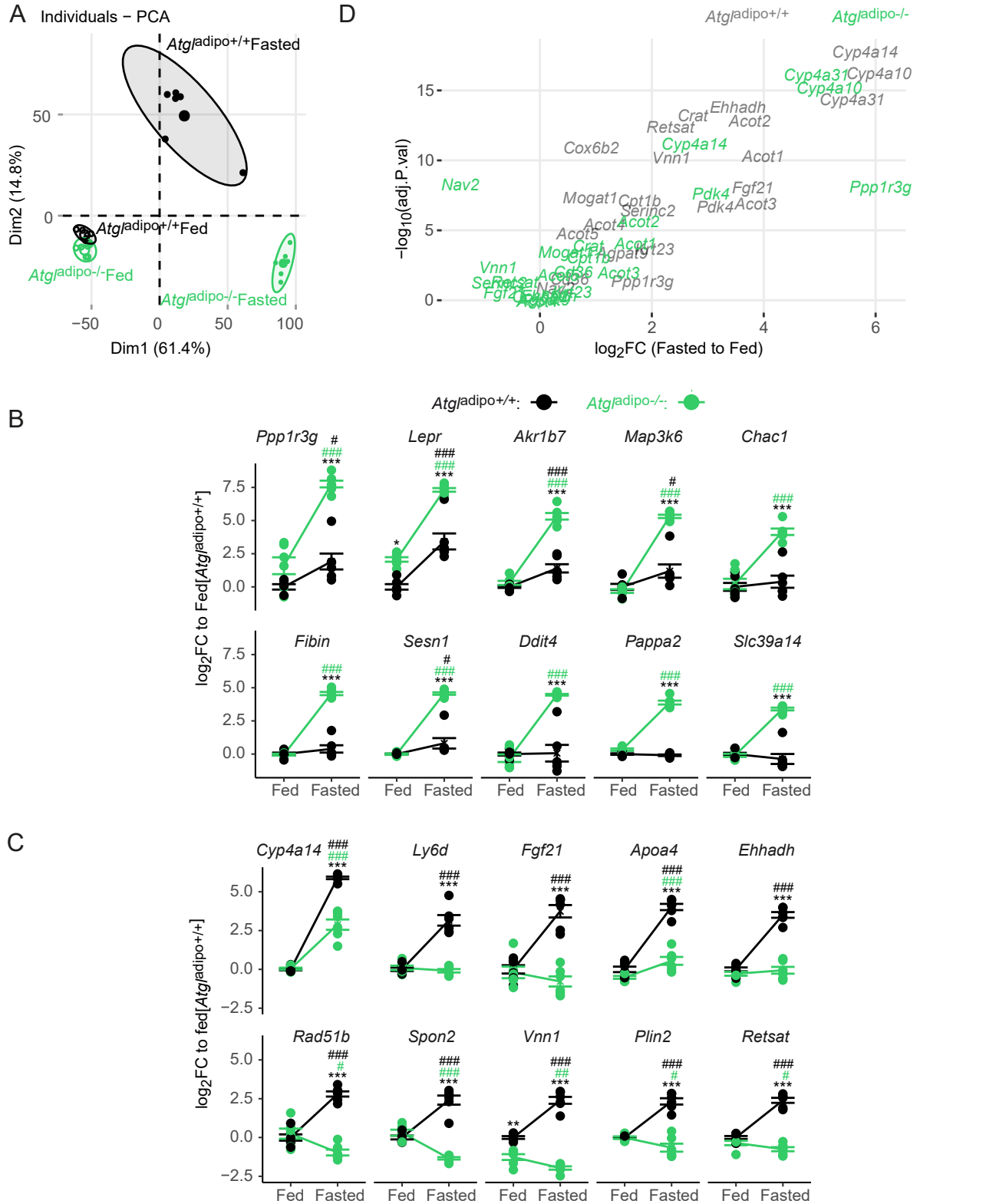


Supplemental information

ATGL-dependent white adipose tissue lipolysis

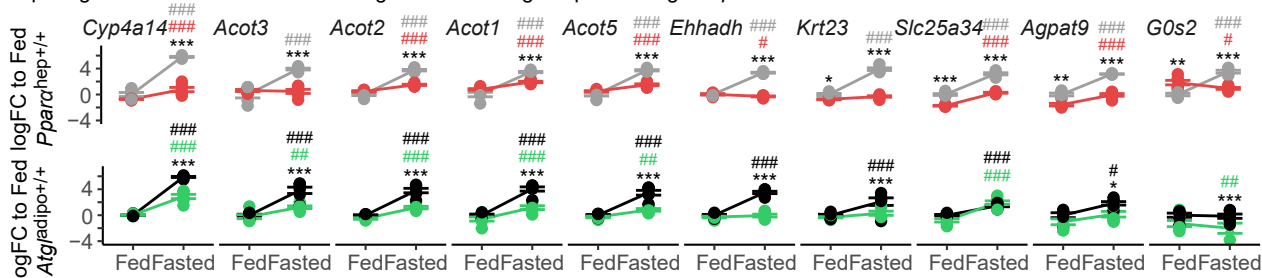
controls hepatocyte PPAR α activity

Anne Fougerat, Gabriele Schoiswohl, Arnaud Polizzi, Marion Régnier, Carina Wagner, Sarra Smati, Tiffany Fougeray, Yannick Lippi, Frederic Lasserre, Ilyès Raho, Valentine Melin, Blandine Tramunt, Raphaël Métivier, Caroline Sommer, Fadila Benhamed, Chantal Alkhoury, Franziska Greulich, Céline Jouffe, Anthony Emile, Michael Schupp, Pierre Gourdy, Patricia Dubot, Thierry Levade, Delphine Meynard, Sandrine Ellero-Simatos, Laurence Gamet-Payrastre, Ganna Panasyuk, Henriette Uhlénhaut, Ez-Zoubir Amri, Céline Cruciani-Guglielmacci, Catherine Postic, Walter Wahli, Nicolas Loiseau, Alexandra Montagner, Dominique Langin, Achim Lass, and Hervé Guillou

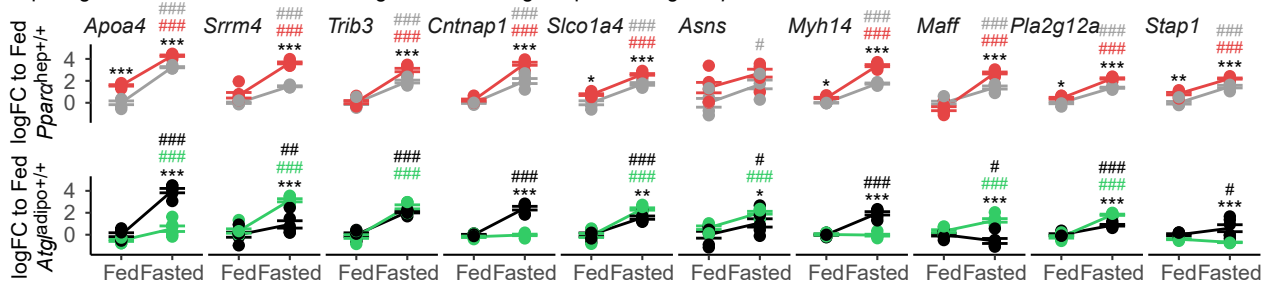


Ppar^{hep+/+}: *Ppar*^{hep-/-}: *Atgl*^{adipo+/+}: *Atgl*^{adipo-/-}:

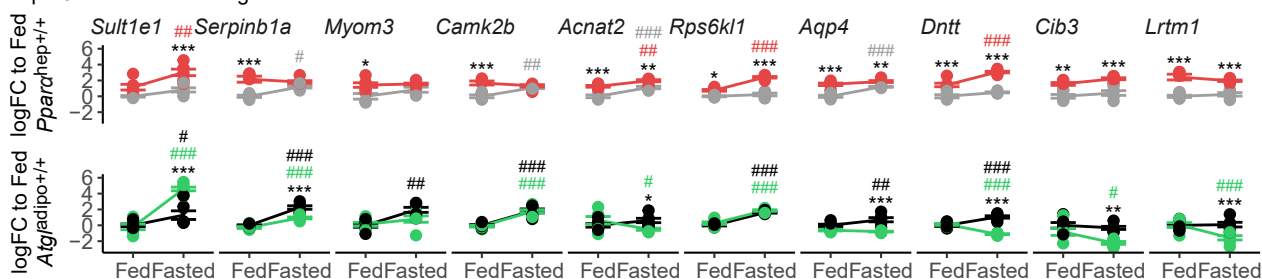
Top 10 genes from cluster 3 with the highest fold-changes upon fasting in *Ppar*^{hep+/+} mice.



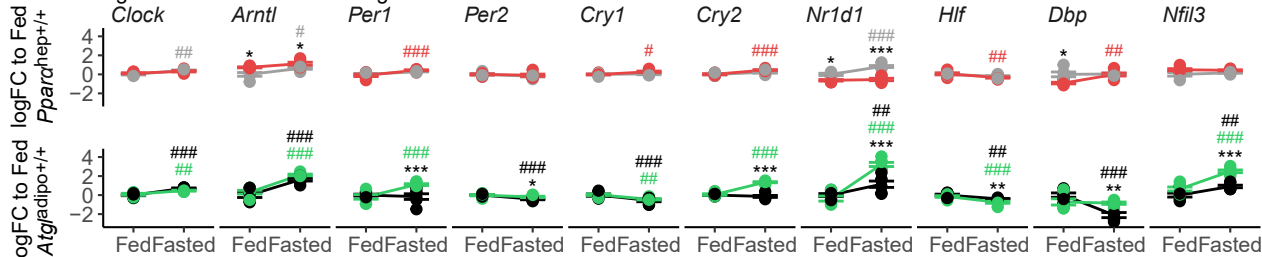
Top 10 genes from cluster 5 with the highest fold-changes upon fasting in *Ppar*^{hep-/-} mice.



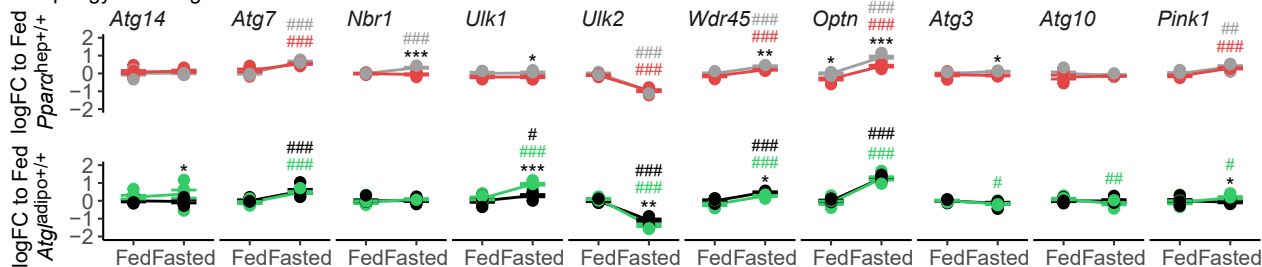
Top 10 most contrasted genes from cluster 4.



Core clock genes and clock-controlled genes.



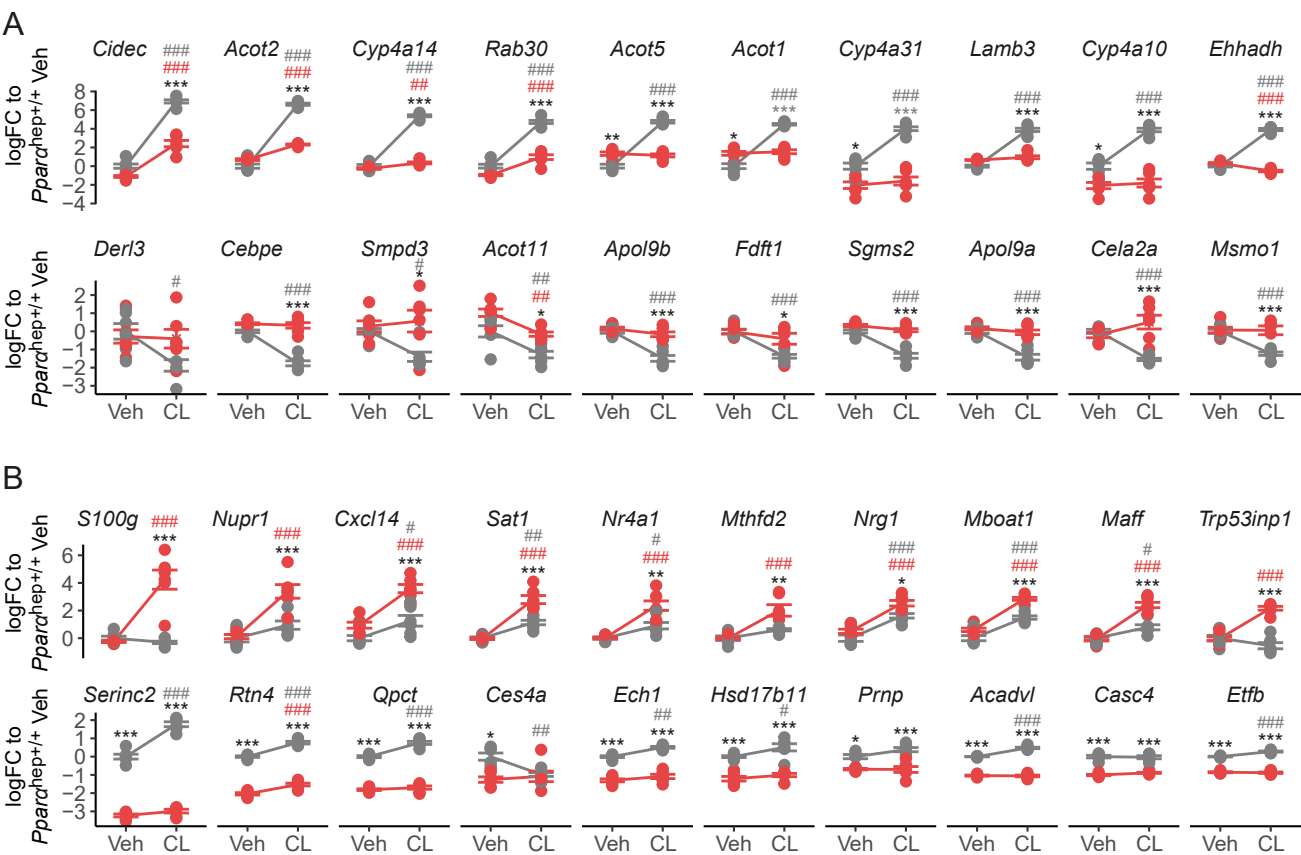
Autophagy-related genes.



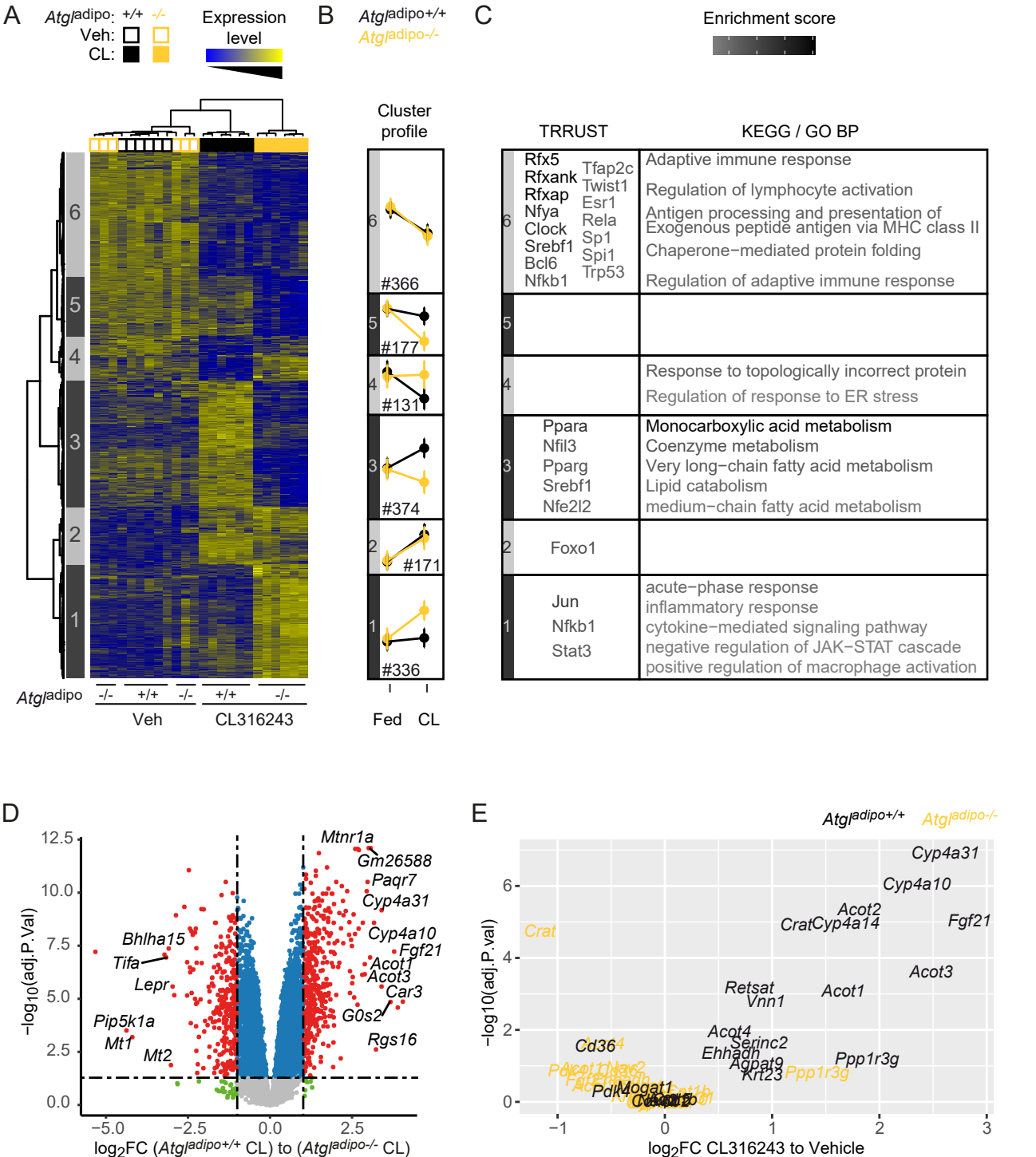
Supplementary Figure S2: Fasting-induced PPARG-dependent hepatic gene expression analyzed in the *Atgl* deficient model.

Related to Figure 2. Microarray experiments performed with liver samples from *Atgl*^{adipo+/+} and *Atgl*^{adipo-/-} mice fed *ad libitum* or fasted for 24 h, and from *Ppar*^{hep+/+} and *Ppar*^{hep-/-} mice fed *ad libitum* or fasted for 24 h (n = 6/group). # fasting effect (colored by genotype), * genotype effect, * or # *adj.p* < 0.05, ** or ## *adj.p* < 0.01, *** or ### *adj.p* < 0.001.

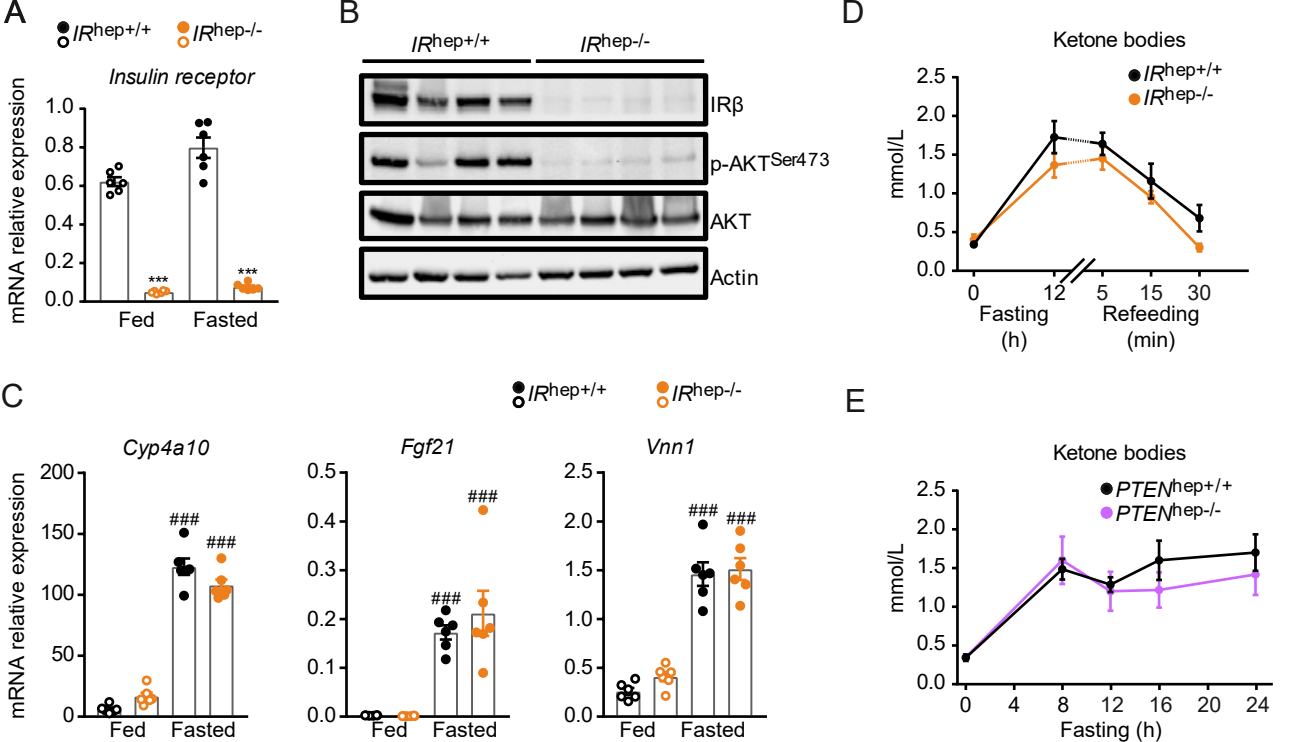
Ppara^{hep+/+}: ● *Ppara*^{hep-/-}: ●



Supplementary Figure S3: Hepatocyte *Ppara* deficiency altered hepatic gene expression in response to β_3 -adrenergic receptor stimulation. Related to Figure 3. **(A-B)** Microarray experiment performed with liver samples from *Ppara*^{hep+/+} and *Ppara*^{hep-/-} fed mice treated with CL316243 (3 mg/kg body weight) or vehicle by gavage for 6 hours (n=6/group). **(A)** Fold-changes of the 10 genes most upregulated (cluster 2) and of the 10 genes most downregulated by CL316243 (cluster 5) in *Ppara*^{hep+/+} mice. **(B)** Fold-changes of the 10 genes most upregulated (cluster 6) and of the 10 genes most downregulated (cluster 3) by CL316243 in *Ppara*^{hep-/-} mice. # CL316243 effect (colored by genotype), * genotype effect, * or # *adj.p* < 0.05, ** or ## *adj.p* < 0.01, *** or ### *adj.p* < 0.001.

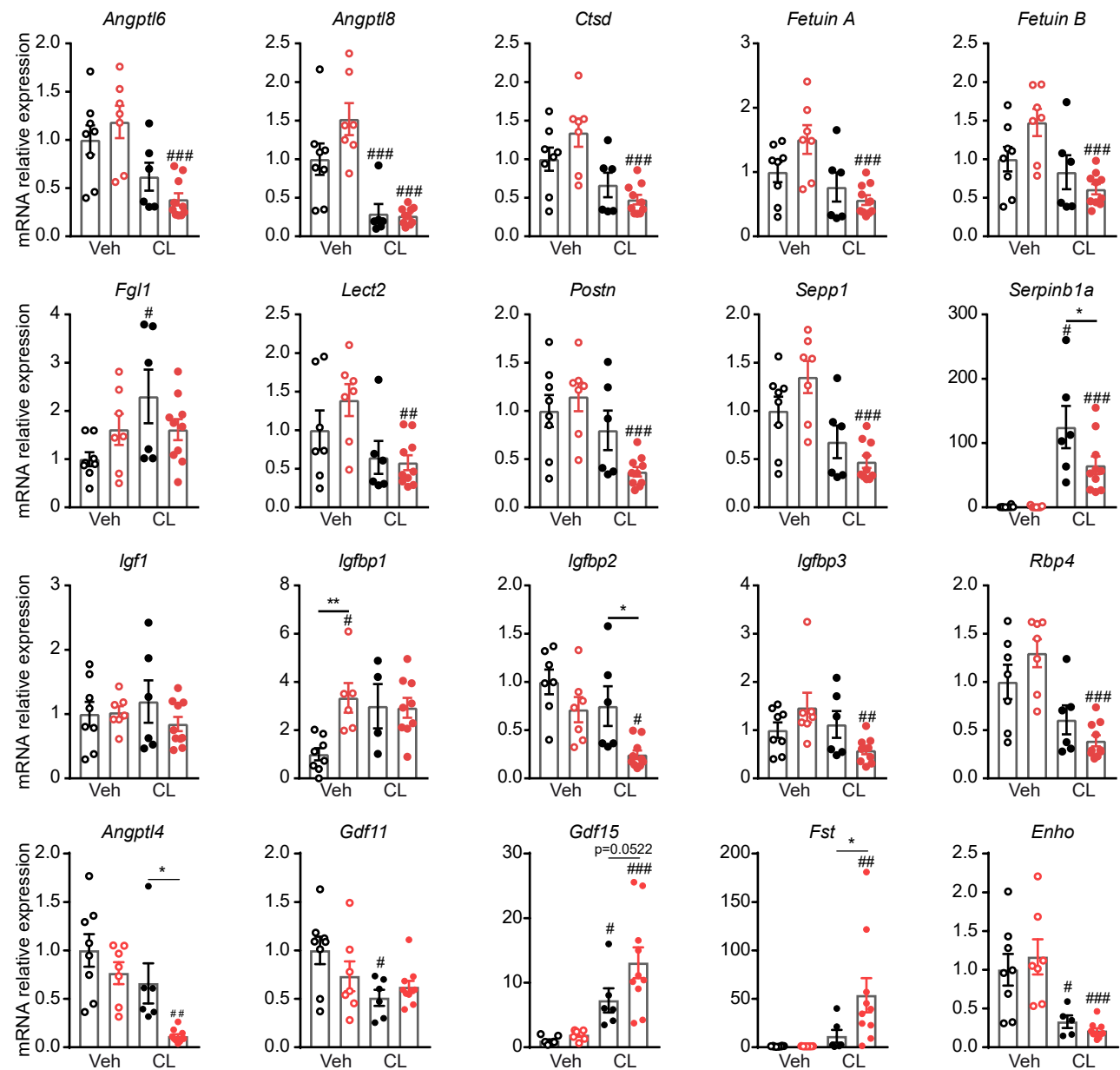


Supplementary Figure S4: Adipocyte *Atgl* deficiency altered hepatic gene expression in response to β 3-adrenergic receptor stimulation. Related to Figure 3. **(A-E)** Microarray experiment performed with liver samples from *Atgl*^{adipo}+/+ and *Atgl*^{adipo}-/- fed mice treated with CL316243 (3 mg/kg body weight) or vehicle by gavage for 6 hours (n = 6/group). **(A)** Heatmap with hierarchical clustering shows the definition of 6 gene clusters (FC > 2; $p \leq 0.05$). **(B)** Schematic representation of the mean cluster profiles in each cluster (unique Entrez gene ID from Metascape). **(C)** Gene Ontology (GO) analysis and enrichment of transcription factors (TF) of genes in each heatmap clusters (FC > 2; $adj.p < 0.05$). **(D)** Volcano plot of differences in gene expression between *Atgl*^{adipo}+/+ and *Atgl*^{adipo}-/- in response to CL316243 treatment. **(E)** Volcano plot representing differences in gene expression between *Atgl*^{adipo}+/+ and *Atgl*^{adipo}-/- in response to CL316243 treatment of selected target genes of PPAR α .

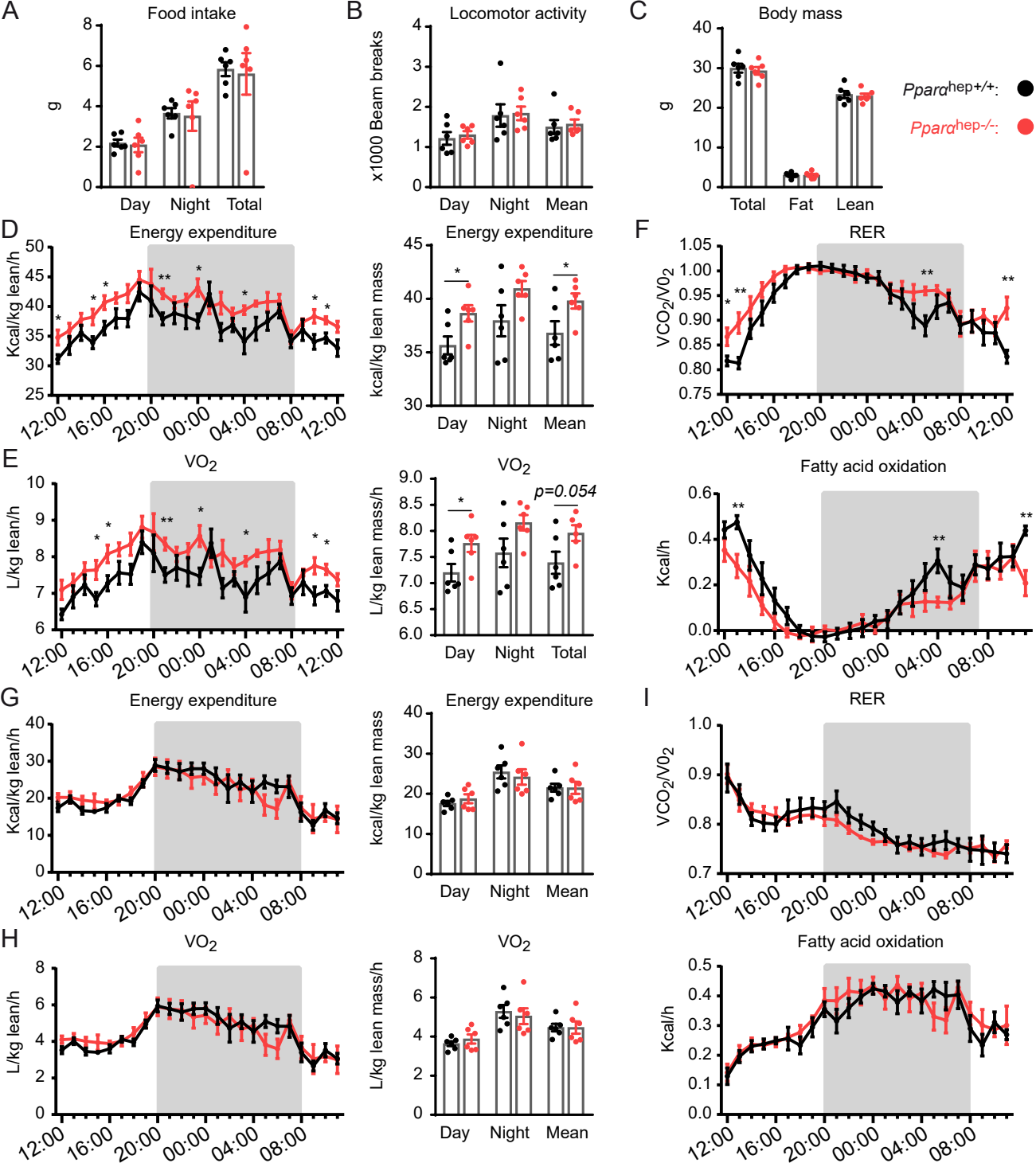


Supplementary Figure S5: Modulation of hepatocyte insulin signaling does not influence hepatocyte PPAR α -dependent responses in the liver during fasting and refeeding. Related to STAR Methods. **(A)** mRNA relative expression of Insulin receptor measured by qRT-PCR in the liver of $IR^{hep+/+}$ and $IR^{hep-/-}$ mice fed *ad libitum* or fasted for 24 h. **(B)** Western blot analysis of Insulin receptor β (IR β), phosphorylated AKT, total AKT and β -actin in the liver of $IR^{hep+/+}$ and $IR^{hep-/-}$ mice fed *ad libitum*. **(C)** mRNA relative expression of *Cyp4a10*, *Vnn1* and *Fgf21* measured by qRT-PCR in the liver of $IR^{hep+/+}$ and $IR^{hep-/-}$ mice fed *ad libitum* or fasted for 24 h. **(D)** Circulating levels of ketone bodies (β -hydroxybutyrate) of $IR^{hep+/+}$ and $IR^{hep-/-}$ in the fed and fasted state, and after 5, 15 and 30 min of refeeding. **(E)** Circulating levels of ketone bodies (β -hydroxybutyrate) in $PTEN^{hep+/+}$ and $PTEN^{hep-/-}$ fasted for 0, 8, 12, 16 and 24 h. Results are the mean \pm SEM. # fasting effect, * genotype effect. * or # $p < 0.05$, ** or ## $p < 0.01$, *** or ### $p < 0.001$.

Ppara^{hep+/+}: Veh ○ CL ● *Ppara*^{hep-/-}: Veh ○ CL ●



Supplementary Figure S6: Relative gene expression of *Angptl6*, *Angptl8*, *Ctsd*, *Fetuin A*, *Fetuin B*, *Fgl1*, *Lect2*, *Postn*, *Sepp1*, *Serpinb1a*, *Igf1*, *Igfbp1*, *Igfbp2*, *Igfbp3*, *Rbp4*, *Angptl4*, *Gdf11*, *Gdf15*, *Fst* and *Enho*. Related to Figure 4. Gene expression was measured by qRT-PCR in fasted *Ppara*^{hep+/+} and *Ppara*^{hep-/-} mice treated with CL316243 (3 mg/kg body weight) or vehicle by gavage for 6 hours. Data are means \pm SEM. # CL316243 effect, * genotype effect, * or # $p < 0.05$, ** or ## $p < 0.01$, *** or #### $p < 0.001$.



Supplementary figure S7: Calorimetry for *Ppara*^{hep+/+} and *Ppara*^{hep-/-} mice during 24 h of cold exposure at 7°C or 24 h of fasting. (Related to Figure 4. (A–F) *Ppara*^{hep+/+} and *Ppara*^{hep-/-} mice were individually housed in a calorimetric cage and exposed to 7°C for 24 h. (A) Cumulative food intake calculated in total and during the light and dark phase. (B) Locomotor activity calculated in mean and during the light and dark phase. (C) Body composition. (D) Energy expenditure normalized per lean body mass. Bar graph (right panel) represents the average of energy expenditure during the light and dark phase in each group. (E) Rate of VO_2 consumption normalized per lean body mass. Bar graph (right panel) represents the average of O_2 consumption during the light and dark phase in each group. (F) Respiratory exchange ratio (RER) and fatty acid oxidation rate. (G–L) *Ppara*^{hep+/+} and *Ppara*^{hep-/-} mice were individually housed in a calorimetric cage and fasted for 24 h. (G) Energy expenditure normalized per lean body mass. Bar graph (right panel) represents the average of energy expenditure during the light and dark phase in each group. (H) Rate of VO_2 consumption normalized per lean body mass. Bar graph (right panel) represents the average of O_2 consumption during the light and dark phase in each group. (I) Respiratory exchange ratio (RER) and fatty acid oxidation rate. Results are the mean \pm SEM. * genotype effect, * $p < 0.05$, ** $p < 0.01$.

**Supplementary Table S1. Oligonucleotide sequences for real-time qPCR.
Related to STAR methods**

Gene	NCBI Refseq	Forward primer	Reverse primer
<i>Angptl4</i>	NM_020581.2	TTCCCTGCCCTTCTCTACTTG	TACAGGTACCAAACCACCAGCC
<i>Angptl6</i>	NM_145154.2	GAATTGCCGCAAACCTCACT	ATGGCCGTCACCTCTCACAG
<i>Angptl8</i>	NM_001080940.1	CCCACCAAGAATTTGAGACCTT	ACTGTTGCTGCTCTGCCATCT
<i>Ctsd</i>	NM_009983	CTTCGTCTCCTTCGCGATTAT	GTCCGACGGATAGATGTGAACTT
<i>Cyp4a10</i>	NM_010011	TCCAGCAGTTCCTCATCACCT	TTGCTTCCCAGAACCATCT
<i>Cyp4a14</i>	NM_007822	TCAGTCTATTTCTGGTGTGTTT	GAGCTCCTTGCTCTCAGATGGT
<i>Dio2</i>	NM_010050.4	ACAGCTTCCTCTAGATGCCTACA	GGGAGCATCTTCACCCAGTTT
<i>Ehhadh</i>	NM_023737	CGTCTCCTCGGTTGGTGTTT	ATTATCTTCTTTGCAGTATCTAGCTGCTT
<i>Elovl3</i>	NM_007703	GCCTCTCATCCTCTGGTCCT	TGCCATAAACTTCACATCCT
<i>Enho</i>	NM_027147	CCGGGCTCAACTCAGGC	TGGTGCTCTGTCCACACAC
<i>Fetuina</i>	NM_013465	ATCGACAAAGTCAAGGTGTGGTCT	TGTCAACTTCCATCTCATACACCACT
<i>Fetuinb</i>	NM_021564	CTCGTCAAAGTCACCAAGGCTAT	CACATAGTAAGCAGGGCCAGAC
<i>Fgl1</i>	NM_145594.2	TGCAAACCTGAACGGTGTGTTT	TTCAAGGAATACCACCACCCA
<i>Fgf21</i>	NM_020013.4	AAAGCCTCTAGGTTTCTTTGCCA	CCTCAGGATCAAAGTGAGGCG
<i>Fst</i>	NM_008046.2	TGCTGCTACTCTGCCAGTTCAT	CACTCTTCTTGCTCAGTTCTGTC
<i>Gadd45a</i>	NM_007836	GCGCAGACCCCGGAC	TCCATGTAGCGACTTTCCCG
<i>Gdf15</i>	NM_011819	GCTGTCCGGATACTCAGTCCA	TTGACGCGGAGTAGCAGCT
<i>Igf1</i>	NM_0105124	GATCTGCCTCTGTGACTTCTTGAA	CAGGTAGAAGAGGTGTGAAGACGA
<i>Igfbp1</i>	NM_008341.4	CCTGCCAACGAGAACTCTAT	AGGGATTTTCTTTCCACTCC
<i>Igfbp2</i>	NM_008342	GCATGGCCGGTACAACCTTA	GCTGTCCGTTTACAGACATCTT
<i>Igfbp3</i>	NM_008343	CAGGCAGCCTAAGCACCTAC	CTCCTCGGACTCACTGATGTTTC
<i>Inhbe</i>	NM_008382.3	TCAGCTTTGCTACCATCATAGACA	CATGGAGCGGTAGGTTGAAGT
<i>Lect2</i>	NM_010702	GTGGACAGTACTCTGCTCAAA	TCCCAGTGAATGGTGCATAC
<i>Pgc1α</i>	NM_008904	CAATCGGAAATCATATCCAACCA	CTGTGAGGACCGTAGGAAGT
<i>Pparα</i>	NM_011144	CCCTGTTTGTGGCTGCTATAATTT	GGGAAGAGGAAGGTGTCATCTG
<i>Pparα (genotyping)</i>	NM_011144	GTACCACTACGGAGTTC	GAATAGTTCGCCGAAAG
<i>Postn</i>	NM_015784	GAATGCTGCCCTGGCTATATGA	AATGCCAGCGTGCCATAAA
<i>Prdm16</i>	NM_027504.3	TCCGCGGTCAAGATGAAGTACTGG	TCACTGCCATCCGACATGTC
<i>Rbp4</i>	NM_011255	GCCAAGTTCAAGATGAAGTACTGG	TGTCGTAGTCCGTGTCGATGA
<i>Sepp1</i>	NM_009155	AAGATCGCTTACTGTGAGGAGAGG	GCTGAGGTCACAGTTTACAGAAGTC
<i>Serpina1a</i>	NM_025429	GGACGAGTCCACGGGCTCTTA	AGTTTGACGTGGACATCAATGAATTC
<i>Tbp</i>	NM_013684	ACTTCGTGCAAGAAATGCTGAA	GCAGTTGTCCGTGGCTCTCT
<i>Ucp1</i>	NM_009463.3	CCTGCCTCTCTCGGAAACAA	TGTAGGCTGCCCAATGAACA