



The amyloid precursor protein of Alzheimer disease Precursor of the amyloid peptide What else?

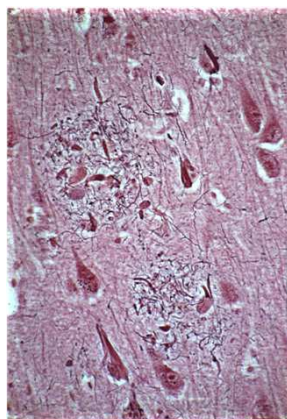
Jean-Noël OCTAVE
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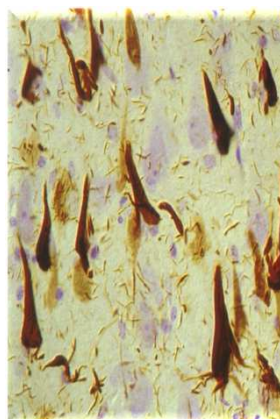
June 20, 2013

Neuropathological lesions of Alzheimer disease

Neurofibrillary tangles

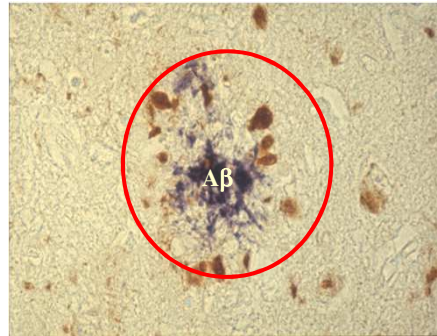


labeled by anti-tau antibodies



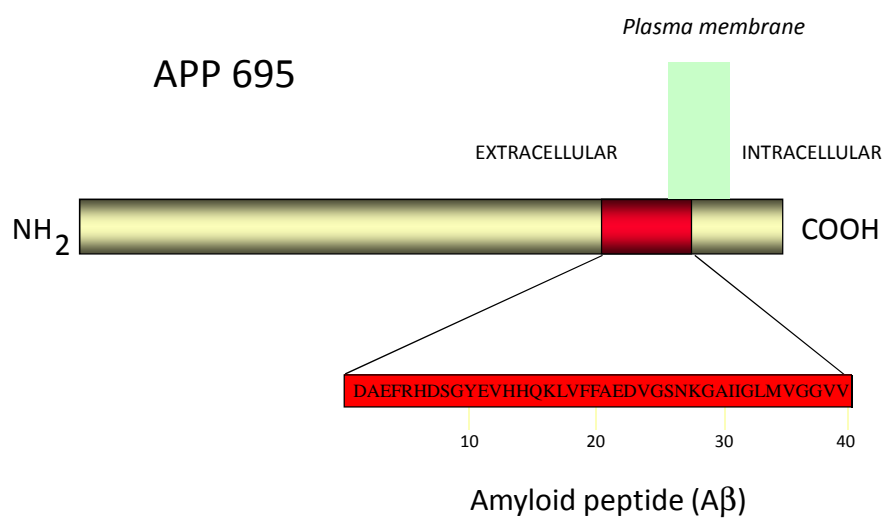
Neuropathological lesions of Alzheimer disease

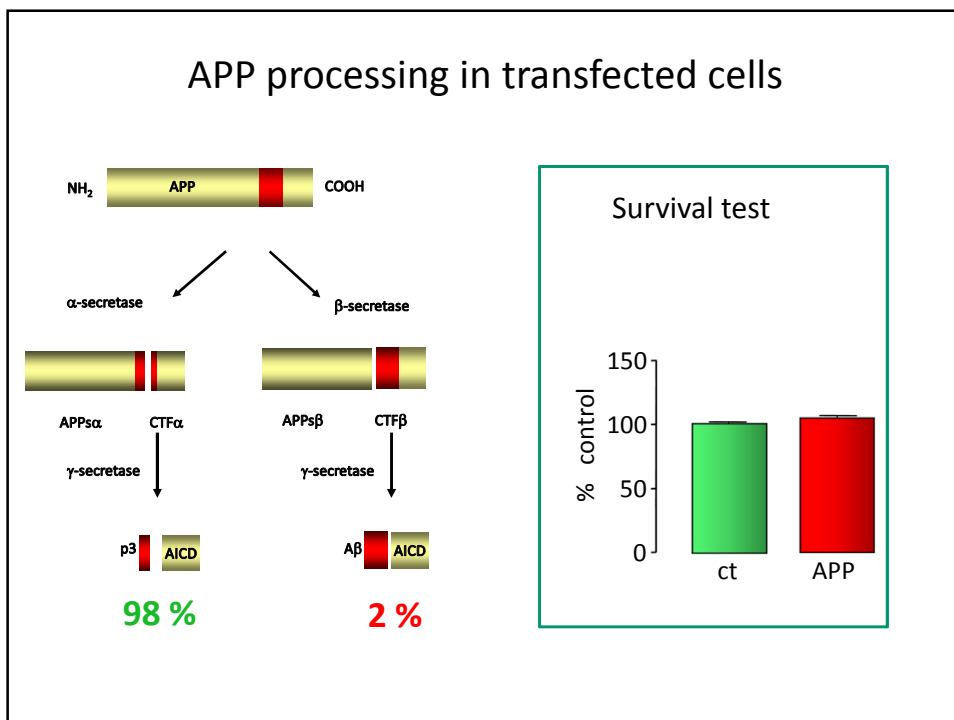
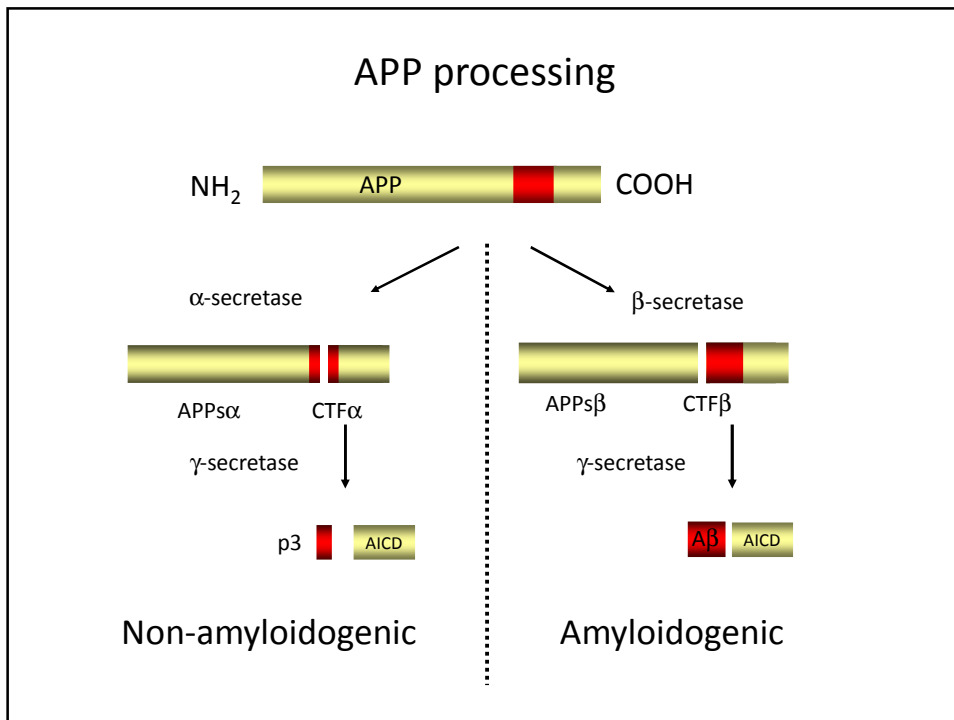
Senile plaques



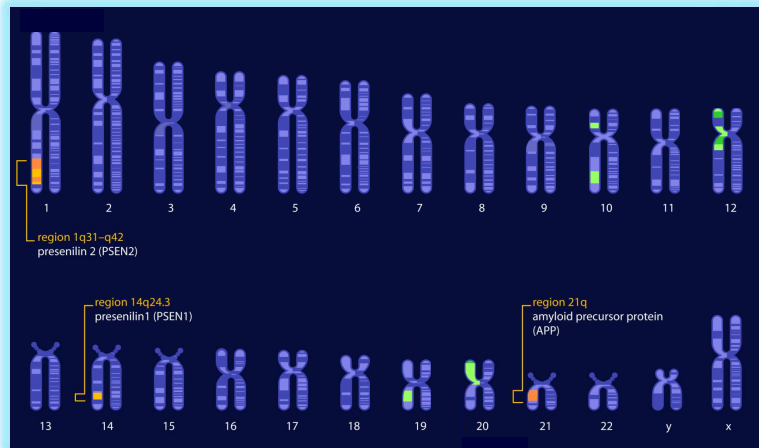
Senile plaques contain an amyloid core of Aβ peptide

The Amyloid Precursor Protein : APP

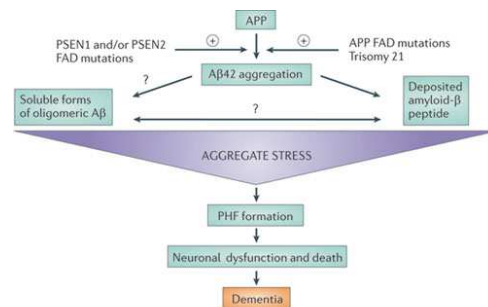




Inheritance of Early Onset Alzheimer Disease

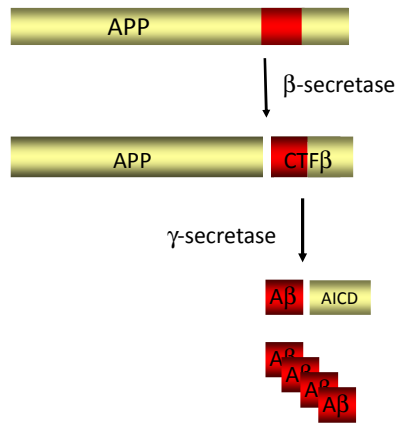


The Amyloid Cascade Hypothesis



E. Karran et al.
Nature Reviews Drug Discovery 10, 698-712 (2011)

A β as therapeutic target



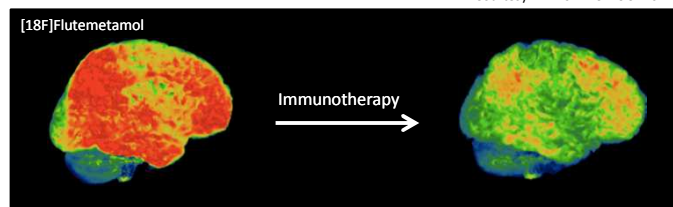
Clinical trials

March 2013 : 102 phase III clinical trials completed.

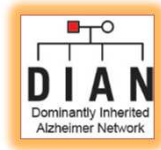
γ -secretase inhibitors : tumorigenic.

β -secretase inhibitors

Immunotherapy



Up to now, all these clinical trials failed



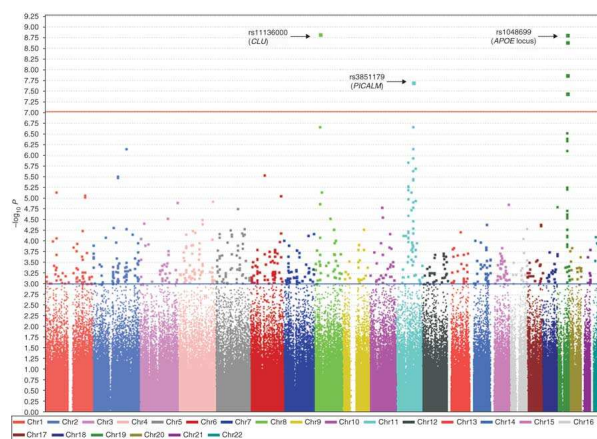
Inheritance of Early Onset Alzheimer Disease

330 patients with inherited early onset Alzheimer disease

Abnormal brain amyloid load 15-20 years before first symptoms

Passive immunotherapy with 2 different antibodies and a β -secretase inhibitor

GWAS in Late Onset Alzheimer Disease



D. Harold et al. Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer's disease. *Nat Genet.* 2009, 41(10):1088-1093

GWAS in Late Onset Alzheimer Disease

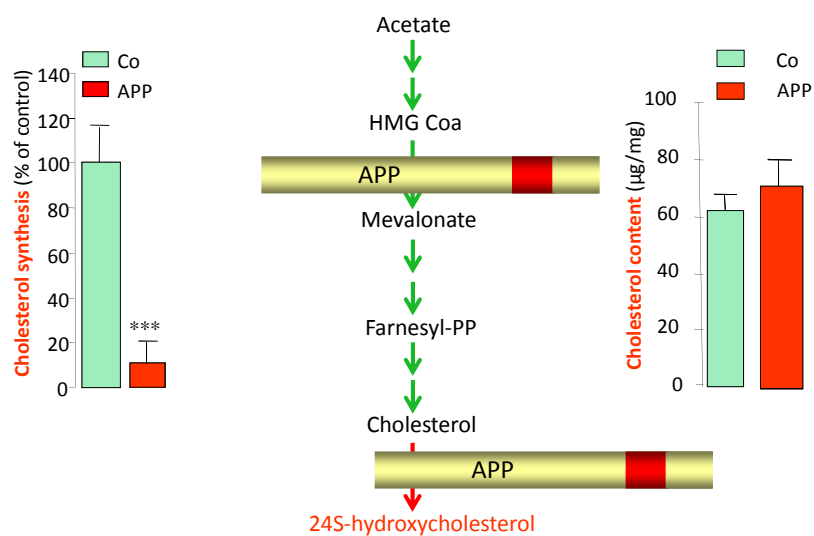
E.H. Corder et al. Gene dose of **apolipoprotein E type 4 allele** and the risk of Alzheimer's disease in late onset families. *Science*. 1993, 261 (5123) : 921-923

D. Harold et al. Genome-wide association study identifies variants at **CLU** and **PICALM** associated with Alzheimer's disease. *Nat Genet*. 2009, 41(10):1088-1093.

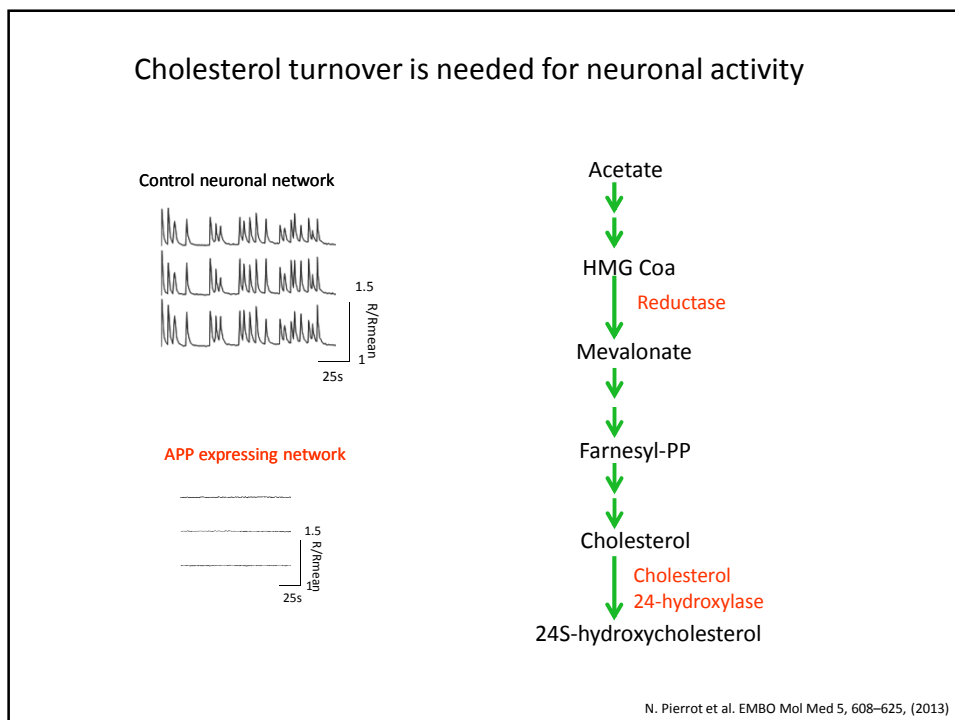
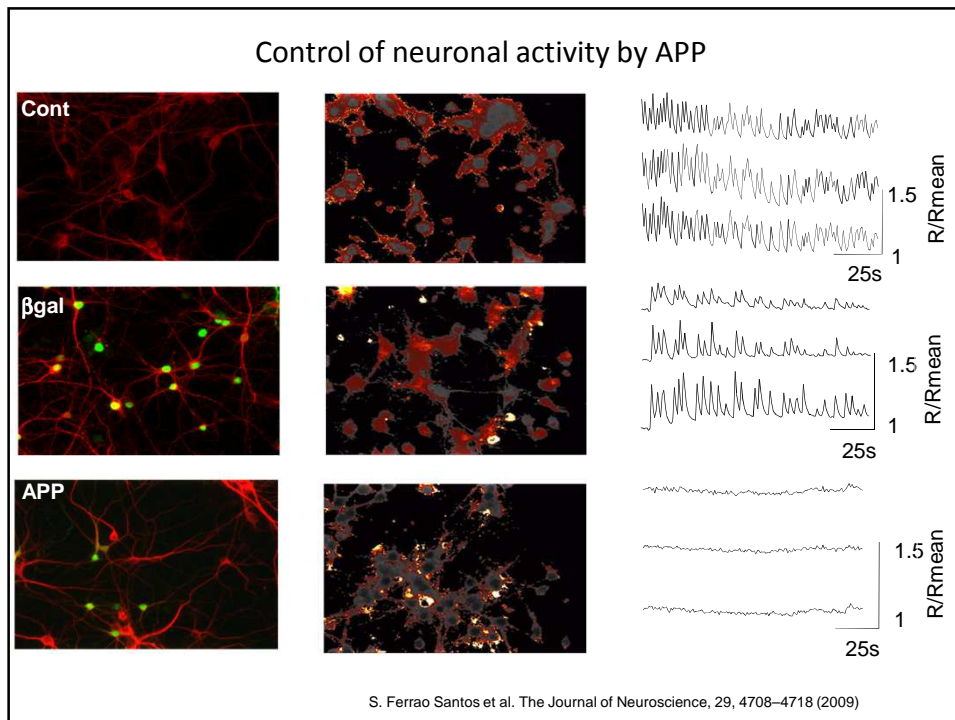
P. Hollingworth et al. Common variants in **ABCA7**, **MS4A6A/MS4A4E**, **EPHA1**, **CD33** and **CD2AP** are associated with Alzheimer's disease. *Nat Genet*. 2011, 43(5): 429-435.

Alzheimer Disease and Cholesterol

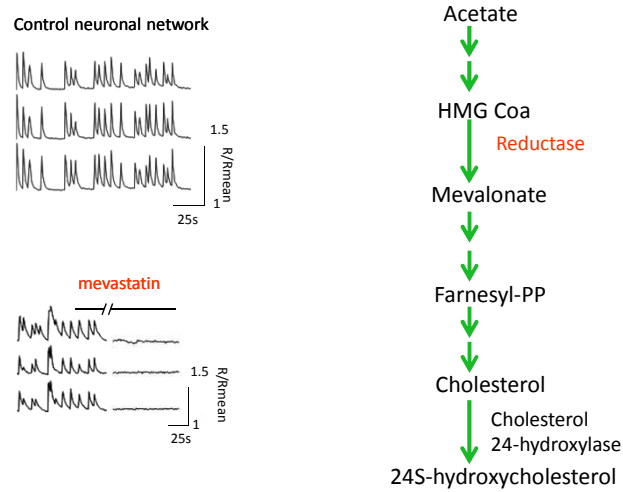
APP controls neuronal cholesterol turnover



N. Pierrot et al. *EMBO Mol Med* 5, 608-625, (2013)



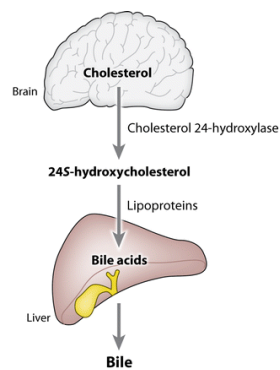
Cholesterol turnover is needed for neuronal activity



N. Pierrot et al. EMBO Mol Med 5, 608–625, (2013)

Cholesterol turnover in Alzheimer disease

A.N. Lazar et al. Time-of-flight secondary ion mass spectrometry (TOF-SIMS) imaging reveals **cholesterol overload in the cerebral cortex of Alzheimer disease patients**. Acta Neuropathol. 125, 133-144 (2013).



Conclusions

Should the amyloid cascade hypothesis be revisited?

How are genetic risk factors favoring progression of Alzheimer disease?

How is APP involved in the progression of Alzheimer disease?