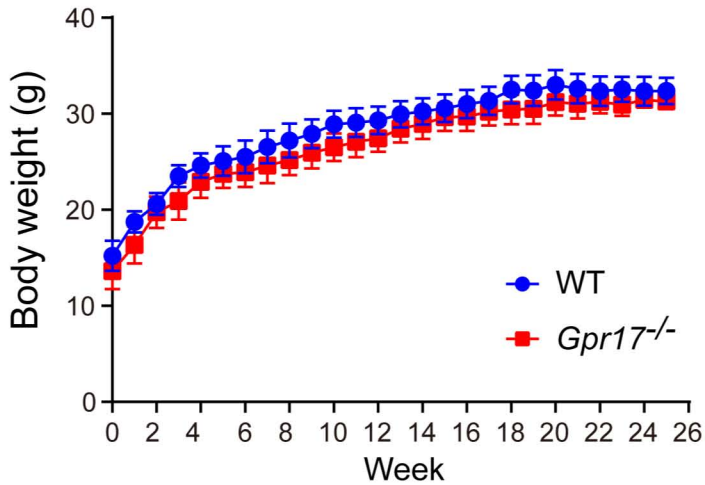
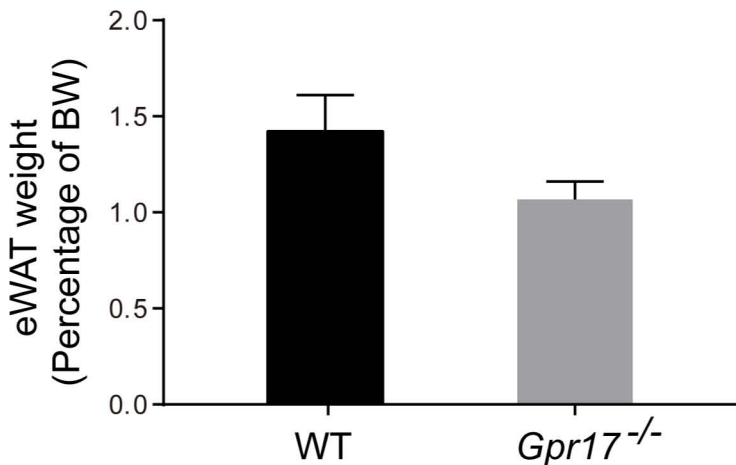


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**Supplemental Information**

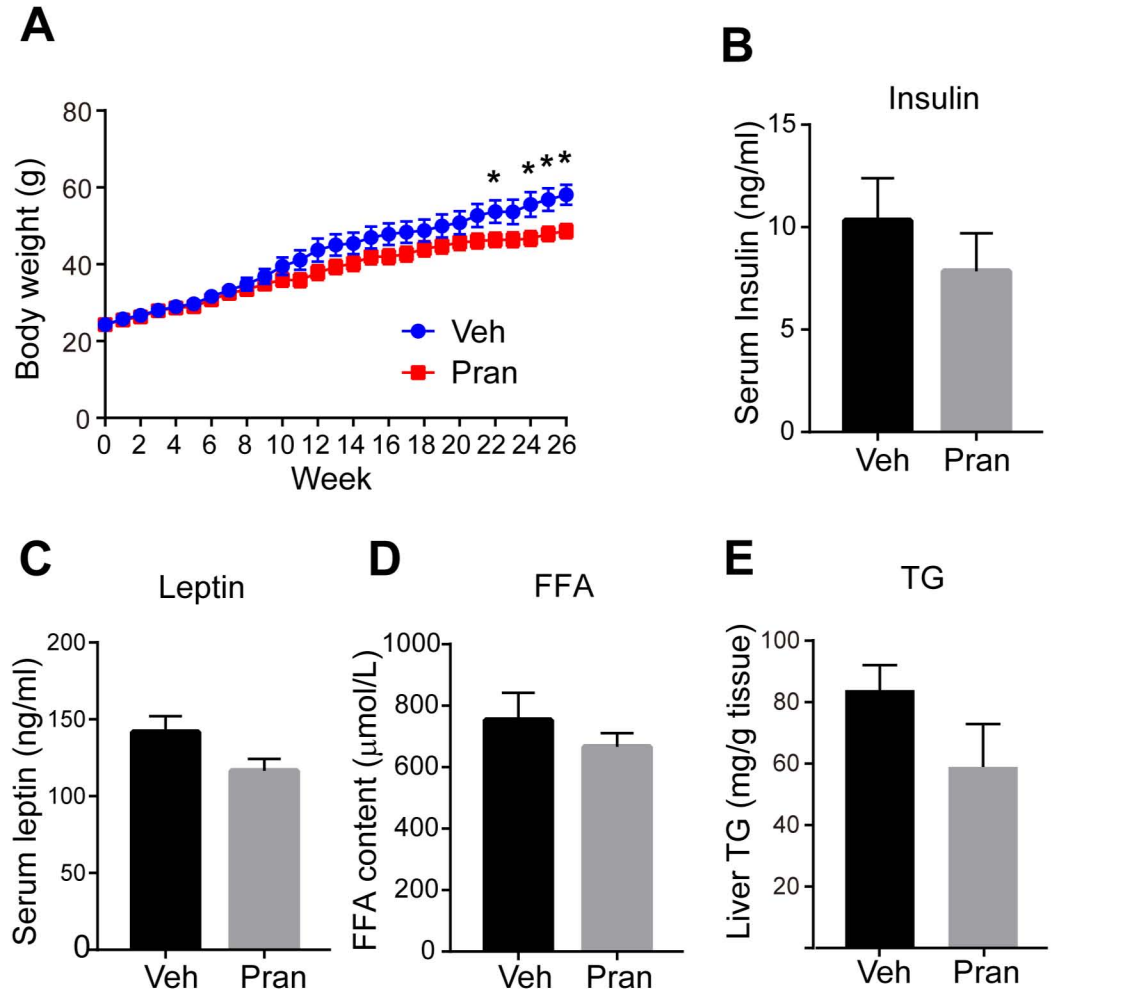
**A GPR17-cAMP-Lactate Signaling Axis  
in Oligodendrocytes Regulates  
Whole-Body Metabolism**

**Zhimin Ou, Yanchen Ma, Yuxia Sun, Gege Zheng, Shiyun Wang, Rui Xing, Xiang Chen, Ying Han, Jiajia Wang, Q. Richard Lu, Tong-Jin Zhao, and Ying Chen**

**A****B**

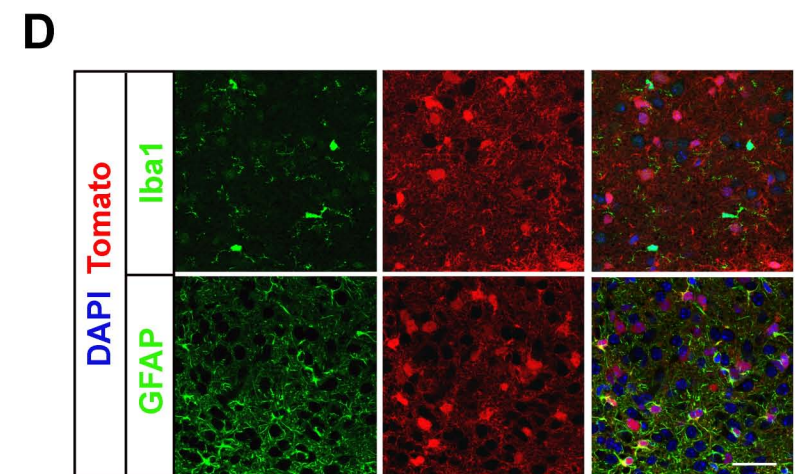
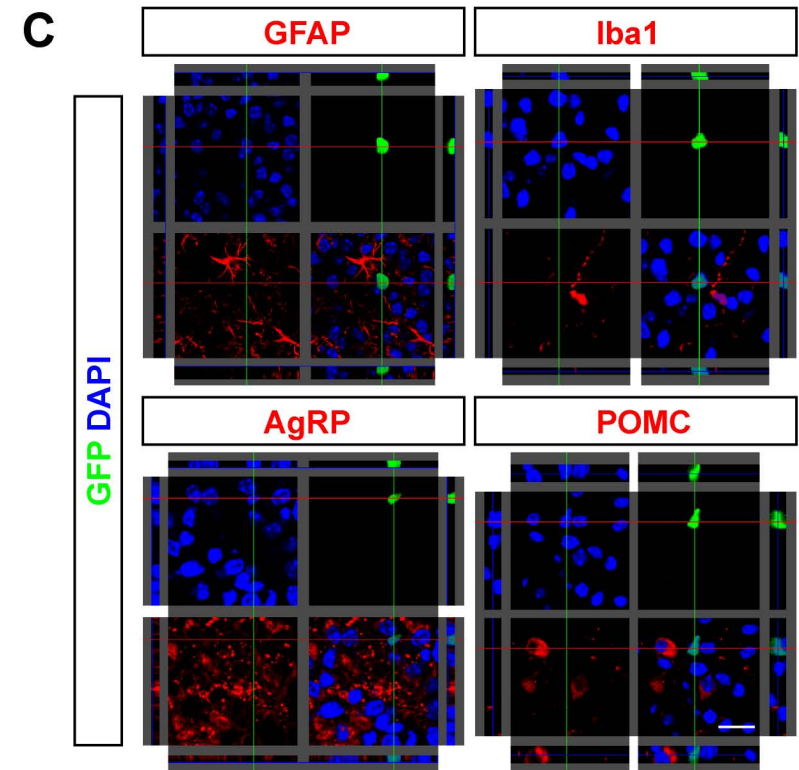
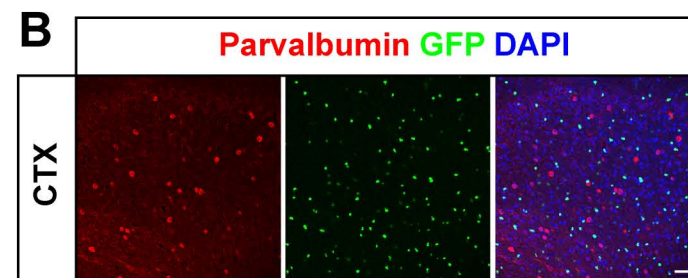
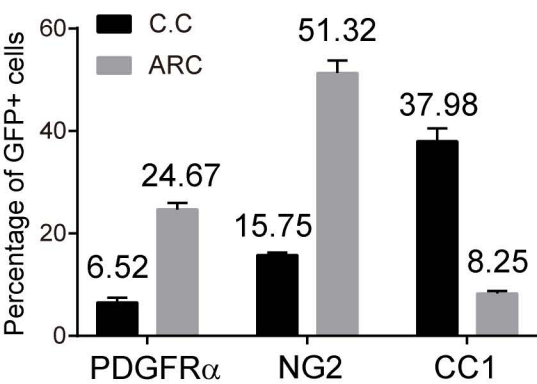
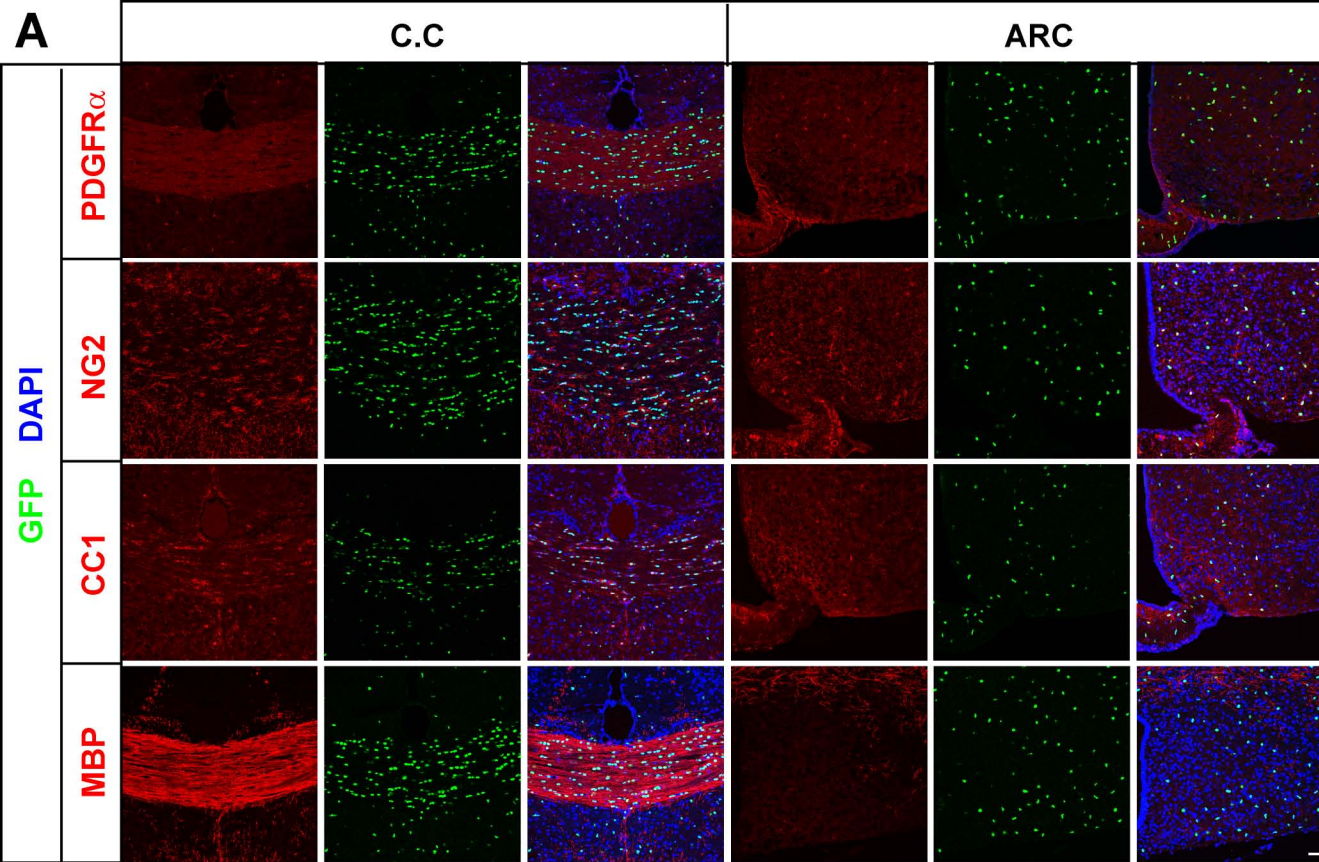
**Supplementary Figure 1. *Gpr17* ablation has little effect on body weight in mice fed with NCD. Related to Figure 1**

*Gpr17*<sup>-/-</sup> mice and their WT littermates were fed NCD. (A) Body weights were recorded weekly from 4 weeks of age. (B) At the age of 30 weeks, mice were sacrificed and the weight of eWAT was measured. Each value represents mean  $\pm$  SEM of 5 mice.



**Supplementary Figure 2. Pranlukast-treated WT mice are resistant to HFD-induced obesity. Related to Figure 1**

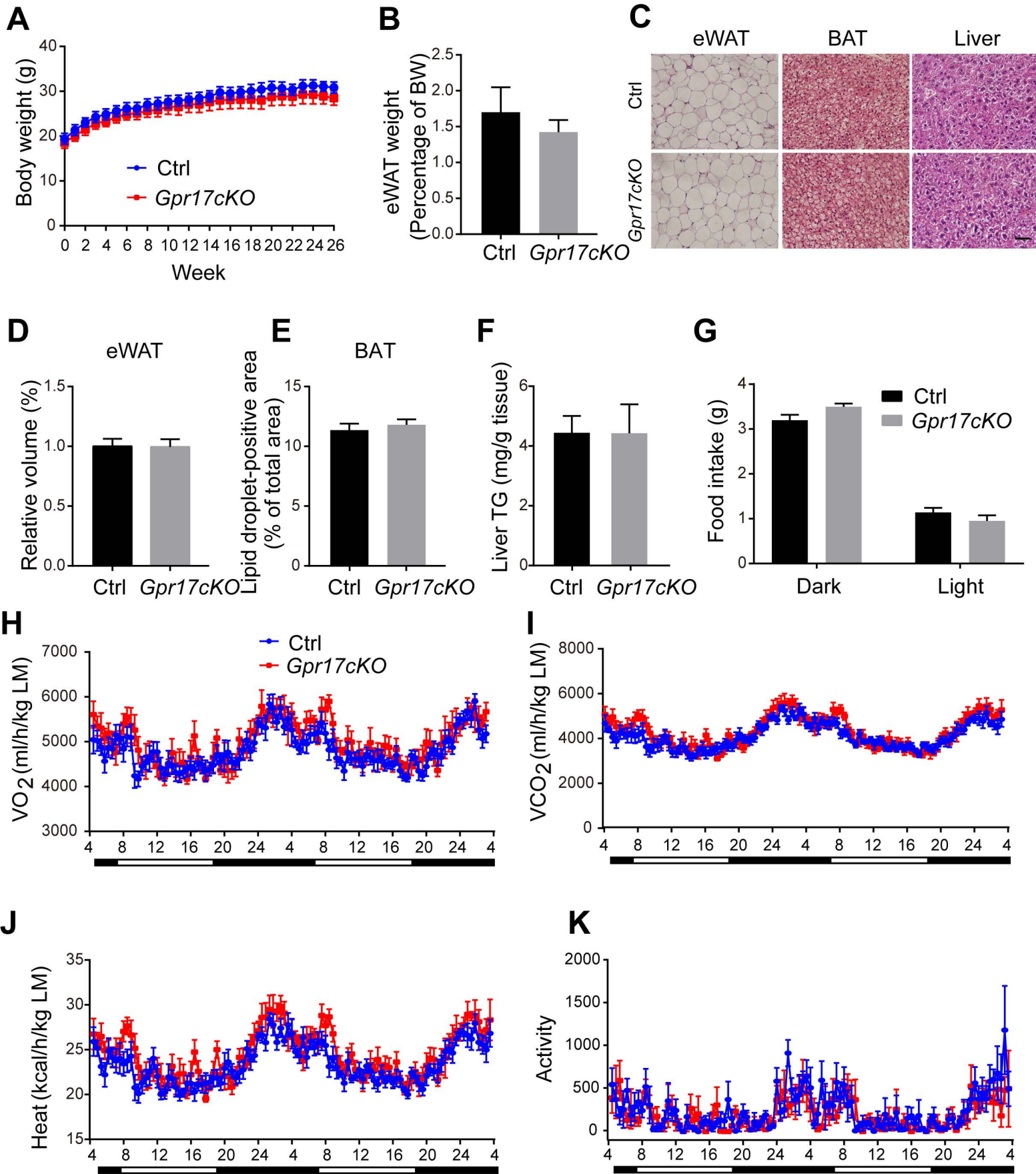
WT mice fed with HFD from the age of 8 weeks received daily intraperitoneal injection of vehicle or 0.2 mg/kg pranlukast for 26 weeks. (A) Body weight was recorded weekly. (B-E) Serum parameters including B) insulin, C) leptin, and D) free fatty acids, and F) liver triglyceride (E) were measured after 26 weeks of HFD feeding. Each value represents mean  $\pm$  SEM of 5 mice. \*,  $p < 0.05$ ; Student's t test.



**Supplementary Figure 3. *Gpr17* is not expressed in astrocytes or microglia. Related to Figure 2**

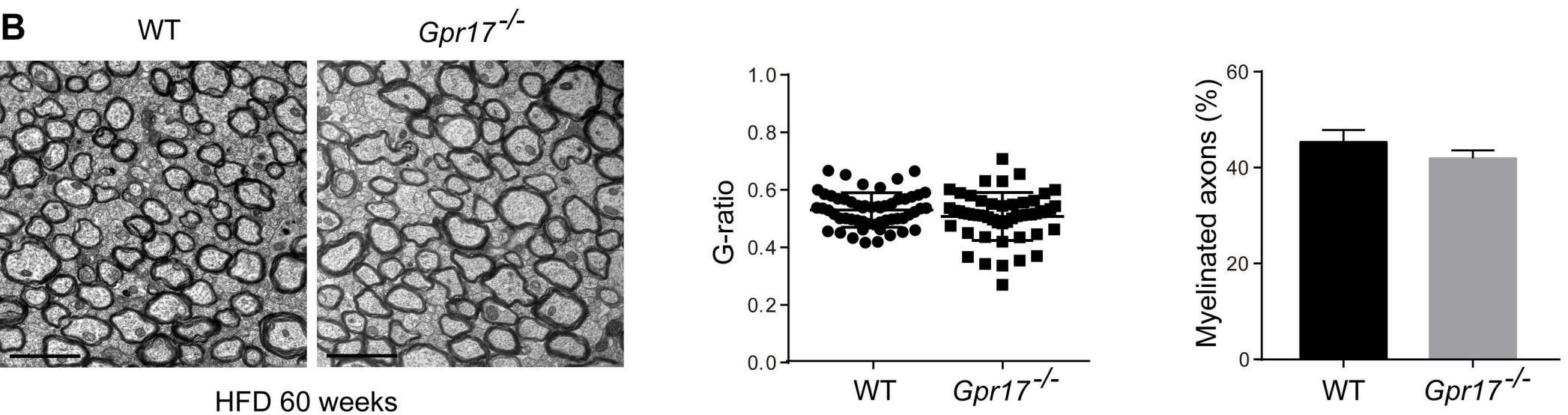
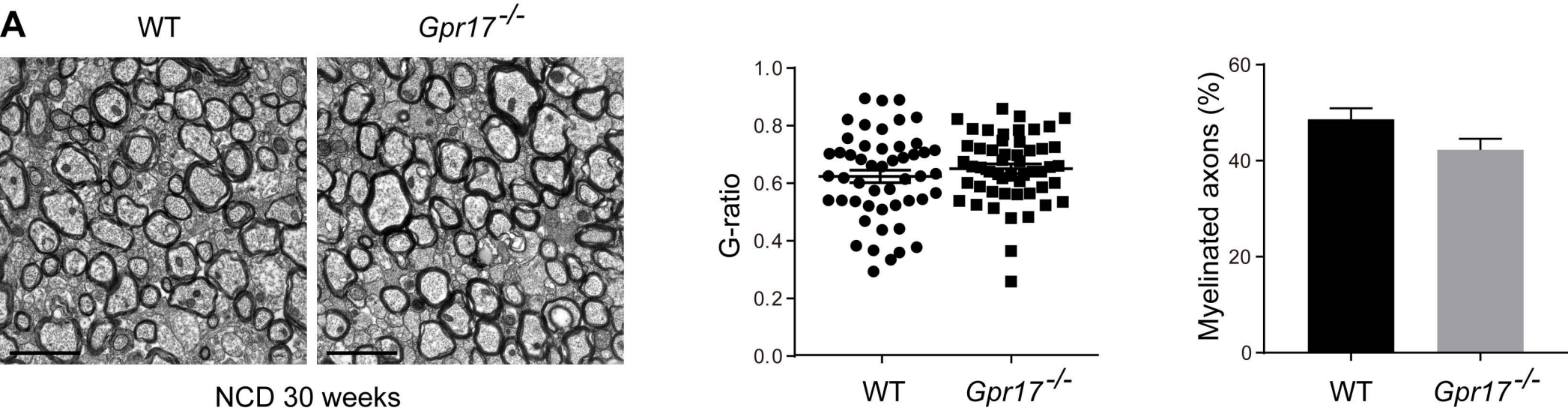
(A-C) Immunofluorescence analysis showing the expression pattern of GFP in MBP, CC1, PDGFR $\alpha$ , and NG2+ oligodendrocytes in the C.C or ARC (A), parvalbumin+ neurons in the cortex (CTX) (B), and GFAP+ astrocytes, Iba1+ microglia and AgRP+ or POMC+ neurons in the ARC (C) of *Gpr17*<sup>-/-</sup> mice. The numbers of the PDGFR $\alpha$  Olig2 or CC1 positive cells were quantified as indicated. Scale bar, 50  $\mu$ m (A and B) or 25  $\mu$ m (C). (D) Immunofluorescent analysis showing the expression of tdTomato in GFAP-positive astrocytes or Iba1-positive microglia in the ARC of *Olig1cre*<sup>+/+</sup>;tdTomato mice as described in STAR Methods. Scale bar, 25  $\mu$ m.





**Supplementary Figure 4. Depletion of *Gpr17* in oligodendrocytes has no significant effect on energy homeostasis of mice fed NCD. Related to Figure 3**

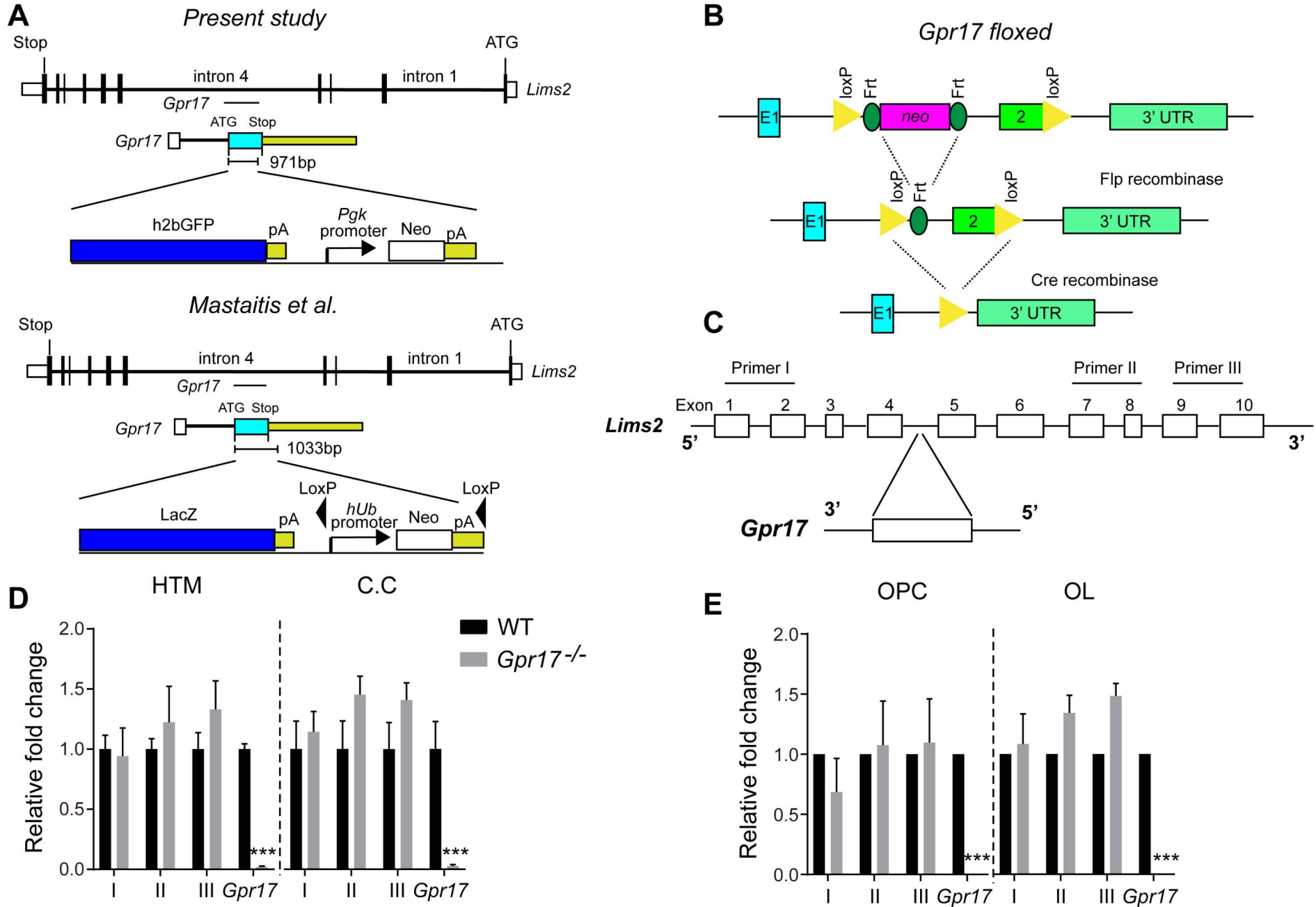
(A-F) *Gpr17cKO* and the control (*Gpr17<sup>fl/fl</sup>*) mice were fed NCD. Mice were sacrificed at 34 weeks of age and the tissue samples were collected. A) Body weight recorded weekly beginning at 8 weeks of age. B) Weight of eWAT. C) H&E stained images of eWAT, BAT, and liver, Scale bar, 50  $\mu$ m. D) The volume of the adipocytes in eWAT. E) Lipid droplet-positive area in the BAT quantified by Image J. F) Triglyceride content in the liver. (G-K) Metabolic parameters of the *Gpr17cKO* and the control mice at 31 weeks of age including G) food intake, H)  $O_2$  consumption, I)  $CO_2$  production, J) heat production, and K) ambulatory activity were recorded during 48 hours of dark and light cycles. Open and filled bars represent light and dark phases, respectively. Each value represents mean  $\pm$  SEM of 8 mice.



**Supplementary Figure 5. Loss of *Gpr17* does not alter the myelination in mice. Related to Figure 1**

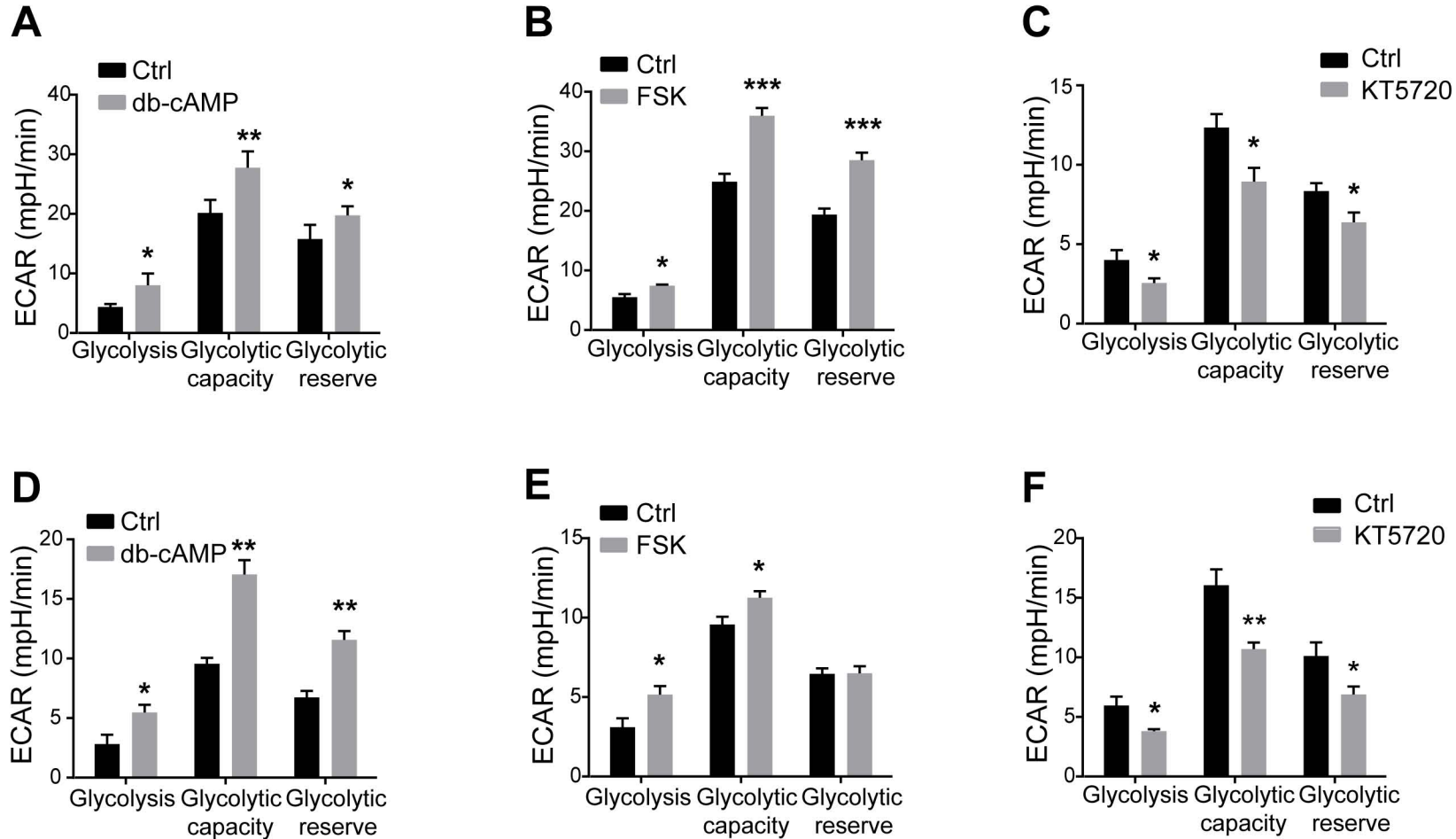
(A-B) Electron microscopic examination of the C.C of WT and *Gpr17*<sup>-/-</sup> mice fed NCD for A) 30 weeks or B) HFD for 60 weeks. The G-ratio and the myelinated axon numbers were quantified. Scale bar, 2  $\mu$ m.





**Supplementary Figure 6. Deletion of *Gpr17* gene did not affect the expression of *Lims2*. Related to Figure 1**

(A-B) Schematic strategies of generating the *Gpr17*<sup>-/-</sup> (A, upper panel: adapted from Chen et al., 2009; lower panel: adapted from Mastaitis et al., 2015) and *Gpr17*<sup>cKO</sup> mice (B, adapted from Ou et al., 2016). (C) Schematic of the *Lims2* gene with the location of *Gpr17* indicated. The positions of the real-time PCR primers are also indicated. (D-E) The relative mRNA levels of *Lims2* and *Gpr17* in D) the hypothalamus and C.C. of *Gpr17*<sup>-/-</sup> mice and their WT littermates (n = 5 animals/genotype) or E) isolated OPCs and OLs from *Gpr17*<sup>-/-</sup> mice and their WT littermates (n = 3 independent experiments). Each value represents mean ± SEM \*\*\*, p<0.001; Student's t test.



**Supplementary Figure 7. GPR17 regulates oligodendrocyte glycolysis in a PKA-dependent manner. Related to Figure 5**

(A-F) Quantifications of the ECAR results in Figures 5E to 5J. Each value represents mean  $\pm$  SEM of three independent experiments. \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ; \*\*\*,  $p < 0.001$ , Student's t test.