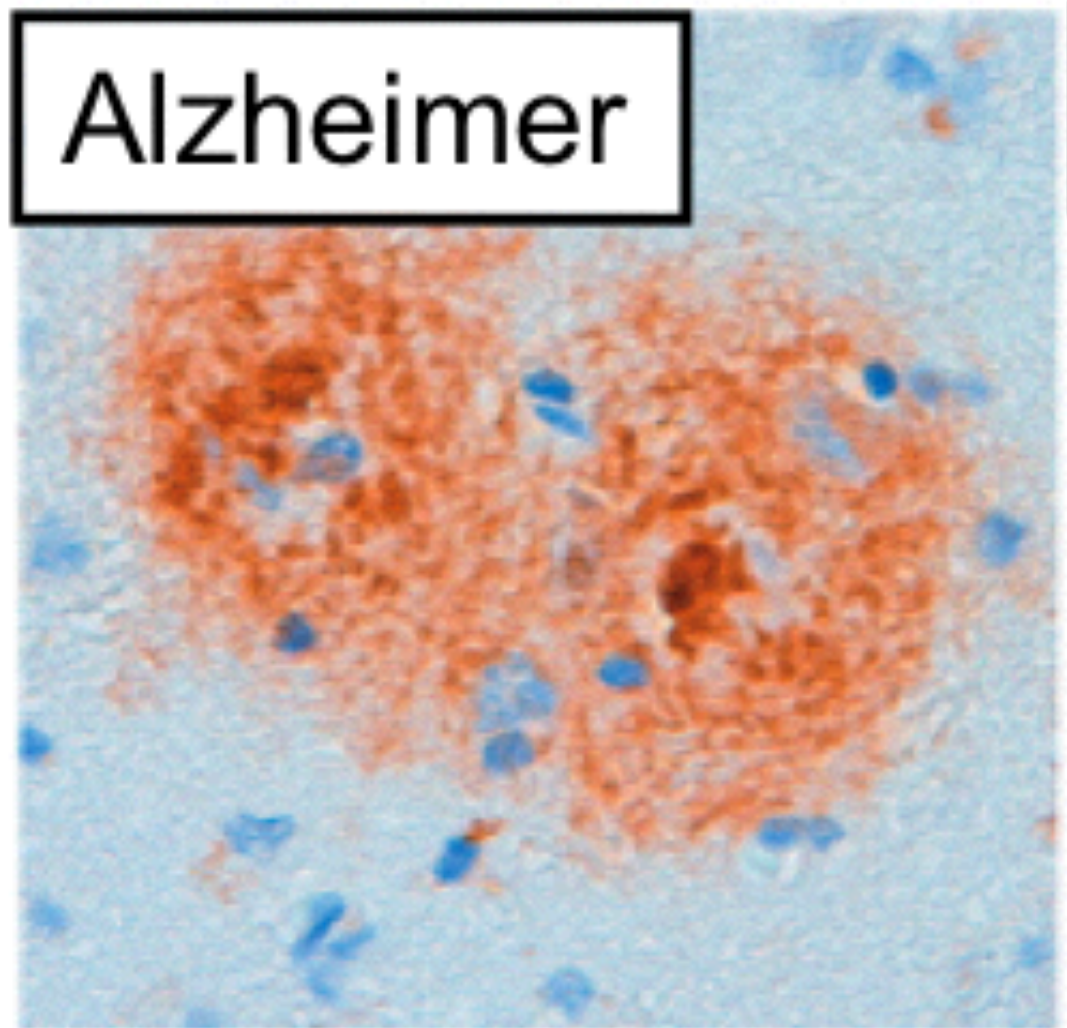
Mendelian Genes for Alzheimer's Disease

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



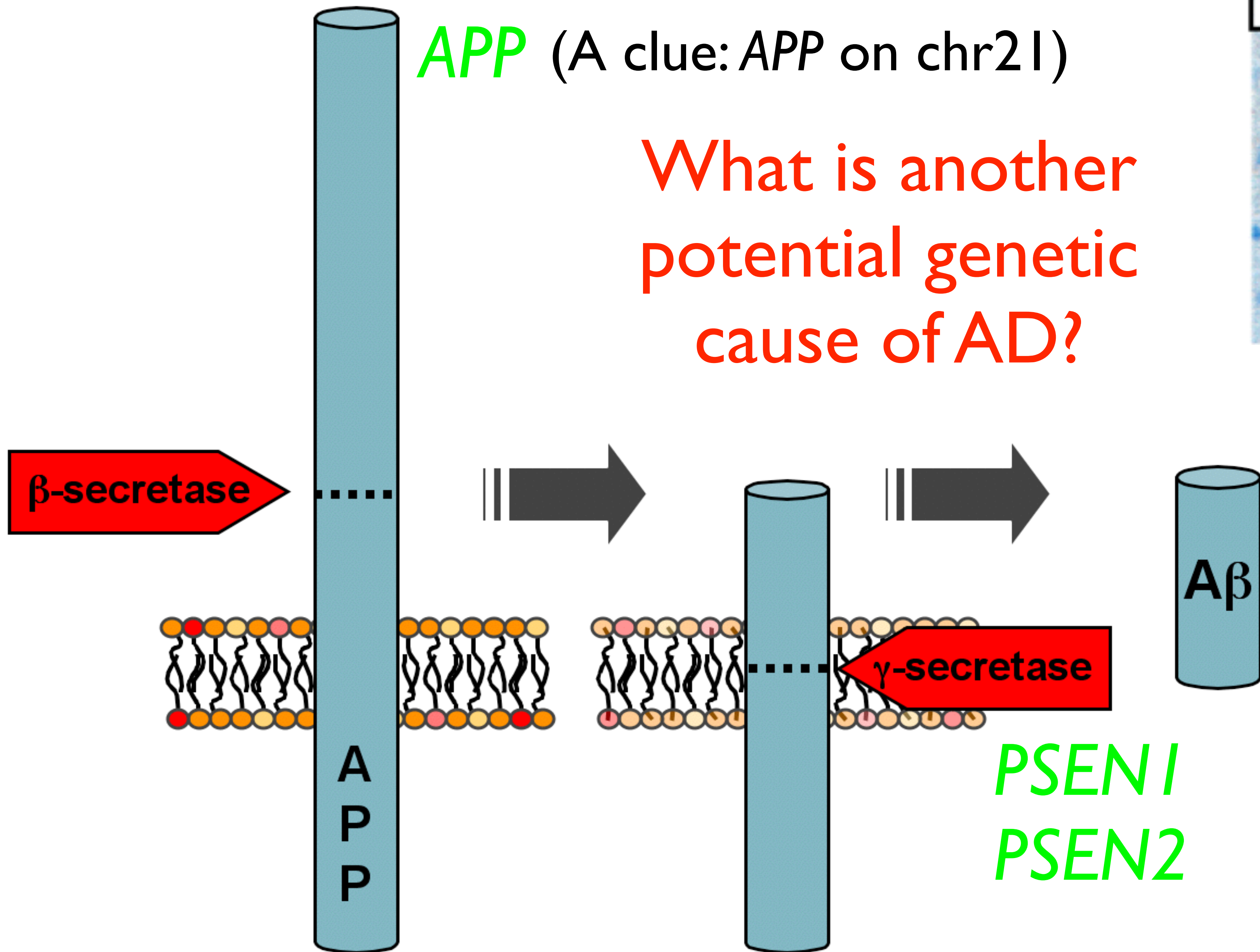
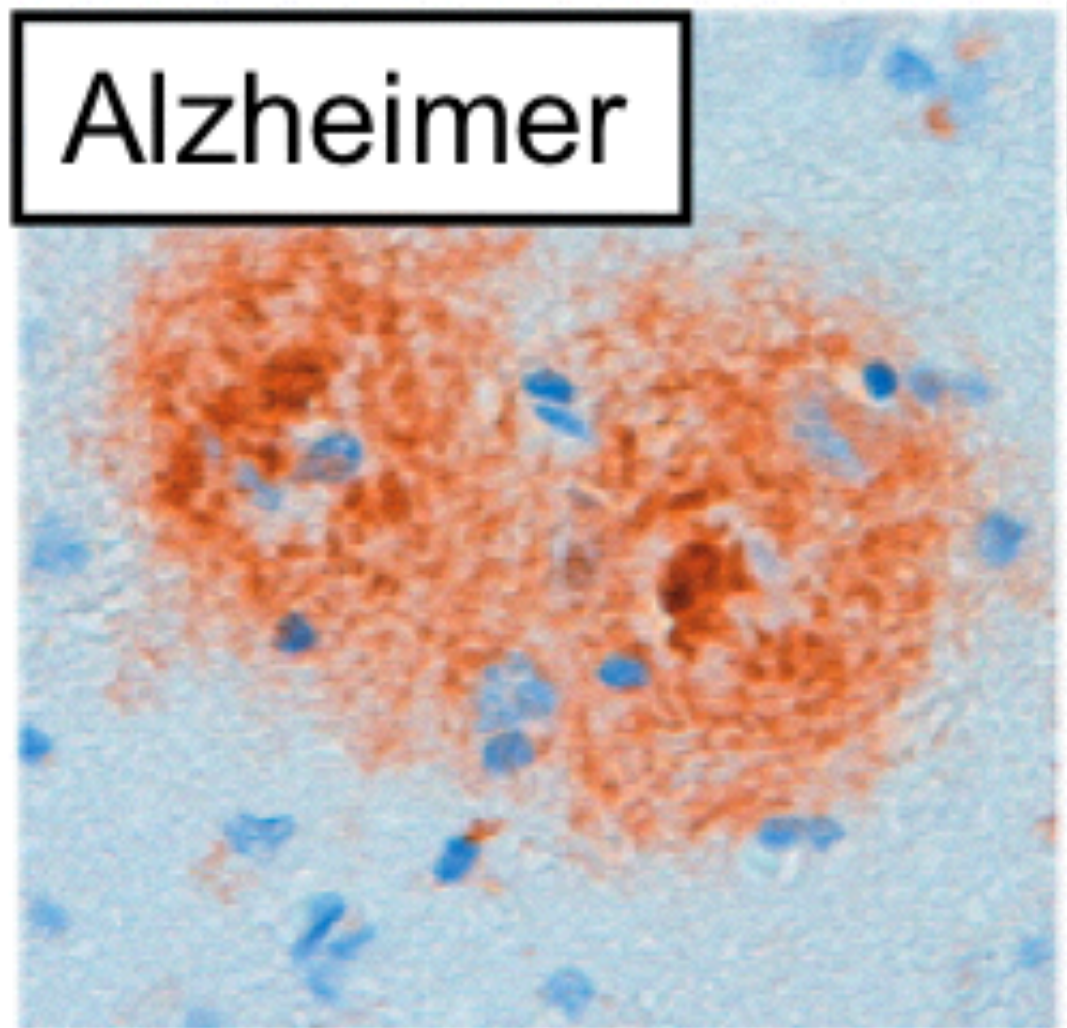


What is another
potential genetic
cause of AD?



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

A mutation in *APP* protects against Alzheimer's disease and age-related cognitive decline

Thorlakur Jonsson¹, Jasvinder K. Atwal², Stacy Steinberg¹, Jon Snaedal³, Palmi V. Jonsson^{3,8}, Sigurbjorn Bjornsson³, Hreinn Stefansson¹, Patrick Sulem¹, Daniel Gudbjartsson¹, Janice Maloney², Kwame Hoyte², Amy Gustafson², Yichin Liu², Yanmei Lu², Tushar Bhangale², Robert R. Graham², Johanna Huttenlocher^{1,4}, Gyda Bjornsdottir¹, Ole A. Andreassen⁵, Erik G. Jönsson⁶, Aarno Palotie⁷, Timothy W. Behrens², Olafur T. Magnusson¹, Augustine Kong¹, Unnur Thorsteinsdottir^{1,8}, Ryan J. Watts² & Kari Stefansson^{1,8}

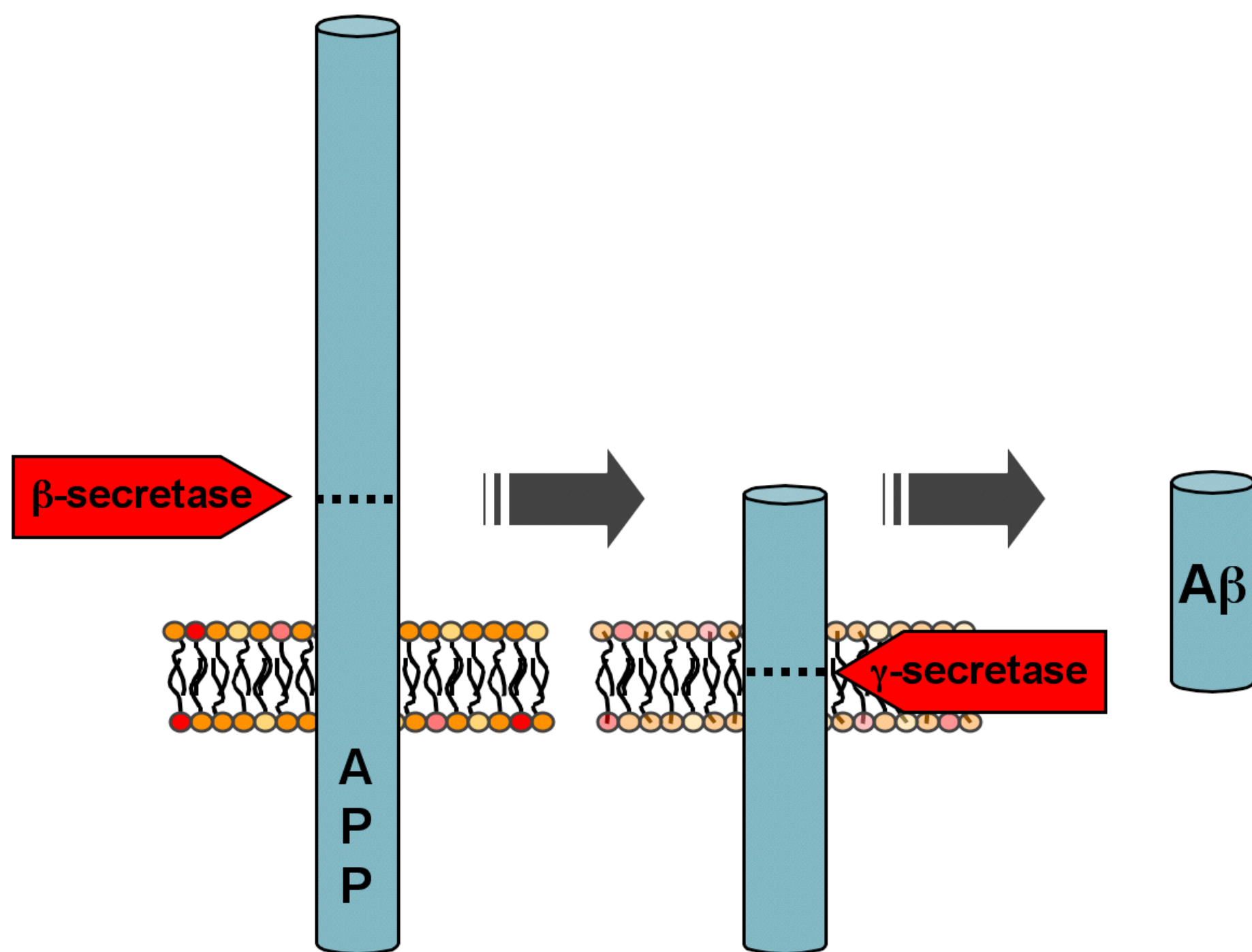
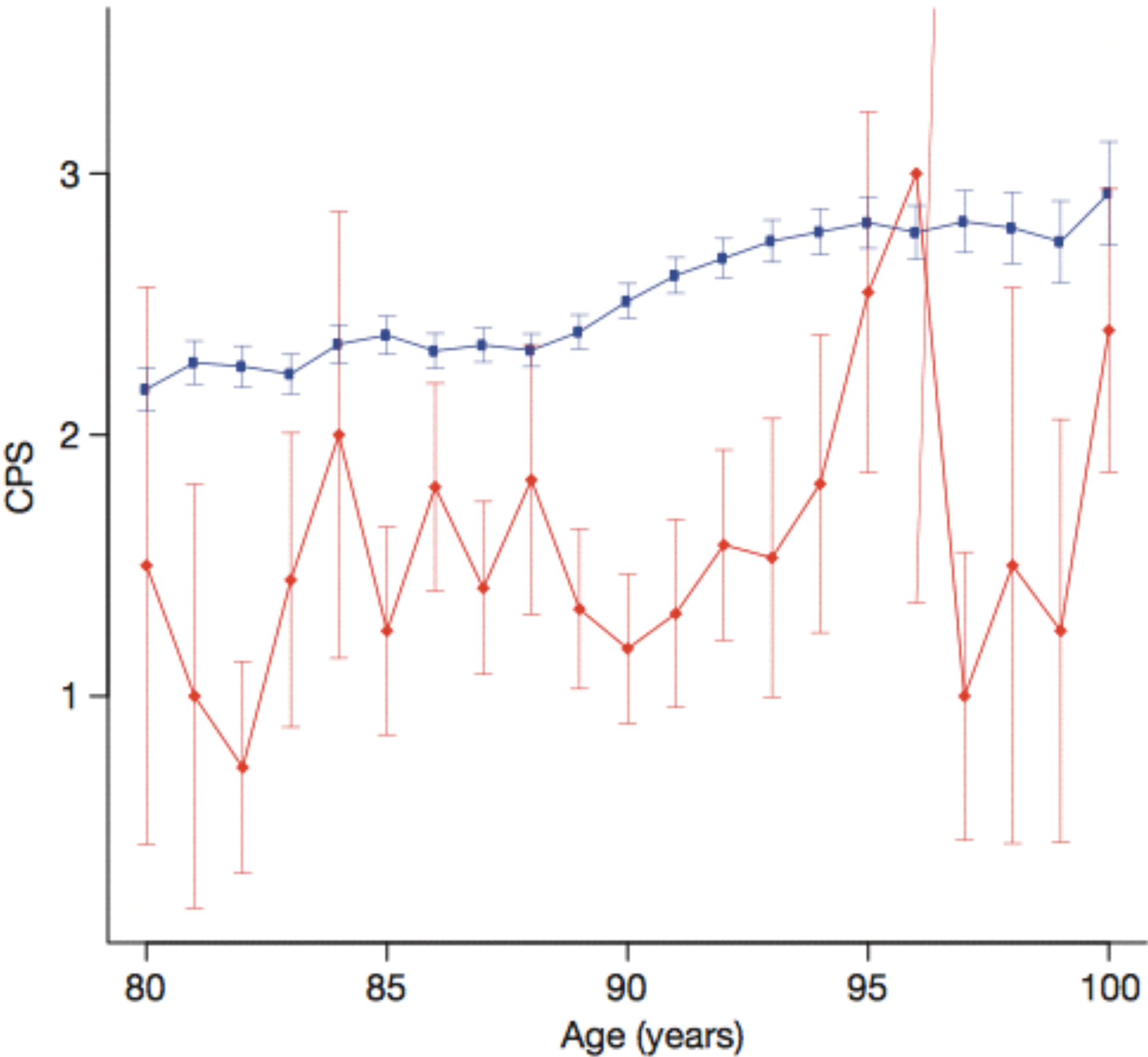


Table 1 | APP A673T protects against Alzheimer’s disease

Analysis	1/OR	OR	P value	Controls		
				Frequency (%)	<i>N</i> _{chip}	<i>N</i> _{in silico}
AD	-	-	-	0.13	2,199	849
AD versus population controls	4.24	0.236	4.19×10^{-5}	0.45	57,174	22,074
AD versus population controls aged 85 or greater	5.29	0.189	4.78×10^{-7}	0.62	7,653	1,350
AD versus cognitively intact controls at age 85	7.52	0.133	6.92×10^{-6}	0.79	827	407

The table shows association results, comparing patients with Alzheimer’s disease (AD) to three different control groups (top line gives numbers for patients with Alzheimer’s disease only). *N*_{chip}, number of individuals with chip-based genotype information; *N*_{in silico}, number of individuals with genealogy-based genotype information.



odds for carriers of rs63750847-A of reaching age 85 are 1.47-fold the odds of non-carriers.

Effects of rs63750847-A on cognitive ability extend beyond Alzheimer’s disease.

Variant of *TREM2* Associated with the Risk of Alzheimer's Disease

Thorlakur Jonsson, Ph.D., Hreinn Stefansson, Ph.D., Stacy Steinberg, Ph.D., Ingileif Jonsdottir, Ph.D., Palmi V. Jonsson, M.D., Jon Snaedal, M.D., Sigurbjorn Bjornsson, M.D., Johanna Huttenlocher, B.S., Allan I. Levey, M.D., Ph.D., James J. Lah, M.D., Ph.D., Dan Rujescu, M.D., Harald Hampel, M.D., Ina Giegling, Ph.D., Ole A. Andreassen, M.D., Ph.D., Knut Engedal, M.D., Ph.D., Ingun Ulstein, M.D., Ph.D., Srdjan Djurovic, Ph.D., Carla Ibrahim-Verbaas, M.D., Albert Hofman, M.D., Ph.D., M. Arfan Ikram, M.D., Ph.D., Cornelia M van Duijn, Ph.D., Unnur Thorsteinsdottir, Ph.D., Augustine Kong, Ph.D., and Kari Stefansson, M.D., Ph.D.
N Engl J Med 2013; 368:107-116 | [January 10, 2013](#) | DOI: 10.1056/NEJMoa1211103

TREM2 Variants in Alzheimer's Disease

Rita Guerreiro, Ph.D., Aleksandra Wojtas, M.S., Jose Bras, Ph.D., Minerva Carrasquillo, Ph.D., Ekaterina Rogaeva, Ph.D., Elisa Majounie, Ph.D., Carlos Cruchaga, Ph.D., Celeste Sassi, M.D., John S.K. Kauwe, Ph.D., Steven Younkin, M.D., Ph.D., Lilinaz Hazrati, M.D., Ph.D., John Collinge, M.D., Jennifer Pocock, Ph.D., Tammaryn Lashley, Ph.D., Julie Williams, Ph.D., Jean-Charles Lambert, Ph.D., Philippe Amouyel, M.D., Ph.D., Alison Goate, Ph.D., Rosa Rademakers, Ph.D., Kevin Morgan, Ph.D., John Powell, Ph.D., Peter St. George-Hyslop, M.D., Andrew Singleton, Ph.D., and John Hardy, Ph.D. for the Alzheimer Genetic Analysis Group
N Engl J Med 2013; 368:117-127 | [January 10, 2013](#) | DOI: 10.1056/NEJMoa1211851

A rare missense mutation (rs75932628-T) in the gene encoding the triggering receptor expressed on myeloid cells 2 (*TREM2*), which was predicted to result in an R47H substitution, was found to confer a significant risk of Alzheimer's disease

odds ratio, 2.92; 95% confidence interval [CI], 2.09 to 4.09; P=3.42×10^{−10}

Today's Plan

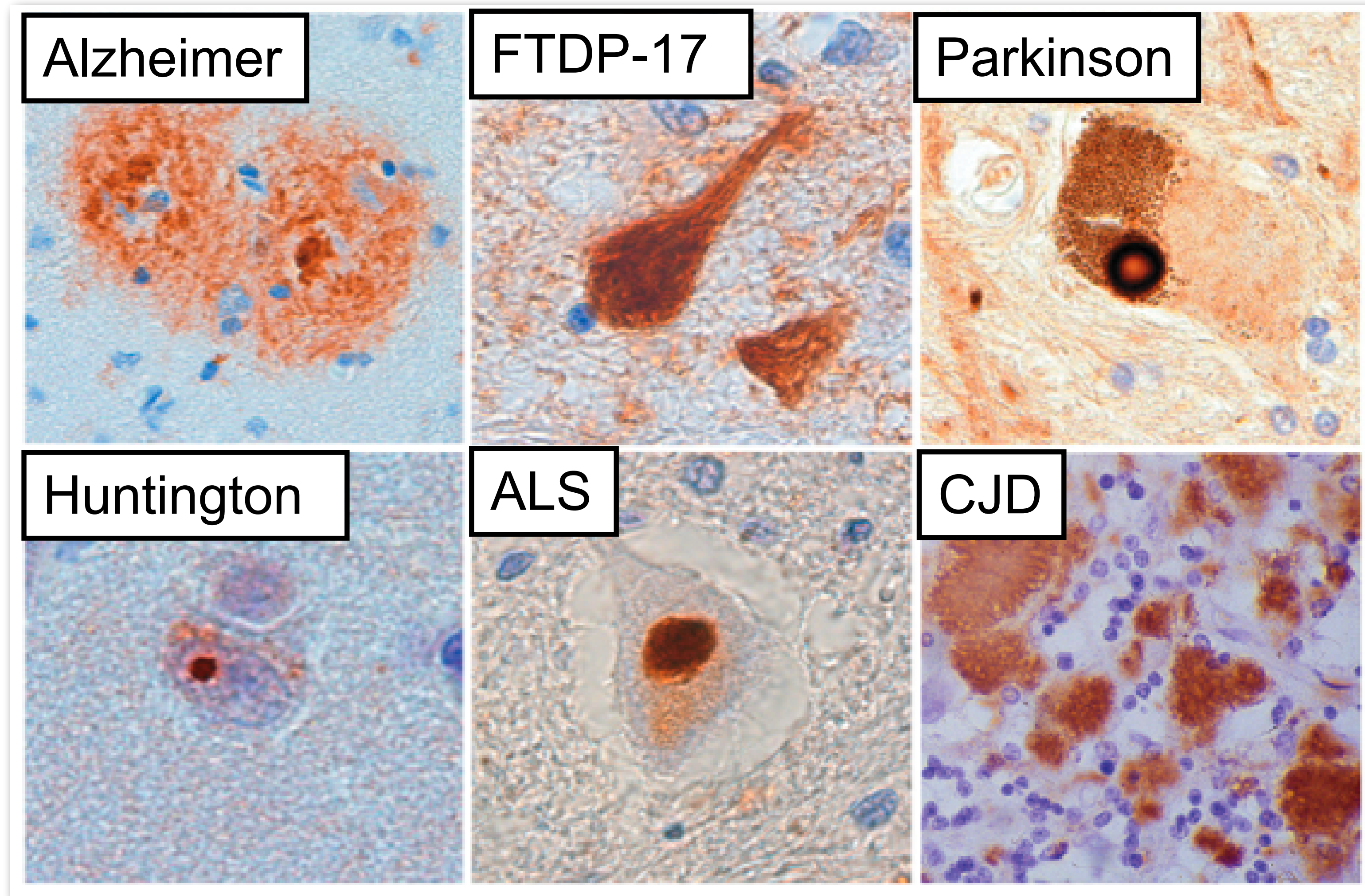
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(Gitler)
5. Parkinson's Disease (Chuang)

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

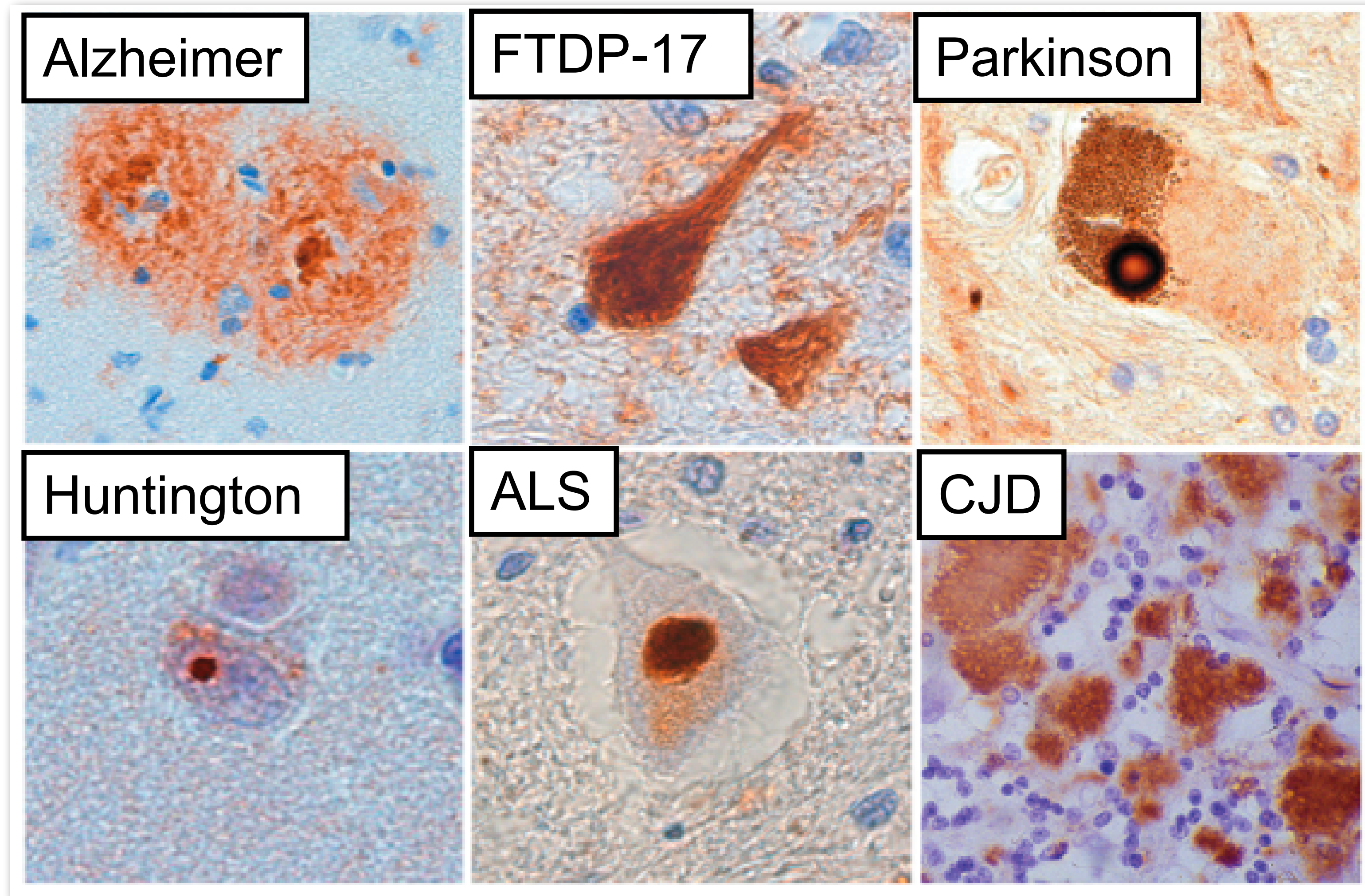
Protein Aggregates in Neurodegenerative Diseases



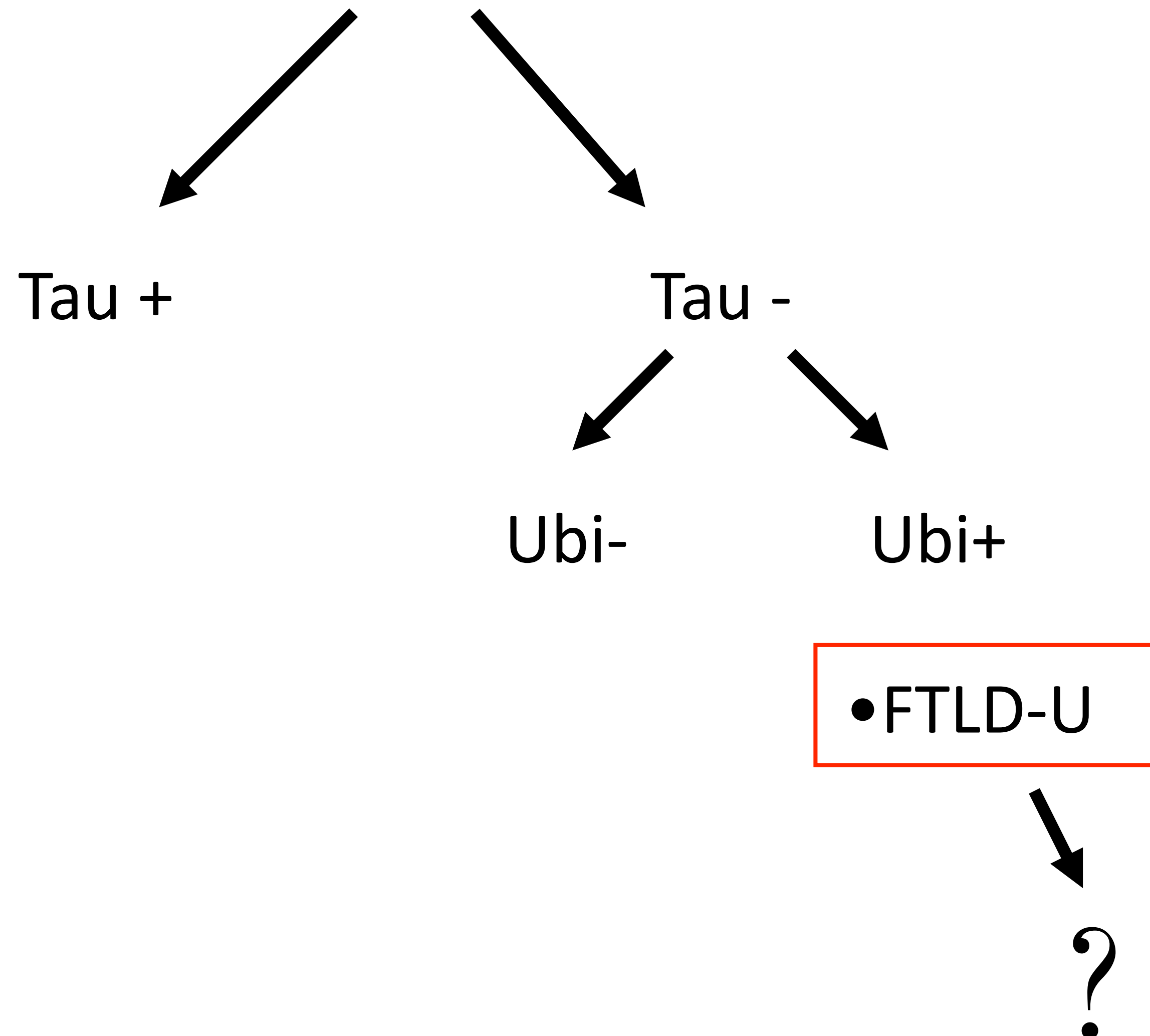
Mendelian Genes for FTD

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)



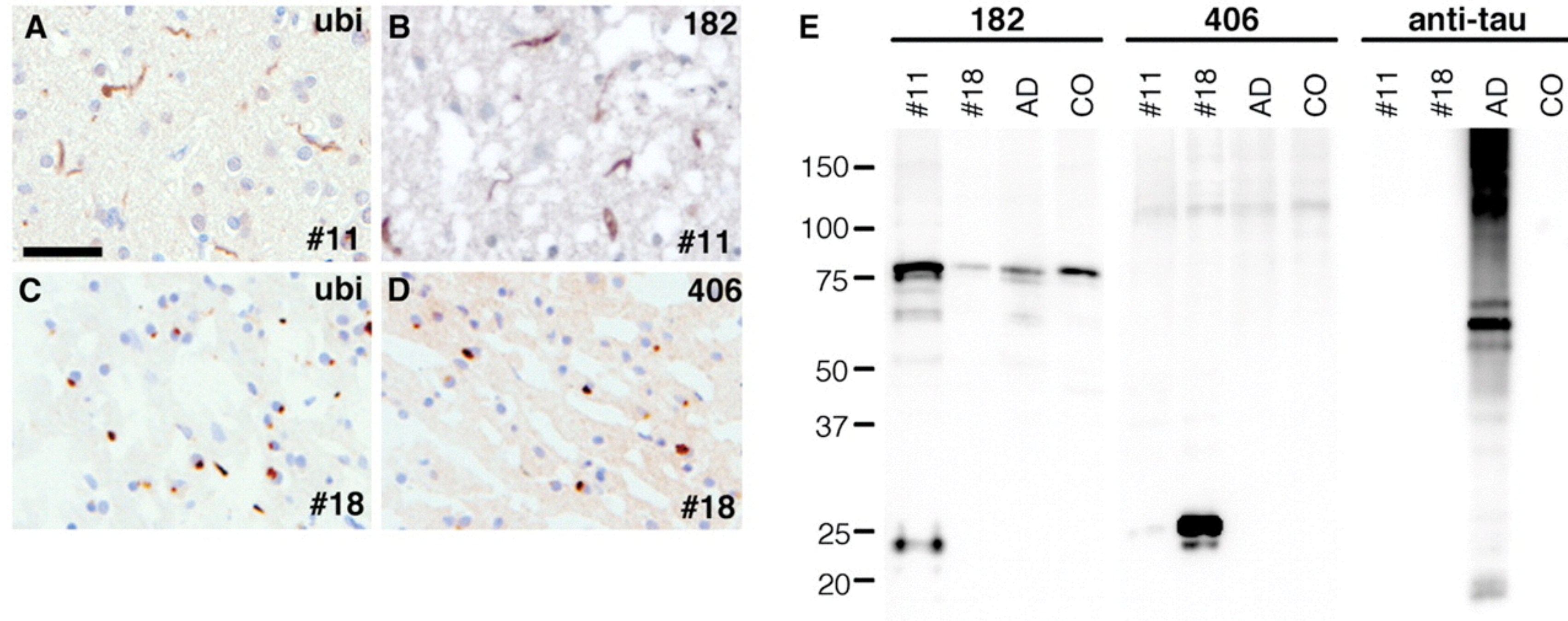
REPORTS

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**

TDP-43



F

1 MSEYIRVTEDENDIEPIEIPSEDDGTVLLSTVTAQFPGACGLRYRNPVSQCMRGVRLVEGILHAPDAGWGN

71 LVYVVNYPKDNKRKMDDETDAASSAVKVKRAVQKTS~~DLIVLGLPWKTTEODLKEYFSTFGEVLMVOVKKDLK~~

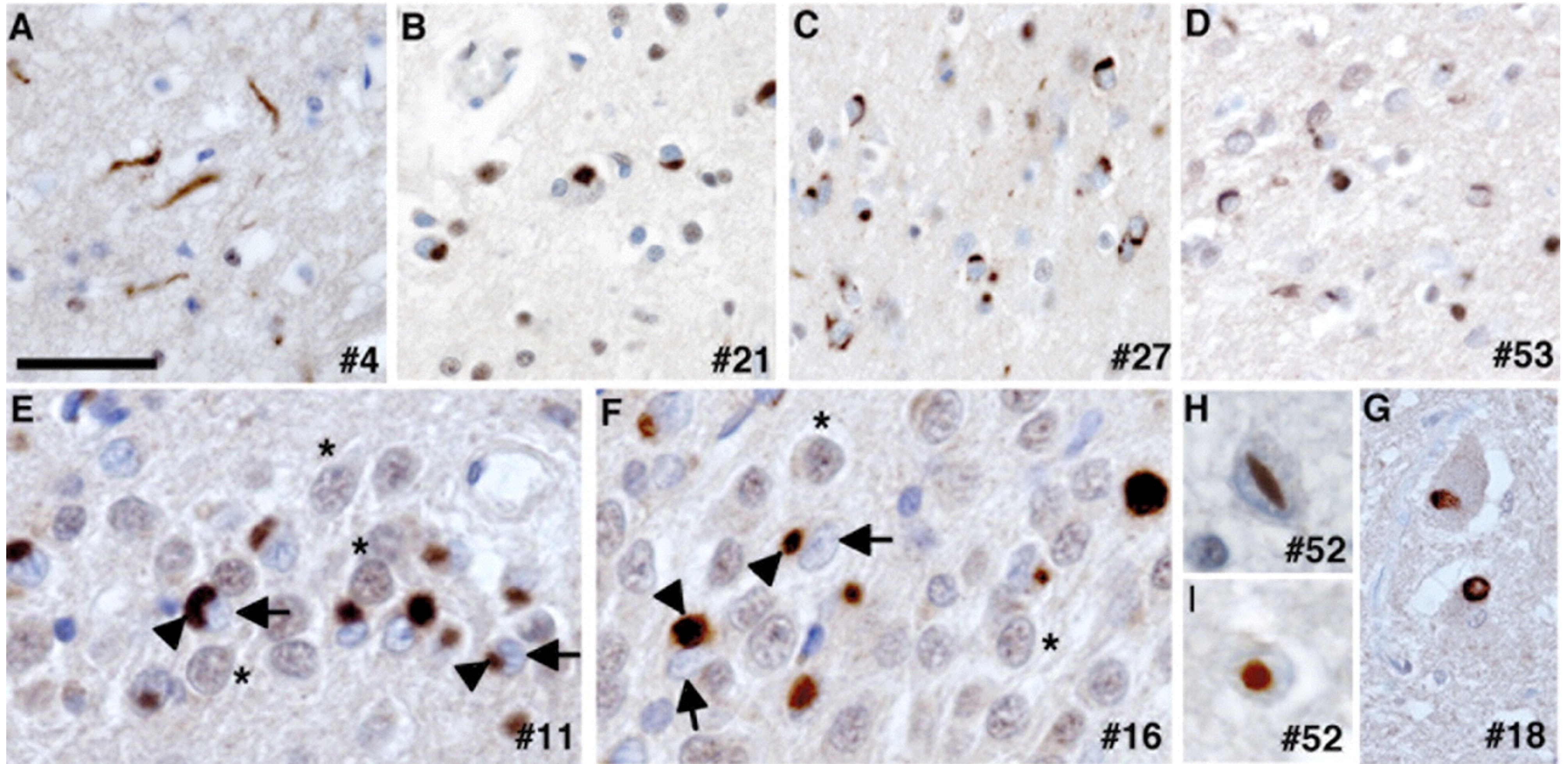
141 ~~TGHSKGFGFVRFTTEYETOVKVMSORHMIDGRWCDCKLPNSKQSQDEPLRSRKVFVGRCTEDMTEDELREF~~

211 ~~FSOYGDVMDVFI~~PKPFRAFAFVTFADDOIAOSLCGEDLIIK~~GISVHISNAEPKHNSNRQLERS~~~~GRFGGNP~~

281 ~~GGFGNQGGFGNSR~~GGGAGLGNNQGSNMGGGMNFGAFSINPAMMAAAQAALQSSWGMMGLASQQNQSGPS

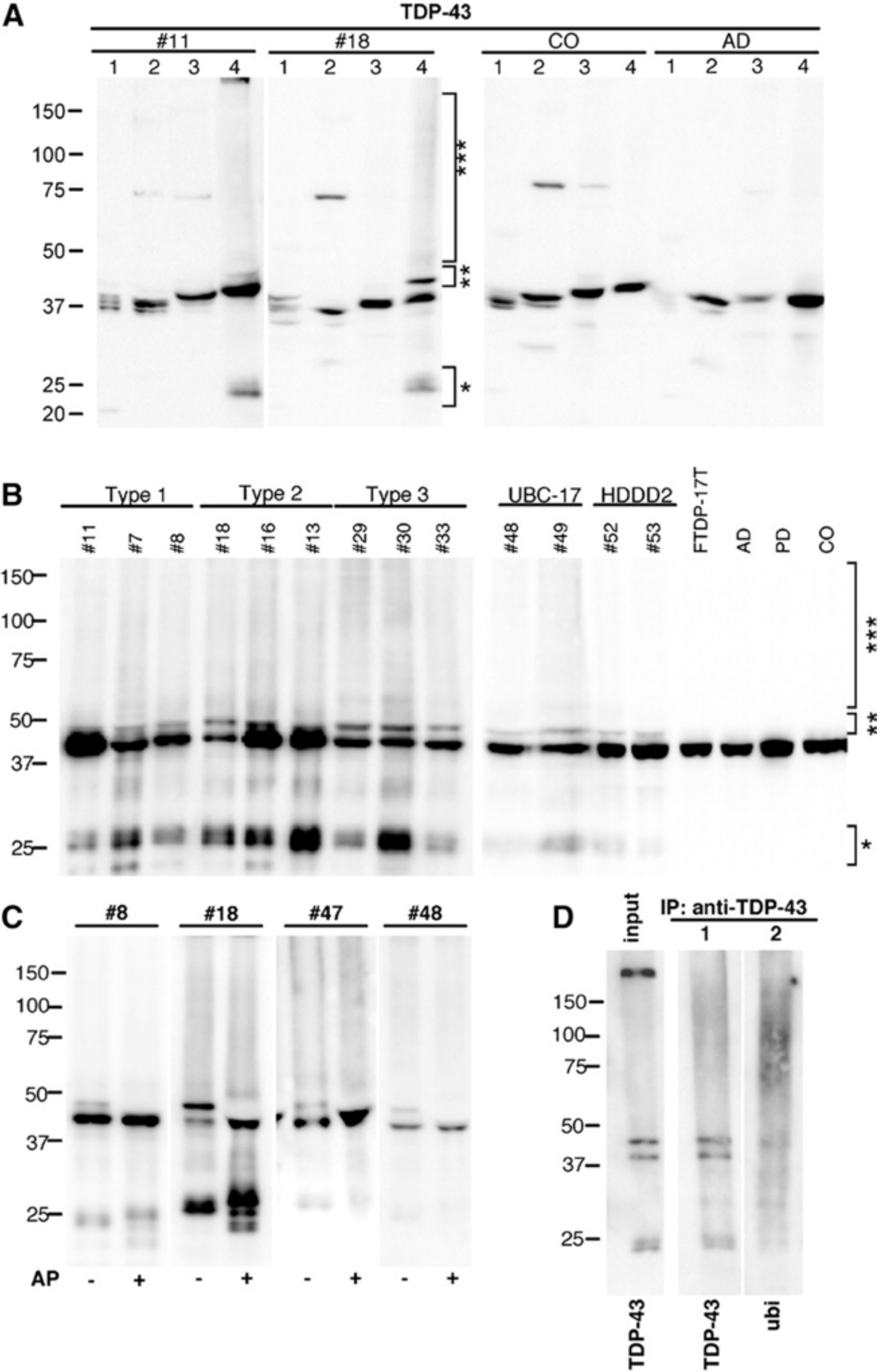
351 GNNQNQGNMQREPNQAFGSGNNSYSGSNSGAAIGWGSASNAGSGSGFNGGFGSSMDSKSSGWGM

TDP-43 pathology in FTLD-U



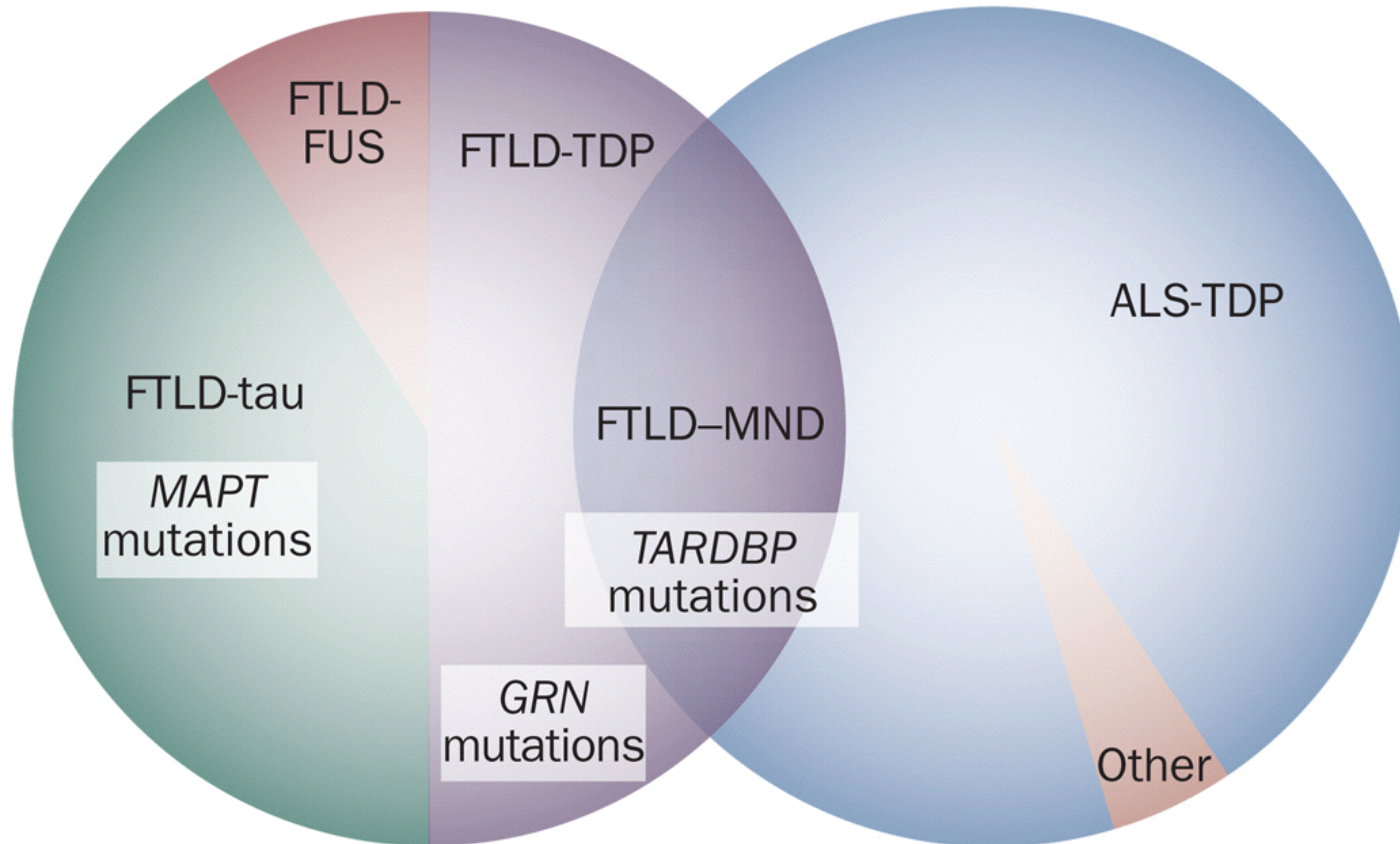
TDP-43

“biochemical signature”

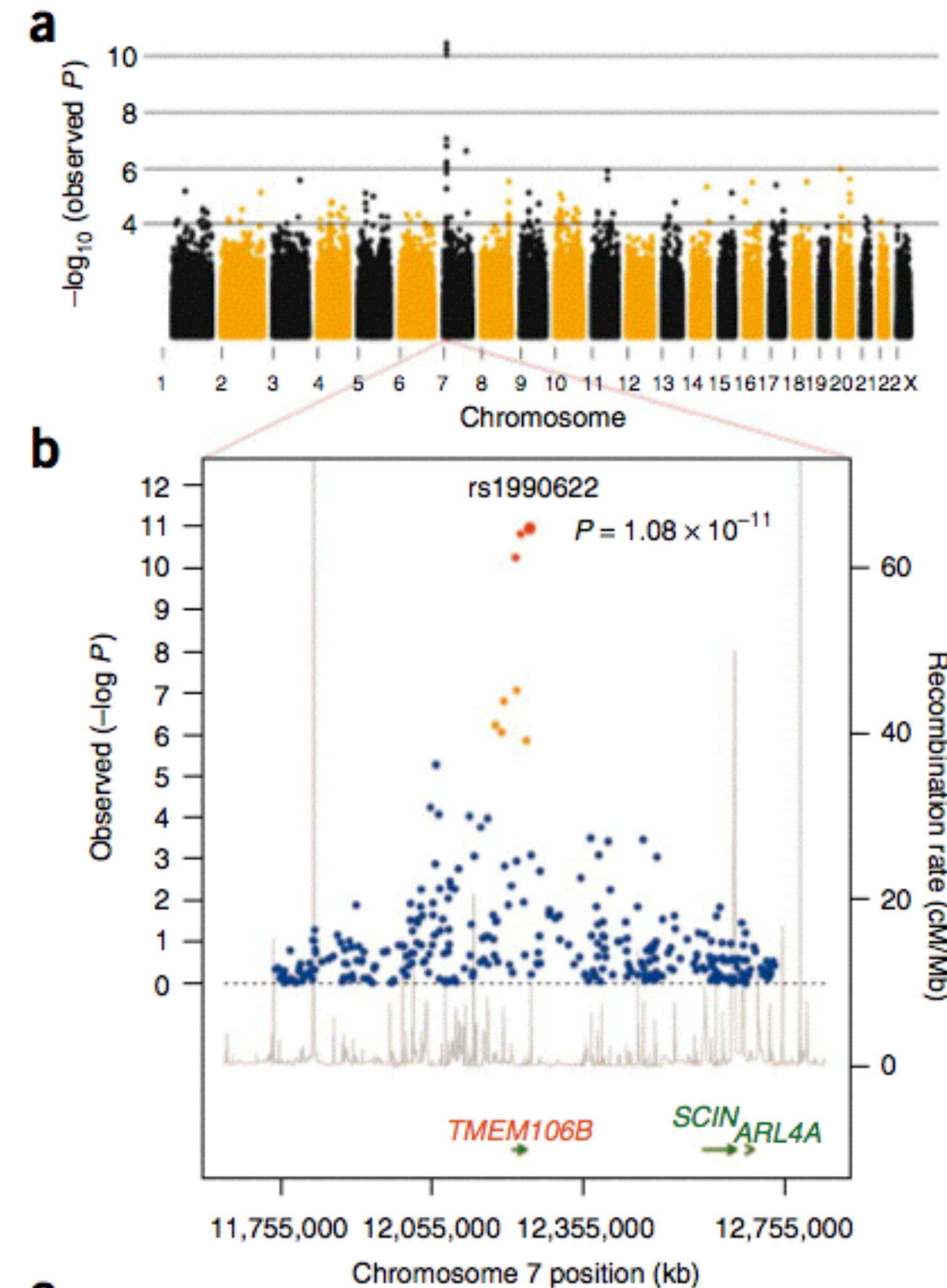


Neumann et al.,
Science 2006

Pathological subtypes of FTLD and ALS



GWAS for frontotemporal dementia susceptibility loci

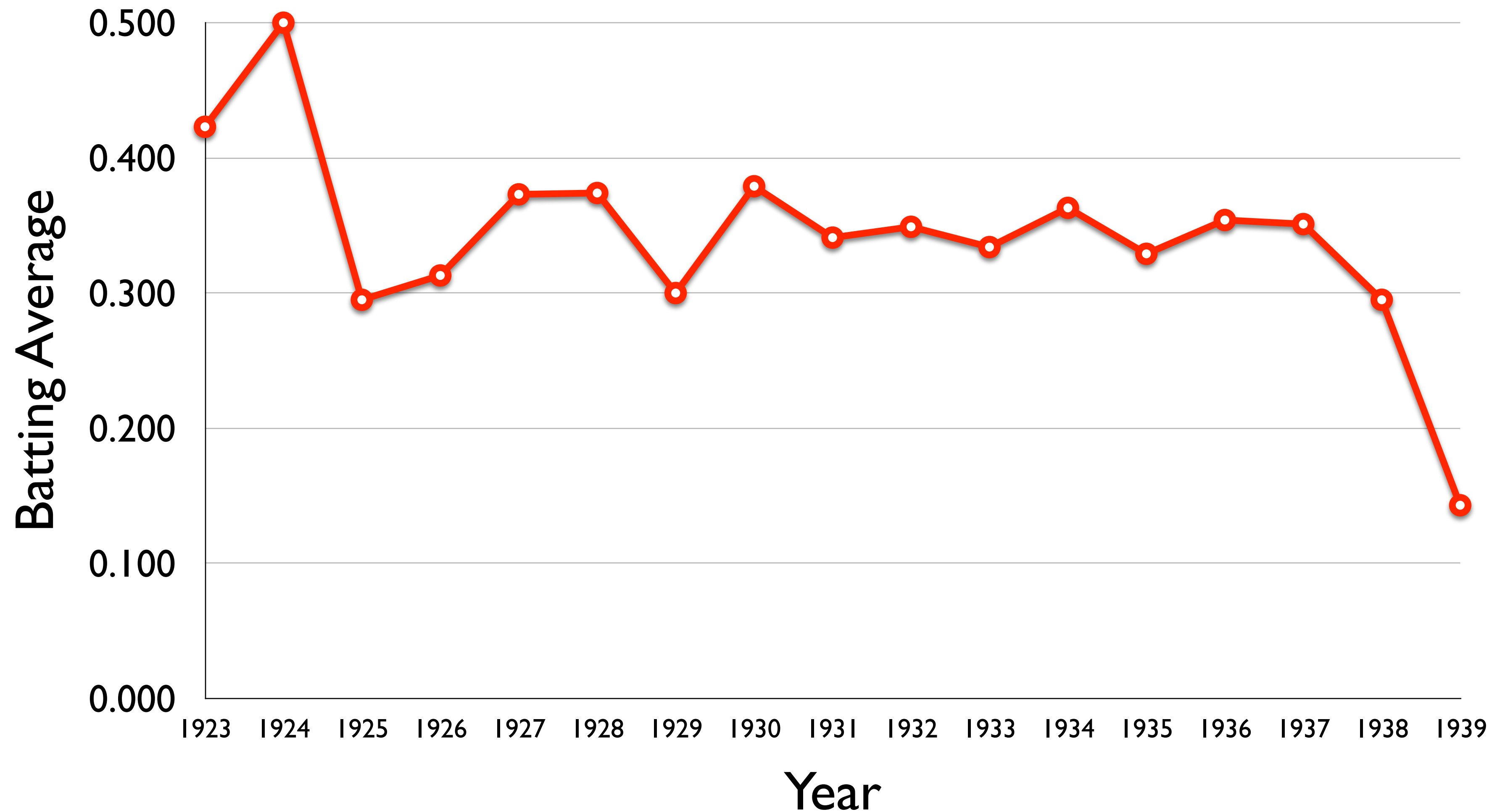


rs1990622
TMEM106B
OR 1.64 (1.41-1.89)

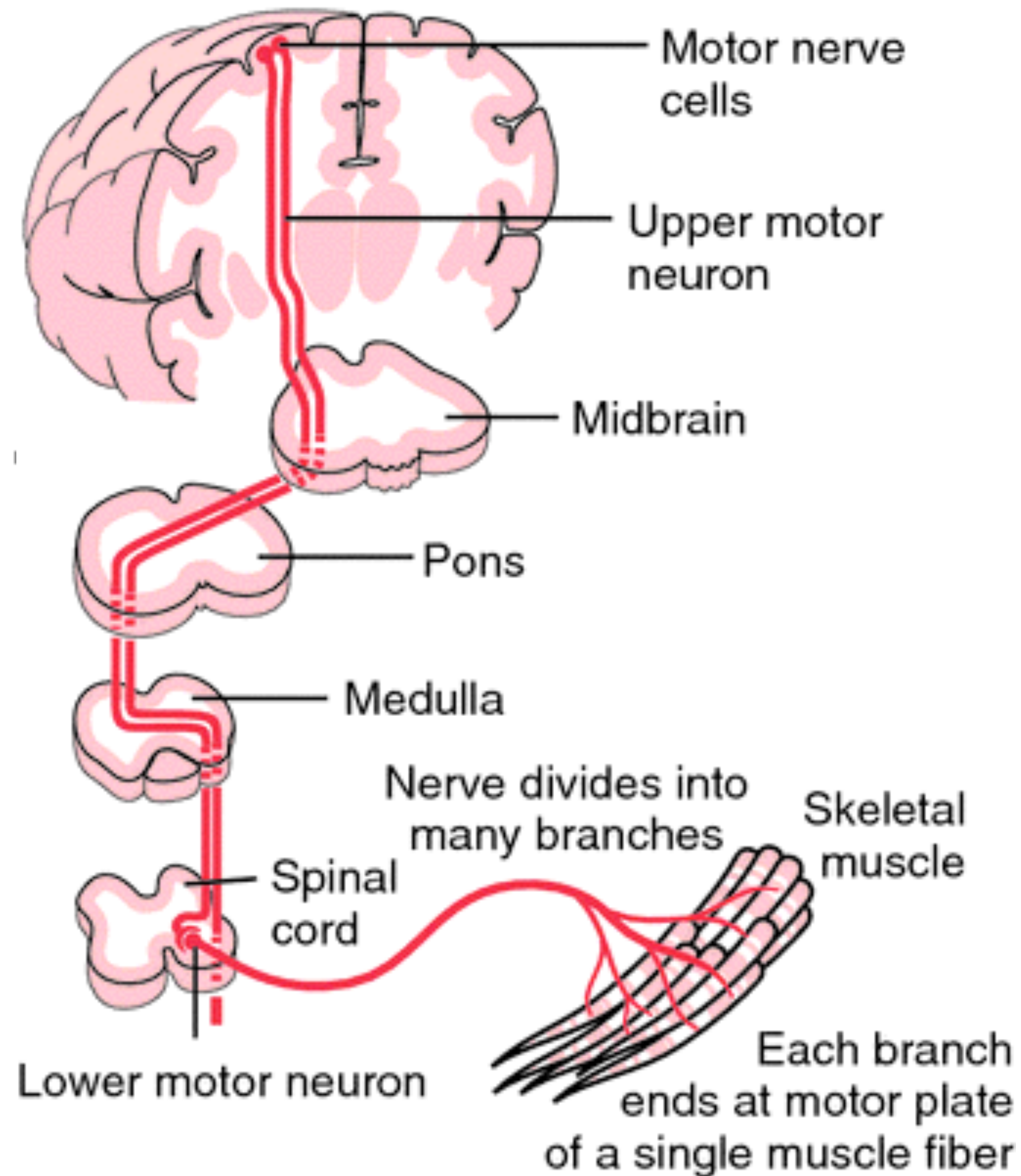
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4. Amyotrophic lateral sclerosis (ALS)
(Gitler)
5. Parkinson's Disease (Chuang)

Lou Gehrig's career batting average

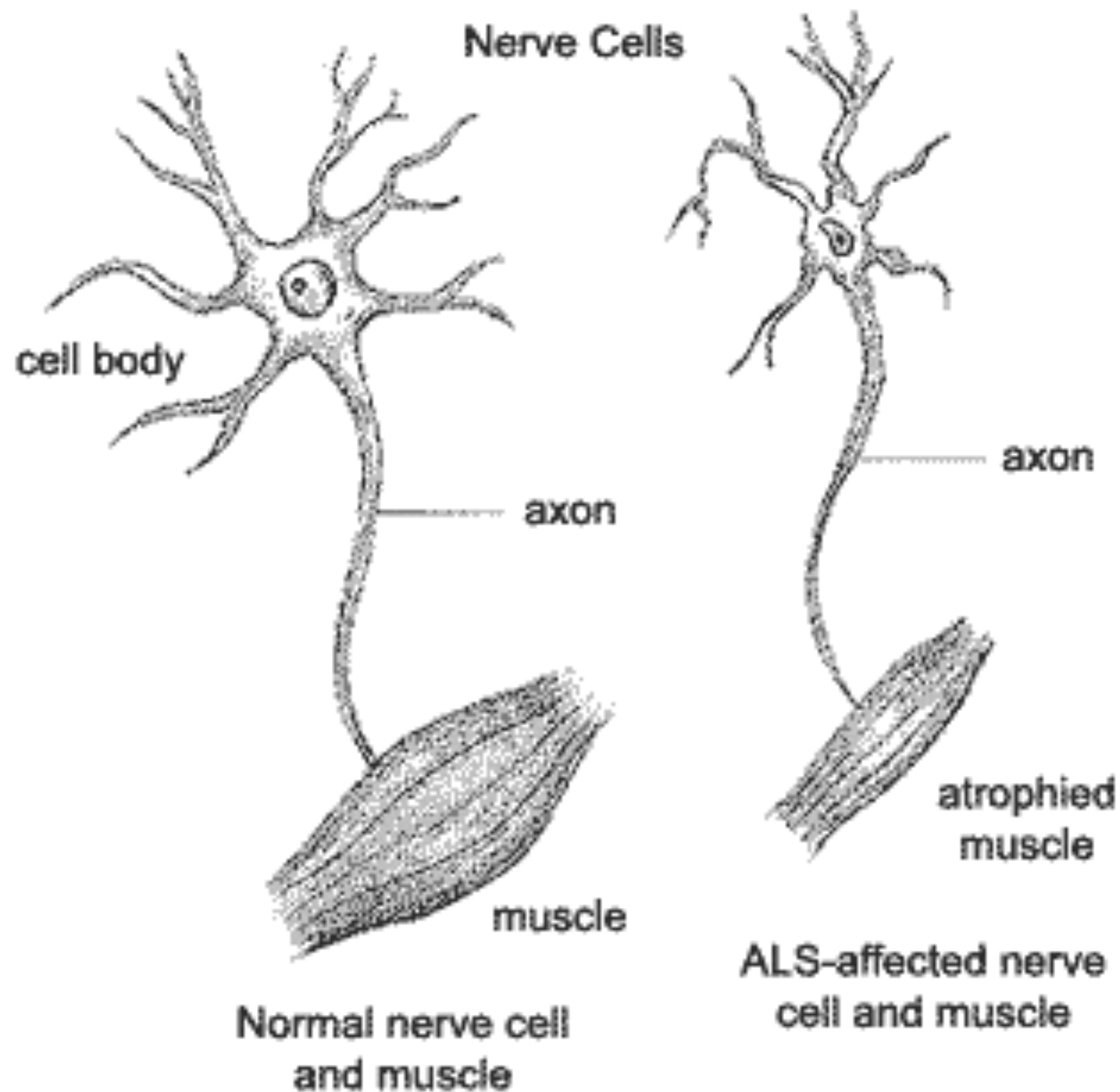


Amyotrophic Lateral Sclerosis (ALS)



- 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?

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Stephen Hawking

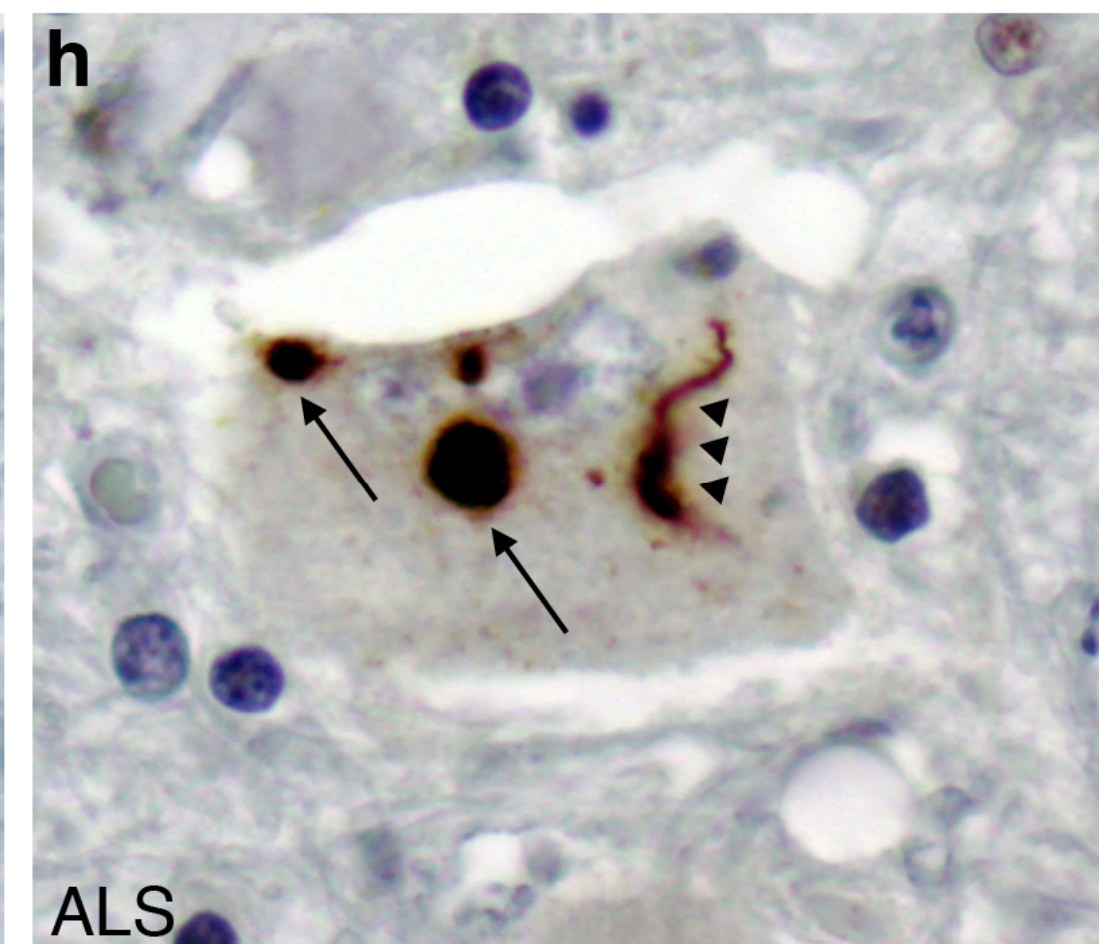
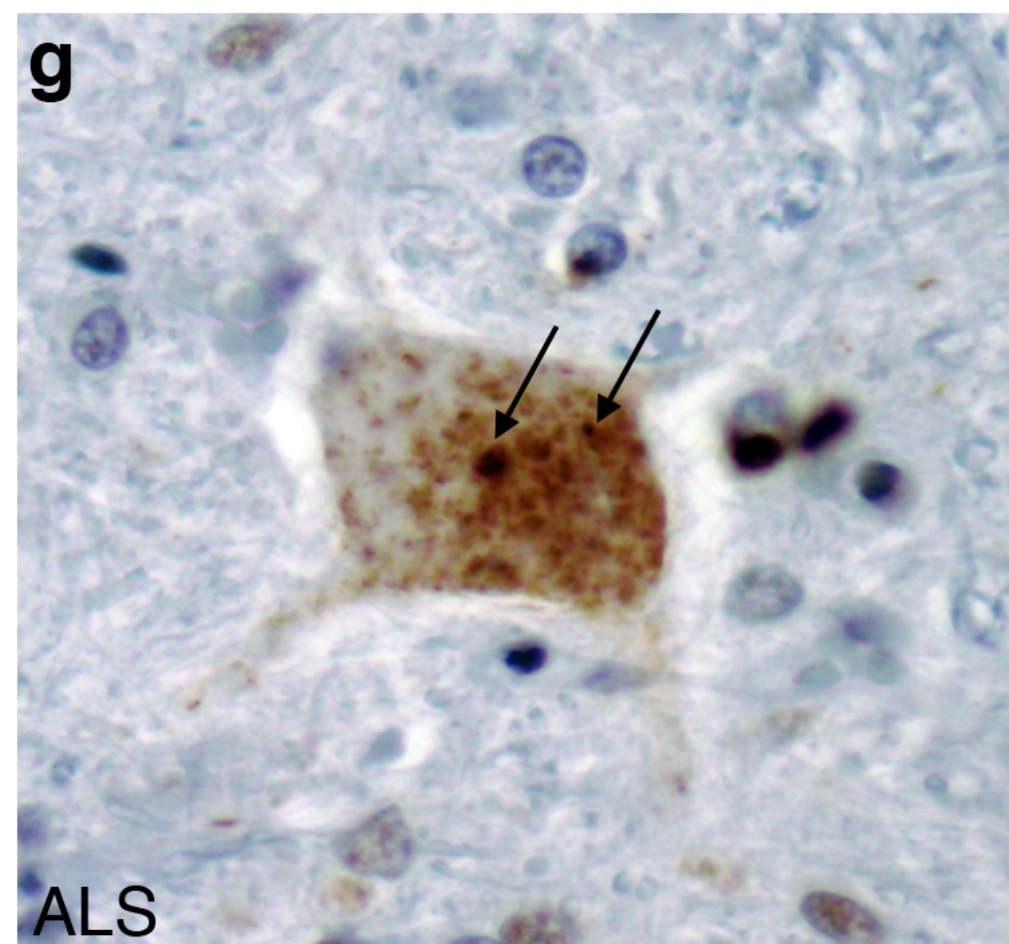
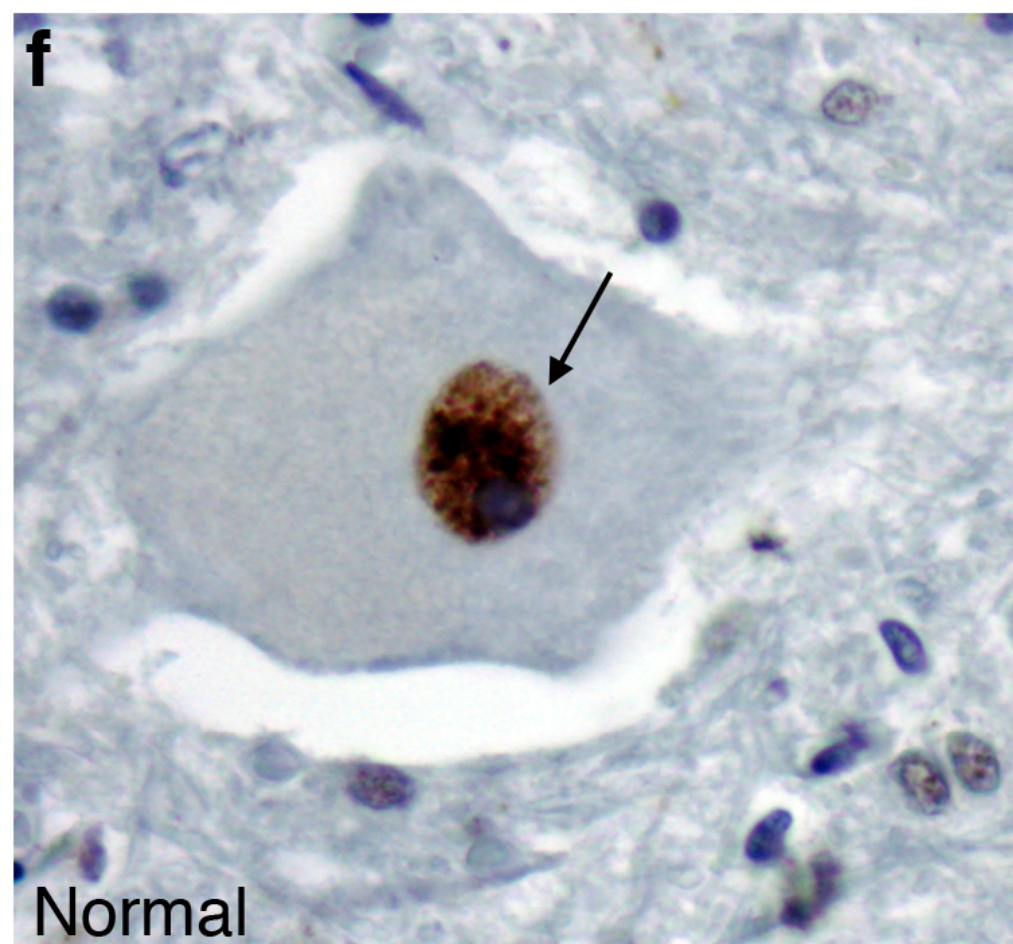
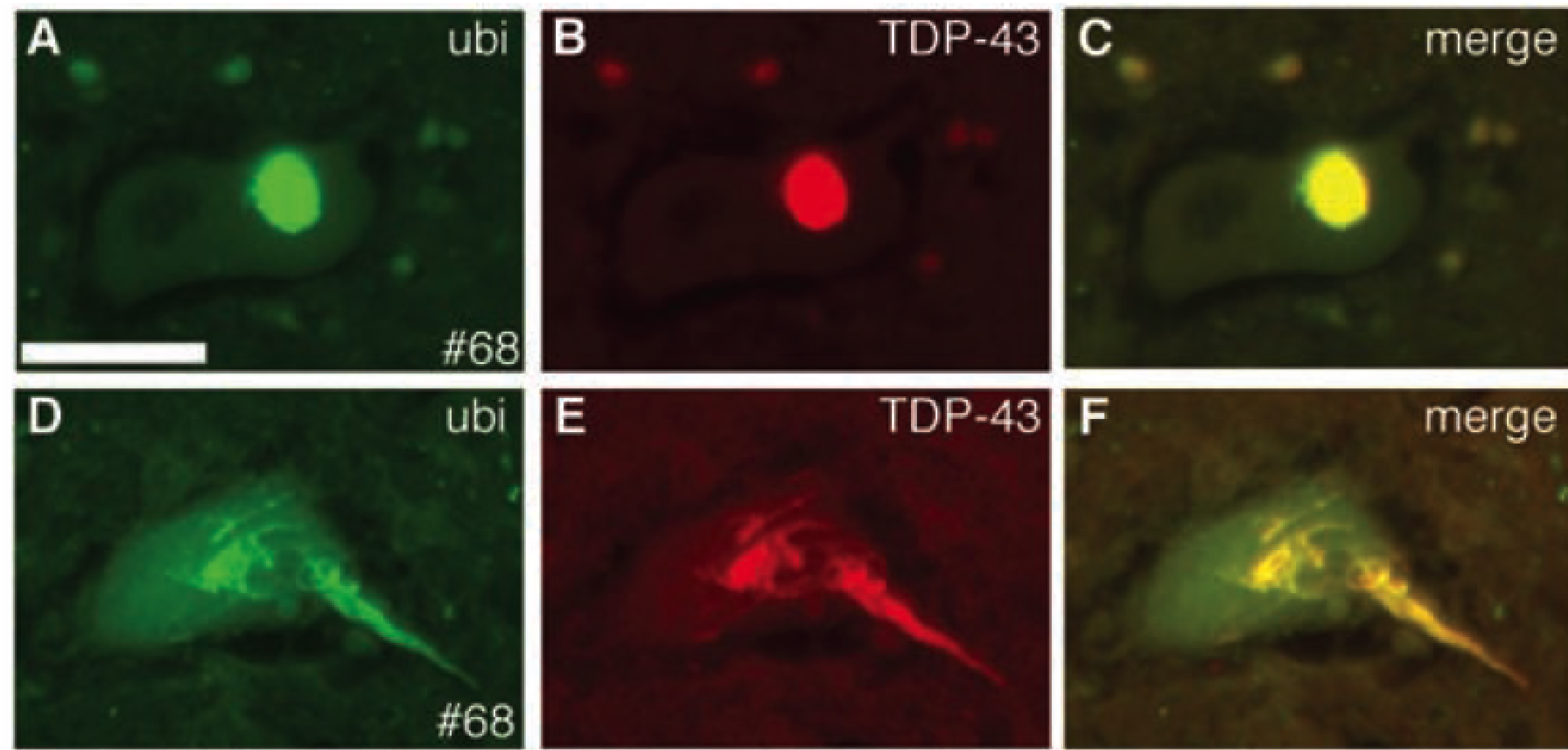




New Orleans Saints
safety Steve Gleason
blocks punt vs. Falcons
Sept. 2006



TDP-43 pathology in sporadic ALS

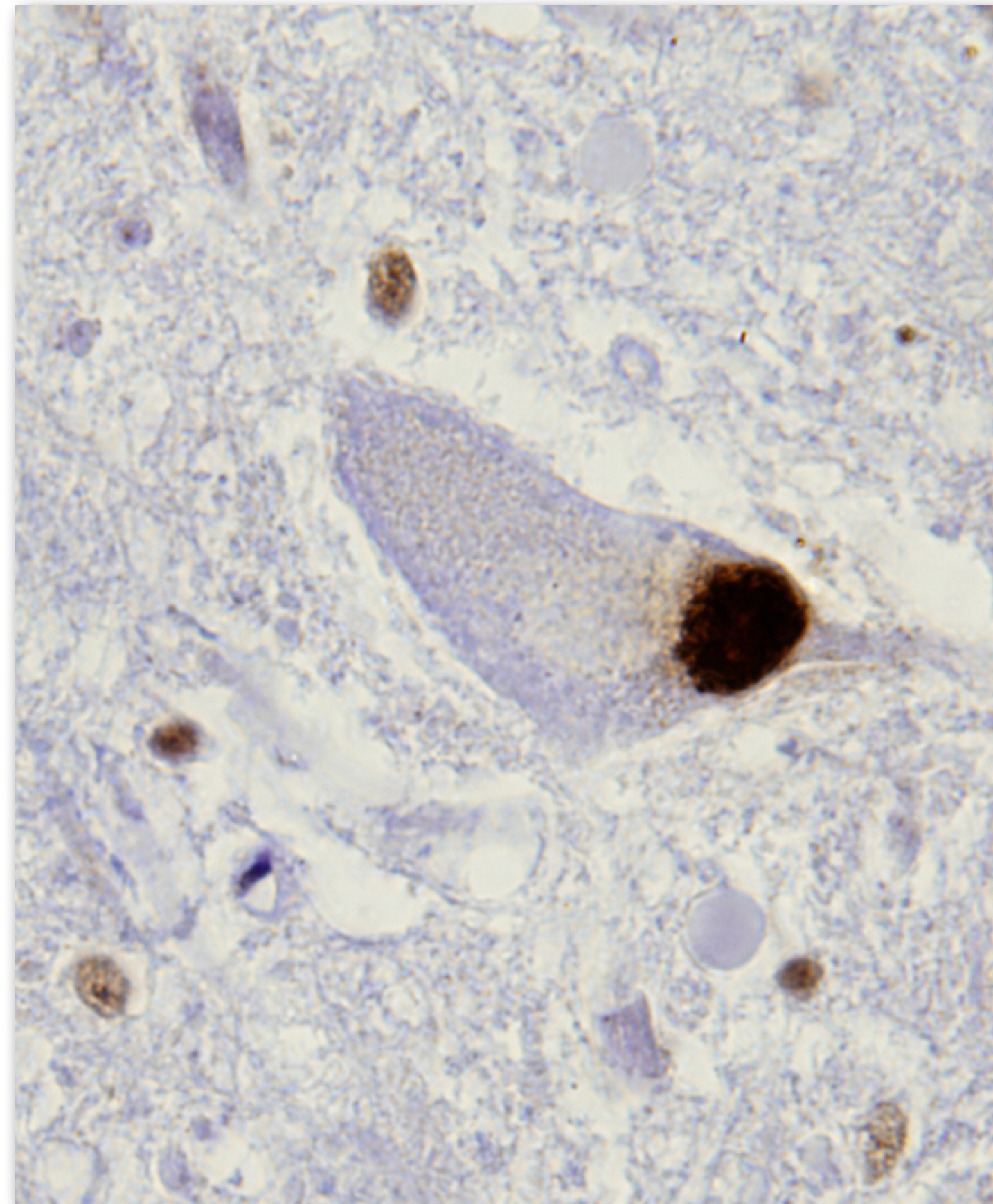


Editorial

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



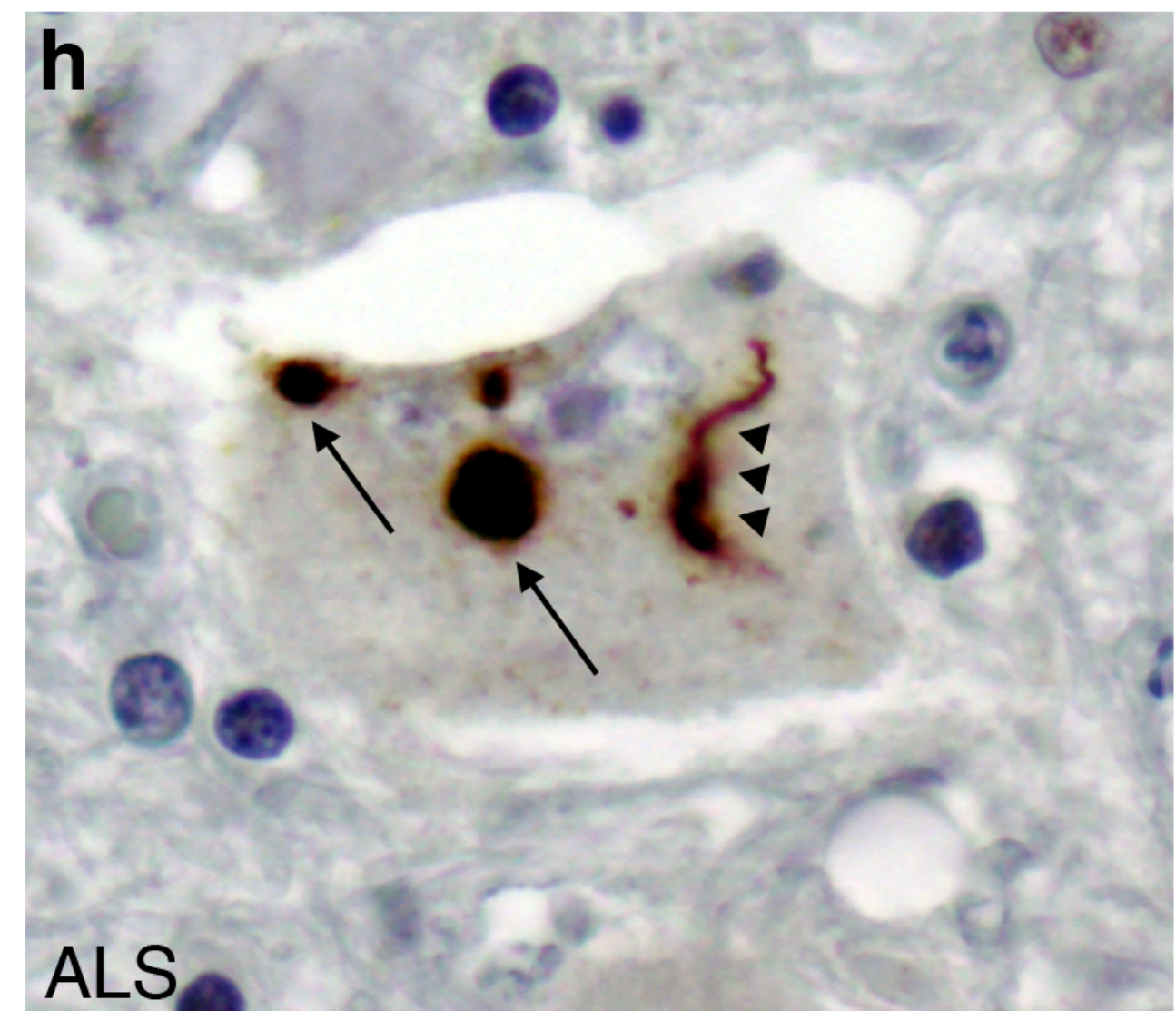
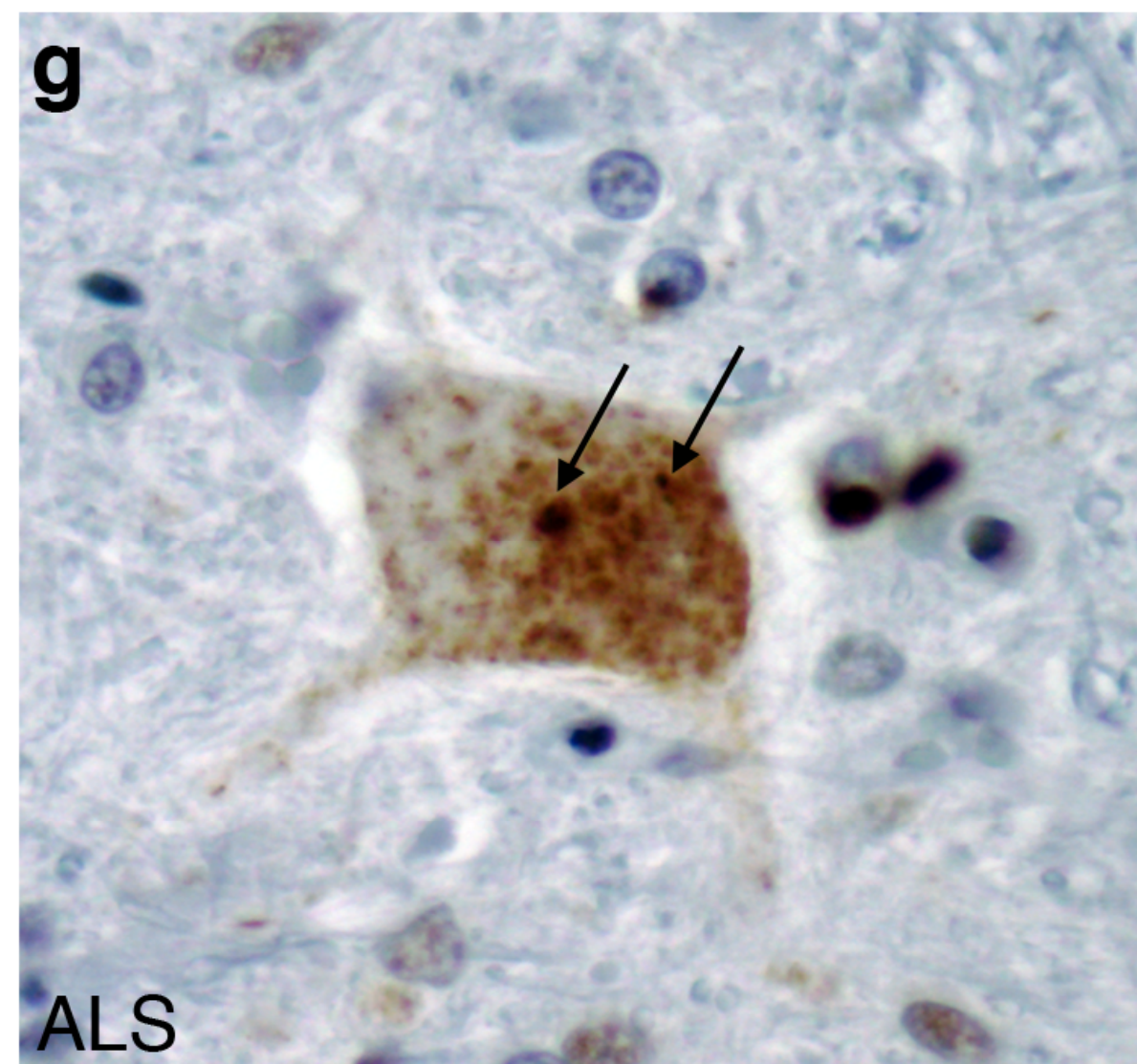
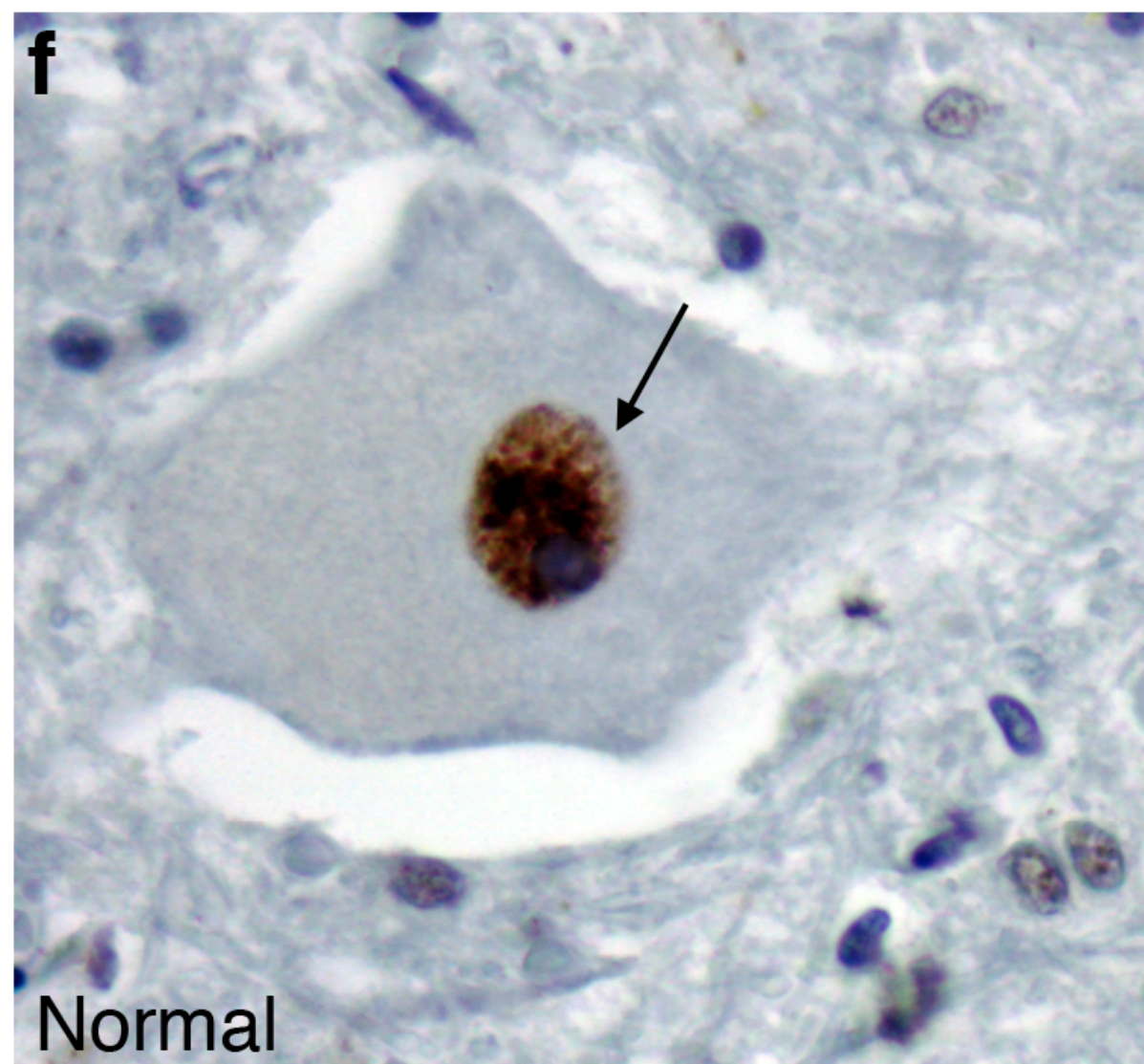
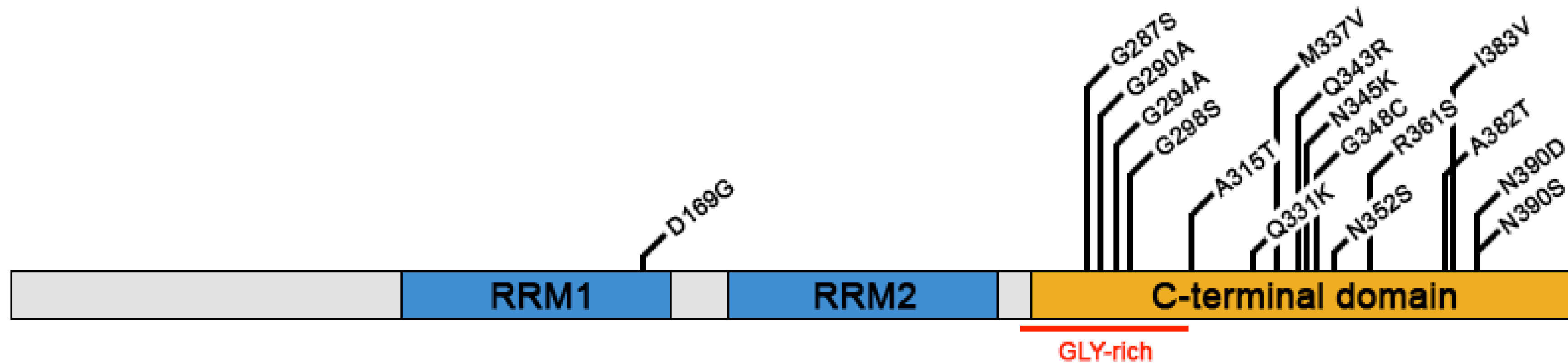
TDP-43 Mutations in Familial and Sporadic Amyotrophic Lateral Sclerosis

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*†}

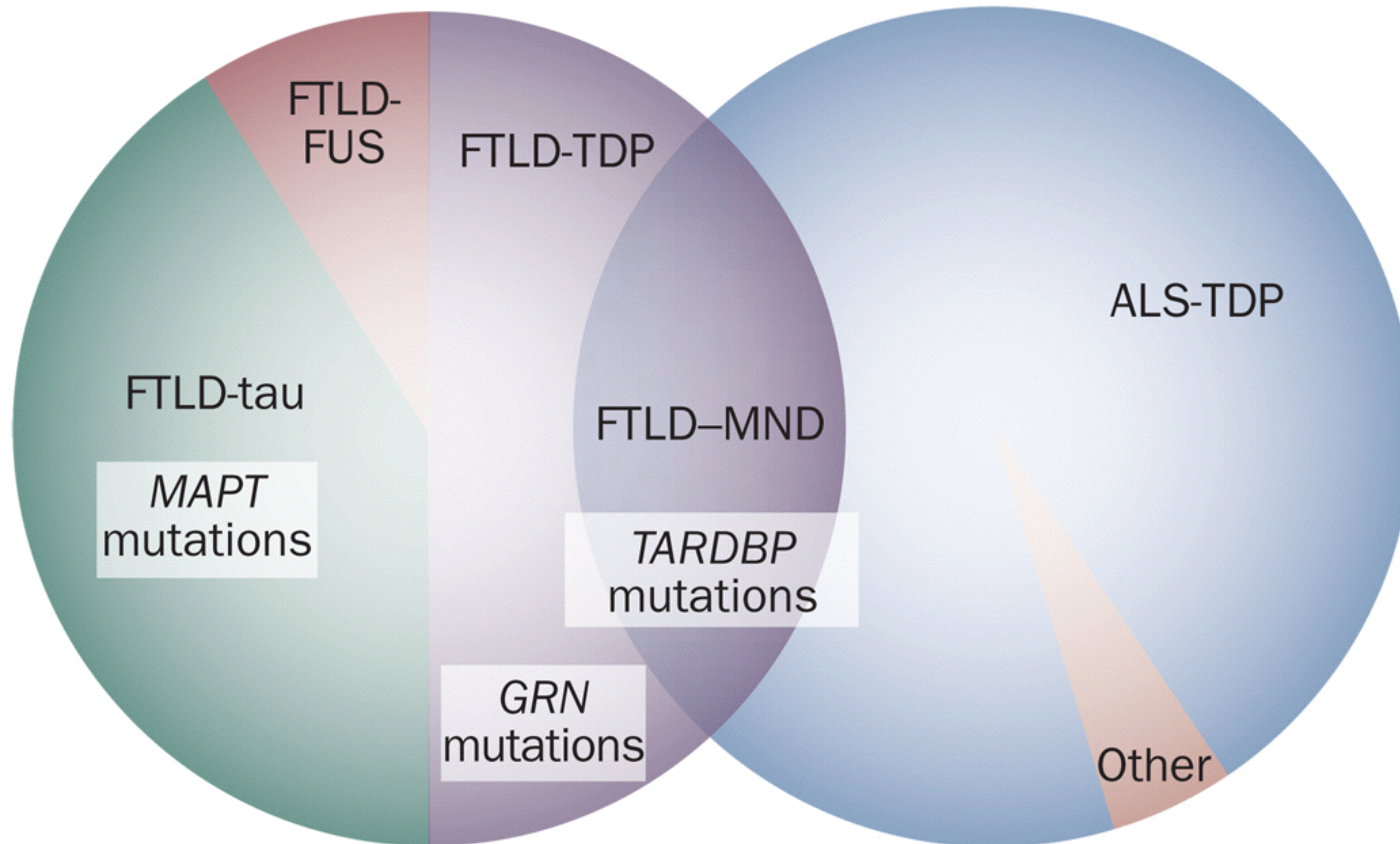
TARDBP mutations in amyotrophic lateral sclerosis with TDP-43 neuropathology: a genetic and histopathological analysis

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?



Pathological subtypes of FTLD and ALS



Mendelian Genes for ALS

Gene	Protein	Location	Inheritance
ANG	Angiogenin	14q11.2	dominant
ALS2	alsin	2q33.1	recessive
FIG4	SAC1 lipid phosphatase domain containing	6q21	recessive
FUS	Fused in sarcoma	16p11.2	both
OPTN	Optineurin	10p13	both
SETX	Senataxin	9q34.13	dominant
SOD1	Superoxide dismutase 1	21q22.11	both
SPG11	Spastic paraplegia 11	15q21.1	recessive
TARDBP	TDP-43	1p36.22	dominant
UBQLN2	Ubiquilin 2	Xp11.21	x-linked dominant
VAPB	VAMP	20q13.32	dominant
VCP	Valosin-containing protein	9p13.3	dominant
PFN1	profilin 1	17p13.3	dominant
C9ORF72	C9Orf72	9p21	dominant

~70% of FALS causative genes are now known
but only 5-10% of SALS causative genes are known

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.

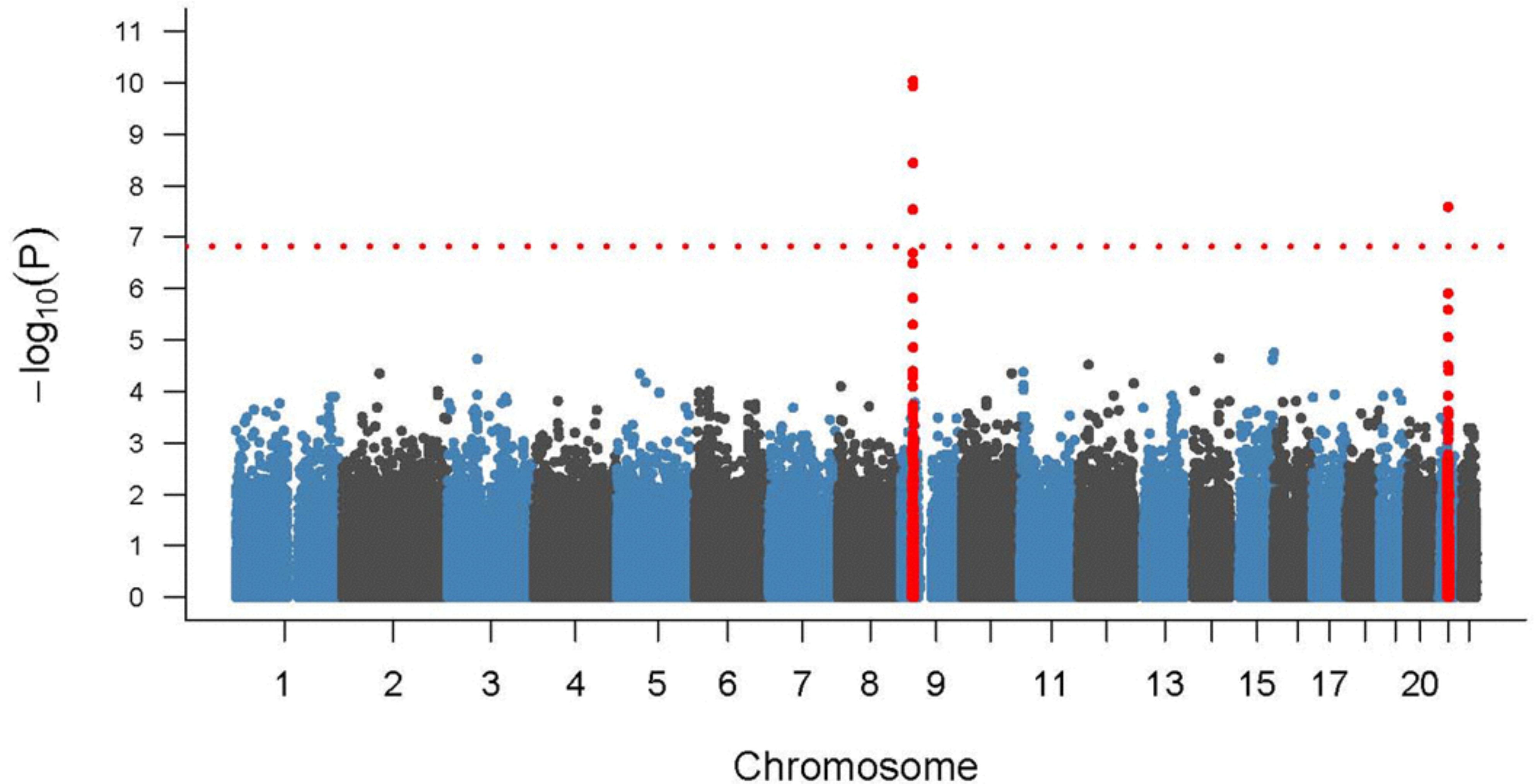
Susceptibility Loci for ALS

(Han Chinese)

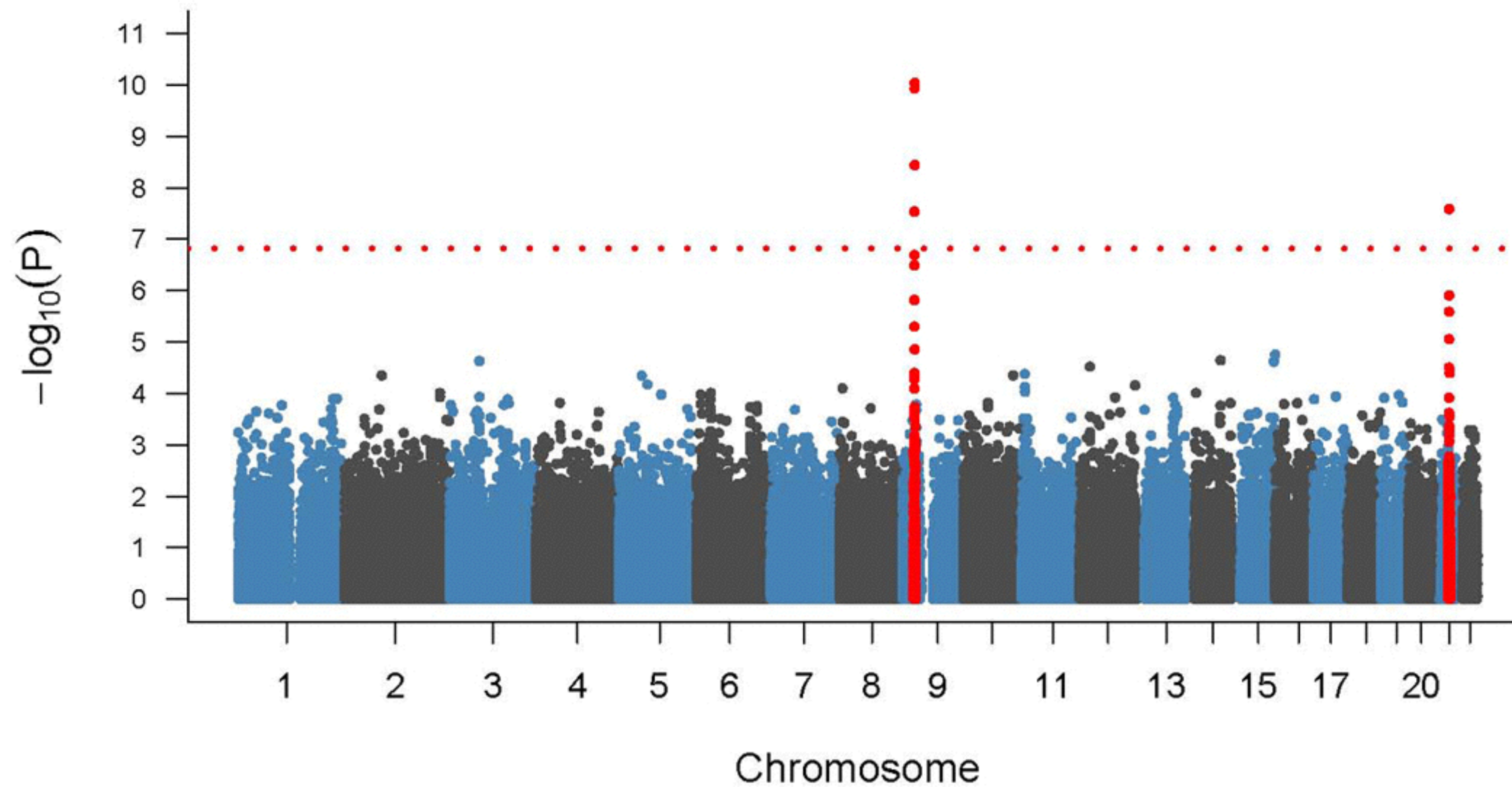
Gene	Protein	Location	Polymorphism	Odds Ratio
<i>CAMK1G</i>	CAMK1G	1q32	rs6703183	1.31
CABIN1 and SUSD2	Unknown	22p11	rs8141797	1.52

Deng et al., *Nat Genet* 2013

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



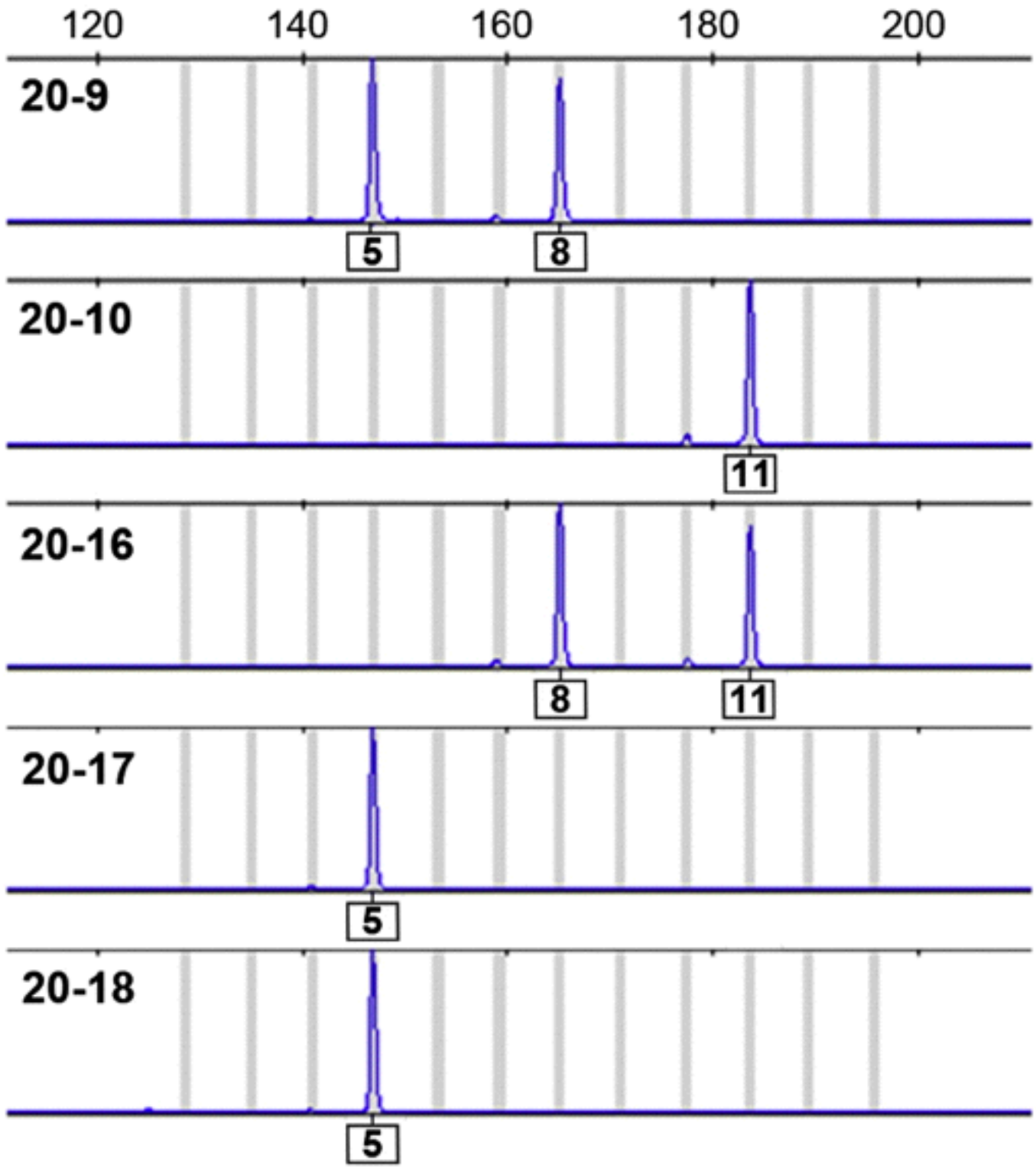
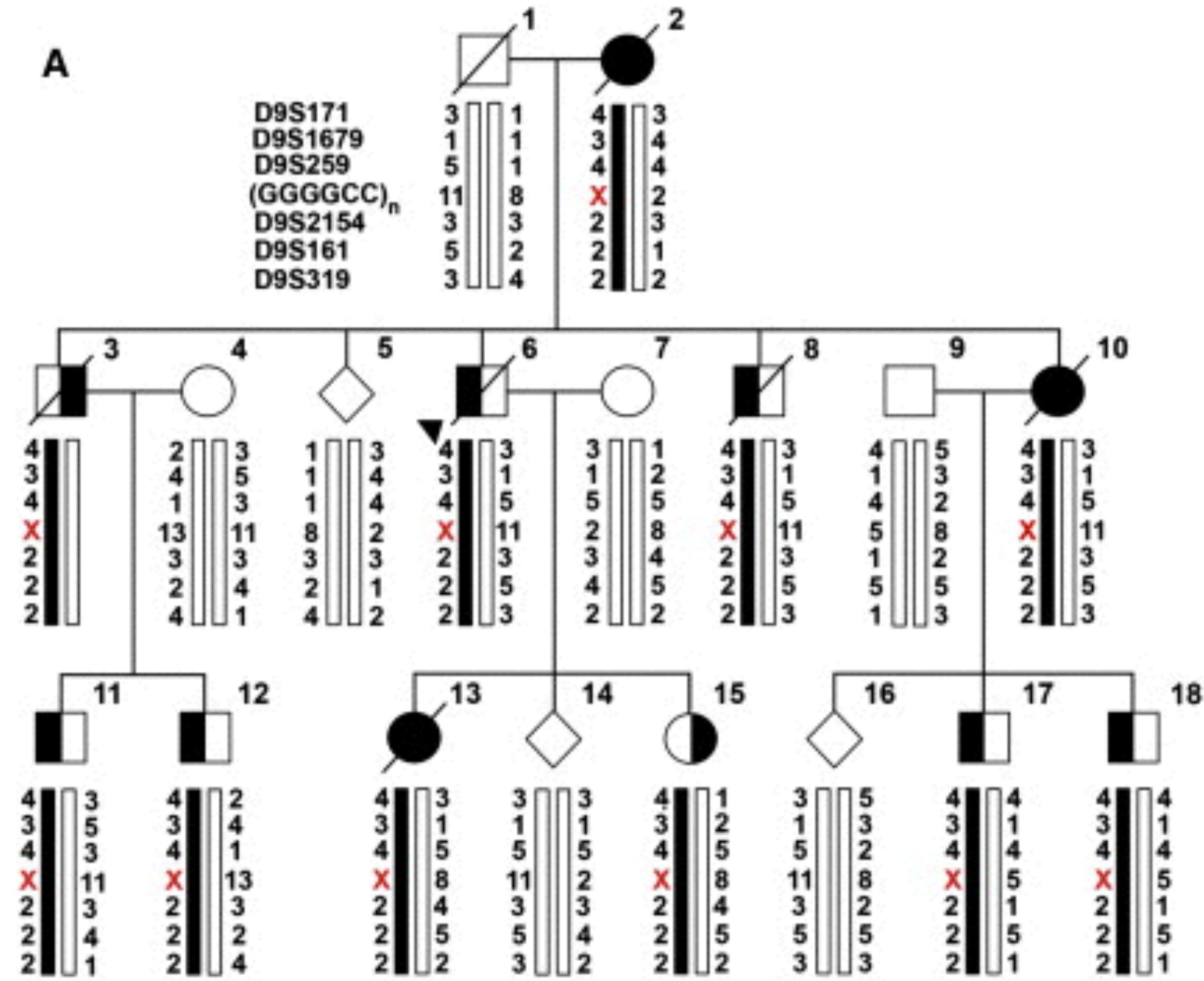
How would you identify the
mutated gene(s) on 9p21?

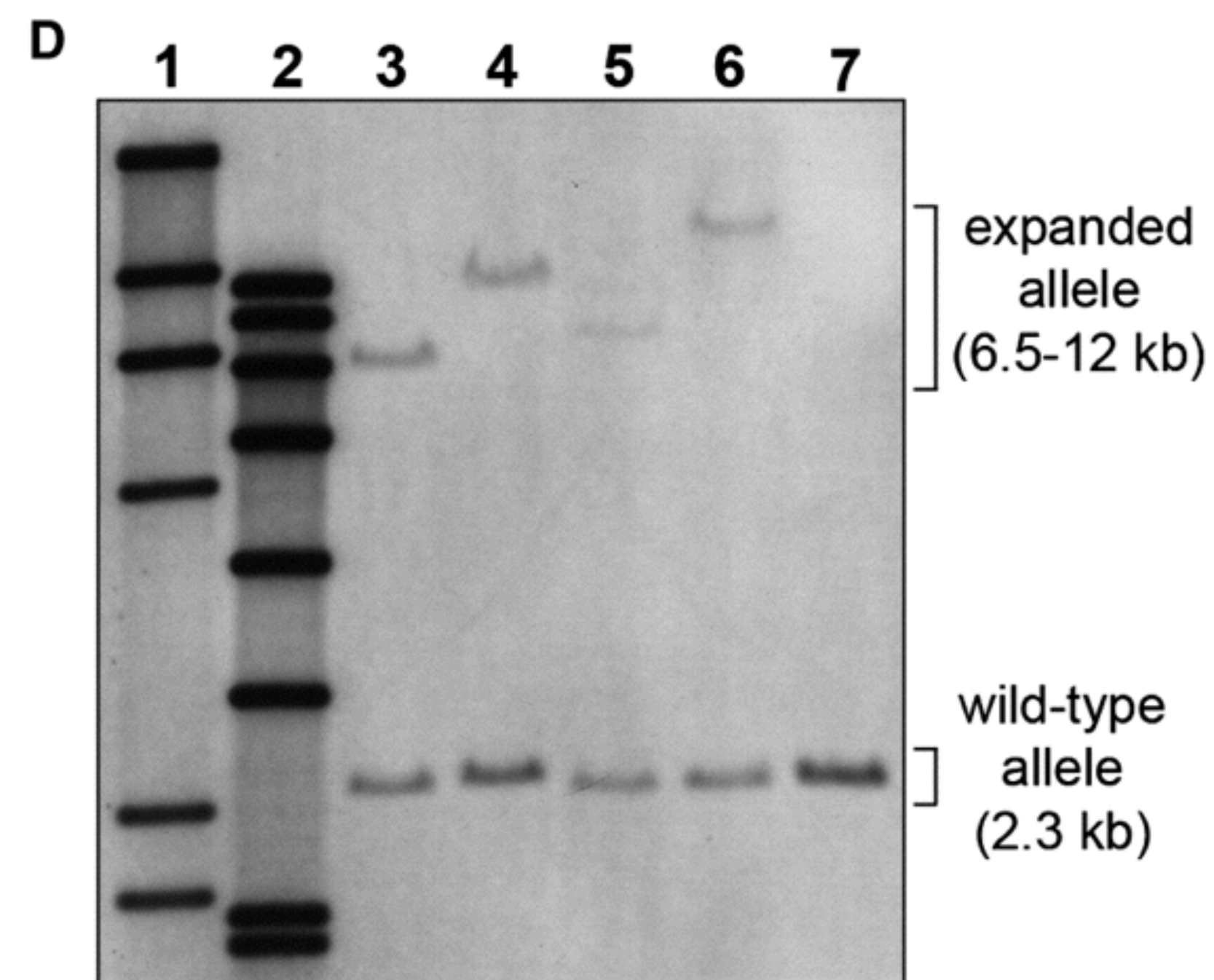
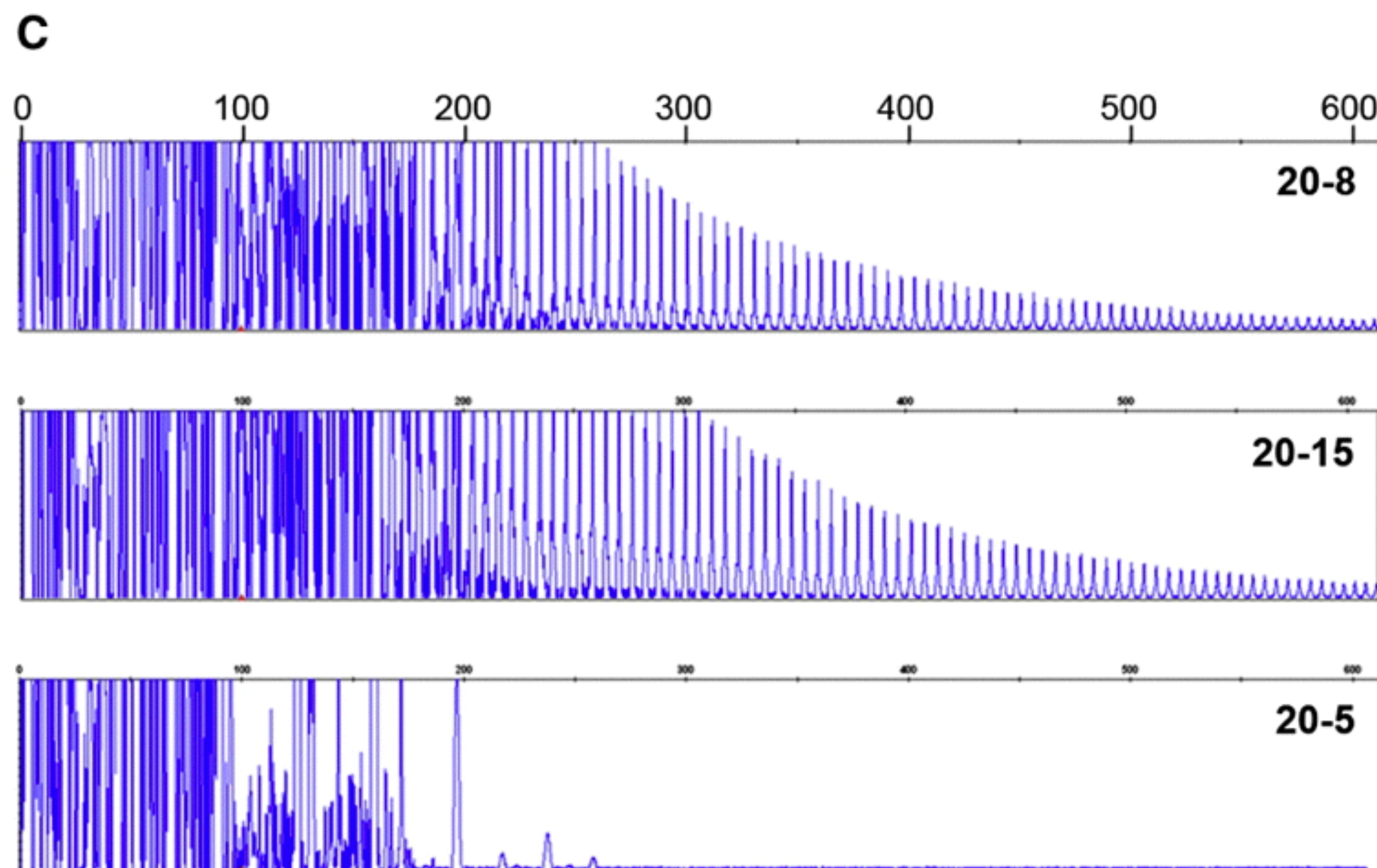
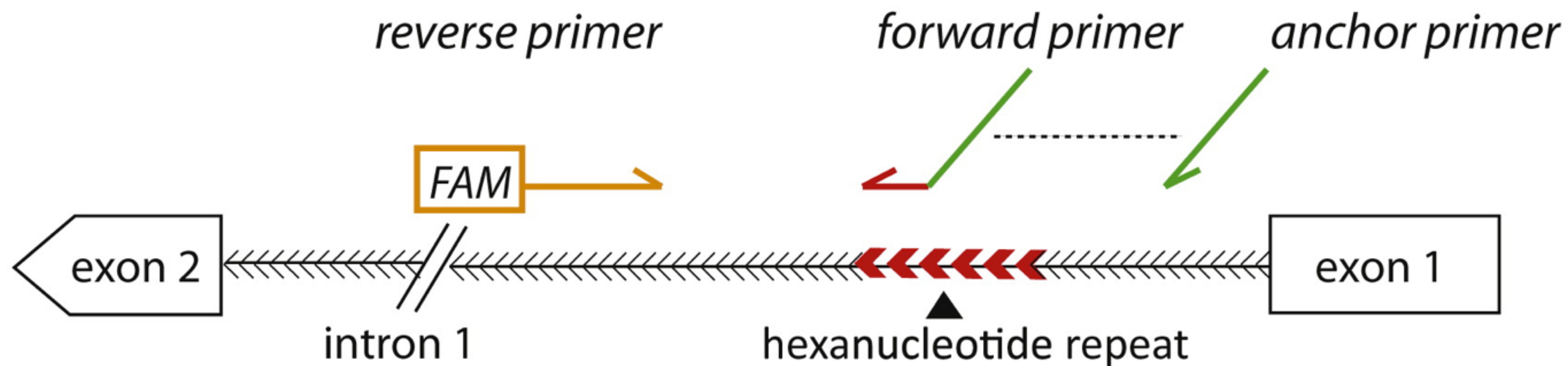


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GACCTGATAAAGATTAACCAAGAAGAAAACAAGGAGGGAAAC
AACCGCAGCCTGTAGCAAGCTCTGGAACCTCAGGAGTCGCG
CGCTAGGGGGCCGGGGGCCGGGGCCGGGGCGTGGTCCGGGG
CGGGCCCGGGGGCGGGCCCGGGGCGGGGGCTGCGGGTTGC
GGTGCCTGCGCCCGCGGCGGCGGAGGCGCAGGCGGGTGG
CGAGTGGGTGAGTG

CTCTTTTGGGGGCGGGGTCTAGCAAGAGCAGGTGTGGGT
TAGGAGGTGTGTGTTTTTGTTCACCTCTCTCCCA
CTACTTGCTCTCACAGTACTCGCTGAGGGTGAACAAGAAA
GACCTGATAAAGATTAACCAAGAAACAAAGGAGGGAAAC
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CGAGTGGGTGAGTG

CTCTTTTGGGGGCGGGGTCTAGCAAGAGCAGGTGTGGGTTTAGGAGGTGTGTGTTTTTGT
TTCCCACCCTCTCTCCCCACTACTTGCTCTCACAGTACTCGCTGAGGGTGAACAAGAAAAGA
CCTGATAAAGATTAACCAGAAGAAAACAAGGAGGGAAACAACCGCAGCCTGTAGCAAGCTCT
GGAAGTCAGGAGTCGCGCGCTA**GGGGCCGGGGCCGGGGCC**GGGGCGTGGTCGGGGCGGG
CCCGGGGGCGGGCCCGGGGCGGGGCTGCGGTTGCGGTGCCTGCGCCCGCGGGCGGGCGGA





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

Mariely DeJesus-Hernandez,^{1,10} Ian R. Mackenzie,^{2,10,*} Bradley F. Boeve,³ Adam L. Boxer,⁴ Matt Baker,¹ Nicola J. Rutherford,¹ Alexandra M. Nicholson,¹ NiCole A. Finch,¹ Heather Flynn,⁵ Jennifer Adamson,¹ Naomi Kouri,¹ Aleksandra Wojtas,¹ Pheth Sengdy,⁶ Ging-Yuek R. Hsiung,⁶ Anna Karydas,⁴ William W. Seeley,⁴ Keith A. Josephs,³ Giovanni Coppola,⁷ Daniel H. Geschwind,⁷ Zbigniew K. Wszolek,⁸ Howard Feldman,^{6,9} David S. Knopman,³ Ronald C. Petersen,³ Bruce L. Miller,⁴ Dennis W. Dickson,¹ Kevin B. Boylan,⁸ Neill R. Graff-Radford,⁸ and Rosa Rademakers^{1,*}

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¹⁰These authors contributed equally to this work

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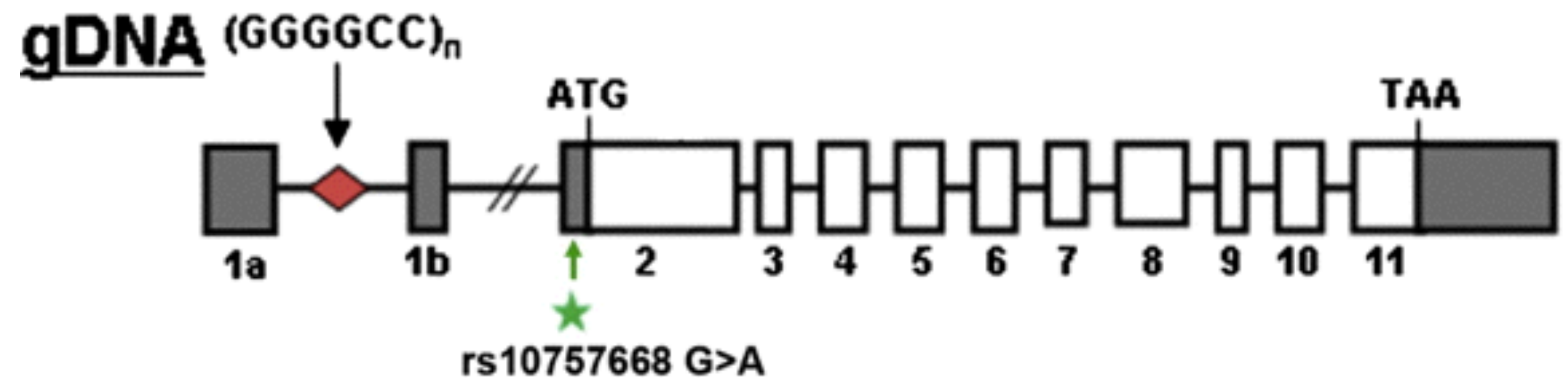
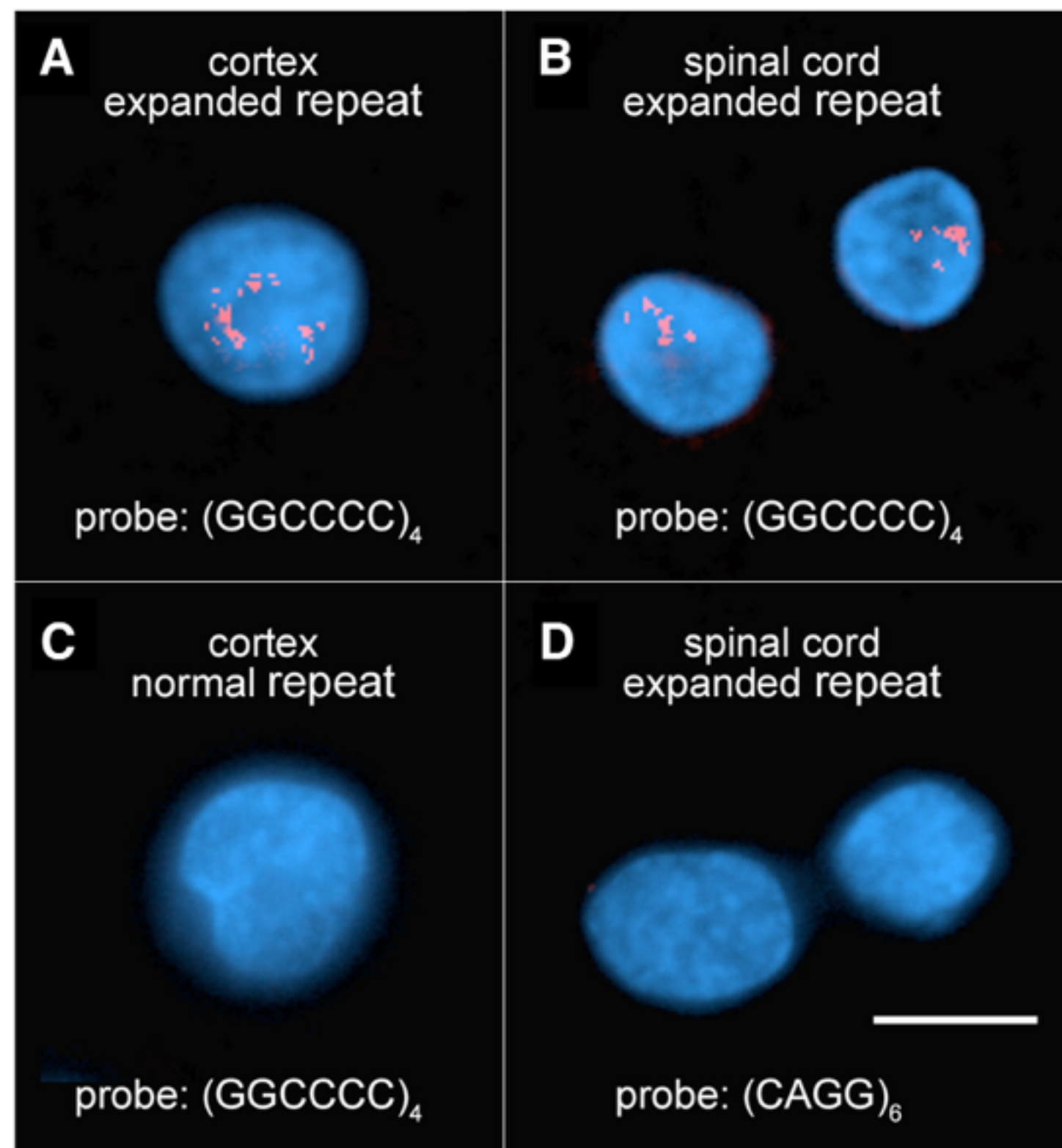
DOI 10.1016/j.neuron.2011.09.011

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. Kristen Powers and Katie Moser
2. Alzheimer's Disease (Gitler)
3. Frontotemporal Dementia (Gitler)
4. Amyotrophic lateral sclerosis (ALS)
(Gitler)
5. Parkinson's Disease (Chuang)

Parkinson's Disease

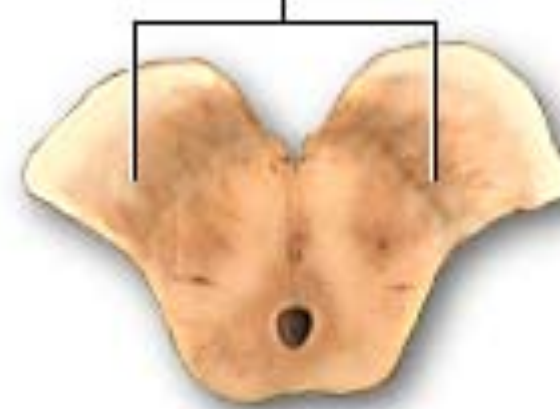


Cut section
of the midbrain
where a portion
of the substantia
nigra is visible

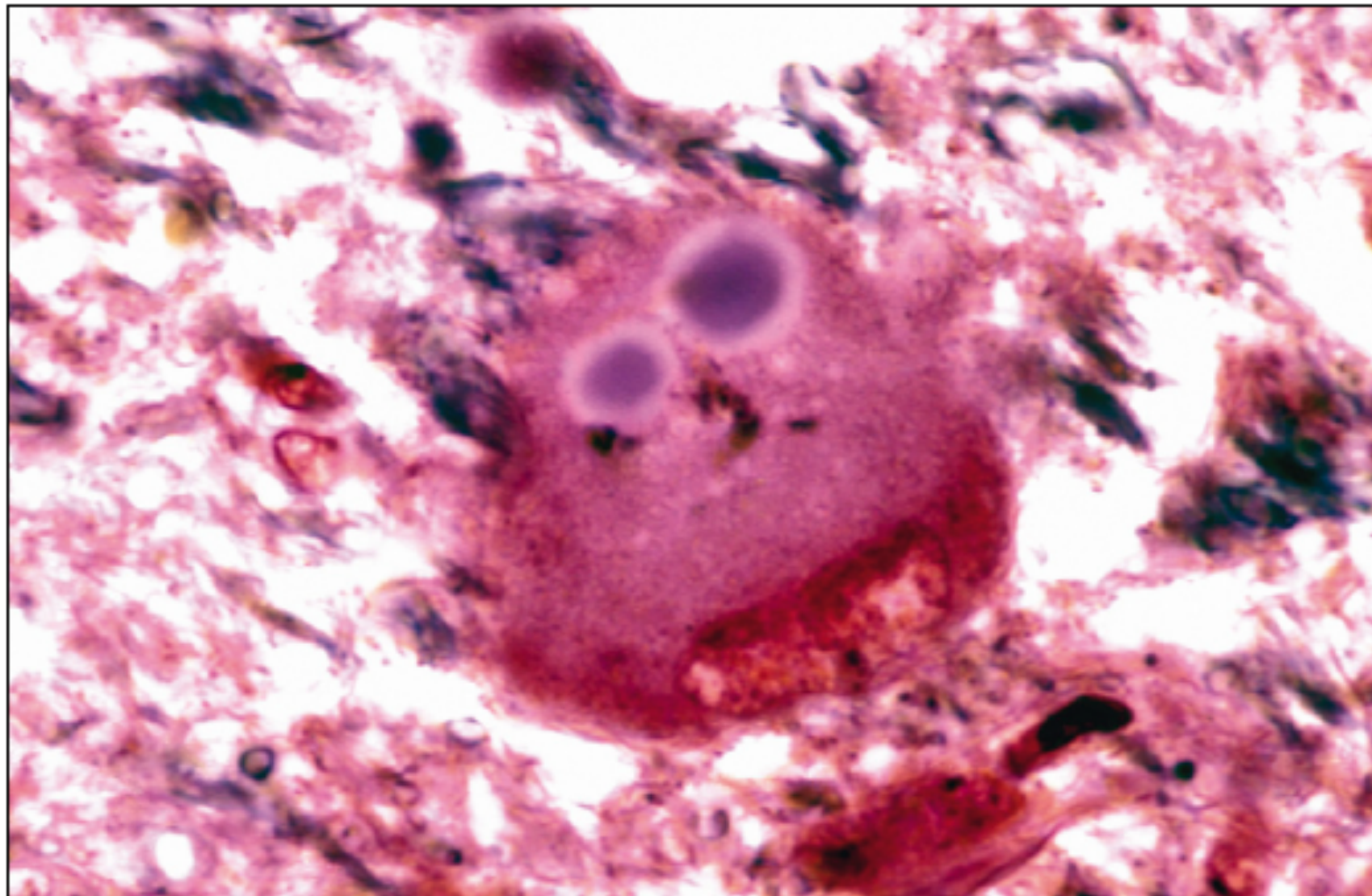
Substantia nigra



Diminished substantia
nigra as seen in
Parkinson's disease



ADAM.

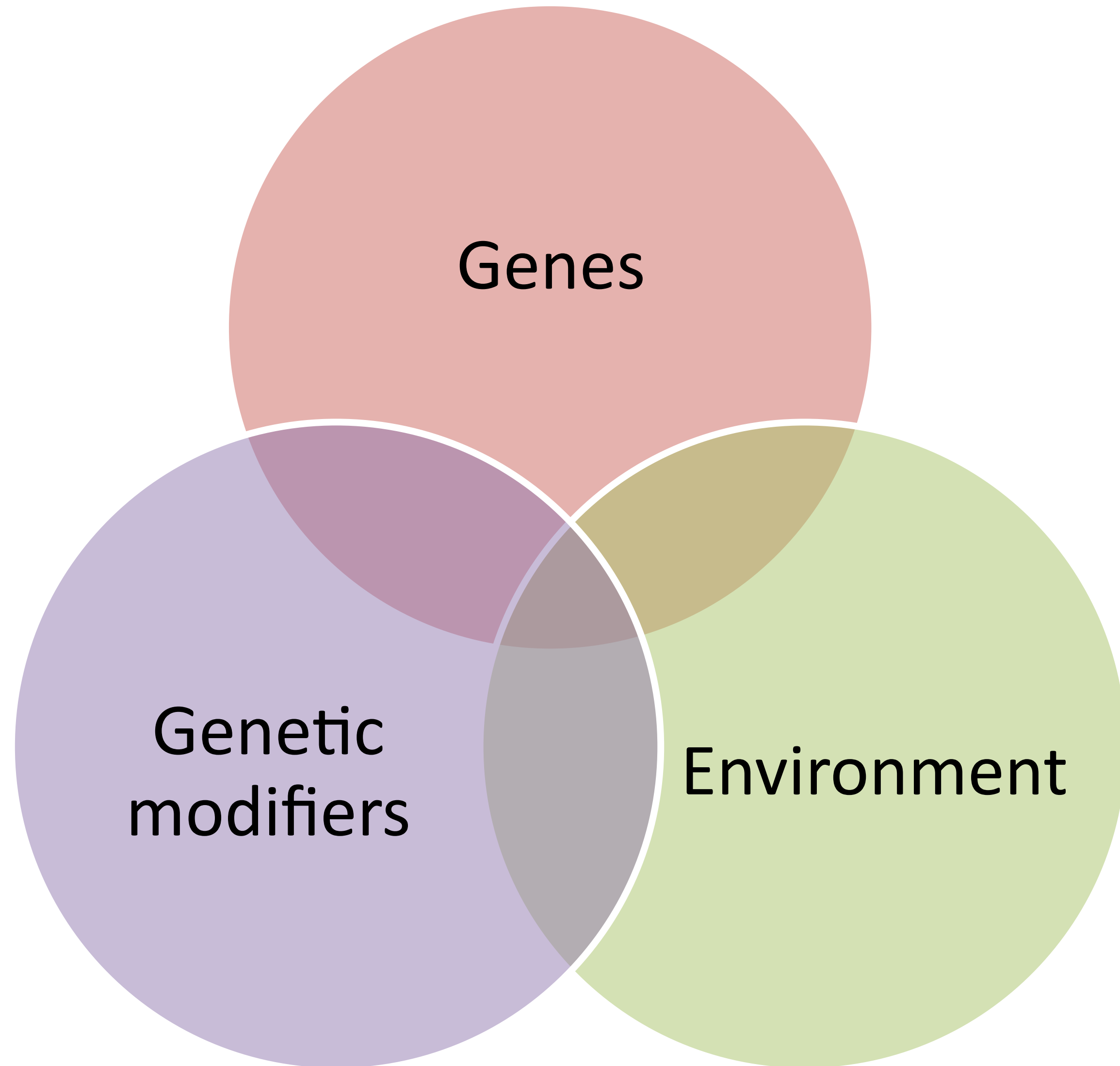


Science Photo Library

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



What causes Parkinson's Disease?



Using genome-wide complex trait analysis to quantify ‘missing heritability’ in Parkinson’s disease

Margaux F. Keller^{1,2}, Mohamad Saad^{3,4}, Jose Bras⁵, Francesco Bettella⁷, Nayia Nicolaou⁸, Javier Simón-Sánchez⁸, Florian Mittag³, Finja Büchel³, Manu Sharma^{9,10}, J. Raphael Gibbs^{1,5}, Claudia Schulte^{9,10}, Valentina Moskvina^{11,12}, Alexandra Durr^{13,14,15,16}, Peter Holmans^{11,12}, Laura L. Kilarski^{11,12}, Rita Guerreiro⁵, Dena G. Hernandez^{1,5}, Alexis Brice^{13,14,15,16}, Pauli Ylikotila¹⁷, Hreinn Stefánsson⁷, Kari Majamaa¹⁸, Huw R. Morris^{11,12}, Nigel Williams^{11,12}, Thomas Gasser^{9,10}, Peter Heutink⁷, Nicholas W. Wood^{5,6}, John Hardy⁵, Maria Martinez^{3,4}, Andrew B. Singleton¹ and Michael A. Nalls^{1,*} for the International Parkinson’s Disease Genomics Consortium (IPDGC) and The Wellcome Trust Case Control Consortium 2 (WTCCC2)[†]

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ORIGINAL RESEARCH ARTICLE

**Genetics
in Medicine**

Risk prediction for complex diseases: application to Parkinson disease

Taryn O. Hall, MPH¹, Jia Y. Wan, MS², Ignacio F. Mata, PhD³, Kathleen F. Kerr, PhD⁴, Katherine W. Snapinn, MS², Ali Samii, MD³, John W. Roberts, MD⁵, Pinky Agarwal, MD⁶, Cyrus P. Zabetian, MD, MS³ and Karen L. Edwards, PhD^{1,2}

Parkinson's Disease Heritability

- Overall heritability is estimated at 0.27
- Currently known variants account for ~10% of heritability
- Best current predictor of PD is family history rather than genetics
 - Family history incorporates additional genetic risk factors different from risk factors identified by current GWAS

Parkinson's Disease

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

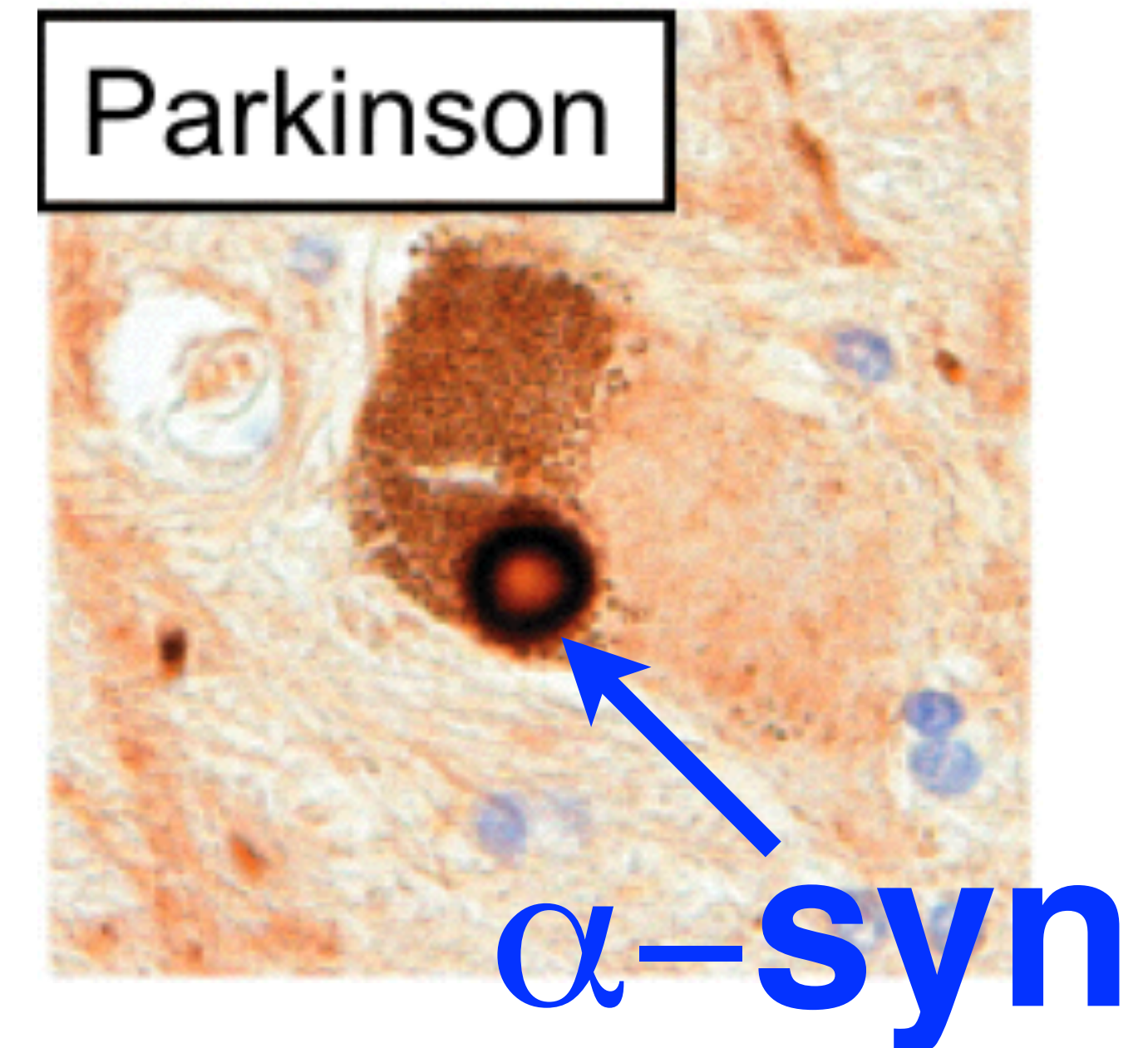
*Some papers suggest 5-10% of PD patients have a gene mutation

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

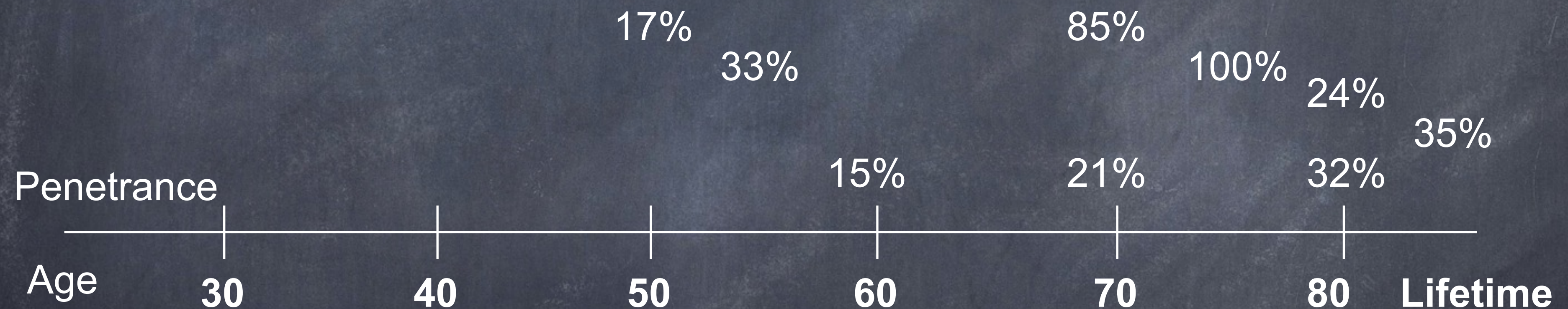
Locus	Chromosomal Location	Protein	Function	Inheritance
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<i>PARK9</i>	1p36	ATP13A2	Transmembrane Cationic ATPase	recessive

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
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<i>PARK4</i>	4p15*			
<i>PARK5</i>	4p14	UCH-L1	Ubiquitin C-terminal hydrolase	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, Tatsuishi 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?

