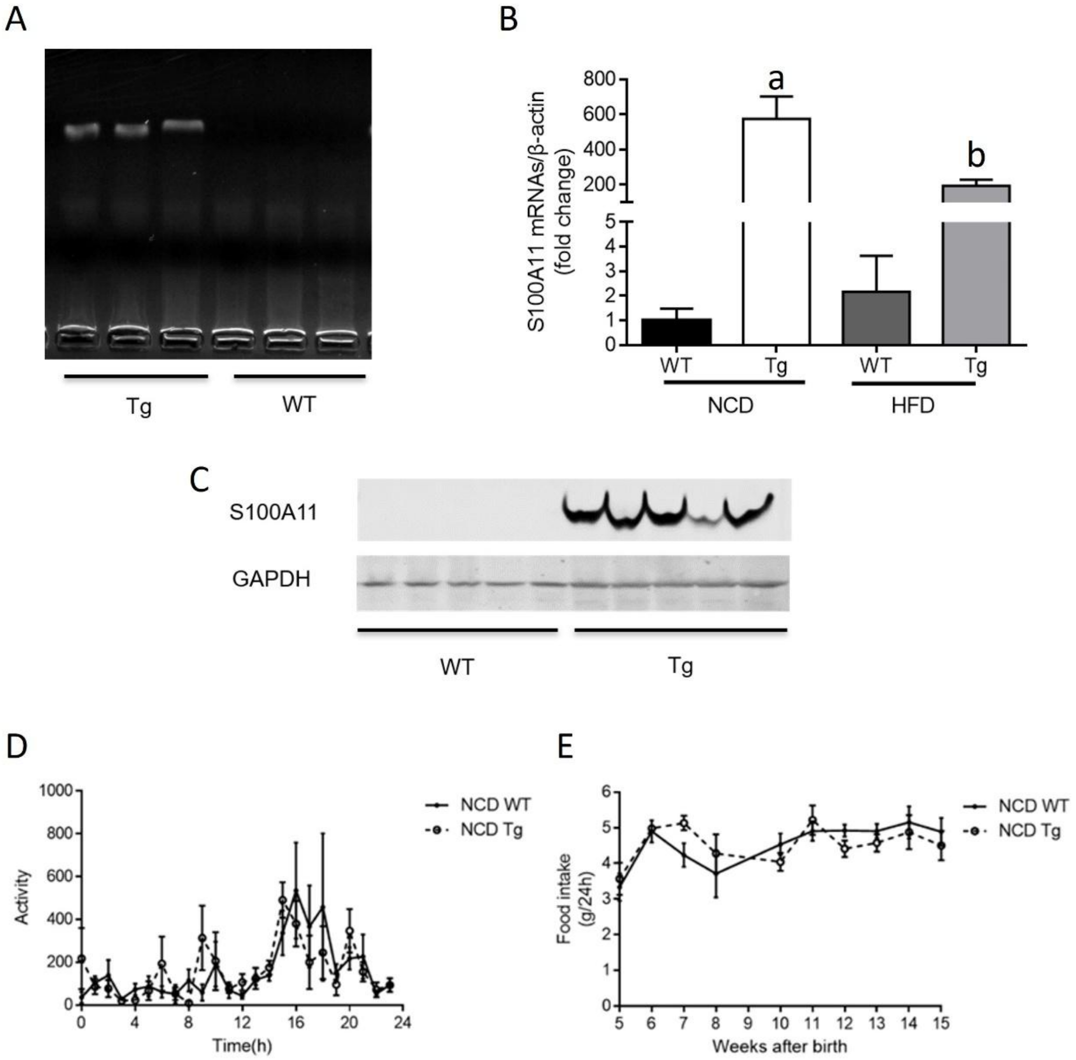
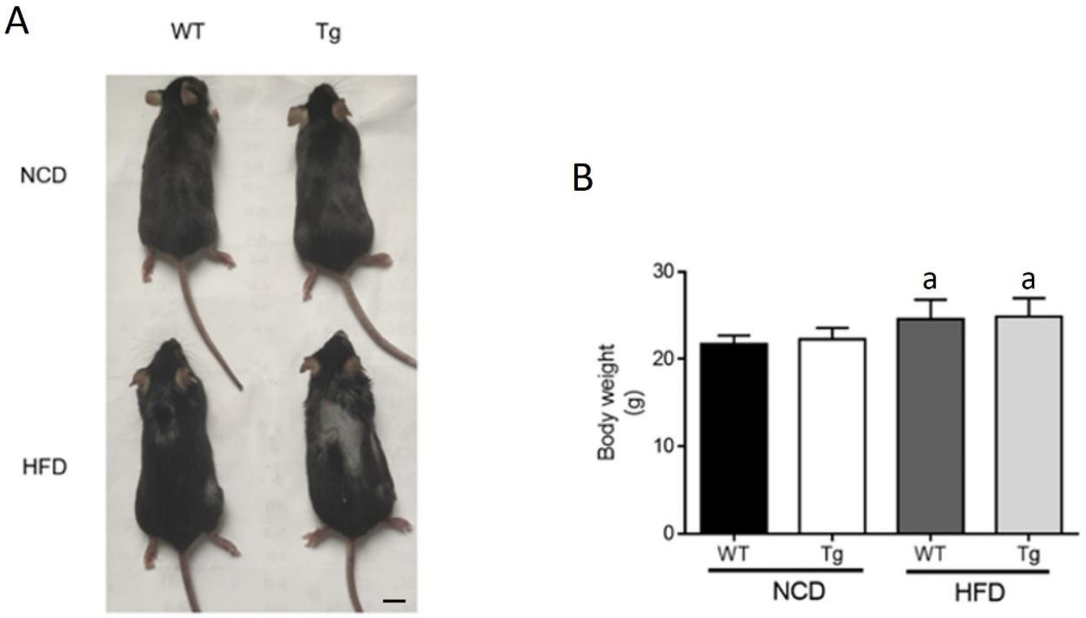
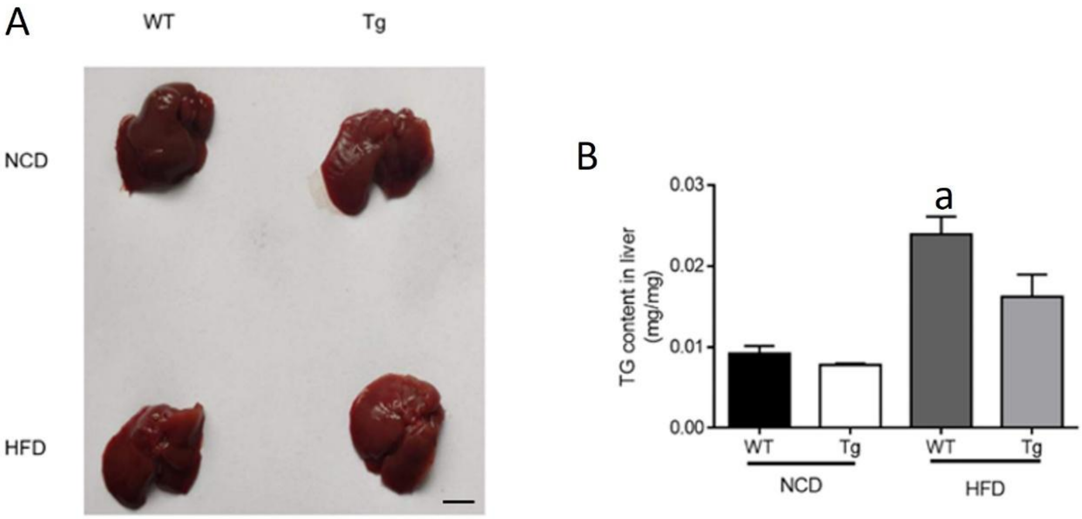


Supplementary Figure 1 Activity and food intake of mice under normal-chow diet. A: Genotyping results of mouse tail DNA; B: Hepatic mRNA expression levels of S100A11 in mice; C: Hepatic protein expression levels of S100A11 in mice. D: Activity of mice under normal-chow diet; E: Food intake of mice under normal-chow diet. All data are presented as means ± SE. n = 6 mice/group. Statistical analysis was performed using one-way analysis of variance. *P* values were adjusted for multiple testing using the Bonferroni correction: $^{a}P < 0.05$ vs NCD WT, $^{b}P < 0.05$ vs HFD WT.

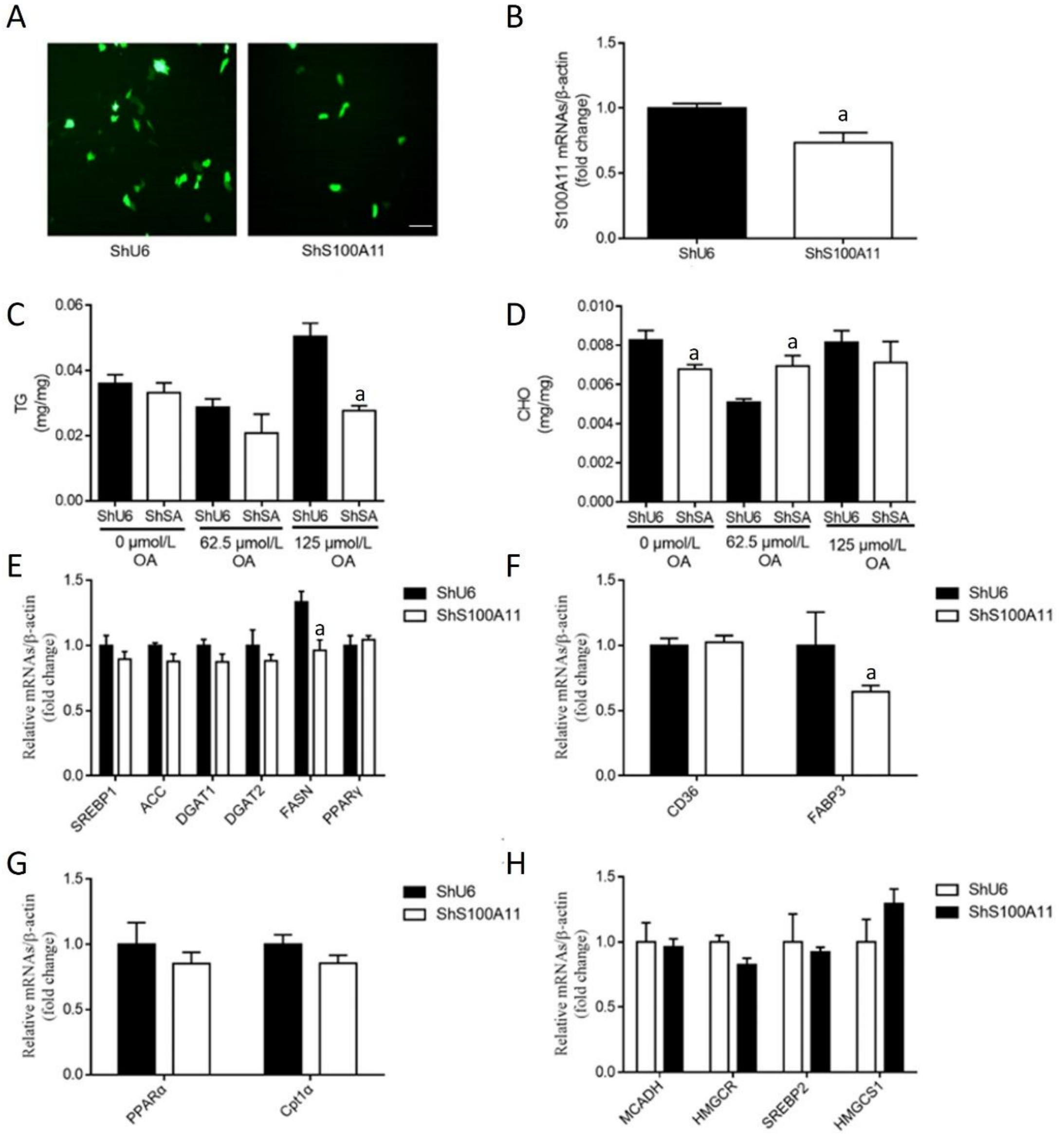


Supplementary Figure 2 Body weight of female S100A11-hTg mice. Five-week-old female S100A11-hTg mice and littermate control mice were fed normal diet or high-fat diet for 12 weeks. A: General picture of mice at 17 weeks of age, scale bar: 1 cm; B: Body weight of mice at 17 weeks of age. All data are presented as means ± SE. $n = 6$ mice/group. Statistical analysis was performed using one-way analysis of variance, P values were adjusted for multiple testing using the Bonferroni correction: $^{a}P < 0.05$ versus NCD wild type (WT).

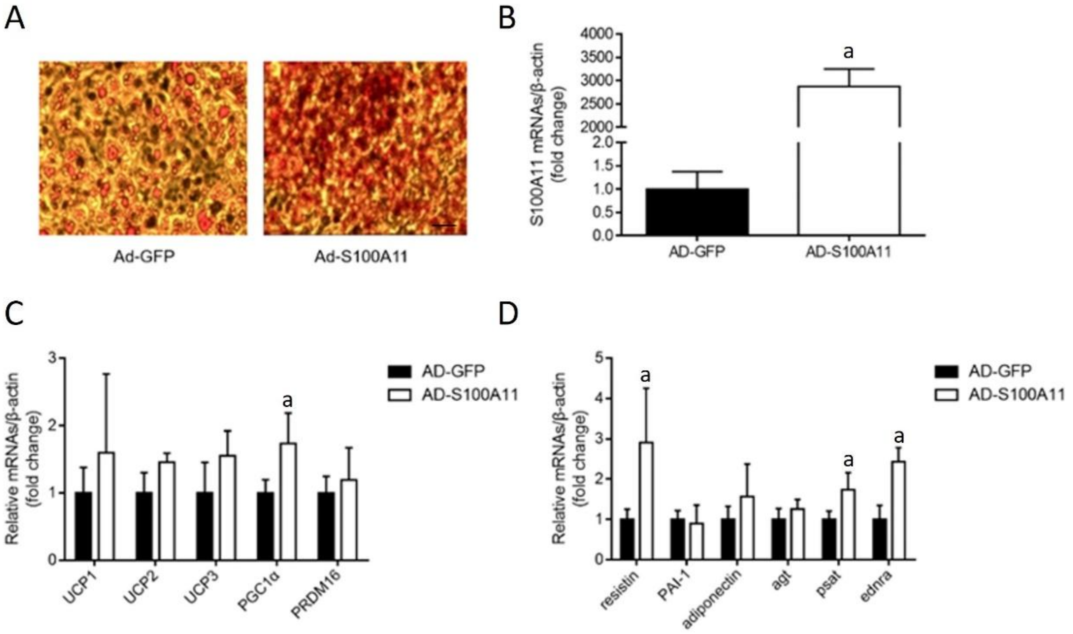


Supplementary Figure 3 Liver lipid accumulation in female S100A11-hTg mice.

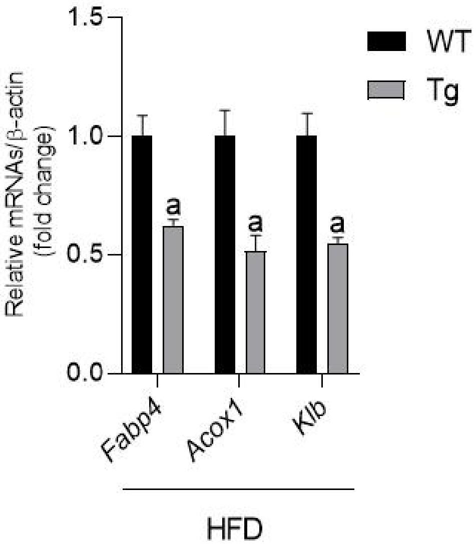
Five-week-old female S100A11-hTg mice and littermate control mice were fed normal-chow diet (NCD) or high-fat diet (HFD) for 12 weeks. A: General liver image of mice at 17 weeks of age, scale bar: 1 cm; B: Triglyceride (TG) concentration in the liver of mice at 17 weeks of age. All data are presented as means ± SE. $n = 6$ mice/group. Statistical analysis was performed using one-way analysis of variance, P values were adjusted for multiple testing using the Bonferroni correction: $^{a}P < 0.05$ versus NCD wild type (WT).



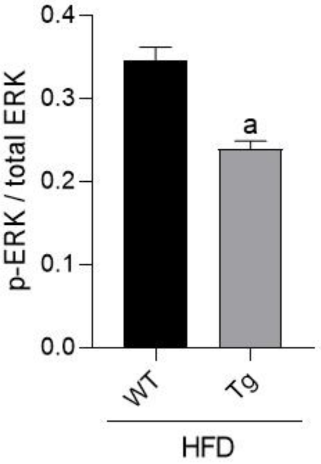
Supplementary Figure 4 Knockdown of S100A11 gene inhibits lipid accumulation in mouse-derived normal liver cell line AML12 cells. A: AML12 cells infected with shS100A11, shU6 as a control group, and observed under a fluorescent microscope after 48 h, scale bar: 50 μm; B: Real-time PCR was used to detect expression of *S100a11* mRNA; C: AML12 cells were transfected with shS100A11, or shU6 as a control, and treated with 0, 62.5, or 125 nmol/L oleic acid for 36 h to detect triglyceride (TG) concentration; D: AML12 cells were transfected with shS100A11, or shU6 as a control, and treated with 0, 62.5, or 125 nmol/L oleic acid for 36 h to detect cholesterol (CHO) concentration; E–H: Real-time PCR was used to detect expression level of liver lipid metabolism. All data are presented as mean ± SE. n = 3–5 biological repeats. Statistical analysis was performed using unpaired two-tailed Student's t test: $^{a}P < 0.05$ versus shU6.



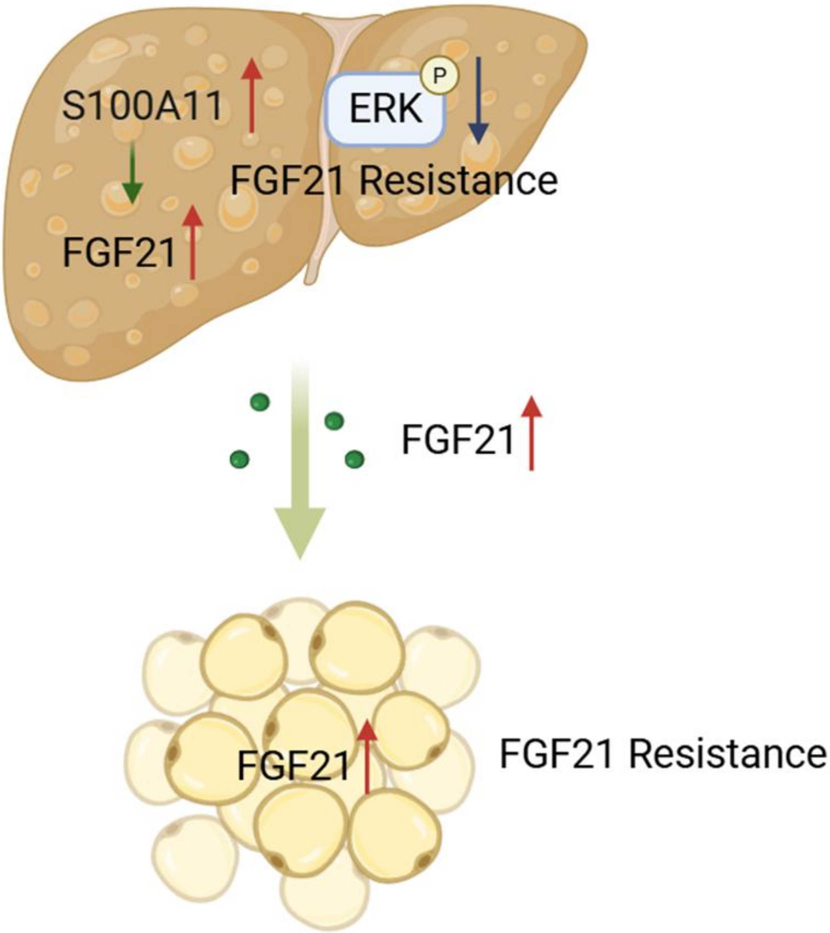
Supplementary Figure 5 Effect of overexpression of S100A11 on lipid accumulation in brown adipocytes. Ad-S100A11 was used to infect fused brown adipocytes and differentiated simultaneously. After 6 days: A: Oil Red O staining was detected, scale bar: 100 μm; B Real-time PCR was used to detect expression of S100A11 mRNA; C, D: Real-time PCR was used to detect expression of genes related to brown adipocytes. All data are presented as means ± SE. *n* = 4–6 biological repeats. Statistical analysis was performed using unpaired two-tailed Student’s *t* test: $^{a}P < 0.05$ versus Ad-GFP.



Supplementary Figure 6 qPCR validation of key genes in liver tissues. All data are presented as means ± SE. *n*=6 biological repeats. Statistical analysis was performed using unpaired two-tailed Student's t-test: $^{a}P < 0.05$ vs HFD WT.



Supplementary Figure 7 p-ERK/total ERK ratio of liver tissue. All data are presented as means ± SE. *n*=6 biological repeats. Statistical analysis was performed using unpaired two-tailed Student's t-test: $^{a}P < 0.05$ vs HFD WT.



Supplementary Figure 8 Schematic diagram. Upregulation of S100A11 in the liver under our experimental conditions, the consequent elevation of circulating FGF21 levels, the development of FGF21 resistance as evidenced by decreased ERK phosphorylation in target tissues, and the proposed downstream effects on hepatic lipid accumulation and adipose tissue browning.

Supplementary Table 1 List and sequence of primers

	Upstream primer (5-3)	Downstream primer (5-3)
UCP1	GGACGACCCCTAATCTAATG	CATTAGATTAGGGGTCGTCC
PGC1a	GATTGAAGTGGTGTAGCGAC	GTCGCTACACCACTTCAATC
PRDM16	CCACCAGCGAGGACTTCAC	GGAGGACTCTCGTAGCTCGAA
Ednra	CGGAGATCAACTTTCTGG	TGGAGACGATTTCAATGG
resistin	TCCTTGTCCCTGAACTGC	ACGAATGTCCCACGAGC
adiponectin	TGTTGGAATGACAGGAGCTG	CGAATGGGTACATTGGGAAC
PAI-1	AGGGCTTCATGCCCCACTTCTTCA	AGTAGAGGGCATTCACCAGCACCA
HMGCS1	AACTGTGGTCTCCAGGTCGGT	AGTCTGCGGTCTCCTTGCTTT
HMGCR	TGATTGACCTTTCCAGAGCAAG	CTAAAATTGCCATTCCACGAGC
SREBP2	CCTGGGAGACATCGACGAGAT	TGAATGCCGTTGCACTGAAG
SREBP1	ACAGTGACTTCCCTGGCCTAT	GCATGGACGGGTACATCTTCAA
DGAT1	TTCCGCCTCTGGGCATT	AGAATCGGCCCACAATCCA
DGAT2	ATTGCTGGCTCATCGCTGT	GGGAAAGTAGTCTCGAAAGTAGC
ACC	TGGTCGTGACTGCTCTGTGC	GTAGCCGAGGGTTCAGTTCC
CD36	TGGTCAAGCCAGCTAGAAA	CCCAGTCTCATTTAGCCAC
FABP3	GAACTCGACTCCCAGCTTGAA	AAGCCTACCACAATCATCGAAG
FASN	TGGGTTCTAGCCAGCAGAGT	ACCACCAGAGACCGTTATGC
ACSL1	CAAGCCTCCAGTACCTGAAGATC	AACGTGTTCTCTGTCATTTTCACAA
aSMA	CCCAGACATCAGGGAGTAATGG	TCTATCGGATACTTCAGCGTCA
Collagen1	CAATGGCACGGCTGTGTGCG	AGCACTCGCCCTCCCGTCTT
Collagen4	ATCCGGCCCTTCATTAGC	ACTGCGGAATCTGAATGGTC
Klb	TGTTCTGCTGCGAGCTGTTAC	TACCGGACTCACGTACTGTTT
Acox1	TAACTTCCTCACTCGAAGCCA	AGTTCCATGACCCATCTCTGTC
Fabp4	AAGGTGAAGAGCATCATAACCCT	TCACGCCTTTCATAACACATTCC
β-actin	ATCTGGCACCACACCTTC	AGCCAGGTCCAGACGCA
GAPDH	ATGACATCAAGAAGGTGGTG	CATACCAGGAAATGAGCTTG

Supplementary Table 2 Proteomics analysis of liver tissues from wild-type and S100A11 transgenic mice

Gene Symbol	Protein Name	WT Mean	TG Mean	Fold Change (TG/WT)	Regulation
Fgf21	Fibroblast growth factor 21	8853.87	69340.84	7.83	Up
Me1	Malic enzyme 1	8817.54	36705.93	4.16	Up
Fabp1	Fatty acid-binding protein 1	7990.58	12488.06	1.56	Up
Scd3	Stearoyl-CoA desaturase 3	11086.27	13481.43	1.22	Up
Cpt1a	Carnitine palmitoyltransferase 1A	12810.38	13885.68	1.08	Up
Cyp4a14	Cytochrome P450 4a14	17213.71	10969.18	0.64	Down
Scd4	Stearoyl-CoA desaturase 4	27130.91	13134.68	0.48	Down