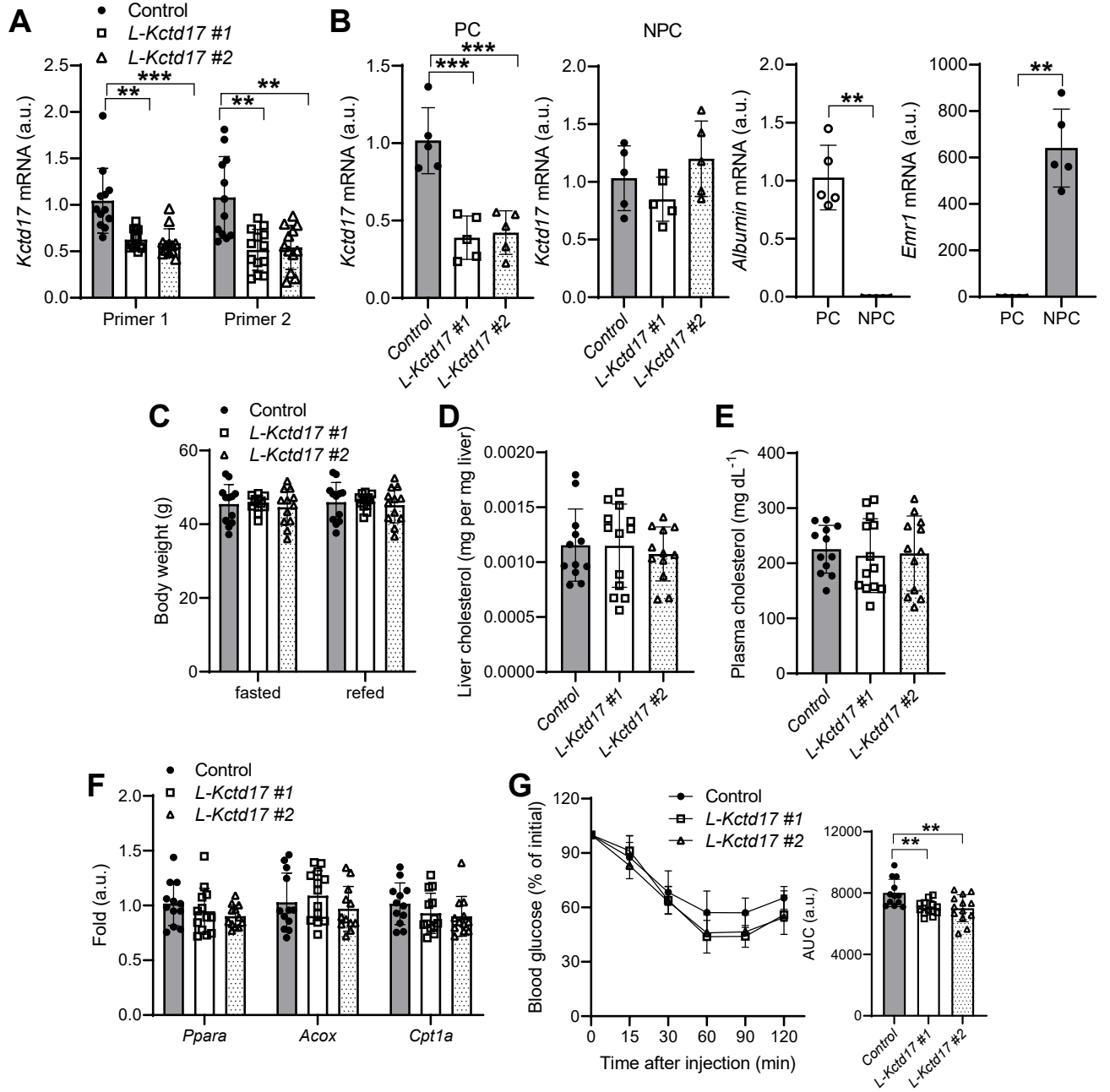
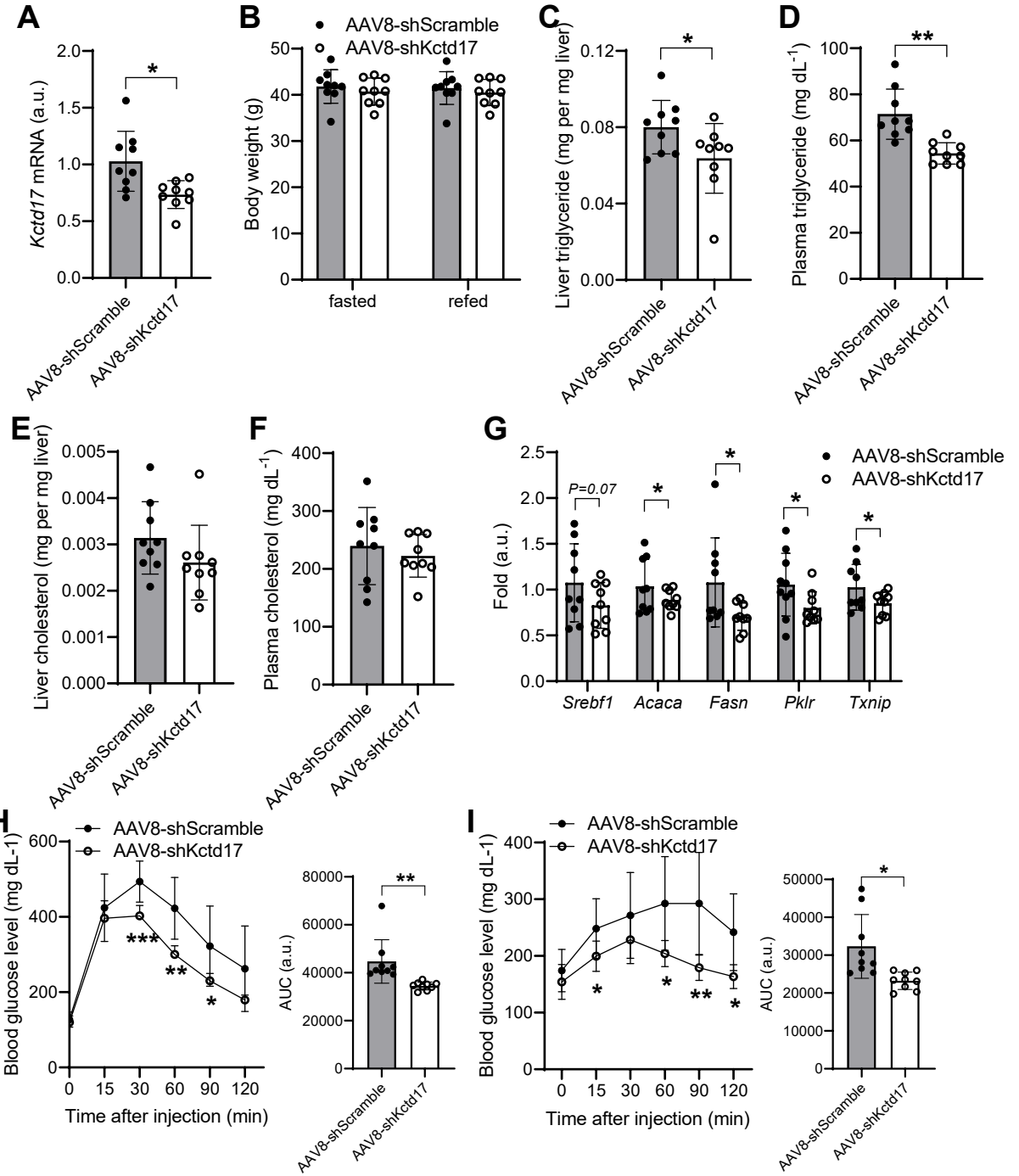
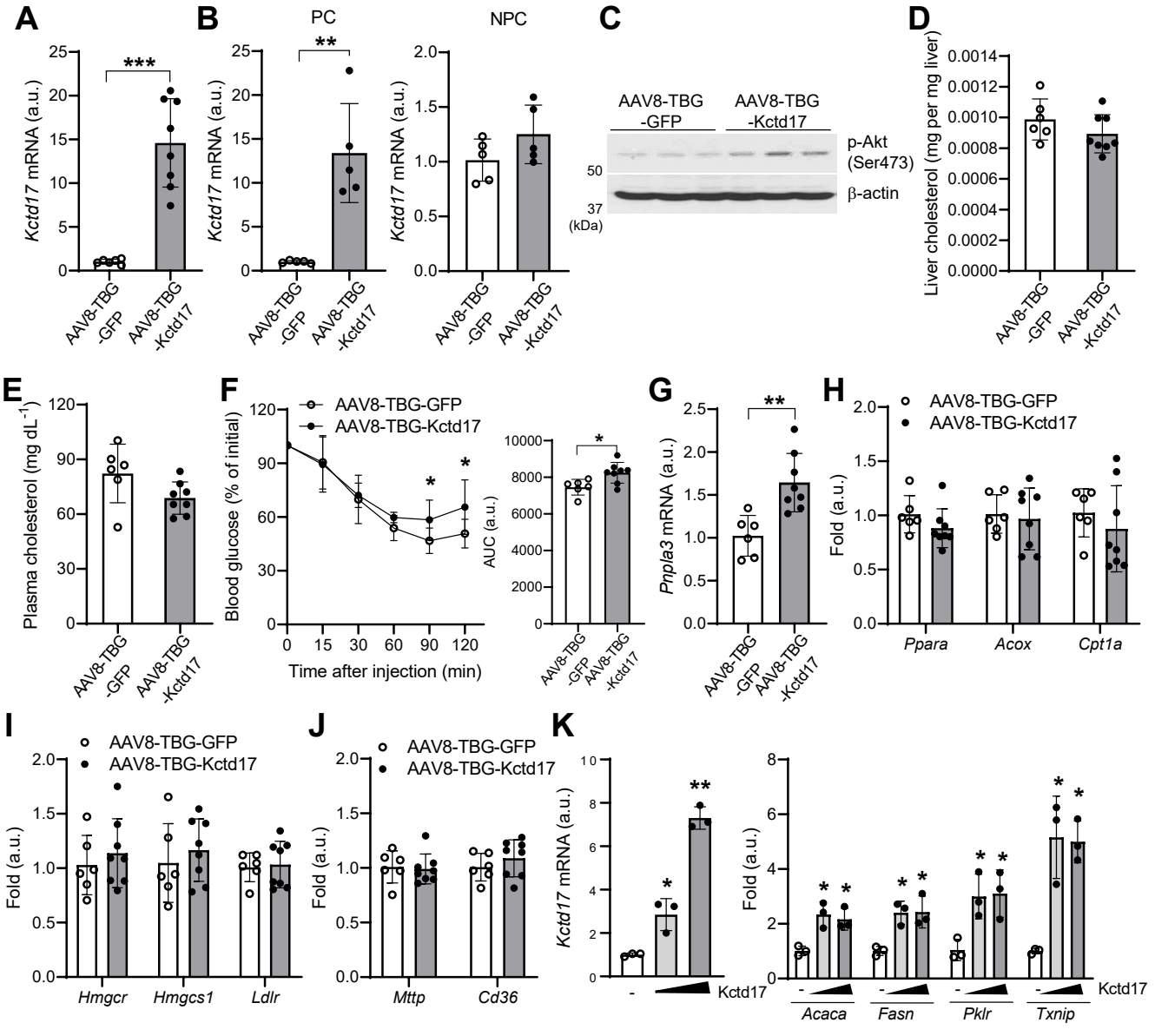


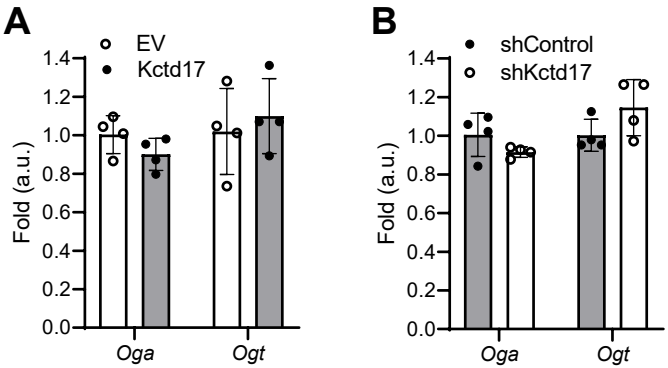
Supplementary Figure 1. Further characterization of hepatocyte-specific *Kctd17* KO mice. This figure corresponds to Figure 1. (A, B) *Kctd17* expression in (A) total liver and (B) parenchymal (PC) or nonparenchymal cells (NPC). *Albumin* or *Emr1* gene expression shown as representative markers of either PC or NPC. (C) Body weight, (D) liver and (E) plasma cholesterol, (F) hepatic expression of fatty acid oxidation machinery, and (G) insulin tolerance test (ITT; left), AUC of ITT (right) from HFD-fed, control and hepatocyte-specific *Kctd17* knockout (*L-Kctd17 #1* or *#2*) mice (n=12 to 13 per group). **P* < 0.05, ***P* < 0.01, ****P* <0.001 as compared to the indicated control by two-way ANOVA. All data are shown as the means ± s.d.



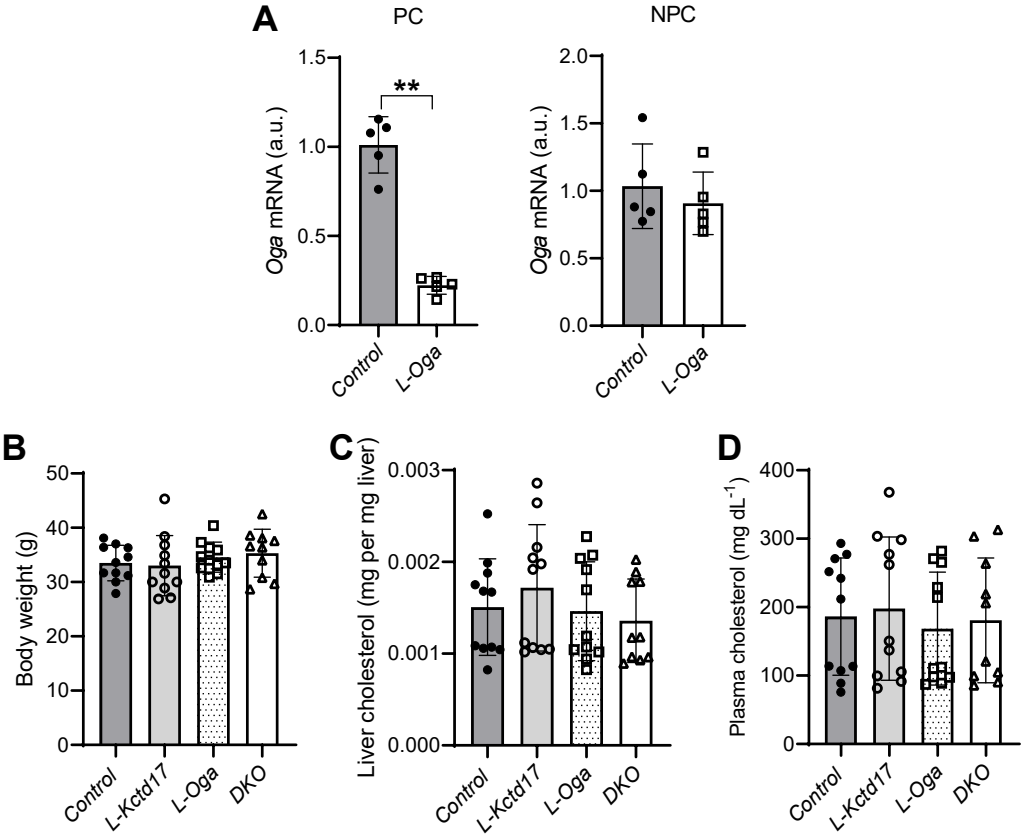
Supplementary Figure 2. Characterization of *Kctd17*-knockdown mice. (A) *Kctd17* expression, (B) body weight, (C) liver and (D) plasma triglyceride, (E) liver and (F) plasma cholesterol, (G) lipogenic and glycolytic gene expression, (H) GTT (left), AUC of GTT (right) and (I) PTT (left), AUC of PTT (right) in HFD-fed AAV8-shScramble or AAV8-shKctd17-transduced mice (n=9 per group). **P* < 0.05, ***P* < 0.01, ****P* <0.001 as compared to the indicated control by two-way ANOVA. All data are shown as the means ± s.d.



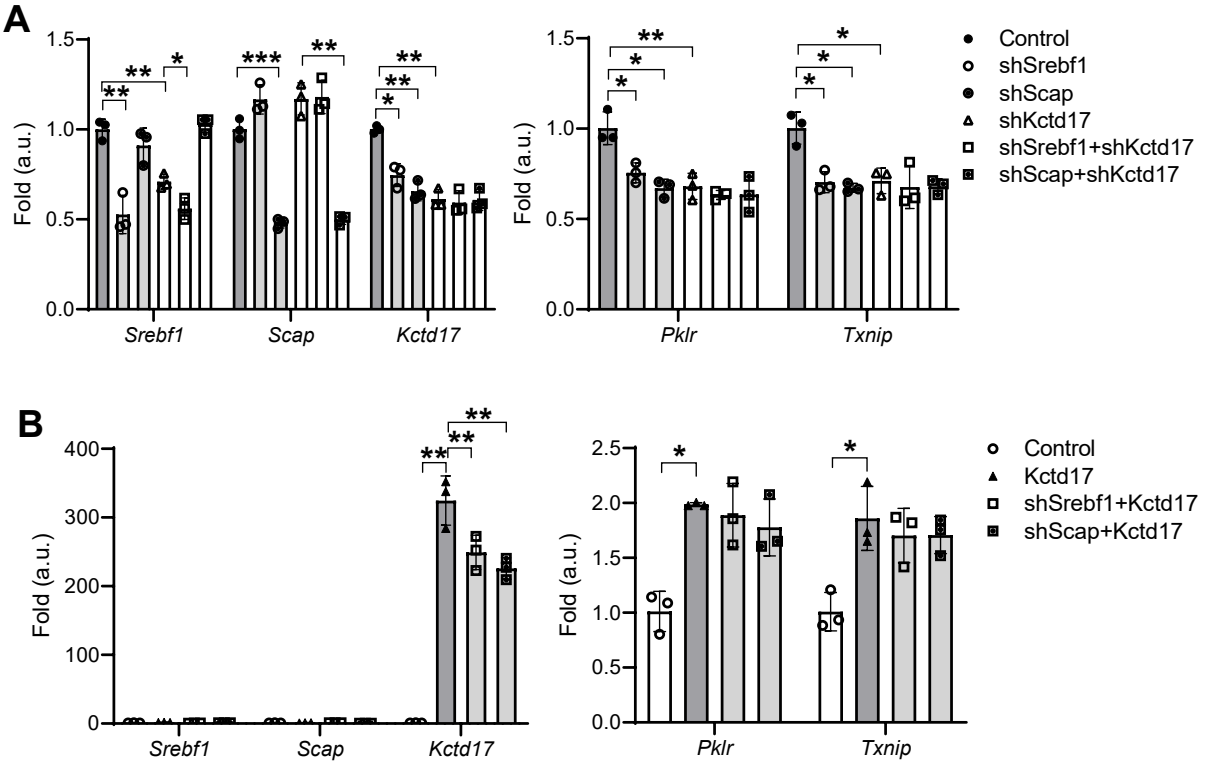
Supplementary Figure 3. Further characterization of Kctd17-overexpressed mice. This figure corresponds to Figure 2. (A) *Kctd17* expression, in total livers and (B) parenchymal or nonparenchymal cells, (C) phosphorylation of Akt (Ser473) in liver, (D) liver and (E) plasma cholesterol, (F) ITT (left), AUC of ITT (right), and expression of (G) *Pnpla3*, (H) fatty acid oxidation machinery, (I) *Srebpf2* targets, (J) and *Mttp* and *Cd36* in NCD-fed AAV8-TBG-GFP-transduced control (AAV8-TBG-GFP) or hepatocyte-specific Kctd17 overexpressed (AAV8-TBG-Kctd17) mice (n=6 to 8 per group). (K) *Kctd17* (left) and lipogenic and glycolytic gene expression (right) with Kctd17 overexpression. **P* < 0.05, ***P* < 0.01, ****P* <0.001 as compared to the indicated control by two-way ANOVA. All data are shown as the means ± s.d.



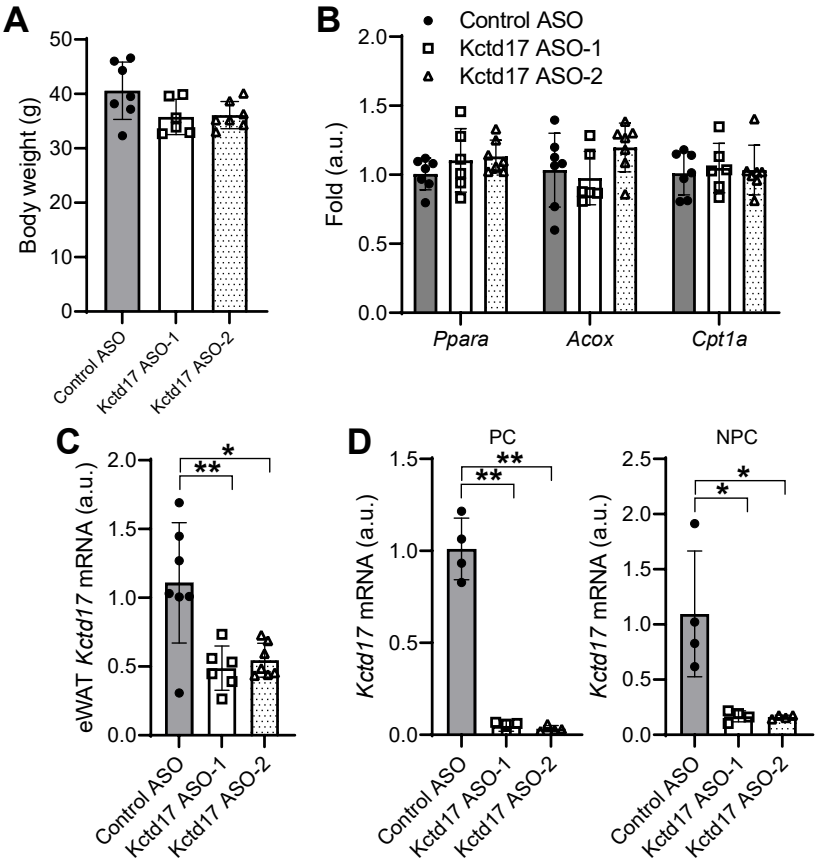
Supplementary Figure 4. Kctd17 regulates the Oga-Chrebp pathway. This figure corresponds to Figure 3. (A, B) *Oga* and *Ogt* gene expression in Hepa1c1c7 cells transfected with Kctd17 (A), or primary hepatocytes transduced with adenovirus expressing shControl or shKctd17 (n=4 per group).



Supplemental Figure 5. Hepatocyte Oga is required for Kctd17-mediated liver steatosis in DIO. This figure corresponds to Figure 4. (A) *Oga* expression in parenchymal or nonparenchymal cells, (B) body weight, (C) liver and (D) plasma cholesterol in HFD-fed Cas9 KI mice transduced with AAV8 expressing TBG-Cre (Control) or U6-driven Kctd17 (*L-Kctd17*) or Oga (*L-Oga*), or both Kctd17/Oga (*DKO*) sgRNA (n=10 to 11 per group). $^{**}P < 0.01$ as compared to the indicated control by two-way ANOVA. All data are shown as the means ± s.d.



Supplementary Figure 6. Kctd17 actions depend on the Srebp1c activity. This figure corresponds to Figure 5. (A, B) *Kctd17, Srebf1, Scap* and glycolytic gene expression in the presence of Kctd17 knockdown (A) or overexpression (B), in Hepa1c1c7 cells lacking *Srebf1* or *Scap*. **P* < 0.05, ***P* < 0.01, ****P* <0.001 as compared to the indicated control by two-way ANOVA. All data are shown as the means ± s.d.



Supplementary Figure 7. Further characterization of *Kctd17* ASO-administered mice. This figure corresponds to Figure 7. (A, B) Body weight (A), fatty acid oxidation-related gene expression (B), *Kctd17* gene expression in eWAT (C) in control or two different Kctd17 ASO (ASO-1 or ASO-2)-treated HFD-fed C57BL/6 mice (n=6 to 7 per group). (D) *Kctd17* expression in isolated parenchymal or nonparenchymal cells (D) (n=4 per group). **P* < 0.05, ***P* < 0.01 as compared to the indicated control by two-way ANOVA. All data are shown as the means ± s.d.