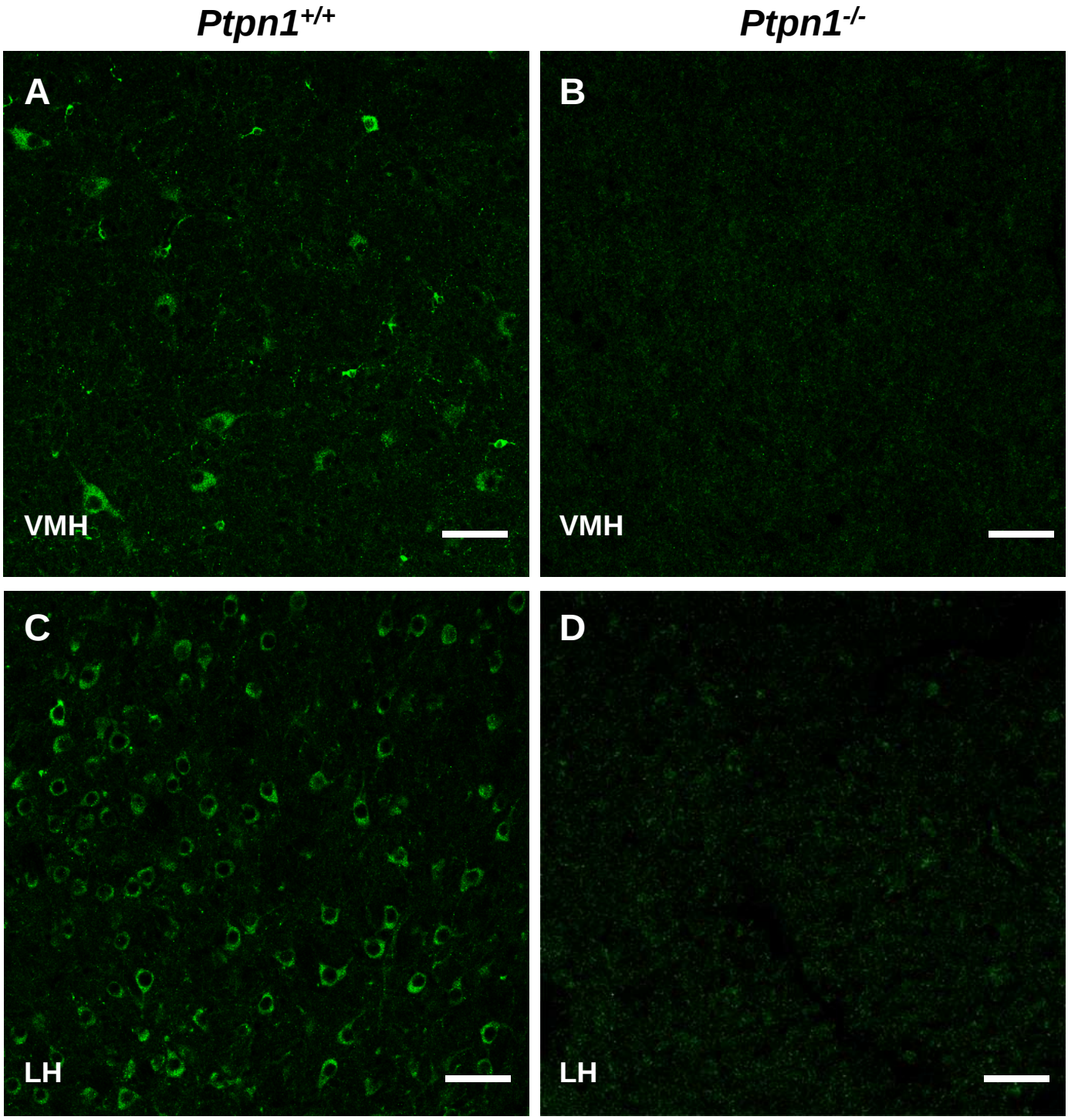
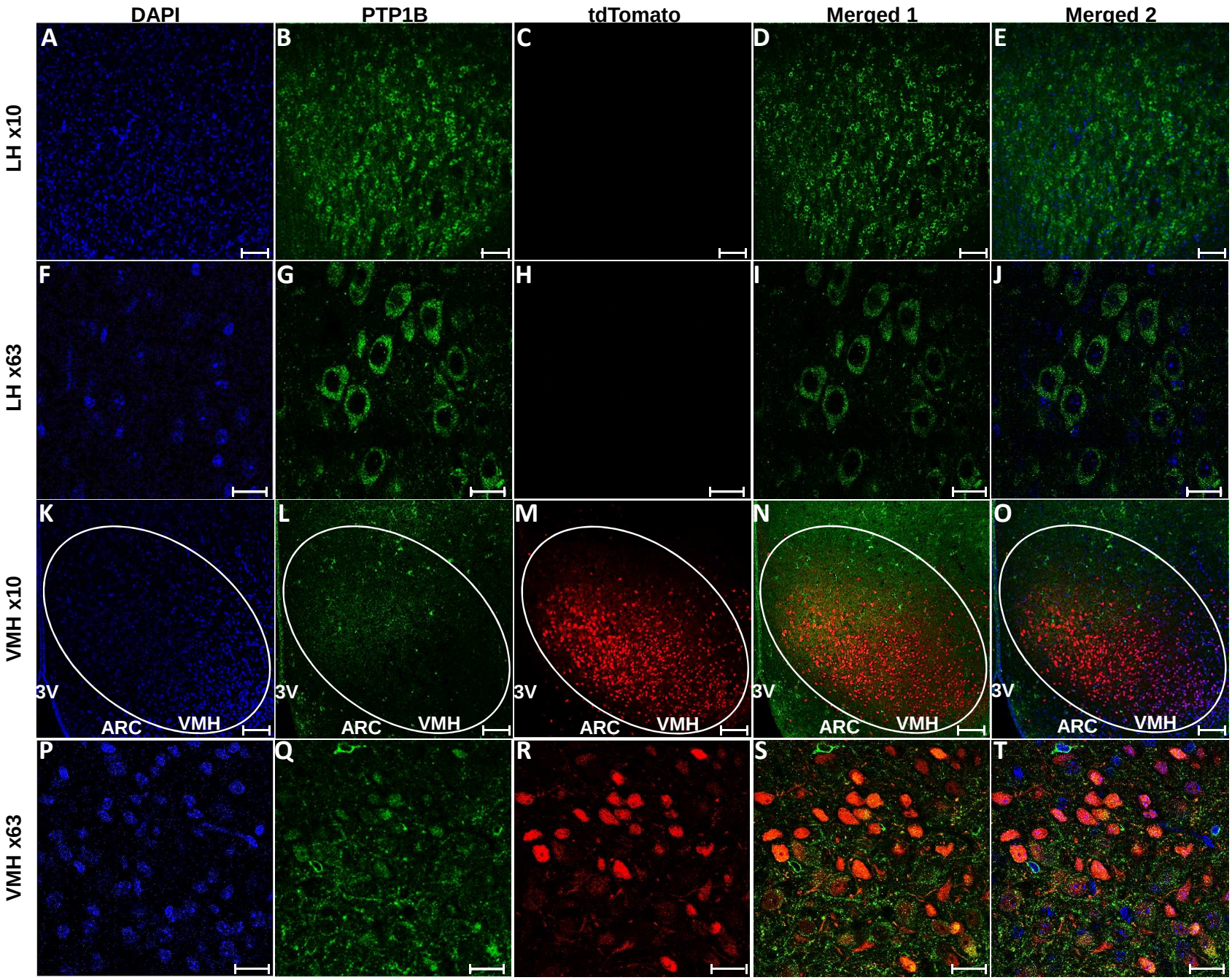
	Age (weeks)	**Controls** (n=9-21)	***Sf1-Ptpn1*$^{-/-}$** (n=4-9)	**p-value**
Blood glucose (mg/dl) in fed state	18	141 ± 5	143 ± 5	0.85
Blood glucose (mg/dl) 5 hrs after food removal	14	137 ± 3	141 ± 5	0.11
	16	***142 ± 6***	***170 ± 7***	***0.042***
	27	***130 ± 8***	***172 ± 2***	***0.026***
	28	143 ± 1	162 ± 2	0.29
Plasma insulin (ng/ml) 5 hrs after food removal	***28***	***0.30 ± 0.07***	***0.99 ± 0.34***	***0.015***

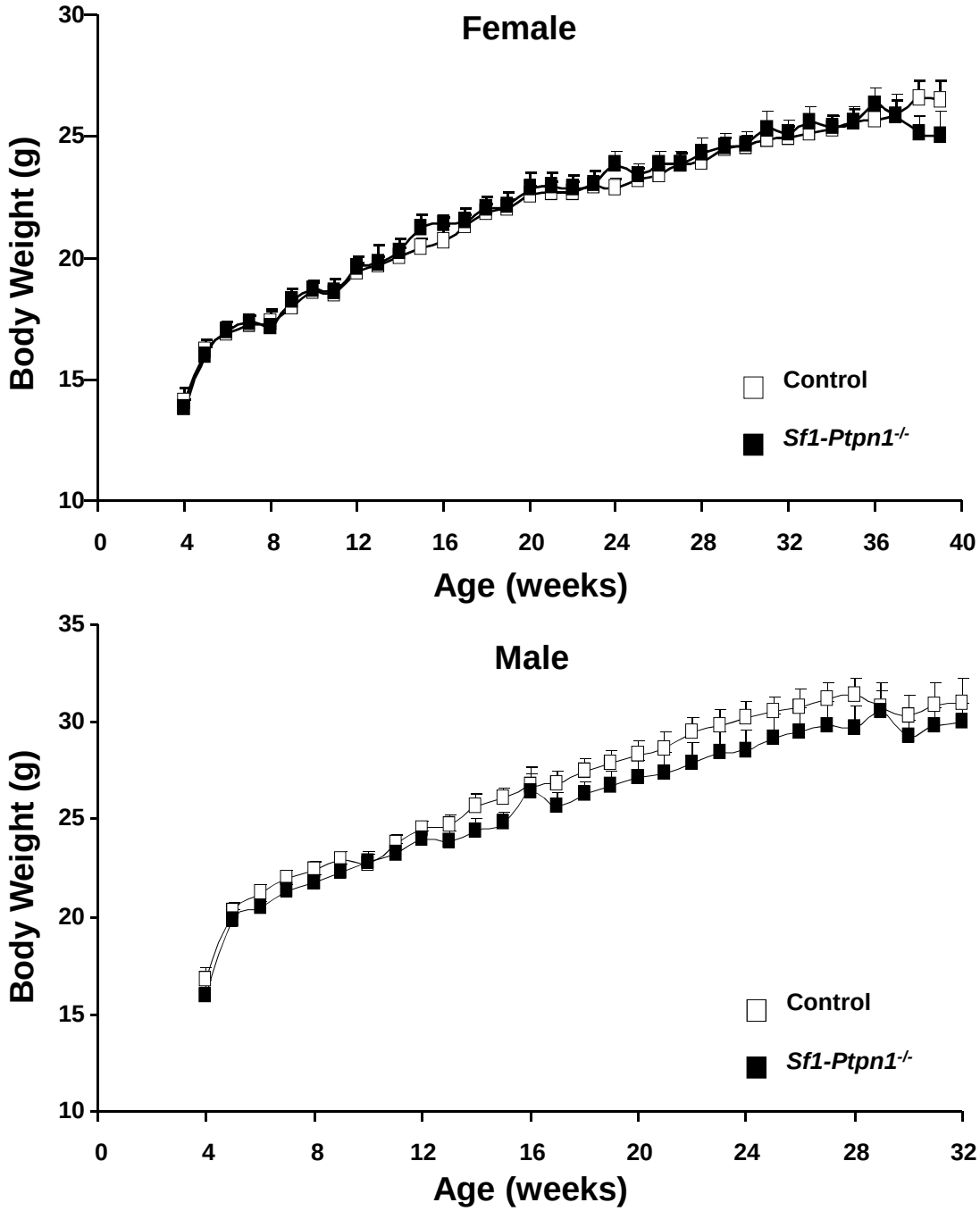
Supplemental Table 1. Blood glucose and plasma insulin levels in female mice on HFD in the fed state at 10 am and 5 hours after food removal. Data are means ± SEM. The values in bold and italics are statistically different between genotypes.



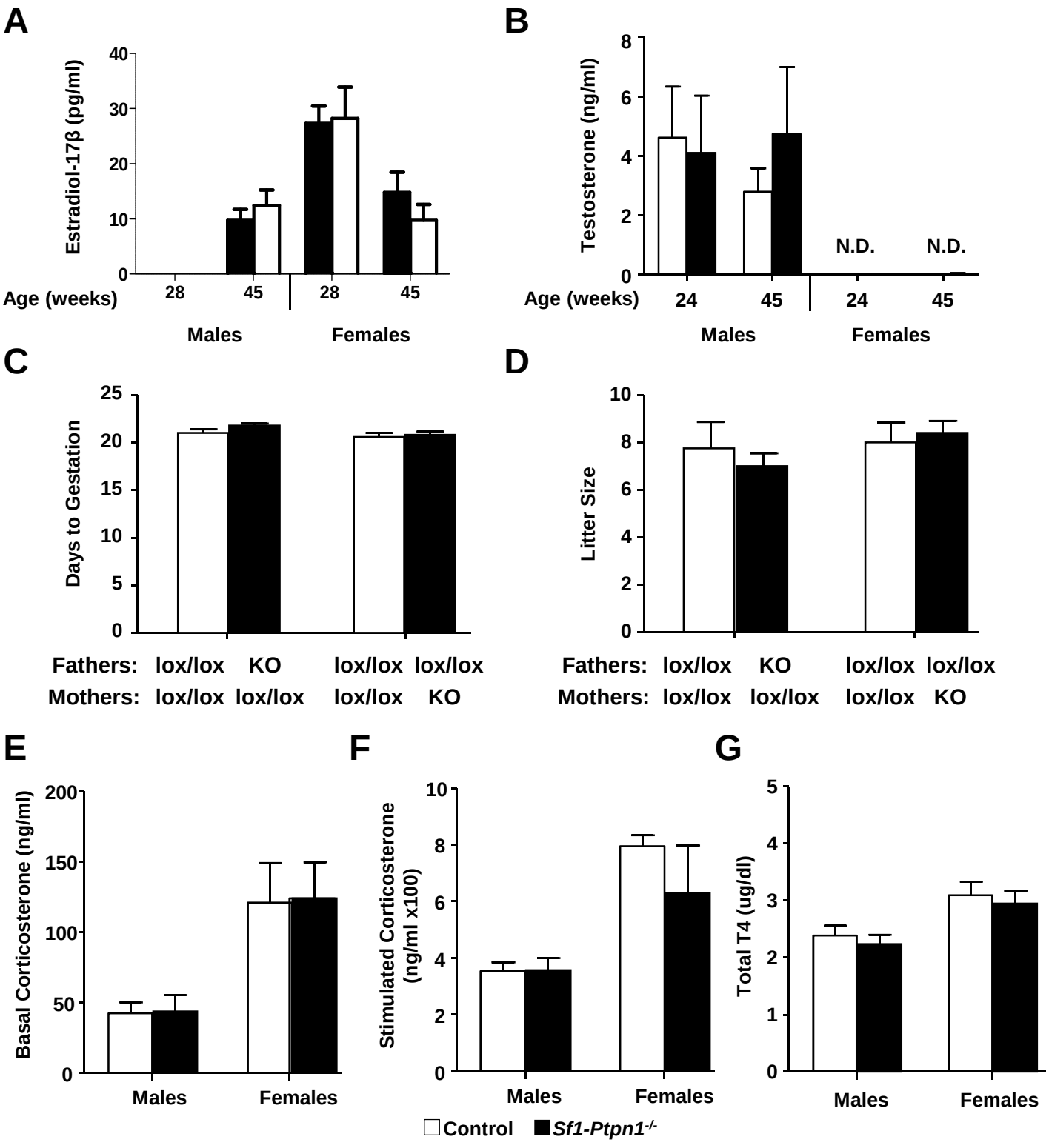
Supplemental Figure 1. PTP1B expression in wild-type mice. Immunostaining of coronal sections of hypothalami from *Ptpn1*$^{+/+}$ **(A, C)** and *Ptpn1*$^{-/-}$**(B, D)** mice shows PTP1B levels in VMH **(A, B)** and LH **(C, D)** neurons and demonstrates specificity of anti-PTP1B antibodies. Scale bars: 50µm. Original magnification: x20



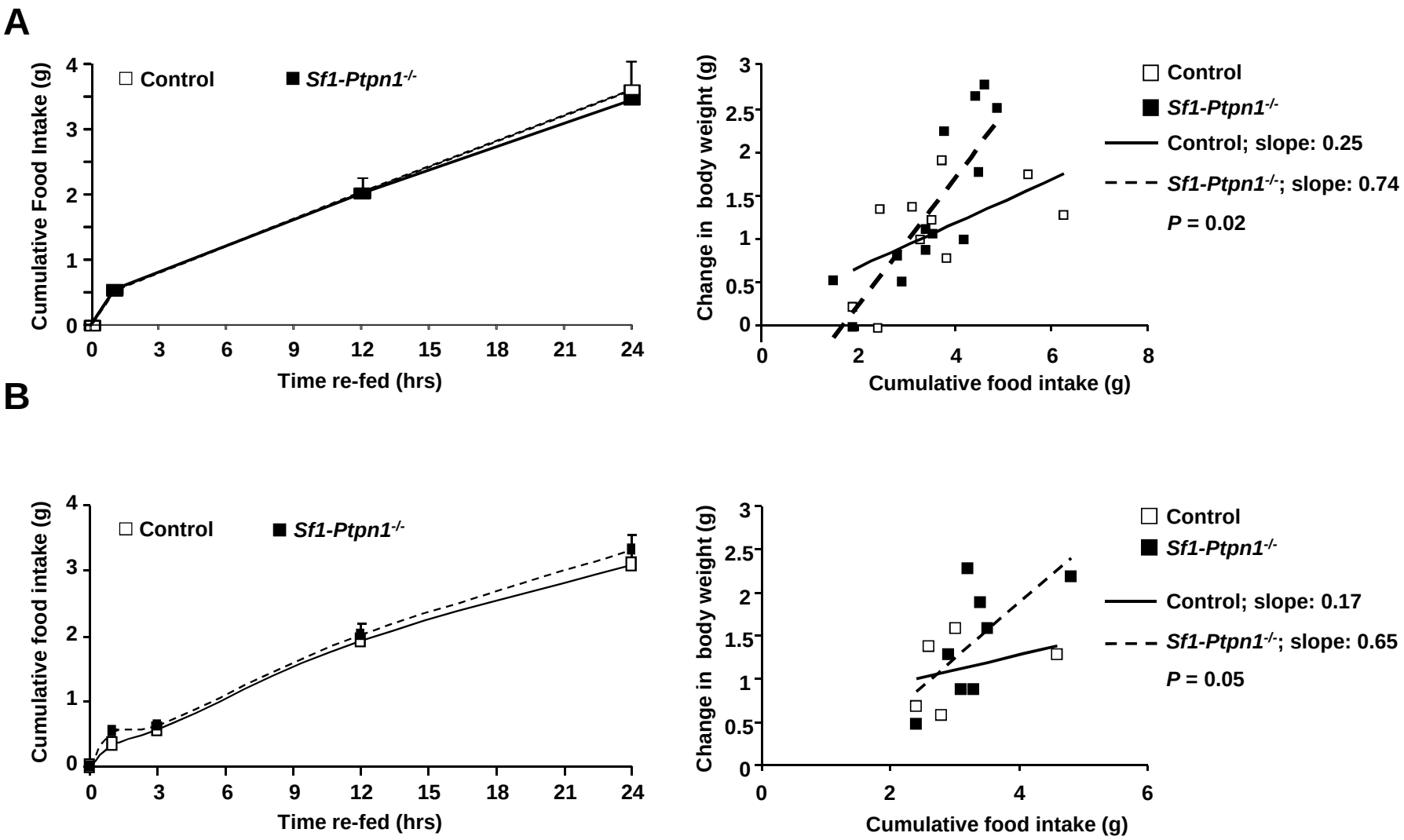
Supplemental Figure 2. PTP1B is expressed in VMH and LH neurons of *Sf1-Cre:Ptpn1$^{lox/+}$:Isl-tdTomato* mice. Coronal sections of hypothalami from *Sf1-Cre:Ptpn1$^{lox/+}$:Isl-tdTomato* mice showing immunostaining for PTP1B (green) and tdTomato (red) . Panels A-J and K-T demonstrate that PTP1B is expressed in LH and VMH neurons, respectively. Note the absence of tdTomato fluorescence in LH sections indicating the absence of *Sf1-Cre* expression in LH, which lacks Sf1 neurons. All immunofluorescence was performed on the same brains. These images are representative of data on 3 brains. **A**, **F**, **K** and **P** show DAPI staining of cell nuclei. Merged 1 corresponds to the overlay of the anti-PTP1B (green) and tdTomato (red) images. Merged 2 corresponds to the overlay of the DAPI, anti-PTP1B (green) and tdTomato (red) images. Scale bars: 100µm **(A-E, K-O)**; 20µm **(F-J, P-T)**. Original magnification: x10 **(A-E, K-O);** x63 **(F-J, P-T)**.



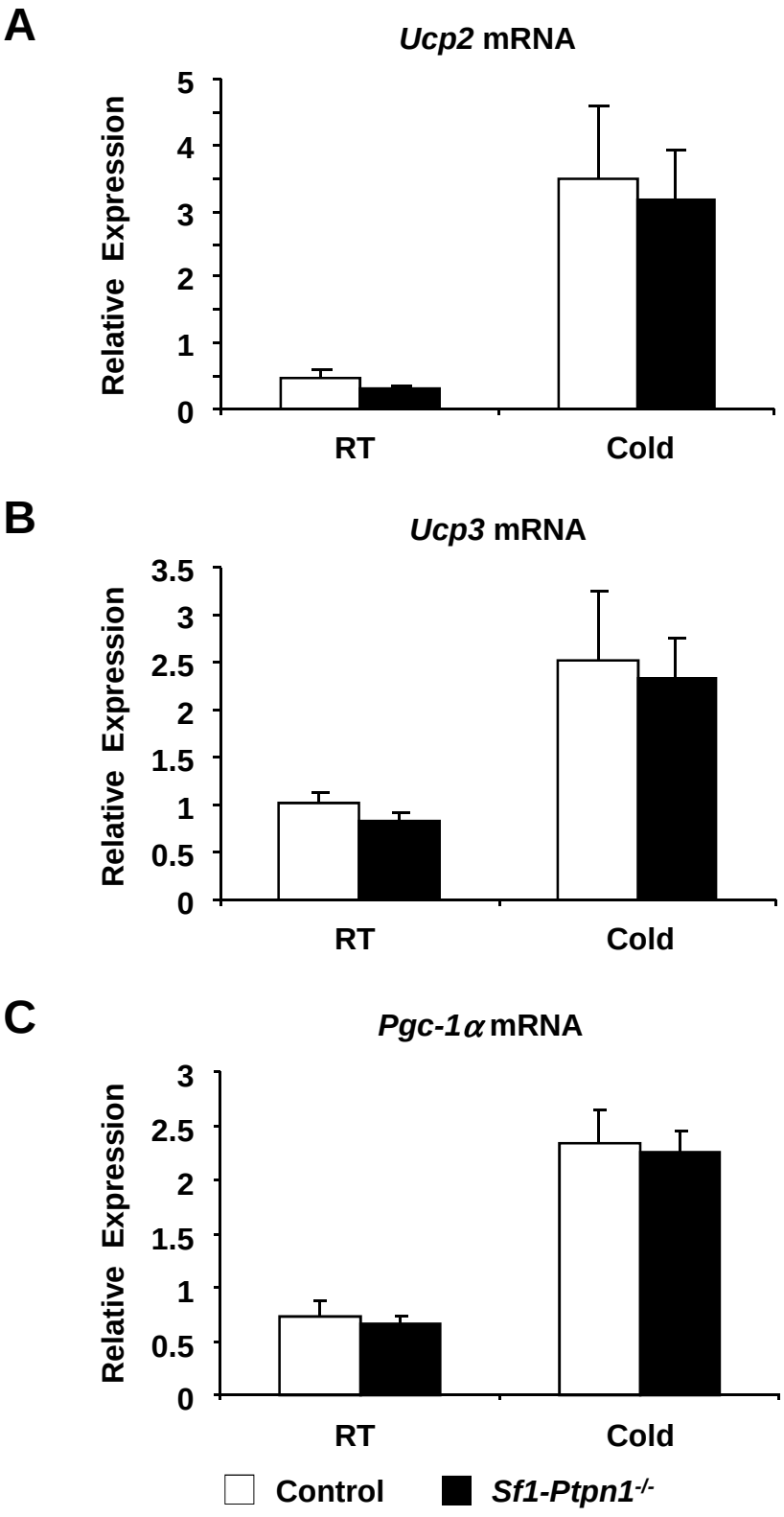
Supplemental Figure 3. *Sf1-Ptpn1*$^{-/-}$ mice have normal body weight on chow diet. Data shown are means ± SEM. n=11-22 per group.



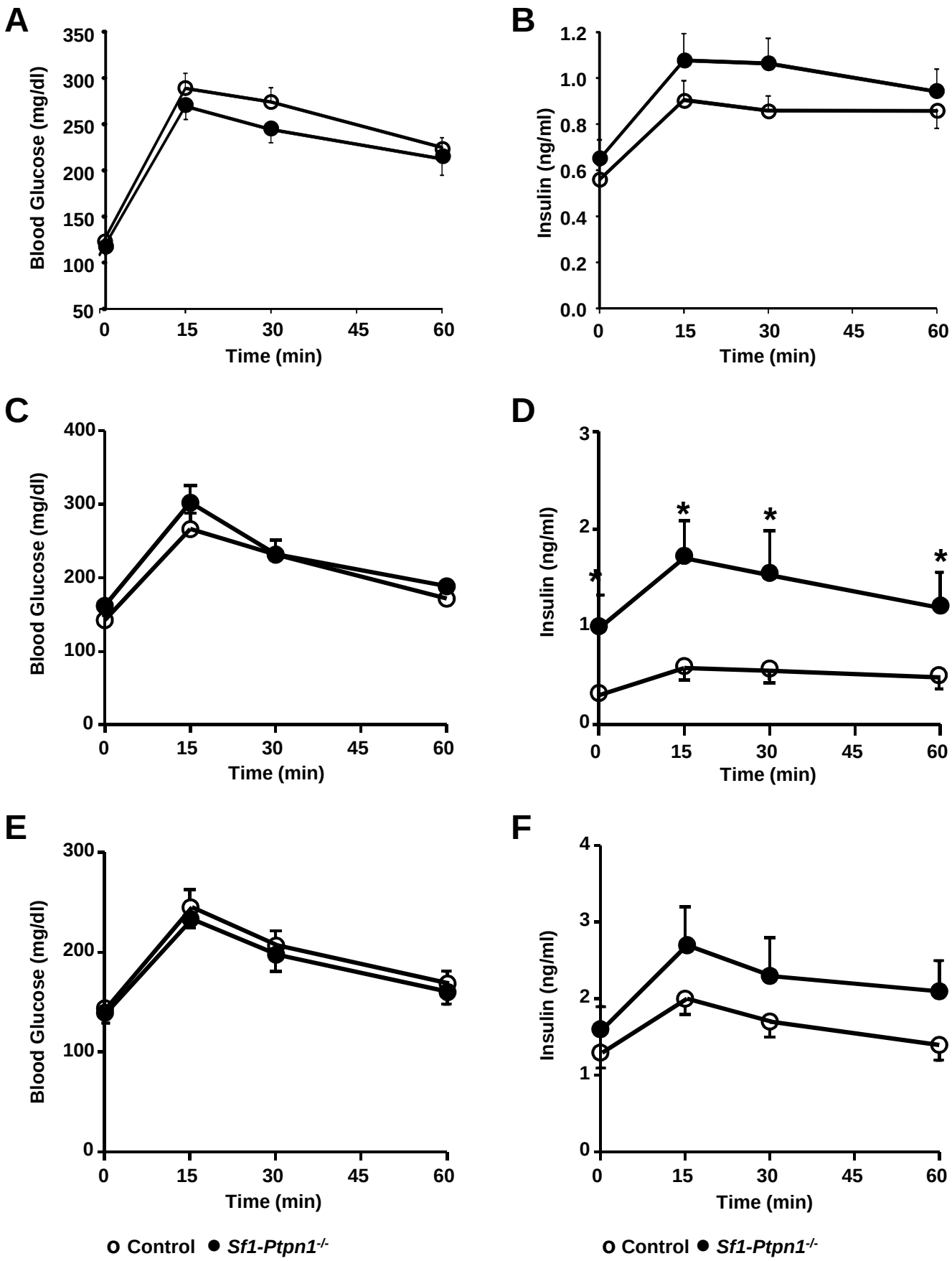
Supplemental Figure 4. Reproductive function and hormone levels are normal in *Sf1-Ptpn1*$^{-/-}$ mice on HFD. (A) Serum estradiol-17β levels at 28 and 45 weeks (n=6-16 per group). **(B)** Serum testosterone levels at 24 weeks (n=4-11) and 45 weeks (n=6-17); ND=not detected. **(C)** Days to gestation and **(D)** litter size for the indicated breeding pairs (n=5 per genotype combination). **(E)** Basal serum corticosterone, **(F)** serum corticosterone after 15 min of restraint, and **(G)** serum T4 levels (n=4-8). Data shown are means ± SEM.



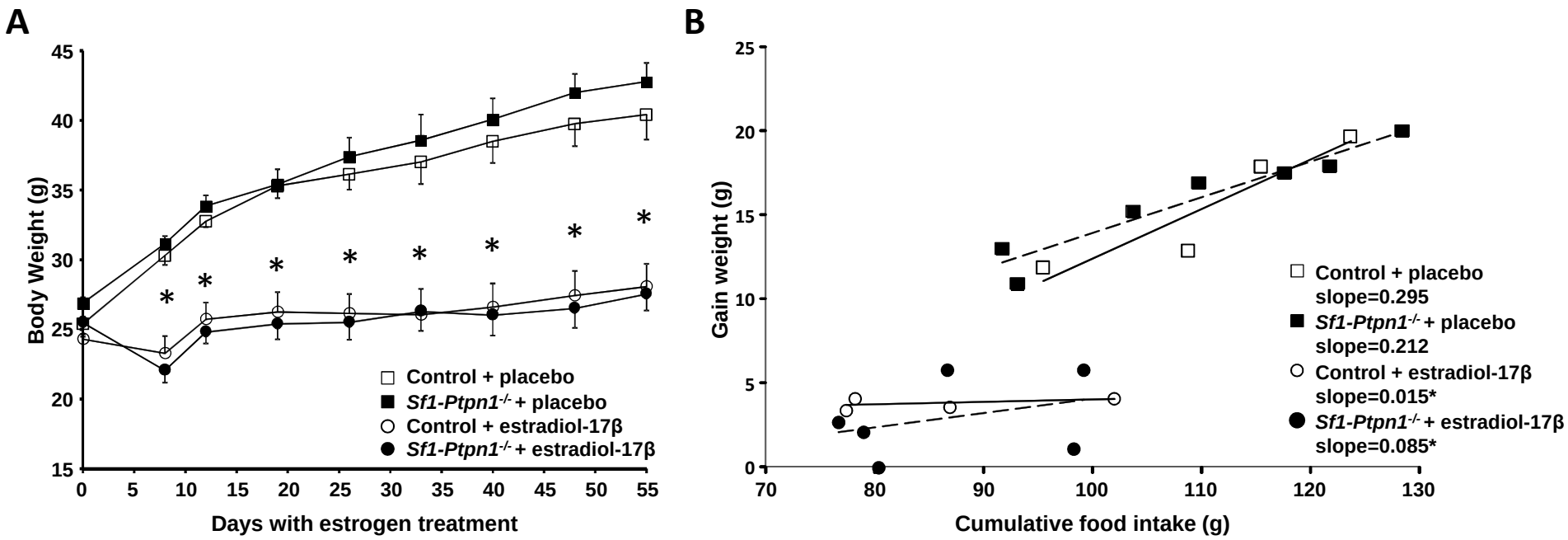
Supplemental Figure 5. ***Sf1-Ptpn1*$^{-/-}$ mice have increased feed efficiency. (A)** Cumulative food intake after 24h fast, followed by re-feeding of HFD for the indicated times (left panel); and feed efficiency during 24h of re-feeding (right panel) HFD to 18-20 week-old female mice (before body weight divergence); n=10-13. **(B)** The same experiment as in **(A)** was repeated in 36 week-old female mice; n=5-8. Slopes are compared by ANCOVA. Data represent means ± SEM.



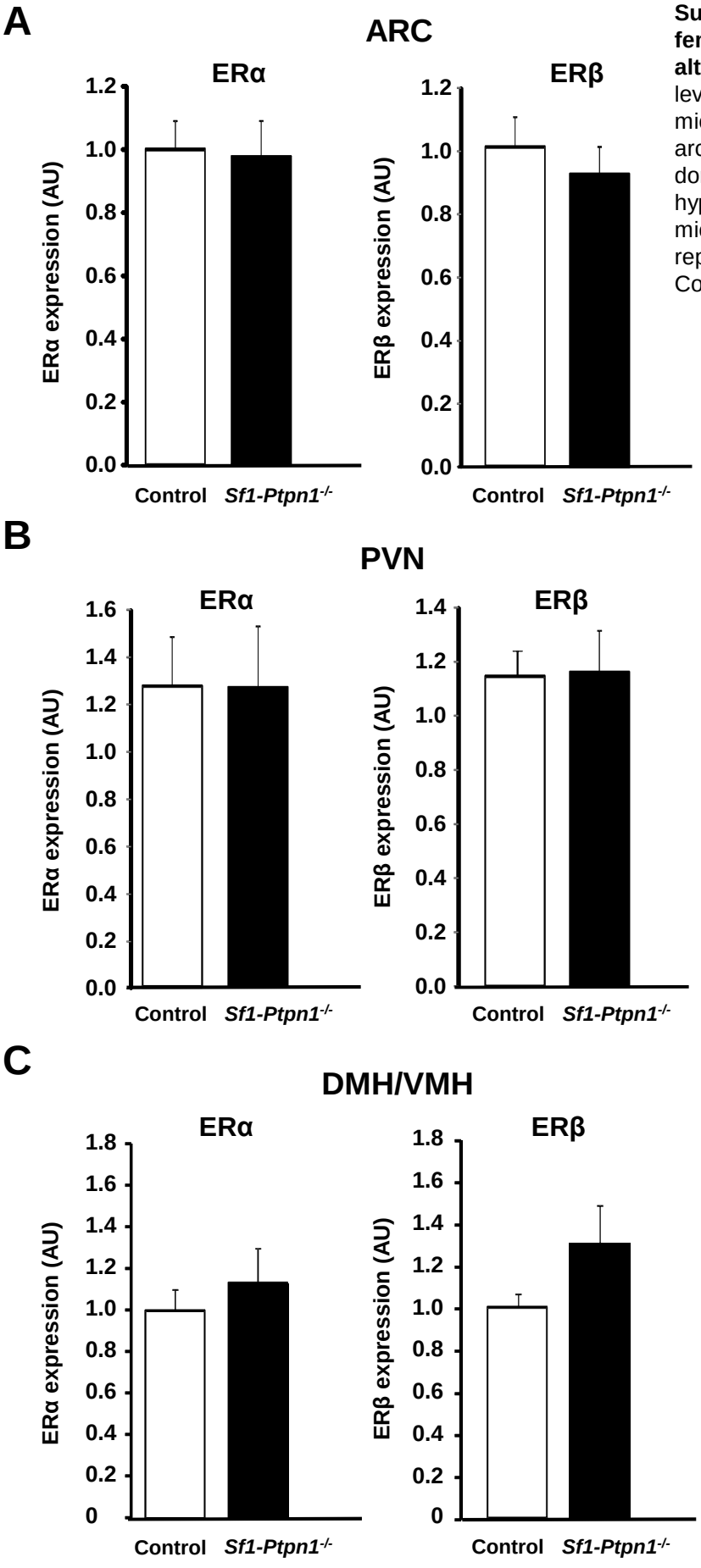
Supplemental Figure 6. *Sf1-Ptpn1*$^{-/-}$ mice show normal expression of genes involved in thermogenesis. (A) *Ucp2*, **(B)** *Ucp3*, and **(C)** *Pgc-1α* mRNA levels in BAT from Control and *Sf1-Ptpn1*$^{-/-}$ mice at room temperature (RT) and after 3 days of cold exposure (4°C). All mice are females on HFD at 33-35 weeks of age. Data represent means ± SEM. n=5/8 per genotype.



Supplemental Figure 7. Glucose and insulin levels during glucose tolerance tests in *Sf1-Ptpn1*$^{-/-}$ mice. Blood glucose response and insulin release during glucose tolerance tests (1mg/kg IP) performed at 18 weeks (**A, B**; n=16 per group), 28 weeks (**C, D**; n=4-10), and 45 weeks of age (**E, F**; n=9-18). All mice were females on HFD. Data are means ± SEM. **P* < 0.05 by unpaired *t* test.



Supplemental Figure 8. Estradiol-17β treatment causes weight loss and decreased feed efficiency in Control and *Sf1-Ptpn1*$^{-/-}$ male mice on HFD. (A) Body weights on HFD of Control (open squares, n=5) and *Sf1-Ptpn1*$^{-/-}$ (black squares, n=7) male mice, treated with placebo, and Control (open circle, n=4) and *Sf1-Ptpn1*$^{-/-}$ (black circle, n=7) mice, treated with subcutaneous estrogen pellet (2µg/day/mouse). Data represent means ± SEM. **P* <0.05 for placebo versus estrogen groups for each genotype, using ANOVA with unpaired *t*-test for individual comparisons. **(B)** Feed efficiency in HFD-fed Control and *Sf1-Ptpn1*$^{-/-}$ male mice administered placebo or subcutaneous estrogen pellet. **P* <0.05 versus the respective placebo group for each genotype; slopes compared by ANCOVA.



Supplemental Figure 9. Increased adiposity in female *Sf1-Ptpn1*$^{-/-}$ cannot be explained by altered hypothalamic ER levels. ERα and ERβ levels in hypothalamic nuclei of female *Sf1-Ptpn1*$^{-/-}$ mice on HFD. ERα and ERβ mRNA levels in **(A)** arcuate (ARC), **(B)** paraventricular (PVN) and **(C)** dorso- and ventromedial (DMH/VMH) nuclei of the hypothalamus of Control and *Sf1-Ptpn1*$^{-/-}$ female mice on HFD were quantified by RT-qPCR. Data represent means of gene expression/18S ± SEM. Controls, n=6; *Sf1-Ptpn1*$^{-/-}$, n=8.