

ABCA7 loss of function variants induce lipid disruption and DNA damage in neurons

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Tsai Lab, MIT

Disclosure:

Patent application for cyclodextrin and analogues as an Alzheimer's disease therapeutic
(Provisional Patent Application No. 63/160,877)

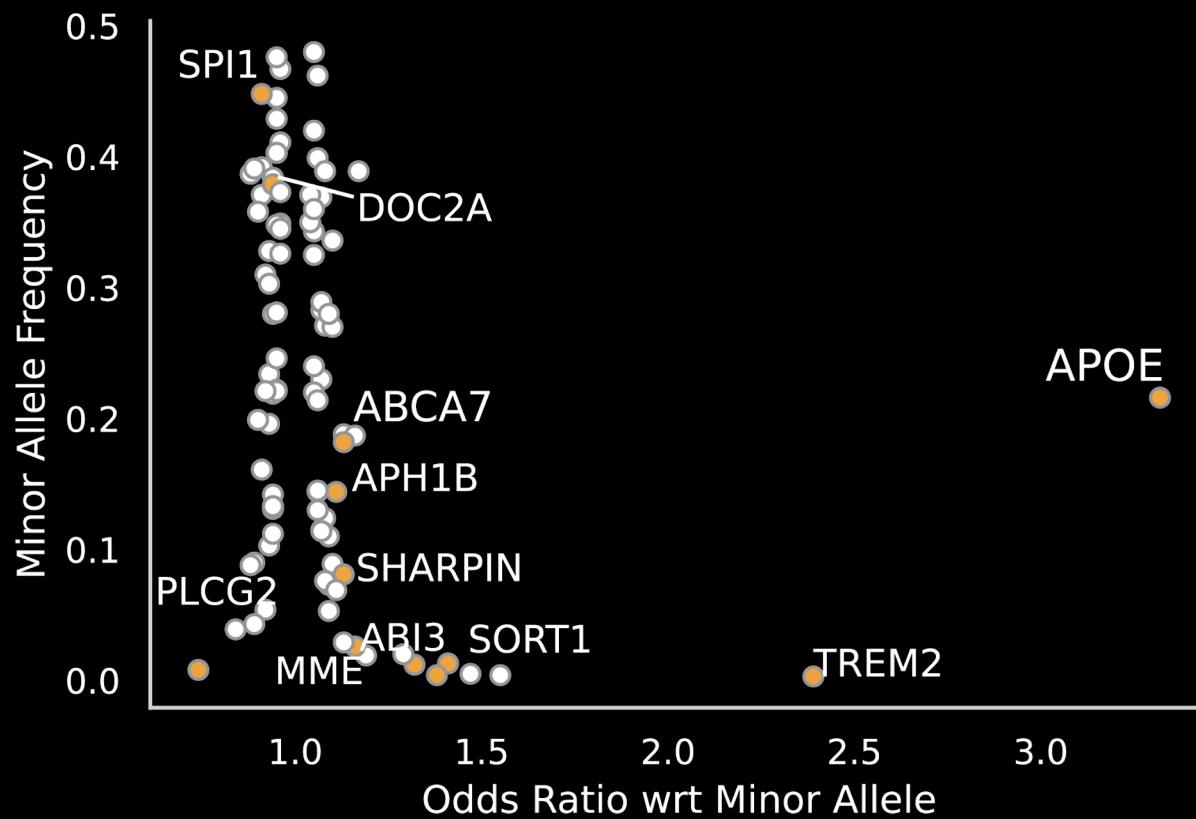


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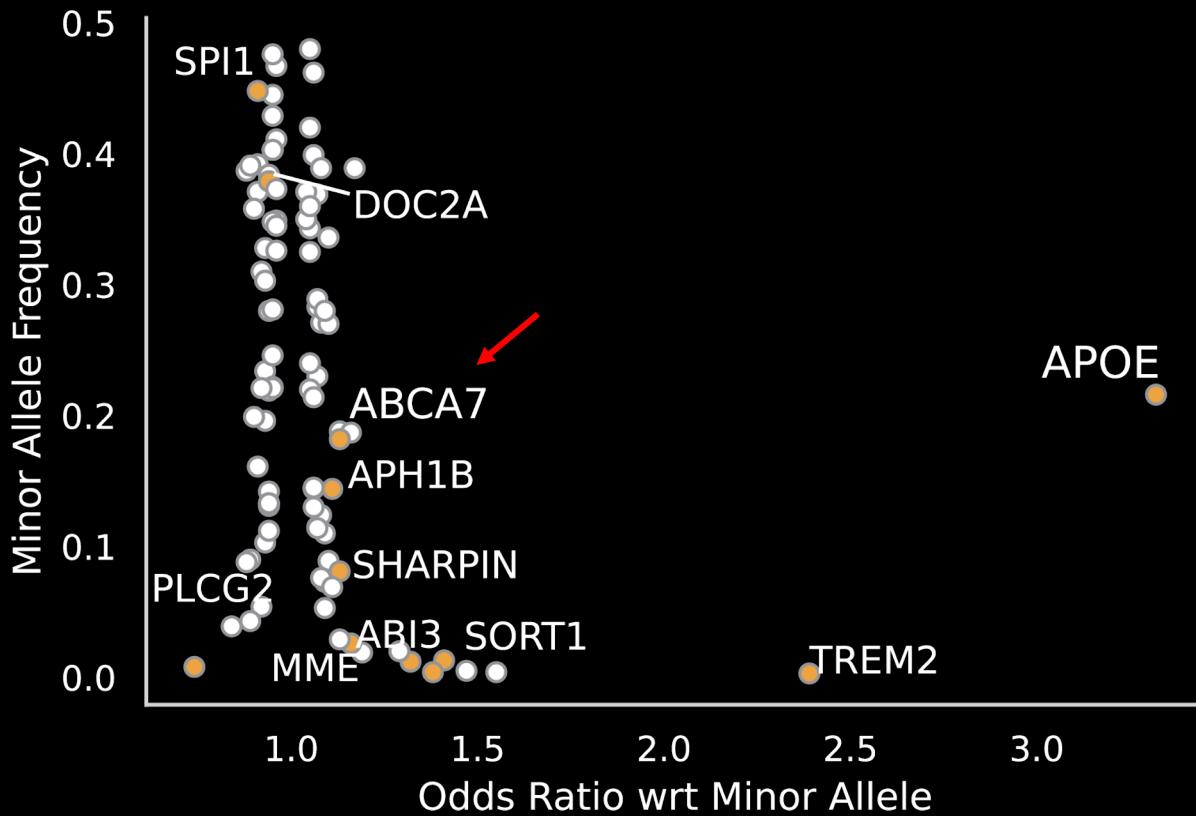
Coding variants implicated in Alzheimer's disease through genome-wide association studies (GWAS)



● Protein-coding variant

Data source: Kunkle et al, Table 1, Nat Genet 51, 414–430 (2019)

GWAS implicate ABCA7 in Alzheimer's disease risk

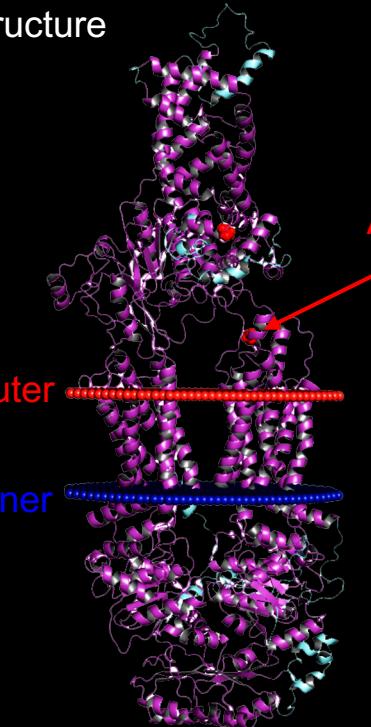


● Protein-coding variant

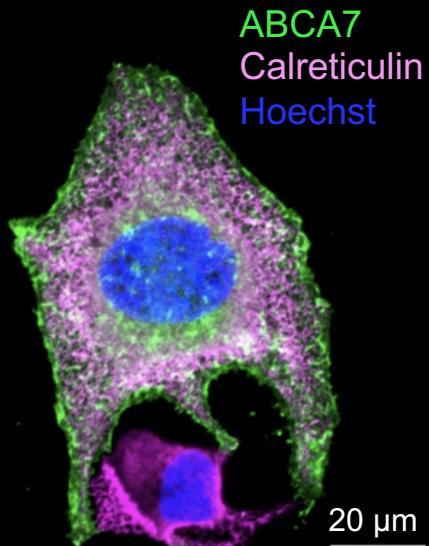
Data source: Kunkle et al, Table 1, Nat Genet 51, 414–430 (2019)

ABCA7 mediates inter-cellular lipid transport

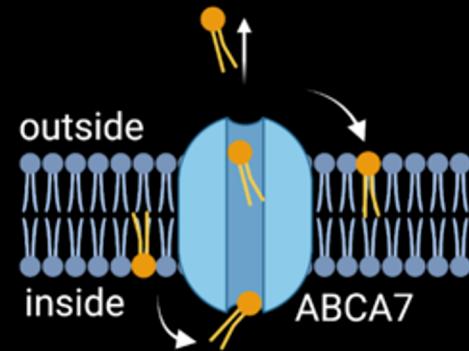
Structure



Localization



Function



See also:

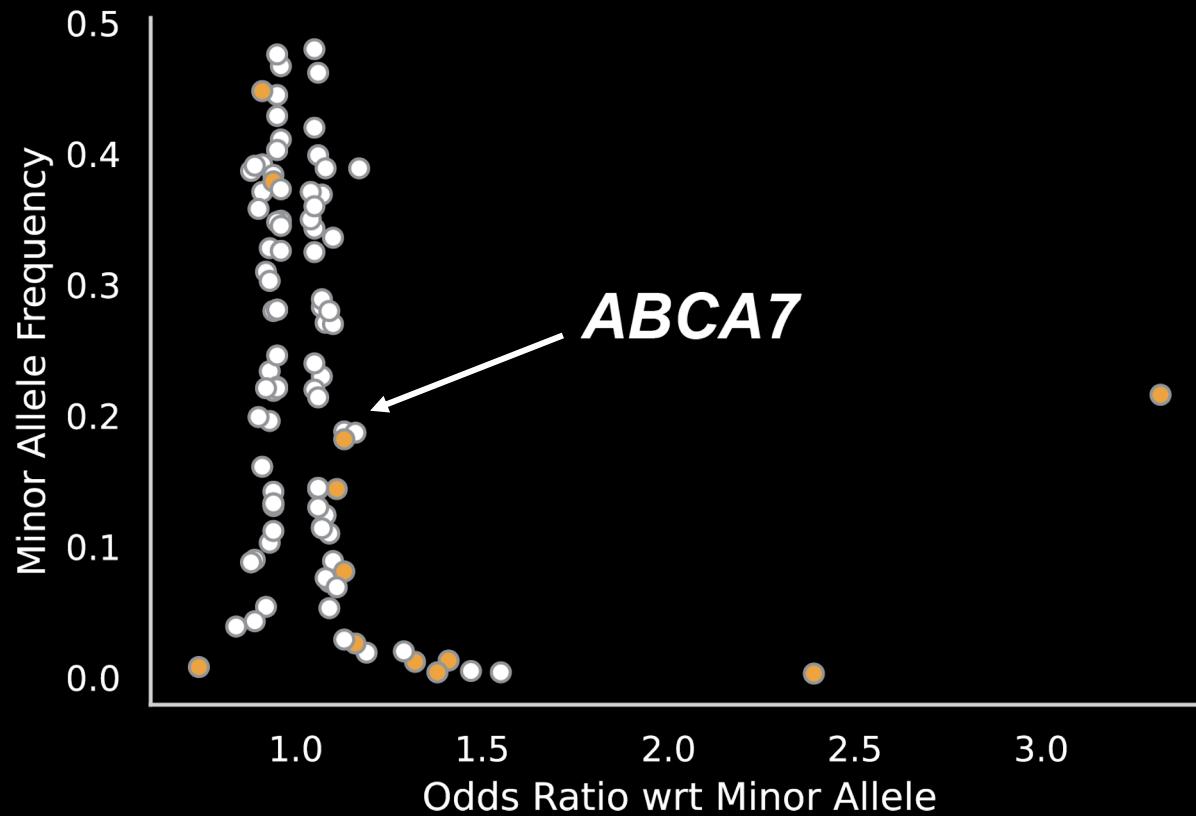
- Let et al, *he EMBO Journal* (2023)42:e111065
Quazi et al, *J Biol Chem.* 2013 Nov 29; 288(48):
34414–34426.
Daleke, , *JBC Papers in Press*, November 27, 2006,
DOI 10.1074/jbc.R600035200

(left) Structural representation of ABCA7 (PDB ID 8EEB) in intermediate open conformation, Andrea Spitaleri

(middle) Adapted from Bossaerts et al, *acta neuropathol commun* 10, 43 (2022), Permissions: CC BY 4.0, <http://creativecommons.org/licenses/by/4.0/>.

(right) Created with BioRender.com

Rare loss-of-function (LoF) variants in ABCA7 increase risk of Alzheimer's disease



See also:

Holstege et al, Nat Genet 54, 1786–1794 (2022). <https://doi.org/10.1038/s41588-022-01208-7>

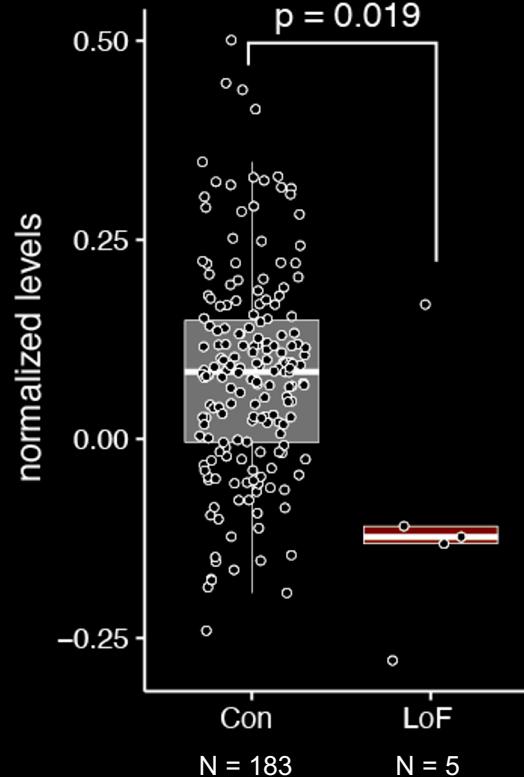
Steinberg et al, Nat Genet 47, 445–447 (2015). <https://doi.org/10.1038/ng.3246>

Data source: Kunkle et al, Table 1, Nat Genet 51, 414–430 (2019)

ABCA7 LoF variants likely increase risk through haploinsufficiency

	c.3641G>A	<i>stop gained</i>
	c.3255G>A	
	c.4208delT	<i>frameshift</i>
	c.2126_2132del	
	c.5570+5G>C	<i>splice region</i>
	c.4416+2T>G	

ABCA7 protein levels in human PFC



See also:

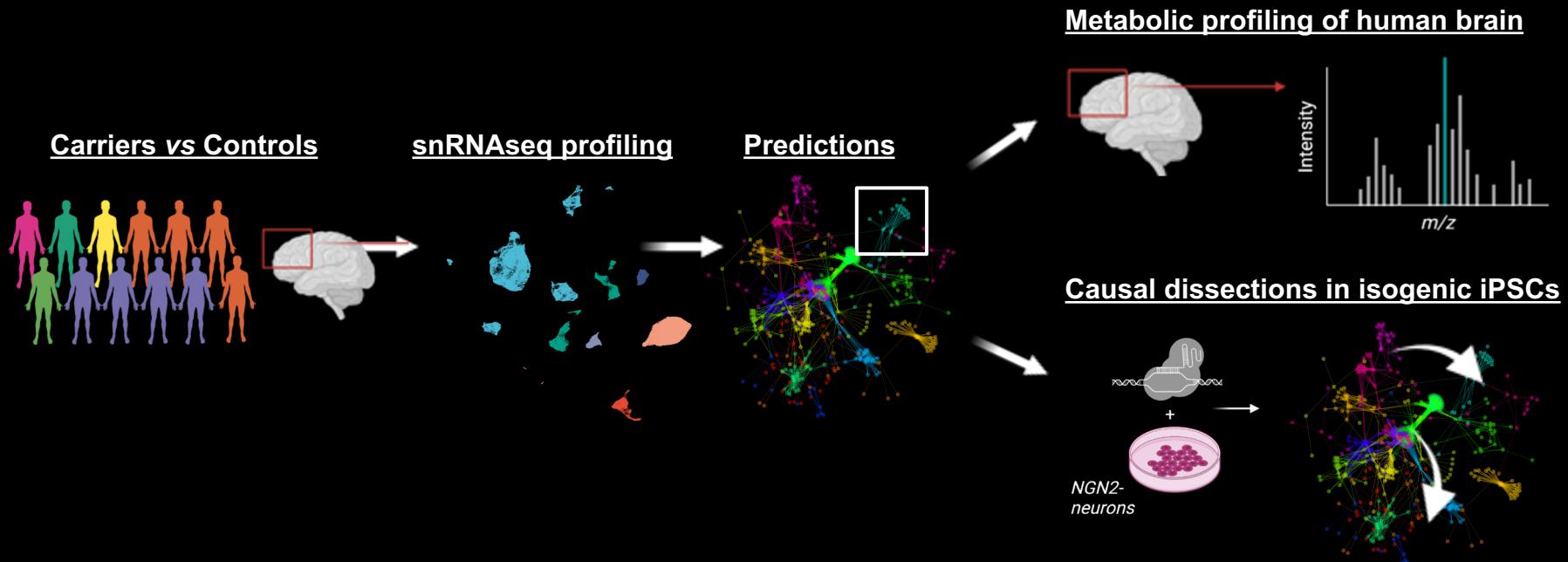
Bossaerts et al, *acta neuropathol commun* 10, 43 (2022)

De Roeck et al, *Acta Neuropathol* 2019 Aug;138(2):201-220. doi: 10.1007/s00401-019-01994-1

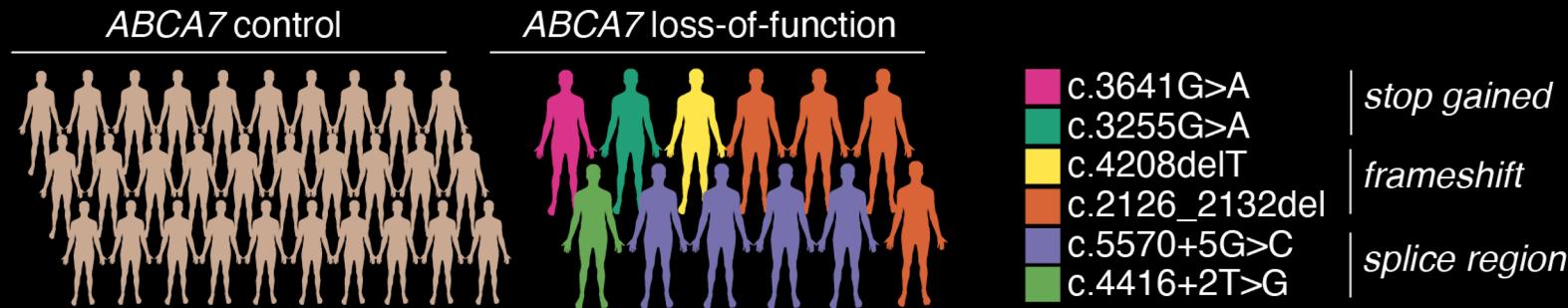
Proteomics data available at:

<https://www.synapse.org/#!Synapse:syn26452612> (syn26452612) (Emory University)

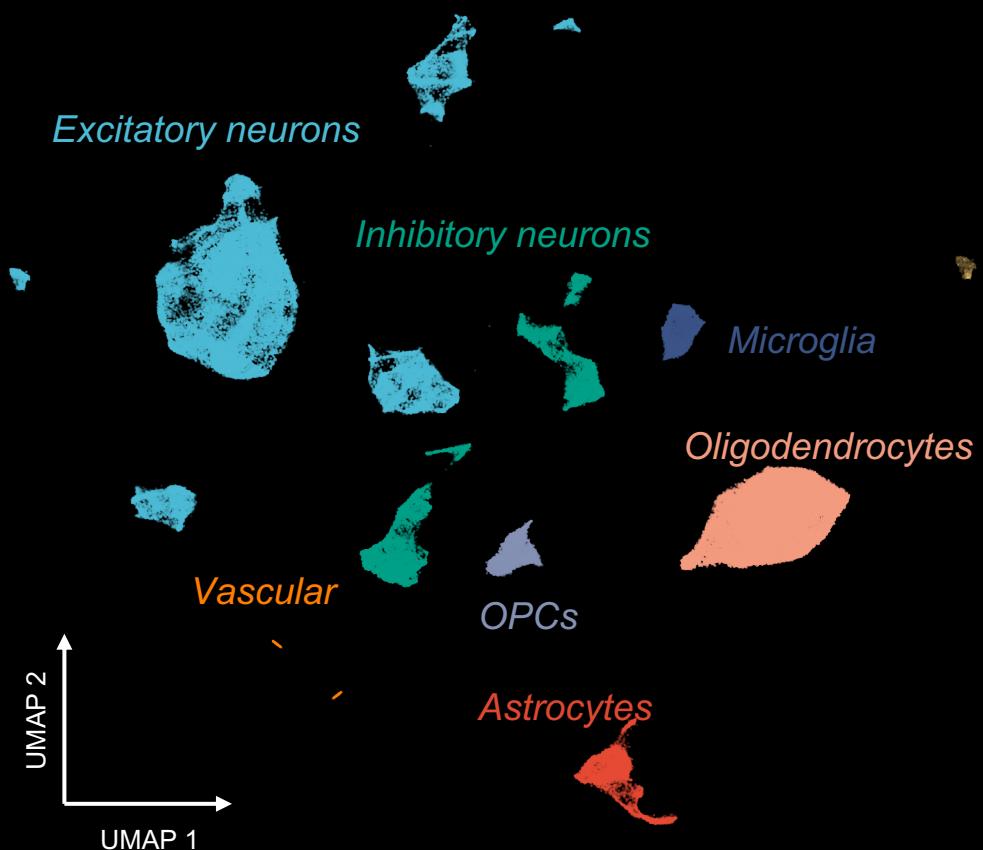
What are the cell-type-specific consequences of ABCA7 LoF variants?



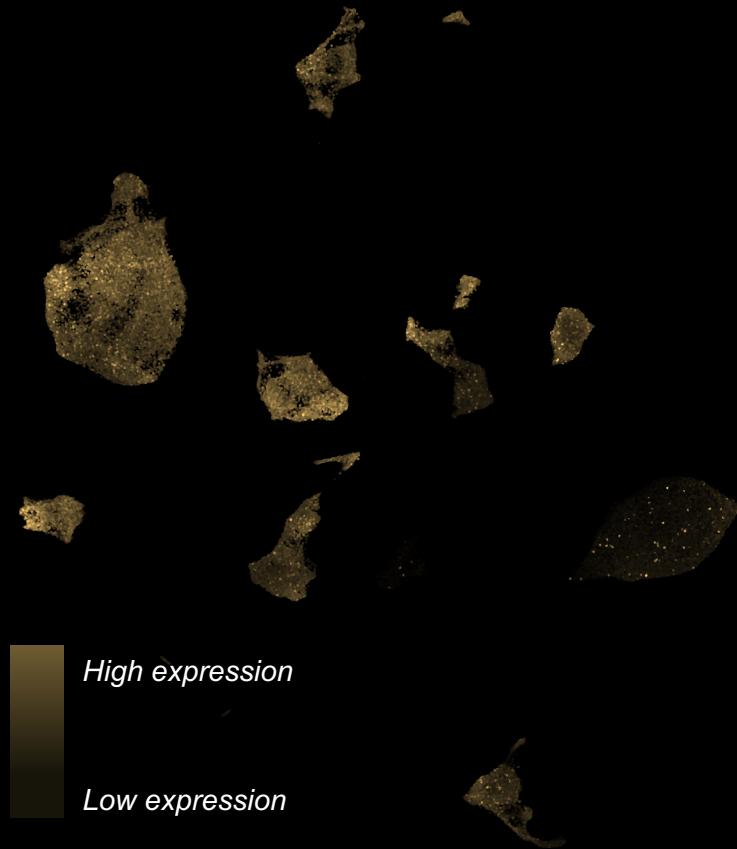
Assembling a cohort of ABCA7 LoF variant-carriers with available *postmortem* brain samples



Major cell types

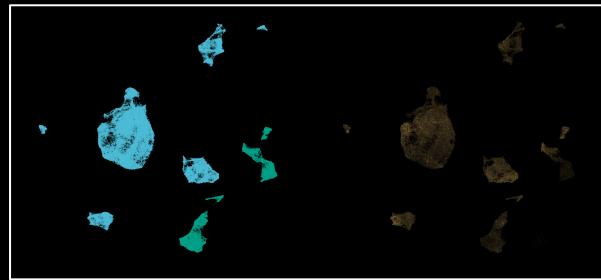


ABCA7 expression

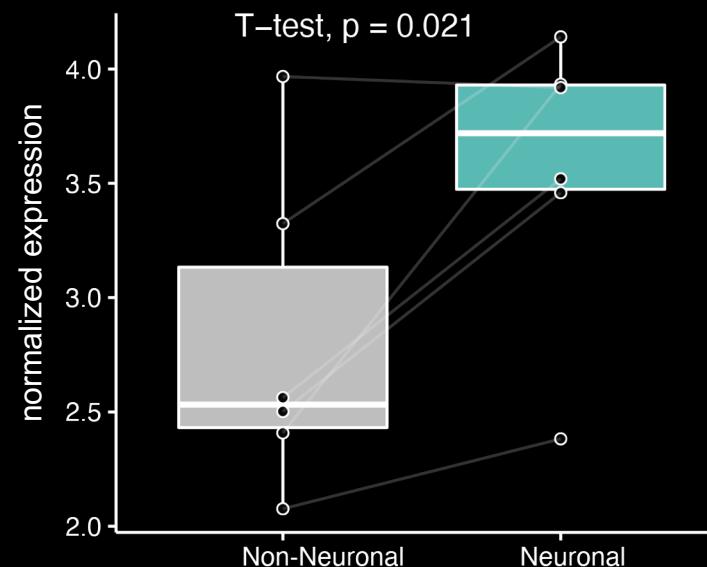
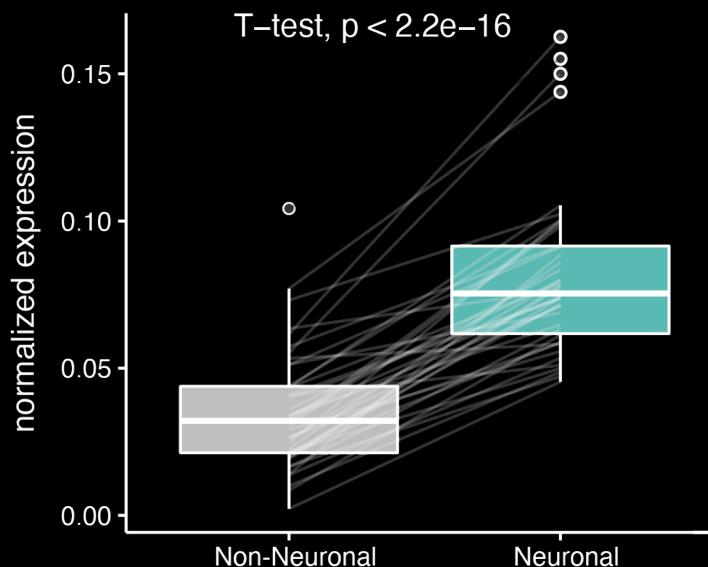
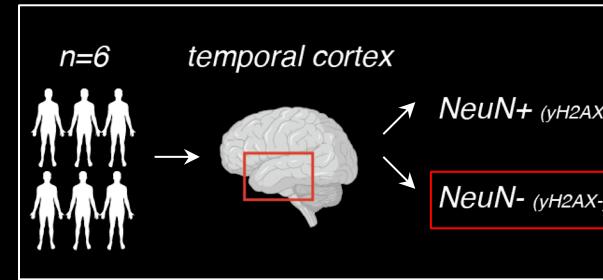


ABCA7 expression is higher in neurons vs non-neuronal cells in human brain

snRNAseq

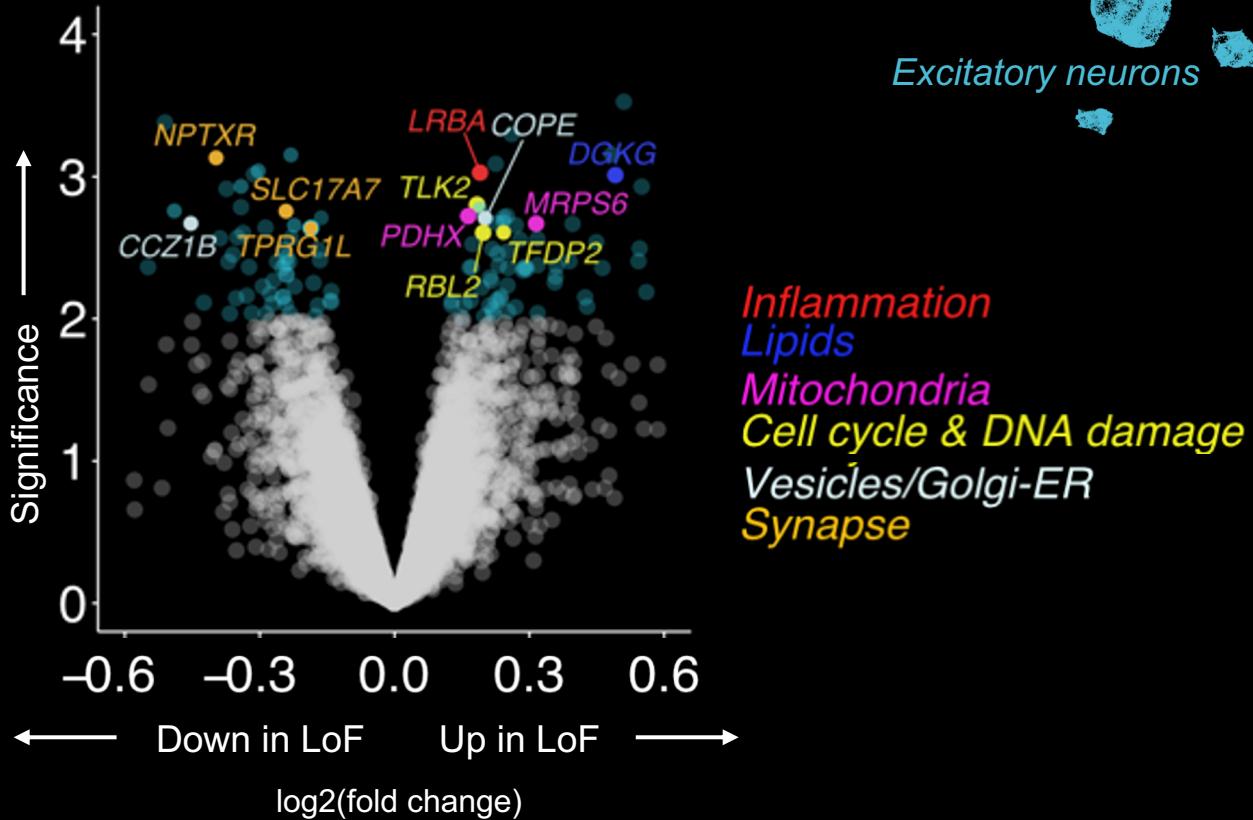


Bulk RNA-seq

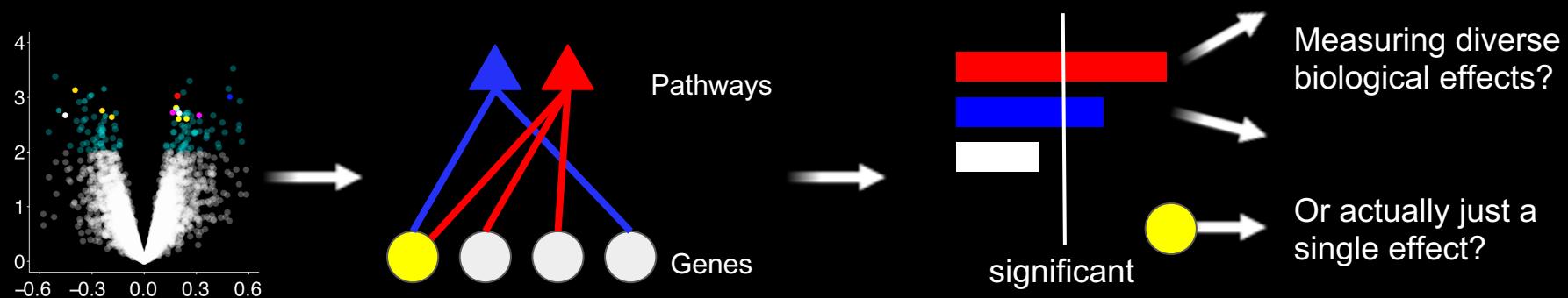


Data source (right):
Welch et al, SCIENCE
ADVANCES
28 Sep 2022
Vol 8, Issue 39
DOI: 10.1126/sciadv.abo4662

ABCA7 LoF - associated gene changes in excitatory neurons

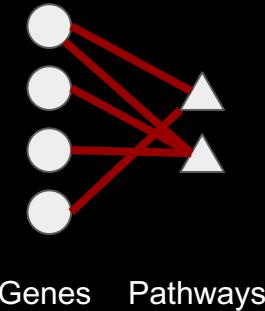


Gene redundancy in biological pathway databases

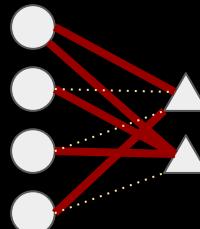


Partitioning bipartite graph into non-overlapping gene groups

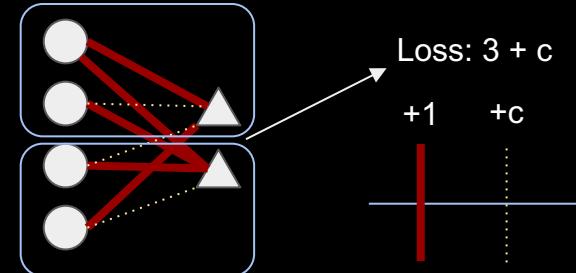
1 Load input



2 Add missing edges

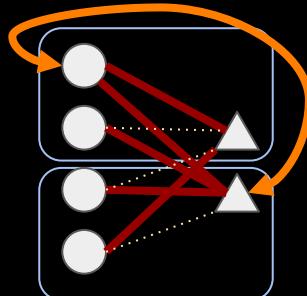


3 Initialize random solution



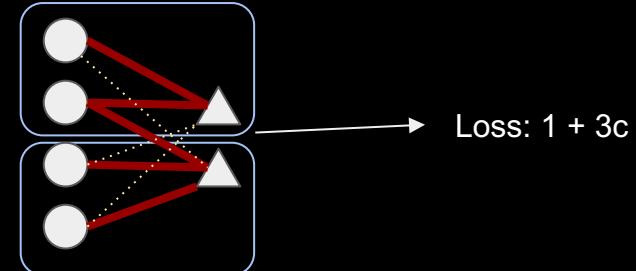
Genes Pathways

4 Swap to minimize loss

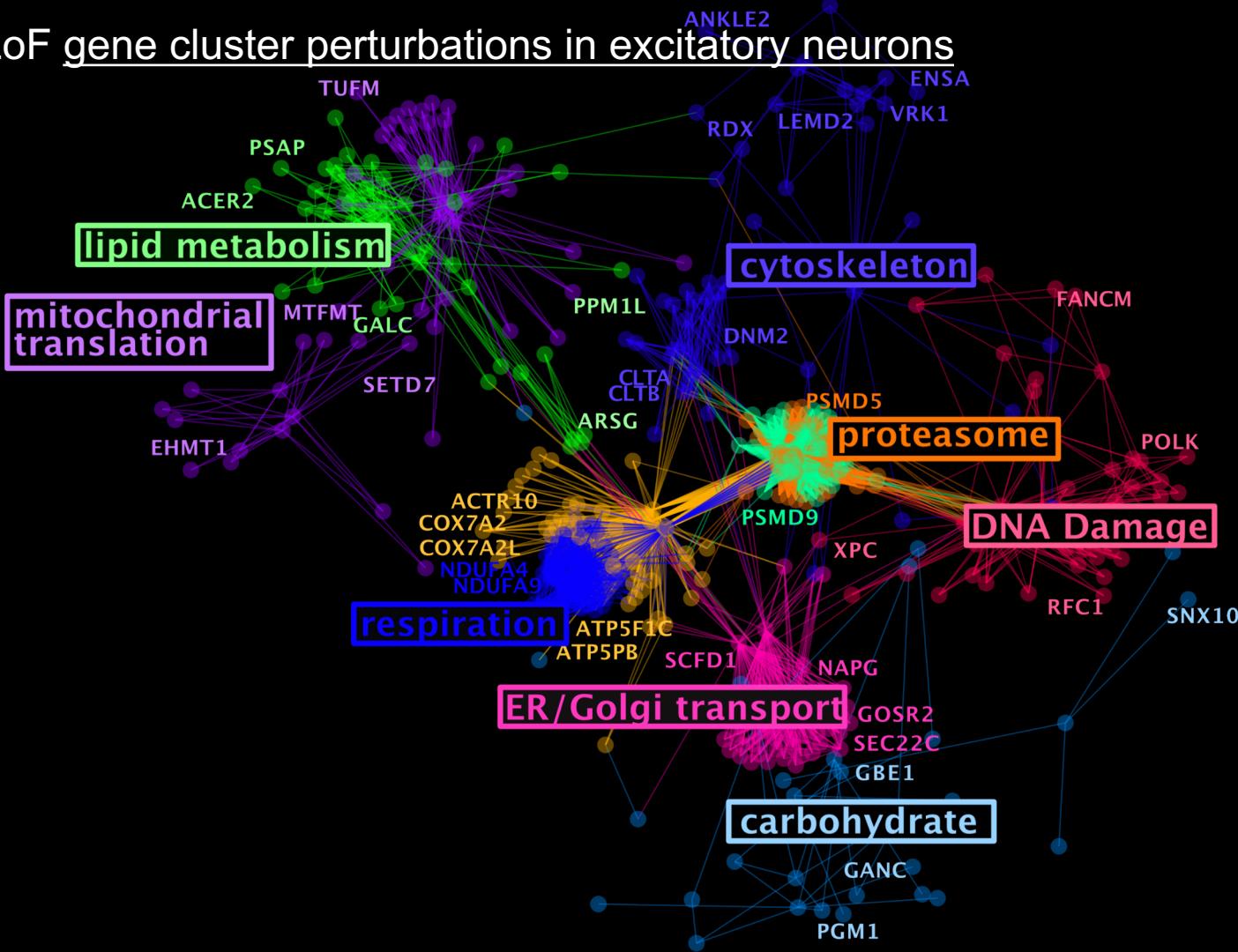


Use
Kernighan–Lin
heuristic

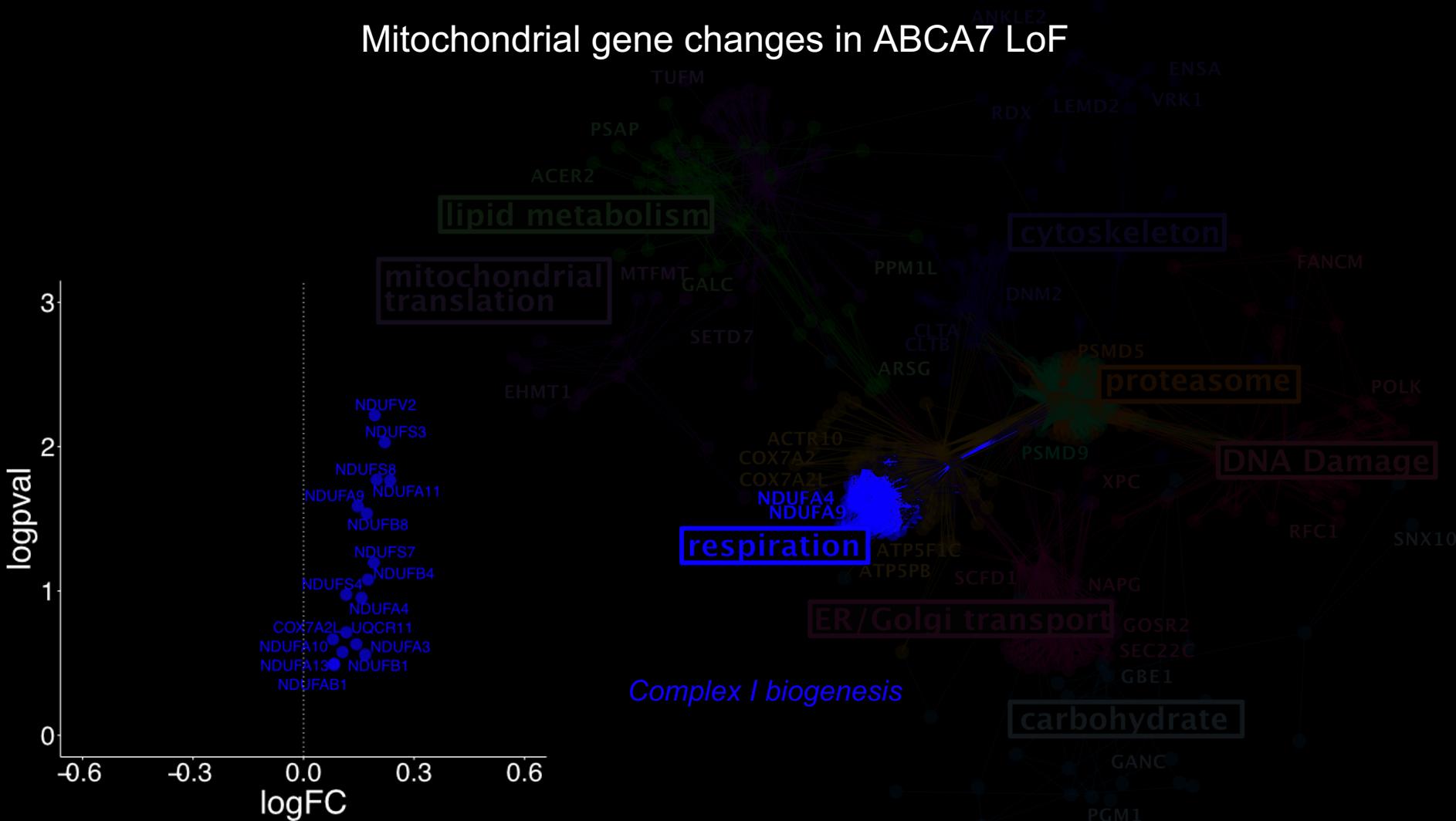
5 Repeat 4 to convergence



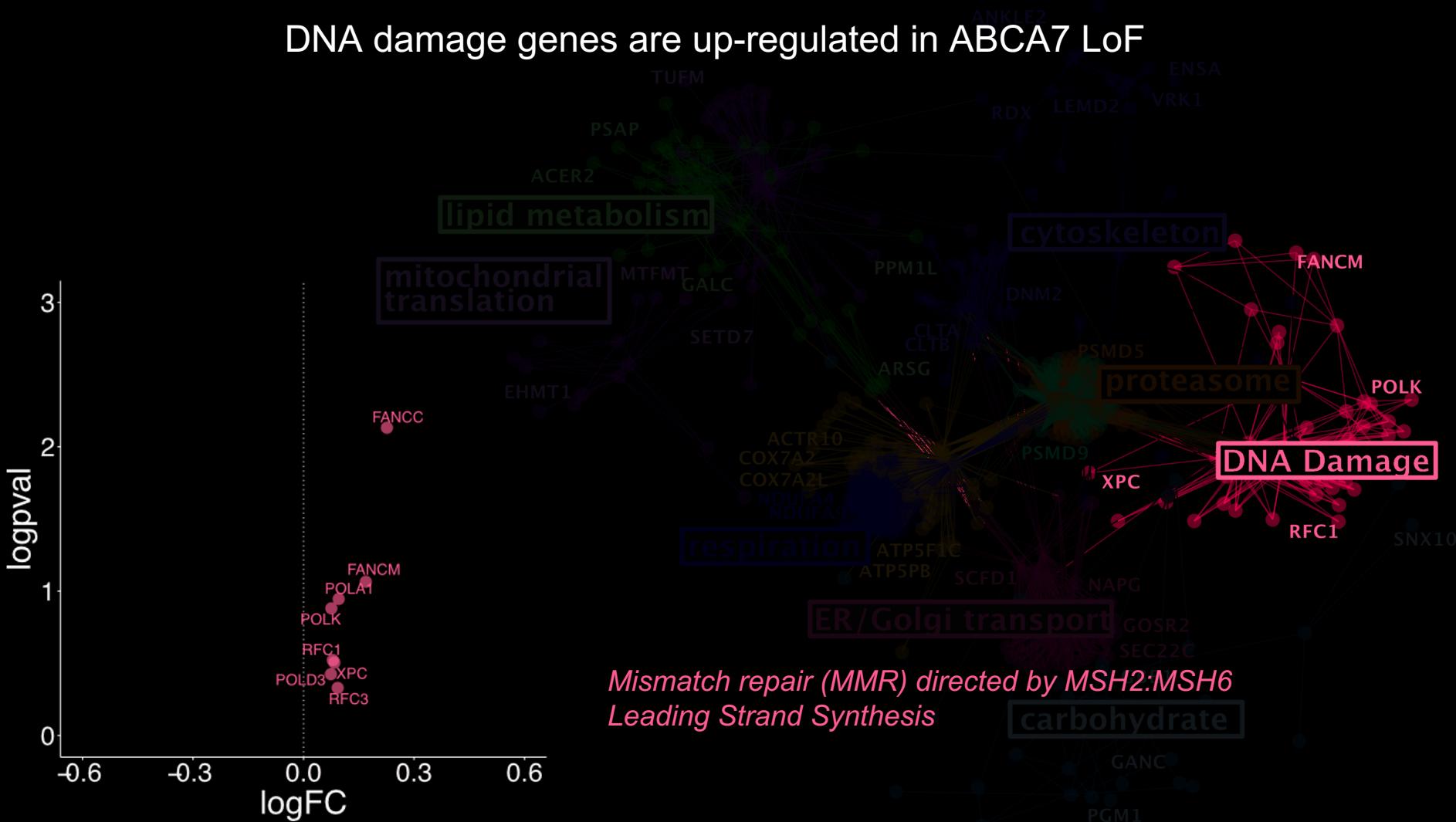
ABCA7 LoF gene cluster perturbations in excitatory neurons



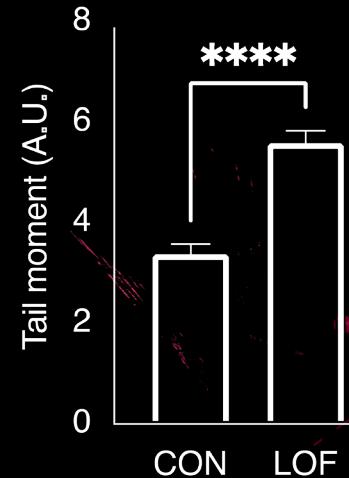
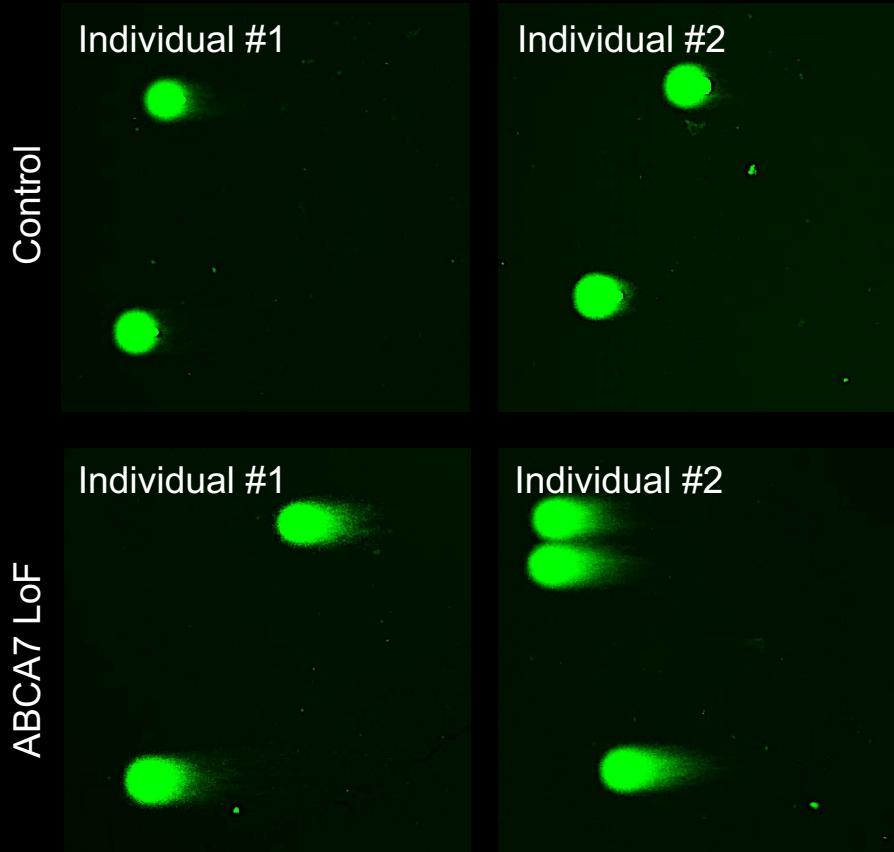
Mitochondrial gene changes in ABCA7 LoF



DNA damage genes are up-regulated in ABCA7 LoF



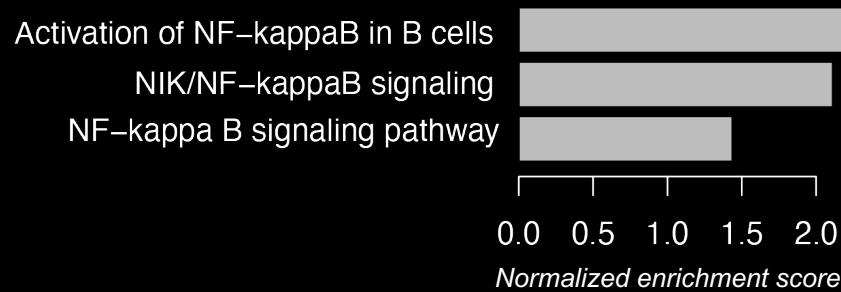
Increased DNA damage in ABCA7 LoF human brain



1187 vs 1352 nuclei

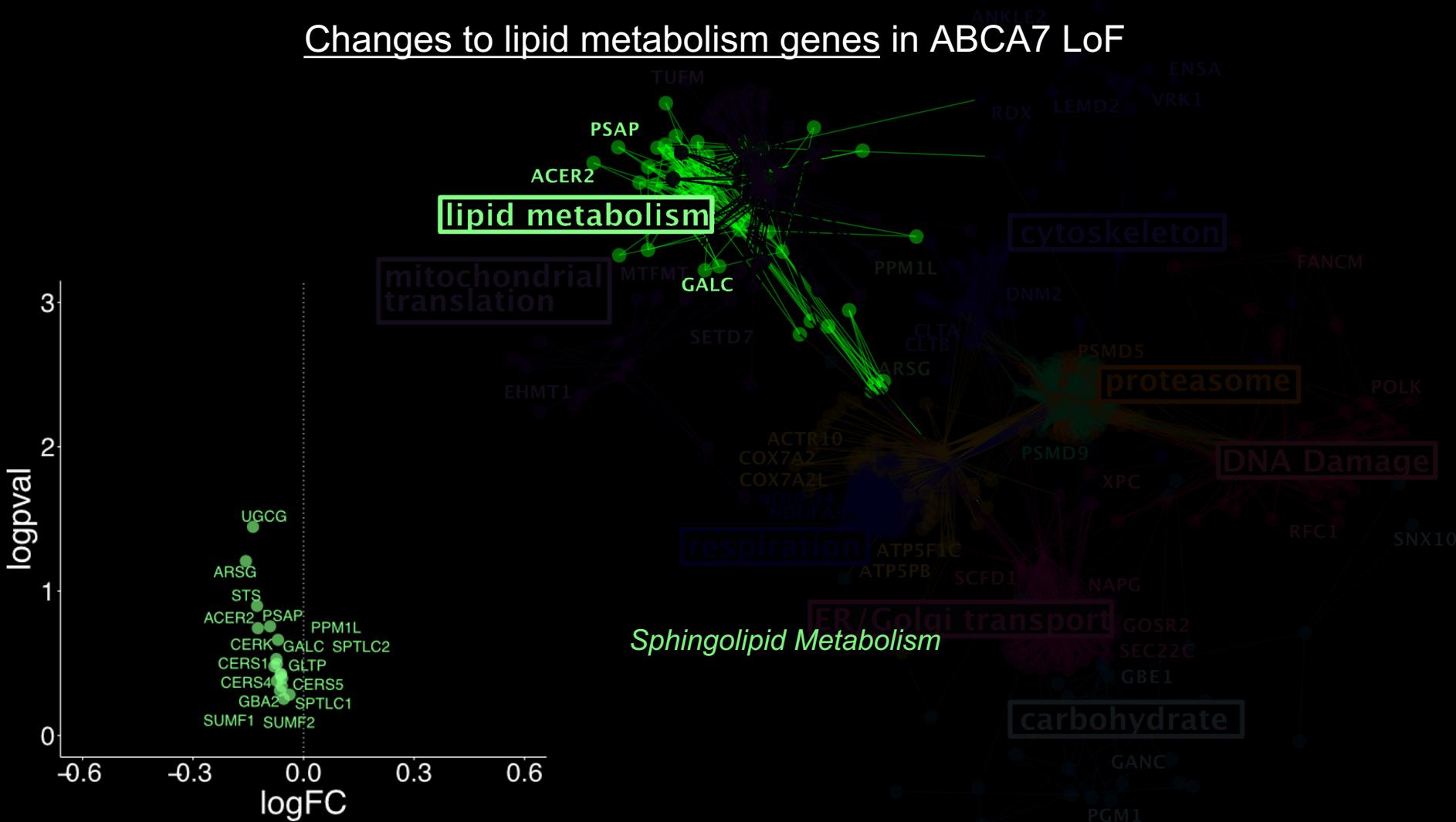


Increased nuclear localization of NFKB in ABCA7 LoF human brain



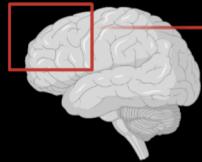
See also for DNA damage & inflammatory signaling in neurons:
Welch et al, SCIENCE ADVANCES, 2022, Vol 8, Issue 39 DOI:
[10.1126/sciadv.abo4662](https://doi.org/10.1126/sciadv.abo4662)

Changes to lipid metabolism genes in ABCA7 LoF

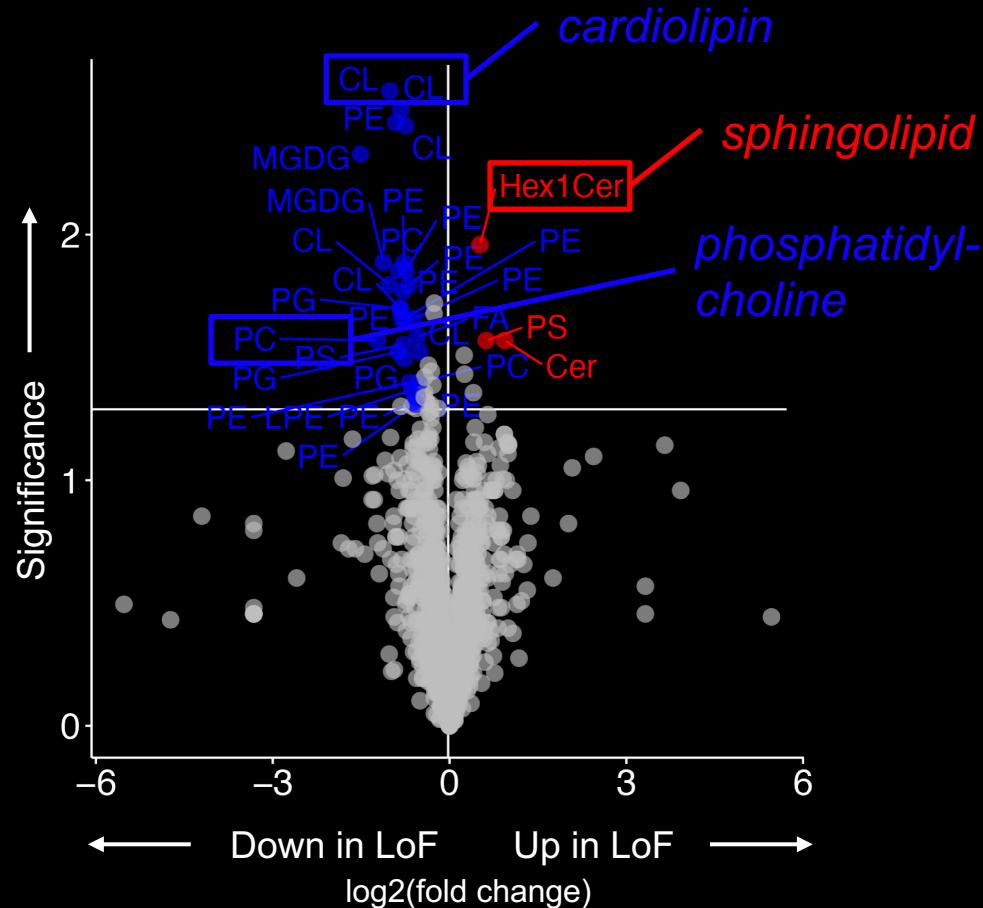
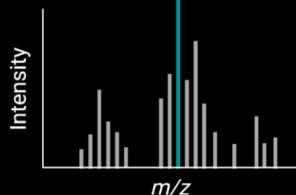


Is the lipidome altered in ABCA7 LoF brains?

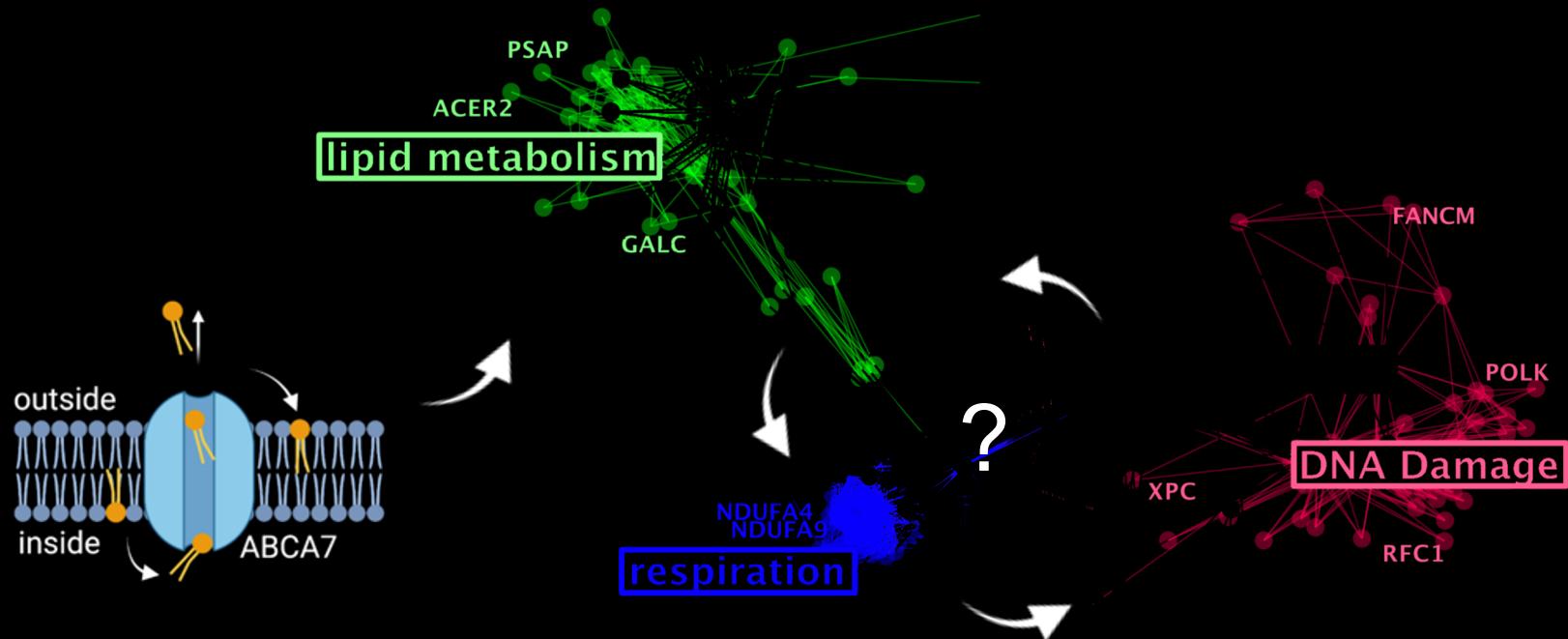
lipidome profiling



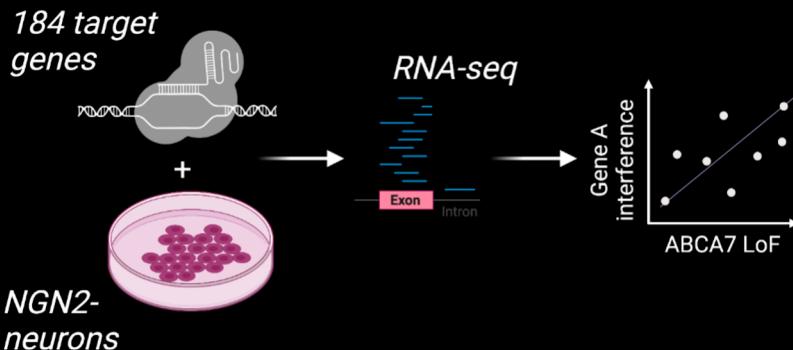
ABCA7 Con (N=8)
ABCA7 LoF (N=8)



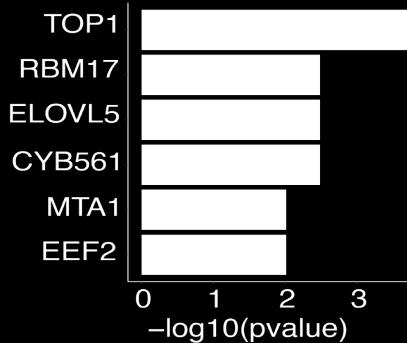
How do these perturbations causally relate to one another?



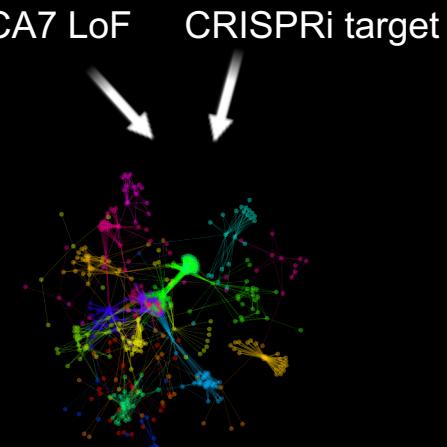
How do these perturbations relate to one another?



CRISPRi target



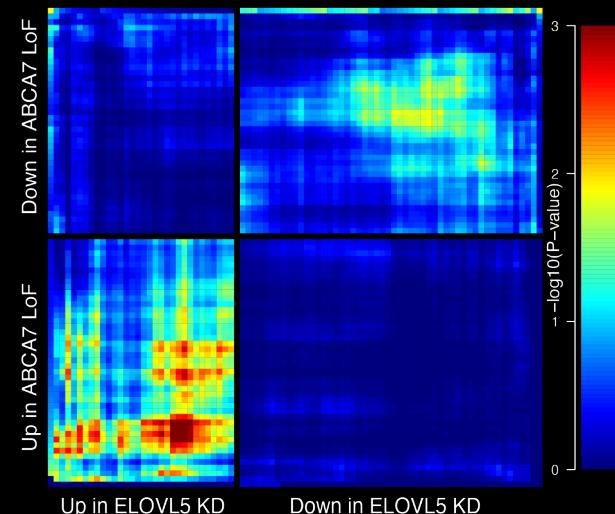
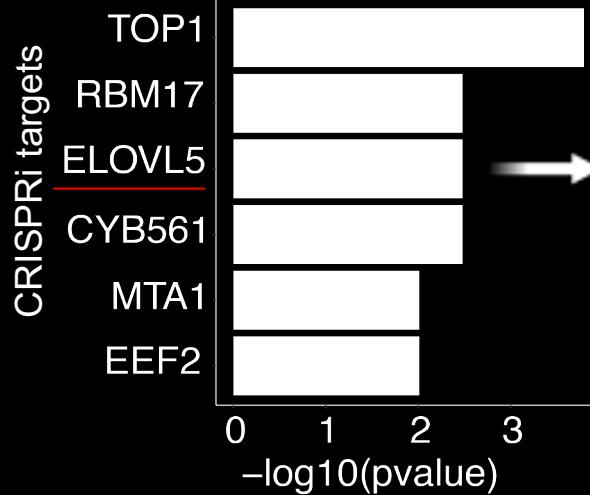
ABCA7 LoF



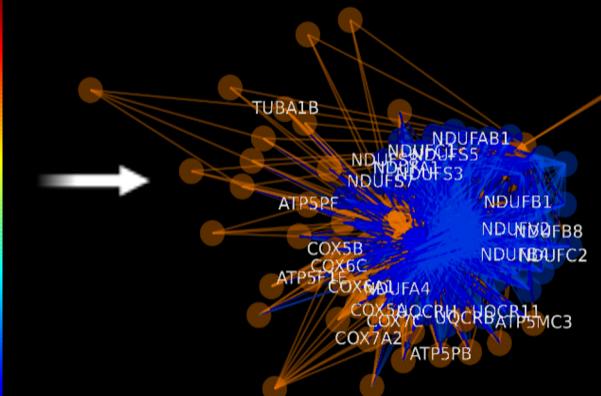
CRISPRi data source: Tian *et al* *Nat Neurosci* 24, 1020–1034 (2021).
Available through www.crisprbrain.org; Glutamatergic Neuron-RNA-Seq-CRISPRi-2020

Fatty acid elongase knock-down mimics transcriptional effects of ABCA7 LoF

Transcriptional Overlap between ABCA7 LoF (Ex, brain) and ELOVL5 (NGN2)

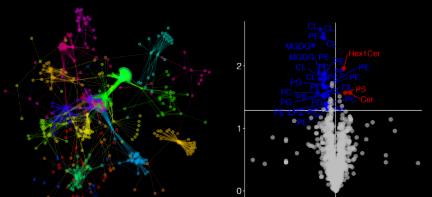
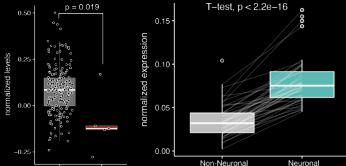


mitochondrial gene clusters

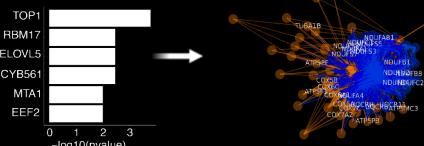


Does ABCA7 LoF induce high-risk cell states by disrupting the lipidome?

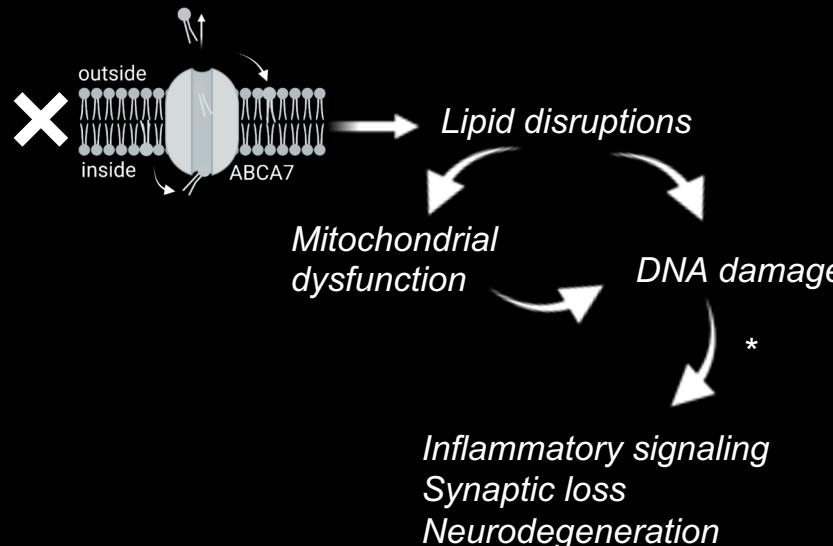
Observations



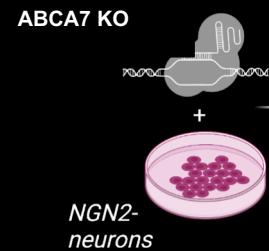
- Altered mitochondrial function
- DNA damage



Model



Testing



Acknowledgments

Thank you to the ROSMAP participants, their families, and the scientists and clinicians enabling the ROSMAP study - This research is not possible without you!



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Jenny Pao (Current: Sanofi)
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