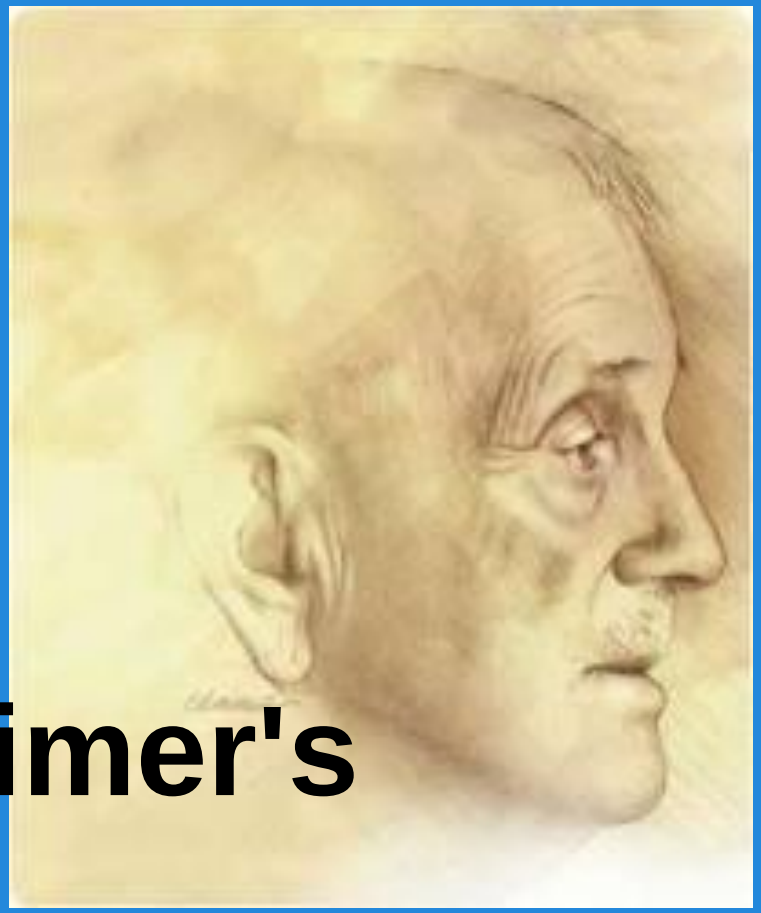
Genetics of Alzheimer's Disease



Kim Kukurba, Emma Xi Li

Overview of Alzheimer's Disease

- Epidemiology
  - Alzheimer's disease (AD) is a neurodegenerative condition.
    - Decline in thinking and reasoning skills.
    - Eventually unable to perform the basic activities.
  - ***Most*** common cause of dementia in people over 65
    - ***~5 million*** people in the United States now.
    - ***~14 million*** Americans will have the disease by 2050.
  - Currently ***no cure*** for AD, scientists and physicians are working
    - To understand disease mechanism
    - Improve the management of its symptoms
    - Ultimately to develop ways of slowing or stopping its progression.

Overview of Alzheimer's Disease

- 2 Types of Alzheimer's Disease
  - **Early-Onset AD**
    - Occurs in people age 30 to 60 (5% of total AD)
    - Mostly inherited, known as familial Alzheimer's disease (FAD)
    - Single mutations cause abnormal protein formation.
  - **Late-Onset AD**
    - Occurs in people after age 60 (majority of AD)
    - Combination of genetic, environmental, and lifestyle factors.
    - Increased risk associated with APOE ε4 allele.

Clinical Presentation

- **10 Warning Signs of Alzheimer's**
  - Memory loss that disrupts daily life
  - Challenges in planning or solving problems
  - Difficulty completing familiar tasks at home, at work or at leisure
  - Confusion with time or place
  - Trouble understanding visual images and spatial relationships
  - New problems with words in speaking or writing
  - Misplacing things and losing the ability to retrace steps
  - Decreased or poor judgment
  - Withdrawal from work or social activities
  - Changes in mood and personality

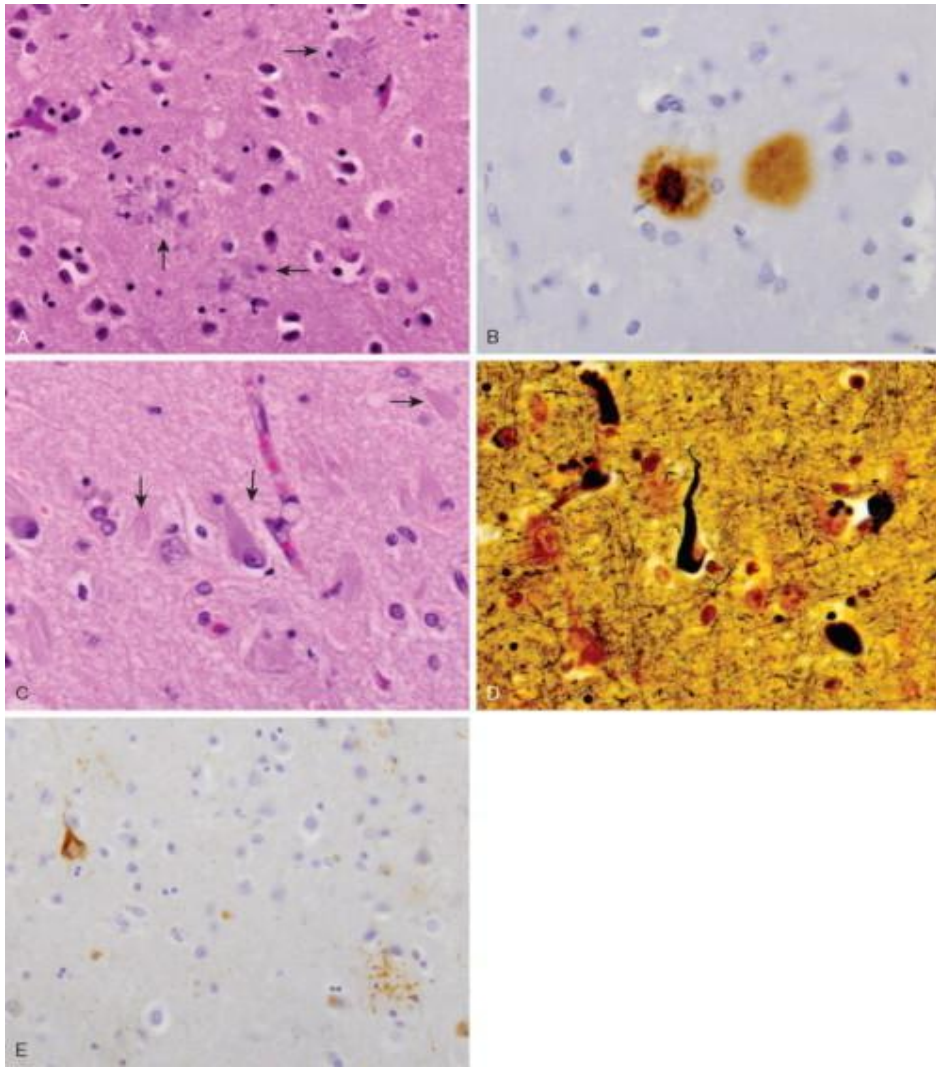
link

Pathological Changes

-Diagnosis made postmortem

-Hallmark features

- **Abnormal morphology**
  - Cortical atrophy (widened sulci)
  - Severe neuronal loss
- **Neuritic Plaques**
  - Dystrophic neurites around amyloid plaques made of **Aβ40/42** (APP derivative)
  - Diffuse plaques (**Aβ42 dominant**)
- **Neurofibrillary Tangles**
  - Hyperphosphorylated forms of the **tau protein.**



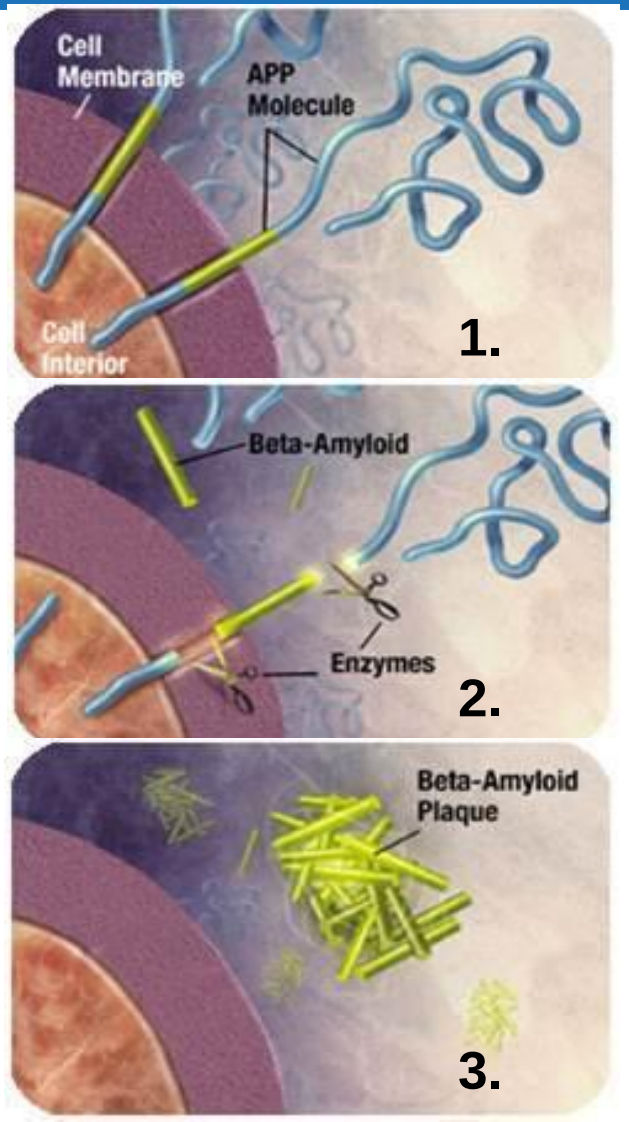
Pathological Changes: Neuritic Plaques

Amyloid precursor protein (APP) is the precursor to ***amyloid plaque***.

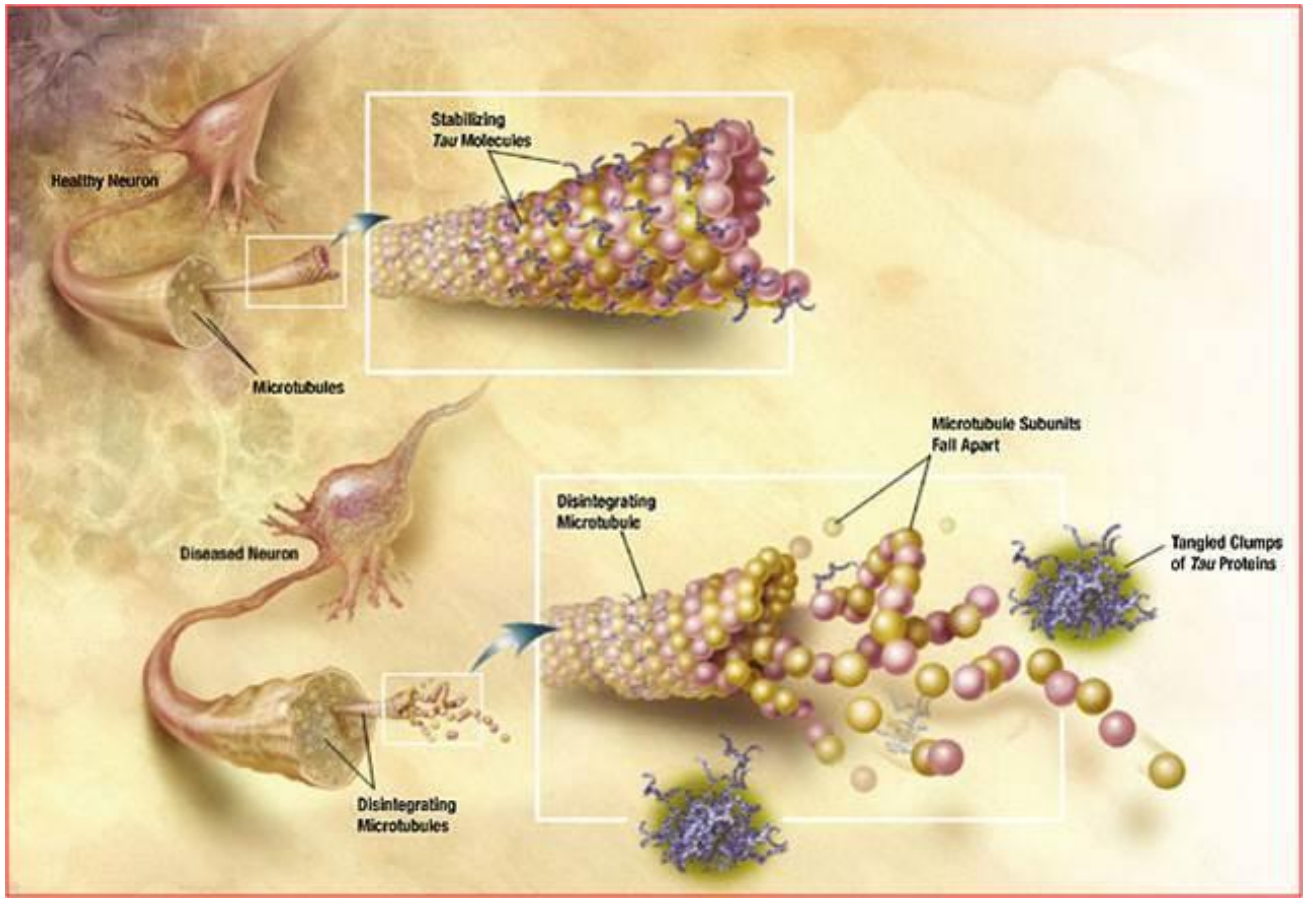
1. APP sticks through the neuron membrane.

2. Enzymes cut the APP into fragments of protein, including beta-amyloid(Aβ).

3. Aβ fragments come together in clumps to form plaques.

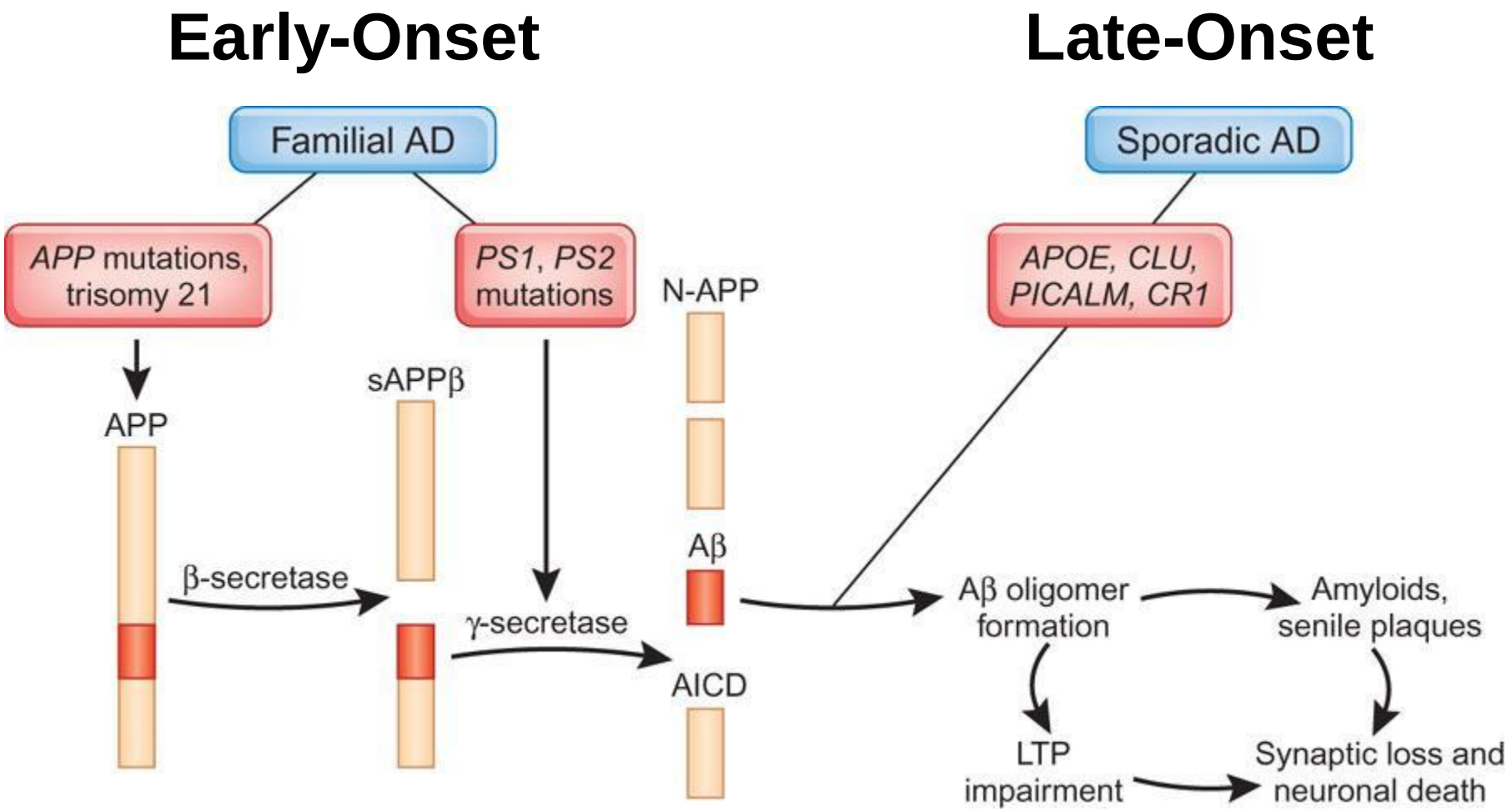


Pathological Changes:
Neurofibillary Triangles



MT are stablized by the ***tau* protein**. Mutated *tau* proteins cause microtubules to collapse, and the *tau* proteins clump together to form **neurofibrillary tangles**.

Genetic Contribution of the Disease



Genetic Contribution of the Disease

Early-onset Alzheimer's Disease

- Autosomal dominant inheritance
- Associated with SNPs in:
  - Amyloid precursor protein (APP) gene
  - Presenilin (PS1) gene
  - Presenilin (PS2) gene
- Single amino-acid changes result abnormal protein function and abnormal amyloid protein breakdown, which generates harmful amyloid plaques, a hallmark of the disease.

Genetic Contribution of the Disease

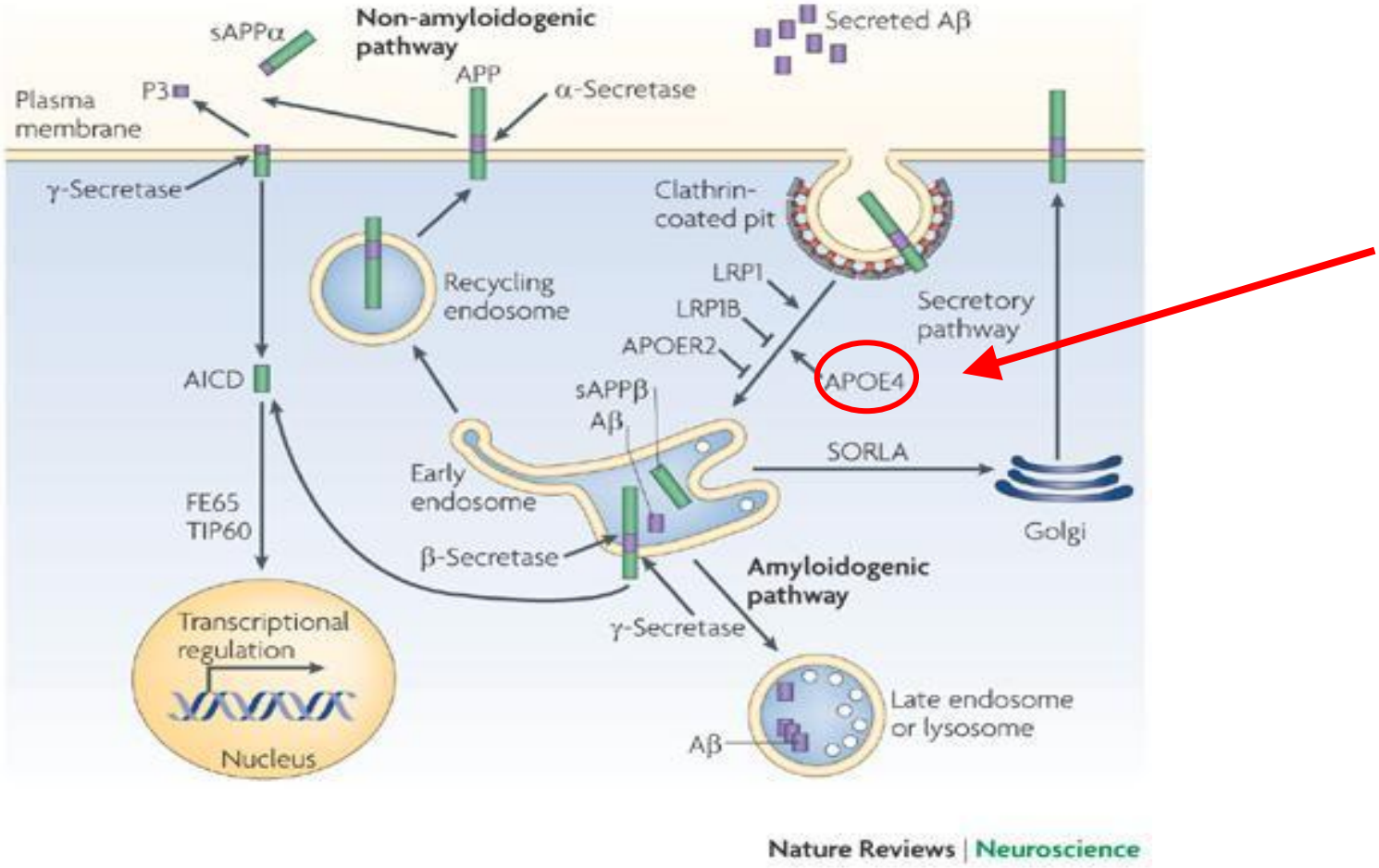
Late-onset Alzheimer's Disease (60%genetic)

- **ApoE gene**
  - Encodes a very low-density lipoprotein that helps remove cholesterol from the bloodstream and their exact role in AD is unclear
  - Different alleles (ε2,ε3, ε4) have different phenotypes
- **Microtubule associated protein tau (MAPT) gene**
  - SNPs in this gene do not influence the risk of Alzheimer's.
  - Increased tau proteins CSF correlate with early onset.
- **Tumor necrosis factor (TNF) gene**

  Both an independent risk factor for disease development and a modifier of the risk for ApoE4 carriers
- GWASs have identified more candidates: BIN1, CLU, PICALM, CR1.

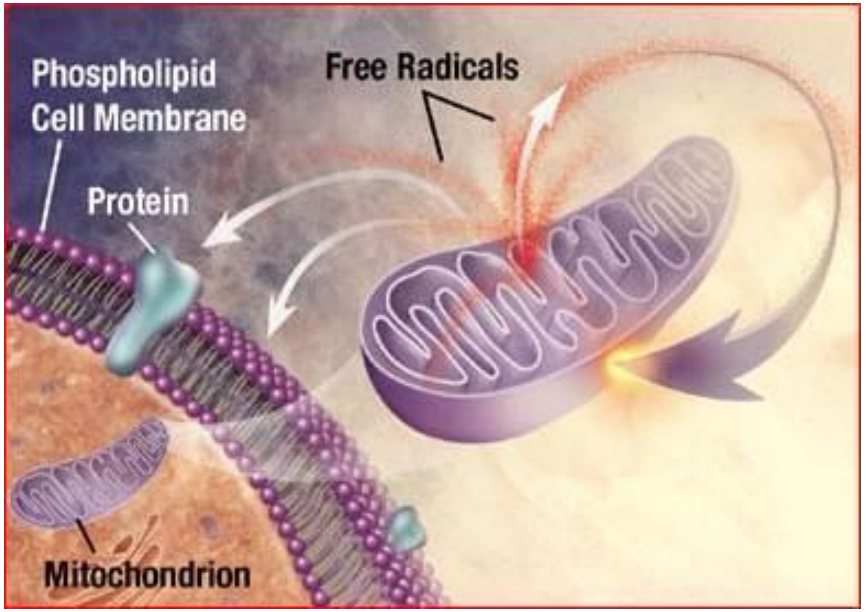
Genetic Contribution of the Disease

Late-onset Alzheimer's Disease

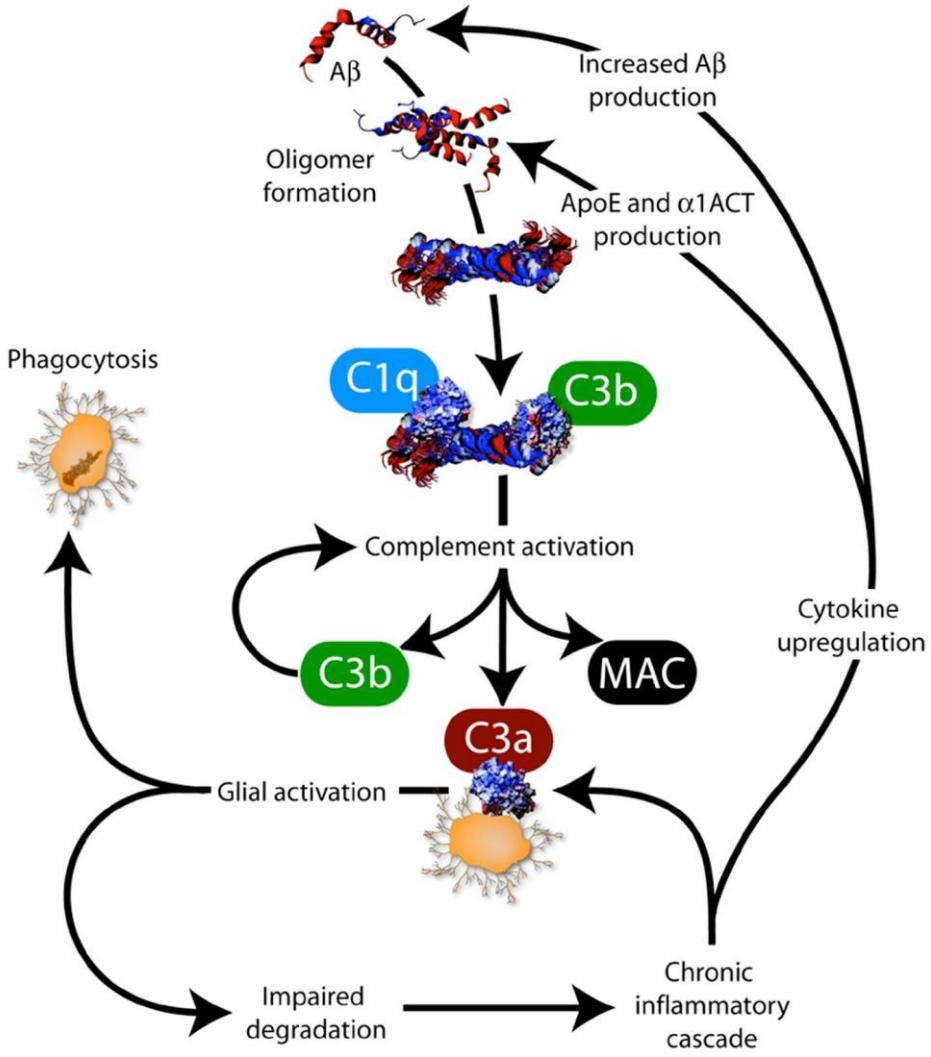


Non-genetic Factors

- Most cases of AD (90%) are non-familial.
- Interaction of multiple susceptibility genes and unknown environmental factors.
- Oxidative stress
  - Contributing factor
  - Significant increase in markers of oxidative damage found in AD tissue
- Inflammation



Non-genetic Factors



Inflammation

- Pro-inflammatory cytokines & reactive microglia in AD brains
- Anti-inflammatory agents
  -reduced AD risk
  -limited plaque production.
- No positive effects of anti-IF agents on established AD
  -already established pathology cannot be reversed.

Genetic Testing-Which SNPs?

ApoE gene

- Located on chromosome 19
- 3 common variants (**ε2**, **ε3**, **ε4**) produce different phenotypes
- 3 common variants are determined by two SNPs (**rs429358** & **rs7412**)

- **rs429358**
  - Common allele: T Variant allele: C
  - Encodes amino acid change (Cys130Arg) in exon 4
- **rs7412**
  - Common allele: C Variant allele: T
  - Encodes amino acid change (Arg176Cys) in exon 4

Genetic Testing-What SNPs?

How are three ApoE variants determined by the two SNPs?

	rs429358	rs7412	Prognosis
ApoE ε2	T	T	uncommon; possible protection
ApoE ε3	T	C	most common; neutral role
ApoE ε4	C	C	20% in population; risk variant
Not Observed	C	T	

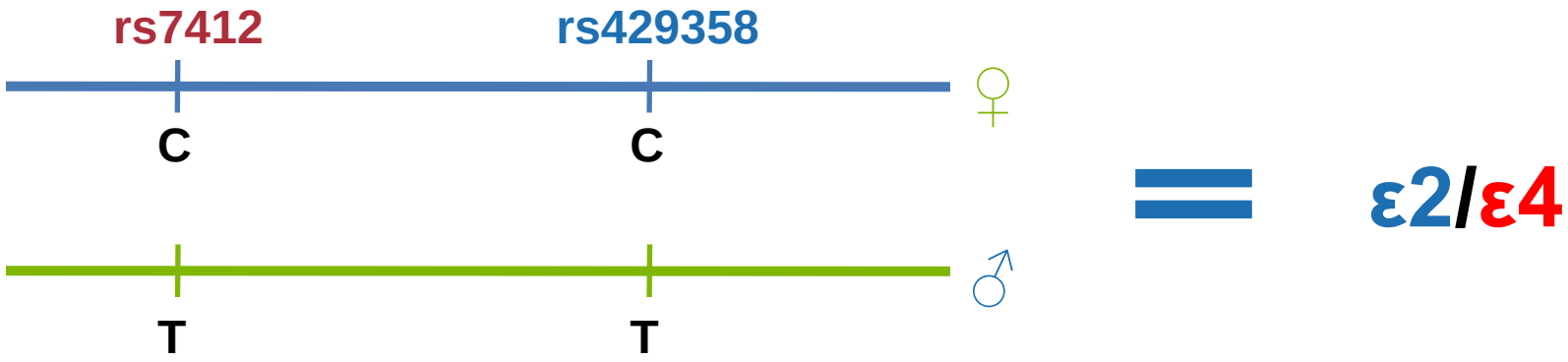
Genetic testing - Imputing rs429358

- rs429358 is notoriously difficult to genotype
- Old 23&me arrays have genotyped rs4420638, which is situated 14kb away from ApoC and co-inherited with ApoE, and used it to impute rs429358
- Strong linkage disquilibrium between rs4420638 and rs429358 based on Caucasian allele frequency
  - D' = 0.86
  - R^2 = 0.60
- A at rs4420638 indicates a high probability of T at rs429358
- G at rs4420638 indicates a high probability of C at rs429358

Genetic Testing-What SNPs?

Exercise!

(1) What is the variant combination of people with the CT genotype at both SNPs?



Genetic Testing-What SNPs?

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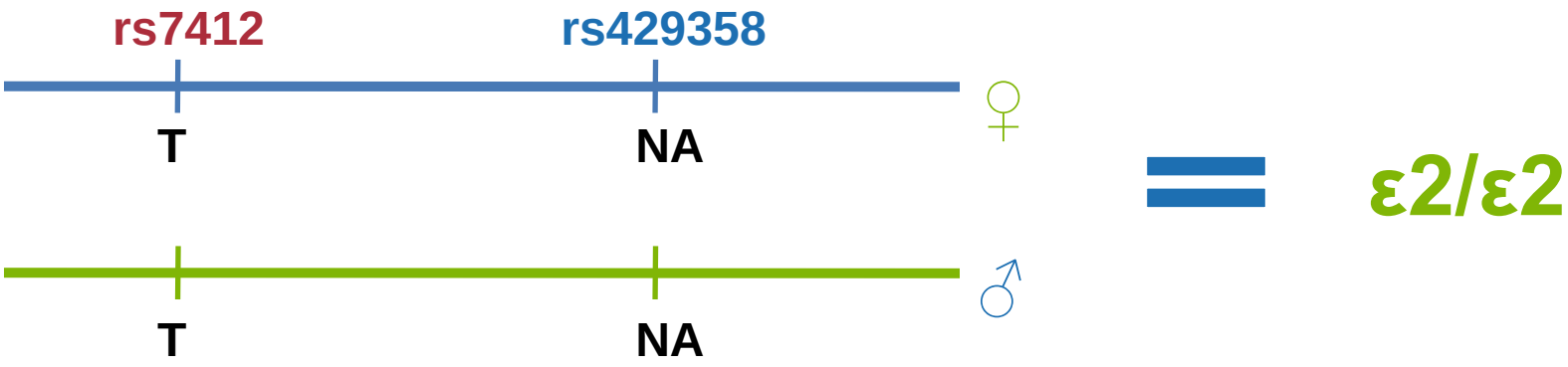
Not Observed	C	T	

Genetic Testing-What SNPs?

(2) What is the variant combination of people with TT at rs7412?



Genetic Testing-What does it mean?

- Risk associated with ε4 variant
  - The odds of developing AD increases with each copy of the ε4 variant of APOE
  - **1 copy** is associated with about **2** times increased odds
  - **2 copies** is associated with about **11** times increased odds

- However, ε4 does not tell the whole story...
  - Many people who carry the ε4 variant ***never*** develop AD.
  - more than half of the people with AD have ***no*** copies of ε4 at all.
  - Family History is a more significant factor than carrying a ε4 copy.
  - The number of ppl diagnosed increases with age. However, the residual risk decreases as an individual gets older.
  - The effect of APOE ε4 is not well-established for non-European populations.

Genetic Testing-what can you do?

- Know the symptoms
- Take care of your heart
- Exercise body and mind
- Eat Right
- Learn your family history