

The Amyloid Hypothesis

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The beginning.....

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

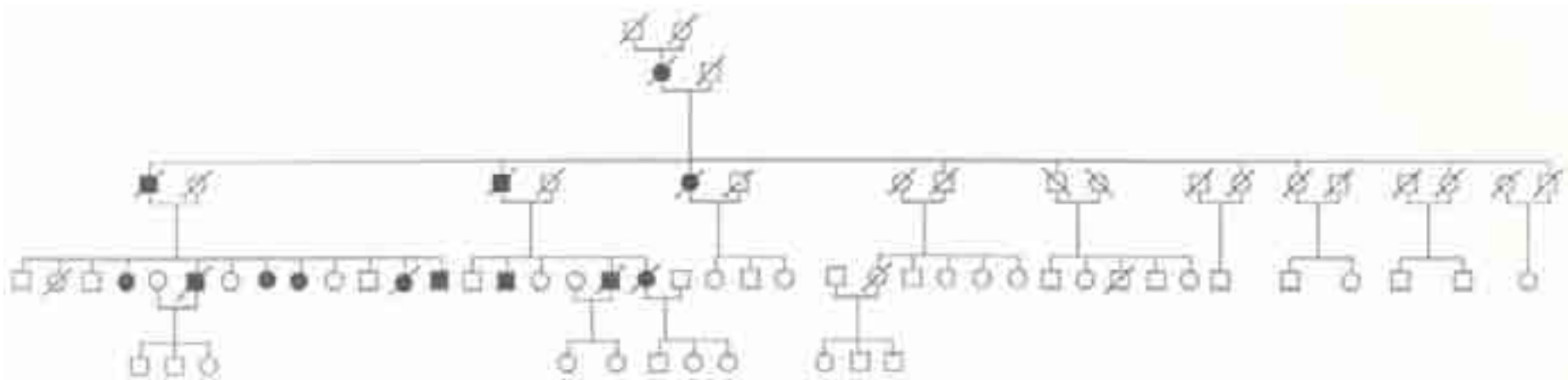
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Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein.

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

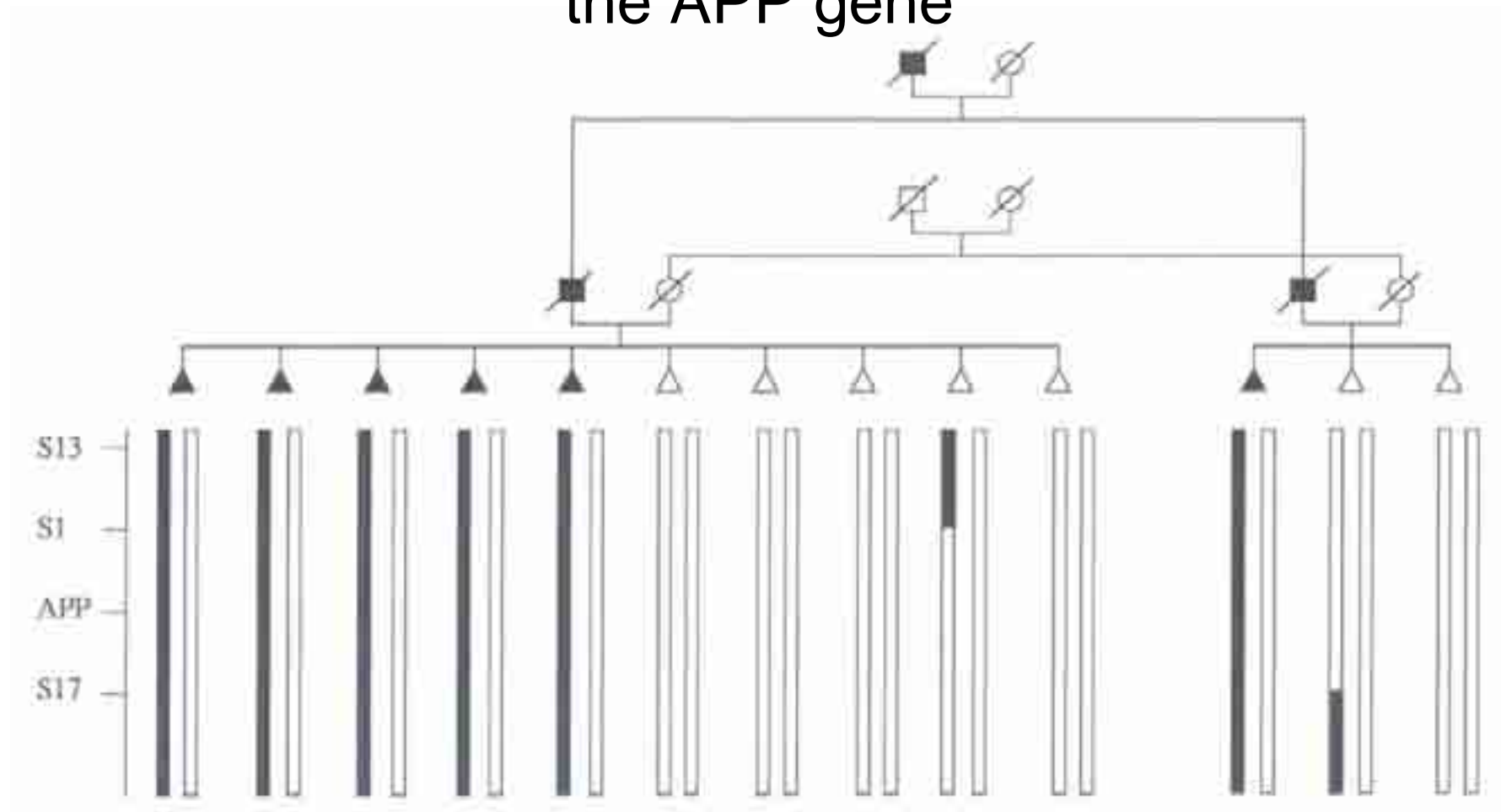


Mean AOO= 57yrs

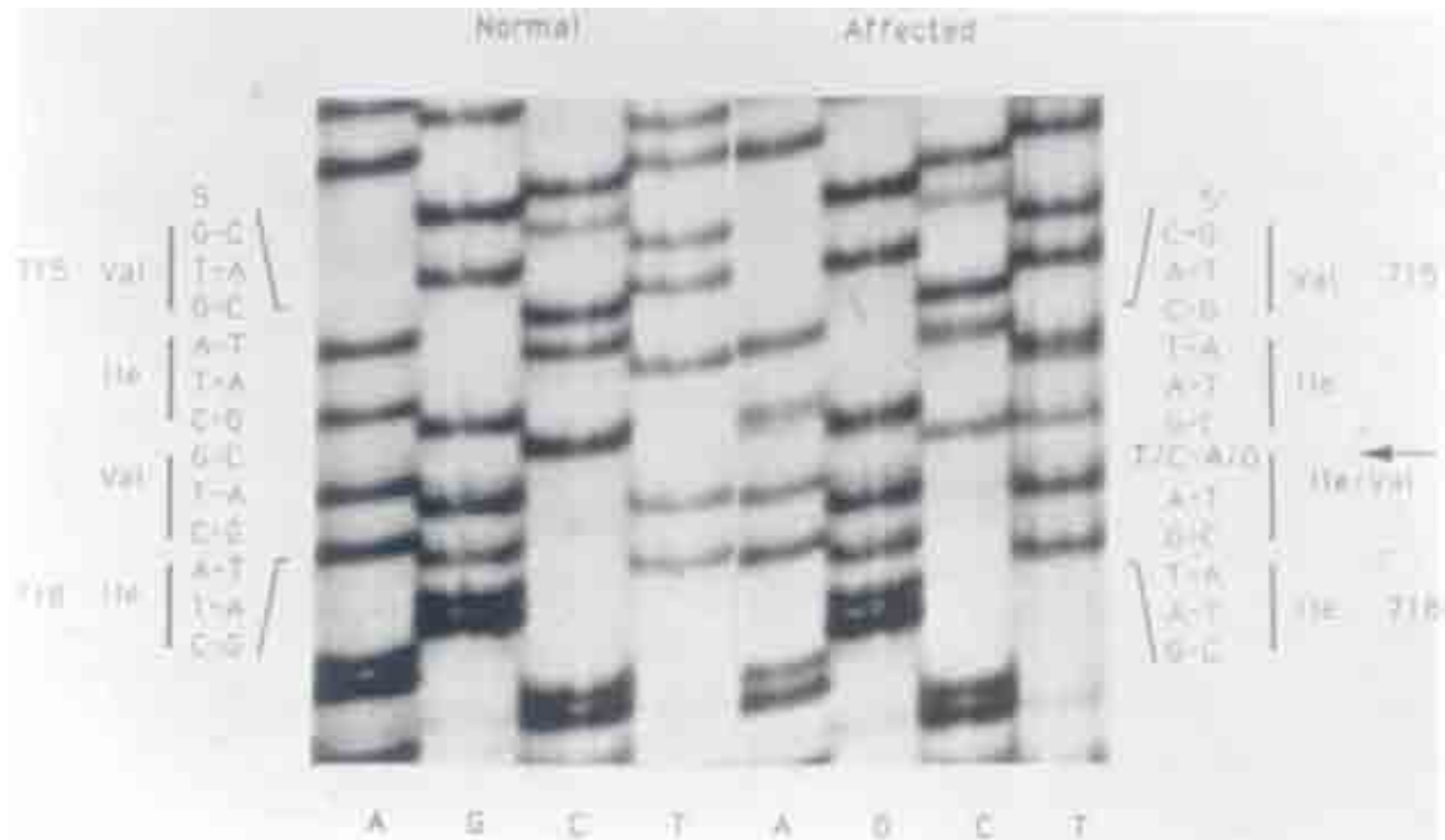
Range (52-66yrs)

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



C/T mutation in exon 17 of APP in affected individual from F23 causes a Valine to Isoleucine substitution at codon 717

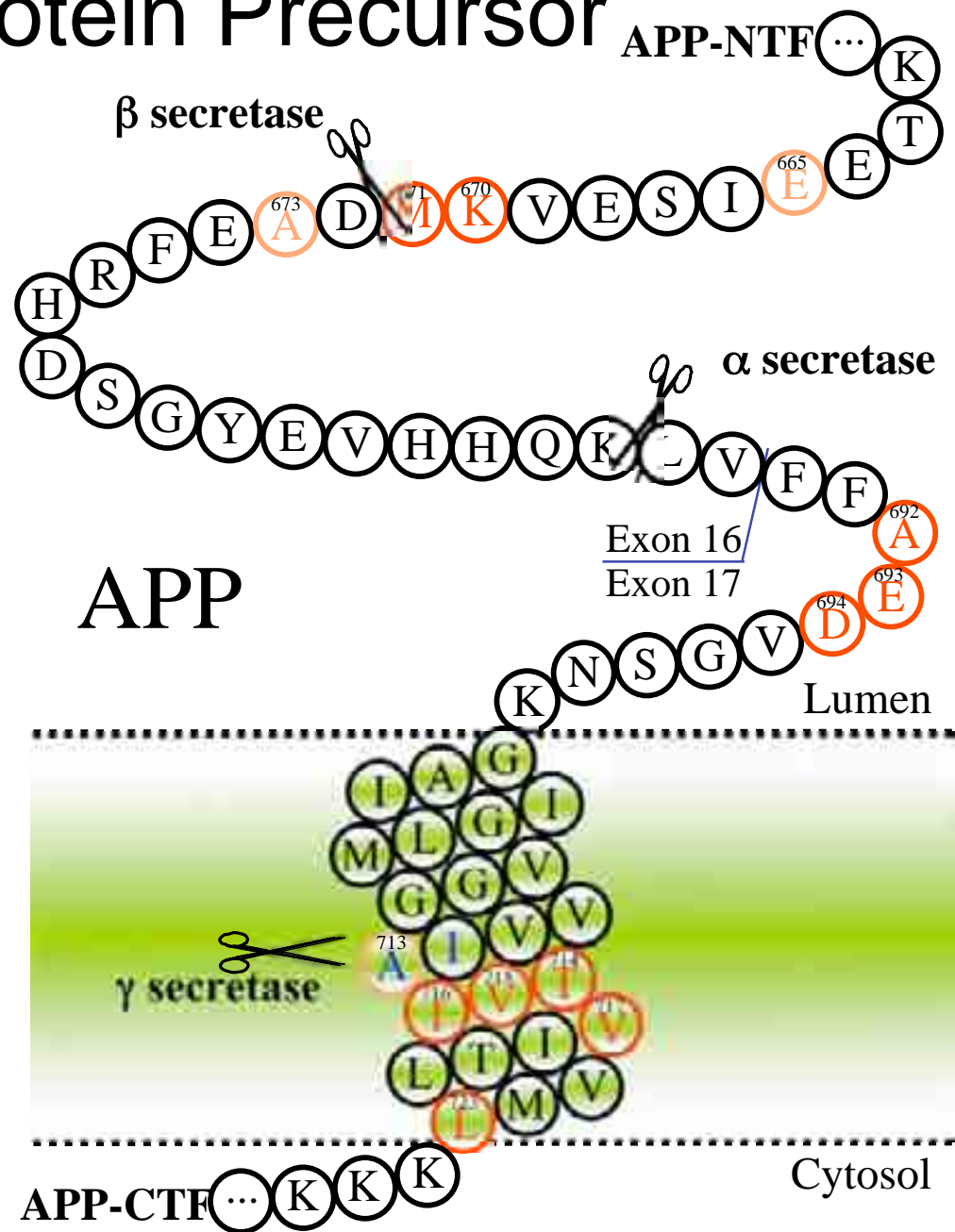
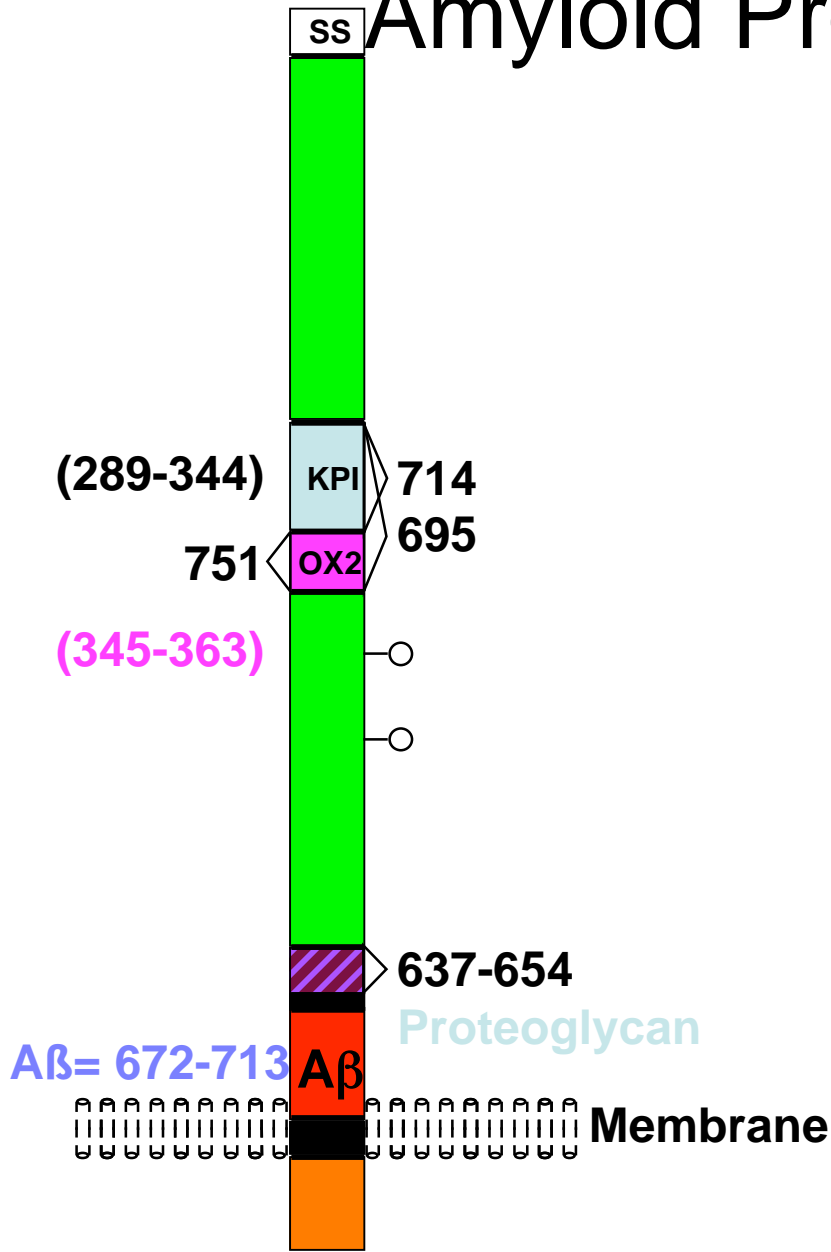


“It’s marvellous. In future it may be possible to prevent the disorder happening. While it will not help me. I hope it will help ...y children”
Carol Jennings, The Times, February 16th, 1991



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

Amyloid Protein Precursor



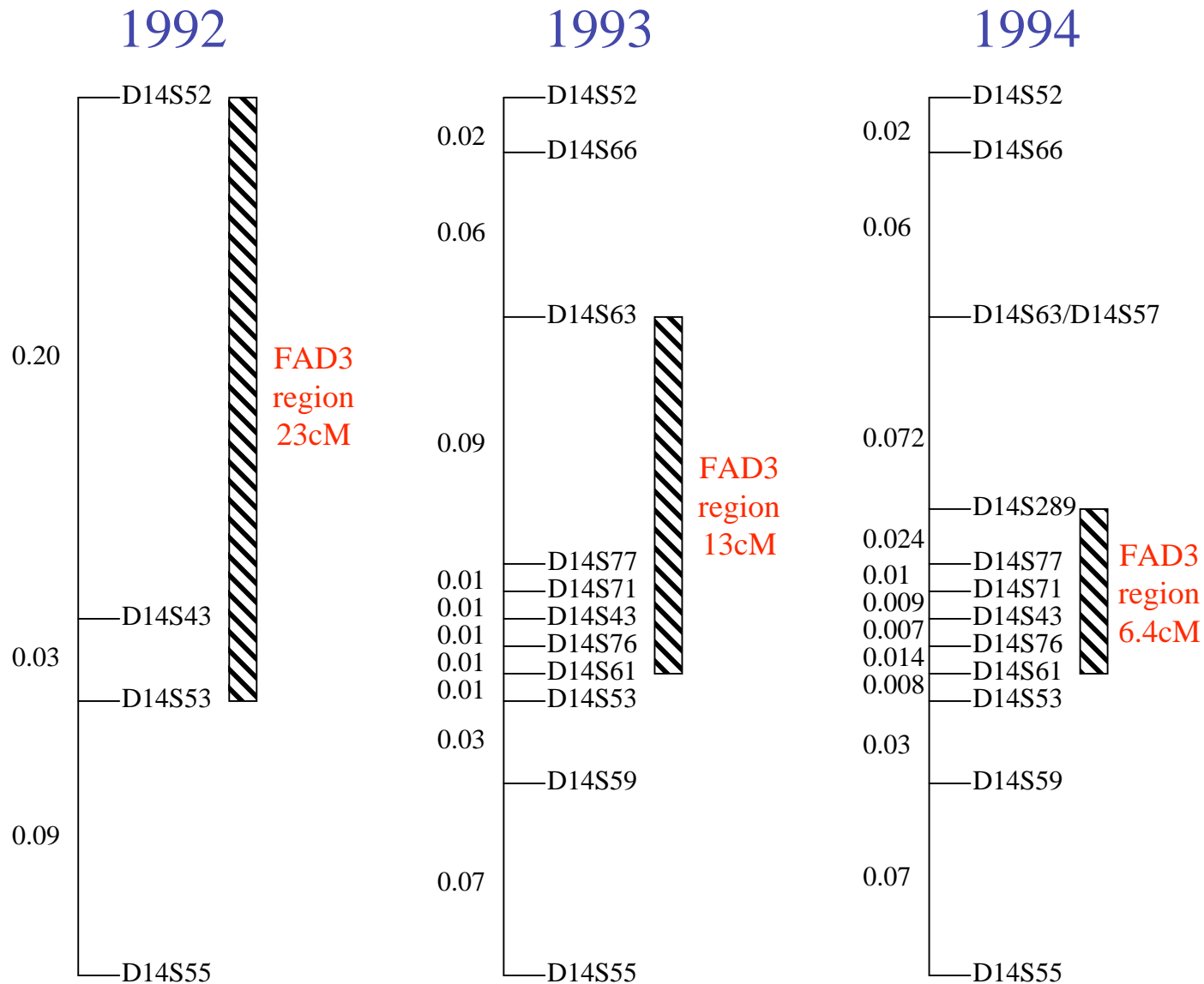
Only a Small Proportion of families
had APP mutations (~10%):-

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

Genetic Maps around the FAD locus on Chromosome 14



**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. Rogaev¹, R. Sherrington¹, E. A. Rogaeva¹,
G. Levesque¹, M. Ikeda¹, Y. Liang¹, H. Chi¹,
C. Lin¹, K. Holman¹, T. Tsuda¹, L. Mar¹, S. Sorbi²,
E. Nacmias³, S. Piacentini⁴, L. Amaducci⁵,
I. Chumakov⁶, D. Cohen⁷, L. Lamfelt⁸,
P. E. Fraser⁹, J. M. Rommens¹⁰
& P. H. St George-Hyslop¹¹*

nature
Aug. 1995

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

R. Sherrington¹, E. I. Rogaev¹, Y. Liang¹, E. A. Rogaeva¹, G. Levesque¹,
M. Ikeda¹, H. Chi¹, C. Lin¹, G. Li¹, K. Holman¹, T. Tsuda¹, L. Mar¹,
J.-F. Foncin², A. C. Brunl³, M. P. Montesi⁴, S. Sorbi⁵, I. Rainero⁶, L. Pinessi⁷,
L. Nee⁸, I. Chumakov⁹, D. Pollen¹⁰, A. Brookes¹¹, P. Sanseau¹²,
R. J. Polinsky¹³, W. Wasco¹⁴, H. A. R. Da Silva¹⁵, J. L. Haines¹⁶,
M. A. Pericak-Vance¹⁷, R. E. Tanzi¹⁸, A. D. Roses¹⁹, P. E. Fraser²⁰,
J. M. Rommens²¹ & P. H. St George-Hyslop²²*

nature
June 1995

**A Familial Alzheimer's Disease
Locus on Chromosome 1**

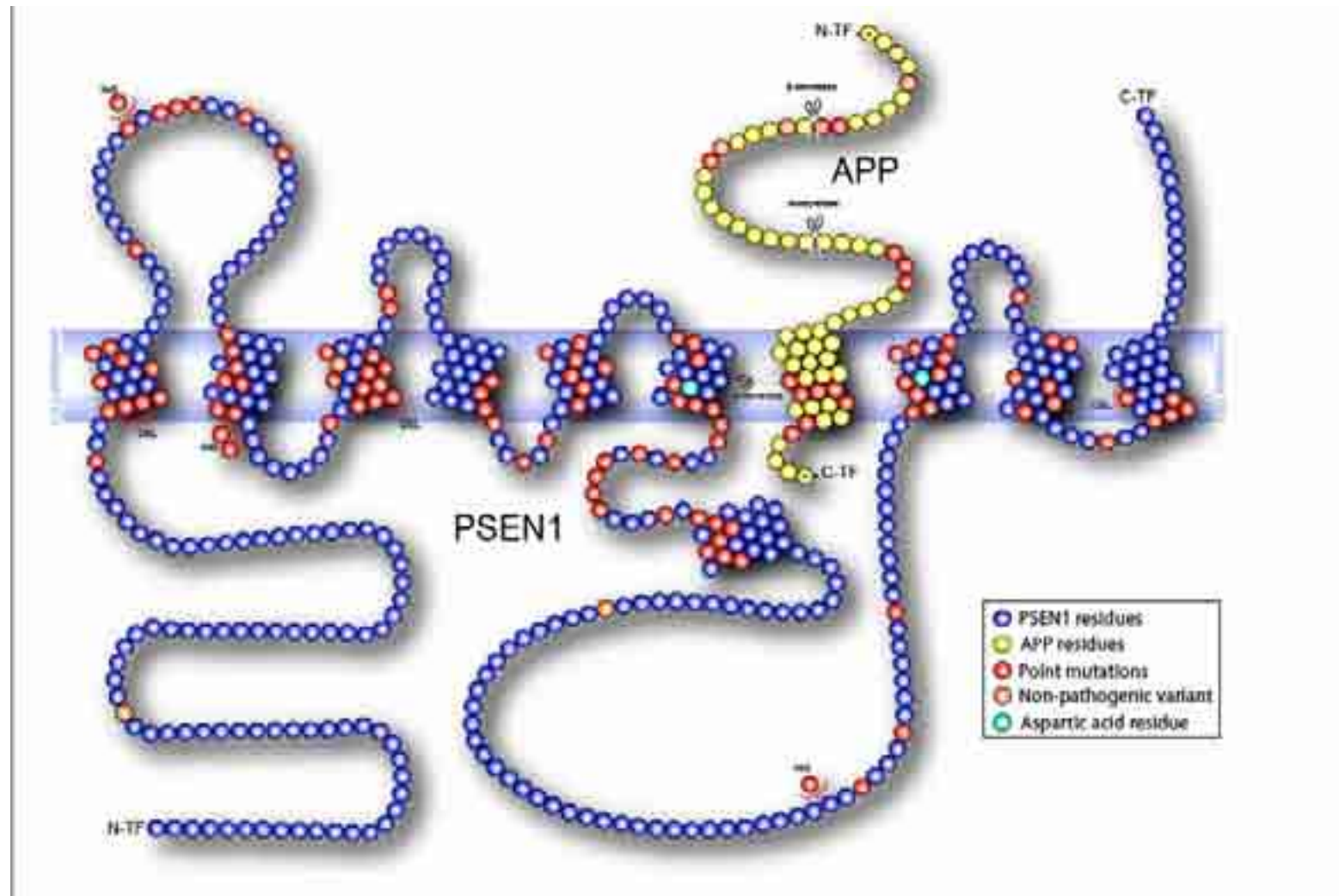
Ephrat Levy-Lahad, Ellen M. Wijsman, Ellen Nemens,
Leojean Anderson, Katrina A. B. Goddard, James L. Weber,
Thomas D. Bird, Gerard D. Schellenberg*

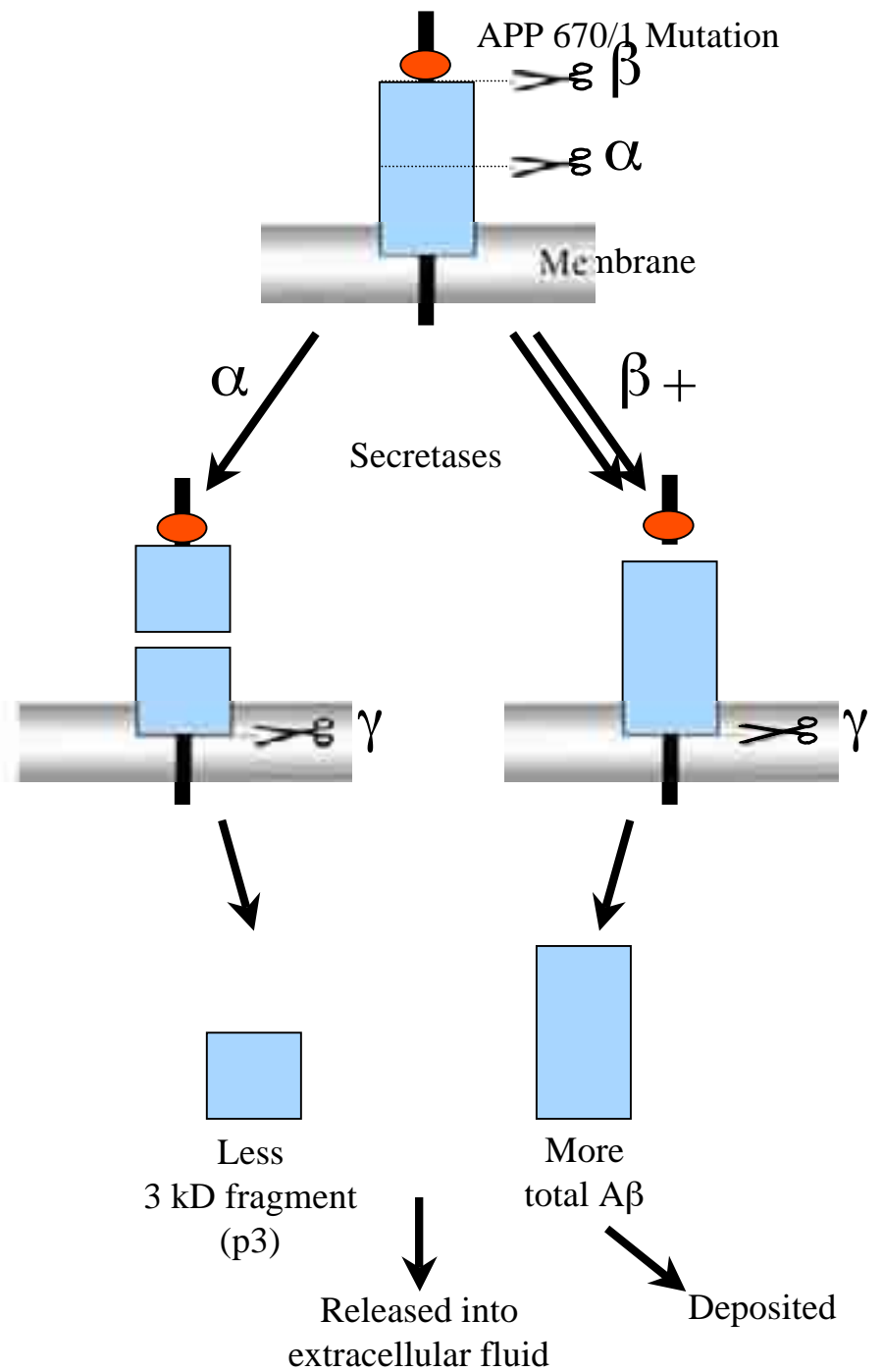
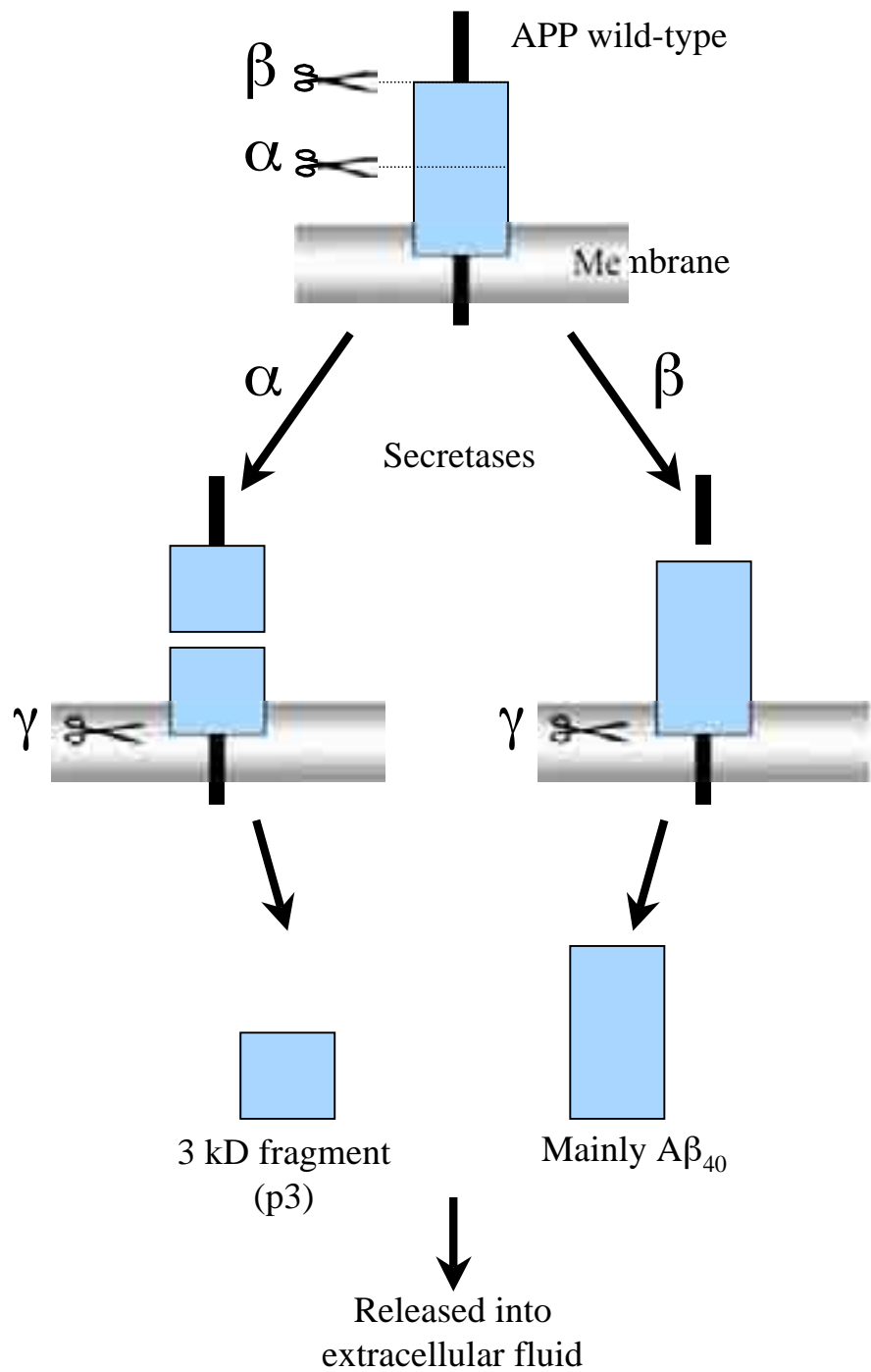
Science
Aug. 1995

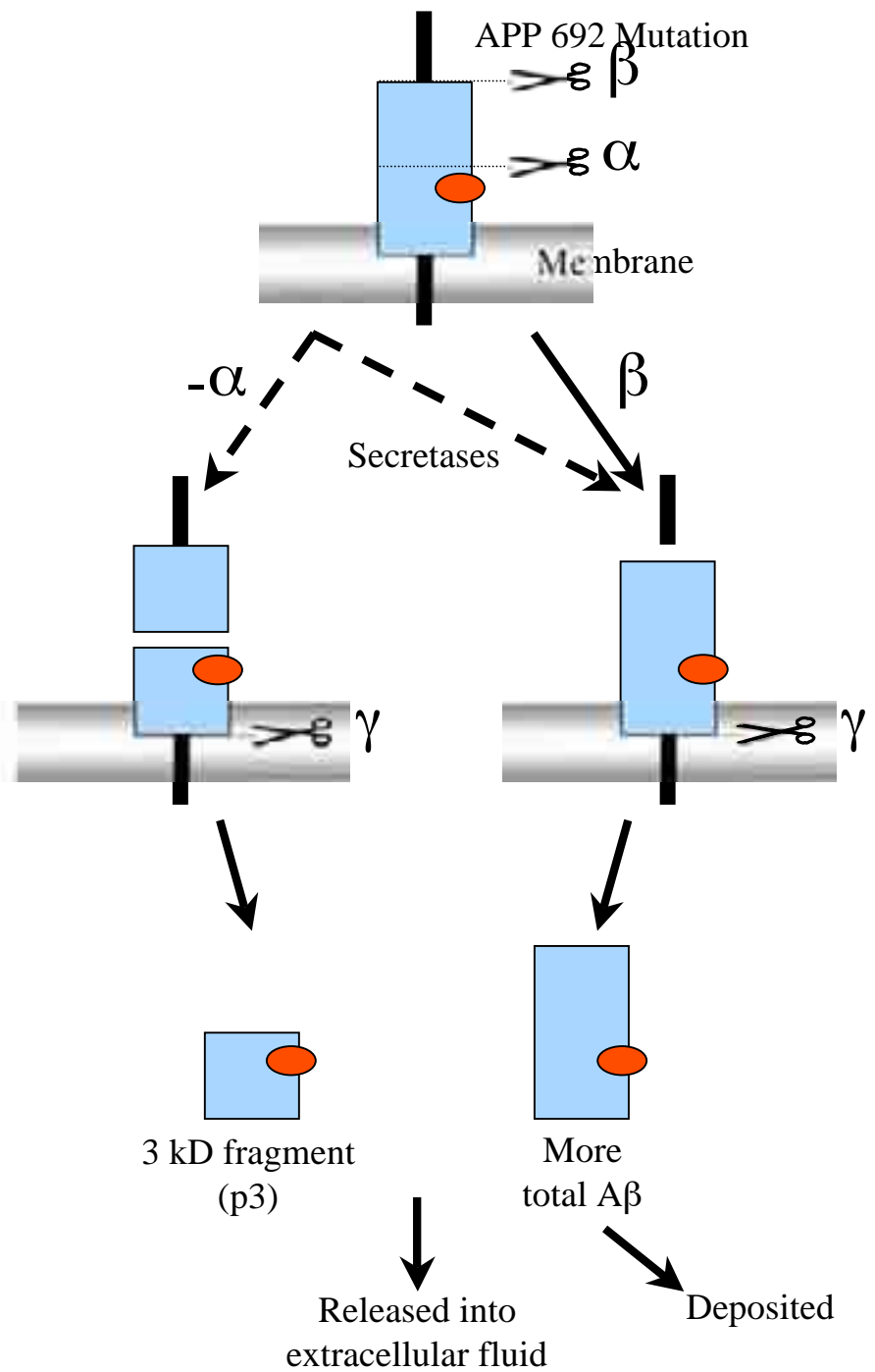
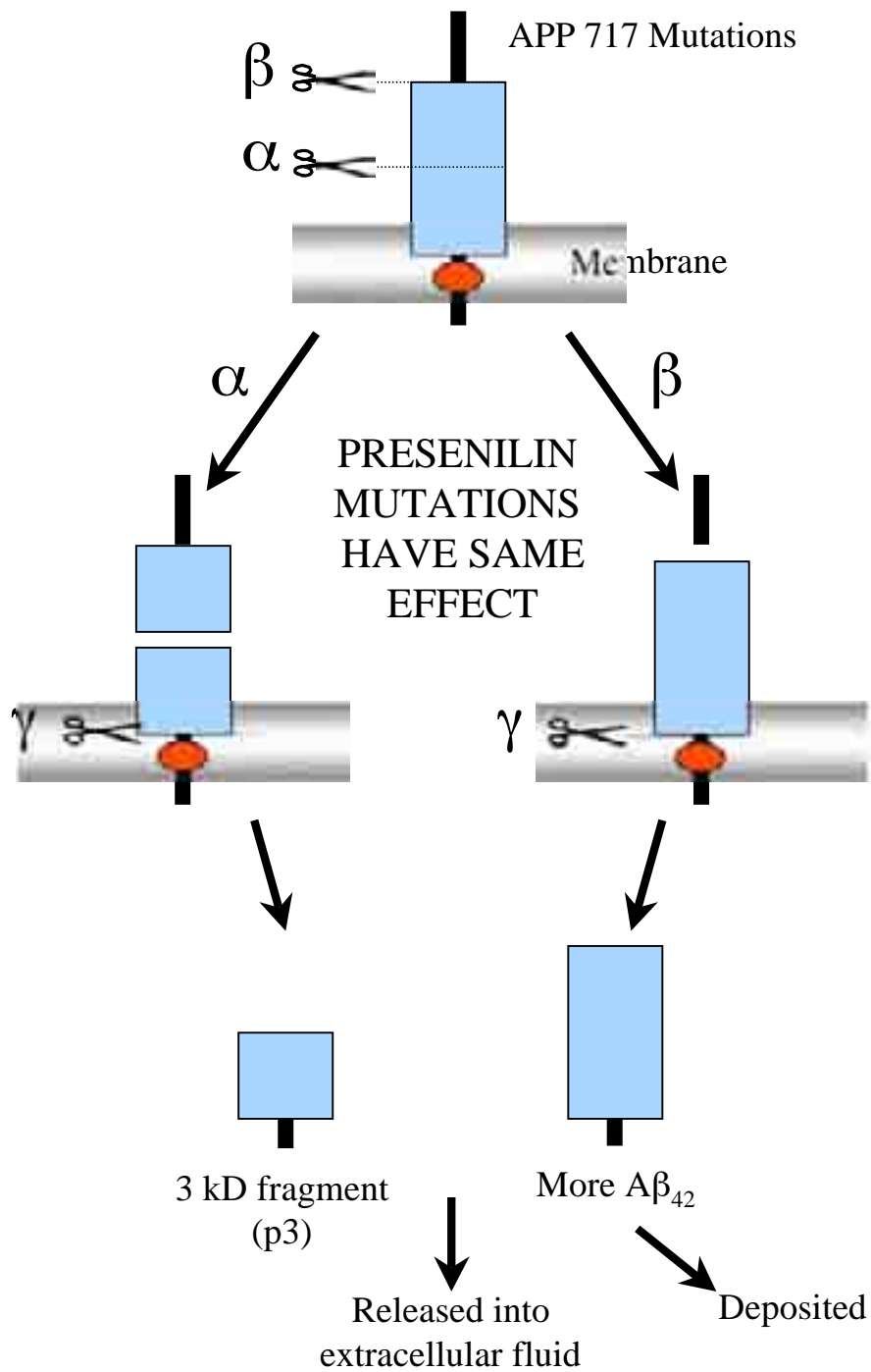
**Candidate Gene for the Chromosome 1 Familial
Alzheimer's Disease Locus**

Ephrat Levy-Lahad,¹ Wilma Wasco,² Parvoneh Poorkaj,
Donna M. Romano, Junko Oshima, Warren H. Pettingell,
Chang-shi Yu, Paul D. Jondro, Stephen D. Schmidt, Kai Wang,
Annette G. Crowley, Ying-Hui Fu, Suzanne Y. Guenette,
David Galas, Ellen Nemens, Ellen M. Wijsman, Thomas D. Bird,
Gerard D. Schellenberg, & Rudolph E. Tanzi³*

Presenilin with APP in the Active Site







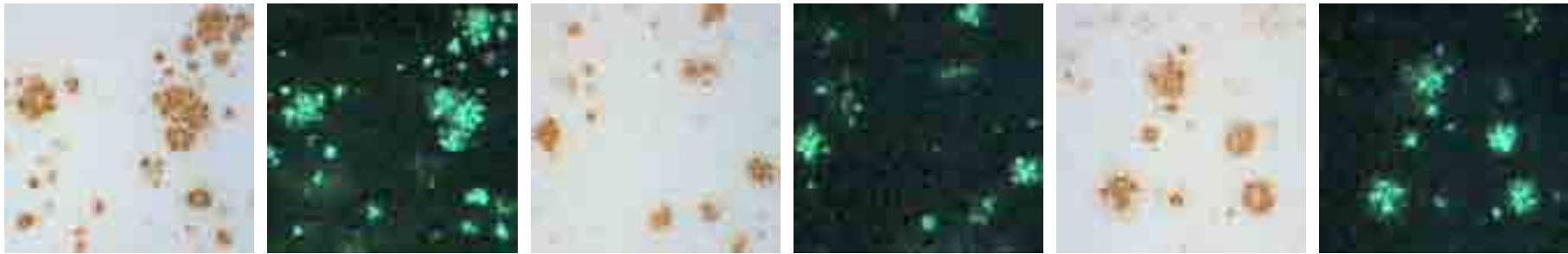
Presenilin accelerates amyloid pathology.

Hippocampus

Cingulate cortex

Entorhinal cortex

PSAPP



APP (Tg2576)

A β

ThioS

A β

ThioS

A β

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^{b, d}, Debomoy K. Lallari^b,
Shantia Shears^{c, d}, Jeremy Booth^{c, d}, William Wu^{c, d}, Alison Goate^{c, d},
Marie Christine Chartier-Harlin^f, John Hardy^{a, e}, Jordi Pérez-Tur^a

**Neuroscience
Letters**
July 1999

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

Jane M. Olson, Katrina A. B. Coddard, and Doreen M. Durick

**The American Journal of
Human Genetics**

Oct. 2001

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

The American Journal of
Human Genetics

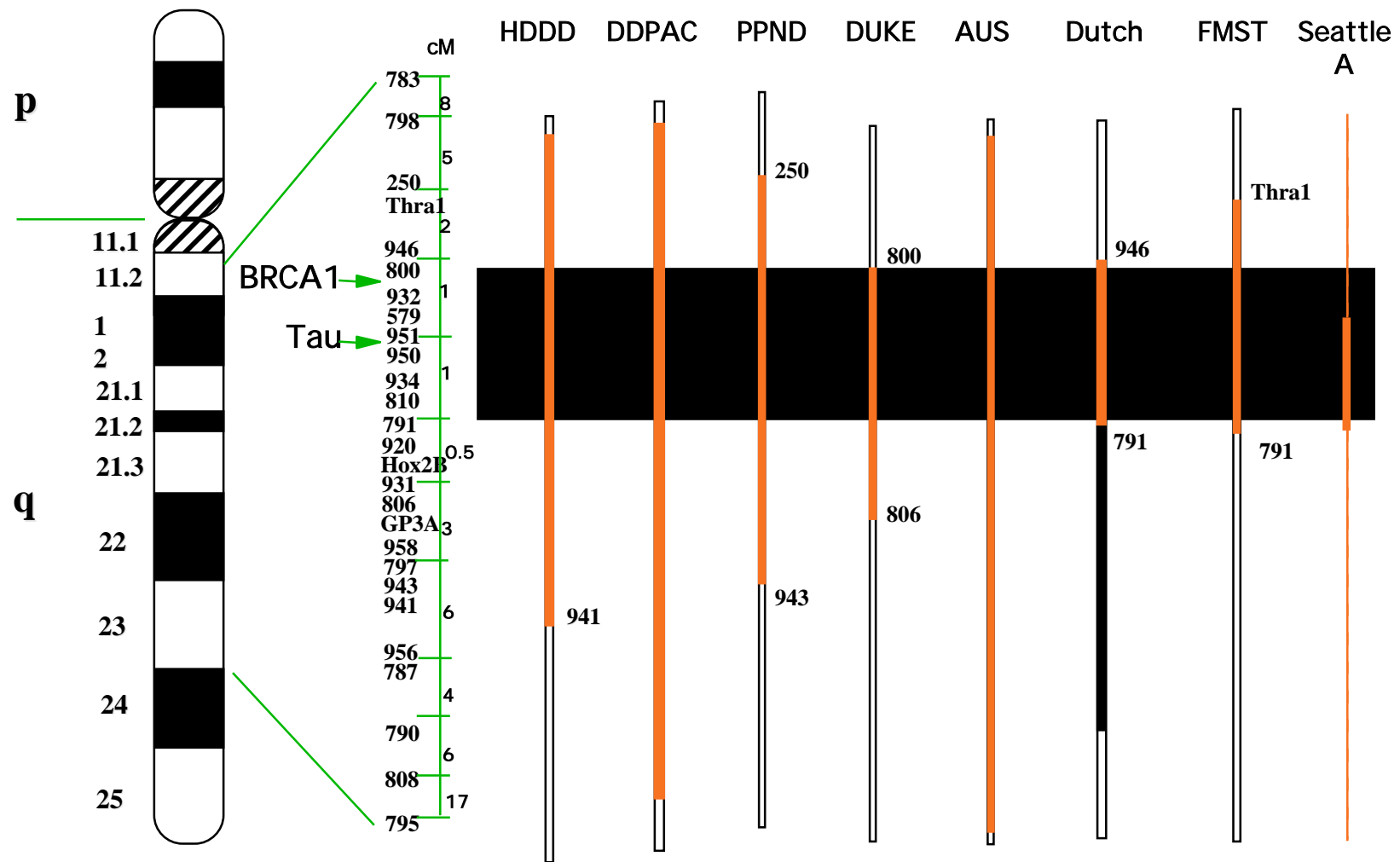
Dec. 1994

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

Norman L. Foster, MD,¹ Kirk Wilhelmsen, MD, PhD,¹ Anders A. E. Sarna, MD, PhD,^{1,5}
Margaret Z. Jones, MD,¹ Constance J. D'Amato, BS,¹ Sid Gilman, MD,⁶ and Conference Participants¹

Annals of Neurology
June 1997

Families with linkage to the FTDP-17 Locus



Tau Is a Candidate Gene for Chromosome 17 Frontotemporal Dementia

Parvoneh Poojary, PhD,*† Thomas D. Bird, MD,*‡ Ellen Wijman, 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*†‡§§

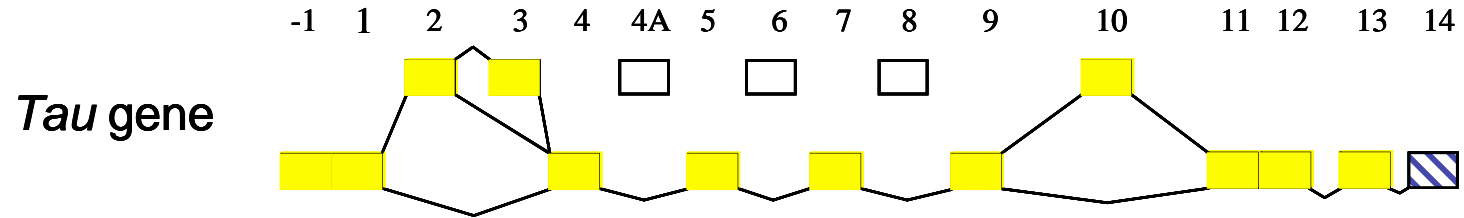
Annals of Neurology
June 1998

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

nature
June 1998

Mike Hutton¹, Corinne L. Lendon², Patrizia Rizzu^{3,4}, 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 Graaf², Erwin Wauters³,
Jeltje van Baren³, Marcel Hillebrand², Marijke Joosse³,
Jennifer M. Kwon⁹, Petra Nowotny², Lien Kuel Che², Joanne Norton⁹,
John C. Morris⁹, Lee A. Reed¹⁰, John Trojanowski¹⁰, Hans Basun⁹,
Lars Lannfelt⁹, 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 Craufurd¹⁸, David Neary¹⁸, Frank Owen⁹,
Ben A. Oostra³, John Hardy¹, Alison Goate², John van Swieten⁴,
David Mann²⁹, Timothy Lynch¹¹ & Peter Heutink²

The microtubule associated protein tau



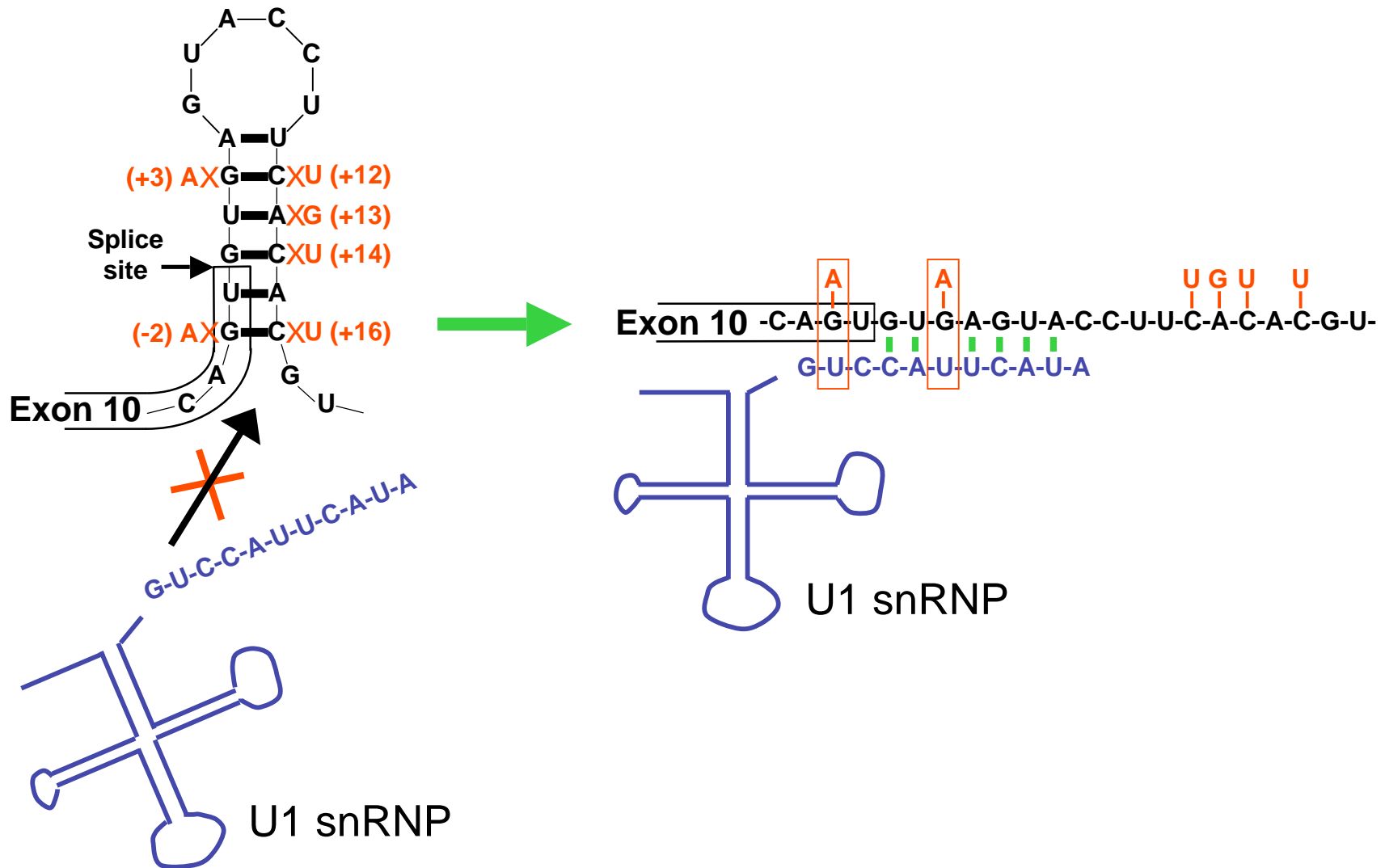
Tau 3 repeat protein isoforms



Tau 4 repeat protein isoforms

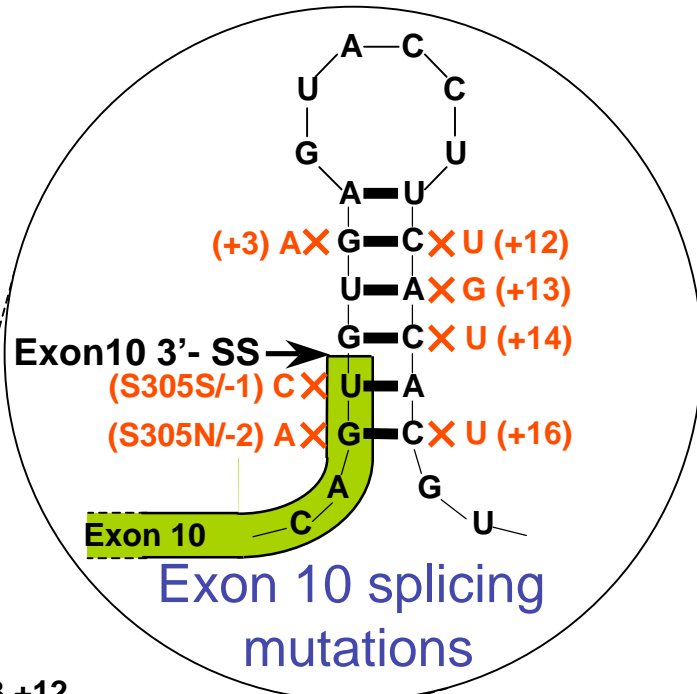
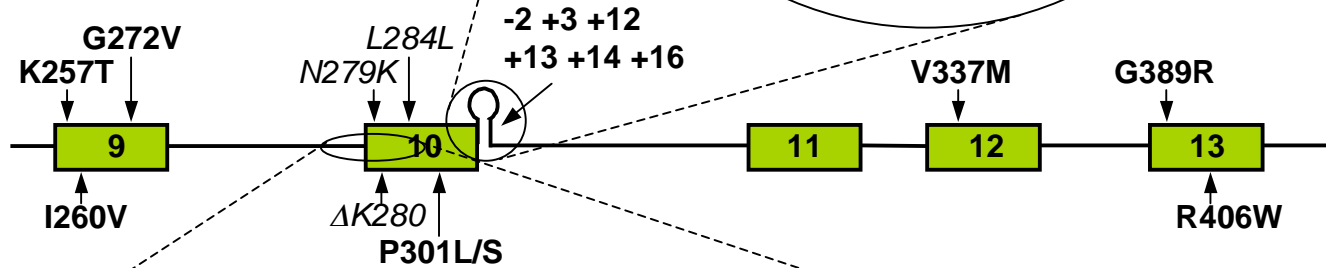


Tau Exon 10 3' splice site mutations increase U1 snRNP binding and splicing of Exon 10

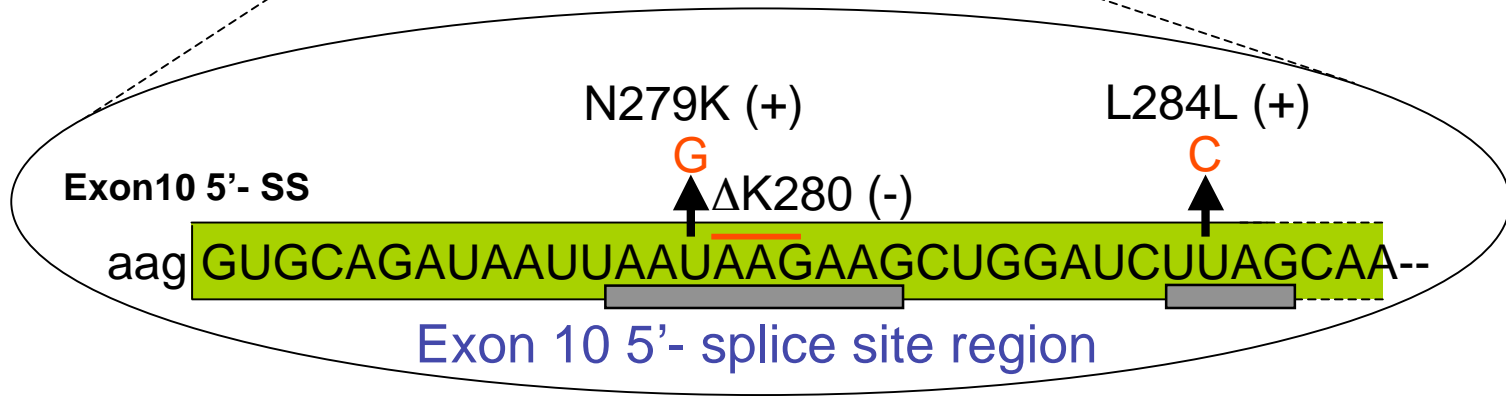


FTDP-17 - missense and splicing mutations in tau

All tau mutations



Exon 10 splicing mutations



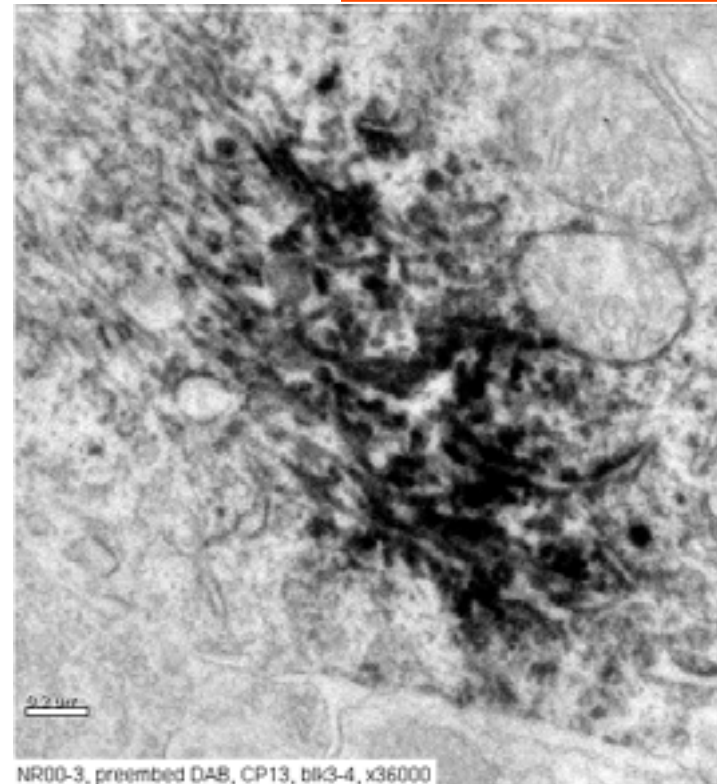
Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein

Jada Lewis¹, Eileen McGowan¹, Julia Rockwood², Heather Metrose¹, Parimata Nacharaju¹, Marjon Van Segrenhorst¹, Katrina Gwynn-Hardy¹, M. Paul Murphy¹, Matt Baker¹, Xin Yu¹, Karen Duff¹, John Hardy¹, Anthony Corral¹, Wen-Lang Lin¹, Shu-Hui Yen³, Dennis W. Dickson¹, Peter Davies² & Mike Hutton¹

nature
genetics
Aug. 2000



- Thioflavin-S positive NFT
- brain stem

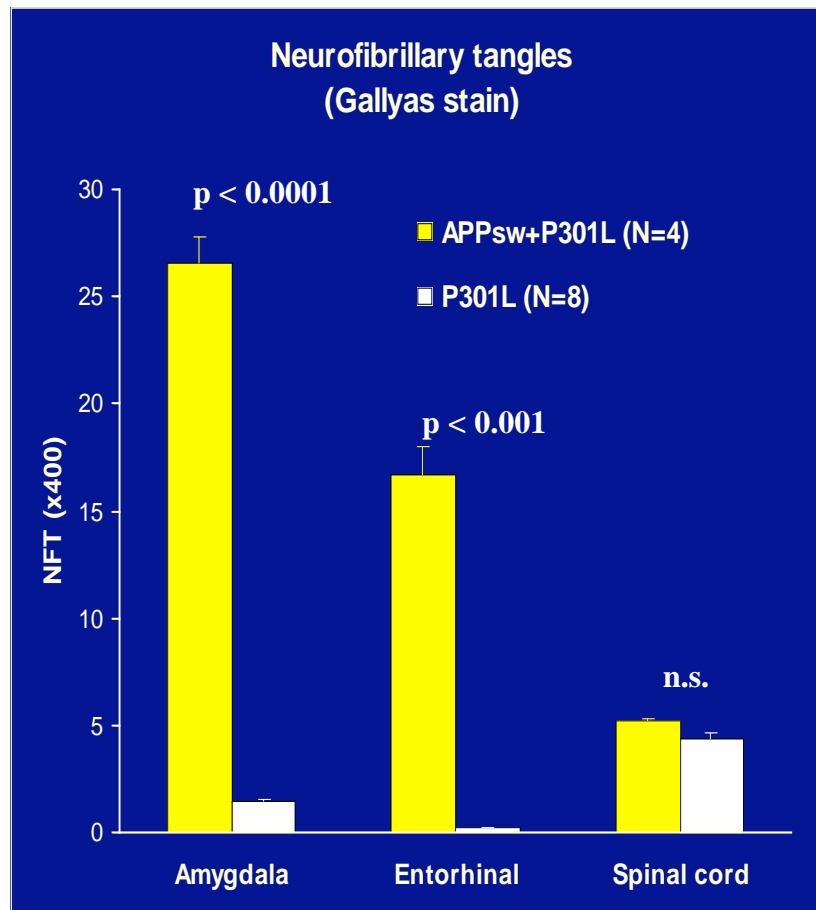


- Tau immuno-EM (22-24-nm twisted ribbons)

Enhanced Neurofibrillary Degeneration in Transgenic Mice Expressing Mutant Tau and APP

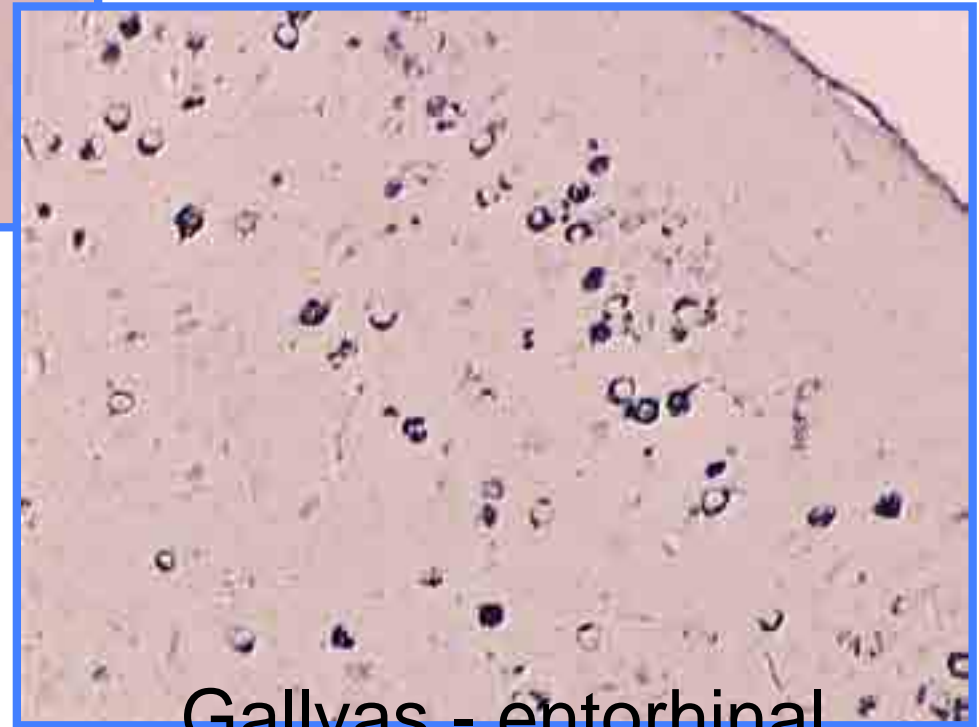
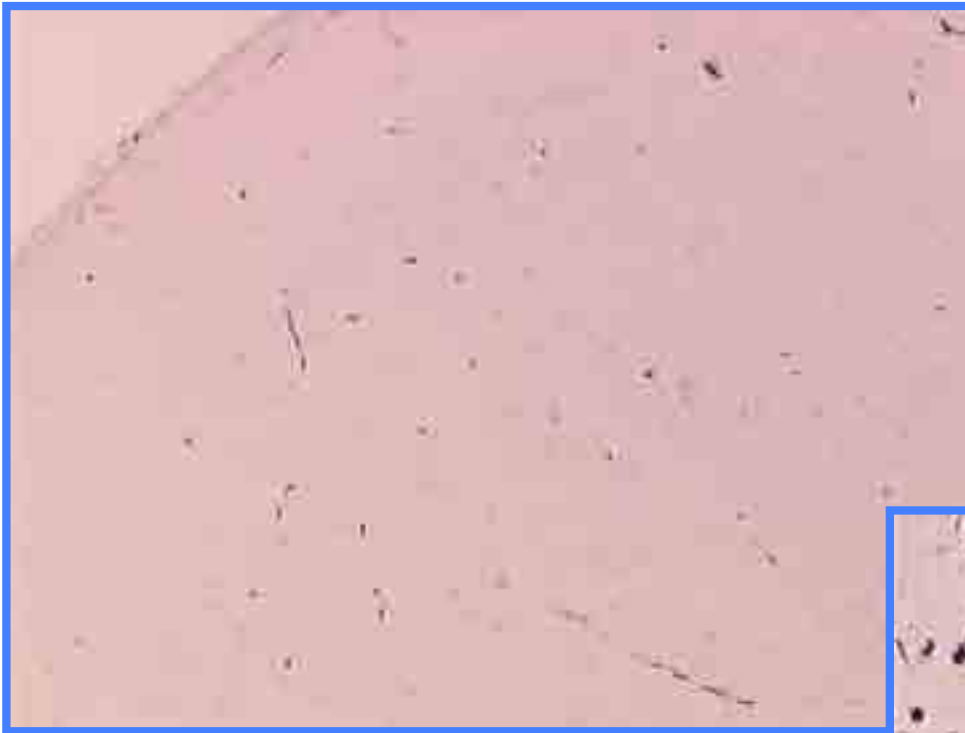
Jada Lewis,* Dennis W. Dickson,* Wen-Lang Lin, Louise Chisholm, Anthony Corral, Graham Jones, Shu-Hui Yen, Naruhiko Sahara, Lisa Skipper, Debra Yager, Chris Eckman, John Hardy, Mike Hutton,† Eileen McGowan

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-A β (β -amyloid peptide) environment. The resulting double mutant (tau/APP) progeny and the Tg2576 parental strain developed A β 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 A β influences the formation of neurofibrillary tangles. The interaction between A β and tau pathologies in these mice supports the hypothesis that a similar interaction occurs in Alzheimer's disease.



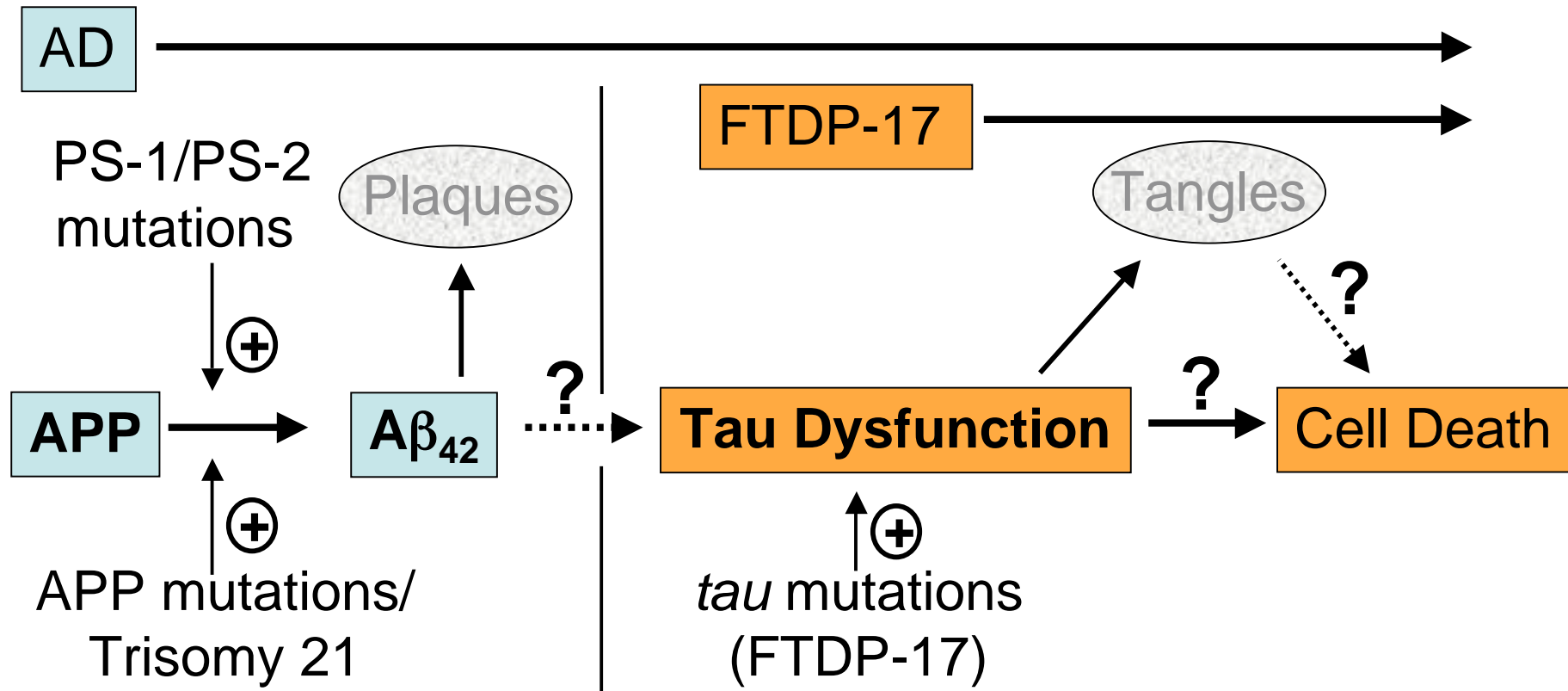
Science
Aug. 2001

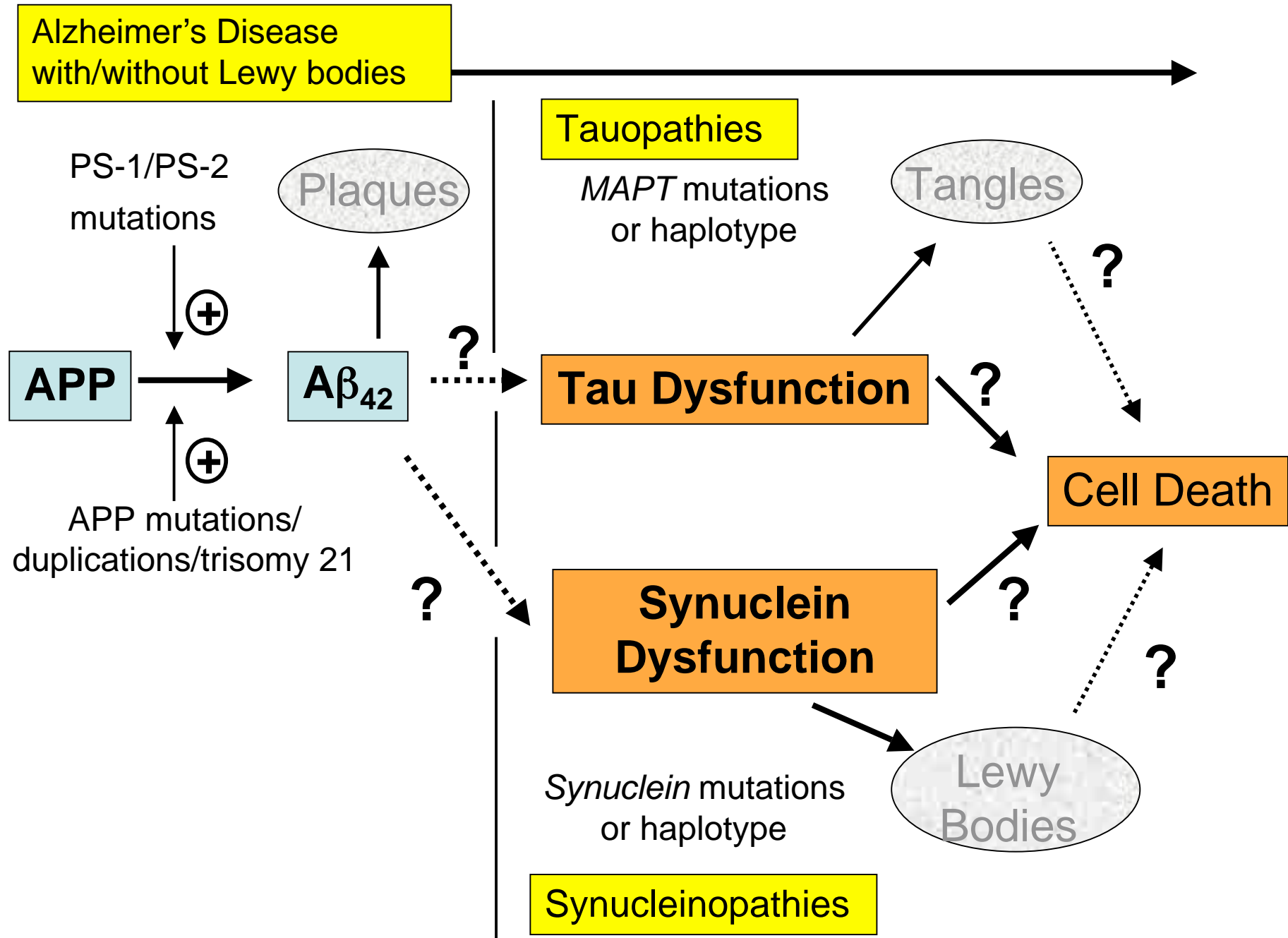
Gallyas - entorhinal P301L



Gallyas - entorhinal
APP/P301L

AD/FTDP-17 - Pathways to neurodegeneration

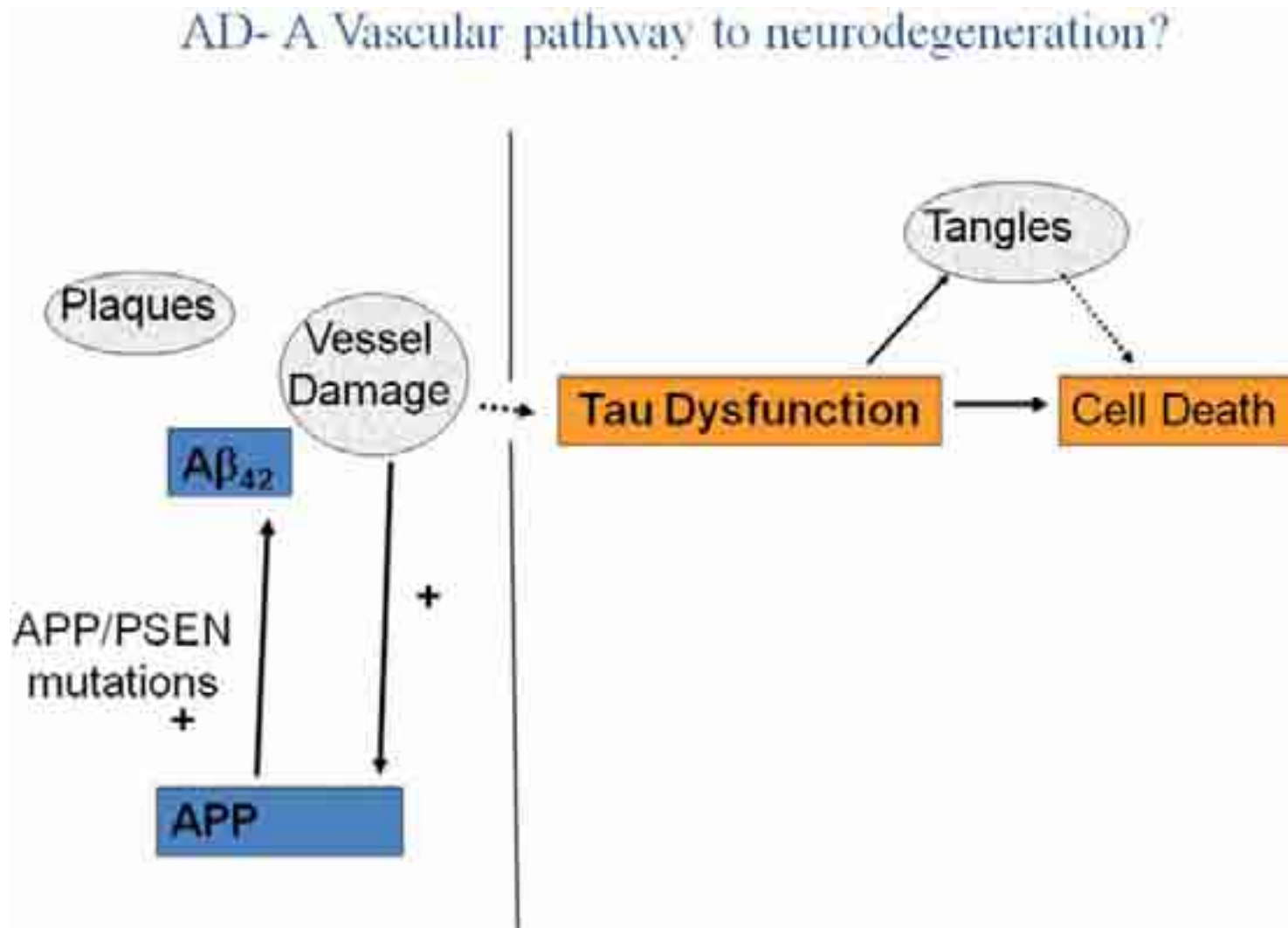




Concerns:-

- 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?
- By the time diagnosis is made, is it too late to stop the pathogenesis?

Is this the problem



Evidence?

- All plaques have a blood vessel at their core (Miyakawa 1980, Kumar-Singh 2005)
- All plaques are the site of microhaemorrhages (Cullen 2006)
- APP is a clotting cascade inhibitor
- Side effect of some vaccines: encephalitis (tearing the bandage off a sore?)