Alzheimer's Disease Apolipoprotein Pathology for Treatment Elucidation and Development

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The Biomedical Research Centre Network for Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, Spain.

on behalf of ADAPTED
Project Objectives

1. **Increased APOE understanding**: Clarification of the role of APOE as a risk factor in the development of AD
   - unbiased
   - human focus
   - leveraging current technologies, e.g. large data sets, -omics, iPSC

2. Identification of promising entry points (*targets*) for the treatment of AD

3. Generation and validation of selected high value *APOE-related model systems*

4. Uncover the basic scientific evidence required to progress the development of a *stratified* approach
Project Specifics

Total budget, duration and current status

- Committed EFPIA in-kind contribution: € 3 million
- IMI-JU funding: € 3.5 million
- 3 year project: Oct 1, 2016 - Sept 30, 2019

Project Participants & Organization

- Project jointly led by
  - Fundació ACE (Institut Català de Neurociències Aplicades, Barcelona (coordinator)
  - AbbVie (leader)
- 3 EFPIA participants (AbbVie, Janssen and Biogen)
- 10 Academic/non-profit research organizations/SMEs
- 6 Countries (Belgium, Germany, Netherlands, Spain, UK, USA)
- 5 Work Packages
WP1 - Consortium Management & Governance

WP2 – APOE Models
LEAD: CSIC/ABBVIE

WP3 – APOE Pathways and Neurodegeneration
LEAD: EMC/JANSSEN

WP4 – APOE and AD Risk Factor Validation
LEAD: UKB/BIOGEN

WP5 – Data & Knowledge Management
LEAD: CAEBi

→ Integral part:
APOE stratified analysis and integration of human OMICS data

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115975. This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations
APOE stratified analysis and integration of human OMICS data

Differences by disease status

- AD vs controls
- AD vs controls
- AD vs controls

Differences by ApoE status:

- ApoE2
- ApoE3
- ApoE4

- AD cases
- Controls
- all

[Yugi et al (2016), Trends in Biotechnology]
Stratified GWAS analysis on AD status:
• in two stages (stage I and stage II)
• In total 27,841 samples: ApoE2:2447, ApoE3 14,404, ApoE4: 10,990
• adjusted gender, PMI, age and race

Significant loci of combined analysis (p-value(Stage I)<0.001, p-value(Stage II)<0.05 and p-value(Stage I+II)<0.0001):
• ApoE2: 1 locus
• ApoE3: 10 loci
• ApoE4: 6 loci

Manhattan plot of ApoE3 GWAS (stage I and II)
Filtered for maf >0.5
Integrative analysis - Scoring
• robust rank aggregation (RRA) used to integrate ranked gene lists from the GWAS metaanalysis, the brain and blood expression analysis
• genes were given a final rank according to the calculated RRA scores sorted in ascending order

Pathway analysis:
• performed on top 200 genes scored by RRA with WebGestalt
• Immune pathways were enriched in top genes from ApoE2 and ApoE4 stratum

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Network analysis to investigate genotype specific processes

Co-Expression network analysis:

- performed for the largest gene expression data set (ROS/MAP study) for cases and controls
  - Most co-expression modules are preserved in case and controls
  - few modules show poor evidence of preservation between co-expression in controls and cases
  - are enriched for immune related pathways
  - include genes that are differentially expressed between cases with ApoE2 and cases with ApoE4
Looking for therapeutic entry points for Alzheimer's disease: lessons learned from agnostic trans-co-regulatory network analyses of APOE, TREM2, PLCG2 and ABI3 loci.

Table 1: Top ten pathways associated to AD risk genes agnostic trans-coregulatory networks

<table>
<thead>
<tr>
<th>geneset</th>
<th><strong>Top 10 APOE</strong> co-regulated pathways</th>
<th>Enrichment</th>
<th>FDR p-value</th>
<th>geneset</th>
<th><strong>TOP 10 TREM2</strong> co-regulated pathways</th>
<th>Enrichment</th>
<th>FDR p-value</th>
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<tr>
<td>GO: 0072376</td>
<td>protein activation cascade</td>
<td>20,09</td>
<td>4.34E-07</td>
<td>GO: 0002683</td>
<td>negative regulation of immune system process</td>
<td>8,29</td>
<td>1.17E-05</td>
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<td>GO: 0006959</td>
<td>humoral immune response</td>
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<td>9.41E-06</td>
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<td>activation of immune response</td>
<td>6,56</td>
<td>2.17E-05</td>
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<td>GO: 0050727</td>
<td>regulation of inflammatory response</td>
<td>5,99</td>
<td>1.53E-03</td>
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<td>regulation of cell activation</td>
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<td>GO: 1901342</td>
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<td>response to inorganic substance</td>
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<td>GO: 0002253</td>
<td>activation of immune response</td>
<td>4,08</td>
<td>7.95E-03</td>
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<td>protein activation cascade</td>
<td>15,20</td>
<td>2.04E-03</td>
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<td>GO: 0002526</td>
<td>acute inflammatory response</td>
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<td>9.44E-03</td>
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<td>GO: 0007568</td>
<td>aging</td>
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<td>1.29E-02</td>
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<td>GO: 1901565</td>
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<td>regulation of cell activation</td>
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<td>GO: 0002683</td>
<td>negative regulation of immune system process</td>
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<td>0</td>
<td>GO: 0006909</td>
<td>phagocytosis</td>
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<td>6.43E-02</td>
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<td>GO: 0002976</td>
<td>negative immunity effect on effector process</td>
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<td>0</td>
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<td>homeostasis of number of cells</td>
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<td>0</td>
<td>GO: 0033627</td>
<td>cell adhesion mediated by integrin</td>
<td>43,55</td>
<td>7.05E-02</td>
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</tbody>
</table>

Kleineidam et al. (manuscript in preparation)

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**Figure 1**: Venn diagram. Shared co-regulated networks of genes observed in four AD risk loci. APOE-PLCG2 (n=43) and APOE-PLCG2-TREM2 (n=21) gene sets were selected for additional enrichment analyses.

**Figure 2**: STRING results only using common genes observed in APOE, PLCG2 and TREM2 agnostic coregulatory networks. FDR p-value=0. Top Pathway predicted was complement activation (FDR p-value=1.09E-11, proteins in red)

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Thanks for your attention

Questions?

Ideas?