

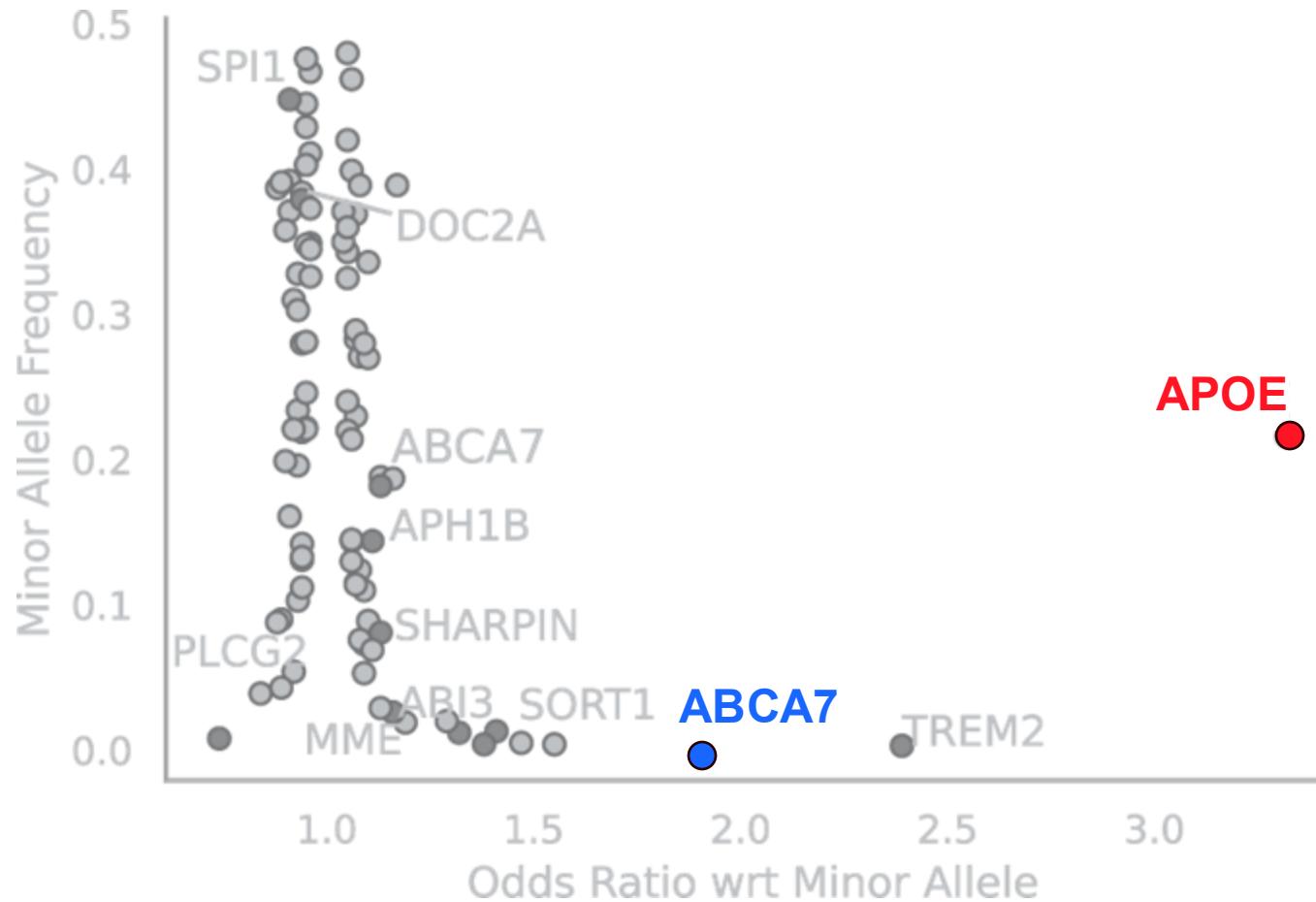
ABCA7 variants impact phosphatidylcholine and mitochondria in neurons

Alzheimer's Association International Conference 2025

Djuna von Maydell
PhD Candidate, Tsai Lab

July 27th 2025

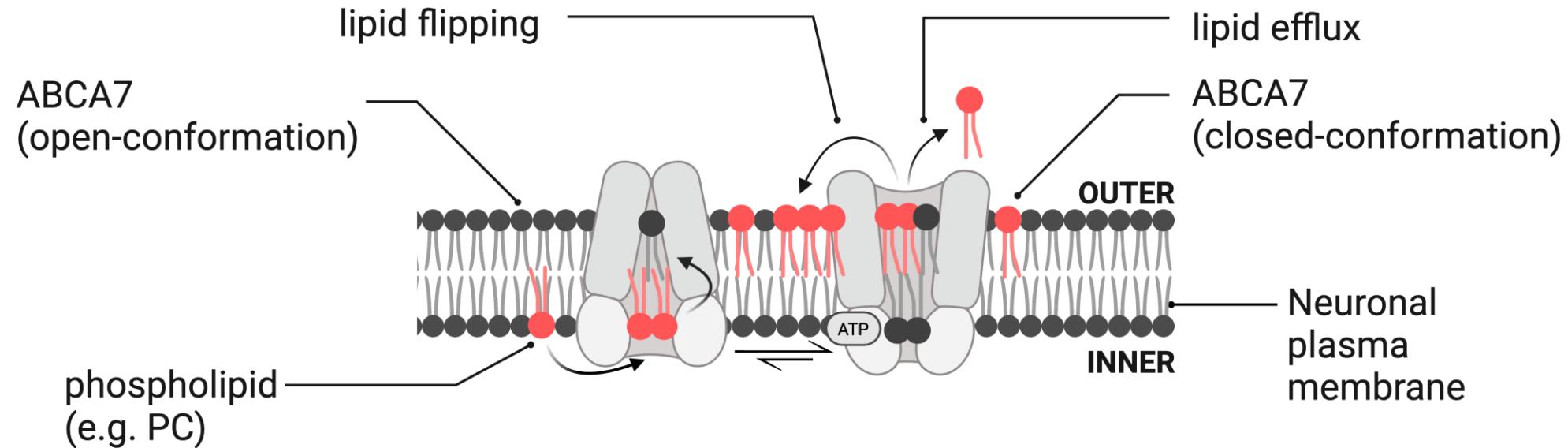
ABCA7 loss-of-function variants in Alzheimer's disease



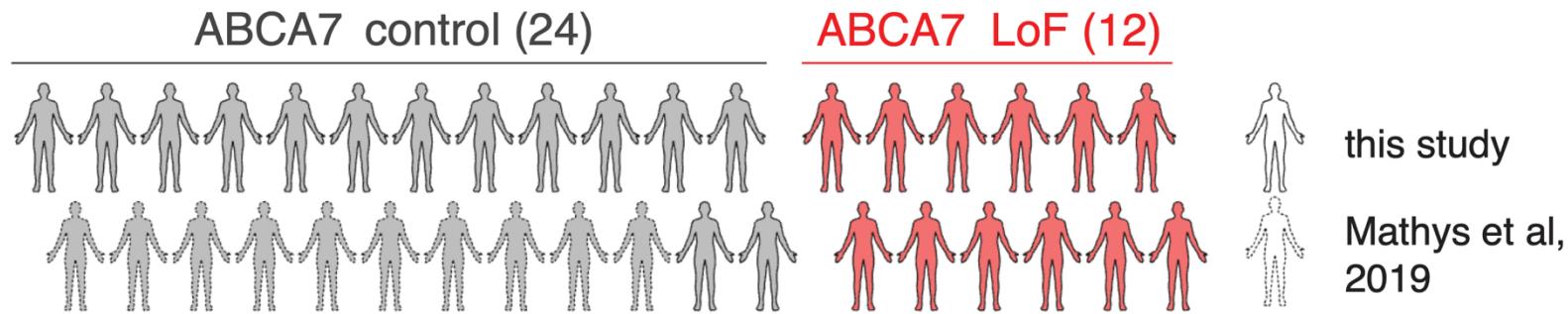
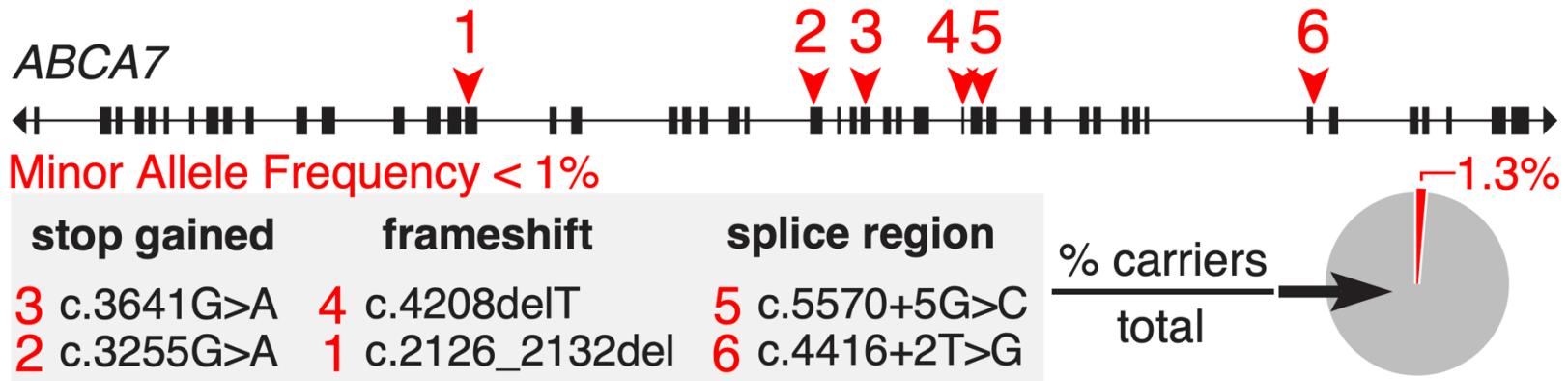
Data source: Kunkle et al, Table 1, Nat Genet 51, 414–430 (2019)

ABCA7 in blue: Steinberg et al, Nat Genet (2015); Holstege et al, Nat Genet (2022)

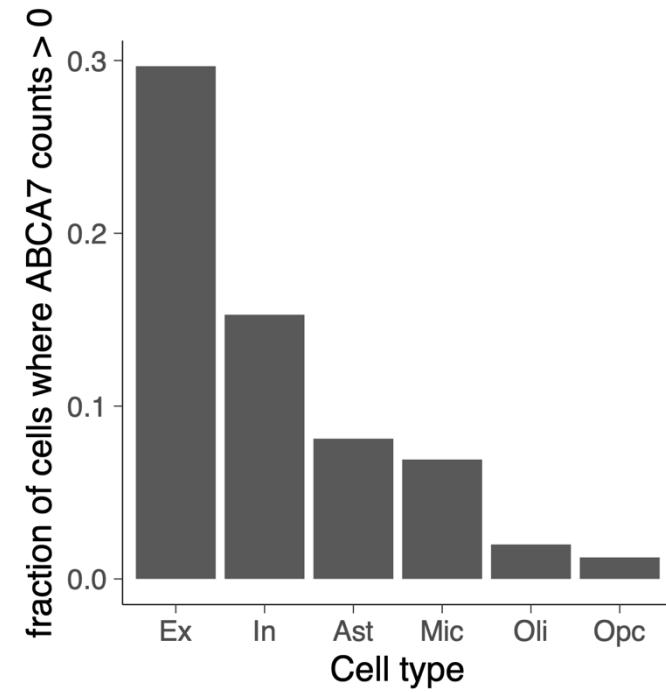
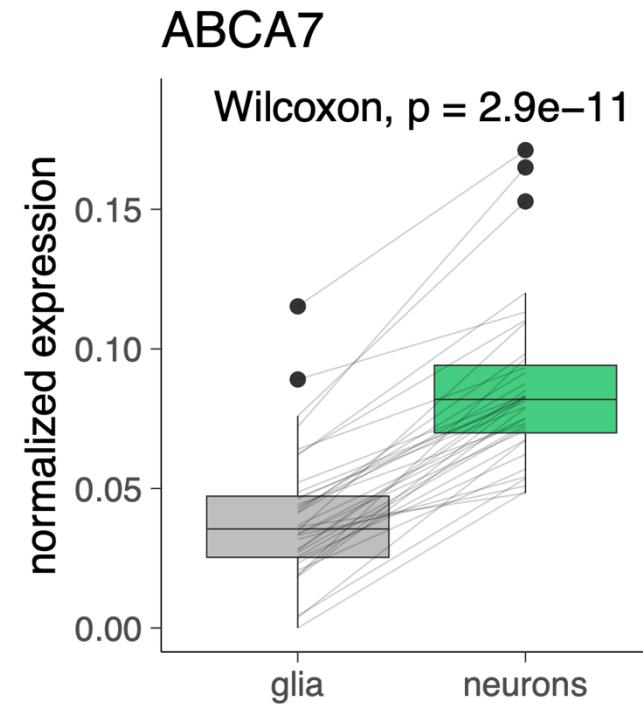
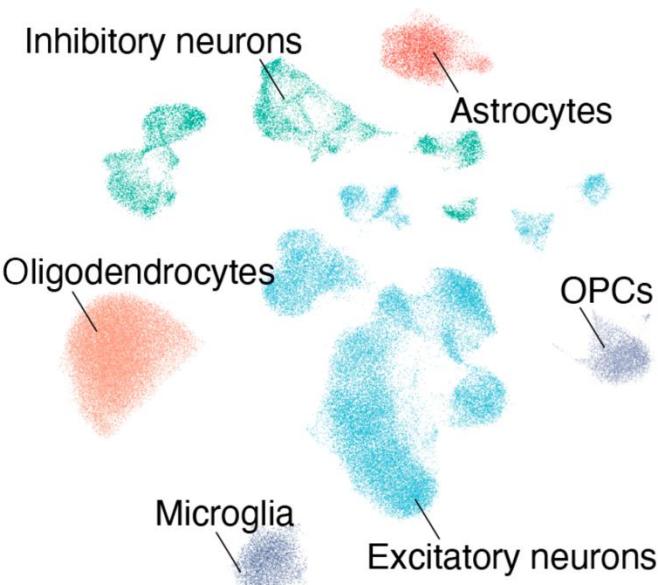
ABCA7 transfers phospholipids across membranes



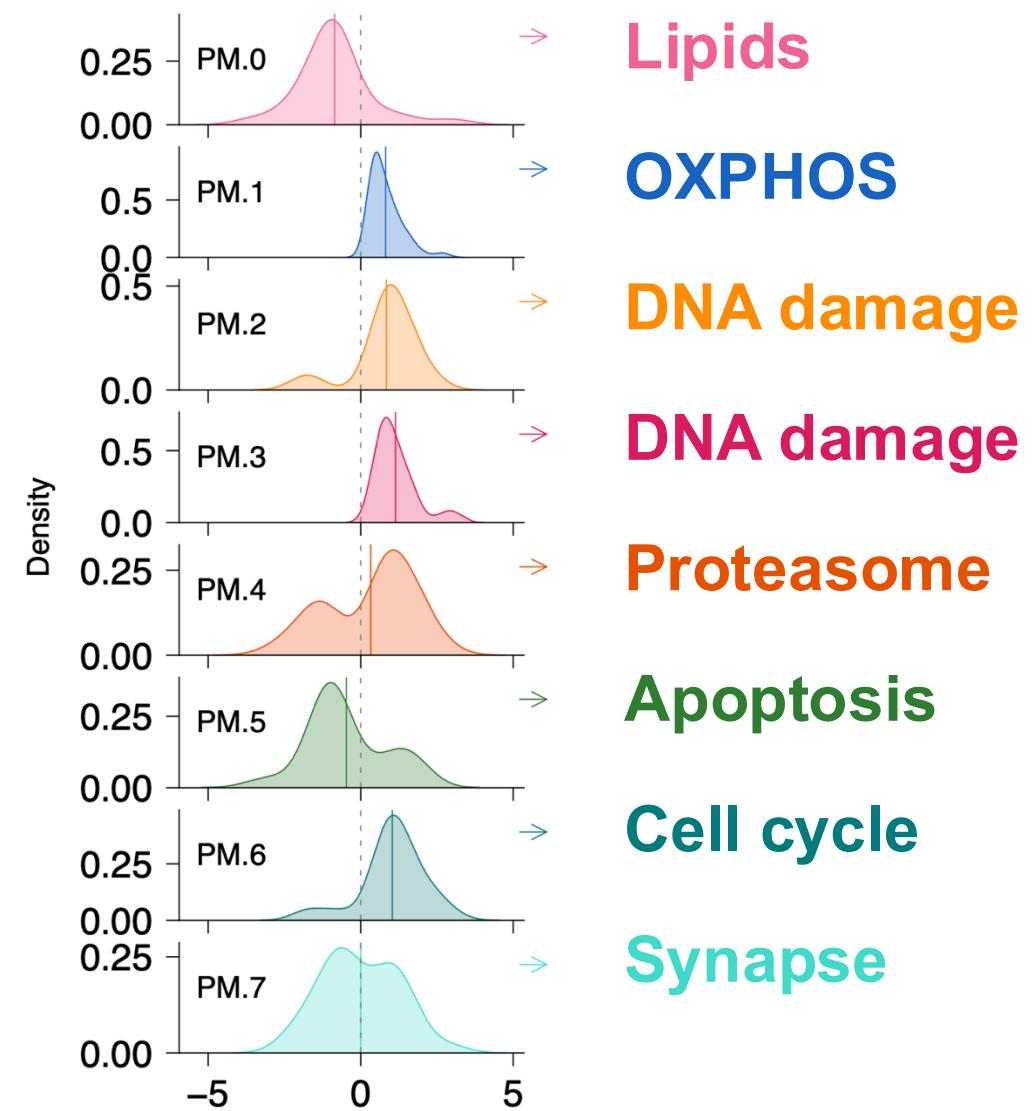
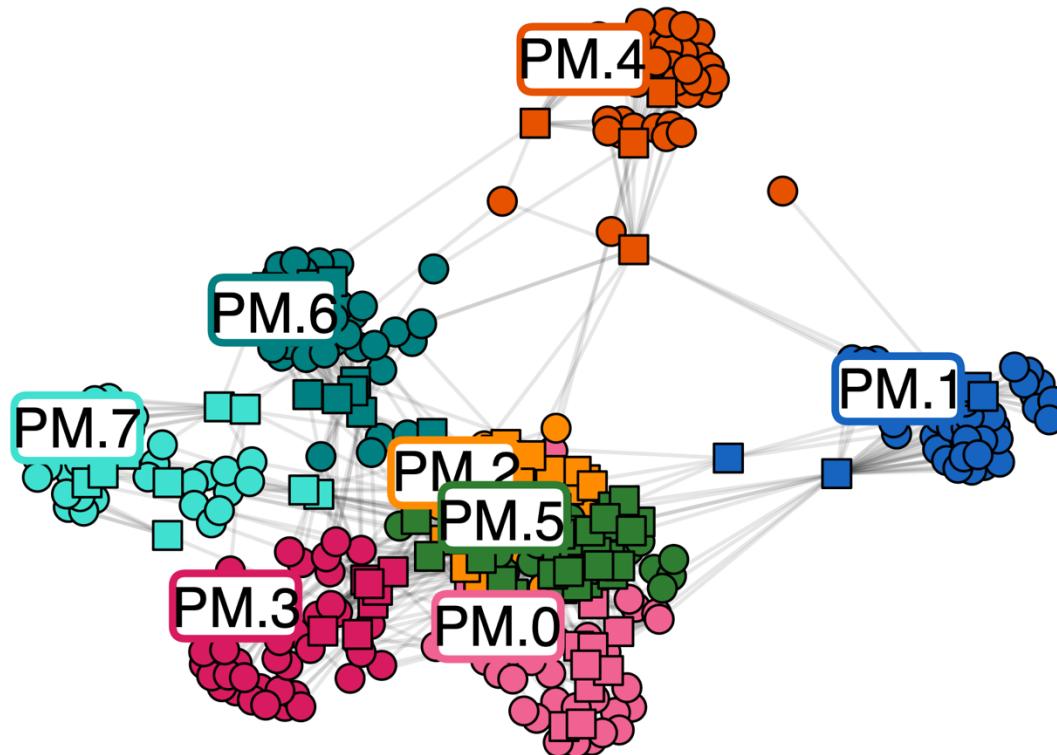
A single-cell atlas of ABCA7 loss-of-function variants



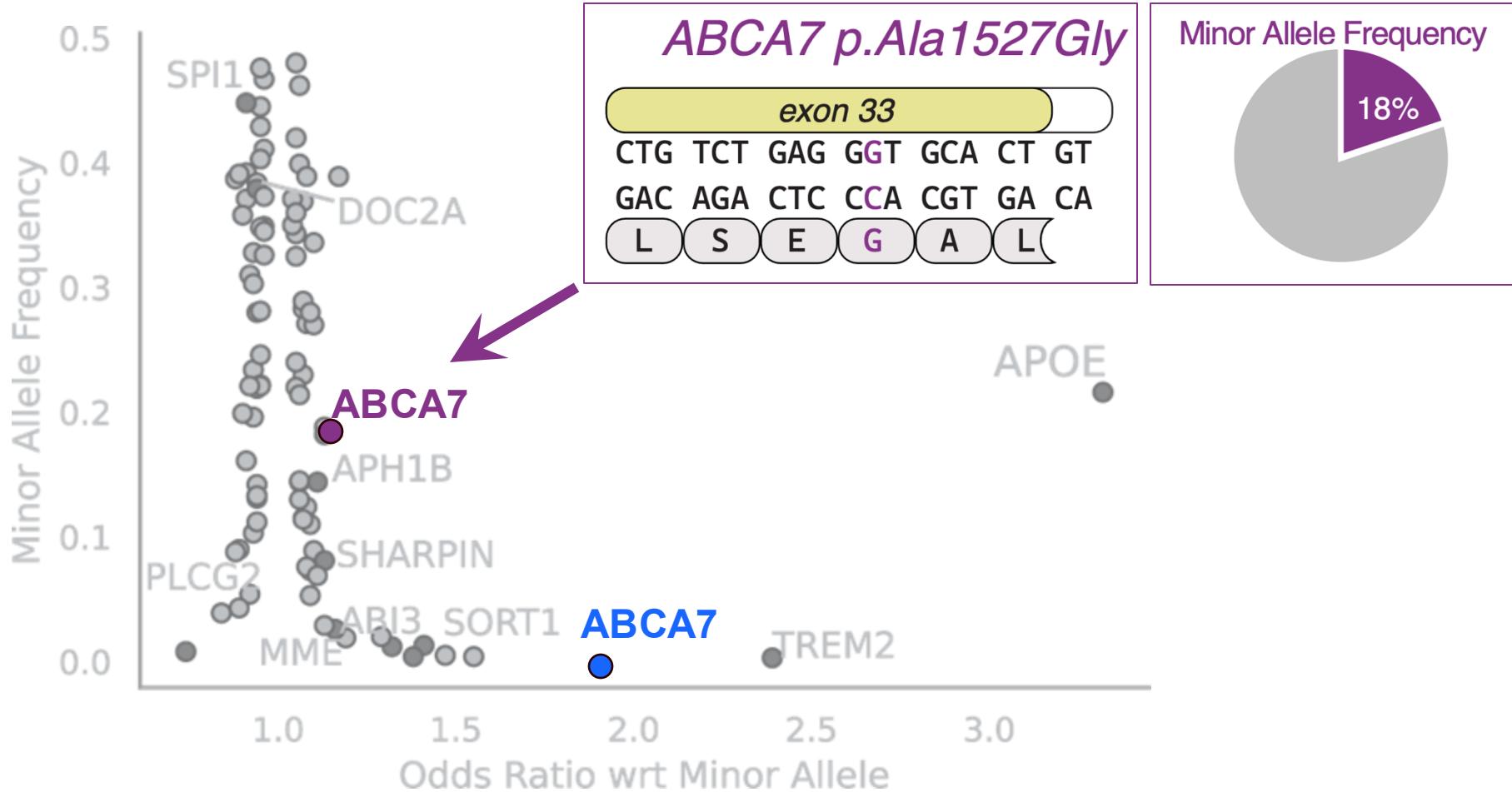
Highest ABCA7 expression is in excitatory neurons



Transcriptional correlates in excitatory neurons



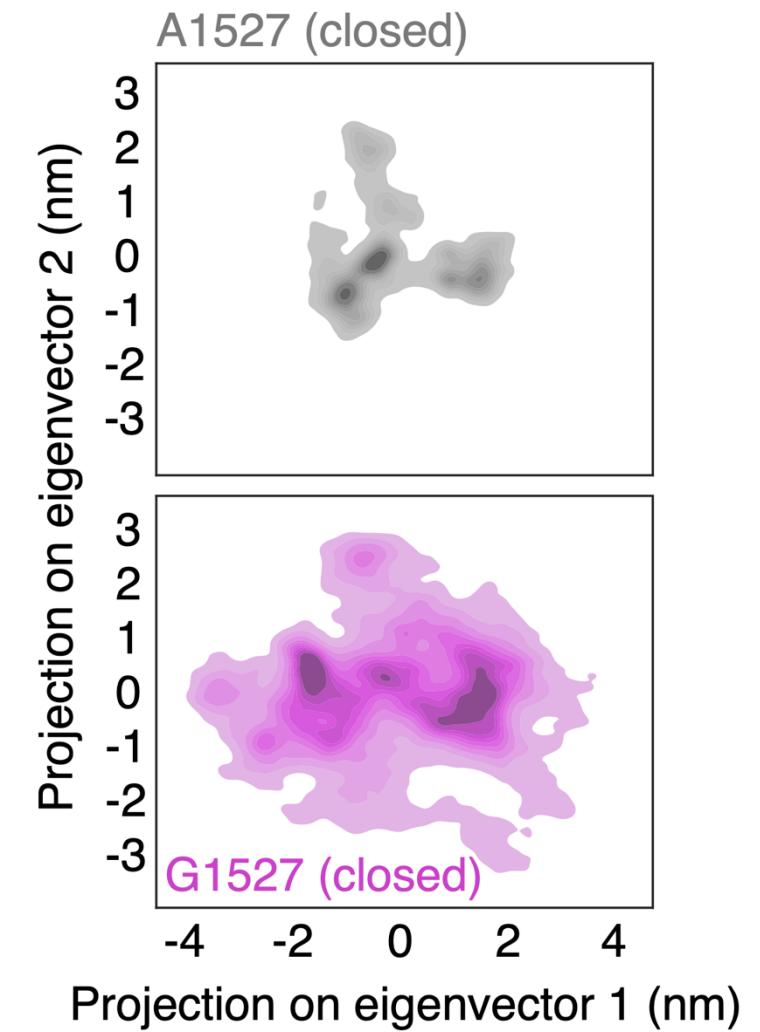
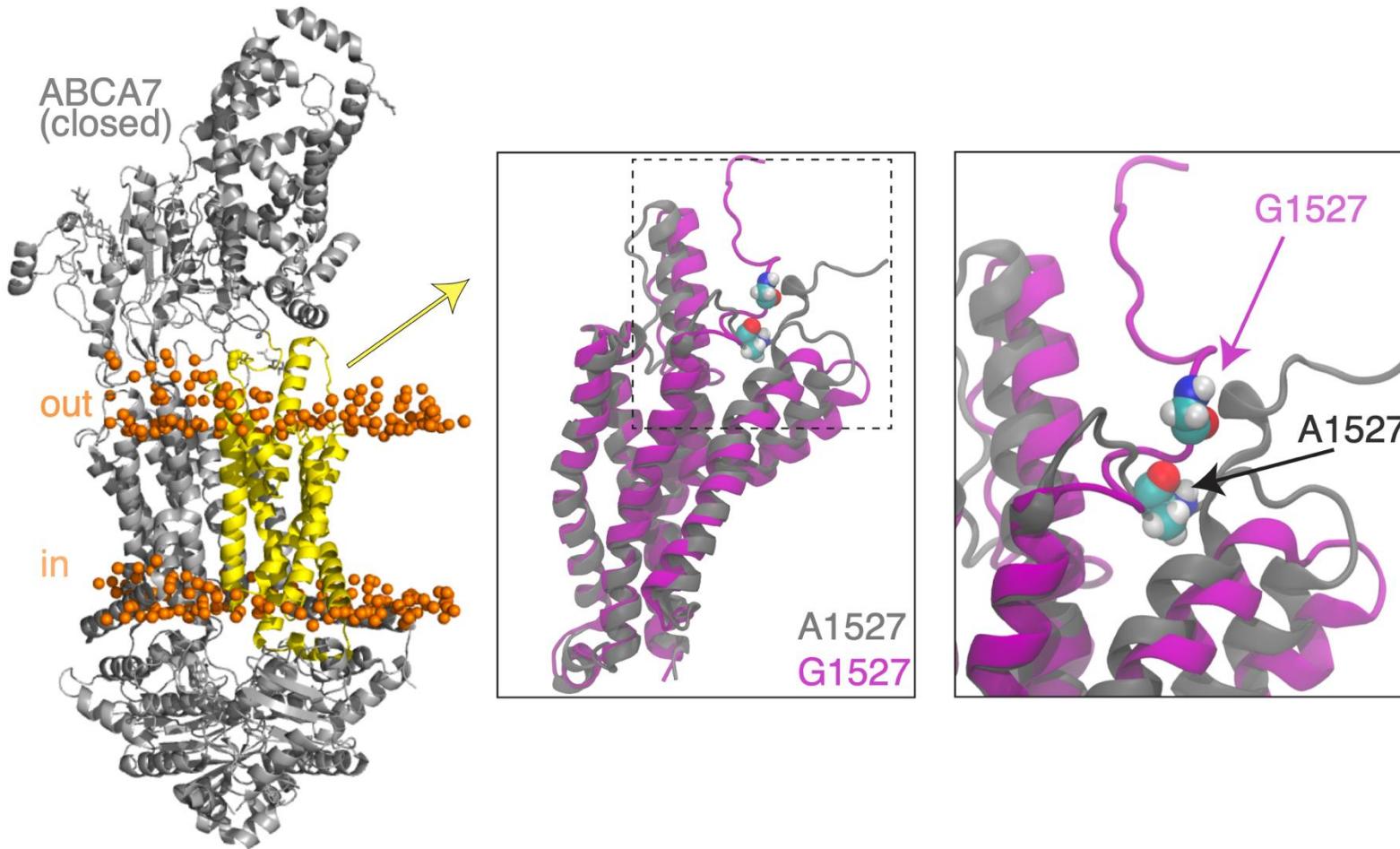
Common missense variant in ABCA7 increases risk



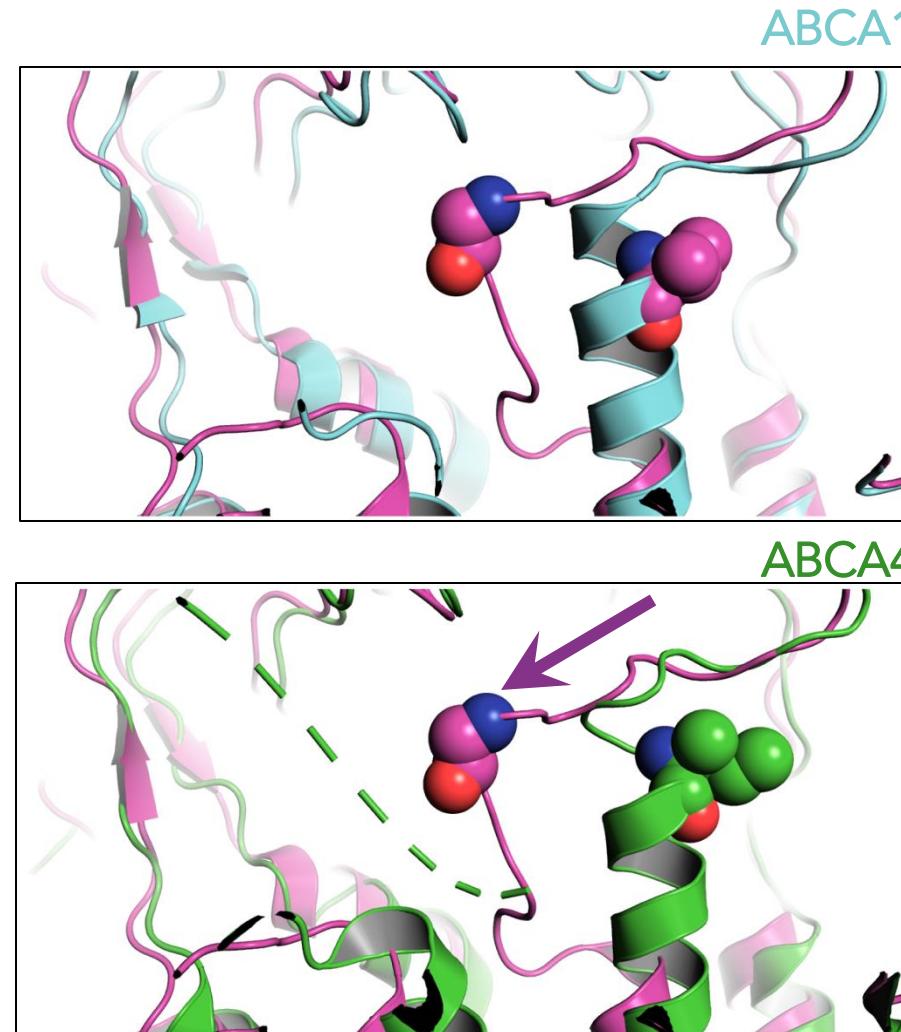
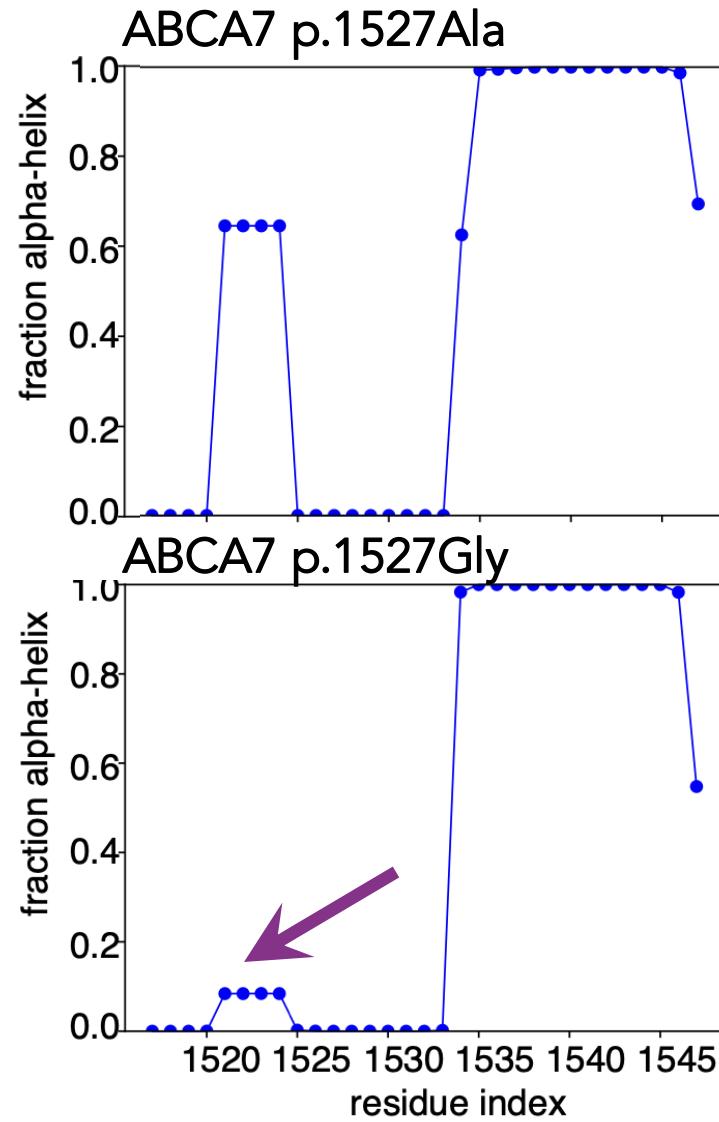
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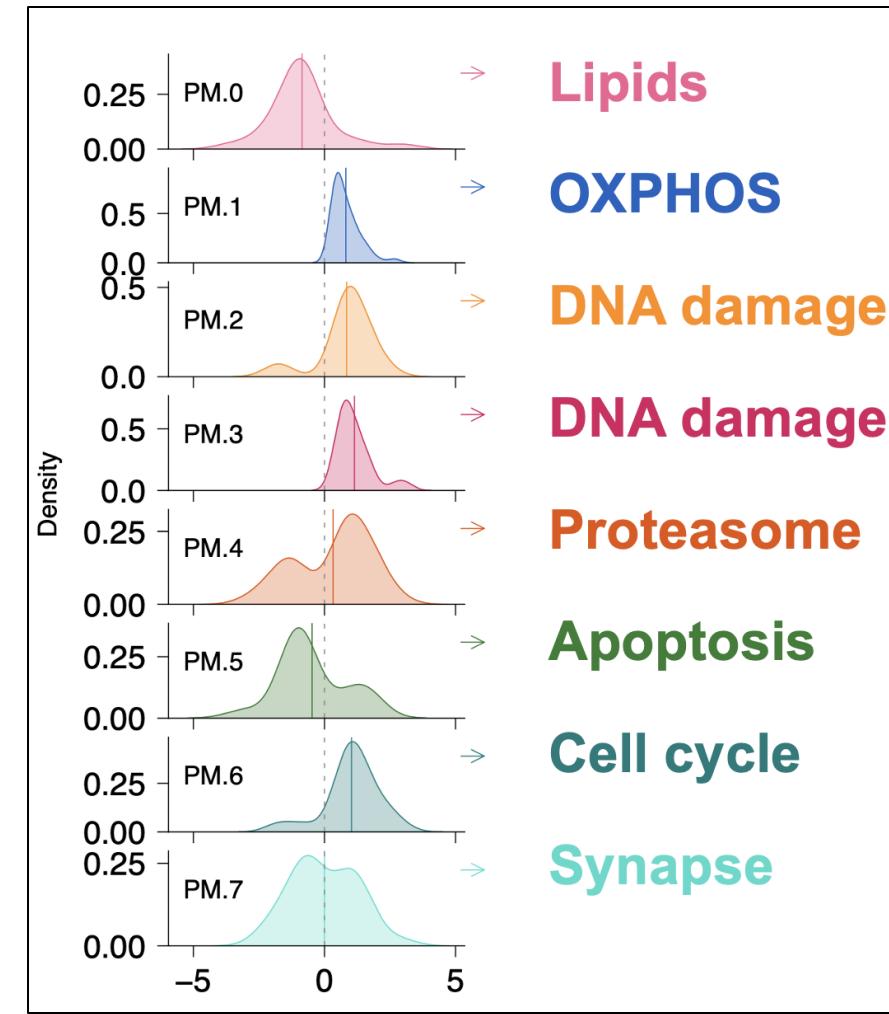
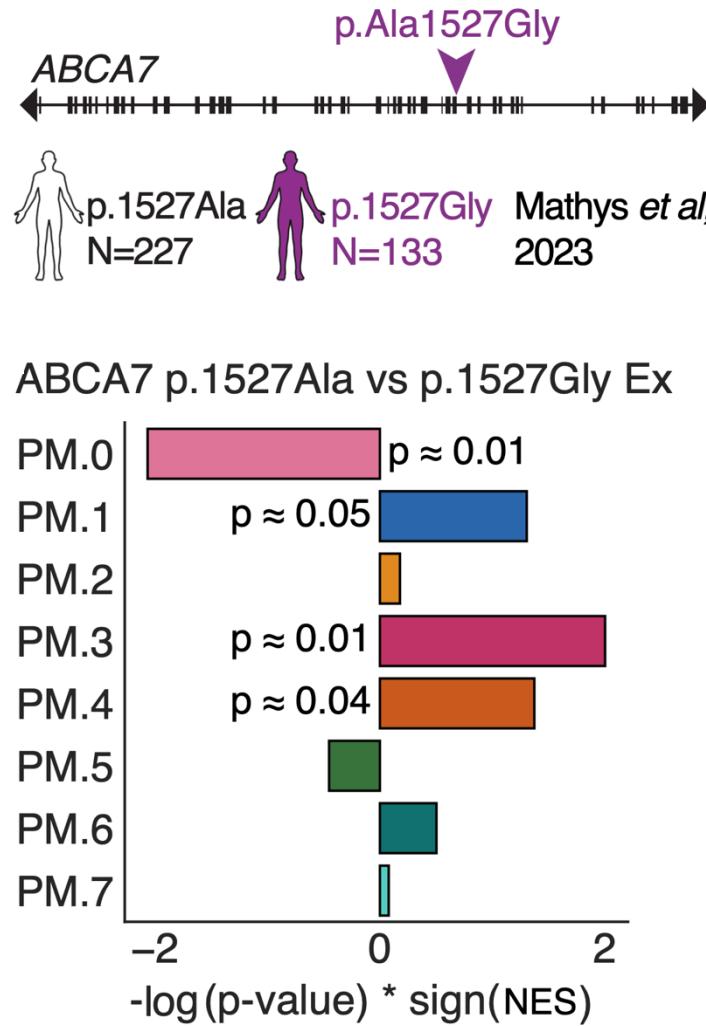
Structural impact of ABCA7 p.Ala1527Gly



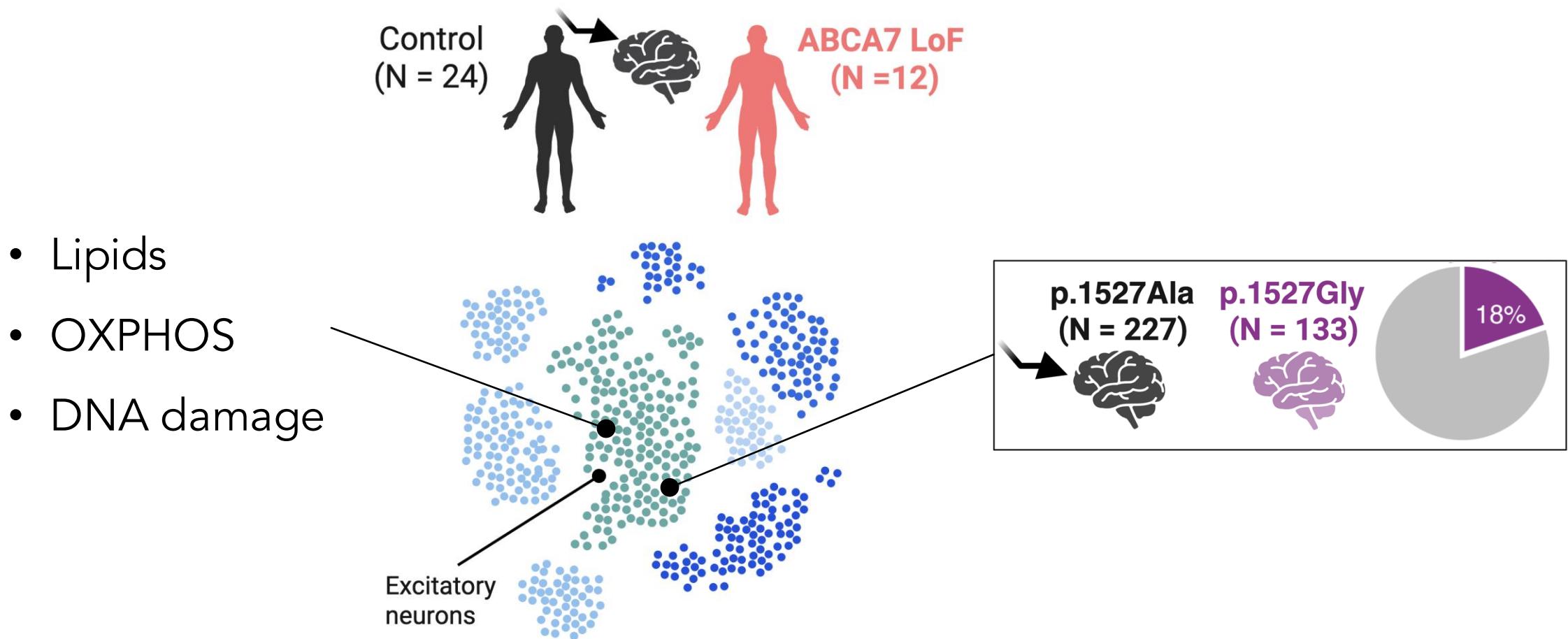
Structural impact of ABCA7 p.Ala1527Gly



Transcriptional overlap of loss-of-function and p.Ala1527Gly



Summary: Single-nuclear RNA-seq atlas



Deriving human neurons with ABCA7 loss-of-function variants

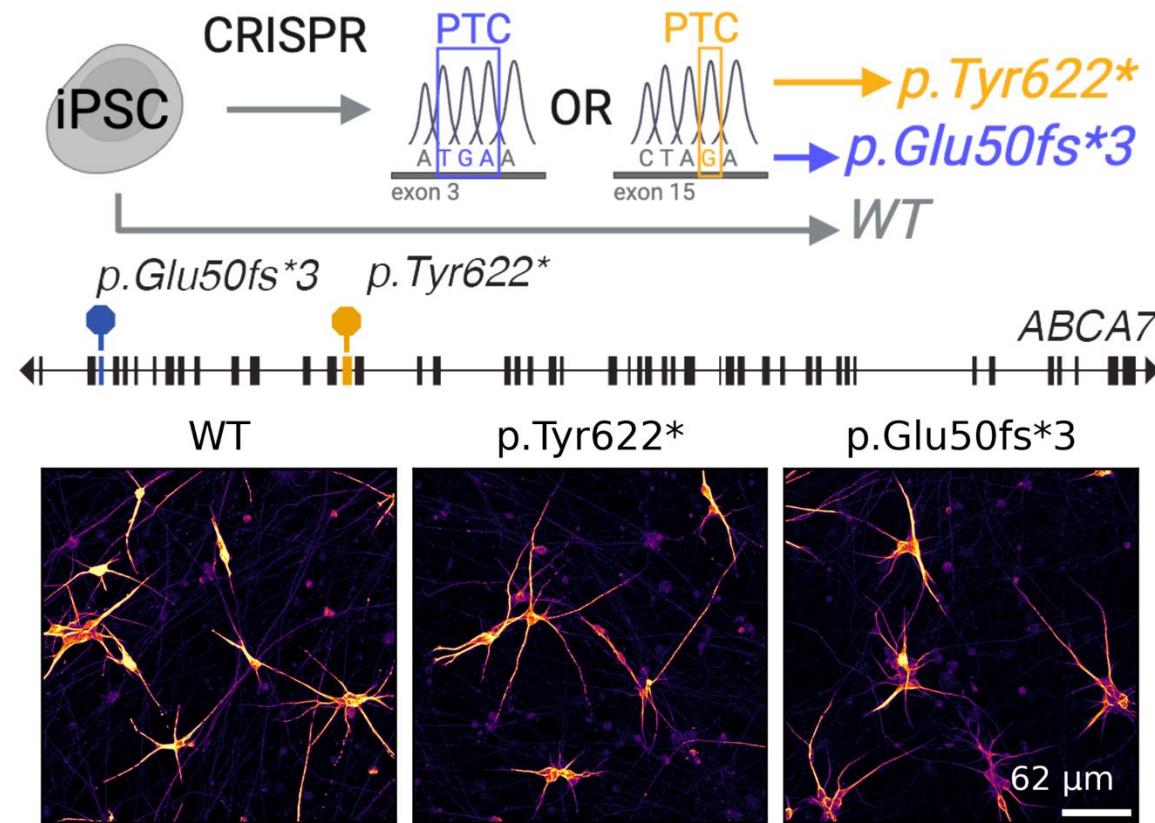
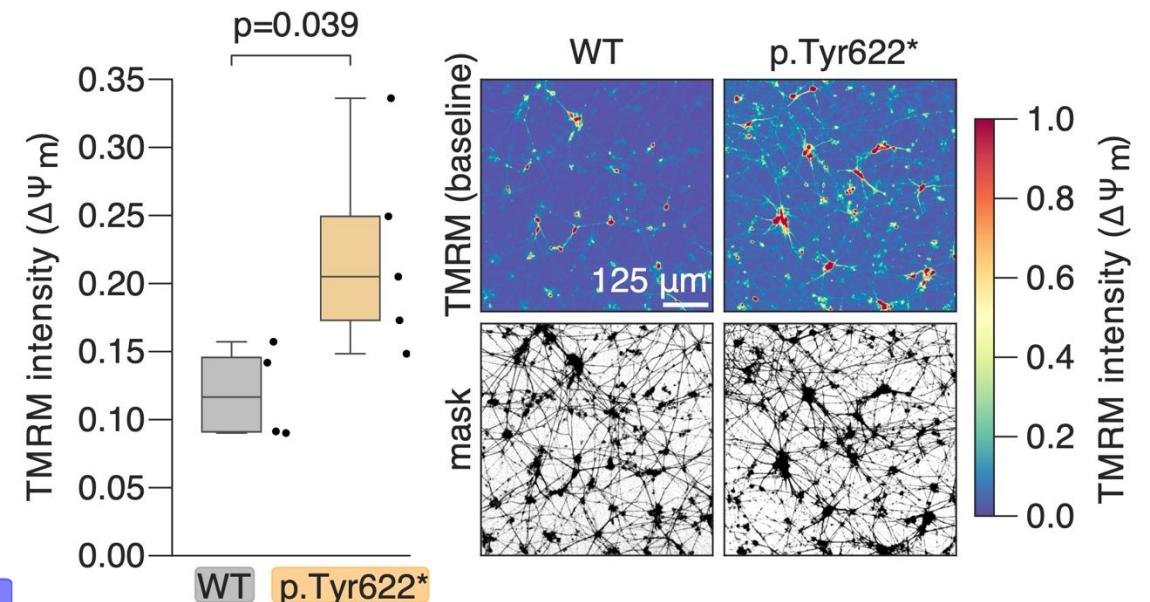
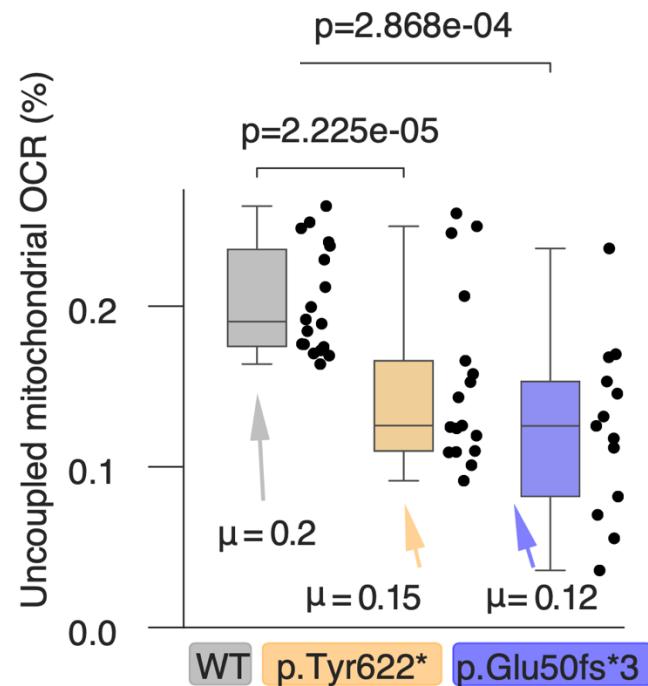
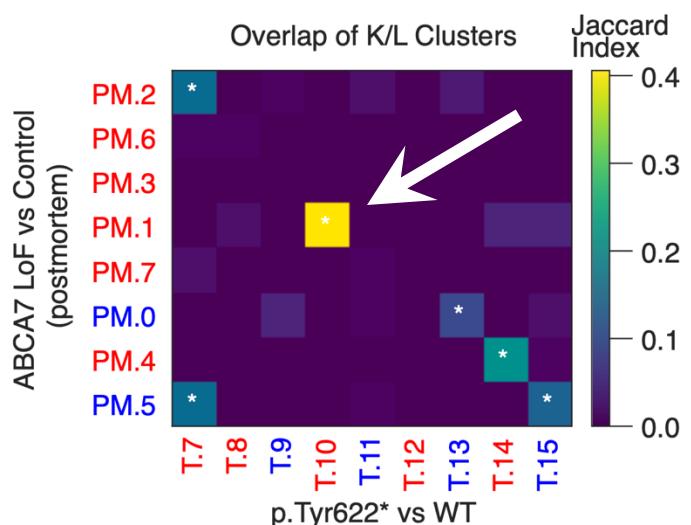


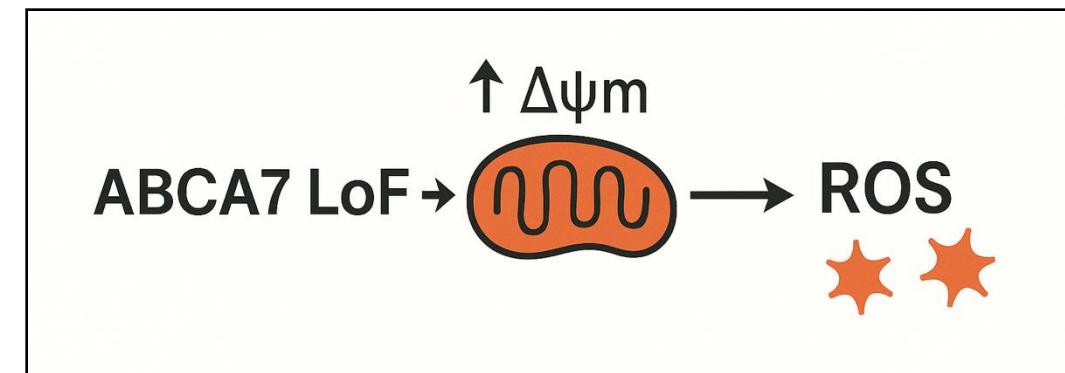
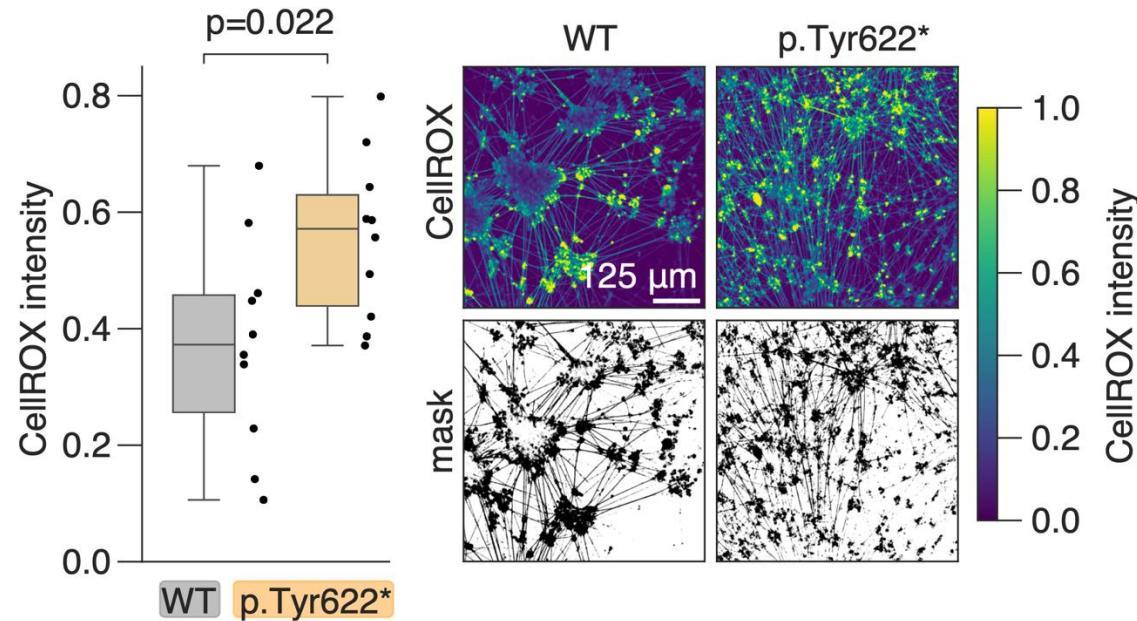
Table 1 Association of loss-of-function variants in *ABCA7* with Alzheimer's disease in Iceland

Variant	Position ^a	Rs ID	MAF (%)	OR	P	Info
p.Tyr622*	Chr19:998,176	-	0.041	4.42	0.0034	0.98

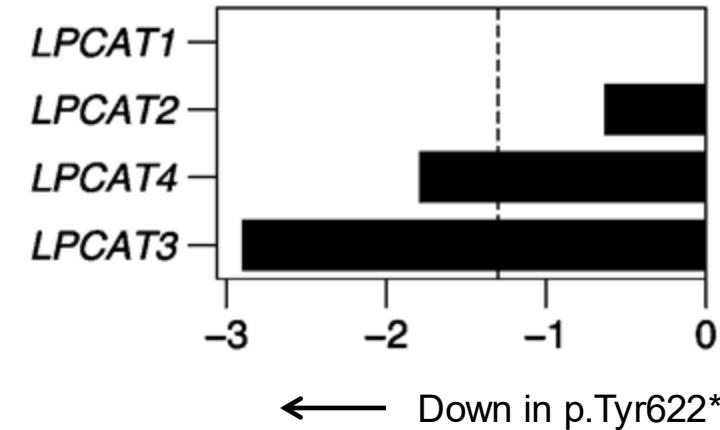
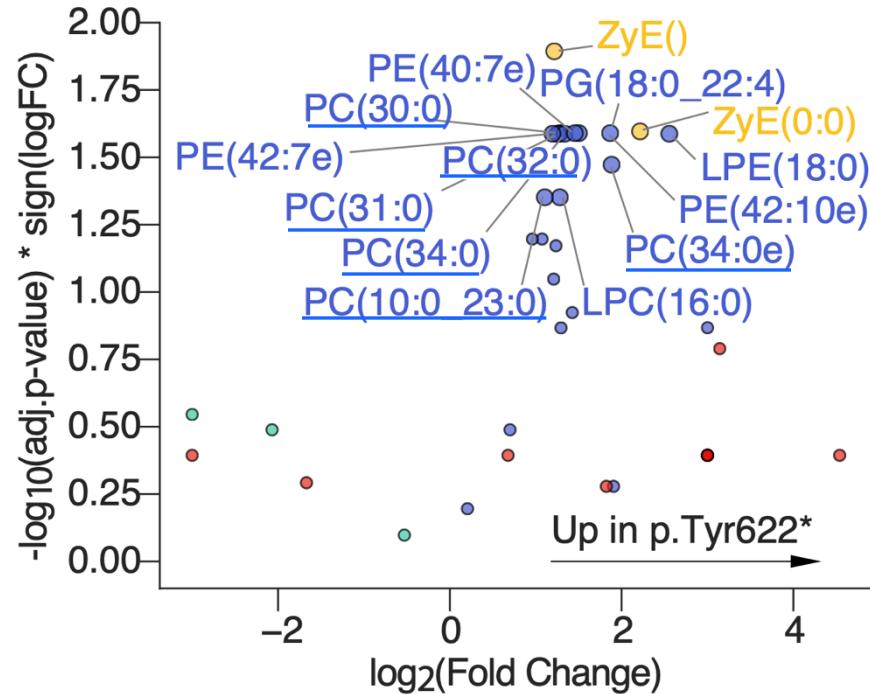
ABCA7 loss-of-function variants impact mitochondrial function



ABCA7 loss-of-function variants impact mitochondrial function

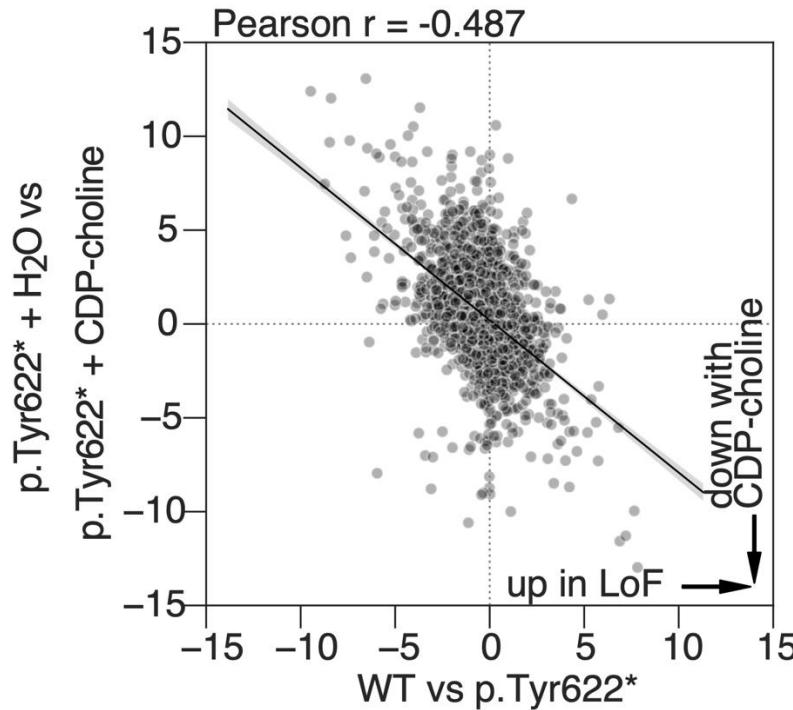
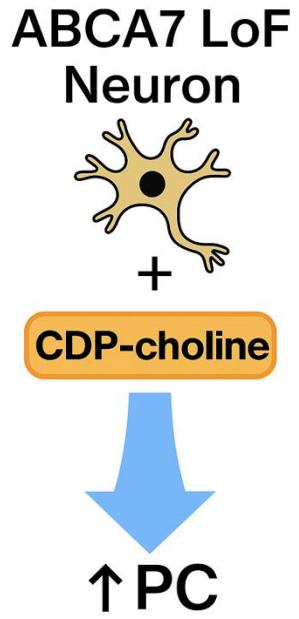


Shift towards saturated phosphatidylcholine in ABCA7 loss-of-function



Also \uparrow SFA PC in p.Glu50fs*3 along with \downarrow PUFA PC and \uparrow PUFA TG

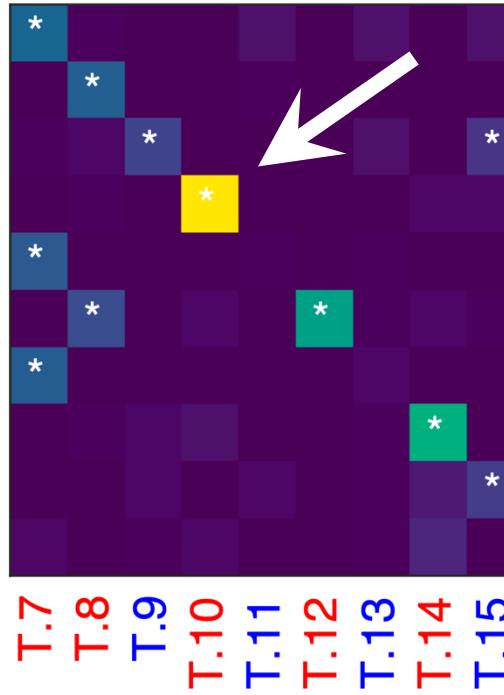
Boosting *de novo* PC synthesis reverses transcriptional signature



p.Tyr622* +/- CDP-choline

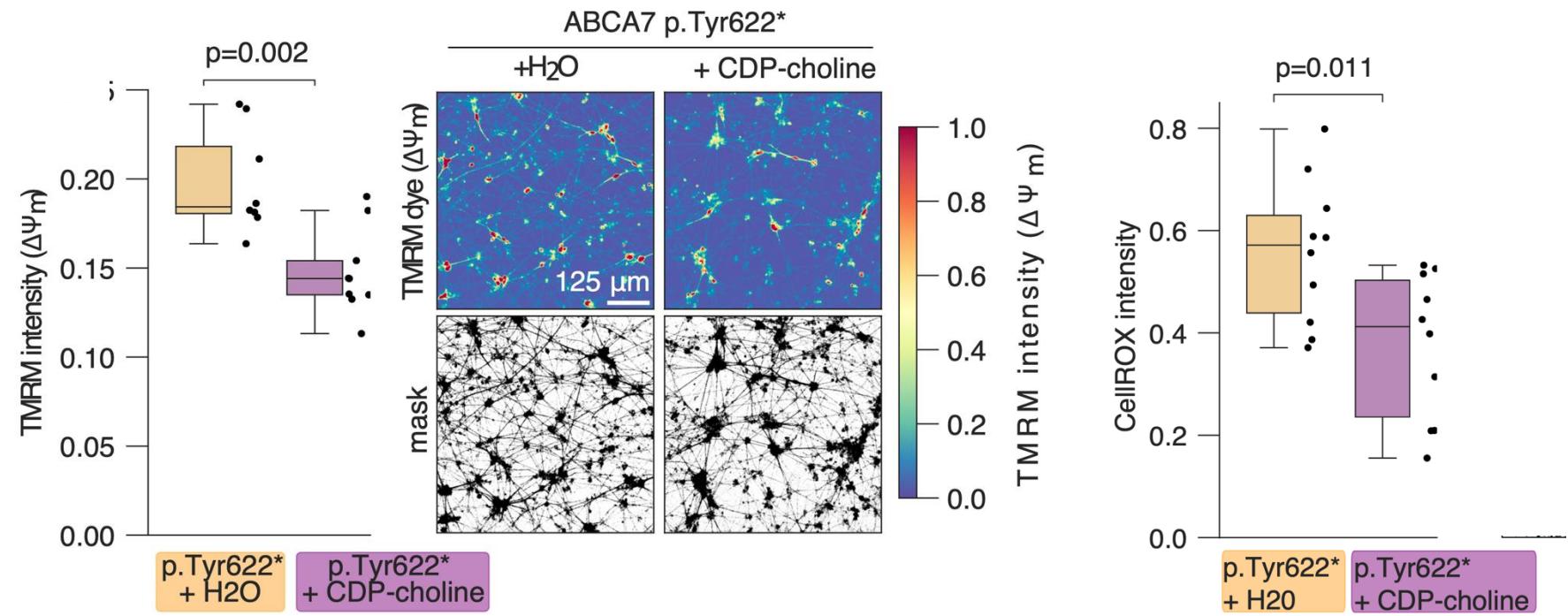
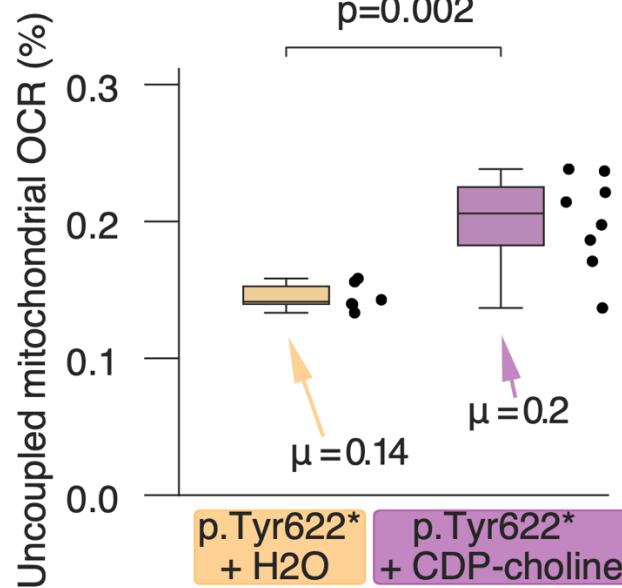
T+C.28
T+C.27
T+C.30
T+C.26
T+C.33
T+C.31
T+C.24
T+C.25
T+C.32
T+C.29

Overlap of K/L Clusters

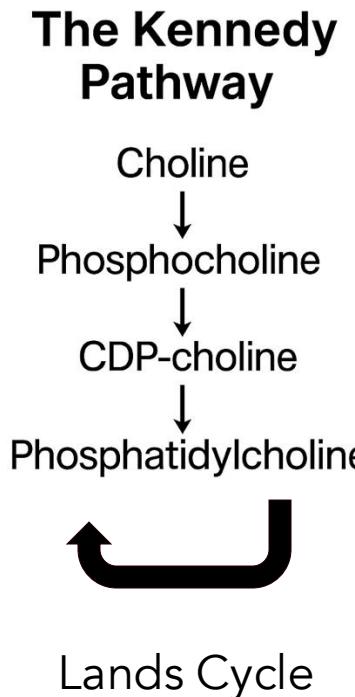
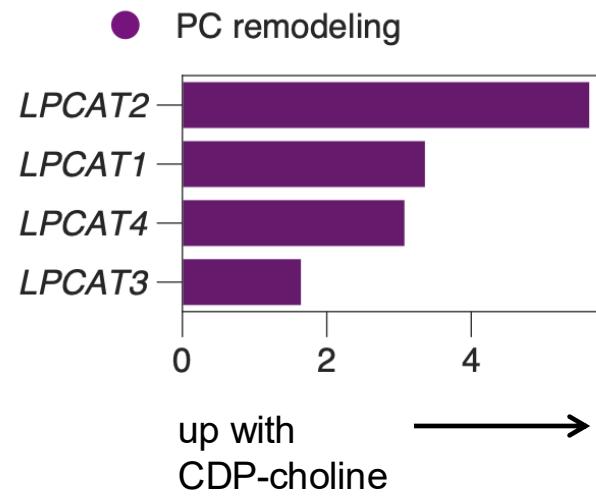
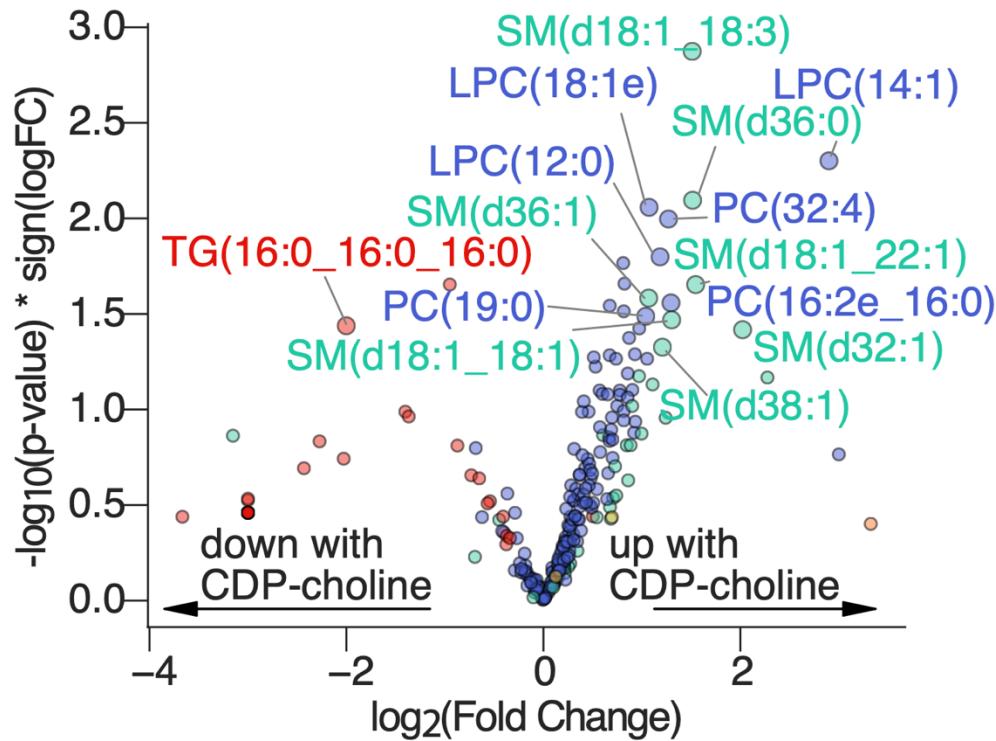


WT vs p.Tyr622*

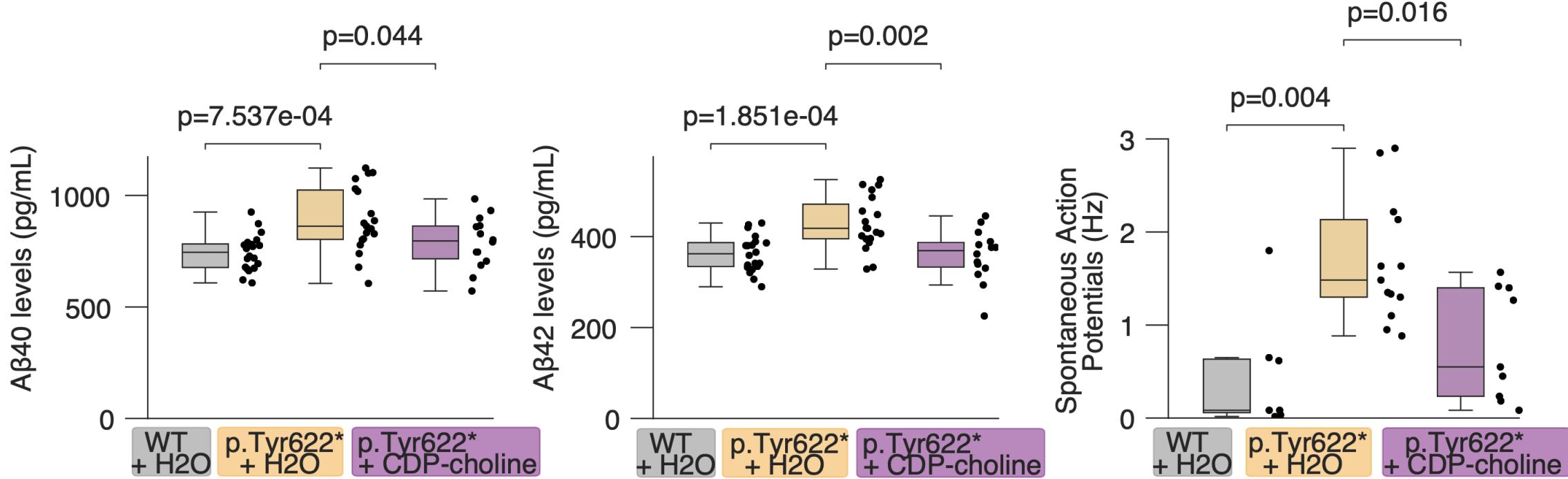
CDP-choline supplementation rescues mitochondrial defects



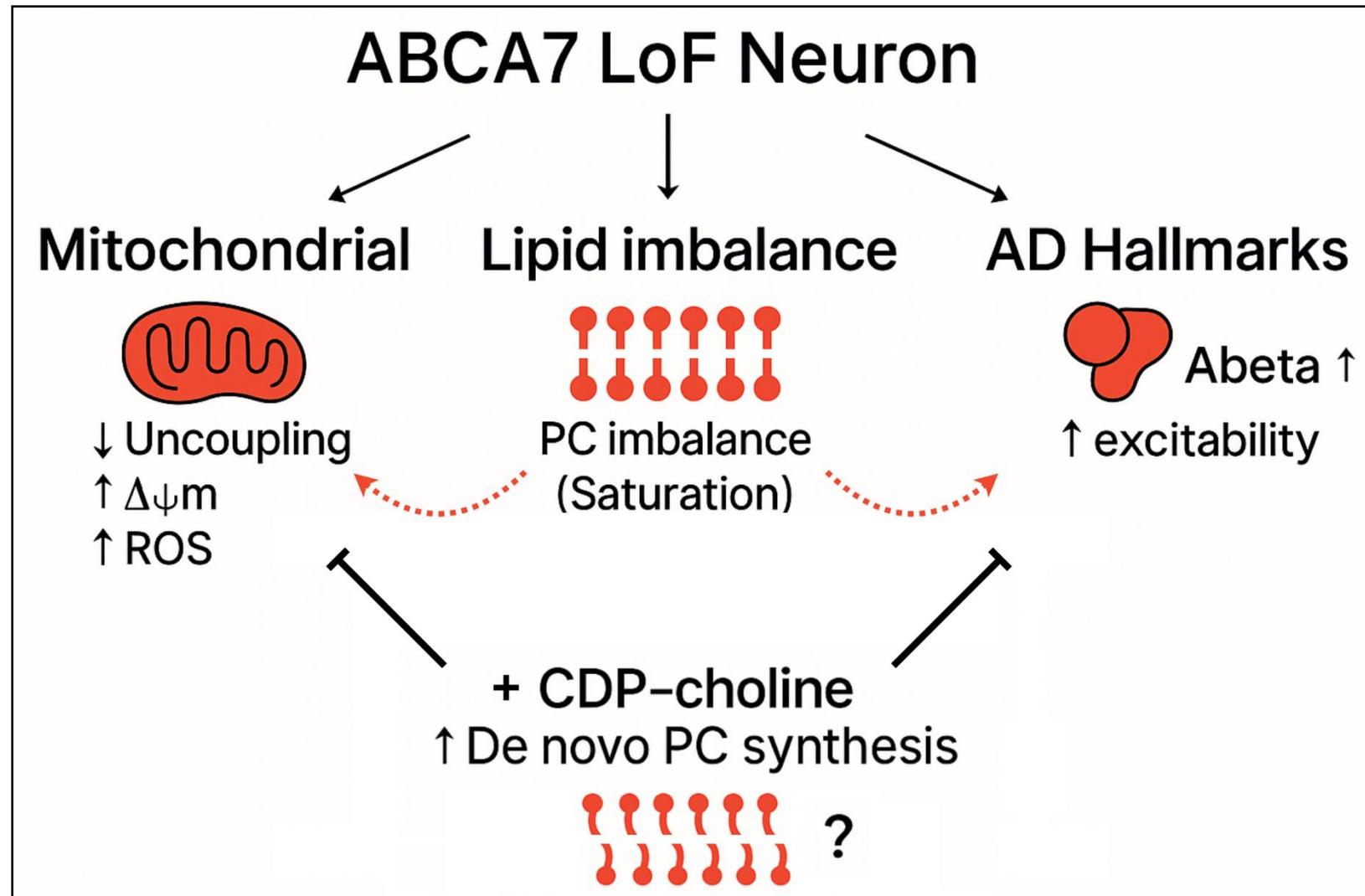
Intervening on de novo phosphatidylcholine synthesis



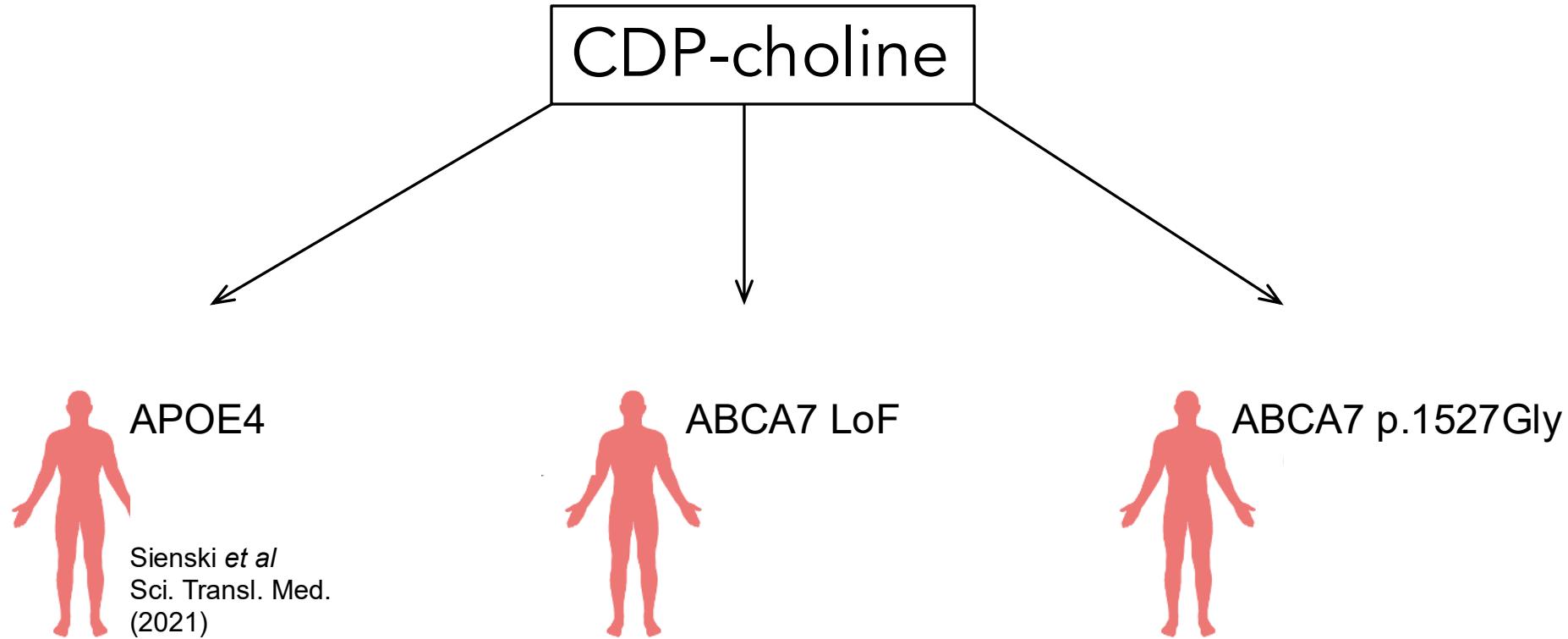
CDP-choline supplementation rescues AD phenotypes in cortical organoids



Summary: ABCA7 loss-of-function in neurons



Reducing risk in multiple genotypes with CDP-choline



Thank you!



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MIT

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Sanofi (prev. MIT)

Shannon Wright
OurAlis (prev. MIT)

Colin Staab
MIT

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MIT

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Sanofi (prev. MIT)

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MIT

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