APOE4 impairs myelination via cholesterol dysregulation in oligodendrocytes

Dissecting mechanisms of APOE4 risk using the ROSMAP cohort

Joel Blanchard, Leyla Akay, Jose Davila, Djuna von Maydell

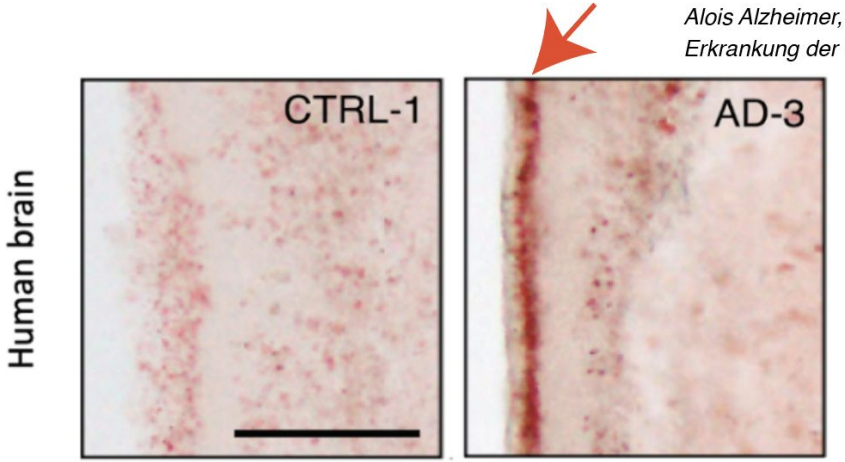
Tsai & Kellis labs

Lipid dyshomeostasis is a key feature of AD

"..., daneben zeigen viele Gliazellen große Fettsäcke."

Glial cells had accumulated large lipid droplets.

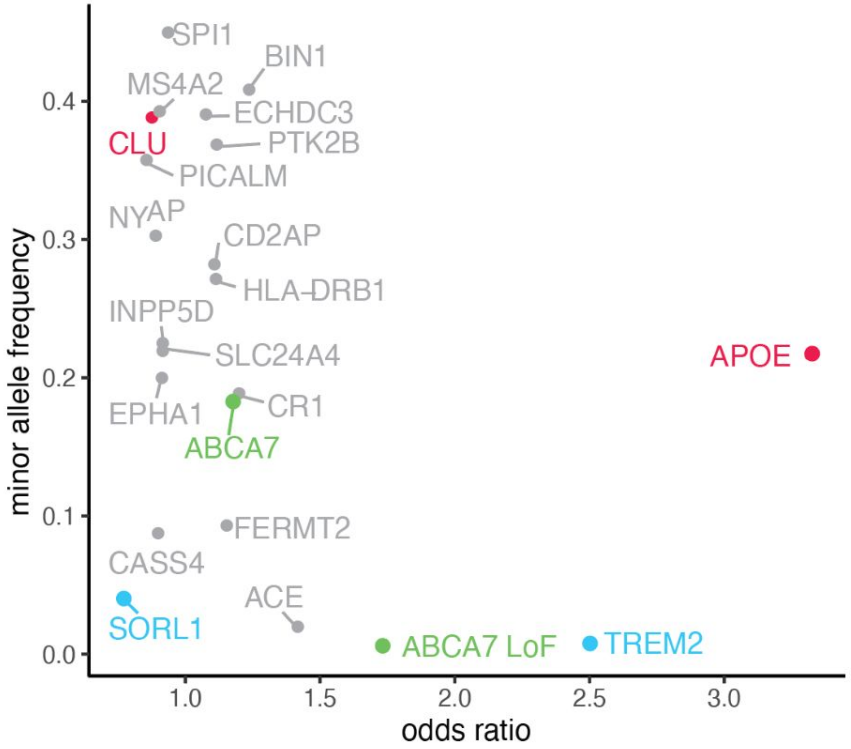
Alois Alzheimer, 'Uber eine eigenartige Erkrankung der Hirnrinde' (1906)

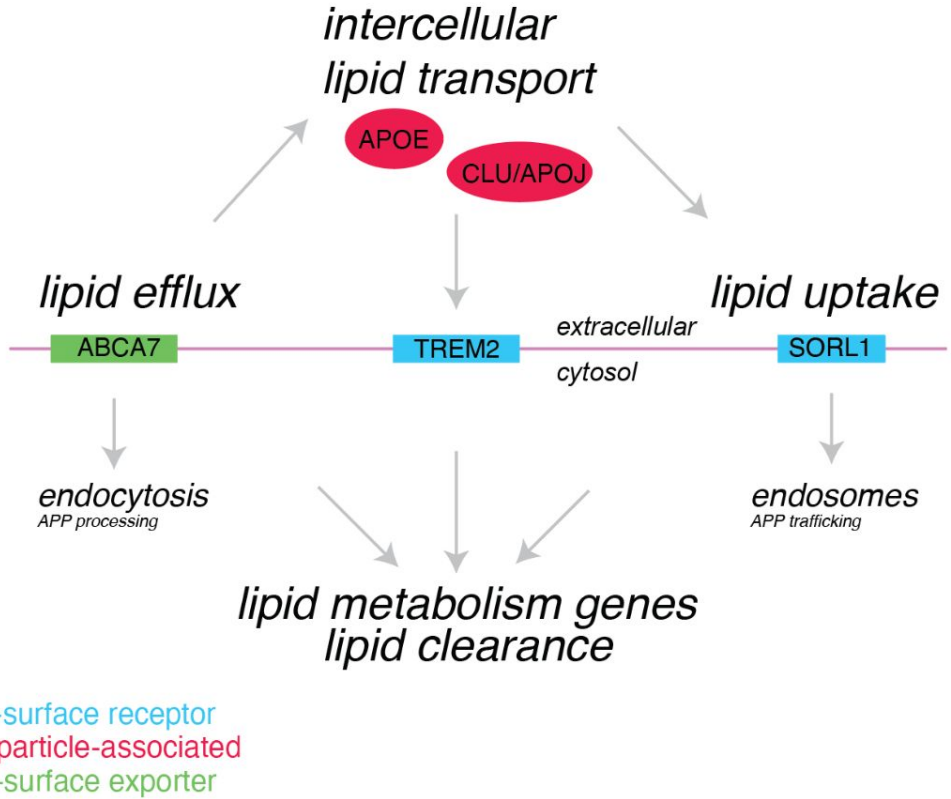


Hamilton et al, Cell Stem Cell (2015)

Top right: Kunkle *et al*, Nature Genetics (2019)

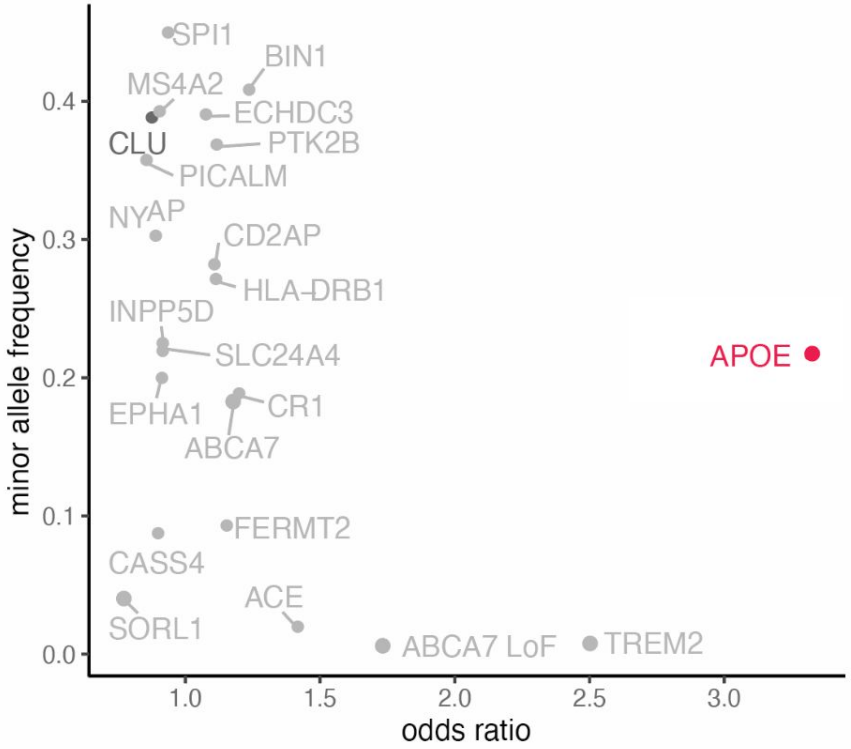
Genetic Risk Variants Implicate Lipid Dyshomeostasis in AD Etiology

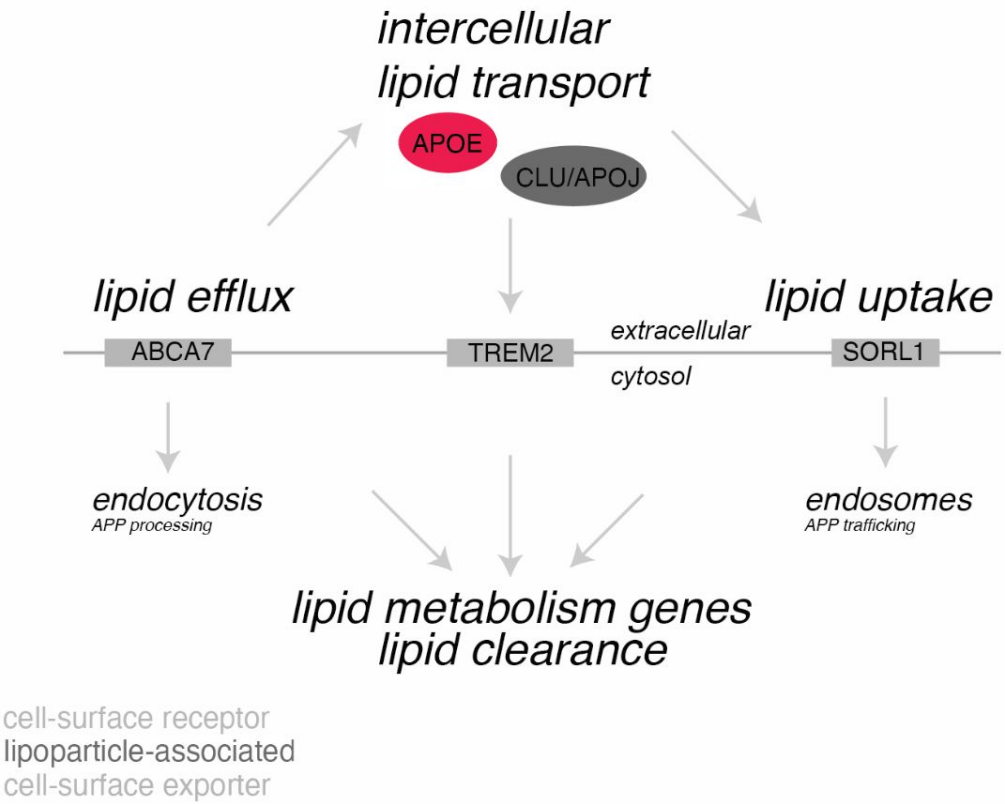




Adapted from Kunkle *et al*, Nature Genetics (2019)

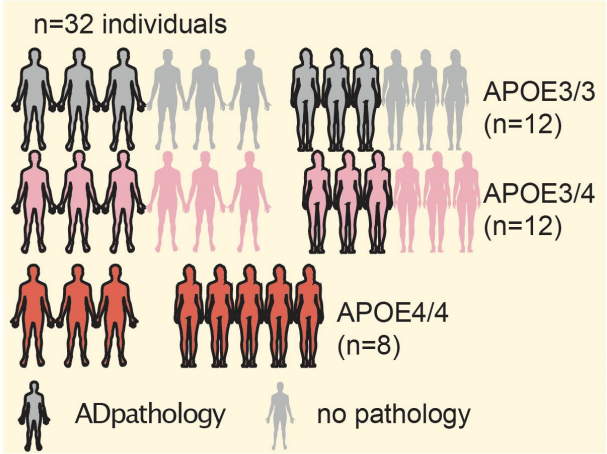
APOE4 is the Strongest Genetic Risk Factor for AD

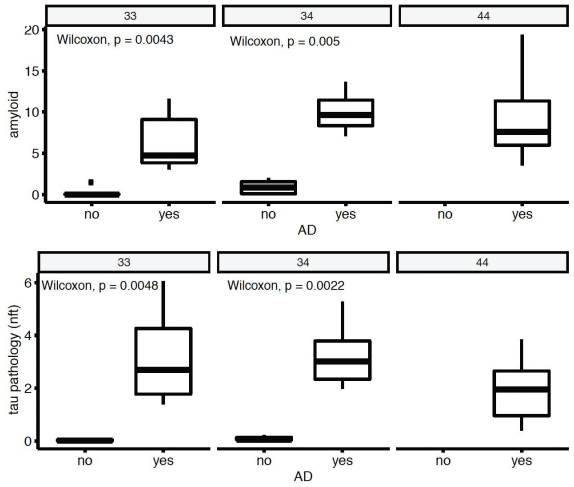


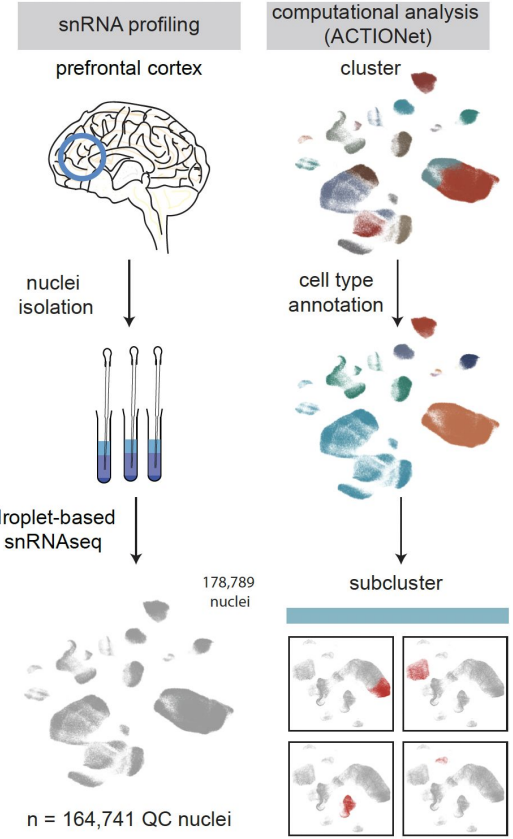


Adapted from Kunkle *et al*, Nature Genetics (2019)

Single-Nuclear Transcriptomic Profiling of APOE4 Post-Mortem Human Brains

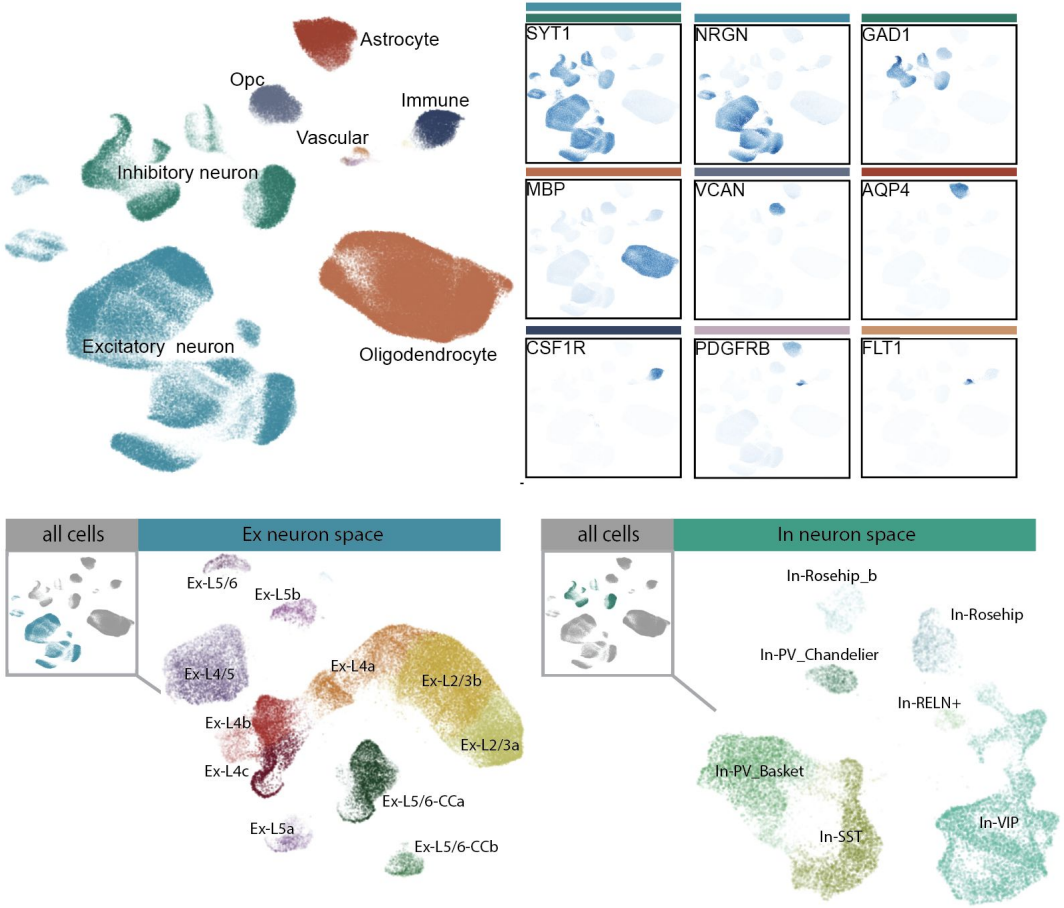




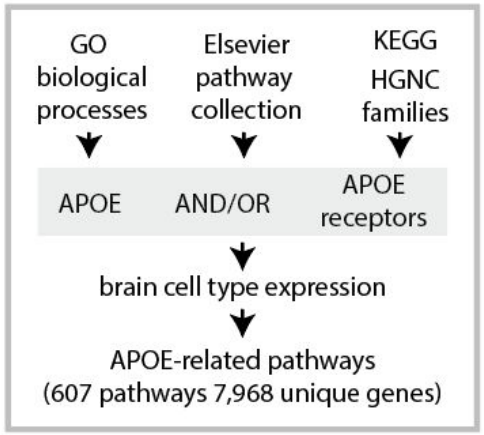


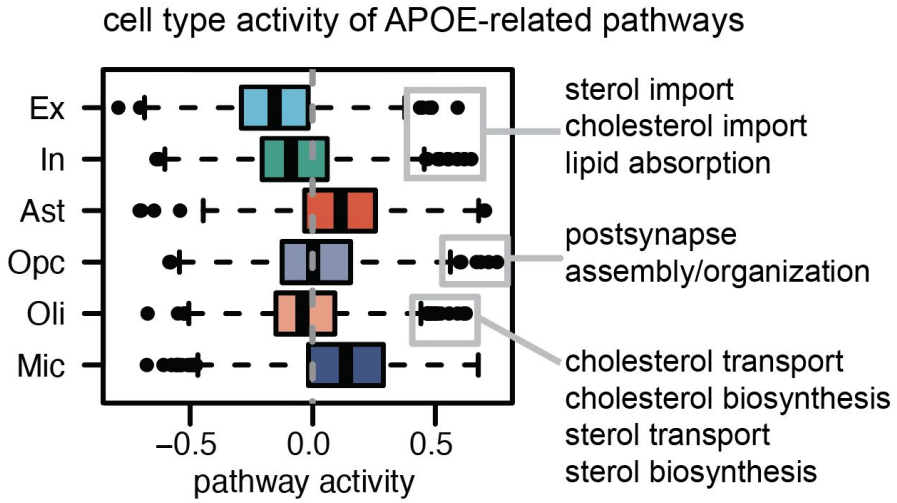
Blanchard, Akay, Davila-Velderrain, von Maydell *et al.*, submitted

snRNAseq Captures Cellular Diversity of the Pre-Frontal Cortex

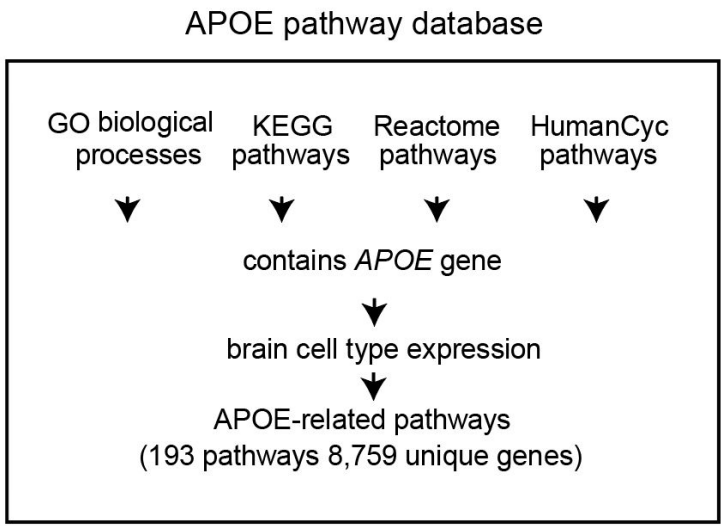


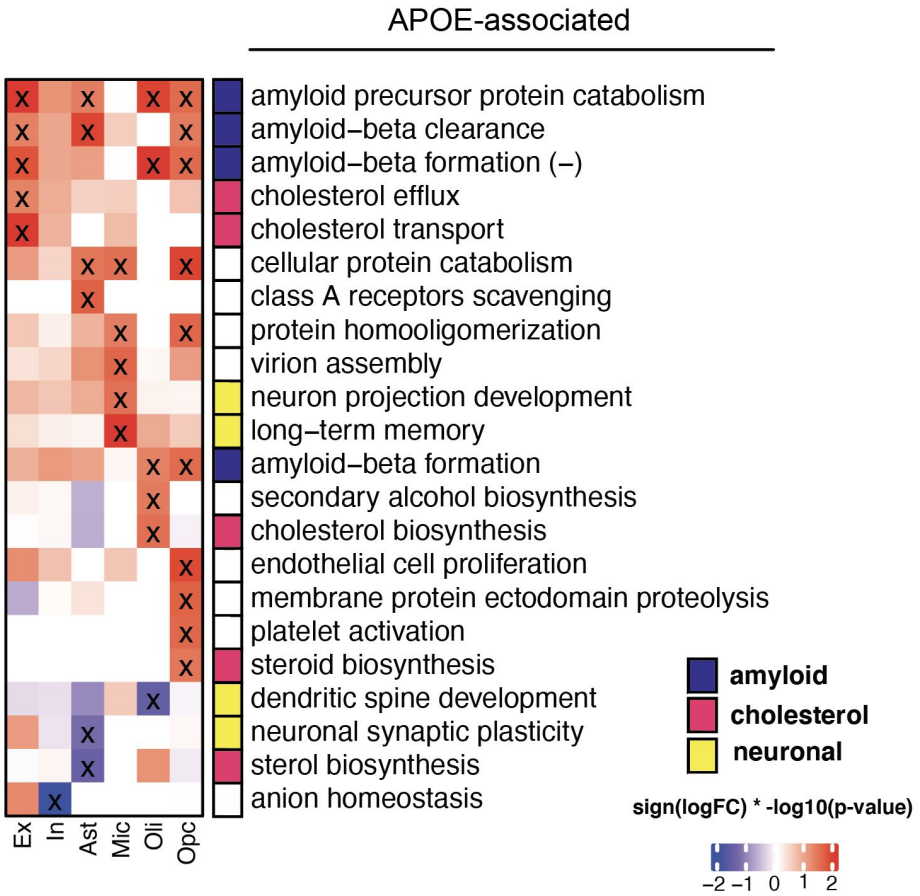
Distinct APOE-related pathways are active in multiple cell types





Cholesterol-related pathways are frequently perturbed in APOE4





Blanchard, Akay, Davila-Velderrain, von Maydell *et al.*, submitted

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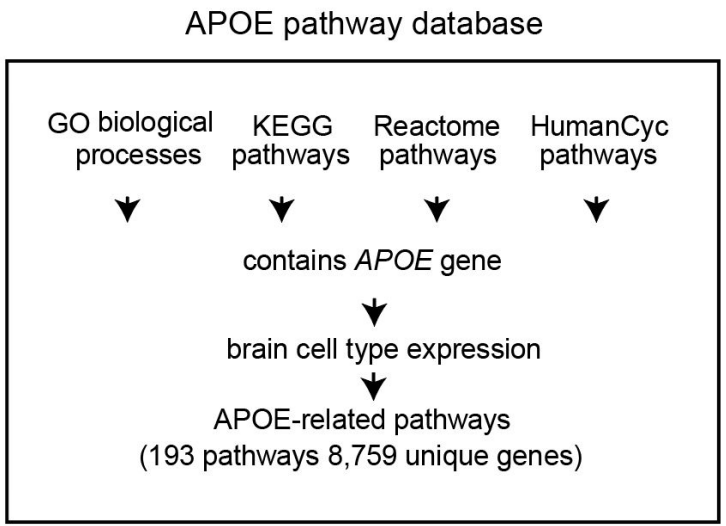

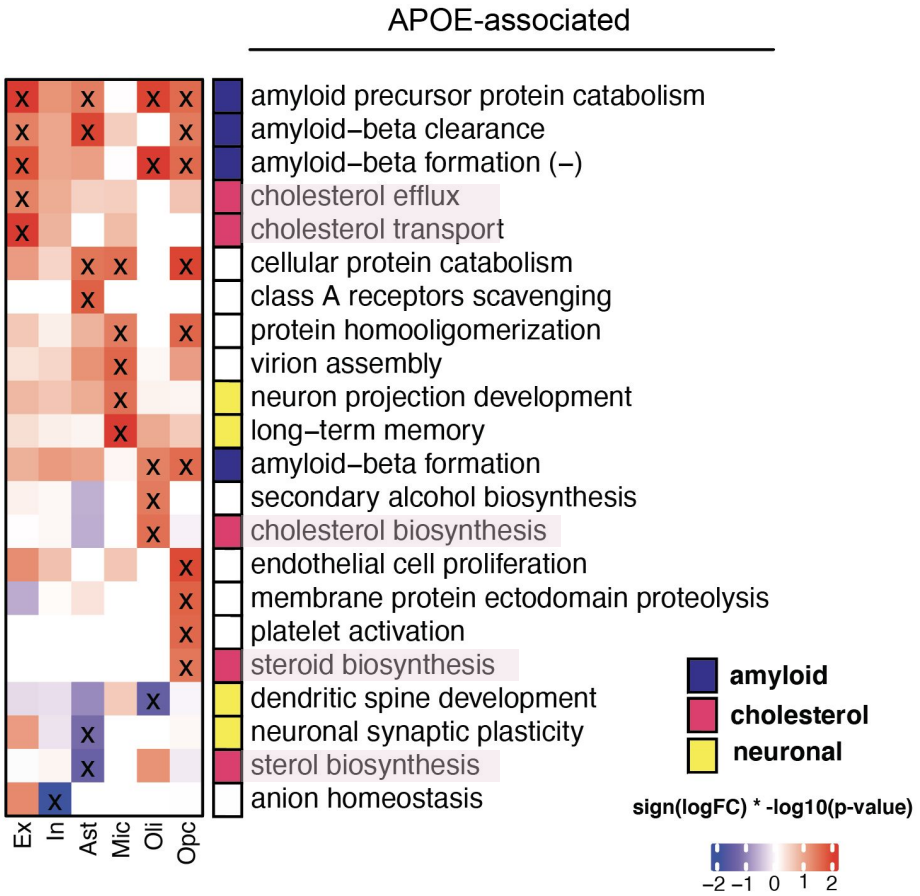

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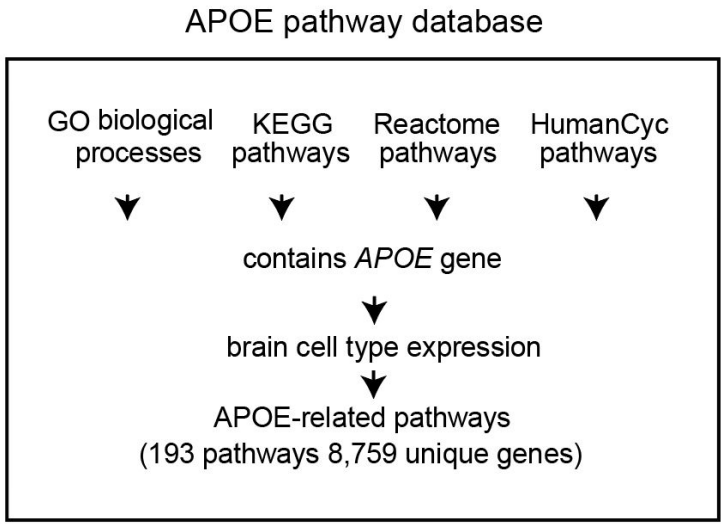
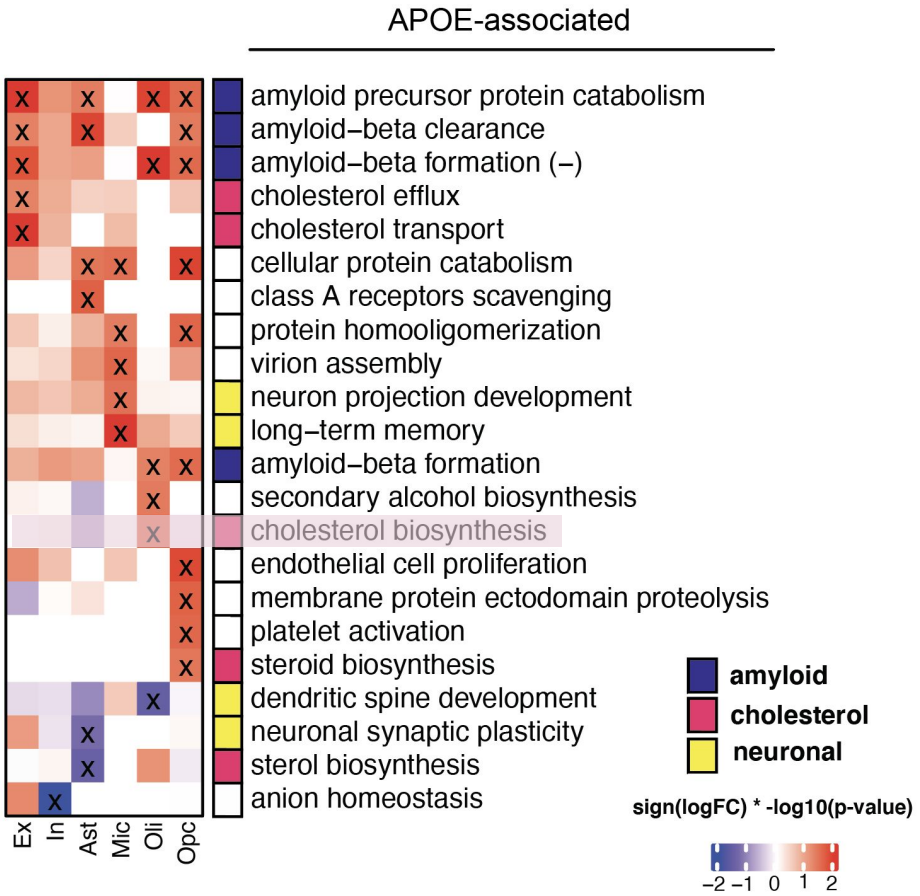
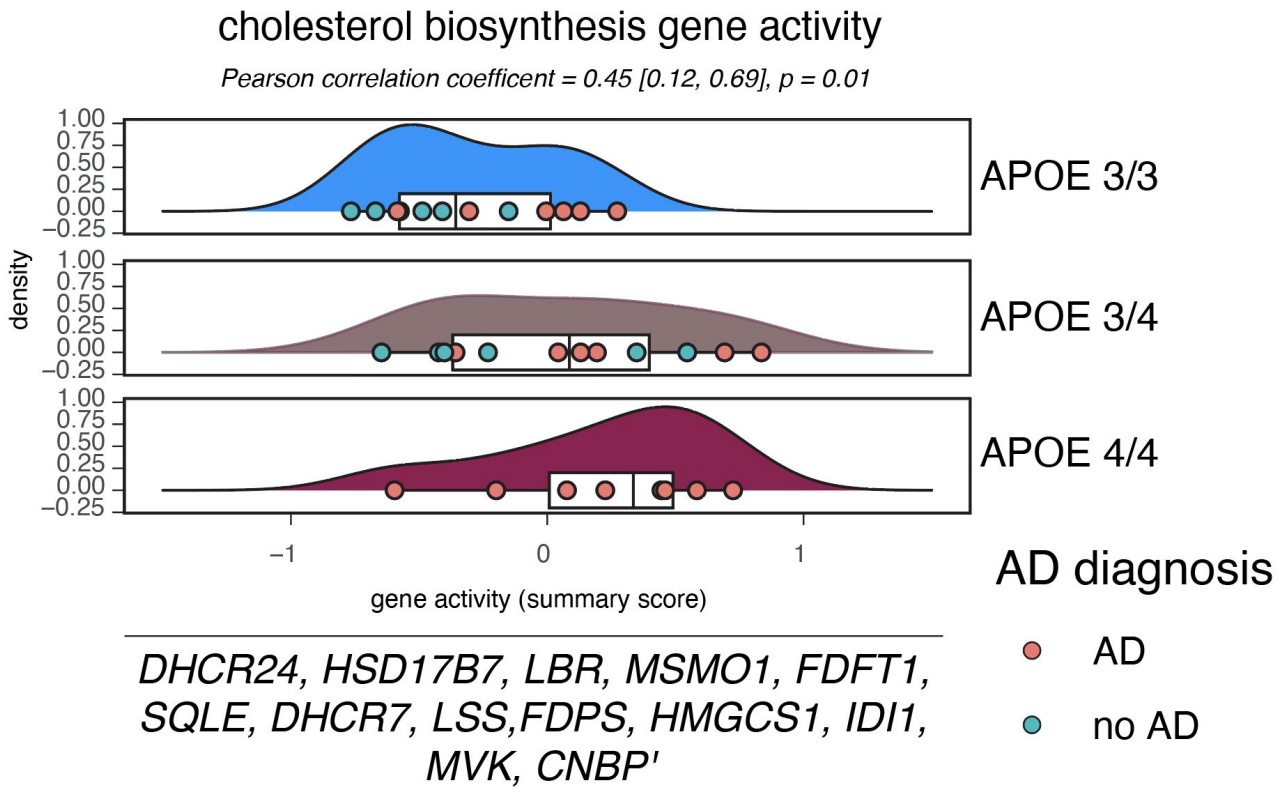




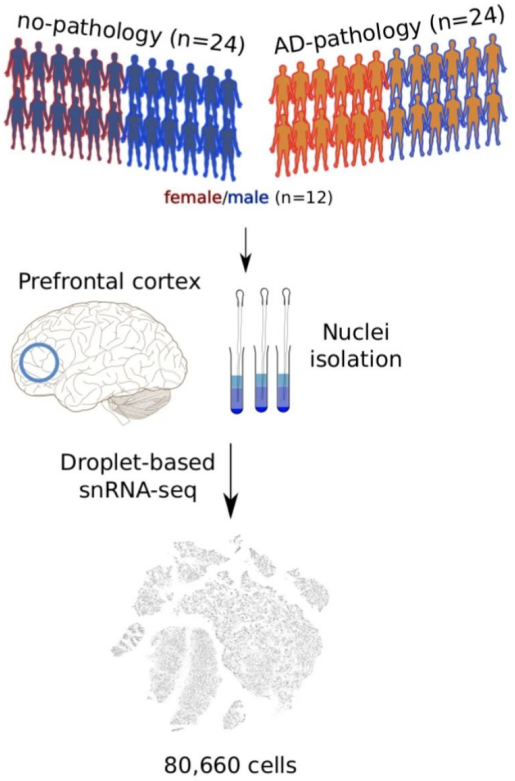
Blanchard, Akay, Davila-Velderrain, von Maydell *et al.*, submitted

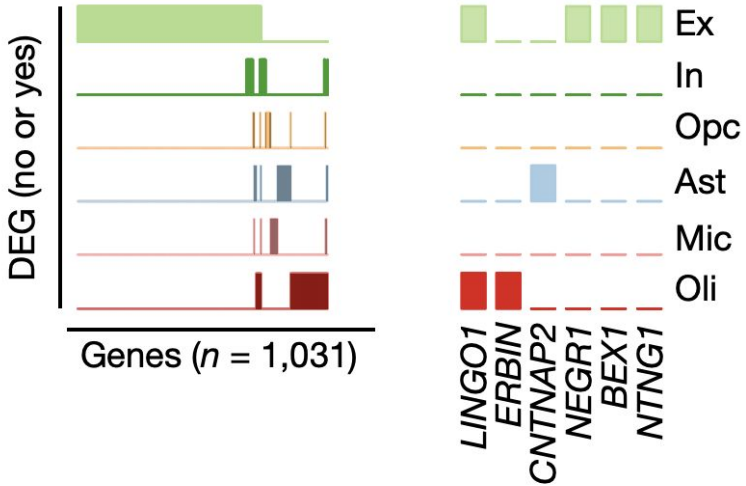
Perturbation of cholesterol biosynthesis genes in APOE4 Oligodendrocytes



Blanchard, Akay, Davila-Velderrain, von Maydell *et al.*, submitted

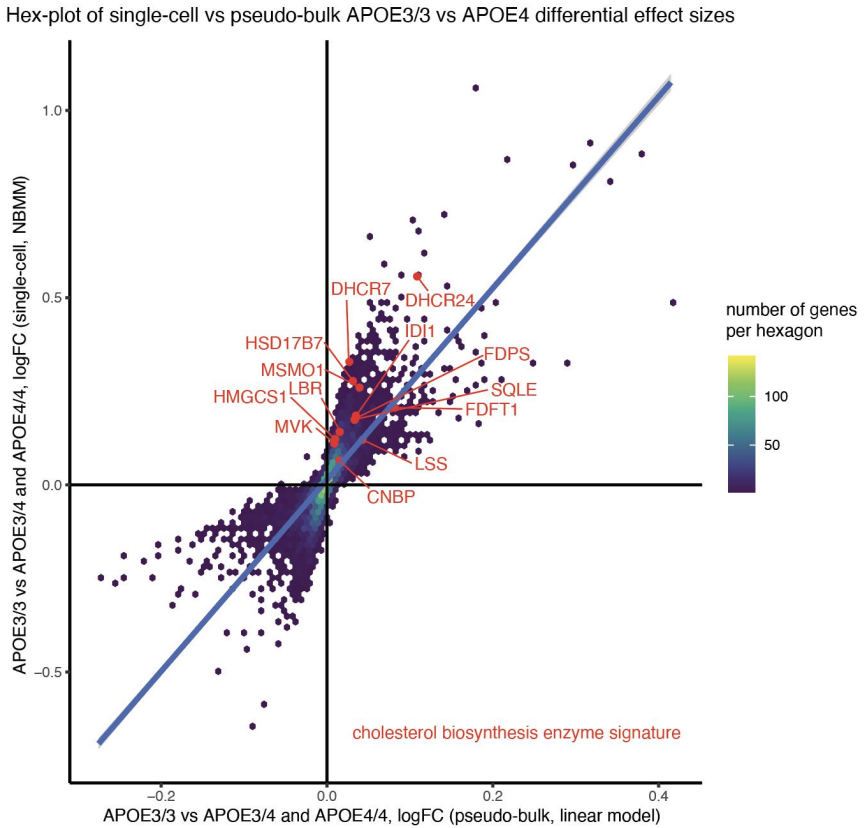
Previous Work Suggesting Altered Myelination in AD Oligodendrocytes

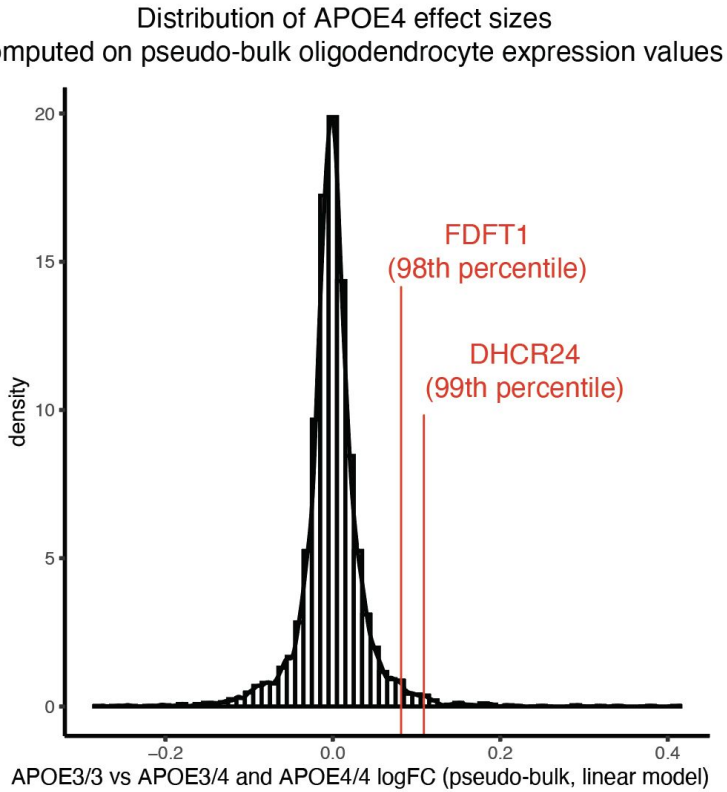




Mathys, Davilla-Velderrain *et al*, Nature, 2019

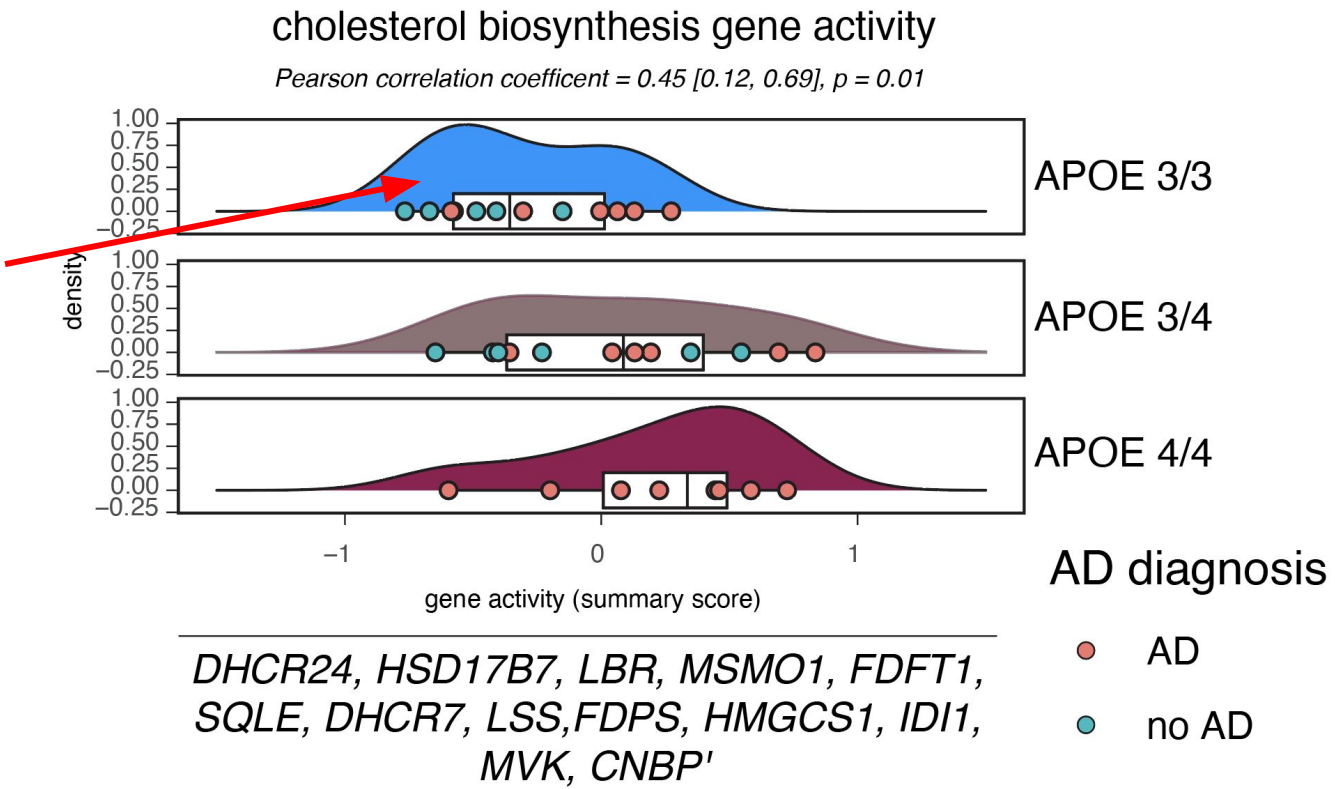
Perturbation of cholesterol biosynthesis genes in APOE4 Oligodendrocytes





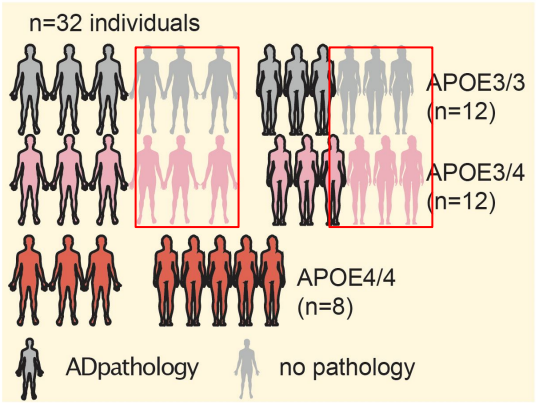
Blanchard, Akay, Davila-Velderrain, von Maydell *et al.*, submitted

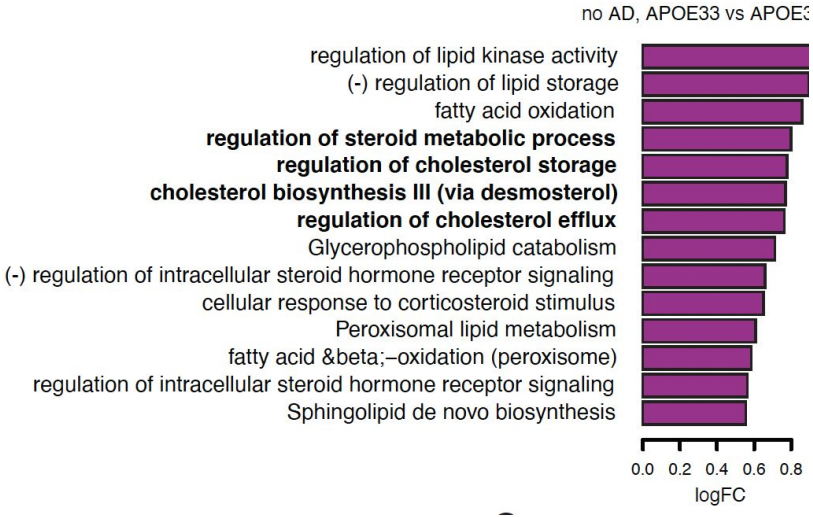
Perturbation of cholesterol biosynthesis genes in APOE4 Oligodendrocytes

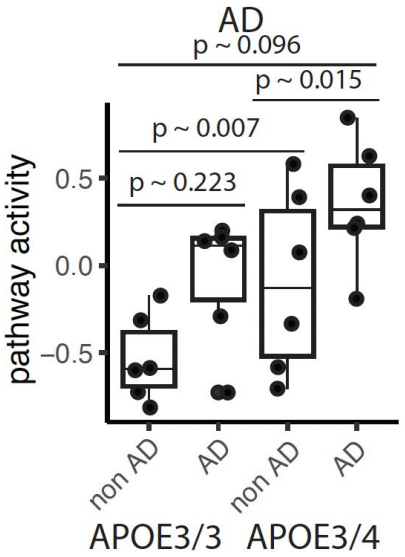


Blanchard, Akay, Davila-Velderrain, von Maydell *et al.*, submitted

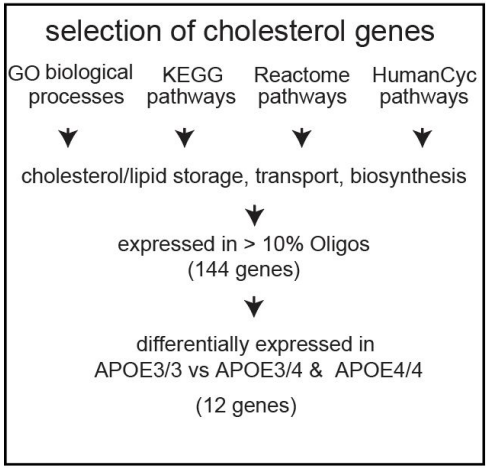
Convergence of Pathology and APOE4 Perturbations on Cholesterol Homeostasis in Oligodendrocytes

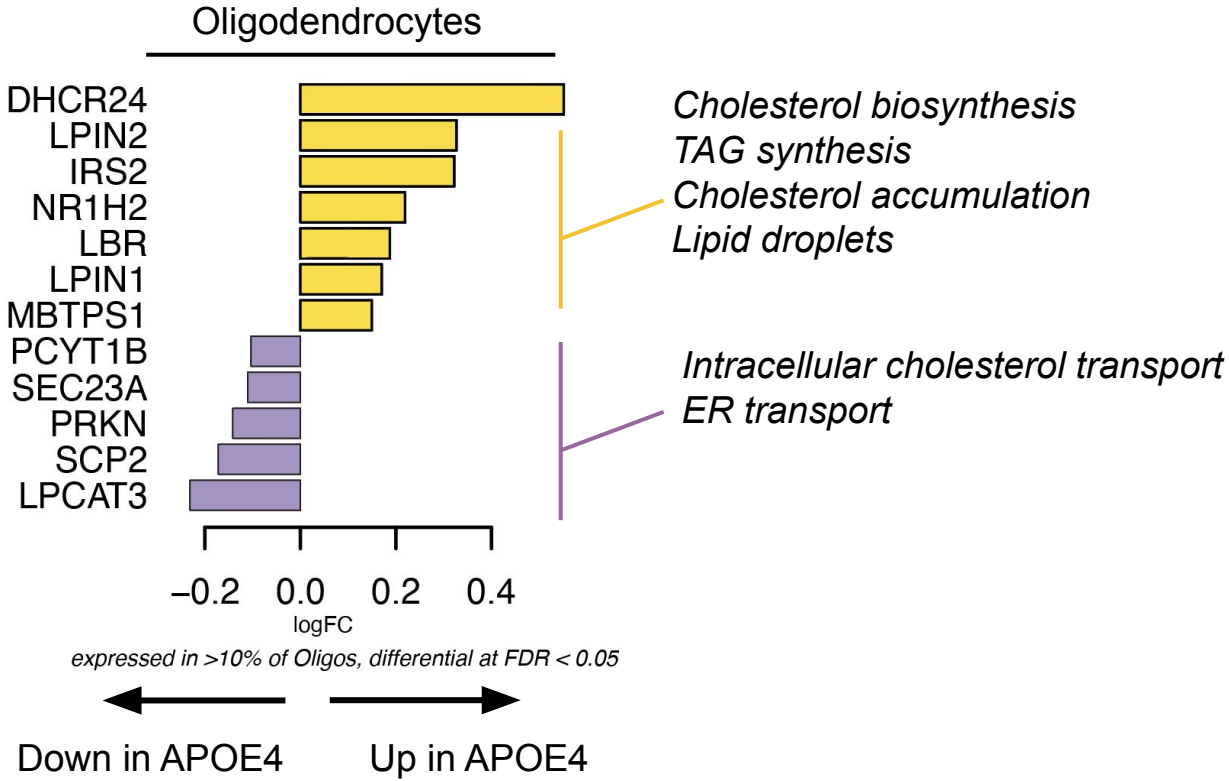






Differentially expressed genes related to cholesterol accumulation and transport

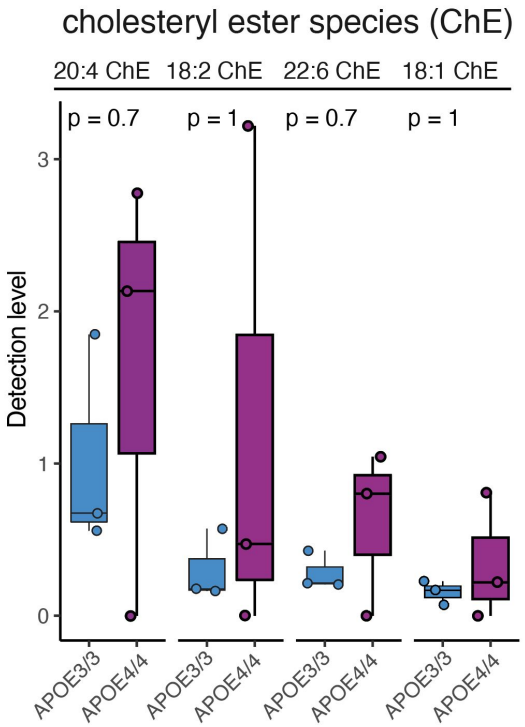




Blanchard, Akay, Davila-Velderrain, von Maydell *et al.*, submitted

Elevated Cholesteryl Ester Species in APOE4 brains

Post-mortem corpus callosum



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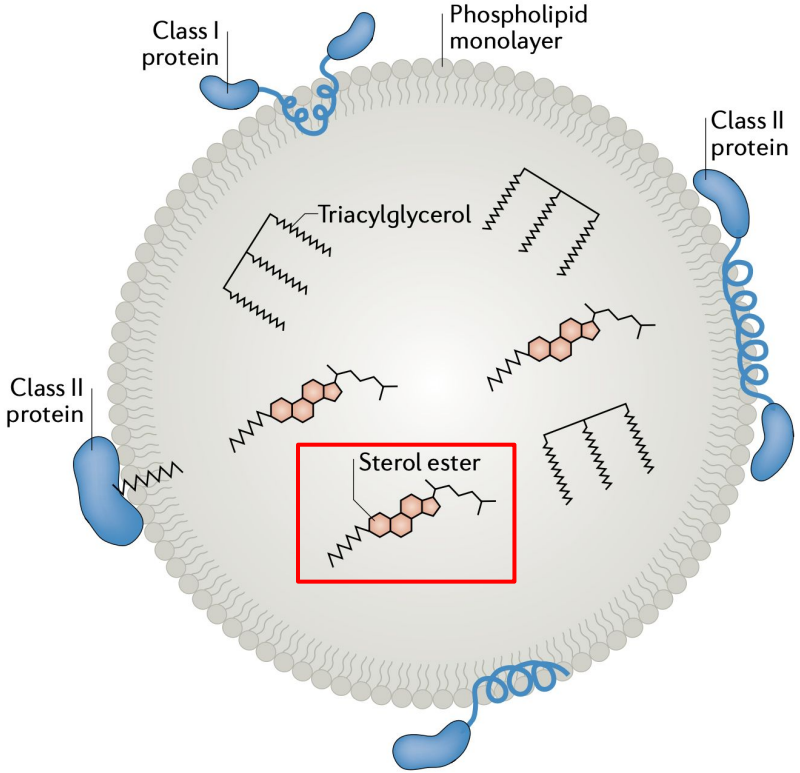

Olzmann and Carvalho, Nature Reviews Molecular Cell Biology, 2019

Elevated Cholesteryl Ester Species in APOE4 brains

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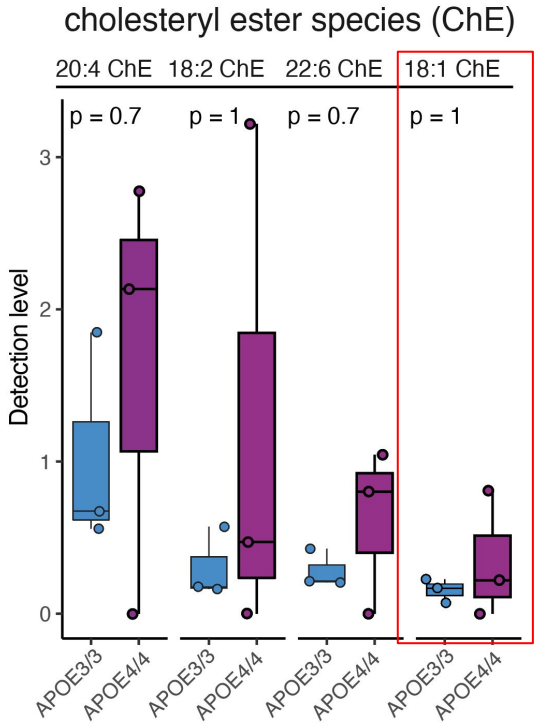
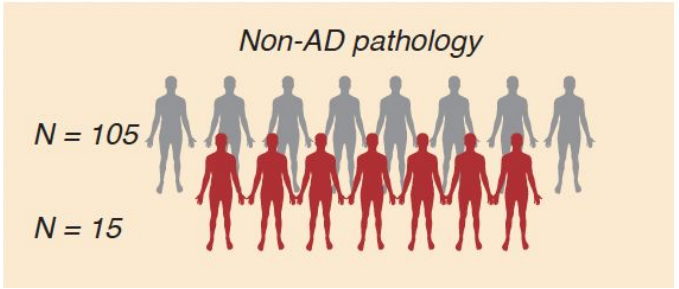
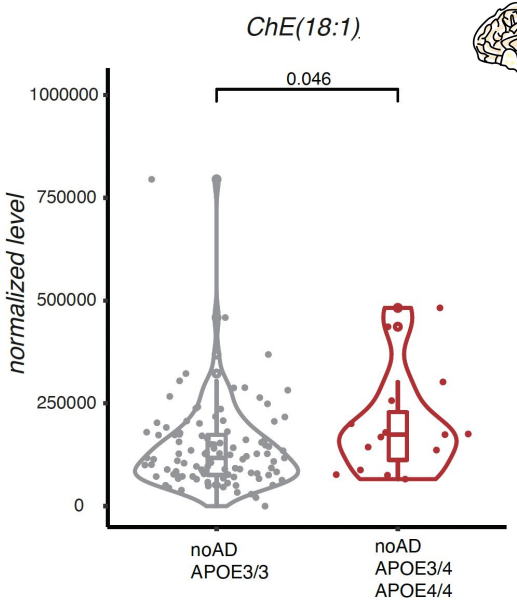




Post-mortem PFC

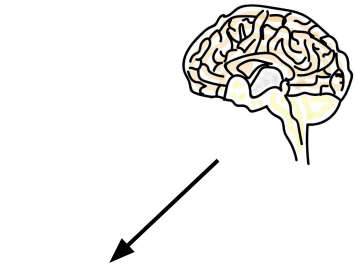


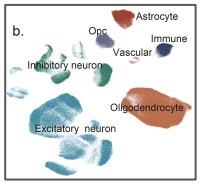
Blanchard, Akay, Davila-Velderrain, von Maydell *et al.*, submitted

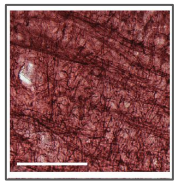
Emory University:
Chih-Yu Chen, Kristal Maner-Smith, Ihab Hajjar, Eric A Ortlund

Predicting and Validating APOE4-Associated Effects in post-mortem Human Brain

Human post-mortem brains



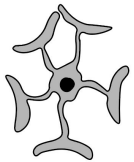




predictions

validation

iPSC-derived oligodendroglia

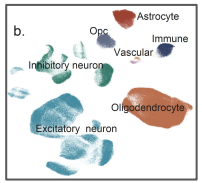


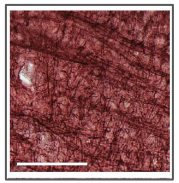
Oligos E3 E4

Isolate APOE4 effects

Predicting and Validating APOE4-Associated Effects in Multiple Systems

Human post-mortem brains





predictions

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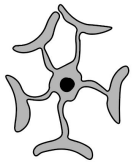
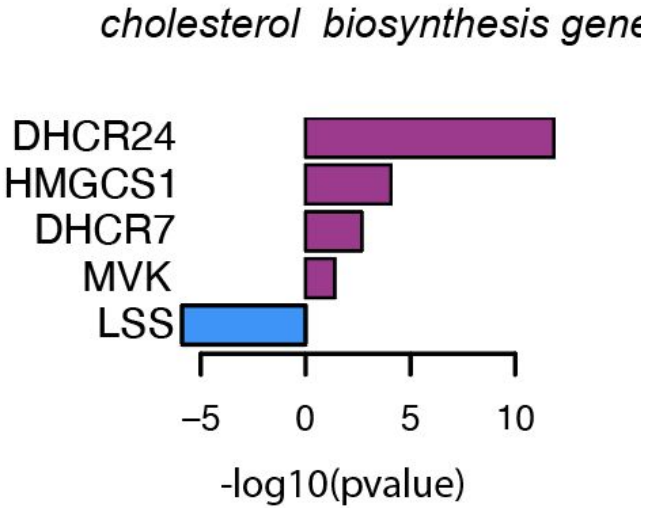
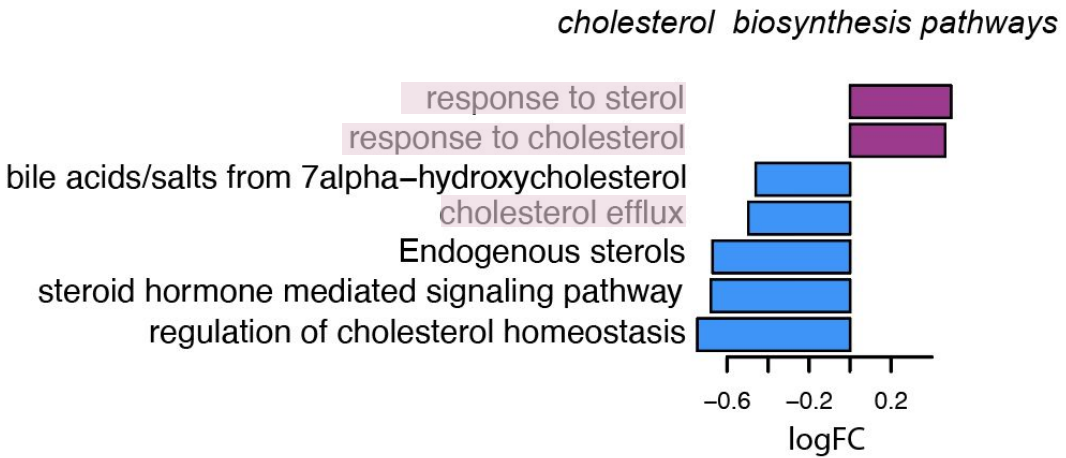


Oligos E3 E4

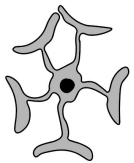
Isolate APOE4 effects

iPSC-derived APOE4 Oligodendroglia Also Show Transcriptional Changes Related to Cholesterol Biosynthesis, Accumulation, and Transport



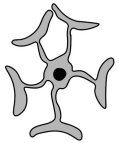


iPSC-derived Oligodendroglia

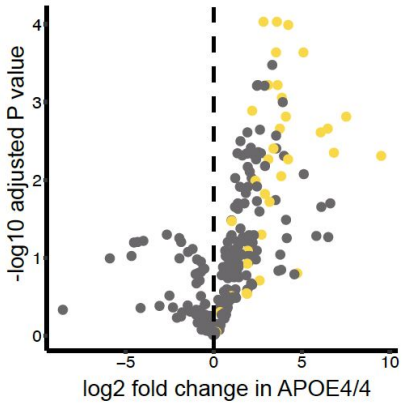


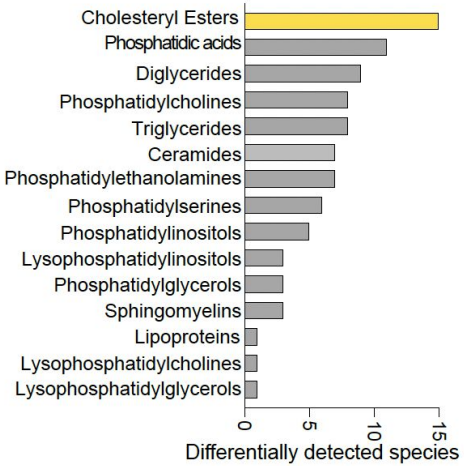
→ Increased cholesterol biosynthesis?
→ decreased cholesterol efflux?
→ Increased cholesterol accumulation?

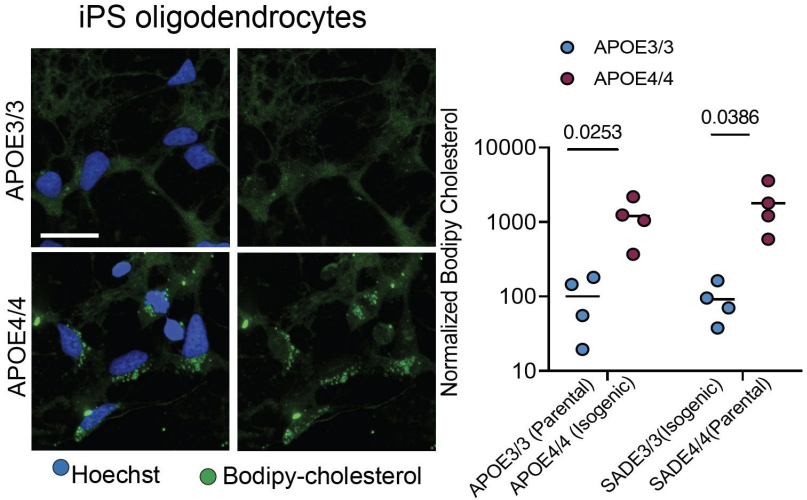
Elevated Cholesteryl Ester Species in iPSC-derived APOE4 Oligodendroglia



iPSC-derived Oligodendroglia







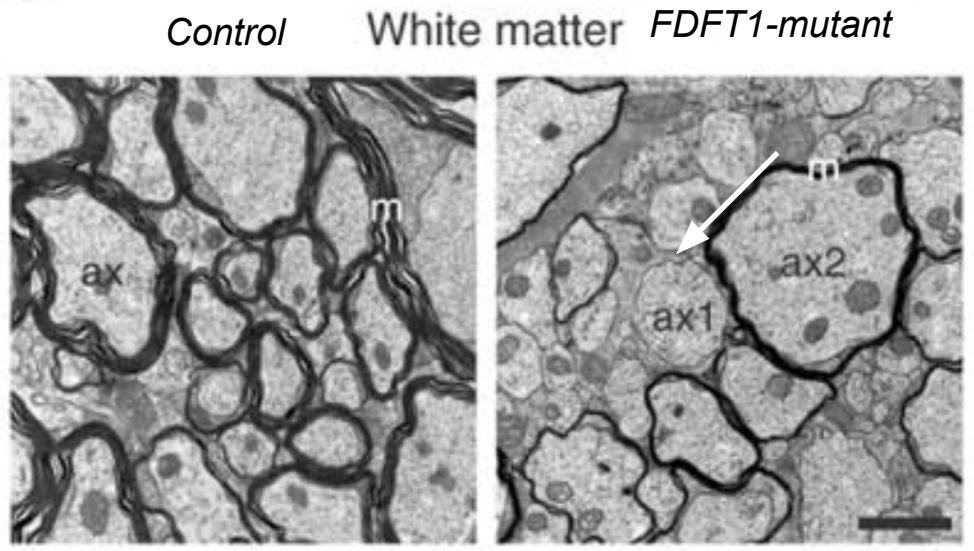
Blanchard, Akay, Davila-Velderrain, von Maydell *et al.*, submitted

Cholesterol is a Necessary Component of Myelin

Approx. myelin composition

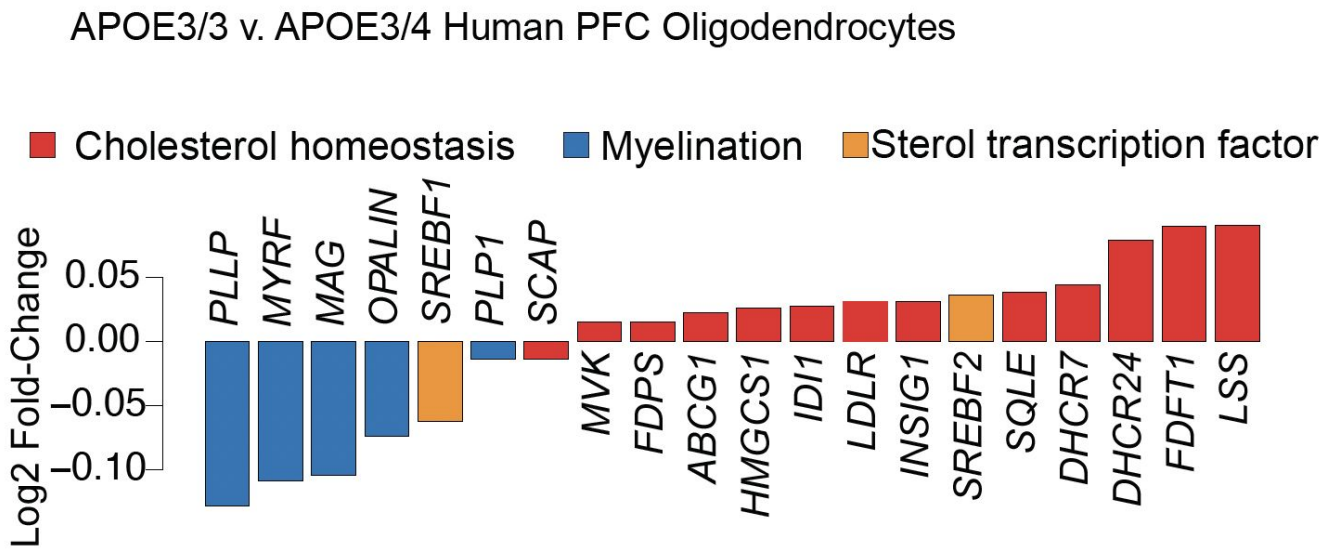
	Myelin Membrane[a]
Lipid content (dry weight)	**71%**
Lipid class	
Cholesterol	**26%**
Phospholipids	
PE	16%
PS	6%
PC	12%
PI	1%
SM	3%
Glycolipids	**31%**
Other lipids	5%

Chrast *et al*, 2011, Journal of lipid res



Saher *et al*, 2005, Nature Neuroscience

Down-Regulation of Myelin Genes is Inversely Correlated With Changes to Cholesterol Regulators



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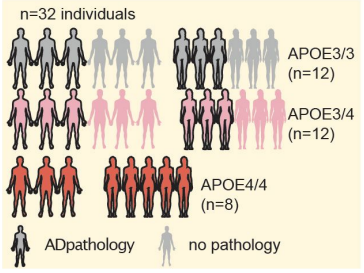
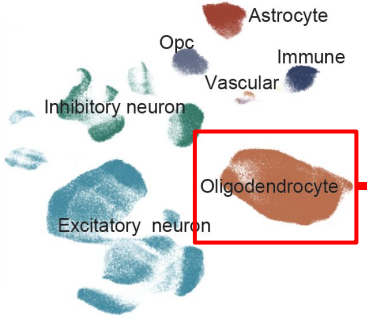
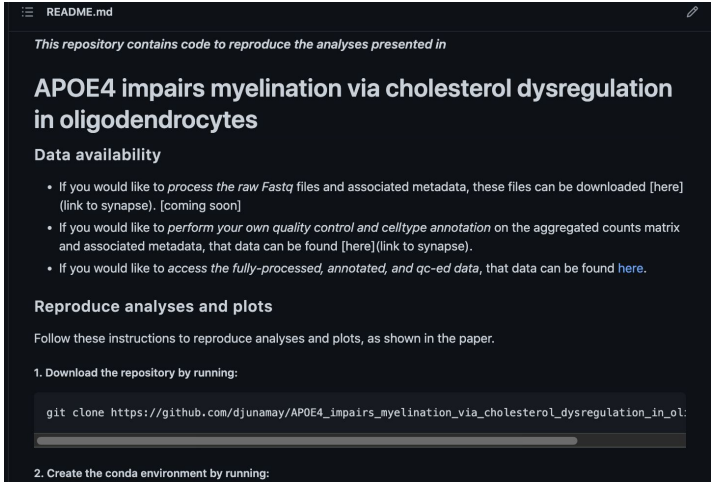
A Resource For Mechanistic Insights

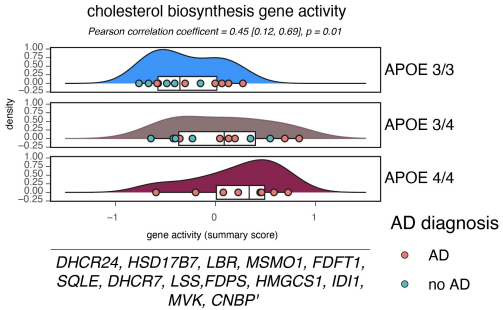




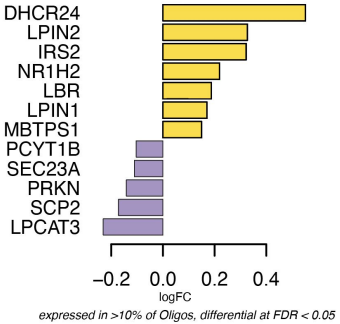
All Code and Data Available Through [Github]



(i) Perturbed Cholesterol Signature

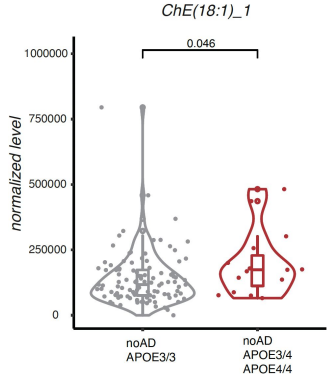


DHCR24, HSD17B7, LBR, MSMO1, FDFT1, SQLE, DHCR7, LSS,FDPS, HMGCS1, IDI1, MVK, CNBP'

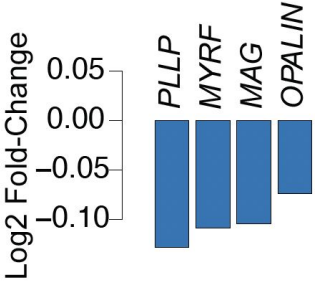


expressed in >10% of Oligos, differential at FDR < 0.05

(ii) Cholesterol Accumulation



(iii) Decreased Myelin Genes



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