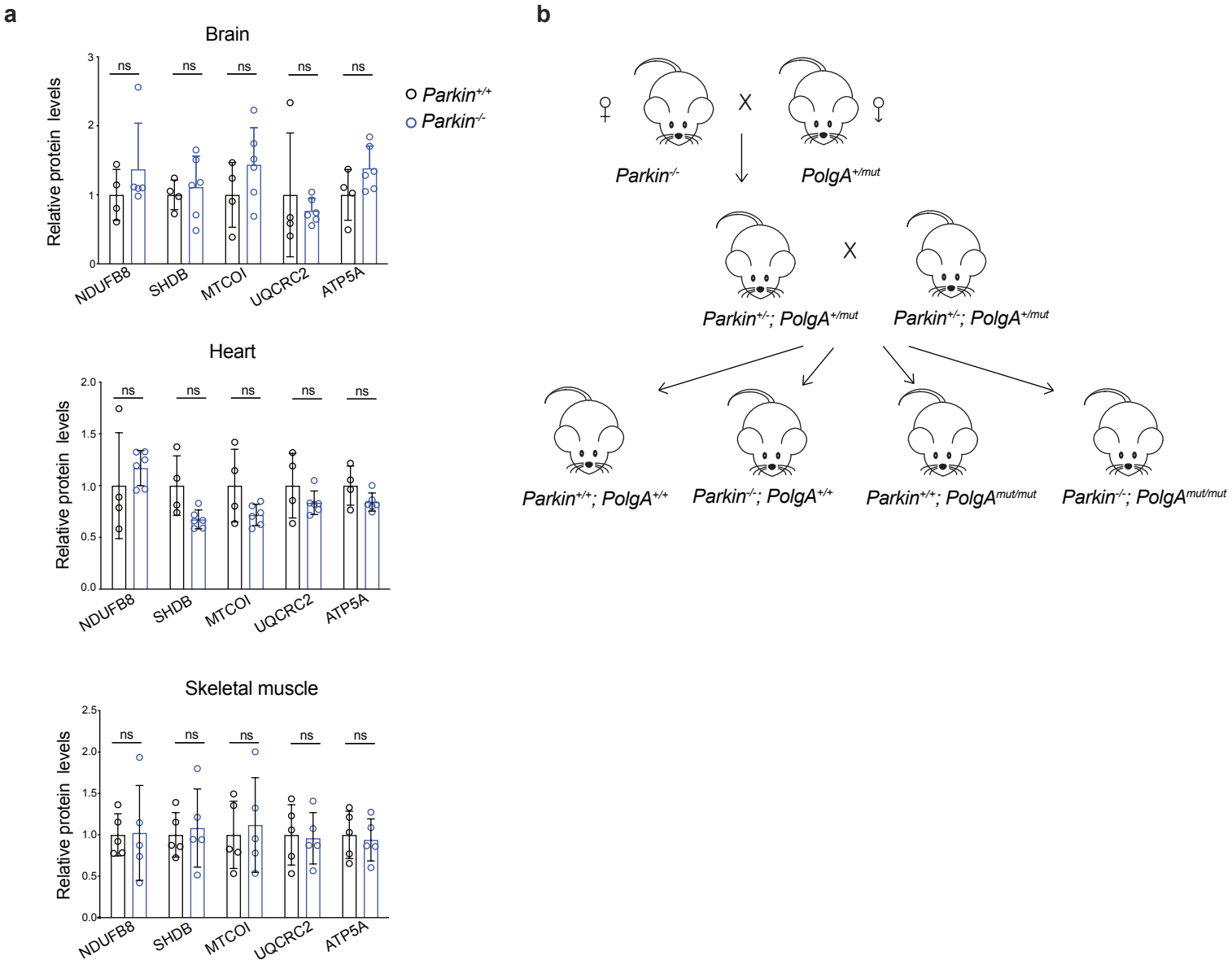
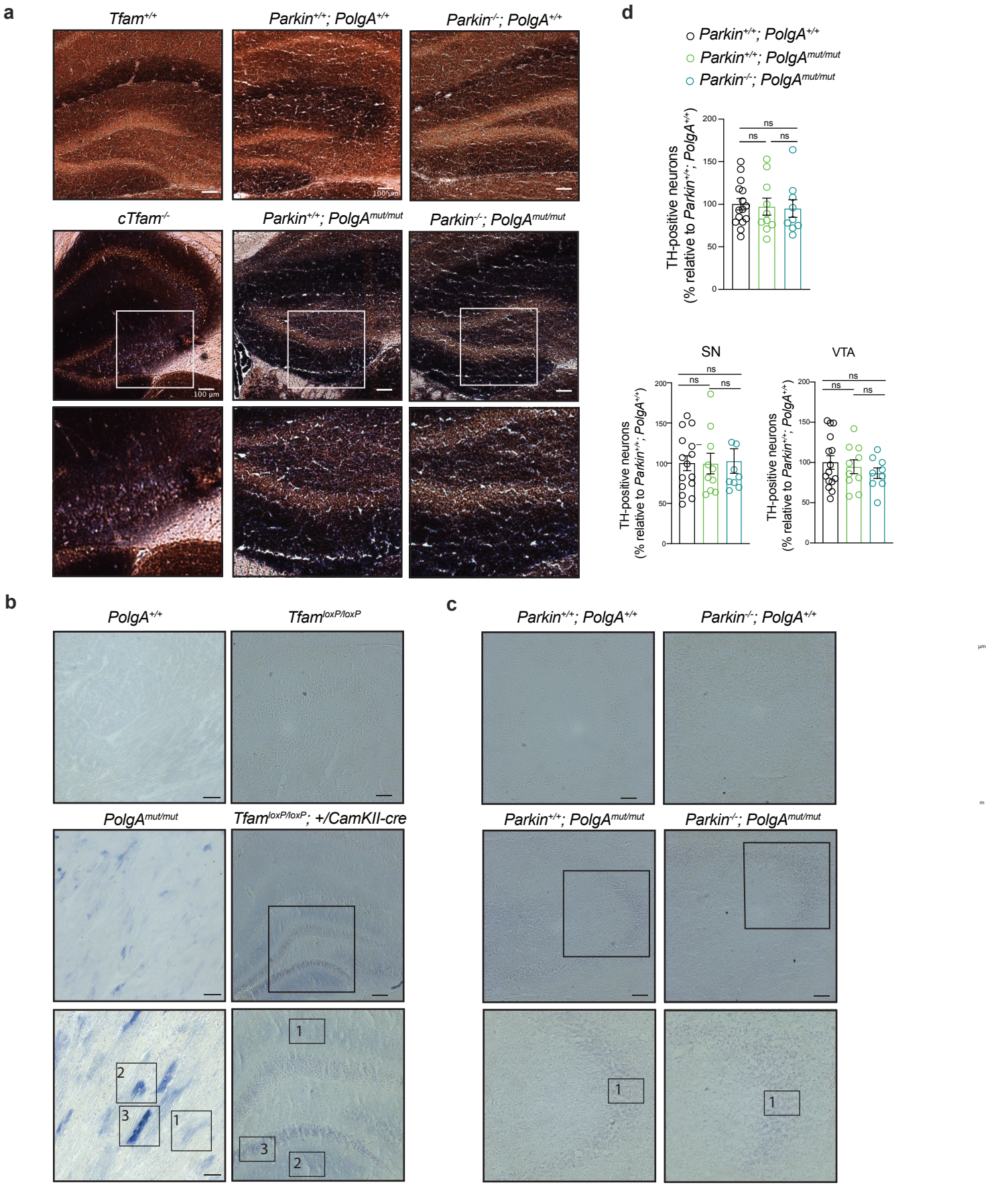
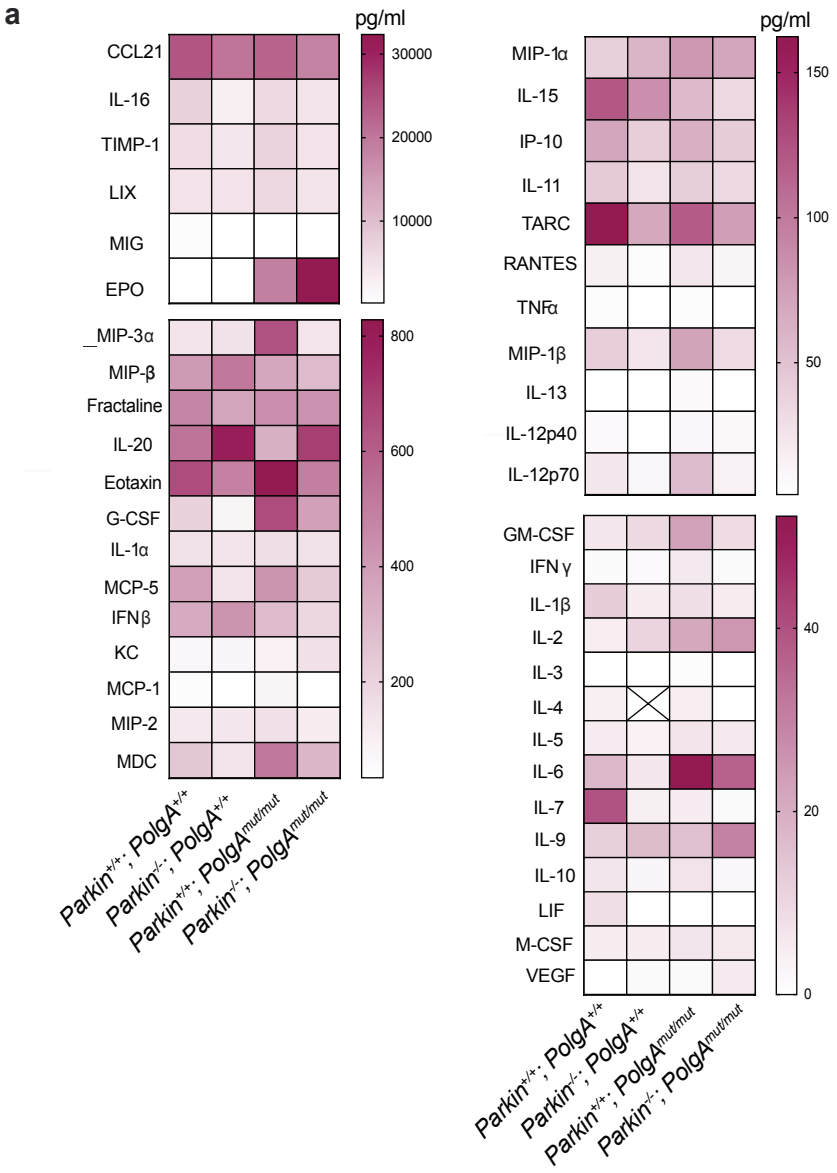


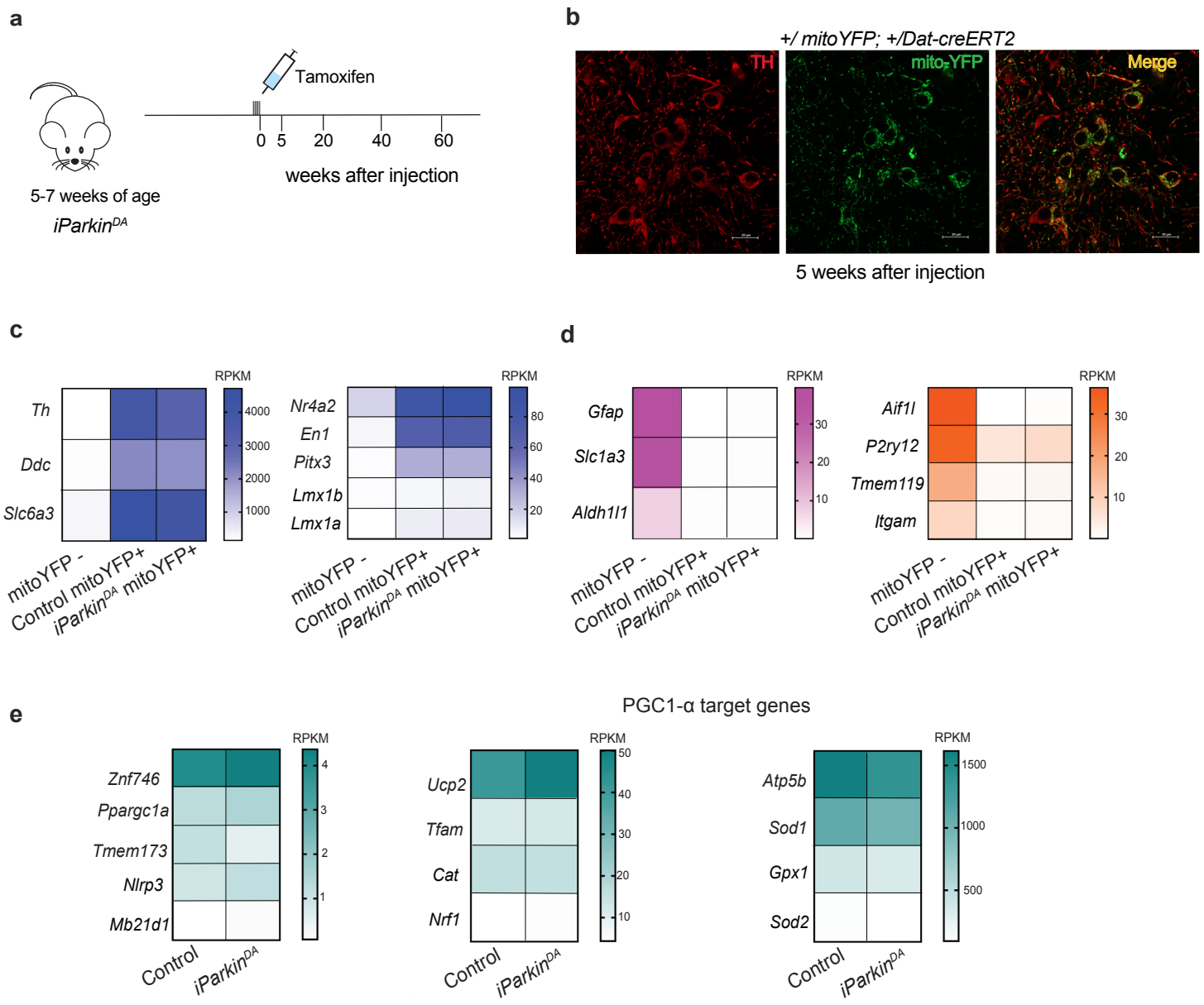
Supplementary Fig. 1. Ablation of *Parkin* in mouse models. a. Densitometric quantification of the steady-state levels of OXPHOS subunits in brain, heart, and skeletal muscle as determined by Western blots. Data are represented as mean ± s.e.m.; n≥4; ns= not significant. **b.** Breeding strategy used to generate the transgenic mouse line homozygous for both the whole-body *Parkin* knockout allele and the mtDNA mutator allele.



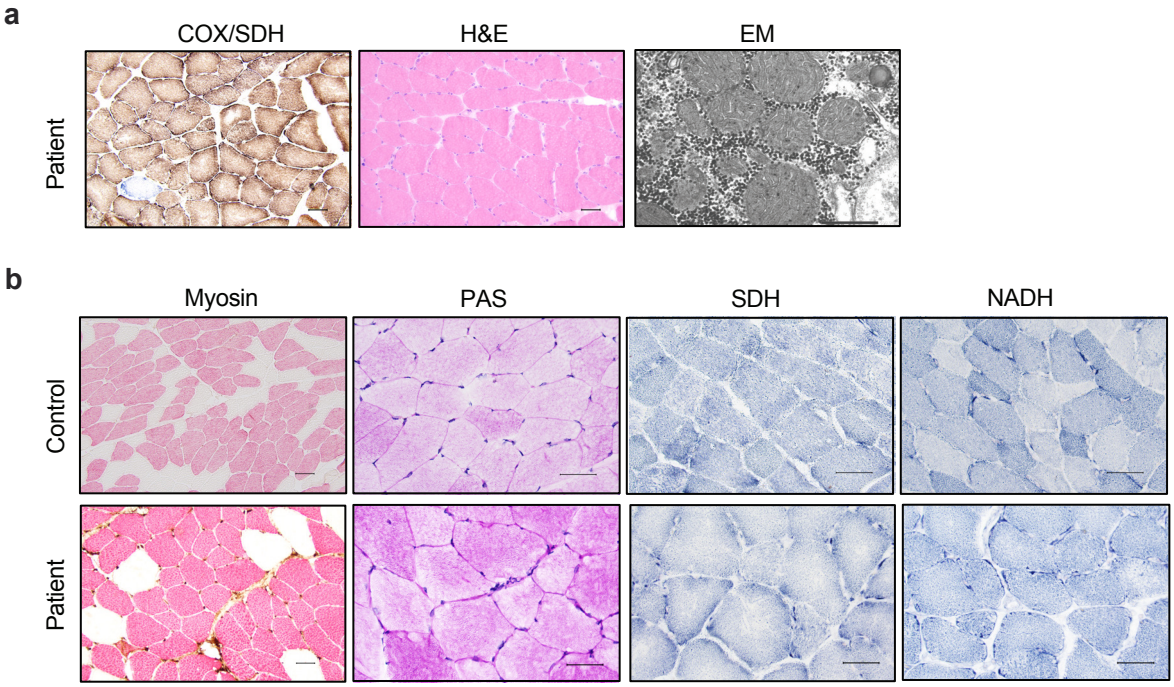
Supplementary Fig.2. COX activity of *Parkin*$^{-/-}$; *PolgA* $^{mut/mut}$ mice. COX enzyme activity measured using **a.** COX/SDH in brain sections of MILON mice (conditional *Tfam* KO in forebrain neurons, *Tfam*$^{loxP/loxP}$*; +/CamKII-cre*) at 5 months of age and in hippocampal section of *Parkin* KO mice carrying WT mtDNA (*Parkin*$^{-/-}$*; PolgA*$^{+/+}$) or mutant mtDNA (*Parkin*$^{-/-}$*; PolgA*$^{mut/mut}$) . NBTx staining in **b.** the heart of mtDNA mutator mice (*PolgA*$^{mut/mut}$), which was used as positive controls with different levels of COX deficiency (1 to 3), and **c.** in the hippocampal section of *Parkin* KO mice carrying WT mtDNA (*Parkin*$^{-/-}$*; PolgA*$^{+/+}$) or mutant mtDNA (*Parkin*$^{-/-}$*; PolgA*$^{mut/mut}$). (Scale bars: 500 µm, 100 µm and 50 µm). **d.** Quantification of TH-positive DA neurons in ventral midbrain (SN and VTA) performed in midbrain sections using Cell Counter plugin. Data are represented as mean ± s.e.m.; n≥5 slices from 2-3 mice per genotype; ns= not significant.



Supplementary Fig.3. Levels of pro-inflammatory mediators in *Parkin* $^{-/-}$*; PolgA* $^{mut/mut}$ mice. a. Heatmaps showing the levels (pg/ml) of 45 inflammatory cytokines and chemokines in plasma samples collected from 36-week-old mice; n ≥5 per genotype.

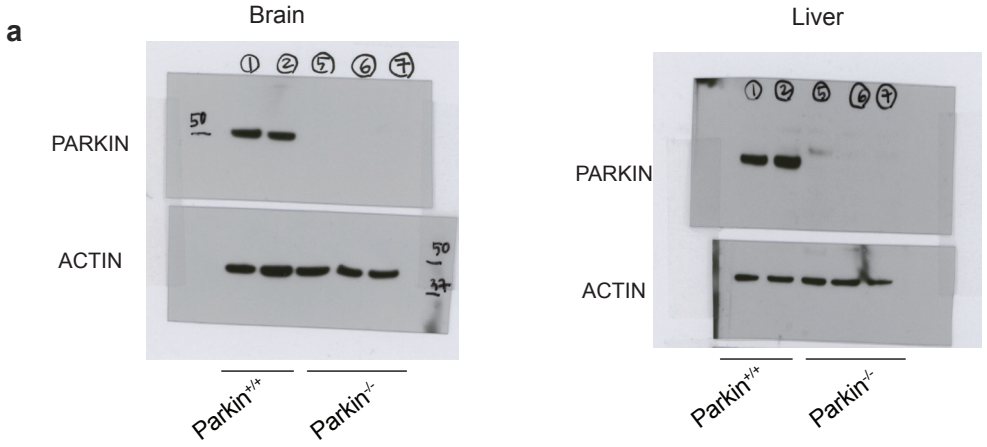


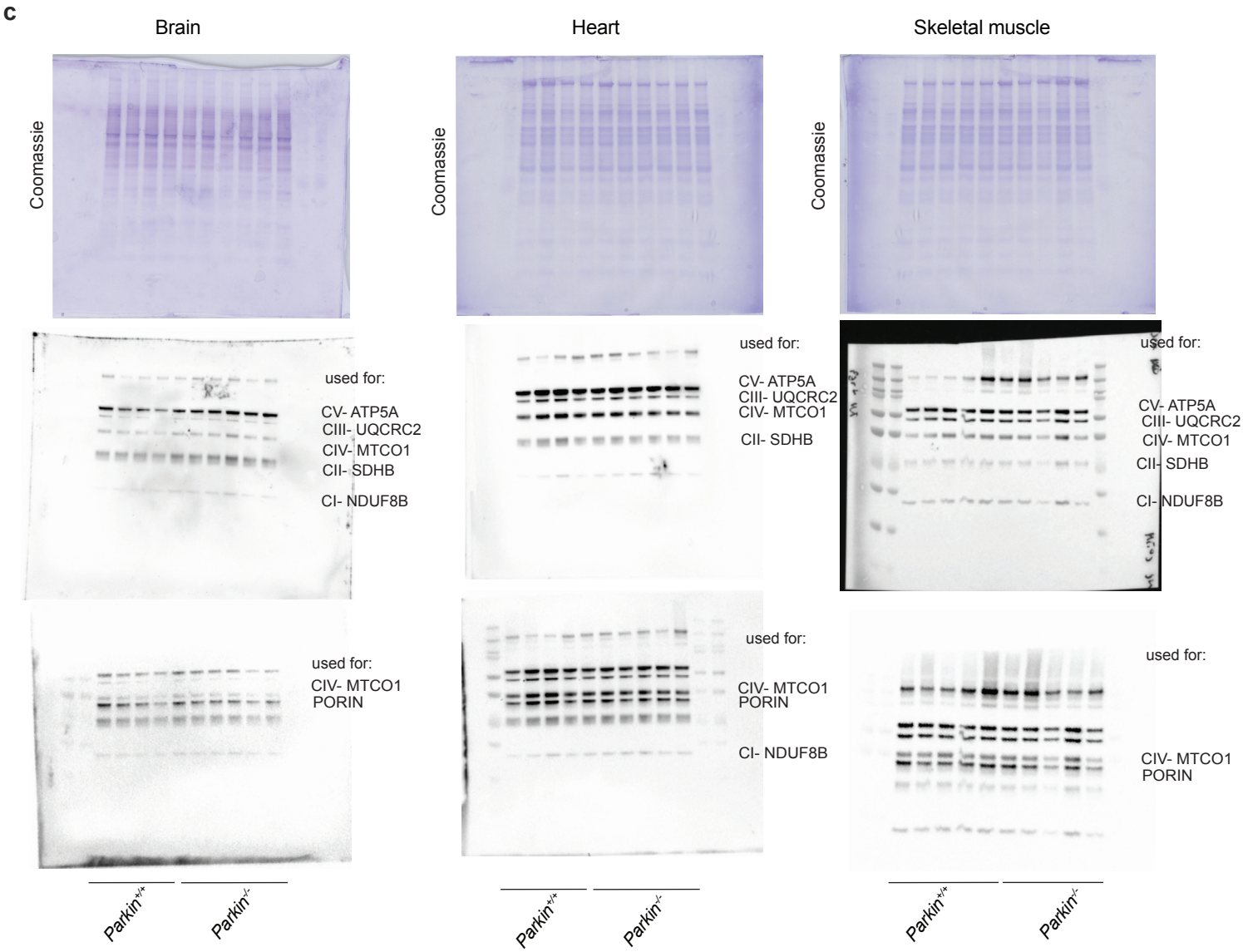
Supplementary Fig.4. Induction of PARKIN loss in adult DA neurons and transcriptomics analysis at 5 weeks after tamoxifen injection. a. Diagram depicting tamoxifen-induced inactivation of *Parkin* gene in adult mice. Mice at 5–7 weeks of age were intraperitoneally injected with tamoxifen for 5 consecutive days and examined up to 60 weeks after injection. **b.** Representative confocal microscopy images of mitoYFP-labelled mitochondria (green) in TH immunoreactive neurons (red) at 5 weeks after tamoxifen injection (Scale bar: 20 µm). **c-d.** Heatmaps showing the expression levels of genes encoding **c.** DA neuronal markers, **d.** astrocyte and microglial markers in mitoYFP+ and mitoYFP- samples (Reads Per Kilobase Million, RPKM) at 5 weeks after injection. **e.** Heatmap showing the expression of genes involved in mitochondrial biogenesis and inflammation in mitoYFP+ cells isolated from *iParkinDA* and control mice at 5 weeks after injection. n>5 per genotype.



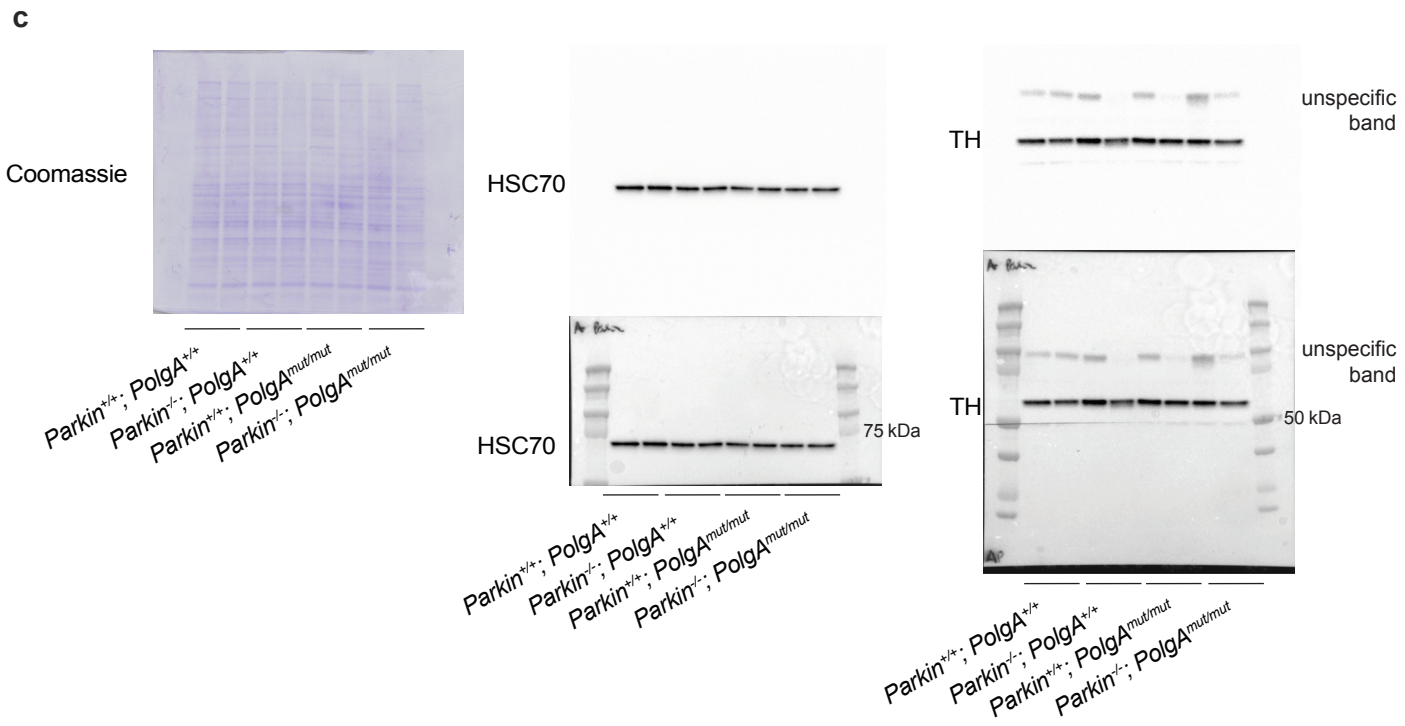
Supplementary Fig.5. Histochemistry and histology of skeletal muscle from the PARKIN-deficient patient. a. A skeletal muscle biopsy specimen from the *PRKN* patient stained with H&E for tissue morphology, COX/SDH for COX activity. High magnification transmission electron microscopy analysis was performed to define mitochondrial ultrastructure in skeletal muscle (Scale bar: 500 nm). **b.** Skeletal muscle biopsy specimens from the PRKN patient and an age- and gender-matched healthy donor were stained for myosin to discriminate between type 1 fibers (red) and type 2 fibers (white), Periodic acid schiff (PAS) staining to detect glycogen. Staining for succinate dehydrogenase (SDH) and nicotinamide adenine dinucleotide (NADH) to reveal myofibrillar architecture. (Scale bar: 50 µm).

Uncropped WB Fig. 1





Uncropped WB Fig. 3



Uncropped WB Fig. 6