SAPAP3 scaffolding protein as a regulator of mitochondrial function in Huntington's Disease

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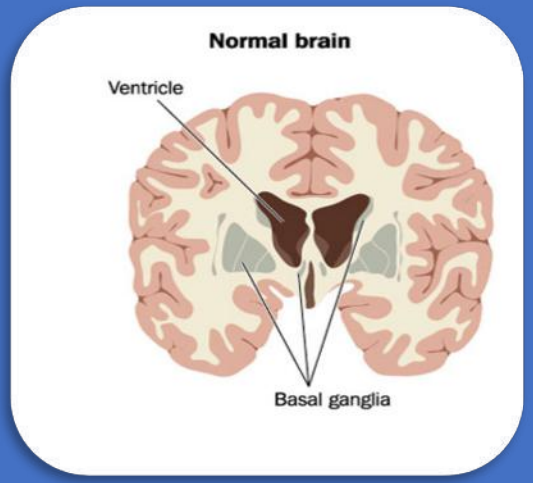
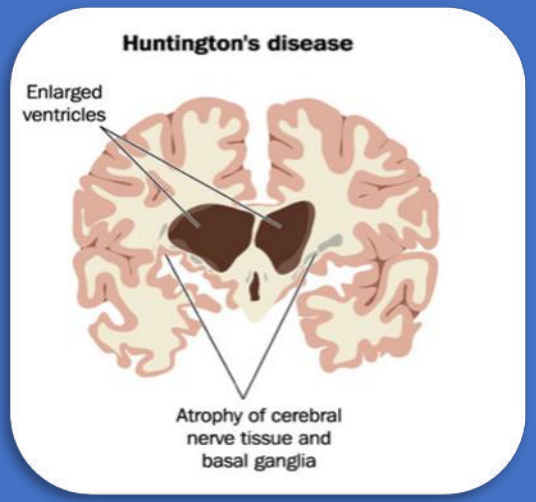
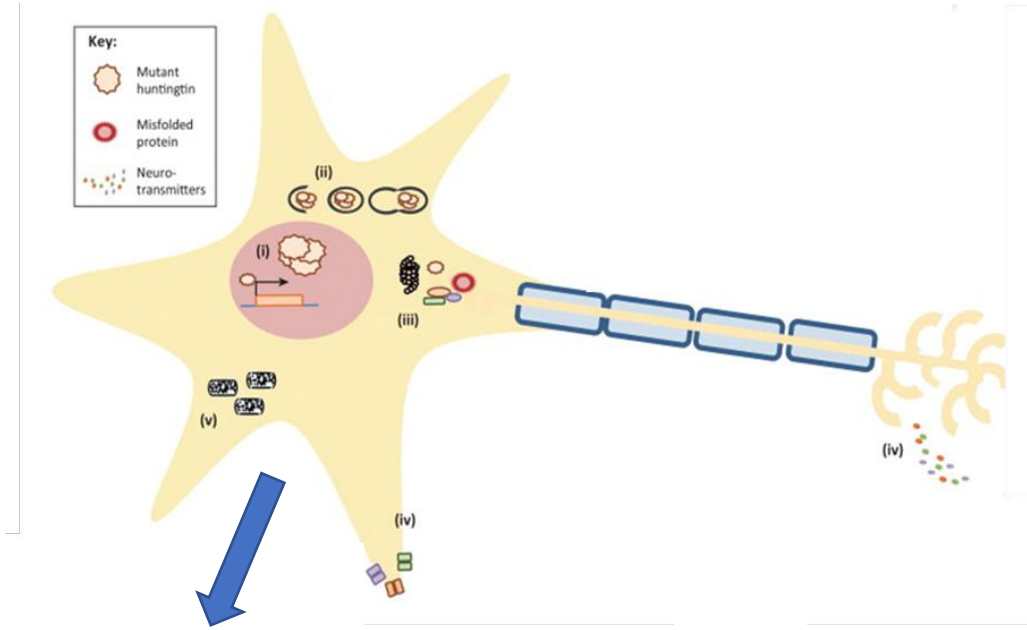
Huntington's Disease

Adapted from: Myers *et al.* (1998)

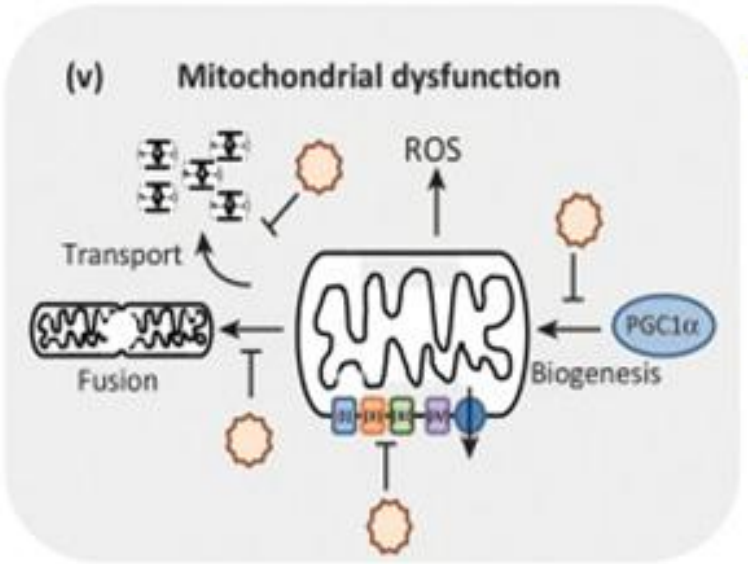




- *Huntington's disease (HD):*
  - Autosomal dominant neurodegenerative disorder
  - CAG repeat expansion in the *HTT* gene.
  - Affects the striatum and later the cortex

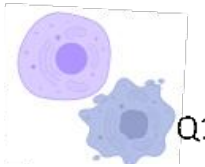


- HD clinical symptoms include:
  - Uncontrolled motor movements
  - Dementia
  - Cognitive dysfunction
  - Psychiatric disturbances

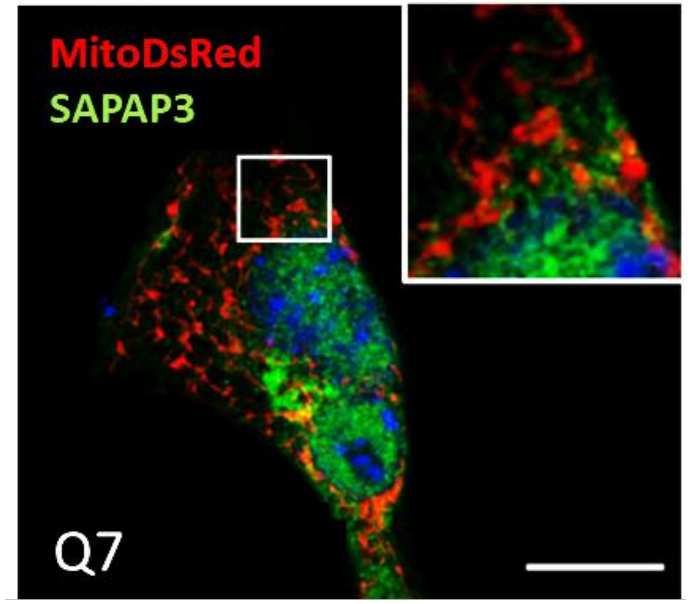


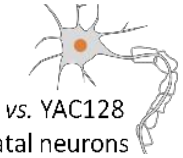
Adapted from: Labbadia *et al.* (2013)

SAPAP3 is present in mitochondria

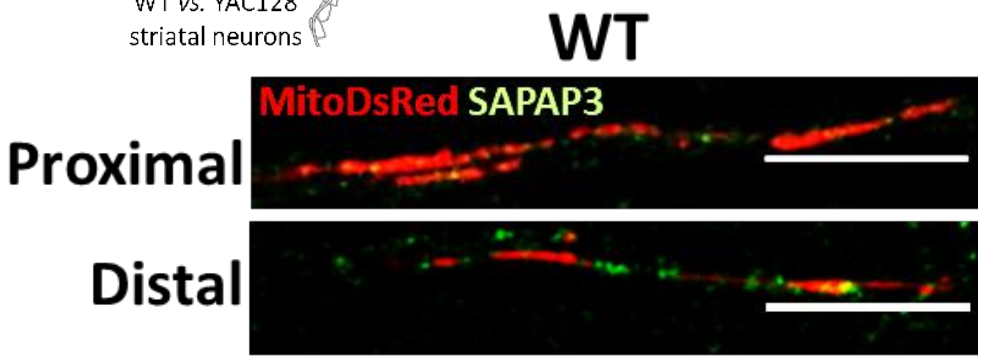


Q7/Q7 *vs.*
Q111/Q111 cells





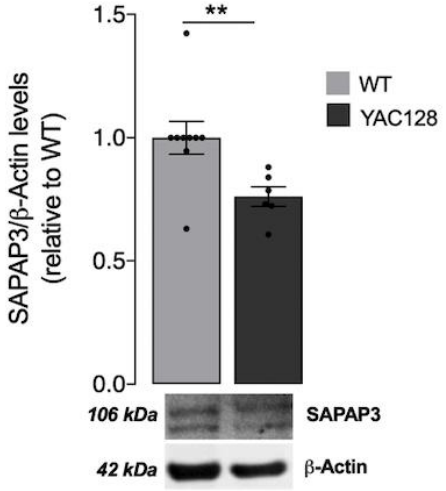
WT *vs.* YAC128
striatal neurons



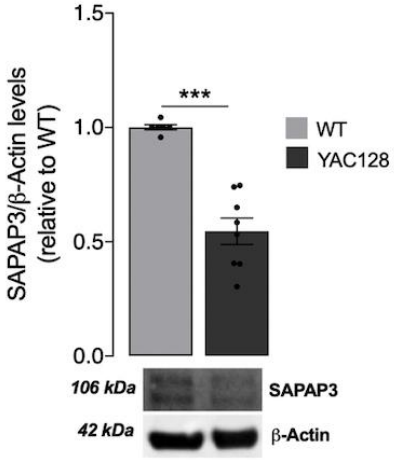
SAPAP3 is diminished in HD YAC128 neurons

Primary cultures: Extracts

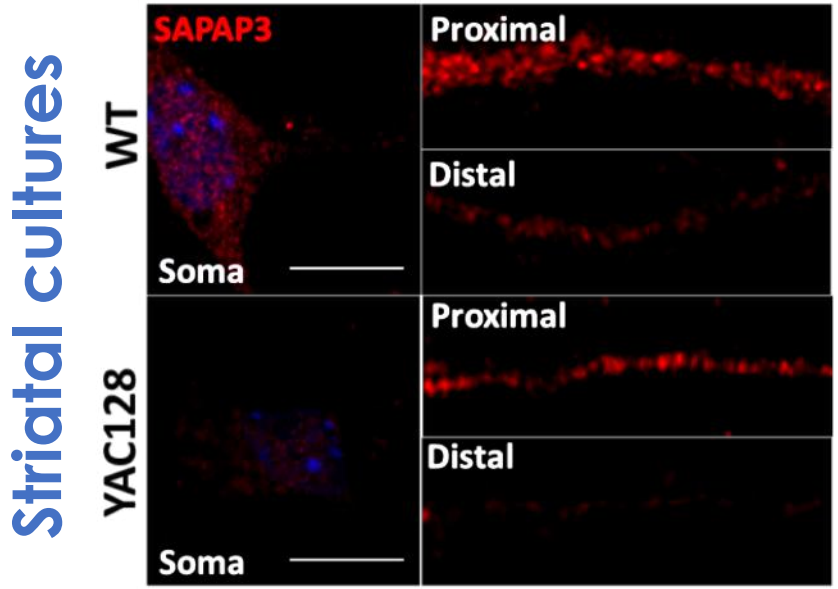
Striatal cultures



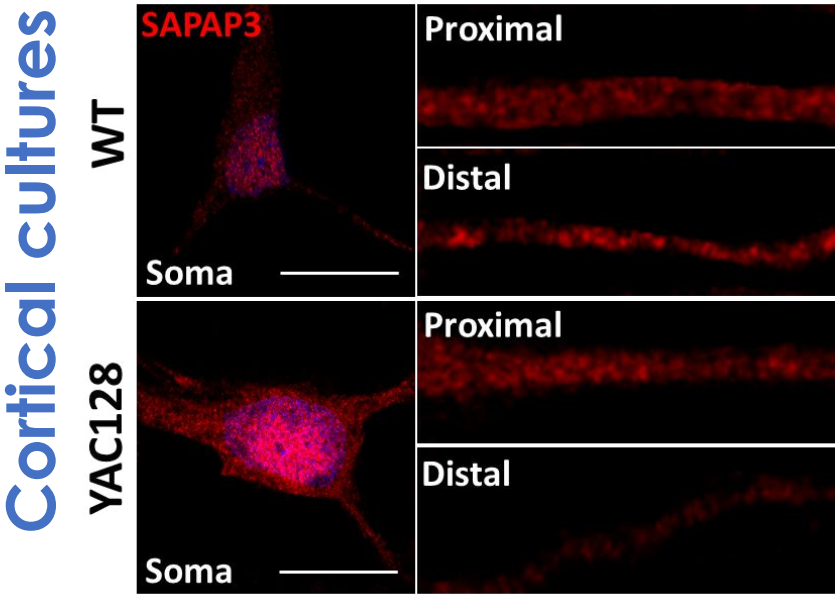
Cortical cultures

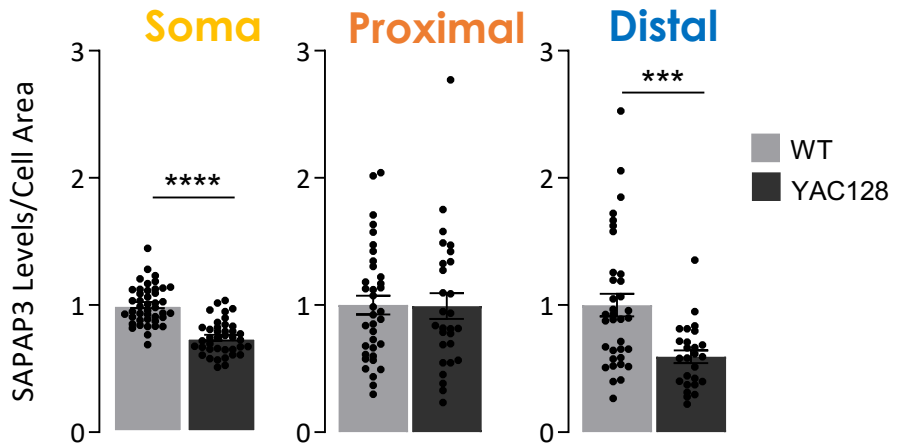


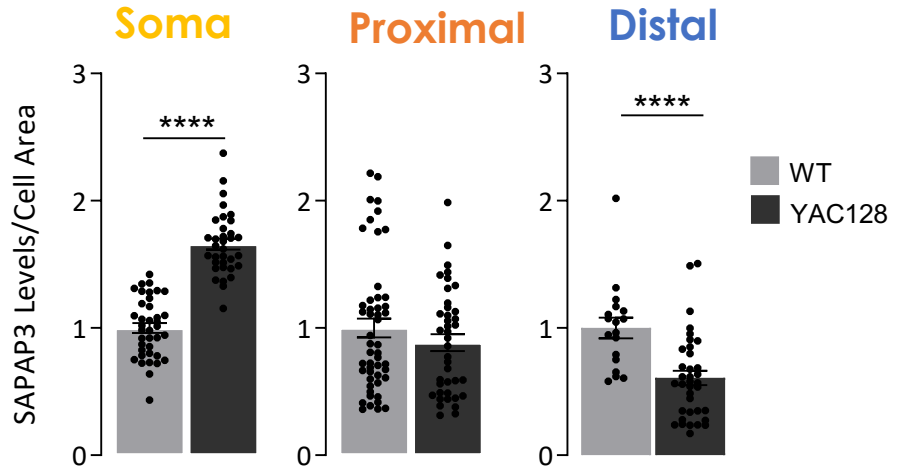
Striatal cultures



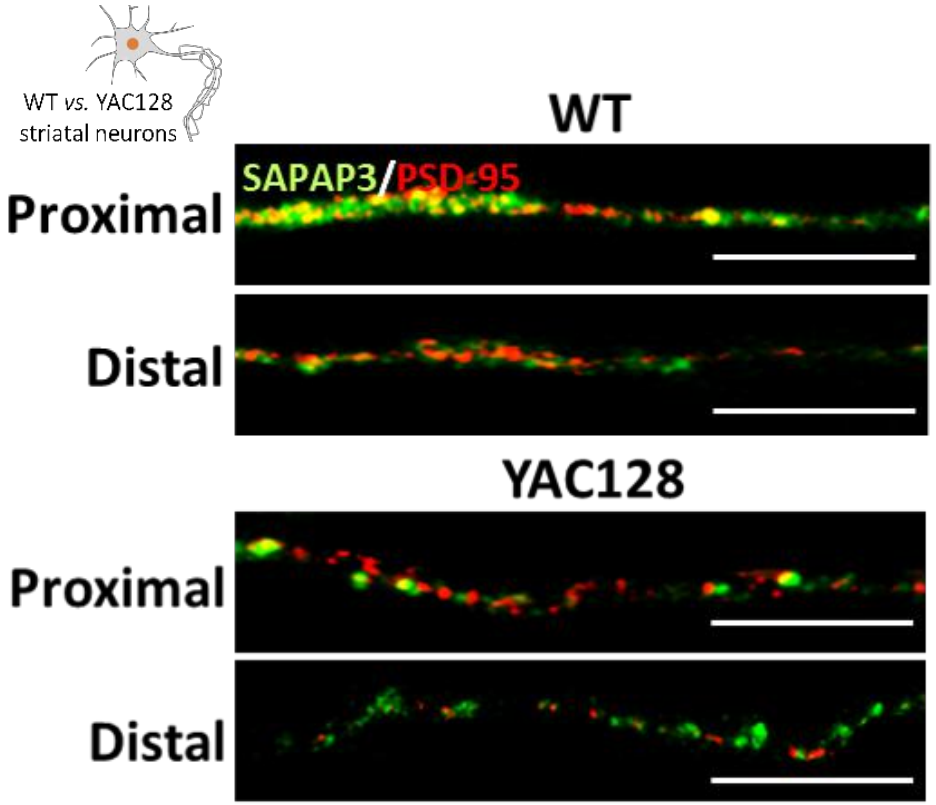
Cortical cultures



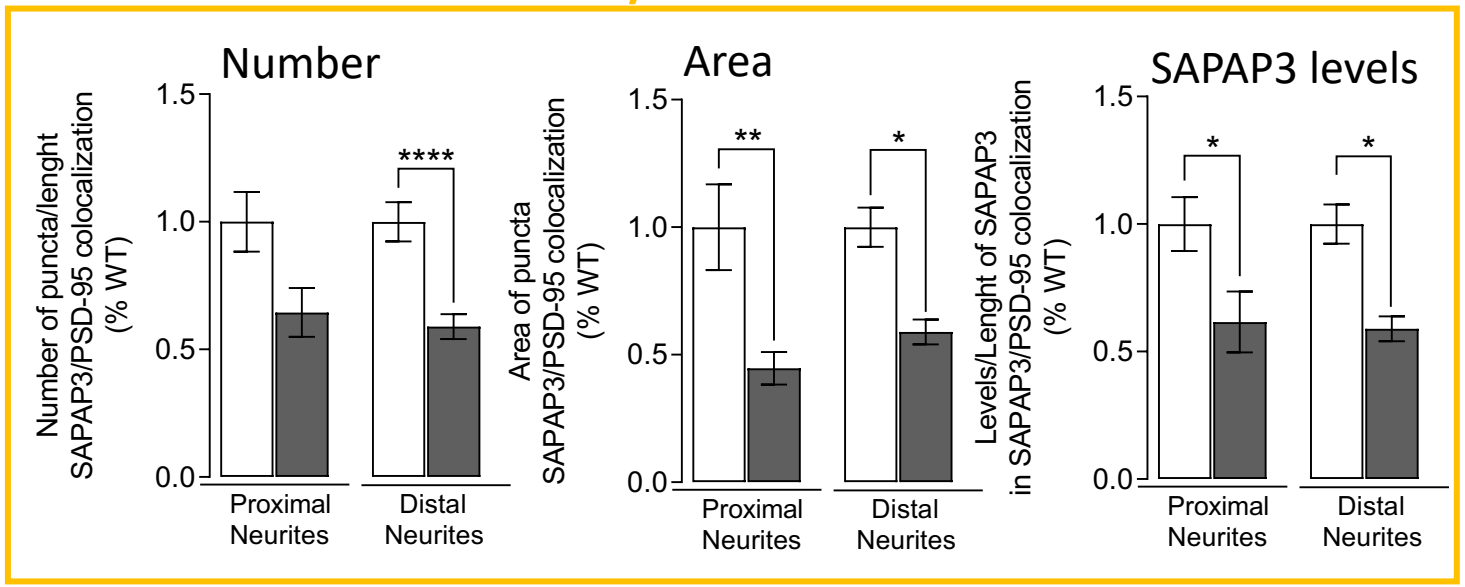


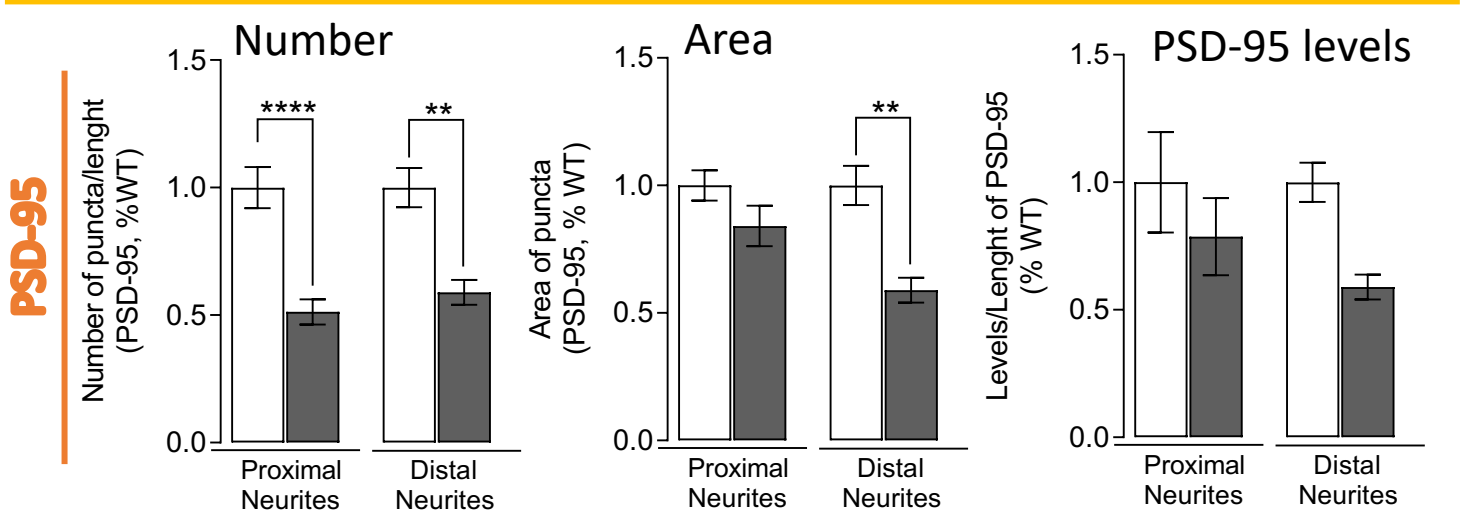


SAPAP3 distinctly colocalizes with PSD-95 in HD YAC128 striatal neurons



SAPAP3/PSD-95 colocalization





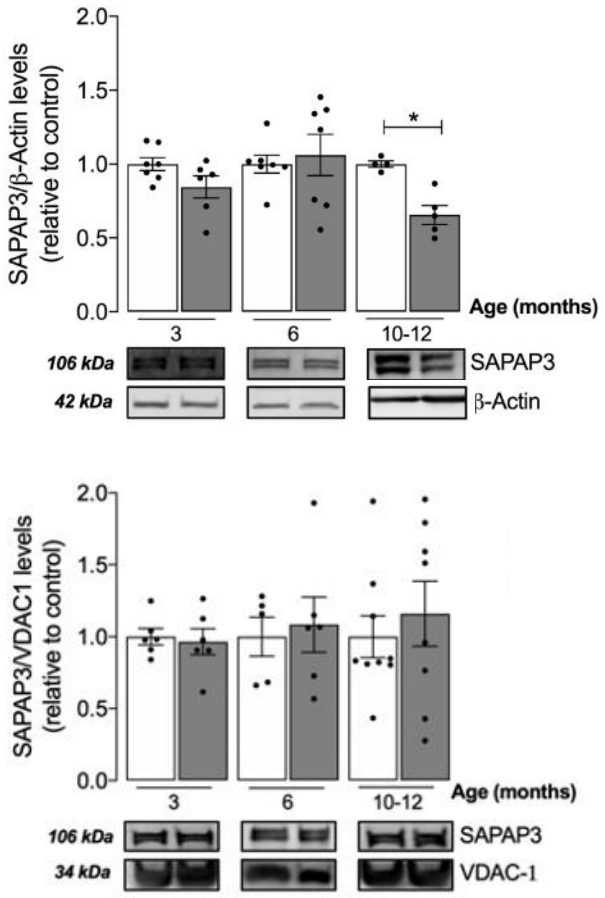
SAPAP3-mitochondrial colocalization is altered in HD models

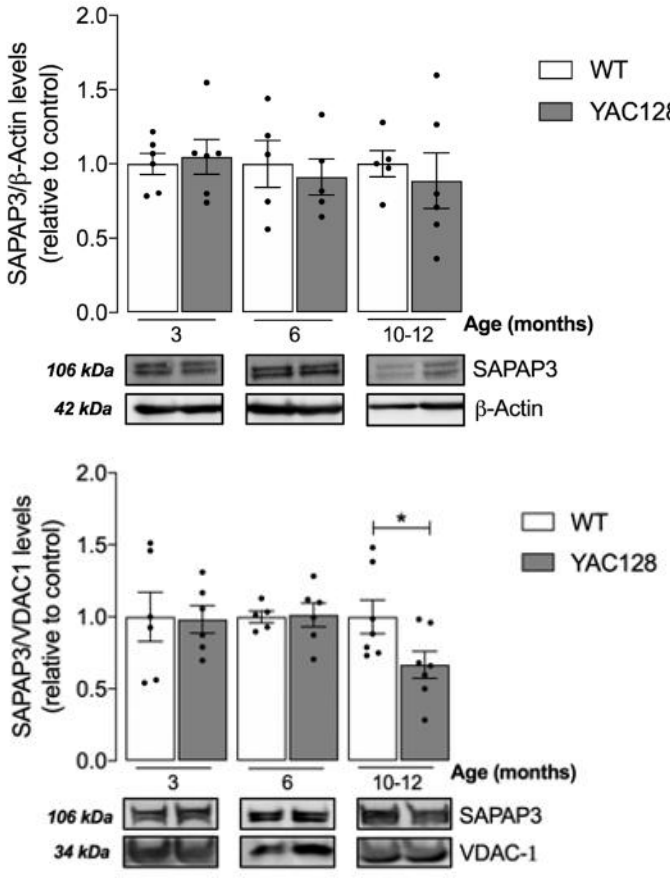
Striatum

Cortex

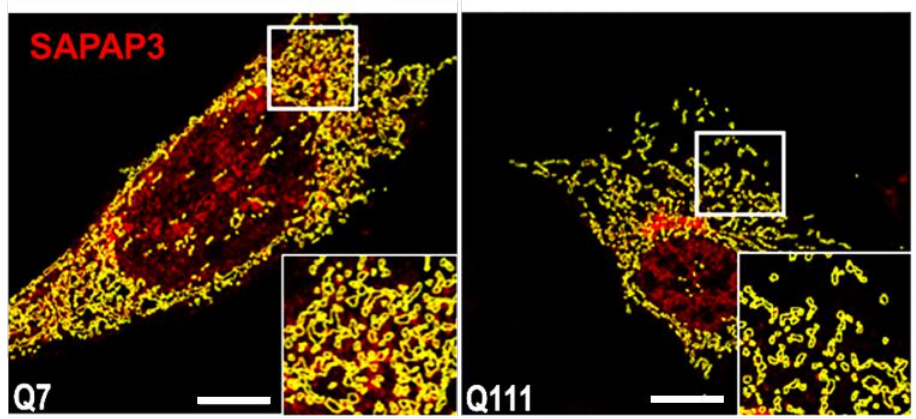
Total Brain

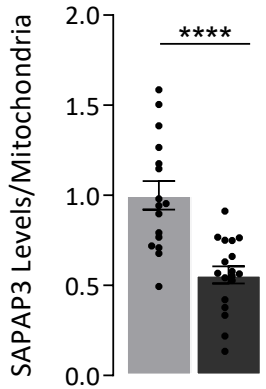
Mitochondrial Brain Isolates



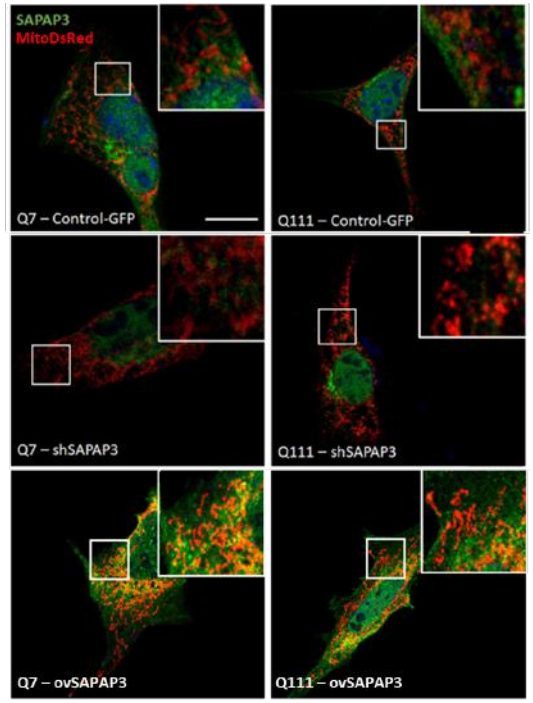


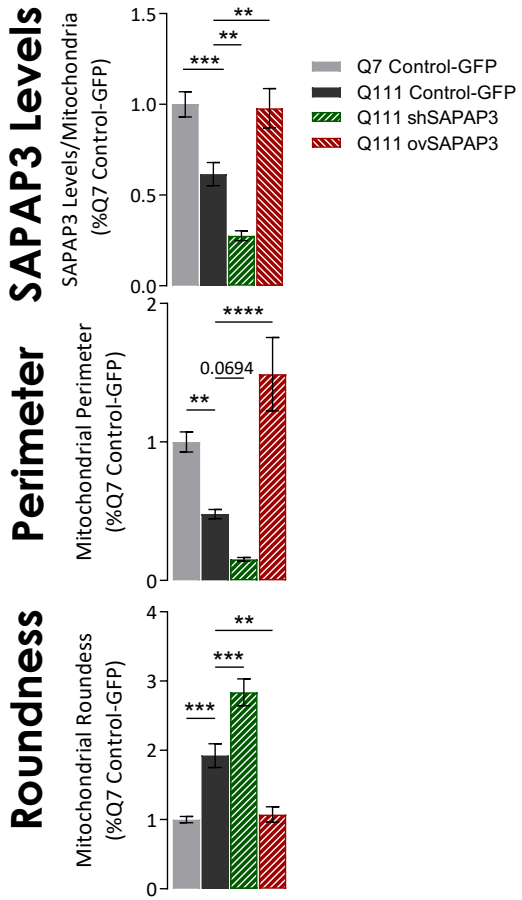
Mitochondrial SAPAP3 levels in Q7/Q7 *vs.* Q111/Q111 cells

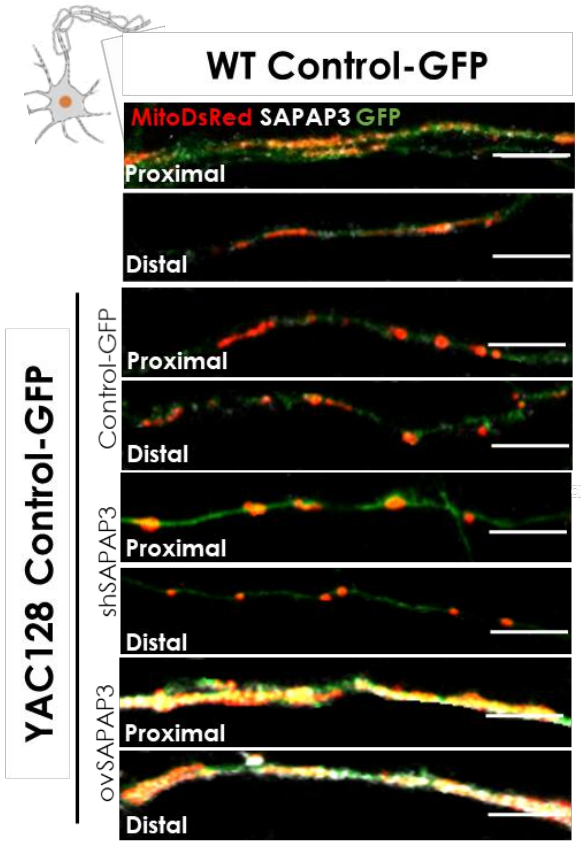


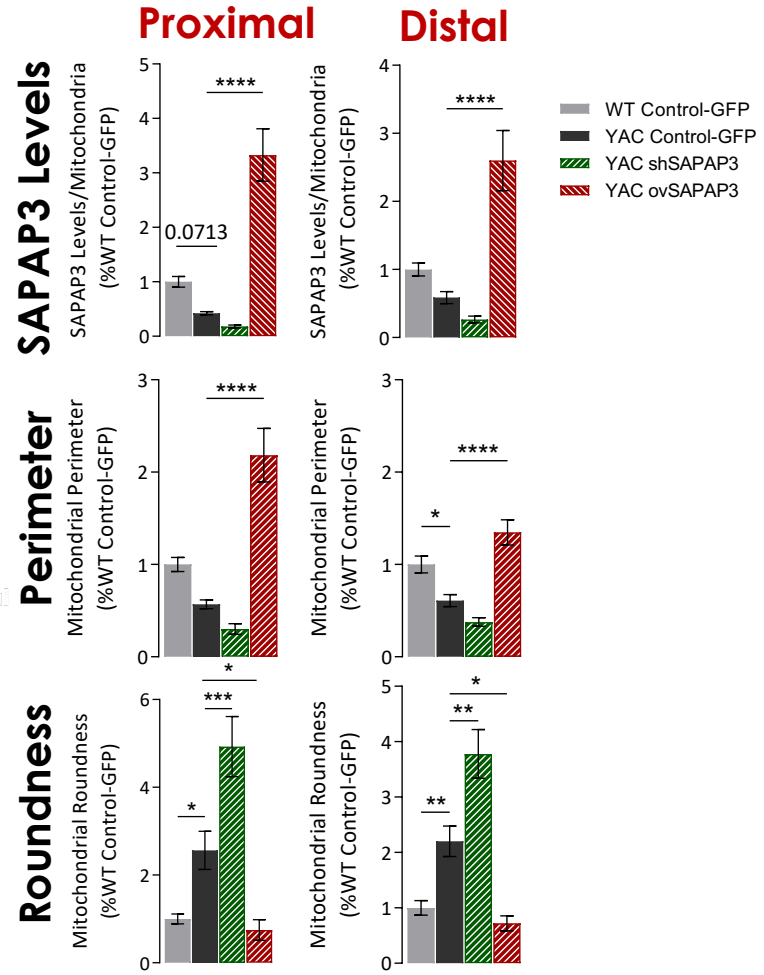


SAPAP3 modulation alters mitochondrial morphology and fission/fusion events

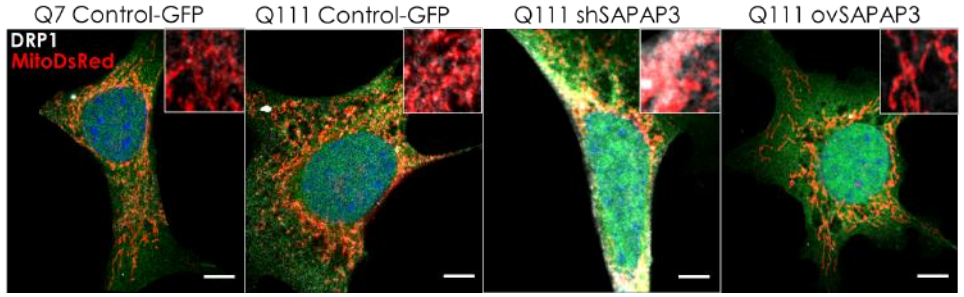




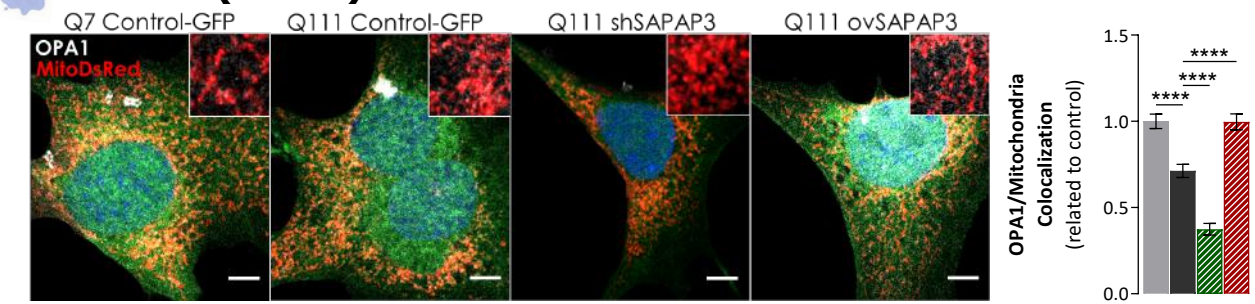




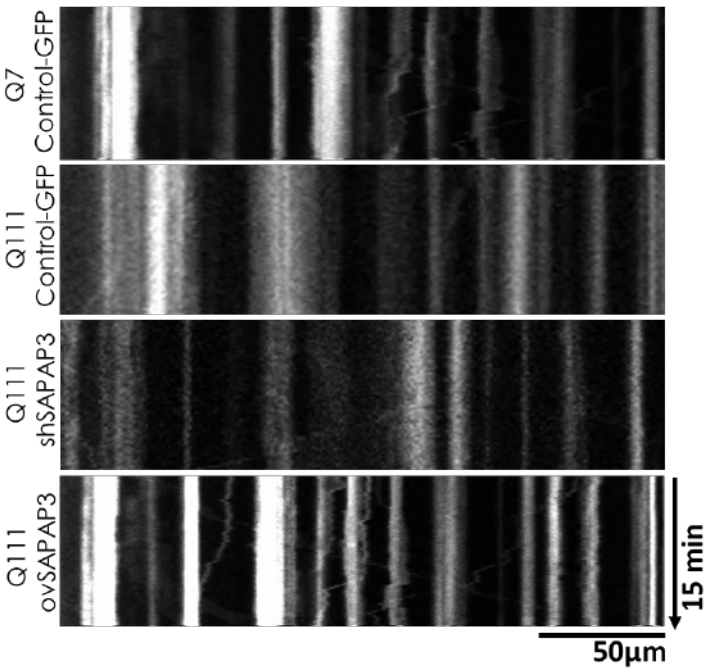
Fission (Drp1)

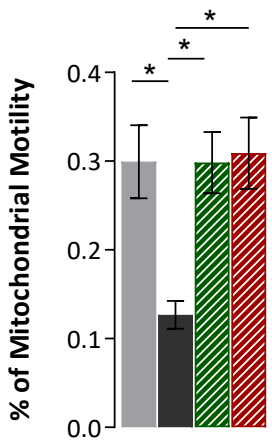


Fusion (OPA1)

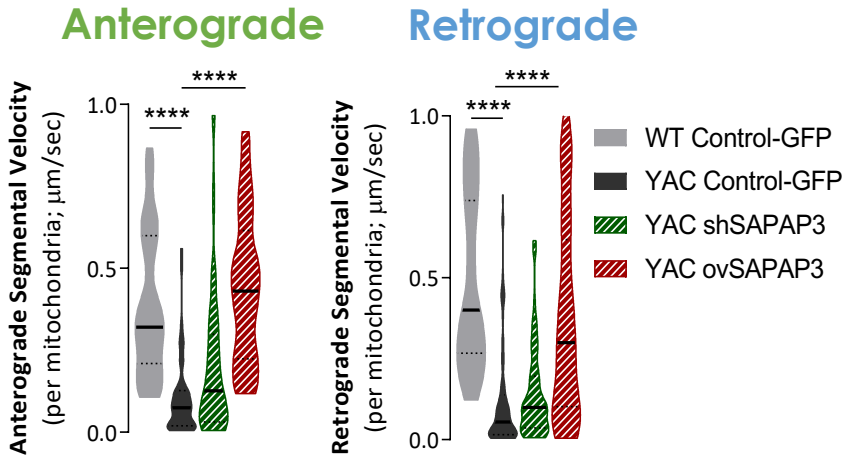


Mitochondrial Movement

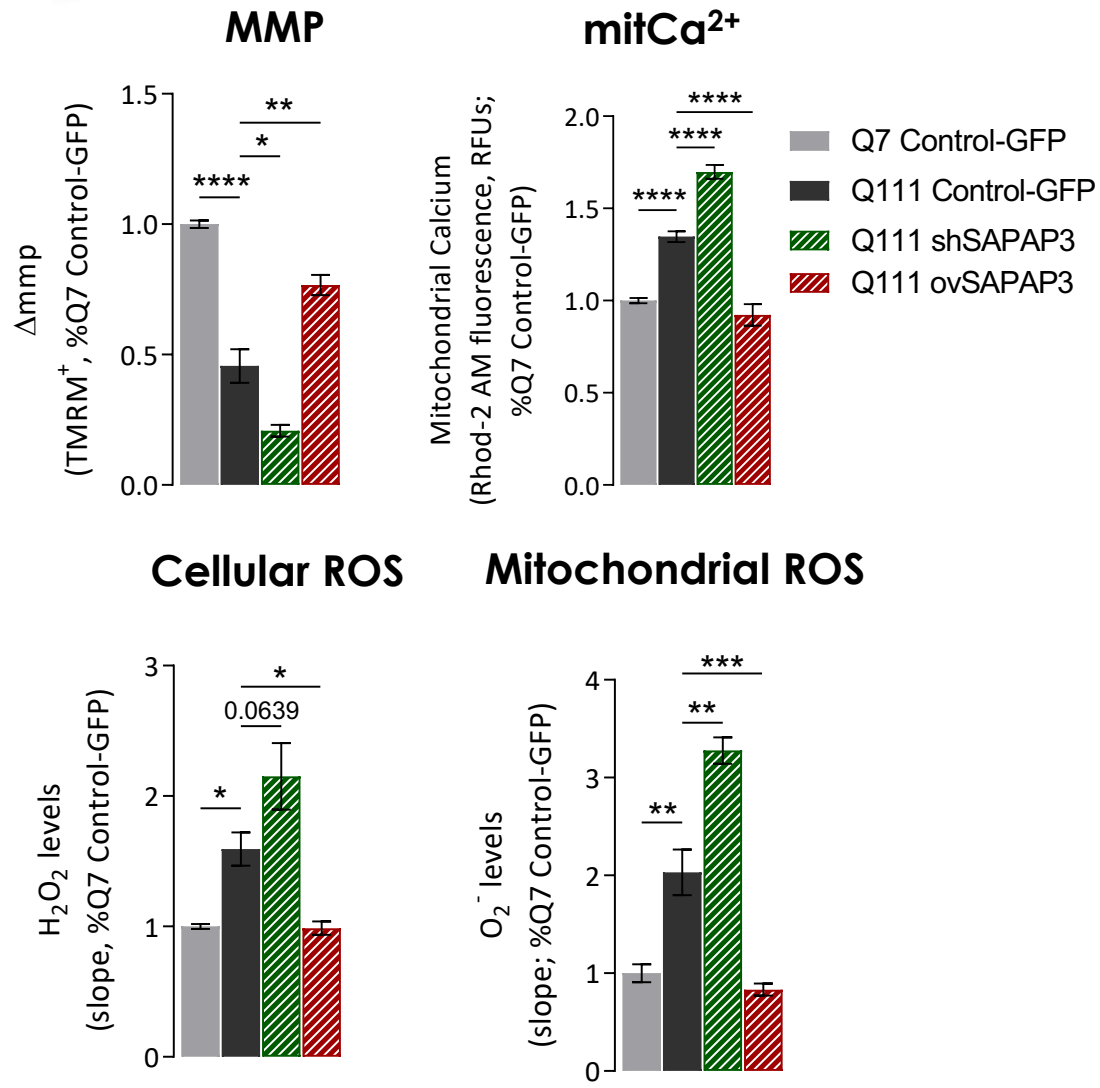




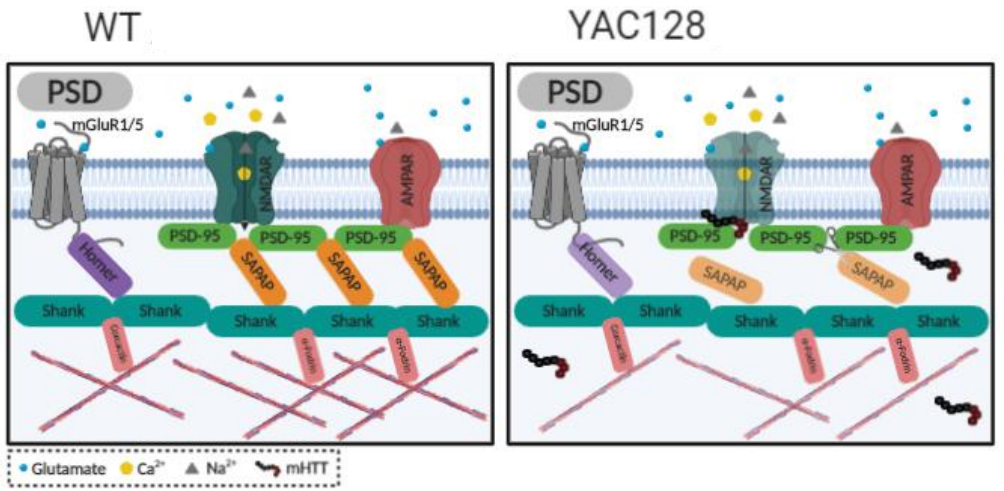
Velocity



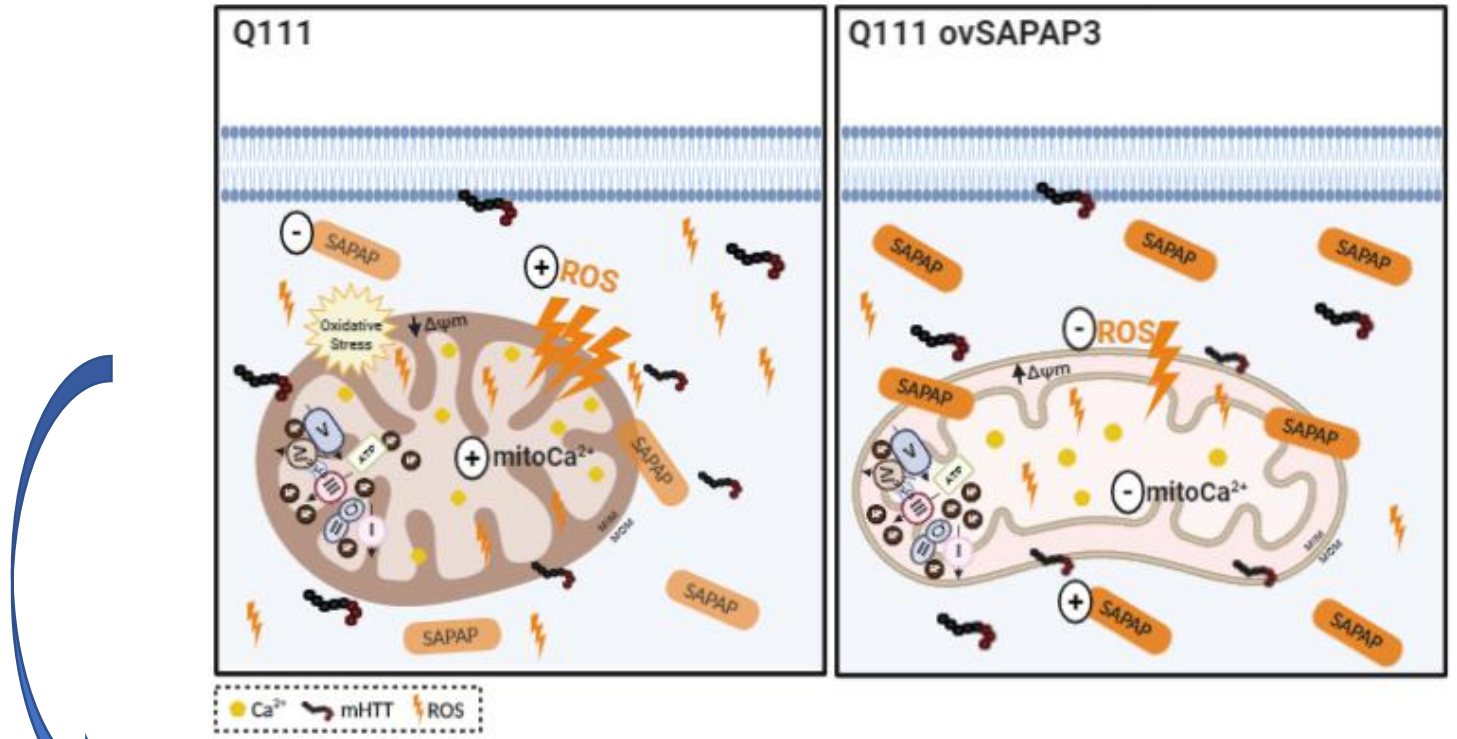
Mitochondrial Function



Conclusions



PSD destabilization in HD might involve SAPAP3 defects



SAPAP3 might have a **protective effect in mitochondrial dysfunction** in HD