Supplement

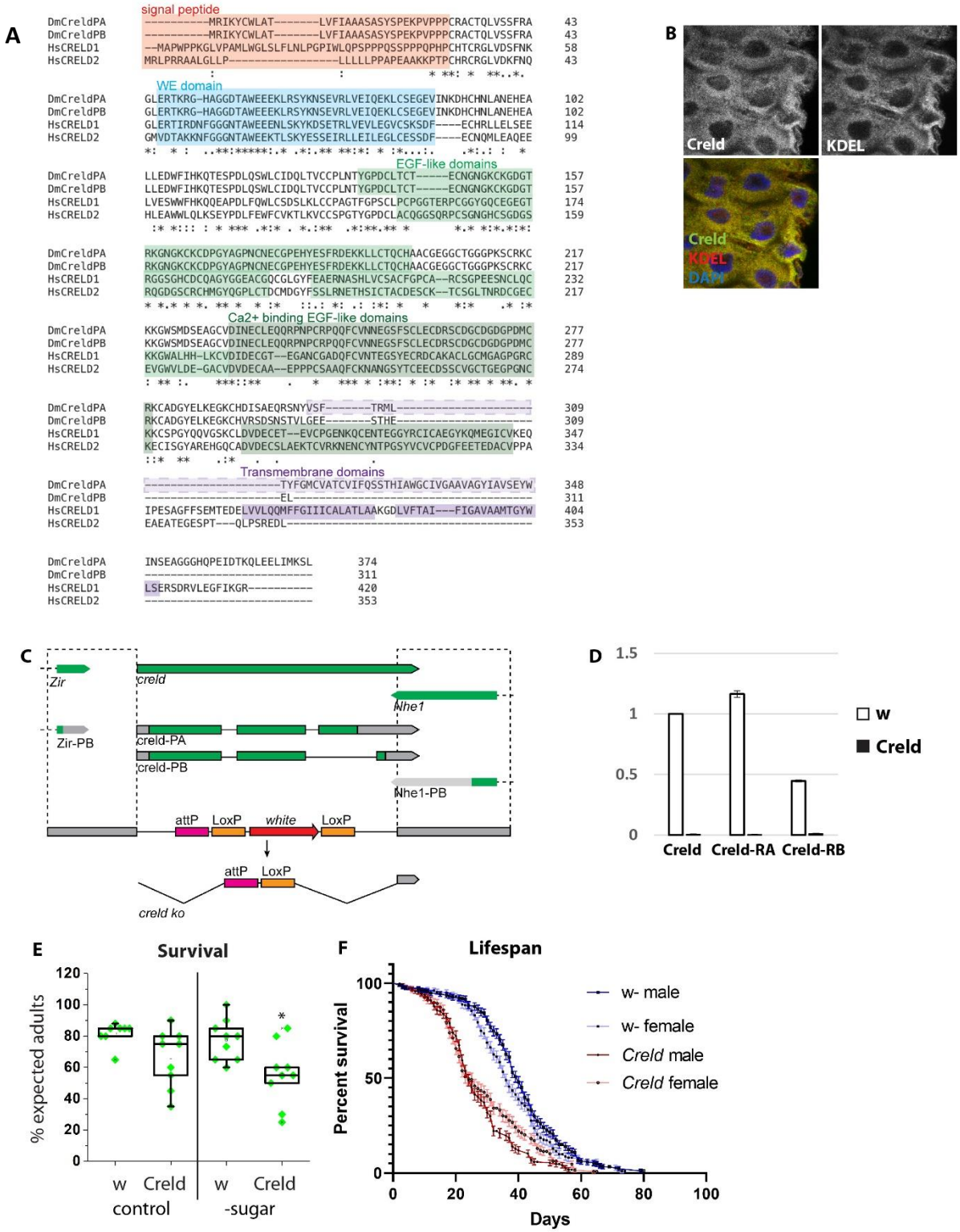

Figure S1: A) Representation of the domains and conservation of the Drosophila Creld peptides PA and PB and human CRELD1 and 2. B) Creld primarily colocalizes with the ER marker KDEL in Drosophila gut tissue. C) Representation of the generation of the Creld$^{\Delta 51}$ mutant by homologous recombination. D) Transcript levels determined by real-time qPCR of the Creld isoforms RA and RB. E) Survival rate of Creld mutants on food containing sugar and protein or sugar-depleted food

compared to w1118. F) Lifespan of w1118 and Creld mutant male and female flies. Asterisks represent * $p < 0.05$

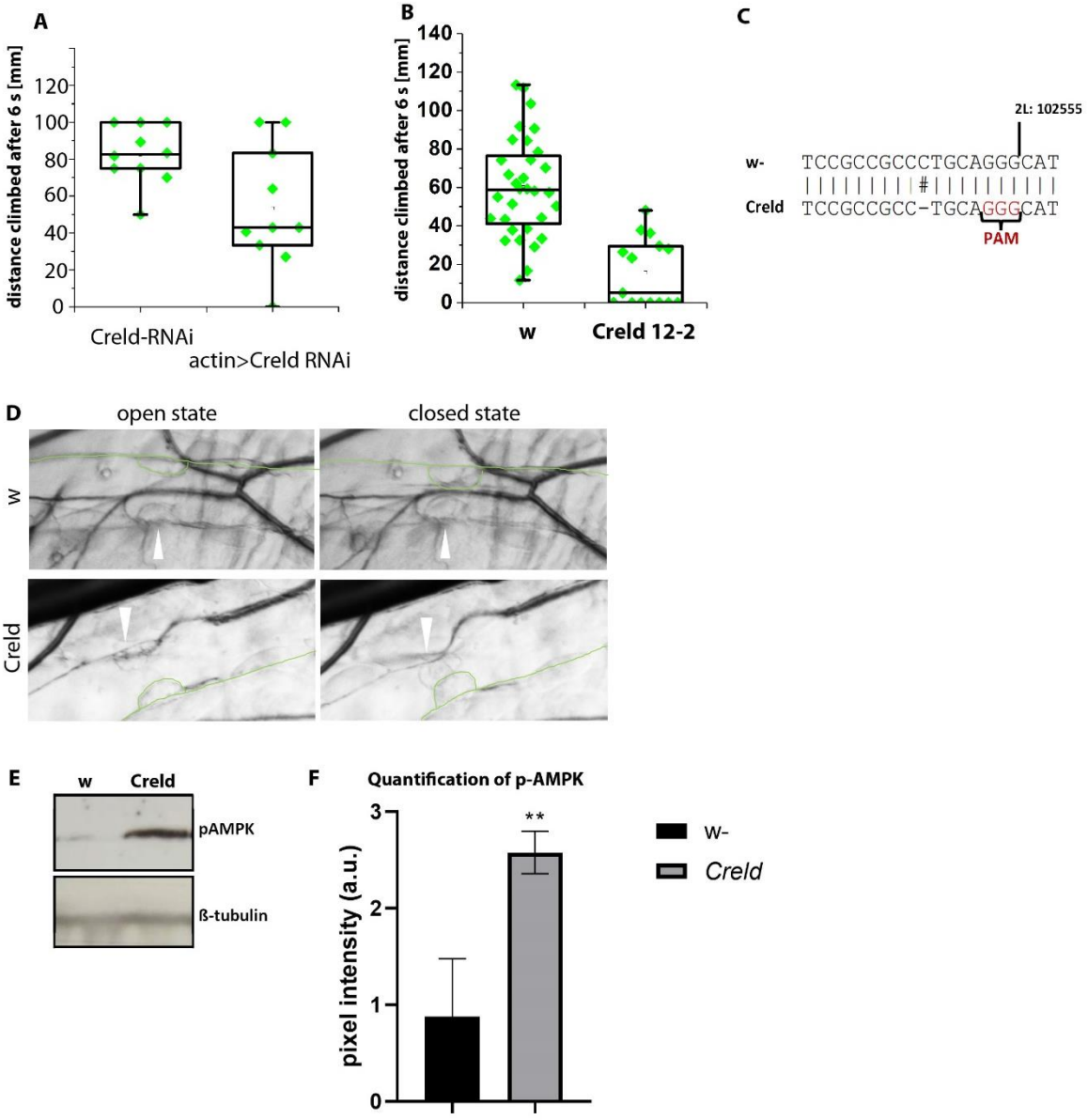

Figure S2: A) SING assay of flies expressing 2 copies of Creld RNAi under the control of the ubiquitous actin-Gal4 driver. Genotypes are Creld-RNAi (KK100565)/+; Creld-RNAi (TRiP.GLC0179)/+ and actin-Gal4/Creld-RNAi (KK100565); Creld-RNAi (TRiP.GLC0179)/+. B) SING assay of w1118 and Creld 12-2 mutants, the latter generated by Crispr/Cas9-mediated non-homologous end-joining. C) Representation of the Creld Crispr/Cas9 point mutation. D) Heart-valve ostial cells in the open and closed state of w1118 and Creld mutant 3rd instar larvae. E) Western Blot of protein extracts from adult w^{1118} and Creld mutants. Detection of phosphorylated AMPK. F) Quantification of the band intensity, n = 5. Asterisks represent ** $p < 0.01$

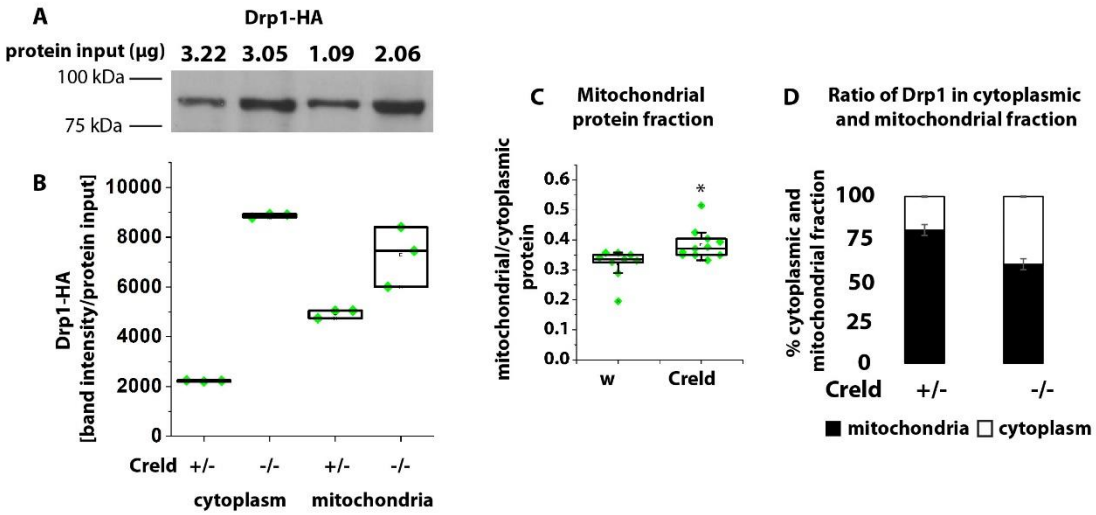

Figure S3: A) Western blot of the cytoplasmic and mitochondrial fraction of Creld+/-; tubulin Gal4/UAS Drp1-HA and Creld-/-; tubulin Gal4/UAS Drp1-HA, protein detected with anti-HA. B) Band intensity normalized to the protein input indicated in A). C) Ratio of the protein content of the mitochondrial versus cytoplasmic fraction of adult w1118 and Creld mutants. D) Ratio of the normalized band intensity in the cytoplasmic and mitochondrial fraction of Western blot of the cytoplasmic and mitochondrial fraction of Creld+/-; tubulin Gal4/UAS Drp1-HA and Creld-/-; tubulin Gal4/UAS Drp1-HA. Asterisks represent *$p < 0.05$.

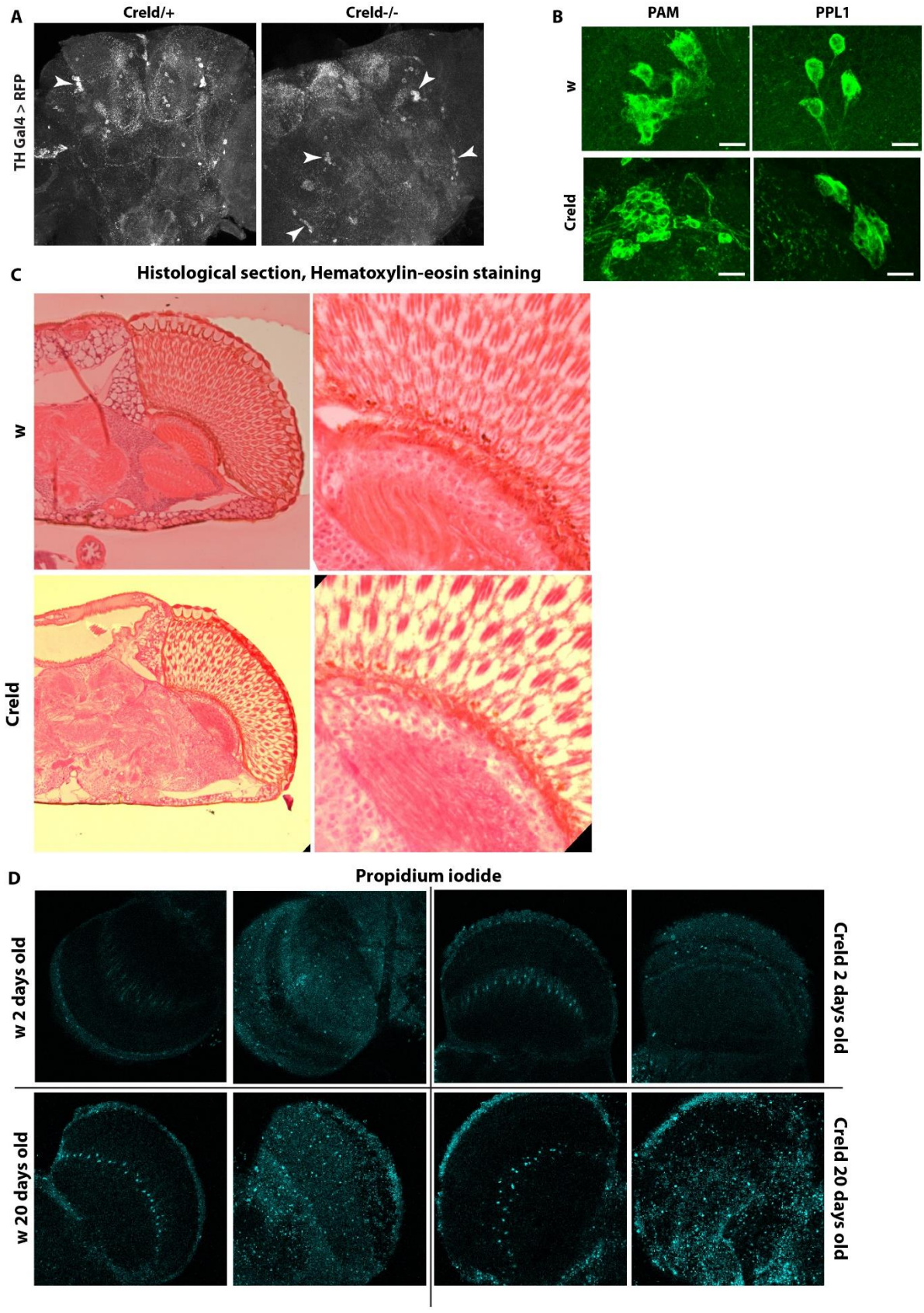

Figure S4: A) Immunofluorescent staining of adult brains with RFP under the control of TH-Gal4 to label dopaminergic neurons. B) Selected clusters of dopaminergic neurons stained with α-TH. C)

Histological sections of adult brains stained with hematoxylin-eosin (HE). D) Staining of apoptotic cells in optical lobes of young and old w and Creld adult flies with propidium iodide.

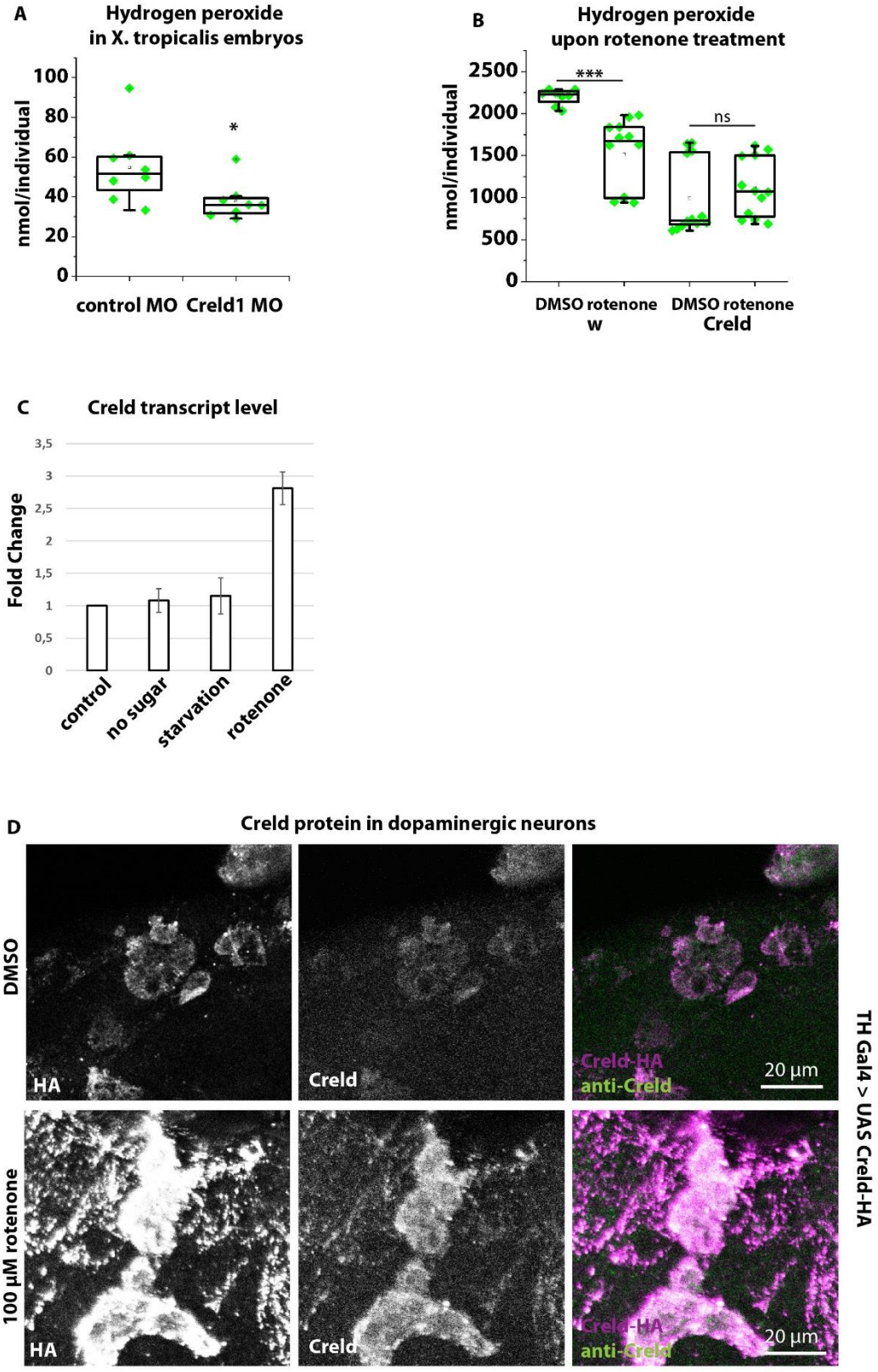

Figure S5: A) Hydrogen peroxide in extracts of *X. tropicalis* embryos. B) Hydrogen peroxide levels from extracts from adult flies fed on DMSO or 100 µM rotenone. C) Quantitative real-time PCR of Creld in wildtype adult flies. Fold Change normalized to control feeding condition. Error bars

represent standard deviation. D) Immunofluorescent staining of PPL1 cluster of dopaminergic neurons in the adult brain of female flies. Creld is tagged with HA, and endogenous Creld is detected with anti-Creld. Genotype: +/+; TH Gal4/UAS-Creld-HA. Flies were fed for 24 h on 10 % sugar with 100 µM rotenone or vehicle (DMSO).