Dementia

- severe cognitive decline
- age related: <1% under 65
  +13% of those aged 65
  +20% of those aged 85+
- US Medicare cost/year $189 billion by 2015
  not including cost to family, friends, insurance
- 3rd leading cause of death

Alzheimer's disease (AD)
- 50% of all dementia cases
- early and late-onset types
- recent memory loss
- loss of independence, death
- extensive changes in the brain: amyloid peptide buildup, tangles of fibers, plaques

Multiple infarct dementia (MID) (vascular dementia)
- numerous small strokes
- infarcts lead to brain damage
- more abrupt onset, focal symptoms

1/3 of all dementia cases involve both AD and MID
Alzheimer’s disease

Late-onset form
- first degree relative risk = 50% (by age 85)
- twin studies indicate a moderate genetic influence:

Early-onset form
- clearly influenced by genes, runs in families in a Mendelian way, several single genes found
- only 10% of Alzheimer’s cases are early onset

Current treatments: 5 drugs slow progress for 6-12 months in ½ of those treated. 9 drugs in test.

Risk factors for late-onset AD
- all known genetic risk alleles only account for ~50% of genetic variation for AD
- expected than ~5 more risk alleles will be found candidates at 13 loci across genome (progress tracked on AlzGene database)
  small effects only – estimated sample size of +1000 needed alleles have relatively low penetrance but high prevalence

Apolipoprotein E gene chromosome 19
- associated with 50% of all AD cases
3 alleles: E2 E3 E4

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Frequency</th>
<th>Mean age of onset</th>
<th>Risk of AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>E4/E4</td>
<td>2% population</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>E4/ -</td>
<td>15%</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>no E4</td>
<td>83%</td>
<td>84</td>
<td></td>
</tr>
</tbody>
</table>

• environmental factors also play a role
## Genes associated with risk for Alzheimer's disease

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene Type</th>
<th>Onset</th>
<th>% Cases Familial</th>
<th>% Cases All</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>QTL</td>
<td>60+</td>
<td>40-50%</td>
<td></td>
<td>ApoE4</td>
</tr>
<tr>
<td>14</td>
<td>dominant</td>
<td>30-60</td>
<td>70-80%</td>
<td>5-10%</td>
<td>Presenilin 1 (membrane protein)</td>
</tr>
<tr>
<td>1</td>
<td>dominant</td>
<td>40-70</td>
<td>20%</td>
<td>2-3%</td>
<td>Presenilin 2</td>
</tr>
<tr>
<td>21</td>
<td>dominant</td>
<td>45-65</td>
<td>2-3%</td>
<td>&lt;1%</td>
<td>APP (amyloid precursor protein)</td>
</tr>
</tbody>
</table>

SORL1 gene Chr 11  lipoprotein receptor
? ApoE receptor gene
? A2M gene  macroglobulin, removes toxins

No mouse model that shows all AD characteristics

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**Diagram:**

- **Genetic:**
  - APP (chromosome 21)
  - Down's syndrome (trisomy 21)
  - PS1 (chromosome 14)
  - PS2 (chromosome 1)
  - Other genes (?)

- **Nongenetic:**
  - Toxins
  - Viruses
  - Prions
  - Low level of education
  - Head trauma
  - Environment + genes [APOE, others] + aging

**Notes:**

- PS1 = presenilin 1
- PS2 = presenilin 2

Left side: genetic factors shown are KNOWN causes
Right side: nongenetic risks are speculative – none proven
Bottom: most likely pathway to AD in general population