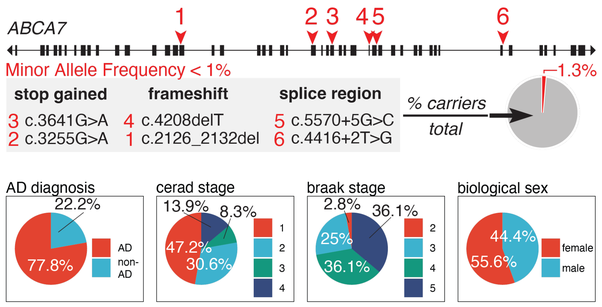
Single-cell atlas of ABCA7 loss-of-function reveals impaired neuronal respiration via choline-dependent lipid imbalances

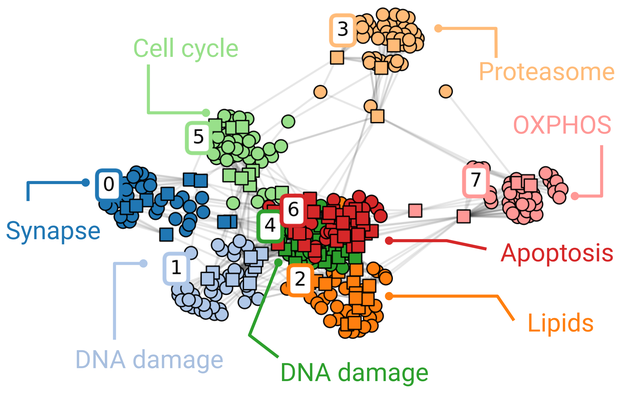
Why should we care about ABCA7?

- Rare ABCA7 LoF variants (MAF < 1%) increase Alzheimer's risk (OR ~2).
- Common ABCA7 variant (MAF *circa* 18%) p.Ala1527Gly raises Alzheimer's risk.
- ABCA7 effluxes phospholipids to maintain lipid balance (via transfer to apolipoproteins and "lipid flipping")

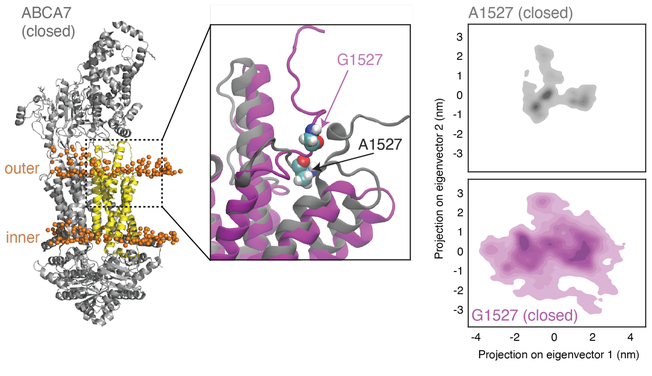
A human brain single-cell atlas of ABCA7 LoF



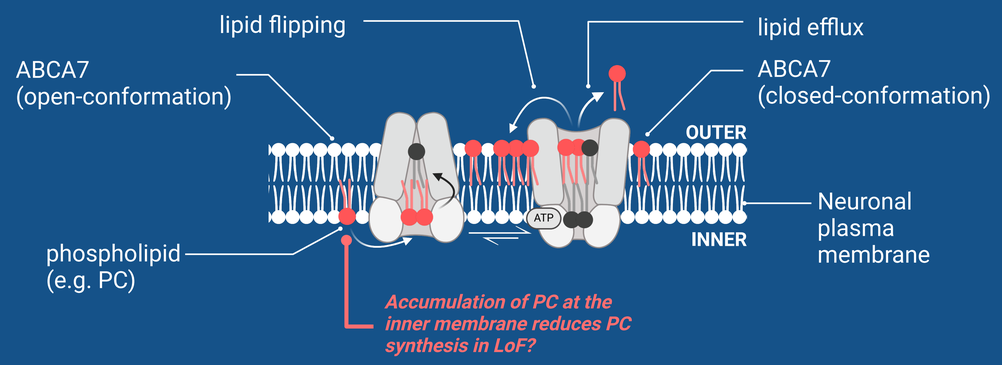
Transcriptional signatures of ABCA7 LoF in excitatory neurons, the top ABCA7-expressing cell type

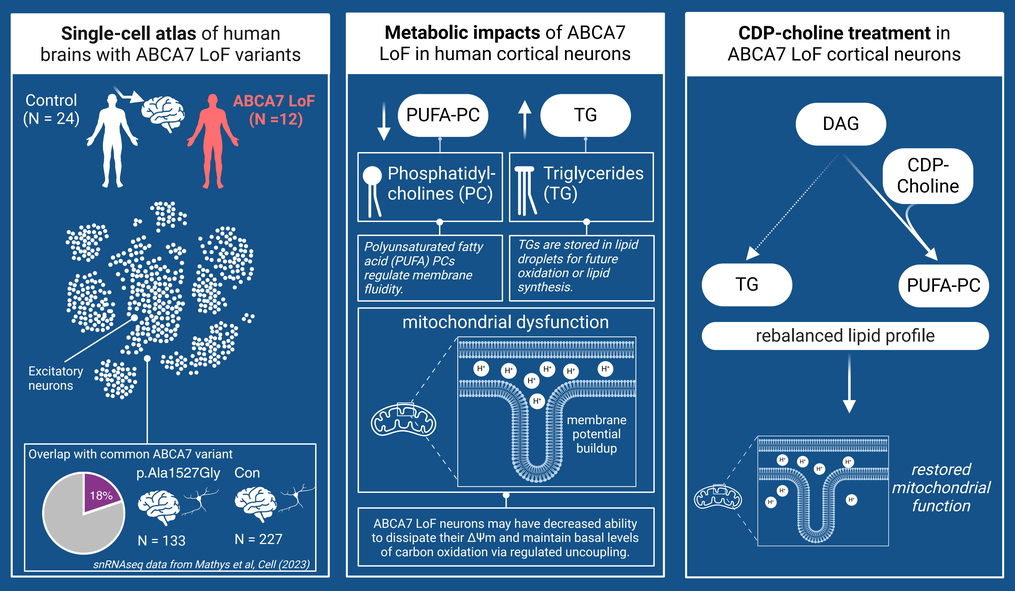


p.Ala1527Gly disrupts ABCA7 helical structure and shares transcriptional perturbations with LoF neurons



ABCA7 loss-of-function variants disrupt neuronal lipid metabolism and respiration





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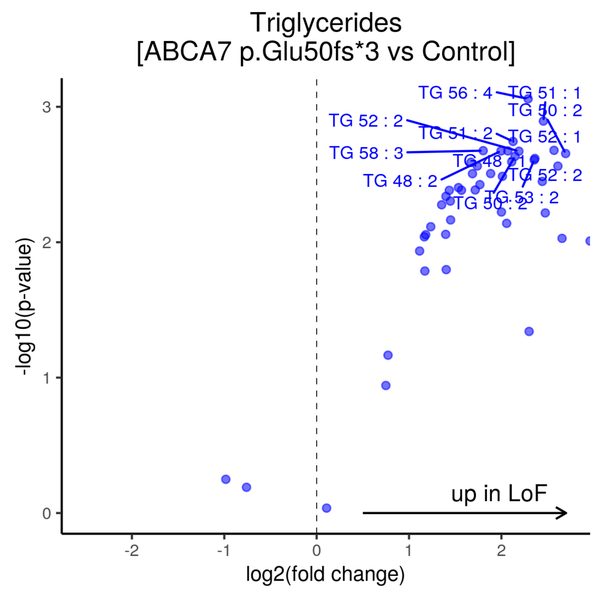
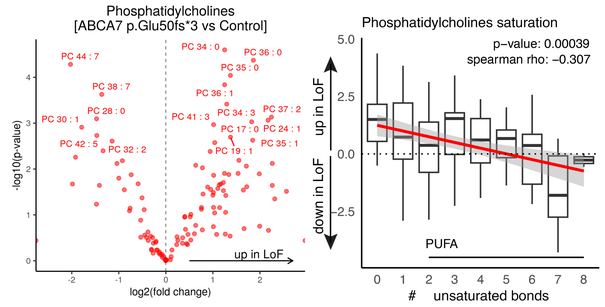
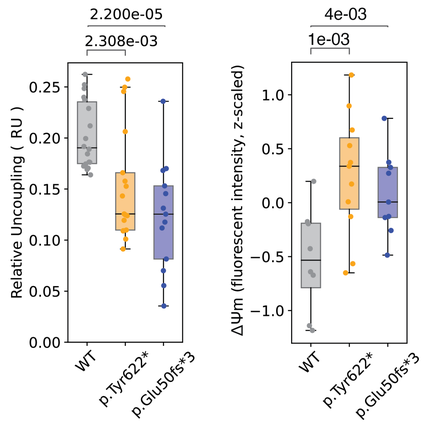
ABCA7 LoF human iPSC neurons accumulate unsaturated triglycerides ...



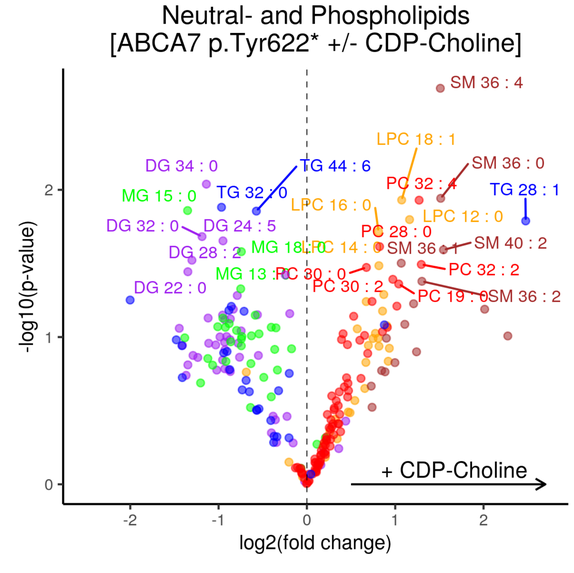
... have reduced polyunsaturated phosphatidylcholines



... and mitochondrial impairments



CDP-choline supplementation restores lipid balance and mitochondrial functions



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