# Neurodegenerative Disease:
## Too much of a bad thing, kills you

John Hardy Ph.D. NIA

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# The law of mass action applied to neurodegenerative disease: a hypothesis concerning the etiology and pathogenesis of complex diseases

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**Loci underlying autosomal dominant forms of most neurodegenerative disease have been identified: prion mutations cause Gerstmann Straussler syndrome and hereditary Creuzfeldt–Jakob disease, tau mutations cause autosomal dominant frontal temporal dementia, and α-synuclein mutations cause autosomal dominant Parkinson's disease. In all these cases, the pathogenic mutation is in the protein that is deposited in the diseased tissue and in these cases the whole protein is deposited. In Alzheimer's disease, mutations in APP or presenilin 1 or 2 cause autosomal dominant disease and these are the substrate and proteases, respectively, which are responsible for the production of the deposited peptide, Aβ. Thus, in all cases, the mutations lead to the disease by a mechanism that involves the deposition process. We briefly review this remarkably predictable biology, but also point out that it seems sporadic forms of all these diseases are predisposed to by genetic variability at the same loci, strongly suggesting that the quantity of the normal protein produced influences risk for the sporadic forms of the disease. The evidence for this assertion is strongest in Parkinson's disease (PD), where genetic variability in α-synuclein expression affects risk of developing disease, although the oldest evidence for the notion that increased expression of normal sequence protein can lead to disease comes from the observation of Alzheimer's disease in trisomy 21 cases. From these observations, we make predictions concerning the etiology and pathogenesis of neurodegenerative diseases in general.**

# Pathology of Diseases

- Alzheimer's disease: plaques (Aβ), 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).
- Progressive Supranuclear Palsy and Corticobasal Degeneration (tangles).
- Parkinson's disease/Lewy body dementia: Lewy bodies.

# A Prescient Suggestion

: 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.

: Brain. 1969 Mar;92(1):147-56.

## Presenile dementia and Alzheimer's disease in mongolism.

**Olson MI, Shaw CM.**

: Ann Neurol. 1998 Mar;43(3):380-3. Related Articles, Links

## Molecular mapping of Alzheimer-type dementia in Down's syndrome.

**Prasher VP, Farrer MJ, Kessling AM, Fisher EM, West RJ, Barber PC, Butler AC.**

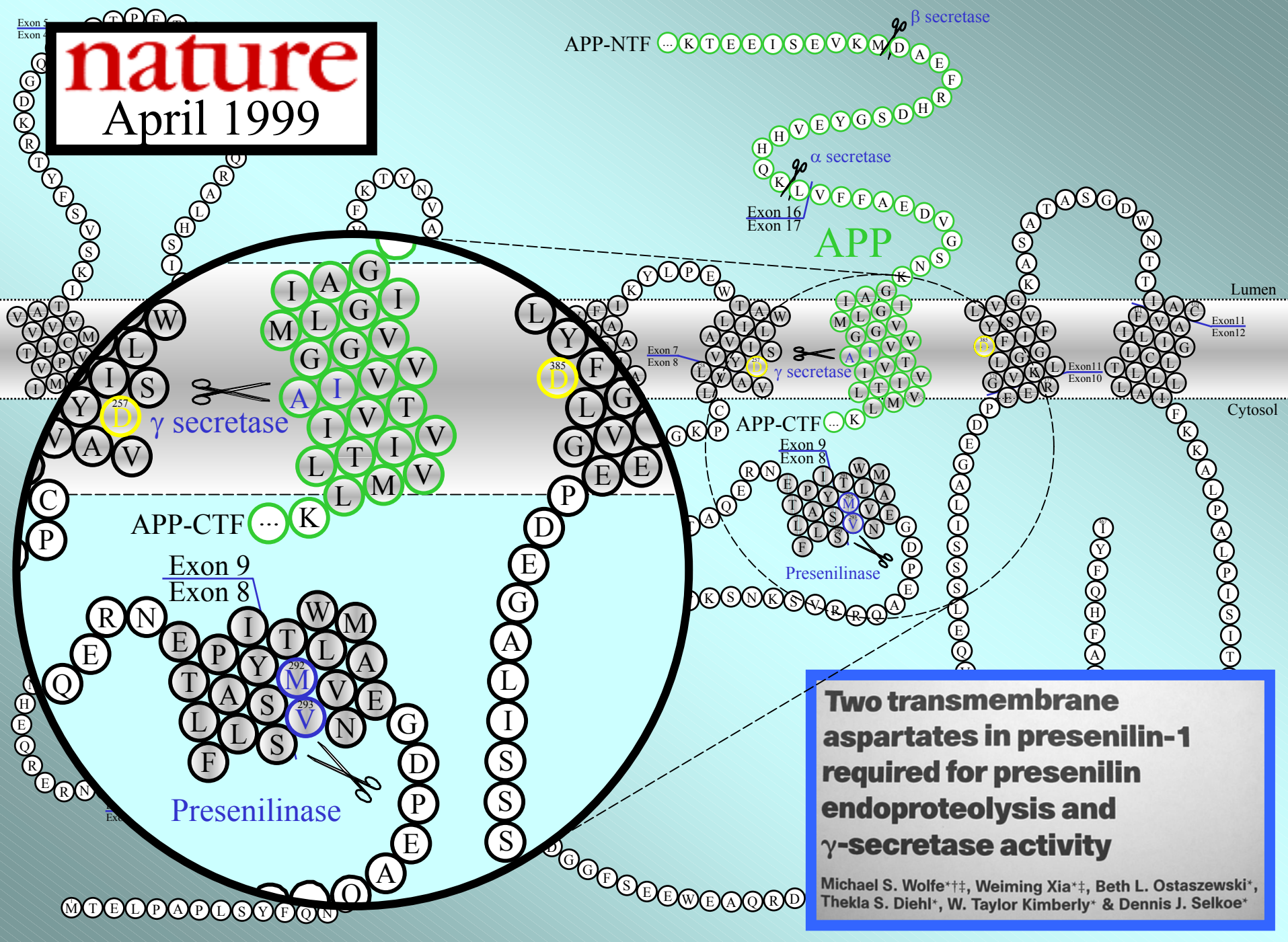
Department of Psychiatry, University of Birmingham, United Kingdom.

Previous research has hypothesized an association between Alzheimer's disease and the amyloid precursor protein (APP) gene found on chromosome 21. We report the case of a 78-year-old woman with Down's syndrome with partial trisomy 21 [46,XX,rec(21)dup q, inv(21) (p12q22.1)]. No evidence of Alzheimer's disease was found on neuropsychological, magnetic resonance imaging, and neuropathological assessment. The gene sequence for APP was present in only two copies. This case further supports the hypothesis that Alzheimer's disease is associated with trisomy for proximal chromosome 21q, including the APP gene.

# Alzheimer's Disease

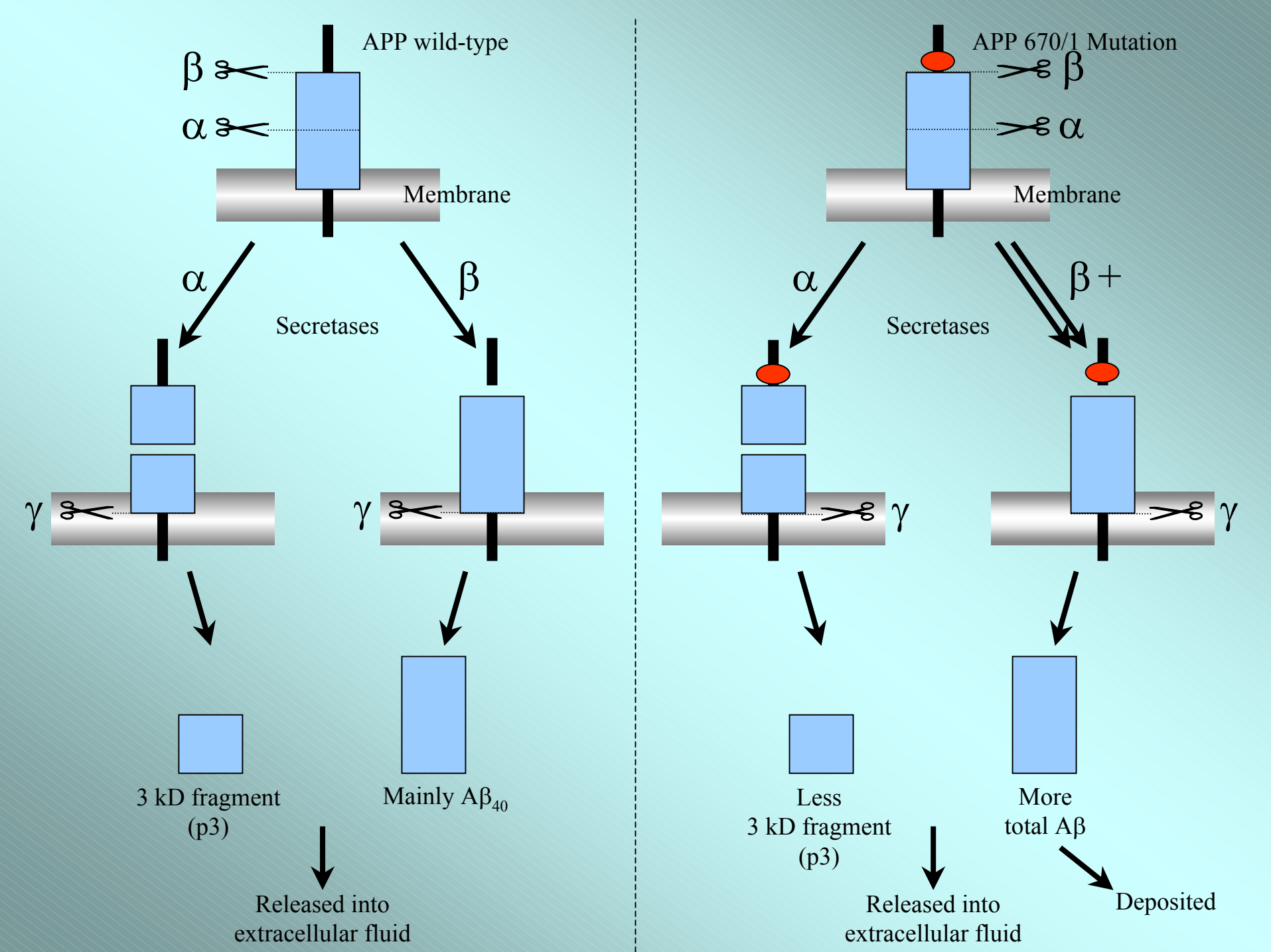
- Primary Deposited Protein is Aβ
- Genes for Mendelian Forms are
  - APP: precursor of Aβ
  - Presenilin 1 and 2: enzymes catalysing production of Aβ from APP
- Tangle (tau) and Lewy Bodies (α-synuclein) are Secondary Pathologies.

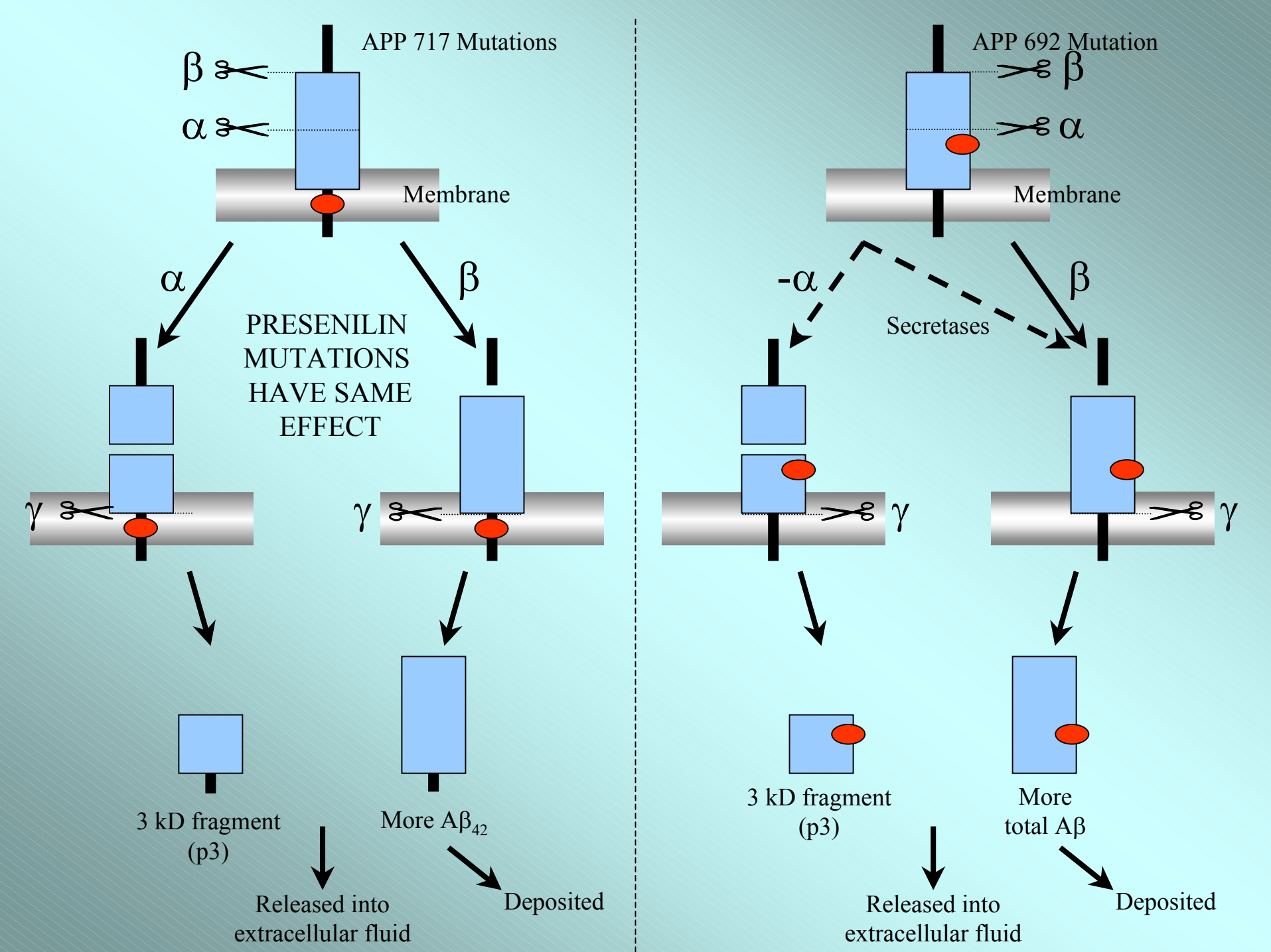
nature
April 1999




# Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and γ-secretase activity

Michael S. Wolfe*†‡, Weiming Xia*‡, Beth L. Ostaszewski*, Thekla S. Diehl*, W. Taylor Kimberly* & Dennis J. Selkoe*

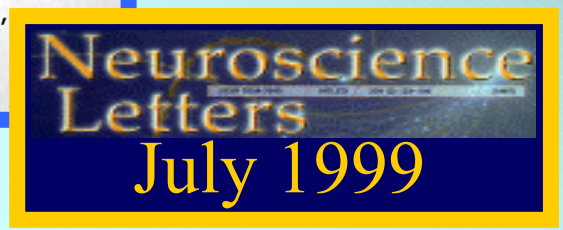

APP wild-type
β
α
Membrane
α
β
Secretases
γ
γ
3 kD fragment
(p3)
Mainly Aβ40
Released into
extracellular fluid
APP 670/1 Mutation
β
α
Membrane
α
β +
Secretases
γ
γ
Less
3 kD fragment
(p3)
More
total Aβ
Released into
extracellular fluid
Deposited


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

# 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]



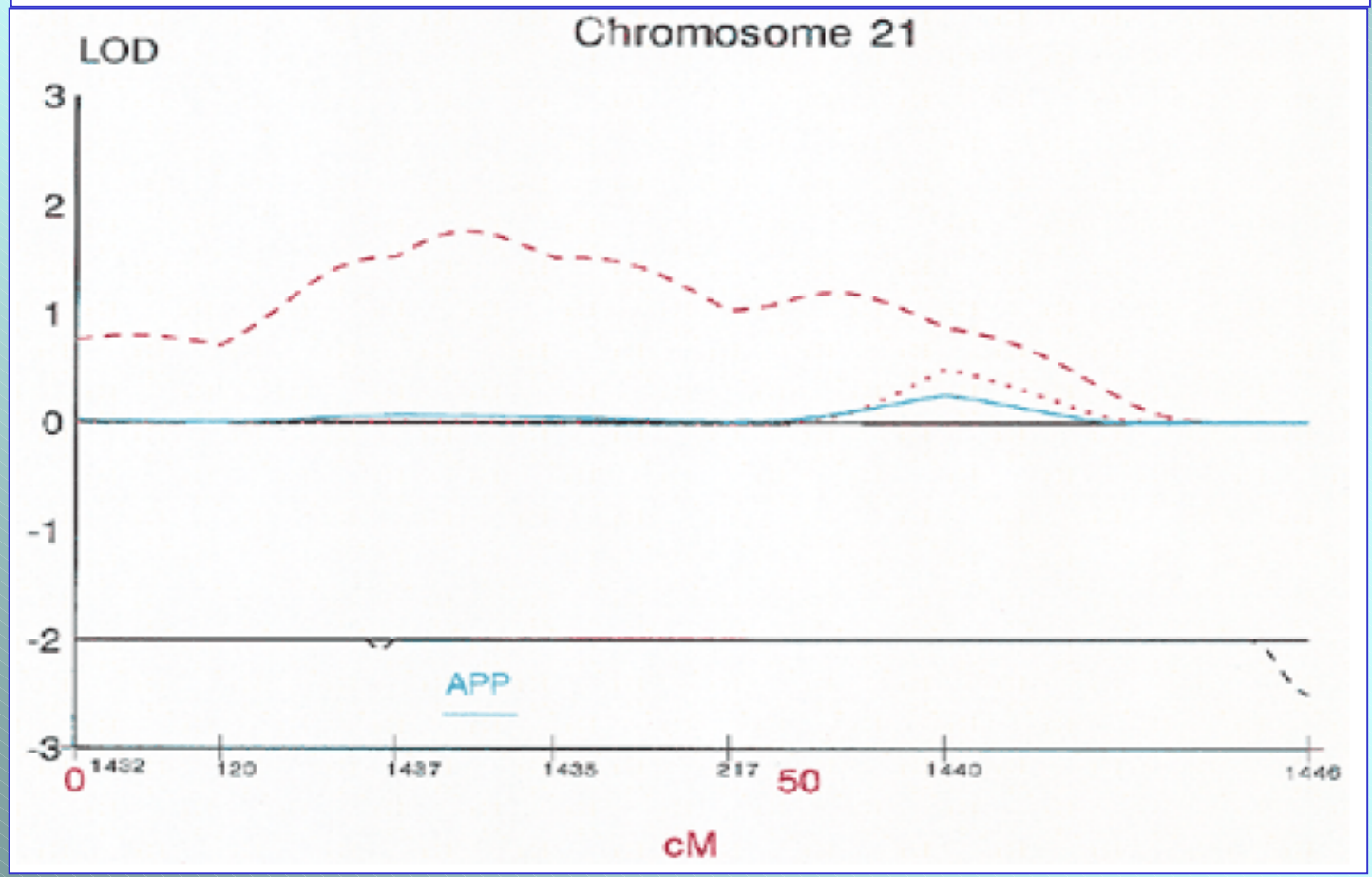

**The Amyloid Precursor Protein Locus and Very-Late-Onset Alzheimer Disease**

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

Human Molecular Genetics, 1999, Vol. 8, No. 2 237–245

# A full genome scan for late onset Alzheimer's disease

Patrick Kehoe+, Fabienne Wavrant-De Vrieze[1,+], Richard Crook[1,+], William S. Wu[2,+], Peter Holmans+, Iain Fenton, Gillian Spurlock, Nadine Norton, Hywel Williams, Nigel Williams, Simon Lovestone[3], Jordi Perez-Tur[1], Mike Hutton[1], Marie-Christine Chartier-Harlin[4], Shantia Shears[2], Kimberly Roehl[2], Jeremy Booth[2], Wendy Van Voorst[2], Dzanan Ramic[2], Julie Williams, Alison Goate[2], John Hardy[1] and Michael J. Owen*



# Conclusion 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.
- Genetic variability in 'normal' APP expression contributes to disease risk.
  - (not clear whether variability in presenilin expression also contributes).

# Prion Diseases

- Primary protein deposit is $PrP^{Sc}$: sometimes as plaques, more often much more subtle.
- Hereditary (caused by prion gene mutations).
- Sporadic (of unknown cause)
- Infectious (iatrogenic, cannibalistic or infectious)
- Tangle (tau) and Lewy Bodies ($\alpha$-synuclein) can be Secondary Pathologies.

# The First Family with a Prion Mutation

Brain Res Mol Brain Res. 1990 Apr;7(3):273-6.



**An in-frame insertion in the prion protein gene in familial Creutzfeldt-Jakob disease.**

**Owen F, Poulter M, Shah T, Collinge J, Lofthouse R, Baker H, Ridley R, McVey J, Crow TJ.**

Division of Psychiatry, Clinical Research Centre, Harrow, Middlesex, U.K.

In a pedigree with Creutzfeldt-Jakob disease we identified a 144-bp insertion in the open reading frame of the prion protein (PrP) gene. The insertion is in-frame and codes for 6 extra uninterrupted octapeptide repeats in addition to the 5 that are normally present in the N-terminal region of the protein. The possibility that this mutation may prove relevant to elucidating the mechanism of horizontal transmission of the spongiform encephalopathies is discussed.

: Lancet. 1991 Jun 15;337(8755):1441-2.

Related Articles, Links

**Genetic predisposition to iatrogenic Creutzfeldt-Jakob disease.**

**Collinge J, Palmer MS, Dryden AJ.**

Department of Biochemistry and Molecular Genetics, St Mary's Hospital Medical School, London, UK.

The spongiform encephalopathy Creutzfeldt-Jakob disease (CJD) has been transmitted to man via administration of growth hormone and gonadotropin extracted from large pooled batches of human cadaveric pituitary glands. In the UK, 1908 individuals were exposed to potentially contaminated growth hormone, of whom 6 have so far manifested CJD. Examination of the prion protein genes of all these cases and of a single case of gonadotropin-related CJD showed that 4 had the uncommon valine 129 homozygous genotype indicating genetic susceptibility to prion infection. Such genetic susceptibility may be important in the aetiology of sporadic CJD disease.

# Variant Creutzfeldt-Jakob disease

John Collinge

**The Lancet**
Volume 354, Issue 9175 , 24 July 1999, Pages 317-323

"The unremarkable history of exposure to BSE among patients with variant CJD to date suggests that these susceptibility factors are more important than the degree of exposure. Susceptibility could be genetic or related to one or more cofactors. All patients with variant CJD analysed to date have been *PRNP* codon 129 methionine homozygotes. All cattle studied are homozygous for methionine at the corresponding bovine codon. About 38% of the normal white population are, however, of this *PRNP* genotype."

1: Nature. 1991 Jul 25;352(6333):340-2. Related Articles, Links

**Homozygous prion protein genotype predisposes to sporadic Creutzfeldt-Jakob disease.**

**Palmer MS, Dryden AJ, Hughes JT, Collinge J.**

Department of Biochemistry and Molecular Genetics, St Mary's Hospital Medical School, London, UK.

The human prion diseases, Creutzfeldt-Jakob disease (CJD) and Gerstmann-Straussler syndrome (GSS), are neurodegenerative diseases that are unique in being both infectious and genetic. Transmission of both diseases and the animal spongiform encephalopathies (for example, scrapie and bovine spongiform encephalopathy) to experimental animals by intracerebral inoculation with brain homogenates is well documented. Despite their experimental transmissibility, missense and insertional mutations in the prion protein gene are associated with both GSS and familial CJD, demonstrating that the human familial cases are autosomal dominant diseases. More than 80% of CJD cases occur sporadically, however, and are not known to be associated with mutations. Here we report that 21 of 22 sporadic CJD cases and a further 19 of 23 suspected sporadic CJD cases are homozygous at the polymorphic amino-acid residue 129; 51% of the normal population are heterozygous at this site. We argue that homozygosity predisposes towards sporadic CJD and that this directly supports the hypothesis that interaction between prion protein molecules underlies the disease process.

*Am. J. Hum. Genet.* 69:1225–1235, 2001

# Sporadic—but Not Variant—Creutzfeldt-Jakob Disease Is Associated with Polymorphisms Upstream of *PRNP* Exon 1

Simon Mead,[1] Sukhvir P Mahal,[1] John Beck,[1] Tracy Campbell,[1] Martin Farrall,[2] Elizabeth Fisher,[1] and John Collinge[1]

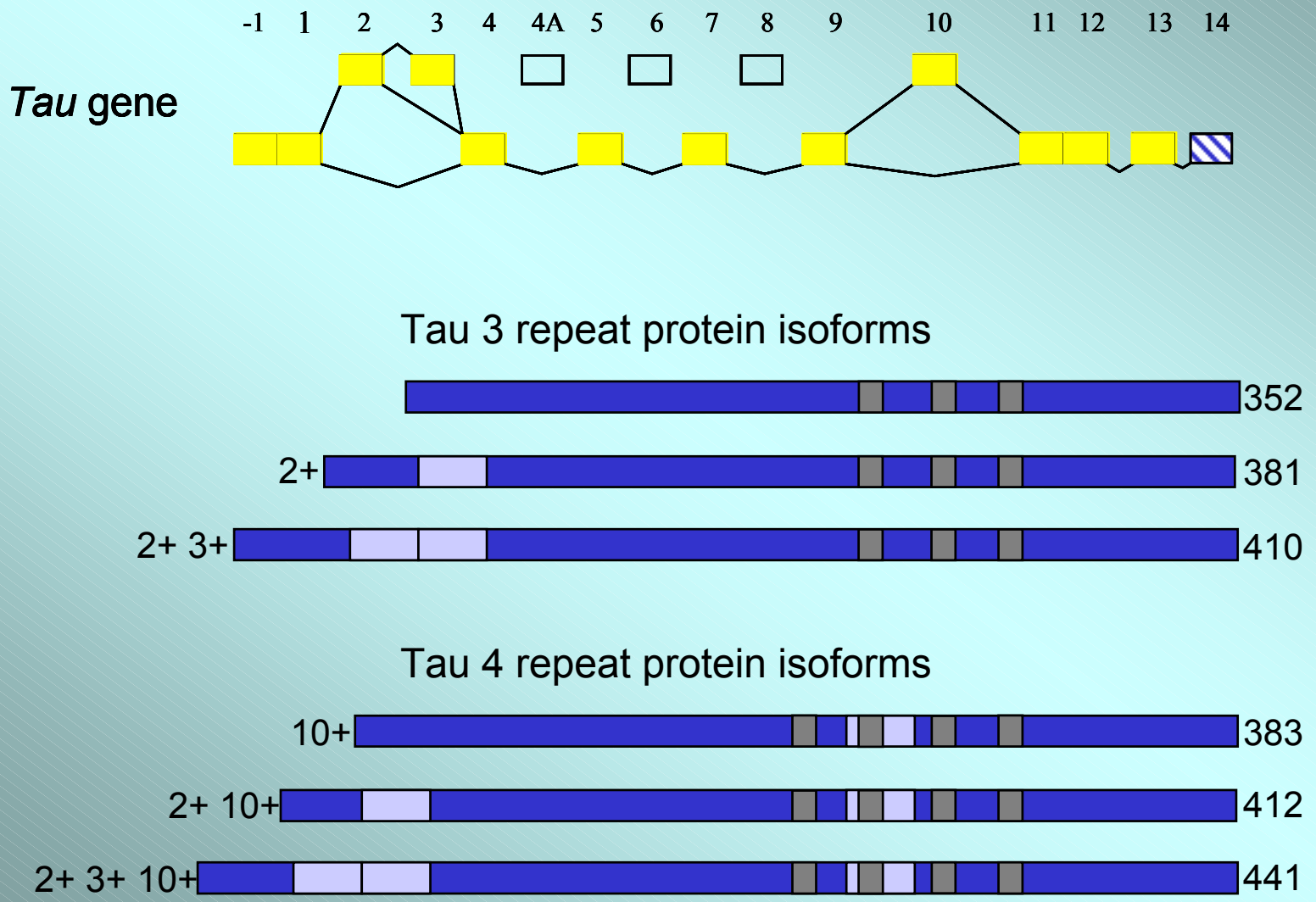
# Prion Disease Conclusions

- Mutations in prion gene cause mendelian disease.
- Homozygosity at codon 129 prediposes to infectious disease: whether it is MM or VV depends on the sequence of the infecting prion.
- Homozygosity of either allele predisposes to sporadic CJD.
- Particular promoters, presumably high expressing ones, also predispose to sporadic CJD.
- But the promoter association does not hold up for infectious disease.
- Thus, the mechanism of initiation of infectious disease is different from that of sporadic disease *(the former is not concentration dependent but the latter is?)*

# Disease with *only* Tau Pathology

- FTDP-17 (previously, many families would have been called Pick's disease): mendelian disease with variable pathology: tangles, Pick bodies or wispy tau filaments.
- Progressive Supranuclear Palsy, Corticobasal degeneration, Argyrophilic Grain Disease
- Parkinson's Dementia Complex of Guam
- Many other rare diseases including von Economo's disease and subacute sclerosing panencephalitis.

# The microtubule associated protein tau



# 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*†‡¶¶

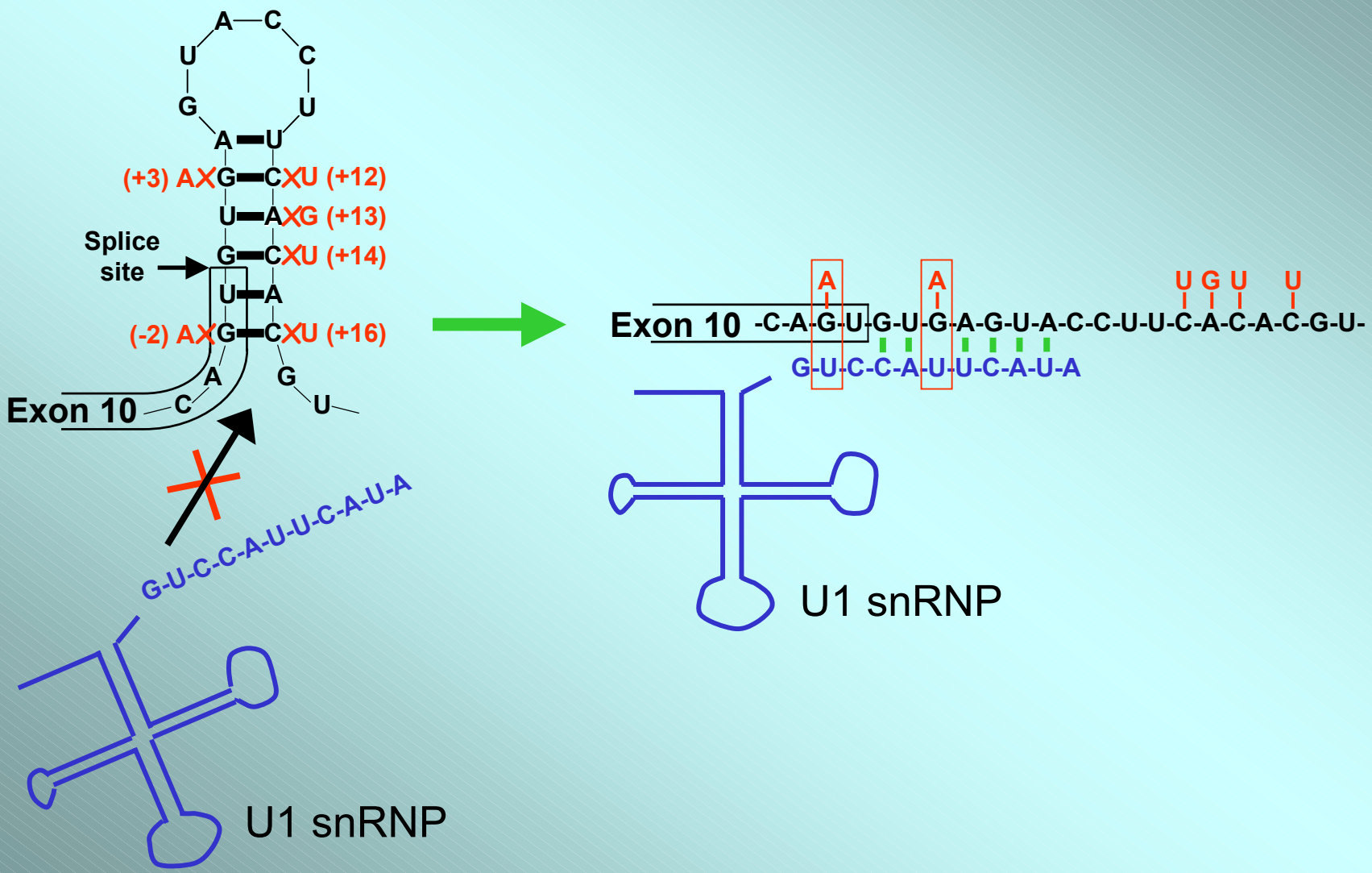
Annals of Neurology
June 1998

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

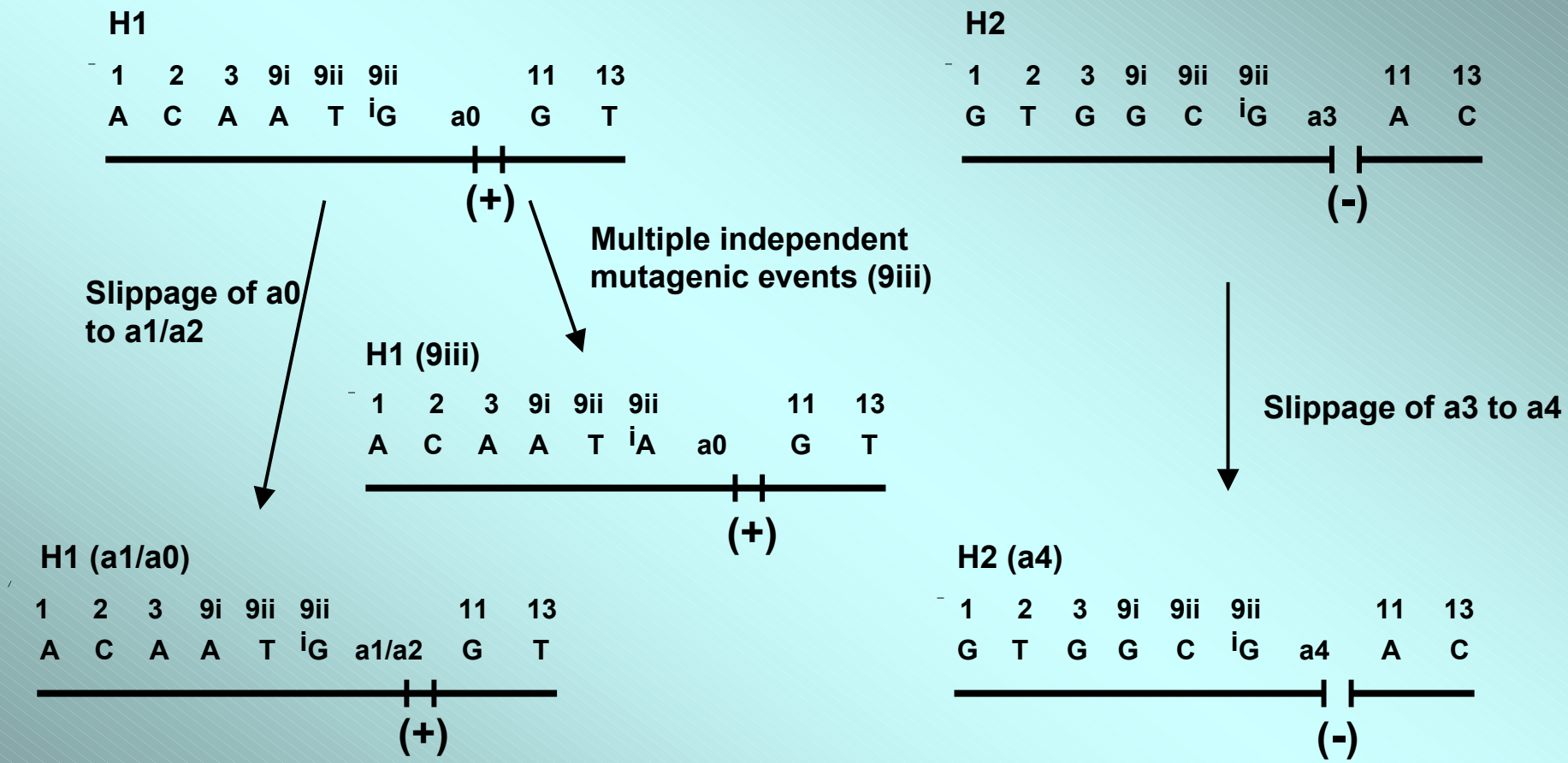
Mike Hutton*[1], Corinne L. Lendon*[2], Patrizia Rizzu*[3,4], Matt Baker[1], Susanne Froelich[3,5], Henry Houlden[1], Stuart Pickering-Brown[6], Sumi Chakraverty[2], Adrian Isaacs[1], Andrew Grover[1], Jennifer Hackett[1], Jennifer Adamson[1], Sarah Lincoln[1], Dennis Dickson[1], Peter Davies[7], Ronald 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

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



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




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

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

Matt Baker, Irene Litvan[1], Henry Houlden, Jennifer Adamson, Dennis Dickson, Jordi Perez-Tur, John Hardy, Timothy Lynch[2], Eileen Bigio[3] and Mike Hutton*

**Human Molecular Genetics**
April 1999

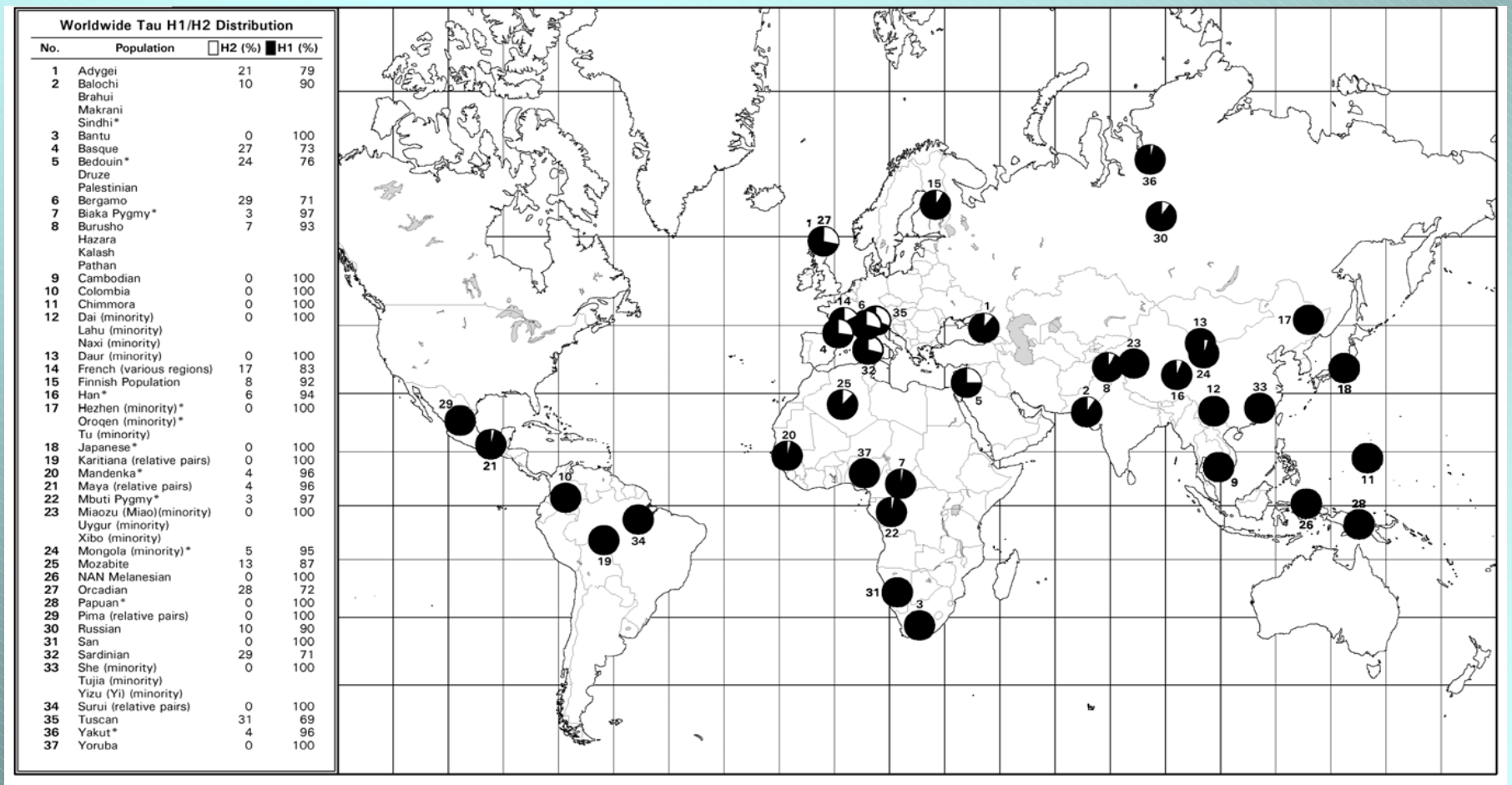
*Neurology* 2001;56:1702-1706


**Articles**

## Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype

H. Houlden, MRCP;, M. Baker, BSc;, H.R. Morris, MRCP;, N. MacDonald, MBBS;, S. Pickering–Brown, PhD;, J. Adamson, BS;, A.J. Lees, MD;, M.N. Rossor, MD;, N.P. Quinn, MD;, A. Kertesz, MD;, M.N. Khan, MSc;, J. Hardy, PhD;, P.L. Lantos, MD;, P. St. George–Hyslop, MD, FRCP(C);, D.G. Munoz, MD;, D. Mann, MD;, A.E. Lang, MD;, C. Bergeron, MD;, E.H. Bigio, MD;, I. Litvan, MD;, K.P. Bhatia, MD;, D. Dickson, MD;, N.W. Wood, FRCP; and M. Hutton, PhD

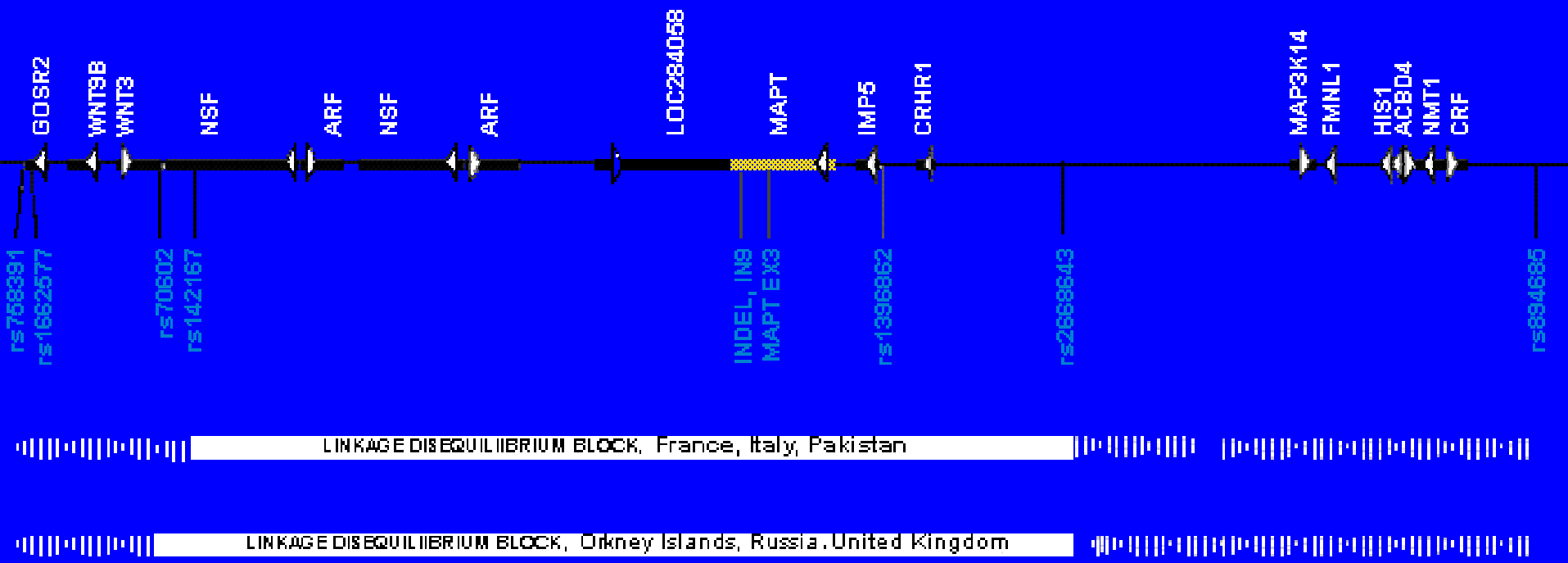
# Worldwide Distribution of Tau Haplotype



**Worldwide Tau H1/H2 Distribution**

| No. | Population | H2 (%) | H1 (%) |
|---|---|---|---|
| 1 | Adygei | 21 | 79 |
| 2 | Balochi | 10 | 90 |
| | Brahui | | |
| | Makrani | | |
| | Sindhi* | | |
| 3 | Bantu | 0 | 100 |
| 4 | Basque | 27 | 73 |
| 5 | Bedouin* | 24 | 76 |
| | Druze | | |
| | Palestinian | | |
| 6 | Bergamo | 29 | 71 |
| 7 | Biaka Pygmy* | 3 | 97 |
| 8 | Burusho | 7 | 93 |
| | Hazara | | |
| | Kalash | | |
| | Pathan | | |
| 9 | Cambodian | 0 | 100 |
| 10 | Colombia | 0 | 100 |
| 11 | Chimmora | 0 | 100 |
| 12 | Dai (minority) | 0 | 100 |
| | Lahu (minority) | | |
| | Naxi (minority) | | |
| 13 | Daur (minority) | 0 | 100 |
| 14 | French (various regions) | 17 | 83 |
| 15 | Finnish Population | 8 | 92 |
| 16 | Han* | 6 | 94 |
| 17 | Hezhen (minority)* | 0 | 100 |
| | Oroqen (minority)* | | |
| | Tu (minority) | | |
| 18 | Japanese* | 0 | 100 |
| 19 | Karitiana (relative pairs) | 0 | 100 |
| 20 | Mandenka* | 4 | 96 |
| 21 | Maya (relative pairs) | 4 | 96 |
| 22 | Mbuti Pygmy* | 3 | 97 |
| 23 | Miaozu (Miao)(minority) | 0 | 100 |
| | Uygur (minority) | | |
| | Xibo (minority) | | |
| 24 | Mongola (minority)* | 5 | 95 |
| 25 | Mozabite | 13 | 87 |
| 26 | NAN Melanesian | 0 | 100 |
| 27 | Orcadian | 28 | 72 |
| 28 | Papuan* | 0 | 100 |
| 29 | Pima (relative pairs) | 0 | 100 |
| 30 | Russian | 10 | 90 |
| 31 | San | 0 | 100 |
| 32 | Sardinian | 29 | 71 |
| 33 | She (minority) | 0 | 100 |
| | Tujia (minority) | | |
| | Yizu (Yi) (minority) | | |
| 34 | Surui (relative pairs) | 0 | 100 |
| 35 | Tuscan | 31 | 69 |
| 36 | Yakut* | 4 | 96 |
| 37 | Yoruba | 0 | 100 |

# Results




- LD extends almost the same distance in all populations (1.6Mb)
  - Some breakdown at the teleomeric edge

# Inversion

ARTICLES

nature genetics

## A common inversion under selection in Europeans

Hreinn Stefansson[1,3], Agnar Helgason[1,3], Gudmar Thorleifsson[1], Valgerdur Steinthorsdottir[1], Gisli Masson[1], John Barnard[2], Adam Baker[1], Aslaug Jonasdottir[1], Andres Ingason[1], Vala G Gudnadottir[1], Natasa Desnica[1], Andrew Hicks[1], Arnaldur Gylfason[1], Daniel F Gudbjartsson[1], Gudrun M Jonsdottir[1], Jesus Sainz[1], Kari Agnarsson[1], Birgitta Birgisdottir[1], Shyamali Ghosh[1], Adalheidur Olafsdottir[1], Jean-Baptiste Cazier[1], Kristleifur Kristjansson[1], Michael L Frigge[1], Thorgeir E Thorgeirsson[1], Jeffrey R Gulcher[1], Augustine Kong[1,3] & Kari Stefansson[1,3]

www.nature.com/naturegenetics

# Haplotype dating

- Inversion/LD block implies distinct evolutions for each haplotype because there is suppressed recombination between the two haplotype clades
- Performed 2 analyses to determine the evolutionary distance between H1 and H2

# Comparison of chimp and human sequence

| Position | dbSNP ID | Chimp | H1 | H2 |
|---|---|---|---|---|
| 41301910 | rs1078830 | **C** | T | **C** |
| 41307507 | rs2055794 | **A** | G | **A** |
| 41333623 | rs1864325 | **C** | **C** | T |
| 41334330 | rs1560310 | **G** | **G** | A |
| 41336326 | rs3885796 | C | T | G |
| 41354620 | rs767058 | **C** | **C** | G |
| 41409284 | rs2217394 | **G** | A | **G** |
| 41411483 | rs754512 | **T** | **T** | A |
| 41429726 | rs1052553 | **G** | A | **G** |
| 41432502 | sthQ7R | **G** | A | **G** |
| 41442488 | *ins/del9* | + | + | - |
| 41445400 | rs733966 | **C** | **C** | T |
| 41457408 | rs9468 | **C** | T | **C** |
| 41461242 | rs7521 | **G** | A | **G** |

- neither haplotype is the founder of the other, since chimp at some level resembles either haplotype
- **H1/H2 diverged from ~3 million years ago (also DeCode and Antwerp data)**

# Slippage of dinucleotide repeat markers

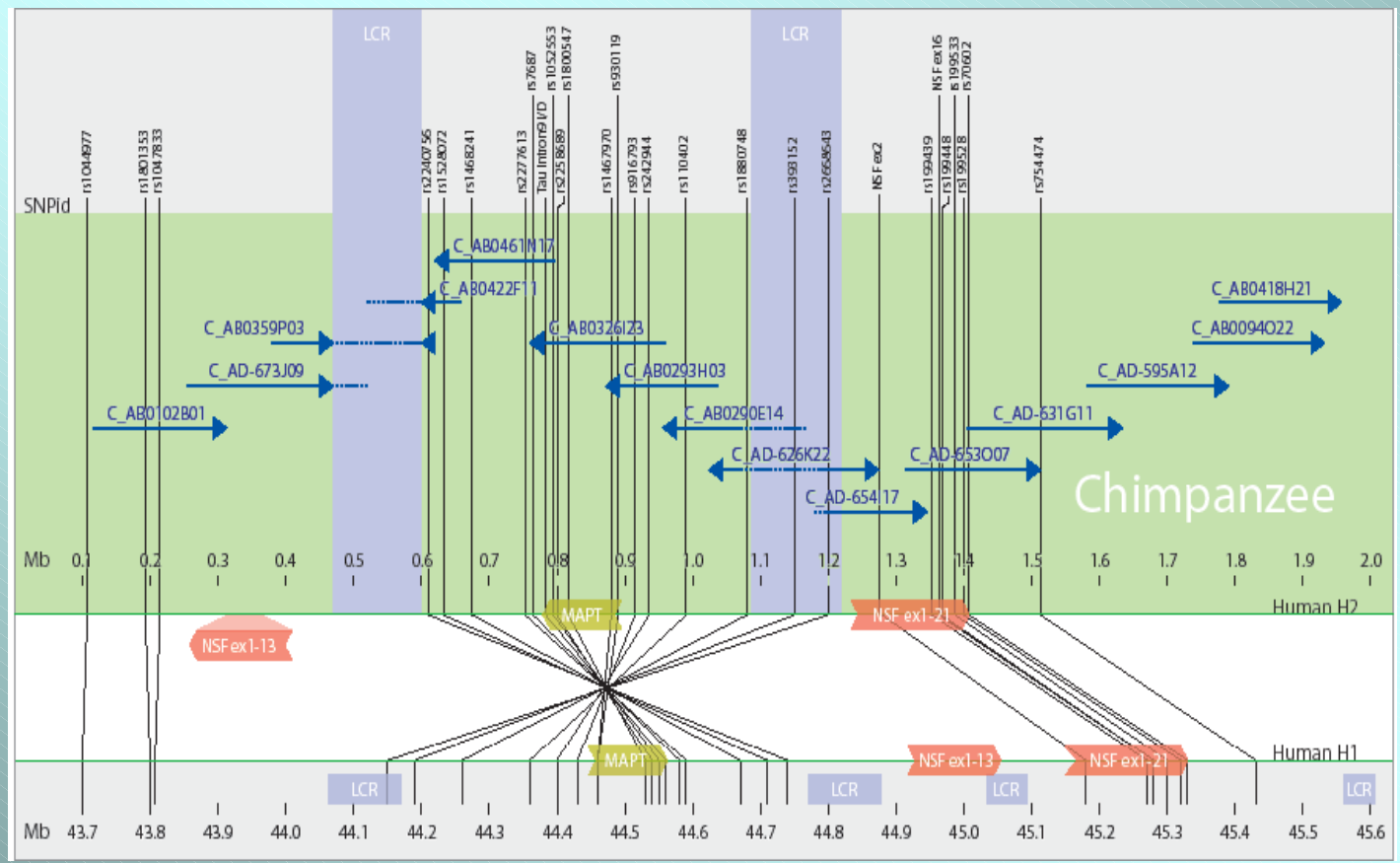
| Marker name | Location | Major Allele Size | Major allele frequency | Predicted Age in Generations (Years) |
|---|---|---|---|---|
| Tau Hap 2 | 44752820 | 182 | 75% | 513 (12,825) |
| Tau Hap 3 | 45289761 | 183 | 74% | 542 (13,550) |
| Tau Hap 5 | 44423308 | 258 | 86% | 267 (6,675) |
| Tau Hap 6 | 44439826 | 496 | 87% | 243 (6,075) |
| Tau Hap 7 | 44475319 | 240 | 62% | 868 (21,700) |

- Assuming that H2 is a single founder event and an average of 25 generations for each slippage event, typed 13 CEPH H2 homozygotes with microsatellite markers mapping to the region.
- **The age of H2 in H. sapiens is ~10,000-30,000 years based on distribution and slippage.**

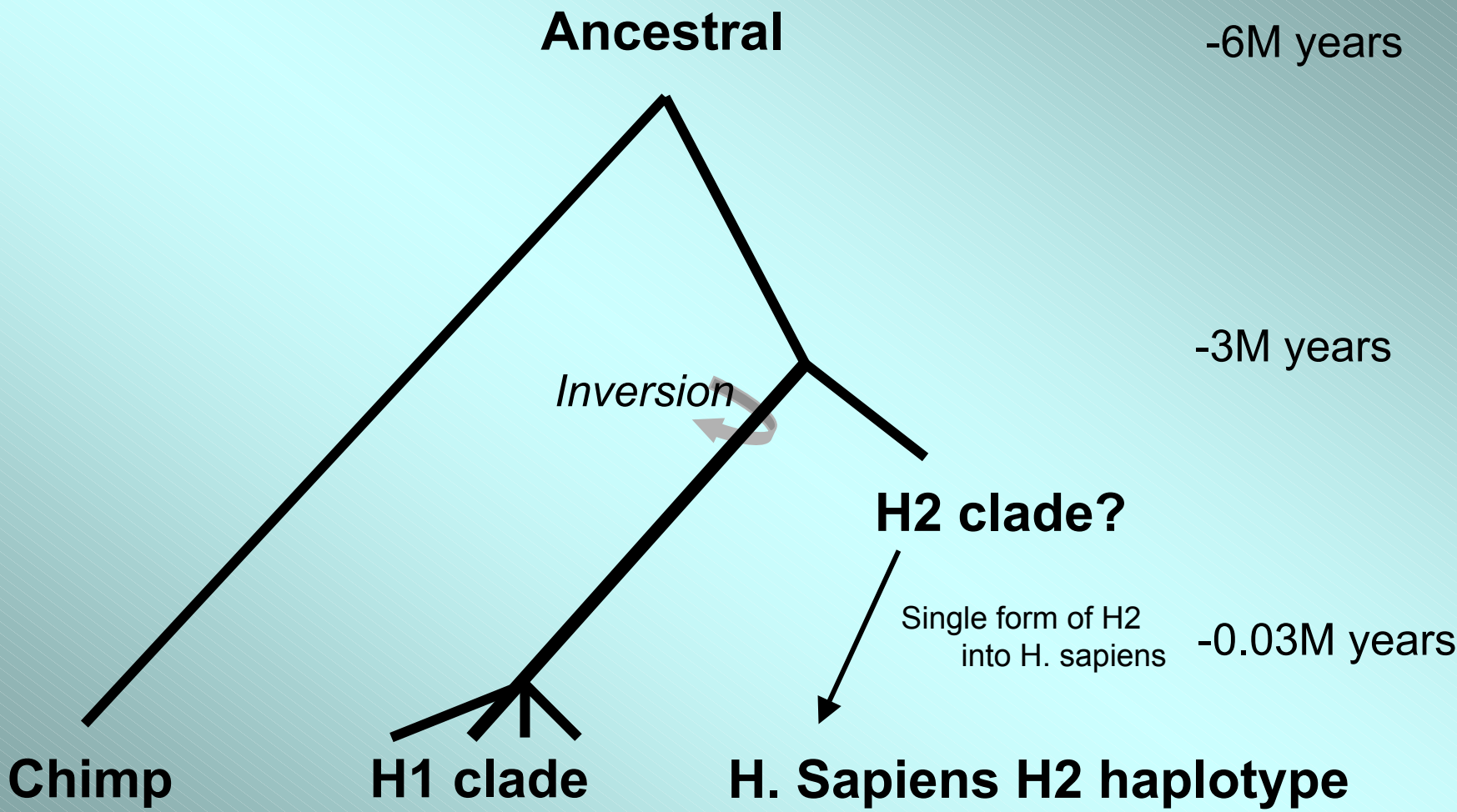
# H2 has been re-introduced once exclusively into European *H. sapiens* populations

- Contradictory evolutionary evidence:
  - H1 and H2 diverged ~ 3M years ago
  - Yet, based on slippage analysis H2 is a recent haplotype within *H. sapiens* (10-30K years ago)
- Further evidence:
  - H2 haplotype has reduced diversity compared with H1
  - H2 distribution reflects the spread of European populations and is not seen within Asian and most African chromosomes

# H1, not H2 is Inverted!

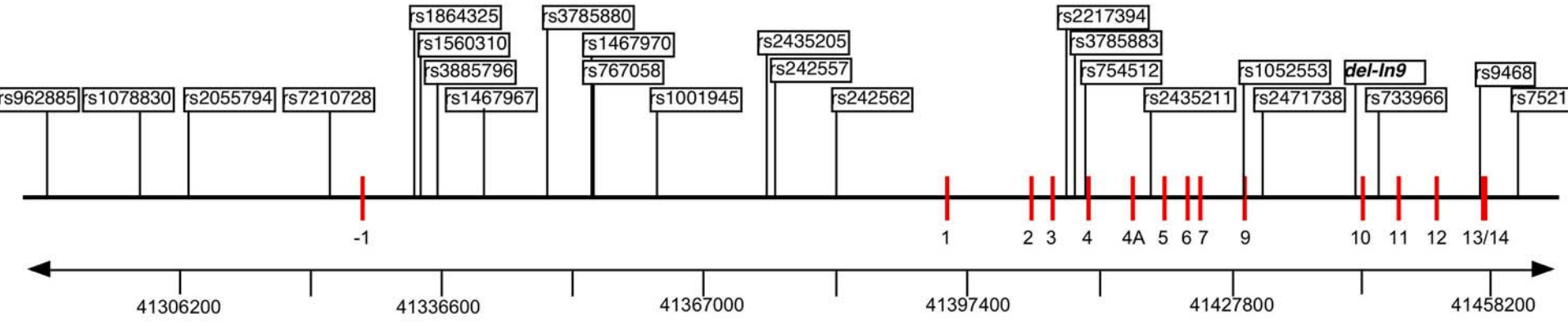


# Model of the evolution of the MAPT locus



*"Neanderthals have moved in next door!"*

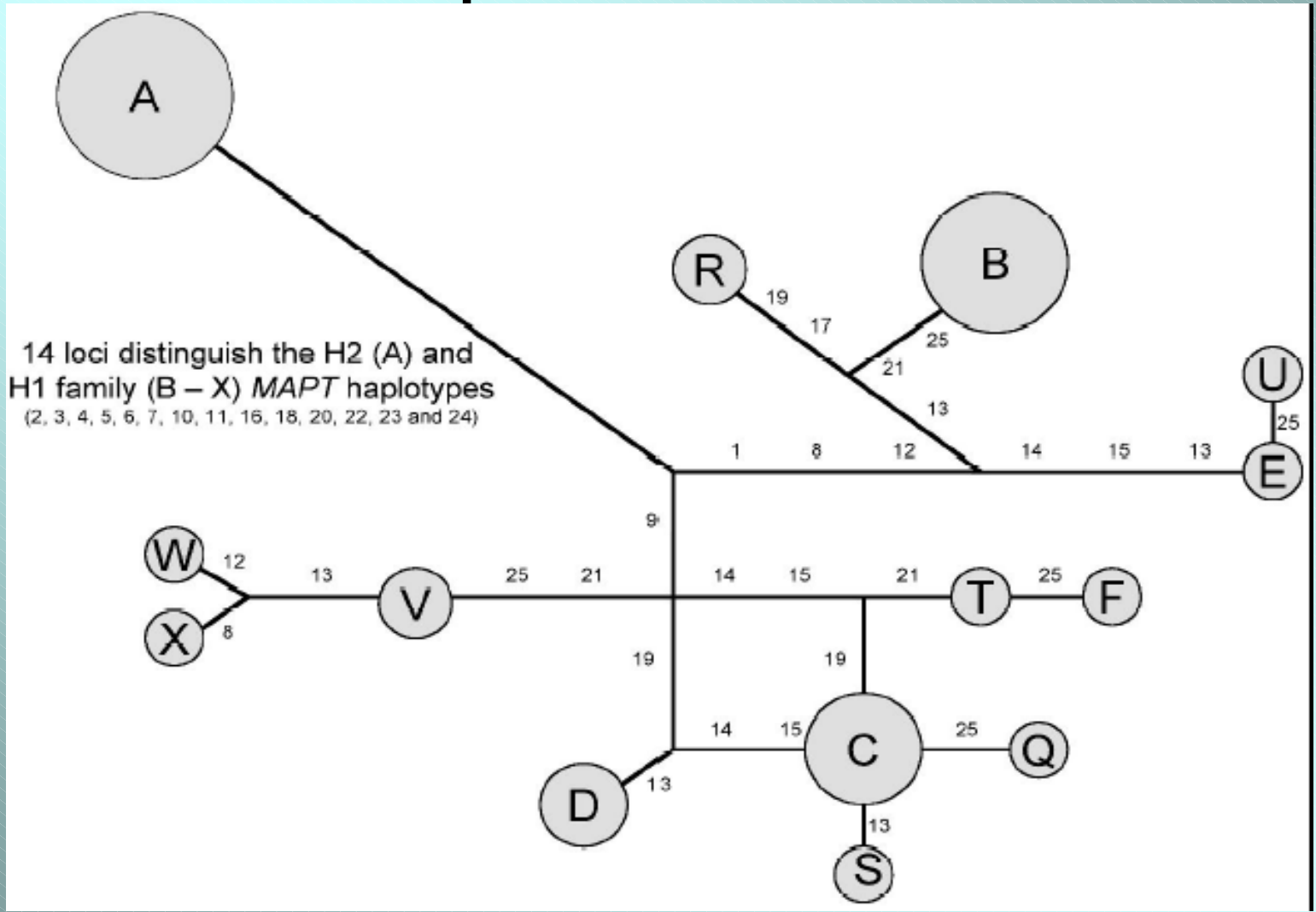
# Tagging SNPs Selection



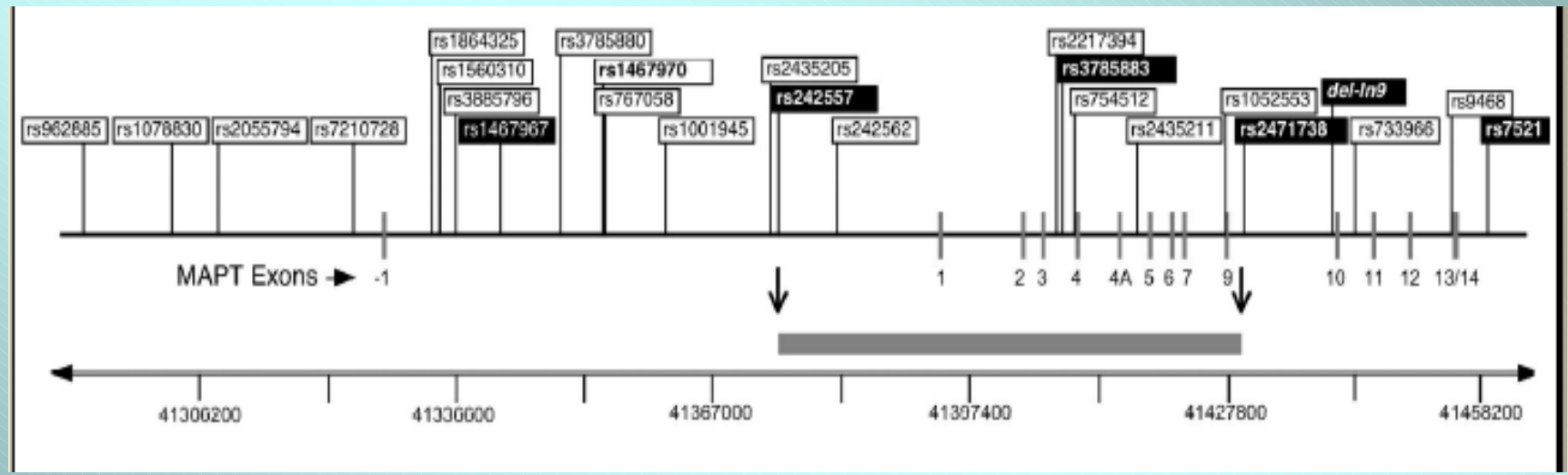

- 25 SNPs spanning the entire locus were selected from the CEPH database (www.hapmap.org)

- Using the program Tagit (popgen.biol.ucl.ac.uk/software) 5 SNPs were identified that captured the haplotype diversity of the *MAPT* locus

# More Complex than Just H1/H2



# Dissecting H1 further…

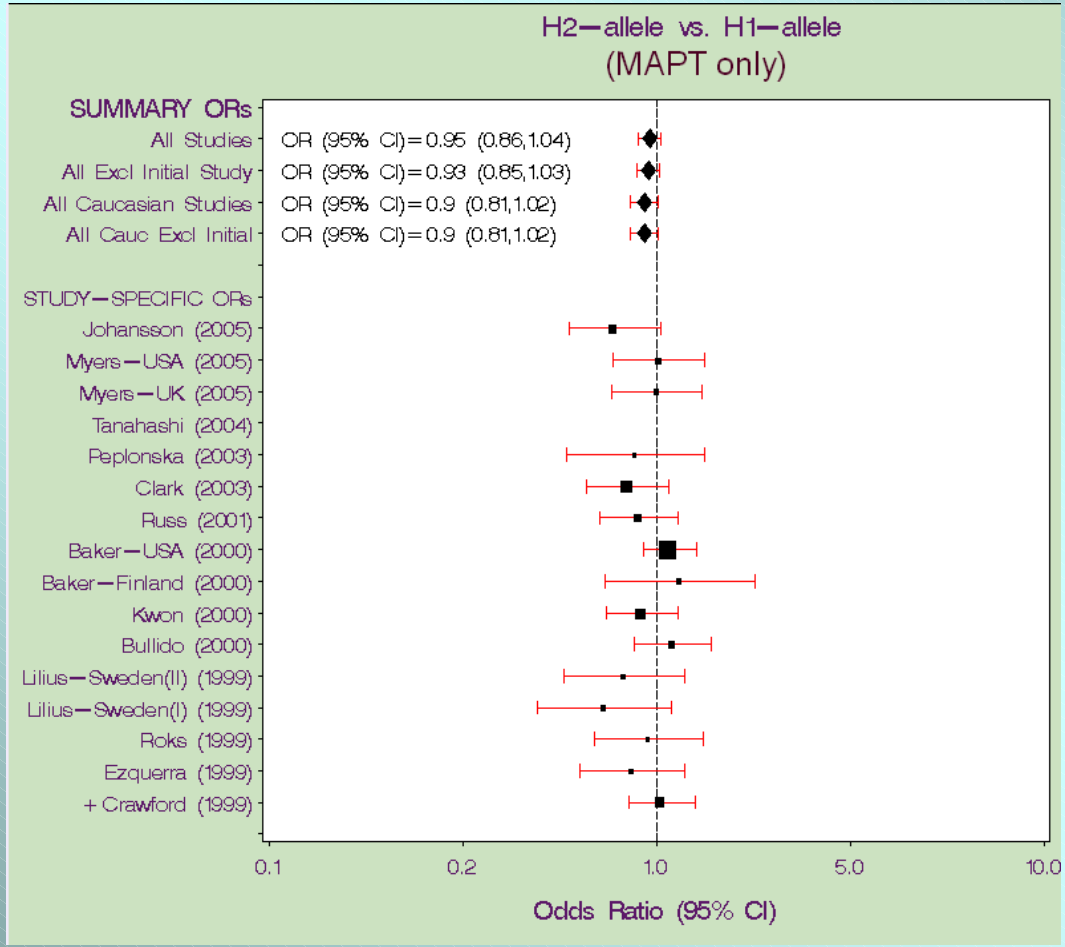


# Associations with PSP… and AD

| | **Controls** | **Alzheimer Disease** | **PSP** |
|---|---|---|---|
| H2a | 23 | 23 | 6 |
| H1b | 13 | 15 | 14 |
| **H1c** | **9** | **14** | **24** |
| Others | 55 | 48 | 56 |
| (n) ‘p’ | (272) | (360)<br>**0.006** | (321)<br>**0.000006** |

# *MAPT* and meta-analysis

http://www.alzforum.org/res/com/gen/alzgene/default.asp



# Primary Tauopathies

- Mutations in the opening reading frame or in the exon 10 splice area cause mendelian tau disease (FTDP-17): the precise tau pathology is largely dependent on the mutation.
- Sporadic tangle diseases, PSP and CBD are predisposed to by the tau H1 haplotype.
- Weaker association of same haplotypes with Alzheimer's disease.
- Other sporadic tangle diseases are either not assessed (too rare) or occur in populations without an H2 allele (Guam).
- Not clear whether haplotype association reflects differences in splicing or in expression (though overexpressing mice get tangles).

# Diseases with *only* Lewy Bodies

- Parkinson's disease
- Lewy body dementia

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, Aglaia Athanassiadou, Theodore Papapetropoulos, William G. Johnson, Alice M. Lazzarini, Roger C. Duvoisin, Giuseppe Di Iorio, Lawrence I. Golbe, Robert L. Nussbaum

# The New Mutation, E46K, of α-Synuclein Causes Parkinson and Lewy Body Dementia

Juan J. Zarranz, MD, PhD,[1] Javier Alegre, MD,[2] Juan C. Gómez-Esteban, MD,[1] Elena Lezcano, PhD,[1] Raquel Ros, PhD,[2] Israel Ampuero, PhD,[2] Lídice Vidal, PhD,[2] Janet Hoenicka, PhD,[2] Olga Rodriguez, MD,[3] Begoña Atarés, MD,[4] Verónica Llorens, MD,[5] Estrella Gomez Tortosa, MD, PhD,[2,6] Teodoro del Ser, MD, PhD,[7] David G. Muñoz, MD, PhD,[2] and Justo G. de Yebenes, MD, PhD[2,6]

**Familial parkinsonism and dementia with cortical and subcortical Lewy bodies is uncommon, and no genetic defect has been reported in the previously described sibships. We present a Spanish family with autosomal dominant parkinsonism, dementia, and visual hallucinations of variable severity. The postmortem examination showed atrophy of the substantia nigra, lack of Alzheimer pathology, and numerous Lewy bodies which were immunoreactive to α-synuclein and ubiquitin in cortical and subcortical areas. Sequencing of the α-synuclein gene showed a novel, nonconservative E46K mutation in heterozygosis. The E46K mutation was present in all affected family members and in three young asymptomatic subjects, but it was absent in healthy and pathological controls. The novel mutation, that substitutes a dicarboxylic amino acid, glutamic acid, with a basic amino acid such as lysine in a much conserved area of the protein, is likely to produce severe disturbance of protein function. Our data show that, in addition to the previously described hereditary α-synucleinopathies, dementia with Lewy bodies is related to mutation of α-synuclein.**

Ann Neurol 2004;55:164–173

Human Molecular Genetics
Aug. 2001

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

Matt Farrer, Demetrius M. Maraganore[1], Paul Lockhart, Andrew Singleton, T.G. Lesnick[2], Mariza de Andrade[2], Andrew West, Rohan de Silva[3], John Hardy* and Dena Hernandez

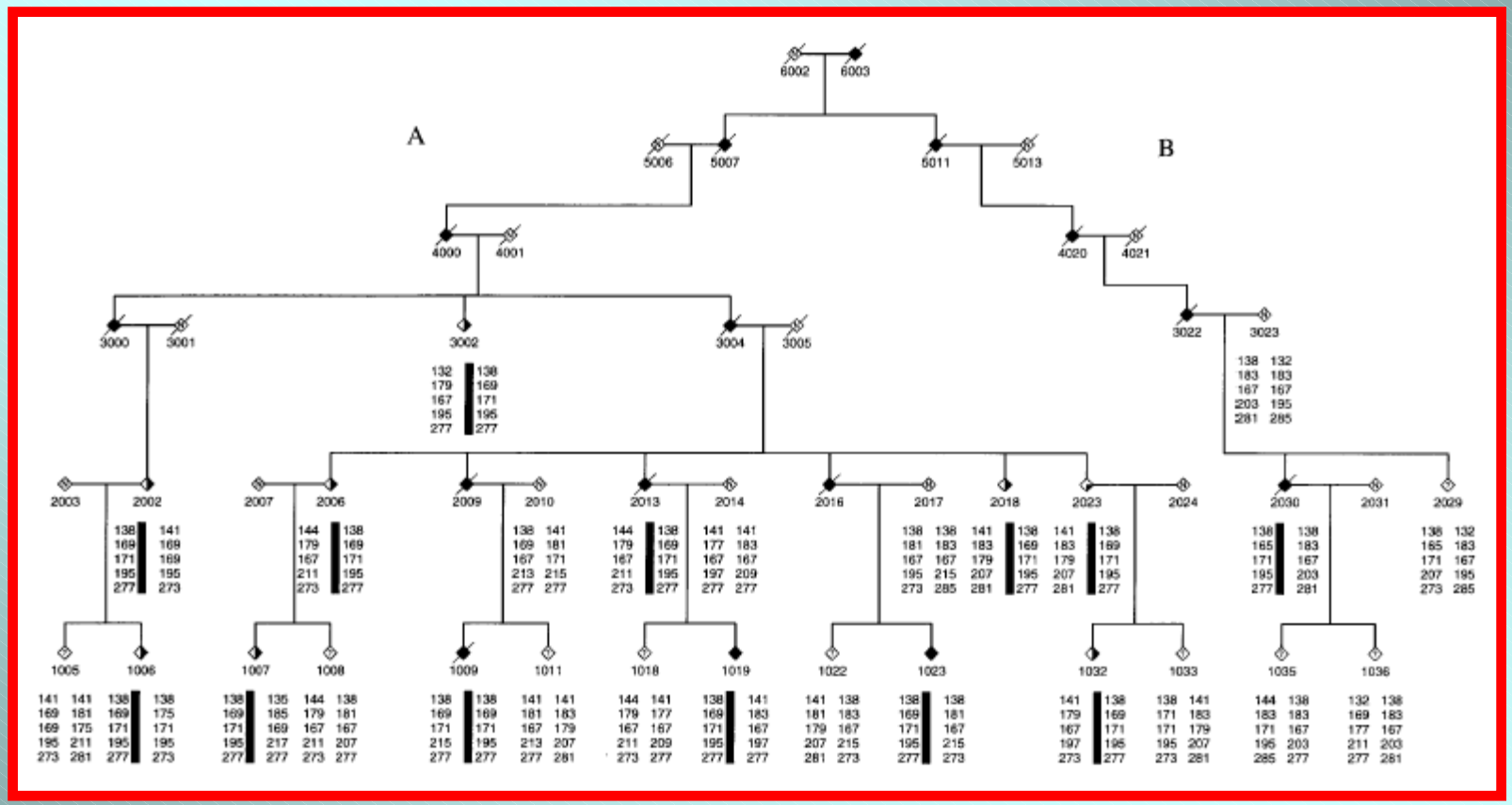
Hum Genet (2003) 113 : 426–431
DOI 10.1007/s00439-003-1002-9

ORIGINAL INVESTIGATION

Ornit Chiba-Falek · Jeffrey W. Touchman
Robert L. Nussbaum

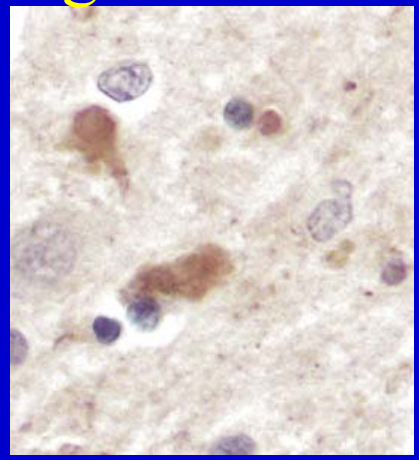
## Functional analysis of intra-allelic variation at NACP-Rep1 in the α-synuclein gene

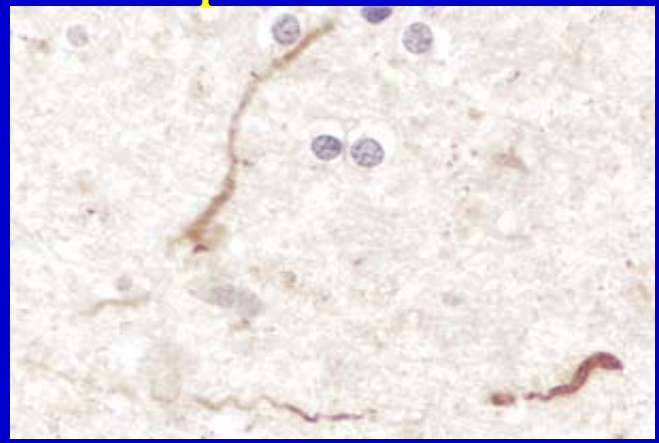
# Iowa Kindred Structure



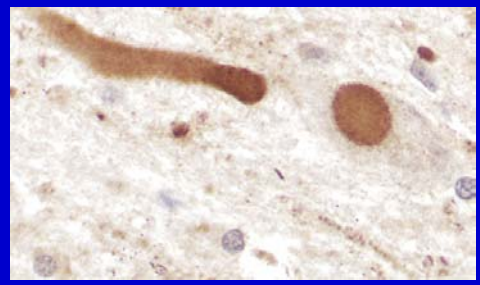
# Diffuse α-synuclein pathologies in male patient: abnormal neuronal and glial inclusions and processes

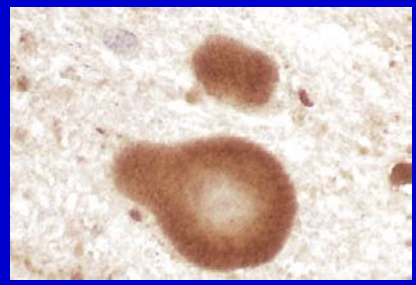
Globus pallidus



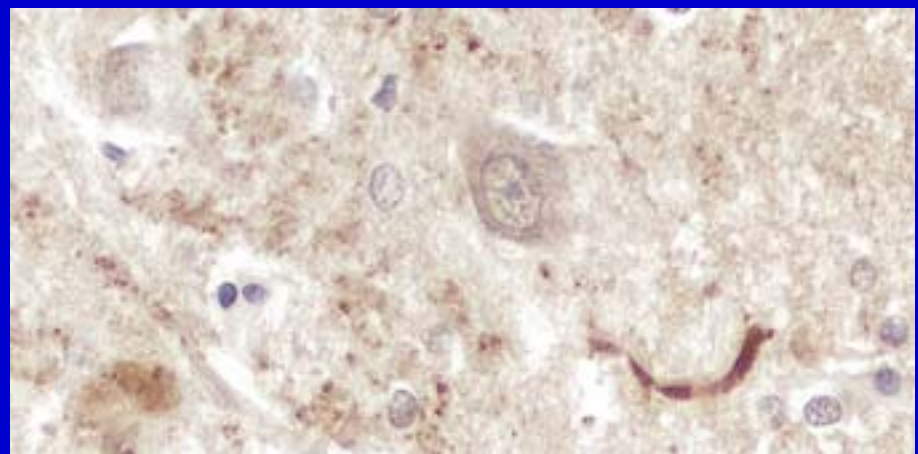


Substantia nigra

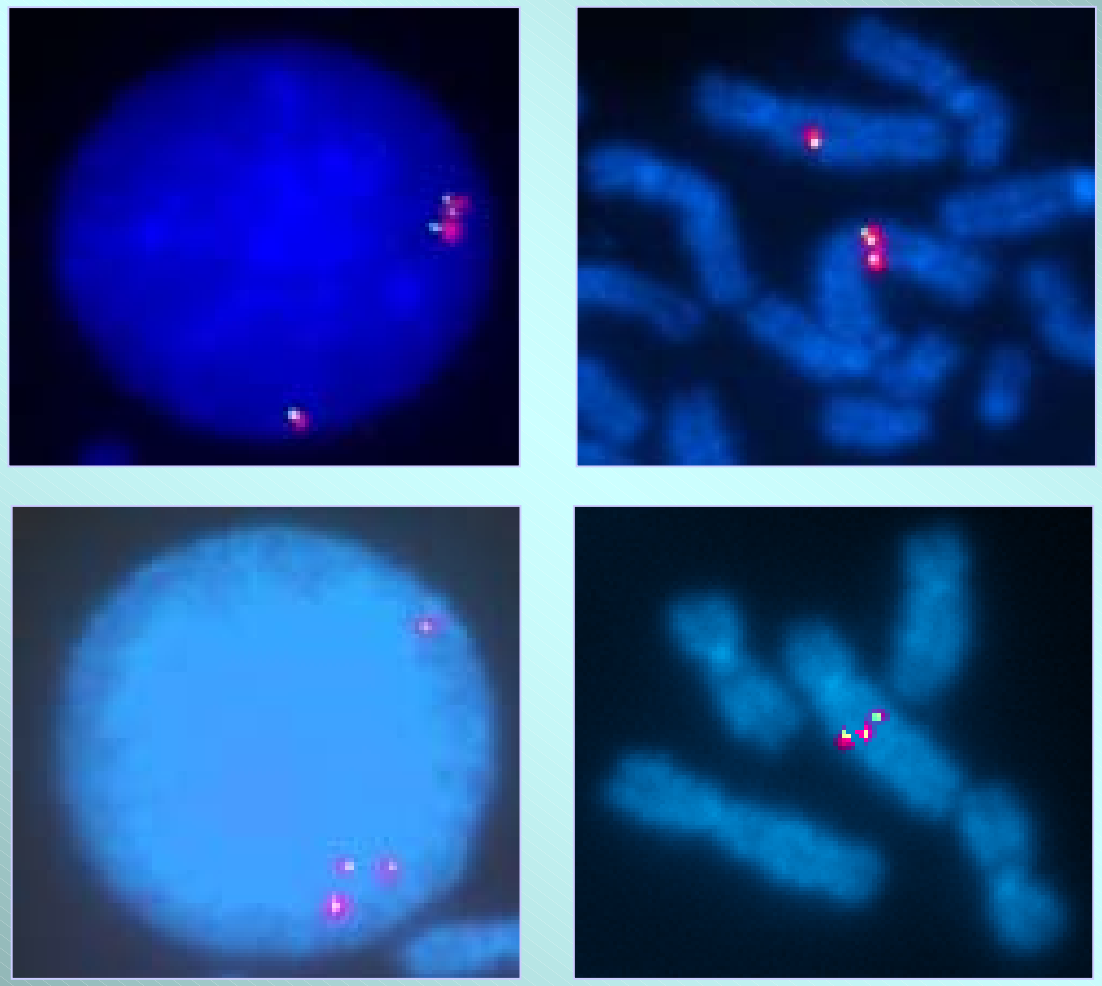




Hippocampus



# Chromosomal Spreads (FISH)



# Lewy Bodies Disease Conclusions

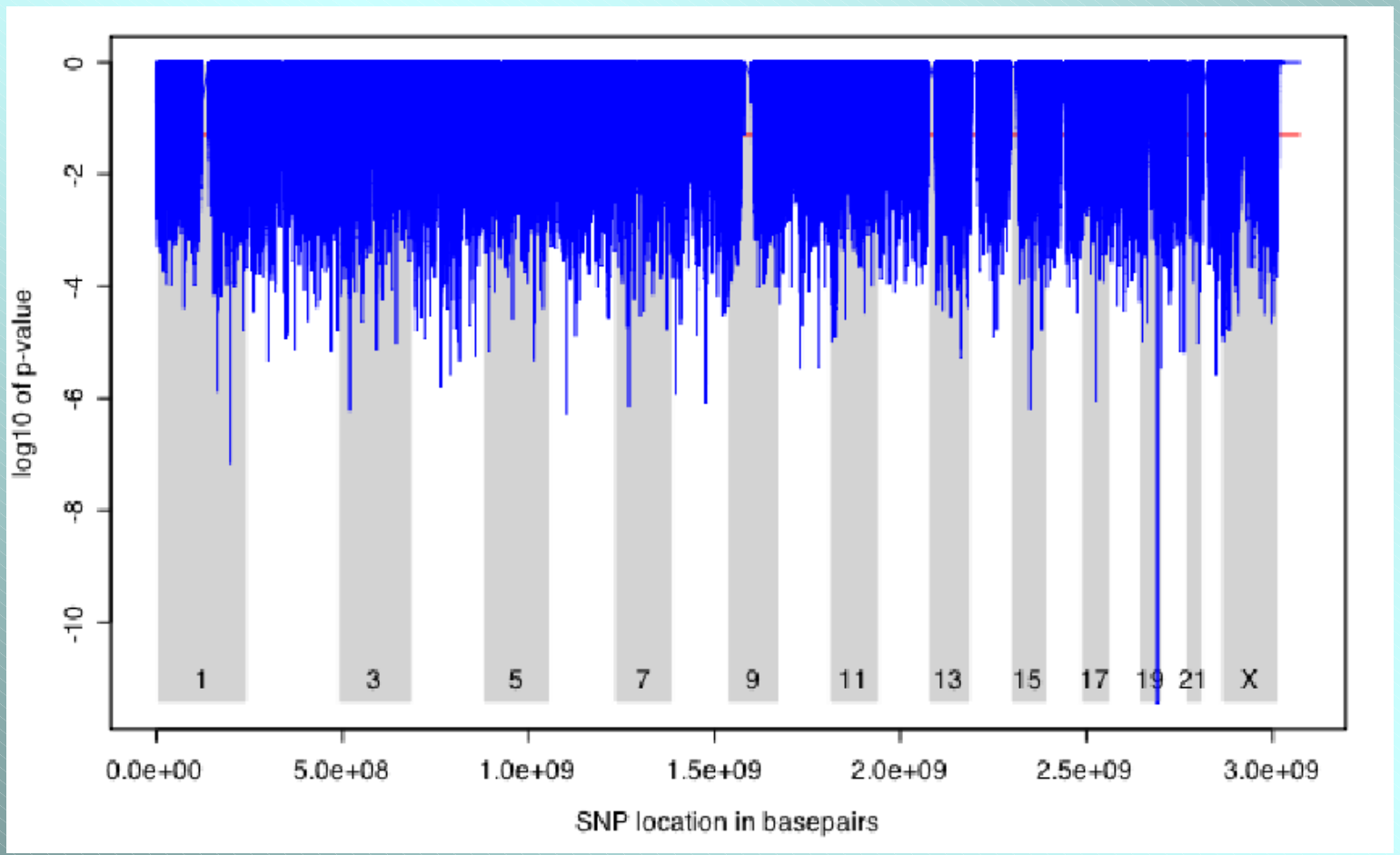
- Mutations in α-synuclein can cause either mendelian Parkinson's disease or Lewy Body dementia, sometimes both in the same family.
- Triplication (overall doubling) of the α-synuclein locus causes disease onset in the 30's (duplication of the locus, causes disease in the 50's)
- Genetic variability in the normal promoter contributes to risk of sporadic disease with high expression promoters being more prone to disease.

# Overall Conclusions

- Analysis of autosomal dominant forms of neurodegenerative diseases in which there is pathological deposition reveal that the causative locus encodes the protein which is deposited (most cases) or the enzymes responsible for the liberation of the deposited peptide (presenilins).
- Normal genetic variability at these same loci contribute to the risk of sporadic forms of these diseases: most likely, high expressors are predisposed to disease.
- Predictions and Implications
  - Deposition is *clearly* important.
  - SOD and sporadic ALS?
  - Genetic variability in degradation may also contribute to risk?

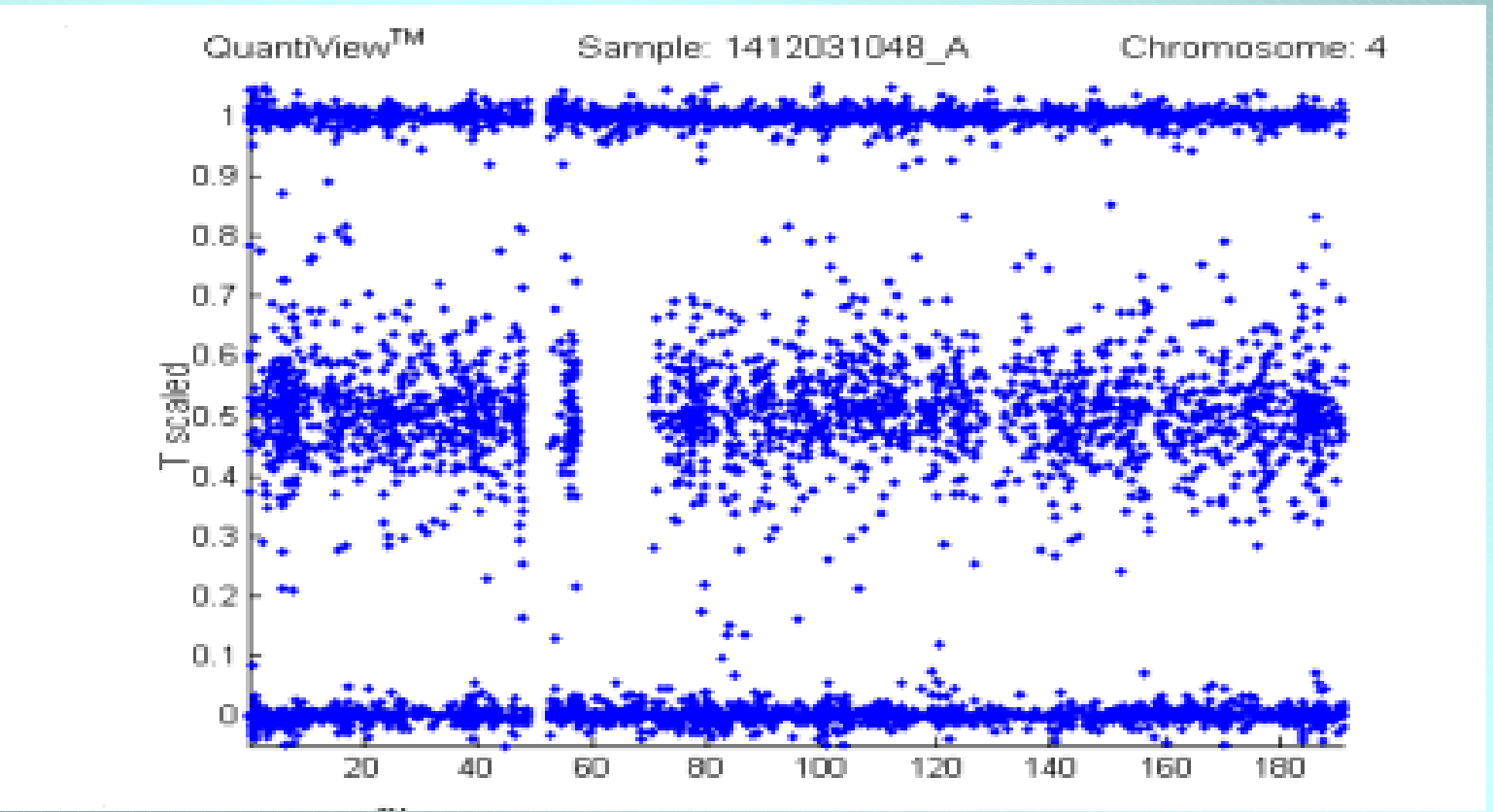
# Whole Genome Study For AD

(presently underpowered ~180 cases and controls)



# Loss of Heterozygosity

## (10% North American Controls Show Evidence for Consanguinity



# Sample Whole Genome Data

## Chromosome 5 Control Male of 65 years