## HIPK2 may be a marker of neuronal stress in ALS/FTLD

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Amyotrophic lateral sclerosis (ALS) and fronto-temporal lobar degeneration (FTLD) are neurodegenerative diseases often characterized by TAR DNA-binding protein-43 (TDP-43) pathology in neurons. Accumulation of misfolded proteins causes endoplasmic reticulum (ER) stress, which may lead to cell death in disease. Here, we aimed to optimise antibodies to enable their use to reliably detect ER stress proteins C/EBP homologous protein (CHOP), protein kinase R-like ER kinase (PERK) and homeodomain-interacting protein kinase-2 (HIPK2) in an ALS/FTLD transgenic mouse model at different stages of the disease course. Tissues from the cerebral cortex and lumbar spinal cord were harvested from two-week off doxycycline NEFH-tTA/tetO-hTDP-43ΔNLS B6C3H mice with neurological manifestations of ALS/FTLD. Paraformaldehyde fixed tissues were immune stained with commercially available CHOP, PERK and HIPK2 primary antibodies with appropriate negative controls and visualized under an epifluorescence microscope. Alpha-motor neurones in the spinal cord of bigenic mice showed nuclear staining for HIPK2, consistent with previous findings where expression of HIPK2 was altered in disease compared to healthy tissue. Conditions for detection of PERK and CHOP require further optimisation. Therefore, we conclude that HIPK2 is expressed in the central nervous system of the bigenic mouse model of ALS/FTLD at an early age of the disease. These findings suggest that activation of HIPK2 may contribute to the early stages of diseases associated with TDP-43 pathology.

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