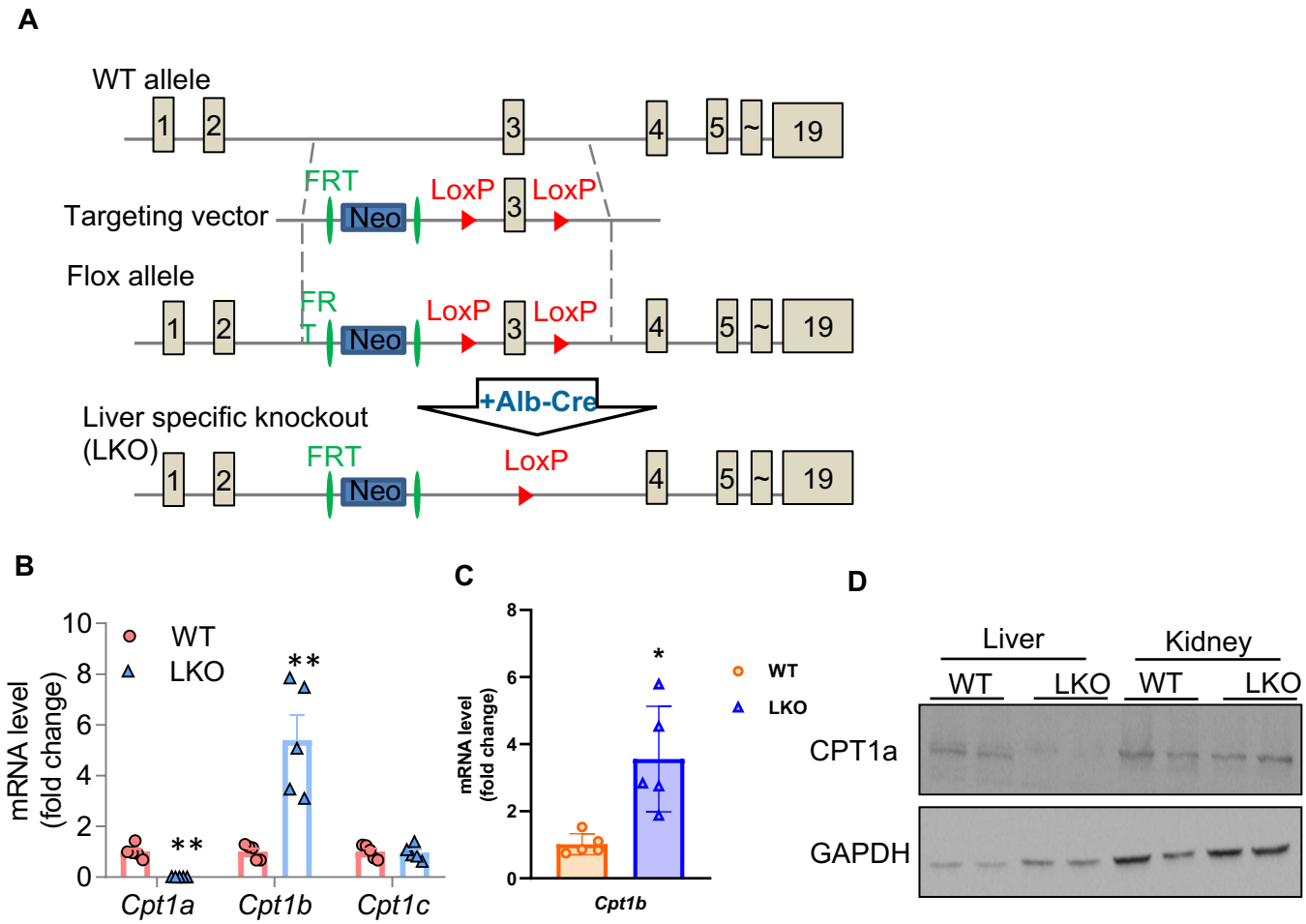
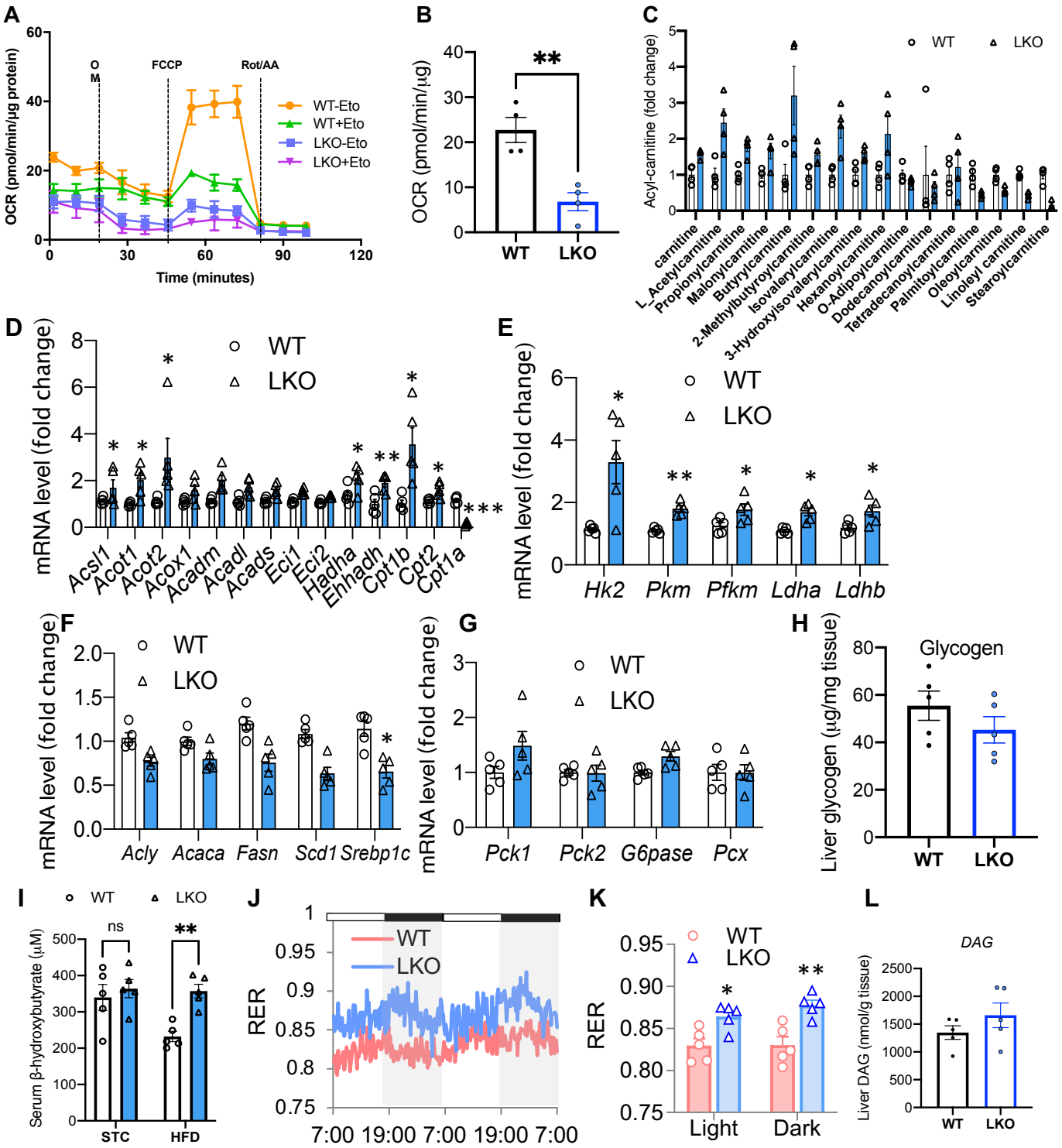
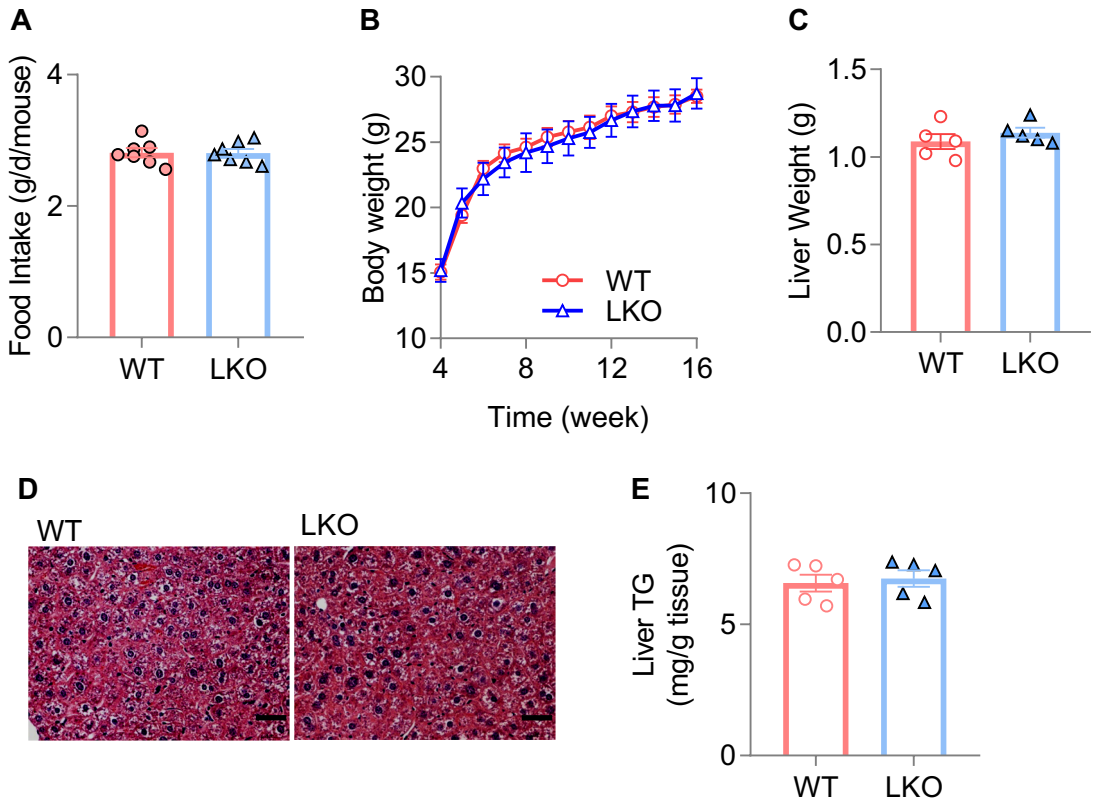


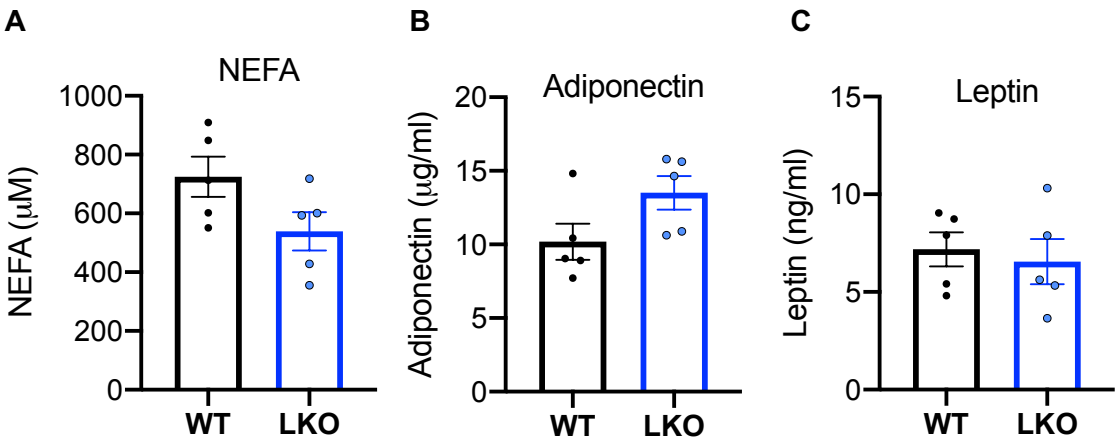
Online Appendix Figure 1. Generation of liver specific knockout of *Cpt1a* mouse model. (A) Schematic diagram showing the strategy for liver specific deletion of *Cpt1a* gene in mice. Homologous recombination-based approach was used to construct *Cpt1a* flox/flox mice. (B) mRNA levels of *Cpt1* isoforms in liver of lean WT and LKO mice. (C) mRNA levels of *Cpt1b* in liver of WT and LKO mice fed on high fat diet for 8 weeks. (D) Western blotting of CPT1A protein expression in lean LKO and WT mice. (E)-(F) Fatty acid oxidation rate in normal and CPT1A deficient hepatocyte determined by seahorse. (n=4) (G) Serum levels of β-hydroxybutyrate in mice (n=5). Data represent mean ± SEM, **p<0.01.



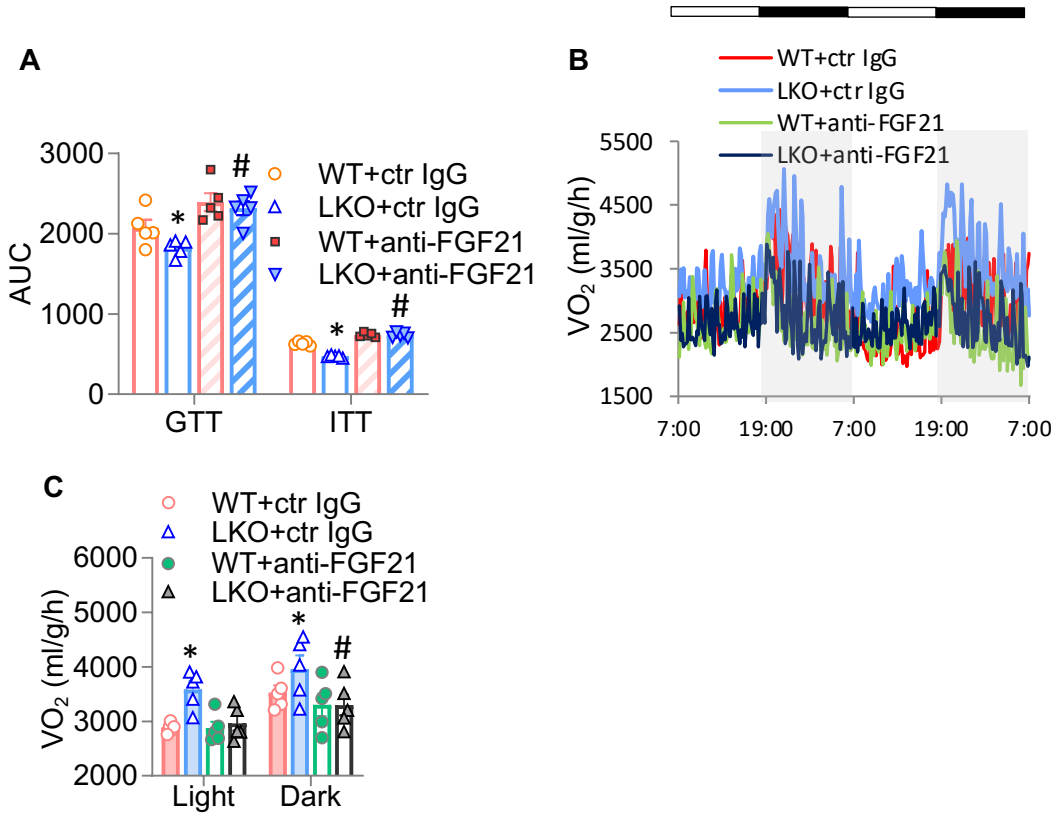
Online Appendix Figure 2. Hepatic deletion of *Cpt1a* led to reduced fatty acid metabolism in mice. WT and LKO mice were subjected to HFD for 8 weeks before analysis. (A) OCR in primary hepatocytes were pre-treated with etomoxir (40uM) or vehicle for 30 min before OCR was measured by seahorse. (B) OCR difference in maximal respiration between vehicle and etomoxir-treated group, indicating the fatty acid oxidation rate of the hepatocytes. (C) Relative fold change of carnitine and acyl-carnitine levels in liver of WT and LKO mice. (D)-(G) mRNA expression of (D) lipid metabolism, (E) lipogenesis, (F) glycolysis, (G) gluconeogenesis in mouse liver. (H) Glycogen content in liver. (I) Ketone body concentration in serum of the mice. (J)-(K) Respiratory exchange ratio (RER) of the mice measured by CLAMS in two consecutive light-dark cycles. (L) Diacyl glycerol level in mouse liver. Data represent mean ± SEM, *p<0.05, **p<0.01, ***p<0.001. OM, oligomycin; FCCP, fluoro-carbonyl cyanide phenylhydrazone; Rot/AA, rotenone and antimycin A. (n=5).



Online Appendix Figure 3. No significant phenotypes were observed in standard chow diet-fed LKO mice. (A) Food intake and (B) Body weight of LKO and WT mice (n=7). (C) Liver weight, (D) HE staining of liver sections and (E) Liver TG content in WT and LKO mice (n=5). Data represent mean ± SEM.



Online Appendix Figure 4. Serum concentration of non-esterified fatty acid (NEFA), adiponectin and leptin in HFD-fed WT and LKO mice. WT and LKO mice were subjected to HFD for 8 weeks and the serum was collected at the fed state. (A) NEFA, (B) Adiponectin and (C) Leptin concentrations were measured. (n=5). Data represent mean ± SEM.



Online Appendix Figure 5. Neutralization of serum FGF21 reverses the insulin sensitivity and increased energy expenditure in LKO mice. HDF-fed WT and LKO mice were i.v. injected with FGF21 neutralizing antibody (anti-FGF21) or control IgG (ctr IgG) every two weeks (n=5). Metabolic phenotypes were examined 8 weeks later. (A) AUC of GTT and ITT of the mice. (B)-(C) Whole body oxygen consumption of the mice (n=5). Data represent mean ± SEM, *p<0.05, vs. WT ctr IgG. #p<0.05 vs. LKO ctr IgG.

Online Appendix Table 1. Primer sequences for RT-qPCR.

Gene	Species	Primer	Sequence
Cpt1a	Mus musculus	forward	CTCCGCCTGAGCCATGAAG
		reverse	CACCAGTGATGATGCCATTCT
Cpt1b	Mus musculus	forward	GCACACCAGGCAGTAGCTTT
		reverse	CAGGAGTTGATTCCAGACAGGTA
Cpt2	Mus musculus	forward	CAACTCGTATACCCAAACCCAGTC
		reverse	GTTCCCATCTTGATCGAGGACATC
Acadm	Mus musculus	forward	AGGGTTTAGTTTTGAGTTGACGG
		reverse	CCCCGCTTTTGTCATATTCCG
Acads	Mus musculus	forward	TGGCGACGGTTACACACTG
		reverse	GTAGGCCAGGTAATCCAAGCC
Acsl6	Mus musculus	forward	AAGTGACAGAGAGTCAGTGGG
		reverse	TAGGGCGGAGAGCCTTCAT
Acat1	Mus musculus	forward	CAGGAAGTAAGATGCCTGGAAC
		reverse	TTCACCCCCTTGGATGACATT
Pgc1a	Mus musculus	forward	CAACATGCTCAAGCCAAACCAACA
		reverse	CGCTCAATAGTCTTGTTCTCAAATGGG
Acsl1	Mus musculus	forward	ATCTGGTGGAACGAGGCAAG
		reverse	TCCTTTGGGGTTGCCTGTAG
Mcad	Mus musculus	forward	AACACTTACTATGCCTCGATTGCA
		reverse	CCATAGCCTCCGAAAATCTGAA
Acot1	Mus musculus	forward	GACAAGAAGAGCTTCATTCCCGTG
		reverse	CATCAGCATAGAACTCGCTCTTCC
Hadha	Mus musculus	forward	TGCATTTGCCGCAGCTTTAC
		reverse	GTTGGCCCAGATTTCGTTCA
Acly	Mus musculus	forward	GCCAGCGGGAGCACATC
		reverse	CTTTGCAGGTGCCACTTCATC
Acaca	Mus musculus	forward	TGTACAAGCAGTGTGGGCTGGCT
		reverse	CCACATGGCCTGGCTTGGAGGG
Fasn	Mus musculus	forward	GCTGCGGAAACTTCAGGAAAT
		reverse	AGAGACGTGTCACTCCTGGACTT
Scd1	Mus musculus	forward	CCCTGCGGATCTTCCTTATC
		reverse	TGTGTTTCTGAGAACTTGTGGTG
Srebf1	Mus musculus	forward	GGAGCCATGGATTGCACATT
		reverse	GGCCCGGGAAGTCACTGT
Pcx	Mus musculus	forward	GGAGCTTATCCCGAACATCC
		reverse	CGGAAGACGTCCATACCATTC
G6pc	Mus musculus	forward	TCTGTCCCGGATCTACCTTG
		reverse	GTAGAATCCAAGCGCGAAAC
Pck1	Mus musculus	forward	TATGCTGATCCTGGGCATAA
		reverse	CACGTTGGTGAAGATGGTGT
Hk2	Mus musculus	forward	TGATCGCCTGCTTATTCACGG
		reverse	AACCGCCTAGAAATCTCCAGA
Pkm1	Mus musculus	forward	GCTGTTTGAAGAGCTTGTGC
		reverse	TTATAAGAGGCCTCCACGCT
Pkm2	Mus musculus	forward	TCGCATGCAGCACCTGATT
		reverse	CCTCGAATAGCTGCAAGTGGTA
Ldha	Mus musculus	forward	GCTCCCCAGAACAAGATTACAG
		reverse	TCGCCCTTGAGTTTGTCTTC
Ldhb	Mus musculus	forward	GGGAAAGTCTCTGGCTGATGAA
		reverse	CTGTCACAGAGTAATCTTTATCGGC
Gapdh	Mus musculus	forward	CCACTCCTCCACCTTTGAC
		reverse	ACCCTGTTGCTGTAGCCA

Online Appendix Table 2. Top up- and down-regulated genes in the liver of LKO mice.

Up		*Down*	
Gm15441	*Zfp628*	*Cpt1a*	*Tkfc*
Tmem86a	*Bglap3*	*Hamp2*	*C230088H06Rik*
B930025P03Rik	*Rufy4*	*Gna14*	*AC160635.2*
Cntnap1	*Sox12*	*Lrtm1*	*Mkx*
Cpt1b	*Peg3*	*Slc22a7*	*Slc30a10*
Igfbp2	*Sema3b*	*Thrsp*	*Lum*
Slc35f2	*Tnfaip8l3*	*Acnat2*	*Sult2a7*
Trpm4	*Tspan17*	*Mmd2*	*Gm28048*
Wdfy4	*Fads2*	*Ppp1r3b*	*Ntrk2*
Gm16759	*Slc16a5*	*Hcn3*	*Khk*
Cebpb	*Esr1*	*Pklr*	*Pygl*
Osbpl3	*Cbx7*	*Trhde*	*9030619P08Rik*
Blnk	*Pnldc1*	*Gck*	*Cyp2c29*
Cyp4a32	*Fgf21*	*Tmie*	*Glipr1*
Oas1g	*Arsg*	*Car14*	*Tlcd2*
Serinc2	*Tmem238*	*Slc10a2*	*Spp1*
Gpc1	*Sik1*	*B430219N15Rik*	*Slc3a1*
C730034F03Rik	*Lysmd2*	*Gm35986*	*Prkar2b*
Slc13a5	*Amigo2*	*Acot11*	*C330021F23Rik*
Meg3	*AC098716.1*	*Derl3*	*Tnfrsf11b*
Gal3st1	*Irf7*	*AC151971.2*	*Serpina12*
Ctcflos	*Aqp7*	*Cyp17a1*	*Gm12718*
Ehhadh	*Ifi27l2b*	*Slc17a8*	*1810011O10Rik*
Sel1l3	*Mfsd7c*	*Slc38a11*	*Sox9*
Oas1a	*Cd276*	*Gstt3*	*Ube2u*
Gm45531	*Prrx1*	*Cyp2c70*	*Slc41a2*
Gstp2	*Brca1*	*Chil1*	*Vmn2r20*
Igsf23	*Lad1*	*Fras1*	*Plcd3*
Agap2	*Zbp1*	*Arhgap26*	*Nupr1*
Cgref1	*Alas1*	*Fam81a*	*Gm26917*
Ntrk1	*Fut1*	*Gm12033*	*Scara3*
Cyp4a12b	*Rgs3*	*Slc26a4*	*Fam198a*
Tbc1d30	*Syne3*	*Prkcg*	*Atp2b2*
Cyp4a31	*Retsat*	*Atp4a*	*Orm2*
Slc41a3	*Fbxo21*	*Scara5*	*Chrnb2*
Hsf2bp	*Scn8a*	*Chic1*	*Sult1d1*
Rian	*Gucy2c*	*Scd1*	*Col15a1*
Gm14097	*2410089E03Rik*	*Cxcl14*	*Bdh2*
Aqp4	*Det1*	*Fam83f*	*Saa3*
Ifi44	*Hhipl2*	*Egfr*	*Mt2*
Emp2	*Hspb1*	*Mt1*	*Gstm2*
Sptlc3	*Gm43863*	*Pde4b*	*Robo1*
Apoa4	*Rarb*	*Srebf1*	*AC153954.2*
Pisd-ps1	*Chrna2*	*AC098712.1*	*Slc22a27*
Itpka	*Gm13375*	*Acpp*	*Hapln4*
Ucp3	*Rdh16f1*	*Orm3*	*Smoc2*
Elovl2	*Rbm24*	*Leap2*	*Robo2*
4833411C07Rik	*Rgs14*	*Clec4d*	*Lcn2*
Gabrd	*N4bp2os*	*Cyp2c55*	*Gpr135*
Nt5dc2	*Mtx3*	*Dusp14*	*Gm15318*