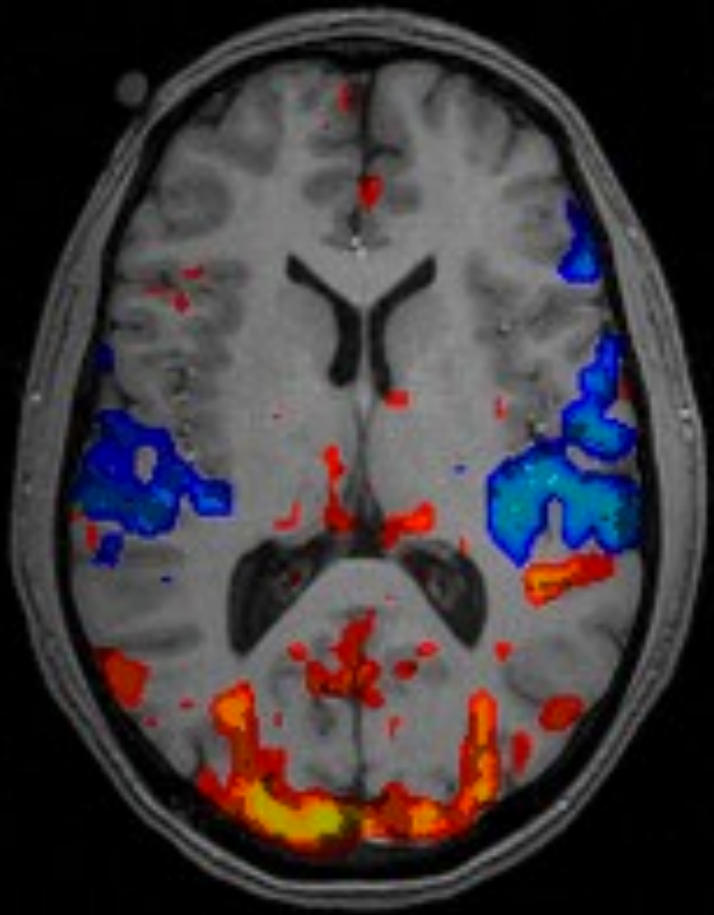
ASHI691:

# Why We Fall Apart: The Neuroscience and Neurophysiology of Aging

Dr. Olav E. Krigolson
krigolson@uvic.ca

Lecture 4:
DEMENTIA AND
ALZHEIMER'S DISEASE



# Dementia

| Normal Aging | Dementia |
| --- | --- |
| Not being able to remember details of a conversation or event that took place a year ago | Not being able to recall details of recent events or conversations |
| Not being able to remember the name of an acquaintance | Not recognizing or knowing the names of family members |
| Forgetting things and events occasionally | Forgetting things or events more frequently |
| Occasionally have difficulty finding words | Frequent pauses and substitutions when finding words |
| You are worried about your memory but your relatives are not | Your relatives are worried about your memory, but you are not aware of any problems |

# What is Dementia?

- Dementia is characterised by a decline of information processing abilities accompanied by changes in personality and behaviour

- Dementia is an umbrella term for progressive disorder of cognition

Dementia has to be distinguished from ***delirium*** which is an acute disturbance of cerebral function with impaired conscious level, hallucinations and autonomic overactivity as a consequence of toxic, metabolic or infective conditions.

**Depression** can mimic the initial phases of dementia and it is termed 'pseudodementia' (which is amenable to antidepressant medication).

Dementia may occur at any age but is **more common in the elderly**, accounting for 40% of long-term psychiatric in-patients over the age of 65 years.

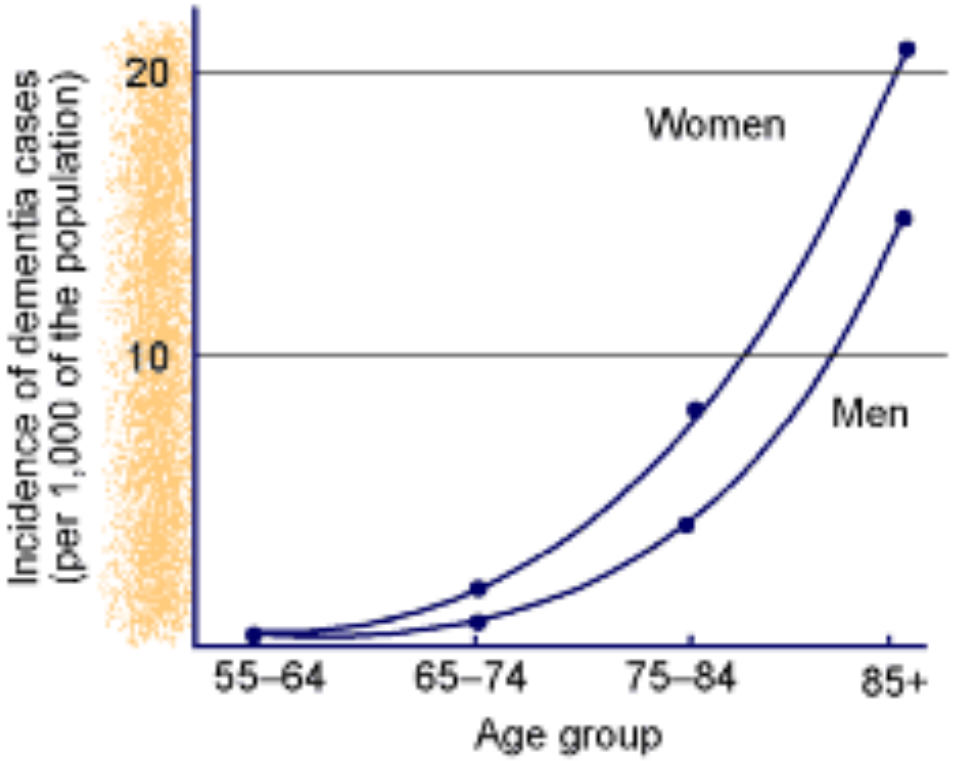
The **prevalence** in persons aged between 50 and 70 years is about 1% and in those approaching 90 years reaches 50%.

An annual incidence rate is 190/100 000 persons.

# *Mild cognitive impairment (MCI)*

- MCI is a relatively recent term, used to describe people who have some **problems with their memory** but do not actually have dementia.
- Some people (80%?) will be in the early stages of Alzheimer's disease or another dementia. Others, however, will have MCI as a result of stress, anxiety, depression, physical illness or just an 'off day'.
- It is estimated that **15% of the population** may be experiencing MCI.
- Currently **extensive research** on MCI is ongoing.
- At the moment there is not enough evidence to recommend any specific treatments.

**The exponential increase in the prevalence of dementia by age group in men and women**

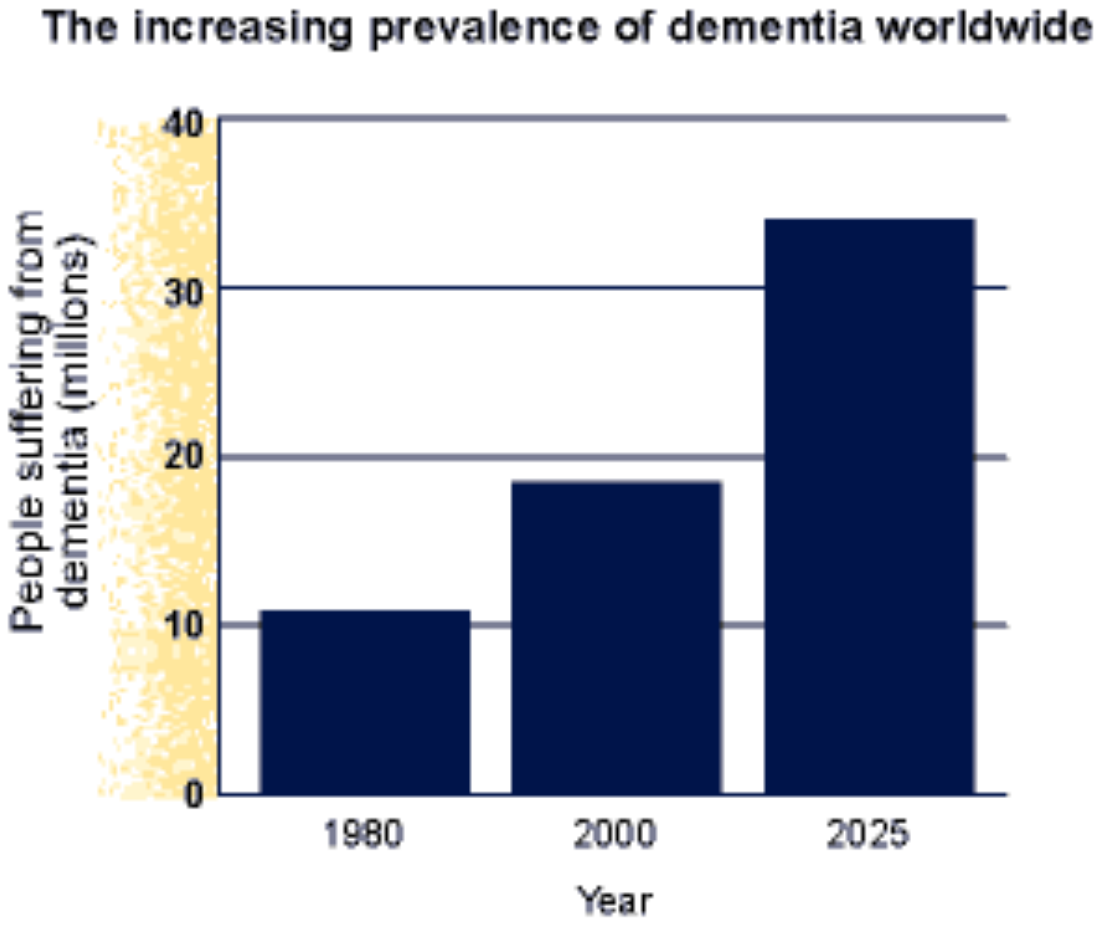


# RISK FACTORS FOR DEMENTIA

- **Age**
- **Family history**
- **Head injury**
- **Fewer years of education**

# Statistics

- 564,000 people in Canada currently with dementia
- 25,000 new cases diagnosed each year


The increasing prevalence of dementia worldwide
People suffering from dementia (millions)
40
30
20
10
0
1980
2000
2025
Year

# Cognitive Symptoms: Changes in Memory

- **Memory is the process of taking in, storing and retrieving information**
- Unable to recall day/ date/ names/ faces
- Repeating questions/ conversations
- Getting lost
- Losing things

# Cognitive Symptoms: Changes in Perception

- **Perception is the process of making sense of information you see (external) and information from your body (internal)**
- Unable to recognise objects
- Unable to judge the position/ location of people/ objects.
- Ignoring one side of the world (including oneself, environment)

# Cognitive Symptoms: Changes in Executive Functioning

- **Executive functioning involves the processing of information in order to plan, sequence, make decisions, prioritize, problem-solve and self-monitor**
- Difficulties with initiating tasks
- Getting stuck on tasks/ repeating actions
- Not thinking through the consequences of actions

# Cognitive Symptoms: Changes in Language

- **Language involves the process of understanding information which is being said by others (receptive language) and the process of expressing information (expressive language)**
- Difficulties understanding (e.g. words, concepts, complex sentences)
- Difficulties finding the word
- Reduced vocabulary

# Non cognitive symptoms of Dementia (BPSD)

- Delusions
- Hallucination
- Agitation / wandering
- Depression / dysphoria
- Anxiety
- Euphoria/elation
- Apathy / Indifference
- Disinhibition
- Irritability / lability / aggression
- Aberrant motor behaviour
- Night-time behaviour
- Appetite / Eating change

# Most common Types of Dementia

In order of prevalence

- Alzheimer's Disease (~ 60%)
- Vascular Dementia
- Lewy Body Dementia
- Frontotemporal

# Rarer forms of Dementia

- Pre-senile Dementia
- Picks Disease
- Korsakov Dementia*
- Pseudo-dementia*
- Endocrine related Dementia*
- Parkinson's Disease
- Huntington's chorea
- Posterior cortical atrophy
- Normal Pressure Hydrocephalus*
- Neurosyphilis*

- **Creutzfeldt-Jakob Disease**
- **Aids-related Dementia**
- **Wernickes**
- **Pernicious anaemia***
- **Subdural haematoma***
- **Subcortical dementias**
- **Progressive supranuclear palsy**
- **Binswangers disease**
- **Semantic dementia**
- **Dementia Pugilistica**

* Reversible

# Vascular Dementia

- Refers to the pathology – many different types
- Early symptoms are memory difficulties and executive difficulties
- Often history of stroke / falls
- Stepwise progression
- Vascular risk factors usually present (High blood pressure, high cholesterol, diabetes) (Salmon & Bondi, 2009)

# Lewy Body Dementia

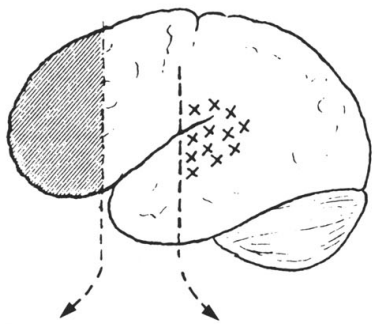
- Under umbrella of disease related to Parkinson's disease
- Early symptoms include executive difficulties
- Visuospatial problems
- Hallucinations of animals and children common (Salmon & Bondi, 2009)

# Frontotemporal dementia

- Frontotemporal variant
- Umbrella term – may different variants including Picks, semantic dementia, primary progressive aphasia (PPA)
- Main cognitive deficits are in executive functioning and attention
- Memory and visuospatial abilities mostly spared (Lezak, 2004)

# Dementias – classification

*Based on site*



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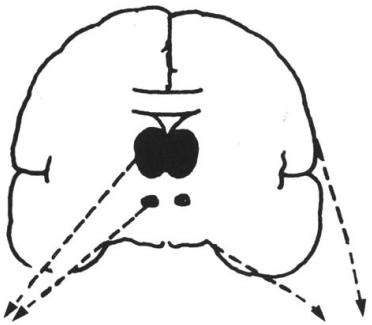


**Anterior**
(Frontal premotor cortex)
↓
Behavioural changes/loss of inhibition, antisocial behaviour, facile and irresponsible
↓
e.g. Normal pressure Hydrocephalus
Huntington's chorea
Metabolic disease

**Posterior**
(Parietal and temporal lobes)
↓
Disturbance of cognitive function (memory and language)
without marked changes in behaviour
↓
ALZHEIMER'S DISEASE

**Subcortical**
Apathetic
Forgetful and slow, poor ability to use knowledge
Associated with other neurological signs and movement disorders
↓
e.g. PARKINSON'S DISEASE
AIDS DEMENTIA COMPLEX

**Cortical**
Higher cortical abnormalities
– dysphasia
– agnosia
– apraxia
↓
e.g. ALZHEIMER'S DISEASE

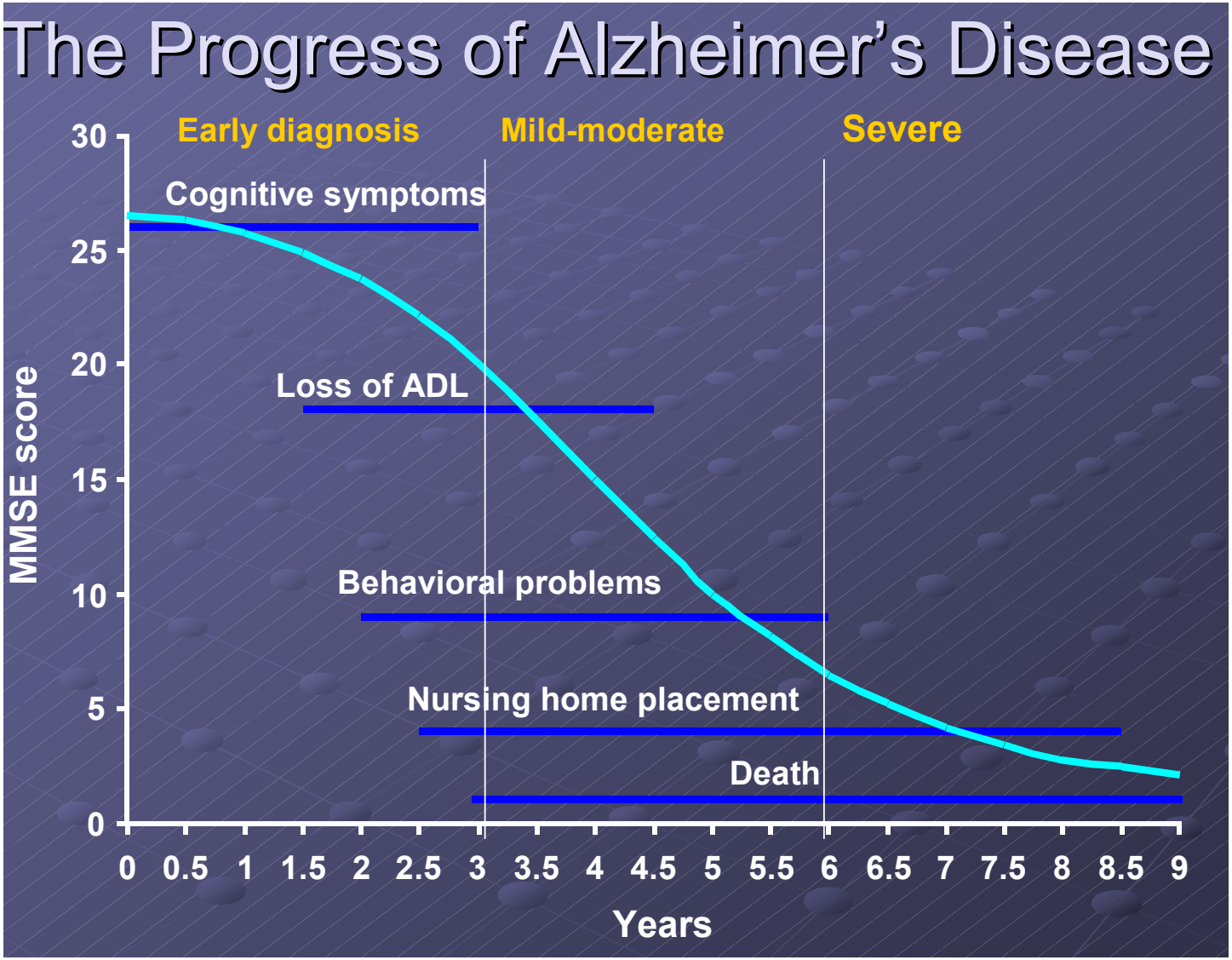
# Alzheimer’s Disease

# ***Alzheimer's disease***

- The commonest cause of dementia.
- The disorder rarely occurs under the age of 45 years.
- The incidence increases with age.
- The cause of AD is not known for sure
- Up to 30% of cases are familial (the loci were found on chromosome 21 and 19).
- Pathology – the presence of senile plaques and neurofibrillary tangles in the brain.
- Diagnosis of AD may be established during life by early memory failure, slow progression and exclusion of other causes.

## Signs & Symptoms:

- Memory loss for recent events
- Progresses into dementia → almost total memory loss
- Inability to converse, loss of language ability
- Affective/personality disturbance (fatuous, hostile)
- Death from opportunistic infections, etc.


The Progress of Alzheimer's Disease
Early diagnosis
Mild-moderate
Severe
Cognitive symptoms
Loss of ADL
Behavioral problems
Nursing home placement
Death
MMSE score
30
25
20
15
10
5
0
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9
Years

# Alzheimer's Disease Progresses Through Distinct Stages

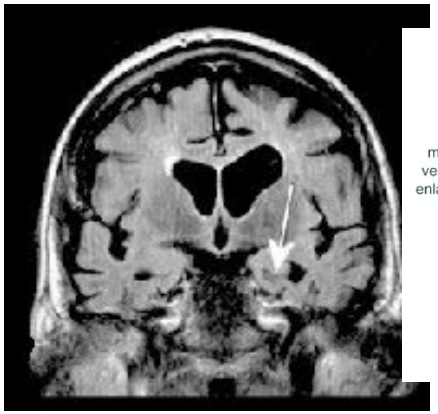

| Symptoms | Memory loss<br>Language problems<br>Mood swings<br>Personality changes<br>Diminished judgment | Behavioral, personality changes<br>Unable to learn/recall new info<br>Long-term memory affected<br>Wandering, agitation, aggression, confusion<br>Require assistance w/ADL | Gait, incontinence, motor disturbances<br>Bedridden<br>Unable to perform ADL<br>Placement in long-term care needed |
|---|---|---|---|

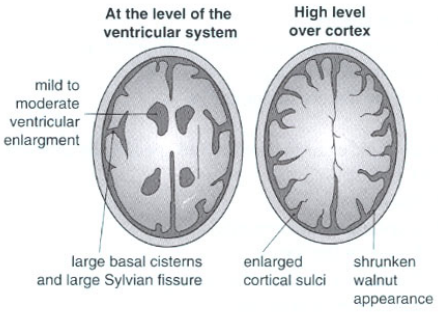
## Confirmation of Diagnosis:

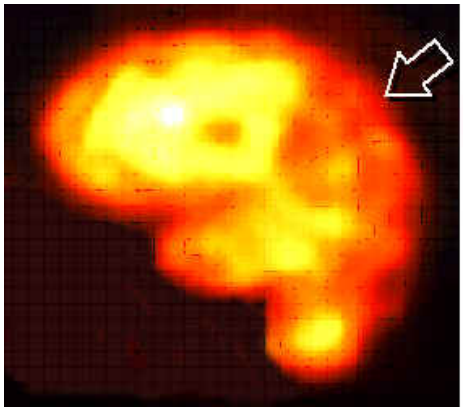
- Neuronal (amyloid, β amyloid, Aβ amyloid) plaques
- Neurofibrillary tangles
- Brain Atrophy

# *Alzheimer's disease*

- **CT scanning** aids diagnosis by excluding multiple infarction or a mass lesion.
- **MRI** shows bilateral temporal lobe atrophy.
- **SPECT** usually shows temporoparietal hypoperfusion.





# Stages of Alzheimer's Disease 1

## Mild

Primary early symptom is forgetfulness
- names/words
- addresses
- shopping items

Main deficit is in recent memory

Intellectual deficits confirmed by neuropsychological testing

Some awareness of their symptoms, so the person may become anxious, depressed and may be in denial

No distinguishing features on physical examination

# Stages of Alzheimer's Disease 2

## Moderate

Significant memory loss – close family members / well known routes/places

Personality and behavioural changes

Self-neglect

Disorientation in time and space

Inability to undertake simple tasks i.e. dressing

Reduced range of thinking
(intellectual deficits)

Language problems start

Disinhibition

# Stages of Alzheimer's Disease 3

## Severe

Dysphasia with disordered and fragmented speech

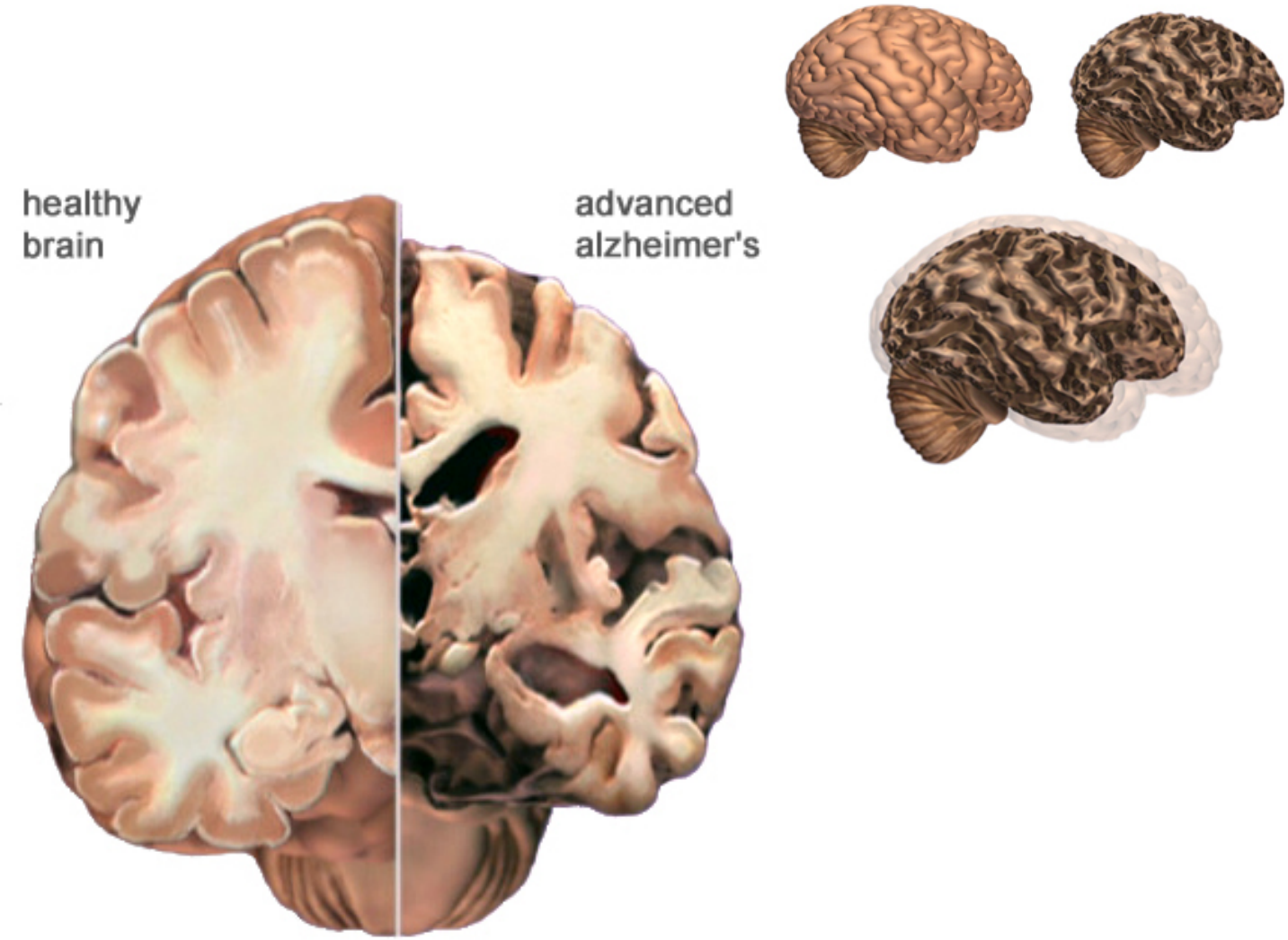
Aggression, restlessness and wandering

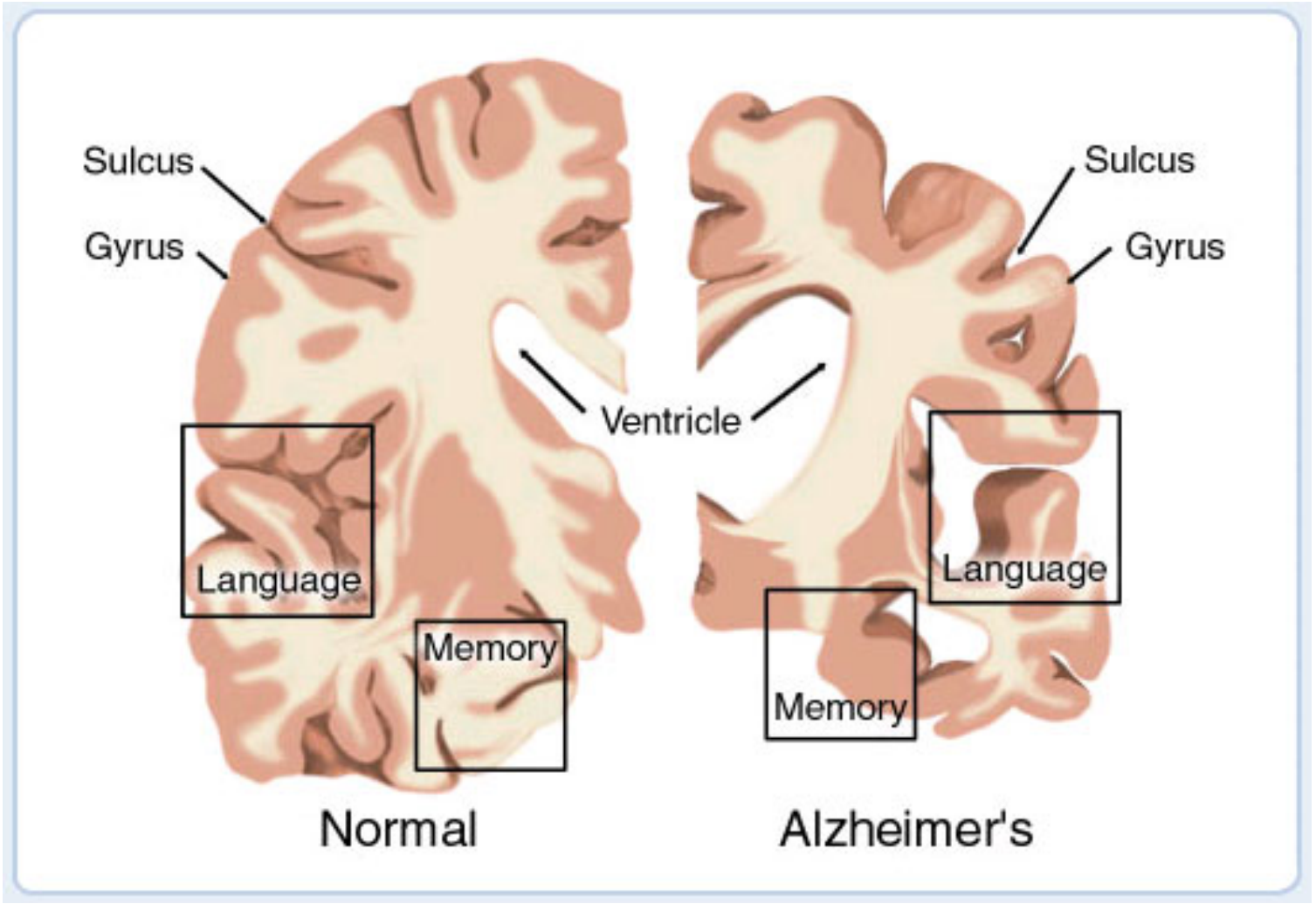
Hallucinations and delusions

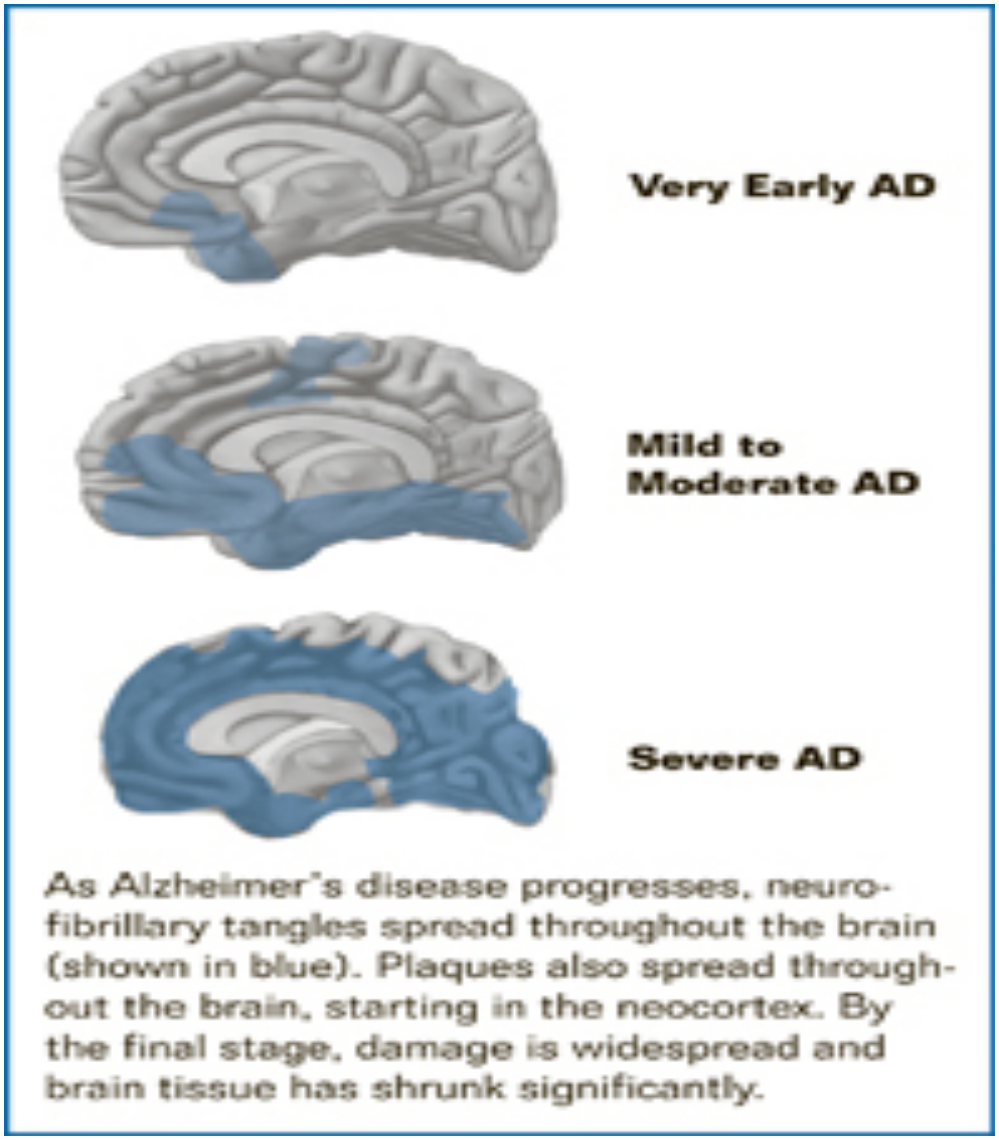
Incontinence

Immobility, rigidity and recurrent falls

General physical deterioration

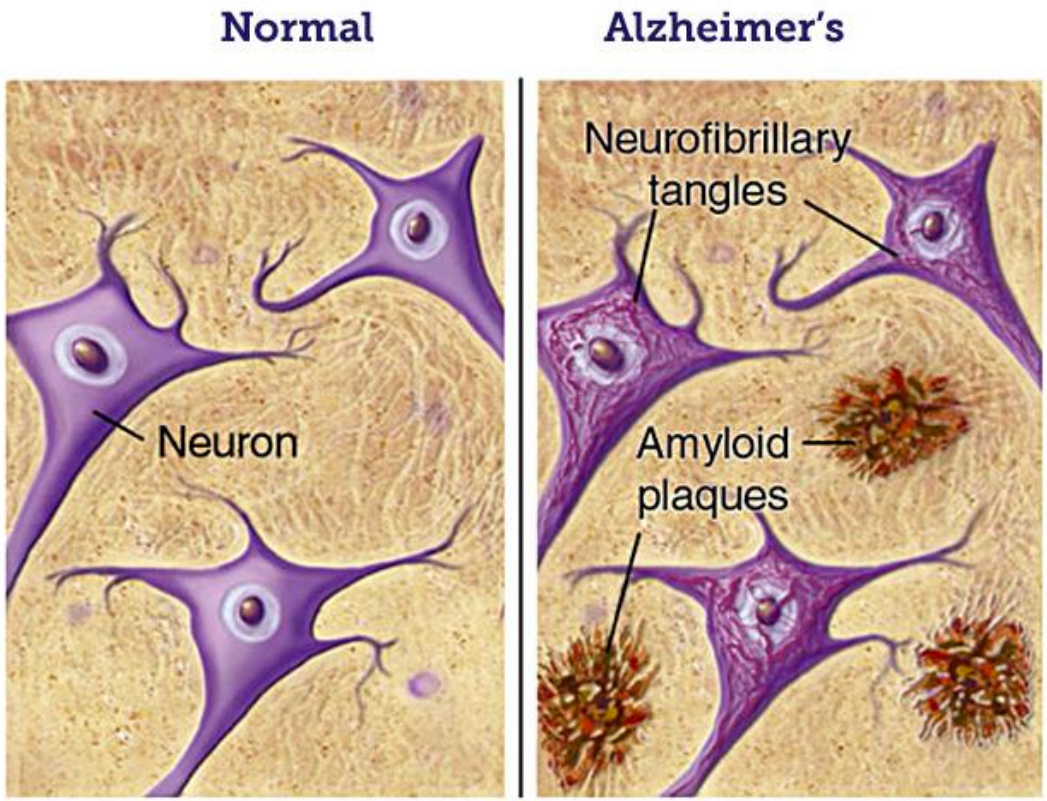

healthy
brain
advanced
alzheimer's


Sulcus
Gyrus
Ventricle
Language
Memory
Sulcus
Gyrus
Language
Memory
Normal
Alzheimer's




As Alzheimer's disease progresses, neurofibrillary tangles spread throughout the brain (shown in blue). Plaques also spread throughout the brain, starting in the neocortex. By the final stage, damage is widespread and brain tissue has shrunk significantly.

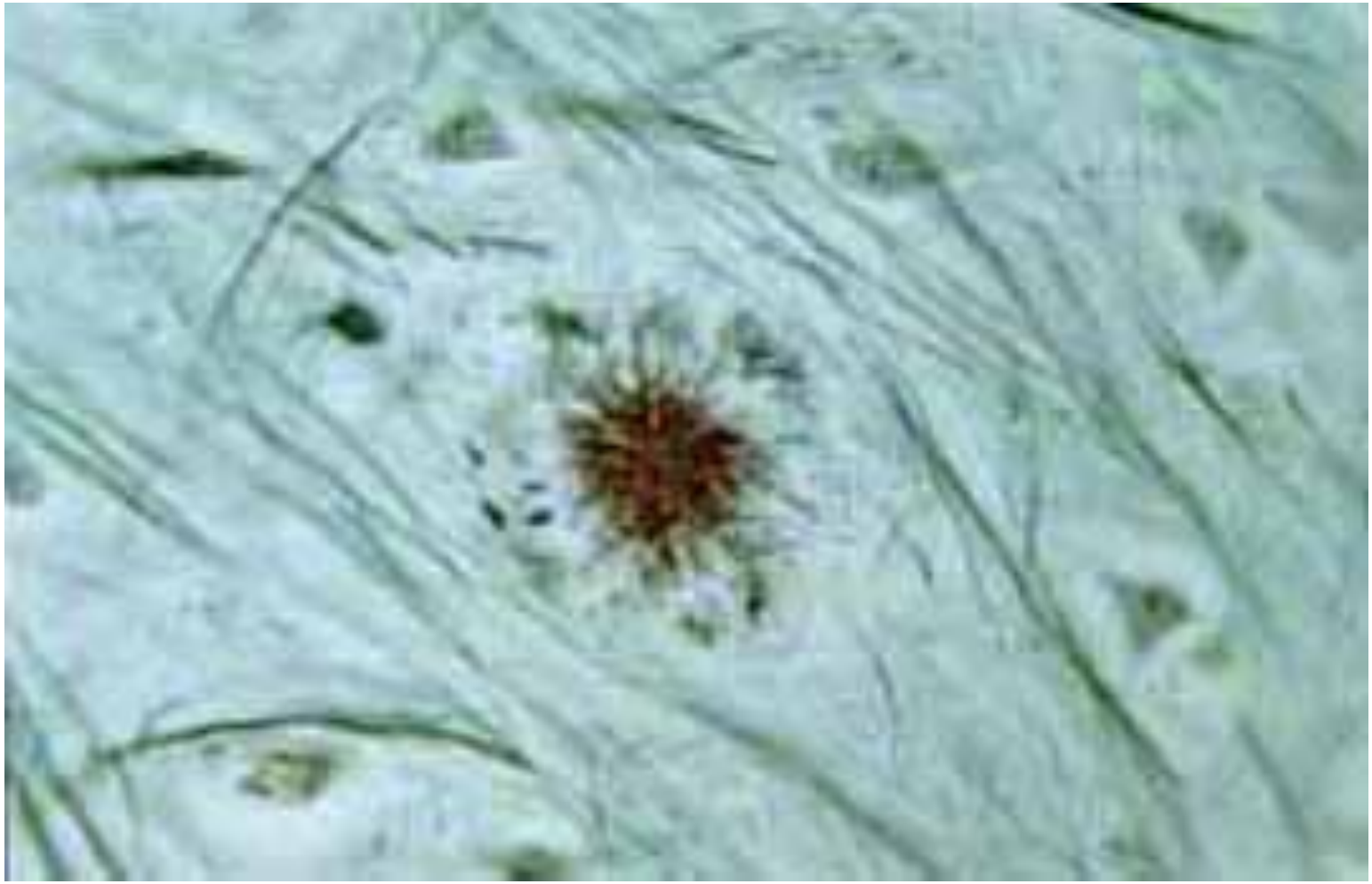
# Normal vs. Alzheimer's Diseased Brain



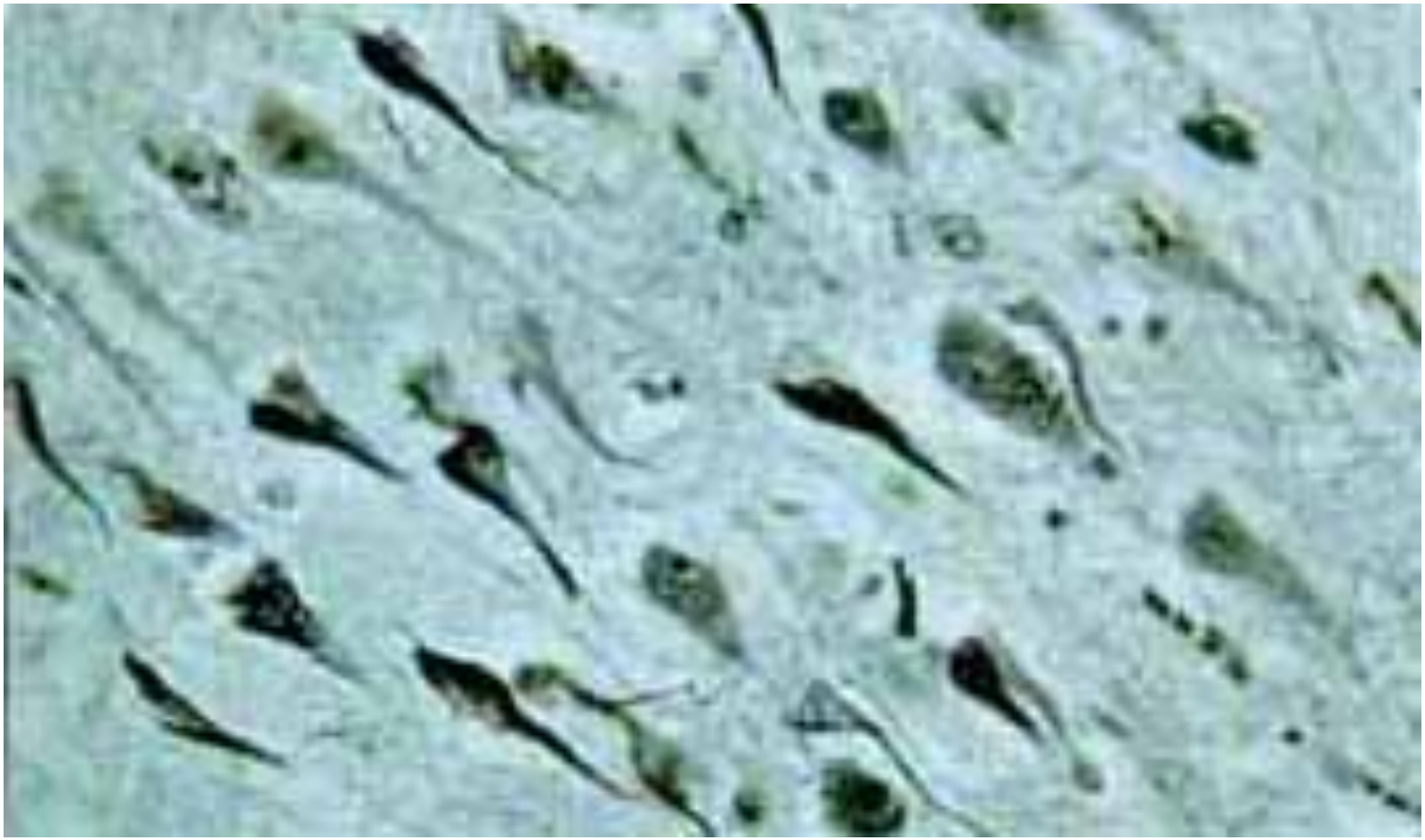



BrightFocus® Foundation
Cure in Mind. Cure in Sight.

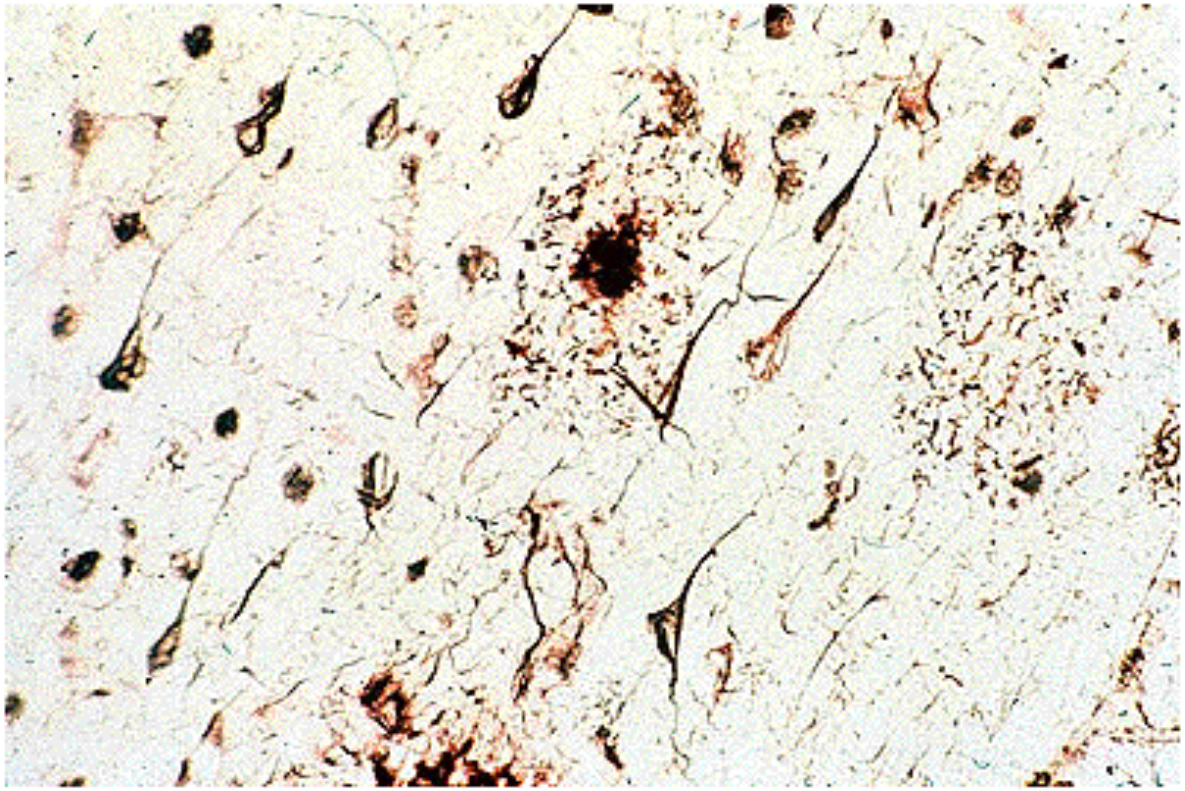
Neuronal Plaques  in Alzheimer's Disease

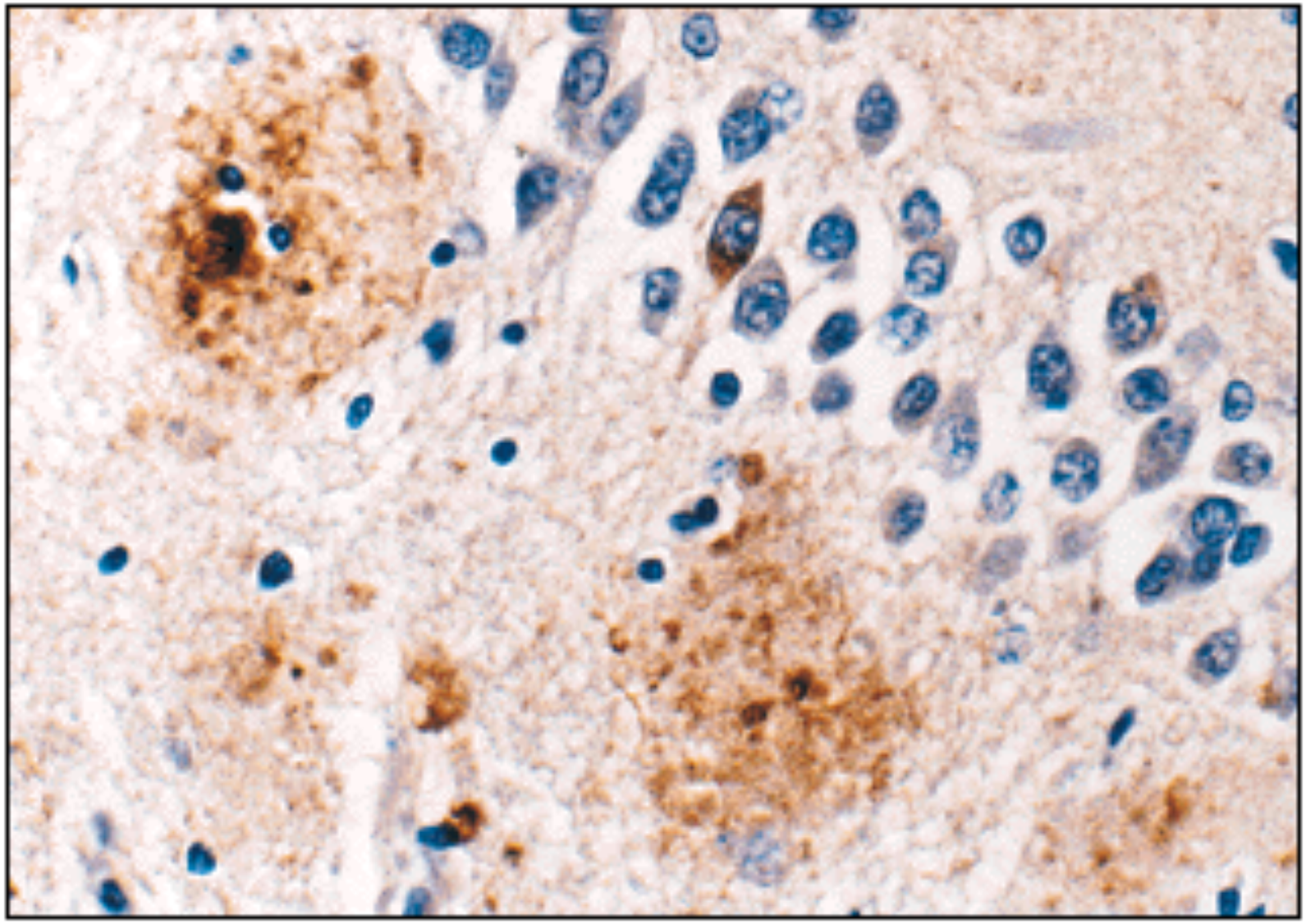


Neurofibrillary Tangles in Alzheimer's Disease



# Plaques and neurofibrillary tangles





**Alzheimer's Disease, Type 1:**

- Several mutations in APP gene on chromosome 21
- Most common = Val717Iso
- Produce abnormal beta amyloid fragment
- 15%-20% of early onset, familial AD
- Autosomal dominant

**Alzheimer's Disease, Type 2:**

- Epsilon 4 (ε4, AKA E4) allele of the Apolipoprotein E (ApoE) gene on chromosome 19 confers risk

- Epsilon 2 (ε2, AKA E2) allele of the Apolipoprotein E gene on chromosome 19 confers protection

- Mechanism unclear; ApoE is a very low density lipoprotein that transports cholesterol

- Most cases are late onset, familial

- Susceptibility Locus

## Alzheimer's Disease, Type 3:

- Mutations (> 130) in the presenilin1 gene on chromosome 14
- Most mutations lead to amino acid substitution
- Overproduction of the beta amyloid fragment
- 30% - 70% of early onset, familial AD
- Autosomal dominant

## Alzheimer's Disease, Type 4:

- Mutations in the presenilin2 gene on chromosome 1
- 2 alleles: Asn141Iso and Met239Val
- Overproduction of the beta amyloid fragment
- < 5% of early onset, familial AD (only a few families world wide)
- Autosomal dominant

# What causes AD?

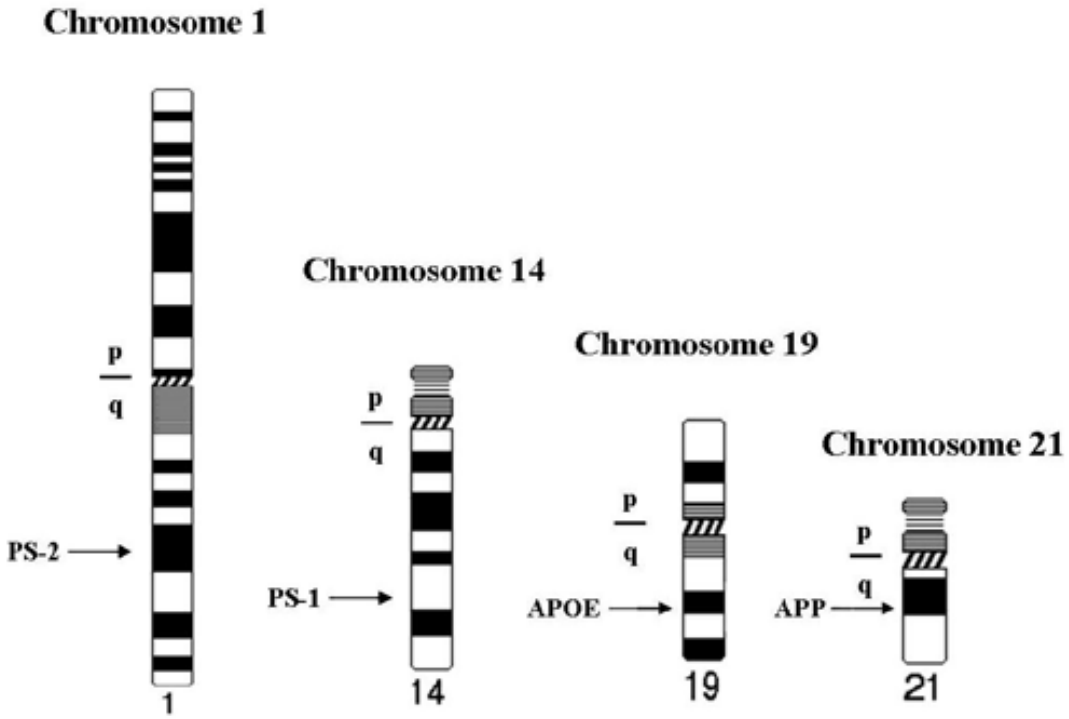
# Classification:

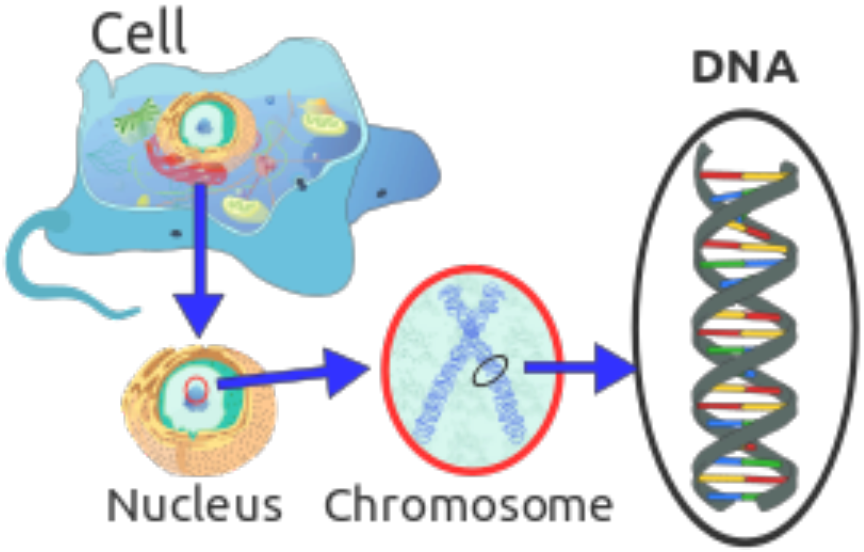
## (1) FAD v SAD: Familial AD versus Sporadic AD

- No complete consensus
- Usually FAD = at least 1 first degree relative affected
- Sometimes 2 second degree relatives

## (2) Early v Late Onset:

- Early onset = usually before 65
- Early onset correlated with FAD
- LOAD = late onset AD




In the nucleus of each cell, the DNA molecule is packaged into thread-like structures called chromosomes. Each chromosome is made up of DNA tightly coiled many times around proteins called histones that support its structure.

# THE GENETICS OF DEMENTIA

- **Mutations of chromosomes 1, 14, 21**
- **Rare early-onset (before age 60) familial forms of dementia**
- **Down syndrome**

- **Apolipoprotein E4 on chromosome 19**
- **Late-onset AD**
- **APOE*4 allele ↑ risk & ↓ onset age in dose-related fashion**
- **APOE*2 allele may have protective effect**

Allele: one of two or more alternative forms of a gene that arise by mutation and are found at the same place on a chromosome.

# Two Major Hypotheses for AD:

## β amyloid protein (BAP) v. tau

1. **BAPtists: The accumulation of a fragment of the amyloid precursor protein or APP (the amyloid beta 42 residue fragment or Ab-42) leads to the formation of plaques that someone kill neurons.**

2. **TAUists: Abnormal phosphorylation of tau proteins makes them "sticky," leading to the break up of microtubules. The resulting loss of axonal transport causes cell death.**

# Amyloid Hypothesis

## (it's the plaques)

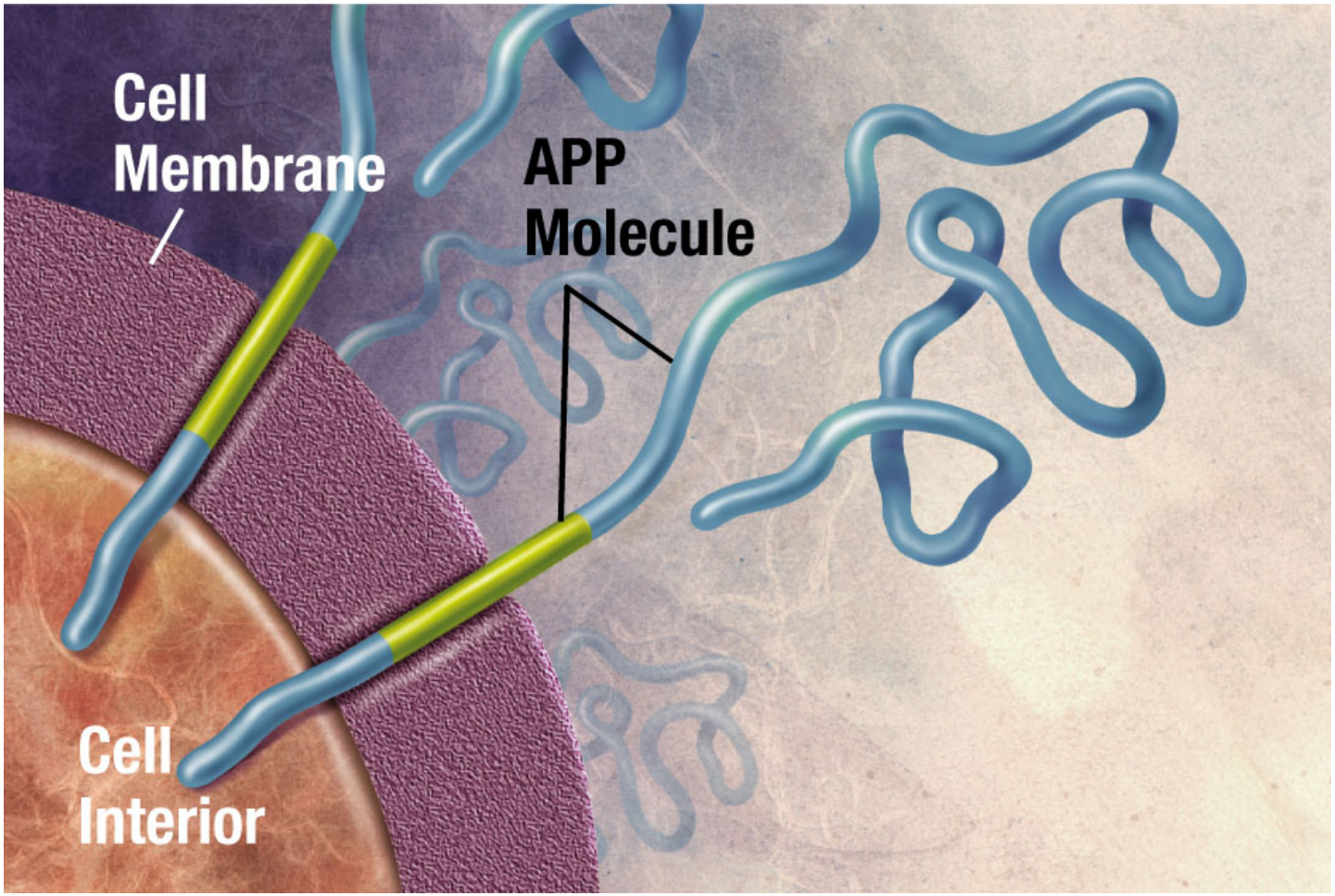
1. The amyloid precursor protein (APP) is broken down by a series of secretases (see next two slides).

2. During this process, a nonsoluble fragment of the APP protein (called Aβ-42) accumulates and is deposited outside the cell.

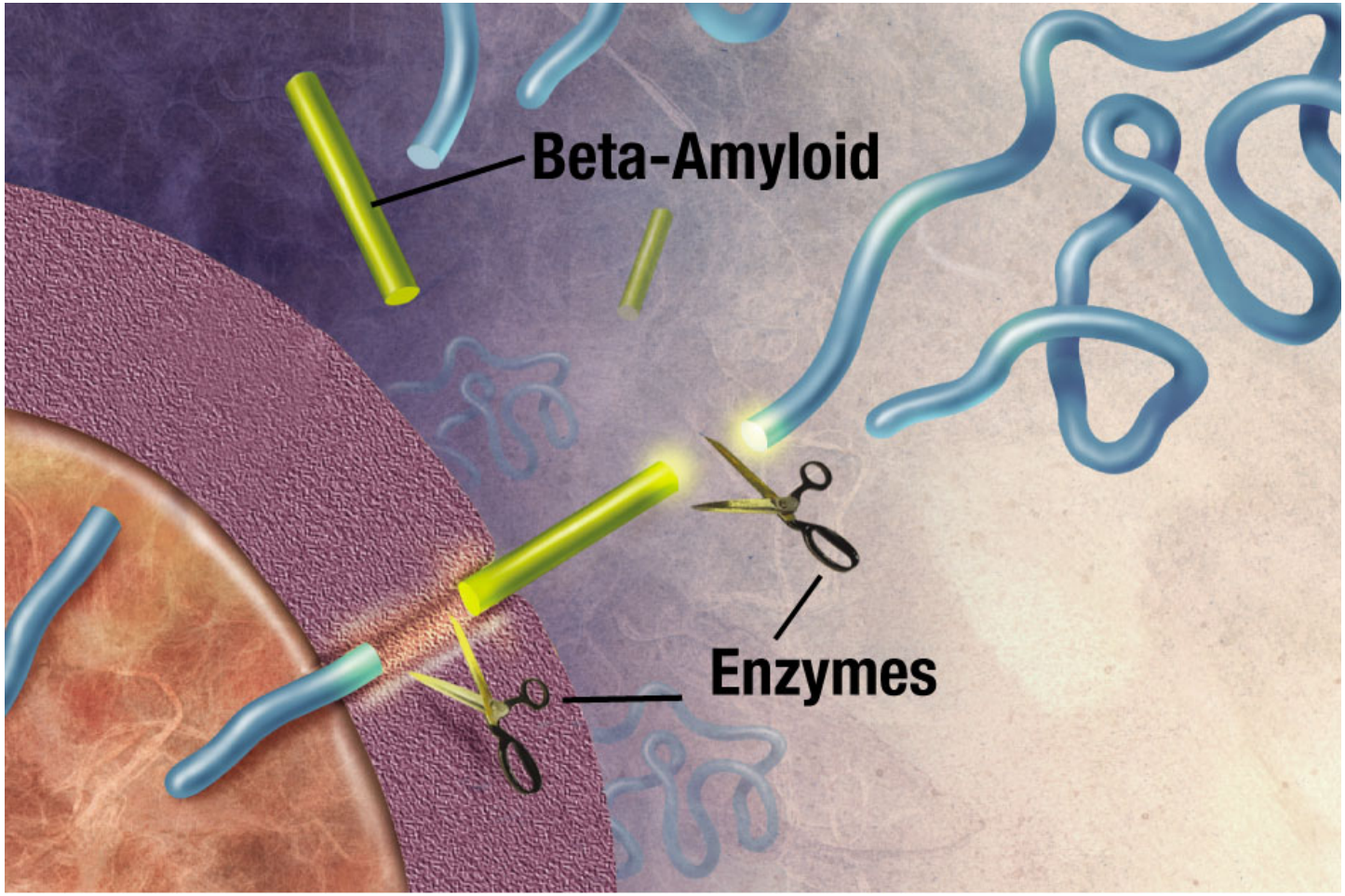
3. The nonsoluble or "sticky" nature of Aβ-42 helps other protein fragments (including apoE) to gather into plaques.

4. Somehow the plaques (or possible the migration of Aβ-42 outside the cell) cause neuronal death.

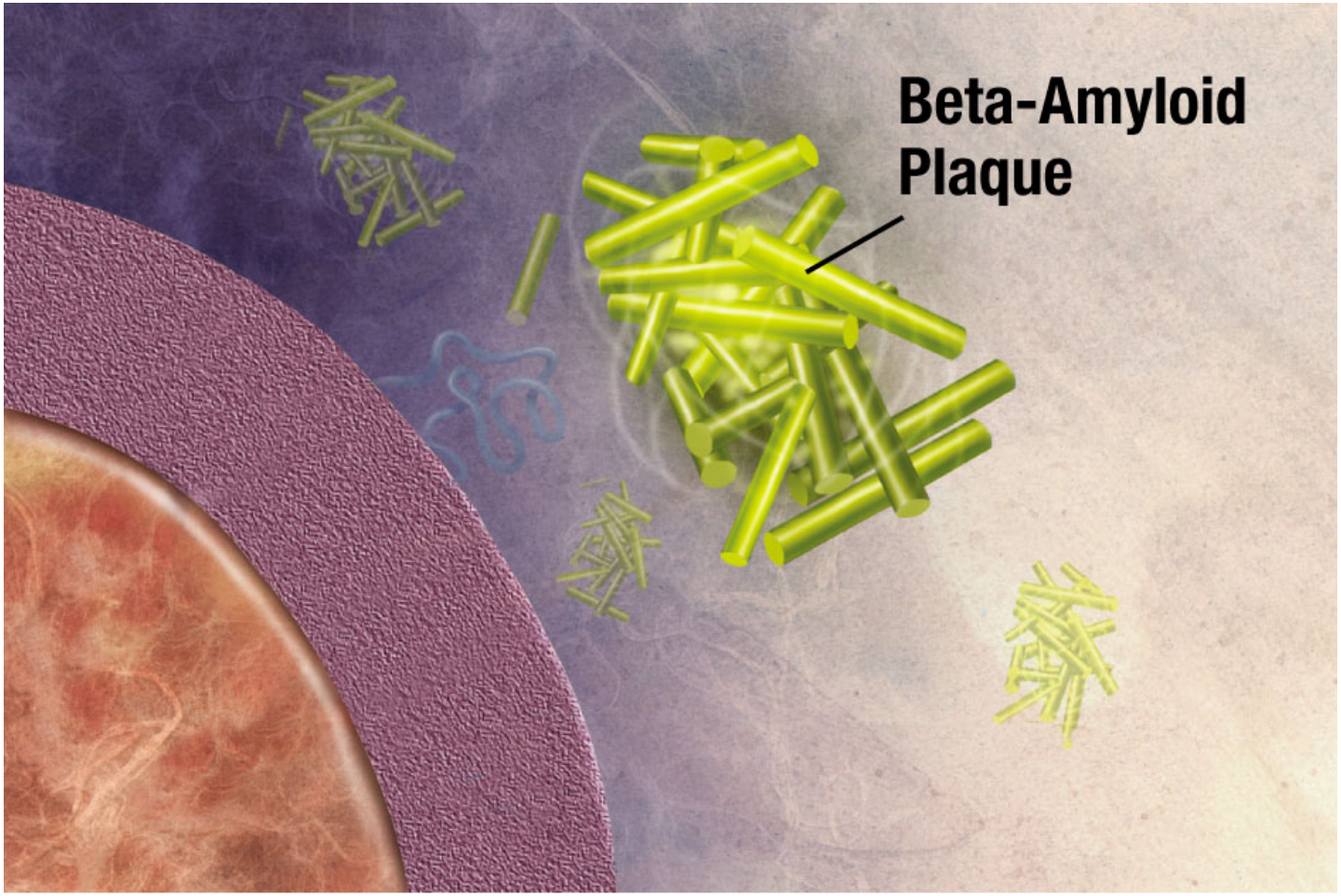
5. May be due to PSEN1 & PSEN2 genes




Amyloid precursor protein (APP) is membrane protein that sits in the membrane and extends outward. It is though to be important for neuronal growth, survival, and repair.




Enzymes cut the APP into fragments, the most important of which for AD is called β-amyloid (beta-amyloid) or Aβ.

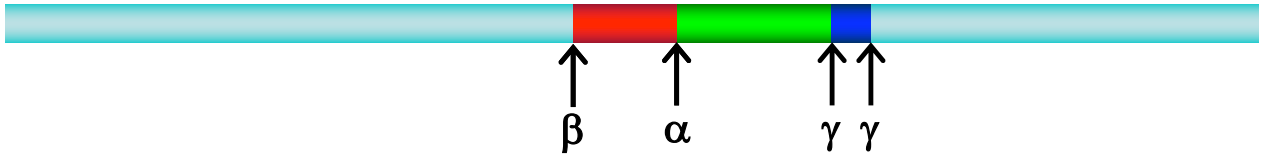



Beta-amyloid is “sticky” so the fragments cling together along with other material outside of the cell, forming the plaques seen in the AD brain.

# β-secretase Pathway:

(not drawn to scale)

**APP Protein:**




**(1) β-secretase cuts APP protein, giving:**

**(2) γ-secretase cuts this residue, giving:**


Soluble

or


Unsoluble, aggregates into plaques

# Tau Hypothesis
## (it's the tangles)

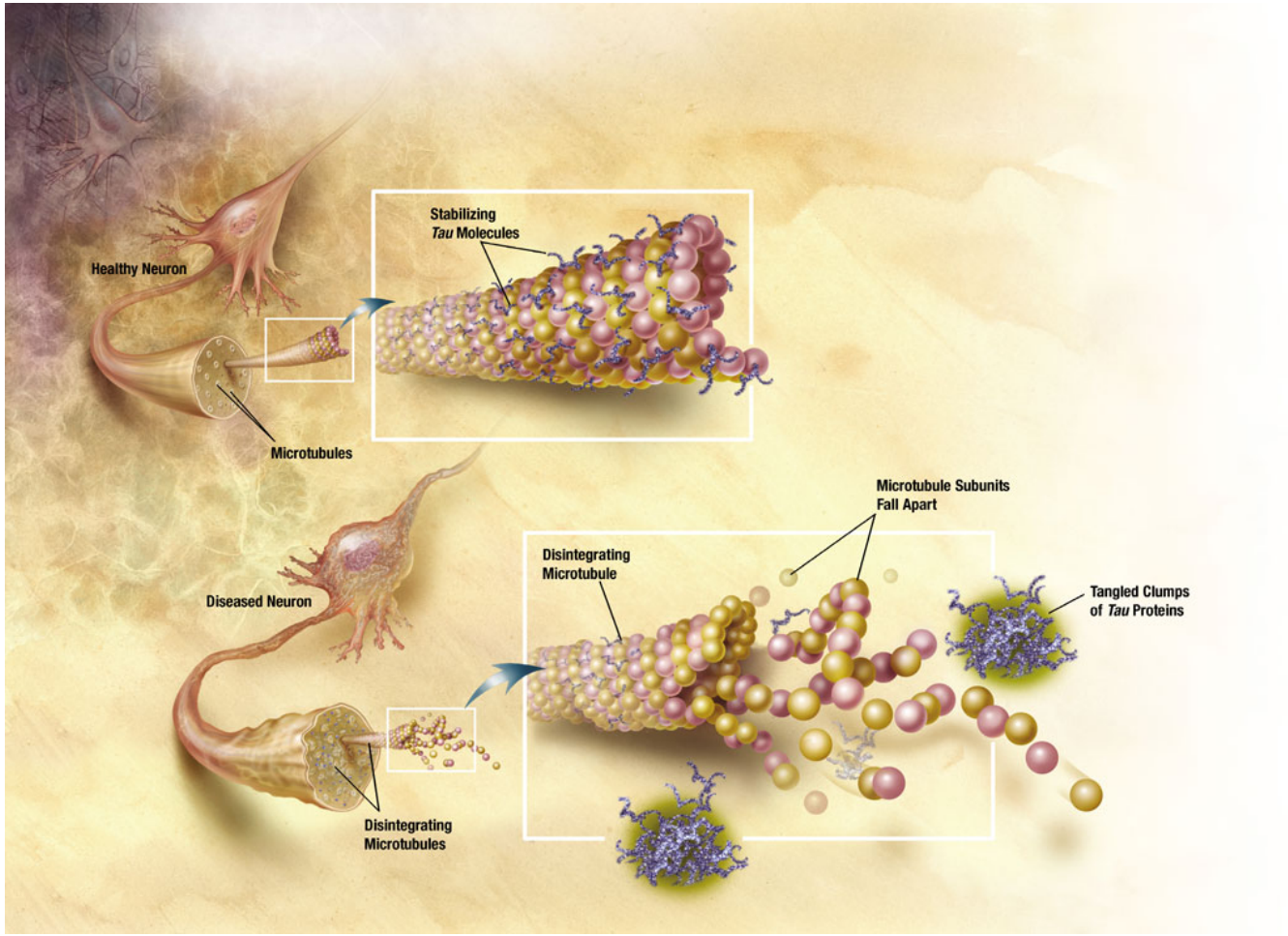
1. Ordinarily, the $\tau$ (tau) protein is a microtubule-associated protein that acts as a three-dimensional "railroad tie" for the microtubule. The microtubule is responsible for axonal transport.

2. Accumulation of phosphate on the tau proteins cause "paired helical filaments" or PHFs (like two ropes twisted around each other) that accumulate and lead to the neurofibrillary tangles (NFT). PHFs are the main component in NFTs.

3. Impaired axonal transport is the probable cause of cell death.

4. Focus on MAPT gene (microtubule-associated protein tau)

5. Not as supported as the other hypothesis




Microtubules are like railroad tracks that transport nutrition and other molecules. Tau-proteins act as "ties" that stabilize the structure of the microtubules. In AD, tau proteins become tangled, unstabilizing the structure of the microtubule. Loss of axonal transport results in cell death.

Current theory: Multifactorial, involving several pathways.

- Protein accumulation: → plaques & tangles
- Inflammation: Unregulated activation of glia
- Lipid distribution: Lipid membrane site of APP cleavage.

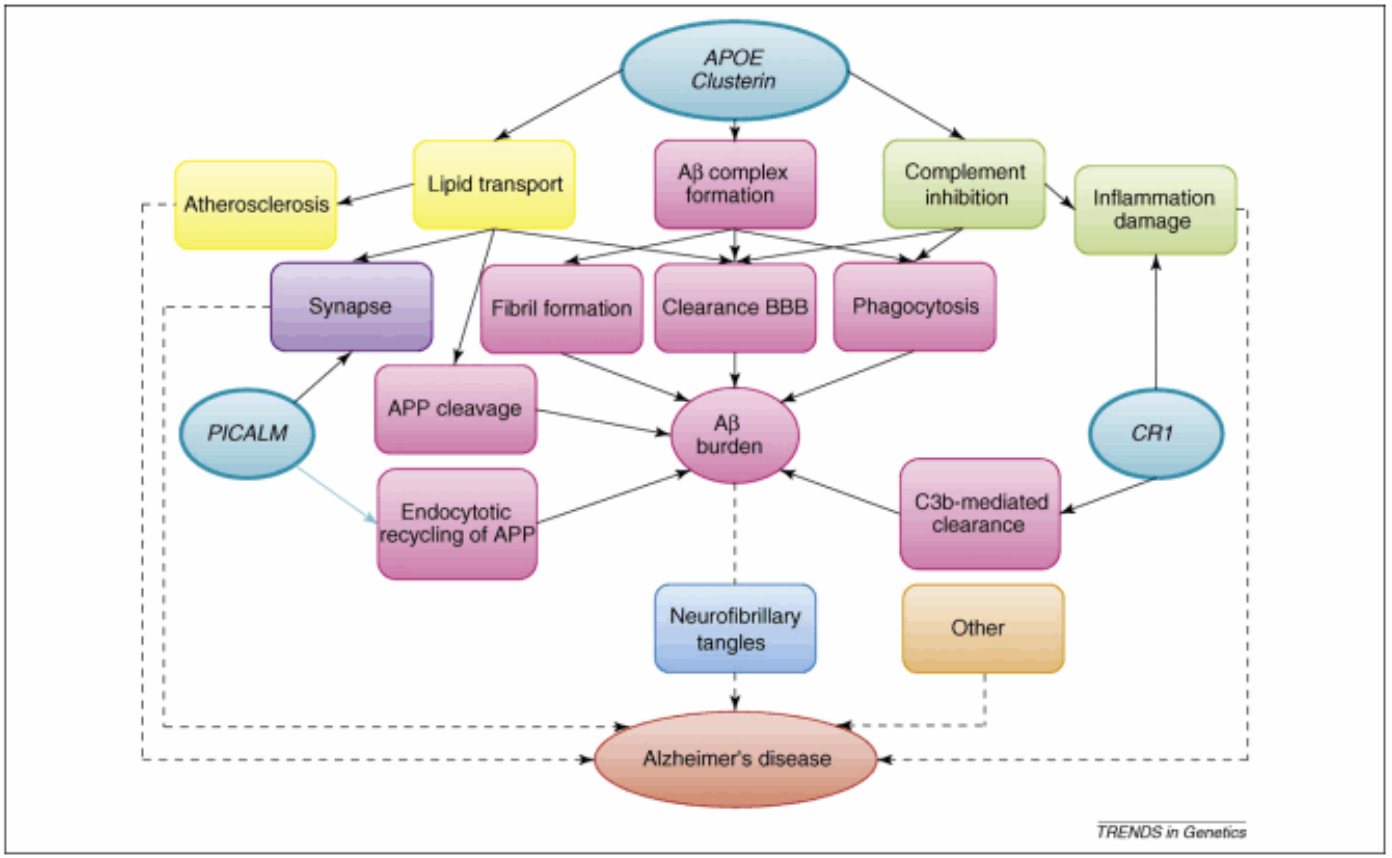



**Figure 1**. Linking the genes to the pathophysiology of AD. An overview of how *APOE*, *CLU*, *PICALM* and *CR1* are implicated in AD susceptibility. The information based on current experimental or observational evidence is depicted by solid black arrows, with hypotheses shown by blue arrows. Several pathophysiological pathways thought to contribute to disease (Aβ (in pink), neurofibrillary tangles (blue), chronic inflammation (green), atherosclerosis (yellow), loss of physiological function at the synapse (purple) and others (orange)) are indicated by interrupted arrows. Note that neurofibrillary tangles are not necessarily downstream of Aβ deposition. Abbreviation: BBB, blood–brain barrier.

Current gene candidates for AD:

- Changes too rapidly to keep track of.
- Go to http://Alzgene.org for latest list

# AD: The Great Unknown

## What is causing the majority of AD cases?

## Cases with no known cause (theoretical extremes):

**Inherited** **Multifactorial**

**Disease is genetic)**

**CDCV**
**Common disease/**
**common variant**

# Inherited/Phenocopy

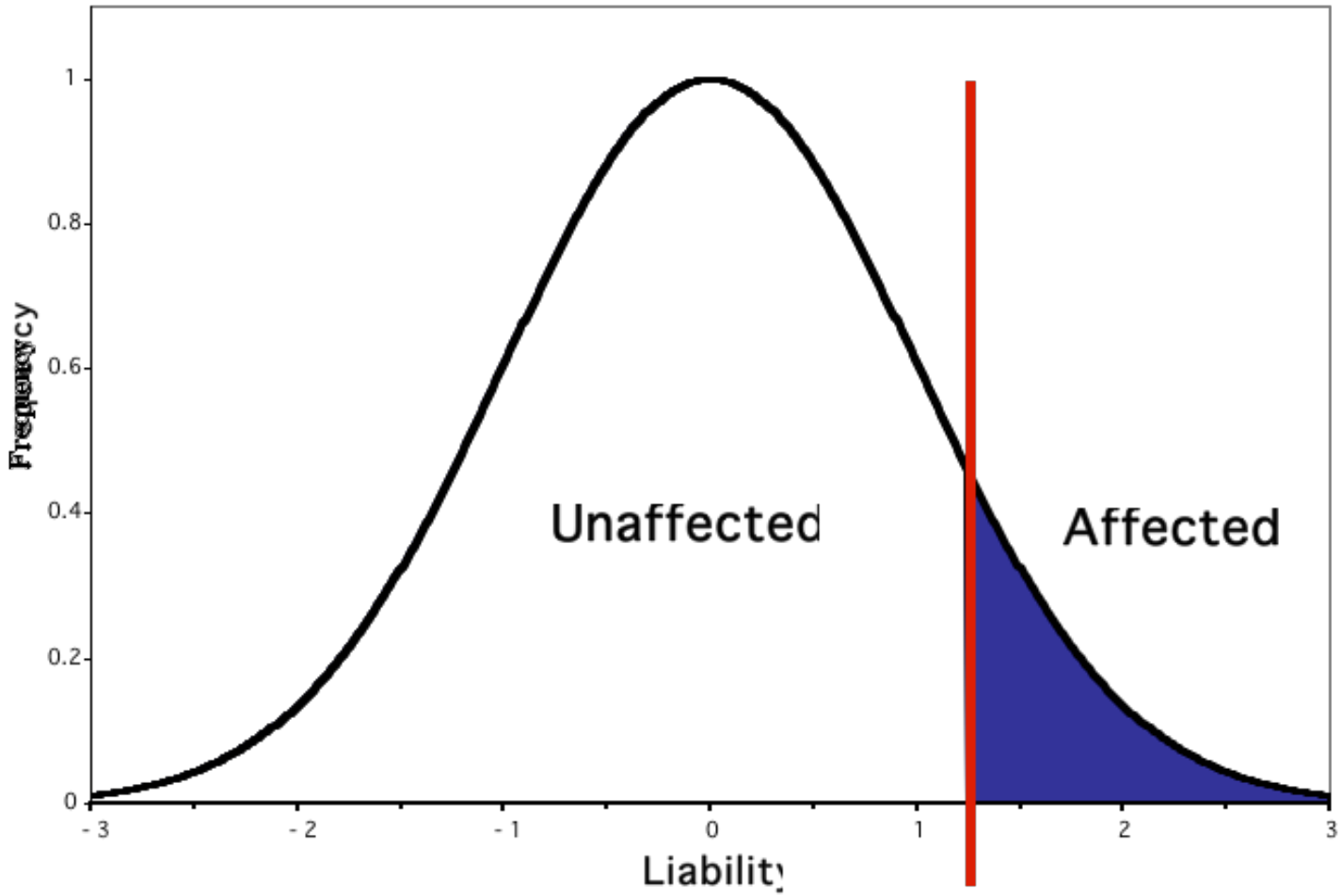
- Many rare alleles with high penetrance ("Mendelian" forms of the disorder).

- Almost no person will get two or more of these AD alleles.

- Non familial cases due to phenocopies.

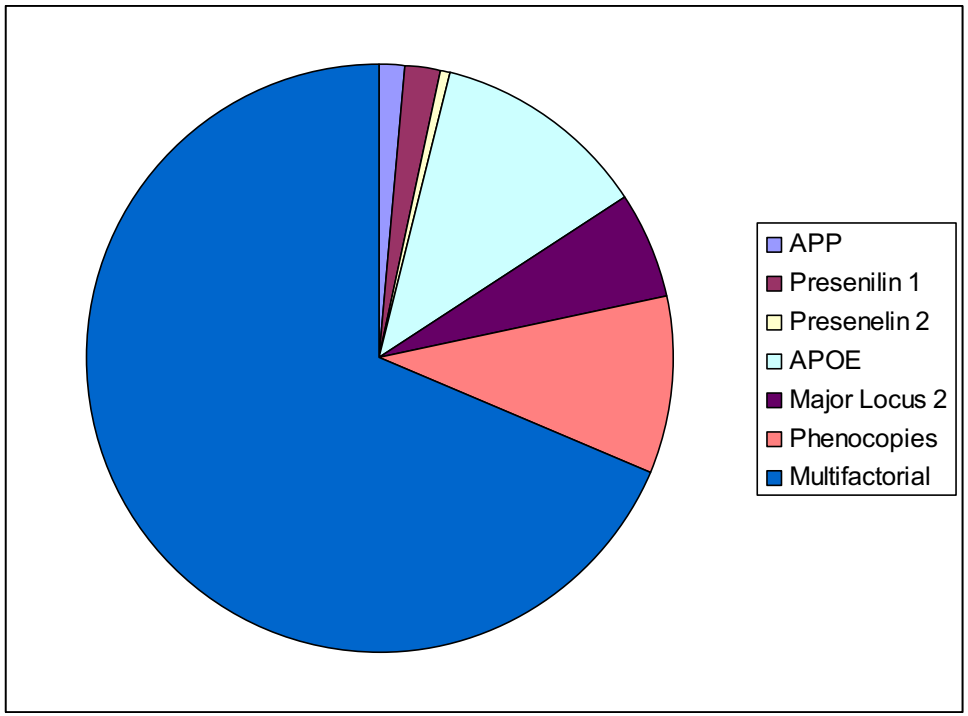
# Multifactorial Threshold Model

- Many common alleles with “low” penetrance.
- Most people will have several risk alleles.
- Risk alleles are additive (multiplicative).
- Many additive environmental factors.
- Genes and environment → ***liability***.
- Once liability reaches a certain value (i.e., the ***threshold***) a disease process begins.




HGSS: Carey: Figure 6.1

# Theoretical major causes of AD:



# DIFFERENTIAL DIAGNOSIS

- **Alzheimer's disease**
- **Vascular (multi-infarct) dementia**
- **Dementia associated with Lewy bodies**
- **Delirium**
- **Depression**
- **Other (alcohol, Parkinson's disease [PD], Pick's disease, frontal lobe dementia, neurosyphilis)**

# ASSESSMENT: HISTORY (1 of 4)

- Ask both the patient & a reliable informant
- about the patient's:

- Current condition
- Medical history
- Current medications & medication history
- Patterns of alcohol use or abuse
- Living arrangements

# ASSESSMENT: PHYSICAL
## (2 of 4)

- **Examine:**
- **Neurologic status**
- **Mental status**
- **Functional status**

- **Include:**
- **Quantified screens for cognition**
  - **e.g., Folstein's MMSE, Mini-Cog**
- **Neuropsychologic testing**

# ASSESSMENT: LABORATORY (3 of 4)

- **Laboratory tests should include:**

- **Complete blood cell count**
- **Blood chemistries**
- **Liver function tests**
- **Serologic tests for:**

  Syphilis, TSH, Vitamin $B_{12}$ level

# ASSESSMENT: BRAIN IMAGING (4 of 4)

- **Use imaging when:**
- **Onset occurs at age < 65 years**
- **Symptoms have occurred for < 2 years**
- **Neurologic signs are asymmetric**
- **Clinical picture suggests normal-pressure hydrocephalus**

- **Consider:**
- **Noncontrast computed topography head scan**
- **Magnetic resonance imaging**
- **Positron emission tomography**

# TREATMENT & MANAGEMENT

- **Primary goals: to enhance quality of life & maximize functional performance by improving cognition, mood, and behavior**
  - **Nonpharmacologic**
  - **Pharmacologic**
  - **Specific symptom management**
  - **Resources**