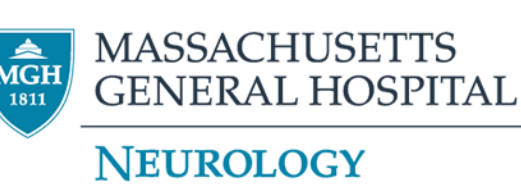


Disruption of Autophagy and Endosomal Pathways Promotes TDP-43 Pathology



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What Causes TDP-43 Pathology?

Normal TAR DNA-binding protein 43 (TDP-43) function:

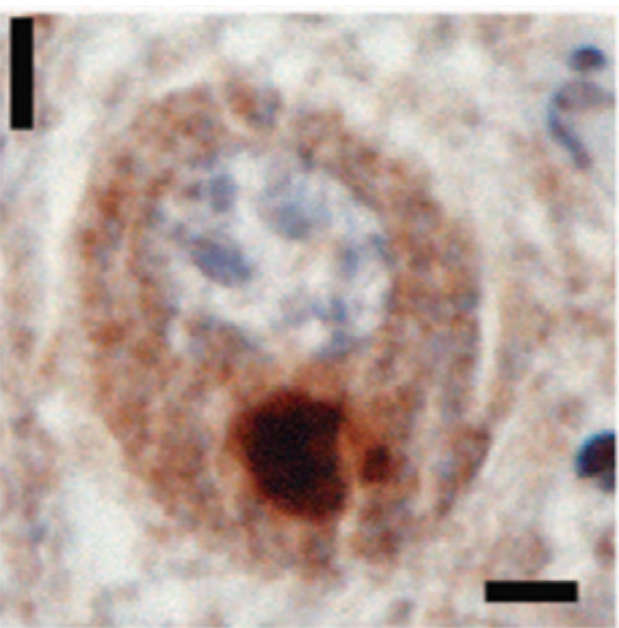
- pre-mRNA splicing
- Micro-RNA (miRNA) and long non-coding RNA (lncRNA) metabolism

Features of TDP-43 pathology:

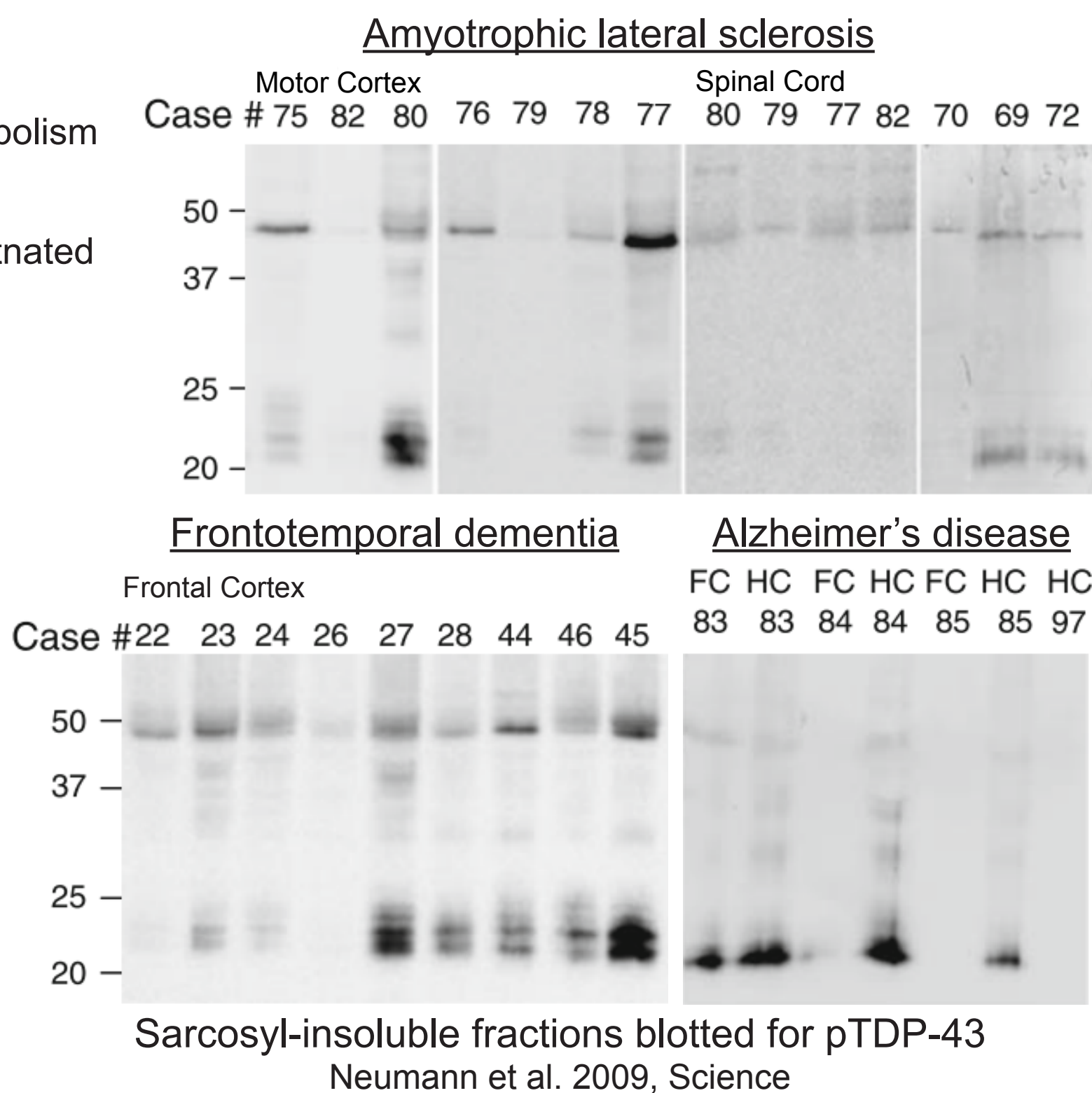
- Becomes insoluble, cleaved, hyperphosphorylated, and ubiquitinated
- Shift from nuclear to cytoplasmic localization
- Both TDP-43 overexpression and knockdown are toxic

Pathological TDP-43 appears in...

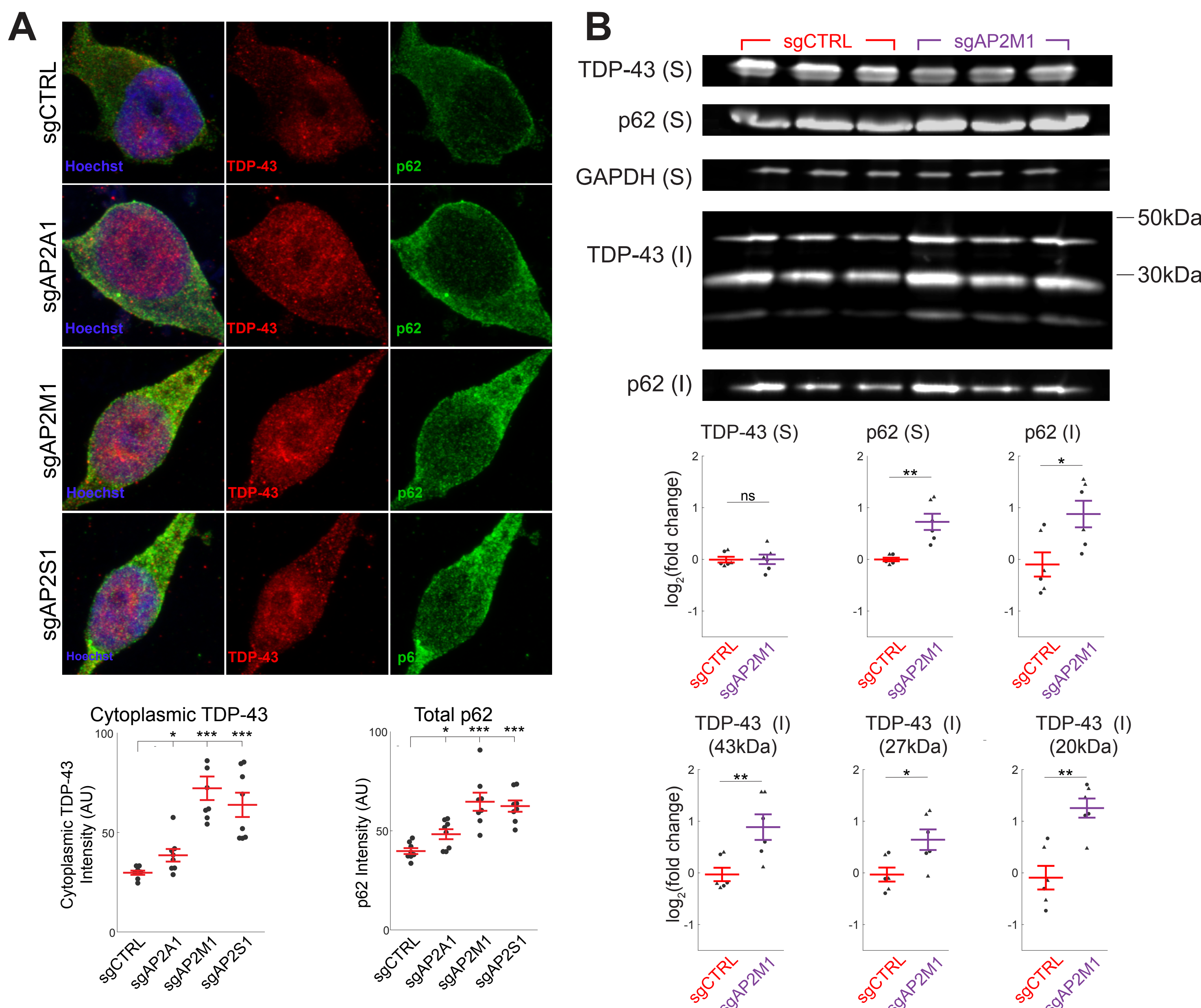
- 97% of amyotrophic lateral sclerosis (ALS) cases
- 50% of Alzheimer's disease (AD) cases
- 50% of frontotemporal dementia (FTD) cases



Lower motor neuron from ALS patient
Cairns et al. 2007, Amer. J. of Path.

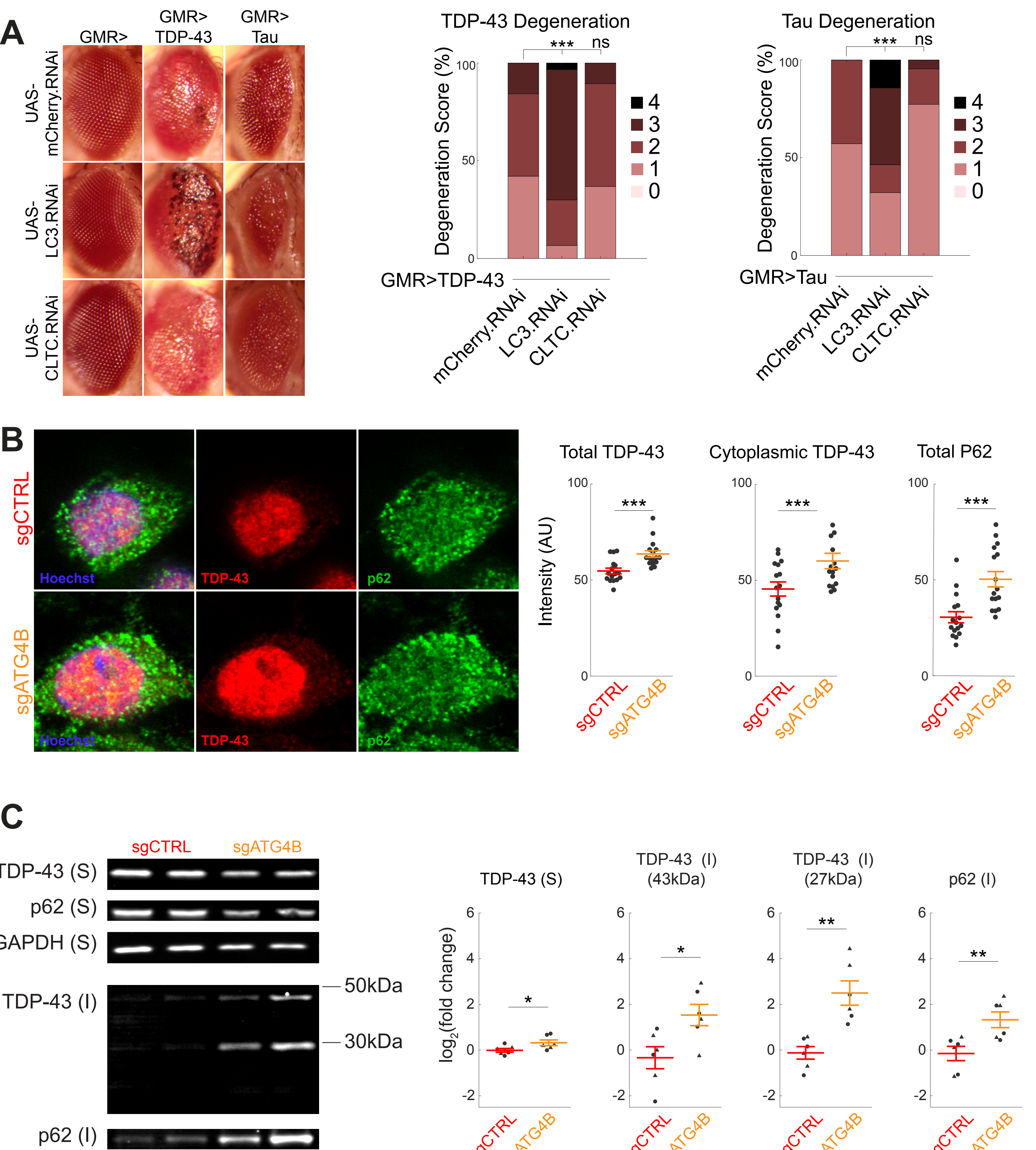


AP2A1 Affects TDP-43 through the AP2 Complex



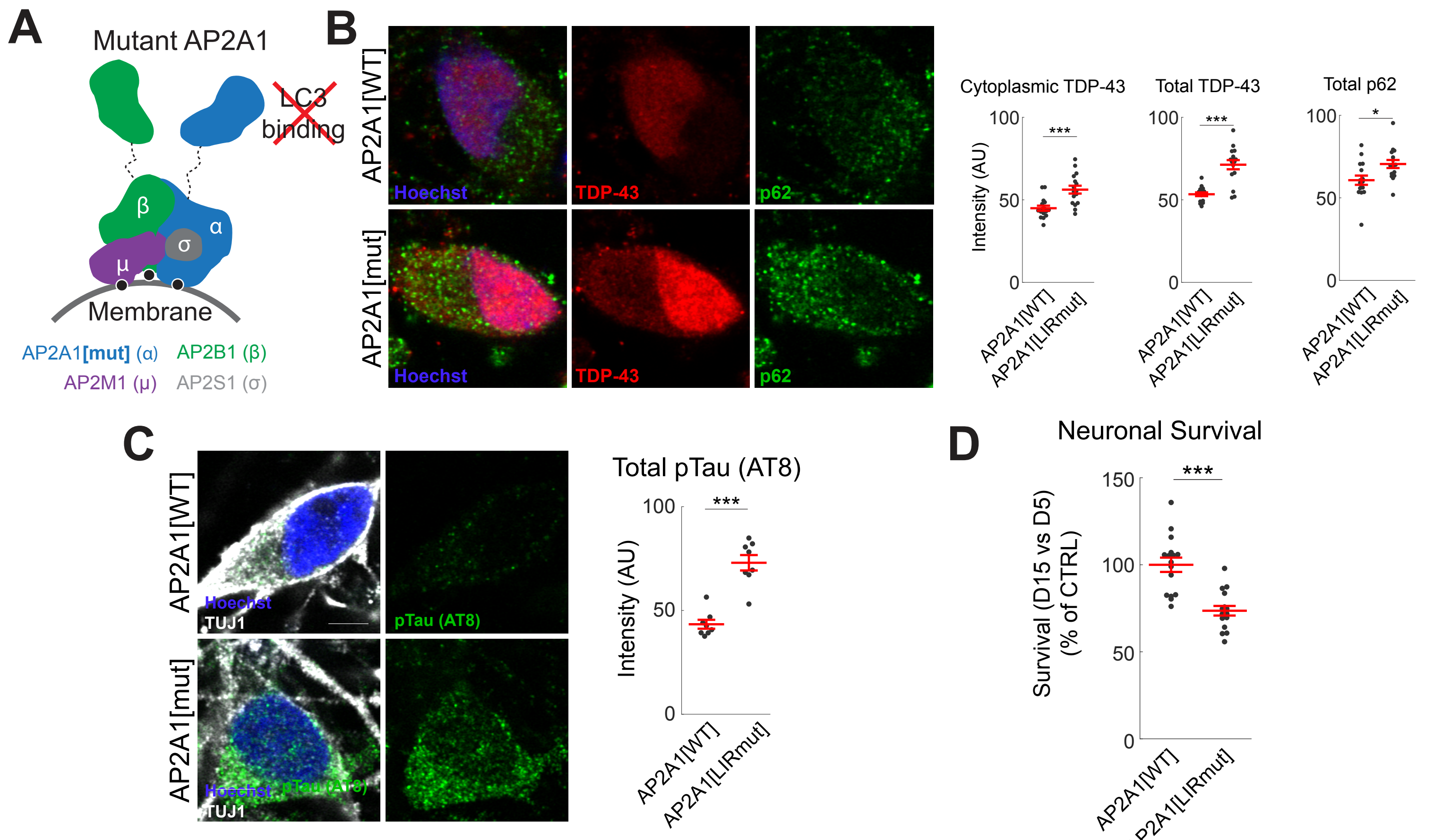
(A) Knocking down *AP2A1*, *AP2M1*, or *AP2S1* increases cytoplasmic TDP-43 and p62 in iPSC-neurons. (B) Knocking down *AP2M1* increases insoluble TDP-43 and insoluble p62, similar to *AP2A1* knockdown.

Autophagy Impairment Disrupts TDP-43 and Tau



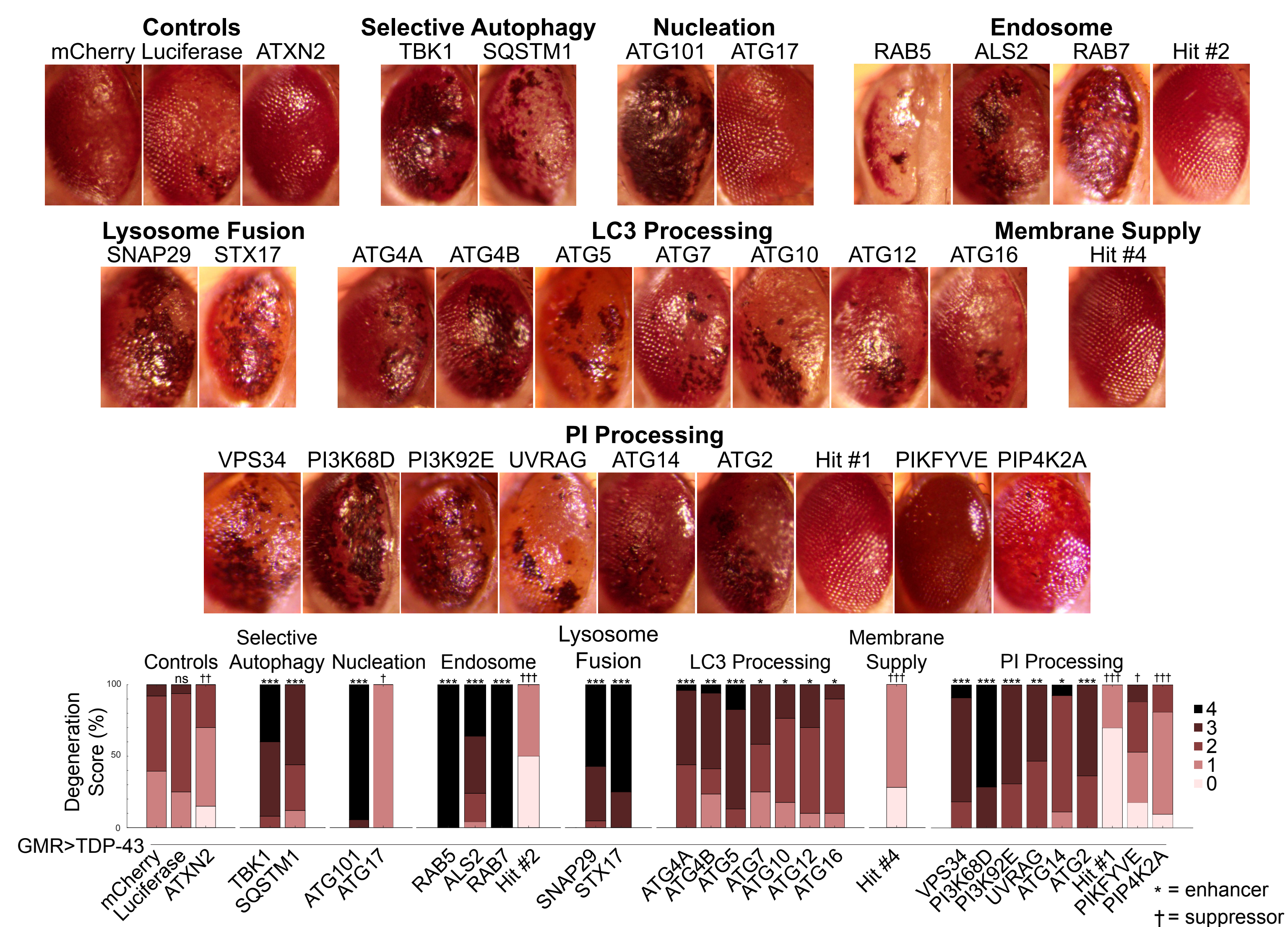
(A) Knocking down LC3 increases neurodegeneration in the TDP-43 and Tau models, while knocking down the clathrin heavy chain (CLTC) has no effect, suggesting that AP2A1 may regulate TDP-43 through its interaction with LC3. (B) Knocking down the critical LC3 processing gene *ATG4B* increases cytoplasmic TDP-43 and p62 in iPSC-neurons. (C) Knocking down *ATG4B* increases insoluble TDP-43 and insoluble p62, similar to *AP2A1* and *AP2M1* knockdowns.

AP2A1-LC3 Binding Regulates TDP-43 and Tau Pathology



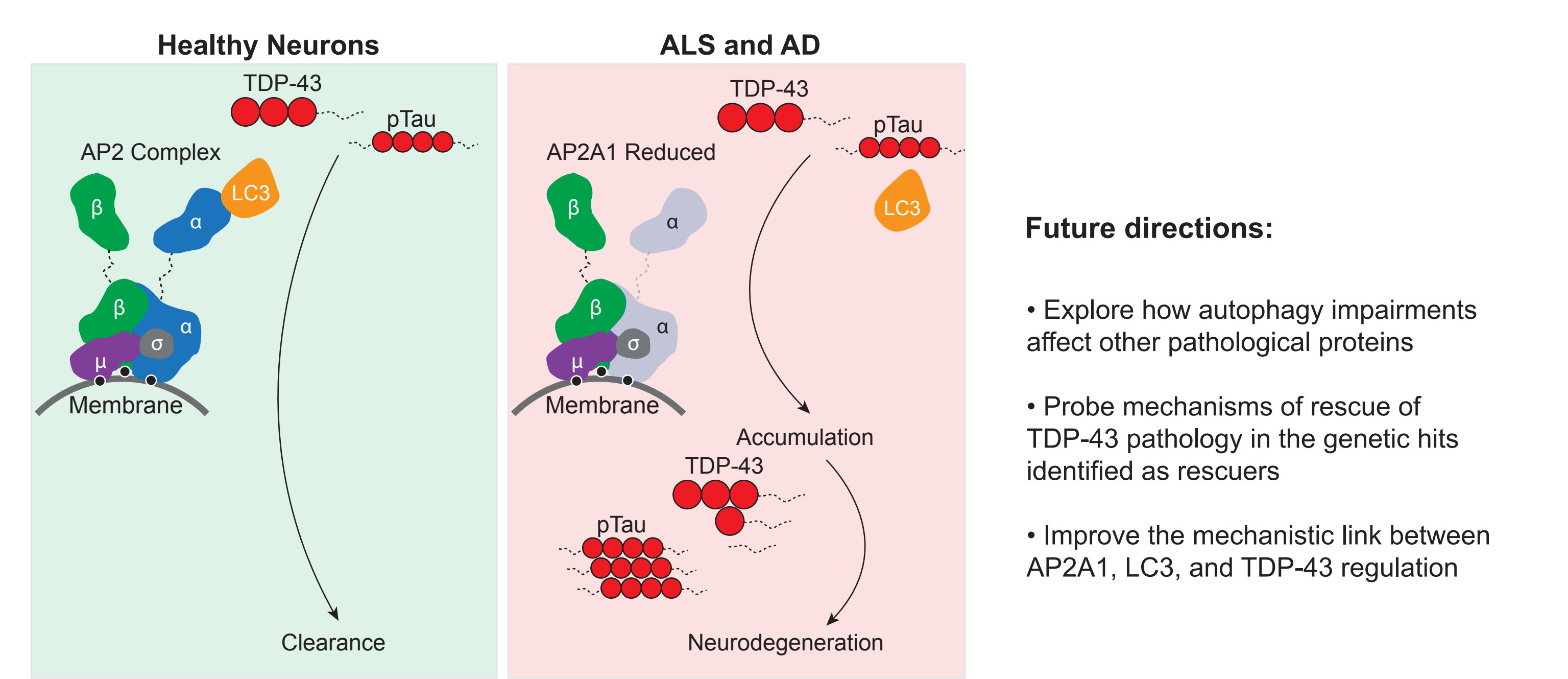
(A) AP2A1 LC3-interacting region (LIR) is mutated to prevent LC3 binding. (B) Mutating the AP2A1 LIR increases cytoplasmic TDP-43. (C) increases total pTau, and (D) decreases lifespan.

Autophagy Disruption Increases TDP-43 Degeneration



Screen for genetic modifiers of TDP-43 expression in *Drosophila* eyes. Knocking down several genes in the autophagy and endosomal pathways increases neurodegeneration caused by TDP-43 expression. Notable hits include TBK1, SQSTM1, and ALS2, which can cause familial ALS when mutated. Several hits also mitigate neurodegeneration, and some have a stronger effect than the positive control ATXN2.

Model and Future Directions



- Future directions:**
- Explore how autophagy impairments affect other pathological proteins
 - Probe mechanisms of rescue of TDP-43 pathology in the genetic hits identified as rescuers
 - Improve the mechanistic link between AP2A1, LC3, and TDP-43 regulation

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