Alzheimer Disease

Prof Vandana Rai
Department of Biotechnology
VBS Purvanchal University
Jaunpur

Alois Alzheimer

Alois Alzheimer was a medical officer at the state asylum in Frankfurt am Main, Germany.
He became a leading neurologist, publishing papers on epilepsy, brain tumors, syphilis, cerebro arterio-sclerosis & Huntington's chorea.

- In 1901, Alzheimer met a 51 year old man, Auguste D, who he cared for at the asylum for the next four years.

- Her condition steadily deteriorated from memory loss, speech difficulty, confusion, suspicion, agitation, wandering and screaming to being bedridden, incontinent, and unaware of her surroundings.

- In 1905, at autopsy he found the brain had shriveled, and neurons had disappeared. He discovered thread-like spindle-shaped objects "neurofibrillary tangles", as well as thick viscous-looking blobs "senile plaques" .
- In 1907, Alzheimer published a monumental paper on the first description of this new dementia AD.
- In 1912, on his way to assuming the position of full professor at the University Hospital in Breslau, Alzheimer became ill with strep throat, complicated by rheumatic fever and heart disease.

- In 1915, at the age of 51, Alzheimer died of endocarditis (heart valve infection) and kidney failure.

Auguste D

What is Alzheimer's Disease?

- An irreversible, progressive brain disorder
- The fourth leading cause of death among the elderly in developed nations
- AD advances by stages, from early, mild forgetfulness to a severe loss of mental function (dementia). Symptoms usually first appear after age 60.
- The earliest symptoms often include loss of recent memory (names of people & common objects) , faulty judgment, changes in personality and loss of clear thinking.

o Later in the disease, they may forget how to do simple tasks, such as washing their hands. Eventually, people with AD lose all reasoning ability and become dependent on other people for their everyday care.

- Finally, the disease becomes so debilitating that patients are bedridden and likely to develop other illnesses and infections. Most commonly, people with AD die from pneumonia.

- The course varies from person to person, as does the rate of decline. On average, AD patients live for 8 to 10 years after they are diagnosed, though the disease can last for up to 20 years.

Symptoms

- Many different clinical features are associated with AD. Among the first symptoms are the inability to create new memories and the loss of short-term memory.
- The ability to concentrate and recall past events worsens as the disease progresses.
- Alzheimer disease patients often have no accurate sense of time and are unable to correctly identify the day, month, or year.
- Although standard speech patterns and clichés are retained in the early stages, both sentence formation and coherent verbal communication diminish and are eventually lost.
- Some AD patients become extremely passive, others very hostile, and some abnormally suspicious. Delusions are prevalent in 50% of the cases.
- In the end, AD patients are mute, immobilized, and uncomprehending. Death is often the result of respiratory failure.
- For AD patients diagnosed at 65 years or older, the disease lasts from about 8 to 20 years.

Features of AD patients

- Many different clinical features are associated with AD.
- Among the first symptoms are the inability to create new memories and the loss of short-term memory.
- AD patients often have no accurate sense of time and are unable to correctly identify the day, month or year.
- Although standard speech patterns and clichés are retained in the early stages, both sentence formation and coherent verbal communication diminish and are eventually lost.
- AD patients becomes extremely passive, others very hostile, and some abnormally suspicious.
- Delusions are prevalent in 50% of the cases.
- In the end, AD patients are mute, immobilized and uncomprehending.
- Death is often the result of respiratory failure

- AD is classified as

  familial or sporadic

  and early –onset (generally before 60 years) or late-onset (after 60), with early-onset primarily occurring in familial cases and late-onset in both familial and sporadic cases.

- Familial, early –onset AD is very rare, estimated to comprise only 1-2% of all AD cases. The remaining 98% of AD patients are clinically classified as late-onset familial or sporadic.

Progression of Alzheimer's Disease

Drew L., 2018. An age-old story of dementia. Nature 559 (7715), S2-S3. https://doi.org/10.1038/d41586-018-05718-5

Some sobering facts about Alzheimer's

- More than 44 million suffer from AD today.
- Neither Medicare nor most private health insurance covers the long-term care most patients need.
- Alzheimer's disease is the most common cause of senile dementia and is estimated to affect 50 million people worldwide by year 2025 and other age-related neurodegenerative disorders leading to dementia are on the rise because of increase in life expectancy and decrease in human mortality.

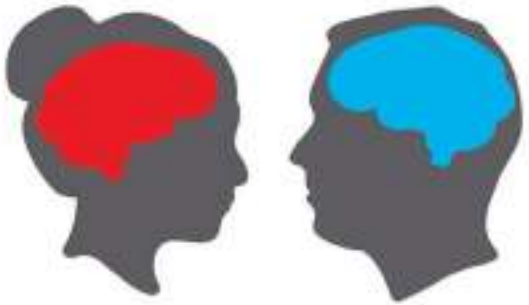
Risk factors

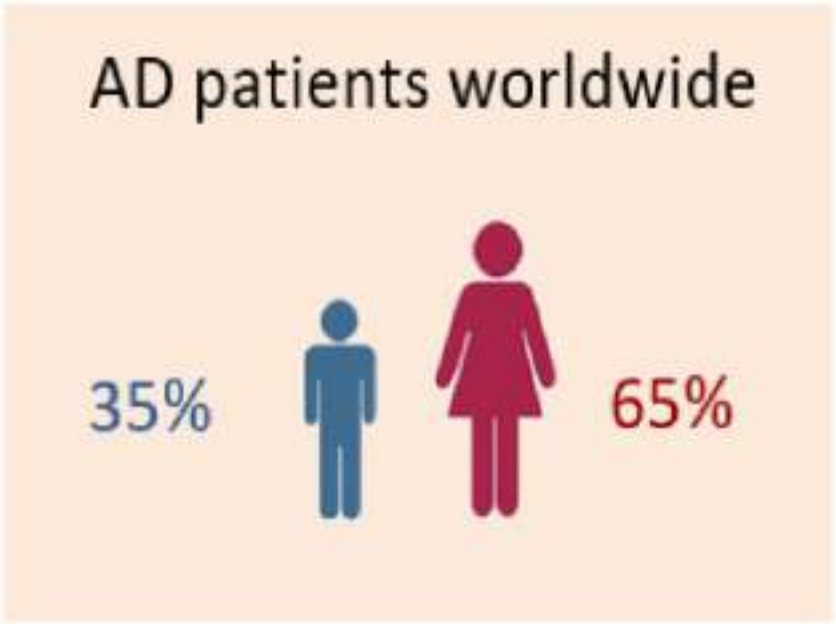
Genetic factor

- Around **1%** of cases of Alzheimer's disease are caused by mutations in the genes *which affect amyloid-processing*
- *APP*,
- *PSEN1 or PSEN2*,.

https://ghr.nlm.nih.gov/condition/alzheimer-disease#inheritance

Gender





The overall incidence of Alzheimer's disease in women is up to twice that of men.

https://www.brightfocus.org/alzheimers/news/scientists-shed-new-light-gender-differences-alzheimers

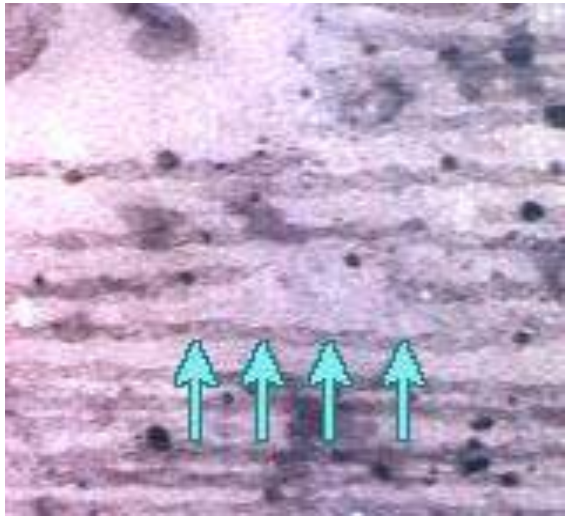
http://www.womensbrainproject.com/facts/

LIFESTYLE

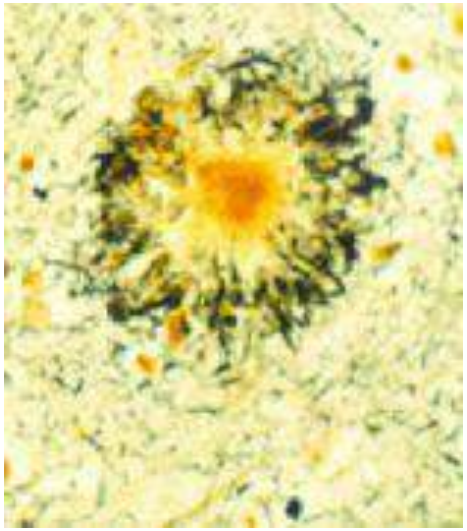
- Potentially modifiable risk factors for Alzheimer's disease have been identified.
- Diabetes
- Obesity
- Depression
- Smoking and
- Low educational attainment.

Alzheimer's Disease

AD occurs when nerve cells in key areas of the brain are damaged or destroyed. The changes disrupt the normal flow of information between body and brain resulting in a steady decline in mental function.



tangles, helical filament**s**



neuron tangles surround an amyloid plaque

It has been postulated that nerve deterioration is most likely caused by formation of neurofibrillary tangles (knots) and senile plaques (clumps) commonly found in diseased brain during an after-death biopsy.

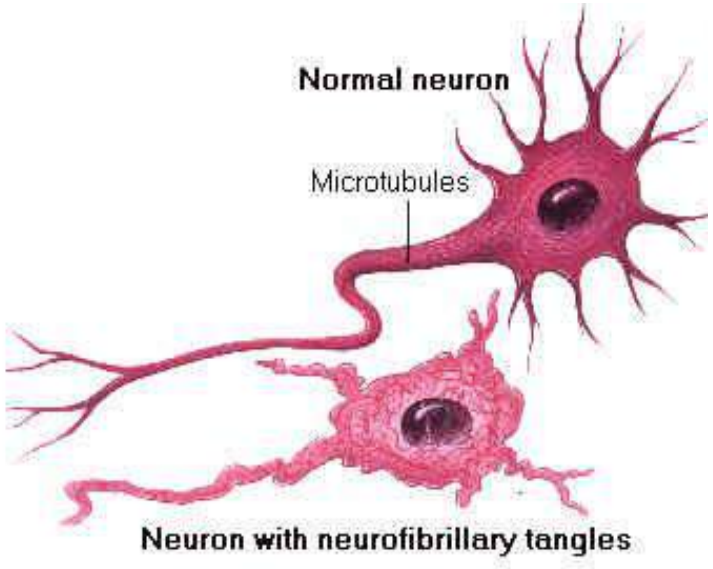
Plaques and knots form primarily in areas controlling memory and retention of learned information

Amyloid plaques (20–200mm in diameter)

- One of the hallmarks of Alzheimer's disease is the accumulation of amyloid plaques *between* nerve cells (neurons) in the brain. Amyloid is a general term for protein fragments that the body produces normally. Beta-amyloid is a fragment of a protein that is snipped from another protein called amyloid precursor protein (APP).
- In a healthy brain, these protein fragments would be broken down and eliminated. In Alzheimer's disease, the fragments accumulate to form hard, insoluble plaques.

- Neurofibrillary tangles consist of insoluble twisted fibers that are found *inside* of the brain's cells. They primarily consist of a protein called tau, which forms part of a structure called a microtubule.

- The microtubule helps transport nutrients and other important substances from one part of the nerve cell to another (the axon is the long threadlike extension that conducts nerve impulses *away* from the body of a nerve cell, and dendrites are any of the short branched threadlike extensions that conduct nerve impulses *towards* the nerve cell body.
- In Alzheimer's disease the tau protein is abnormal and the microtubule structures collapse



Senile plaques/Amyloid plaques

- The amyloid plaques are almost exclusively composed of a small peptide called b-amyloid (Ab), which is derived from a larger integral membrane protein called b-amyloid precursor protein (bAPP).
- Biochemical analysis on how bAPP is produced revealed the generation of the toxic Ab peptide.
- Some of the bAPP in the membrane are internalized and degraded. A small subset of the APP molecules is found to be degraded initially by a-secretase enzyme to produce 83-residue COOH-terminal fragment (C83) and a soluble version of bAPP (a-APP), and then by g-secretase enzyme to give rise to a harmless peptide of 3kDa called p3.

- However, when βAPP is cleaved initially by βsecretase enzyme to produce a 99-residue COOH terminal fragment (C99) and βAPPs, followed by g-secretase cleavage, either a 40 amino acids Ab peptide (Aβ40) or a 42 amino acids Aβ peptide (Aβ42) of a 4kDa is formed.
- The more toxic version is Aβ42 as it is hydrophobic and rapidly forms aggregates in the extra cellular space

Neurofibrillary tangles (NFTs)

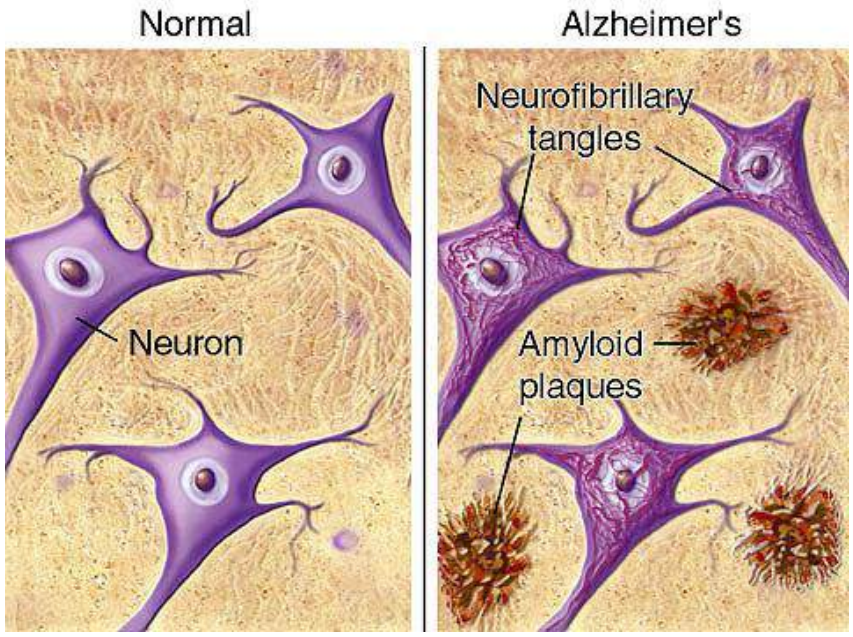
- The main fibrous elements of NFTs are numerous paired helical filaments (PHFs). A PHF consists of two cross –linked, interwined protein strands, with each strand made up of a number of joined tau (t) protein molecules forming a tau filament.

- *The MAPT gene encodes the tau protein and is located at chromosome site 17q21.*

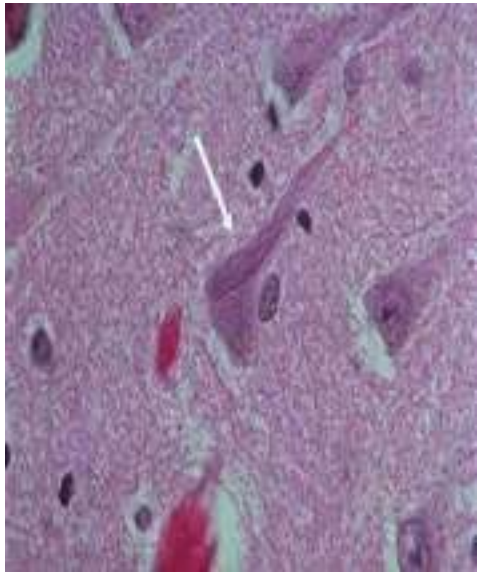
- The main tau protein binds to tubulin molecules and facilitates the assembly of tubulin into microtubules and, in combination with other microtubule –associated proteins (MAPs), tau protein maintains the stability of microtubules.
- In contrast to tau molecues under normal conditions, those that make up NFTs are hyper-phosphorylated (HP-tau).

HP-tau does not bind to tubulin but attaches to other MAPs. Consequently, HP-tau blocks the formation of microtubules and undermines the stability of existing microtubules. HP-tau probably dissembles microtubules and acts as an aggregation center for the formation of PHFs and NFTs.

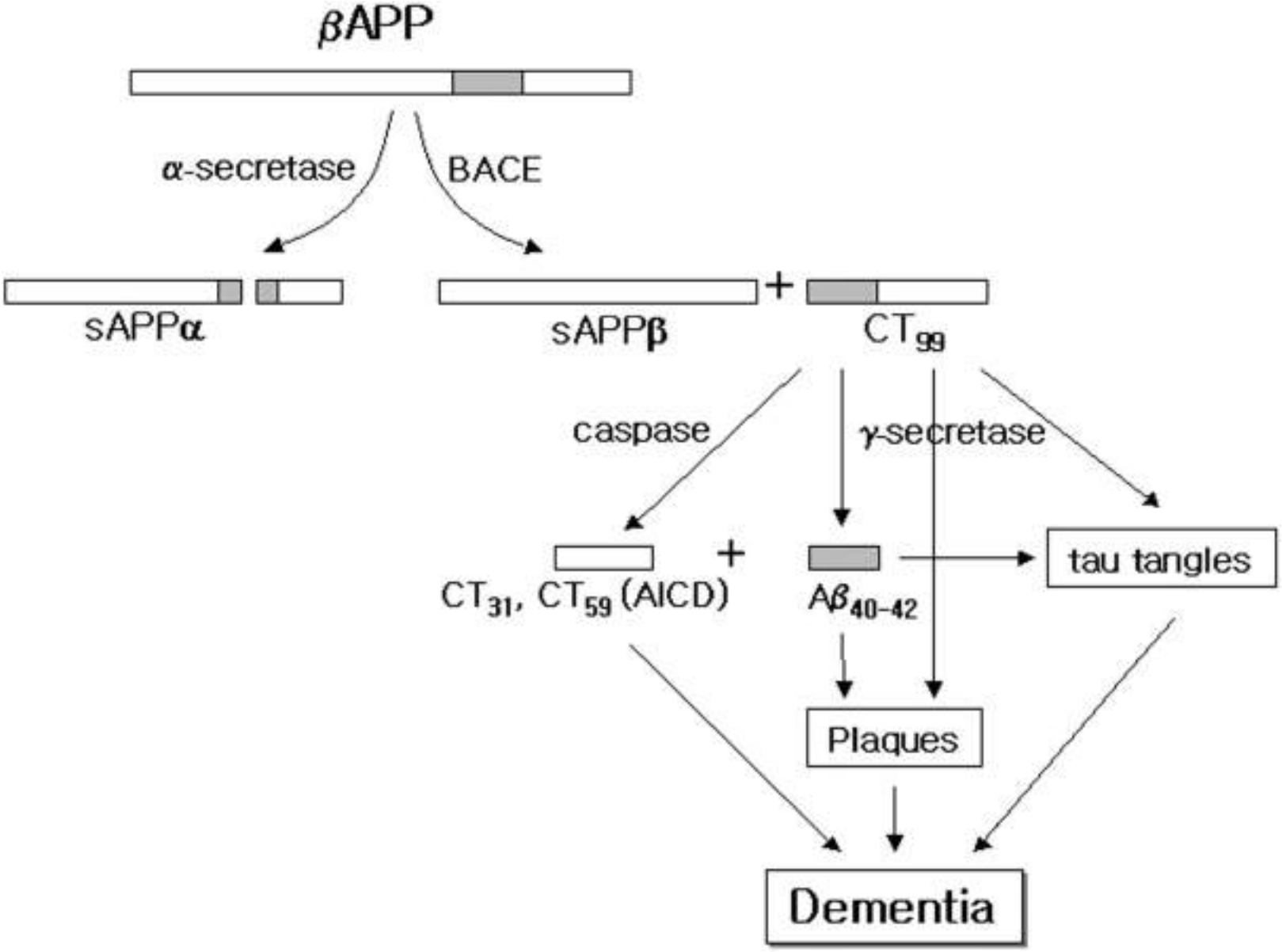
The dissolution of the neuronal microtubule system would prevent axonal transport, which in turn would cause the loss of synapses and lead eventually to the degeneration of synaptic bulbs.



Hard, insoluble plaques are not broken down and not eliminated in AD; Insoluble twisted tangles made up of misfolded tau proteins



Nerve fiber tangle of Alzheimer's victim

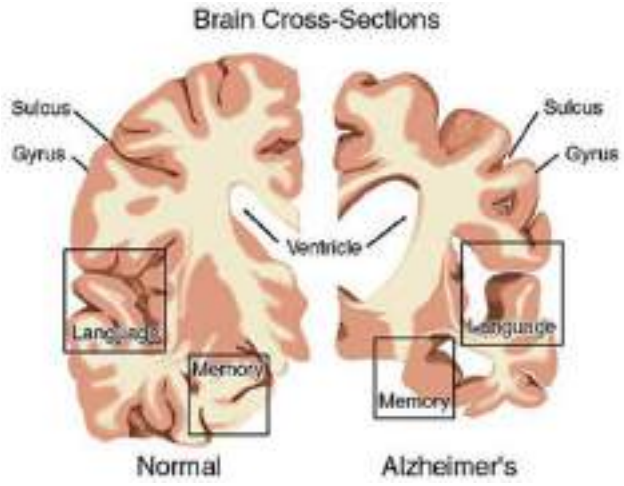

βAPP
α-secretase
BACE
sAPPα
sAPPβ
+
CT99
caspase
γ-secretase
CT31, CT59 (AICD)
+
Aβ40-42
tau tangles
Plaques
Dementia

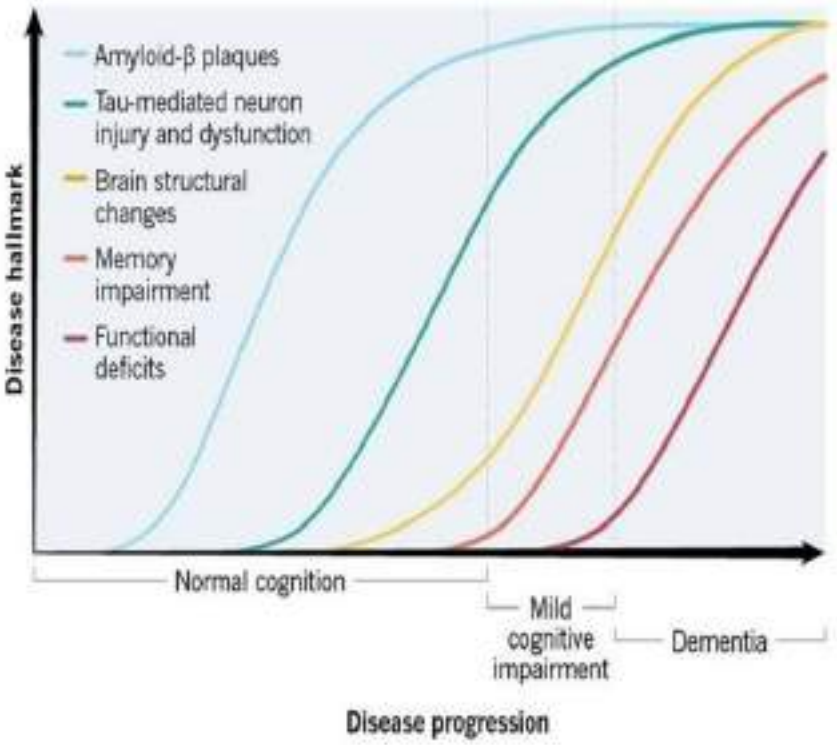
A Slow March

By the time that a person begins to experience the symptoms of Alzheimer's disease, the condition is already well-established in the brain.

- The accumulation of amyloid-b, generally thought to be the first step in disease progression, could precede symptoms by 10–15 years.

- Tau accumulation occurs later, much closer to the onset of neurodegeneration.





Drew L. Nature 2018;559:S2-3

Biochemistry of Senile Plaques and Neurofibrillary Tangles

- The core of a senile plaque is a densely packed fibrous structure that historically has been described as an amyloid body.
- Originally, amyloid bodies were thought to be made up of carbohydrates.
- More definitive chemical analyses established that the major component(s) was protein.
- The principal protein of AD amyloid bodies is a 4-kDa peptide (Ab protein; b-protein; A4, b/A4).
- Within AD amyloid bodies, the Ab protein (amyloid b-protein) consists of isoforms that range in amino acid number from 39 to 43.
- Of these, the two main isoforms contain 40 and 42 amino acids and are designated Ab1–40 (Ab40) and Ab1–42 (Ab42), respectively.

Amyloid precursor protein (APP)

- The amyloid precursor protein (*APP*) has a single transmembrane domain and commonly occurs as three **isoforms with 695, 751, and 770 amino acids.**
- The 695-amino acid APP isoform is found in neurons throughout the CNS.
- Some of these APP molecules are found in the membrane at the terminal ends of axons and others in intracellular membranes including the Golgi network.
- The 751- and 770-amino acid isoforms are produced, for the most part, by glial cells.
- Some complete versions and processed segments of the 751- and 770-APP isoforms are secreted.

APP processing

- For convenience, the amino acid numbering system for APP and Ab isoforms is based on the 770-amino acid isoform.
- The Ab43 isoform encompasses amino **acid sites 672 to 714 of the APP** molecule. Under normal conditions, APP molecules are processed by proteolytic enzymes .
- An enzyme called **a-secretase** cleaves the APP molecule after the amino acid at **site 687**, which lies within the Ab region.
- Neither of the fragments produced by this cleavage are fibrillogenic (amyloidogenic).
- Cleavage by **b-secretase** (BACE-1, b-site APP-cleaving enzyme) after amino acid **site 671** also produces two nonamyloidogenic fragments.
- Both a- and b-secretase cleavages of APP are normal processes and occur in almost all cells.
- When some APP molecules are doubly cleaved by **b-secretase and by g-secretase**, which cuts after either site 711 or site 713, then Ab40 and Ab42 isoforms are released.
- Cleavage of APP by both a and g-secretases releases an internal piece of the APP protein that has 24 amino acids (Ab17-40; p3) and is not amyloidogenic.

Function of APP

- The functional roles of APP and the various fragments of APP in the nervous system are not well understood.
- The cell membrane-bound 695-amino acid APP isoform may facilitate **cell-to-cell contact, adhesion to the extra neuronal matrix, and/or synaptic stability.**
- Intracellular APP may be associated with the **cytoskeletal system, which is composed of filaments and microtubules conveying vesicles and other components from one part of a cell to another.**
- The two types of secreted APP fragments [**APP 1–671 (bAPPs); APP 1–687 (aAPPs)]** may protect neurons from damage and modulate events at synapses.
- Atypical processing of APP that leads to an excess of the Ab42 isoform is probably responsible for the destruction of synapses during the early stages of AD, the formation of senile plaques, and, eventually, degradation of neurons.

Brain autopsy of AD patients shows three distinctive neuropath-logical features.

•First, there are devastating loses of synapses and neurons within the hippocampus and entorhinal cortex, which is the region of the cerebral cortex (neocortex). Many cerebral cortex neurons that connect with other cortical neurons that also degenerate. By the final stage of the diseases, the overall width of most of the neocortex is dramatically reduced.

•Second, dense spherical structures (20-200um in diameter), senile plagues (SPs) or amyloid plaques are prevalent outside the neurons of the hippocampus and other regions of the brain.

•Third, aggregation of fibrils (neurofibrillary tangles, NFTs) accumulate within the cell bodies and dendritic processes of the neurons of the hippocampus, the neocortex including the entorhinal region, the amygdala, and other parts of the brain

Pathophysiology

- There is an overall shrinkage of brain tissue as Alzheimer's disease progresses. In addition, the ventricles, or chambers within the brain that contain cerebrospinal fluid, are noticeably enlarged.

- In the early stages of Alzheimer's disease, short-term memory begins to decline when the **cells in the hippocampus**, which is part of the limbic system, degenerate. The ability to perform routine tasks also declines.

- As Alzheimer's disease spreads through the cerebral cortex (the outer layer of the brain), judgment declines, emotional outbursts may occur and language is impaired.

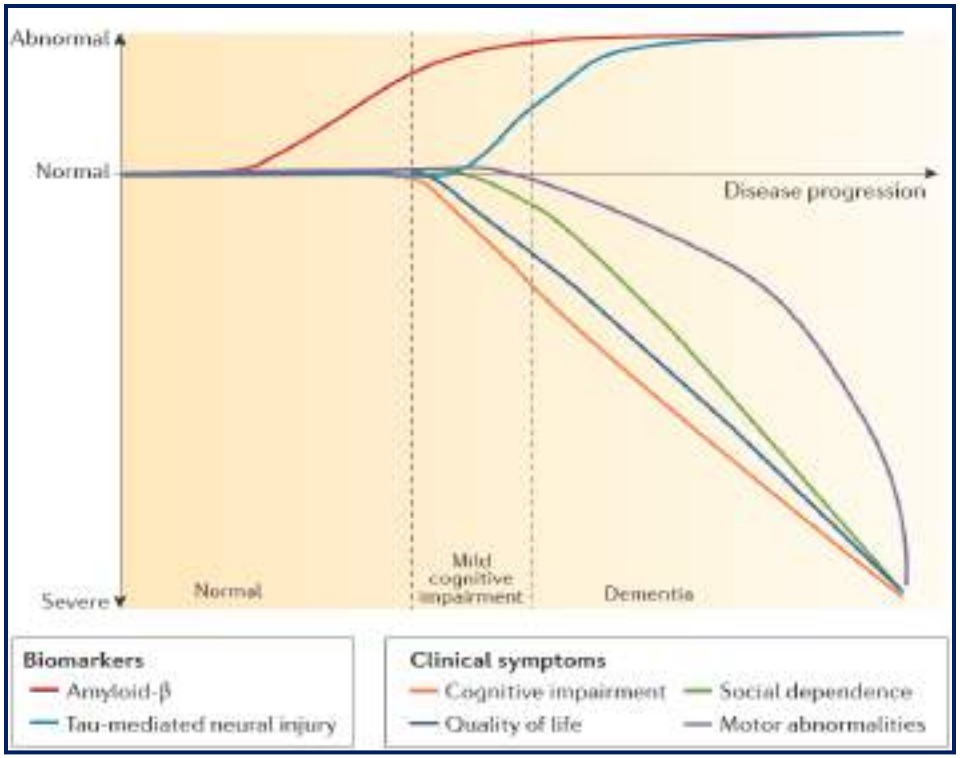
- Progression of the disease leads to the death of more nerve cells and subsequent behavior changes, such as wandering and agitation. The ability to recognize faces and to communicate is completely lost in the final stages.

- Patients lose bowel and bladder control, and eventually need constant care. This stage of complete dependency may last for years before the patient dies. The average length of time from diagnosis to death is 4 to 8 years, although it can take 20 years or more for the disease to run its course.

Stages of Alzheimer Disease

Stages	Patients condition	Duration	Brain regions	Symptoms	Disease
Stage 1	Normal	7 years	Disease begins in Medial Temporal lobe	Short Term memory loss	**Mild Cognitive impairments**
Stage 2	Normal age forgetfulness				
Stage 3	Mild cognitive impairments				
Stage 4	A diagnosis of Alzheimer's disease is possible, patients have trouble with memory and every day task	2 years	Disease spreads to lateral Temporal and parital lobes	Reading problems, Poor Object recognition, Poor direction sense	**Mild Alzheimer's disease**
Stage 5	Patients can no longer live independently as their memory and ability to communicate deteriorates	2 years	Disease spreads to frontal lobe	Poor Judgement, Impulsivity, Short Attention	**Moderate Alzheimer's disease**
Stage 6	Memory is severely impaired, patients confused, Patients will need family members for personal hygiene	3 Years	Disease Spreads to Occipital lobe	Visual problems	**Severe Alzheimer's disease**
Stage 7	Patient can no longer respond to their environment and become infantile				

Quality of life of patients with Alzheimer's disease.



Schematic depiction of relative rates of change of cognitive impairment, social dependence and motor abnormalities that adversely affect the general quality of life in people who develop dementia due to Alzheimer's disease.

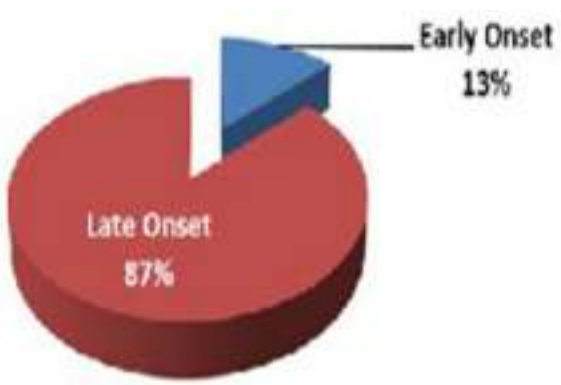
Alzheimer's disease. *Nat Rev Dis Primers* **1,** 15059 (2015)

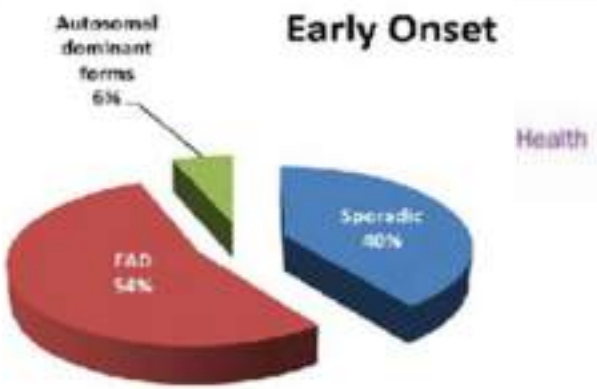
Genetics of Alzheimer Disease

- Alzheimer disease is a complicated genetic disorder.
- Only about 10% of cases occur as well-defined, fully penetrant autosomal dominant inheritance. In these families, the onset of the disease is between 55 and 60 years of age, which is considered early for a condition that usually affects much older people.
- Because of the relatively young age of occurrence of these symptoms, the condition was originally designated as “presenile dementia.” Patients with early-onset AD (EOAD) show the same clinical and neuropathological features as those with late-onset AD (LOAD), that is, >65 years, except that the time course of EOAD is usually more rapid than LOAD.
- Approximately >90% of AD cases are late onset, and many of these are nonfamilial (sporadic).
- However, 25% to 40% of those with LOAD have at least one close relative with the

Genetics and Alzheimer's Disease

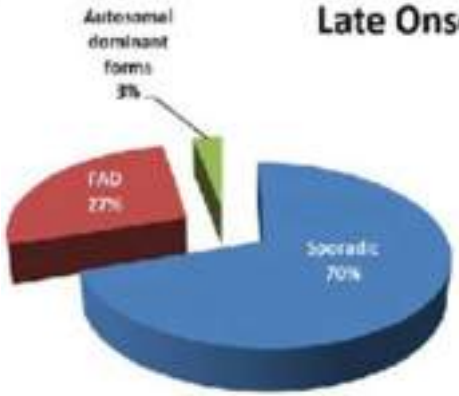
	Early-Onset AD (Dominantly Inherited)	Early-Onset AD (Complex Inheritance)	Late-Onset AD (Complex Inheritance)
Cause:	Inherited Genetic Mutations	Genetic and Environmental Risk Factors	Genetic and Environmental Risk Factors
Age at Onset:	Usually 30-60 years	<65 years	>65 years
Proportion of Cases:	~1%	~4%	~95%





Early Onset

Late Onset



Genes involved in early-onset familial Alzheimer disease (bold) and susceptibility genes for AD

Gene name	Chromosomal location	Onset	Familial and/or sporadic	Involvement in AD
APP	**21q21.3–q22.05**	**Early**	**F**	**Certain**
_PS1_	**14q24.3**	**Early**	**F**	**Certain**
_PS2_	**1q31–q42**	**Early**	**F**	**Certain**
APOE	19q32.2	Late	S and F	Certain
α2M	12p	Late	S	Uncertain
LRP	12	Late	S	Uncertain
LBP-1c/CP2/LSF	12	Late	S	Uncertain
ACE	17q23	Late	S	Uncertain
VLDL-R	9pter–p23	Late	S	Uncertain
BChE	3q26.1–q26.2	Late	S	Uncertain
ACT	14q32.1	Late	S	Uncertain
IDE	10q23–q25	Late/early	S and F (?)	Uncertain
Tf C2	3q21	Late	S	Uncertain
catD	11p15.5	Late/early	S and F	Uncertain
BH	17q11.1–q11.2	Late/early	S	Uncertain
TGF-β1	19q13.1–q13.3	Late	S	Uncertain
5-HTT	17q11.1–q12	Late	S	Uncertain
APOE promoter	19q32.2	Late/early	S	Uncertain
NOS3	7q35	Late	S	Uncertain
CST3	20p11.2	Late	S	Uncertain
PS1 promoter	14q24	Early	S and F	Uncertain

Rocchi et al. / Brain Research Bulletin 61 (2003) 1–24

Confirmed genetic factors predisposing to Alzheimer's disease: relationships to the β-amyloid phenotype

Chromosome	Gene Defect	Phenotype
21	β-APP mutations	↑ Production of all Aβ peptides or $A\beta_{40}$ peptides
19	ApoE4 polymorphism	↑ Density of Aβ plaques and vascular deposits
14	Presenilin 1 mutations	↑ Production of $A\beta_{42}$ peptides
1	Presenilin 2 mutation	↑ Production of $A\beta_{42}$ peptides

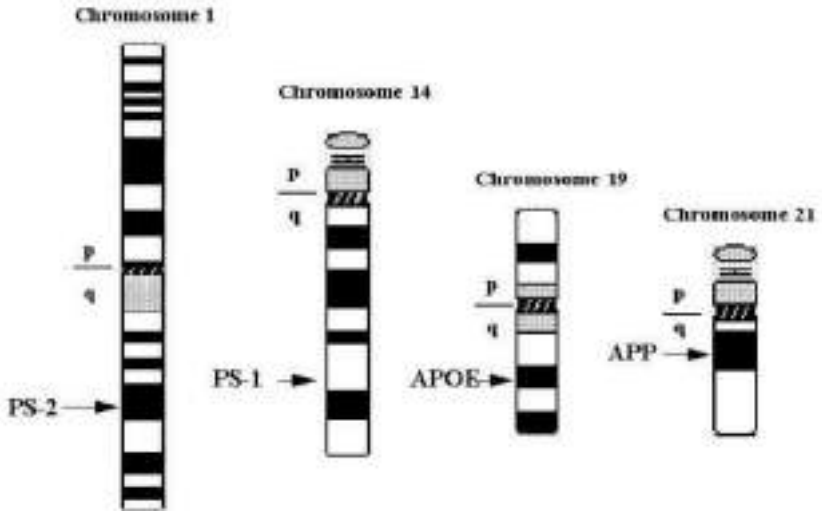
β-APP, β-amyloid precursor protein; Aβ, amyloid β-protein.

Rocchi et al.,Brain Research Bulletin 61 (2003) 1–24

Alzheimer's Disease

Genes

- **Chrom. 21, APP** = amyloid precursor protein gene (-> a protease inhibitor in the membrane)
  - Incorrect processing -> ~40aa beta-amyloid.
  - May poison cholinergic neurons
  - The inherited mutation in some families, but also in many sporatic cases of Alzheimer's
- **Chrom. 19, apoE** (apolipoprotein E) gene
  - Early onset, inherited; also sporatic
  - The mutation apoE4 product binds tightly to beta-amyloid
- **Chrom. 14.PSEN1**
  - Early onset, inherited
- Treatment (none)
  - April 2002, mice, vaccination w/ beta-amyloid helps
  - Inhibitors of neurotransmitter acetylcholinesterase delay symptoms but don't cure.



Mutations of the Amyloid Precursor Protein (APP) Gene

- Mutation screening of the *APP* gene in members of a large family with earlyonset AD revealed a missense mutation changing the amino acid at APP site 717 (V717I) (Valine717Isoleucine).
- The V717I and two other missense mutations at the same site (V717G, V717F) have been found in AD individuals in various families in different parts of the world.
- One individual with AD in a single family had an *APP* gene mutation that affected site 716 (I716V) of APP.
- In another family,those with AD had a double mutation that altered APP sites 670 (K670N) and 671 (M671L). This double mutation is adjacent to the g-secretase cleavage site.
- The age of onset of AD in families with *APP* gene mutations is between 45 and 60 years. Except for the difference in time of onset, AD individuals with *APP* gene

Mutations in the Presenilin Genes

- Linkage studies mapped a locus for AD in six large families with early-onset AD to 14q24.3.
- On this basis, both the gene and the protein it encodes were identified. Because of the early onset of AD in these families, the gene is designated as presenilin 1 and assigned gene symbol *PSEN1*.
- The protein is called presenilin-1 (PSEN1, ps-1, PS1). *PSEN1* mutations account for approximately 40% of all cases of familial early-onset AD, with the first clinical signs of the disorder ranging from 30 to 55 years of age.

- Another site for familial early-onset AD was localized to 1q32-q42 shortly after the *PSEN1* gene was discovered.
- This gene is called presenilin 2 (*PSEN2*), and the protein is presenilin-2 (PSEN2, ps-2, PS2). *PSEN2* mutations occur in less than 1% of families with early-onset AD, and commencement of AD ranges from 40 to 75 years of age. The presenilins participate in g-secretase cleavage of APP. Mutant PSEN1 and PSEN2 proteins likely increase the production of the Ab42 peptide and, in addition, may have deleterious effects on neurons. Together the *APP*, *PSEN1*, and *PSEN2* mutations represent approximately 50% of all familial early-onset AD.

Genetic Risk Factor for Alzheimer Disease

- Linkage between AD and 19q13.2 was observed in a group of families with late-onset AD.
- Because the gene (*APOE*) for apolipoprotein E is in this region,it became a candidate for familial late-onset AD.
- The *APOE* gene is polymorphic for three common alleles, *APOE**2*, *APOE**3*, and *APOE**4*, that occur in most populations with frequencies of about 8%, 78%, and 14%, respectively.
- Each *APOE* allele encodes a distinctive isoform: ApoE2, ApoE3, and ApoE4.
- Apolipoprotein is synthesized primarily in the brain by astrocytes. Among other functions, apolipoprotein E sequesters cholesterol and triglycerides from cellular debris and transports these molecules into neurons, where they are used for the formation of synaptic membranes.

- After a number of extensive studies of clinical and autopsy material from AD individuals and large samples of individuals with late-onset AD, it became clear the *APOE*4* allele was significantly associated with the occurrence of AD.
- This allele may account for approximately 50% of the genetic component of AD.
- However, it is neither sufficient nor necessary for AD, because many individuals with either one or two *APOE*4* alleles never show any signs of AD.
- For example, about 50% of persons homozygous for *APOE*4* who survive to be 80 years old never develop any signs of AD.
- In genetic parlance, the *APOE*4* allele is a risk factor that, in combination with other genes and/or environmental factors, significantly increases the likelihood that AD will occur.

Apolipoprotein E

Apolipoprotein E (ApoE) is a plasma glycoprotein with a molecular mass of 34,200 Da synthesized mainly by the liver, by both neurons and astrocytes in the brain, and also by other cell types including macrophages and monocytes.

ApoE is involved in the mobilization and redistribution of cholesterol during neuronal growth and after injury.

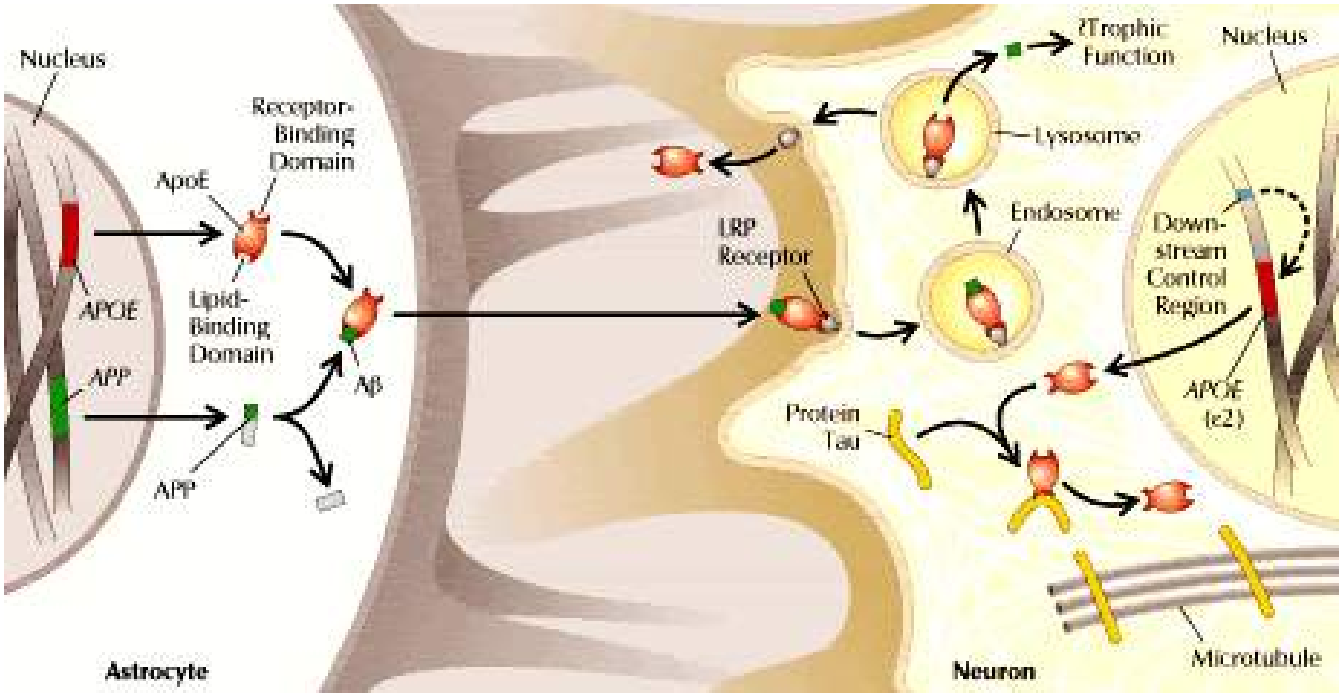
It is also involved in many other functions in human beings, like nerve regeneration, immunoregulation and activation of several lipolytic enzymes.

ApoE contains 299 amino acids, the amino terminal domain (residues 1–191) is a stable globular structure containing the receptor binding site, while the carboxy-terminal domain (residues 216–299) is helical, less stable, and contains the lipoprotein binding functions.

Zannis et al.(1981) identified by isoelectric focusing the three major isoforms of ApoE (ApoE2, ApoE3, and ApoE4) and concluded that a single locus with three alleles (ε2, ε3, and ε4) is responsible for this pattern.

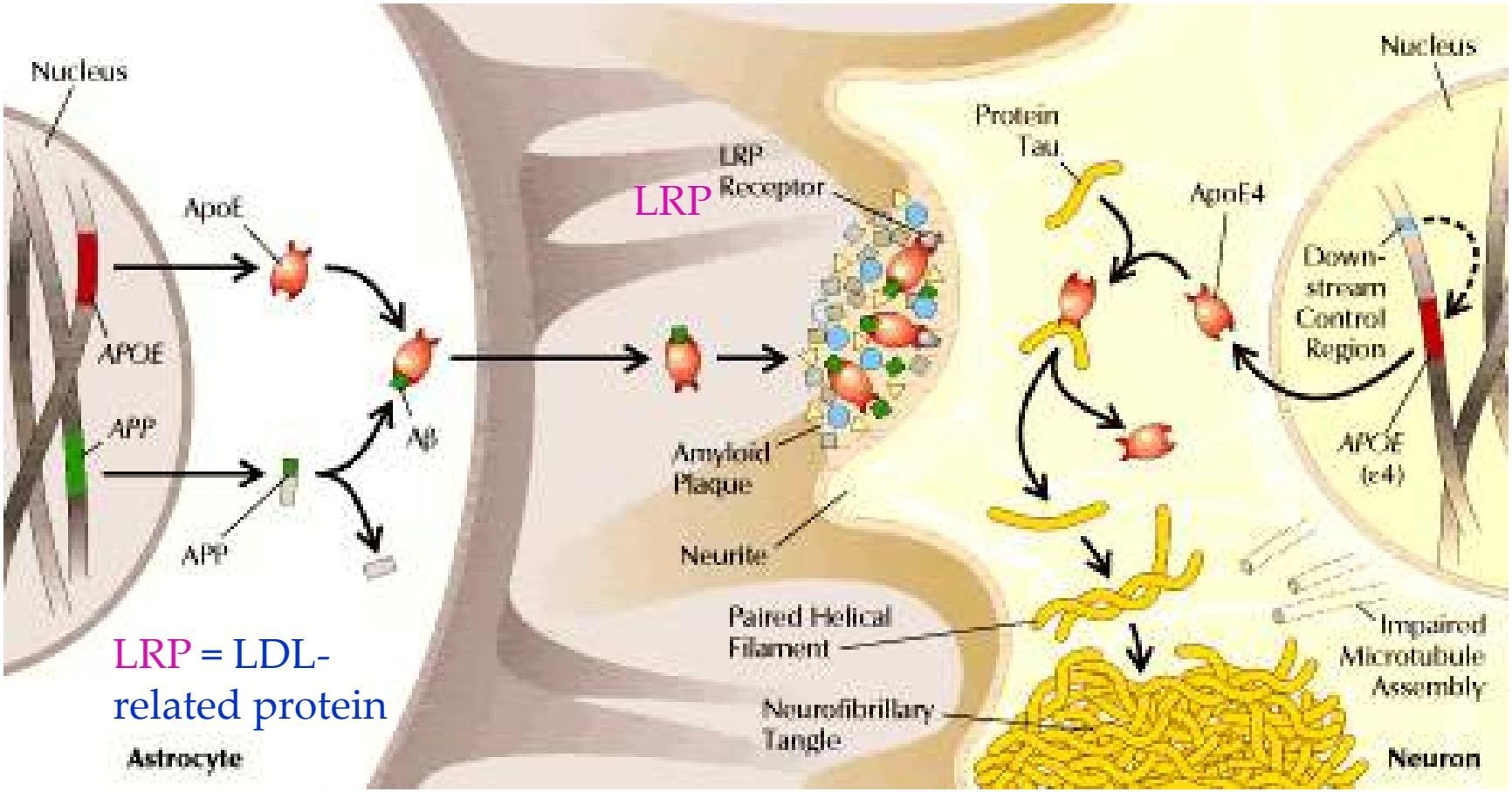
The ApoE2, ApoE3, and ApoE4 isoforms differ in amino acid sequence at two sites, residue

Gene on chromosome 19 codes for apolipoprotein E (apoE), a lipid carrier that binds to low-density lipoprotein (LDL) receptor ("bad" cholesterol) in human plasma



In the brain apoE appears to ferry the Ab peptide to neurons and to facilitate the MAP protein tau's binding to microtubules (important structural and transport proteins for the neurons)

In the AD brain, apoE is postulated to get trapped by LRP in plaques (along with 30+ other proteins including apoE)



The lack of “protection” of the tau MAP protein may allow it to dimerize and form tangles. Then microtubles cannot assemble, destroying the neuron’s shape and synaptic integrity.

Diagnosis

- Difficult.

  Tangles and plaques permitting a definitive diagnosis, can only result from examination of brain tissue.

- Recent evidence suggests altered brain function, in the form of decreased glucose metabolism, at least two decades before symptoms would be expected. Thus, the genetic factors promoting or causing the disease appear to be long-smoldering.

Current Diagnostic Practice

A patient history, physical exam, a series of tests that measure memory, language skills, and other abilities related to brain functioning

- Analysis of cerebrospinal fluid for levels of "sticky“ beta-amyloid peptide and tau protein.

- PET scanning (positron emission tomography), an imaging method in living patients, detects AD-related changes in glucose metabolism in the brain.

MRI (magnetic resonance imaging) gauges the size of structures in the brain; e.g. hippocampus shrinkage - measure of memory/learning damage

-

Therapy

Drugs

Current Alzheimer's medications can help for a time with memory symptoms and other cognitive changes. Two types of drugs are currently used to treat cognitive symptoms:

Cholinesterase inhibitors. These drugs work by boosting levels of cell-to-cell communication by preserving a chemical messenger that is depleted in the brain by Alzheimer's disease. The improvement is modest.

Cholinesterase inhibitors may also improve neuropsychiatric symptoms, such as agitation or depression. Commonly prescribed cholinesterase inhibitors include donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon).

The main side effects of these drugs include diarrhea, nausea, loss of appetite and sleep disturbances. In people with cardiac conduction disorders, serious side effects may include cardiac arrhythmia.

Memantine (Namenda). This drug works in another brain cell communication

Suggested Reading

1. Human Molecular Genetics – Tom Stratchen & Andrew P. Read. Pub: John Wiley & Sons.
2. An introduction to Genetic Analysis – Griffith, Miller, Suzuki, Lewontin, Gelbard. Pub: W.H. Freeman & Co.
3. Genomes 2 – T.A. Brown, Pub: Wiley-Liss. John W. & Sons.
4. Emery's Elements of Medical Genetics– R.F. Mueller, I.D. Young, Pub: Churchill
5. An Introduction to Human Molecular Genetics – J.J. Pasternak, Pub: Fitzgerald Science.

Alzheimer Disease

Prof Vandana Rai
Department of Biotechnology
VBS Purvanchal University
Jaunpur

Alois Alzheimer

Alois Alzheimer was a medical officer at the state asylum in Frankfurt am Main, Germany.
He became a leading neurologist, publishing papers on epilepsy, brain tumors, syphilis, cerebro arterio-sclerosis & Huntington's chorea.

- In 1901, Alzheimer met a 51 year old man, Auguste D, who he cared for at the asylum for the next four years.

- Her condition steadily deteriorated from memory loss, speech difficulty, confusion, suspicion, agitation, wandering and screaming to being bedridden, incontinent, and unaware of her surroundings.

- In 1905, at autopsy he found the brain had shriveled, and neurons had disappeared. He discovered thread-like spindle-shaped objects "neurofibrillary tangles", as well as thick viscous-looking blobs "senile plaques" .
- In 1907, Alzheimer published a monumental paper on the first description of this new dementia AD.
- In 1912, on his way to assuming the position of full professor at the University Hospital in Breslau, Alzheimer became ill with strep throat, complicated by rheumatic fever and heart disease.

- In 1915, at the age of 51, Alzheimer died of endocarditis (heart valve infection) and kidney failure.

Auguste D

What is Alzheimer's Disease?

- An irreversible, progressive brain disorder
- The fourth leading cause of death among the elderly in developed nations
- AD advances by stages, from early, mild forgetfulness to a severe loss of mental function (dementia). Symptoms usually first appear after age 60.
- The earliest symptoms often include loss of recent memory (names of people & common objects) , faulty judgment, changes in personality and loss of clear thinking.

o Later in the disease, they may forget how to do simple tasks, such as washing their hands. Eventually, people with AD lose all reasoning ability and become dependent on other people for their everyday care.

- Finally, the disease becomes so debilitating that patients are bedridden and likely to develop other illnesses and infections. Most commonly, people with AD die from pneumonia.

- The course varies from person to person, as does the rate of decline. On average, AD patients live for 8 to 10 years after they are diagnosed, though the disease can last for up to 20 years.

Symptoms

- Many different clinical features are associated with AD. Among the first symptoms are the inability to create new memories and the loss of short-term memory.
- The ability to concentrate and recall past events worsens as the disease progresses.
- Alzheimer disease patients often have no accurate sense of time and are unable to correctly identify the day, month, or year.
- Although standard speech patterns and clichés are retained in the early stages, both sentence formation and coherent verbal communication diminish and are eventually lost.
- Some AD patients become extremely passive, others very hostile, and some abnormally suspicious. Delusions are prevalent in 50% of the cases.
- In the end, AD patients are mute, immobilized, and uncomprehending. Death is often the result of respiratory failure.
- For AD patients diagnosed at 65 years or older, the disease lasts from about 8 to 20 years.

Features of AD patients

- Many different clinical features are associated with AD.
- Among the first symptoms are the inability to create new memories and the loss of short-term memory.
- AD patients often have no accurate sense of time and are unable to correctly identify the day, month or year.
- Although standard speech patterns and clichés are retained in the early stages, both sentence formation and coherent verbal communication diminish and are eventually lost.
- AD patients becomes extremely passive, others very hostile, and some abnormally suspicious.
- Delusions are prevalent in 50% of the cases.
- In the end, AD patients are mute, immobilized and uncomprehending.
- Death is often the result of respiratory failure

- AD is classified as

  familial or sporadic

  and early –onset (generally before 60 years) or late-onset (after 60), with early-onset primarily occurring in familial cases and late-onset in both familial and sporadic cases.

- Familial, early –onset AD is very rare, estimated to comprise only 1-2% of all AD cases. The remaining 98% of AD patients are clinically classified as late-onset familial or sporadic.

Progression of Alzheimer's Disease

Drew L., 2018. An age-old story of dementia. Nature 559 (7715), S2-S3. https://doi.org/10.1038/d41586-018-05718-5

Some sobering facts about Alzheimer's

- More than 44 million suffer from AD today.
- Neither Medicare nor most private health insurance covers the long-term care most patients need.
- Alzheimer's disease is the most common cause of senile dementia and is estimated to affect 50 million people worldwide by year 2025 and other age-related neurodegenerative disorders leading to dementia are on the rise because of increase in life expectancy and decrease in human mortality.

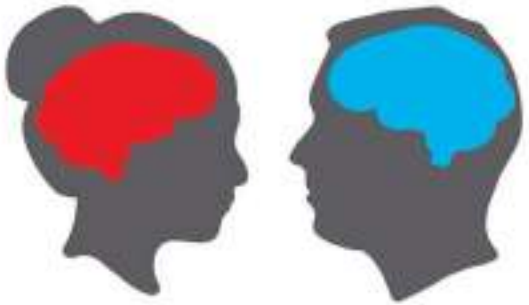
Risk factors

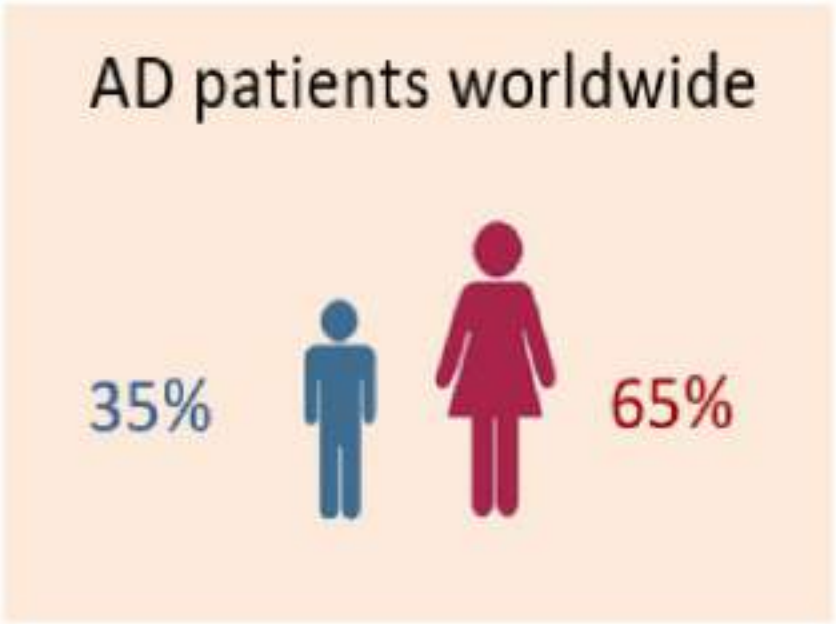
Genetic factor

- Around **1%** of cases of Alzheimer's disease are caused by mutations in the genes *which affect amyloid-processing*
- *APP*,
- *PSEN1 or PSEN2*,.

https://ghr.nlm.nih.gov/condition/alzheimer-disease#inheritance

Gender





The overall incidence of Alzheimer's disease in women is up to twice that of men.

https://www.brightfocus.org/alzheimers/news/scientists-shed-new-light-gender-differences-alzheimers

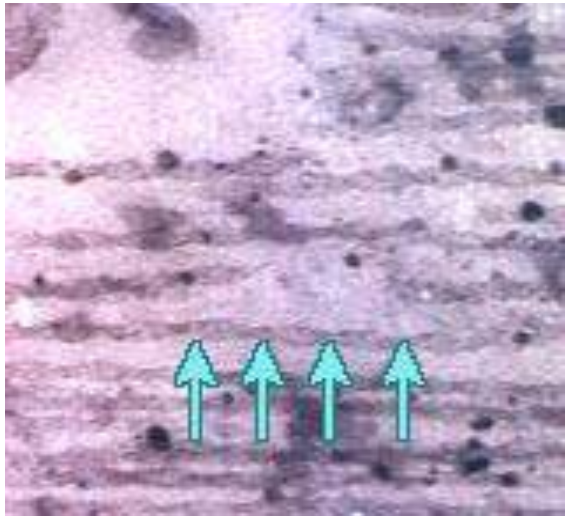
http://www.womensbrainproject.com/facts/

LIFESTYLE

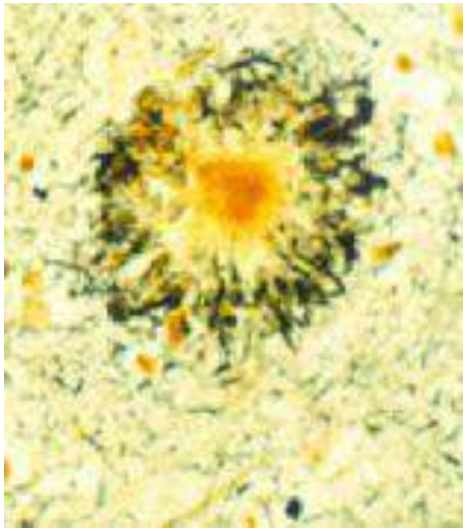
- Potentially modifiable risk factors for Alzheimer's disease have been identified.
- Diabetes
- Obesity
- Depression
- Smoking and
- Low educational attainment.

Alzheimer's Disease

AD occurs when nerve cells in key areas of the brain are damaged or destroyed. The changes disrupt the normal flow of information between body and brain resulting in a steady decline in mental function.



tangles, helical filament**s**



neuron tangles surround an amyloid plaque

It has been postulated that nerve deterioration is most likely caused by formation of neurofibrillary tangles (knots) and senile plaques (clumps) commonly found in diseased brain during an after-death biopsy.

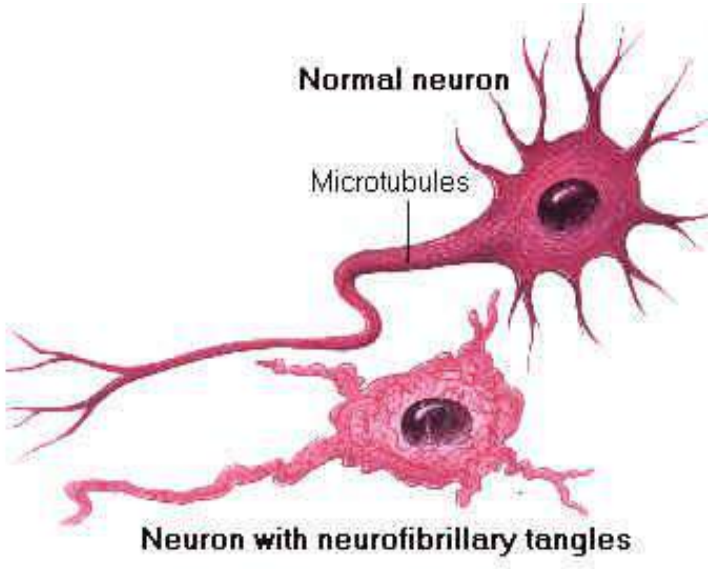
Plaques and knots form primarily in areas controlling memory and retention of learned information

Amyloid plaques (20–200mm in diameter)

- One of the hallmarks of Alzheimer's disease is the accumulation of amyloid plaques *between* nerve cells (neurons) in the brain. Amyloid is a general term for protein fragments that the body produces normally. Beta-amyloid is a fragment of a protein that is snipped from another protein called amyloid precursor protein (APP).
- In a healthy brain, these protein fragments would be broken down and eliminated. In Alzheimer's disease, the fragments accumulate to form hard, insoluble plaques.

- Neurofibrillary tangles consist of insoluble twisted fibers that are found *inside* of the brain's cells. They primarily consist of a protein called tau, which forms part of a structure called a microtubule.

- The microtubule helps transport nutrients and other important substances from one part of the nerve cell to another (the axon is the long threadlike extension that conducts nerve impulses *away* from the body of a nerve cell, and dendrites are any of the short branched threadlike extensions that conduct nerve impulses *towards* the nerve cell body.
- In Alzheimer's disease the tau protein is abnormal and the microtubule structures collapse



Senile plaques/Amyloid plaques

- The amyloid plaques are almost exclusively composed of a small peptide called b-amyloid (Ab), which is derived from a larger integral membrane protein called b-amyloid precursor protein (bAPP).
- Biochemical analysis on how bAPP is produced revealed the generation of the toxic Ab peptide.
- Some of the bAPP in the membrane are internalized and degraded. A small subset of the APP molecules is found to be degraded initially by a-secretase enzyme to produce 83-residue COOH-terminal fragment (C83) and a soluble version of bAPP (a-APP), and then by g-secretase enzyme to give rise to a harmless peptide of 3kDa called p3.

- However, when βAPP is cleaved initially by βsecretase enzyme to produce a 99-residue COOH terminal fragment (C99) and βAPPs, followed by g-secretase cleavage, either a 40 amino acids Ab peptide (Aβ40) or a 42 amino acids Aβ peptide (Aβ42) of a 4kDa is formed.
- The more toxic version is Aβ42 as it is hydrophobic and rapidly forms aggregates in the extra cellular space

Neurofibrillary tangles (NFTs)

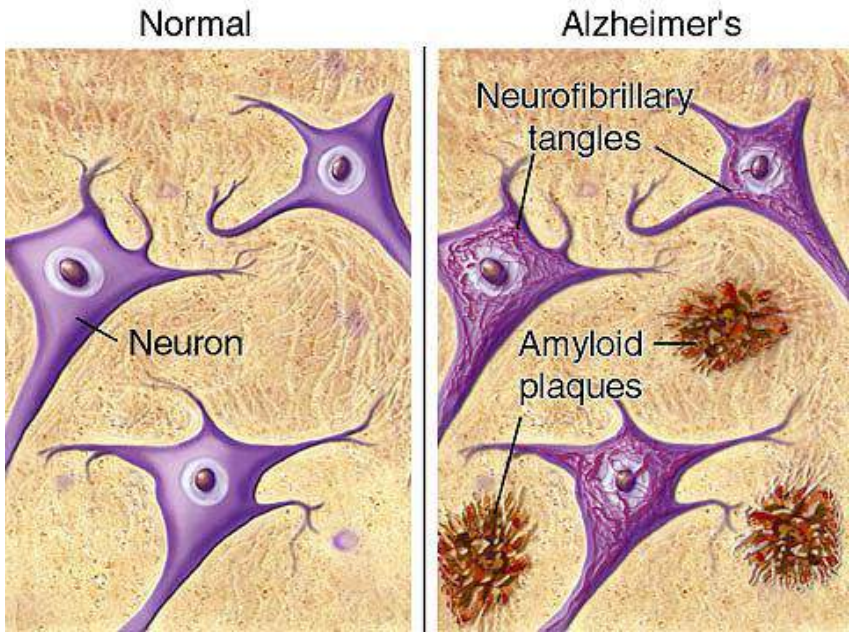
- The main fibrous elements of NFTs are numerous paired helical filaments (PHFs). A PHF consists of two cross –linked, interwined protein strands, with each strand made up of a number of joined tau (t) protein molecules forming a tau filament.

- *The MAPT gene encodes the tau protein and is located at chromosome site 17q21.*

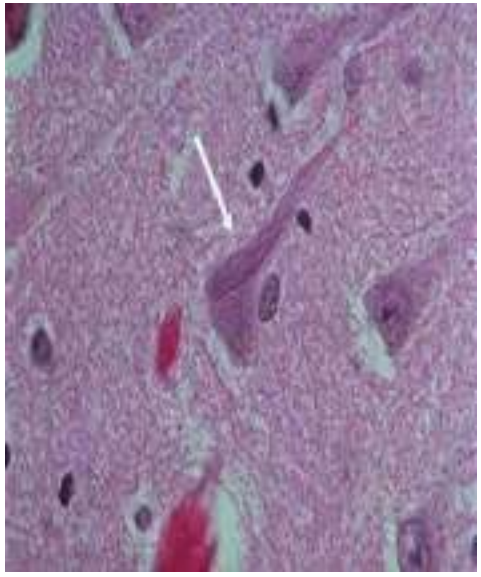
- The main tau protein binds to tubulin molecules and facilitates the assembly of tubulin into microtubules and, in combination with other microtubule –associated proteins (MAPs), tau protein maintains the stability of microtubules.
- In contrast to tau molecues under normal conditions, those that make up NFTs are hyper-phosphorylated (HP-tau).

HP-tau does not bind to tubulin but attaches to other MAPs. Consequently, HP-tau blocks the formation of microtubules and undermines the stability of existing microtubules. HP-tau probably dissembles microtubules and acts as an aggregation center for the formation of PHFs and NFTs.

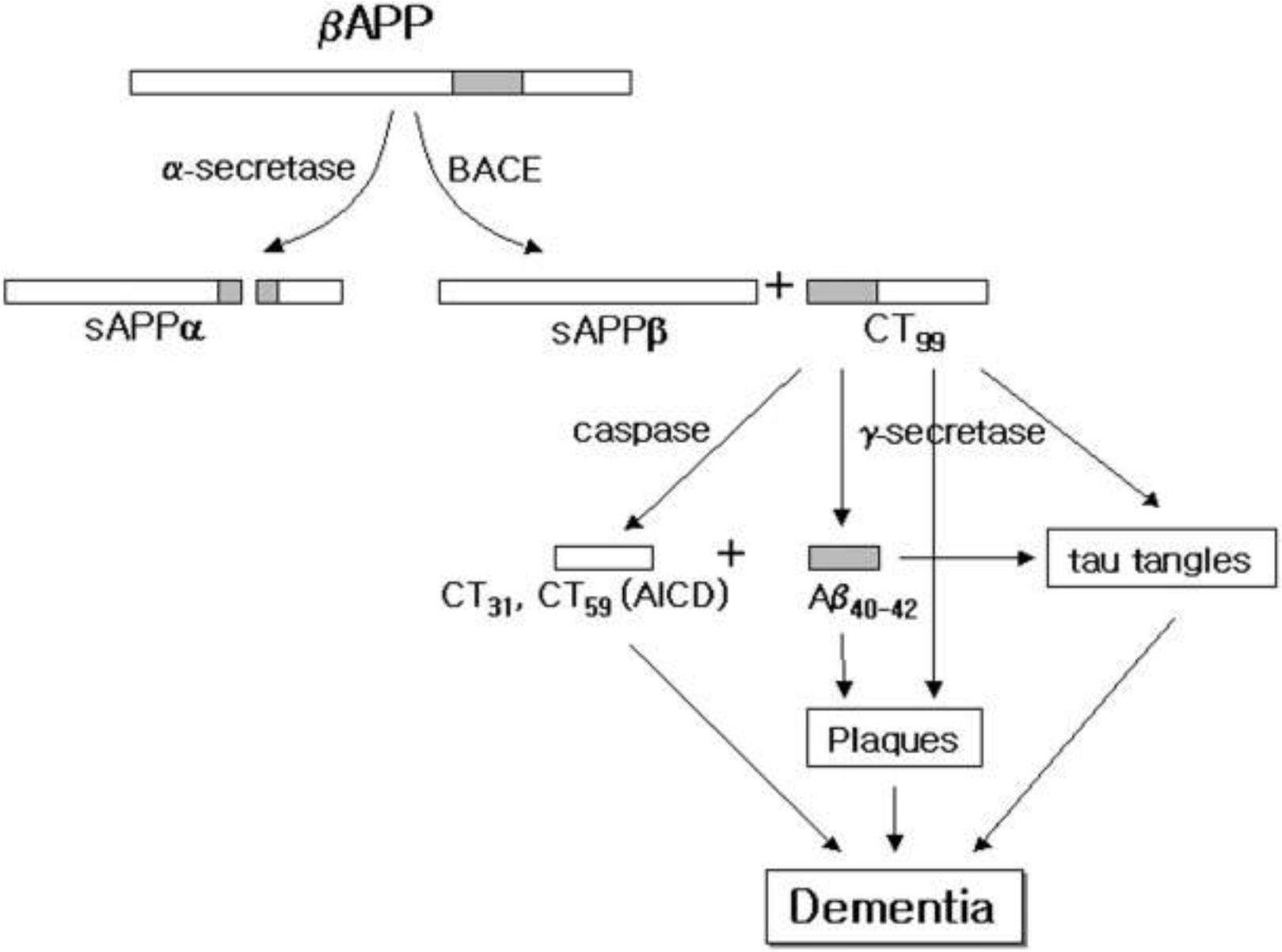
The dissolution of the neuronal microtubule system would prevent axonal transport, which in turn would cause the loss of synapses and lead eventually to the degeneration of synaptic bulbs.



Hard, insoluble plaques are not broken down and not eliminated in AD; Insoluble twisted tangles made up of misfolded tau proteins



Nerve fiber tangle of Alzheimer's victim

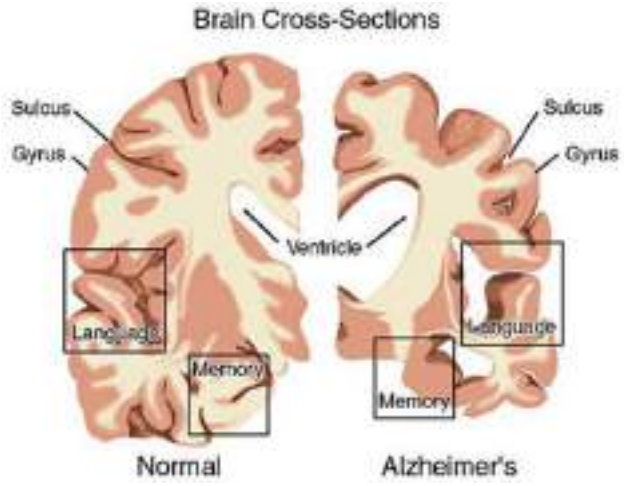

βAPP
α-secretase
BACE
sAPPα
sAPPβ
+
CT99
caspase
γ-secretase
CT31, CT59 (AICD)
+
Aβ40-42
tau tangles
Plaques
Dementia

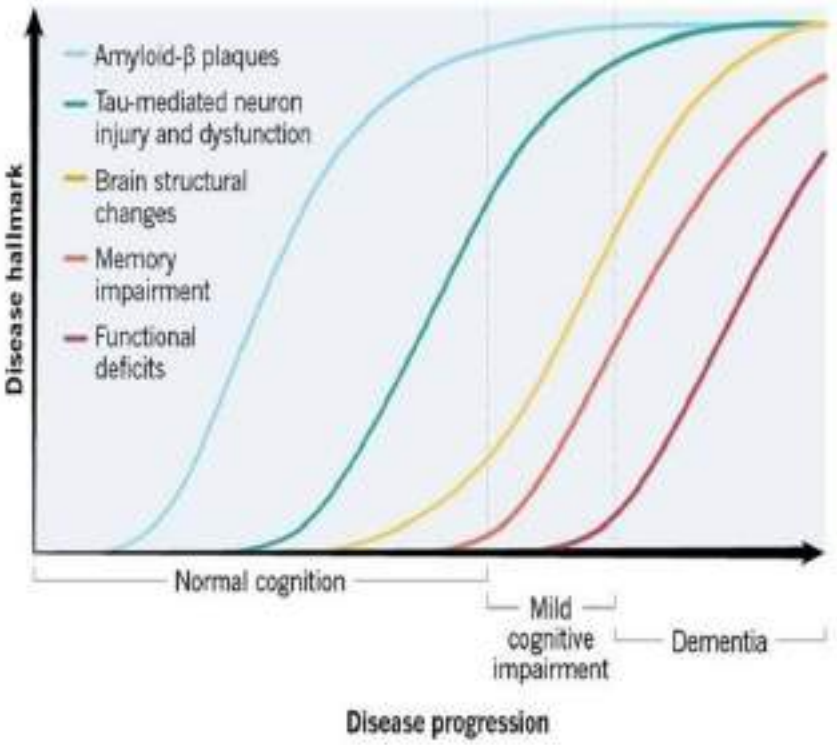
A Slow March

By the time that a person begins to experience the symptoms of Alzheimer's disease, the condition is already well-established in the brain.

- The accumulation of amyloid-b, generally thought to be the first step in disease progression, could precede symptoms by 10–15 years.

- Tau accumulation occurs later, much closer to the onset of neurodegeneration.





Drew L. Nature 2018;559:S2-3

Biochemistry of Senile Plaques and Neurofibrillary Tangles

- The core of a senile plaque is a densely packed fibrous structure that historically has been described as an amyloid body.
- Originally, amyloid bodies were thought to be made up of carbohydrates.
- More definitive chemical analyses established that the major component(s) was protein.
- The principal protein of AD amyloid bodies is a 4-kDa peptide (Ab protein; b-protein; A4, b/A4).
- Within AD amyloid bodies, the Ab protein (amyloid b-protein) consists of isoforms that range in amino acid number from 39 to 43.
- Of these, the two main isoforms contain 40 and 42 amino acids and are designated Ab1–40 (Ab40) and Ab1–42 (Ab42), respectively.

Amyloid precursor protein (APP)

- The amyloid precursor protein (*APP*) has a single transmembrane domain and commonly occurs as three **isoforms with 695, 751, and 770 amino acids.**
- The 695-amino acid APP isoform is found in neurons throughout the CNS.
- Some of these APP molecules are found in the membrane at the terminal ends of axons and others in intracellular membranes including the Golgi network.
- The 751- and 770-amino acid isoforms are produced, for the most part, by glial cells.
- Some complete versions and processed segments of the 751- and 770-APP isoforms are secreted.

APP processing

- For convenience, the amino acid numbering system for APP and Ab isoforms is based on the 770-amino acid isoform.
- The Ab43 isoform encompasses amino **acid sites 672 to 714 of the APP** molecule. Under normal conditions, APP molecules are processed by proteolytic enzymes .
- An enzyme called **a-secretase** cleaves the APP molecule after the amino acid at **site 687**, which lies within the Ab region.
- Neither of the fragments produced by this cleavage are fibrillogenic (amyloidogenic).
- Cleavage by **b-secretase** (BACE-1, b-site APP-cleaving enzyme) after amino acid **site 671** also produces two nonamyloidogenic fragments.
- Both a- and b-secretase cleavages of APP are normal processes and occur in almost all cells.
- When some APP molecules are doubly cleaved by **b-secretase and by g-secretase**, which cuts after either site 711 or site 713, then Ab40 and Ab42 isoforms are released.
- Cleavage of APP by both a and g-secretases releases an internal piece of the APP protein that has 24 amino acids (Ab17-40; p3) and is not amyloidogenic.

Function of APP

- The functional roles of APP and the various fragments of APP in the nervous system are not well understood.
- The cell membrane-bound 695-amino acid APP isoform may facilitate **cell-to-cell contact, adhesion to the extra neuronal matrix, and/or synaptic stability.**
- Intracellular APP may be associated with the **cytoskeletal system, which is composed of filaments and microtubules conveying vesicles and other components from one part of a cell to another.**
- The two types of secreted APP fragments [**APP 1–671 (bAPPs); APP 1–687 (aAPPs)]** may protect neurons from damage and modulate events at synapses.
- Atypical processing of APP that leads to an excess of the Ab42 isoform is probably responsible for the destruction of synapses during the early stages of AD, the formation of senile plaques, and, eventually, degradation of neurons.

Brain autopsy of AD patients shows three distinctive neuropath-logical features.

•First, there are devastating loses of synapses and neurons within the hippocampus and entorhinal cortex, which is the region of the cerebral cortex (neocortex). Many cerebral cortex neurons that connect with other cortical neurons that also degenerate. By the final stage of the diseases, the overall width of most of the neocortex is dramatically reduced.

•Second, dense spherical structures (20-200um in diameter), senile plagues (SPs) or amyloid plaques are prevalent outside the neurons of the hippocampus and other regions of the brain.

•Third, aggregation of fibrils (neurofibrillary tangles, NFTs) accumulate within the cell bodies and dendritic processes of the neurons of the hippocampus, the neocortex including the entorhinal region, the amygdala, and other parts of the brain

Pathophysiology

- There is an overall shrinkage of brain tissue as Alzheimer's disease progresses. In addition, the ventricles, or chambers within the brain that contain cerebrospinal fluid, are noticeably enlarged.

- In the early stages of Alzheimer's disease, short-term memory begins to decline when the **cells in the hippocampus**, which is part of the limbic system, degenerate. The ability to perform routine tasks also declines.

- As Alzheimer's disease spreads through the cerebral cortex (the outer layer of the brain), judgment declines, emotional outbursts may occur and language is impaired.

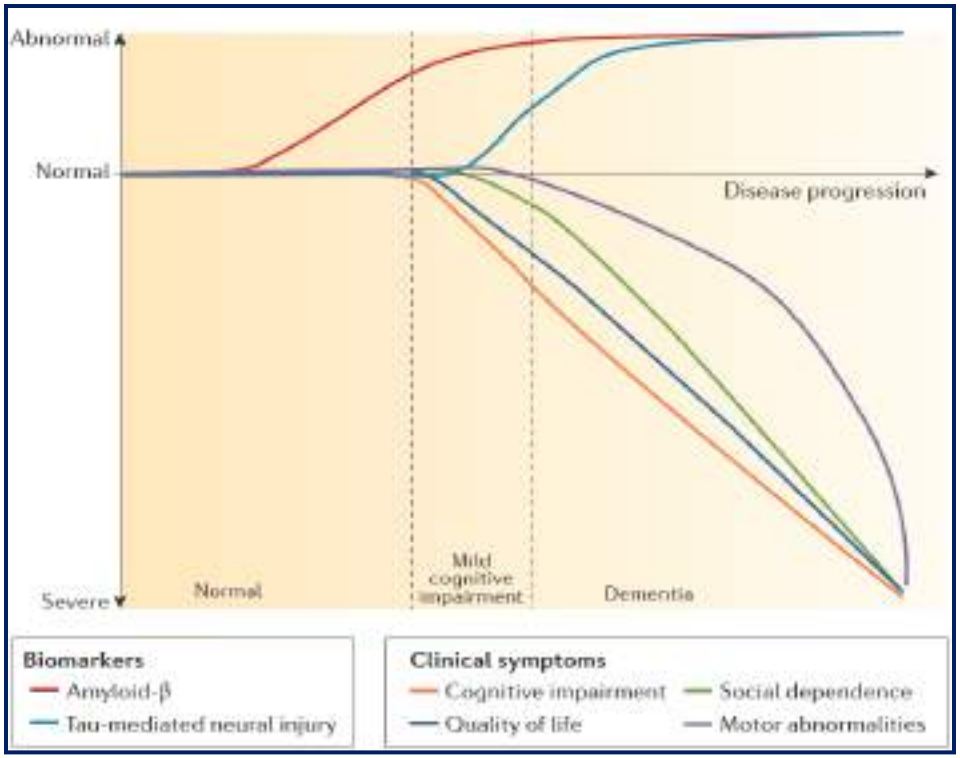
- Progression of the disease leads to the death of more nerve cells and subsequent behavior changes, such as wandering and agitation. The ability to recognize faces and to communicate is completely lost in the final stages.

- Patients lose bowel and bladder control, and eventually need constant care. This stage of complete dependency may last for years before the patient dies. The average length of time from diagnosis to death is 4 to 8 years, although it can take 20 years or more for the disease to run its course.

Stages of Alzheimer Disease

Stages	Patients condition	Duration	Brain regions	Symptoms	Disease
Stage 1	Normal	7 years	Disease begins in Medial Temporal lobe	Short Term memory loss	**Mild Cognitive impairments**
Stage 2	Normal age forgetfulness				
Stage 3	Mild cognitive impairments				
Stage 4	A diagnosis of Alzheimer's disease is possible, patients have trouble with memory and every day task	2 years	Disease spreads to lateral Temporal and parital lobes	Reading problems, Poor Object recognition, Poor direction sense	**Mild Alzheimer's disease**
Stage 5	Patients can no longer live independently as their memory and ability to communicate deteriorates	2 years	Disease spreads to frontal lobe	Poor Judgement, Impulsivity, Short Attention	**Moderate Alzheimer's disease**
Stage 6	Memory is severely impaired, patients confused, Patients will need family members for personal hygiene	3 Years	Disease Spreads to Occipital lobe	Visual problems	**Severe Alzheimer's disease**
Stage 7	Patient can no longer respond to their environment and become infantile				

Quality of life of patients with Alzheimer's disease.



Schematic depiction of relative rates of change of cognitive impairment, social dependence and motor abnormalities that adversely affect the general quality of life in people who develop dementia due to Alzheimer's disease.

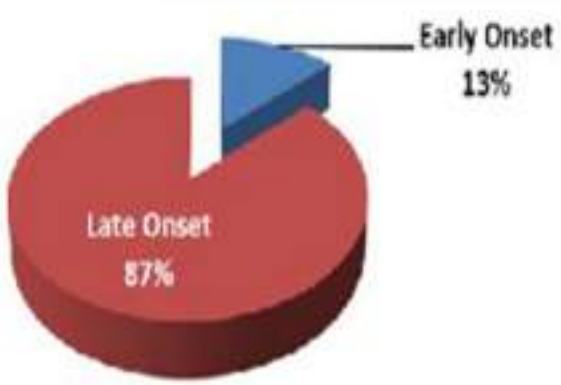
Alzheimer's disease. *Nat Rev Dis Primers* **1,** 15059 (2015)

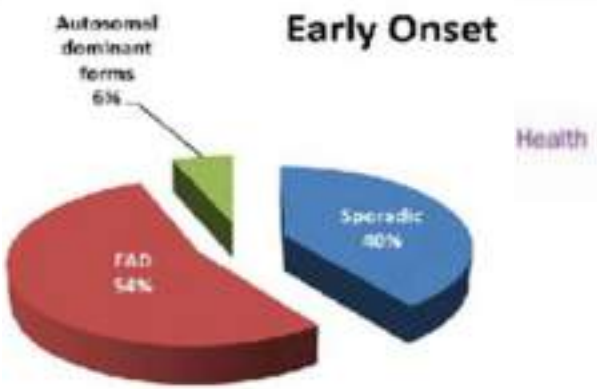
Genetics of Alzheimer Disease

- Alzheimer disease is a complicated genetic disorder.
- Only about 10% of cases occur as well-defined, fully penetrant autosomal dominant inheritance. In these families, the onset of the disease is between 55 and 60 years of age, which is considered early for a condition that usually affects much older people.
- Because of the relatively young age of occurrence of these symptoms, the condition was originally designated as “presenile dementia.” Patients with early-onset AD (EOAD) show the same clinical and neuropathological features as those with late-onset AD (LOAD), that is, >65 years, except that the time course of EOAD is usually more rapid than LOAD.
- Approximately >90% of AD cases are late onset, and many of these are nonfamilial (sporadic).
- However, 25% to 40% of those with LOAD have at least one close relative with the

Genetics and Alzheimer's Disease

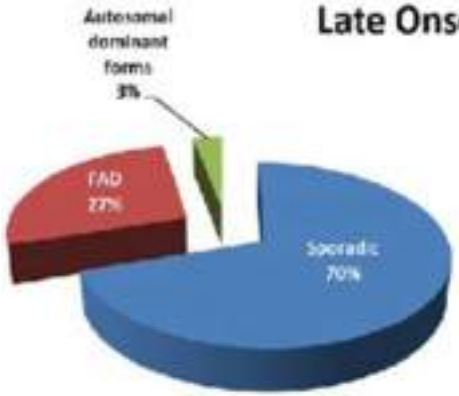
	Early-Onset AD (Dominantly Inherited)	Early-Onset AD (Complex Inheritance)	Late-Onset AD (Complex Inheritance)
Cause:	Inherited Genetic Mutations	Genetic and Environmental Risk Factors	Genetic and Environmental Risk Factors
Age at Onset:	Usually 30-60 years	<65 years	>65 years
Proportion of Cases:	~1%	~4%	~95%





Early Onset

Late Onset



Genes involved in early-onset familial Alzheimer disease (bold) and susceptibility genes for AD

Gene name	Chromosomal location	Onset	Familial and/or sporadic	Involvement in AD
APP	**21q21.3–q22.05**	**Early**	**F**	**Certain**
_PS1_	**14q24.3**	**Early**	**F**	**Certain**
_PS2_	**1q31–q42**	**Early**	**F**	**Certain**
APOE	19q32.2	Late	S and F	Certain
α2M	12p	Late	S	Uncertain
LRP	12	Late	S	Uncertain
LBP-1c/CP2/LSF	12	Late	S	Uncertain
ACE	17q23	Late	S	Uncertain
VLDL-R	9pter–p23	Late	S	Uncertain
BChE	3q26.1–q26.2	Late	S	Uncertain
ACT	14q32.1	Late	S	Uncertain
IDE	10q23–q25	Late/early	S and F (?)	Uncertain
Tf C2	3q21	Late	S	Uncertain
catD	11p15.5	Late/early	S and F	Uncertain
BH	17q11.1–q11.2	Late/early	S	Uncertain
TGF-β1	19q13.1–q13.3	Late	S	Uncertain
5-HTT	17q11.1–q12	Late	S	Uncertain
APOE promoter	19q32.2	Late/early	S	Uncertain
NOS3	7q35	Late	S	Uncertain
CST3	20p11.2	Late	S	Uncertain
PS1 promoter	14q24	Early	S and F	Uncertain

Rocchi et al. / Brain Research Bulletin 61 (2003) 1–24

Confirmed genetic factors predisposing to Alzheimer's disease: relationships to the β-amyloid phenotype

Chromosome	Gene Defect	Phenotype
21	β-APP mutations	↑ Production of all Aβ peptides or $A\beta_{40}$ peptides
19	ApoE4 polymorphism	↑ Density of Aβ plaques and vascular deposits
14	Presenilin 1 mutations	↑ Production of $A\beta_{42}$ peptides
1	Presenilin 2 mutation	↑ Production of $A\beta_{42}$ peptides

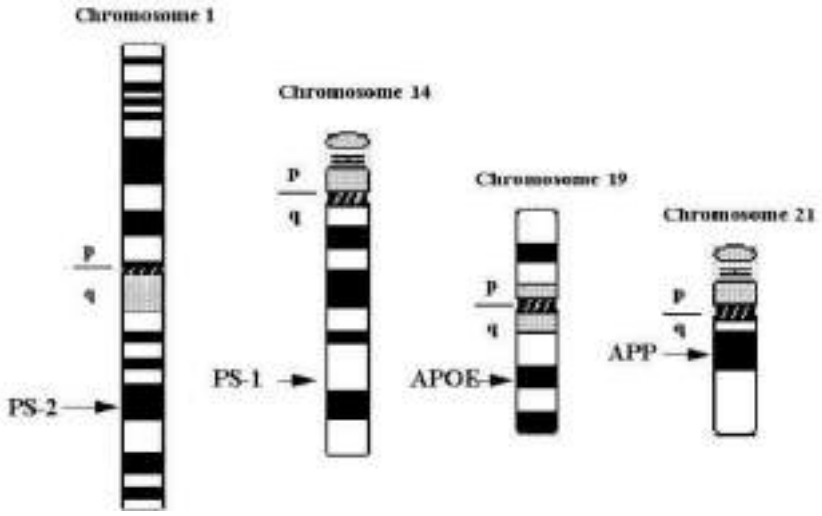
β-APP, β-amyloid precursor protein; Aβ, amyloid β-protein.

Rocchi et al.,Brain Research Bulletin 61 (2003) 1–24

Alzheimer's Disease

Genes

- **Chrom. 21, APP** = amyloid precursor protein gene (-> a protease inhibitor in the membrane)
  - Incorrect processing -> ~40aa beta-amyloid.
  - May poison cholinergic neurons
  - The inherited mutation in some families, but also in many sporatic cases of Alzheimer's
- **Chrom. 19, apoE** (apolipoprotein E) gene
  - Early onset, inherited; also sporatic
  - The mutation apoE4 product binds tightly to beta-amyloid
- **Chrom. 14.PSEN1**
  - Early onset, inherited
- Treatment (none)
  - April 2002, mice, vaccination w/ beta-amyloid helps
  - Inhibitors of neurotransmitter acetylcholinesterase delay symptoms but don't cure.



Mutations of the Amyloid Precursor Protein (APP) Gene

- Mutation screening of the *APP* gene in members of a large family with earlyonset AD revealed a missense mutation changing the amino acid at APP site 717 (V717I) (Valine717Isoleucine).
- The V717I and two other missense mutations at the same site (V717G, V717F) have been found in AD individuals in various families in different parts of the world.
- One individual with AD in a single family had an *APP* gene mutation that affected site 716 (I716V) of APP.
- In another family,those with AD had a double mutation that altered APP sites 670 (K670N) and 671 (M671L). This double mutation is adjacent to the g-secretase cleavage site.
- The age of onset of AD in families with *APP* gene mutations is between 45 and 60 years. Except for the difference in time of onset, AD individuals with *APP* gene

Mutations in the Presenilin Genes

- Linkage studies mapped a locus for AD in six large families with early-onset AD to 14q24.3.
- On this basis, both the gene and the protein it encodes were identified. Because of the early onset of AD in these families, the gene is designated as presenilin 1 and assigned gene symbol *PSEN1*.
- The protein is called presenilin-1 (PSEN1, ps-1, PS1). *PSEN1* mutations account for approximately 40% of all cases of familial early-onset AD, with the first clinical signs of the disorder ranging from 30 to 55 years of age.

- Another site for familial early-onset AD was localized to 1q32-q42 shortly after the *PSEN1* gene was discovered.
- This gene is called presenilin 2 (*PSEN2*), and the protein is presenilin-2 (PSEN2, ps-2, PS2). *PSEN2* mutations occur in less than 1% of families with early-onset AD, and commencement of AD ranges from 40 to 75 years of age. The presenilins participate in g-secretase cleavage of APP. Mutant PSEN1 and PSEN2 proteins likely increase the production of the Ab42 peptide and, in addition, may have deleterious effects on neurons. Together the *APP*, *PSEN1*, and *PSEN2* mutations represent approximately 50% of all familial early-onset AD.

Genetic Risk Factor for Alzheimer Disease

- Linkage between AD and 19q13.2 was observed in a group of families with late-onset AD.
- Because the gene (*APOE*) for apolipoprotein E is in this region,it became a candidate for familial late-onset AD.
- The *APOE* gene is polymorphic for three common alleles, *APOE**2*, *APOE**3*, and *APOE**4*, that occur in most populations with frequencies of about 8%, 78%, and 14%, respectively.
- Each *APOE* allele encodes a distinctive isoform: ApoE2, ApoE3, and ApoE4.
- Apolipoprotein is synthesized primarily in the brain by astrocytes. Among other functions, apolipoprotein E sequesters cholesterol and triglycerides from cellular debris and transports these molecules into neurons, where they are used for the formation of synaptic membranes.

- After a number of extensive studies of clinical and autopsy material from AD individuals and large samples of individuals with late-onset AD, it became clear the *APOE*4* allele was significantly associated with the occurrence of AD.
- This allele may account for approximately 50% of the genetic component of AD.
- However, it is neither sufficient nor necessary for AD, because many individuals with either one or two *APOE*4* alleles never show any signs of AD.
- For example, about 50% of persons homozygous for *APOE*4* who survive to be 80 years old never develop any signs of AD.
- In genetic parlance, the *APOE*4* allele is a risk factor that, in combination with other genes and/or environmental factors, significantly increases the likelihood that AD will occur.

Apolipoprotein E

Apolipoprotein E (ApoE) is a plasma glycoprotein with a molecular mass of 34,200 Da synthesized mainly by the liver, by both neurons and astrocytes in the brain, and also by other cell types including macrophages and monocytes.

ApoE is involved in the mobilization and redistribution of cholesterol during neuronal growth and after injury.

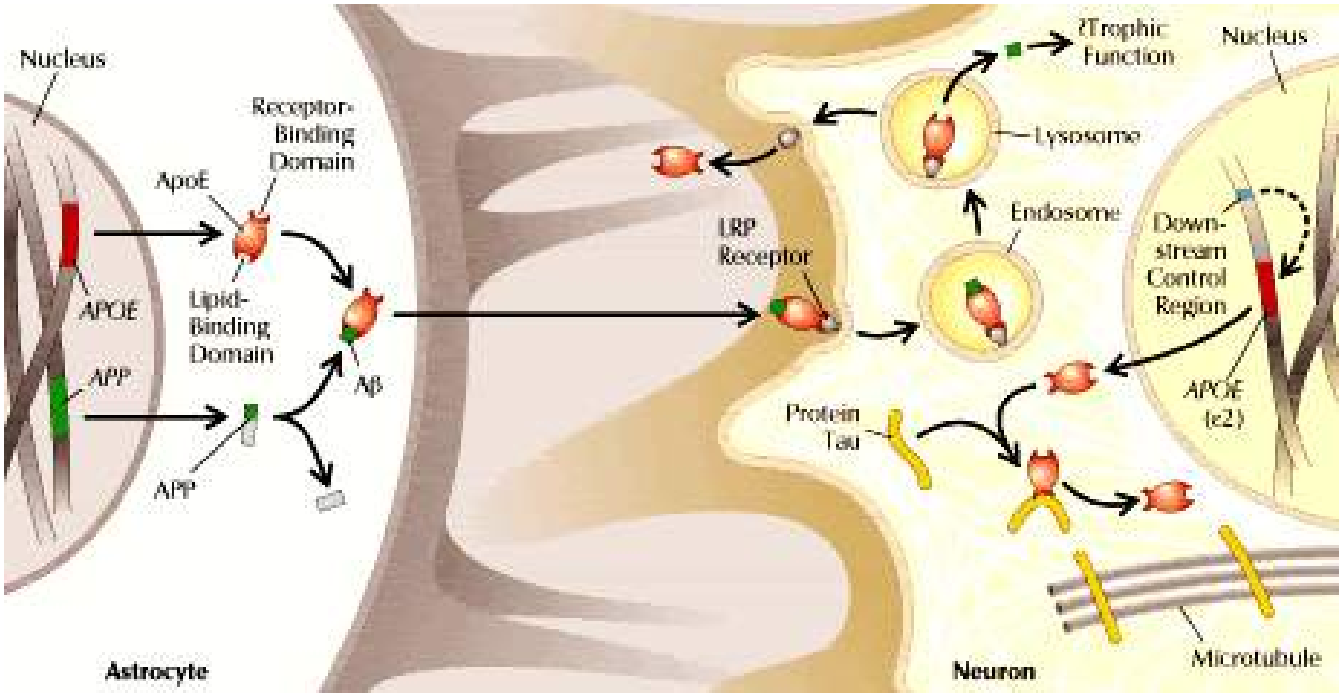
It is also involved in many other functions in human beings, like nerve regeneration, immunoregulation and activation of several lipolytic enzymes.

ApoE contains 299 amino acids, the amino terminal domain (residues 1–191) is a stable globular structure containing the receptor binding site, while the carboxy-terminal domain (residues 216–299) is helical, less stable, and contains the lipoprotein binding functions.

Zannis et al.(1981) identified by isoelectric focusing the three major isoforms of ApoE (ApoE2, ApoE3, and ApoE4) and concluded that a single locus with three alleles (ε2, ε3, and ε4) is responsible for this pattern.

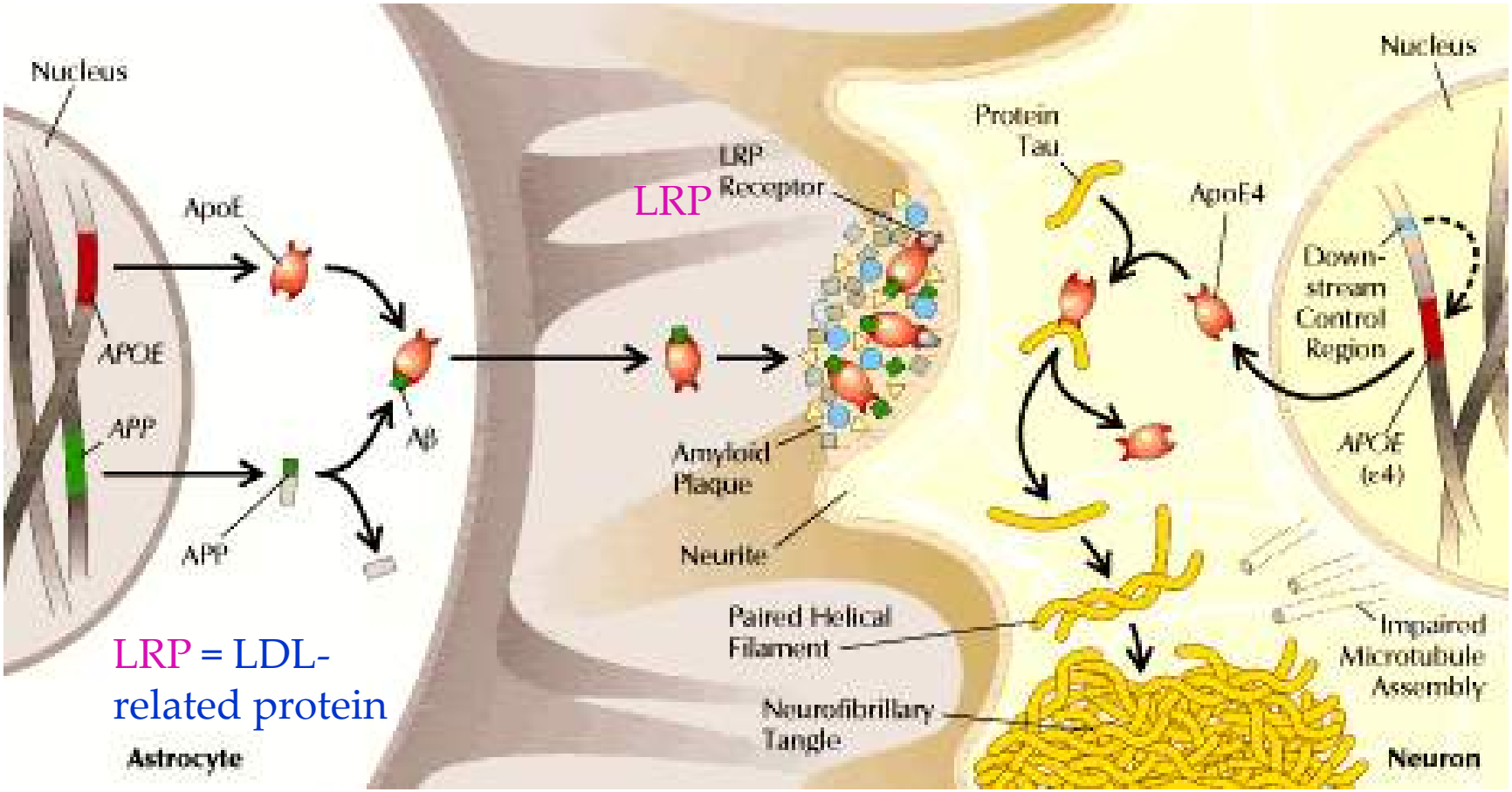
The ApoE2, ApoE3, and ApoE4 isoforms differ in amino acid sequence at two sites, residue

Gene on chromosome 19 codes for apolipoprotein E (apoE), a lipid carrier that binds to low-density lipoprotein (LDL) receptor ("bad" cholesterol) in human plasma



In the brain apoE appears to ferry the Ab peptide to neurons and to facilitate the MAP protein tau's binding to microtubules (important structural and transport proteins for the neurons)

In the AD brain, apoE is postulated to get trapped by LRP in plaques (along with 30+ other proteins including apoE)



The lack of “protection” of the tau MAP protein may allow it to dimerize and form tangles. Then microtubles cannot assemble, destroying the neuron’s shape and synaptic integrity.

Diagnosis

- Difficult.

  Tangles and plaques permitting a definitive diagnosis, can only result from examination of brain tissue.

- Recent evidence suggests altered brain function, in the form of decreased glucose metabolism, at least two decades before symptoms would be expected. Thus, the genetic factors promoting or causing the disease appear to be long-smoldering.

Current Diagnostic Practice

A patient history, physical exam, a series of tests that measure memory, language skills, and other abilities related to brain functioning

- Analysis of cerebrospinal fluid for levels of "sticky“ beta-amyloid peptide and tau protein.

- PET scanning (positron emission tomography), an imaging method in living patients, detects AD-related changes in glucose metabolism in the brain.

MRI (magnetic resonance imaging) gauges the size of structures in the brain; e.g. hippocampus shrinkage - measure of memory/learning damage

-

Therapy

Drugs

Current Alzheimer's medications can help for a time with memory symptoms and other cognitive changes. Two types of drugs are currently used to treat cognitive symptoms:

Cholinesterase inhibitors. These drugs work by boosting levels of cell-to-cell communication by preserving a chemical messenger that is depleted in the brain by Alzheimer's disease. The improvement is modest.

Cholinesterase inhibitors may also improve neuropsychiatric symptoms, such as agitation or depression. Commonly prescribed cholinesterase inhibitors include donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon).

The main side effects of these drugs include diarrhea, nausea, loss of appetite and sleep disturbances. In people with cardiac conduction disorders, serious side effects may include cardiac arrhythmia.

Memantine (Namenda). This drug works in another brain cell communication

Suggested Reading

1. Human Molecular Genetics – Tom Stratchen & Andrew P. Read. Pub: John Wiley & Sons.
2. An introduction to Genetic Analysis – Griffith, Miller, Suzuki, Lewontin, Gelbard. Pub: W.H. Freeman & Co.
3. Genomes 2 – T.A. Brown, Pub: Wiley-Liss. John W. & Sons.
4. Emery's Elements of Medical Genetics– R.F. Mueller, I.D. Young, Pub: Churchill
5. An Introduction to Human Molecular Genetics – J.J. Pasternak, Pub: Fitzgerald Science.