Supporting Information

Supporting Patients and Methods

HUMAN COHORTS

In brief, mucosal biopsy samples of the terminal ileum were taken from individuals who were not diagnosed with inflammatory bowel disease or colorectal cancer during routine endoscopy, and frozen immediately for further mRNA analyses. The sex and ages were at similar levels between the obese group (BMI≥26; n=7) and nonobese group (BMI<26; n=7), with clinical variables listed in Table S1 for Human cohort 1. Paraffin-embedded tissues of terminal ileum were obtained from Cancer Hospital Chinese Academy of Medical Sciences for Human cohort 2 (Beijing, China) or duodenum tissues from Beijing Friendship Hospital (Affiliated to Capital Medical University, Beijing, China) and used for immunofluorescence staining for obese (BMI≥26) and nonobese group (BMI<26), with detailed information listed in Table S2 and Table S3. All individuals met the following inclusion criteria: (1) no inflammatory bowel disease; (2) no small intestine or colorectal cancer; (3) no thyroid dysfunction; (4) no acute or chronic viral hepatitis; (5) no pregnancy; (6) no alcoholic liver disease or daily drinking habits; and (7) no disease judged by clinicians as unsuitable for biopsy.

IMMUNOFLUORESCENCE STAINING

Paraffin-embedded human ileum or duodenum biopsies were cut into 4 μm sections and used for analyses of immunofluorescence staining at the same time. Slices were deparaffinized with xylene (Peking Reagent, Beijing, China) and hydrated using an ethanol gradient, and then washed three

times with PBST (PBS+0.002% Tween 20, V900548, Sigma, Saint Louis, USA), permeabilized with 0.5% Triton X-100 (9002-93-1, Sigma, MA, UK) for 15 min. For antigen retrieval, the sections were autoclaved at 120 °C for 10 min in 0.01 M sodium citrate buffer (pH=6.0, C1010, Solarbio, Beijing, China) and cooled at room temperature for 30 min. After antigen retrieval, the sections were washed 3 times with PBST and blocked with 1% BSA/PBS solution (0332-100G, Amersco, Washington, D.C.) for 40 min at room temperature followed by incubation with anti-PPARα primary antibody (1:100, PA1-822A, Invitrogen, Waltham, MA) or anti-FABP primary antibody (1:100, sc-271591, Santa Cruz, Dallas, TX) in PBS overnight at 4 °C. After three times washing with PBST, the sections were incubated with goat anti-rabbit/mouse TRITC/FITC secondary antibody (ZF-0136 or ZF-0312, zsjqbio, Beijing, China) at room temperature for 1 h. Tissue sections were covered with DAPI-contained mountant (H-1200, Vector Labs, Burlingame, CA). Images were acquired using OLYMPUS microscope (BX53, Tokyo, Japan). Quantitation of the immunofluorescence was performed with Image-Pro Plus software (6.0, NIH, Bethesda, MD, USA).

ANIMALS BREEDING

PPRE-Luc mice were bred with *PPARA*-humanized mice to replace the mouse *Ppara* allele with the *PPARA* transgene and $Ppara^{-/-}$ allele to generate the global human PPARα mice or its strain-matched $Ppara^{-/-}$-PPRE-Luc mice. Small intestines were collected and extracted with lysis buffer, and luciferase activities measured with a luciferase assay system (Promega, Madison, WI). $Ppara^{\Delta IE,\ ERT2}$ mice were generated by crossing the $Ppara^{fl/fl}$ mice with the villin-ERT2-cre mice. $Fabp1^{\Delta IE}$ mice were produced by breeding $Fabp1^{fl/fl}$ mice with villin-cre transgenic mice. Intestinal PPARα and FABP1 double-knockout mice ($Ppara/Fabp1^{\Delta IE}$) were generated by breeding $Fabp1^{fl/fl}$

mice with *Ppara*$^{\Delta IE}$ mice. All mice were maintained under a standard 12-hour light/12-hour dark cycle with water and diet provided ad libitum.

IN VIVO LUMINOFLUORESCENCE IMAGING

D-Luciferin was purchased from Cayman (25836, Ann Arbor, MI). Five-week-old female *PPARA*-humanized-PPRE-Luc mice and *Ppara*$^{-/-}$-PPRE-Luc mice were fed a chow diet or HFD for 2 weeks. The mice were intraperitoneally injected with D-Luciferin at 150 mg/kg in saline. The mice were then anesthetized with isoflurane and images were taken using IVIS Imaging system (PerkinElmer, Waltham, MA) at 30 min after D-luciferin dosing. The mice will then be killed by CO_2 inhalation and tissues (small intestines, livers and adipose) taken for further imaging. Quantitation of luminofluorescence was performed using IVIS system-equipped software.

ANIMAL STUDIES

High-fat diet (HFD, 60 kcal% from fat, S3282) was purchased from Bioserv (Frenchtown, NJ) and high-fat, high-cholesterol, high-fructose diet (HFCFD, 40 kcal% from fat-mostly palm oil, 20 kcal% from fructose and 2 kcal% from cholesterol, D09100310) was obtained from Research Diets (New Brunswick, NJ). GW6471 was purchased from Tocris (4618, Bio-Techne Corporation, Minneapolis, MN). In mice, HFD was used for inducing obesity and fatty liver, while HFCFD was employed for the development of NASH and fibrosis. Six-8-week-old age-matched male mice were fed a chow diet, HFD, or HFCFD for the indicated time. GW6471 (10 mg/kg) by gavage was used to test the preventive effects and therapeutic effects in both the HFD and HFCFD-induced dietary NAFLD models.

GW6471 was dissolved in DMSO and then diluted 40 times in 0.5% sodium carboxymethyl cellulose containing 2.5% Tween 80. For testing the preventive effect of GW6471, mice were fed a HFD and treated with GW6471 at 10 mg/kg body weight via gavage once daily for 12 weeks starting since the first day of HFD treatment. For testing the therapeutic effects, mice were fed a HFD or HFCFD for 8 weeks first to establish obesity and fatty liver or early NASH and then treated with GW6471 at 10 mg/kg via gavage once daily for another 5 weeks for the HFD-fatty liver model or another 8 weeks for HFCFD-NASH model. For inducing temporal intestinal *Ppara* knockout, the $Ppara^{\Delta IE,\ ERT2}$ mice were intraperitoneally injected with tamoxifen (T5648, Sigma, St. Louis, MO). at 100 mg/kg in corn oil for three consecutive days first and then once weekly until the end of experiment. Tamoxifen was dosed in the animal facility room that equipped with Biosafety Level 2 chemical hood. Feces were collected in housed cages with one mouse in each cage for 48 h at the indicated time. For testing the effect of GW6471 in inhibiting PPRE-Luc activity *in vivo*, the *PPARA*-humanized PPRE-Luc mice were fed a HFD and administered GW6471 at 10 mg/kg once daily for 1 week, and then all mice killed by CO_2 inhalation to collect the small intestines for analyses of luciferase activity using the dual-luciferase assay system (E1960, Promega, Madison, WI).

METABOLIC ASSAYS

For the glucose-tolerance test, mice were fasted overnight for 16 h, except the *PPARA*-humanized mice and their matched $Ppara^{-/-}$ mice that were fasted for 12 h, since global $Ppara^{-/-}$ mice are susceptible to fasting-induced hypoglycemia, hypoketonemia, and hypothermia as described previously[1, 2]. Mice were dosed with glucose (2 g/kg) in saline via intraperitoneal injection. For the insulin-tolerance test, mice were fasted for 6 h and injected intraperitoneally with insulin in

saline (Eli Lilly; 0.9 U/kg) . For both glucose-tolerance test and insulin-tolerance test, glucose was measured with a glucometer (Bayer, Washington, D.C.) from tail vein blood at 0, 15, 30, 60 and 90 min after injection. For the oral postprandial TG absorption test, mice were fasted overnight for 16 h. At 30 min before olive oil gavage (O1514, Sigma, St. Louis, MO), the mice were treated by intravenous injection of tyloxapol (T8761, Sigma, St. Louis, MO) at 500 mg/kg in saline. Blood was collected from the tail vein at 0, 1, 2, 4, and 6 h after olive oil gavage at 10 mL/kg.

BODY COMPOSITION AND INDIRECT CALORIMETRY

Body fat and lean mass of non-anesthetized live mice were determined using an EchoMRI 3-in-1 mouse scanner (EchoMRI, Houston, TX) following manufacturer's protocol. Indirect calorimetry was carried out using a 12-chamber Environment Controlled CLAMS (Columbus Instruments, Columbus, OH) with one mouse per chamber as previously described[3]. Mice were tested every 13 minutes for 3 days at 22 °C and 1 day at 30 °C. Temperature was changed on Day 4 at 6:00 AM. During testing, food and water were provided ad libitum. 24 h average parameters were analyzed from data collected at Day 3 for 22 °C and Day 4 for 30 °C (excluding the first hour after temperature changes).

QUANTITATIVE REAL-TIME POLYMERASE CHAIN REACTION ANALYSIS

Tissues were flash frozen in liquid nitrogen and stored at -80 °C. Total RNA from frozen tissues was extracted with TRIzol reagent (Invitrogen, Carlsbad, CA). cDNA was synthesized from 1 μg of total RNA using qScript cDNA SuperMix (Gaithersburg, MD). Analysis was performed by using the ABI PRISM 7900 Sequence Detection System (Applied Biosystems, Bedford, MA). Values were normalized to *β-Actin* (*Actb*) mRNAs and the results expressed as fold change relative

to the control group. Primer sequences are provided in the Table S4.

WESTERN BLOTTING

Tissues or cultured organoids were lysed with RIPA lysis buffer in the presence of protease inhibitors. To isolate nuclear and cytoplasm protein, the NE-PER™ Nuclear and Cytoplasmic Extraction Reagents kit (78835, Thermo Fisher Scientific, Waltham, MA) was used following the manufacturer's instruction. Protein concentrations were determined by the BCA protein assay kit (23227, Pierce Chemical, Rockford, IL). The samples were subjected to SDS-polyacrylamide gel electrophoresis, transferred to polyvinylidene fluoride membranes, and incubated overnight at 4 °C with antibodies against FABP1 (sc-271591, Santa Cruz, Dallas, TX), PPARα (ab126285, Abcam, Cambridge, MA), β-ACTIN (ACTB, 4970, Cell Signaling Technology, Danvers, MA) and LAMIN-B1 (LMNB1, 13435, Cell Signaling Technology, Danvers, MA). Proteins were visualized using the SuperSignal^{TM} West Dura Extended Duration Substrate (34076, Thermo Fisher Scientific, Waltham, MA) with an image analyzer (Alpha Innotech Corp., San Leandro, CA).

HISTOLOGICAL ANALYSIS

Formalin-fixed paraffin-embedded liver and intestine sections were stained with H&E or Sirius red, and OCT compound-embedded frozen liver sections were stained by oil red O in VitroVivo Biotech (Rockville, MD) or Histoserv Inc. (Germantown, MD) according to standard protocols followed by microscopic examination.

BIOCHEMICAL ANALYSIS

Hepatic TC/TG and serum TC/TG/NEFA were measured with assay kits from Wako Diagnostics

(Wako Chemicals USA, Richmond, VA) following the manufacturer's instruction. To measure fecal lipids, mice were housed individually in separate cages, and feces collected during a 48-h period and then dried and stored at -80 °C. Dried feces were weighed and extracted with chloroform : methanol (2:1) solution and dissolved in PBS containing 1% Triton X-100 after evaporation. Fecal NEFA levels were determined with assay kits from Wako Diagnostics (Wako Chemicals USA, Richmond, VA) following the manufacturer's instruction. Serum ALT levels were assessed using commercial ALT kit (CA164-0A; Catachem, Bridgeport, CT) and monitored at 340 nm for 15 min by a kinetic reading every 30 s with a microplate reader (BioAssay Systems, Harvard, CA).

LUCIFERASE REPORTER ASSAYS

PPRE sequences in the promoter region of *Fabp1* were identified by Genomatix software (Genomatix, Munchen, Germany). Custom GeneBlocks containing the predicted PPREs were synthesized by IDT DNA Technologies (Coralville, IA) and cloned into the pGL4.11 luciferase vector (E6661, Promega, Madison, WI). The mouse colon cancer cell line MC38 was obtained from James W. Hodge, National Cancer Institute, National Institutes of Health. MC38 cells were seeded into 12-well plate and cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% FBS and 1% antibiotic. *Fabp1* promoter reporter vector and phRL-TK Renilla luciferase control vector (E2241, Promega, Madison, WI) were co-transfected into MC38 cells by use of Lipofectamine 3000 transfection reagent (L3000-015, Thermo Fisher Scientific, Waltham, MA). In addition, either a PPARα expression vector[4] or the empty backbone vector (pSG5) were co-transfected into the cells and a final concentration of 100 μM WY14643 (MedChem Express, Monmouth Junction, NJ, HY-16995) or together with 6 μM GW6471 (4618,

Tocris, Minneapolis, MN) was added to the culture medium to activate or inhibit PPARα activity, respectively. Empty vector (pGL4.11) was used as a negative control and a validated PPRE reporter vector from Addgene[5] served as a positive control. Twenty-four hours after transfection, luciferase assays were performed by use of the dual-luciferase assay system (E1960, Promega, Madison, WI). Firefly and Renilla luciferase activities were measured by Veritas microplate luminometer (Turner Biosystems, Sunnyvale, CA).

CHROMATIN IMMUNOPRECIPITATION ASSAY

ChIP for PPARα binding was performed according to the ChIP-IT High Sensitivity ® Kit protocol (53040, Active Motif, Carlsbad, CA). Chromatin was prepared from isolated nuclei of formaldehyde cross-linked MC38 cells and sheared to between 200 and 500 bp. Sheared chromatin was immunoprecipitated with anti-PPARα antibody (ab24509, Abcam, Cambridge, MA, ab24509), or anti-pan-H3 antibody (4620, Cell Signaling Technology, Danvers, MA), or normal rabbit IgG (2729, Cell Signaling Technology, Danvers, MA). Precipitated DNA samples were incubated with RNase A and proteinase K, purified using MinElute Reaction Cleanup Kit (28204, QIAGEN, Germantown, MD), and subjected to qPCR using primers listed in Table S5. H3 was used as a positive control and IgG as a negative control.

INTESTINAL ORGANOID ISOLATION AND TREATMENT

Primary intestinal organoids were isolated from the jejunum part for palmitic acid/oleic acid (Sigma, St. Louis, MO, 76119 and O1383) treatment and fatty acid uptake assays using NBD-stearate (Avanti, Birmingham, AL, 810110P-1mg) or BODIPY-C_{12} (Invitrogen, Waltham, MA, D3823) as substrates. MC38 cells were cultured in DMEM (10% FBS and 1% antibiotics) and

used for luciferase reporter and chromatin-immunoprecipitation (ChIP) assays. Intestinal organoids were isolated as described previously[6]. The jejunum part of the small intestines was removed from mice, opened longitudinally and washed with ice-cold PBS. Crypts and villi were exposed by dicing the intestines into 2 mm segments followed by extensive washing to remove contaminants. Then, the intestinal pieces were incubated with Gentle Cell Dissociation Reagent (7174, Stemcell Technologies, Cambridge, MA) on a gently rotating platform for 15 min. Subsequently, the dissociation reagent was removed and intestine segments were washed with PBS containing 0.1% BSA by vigorous pipetting. The washing step was repeated four times and the supernatant collected from each wash and labeled as fraction 1-4. The first and second fractions that usually contain loose pieces of mesenchyme and villi were not used. Fractions three and four containing the intestinal crypts were pooled and filtered through a 70 μm nylon cell strainer (352350, Corning, New York, NY). Crypts were counted, then embedded in Matrigel (354230, Corning, New York, NY), and cultured in IntestiCult Organoid Growth Medium (6005, Stemcell Technologies, Cambridge, MA). Medium was changed every two or three days. On day 6, the intestinal organoids were treated with DMSO, 100 μM WY14643 (HY-16995, MedChem Express, Monmouth Junction, NJ), 6 μM GW6471 (4618, MedChem Express), control BSA, or BSA-conjugated fatty acid (BSA-FA, 0.2 mM palmitic acid + 0.4 mM oleic acid or 0.4 mM palmitic acid + 0.8 mM oleic acid) (76119 and O1383, Sigma, St. Louis, MO). Intestinal organoids were harvested 24 h post treatment for RNA and protein analysis.

For lentiviral transduction experiments, organoids were harvested and placed in 15 mL Corning tubes. Supernatant was removed by centrifugation and control lentiviruses or lentiviruses carrying the *Fabp1* cDNA (VectorBuilder, Chicago, IL; sequence available upon request) was added at 10^6 PFU/100 crypts. The organoid-virus mixture was placed in an incubator at 37 °C for

1 h. Then, 500 µl culture medium was added to the organoid-virus mixture, centrifugation carried out and the supernatant discarded. Finally, the organoids were embedded in Matrigel and cultured as described above. Three days after viral transduction, the organoids were supplemented with puromycin (3 µg/ml) for antibiotic selection for one week. After selection, the organoids were grown in normal culture medium for RNA, protein analysis and fatty acid uptake assay.

FATTY ACID UPTAKE IN ORGANOIDS

Three types of intestinal organoid experiments were performed. 1. Intestinal organoids were isolated from *PPARA*-humanized mice. On Day 6 after isolation, the organoids were pre-treated with DMSO or WY14643 (100 µM) or WY14643 + GW6471 (6 µM) for 24 h. 2. Intestinal organoids were isolated from *Ppara*$^{fl/fl}$, *Ppara*$^{\Delta IE}$, *Fabp1*$^{fl/fl}$ and *Fabp1*$^{\Delta IE}$ mice fed a HFD for 10 days. On Day 6 after isolation, the organoids were pre-treated with DMSO or GW6471 (6 µM) for 24 h. 3. Intestinal organoids were isolated from *Ppara*$^{fl/fl}$ and *Ppara*$^{\Delta IE}$ mice and transduced with control lentivirus (Lv-ctrl) or lentivirus overexpressing Fabp1 (Lv-Fabp1). Viral-transduced organoids were pre-treated with 0.4 mM oleic acid + 0.2 mM palmitic acid 24 h before fatty acid uptake assay. To measure fatty acid uptake in the above organoids, the organoids were starved for 4 h, and then treated with 2 µM BODIPY-C_{12} (middle-long chain FA, in 1% BSA) (D3823, Invitrogen, Waltham, MA) or 25 µM NBD-stearate (long chain FA, in 1% BSA) (810110P-1mg, Avanti, Birmingham, AL) for 30 min. Photos were taken under fluorescent microscope. Organoids were homogenized with RIPA buffer and the fluorescent intensity in the supernatant measured with a microplate reader and fluorescent intensity normalized to protein concentrations.

RNA-SEQ LIBRARY PREPARATION AND DATA ANALYSIS

Total RNA was isolated from jejunum using RNeasy Plus Mini Kit (#74136, Qiagen, Germantown, MD) according to the manufacturer's instructions. RNA-seq libraries were prepared using Illumina TruSeq Stranded mRNA Library Prep (#20020596, Illumina, San Diego, CA). Samples were pooled and sequenced on HiSeq4000 (Illumina, San Diego, CA) using paired-end protocol. For RNA-seq data analysis, reads of the samples were trimmed for adapters and low-quality bases using Trimmomatic 0.36 software before alignment with the reference genome (Mouse-mm10) and the annotated transcripts using STAR 2.5.1. The mapping statistics were calculated using Picard 1.84 software. Library complexity was measured in terms of unique fragments in the mapped reads using Picard's MarkDuplicate utility. The gene expression quantification analysis was performed for all samples using STAR/RSEM 1.2.22 tools. Differential gene expression was assessed with DESeq2 with the parameters *P-adj* 0.05 and log2 fold 1 (for 2-fold differentially expressed genes).

MASS SPECTROMETRY-BASED ANALYSES

Total fatty acids were detected after acid hydrolysis and measured with an Agilent 8890 gas chromatograph (8890 GC system) coupled to a 5977B GC/mass-selective detector (MSD) (Agilent Technologies, Santa Clara, CA) with a method described previously. [1] In brief, 50 µL of serum were mixed with 400 µL acetonitrile and 400 µL CH_2Cl_2 including 20 µM of myristic-d_{27} acid as internal standard (#366889, Sigma, St. Louis, MO), then 750 µL supernatant were transferred to a new tube and dried under vacuum. The dried samples were resuspended in 300 µL of hydrogen chloride-methanol solution (#17935, Sigma, St. Louis, MO) and then transferred to a glass bottle for one-hour incubation at 100 °C. Finally, 300 µL of hexane was added to extract the formed fatty acid esters and 100 µL supernatant was used for GC-MS injection. Fatty acid standards were

purchased from Sigma (#CRM47885, Sigma, St. Louis, MO). The chromatography for these fatty acids were carried out on a HP-5MS capillary column (30 m× 0.250 mm, 0.25 μm; Agilent Technologies, Santa Clara, CA), while GC-MS detection parameters for the tested fatty acid analytes were as described previously.[1] The data were acquired and processed using Agilent MassHunter WorkStation Quantitative analyses version 10.1 software (Agilent Technologies, Santa Clara, CA).

Intestinal bile acids were tested using the matched part of jejunum tissues using the LC-MS/MS as described previously.[7, 8] In brief, about 20-40 mg intestine tissues were homogenized in 500 μL acetonitrile containing 1 μM ursodeoxycholic acid (UDCA)-d_4 (U-002, Sigma, St. Louis, MO) as internal standard. Two hundred μL of supernatant were dried using speed vacuum and the dried samples were suspended in 400 μL 30% methanol (Methanol: water=3:7). The reconstituted samples were vortexed for 3 min, sonicated on ice water for 3 min and then vortexed for 30 s. All samples were then centrifuged at 15000 g for 10 min. One hundred and fifty μL supernatant were transferred for the LC-MS/MS injection. Bile acids were detected by a Waters Acquity I-Class UPLC/Synapt-G2Si QTOFMS system, as described previously. [7, 8]

The fat-soluble vitamins of serum were detected using LC-MS/MS similarly as described.[9] The standards including vitamin A (V-011-1 ML), vitamin D3 (739650-1ML), vitamin E (V-020-1 ML), D_6-25-hydroxyvitamin D3 (H-074-1ML) and hexane (34859-2.5 L) were purchased from Sigma (St. Louis, MO). Formic acid, methanol and acetonitrile were of HPLC grade from Fischer Scientific (Hampton, NH). Fifty μL of serum were mixed with 100 μL acetonitrile containing D_6-25-hydroxyvitamin D3 0.25 μM and vortexed for 1 min, followed by 10-min centrifugation at 14000 g at 4 °C. One hundred μL of supernatant were taken into the glass tube for LC-MS/MS injection. LC-MS/MS conditions are same as described[9], with exceptions noted below. The

samples were injected onto a Waters Acquity HSS PFP column (2.1× 100 mm) connected to a Waters I-Class UPLC system (Waters Corporation, Milford, MA). Eluting analytes were measured using a Waters Xevo-TQS MS/MS system monitoring the following MRM transitions: vitamin A (269.1>93.1), 25-Hydroxyvitamin D3 (383.2>365.2), vitamin E (430.7>165.0), and D6-25-hydroxyvitamin D3 (389.3>107.1).

Supporting Figures and Tables

Supporting figures

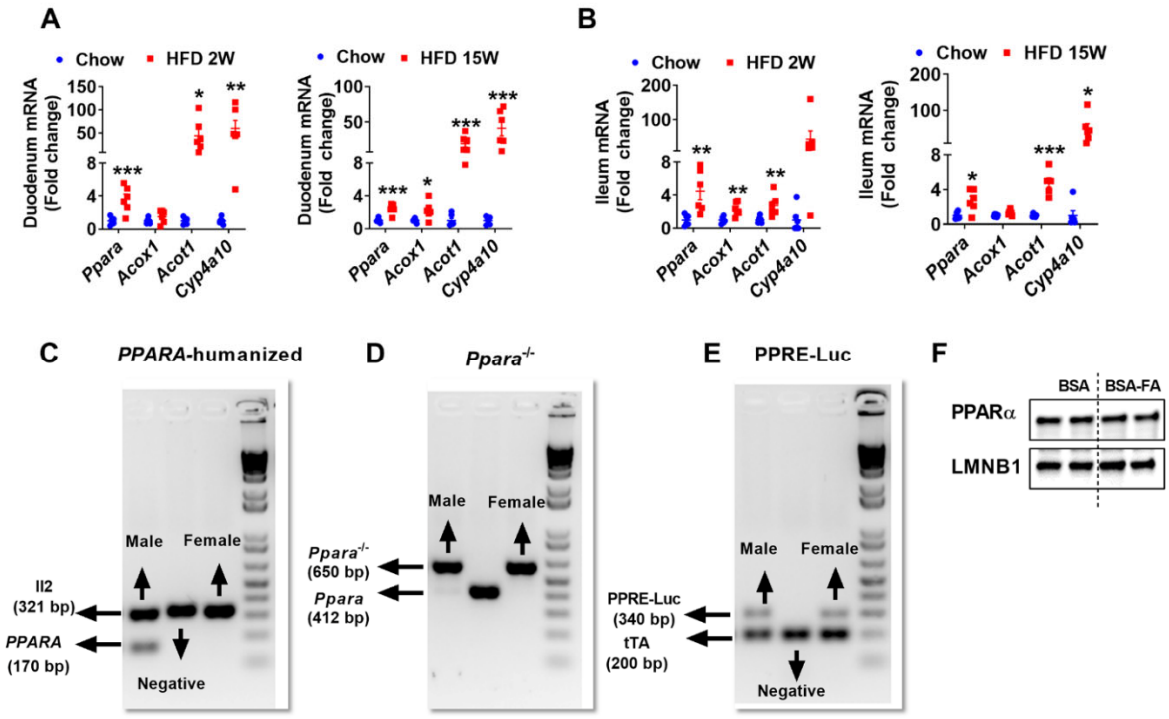

FIGURE S1 (related to FIGURE 1).

(A-B) mRNA expression of indicated genes in the mouse duodenum (A) and ileum (B) after HFD feeding for 2 weeks or 15 weeks, N=6.

(C-E) Genotyping of *PPARA*-humanized PPRE-Luc mouse strains. One male *PPARA*-humanized PPRE-Luc mouse on *Ppara*$^{-/-}$ background was bred with one female non-humanized PPRE-Luc mouse on *Ppara*$^{-/-}$ background. C, Humanized PPARA allele band with IL2 as internal standard. Genomic tail DNA from a wild-type mouse was used as a control. D, *Ppara*$^{-/-}$ allele band with mouse *Ppara* band as a control. E, PPRE-Luc allele band with tTA (oIMR8744 and 8745 from The Jackson Laboratory) as internal standard. C57bl/6N mice was used as the control.

(F) PPARα protein levels in FA-treated intestinal organoids isolated from *PPARA*-humanized mice.

*P<0.05; **P<0.01, ***P<0.001. FA, fatty acids.

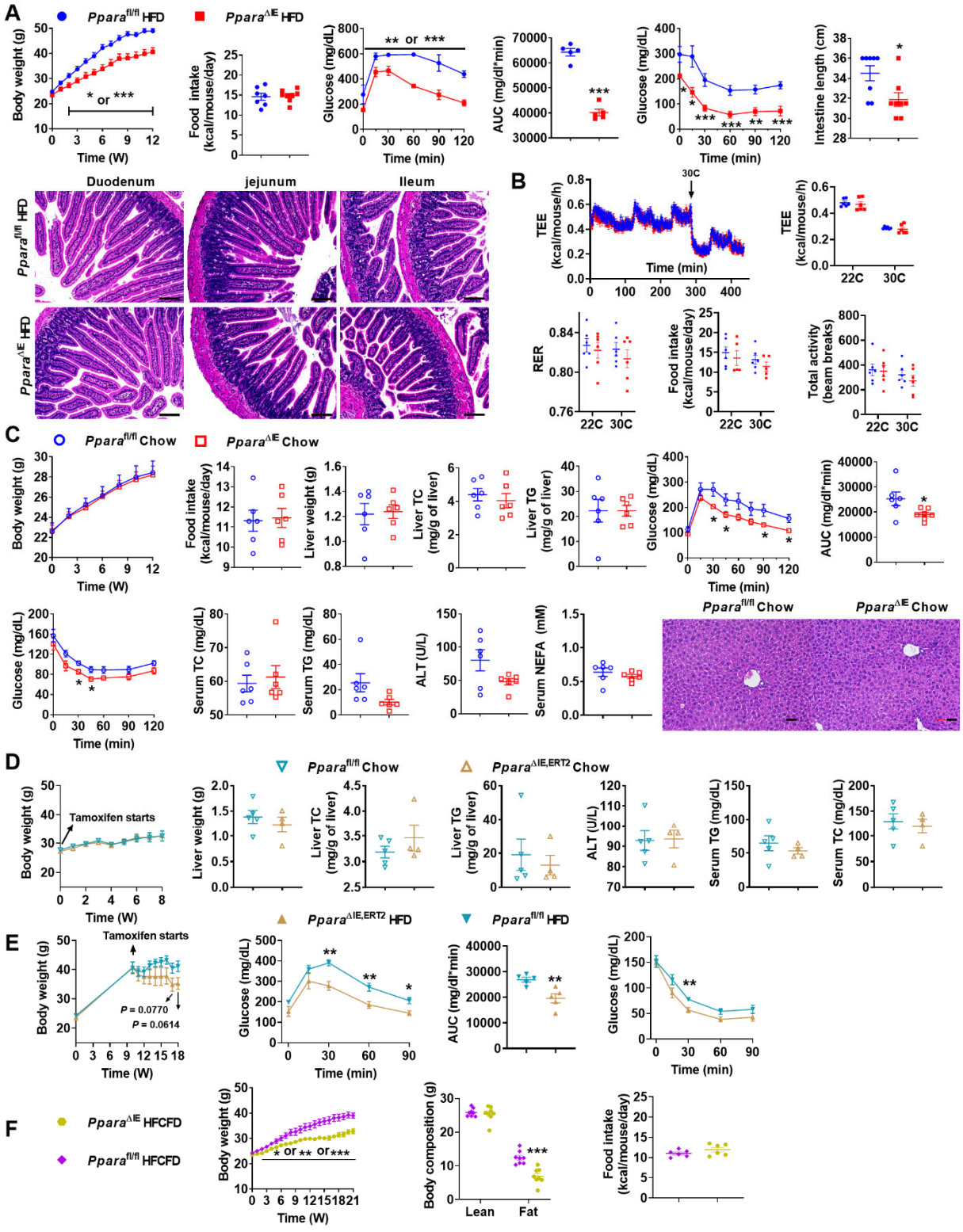
A
Ppara fl/fl HFD
Ppara ΔIE HFD
Body weight (g)
Time (W)
* or ***
Food intake (kcal/mouse/day)
Glucose (mg/dL)
** or ***
Time (min)
AUC (mg/dl*min)
Intestine length (cm)
Duodenum
jejunum
Ileum
B
TEE (kcal/mouse/h)
30C
22C
RER
Food intake (kcal/mouse/day)
Total activity (beam breaks)
C
Ppara fl/fl Chow
Ppara ΔIE Chow
Liver weight (g)
Liver TC (mg/g of liver)
Liver TG (mg/g of liver)
Serum TC (mg/dL)
Serum TG (mg/dL)
ALT (U/L)
Serum NEFA (mM)
D
Tamoxifen starts
Ppara ΔIE,ERT2 Chow
E
Ppara ΔIE,ERT2 HFD
Ppara fl/fl HFD
P = 0.0770
P = 0.0614
F
Ppara ΔIE HFCFD
Ppara fl/fl HFCFD
Body composition (g)
Lean
Fat

FIGURE S2 (related to FIGURE 2):

(A) *Ppara*$^{\Delta IE}$ mice and *Ppara*$^{fl/fl}$ mice were fed a HFD for 12 weeks. Body weight curve (N=8), food intake (N=7), glucose tolerance test (GTT) curve and area under the curve (AUC) (N=5), insulin tolerance test (ITT) curve (N=5), small intestine length (N=8), and histological analyses of duodenum, jejunum, and ileum; scale bar 100 μm.

(B) *Ppara*$^{\Delta IE}$ mice and *Ppara*$^{fl/fl}$ mice were fed a HFD for 2 weeks and energy expenditure tested at 22 °C (22C) or 30 °C (30C), N=6. Total energy expenditure curve (left upper) and statistical analyses (right upper), and respiratory exchange ratio (RER), food intake and total activity (bottom).

(C) Eight-week-old *Ppara*$^{\Delta IE}$ mice and *Ppara*$^{fl/fl}$ mice were fed a chow diet for 12 weeks. N=6. Body weight curve, food intake, liver weight, hepatic TC and TG, GTT curve and AUC, ITT curve, serum TC/TG/ALT/NEFA, and H&E staining of livers, scale bar 50 μm.

(D) Eight-week-old *Ppara*$^{\Delta IE,ERT2}$ mice and *Ppara*$^{fl/fl}$ mice were fed a chow diet for 10 weeks and then injected weekly with tamoxifen for another 8 weeks, N=4-5. Body weight curve, liver weight, hepatic TC and TG, serum ALT, TG and TC.

(E) Eight-week-old *Ppara*$^{\Delta IE,ERT2}$ mice and *Ppara*$^{fl/fl}$ mice were fed a HFD diet for 10 weeks and then injected weekly with tamoxifen for another 8 weeks; N=5. Body weight curve, GTT curve and AUC, ITT curve.

(F) *Ppara*$^{\Delta IE}$ mice and *Ppara*$^{fl/fl}$ mice were fed a HFCFD for 21 weeks. Body weight curve (N=8), body composition (N=8), food intake (N=6).

*P<0.05; **P<0.01, ***P<0.001.

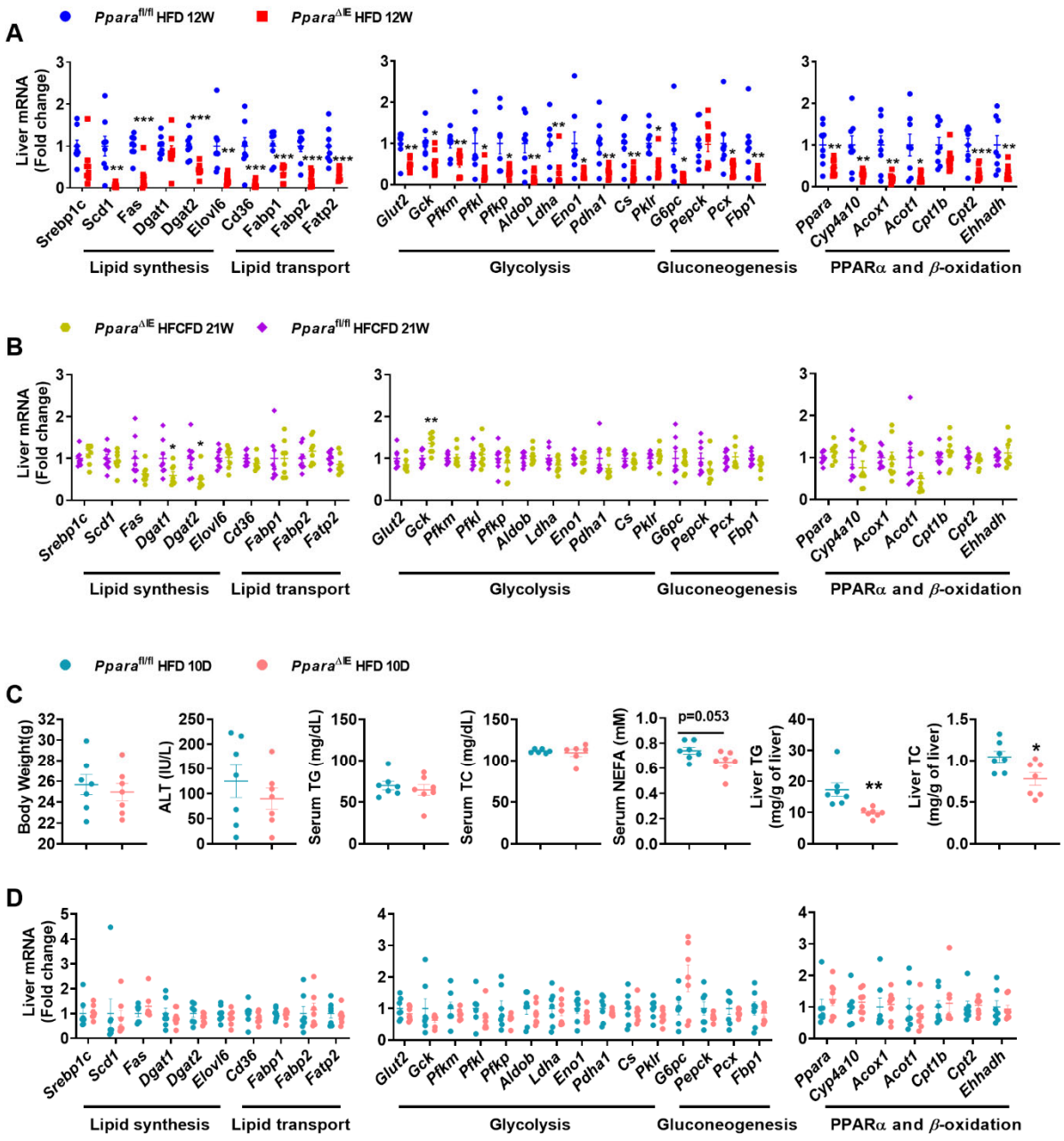

FIGURE S3 (related to FIGURE 2):

(A-B) Hepatic mRNA levels for genes involved in lipogenesis and transport, glycolysis and gluconeogenesis, *β*-oxidation and PPARα signaling in *Ppara*$^{\Delta IE}$ mice and *Ppara*$^{fl/fl}$ mice fed a HFD for 12 weeks (A) or fed a HFCFD for 21 weeks (B). N=8.

(C) *Ppara*$^{\Delta IE}$ mice and *Ppara*$^{fl/fl}$ mice were fed a HFD for 10 days. Body weight, serum ALT, TG, TC and NEFA, hepatic TC and TG levels. N=7.

(D) Hepatic mRNA levels for genes involved in lipogenesis and transport, glycolysis and gluconeogenesis, *β*-oxidation and PPARα signaling in *Ppara*$^{\Delta IE}$ mice and *Ppara*$^{fl/fl}$ mice fed a HFD for 10 days. N=7.

**P*<0.05; ***P*<0.01, ****P*<0.001.

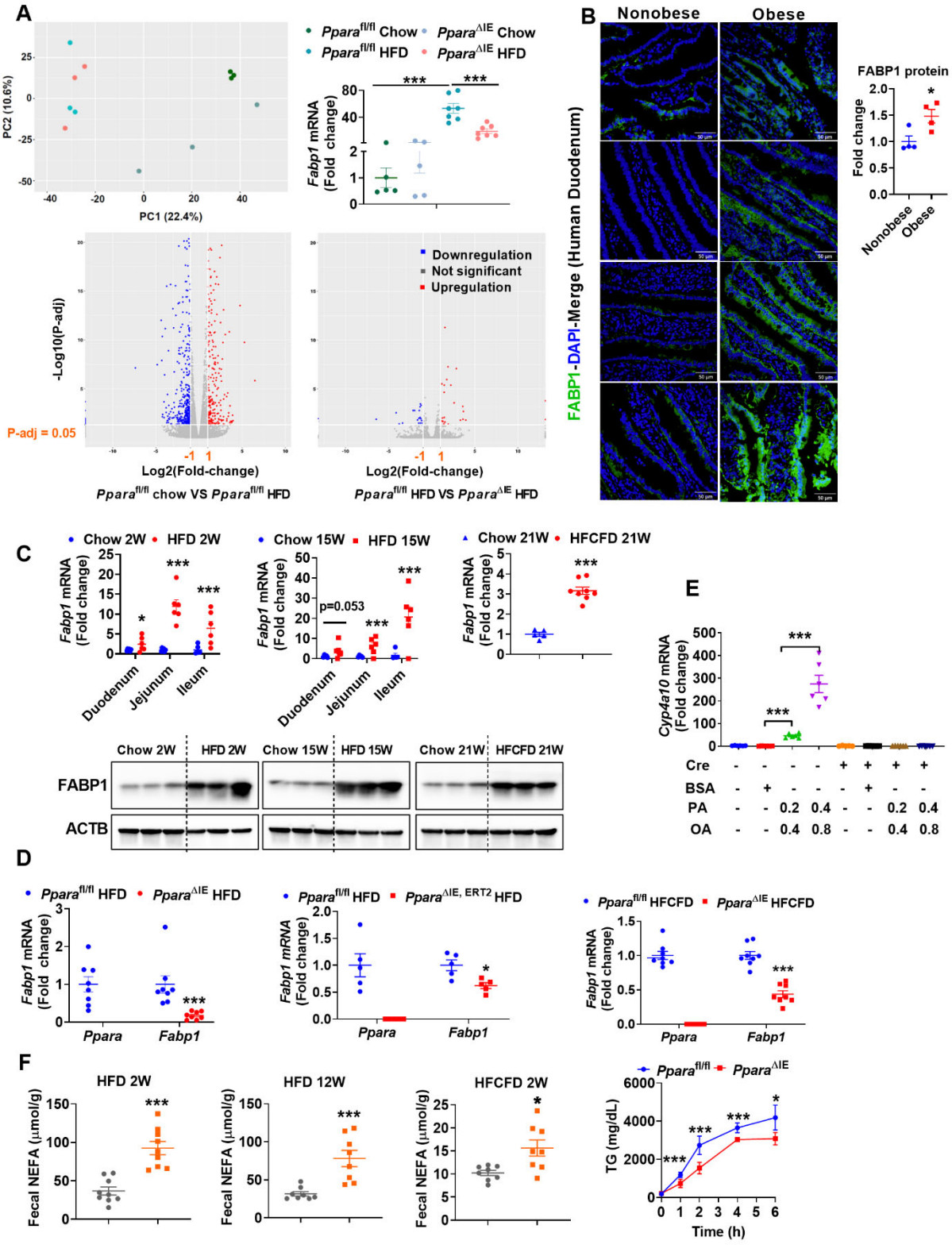
A
PC2 (10.6%)
PC1 (22.4%)
Ppara fl/fl Chow
Ppara ΔIE Chow
Ppara fl/fl HFD
Ppara ΔIE HFD
Fabp1 mRNA (Fold change)
-Log10(P-adj)
P-adj = 0.05
Log2(Fold-change)
Ppara fl/fl chow VS Ppara fl/fl HFD
Downregulation
Not significant
Upregulation
Ppara fl/fl HFD VS Ppara ΔIE HFD
B
Nonobese
Obese
FABP1-DAPI-Merge (Human Duodenum)
FABP1 protein
Fold change
C
Chow 2W
HFD 2W
Chow 15W
HFD 15W
Chow 21W
HFCFD 21W
Duodenum
Jejunum
Ileum
p=0.053
FABP1
ACTB
D
Ppara
Fabp1
E
Cyp4a10 mRNA (Fold change)
Cre
BSA
PA
OA
F
HFD 2W
HFD 12W
HFCFD 2W
Fecal NEFA (μmol/g)
TG (mg/dL)
Time (h)

FIGURE S4 (related to FIGURE 3):

(A) PCA plot, Volcano plot, qPCR quantitation of *Fabp1* mRNA levels in the small intestines from the batch of mice same used for RNAseq analyses (N=5-7, left).

(B) Immunofluorescence images of human duodenum from nonobese (BMI<26) and obese (BMI≥26) humans (N=4, left), and quantitation of FABP1 immunofluorescence (N=4, right).

(C) *Fabp1* mRNA levels (N=6-8) and FABP1 protein levels in the small intestines of C57BL/6N mice fed a chow or HFD for 2 or 15 weeks or HFCFD for 21 weeks.

(D) qPCR analyses of *Ppara* and *Fabp1* mRNA in 12-week HFD-fed mice (left) or 16-week HFD-fed $Ppara^{\Delta IE,\ ERT2}$ mice dosed with tamoxifen for the last 8 weeks (middle) or 21-week HFCFD-fed mice (right), N=5=8.

(E) *Cyp4a10* mRNA levels of fatty acids-treated organoids, N=6.

(F) Fecal NEFA levels of 2-week-HFD-fed mice, 12-week-HFD-fed mice and 2W-HFCFD-fed mice (N=8-9), oral postprandial TG absorption test in HFD-fed $Ppara^{fl/fl}$ and $Ppara^{\Delta IE}$ mice (N=5). **P*<0.05; ***P*<0.01, ****P*<0.001.

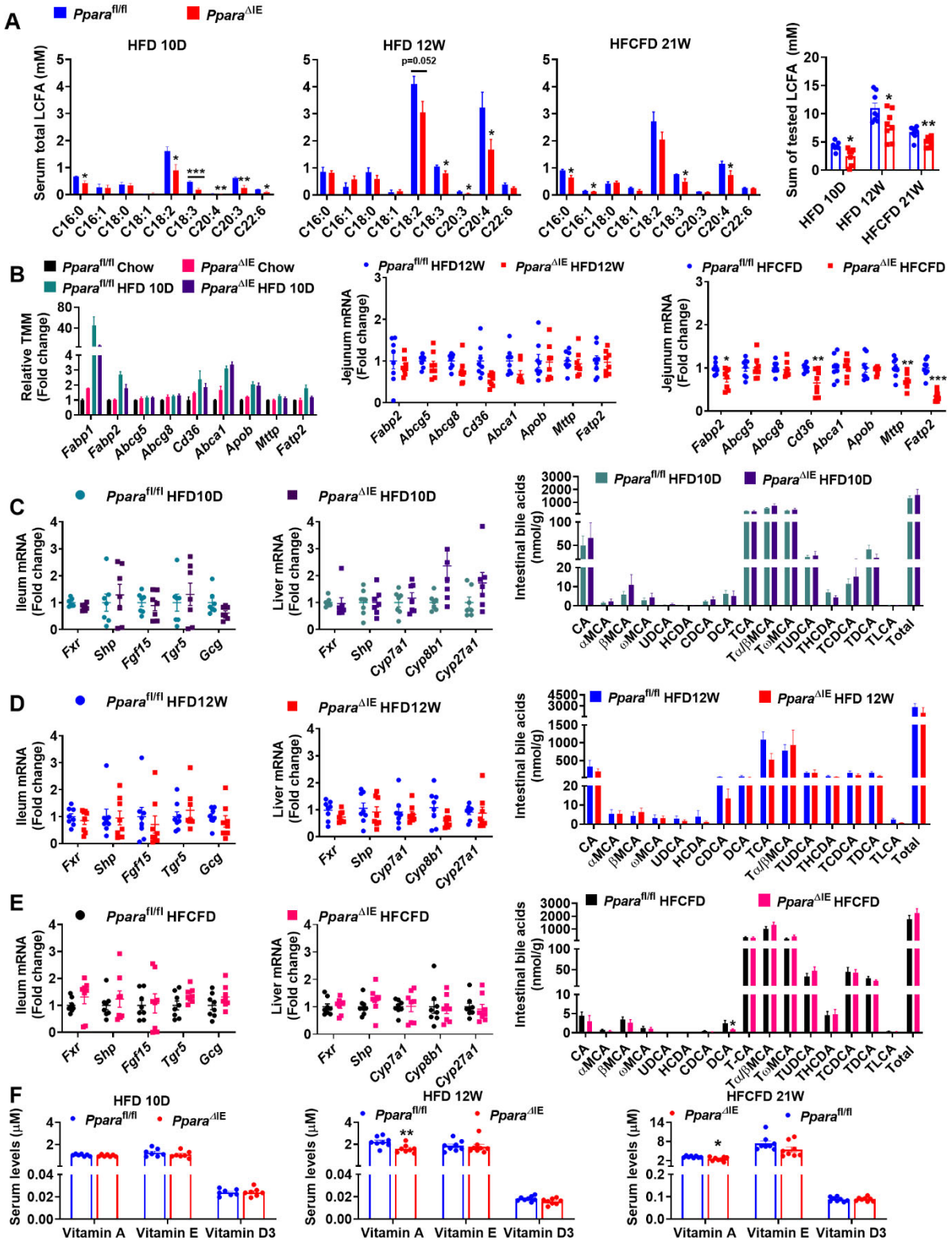
A
Ppara fl/fl
Ppara ΔIE
HFD 10D
HFD 12W
p=0.052
HFCFD 21W
Serum total LCFA (mM)
Sum of tested LCFA (mM)
C16:0
C16:1
C18:0
C18:1
C18:2
C18:3
C20:3
C20:4
C22:6
HFD 10D
HFD 12W
HFCFD 21W
B
Ppara fl/fl Chow
Ppara ΔIE Chow
Ppara fl/fl HFD 10D
Ppara ΔIE HFD 10D
Relative TMM (Fold change)
Fabp1
Fabp2
Abcg5
Abcg8
Cd36
Abca1
Apob
Mttp
Fatp2
Ppara fl/fl HFD12W
Ppara ΔIE HFD12W
Jejunum mRNA (Fold change)
Ppara fl/fl HFCFD
Ppara ΔIE HFCFD
C
Ppara fl/fl HFD10D
Ppara ΔIE HFD10D
Ileum mRNA (Fold change)
Liver mRNA (Fold change)
Fxr
Shp
Fgf15
Tgr5
Gcg
Cyp7a1
Cyp8b1
Cyp27a1
Intestinal bile acids (nmol/g)
CA
αMCA
βMCA
ωMCA
UDCA
HCDA
CDCA
DCA
TCA
TαβMCA
TωMCA
TUDCA
THCDA
TCDCA
TDCA
TLCA
Total
D
Ppara fl/fl HFD12W
Ppara ΔIE HFD 12W
E
Ppara fl/fl HFCFD
Ppara ΔIE HFCFD
T-CA
F
HFD 10D
HFD 12W
HFCFD 21W
Serum levels (μM)
Vitamin A
Vitamin E
Vitamin D3

FIGURE S5 (related to FIGURE 3):

(A) Serum LCFA profiles (left) and serum total LCFA levels (a sum of the tested LCFAs, right) of *Ppara*$^{fl/fl}$ mice and *Ppara*$^{\Delta IE}$ mice fed a HFD for 10 days (N=7), 12 weeks (N=8) or fed a HFCFD for 21 weeks (N=8).

(B) Relative TMM levels of common genes involved in intestinal lipid transport derived from RNAseq analyses for 10-day HFD or chow-fed mice (left, N=7), jejunum mRNA levels of genes involved in intestinal lipid transport for 12-week HFD-fed mice (middle, N=8), and jejunum mRNA levels of genes involved in intestinal lipid transport for 21-week HFCFD-fed mice (right, N=8).

(C) Relative mRNA levels of genes involved in FXR and/or TGR5 pathways in the ileum (left) and liver (middle), as well as the intestinal bile acid profiles for mice fed a HFD for 10 days. N=7.

(D) Relative mRNA levels of genes involved in FXR and/or TGR5 pathways in the ileum (left) and liver (middle), as well as the intestinal bile acid profiles for mice fed a HFD for 12 weeks. N=8.

(E) Relative mRNA levels of genes involved in FXR and/or TGR5 pathways in the ileum (left) and liver (middle), as well as the intestinal bile acid profiles for mice fed a HFCFD for 21 weeks. N=8.

(F) Serum levels of fat-soluble vitamins including vitamin A, E and D3 in *Ppara*$^{fl/fl}$ mice and *Ppara*$^{\Delta IE}$ mice fed a HFD for 10 days (left), 12 weeks (middle) or a HFCFD for 21 weeks (right). **P*<0.05; ***P*<0.01, ****P*<0.001. LCFA, long-chain fatty acid.

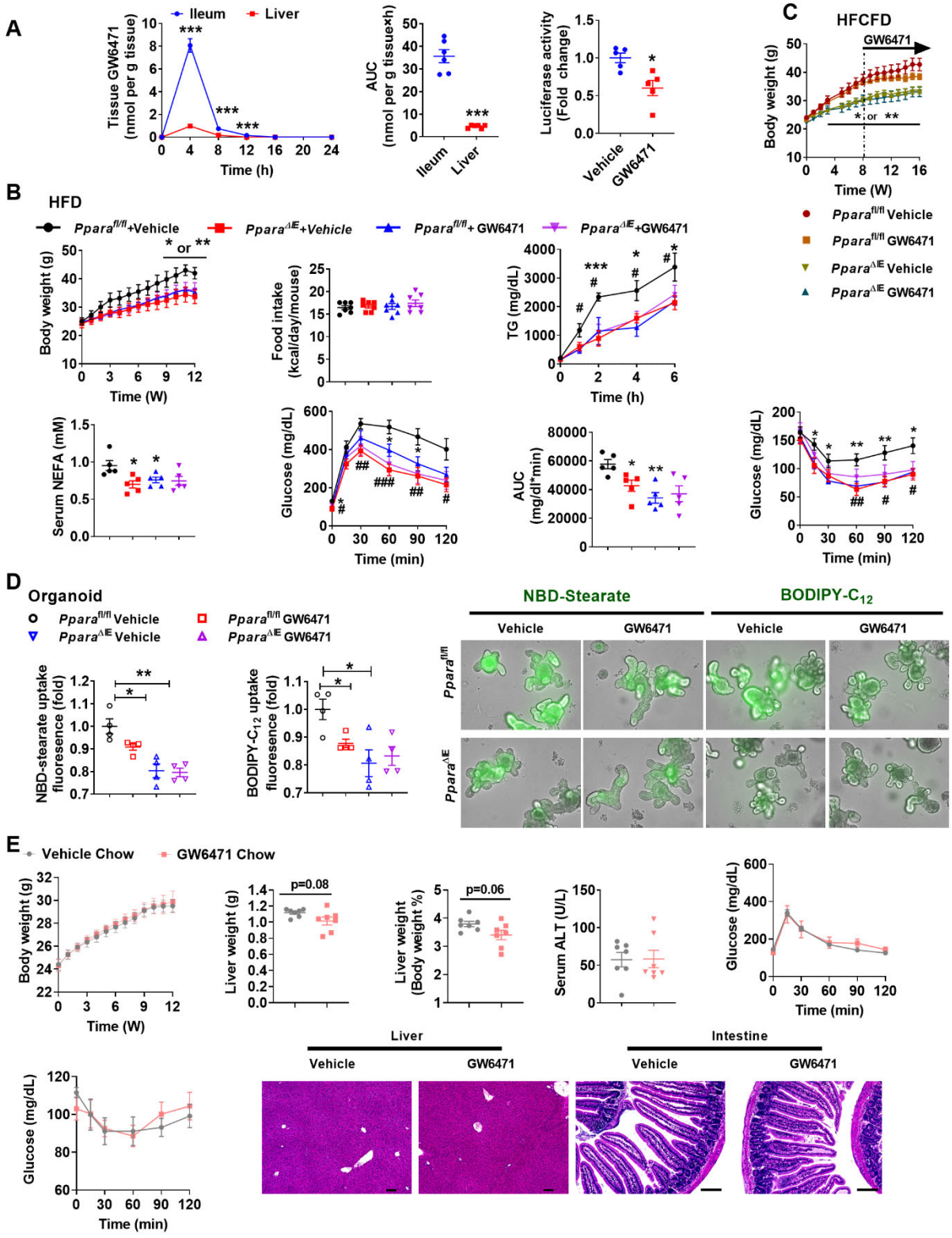
A
Ileum
Liver
Tissue GW6471 (nmol per g tissue)
Time (h)
AUC (nmol per g tissue×h)
Luciferase activity (Fold change)
Vehicle
GW6471
C
HFCFD
GW6471
Body weight (g)
Time (W)
B
HFD
Ppara^fl/fl+Vehicle
Ppara^ΔIE+Vehicle
Ppara^fl/fl+ GW6471
Ppara^ΔIE+GW6471
Food intake (kcal/day/mouse)
TG (mg/dL)
Serum NEFA (mM)
Glucose (mg/dL)
AUC (mg/dl*min)
D
Organoid
NBD-Stearate
BODIPY-C12
NBD-stearate uptake fluoresence (fold)
BODIPY-C12 uptake fluoresence (fold)
E
Vehicle Chow
GW6471 Chow
p=0.08
p=0.06
Liver weight (g)
Liver weight (Body weight %)
Serum ALT (U/L)
Liver
Intestine

FIGURE S6 (related to FIGURE 4):

(A) Pharmacokinetic distribution of GW6471 in liver and intestine, AUC of GW6471 in liver and intestine (N=6) and HFD-fed PPRE-Luc mice were treated with GW6471 at 10 mg/kg via gavage once daily for 1 week and then intestines collected to evaluate the luciferase activity (N=5).

(B), *Ppara*$^{fl/fl}$ mice and *Ppara*$^{\Delta IE}$ mice were fed a HFD for 12 weeks and dosed with GW6471 at 10 mg/kg via gavage once daily until the end of experiments, N=5 unless otherwise indicated. Body weight curve, food intake (N=7), serum NEFA levels, oral postprandial TG absorption test of GW6471-treated *Ppara*$^{fl/fl}$ mice and *Ppara*$^{\Delta IE}$ mice fed a HFD for 2 weeks (N=5), GTT curve and AUC, ITT curve. (C) Body weight curve of HFCFD-fed mice. N=5-8.

(D) Quantitation (N=4) (left) and representative images (right) of NBD-stearate and BODIPY-C_{12} uptake in intestinal organoids isolated from *Ppara*$^{fl/fl}$ and *Ppara*$^{\Delta IE}$ mice and treated with control DMSO or 6 μM GW6471 for 24 h.

(E) C57BL/6N mice were treated with vehicle or GW6471 at 10 mg/kg by gavage once daily and fed a chow diet for 12 weeks. N=6. Body weight curve, liver weight, liver index, serum ALT levels, GTT curve, ITT curve, and representative H&E staining for liver and small intestine (scale bar 100 μm).

**P*<0.05; ***P*<0.01, ****P*<0.001. For S4B, postprandial TG and GTT/ITT curve, **P*<0.05; ***P*<0.01 indicate comparisons between *Ppara*$^{fl/fl}$ + Vehicle and *Ppara*$^{fl/fl}$ + GW6471 groups, while $^{\#}P$<0.05, $^{\#\#}P$<0.01, $^{\#\#\#}P$<0.001 indicate comparisons between *Ppara*$^{\Delta IE}$ + Vehicle and *Ppara*$^{fl/fl}$ + Vehicle groups.

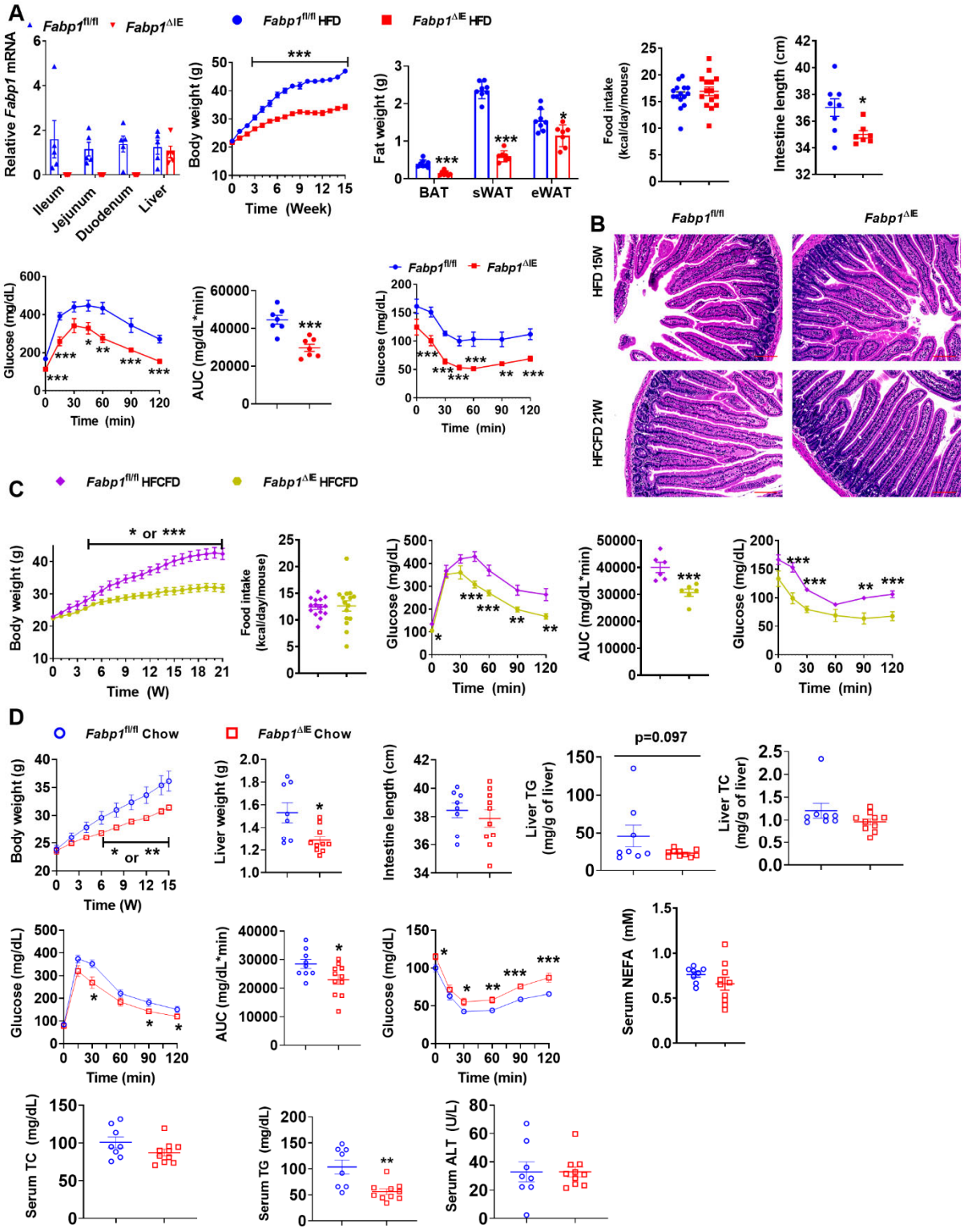
A
Fabp1fl/fl
Fabp1ΔIE
Relative Fabp1 mRNA
Ileum
Jejunum
Duodenum
Liver
Fabp1fl/fl HFD
Fabp1ΔIE HFD
Body weight (g)
Time (Week)
Fat weight (g)
BAT
sWAT
eWAT
Food intake (kcal/day/mouse)
Intestine length (cm)
Glucose (mg/dL)
Time (min)
AUC (mg/dL*min)
B
HFD 15W
HFCFD 21W
C
Fabp1fl/fl HFCFD
Fabp1ΔIE HFCFD
Time (W)
D
Fabp1fl/fl Chow
Fabp1ΔIE Chow
Liver weight (g)
Liver TG (mg/g of liver)
p=0.097
Liver TC (mg/g of liver)
Serum NEFA (mM)
Serum TC (mg/dL)
Serum TG (mg/dL)
Serum ALT (U/L)

FIGURE S7 (related to FIGURE 5):

(A) mRNA expression of *Fabp1* in indicated tissues (N=5, upper left). *Fabp1*$^{\Delta IE}$ and *Fabp1*$^{fl/fl}$ mice were fed a HFD for 15 weeks (N=7-8 unless otherwise indicated). Body weight curve, fat mass, food intake on a HFD for the first week (N=15), small intestine length, GTT curve and AUC, ITT curve.

(B) H&E staining of duodenum from 15-week HFD-fed mice (upper) and 21-week HFCFD-fed mice (bottom), scale bar 100 μm.

(C) Body weight curve on a HFCFD (N=6), food intake on a HFCFD (N=15), GTT curve and AUC on a HFCFD (N=6), and ITT curve (N=6).

(D) *Fabp1*$^{\Delta IE}$ and *Fabp1*$^{fl/fl}$ mice were fed a chow diet for 15 weeks. N=9-11. Body weight curve, liver weight, small intestine length, hepatic TG and TC, GTT curve and AUC, ITT curve, serum ATL, TC, TG and NEFA levels.

**P*<0.05; ***P*<0.01, ****P*<0.001. BAT, brown adipose tissue. sWAT, subcutaneous tissue. eWAT, epididymal white adipose.

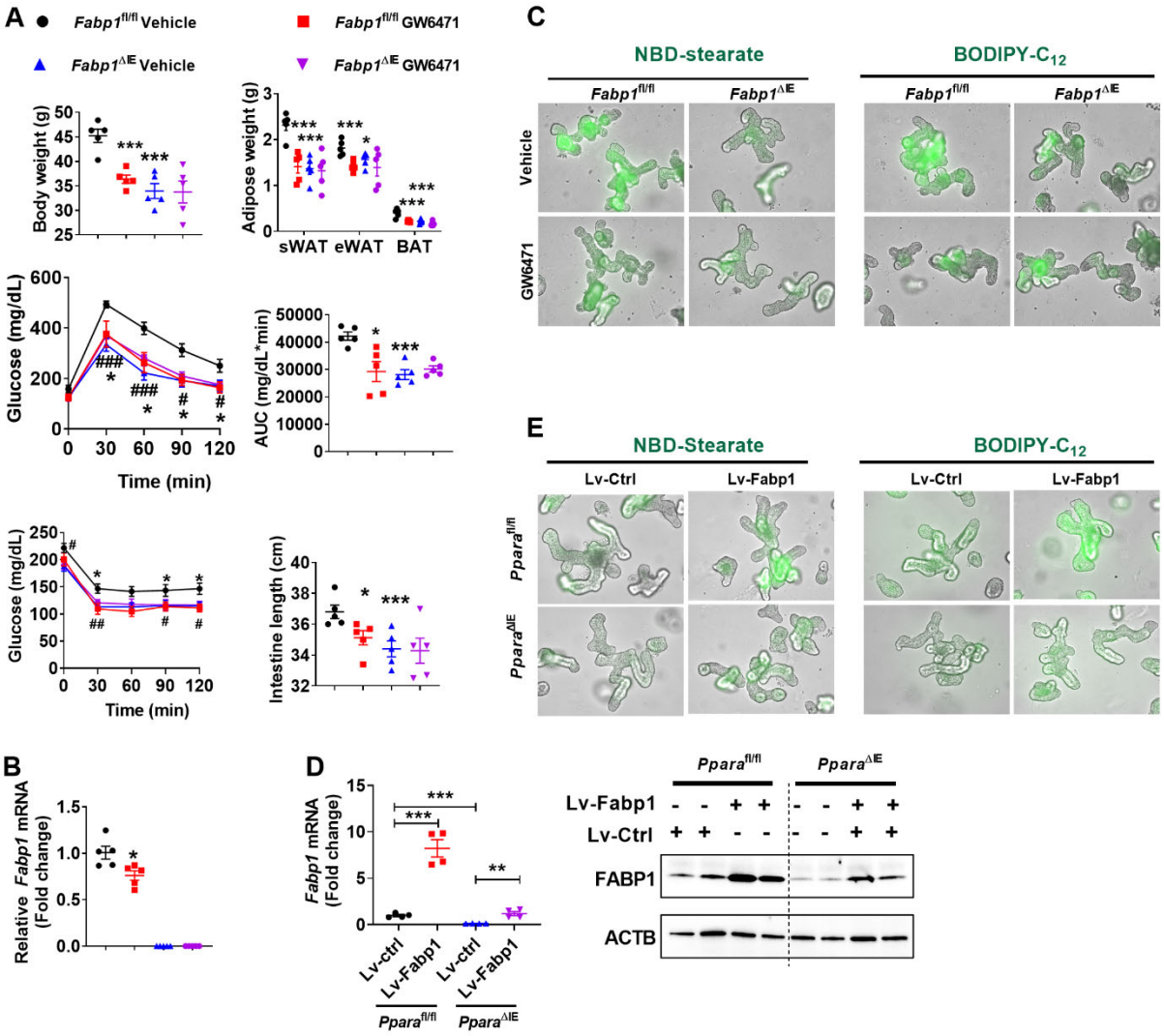

FIGURE S8 (related to FIGURE 6):

(A) *Fabp1*$^{\Delta IE}$ mice and *Fabp1*$^{fl/fl}$ mice were first fed a HFD for 8 weeks and then treated with GW6471 at 10 mg/kg or control vehicle once daily for another 8 weeks while maintained on a HFD feeding, N=5. Body weight at the final day, fat mass, GTT curve and AUC, ITT curve, and small intestine length.

(B) Intestinal *Fabp1* mRNA expression. N=5.

(C) Representative images of NBD-stearate (left) and BODIPY-C_{12} (right) in Vehicle or GW6471-treated organoids isolated from *Fabp1*$^{\Delta IE}$ or *Fabp1*$^{fl/fl}$ mice.

(D) *Fabp1* mRNA (left) (N=4) and FABP1 protein (right) levels in intestinal organoids infected with control lentivirus (Lv-ctrl) or FABP1-overexpressing lentivirus (Lv-Fabp1).

(E) Representative images of NBD-stearate (left) or BODIPY-C_{12} uptake (right) in intestinal organoids infected with control lentivirus (Lv-ctrl) or FABP1-overexpressing lentivirus (Lv-Fabp1).

**P*<0.05; ***P*<0.01, ****P*<0.005 versus each control. For GTT and ITT curve, **P*<0.05, ***P*<0.01, ****P*<0.005 indicate comparisons between *Fabp1*$^{fl/fl}$ + Vehicle and *Fabp1*$^{fl/fl}$ + GW6471 groups, while $^{\#}P$<0.05, $^{\#\#}P$<0.01, $^{\#\#\#}P$<0.001 indicate comparisons between *Fabp1*$^{\Delta IE}$ + Vehicle and *Fabp1*$^{fl/fl}$ + Vehicle groups)

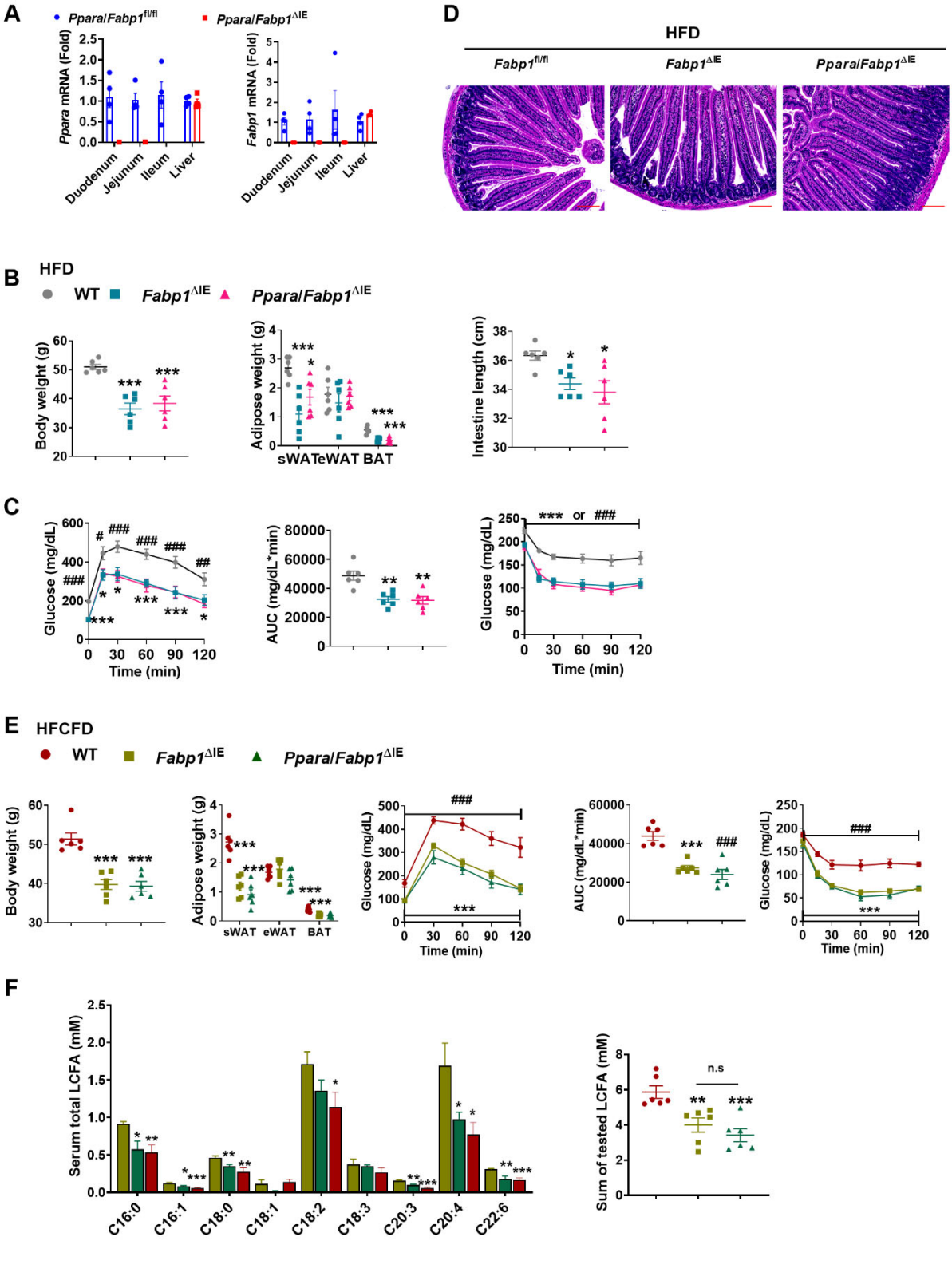
A
Ppara/Fabp1fl/fl
Ppara/Fabp1ΔIE
Ppara mRNA (Fold)
Fabp1 mRNA (Fold)
Duodenum
Jejunum
Ileum
Liver
D
HFD
Fabp1fl/fl
Fabp1ΔIE
Ppara/Fabp1ΔIE
B
HFD
WT
Fabp1ΔIE
Ppara/Fabp1ΔIE
Body weight (g)
Adipose weight (g)
sWAT
eWAT
BAT
Intestine length (cm)
C
Glucose (mg/dL)
Time (min)
AUC (mg/dL*min)
*** or ###
E
HFCFD
WT
Fabp1ΔIE
Ppara/Fabp1ΔIE
Body weight (g)
Adipose weight (g)
sWAT
eWAT
BAT
Glucose (mg/dL)
Time (min)
AUC (mg/dL*min)
F
Serum total LCFA (mM)
C16:0
C16:1
C18:0
C18:1
C18:2
C18:3
C20:3
C20:4
C22:6
Sum of tested LCFA (mM)
n.s

FIGURE S9 (related to FIGURE 7):

(A) mRNA expression of *Ppara* and *Fabp1* in duodenum, jejunum, ileum and liver (N=4).

(B-C) *Fabp1*/*Ppara*$^{\Delta IE}$ mice, *Fabp1*$^{\Delta IE}$ mice, and *Fabp1*$^{fl/fl}$ mice were fed a HFD for 15 weeks. Body weight curve, fat mass, small intestine length (B) and GTT curve and AUC, ITT curve (C). N=6.

(D) H&E staining of small intestines from 15-week HFD-fed mice, scale bar 100 μm.

(E) *Fabp1*/*Ppara*$^{\Delta IE}$ mice, *Fabp1*$^{\Delta IE}$ mice, and *Fabp1*$^{fl/fl}$ mice were fed a HFCFD for 21 weeks. Body weight at the final day, fat mass, GTT curve and AUC, ITT curve. N=6.

(F) Serum LCFA profiles detected by GC-MS (left) and total serum LCFA levels (a sum of the tested LCFAs, right). N=8.

**P*<0.05; ***P*<0.01, ****P*<0.001 compared with control group. For GTT and ITT curve, **P*<0.05, ***P*<0.01, ****P*<0.001 indicates comparison between *Fabp1*$^{\Delta IE}$ and *Fabp1*$^{fl/fl}$ groups; $^{\#}$*P*<0.05, $^{\#\#}$*P*<0.01, $^{\#\#}$*P*<0.001 indicate comparison between WT and *Ppara*/*Fabp1*$^{\Delta IE}$ groups. WT, wild-type. LCFA, long-chain fatty acid.

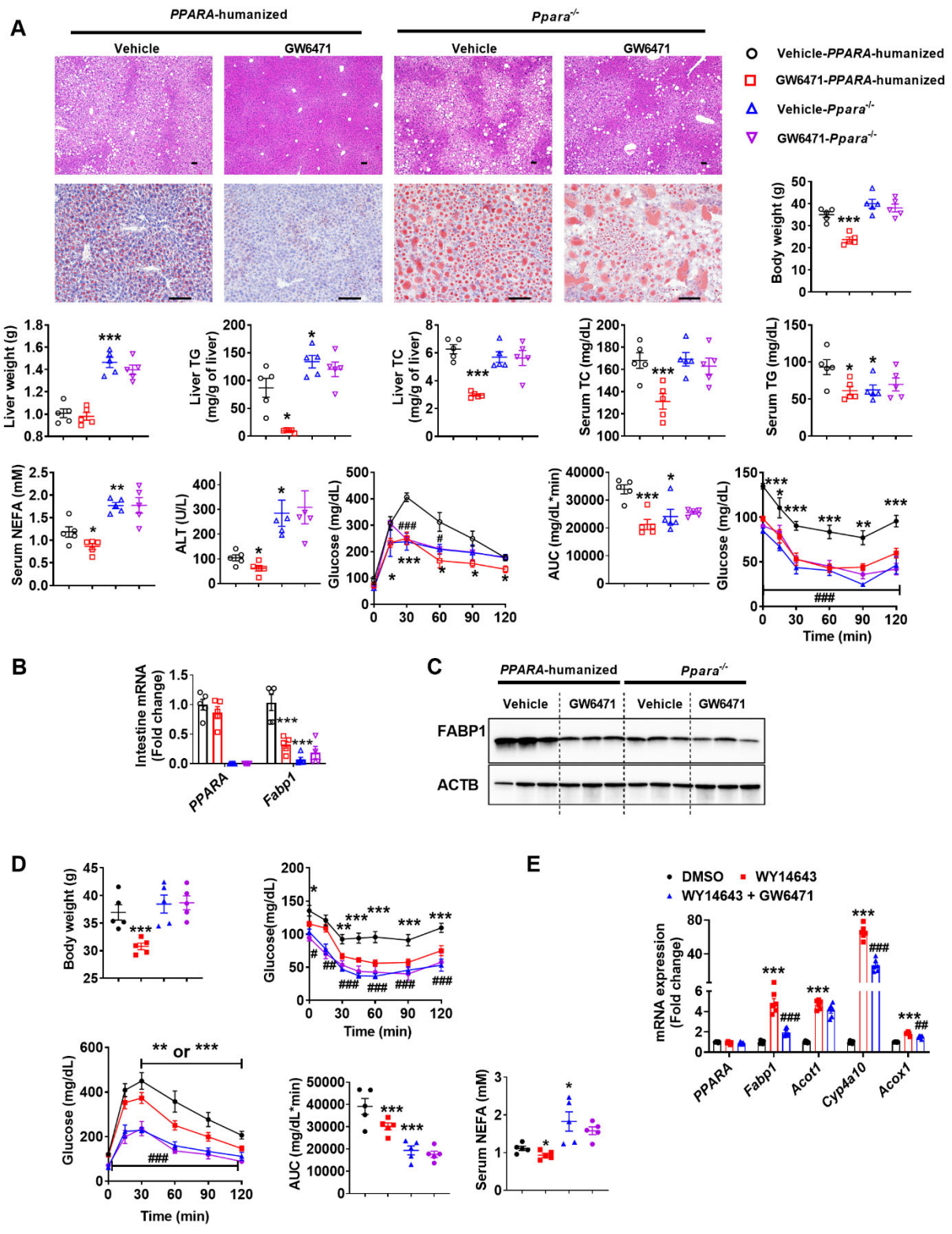
A
PPARA-humanized
Ppara-/-
Vehicle
GW6471
Vehicle
GW6471
Vehicle-PPARA-humanized
GW6471-PPARA-humanized
Vehicle-Ppara-/-
GW6471-Ppara-/-
Body weight (g)
Liver weight (g)
Liver TG (mg/g of liver)
Liver TC (mg/g of liver)
Serum TC (mg/dL)
Serum TG (mg/dL)
Serum NEFA (mM)
ALT (U/L)
Glucose (mg/dL)
AUC (mg/dL*min)
Glucose (mg/dL)
Time (min)
B
Intestine mRNA (Fold change)
PPARA
Fabp1
C
PPARA-humanized
Ppara-/-
Vehicle
GW6471
Vehicle
GW6471
FABP1
ACTB
D
Body weight (g)
Glucose(mg/dL)
Time (min)
Glucose (mg/dL)
** or ***
Time (min)
AUC (mg/dL*min)
Serum NEFA (mM)
E
DMSO
WY14643
WY14643 + GW6471
mRNA expression (Fold change)
PPARA
Fabp1
Acot1
Cyp4a10
Acox1

FIGURE S10 (related to FIGURE 8):

(A) *PPARA*-humanized mice and *Ppara*$^{-/-}$ mice were fed a HFD and treated with vehicle or GW6471 for 12 weeks (N=5). Representative H&E staining (scale bar 50 μm) and oil red O staining (scale bar 100 μm), body weight at the final day, liver weight, hepatic TG and TC, serum TC, TG, NEFA and ALT, GTT curve and AUC, and ITT curve.

(B) qPCR analyses of *PPARA* and *Fabp1* in the intestine. N=5.

(C) Intestinal FABP1 protein levels.

(D) *PPARA*-humanized mice and *Ppara*$^{-/-}$ mice were first fed a HFD for 8 weeks and then treated with GW6471 for another 8 weeks while maintained on HFD feeding, N=5. Body weights at the final day, GTT curve and AUC, ITT curve and serum NEFA levels. N=5.

(E) qPCR analyses of *PPARA* mRNA and its target gene mRNAs in organoids. N=3.

**P*<0.05, ***P*<0.01, ****P*<0.001 compared with Vehicle-*PPARA*-humanized group. For GTT and ITT curve, **P*<0.05, ***P*<0.01, ****P*<0.001 indicates comparison between Vehicle-*PPARA*-humanized group and GW6471-*PPARA*-humanized group. $^{\#}P$<0.05, $^{\#\#}P$<0.01, $^{\#\#\#}P$<0.001 indicates comparison between Vehicle-*PPARA*-humanized and Vehicle-*Ppara*$^{-/-}$.

Supporting Tables

Table S1. Patients' information for human cohort 1

	Non-obese	Obese
Gender, *%*		
Male	43% (3/7)	57% (4/7)
Female	57% (4/7)	43% (3/7)
Age, *year*		
Mean (sem)	57.6 (3.78)	45.1 (4.88)
Range	44-70	31-61
Body mass index, kg/m^2		
Mean (sem)	22.0 (0.82)	28.5 (1.81) ***
Range	19.1-25.6	26.7-31.6
ALT, *U/L*		
Mean (sem)	16.9 (2.52)	43.9 (6.42) **
Range	8.0-27	14-61

*P=0.0021 (ALT), ***P<0.0001 (Body mass index) versus nonobese individuals, by two-tailed Student's t-test. BMI≥26.0, obese; BMI<26.0, nonobese. BMI, Body mass index.

Table S2. Patients' information for human cohort 2

Gender	Age, *year*	BMI, kg/m^2	Group
Male	47	22.6	Nonobese
Male	64	22.5	Nonobese
Male	59	22.4	Nonobese
Male	48	20.8	Nonobese
Male	64	28.3	Obese
Male	61	29.1	Obese
Male	46	29.2	Obese
Male	60	30.4	Obese

BMI, Body mass index. BMI≥26.0, obese; BMI<26.0, nonobese.

Table S3. Patients' information for human cohort 3

Gender	Age, *year*	BMI, kg/m^2	Group	Tissue
Male	59	23.1	Nonobese	Ileum
Female	66	22.5	Nonobese	Ileum
Female	40	26.5	Obese	Ileum
Male	52	26.2	Obese	Ileum
Female	42	27.9	Obese	Ileum
Male	51	29.4	Obese	Ileum

BMI, Body mass index. BMI≥26.0, obese; BMI<26.0, nonobese.

Table S4. Primers for qPCR and ChIP

Human primers	Forward sequence	Reverse sequence
PPARA	TCATCACGGACACGCTTTCA	TCAATGCTCCACTGGGAGAC
FABP1	GTGTCGGAAATCGTGCAGAAT	GACTTTCTCCCCTGTCATTGTC
ACTB	CATGTACGTTGCTATCCAGGC	CTCCTTAATGTCACGCACGAT
GAPDH	GGAGCGAGATCCCTCCAAAAT	GGCTGTTGTCATACTTCTCATGG
ChIP primers		
Fabp1	CGTTGACCATTGCTCTCAGG	GGTCACCCACTGTTGCCTAT
Fscn2	CATCCAGGAGCCACTGAAAT	GACATGGACGCTACCTGCTC
Mouse primers		
Srebp1c	GGAGCCATGGATTGCACATT	GCTTCCAGAGAGGAGGCCAG
Scd1	TTCTTGCGATACACTCTGGTGC	CGGGATTGAATGTTCTTGTCGT
Fas	AAGTTGCCCGAGTCAGAGAACC	ATCCATAGAGCCCAGCCTTCCAT
Dgat1	GACGGCTACTGGGATCTGA	TCACCACACACCAATTCAGG
Dgat2	CGCAGCGAAAACAAGAATAA	GAAGATGTCTTGGAGGGCTG
Elovl6	GAAAAGCAGTTCAACGAGAACG	AGATGCCGACCACCAAAGATA
Cd36	AGATGACGTGGCAAAGAACAG	CCTTGGCTAGATAACGAACTCTG
Fabp2	GTGGAAAGTAGACCGGAACGA	CCATCCTGTGTGATTGTCAGTT
Fatp2	TCCTCCAAGATGTGCGGTACT	TAGGTGAGCGTCTCGTCTCG
Mttp	CCCACTCAGGCAATTCGAGA	TGATGGAGGGGGAGTTCACA
Abca1	TTGTCCGGACGCTGTTAGAC	ACAGAGCCATTTGGGGACTG
Apob	GGTGTATGGCTTCAACCCTGA	GCTTGAGTTCGTACCTGGACA
Abcg5	CGTGGCGGACCAAATGATTG	TAGCATCATGACCTTGGGGT
Abcg8	CTGATGACATCTGGCACCCC	AAGTCCACGTAGAAGTCCGC
Glut2	TCCCTTGGTTCATGGTTGCT	CCCAAGGAAGTCCGCAATGT
Gck	TAGCGGGGGTCATAAATCGC	CTCCTTGAAGCTCGGGTGC
Pfkm	AGCATTCATACCTTGGGCAT	CCATGAAGAGCATCATGCAG
Pfkl	ACGTGAAGGATCTGGTGGTTC	ATTCGGTCGAAGGCTGAAGG
Pfkp	TAAAGTACACTTTGGCCCCC	AGCTATCGGTGTCCTGACCA
Pklr	CTTCCCCTTGCTCTACCGTG	AGCCACGAAGCTTTCCACTT
Aldob	GCTGGGCAATTTCAGAGAGC	GAGGACTCTTCCCCTTTGCT
Ldha	GTGCCCAGTTCTGGGTTAAG	CTGGGTCCTGGGAGAACAT
Eno1	GAGGTCGATCTGTACACCGC	GAGACACCCTTCCCCATGAA
Pdha1	TCATTTGCAAAATTACGGGA	AAGATGCTTGCCGCTGTATC
Cs	GGACAATTTTCCAACCAATCTGC	TCGGTTCATTCCCTCTGCATA
G6pc	GTCTTGTCAGGCATTGCTGTG	GAATCCAAGCGCGAAACCAA
Pepck	ATGAAAGGCCGCACCATGTA	GGGCGAGTCTGTCAGTTCAA
Pcx	GTGCATTAAGGACATGGCGG	TGGGTATGGATGTGCAGTGG
Fbp1	GCACAGCTCTATGGTATCGCT	CACAGGTAGCGTAGGACGAC

Ppara	CCCTGAACATCGAGTGTCGAA	TTCGCCGAAAGAAGCCCTTA
Fabp1	ATGAACTTCTCCGGCAAGTACC	CTGACACCCCCTTGATGTCC
Acox1	GGGCACGGCTATTCTCACAG	CATCAAGAACCTGGCCGTCT
Cyp4a10	AAGGGTCAAACACCTCTGGA	GATGGACGCTCTTTACCCAA
Acot1	CGATGACCTCCCCAAGAACAT	CTTTTACCTCGGGGTGGCT
Cpt1b	GAACACAAATGTGCAAGCAGC	GCCATGACCGGCTTGATCTC
Ehhadh	CGGTCAATGCCATCAGTCCAA	TGCTCCACAGATCACTATGGC
Cpt2	CGTACCCACCATGCACTACC	TTCTGTCTTCCTGAACTGGCTG
Fxr	TGGGCTCCGAATCCTCTTAGA	TGGTCCTCAAATAAGATCCTTGG
Shp	TCTGCAGGTCGTCCGACTATTC	AGGCAGTGGCTGTGAGATGC
Fgf15	GCCATCAAGGACGTCAGCA	CTTCCTCCGAGTAGCGAATCAG
Cyp7a1	TTCTGCGAAGGCATTTGGAC	AGCATCTCCCTGGAGGGTTT
Cyp8b1	TTGCAAATGCTGCCTCAACC	TAACAGTCGCACACATGGCT
Cyp27a1	CAGGAGGGCAAGTACCCAAT	CATTGCTCTCCTTGTGCGATG
Tgr5	CTGTGTGAGATCCGCCGAC	CGACGCTCATAGGCCAAGA
Gcg	GATCATTCCCAGCTTCCCAG	CTGGTAAAGGTCCCTTCAGC
Col1a1	TAGGCCATTGTGTATGCAGC	ACATGTTCAGCTTTGTGGACC
Col12a1	GGGTCACAGAGGTTACCCAG	ACCAGGGGAACCACTCTCAC
Col3a1	TAGGACTGACCAAGGTGGCT	GGAACCTGGTTTCTTCTCACC
Tgfb	GTCACTGGAGTTGTACGGCA	GGGCTGATCCCGTTGATTTC
Acta2	CCAGCCATCTTTCATTGGGATG	TACCCCCTGACAGGACGTTG
Tnfa	CCACCACGCTCTTCTGTCTAC	AGGGTCTGGGCCATAGAACT
Il6	TAGTCCTTCCTACCCCAATTTCC	TTGGTCCTTAGCCACTCCTTC
Il1b	GCCACCTTTTGACAGTGATGAG	GACAGCCCAGGTCAAAGGTT
Ccl2	TTAAAAACCTGGATCGGAACCAA	GCATTAGCTTCAGATTTACGGGT
Tgm2	GGTAGATGAAGCCCTGTTGC	GGCCACTTCATCCTGCTCTA
Actb	GGCTGTATTCCCCTCCATCG	CCAGTTGGTAACAATGCCATGT
Gapdh	AGGTCGGTGTGAACGGATTTG	TGTAGACCATGTAGTTGAGGTCA

Table S5. Genotyping primers

Strains	Product size	Name	Primer Sequence
***Ppara*-null**	null=650 bp	For	GAGAAGTTGCAGGAGGGGATTGTG
	WT=412 bp	Rev	CCCATTTCGGTAGCAGGTAGTCTT
		Neo	GCAATCCATCTTGTTCAATGGC
***Ppara*-flox**	flox=700 bp	For	CAAGGCCATGTCTAATCATCCTGG
	WT=550 bp	Rev	TCTCATGGATTCAATTGACTGACTGG
		Lar	CAACGGGTTCTTCTGTTAGTCC
human *PPARA*	170 bp	For	CCAATCTGGAAACAGTAAATTAAACC
		Rev	GCATCCAGAGAACAACCGTAA
Il2	321 bp	For	CTAGGCCACAGAATTGAAAGATCT
		Rev	GTAGGTGGAAATTCTAGCATCATCC
PPRE-Luc	340bp	For	GGCAGAAGCTATGAAACGAT
		Rev	CGACTGAAATCCCTGGTAAT
tTA	200bp	For	CAAATGTTGCTTGTCTGGTG
		Rev	GTCAGTCGAGTGCACAGTTT
Cre	195 bp	For	GATTTCGACCAGGTTCGTTC
		Rev	GCTAACCAGCGTTTTCGTTC
***Fabp1*-flox**	flox~580 nt	For	GAATTGAGGAGTTCTCCAGTG
	WT ~480 nt	Rev	CAAACACTCTCTAAACTGTGAG

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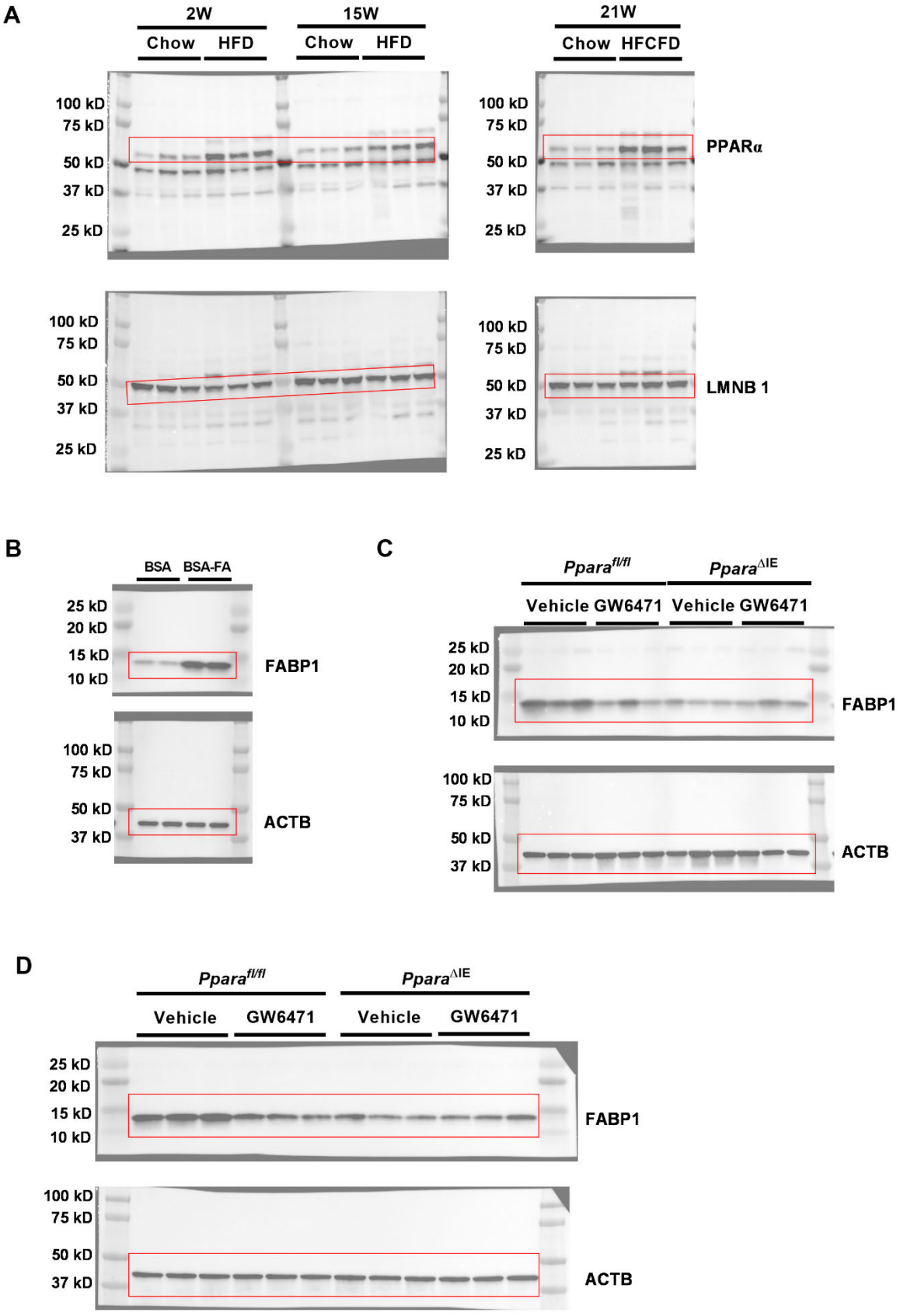
Original images for Blots

Full western blot gel panels.

(A) PPARα and LMNB1 from which the data in Figure 1B were derived.
(B) FABP1 and ACTB from which the data in Figure 3D were derived.
(C) FABP1 and ACTB from which the data in Figure 4B were derived.
(D) FABP1 and ACTB from which the data in Figure 4F were derived.
(E) FABP1 and ACTB from which the data in Figure 5A were derived.
(F) FABP1 and ACTB from which the data in Figure 6C were derived.
(G) FABP1 and ACTB from which the data in Figure 6E were derived.
(H) PPARα, LMNB1, FABP1, and ACTB from which the data in Figure 7A were derived.
(I) FABP1 and ACTB from which the data in Figure 8C were derived.
(J) FABP1 and ACTB from which the data in Figure 8D were derived.
(K) PPARα and LMNB1 from which the data in Figure S1H were derived.
(L) FABP1 and ACTB from which the data in Figure S3C were derived.
(M) FABP1 and ACTB from which the data in Figure S8C were derived.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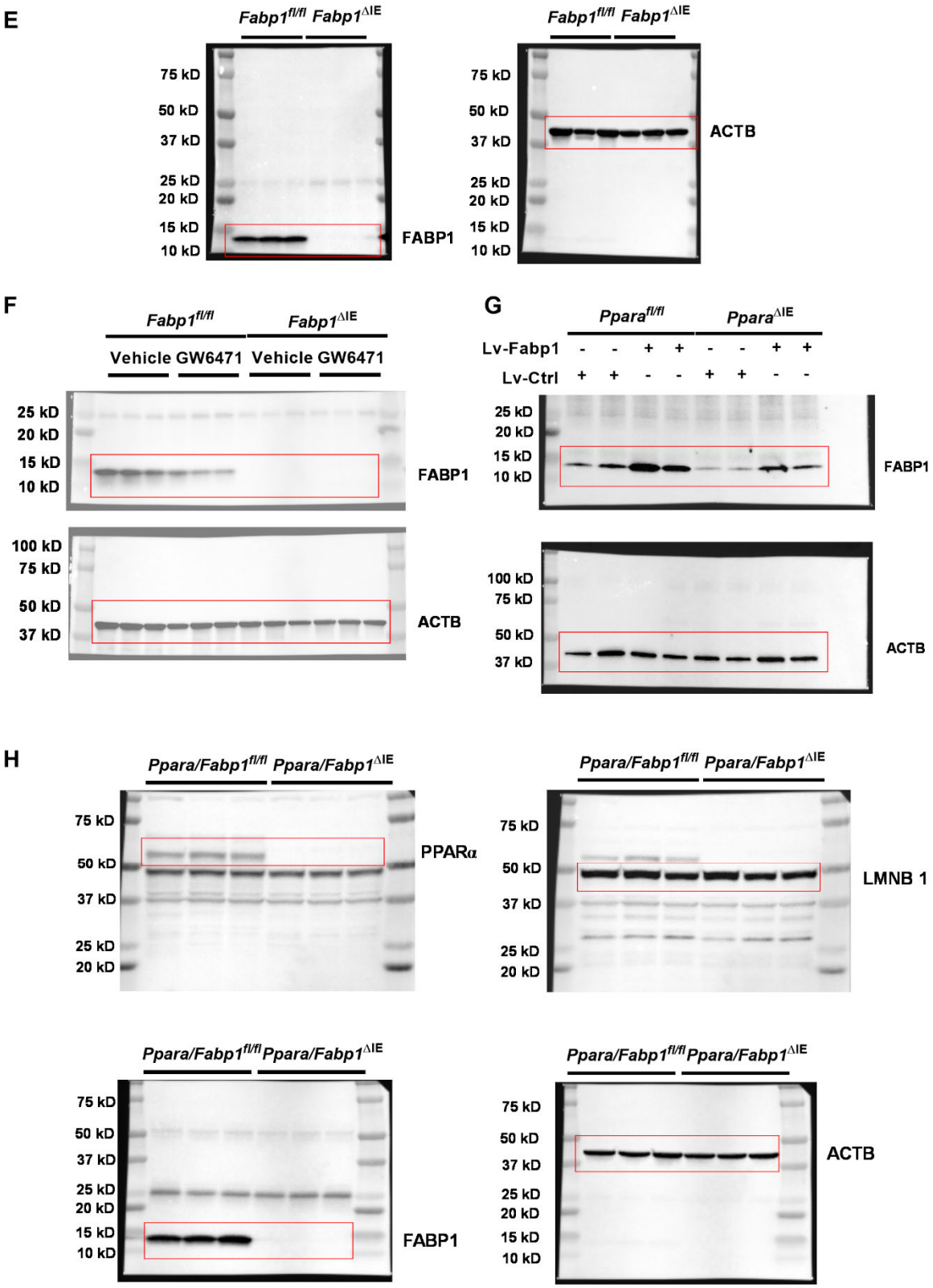
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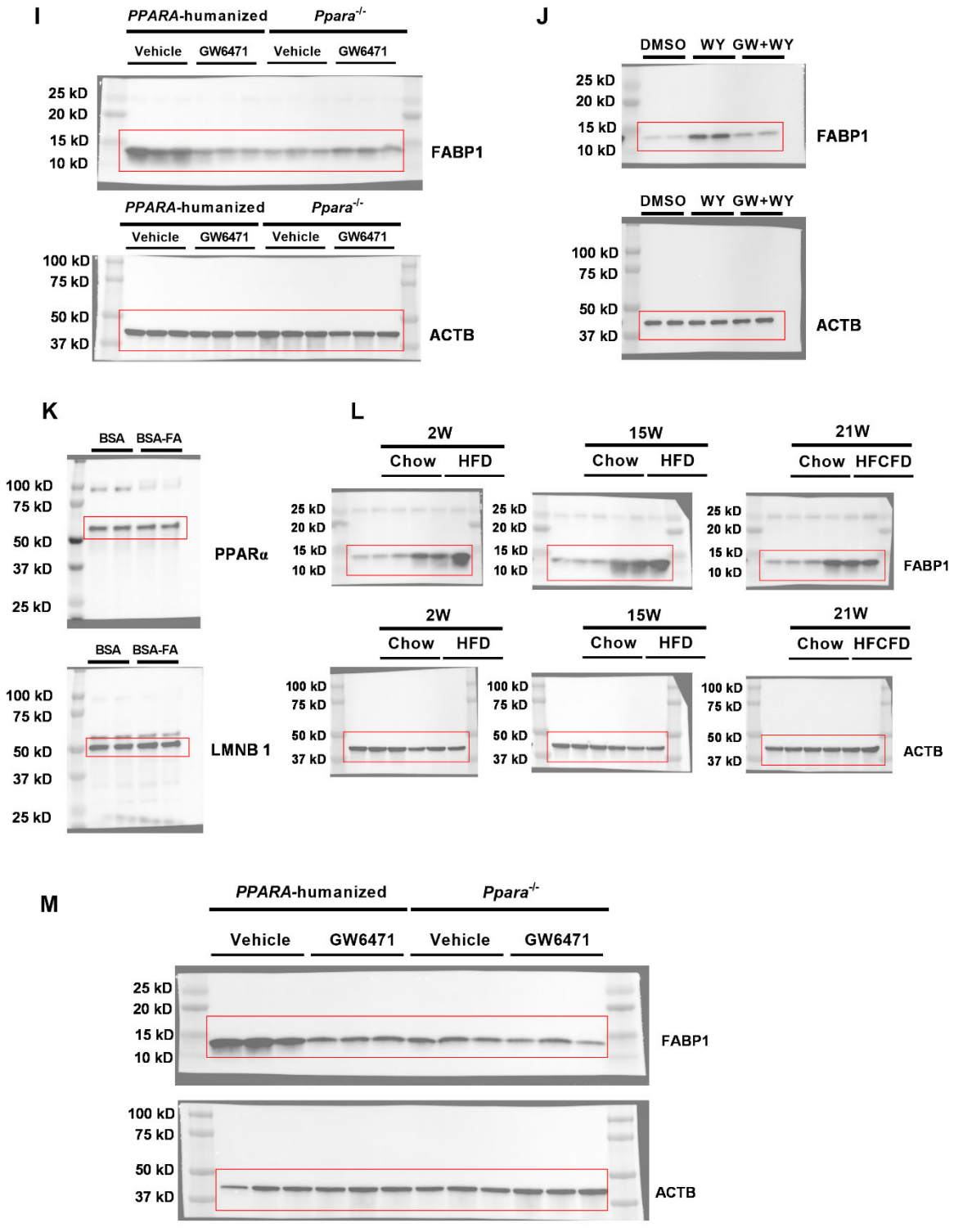
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