ABCA7 loss of function induces DNA damage in neurons

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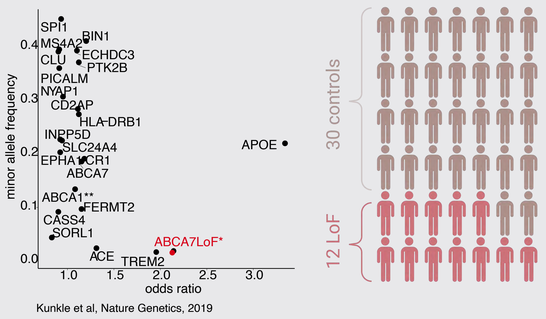
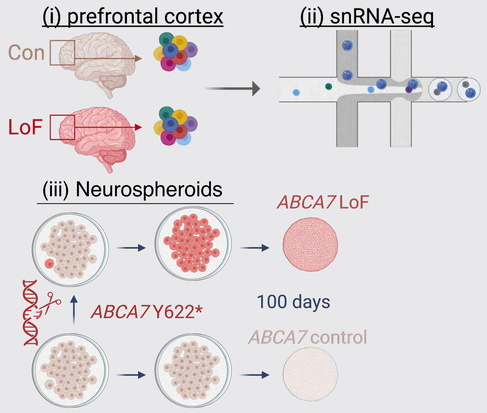
Summary:

MOTIVATION. ABCA7 loss of function (LoF) variants are one of the strongest genetic risk factors for sporadic Alzheimer's disease (sAD). The mechanisms and affected brain cell types remain largely unknown.



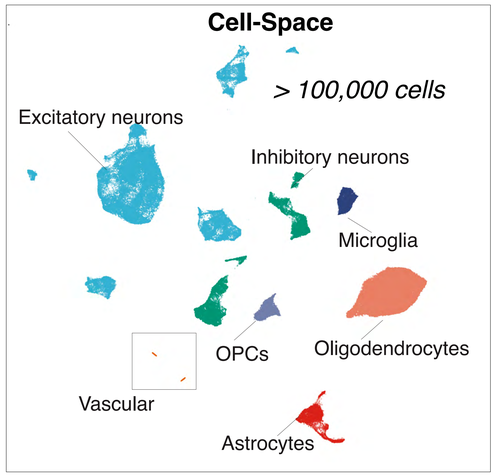
Kunkle et al, Nature Genetics, 2019

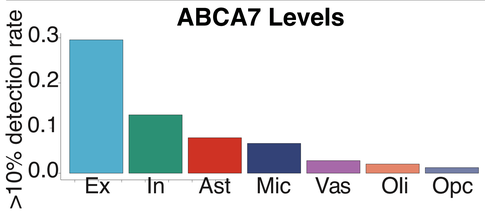
METHOD. We profiled >100,000 brain cells from human post-mortem ABCA7 LoF variant carriers and matched controls by single-nuclear RNA-sequencing, performed biochemical experiments on post-mortem brain sampes and isogenic iPSC-derived neurospheroids. .

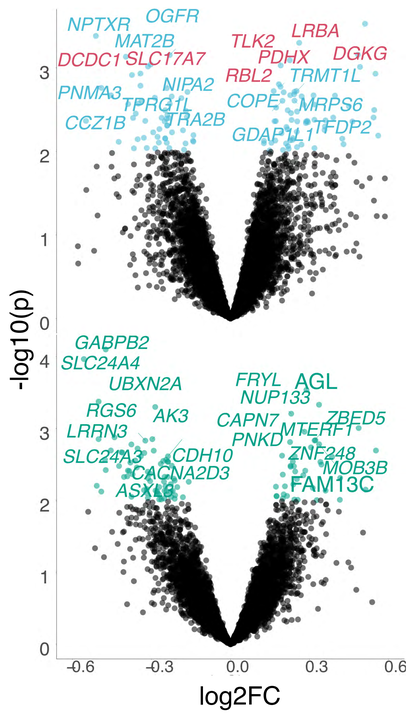


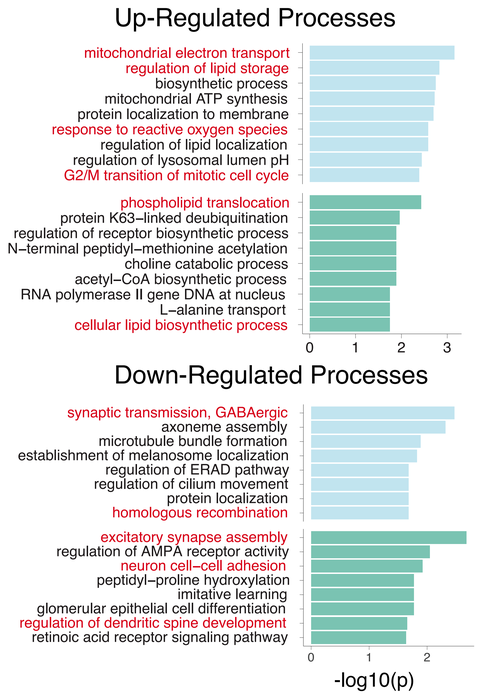
RESULTS.
Neurons expressed highest levels of ABCA7 and showed evidence for elevated expression of oxidative stress, DNA damage, and NF KB-inflammatory genes signatures. Multiple (phospho)-lipid-related processes were perturbed. Assays on post-mortem tissues and iPSC-derived neurospheroids showed increased levels of DNA damage, NF KB activation, and lipid peroxidation in ABCA7 LoF neurons.

snRNAseq on Human Brain from ABCA7 LoF-Carriers and non-Carriers

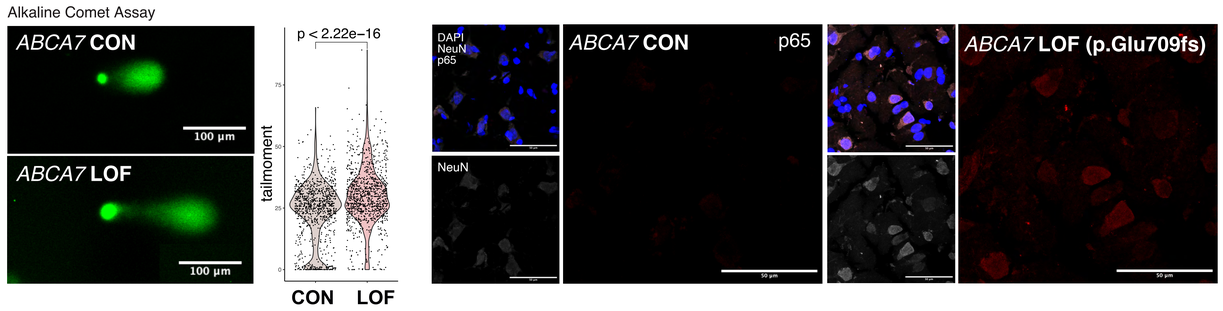




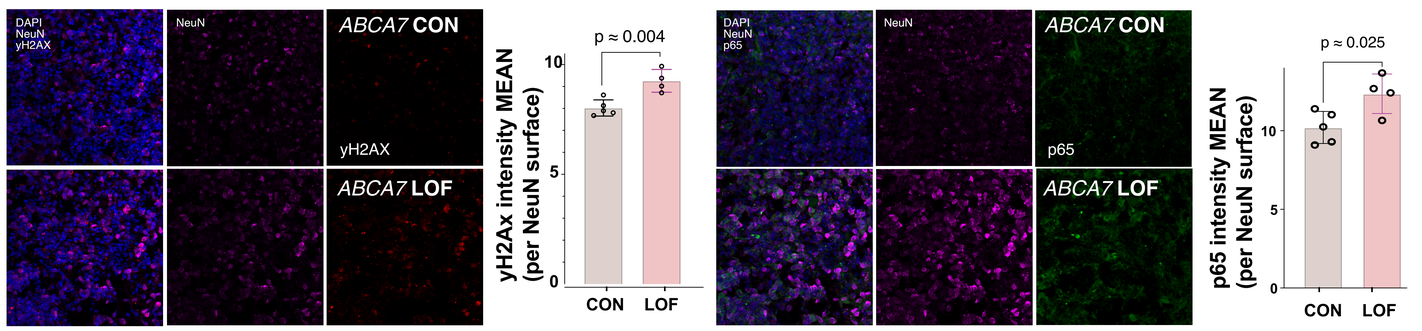




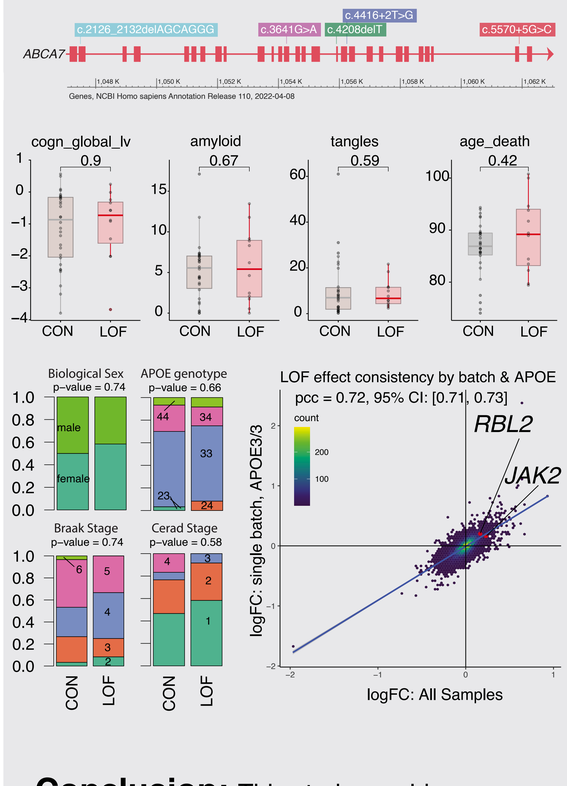
Post-Mortem Human Brain



ABCA7 LoF Neurospheroids (100 Days)



Cohort Metadata:



Conclusion:

This study provides a cell-type-specific atlas of ABCA7 LoF disruption in the human brain and suggests mechanisms, by which ABCA7 might increase sAD risk through DNA damage, inflammation, and lipid disruption in neurons.

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