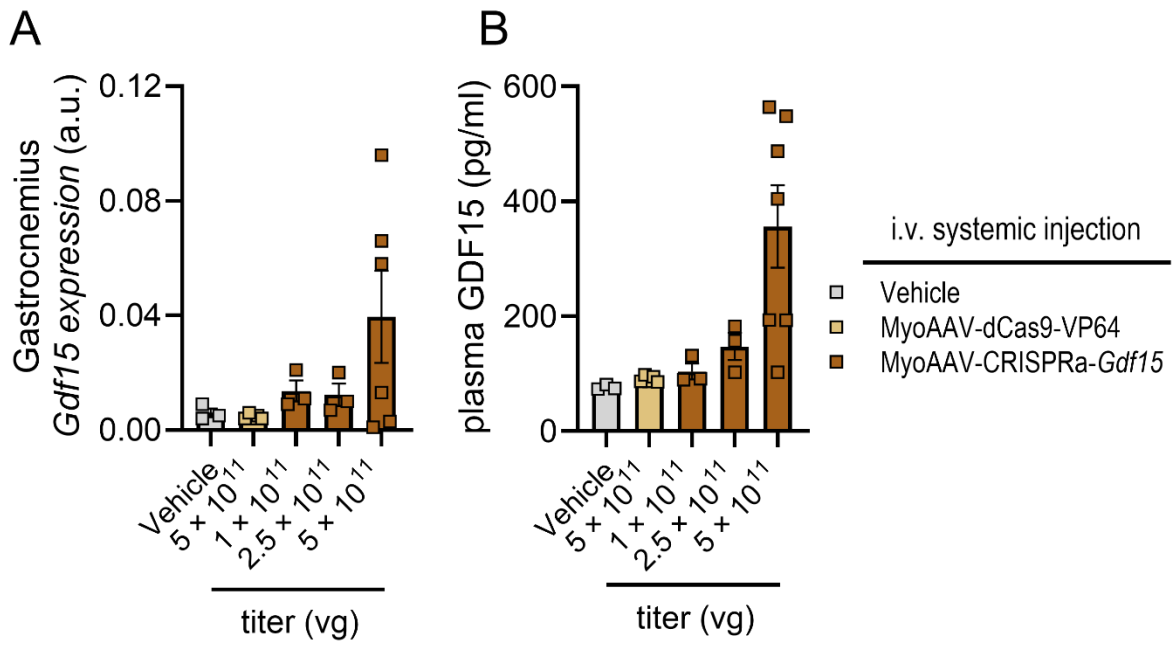

Figure S1. Chow-fed 7–10-week-old male C57BL/6J mice were injected intravenously with vehicle or MyoAAV-dCas9-VP64 control vectors (MyoAAV2a-C-dCas9-VP64 plus MyoAAV2a-N-dCas9; 5 × 10^{11} vg). Treatment groups received MyoAAV-CRISPRa-Gdf15 (MyoAAV2a-C-dCas9-VP64, MyoAAV2a-N-dCas9, and MyoAAV2a-SAM-gRNA5+7) at low (1 × 10^{11} vg), medium (2.5 × 10^{11} vg), or high (5 × 10^{11} vg) doses. Three weeks later mice were euthanized and (a) Gdf15 mRNA were determined in gastrocnemius muscle and (b) plasma GDF15 was measured by ELISA.

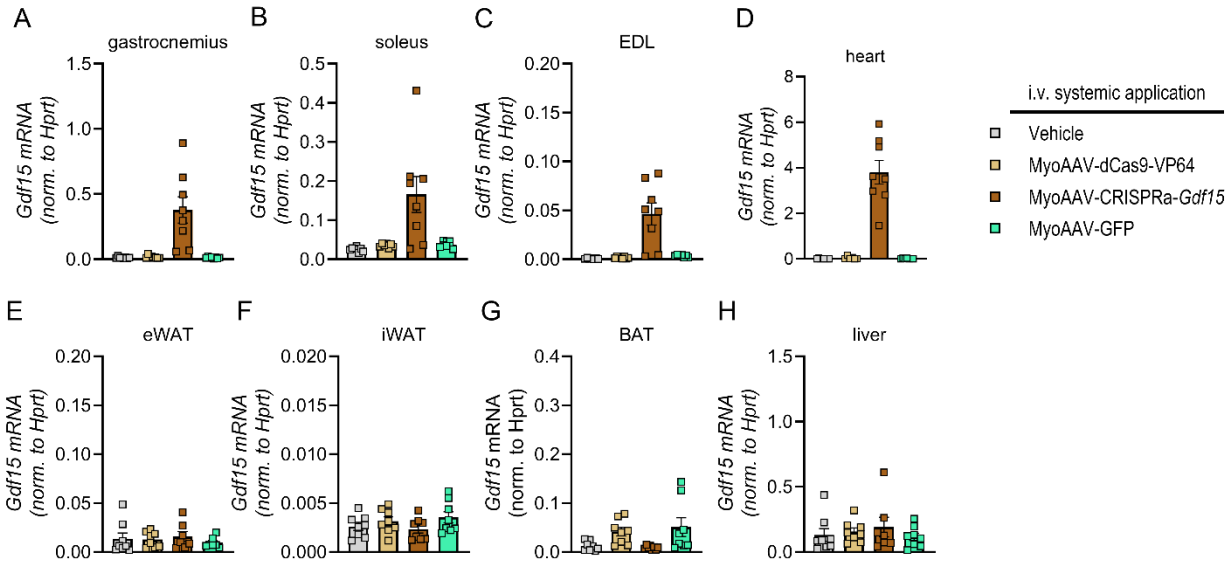

Figure S2. Effect of intravenous delivery of CRISPRa-Gdf15 on *Gdf15* expression in different tissues in wildtype mice. Gdf15 mRNA abundance was determined in the indicated (a-h) tissues from the study described in Figure 2.

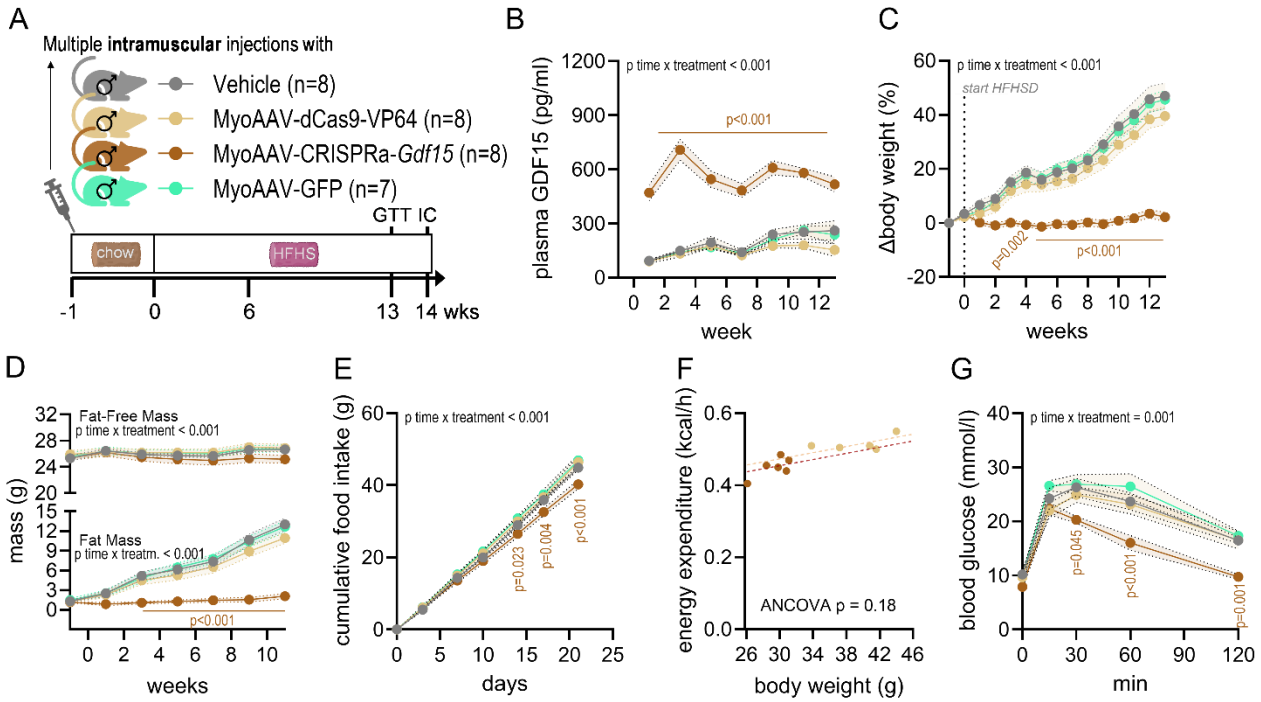

Figure S3. Metabolic phenotyping after intramuscular delivery of CRISPRa-Gdf15 in wildtype mice. (A) Schematic of study design with chow-fed male mice receiving intramuscularly injections with vehicle or MyoAAV2a encoding for eGFP or MyoAAV2a encoding for different component of the CRISPRa system. One week later all mice were switched to a HFHSD (EF D12331, ssniff Spezialdiäten GmbH, Germany) containing 58 kcal% fat. Over the course of the experiment, (B) plasma GDF15 levels, (C) body weight change, (D) fat-free mass and fat mass, and (E) cumulative food intake, were measured. (F) Energy expenditure was determined by indirect calorimetry in week 14. (H) Glucose tolerance was tested in week 13. (B-E, H) data are presented as mean values +/− SEM. Statistic: (B-E, H) repeated measures two-way (time x treatment) ANOVA with Šidák post hoc testing. Data in (F) were analyzed using ANCOVA with body weight as co-variate.

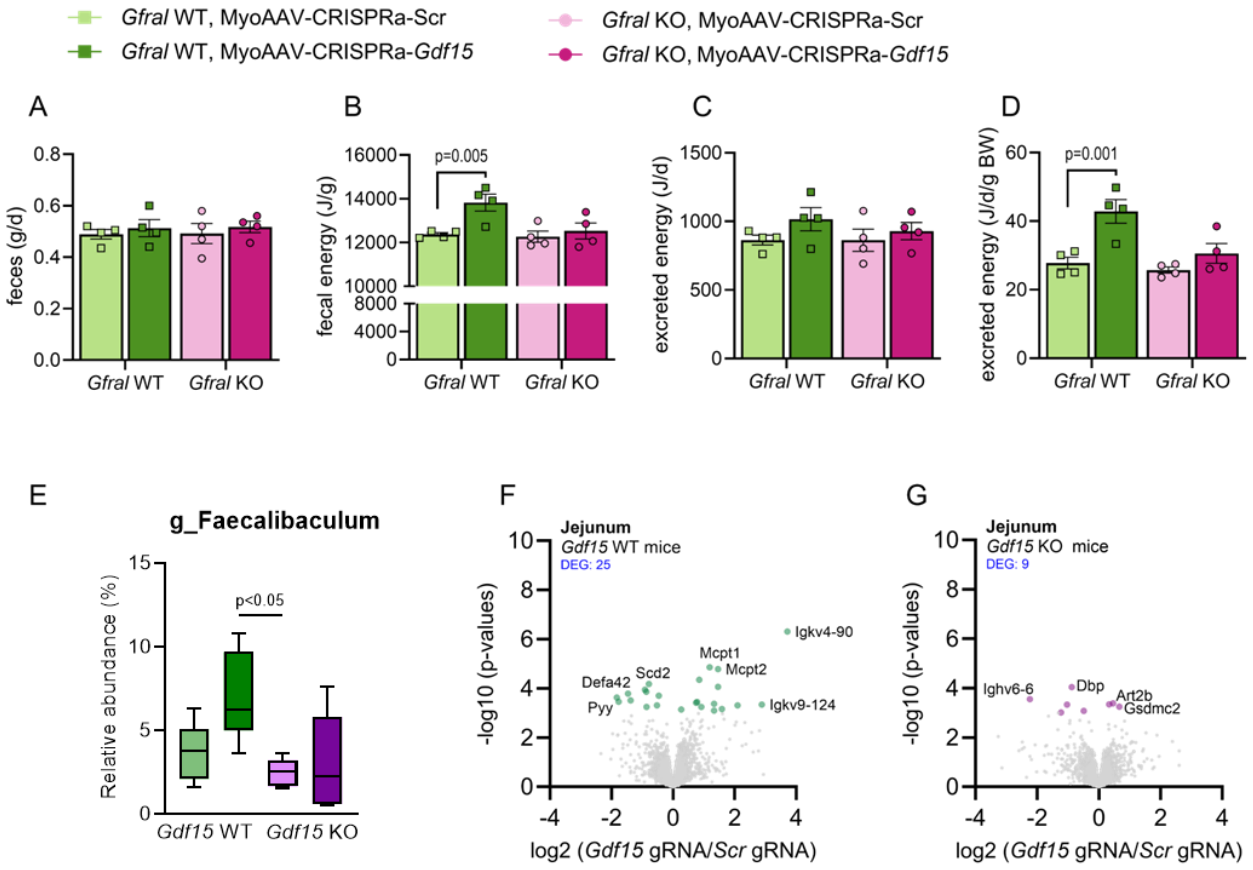

Figure S4. Effect of intravenous delivery of CRISPRa-*Gdf15* on energy excretion in *Gfral* WT and *Gdf15* KO mice (A-D): In the study shown in Figure 3, feces were collected in week 11 to determine (A) total feces mass, (B) fecal energy density and (C,D) overall energy excreted. (E) differential abundance of microbial genera in cecum as described in Figure 5 and and on (F,G) gene expression (RNAseq) in jejunum from *Gdf15* WT and *Gdf15* KO mice as described in Figure 5. (A-D) data are presented as mean values +/− SEM. (E) data are presented as Tukey box plots with median, IQR, and whiskers. Statistic: (A-D) Two-way (genotype x treatment) ANOVA with with Šidák post hoc testing. (E) Wilcoxon Rank Sum Test with multiple testing correction by the Benjamini–Hochberg method for adjusted p-values.