The Amyloid Hypothesis

John Hardy Ph.D.

Department of Molecular Neuroscience and Reta Lila Weston Laboratories, Institute of Neurology

The beginning……

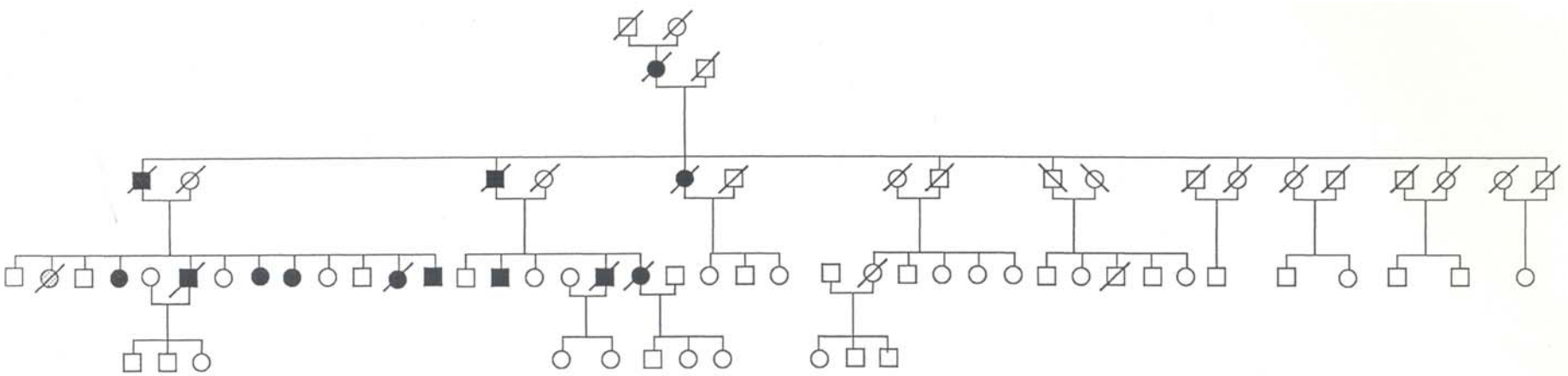
: Biochem Biophys Res Commun. 1984 Aug 16;122(3):1131-5.

Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein.

Glenner GG, Wong CW.

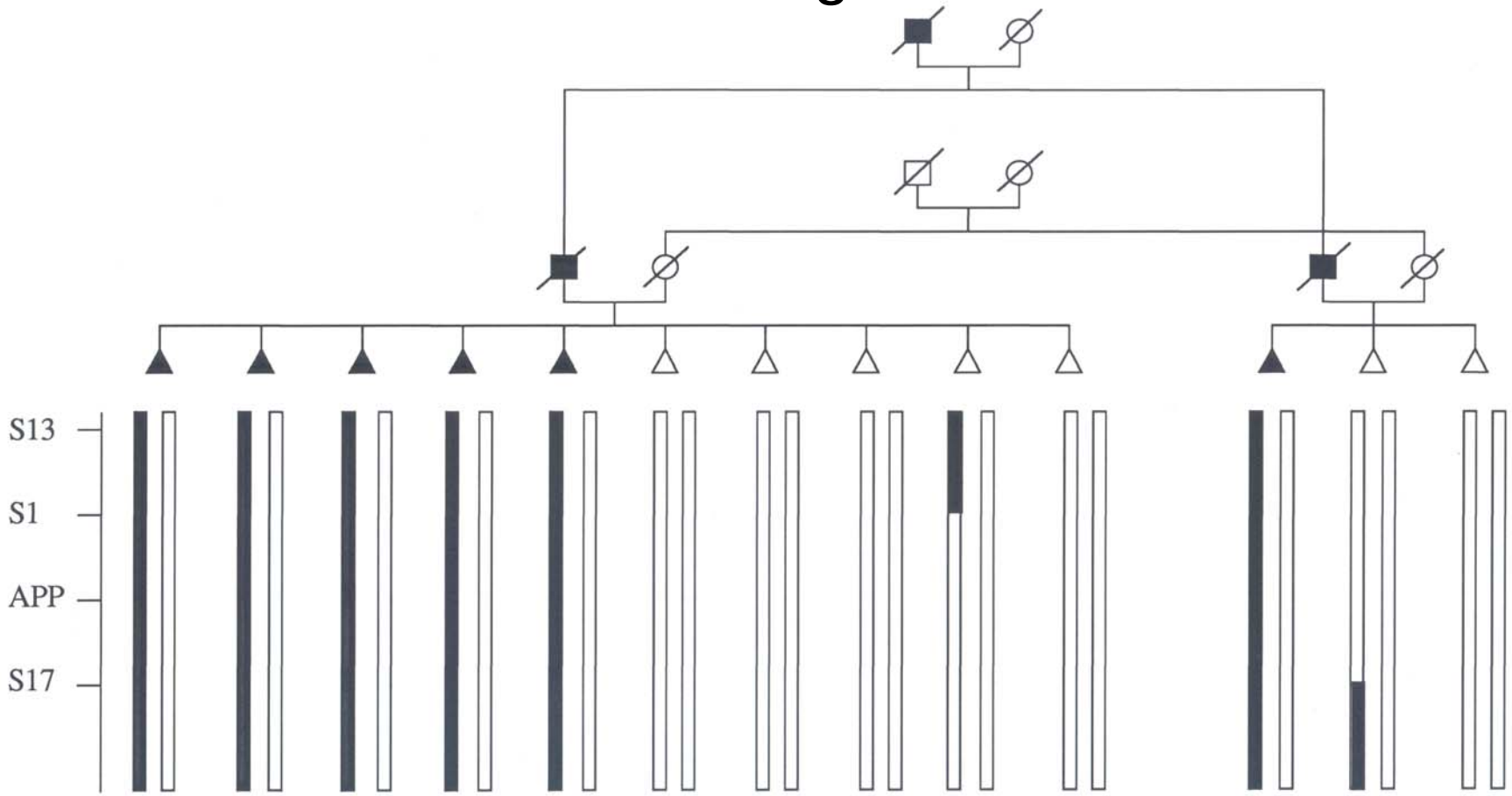
The cerebrovascular amyloid protein from a case of adult Down's syndrome was isolated and purified. Amino acid sequence analysis showed it to be homologous to that of the beta protein of Alzheimer's disease. This is the first chemical evidence of a relationship between Down's syndrome and Alzheimer's disease. It suggests that Down's syndrome may be a predictable model for Alzheimer's disease. Assuming the beta protein is a human gene product, it also suggests that the genetic defect in Alzheimer's disease is localized on chromosome 21.

F23, a multi-generational UK pedigree with early onset AD



Mean AOO= 57yrs
Range (52-66yrs)
Neuropathologically confirmed AD with cortical Lewy bodies

Recombination events in F23 localize the disease locus to a region between S1 and S17 that includes the APP gene

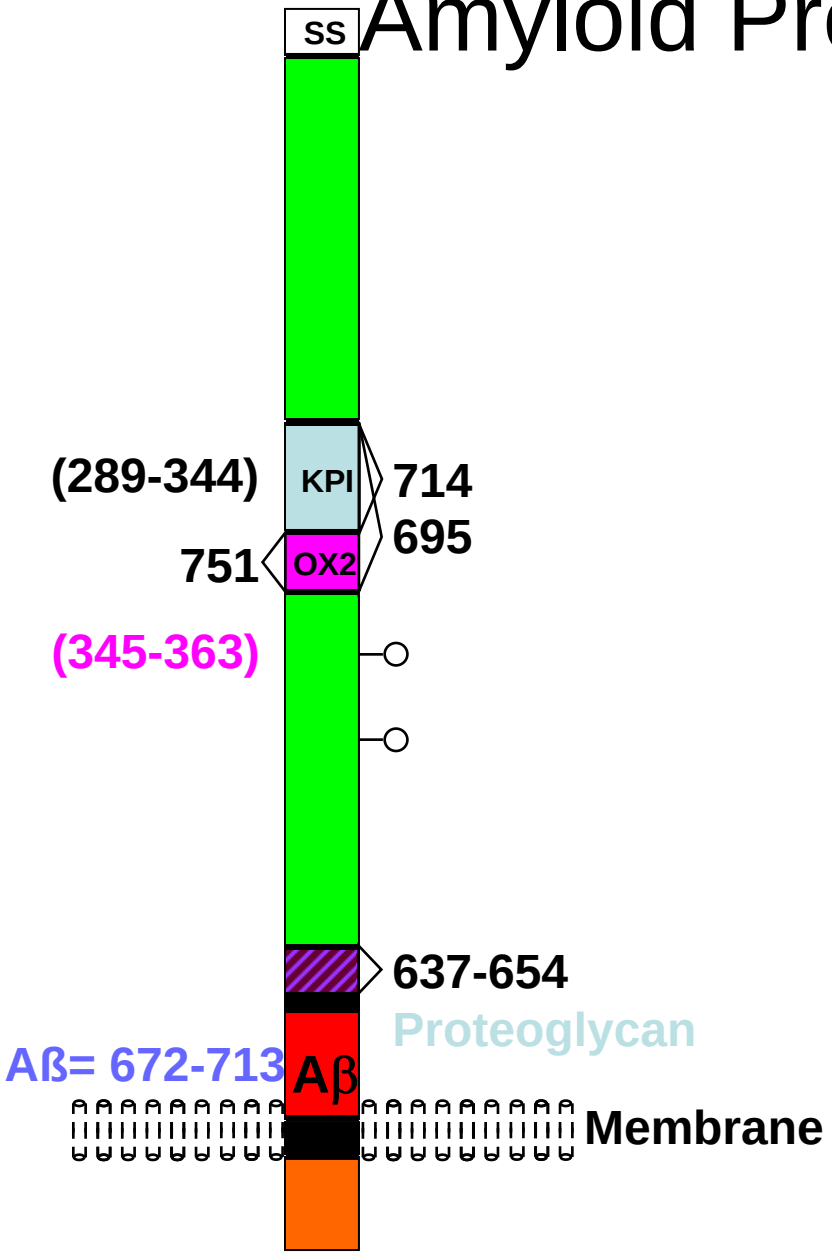


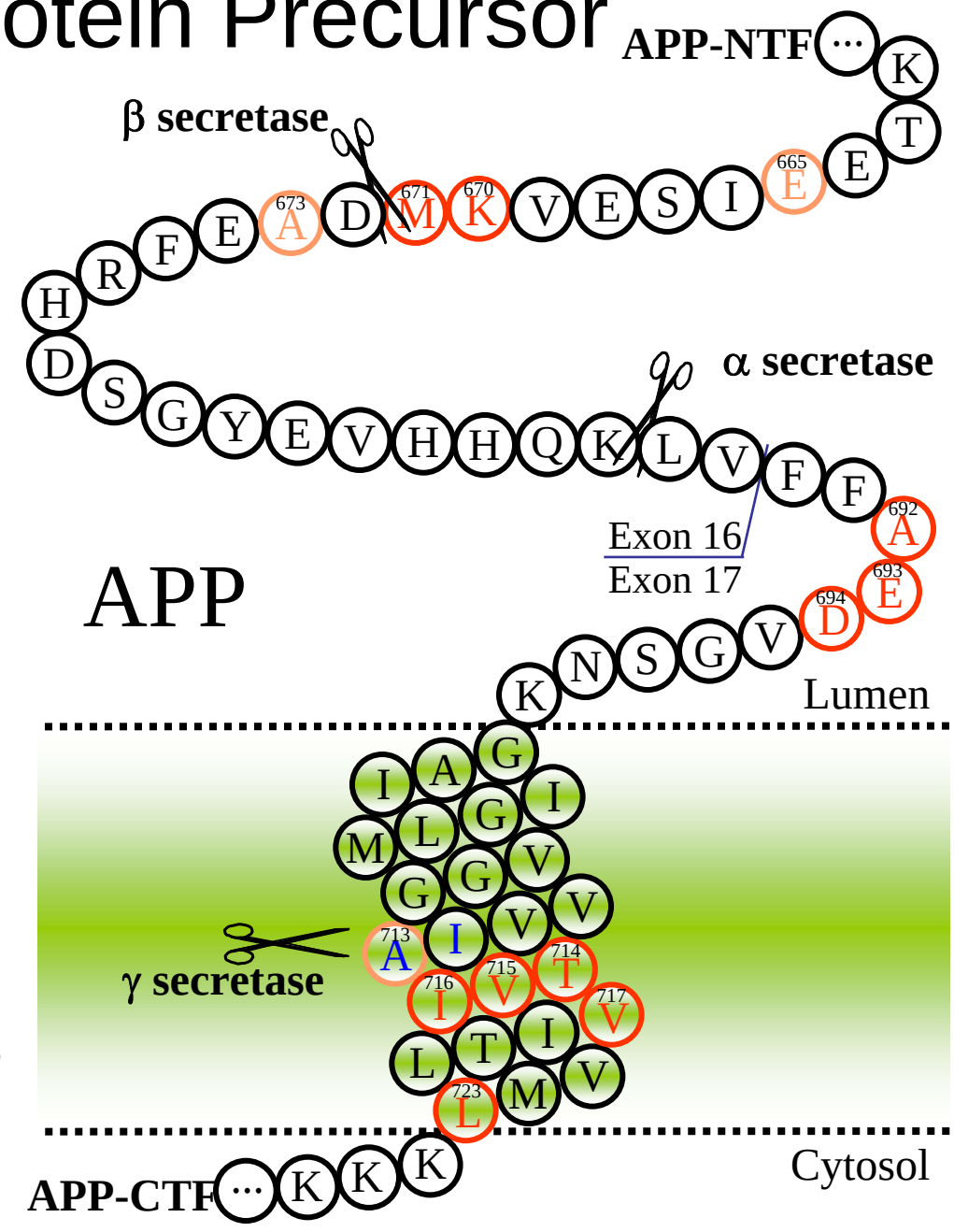
“It’s marvellous. In future it may be possible to prevent the disorder happening. While it will not help me. I hope it will help my children” Carol Jennings, The Times, February 16th, 1991

STEVE ETHERINGTON

Carol Jennings and her children Emily and John who have been involved in research into Alzheimer's disease

Amyloid Protein Precursor

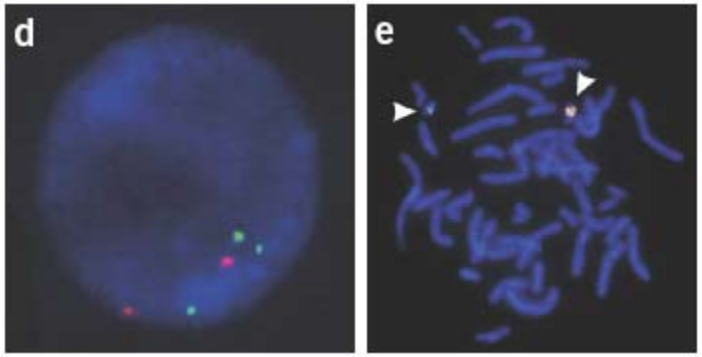


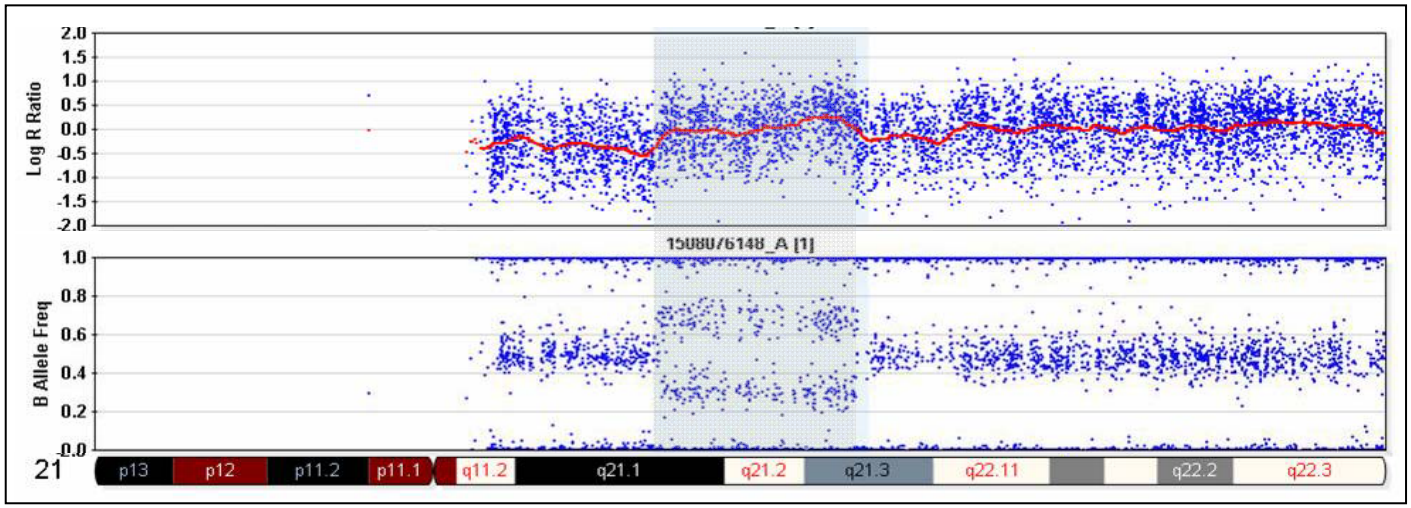


7Mb duplication of locus around APP

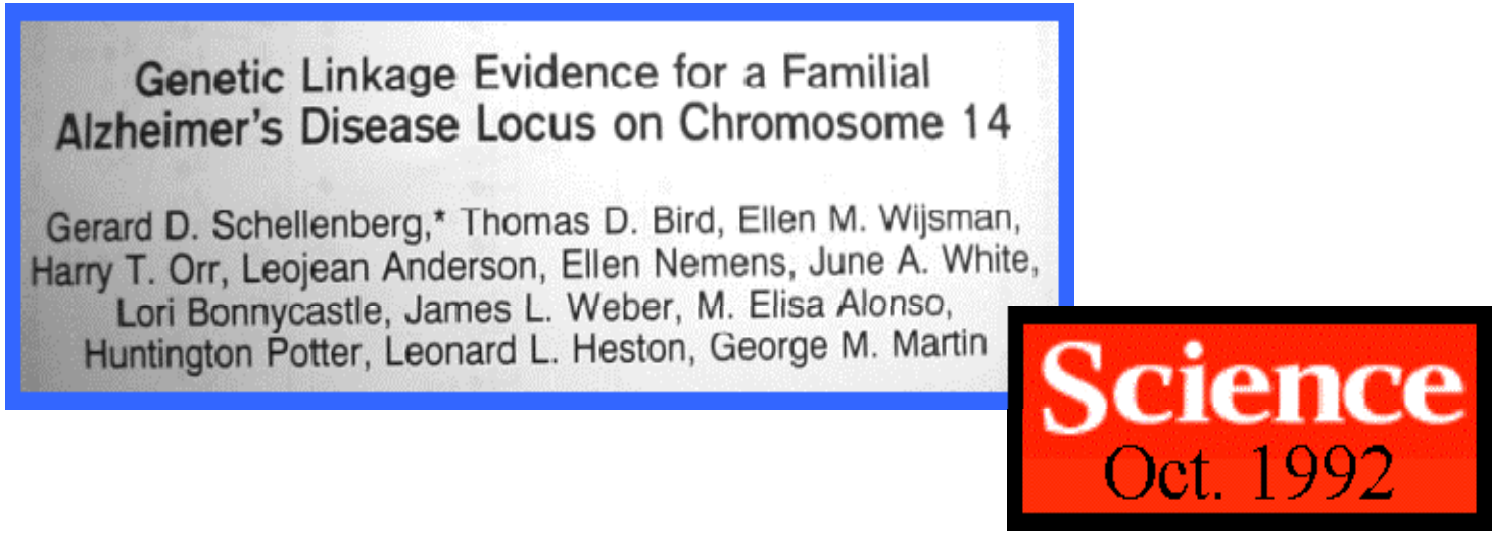
APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy

Anne Rovelet-Lecrux[1], Didier Hannequin[1,2], Gregory Raux[1], Nathalie Le Meur[3], Annie Laquerrière[4], Anne Vital[5], Cécile Dumanchin[1], Sébastien Feuillette[1], Alexis Brice[6], Martine Vercelletto[7], Frédéric Dubas[8], Thierry Frebourg[1] & Dominique Campion[1,9]





Only a Small Proportion of families had APP mutations (~10%):-



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

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 I

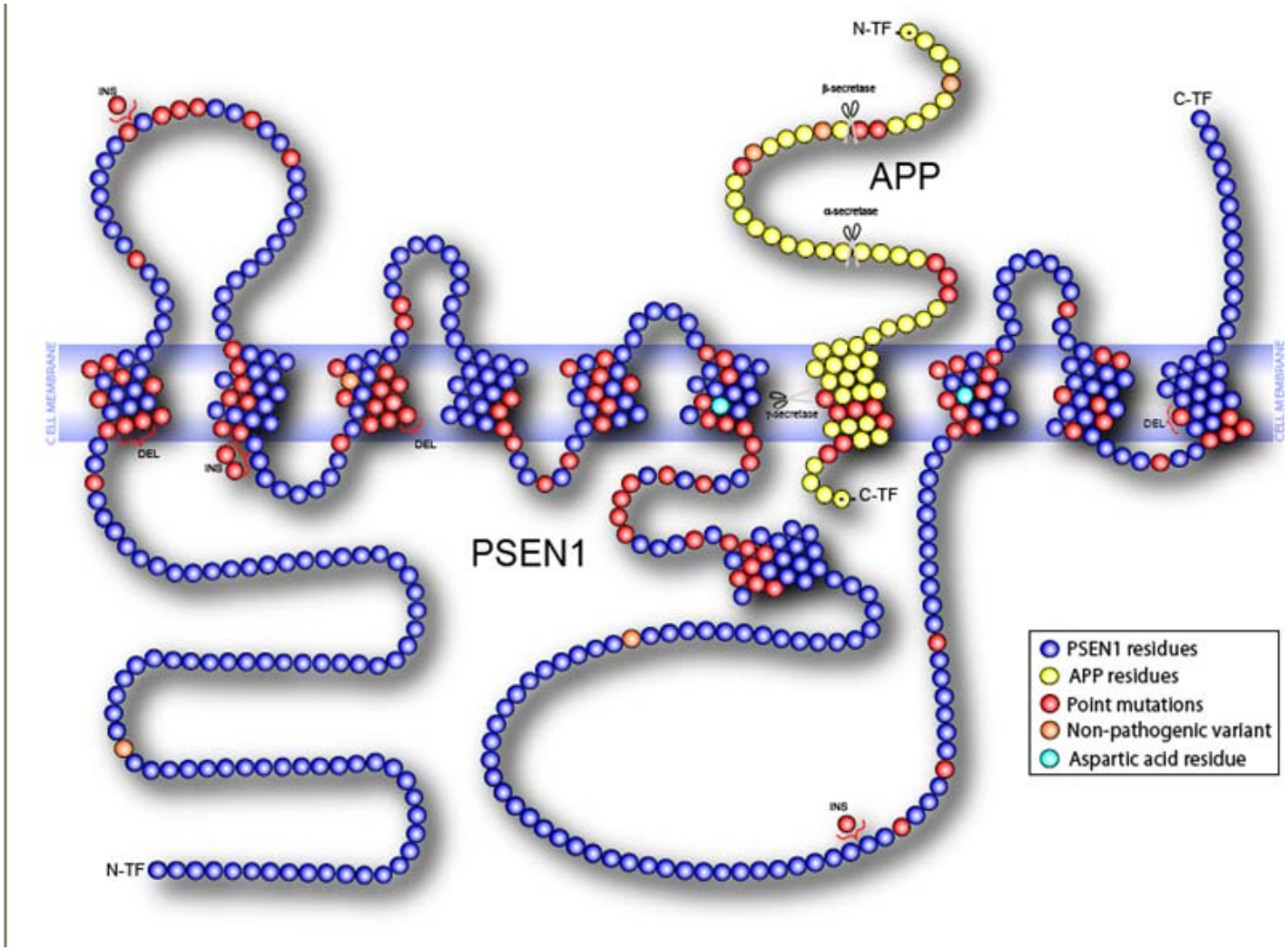
Ephrat Levy-Lahad, Ellen M. Wijsman, Ellen Nemens, Leojean Anderson, Katrina A. B. Goddard, James L. Weber, Thomas D. Bird, Gerard D. Schellenberg*

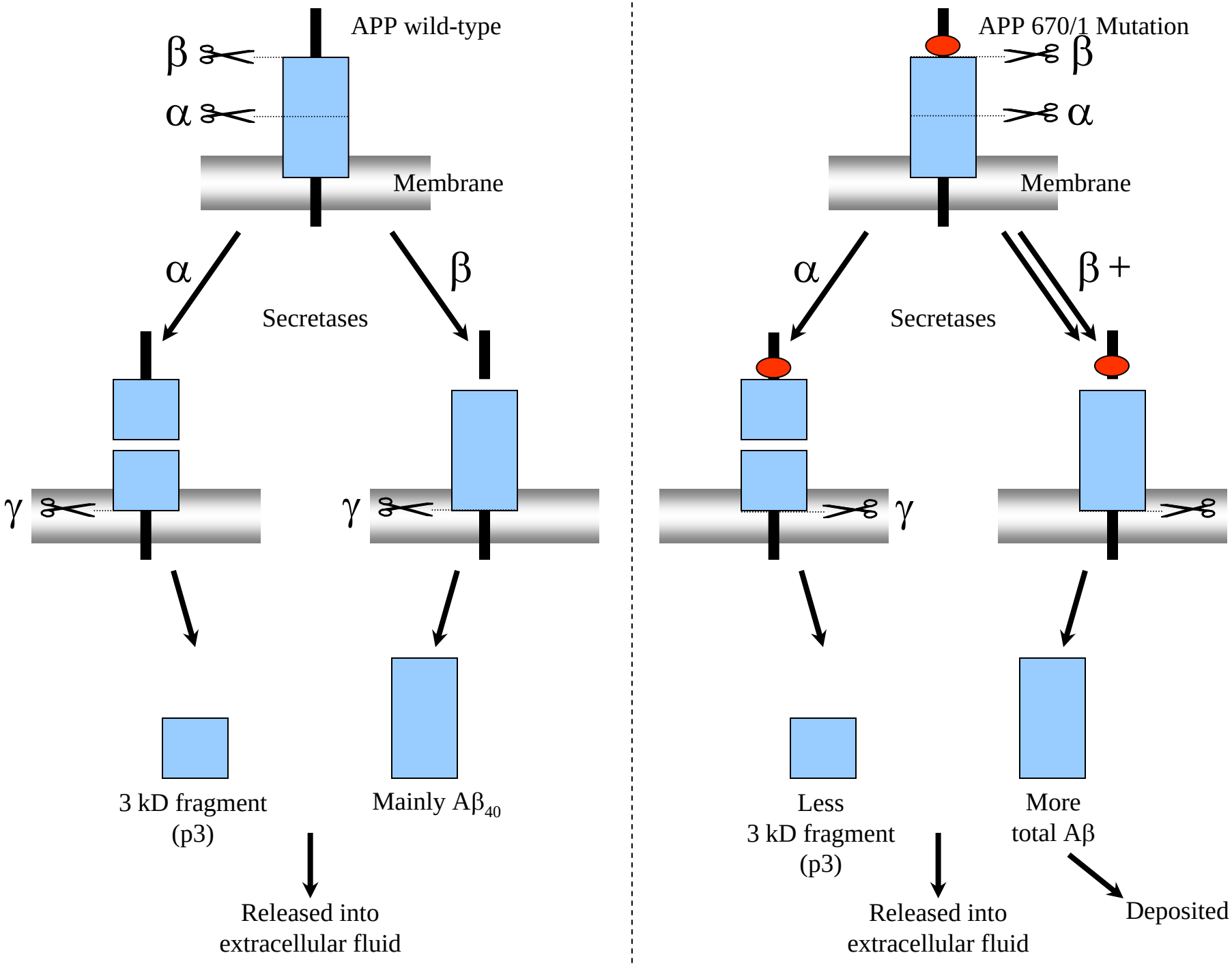
Science
Aug. 1995

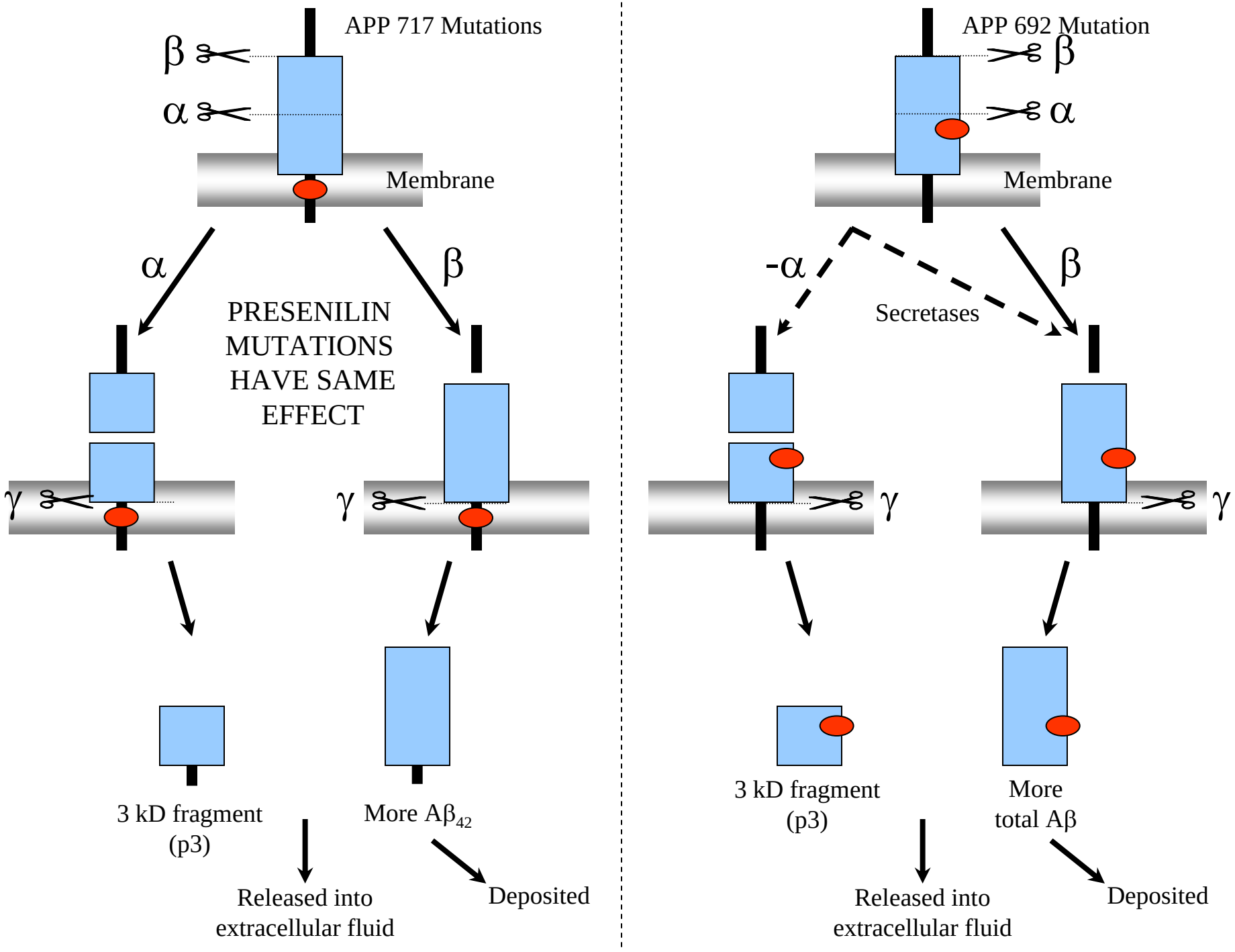
Candidate Gene for the Chromosome 1 Familial *Alzheimer's Disease Locus*

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

Presenilin with APP in the Active Site



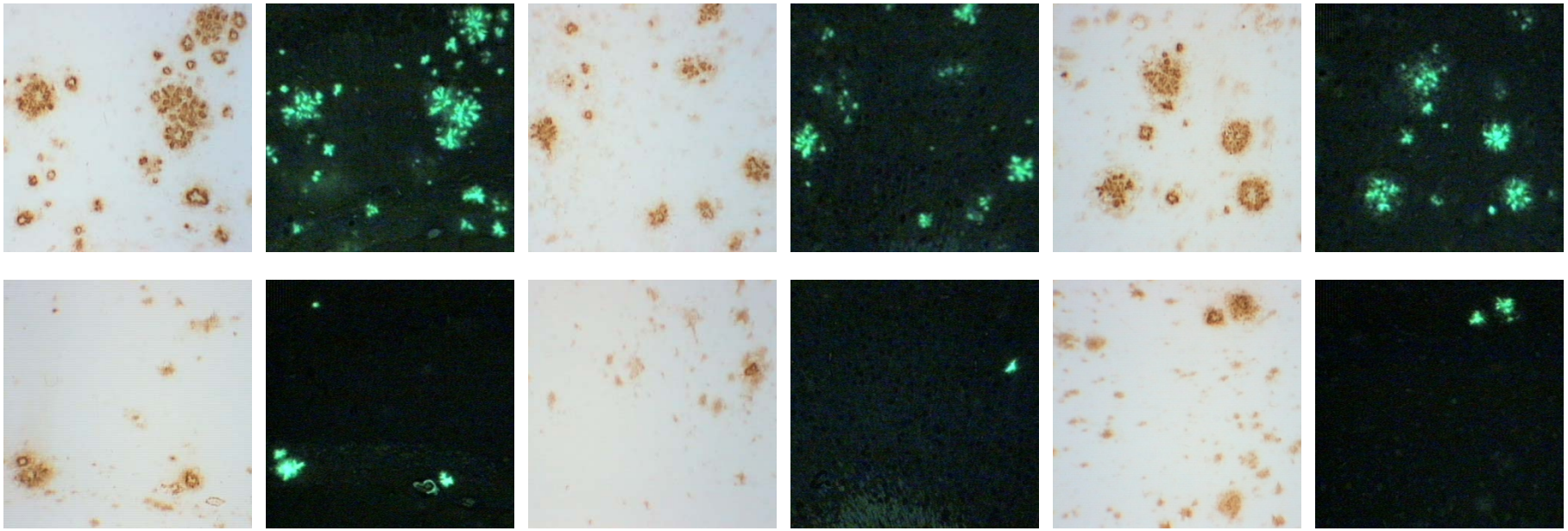

APP wild-type
β
α
Membrane
α
β
Secretases
γ
γ
3 kD fragment
(p3)
Mainly Aβ40
Released into
extracellular fluid
APP 670/1 Mutation
β
α
Membrane
α
β +
Secretases
γ
γ
Less
3 kD fragment
(p3)
More
total Aβ
Released into
extracellular fluid
Deposited


APP 717 Mutations
β
α
Membrane
α
β
PRESENILIN
MUTATIONS
HAVE SAME
EFFECT
γ
γ
3 kD fragment
(p3)
More Aβ42
Released into
extracellular fluid
Deposited
APP 692 Mutation
β
α
Membrane
-α
β
Secretases
γ
γ
3 kD fragment
(p3)
More
total Aβ
Released into
extracellular fluid
Deposited

Presenilin accelerates amyloid pathology.

Hippocampus Cingulate cortex Entorhinal cortex

PSAPP



APP (Tg2576)

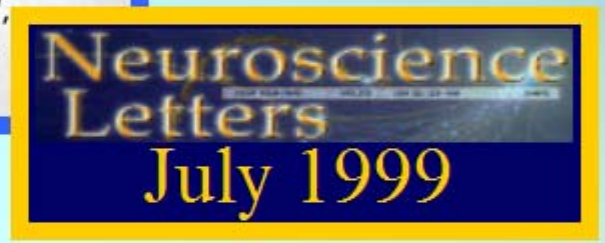
Aβ ThioS Aβ ThioS Aβ ThioS

17 month old mice

APP Probably a Locus for "Sporadic" Alzheimer's Disease

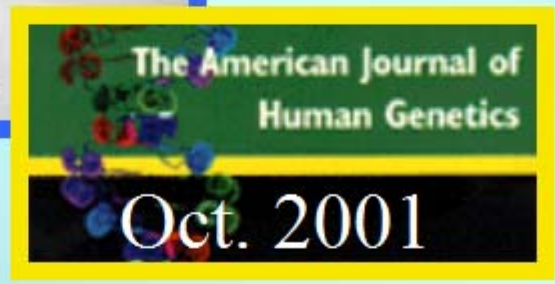
Genetic variability at the amyloid-β precursor protein locus may contribute to the risk of late-onset Alzheimer's disease

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



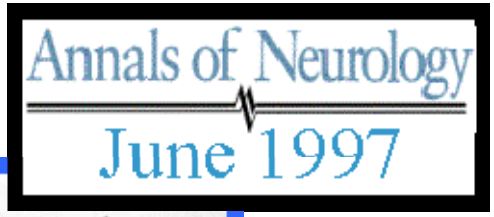
Conclusions on Alzheimer's Disease

- Overexpression of APP in Down syndrome causes disease.
- Overproduction of $A\beta_{42}$ because of APP or presenilin mutations causes disease in a mendelian fashion.
- Overexpression because of gene duplication causes mendelian disease.
- Genetic variability in 'normal' APP expression contributes to disease risk.
  - (not clear whether variability in presenilin expression also contributes).

All Autosomal Dominant Alzheimer's Disease can be Explained through $A\beta$

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¶

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*†‡¶¶

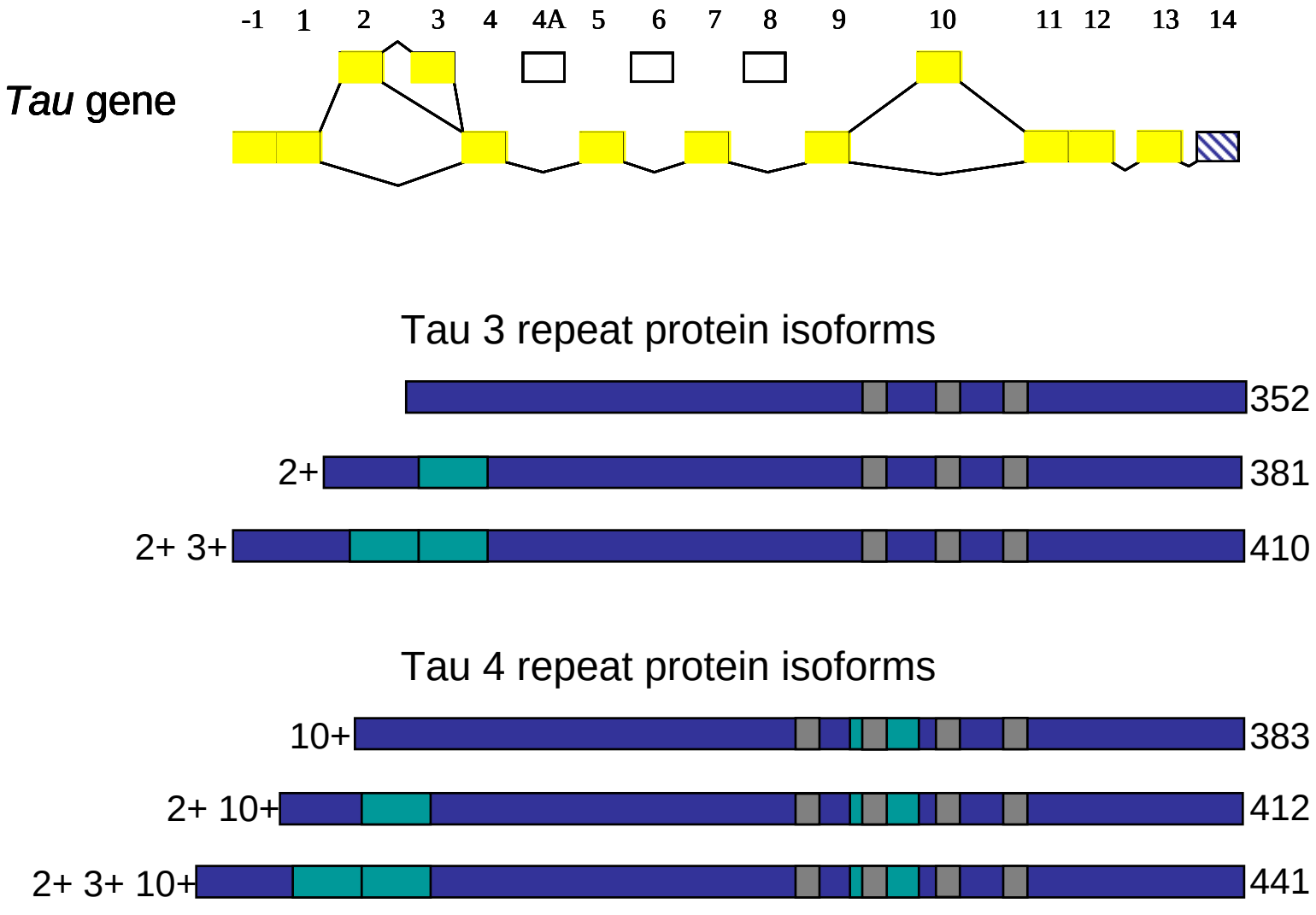
Annals of Neurology
June 1998

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

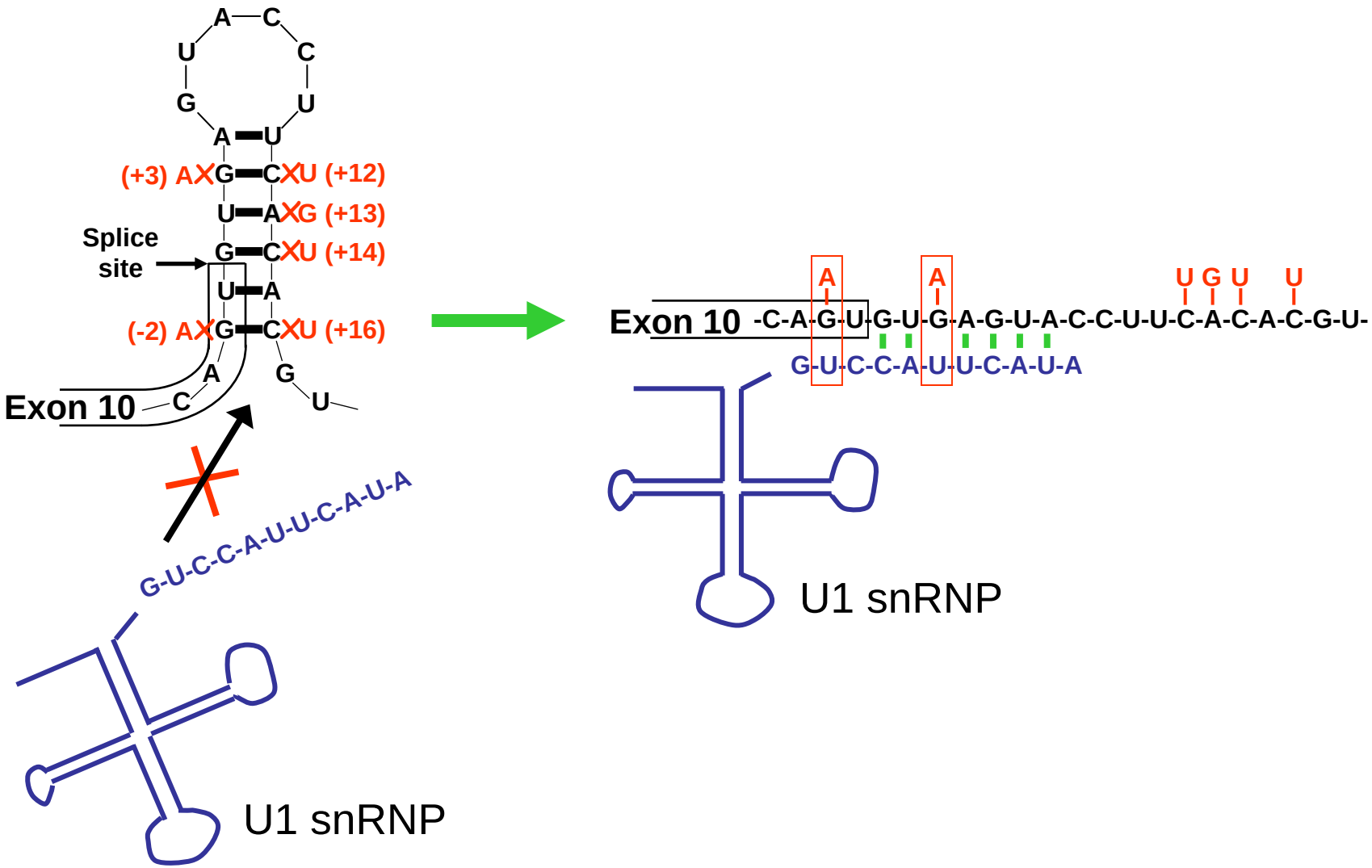
Mike Hutton*[1], Corinne L. Lendon*[2], Patrizia Rizzu*[3,4], Matt Baker[1], Susanne Froelich[3,5], Henry Houlden[1], Stuart Pickering-Brown[6], Sumi Chakraverty[2], Adrian Isaacs[1], Andrew Grover[1], Jennifer Hackett[1], Jennifer Adamson[1], Sarah Lincoln[1], Dennis Dickson[1], Peter Davies[7], Ronald C. Petersen[8], Martijn Stevens[4], Esther de Graaff[3], Erwin Wauters[3], Jeltje van Baren[3], Marcel Hillebrand[3], Marijke Joosse[3], Jennifer M. Kwon[9], Petra Nowotny[2], Lien Kuei Che[2], Joanne Norton[9], John C. Morris[9], Lee A. Reed[10], John Trojanowski[10], Hans Basun[5], Lars Lannfelt[5], Michael Neystat[11], Stanley Fahn[11], Francis Dark[12], Tony Tannenberg[13], Peter R. Dodd[14], Nick Hayward[15], John B. J. Kwok[16], Peter R. Schofield[16], Athena Andreadis[17], Julie Snowden[18], David Craufurd[19], David Neary[18], Frank Owen[6], Ben A. Oostra[3], John Hardy[1], Alison Goate[2], John van Swieten[4], David Mann[20], Timothy Lynch[11] & Peter Heutink[3]

nature
June 1998

The microtubule associated protein tau



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



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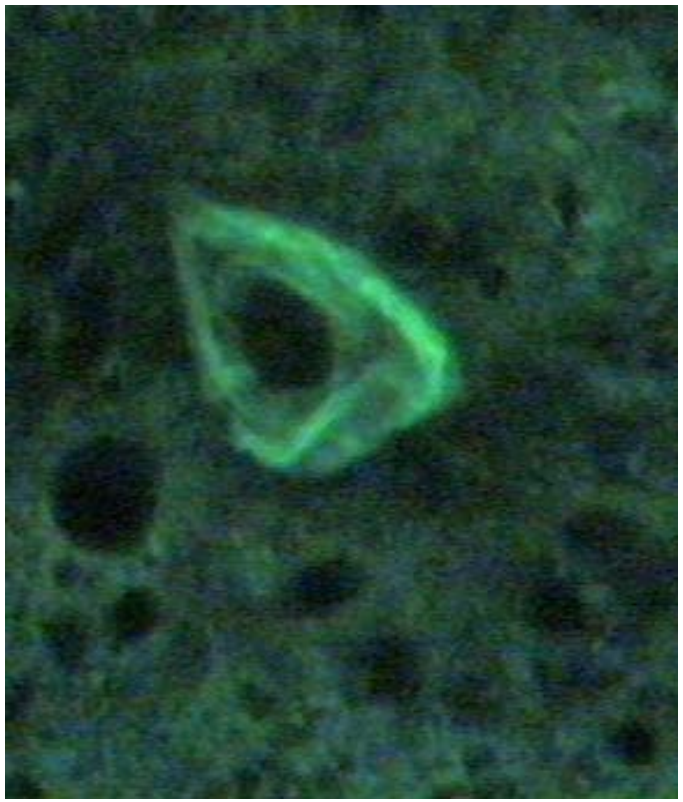
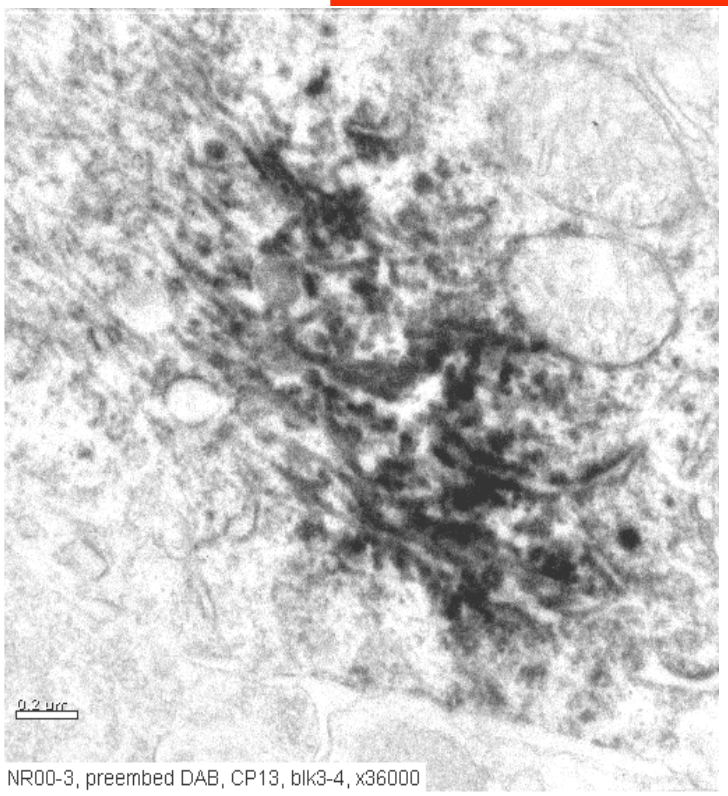
Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein

Jada Lewis[1], Eileen McGowan[1], Julia Rockwood[2], Heather Melrose[1], Parimala Nacharaju[1], Marjon Van Slegtenhorst[1], Katrina Gwinn-Hardy[1], M. Paul Murphy[1], Matt Baker[1], Xin Yu[1], Karen Duff[1], John Hardy[1], Anthony Corral[1], Wen-Lang Lin[1], Shu-Hui Yen[1], Dennis W. Dickson[1], Peter Davies[2] & Mike Hutton[1]

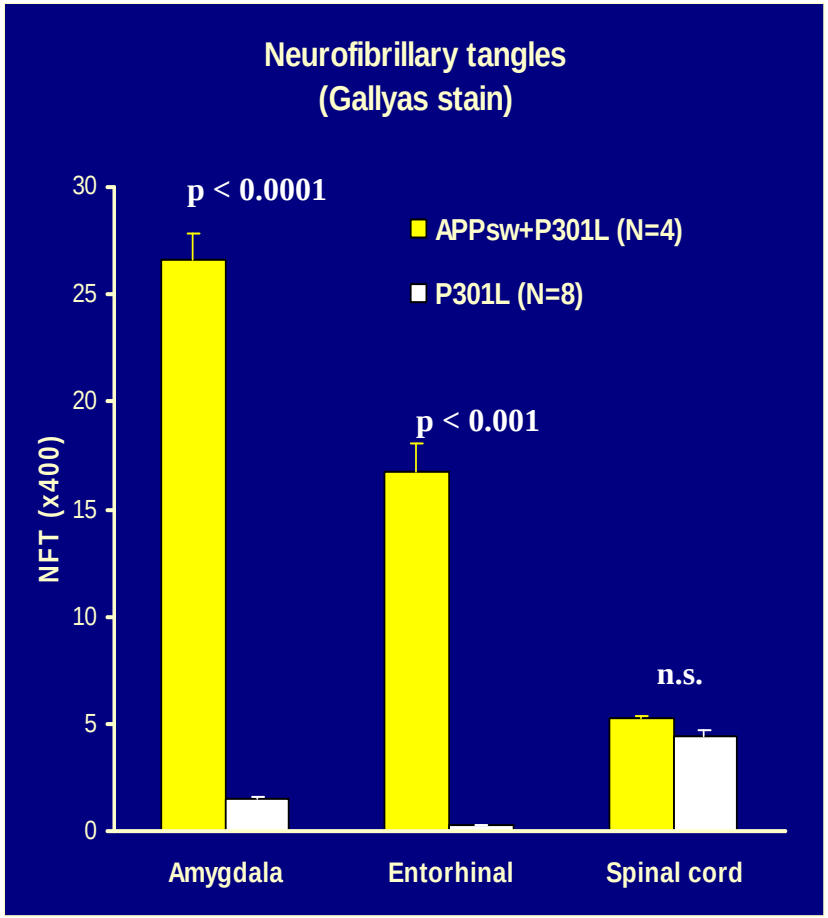
nature genetics Aug. 2000



- Thioflavin-S positive NFT
- brain stem



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



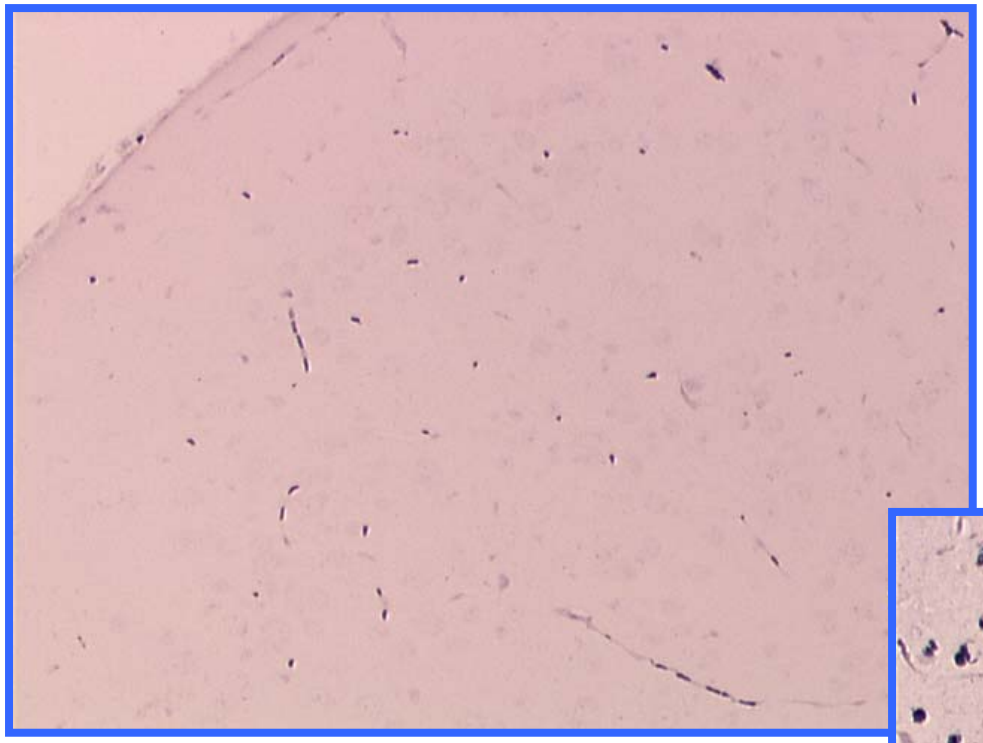
Enhanced Neurofibrillary Degeneration in Transgenic Mice Expressing Mutant Tau and APP

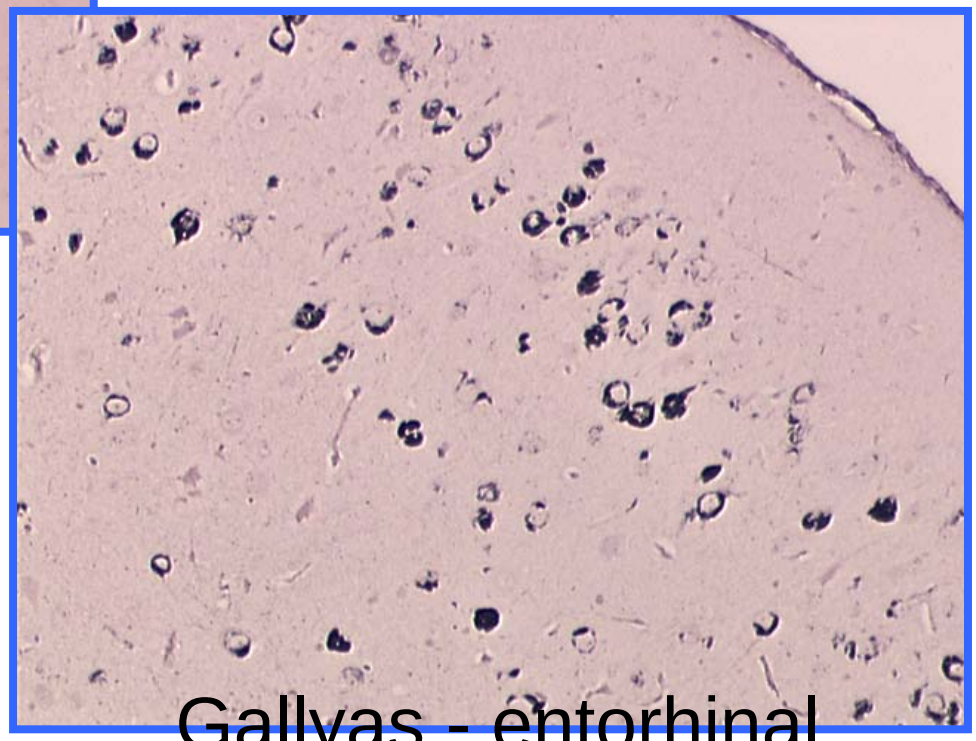
Jada Lewis,* Dennis W. Dickson,* Wen-Lang Lin, Louise Chisholm, Anthony Corral, Graham Jones, Shu-Hui Yen, Naruhiko Sahara, Lisa Skipper, Debra Yager, Chris Eckman, John Hardy, Mike Hutton,† Eileen McGowan

JNPL3 transgenic mice expressing a mutant tau protein, which develop neurofibrillary tangles and progressive motor disturbance, were crossed with Tg2576 transgenic mice expressing mutant β-amyloid precursor protein (APP), thus modulating the APP-Aβ (β-amyloid peptide) environment. The resulting double mutant (tau/APP) progeny and the Tg2576 parental strain developed Aβ deposits at the same age; however, relative to JNPL3 mice, the double mutants exhibited neurofibrillary tangle pathology that was substantially enhanced in the limbic system and olfactory cortex. These results indicate that either APP or Aβ influences the formation of neurofibrillary tangles. The interaction between Aβ and tau pathologies in these mice supports the hypothesis that a similar interaction occurs in Alzheimer's disease.

Science
Aug. 2001

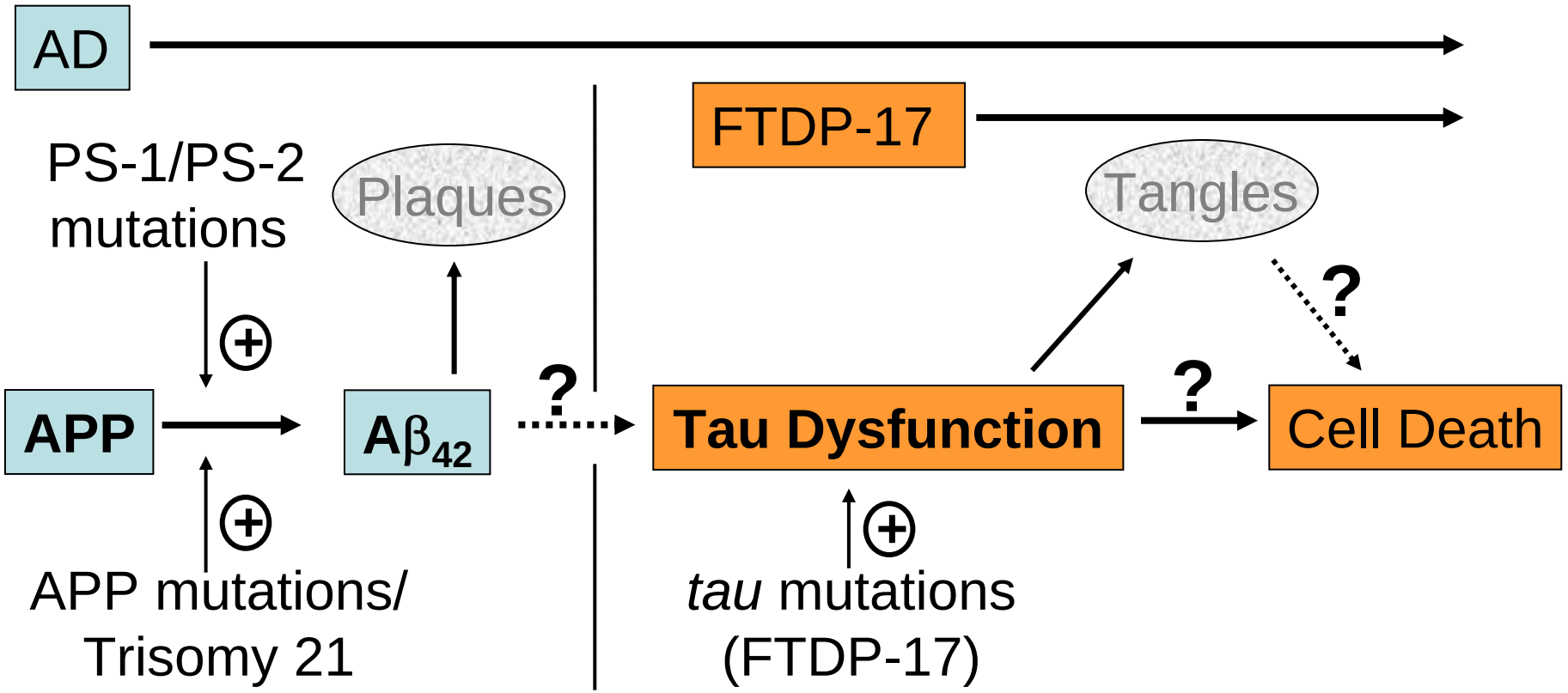
Gallyas - entorhinal P301L





Gallyas - entorhinal APP/P301L

AD/FTDP-17 - Pathways to neurodegeneration



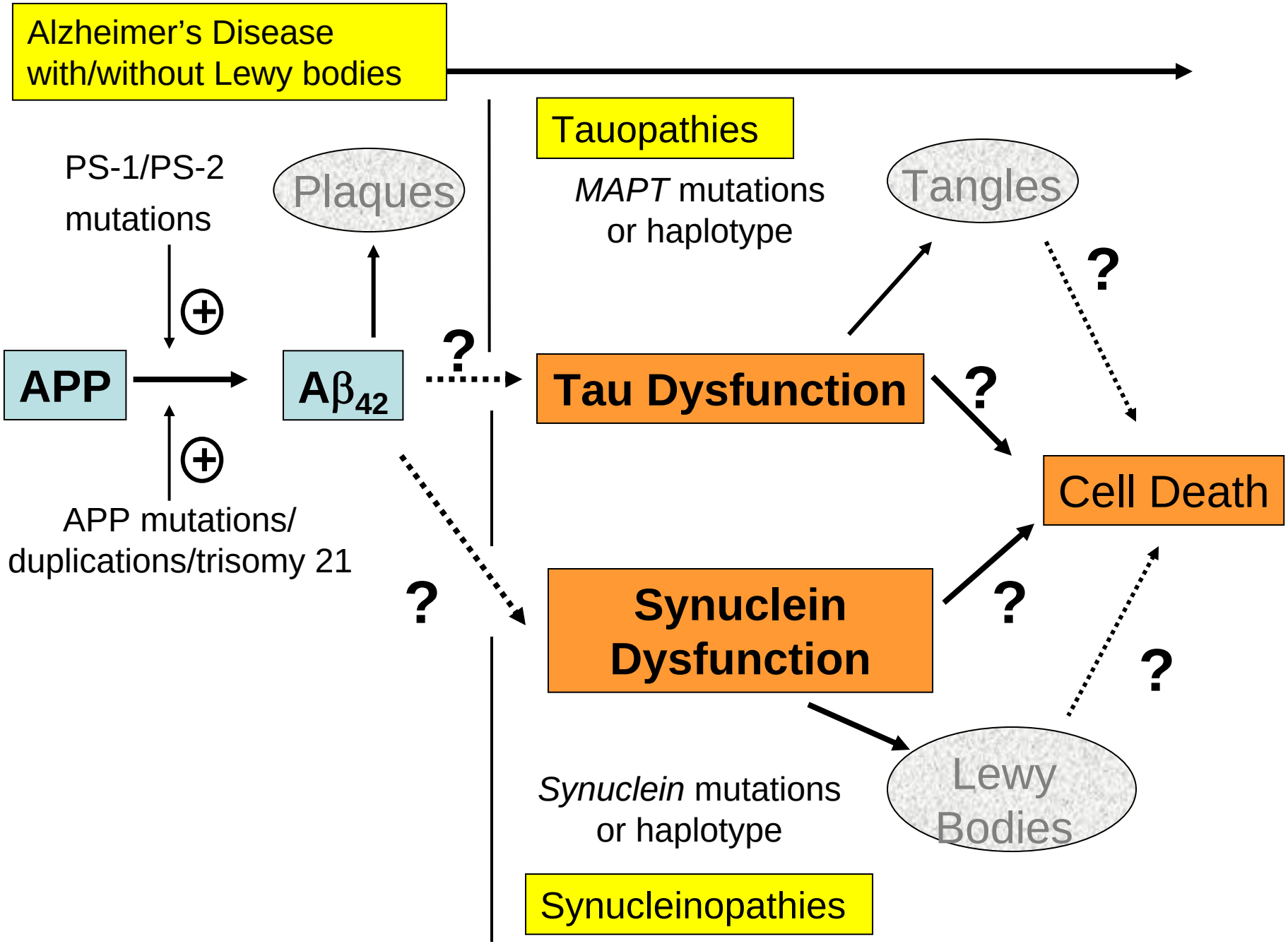
review

nature neuroscience
Sept. 1998

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

Neurogenetics and Transgenics Laboratories, Mayo Clinic Jacksonville, Jacksonville, Florida 32224, USA
Correspondence should be addressed to J.H. (hardy.john@mayo.edu)


Alzheimer's Disease
with/without Lewy bodies
Tauopathies
PS-1/PS-2
mutations
Plaques
MAPT mutations
or haplotype
Tangles
?
APP
Aβ42
?
Tau Dysfunction
?
Cell Death
APP mutations/
duplications/trisomy 21
?
Synuclein
Dysfunction
?
?
Synuclein mutations
or haplotype
Lewy
Bodies
Synucleinopathies

Concerns:-

- What is the function of APP?
- Is it appropriate to extrapolate from the <5% of cases with autosomal dominant disease to Alzheimer's disease in general?
  - Should we be designing trials in APP mutation carriers? Presenilin mutation carriers? Down Syndrome because we "know" the amyloid hypothesis is operative in their disease?
- By the time diagnosis is made, is it too late to stop the pathogenesis?
  - The families offer one appropriate solution.