ApoE Genotype Directed Drug Repositioning and Combination Therapy for Alzheimer’s Disease

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UCSF, the Gladstone Institutes
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The Multifactorial Nature of Alzheimer’s Disease

[Diagram showing the multifactorial nature of Alzheimer's Disease, with nodes for Aβ, ApoE4, and Tau, and multiple connections between them.]

[Text along the right side of the diagram: Alzheimer’s Disease, Alzheimer’s Disease, Alzheimer’s Disease, and Alzheimer’s Disease.

[Color coding: Aβ in blue, ApoE4 in red, and Tau in green.]

[Red and blue arrows connecting the nodes, indicating interactions between Aβ, ApoE4, and Tau.]
The Multifactorial Nature of Alzheimer’s Disease
(Targeting/Removing One Factor Would not Work Well)
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The Network Concept of Drug Targets for Alzheimer’s Disease

One or more therapeutic agents to perturb entire molecular networks away from the disease states.
Four Major Publically Available Transcriptional Studies in the Temporal Cortex of Control and AD Patients with ApoE Genotype Information (Total N = 956)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Online Source</th>
<th>Data Source</th>
<th>n</th>
<th>ApoE Genotype</th>
<th>Brain Region</th>
<th>Analytic Method</th>
<th>Quality Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSE15222a</td>
<td>GEO expression Omnibus</td>
<td>U. Miami Myers Lab</td>
<td>240</td>
<td>Yes</td>
<td>Temporal cortex</td>
<td>Illumina, microarray</td>
<td>Yesa</td>
</tr>
<tr>
<td>Syn3157255b</td>
<td>Sage synapse Amp-AD</td>
<td>UFL-MAYO-ISB (MayoEGWAS)</td>
<td>399</td>
<td>Yes</td>
<td>Temporal cortex</td>
<td>Illumina, whole genome DASL</td>
<td>Yesb</td>
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<tr>
<td>Syn5550404c</td>
<td>Sage synapse Amp-AD</td>
<td>UFL-MAYO-ISB (MayoRNA-seq)</td>
<td>192</td>
<td>Yes</td>
<td>Temporal cortex</td>
<td>RNA-Seq, HiSeq 200</td>
<td>Yes</td>
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<tr>
<td>Syn3157743d</td>
<td>Sage synapse Amp-AD</td>
<td>Mt. Sinai Brain Bank</td>
<td>125</td>
<td>Yes</td>
<td>Temporal cortex</td>
<td>RNA-Seq 2500, HiSeq 2500</td>
<td>Yes</td>
</tr>
</tbody>
</table>

c. For Syn5550404 (MayoRNA-seq), temporal lobar brain samples were taken from the Mayo Clinic Brain Bank and Banner Sun Health Research Institute.
d. For Syn3157743 (MSBB), temporal cortex samples were taken from the Mt. Sinai Brain Bank.
Precision Medicine is Paramount to Accuracy in Mapping Disease Networks

Genotype Enrichment in Datasets

- GSE15222 Ctrl
- MayoEGWAS Ctrl
- GSE15222 AD
- MayoEGWAS AD

Legend:
- E3/3
- E3/4
- E4/4
First Step: Identifying ApoE Genotype-Specific Gene Expression Signatures of Alzheimer’s Disease

Gene Expression Microarray or RNA-Seq Dataset-A

Gene Expression Microarray or RNA-Seq Dataset-B

Combine Shared Genes

Batch Correction

Genotype Separation

E3/E3

E3/E4

E4/E4

Analysis of Differentially Expressed Genes
ApoE Genotype-Specific Gene Expression Signatures of Alzheimer’s Disease (N=639)

Sample Numbers

- **E3/E3**
  - AD: 106
  - CTRL: 236

- **E3/E4**
  - AD: 147
  - CTRL: 69

- **E4/E4**
  - AD: 46
  - CTRL: 7

**Upregulated Genes**
- E3/E3: 295
- E3/E4: 43
- E4/E4: 142

**Downregulated Genes**
- E3/E3: 186
- E3/E4: 7
- E4/E4: 22
ApoE Genotype-Specific Gene Expression Signatures of Alzheimer’s Disease (N=639)

Dysregulated Pathways in ApoE4/4 AD

E4/E4
AD  CTRL
46  7

E3/E4
AD  CTRL
147 69

E3/E3
AD  CTRL
106 236

Dysregulated
Pathways in
ApoE4/4 AD

<table>
<thead>
<tr>
<th>Ingenuity Canonical Pathways</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate Dependent Acid Resistance</td>
<td>0.000200</td>
</tr>
<tr>
<td>GABA Receptor Signaling</td>
<td>0.000437</td>
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<tr>
<td>Coagulation System</td>
<td>0.001480</td>
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<tr>
<td>cAMP-mediated signaling</td>
<td>0.001550</td>
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<tr>
<td>Neuroinflammation Signaling Pathway</td>
<td>0.001740</td>
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<tr>
<td>Glutamate Degradation III (via 4-aminobutyrate)</td>
<td>0.001950</td>
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<tr>
<td>G-Protein Coupled Receptor Signaling</td>
<td>0.002040</td>
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<tr>
<td>G-alpha-s Signaling</td>
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<tr>
<td>IL-12 Signaling and Production in Macrophages</td>
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<tr>
<td>VDR/RXR Activation</td>
<td>0.005010</td>
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<tr>
<td>Synaptic Long Term Depression</td>
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<tr>
<td>Pathogenesis of Multiple Sclerosis</td>
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<tr>
<td>Glutamate Receptor Signaling</td>
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<td>Phagosome Formation</td>
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<td>Cholesterol Biosynthesis I</td>
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<tr>
<td>Cholesterol Biosynthesis II (via 24,25-dihydranolasterol)</td>
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<tr>
<td>Cholesterol Biosynthesis III (via Desmosterol)</td>
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<td>Agranulocyte Adhesion and Diapedesis</td>
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<td>Mechanisms of Viral Exit from Host Cells</td>
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<td>NRF2-mediated Oxidative Stress Response</td>
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<td>Role of Hypercytokinemia/hyperchemokininemia in the Pathogenesis of Influenza</td>
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<td>Tight Junction Signaling</td>
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<td>Cell Cycle: G2/M DNA Damage Checkpoint Regulation</td>
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<td>CCR3 Signaling in Eosinophils</td>
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<td>L-serine Degradation</td>
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<tr>
<td>N-acetylglucosamine Degradation I</td>
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<tr>
<td>Factors Promoting Cardiogenesis in Vertebrates</td>
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<tr>
<td>Actin Cytoskeleton Signaling</td>
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</tbody>
</table>
Drug Repositioning Pipeline

Gene Expression Signatures of AD

Drug Repositioning with Full Gene Signature
CMAP Compound Library

a

b

Study 1
Control 1
Control 2
Control 3
AD 1
AD 2
AD 3

Study 2
Control 4
Control 5
Control 6
AD 4
AD 5
AD 6

Microarray

C

Drug
Signature

gene 1

gene 2

gene 3

gene 4

gene 5

gene 6

D

Opposite Drug Signature

CMAP Score

Predicted as a therapeutic agent
Precision Medicine and Combination Therapy of Repurposed Drugs based on ApoE Genotype-Specific Gene Expression Signatures of AD

Drug A
- Unique E3/E3 DE Gene Signature of AD
- E4/E4

Drug B
- E3/E3 and E4/E4 Shared DE Gene Signature of AD
- E3/E3
- E4/E4

Drug C
- Unique E4/E4 DE Gene Signature of AD
- E3/E3
- Unique E4/E4 Signature

Treat E3/E3 AD Patients
Treat E4/E4 AD Patients

DE: Differentially Expressed
Conclusions and Further Directions

• Network approach to drug targeting to treat complex disease
• Precision medicine is paramount to efficacious targeting of disease networks
• Developing unique and combinatorial precision medicine-led methods for drug repositioning
• Currently testing lead compounds
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