



University of Thessaly



School of Medicine



# Μοριακή βάση της νόσου Alzheimer

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Πανεπιστήμιο Θεσσαλίας*

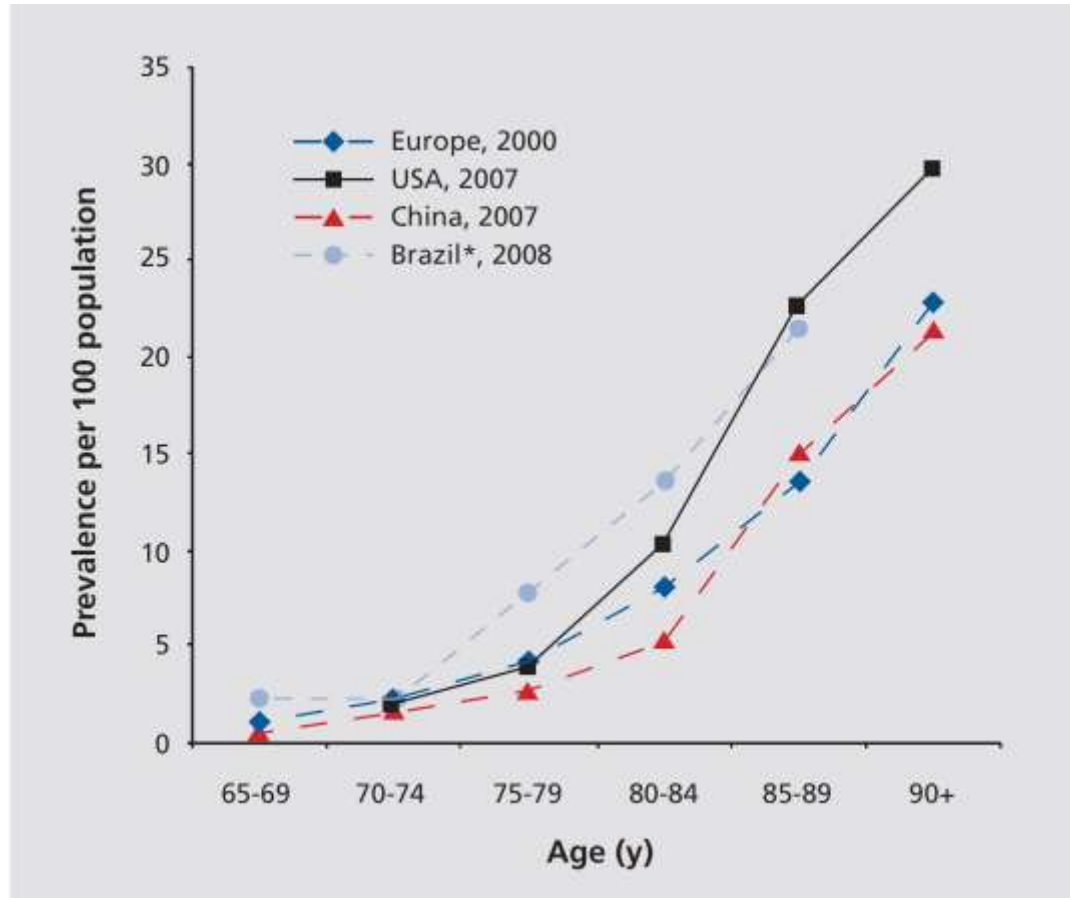
# Νόσος Alzheimer

Disorder	Class of evidence	Range of ages included (y)	Median estimates				Rate ratio, M/F†	Age(s), y, of peak incidence
			Annual incidence		Prevalence			
			Rate/100,000	No.*	Rate/1,000	No.*		
Alzheimer disease	I,II	≥65	1,275	468,000	67	2,459,000	0.5	≥80

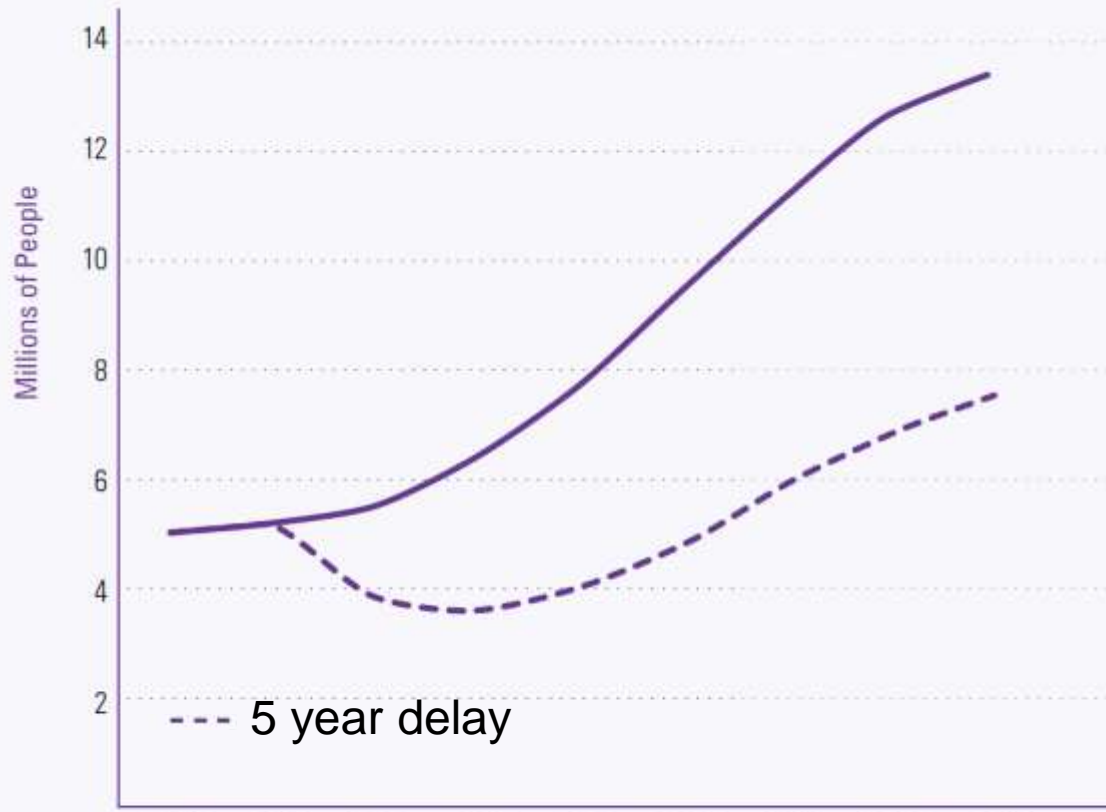
## Πληθυσμό >65 ετών

- Επίπτωση: 1.275 νέα περιστατικά/100.000/έτος
- Επιπολασμός: 6.700 /100.000

# Νόσος Alzheimer



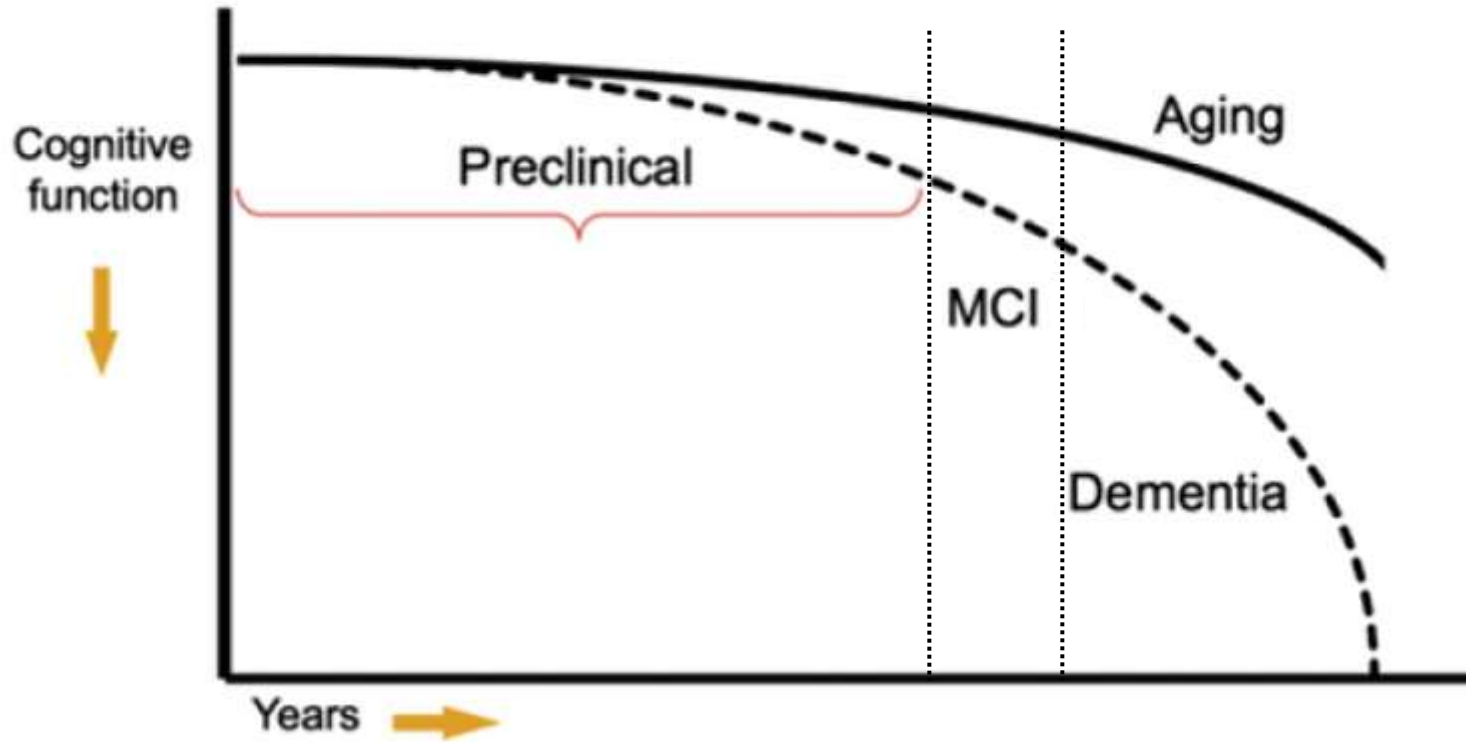
Americans Age 65 and Older with Alzheimer's Disease, 2010–2050



	2010	2015	2020	2025	2030	2035	2040	2045	2050
— Current Trajectory	5.1	5.3	5.6	6.5	7.8	9.5	11.2	12.7	13.5
- - - Delayed Onset	5.1	5.3	4.0	3.8	4.2	5.1	6.1	7.1	7.7
Decrease		0.0	1.6	2.7	3.6	4.4	5.1	5.6	5.8

# **Κλινική εικόνα της νόσου διαγνωστικά κριτήρια**

## The continuum of Alzheimer's disease



## **Panel: Imaging and CSF biomarker categories in Alzheimer's disease**

### **Brain A $\beta$ -plaque deposition**

- CSF A $\beta_{1-42}$
- PET A $\beta$  imaging

### **Neurodegeneration**

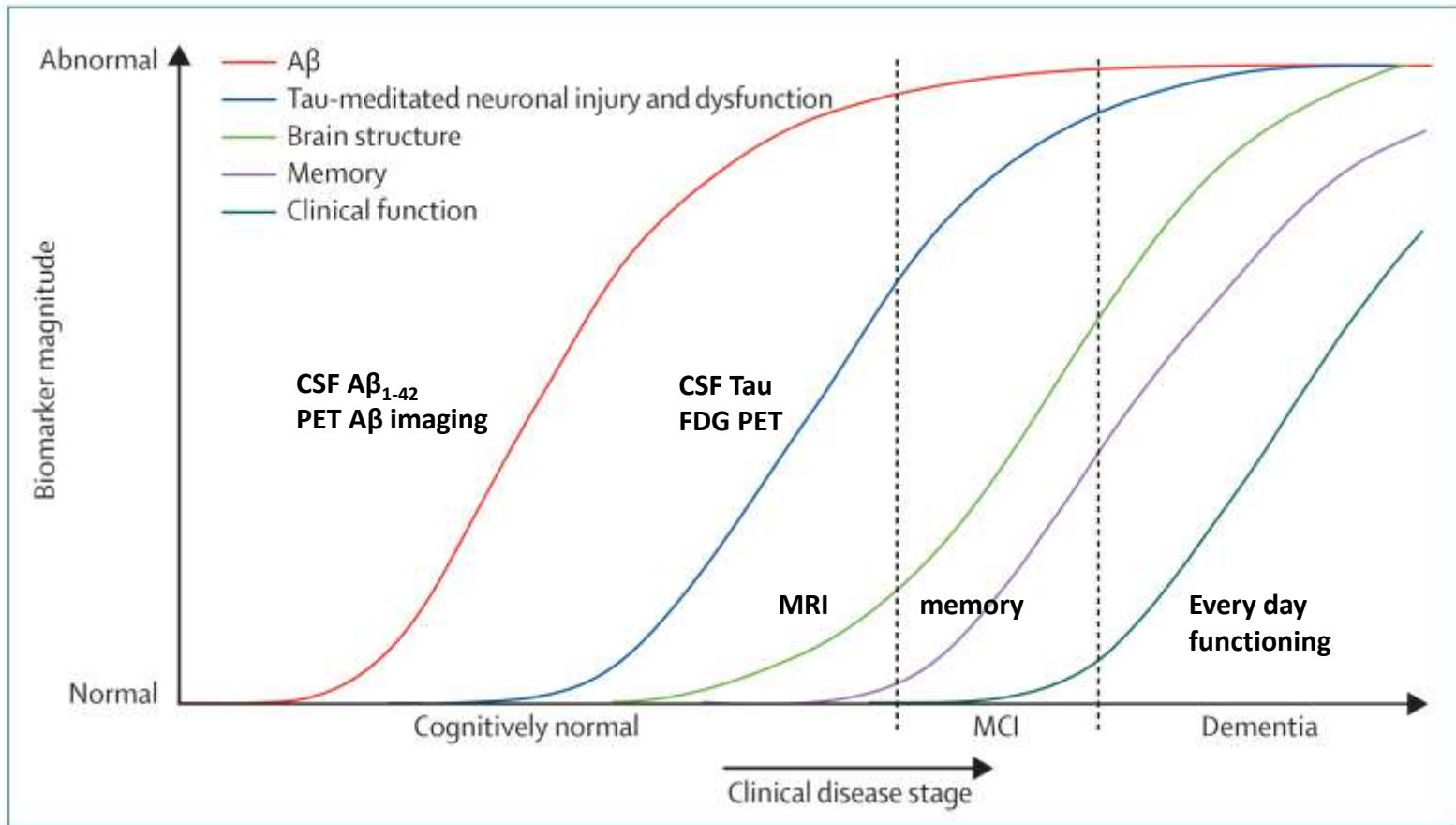
- CSF tau
- Fluorodeoxyglucose-PET
- Structural MRI

A $\beta$ = $\beta$ -amyloid.

Preclinical stage

MCI

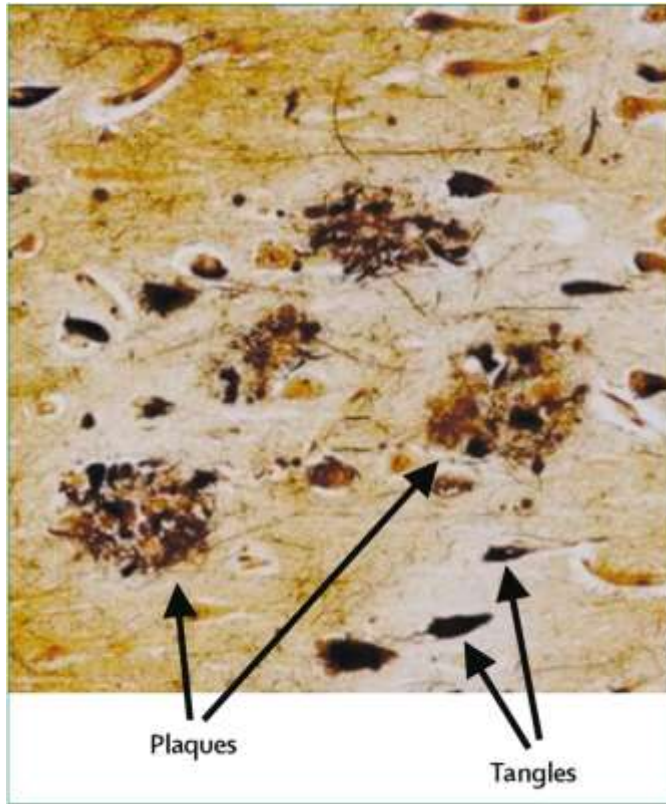
AD



*Lancet Neurol 2010; 9: 119–28. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade*



# Παθοφυσιολογία της νόσου Alzheimer



Plaques

Tangles

Neuronal loss

Loss of synapses

Dystrophic neurites

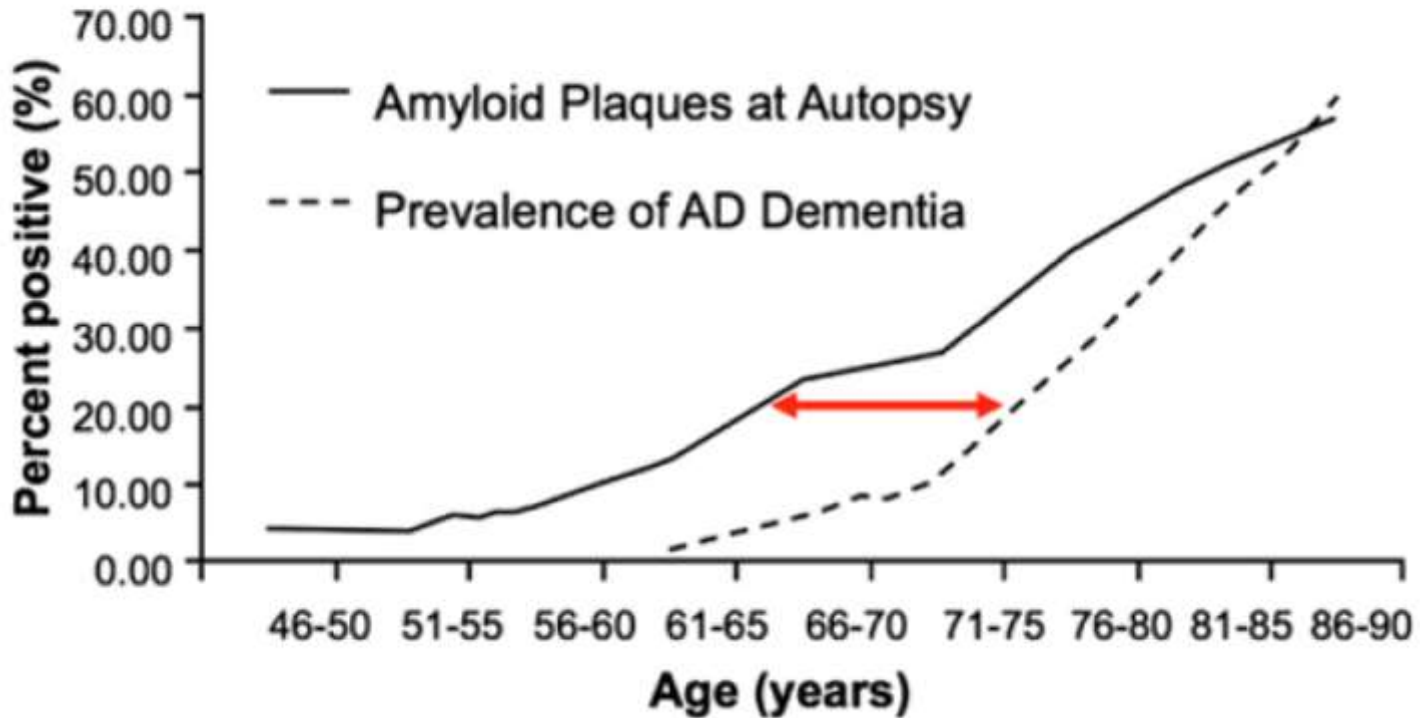
neuropil threads

amyloid angiopathy

Gross atrophy

Gliosis

## Appearance of Plaques vs. Dementia



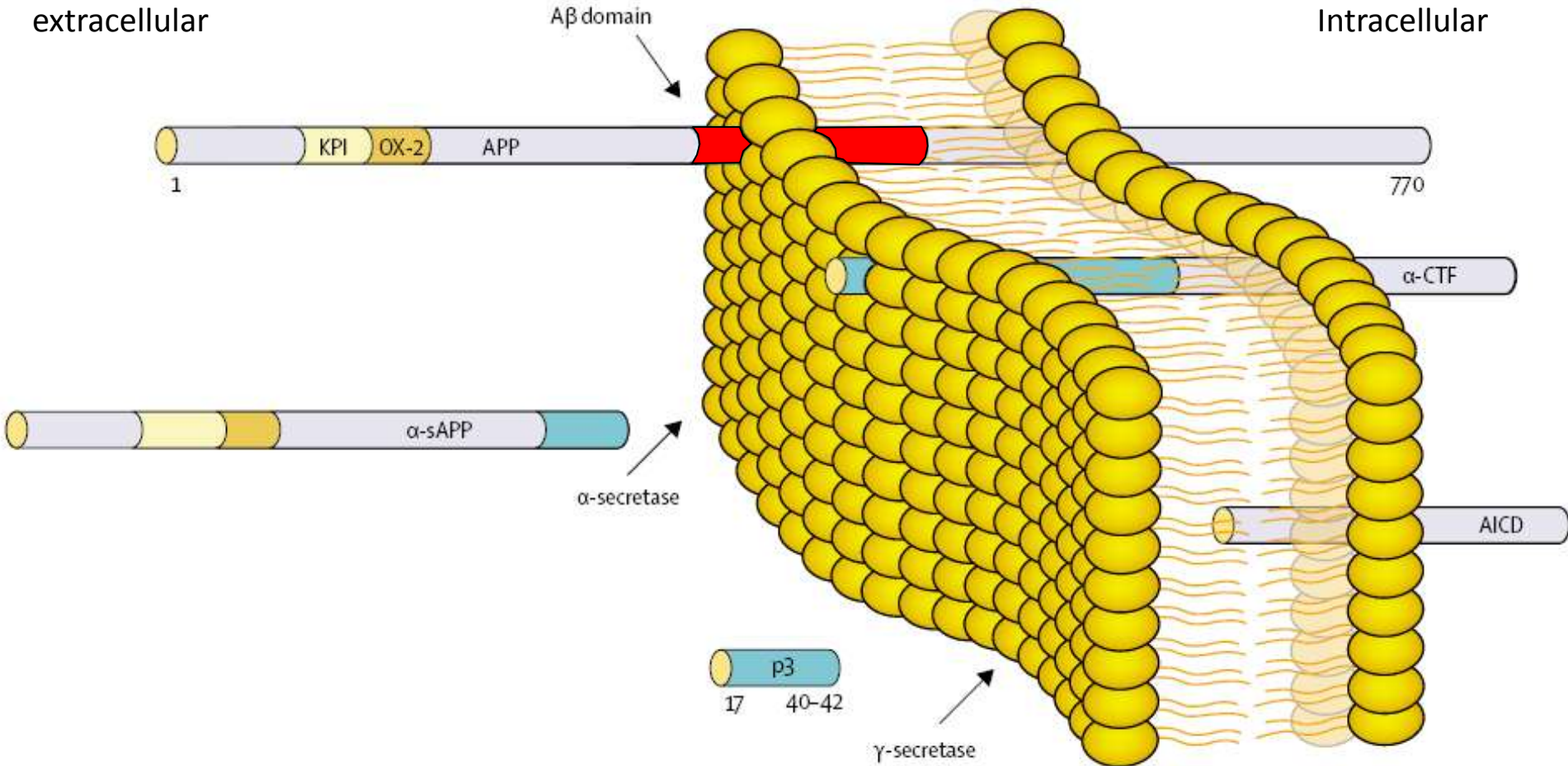
# Παραγωγή Αβ αμυλοειδούς

α-secretase pathway (non-amyloidogenic)

extracellular

Aβ domain

Intracellular



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α-secretase pathway (non-amyloidogenic)

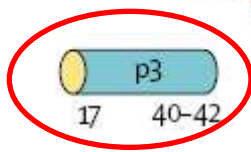
extracellular

Aβ domain

Intracellular



α-secretase



γ-secretase

α-CTF

AICD

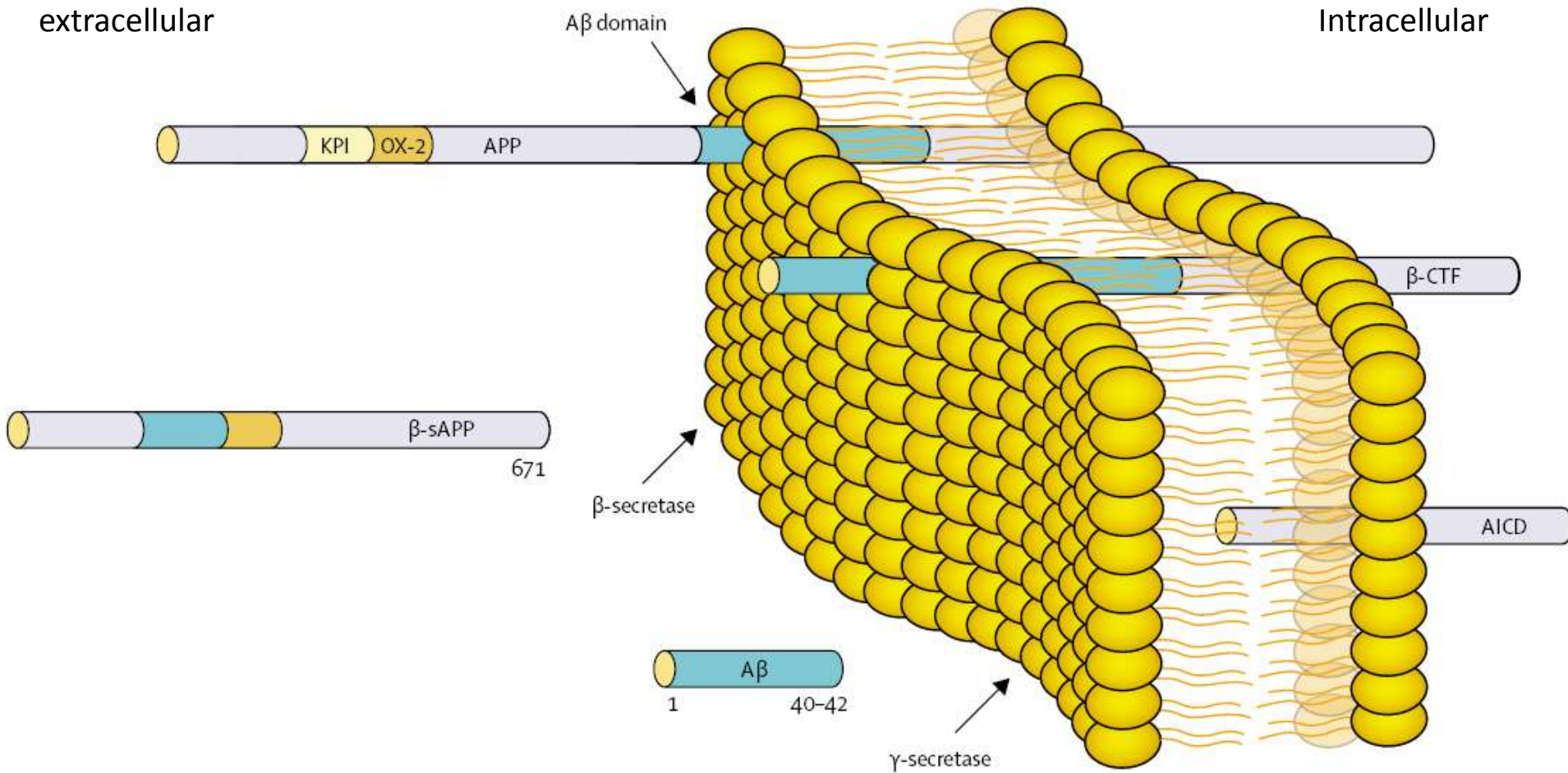


# Παραγωγή Αβ αμυλοειδούς

β-secretase pathway (amyloidogenic)

extracellular

Intracellular

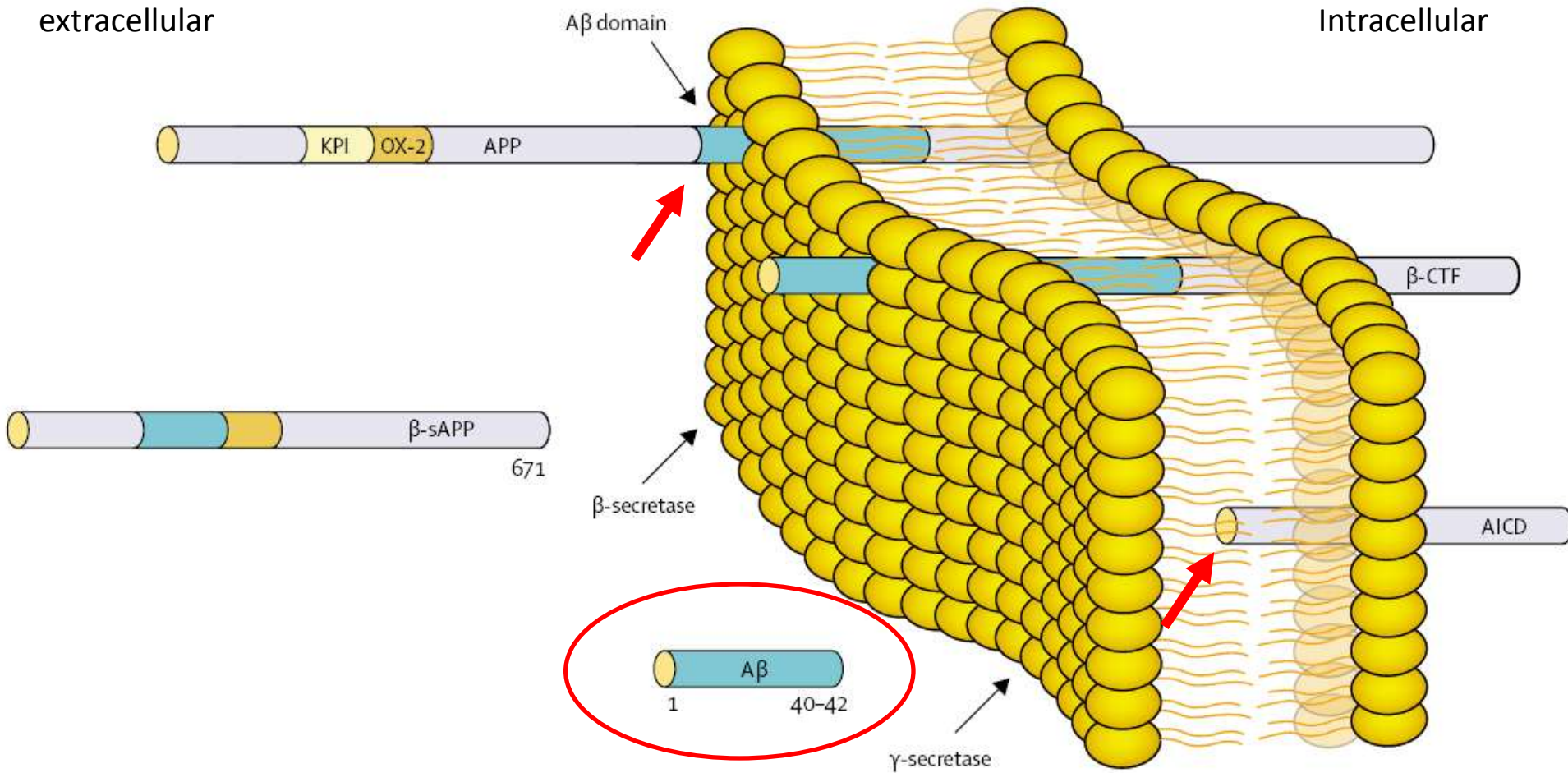


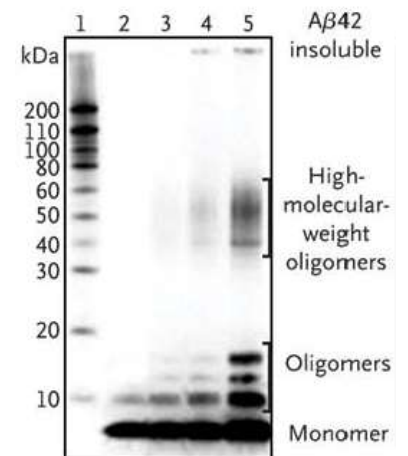
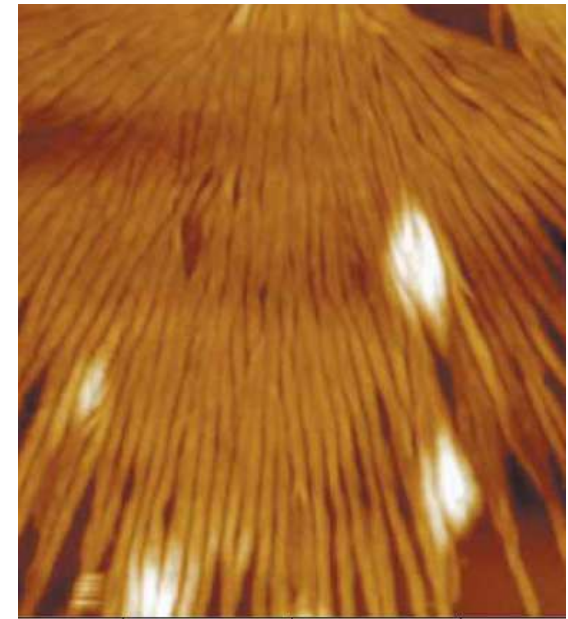
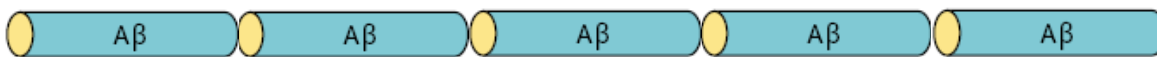
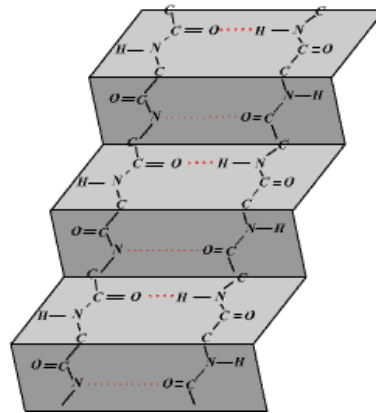
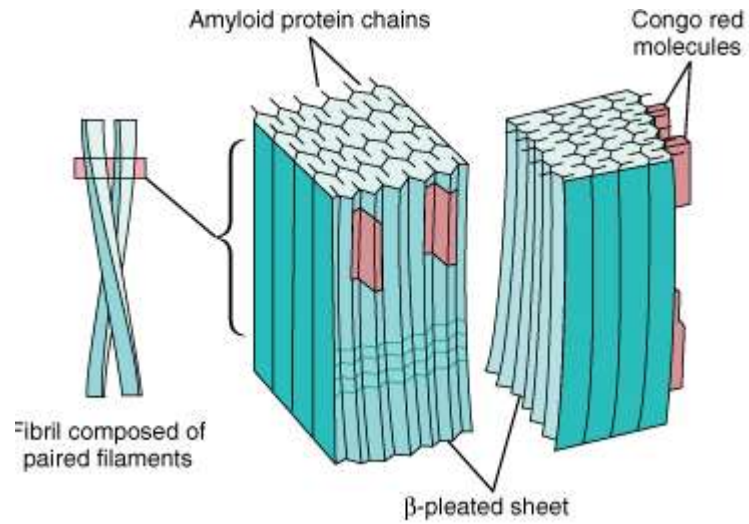
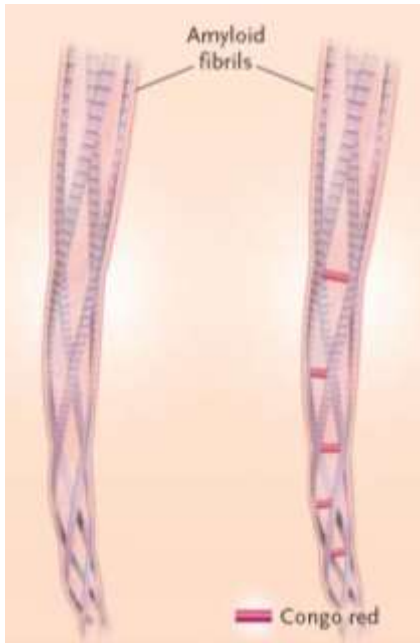
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extracellular

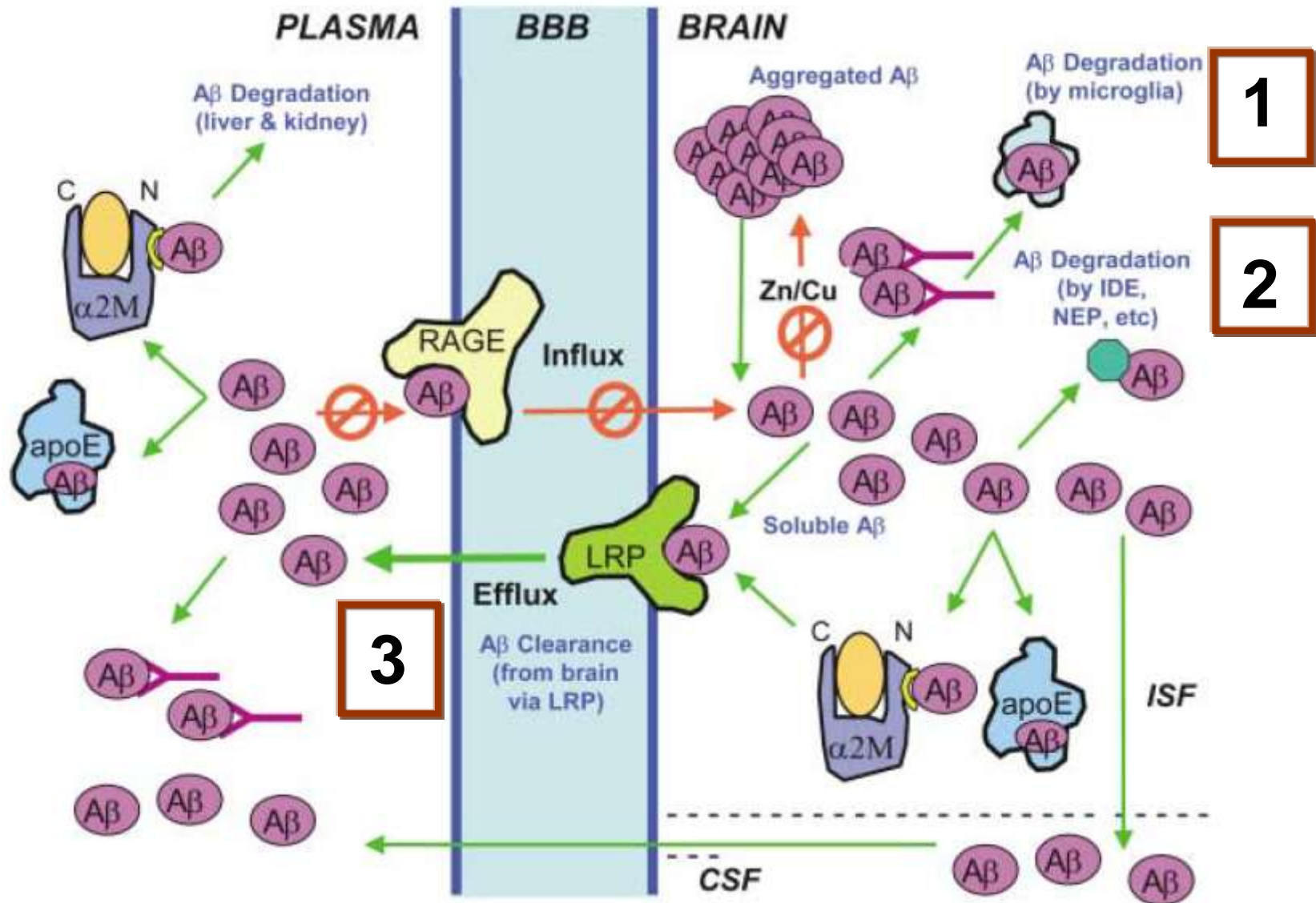
Intracellular





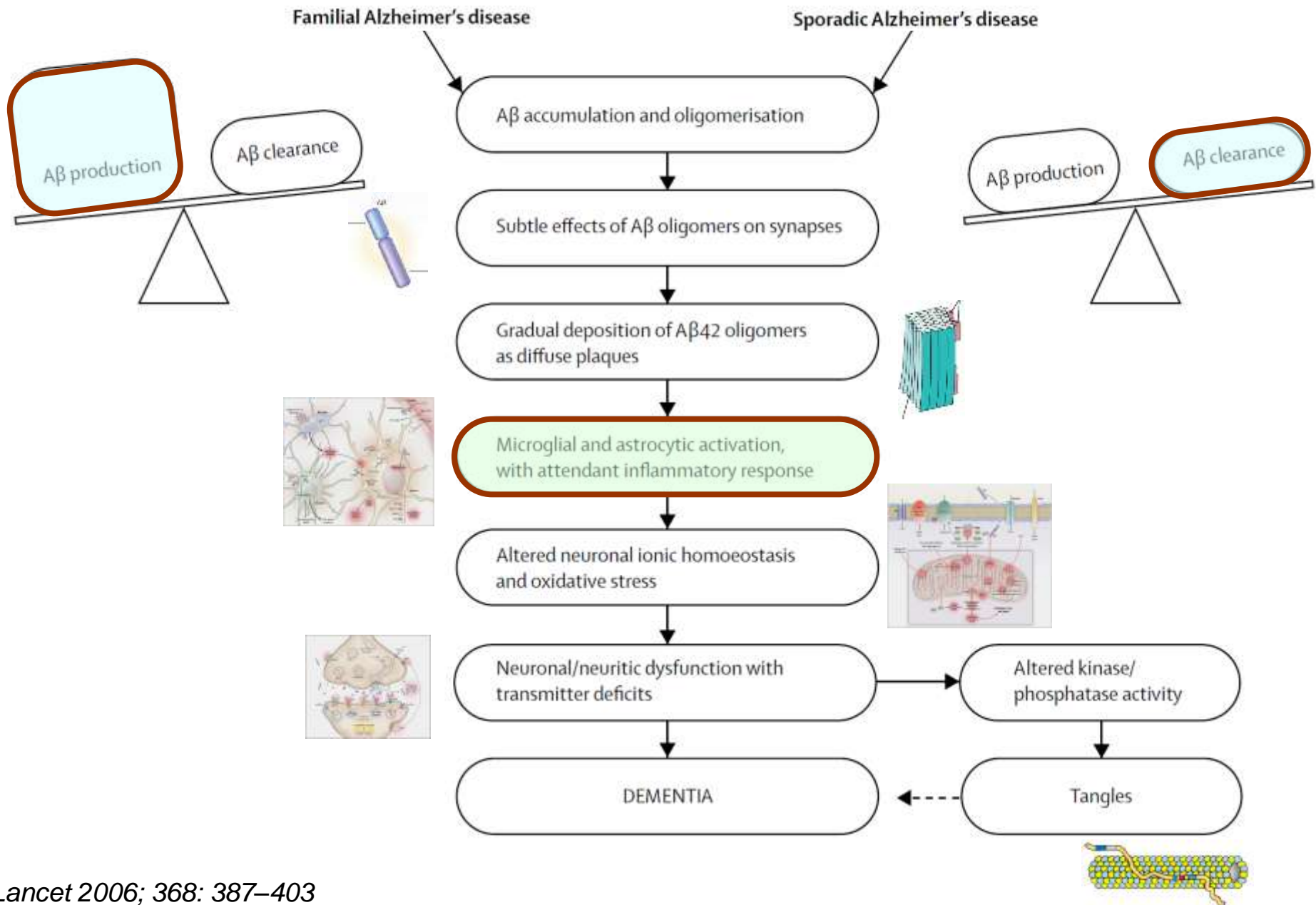


# Κάθαρση Αβ αμυλοειδούς

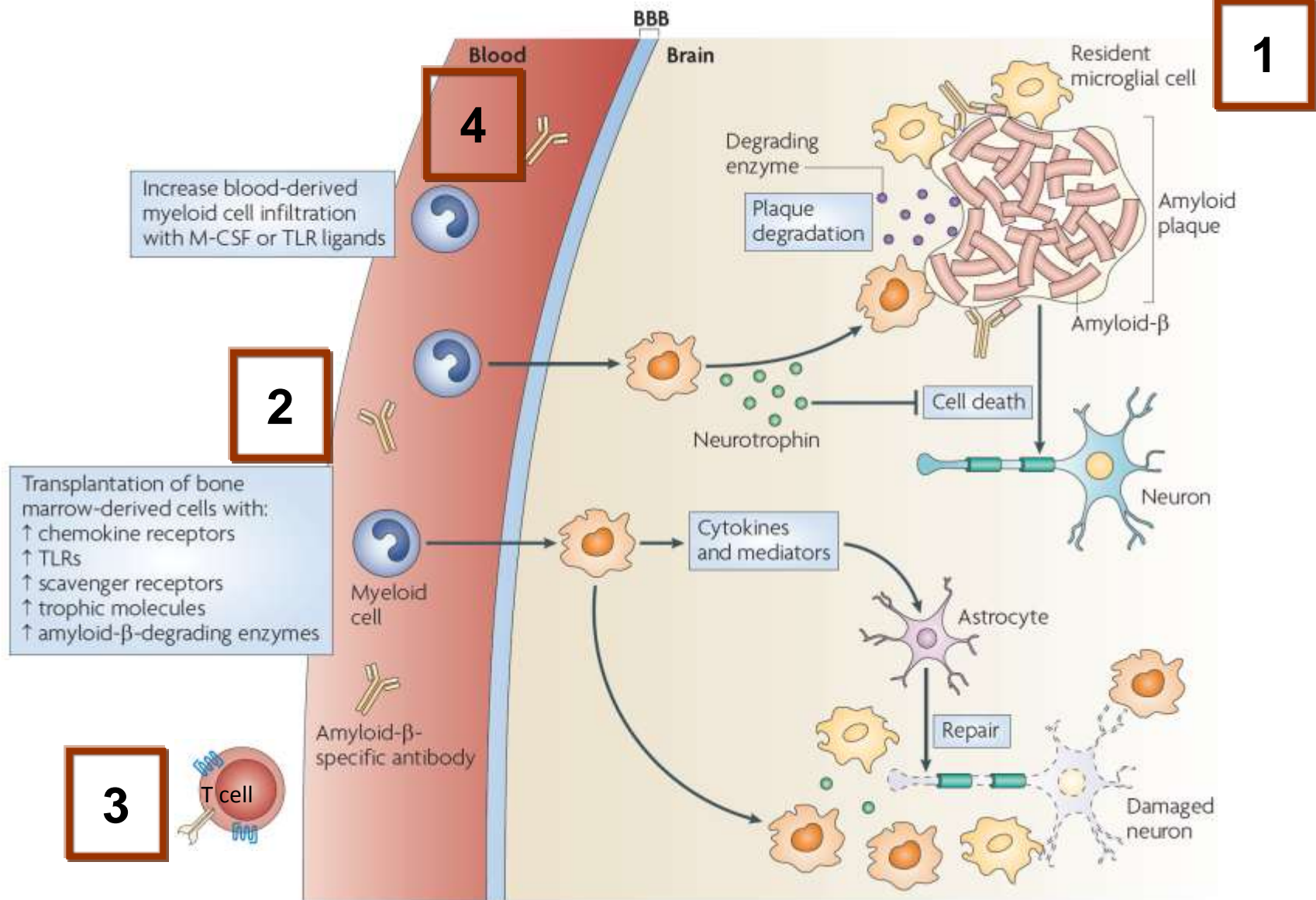


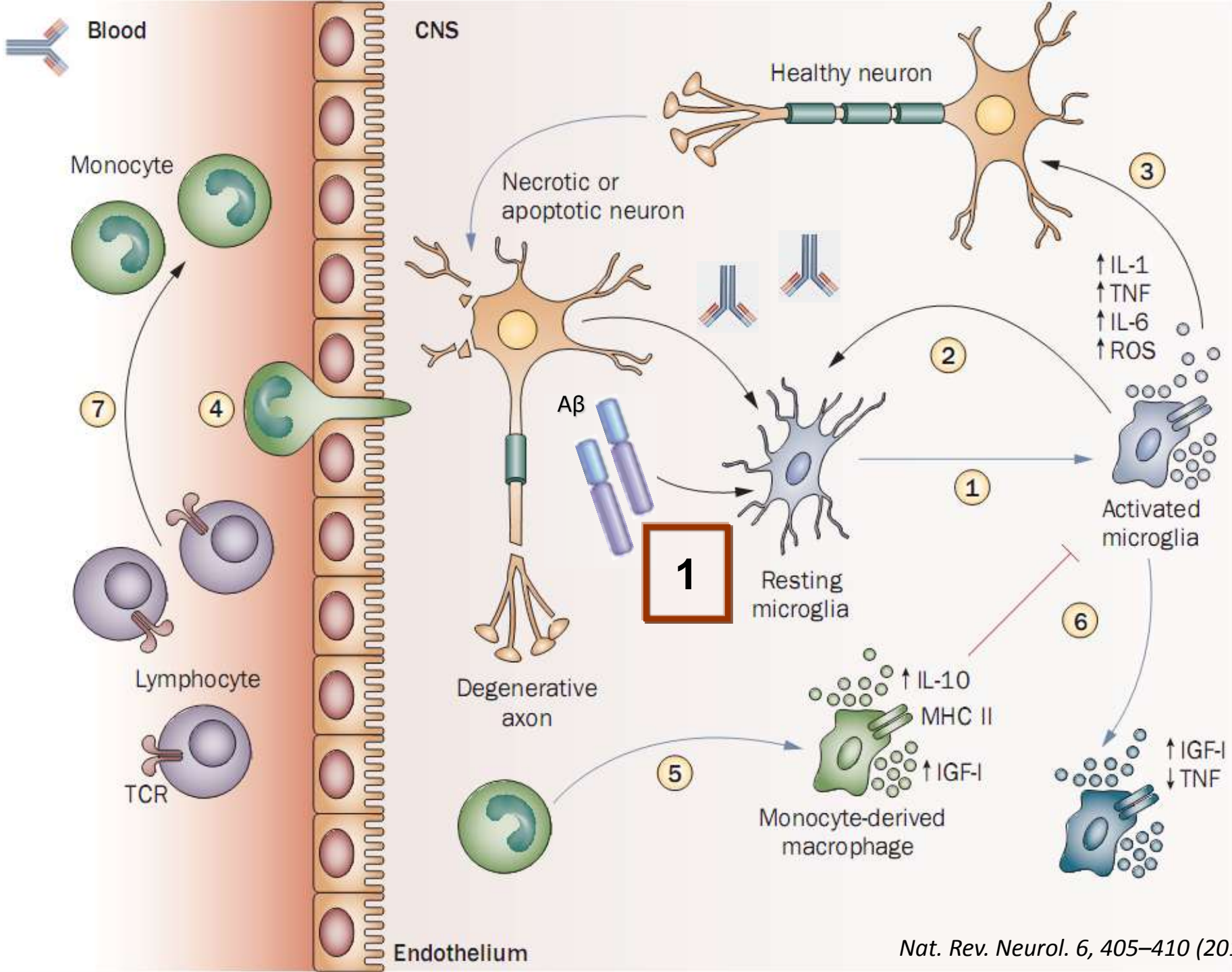


# Amyloid hypothesis

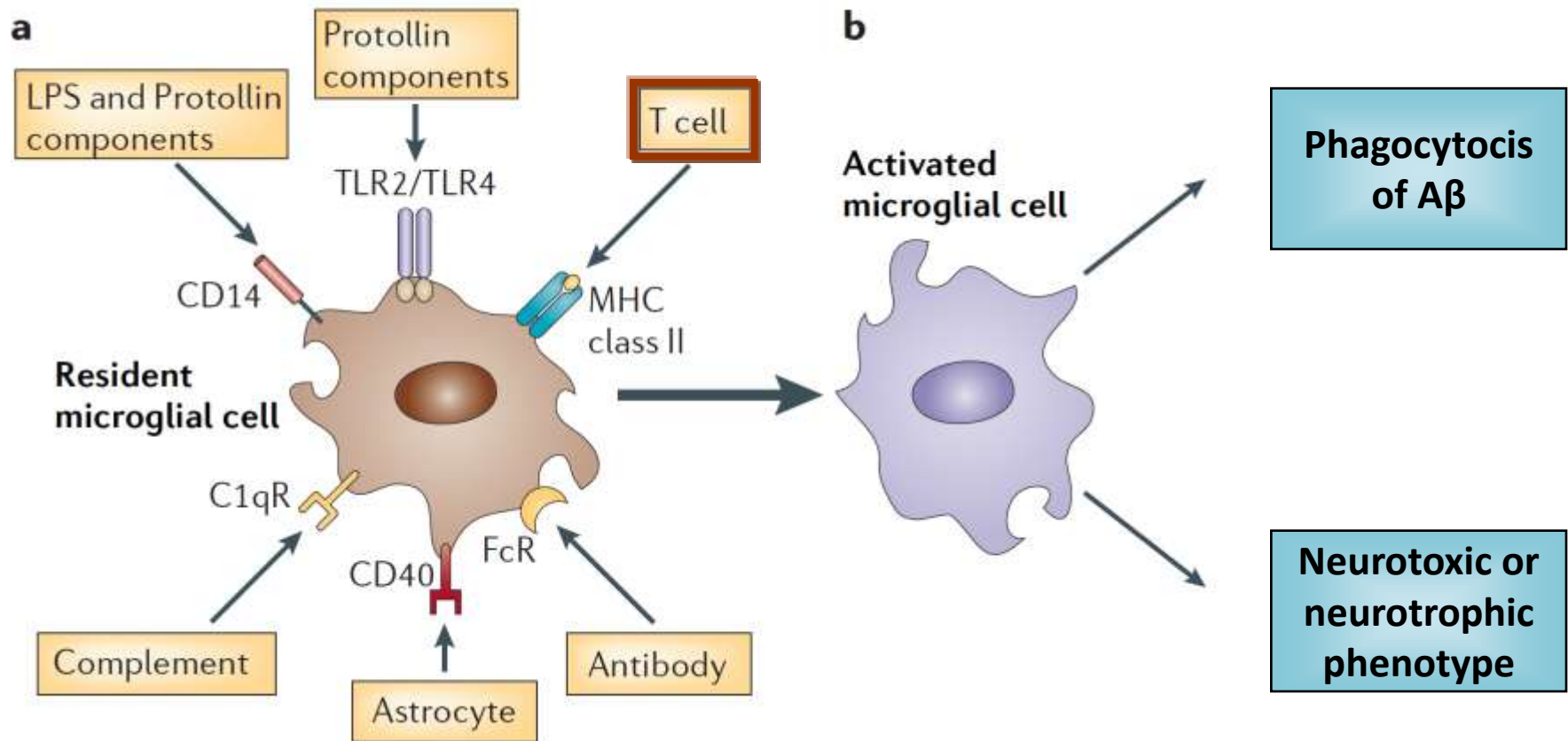


# Ανοσιακή απάντηση στο Αβ-πεπτίδιο





# Th1 vs Th2



# Familial AD

1 to 2 percent of AD cases



# Γονίδια που εμπλέκονται στην παθογένεια της νόσου Alzheimer

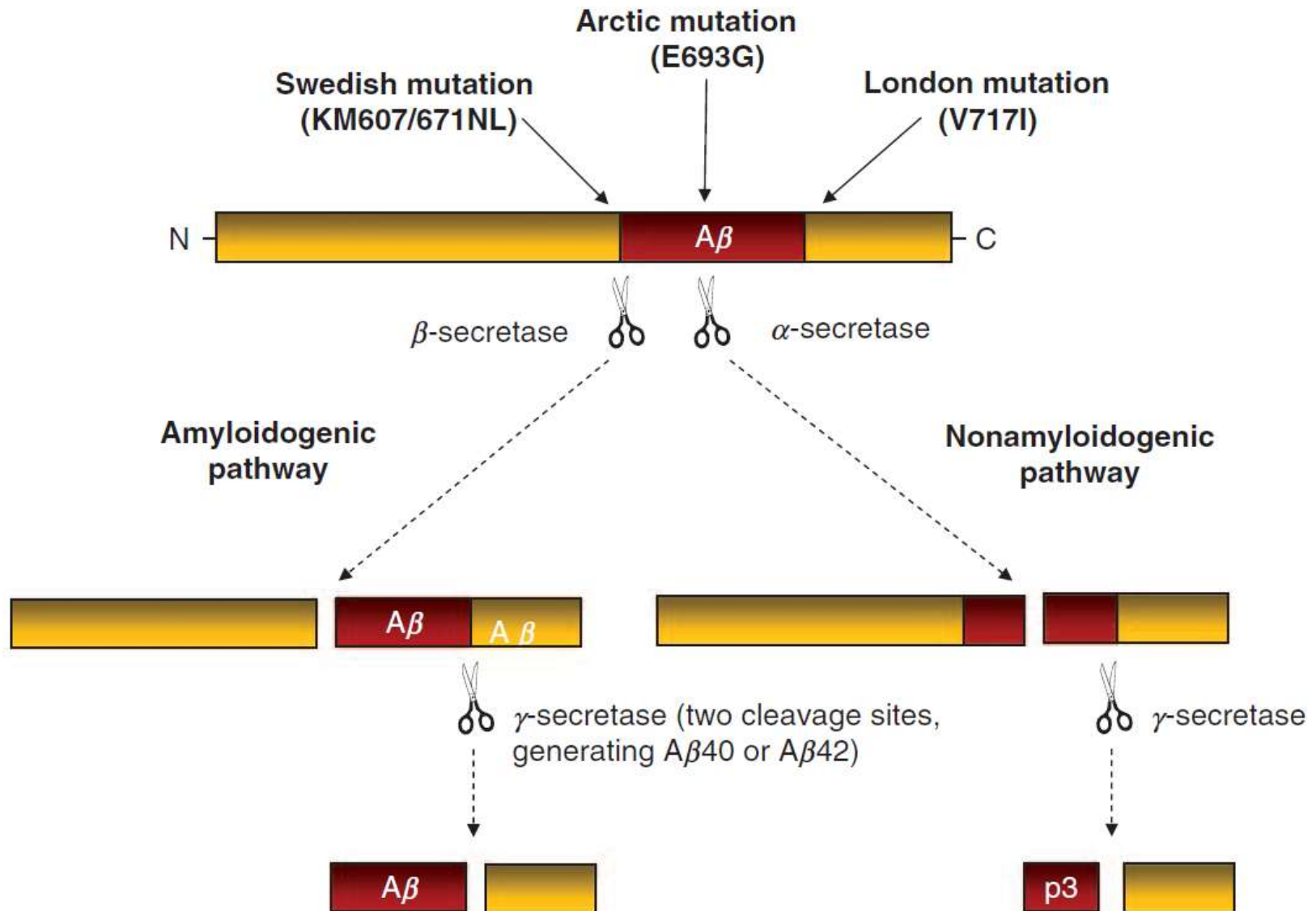
Γονιδιακό προϊόν	Χρωμόσ.	Είδος Βλάβης	Διάρκεια νόσου (έτη)	% EOAD	%FAD
APP	21	Τρισωμία	30-50 χρ.	-	-
APP	21	Μεταλλαγή	45-66	<1	<0.1
PS1	14	Μεταλλαγή	28-62	<30-50	1-2
PS2	1	Μεταλλαγή	40-85	<1	<0.1

# amyloid precursor protein

linkage analyses chromosome 21

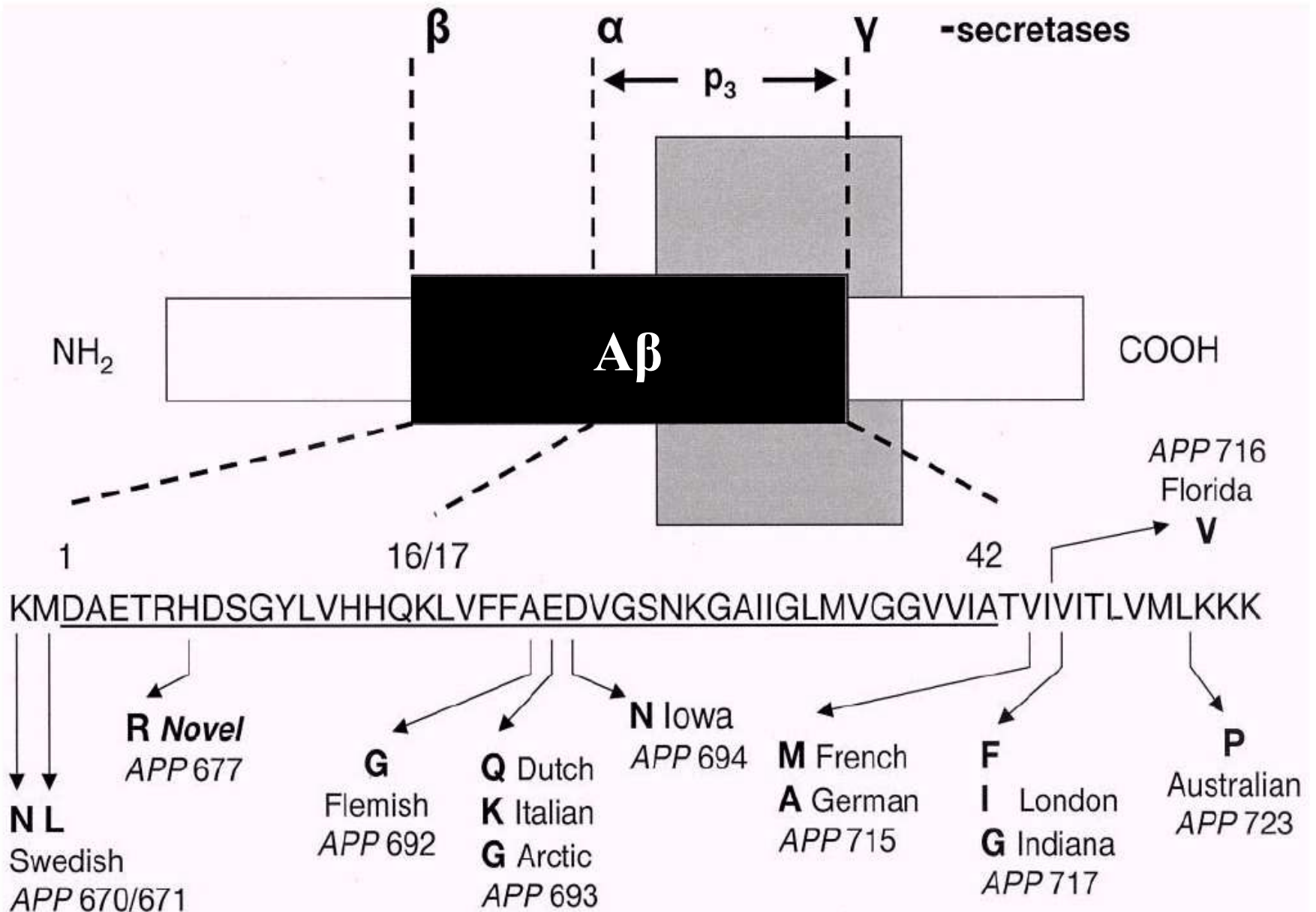
Down' s syndrome (trisomy 21)

# amyloid precursor protein





Mutation Name	Mutation Locus	Mutational Effect	Neuropathological Features
Swedish	Lys670Met/Asn671Leu	Increases A $\beta$ 40, A $\beta$ 42	AD pathology
	His677Arg	Unknown	AD pathology
	Asp678Asn	Unknown	N/A
Flemish	Ala692Gly	Increases A $\beta$ 40, A $\beta$ 42	Cerebral hemorrhage with amyloid angiopathy
Arctic	Glu693Gly	Increases total A $\beta$ , increases protofibril formation	AD pathology
Dutch	Glu693Gln	Decreases A $\beta$ 42, increases protofibril formation	Cerebral hemorrhage with amyloid angiopathy
Italian	Glu692Lys	Altered fibrillization	Cerebral hemorrhage with amyloid angiopathy
Iowa	Asp694Asn	Altered fibrillization	Severe amyloid angiopathy
Iranian	Thr714Ala	Unknown	AD pathology
Austrian	Thr714Ile	Increases A $\beta$ 42	AD pathology
French	Val715Met	Decreases A $\beta$ 40, increases A $\beta$ 42	AD pathology
German	Val715Ala	Unknown	AD pathology
Florida	Ile716Val	Increases A $\beta$ 42	AD pathology
London	Val717Ile	Increases A $\beta$ 42	AD pathology
Indiana	Val717Phe	Increases A $\beta$ 42	AD pathology
	Val717Gly	Unknown	AD pathology
	Val717Leu	Increases A $\beta$ 42	AD pathology
Australian	Leu723Pro	Increases A $\beta$ 42, induces apoptosis	AD pathology

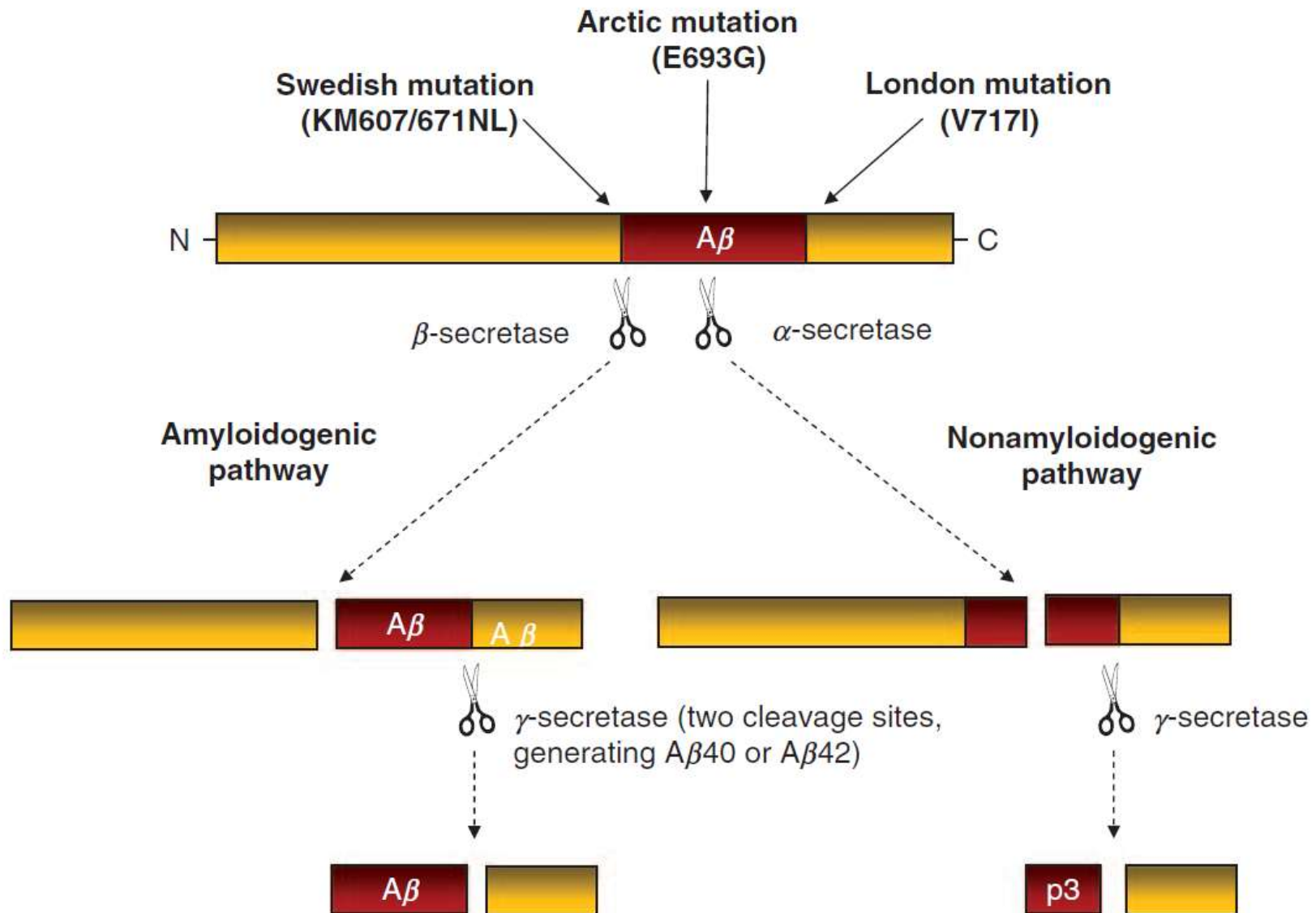


Να δείξω εικόνα με λοιπές μεταλλάξεις στο πρόδρομο μόριο του β-αμυλοειδούς που σχετίζονται με αμυλοειδωσική αγγειοπάθεια.

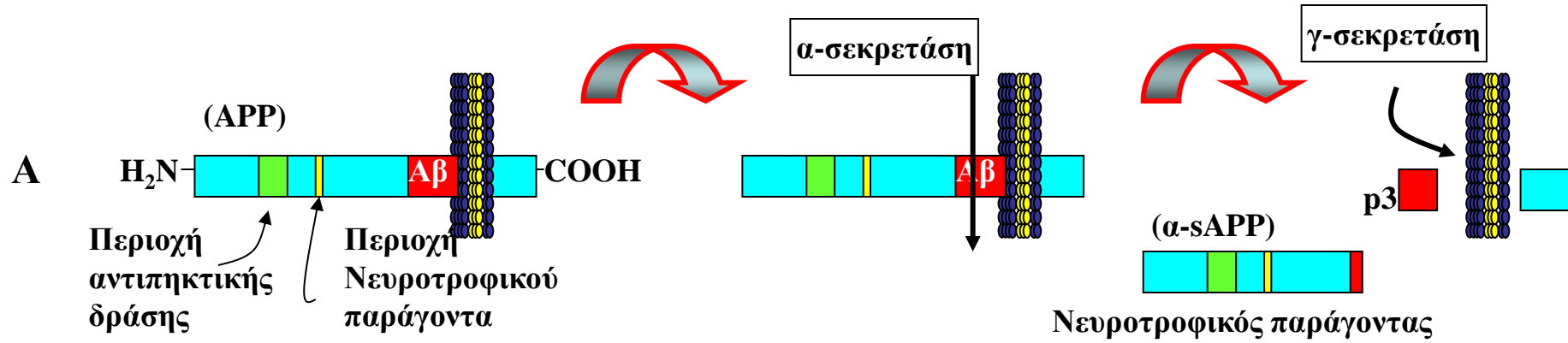
*Presenilin 1 (PS1) chromosome 14*  
*Presenilin 2 (PS2) chromosome 1*

Apart from the presenilins, the  $\gamma$ -secretase enzyme complex consists of nicastrin, aph-1, and pen-2

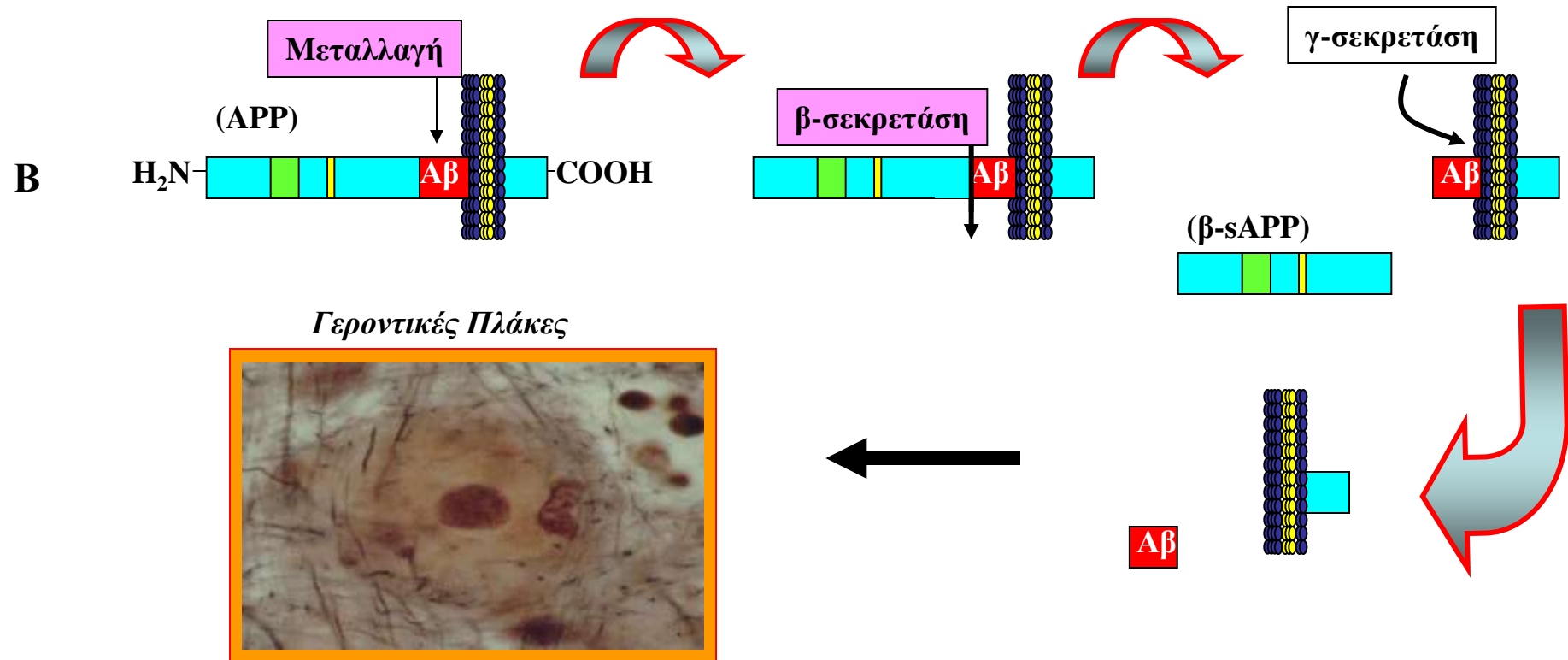
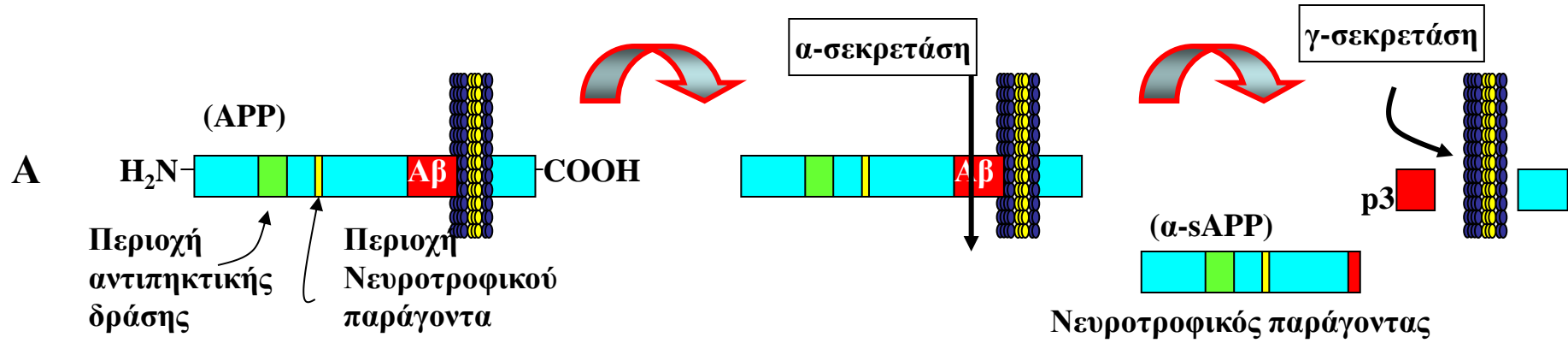
# $\gamma$ -secretase



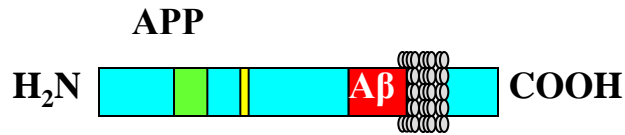
# Επίδραση των μεταλλαγών (APP) στη δημιουργία των εναποθέσεων του αμυλοειδούς



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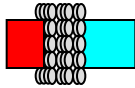




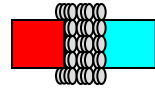
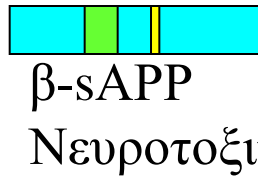


**α-σεκρετάση**

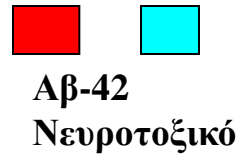
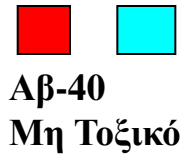
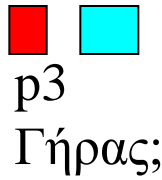
**β-σεκρετάση**

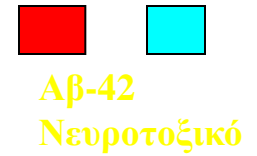
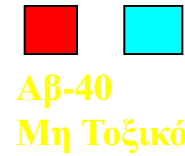
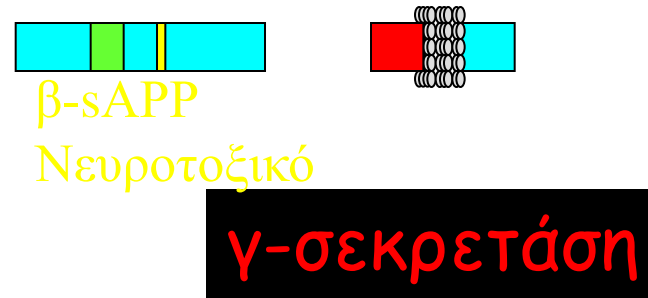
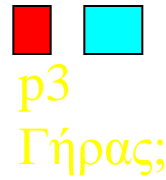
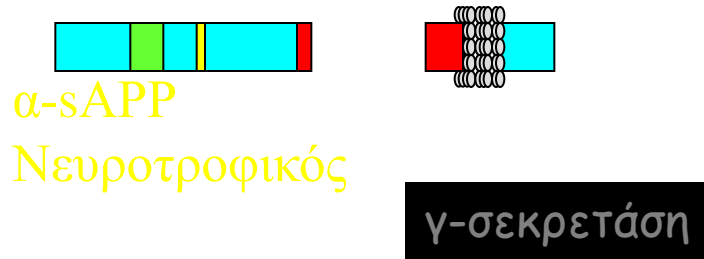
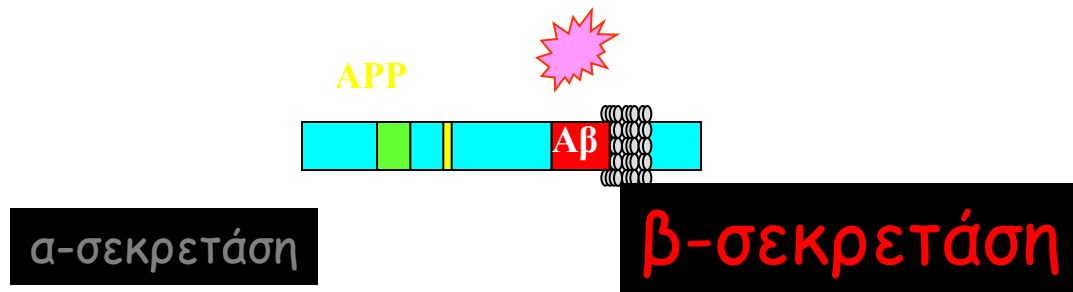


**γ-σεκρετάση**



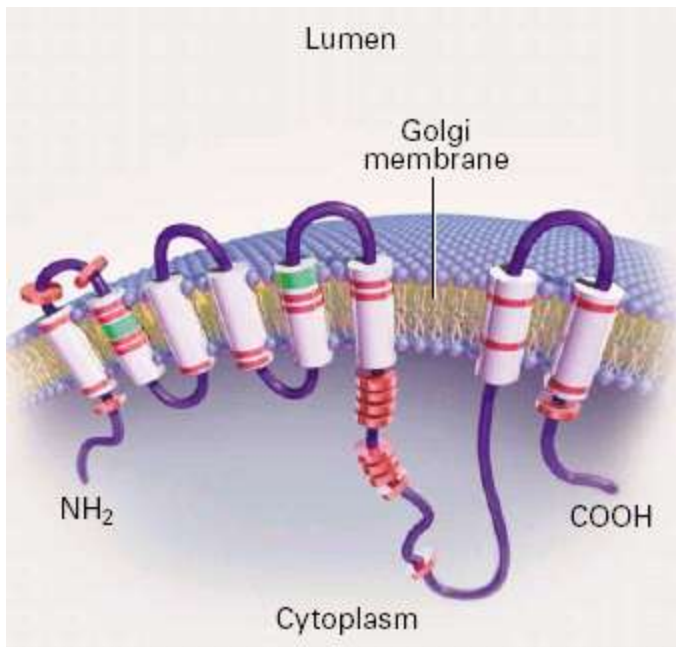
**γ-σεκρετάση**





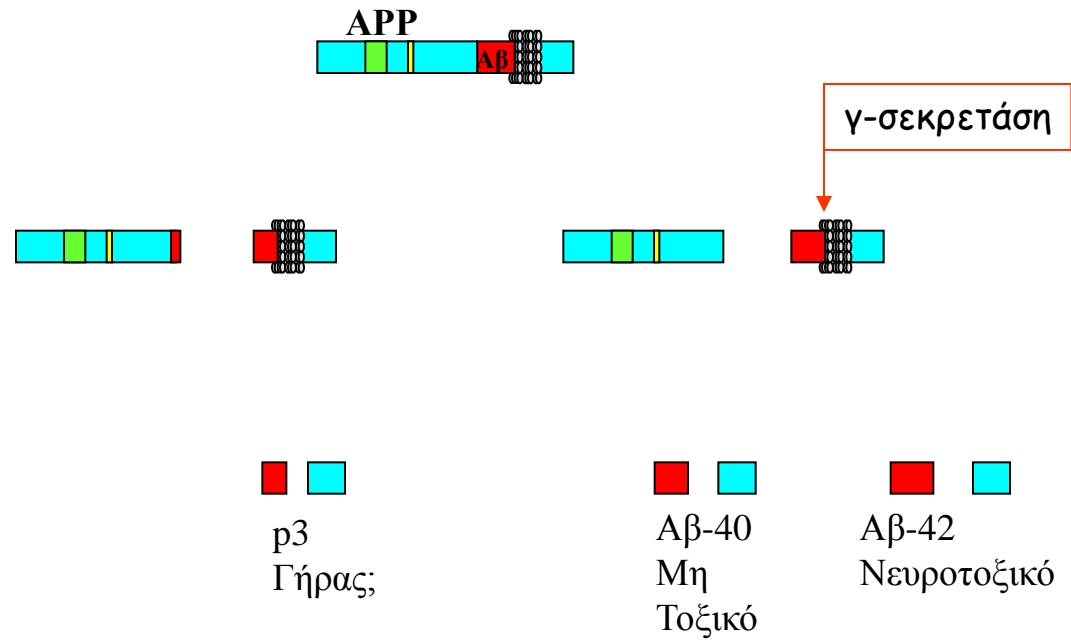
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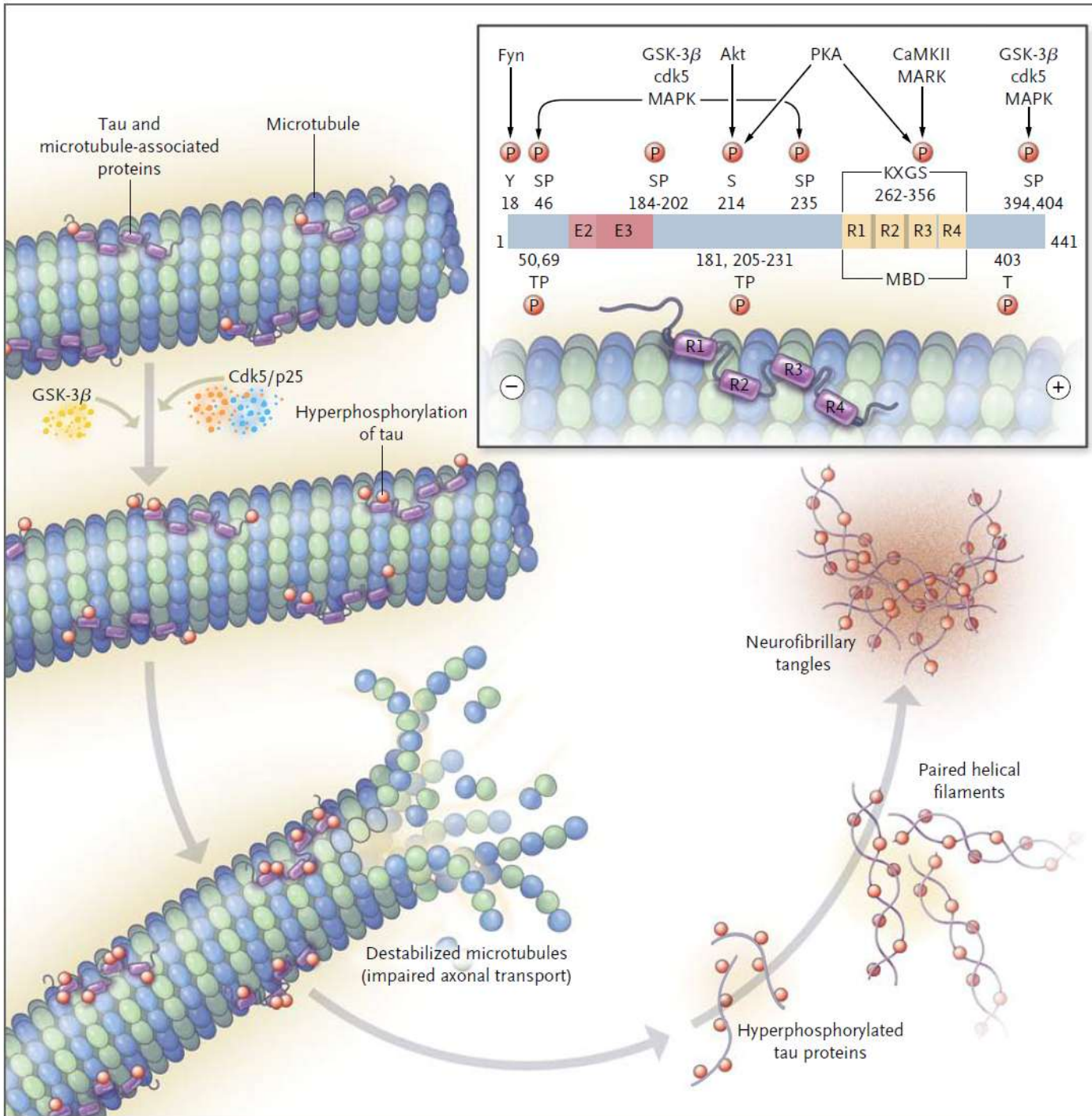


Presenilin 1

Presenilin 2



# Tau protein



# Tau protein

The number of neurofibrillary tangles is a pathologic marker of the severity of Alzheimer's disease.

Nevertheless, increased levels of phosphorylated and total tau in the cerebrospinal fluid correlate with reductions in scores on cognitive examinations. 34 Elevated levels of phosphotau amino acids T181, T231, and total tau in the cerebrospinal fluid together constitute a biomarker test with good accuracy for predicting incipient Alzheimer's disease in patients with mild cognitive impairment

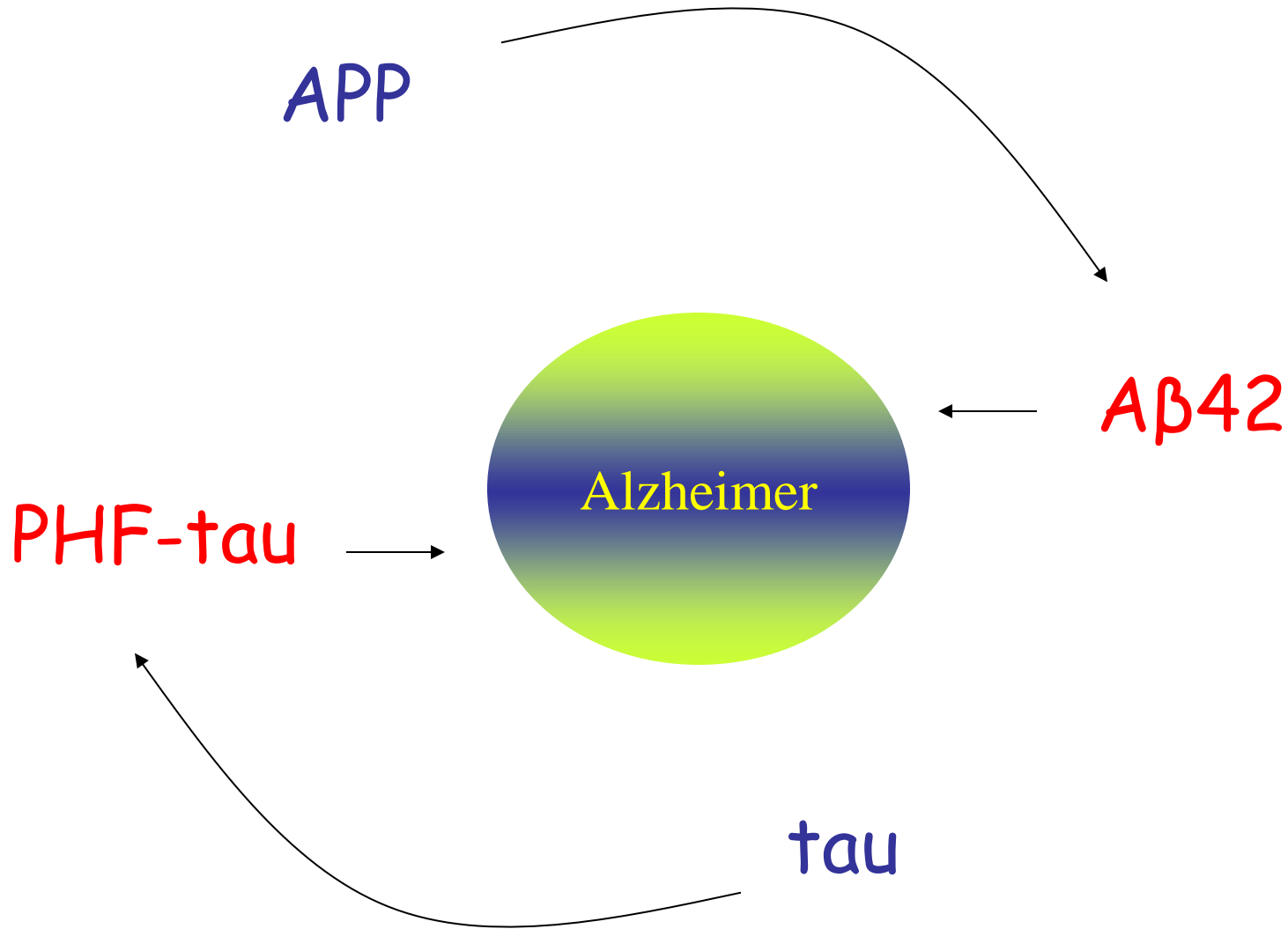
Tangles are known to evolve in an anatomically stereotypical fashion with the CA1 subfield of hippocampus, subiculum, layers II/IV of the entorhinal cortex, and the perirhinal region being the earliest affected brain areas

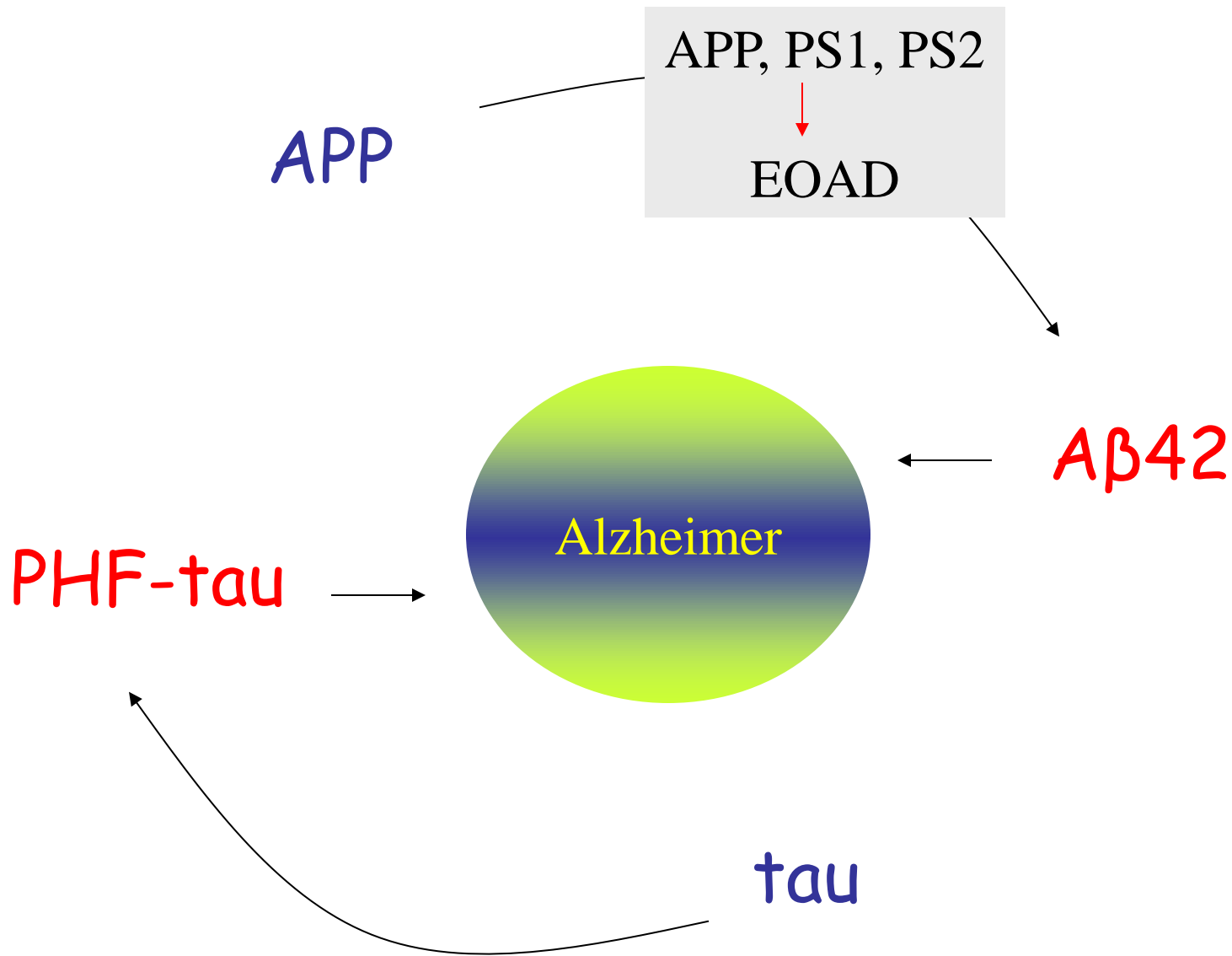
# Tau protein

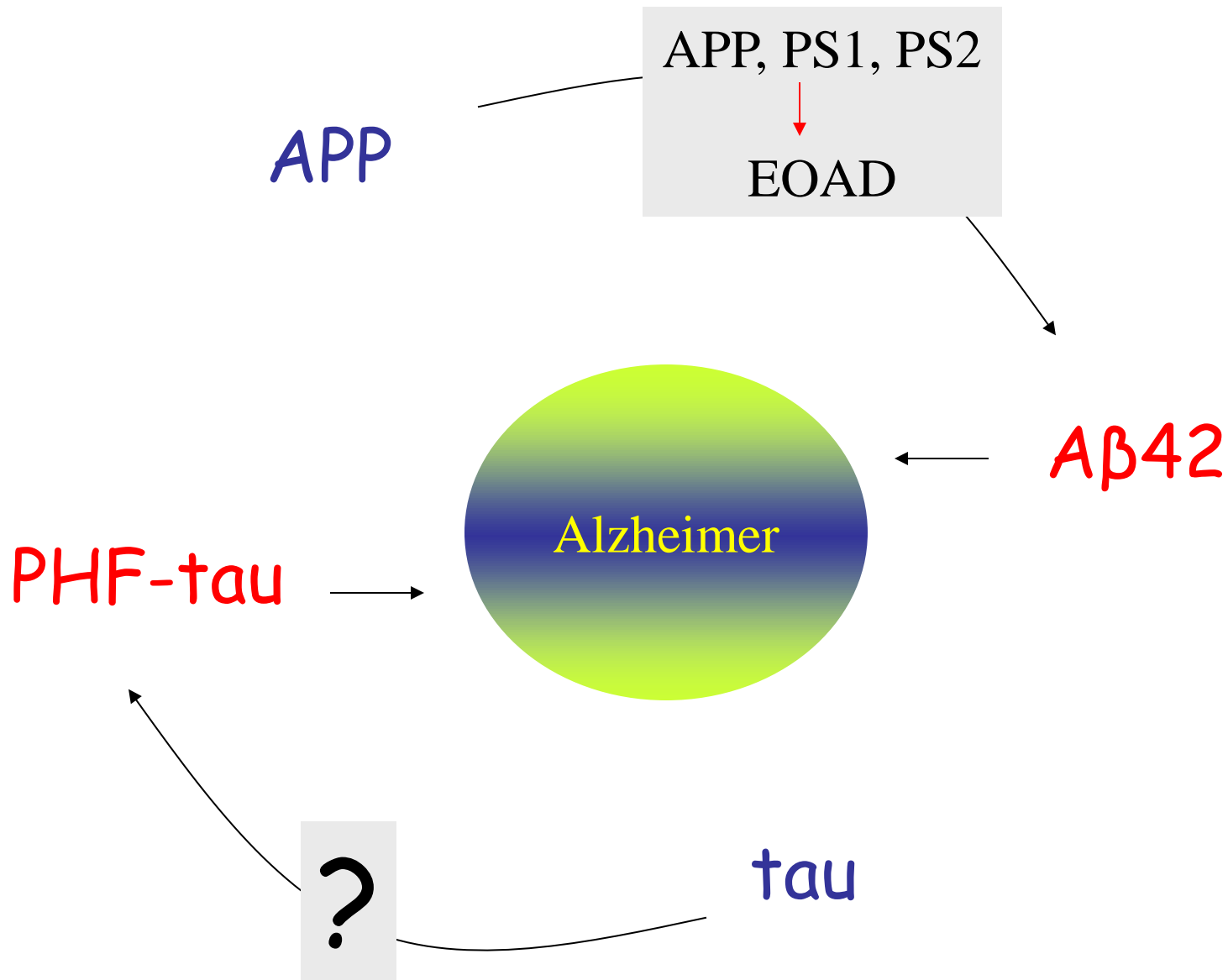
More than 40 mutations of *Tau* on chromosome 17 have been detected in frontotemporal dementia with parkinsonism. By contrast, *Tau* mutations do not occur in Alzheimer's disease

# **Genetics of Late-Onset Alzheimer's Disease**









APP

APP, PS1, PS2

EOAD

A $\beta$ 42

Alzheimer

PHF-tau

tau

LOAD

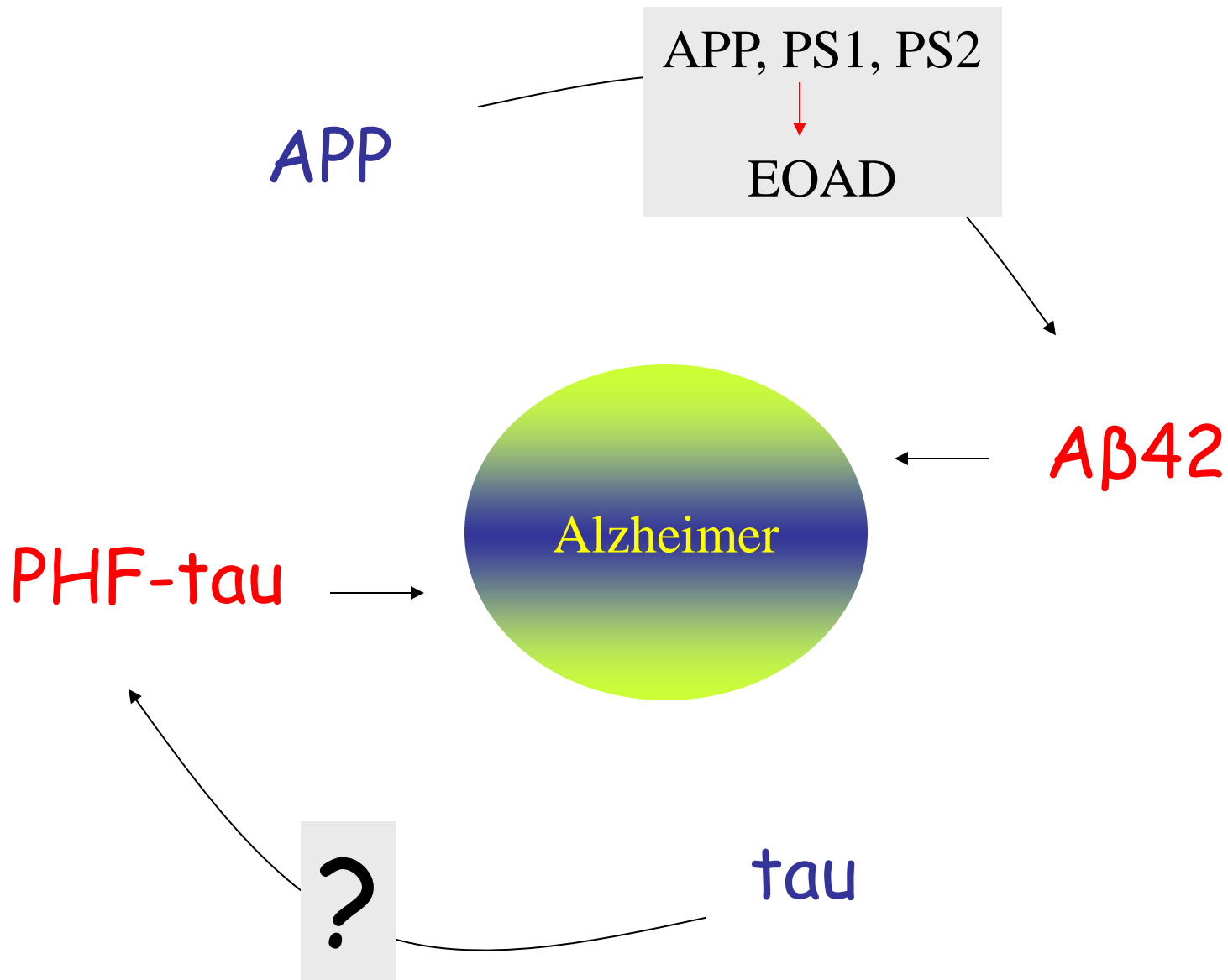
Χρωμόσωμα

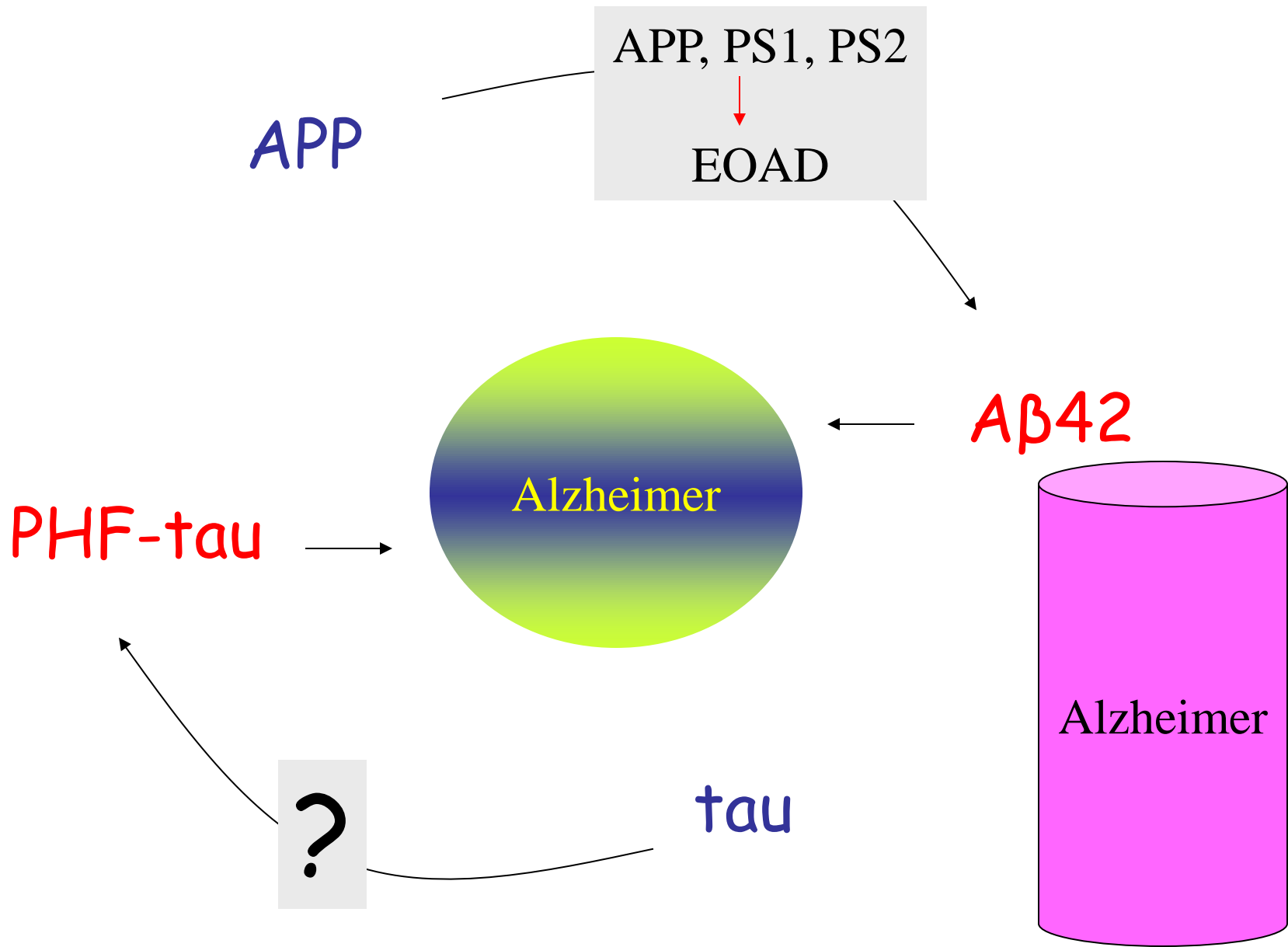
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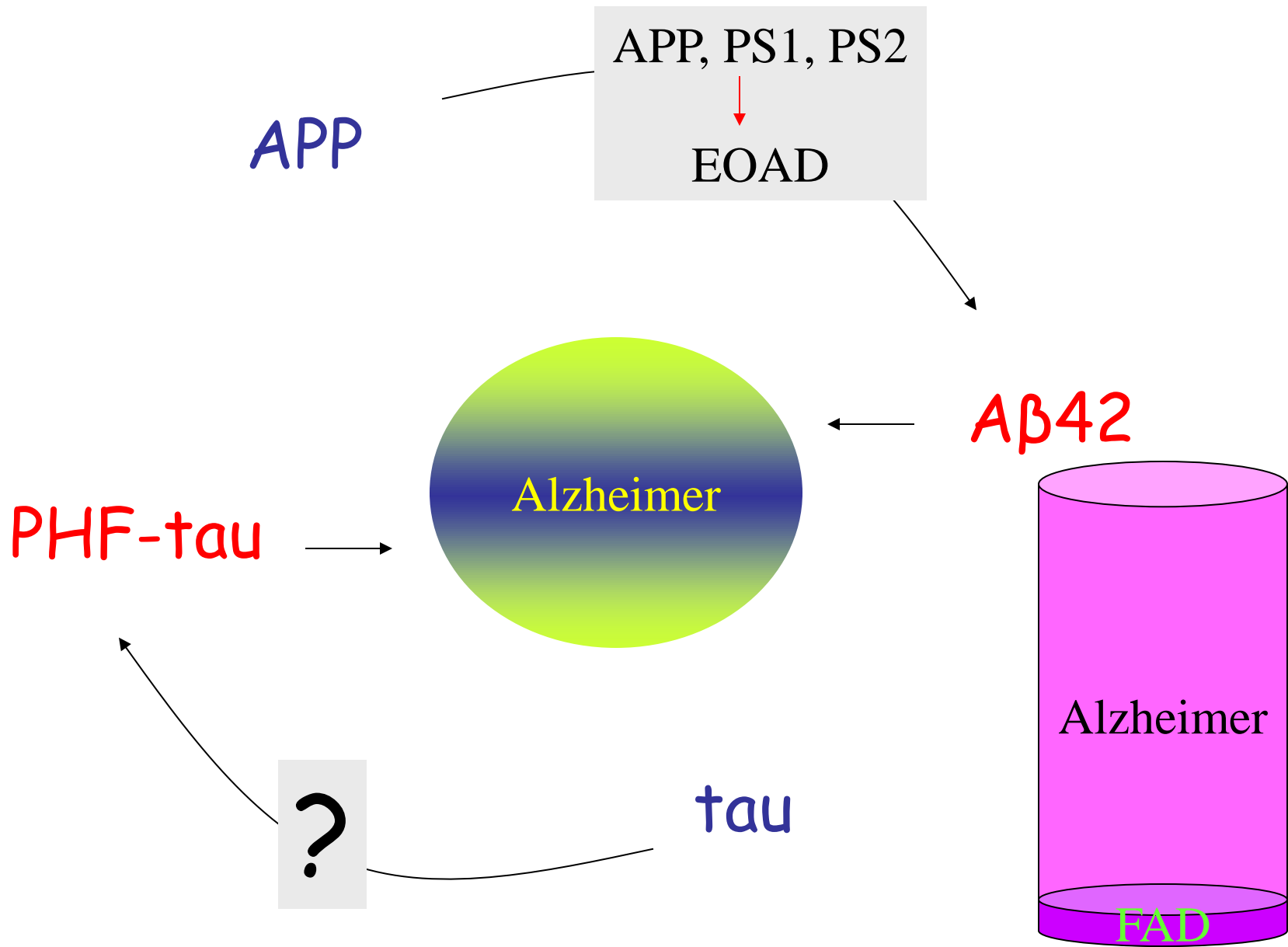
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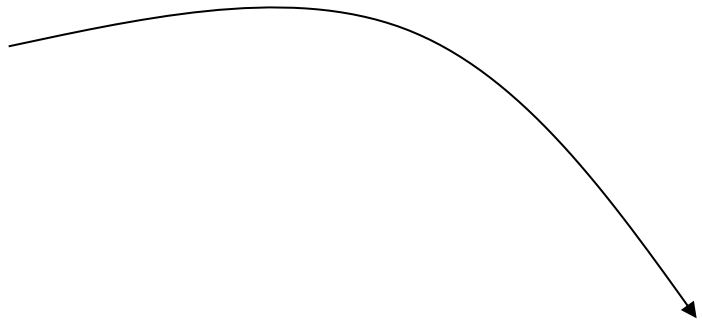






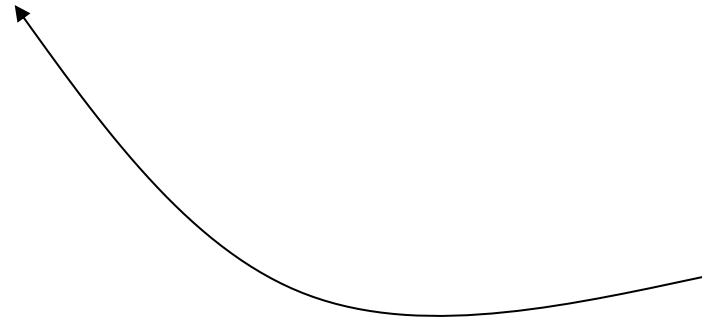


APP



Aβ42

PHF-tau



tau

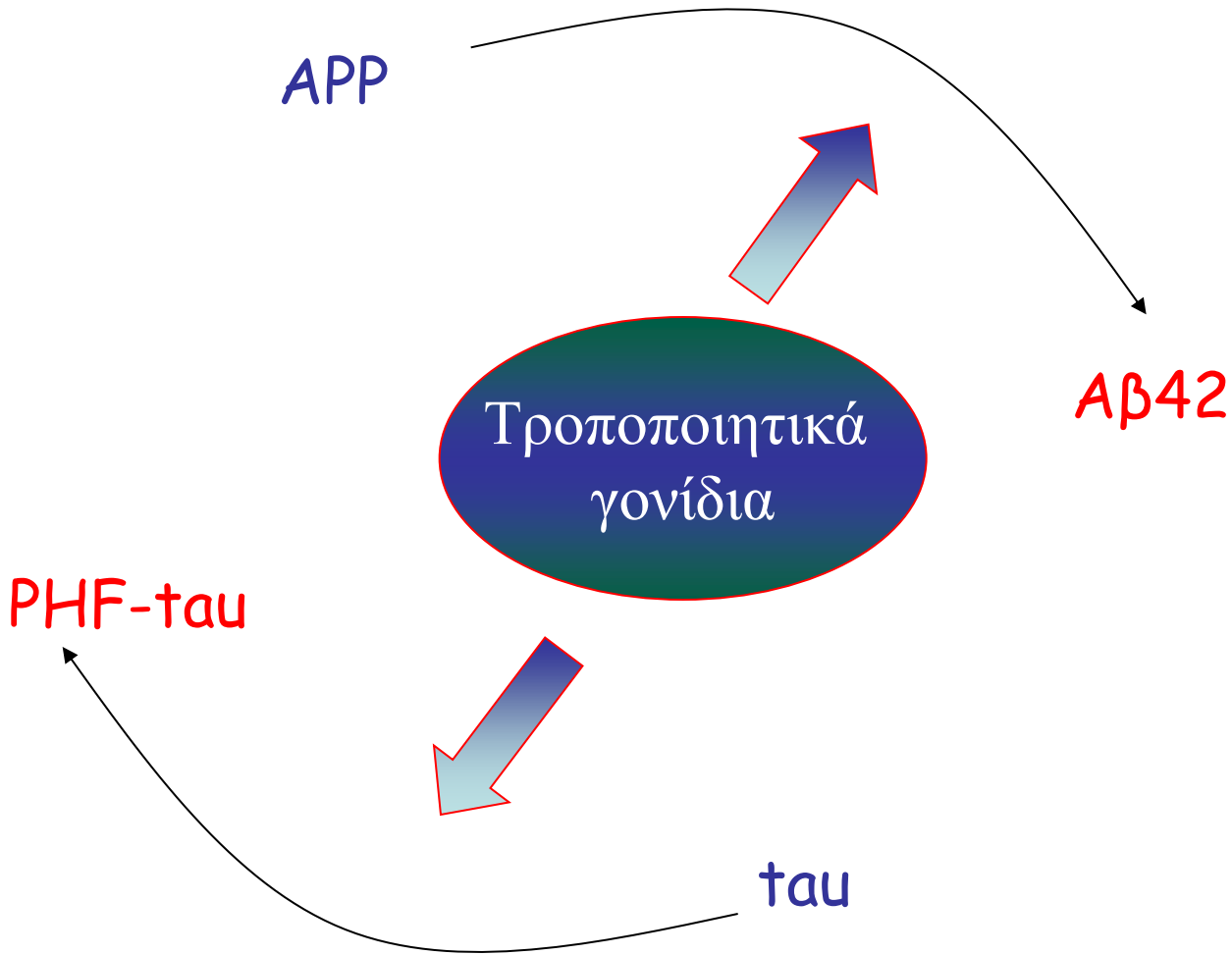
APP



Aβ42

PHF-tau

tau



APP



PHF-tau

tau

**Table 1.** Case-control studies of genetic polymorphisms in sporadic AD

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Genes involved in A $\beta$  metabolism

Apolipoprotein E (APOE)  
Presenilin 1 (PS1)  
Presenilin 2 (PS2)  
 $\alpha_2$ -Macroglobulin (A2M)  
Low-density lipoprotein receptor-related protein (LRP)  
LRP-associated protein (LRPAP1)  
Very-low-density lipoprotein receptor (VLDLR)  
Lipoprotein lipase (LPL)  
Cathepsin D (catD)  
FE65  
LBP-1c/CP2/LSF  
Bleomycin hydrolase (BH)  
 $\alpha$ 1-antichymotrypsin (ACT)  
Butyrylcholinesterase (BCHE)

---

Genes involved in oxidative stress

Endothelial nitric oxide synthase (NOS3)  
Inducible nitric oxide synthase (NOS2)  
Dihydropyridyl succinyltransferase (DLST)  
CYP2D6  
Transferrin  
HFE

---

Genes involved in inflammation/apoptosis

HLA-A2  
Interleukin-1A and -1B (IL-1A/-1B)  
Interleukin-6 (IL-6)  
Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )  
FAS receptor (TNFRSF6)

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Genes involved in vascular disease

Angiotensin-converting enzyme (ACE)  
Cystatin C

---

Other putative genes

Tau  
NACP/ $\alpha$ -synuclein  
Prion protein (PRNP)  
5-HT transporter  
Estrogen receptor- $\alpha$

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*Shastry BS, J Hum Genet, 2001*

*Combarros O et al, DGCD, 2005*

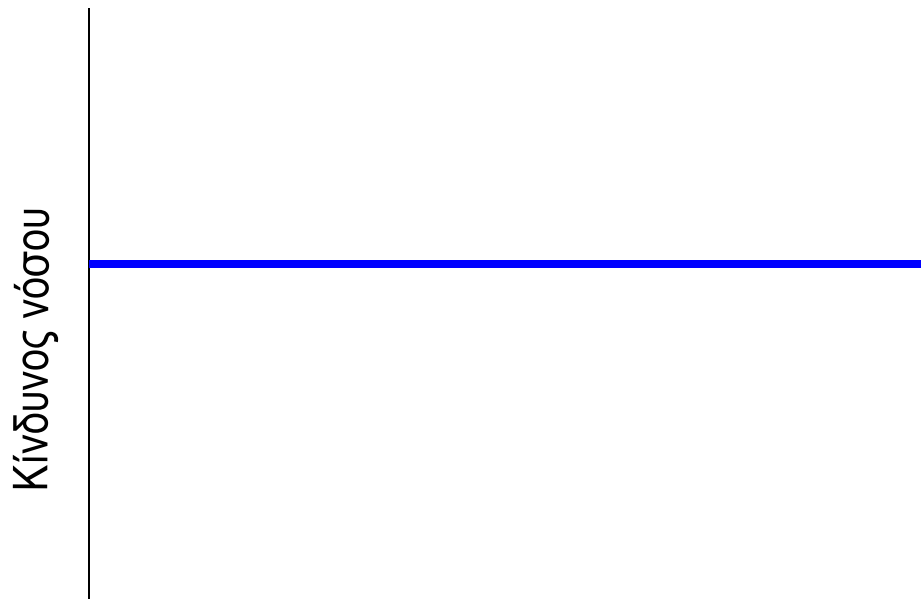
Ένας πολυμορφισμός

▶ 1-8% κινδύνου νόσου

Προσθετική δράση  
πολλών πολυμορφισμών

▶ 20-70% κινδύνου νόσου

*Trends Mol Med 2003*



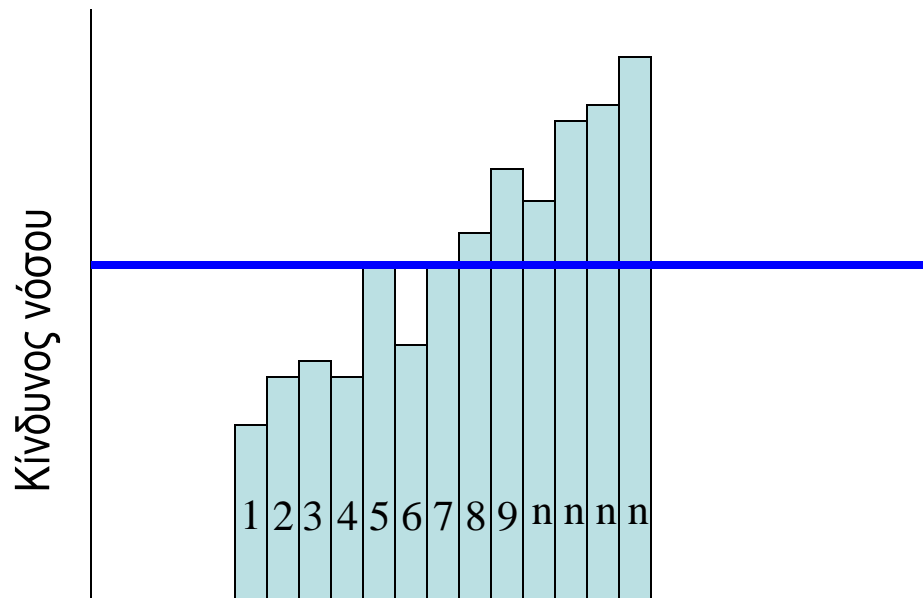
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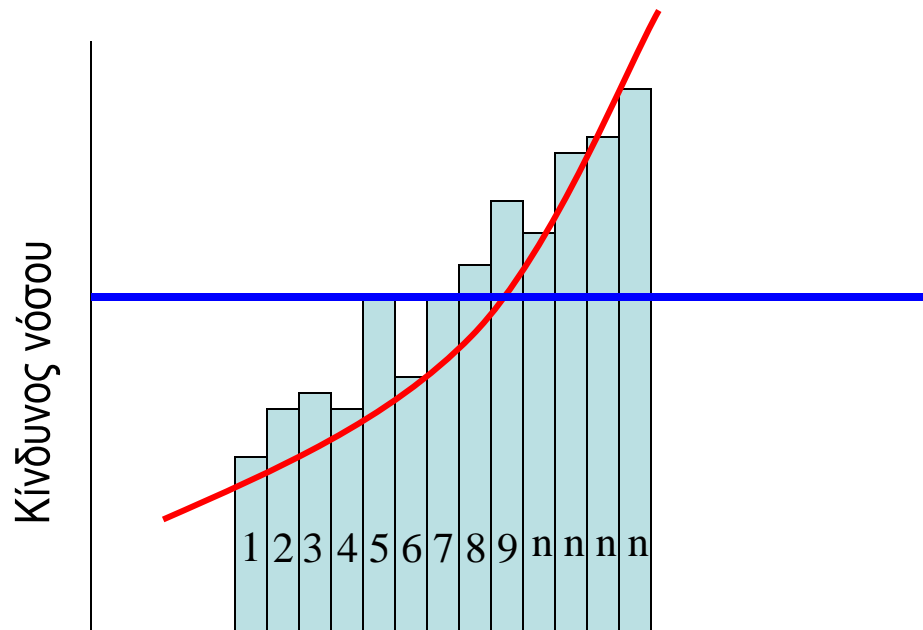
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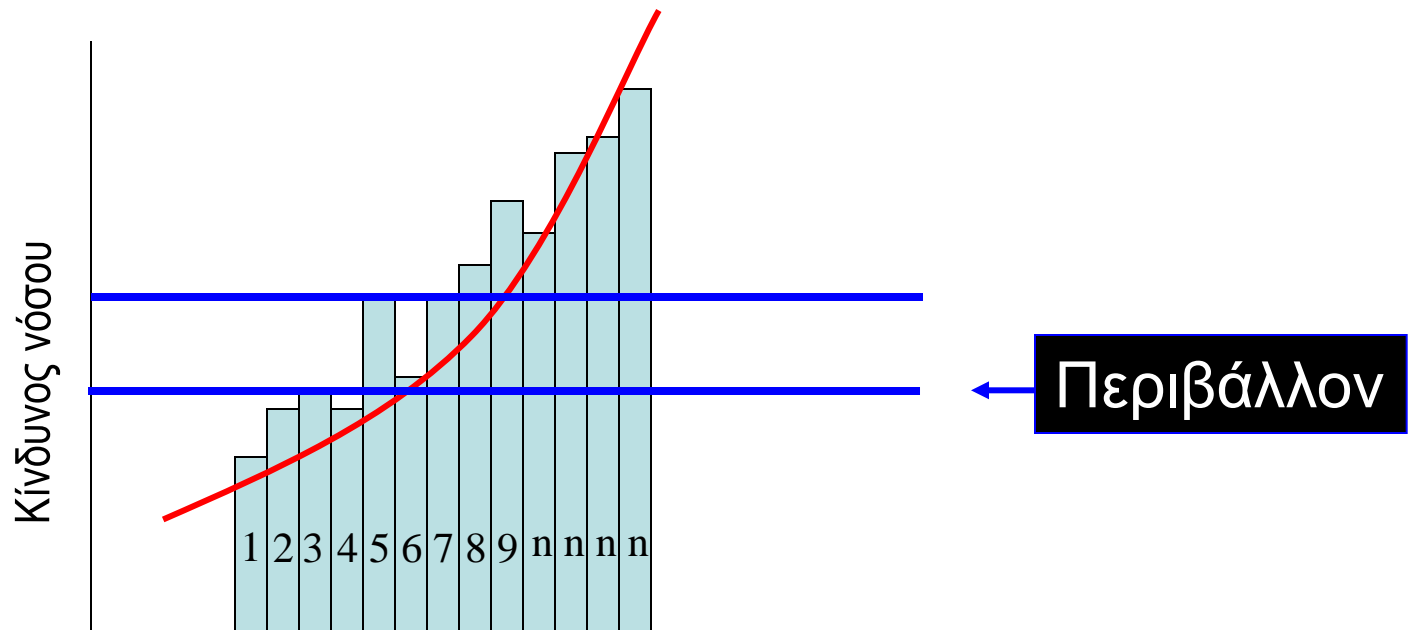
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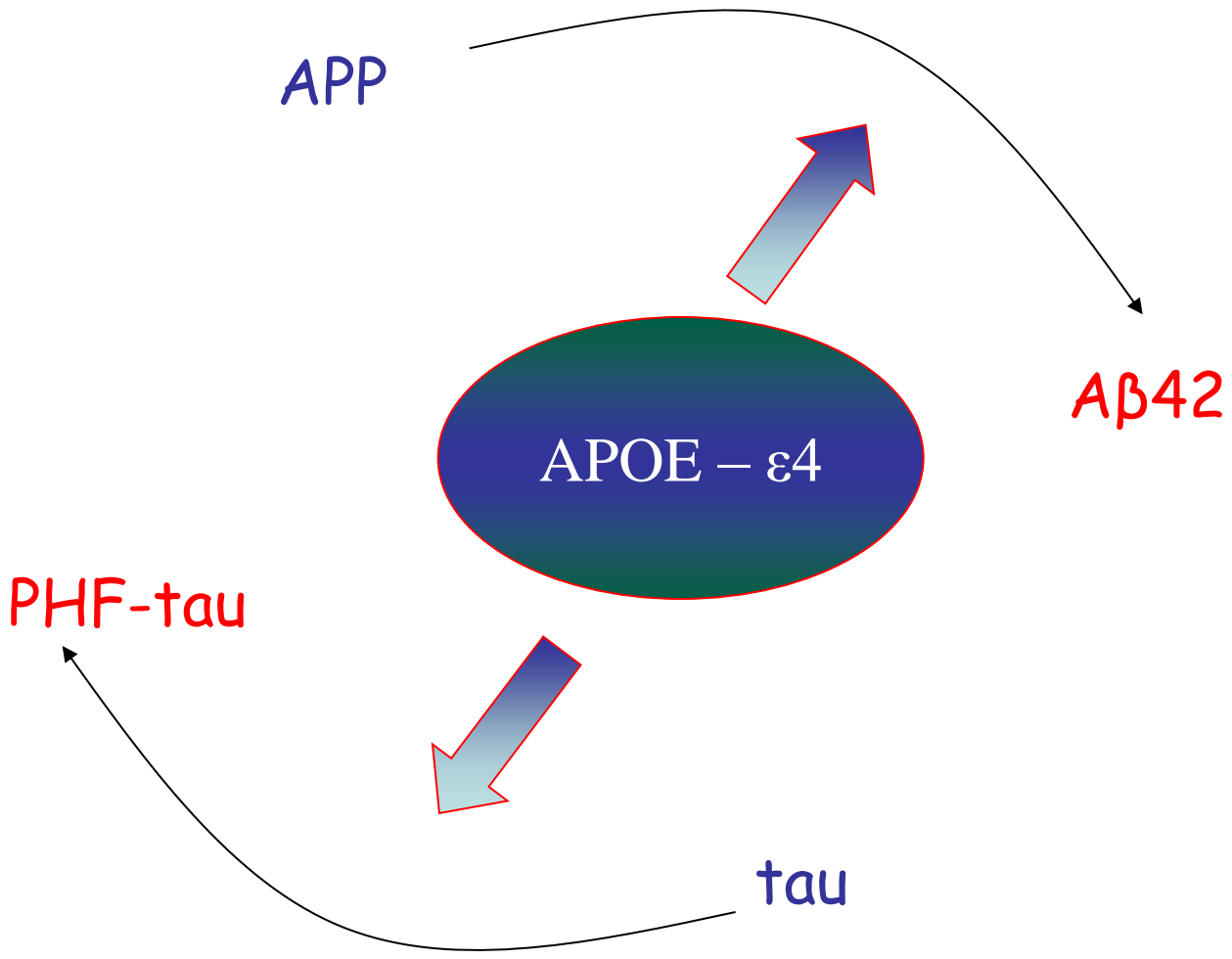
Προσθετική δράση  
πολλών πολυμορφισμών

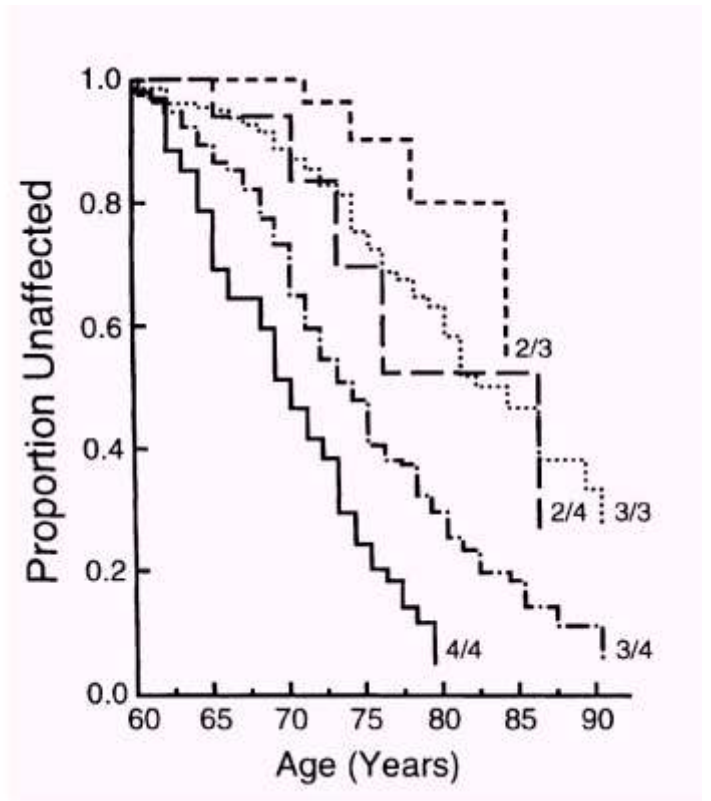
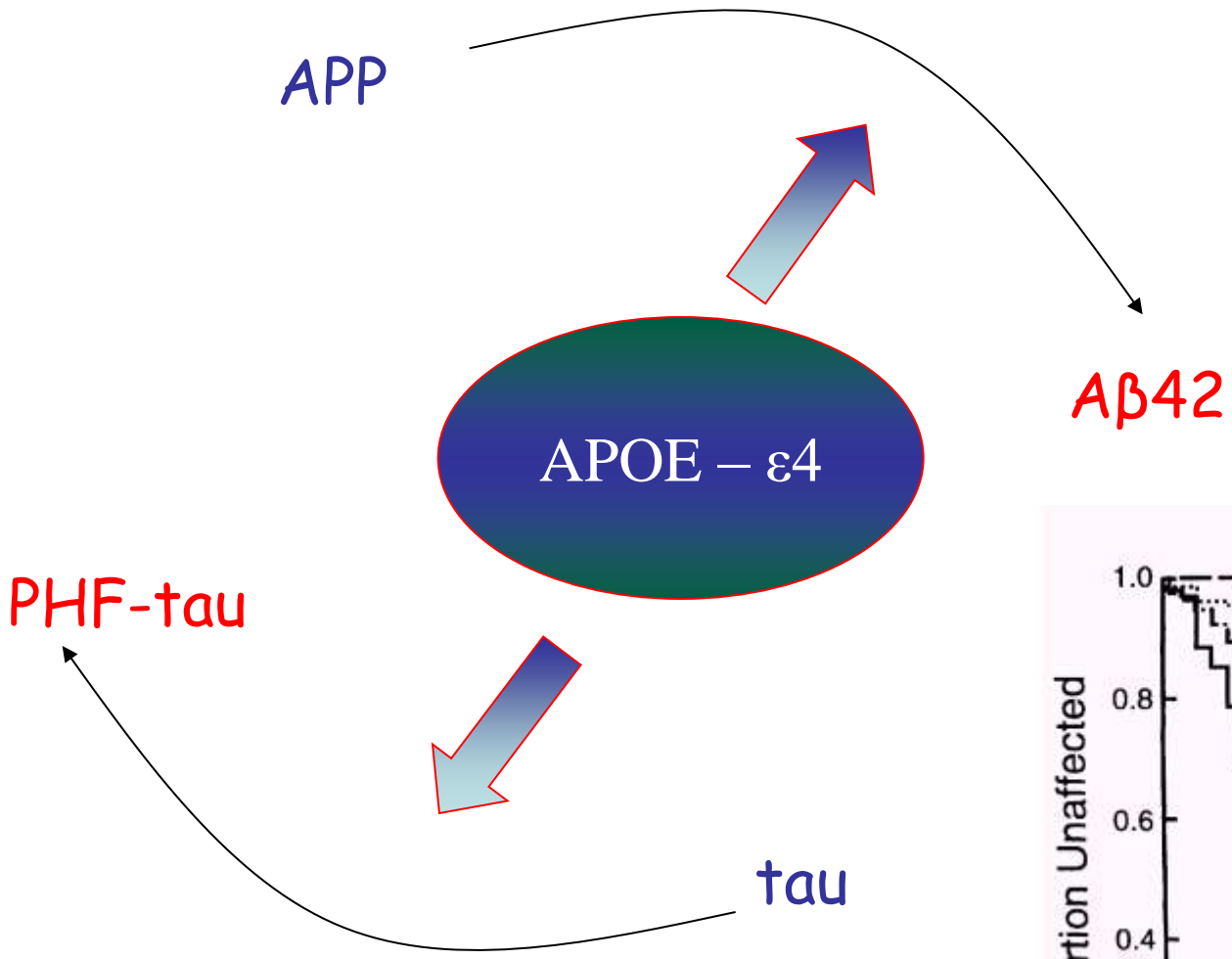
▶ 20-70% κινδύνου νόσου

*Trends Mol Med 2003*









*Roses AD. Neurogenetics 1997*

APP



Aβ42

X3 - ε4/-  
X8 - ε4/ε4

PHF-tau

tau



Gene	Chromosome (Polymorphism [Alias])	Protein Name	Proposed Functional Relevance of Protein / Polymorphism to AD Pathogenesis
<i>APOE</i>	19q13 ( $\epsilon 2$ , $\epsilon 3$ , $\epsilon 4$ )	Apolipoprotein E	May influence A $\beta$ metabolism. Risk allele ( $\epsilon 4$ ) causes 3x increased disease risk
<i>APOE</i> (promoter)	19q13 (rs 449647 and others)	Apolipoprotein E	May influence A $\beta$ metabolism
<i>APOC1</i>	19q13 (HpaI ins/del)	Apolipoprotein C1	Unknown
<i>ACE</i>	17q23 (Intron 16 ins/del and others)	Angiotensin converting enzyme	Unknown
<i>CST3</i>	20p11 (rs1064039 [A25T] and others)	Cystatin C	Unknown
<i>ESR1</i>	6q25 (PvuII (rs2234693))	Estrogen receptor 1	May confer a disease protective effect (as suggested by epidemiological studies)
<i>IDE</i>	10q23 (rs2251101 [IDE_7])	Insulin degrading enzyme	Degrades A $\beta$ ; risk allele may render the enzyme inefficient
<i>PRNP</i>	20p13 (rs1799990 [M129V])	Prion protein	Unknown
<i>PS1</i>	14q24 (rs 165932 [intron 8])	Presenilin 1	A component of the $\gamma$ -secretase complex in the amyloidogenic pathway; risk allele may make the enzyme more efficient
<i>TF</i>	3q22 (rs1049296 [P570S])	Transferrin	Unknown

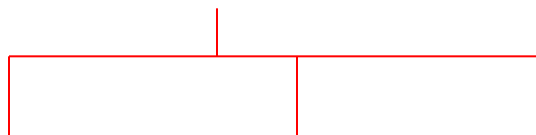
For up-to-date summaries and meta-analyses of these and over 400 additional putative AD genes, please visit the AlzGene web site at [www.alzgene.org](http://www.alzgene.org) (Bertram et al., 2007).

Early-onset, <60

Προγεροντικές



Οικογενείς



APP (21)

PS1 (14)

PS2 (1)

% <1

50

<1

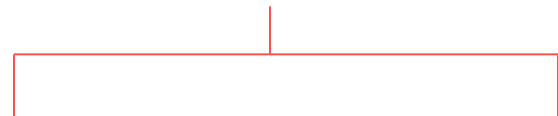
<0.1

1-2

<0.1

Late-onset, >60

Γεροντικές



Οικογενείς

Σποραδικές

(6,9,10,12)



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Προγεροντικές

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Γεροντικές

Οικογενείς

Οικογενείς

Σποραδικές

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PS1 (14)

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(6,9,10,12)

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<0.1

1-2

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Τροποποιητικά γονίδια + περιβάλλον

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Προγεροντικές

Late-onset, >60

Γεροντικές

Οικογενείς

Οικογενείς

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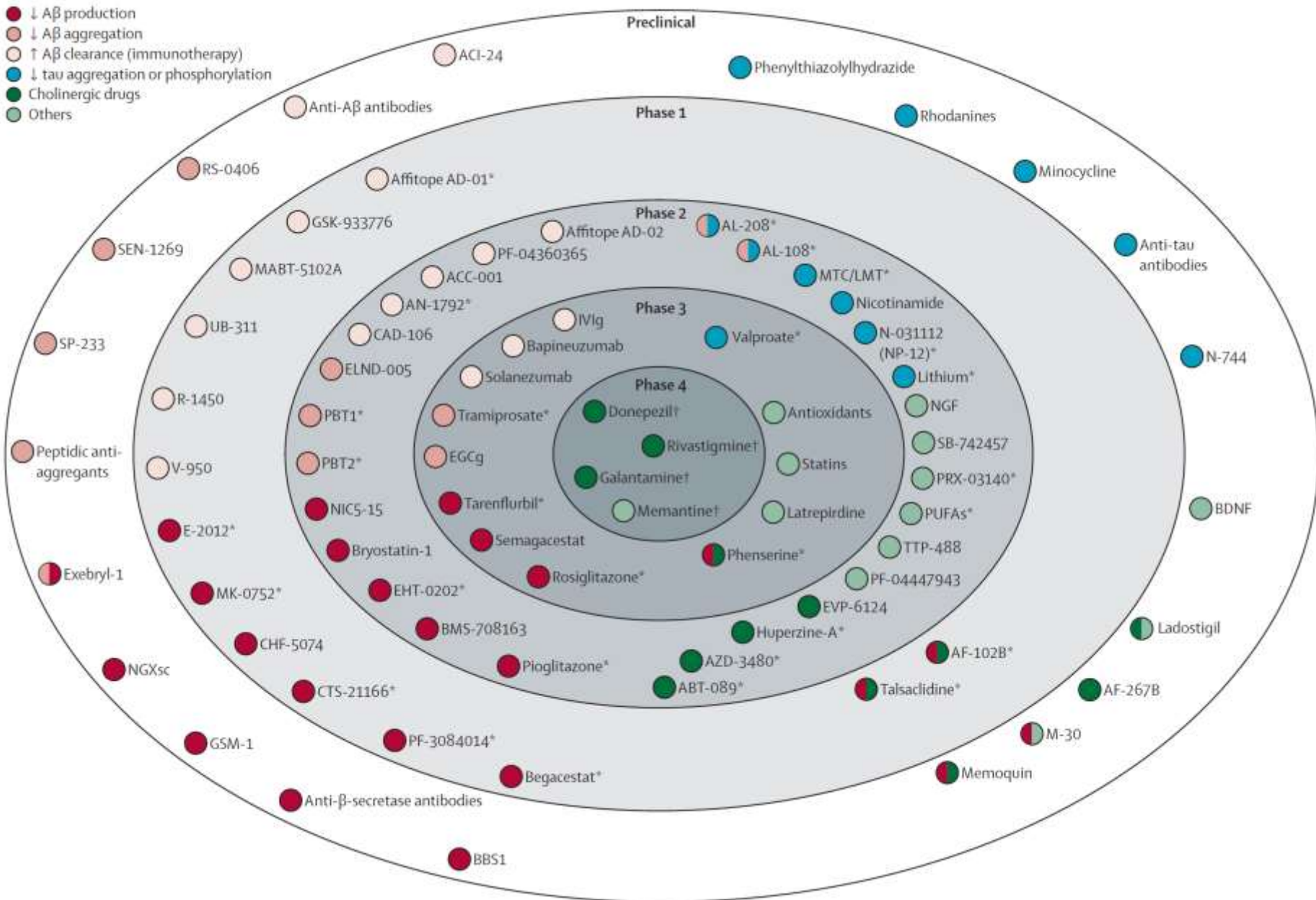
<1

<0.1

1-2

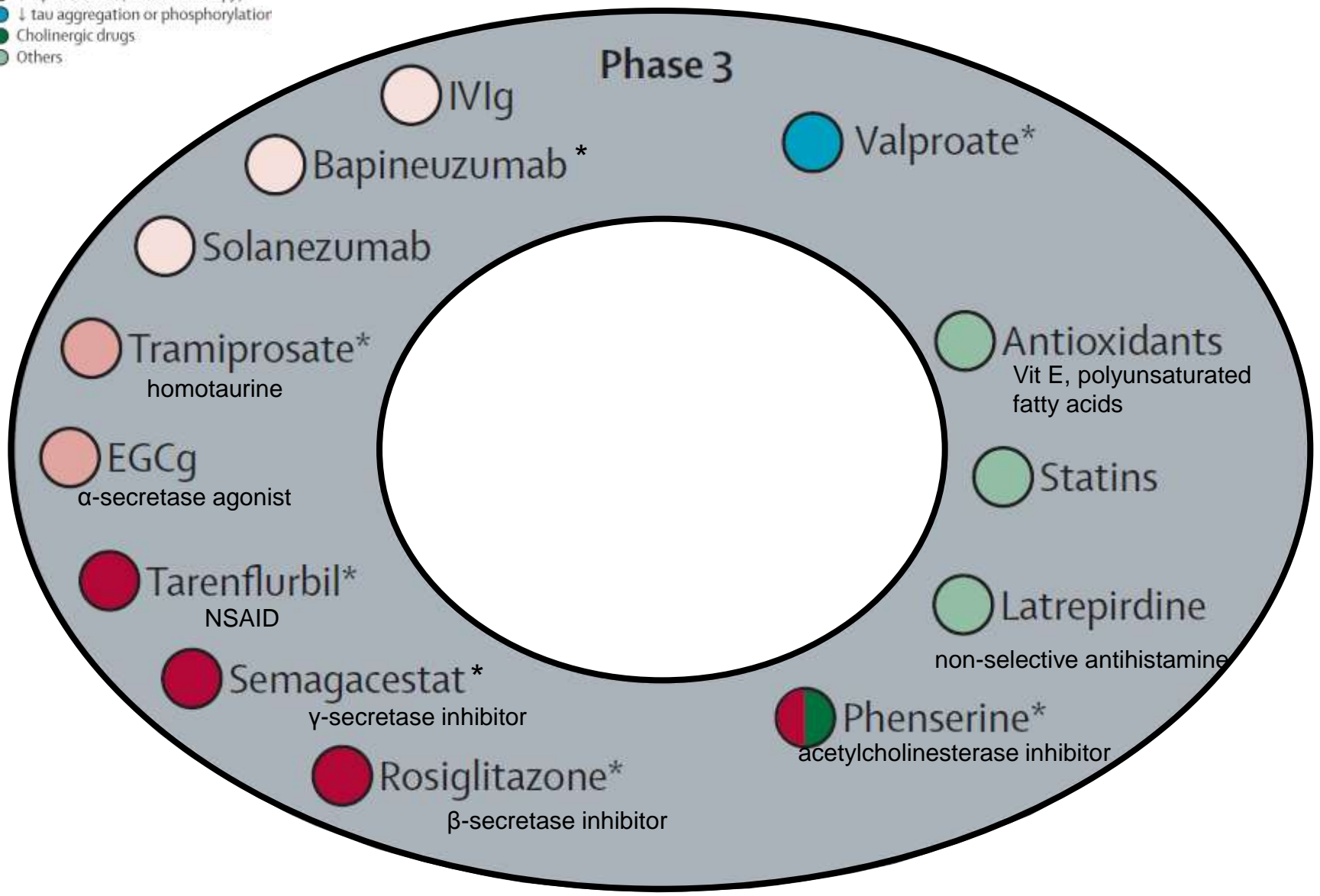
<0.1

Τροποποιητικά γονίδια + περιβάλλον



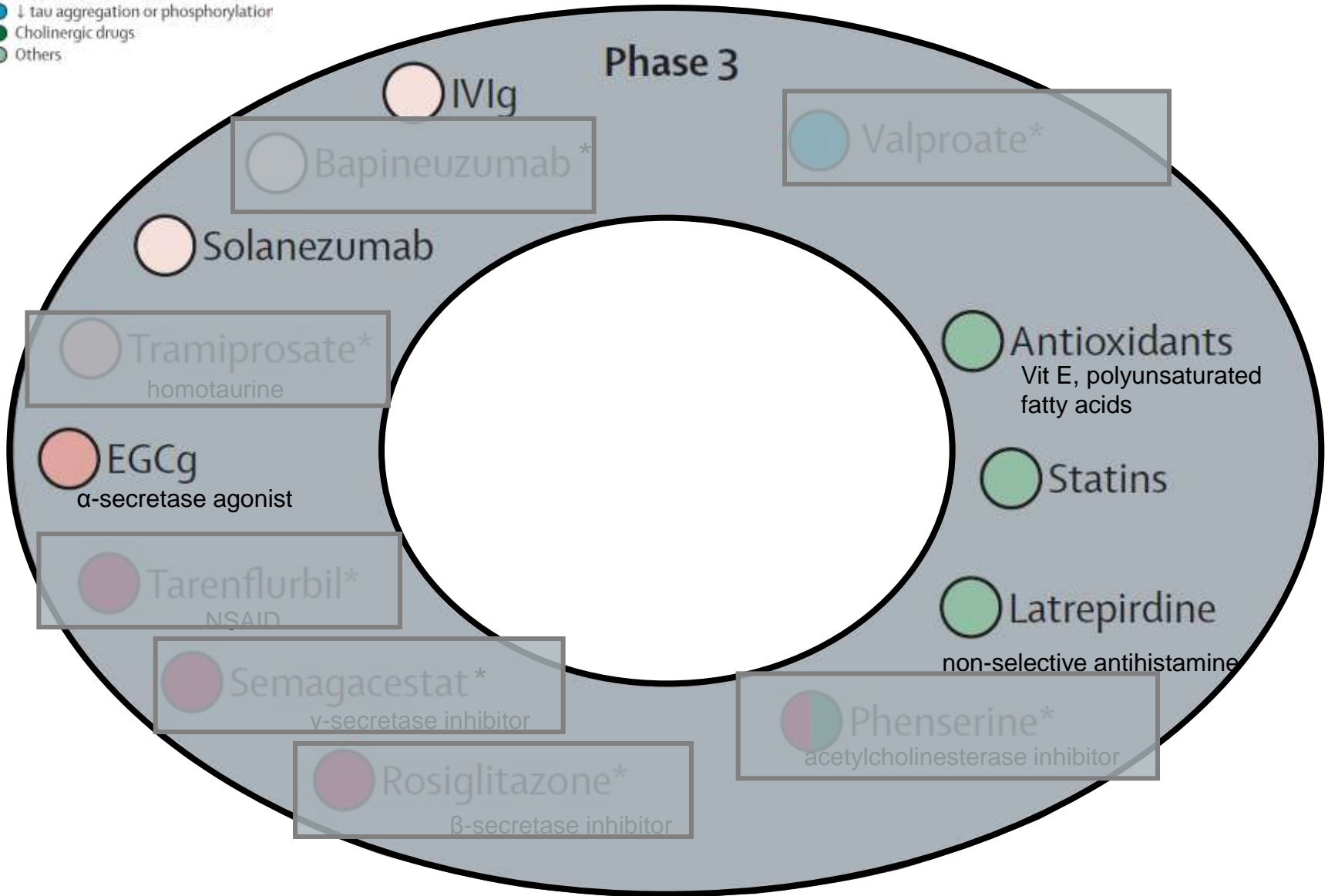
- ↓ Aβ production
- ↓ Aβ aggregation
- ↑ Aβ clearance (immunotherapy)
- ↓ tau aggregation or phosphorylation
- Cholinergic drugs
- Others

### Phase 3

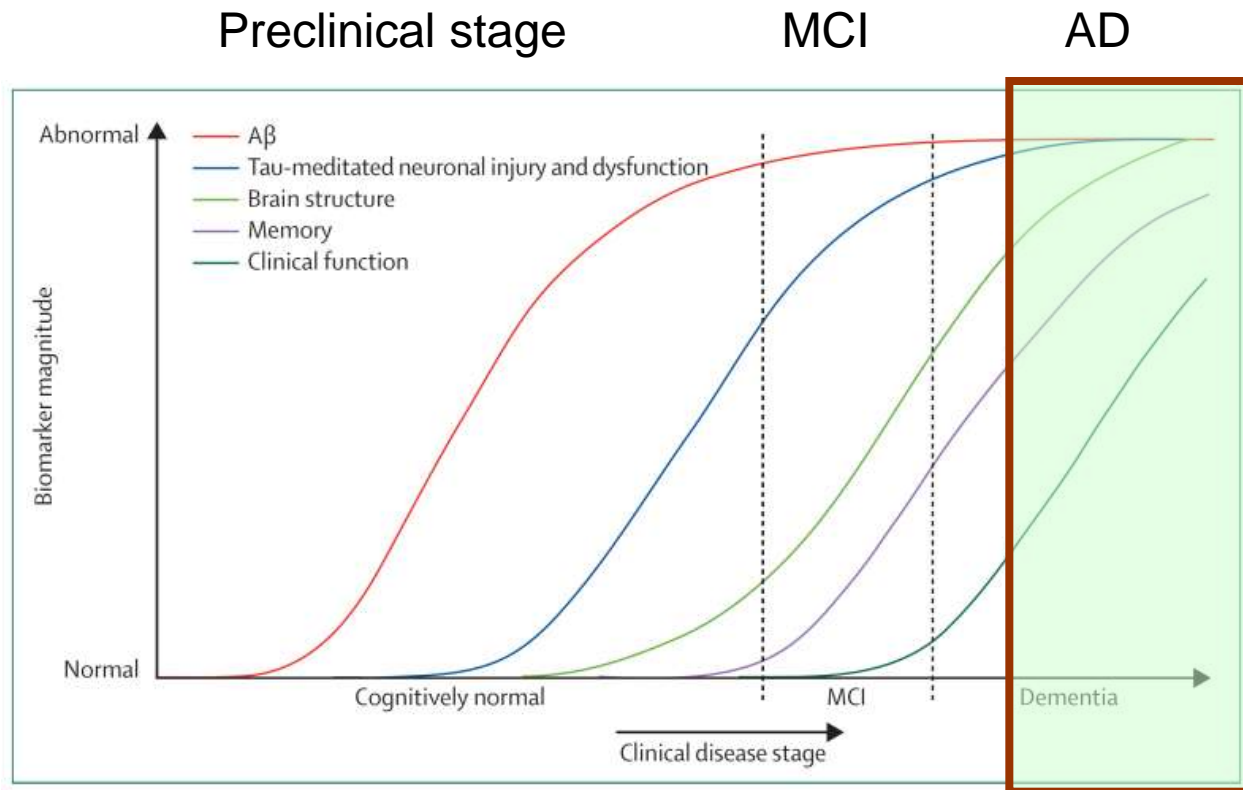


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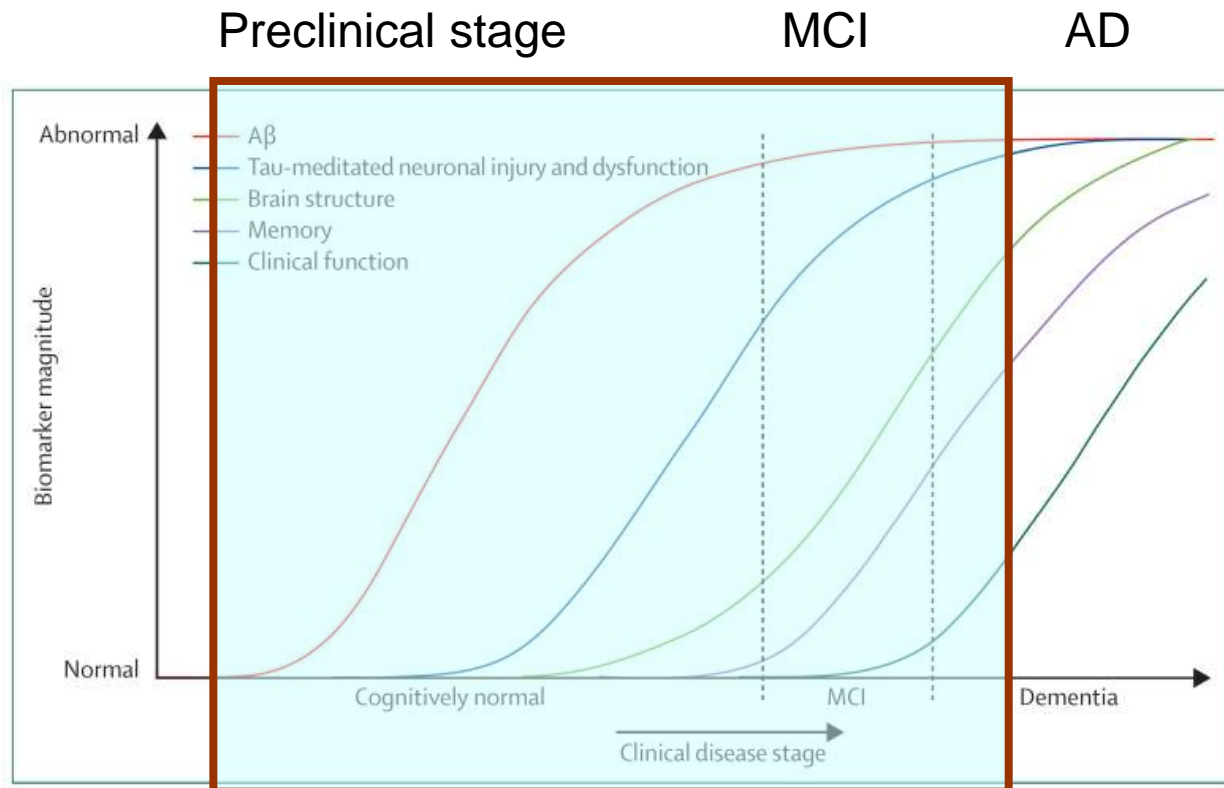
### Phase 3



# AD therapies



# AD therapies





# Preclinical stage

## Alzheimer's Prevention Trials at a Glance

Trial	Participants	Treatment	Outcome Measures
<b>API:</b> Alzheimer's Prevention Initiative	300 members of Colombian families, including 100 carriers of a mutated <i>PSEN1</i> gene	Crenezumab (Genentech)	Primary: Cognitive. Secondary: Biomarkers, including brain scans to measure amyloid accumulation and brain atrophy
<b>DIAN:</b> Dominantly Inherited Alzheimer Network	240 members of families with early-onset Alzheimer's; 60 have a mutation in one of three genes	Three anti-amyloid therapies to be determined	An initial phase will use biomarkers to identify the most promising drug candidate for a follow-up phase to examine cognitive effects
<b>A4:</b> Anti-Amyloid Treatment of Asymptomatic Alzheimer's	1500 healthy seniors, including 500 with amyloid-positive brain scans	One anti-amyloid therapy to be determined	Primary: Cognitive Secondary: Biomarkers