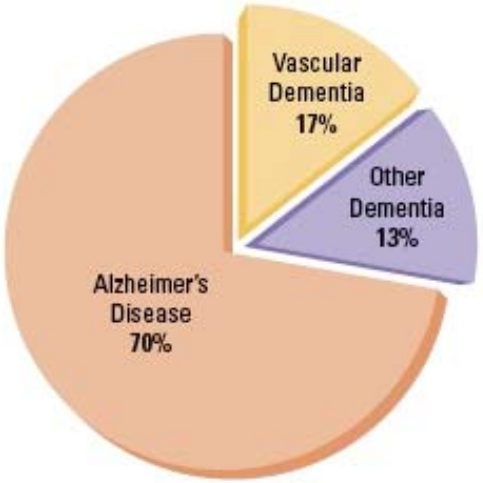
Dementia

To be classified as dementia, there must be decline in memory and impairment in at least one of the following cognitive abilities:

Ability to generate coherent speech and understand spoken or written language
Ability to recognize or identify objects, assuming intact sensory function
Ability to execute motor activities, assuming intact motor abilities, sensory function and comprehension of the required task
Ability to think abstractly, make sound judgments and plan and carry out complex tasks

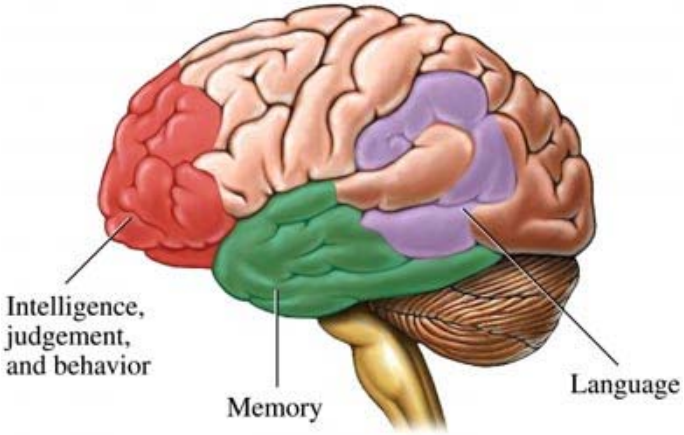
Types of dementia



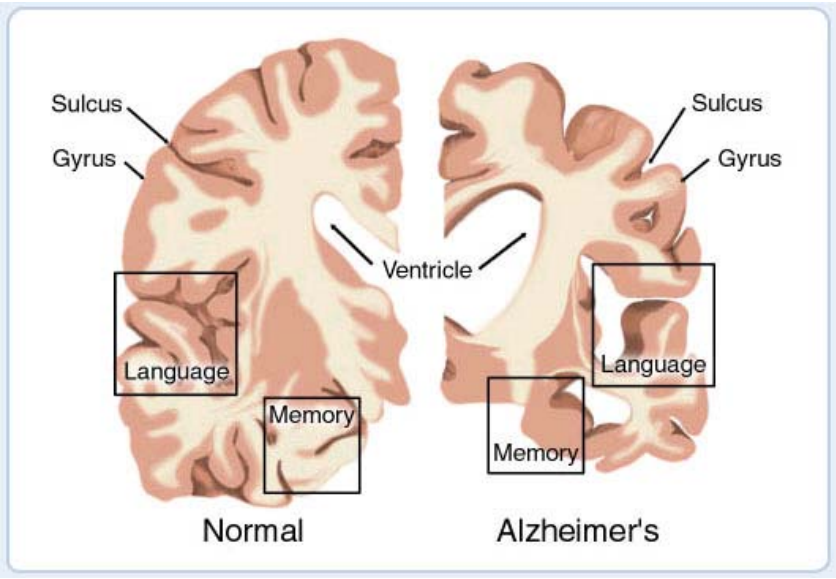
Parkinson's disease, Lewy body disease, frontotemporal dementia and normal pressure hydrocephalus

Source: Plassman, BL; Langa, KM; Fisher, GG; Heeringa, SG; Weir, DR; Ofstedal, MB, et al. "Prevalence of Dementia in the United States: The Aging Demographics, and Memory Study. *Neuroepidemiology* 2007; 29:125-132.[31]

http://cadc.ucsf.edu/cadc/resources/dementia



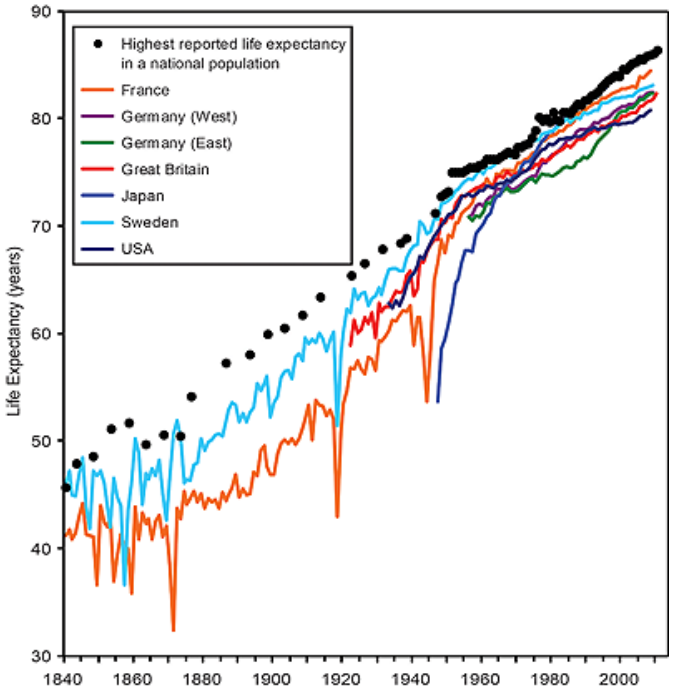
http://www.topnews.in/health/diseases/dementia



The Prevalence of Dementia	
Age Group	International Prevalence Rate
60 – 64	1.3 %
65 – 69	2.2 %
70 – 74	3.8 %
75 – 79	6.5 %
80 – 84	11.6 %
85 – 89	20.1%
90 +	41.5%

http://www.dementiaguide.com/aboutdementia/typesofdementia/alzheimers/

Female Life Expectancy in Developed Countries: 1840-2009



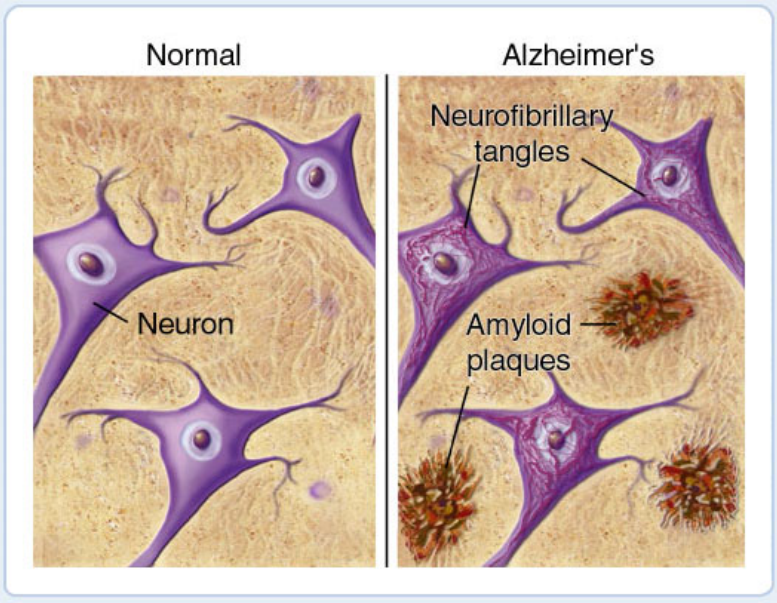
http://www.nia.nih.gov/research/publication/global-health-and-aging/living-longer

Alzheimer's disease (AD)

AD is an insidious neurodegenerative disorder and the primary cause of dementia in the elderly. There is presently no treatment to stop the disease progression. The primary clinical features of AD are characterized by deterioration of memory and cognitive function, progressive impairment of activities of daily living, and several neuropsychiatric symptoms (Cummings, 2004). At the cellular and molecular levels, the pathological features of AD are characterized by two distinctive hallmarks: **amyloid plaques** primarily comprised of a small protein Aβ (Bertram and Tanzi, 2008; Gandy, 2005; Hardy and Selkoe, 2002), and **neurofibrillary tangles** composed of hyperphosphorylated protein tau. While Aβ42 and Aβ40 are the two primary Aβ species, Aβ42 is more prevalent than Aβ40 in amyloid plaques (Bertram and Tanzi, 2008; Gandy, 2005; Hardy and Selkoe, 2002).

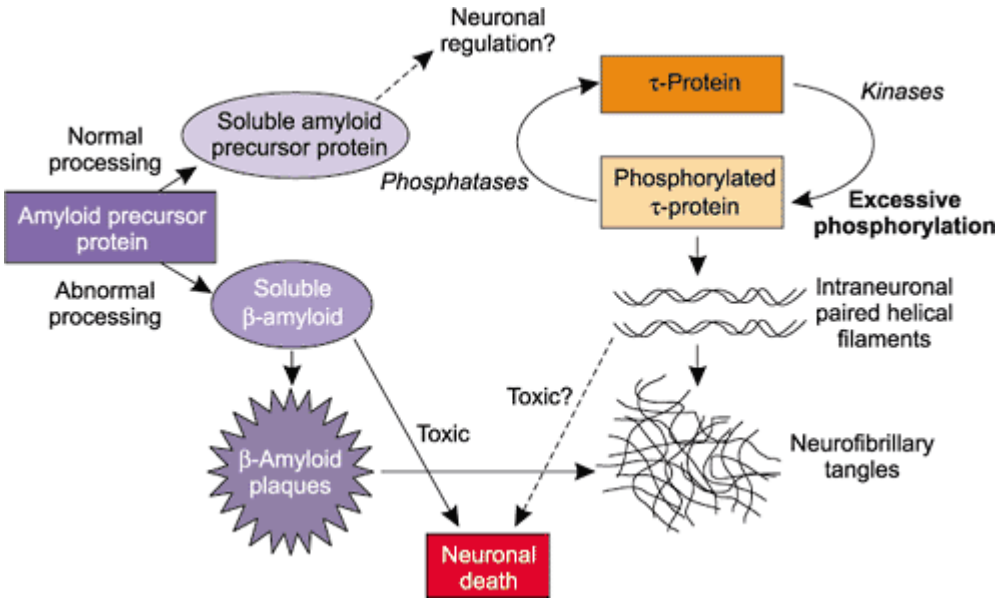
AD is a genetically complex and heterogeneous disorder. Based on the age of onset, it has two primary forms: early-onset and late-onset AD. More than 200 fully penetrant mutations in the amyloid β-protein precursor (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) have been linked to early-onset familial AD (<60 years old; 5-10% cases) (Bertram and Tanzi, 2008; Tanzi and Bertram, 2005), whereas **90-95% cases are late-onset AD** (>60 years old) and a variant (ε4) of the gene encoding apolipoprotein E (*APOE*) has been associated with this disease type (Strittmatter *et al.*, 1993). All of these four confirmed AD genes increase the cerebral Aβ levels, with the majority of early-onset familial AD mutations increasing the ratio of Aβ42 to Aβ40, which enhances the oligomerization of Aβ into neurotoxic assemblies (Hardy and Selkoe, 2002; Tanzi and Bertram, 2005). To date approximately 80% of the late-onset AD genetic variance still remains elusive (Gatz *et al.*, 2006). Recently several genome-wide association studies have identified several novel AD candidate genes (Bertram *et al.*, 2010) and functional characterization of these AD candidate genes has provided insights into the pathogenesis of AD (Zhang *et al.*, 2010a).

Aβ Hypothesis



Considerable evidence from genetics, biochemistry, and molecular biology supports the "**amyloid-cascade hypothesis**," which states that Aβ production and excessive accumulation are the principal pathogenetical events leading to AD (Hardy and Selkoe, 2002; Tanzi and Bertram, 2005). Specifically, Aβ accumulation and aggregation induce a series of "*gain-of-function*" activities, e.g., inflammatory and oxidative activities, followed by tau hyperphosphorylation, fibrillary tangle formation, and apoptotic reaction potentiation (Bertram and Tanzi, 2008; Hardy and Selkoe, 2002). In parallel, these gained and often toxic activities contribute to "*loss-of-function*" activities in proteasomes and lysosomes (Zhang and Saunders, 2009), as well as mitochondria (Bertram and Tanzi, 2008; Selkoe, 2004). Ultimately, these abnormal and usually unbalanced functional activities lead to neuronal dysfunction and cell death (Bertram and Tanzi, 2008; Selkoe, 2004).

Aβ accumulation and aggregation
Gain-of-function
Loss-of-function
Neuronal dysfunction and cell death



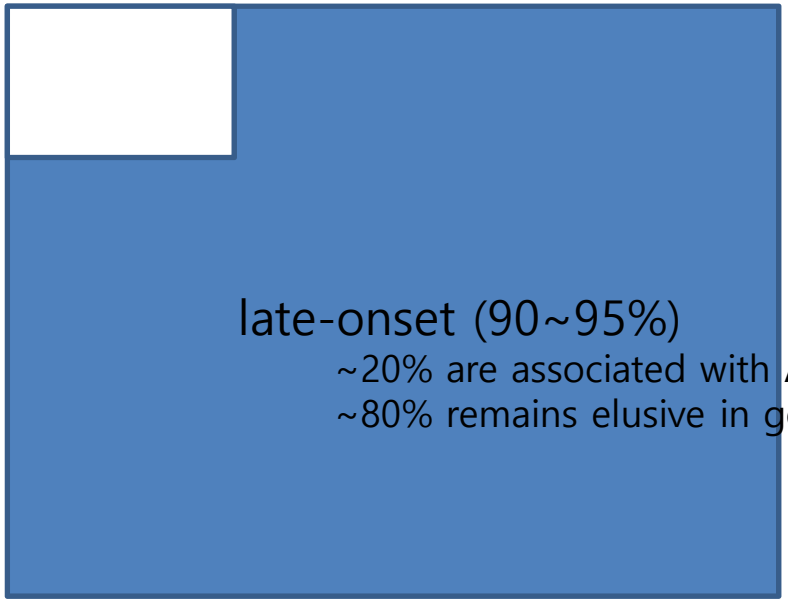
AD is a genetically complex and heterogeneous disorder. Based on the age of onset, it has two primary forms: early-onset and late-onset AD. More than 200 fully penetrant mutations in the amyloid β-protein precursor (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) have been linked to early-onset familial AD (<60 years old; 5-10% cases) (Bertram and Tanzi, 2008; Tanzi and Bertram, 2005), whereas **90-95% cases are late-onset AD** (>60 years old) and a variant (ε4) of the gene encoding apolipoprotein E (*APOE*) has been associated with this disease type (Strittmatter *et al.*, 1993). All of these four confirmed AD genes increase the cerebral Aβ levels, with the majority of early-onset familial AD mutations increasing the ratio of Aβ42 to Aβ40, which enhances the oligomerization of Aβ into neurotoxic assemblies (Hardy and Selkoe, 2002; Tanzi and Bertram, 2005). To date approximately 80% of the late-onset AD genetic variance still remains elusive (Gatz *et al.*, 2006). Recently several genome-wide association studies have identified several novel AD candidate genes (Bertram *et al.*, 2010) and functional characterization of these AD candidate genes has provided insights into the pathogenesis of AD (Zhang *et al.*, 2010a).

early-onset (5~10%): familial mutations

Amyloid β-protein precursor (*APP)*

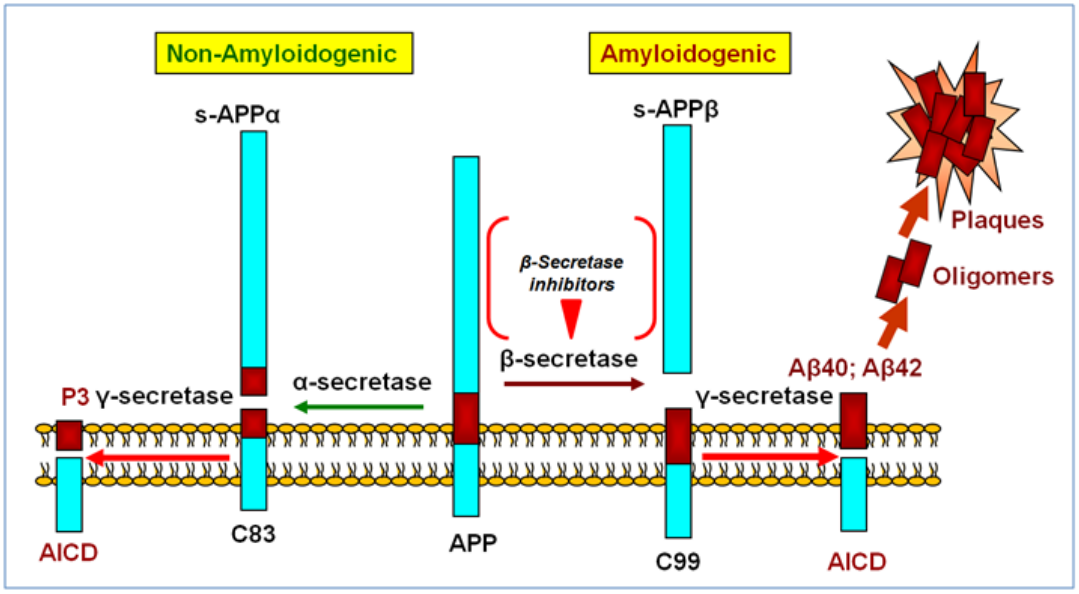
presenilin 1 (*PSEN1*)

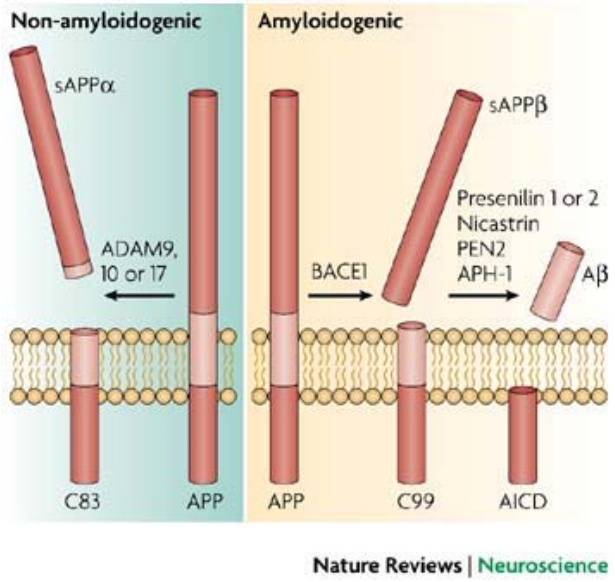
presenilin 2 (*PSEN2)*



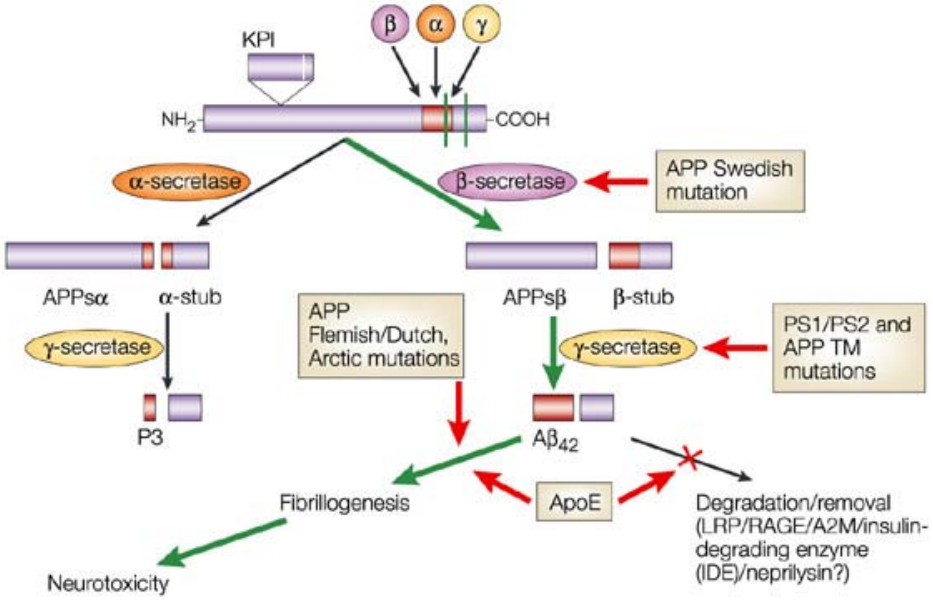
BACE1: beta-secretase 1 (beta-site amyloid precursor protein cleaving enzyme 1)
ADAM: a disintegrin and metalloproteinase domain
ADAM9: ADAM-containing protein 9, membrane protein structurally related to snake venome disintegrins

γ-secretase: a multi-subunit proteases containing presenilin 1, nicastrin, PEN2, APH-1
(an integral membrane protein that cleaves single-pass transmembrane proteins)
AICD: amyloid precursor protein intracellular domain
APPsβ: a soluble NH2-terminal fragment of amyloid precursor protein

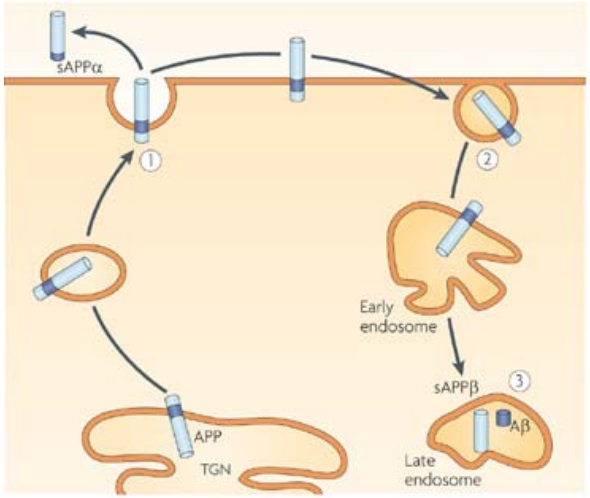




Schematic of the proteolytic events and cleavage products that are generated during the processing of APP



trafficking



Nature Reviews | Neuroscience

The amyloid precursor protein (APP) Swedish mutation makes APP a more favoured substrate for β-secretase (β -site APP-cleaving enzyme, or BACE) cleavage, thereby increasing the flux of APP down the β-secretase–γ-secretase cleavage pathway to generate amyloid-β (Aβ) (wild-type APP is predominantly processed by the α-secretase pathway). The mutations in presenilin 1 (PS1) and PS2 alter γ-secretase cleavage and promote the overproduction of Aβ42. Similarly, mutations within the transmembrane (TM) domain of APP (for example, APPV717I) serve as an improved substrate for γ-secretase, leading to the overproduction of Aβ42. The APP Flemish/Dutch and Arctic mutations seem to alter the propensity of A fibril formation. Apolipoprotein 4 (ApoE4) might have several effects, including competing with A for clearance through the low-density-lipoprotein-related protein 1 (LRP1) receptor, and enhancing aggregation and fibrillogenesis of extracellular A. In addition, because of the role of ApoE in lipid metabolism and repair mechanisms, it is conceivable that the 4 allele might not support these functions as well in response to various noxious stimuli when compared with ApoE3 or ApoE2. APPsβ, β-secretase-derived secreted APP; KPI, Kunitz protease inhibitor domain. Nature Reviews Neuroscience 3, 281-290 (April 2002)

Intracellular proteolysis: UPS and Autophagy

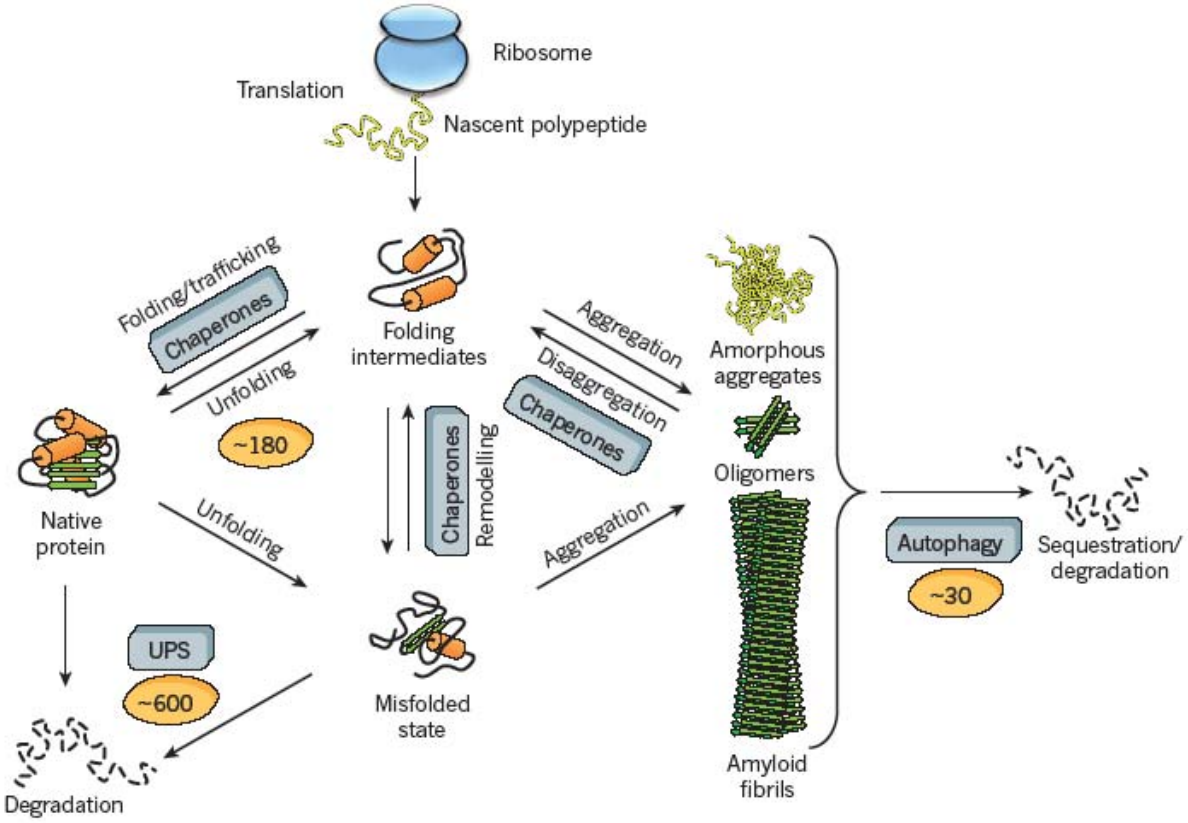


Figure 6 | Protein fates in the proteostasis network. The proteostasis network integrates chaperone pathways for the folding of newly synthesized proteins, for the remodelling of misfolded states and for disaggregation with the protein degradation mediated by the UPS and the autophagy system. Approximately 180 different chaperone components and their regulators orchestrate these processes in mammalian cells, whereas the UPS comprises ~600 and the autophagy system ~30 different components. The primary effort of the chaperone system is in preventing aggregation, but machinery for the disaggregation of aggregated proteins has been described in bacteria and fungi, involving oligomeric AAA^{+}-proteins such as HSP104 and the *E. coli* molecular chaperone protein ClpB, which cooperate with HSP70 chaperones[25]. A similar activity has been detected in metazoans, but the components involved have not yet been defined[83].

ApoE4 and Alzheimer's disease (AD)

Apolipoprotein E (ApoE) is 299 amino acids long and transports lipoproteins, fat-soluble vitamins, and cholesterol into the lymph system and then into the blood.

ApoE is a class of apolipoprotein found in the chylomicron and Intermediate-density lipoprotein (IDLs) that is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. In peripheral tissues, ApoE is primarily produced by the liver and macrophages, and mediates cholesterol metabolism in an isoform-dependent manner. In the central nervous system, ApoE is mainly produced by astrocytes, and transports cholesterol to neurons via ApoE receptors, which are members of the LDL receptor gene family.

Papers

1. **Apolipoprotein E and Apolipoprotein E Receptors: Normal Biology and Roles in Alzheimer Disease**

2. **The Genetics of Alzheimer Disease**

3. **Proteolytic Degradation of Amyloid β-Protein**

The genetics of AD

Early onset AD (EO-FAD): before 65, ~5%
mostly dominant, except one
Late onset AD (LO-FAD): ApoE genotype is the strongest genetic factor

Table 1. Early-onset familial Alzheimer disease genes and their pathogenic effects

Gene	Protein	Chromosome	Mutations	Molecular phenotype
APP	Amyloid β (A4) protein precursor	21q21	24 (duplication)	Increased $A\beta_{42}/A\beta_{40}$ ratio Increased Aβ production Increased Aβ aggregation
PSEN1	Presenilin 1	14q24	185	Increased $A\beta_{42}/A\beta_{40}$ ratio
PSEN2	Presenilin 2	1q31	14	Increased $A\beta_{42}/A\beta_{40}$ ratio

The E4 variant is the largest known genetic risk factor for late-onset sporadic AD in a variety of ethnic groups

Estimated worldwide human allele frequencies of ApoE			
Allele	ε2	ε3	ε4
General Frequency	8.4%	77.9%	13.7%
AD Frequency	3.9%	59.4%	36.7%

Increased risk with one and two E4 allele is ~3x and ~12x, respectively.

Cerebral amyloid angiopathy (CAA)

a form of angiopathy in which amyloid deposits form in the walls of the blood vessels of the central nervous system

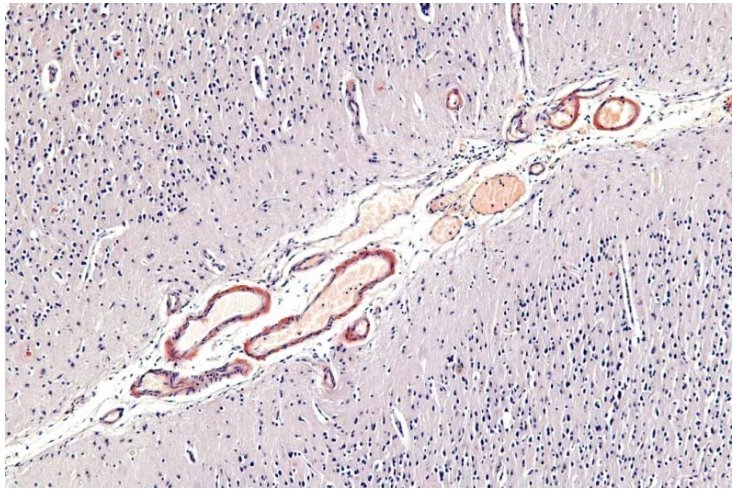
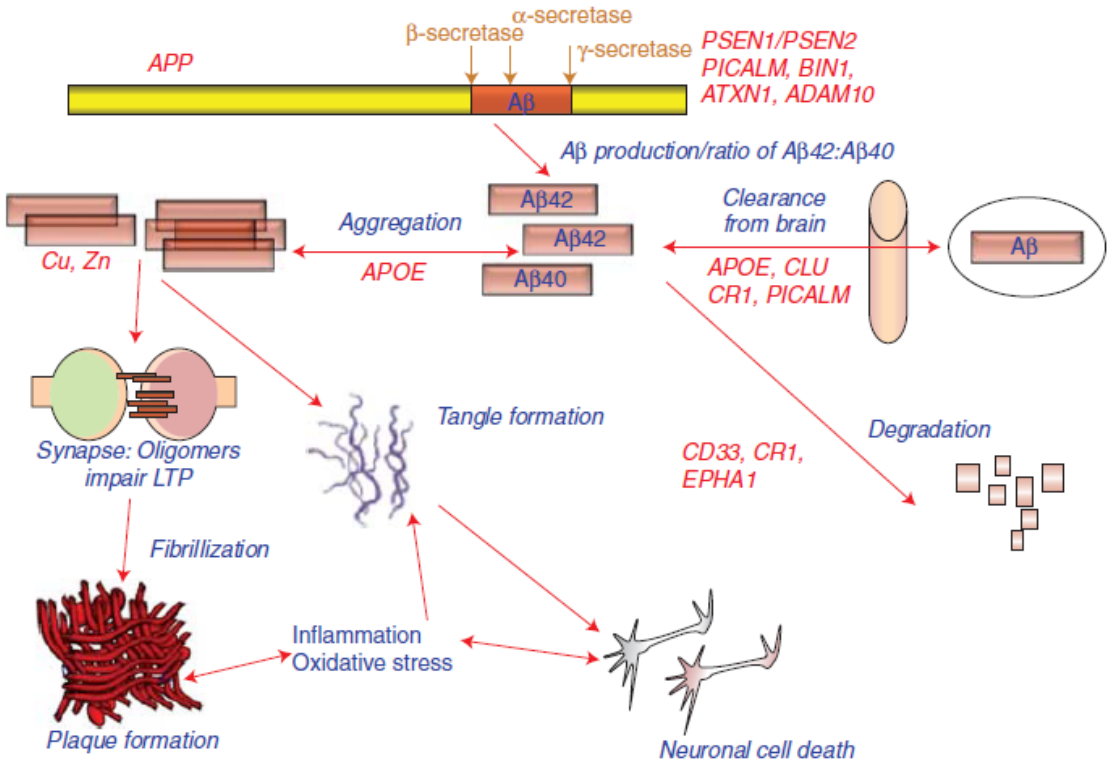


Table 2. Results of select genome-wide association studies of late-onset Alzheimer disease

Genome-wide association studies	Study design	Population	Major genes identified
Reiman et al. 2007	Case–control	US	*APOE*, *GAB2*
Bertram 2008	Family-based	US	*APOE*, *ATXN1*, *CD33*, *GWA_14q31*
Lambert et al. 2009	Case–control	US, Europe	*APOE*, *CLU*, *CR1*
Harold et al. 2009	Case–control	US, Europe	*APOE*, *CLU*, *PICALM*
Seshadri et al. 2010	Case–control	US, Europe	*APOE*, *BIN1*
Naj et al. 2011	Case–control	US, Europe	*MS4A6A/MS4A4E*, *EPHA1*, *CD33*, *CD2AP*
Hollingworth et al. 2011	Case–control	US, Europe	*ABCA7*, *MS4A6A/MS4A4E*, *EPHA1*, *CD33*, *CD2AP*

Table 3. Predicted pathogenic mechanisms of late-onset Alzheimer disease genes from GWASs

Gene	Protein	Location	Risk change (%)	Proposed molecular phenotype
APOE	Apolipoprotein E	19q13	~400%–1500%	Clearance of Aβ; lipid metabolism
CD33	CD33 (Siglec 3)	19q13.3	~10%	Innate immunity; degradation of Aβ
CLU	Clusterin	8p21.1	~10%	Clearance of Aβ; innate immunity
CR1	Complement component (3b/4b) receptor 1	1q32	~15%	Clearance of Aβ; innate immunity
PICALM	Phosphatidylinositol binding clathrin assembly molecule	11q14	~15%	Production and clearance of Aβ; cellular signaling
BIN1	Bridging integrator 1	2q14	~15%	Production and clearance of Aβ; cellular signaling
ABCA7	ATP-binding cassette subfamily A member 7	19p13.3	~20%	Lipid metabolism; cellular signaling
CD2AP	CD2-associated protein	6p12.3	~10%	Cellular signaling
EPHA1	EPH receptor A1	7q34	~10%	Cellular signaling; innate immunity
MS4A6A/MS4A4E	Membrane-spanning 4-domains, subfamily A, members 6A and 4E	11q12.1	~10%	Cellular signaling
ATXN1	Ataxin 1	6p22.3	NA	Production of Aβ

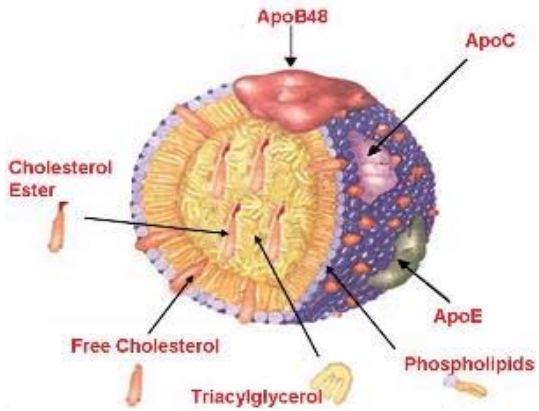


Potential roles of select Alzheimer disease (AD) genes in Aβ-related pathogenesis of AD. (Modified from Bertram and Tanzi 2008; reprinted with permission from the author.) Cold Spring Harbor Perspectives in Medicine (2012)

Apolipoproteins

2 major classes: ApoB form LDL, while others form HDL
6 classes and several subgroups

- A: apo A-1, apo A-II, apo A-IV, apo A-V
- B: apo B48, apo B100
- C: apo C-I, apo C-II, apo C-III, apo C-IV
- D:
- E: polymorphic with 3 major isoforms
- H:

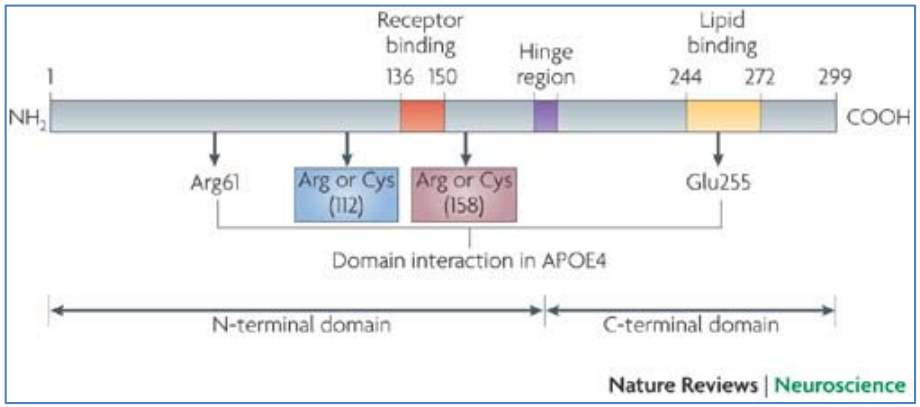


ApoE polymorphism

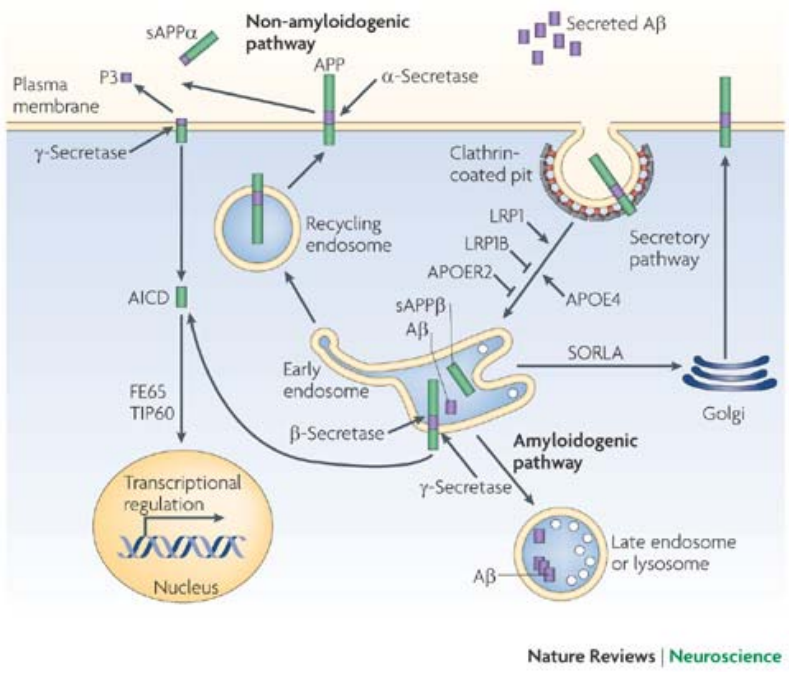
ApoE2 (cys112, cys158), ApoE3 (cys112, arg158), and ApoE4 (arg112, arg158). Although these allelic forms differ from each other by only one or two amino acids at positions 112 and 158, these differences alter apoE structure and function. These have physiological consequences:

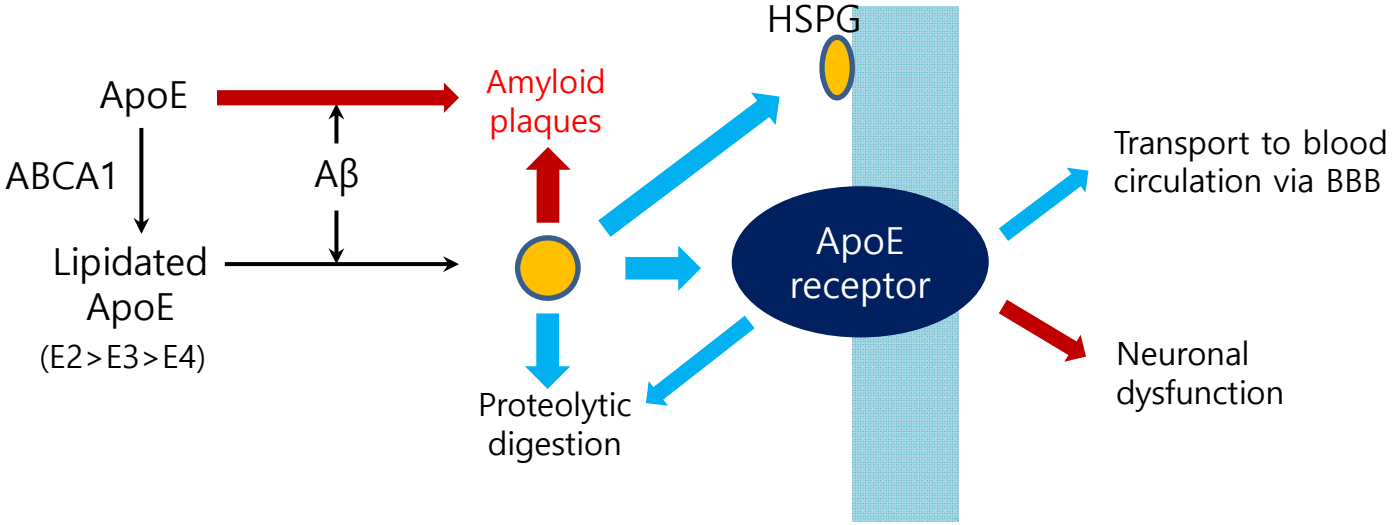
E2 is found in approximately 7 percent of the population. E3 is found in approximately 79 percent of the population. E4 is found in approximately 14 percent of the population.

6 genotypes: E2/2, E3/3, E4/4, E2/3, E2/4, E3/4



Effects of ApoE & ApoE receptors on
- Neuronal trafficking
- Aggregation
- Clearance



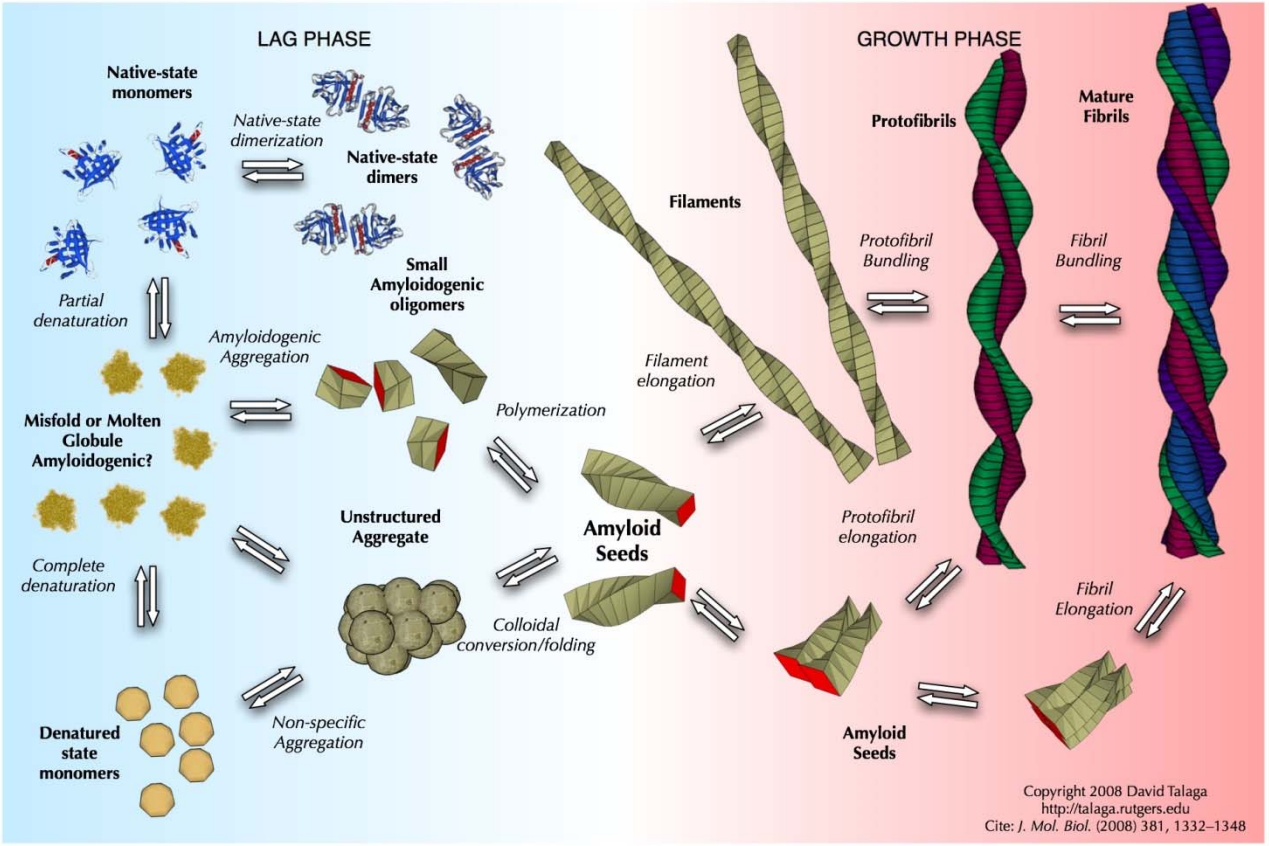


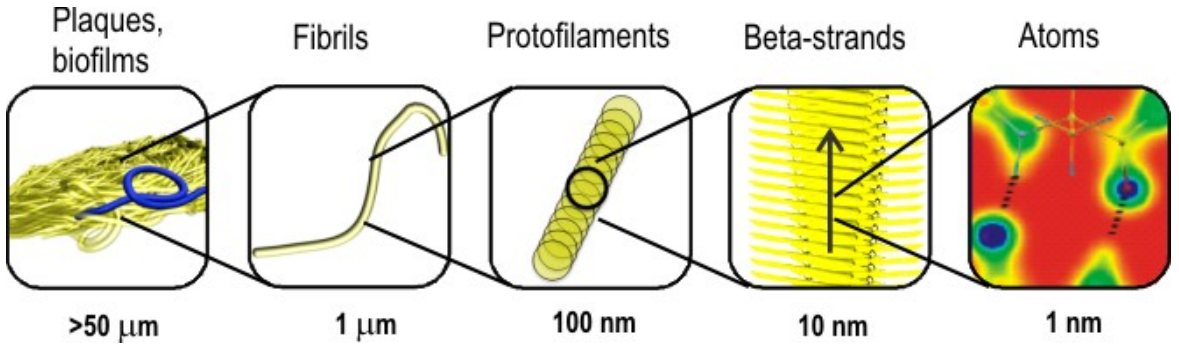
FDA-approved drugs

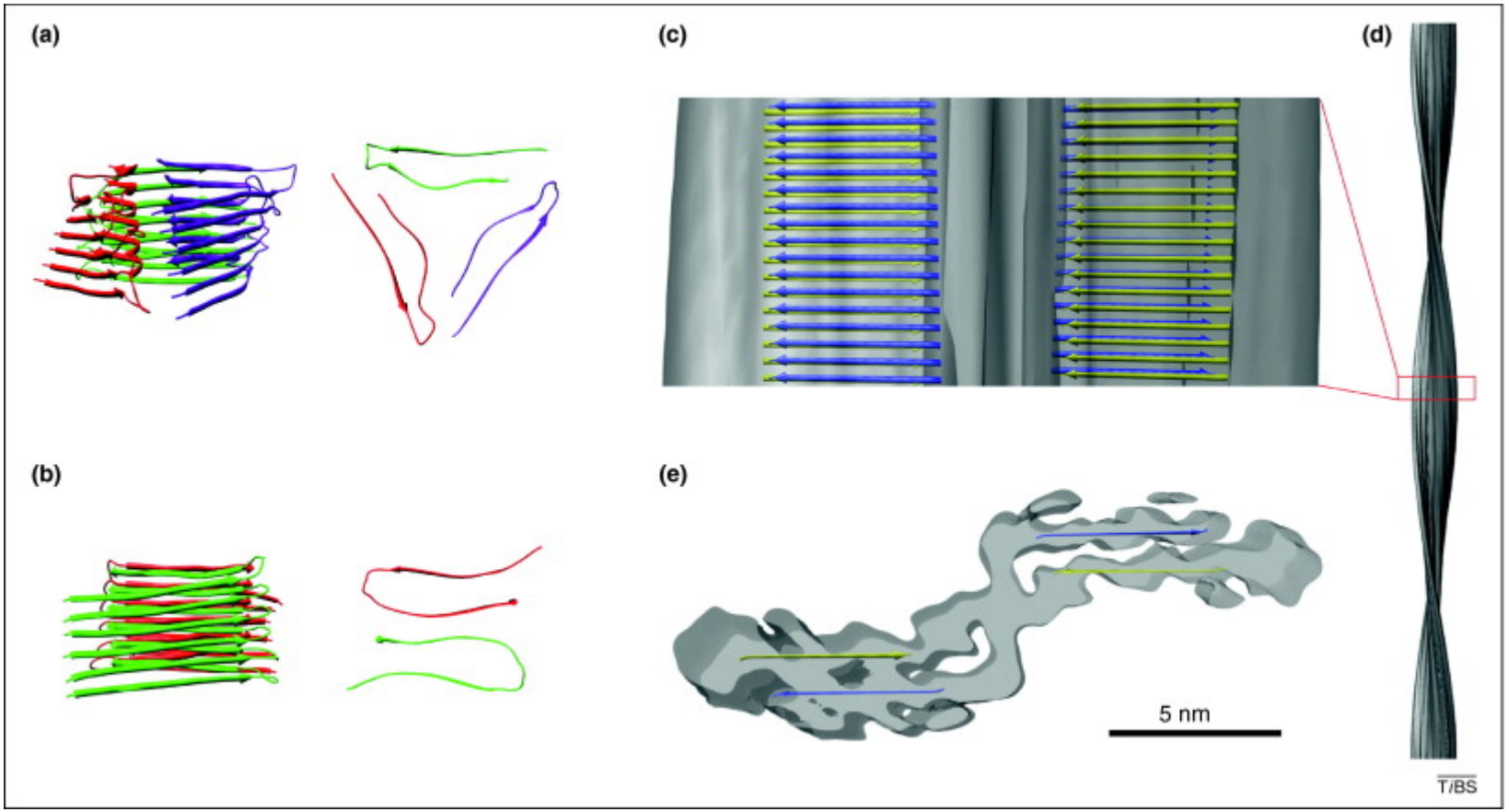
Drug name	Brand name	Approved For	FDA Approved
1. donepezil	Aricept	All stages	1996
2. galantamine	Razadyne	Mild to moderate	2001
3. memantine	Namenda	Moderate to severe	2003
4. rivastigmine	Exelon	All stages	2000
5. donepezil and memantine	Namzaric	Moderate to severe	2014

1) Cholinesterase inhibitors work by slowing down the process that breaks down a key neurotransmitter. Donepezil, galantamine and rivastigmine are cholinesterase inhibitors.

2) Memantine, the fifth Alzheimer's drug, is an NMDA (N-methyl-D-aspartate) receptor antagonist, which works by regulating the activity of glutamate, an important neurotransmitter in the brain involved in learning and memory. Attachment of glutamate to cell surface "docking sites" called NMDA receptors permits calcium to enter the cell. This process is important for cell signaling, as well as learning and memory. In Alzheimer's disease, however, excess glutamate can be released from damaged cells, leading to chronic overexposure to calcium, which can speed up cell damage. Memantine helps prevent this destructive chain of events by partially blocking the NMDA receptors.


LAG PHASE
GROWTH PHASE
Native-state monomers
Native-state dimerization
Native-state dimers
Small Amyloidogenic oligomers
Partial denaturation
Amyloidogenic Aggregation
Misfold or Molten Globule Amyloidogenic?
Unstructured Aggregate
Complete denaturation
Denatured state monomers
Non-specific Aggregation
Polymerization
Colloidal conversion/folding
Amyloid Seeds
Filaments
Filament elongation
Protofibrils
Protofibril Bundling
Mature Fibrils
Fibril Bundling
Protofibril elongation
Fibril Elongation
Amyloid Seeds
Copyright 2008 David Talaga
http://talaga.rutgers.edu
Cite: J. Mol. Biol. (2008) 381, 1332–1348


Plaques, biofilms
Fibrils
Protofilaments
Beta-strands
Atoms
>50 μm
1 μm
100 nm
10 nm
1 nm

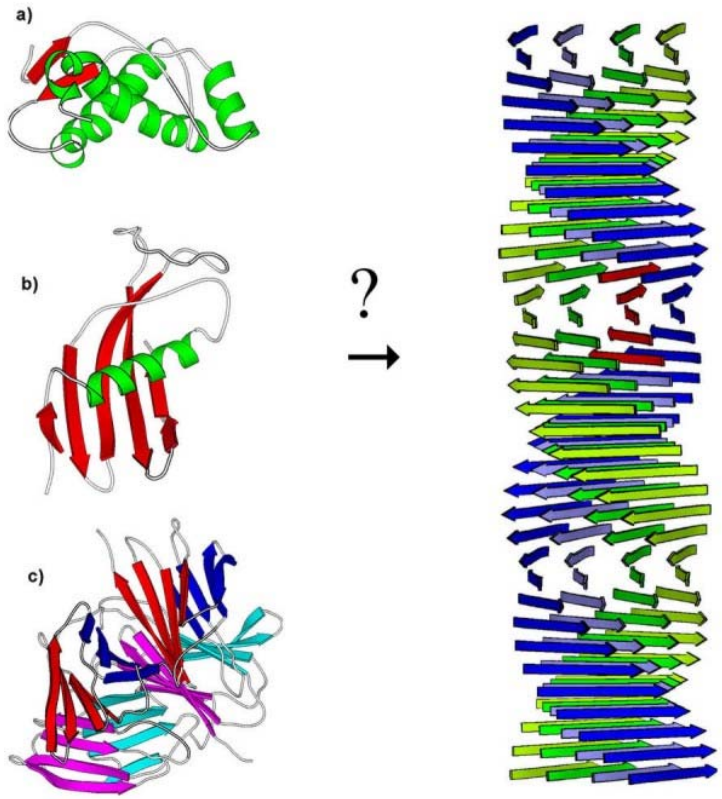


Recent progress in understanding Alzheimer's β-amyloid structures
TIBS Volume 36, Issue 6, June 2011, Pages 338–345

Figure 4. Structural models of Aβ fibrils. Previous structural models deviate significantly for the most highly resolved Aβ fibril structures, which were obtained by cryo-EM. Hence, the latter encompass a different peptide assembly. (a,b) Structural models assuming a U-shaped peptide fold; side views and top views shown; only residues 9–40 modeled. (a) Three Aβ(1–40) molecules per cross-sectional layer [29]. (b) Two Aβ(1–40) molecules per cross-sectional layer [24]. (c,d) Cryo-EM structure of an Aβ(1–40) fibril (0.8 nm). (c,d) side views, (e) cross-section. Images in (c,e) are superimposed with a β-sheet model, which is derived from these cryo-EM data, and highlights the peptides forming the cross-β regions in yellow or blue (the lines are not meant to imply continuous β-strands over their entire length; these regions might instead contain several shorter strands). Images in (a–c) and (e) are displayed with the same scale.

Amyloid fibrils

There are at least 21 distinct human diseases that are associated with amyloid fibril formation



Three different proteins, **(a)** prion protein, **(b)** cystatin C and **c)** transthyretin, with three different three-dimensional structures which are known to form amyloid fibres in vivo. On the right is a proposed model for the structure of an amyloid fibril.

Amyloidoses

mutant forms of normally occurring proteins
amyloid fibrils are beta sheet structures
extension of partial beta domains

Under the appropriate conditions

almost any protein can be induced to aggregate

It seems likely that protein folding pathways have evolved not only to allow polypeptides to assume stable native structures but also to avoid forming interchain H bonds that would lead to fibril formation

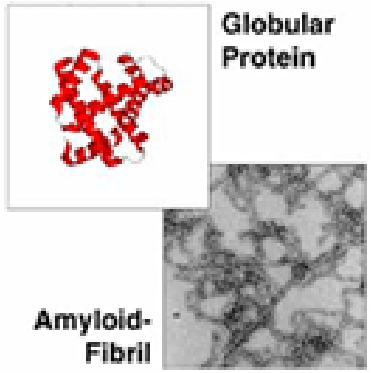


Figure 6-50 Fundamentals of Biochemistry, 2/e

A model, based on X-ray fiber diffraction measurements, of an amyloid fibril