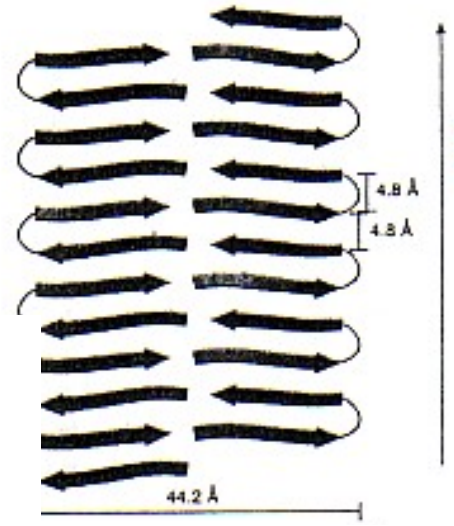
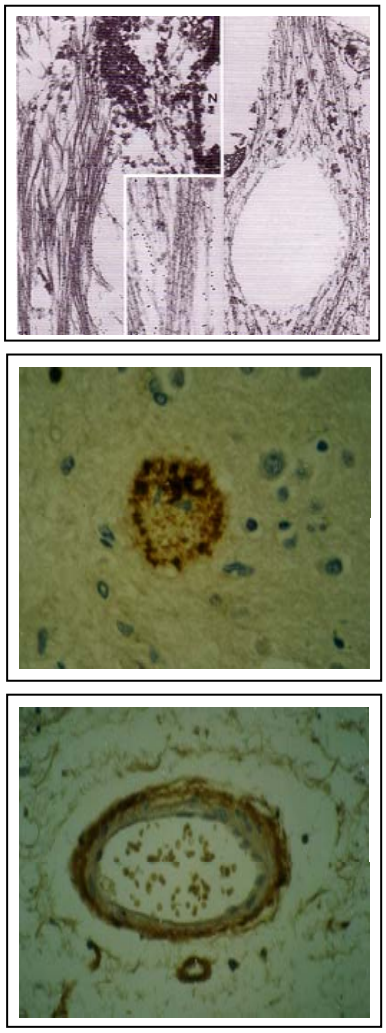
Several proteins accumulate as amyloid in the CNS

Cystatin C variant
Aβ
PrP
Tau
α-synuclein
ABri
ADan
TTR variant
PoliQ?





Human diseases associated with Aβ deposition

Sporadic

- **Alzheimer's disease**
- **Down syndrome**
- **Cerebral amyloid angiopathy**
- **Dementia pugilistica**

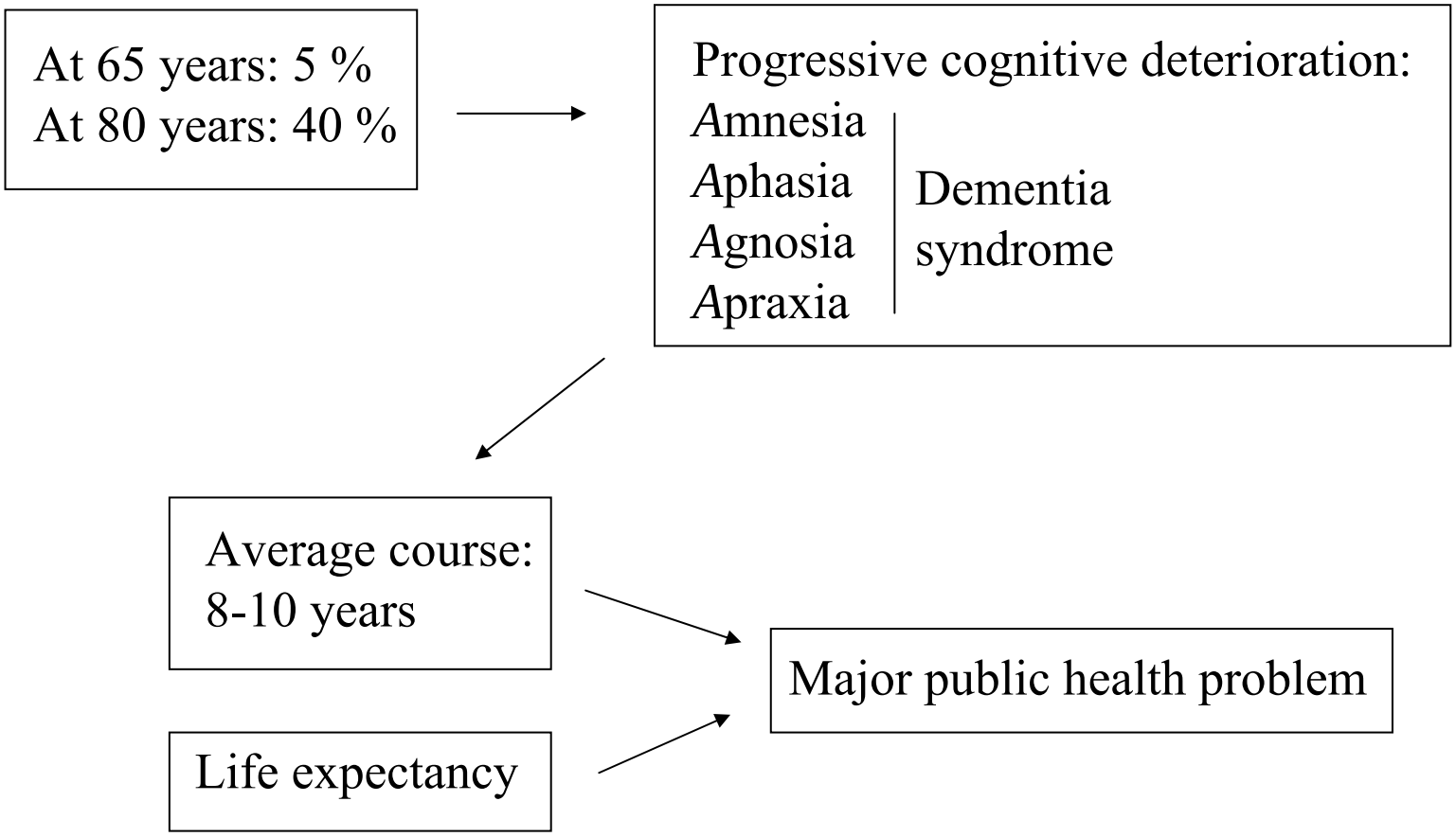
APOE genotype
Chronic trauma
Cholesterol

Familial *(autosomal dominant)*

- **Early-onset Alzheimer's disease**
- **Hereditary cerebral hemorrhage (Dutch and Italian types)**
- **Dementia with amyloid angiopathy (Flemish, Arctic and Iowa types)**

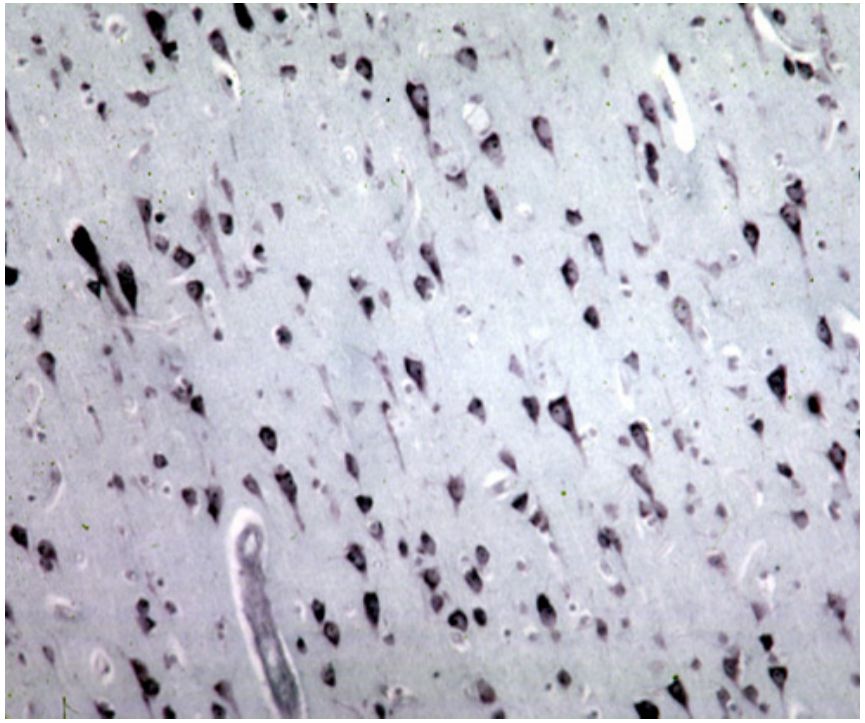
Mutations in APP and Presenilin genes

Alzheimer's disease: the most prevalent form of dementia

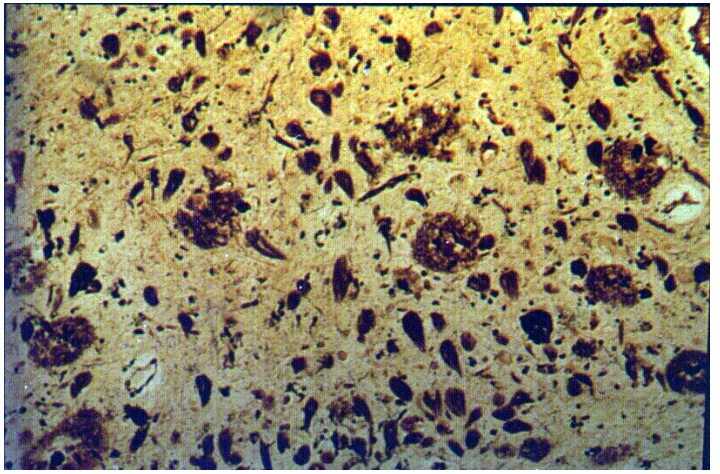


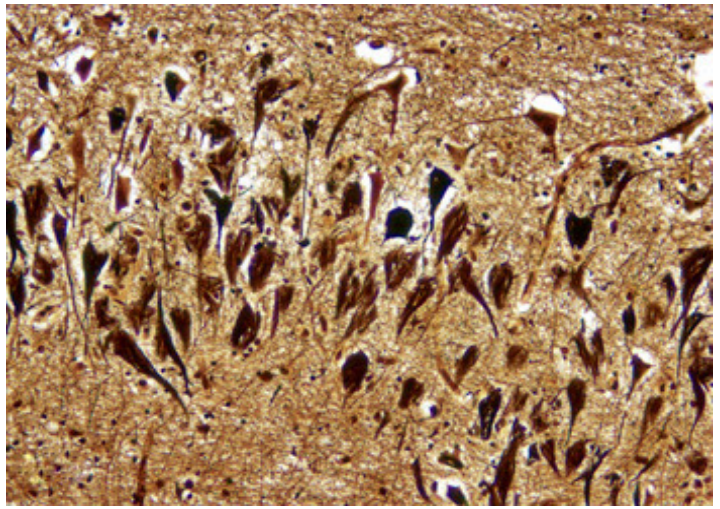
Normal vs Alzheimer histopathology

Normal

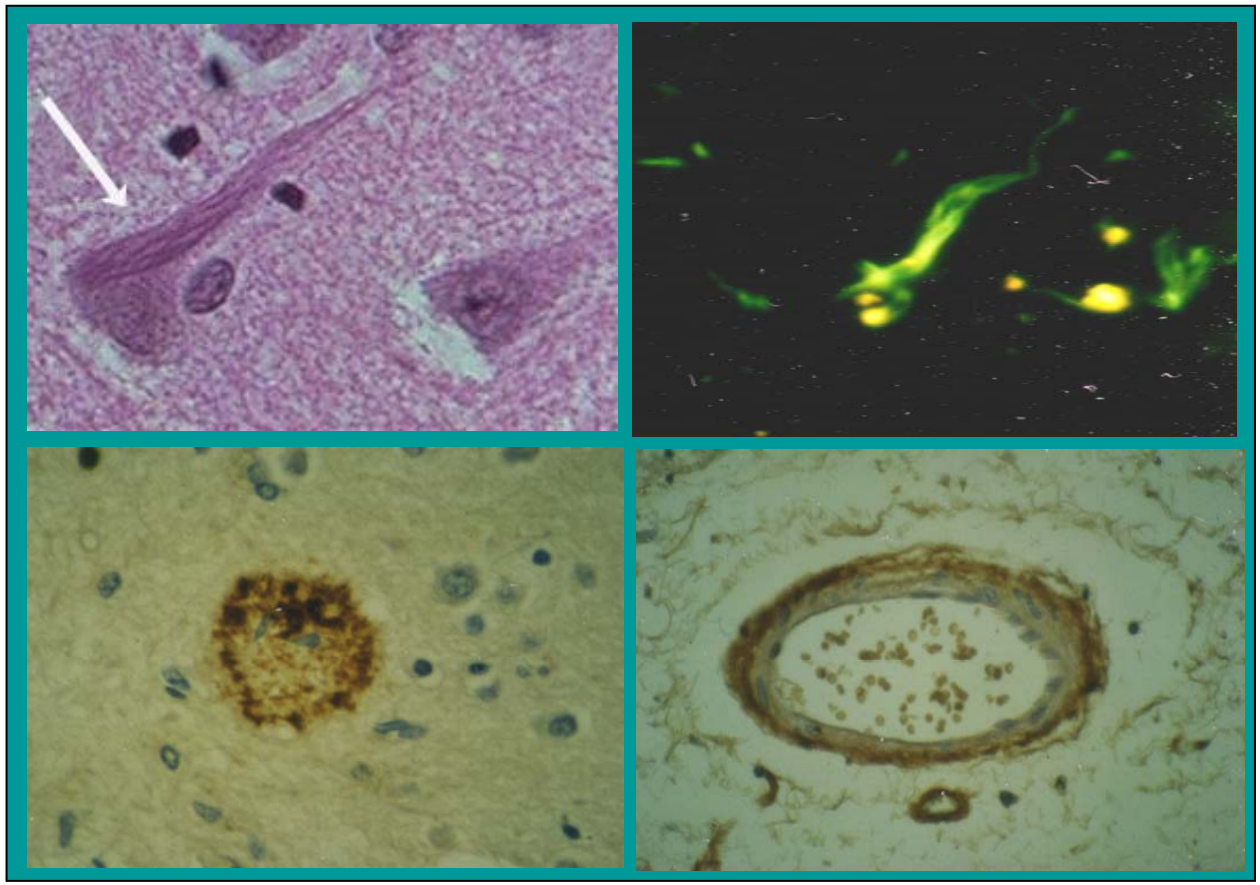


Alzheimer





Abnormal protein deposits in Alzheimer's disease brain: amyloid β and phospho-tau



Alzheimer's disease: distribution of senile plaques

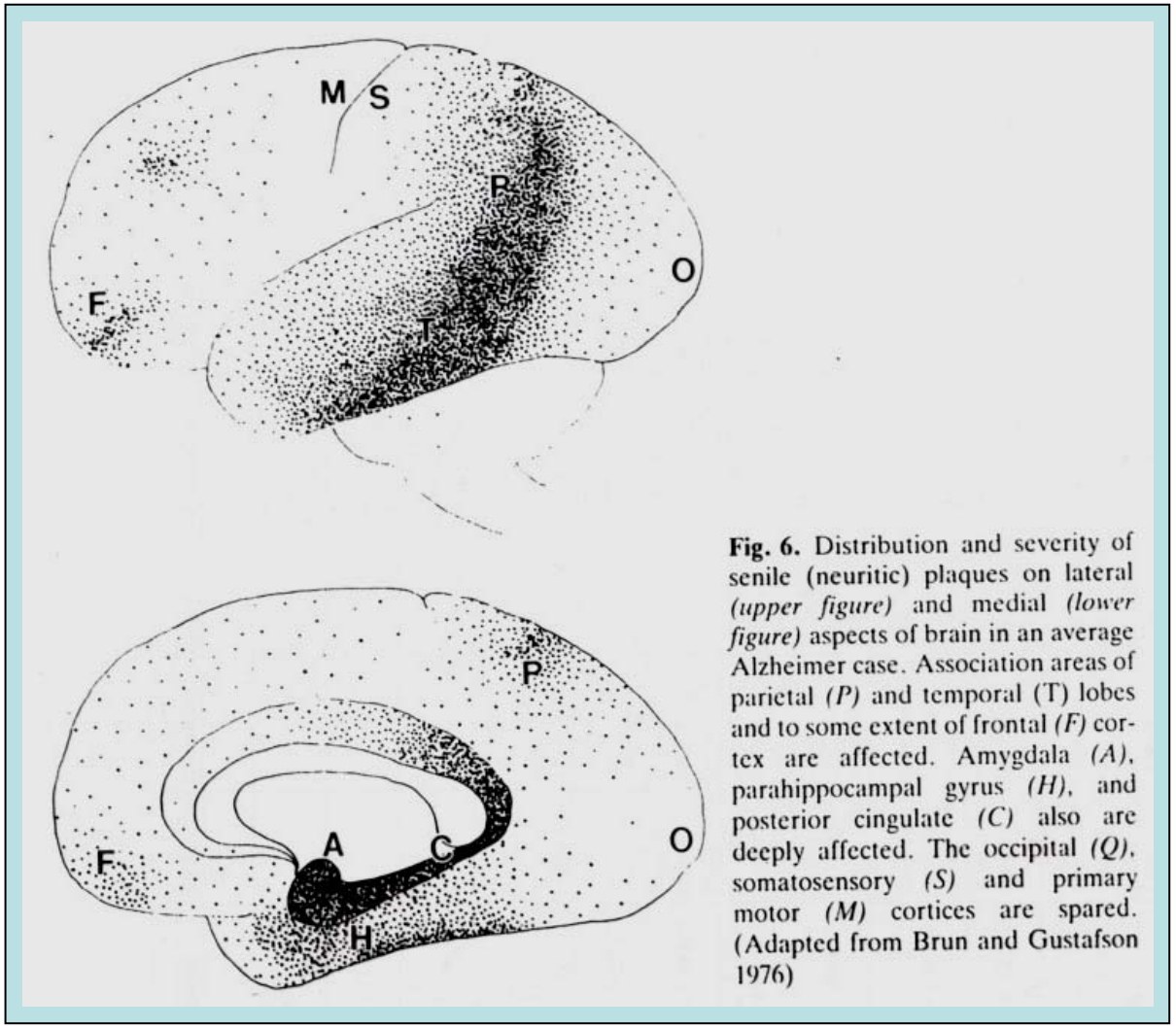
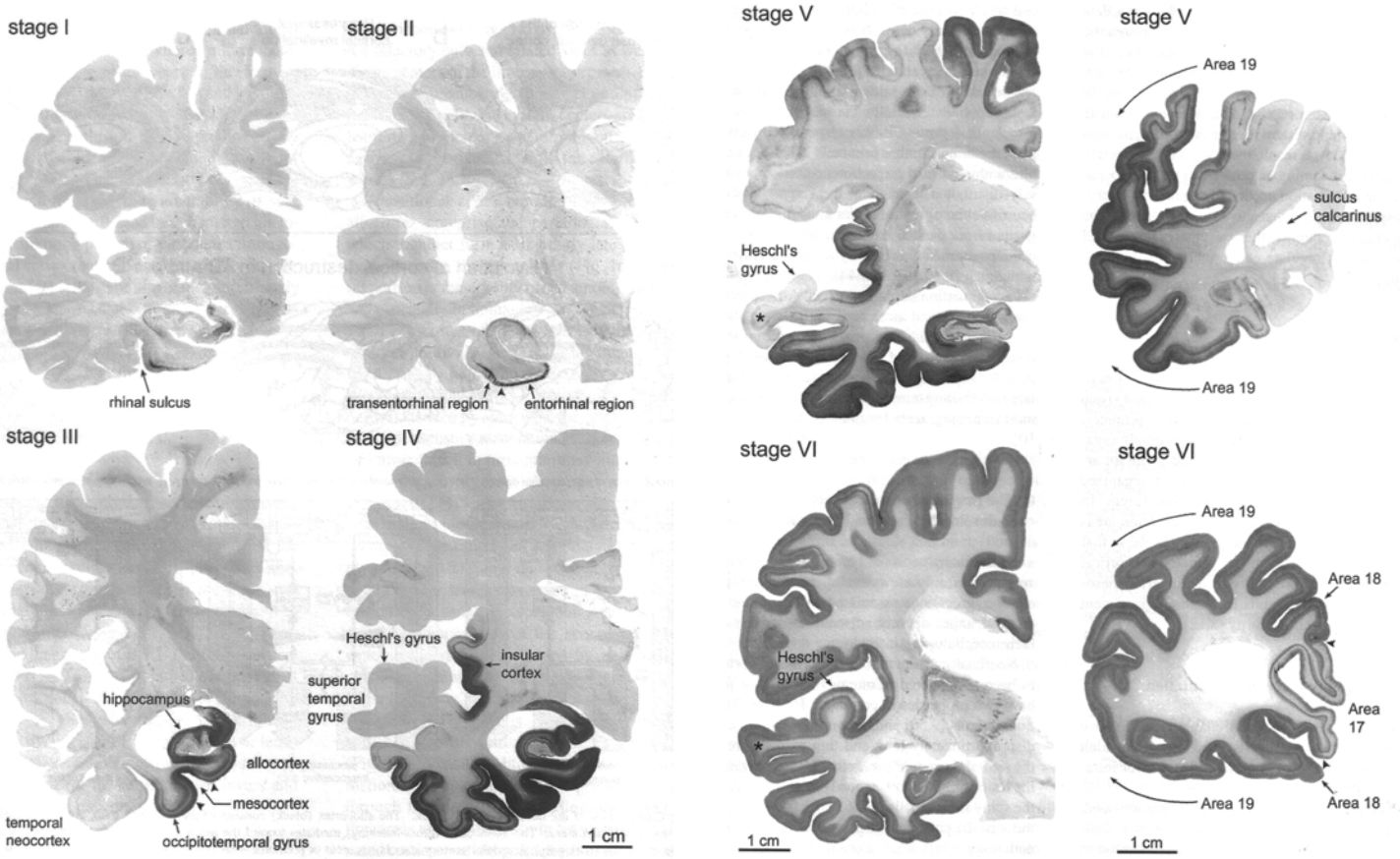
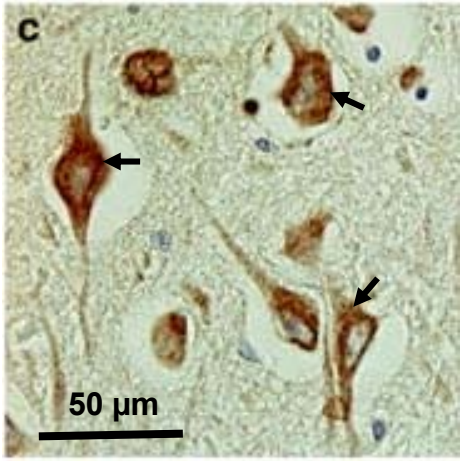


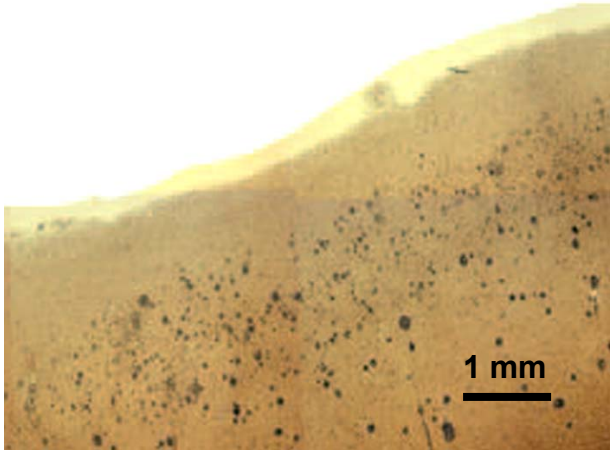
Fig. 6. Distribution and severity of senile (neuritic) plaques on lateral *(upper figure)* and medial *(lower figure)* aspects of brain in an average Alzheimer case. Association areas of parietal *(P)* and temporal (T) lobes and to some extent of frontal *(F)* cortex are affected. Amygdala *(A)*, parahippocampal gyrus *(H)*, and posterior cingulate *(C)* also are deeply affected. The occipital *(Q)*, somatosensory *(S)* and primary motor *(M)* cortices are spared. (Adapted from Brun and Gustafson 1976)

Posssible sequence of neuronal pathology in AD

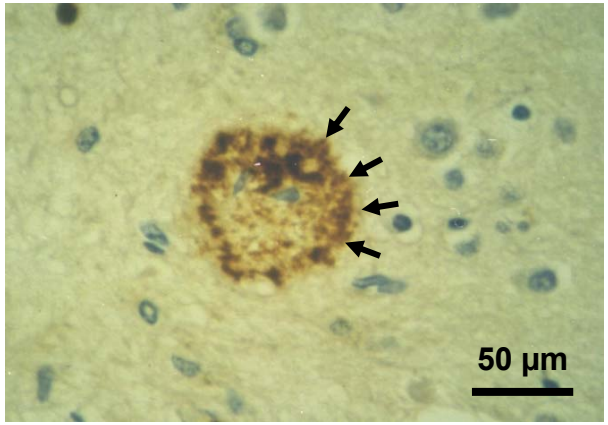


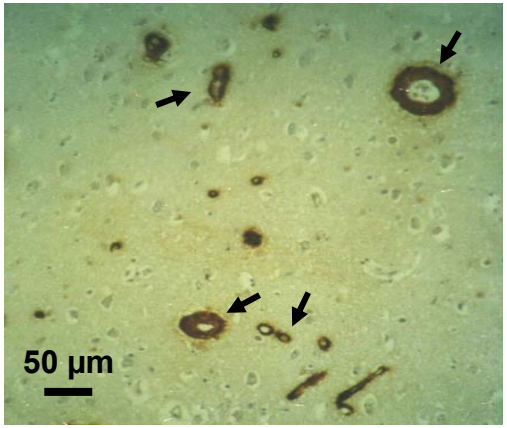
Massive Aβ accumulation in the AD brain

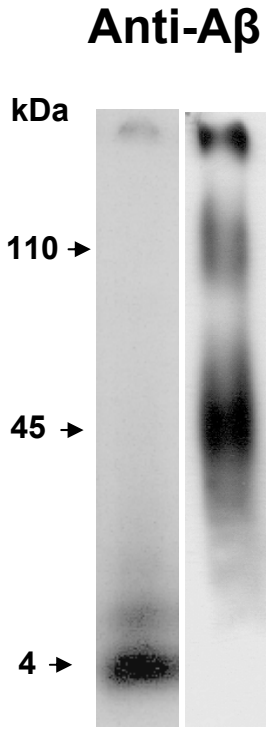




Christensen et al *Acta Neuropathol.* 2010 119: 555



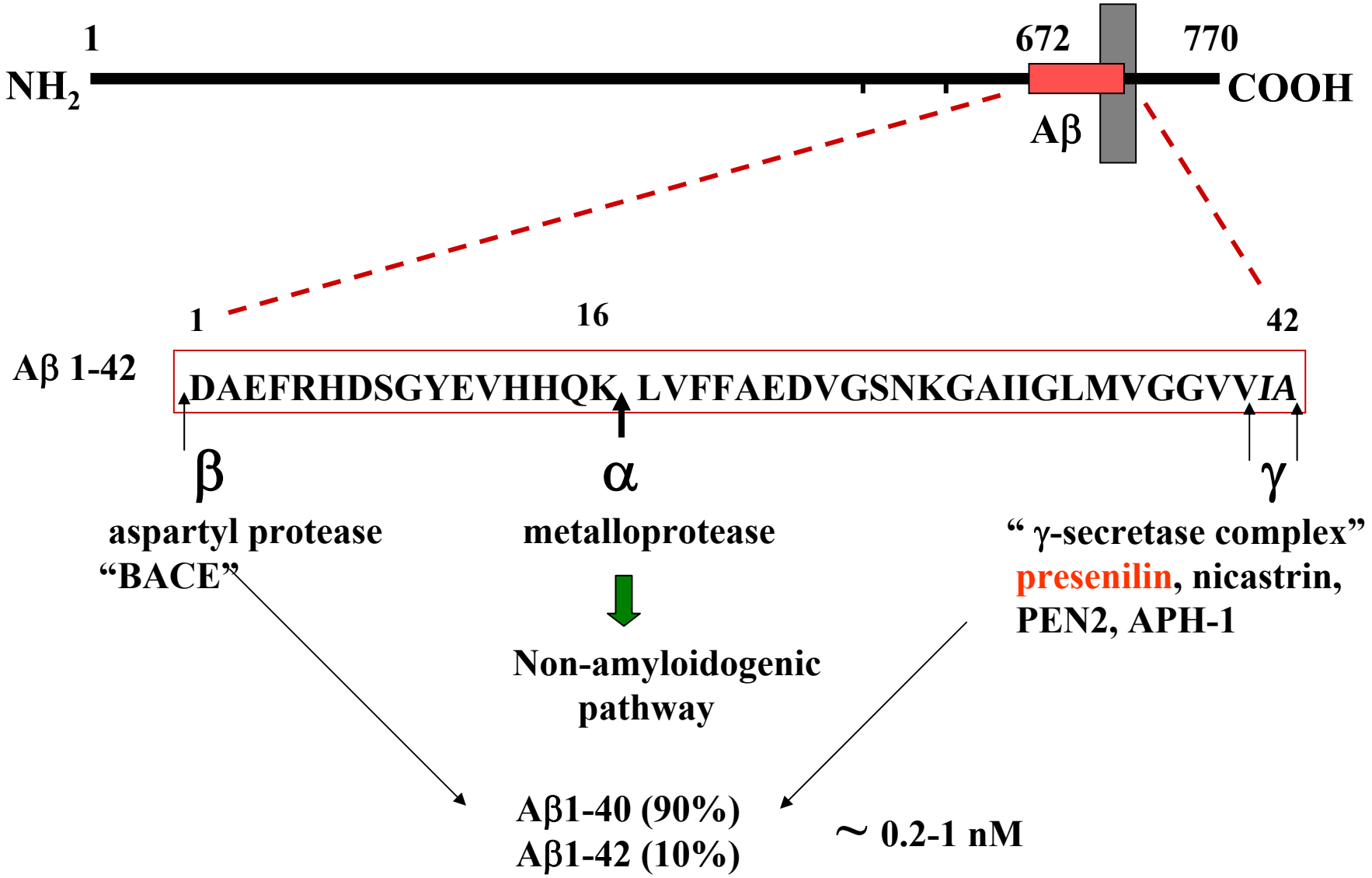




AMYLOID β

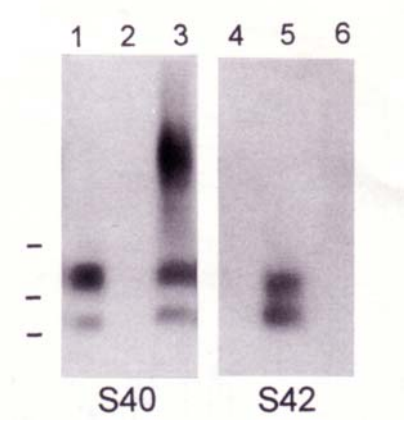
1) Generation
2) Mechanisms of accumulation
3) Possible toxicity

Limited proteolysis of AβPP generates soluble Aβs

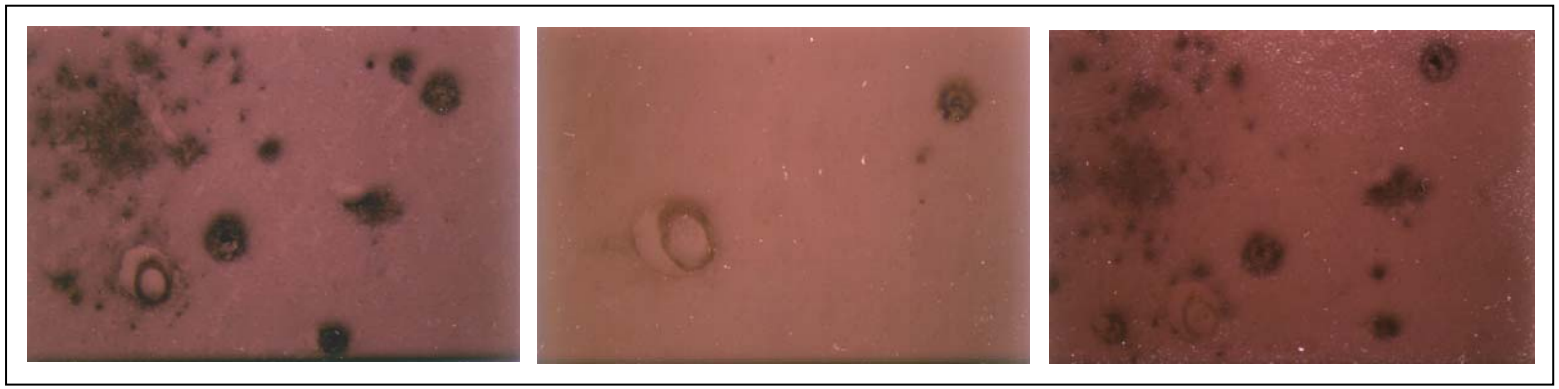


Differential deposition of Aβ 40/42 in Alzheimer's disease brains

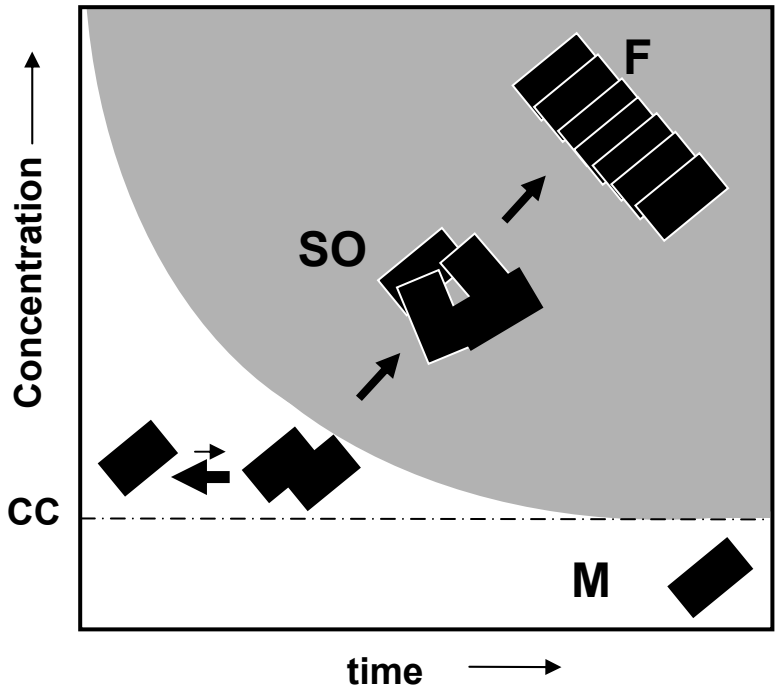
^{1}DAEFRHDSGYEVHHQK LVFFAEDVGSNKGAIIGLMVGGVVIA^{42}



4G8 **S40** **S42**



Aβ aggregation is a nucleation-dependent process

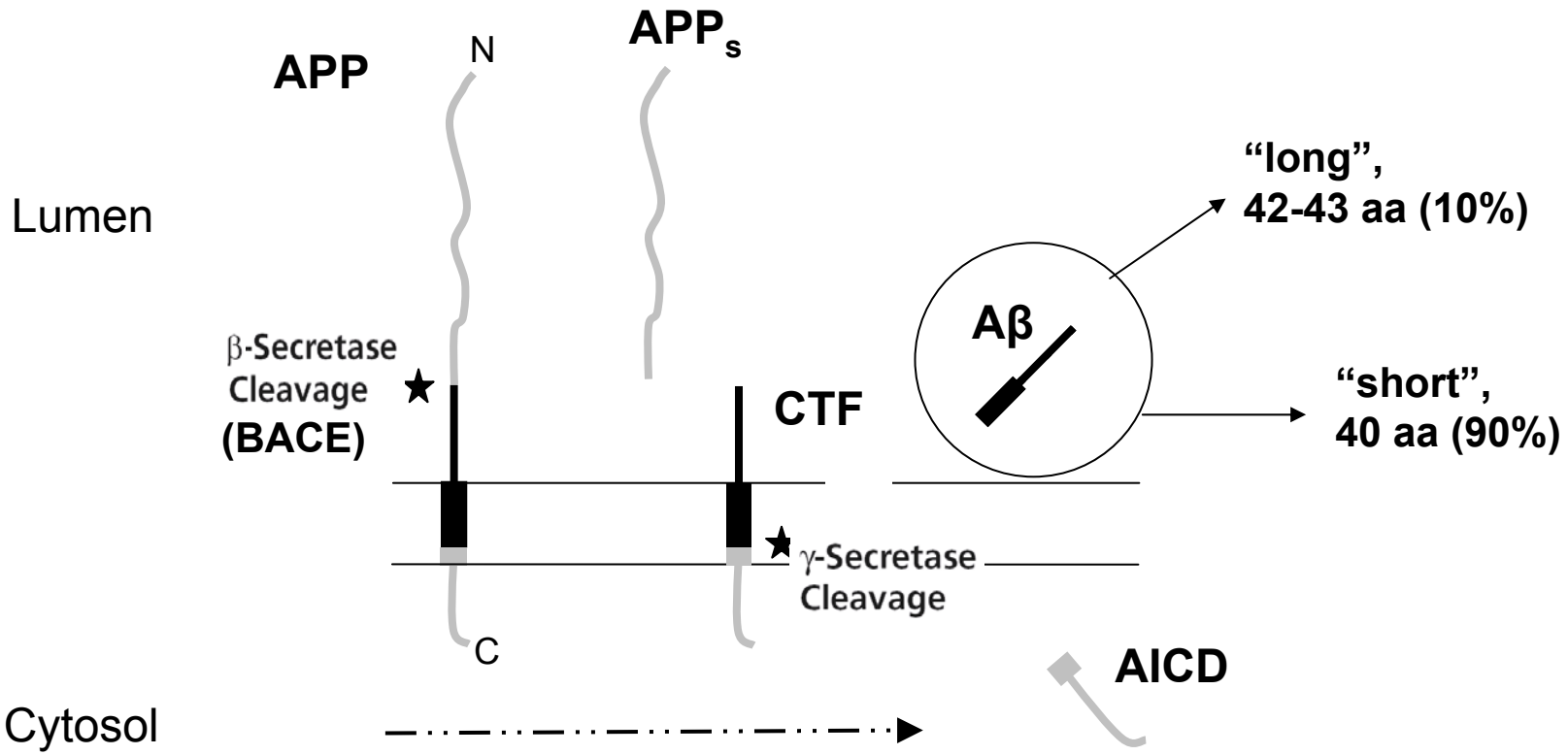


Monomer (M)

Soluble oligomer (SO)

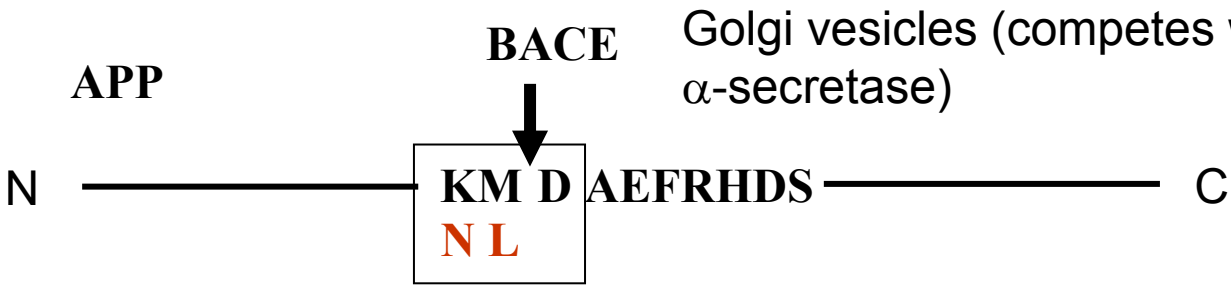
Fibril (F)

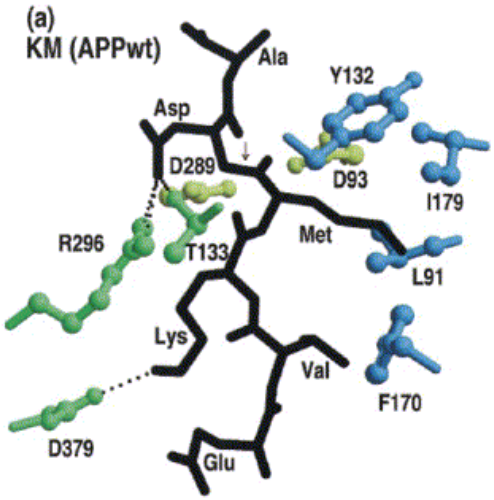
Amyloid β production



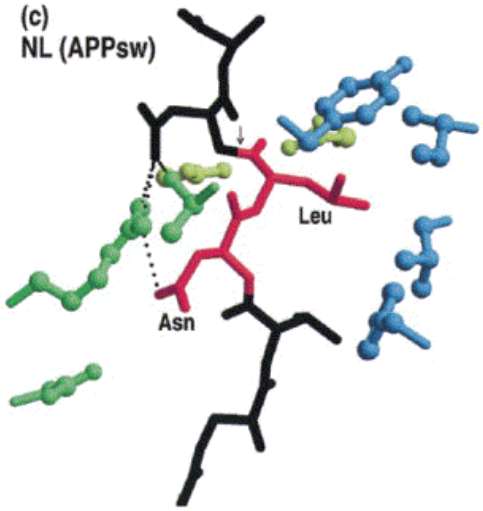
Secretory-endocytic pathway

Swedish ("BACE site") mutation associated with FAD accelerates Aβ generation



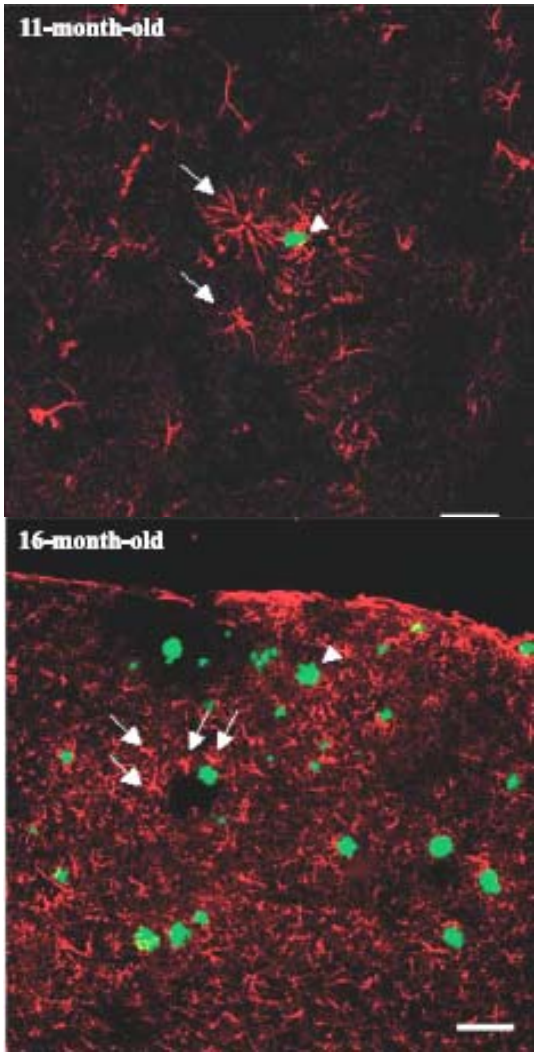


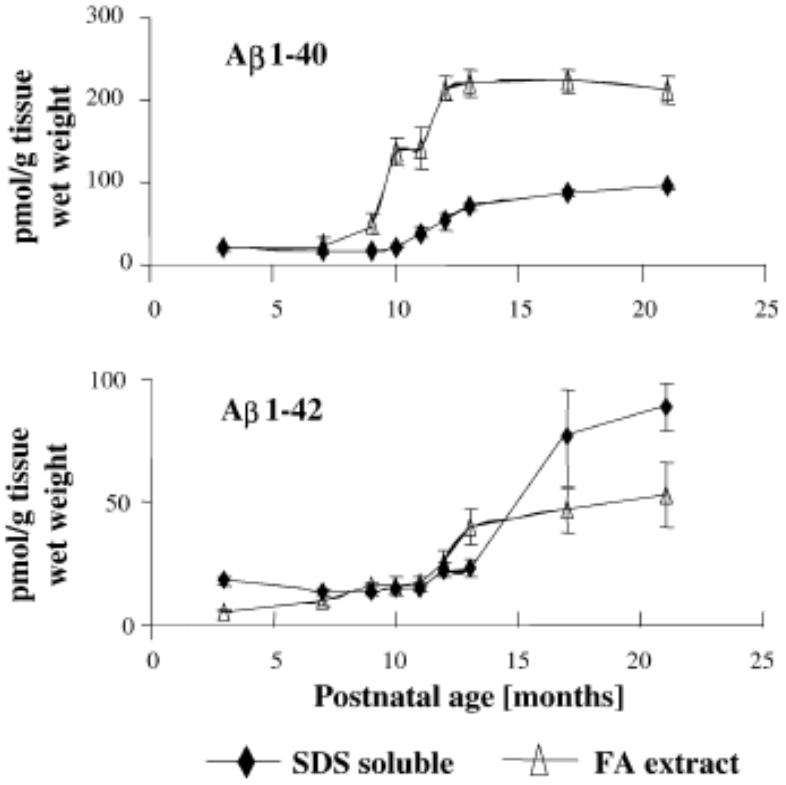
Total Aβ (5-10 fold)



Citron M, Nature 1992 360:672 Sauder JM, J Mol Biol. 2000 300:241

Transgenic mice carrying APPswe mutation

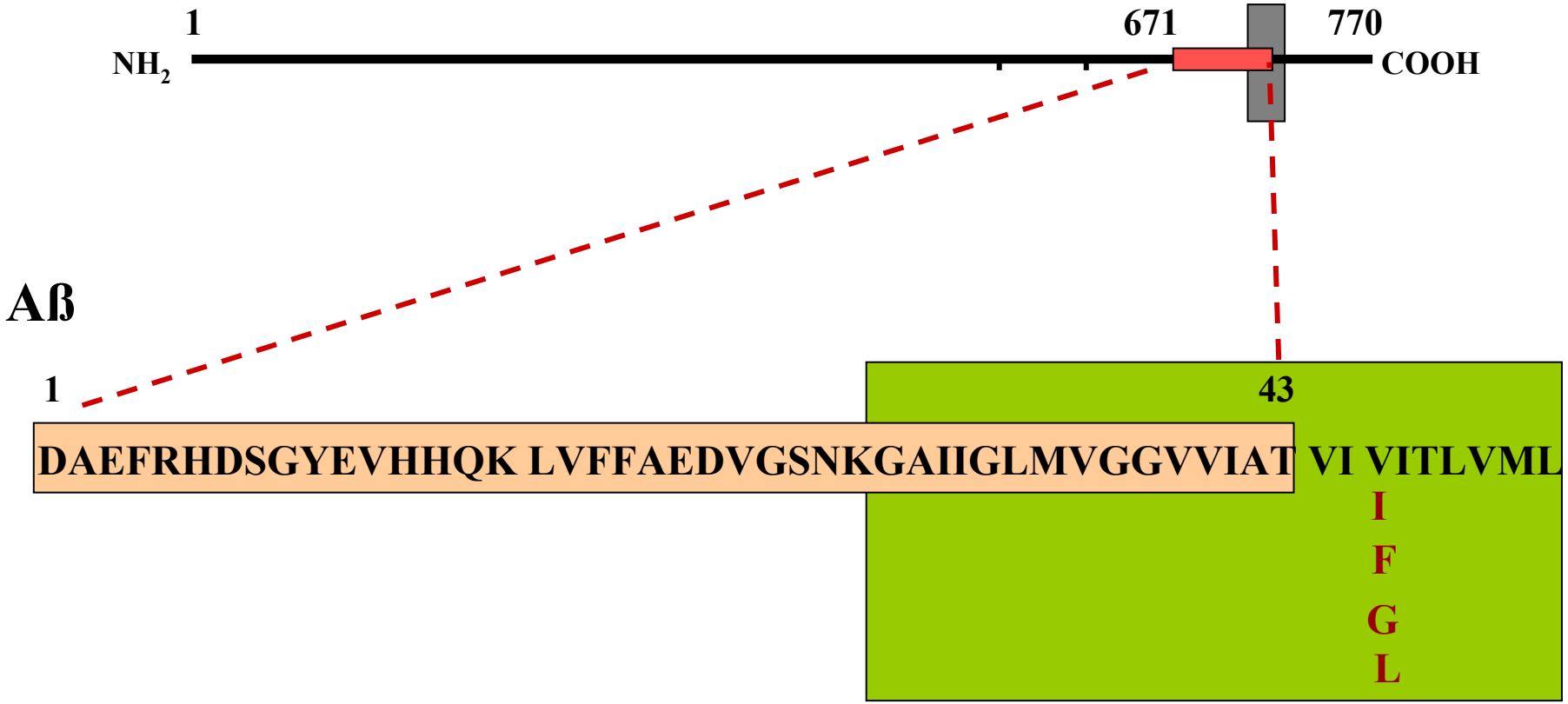




Apelt J. et al. Int J Dev Neurosci. 2004; 22:475

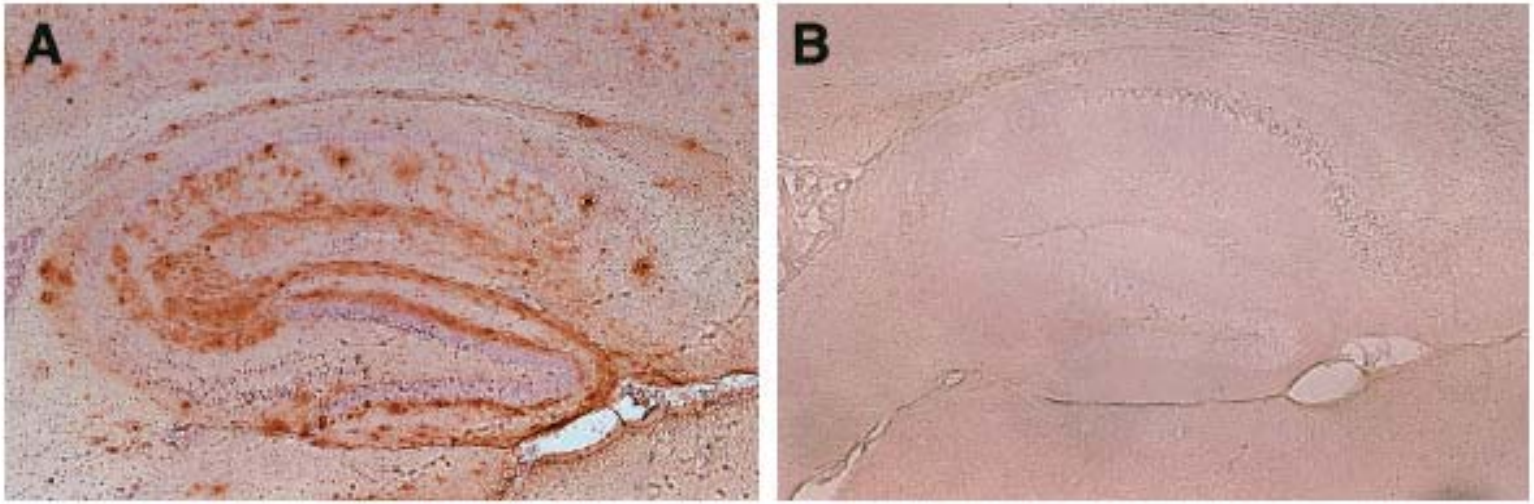
Leal MC. et al. J Neuropathol. Exp. Neurol. 2006;65:976

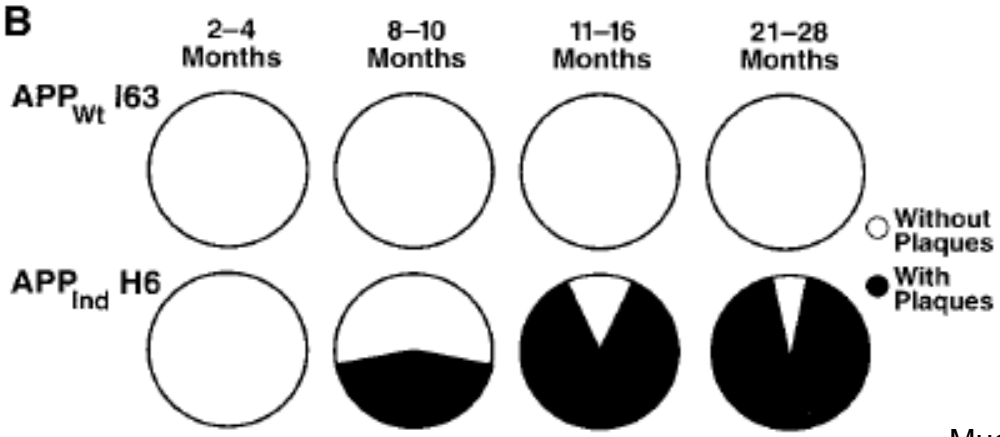
Mutations in AβPP associated with early onset Alzheimer disease at position 717



APP 717 V>F(Indiana) transgenic mice

hAPP ind **18 months** **hAPP wt**

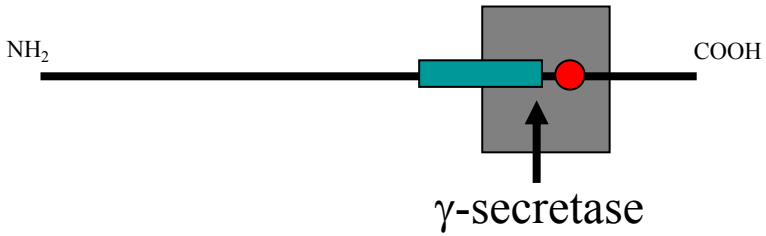




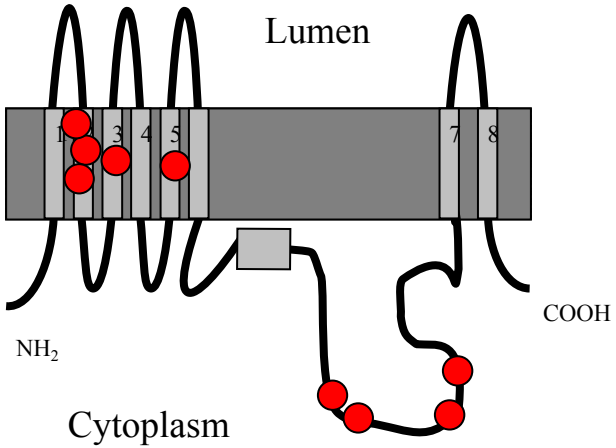
Mucke L, J Neurosci 20:4050, 2000

AβPP-717 and PRESENILIN 1-2 mutations promote the overproduction of Aβ ending at 42/43

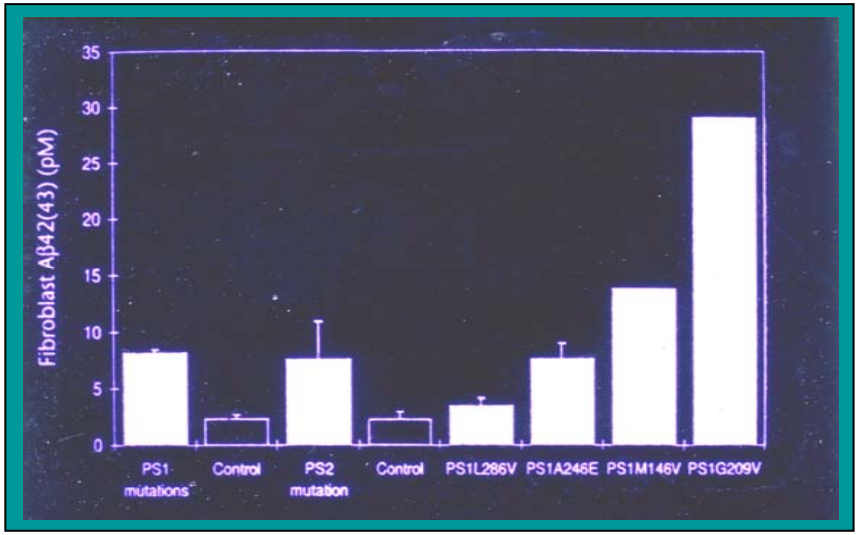
AβPP



PS1-PS2



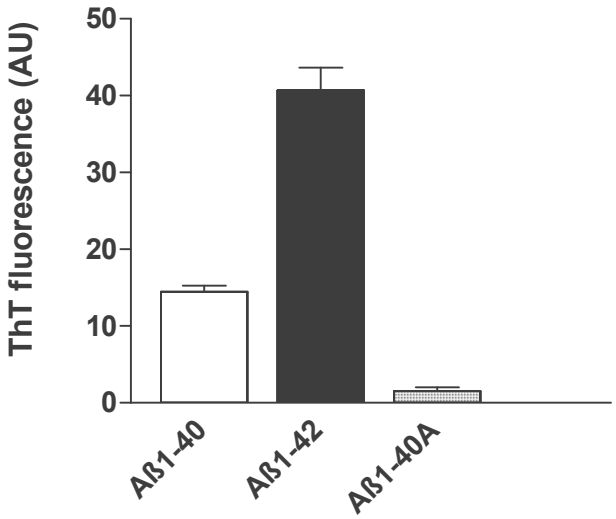
Primary fibroblasts EOAD

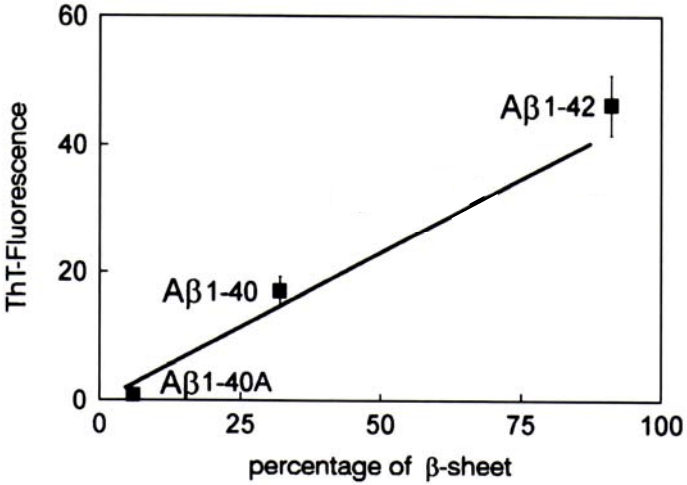


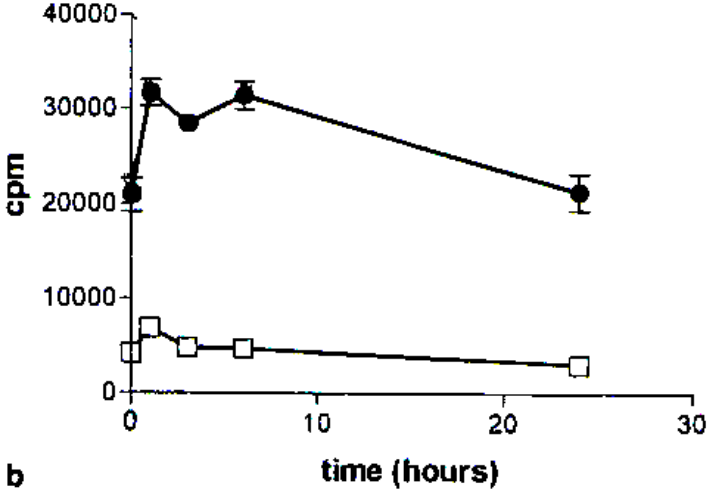
AβPP TM domain

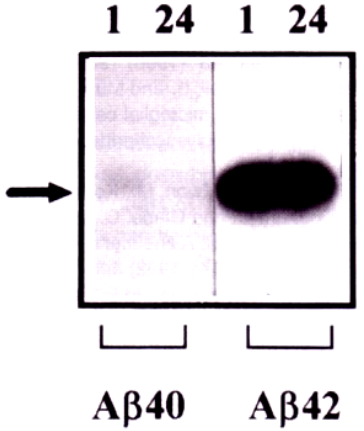
GAIIGLMVGGVV IA T VIVITLVML

Aβ1-42 vs Aβ1-40: amyloid formation *in vitro* and accumulation in a human monocytic cell line







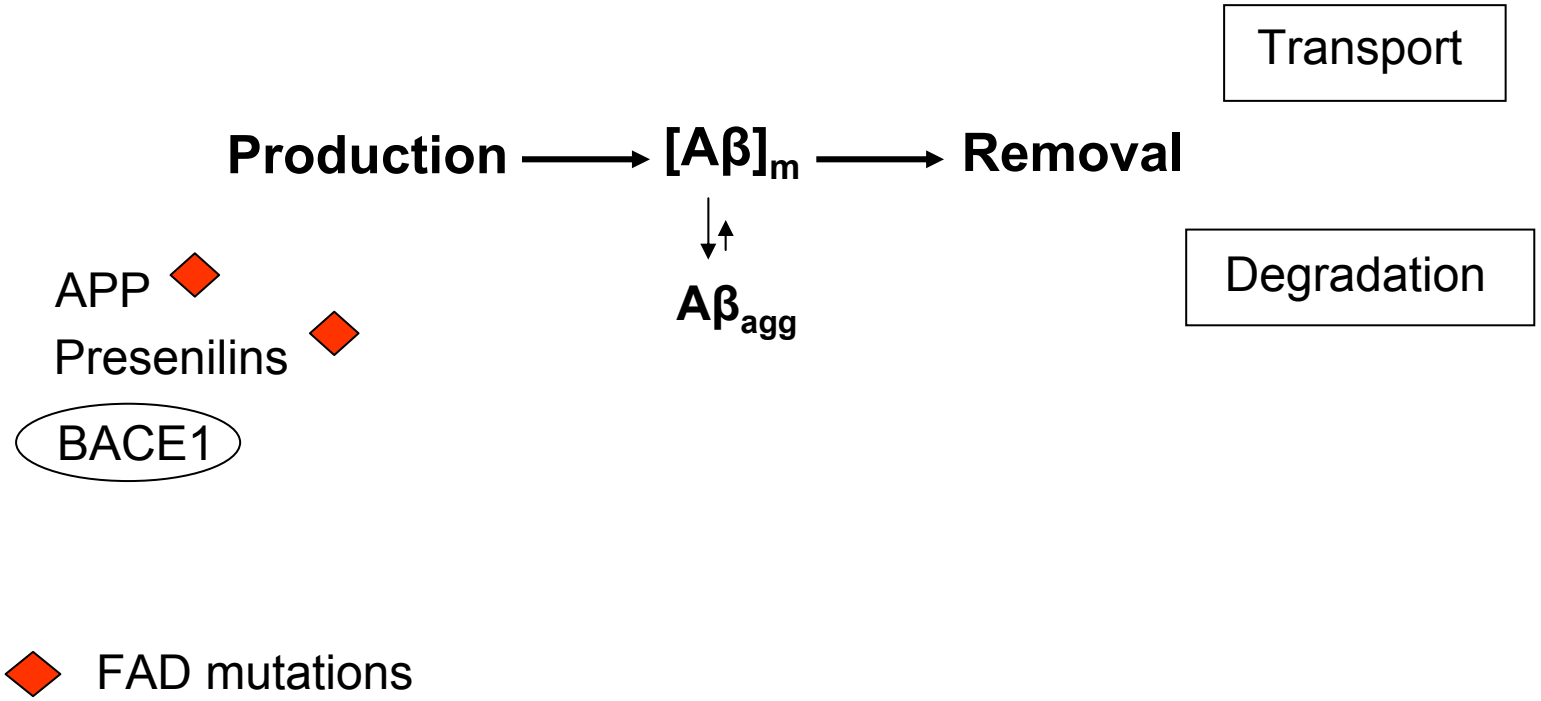


Factors that promote Aβ accumulation

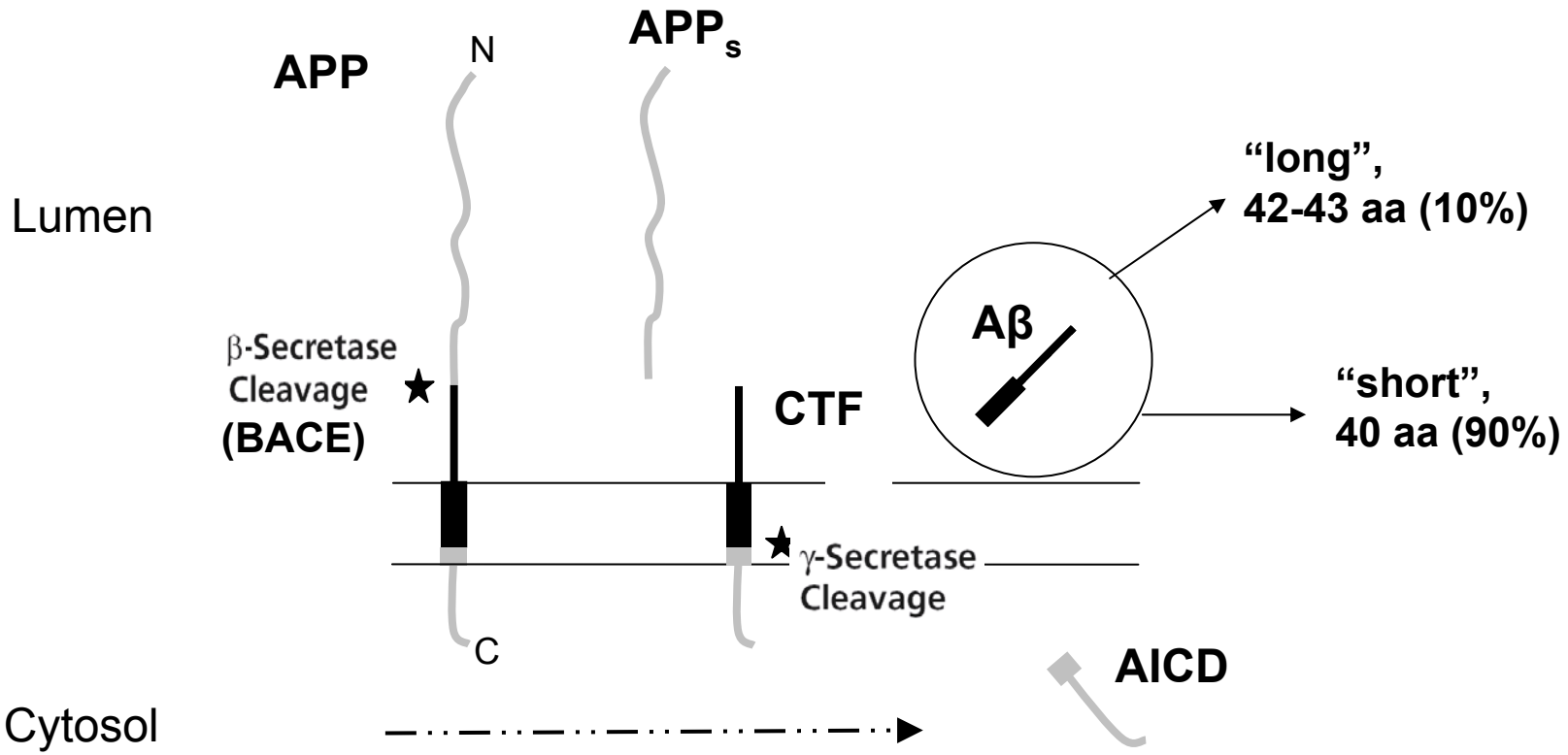
Early onset familial AD → 1) Aβ overproduction
2) Length of Aβ C-terminus
3) Amino acid substitutions

Sporadic AD ?

The steady state of monomeric Aβ: a tightly controlled balance between production and removal



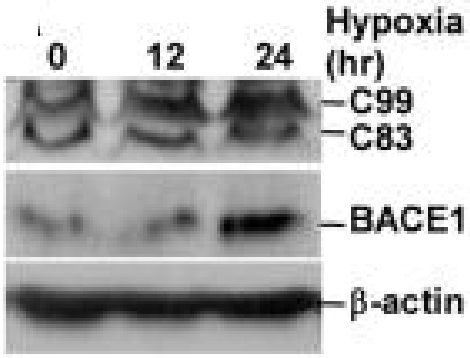
Amyloid β production

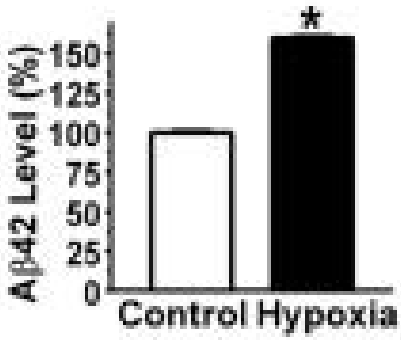


Secretory-endocytic pathway

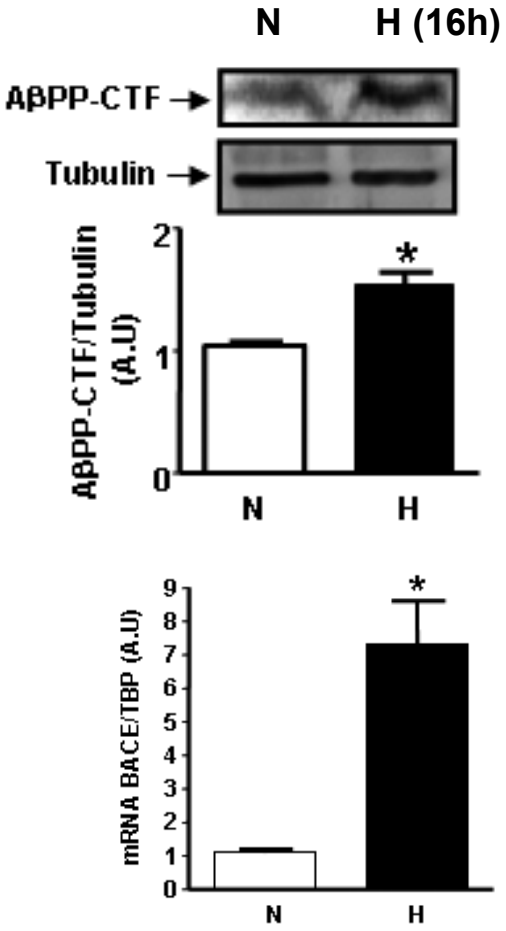
BACE1 expression is increased by hypoxia and oxidative stress *in vitro* and *in vivo*

Cell cultures



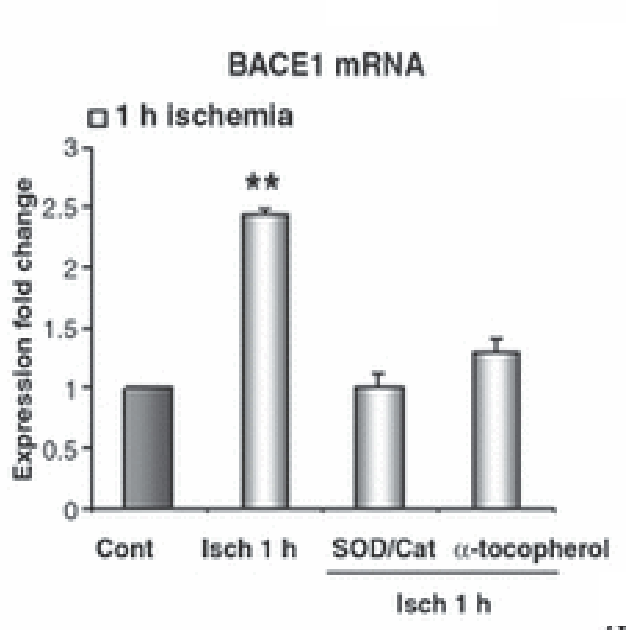


Sun X, et al
PNAS. 2006 103:18727



Bulloj et al. J Alzheimer Dis 2010 19:79

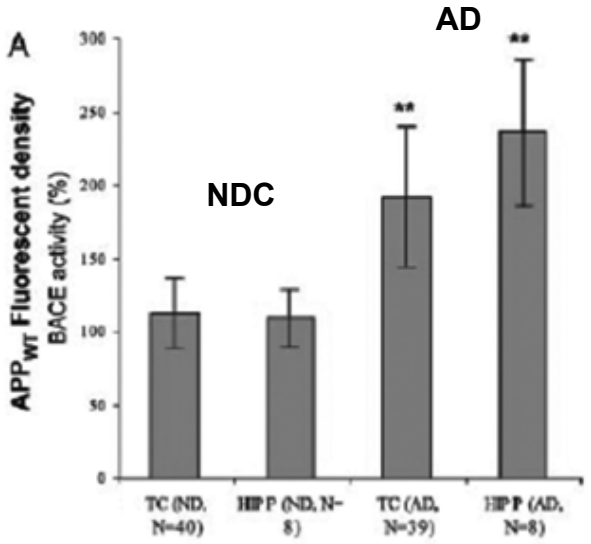
Rat brain



Guglielmotto M,et al
J Neurochem. 2009 108:1045

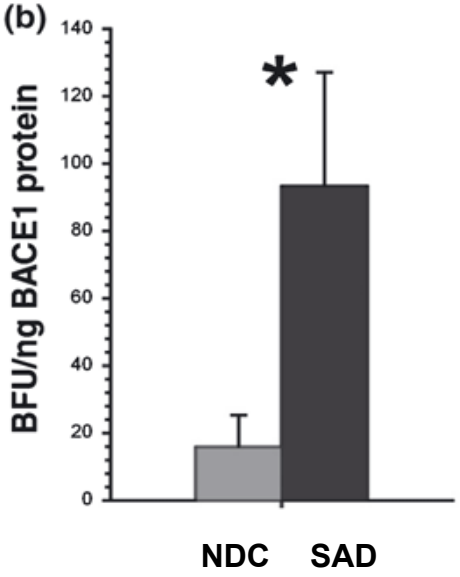
BACE1 activity is increased in the brain of sporadic AD vs ND controls

Temporal cortex/ Hippocampus



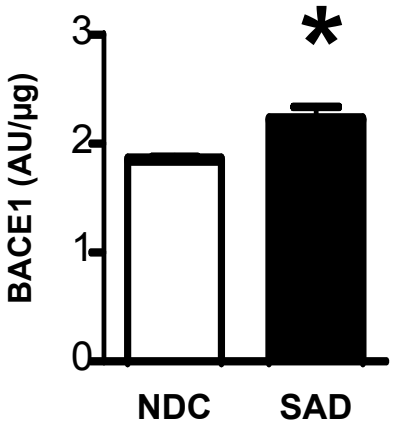
Li R. et al. PNAS. 2004; 101:3632

Frontal cortex



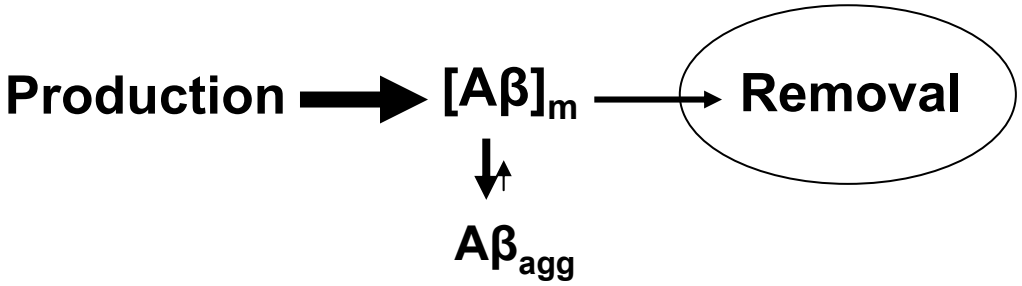
Ahmed RR et al
J Neurochem. 2010 112:1045

Hippocampus



Morelli I. et al
unpublished

The steady state of monomeric Aβ in SAD: increased production by BACE1



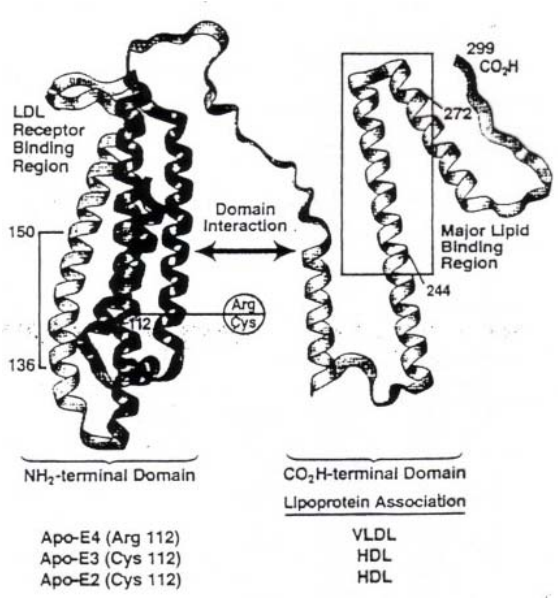
BACE1

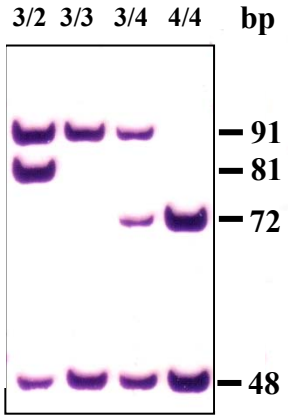
Increased Activity in SAD
(Hypoxia/oxidative stress?)

Major Aβ-degrading proteases

Protease	Type	Cellular localization	Overexpression (transfected cells)	K.O mice
Neprilysin	Neutral, Zn-metallo	Plasma membrane	↓Aβ (IC,EC)	↑Aβ, gene-dose effect
Endothelin-Converting Enzymes	Neutral, acidic Zn-metallo	Plasma Membrane, Internal membranes	↓ Aβ (EC)	↑Aβ, gene-dose effect
Insulin-Degrading Enzyme	Neutral, Zn-metallo	Cytosol, Membranes Peroxisomes Secreted?	↓ Aβ (IC, EC)	↑Aβ, gene-dose effect ↑ Insulin

Apolipoprotein E: domain structure, human isoforms and risk for Alzheimer's disease



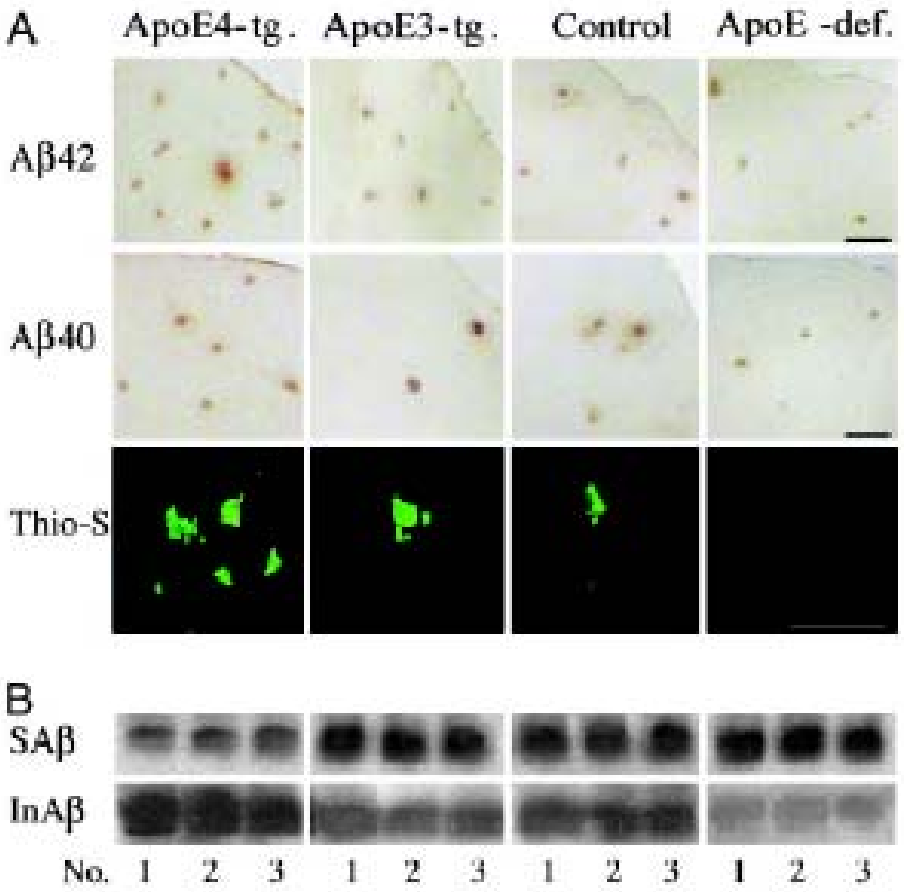


Genotype and allele frequency of APOE in patients with late onset Alzheimer's disease (LOAD), controls, and general population in Argentina

Group (n)	*Mean age (y)*	*2/2*	*2/3*	*2/4*	*3/3*	*3/4*	*4/4*	*ε2*	*ε3*	*ε4*
LOAD (45)	74·72	0	0	0	28	14	3	0 (0)	0·62 (70)	0·22 (20)*
Controls (45)	71·89	0	1	0	37	7	0	0·011 (1)	0·911 (82)	0·077 (7)
General population (101)	33·81	0	5	7	65	24	0	0·059 (12)	0·787 (159)	0·153 (31)

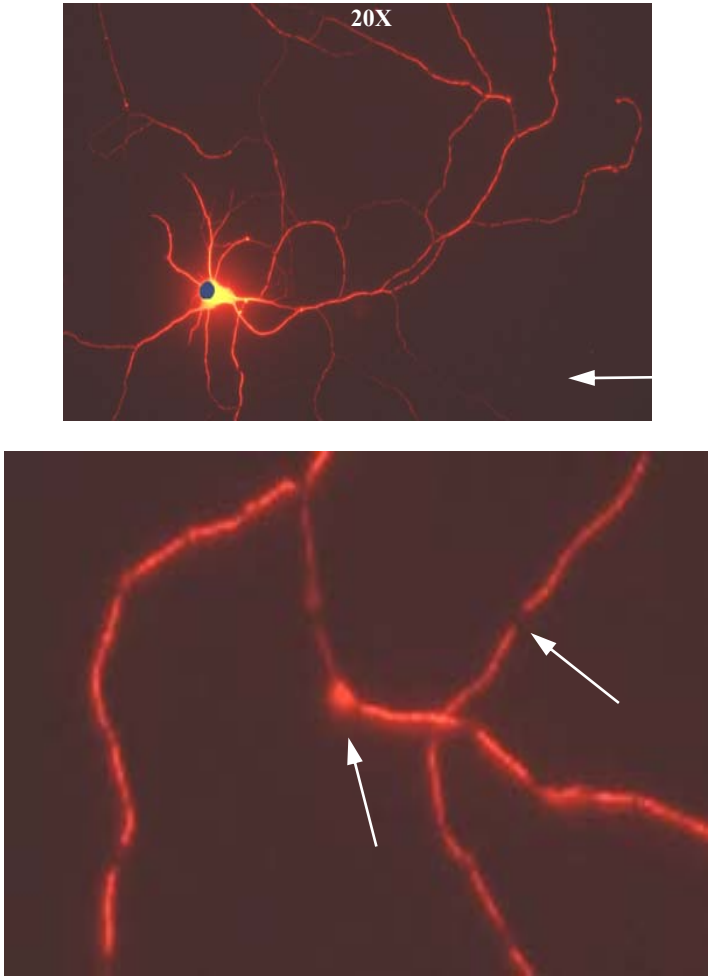
*P = 0·015 (Fisher's exact statistics), LOAD *v* controls.
Allele numbers are in parenthesis.

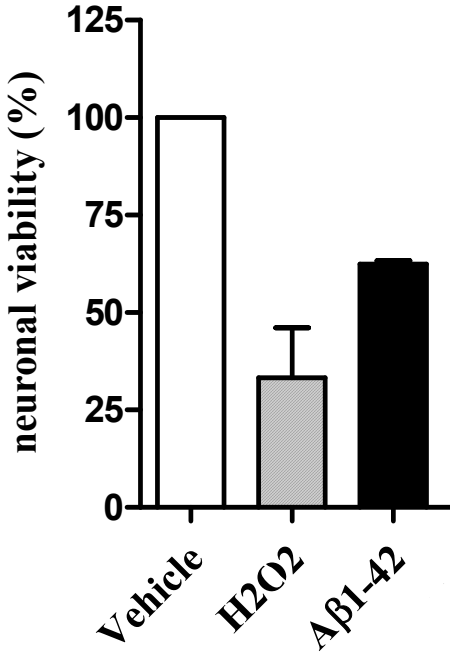
Aβ accumulation in Tg mice as a function of human apoE allele expression



Amyloid β oligomers are toxic to primary neurons in culture

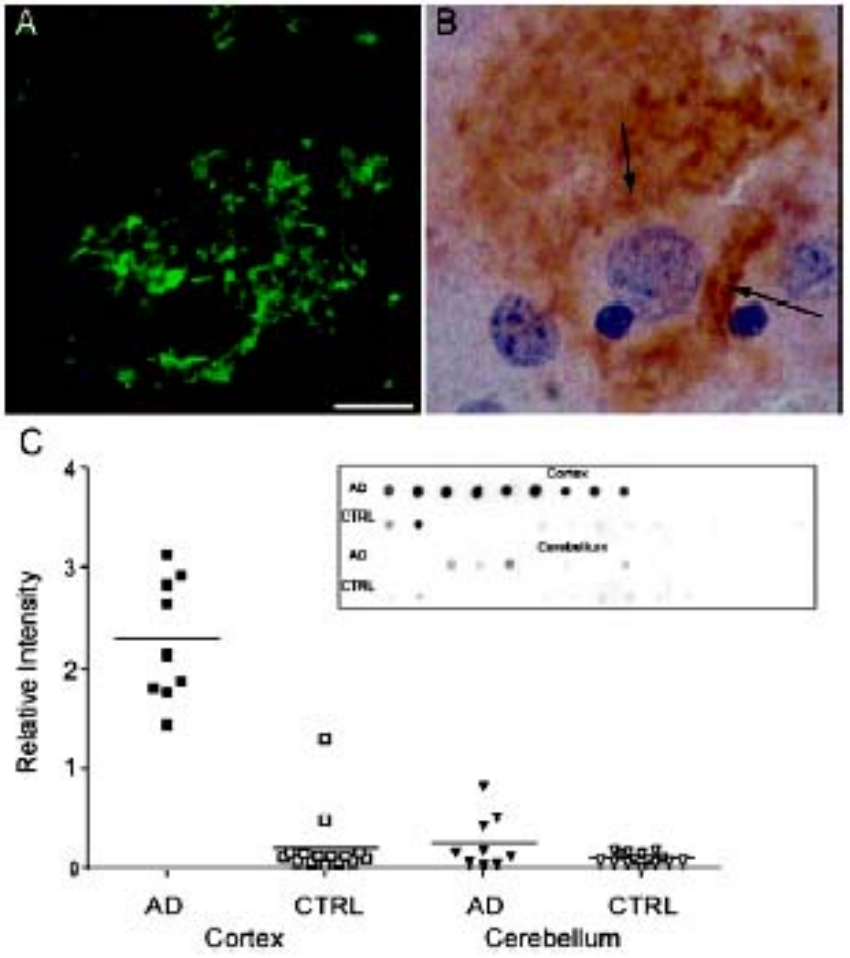
Oligomeric Aβ



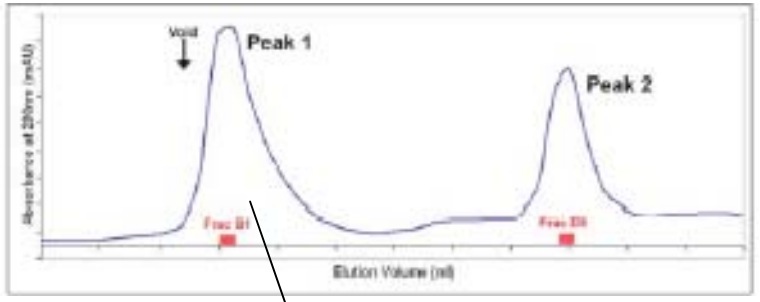


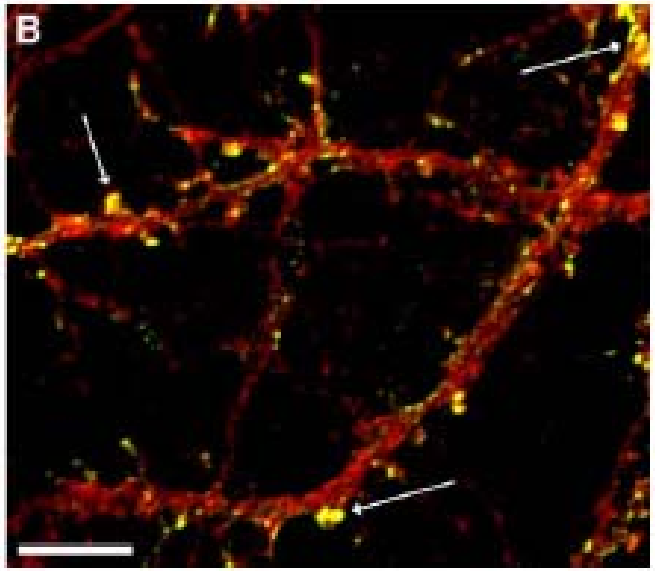
Soluble Aβ42 oligomers in AD brains: targeting to dendritic spines

Anti-Aβ oligomer staining AD brain



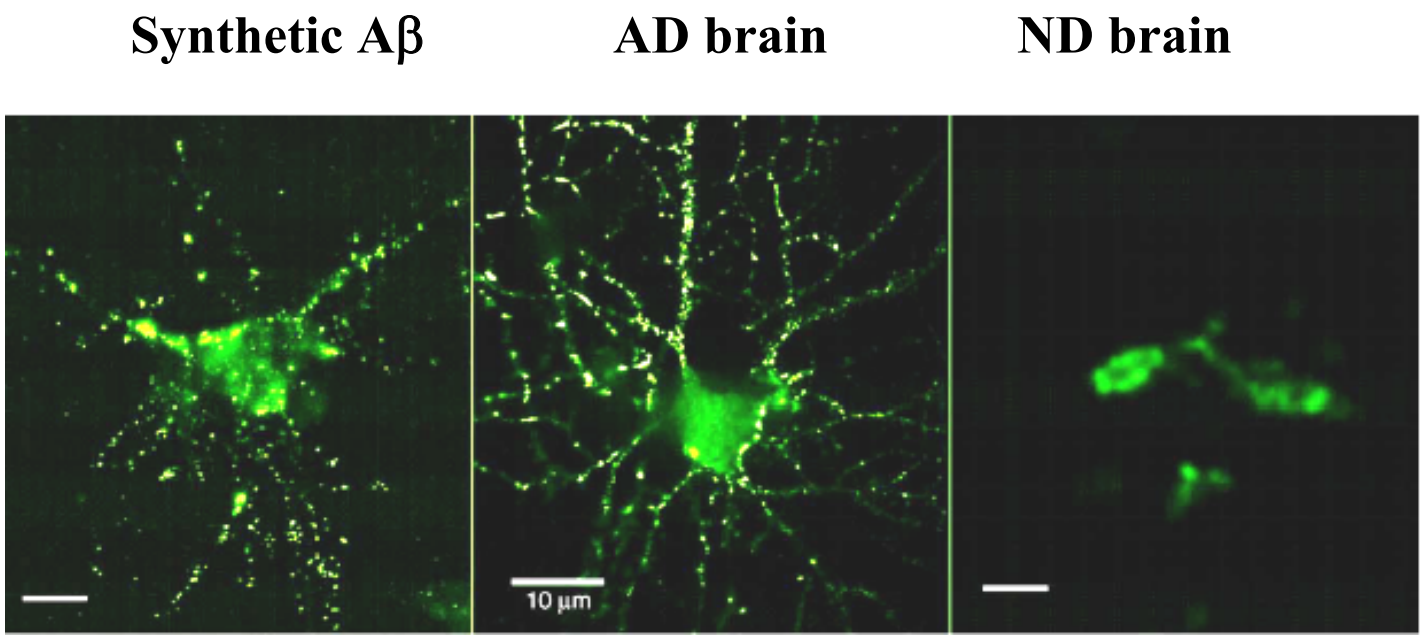
Synthetic Aβ oligomers



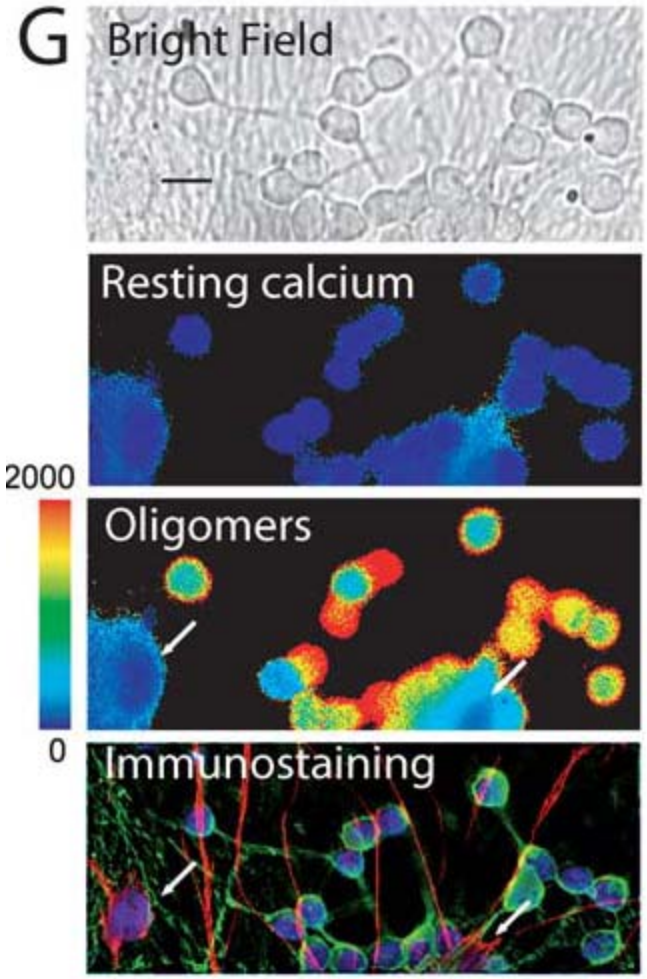


Anti-Ca^{2+}/Calmod.PKII-anti-Aβoligomer

Soluble Aβ42 oligomers bind with high avidity to membrane domains in hippocampal neurons

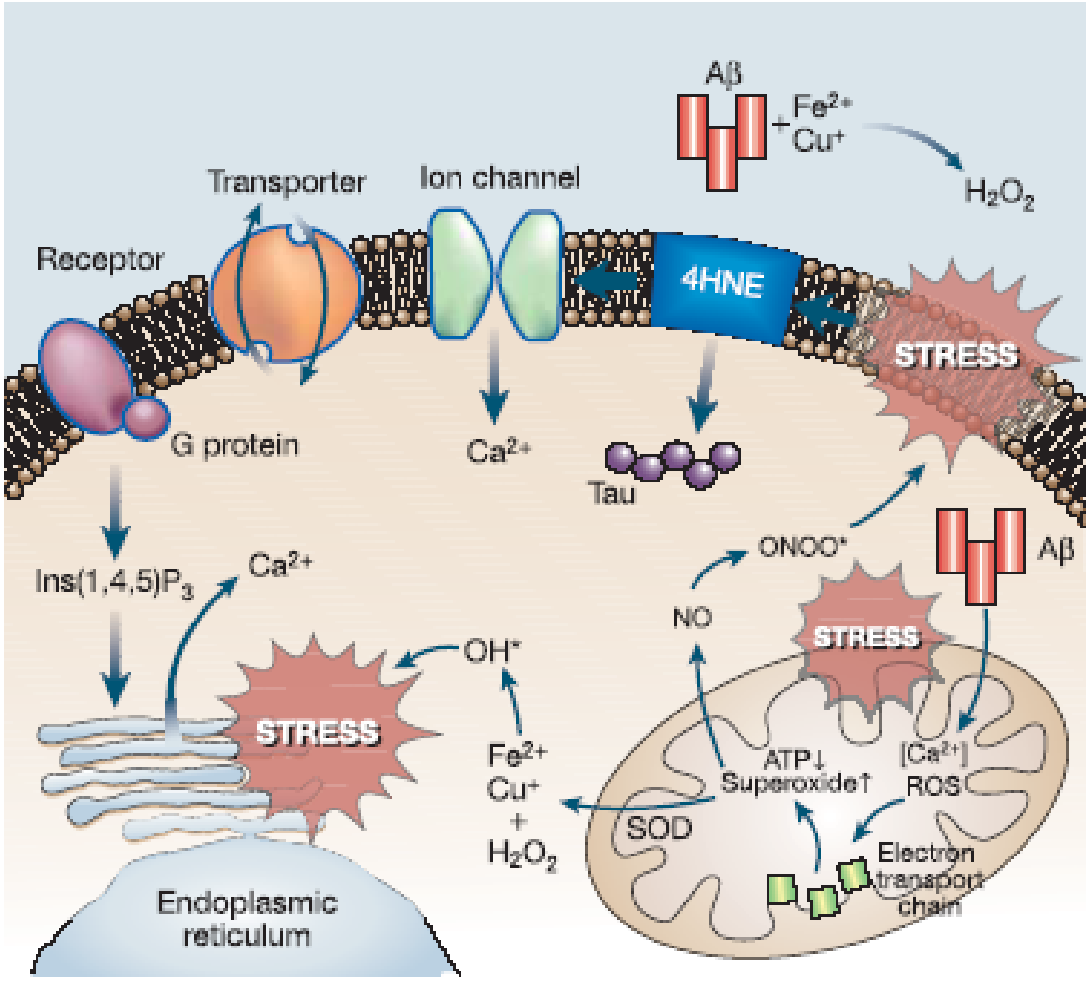


Increased neuronal intracytoplasmic calcium induced by amyloid β oligomers

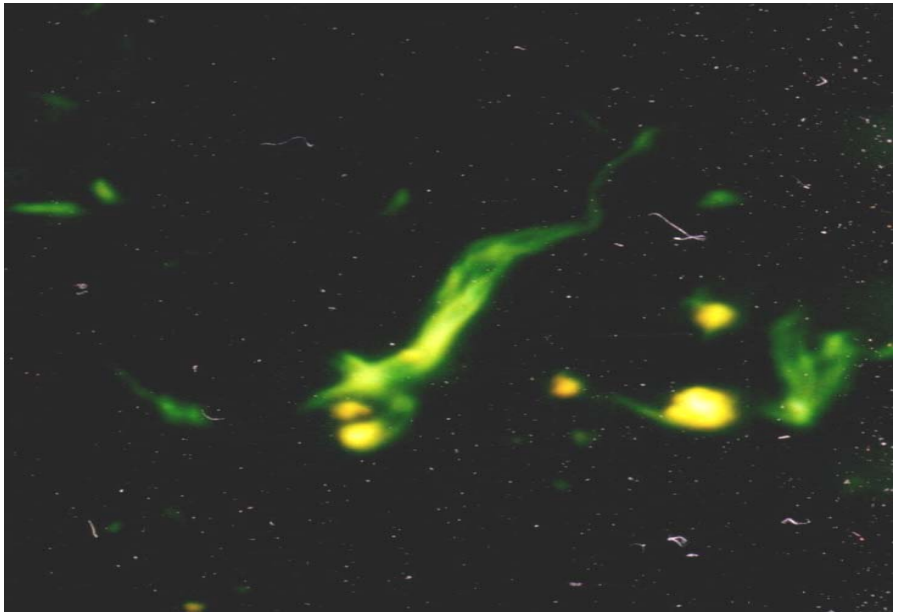


San Blasco S et al Plos one 2008

Mechanisms of cellular toxicity triggered by Aβ



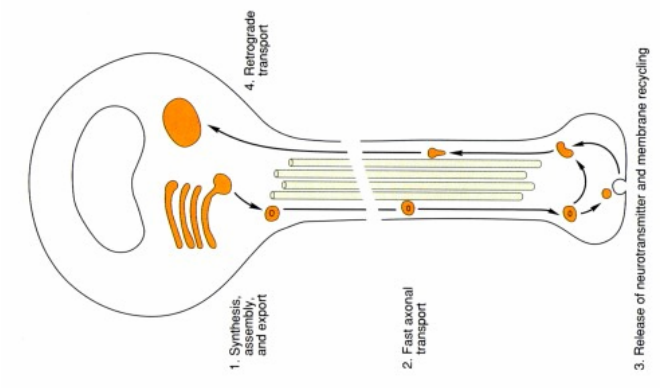
The neurofibrillary tangle (NFT) : role of tau

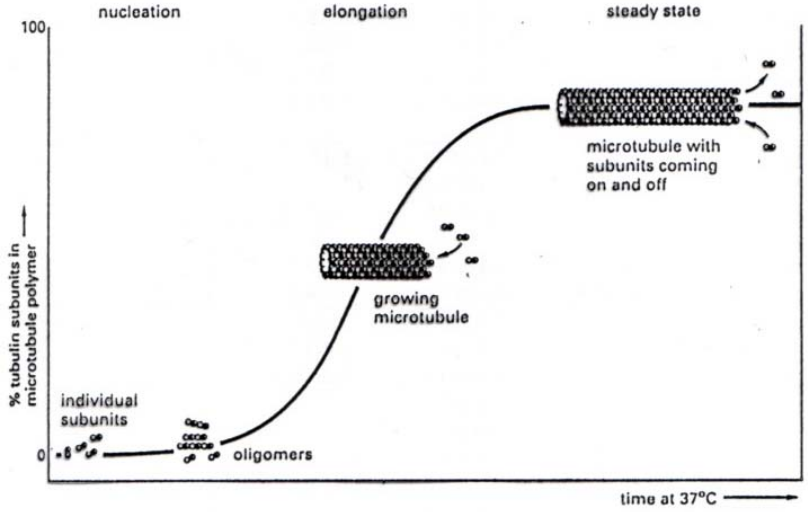


MICROTUBULE ASSOCIATED-TAU

1) Function
2) Phosphorylation
3) Association with AD and other dementias
4) Mutations

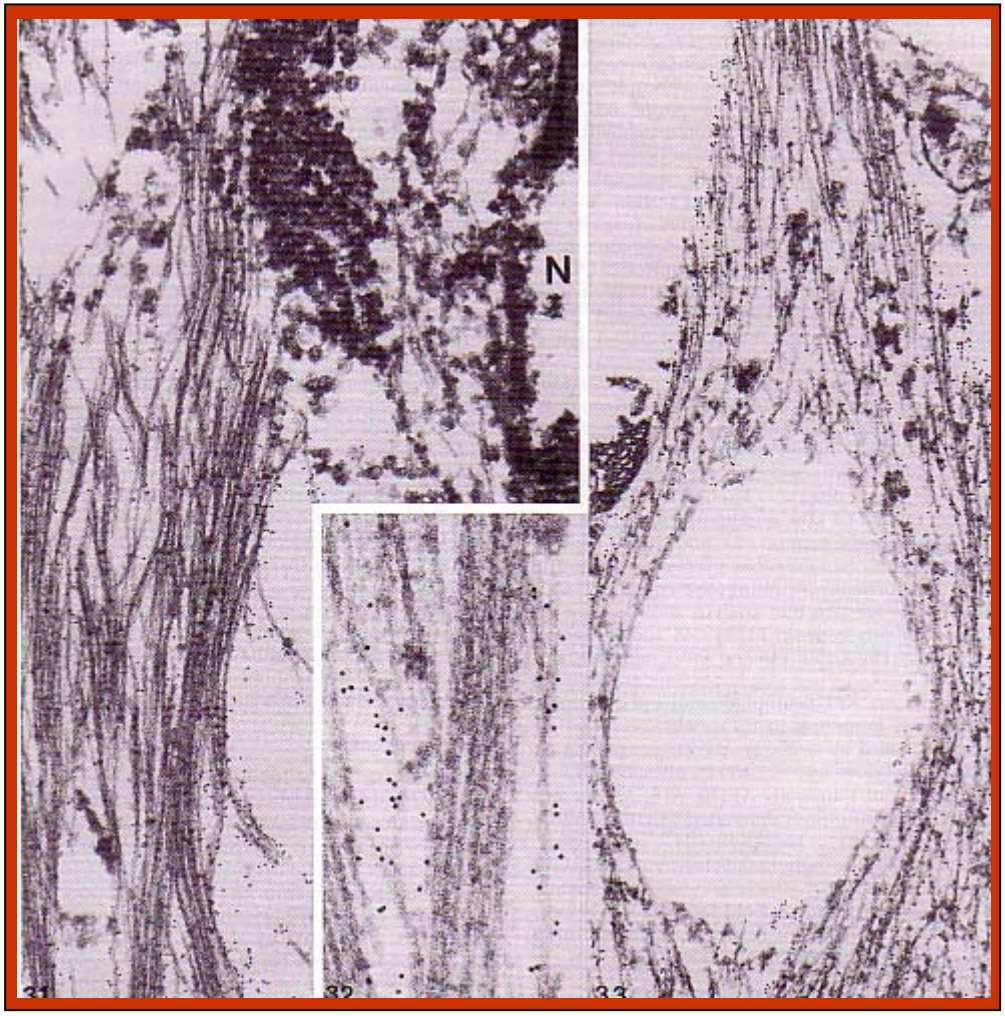
Tau is a microtubule-associated protein: axonal transport



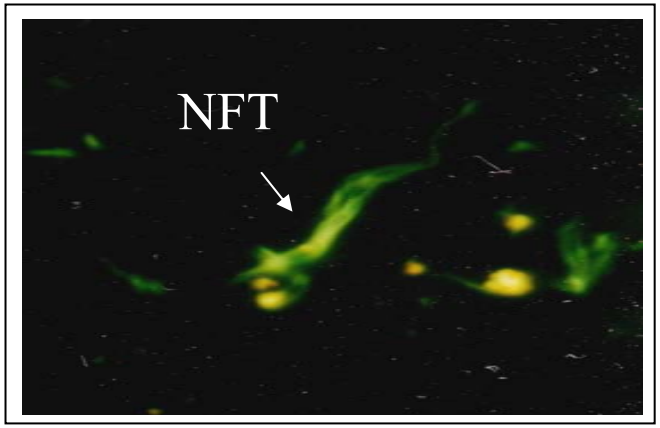


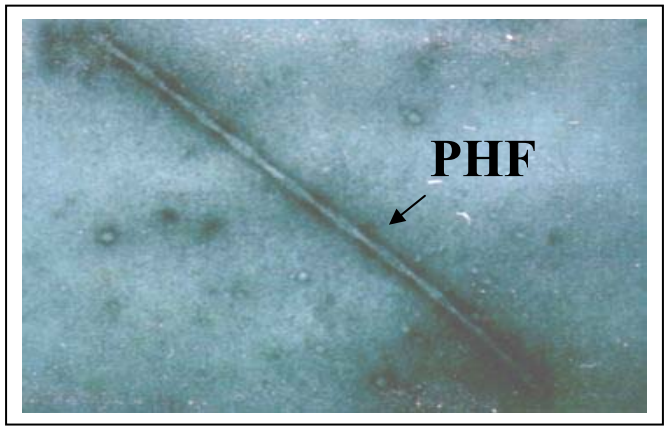
	Exon structure (variable exons)										Amino acids	Isoform
Adult tau isoforms	2+	3+	10+	E2	E3	R1	R2	R3	R4		441	4R/2N
	2+	3-	10+	E2		R1	R2	R3	R4		412	4R/1N
	2-	3-	10+			R1	R2	R3	R4		383	4R/0N
	2+	3+	10+	E2	E3	R1		R3	R4		410	3R/2N
	2+	3-	10-	E2		R1		R3	R4		381	3R/1N
Fetal tau isoform	2-	3-	10-			R1		R3	R4		352	3R/0N

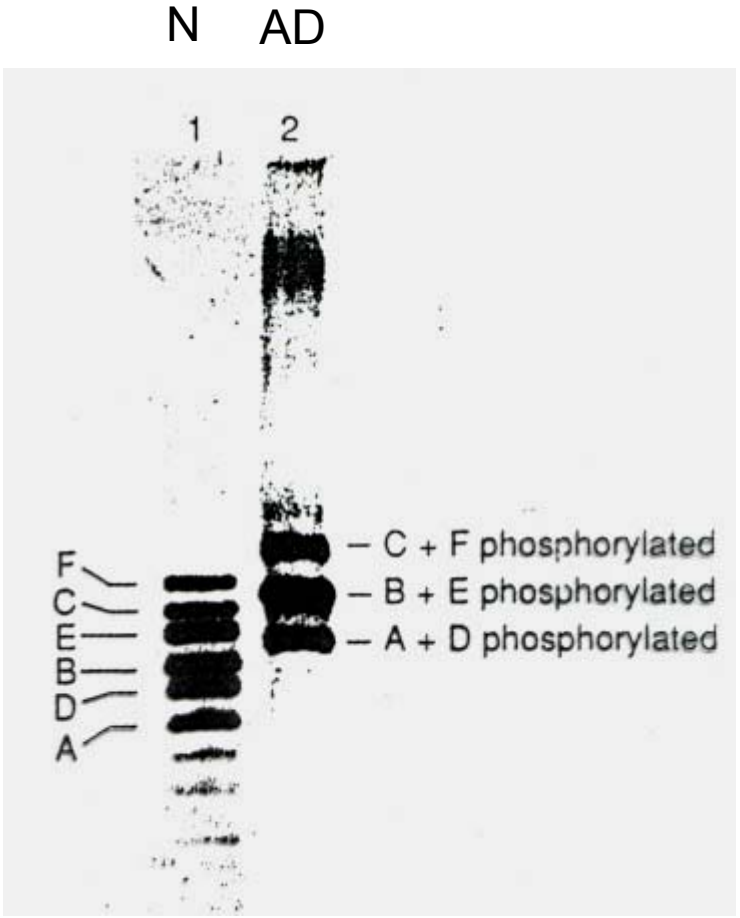
Intraneuronal amyloid fibrils made of *tau* protein



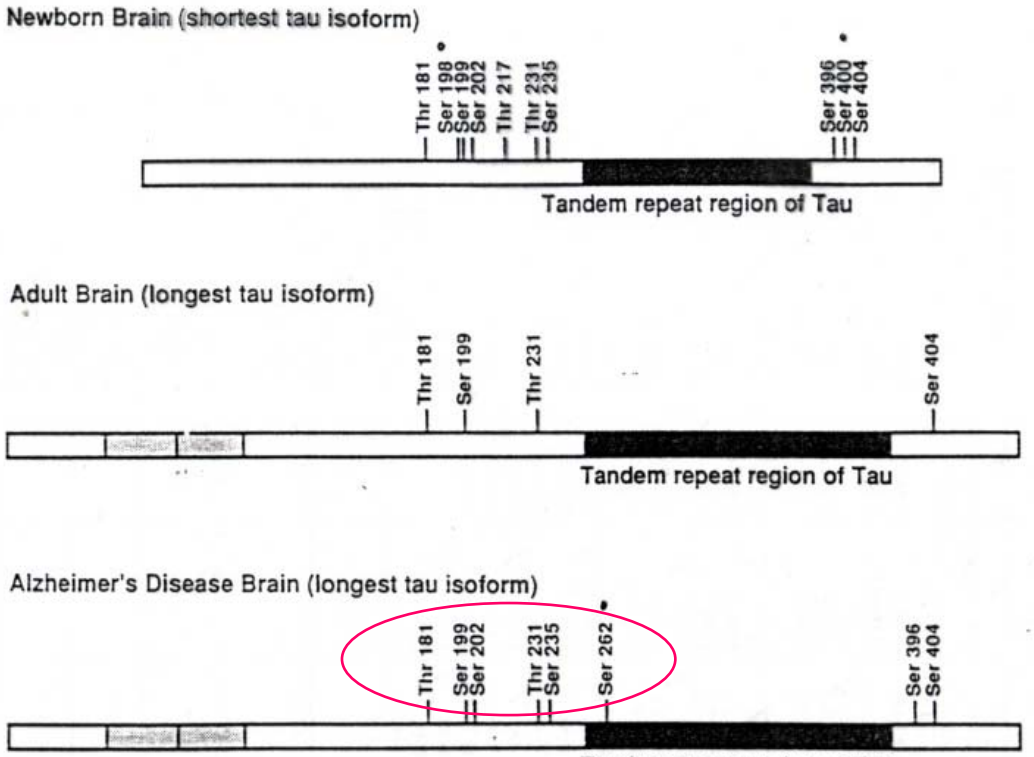
NFTs are composed of paired helical filaments of hyperphosphorylated *tau*



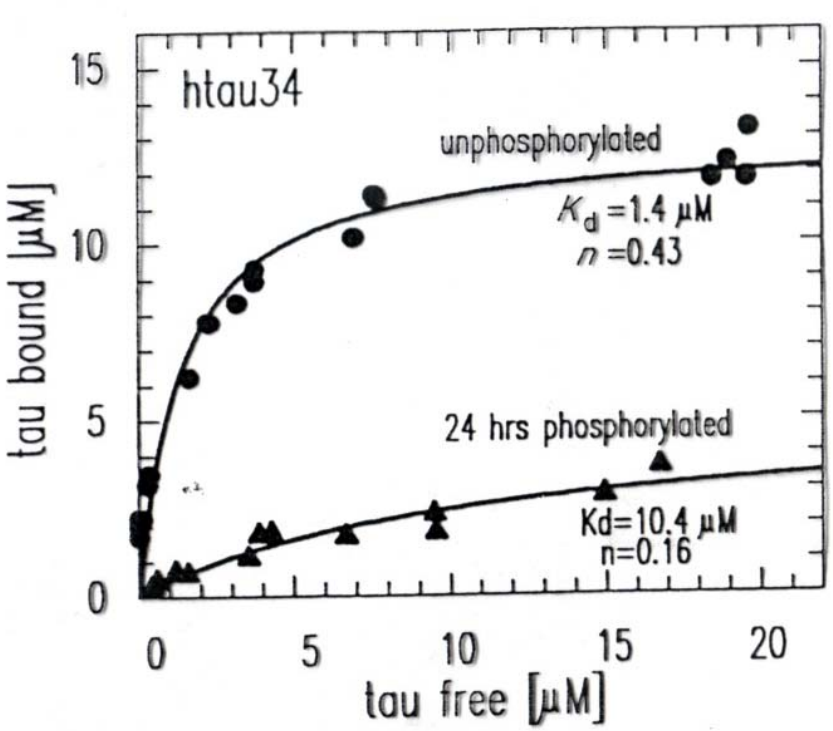




Hyperphosphorylation of *tau* in AD

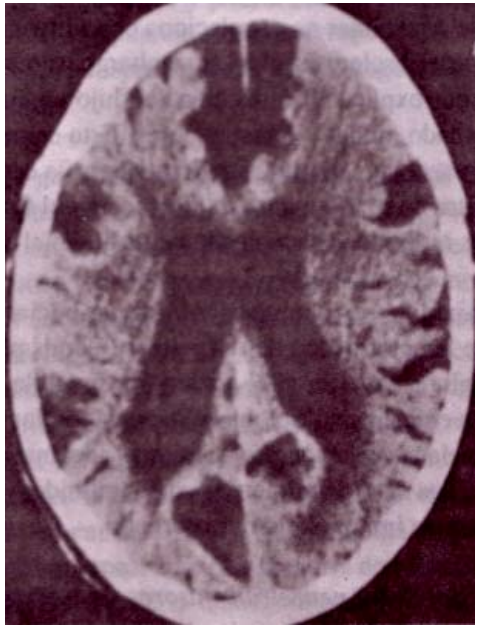


Hyperphosphorylation of *tau* affects its binding to microtubules



Frontotemporal dementia-parkinsonism (FTDP-17)

- **Autosomal dominant**
- **Onset in the 5th-6th decade of life**
- **Dementia, aphasia, rigidity**
- **Selective atrophy: frontal and temporal lobes**
- **Inclusions of P-tau in neocortex, subcortical nuclei**
- **Associated with more than 30 mutations in TAU gene**



Mutations in the *tau* gene cause FTDP

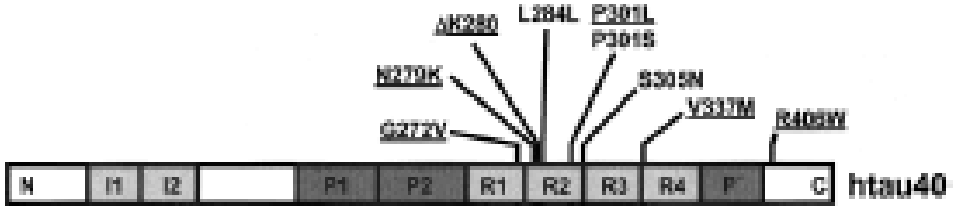
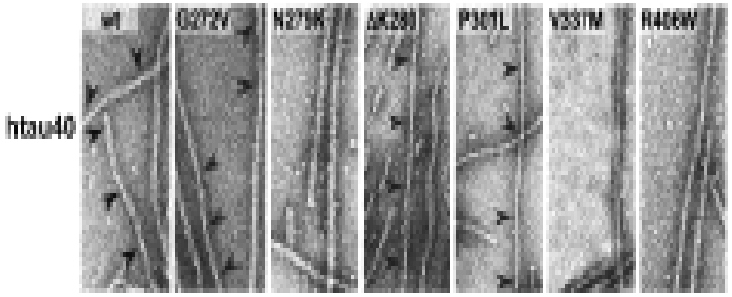
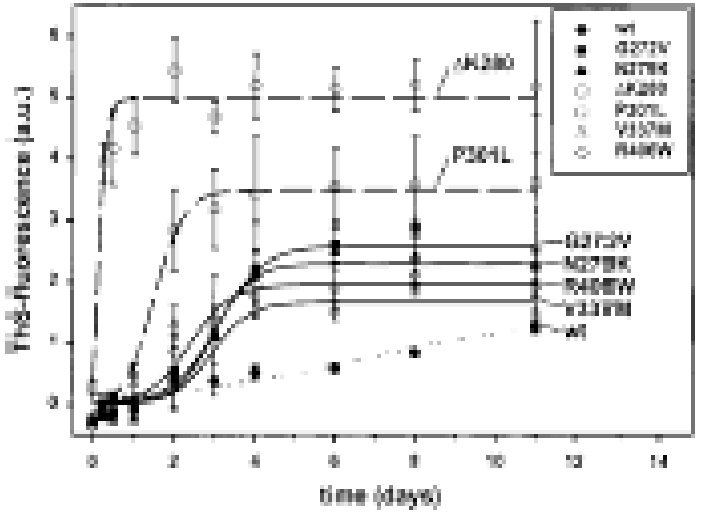
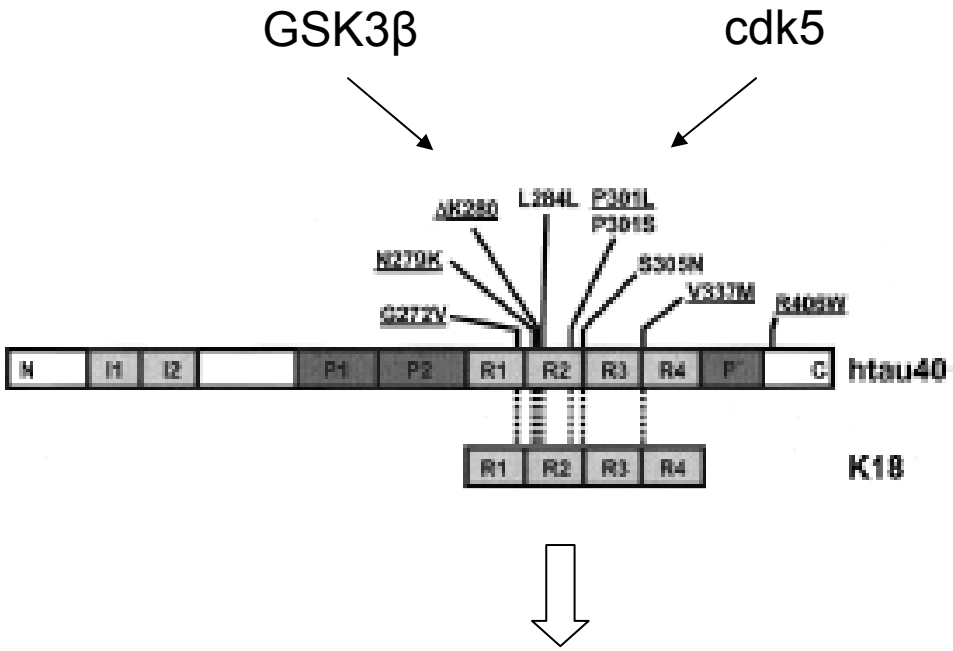


FIGURE 1:





Some tau mutations promote phosphorylation



Unbound to microtubules

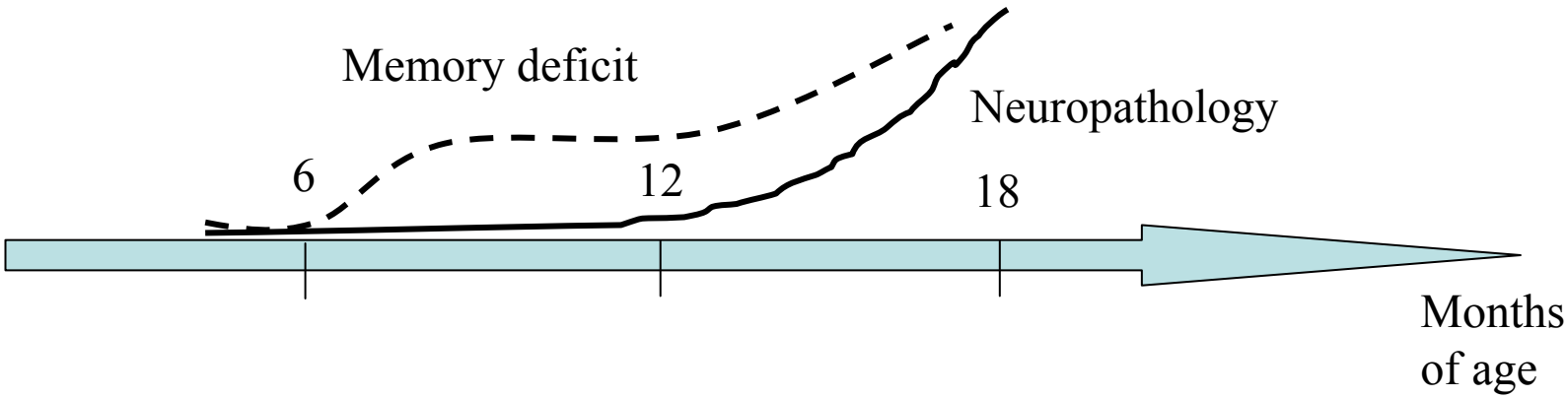
Mouse models of Aβ-related pathology

PDAPP: human APP "Indiana" mutation V717F

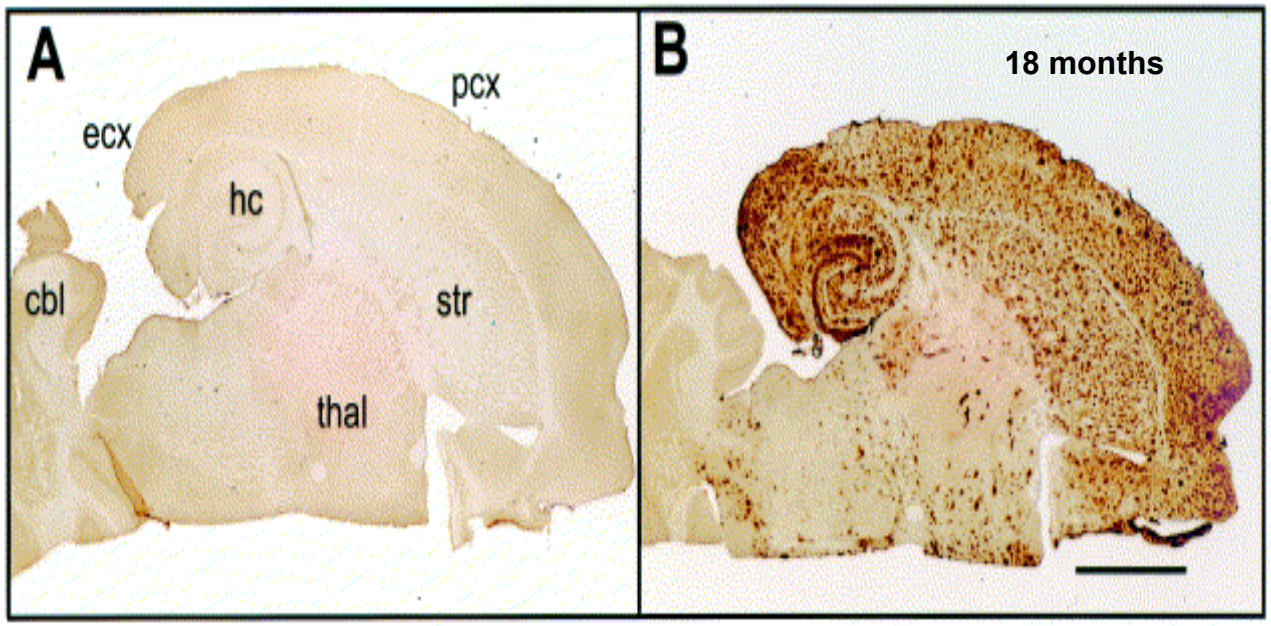
Tg2576: human APP "Swedish" double mutation (PrP promoter)

APP23: same as Tg2576 with Thy1 promoter

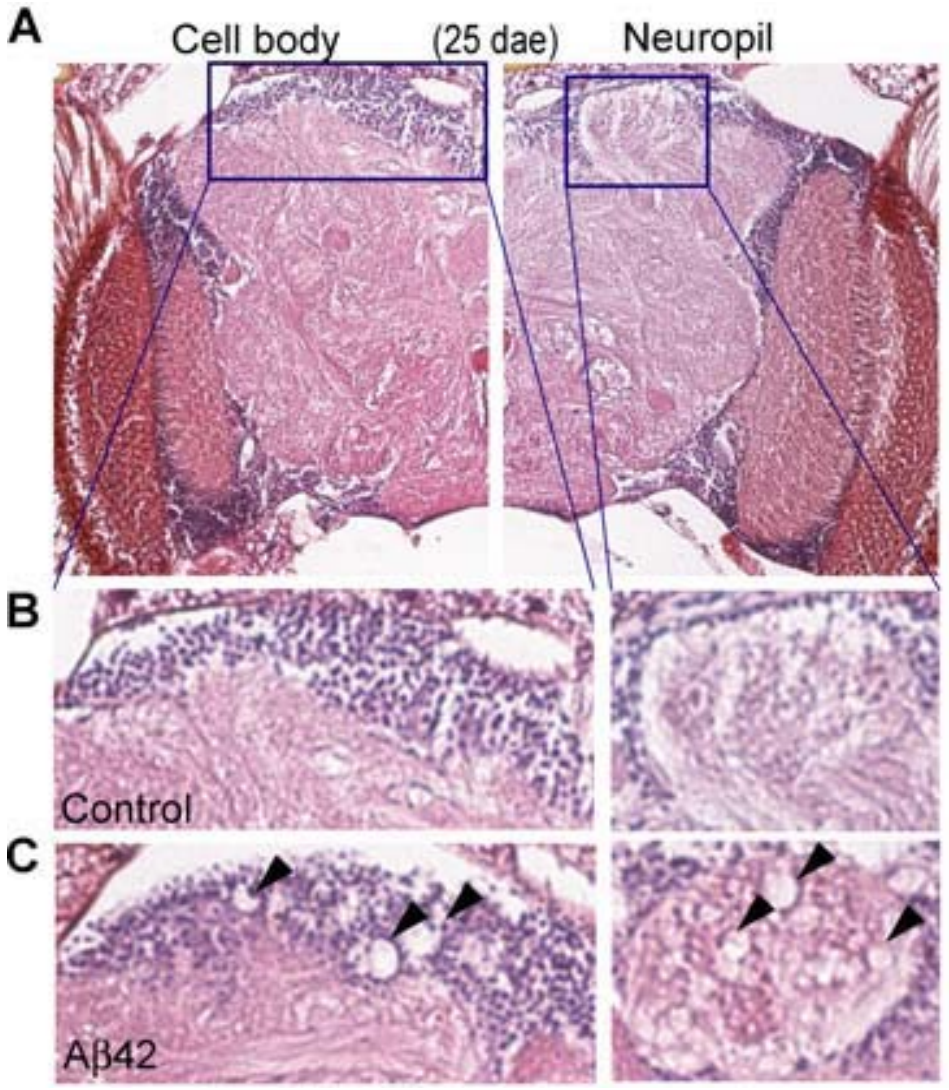
PSAPP: human APP "swedish"+ human PS1 M146L



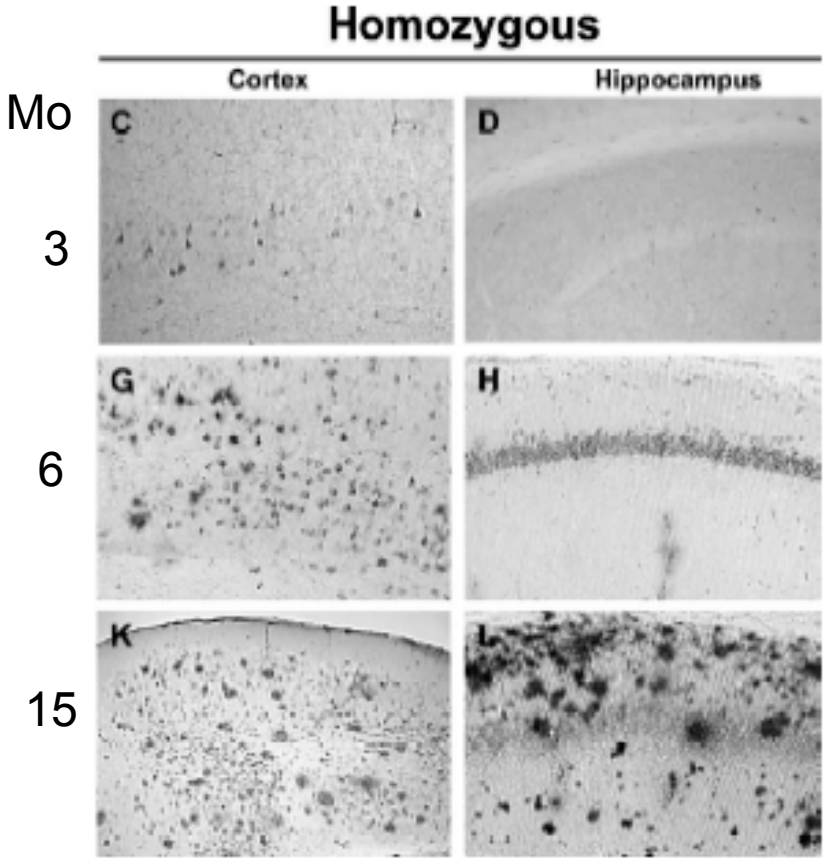
APP Transgenic mice accumulate amyloid β with little neurotoxicity



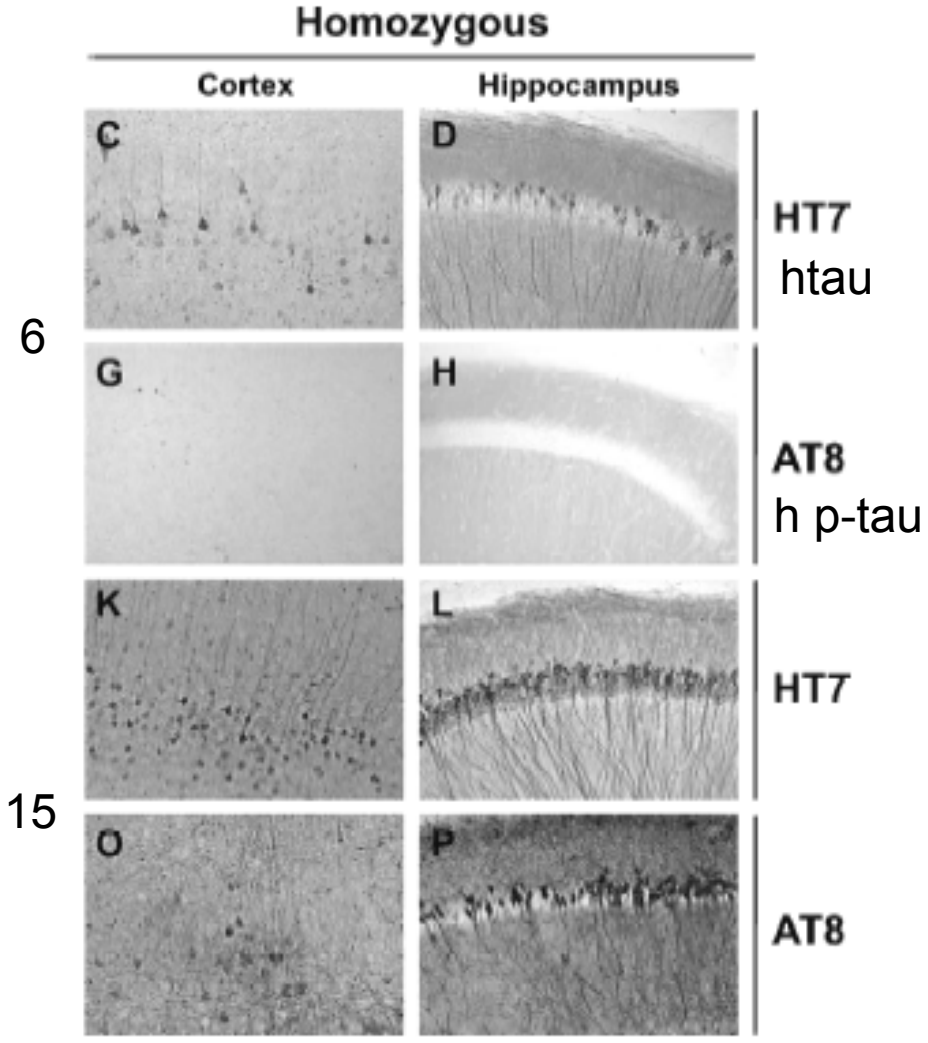
Amyloid β is neurotoxic in transgenic flies



Alzheimer disease animal models: triple transgenic mice PS1M146V-APPsw-TauP301L



Anti-Aβ



Summary

1) AD is heterogeneous (95% “sporadic”, 5% familial)
2) Age and apoE4 are the major risk factors in sporadic AD
3) Amyloid β accumulates due to an imbalance in production/removal
4) Intraneuronal tau is hyperphosphorylated
5) Amyloid β oligomers and soluble p-tau may be neurotoxic