

Supplementary Informations

Hepatocyte-specific deletion of *Ppar* α promotes NAFLD in the context of obesity

Marion Régnier¹, Arnaud Polizzi¹, Sarra Smati^{1,2}, Céline Lukowicz¹, Anne Fougerat¹, Yannick Lippi¹, Edwin Fouché¹, Frédéric Lasserre¹, Claire Naylies¹, Colette Bétoulières¹, Valentin Barquissau², Etienne Mouisel², Justine Bertrand-Michel³, Aurélie Batut³, Talal Al Saati⁴, Cécile Canlet¹, Marie Tremblay-Franco¹, Sandrine Ellero-Simatos¹, Dominique Langin^{2,5}, Catherine Postic⁶, Walter Wahli^{1,7,8}, Nicolas Loiseau¹, Hervé Guillou^{1*}, Alexandra Montagner^{1,2*}

1. Toxalim, INRAE UMR 1331, ENVT, INP-Purpan, University of Toulouse, Paul Sabatier University, F-31027 Toulouse, France

2. Institut National de la Santé et de la Recherche Médicale (INSERM), UMR1048, Institute of Metabolic and Cardiovascular Diseases, University of Toulouse, Paul Sabatier University, Toulouse, France

3. Metatoul-Lipidomic Facility, MetaboHUB, Institut National de la Santé et de la Recherche Médicale (INSERM), UMR1048, Institute of Metabolic and Cardiovascular Diseases, Toulouse, France

4. Service d'Histopathologie Expérimentale Unité INSERM/UPS/ENV-T-US006/CREFRE Inserm, CHU Purpan, 31024 Toulouse cedex 3, France

5. Toulouse University Hospitals, Laboratory of Clinical Biochemistry, Toulouse, France

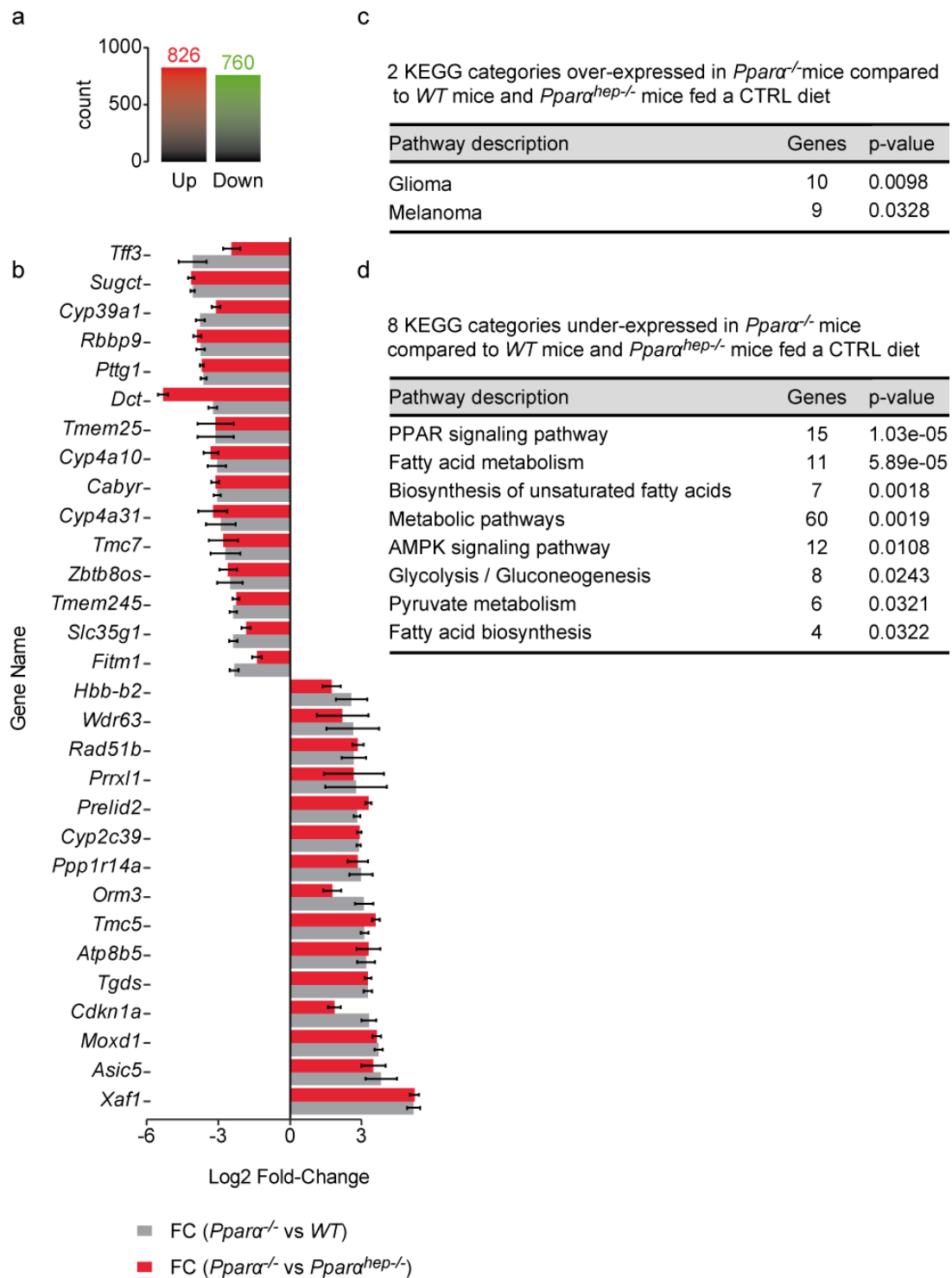
6. Institut National de la Santé et de la Recherche Médicale (INSERM), U1016, Institut Cochin, Paris, France

7. Lee Kong Chian School of Medicine, Nanyang Technological University Singapore, Clinical Sciences Building, 11 Mandalay Road, Singapore

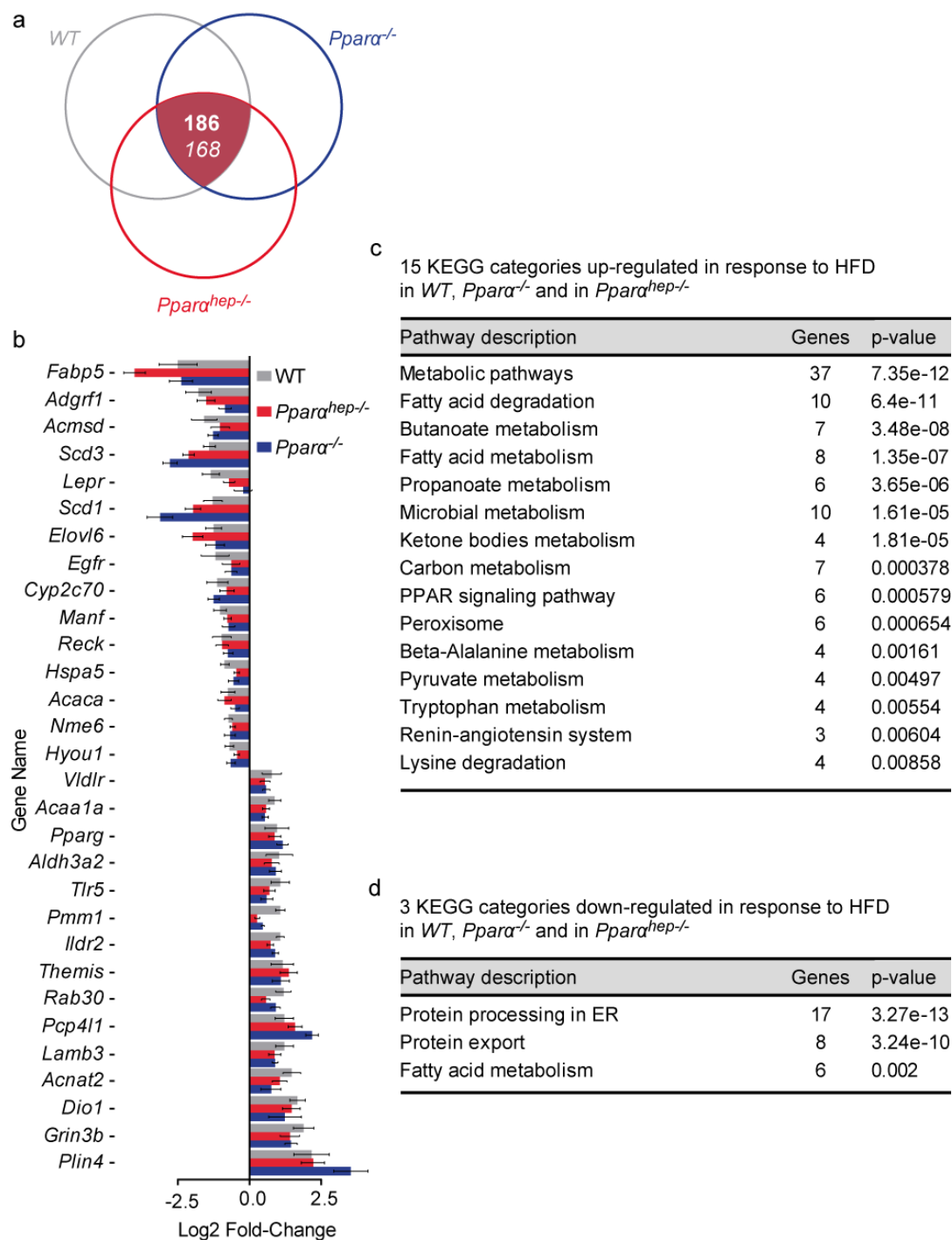
8. Center for Integrative Genomics, Université de Lausanne, Le Génopode, Lausanne, Switzerland

Supplementary Table 1. Oligonucleotide sequences for real-time qPCR. Oligonucleotides (Sigma-Aldrich) were designed using Primer Express 2.0 software (Applied Biosystems). Couples of primers have a T_m of 60°C, exhibit no amplification with genomic DNA, and the derivative from each dissociation curve of amplicons from cDNA exhibits a single specific peak.

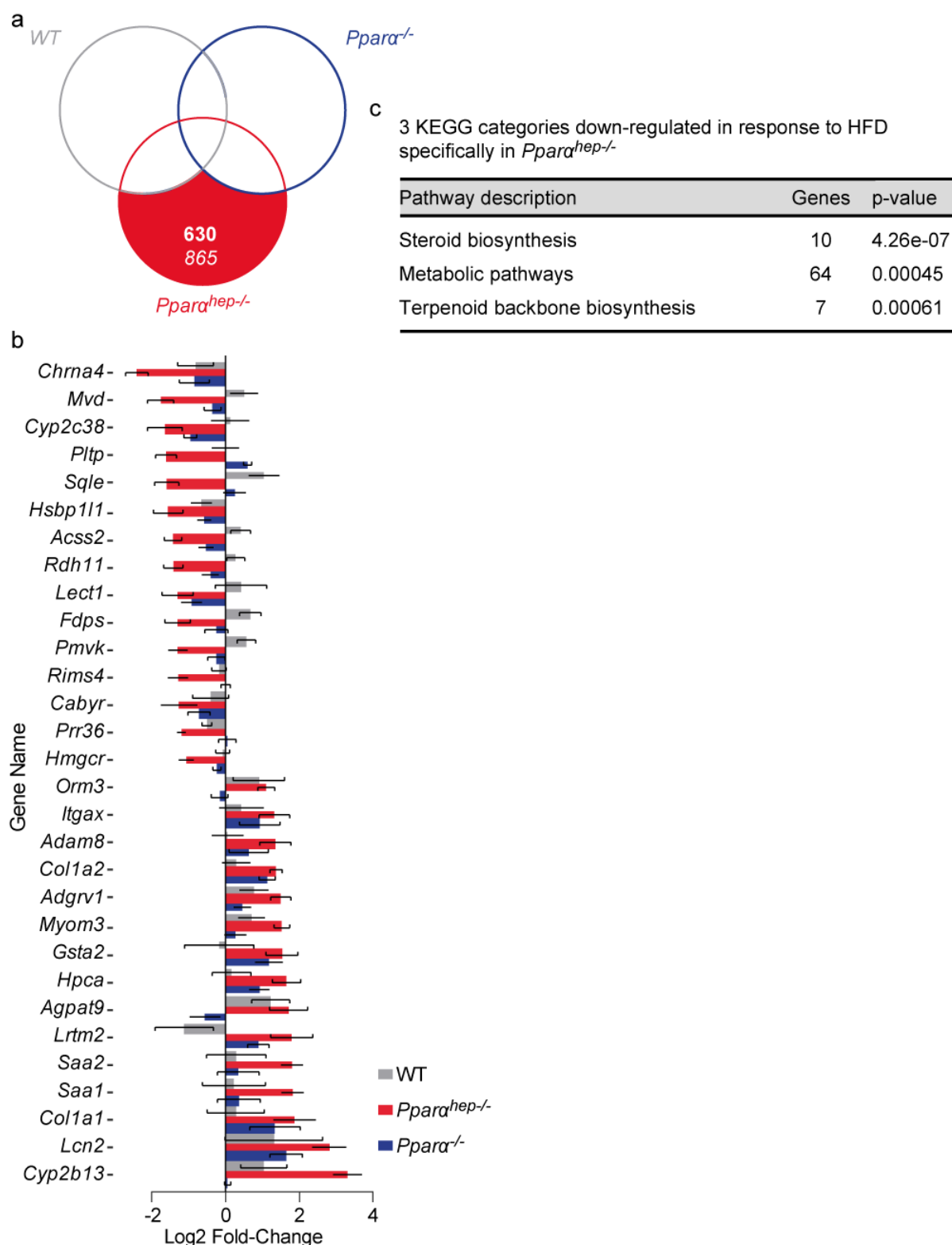
Gene	NCBI Refseq	Forward primer (5'-3')	Reverse primer (5'-3')
<i>Col1a1</i>	NM_007742	GGCTCCTGCTCCTTAGGG	TCGGGTTTCCACGTCTCAC
<i>Fmo3</i>	NM_008030	AAGAAAGGAAGACAAAGAAAAGGCA	AGCTCCAATGATGGCCACTT
<i>Ppar-γ2</i>	NM_011146	GATGCACTGCCTATGAGCACTT	GAATGGCATCTCTGTGCAACC
<i>Vnn1</i>	NM_011704	ATGAGGTTTATGCCTTTGGAGC	CCACAGGTGCGTAAATTGGTAG



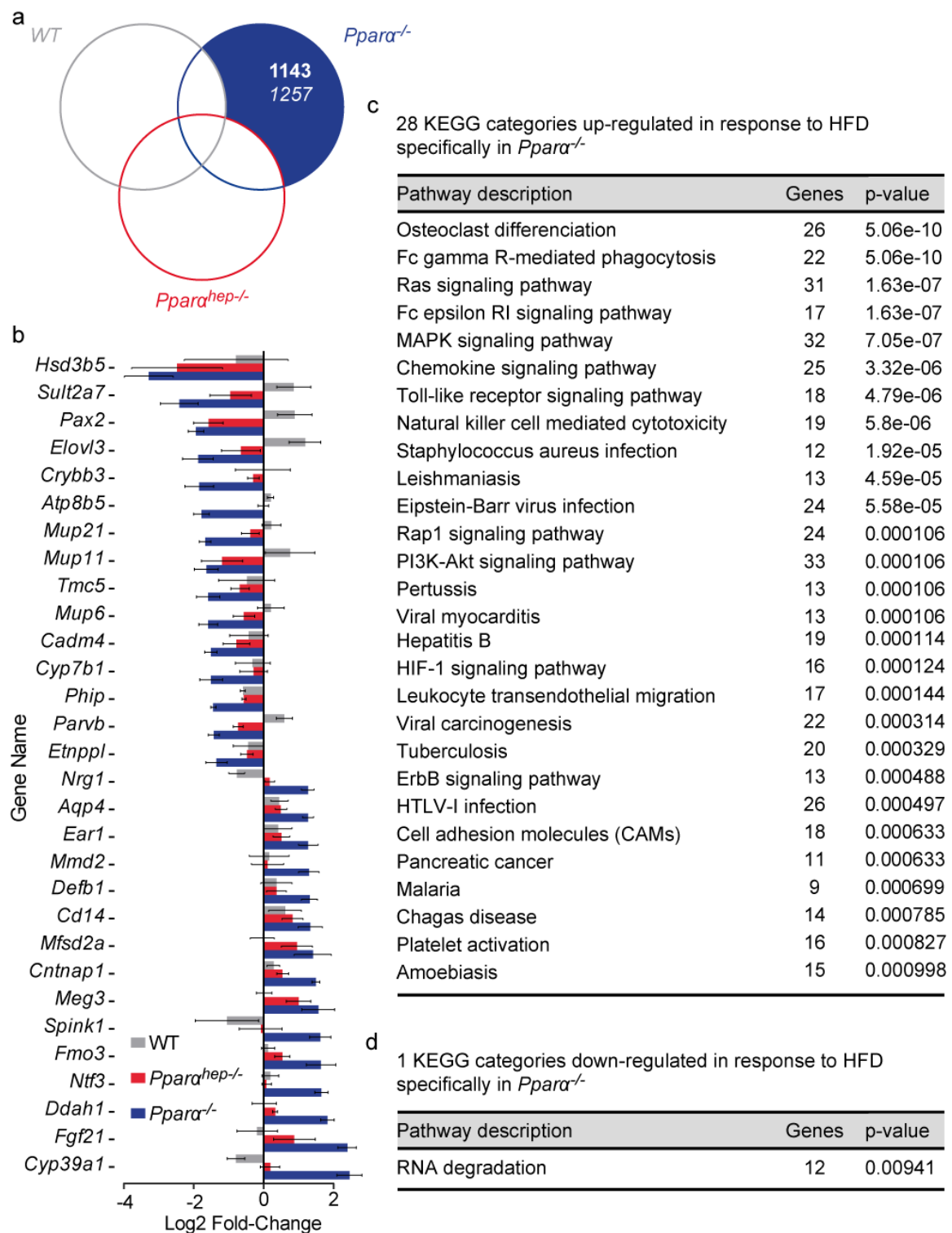
Supplementary Figure 1. Differential hepatic gene expression profiles by comparing *Ppara*^{-/-} to both *WT* and *Ppara*^{hep-/-} mice. (a) Number of differentially expressed genes by comparing *Ppara*^{-/-} to both *WT* and *Ppara*^{hep-/-} mice (adjusted $p \leq 0.05$) (b) Grey bars represent the top 15 induced and repressed genes specifically in *WT* mice compared to *Ppara*^{-/-} mice fed a CTRL diet. Red bars represent the differentially expressed genes between *Ppara*^{hep-/-} and *Ppara*^{-/-} mice fed a CTRL diet ($p \leq 0.05$). (c) Analysis of KEGG categories over-expressed in *Ppara*^{-/-} mice compared to both *WT* mice and *Ppara*^{hep-/-} mice fed a CTRL diet ($p \leq 0.05$). (d) Analysis of KEGG categories under-expressed in *Ppara*^{-/-} mice compared to both *WT* mice and *Ppara*^{hep-/-} mice fed a CTRL diet ($p \leq 0.05$).



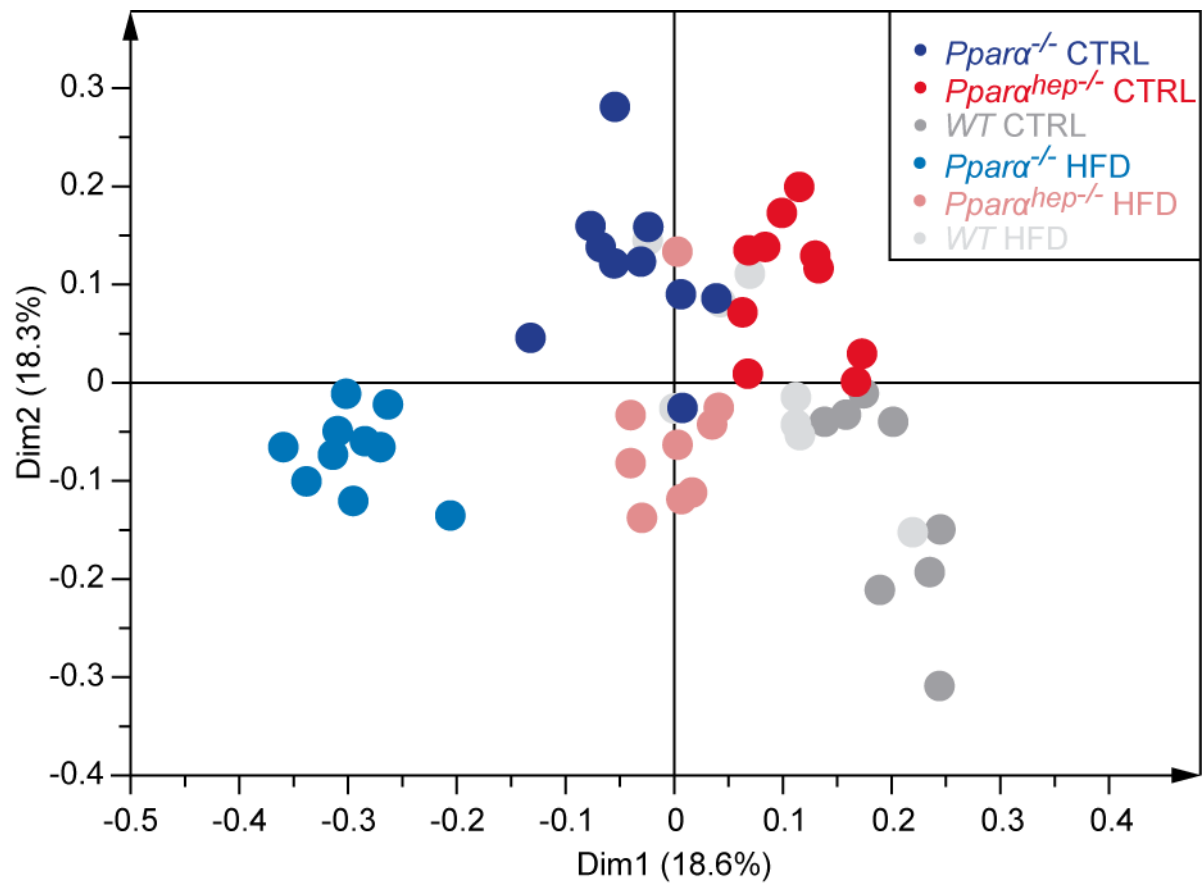
Supplementary Figure 2. Common changes in the hepatic gene expression profiles of WT, *Ppara*^{hep-/-}, *Ppara*^{-/-} mice in response to HFD. (a) Venn diagram presenting the number of overlapping hepatic genes up-regulated (bold) and down-regulated (regular) in response to HFD in WT, *Ppara*^{hep-/-}, and *Ppara*^{-/-} mice (adjusted $p \leq 0.05$) (b) Grey bars represent the top 15 induced and repressed genes specifically in WT mice exposed to CTRL diet vs HFD. Red and blue bars represent the HFD-induced responses in *Ppara*^{hep-/-} and *Ppara*^{-/-}, respectively. (c) Analysis of KEGG categories up-regulated in WT, *Ppara*^{hep-/-} and *Ppara*^{-/-} mice fed a HFD vs. CTRL diet ($p \leq 0.01$). (d) Analysis of KEGG categories down-regulated in WT, *Ppara*^{hep-/-} and *Ppara*^{-/-} mice fed a HFD ($p \leq 0.01$).



Supplementary Figure 4. Specific changes in liver gene expression profiles in *Ppara*^{hep-/-} mice fed a HFD. (a) Venn diagram presenting the number of hepatic genes up-regulated (bold) and down-regulated (regular) in response to HFD in WT, *Ppara*^{hep-/-} and *Ppara*^{-/-} mice (adjusted p-value; $p \leq 0.05$) (b) Red bars represent the top 15 induced and repressed genes in *Ppara*^{hep-/-} mice fed a HFD vs CTRL diet. Grey bars represent the gene expression profile in WT mice and blue bars the gene expression profile in *Ppara*^{-/-} mice (c) Analysis of KEGG categories specifically down-regulated in *Ppara*^{hep-/-} mice fed a HFD ($p \leq 0.01$).



Supplementary Figure 5. Specific changes in liver gene expression profiles in *Ppara*^{-/-} mice fed a HFD. (a) Venn diagram presenting the number of hepatic genes up-regulated (bold) and down-regulated (regular) in response to HFD in WT, *Ppara*^{hep-/-} and *Ppara*^{-/-} mice (adjusted $p \leq 0.05$). (b) Blue bars represent the top 15 induced and repressed genes in *Ppara*^{-/-} mice fed a HFD vs. CTRL diet. Grey bars represent the gene expression profile in WT mice and red the gene expression profile in *Ppara*^{hep-/-} mice (c) Analysis of KEGG categories specifically up-regulated in *Ppara*^{-/-} mice fed a HFD ($p \leq 0.001$).



Supplementary Figure 6. Liver metabolome discriminates whole-body *Ppara* deletion from hepatocyte-specific PPAR α deletion in mice fed a HFD. Two-dimensional PLS-DA score plot of liver extract integrated ¹H-NMR spectra. Each dot represents an observation (animal), projected onto first (horizontal axis) and second (vertical axis) PLS-DA variables.