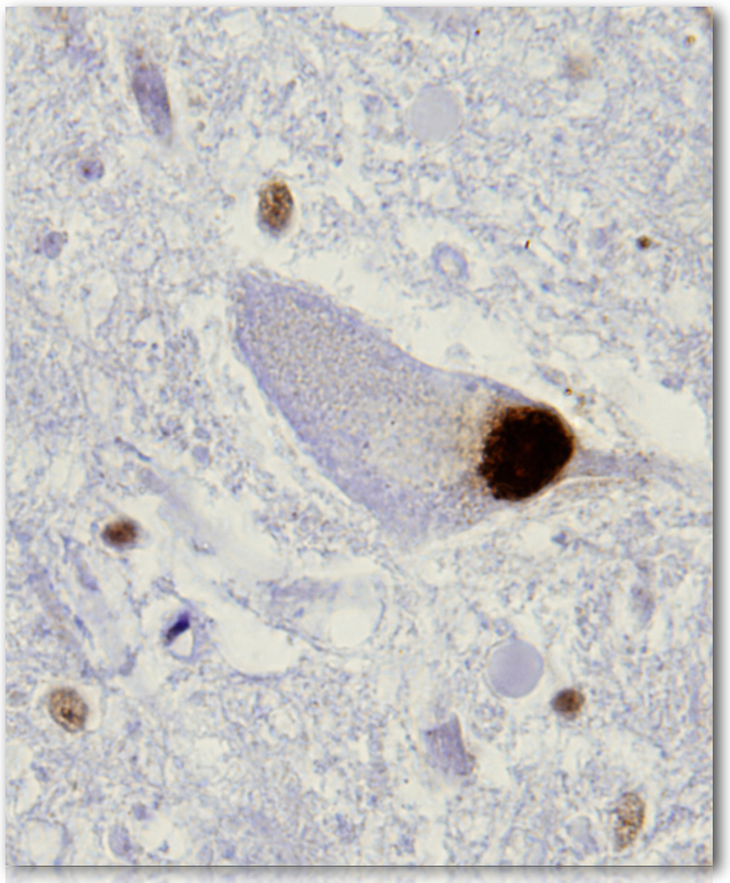
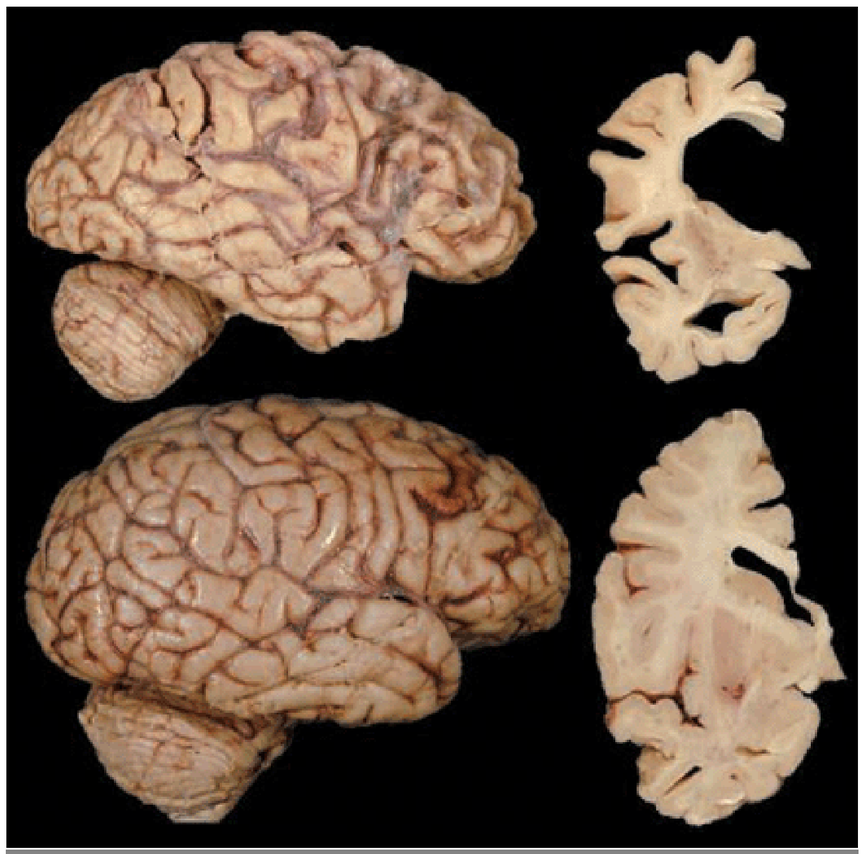
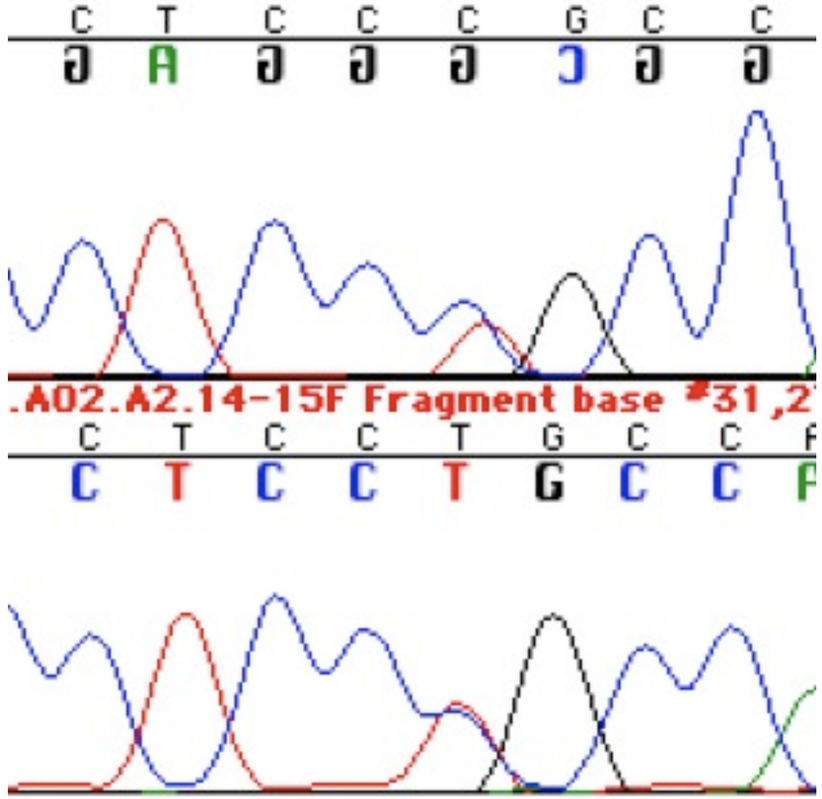
Genetics of human neurodegenerative disease

Aaron D. Gitler, Ph.D.
Rosalind Chuang, M.D.







Today's Plan

1. Kristen Powers and Katie Moser

2. Alzheimer's Disease (Gitler)

3. Frontotemporal Dementia (Gitler)

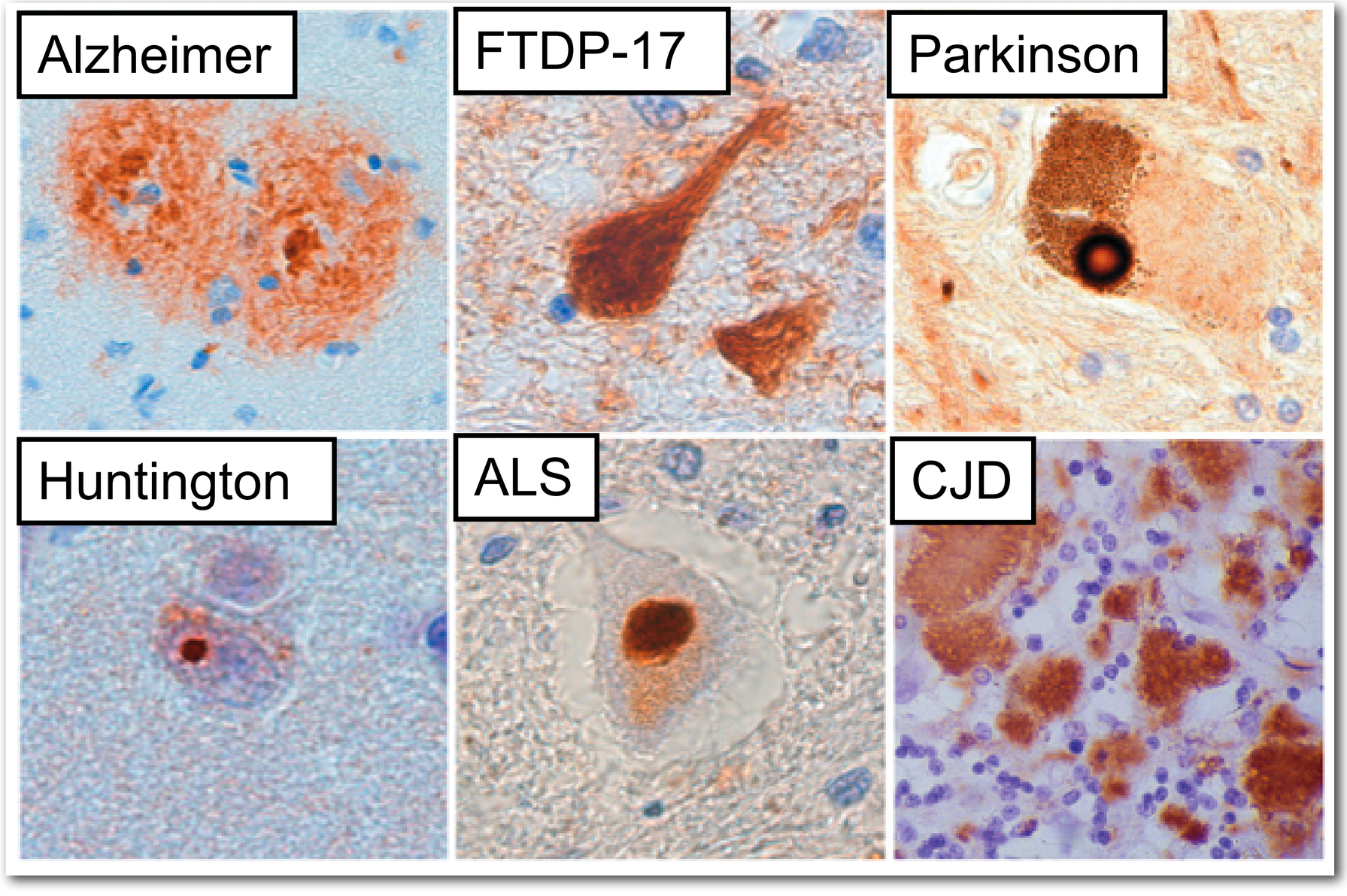
4. Amyotrophic lateral sclerosis (ALS) (Gitler)

5. Parkinson's Disease (Chuang)

Neurodegenerative Diseases

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

Protein Aggregates in Neurodegenerative Diseases



Adapted from Forman, Trojanowski, and Lee 2004

Protein Aggregates in Neurodegenerative Diseases

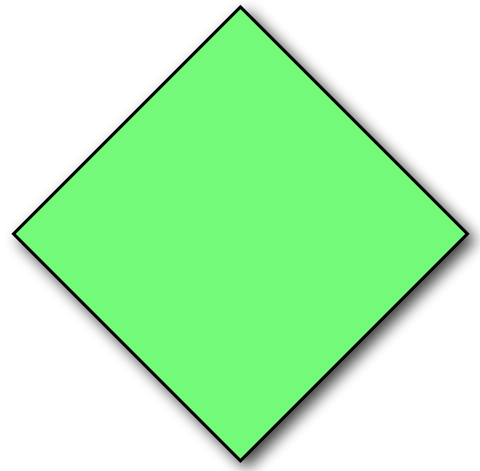
Protein Aggregates in Neurodegenerative Diseases

Normal Protein

Protein Aggregates in Neurodegenerative Diseases

Normal Protein

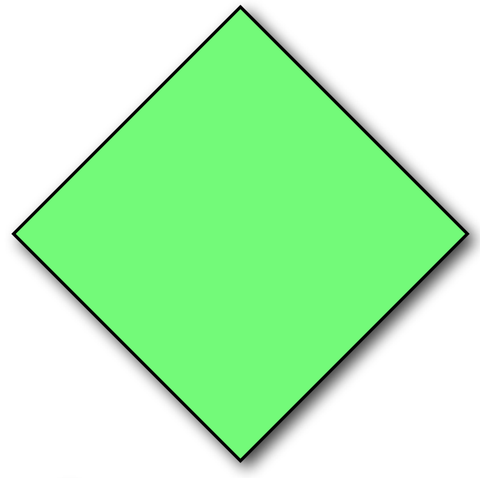
Misfolded Protein

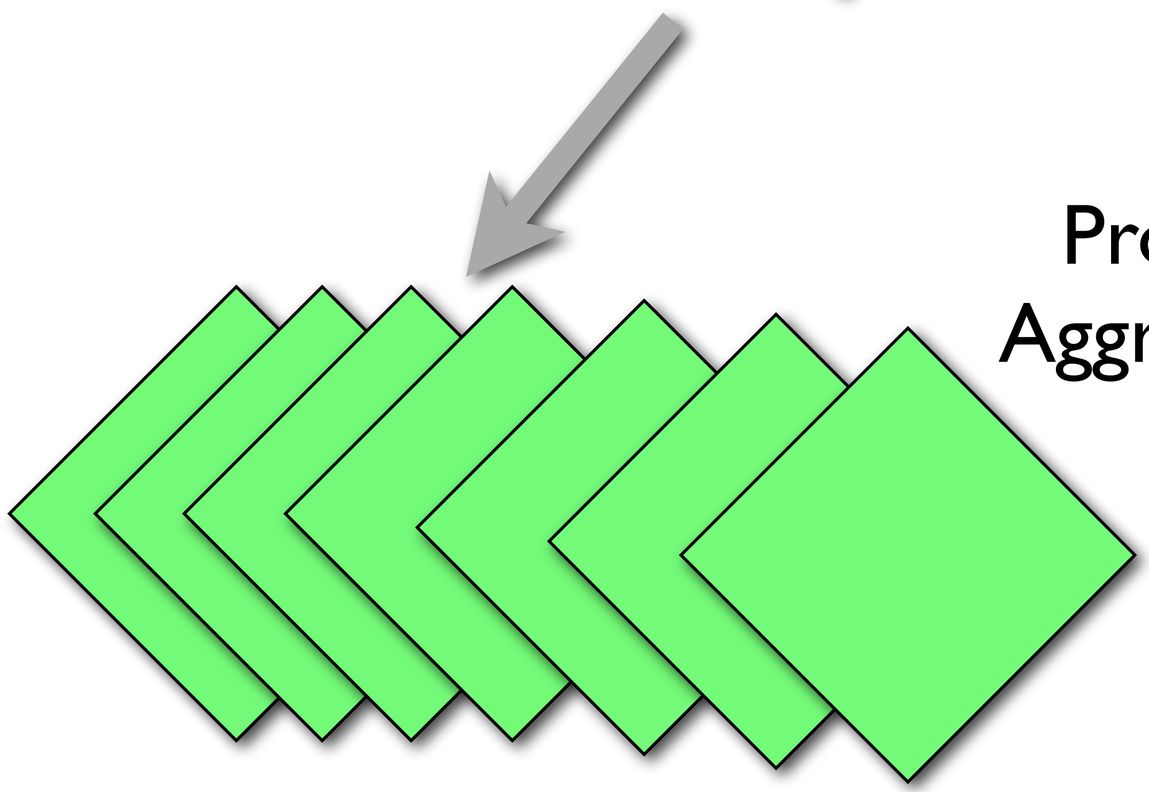


Protein Aggregates in Neurodegenerative Diseases

Normal Protein

Misfolded Protein





Protein
Aggregates

Protein Aggregates in Neurodegenerative Diseases

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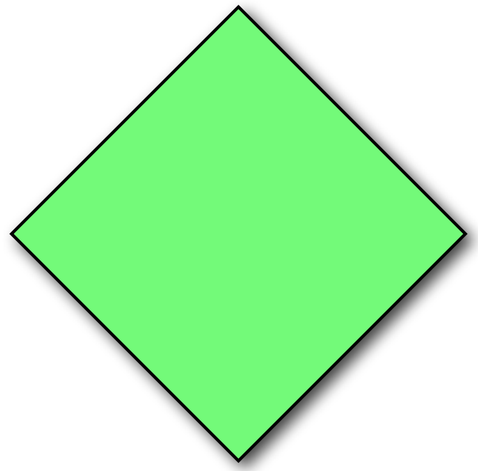
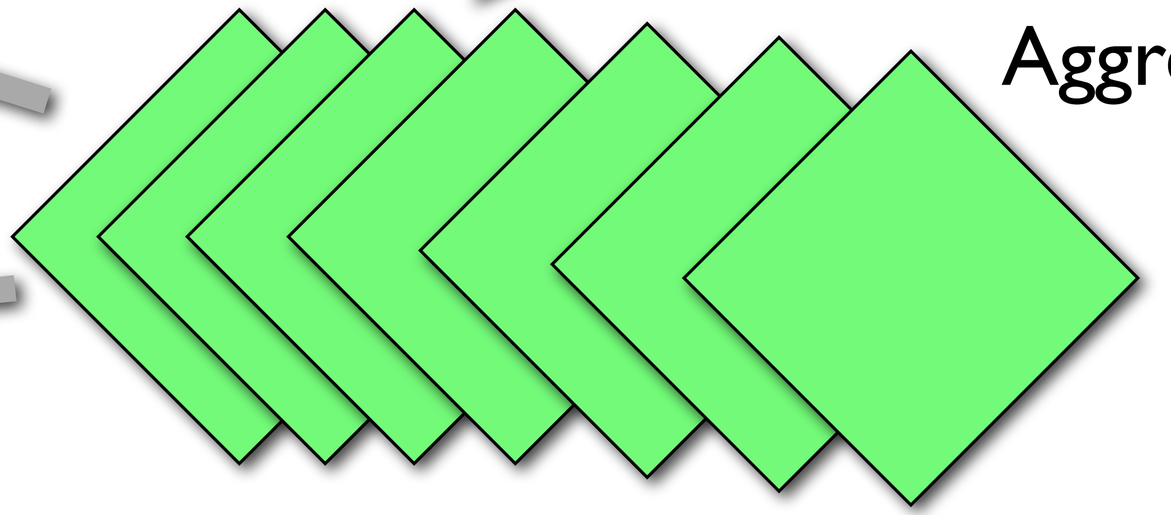


Loss of Protein's Normal Function

Toxic Gain of Function



Protein Aggregates

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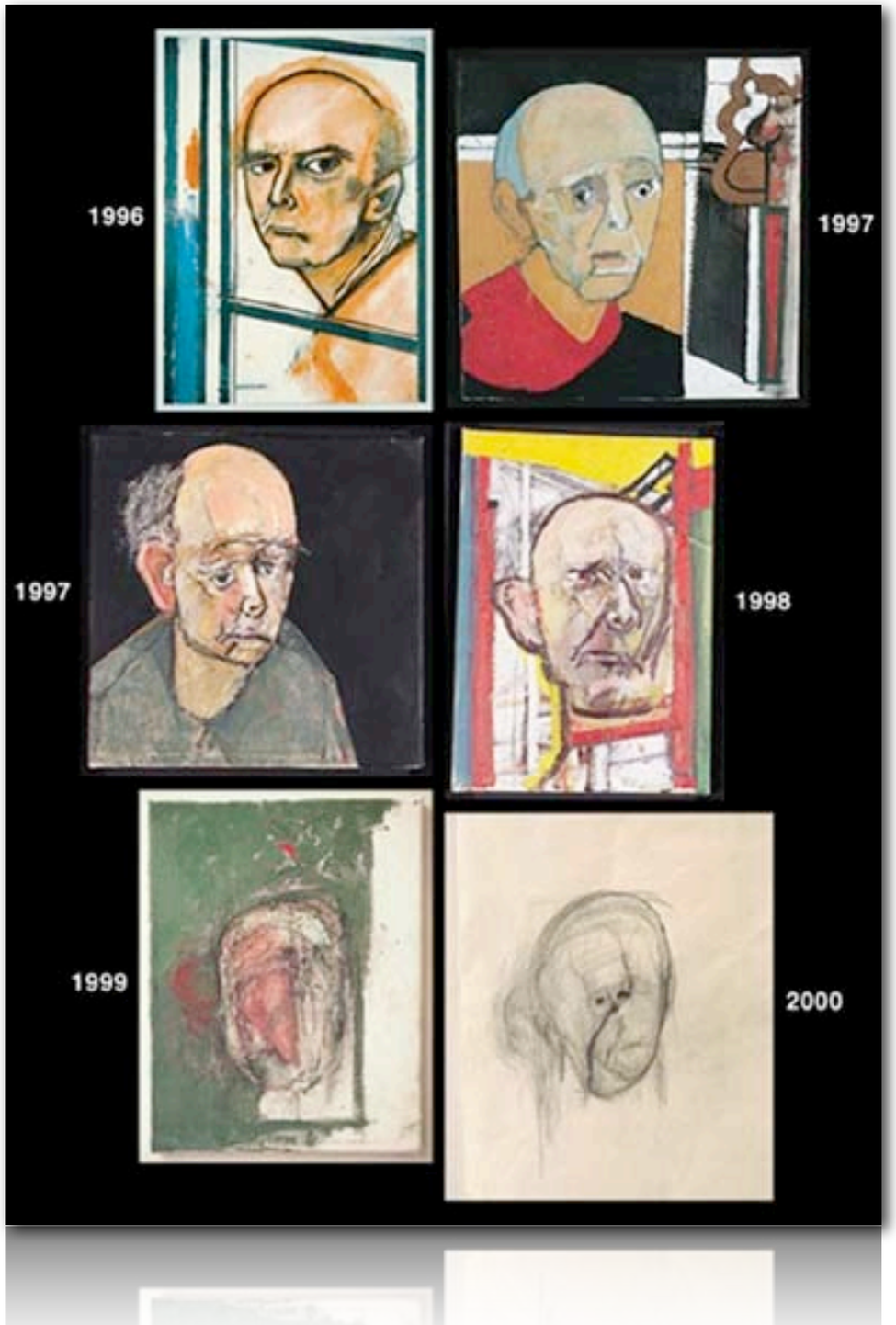
Alzheimer's Disease

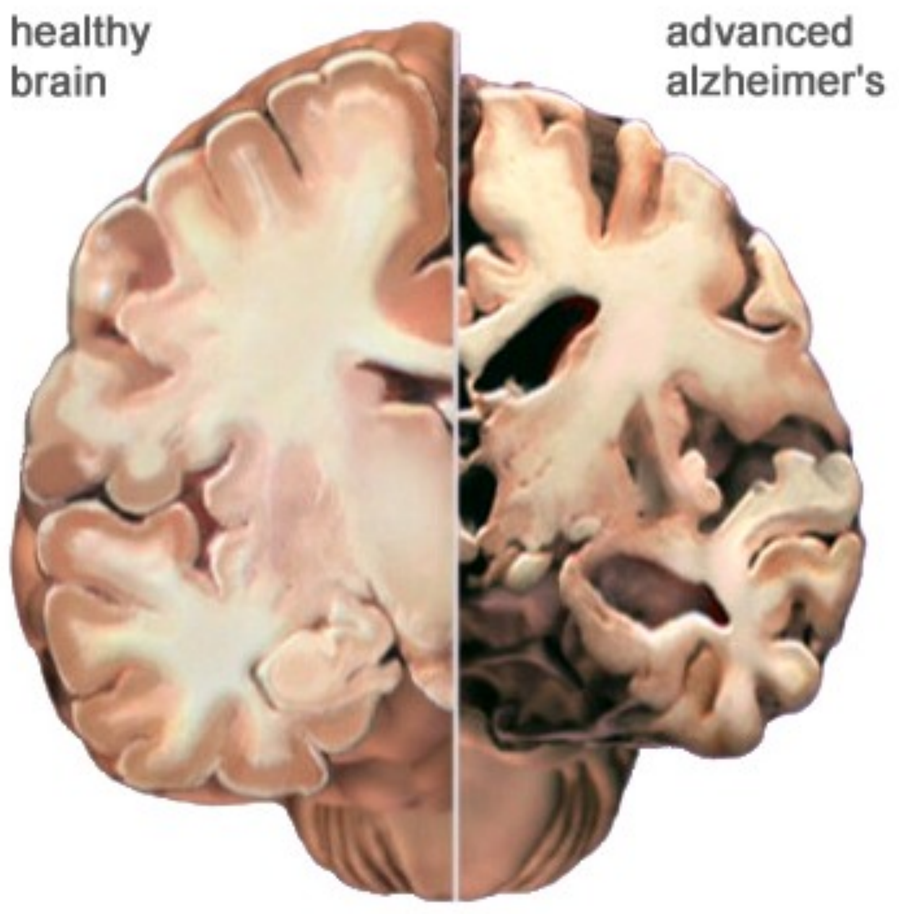


Artist charts his slide into dementia

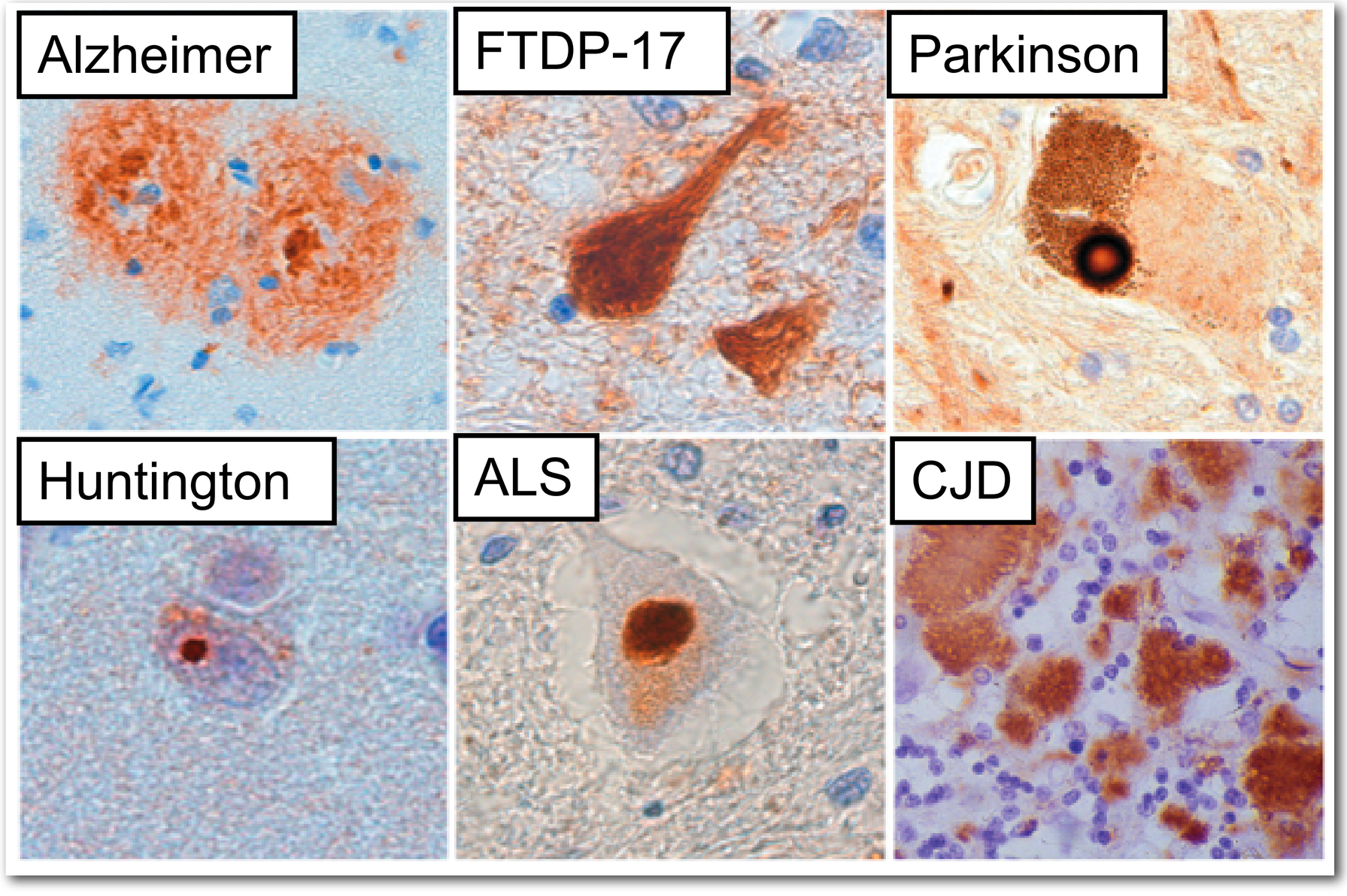
Six self-portraits by artist William Utermohlen chronicle his experience with Alzheimer's disease.

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?



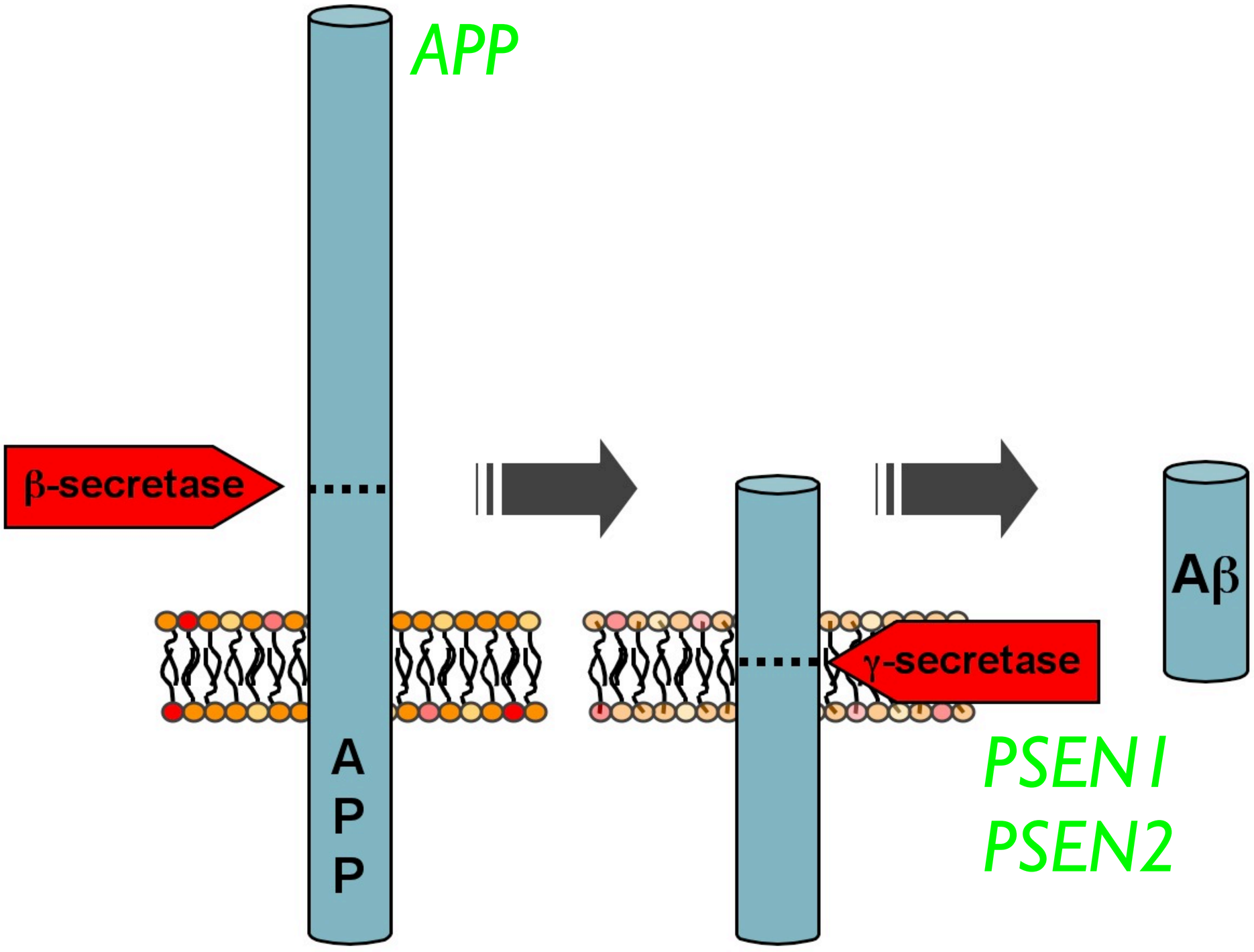
Protein Aggregates in Neurodegenerative Diseases



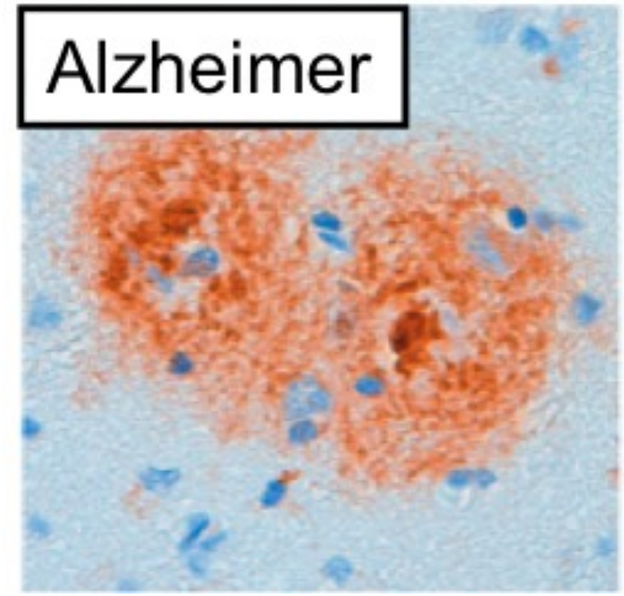
Adapted from Forman, Trojanowski, and Lee 2004

Mendelian Genes for Alzheimer's Disease

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


APP
β-secretase
APP
γ-secretase
Aβ
PSEN I
PSEN2

Alzheimer



APP

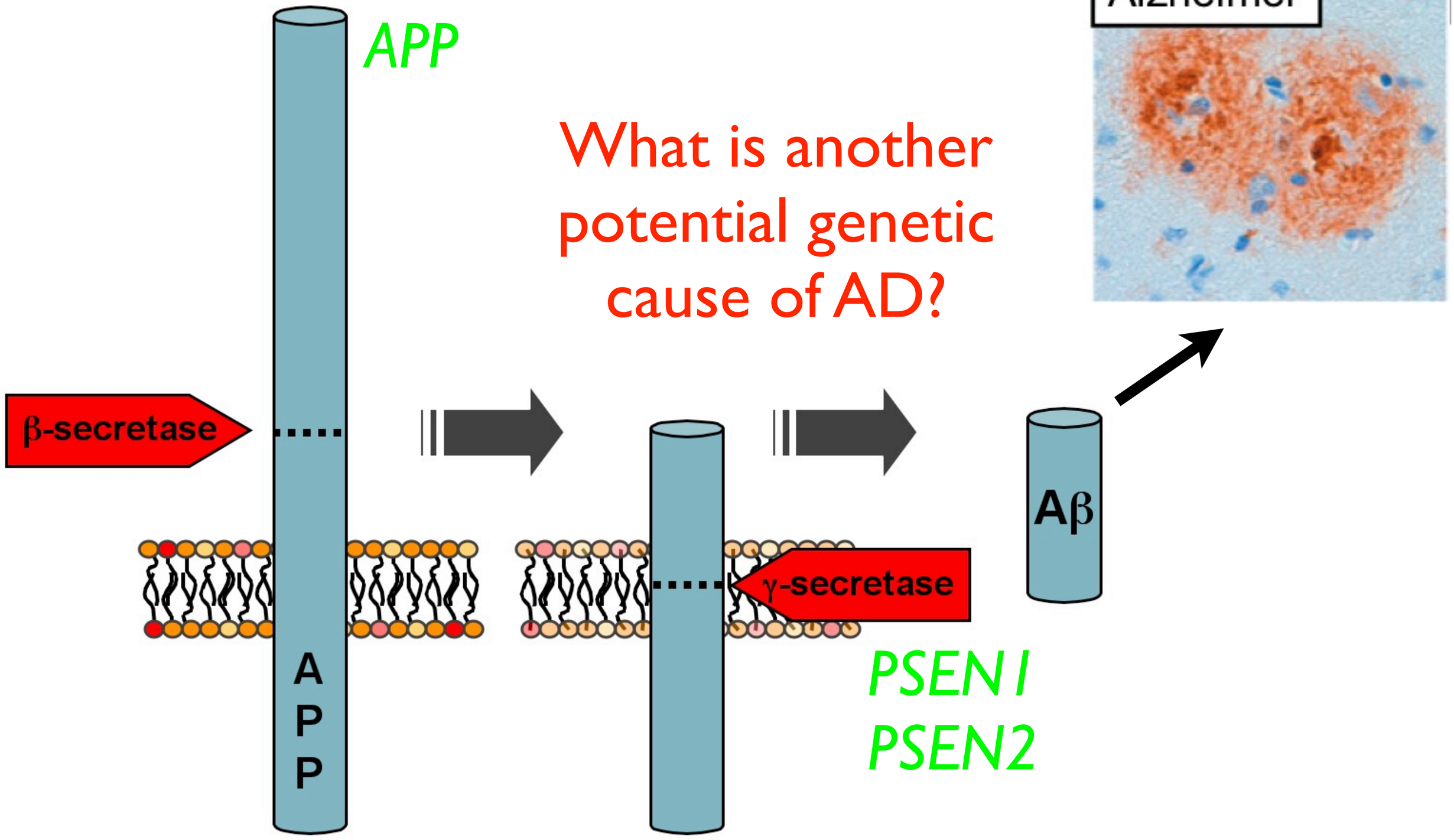
β-secretase

A
P
P

γ-secretase

Aβ

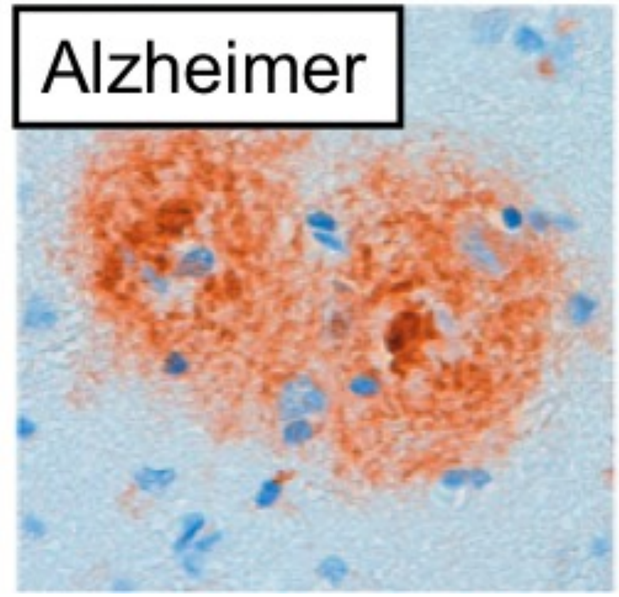
PSEN I
PSEN2

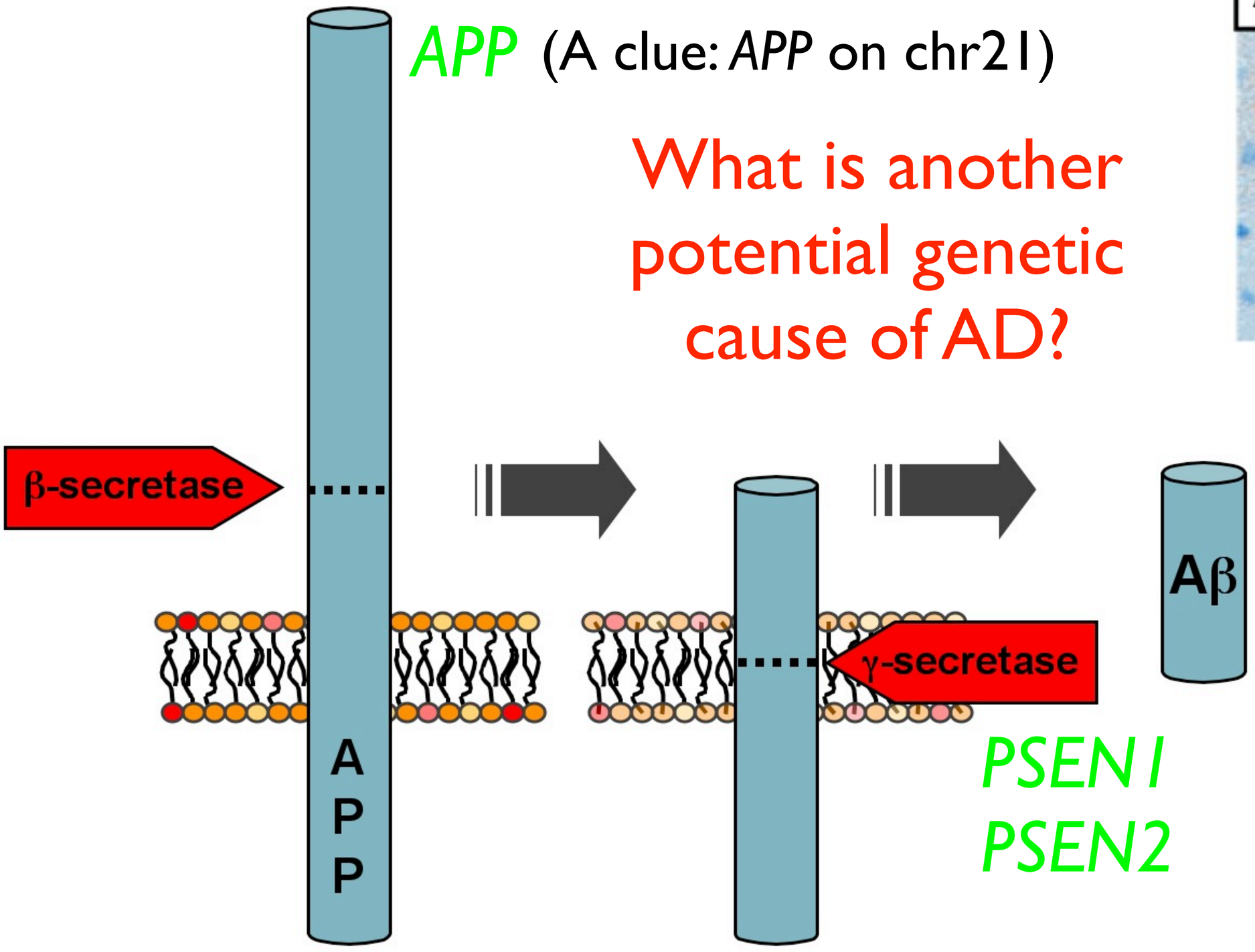


What is another potential genetic cause of AD?

APP (A clue: *APP* on chr21)

What is another potential genetic cause of AD?





PSEN1
PSEN2

Susceptibility Loci for Alzheimer's Disease

Gene	Protein	Polymorphism	OR (95% CI)
ABCA7	ATP-binding cassette, A7	rs3764650	1.23 (1.18-1.28)
APOE	Apolipoprotein E	rs429358 (E4)	3.81 (3.37-4.30)
BIN1	Bridging integrator 1	rs744373	1.17 (1.13-1.2)
CD2AP	CD2-associated protein	rs9349407	1.12 (1.08-1.16
CD33	CD33 molecule (siglec 3)	rs3865444	1.12 (1.08-1.16
CLU	Clusterin	rs1136000	1.14 (1.11-1.17)
CR1	Complement component receptor	rs3818361	1.17 (1.14-1.21)
MS4A4E	Membrane-spanning 4-domain A4E	rs670139	1.08 (1.05-1.11)
MS4A6A	Membrane-spanning 4-domain A6A	rs610932	1.11 (1.07-1.14)
PICALM	Phosphatidylinositol binding clathrin assembly protein	rs3851179	1.14 (1.11-1.17)

Two SNPs determine APOE variants

Variant	rs429358	rs7412
ε2	T	T
ε3	T	C
ε4	C	C

1 copy of ε4 allele = ~2 times increased risk for AD

2 copies of ε4 allele = ~11 times increased risk for AD

ORIGINAL ARTICLE

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

ORIGINAL ARTICLE

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

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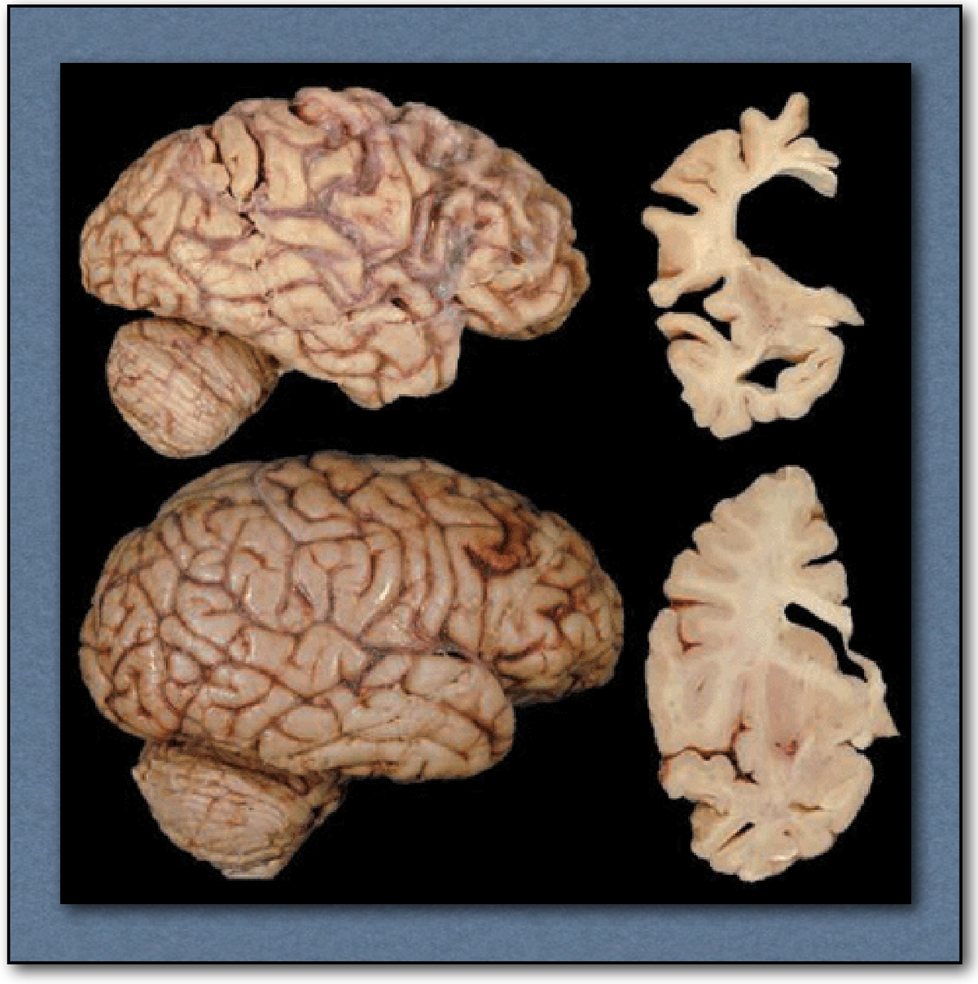
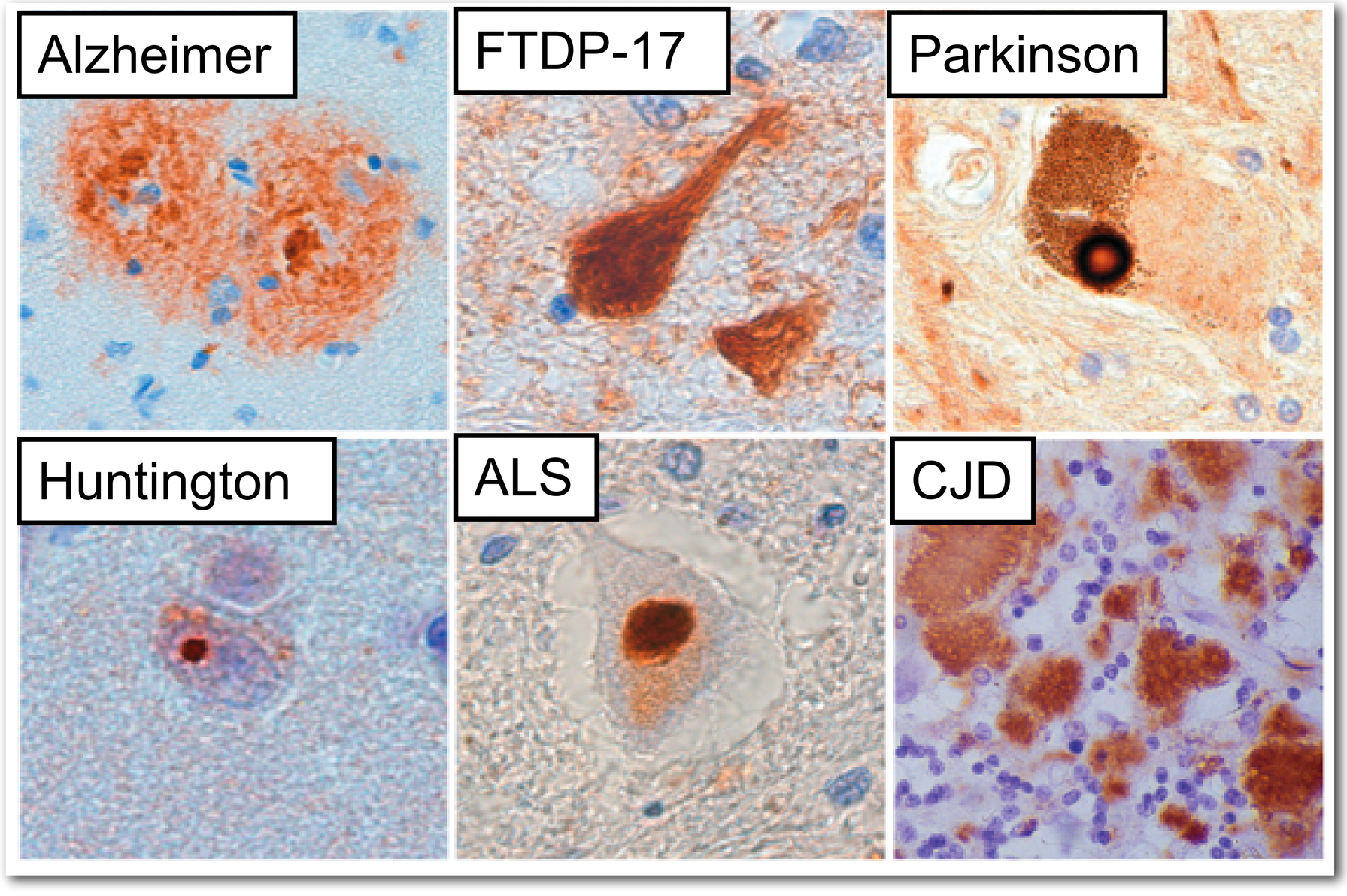
Frontotemporal lobar dementias (FTLDs)



- 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

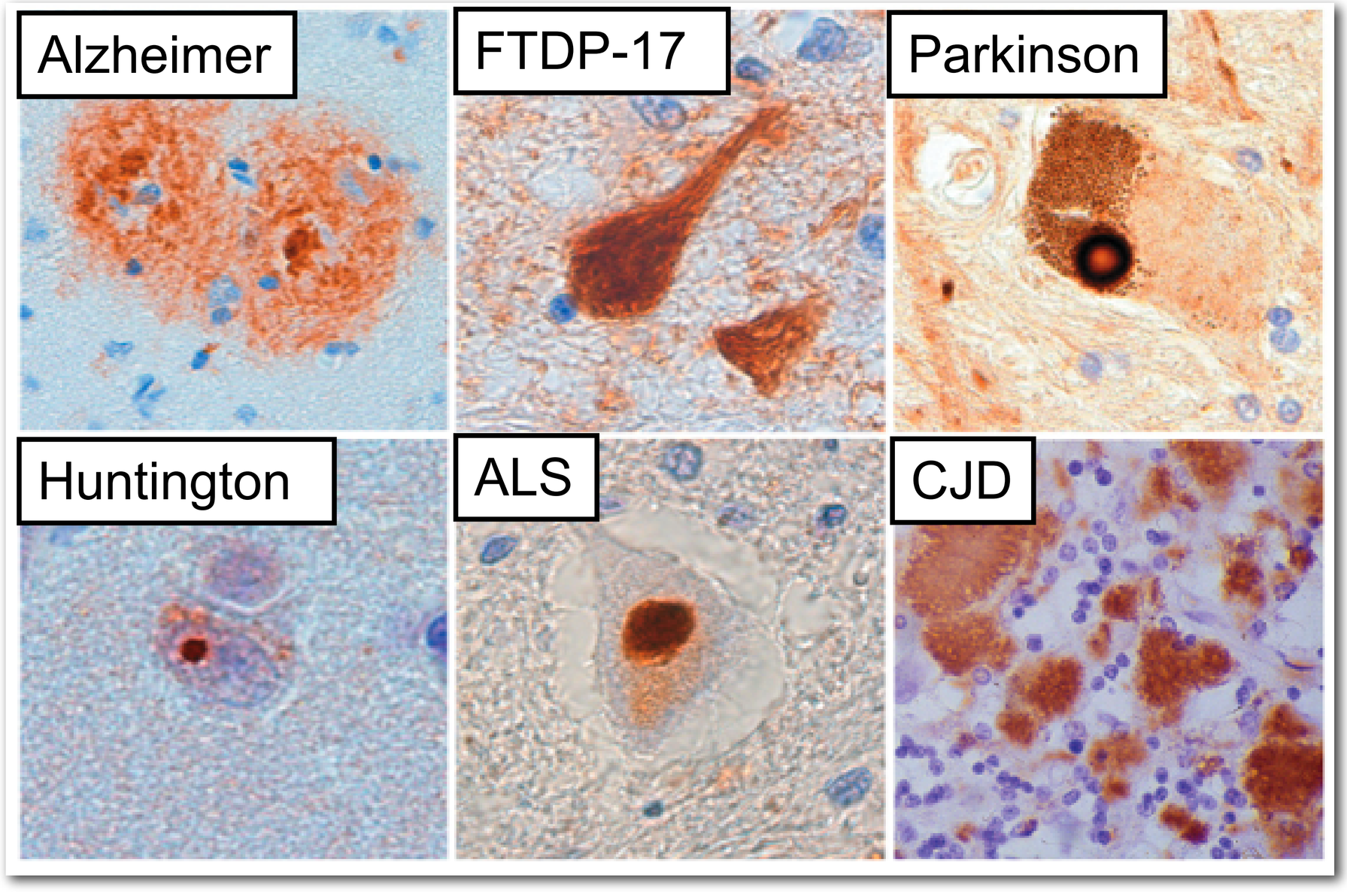


Adapted from Forman, Trojanowski, and Lee 2004

Mendelian Genes for FTD

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

Protein Aggregates in Neurodegenerative Diseases



Adapted from Forman, Trojanowski, and Lee 2004

Frontotemporal lobar dementias (FTLDs)

Tau +

Tau -

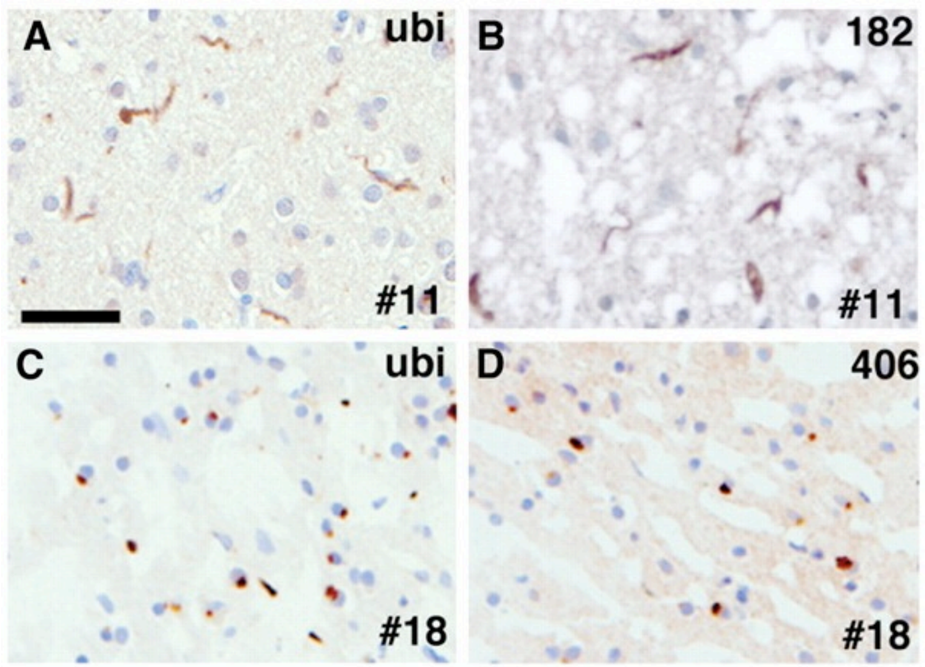
Ubi-

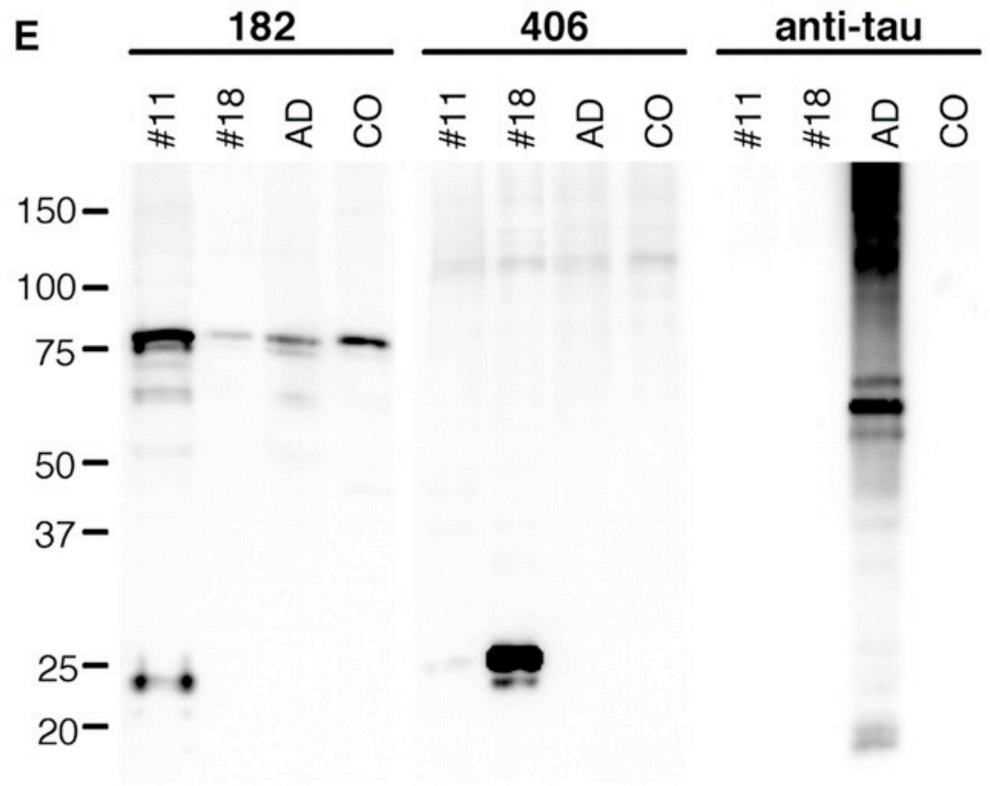
Ubi+

- FTLD-U

?

TDP-43





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211  FSQYGDVMDVFIPKPFRAFAFVTFADDQIAQSLCGEDLIIKGISVHISNAEPKHNSNRQLERSGRFGGNP
281  GGFGNQGGFGNSRGGGAGLGNNQGSNMGGGMNFGAFSINPAMMAAAQAALQSSWGMMGMLASQQNQSGPS
351  GNNQNQGNMQREPNQAFGSGNNSYSGSNSGAAIGWGSASNAGSGSGFNGGFGSSMDSKSSGWGM
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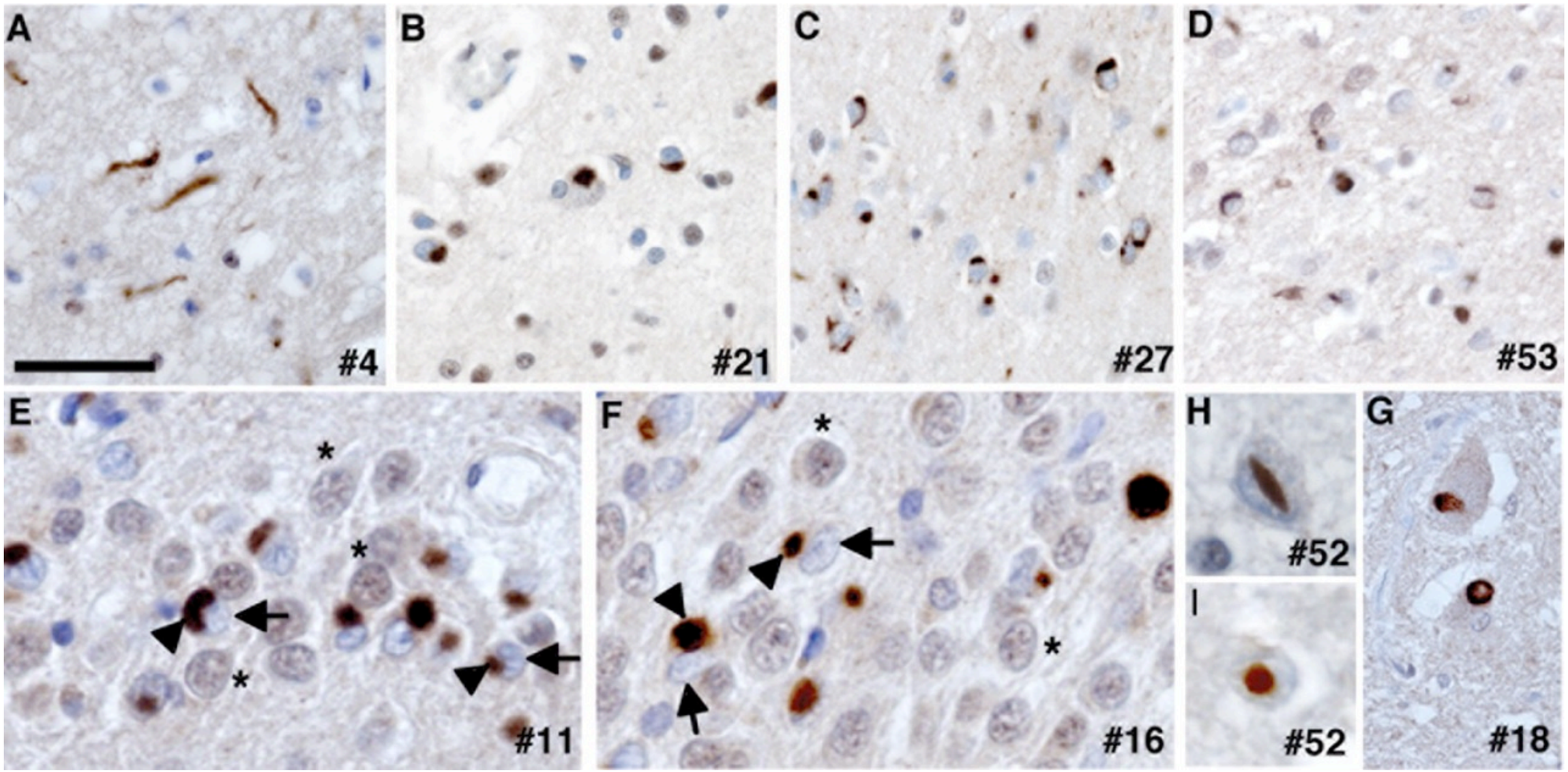
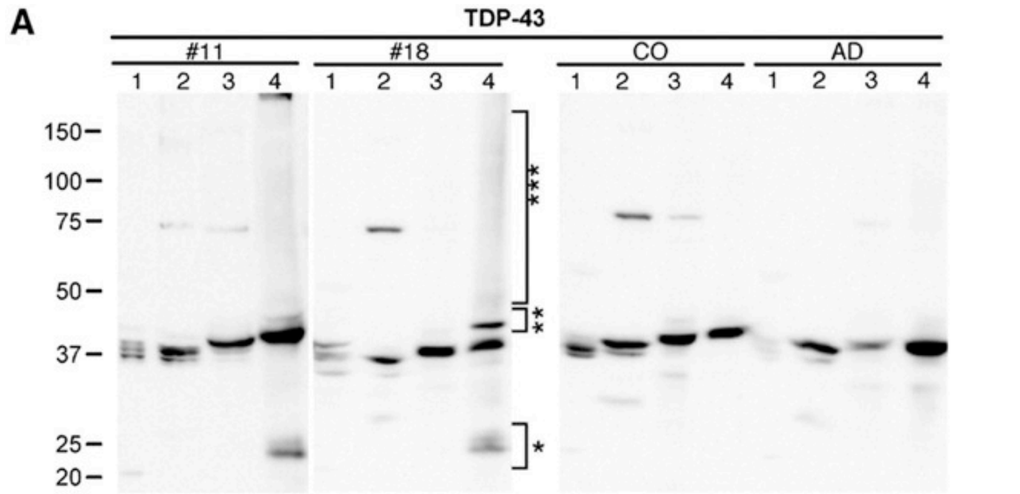
Neumann et al.,
Science 2006

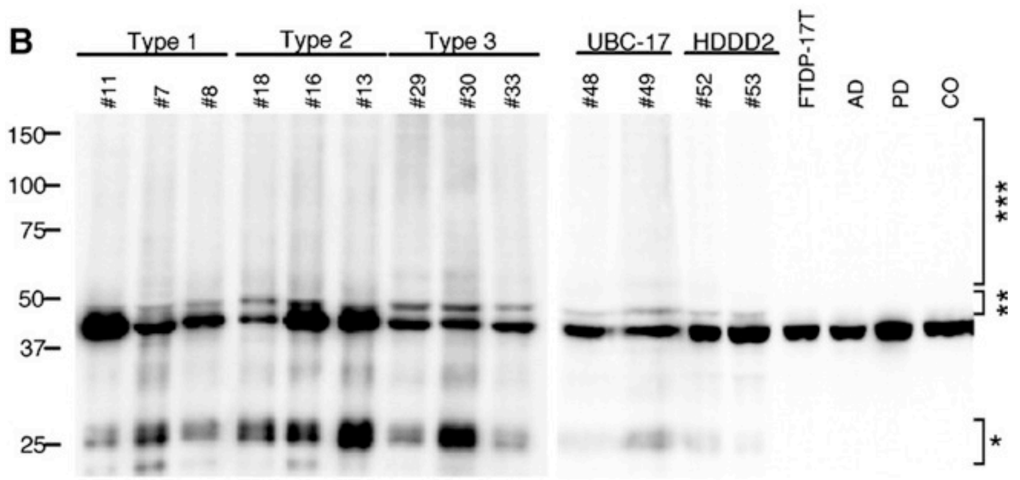
TDP-43 pathology in FTLD-U

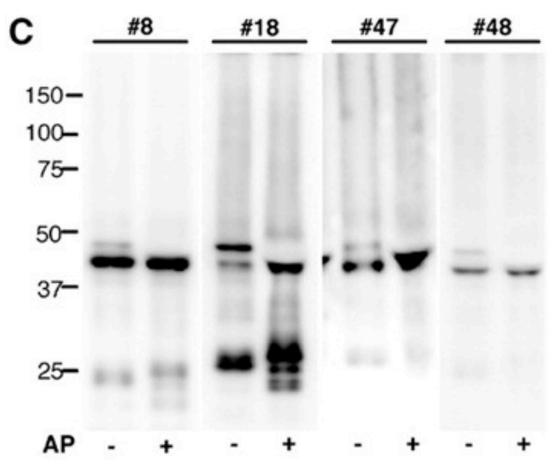


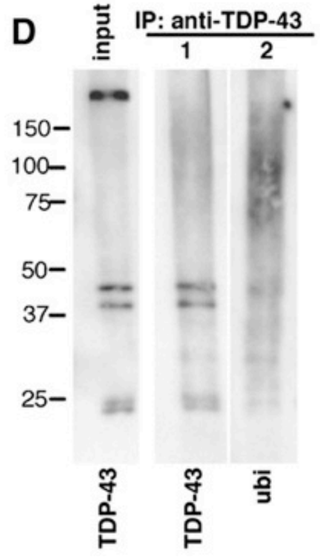
Neumann et al.,
Science 2006

TDP-43 "biochemical signature"



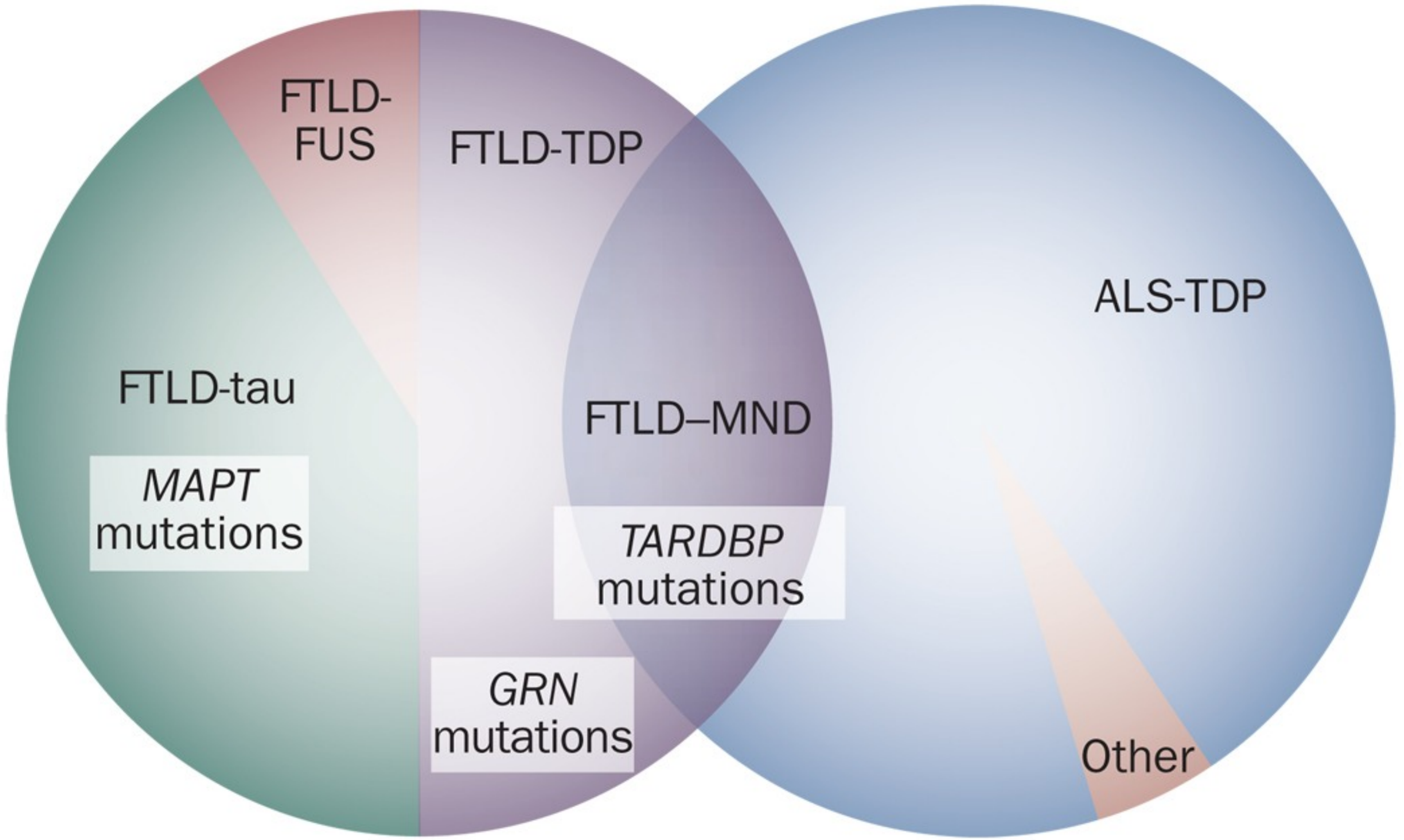




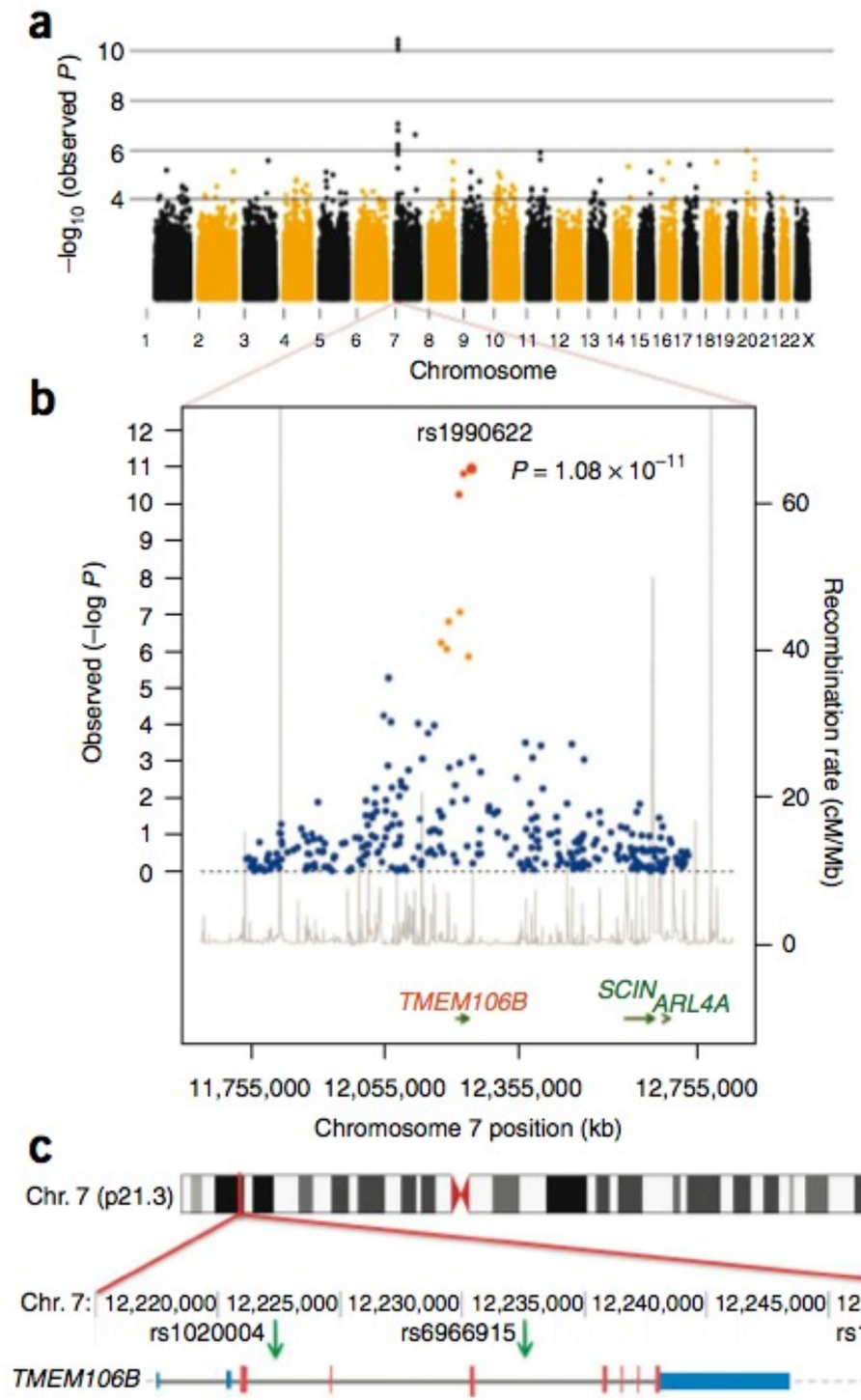


Neumann et al.,
Science 2006

Pathological subtypes of FTLD and ALS



GWAS for frontotemporal dementia susceptibility loci



rs1990622
TMEM106B
OR 1.64 (1.41-1.89)

Van Deerlin et al
Nature Genetics 2010

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**

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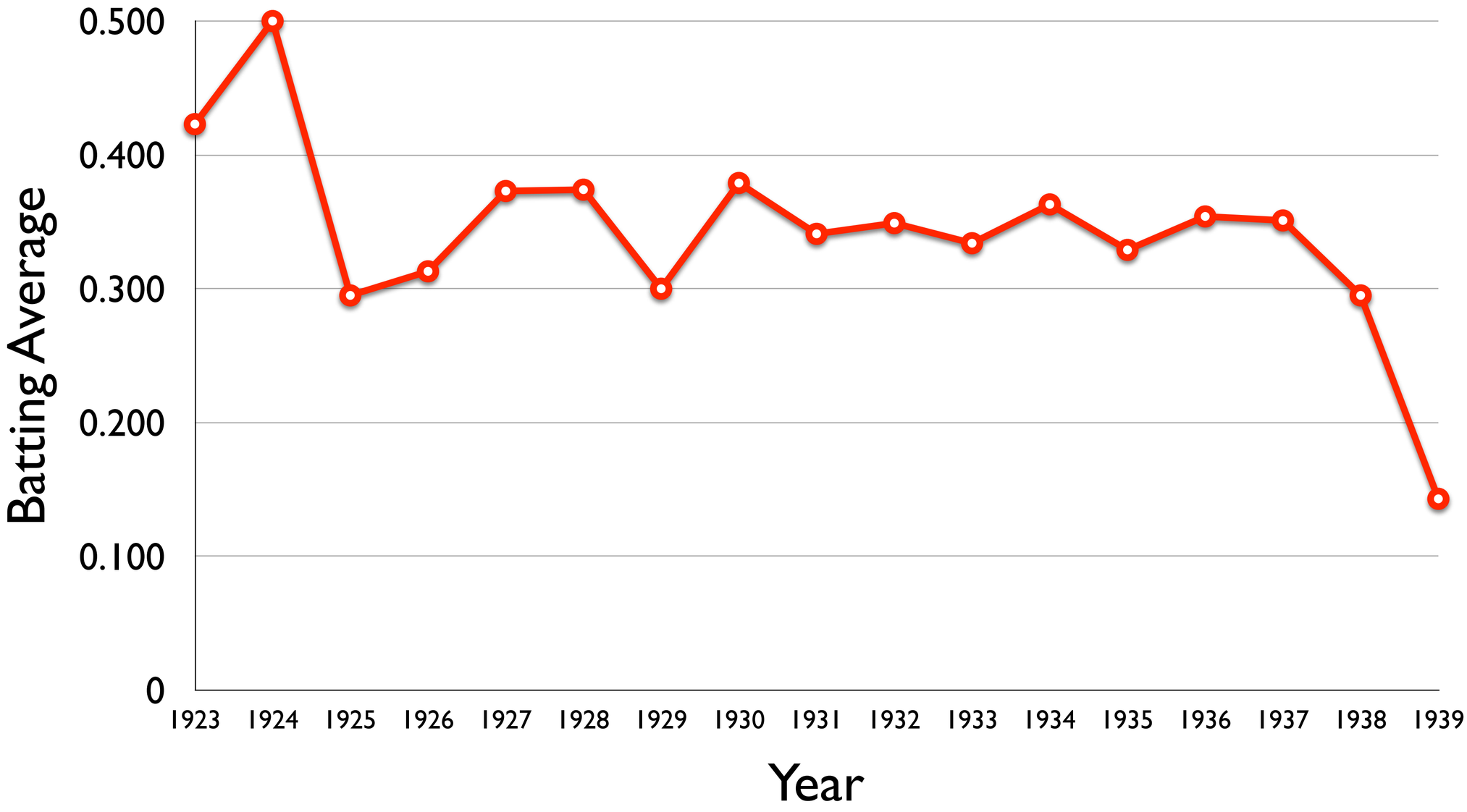
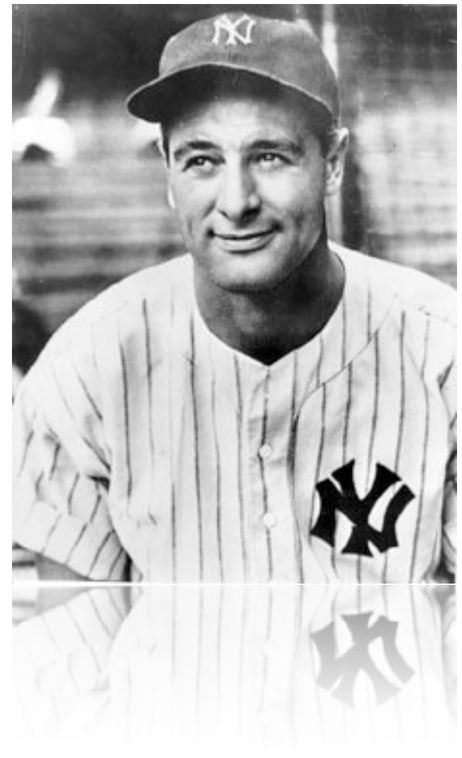
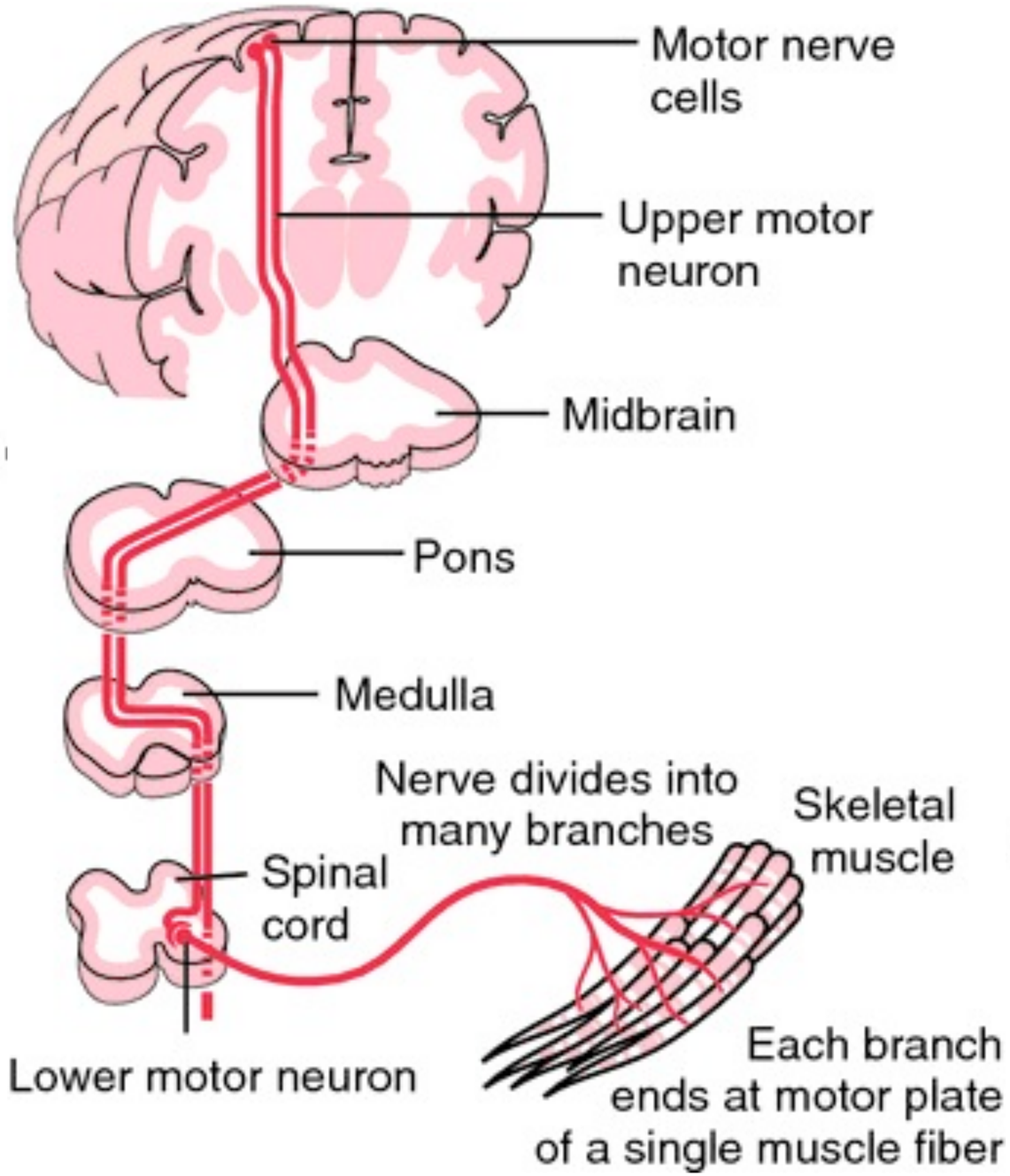
Lou Gehrig's career batting average



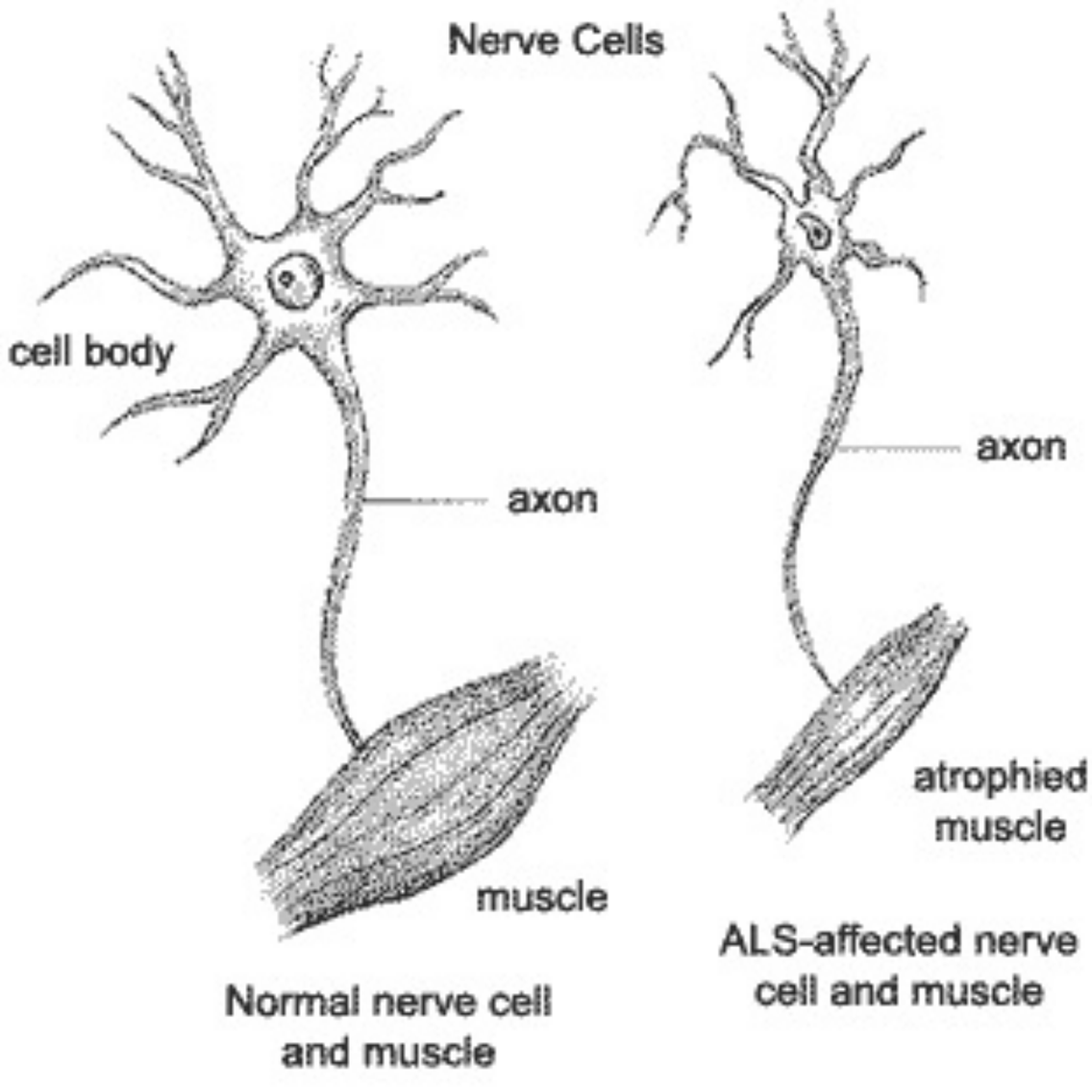


Amyotrophic Lateral Sclerosis (ALS)



- 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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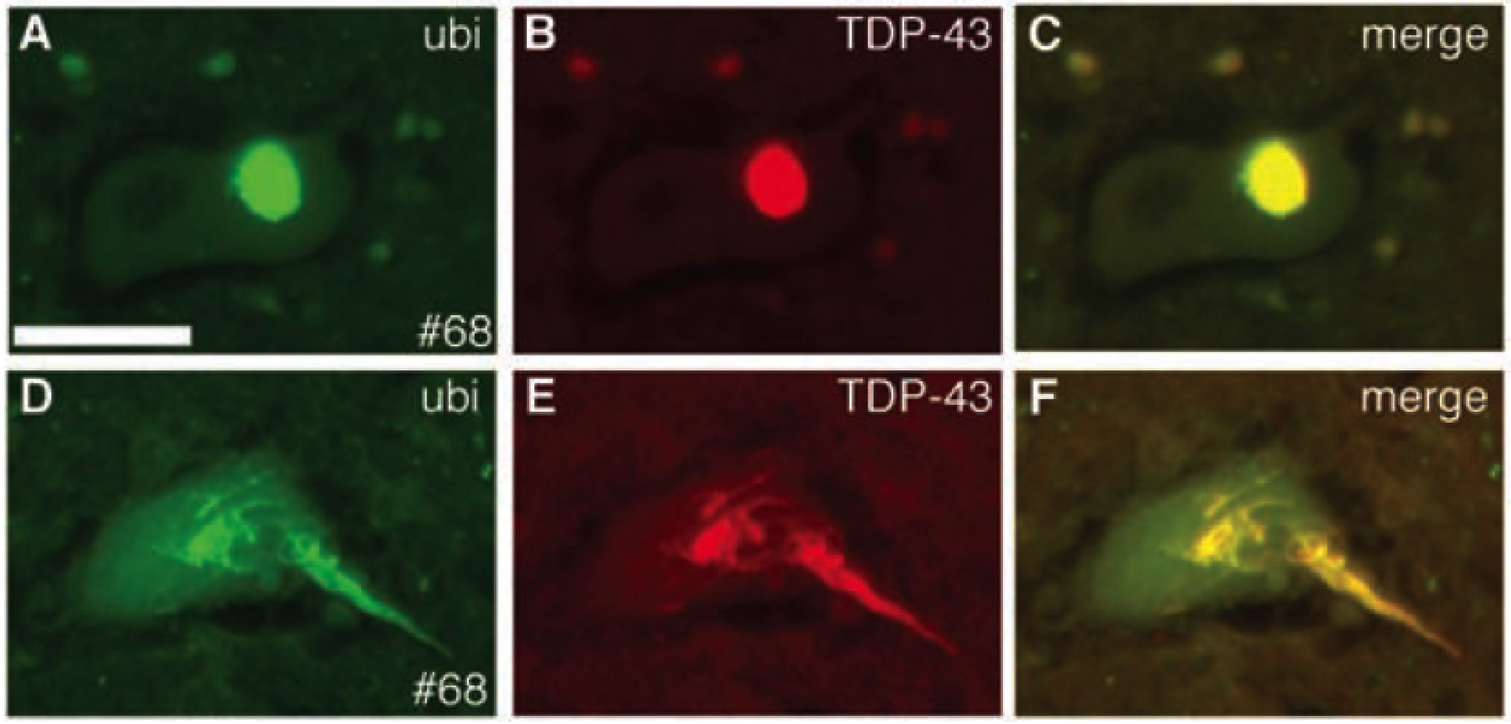
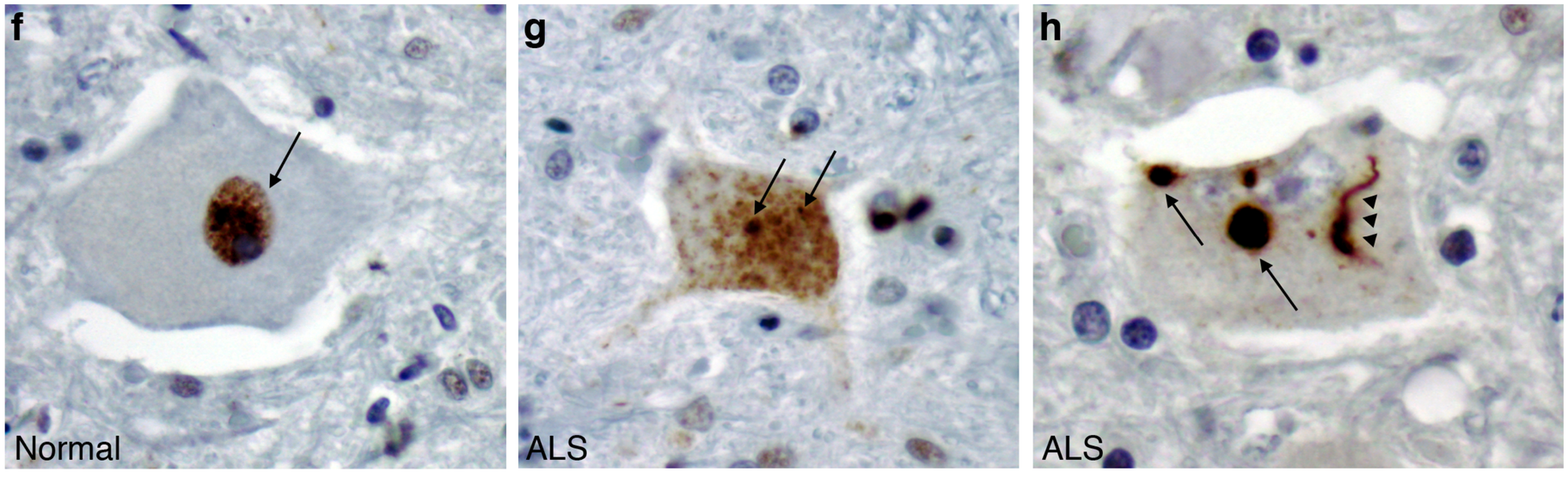
Stephen Hawking

TDP-43 pathology in sporadic ALS



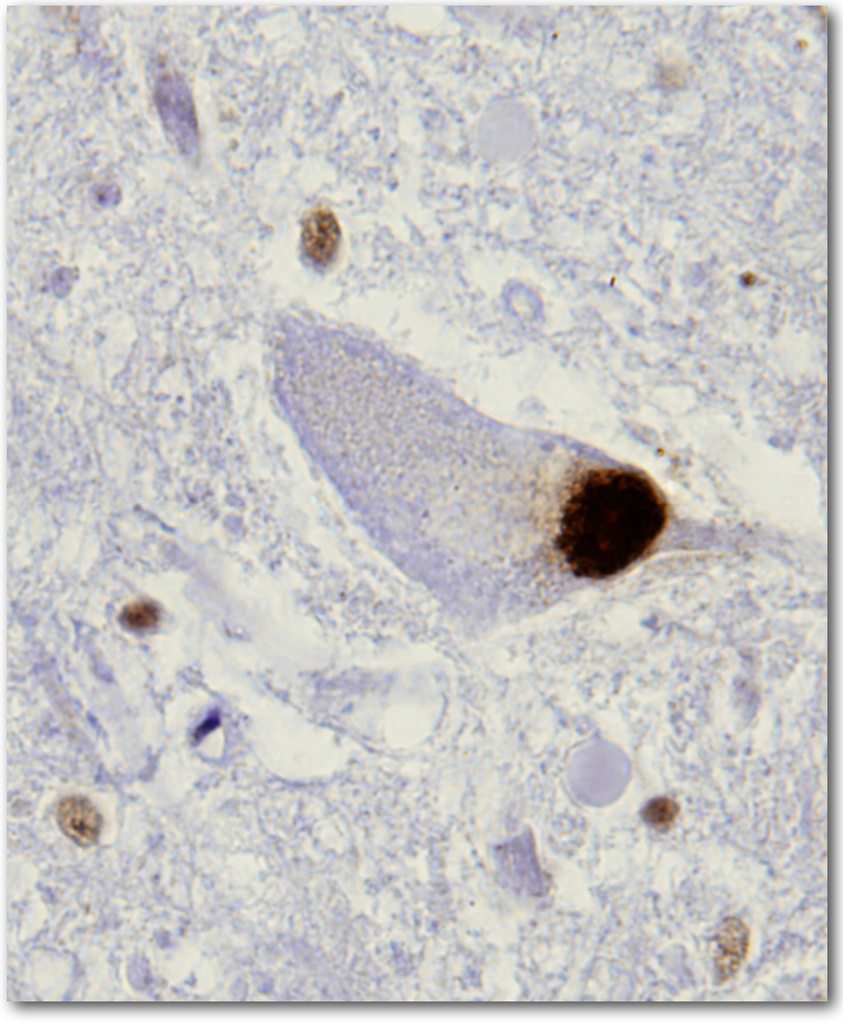


Editorial

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

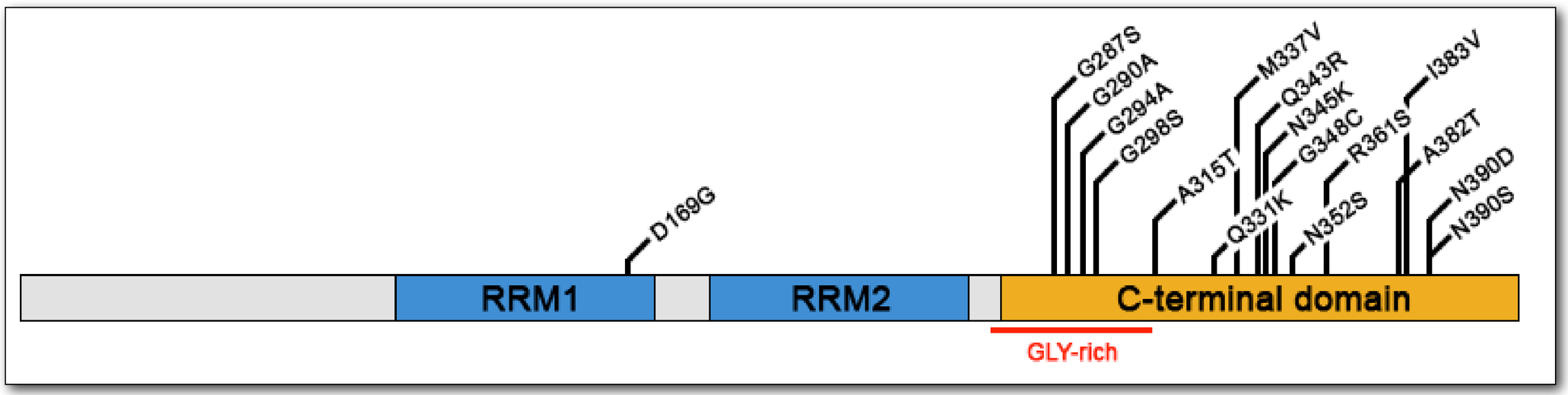
Michael A. Gitcho, PhD,[1,2] Robert H. Baloh, MD, PhD,[2] Sumi Chakraverty, MS,[1,3] Kevin Mayo, BS,[3] Joanne B. Norton, RN,[1,3] Denise Levitch, RN,[1,3] Kimmo J. Hatanpaa, MD, PhD,[4] Charles L. White III, MD,[4] Eileen H. Bigio, MD,[5,6] Richard Caselli, MD,[7] Matt Baker, BSc,[8] Muhammad T. Al-Lozi, 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] Akihide 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, PhD[2]

TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis

Edor Kabashi[1,6], Paul N Valdmanis[1,6], Patrick Dion[1], Dan Spiegelman[1], Brendan J McConkey[2], Christine Vande Velde[1], Jean-Pierre Bouchard[3], Lucette Lacomblez[4], Ksenia Pochigaeva[4], Francois Salachas[4], Pierre-Francois Pradat[4], William Camu[5], Vincent Meininger[4], Nicolas Dupre[1,3] & Guy A Rouleau[1]



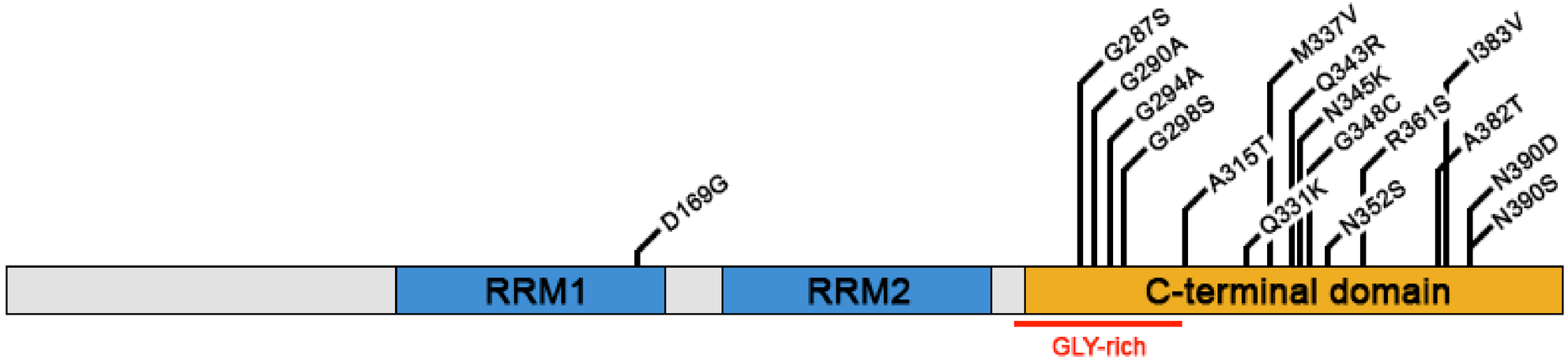
TDP-43 Mutations in Familial and Sporadic Amyotrophic Lateral Sclerosis

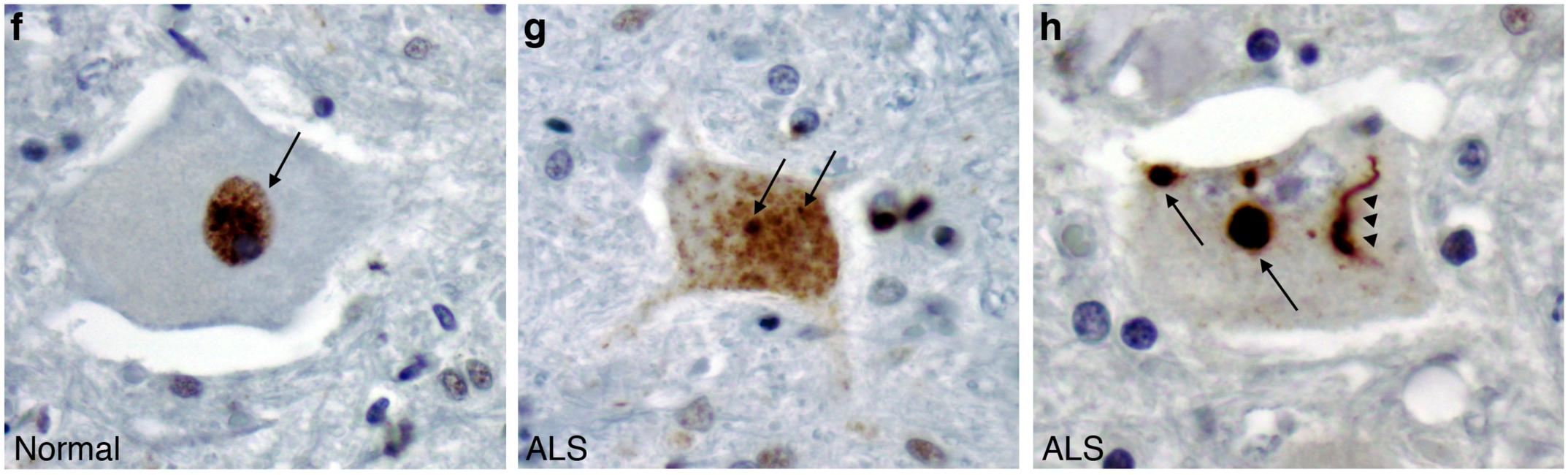
Jemeen Sreedharan,[1*] Ian P. Blair,[3,4*] Vineeta B. Tripathi,[1*] Xun Hu,[1] Caroline Vance,[1] Boris Rogelj,[1] Steven Ackerley,[1,2] Jennifer C. Durnall,[3] Kelly L. Williams,[3] Emanuele Buratti,[5] Francisco Baralle,[5] Jacqueline de Belleroche,[6] J. Douglas Mitchell,[7] P. Nigel Leigh,[1] Ammar 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

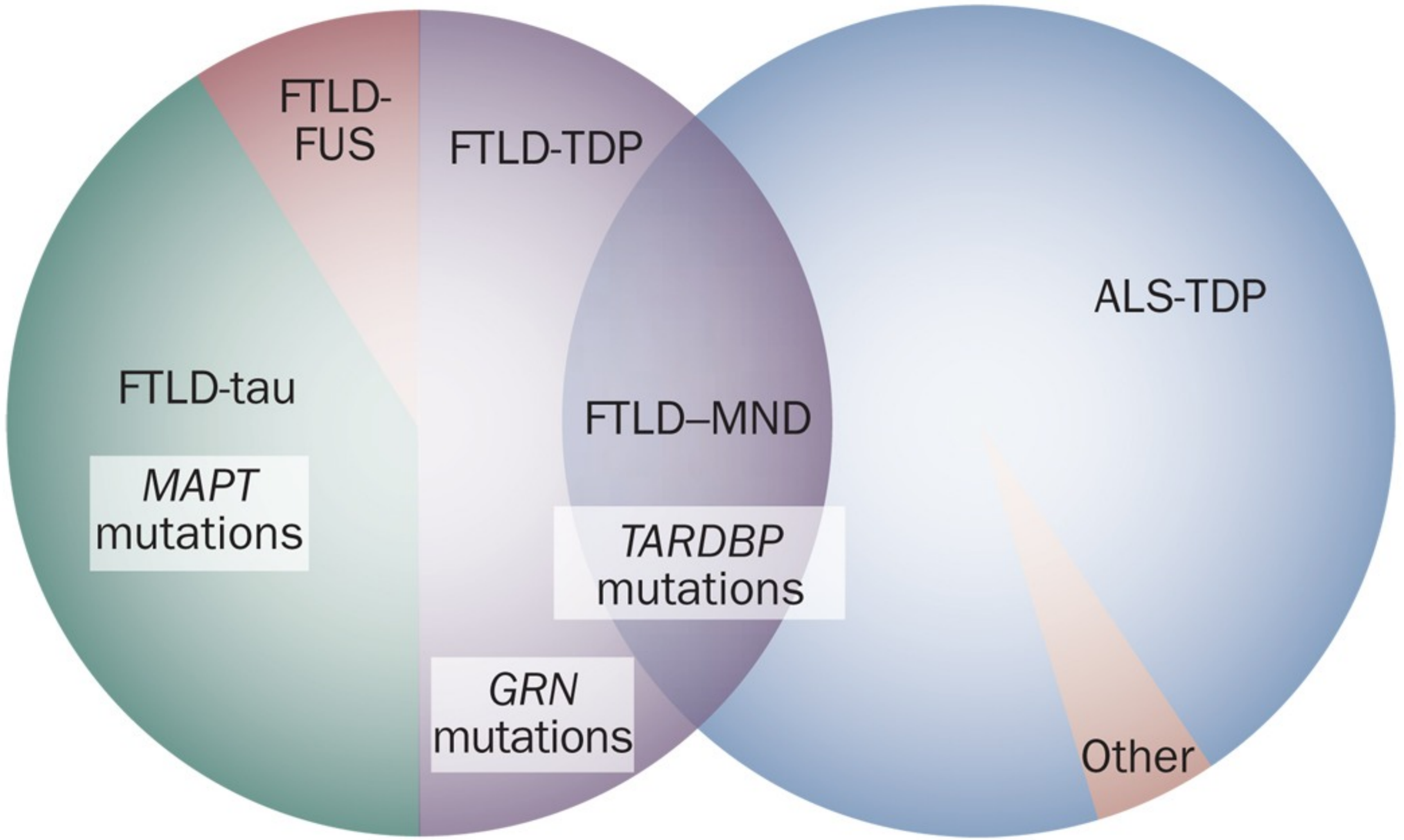
Vivianna M Van Deerlin, James B Leverenz, Lynn M Bekris, Thomas D Bird, Wuxing Yuan, Lauren B Elman, Dana Clay, Elisabeth McCarty Wood, Alice S Chen-Plotkin, Maria Martinez-Lage, Ellen Steinbart, Leo McCluskey, Murray Grossman, Manuela Neumann, I-Lin Wu, Wei-Shiung Yang, Robert Kalb, Douglas R Galasko, 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

~50% of FALS causative genes are now known
but only 5-10% of SALS causative genes are known

Susceptibility Loci for ALS

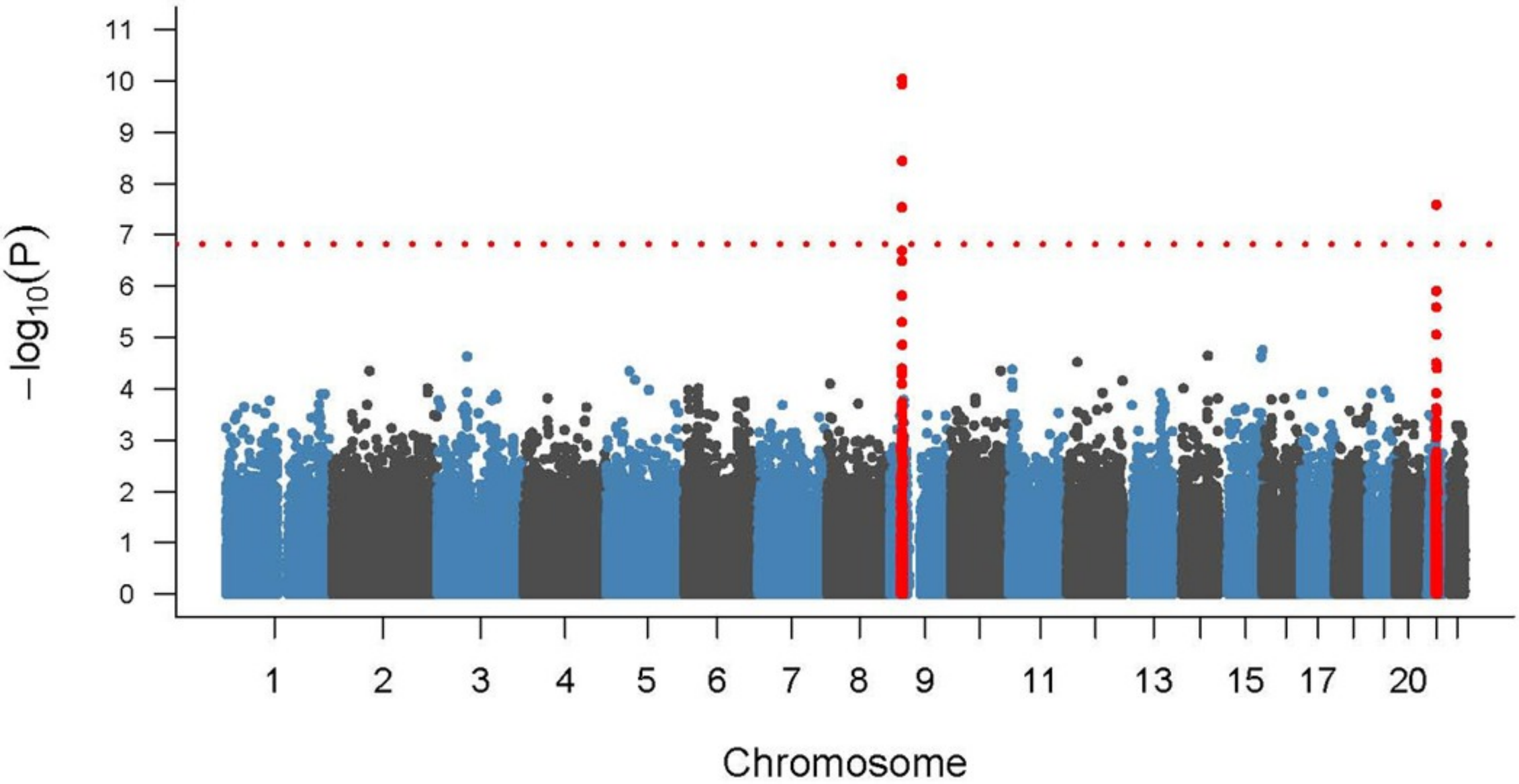
Gene	Protein	Location	Polymorphism	OR (95% CI)
UNC13A	unc-13 homolog A	19p13.11	rs12608932	1.18 (1.13-1.24)
GWA_9p21.2	Unknown	9p21.2	rs2814707	1.25 (1.19-1.32)
ATXN2	ataxin 2	12q24.12	PolyQ	n.a.

Susceptibility Loci for ALS (Han Chinese)

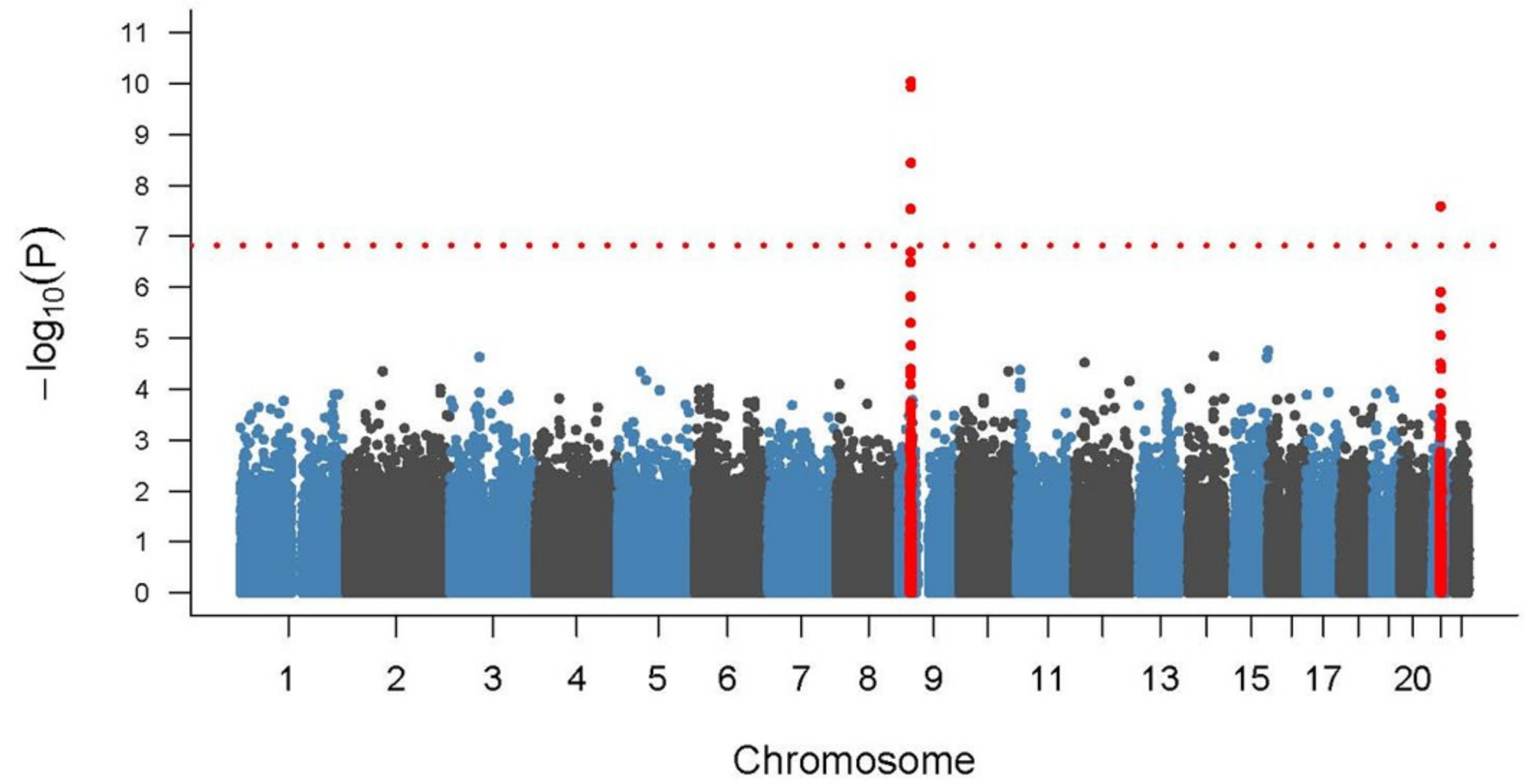
Gene	Protein	Location	Polymorphism	Odds Ratio
CAMK1G	CAMK1G	1q32	rs6703183	1.31
CABIN1 and SUSD2	Unknown	22p11	rs8141797	1.52

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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AACCGCAGCCTGTAGCAAGCTCTGGAACTCAGGAGTCGCG
CGCTAGGGGCCGGGGCCGGGGCCGGGGCGTGGTCGGGG
CGGGCCCGGGGGCGGGCCCGGGGCGGGGCTGCGGTTGC
GGTGCCTGCGCCCGCGGCGGCGGAGGCGCAGGCGGTGG
CGAGTGGGTGAGTG

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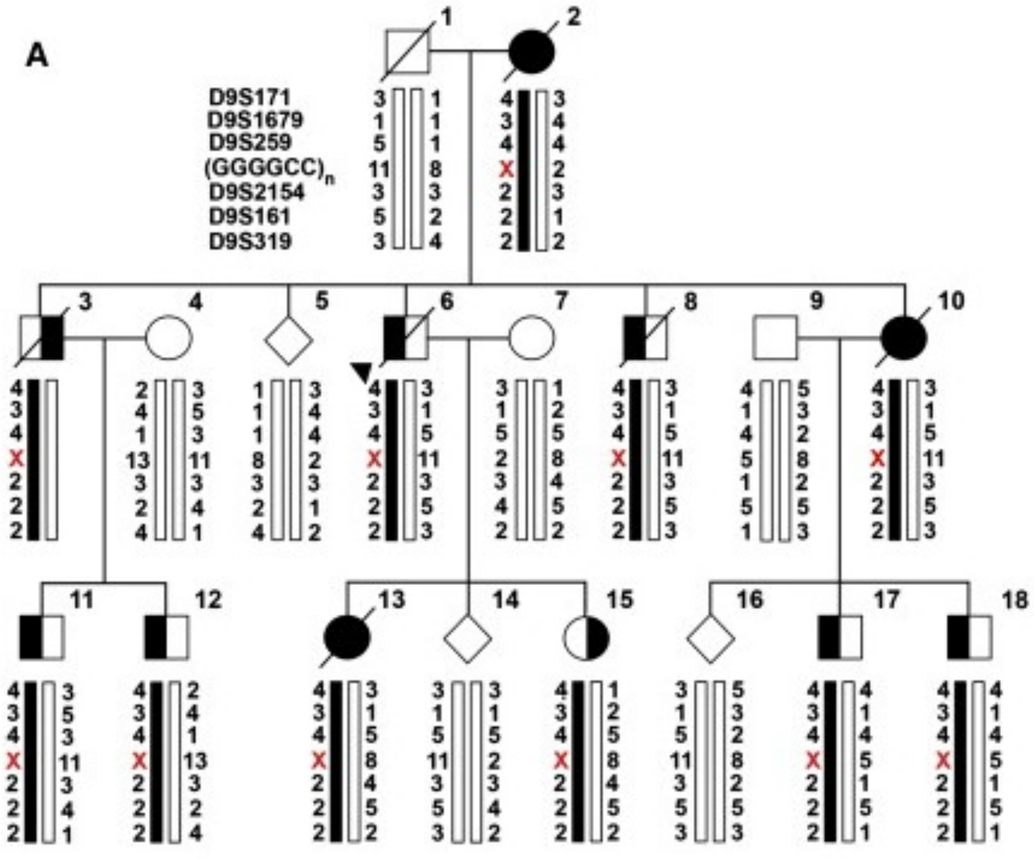
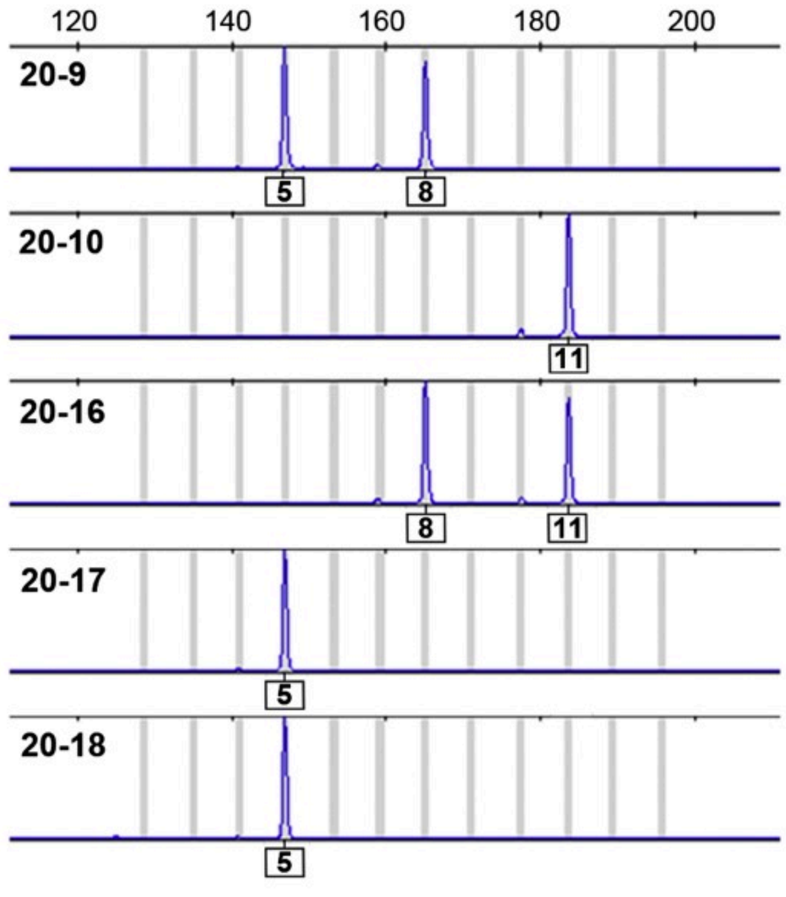
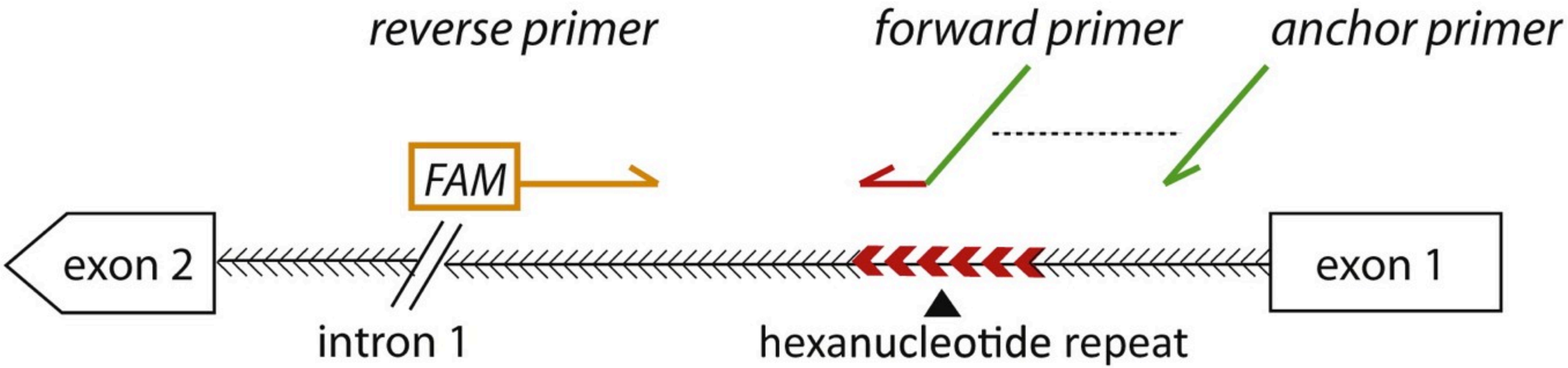
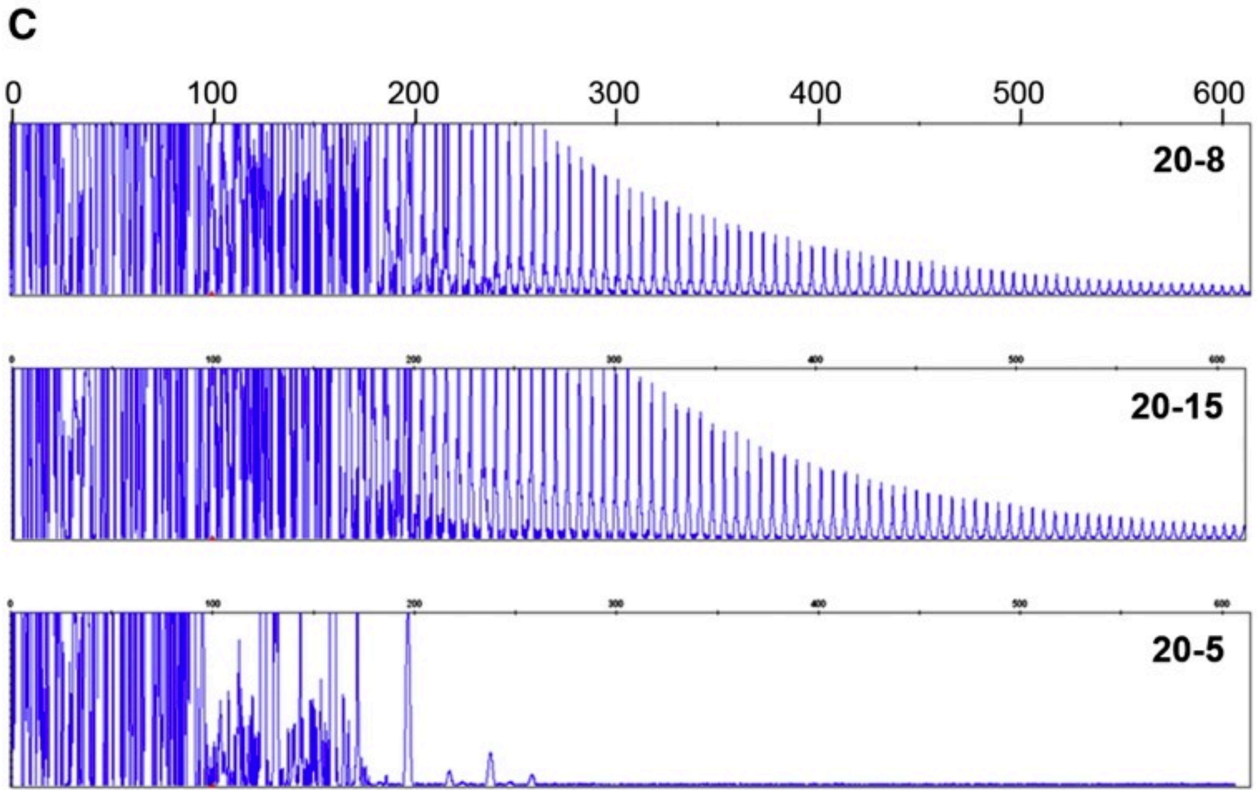





reverse primer
forward primer
anchor primer
FAM
exon 2
exon 1
intron 1
hexanucleotide repeat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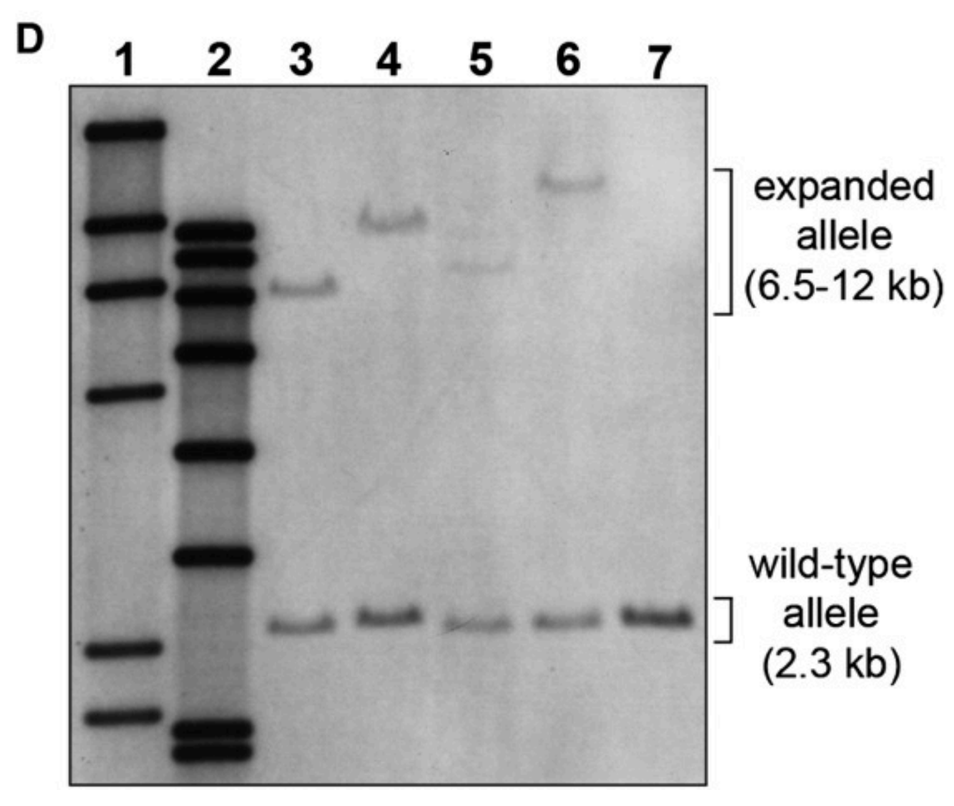
D
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expanded allele (6.5-12 kb)
wild-type allele (2.3 kb)

Neuron
Article

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

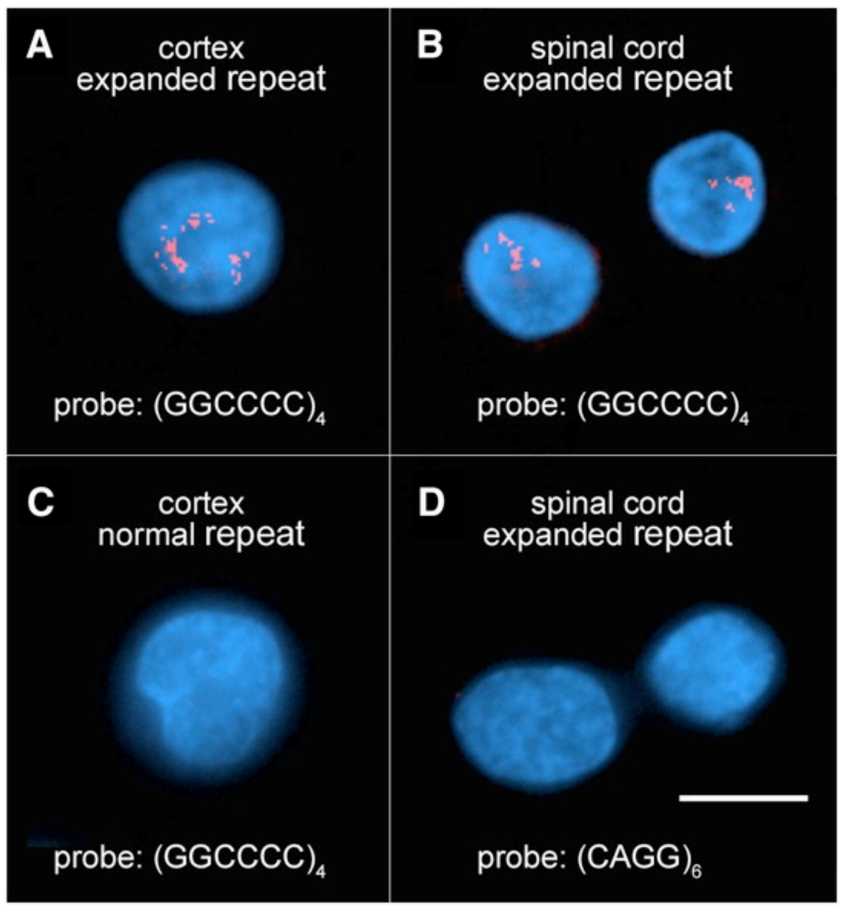
Neuron
Article

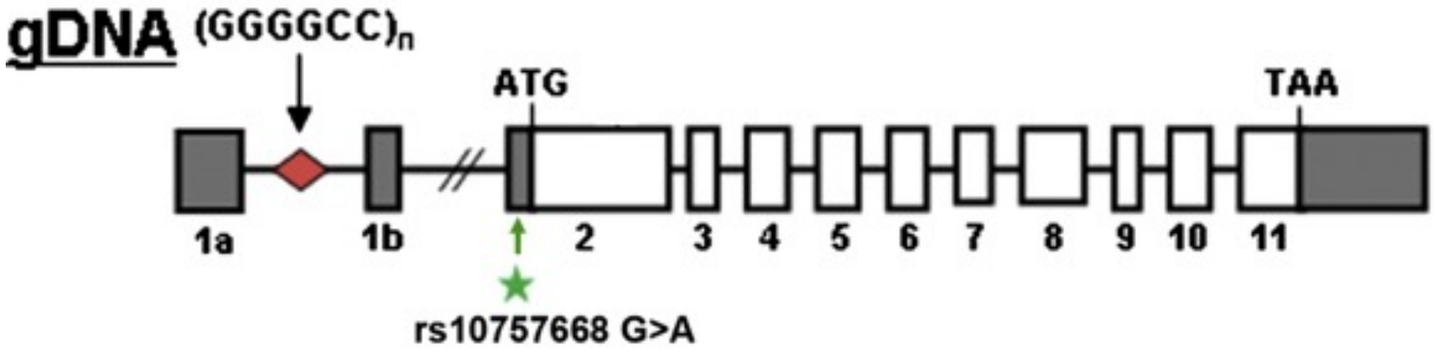
A Hexanucleotide Repeat Expansion in *C9ORF72* Is the Cause of Chromosome 9p21-Linked ALS-FTD

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 Wuu,[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 GGGGCC expansions in *C9ORF72* cause FTLD/ALS?

Clues





Today's Plan

1. Kristen Powers and Katie Moser

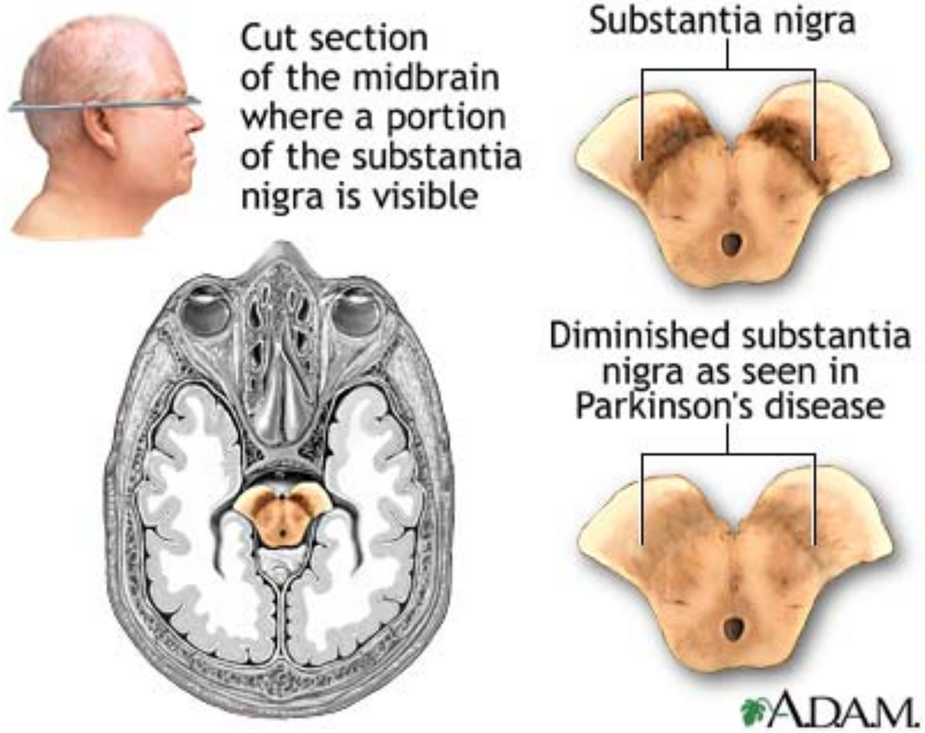
2. Alzheimer's Disease (Gitler)

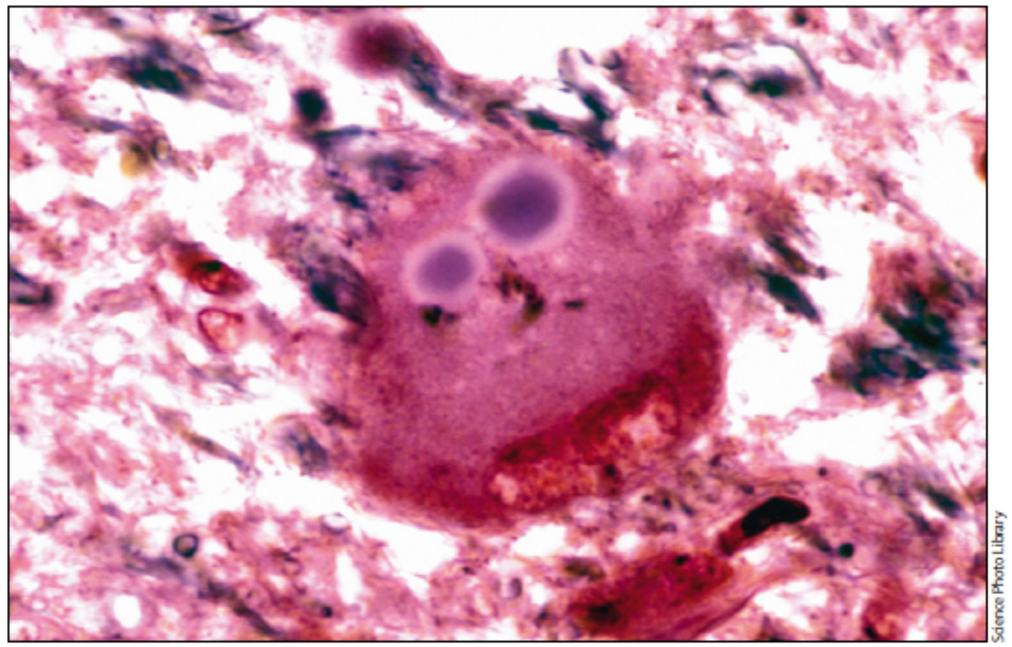
3. Frontotemporal Dementia (Gitler)

4. Amyotrophic lateral sclerosis (ALS) (Gitler)

5. Parkinson's Disease (Chuang)

Parkinson's Disease

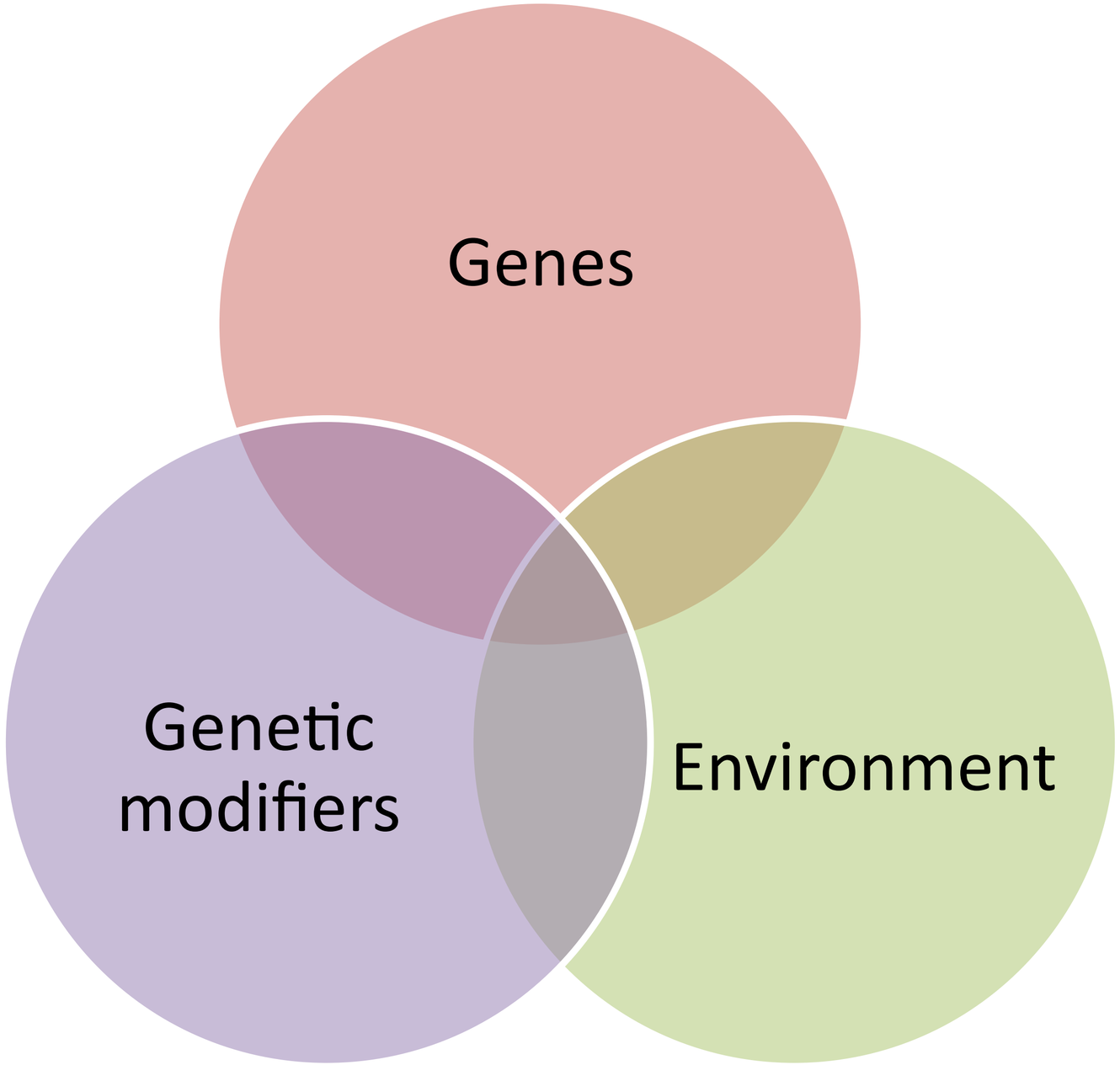




Science Photo Library

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

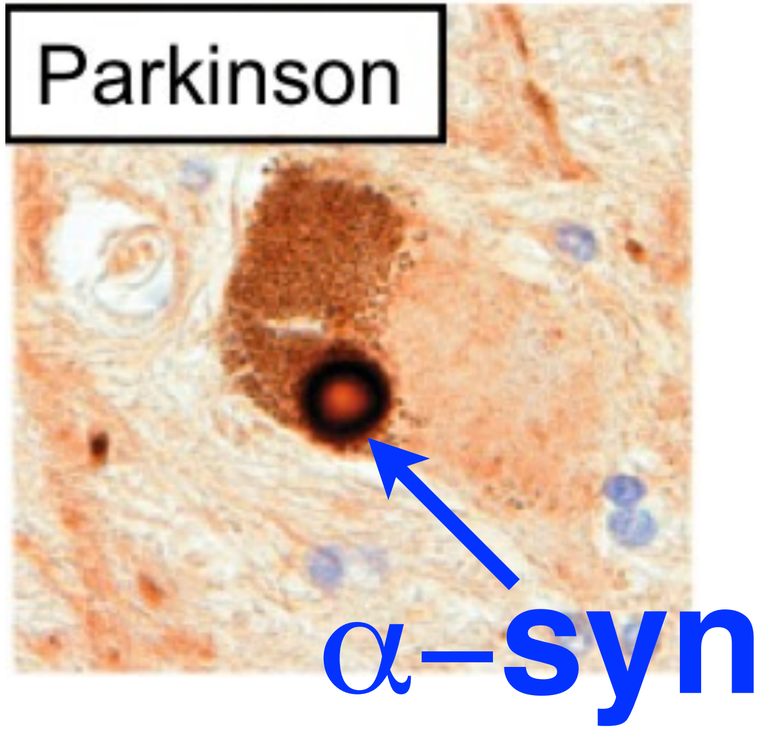
*Some papers suggest 5-10% of PD patients have a gene mutation

Monogenic parkinsonism

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



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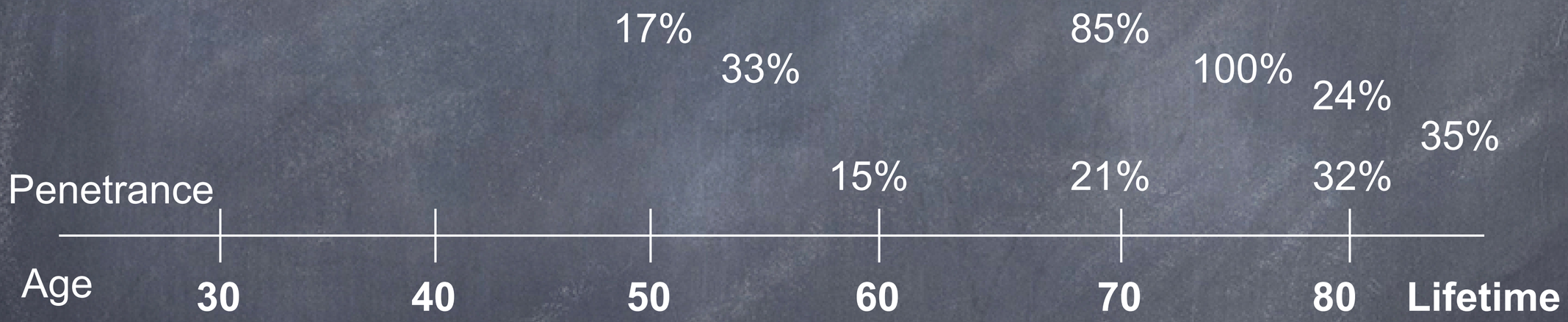
PARK7	1p36	DJ-1	Similar to Hsp31; oxidative stress sensor or antioxidant	recessive
PARK8	12p11.2-q13.1	LRRK2	Contains kinase (plus other domains)	dominant
PARK9	1p36	ATP13A2	Transmembrane Cationic ATPase	recessive

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 ancest
- 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

Slide courtesy of Dr. Connie Marras

Monogenic parkinsonism

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PARK8	12p11.2-q13.1	LRRK2	Contains kinase (plus other domains)	dominant
PARK9	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

OPEN ACCESS Freely available online

PLoS GENETICS

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

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The Internat
Consortium[1]
Tanzi[2], Muir

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 artides from which relevant data were extracted. In addition, individual-level data from three publidy 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 ($P<5\times10^{-8}$) 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, $P=1.3\times10^{-8}$). 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.

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

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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* ($p=7.6\times10^{-10}$, OR = 0.84) and rs11868035 near *SREBF1/RAI1* ($p=5.6\times10^{-8}$, 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.

Susceptibility Loci for Parkinson's Disease

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