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

Angela Wei[1,2], Dominic Tringali[1,2], Gabriella MacDougall[1,2], Ashley Kilgore[1,2], Ornit Chiba-Falek[1,2]

[1]Division of Translational Brain Sciences, Department of Neurology, Duke University Medical Center, Durham, NC 27710, USA; [2]Center for Genomic and Computational Biology, Duke University Medical Center, Durham, NC 27710, USA

Duke UNIVERSITY | BASS CONNECTIONS
Brain & Society

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?

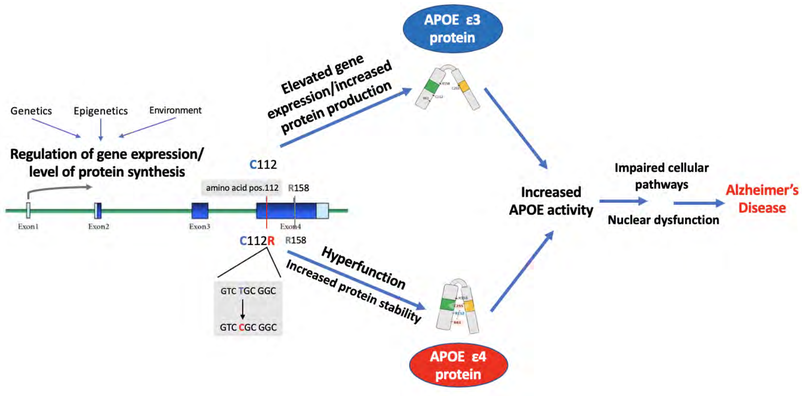
- AD affects nearly 6 million people in the U.S. and is projected to affect 14 million by 2050
- Causative factors and the mechanism behind its onset and progression remain unknown; no cure currently exists

The APOE gene can modify your risk of developing Alzheimer's

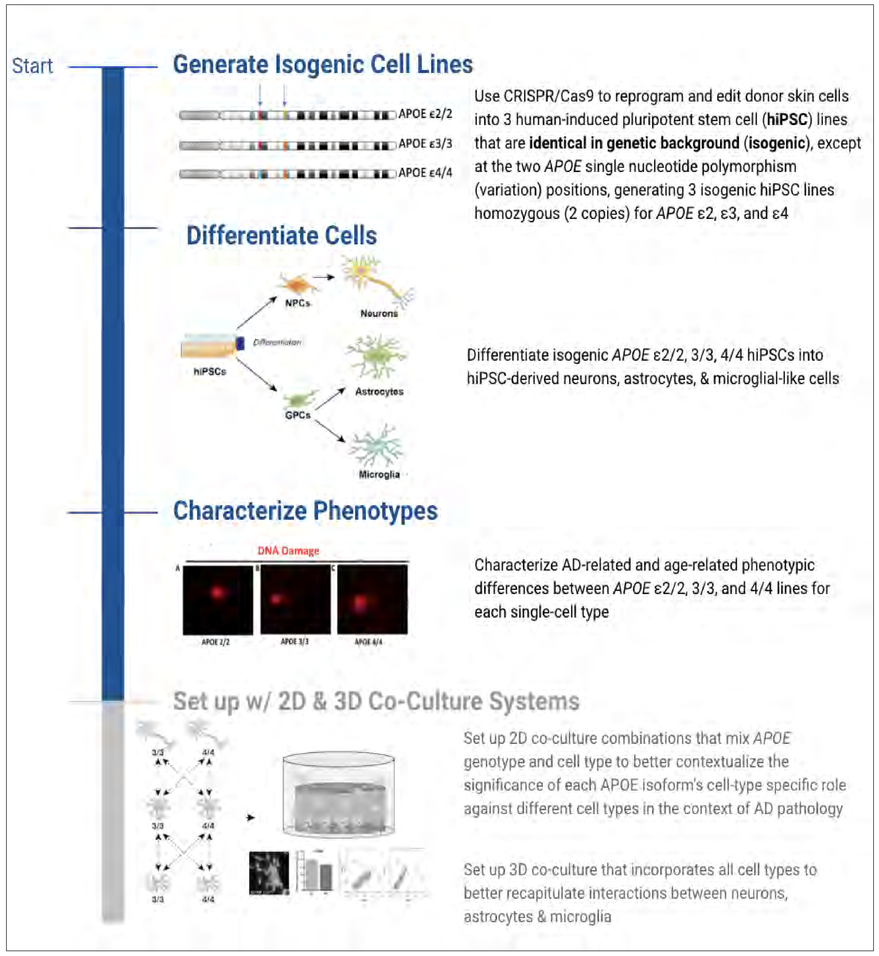
- *APOE* ε4 has been identified as the strongest and most reproducible genetic risk factor for LOAD
- *APOE* has 3 protein variants (isoforms) that vary by a single nucleotide in two possible positions in their DNA sequence, results in the coding of different amino acids in the protein

Isoform	Frequency	LOAD Risk	
ε4 (R112, R158)	Less common (~14)	Higher (risk)	1 copy= 3-4 x
			2 copies = 8-12 x
ε3 (C112, R158)	Most common (~79)	Normal (neutral)	
ε2 (C112, C158)	Rare (~4)	Lower (resilience)	

Our Hypothesis



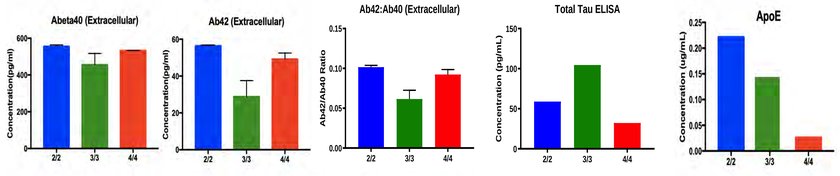
Methods



Results

AD-Related Phenotypes

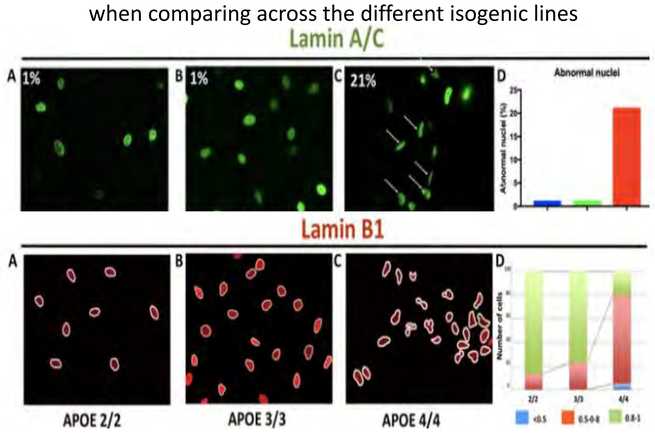
APOE ε4 hiPSC-derived neurons show increased levels of Ab40, Ab42, and lower levels of total tau and APOE



Quantification of secreted Ab40, Ab42, total tau, and APOE

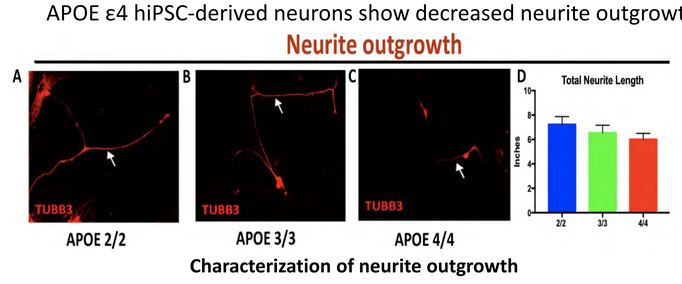
Age-Related Phenotypes

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



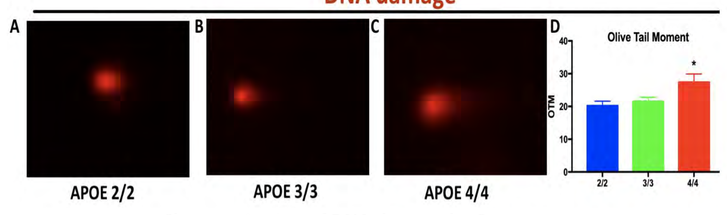
Characterization for the nuclear envelop markers for Lamin A/C (top) and Lamin B1 (bottom)

APOE ε4 hiPSC-derived neurons show decreased neurite outgrowth



Characterization of neurite outgrowth

APOE ε4 hiPSC-derived neurons show increased DNA damage



Characterization of DNA damage by Comet assay

Conclusion

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.

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