Genetics of Alzheimer’s disease and other dementias

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Normal Aging vs. Dementia

• Convincing evidence is accumulating that cognitive impairment is not an inevitable part of aging. It is possible to maintain “normal” mental skills well into the 9th decade (Morris, 1999).

• Dementia results from a disease process which interacts with aging and other risk factors to cause a significant decline in mental performance.
Age is a Risk Factor for Alzheimer’s Disease (AD)
Do genes play a role in Alzheimer’s disease?

- A single gene disorder
  - Probably <1% of AD cases are caused by mutation in a single gene

- A complex disorder
  - Most cases of AD probably result from a mixture of genetic and environmental risk factors
Familial Alzheimer’s disease is a dominant trait

50% of the offspring of affected individuals develop AD
Inherited forms of Alzheimer’s disease

- Mutations in 3 genes
  - β-amyloid precursor protein (APP) on chromosome 21
  - Presenilin 1 (PS1) on chromosome 14
  - Presenilin 2 (PS2) on chromosome 1
Most mutations causing FAD are in PS1

<table>
<thead>
<tr>
<th>Gene</th>
<th># Mutations</th>
<th># Families</th>
</tr>
</thead>
<tbody>
<tr>
<td>APP</td>
<td>16 (10.39 %)</td>
<td>43 (13.52 %)</td>
</tr>
<tr>
<td>PSEN1</td>
<td>129 (83.77 %)</td>
<td>260 (81.76 %)</td>
</tr>
<tr>
<td>PSEN2</td>
<td>9 (5.84 %)</td>
<td>15 (4.72 %)</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td>318</td>
</tr>
</tbody>
</table>

From AD mutations database:
## Age at Onset overlaps for these genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Onset (range)</th>
<th>Death (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenilin 1 (n=60)</td>
<td>44.1 ± 7.8 (26-78)</td>
<td>52.7 ± 9.3 (37-89)</td>
</tr>
<tr>
<td>Presenilin 2 (n=17)</td>
<td>58.6 ± 7.0 (45-73)</td>
<td>69.9 ± 7.6 (54-80)</td>
</tr>
<tr>
<td>APP (n=17)</td>
<td>48.9 ± 6.7 (39-59)</td>
<td>61.2 ± 7.2 (46-72)</td>
</tr>
</tbody>
</table>

Causes of familial early onset AD

- **PS1 mutations** are the most common form of familial AD (FAD), may account for 50% of FAD cases
  - >160 mutations in over 200 families, age of onset 26-78yrs
- **APP** encodes precursor of amyloid in plaques
  - 25 mutations mostly in single families, age of onset 40-65yrs
- **PS2 mutations** rarest form of FAD identified
  - 10 mutations often showing wide variation in age of onset in a family (40-75yrs)
Age of onset is variable even in families carrying FAD mutations

- Colombian kindreds carrying E280A mutation in Presenilin 1
  - >20 extended families carry E280A mutation
  - 52 individuals with diagnosis of probable or definite AD
  - Mean age of onset 45.2yrs, SD 5.7yrs
  - Age of onset in these families shows wide range (35-62 yrs) suggesting that genes and/or environmental factors may influence age of onset
Two pathways of APP metabolism

- **α-secretase pathway**
  - sAPP\(\alpha\)
  - CTF\(\alpha\)
  - γ-secretase
  - p3

- **β-secretase pathway**
  - sAPPβ
  - CTFβ
  - γ-secretase
  - Aβ

- **γ-secretase**
  - generates Aβ and CTFγ

**APP**

- β
- α
- γ

- 1
- 770
β-Amyloid Precursor Protein

TEEISEV**K**MĐAEFRHD**S**GYE**V**HHQKLVFF**A**EDVGSNKGAIIGLMVG**G**VVIA**T**VIVITLVM**L**KKK
Effect of FAD mutations on Aβ levels

- Control
- βAPP Swedish mutation
- PS1 several mutations
- βAPP London mutation
- PS-2 Volga german mutation
Genetic Risk factors for sporadic Alzheimer’s disease

A complex trait

• Most cases have age of onset > 65 yrs
• 40% of cases have one or more affected first degree relatives
• Single known genetic risk factor
  – *Apolipoprotein E4*
• 50% of AD cases do not carry *APOE4* alleles
Apolipoprotein E

- Encoded by a gene on chromosome 19
- Exists as three variants: $\varepsilon_2$, $\varepsilon_3$, $\varepsilon_4$
- $APO\varepsilon_4$ increases risk for AD
- $APO\varepsilon_2$ decreases risk for AD
- Binds to A$\beta$ in cerebrospinal fluid
- Found in plaques in AD brains
**APOE4** allele distribution in early onset AD cases and controls

<table>
<thead>
<tr>
<th># of APOE4 alleles</th>
<th>Frequency of APOE4 in AD Cases</th>
<th>Frequency of APOE4 in Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>17%</td>
<td>3%</td>
</tr>
<tr>
<td>1</td>
<td>36%</td>
<td>24%</td>
</tr>
<tr>
<td>0</td>
<td>47%</td>
<td>73%</td>
</tr>
</tbody>
</table>

From: Van Duijn et al., Nat. Genet. 7: 74-78 (1994)
**APOE4 in early onset AD**

- **APOE4** is the most common known risk factor for early onset AD
  - Dose dependent increase in risk
  - 2.3 fold increase in risk with one **APOE4** allele and 8.1 fold increase for 2 **APOE4** alleles

- Among those without an **APOE4** allele cases with a family history still have higher risk
  - **APOE4** does not fully explain familial aggregation in early onset AD suggesting there are other genetic risk factors
# APOE4 and the risk for late onset AD

<table>
<thead>
<tr>
<th>APOE allele</th>
<th>AD Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>3</td>
<td>63%</td>
<td>81%</td>
</tr>
<tr>
<td>4</td>
<td>34%</td>
<td>13%</td>
</tr>
</tbody>
</table>
APOE genotype and risk for AD

- *APOE4* shows a dose dependent effect on age of onset of AD
  - Each allele reduces age of onset by 5yrs
- **Evidence for gene-environment interaction**
  - Risk for AD after severe head injury with loss of consciousness is much greater in individuals with one or more *APOE4* alleles
  - Boxers with ”punch-drunk syndrome” tend to have *APOE4* alleles
Effect of $APOE4$ allele on age of onset in a presenilin mutation family
Protective effect of *APOE2* allele on age of onset in presenilin mutation family
How does identifying deterministic mutations help?

• Clinical Utility
  – Presymptomatic diagnosis
  – Preimplantation embryo selection
  – Monitoring and early treatment

• Basic and Clinical Research
  – Greater understanding of pathogenesis of disease
  – Development of animals models
  – Development of new treatments for disease
How does knowledge of genetic risk factors help?

• Development of animals models
• Greater understanding of disease pathogenesis
• *APOE* genotyping is not recommended for presymptomatic testing or diagnosis
  – Modification of genetic risk by life-style changes or drug treatment
• Identify subgroups who respond differently to treatment (pharmacogenomics)
  – Personalize treatment
Fronto-temporal dementia

- Characterized clinically by early changes in personality or behavior that may precede memory changes or changes in speech output that may precede memory changes
  - Often accompanied by parkinsonism or motor neuron degeneration
  - No plaques, these disorders may be associated with tangles or with ubiquitin inclusions
Genetics of Frontotemporal Dementia

- FTD characterized by behavior and personality changes often with Parkinsonism often carries mutations in the “tau” gene, the protein found in tangles
- FTD characterized by language impairment and ubiquitin positive inclusions is often caused by mutations in the “progranulin” gene
Prion dementias

- Can be misdiagnosed as both AD and FTD
- Rapid course of disease (6 months-2 yrs) is common for Prion dementias (CJD)
- Familial prion dementia caused by mutations in the Prion protein gene
- Risk for sporadic prion dementia is associated with a common variant in the prion protein gene
- Prion dementia is transmissible (Scrapie in sheep, BSE in cattle, sporadic CJD in humans)
Summary

- Dementia causing diseases may be sporadic or familial
- Mutations in APP, PS1 and PS2 cause FAD
- \textit{APOE4} increases risk for AD
- 50% of AD cases have unknown genetic risk factors
- Frontotemporal dementia is caused by mutations in several genes including tau and progranulin
- Familial Prion dementias are caused by mutations in the prion protein