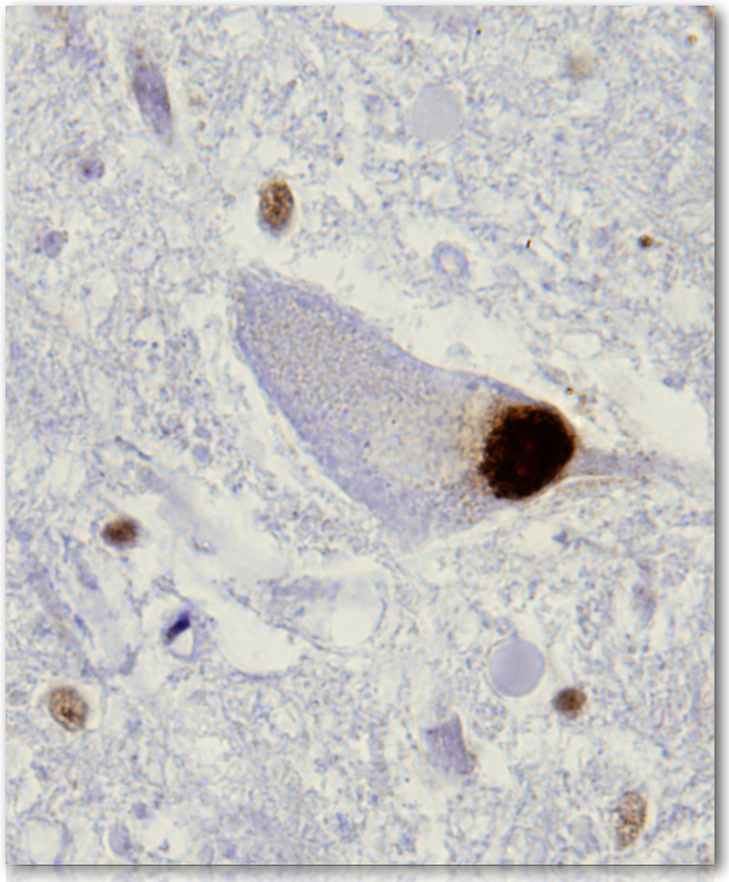
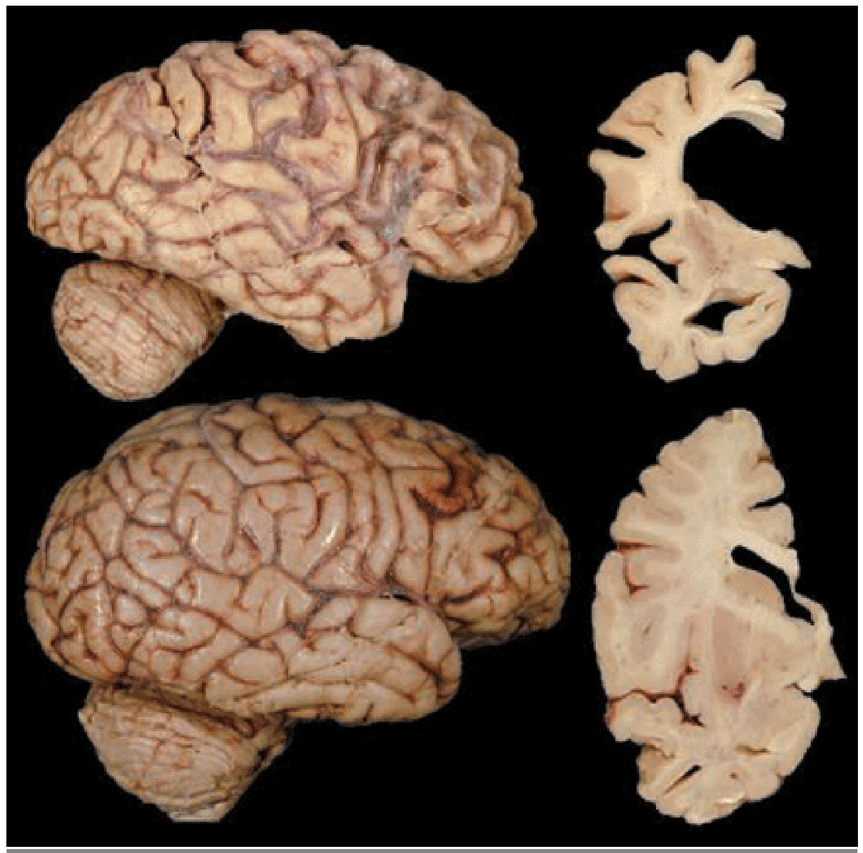
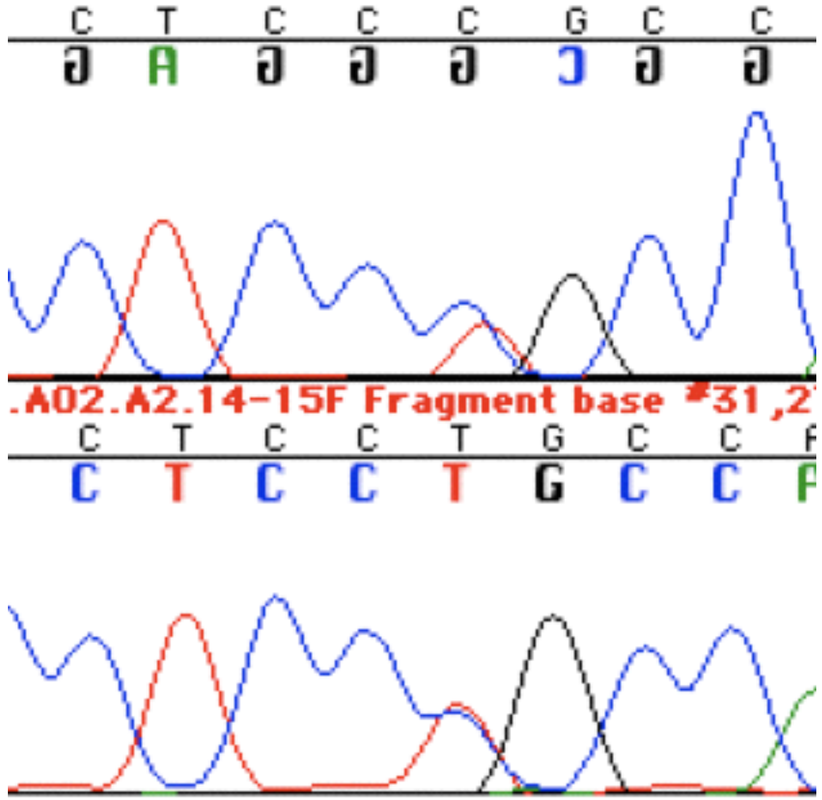
Genetics of human neurodegenerative disease

Gene 210
April 21, 2015
Aaron D. Gitler, Ph.D.







Today's Plan

1. Alzheimer's Disease

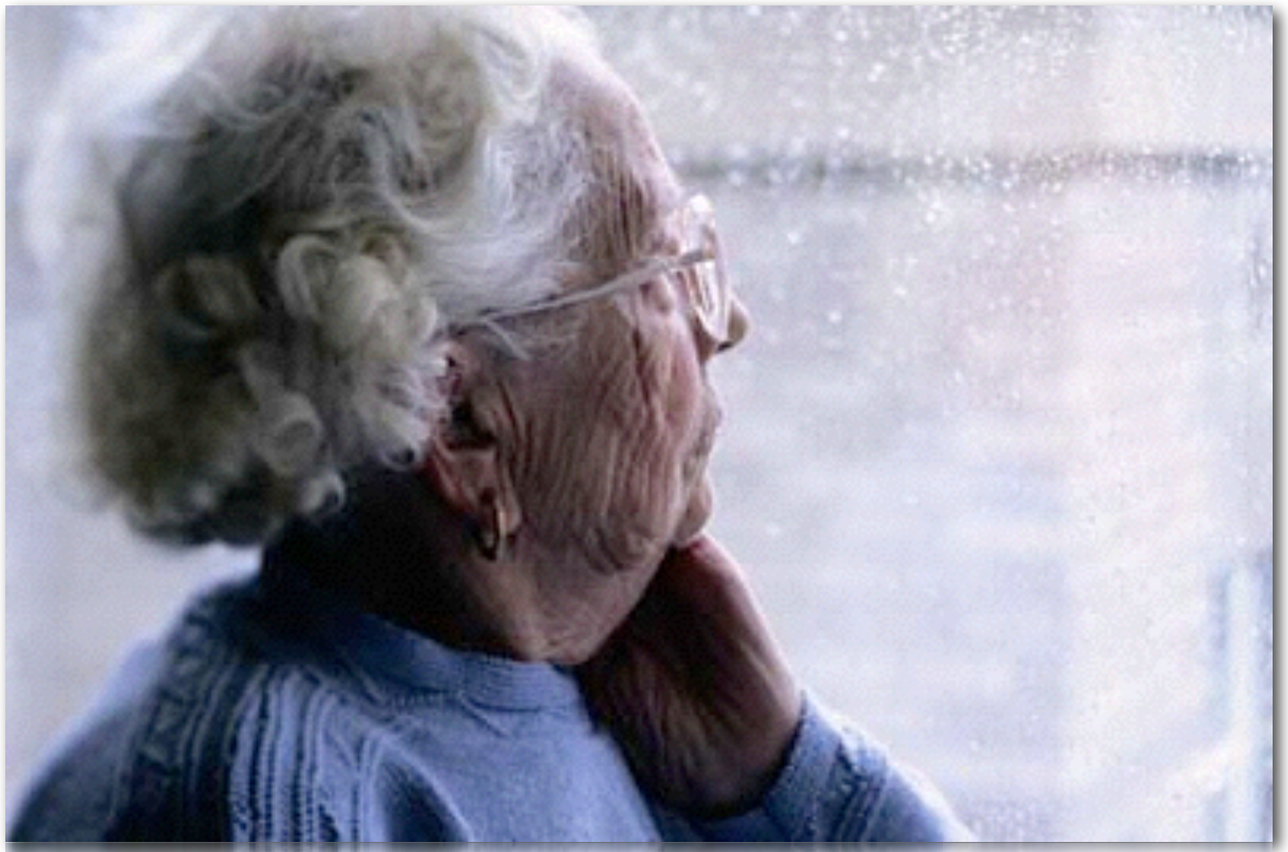
2. Frontotemporal Dementia

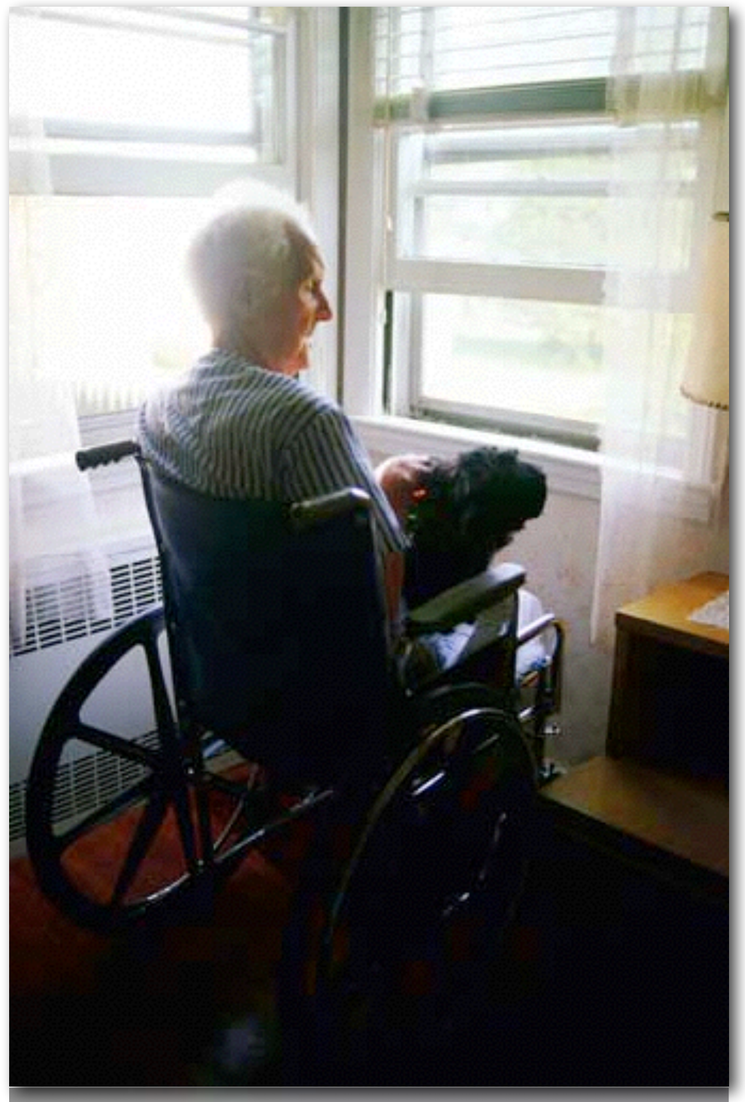
3. Amyotrophic lateral sclerosis (ALS)

4. Parkinson's Disease

5. Polyglutmaine Diseases (HD, SCA)

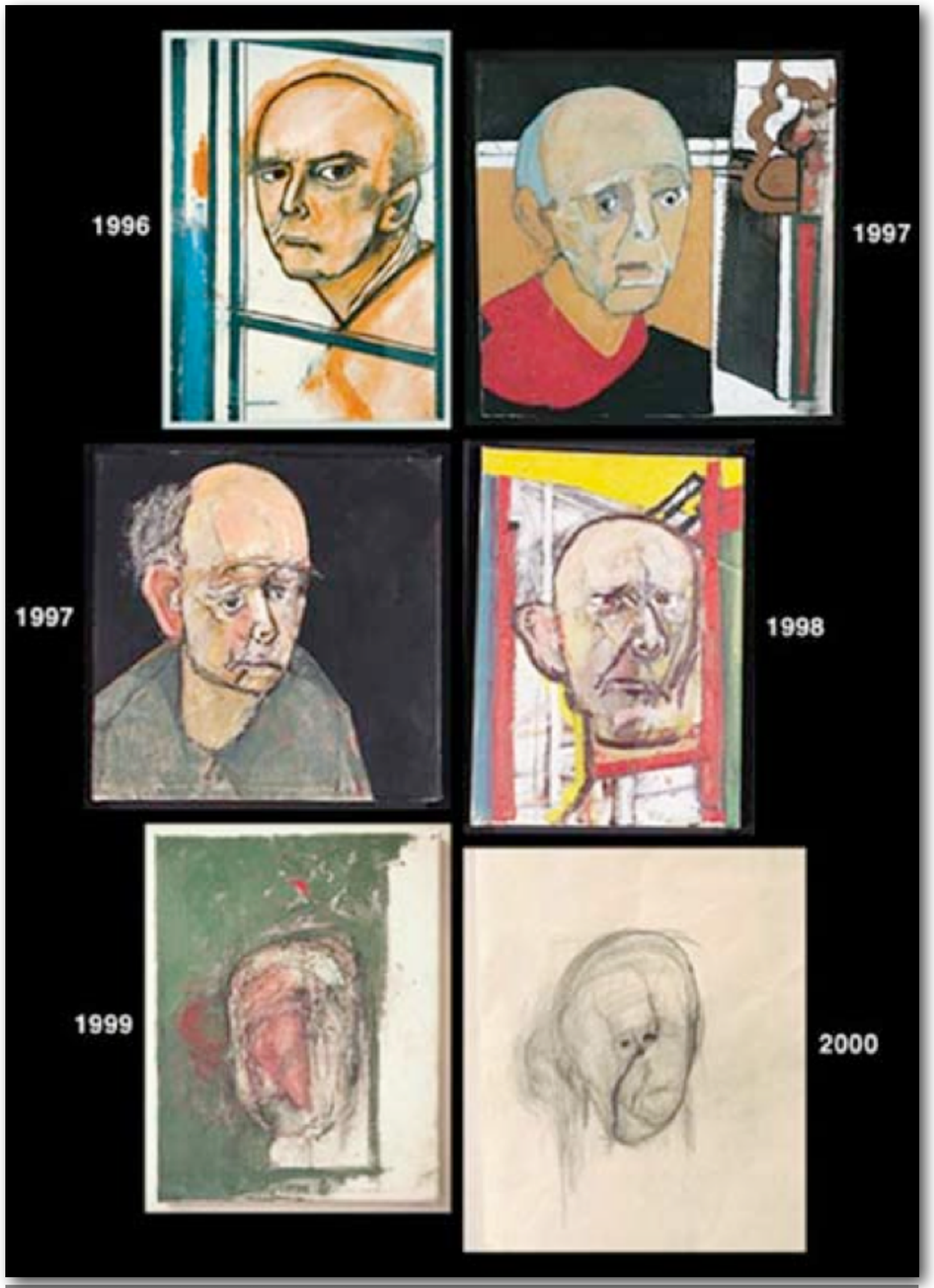
Neurodegenerative Diseases



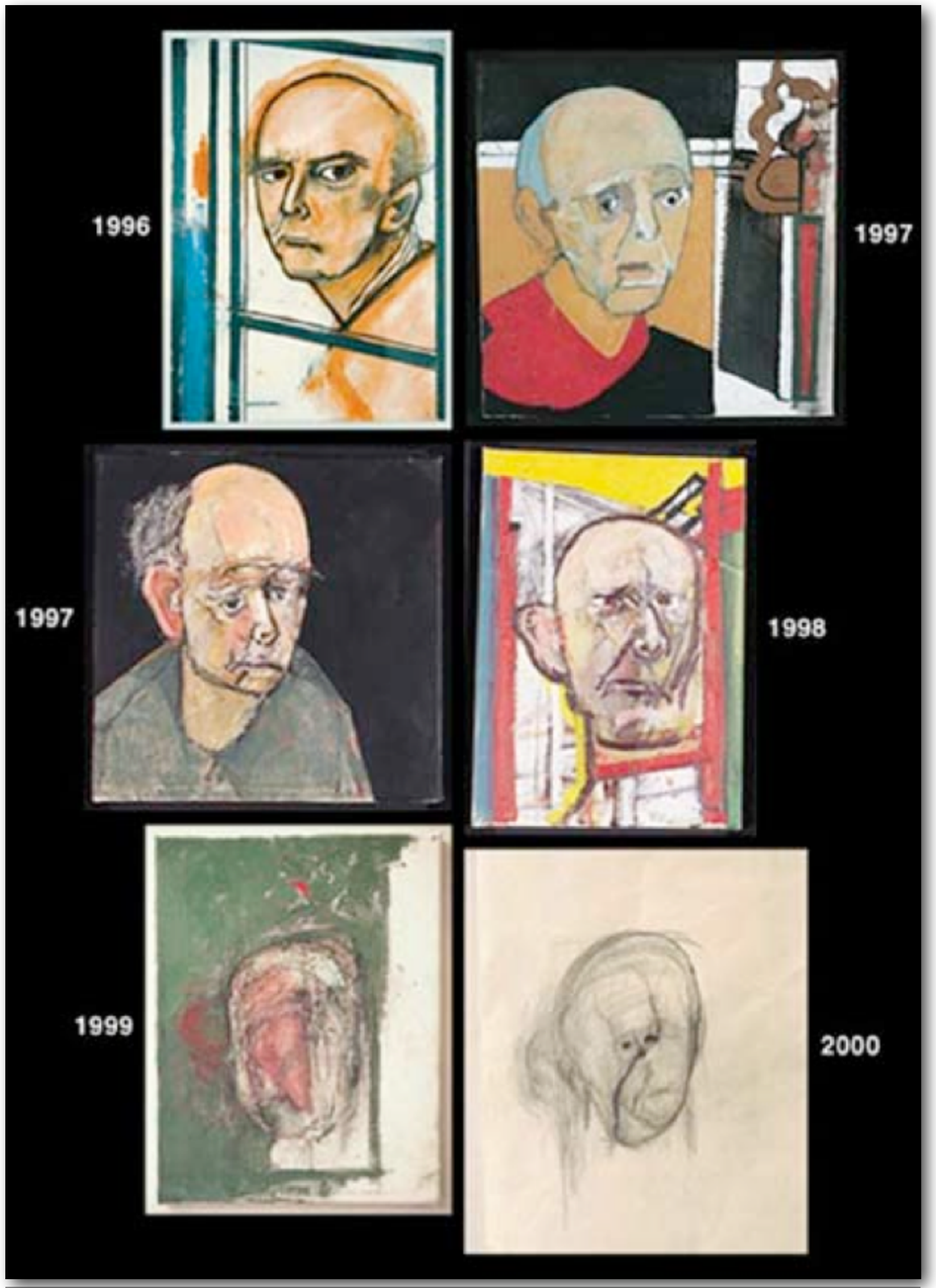


Alzheimer Disease
Parkinson Disease
Huntington Diseae
Frontotemporal Dementia
Lou Gehrig's Disease (ALS)

Alzheimer’s disease

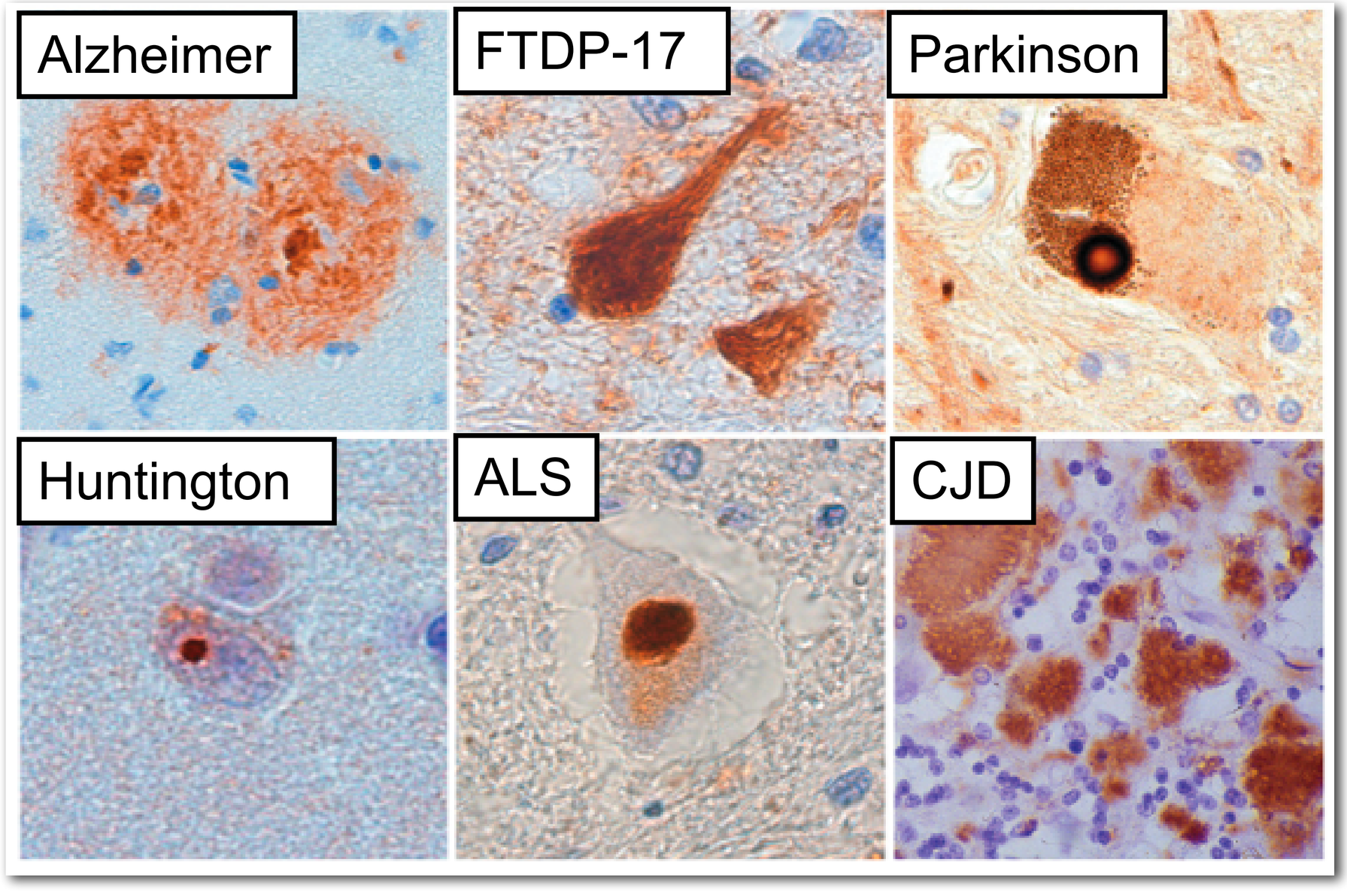


Alzheimer's disease



Parkinson's disease

Protein Aggregates in Neurodegenerative Diseases



Adapted from Forman, Trojanowski, and Lee 2004

Protein Aggregates in Neurodegenerative Diseases

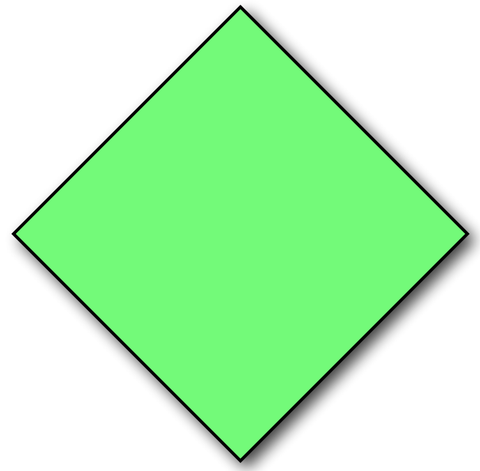
Protein Aggregates in Neurodegenerative Diseases

Normal Protein

Protein Aggregates in Neurodegenerative Diseases

Normal Protein

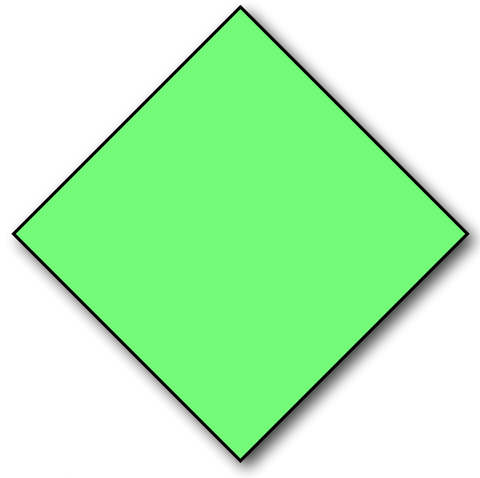
Misfolded Protein

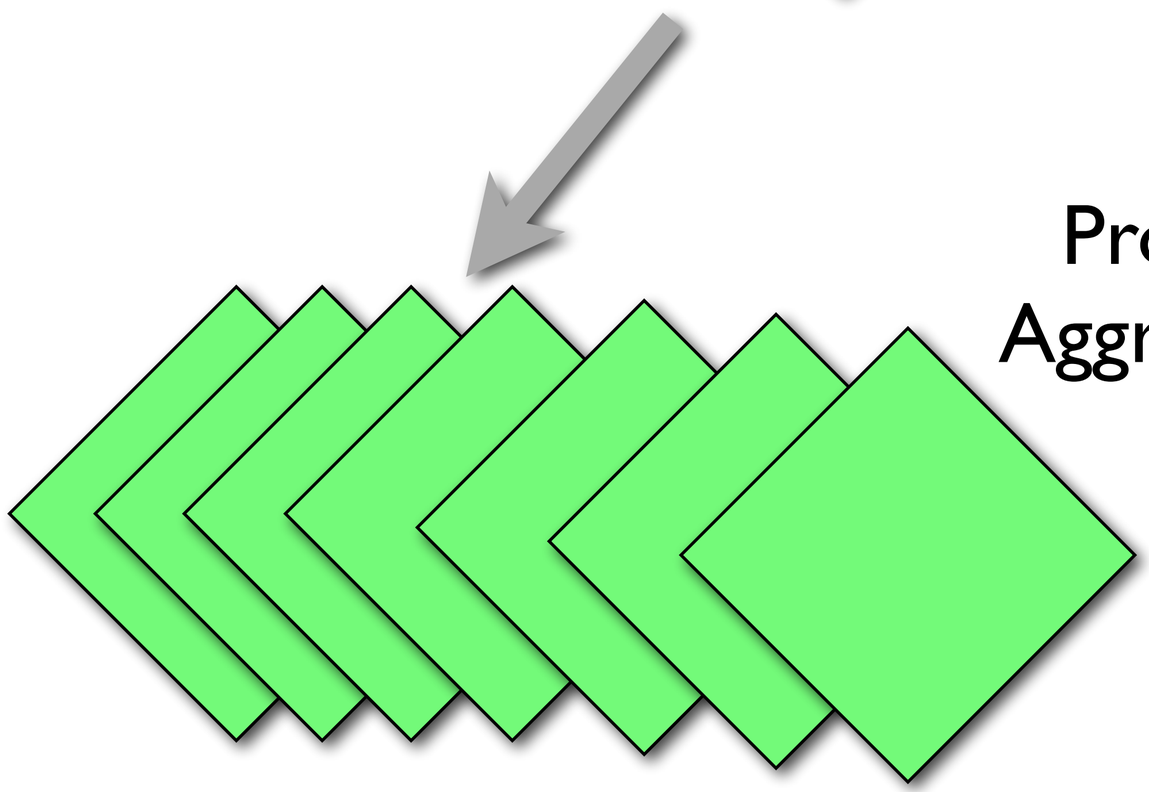


Protein Aggregates in Neurodegenerative Diseases

Normal Protein

Misfolded Protein



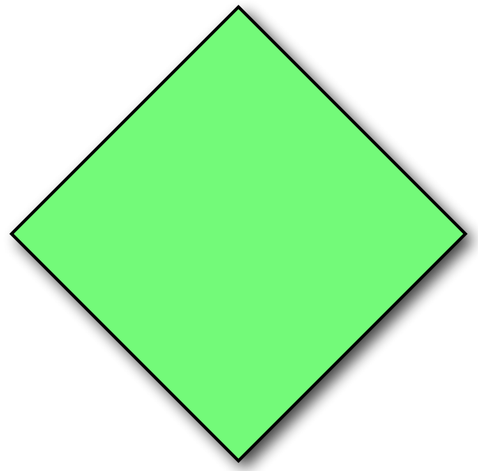


Protein
Aggregates

Protein Aggregates in Neurodegenerative Diseases

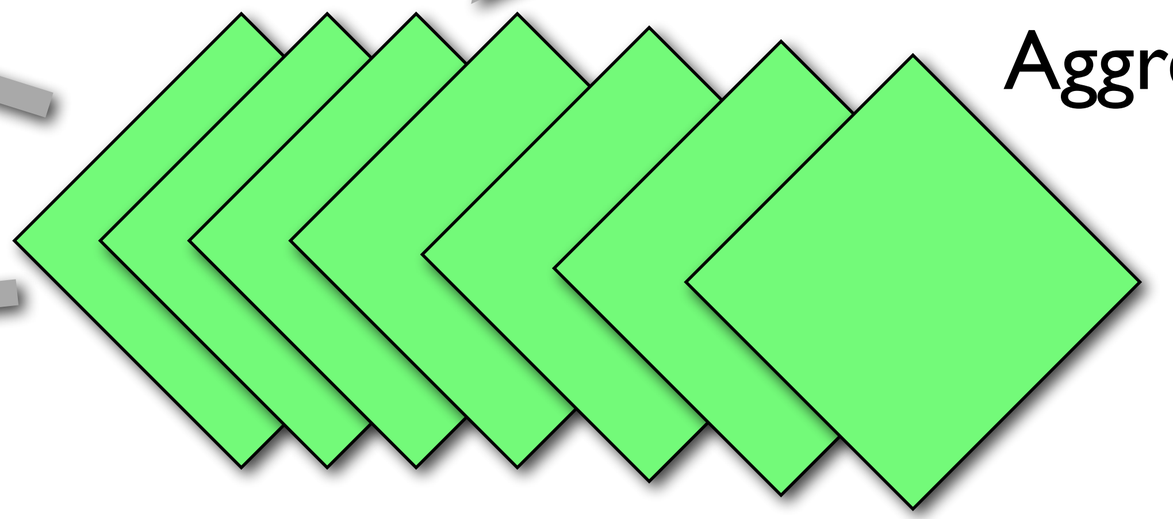
Normal Protein

Misfolded Protein



Loss of Protein's Normal Function

Toxic Gain of Function



Protein Aggregates

Today's Plan

1. Alzheimer's Disease

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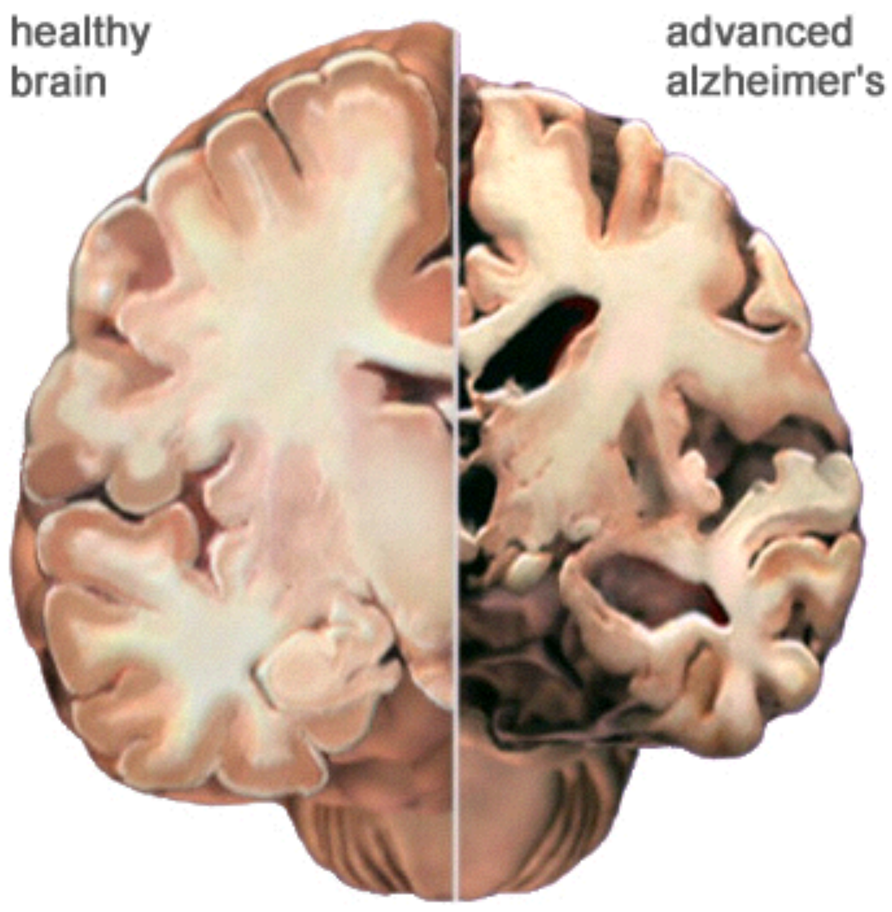
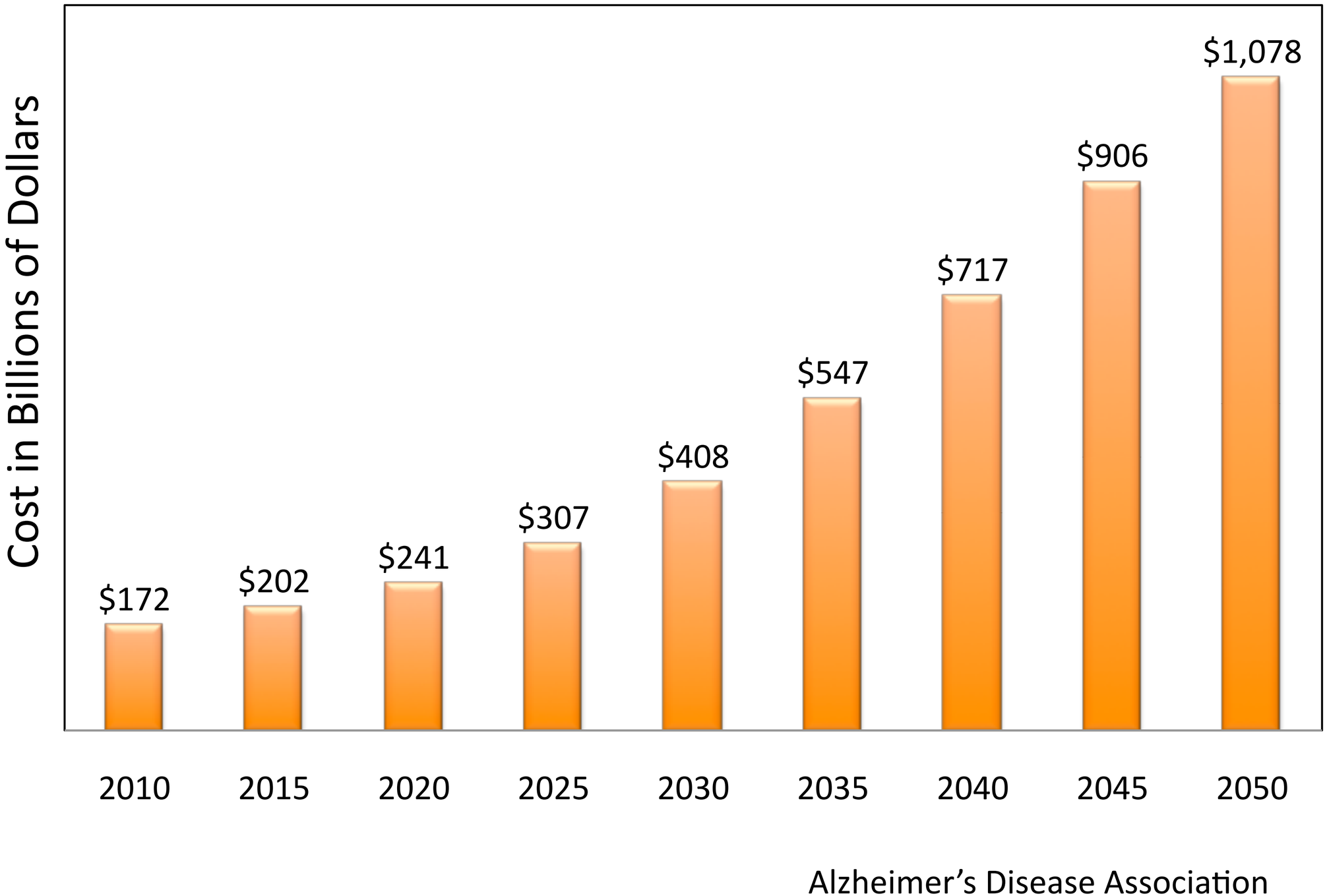
Alzheimer's Disease

- 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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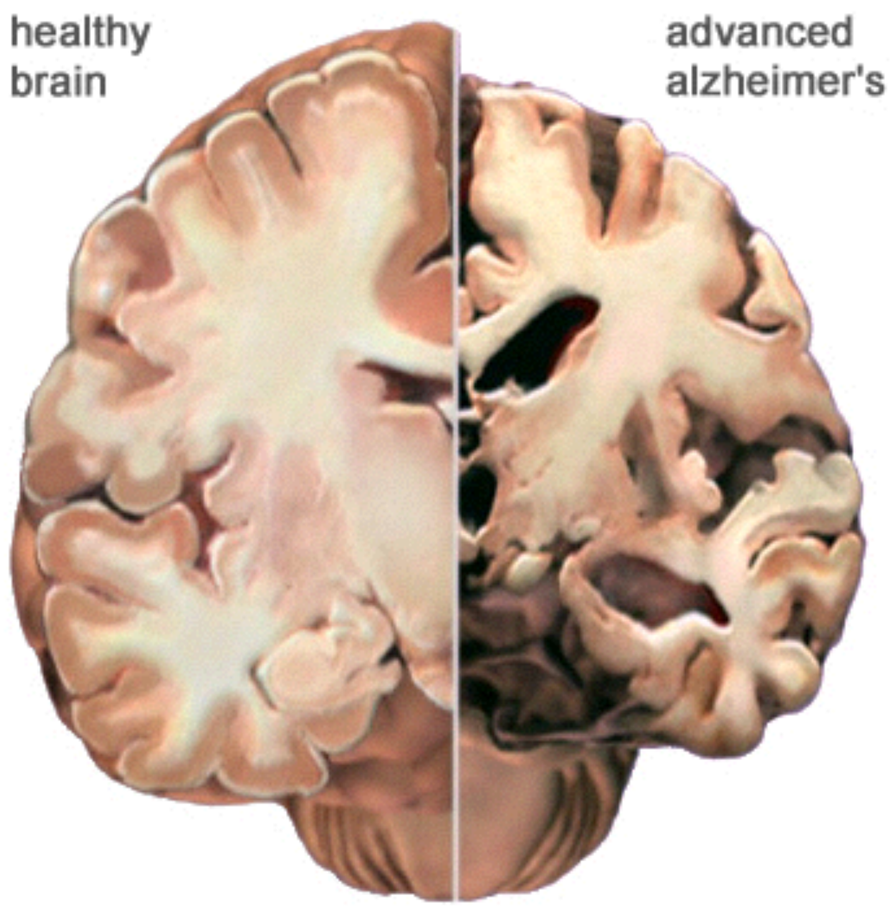
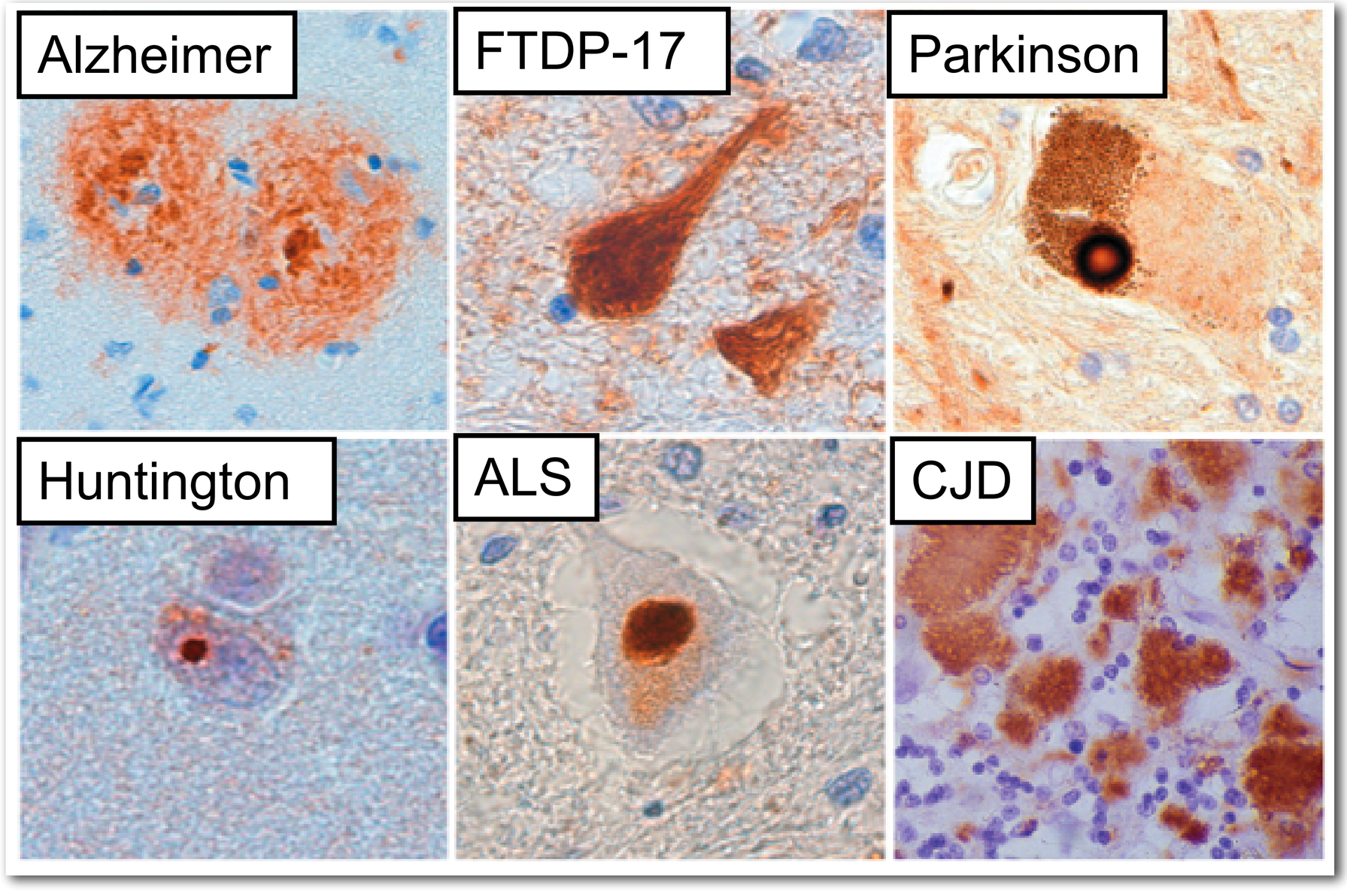


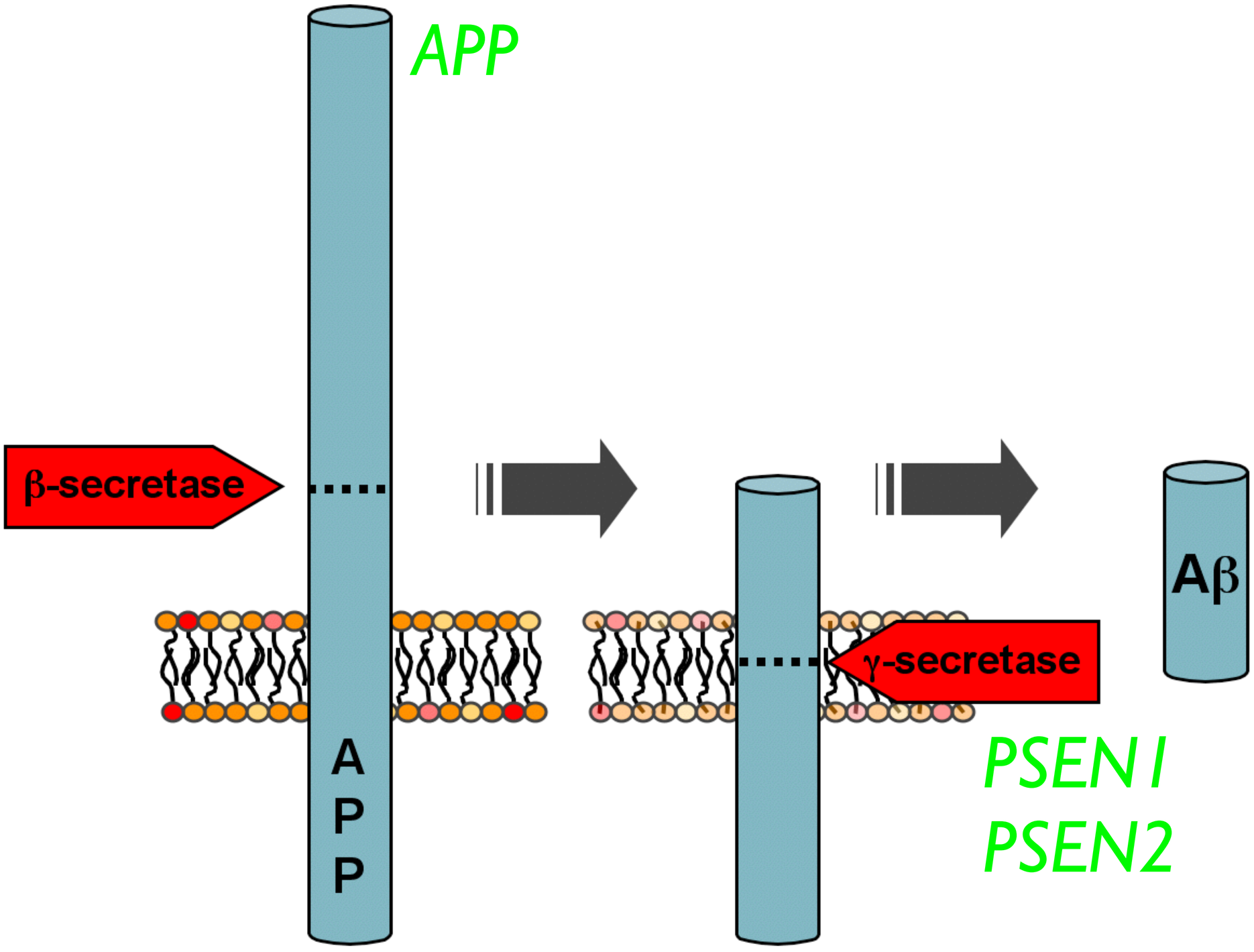
Protein Aggregates in Neurodegenerative Diseases

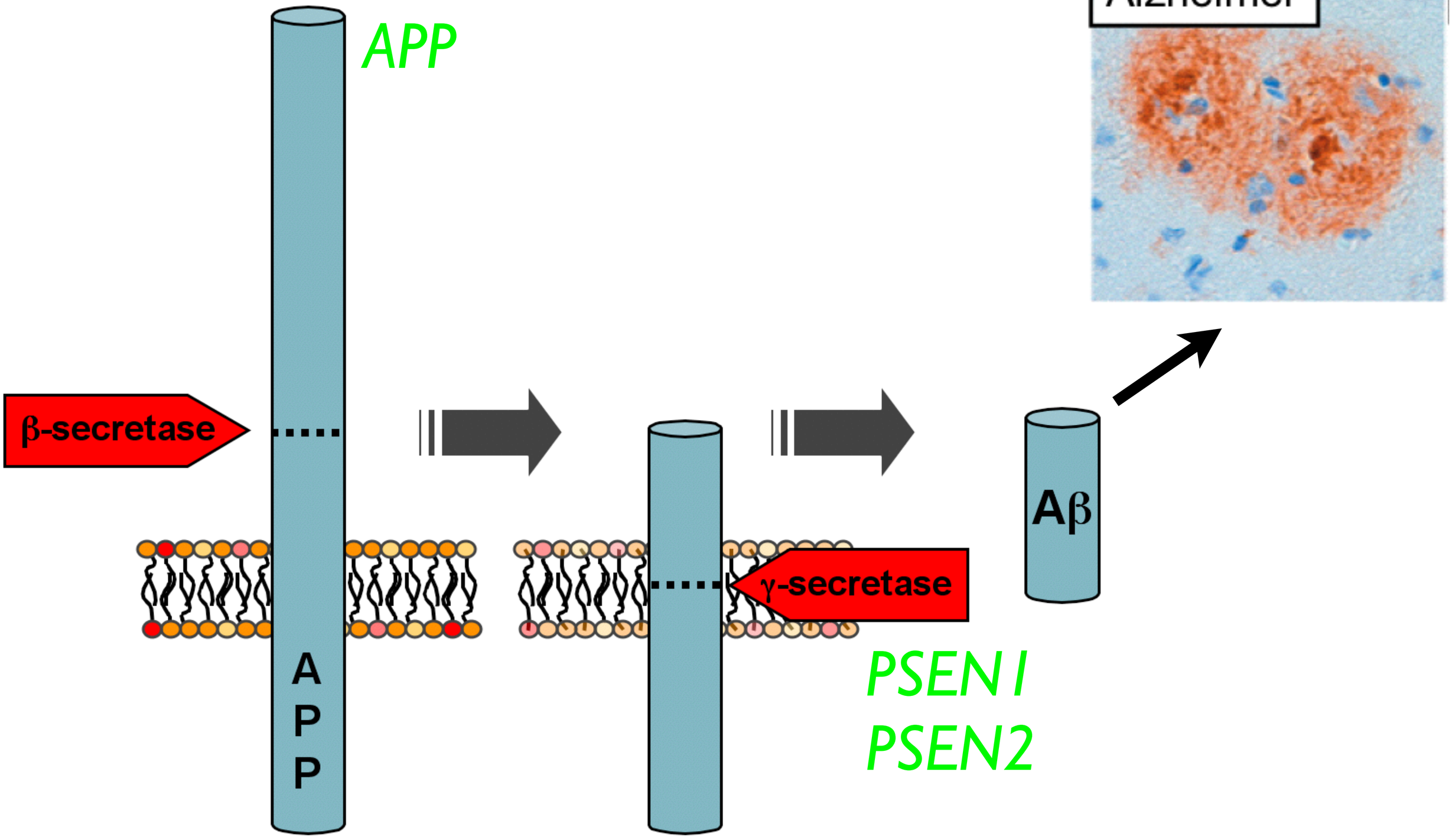


Adapted from Forman, Trojanowski, and Lee 2004

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
A
P
P
γ-secretase
Aβ
PSEN I
PSEN2


APP
β-secretase
A
P
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γ-secretase
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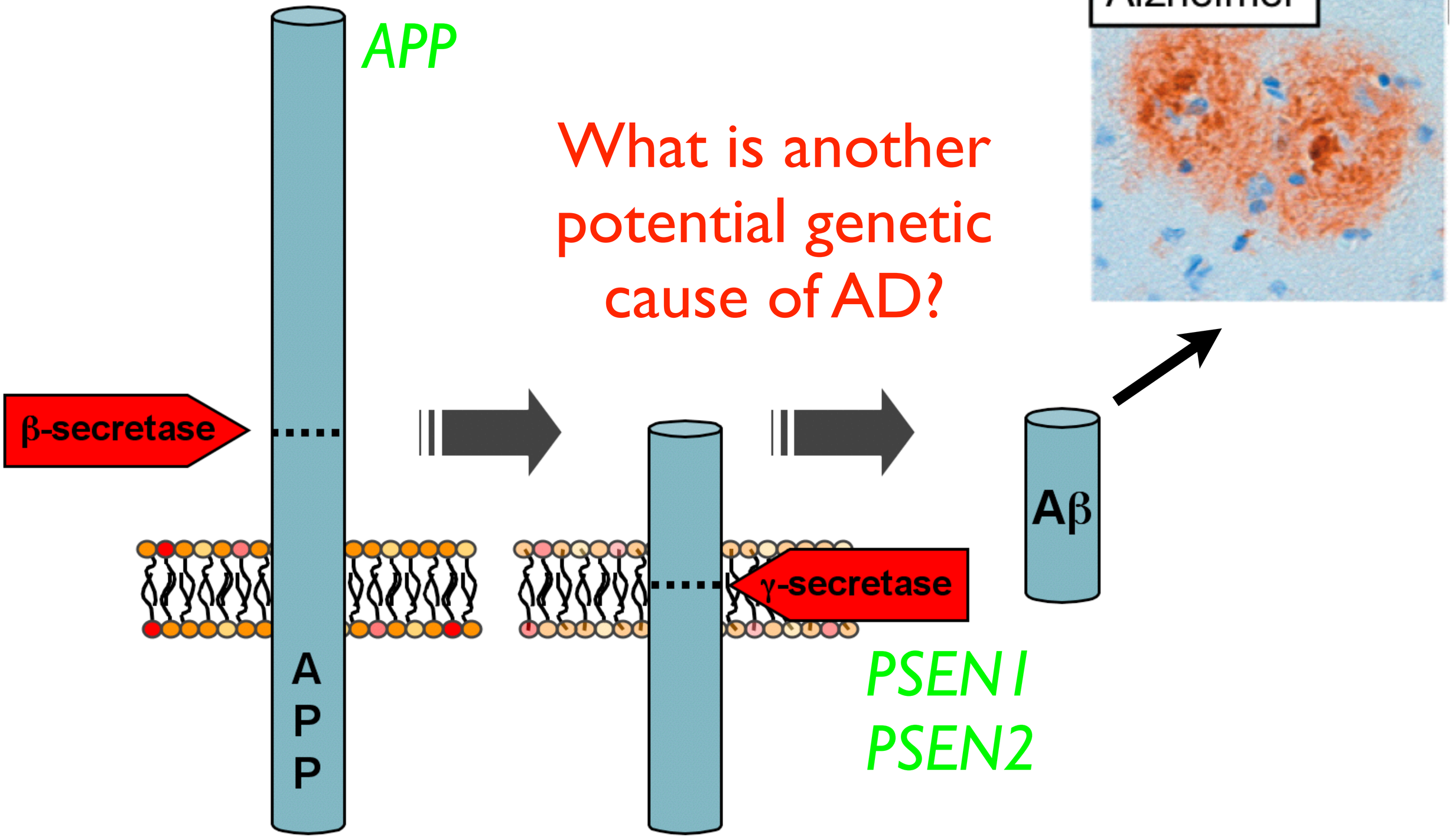
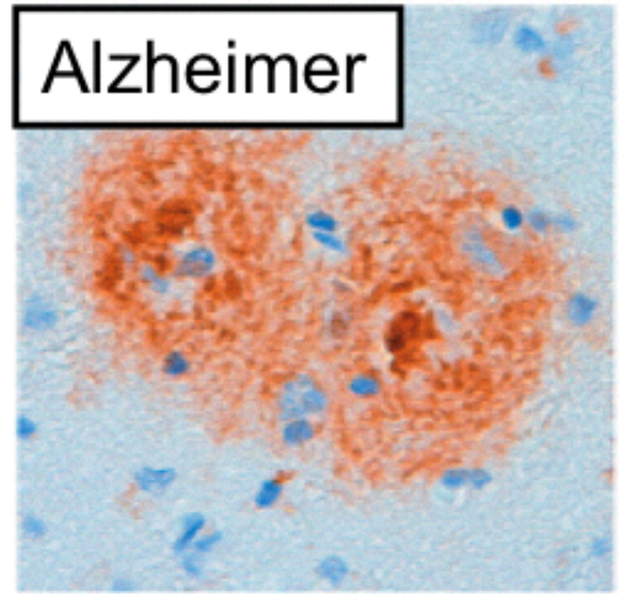


What is another potential genetic cause of AD?

APP (A clue: *APP* on chr21)

What is another potential genetic cause of AD?



β-secretase

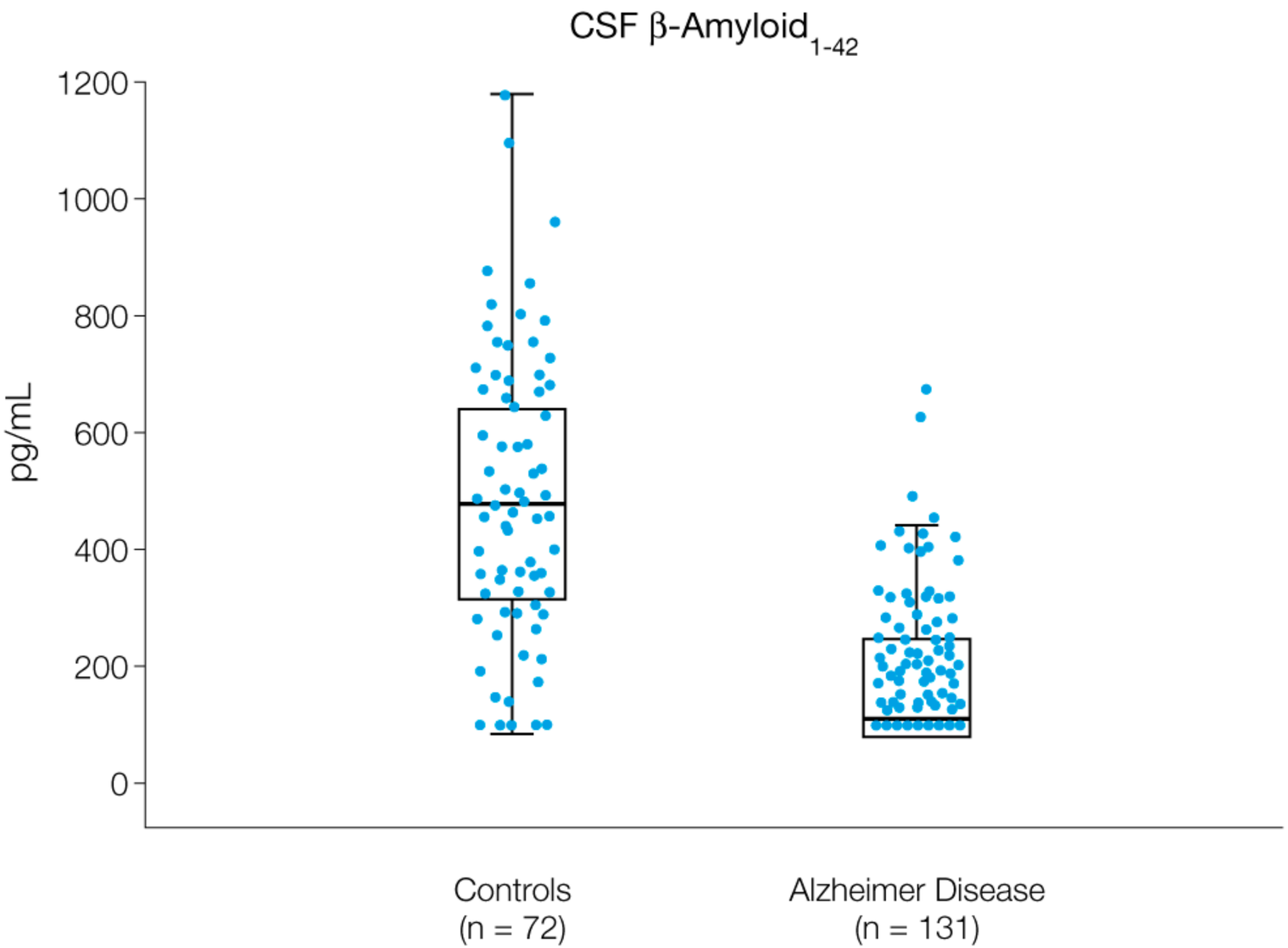
A P P

γ-secretase

Aβ

PSEN1
PSEN2

Spinal Fluid Markers:
Beta-Amyloid Is Reduced



Sunderland et al., *JAMA*, 2003

LETTER

doi:10.1038/nature11283

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

Thorlakur Jonsson[1], Jasvinder K. Atwal[2], Stacy Steinberg[1], Jon Snaedal[3], Palmi V. Jonsson[3,8], Sigurbjorn Bjornsson[3], Hreinn Stefansson[1], Patrick Sulem[1], Daniel Gudbjartsson[1], Janice Maloney[2], Kwame Hoyte[2], Amy Gustafson[2], Yichin Liu[2], Yanmei Lu[2], Tushar Bhangale[2], Robert R. Graham[2], Johanna Huttenlocher[1,4], Gyda Bjornsdottir[1], Ole A. Andreassen[5], Erik G. Jönsson[6], Aarno Palotie[7], Timothy W. Behrens[2], Olafur T. Magnusson[1], Augustine Kong[1], Unnur Thorsteinsdottir[1,8], Ryan J. Watts[2] & Kari Stefansson[1,8]

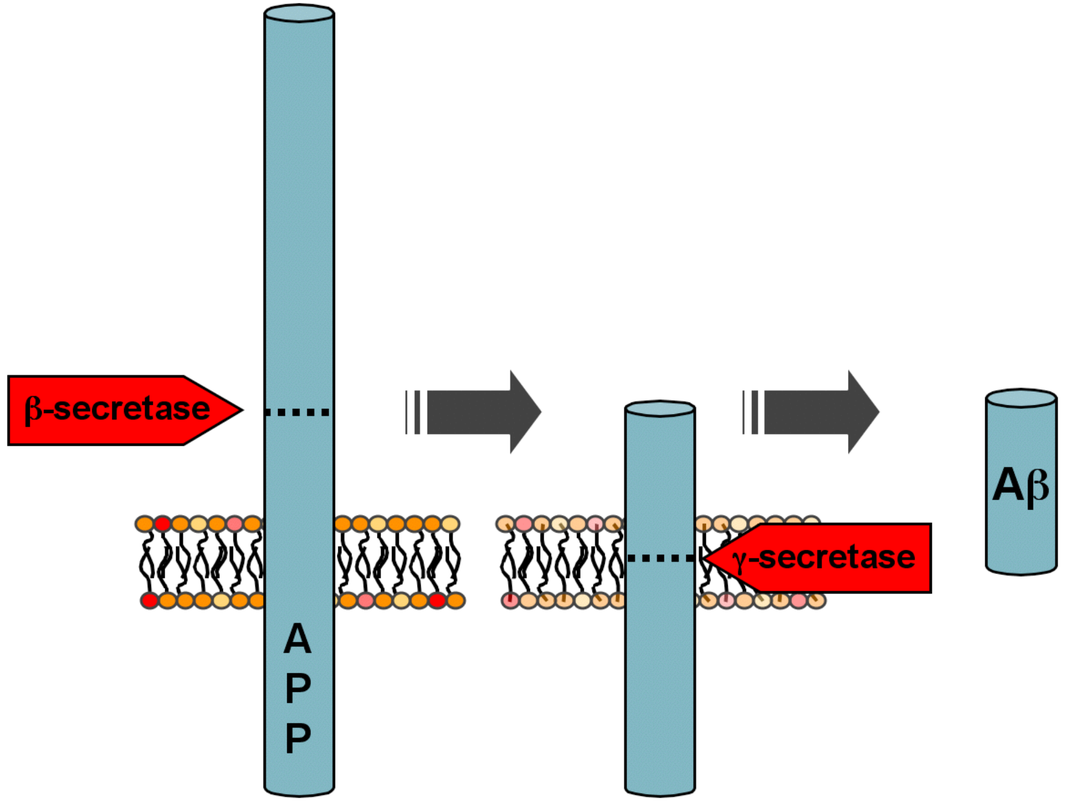
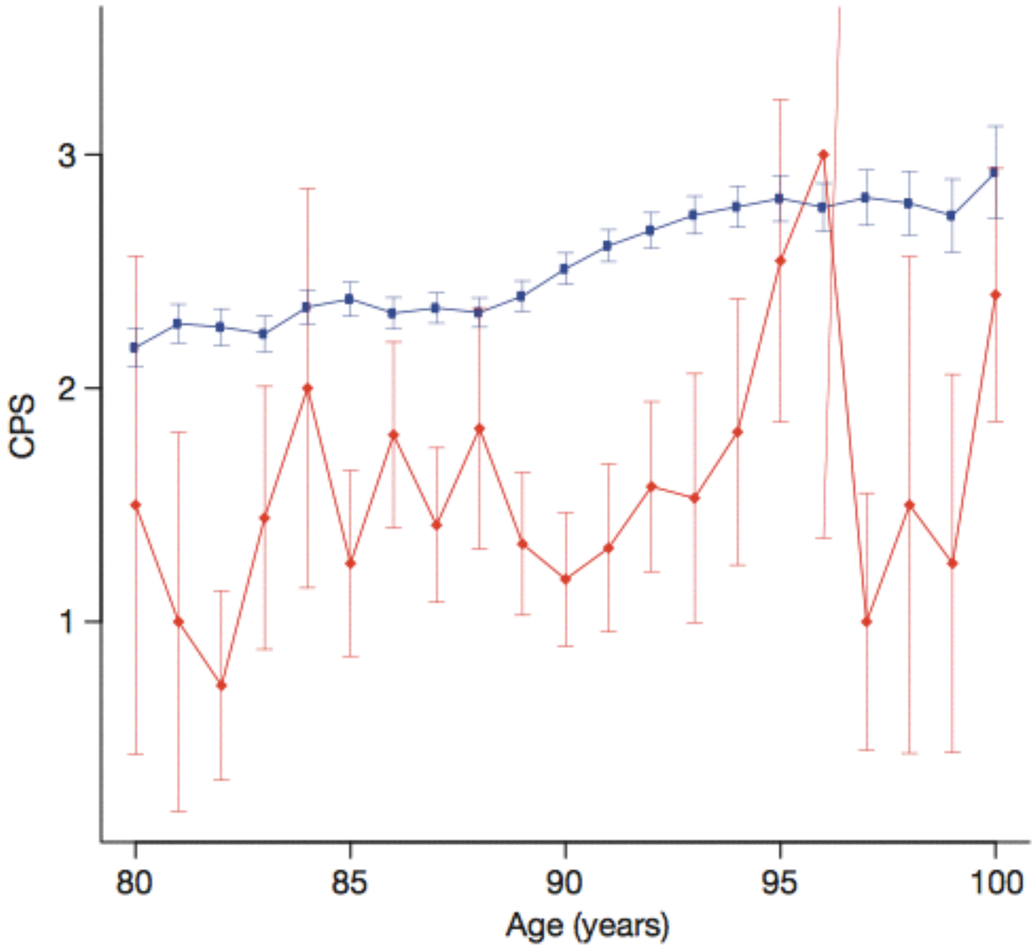


Table 1 | APP A673T protects against Alzheimer's disease

Analysis	1/OR	OR	*P* value	Controls		
				Frequency (%)	N_{chip}	$N_{in\ silico}$
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

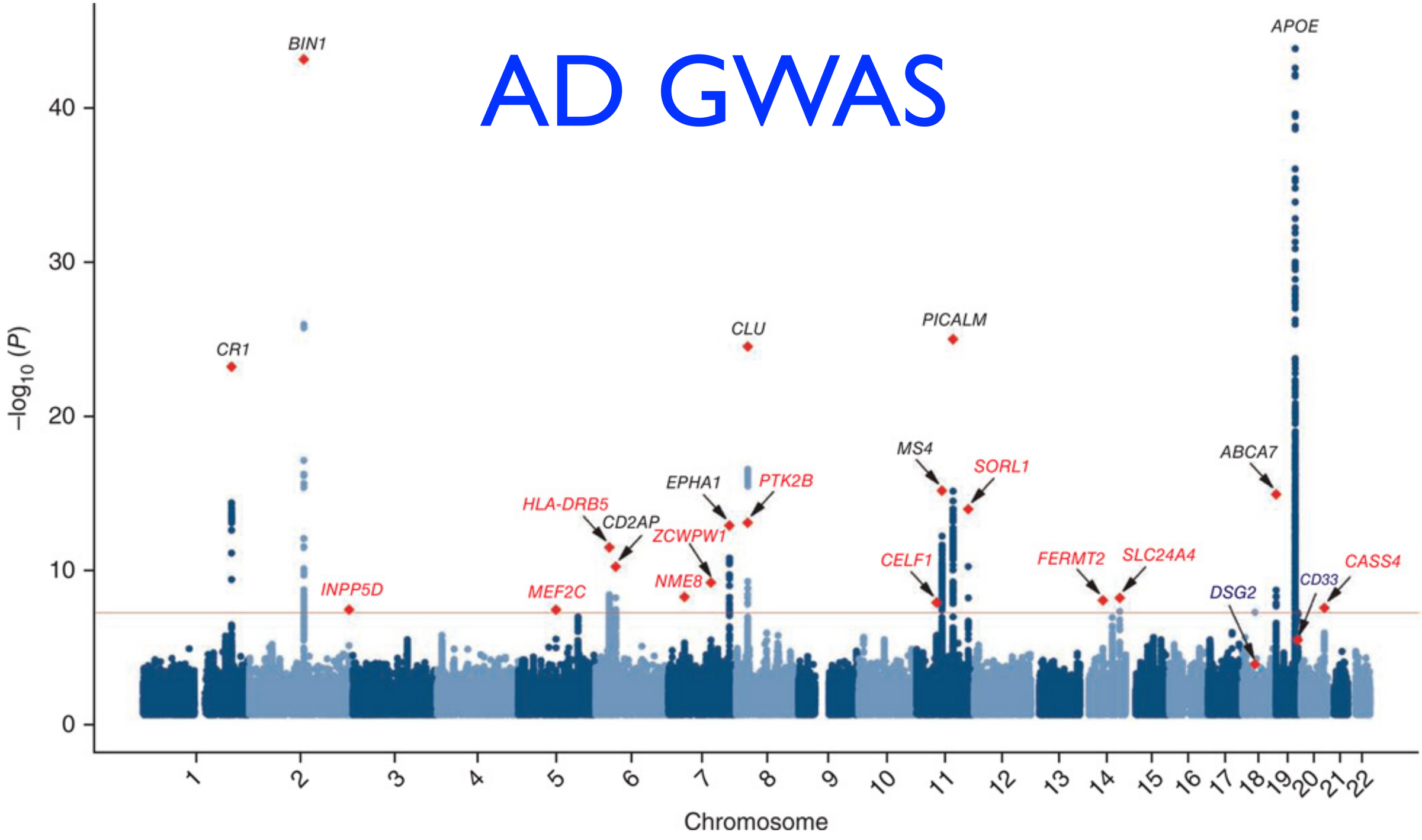
The table shows association results, comparing patients with Alzheimer's disease (AD) to three different control groups (top line gives numbers for patients with Alzheimer's disease only). N_{chip}, number of individuals with chip-based genotype information; $N_{in\ silico}$, number of individuals with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

AD GWAS



Lambert et al., *Nat Genet* 2013

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	rs11136000	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)

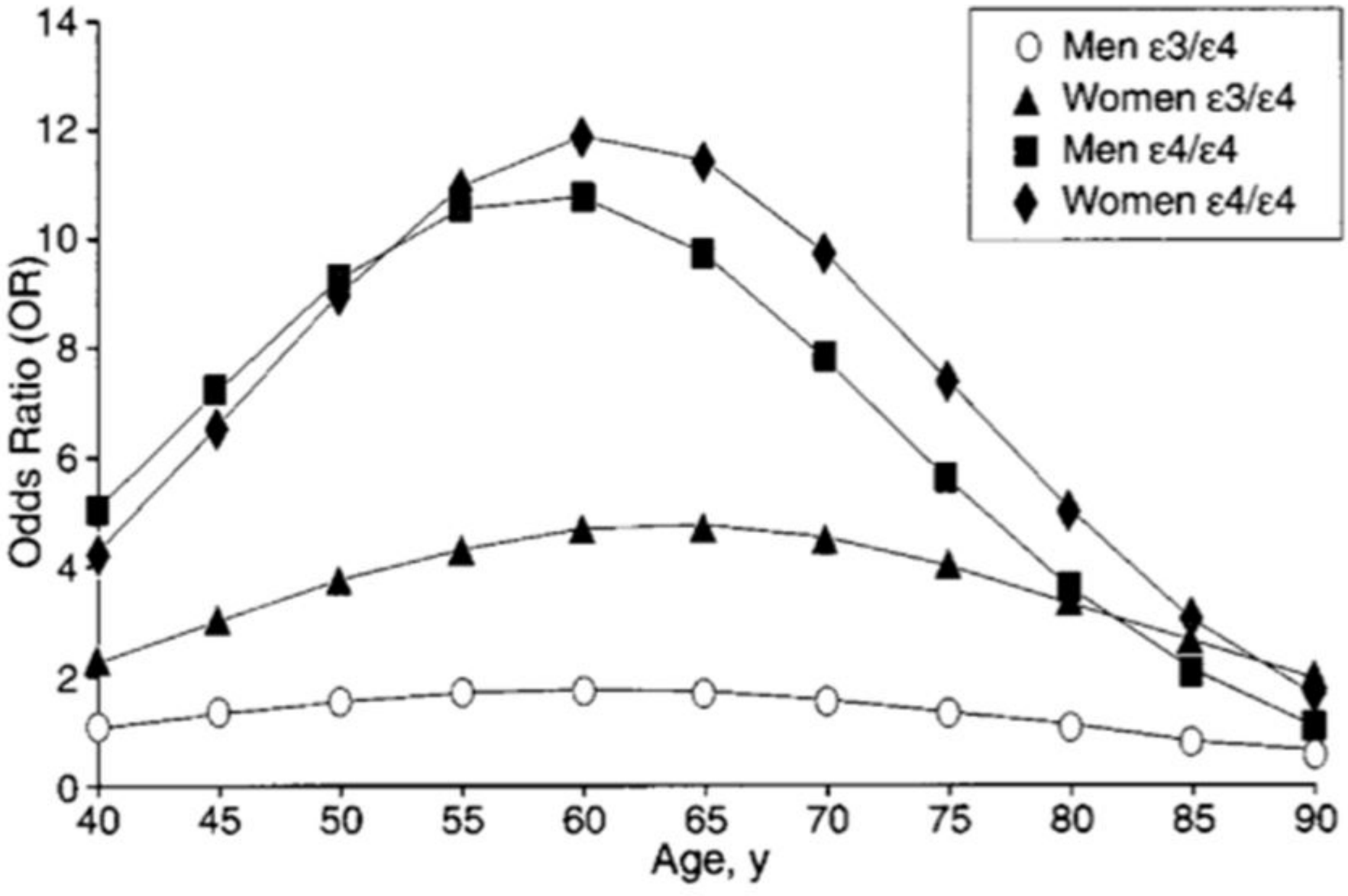
Two SNPs determine APOE variants

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

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

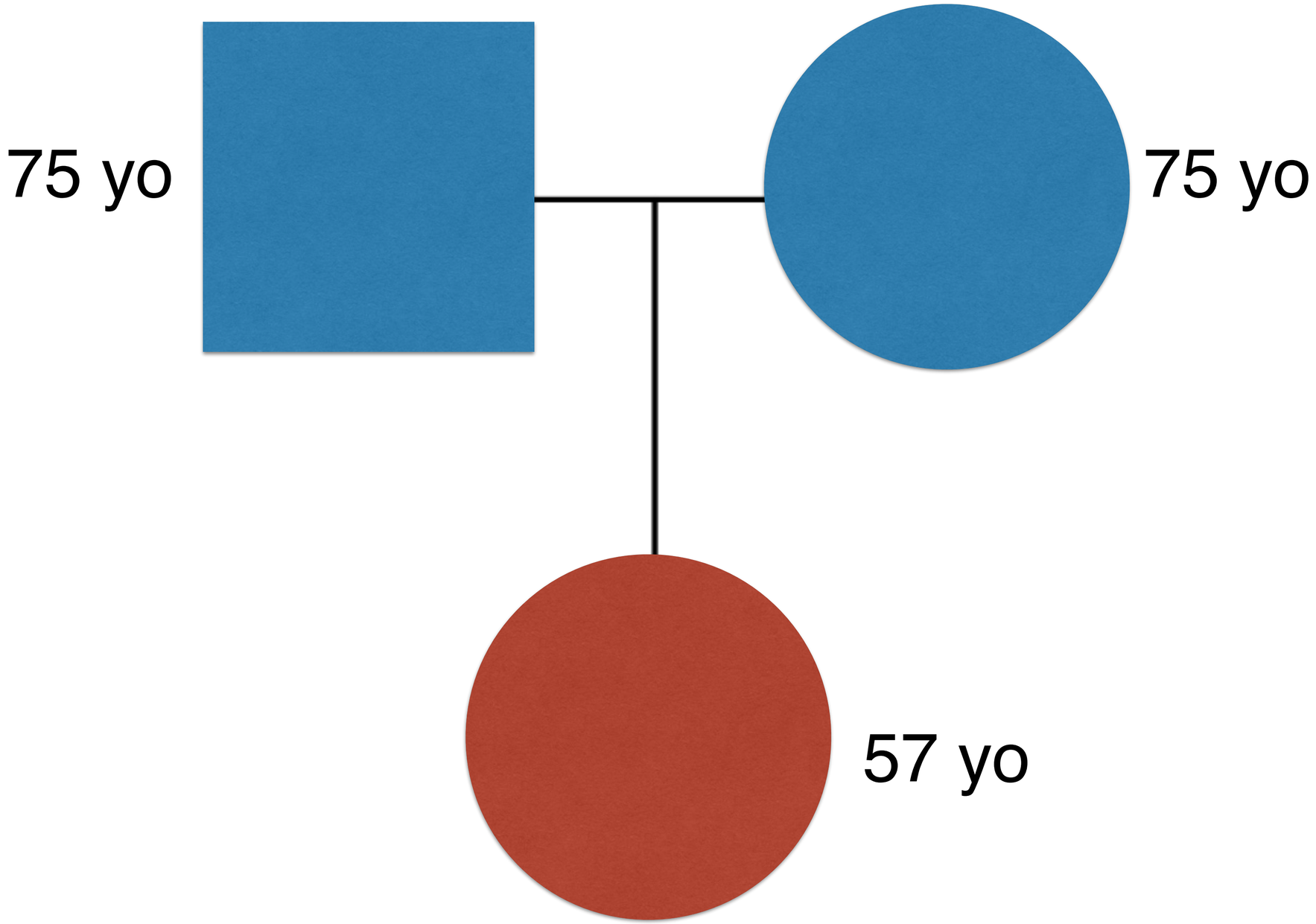
2 copies of ε4 allele = ~11 times increased risk for AD

Sex Modifies the APOE4 Effect (case-control data)



Farrer et al, *JAMA*, 1997

An interesting AD trio



collaboration w/ Mike Greicius, M.D. (Neurology)

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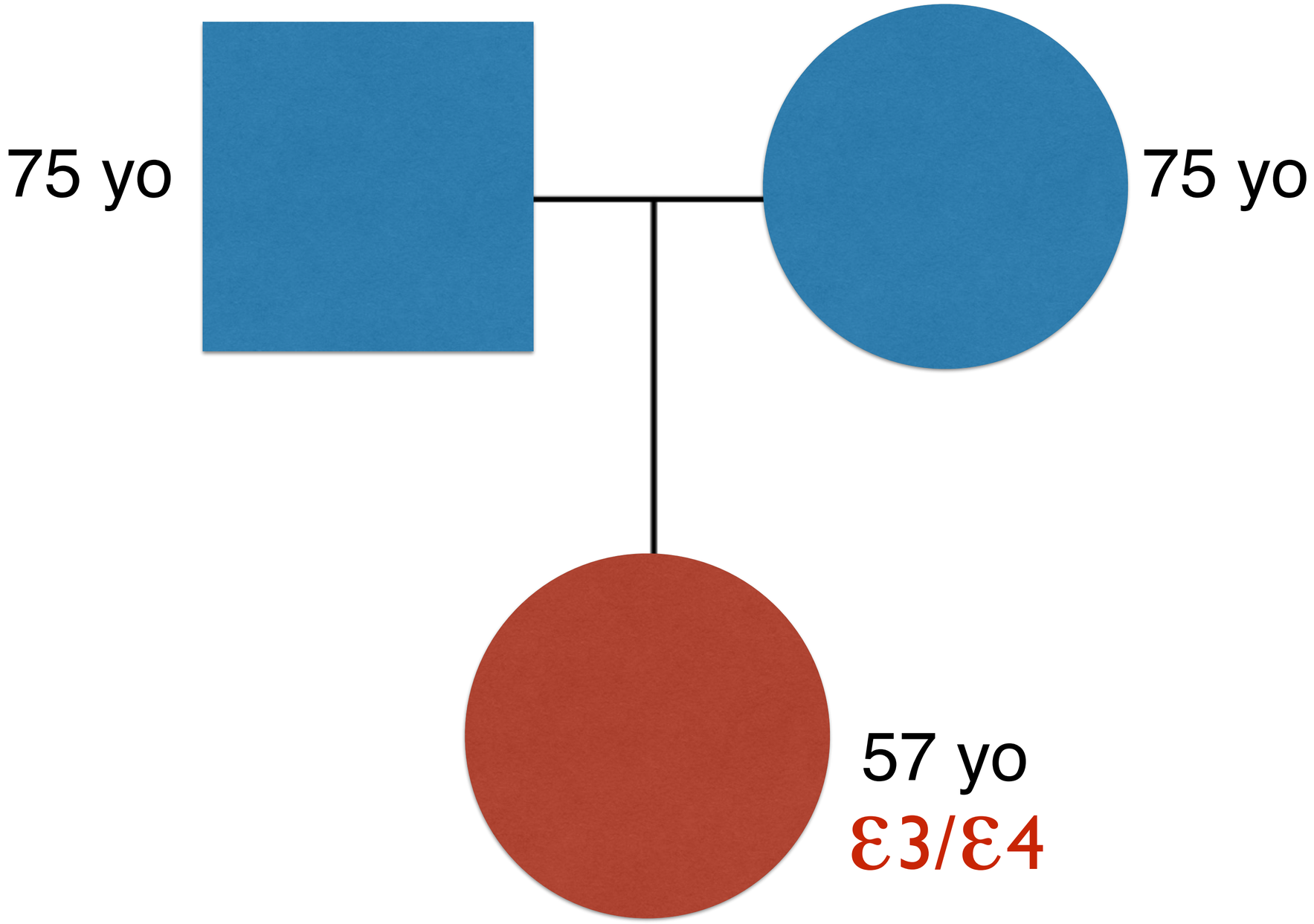

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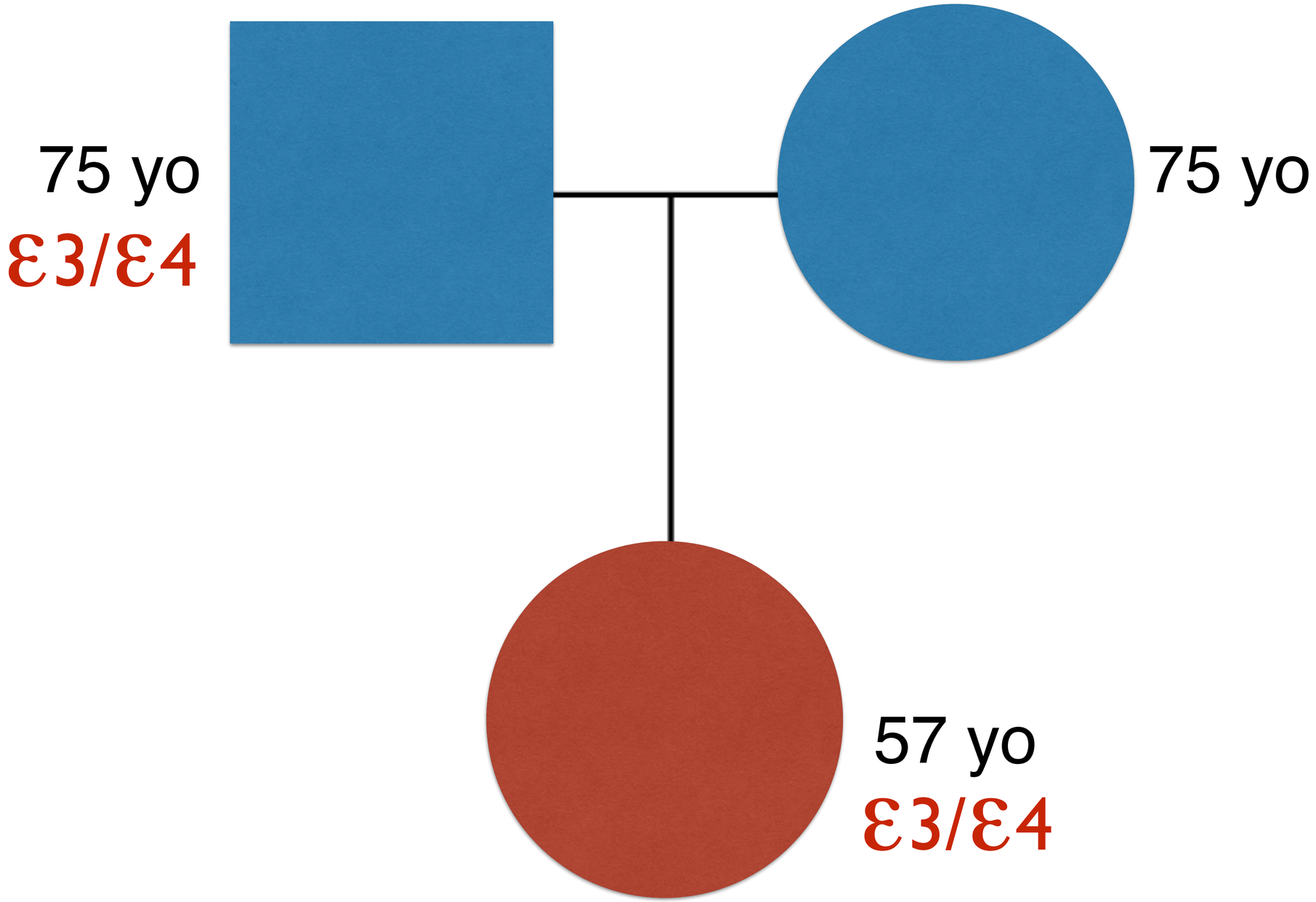

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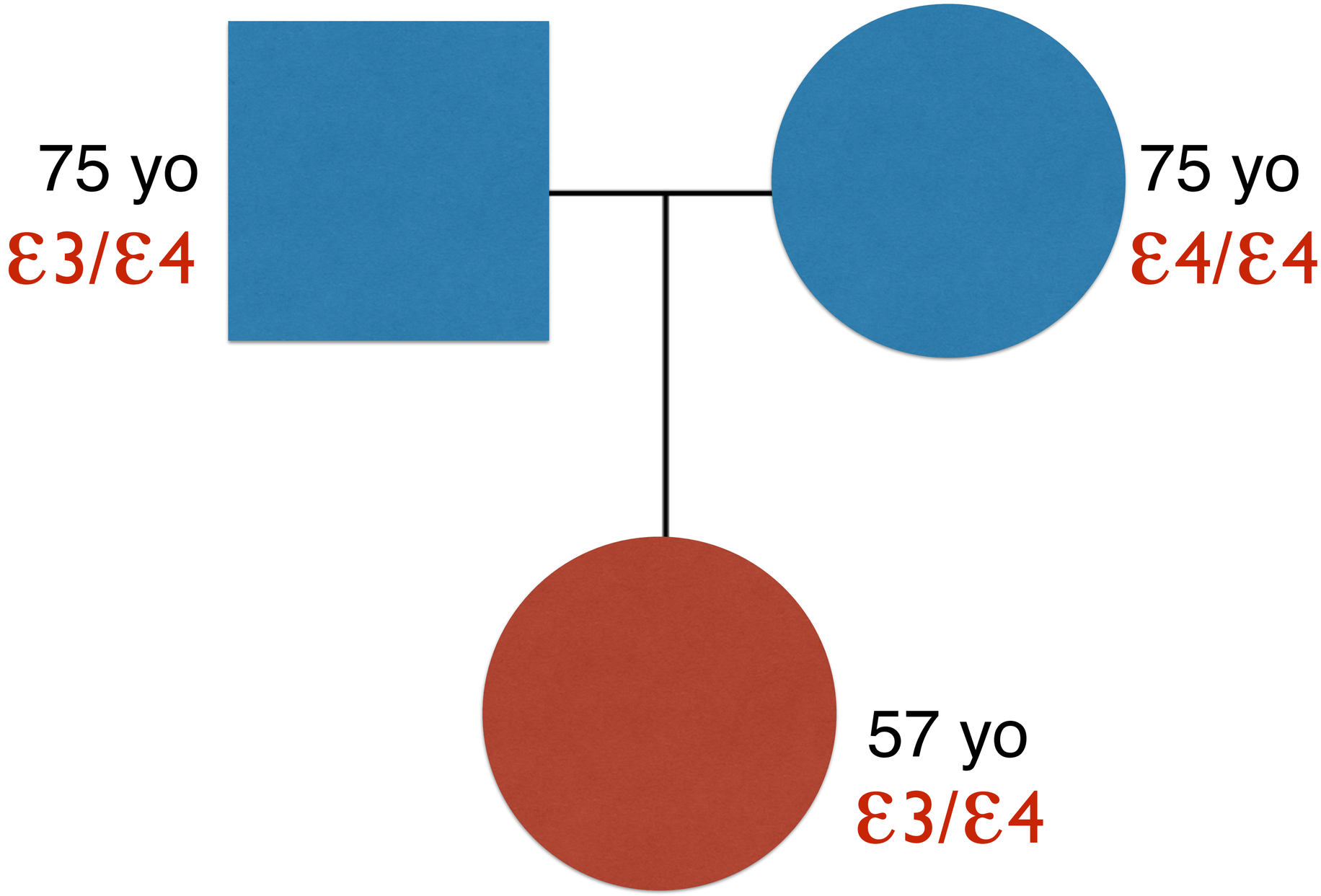

collaboration w/ Mike Greicius, M.D. (Neurology)

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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1. Alzheimer's Disease

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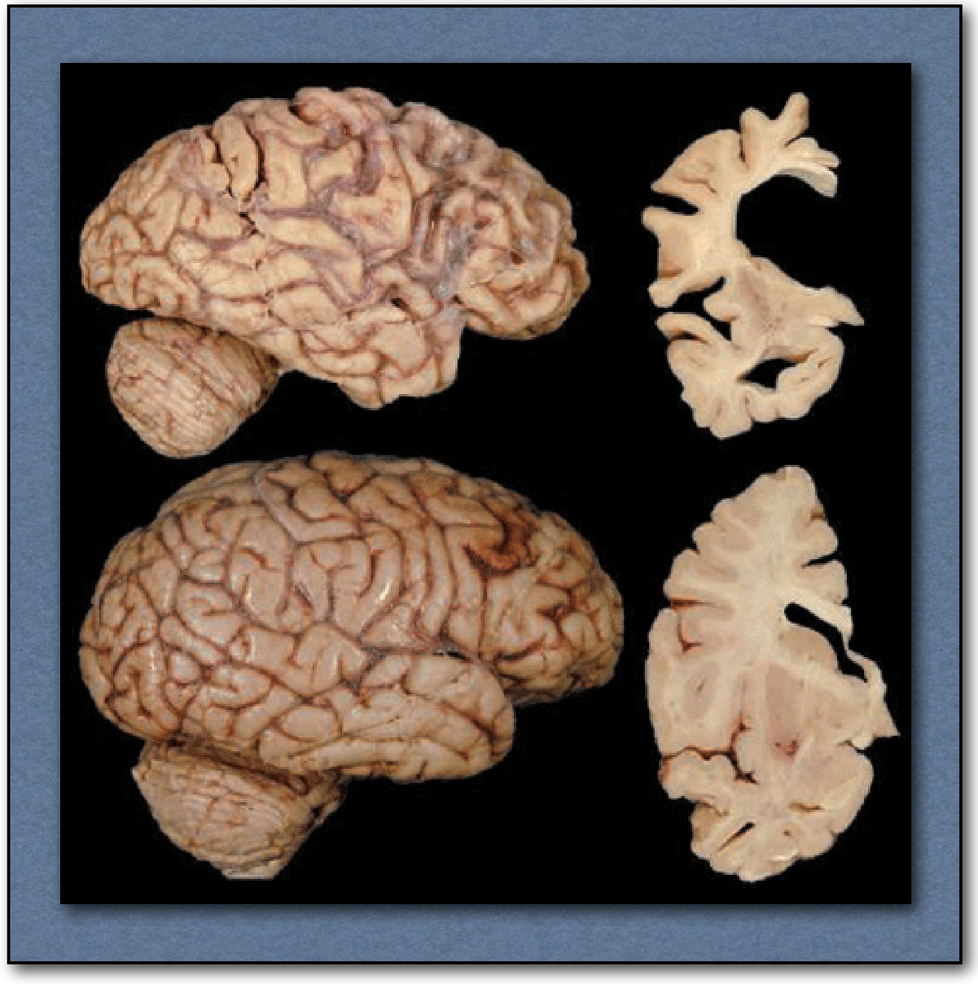
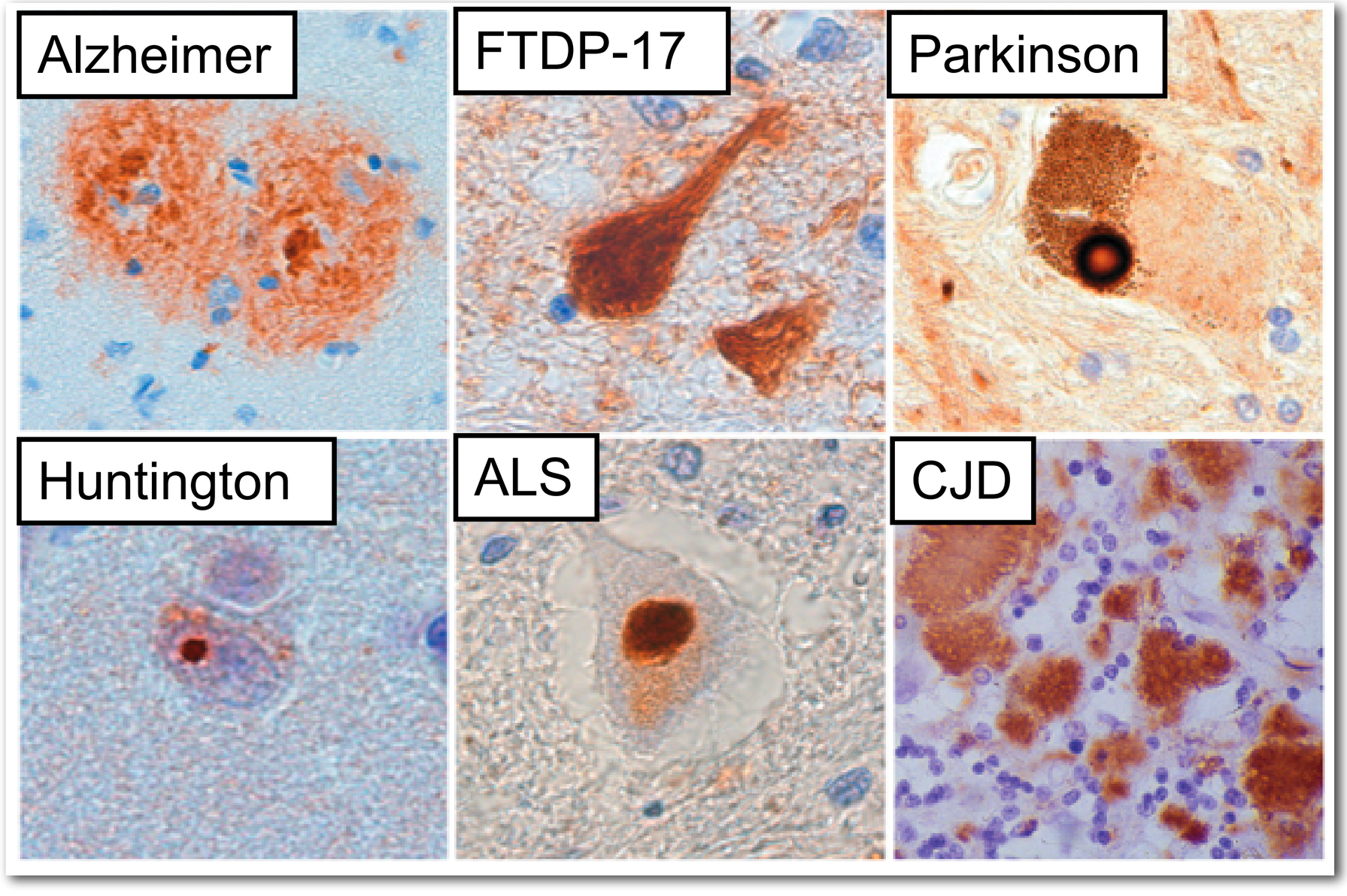
Frontotemporal lobar dementias (FTLDs)



- 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

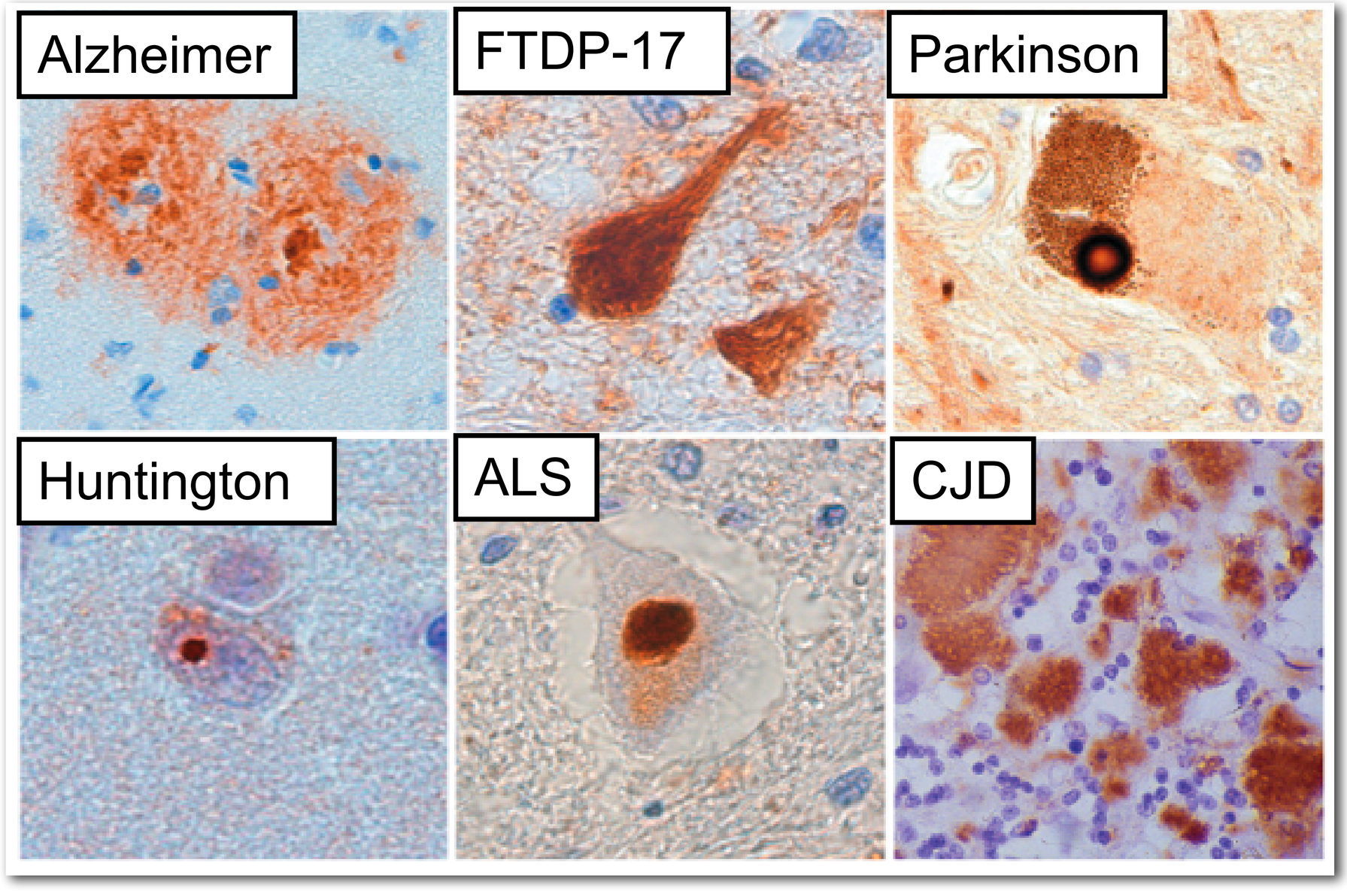


Adapted from Forman, Trojanowski, and Lee 2004

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

?

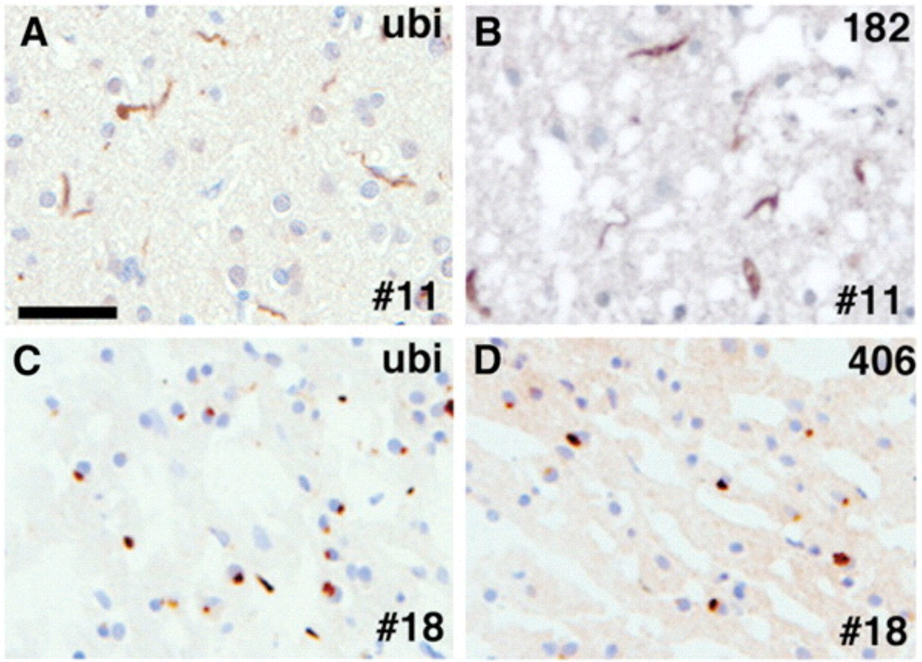
REPORTS

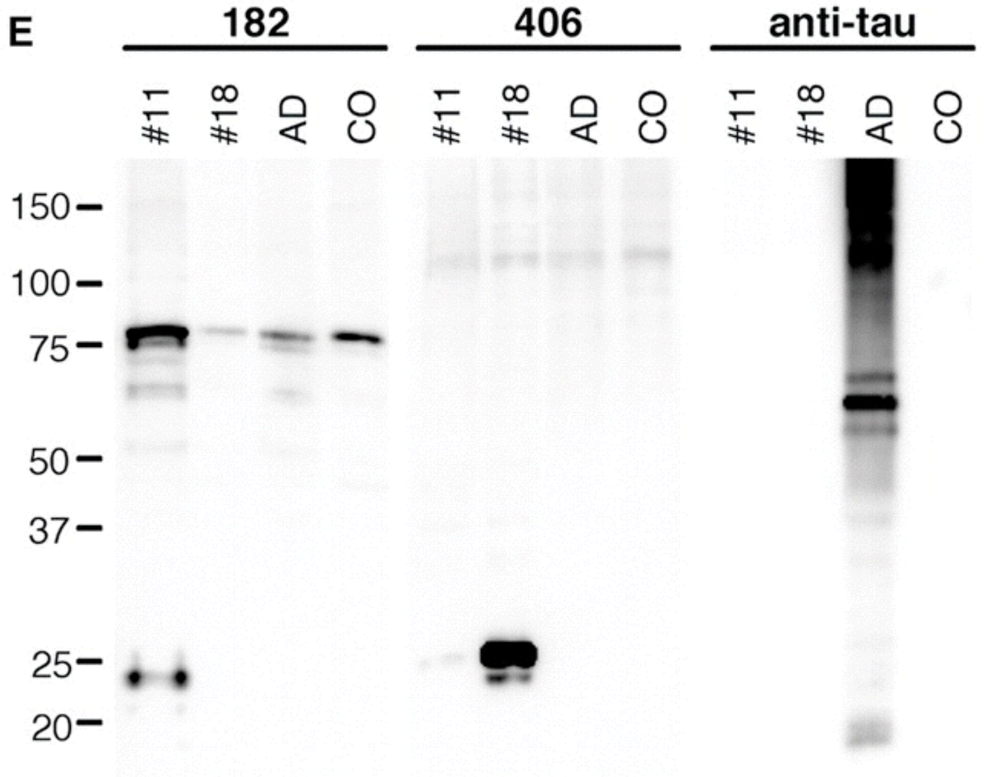
Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

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





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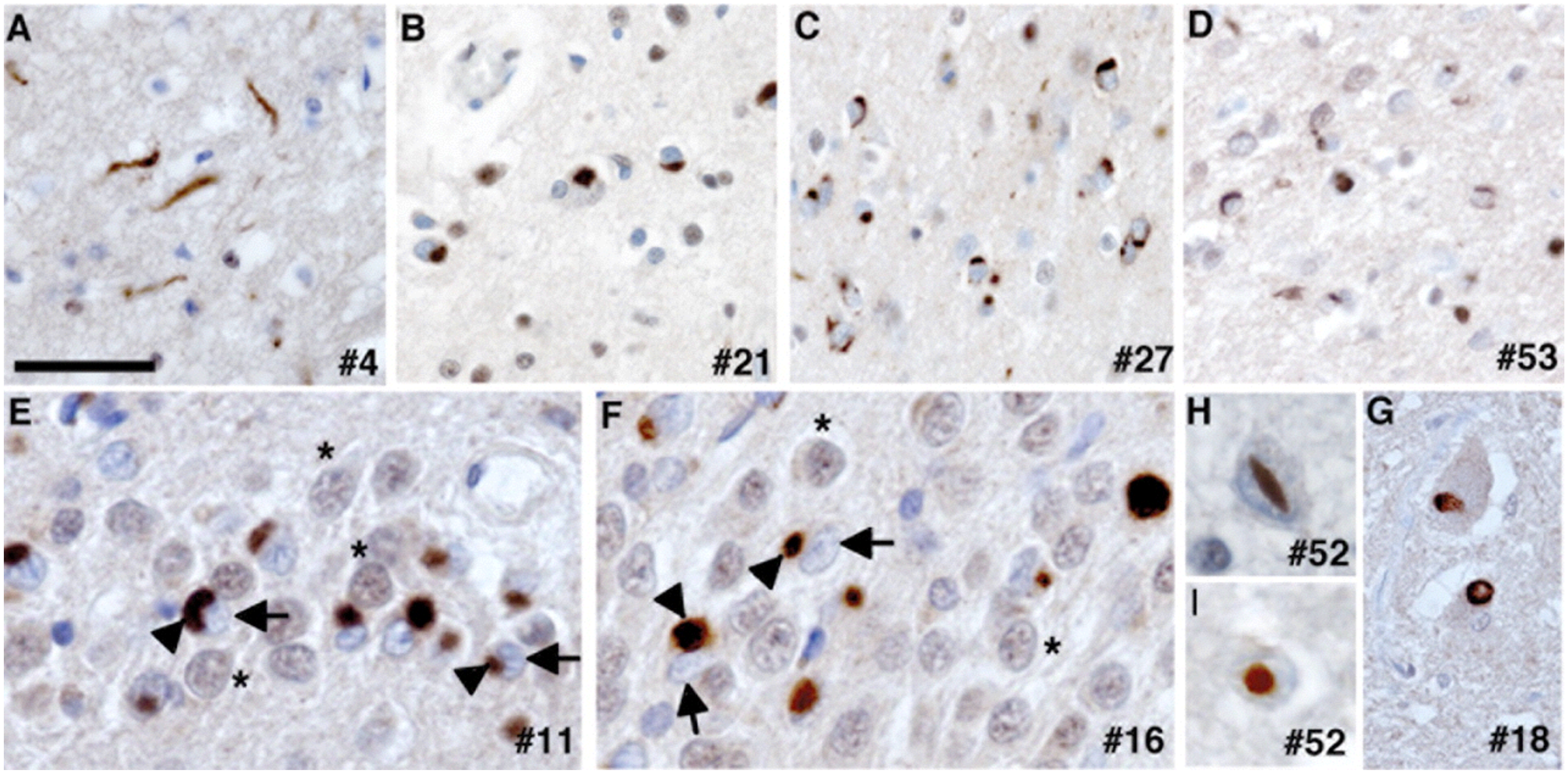
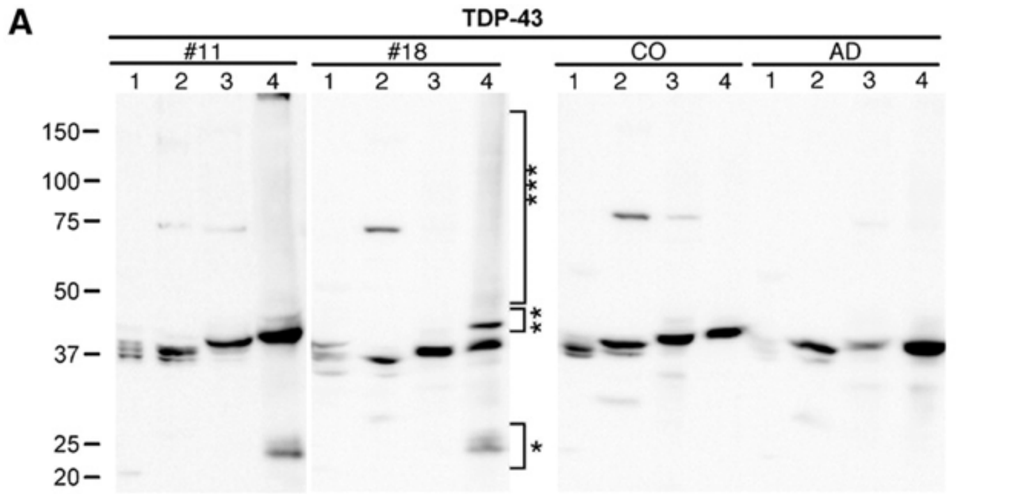
Neumann et al., *Science* 2006

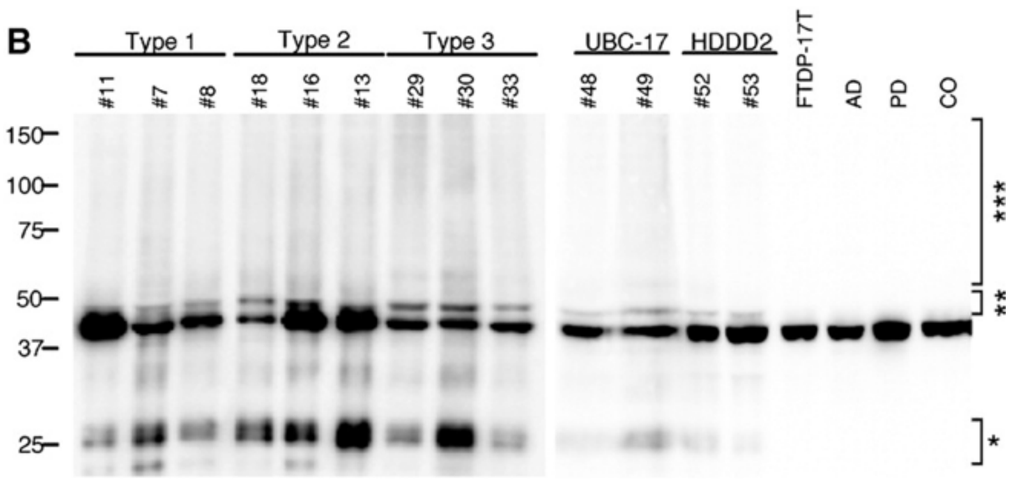
TDP-43 pathology in FTLD-U

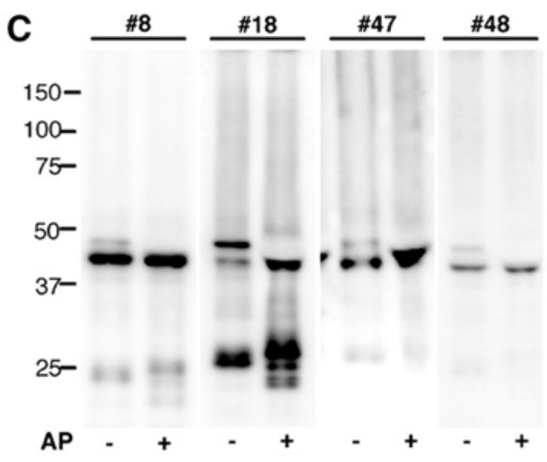


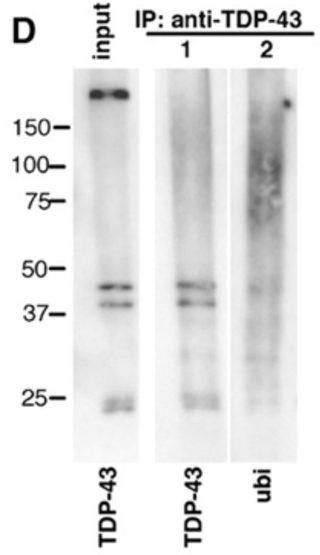
Neumann et al.,
Science 2006

TDP-43 "biochemical signature"









Neumann et al.,
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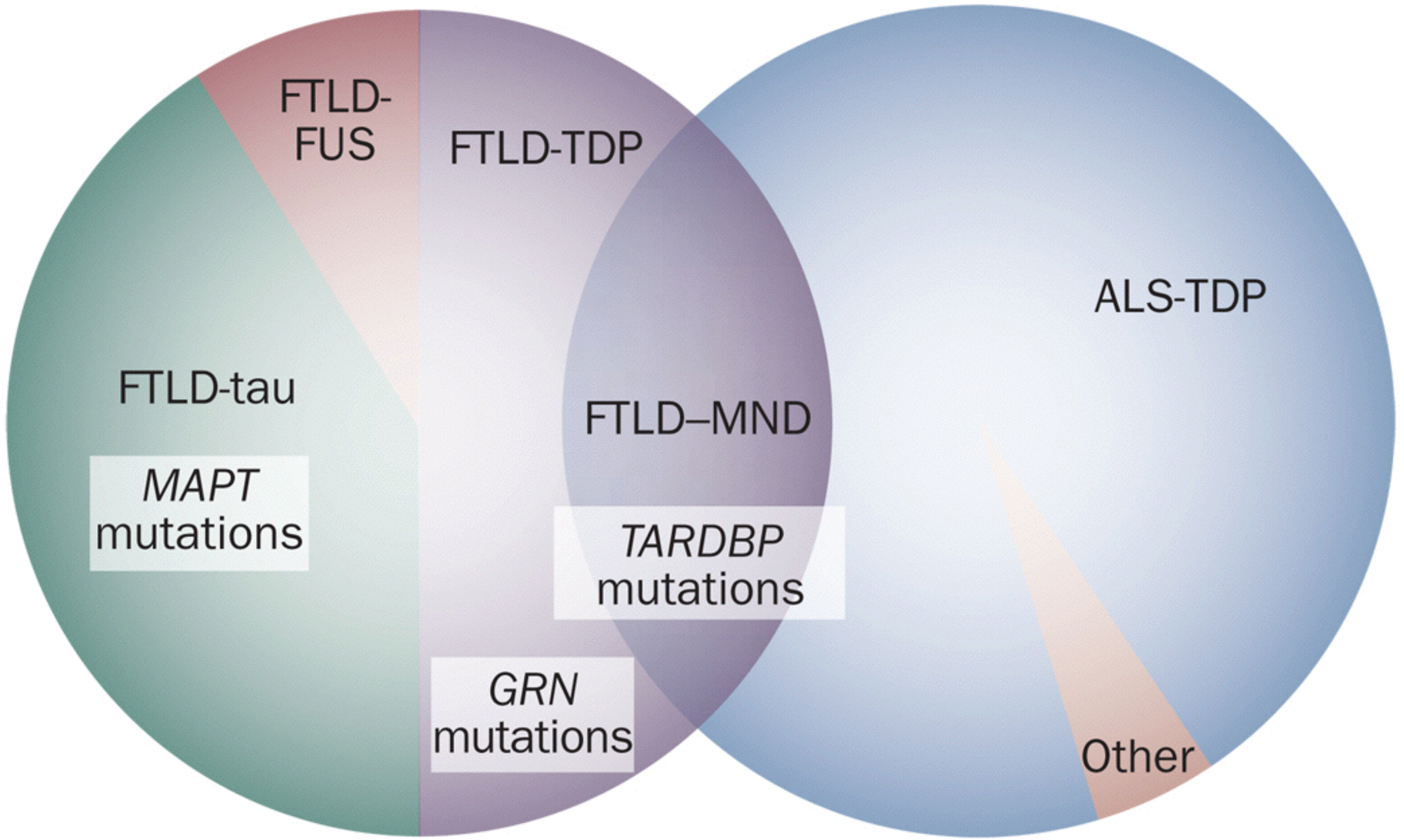
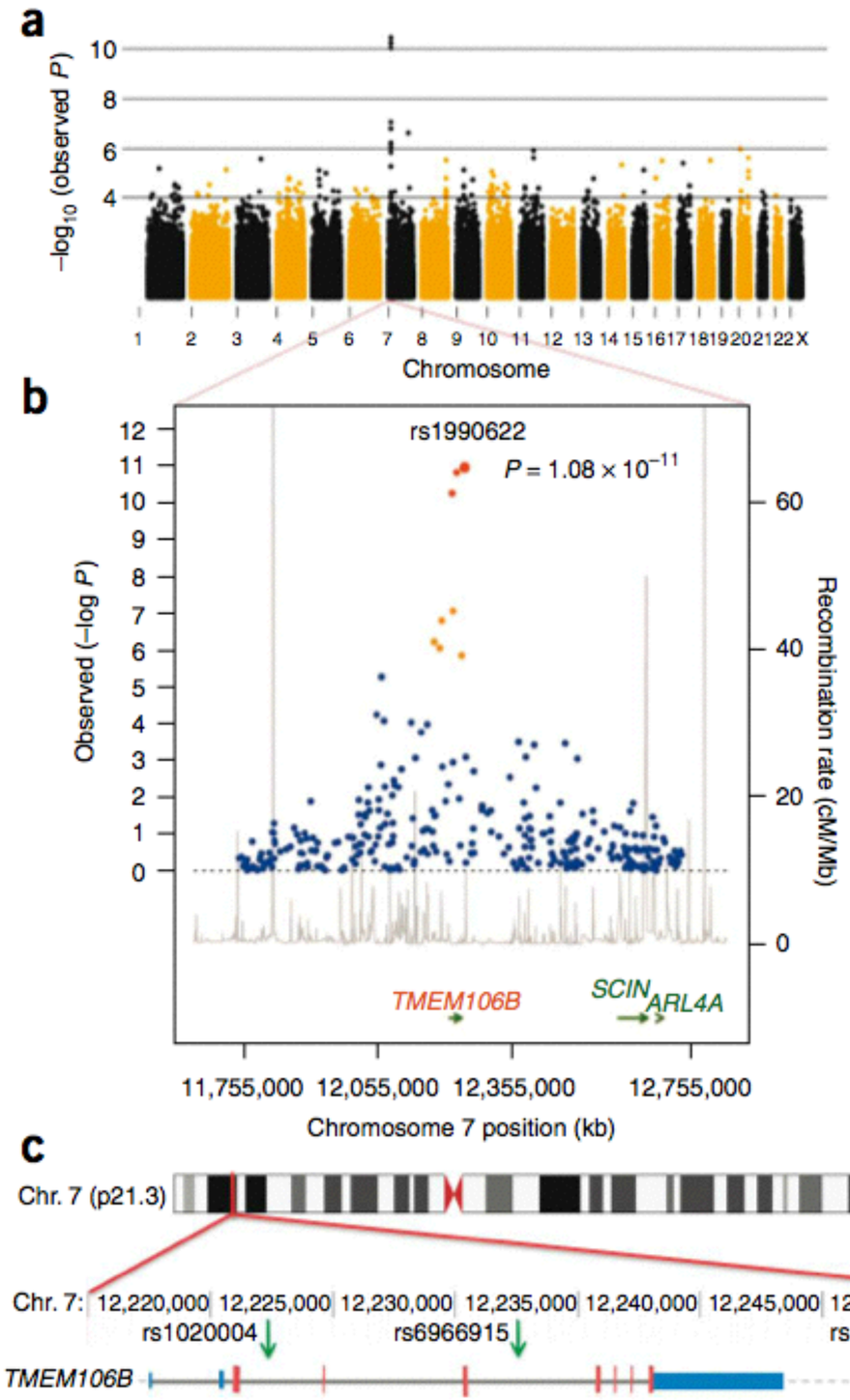
Pathological subtypes of FTLD and ALS



GWAS for frontotemporal dementia susceptibility loci



rs1990622
TMEM106B
OR 1.64 (1.41-1.89)

Van Deerlin et al
Nature Genetics 2010

Today's Plan

1. Alzheimer's Disease

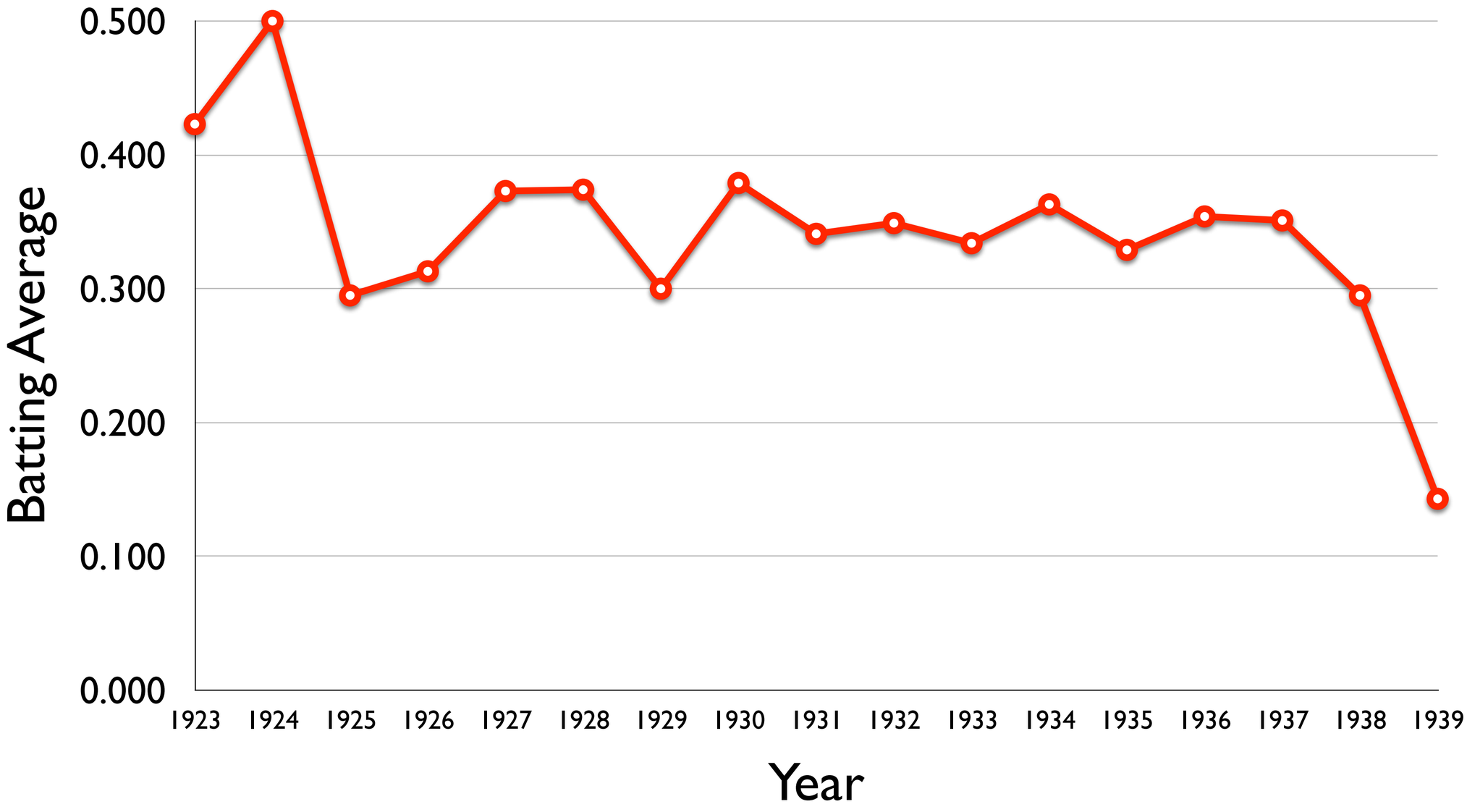
2. Frontotemporal Dementia

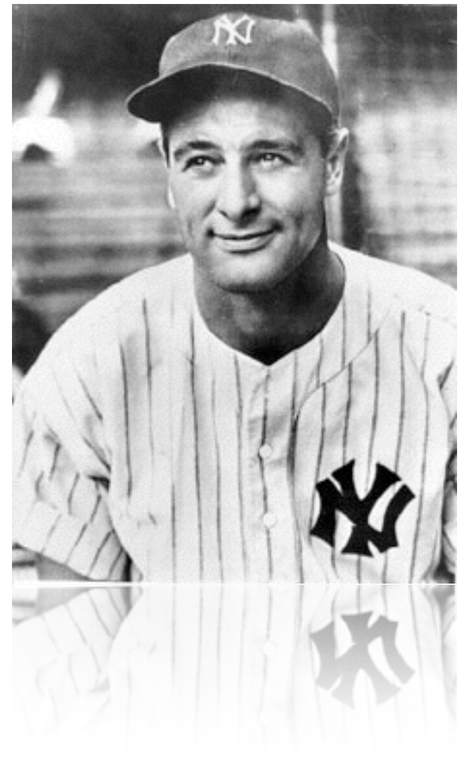
3. Amyotrophic lateral sclerosis (ALS)

4. Parkinson's Disease

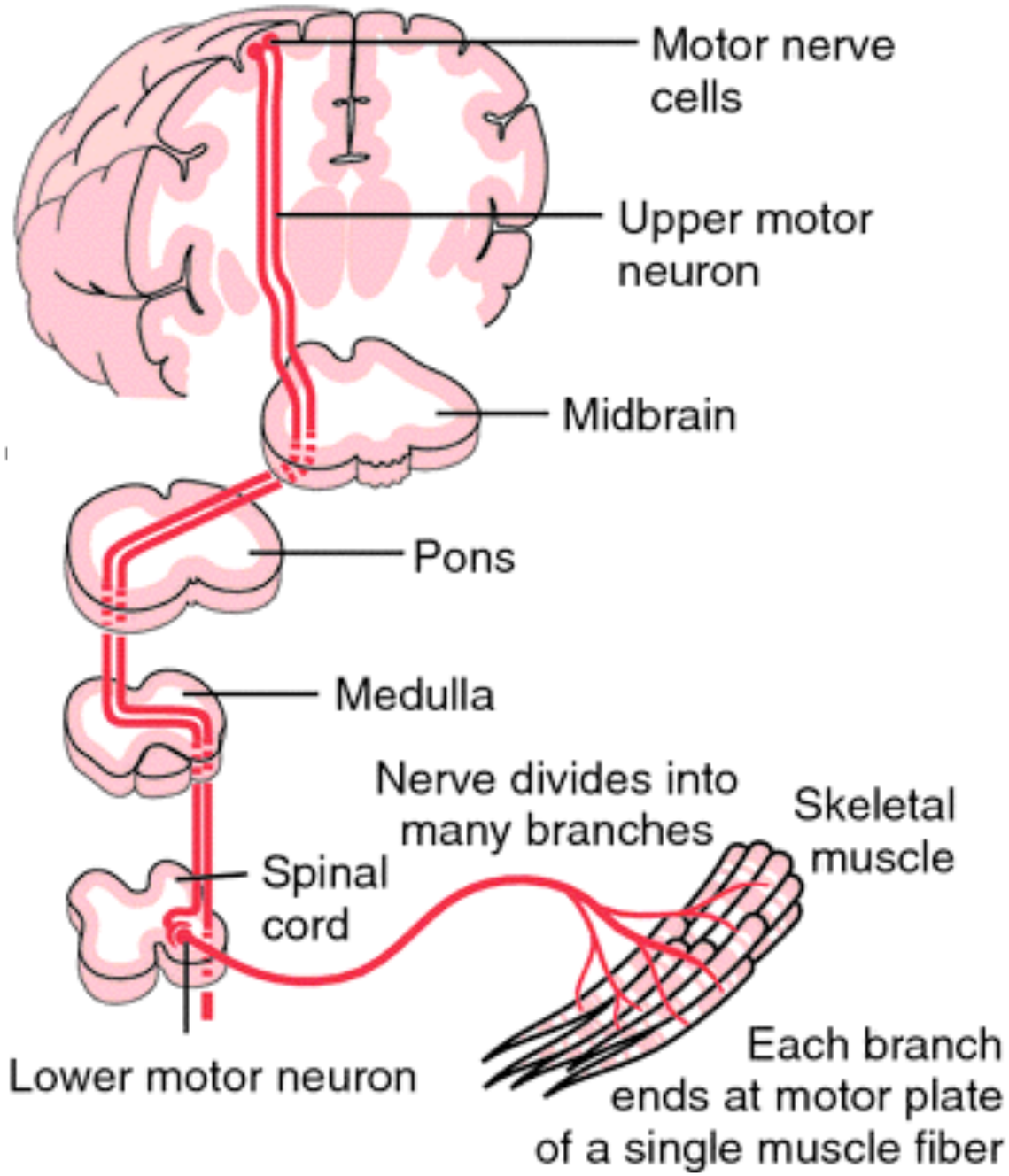
5. Polyglutmaine Diseases (HD, SCA)

Lou Gehrig's career batting average



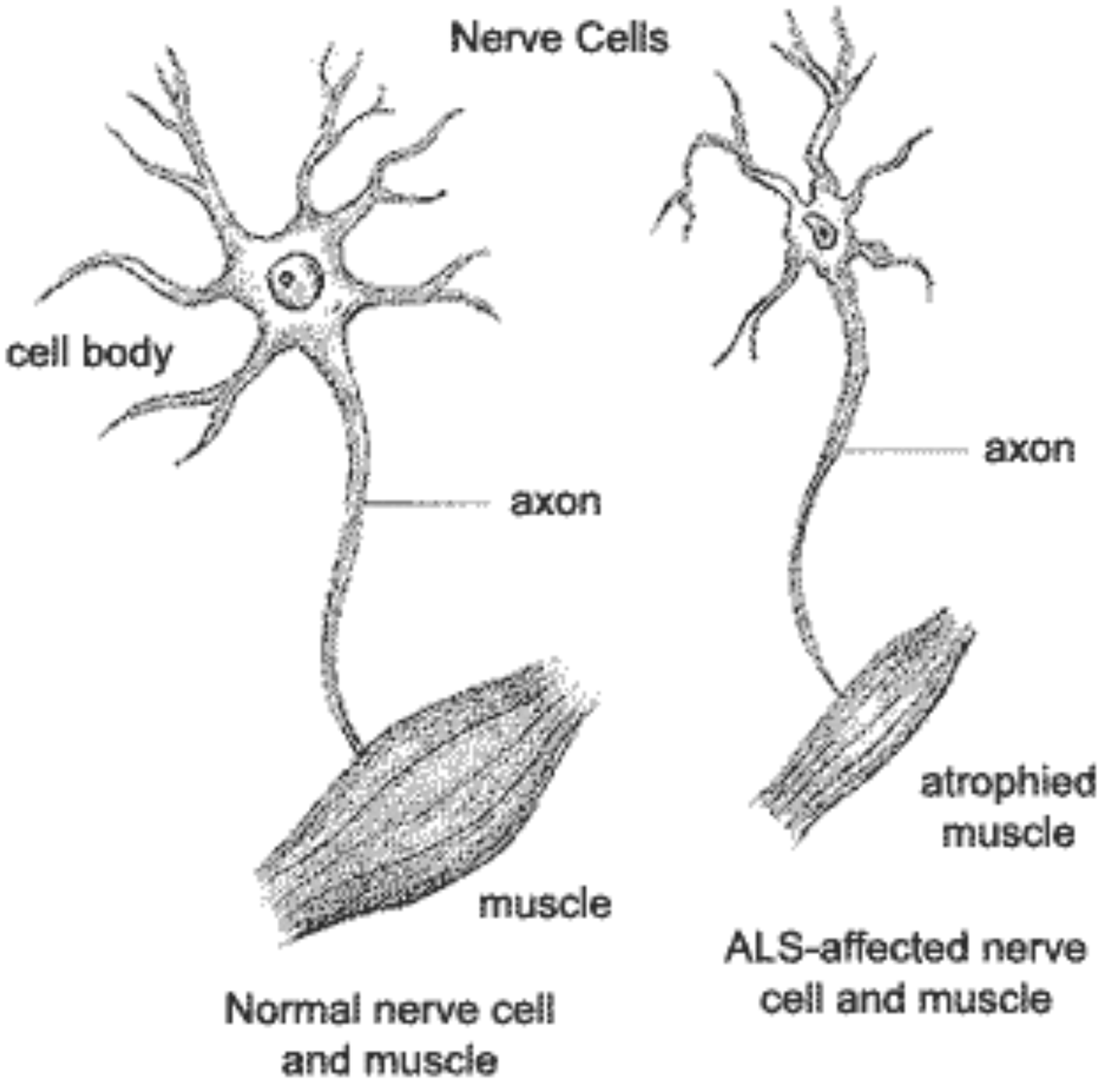


Amyotrophic Lateral Sclerosis (ALS)



- 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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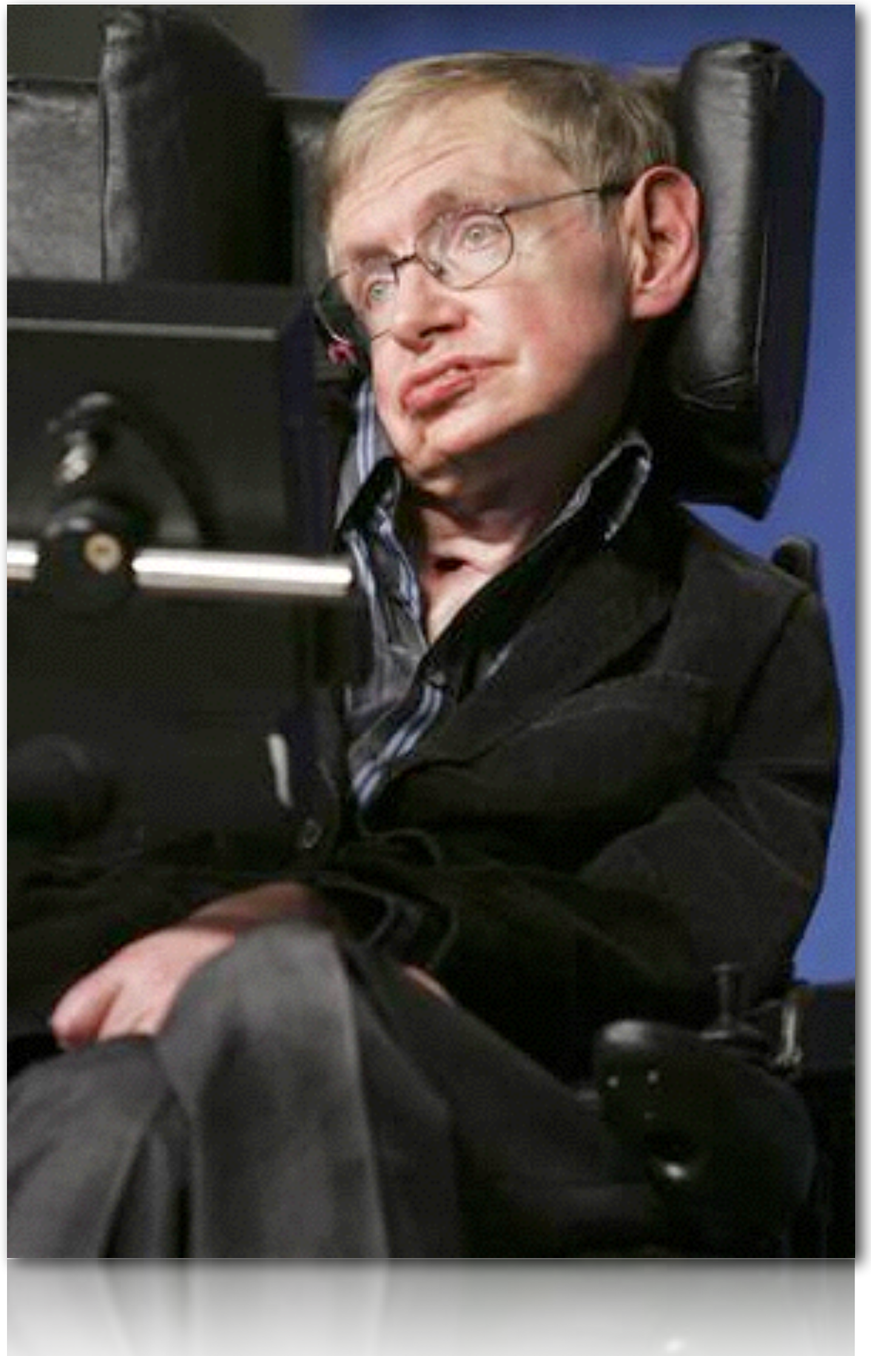
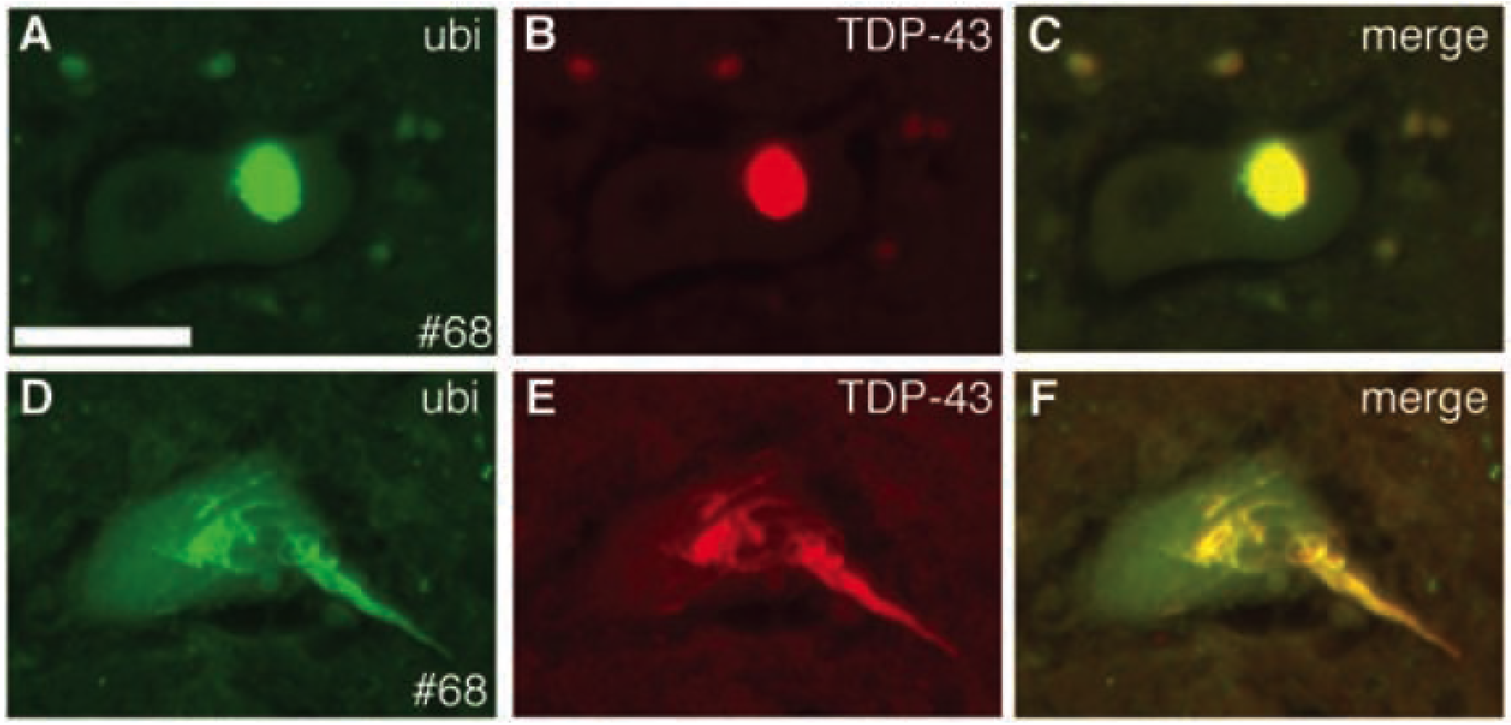
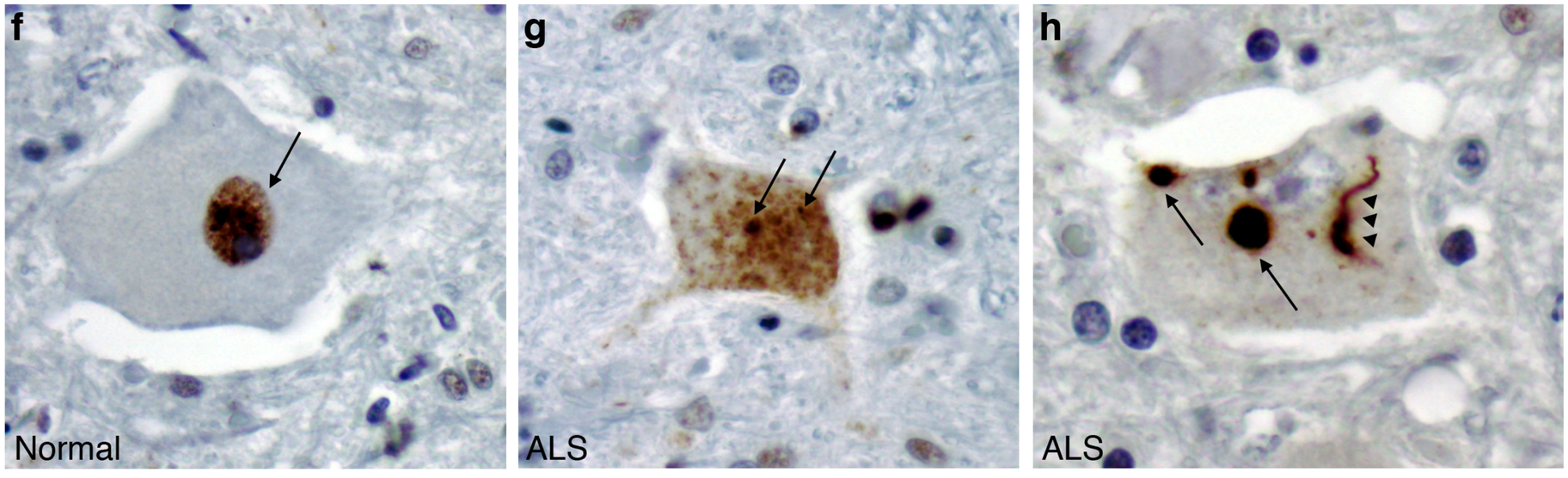
Stephen Hawking



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

TDP-43 pathology in sporadic ALS



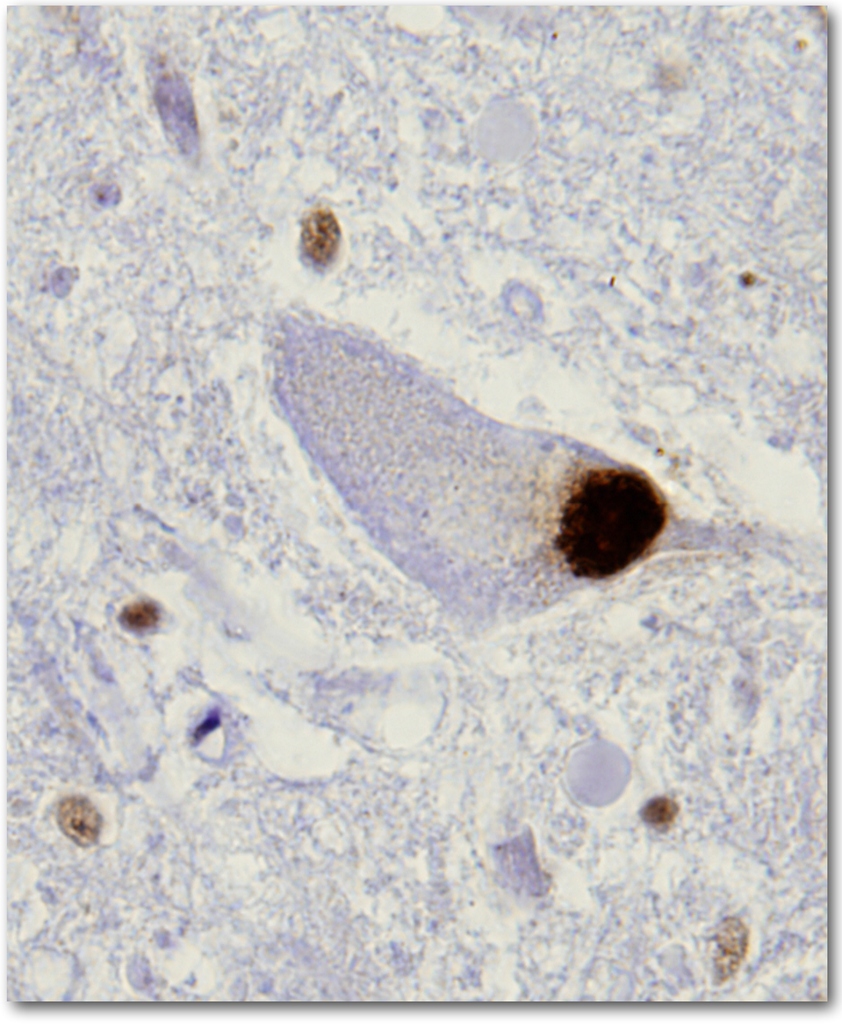


Editorial

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

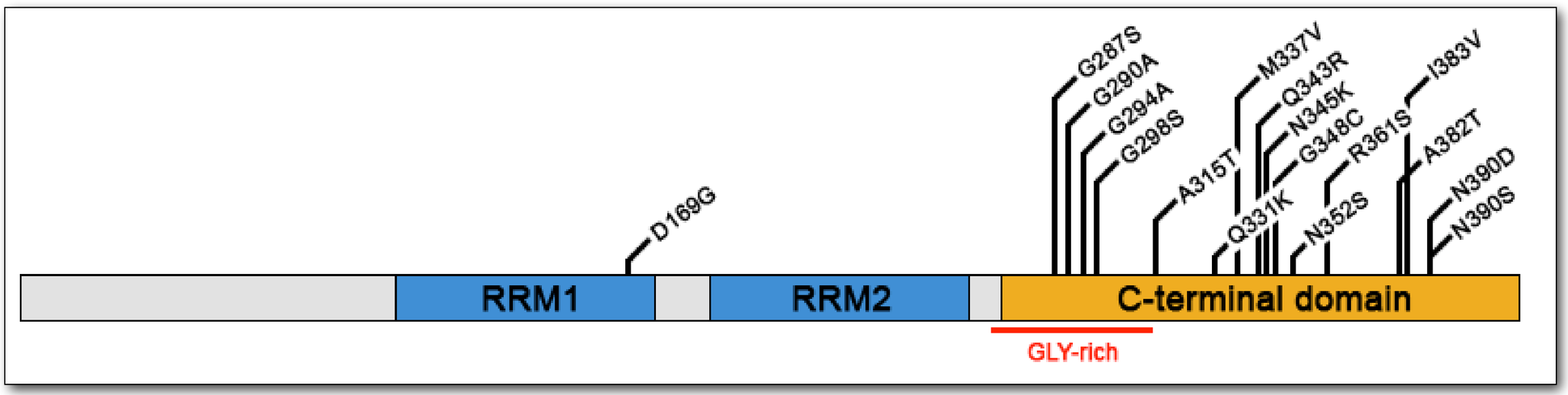
Michael A. Gitcho, PhD,[1,2] Robert H. Baloh, MD, PhD,[2] Sumi Chakraverty, MS,[1,3] Kevin Mayo, BS,[3] Joanne B. Norton, RN,[1,3] Denise Levitch, RN,[1,3] Kimmo J. Hatanpaa, MD, PhD,[4] Charles L. White III, MD,[4] Eileen H. Bigio, MD,[5,6] Richard Caselli, MD,[7] Matt Baker, BSc,[8] Muhammad T. Al-Lozi,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



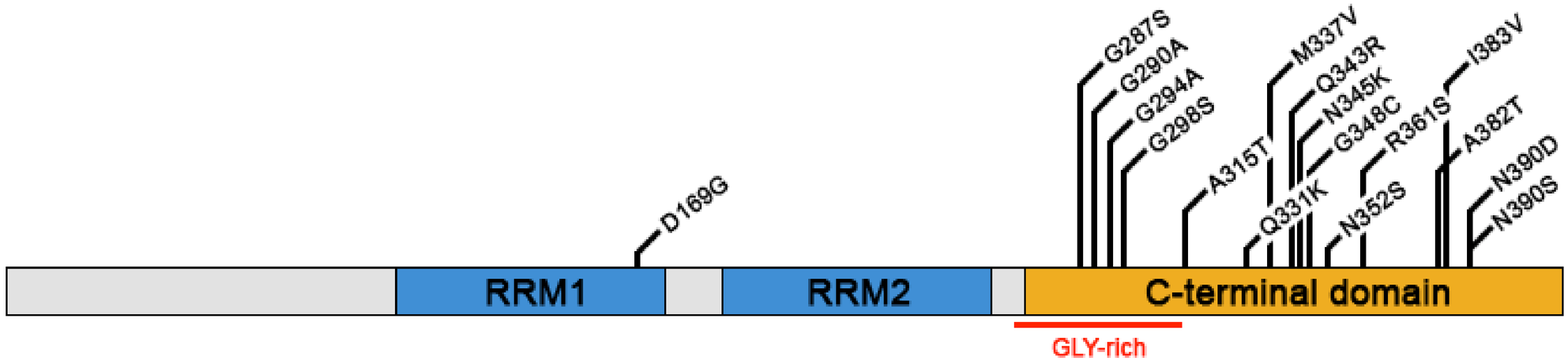
TDP-43 Mutations in Familial and Sporadic Amyotrophic Lateral Sclerosis

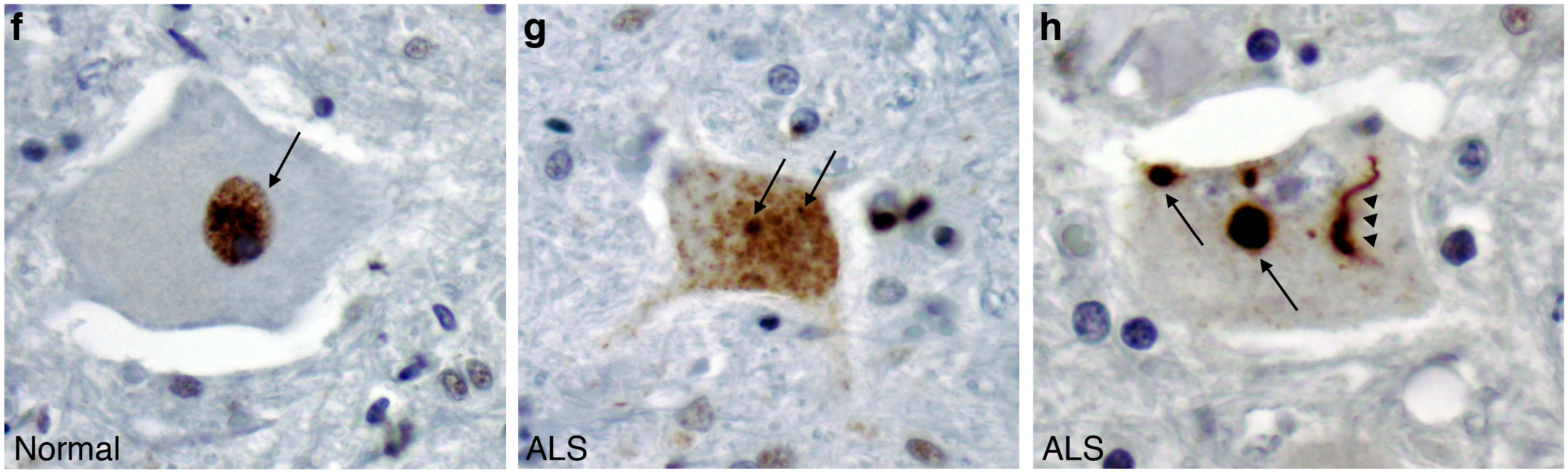
Jemeen Sreedharan,[1*] Ian P. Blair,[3,4*] Vineeta B. Tripathi,[1*] Xun Hu,[1] Caroline Vance,[1] Boris Rogelj,[1] Steven Ackerley,[1,2] Jennifer C. Durnall,[3] Kelly L. Williams,[3] Emanuele Buratti,[5] Francisco Baralle,[5] Jacqueline de Belleroche,[6] J. Douglas Mitchell,[7] P. Nigel Leigh,[1] Ammar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

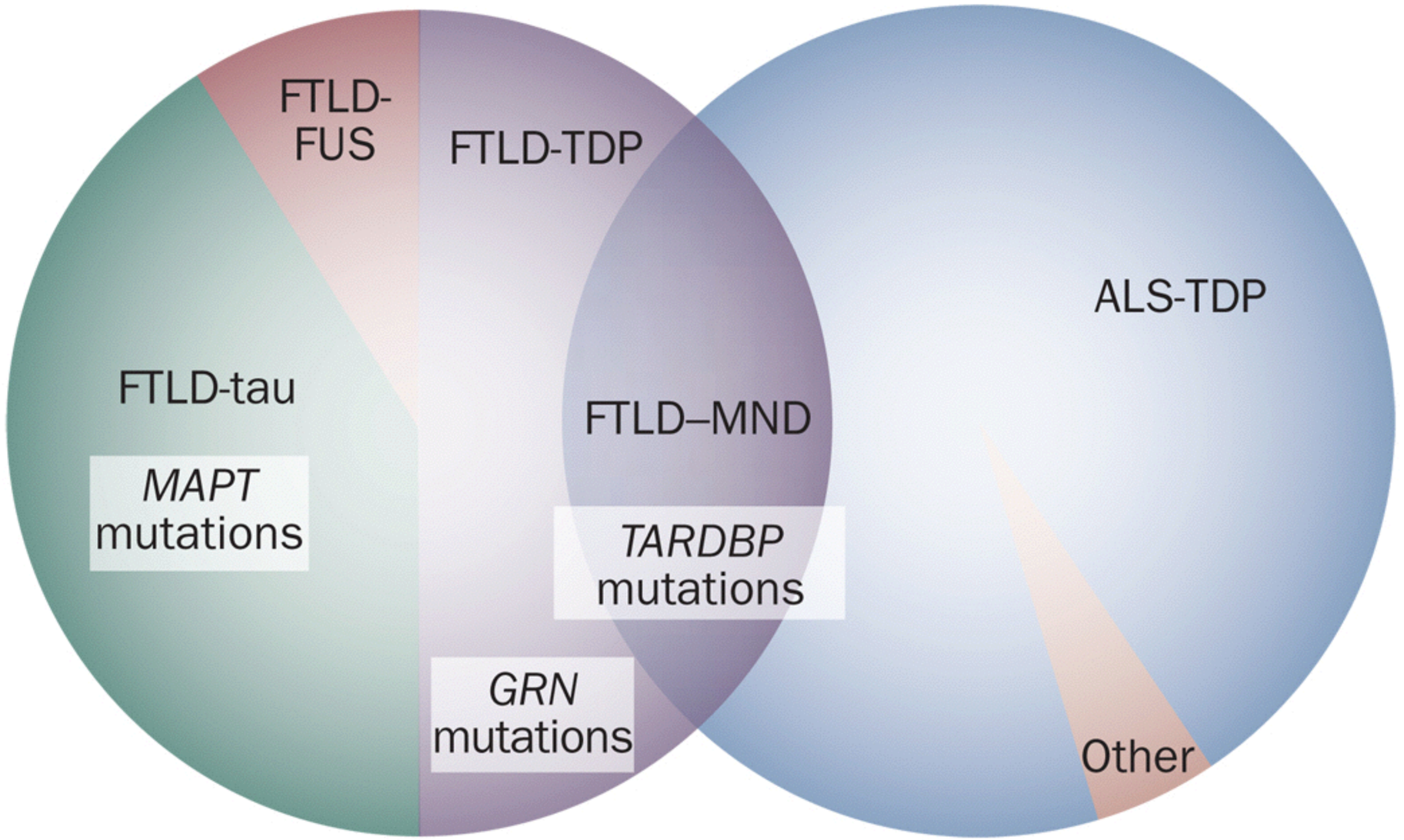
Vivianna M Van Deerlin, James B Leverenz, Lynn M Bekris, Thomas D Bird, Wuxing Yuan, Lauren B Elman, Dana Clay, Elisabeth McCarty Wood, Alice S Chen-Plotkin, Maria Martinez-Lage, Ellen Steinbart, Leo McCluskey, Murray Grossman, Manuela Neumann, I-Lin Wu, Wei-Shiung Yang, Robert Kalb, Douglas R Galasko,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

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

Susceptibility Loci for ALS

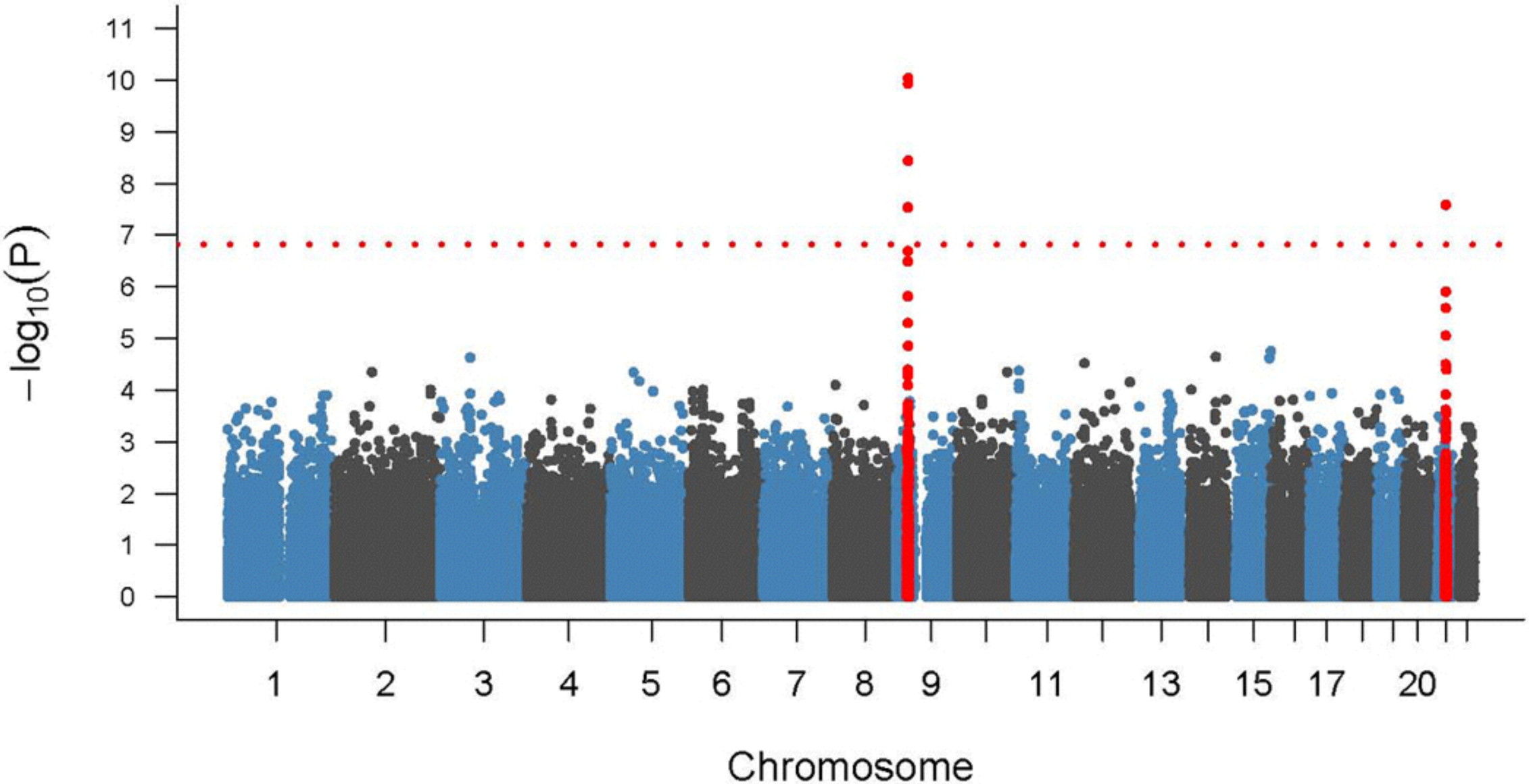
Gene	Protein	Location	Polymorphism	OR (95% CI)
UNC13A	unc-13 homolog A	19p13.11	rs12608932	1.18 (1.13-1.24)
GWA_9p21.2	Unknown	9p21.2	rs2814707	1.25 (1.19-1.32)
ATXN2	ataxin 2	12q24.12	PolyQ	n.a.

Susceptibility Loci for ALS (Han Chinese)

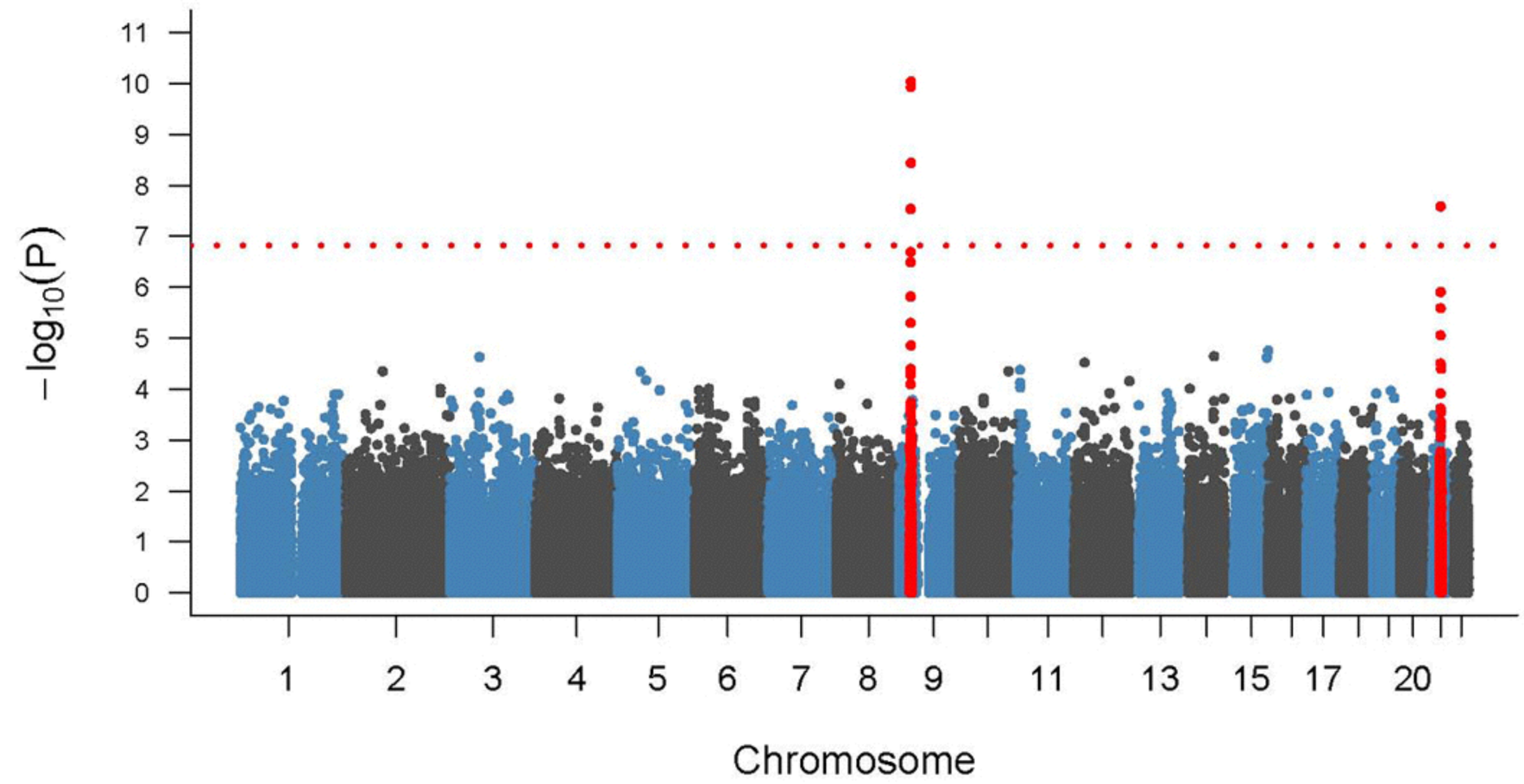
Gene	Protein	Location	Polymorphism	Odds Ratio
CAMK1G	CAMK1G	1q32	rs6703183	1.31
CABIN1 and SUSD2	Unknown	22p11	rs8141797	1.52

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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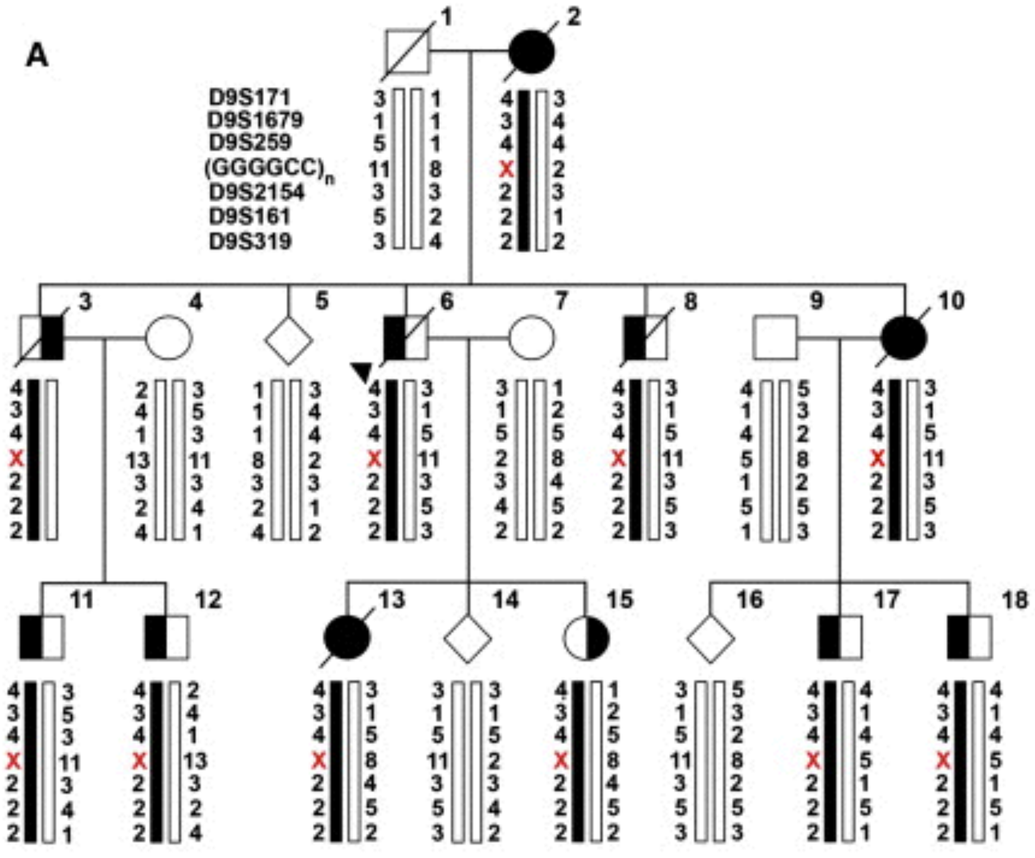

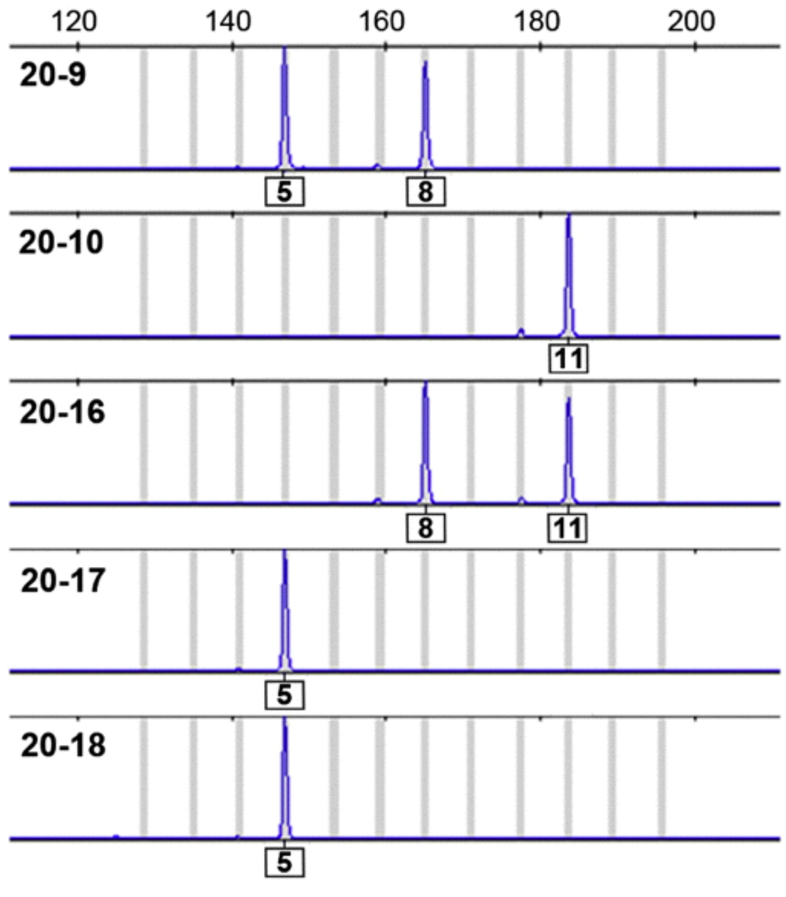

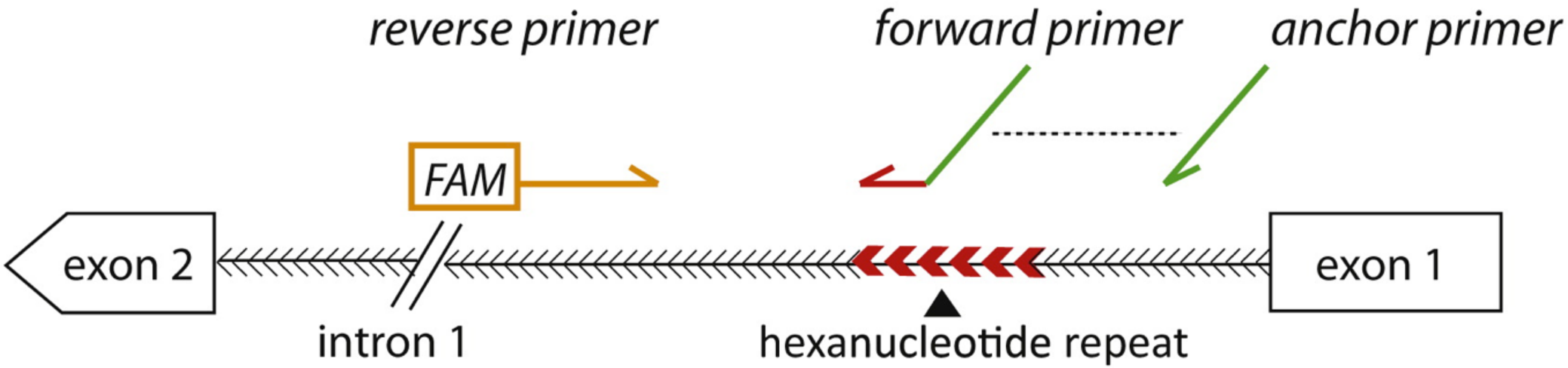
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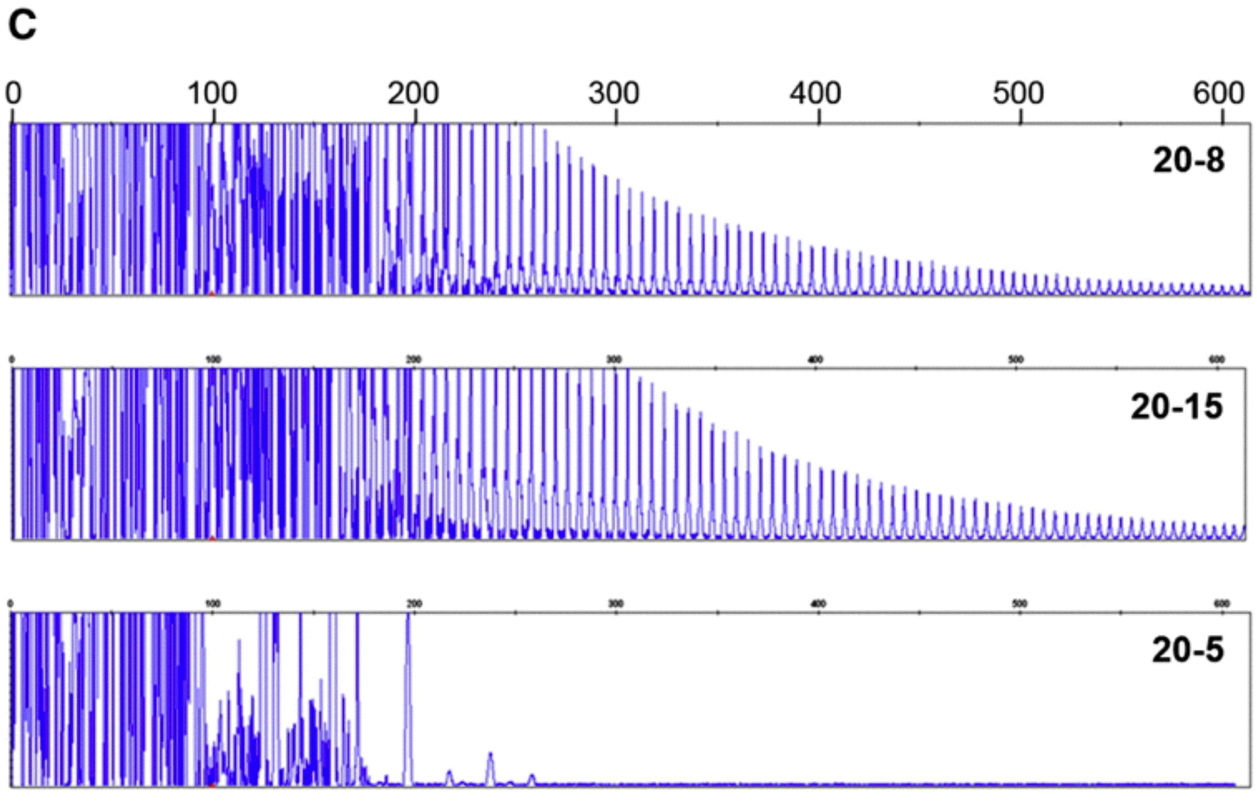
forward primer
anchor primer
FAM
exon 2
exon 1
intron 1
hexanucleotide repeat

C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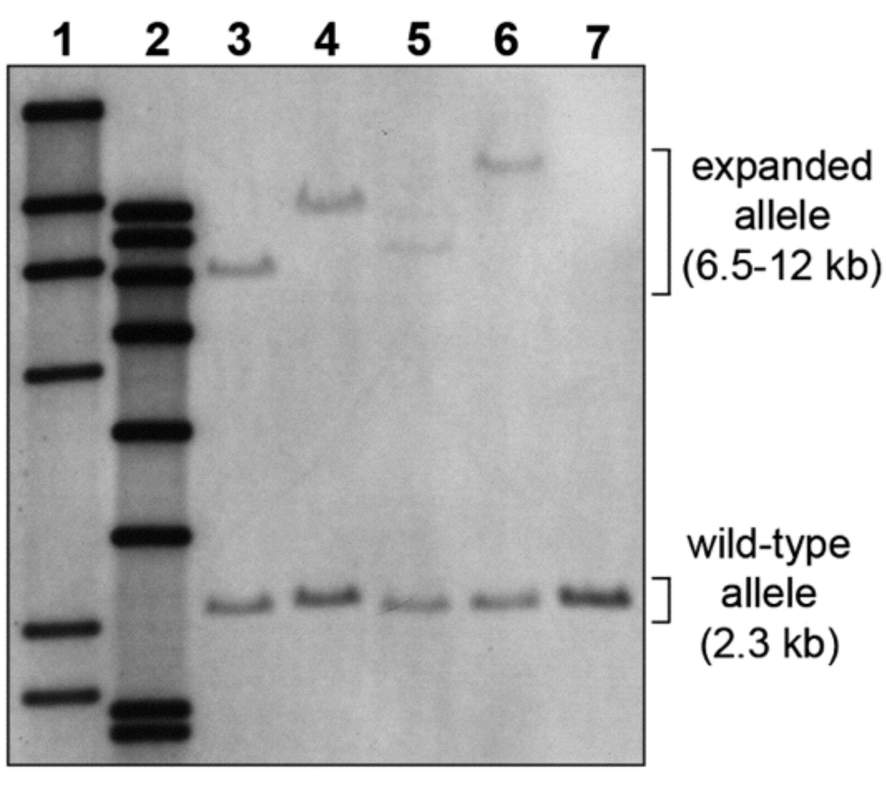
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2
3
4
5
6
7
expanded allele (6.5-12 kb)
wild-type allele (2.3 kb)

Neuron
Article

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

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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[6]Division of Neurology, University of British Columbia, Vancouver, BC V6T 2B5, Canada
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[10]These authors contributed equally to this work
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DOI 10.1016/j.neuron.2011.09.011

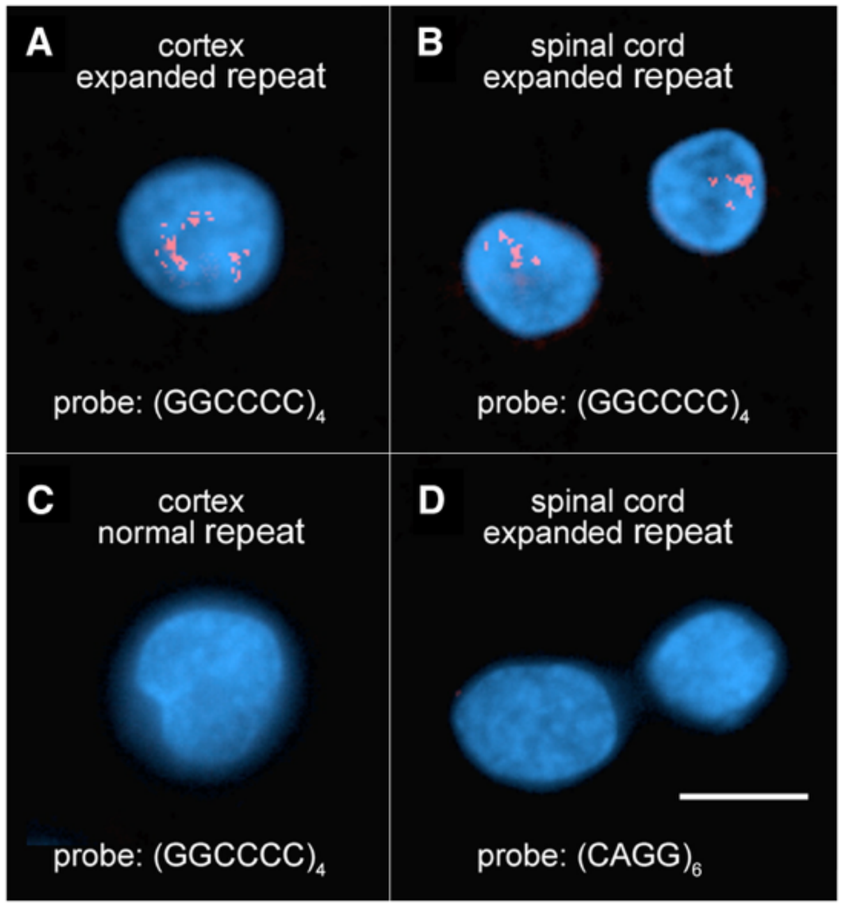
Neuron
Article

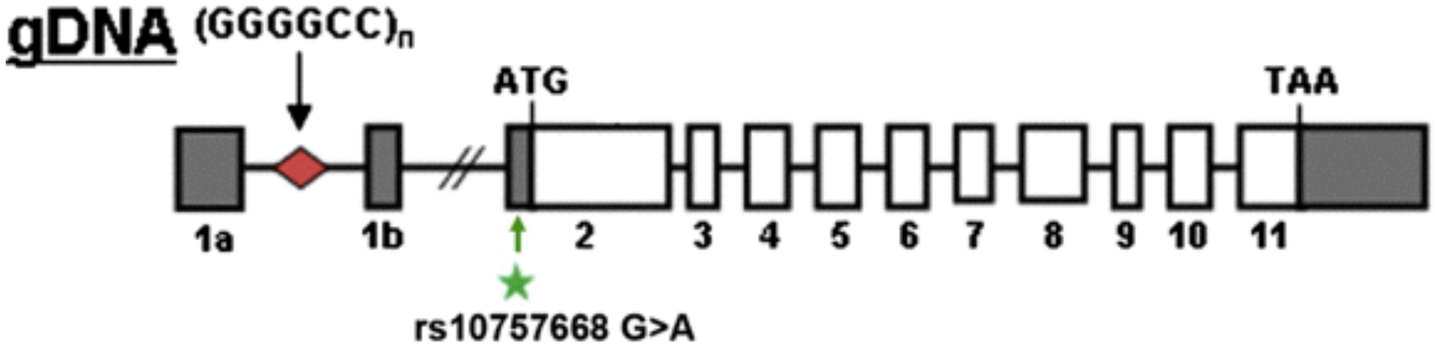
A Hexanucleotide Repeat Expansion in *C9ORF72* Is the Cause of Chromosome 9p21-Linked ALS-FTD

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





Sciencexpress

The *C9orf72* GGGGCC Repeat Is Translated into Aggregating Dipeptide-Repeat Proteins in FTLD/ALS

Kohji Mori,[1]* Shih-Ming Weng,[2]* Thomas Arzberger,[3] Stephanie May,[2] Kristin Rentzsch,[2] Elisabeth Kremmer,[4] Bettina Schmid,[2,5] Hans A. Kretzschmar,[3] Marc Cruts,[6,7] Christine Van Broeckhoven,[6,7] Christian Haass,[1,2,5] Dieter Edbauer[1,2,5]†

Neuron
Report

Unconventional Translation of *C9ORF72* GGGGCC Expansion Generates Insoluble Polypeptides Specific to c9FTD/ALS

Peter E.A. Ash,[1,3,4] Kevin F. Bieniek,[1,3,4] Tania F. Gendron,[1] Thomas Caulfield,[1] Wen-Lang Lin,[1] Mariely DeJesus-Hernandez,[1,3] Marka M. van Blitterswijk,[1] Karen Jansen-West,[1] Joseph W. Paul III,[1] Rosa Rademakers,[1] Kevin B. Boylan,[2] Dennis W. Dickson,[1] and Leonard Petrucelli[1,*]
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[4]These authors contributed equally to this work
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http://dx.doi.org/10.1016/j.neuron.2013.02.004

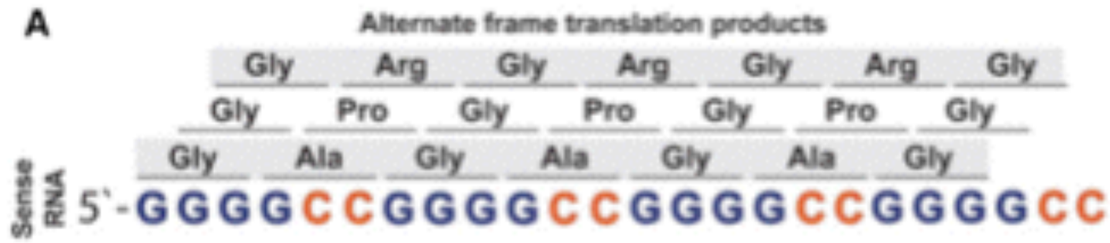
RAN proteins and RNA foci from antisense transcripts in *C9ORF72* ALS and frontotemporal dementia

Tao Zu[a,b,1], Yuanjing Liu[a,b,1], Monica Bañez-Coronel[a,b,2], Tammy Reid[a,b,2], Olga Pletnikova[c], Jada Lewis[d], Timothy M. Miller[e], Matthew B. Harms[e], Annet E. Falchook[f], S. H. Subramony[a,f], Lyle W. Ostrow[g], Jeffrey D. Rothstein[g], Juan C. Troncoso[c], and Laura P. W. Ranum[a,b,f,h,3]

Sciencexpress

The *C9orf72* GGGGCC Repeat Is Translated into Aggregating Dipeptide-Repeat Proteins in FTLD/ALS

Kohji Mori,[1]* Shih-Ming Weng,[2]* Thomas Arzberger,[3] Stephanie May,[2] Kristin Rentzsch,[2] Elisabeth Kremmer,[4] Bettina Schmid,[2,5] Hans A. Kretzschmar,[3] Marc Cruts,[6,7] Christine Van Broeckhoven,[6,7] Christian Haass,[1,2,5] Dieter Edbauer[1,2,5]†



Neuron
Report

Unconventional Translation of *C9ORF72* GGGGCC Expansion Generates Insoluble Polypeptides Specific to c9FTD/ALS

Peter E.A. Ash,[1,3,4] Kevin F. Bieniek,[1,3,4] Tania F. Gendron,[1] Thomas Caulfield,[1] Wen-Lang Lin,[1] Mariely DeJesus-Hernandez,[1,3] Marka M. van Blitterswijk,[1] Karen Jansen-West,[1] Joseph W. Paul III,[1] Rosa Rademakers,[1] Kevin B. Boylan,[2] Dennis W. Dickson,[1] and Leonard Petrucelli[1,*]
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http://dx.doi.org/10.1016/j.neuron.2013.02.004

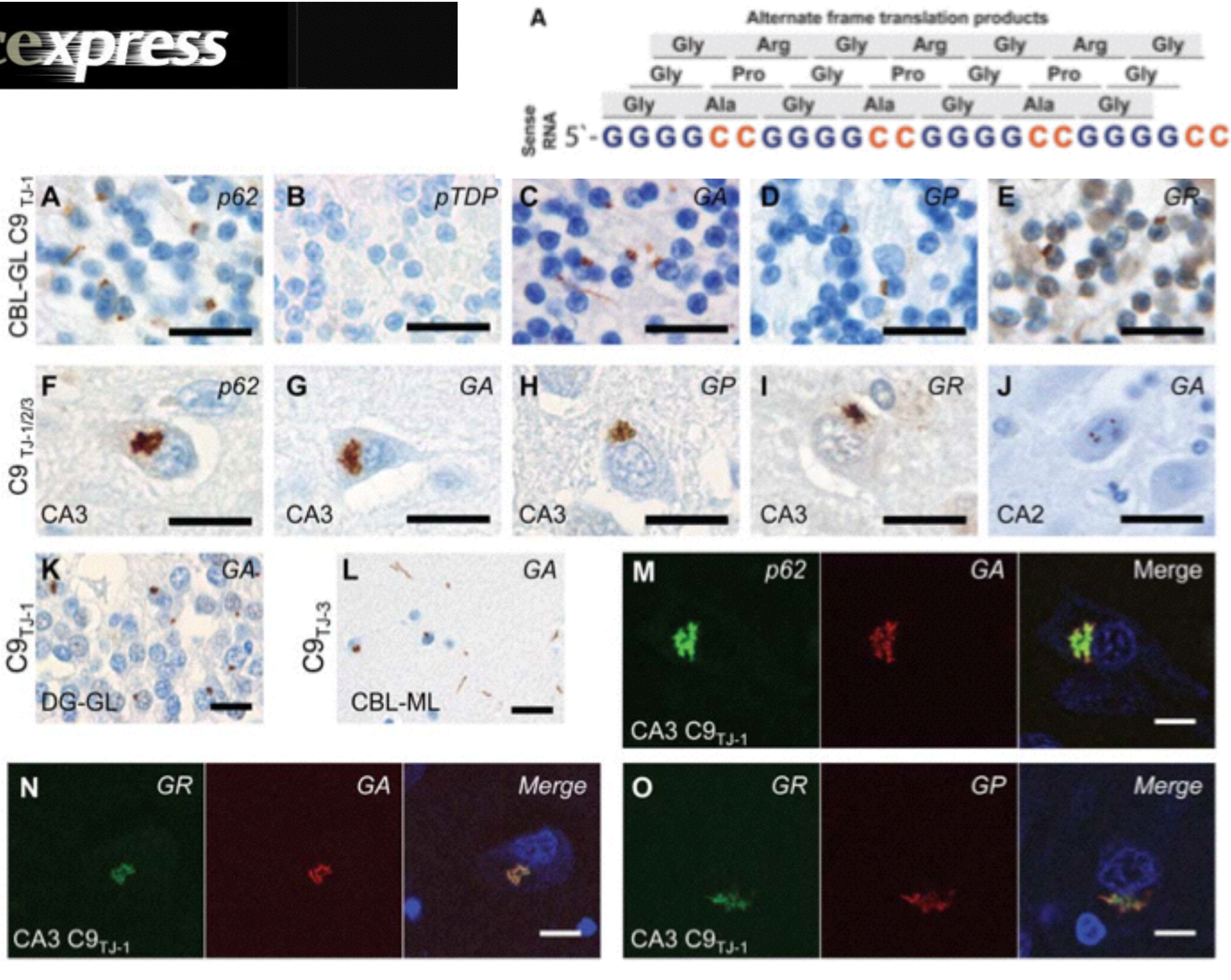
RAN proteins and RNA foci from antisense transcripts in *C9ORF72* ALS and frontotemporal dementia

Tao Zu[a,b,1], Yuanjing Liu[a,b,1], Monica Bañez-Coronel[a,b,2], Tammy Reid[a,b,2], Olga Pletnikova[c], Jada Lewis[d], Timothy M. Miller[e], Matthew B. Harms[e], Annet E. Falchook[f], S. H. Subramony[a,f], Lyle W. Ostrow[g], Jeffrey D. Rothstein[g], Juan C. Troncoso[c], and Laura P. W. Ranum[a,b,f,h,3]

Sciencexpress

The *C9orf*
Translated
Repeat Pr

Kohji Mori,[1]* Shih-Ming
Elisabeth Kremmer,[4] Be
Broeckhoven,[6,7] Christia



RAN prot
in *C9ORF*

Tao Zu[a,b,1], Yuanjin
Timothy M. Miller[e],
Jeffrey D. Rothstein

nakers,[1]

Today's Plan

1. Alzheimer's Disease

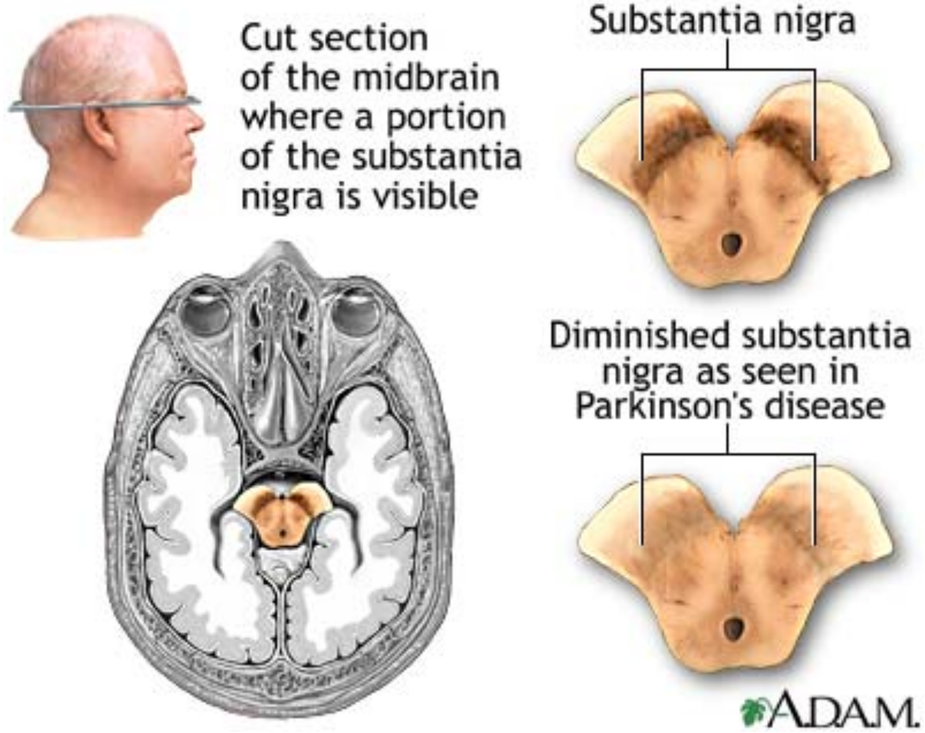
2. Frontotemporal Dementia

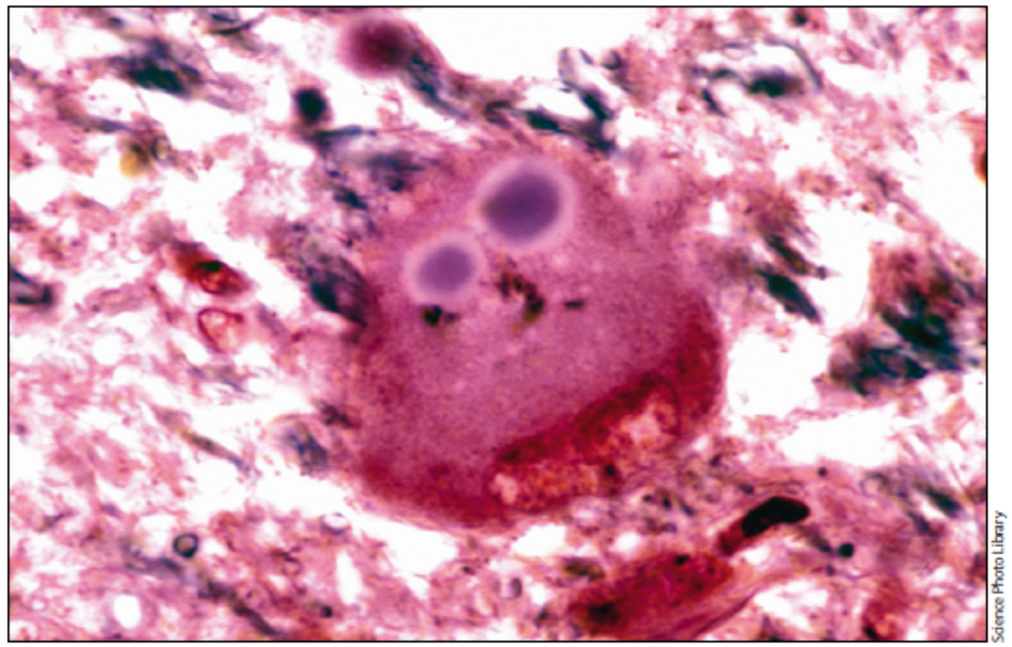
3. Amyotrophic lateral sclerosis (ALS)

4. Parkinson's Disease

5. Polyglutmaine Diseases (HD, SCA)

Parkinson's Disease

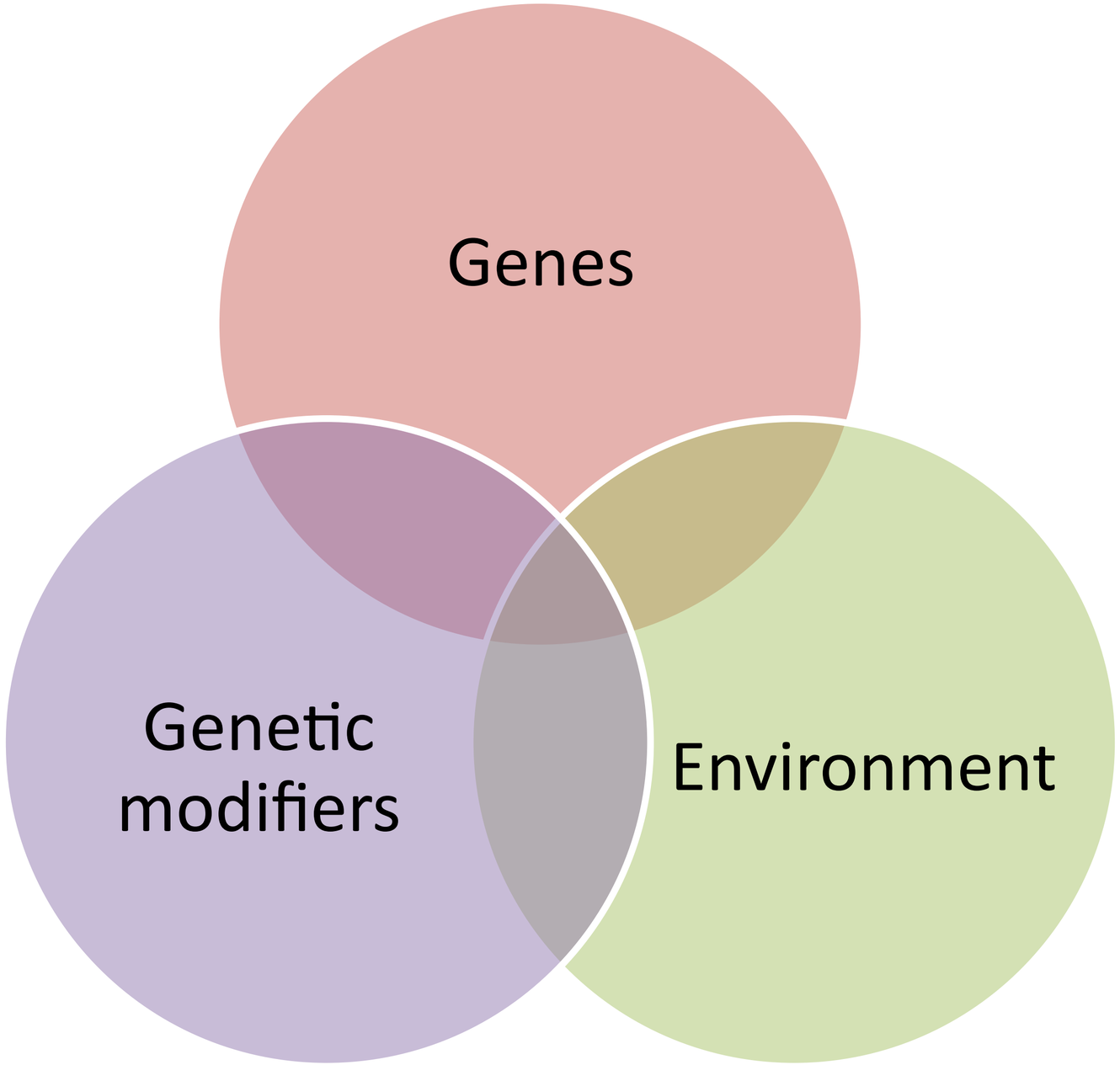




Science Photo Library

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

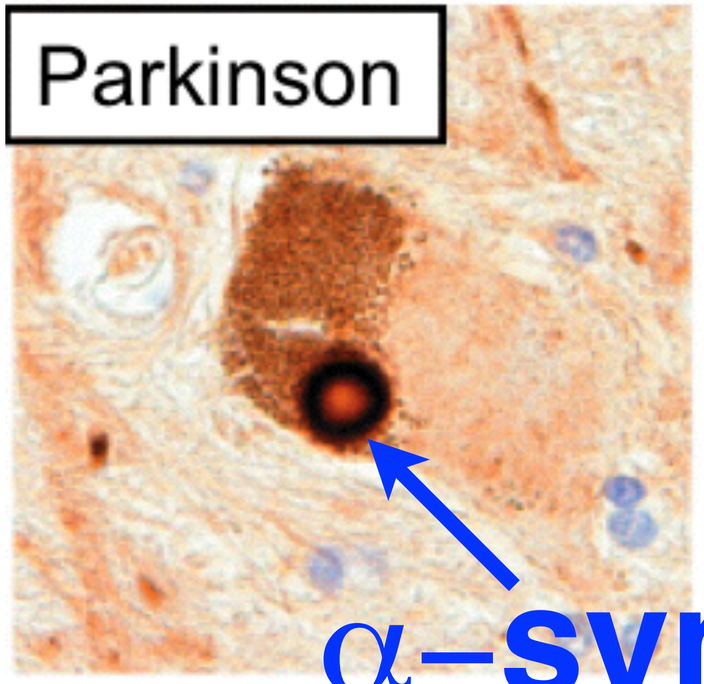
*Some papers suggest 5-10% of PD patients have a gene mutation

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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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”

Monogenic parkinsonism

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Susceptibility Loci for Parkinson's Disease

SNP	Gene	Major Allele	Minor Allele	Risk Allele	OR	P Value
rs35749011	GBA-SYT11	G	A	A	1.824	1.37 × 10−29
rs823118	RAB7L1-	T	C	T	1.122	1.66 × 10−16
rs10797576	SIPA1L2	C	T	T	1.131	4.87 × 10−10
rs6430538	ACMSD-	C	T	T	0.875	9.13 × 10−20
rs1474055	STK39	C	T	T	1.214	1.15 × 10−20
rs12637471	MCCC1	G	A	A	0.842	2.14 × 10−21
rs34311866	TMEM175-	T	G	T	0.786	1.02 × 10−43
rs11724635	BST1	A	C	A	1.126	9.44 × 10−18
rs6812193	FAM47E-	C	T	T	0.907	2.95 × 10−11
rs356182	SNCA	A	G	A	0.76	4.16 × 10−73
rs9275326	HLA-DQB1	C	T	T	0.826	1.19 × 10−12
rs199347	GPNMB	A	G	A	1.11	1.18 × 10−12
rs117896735	INPP5F	G	A	A	1.624	4.34 × 10−13
rs329648	MIR4697	C	T	T	1.105	9.83 × 10−12
rs76904798	LRRK2	C	T	T	1.155	5.24 × 10−14
rs11060180	CCDC62	A	G	A	1.105	6.02 × 10−12
rs11158026	GCH1	C	T	T	0.904	5.85 × 10−11
rs1555399	TMEM229B	T	A	A	0.897	6.63 × 10−14
rs2414739	VPS13C	A	G	A	1.113	1.23 × 10−11
rs14235	BCKDK-	G	A	A	1.103	2.43 × 10−12
rs17649553	MAPT	C	T	T	0.769	2.37 × 10−48
rs12456492	RIT2	A	G	A	0.904	7.74 × 10−12
rs8118008	DDRGK1	G	A	A	1.111	3.04 × 10−11

Google's Brin has gene mutation linked to Parkinson's

Sergey Brin
(Google co-founder)

LRRK2 G2019S

rs34637584
(major allele = G, risk allele = A)
odds ratio, 9.62
(6.43-14.37)

rs34637584(A) allele confers PD risk of 28% at age 59, 51% at 69, and 74% at 79
(Healy et al., *Lancet Neurol* 2008)

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.)

Today's Plan

1. Alzheimer's Disease

2. Frontotemporal Dementia

3. Amyotrophic lateral sclerosis (ALS)

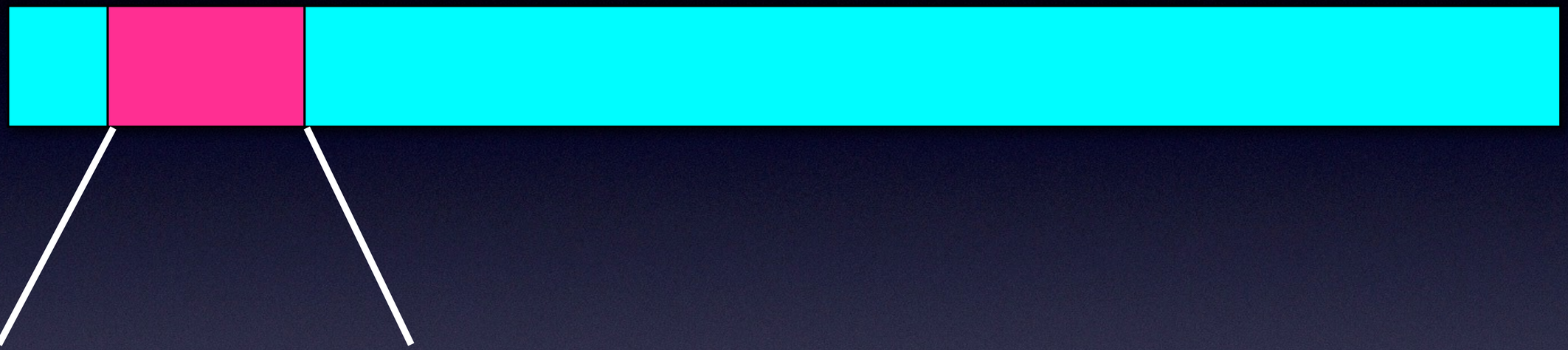
4. Parkinson's Disease

5. Polyglutamine Diseases (HD, SCA)

Huntington's Disease

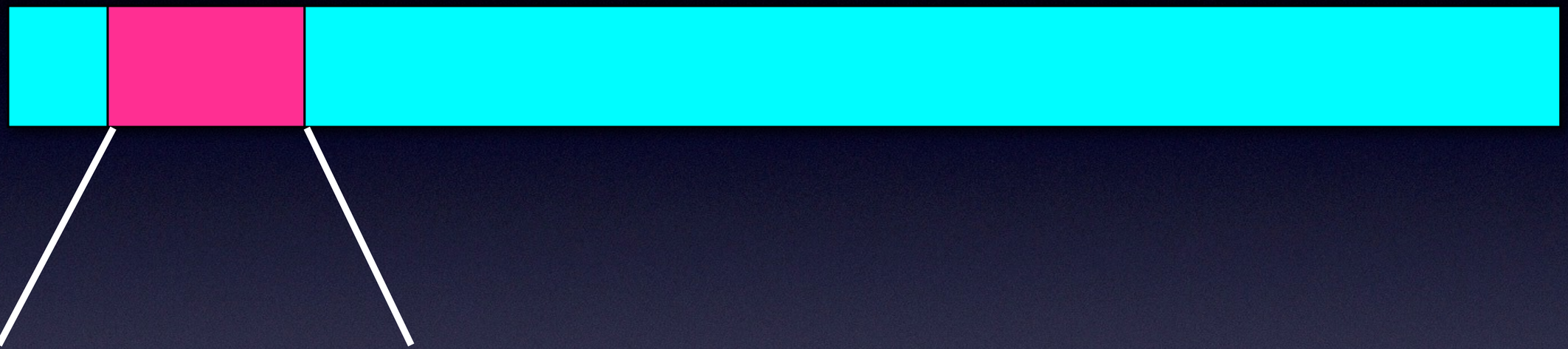
- A devastating, hereditary, degenerative brain disorder
- Affects 1 out of 10,000 individuals
- Usually begins in mid-life - Between age 30 and 45
- Involuntary movements, difficulties with speech, balance and swallowing, depression, mood swings
- Autosomal dominant genetic disorder: A parent with HD has 50% chance of passing disease gene to child
- No effective treatment or cure
- Huntington's Disease gene identified in 1993

The Huntington's Gene



CAG CAG CAG CAG CAG CAG CAG CAG CAG

The Huntington's Gene



CAG CAG CAG CAG CAG CAG CAG CAG CAG

QQQQQQQQ polyQ (Normally ~5-20)

The Huntington's Gene

The Huntington's Gene

The Huntington's Gene

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

Expanded polyQ causes Huntington's Disease
(~38 Q's or more)

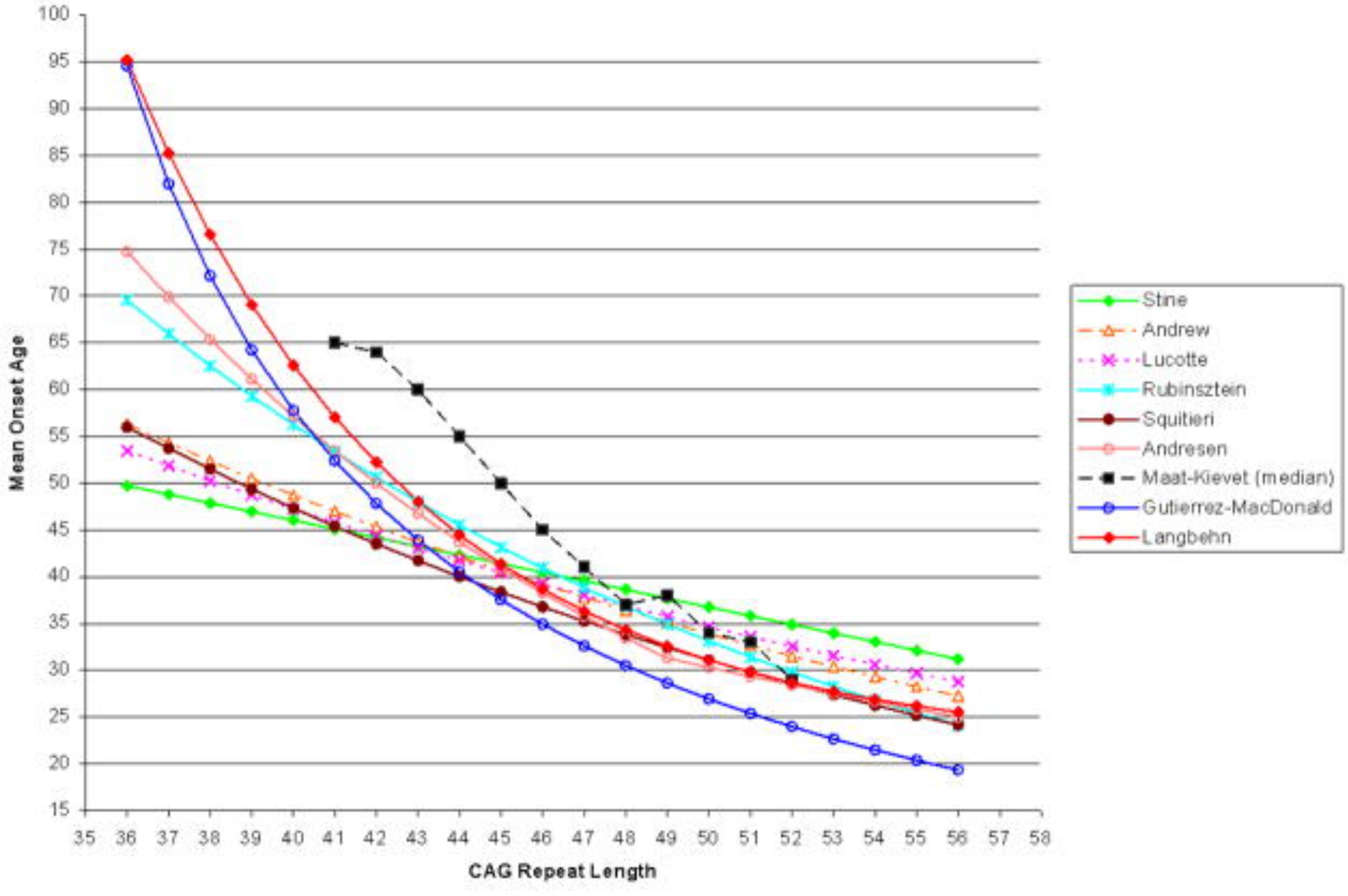
QQQQQQQQQQQQQQQQQQQQ
QQQQQQQQ QQQQQQQQQQQQ

Polyglutamine Disease Genes

Disease	Mutation/ repeat unit	Gene name (protein product)	Putative function	Normal repeat length	Pathogenic repeat length
SCA1	$(CAG)_n$	*SCA1* (ataxin 1)	Transcription	6–39	40–82
SCA2	$(CAG)_n$	*SCA2* (ataxin 2)	RNA metabolism	15–24	32–200
SCA3 (MJD)	$(CAG)_n$	*SCA3* (ataxin 3)	De-ubiquitylating activity	13–36	61–84
SCA6	$(CAG)_n$	*CACNA1A* ($CACNA1_A$)	P/Q-type α1A calcium channel subunit	4–20	20–29
SCA7	$(CAG)_n$	*SCA7* (ataxin 7)	Transcription	4–35	37–306
SCA17	$(CAG)_n$	*SCA17* (TBP)	Transcription	25–42	47–63
DRPLA	$(CAG)_n$	*DRPLA* (atrophin 1)	Transcription	7–34	49–88
SBMA	$(CAG)_n$	*AR* (androgen receptor)	Steroid-hormone receptor	9–36	38–62
HD	$(CAG)_n$	*HD* (huntingtin)	Signalling, transport, transcription	11–34	40–121

Gatchel and Zoghbi, 2005

Age of onset correlates to repeat numbers



Langbehn for PREDICT-HD group 2010

J Med Genet 1993; **30**: 293–295

Suicide risk in Huntington's disease

Luigi Di Maio, Ferdinando Squitieri, Gioacchino Napolitano, Giuseppe Campanella, James A Trofatter, P Michael Conneally

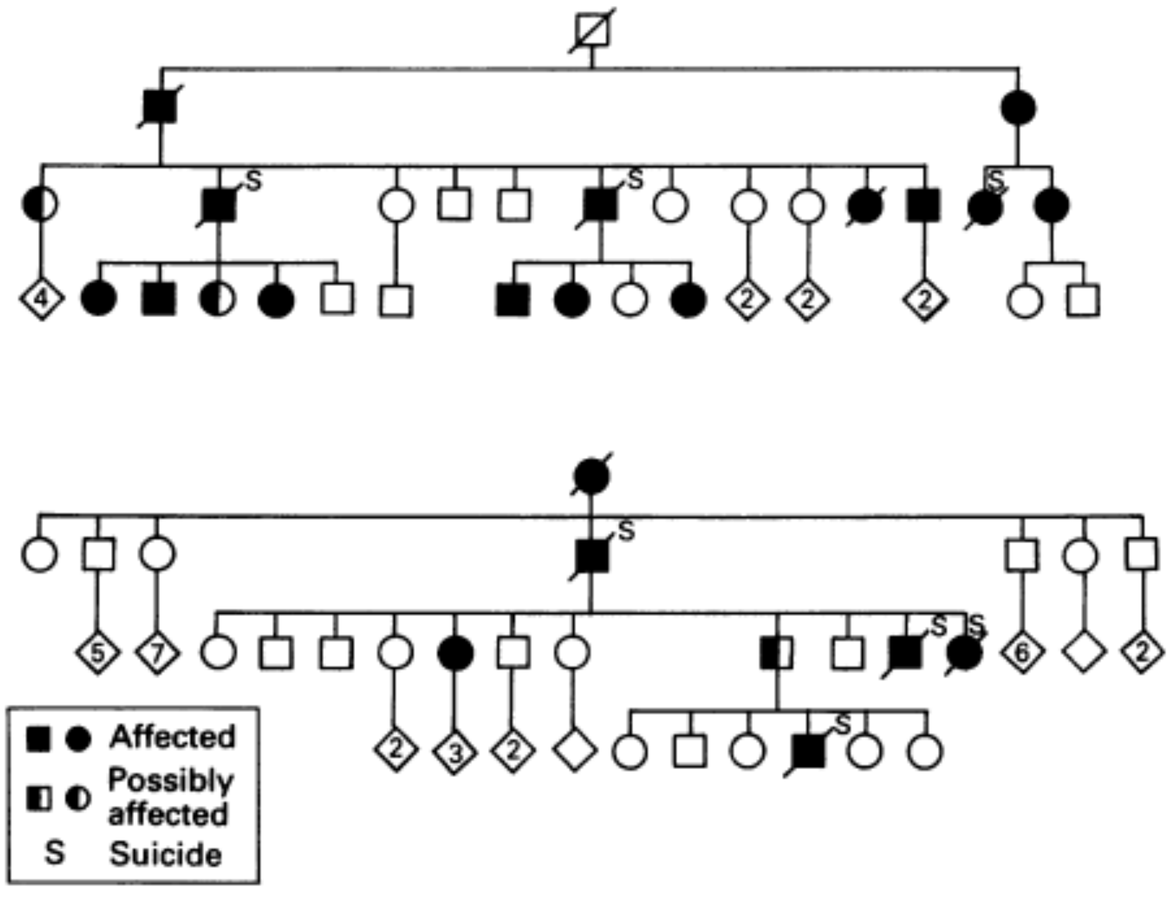


Figure 2 Pedigrees of two families in which several cases of suicide occurred.

Abstract

In order to evaluate the relevance of suicide risk in families affected by Huntington's disease (HD), 2793 subjects registered with the National Huntington's Disease Research Roster were studied. Suicide was the reported cause of death in 205 subjects (7·3%). This group included affected and possibly affected subjects, subjects at 50% and 25% risk, possibly at risk subjects, and normal relatives. In all categories suicide was more frequent than in the general US population. The data suggest that suicide is quite frequent in some families with HD. This increased suicide risk must be carefully considered in planning genetic counselling for predictive testing in HD.

(*J Med Genet* 1993;**30**:293–5)

Ethics of HD testing

- 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 currently does not test for HD
    - Would *you* want to know?

Other HD in the news

- Episode 492: “Dr. Gilmer and Mr. Hyde” on This American Life, April 14, 2013.
- *“Dr. Benjamin Gilmer gets a job at a rural clinic. He finds out he’s replaced someone — also named Dr. Gilmer— who went to prison after killing his own father. But the more Benjamin’s patients talk about the other Dr. Gilmer, the more confused he becomes. Everyone loved the old Dr. Gilmer. So Benjamin starts digging around, trying to understand how a good man can seemingly turn bad.”*

http://www.thisamericanlife.org/radio-archives/episode/492/dr-gilmer-and-mr-hyde

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Gatchel and Zoghbi, 2005