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Et al.

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POLY (GR) IN C9ORF72-RELATED ALS/FTD COMPROMISES MITOCHONDRIAL FUNCTION AND INCREASES OXIDATIVE STRESS AND DNA DAMAGE IN IPSC-DERIVED MOTOR NEURONS

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GGGGCC repeat expansions in C9ORF72 are the most common genetic cause of both ALS and FTD. To uncover underlying pathogenic mechanisms, we found that DNA damage was greater, in an age dependent manner, in motor neurons differentiated from iPSCs of multiple C9ORF72 patients than control neurons. Ectopic expression of the dipeptide repeat (DPR) protein (GR)80 in iPSC-derived control neurons increased DNA damage, suggesting poly(GR) contributes to DNA damage in aged C9ORF72neurons. Oxidative stress was also increased inC9ORF72 neurons in an age-dependent manner. Pharmacological or genetic reduction of oxidative stress partially rescued DNA damage in C9ORF72neurons and control neurons expressing (GR)80 or (GR)80-induced toxicity in flies. Moreover, interactome analysis revealed that (GR)80 preferentially bound to mitochondrial ribosomal proteins and caused mitochondrial dysfunction. Thus, poly(GR) in C9ORF72 neurons compromises mitochondrial function and causes DNA damage in part by increasing oxidative stress, revealing another pathogenic mechanism in C9ORF72-related ALS and FTD.

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