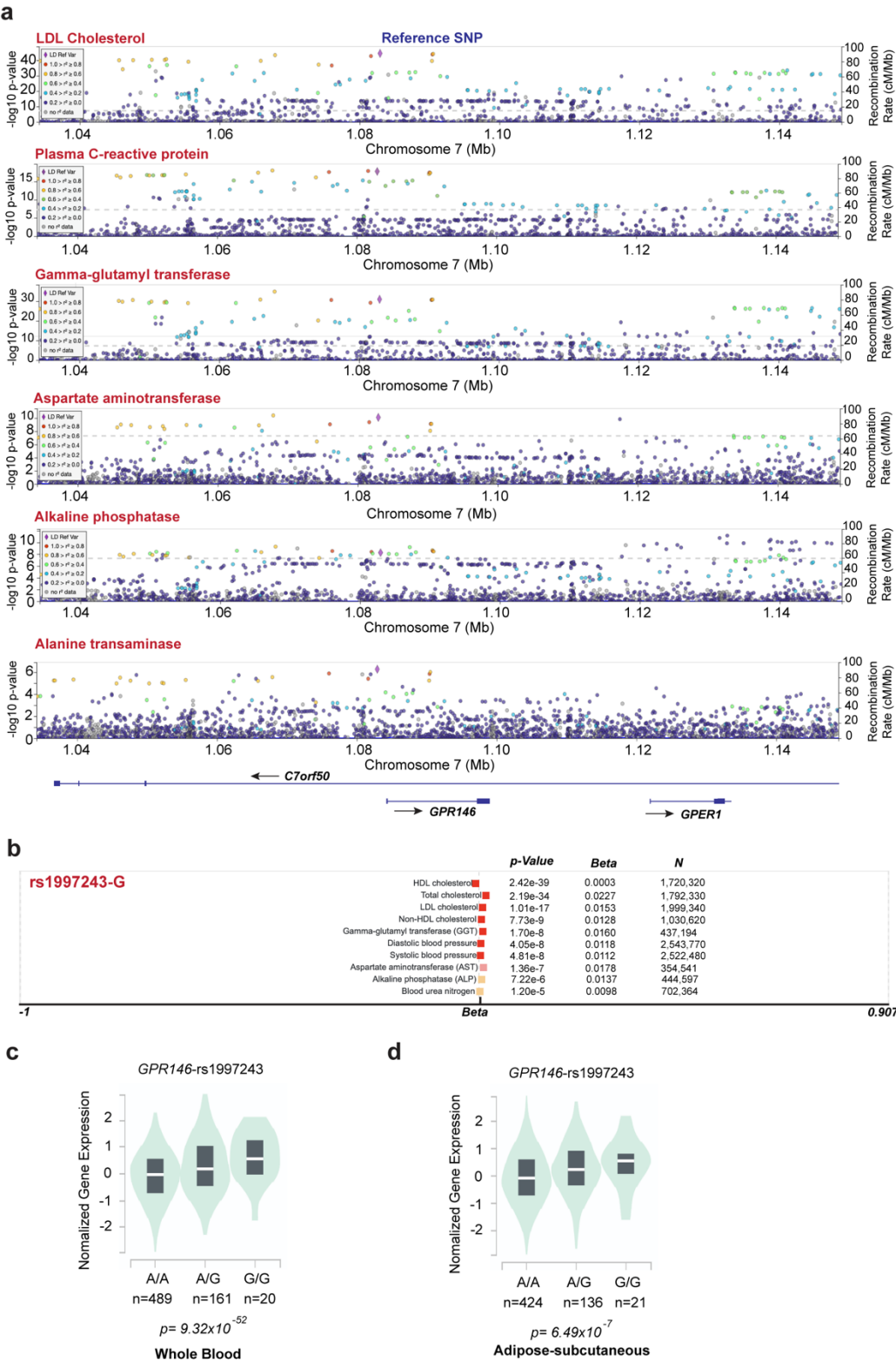


SUPPLEMENTARY INFORMATION

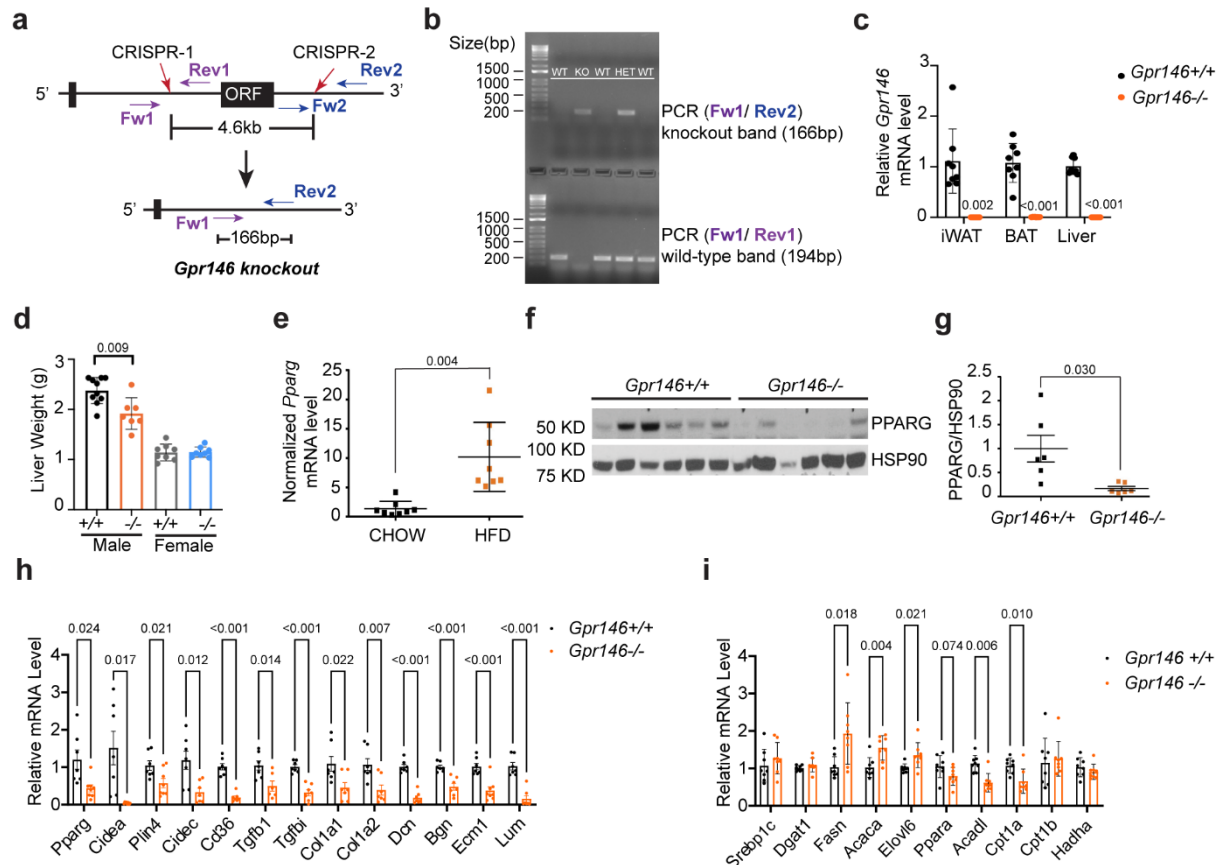
Supp\_Figure1



Supplementary Figure 1. Variants in the *GPR146* Gene Are Associated with Plasma Liver Inflammation Enzyme Levels. a, Regional (7p22 locus) association of

1 GWAS variants with plasma LDL-C, C-reactive protein, gamma-glutamyl transferase  
2 (GGT), Aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine  
3 aminotransferase (ALT) levels in humans. **b**, Lipoproteins, blood pressure, liver  
4 inflammation enzymes as a function of the G-allele of rs1997243 in individuals from  
5 T2D Portal meta-analysis. The effects are shown as beta-coefficients per G-allele  
6 compared with noncarriers. **c,d** eQTL studies using 670 human blood samples (**c**) and  
7 591 human subcutaneous adipose samples (**d**) from GTEx database revealed a highly  
8 significant dose-dependent relation between the rs1997243 G-allele and GPR146  
9 expression in both tissues. Source data are provided as a Source Data file.

## Supp\_Figure2



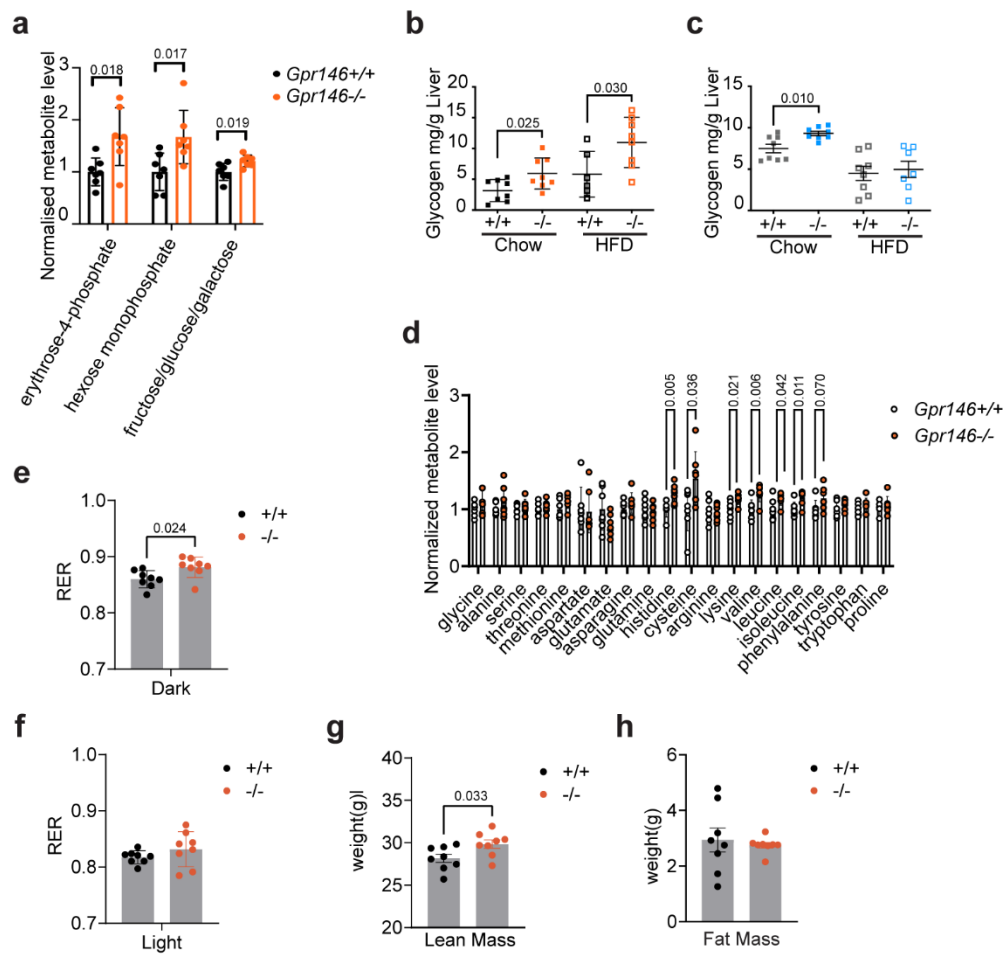
## Supplementary Figure 2. GPR146 Deficiency Downregulates PPAR $\gamma$ Signalling

**Pathway in Mouse Liver, Related to Fig.1.** **a**, Schematic diagram showing the generation of *Gpr146* whole-body knockout mouse model using the CRISPR/Cas9 system, along with the genotyping strategy. **b**, Representative gel images showing PCR products amplified with Fw1/Rev2 and Fw1/Rev1, enabling distinction of wild-type (WT), heterozygous (HET), and homozygous (KO) mice. **c**, qPCR analysis confirming efficient depletion of GPR146 across multiple tissues, including iWAT, BAT, and liver. **d**, Weights of whole liver from male and female *Gpr146* wild-type (+/+) mice and knockout (-/-) littermates fed HFD for 3 months (n=7-10mice per group). **e**, Quantitative polymerase chain reaction (qPCR) expression analysis of *Pparg* mRNA levels in liver of mice fed chow or HFD for 3 months (n=8 mice per group). **f, g**, Western blot (**f**) and relative quantification (**g**) of PPARG in liver of 16 h fasted male *Gpr146*<sup>+/+</sup> mice and *Gpr146*<sup>-/-</sup> littermates fed HFD for 3 months (n=6 mice per group). **h**, qPCR expression analysis of adipogenesis and extracellular matrix genes in liver of 16 h fasted male *Gpr146*<sup>+/+</sup> and *Gpr146*<sup>-/-</sup> littermates fed HFD for 3 months (n=8 mice per group). **i**, qPCR expression analysis of fatty acid biosynthesis or b-oxidation genes in

1 liver of 16 h fasted male *Gpr146*<sup>+/+</sup> and *Gpr146*<sup>-/-</sup> littermates fed HFD for 3 months (n=8  
2 mice per group). Bars in c, d and e indicate mean  $\pm$  s.d., bars in g-i indicate mean  $\pm$   
3 s.e.m.. Statistical analyses were performed using two-sided unpaired t-tests, with P  
4 values (c–e, g–i) indicated. Source data are provided as a Source Data file.

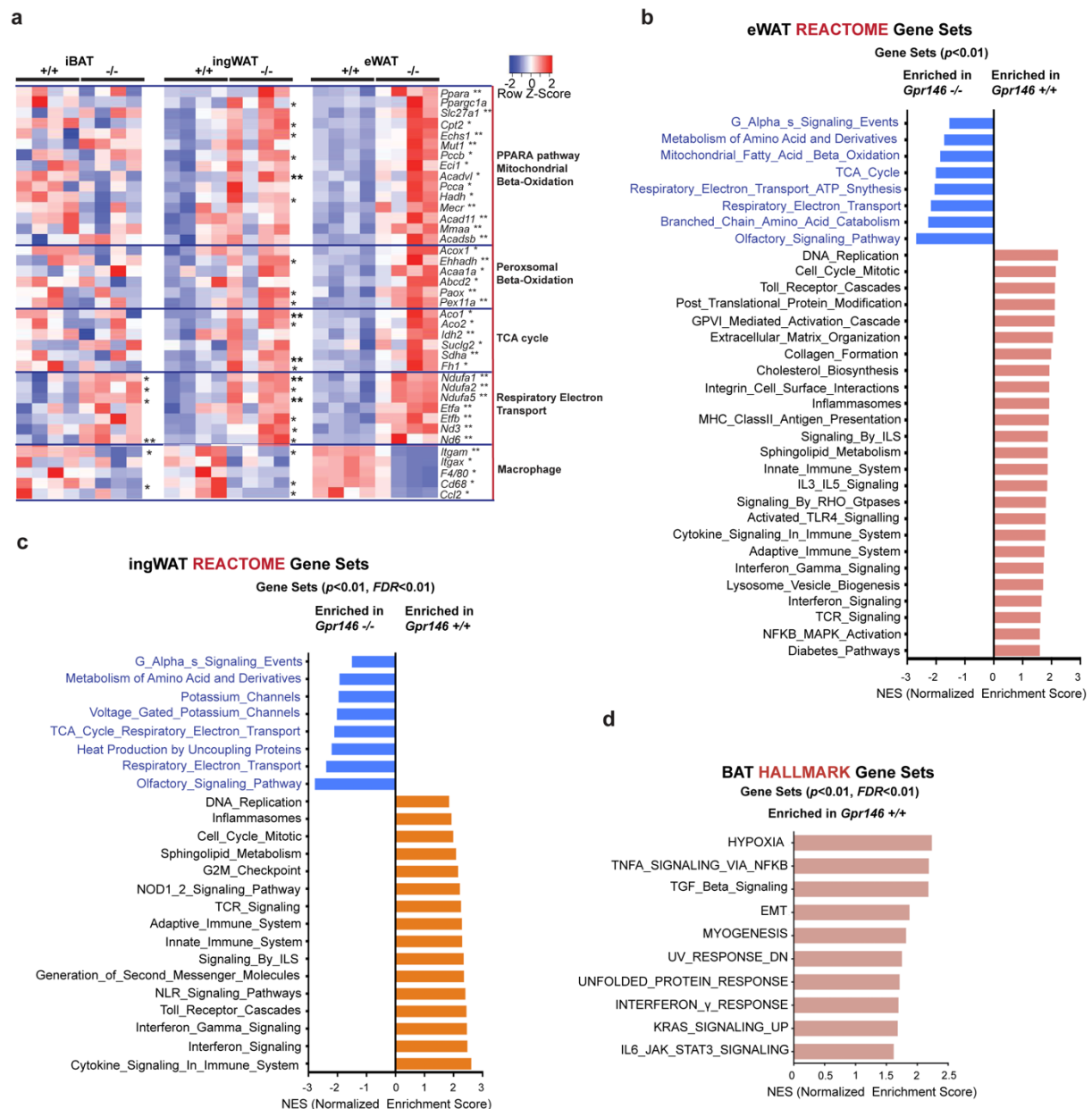
5

# Supp\_Figure3



**Supplementary Figure 3. GPR146 deficiency reprograms hepatic glucose and amino acid metabolism.** **a**, Hepatic erythrose-4-phosphate, hexose monophosphate, and hexose of 16 h fasted male *Gpr146* wild-type (+/+) mice and knockout (-/-) littermates fed an HFD (n=7 mice per group). **b,c**, Hepatic glycogen content of 16 h fasted male (**b**) and female (**c**) *Gpr146* wild-type (+/+) mice and knockout (-/-) littermates fed chow or HFD as indicated (n= 8-13 mice per group). **d**, Relative abundance of hepatic amino acids in 16 h fasted male mice fed an HFD (n=7 mice per group). **e.f**, Respiratory exchange ratio (RER) measured during the **dark** (**e**) and **light** (**f**) phases by indirect calorimetry in chow-fed *Gpr146*<sup>+/+</sup> and *Gpr146*<sup>-/-</sup> male mice. **g,h**, Magnetic resonance imaging (MRI) analysis of lean mass (**g**) and fat mass (**h**) of *Gpr146*<sup>+/+</sup> and *Gpr146*<sup>-/-</sup> littermates on chow diet. Bars in a-d indicate mean ± s.d., bars in e-h indicate mean ± s.e.m.. Statistical analyses were performed using two-sided unpaired t-tests, with P values indicated. Source data are provided as a Source Data file.

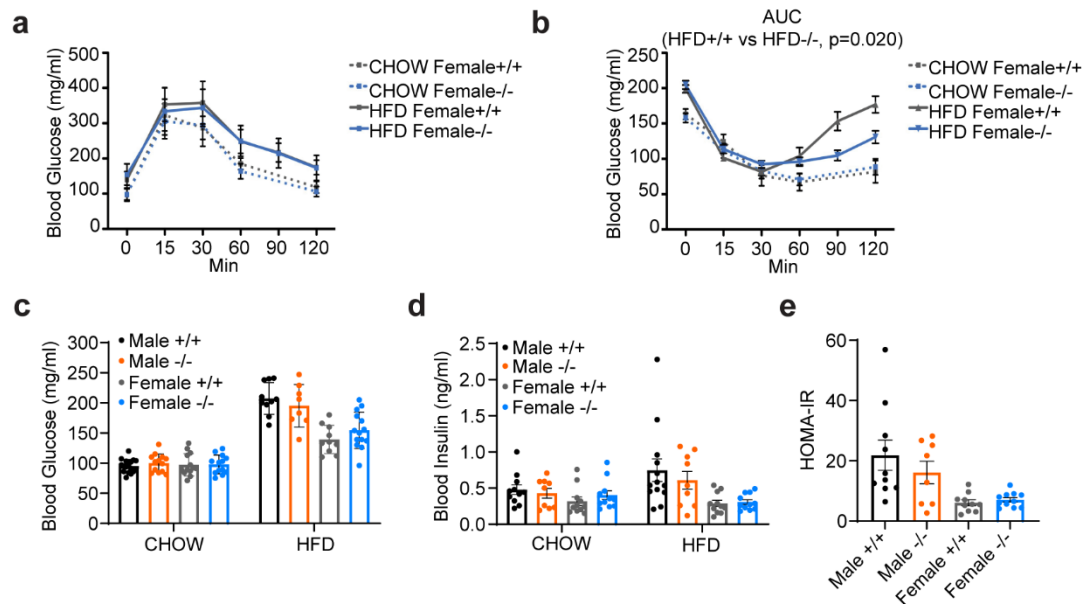
## Supp\_Figure4



**Supplementary Figure 4. Transcriptomic remodeling and pathway alterations in adipose tissues associated with GPR146 deficiency, Related to Fig.2.** **a.** Heatmap of Beta-oxidation, TCA cycle, and electron transport chain (HALLMARK Pathway Database)-related genes in ingWAT, eWAT, and iBAT of male *Gpr146*<sup>+/+</sup> and *Gpr146*<sup>-/-</sup> littermates fed HFD for 3 months (n=4 per group, by two-sided unpaired t-test). **b-d,** Top ranking REACTOME or HALLMARK pathway gene sets discovered from gene set enrichment analysis (GSEA) of genes that are differentially expressed in eWAT (**b**), iWAT (**c**), and BAT (**d**) of 16 h fasted male *Gpr146*<sup>+/+</sup> and *Gpr146*<sup>-/-</sup> littermates fed

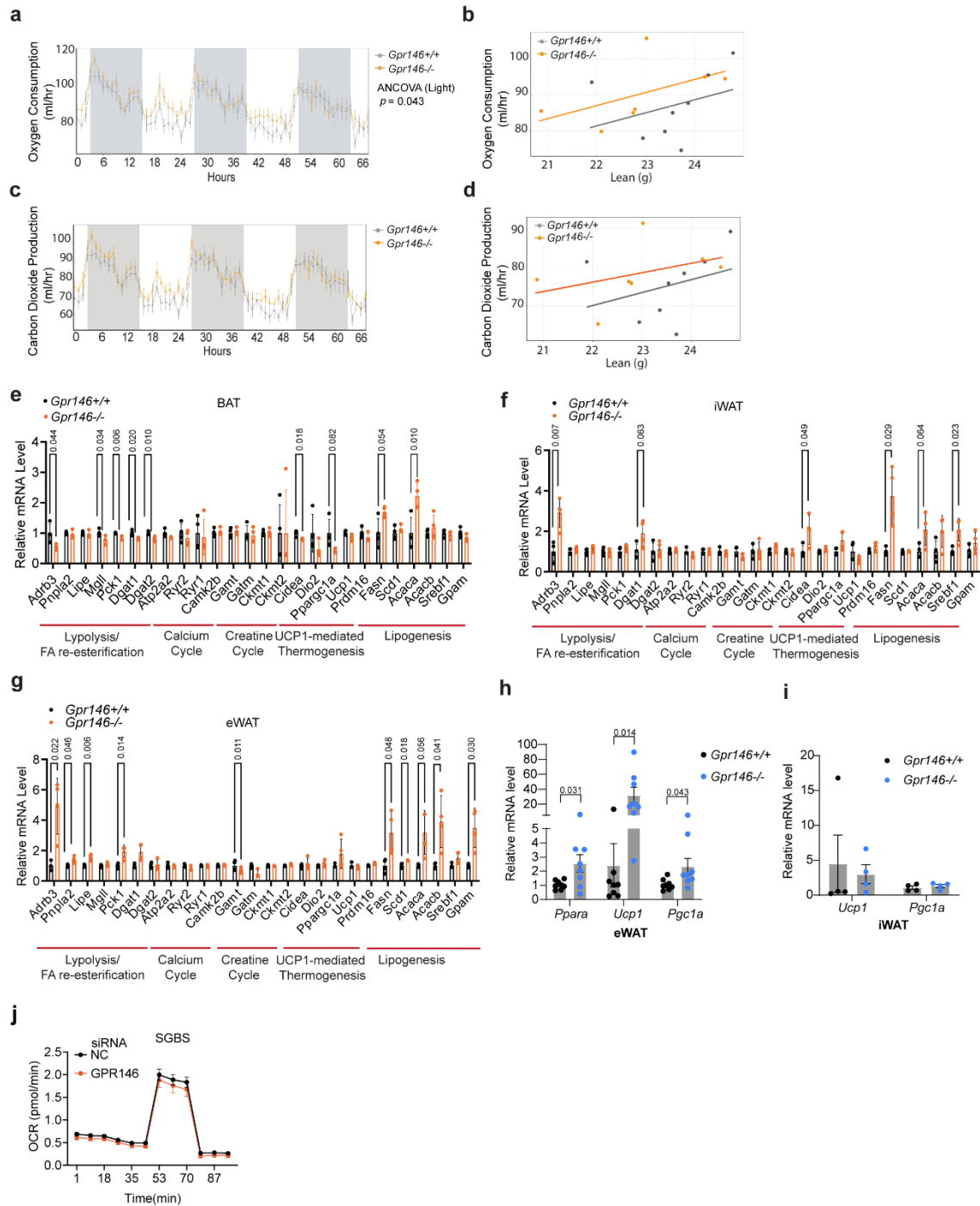
- 1 HFD for 3 months (n=4 mice per group), with significance assessed by permutation-
- 2 based testing and false discovery rate (FDR) correction. \*,  $p < 0.05$ , \*\*,  $p < 0.01$ .

## Supp\_Figure5



**Supplementary Figure 5. GPR146 deficiency alters systemic glucose metabolism, Related to Fig.2.** **a,b**, Plasma glucose during glucose tolerance test (**a**) and insulin tolerance test (**b**) of female *Gpr146*<sup>+/+</sup> and *Gpr146*<sup>-/-</sup> littermates fed chow or HFD for 2 months (n=10-15 mice per group). **c,d**, Plasma glucose (**c**) and insulin (**d**) levels of 16 h fasted mice fed chow or HFD for 2 months (n=7-10 mice per group). **e**, HOMA-IR calculated from fasting glucose and insulin levels in mice fed HFD for 1 month (n = 8–11 mice per group). Bars in a, b and e indicate mean ± s.e.m.; bars in c and d indicate mean ± s.d.. Statistical analyses were performed using two-sided unpaired t-tests(c-e). For panel a, b, AUC was calculated and compared between HFD-fed female *Gpr146*<sup>+/+</sup> and *Gpr146*<sup>-/-</sup> mice using two-sided unpaired t-test with P value indicated. Source data are provided as a Source Data file.

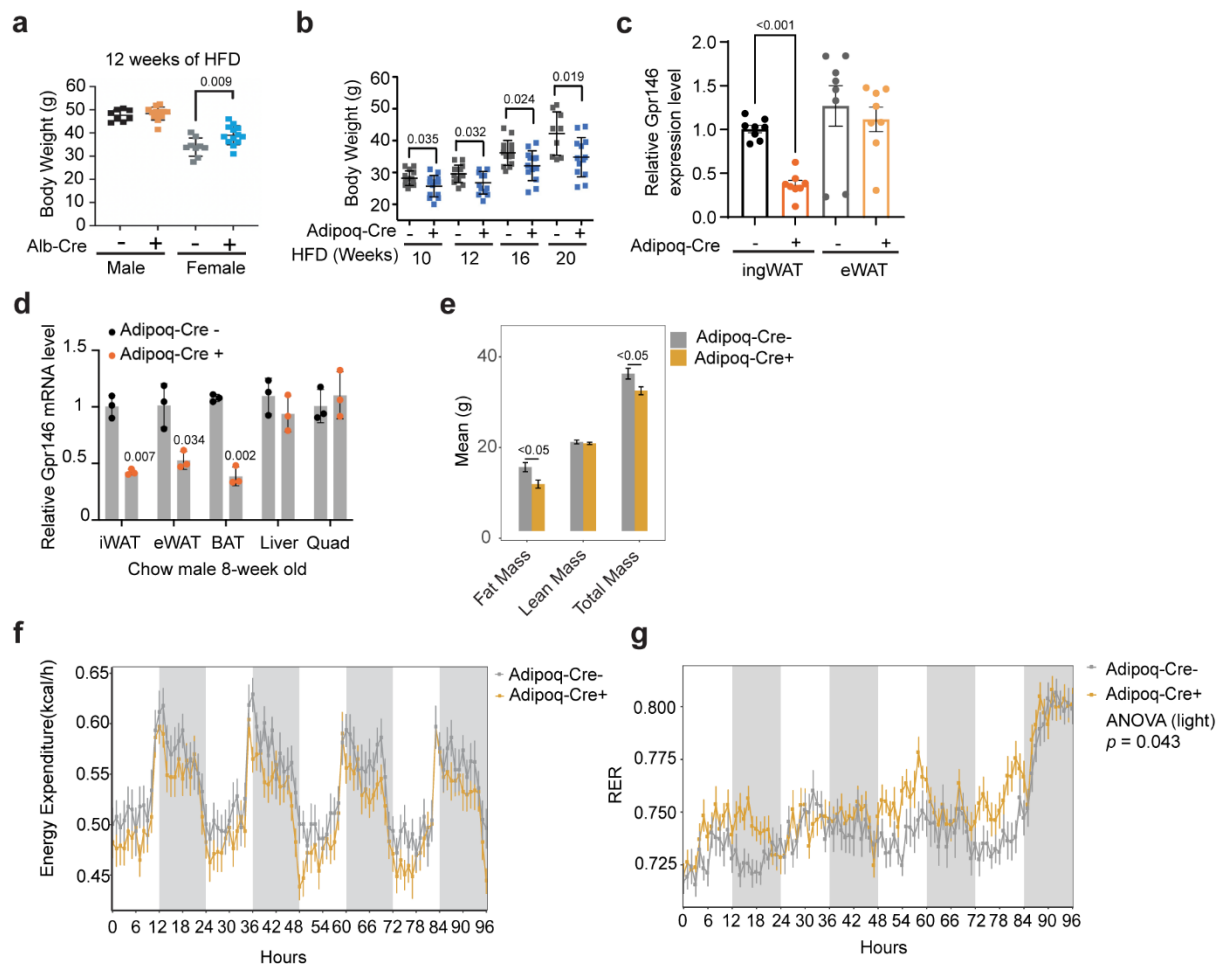
# 1 Supp\_Figure6



**Supplementary Figure 6, Metabolic phenotyping and thermogenic pathway regulation in adipose tissue of GPR146-deficient and control mice, Related to Fig3.** **a-d**, Oxygen consumption (**a**), regression plots for analysis of oxygen consumption versus lean mass (**b**), carbon oxygen consumption (**c**), and regression plots for analysis of carbon oxygen consumption versus lean mass (**d**) for *Gpr146*<sup>+/+</sup> and *Gpr146*<sup>-/-</sup> littermates (n = 8 mice per group). **e-g**, Relative mRNA expression levels

1 of selected genes associated with three major thermogenic pathways in BAT (**e**), iWAT  
2 (**f**), eWAT (**g**) of male *Gpr146*<sup>+/+</sup> and *Gpr146*<sup>-/-</sup> littermates fed HFD for 3 months (n=4  
3 per group). **h,i**, qPCR expression analysis of *Ucp1*, *Pgc1a* and *Ppara* in eWAT (**h**) and  
4 iWAT (**i**) from female *Gpr146*<sup>+/+</sup> and *Gpr146*<sup>-/-</sup> littermates fed HFD (n=4-8 mice per  
5 group). **j**, Oxygen consumption rate (OCR) measured by Seahorse XF mitochondrial  
6 stress test in SGBS adipocytes transfected with control (NC) or GPR146 siRNA. Bars  
7 in a-d, h and i indicate mean± s.d.; bars in e,f and g indicate mean ± s.e.m.. Statistical  
8 significance was determined by two-way ANCOVA (a-d), two-sided unpaired t-tests  
9 (e-j), with adjusted P values or P values indicated. Source data are provided as a  
10 Source Data file.

## Supp\_Figure7

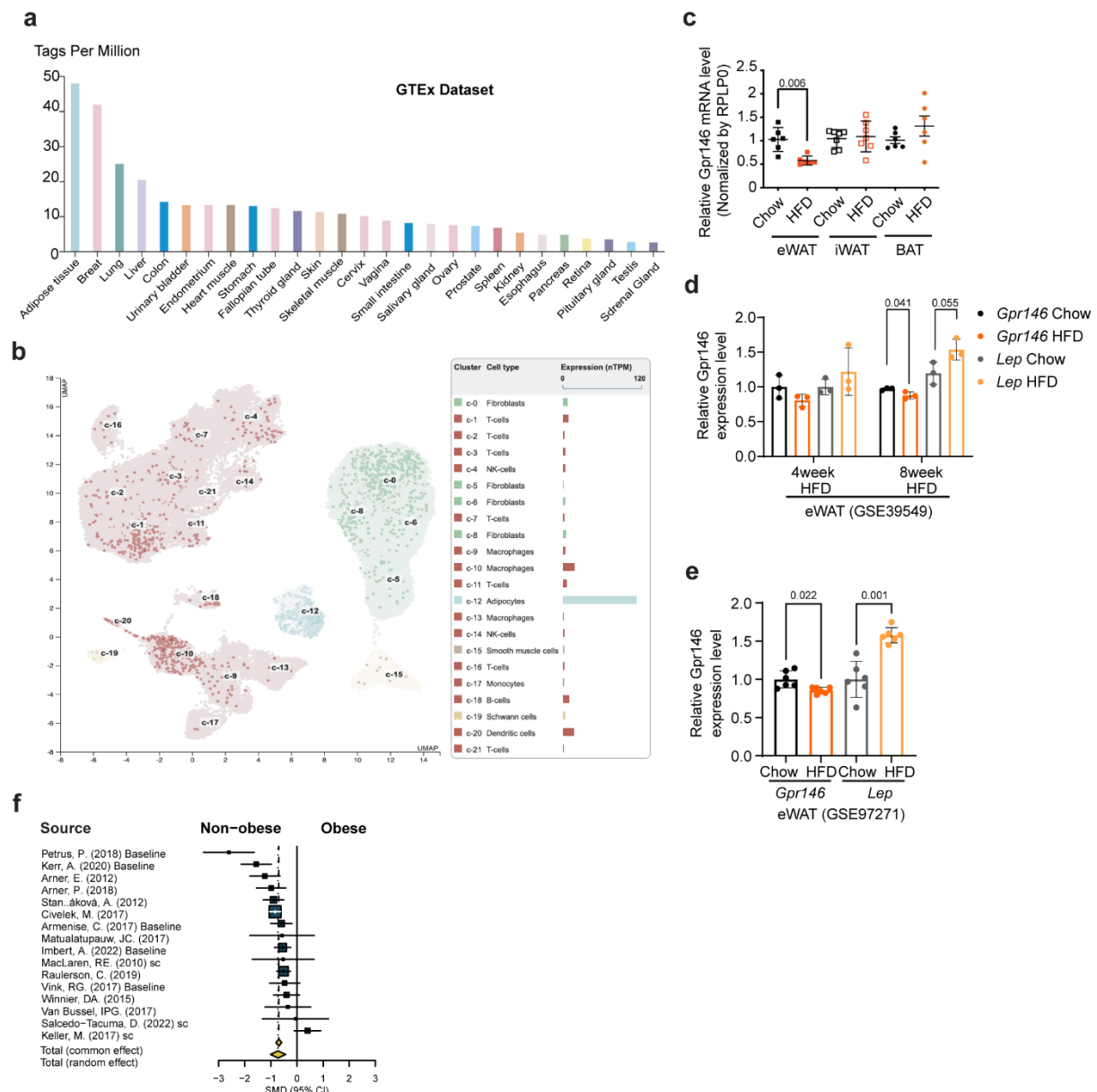


**Supplementary Figure 7, Adipose GPR146 mediates protection against diet-induced obesity and liver steatosis, Related to Fig.4.** **a**, Body weight of male or female liver-specific knockout mice (Alb-Cre<sup>+</sup>) and control littermates (Alb-Cre<sup>-</sup>) fed HFD for 3 months (n = 8-15 mice per group). **b**, Body weight of female adipose-specific knockout mice (Adipoq-Cre<sup>+</sup>) and control littermates (Adipoq-Cre<sup>-</sup>) fed HFD as indicated (n = 9-14 mice per group). **c,d**, Relative expression of *Gpr146* mRNA in ingWAT and eWAT from male mice at 8-week-old (**d**) and after fed HFD for 4 months (**c**) (n = 8 mice per group). **e**, MRI analysis of fat mass and lean mass from female adipose-specific knockout mice (Adipoq-Cre<sup>+</sup>) and control littermates (Adipoq-Cre<sup>-</sup>) fed HFD for 5 months. **f**, Energy Expenditure measured by indirect calorimetry in Adipoq-Cre<sup>+</sup> and control mice (Adipoq-Cre<sup>-</sup>) fed HFD for 4 months. **g**, Hourly respiratory exchange ratio (RER) measured in the same cohort of male Adipose specific knockout and the control littermates. Bars in all panels indicate mean ± s.d..

1 Statistical significance was determined by two-sided unpaired t-tests (a–d) or two-way  
2 ANCOVA (e–g), with P values or adjusted P values indicated. Source data are  
3 provided as a Source Data file.

4

## Supp\_Figure8

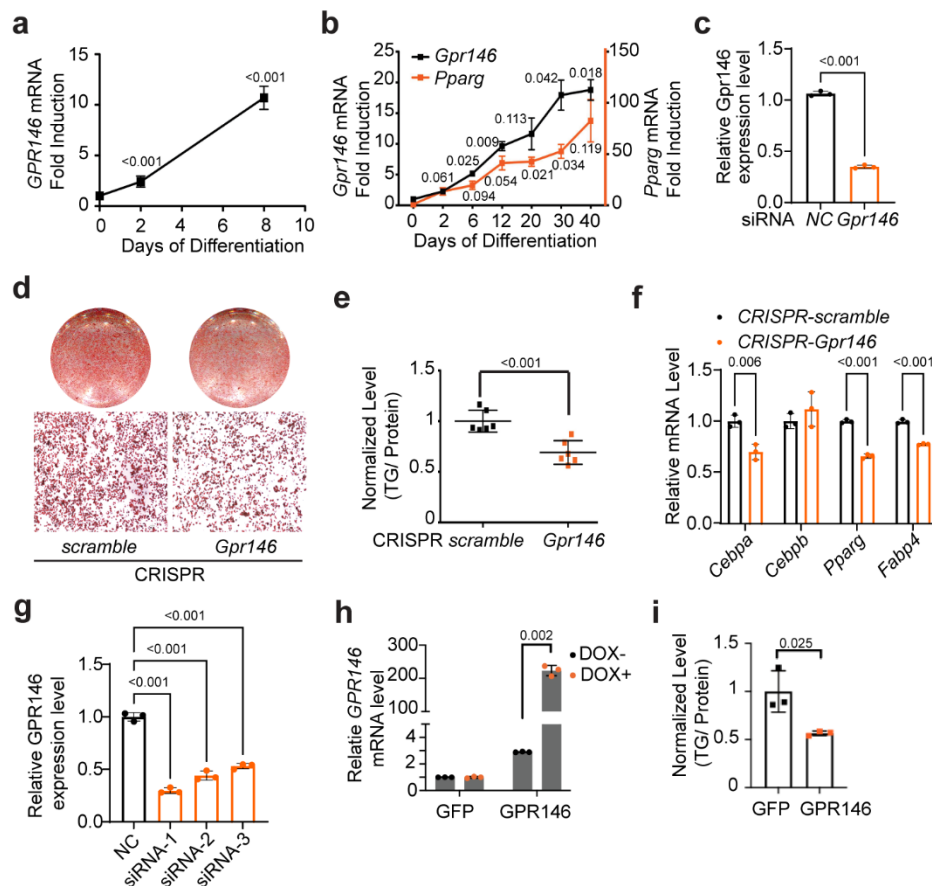


**Supplementary Figure 8, GPR146 expression in adipose tissue is modulated by nutritional and physiological context in mice and humans, Related to Fig.4. a,** Profiling of GPR146 expression in a variety of human tissues (The Human Protein ATLAS). **b,** Single cell profiling of *GPR146* expression in human adipose tissue (The Human Protein ATLAS). **c,** *Gpr146* mRNA expression in eWAT, iWAT, and BAT from WT C57/BL6 mice fed a chow or high-fat diet (HFD) for 3 months (n = 6–10 per group). **d, e,** Analysis of mouse eWAT transcriptomic data from two publicly available datasets, GSE39549 (**d**) and GSE97271 (**e**), comparing *Gpr146* expression before and after HFD feeding, and its relationship with *Lep* (leptin) expression. **f,** Forest plots

1 summarizing GPR146 expression across multiple human transcriptomic cohorts (data  
2 adapted from the Adipose Tissue Knowledge Portal), comparing individuals with and  
3 without obesity. Source studies included in the meta-analysis are listed alongside each  
4 plot. Standardized mean differences (SMD) with 95% confidence intervals were  
5 calculated for each cohort and combined using a random-effects meta-analysis. Bars  
6 in d, e indicate mean  $\pm$  s.e.m.. Statistical significance was determined by two-sided  
7 unpaired t-tests (c–e), with P values indicated. Source data are provided as a Source  
8 Data file.

9

## Supp\_Figure9

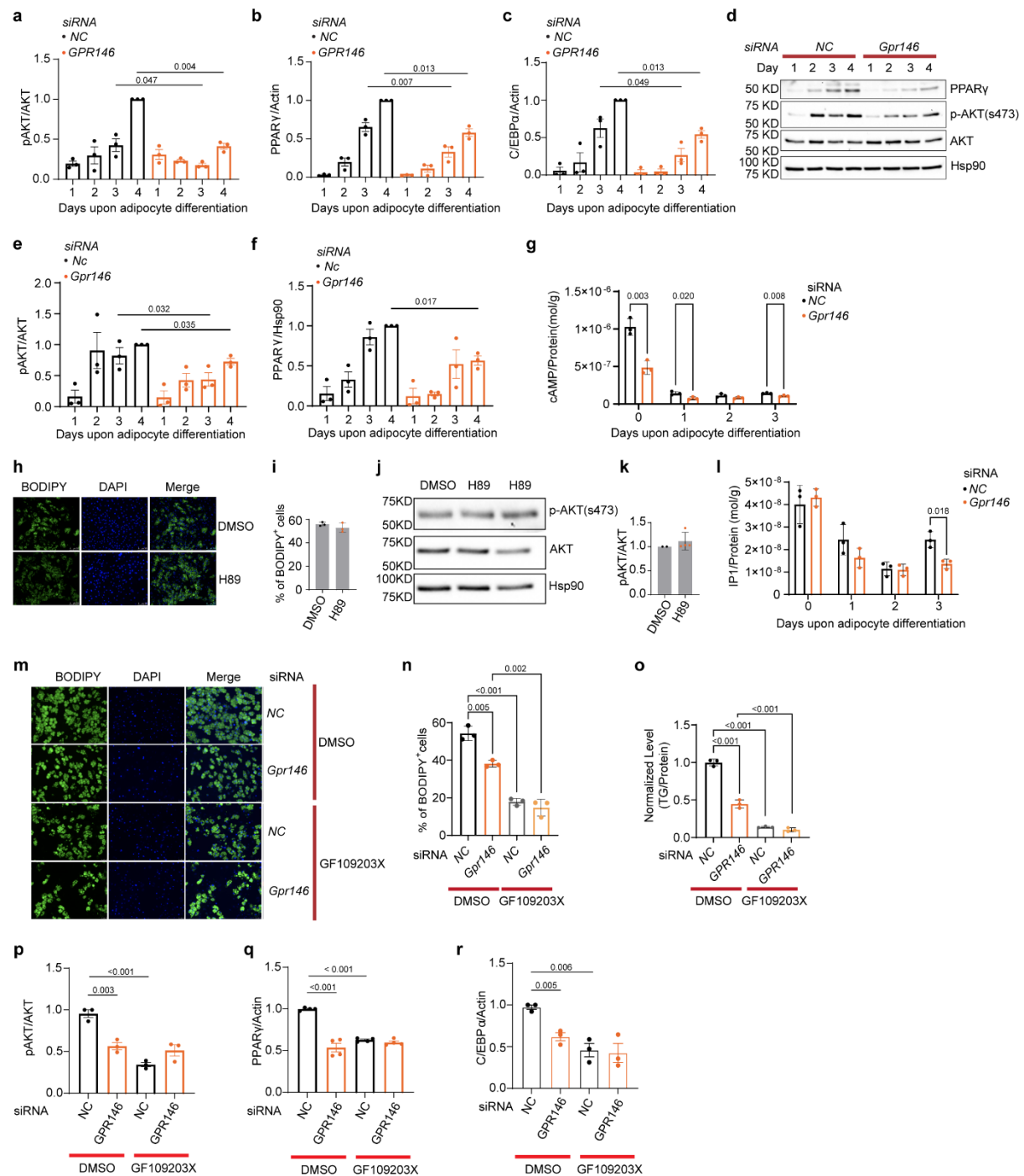


**Supplementary Figure 9, GPR146 promotes differentiation of both mouse and human preadipocytes, Related to Fig.6.** **a**, Relative expression of *GPR146* messenger RNA during adipocyte differentiation of SGBS pre-adipocytes (n=3 replicates per experiment, representative of 3 independent experiments). **b**, Relative expression of *Gpr146* and *Pparg* messenger RNA during adipocyte differentiation of SVF-derived pre-adipocytes (n=3 replicates per experiment, representative of 3 independent experiments). **c**, Relative expression of *Gpr146* mRNA in mouse SVF upon siRNA-induced knockdown of *GPR146* (n=3 replicates per experiment, representative of 3 independent experiments). **d,e**, Oil Red O-staining (**d**) and TG content (**e**) of mouse SVF-differentiated adipocytes upon CRISPR/Cas9-based knockout of *Gpr146* (n=3 replicates per experiment, representative of 3 independent experiments). **f**, Quantitative qPCR expression analysis of adipogenesis genes at day 4 of adipocyte differentiation (n=3 replicates per experiment, representative of 3 independent experiments). **g,h**, Relative *GPR146* mRNA expression in human SGBS cells following siRNA-mediated knockdown (**g**) or doxycycline-induced overexpression

1 of *GPR146* (h) (n = 3 replicates per condition, representative of 3 independent  
2 experiments). i, Triglyceride content in SGBS-differentiated adipocytes  
3 overexpressing *GPR146* or GFP (control). Bars in a-e, g, h, and i indicate mean $\pm$  s.d.,  
4 bars in f indicate mean  $\pm$  s.e.m.. Statistical significance was determined by two-sided  
5 unpaired t-tests (a,c and e-i) or two-way ANOVA (b), with P values or adjusted P  
6 values indicated. Source data are provided as a Source Data file.

7

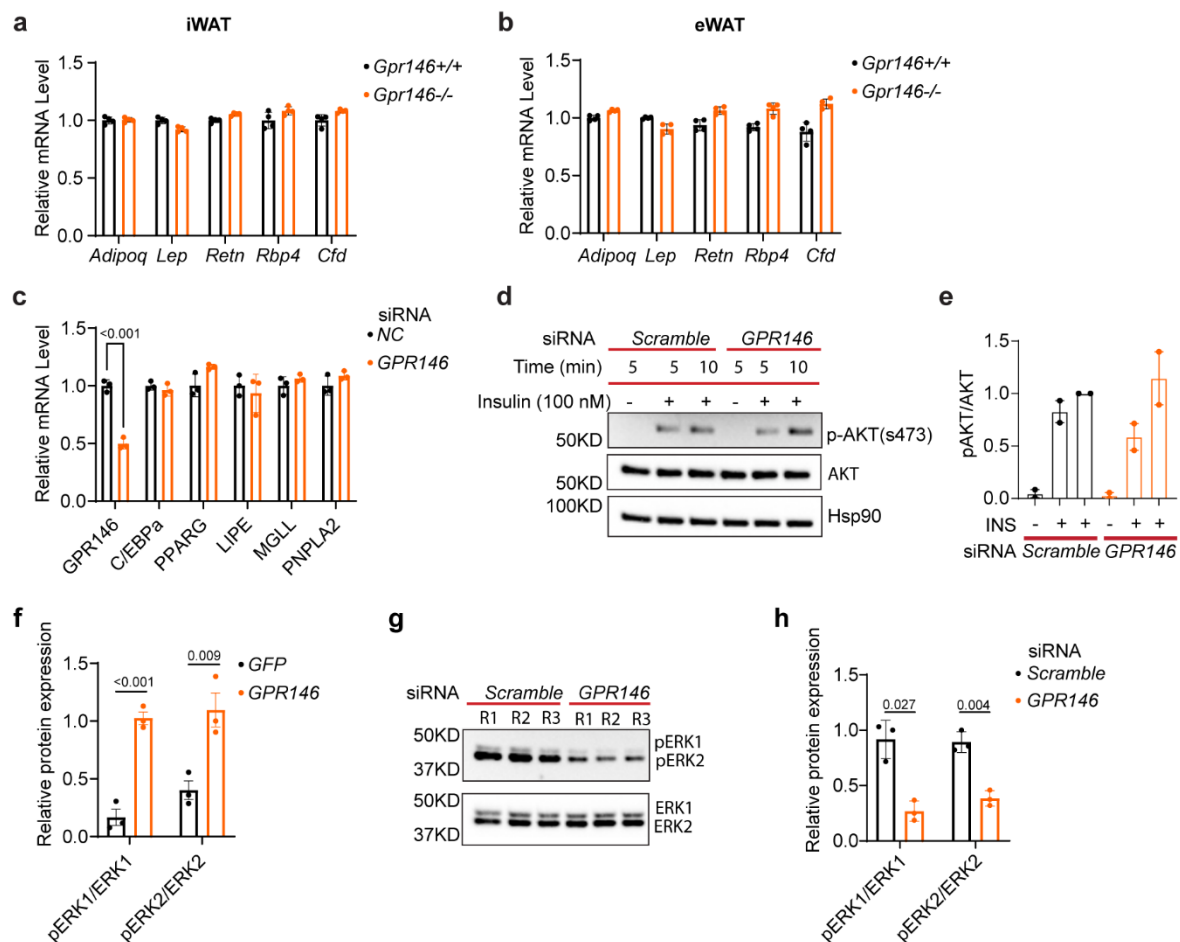
## Supp\_Figure10



**Supplementary Figure 10, GPR146 Regulates Adipogenesis through Gαq-mediated Activation of PKC Signaling Pathway in both human and mouse preadipocytes, Related to Fig.7.** **a-c**, Relative quantification of western blots (Fig. 7c) for p-AKT (s473), AKT, PPAR $\gamma$ , C/EBP $\alpha$  and Actin in *GPR146* knockdown or control SGBS pre-adipocytes upon differentiation for the time indicated. **d-f**, Representative western blots (**d**) and relative quantification for p-AKT (s473), AKT (**e**), and PPAR $\gamma$  (**f**)

1 in *Gpr146* knockdown or control SVF pre-adipocytes upon differentiation for the time  
2 indicated. **g**, Cellular cAMP level in *Gpr146* knockdown or control SVF pre-adipocytes  
3 upon differentiation for the time indicated (n=3 replicates per experiment,  
4 representative of 3 independent experiments). **h,i**, BODIPY-staining (**h**) and  
5 percentage of BODIPY+ cells (**i**) of mouse SVF-differentiated adipocytes in the  
6 presence or absence of H89 (n=3 replicates per experiment, representative of 3  
7 independent experiments). **j,k**, Representative western blots (**j**) and relative  
8 quantification(**k**) of p-AKT (s473) and ATK in SVF at day 4 of adipocyte differentiation  
9 in the presence or absence of H89 (representative of 2 independent experiments). **l**,  
10 Cellular IP1 levels in *Gpr146* knockdown or control SVF pre-adipocytes upon  
11 differentiation for the time indicated (n=3 replicates per experiment, representative of  
12 3 independent experiments). **m-o** BODIPY-staining (**m**), percentage of BODIPY+ cells  
13 (**n**), and triglyceride (TG) content (**o**) of mouse SVF-differentiated adipocytes upon  
14 siRNA-induced knockdown of *Gpr146* in the presence or absence of GF109203X (n=3  
15 replicates per experiment, representative of 3 independent experiments). **p-r**, Relative  
16 quantification of western blot (**Fig. 7h**) for p-AKT(s473), AKT (**p**), PPAR $\gamma$  (**q**), C/EBP $\alpha$   
17 (**r**), and Actin (**q, r**) in GPR146 knockdown or control SGBS pre-adipocytes upon  
18 differentiation for 4 days in the presence or absence of GF109203X. Bars in a, b, c,  
19 e, f, k, p, q and r indicate mean $\pm$  s.e.m., bars in g, i, l, n and o indicate mean $\pm$  s.d..  
20 Statistical significance was determined by two-sided paired tests (a-c, e and f)  
21 unpaired t-tests (g, i, k and l) or two-way ANOVA (n-r), with P values or adjusted P  
22 values indicated. Source data are provided as a Source Data file.

## Supp\_Figure11



**Supplementary Figure 11, GPR146 regulates mature adipocyte lipolysis through ERK signaling, Related to Fig. 8.** **a,b**, Relative mRNA expression of genes encoding major adipokines in iWAT(**a**) and eWAT(**b**) from male *Gpr146*<sup>+/+</sup> and *Gpr146*<sup>-/-</sup> littermates fed HFD for 3 months (n=4 mice per group). **c**, qPCR expression analysis of key transcriptional regulators of adipogenesis and lipases involved in lipolysis in mature adipocyte with *GPR146* knockdown by siRNA (n=3 mice per group). **d,e**, Representative western blots (**d**) and relative quantification (**e**) of p-AKT (s473) and AKT in mature adipocytes derived from SGBS cells following *GPR146* knockdown and Insulin stimulation (100nM) at indicated time points. **f**, Relative quantification of western blot (**Fig. 8d**) for phosphorylated ERK (p-ERK) and total ERK in SGBS cells with doxycycline-induced GFP or GPR146 expression. **g,h**, Representative western blots (**g**) and relative quantification (**h**) of p-ERK and ERK in *GPR146* knockdown SGBS-derived mature adipocytes. Bars in a, b and c indicate mean±s.d.. bars in e, f and h indicate mean±s.e.m.. Statistical significance was determined by two-sided

1 unpaired t-tests (a–c), paired t-tests (f and h), with P values indicated. Source data are  
2 provided as a Source Data file.  
3  
4

## Supplementary Table 1

| REAGENT or RESOURCE                                                 | SOURCE                    | IDENTIFIER                      |
|---------------------------------------------------------------------|---------------------------|---------------------------------|
| <b>Antibodies</b>                                                   |                           |                                 |
| Mouse monoclonal anti-HSP90                                         | Santa Cruz Biotechnology  | Cat# sc-13119; RRID: AB_675659  |
| Rabbit polyclonal anti- Akt                                         | Cell Signaling Technology | Cat#9272; RRID:AB_AB_329827     |
| Rabbit monoclonal anti-phospho-Akt(Ser473)(D9E)                     | Cell Signaling Technology | Cat#9271; RRID:AB_2315049       |
| Rabbit monoclonal anti-PPAR $\gamma$ (C26H12)                       | Cell Signaling Technology | Cat# 2435                       |
| Rabbit polyclonal anti-C/EBP $\alpha$ [EP708Y]                      | Abcam                     | Cat#ab40761; RRID:AB_1140761    |
| Mouse monoclonal anti-C/EBP $\alpha$ (D5)                           | Santa Cruz Biotechnology  | Cat#sc-365318; RRID:AB_10846948 |
| Mouse monoclonal anti- $\beta$ -actin                               | Sigma-Aldrich             | Cat# A5316; RRID: AB_476743     |
| Rabbit monoclonal anti-p44/42 MAPK (Erk1/2)                         | Cell Signaling Technology | Cat# 4695; RRID:AB_390779       |
| Rabbit monoclonal anti-phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) | Cell Signaling Technology | Cat# 4370; RRID: AB_2315112     |
| <b>Chemicals</b>                                                    |                           |                                 |
| PKC inhibitor (GF109203X)                                           | Sigma-Aldrich             | Cat#G2911                       |
| Dexamethasone                                                       | Sigma-Aldrich             | Cat#D1756                       |
| Insulin                                                             | Sigma-Aldrich             | Cat# I9278                      |
| 3-Isobutyl-1-methylxanthine (IBMX)                                  | Sigma-Aldrich             | Cat#I5879                       |
| Rosiglitazone                                                       | Sigma-Aldrich             | Cat#R2408                       |
| Panhotenat                                                          | Sigma-Aldrich             | Cat#P5155                       |
| Cortisol                                                            | Sigma-Aldrich             | Cat#H0888                       |
| Triiodothyronine (T3)                                               | Sigma-Aldrich             | Cat# T6397                      |
| BODIPY® 493/503                                                     | Thermo Fisher Scientific  | Cat# D3922                      |
| Hoechst 33342                                                       | Thermo Fisher Scientific  | Cat# 62249                      |
| Oil Red O                                                           | Sigma-Aldrich             | Cat# O0625                      |
| Eosin Y solution                                                    | Sigma-Aldrich             | Cat# 318906                     |
| Hematoxylin Solution, Mayer's                                       | Sigma-Aldrich             | Cat# MHS32                      |
| PD0325901                                                           | Selleckchem               | Cat#S1036                       |
| CL316,243                                                           | MCE                       | Cat#HY-116771A                  |
| Collagenase A                                                       | Sigma-Aldrich             | Cat#H3023                       |
| PD98059                                                             | Selleckchem               | Cat#S1036                       |
| Foskolin                                                            | Sigma-Aldrich             | Cat#F6886                       |
| <b>Critical Commercial Assays</b>                                   |                           |                                 |
| Infinity Triglycerides Reagent                                      | Thermo Fisher Scientific  | Cat# TR22421                    |
| Infinity Triglycerides Reagent                                      | Thermo Fisher Scientific  | Cat# TR13421                    |
| cAMP-Gs dynamic kit                                                 | PerkinElmer               | Cat# 62AM4PEB                   |
| IP-One Gq Kit                                                       | PerkinElmer               | Cat# PKE_62IPAPEB               |
| ALT kit                                                             | Sigma-Aldrich             | Cat# MAK052                     |
| BrdU Cell Proliferation Assay Kit                                   | Cell Signaling Technology | Cat# 6813                       |
| Free Glycerol Reagent                                               | Sigma-Aldrich             | Cat# F6428                      |
| Mouse insulin ELISA kit                                             | Abcam                     | Cat# ab277390                   |
| <b>Deposited Data</b>                                               |                           |                                 |
| Microarray raw data                                                 | This paper                | GEO(GSE316218)                  |
| <b>Experimental Models: Cell Lines</b>                              |                           |                                 |

|                                                                                                                        |                            |                                                                     |
|------------------------------------------------------------------------------------------------------------------------|----------------------------|---------------------------------------------------------------------|
| Human: Human Simpson–Golabi–Behmel syndrome (SGBS) cell line                                                           | University of Ulm, Germany |                                                                     |
| <b>Experimental Models:</b><br><b>Organisms/Strains</b>                                                                |                            |                                                                     |
| Mouse: <i>Gpr146</i> <sup>-/-</sup>                                                                                    | This paper                 | N/A                                                                 |
| Mouse: B6.Cg-Speer6- <sup>ps1Tg(Alb-cre)21Mgn/J</sup>                                                                  | The Jackson Laboratory     | RRID: IMSR_JAX:003574                                               |
| Mouse: B6.FVB-Tg(Adipoq-cre) <sup>1Evdr/J</sup>                                                                        | The Jackson Laboratory     | RRID: IMSR_JAX:010803                                               |
| Mouse: <i>Gpr146</i> -LKO                                                                                              | This paper                 | N/A                                                                 |
| Mouse: <i>Gpr146</i> -FKO                                                                                              | This paper                 | N/A                                                                 |
| Mouse: B6J.129(Cg)-Gt(ROSA) <sup>26Sor</sup> <sup>tm1.1(CAG-cas9*,-EGFP)Fezh/J</sup>                                   | The Jackson Laboratory     | RRID: IMSR_JAX:026179                                               |
| Mouse : C57BL6/J                                                                                                       | The Jackson Laboratory     | RRID: IMSR_JAX:000664                                               |
| <b>Oligonucleotides (5' to 3' orientation)</b>                                                                         |                            |                                                                     |
| Mouse <i>Gpr146</i> sgRNA1 sequence (for generating whole-body knockout mouse model): GCTACCTTTTGGCACGGGTT             | This paper                 | N/A                                                                 |
| Mouse <i>Gpr146</i> sgRNA2 sequence (for generating whole-body knockout mouse model): GTGGCTAAGGGATTATATGG             | This paper                 | N/A                                                                 |
| Mouse <i>Gpr146</i> sgRNA1 sequence (for knockout of <i>Gpr146</i> in adipose-derived SVF cells): GCCCACGCTGTGCTGTTGAG | This paper                 | N/A                                                                 |
| Mouse <i>Gpr146</i> sgRNA2 sequence (for knockout of <i>Gpr146</i> in adipose-derived SVF cells): CCCCCAGGTAGAGCAGCGAG | This paper                 | N/A                                                                 |
| Mouse <i>Gpr146</i> sgRNA3 sequence (for knockout of <i>Gpr146</i> in adipose-derived SVF cells): GTACTTCGTGAACATGGCCG | This paper                 | N/A                                                                 |
| Mouse <i>Gpr146</i> siRNA                                                                                              | Thermo Scientific Fisher   | s206895                                                             |
| Human <i>GPR146</i> siRNA                                                                                              | Thermo Scientific Fisher   | s41795                                                              |
| Mouse <i>Gpr146</i> AAV8-shRNA targeting sequence: GCATTATC TGGGCATCCTACA                                              | This paper                 | N/A                                                                 |
| <b>Software and Algorithms</b>                                                                                         |                            |                                                                     |
| ImageJ                                                                                                                 | NIH                        | <a href="https://imagej.nih.gov/ij/">https://imagej.nih.gov/ij/</a> |
| GraphPad Prism9                                                                                                        | GraphPad Software          | <a href="https://www.graphpad.com/">https://www.graphpad.com/</a>   |
| Adiposoft                                                                                                              | 46                         |                                                                     |
| KSEA                                                                                                                   | 37                         |                                                                     |

1

2

**Supplementary Table 2: qPCR primers****Mouse**

| <b>Gene</b>    | <b>Forward</b>                    | <b>Reverse</b>                   |
|----------------|-----------------------------------|----------------------------------|
| <i>Gpr146</i>  | ACGCACCTACATGGCCAGTGTGTAC         | CGATTCTAGAAGACACGTGACTGCAGATGT   |
| <i>Rplp</i>    | GAAGACAGGGCGACCTGGAAGTCCAACTAC    | GATCTGCTGCATCTGCTTGAGCCCACTC     |
| <i>Pparg</i>   | TTCACAAGAGCTGACCCAATGGTTGCTGATTAC | ATGAGGCCTGTTGTAGAGCTGGGTCTTTTCAG |
| <i>Cidea</i>   | AGTTTCAAACCATGACCGAAGTAGCCGGCG    | ACCAGCGTAACCAGGCCAGTTGTGATGAC    |
| <i>Plin4</i>   | GATGAGTTGAAAGGGCTGGGTGATATCTTTC   | GACGGATGTAGTAGCTTCCCCGGTCACTGC   |
| <i>Cd36</i>    | GAGCCTTCACTGTCTGTTGGAACAGAGGATG   | ATAAGAGAGTTGAGCACAACTTGAACAATG   |
| <i>Col1a1</i>  | ATGTTTCAGCTTTGTGGACCTCCGGCTCTC    | GTTTCCACGTCTCACCATTGGGGAC        |
| <i>Col1a2</i>  | GAGGCAGAGATGGTGTGATGGTCCCATGTG    | ATTGGTCCAGGGCCAGATGAAACTCCTTTG   |
| <i>Il6</i>     | CCACTTCACAAGTCGGAGGCTTAATTACAC    | CAGATTGTTTTCTGCAAGTGCATCATCTTG   |
| <i>Tnfa</i>    | TGCCTATGTCTCAGCCTCTTCTCATTCTGC    | TGAGTGTGAGGGTCTGGGCCATAGAACTG    |
| <i>Il1b</i>    | GCCCATCCTCTGTGACTCAT              | AGGCCACAGGTATTTTGTCTG            |
| <i>Cebpa</i>   | CAAAGCCAAGAAGTCGGTGGACAAGAACAG    | CCTTCTGTTGCGTCTCCACGTTGCGTTG     |
| <i>Cebpb</i>   | AAGCTGAGCGACGAGTACAAGATGCGG       | TCGTTCTCCGCCGTCAGCTCCAGC         |
| <i>Fasn</i>    | TGGTGTGGACATGGTCACAGATGATGACAGG   | TGGACCCCAAAAAAGGAGGCGTCGAACTC    |
| <i>Fabp4</i>   | TAAAAACACCGAGATTTCTTCAAACCTGGG    | ATTGTGGTCGACTTTCCATCCCACCTTCG    |
| <i>F4/80</i>   | TTGGGATCTGCCCTAAGTATTCCAACCTGC    | AGGGCAAACGTCTCGAGTCACACATTCTC    |
| <i>Mcp1</i>    | ATGATCCCAATGAGTAGGCTGGAGAGCTACAAG | ATTCCTTCTTGGGGTCAGCACAGACCTCTC   |
| <i>Lpl</i>     | GAGTTTGGCTCCAGAGTTTGACCGCCTTCC    | AGCTGTGTCTTCAGGGGTCTTAGGGCTC     |
| <i>Ppara</i>   | TGCAGACTACCAGTACTTAGGAAGCTGTCC    | GACTGAGGAAGGGCTGGAAGCTGGAGAGAG   |
| <i>Adipoq</i>  | GCAGAGATGGCACTCCTGGAGAGAAGGG      | CCTTCAGCTCCTGTCAATCCAACATCTCTC   |
| <i>Tgfb1</i>   | TACCAGCTGGTGCTGCAGCATAGC          | CTTCCTCTGGTACCACTGCTTGCAGTTG     |
| <i>Dcn</i>     | GATGCCAGTGTCTATCTTCGAGTGGTGCAGT   | ATGCAAGTCCTTCAGGTTCTTGAAGGCTCC   |
| <i>Bgn</i>     | GACTCTGTCACACCTACCTTCAGTGCCATG    | TCTGCAGGTCTAGCAGTGTGGTGTCAAGTG   |
| <i>Ecm1</i>    | GACCGTATCCAGAGCAGCCTTGATCTTGGC    | CTTCATGGAGGTGCTGGAAGAGGGCGCTC    |
| <i>Lum</i>     | GAGTATACCAACAGTTAATGAAAATCTTG     | GCTTGATCTTGGAGTAAGACAGTGGTCTCCA  |
| <i>Srebp1c</i> | TGACAGGTGAAATCGGCGCGGAAGCTG       | GTCTTGTTGTTGATGAGCTGGAGCAT       |
| <i>Dgat1</i>   | AATCATCTGCTTCCCAGCAGCTGTGGCTC     | CACCACAGGTTGACATCCCGGTAGGAATAAAG |
| <i>Acaca</i>   | CAGATACACTTTCTGATTTGGGGATCTCTG    | GTGAGTCTATTTTCTTTCTGTCTCGACCTTG  |

|               |                                     |                                       |
|---------------|-------------------------------------|---------------------------------------|
| <i>Elovl6</i> | GAATTCGAAAAGCAGTTCAACGAGAAC<br>GAAG | GATGCCGACCACCAAAGATAAAGGCA<br>GC      |
| <i>Acadl</i>  | CGGGAGAGTGTAAGGAAGTTTTTCCAA<br>GAAG | ATGTTGATGCCAAGCAAGCCCTGCTTG<br>C      |
| <i>Cpt1a</i>  | CAAACAGATCTGCCTGTCAGGGCTGCA<br>CT   | GTATGCATGGATGATATCACACCCACC<br>ACC    |
| <i>Cpt1b</i>  | CGGGAGGCTCTGAGACACATCTACCTG         | GTAGTTGGAACCAACTGTTGCCATGAC<br>AAC    |
| <i>Hadha</i>  | TGCATTTGCCGCAGCTTTAC                | GTTGGCCCAGATTTTCGTTCA                 |
| <i>Ucp1</i>   | GGAGTTTCAGCTTGCCTGGCAGATATC<br>ATC  | GTGATGGTCCCTAGGACACCTTTATAC<br>CTAATG |
| <i>Pgc1a</i>  | CAGCTCAGCTACAATGAATGCAGCGGT<br>C    | AATGCTCTTCGCTTTATTGCTCCATGA<br>ATTC   |

1

#### Human

| Gene          | Forward                             | Reverse                             |
|---------------|-------------------------------------|-------------------------------------|
| <i>GPR146</i> | ACACAGCAAGGCCAGCATGACCATG           | TGGACTTCGCCGCCACACTCCAC             |
| <i>RPLP</i>   | CGACCTGGAAGTCCAACACTTCCTT<br>AAG    | CATGCGGATCTGCTGCATCTGCTTGGA<br>G    |
| <i>CEBPA</i>  | GGTGCTGGAGCTGACCAGTGACAAT<br>GAC    | AGTTGCCCATGGCCTTGACCAAGGAGC         |
| <i>CEBPB</i>  | GACAAGCACAGCGACGAGTACAAGA<br>TCC    | TTCTCGGCCGTGAGCTCCAGGACCTTG         |
| <i>PPARG</i>  | ACAAGAACAGATCCAGTG GTTGCAG<br>ATTAC | CATGAGGCTTATTGTAGAGCTGAGTCT<br>TCTC |
| <i>FASN</i>   | CAAGCAGGCACACACGATGGACCCT<br>CAG    | CGCCAGTGTGTGTTCTCGGAGTGAAT<br>C     |
| <i>FABP4</i>  | GAAGTAGGAGTGGGCTTTGC                | TTCTGGCCCAGTATGAAGG                 |
| <i>LIPE</i>   | CCGACTGAATCTACGTCCCA                | TAGGGCTGATCGCTGTATGG                |
| <i>MGLL</i>   | AAAGACTACCCTGGGCTTCC                | CAGCACAAGGTTGAGCACTT                |
| <i>PNPLA2</i> | AAGGTCCTGCCTGCTGATAG                | GATGAAACCGCTGCAGACAT                |

2

3