Monogenic vs. Complex Disorders: Isolating the molecular defects of Alzheimer’s Disease

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Monogenic
- Fragile X Syndrome
- Tay-Sachs
- Dystonia
- Hereditary Ataxias
- Wilson Disease
- Huntington Disease

Complex
- Autism
- Schizophrenia
- Epilepsy
- Alzheimer disease
- Parkinson disease
- ALS

Brain Disease
Alzheimer Disease

Monogenic
• Early Onset Alzheimer Disease (EOAD)
  • Familial
  • 5%

Complex
• Late-Onset Alzheimer Disease (LOAD)
  • Sporadic
  • 95%

Anatomy
**Pathophysiology**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Key feature</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>[Diagram of Normal]</td>
<td></td>
</tr>
<tr>
<td>Cell sickness stage</td>
<td>[Diagram of Cell]</td>
<td>Functional imaging</td>
</tr>
<tr>
<td>Histological stage</td>
<td>[Diagram of Histological]</td>
<td>Histological imaging</td>
</tr>
<tr>
<td>Cell death stage</td>
<td>[Diagram of Cell]</td>
<td>Volumetric imaging</td>
</tr>
</tbody>
</table>

Small SA, Nature Neuroscience, 2005

**Histology**

- Normal
- Alzheimer's

- Neuron
- Neurofibrillary tangles
- Amyloid plaques
**Histology**

- **Aβ peptide**
  - Soluble
  - Insoluble
  - Amyloid Plaques

- **Tau protein**
  - Neurofibrillary Tangles

**Molecular & Cell Biology**

- APP → BACE → β-cleavage → Gamma secretase → γ-cleavage → Aβ
- TGN → Endosome → ER → NUC → Lysosome → Aβ
Molecular Defects in Monogenic Disorders

Molecular Techniques:
Large-Scale Genetic Profiles

Statistical Models:
Pinpointing Genetic Defect

Single Nucleotide Polymorphisms (SNPs)

1. Law of "Segregation of Characteristics."
2. Law of "Independent Assortment."

Molecular Defects in Early-Onset AD

APP(ch21q21.3)  Presenilin1 (ch14q24.13)  Presenilin2 (ch1q31.42)
Molecular Defects in Late-Onset AD

Apolipoprotein E (APOE): ε2, ε3, ε4 (ch19q13.2)

Roberts JS, et al, J Geriatr Psychiatry Neurol, 2005

Brain Cells

Liver Cells

Genes

Gene Products
**Alzheimer’s Disease**

**Healthy**

<table>
<thead>
<tr>
<th>Twin A</th>
<th>Twin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes</td>
<td>Genes</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Gene Products</td>
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</tr>
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</table>

**Molecular Defects in Complex Disorders**

**Molecular Techniques:**
- Large-Scale Genetic Expression Profiles

**Statistical Models:**
- Pinpointing Molecular Defects

**Microarray**
Brain Microarray: Finding Needles in Molecular Haystacks
Nicole M. Lewandowski and Scott A. Small
The Journal of Neuroscience, November 3, 2005 - 23(1)

Spatial Information

Temporal Information

Spatial Information
Model-Guided Microarray Implicates the Retromer Complex in Alzheimer’s Disease

Scott A. Small, Kelly Kent, Aimir Pierce, Conrad Leung, Min Suk Kang, Hirokazu Ohada, Lawrence Honig, Jean-Paul Vonsattel, and Tae-Weon Kim

Annals of Neurology, 2005
A. Manipulate molecules

B. Manipulate molecules

C. Test for polymorphisms

Aβ levels

Memory loss, synaptic dysfunction, Aβ levels

Risk for developing Alzheimer's disease

Cell Culture

Mouse Models

Human Disease

Risk for Late-Onset Alzheimer’s Disease
Model-Guided Microarray Implicates the Retromer Complex in Alzheimer’s Disease

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