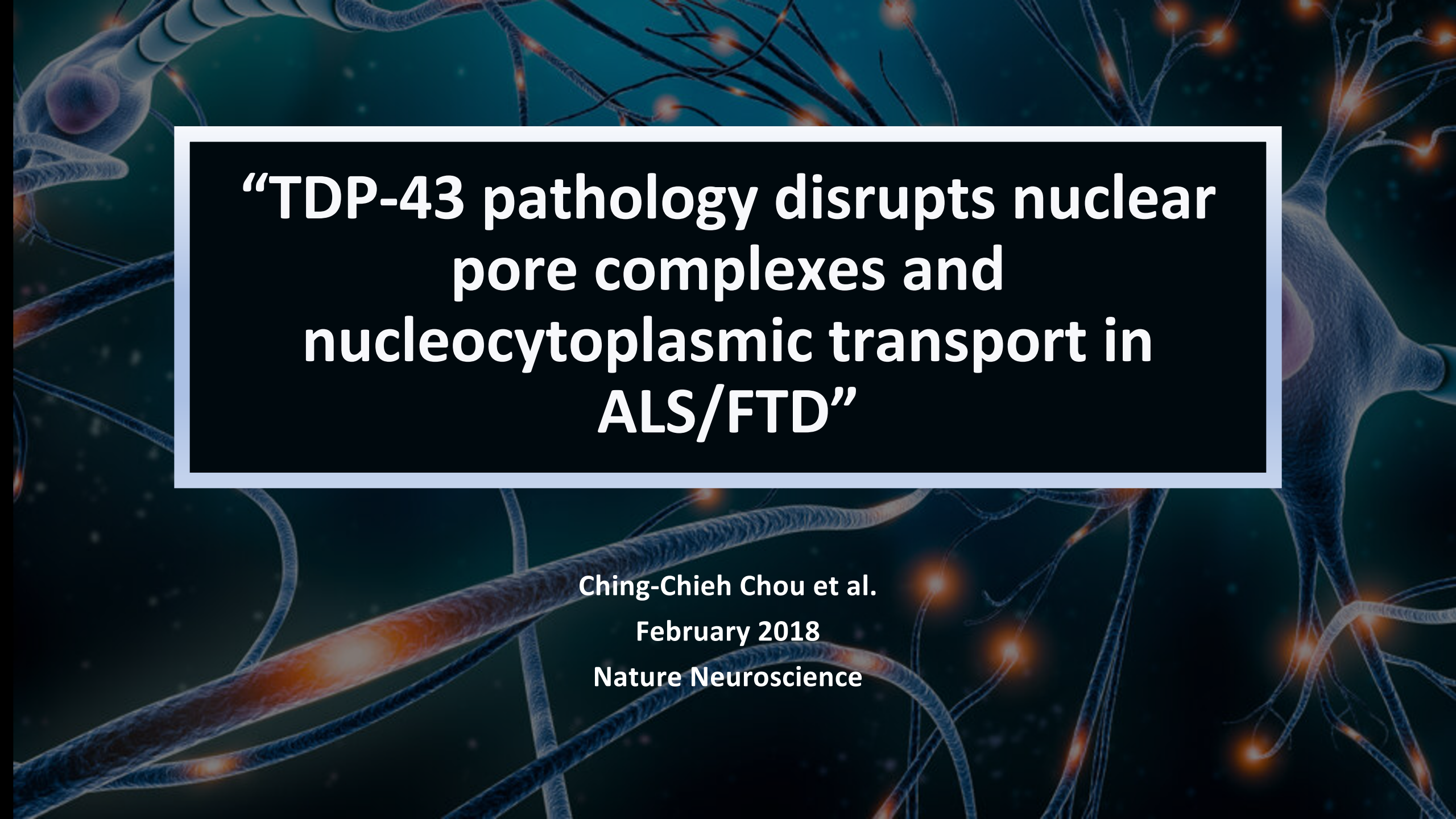


“TDP-43 pathology disrupts nuclear pore complexes and nucleocytoplasmic transport in ALS/FTD”

Ching-Chieh Chou et al.

February 2018

Nature Neuroscience

What is Amyotrophic Lateral Sclerosis (ALS)?

Early Stages of ALS

- Muscle weakness
- Muscle twitching (fasciculation)
- Muscle cramping
- Fatigue
- Poor balance
- Slurred speech

Middle Stages of ALS

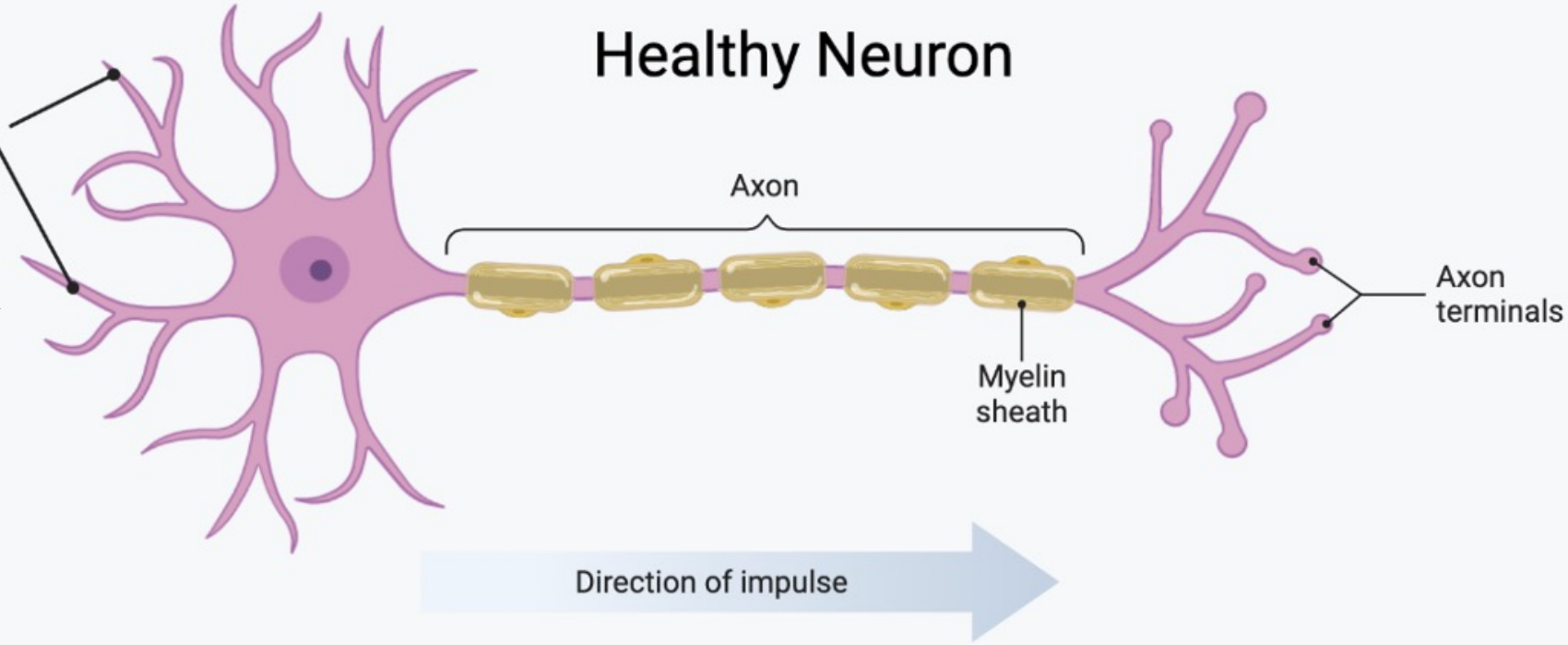
- More severe muscle weakness
- Paralysis in some muscles
- Difficulty in swallowing
- Difficulty in eating/chewing
- Breathing issues
- Bouts of uncontrollable laughter or crying (pseudobulbar affect)

Late Stages of ALS

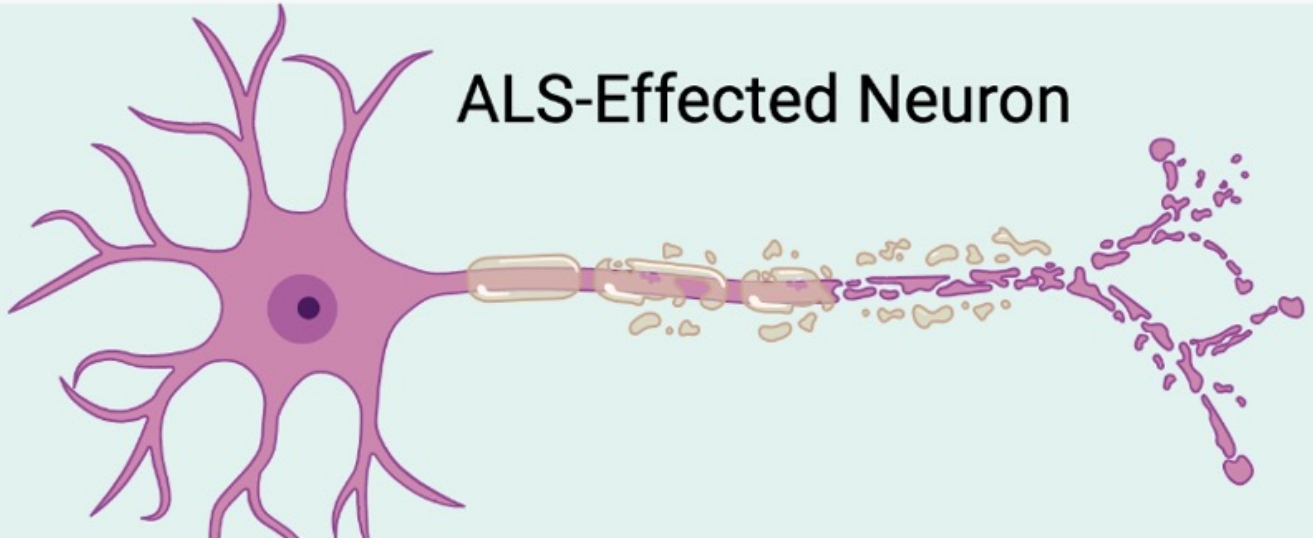
- Paralysis in most muscles
- Extremely limited mobility
- Inability to speak
- Inability to breath without assistance
- Inability to eat without assistance
- Inability to drink without assistance

What gene is associated with ALS?

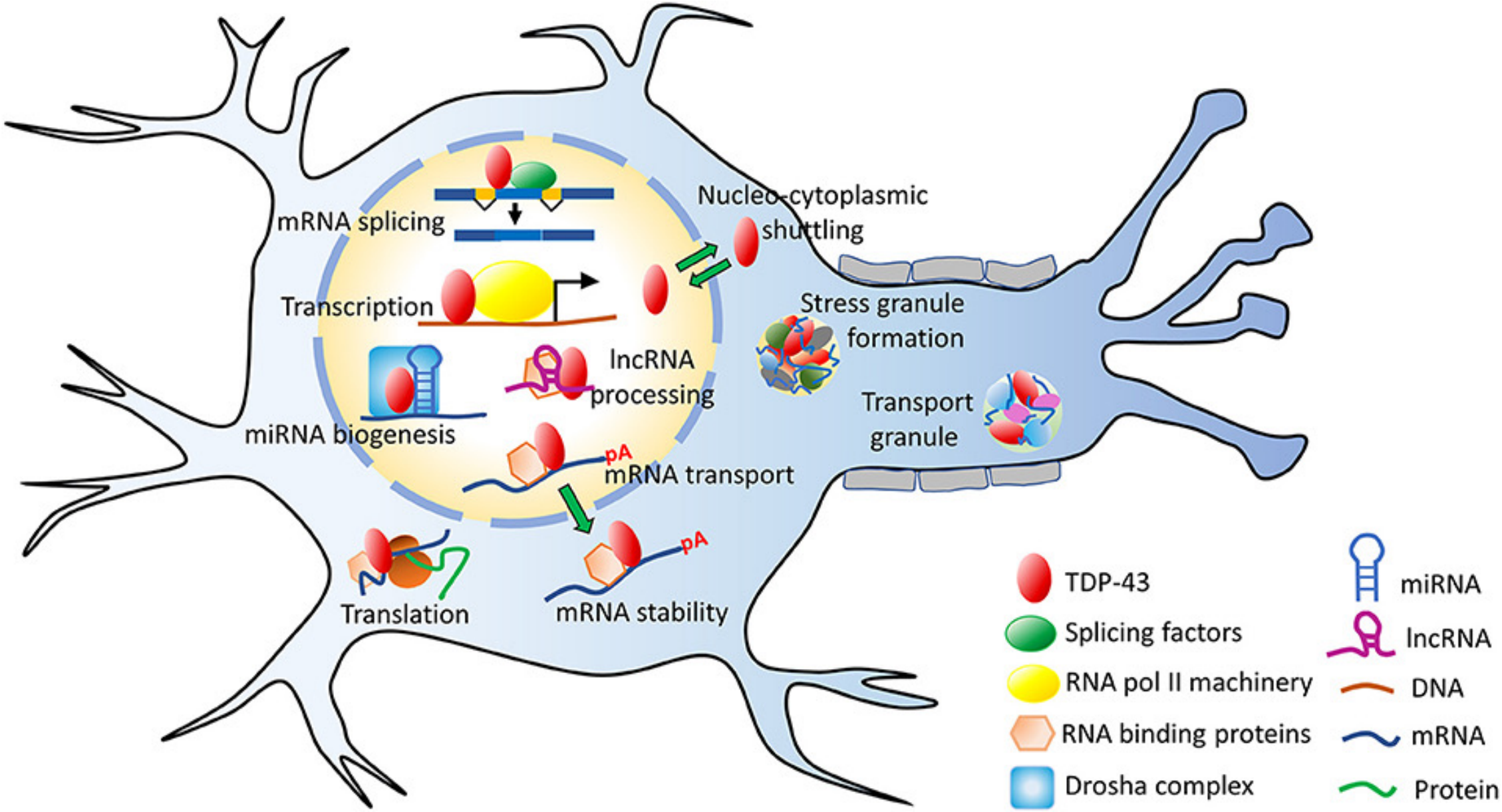
Normal TDP-43



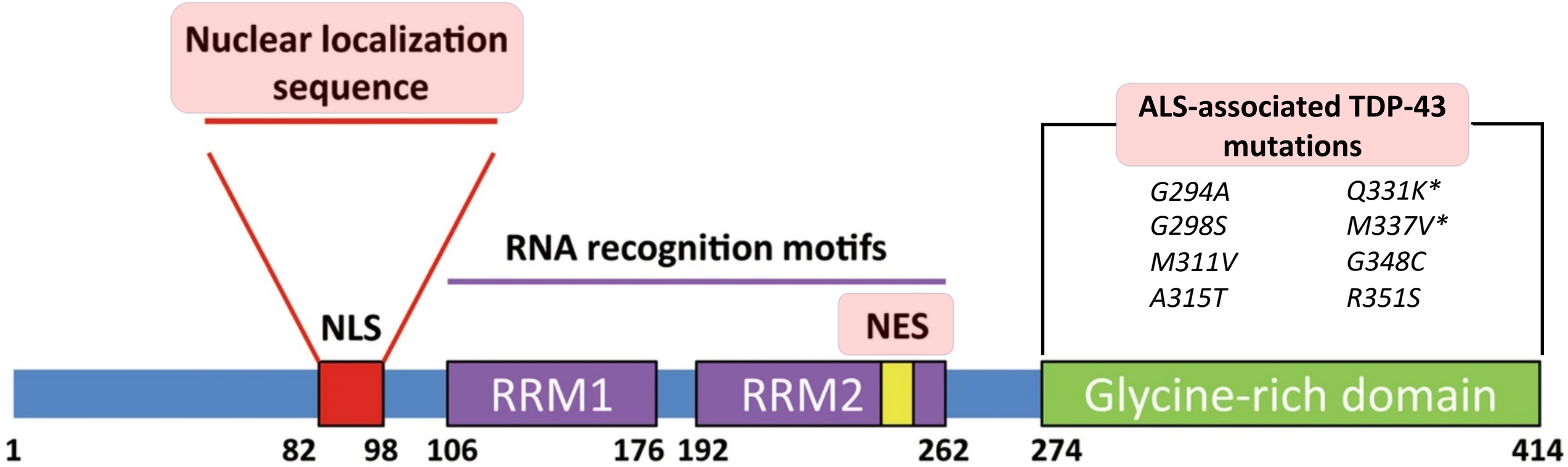
Mutated TDP-43



What is the normal function of TDP-43 in the cell?

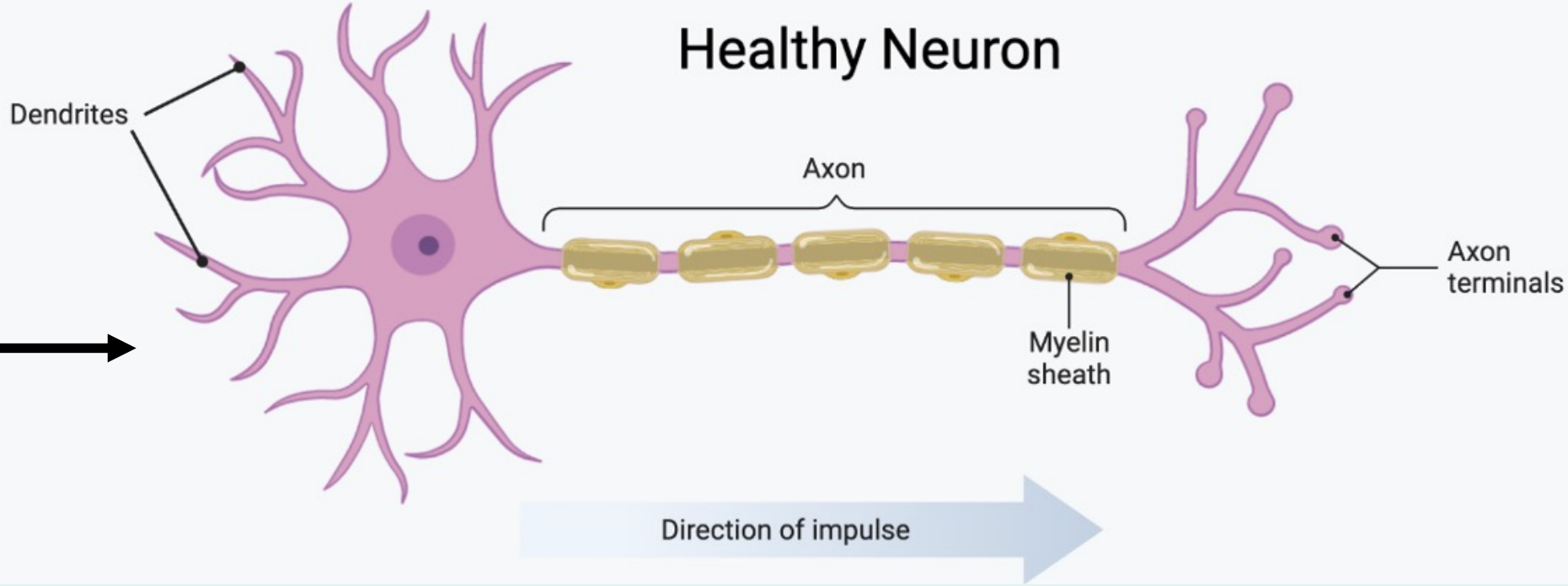


What are the domains of TDP-43?

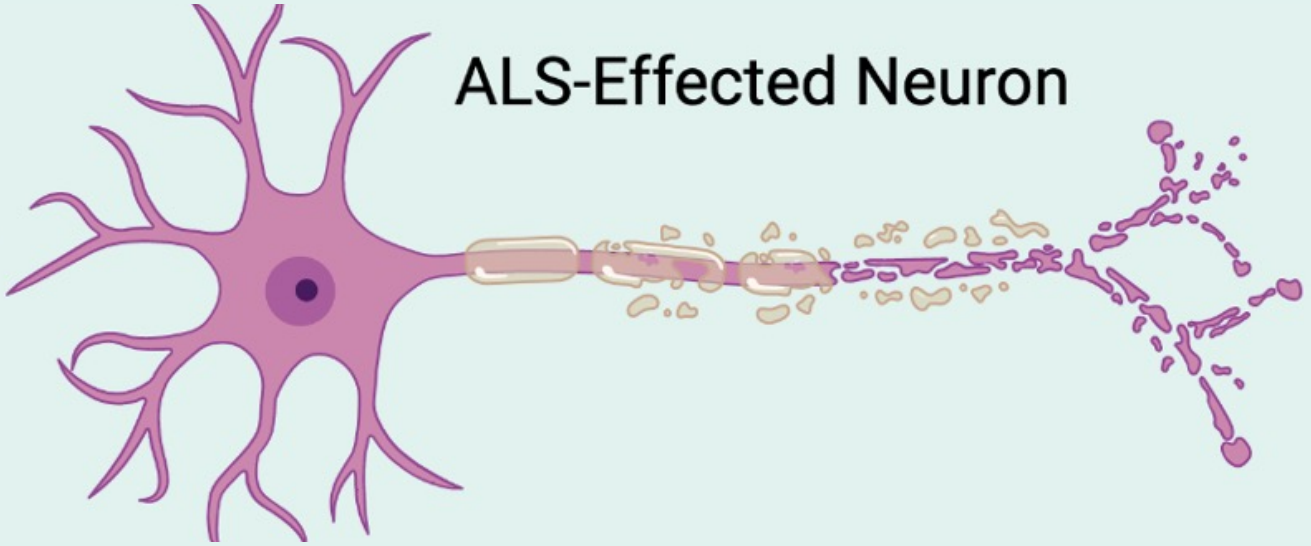


C-terminus mutation → Cytoplasmic mis-localization → TDP-43 neurotoxicity

What are the mechanisms of TDP-43 pathology in neurodegeneration?

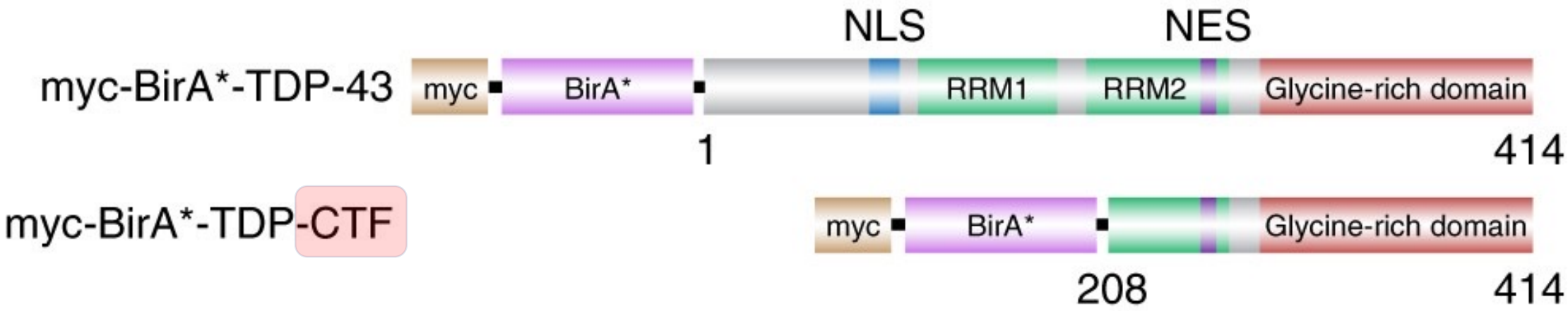


Normal TDP-43 →



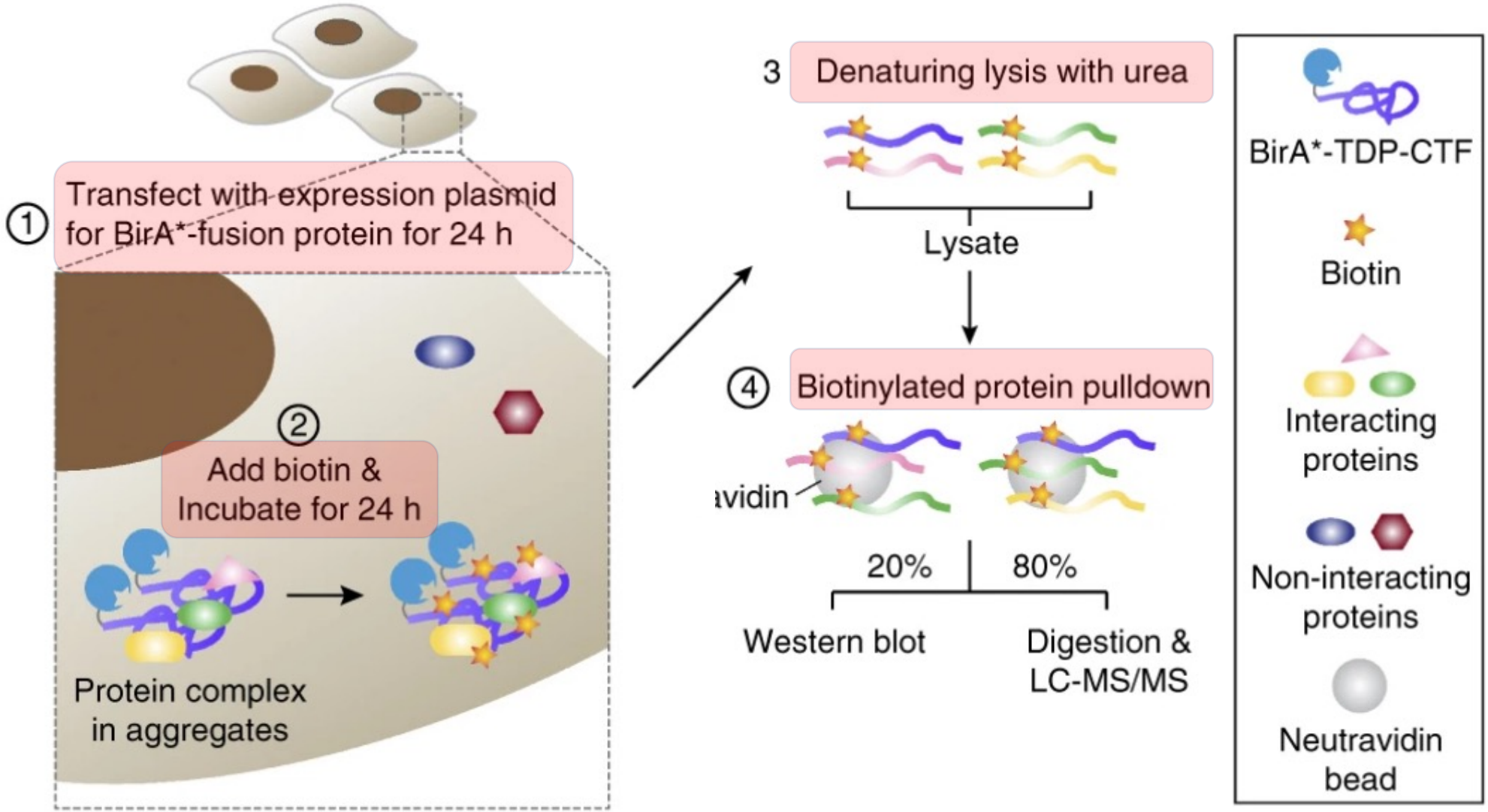
Mutated TDP-43 → ???????? ????????

How can we find interacting proteins of TDP-43?

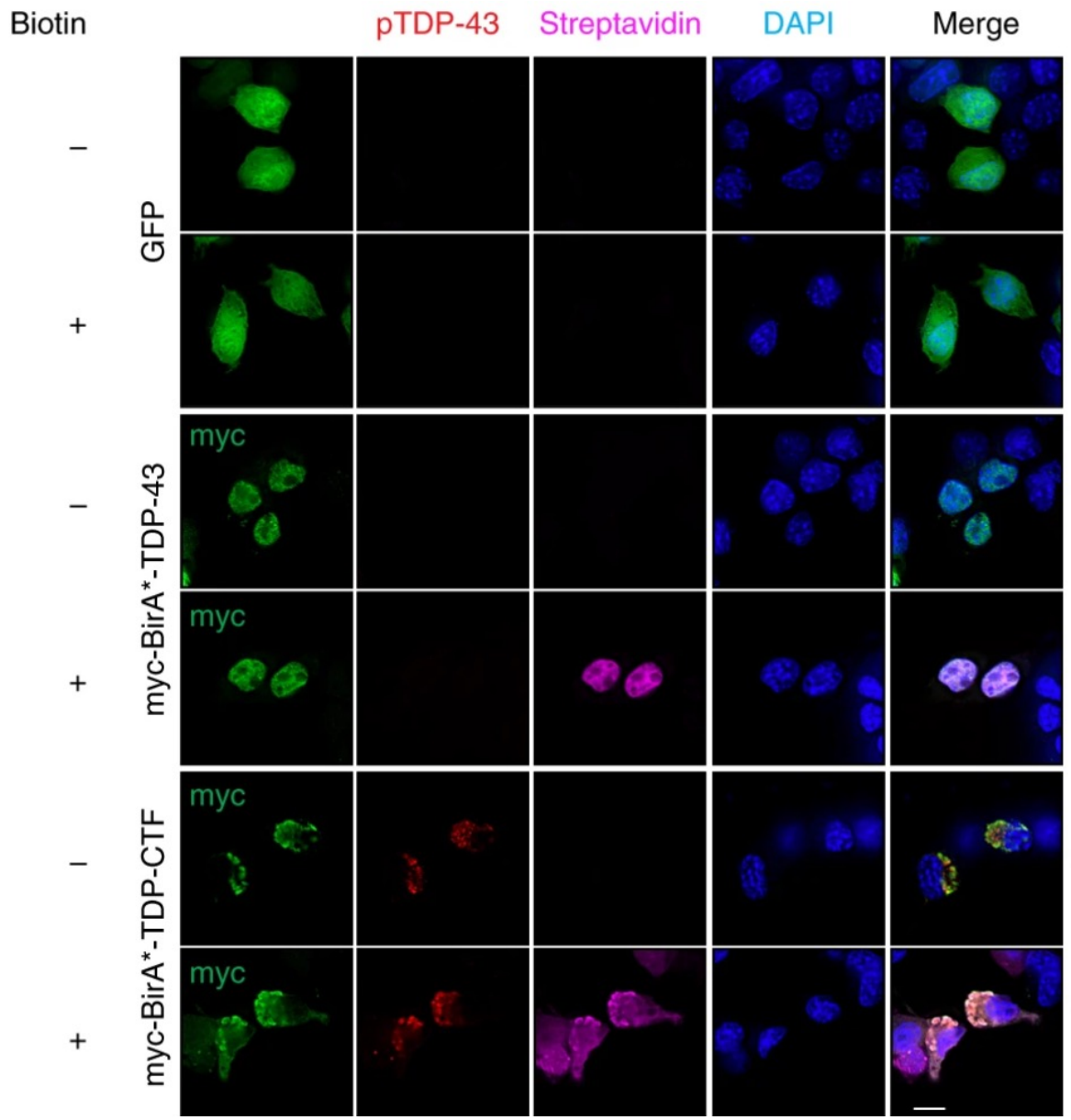


C-terminal fragment

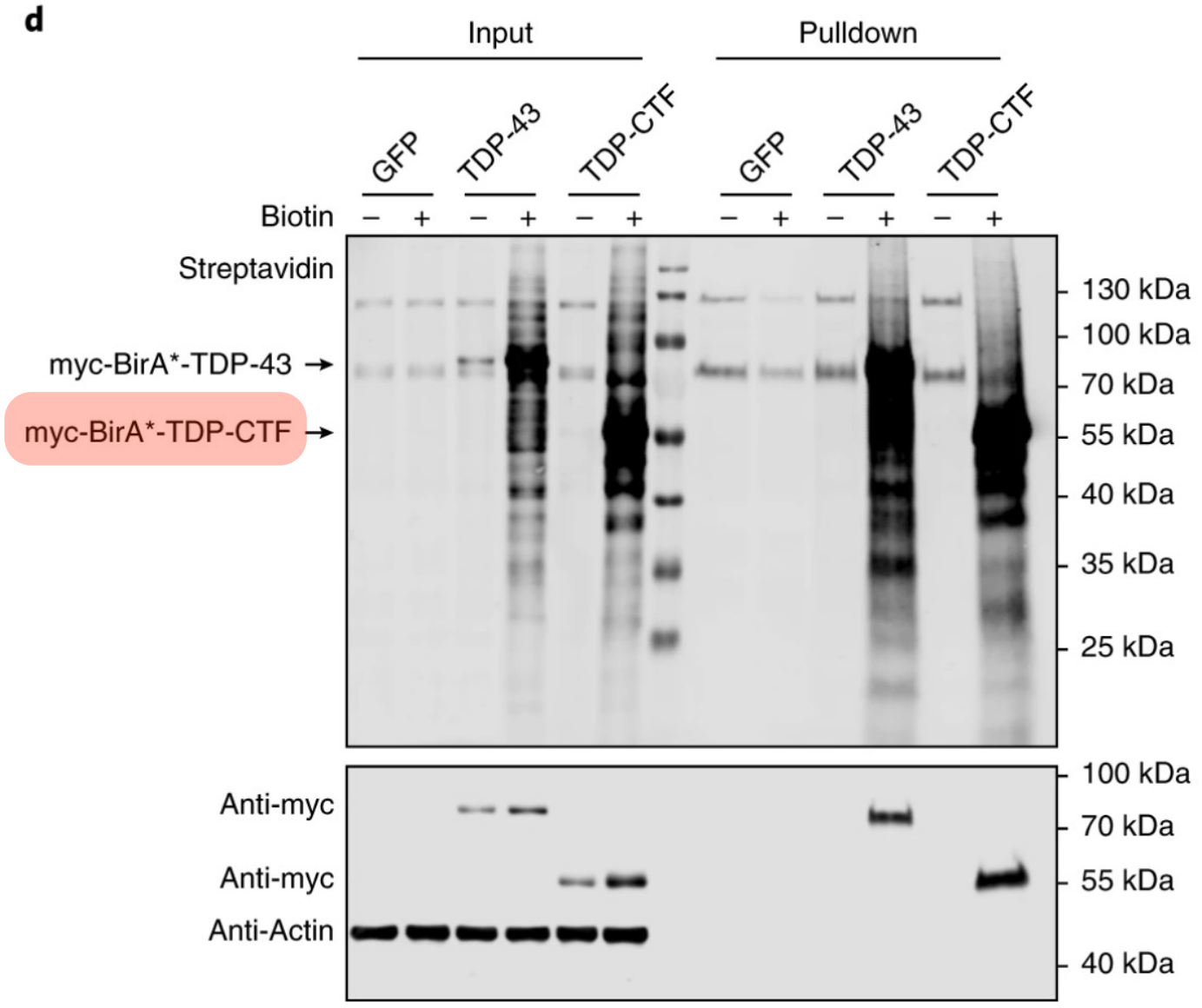
How can we tag proximity-dependent proteins associated with TDP-CTF?



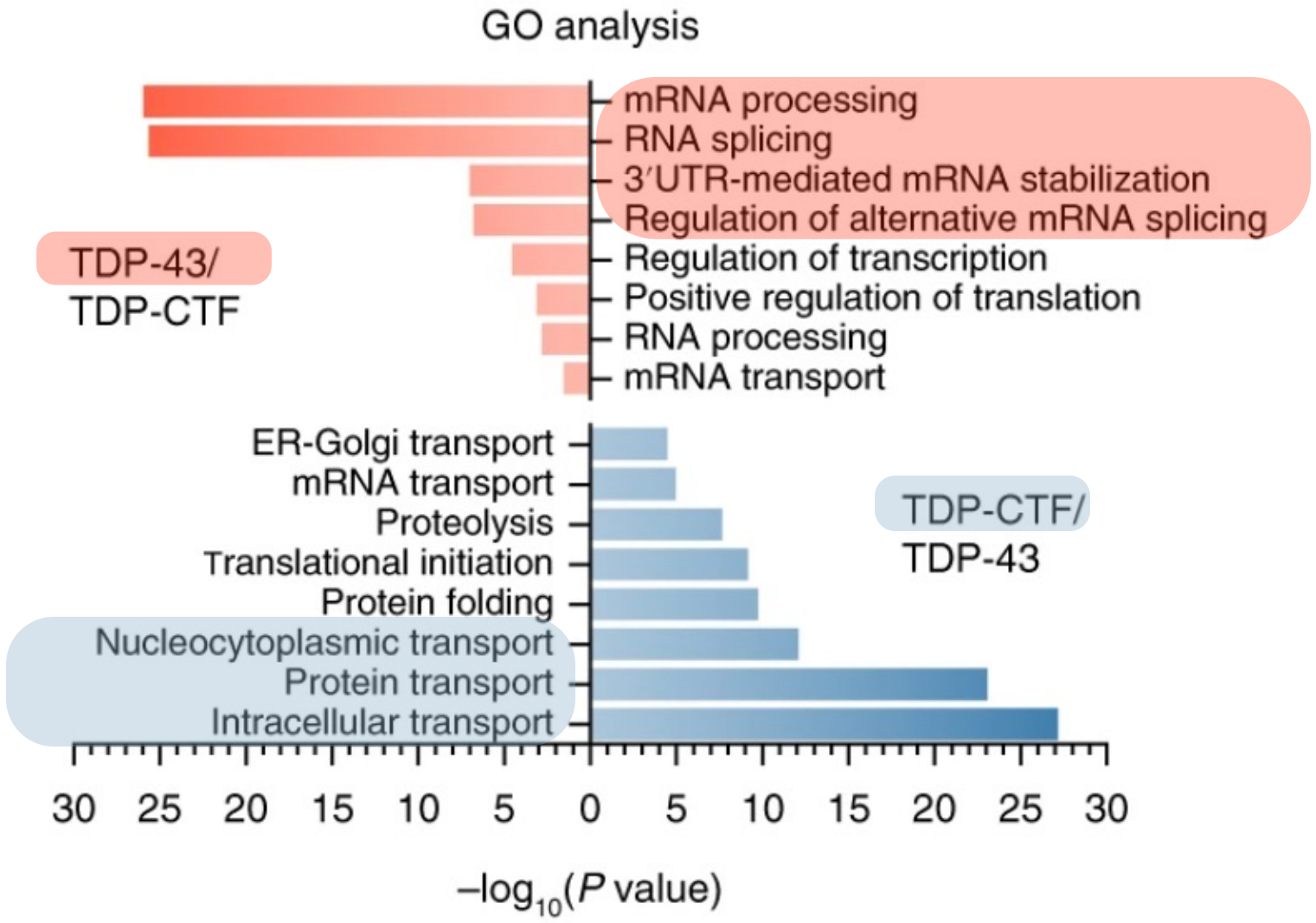
What do GFP patterns show of TDP-43 constructs?



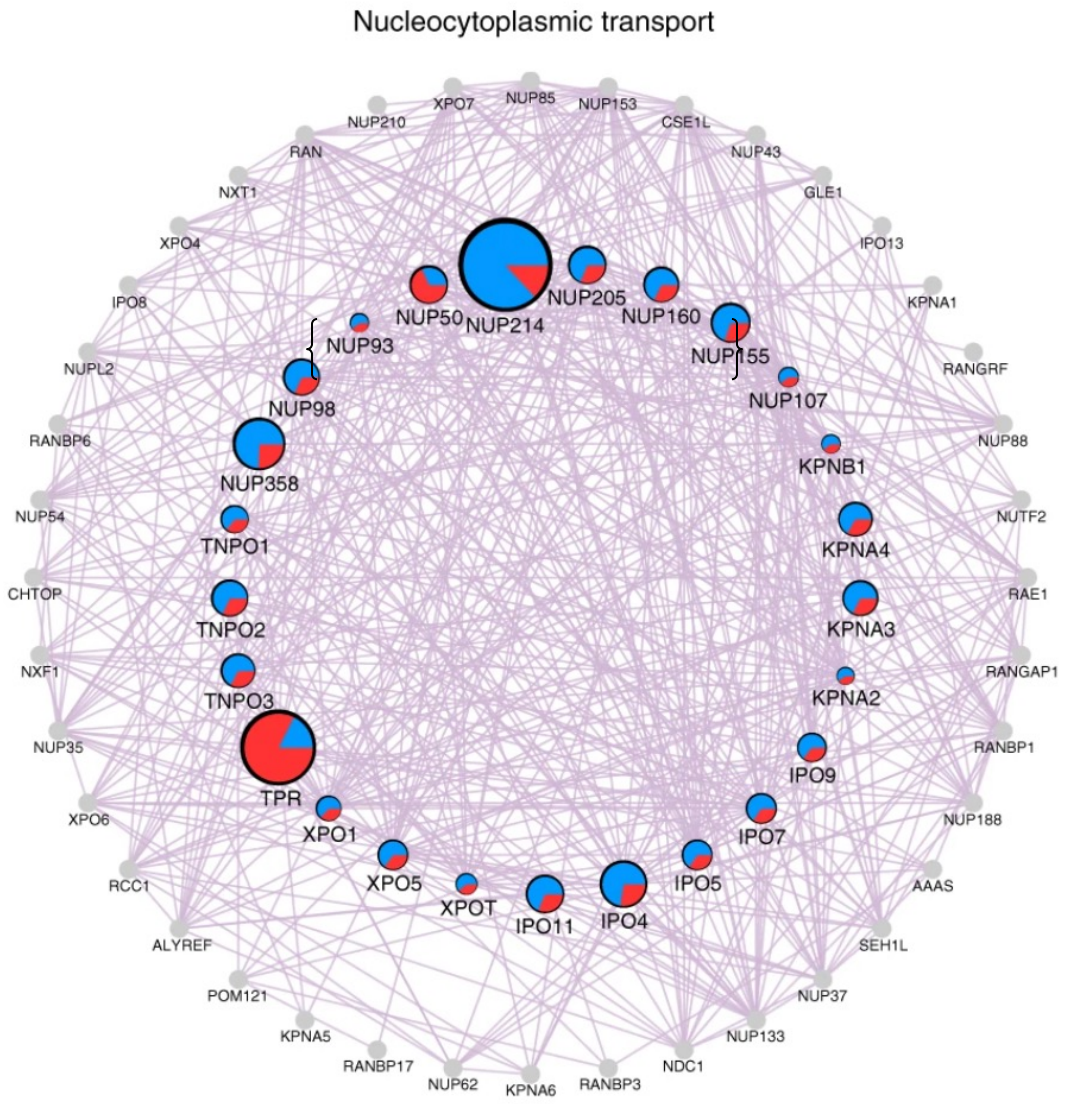
Are there distinct patterns between TDP-43/TDP-CTF protein interactions?



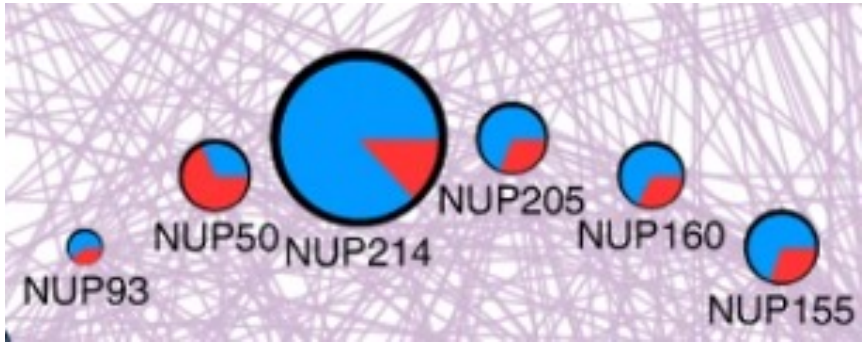
What did proteomic analysis of TDP-43/CTF interactive proteins reveal?



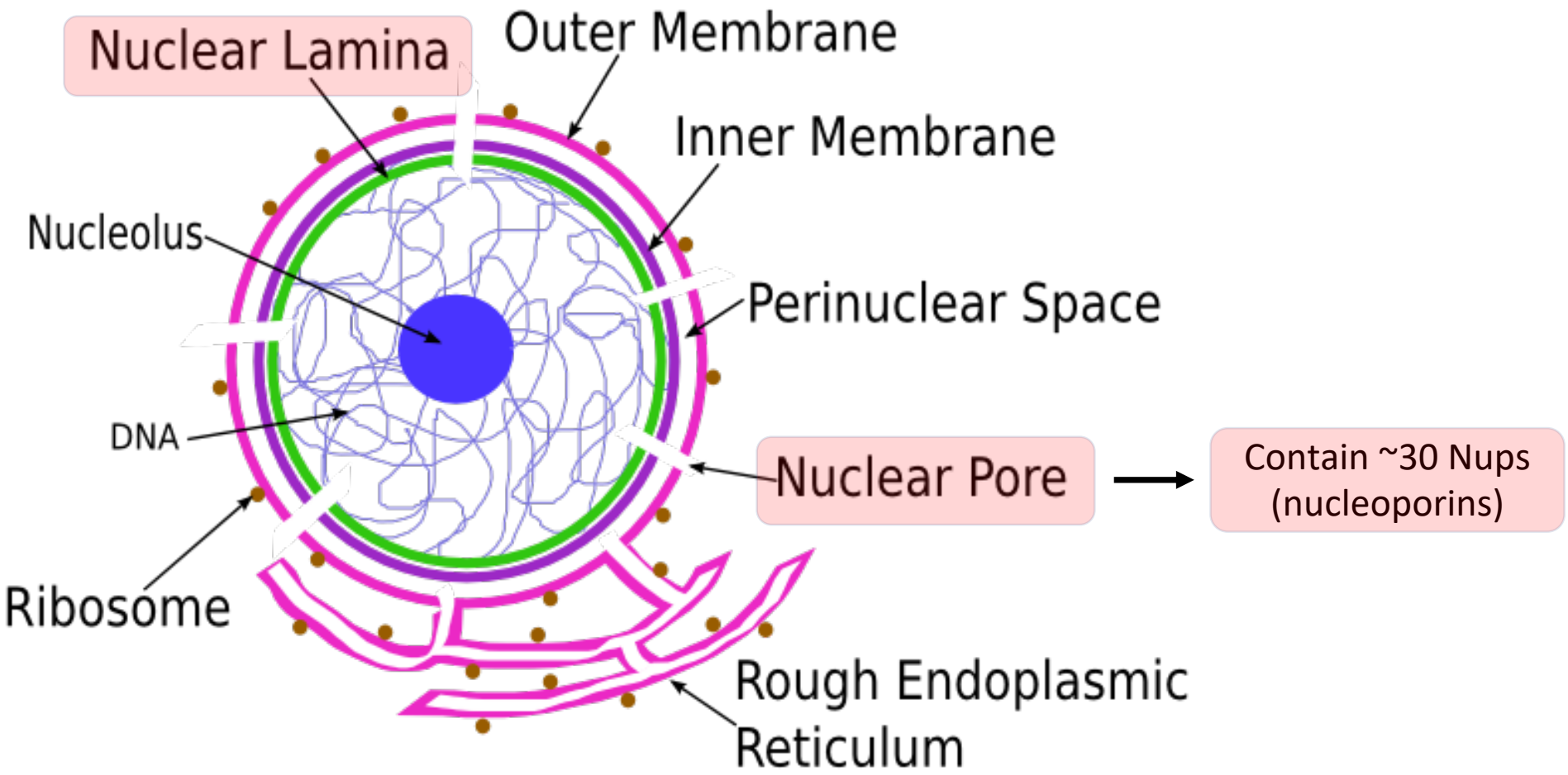
What is the function-specific enrichment and interaction network of TDP-CTF and TDP-43?



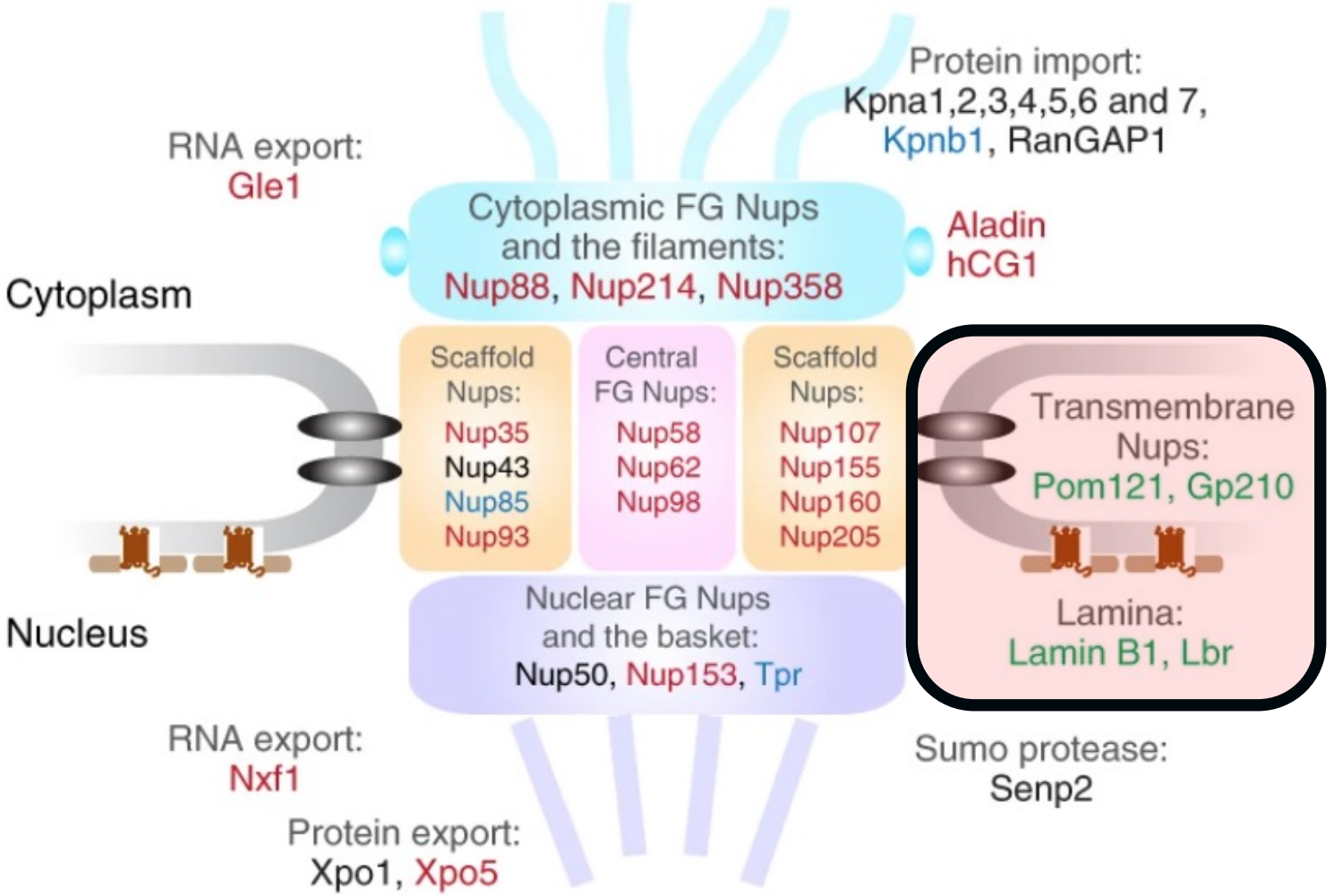
Nups



What are nucleoporins (Nups) and nuclear lamina?



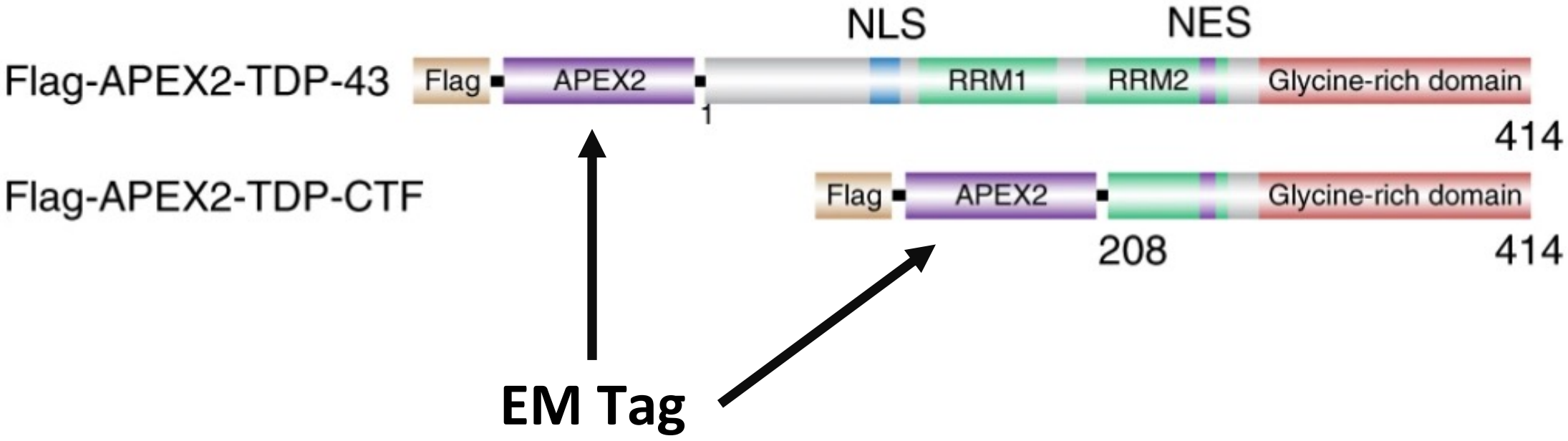
Does TDP-43 pathology cause aggregation of transmembrane Nups?



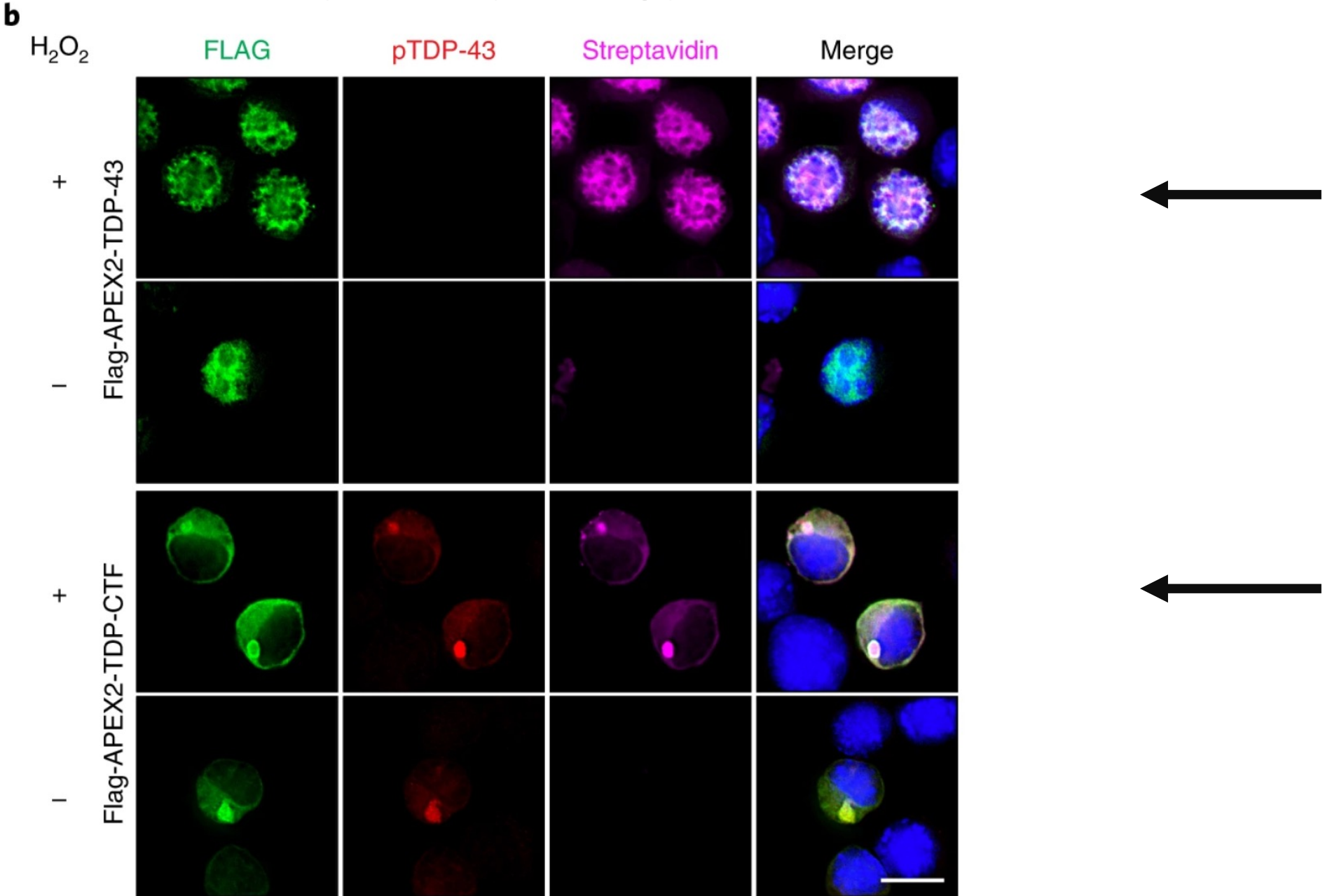
Interaction patterns

Coaggregation | Mislocalization | Disaggregation | Not affected

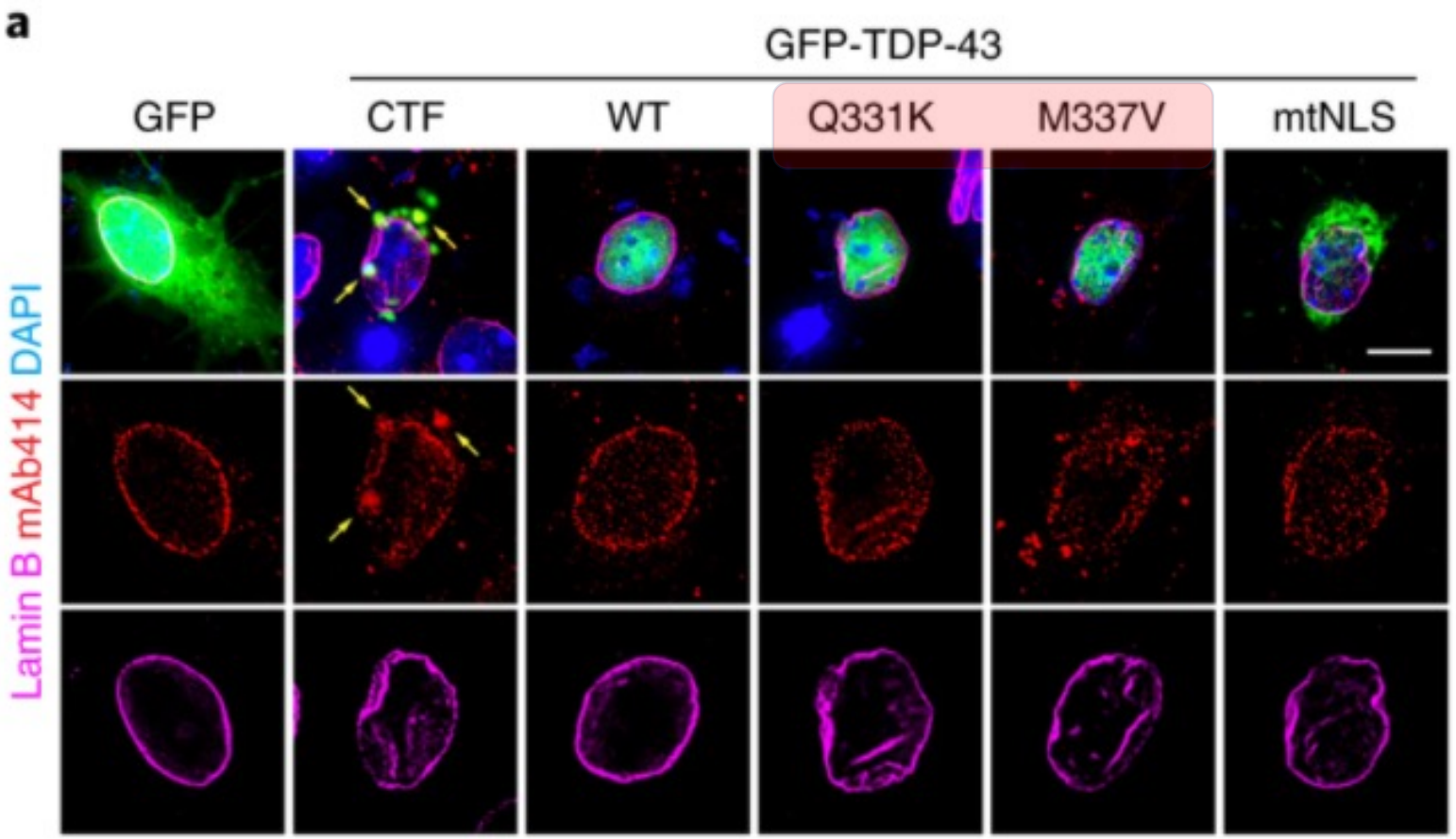
Does TDP-43 disrupt morphology of the NM and NPC?

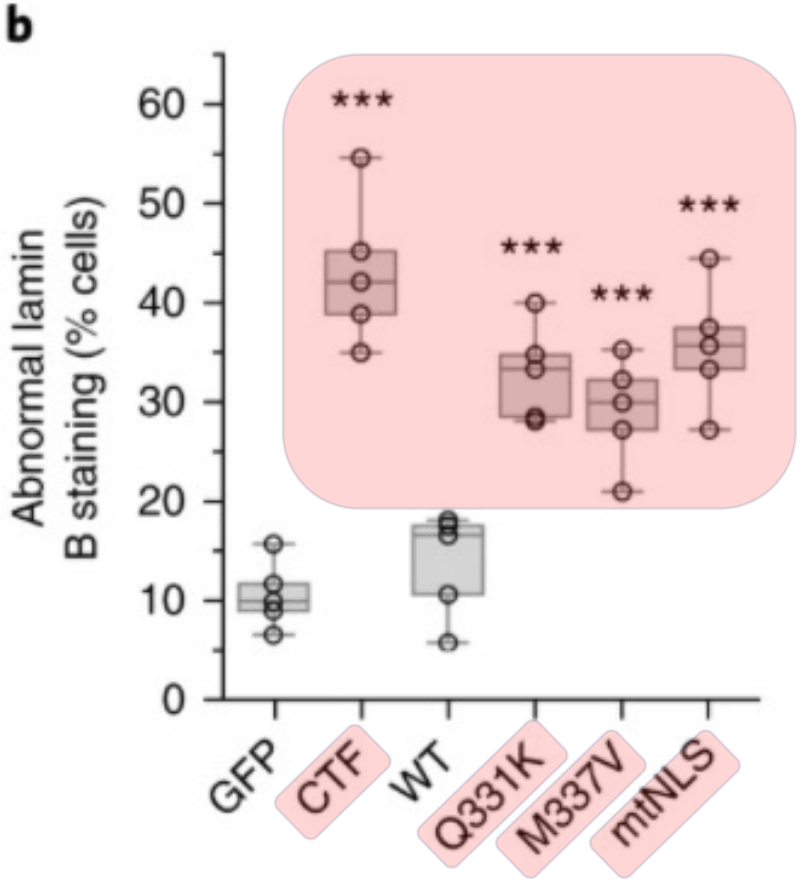


Does TDP-43 disrupt morphology of the NM and NPC?



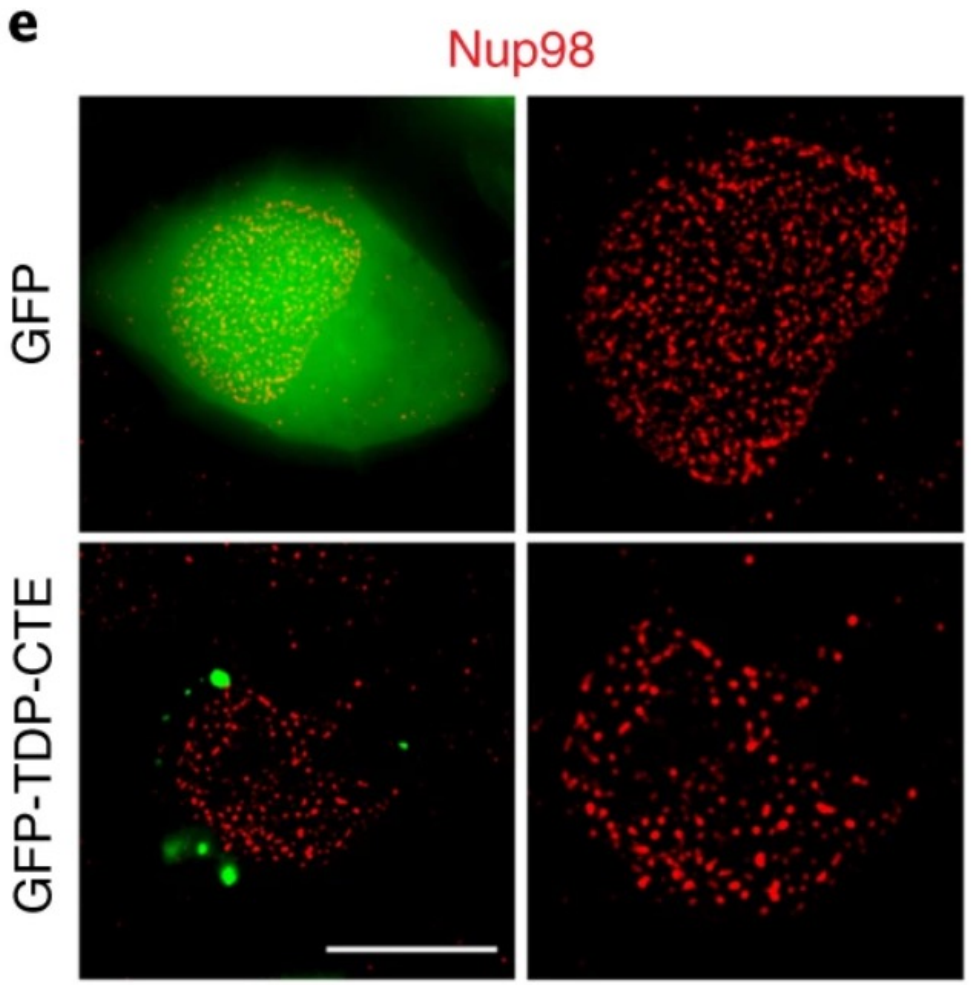
Do mutations in TDP-43 disrupt morphology of the nuclear membrane and nuclear protein channels?



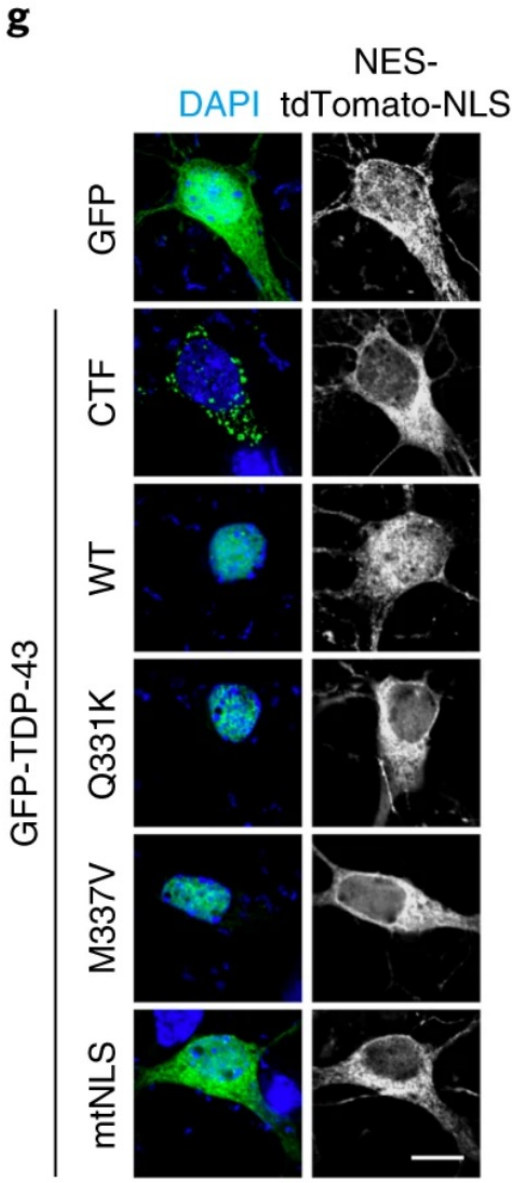


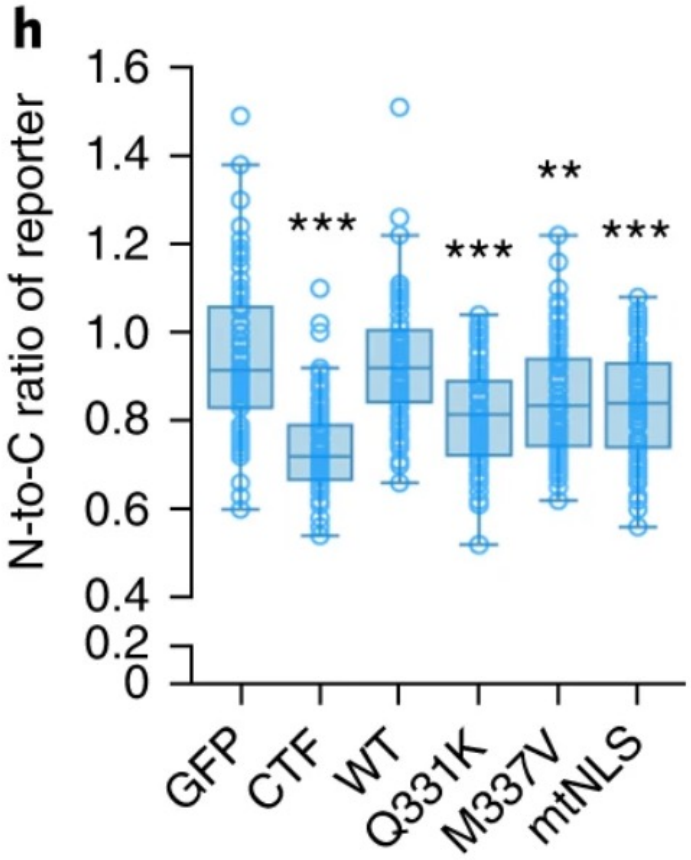
Mutations of TDP-43 glycine-rich domain

How is distribution of Nup98 affected in the nuclear membrane of N2a cells expressing GF-TDP-CTF?

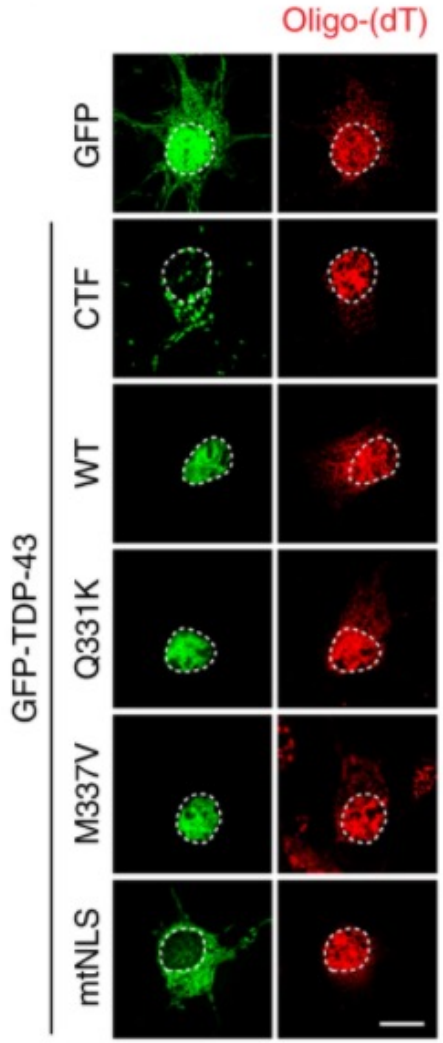


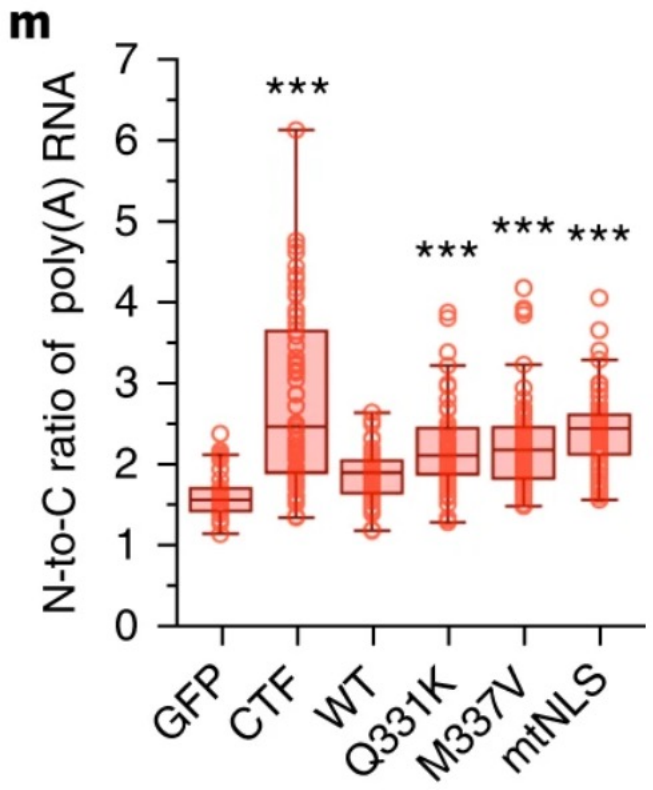
Does TDP-43 pathology disrupt nuclear import of proteins?



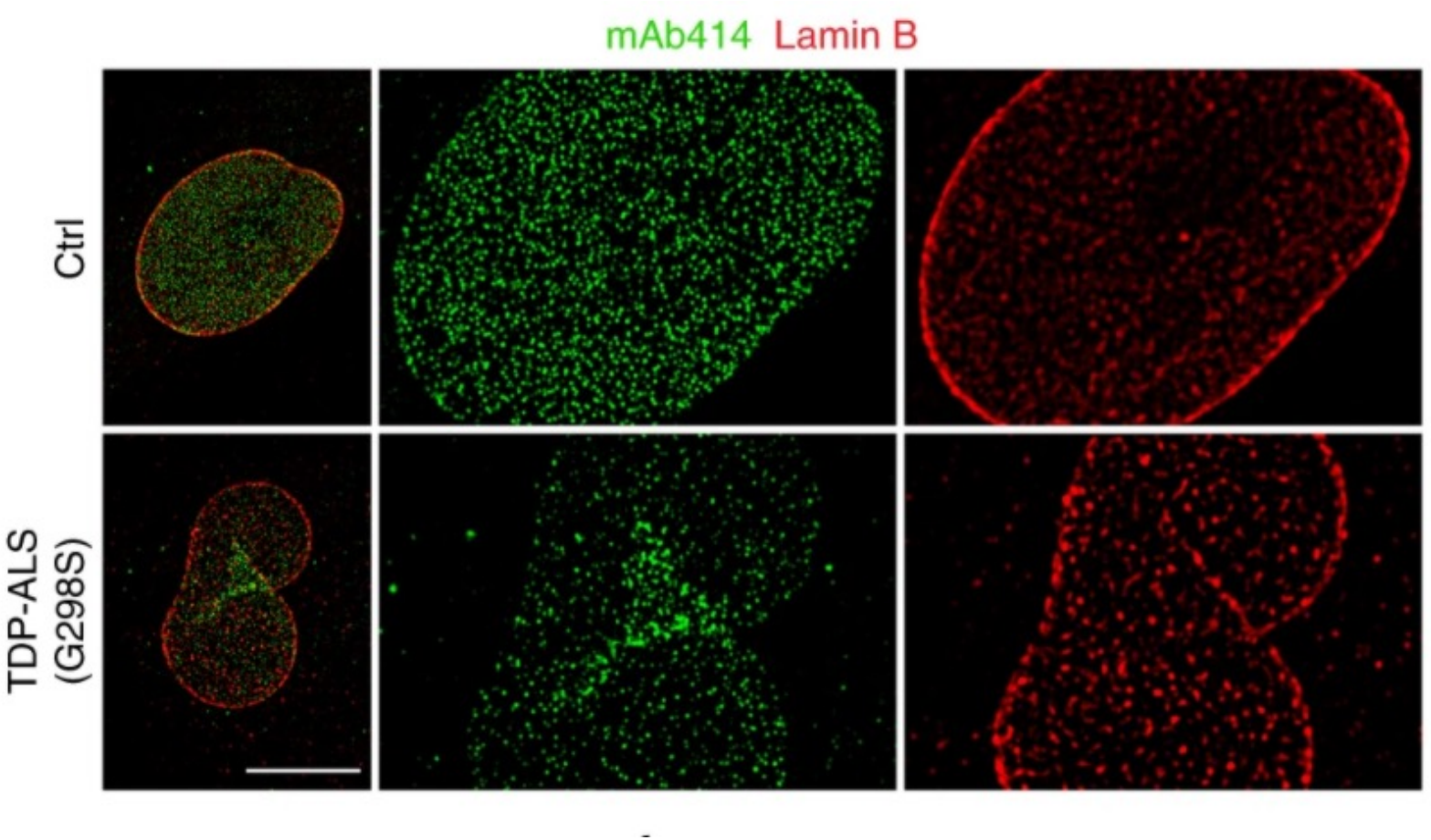


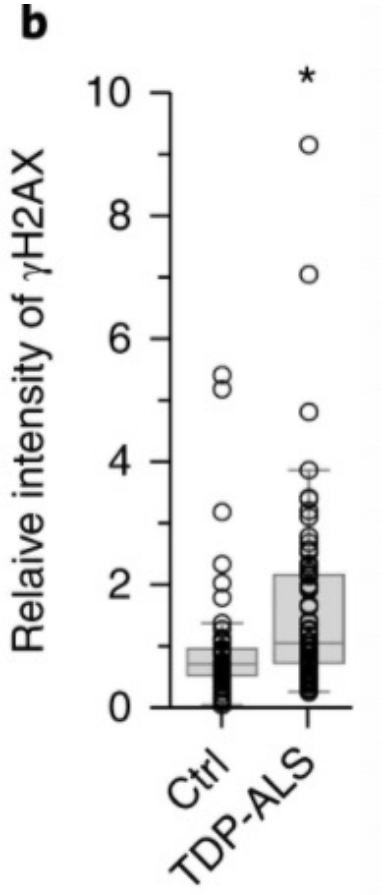
Does TDP-43 pathology disrupt nuclear export of mRNA?



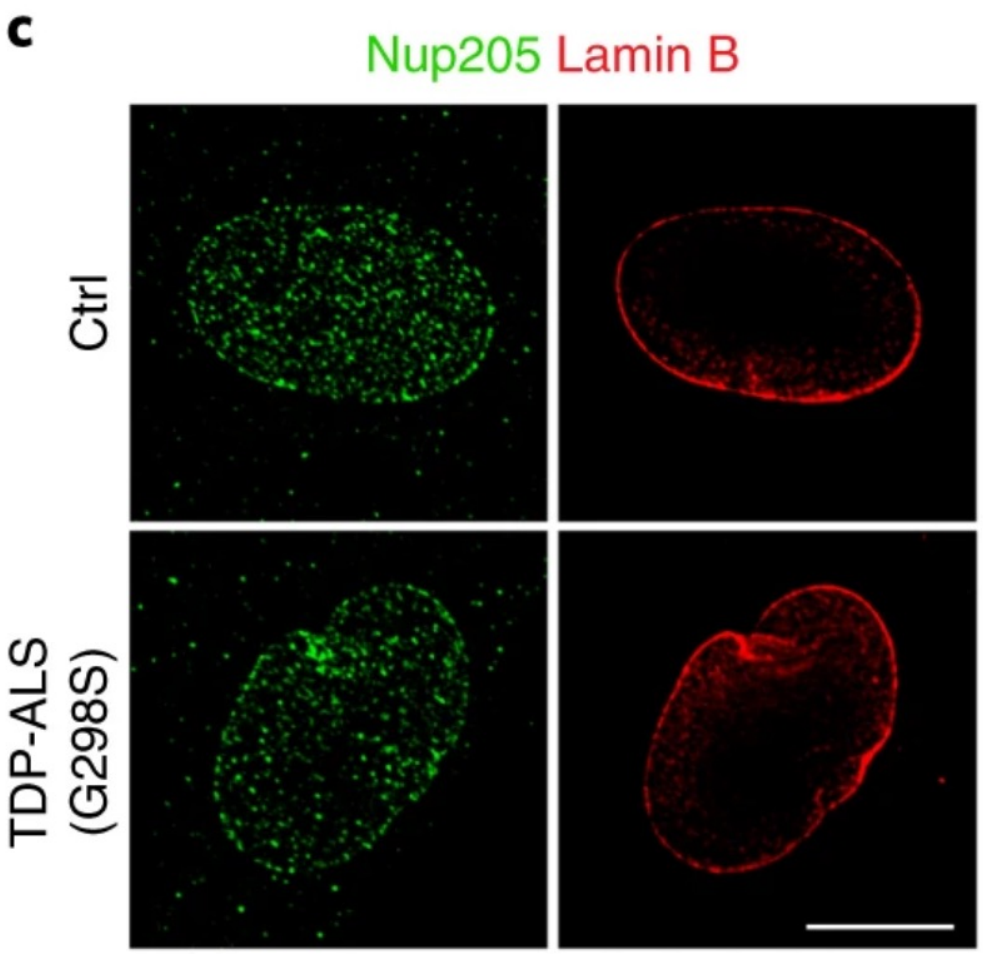


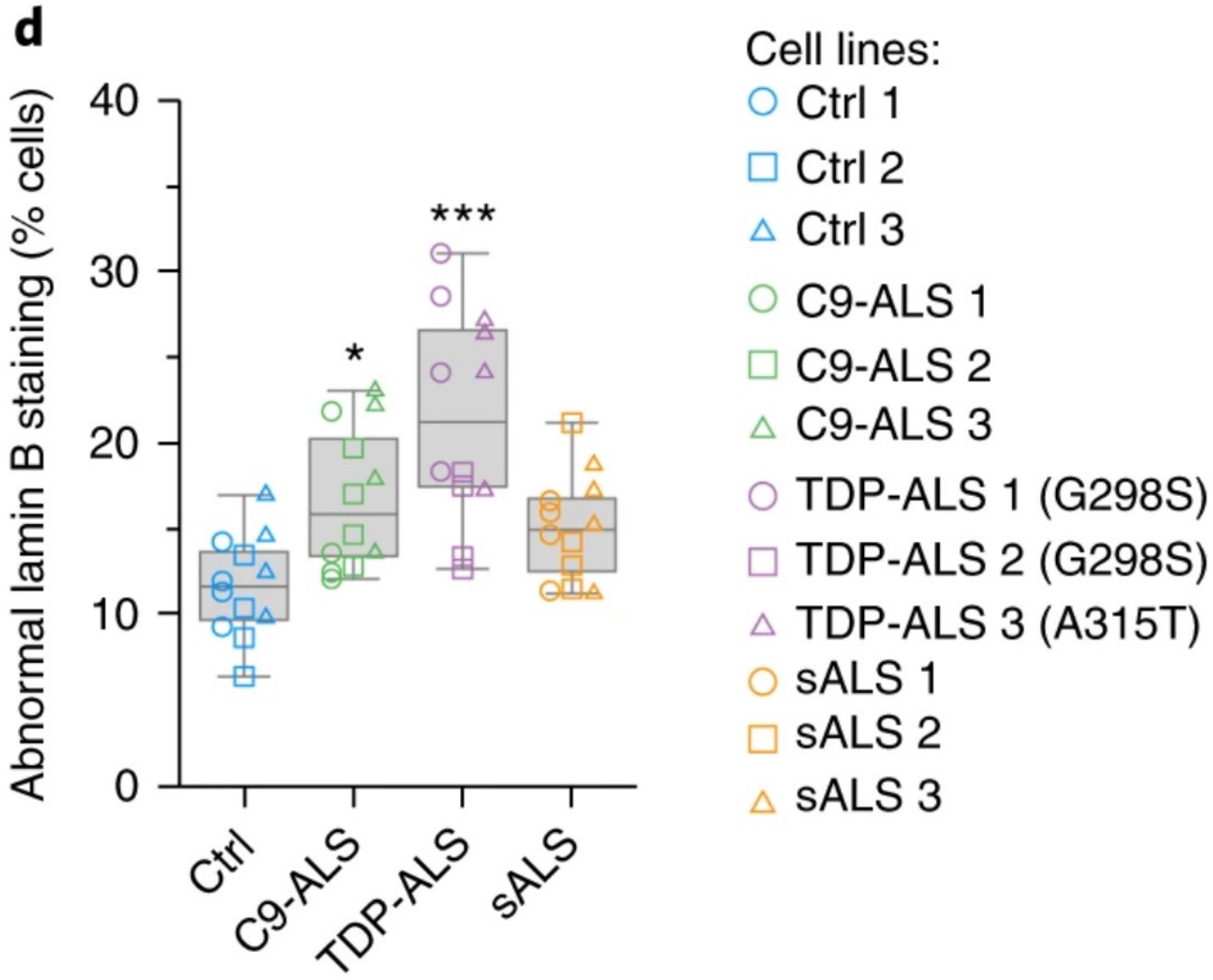
What do defects in NCP in the cells of human ALS patients?



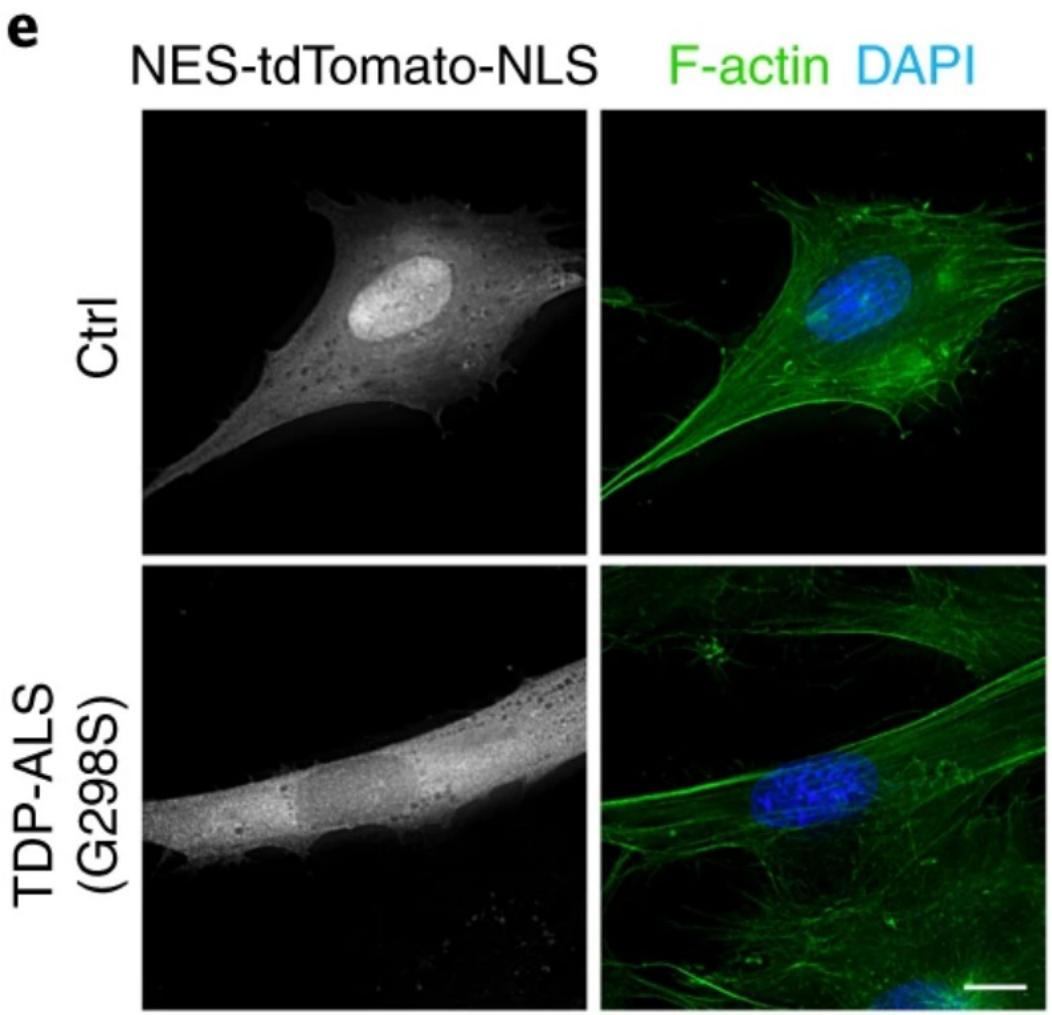


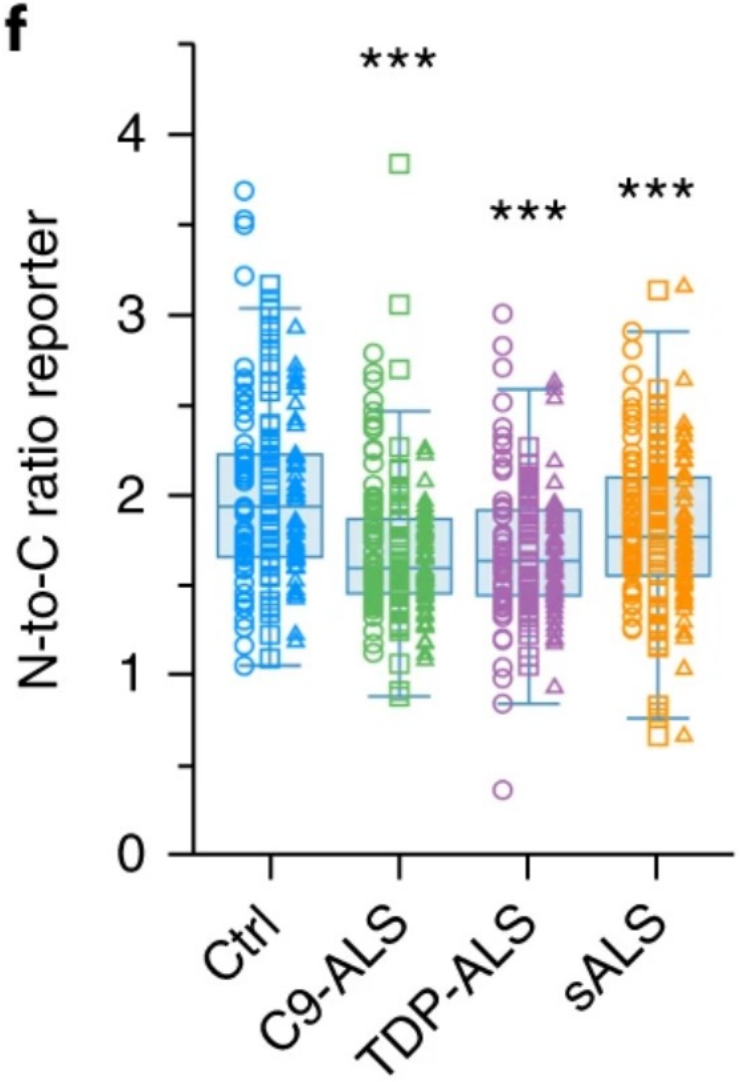
How do cells from human ALS patients show defects in lamina morphology?





How do cells from human ALS patients show defects in nucleocytoplasmic transport?





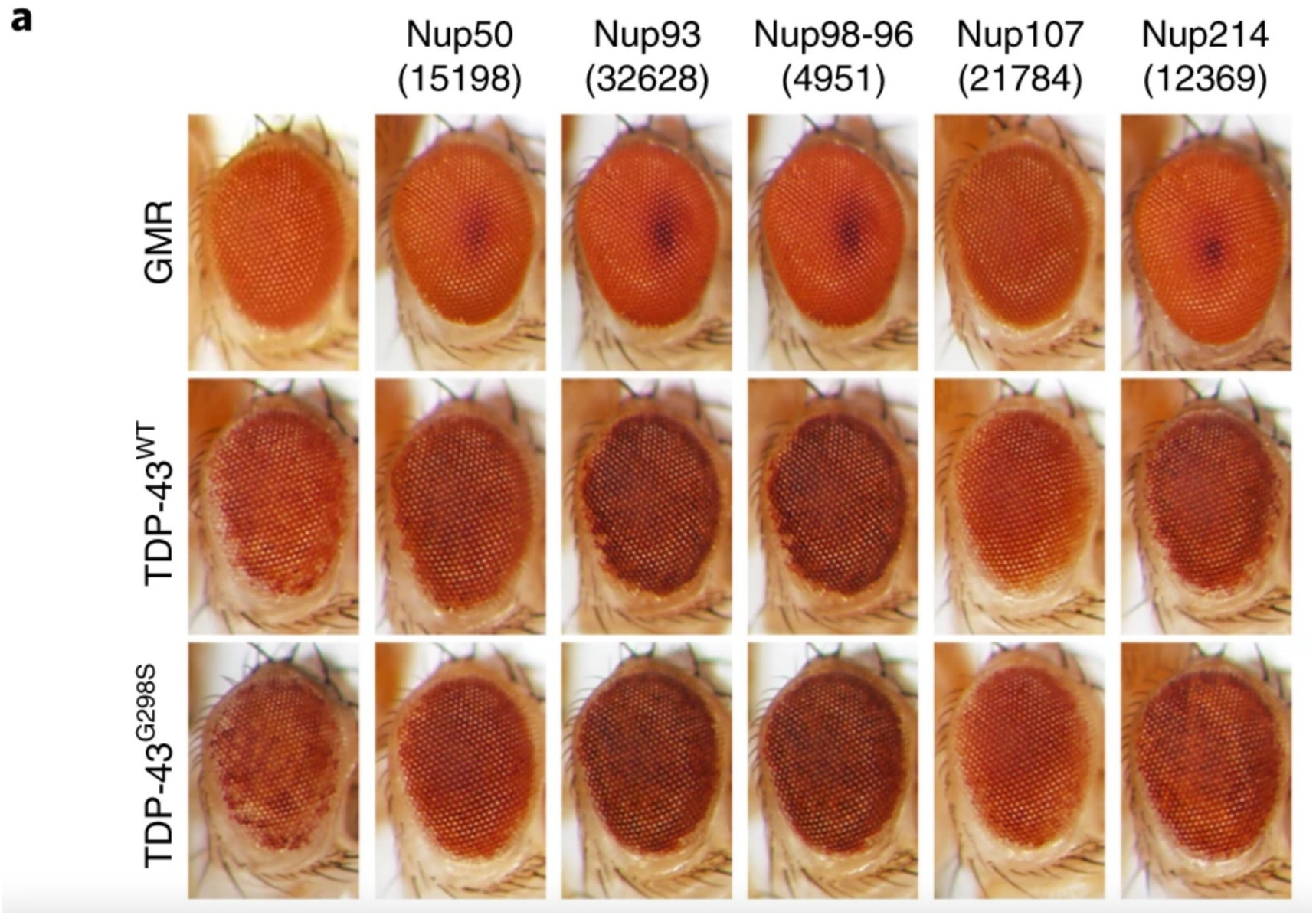
How do we model TDP-43 suppression of *Nup* genes in model organisms?

Drosophila

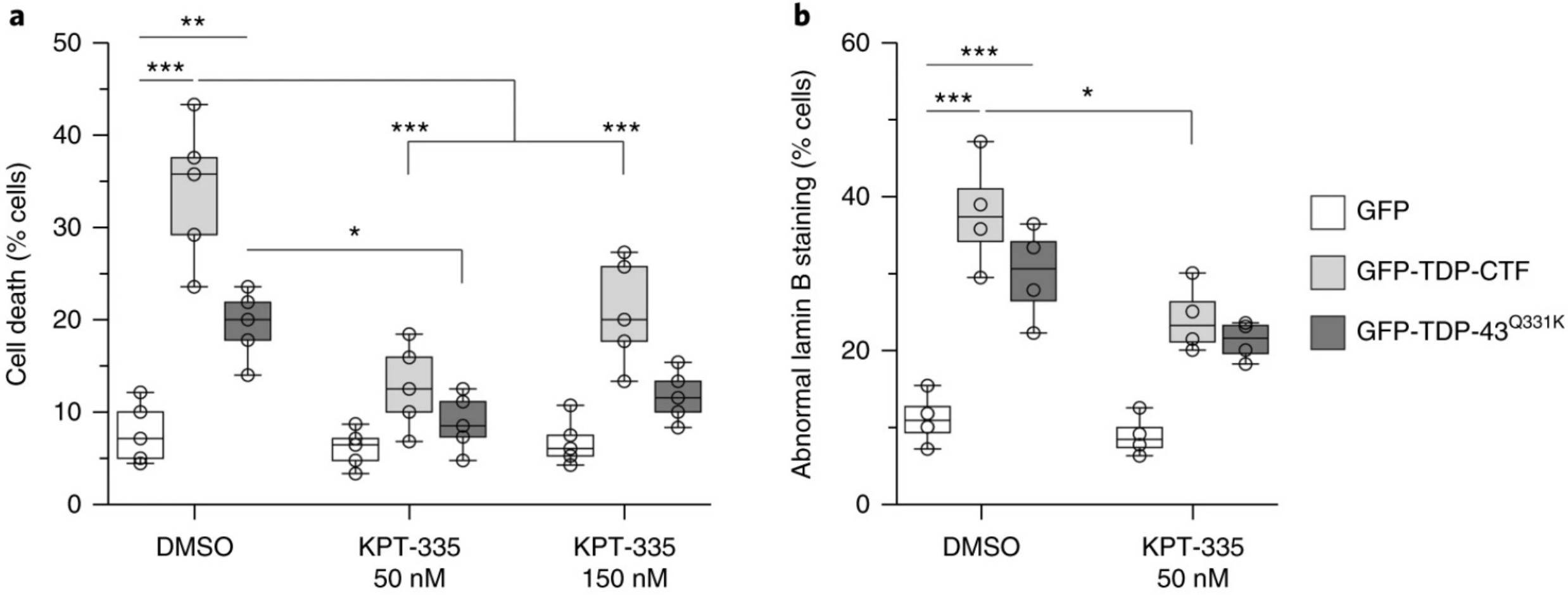
Overexpression of human $TDP-43^{G298S}$ (mutant)

- Retinal degradation
- Larval motor dysfunction
- *Nup50* mutation

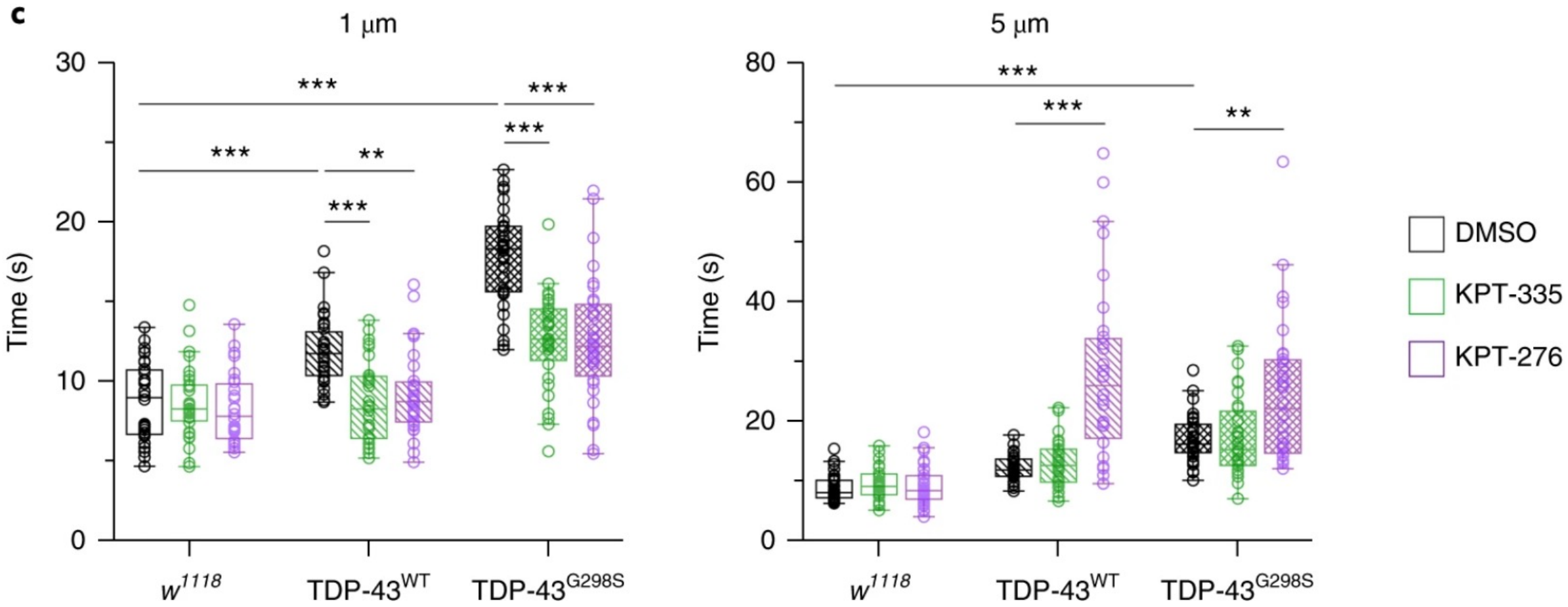
How do we model TDP-43 suppression of *Nup* genes in model organisms?



Does suppression of TDP-43 toxicity rescue nucleocytoplasmic transport defects?



Does suppression of TDP-43 toxicity rescue nucleocytoplasmic transport defects?



Summary

BioID can be modified in order to better “interrogate the genome” to understand TDP-43 protein interaction aggregate neurotoxicity

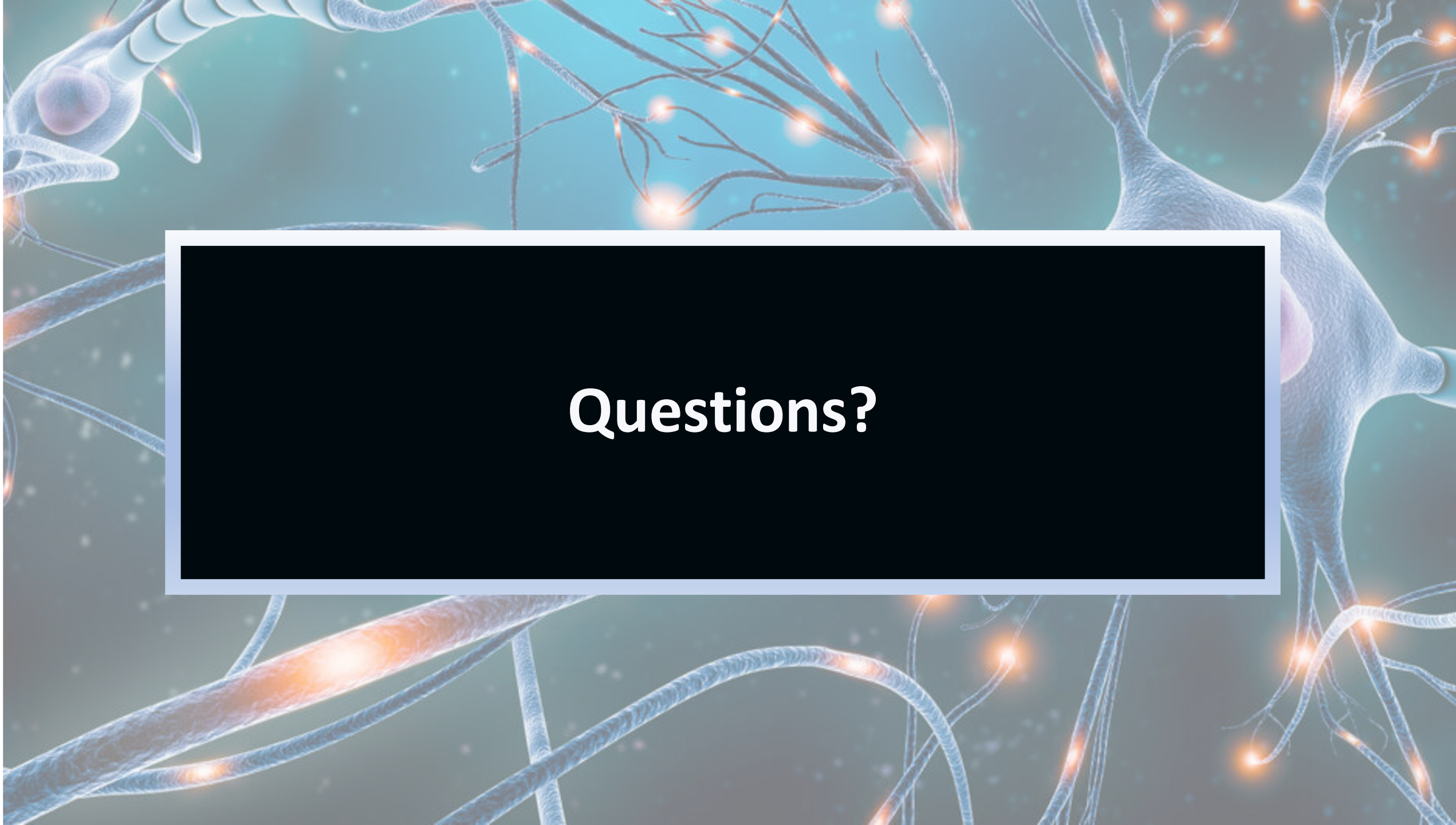
Interacting proteins of TDP-43 were highly associated with the nuclear membrane and nucleocytoplasmic transport proteins and transport factors

The Drosophila model of nucleoporin defects showed that the *Nup* knockout could reduce TDP-43 cytoplasmic shuttling, successfully suppressing TDP-43 toxicity

Overall, NM, NPCs, and nucleocytoplasmic transport may play a pathogenic role in most ALS with TDP-43 retinopathy

Image Sources

- https://www.google.com/search?q=tdp-43+proteinopathy&tbm=isch&ved=2ahUKEwjvjPeVv9PvAhXIK6wKHfEtAtsQ2-cCegQIABAA&oq=TDP-43+&gs_lcp=CgNpbWcQARgEMgIIADICCAAyAggAMgIIADICCAAyAggAMgIIADICCAAyAggAMgIIADoECAAQQzoFCAAQsQM6CAgAELEDEIMBUOmrAViOxgFgu9cBaABwAHgAgAH2AYgBlwaSAQU3LjAuMZgBAKABAaoBC2d3cy13aXotaW1nsAEAwAEB&sclient=img&ei=TbpgYK-yEcjXsAXx24jYDQ&bih=689&biw=778#imgrc=1U2WPUo8sCu4ZM
- https://translationalneurodegeneration.biomedcentral.com/articles/10.1186/s40035-020-00219-w/figures/2
- https://www.google.com/url?sa=i&url=https%3A%2F%2Fnews.harvard.edu%2Fgazette%2Fstory%2F2020%2F12%2Fhow-neurons-form-long-term-memories%2F&psig=AOvVaw1dddatPvDlPeJ74ejh4vw4&ust=1617137728423000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCKD1jNex1u8CFQAAAAAdAAAAABAD


Questions?