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

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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 $\text{Aβ40/42}$ (APP derivative)
    - Diffuse plaques ($\text{Aβ42 dominant}$)
  - **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.
MT are stabilized by the \textit{tau protein}. Mutated \textit{tau} proteins cause microtubules to collapse, and the \textit{tau} proteins clump together to form \textit{neurofibrillary tangles}.
Genetic Contribution of the Disease

**Early-Onset**
- Familial AD
  - APP mutations, trisomy 21
  - sAPPβ
  - APP
  - β-secretase
  - γ-secretase
  - Aβ
  - AICD

**Late-Onset**
- Sporadic AD
  - APOE, CLU, PICALM, CR1
  - Aβ oligomer formation
  - Amyloids, senile plaques
  - LTP impairment
  - Synaptic loss and neuronal death
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 in abnormal protein function and abnormal amyloid protein breakdown, which generates harmful amyloid plaques, a hallmark 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

[Diagram showing the genetic pathways involved in Alzheimer's disease, highlighting the role of APOE4.]
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?

<table>
<thead>
<tr>
<th>ApoE ε</th>
<th>rs429358</th>
<th>rs7412</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ε2</td>
<td>T</td>
<td></td>
<td>uncommon; possible protection</td>
</tr>
<tr>
<td>ε3</td>
<td>T</td>
<td>C</td>
<td>most common; neutral role</td>
</tr>
<tr>
<td>ε4</td>
<td>C</td>
<td>C</td>
<td>20% in population; risk variant</td>
</tr>
<tr>
<td>Not Observed</td>
<td>C</td>
<td>T</td>
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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 disequilibrium 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
Exercise!

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

**Exercise Solution:**

- **rs7412:** C
- **rs429358:** C

**Result:** ε2/ε4
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(2) What is the variant combination of people with TT at rs7412?

\[ \text{rs7412} \text{ (TT)} \quad \text{rs429358} \text{ (NA)} \]

\[ \text{♂} \quad \text{♀} \quad \varepsilon2/\varepsilon2 \]
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