Gene Therapy in Alzheimer's Disease: Understanding the Role of Apolipoprotein E in Late Onset Alzheimer's Disease

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Background

What is Alzheimer's Disease (AD)?
- A progressive neurodegenerative disease that causes memory loss and cognitive decline
- Late onset Alzheimer's disease (LOAD) is the most common form (affects people ages 65 and older)
- Pathological hallmarks of AD are amyloid plaques and neurofibrillary tangles, associated with amyloid-β protein clustering and tau protein misfolding respectively

Why Study It?
- AD affects nearly 6 million people in the U.S. and is projected to affect 14 million by 2050
- Causative factors and the mechanism behind its onset and progression remain unknown; no cure currently exists

The APOE gene can modify your risk of developing Alzheimer’s
- APOE ε4 has been identified as the strongest and most reproducible genetic risk factor for LOAD
- APOE has 3 protein variants (isoforms) that vary by a single nucleotide in two possible positions in their DNA sequence, resulting in the coding of different amino acids in the protein

<table>
<thead>
<tr>
<th>Isoform</th>
<th>Frequency</th>
<th>LOAD Risk</th>
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<tbody>
<tr>
<td>ε4 (R112, R158)</td>
<td>Less common (14%)</td>
<td>Higher (risk)</td>
</tr>
<tr>
<td>ε3 (C112, R158)</td>
<td>Most common (79%)</td>
<td>Normal (neutral)</td>
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<tr>
<td>ε2 (C112, C158)</td>
<td>Rare (4%)</td>
<td>Lower (resilience)</td>
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Methods

The hiPSC-derived neurons showed differences in nuclear envelope markers when comparing across the different isogenic lines

Age-Related Phenotypes
- Characterization for the nuclear envelop markers for Lamin A/C (top) and Lamin B1 (bottom)

AD-Related Phenotypes
- APOE ε4 hiPSC-derived neurons show increased levels of Ab40, Ab42, and lower levels of total tau and APOE

Our Hypothesis

Our data suggests a role of APOE in the maintenance of the nuclear envelope integrity that may lead to alterations in the cell homeostasis and cause neuronal loss.

Conclusion

We conclude our model provides a strong & malleable system for evaluating novel therapeutic gene therapy approaches in the APOE gene.