

Genetically Dissecting Neurodegenerative Disease

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**Laboratory of
NeuroGenetics**

The Usefulness of Genetics

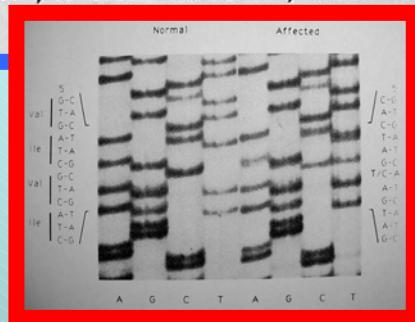
- Is to put order, into pathology.
- Pathology shows you the endpoint of disease... the final credits of the movie.
- Genetics shows the start and means you have a pathway which you can try and stop.
- Using genetics also allows better modeling of disease... and hopefully, earlier and better diagnosis.

Pathology of Diseases

- Alzheimer's disease: plaques ($A\beta$), tangles (tau) and often, Lewy bodies (α -synuclein).
- Prion disease: often PrP plaques; sometimes tangles; sometimes Lewy bodies.
- FTDP-17/Pick's disease: tangles or Pick bodies (3-repeat tau).
- Parkinson's disease/Lewy body dementia: Lewy bodies.
- Progressive Supranuclear Palsy and Corticobasal Degeneration (tangles).

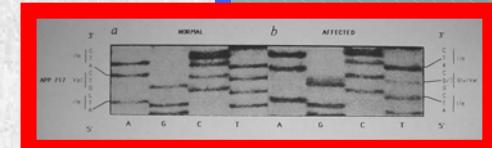
Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease

Alison Goate*, Marie-Christine Chartier-Harlin*, Mike Mullan*, Jeremy Brown*, Fiona Crawford*, Liana Fidani*, Luis Giuffra†, Andrew Haynes‡, Nick Irving*, Louise James‡, Rebecca Mant||, Philippa Newton*, Karen Rooke*, Penelope Roques*, Chris Talbot*, Margaret Pericak-Vance§, Allen Roses§, Robert Williamson*, Martin Rossor*, Mike Owen|| & John Hardy*¶



Early-onset Alzheimer's disease caused by mutations at codon 717 of the β -amyloid precursor protein gene

Marie-Christine Chartier-Harlin, Fiona Crawford, Henry Houlden, Andrew Warren*, David Hughes, Liana Fidani, Alison Goate, Martin Rossor, Penelope Roques, John Hardy & Mike Mullan†

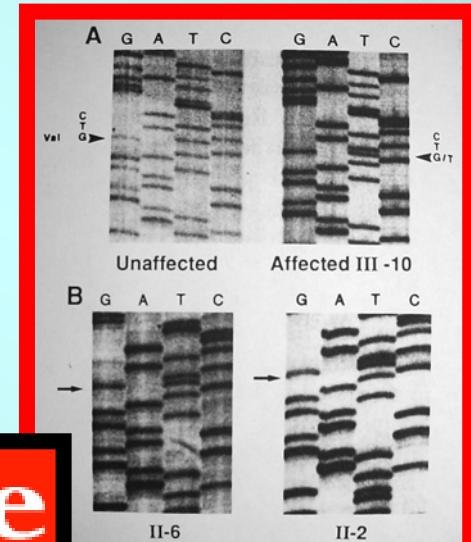


nature
Feb./Oct. 1991

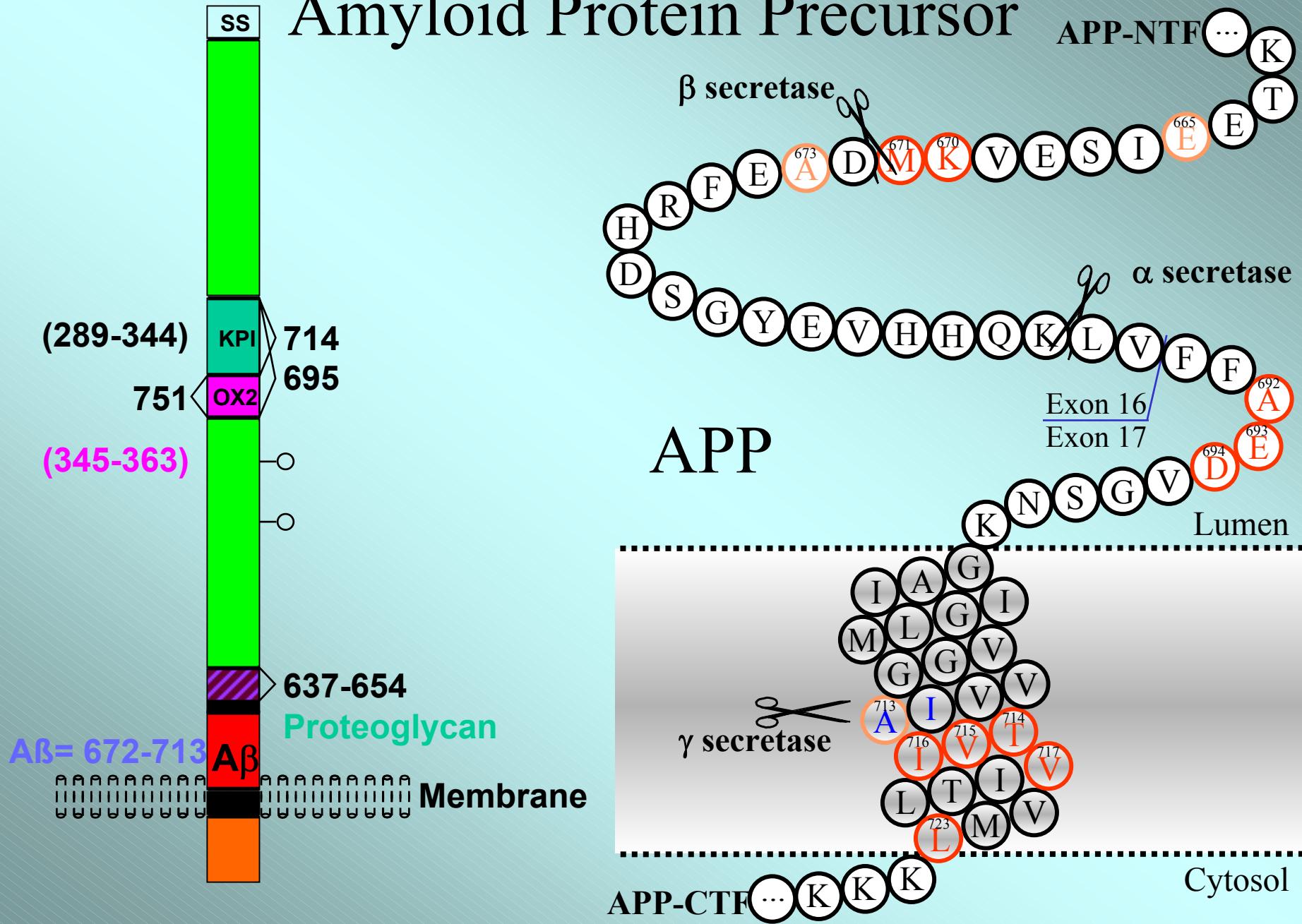
A Mutation in the Amyloid Precursor Protein Associated with Hereditary Alzheimer's Disease

JILL MURRELL, MARTIN FARLOW, BERNARDINO GHETTI, MERRILL D. BENSON*

Science
Oct. 1991



Amyloid Protein Precursor



Mutation of the β -amyloid precursor protein in familial Alzheimer's disease increases β -protein production

Martin Citron[†], Tilman Oltersdorf^{*†}, Christian Haass,
Lisa McConlogue*, Albert Y. Hung, Peter Seubert*,
Carmen Vigo-Pelfrey*, Ivan Lieberburg*
& Dennis J. Selkoe

nature
Dec. 1992

Release of Excess Amyloid β Protein from a Mutant Amyloid β Protein Precursor

Xiao-Dan Cai, Todd E. Golde, Steven G. Younkin*

An Increased Percentage of Long Amyloid β Protein Secreted by Familial Amyloid β Protein Precursor (β APP₇₁₇) Mutants

Nobuhiro Suzuki,* Tobun T. Cheung,* Xiao-Dan Cai,
Asano Odaka, Laszlo Otvos Jr., Christopher Eckman,
Todd E. Golde, Steven G. Younkin†

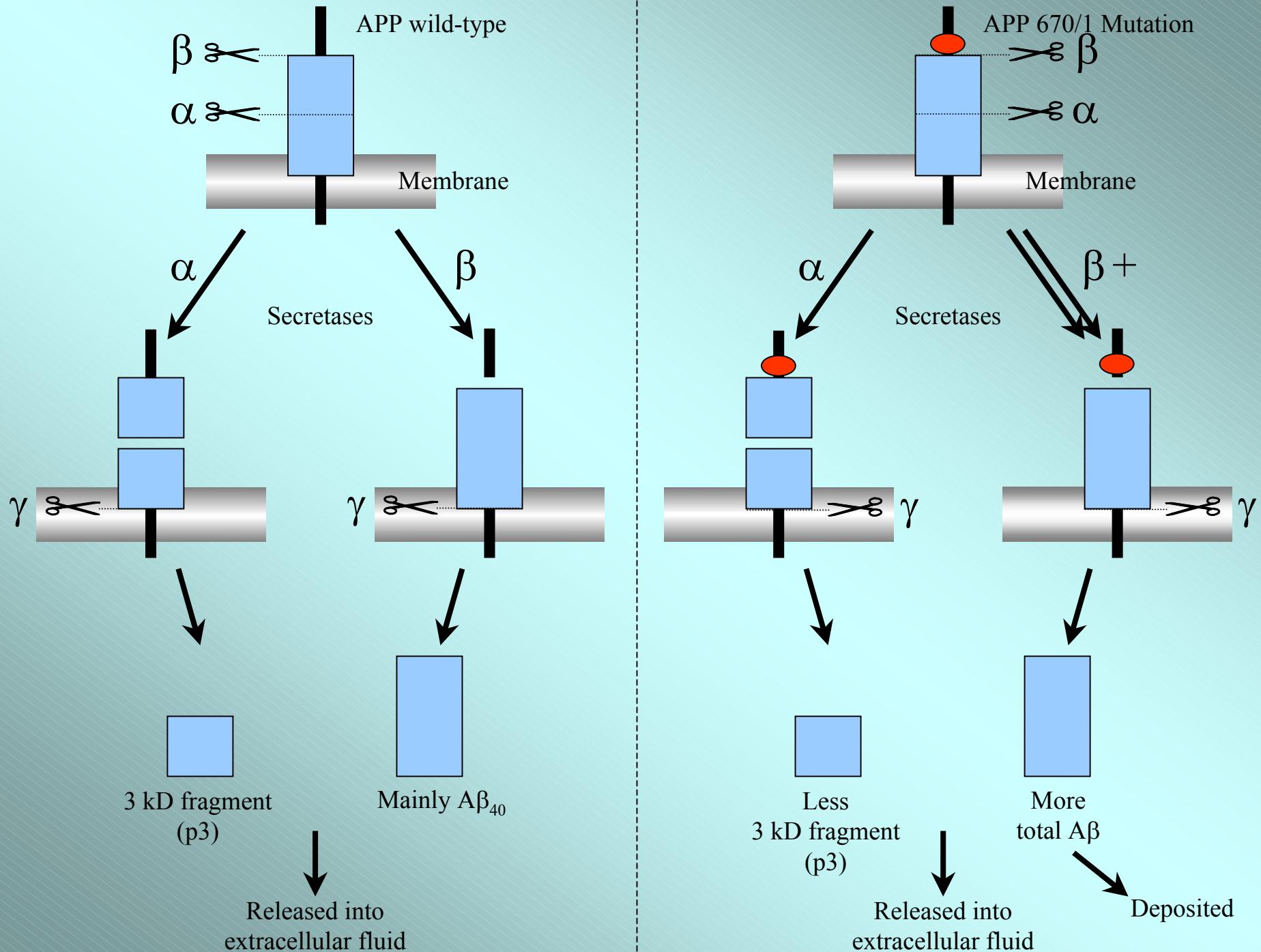
Neuron
March 1995

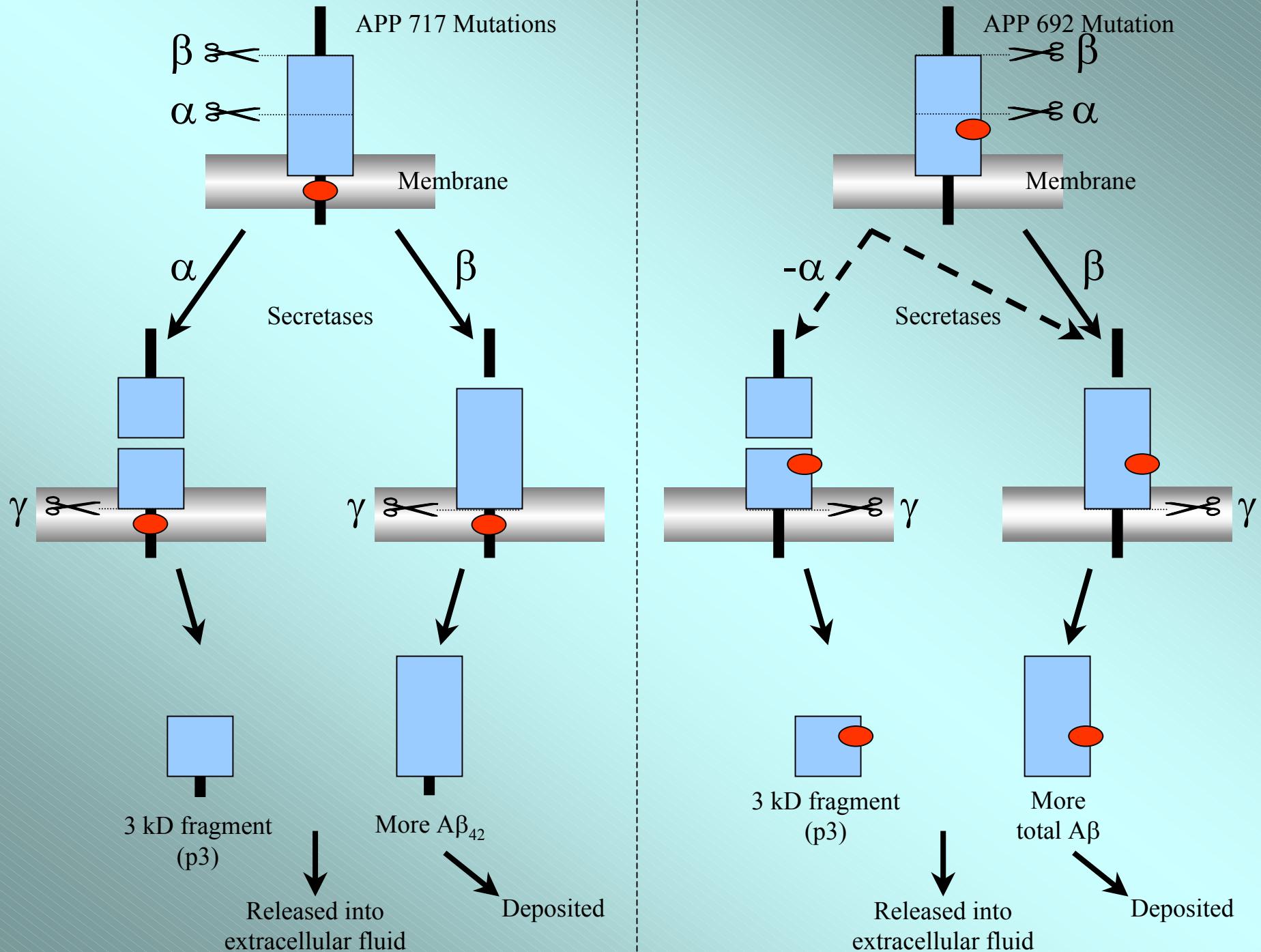
Generation of Amyloid β Protein from Its Precursor Is Sequence Specific

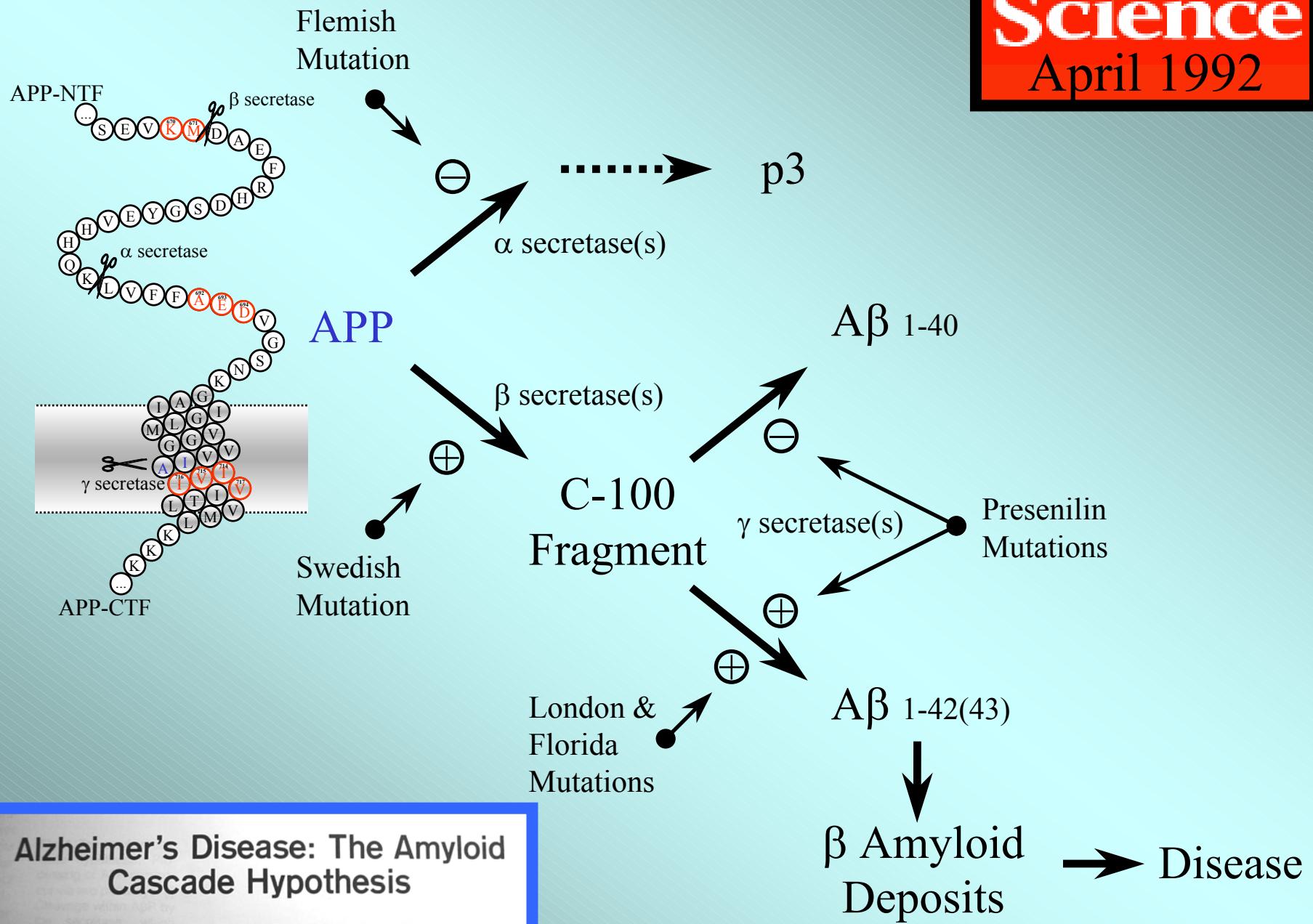
Martin Citron, David B. Teplow,
and Dennis J. Selkoe

Science
Jan. 1993

Science
May 1994







Alzheimer's Disease: The Amyloid Cascade Hypothesis

John A. Hardy and Gerald A. Higgins

Genetic Linkage Evidence for a Familial Alzheimer's Disease Locus on Chromosome 14

Gerard D. Schellenberg,* Thomas D. Bird, Ellen M. Wijsman,
Harry T. Orr, Leojean Anderson, Ellen Nemens, June A. White,
Lori Bonnycastle, James L. Weber, M. Elisa Alonso,
Huntington Potter, Leonard L. Heston, George M. Martin

Science
Oct. 1992

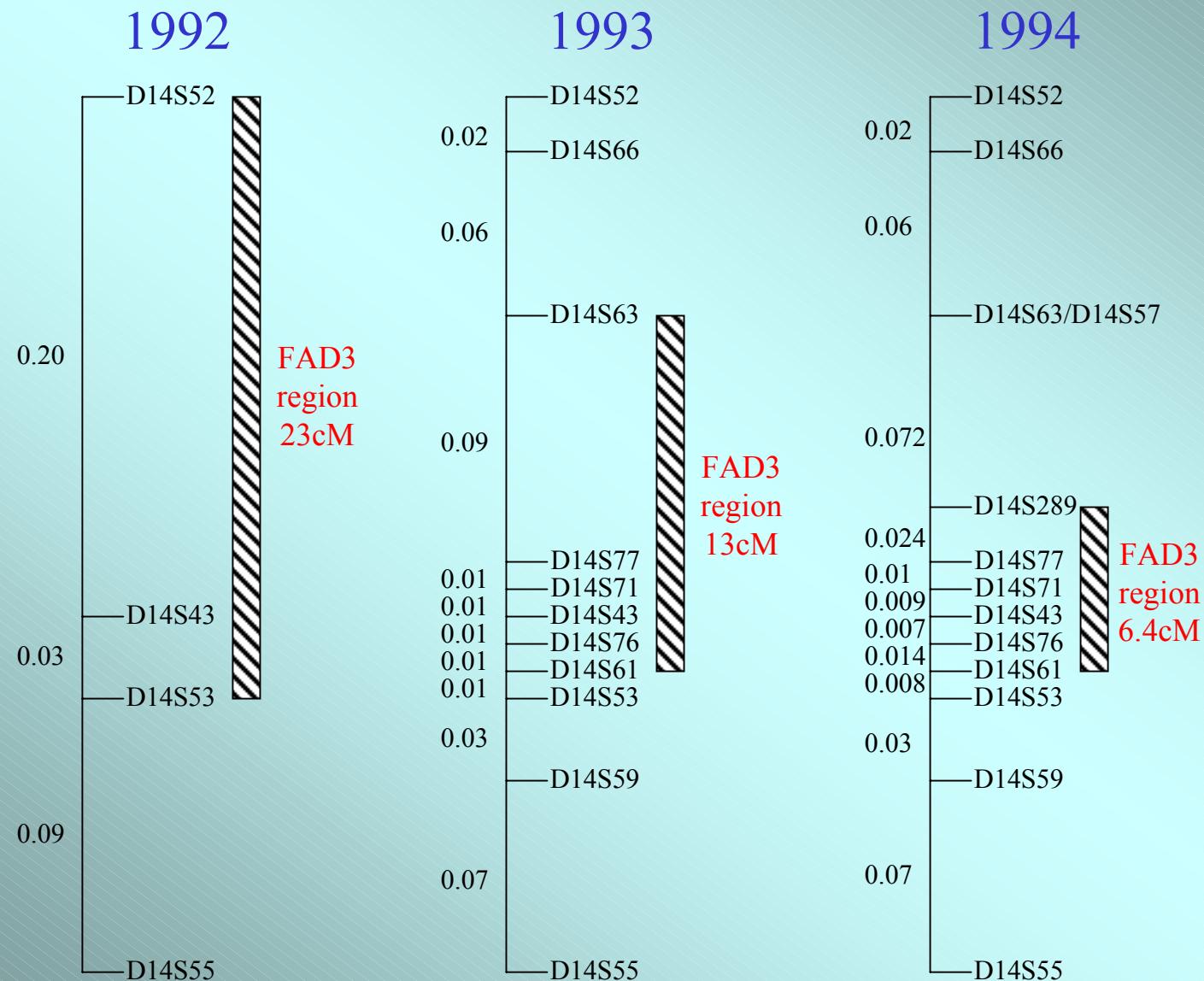
The American Journal of
Human Genetics

May 1983

Alzheimer Disease: Evidence for Susceptibility Loci on Chromosomes 6 and 14

LOWELL R. WEITKAMP,¹ LINDA NEE,² BRONYA KEATS,³ RONALD J. POLINSKY,²
AND SALLY GUTTORMSEN¹

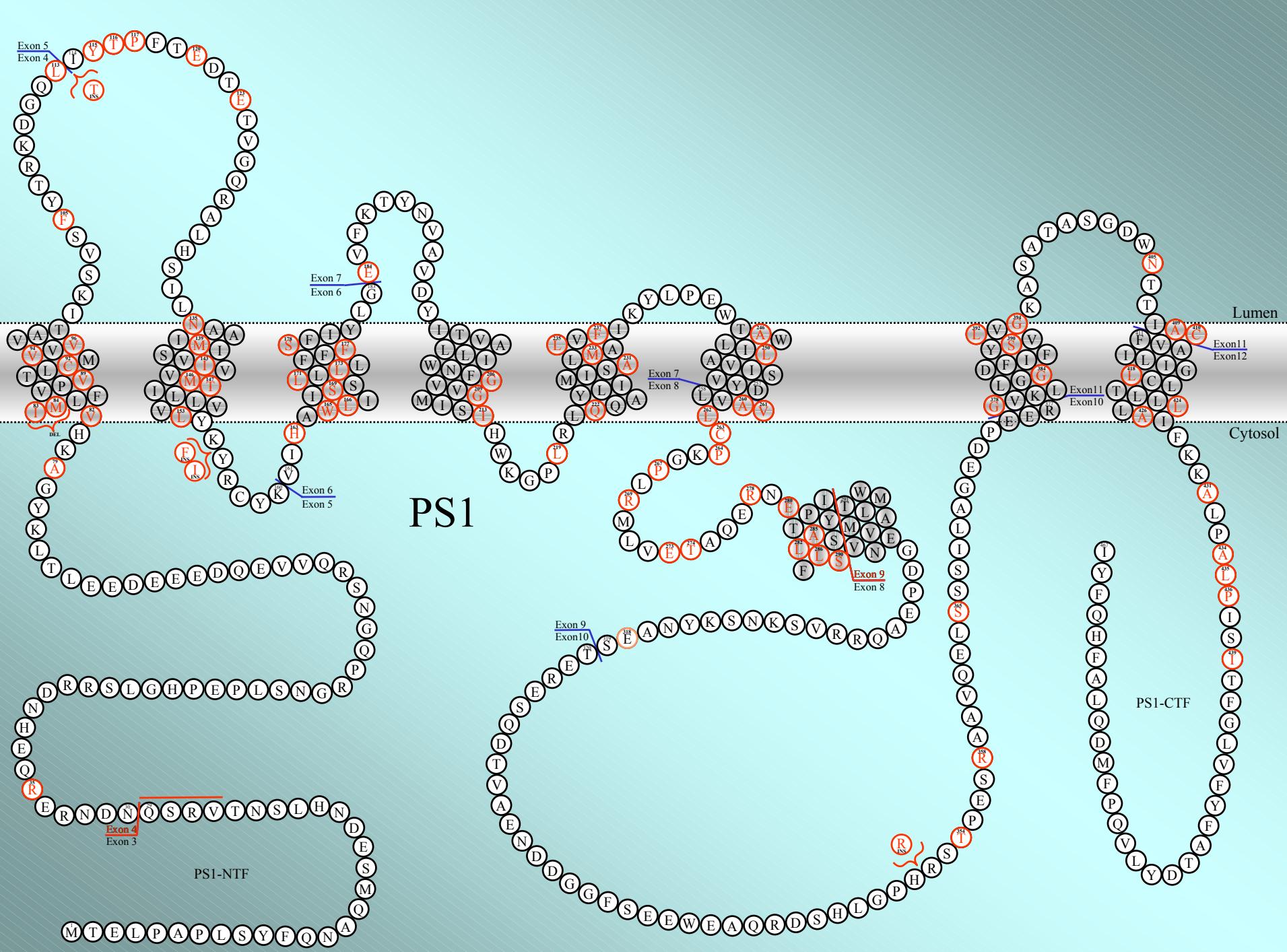
Genetic Maps around the FAD locus on Chromosome 14



Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease

R. Sherrington*, E. I. Rogaev*, Y. Liang*, E. A. Rogaeva*, G. Levesque*,
M. Ikeda*, H. Chi*, C. Lin*, G. Li*, K. Holman*, T. Tsuda*, L. Mar†,
J.-F. Foncin§, A. C. Bruni||, M. P. Montesi||, S. Sorbi†, I. Rainero#, L. Pinessi#,
L. Nee☆, I. Chumakov**, D. Pollen††, A. Brookes†, P. Sanseau††,
R. J. Polinsky#‡, W. Wasco‡‡, H. A. R. Da Silva§§, J. L. Haines‡‡,
M. A. Pericak-Vance§§, R. E. Tanzi‡‡, A. D. Roses§§, P. E. Fraser,
J. M. Rommens† & P. H. St George-Hyslop*||

nature
June 1995



A Familial Alzheimer's Disease Locus on Chromosome 1

Ephrat Levy-Lahad, Ellen M. Wijsman, Ellen Nemens,
Leojean Anderson, Katrina A. B. Goddard, James L. Weber,
Thomas D. Bird, Gerard D. Schellenberg*

Science
Aug. 1995

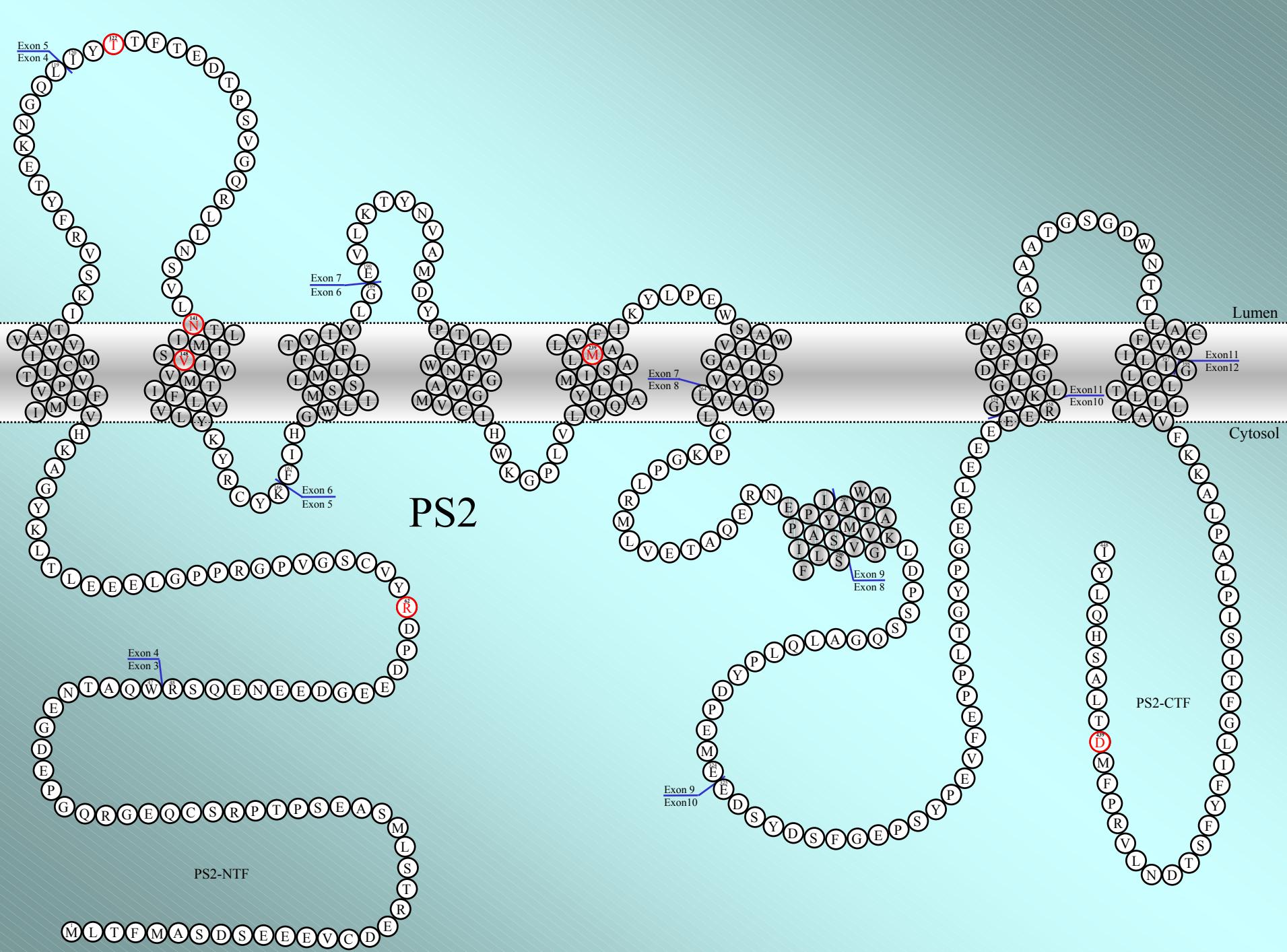
Candidate Gene for the Chromosome 1 Familial Alzheimer's Disease Locus

Ephrat Levy-Lahad,* Wilma Wasco,* Parvoneh Poorkaj,
Donna M. Romano, Junko Oshima, Warren H. Pettingell,
Chang-en Yu, Paul D. Jondro, Stephen D. Schmidt, Kai Wang,
Annette C. Crowley, Ying-Hui Fu, Suzanne Y. Guenette,
David Galas, Ellen Nemens, Ellen M. Wijsman, Thomas D. Bird,
Gerard D. Schellenberg,† Rudolph E. Tanzi

Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene

E. I. Rogaev*, R. Sherrington*, E. A. Rogaeva*,
G. Levesque*, M. Ikeda*, Y. Liang*, H. Chi*,
C. Lin*, K. Holman*, T. Tsuda*, L. Mar†, S. Sorbi‡,
B. Nacmias‡, S. Piacentini‡, L. Amaducci‡,
I. Chumakov§, D. Cohen§, L. Lannfelt||,
P. E. Fraser*, J. M. Rommens†
& P. H. St George-Hyslop*¶

nature
Aug. 1995



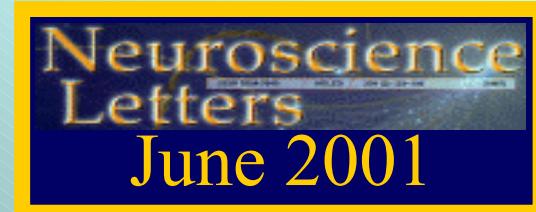
The structure of the presenilin 1 (S182) gene and identification of six novel mutations in early onset AD families

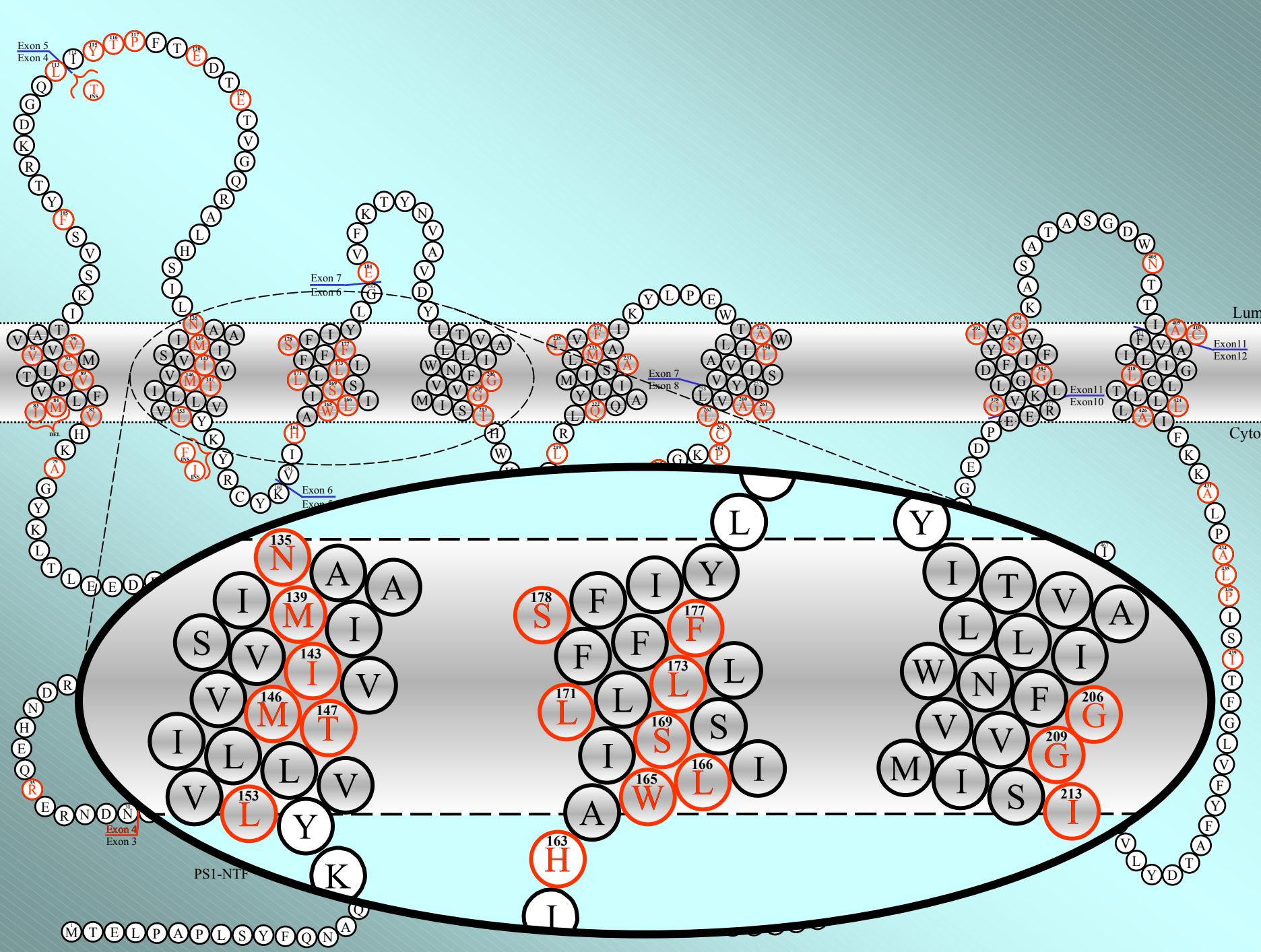
Alzheimer's Disease Collaborative Group.*

nature
genetics
Oct. 1995

Presenilin mutations line up along transmembrane α -helices

John Hardy*, Richard Crook





Secreted amyloid β -protein similar to that in the senile plaques of Alzheimer's disease is increased *in vivo* by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease

nature
medicine

Aug. 1996

Increased amyloid- β 42(43) in brains of mice expressing mutant presenilin 1

Karen Duff*,†, Chris Eckman†, Cindy Zehr*†, Xin Yu*, Cristian-Mihail Prada†, Jordi Perez-tur*†, Mike Hutton*†, Luc Buee†, Yasuo Harigaya†, Debra Yager†, David Morgan§, Marcia N. Gordon§, Leigh Holcomb§, Lawrence Refolo†, Brenda Zenk†, John Hardy*† & Steven Younkin†

nature
Oct. 1996

nature
medicine
Jan. 1997

D. SCHEUNER¹, C. ECKMAN^{1,2}, M. JENSEN³, X. SONG⁴, M. CITRON⁵, N. SUZUKI⁶, T.D. BIRD^{7,12}, J. HARDY¹⁴, M. HUTTON¹⁴, W. KUKULL⁸, E. LARSON⁹, E. LEVY-LAHAD^{9,13}, M. VIITANEN³, E. PESKIND^{10,13}, P. POORKAJ^{7,13}, G. SCHELLENBERG^{7,9,11,13}, R. TANZI¹⁵, W. WASCO¹⁵, L. LANNFELT³, D. SELKOE⁵ & S. YOUNKIN²

Familial Alzheimer's Disease-Linked Presenilin 1 Variants Elevate A β 1-42/1-40 Ratio In Vitro and In Vivo

David R. Borcheit,^{1,4,11} Gopal Thinakaran,^{1,4,11} Christopher B. Eckman,^{5,6,11} Michael K. Lee,^{1,4,11} Frances Davenport,⁴ Tamara Ratovitsky,⁴ Cristian-Mihail Prada,⁶ Grace Kim,⁴ Sophia Seekins,⁴ Debra Yager,⁶ Hilda H. Slunt,⁴ Rong Wang,⁷ Mary Seeger,⁸ Allan I. Levey,⁹ Samuel E. Gandy,⁸ Neal G. Copeland,¹⁰ Nancy A. Jenkins,¹⁰ Donald L. Price,^{1,2,3,4} Steven G. Younkin,^{5,6} and Sangram S. Sisodia,^{1,2,4}

Neuron
Nov. 1996

Mutant presenilins of Alzheimer's disease increase production of 42-residue amyloid β -protein in both transfected cells and transgenic mice

MARTIN CITRON¹, DAVID WESTAWAY², WEIMING XIA¹, GEORGE CARLSON³, THEKLA DIEHL¹, GEORGES LEVESQUE², KELLY JOHNSON-WOOD⁴, MICHAEL LEE¹, PETER SEUBERT⁴, ANGELA DAVIS³, DORA KOLODENKO⁴, RUTH MOTTER⁴, ROBIN SHERRINGTON², BILLIE PERRY³, HONG YAO², ROBERT STROME², IVAN LIEBERBURG⁴, JOHANNA ROMMENS², SOYEON KIM⁵, DALE SCHENK⁴, PAUL FRASER², PETER ST GEORGE HYSLOP² & DENNIS J. SELKOE¹

Is late onset Alzheimer's Disease caused by related mechanisms?

1. Yes: ApoE involved in amyloid deposition

Apolipoprotein E is essential for amyloid deposition
in the APP^{V717F} transgenic mouse model of
Alzheimer's disease

PNAS Dec. 1999
Proceedings of the National Academy of Sciences
of the United States of America

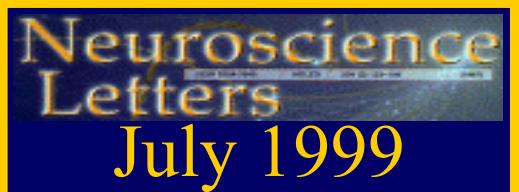
Kelly R. Bales*, Tatyana Verina†, David J. Cummins‡, Yansheng Du§, Richard C. Dodel§¶, Josep Saura§, Cindy E. Fishman*||,
Cynthia A. DeLong*, Pedro Piccardo†, Valerie Petegnief*, Bernardino Ghetti†, and Steven M. Paul*§||

Is late onset Alzheimer's Disease caused by related mechanisms?

1. Yes: ApoE involved in amyloid deposition
2. Yes: APP probably a “late onset gene”

Genetic variability at the amyloid- β precursor protein locus may contribute to the risk of late-onset Alzheimer's disease

Fabienne Wavrant-De Vrièze^{a, f}, Richard Crook^a, Peter Holmans^{b, c}, Patrick Kehoe^b, Michael J. Owen^b, Julie Williams^b, Kim Roehl^{c, d}, Debomoy K. Laliiri^e, Shantia Shears^{c, d}, Jeremy Booth^{c, d}, William Wu^{c, d}, Alison Goate^{c, d}, Marie Christine Chartier-Harlin^f, John Hardy^{a,*}, Jordi Pérez-Tur^a



The Amyloid Precursor Protein Locus and Very-Late-Onset Alzheimer Disease

Jane M. Olson, Katrina A. B. Goddard, and Doreen M. Dudek



Is late onset Alzheimer's Disease caused by related mechanisms?

1. Yes: ApoE involved in amyloid deposition
2. Yes: APP probably a “late onset gene”
3. Yes: Late onset AD & high A β show linkage to the same locus

Susceptibility Locus for Alzheimer's Disease on Chromosome 10

Amanda Myers,¹ Peter Holmans,^{1*} Helen Marshall,¹ Jennifer Kwon,¹ David Meyer,¹ Dzanan Ramic,¹ Shantia Shears,¹ Jeremy Booth,¹ Fabienne Wavrant DeVrieze,² Richard Crook,² Marian Hamshere,³ Richard Abraham,³ Nigel Tunstall,⁴ Francis Rice,³ Stephanie Carty,³ Sara Lillystone,³ Pat Kehoe,³ Varuni Rudrasingham,³ Lesley Jones,³ Simon Lovestone,⁴ Jordi Perez-Tur,⁵ Julie Williams,³ Michael J. Owen,³ John Hardy,² Alison M. Goate^{1†}

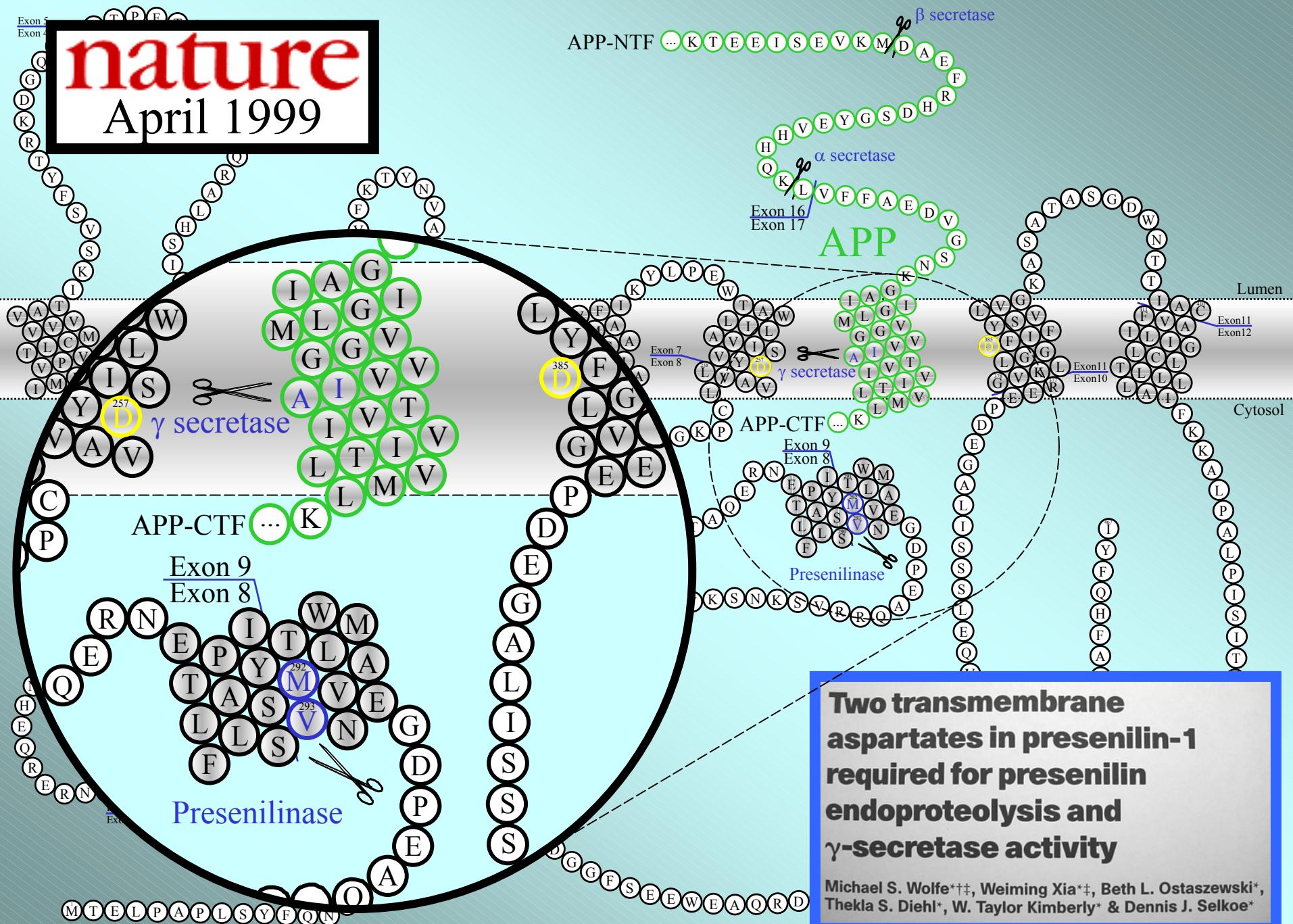
Linkage of Plasma A β 42 to a Quantitative Locus on Chromosome 10 in Late-Onset Alzheimer's Disease Pedigrees

Nilufer Ertekin-Taner,¹ Neill Graff-Radford,¹ Linda H. Younkin,¹ Christopher Eckman,¹ Matthew Baker,¹ Jennifer Adamson,¹ James Ronald,¹ John Blangero,² Michael Hutton,^{1*} Steven G. Younkin¹

Science
Dec. 2000

nature

April 1999



Accelerated Alzheimer-type phenotype in transgenic mice
carrying both mutant *amyloid precursor protein*
and *presenilin 1* transgenes

LEIGH HOLCOMB¹, MARCIA N. GORDON¹, EILEEN MCGOWAN², XIN YU², STAN BENKOVIC¹,
PAUL JANTZEN¹, KRISTAL WRIGHT¹, IRENE SAAD¹, RYAN MUELLER¹, DAVE MORGAN¹,
SUNNY SANDERS², CINDY ZEHR², KASSANDRA O'CAMPO², JOHN HARDY³,
CRISTIAN-MIHAIL PRADA⁴, CHRIS ECKMAN⁴, STEVE YOUNKIN⁴, KAREN HSIAO⁵ & KAREN DUFF²

nature
medicine
Jan. 1998

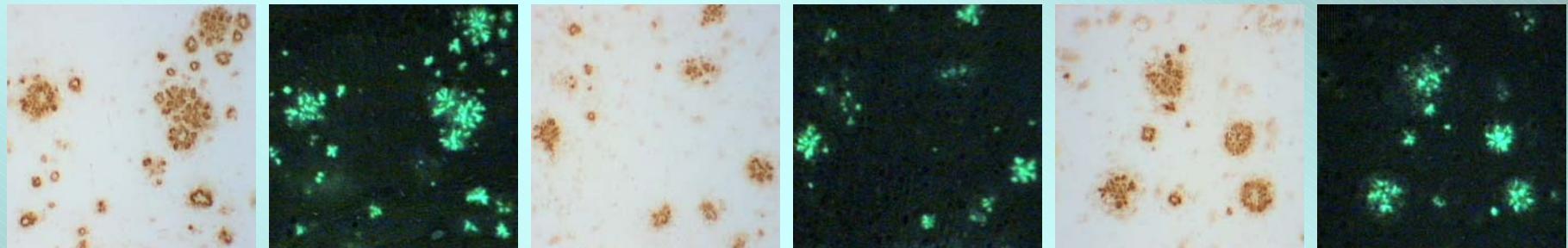
**Accelerated Amyloid Deposition in the Brains
of Transgenic Mice Coexpressing Mutant
Presenilin 1 and Amyloid Precursor Proteins**

David R. Borchelt,*|| Tamara Ratovitski,*
Judy van Lare,* Michael K. Lee,* Vicki Gonzales,*
Nancy A. Jenkins,§ Neal G. Copeland,§
Donald L. Price,*†‡ and Sangram S. Sisodia*†

Neuron
Oct. 1997

Presenilin accelerates amyloid pathology.

Hippocampus
PSAPP



Cingulate cortex

Entorhinal cortex

APP (Tg2576)

A β

ThioS

A β

ThioS

A β

ThioS

17 month old mice

Localization of Disinhibition-Dementia-Parkinsonism-Amyotrophy Complex to 17q21-22

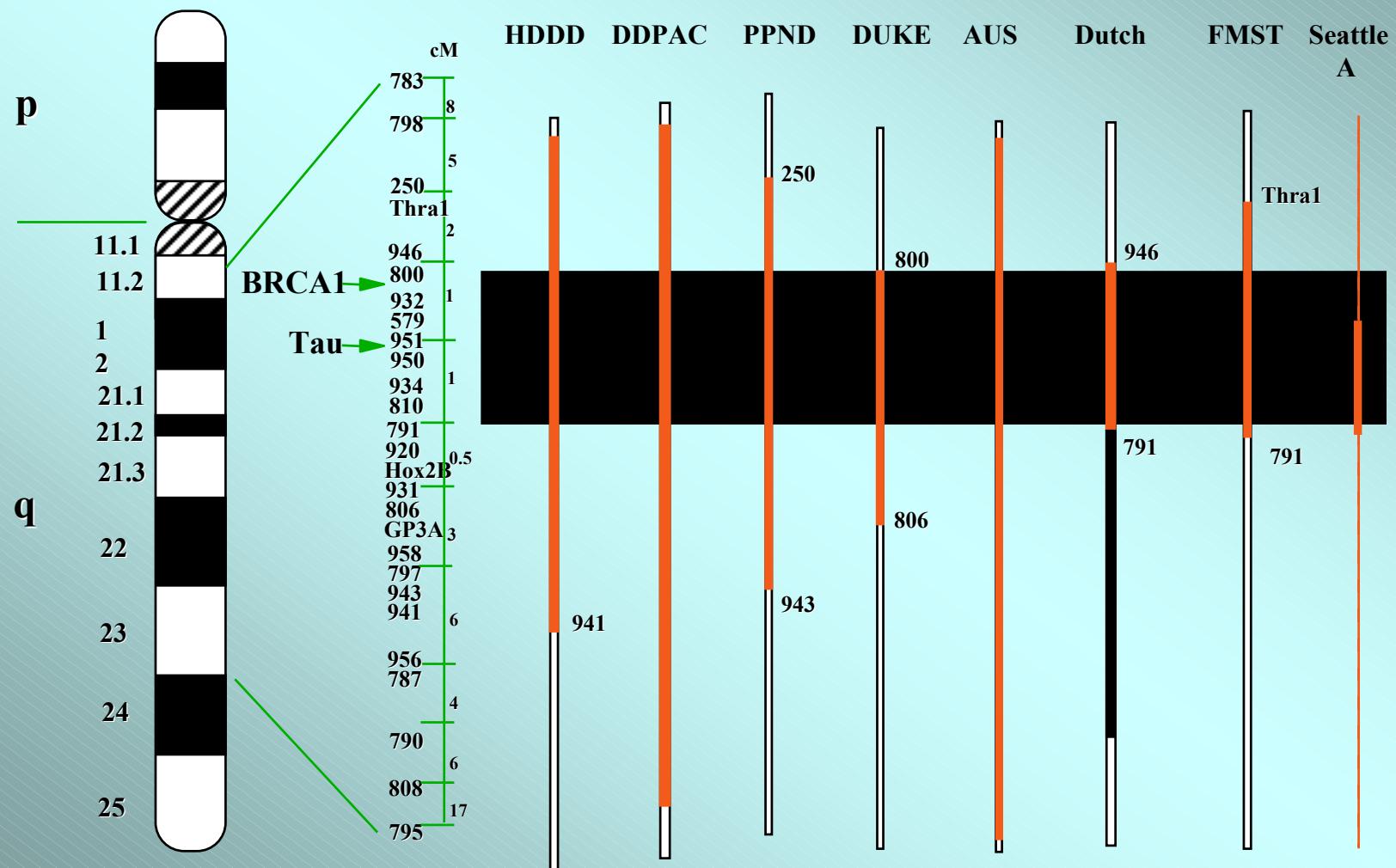
K. C. Wilhelmsen, T. Lynch, E. Pavlou, M. Higgins, and T. G. Nygaard



Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17: A Consensus Conference

Norman L. Foster, MD,* Kirk Wilhelmsen, MD, PhD,† Anders A. F. Sima, MD, PhD,‡§
Margaret Z. Jones, MD,|| Constance J. D'Amato, BS,‡ Sid Gilman, MD,* and Conference Participants¶

Families with linkage to the FTDP-17 Locus

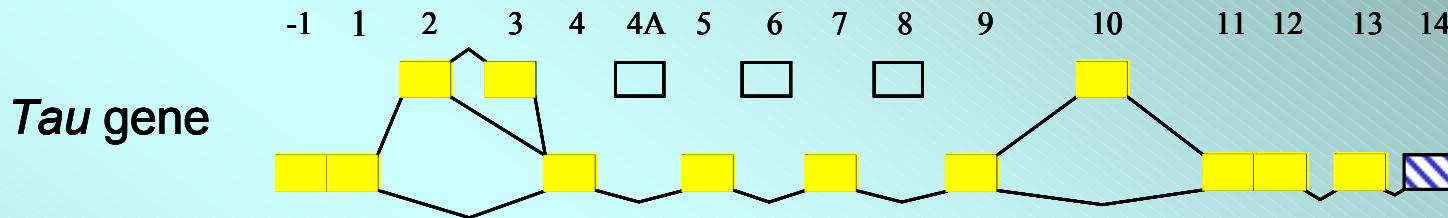


Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17: A New Group of Tauopathies

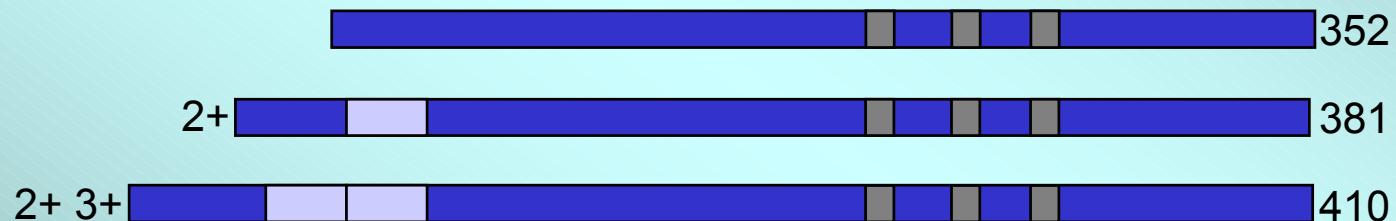
Maria Grazia Spillantini¹, Thomas D. Bird², and
Bernardino Ghetti³

BRAIN PATHOLOGY
The Official Publication of the International Society of Neuropathology
April 1998

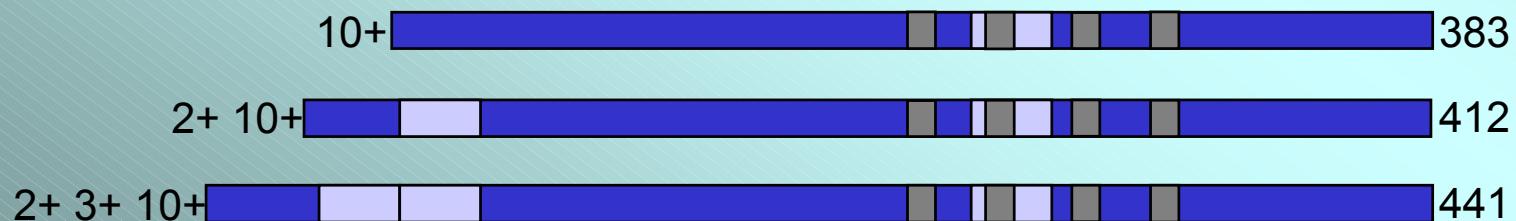
The microtubule associated protein tau



Tau 3 repeat protein isoforms



Tau 4 repeat protein isoforms



Tau Is a Candidate Gene for Chromosome 17 Frontotemporal Dementia

Parvoneh Poorkaj, PhD,*† Thomas D. Bird, MD,*‡ Ellen Wijsman, PhD,§¶|| Ellen Nemens, MS,*
Ralph M. Garruto, PhD,# Leojean Anderson, BS,* Athena Andreadis, PhD,** Wigbert C. Wiederholt, MD,††
Murray Raskind, MD,‡‡§§ and Gerard D. Schellenberg, PhD*††¶¶

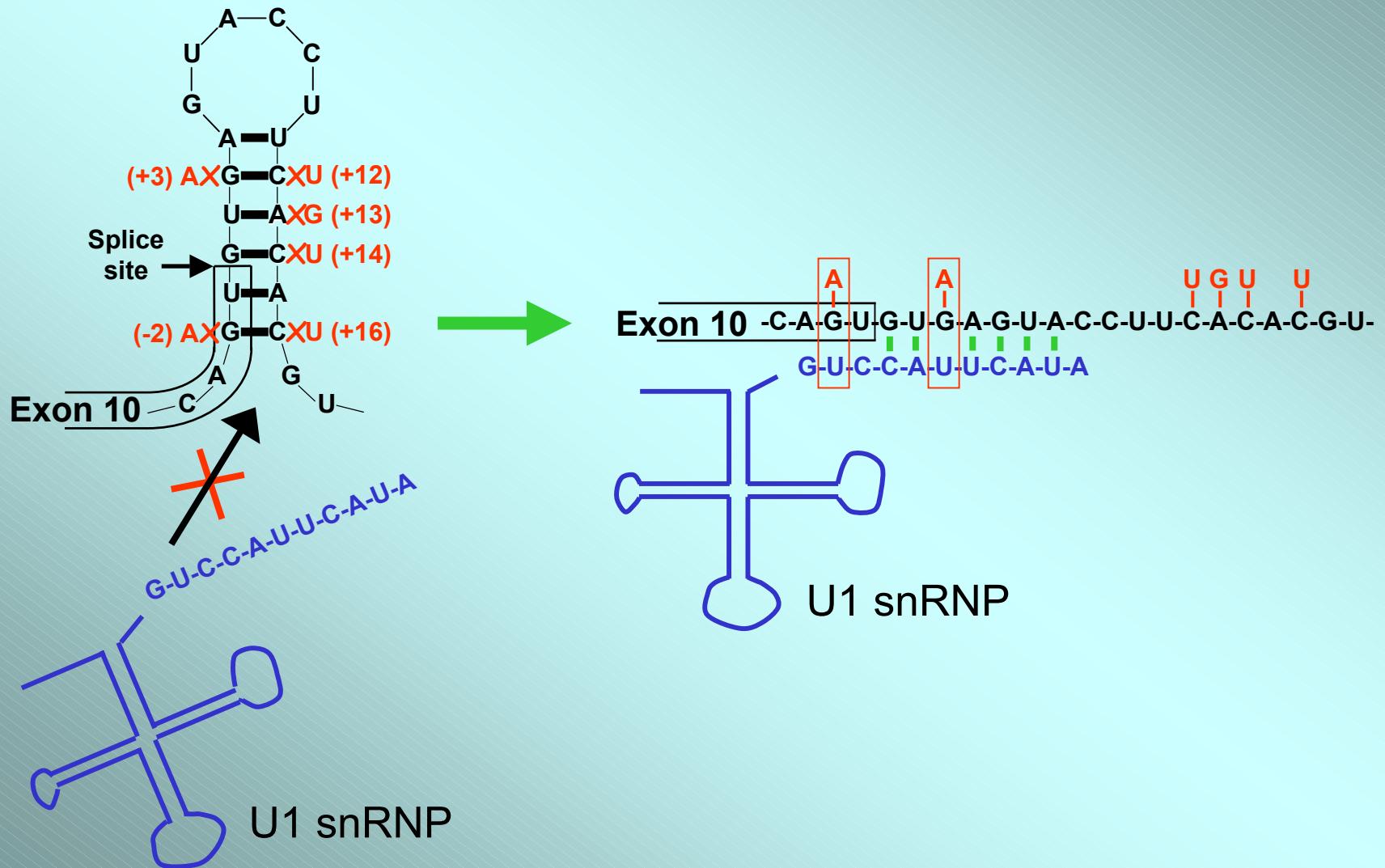
Annals of Neurology
June 1998

Association of missense and 5'-splice-site mutations in *tau* with the inherited dementia FTDP-17

Mike Hutton*, Corinne L. Lendon*, Patrizia Rizzu*, Matt Baker¹,
Susanne Froelich^{3,5}, Henry Houlden¹, Stuart Pickering-Brown⁶,
Sumi Chakraverty², Adrian Isaacs¹, Andrew Grover¹,
Jennifer Hackett¹, Jennifer Adamson¹, Sarah Lincoln¹,
Dennis Dickson¹, Peter Davies⁷, Ronald C. Petersen⁸,
Martijn Stevens⁴, Esther de Graaff³, Erwin Wauters³,
Jeltje van Baren³, Marcel Hillebrand³, Marijke Joosse³,
Jennifer M. Kwon⁹, Petra Nowotny², Lien Kuei Che², Joanne Norton⁹,
John C. Morris⁹, Lee A. Reed¹⁰, John Trojanowski¹⁰, Hans Basun⁵,
Lars Lannfelt⁵, Michael Neystat¹¹, Stanley Fahn¹¹, Francis Dark¹²,
Tony Tannenberg¹³, Peter R. Dodd¹⁴, Nick Hayward¹⁵,
John B. J. Kwok¹⁶, Peter R. Schofield¹⁶, Athena Andreadis¹⁷,
Julie Snowden¹⁸, David Craufurd¹⁹, David Neary¹⁸, Frank Owen⁶,
Ben A. Oostra³, John Hardy¹, Alison Goate², John van Swieten⁴,
David Mann²⁰, Timothy Lynch¹¹ & Peter Heutink³

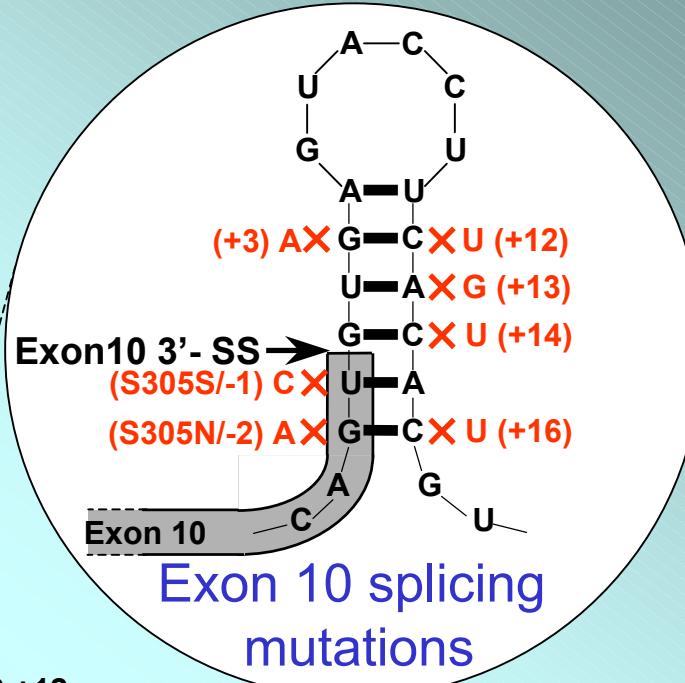
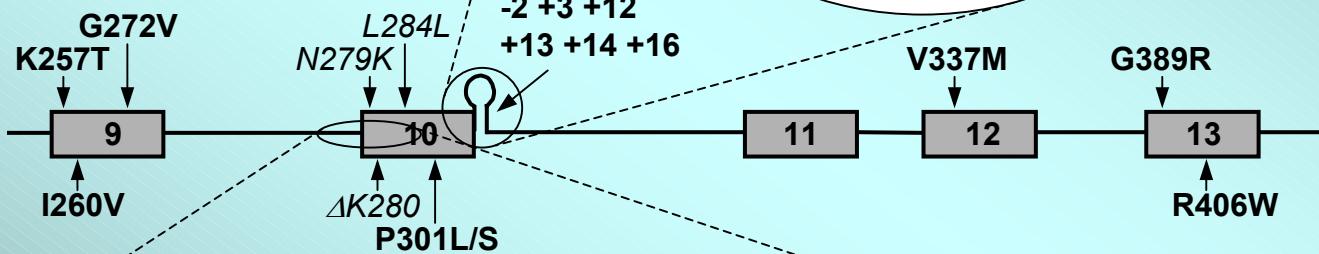
nature
June 1998

Tau Exon 10 3' splice site mutations increase U1 snRNP binding and splicing of Exon 10

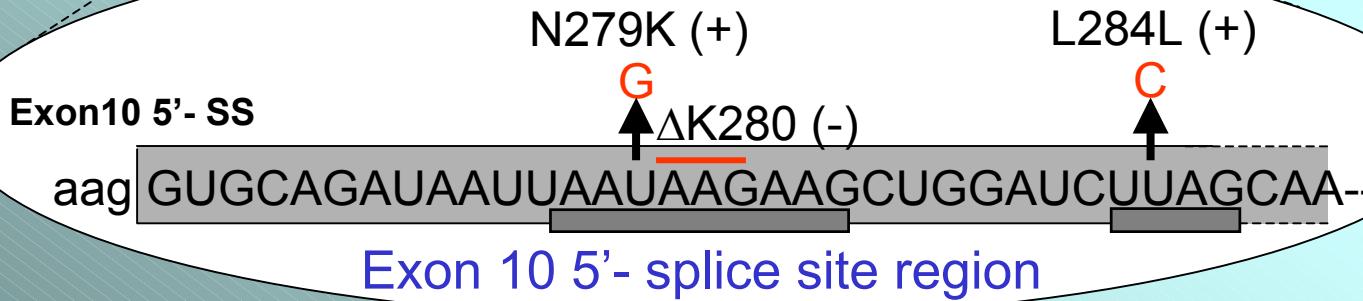


FTDP-17 - missense and splicing mutations in tau

All tau mutations



Exon 10 splicing mutations



Exon 10 5'- splice site region

Genetic Evidence for the Involvement of τ in Progressive Supranuclear Palsy

Chris Conrad, BS,* Athena Andreadis, PhD,† John Q. Trojanowski, MD, PhD,‡ Dennis W. Dickson, MD,§
David Kang, MS,* Xiaohua Chen, MD,* Wigbert Wiederholt, MD,* Larry Hansen, MD,*
Eliezer Masliah, MD,* Leon J. Thal, MD,* Robert Katzman, MD,* Yu Xia, MS,* and Tsunao Saitoh, PhD*||

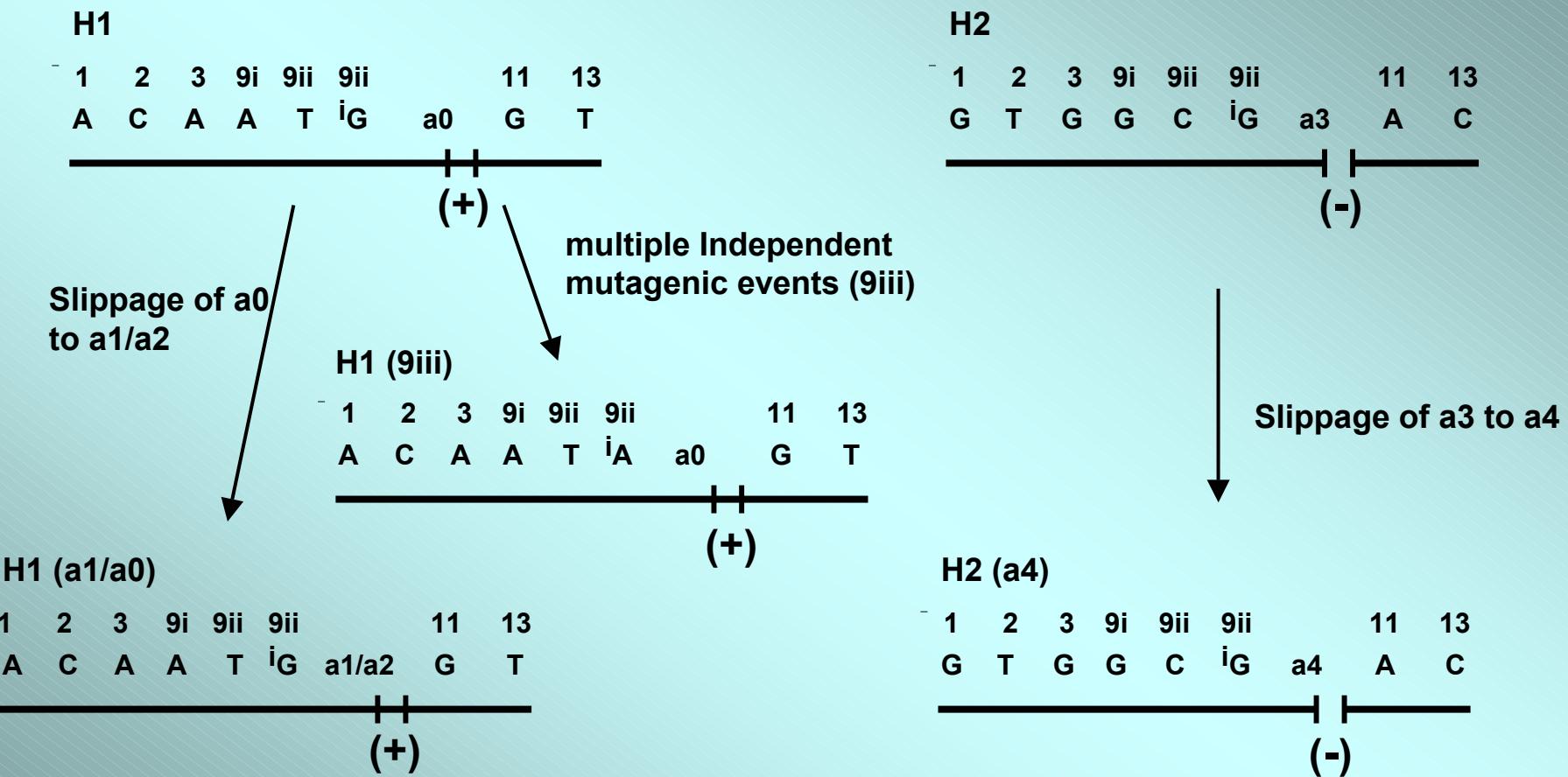
Annals of Neurology
Feb 1997

Association of an extended haplotype in the *tau* gene with progressive supranuclear palsy

Matt Baker, Irene Litvan¹, Henry Houlden, Jennifer Adamson, Dennis Dickson,
Jordi Perez-Tur, John Hardy, Timothy Lynch², Eileen Bigio³ and Mike Hutton*

Human
Molecular
Genetics
April 1999

Evolution of Human *tau* haplotypes (almost no recombination between H1/H2)

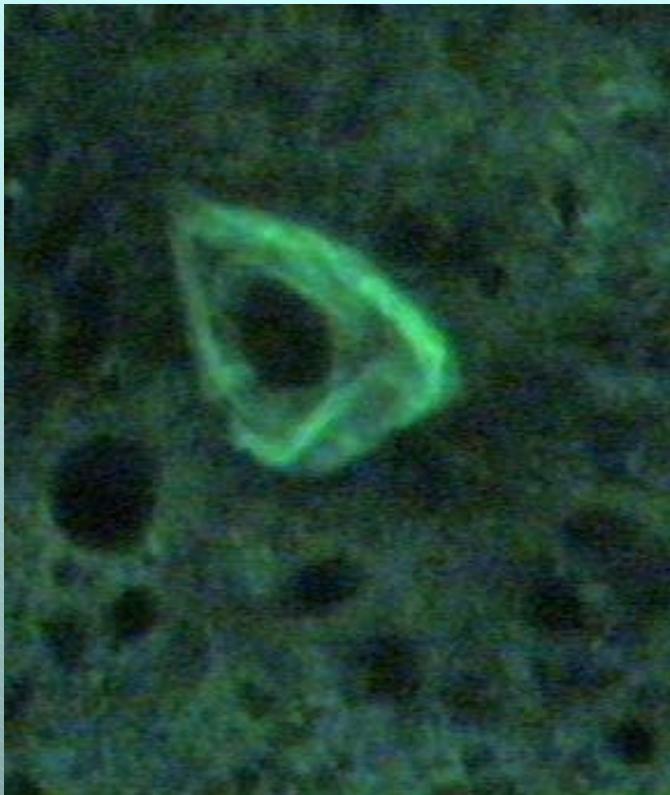


(+)/(-) indicates location of intronic deletion 5' of E10

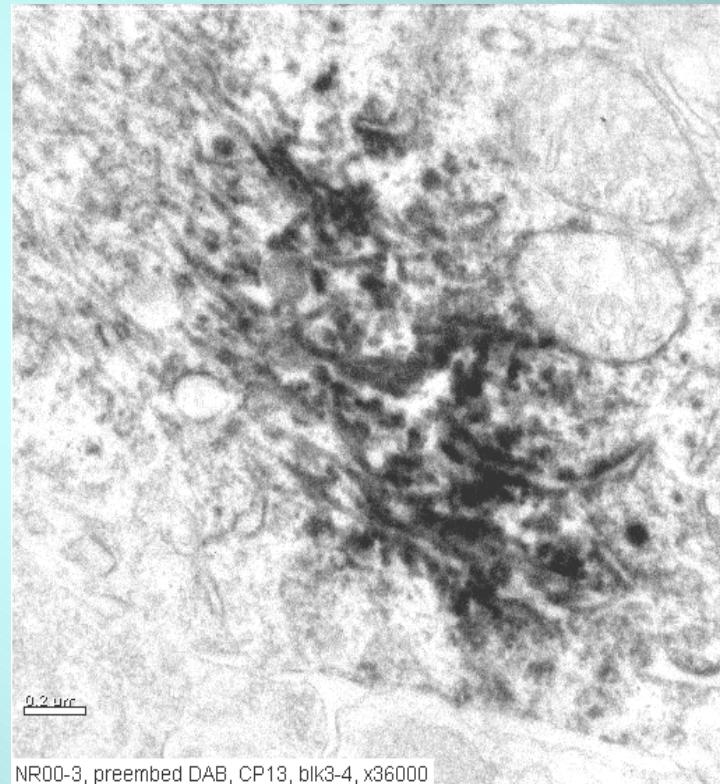
Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein

Jada Lewis¹, Eileen McGowan¹, Julia Rockwood², Heather Melrose¹, Parimala Nacharaju¹, Marjon Van Slegtenhorst¹, Katrina Gwinn-Hardy¹, M. Paul Murphy¹, Matt Baker¹, Xin Yu¹, Karen Duff¹, John Hardy¹, Anthony Corral¹, Wen-Lang Lin¹, Shu-Hui Yen¹, Dennis W. Dickson¹, Peter Davies² & Mike Hutton¹

nature
genetics
Aug. 2000



- Thioflavin-S positive NFT
- brain stem

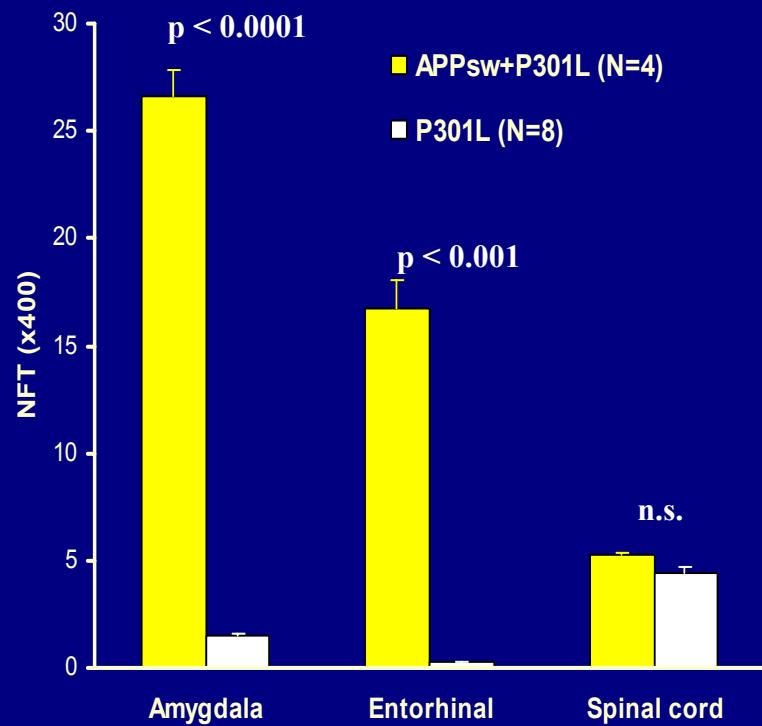


- Tau immuno-EM (22-24-nm twisted ribbons)

Enhanced Neurofibrillary Degeneration in Transgenic Mice Expressing Mutant Tau and APP

Jada Lewis,* Dennis W. Dickson,* Wen-Lang Lin, Louise Chisholm,
Anthony Corral, Graham Jones, Shu-Hui Yen, Naruhiko Sahara,
Lisa Skipper, Debra Yager, Chris Eckman, John Hardy,
Mike Hutton,† Eileen McGowan

Neurofibrillary tangles
(Gallyas stain)

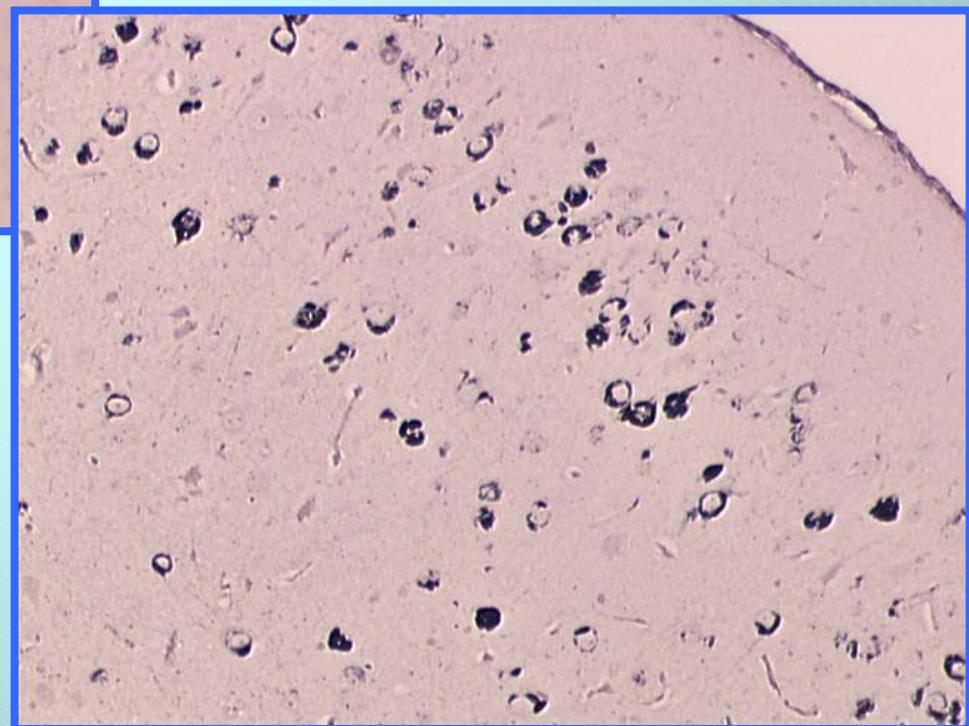
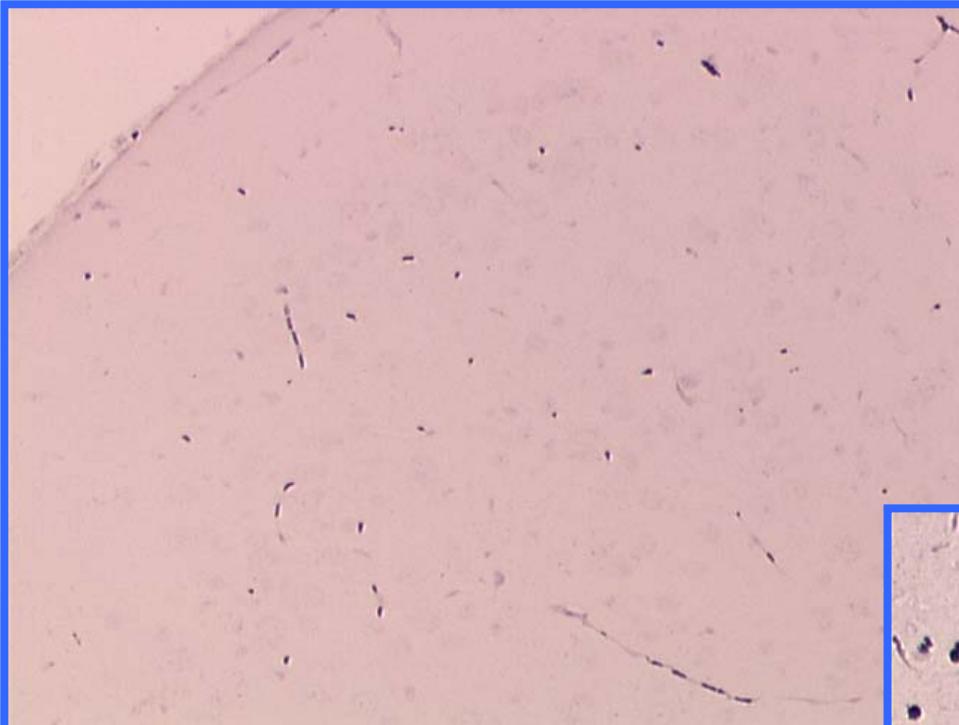


Formation of Neurofibrillary Tangles in P301L Tau Transgenic Mice Induced by A β 42 Fibrils

J. Götz,^{1*}† F. Chen,^{1*} J. van Dorpe,² R. M. Nitsch^{1‡}

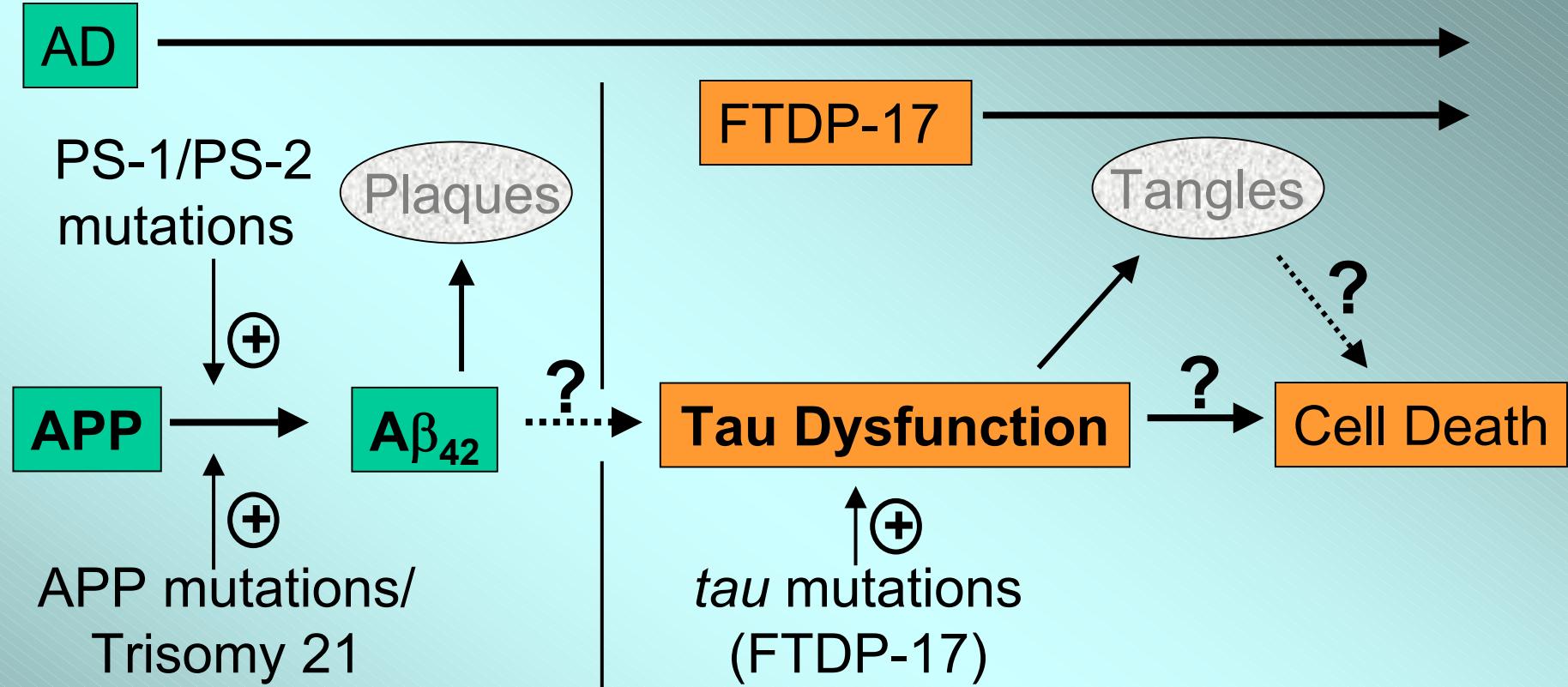
Science
Aug. 2001

Gallyas - entorhinal P301L



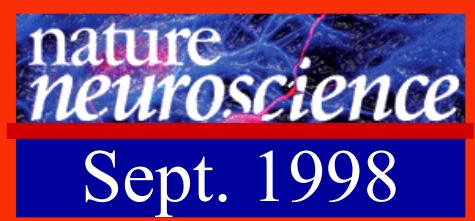
Gallyas - entorhinal APP/P301L

AD/FTDP-17 - Pathways to neurodegeneration



Genetic dissection of Alzheimer's disease and related dementias: amyloid and its relationship to tau

John Hardy, Karen Duff, Katrina Gwinn Hardy, Jordi Perez-Tur and Mike Hutton



α -Synuclein in Lewy bodies

scientific correspo

Maria Grazia Spillantini

Marie Luise Schmidt

Virginia M.-Y. Lee

John Q. Trojanowski

Ross Jakes, Michel Goedert

Science

June 1997

Mutation in the α -Synuclein Gene Identified in Families with Parkinson's Disease

Mihael H. Polymeropoulos,* Christian Lavedan†,
Elisabeth Leroy†, Susan E. Ide, Anindya Dehejia, Amalia Dutra,
Brian Pike, Holly Root, Jeffrey Rubenstein, Rebecca Boyer,
Edward S. Stenroos, Settara Chandrasekharappa,
Aglaja Athanassiadou, Theodore Papapetropoulos,
William G. Johnson, Alice M. Lazzarini, Roger C. Duvoisin,
Giuseppe Di Iorio, Lawrence I. Golbe, Robert L. Nussbaum

nature

Aug. 1997

Dopaminergic Loss and Inclusion Body Formation in α -Synuclein Mice: Implications for Neurodegenerative Disorders

Eliezer Masliah,^{1,2*} Edward Rockenstein,¹ Isaac Veinbergs,²
Margaret Mallory,¹ Makoto Hashimoto,¹ Ayako Takeda,^{1,3}
Yutaka Sagara,² Abbyann Sisk,² Lennart Mucke⁴

Science

Feb. 2000

β -Amyloid peptides enhance α -synuclein accumulation and neuronal deficits in a transgenic mouse model linking Alzheimer's disease and Parkinson's disease

Eliezer Masliah*†‡, Edward Rockenstein*, Isaac Veinbergs†, Yutaka Sagara*, Margaret Mallory*, Makoto Hashimoto*, and Lennart Mucke§

PNAS

Oct. 2001
Proceedings of the National Academy of Sciences
of the United States of America

Increased Susceptibility to Sporadic Parkinson's Disease by a Certain Combined α -Synuclein/Apolipoprotein E Genotype

Rejko Krüger, MD,*† Ana Maria Menezes Vieira-Saecker,* Wilfried Kuhn, MD,† Daniela Berg, MD,‡
Thomas Müller, MD,† Natalia Kühnl, MD,§ Gerd A. Fuchs, MD,§ Alexander Storch, MD,||
Marcel Hungs, MD,¶ Dirk Woitalla, MD,† Horst Przuntek, MD,† Jörg T. Epplen, MD,*
Ludger Schöls, MD,† and Olaf Riess, MD*

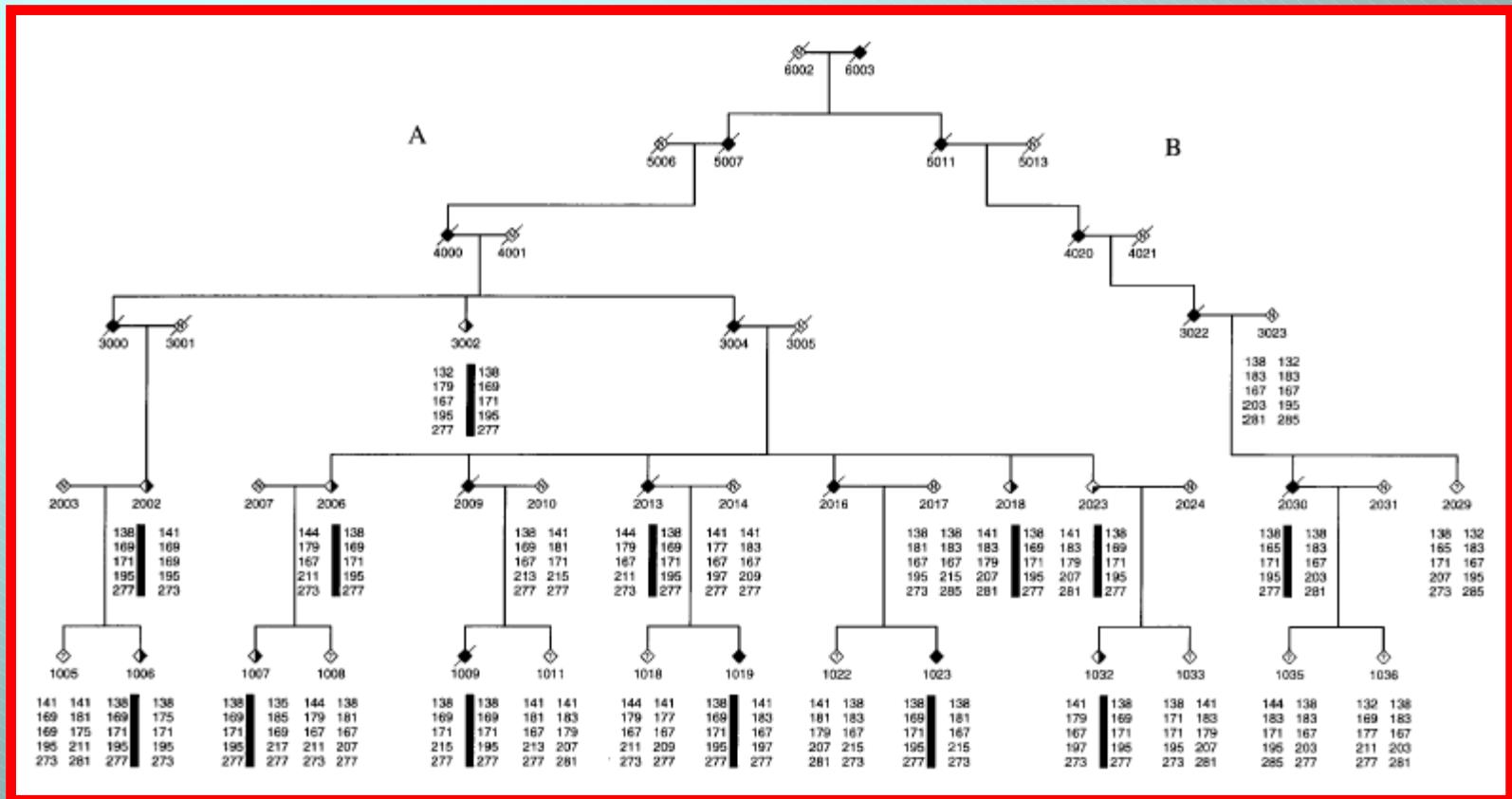
Annals of Neurology
May 1999

α -synuclein gene haplotypes are associated with Parkinson's disease

Matt Farrer, Demetrius M. Maraganore¹, Paul Lockhart, Andrew Singleton, T.G. Lesnick²,
Mariza de Andrade², Andrew West, Rohan de Silva³, John Hardy* and Dena Hernandez

Human
Molecular
Genetics
Aug. 2001

Iowa Kindred Structure



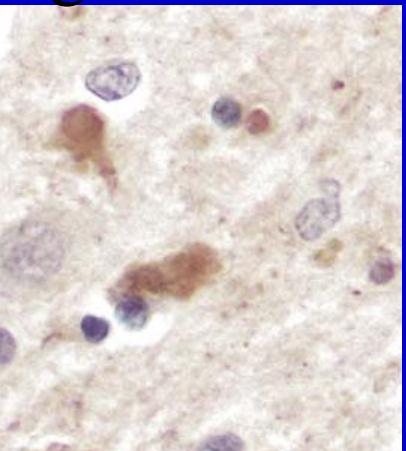
Laboratory of Neurogenetics, National Institute on Aging



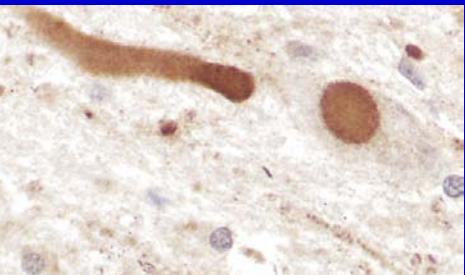


Diffuse α -synuclein pathologies in male patient: abnormal neuronal and glial inclusions and processes

Globus pallidus



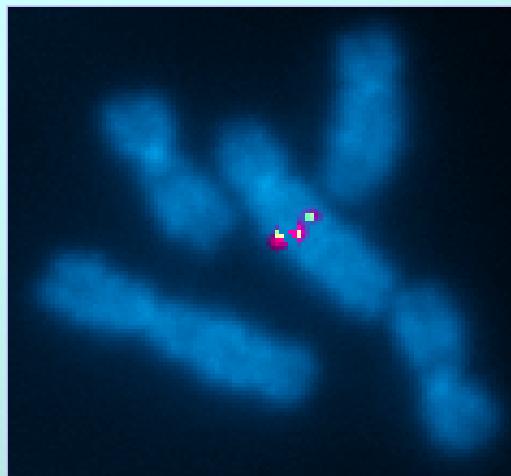
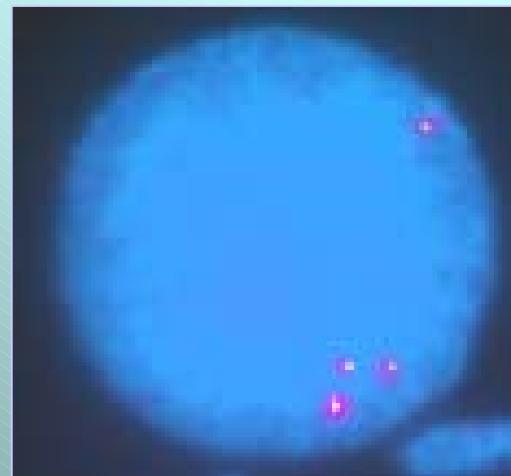
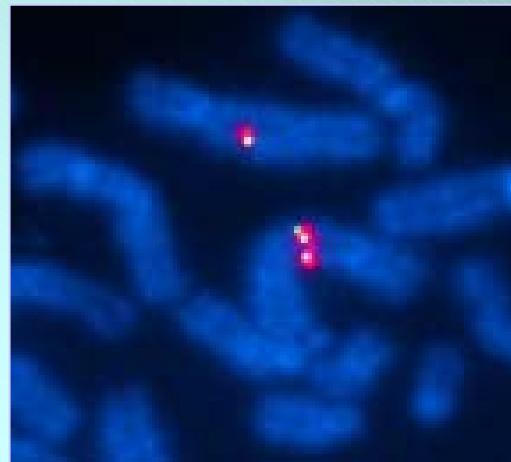
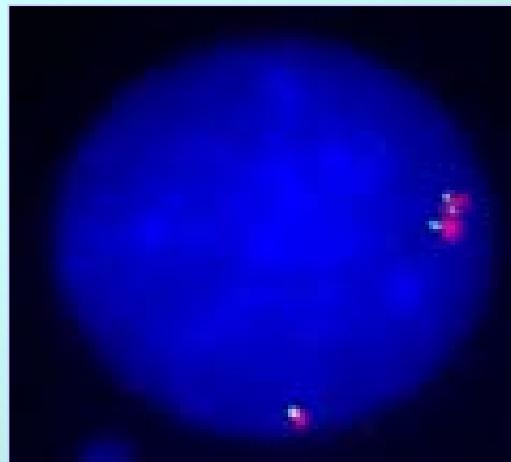
Substantia nigra



Hippocampus



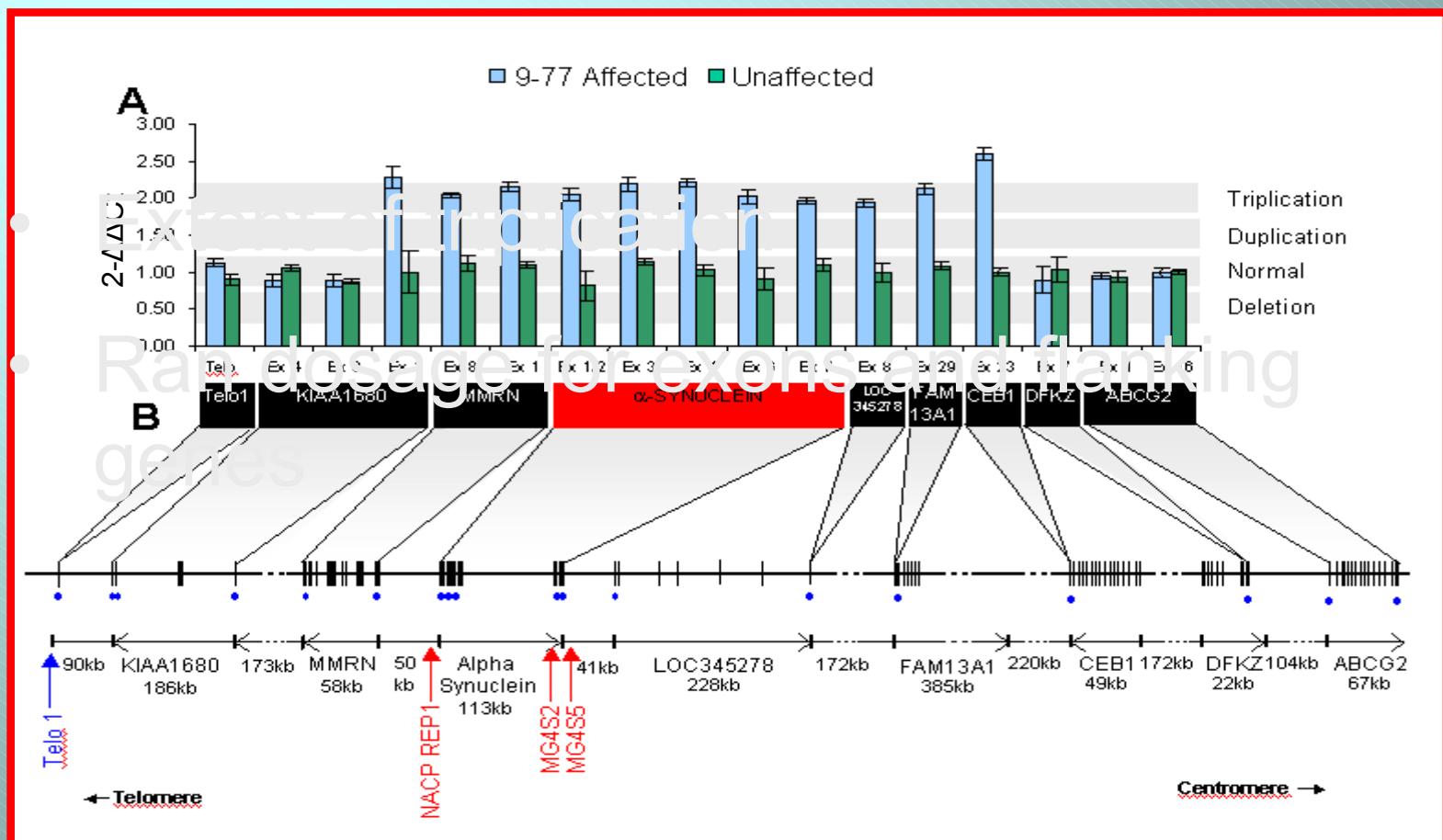
Chromosomal Spreads (FISH)



Laboratory of Neurogenetics, National Institute on Aging



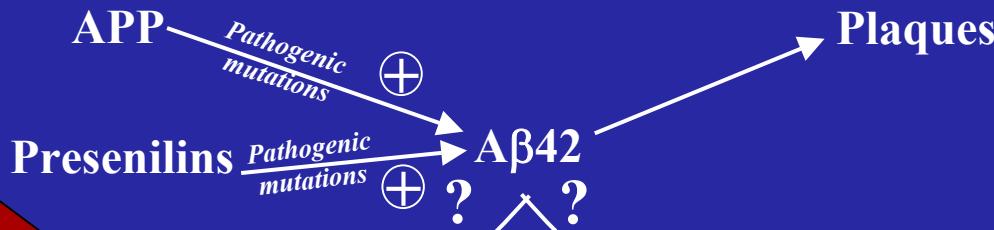
Gene Dosage Analysis



Tau and Synucleinopathies: similarities

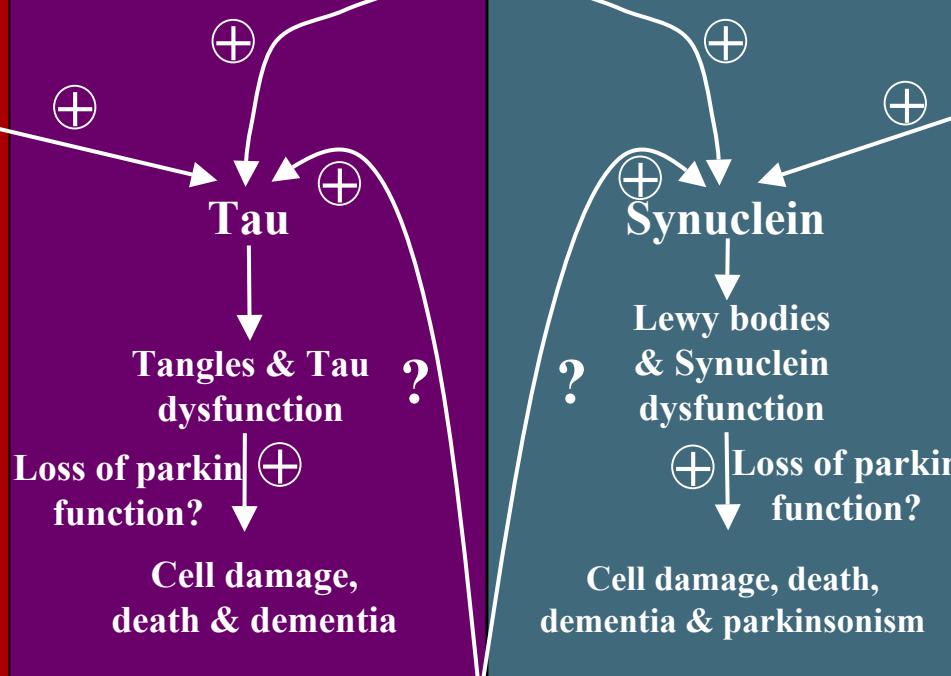
- Both intracellular inclusion diseases
- Familial forms of both diseases can be caused by mutations in the cognate proteins
- Sporadic forms of both diseases can be predisposed to by gene haplotypes.
- Both can be caused by A β or PrP^{Sc} in humans and in animals.

Alzheimer's Diseases



Pathogenic
Tau mutations or tau
haplotype

**FTDP-17
Diseases,
PSP and
CBD**



Chromosome
1q(2), 2p & 4p loci
Synuclein
mutations or synuclein
haplotype

**Lewy Body
Diseases**

